The Chemistry of Diphenyl N-Cyanocarbonimidate

by

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A thesis presented to the University of London in partial fulfilment of the requirements for the degree of Doctor of Philosophy

Department of Chemistry
University College London
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Dedicated with love to
my parents

The Road goes ever on and on
Down from the door where it began.
Now far ahead the Road has gone,
And I must follow, if I can,
Pursuing it with weary feet,
Until it joins some larger way,
Where many paths and errands meet.
And whither then? I cannot say.

Frodo Baggins in 'The Lord of the Rings'

All knowledge is of itself of some value.
There is nothing so minute or inconsiderable,
that I would not rather know it than not.

Dr Johnson in Boswell's 'Life of Johnson'

Acknowledgements

I wish to thank Dr's Peter Garratt and Roger Wrigglesworth for suggesting this research problem, for their enthusiasm, encouragement, and friendship throughout this work. Thanks are also due to all members of the Sandoz Institute for Medical Research who have given so freely of their time, but especially the members of the Chemistry Department who have bourne the brunt of my intrusions over the last three years. Thanks also to Deirdre for her help with binding.

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To Richard 'The Beadle' Towle thanks for all the fun and games over the last three years, and to Peter Leighton thanks for not 'throwing the book' at me on several occasions.

I am grateful to Mary and Eileen for providing the fuel to keep the boiler stoked over the last three years.

Finally, I am indebted to my parents, for all their love, encouragement, support, understanding and help throughout my life, and it is to them that I dedicate this thesis.

Abstract

The synthesis of a variety of heterocyclic compounds by the sequential addition of two nucleophiles to a one carbon equivalent is described. Treatment of this one carbon equivalent, diphenyl N-cyanocarbonimidate **53**, with the first nucleophile leads to N-cyano-O-phenylisourea intermediates. These compounds were shown to be a mixture of isomers by variable temperature ^{1}H n.m.r. spectroscopy and the origin of the stereoisomerism is discussed. The N-cyano-O-phenylisoureas were then treated with a second nucleophile which displaced phenol, giving an intermediate which spontaneously cyclised to produce a heterocyclic ring.

In this way 6-substituted and 5,6-disubstituted-dihydro-4(3H)-pyrimidinones were synthesised together with 5,6-dihydro-4(3H)-pyrimidinones and imidazolidin-5-ones substituted with carbocyclic sugar analogues at N-3. An attempt to synthesise pyrimidine isonucleosides failed due to the steric hindrance present in the sugar.

Several of the imidazolidin-5-ones were rearranged to dihydro-4(3H)-pyrimidinone-6-carboxylic acids by a ring expansion reaction.

Investigations into the hydrolysis of the cyanoimine portion of several molecules using trifluoroacetic acid are reported.

The synthesis of several triazoles, using the bifunctional nucleophile hydrazine and its analogues, is reported. A temperature dependent competition between synthesis of the triazole and the corresponding imidazole, *via* different cyclisation modes, is described, and a mechanism for the reaction is discussed.

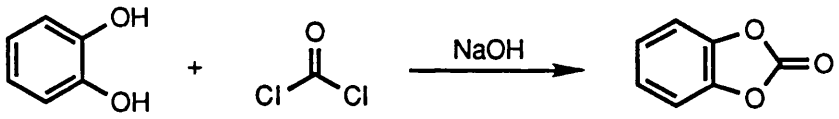
Contents

Introduction

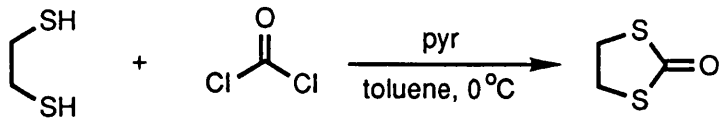
For most of the common heterocyclic ring systems there are a wide range of synthetic routes available.[1] These syntheses can be broadly divided into two groups, those involving transformations on preformed heterocycles and those involving cyclisation of acyclic precursors. The latter group can be further sub-divided into cyclisation reactions in which two ring bonds are formed in the ring closure process and cyclisation reactions in which a single bond is formed. This theses is partly concerned with the latter type, in particular the sequential addition to one carbon compounds. One carbon compounds in which the carbon atom is sp^2 hybridised and is bonded to two potential leaving groups have long been known. The synthesis and reaction of some of the more common examples is now described.

1.1 Phosgene, thiophosgene and related compounds

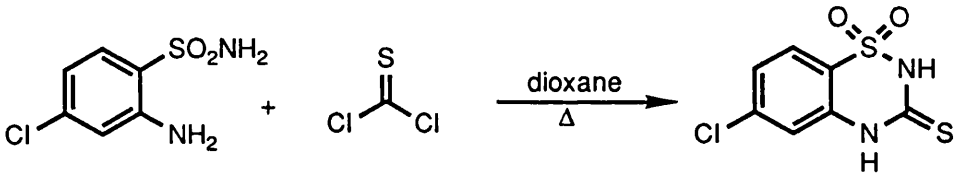
Phosgene **1** and thiophosgene **2** were probably the first one carbon compounds to be used in the preparation of heterocycles and their use is now commonplace. Phosgene **1** reacts with primary amines to give N-substituted carbamyl chlorides, N-substituted isocyanates or N, N'-disubstituted ureas depending on the amine used. The carbamyl chlorides are highly unstable with respect to loss of hydrogen chloride and give the corresponding isocyanates. Phosgene reacts with bifunctional nucleophiles such as catechol **3**[2] and 1,2-ethanediol **4**[3] to form phenylene carbonate **5** and 1,3-dithiolan-2-one **6**, respectively. Its main use, therefore, is to introduce an oxo substituent between two heteroatoms. Thiophosgene **2** shows analogous reactions to phosgene **1**, thus the aminobenzenesulphonamide **7** condenses with **2** to give the benzothiadiazene **8**.[4]



3 **1** **5**

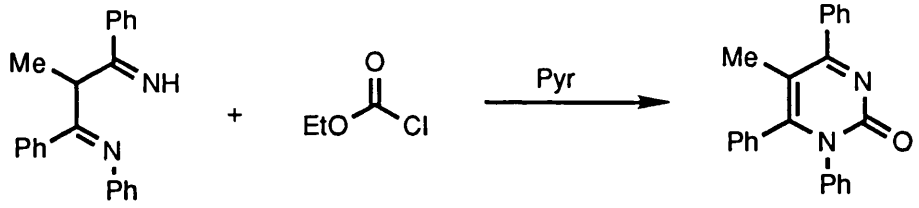


4 **1** **6**



7 2 8

Derivatives of phosgene **1** and thiophosgene **2** can also be condensed with bifunctional nucleophiles in a similar fashion. Ethyl chloroformate **9** and 1-imino-2-methyl-1,3-diphenyl-3-phenyliminopropane **10** in pyridine at 0 °C give 5-methyl-1,4,6-triphenyl-2(1H)-pyrimidinone **11**.[5] Diethyl carbonate **12** and 2-(*m*-chlorophenyl)-2-ethylmalondiamide **13** react to give the barbituric acid **14**.[6] Similarly **12** condenses with the 1,3-diamine **15** to give the isoquinoline derivative **16**.[7]



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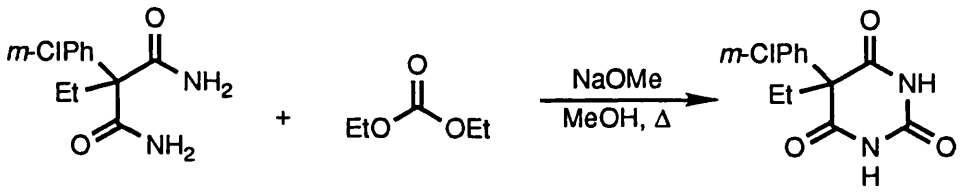

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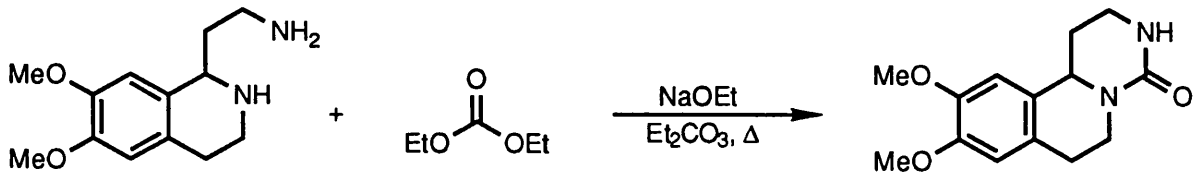
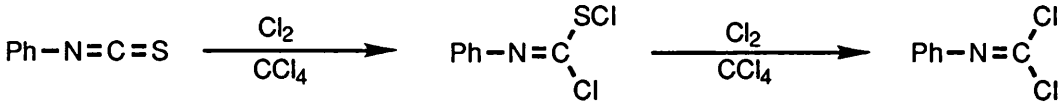


15 12 16

1.2 The isocyanide dihalides

The oldest method for the preparation of alkyl and aryl isocyanide dihalides is the chlorination of isothiocyanates.[8] Chlorination of phenylisothiocyanate **17** at low temperature in chloroform led to the elimination of sulphur dichloride and the formation of phenylisocyanide

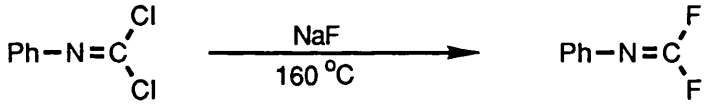
dichloride **18**. Nuclear chlorination products are also obtained in this reaction, but this problem can be avoided by using carbon tetrachloride as the solvent. The reaction has a multistep mechanism; the primary chlorinated adduct **19** is formed in a strongly exothermic reaction; further chlorination of this intermediate leads to the elimination of sulphur dichloride and the formation of **18** with no appreciable evolution of heat.



17 **19** **18**

The chlorination of isothiocyanates is not generally applicable for the synthesis of isocyanide dichlorides, thus a wide range of complementary reactions have been developed including the addition of halogen to isocyanides,[9,10] the chlorination of monosubstituted formanilides in the presence of sulphuryl chloride/thionyl chloride,[11] and the chlorination of isocyanates with phosphorus pentachloride.[12] These and other special methods have been reviewed by Kühle *et al.*[13a]

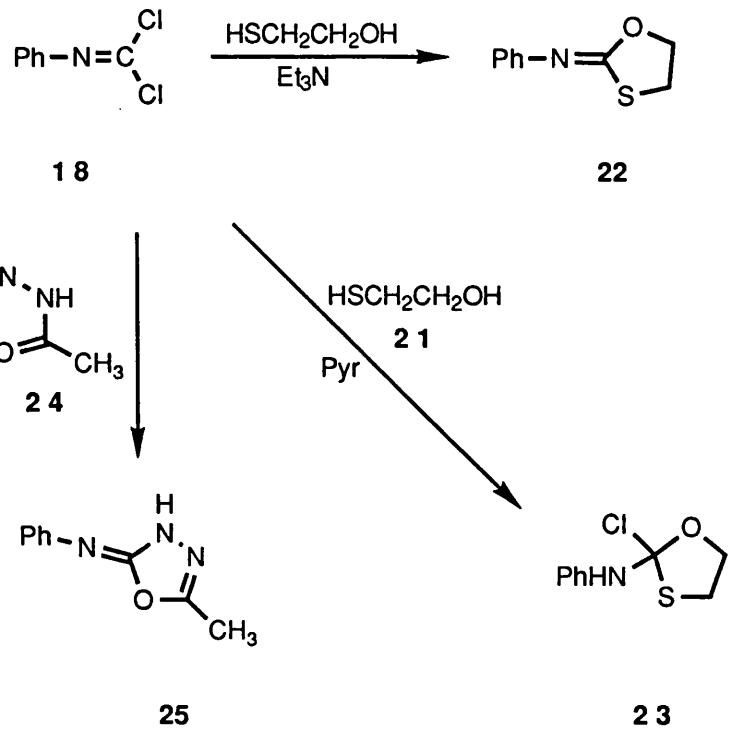
Isocyanide difluorides can generally only be obtained from the corresponding isocyanide dichlorides, for example phenyl isocyanide dichloride **18** reacts with an excess of sodium fluoride at 160 °C to give phenyl isocyanide difluoride **20**.[14]



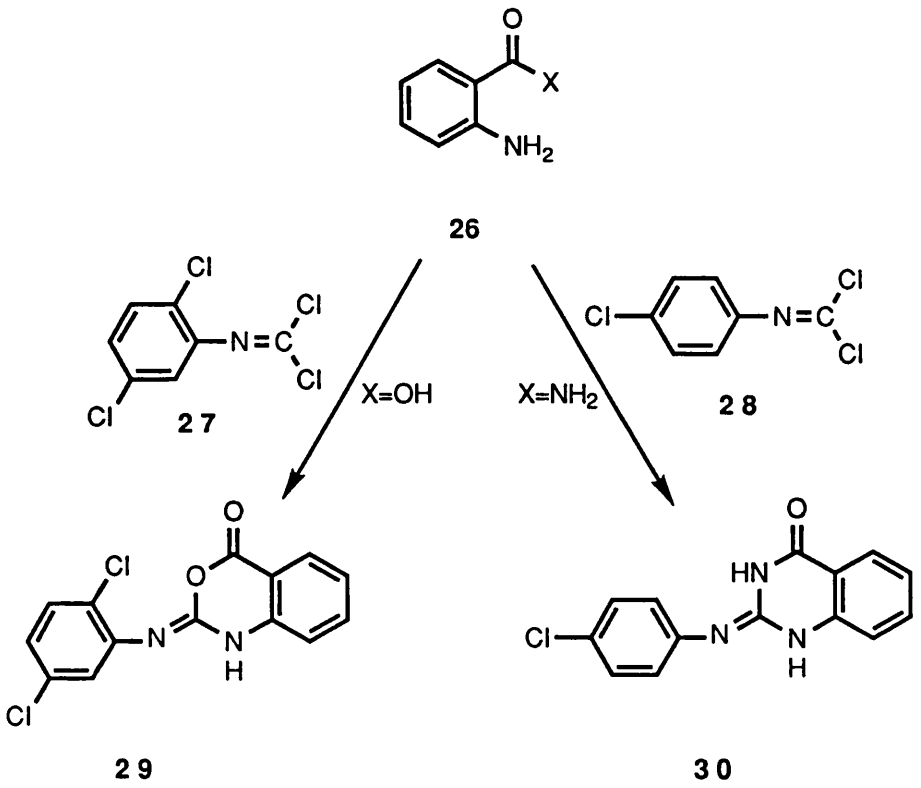
18 **20**

The preparation of acyl isocyanide dihalides is similar to the preparation of alkyl and aryl isocyanide dihalides and is encompassed in the review by Kühle *et al.*[13a] In addition, isocyanide dichlorides with a variety of other substituents on the imine nitrogen are also available, one example being the sulphonate group.[13a]

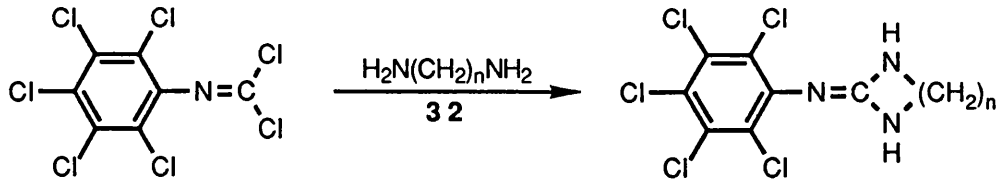
The cyclisation of isocyanide dichlorides requires a variety of reaction conditions depending on the starting materials, and different conditions can lead to different cyclisation products. Thus the reaction of phenyl isocyanide dichloride **18** with mercaptoethanol **21** in the presence of triethylamine yields 2-phenylimido-1,3-oxathiolane **22**, while in the presence of pyridine 2-chloro-2-phenylimido-1,3-oxathiolane **23** is obtained.[15] The 5-membered heterocycles produced from isocyanide dichlorides have been extensively studied, and the reaction appears to accept almost any combination of heteronucleophiles, for instance N-aminoethanamide **24** reacts with phenyl isocyanide dichloride **18** to give the 1,3,4-oxadiazine **25**.[13b]



More complex heterocycles have been prepared from isocyanide dichlorides in isolated cases. Anthranilic acid **26a** (X=OH) and anthranilamide **26b** ($X=NH_2$) react with the isocyanide dihalides **27** and **28** to yield the benzoxazine **29** and the quinazoline **30** respectively.[13b]

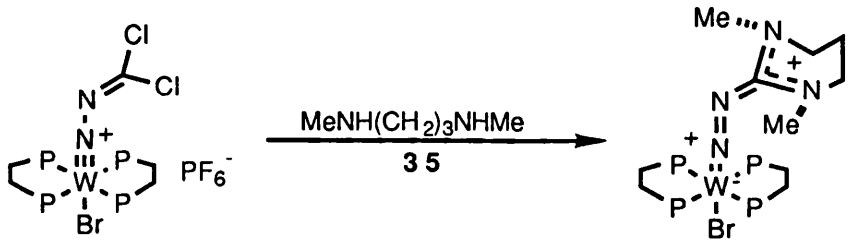


Isocyanide dihalides give 6-membered heterocycles on reaction with 1,3-diamines, 1,3-dithiols or 3-amino-1-propanols. Pentachlorophenyl isocyanide dichloride **31** reacts with 1,4-diaminobutane **32** (n=4) and 1,6-diaminohexane **32** (n=6) to give 7-membered heterocycles **33** (n=4) and 9-membered heterocycles **33** (n=6) respectively.[13b]



31 **33**

Dichlorodiazomethane does not exist in the free state but it can be stabilised within the coordination sphere of tungsten to give the dichlorodiazomethane complex **34**, which can be condensed with N,N'-dimethyl-1,3-diaminopropane **35** to give the hexahydropyrimidine complex **36**.[16] This was proposed to have the structure shown on the basis of the ^1H n.m.r. spectrum which showed that the N-methyl signals were equivalent down to -100 °C.



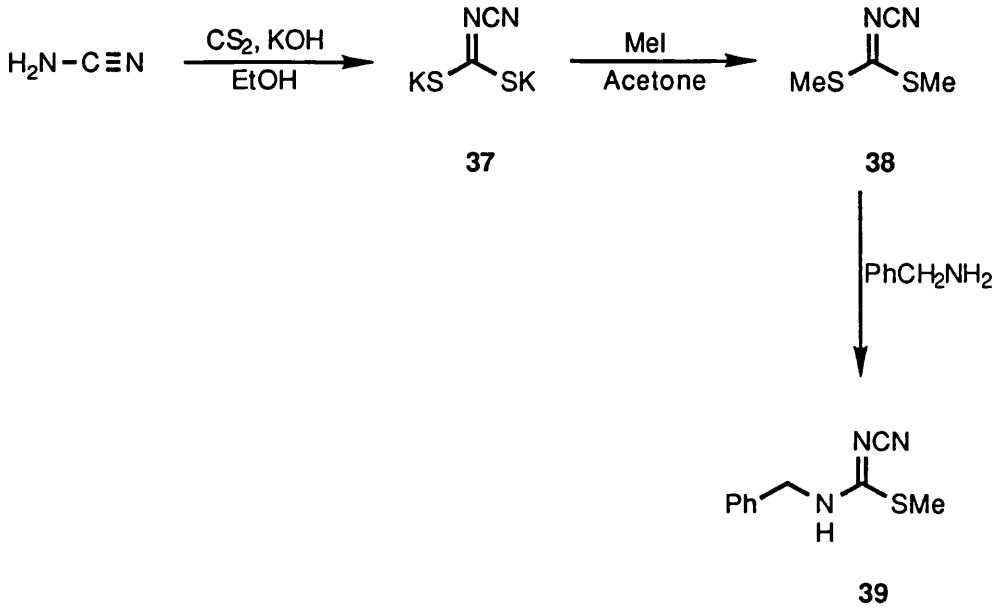
34 **36**

In a similar way to phosgene, the isocyanides have the disadvantage that they are extremely toxic. Their vapours are extremely irritating to the eyes and prolonged exposure to phenyl isocyanide dichloride **18** is reported to cause corneal ulceration and temporary loss of vision, which led to its limited use as a 'blinding gas' during the First World War. There is again the disadvantage of not being able to control the reaction and isolate the product of the first nucleophilic addition-elimination, since this is still highly reactive.

1.3 Dimethyl cyanodithiocarbonimidate and related compounds

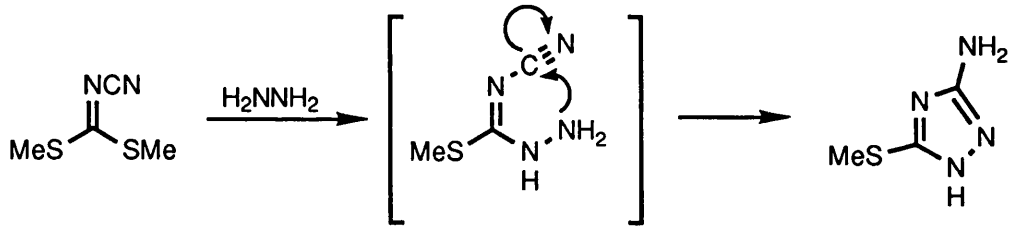
Dimethyl cyanodithiocarbonimidate **38** has found widespread use in the synthesis of heterocyclic compounds in recent years. It is prepared in two steps by first condensing carbon disulphide with cyanamide in the presence of potassium hydroxide, and then treating the intermediate cyanodithiocarbonimidate dianion with methyl iodide.[17] Treatment of **38** with mono functional nucleophiles results in the displacement of methanethiol to give N-substituted-N'-

cyano-S-methylisothioureas, which are stable solids. Primary aliphatic amines react with **38** at room temperature. Benzylamine, for example, reacts with **38** to give N-benzyl-N'-cyano-S-methylisothiourea **39**.[18] Primary aromatic amines require boiling in ethanol to effect the reaction and the attachment of electron withdrawing groups to the phenyl ring often results in a failure of the nucleophile to react. t-Butylamine and secondary amines also fail to react with **38**.



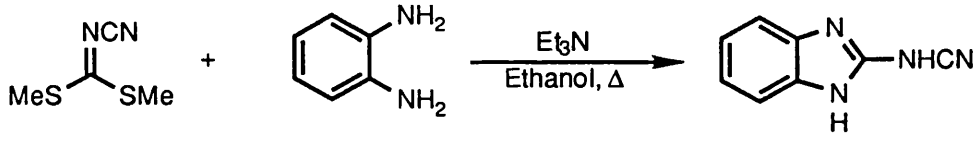
37 **38** **39**

Treatment of **38** with bifunctional nucleophiles such as hydrazine, leads to displacement of one molecule of methanethiol to give the isothiourea **40**, which cyclises spontaneously by attack of the NH_2 group at the nitrile carbon, rather than the imine carbon, to give the thermodynamically more favoured 5-membered ring.[19]



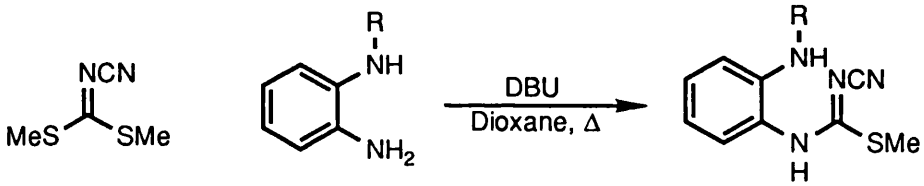
38 **40** **41**

Bifunctional nucleophiles, such as *o*-phenylenediamine **42**, react with **38** by sequential displacement of the two molecules of methanethiol to afford the 2-cyanoaminobenzimidazole **43**.[17] The reaction fails completely when electron withdrawing groups are attached to the aromatic ring.

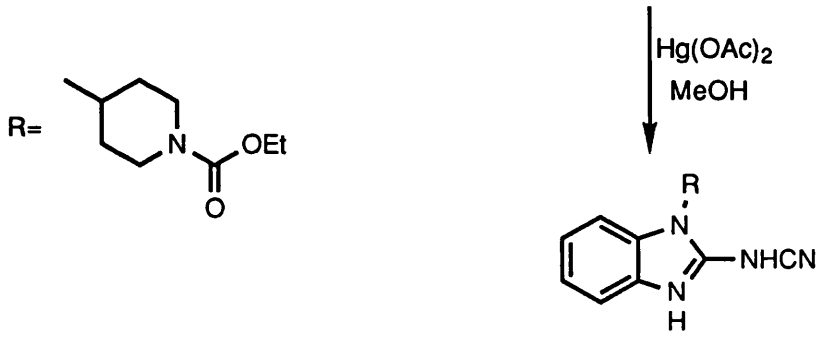


38 **42** **43**

Treatment of **38** with the sterically hindered phenylenediamine **44** yielded none of the desired benzimidazole **46**[20] using the conditions described by Wittenbrook.[17] When the reaction was carried out in the presence of 1,8-diazabicyclo-[5,4,0]-undec-7-ene (DBU) at 80 °C only the acyclic isothiourea **45** was obtained. A variety of conditions were tried in an attempt to cyclise **45**, but success was only achieved using mercuric acetate in methanol, which resulted in an essentially quantitative conversion.

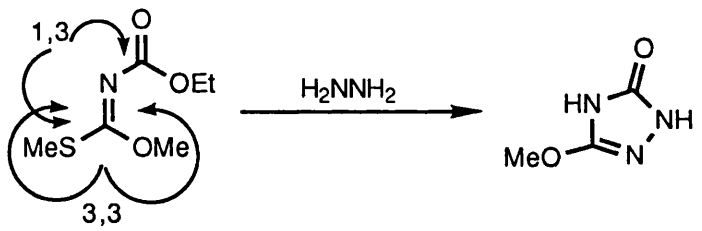


38 **44** **45**



46

There are isolated cases of one carbon compounds related to **38** being used for heterocyclic syntheses. The carbamate **47** can either undergo 1,3- or 3,3- cyclisations with bifunctional nucleophiles depending on the nature of the nucleophile. Thus hydrazine gives the 1,3-cyclisation product **48** while 1,3-diaminopropane **32** (n=2) gives the pyrimidine derivative **49**.[21]



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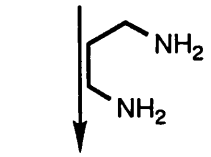
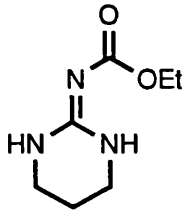
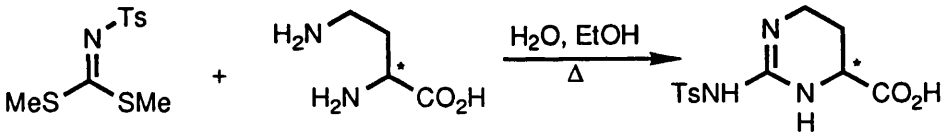




49

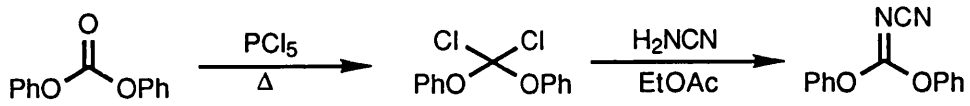
Dimethyl N-tosyldithiocarbonimidate **50** reacts with aliphatic diamines in refluxing aqueous ethanol to give cyclic tosyl guanidines in high yields.[22] Thus **50** reacts with (S)-(+)-2,4-diaminobutanoic acid **51** to give the optically active, cyclic guanidine **52**, which was detosylated by treatment with anhydrous hydrogen fluoride.



50 51 52

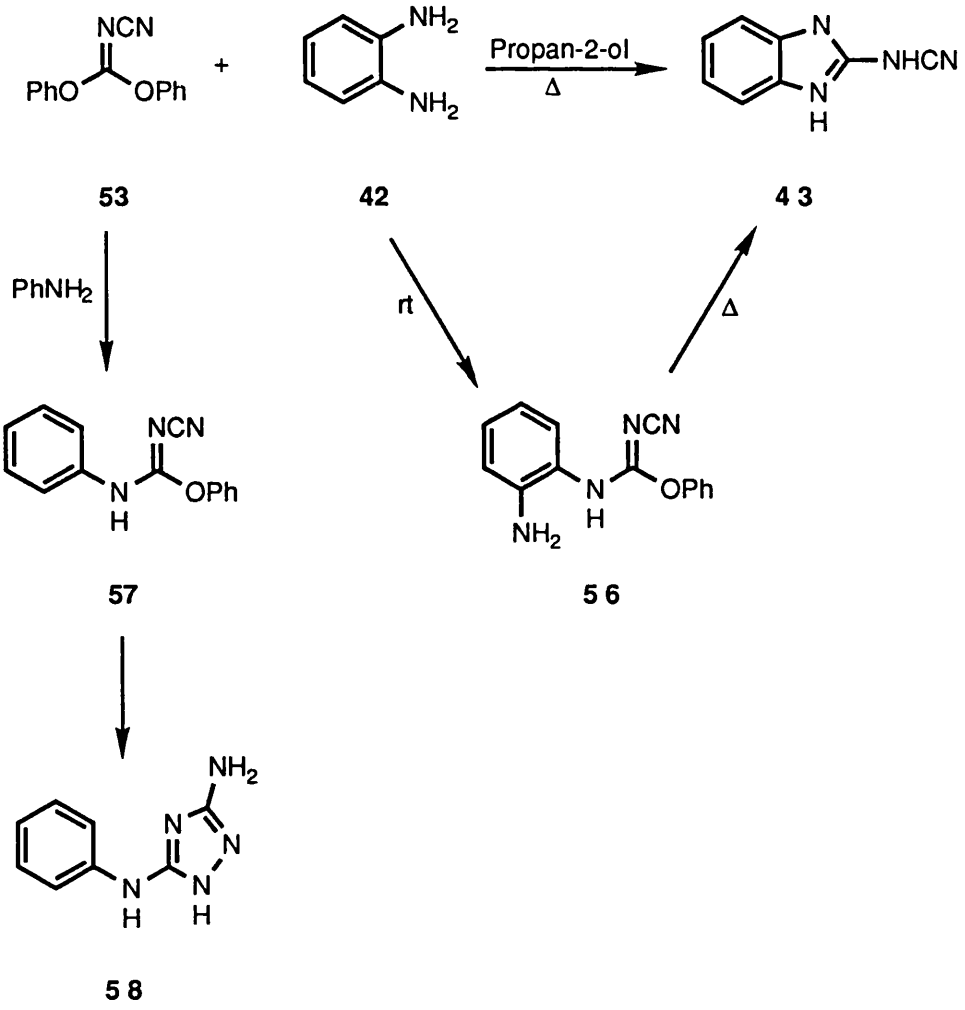
1.4 Diphenyl cyanocarbonimidate and related compounds

The potential of diphenyl cyanocarboimidate **53** as a synthon for heterocyclic compounds has been known for several years,[23] but until recently little use was made of it in this field. It can be prepared on a large scale in high yield. Treatment of diphenyl carbonate **54** with phosphorus pentachloride, with continuous removal of the phosphorus oxychloride formed, gives 1,1-dichloro-1,1-diphenoxymethane **55**. Condensation of **55** with cyanamide affords **53**. This reagent has a number of advantages over dimethyl cyanodithiocarbonimidate **38**. The first advantage is that bifunctional nucleophiles attack the imine carbon under extremely mild conditions allowing the isolation of O-phenylisoureas. Slightly more vigorous conditions then lead to the displacement of a second molecule of phenol to give heterocyclic compounds.



54 **55** **5 3**

o-Phenylenediamine **42** condenses with **53** at room temperature in propan-2-ol to give the O-phenylisourea **56**, which cyclises to the benzimidazole **43** on refluxing in propan-2-ol. Alternatively, the benzimidazole **43** can be obtained directly by refluxing the two reagents together.[23] Another major advantage of the phenoxy reagent is that the production of foul smelling mercaptans is avoided.



53 **42** **4 3**

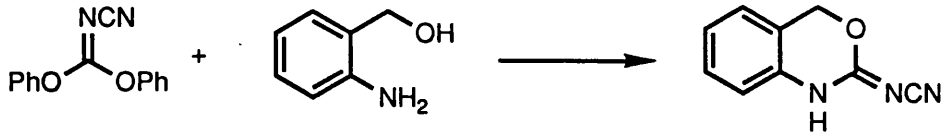
57 **5 6**

5 8

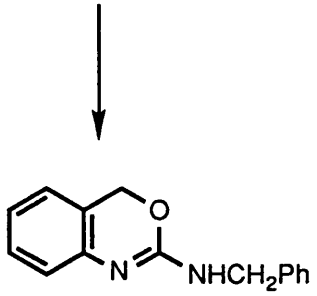
It has been suggested that the ease with which transformations take place is largely due to the stability of the phenoxide ion as a leaving group and its weak nucleophilicity.[23] Even poor nucleophiles such as *p*-chlorophenylenediamine condense with **53** almost quantitatively on simply stirring in propan-2-ol at room temperature. In addition, the O-phenylisoureas are much more easily attacked by a second nucleophile than the S-methylisothioureas. The O-

phenylisoureas are attacked by hydrazine, in a similar way to the isothioureas. Thus reaction of **53** with aniline gives N-cyano-N'-phenyl-O-phenylisourea **57**, which cyclises to give the triazole **58** on treatment with hydrazine.

Further advances in the use of diphenyl cyanocarbonimidate **53** in heterocyclic synthesis have recently been made.[24,25] Thus treatment of **53** with 2-aminobenzyl alcohol **59** gave the 2-N-cyanoimino-4H-1,3-benzoxazine **60**. Compound **60** could be further modified by treatment with an amine in boiling propan-2-ol, for example **60** with benzylamine gave 2-benzylamino-1,3-benzoxazine **61** *via* loss of H_2NCN.[25]

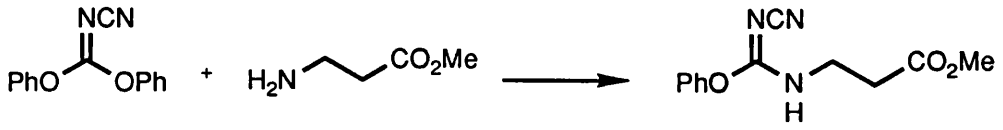


53 **59** **60**

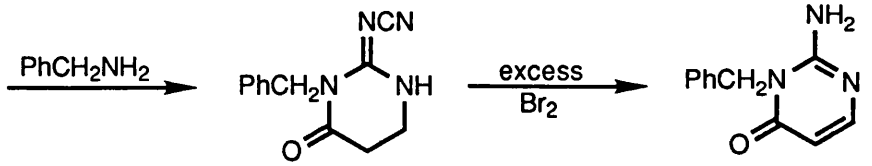


61

Treatment of **53** with a β-amino ester has been used as a method of synthesising dihydropyrimidines. Thus use of β-alanine methyl ester **62** gave the dihydropyrimidine **64** *via* the O-phenylisourea **63**, which could be further modified to the pyrimidine **65** by a bromination-dehydrobromination sequence.[24]

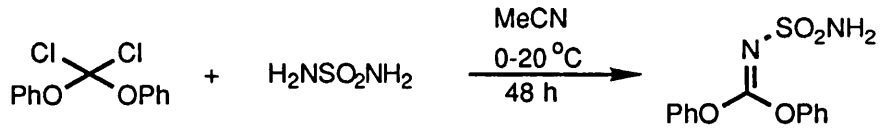


5 3 **62** **6 3**



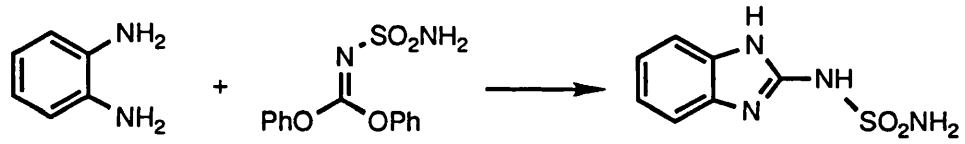
64 **65**

Recently a new one carbon synthon, diphenyl N-sulphamoylcarbonimidate **66** has been reported[26] as a versatile building block for the construction of heterocycles. Diphenyl N-sulphamoylcarbonimidate **66** is prepared from dichlorodiphenoxymethane **55** by condensation with sulphamide **67** in acetonitrile at 0 °C.



55 **67** **66**

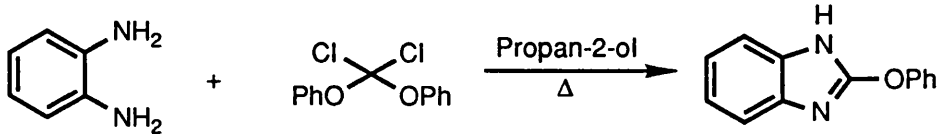
As with the previous reagent, nucleophilic displacement of phenol is easily achieved, for example reaction of *o*-phenylenediamine **42** with **66** gives the bicyclic benzimidazole **68**.



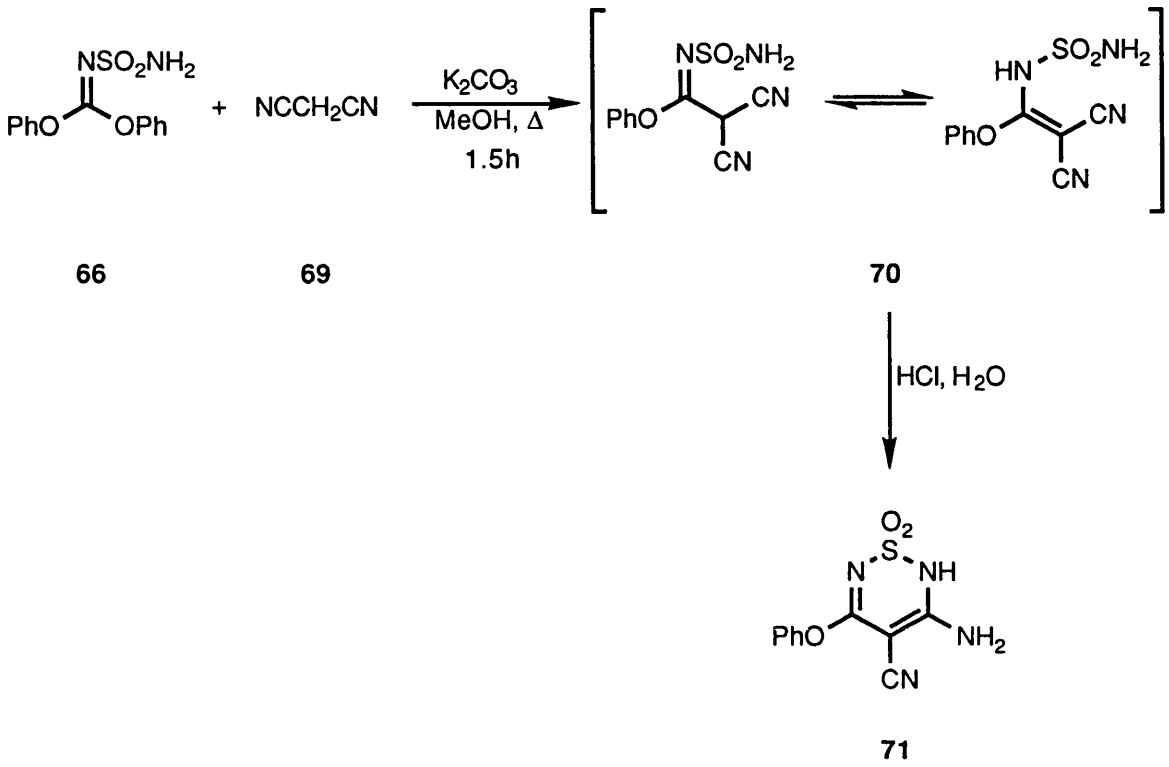
42 **66** **68**

Furthermore, N-sulphamoylcarbonimidate **66** has been shown to undergo nucleophilic phenoxy group displacement with C-nucleophiles. With malononitrile **69** in the presence of potassium carbonate, for example, the primary condensation product **70** may either be isolated or cyclized by subsequent addition of 6N hydrochloric acid solution to give the 2H-1,2,6-thiadiazine 1,1-dioxide **71**.

1,1-Dichloro-1,1-diphenoxymethane **55** has also been shown to have potential as a reagent for heterocyclic synthesis. Treatment of **55** with *o*-phenylenediamine **42** yields 2-phenoxybenzimidazole **72**.[27]



42 **55** **72**



66 69 70 71

1.5 Aims of the present work

The use of diphenyl cyanocarbonimidate **53** in the synthesis of various heterocyclic systems is investigated and described. Chapters 2 and 3 describe the synthesis of 6-substituted and 5,6-disubstituted dihydropyrimidinones. Chapter 4 describes the synthesis of carbocyclic dihydropyrimidinones and imidazolones. Chapter 5 describes reactions at the N-cyanoimine functional group, whilst Chapter 6 describes the preparation of 1,2,4-triazoles. Chapter 7 details investigations into the stereoisomerism of some of the compounds synthesised. The experimental sections are grouped together in Chapter 8.

Synthesis of 6-Substituted and 5,6-Disubstituted - dihydro-4(3H)-Pyrimidinones

2.1 Introduction

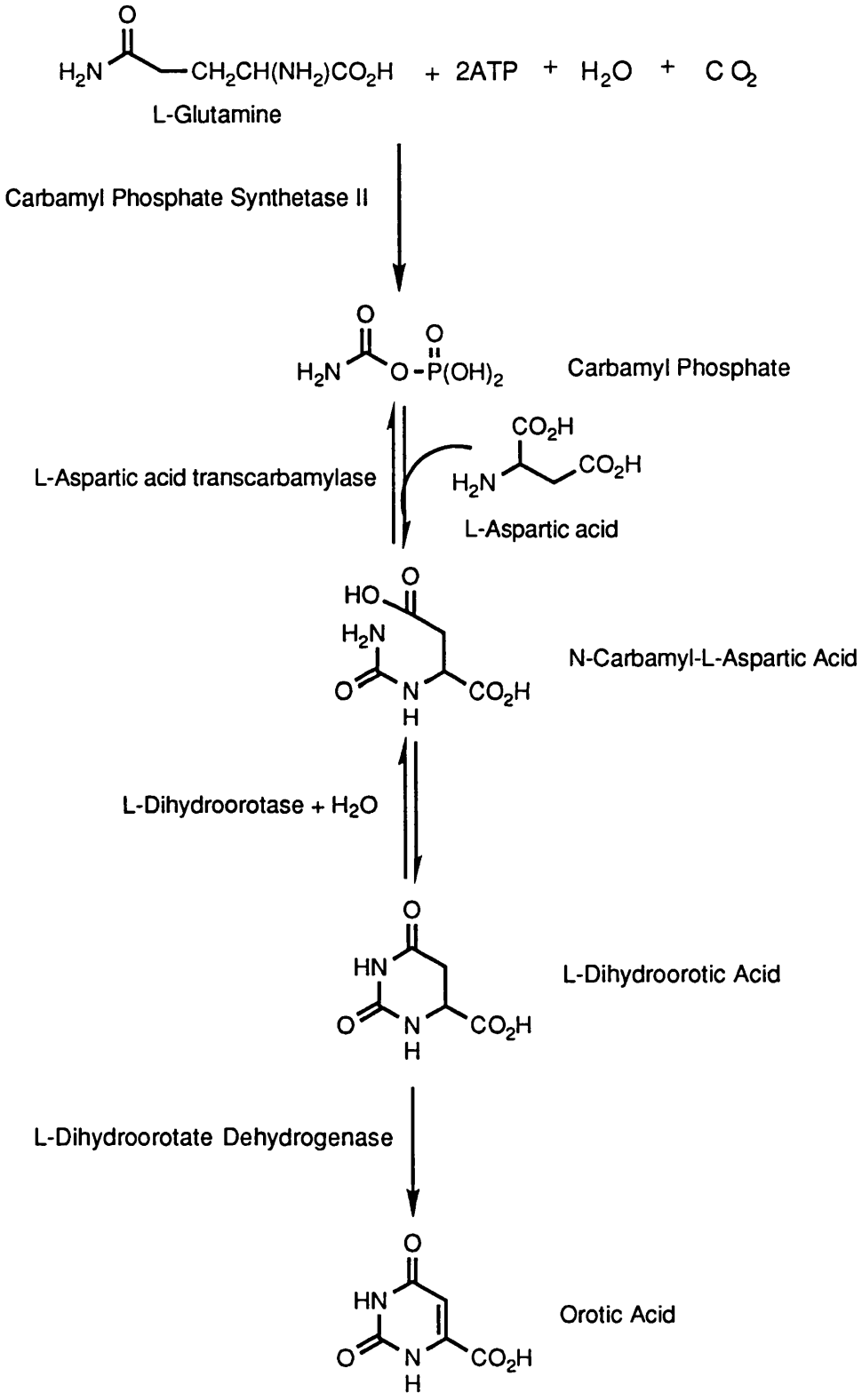
Pyrimidines are an essential component of life and they are distributed throughout the spectrum of living organisms. The requirement for pyrimidines can be fulfilled by two synthetic pathways: a *de novo* route and a salvage pathway. Uridine-5'-monophosphate (UMP) is a common product of both of these pathways. The *de novo* pathway is generally considered to consist of six enzymes: carbamyl phosphate synthetase II (CPS II); L-aspartate transcarbamylase (ATCase); L-dihydrorotase (DHOase); L-dihydroorotate dehydrogenase (DHO deHase); orotate phosphoribosyl transferase (OPRTase); and orotidine-5'-monophosphate decarboxylase (OMP deCase). A brief overview of the biosynthetic pathway is given here. For a more detailed account the reader is directed to the reviews of Shambaugh[28] and Jones.[29] The main components of the pyrimidine ring are derived from L-aspartic acid and L-glutamine, while the ribosyl and phosphoryl moieties are transferred from phosphoribosyl pyrophosphate (Scheme 2.1).

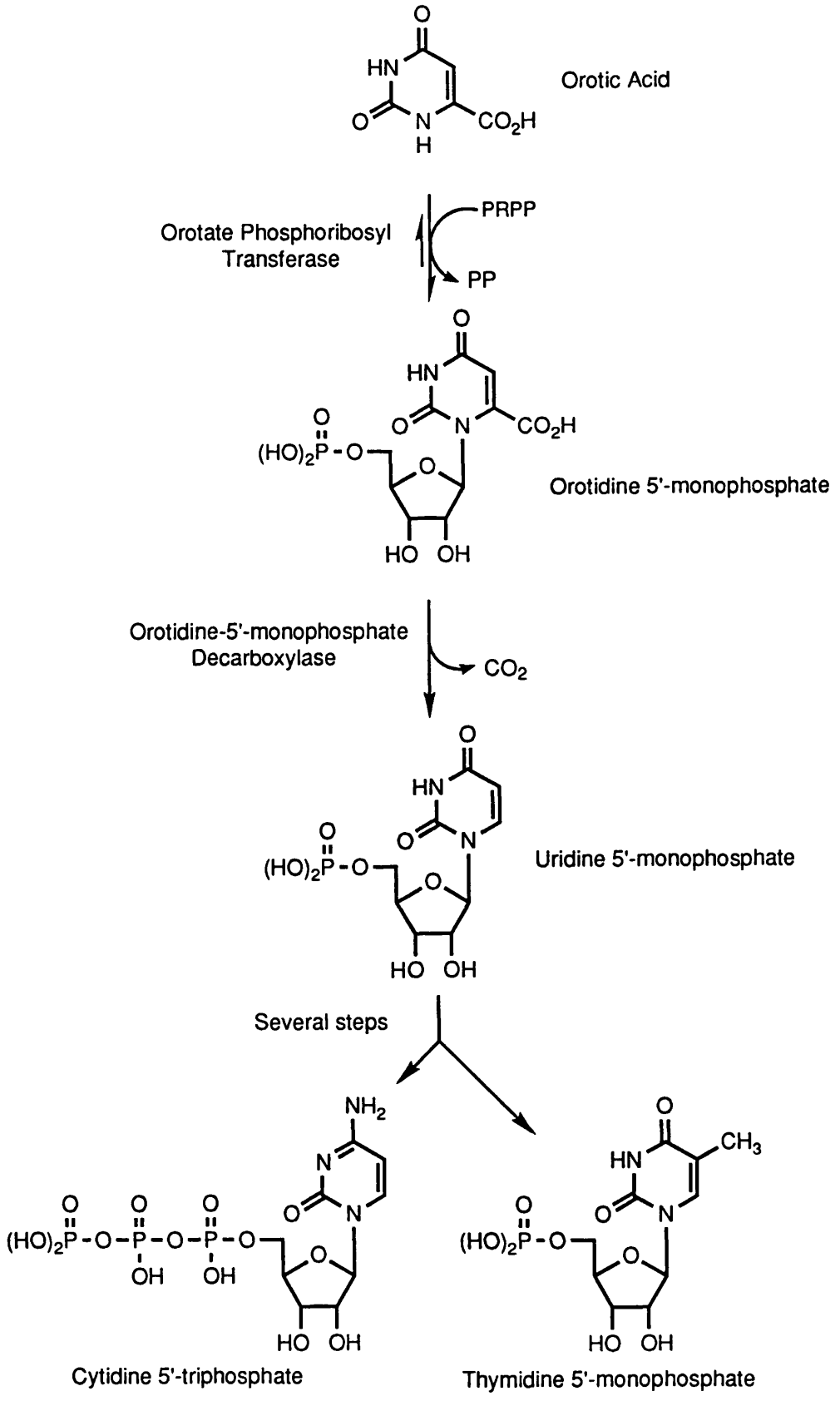
So far as is known, this 'genealogy' of the pyrimidine ring is universal and serves to underscore the intimate relationship of the dicarboxylic amino acids and their amides with nucleic acid biosynthesis. The salvage pathway, by contrast, utilizes preformed nucleosides or bases in the biosynthesis of pyrimidine nucleotides.[188] Two additional enzymes, namely thymidylate synthetase (TS) and cytidylate synthetase (CTP synthetase), catalyze modification of the pyrimidine ring to yield the two other major pyrimidine nucleotides, cytidine-5'-triphosphate and thymidine-5'-monophosphate (TMP).

The intracellular localisation of the six catalytic activities of the *de novo* pathway appear to be optimized to ensure efficient flux and to permit changing of the output in response to physiological needs.[30] CPS II, ATCase and DHOase exist as a large cytosolic multienzyme complex (*pyr* 1-3). The proximity of consecutive catalysts serves to channel products from one active site to another without undue dilution by diffusion into the cytoplasmic milieu. The fourth enzyme of the pathway, DHO deHase, is particulate and is sequestered on the outer face of the inner mitochondrial membrane. Thus this enzyme is ideally sited to exert regulatory control over the velocity of pyrimidine ring assembly because both its substrate and product must diffuse across the mitochondrial membrane. Another cytosolic multienzyme complex, (*pyr* 5,6), composed of OPRTase and OMP deCase, effects the last two steps of pyrimidine biosynthesis, producing UMP as the final product for use as such or for further transformation into cytidine and thymidine nucleotides.

The pyrimidine biosynthetic pathway is subject to complex regulation by its products and substrates; as a result, physiological or drug induced alterations in the levels of these

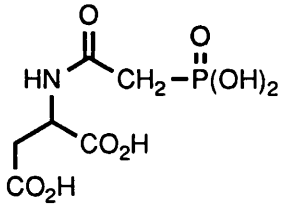
Scheme 2.1


L-Glutamine
+ 2ATP + H_2O + CO_2
Carbamyl Phosphate Synthetase II
Carbamyl Phosphate
L-Aspartic acid transcarbamylase
L-Aspartic acid
N-Carbamyl-L-Aspartic Acid
L-Dihydroorotase + H_2O
L-Dihydroorotic Acid
L-Dihydroorotate Dehydrogenase
Orotic Acid


Orotic Acid
Orotate Phosphoribosyl Transferase
PRPP
PP
Orotidine 5'-monophosphate
Orotidine-5'-monophosphate Decarboxylase
CO2
Uridine 5'-monophosphate
Several steps
Cytidine 5'-triphosphate
Thymidine 5'-monophosphate

regulators can provoke important changes in the *de novo* output of UMP. A more detailed account of this control process can be found elsewhere.[30] Inasmuch as the specific activities of five of the six enzymes of the central pathway are similar and low, only that of ATCase being disproportionately high, the system is an attractive one in terms of pharmacological intervention.

This having been said, there are currently no good inhibitors of any step in the pyrimidine biosynthetic pathway. Perhaps the best inhibitor to date is PALA (N-(phosphonoacetyl)-L-aspartic acid) **73**, which was synthesised as a stable "transition state analogue" of the reaction catalysed by ATCase[31] and, as such, combines the structural features of the two natural substrates, carbamyl phosphate and L-aspartic acid.

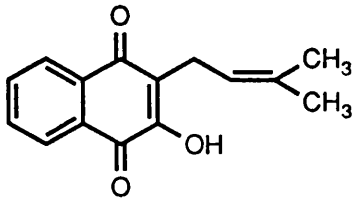


73

PALA is reported to have a high inhibitory potency *in vitro*[32] but the *in vivo* activity has been disappointing. It is expected, however, that PALA will be used in combination chemotherapeutic strategies.

To date there are no good inhibitors of DHOase. Christopherson and Jones[33] have presented a very systematic evaluation of the inhibitory effects of 5-substituted analogues of orotate against mammalian DHOase *in vitro*. However, only two moderately potent substrate analogues have been identified as chemotherapeutic: 5-fluoroorotate and 5-aminoorotate, which were active against several transplantable murine leukaemias. Hence, L-dihydroorotase is an enzyme awaiting 'attack'.

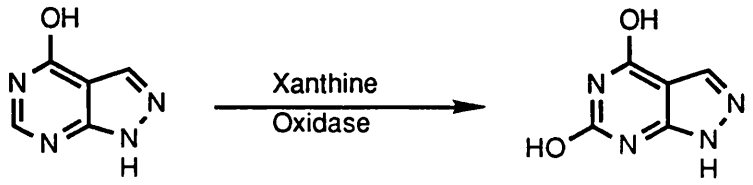
L-dihydroorotate dehydrogenase is subject to product inhibition hence orotic acid and some of its analogues, particularly dihydro-5-azaorotic acid, are effective inhibitors. Additionally, naphthoquinones, for example lapachol **74**, have been identified as potent inhibitors of DHO deHase. They are believed to act as analogues of the cofactor, ubiquinone, and serve as electron acceptors that alter electron flow.[192]



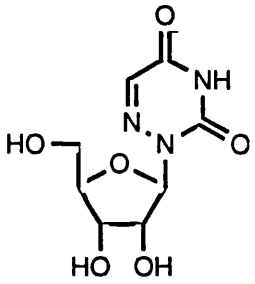
74

A number of orotate analogues have been described as inhibitors of OPRTase; many are also substrates for the enzyme and can form fraudulent nucleotides which, in turn, are potent inhibitors of OMP deCase. By contrast, potent inhibitors of OPRTase are scarce. 5-Fluoroorotate is a good inhibitor of OPRTase prepared from mouse Ehrlich ascites cells: 50 μM 5-fluoroorotate inhibited acivity by 75%.[34,35]

Synthetic pyrimidine and purine analogues which, after monophosphorylation, are extremely potent OMP deCase inhibitors (see below) are in general inhibitors of OPRTase, for example allopurinol **75**, oxipurinol **76** and 6-azauridine **77**.

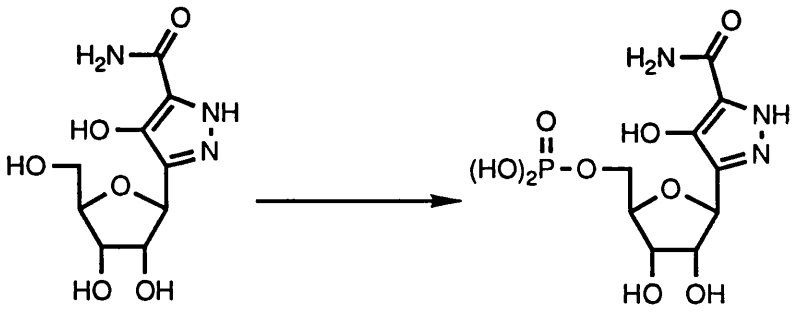


75 **76**



77

Two potent antimetabolites, 6-azauridine **77** and pyrazofurin **78**, are available for the inhibition of OMP deCase which is involved in the last step in the assembly of the pyrimidine ring. Both agents are phosphorylated *in vivo* to 5'-monophosphate derivatives through the actions of uridine, cytidine and adenosine kinases, respectively, and it is these anabolites that strongly impede the decarboxylation of orotidine-5'-monophosphate.



78 **79**

At this point in the development of inhibitors of enzymes of the pyrimidine biosynthetic pathway, however, the present generation of drugs are, for the most part, without significant therapeutic value in humans, particularly in the management of neoplasia. The parent inhibitors are non-specific with the notable exception of PALA, and in no instances have they been demonstrated completely to block precursor flow through the pathway.

Use of the chemistry of diphenyl cyanocarbonimidate **53** allows the construction of pyrimidines, and particularly dihydropyrimidines[24] which are difficult to construct by conventional methods.

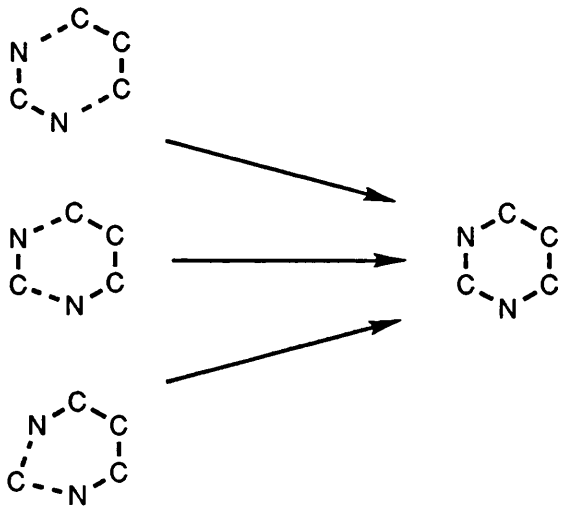
A brief survey of the common methods for the synthesis of pyrimidines and dihydropyrimidines follows.

2.1.1 Synthesis of Pyrimidines

The pyrimidine ring has been synthesized by a wide variety of methods. Syntheses starting from acyclic precursors are most common, but pyrimidines may also be obtained by ring expansion, isomerization or degradation.

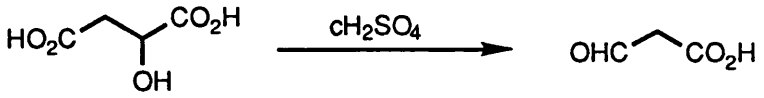
The 'principal' synthesis, as the name implies, is the most useful and widely used method. It involves the combination of an N-C-N fragment and a C-C-C fragment. Other useful syntheses involve the combination of a C-C-C-N fragment with a C-N fragment and an N-C-C-C-N fragment with a C fragment (Scheme 2.2). The ring has been constructed from other fragments, but these syntheses are generally of limited use.

Scheme 2.2

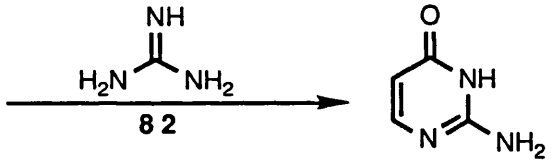


2.1.2 The Principal Synthesis

The N-C-N fragment used in this approach is commonly urea **80**, thiourea **81** or guanidine **82** and the C-C-C fragment is typically a 1,3-diketone, diester or dinitrile. The choice of reagents depends on the substituents required in the product. For instance, the treatment of malic acid **83** with concentrated sulphuric acid resulted in the formation of formyl acetic acid **84**, which was condensed with guanidine **82** to give 2-amino-4(3H)-pyrimidinone **85** (isocytosine).[36]

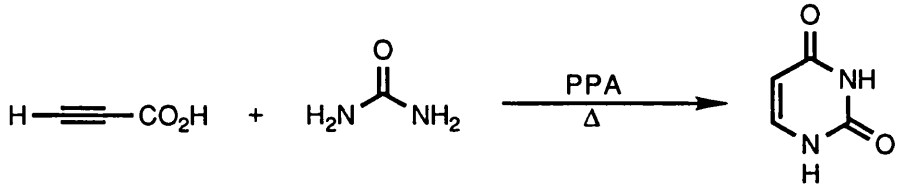


83 **84**

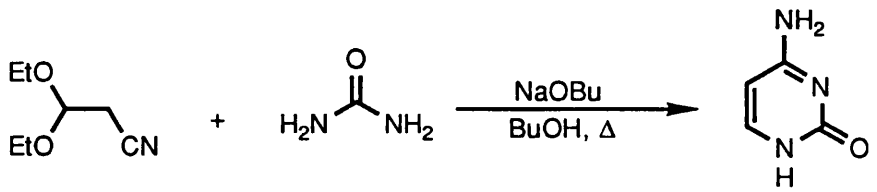


85

Heating propiolic acid **86** with urea **80** in the presence of polyphosphoric acid gives 2,4-(1H,3H)-pyrimidinedione **87** (uracil).[37] The condensation of 1-cyano-2,2-diethoxyethane **88** with urea **80** in the presence of sodium butoxide gave 4-amino-2(1H)-pyrimidinone **89** (cytosine).[38]

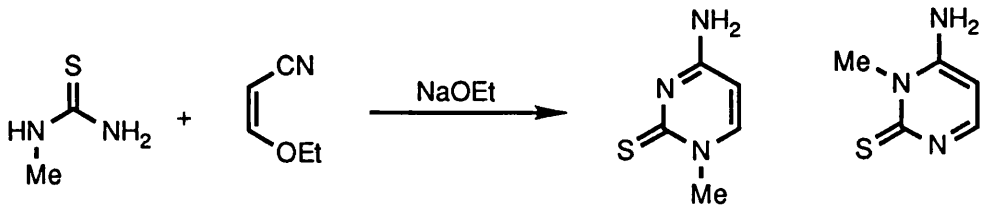


86 **80** **87**



88 **80** **89**

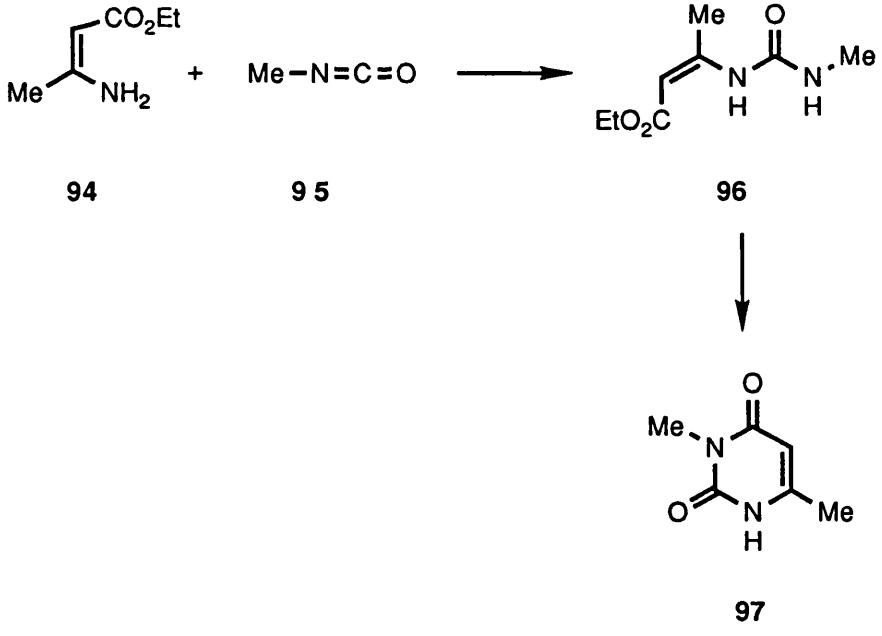
In these examples the N-C-N fragment is symmetrical and there is no ambiguity in the structure of the product. When unsymmetrical N-C-N fragments are condensed with unsymmetrical C-C-C fragments the structure of the product is ambiguous and care must be taken to obtain absolute proof of the structure. This is exemplified by the condensation of N-methyl thiourea **90** with Z-1-cyano-2-ethoxyethene **91**, which gives 4-amino-1-methyl-2(1H)-pyrimidinethione **92** instead of the expected 4-amino-3-methyl-2(1H)-pyrimidinethione **93**.[39]



90 **91** **92** **93**

2.1.3 Other Primary Syntheses

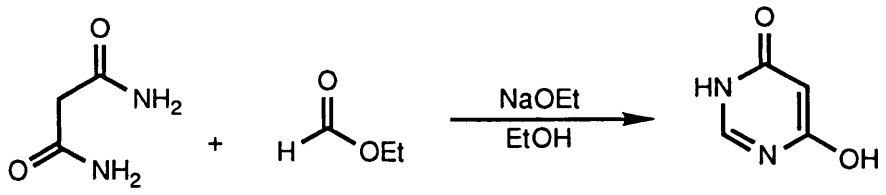
The synthesis of a pyrimidine ring from a C-C-C-N fragment and a C-N fragment is exemplified by the reaction between ethyl 2-aminocrotonate **94** and methylisocyanate **95**.[40] The substituted urea **96** is first formed, which then cyclises to 3,6-dimethyl-2,4-(1H,3H)-pyrimidinedione **97**.



94 **95** **96**

97

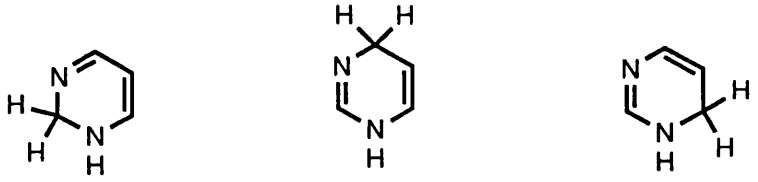
The condensation of an N-C-C-C-N fragment with a C fragment is exemplified by the Remfry-Hull synthesis,[41] in which malondiamide **98** reacts with ethyl formate **99** to give 6-hydroxy-4(3H)-pyrimidinone **100**.



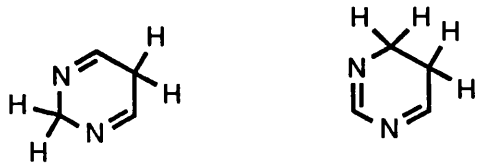
98 **99** **100**

2.1.4 Dihydropyrimidines

In theory there are five possible isomers of dihydropyrimidine, but the situation is complicated by the mobile nature of the hydrogen atoms bound to nitrogen. Thus 1,4- **102** and 1,6-dihydropyrimidine **103** are in tautomeric equilibrium with each other.



101 **102** **103**



104 **105**

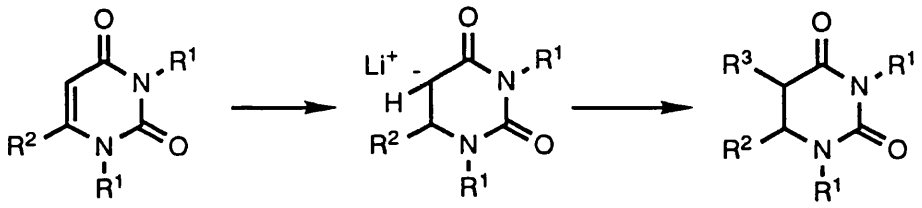
Dihydropyrimidines may be prepared by the addition of hydrogen to the pyrimidine nucleus[42-44] but, in many cases, the pyrimidine nucleus is inert to attack by a variety of reducing agents. The dihydropyrimidines are often unstable under the reaction conditions, with only decomposition products resulting. They can also be prepared by the addition of reagents other than hydrogen, for example alkyl lithiums, to the pyrimidine nucleus.

The most common method of synthesis is from acyclic precursors, as for the pyrimidines, but with starting materials modified appropriately. Having said this, the number of publications regarding pyrimidines far outweighs those regarding dihydropyrimidines. The paucity of publications in this field is attributed to the fact that many dihydropyrimidines are unstable and are difficult to separate and purify. This problem has been noted particularly for 1,4- and 1,6-dihydropyrimidines,[45-47] but has also been reported for 5,6-dihydropyrimidines.[48,49]

2.1.5 Synthesis of 5,6-Dihydropyrimidines

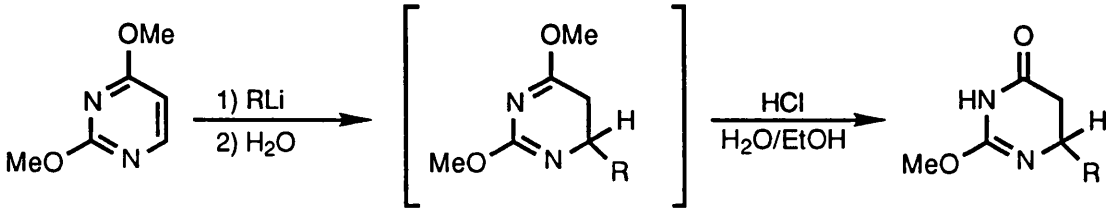
The catalytic hydrogenation of 4(3H)-pyrimidinones has been used to prepare the corresponding dihydropyrimidines, but this method is of limited use since it is difficult to control the degree of hydrogenation and the formation of side products is often a problem.[50-52]

Complex metal hydrides have been used with some success. For example the 5,6-double bond of the N,N'-disubstituted uracils **106** (R^1=Me, CH_2Ph, CH_2OCH_2Ph, R^2=H) and the methyl orotates **106** (R^1=Me etc, R^2 =CO_2Me) is specifically reduced by lithium tri-s-butyl borohydride, 'L-selectride', to give the corresponding derivatives **108**.[53] Substituents such as F or C=CSiMe_3 in the 5-position, which might not survive alternative hydrogenation methods like catalytic reduction, remained unaffected. An additional advantage is that the intermediate anion **107** can be trapped by an alkylating agent, for example ethyl or benzyl bromide with the formation of the 5-substituted uracil **108** (R^2=H, R^3=Et or CH_2Ph).



106 **107** **108**

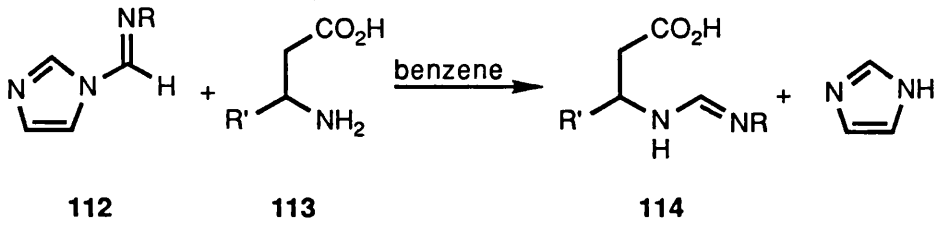
Since pyrimidine is an electron deficient nucleus, it is susceptible to attack by a variety of nucleophiles and this has been exploited in the preparation of a number of dihydropyrimidines using carbanions as nucleophiles.[193] Treatment of 2,4-dimethoxypyrimidine **109** with organolithium reagents, followed by selective hydrolysis of the resultant dihydropyrimidines **110** leads to 5,6-dihydro-2-methoxy-4(3H)-pyrimidinones **111**.



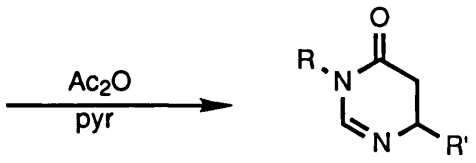
109 **110** **111**

3-Alkyl-5,6-dihydro-4(3H)-pyrimidinones **115** have been prepared by transformidoylation of 1-(N-alkyliminoformyl)-imidazoles **112** with amino acids **113**, followed by

cyclisation of the intermediate N-(N'-alkyliminoformyl)-amino acid **114** with acetic anhydride in pyridine.[54]

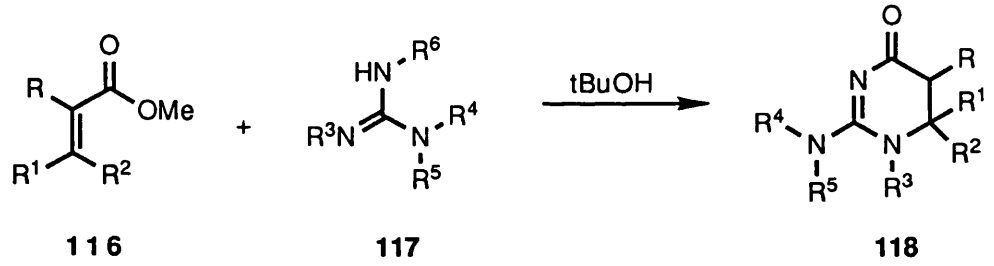


112 **113** **114**

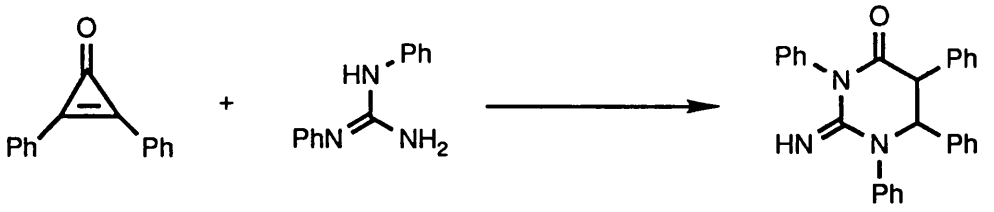


115

Dihydropyrimidine derivatives have been obtained by cyclisation under acetic acid conditions of α,β-unsaturated carboxylic acids with urea.[55] The yields are usually low, however, due to the instability of the products[48] and the formation of bi-products. This synthesis has recently been modified,[49] an α,β-unsaturated ester **116** being condensed with an N-alkyl guanidine **117** (R^6=H) in t-butanol or propan-2-ol to give 2-amino-5,6-dihydro-4(1H)-pyrimidinone **118**. The 2-amino-5,6-dihydro-4(1H)-pyrimidinone **120** is formed in an interesting ring expansion reaction when diphenylcyclopropenone **119** is treated with the alkylguanidine **117** (R^4, R^5=H, R^3, R^6=Ph)[56] but this reaction is somewhat limited in its applicability.



116 **117** **118**



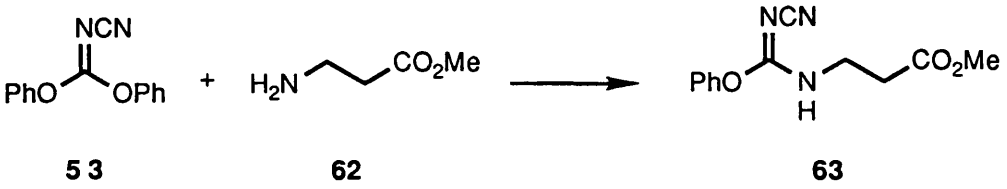
119 **117** **120**

The synthesis described in this work involves a skeletal assembly which appears to be novel, and is potentially of general applicability. It involves the condensation of a C-C-C-N fragment sequentially with a C fragment and an N fragment. This route differs slightly from the conventional synthesis in that a dihydropyrimidine results from the sequential condensations as opposed to the usual pyrimidine. However, the dihydropyrimidines can easily be converted to pyrimidines,[24] and the synthesis offers scope for directly synthesising pyrimidines by introducing unsaturation into the C-C-C-N fragment.

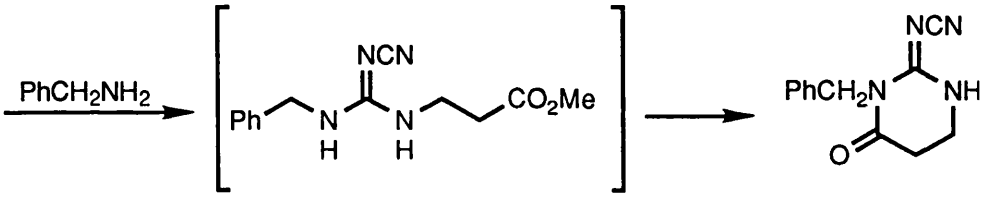
Chapters 2 and 3 describe the synthesis of 6- and 5,6-disubstituted dihydropyrimidines by this method and Chapter 4 describes the synthesis of pyrimidine and imidazolidine analogues substituted at N-3 by a carbocyclic sugar analogue. That the N-cyanoguanidine moiety has been proposed to be an isostere for urea,[57,58] suggests that these pyrimidines will act as analogues that are accepted by various enzymes of the pyrimidine biosynthetic pathway, leading to inhibition by product/substrate feedback pathways, in particular for the enzymes L-dihydroorotate dehydrogenase and orotate phosphoribosyl transferase.

2.2 Results and Discussion

Synthesis of the simplest dihydropyrimidine in the series from β-alanine methyl ester has already been described.[24,59] Thus reaction of β-alanine methyl ester **62** with diphenyl cyanocarbonimidate **53** gives the intermediate O-phenylisourea **63**, which upon treatment with benzylamine gave the cyclised product **64**, presumably *via* the acyclic adduct **121**.

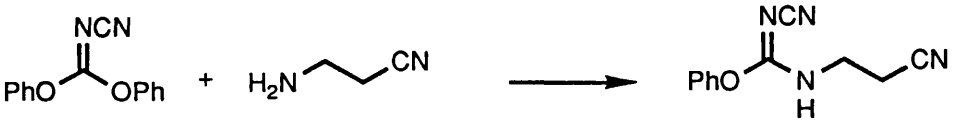


53 **62** **63**

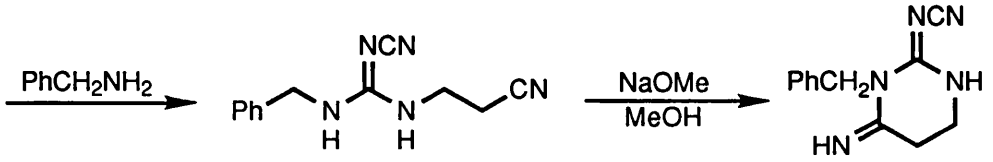


121 **64**

Similarly the 2-cyanoethylamine **122** could be coupled to **53** to give the intermediate **123** which when reacted with benzylamine gave N-cyanoguanidine **124**. Cyclization was then achieved by the use of sodium methoxide in methanol, to give the dihydropyrimidine **125**.

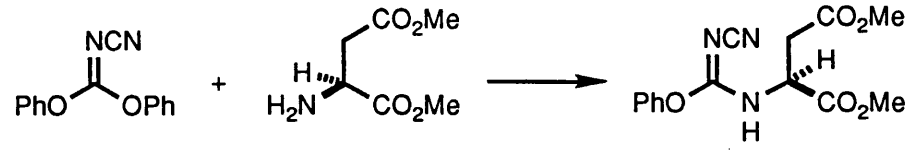


53 **122** **123**

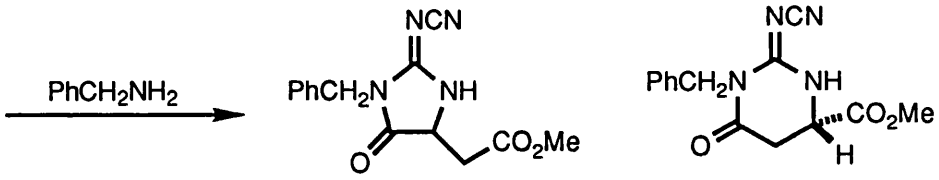


124 **125**

When the synthesis is applied to dimethyl aspartate however, a problem occurs, in that two modes of cyclisation are possible.[24] The structure of the product was assigned by comparison of the I.R. stretching frequencies of the ring carbonyl, this being diagnostic of ring size.[60] Hence the intermediate O-phenylisourea **127** reacts with benzylamine to give the imidazolidin-5-one **128** and not the dihydropyrimidinone **129**.



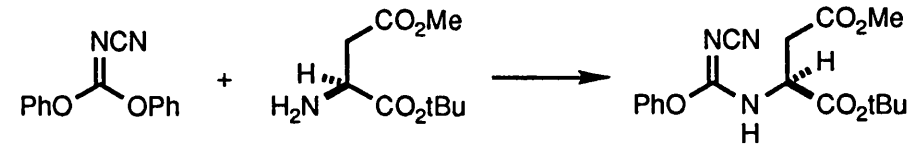
53 126 127



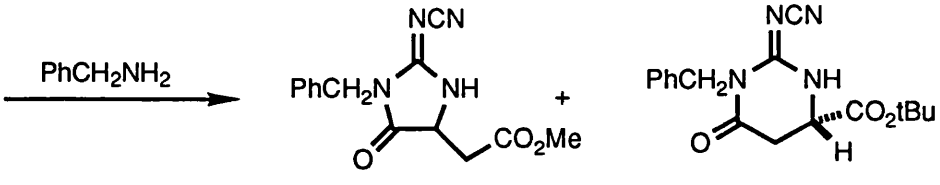
128 129

In an attempt to alter this preference for ring closure to a 5-membered ring system, we have investigated the effect of changing the nature of the ester, presuming that a more hindered alcohol would be less likely to act as a leaving group in the cyclisation step.

(S)-α-tert-Butyl-β-methyl aspartate **130**,[61] prepared from (S)-α-tert-butyl aspartate and diazomethane, was treated with diphenyl cyanocarbonimidate **53** in propan-2-ol to give the isourea **131** in 84% yield. HPLC, using (R)-N-3,5-dinitrobenzoyl phenylglycine chiral stationary phase (CSP) as a chiral support,[62-65] showed that the compound had *ca* 100% ee and it had an optical rotation $[\alpha]_D$=-7.39 °. It was found, however, that upon storing racemization occured, and a 3:1 mixture of stereoisomers was noted by HPLC. A corresponding reduction in the value of the optical rotation was also noted with time. Treatment of **131** in propan-2-ol with benzylamine gave a *ca* 1:1 mixture (*ca* 68% yield) of the dihydroimidazole **128** and the dihydropyrimidine **132**.



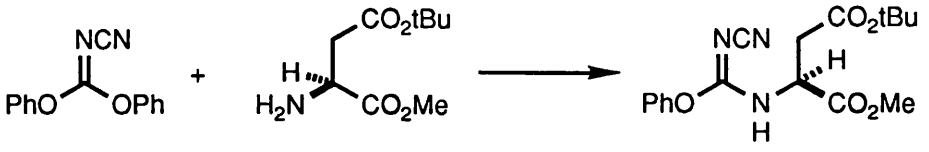
53 130 131



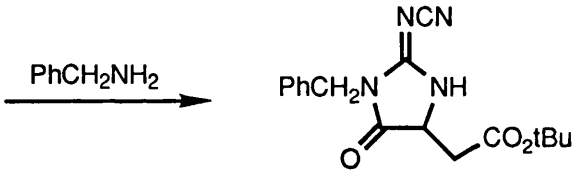
128 132

As was predicted, substitution of tert-butyl for methyl at the α-ester group has decreased cyclisation through this centre and allowed cyclisation at the β-ester to become competitive.

Structural assignments were made on the basis of I.R. absorptions in comparison to known compounds[60] and to the imidazole **135**, prepared in 40% yield from the O-phenylisourea **134**, which was itself prepared from α-methyl-β-tert-butyl aspartate **133**.



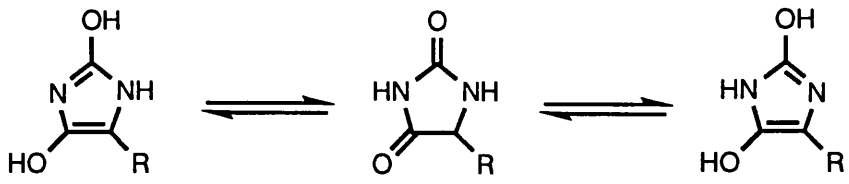
53 **133** **134**



135

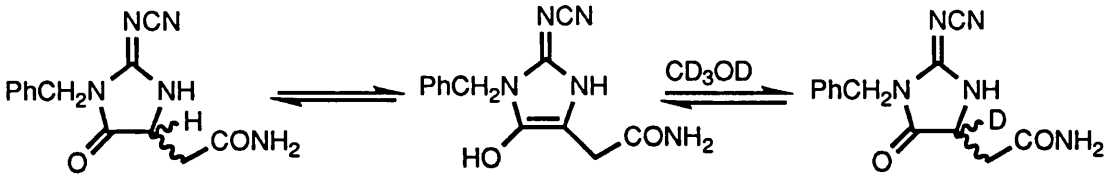
The imidazole **128** showed I.R. absorptions at 2190 cm^{-1} (CN) and 1759 cm^{-1} (C=O) compared to 2194 cm^{-1} (CN) and 1778 cm^{-1} (C=O) for the imidazole **135**. In both cases the values were within the range found for imidazoles.[60] The pyrimidine **132** had absorptions at 2183 cm^{-1} (CN) and 1700 cm^{-1} (C=O) which were in fairly close agreement with previous findings.[60] However, it seems that for the substituted pyrimidines the range of frequencies over which the ring carbonyl stretch occurs should be extended from 1710-1716 cm^{-1} to 1700-1720 cm^{-1} (see later).

Measurement of the optical activity of the 5-membered ring **128** showed that, as expected, racemization had occured at position C-5 of the ring. This is to be expected since keto-enol tautomerization is a well known phenomenum in the related hydantoin system.[66,67]



HPLC measurements using the chiral support indicated, however, that racemization was not complete since two peaks in the ratio 2.5:1 were resolved. Proof that the racemization

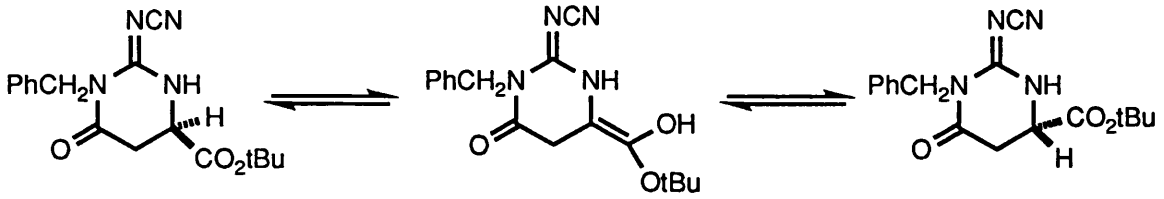
was occuring slowly, over a period of several days in solution, came from an examination of the ^1H n.m.r. spectrum of the amide **136** in d_4-methanol. Initially the spectrum showed the C-5 proton at δ 4.4 ppm but after a period of 7 days in d_4-methanol this signal had disappeared due to the keto-enol tautomerizm process, deuterium being more readily available to add back to the enol than hydrogen.



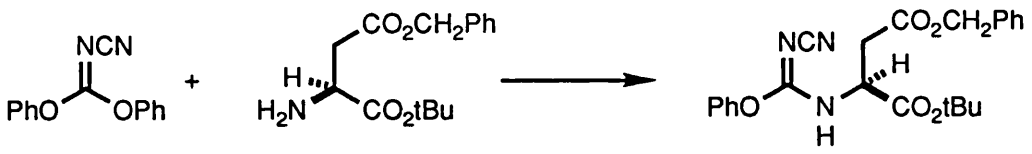
136a **136b**

The (S)-dihydropyrimidine **132** was found to be optically active with $[\alpha]_D$=-92.8 °. The retention of optical activity is to be expected in the 6-membered derivatives since the chiral centre is now one carbon removed from the ring carbonyl and the exocyclic form of the double bond in the 6-membered ring is less likely. HPLC using the chiral support showed the S enantiomer was eluted after the R enantiomer from the column, and the enantiomeric excess was found to be 80%, which gave a calculated $[\alpha]_D$=-114 ° for the pure enantiomer.

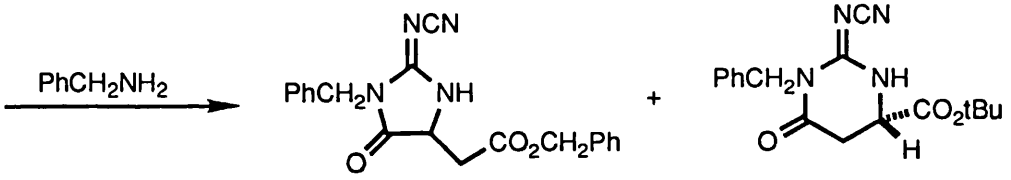
Repetition of the synthesis with (R)-α-tert-butyl-β-methyl aspartate gave the enantiomer of **132**. This was found to have $[\alpha]_D$=+108.4 ° and an enantiomeric excess of 96%, giving a calculated $[\alpha]_D$=+113 °. The close agreement of the two calculated $[\alpha]_D$ values seems to suggest that the chiral HPLC column separations observed are real and that the peaks observed are those due to the enantiomers present in the sample. It should be noted, however, that the optical purity of the dihydropyrimidine **132** varied quite widely from reaction to reaction. This suggests that racemization is occurring either during the reaction, or in the O-phenylisourea **131**, or both, hence old samples of this isourea should be avoided. Racemization during the reaction could be attributed to a keto-enol tautomerizm involving the exocyclic ester group.



The regioselectivity of the cyclisation could be improved by substituting benzyl for the methyl group in **130**. Thus the α-tert-butyl-β-benzyl aspartate **137** was prepared from β-benzyl aspartate by the method of Roeske.[68] Coupling with diphenyl cyanocarbonimidate **53** followed by reaction with benzylamine and cyclisation gave the dihydropyrimidine **132** and the imidazolidinone **139** in the ratio 3.75:1.



53 **137** **138**



139 **132**

It was found, however, that the products could not be separated by conventional chromatography, hence the product ratios are based on signals in the ^1H n.m.r. spectrum of the combined purified products.

An examination of the solvent dependance of this reaction showed that whilst the product ratio was in favour of the 6-membered ring **132** in propan-2-ol, carrying out an identical reaction in THF gave very little reaction in a similar time period. The reaction was faster in acetonitrile as solvent at lower temperatures (room temperature compared to 50 °C), but the product ratio was now found to be only 1.18:1 in favour of **132**. Presumably the difference in rates of reaction reflect the different solvating abilities of the three solvents towards the different transition states of the reaction, the use of acetonitrile leading to the two transition states being nearly equal in energy, whilst propan-2-ol as solvent leads to a lowering of the energy of the transition state leading to the 6-membered ring.

Attempts to synthesis α–tert-butyl-β-allyl aspartate from the Z-protected aspartate[69] were unsuccessful owing to the difficulty of removal of the protecting group in the presence of the allyl ester.

Following on from this work the synthesis of 5,6-disubstituted dihydropyrimidines was investigated. The required β-substituted amino acids were prepared by the method of Baldwin *et al.*[70] (Scheme 2.3).

Thus (S)-aspartic acid **140** was converted to its β-methyl ester **141** by the method of Coleman,[71] the amine function protected with benzyl chloroformate and potassium carbonate, and **142** converted to the required diester **143** by treatment with isobutene and sulphuric acid.[61,68,72] The protected amino acid **143** was alkylated to a mixture of **144a** and **144b** by treatment with lithium hexamethyldisilazide at -78 °C followed by benzyl bromide. Whilst a claim of a diastereomeric excess of 5:1 has been made for this reaction,[70] in our hands the best diastereomeric ratio obtained for **144a**:**144b** was estimated by ^{1}H n.m.r. spectroscopy to be 3:1. The diastereomers were separated by column chromatography and the benzyloxycarbonyl group removed by hydrogenation over palladium to give **145a** and **145b** as separate compounds. Reaction of each with diphenyl cyanocarbonimidate **53** in propan-2-ol at 40 °C gave the O-phenylisoureas **146a** and **146b**. HPLC on the chiral support indicated that **146a** was greater than 98% enantiomerically pure whilst **146b** appeared to be approximately 85% enantiomerically pure. This would seem to indicate that, as had been noted previously for **134**, a small amount of racemization at the α centre was occurring with time.

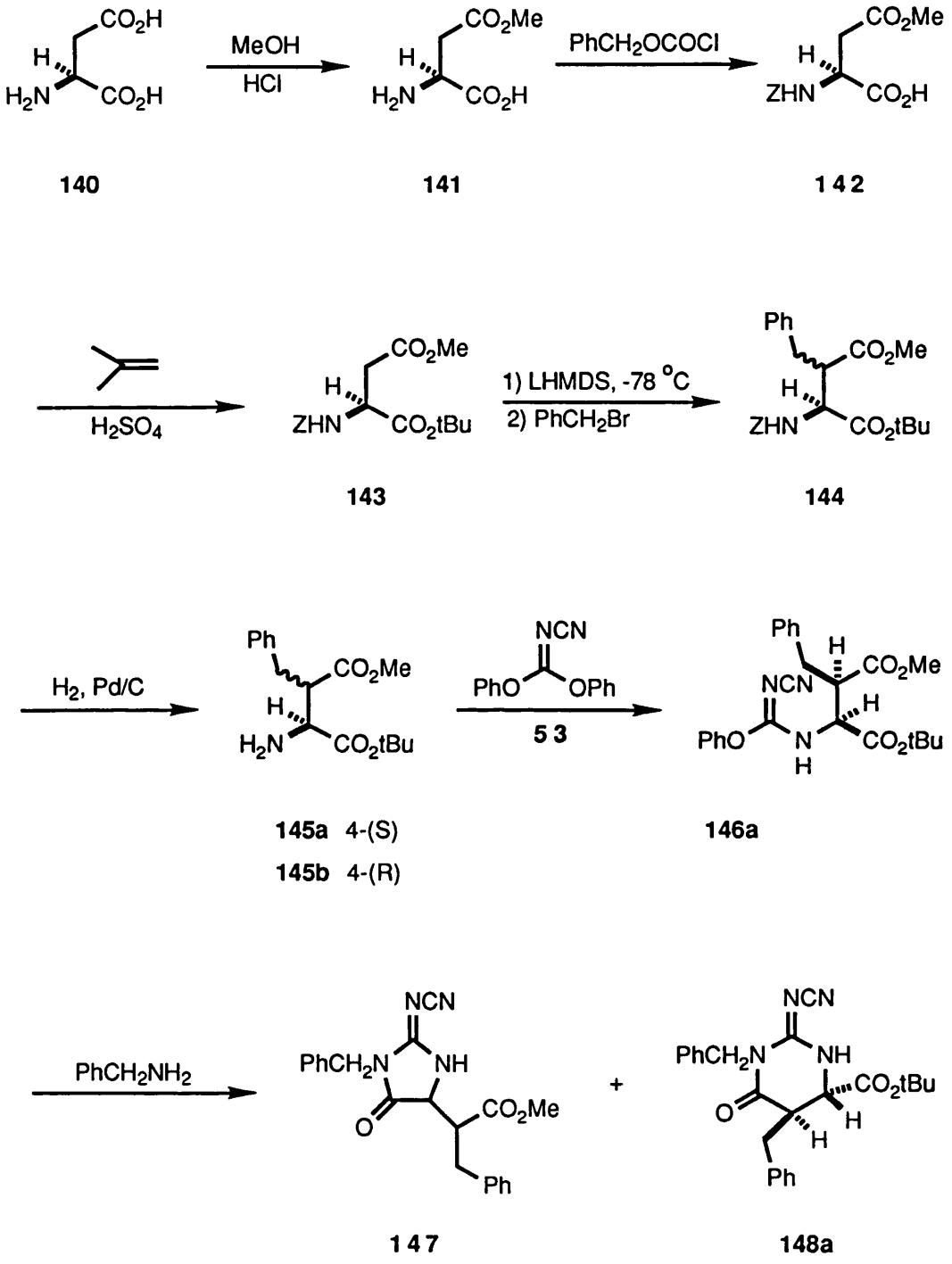
It was noted, by comparison with the reaction of the unseparated diastereomers **145**, that diphenyl cyanocarbonimidate **53** reacted approximately twice as fast with the major diastereomer, so that for the diastereomeric mixture the diastereomeric ratio in the O-phenylisourea **146** was 6:1 and not the 3:1 seen in **144**.

Reaction of O-phenylisourea **146a** with benzylamine gave a 4:1 mixture of **148a** and **147**. HPLC on the chiral support of **148a** showed that it was a 5.2:1 mixture of diasteroisomers and this was confirmed by ^{1}H n.m.r. spectroscopy. As expected, the imidazole **147** was a 1:1 racemic mixture of diasteroisomers due to racemization at C-5 of the ring. This was again confirmed by HPLC. No evidence for racemization at the benzyl substituted carbon was seen, however, since separation of enantiomers was not observed on the chiral support.

Repetition of the latter reaction with O-phenylisourea **146b** led to the pyrimidinone **148b** as the only isolated product. This is probably merely a reflection of the smaller amount of **146b** used. ^{1}H n.m.r. spectroscopy showed this compound to be diastereomerically pure, only a single set of peaks being seen, and HPLC on the chiral support showed that **148b** was enantiomerically pure, only a single peak being seen.

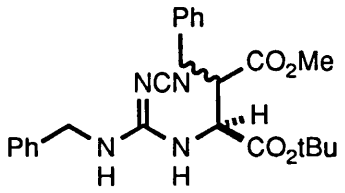
Attempts to grow crystals of **148** failed, hence an X-ray structure could not be obtained. The ^{1}H n.m.r. coupling constants do not allow an assignment of relative srereochemistry of the C-5 and C-6 centres, so neither absolute or relative stereochemistry can be defined. Hence the structures shown for compounds **145a** and **145b** and all compounds derived from these amino acids are arbitary and are used for illustrative purposes only.

Scheme 2.3



That racemization in **148a** had occurred at C-6 and not at C-5 (a keto-enol tautomerizm mechanism similar to the imidazoles could be imagined at this position) was shown by HPLC, using the chiral support. If racemization had occurred at C-5 than the product should have been **148b**. That the retention time of the minor isomer present in **148a** was different from that of **148b** (18 min compared to 12 min) showed this was not the case.

Repetition of the latter reaction on a large scale using a diastereomeric mixture of **146** lead to the isolation to the guanidine **149**. That this product does not spontaneously cyclize and can be isolated seems to reflect the increased steric hindrance present in the aspartate portion of the molecule.



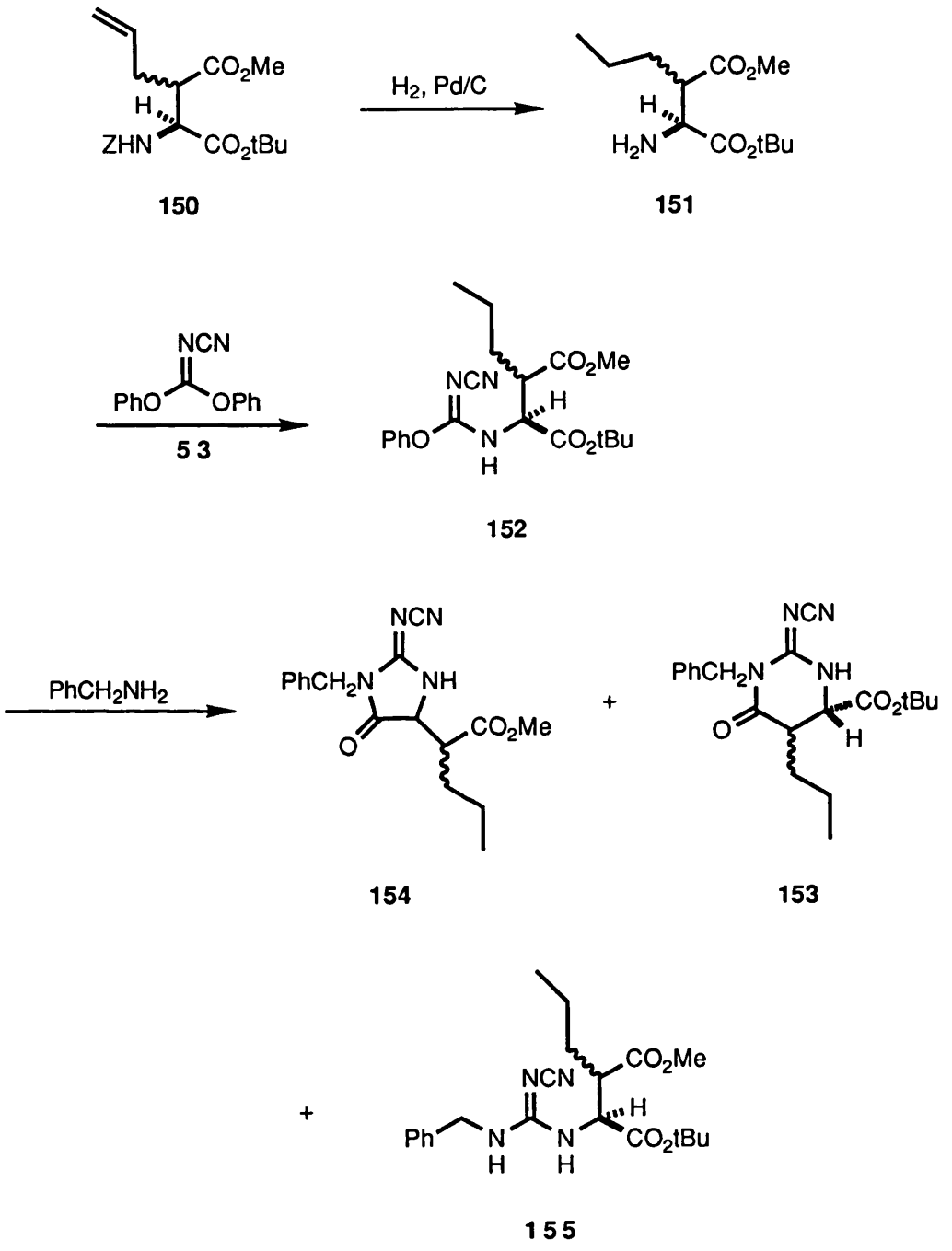
149

Interestingly, the HPLC of the diastereomeric mixture of pyrimidines **148** resulting from this reaction showed that most of the product resulted from the major diasteromer **146a** and only 2% came from the minor diastereomer, suggesting again that the minor diastereomer **146b** reacts with benzylamine much more slowly. This was also borne out by the longer reaction time needed for complete reaction with the minor diastereoisomer **146b**. A clue to the point at which racemization occurs was also obtained from this reaction, which was carried out at 70 °C as opposed to 40 °C for the separated diastereoisomers. HPLC on the chiral support revealed that approximately 30% of the major isomer **148a** had racemized at C-6, indicating that lower reaction temperatures and longer reaction times are required to give products of high optical purity. Higher temperatures must lead to more keto-enol tautomerism in the products hence lower product optical purity.

The reaction sequence was repeated for the 3-propyl substituted derivative **151**, obtained by catalytic reduction from the corresponding allyl N-protected derivative **150**, that was itself prepared by the method of Baldwin[70] (Scheme 2.4). Reaction of a 2.8:1 diastereomeric mixture of **151** with diphenyl cyanocarbonimidate **53** gave the isourea **152** as a 3.7:1 mixture of diastereomers as assessed by HPLC. This was found to be in agreement with the ^{1}H n.m.r. spectrum of the mixture **152**. Once again apparently reaction of one diastereomer is favoured over reaction of the other. Treatment of **152** with benzylamine gave a mixture of three products from which **153** was separated by chromatography. Imidazolone **154** was separated from the guanidine **155** by fractional crystallisation from the column eluant, and then **155** was completely purified by a second chromatographic separation. The pyrimidine **153** was initially isolated as an oil but, on standing, one crystalline diastereoisomer was deposited. HPLC of the crystalline material on the chiral support showed the presence of one diastereoisomer with about 6% of the other. Interestingly, there appears to be no sign of racemization at C-6 for this compound.

The imidazolidinone **154** was isolated as a mixture of diastereoisomers, as expected, in the ratio 1.67:1. This seemed to suggest that, in this reaction, the minor isomer of **152** is the more reactive, unlike the case for the β-benzyl aspartate. This was borne out by the observation that a large proportion of the pyrimidine **153** seemed to be from the minor diastereoisomer.

Scheme 2.4



150 151 152 154 153 155

HPLC of **154** on the chiral support showed that racemization had occured at C-5 of the ring since three peaks were observed. The fact that a fourth peak was not seen is probably a reflection of the limits of the chiral column to efficiently separate enantiomers rather than as a result of the forth enantiomer not being present.

Similarly, the guanidine **155** was found to be a 1.7:1 mixture of diastereoisomers by ^{1}H n.m.r. spectroscopy. HPLC on the chiral support seemed to show that some racemization had

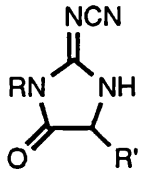
occured at the α centre. The resolution obtained was not, however, sufficiently good to quantify this. That the diastereoisomer ratio was the same as for the imidazolidinone **154** seems to suggest that it is at the formation of the guanidine that the differential reaction rates occur and not at the subsequent cyclisation step.

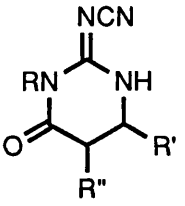
A comparison of the I.R. stretching frequencies of the ring carbonyl group (Table 2.1) shows that the previous findings[60] still hold over this wider range of compounds. For the 5-membered rings the ring carbonyl stretching frequency is between 1748 and 1778 cm^{-1} whereas for the 6-membered ring compounds the ring carbonyl stretch is between 1700 and 1730 cm^{-1}. The correlation of ring size with the position of the nitrile stretching frequency is, however, less reliable.

A further method for determining ring size becomes apparent on inspecting the position in the ^1H n.m.r. spectrum of the CH_2 group of the benzylamine portion of the molecules containing this group (Table 2.1). It is found that for the compounds with an ester side chain the CH_2 group occurs at *ca* 4.7 ppm for the 5-membered ring compounds and *ca* 5.0 ppm for the 6-membered ring compounds. This relationship does not seem to hold for the 6-membered ring carboxylic acids, however, when the CH_2 moves upfield to *ca* 4.68 ppm.

2.3 Conclusion

It has been shown that 6-membered rings can be synthesised by differentiating the two esterifying alcohols on the two carboxylic acid groups of aspartic acid, even though there is a preference for the formation of the 5-membered ring. This is reasonable in terms of a kinetic effect, fewer degrees of freedom being lost on forming a 5-membered ring. Cyclisation to the 6-membered dihydropyrimidine occurs enantiospecifically whereas cyclisation to the 5-membered ring occurs with a considerable degree of racemization. A β-substitutuent favours 6-membered ring formation and enhances the enantiospecificity. Given the ready availability of β-substituted amino acids[69,73-76] this synthesis should be applicable to a wide range of substituted dihydropyrimidines.





156 R=CH_2CO_2Me, R'=H

157 R=$PhCH_2$, R'=H

158 R=$CH_2CH_2CO_2Me$, R'=H

128 R=$PhCH_2$, R'=CH_2CO_2Me

135 R=$PhCH_2$, R'=CH_2CO_2tBu

159 R=H, R'=CH_2CO_2Me

160 R=H, R'=CH_2CONH_2

166 R=R'=CH_2Ph

161 R=$CH_2CH_2CO_2Me$
R'=H, R"=H

64 R=$PhCH_2$, R'=R"=H

132 R=$PhCH_2$, R'=CO_2tBu, R"=H

148a R=R"=$PhCH_2$, R'=CO_2tBu

148b R=R"=$PhCH_2$, R'=CO_2tBu

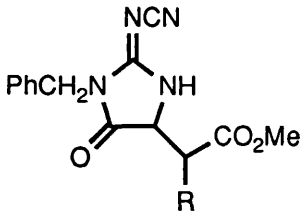
153 R=$PhCH_2$, R'=CO_2tBu,
R"=$CH_2CH_2CH_3$

162 R=R"=H, R'=CO_2H

163 R=$PhCH_2$, R'=CO_2H, R"=H

164 R=R"=$PhCH_2$, R'=CO_2H

165 R=$PhCH_2$, R'=CO_2H
R"=$CH_2CH_2CH_3$



147 R=CH_2Ph

154 R=$CH_2CH_2CH_3$

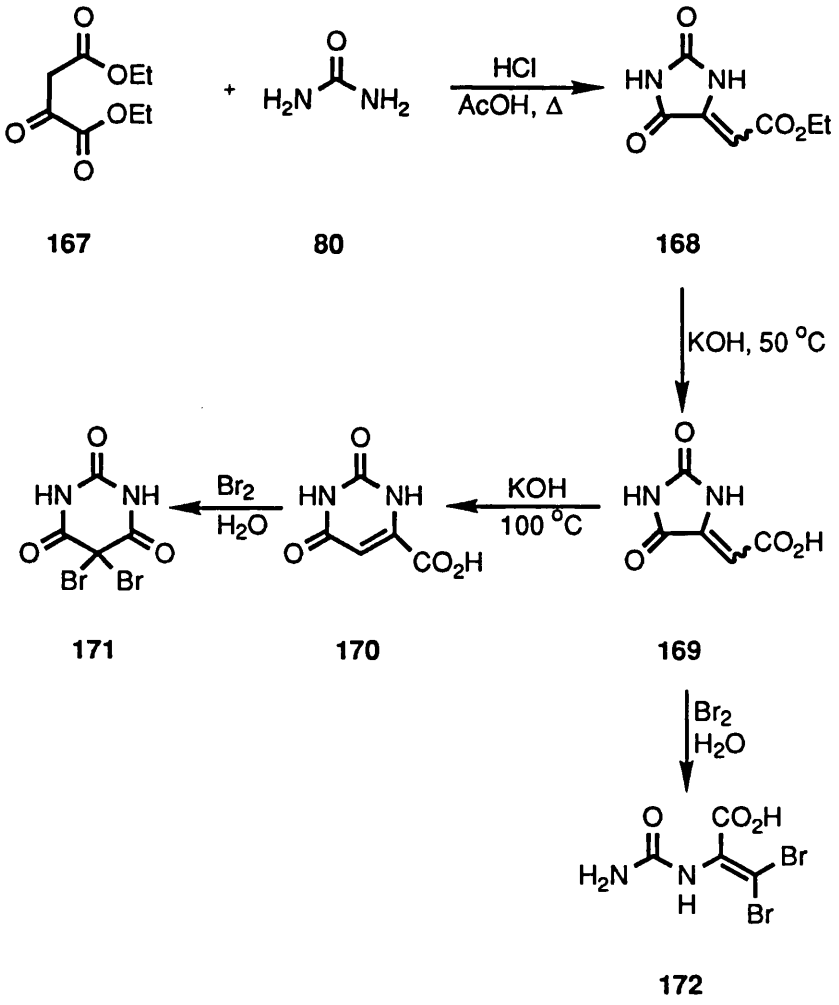
Table 2.1

	CN Stretch/cm^{-1}	CO Stretch/cm^{-1}	CH_2 resonance/ppm
156	2200	1768	-
157	2201	1748	4.60
166	2180	1749	4.51
159	2207	1776	-
160	2207	1749	-
158	2202	1760	-
128	2190	1759	4.70
135	2194	1778	4.75
147	2197	1761	4.68
154	2191	1755	4.70
132	2183	1700	5.02
148a	2184	1721	5.02
148b	2184	1718	4.96
153	2184	1718	5.02
161	2182	1710	-
64	2184	1716	4.90
162	2207	1706	-
163	2198	1730	4.67
164	2195	1718	4.70
165	2176	1718	4.67

Rearrangement of 5-Methoxycarbonylmethyl-2-cyanoiminoimidazolones. Synthesis of 6-Carboxydihydropyrimidines

3.1 Introduction

In 1897 Müller[77] reported the synthesis of a compound through the condensation of oxaloacetic acid diethyl ester **167** and urea **80** to which he assigned a 6-membered ring structure, but much later it was shown that the product of the reaction was a 5-membered ring hydantoin **168**.[78] Treatment of **168** with potassium hydroxide solution resulted in hydrolysis of the ester without ring expansion, to give the carboxylic acid **169**. Treatment of **169** with aqueous potassium hydroxide at 100 °C resulted in rearrangement to 4-carboxy-2,6-pyrimidinedione (orotic acid) **170**. This assignment was confirmed by examining the reactions of **169** and **170** with bromine. Treatment of **170** with aqueous bromine gave 5,5-dibromo-2,4,6-pyrimidinetrione (5,5-dibromobarbituric acid) **171**, whereas 5-(carboxymethylidine)-hydrantoin **169** gave 2-ureido-1,1-dibromoacrylic acid **172** under similar conditions.



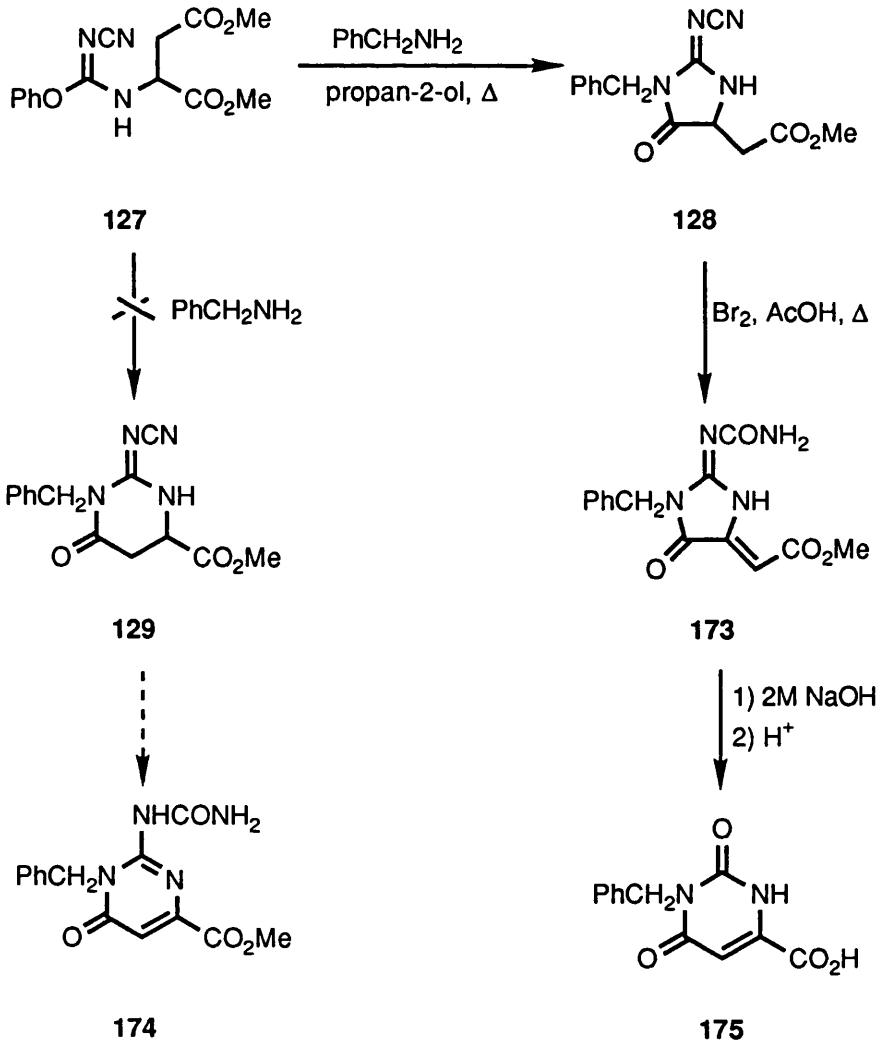
167 **80** **168**

171 **170** **169**

172

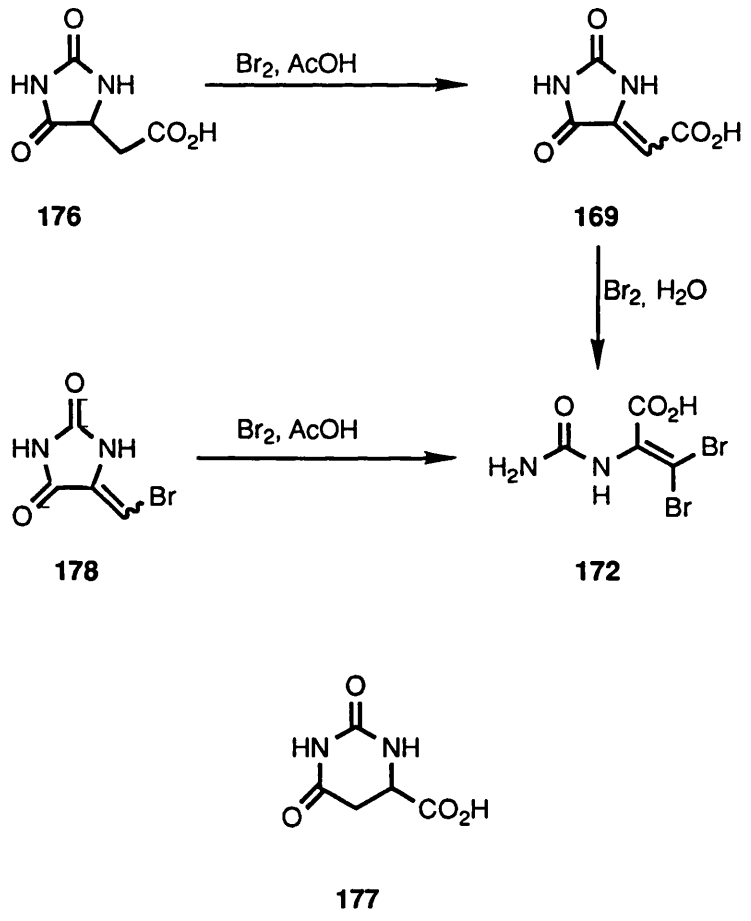
Hobbs[24] initially assigned the structure of the product of the reaction between O-phenylisourea **127** and benzylamine to the 6-membered ring pyrimidinone **129** (Scheme 3.1). The correct structure of the product was subsequently shown, using a variety of spectroscopic techniques, to be that of the 2-cyanoimino-imidazolidin-5-one **128**.[60] Hobbs reacted **128** with bromine in the belief that a pyrimidine **174** would be produced, but it is now known that the product had the 5-membered ring structure **173**, produced as a result of the bromination-dehydrobromination sequence together with hydrolysis of the cyanoimino group catalysed by the acetic acid present (see Chapter 7). Treatment of **173** with boiling 2M sodium hydroxide solution, followed by acidification with hydrochloric acid solution resulted in hydrolysis of the ureido group and also rearrangement to the 6-carboxypyrimidine **175**, a known compound. The fact that the product was produced under such mild conditions was taken by Hobbs as evidence for the 6-membered nature of **173**, since previous rearrangements had required much more vigorous conditions. It is now known that rearrangement had indeed occured under these mild conditions.

Scheme 3.1



The product of the bromination-dehydrobromination was in fact closely related to the previously reported system **169** (Scheme 3.2).[79-81] Guareschi and Grimeau had independently synthesised malyureidic acid, but the two authors assigned different structures to this compound. Guareschi assigned a 5-membered ring structure **176**, whilst Grimeau assigned a 6-membered ring structure **177**. Gabriel[82] repeated the synthesis and treated the product with bromine in acetic acid to give a 'bromine free' product, pyvureidic acid **169**, which was assigned a 5-membered ring structure, since when treated with aqueous bromine it yielded 2-ureido-1,1-dibromoacrylic acid **172**, the same product that was obtained by treatment of hydrantoin **178** with aqueous bromine. This was taken as evidence for a 5-membered ring structure for pyvureidic acid **169**, and since **169** was obtained from malyureidic acid it was concluded that it must also have the 5-membered ring structure **176**.

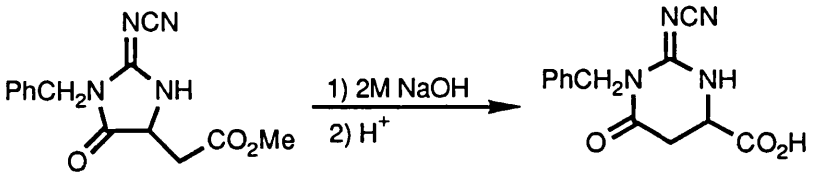
Scheme 3.2



176 **169** **178** **172**

177

Hobbs[83] also treated 2-cyanoimino-imidazolidin-5-one **128** with 2M sodium hydroxide solution at room temperature for 2 min, and observed the carboxylic acid **163**. This was originally taken as evidence for the 6-membered ring structure for **128**. Since **128** was subsequently shown to have a 5-membered ring structure a ring expansion reaction must have taken place.



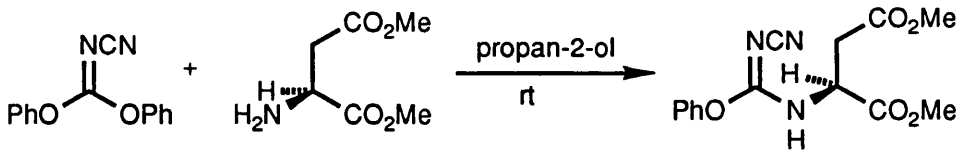
128 **163**

In conjunction with Delisser[84,85] a number of ring expansion reactions have been performed, and from the results it can be concluded that this is a general method for the rearrangement of 2-cyanoimino-5-carboxymethyl substituted imidazolidin-5-ones to the corresponding 6-carboxydihydropyrimidines under very mild conditions.

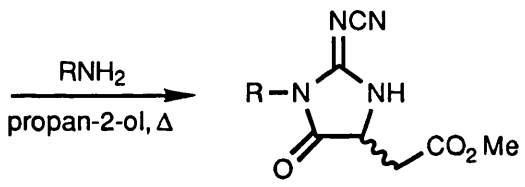
3.2 Results and Discussion

A number of simple imidazolidin-5-ones were prepared by the reaction of diphenyl cyanocarbonimidate **53** with S-aspartic acid dimethyl ester **126**, followed by subsequent reaction with various amines, nucleophilic addition with concomitant cyclisation occuring to give the desired products (Scheme 3.3).

Scheme 3.3

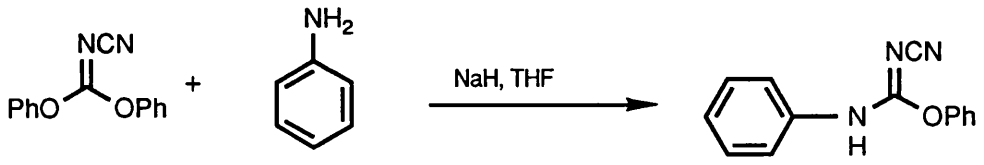


53 **126** **127**

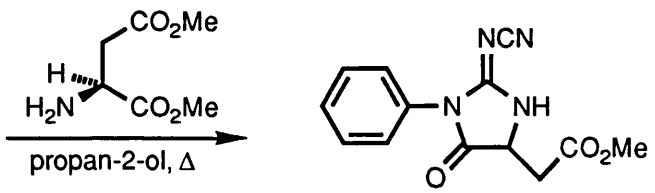


178 R=$CH_3CH_2CH_2$, **179** R=cC_6H_{11}, **180** R=$CH_3(CH_2)_6$,
181 R=cC_5H_9, **128** R=$PhCH_2$

In order to prepare the aniline analogue **182**,[85] the addition had to be performed in the reverse order, that is the aniline was added first. Since the nitrogen of aniline is also significantly less nucleophilic than that of the other amines used, it was also necessary to generate the anion using sodium hydride in order for addition to occur.

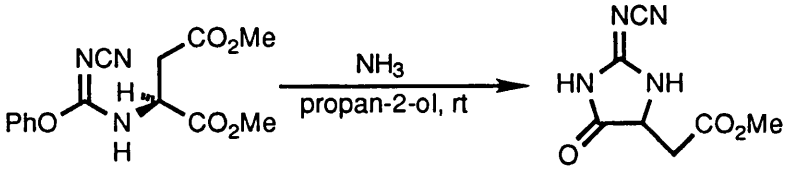


53 **57**

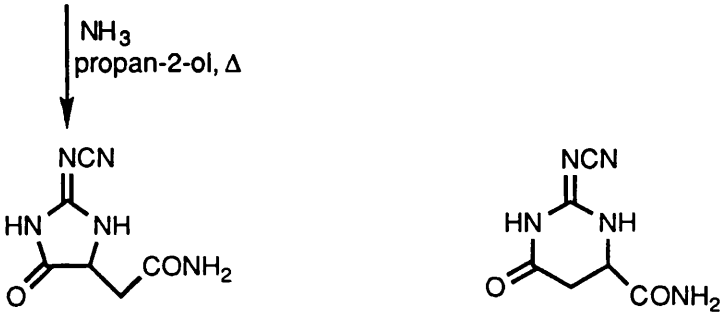


126 **182**

The parent imidazolidin-5-one **159** could also be prepared using aqueous ammonia but it was found that careful monitoring of the reaction was required to prevent further reaction at the ester, leading to the unwanted amide **160**.

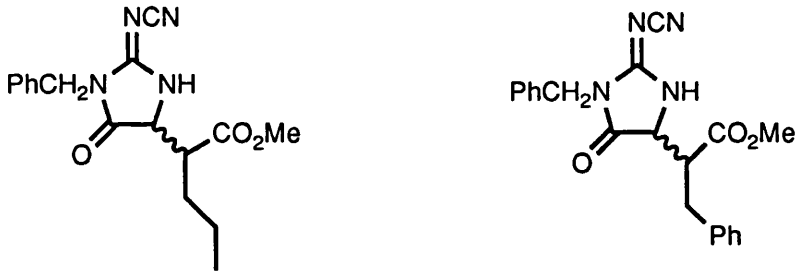


127 **159**



160 **183**

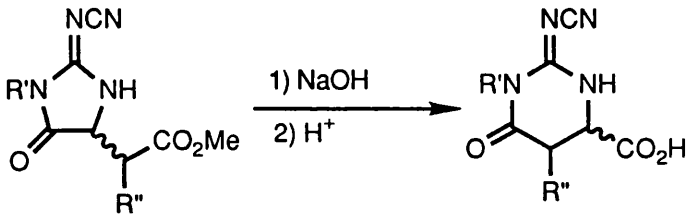
A further two imidazolidin-5-ones **154** and **147**, prepared from β-substituted aspartic acids as described previously, were also used to test the scope of the reaction.



154 **147**

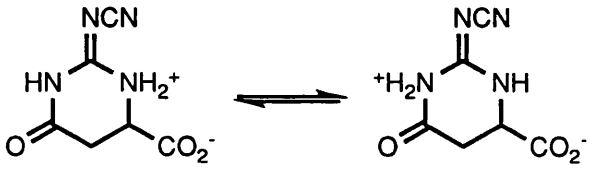
Rearrangements of the imidazolidinones to the corresponding pyrimidinone carboxylic acids were all carried out under similar conditions (Scheme 3.4). Stirring of the imidazolidinone in 2M sodium hydroxide solution for 5-10 min followed by acidification with concentrated hydrochloric acid and cooling to 4 °C precipitated a product that yielded the pure carboxylic acid on recrystallisation from water. In most cases good yields were obtained although for the substituted imidazolidinones **154** and **147** the yields were lower, probably due to the extremely small scale reactions that had to be performed which led to product isolation difficulties.

Scheme 3.4



178	R'=$CH_3CH_2CH_2$, R"=H	**184**
179	R'=cC_6H_{11}, R"=H	**185**
180	R'=$CH_3(CH_2)_6$, R"=H	**186**
181	R'=cC_5H_9, R"=H	**187**
128	R'=$PhCH_2$, R"=H	**163**
182	R'=PhNH, R"=H	**188**
159	R'=R"=H	**162**
147	R'=R"=CH_2Ph	**164**
154	R'=$PhCH_2$, R"=$CH_3CH_2CH_2$	**165**

In all cases the ^1H n.m.r. spectrum of the product was consistent with the dihydropyrimidine carboxylic acid as shown, except for **162** which had an unusual spectrum. Compound **162** showed two sets of peaks in the ratio 1.8:1 for each proton signal present. Since the product has only one chiral centre this can only be explained as being the result of two zwitterionic species **162/1** and **162/2** existing in equilibrium in solution.

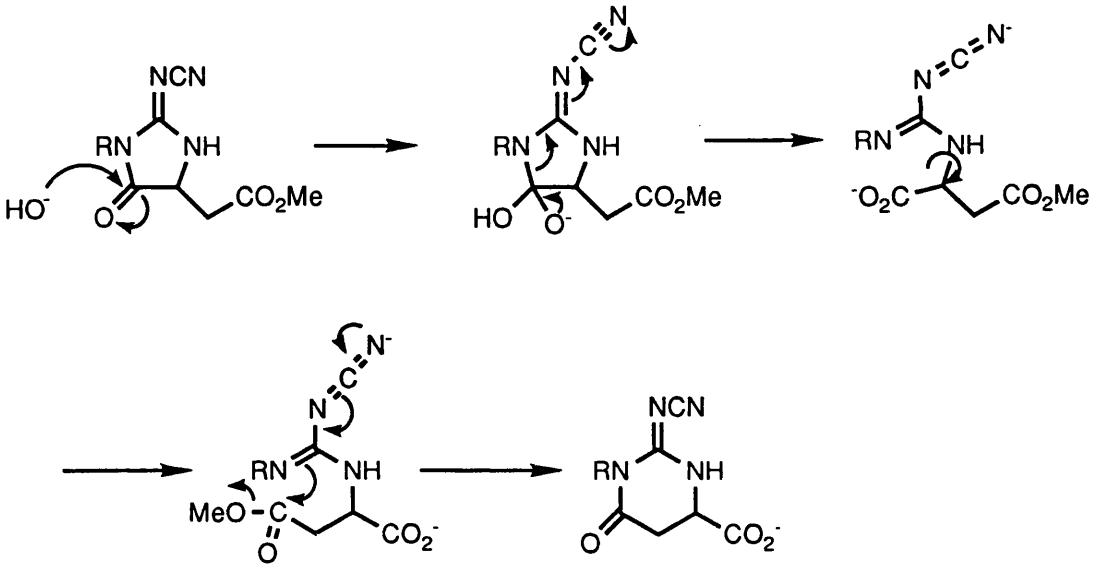


162/1 **162/2**

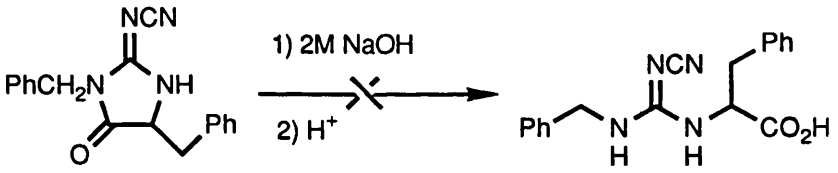
Due to the low solubility of **162** a mixture of D_2O and DMSO was required as n.m.r. solvent in this case, as opposed to all other cases where the n.m.r. spectra were obtained in DMSO alone. This may account for the appearance of two products in the ^1H n.m.r. spectrum since ionisation is more likely in a solvent containing a significant proportion of D_2O.

The mechanism proposed for the rearrangement reaction is as shown (Scheme 3.5).

Scheme 3.5



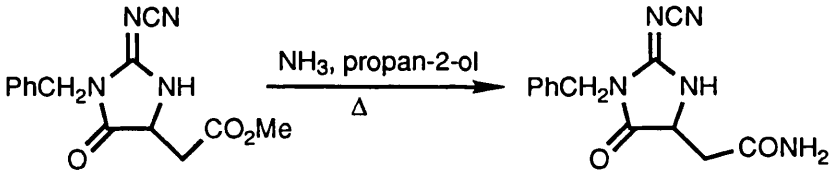
The driving force for this reaction appears to be the reclosure of the linear intermediate to give the 6-membered ring structure. Evidence for this comes from the observation that imidazolidin-5-one **166** is stable in 2M sodium hydroxide solution, as would be expected since the ring closure step is not possible in this case.



166 **189**

Whilst this methodology readily provides high yields of pyrimidinone carboxylic acids it should be noted that since the starting imidazolidin-5-ones are racemic the product pyrimidinones are also racemic. For the preparation of carbocyclic nucleoside analogues (Chapter 4) this seems, however, to be the only viable method for the synthesis of pyrimidinones.

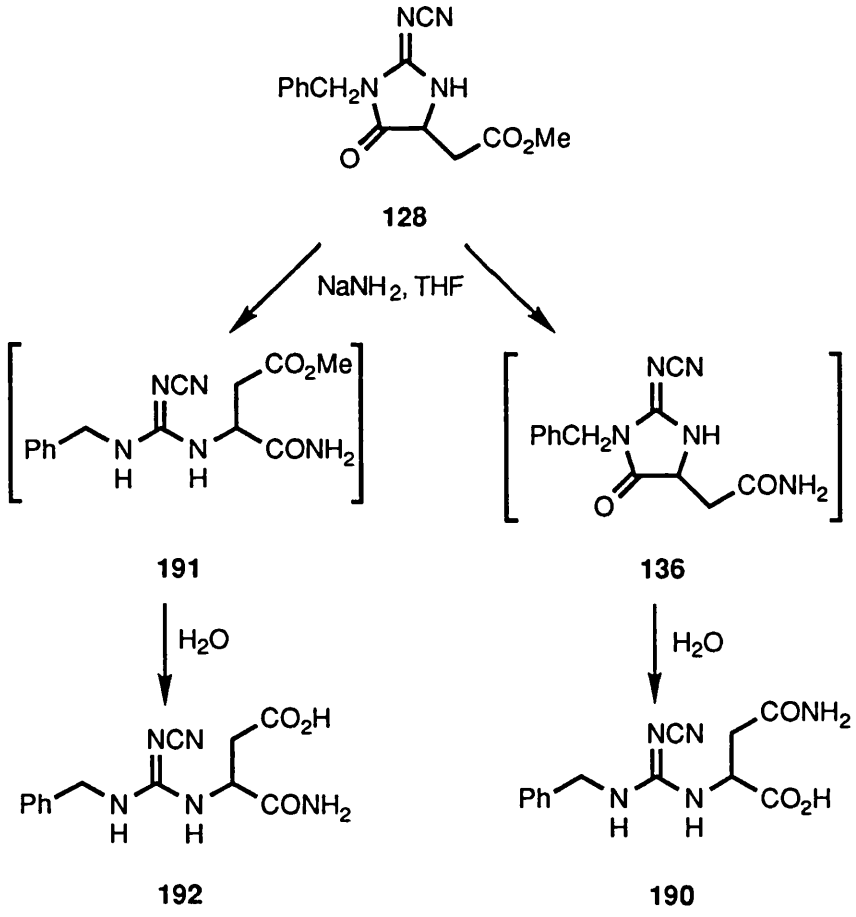
It is conceivable that the amide **160** has a 5- or 6-membered ring structure since the initially formed ester **159** could have been ring opened again by attack of ammonia at the ring carbonyl in a similar manner to the hydroxide mechanism. That the product **160** had a 5-membered ring structure and is not the 6-membered ring structure **183** was confirmed by comparison of the IR frequencies of the ring carbonyl and cyanide groups to those of the imidazolidinone esters already prepared and also to the frequencies for the amide **136**, prepared directly from the imidazolidin-5-one **128**.



128 **136**

Imidazolidin-5-one **128** could also be ring opened with sodium amide in THF, followed by aqueous workup (Scheme 3.6). In light of the fact that ammonia readily reacts with methyl esters in this series to give the corresponding amides it seems likely that initially an amide is formed and that ring opening occurs under the strongly basic conditions that exist when the reaction is quenched, giving as product the guanidine **190**. However it should be noted that quenching the reaction with 2M hydrochloric acid solution also leads to the same product.

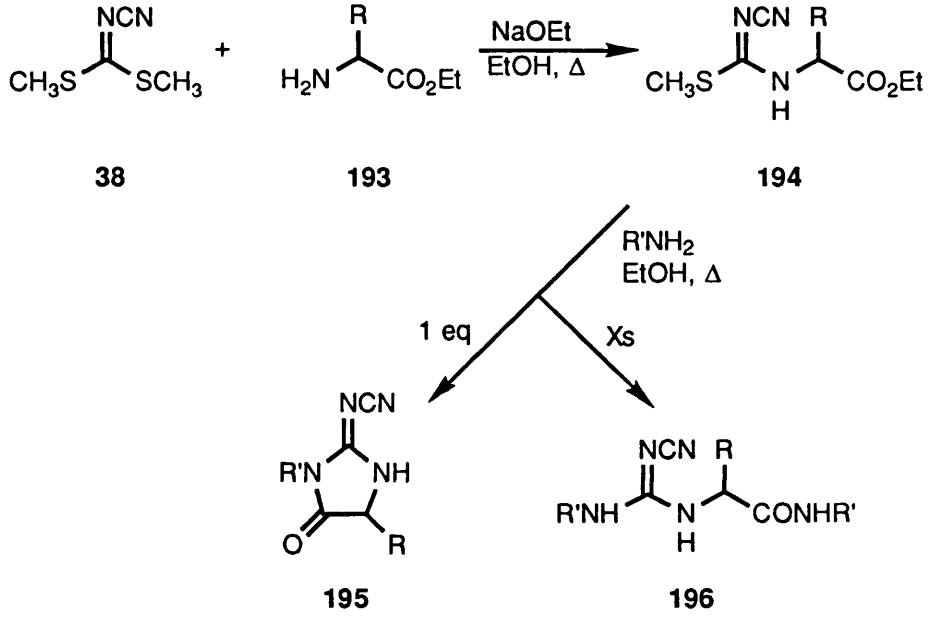
Scheme 3.6



The possibility exists that the sodium amide first attacks at the ring carbonyl leading to ring opening. 2-Imidazolidin-5-ones similar to **128** have been ring opened using excess ammonia (Scheme 3.7).[86] Thus α-amino esters **193** (R=H, $-(CH_2)_2SCH_3$) have been condensed with dimethyl cyanothiocarbonimidate **38**, to give the isothioureas **194**, by heating the two

compounds in the presence of sodium ethoxide. Prolonged heating of the isothioureas **194** with a series of aliphatic amines resulted in the displacement of methanethiol and the concomitant cyclisation to give the 2-imidazolidin-5-one derivatives **195**. Treatment of **194** with an excess of the amine resulted in the formation of the acyclic amides **196**, presumably via the initial ring closure followed by ring cleavage with excess amine. In this case, however, forcing conditions were required and the possibility exists that the amide forms first and then substitution via elimination of methanethiol occurs.

Scheme 3.7



38 **193** **194**

195 **196**

In our case if amide attack occurred first to open the ring the possibility exists for ring closure to a 6-membered ring, which is then reopened during workup, or the acyclic intermediate does not reclose but ester hydrolysis occurs to give the acyclic product.

A fourth possibility exists that the initial product is a di-amide produced from a combination of reaction of the ester and also ring opening, and that at the quenching step one of the amides is selectively hydrolysed to the carboxylic acid seen in the product. At present the product cannot be confidently assigned to either of the two possible structures **190** or **192**.

3.3 Conclusion

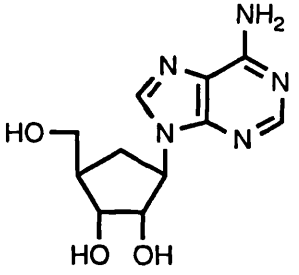
It can be seen that the rearrangement reaction of imidazolidin-5-ones offers a simple and convenient route to pyrimidinone 6-carboxylic acids and, for pyrimidinones with more hindered substituents at N-1, this seems to be a better method of synthesis than attempts to construct them directly, but with the corollary that the products will be racemic.

Synthesis of Carbocyclic Isonucleosides

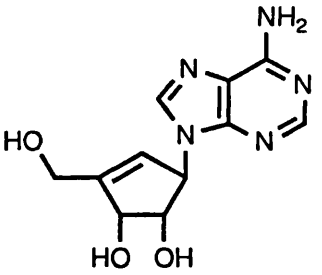
4.1 Introduction

Nucleoside analogues display a wide range of biological activities[87] and have attracted particular attention as anti-tumour[88,89] and anti-viral[90] agents. Consequently, extensive modifications have been made to both the heterocyclic base and the sugar moiety. Replacement of the furanose ring oxygen by carbon is of particular interest since the resulting carbocyclic nucleosides possess greater metabolic stability to the phosphorylase enzymes which cleave the glycosidic linkage of normal nucleosides.

Although certain carbocyclic nucleosides occur in nature they were first described in 1966 with Sheally and Clayton's synthesis[91] of the racemic carbocyclic analogue (±) **197** of adenosine. Two years later the (-) enantiomer, named aristeromycin, was isolated as a metabolite of *Streptomyces citricolo*.[92] Synthetic interest was renewed in 1981 with the isolation of the structurally more diverse neoplanocin family of carbocyclic nucleosides,[93] and, in particular, the cyclopentenyl derivative neoplanocin A **198**.



(±)197
Aristeromycin

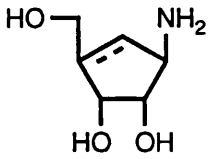


198
Neoplanocin A

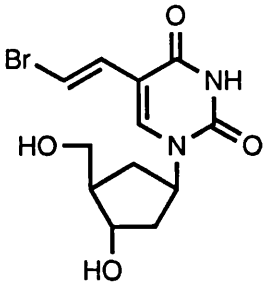
The first enantiospecific synthesis was provided by Ohno *et al*[94] with a chemicoenzymatic approach to (-) aristeromycin **197** and (-) neoplanocin **198**. This synthesis again utilised the stepwise construction of the heterocyclic base onto a cyclopentylamine **199** which was a feature of Shealy and Clayton's approach. This method has been extensively employed in providing a wide range of racemic carbocyclic nucleoside analogues.[95]

In the last five years nucleoside analogues have been investigated with renewed urgency in the search for agents effective against the Human Immunodeficiency Virus (HIV), the causative agent in the AIDS epidemic. More effective treatment has also been sought for other viral infections, in particular Herpes Simplex virus (HSV types 1 and 2), Varicella Zoster virus (VZV), Cytomegalovirus (CMV) and Epstein Barr virus (EBV), which can prove lethal to AIDS patients and other immunocompromised individuals. This has resulted in an explosion in synthetic activity in the field of carbocyclic nucleosides and the discovery of several derivatives with potent anti-viral

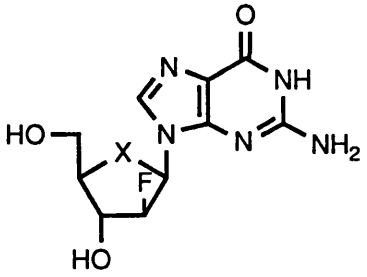
activity. Thus, carbocyclic BVDU **200** is being developed for the treatment of HSV1 and VZV infections[96] while carbocyclic 2'-ara-fluoro-guanosine **201** is exceptionally effective against HSV1 and HSV2.[97,98]



199



200

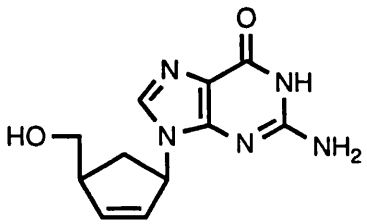


201 X=CH_2

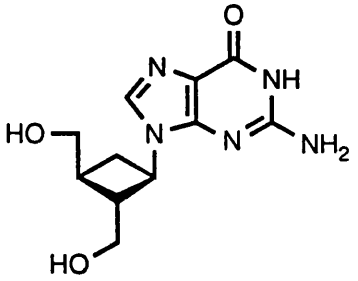
202 X=O

Compound **201** established carbocyclic nucleosides as more than simply metabolically stable versions of the active furanose nucleosides since its furanose parent **202** is only weakly active against herpes.

The unsaturated derivative carbovir **203** has also attracted much attention[99] with activity against HIV comparable to that of AZT. Carbocyclic derivatives now include cyclohexyl and cyclobutyl derivatives with the latter showing promising anti-viral properties. For example, carbocyclic oxetanocin G **204** displays broad spectrum anti-viral activity against HIV and herpes viruses.[100,101]



203



204

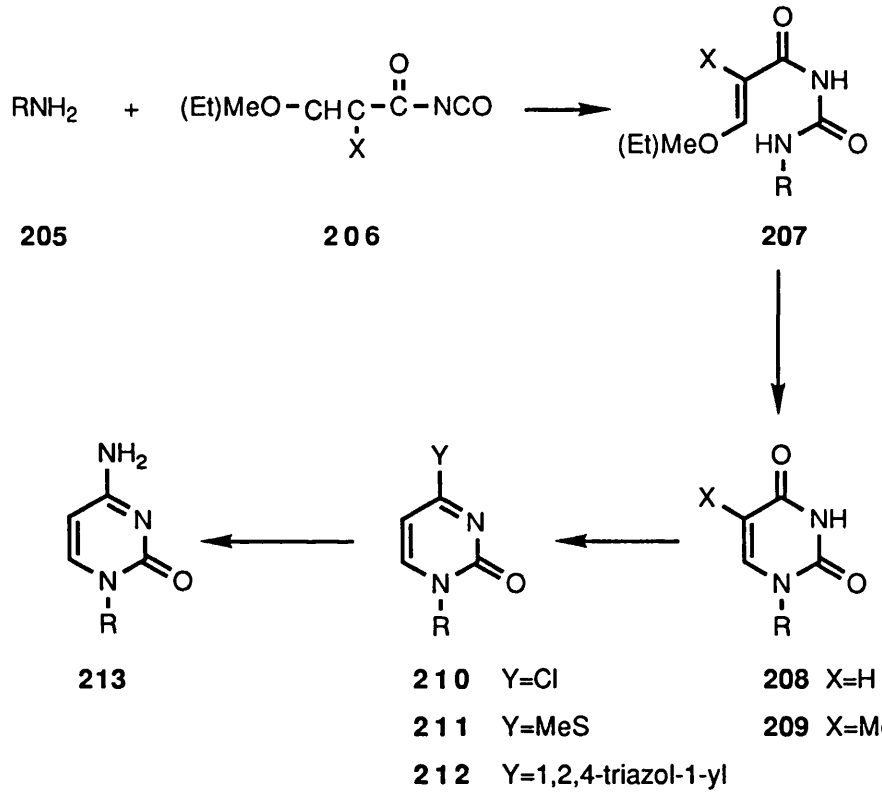
The pharmacological importance of these newer analogues has focussed attention on more efficient and flexible syntheses. There are two approaches that can be used, linear or the convergent. The realisation that the biological activity normally resides in one enantiomer,[97,102-104] and the increasing demand for the new drug substance to be enantiomerically pure has made the development of routes to chiral carbocyclic nucleosides of paramount importance. Both the approaches used will be described briefly with examples, followed by a description of our proposed approach to the synthesis of carbocyclic isonucleosides and nucleosides. For more examples of currently used synthetic methods see Borthwick and Biggadike.[105]

4.1.1 Linear Approaches

Linear approaches to chiral carbocyclic nucleosides rely on the construction of the heterocyclic base onto a suitable chiral cyclopentylamine. The chemistry involved in the construction of the pyrimidine and purine moieties is as follows.

a) Pyrimidines

Synthesis of uridine and thymidine derivatives employs methodology developed originally by Shaw and Warrener.[106] Thus reaction of the carbocyclic amine **205** with an acryloyl isocyanate **206** provides the intermediate acryloyl urea **207** which is then cyclised with concentrated ammonia or with acid catalysis, to afford the uridine **208** and thymidine **209** analogues.

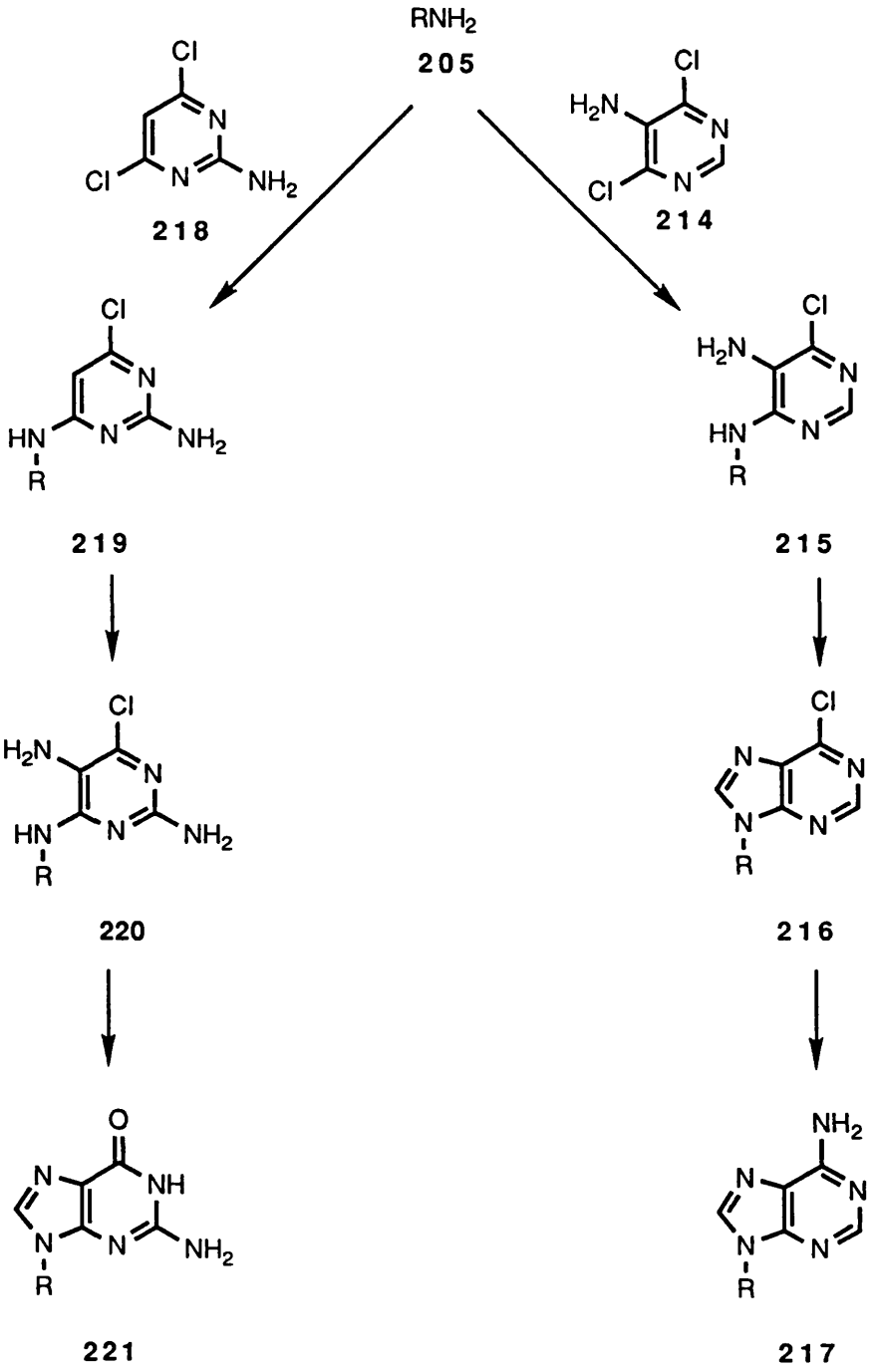


Cytidine derivatives **213** are derived from the corresponding uridines **208** by ammonolysis of either the 4-chloro **210**, 4-methylthio **211**, or 4-(1,2,4-triazol-1-yl) **212** intermediates.

b) Purines

Construction of the purine derivatives is based on the Traube synthesis.[194] Adenosine derivatives are prepared from the cyclopentylamine **205** in three stages. Thus,

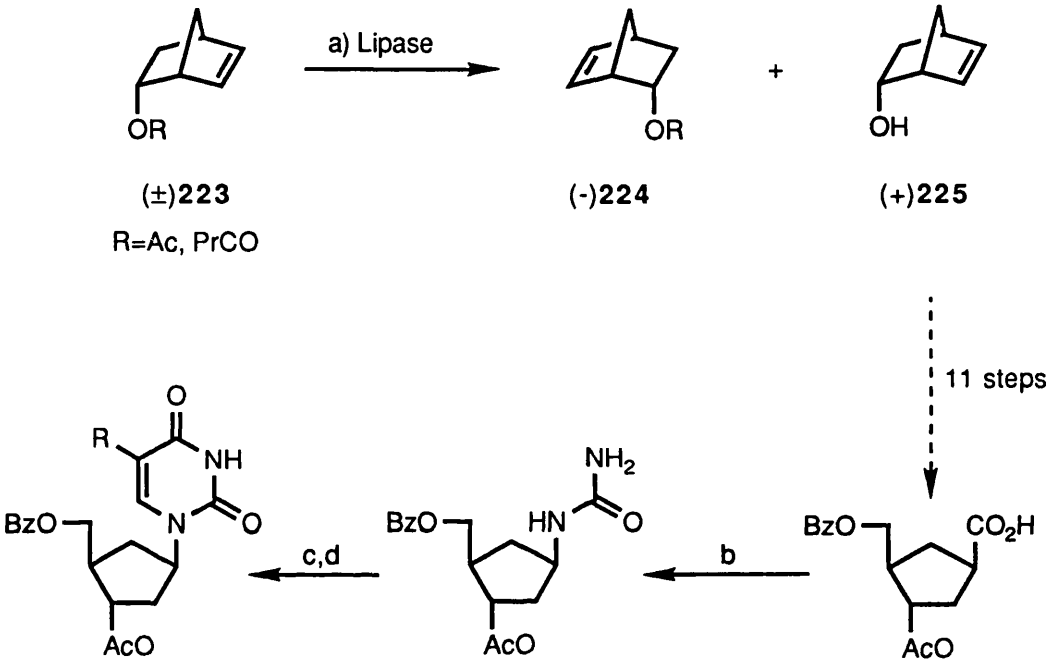
reaction with the dichloropyrimidine **214** affords the diamino derivative **215** which is then cyclised with triethylorthoformate to give the 6-chloropurine **216**. Aminolysis of the chloro function then provides adenosine analogues **217**.



Synthesis of the guanidine base requires two extra steps to introduce the 5-amino moiety. Reaction of **205** with the pyrimidine **218** affords the diamine **219** and the 5-amino group is then introduced by a diazotization/reduction sequence. The resulting triamine **220** is then

cyclised and the chloro function hydrolysed to provide guanosine analogues **221**.

Griengl *et al*[107,108] have gained access to either enantiomer of 2'-deoxy carbocyclic nucleosides *via* enzymatic resolution of an *endo* norbornenyl ester (±) **223**. After 11 steps they arrived at the carboxylic acid **226**. Curtius degradation and trapping of the resulting isocyanate with gaseous ammonia afforded the urea **227** which was converted in two stages into (+) carbocyclic 2'-deoxy-uridine **228** (overall yield 3.5% for 14 steps from (±) **223**). Further elaboration of the pyrimidine base afforded (+) carbocyclic IDU **229** and (+) carbocyclic BVDU **200**.



(±)**223**
R=Ac, PrCO

(-)**224**

(+)**225**

228 R=H
229 R=I
200 R=(E)CH:CHBr

227

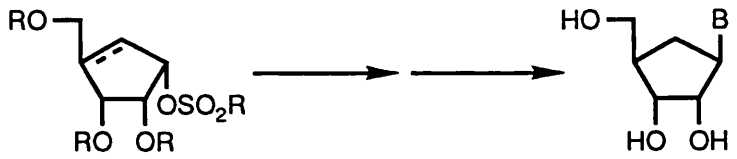
226

Reagents: b) DPPA, NH_3; c) 3-ethoxyacryloyl chloride; d) aq NH_3; e) R=I, I_2, HNO_3;
f) R=(E)CH:CHBr, methyl acrylate, $Pd(OAc)_2$, PPh_3, NEt_3; KOH; NBS, $KHCO_3$

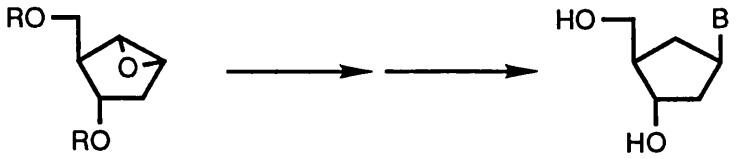
4.1.2 Convergent Approaches

Convergent syntheses of carbocyclic nucleosides bring together the functionalised carbocyclic ring and the intact heterocyclic base. The convergent approaches that have been developed have employed three distinct stratergies. These involve coupling the heterocyclic base with the carbocycle moiety by:

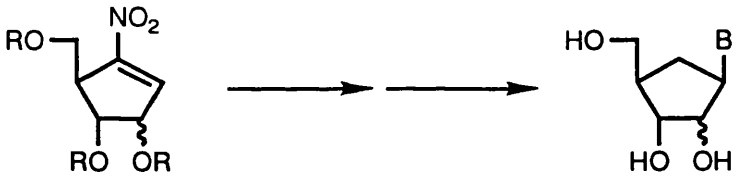
a) Nucleophilic displacement of an activated hydroxyl group.



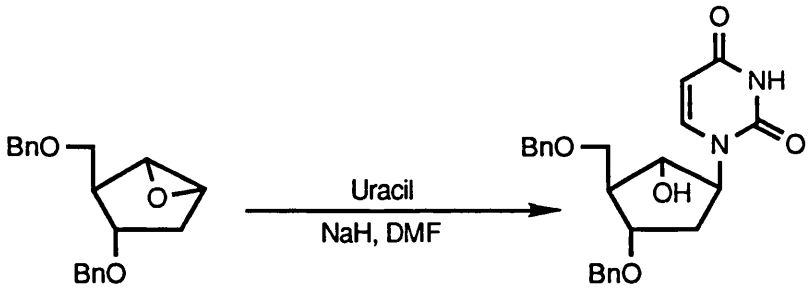
b) Nucleophilic opening of an epoxide



c) Michael addition to an α,β unsaturated nitro compound



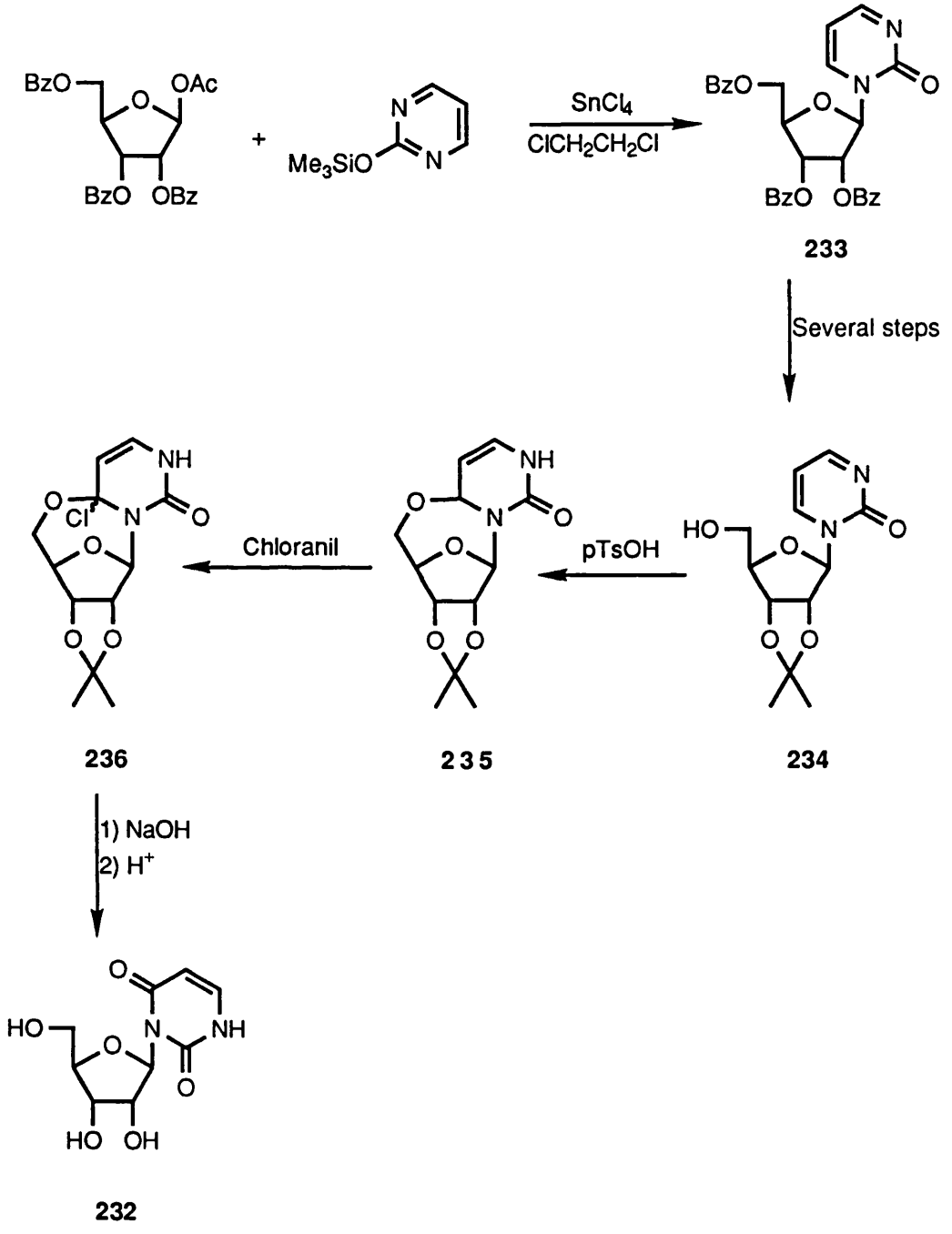
An example of the convergent approach is the opening of the epoxide **230** with uracil to give the alcohol **231**.[109]



230 **231**

In comparison to the number of reports on the synthesis of nucleosides and carbocyclic nucleosides very little work has been done in the field of isonucleosides. Isouridine **232** was not screened for anti-tumour activity by the NIH until 1983 despite its characterisarion and synthesis over 30 years before.[110,111] The most complete biological investigation of isouridine was conducted by Holy and his collaborators who studied the behavior of the nucleotide derivative as well as its 2', 3'-cyclic phosphate, with respect to a range of nucleolytic enzymes.[112-114] In addition, the same group found that, in a reaction catalyzed by ribonuclease, **232** behaved as a good acceptor with adenosine 2',3'-cyclic phosphate to form the

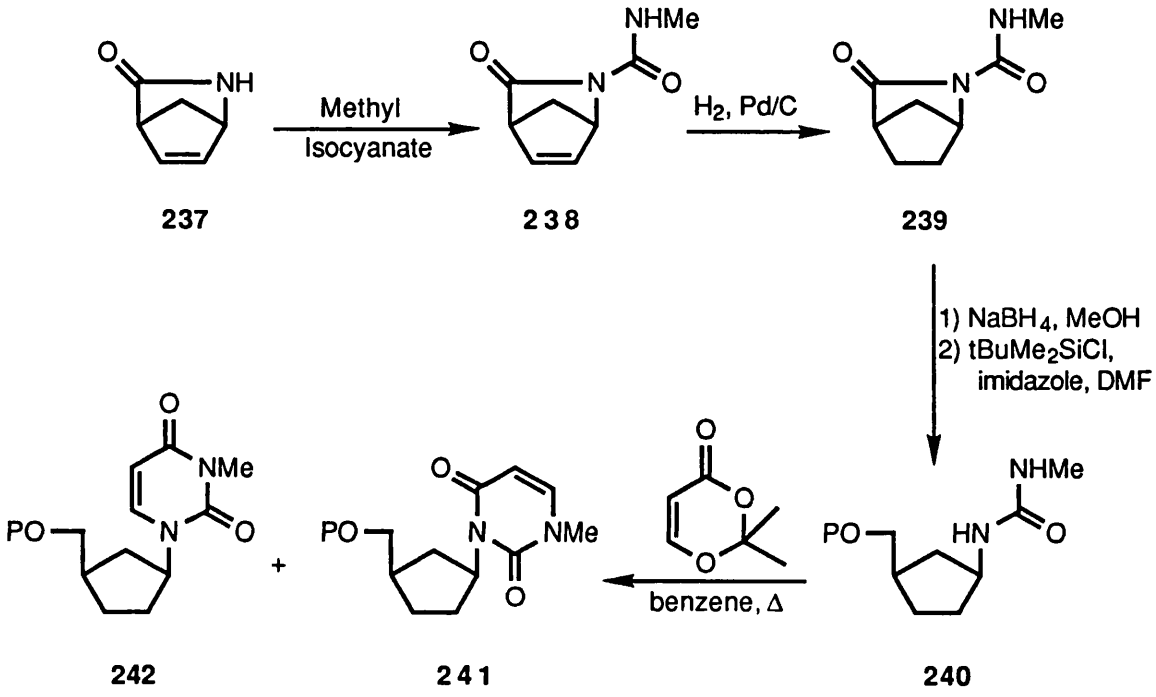
corresponding dinucleotide monophosphates.[115] The most recent report on the synthesis of isouridine[189,190] used a convergent approach similar to that of the carbocyclic nucleosides. Thus the dihydropyrimidinone **234** was readily converted to the cyclic nucleoside **235**, which was oxidised to the chlorine containing intermediate **236** *via* an unknown mechanism. Exchange of the chlorine by hydroxide, together with spontaneous rearrangement led to the desired product, isouridine **232.**



Biological testing of isouridine **232** against P388 cell culture showed, however, no inhibition of cell growth at concentrations as high as $5x10^{-4}$ M. In addition at $1x10^{-4}$ M, $1x10^{-3}$ M and $1x10^{-2}$ M concentrations it failed to inhibit uridine kinase extracted from the P388 cells. The

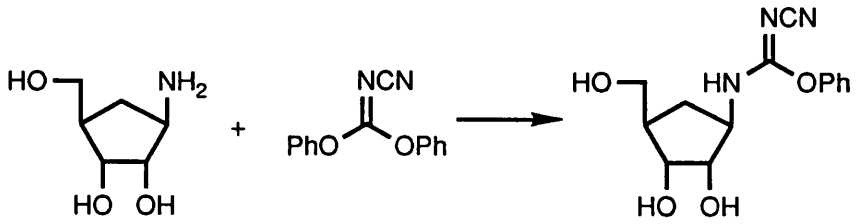
lack of activity is not surprising when one considers that the pyrimidine ring is now in an orientation that is unlikely to be recognized by most enzymes that utilize pyrimidine nucleosides.

A recent report on the synthesis of carbocyclic nucleosides[116] led us to believe that the chemistry of diphenyl cyanocarbonimidate **53** might be applicable to the synthesis of carbocyclic nucleosides. Amide **237** was treated with methyl isocyanate to give the urea **238**. Reductive cleavage of its dihydro derivative **239** gave **240** which, after protection, was reacted with 2,2-dimethyl-1,3-dioxin-4-one to give the carbocyclic nucleosides **241** and **242**.

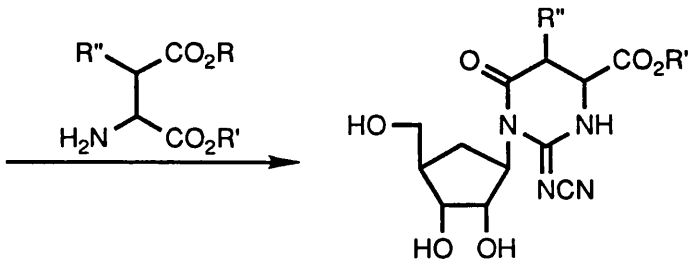


237 **238** **239** **240** **241** **242**

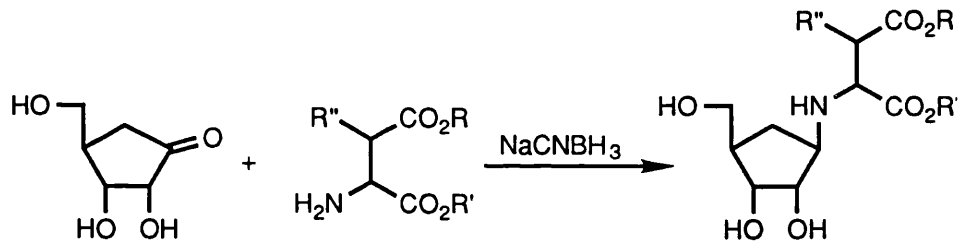
It was envisaged that a sequence in which cyclopentylamine derivatves were treated with diphenyl cyanocarbonimidate **53** followed by reaction with an aspartic acid derivative would give carbocyclic isonucleosides with a variety of functionality on the base. In this way it was hoped that biological activity might be seen even though the products are closer in structure to isouridine than to uridine.

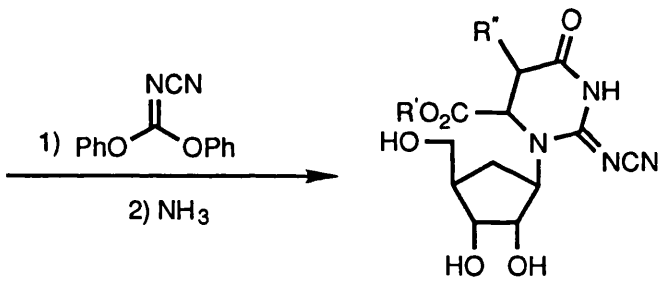


53



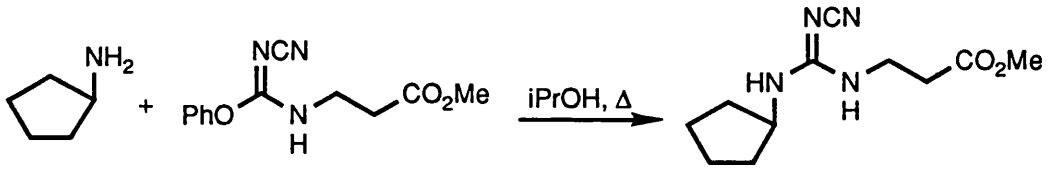
Subsequent reverse order addition was also envisaged that would lead to carbocyclic nucleosides, joined at N-1 of the heterocyclic base.





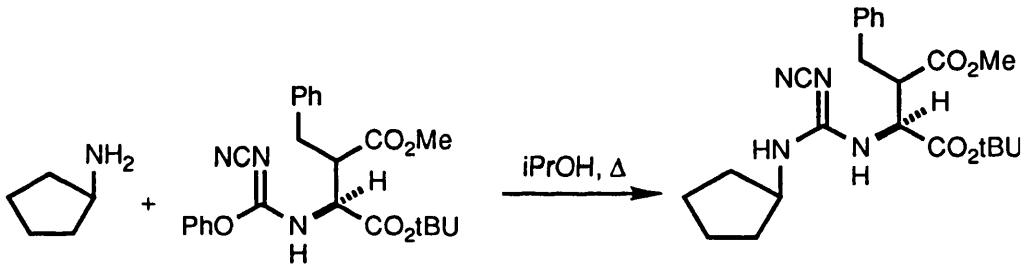
4.2 Results and Discussion

Initial model studies were carried out using cyclopentylamine **243** as the 'sugar mimic'. It was found that substantially different behaviour occured with this amine to the comparable reaction in which benzylamine was used. Thus O-phenylisourea **63** reacted with cyclopentylamine **243**, but only to give the guanidine **244**, further cyclisation which occurred with benzylamine not being observed.



243 **63** **244**

Similarly, the more substituted O-phenylisourea **146** also gave only the linear product **245**, the yield, however, being considerably worse.



243 **146** **245**

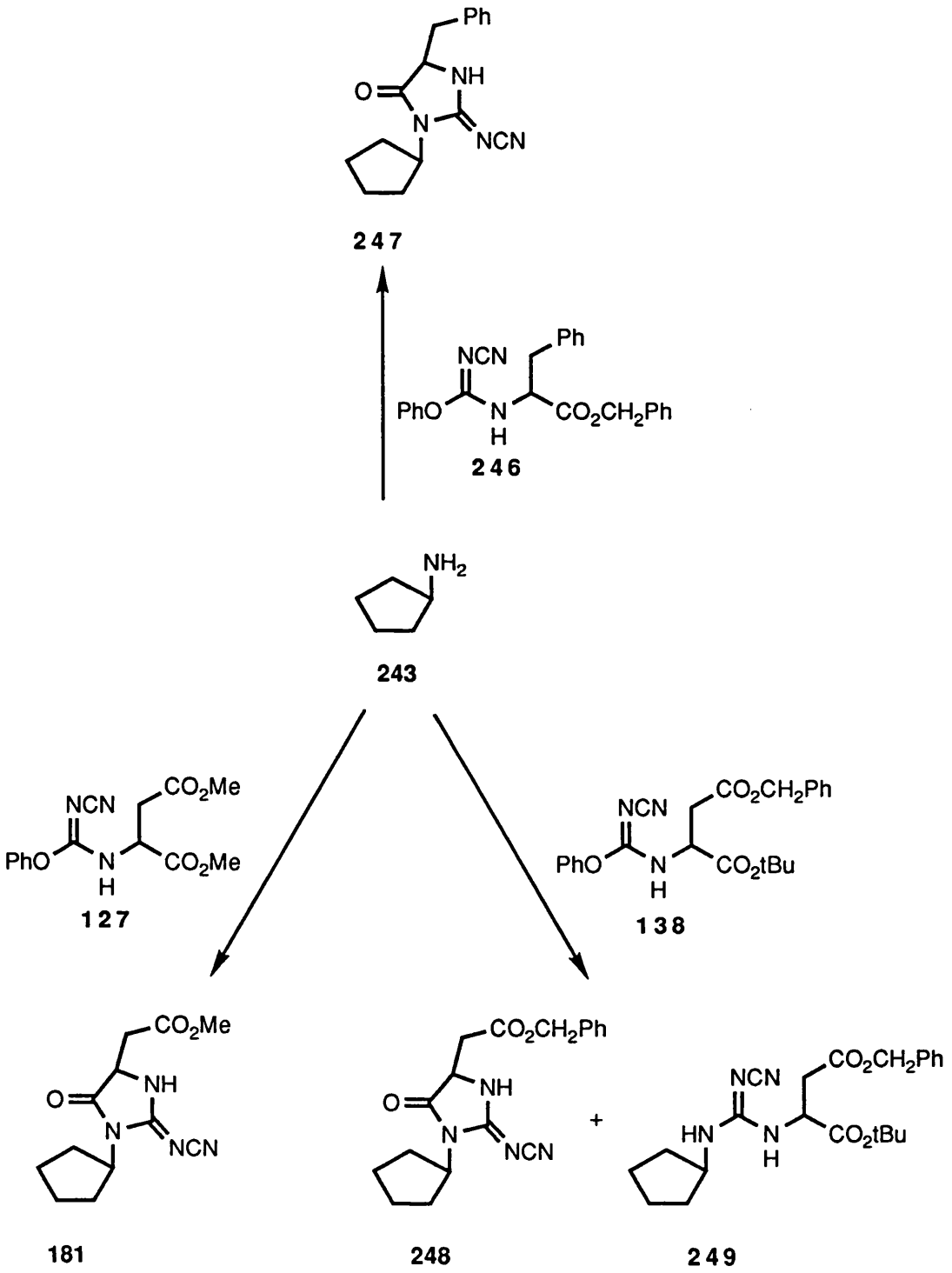
Imidazolidin-5-ones did readily form however, albeit with reduced yields, when compared to the corresponding benzylamine reactions (Scheme 4.1). This once again demonstrates that formation of a 5-membered ring is the favoured ring closure reaction in this system. Reaction of cyclopentylamine with a variety of α-amino acid esters led to the imidazolidin-5-ones shown.

Perhaps the most significant result is that reaction of cyclopentylamine with the O-phenyisourea **138** derived from α-tBu-β-Bzl-Asp **137** led only to the imidazolidinone **248** together with the guanidine **249**. In this system therefore cyclisation onto a t-butyl ester is favoured over any cyclisation to any group that would lead to the pyrimidinone system.

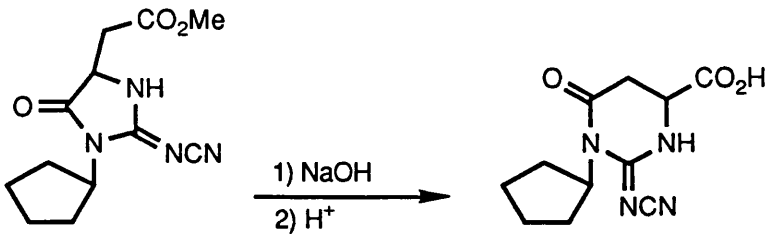
These results seem to indicate that a fine line exists between benzylamine and the cyclopentylamine derivatives, with formation of a 6-membered ring being possible for the former but not the latter. The reduced yields and absence of pyrimidinone products can be attributed to the greater steric hindrance that is present in the cyclopentyl structure at the amine nitrogen as compared to benzylamine. This is a recurring theme in the chemistry of diphenyl

cyanocarbonimidate **53** where any substitution that leads to increased steric crowding at the amine centre results in rapidly decreasing product yields.This increased steric hindrance at the amine centre must lead to the transition state for the 6-membered ring product being more disfavoured than it is in the case of benzylamine. Hence it seems that any amine will present problems at the initial substitution or subsequent cyclisation step if it is more complex at the nitrogen than a primary amine.

Scheme 4.1



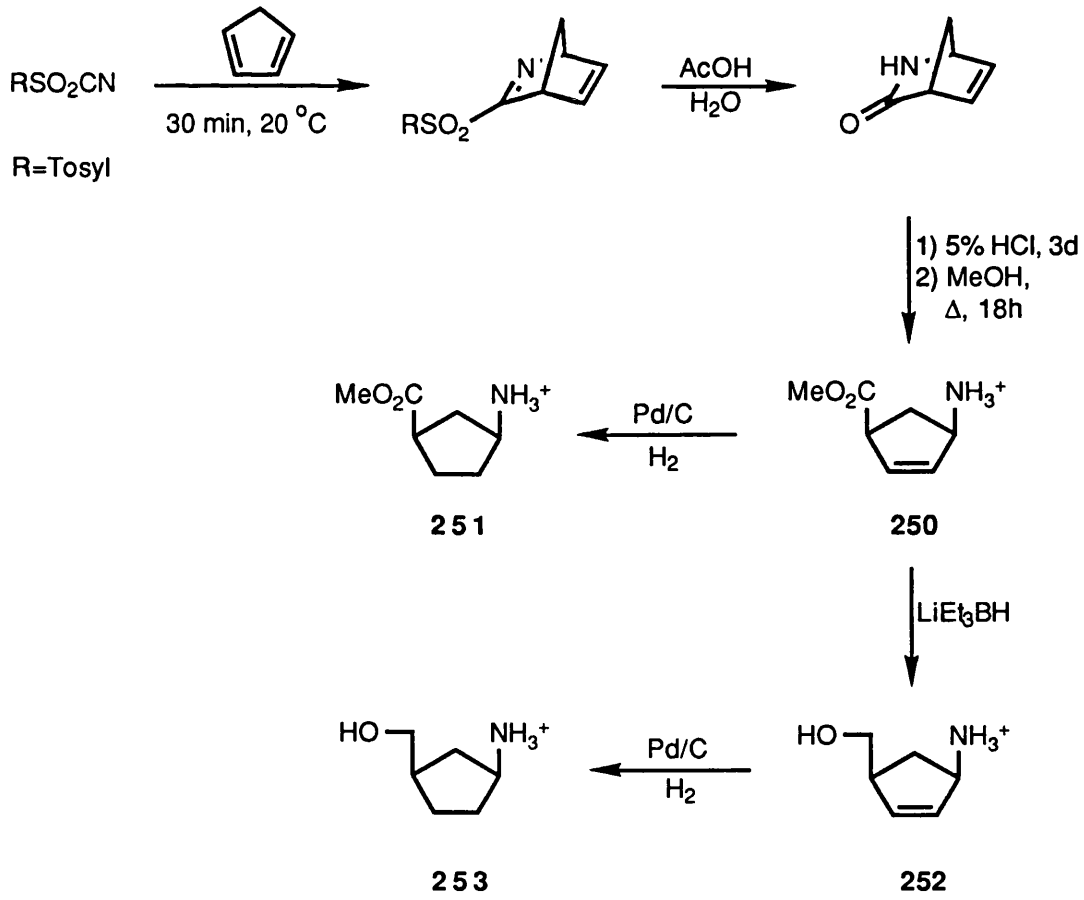
The imidazolidin-5-one **181** derived from dimethyl aspartic acid could, however, be rearranged to the pyrimidine carboxylic acid **187** by making use of the rearrangement reaction as previously stated (Chapter 3). The spectral changes in going from **181** to **187** were competely consistent with the changes in structure.



181 **187**

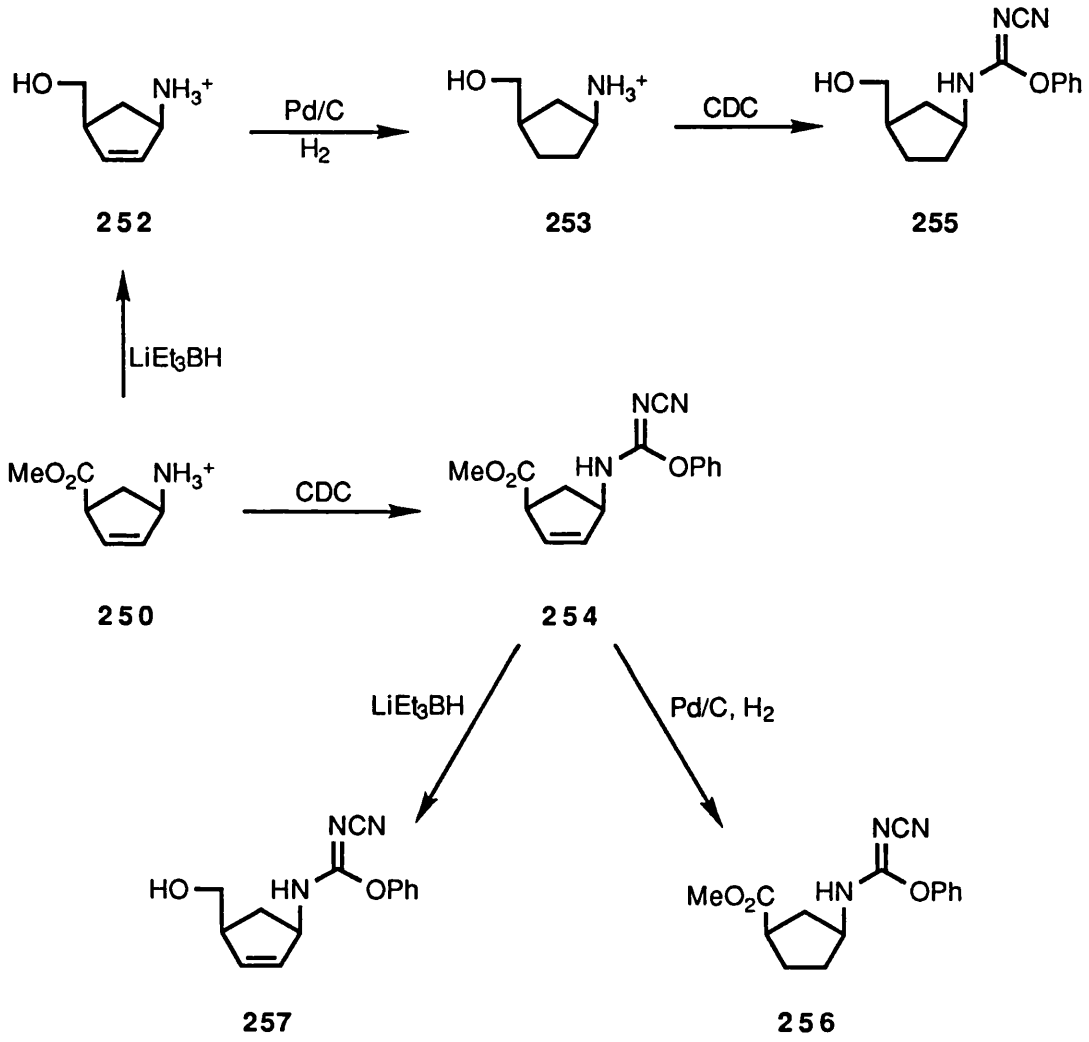
With these model results in hand attention was turned to the synthesis of 1,4-disubstituted carbocyclic pyrimidinones. The cyclopentylamines required for this chemistry were constructed using literature methods[117,118] (Scheme 4.2).

Scheme 4.2

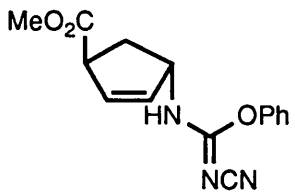


All four racemic carbocyclic amines **250-253** were effectively coupled to diphenyl cyanocarbonimidate **53**, either by direct coupling or by modification of a preformed O-phenyisourea (Scheme 4.3).

Scheme 4.3



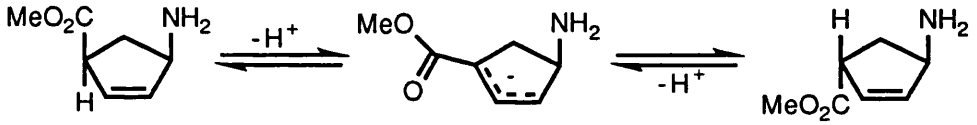
Interestingly, amine **250** reacted to give only the *cis* isomer **254** and not the corresponding *trans* isomer **258**.



258

That only one isomer was formed was confirmed by n.O.e. measurements. These clearly showed that on irradiating one of the C-5 protons an enhancement occured only at the NH proton and the other C-5 proton, whilst irradiating at the second C-5 proton led to an enhancement at both the C-1 and C-4 protons. These results are those that would be expected for **254** and not **258**.

This result seems to contradict the literature[117] where it has been reported that the cyclopentylamine **250** readily undergoes base catalysed epimerization on stirring the amine hydrochloride with triethylamine in THF. The site of inversion was clearly shown by incubation of **250** with sodium deuteroxide in CD_3OD to be C-4, as would be expected since this is the most acidic proton, being α to both an ester and olefin.

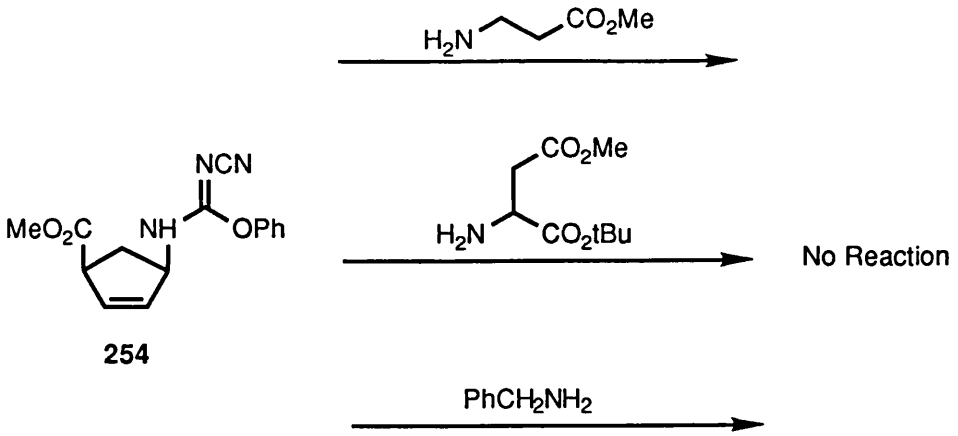


250 **250a**

Since this result seemed to contradict our own observations, the epimerization was reinvestigated by monitoring the reaction using ^1H n.m.r. spectroscopy. Thus the free amine of **250** was generated using triethylamine in THF and the salt subsequently regenerated with HCl gas. The ^1H n.m.r. spectrum of the regenerated salt clearly indicated the presence of the second isomer, a new set of peaks being seen.

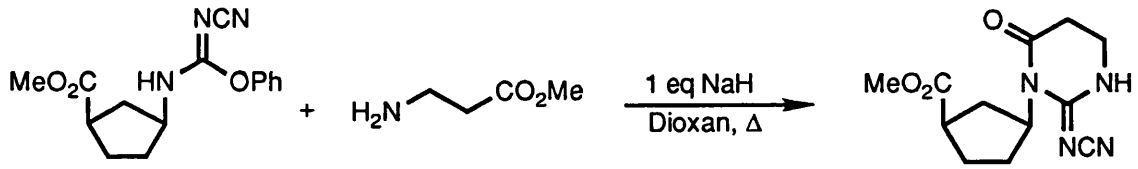
The reason for only one isomer being seen on reaction with diphenyl cyanocarbonimidate **53** is unclear. Since epimerization is apparently occurring during the reaction it must be concluded that either only the *cis* isomer can react or, as seems more likely, the *cis* isomer is the more stable of the two possible products and any *trans* isomer that is produced is converted to the more thermodynamically stable *cis* isomer by epimerization susbequent to its formation.

Attempts to react O-phenylisourea **254** with a number of amine nucleophiles under a variety of conditions (Et_3N, NaH, or BuLi) to give pyrimidinones directly proved to be unsuccessful. No reaction was obtained with β-alanine-methyl ester, α-tBu-β-Me Aspartate, or even benzylamine.

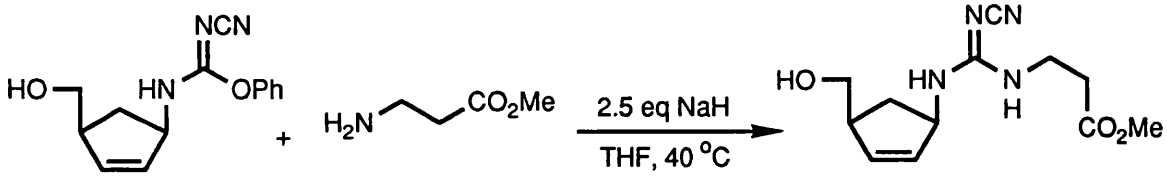


254

O-Phenylisoureas **256** and **257** did, however, react with β-alanine-methyl ester **62** when the anion of the amine was generated using sodium hydride. In the case of **256** dioxan was used as the solvent and a small amount of the cyclised product **259** was obtained. For **257** THF was used as the solvent and the guanidine **260** was obtained. However, yields were low at less than 10% in both cases.



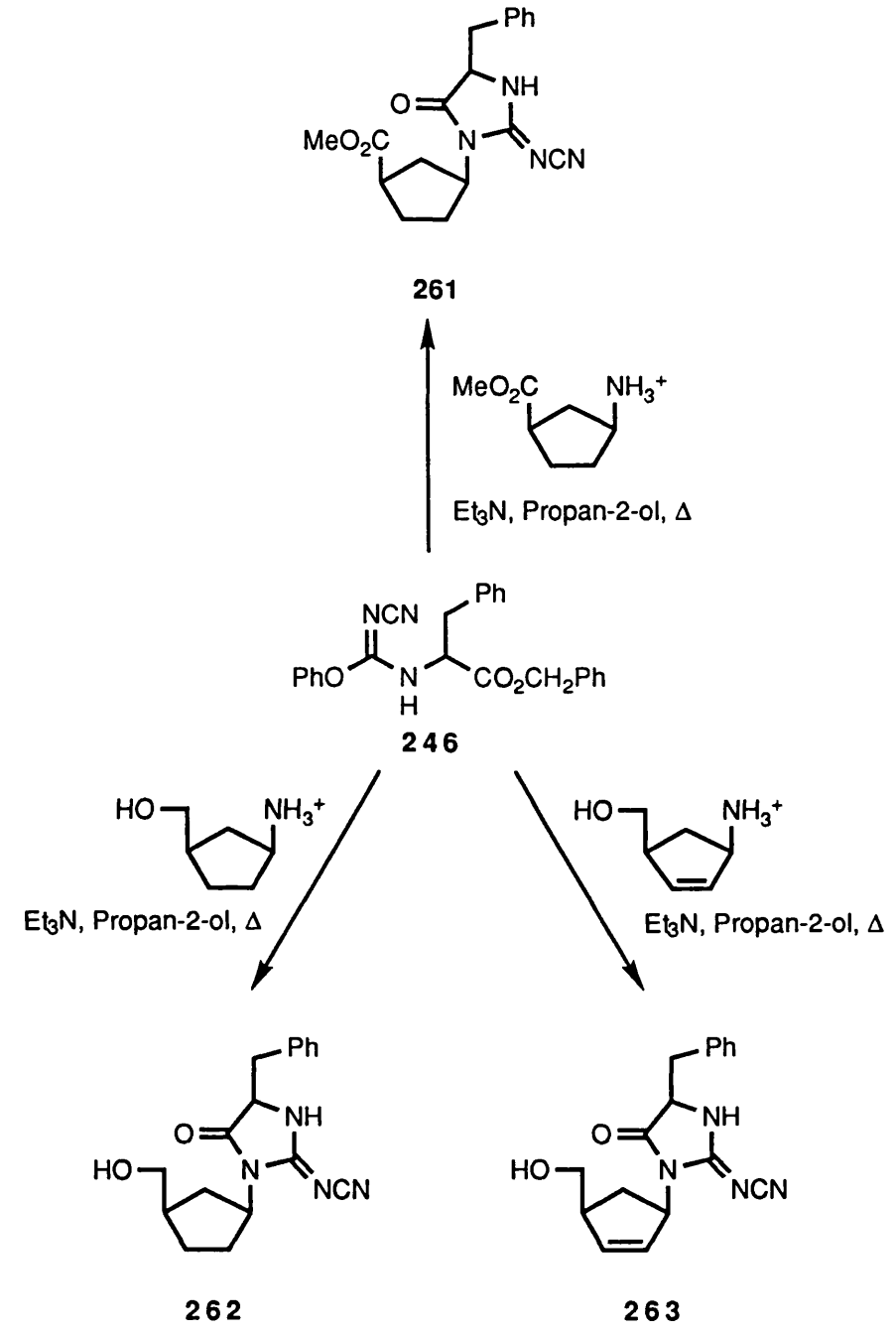
256 **62** **259**



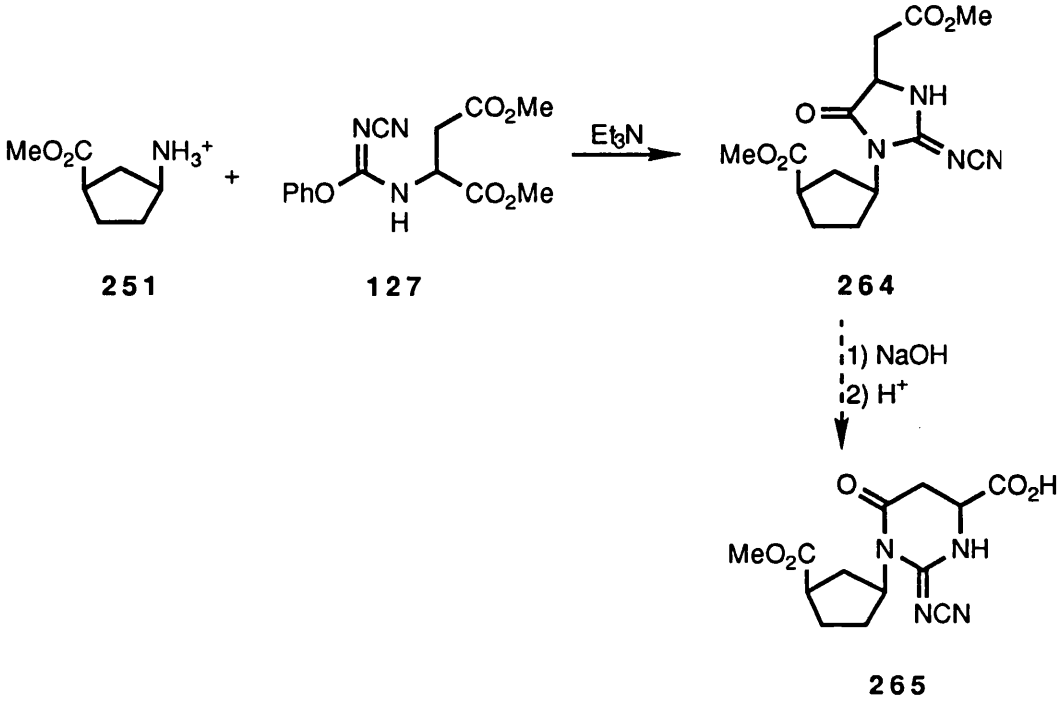
257 **62** **260**

Once again, however, imidazolidin-5-ones could be formed (Scheme 4.4) but even in these cases yields were greatly reduced (10-15%) in comparison to those observed where the carbocycle was not substituted at C-4. Phenylalanine benzyl ester was generally used since the resulting imidazolidinones still contained a chromophore, making isolation of the products easier. The products were mixtures of diastereoisomers as seen by ^{13}C n.m.r.

Scheme 4.4



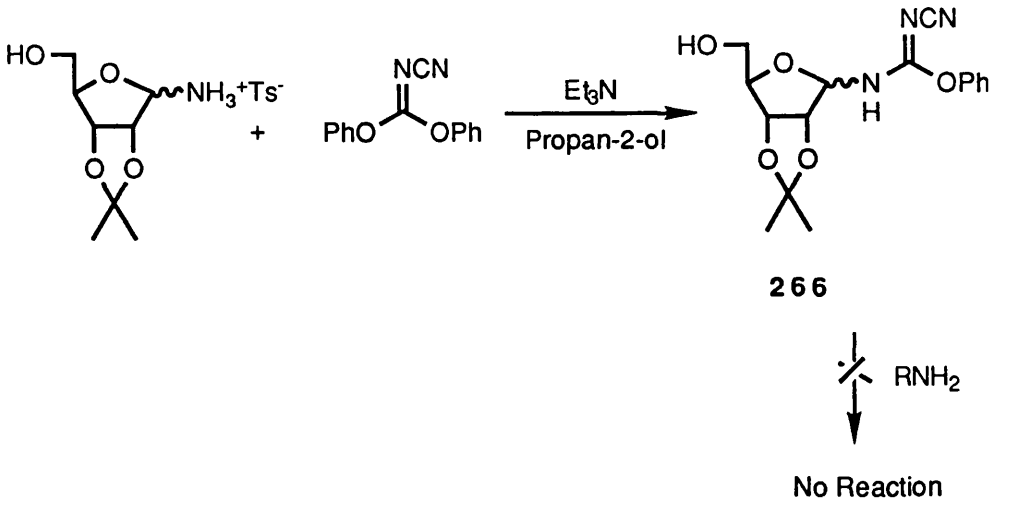
As a result of the low yields it proved to be impossible to obtain enough of the carbocyclic imidazolidin-5-one methyl ester **264** to perform the ring rearrangement reaction. Given that this reaction was successful in all other cases it would be predicted that, given sufficient of the imidazolidinone, it would be successful in this case.



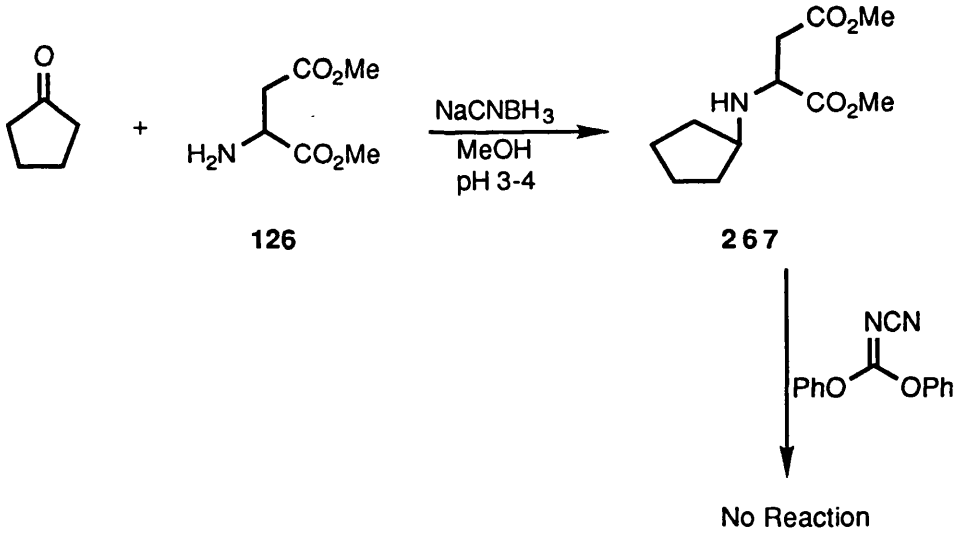
251 **127** **264** **265**

From these results it is seen that further increasing the steric bulk of the cyclopentylamine by the introduction of a second group at C-4 led to a substantial decrease in product yield, such that either no product is formed or the yield of product is synthetically unacceptable.

Attention was then turned to the use of ribitylamine[119] as the amine source. It was hoped that the oxygen now present in the ring would lead to a conformation sufficiently different for reaction with a second nucleophile to be possible. However it was found that whilst the protected ribitylamine would readily react with diphenyl cyanocarbonimidate **53** to give the intermediate O-phenylisourea **266**, further reaction with a second amine such as benzylamine or β-alanine methyl ester did not occur. In the light of the previous results with cyclopentylamine derivatives it seemed unlikely that this even more hindered amine source would give better results, hence this was not pursued further.



Attempts to perform the reverse addition were also investigated. Reductive amination[195] of cyclopentanone with dimethyl aspartate **126** occured smoothly to give the cyclopentylamine derivitive **267** but again this was found not to react with diphenyl cyanocarbonimidate **53** even when sodium amide was used to generate the amine anion. This is again attributed to the steric hindrance present in the amine.



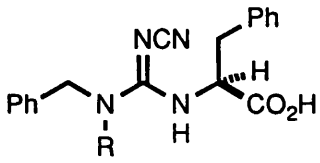
4.3 Conclusion

Once again it can be seen from the model studies that the formation of imidazolidin-5-ones is favoured over formation of pyrimidinones. It seems that the steric hindrance present in these cyclic amines is sufficiently large to prevent the efficient addition of the second amine group and that where addition does occur the subsequent cyclisation is now inhibited.

Reactions of the N-cyanoimine Functional Group

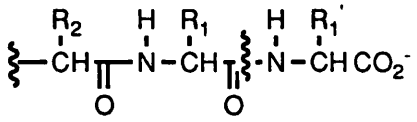
5.1 Design of Enzyme Inhibitors of Carboxypeptidase A

During attempts to prepare a potential inhibitor **268** of the enzyme Carboxypeptidase A, an unusual cyclisation reaction was observed. Further investigation of similar systems led to a mechanism that explains the observation.



268

Carboxypeptidase A is a zinc-containing proteolytic enzyme which removes the C-terminal amino acid from a peptide chain if the C-terminal carboxylate is free. In order that a substrate may be susceptible to lysis by carboxypeptidase A, certain requirements and preferences are exerted by the enzyme.[120] Firstly, the peptide bond which is to undergo hydrolysis must be adjacent to a terminal free carboxyl group, as for **269**. Secondly, the rate of hydrolysis is usually enhanced if the terminal residue has an aromatic or branched aliphatic side chain. Thirdly, dipeptides having a free amino group are hydrolysed slowly, but if this group is blocked by N-acylation, the hydrolysis is rapid. Fourthly, the carboxyl-terminal residue must be in the L-configuration. Fifthly, substitution of a methyl group for the H atom of the NH group of the peptide bond to be split either prohibits or greatly reduces hydrolysis.

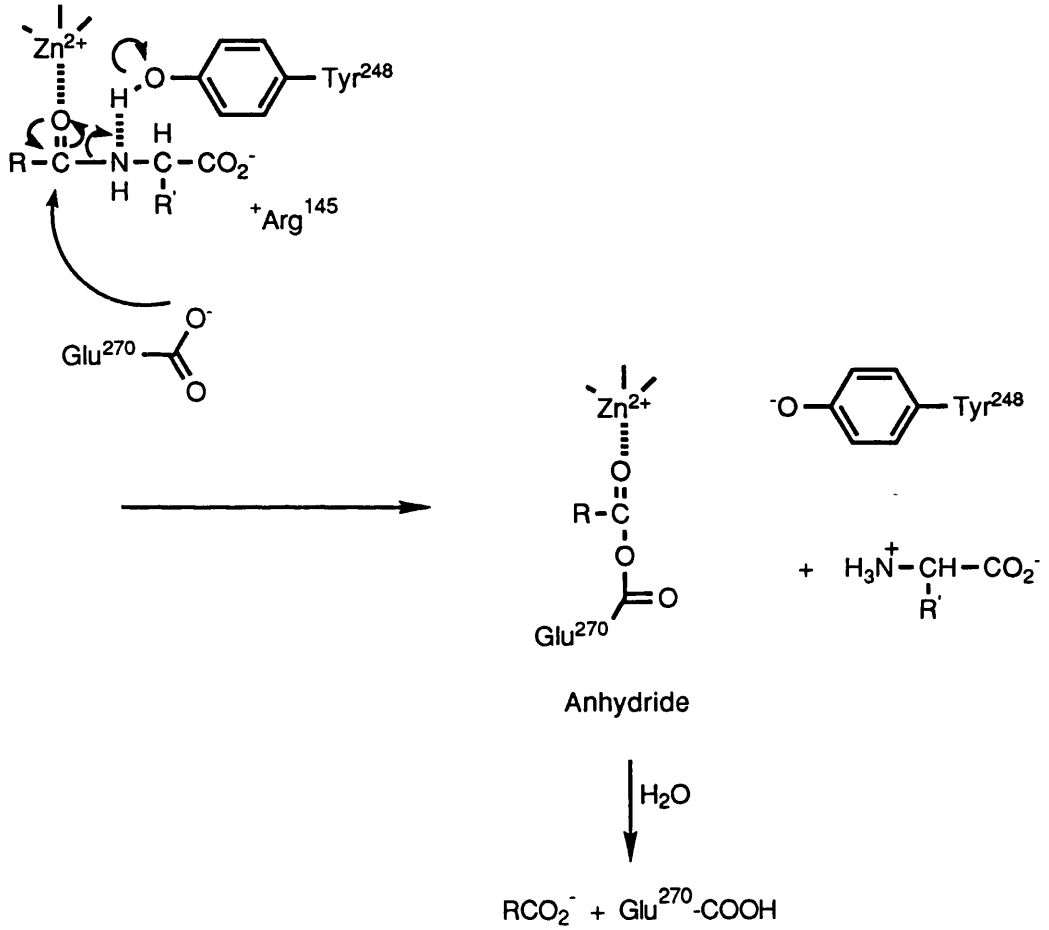


269

The detailed mechanism of action of Carboxypeptidase A remains controversial. Binding of the substrate is believed to involve charge pairing of the terminal carboxylate group with the guanidinium of Arg^{145}, setting up the carbonyl oxygen of the terminal peptide bond to become a ligand of the active site zinc.[121] This liganding polarizes the carbonyl group, increasing the electrophilicity of the carbonyl carbon and facilitating nucleophile mediated hydrolysis. The phenolic hydroxyl of Tyr^{248} is in sufficient proximity to the susceptible amide linkage in the substrate to donate a proton to the amine fragment on cleavage, facilitating its expulsion as a leaving group by general acid catalysis.

However the distinction between the so-called 'anhydride' mechanism (Scheme 5.1), where Glu^{270} attacks the carbonyl of the substrate to form an acyl-enzyme intermediate (an anhydride), and the 'direct' mechanism (Scheme 5.2), where Glu^{270} acts as a general base to activate a water molecule which directly cleaves the substrate, cannot be made.[122]

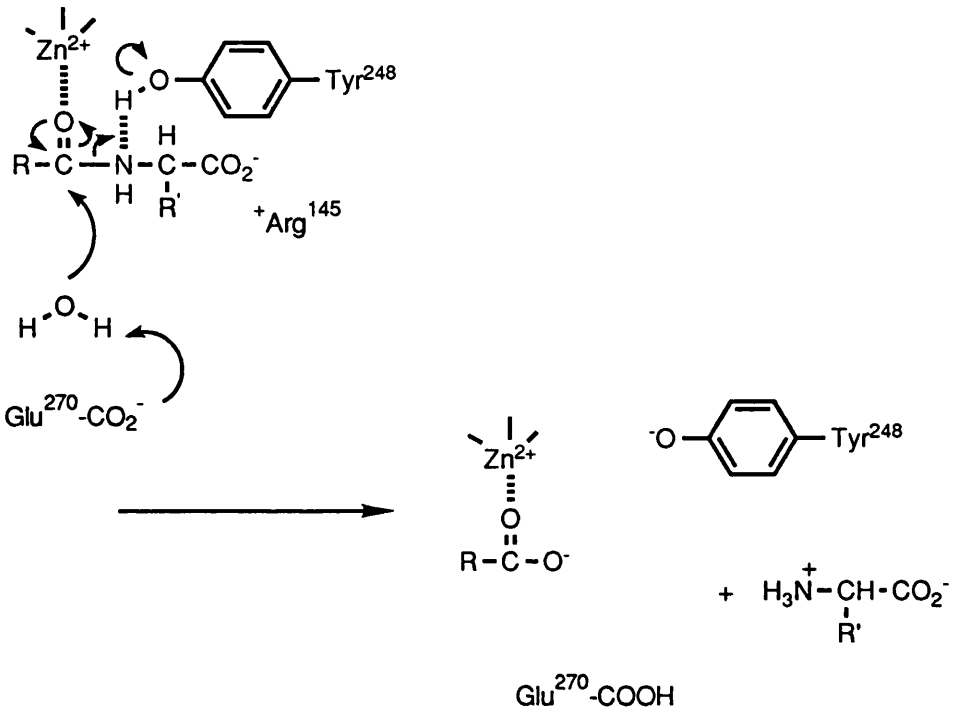
Scheme 5.1



Various mechanistic claims have been made for particular substrates, but even these have been disputed.[123,124] Combined with the observation that this enzyme can catalyse stereospecific enolisation of a ketonic substrate,[125] and α,β-elimination reactions[126] it is perhaps a moot point to attempt to formulate a general mechanism for all substrates for this enzyme.

Our potential substrate/inhibitor seemed to satisfy many of the criteria for a good substrate for carboxypeptidase A. The 'peptide' bond to be hydrolysed is adjacent to an L-aromatic terminal residue with a free carboxylate group. There is no free amino group which is known to slow down hydrolysis. The fact that the peptide bond oxygen has been replaced by the

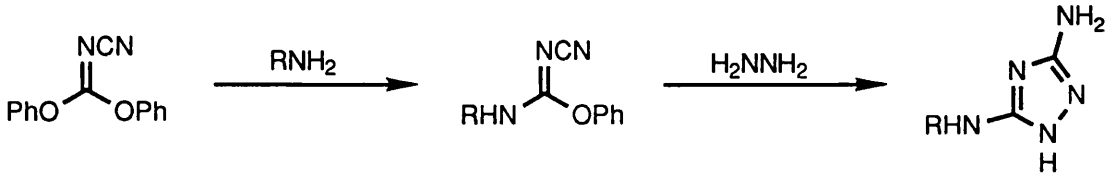
Scheme 5.2



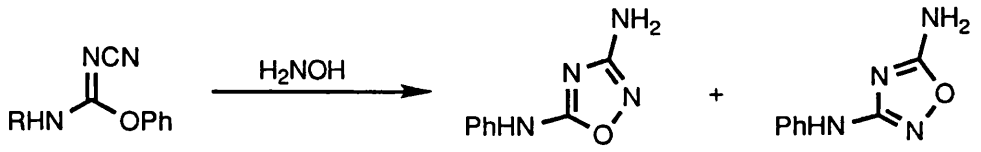
N-cyanoimino group leads to uncertainty over whether **268** would behave as an inhibitor or substrate. Whilst this group is known to be an isostere for the carbonyl group[57,58] it is uncertain whether the enzyme would accept this group and carry out the hydrolysis, thus removing the phenylalanine and leaving behind a group that could act as an inhibitor of the enzyme, or whether the enzyme would accept the substrate **268** but then be unable to carry out the peptide bond hydrolysis, thus inhibiting the enzyme at this earlier stage.

5.2 Reactions of the N-cyanoimine group

N-cyanoimines react with hydrazine to give 1,2,4-triazoles **271** (Chapter 6), and also with hydroxylamine to give 1,2,4-oxadiazoles **272** and **273**.[27]

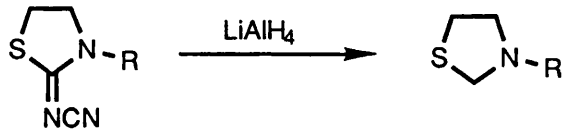


53 **270** **271**

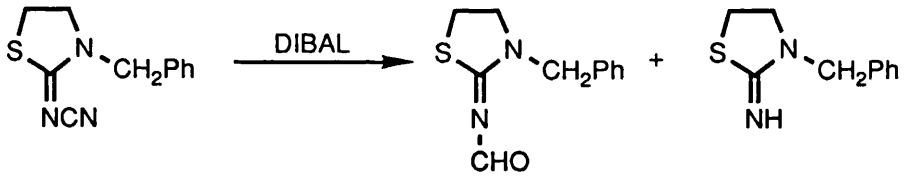


270 **272** (10%) **273** (90%)

The N-cyanoimine group can also be converted to other groups once the heterocycle has been formed. Recently, the regioselective hydride reduction of 2-(N-cyanoimino)-thiazole derivatives has been reported.[127] Hence reductive cleavage of the imino double bond was achieved using lithium aluminium hydride, and reduction of the nitrile group and/or the cleavage of the imino nitrile bond was achieved with diisobutylaluminium hydride.

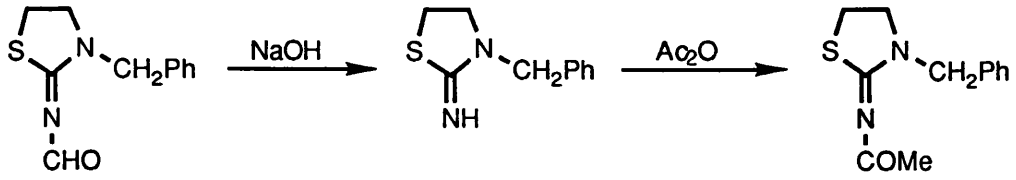


274 **275**



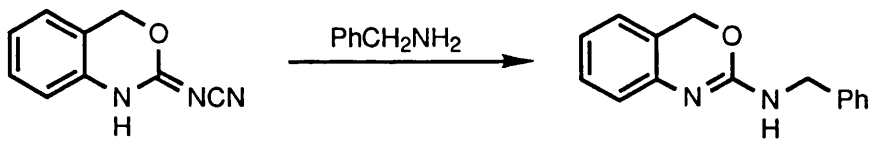
276 **277** **278**

The 2-formylimino compound **277** was easily converted to the 2-imino derivative **278** by hydrolysis with aqueous sodium hydroxide, and treatment of **278** with acetic anhydride gave the 2-acetyliminothiazolidine **279**.



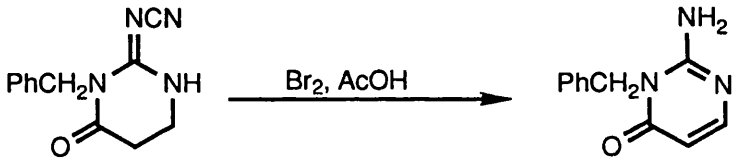
277 **278** **279**

Treatment of 2-N-cyanoimino-4H-1,3-benzoxazine **60** with benzylamine in boiling propan-2-ol gave the 2-benzylamino-1,3-benzoxazine **61** by nucleophilic addition to the C=N carbon with subsequent ejection of H_2NCN.[25]



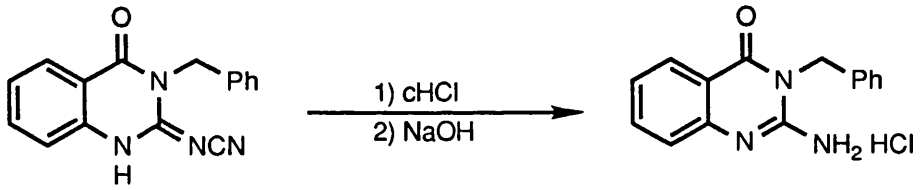
60 **61**

The N-cyanoimine group can also be hydrolysed. During the course of a reaction to introduce a double bond into the dihydropyrimidine **64** using bromine in acetic acid, the N-cyanoimine group was also hydrolysed to the amine **65**.[24]



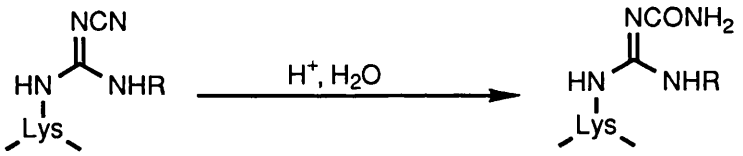
64 **65**

Similarly treatment of 3-benzyl-2-cyanoimino-4(1H, 3H)-quinazolinone **280** with concentrated hydrochloric acid resulted in hydrolysis of the N-cyanoimino group to give 2-amino-3-benzyl-4(3H)-quinazolinone hydrochloride **281**.



280 **281**

Recently it has been reported that gonadotropin-releasing hormone (GnRH) antagonists containing modified N^{ω}-cyano-$N^{\omega'}$-alkyl or arylguanidino moieties on homoarginine, when stored in lyophilized form as the trifluoroacetate salts decompose into a major hydrophobic impurity.[128] From infra-red and mass spectrometry data it was concluded that, in the presence of water of hydration, hydrolysis of the nitrile had occured under the acidic conditions induced by the TFA counter-ion, yielding the corresponding guanylurea derivative. In order to assess the lability of the cyanoguanidino function in acid, the hydrolysis of **282** in 0.1% TFA was monitored by HPLC and was found to be complete within 4 days at room temperature.

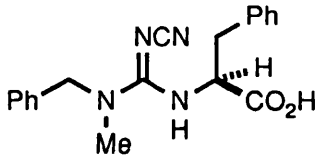


282 **283**

We have investigated this reaction under both anhydrous and hydrated conditions and have found that the results can be used to explain the formation of unusual cyclisation products upon attempts to synthesise inhibitors of the enzyme carboxypeptidase A.

5.3 Results and Discussion

It was envisaged that synthesis of the benzyl ester **284** followed by subsequent deprotection would give the required guanidine **285**. Hence diphenyl cyanocarbonimidate **53** was coupled with L-phenylalanine benzyl ester **286** to give the O-phenylisourea **246** (Scheme 5.3). Reaction of this with N-methyl benzylamine then gave the guanidine **284**. It was found, however, that use of this secondary amine led to a poor yield of the guanidine **284**, the best yield obtained being 56%. This is believed to be due to the fact that the more hindered secondary amine cannot readily approach the imine carbon. Deprotection of the benzyl ester **284** by hydrogenation over palladium did not, however, give the desired free carboxylic acid **285**, but instead led to a compound whose spectral properties were consistent with those of the imidazole **287**. This compound showed broad peaks in the ^1H n.m.r. spectrum at room temperature and heating the sample caused these peaks to coalesce (T_c=393 K, $\Delta\upsilon$=169 Hz, K'=375 s^{-1}, $\Delta G^{\ddagger}$=18.6 Kcal/mol). These spectral properties are believed to arise as a result of restricted rotation about the N-methyl benzyl carbon due to it coming into close proximity in some positions with the hydrogen attached to the ring nitrogen.



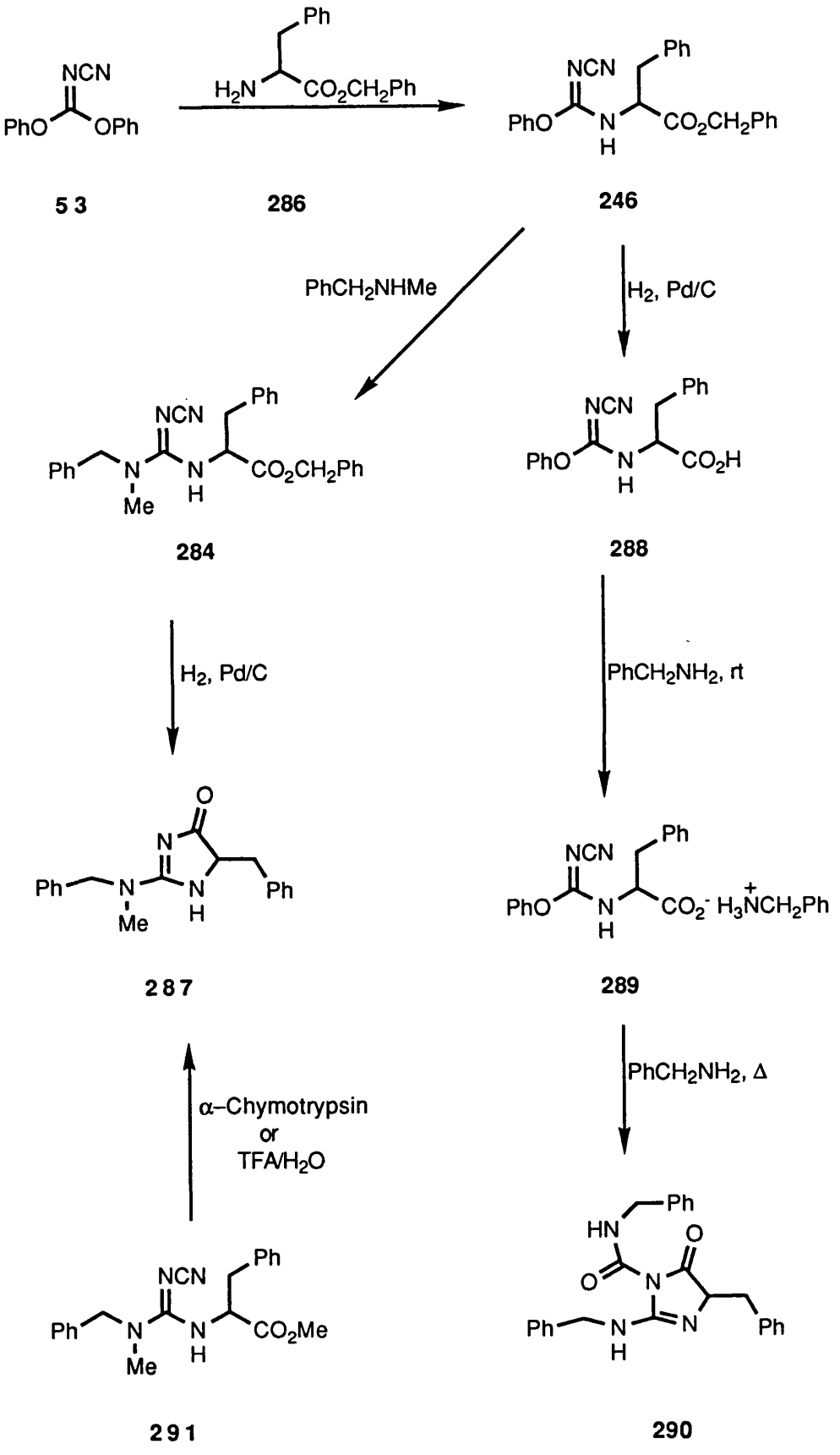
285

Deprotection of the intermediate O-phenylisourea **246** using identical conditions did not, however, lead to a similar cyclisation reaction. In this case the carboxylic acid **288** was isolated. Subsequent reaction with benzylamine at room temperature led to a compound whose spectral data were consistent with those of the benzylamine salt **289**. Reaction of this salt with benzylamine at 100 °C gave another imidazole **290**. Interestingly this compound did not show the presence of hindered rotation, which reflects the absence of both the N-Me and N-H groups from this molecule.

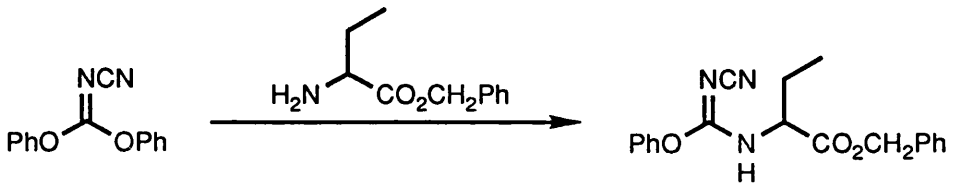
A similar product **295** could also be obtained from the corresponding 2-amino butyric acid benzyl ester **292**. Thus coupling with diphenyl cyanocarbonimidate **53** gave the O-phenylisourea **293** which was reacted with N-methyl benzylamine to give the guanidine **294**. Deprotection of the guanidine **294** by hydrogenation over palladium led to the imidazole **295** which again showed the presence of hindered rotation in its ^1H n.m.r. spectrum (T_c=293 K, $\Delta\upsilon$=22.8 Hz, K'=50.6 s^{-1}, $\Delta G^{\ddagger}$=14.8 Kcal/mol).

The imidazole **287** could also be synthesised from the methyl ester **291** either by deprotection using trifluoroacetic acid/water in boiling THF, or chymotrypsin in a phosphate buffer at pH=7.8. Cleavage of methyl esters is usually achieved under basic or neutral

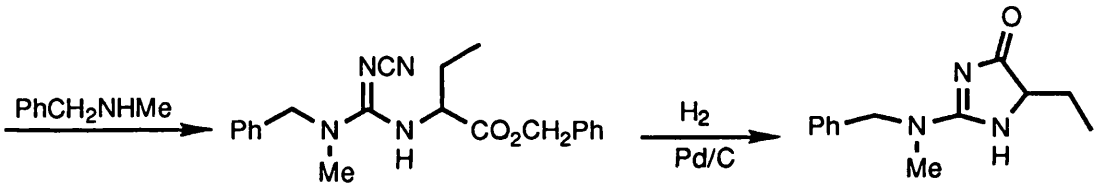
Scheme 5.3


NCN
PhO
OPh
Ph
H2N
CO2CH2Ph
53
286
246
PhCH2NHMe
H2, Pd/C
284
288
H2, Pd/C
PhCH2NH2, rt
287
289
α–Chymotrypsin
or
TFA/H2O
PhCH2NH2, Δ
291
290

conditions,[129] however anhydrous TFA has been used to cleave methyl esters,[130] though under the more vigorous conditions of heating the ester in a sealed tube to 105 °C for 20 h. That chymotrypsin cleaves the methyl ester is to be expected, since there are many reports of the use of chymotrypsin to cleave esters,[131] and also because **291** resembles a dipeptide with a phenylalanine as its terminal residue; phenylalanyl peptide bonds are among those that are primarily attacked by chymotrypsin. In this case, however, evidence was found for the intermediacy of the free carboxylic acid **285**. Monitoring the reaction by TLC showed a more polar product spot below that of the imidazole **287**. Attempts to isolate this product however, by either extraction or flash chromatography failed. In both cases the acid was apparently converted to the imidazole during the work-up procedure.



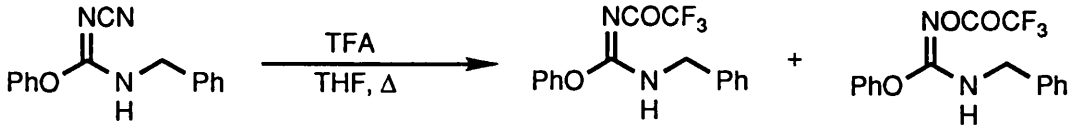
53 **292** **293**



294 **295**

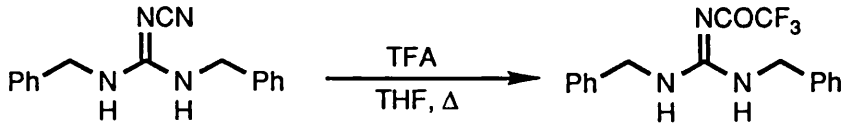
It would seem, therefore, that once the ester protecting group has been removed an unstable intermediate acid **285** is formed which readily reacts further to give the imidazole **287**. A clue as to the possible mechanism of formation of these cyclisation products came from an investigation of the reaction of simple cyanoimines with TFA under anhydrous and hydrous conditions.

Under anhydrous conditions reaction of the O-phenylisourea **296** with 6-equivalents of TFA in boiling THF led to two products, the trifluoroacetyl compound **297** and the trifluoroacetoxy compound **298**, **297** being the major product.



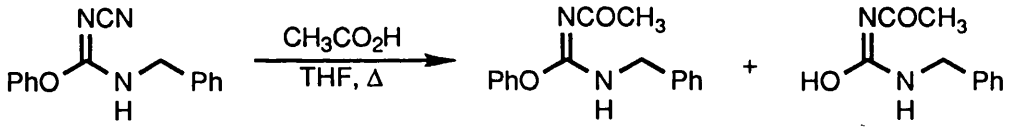
296 **297** **298**

The guanidine **299**, however, under identical conditions yielded only the trifuoroacetyl product **300**.

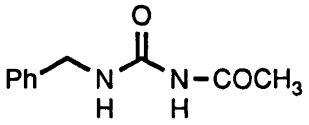


299 **300**

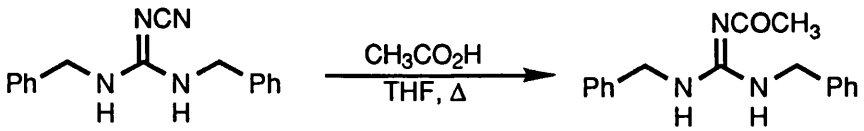
A similar set of products were observed when glacial acetic acid was used in place of TFA. However reaction times were considerably longer and, in the case of the O-phenylisourea **296**, some hydrolysis of the phenoxy group was seen, probably as a consequence of the longer reaction times allowing moisture to get into the system.



296 **301** **302**



303



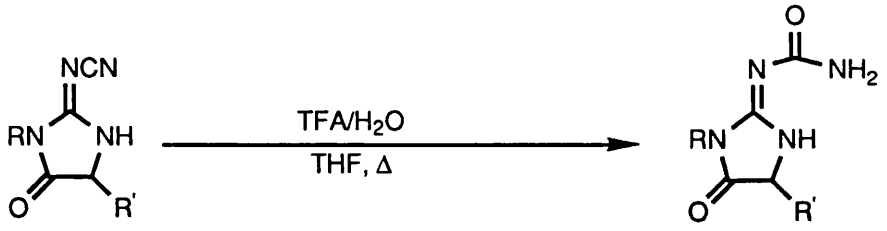
299 **304**

The presence of rotamers in the ^{1}H and ^{13}C n.m.r. spectra of **302** together with an absorption in the IR spectrum consistent with an imine stretch suggest that **302** has the structure shown and not the corresponding tautomeric urea structure **303**.

Addition of an equivalent amount of water to the TFA present in the reaction mixture led to a change in the course of the reaction. Hydrolysis products similar to those obtained

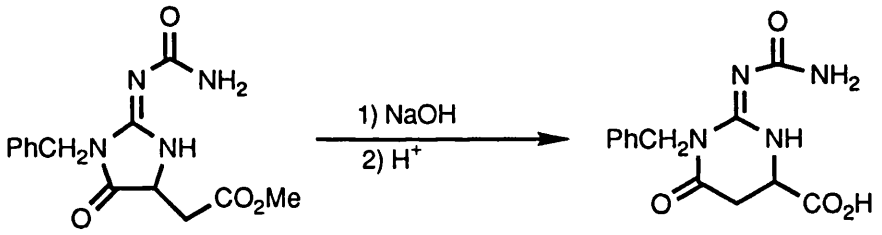
previously[128] were seen. Thus several imidazoles were converted to their corresponding urea derivatives (Scheme 5.4).

Scheme 5.4



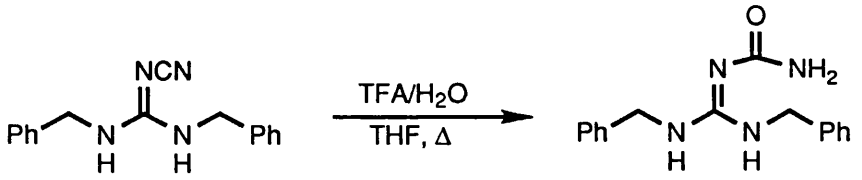
166	$R=R'=CH_2Ph$	**306**
128	$R=CH_2Ph$, $R'=CH_2CO_2Me$	**307**
181	$R=cC_5H_9$, $R'=CH_2Ph$	**308**
305	$R=NH_2$, $R'=Et$	**310**

Urea **307** could also be rearranged to give the dihydropyrimidine **309** using the rearrangement reaction described previously (Chapter 3).

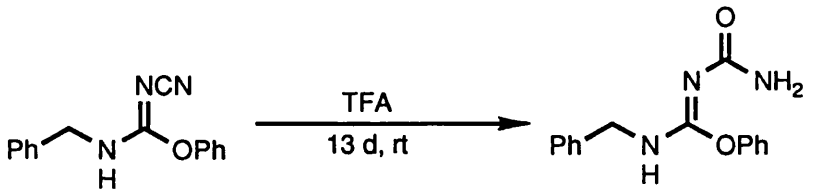


307 **309**

The guanidine **299** could also be converted to its urea derivative **311**, but in the case of the O-phenylisourea **296** it was found that under reflux conditions hydrolysis of the phenoxy group occured. Hence the O-phenylisourea **296** was stirred with TFA alone in THF at room temperature for 13 days to give the urea **312**. Presumably during the reaction water is slowly absorbed into the reaction mixture from the atmosphere, thus allowing the hydrolysis of the N-cyanoimine to occur, but insufficient water is present for hydrolysis of the phenoxy group.

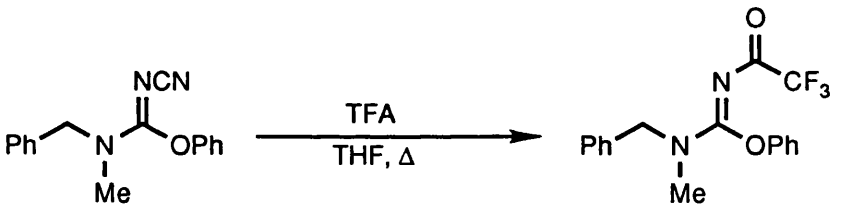


299 311



296 312

That the NH proton is not necessary for the anhydrous reaction to proceed is evident from the fact that the O-phenylisourea **313** can be converted to its corresponding trifluoroacetyl derivative **314** by reaction with TFA in boiling THF.



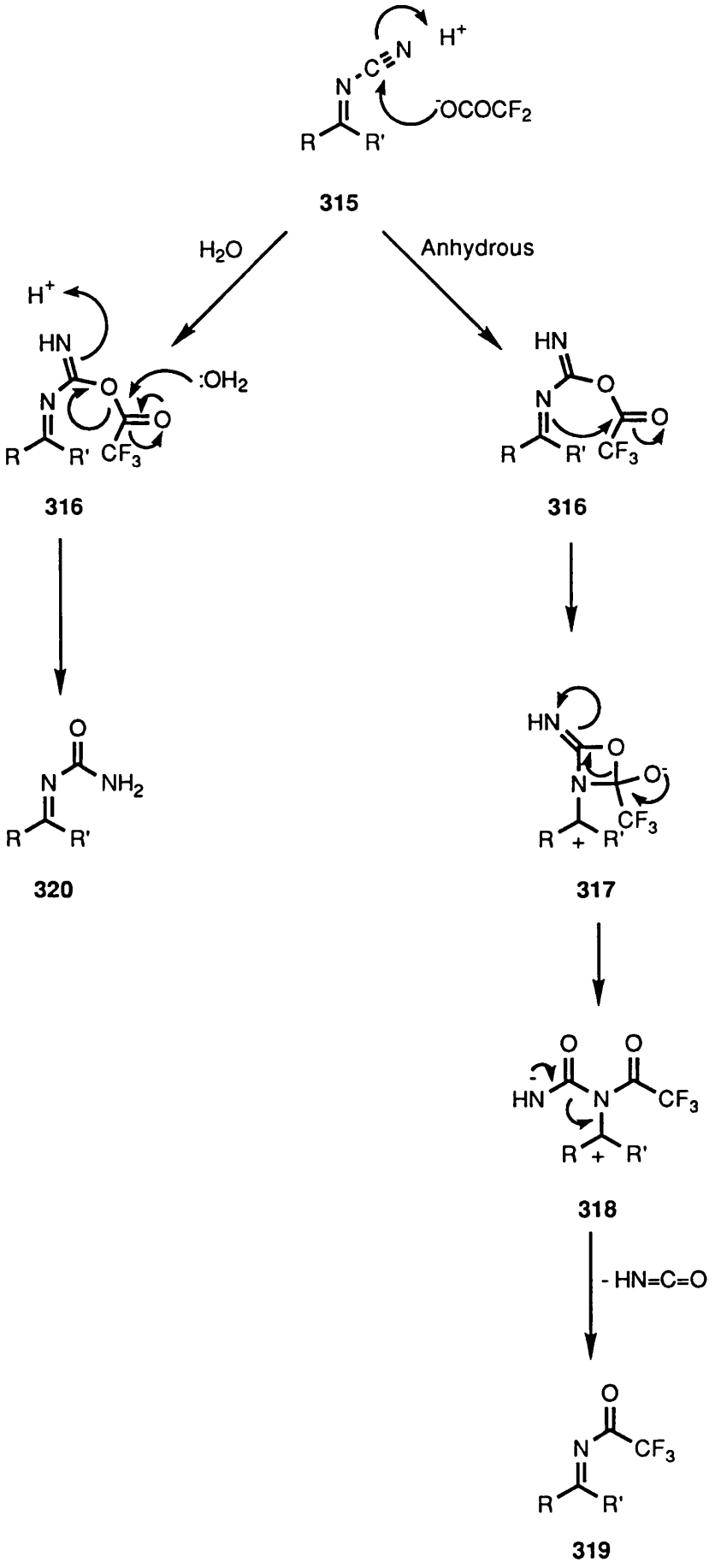
313 314

A common mechanism can be postulated to explain all of these results (Scheme 5.4). Initial attack of the acid upon the nitrile carbon gives an intermediate **316** which under anhydrous conditions collapses to the product due to intramolecular electron transfer from the imine bond, but under aqueous conditions is attacked by the more nucleophilic water present, with resulting collapse to the urea **320**.

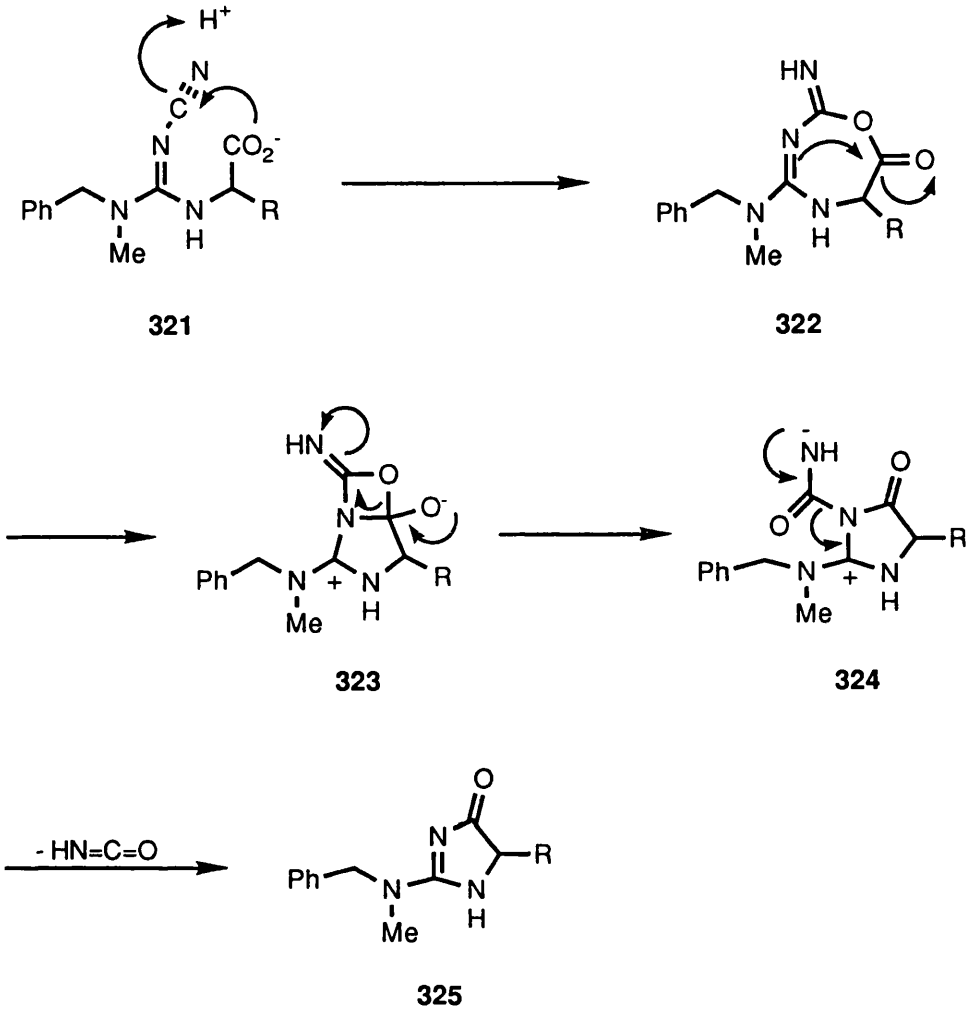
Presumably **298** which does not fit into this reaction scheme must result from the nucleophilic displacement of the cyanide group from **296** to give the trifluoroacetoxy product.

Formation of the imidazole during attempts to prepare carboxypeptidase A inhibitors can also be explained by this mechanism (Scheme 5.5).

Scheme 5.4


H+
N
C
N
R
R'
OCOCF2
315
H2O
Anhydrous
H+
HN
:OH2
O
N
O
R
R'
CF3
316
HN
O
N
O
R
R'
CF3
316
O
N
NH2
R
R'
320
HN
O
N
O-
CF3
R
+
R'
317
O
O
HN
N
CF3
R
+
R'
318
- HN=C=O
O
N
CF3
R
R'
319

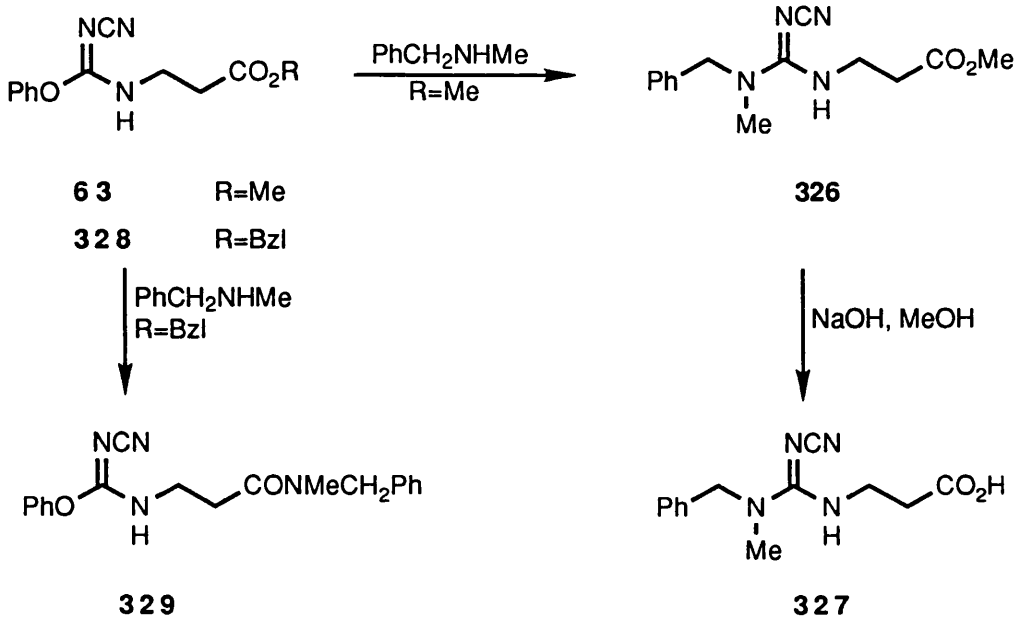
Scheme 5.5



321 322 323 324 325

In the presence of an excess of amine the intermediate urea **324** formed can react further by an amine exchange mechanism thus explaining the formation of **290**.

Attempts to extend this synthesis to dihydropyrimidines were unsuccessful. O-phenylisourea **63** was readily coupled with N-methylbenzylamine to give the guanidine **326**, but on deprotection of the ester using sodium hydroxide in methanol the carboxylic acid **327** was obtained and no cyclic product was observed. The corresponding benzyl ester could not be prepared since in this case the N-methylbenzylamine reacted with the ester group of **328** in preference to the phenoxyimine to give the amide **329**. This is again a reflection of the fact that O-phenylisoureas are not very reactive toward secondary amines, and in this case the relatively reactive and unhindered ester is much more readily attacked.



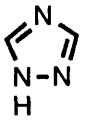
5.4 Conclusion

It can be seen that the N-cyanoimine compound can readily be converted either to the trifluoroacetyl or the urea analogue. A different class of imidazoles can also be formed in a related reaction, the only restriction apparently being the coupling of the O-phenylisourea to a secondary amine, this step giving the lowest yield in the sequence. This synthesis does not, however, appear to be applicable to dihydropyrimidines, probably because the putative transition state would be an 8-membered ring in this case, once again illustrating that the 5-membered ring is the favoured product.

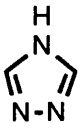
Synthesis of 1,2,4-Triazoles

6.1 Introduction

The heteroaromatic triazole ring system is composed of five atoms, two carbons and three nitrogens which can be arranged in two combinations to give either 1,2,3-triazole or 1,2,4-triazole. Although two NH (**330** and **331**) and one CH_2 (**332**) tautomeric forms are possible for 1,2,4-triazoles, this structure is best represented as a positively charged hydrogen associated with a resonance stabilised triazole anion.[132]



330

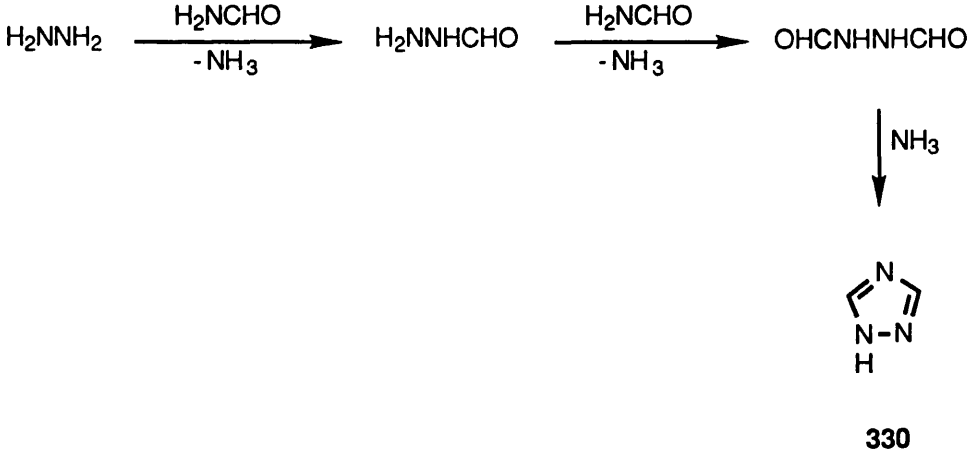


331

332

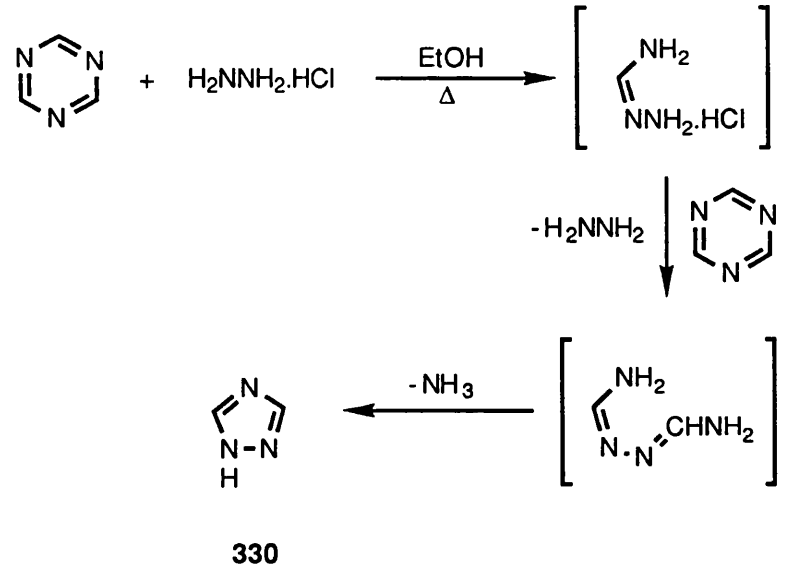
In Chemical Abstracts 3-substituted and 3,5-disubstituted 1,2,4-triazoles are usually indexed as s-triazoles.

Bladin reported the preparation of derivatives of s-triazole **330** in 1885[133] and soon thereafter Pellizzari obtained the parent ring system from the reaction of formylhydrazine with formamide.[134]



330

These reactions gave low yields of s-triazoles. Subsequent methods led to improved yields, culminating in a 95% yield using the method of Grundmann and Rätz.[135] This method involved the treatment of s-triazine with hydrazine hydrochloride.

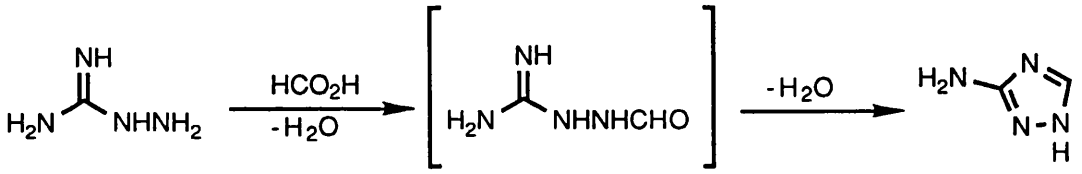


330

6.1.1 3(or 5)-Amino(unsubstituted)-s-Triazoles

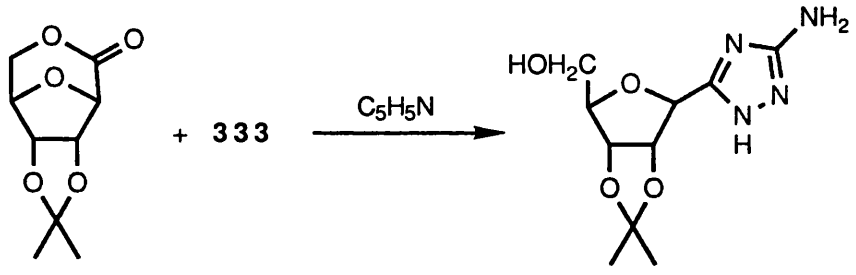
Many related methods for the preparation of amino-1,2,4-triazoles have been reported in the literature, a few of which are illustrated.

The preparation of 3-aminotriazole **335** via N-(formylamino)-guanidine **334** was accomplished by heating a mixture of an aminoguanidine **333** salt (HCl, HNO_3) and formic acid in toluene and separating the water generated in the reaction.[136]



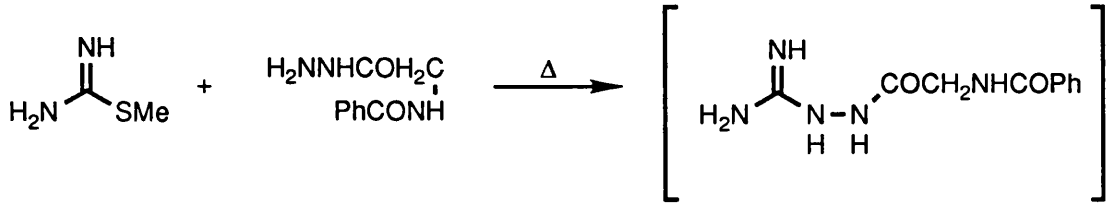
333 **334** **335**

Extensive work has been reported on the condensation of aliphatic carboxylic acids and lactones with N-aminoguanidine **333**, of which one example is the conversion of **336** to the C-nucleoside **337**.[137,138]

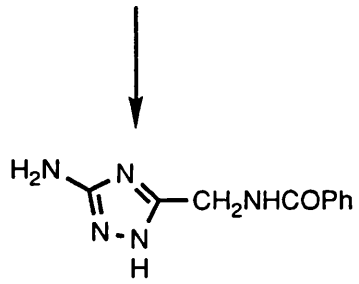


336 **337**

In the reaction of hydrazides with 2-methyl-2-thiopseudourea **338** under mild conditions, the intermediate N-(acylamino) guanidines **340** are usually not isolated, but undergo cyclisation to triazoles, as demonstrated by the reaction of (benzamido)-acetylhydrazide **339** with **338** to give 3-amino-5-(benzamidomethyl)-triazole **341**.[139]

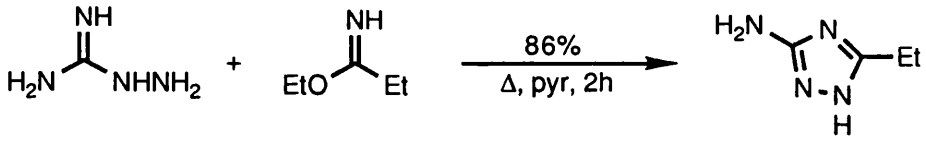


338 **339** **340**



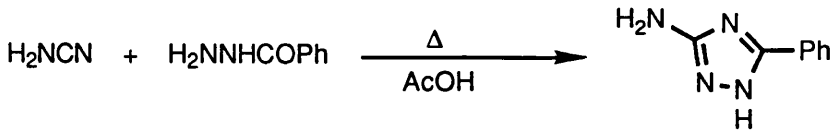
341

Good yields of 3-amino-5-alkyltriazoles resulted from the condensation of imino ethers with N-aminoguanidine in refluxing pyridine. For example, ethyl propionimidate hydrochloride **342** and N-aminoguanidine **333** gave 3-amino-5-ethyltriazole **343**.[140]



333 **342** **343**

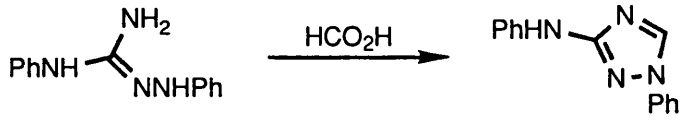
The 3-amino-5-aryltriazoles are prepared via similar types of intermediates. For example treatment of the aroylhydrazine **344** with cyanamide in refluxing acetic acid gave 3-amino-5-phenyltriazole **345**.[141]



344 **345**

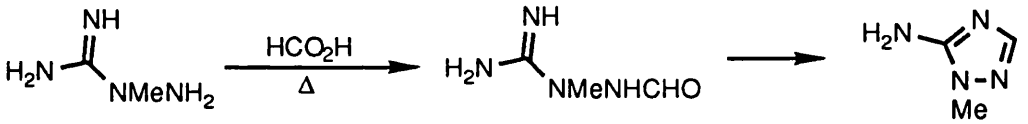
6.1.2 3(or 5)-Amino-1H-1,2,4-Triazoles

The cyclisation of N-aminoguanidine derivatives to give 1-substituted aminotriazoles has been directed toward the preparation of both 1-alkyl- and 1-aryl-3-amino- or 5-amino-1H-1,2,4-triazoles. Treatment of N-anilino-N'-phenylguanidine **346** with formic acid gave 3-anilino-1-phenyltriazole **347** in good yield.[142]



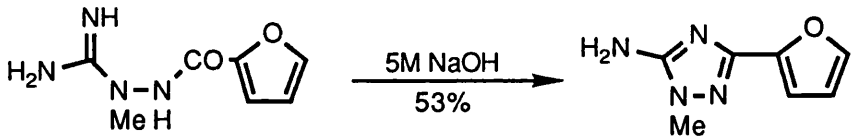
346 **347**

In the cyclisation of N-amino-N-methylguanidine **348** with formic acid, a good yield of 5-amino-1-methyltriazole **350** was obtained.[143]



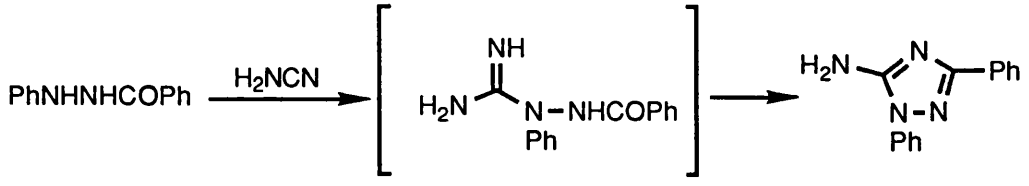
348 **349** **350**

Another method for the preparation of 1-(substituted)-5-aminotriazoles involves the cyclisation of N-(acylamino) guanidines in a basic medium, for example the conversion of **351** to **352**.[144]



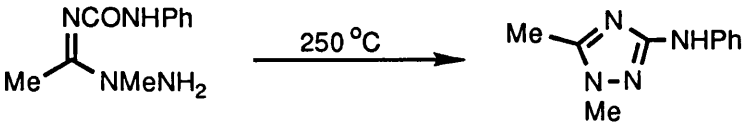
351 **352**

The N-(acylamino) guanidines (for example **354**) can also be generated *in situ* and converted directly to triazoles, as demonstrated by the condensation of the hydrazide **353** with cyanamide to give **355**.[145]



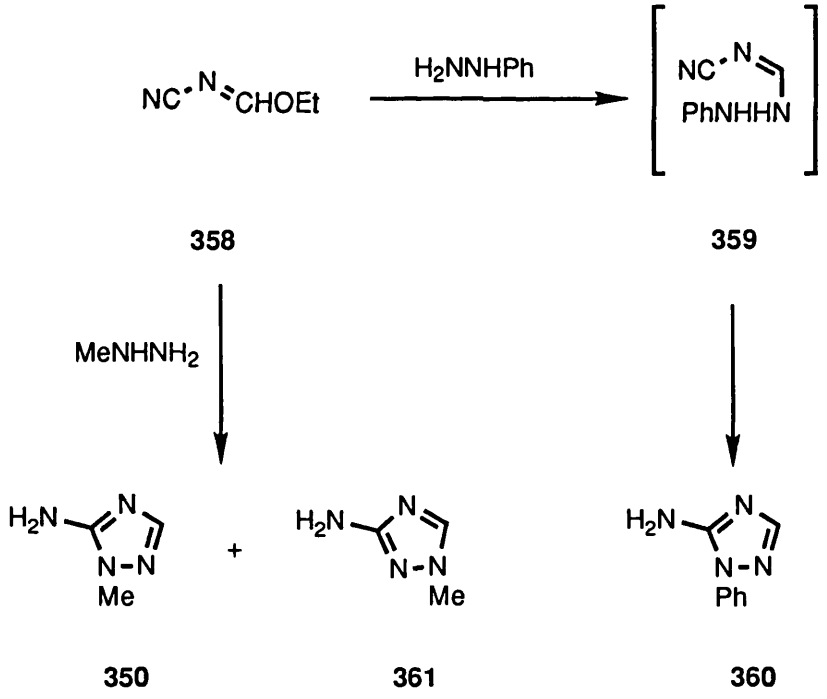
353 **354** **355**

In the thermal cyclisation of the amidrazone derivative **356**, it was found that water rather than aniline was eliminated to give a good yield of **357**.[145]



356 **357**

The N-cyanoamidrazones are implicated in several conversions to give aminotriazoles in good yields under mild conditions. For example, the reaction of phenylhydrazine with ethoxymethylene cyanamide **358** gave **360**, presumably *via* the formation of **359**.[146] However, treatment of **358** with methylhydrazine produced a mixture of the 1-methyl-5-amino and 1-methyl-3-aminotriazoles (**350** and **361**), respectively in which **350** was the major product.[147]

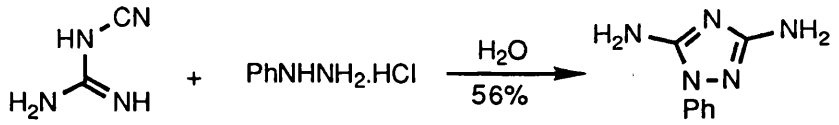


358 **359**

350 **361** **360**

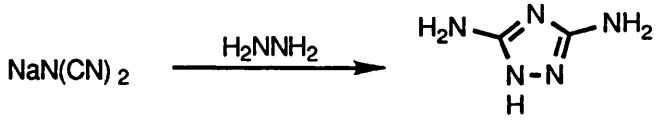
6.1.3 3,5-Diamino-1,2,4-Triazoles

The preparation of a variety of 1-aryl-3,5-diaminotriazoles (1-arylguanazoles) was accomplished in good yield by the treatment of the hydrochlorides of aryl hydrazines with the dicyanamide **362** in boiling water, as shown for the preparation of 1-phenyltriazole **363**.[148-150]

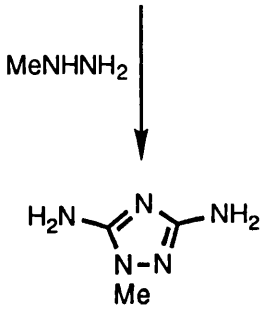


362 **363**

Variations on this method include the interaction of the alkaline salts of dicyanamide **364** with hydrazine and its alkyl and aryl derivatives to give 3,5-diamino-s-triazole (guanazole) **365** and the 1-substituted derivative **366**.[151,152]

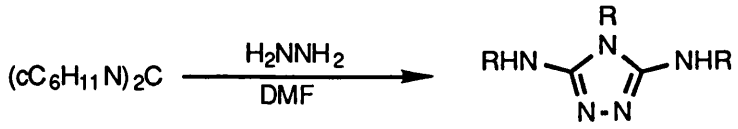


364 **365**



366

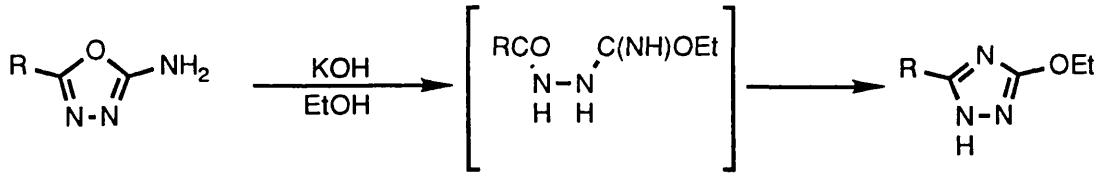
A number of 3,5-diaminotriazoles have been prepared from carbodiimides. Treatment of N,N'-dicyclohexylcarbodimide **367** with hydrazine in hot DMF gave a 75% yield of **368**.[153]



367 **368** R=cC$_6$H$_{11}$

6.1.4 O-substituted Oxy-1,2,4-Triazoles

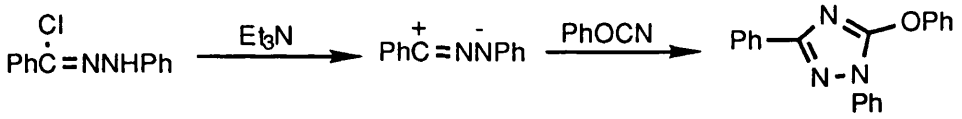
Alcoholysis of a variety of 5-alkyl and aryl-2-amino-1,3,4-oxadiazoles (eg **369**, **370**) in the presence of potassium hydroxide gave good yields of alkoxytriazoles (**373**, **374**), presumably formed *via* the corresponding imino ether intermediates (**371**, **372**).[154,155]



369 R=Me **371** **373**

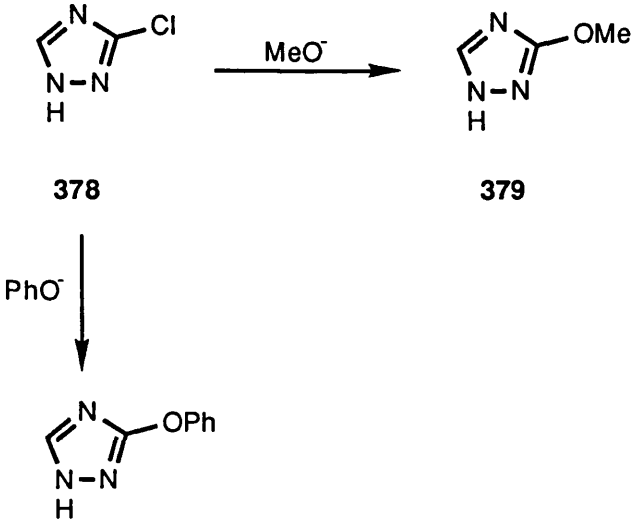
370 R=Ph **372** **374**

Aryl ethers of 1,2,4-triazoles have been prepared by the 1,3-dipolar addition of nitrilimines to aryl cyanates.[156] For example, refluxing a benzene solution of **375** in the presence of triethylamine generated the nitrilimine **376**, which reacted with phenyl cyanate to give **377** in 48% yield.



375 **376** **377**

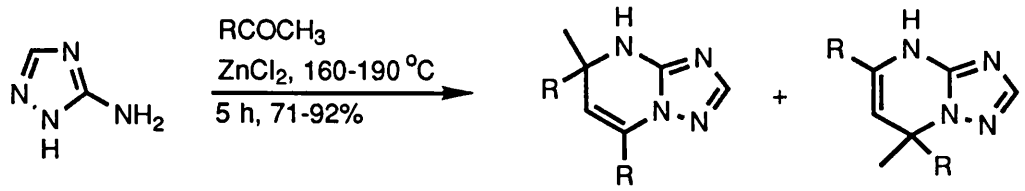
Nucleophilic displacement of the halogen of halotriazoles also gives O-1,2,4-triazoles. For example, treatment of **378** with methoxide or phenoxide gave **379** and **380** respectively.[145,157]



378 **379**

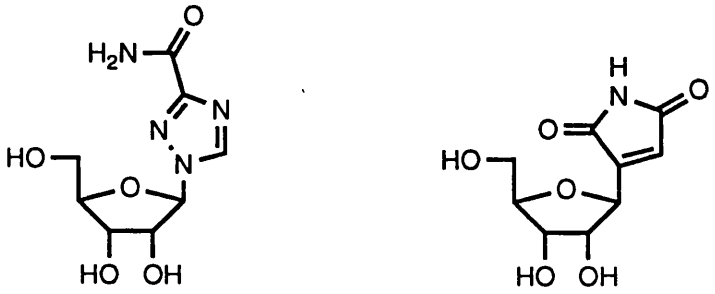
380

Recently a new method for the synthesis of dihydro-1,2,4-triazolo[1,5-a]pyrimidines has been reported.[158] This involves heating acetophenones with 5-amino-1H-1,2,4-triazole **335** in the presence of a catalytic amount of zinc chloride, giving rise to a mixture of condensation products, 5,7-diaryl-4,5-dihydro-5-methyl-1,2,4-triazolo[1,5-a] pyrimidines **381** and 5,7-diaryl-4,7-dihydro-7-methyl-1,2,4-triazolo[1,5-a] pyrimidines **382**, which were easily separated by column chromatography or fractional crystallisation.



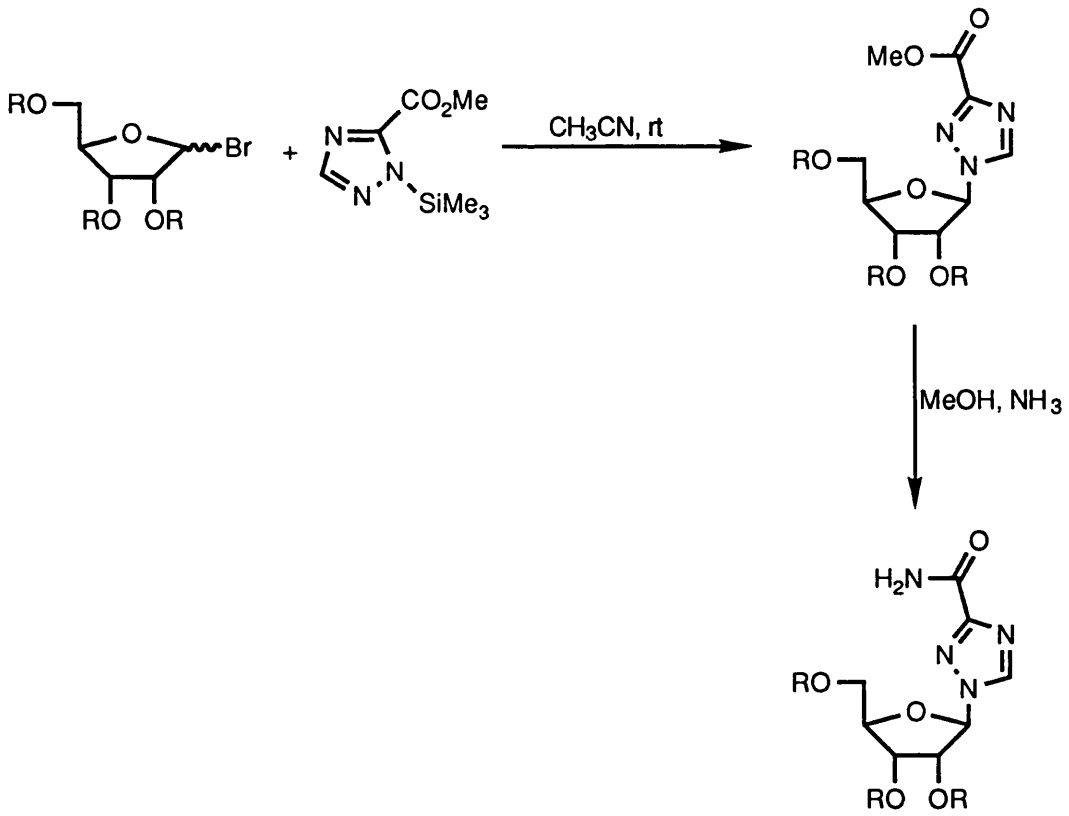
335 **381** **382**

Several 1,2,4-triazoles have been found to have interesting therapeutic actions, amongst which is included 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (virazole) **383**.[159-161] It has been suggested that 1,2,4-triazole nucleoside analogues resemble the natural nucleosides in various biochemical systems, on the basis that the five membered ring in showdomycin **384** results in an antibiotic that specifically inhibits uridine monophosphate kinase and uridine phosphorylase. Virazole has been found to be inhibitory to both RNA and DNA viruses *in vitro* and *in vivo*.[161]



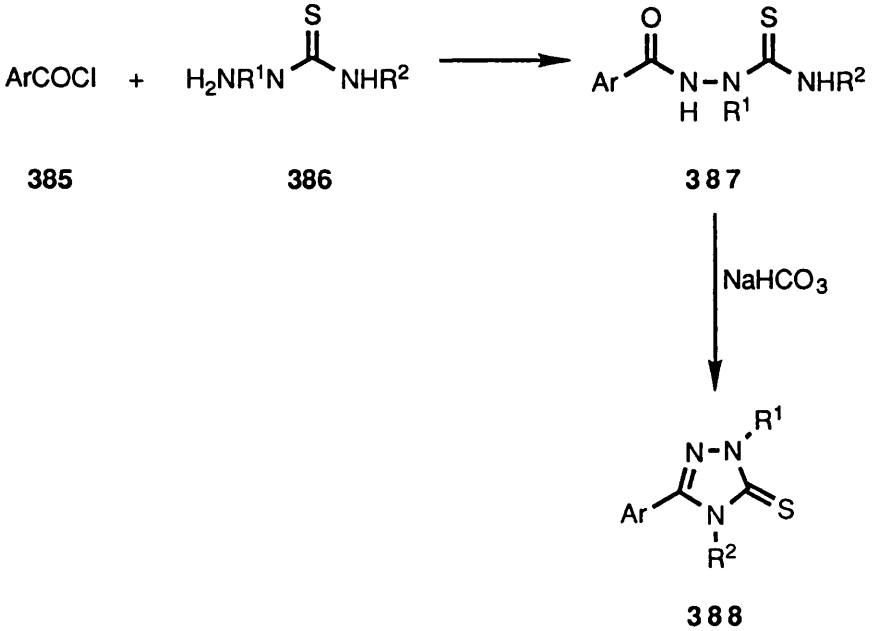
383 **384**

Synthesis of virazole **383** was achieved by treatment of an acyl-blocked ribofuranosyl bromide with the tetramethylsilyl derivative of methyl 1,2,4-triazole-3-carboxylate, followed by treatment of the purified product with methanolic NH_3.



383

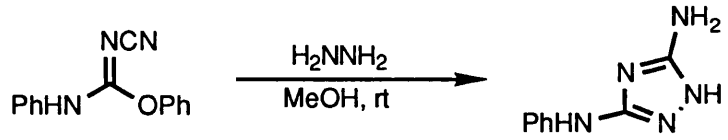
A number of potential antidepressant agents with a general 2,4-dihydro-3H-1,2,4-triazole-3-thione structure **388** have been prepared[162] using the methodology of Sandström and Wennerbeck.[163] The reaction of aroyl chlorides **385** and thiosemicarbazides **386** in either chloroform or pyridine gave 1-aroylthiosemicarbazides **387** which, without purification, were cyclised in refluxing aqueous sodium bicarbonate to yield the desired 2,4-dihydro-3H-1,2,4-triazole-3-thiones **388**.



385 **386** **387**

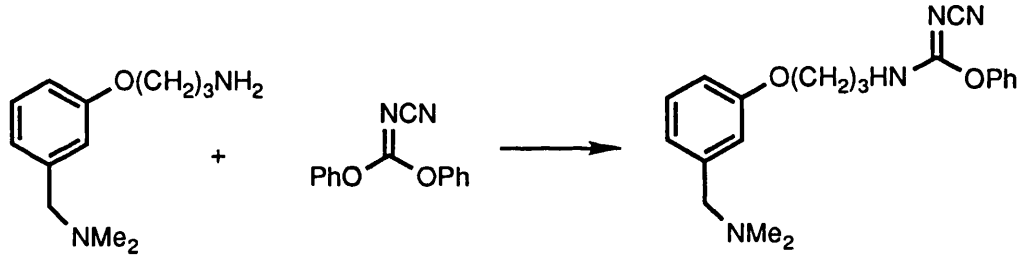
388

Webb and Labaw[23,27] have reported that diphenyl cyanocarbonimidate **53** and derivatives of this compound can be treated with hydrazine nucleophiles to give triazoles, for example **57** is smoothly converted to triazole **58** with hydrazine in methanol at room temperature.[23]

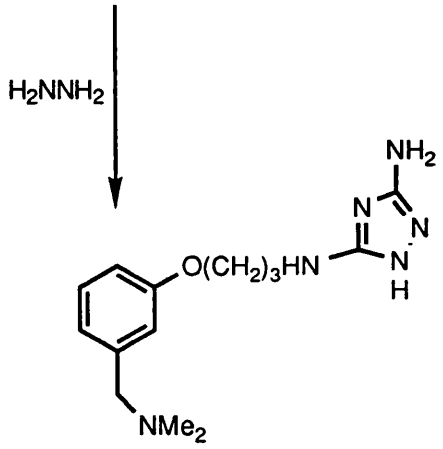


57 **58**

Compound **389**, a potent antagonist of the H_2-receptor of histamine has been synthesised using the same reaction sequence.



53

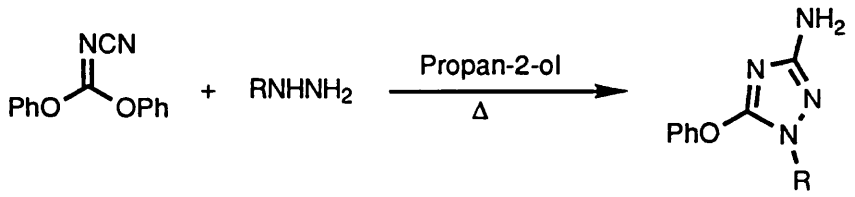


389

Using this reaction of diphenyl cyanocarbonimidate **53** we set out to develop the methodology to allow synthesis of bicyclic triazoles, and also to conduct an investigation into the regioselectivity of attack when using substituted hydrazines.

6.2 Results and Discussion

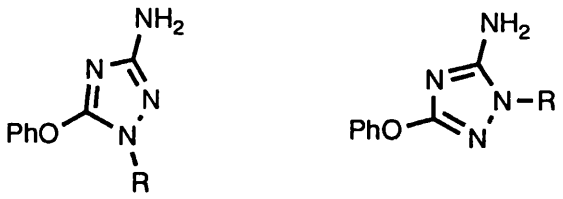
It was initially envisaged that reaction of diphenyl cyanocarbonimidate **53** with hydrazine, followed by nucleophilic displacement of the remaining phenoxy group with an amine, would give the desired products. However, whilst it was found that **53** readily reacted with hydrazine to give the triazole **390** in 59.5% yield, further reaction with a second amine did not occur.[164]



53

390 R=H
391 R=Me
392 R=Ph

Similar treatment of **53** with methylhydrazine and phenylhydrazine gave **391** and **392**, respectively, both in 63% yield. It would be expected that the orientation of the substituents in **391** and **392** would be that with the substituent at position 1 of the ring system, and not position 2, since attack on the phenoxy group is expected to occur *via* the substituted nitrogen which is the more nucleophilic. That this was the case was shown from n.O.e. experiments on the ^1H n.m.r spectrum of **391**.[165] Irradiation at the position of the methyl signal led to an enhancement of the O-phenyl *ortho* proton resonance, whereas irradiation of the NH_2 signal showed no enhancement of the methyl signal.



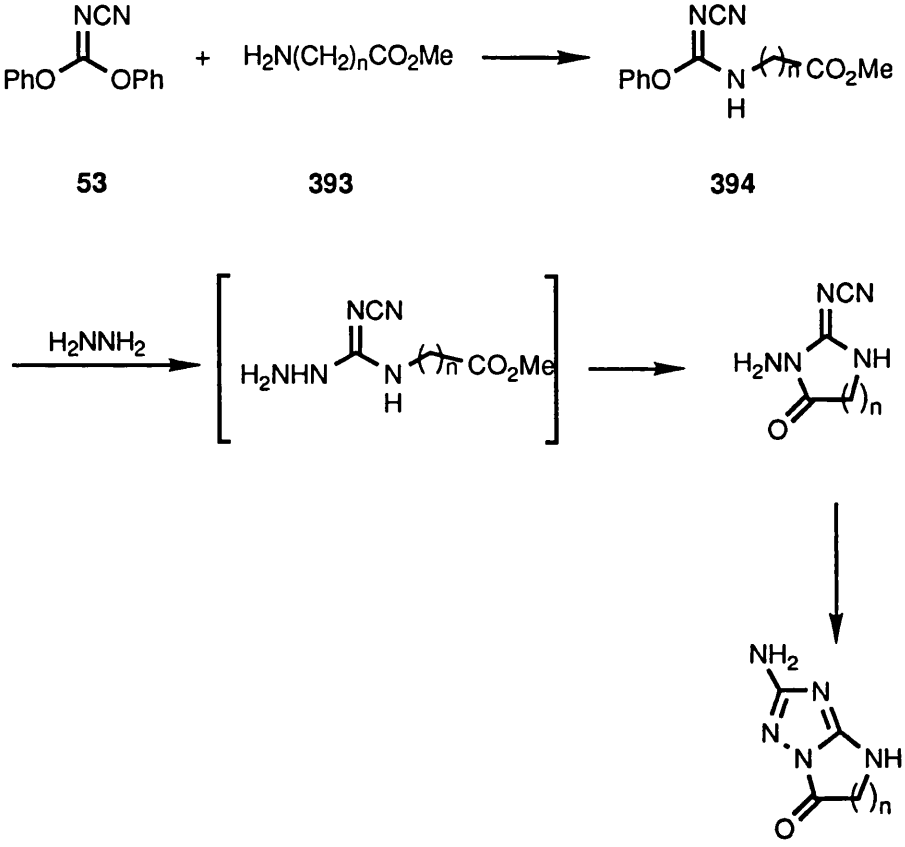
1-Substituted 2-Substituted

The alternative method of synthesis was then investigated. It was envisaged that the reaction of **53** with ω-aminoesters **393** would give the monosubstituted compounds **394** which, on treatment with hydrazine should give the N-cyanoguanidine that could, in principle, cyclise twice (Scheme 6.1).

The ester **395**, obtained from the reaction of **53** with methyl glycine, was treated with hydrazine in propan-2-ol at reflux when the triazole **396** was obtained in 97% yield. The

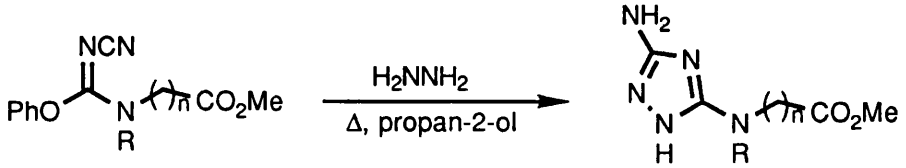
reaction had proceeded as expected, in that the triazole ring formed, but the second cyclisation has not occurred.

Scheme 6.1



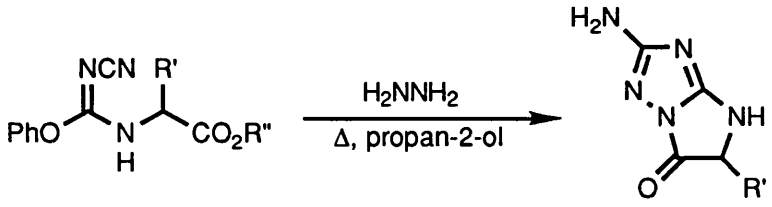
53 **393** **394**

Similarly, treatment of **63** and **398** with hydrazine also gave only the monocyclic products **397** and **399** respectively. Compound **399** was not expected to cyclise further as this requires the formation of a 7-membered ring,[166] but the failure to form the 5- and 6-membered rings in **396** and **397** suggests that the nitrogen in the triazole ring is less nucleophilic than the amines previously used.



395	n=1, R=H	**396**	n=1, R=H
63	n=2, R=H	**397**	n=2, R=H
398	n=3, R=Me	**399**	n=3, R=Me

Turning to the reaction of the derivative **246** prepared from **53** and the benzyl ester of phenylalanine **286**, indicated, however that this was not the sole influence on the reaction. Treatment of **246** with hydrazine in propan-2-ol at reflux gave the bicyclic product **400** in 67% yield. The spectral properties of **400** clearly showed the loss of both the phenoxy and benzyl groups from the precursor **246**.



246 R'=R"=CH_2Ph **400** R'=CH_2Ph

127 R'=CH_2CO_2Me, R"=Me **401** R'=CH_2CO_2Me

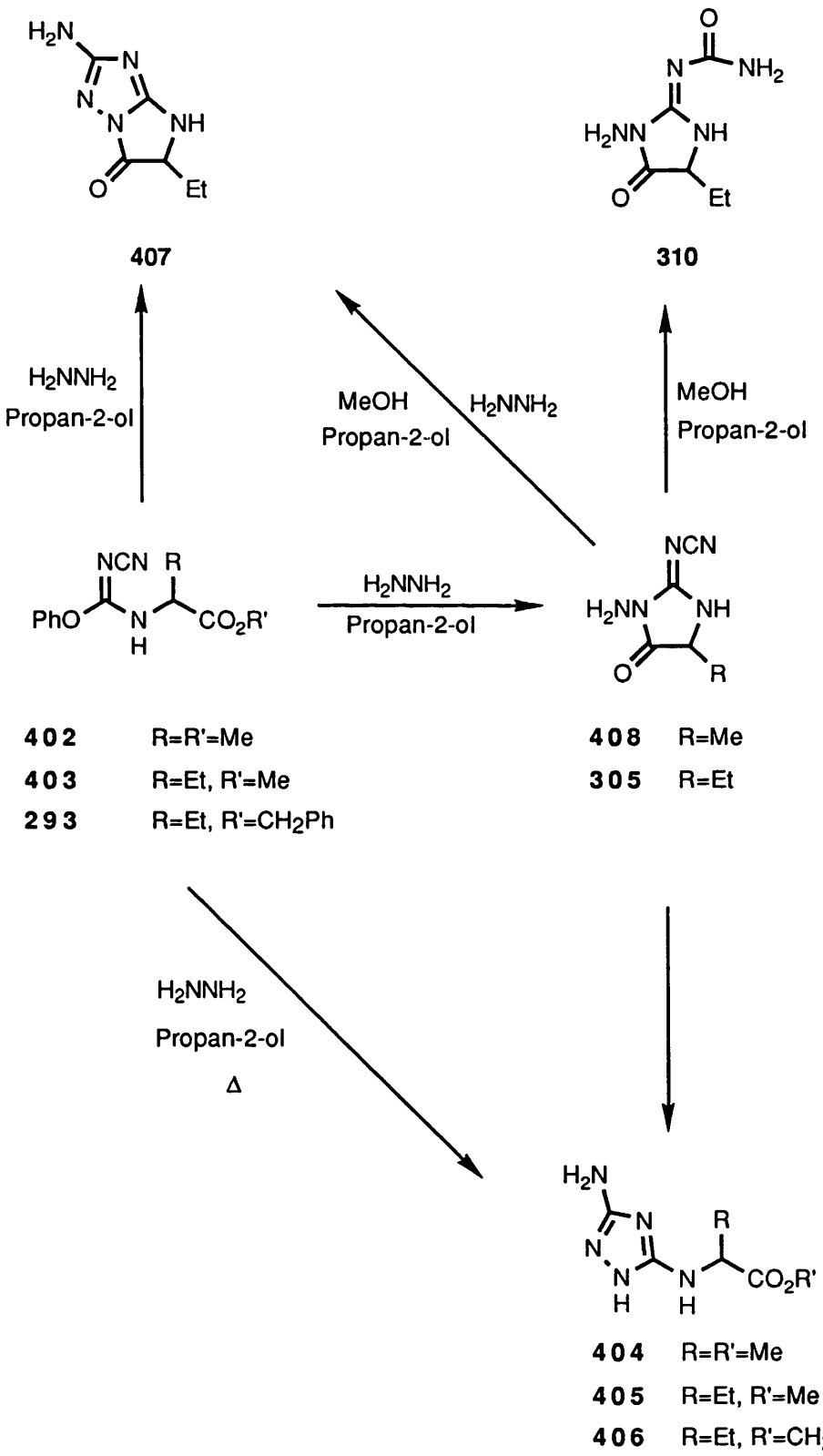
Similarly, **127**, obtained from **53** and dimethyl aspartate **126**, on treatment with hydrazine in propan-2-ol at 60 °C gave **401** in 43% yield. In this case, if the reaction was carried out at reflux, some ester exchange occurred and a mixture of the methyl and 2-propyl esters was formed.

Presumably with both **400** and **401** the conformation required for ring closure is less disfavoured than in the case of **396** and **397** because of the substituent R'. However the question as to which ring forms first is not clear, and it might be considered that these double cyclisations are observed because the rate of closure to the imidazole is increased so that this ring is formed first and the triazole second, whereas in the previous system the triazole ring is formed first and this precludes the formation of the imidazole ring. Subsequent experiments suggested, however, that the process is more complex than this.

Treatment of **402**, prepared from **53** and L-alanine methyl ester, with hydrazine in propan-2-ol at reflux gave the triazole **404** (71%), apparently reproducing the behaviour of the non-substituted derivative **395** Treatment of **403**, prepared from **53** and methyl 2-aminobutanoate, gave a 9:1 mixture of **405** and **407**, from which **405** could be isolated in 70% yield. When the reactions were carried out at 0 °C, however, the imidazoles **408** and **305** were obtained in 77% and 85% yields respectively. Attempts to react **246** with hydrazine at room temperature lead only to the bicyclic triazole product **400**, and the dimethyl ester **127** did not react with hydrazine at this temperature, only starting material being isolated from the reaction mixture. In a further experiment, after **305** had been formed at 0 °C the reaction mixture was heated to reflux and monitored by TLC. The imidazole slowly decreased in concentration with time and the triazole concentration increased, so that after a period of 5 h only the triazole **405** could be isolated from the reaction mixture.

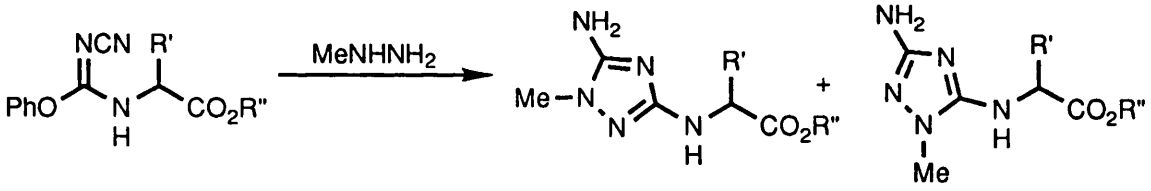
These reactions are clearly delicately balanced and therefore the benzyl ester **293** was prepared, since it was expected that the leaving propensity of the benzyl group would

encourage the formation of **407**. Treatment of **293** with hydrazine in boiling propan-2-ol gave a 1:1.2 mixture of **406** and **407**, which was transformed into a 1:9 mixture, from which **407** could be isolated in 72% yield, when the reaction was carried out at 25 °C.



Finally, further insight into the reaction came from examination of the transformations of the imidazolone **305**. Treatment of **305** with hydrazine and methanol in propan-2-ol at 80 °C gave the bicyclic tetraazaoctane **407**, whereas a similar treatment without hydrazine gave the urea **310**. Each of these reactions, and that in which the reaction mixture containing **305** is converted to **405**, differs in the components dissolved in the propan-2-ol and it is this difference that presumably results in the different transformations that occur. The reaction mixture from **403** contains a mole equivalent of phenol and 0.2 mole equivalents of hydrazine and is presumably acidic, whereas the direct reaction of **305** contains a mole equivalent of hydrazine and is basic while the reaction mixture leading to **310** is approximately neutral. Finally attempts to convert the tetraazaoctane **407** to the monocyclic triazole **405** by heating to reflux in propan-2-ol containing a mole excess of methanol failed to have any effect. The simplest coherent reaction scheme would be that in which the primary reaction is to form the imidazolone which can then ring close to the bicyclic tetraazaoctane. The formation of the monocyclic triazole arises *via* ring opening of the imidazolone and reclosure to the thermodynamically more stable triazole ring system.

Treatment of **246** with methylhydrazine gave two products, neither of them bicyclic. One compound was the expected triazole **411** while the other was identified as the isomer **409**, in which the nonsubstituted nitrogen of the methylhydrazine had acted as the initial nucleophile. The structures of **409** and **411** were determined by n.O.e. experiments. Irradiation of the Me group protons in **411** caused enhancement of the NH, CH_2 and aromatic protons whereas irradiation of the Me group in **409** gave only enhancement of the NH_2 protons. These observations were supported by other n.O.e. experiments in which the NH resonance signals were irradiated. Treatment of **403** with methylhydrazine gave only **410**.

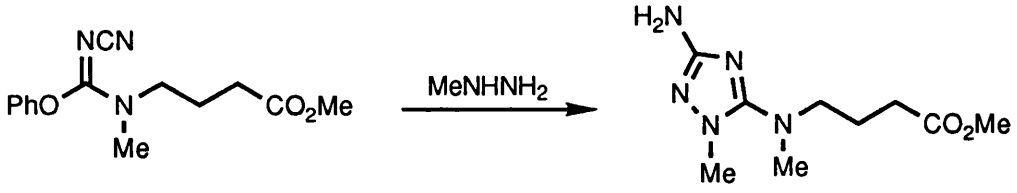


246 R'=R"=CH_2Ph **409** R'=R"=CH_2Ph **411** R'=R"=CH_2Ph

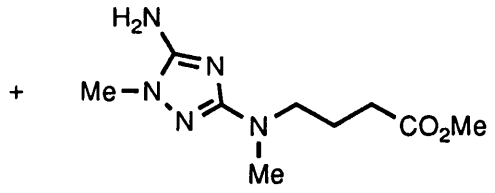
403 R'=Et, R"=Me **410** R'=Et, R"=Me

The formation **391**, **392**, **410**, and **411** indicates that the substituted nitrogen of the hydrazine is the most nucleophilic and the failure to observe the products of ester hydrazine cyclisation can be attributed to this mode of reaction requiring the formation of a quaternary nitrogen. Presenting a more sterically hindered centre to the substituted hydrazine may lead to the formation of more of the product from the initial reaction of the unsubstituted nitrogen. The N-methyl substituted derivitive **398**, however, on treatment with methylhydrazine gives a *ca* 50:50 mixture of **412** and **413**, the former arising from initial nucleophilic addition of the N-methyl group

and the latter from the N-H group, a similar ratio to that found for the reaction of **246** with methylhydrazine. The triazoles **412** and **413** were again distinguished by n.O.e. experiments. Irradiation of the exocyclic N-Me group causing enhancement of the ring N-Me signal in **412** and irradiation of the ring N-Me group showing enhancement of the exocyclic N-Me and the acyclic methylene signals, whereas irradiation of the exocyclic N-Me in **413** gave only enhancement of the acyclic methylene signals and irradiation of the ring N-Me gave enhancement only of the NH_2 signals.



398 **412**



413

6.3 Conclusion

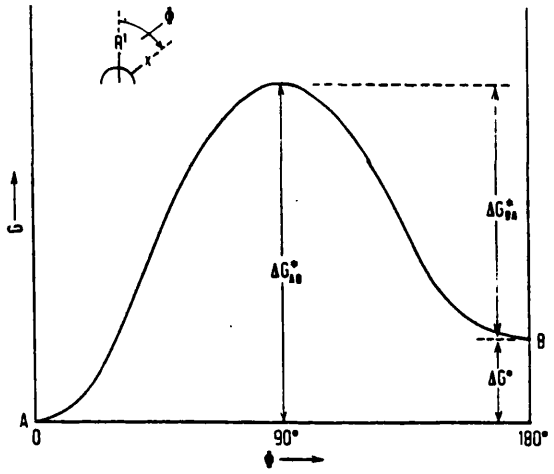
The reaction of hydrazines with pseudoureas of the type **394** is clearly influenced by both the nature of **394** and that of the specific hydrazine involved. Careful control of the reaction conditions and the leaving group propensities on the substrate can, however, give the desired bicyclic tetraazaoctanes in most cases in which there will be a substituent on C-7 of the tetraazabicyclooctane. However, it appears that once again in this system the formation of bicyclic molecules containing 6-membered rings is precluded. In all of the examples investigated the triazole appears to be the thermodynamically preferred product while, at least in some cases, the imidazole is kinetically preferred.

Stereoisomerism of N-cyano-O-phenylisoureas

7.1 Introduction

A variety of N-cyano-O-phenylisoureas show, in their ^{1}H n.m.r. and ^{13}C n.m.r. spectra, the presence of two isomers at ambient temperature. Gradual heating of the samples causes the peaks to broaden, coalesce, and eventually become sharp at elevated temperatures. This process is reversible, the original isomeric mixture being obtained on cooling to ambient temperature.

N.m.r. spectroscopy provides the means to study intramolecular processes with activation energies of 5 to 25 Kcal/mol. In the rotation about a bond there are certain energetically favoured positions of the substituents. For example, the dependence of the energy on the angle of rotation about a double bond is shown.[167] To convert the isomer A into the isomer B it is necessary to supply the free energy of activation $\Delta G^{\ddagger}_{AB}$. The energy $\Delta G^{\ddagger}_{BA}$ that must be supplied for the reverse isomerisation differs by ΔG^{o} from $\Delta G^{\ddagger}_{AB}$.



The magnitude of the free enthalpy of activation determines the rate of thermal isomerisation. The rate constant k' is related to $\Delta G^{\ddagger}$ in accordance with the Eyring equation.[168]

$$k' = K(K_B T/h)\exp[-\Delta G^{\ddagger}/RT] \qquad 7.1$$

K_B=Boltzman's constant, h=Planck's constant

R=gas constant, T=absolute temperature

K=transmission coefficient

Isomerisation of this nature can be followed particularly readily by ^1H n.m.r. spectroscopy when ΔG^o is small so that the concentration of isomers are comparable.

The shape of the signal in the transition region can be used to determine the rate constants. One simple method is to make use of the line separation $\Delta\nu$ found for the spectrum at low temperature and the coalescence temperature, T_c, this being the temperature at which the two signals just coalesce. The rate constant k' of the chemical exchange at the coalescence temperature T_c is the give by:

$$k' = \pi\Delta\nu/\sqrt{2} \qquad \textbf{7.2}$$

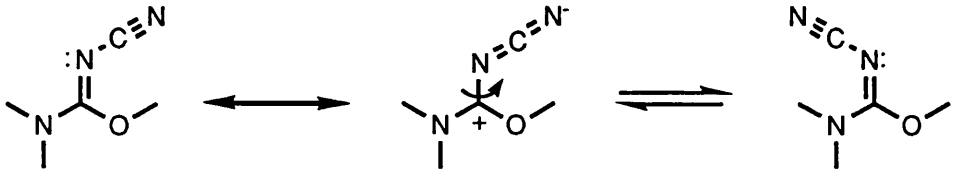
This equation is valid for the two states having equal populations and lifetimes.[169,170] The signal width must be small in comparison with the signal separation.

Combination of equations **7.1** and **7.2** allows approximate free energies of activation for the isomerisation at the temperature of coalescence to be determined, when the transmission coefficient is assumed to be unity.

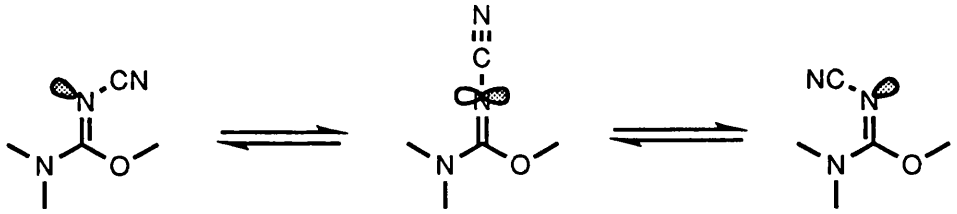
$$\Delta G^{\ddagger} = RT_c[\ln(T_c)-\ln(K')+23.760] \qquad \textbf{7.3}$$

There are in principle three possible mechanisms for the isomerisation observed in N-cyano-O-phenylisoureas and related imines.

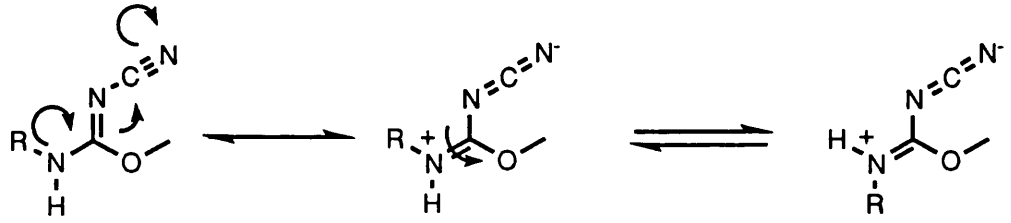
1) Syn-anti isomerisation in which the nitrile substituent describes a circle about the axis of the C=N double bond. This mechanism proceeds via a dipolar intermediate and is favoured by polarisation of the C=N double bond.The sp^2-hybridization of the nitrogen atom, and hence the bond angle (C-N-CN) is retained.



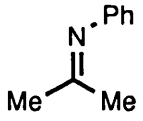
2) Syn-anti isomerisation *via* inversion of the imine nitrogen through a linear C-N-CN transition state in the isourea plane (lateral shift mechanism). The bond angle (C-N-CN) increases to 180 ^{o} in the transition state. The C=N double bond is, to a first approximation, unaffected.



3) E-Z isomerisation via rotation about the C-N single bond



There has been considerable discussion as to which of these mechanisms operates in imine isomers of this sort. The inversion mechanism is favoured for the N-phenylimine **414**,[171] as a result of its remarkably lower barrier to rotation (21 Kcal/mol), since there is no known reason for such a low torsional barrier in a relatively unactivated double bond. However, the N-phenyl group would be expected to stabilise a diagonal transition state.



414

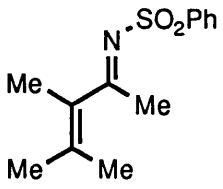
Furthermore, there is a similar effect of the substituent Z on the syn-anti isomerisation in imines ($X_2C=NZ$) and on the inversion of the sp^3 hybridised nitrogen of aziridines.[172] Thus electronegative substituents on nitrogen are expected to decrease the rate of inversion because of the tendency of such substituents to increase the s character of the unshared electron pair on nitrogen. In the planar transition state this electron pair must be in a p orbital. Conjugative or overlap effects, especially of the p-p type, should increase the rate of inversion because such effects are greater in the planar than in the non-planar system.[173] Thus the isomerisation rate increases rapidly as the substituent Z is varied in the order:

$$RO \equiv R_2N < \text{halogen} < \text{alkyl} < \text{aryl} < \text{acyl}$$

The substituents X on the imino carbon atom also increase the inversion rate, the order being:

quinone ring<alkyl<acetyl<alkoxycarbonyl<aryl<
methoxy<alkylthio<dialkylamino

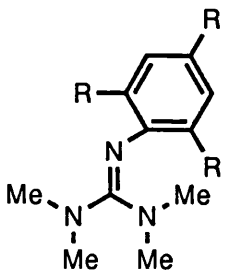
However, care must be taken in taking this analogy with nitrogen inversion too far. The barrier to rotation in N-(1,2,3-trimethyl-2-butenylidene) benzenesulphonamide **415** is considerably lower than that in N-isopropylideneaniline **414** ($\Delta G^{\ddagger}$=16.4 Kcal/mol compared to 20.3 Kcal/mol).[174]



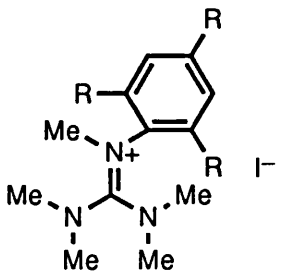
415

This can be attributed to the benzenesulphonyl group being considerably more effective than phenyl in lowering the barrier to rotation by delocalisation of electrons on nitrogen. However, in the corresponding N-substituted aziridines, the free energies of activation, which must correspond to barriers to inversion of pyramidal nitrogen, exhibit a different order in their relative magnitudes. Thus the coalescence temperature of N-phenylaziridine (T_c=-40 °C) is actually somewhat lower than that for N-benzene-sulphonylaziridine (T_c=-30 °C). Clearly different factors are more important in the two systems.

The inversion mechanism is favoured in the guanidines **416**,[175,176] because of steric effects. As the series R=H, CH_3, CH_2CH_3, $CH(CH_3)_2$ is ascended, the isomerisation barrier decreases, while for the guanidinium salts **417** substantial increases in the barrier occur. The introduction of *ortho*-substituents causes the phenyl ring to be twisted out of the plane of the C=N double bond to stabilise the transition state for inversion but not rotation. Rotation would be hindered by the substituents R, as can be seen for the guanidinium salts **417** in which the lone pair of electrons is fixed and inversion is consequently impossible, hence the rapidly increasing barrier.



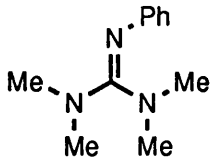
416



417

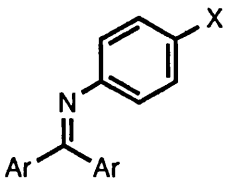
Additionally, good hydrogen bonding solvents, for example methanol, raise the barrier by approximately 1 Kcal/mol compared to that in non-hydrogen bonding solvents, for example chloroform, which is consistent with operation of the inversion mechanism but not with the rotation mechanism.

The small influence of the polarity of the solvent on the rate of isomerisation of tetramethyl-phenylguanidine **418** also points to inversion.[175,177] A polar solvent should facilitate isomerisation by rotation as has been found for example for ketene aminals.[178]



418

In N-arylimines of the type **419** the influence of *para* substituents of the aryl residue on the free enthalpy of activation of the syn-anti isomerisation follows the Hammett relation.[171,177,179,180] Irrespective of the substituent Ar the reaction constant is ρ=1.7.[171] On the other hand a substituent X in benzylideneamines **420** has a much smaller influence (ρ=0.4).[181] The difference in the effects of variations at the N or the C atom has been taken as evidence of inversion,[171] with a linear transition state involving a contribution from a resonance structure of type **421**.



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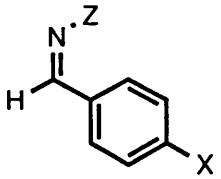
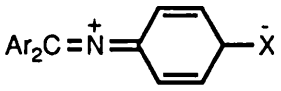


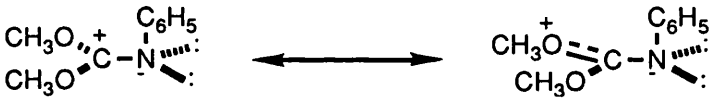
420



421

The rotation mechanism has been favoured by Marullo and Wagener[182,183] on the grounds that the attachment of lone pair bearing substituents to the imino carbon atom dramatically lowers the barrier. Thus they accept that the low activation energy for the isomerisation of imines relative to olefins and the effects of substituents on the rate, particularly the insensitivity of the isomerisation rate to substituents on the aryl group bonded to the imino

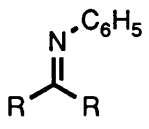
carbon in compounds such as $Ar_1Ar_2C{=}NCH_3$, can be interpreted in terms of a mechanism which proceeds *via* a linear transition state in which the Π bond remains intact and the non-bonded electron pair on nitrogen rehybridises to a p orbital. They contend, however, that the very low activation energy and large isomerisation rate found for iminocarbonates is more easily explained in terms of a mechanism proceeding through a polar transition state in which unpairing of the electrons of the Π bond has occured. Since oxygen is more electronegative than carbon they argue that substitution of methoxy for alkyl or aryl groups attached to the imino carbon might be expected to decrease the extent of polarization of the carbon-nitrogen bond. Resonance effects would operate in an opposite fashion, but can be neglected since they do not make an important contribution to the ground state. The over-all effect would be stabilisation of the ground state. However, resonance effects become important in excited states and, in this case, would be expected to stabilise the transition state by delocalisation of the positive charge being generated on the imino carbon. The expected net effect should be a decrease in the required activation energy.



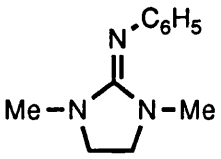
Furthermore, in the series of imines **422** (R=CH_3, OCH_3, SCH_3) and **423**, they report[183] that the isomerization rates parallel the relative conjugative ability of the groups bonded to the imino carbon (X=N>S>O>C) rather than their relative electronegativities (O>N>S>C). This, it is argued, is also evidence for the rotation mechanism.

However, in a similar study[184] on the isomerisation rate of iminocarbonates relative to imines, the rates were interpreted in terms of the greater electron withdrawing ability of oxygen relative to carbon, this being consistent with the lateral shift mechanism.

Also, in a study on N-cyanoimines of type **424** (R=OCH_3, SCH_3, $NDCH_3$), the ability of these groups to stabilise a linear transition state **425** was suggested to be consistent with the lateral shift mechanism.[185] It should be noted that these results also fit with the theory of conjugative ability of the heteroatom, following the scale previously proposed.[183]



422



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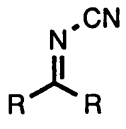
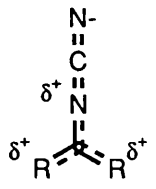


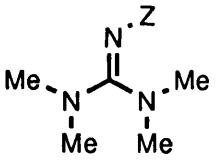
424



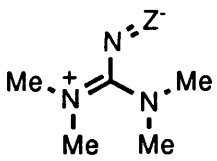
425

Marullo and Wagner[183] do acknowledge that if the lateral shift mechanism is modified to include Π bond participation, then both the rotational and lateral shift mechanisms are consistent with the data, and electronic effects cannot be used to make a choice between the two pathways. The transition states for the two pathways however differ in geometry. From theoretical calculations on the isomerisation barriers of compounds having sp^2 nitrogen of the type $NH=(C=)_nNH$,[186] it was found that the lateral shift pathway requires less energy than the rotational pathway for n=0 or n=2, but for n=1 or n=3 the rotational pathway is slightly favoured.

A detailed study of the isomerisation of compounds of type **426**[172] has revealed that there is a slow process due to restricted rotation about the C-N single bond, and that the syn-anti isomerisation is much more rapid.



426a

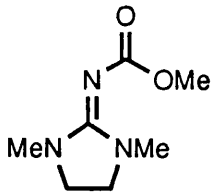


426b

With increasing electronegativity of the Z group in **426a** there is an increasing contribution from the polar form **426b**, resulting in greater double bond character in the C-N single bond. This is supported by the fact that the order of increasing activation enthalpy for Z is:

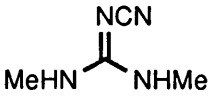
$$COC_6H_5<COCH_3<CN<NO_2$$

For $Z=COCH_3$ one would expect the methyl signal to be split as a result of the double bond character of the C-N bond, which was not the case. This was explained on the ground that the carbonyl group and the C=N double bond adopts a cisoid configuration to minimise steric effects. A strong piece of evidence supporting hindered rotation about the single bond is that in the N-acetylguanidine **427** no splitting was observed above -100 °C.



427

Hindered rotation, however, does not readily explain why N-cyano-N',N"-dimethylguanidine **428** has a higher barrier than N-cyano-N',N',N",N"-tetramethylguanidine **429**.



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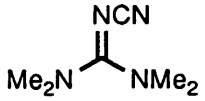


429

These authors[172] then go on to state that a mixed mechanism, as discussed by Raban,[174] is also a possibility, but as yet there is no experimental evidence to support it.

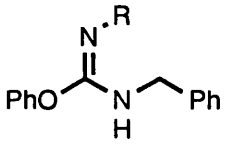
This mixed mechanism[174] is based on the fact that the only differences between the two transition states for the rotation and inversion mechanisms is the C-N-CN bond angle, and associated differences in the hybridization of the nitrogen and its formal charge. The angle is *ca* 109° in the rotation model and 180° in the inversion model. However the angle need not be restricted to one of these two values, but might well adopt values between the two extremes. Thus, a continuum of mechanisms with intermediate bond angles is possible. Substituents such as methoxy, methanethio, and dimethylamino which can stabilize a positive charge would effect a diminution of the bond angle while substituents which lower barriers to nitrogen inversion would result in transition states with larger bond angles.

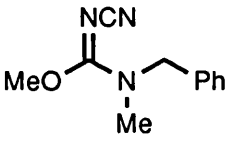
7.2 Results and Discussion

The following tables (Tables 1,3,4) show the results of ^1H n.m.r. spectroscopy experiments to determine the barrier to rotation in N-cyanoimines and related compounds. The $\Delta G^{\ddagger}$ values were calculated using the assumptions implicit in equations **7.2** and **7.3**.

Table 1

	T_c (°K)	ΔV (Hz)	K^{-1} (s^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)	Solvent	Isomer ratio
296	308	34.50	76.6	15.4	$CDCl_3$	10:1
296	322	38.19	84.8	16.0	DMSO	1.2:1
312	279	5.12	11.3	14.9	CD_2Cl_2	1:1
297	>443			>25	DMSO	1:0
301	299	5.92	13.2	16.0	CD_2Cl_2	1:1
298	286	5.96	13.2	15.3	$CDCl_3$	1:1
414	263	140.66	312.5	12.3	$CDCl_3$	2:1
313	283	19.31	42.9	14.4	$CDCl_3$	1:1
314	328	50.42	112.0	16.0	$CDCl_3$	1.5:1





296 R=CN
312 R=$CONH_2$
297 R=$COCF_3$
301 R=$COCH_3$
298 R=$OCOCF_3$

414

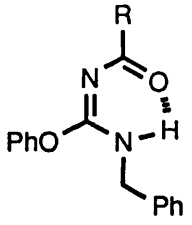
313 R=CN
314 $COCF_3$

From the results (Table 1) it can clearly be seen that increasing the electronegativity of the substituent (as assessed by the Hammett σ_p values,[191] Table 2) attached to the imine nitrogen leads to an increase in the activation barrier, as would be expected on the basis of the nitrogen inversion model, since the s character of the nitrogen lone pair is increased.

Table 2

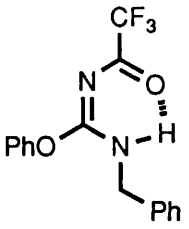
Functional Group	σ_p
$CONH_2$	0.36
$COCH_3$	0.50
CN	0.66
$COCF_3$	0.80
$OCOCH_3$	0.31
$OCOCF_3$	<0.80

However, other factors must also apply since the activation energies for the O-phenylisoureas **296**, **312**, and **301** are all very similar despite the large differences in electronegativity. This seems to suggest that other factors not present in **296** are leading to the increase in $\Delta G^{\ddagger}$ for **312** and **301**. One possibility is that hydrogen-bonding (H-bonding) is occuring between the NH and the carbonyl oxygen groups as shown.



This type of interaction would be expected to be much weaker, in comparison, for the N-cyano compound. This H-bonding would be expected to lead to an increase in the activation energy that must be supplied to convert one isomer to another. However, it would be expected that this would be reflected in the isomer ratio since this represents the stability of one isomer relative to the other, and we would expect that the H-bonded isomer would be more stable. That this is not the case is clearly seen since the isomer ratio for both **312** and **301** is close to unity. The fact that the ratio is not unity in **296** suggests that other factors also play a part. Thus the greater steric hindrance present when the CN group is *cis* to the benzyl group will lead to this being slightly disfavoured but for **312** and **301** this is counter-acted by the H-bonding which brings the isomer ratio back to unity.

The high electronegativity of the trifluoroacetyl group combined with strong H-bonding could explain why in the ^1H n.m.r. spectrum of **297** only one isomer is seen in the temperature range 193 - 443 K. Indeed at high temperatures product breakdown seemed to occur before any stereoisomerisation process. This suggests that the barrier to inversion in this compound is very high, probably greater than 25 Kcal/mol, leading to the conclusion that only the form **297a** exists at ambient temperature.



297a

Further support for the H-bonding theory comes from the fact that for the N-methyl O-phenylisoureas **313** and **314**, the barriers to rotation are lower than for **296** and **297**. In the case of **313** the decrease is small, as would be predicted since only weak H-bonding to the CN functional group is predicted. For **314** the decrease is dramatic, the energy changing from greater than 25 Kcal/mol for **297** to 16.0 Kcal/mol for **314**. This seems to suggest that H-bonding plays a considerable role in stabilising one rotamer of **297** over the other. As would be expected the isomer ratio is also no longer 1:0 but 1.5:1, reflecting this loss of H-bonding. For **313**, however, the isomer ratio has gone to unity from 1.2:1 but the change in solvent makes it difficult to interpret this.

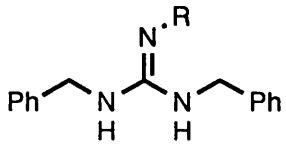
Substitution of the methoxy for the phenoxy group in going from **296** to **414** leads to a decrease in activation energy which suggests that the electrons of the oxygen are more available to stabilise a transition state of the type **425**, as would be expected.

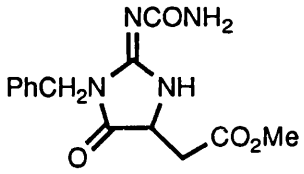
Addition of the extra oxygen in going from **297** to the trifluoroacetoxy derivative **298** leads to a decrease in the activation energy. Based on the fact that acetoxy has a smaller σ_p value than acetyl it is to be expected that trifluoroacetoxy has a smaller σ_p value than trifluoroacetyl, which explains the observed decrease in $\Delta G^{\ddagger}$.

In going from the O-phenylisoureas to the corresponding guanidines a decrease in activation energy is seen (Table 3). This is to be expected since nitrogen has greater conjugative ability than oxygen and so is better able to stabilise the transition state, be it that of the rotation or the inversion mechanism. For N-cyano guanidine **299** this decrease leads to an inversion barrier of less than 5 Kcal/mol which cannot be detected by ^1H n.m.r. spectroscopy, and no line broadening is seen even at temperatures as low as 193 K. For the guanidines **311** and **304** the decrease in activation energy is quite small (<2 Kcal/mol), which suggests that the decrease due to transition state stabilisation is offset by an increase due to H-bonding. However, for the trifluoroacetyl derivative **300** the decrease is apparently very dramatic. The reason for this is unclear, since it would be expected that this compound would also show increased H-bonding to compensate for the decrease of $\Delta G^{\ddagger}$ brought about by adding the second nitrogen. Possibly a steric factor, in that the more bulky trifluoroacetyl group now prefers to adopt a conformation more like the linear transition state of the inversion mechanism now exists.

Table 3

	T_c (°K)	$\Delta\nu$ (Hz)	K^{-1} (S^{-1})	$\Delta G^{\ddagger}$ (Kcal/mol)	Solvent	Isomer ratio
299	<193			<5	CD_2Cl_2	
311	278	65.42	145.3	13.5	$CDCl_3$	1:1
300	301	86.75	192.7	14.5	$CDCl_3$	1:1
304	273	80.86	179.6	13.1	$CDCl_3$	1:1
307	<193			<5	CD_2Cl_2	





299 R=CN

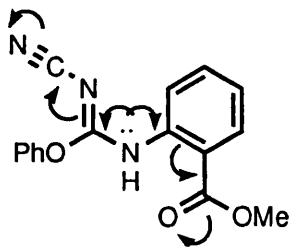
311 R=$CONH_2$

300 R=$COCF_3$

304 R=$COCH_3$

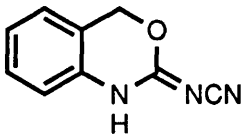
307

Interestingly, the imidazolidinone **307** does not show rotamers in its ^1H n.m.r. spectrum at temperatures down to 193 K. This could be taken as evidence for hindered rotation about the single bond in a similar manner to **427**. Hobbs[83] found further evidence to support hindered rotation about the N-C single bond for the O-phenylisourea **430**. In this case, competition for conjugation of the nitrogen lone pair between the cyanoimino and the *o*-methoxycarbonyl groups would be expected to lower the barrier to isomerisation. This was seen in that only one set of signals was observed in both the ^1H and ^{13}C n.m.r. spectra at ambient temperature. A similar argument can be made in comparing the O-phenylisoureas **398** and **432** (structures on p119), where competition for the nitrogen lone pair due to the presence of the benzyloxycarbonyl group in **432** leads to a lowering of the activation barrier, hence only one set of signals is seen in the ^1H and ^{13}C n.m.r. spectra, even at 213 K.



430

Benzoxazine **433**[83] also exhibited only one set of peaks at ambient temperature which could be interpreted as being consistent with the mechanism involving hindered rotation about the C-N single bond.

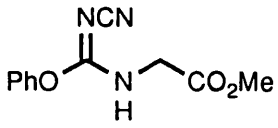


433

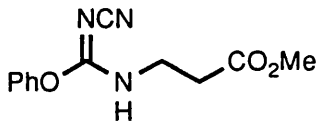
For the N-cyano-guanidines (Table 4) the barrier to rotation is fairly constant at 15-16 Kcal/mol as would be expected if the attached side chains have no actual part in the rotation process. However, the isomer ratios seen at low temperature vary quite widely which indicates that in these cases the two isomers vary considerably in energy. For the relatively unhindered side chains in **395**, **63**, and **398** the ratios are quite close to unity, with the advantage one isomer gains by any H-bonding that is present being offset by the increased steric hindrance in that isomer. In the series **127**, **131**, and **134**, however, the ratio decreases going from 1.3:1 to 1:1. As the steric bulk of the side chain as a whole is increasing down the series, with the steric bulk close to the rotating cyano group increasing most, this seems to suggest that the most stable conformation alters from one with the β-ester closer to the cyano group in **127** to one with the α-ester closer in **134**. This removes the bulky t-butyl group to a more remote position, and simultaneously reduces the steric hindrance around the rotating group. The system apparently finds it much harder to accomodate a phenyl group, as seen for the high isomer ratio of **434**. There must be some degree of steric hindrance no matter what orientation the phenyl group adopts. For the O-phenylisoureas **152** and **146** the bulk of the side chain groups could conceivably lead to a *trans* orientation of the cyano and nitrogen being favoured over *cis* despite the loss of H-bonding in this case, however, the isomer ratios suggest that the whole aspartate portion of the molecules are in positions which allows for both isomers with minimal steric constraint. For the carbocyclic analogues **256** and **254** this *trans* orientation should be favoured on steric grounds, since in the *cis* orientation steric hindrance from the methyl ester group at position 4 is to be expected. The large ratios seen for **402** and **403** are more difficult to explain since the steric bulk of the side chains is less than in the case for **134**. Obviously an interaction, possibly H-bonding, is present in one isomer but not the other leading to the ratio seen. In these cases the side chain must be in positions such that the steric hinderance they present is minimal.

Table 4

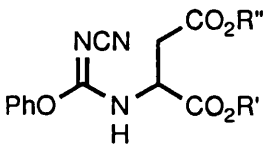
	T_c (°K)	ΔV (Hz)	K^{-1} (s^{-1})	$\Delta G^{\ddagger}$ (Kcal/mol)	Solvent	Isomer ratio
395	343	60.00	133.3	16.8	DMSO	1.3:1
63	323	57.00	126.6	15.9	DMSO	1.2:1
127	333	66.50	147.7	16.3	DMSO	1.3:1
131	318	44.10	98.0	16.0	$CDCl_3$	1.2:1
134	315	31.70	70.4	15.8	$CDCl_3$	1:1
434	315	25.89	57.5	15.9	$CDCl_3$	3:1
152	313	83.89	186.4	15.1	$CDCl_3$	1.2:1
146	348	96.13	213.6	16.8	$CDCl_3$	1:1
256	333	91.53	203.3	16.1	$CDCl_3$	2:1
254	333	94.25	209.4	16.0	$CDCl_3$	1.75:1
398	289	22.18	49.3	14.7	$CDCl_3$	1.05:1
432	<213			<5	$CDCl_3$	
402	301	20.40	45.3	15.3	$CDCl_3$	2.8:1
403	302	19.60	43.5	15.5	$CDCl_3$	2.66:1



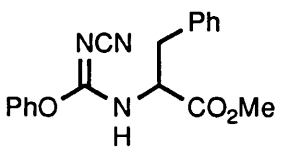
395



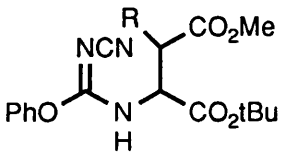
63



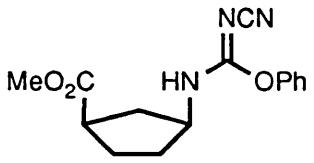
127 R'=Me, R"=Me
131 R'=tBu, R"=Me
134 R'=Me, R"=tBu



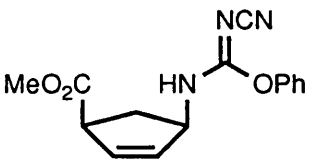
434



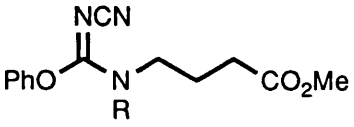
152 R=$CH_3CH_2CH_2$
146 R=$PhCH_2$



256



254



398 R=Me

431 R=H

432 R=$PhCH_2OCO$

402 R=Me

403 R=Et

7.3 Conclusion

It can clearly be seen that altering the electronegativity of the group attached to the imino nitrogen leads to a change in $\Delta G^{\ddagger}$ that can be predicted in a qualitative sense but not in a quantitative sense. Similarly, a prediction can be made on changing the substituent attached to the imino carbon. The actual size of the change depends, however, on both the degree of H-bonding possible, and the steric constraints present within the molecule, since these alter the minimum energies of the two rotamers. The contribution of these factors cannot be easily predicted, hence $\Delta G^{\ddagger}$ values are best obtained by experiment rather than by prediction based on previous work. The results do not point conclusively to any one mechanism. Indeed the complex nature of the variation of $\Delta G^{\ddagger}$ with functional groups seems to point to a spectrum of mechanisms, as first suggested by Raban.[174]

Experimental

8.1 Apparatus and reagents

Microanalyses were carried out by the Microanalytical Section of the Chemistry Department, University College London, except for ^{19}F analyses which were carried out by the microanalytical department of Sandoz, Basel, Switzerland. In cases where a microanalysis could not be obtained high resolution mass spectrometry was used. Melting points were determined on a Reicher melting point apparatus and are uncorrected. The infra-red (I.R.) spectra were recorded on a Perkin-Elmer PE-983 spectrophotometer using potassium bromide pellets (unless otherwise stated); absorptions are recorded in terms of frequency (ν_{max} in cm^{-1}). The proton nuclear magnetic resonance (^1H n.m.r.) spectra were recorded on a Varian Gemini-200 (200 MHz) or a Varian VXR-400 (400 MHz) spectrometer, and are reported in δ values relative to tetramethylsilane as internal standard. The spectra were recorded in deuterochloroform (C), methanol-d_4 (M), or dimethylsulphoxide (D) solution. The following abbreviations are used in signal assignments; s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiple), b (broad). ^{13}C n.m.r. were recorded at 50 MHz on the Varian VXR-400 spectrometer. Mass spectra were recorded on a VG7070H mass spectrometer with Finnigan Incos II data system at University College, or on a VG ZAB-2F (E.I.) or VG 12-250 (C.I.) mass spectrometer at the London School of Pharmacy. Only molecular ions (M^+), if present, base peaks and the next two peaks due to ions of maximum abundance are reported. Optical activity measurements were made on an Optical Activity Ltd polarimeter using a 10 cm cell.

Commercially available Merck Kieselgel 60 F_{254} plates were used for analytical thin layer chromatography (t.l.c.). They were visualised with ultra-violet light or iodine. Column chromatography was performed using Merck flash silica (200-400 mesh) as stationary phase.

t-Butyllithium (in hexanes) was obtained commercially from the Aldrich Chemical Co Ltd and periodically titrated with 2,5-dimethoxybenzylalcohol according to the literature method.[187] All experiments using water sensitive reagents were carried out under an atmosphere of dry argon. Solvents were purified by standard methods. In particular tetrahydrofuran was freshly distilled from sodium-benzophenone-ketyl. Glassware for such reactions was dried by flaming with a Bunsen burner under a vigorous stream of dry argon. All syringes were dried in an oven at 130 °C overnight and flushed with argon prior to use. Temperatures below 0 °C were obtained by cooling acetone with carbon dioxide ("cardice bath").

HPLC was carried out using an (R)-N-2,4-dinitrobenzoyl phenylglycine (CHI-D-PGC 250A, Anachem) stationary phase and a mobile phase composed of hexane:dichloromethane:propan-2-ol in the ratio 92:8:5.

8.2 Preparation of N-cyano-N'-1-t-butyloxycarbonyl-2-methoxycarbonylethyl-O-phenylisourea 131

To a stirred solution of α-tBu-β-Me-aspartate **130** (2.15 g, 10 mmol) in propan-2-ol (200 ml) was added a slurry of diphenyl cyanocarbonimidate **53** (2.15 g, 10 mmol) and the mixture was stirred at room temperature for 72 h. The solvent was removed by evaporation *in vacuo* to yield a

yellow oil which was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:4), to give **131** (3.00 g, 84%) as a pale yellow oil.

M.S. *m/e* : 348 (MH^+), 260 (M^+-87), 246 (M^+-101), 94 (M^+-253).

^1H n.m.r. (C), δ: 7.50-7.00 (m, Ph), 6.10 (bd, NH), 4.80 (m, **CH**CO_2Me), 4.70 (m, **CH**CO_2Me), 3.75 (s, OCH_3), 3.60 (s, OCH_3), 3.10-2.90 (m,**CH**$_2CO_2$), 1.50 (s, C(**CH**$_3$)$_3$), 1.42 (s, C(**CH**$_3$)$_3$).

^{13}C n.m.r. (C), δ: 171.15, 170.52, 167.91, 167.89, 159.40, 150.81, 150.11, 130.70, 129.65, 127.83, 126.92, 121.36, 115.20, 115.18, 83.83, 52.30, 36.19, 35.23, 27.83.

I.R.(neat): 2195, 1740, 1725, 1625 cm^{-1}.

$[\alpha]_D$: -6.14° (c=1.01, MeOH).

8.3 Preparation of 1-benzyl-2-cyanoimino-4-methoxycarbonylmethyl-2-imidazolidin-5-one 128 and 3-benzyl-6-t-butyloxycarbonyl-2-cyanoimino-5,6-dihydro-4(3H)-pyrimidinone 132

To a solution of O-phenylisourea **131** (0.24 g, 0.69 mmol) in propan-2-ol (20 ml) was added benzylamine (0.15 g, 1.43 mmol) and the resulting solution was stirred at room temperature for 25 h. During this time a white precipitate formed. The solvent was removed by evaporation *in vacuo* and the resulting solid dissolved in ethyl acetate and purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:2), to give imidazolidin-5-one **128** (0.051g, 26%), and 4(3H)-pyrimidinone **132** (0.075 g, 38%). Both products were recrystallised from methanol for analytical purposes.

2-Imidazolidin-5-one 128

M.pt: 178-180 °C (lit 171-173 °C[24]).

M.S. *m/e* : 287 (MH^+), 286 (M^+), 105 (M^+-182), 91 (M^+-195).

^1H n.m.r. (C), δ: 8.49 (bs, NH), 7.42-7.28 (m, Ph), 4.70 (d, PhCH', $J_{H'-H''}$=26.8 Hz), 4.69 (d, PhCH", $J_{H''-H'}$=26.8 Hz), 4.41 (dd, **CH**CH_2, $J_{H-H'}$=4.0 Hz, $J_{H-H''}$=7.2 Hz), 3.65(s, O**CH**$_3$), 3.01 (dd, **CH'**CO_2, $J_{H'-H}$=4.0 Hz, $J_{H'-H''}$=17.2 Hz), 2.96 (dd, **CH"**CO_2, $J_{H''-H}$=7.2 Hz, $J_{H''-H'}$=17.2 Hz).

^{13}C n.m.r. (C), δ: 172.15, 169.42, 162.32, 134.71, 128.94, 128.89, 128.74, 115.33, 55.13, 52.49, 43.45, 35.12.

I.R: 2185, 1759, 1739, 1644 cm^{-1}.

$[\alpha]_D$: 0.00°.

Analysis: Calculated for $C_{14}H_{14}O_3N_4$: C, 58.74; H, 4.89; N, 19.58.
Found: C, 58.95; H, 4.80; N, 19.44.

4(3H)-pyrimidinone 132

M.pt: 143.5-145.5 °C.

M.S. *m/e* : 329 (MH^+), 328 (M^+), 272 (M^+-56), 91 (M^+-237).

^1H n.m.r. (C), δ: 7.70 (bs, NH), 7.40-7.24 (m, Ph), 5.02 (s, Ph**CH_2**), 4.17 (t, **CH**CO_2, $J_{H-H'}$=6.0 Hz, $J_{H-H''}$=6.4 Hz), 3.03 (dd, **CH''**CH, $J_{H''-H'}$=16.8 Hz, $J_{H''-H}$=6.4 Hz), 2.95 (dd, **CH'**CH, $J_{H'-H''}$=16.8 Hz, $J_{H'-H}$=6.0 Hz), 1.40 (s, C**$(CH_3)_3$**).

^{13}C n.m.r. (C), δ: 167.34, 165.51, 160.00, 136.19, 128.74, 128.44, 127.78, 115.25, 84.51, 49.83, 44.96, 33.72, 27.76.

I.R: 2183, 1730, 1700, 1590 cm^{-1}.

$[\alpha]_D$: -114° (c=0.30, MeOH).

Analysis: Calculated for $C_{17}H_{20}O_3N_4$: C, 62.20; H, 6.10; N, 17.07.
Found: C, 62.32; H, 6.19; N, 16.84.

8.4 Preparation of N-cyano-N'-(1-methoxycarbonyl-2-t-butoxycarbonylethyl)-O-phenylisourea 134

Triethylamine (0.42 g, 4 mmol) was added to a stirred suspension of α-Me-β-tBu-aspartate-hydrochloride **133** (1.00 g, 4 mmol) in propan-2-ol (30 ml). Diphenyl cyanocarbonimidate **53** (0.99 g, 4 mmol) dissolved in propan-2-ol (10 ml) was added and the resulting mixture stirred at room temperature for 12 h. The propan-2-ol was removed by evaporation *in vacuo* to give a yellow oil, which crystallised on standing for several hours. The crystals were removed by filtration, washed with ether, and dried *in vacuo* to give the O-

phenylisourea **134** (1.07 g, 3.1 mmol, 74%).This material was used for further reactions, but a sample was recrystallised from methanol for analytical purposes.

M.pt: 106-108 °C.

M.S. *m/e* : 348.1716 ($C_{17}H_{21}N_3O_5$ requires 348.3779)
348 (M^++1), 292 (M^+-55), 170 (M^+-177), 95 (M^+-252).

^{1}H n.m.r. (C), δ: 7.50 (m, *m*-Ph), 7.30 (m, *p*-Ph), 7.00 (m, *o*-Ph), 6.14 (bd, NH), 4.80 (m, **CH**CO_2Me), 4.70 (m, **CH**CO_2Me), 3.80 (s, OCH_3), 3.75 (s, OCH_3), 2.95 (m, **CH_2**$CO_2C(CH_3)_3$), 1.40 (s, C(**CH_3**)$_3$), 1.30 (s, C(**CH_3**)$_3$).

^{13}C n.m.r. (C), δ: 169.83, 169.78, 169.33, 168.91, 163.27, 159.39, 156.38, 150.84, 130.74, 129.44, 127.88, 126.87, 121.38, 121.24, 121.08, 119.99, 115.43, 114.31, 53.18, 51.90, 45.98, 37.18, 36.44, 28.00, 27.81.

I.R: 2190, 1745, 1705, 1600 cm^{-1}.

$[\alpha]_D$: -16.19° (c=1.10, MeOH).

8.5 Preparation of 1-benzyl-2-cyanoimino-(4-t-butoxycarbonylmethyl)-2-imidazolidin-5-one 135

A solution of O-phenylisourea **134** (0.30 g, 0.86 mmol) and benzylamine (0.096 g, 0.89 mmol) in propan-2-ol (20 ml) was heated to reflux for 2 h. The volume was reduced, by evaporation *in vacuo*, to one half and then cooled (4 °C, 3 h). The resulting white crystals were removed by filtration, washed with ether, and dried *in vacuo* to give the imidazolidin-5-one **135** (0.11 g, 0.34 mmol, 40%).

M.pt: 161.5-163.0 °C.

M.S. *m/e* : 329 (M^++1), 328(M^+), 255(M^+-73), 91(M^+-237).

^{1}H n.m.r. (C), δ: 7.40-7.25 (m, Ph), 4.75 (s, Ph**CH_2**N), 4.40 (dd, **CH**CH_2, $J_{H-H'}$=8.4 Hz, $J_{H-H''}$=3.6 Hz), 2.94 (dd, **CH''**CO_2, $J_{H''-H}$=3.6 Hz, $J_{H''-H'}$=17.2 Hz), 2.66 (dd, **CH'**CO_2, $J_{H'-H}$=8.4 Hz, $J_{H'-H''}$=17.2 Hz), 1.45 (s, C(**CH_3**)$_3$).

^{13}C n.m.r. (C), δ: 173.41, 167.95, 161.85, 135.47, 128.29, 127.44, 127.41, 115.18, 81.05, 54.94, 42.23, 35.13, 27.51.

I.R: 2194, 1778, 1728, 1645 cm^{-1}.

$[\alpha]_D$: 0.00°.

Analysis: Calculated for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.10; N, 17.06.
Found: C, 62.03; H, 6.22; N, 16.56.

8.6 Preparation of 1-benzyl-2-cyanoimino-4-carbamoylmethyl-2-imidazolidin-5-one 136

Aqueous ammonia (s.g.=0.880, 0.28 ml) was added to a solution of imidazolidin-5-one **128** (0.42 g, 1.47 mmol) in propan-2-ol (20 ml) and the resulting solution was heated to reflux for 3 h. The solvent was removed by evaporation *in vacuo*, the resulting oil redissolved in ethyl acetate (20 ml) and cooled to 4 °C for 6 h. The resulting crystalline product was filtered, washed with ether and dried to give the title compound (0.30 g, 75%).

M.pt: 147-149 °C.

M.S. *m/e* : 272.0945 ($C_{13}H_{14}N_5O_2$ requires 272.0909)
272 (MH^+), 226 (M^+-45), 169 (M^+-102), 91 (M^+-180).

^1H n.m.r. (D), δ: 7.33-7.23 (m, Ph), 4.58 (d, PhCH', $J_{H'-H''}$=15.72 Hz), 4.55 (d, PhCH'', $J_{H''-H'}$=15.72 Hz), 4.32 (dd, **C**HCH_2, $J_{H-H'}$=4.20 Hz, $J_{H-H''}$=4.24 Hz), 2.58 (dd, **CH'**CH, $J_{H'-H}$=4.20 Hz, $J_{H'-H''}$=16.80 Hz), 2.54 (dd, **CH''**CH, $J_{H''-H}$=4.24 Hz, $J_{H''-H'}$=16.80 Hz).

^{13}C n.m.r. (D), δ: 174.93, 171.30, 161.99, 136.09, 128.27, 127.18, 127.13, 115.78, 56.51, 42.08, 37.06.

I.R: 3168, 2207, 1749, 1638, 1574 cm^{-1}.

8.7 Preparation of N-cyano-N'-(1-t-butyloxycarbonyl-2-benzoxycarbonylethyl)-O-phenylisourea 138

A solution of diphenyl cyanocarbonimidate **53** (0.90 g, 3.78 mmol) and α-tBu-β-Bzl-Asp **137** (0.99g, 3.45 mmol) in propan-2-ol (50 ml) was stirred at room temperature for 15 h. The solvent was removed by evaporation *in vacuo* and the resulting brown oil was purified by flash chromatography, eluting with dichloromethane:methanol (9:1), to give the O-phenylisourea **138** as a pale yellow oil (0.8 g, 53%).

M.S. *m/e* : 424 (MH^+), 368 (M^+-55), 188 (M^+-235), 91 (M^+-332).

^{1}H n.m.r. (C), δ: 7.45-7.00 (m, Ph), 6.20 (bs, NH), 6.10 (bd, NH), 5.27 (m, $PhCH_2$), 5.05 (m, $PhCH_2$), 4.76 (m, **C**HCO_2Me), 4.45 (m, **C**HCO_2Me), 3.05 (m, **C**H_2CO_2tBu), 1.44 (bs, C(**C**H_3)$_3$), 1.36 (bs, C(**C**H_3)).

^{13}C n.m.r. (C), δ: 170.30, 169.95, 167.73, 159.28, 156.10, 149.74, 135.00, 130.71, 129.76, 129.63, 128.79, 128.53, 128.45, 127.88, 126.84, 121.32, 121.14, 120.9,9 120.63, 120.15, 115.39, 83.97, 67.38, 67.07, 52.31, 36.21, 35.37, 27.89, 27.79.

I.R.($CHCl_3$): 2200, 1740, 1725, 1630 cm^{-1}.

Analysis: Calculated for $C_{23}H_{25}N_3O_5$: C, 65.24; H, 5.95; N, 9.92.
Found: C, 65.75; H, 5.96; N, 9.14.

8.8 Preparation of 1-benzyl-2-cyanoimino-4-benzyloxycarbonylmethyl-2-imidazolidin-5-one 139 and 3-benzyl-6-t-butoxycarbonyl-2-cyanoimino-5,6-dihydro-4(3H)-pyrimidinone 132

To a solution of O-phenylisourea **138** (0.4 g, 0.95 mmol) in propan-2-ol (10 ml) was added benzylamine (0.2 g, 1.89 mmol), and the resulting solution was stirred at room temperature for 8 h. The solvent was removed by evaporation *in vacuo* and the products separated by column chromatography, eluting with ethyl acetate:cyclohexane (1:2), to give a coeluting mixture of imidazolidin-5-one **139** and pyrimidinone **132**.

2-imidazolidin-5-one 139

^{1}H n.m.r. (C), δ: 8.77 (bs, NH), 7.40-7.20 (m, Ph), 5.15 (d, Ph**CH'**CO_2, $J_{H'-H'}$=12 Hz), 5.10 (d, Ph**CH"**CO_2, $J_{H"-H'}$=12 Hz), 4.61 (s, $PhCH_2N$), 4.40 (dd, **C**HCH_2, $J_{H-H'}$=6.8 Hz, $J_{H-H"}$=4.0 Hz), 3.00 (dd, **CH"**CH, $J_{H"-H}$=4.0 Hz, $J_{H"-H'}$=17.6 Hz), 2.86 (dd, **CH'**CH, $J_{H"-H}$=6.8 Hz, $J_{H"-H'}$=17.6 Hz).

8.9 Preparation of t-Butyl 2-benzyloxycarbonylamino-3-methoxycarbonyl-4-phenyl-(2S)-butanoate 144

The title compound was prepared by the method of Baldwin.[70] The two diastereoisomers of the product were separated by column chromatography eluting initially with hexane, and then gradually increasing the polarity with ether to a final concentration of 15%.

Major diastereoisomer 144a

Yield: 42%.

M.pt: 68-70 °C.

^{1}H n.m.r. (C), δ: 7.41-7.18 (m, Ph), 5.76 (bd, NH, J_{NH-CH}=9.6 Hz), 5.16 (d, Ph**CH'**O, $J_{H'-H''}$=12.4 Hz), 5.15 (Ph**CH''**O, $J_{H''-H'}$=12.4 Hz), 4.45 (dd, NH**CH**CH, J_{H-H}=3.6 Hz, J_{H-NH}=9.6 Hz), 3.63 (s, OCH_3), 3.36 (ddd, **CH**CO_2Me, J_{H-H}=8.0 Hz, $J_{H-H'}$=8.0 Hz, $J_{H-H''}$=7.2 Hz), 3.08 (dd, CH**CH''**Ph, $J_{H''-H}$=7.2 Hz, $J_{H''-H'}$=13.8 Hz), 2.81 (dd, CH**CH'**Ph, $J_{H'-H}$=8.0 Hz, $J_{H'-H''}$=13.8 Hz), 1.50 (s, C(**CH_3**)$_3$).

Minor diasteroisomer 144b

Yield: 15.3%.

M.pt: 51-53 °C.

^{1}H n.m.r. (C), δ: 7.40-7.18 (m, Ph), 5.61 (bd, NH, J_{NH-H}=8.4 Hz), 5.11 (s, PhCH_2O), 4.58 (dd, NH**CH**CH, J_{H-H}=4.4 Hz, J_{NH-H}=8.4 Hz), 3.62 (s, OCH_3), 3.18 (ddd, **CH**CO_2Me, J_{H-H}=4.4 Hz, $J_{H-H'}$=4.7 Hz, $J_{H-H''}$=5.2 Hz), 3.13 (dd, CH**CH'**Ph, $J_{H'-H}$=4.7 Hz, $J_{H'-H''}$=13.2 Hz), 2.86 (dd, CH**CH''**Ph, $J_{H''-H}$=5.2 Hz, $J_{H''-H'}$=13.2 Hz), 1.50 (s, C(**CH_3**)$_3$).

8.10 Preparation of t-butyl 2-amino-3-methoxycarbonyl-4-phenyl-(2S)-butanoate 145a

The title compound was prepared by the method of Baldwin[70] using the purified diastereoisomer **144a**.

^{1}H n.m.r. (C, 200 Mhz), δ: 7.40-7.14 (m, Ph), 3.70-3.65 (m, NH**CH**), 3.53 (s, OCH_3), 3.25-2.85 (m, Ph**CH_2**CH and $CHCO_2$Me), 1.46 (s, C(**CH_3**)$_3$).

8.11 Preparation of t-butyl 2-amino-3-methoxycarbonyl-4-phenyl-(2S)-butanoate 145b

The title compound was prepared by the method of Baldwin[70] using the purified diastereoisomer **144b**.

^{1}H n.m.r. (C, 200 Mhz), δ: 7.30-7.10 (m, Ph), 3.88 (bd, NH**CH**), 3.53 (s, OCH_3), 3.50-3.35 (m, $CHCO_2Me$), 3.20 (dd, PhCH'), 3.00 (dd, PhCH"), 1.49 (s, C(**CH_3**)$_3$).

8.12 Preparation of N-cyano-N'-(t-butyl 3-methoxycarbonyl-4-phenyl-(2S)-butanoate)-O-phenylisourea 146a

To a stirred solution of aspartate **145a** (0.78 g, 2.66 mmol) in propan-2-ol (40 ml) was added diphenyl cyanocarbonimidate **53** (0.69 g, 2.89 mmol) and the resulting solution was stirred at room temperature for 8 h. The solvent was removed by evaporation *in vacuo* to yield a yellow oil which was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:3), to give the O-phenylisourea **146a** (0.97 g, 83%) as a pale yellow oil.

M.S.(C.I.) *m/e* : 438 (MH^+), 382 (M^+-55), 281 (M^+-156), 162(M^+-275).

^{1}H n.m.r. (C), δ: 7.52-6.94 (m, PhO and **Ph**CH_2), 6.31 (bd, NH), 4.47 (dd, NHCH), 4.40 (dd, NHCH), 3.72 (bs, OCH_3), 3.48 (bs, OCH_3), 3.31 (m, $CHCO_2Me$), 3.25 (m, $CHCO_2Me$), 2.95 (m, PhCH'), 2.70 (dd, PhCH"), 1.44 (s, C(**CH_3**)$_3$), 1.39 (s,C(**CH_3**)$_3$).

^{13}C n.m.r. (C), δ: 173.81, 168.86, 164.79, 160.80, 137.49, 137.43, 131.25, 130.12, 129.47, 129.32, 128.36, 127.79, 127.32, 121.68, 84.12, 56.17, 55.31, 52.88, 52.49, 47.70, 47.59, 35.36, 35.04, 28.16, 28.03.

I.R.(neat): 2197, 1738, 1621, 1581 cm^{-1}.

8.13 Preparation of N-cyano-N'-(t-butyl 3-methoxycarbonyl-4-phenyl-(2S)-butanoate)-O-phenylisourea 146b

The O-phenylisourea **146b** was prepared in an analogous manner to O-phenylisourea **146a**, from aspartate **145b** (0.27 g, 9.22 mmol), to give the title compound (0.18 g, 45%).

M.S.(C.I.) *m/e* : 438 (MH^+), 382 (M^+-55), 305 (M^+-132), 91 (M^+-346).

^{1}H n.m.r. (C), δ: 7.43-6.80 (m, PhO and **Ph**CH_2), 5.95 (bd, NH), 4.65 (m, NH**CH**), 4.50 (m, NHCH), 3.64 (s, OCH_3), 3.57 (s, OCH_3), 3.30-2.75 (m, Ph**CH_2** and $CHCO_2Me$), 1.46 (s, C(**CH_3**)$_3$), 1.40 (s, C(**CH_3**)$_3$).

^{13}C n.m.r. (C), δ: 172.52, 172.30, 168.17, 133.13, 131.21, 130.30, 130.05, 129.46, 129.17, 128.32, 127.51, 127.42, 121.73, 121.15, 84.58, 60.67, 56.26, 56.08, 52.49, 49.89, 49.07, 34.61, 34.34, 28.15, 28.02.

I.R.(neat): 2197, 1738, 1621, 1588 cm^{-1}.

8.14 Preparation of 3,5-dibenzyl-6-t-butyloxycarbonyl-2-cyanoimino-5,6-dihydro-4(3H)-pyrimidinone 148a, 1-benzyl-2-cyanoimino-4-ethyl-(1'-methoxycarbonyl-2'-phenyl)-2-imidazolidin-5-one 147 and N-benzyl-N'-cyano-N''-(2-t-butoxycarbonyl-3-methoxycarbonyl-4-phenyl-(2S)-butanoate)-guanidine 149

Benzylamine (0.14 g, 1.31 mmol) was added to a stirred solution of O-phenylisourea **146a** (0.53 g, 1.21 mmol) in propan-2-ol (30 ml) and the resulting solution stirred at 40 °C for 6 days. The solvent was removed by evaporation *in vacuo* and the resulting yellow oil was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:3), to yield pure pyrimidinone **148a** and a mixture of imidazolidin-5-one **147** and guanidine **149**. Imidazolidin-5-one **147** was isolated by fractional crystallisation from the mixture by slow evaporation of the column eluant. The guanidine **149** was then purified from all remaining impurities by flash chromatography, eluting with ethyl acetate:cyclohexane (1:4).

4(3H)-Pyrimidinone 148a

Yield: 0.22g (44%).

M.pt: 186-188 °C.

M.S. *m/e*: 418.2017 ($C_{24}H_{26}N_4O_3$ requires 418.2005)
418 (M^+), 362 (M^+-56), 336 (M^+-82), 91 (M^+-327).

^{1}H n.m.r. (C), δ: 8.30 (bd, NH, J_{NH-H}=4.2 Hz), 7.40-7.17 (m, Ph), 5.02 (s, $PhCH_2$), 5.01 (s, $PhCH_2$)*, 3.79 (dd, NH**C**HCO_2, $J_{H-H'}$=4.8 Hz, J_{H-NH}=4.2 Hz), 3.76 (m, NH**C**HCO_2)*, 3.38 (m, CH_2**C**HCO)*, 3.26 (ddd, CH_2**C**HCO, J_{H-H}=4.8 Hz, J_{H-H}=4.8 Hz, $J_{H-H''}$=10.8 Hz), 3.11 (dd, PhCH', $J_{H'-H}$=4.8 Hz, $J_{H'-H''}$=13.6 Hz), 3.00-2.90 (m, PhCH')*, 2.82 (dd, PhCH'', $J_{H''-H}$=10.8 Hz, $J_{H''-H'}$=13.6 Hz), 2.72-2.64 (m, PhCH'')*, 1.42 (s, C(**C**H_3)$_3$)*, 1.28 (s, C(**C**H_3)$_3$).

*Peaks of the minor diastereoisomer present.

^{13}C n.m.r. (C), δ: 168.31, 168.04, 159.04, 136.16, 135.57, 129.11, 128.97, 128.78, 128.73, 128.64, 128.34, 127.77, 127.67, 127.63, 127.45, 115.75, 83.81, 52.43, 45.25, 44.89, 35.82, 27.54.

I.R: 2184, 1738, 1721, 1611 cm^{-1}.

2-Imidazolidin-5-one 147

Yield: 0.09 g (20%).

M.pt: 173-175 °C.

M.S. *m/e* : 376 (M^+), 345 (M^+-31), 214 (M^+-162), 91 (M^+-285).

^1H n.m.r. (C), δ: 9.07 (bs, NH), 8.52 (bs, NH), 7.54-7.19 (m, Ph), 4.69 (d, PhCH', $J_{H'-H''}$=14.4 Hz)*, 4.67 (d, PhCH'', $J_{H''-H'}$=14.4 Hz)*, 4.53 (d, PhCH', $J_{H'-H''}$=14.4 Hz), 4.46 (d, PhCH'', $J_{H''-H'}$=14.4 Hz), 4.33 (d, NH**C**HCO, J_{H-H}=3.6 Hz), 4.06 (d, NH**C**HCO, J_{H-H}=3.2 Hz)*, 3.64 (s, OCH_3)*, 3.42 (dd, PhCH', $J_{H'-H}$=4.8 Hz, $J_{H'-H''}$=14.0 Hz), 3.38 (s, OCH_3), 3.36-3.30 (m, $CHCO_2$ and $PhCH_2$*), 3.17 (dd, PhCH'', $J_{H''-H}$=6.8 Hz, $J_{H''-H'}$=14.0 Hz), 3.07-3.00 (m, $PhCH_2$)*.

*Peaks of minor diastereoisomer present.

^{13}C n.m.r. (C), δ: 172.63, 171.74, 171.61, 170.21, 162.52, 162.35, 137.36, 136.75, 134.83, 134.71, 130.89, 129.33, 129.23, 129.11, 129.01, 128.96, 128.87, 128.79, 128.68, 128.60, 128.22, 127.16, 127.13, 115.37, 57.86, 57.59, 52.54, 52.19, 48.19, 47.96, 43.35, 43.23, 38.69, 33.45, 30.33, 28.91, 23.72, 22.99.

I.R: 2197, 1761, 1735, 1638, 1601 cm^{-1}.

Analysis: Calculated for $C_{21}H_{20}N_4O_3$: C, 67.00; H, 5.30; N, 14.90.
Found: C, 66.35; H, 5.64; N, 14.37.

Guanidine 149

(The guanidine was prepared using a racemic sample of O-phenyisourea **146**, hence it contains both diastereoisomers).

M.S. *m/e* : 451 (MH^+), 377 (M^+-73), 214 (M^+-236), 91 (M^+-359).

^1H n.m.r. (C), δ: 7.42-7.21 (m, Ph), 5.91 (bd, NH), 4.51 (d, PhCH'), 4.50 (d, PhCH''), 4.45 (m, $PhCH_2$), 4.35 (d, NH**C**H), 4.32 (d, NH**C**H),

3.61 (s, OCH_3), 3.58 (s, OCH_3), 3.20-3.01 (m, **CH**CO_2Me), 2.74 (m, PhCH'), 2.45 (m, PhCH"), 1.38 (s, C(**CH_3**)$_3$), 1.26 (s, C(**CH_3**)$_3$).

^{13}C n.m.r. (C), δ: 173.57, 171.85, 171.68, 168.98, 162.29, 160.02, 137.39, 136.94, 135.84, 134.85, 129.29, 129.25, 129.11, 129.02, 128.94, 128.88, 128.68, 128.35, 127.48, 127.06, 126.88, 121.19, 118.00, 115.99, 82.96, 57.85, 54.78, 52.44, 52.06, 48.32, 47.83, 45.70, 43.17, 35.55, 33.51, 31.72, 30.14, 29.69, 27.82, 27.74.

I.R: 2184, 1762, 1715, 1635 cm^{-1}.

8.15 Preparation of 3,5-dibenzyl-6-t-butyloxycarbonyl-2-cyanoimino-5,6-dihydro-4(3H)-pyrimidinone 148b

The title compound was prepared in an analogous manner to pyrimidinone **148a** from O-phenylisourea **146b** (0.16 g, 0.37 mmol).

Yield: 0.08 g (52%).

M.S. *m/e* : 418 (M^+), 362 (M^+-56), 336 (M^+-82), 91 (M^+-327).

^{1}H n.m.r. (C), δ: 7.83 (bs, NH), 7.30-7.10 (m, Ph), 4.96 (s, $PhCH_2$), 3.71 (bs, NH**CH**CO), 3.22 (ddd, **CH**CO, J_{H-H}=5.12 Hz, $J_{H-H'}$=5.20 Hz, J_{H-H}=10.88 Hz), 3.07 (dd, PhCH', $J_{H'-H}$=5.20 Hz, $J_{H'-H"}$=13.68 Hz), 2.75 (dd, PhCH", $J_{H"-H}$=10.88 Hz, $J_{H"-H'}$=13.68 Hz), 1.28 (s, C(**CH_3**)$_3$).

^{13}C n.m.r. (C), δ: 168.24, 167.96, 159.01, 136.12, 135.58, 129.10, 129.04, 128.71, 127.74, 127.53, 115.37, 84.02, 52.56, 45.21, 44.93, 35.82, 27.58.

I.R: 2184, 1735, 1718, 1608 cm^{-1}.

8.16 Preparation of t-butyl-2-amino-3-methoxycarbonyl-(2S)-hexanoate 151

To a solution of t-butyl-2-benzyloxycarbonylamino-3-methoxycarbonyl-(2S)-5-hexenoate **150**[70] (2.13 g, 5.6mmol) in ethanol (60 ml) was added Pd/C (0.2 g, 10%). The resulting mixture was stirred under an atmosphere of hydrogen (1 atm) for 6 h, diluted with ether (100 ml), filtered through celite and the solvent removed by evaporation *in vacuo* to give the hexanoate **151** as a colourless oil (1.38 g, 99%).

M.S. *m/e* : 245 (M^+), 186 (M^+-59), 144 (M^+-101), 59 (M^+-186).

^{1}H n.m.r. (C, 200 MHz), δ: 4.13 (bs, NH), 3.60-3.51 (m, NH**CH**), 3.57 (s, OCH_3), 2.79-2.74 (m, $CHCO_2$), 1.70-1.00 (m, CH_2CH_2), 1.34 (s, C(**CH_3**)$_3$) 0.79 (t, CH_3).

^{13}C n.m.r. (C, 50 MHz), δ: 174.05, 172.35, 82.37, 56.08, 51.81, 48.24, 30.52, 28.00, 20.81, 13.87.

I.R.($CHCl_3$): 2999, 2925, 1728, 1594 cm^{-1}.

8.17 Preparation of N-cyano-N'-(t-butyl-3-methoxycarbonyl-(2S)-hexanoate)-O-phenylisourea 152

To a stirred solution of aspartate **151** (0.95 g, 3.89 mmol) in propan-2-ol (40 ml) was added diphenyl cyanocarbonimidate **53** (1.11 g, 4.68 mmol) and the resulting mixture stirred at room temperature for 16 h. The solvent was removed by evaporation *in vacuo* and the resulting yellow oil was purified by flash chromatography, eluting with dichloromethane:methanol (99:1), to give O-phenylisourea **152** as a pale yellow oil (1.50 g, 70%).

M.S. *m/e* : 390.2073 ($C_{20}H_{28}N_4O_3$ requires 390.4583)
390 (MH^+), 334 (M^+-55), 302 (M^+-87), 94 (M^+-295).

^{1}H n.m.r. (C), δ: 7.55-7.00 (m, PhO), 6.33 (bd, NH), 4.68-4.52 (m, NH**CH**), 3.74 (s, OCH_3), 3.53 (s, OCH_3), 3.21-2.97 (m, **CH**CO_2Me), 1.90-1.10 (m, CH_2CH_2), 1.49 (s, C(**CH_3**)$_3$), 1.44 (s, C(**CH_3**)$_3$).

^{13}C n.m.r. (C), δ: 174.51, 174.10, 168.68, 168.55, 164.47, 160.91, 131.11, 130.15, 129.69, 128.22, 127.25, 121.66, 121.48, 121.02, 115.83, 81.90, 56.75, 56.23, 52.47, 52.23, 45.48, 31.26, 31.12, 27.89, 21.66, 20.47, 13.82, 13.72.

I.R.($CHCl_3$): 2198, 1738, 1621, 1591 cm^{-1}.

8.18 Preparation of 3-benzyl-5-propyl-6-t-butoxycarbonyl-2-cyanoimino-5,6-dihydro-4(3H)-pyrimidinone 153, 1-benzyl-2-cyanoimino-4-butyl-(1'-methoxycarbonyl)-2-imidazolidin-5-one 154 and N-benzyl-N'-cyano-N"-(2-t-butyl-3-methoxycarbonyl-(2S)-hexanoate)-guanidine 155

Benzylamine (0.47 g, 4.45 mmol) was added to a stirred solution of O-phenyisourea **152** (1.65 g, 4.24 mmol) in propan-2-ol (40 ml) and the resulting solution stirred at 40 °C for 6 days. The solvent was removed by evaporation *in vacuo* and the resulting yellow oil purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:4), to yield pure pyrimidinone **153** and a mixture of imidazolidin-5-one **154** and guanidine **155**. Imidazolidin-5-one **154** was isolated by fractional crystallisation from the mixture by slow evaporation of the column eluant. The guanidine **155** was then purified from all remaining impurities by flash chromatography, eluting with ethyl acetate:cyclohexane (1:4).

4(3H)-Pyrimidinone 153

Yield: 0.85 g (54%).

M.pt: 147-150 °C.

M.S. (C.I.) *m/e*: 371 (MH^+), 315 (M^+-55), 269 (M^+-101), 227 (M^+-143).

^{1}H n.m.r. (C), δ: 8.14 (bs, NH), 7.34-7.23 (m, Ph), 5.03 (d, PhCH', $J_{H'-H''}$=14.4 Hz), 5.00 (d, PhCH", $J_{H''-H'}$=14.4 Hz), 3.91 (dd, NH**CH**, J_{H-NH}=1.8 Hz, J_{H-H}=4.0 Hz), 2.96 (bt, $CHCO_2$, J=7.4 Hz), 1.71-1.63 (m, $\mathbf{CH_2}CH_2$), 1.47-1.32 (m, $CH_2\mathbf{CH_2}$), 1.35 (s, $C(\mathbf{CH_3})_3$), 0.94 (t, CH_3, J_{H-H}=7.2 Hz).

^{13}C n.m.r. (C), δ: 168.75, 168.23, 159.01, 136.25, 128.64, 128.38, 127.54, 116.00, 83.82, 53.92, 44.85, 43.17, 32.18, 27.79, 27.65, 19.70, 13.38.

I.R: 2184, 1735, 1718, 1614 cm^{-1}.

Analysis: Calculated for $C_{20}H_{26}N_4O_3$: C, 64.85; H, 7.07; N, 15.12.
Found: C, 64.62; H, 7.03; N, 14.86.

2-Imidazolidin-5-one 154

Yield: 0.14 g (10%).

M.pt: 153-155 °C.

M.S. (C.I.) *m/e* : 329 (MH^+), 215 (M^+-113), 185 (M^+-143), 91 (M^+-237).

^{1}H n.m.r. (C), δ: 8.76 (bs, NH), 8.37 (bs, NH), 7.44-7.26 (m, Ph), 4.70 (d, PhCH', $J_{H'-H''}$=14.8 Hz), 4.68 (d, PhCH", $J_{H''-H'}$=14.8 Hz), 4.41 (dd, NH**CH**, J_{H-NH}=1.6 Hz, J_{H-H}=4.4 Hz)*, 4.40 (dd, NH**CH**, J_{H-NH}=1.6 Hz, J_{H-H}=4.4 Hz), 3.69 (s, OCH_3)*, 3.42 (s, OCH_3), 3.01-2.92 (m, **CH**CO_2), 2.05-1.90 (m, **CH_2**CH_2), 1.77-1.62 (m, **CH_2**CH_2), 1.44-1.24 (m, CH_2**CH_2**), 0.97 (t, CH_3, J_{H-H}=7.2 Hz)*, 0.84 (t, CH_3, J_{H-H}=7.2 Hz).

*Peaks of the minor diasteroisomer present.

^{13}C n.m.r. (C), δ: 172.56, 172.41, 171.65, 171.25, 162.44, 162.11, 134.84, 134.67, 129.12, 129.00, 128.95, 128.70, 128.67, 128.36, 128.27, 115.23, 115.09, 59.18, 58.64, 52.43, 52.07, 46.31, 45.81, 43.33, 29.80, 29.22, 20.59, 20.31, 13.69.

I.R: 2191, 1755, 1728, 1681, 1638 cm^{-1}.

Analysis: Calculated for $C_{17}H_{20}N_4O_3$: C, 61.99; H, 6.43; N, 17.01.
Found: C, 61.90; H, 6.06; N, 16.82.

Guanidine 155

Yield: 0.13 g (8%).

M.pt: 144-146 °C.

M.S. (C.I.) *m/e* : 403 (MH^+), 371 (M^+-31), 346 (M^+-56), 329(M^+-73).

^{1}H n.m.r. (C), δ: 7.44-7.26 (m, Ph), 5.83 (bd, NH, J_{NH-H}=8.8 Hz), 4.70 (d, PhCH', $J_{H'-H''}$=14.4 Hz), 4.68 (d, PhCH", $J_{H''-H'}$=14.4 Hz), 4.55-4.26 (m, NH**CH**), 3.65 (s, OCH_3), 3.59 (s, OCH_3), 3.02-2.88 (m, $CHCO_2$), 1.79-1.72 (m, **CH_2**CH_2), 1.53-1.21 (m, CH_2**CH_2**), 1.42 (s, C(**CH_3**)$_3$), 0.86 (t, CH_3 J_{H-H}=7.2 Hz), 0.81 (t, CH_3, J_{H-H}=7.2 Hz).

^{13}C n.m.r. (C), δ: 174.40, 172.00, 169.22, 162.24, 160.25, 134.99, 134.86, 129.86, 128.93, 128.90, 128.24, 128.20, 128.01, 127.35, 121.70, 115.67, 115.61, 82.64, 59.19, 58.77, 54.88, 52,29, 51.96, 51.90, 46.69, 45.75,

45.63, 43.26, 31.93, 30.51, 29.77, 29.43, 27.75, 26.91, 20.61, 20.34, 13.72, 13.68.

I.R: 2184, 1755, 1735, 1635, 1588 cm^{-1}.

8.19 Preparation of 2-cyanoimino-4-methoxycarbonylmethyl-2-imidazolidin-5-one 159

To a solution of N-(1,2-dimethoxycarbonylethyl)-N'-cyano-O-phenylisourea **127**[24] (0.70 g, 2.30 mmol) in propan-2-ol (30 ml) was added aqueous ammonia solution (0.880 s.g., 5 ml) and the resulting solution was stirred at room temperature for 2.5 h. The solvent was removed by evaporation *in vacuo* and the product purified by flash chromatography, eluting with ethyl acetate:cyclohexane (7:3), to give the title compound (0.14 g, 31%).

M.pt: 188-190 °C.

M.S. *m/e* : 196.0596 ($C_7H_8N_4O_3$ requires 196.0596)
196 (MH^+), 181 (M^+-15), 137 (M^+-59), 94 (M^+-102).

^1H n.m.r. (M), δ: 4.89 (t, CH, J_{H-H}=5.08 Hz), 3.70 (s, OCH_3), 2.91 (d, CH_2, J_{H-H}=5.08 Hz).

^{13}C n.m.r. (M), δ: 176.26, 171.34, 164.48, 116.66, 57.57, 52.60, 35.51.

I.R: 3132, 2207, 1776, 1724, 1672 cm^{-1}.

8.20 Preparation of 6-carboxy-5,6-dihydro-4(3H)-pyrimidinone 162

A solution of imidazolidin-5-one **159** (0.205 g, 1.05 mmol) in 2 M sodium hydroxide (2 ml) was stirred at room temperature for 15 min. The solution was acidified to pH 1 with concentrated hydrochloric acid. The solvent was reduced to a small volume by evaporation *in vacuo* and ether/methanol (1:1, 5 ml) added. The precipitated product was collected by filtration, washed with ether and dried to give the title compound (0.12 g, 63%).

M.pt: 192-194 °C.

M.S. *m/e* : 182.0445 ($C_6H_6N_4O_3$ requires 182.0440)
182 (M^+), 154 (M^+-28), 129 (M^+-53), 111 (M^+-71).

^1H n.m.r. (D/D_2O), δ: 4.53 (dd, CH, $J_{H-H'}$=4.52 Hz, $J_{H-H''}$=4.30 Hz), 4.38 (dd, CH, $J_{H-H'}$=4.48, $J_{H-H''}$=4.56 Hz), 3.01 (dd, CH', $J_{H'-H''}$=17.97 Hz, $J_{H'-H}$=4.52 Hz), 2.93

(dd, CH", $J_{H"-H'}$=17.97 Hz, $J_{H"-H}$=4.30 Hz), 2.76 (dd, CH', $J_{H'-H"}$=17.86 Hz, $J_{H'-H}$=4.48 Hz), 2.74 (dd, CH", $J_{H"-H'}$=17.86 Hz, $J_{H"-H}$=4.56 Hz).

^{13}C n.m.r. (D/D_2O), δ: 173.89, 170.63, 156.09, 152.27, 115.90, 55.55, 34.22, 33.55.

I.R: 3510, 3425, 2207, 1785, 1761, 1706, 1648 cm^{-1}.

8.21 Preparation of 3,5-dibenzyl-6-carboxy-2-cyanoimino-5,6-dihydro-4(3H)-pyrimidinone 164

A solution of imidazolidin-5-one **147** (0.017 g, 0.04 mmol) in 2 M sodium hydroxide solution (0.6 ml) was stirred at room temperature for 10 min. The solution was acidified to pH 1 with concentrated hydrochloric acid and the precipitated product collected and washed with ether to give the carboxylic acid **164** (0.008 g, 50%).

M.pt: 145-147 °C.

M.S. *m/e* : 362 (M^+), 316 (M^+-46), 225 (M^+-137), 91 (M^+-271).

^{1}H n.m.r. (D), δ: 10.69 (s,CO_2H), 10.60 (s,CO_2H), 7.30-7.05 (m,Ph), 4.70-4.30 (m,Ph**CH_2** and NH**CH**), 3.20-2.97 (m, Ph**CH_2** and **CH**$CHCO_2H$).

I.R: 3418, 2195, 1770, 1718, 1635 cm^{-1}.

8.22 Preparation of 3-benzyl-5-propyl-6-carboxy-2-cyanoimino-5,6-dihydro-4(3H)-pyrimidinone 165

A solution of imidazolidin-5-one **154** (0.045 g, 0.14 mmol) in 2 M sodium hydroxide solution (1 ml) was stirred at room temperature for 7 min. The solution was acidified to pH 1 with concentrated hydrochloric acid and the precipitated product collected and washed with ether to give the carboxylic acid **165** (0.035 g, 82%).

M.pt: 165-167 °C.

M.S. *m/e* : 314.1388 ($C_{16}H_{18}N_4O_3$ requires 314.1379)
314 (M^+), 270 (M^+-32), 212 (M^+-102), 200 (M^+-114).

^{1}H n.m.r. (D), δ: 10.09 (s, CO_2H), 9.95 (s, CO_2H), 7.31-7.24 (m, Ph), 4.67-4.51 (m, Ph**CH_2** and **$CHCO_2H$**), 2.85-2.82 (m, CO**CH**CH_2), 1.80-1.52 (m, CH_2), 1.40-1.29 (m, CH_2), 0.90-0.80 (m, CH_3).

^{13}C n.m.r. (D), δ: 173.46, 172.89, 172.35, 162.01, 161.71, 135.65, 135.61, 128.29, 127.44, 127.33, 126.93, 115.26, 115.10, 58.25, 58.21, 46.30, 46.06, 42.30, 42.20, 29.40, 29.25, 20.19, 20.04, 13.79, 13.65.

I.R: 3412, 2176, 1767, 1718, 1633 cm^{-1}.

8.23 Preparation of 1-cyclopentyl-2-cyanoimino-4-methoxycarbonylmethyl-2-imidazolidin-5-one 181

Cyclopentylamine (0.20 g, 2.35 mmol) was added to a solution of O-phenylisourea **127** (0.70 g, 2.30 mmol) in propan-2-ol (20 ml) and the resulting solution was heated to reflux for 8 h. The solvent was removed by evaporation *in vacuo* and the residue purified by flash chromatography, eluting with ethyl acetate:cyclohexane (2:3), to give the title compound (0.25 g, 41%).

M.pt: 132-133 °C.

M.S. *m/e* : 264.1221 ($C_{12}H_{16}N_4O_3$ requires 264.1222)
264 (M^+), 237 (M^+-27), 208 (M^+-56), 197 (M^+-67).

^{1}H n.m.r. (C), δ: 8.71 (bs,NH), 4.44 (m, NCH), 4.27 (dd, NH**CH**, J_{H-H}=4.00 Hz, J_{H-H}=6.00 Hz), 3.69 (s, OCH_3), 2.93 (dd, CH'CO_2, J_{H-H}=4.00 Hz, J_{H-H}=17.60 Hz), 2.82 (dd, CH"CO_2, J_{H-H}=6.00 Hz, J_{H-H}=17.60 Hz), 2.03-2.01 (m, 2H, CH_2), 1.99-1.83 (m, 3H, CH_2), 1.54-1.52 (m, 3H, CH_2).

^{13}C n.m.r. (C), δ: 172.76, 169.23, 163.08, 115.83, 54.44, 53.01, 52.33, 34.80, 28.61, 28.34, 24.99.

I.R: 3412, 2195, 1758, 1736, 1635 cm^{-1}.

8.24 Preparation of 3-cyclopentyl-6-carboxy-2-cyanoimino-5,6-dihydro-4(3H)-pyrimidinone 187

A solution of imidazolidin-5-one **181** (0.09 g, 0.35 mmol) in 2 M sodium hydroxide (2 ml) was stirred at room temperature for 10 min. The solution was acidified to pH 1 with concentrated

hydrochloric acid and the precipitated product collected and washed with ether to give the carboxylic acid **187** (0.06 g, 68%).

M.pt: 225-227 °C.

M.S. *m/e* : 250.1066 ($C_{11}H_{14}N_4O_3$ requires 250.1071)
250 (M^+), 223 (M^+-23), 194 (M^+-56), 183 (M^+-67).

^{1}H n.m.r. (D), δ: 9.70 (s, CO_2H), 4.38-4.29 (m, CH_2CH_2CH and **CH**CO_2H), 2.83 (dd, **CH'**CH, $J_{CH'-CH}$=3.96 Hz, $J_{CH'-CH''}$=17.44 Hz), 2.73 (dd, **CH''**CH, $J_{H''-H}$=4.28 Hz, $J_{H''-H'}$=17.44 Hz), 2.01-1.97 (m, CH_2), 1.85-1.63 (m, 4H, CH_2), 1.55-1.45 (m, CH_2).

^{13}C n.m.r. (D), δ: 173.79, 170.63, 162.48, 115.56, 54.20, 51.86, 34.21, 28.17, 27.91, 24.81.

I.R: 3327, 2195, 1745, 1710, 1638 cm^{-1}.

8.25 Preparation of N-benzyl-N'-cyano-N''-(1-carboxyethylcarbamate)-guanidine 190

To a solution of imidazolidin-5-one **128** (0.47 g, 1.64 mmol) in dry THF (15 ml) under an atmosphere of argon was added sodium amide (0.38 g, 9.74 mmol) and the resulting solution was stirred at room temperature for 75 min. Ethanol (10 ml) and water (15 ml) were then added sequentially and the resulting mixture extracted with chloroform (3x20 ml). The aqueous layer was then acidified to pH 1.0 with 2M hydrochloric acid solution and extracted with chloroform. The chloroform extracts were dried ($MgSO_4$), the solvent removed by evaporation *in vacuo* and the residue redissolved in methanol (5 ml). Cyclohexane (0.5 ml) was added and the solution cooled to 4 °C for 12 h. The resulting crystalline product was filtered, washed with ether and dried to give the title compound (0.20 g, 42 %).

M.pt: 168-170 °C.

M.S. *m/e* : 289 (M^+), 226 (M^+-63), 103 (M^+-186), 91 (M^+-198).

^{1}H n.m.r. (D), δ: 9.87 (s,CO_2H), 7.31-7.24 (m, Ph), 4.63 (d, PhCH', $J_{H'-H''}$=15.72 Hz), 4.57 (d, PhCH'', $J_{H'-H''}$=15.72 Hz), 4.55 (m, NH**CH**), 3.15 (s, 1.2H, NH_2), 2.89 (dd, CH'CO_2, $J_{H'-H''}$=17.68 Hz, $J_{H'-H}$=4.32 Hz), 2.77 (dd, CH''CO_2, $J_{H''-H'}$=17.68 Hz, $J_{H''-H}$=4.64 Hz).

^{13}C n.m.r. (D), δ: 173.78, 170.70, 162.12, 135.68, 128.37, 127.38, 127.31, 115.40, 55.03, 42.33, 34.04.

I.R: 3547, 3205, 2201, 1755, 1703, 1629 cm^{-1}.

8.26 Preparation of N-cyclopentyl-N'-cyano-N"-(methyl propionate)-guanidine 244

To a solution of O-phenylisourea **63** (0.300 g, 1.21 mmol) in propan-2-ol (20 ml) was added cyclopentylamine (0.103 g, 1.21 mmol) and the resulting solution heated to reflux for 8 h. The solvent was removed by evaporation *in vacuo* and the product purified by flash chromatography, eluting with ethyl acetate:cyclohexane (3:2), to give the title compound (0.090 g, 30%) as a pale yellow oil.

M.S. *m/e* : 238.1433 ($C_{11}H_{18}N_4O_2$ requires 238.1430)
238 (M^+), 215 (M^+-23), 207 (M^+-31), 197 (M^+-41).

^1H n.m.r. (C), δ: 5.85 (bs, NH), 5.60 (bs, NH), 3.77 (m, NCH), 3.67 (s, OCH_3), 3.48 (q, NCH_2, J_{H-H}=5.89 Hz), 2.56 (t, CH_2, J_{H-H}=5.89 Hz), 2.00-1.90 (m, CH_2), 1.71-1.20 (m, 6H, CH_2).

^{13}C n.m.r. (C), δ: 173.63, 159.44, 119.40, 53.45, 52.14, 37.33, 33.83, 33.15, 23.72.

I.R.($CHCl_3$): 3455, 2164, 1718, 1586 cm^{-1}.

8.27 Preparation of N-cyclopentyl-N'cyano-N"-(t-butyl 3-methoxycarbonyl-4-phenyl-(2S)-butanoate)-guanidine 245

Cyclopentylamine (0.036 g, 0.42 mmol) was added to a stirred solution of O-phenylisourea **146** (0.155 g, 0.35 mmol) in propan-2-ol (10 ml) and the resulting solution heated to reflux for 12 h. The solvent was removed by evaporation *in vacuo* and the product purified by flash chromatography eluting with ethyl acetate:cyclohexane (1:2), to give the title compound (0.036 g, 20%) as a pale yellow oil.

M.S. *m/e* : 428.2411 ($C_{23}H_{32}N_4O_4$ requires 428.2423)
428 (M^+), 327 (M^+-101), 266 (M^+-162), 91 (M^+-337).

^1H n.m.r. (C), δ: 7.26-7.08 (m, Ph), 5.93 (d, NH, J_{H-H}=8.72 Hz), 5.47 (d, NH, J_{H-H}=6.12 Hz), 4.53 (dd, $NCHCO_2$, J_{H-H}=3.12 Hz, J_{H-NH}=8.72 Hz), 3.67-3.63 (m, CHNH), 3.58 (s, OCH_3), 3.26 (ddd, $CHCO_2Me$, J_{H-H}=3.12 Hz,

$J_{H-H'}$=7.28 Hz, $J_{H-H''}$=7.96 Hz), 2.97 (dd, CH'CH, $J_{H'-H''}$=13.76 Hz, $J_{H'-H}$=7.28 Hz), 2.76 (dd, CH"CH, $J_{H''-H'}$=13.76 Hz, $J_{H''-H}$=7.96 Hz), 2.03-1.40 (m, 8H, CH_2), 1.36 (s,$C(CH_3)_3$).

^{13}C n.m.r. (C), δ: 174.06, 172.05*, 171.81*, 169.21, 162.76*, 159.99, 137.37, 137.05*, 128.93*, 128.84, 128.71*, 128.67, 126.99*, 126.93, 117.69, 115.90*, 83.07, 57.08, 54.87, 53.45*, 52.84, 52.15*, 48.44*, 47.91, 35.20, 33.27*, 33.23, 27.77, 26.84*, 24.98*, 23.91.

*Peaks of minor diastereoisomer present.

I.R.($CHCl_3$): 3400, 2170, 1733, 1629, 1589 cm^{-1}.

8.28 Preparation of N-cyano-N'-(1-benzyloxycarbonyl-2-phenylethyl)-O-phenylisourea 246

A solution of S-phenylalanine benzylester hydrochloride (0.60 g, 2.05 mmol) and diethylamine (0.22 g, 2.76 mmol) in benzene (20 ml) was stirred for 20 min. Ether (50 ml) was added and the precipitated diethylamine hydrochloride removed by filtration. The filtrate was evaporated *in vacuo* to give S-phenylalanine benzylester (0.52 g, 99%) as a colourless oil. The oil was dissolved in propan-2-ol (20 ml) and diphenyl cyanocarbonimidate **53** (0.48g, 2.05 mmol) was added. The solution was heated to reflux for 5 h and the solvent removed by evaporation. The residual oil was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:4), to give the title compound as a colourless oil (0.75 g, 75%).

M.S. *m/e* : 399.1586 ($C_{24}H_{21}N_3O_3$ requires 399.1583)
399(M^+), 354 (M^+-45), 308 (M^+-91), 91 (M^+-308).

^{1}H n.m.r. (C), δ: 7.40-7.10 (m, 12H, Ph), 6.98-6.80 (m, 2H, Ph), 6.75-6.60 (m, 2H, Ph), 5.58 (bd, NH), 5.23 (bs, **CH'**Ph), 5.15 (bd, **CH"**Ph), 4.85-4.78 (m, NH**CH**), 3.40-3.00 (m, **CH_2**Ph).

^{13}C n.m.r. (C), δ: 170.64, 163.75, 151.36, 136.33, 135.54, 131.11, 130.32, 129.95, 129.26, 128.95, 128.17, 127.58, 127.16, 121.82, 121.20, 116.03, 68.10, 57.37, 56.46, 38.13, 37.96, 36.84, 27.17.

I.R.($CHCl_3$): 3680, 2197, 1745, 1621 cm^{-1}.

Analysis: Calculated for $C_{24}H_{21}O_3N_3$: C, 72.16; H, 5.30; N, 10.52.
Found: C, 71.43; H, 5.54; N, 10.23.

8.29 Preparation of 1-cyclopentyl-2-cyanoimino-4-benzyl-2-imidazolidin-5-one 247

To a solution of O-phenylisourea **246** (0.35 g, 0.88 mmol) in propan-2-ol (20 ml) was added cyclopentylamine (0.15 g, 1.75 mmol) and the resulting solution heated to reflux for 8 h. The solvent was removed by evaporation *in vacuo* and the resulting oil purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:1), to give the title compound (0.17 g, 70%).

M.pt: 152-154 °C.

M.S. *m/e*: 282.1489 ($C_{16}H_{18}N_4O$ requires 282.1481)
282 (M^+), 255 (M^+-27), 215 (M^+-67), 91 (M^+-191).

^{1}H n.m.r. (C), δ: 8.93 (bs, NH), 7.25-7.15 (m, Ph), 4.28 (m, **CH**CH_2Ph, $J_{H-H'}$=4.0 Hz, $J_{H-H''}$=4.4 Hz), 4.20 (qn, **CH**N, J_{H-H}=8.4 Hz), 3.11 (dd, PhCH', $J_{H'-H''}$=14.4 Hz, $J_{H'-H}$=4.0 Hz), 3.09 (dd, PhCH'', $J_{H''-H'}$=14.4 Hz, $J_{H''-H}$=4.4 Hz), 1.73-1.35 (m, 8H, CH_2).

^{13}C n.m.r. (C), δ: 172.93, 162.62, 133.27, 129.86, 128.42, 127.44, 115.90, 58.48, 36.57, 28.37, 28.07, 24.80.

I.R.($CHCl_3$): 3414, 2189, 1755, 1632 cm^{-1}.

8.30 Preparation of 1-cyclopentyl-2-cyanoimino-4-benzyloxycarbonylmethyl-2-imidazolidin-5-one 248 and N-cyclopentyl-N'-cyano-N''-(1-t-butyloxycarbonyl-2-benzoxycarbonylethyl)-guanidine 249

A solution of O-phenylisourea **138** (0.22 g, 0.52 mmol) and cyclopentylamine (0.05 g, 0.59 mmol) in propan-2-ol (20 ml) was heated to reflux for 8 h. The solvent was removed by evaporation *in vacuo* and the resulting oil was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (2:3), to give the imidazolidin-5-one **248** (0.10 g, 57%), and the guanidine **249** (0.05 g, 23%) as an oil.

2-imidazolidin-5-one 248.

M.pt: 110-112 °C.

M.S. *m/e*: 340.1535 ($C_{18}H_{20}N_4O_3$ requires 340.1535)
340 (M^+), 273 (M^+-67), 183 (M^+-157), 91 (M^+-249).

^{1}H n.m.r. (C), δ: 7.35-7.24 (m, Ph), 5.15 (d, CH'Ph, $J_{H'-H''}$=12.0 Hz), 5.10 (d, CH"Ph, $J_{H''-H'}$=12.0 Hz), 4.45 (qn, CHN, J_{H-H}=8.4 Hz), 4.32-4.29 (m, CH_2**CH**N), 3.00 (dd, PhCH', $J_{H'-H''}$=17.44 Hz, $J_{H'-H}$=3.9 Hz), 2.86 (dd, PhCH", $J_{H''-H'}$=17.44 Hz, $J_{H''-H}$=6.4 Hz), 2.03-1.99 (m, 2H, CH_2), 1.87-1.79 (m, 4H, CH_2), 1.55-1.45 (m, 2H, CH_2).

^{13}C n.m.r. (C), δ: 172.63, 168.87, 162.96, 134.98, 128.62, 128.49, 128.40, 115.77, 67.29, 54.49, 53.05, 35.12, 28.35, 24.99.

I.R. ($CHCl_3$): 3412, 2189, 1755, 1733, 1635 cm^{-1}.

Guanidine 249

M.S. *m/e* : 414.2278 ($C_{22}H_{30}N_4O_4$ requires 414.2267)
414 (M^+), 358 (M^+-56), 341 (M^+-73), 91 (M^+-323).

^{1}H n.m.r. (C), δ: 7.34-7.24 (m, Ph), 5.73 (bd, NH), 5.35 (bd, NH), 5.14 (d, PhCH', $J_{H'-H''}$=12.4 Hz), 5.04 (d, PhCH", $J_{H''-H'}$=12.4 Hz) 4.61-4.57 (m, NHCH), 3.63 (qn, NHCH, J_{H-H}=6.0 Hz), 2.97 (dd, CH'Ph, $J_{H'-H''}$=16.4 Hz, $J_{H'-H}$=2.0 Hz), 2.96 (dd, CH"Ph, $J_{H''-H'}$=16.4 Hz, $J_{H''-H}$=2.4 Hz), 2.08-1.85 (m, 2H, CH_2), 1.79-1.49 (m, 6H, CH_2), 1.40 (s, $C(CH_3)_3$).

^{13}C n.m.r.(C), δ: 170.82, 170.77, 169.17, 135.22, 128.59, 128.49, 128.40, 118.90, 83.27, 66.85, 53.40, 51.04, 36.42, 33.29, 27.76, 23.74.

I.R. ($CHCl_3$): 3400, 2170, 1736, 1589 cm^{-1}.

8.31 Preparation of N-cyano-N'-(4-methoxycarbonylcyclopent-2-enyl) O-phenylisourea 254

Triethylamine (0.65 g, 6.47 mmol) was added to a stirred suspension of cyclopentylamine hydrochloride **250** (1.10 g, 6.41 mmol) in propan-2-ol (50 ml). Diphenyl cyanocarbonimidate **53** (1.54 g, 6.47 mmol) was added and the resulting solution was stirred at room temperature for 8 h. The solvent was removed by evaporation *in vacuo* and the product purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:1), to give the title compound as a white solid (1.62 g, 89%).

M.S. *m/e* : 285.1127 ($C_{15}H_{15}N_3O_3$ requires 285.1113)
285 (M^+), 226 (M^+-59), 125 (M^+-160), 94 (M^+-191).

^{1}H n.m.r. (C), δ: 7.45-7.39 (m, 2H, Ph), 7.36-7.30 (m, 1H, Ph), 7.29-7.10 (m, 2H, Ph), 6.62 (bd, NH), 6.08-5.90 (m, CH=CH), 5.08-4.96 (m, CHN), 3.79 (bs, OCH_3), 3.57 (bs, OCH_3)*, 3.61-3.46 (m, $CHCO_2$), 2.60-2.52 (m, CH_2) 2.42-2.33 (m, CH_2)*, 2.26-2.16 (m, CH_2), 1.91-1.88 (m, CH_2)*.

^{13}C n.m.r. (C), δ: 173.74, 162.60, 150.90, 134.09, 133.51*, 132.92*, 132.49, 130.44*, 129.59, 127.35*, 126.71, 121.40, 114.97, 57.92, 52.81, 52.43, 49.59, 49.18*, 34.22, 33.94*.

*Peaks for minor stereoisomer present

I.R.($CHCl_3$): 3052, 2191, 1732, 1718, 1615 cm^{-1}.

8.32 Preparation of N-cyano-N'-(3-hydroxymethylcyclopentyl) O-phenylisourea 255

To a stirred suspension of cyclopentylamine **253** (0.63 g, 4.19 mmol) in propan-2-ol (25 ml) was added triethylamine (0.82 g, 8.11 mmol) and diphenyl cyanocarbonimidate **53** (0.99 g, 4.19 mmol) and the resulting solution was heated to reflux for 8 h. The solvent was removed by evaporation *in vacuo* and the residue purified by flash chromatography, eluting with ethyl acetate:cyclohexane (3:2), to give the title compound as a white solid (0.91 g, 84%).

M.pt: 82-84 °C.

M.S. *m/e* : 259.1321 ($C_{14}H_{17}N_3O_2$ requires 259.1321)
259 (M^+), 225 (M^+-34), 118 (M^+-114), 94 (M^+-165).

^{1}H n.m.r. (C), δ: 8.69 (bd, NH), 7.40-7.37 (m, 2H, Ph), 7.28-7.24 (m, 1H, Ph), 7.09-7.07 (m, 2H, Ph), 4.39 (bs, OH), 4.28 (bs, CHN), 3.64-3.57 (m, CH_2O), 2.40-2.20 (m, **CH**CHO), 2.16-2.00 (m, **CH**CH_2O), 1.90-1.75 (m, 6H, CH_2).

^{13}C n.m.r. (C), δ: 162.63, 151.16, 130.16*, 129.35, 126.70*, 126.24, 121.43, 115.40, 64.13*, 63.86, 54.08, 37.94, 35.42, 34.08, 25.06.

I.R.($CHCl_3$): 3393, 2183, 1621, 1428 cm^{-1}.

8.33 Preparation of N-cyano-N'-(3-methoxycarbonylcyclopentyl) O-phenylisourea 256

To a stirred solution of O-phenylisourea **254** (0.25 g, 0.87 mmol) in degassed ethanol (10 ml) was added palladium on charcoal (10%, 0.01 g) and the resulting suspension was stirred under an atmosphere of hydrogen (1 atm) for 8 h. The reaction mixture was diluted with ethanol (20 ml), filtered through celite, and the solvent removed by evaporation *in vacuo* to give the title compound as a white solid (0.24 g, 95%).

M.S. *m/e* : 288.1361 ($C_{15}H_{18}N_3O_3$ requires 288.1348)
288 (MH^+), 256 (M^+-31), 127 (M^+-160), 67 (M^+-220).

^{1}H n.m.r. (C), δ: 7.47-7.38 (m, 2H, Ph), 7.36-7.25 (m, 1H, Ph), 7.14-7.08 (m, 2H, Ph), 4.44-4.32 (m, NCH), 3.76 (s, OCH_3), 3.54 (s, OCH_3)*, 3.01-2.85 (m, $CHCO_2$), 2.32-1.65 (m, 6H, CH_2).

^{13}C n.m.r. (C), δ: 176.83, 163.09, 150.99, 130.43*, 129.58, 127.24*, 126.65, 121.43, 121.35*, 115.15, 114.90*, 54.98*, 54.47, 52.52, 52.49*, 41.85, 41.48*, 35.90, 35.32*, 33.37, 33.28*, 28.65*, 28.15.

*Peaks for minor stereoisomer present

I.R.($CHCl_3$): 3286, 2191, 1722, 1615 cm^{-1}.

8.34 Preparation of N-cyano-N'-(4-hydroxymethylcyclopent-2-enyl) O-phenylisourea 257

To a solution of O-phenylisourea **254** (0.80 g, 2.79 mmol) in dry THF at 0 °C under an atmosphere of N_2 was added lithium triethylborohydride (8.37 ml, 1M, 8.37 mmol). The resulting solution was stirred at 0 °C for 3 h. The solvent was removed by evaporation *in vacuo* and the residue was dissolved in methanol (15 ml), and treated with 1M HCl at 0 °C to destroy any remaining lithium triethylborohydride. The methanol and resulting trichloroborane were removed by evaporation *in vacuo* and the residue was purified by flash chromatography, eluting with chloroform:methanol (33:1,) to give the title compound as a white solid (0.47 g, 66%).

M.S. *m/e* : 259 (M^+), 241 (M^+-18), 165 (M^+-94), 94 (M^+-165).

^{1}H n.m.r. (C), δ: 7.90 (bd, NH), 7.40-7.34 (m, 2H, Ph), 7.27-7.23 (m, 1H, Ph), 7.10-7.07 (m, 2H, Ph), 5.91-5.71 (m, CH=CH), 4.89 (bt, 0.50H, CHN), 4.81 (bt, 0.15H, CHN), 4.65 (bt, 0.35H, CHN), 4.18 (bs, 0.55H, OH), 3.94 (bs,

0.45H, OH), 3.63-3.35 (m, CH_2O), 2.90-2.85 (m, 0.50H, **CH**CH_2O), 2.84-2.79 (m, 0.25H, **CH**CH_2O), 2.78-2.69 (m, 0.25H, **CH**CH_2O), 2.48-2.28 (m, CH'), 1.78 (bd, 0.50H, CH"), 1.63 (bd, 0.35H, CH"), 1.50 (bd, 0.15H, CH").

^{13}C n.m.r. (C), δ: 162.77*, 162.07, 151.00, 136.70, 136.19*, 130.88*, 130.75, 130.21*, 129.33, 127.08*, 126.28*, 121.35, 121.23*, 115.85*, 115.24, 61.95*, 61.65, 57.50, 56.97, 56.94, 56.27*, 46.00, 45.77*, 34.15, 33.59*.

*Peaks for minor stereoisomers present.

I.R.($CHCl_3$): 3388, 2183, 1617, 1430 cm^{-1}.

8.35 Preparation of 2-cyanoimino-3-(3'-methoxycarbonylcyclopentyl)5,6-dihydro-4(3H)-pyrimidinone 259

To a solution of O-phenylisourea **256** (0.25 g, 0.87 mmol) and β-alanine methyl ester **62** (0.09 g, 0.87 mmol) in dry dioxan (10 ml) under an atmosphere of argon, was added sodium hydride (0.021 g, 0.87 mmol) and the resulting suspension was heated to reflux for 12 h. Water (10 ml) was added followed by 2M HCl solution to bring the pH to 7.0 and the reaction mixture was extracted with chloroform (3x10 ml), dried ($MgSO_4$), and the solvent removed by evaporation *in vacuo*. The residue was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (2:1), to give the title compound as an oil (0.02 g, 8%).

M.S. *m/e* : 264 (M^+), 233 (M^+-31), 205 (M^+-59), 139 (M^+-125).

^{1}H n.m.r. (C), δ: 7.81 (bs, NH), 5.08 (m, CHN), 3.72-3.68 (m, $CHCO_2$), 3.70 (s, OCH_3), 3.50 (dt, NH**CH_2**, J_{H-H}=6.87 Hz, J_{H-NH}=3.21 Hz), 2.74 (t, CH_2CO, J_{H-H}=6.87 Hz), 2.50-2.01 (m, 6H, CH_2).

^{13}C n.m.r. (C), δ: 175.09, 167.71, 159.97, 116.05, 54.43, 51.87, 43.30, 35.84, 32.05, 29.68, 27.93, 27.79.

I.R.($CHCl_3$): 3145, 2178, 1792, 1718, 1601 cm^{-1}.

8.36 Preparation of N-(4-hydroxymethylcyclopent-2-enyl)-N'-cyano-N"-(methyl propionate) guanidine 260

To a solution of O-phenylisourea **257** (0.11 g, 0.43 mmol) and β-alanine-methyl ester hydrochloride **62** (0.078 g, 0.56 mmol) in dry THF (10 ml) was added sodium hydride (0.032 g,

1.07 mmol) and the resulting suspension was heated to 40 °C for 24 h. Water (10 ml) was added and the pH brought to 7.0 with 2M HCl solution. The reaction mixture was extracted with chloroform (3x10 ml), dried ($MgSO_4$), and the solvent removed by evaporation *in vacuo*. The residue was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:2), to give the title compound as a pale yellow oil (0.02 g, 15%).

M.S. *m/e* : 266.1407 ($C_{12}H_{18}N_4O_3$ requires 266.1379)
266 (M^+), 249 (M^+-17), 236 (M^+-30), 162 (M^+-104).

^1H n.m.r. (C), δ: 6.37 (bd, NH, J_{NH-H}=7.92 Hz), 5.91-5.76 (m, 2H, CH=CH), 4.60(bs, CHN), 3.71 (dd, CH'OH, $J_{H'-H''}$=10.56 Hz, $J_{H'-H}$=3.08 Hz), 3.70 (s, OCH_3)), 3.62 (dd, CH"OH, $J_{H''-H'}$=10.56 Hz, $J_{H''-H}$=3.68 Hz), 3.47 (dt, NH**CH_2**, J_{H-H}=5.96 Hz, J_{H-H}=6.12 Hz), 2.89-2.87 (m, **CH**CH_2O), 2.62-2.58 (m, CH_2CO_2), 2.49-2.41 (m, CH'), 1.61 (d, CH", J_{H-H}=14.00 Hz).

^{13}C n.m.r. (C), δ: 173.14, 158.61, 136.17, 131.68, 118.58, 63.18, 56.96, 52.10, 46.48, 37.27, 33.70.

I.R.($CHCl_3$): 3399, 2171, 1722, 1588 cm^{-1}.

8.37 Preparation of 1-(3-methoxycarbonyl-yclopentyl)-2-cyanoimino-4-benzyl-2-imidazolidin-5-one 261

A solution of O-phenylisourea **246** (0.90 g, 2.25 mmol), 3-carboxymethyl-cyclopentylamine hydrochloride **251** (0.44 g, 2.45 mmol) and triethylamine (0.29 g, 2.87 mmol) in propan-2-ol (40 ml) was heated to reflux for 48 h. The solvent was removed by evaporation *in vacuo* and the resulting oil purified by flash chromatography, eluting with ethyl acetate:cyclohexane (2:3), to give the title compound (0.20 g, 26%) as a pale yellow oil.

M.S. *m/e* : 340.1539 ($C_{18}H_{20}N_4O_3$ requires 340.1535)
340 (M^+), 309 (M^+-31), 281 (M^+-59), 91 (M^+-249).

^1H n.m.r. (C), δ: 9.06 (bd, NH, J_{H-H}=2.8 Hz), 7.33-7.22 (m, Ph), 4.38 (m, NH**CH**CH_2, J_{H-H}=4.24 Hz, J_{H-H}=4.48 Hz), 4.24 (m, CHN), 3.71 (s, OCH_3), 3.69 (s,OCH_3), 3.18 (dd, CH'Ph, $J_{H'-H''}$=12.0 Hz, $J_{H'-H}$=2.0 Hz), 3.16 (dd, CH"Ph, $J_{H''-H'}$=12.0 Hz, $J_{H''-H}$=2.4 Hz), 2.67 (m, **CH**CO_2Me), 2.22-2.04 (m, 2H,CH_2), 1.98-1.75 (m, 3H, CH_2), 1.70-1.52 (m, CH_2).

^{13}C n.m.r. (C), δ: 174.86, 172.71, 162.29, 133.16, 129.85, 128.46, 127.52, 115.62, 58.92, 51.87, 51.72, 51.60, 42.42, 36.59, 36.52, 31.42, 31.22, 27.35, 27.11, 26.93.

I.R.($CHCl_3$): 3149, 2195, 1758, 1727, 1635 cm^{-1}.

8.38 Preparation of 1-(3'-hydroxymethylcyclopentyl)-2-cyanoimino-4-benzyl-2-imidazolidin-5-one 262

A solution of O-phenylisourea **246** (0.52 g, 1.30 mmol), 3-hydroxymethylcyclopentylamine hydrochloride **253** (0.12 g, 1.35 mmol) and triethylamine (0.15 g, 1.50 mmol) in propan-2-ol (20 ml) was heated to reflux for 48 h. The solvent was removed by evaporation *in vacuo* and the resulting oil was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:3), to give the title compound (0.10 g, 25%) as a pale yellow oil.

M.S. *m/e* : 313.1666 ($C_{17}H_{21}N_4O_2$ requires 313.1664)
312 (M^+), 241 (M^+-71), 215 (M^+-97), 91 (M^+-221).

^1H n.m.r. (C), δ: 8.50 (bd, NH), 7.25-7.08 (m, Ph), 4.36 (t, NH**CH**CH_2, J_{H-H}=4.54 Hz), 4.26-4.21 (m, CHNH), 3.56 (dd, CH'OH, $J_{H'-H''}$=5.64 Hz, $J_{H'-H}$=1.60 Hz), 3.54 (dd, CH"OH, $J_{H''-H'}$=5.64 Hz, $J_{H''-H}$=1.56 Hz), 3.20 (dd, CH'Ph, $J_{H'-H''}$=14.1 Hz, $J_{H'-H}$=4.4 Hz), 3.10 (dd, CH"Ph, $J_{H''-H'}$=14.1 Hz, $J_{H''-H}$=2.8 Hz), 2.30-1.95 (m, 2H, CH_2), 1.75-1.50 (m, 5H, CH_2).

^{13}C n.m.r. (C), δ: 172.83, 162.40, 133.33, 129.74, 128.60, 127.59, 115.66, 66.60, 58.99, 52.38, 40.57, 36.78, 27.33, 27.05, 26.88.

I.R.($CHCl_3$): 3412, 2189, 1751, 1702, 1629 cm^{-1}.

8.39 Preparation of 1-(4'-hydroxymethylcyclopent-2'-enyl)-2-cyanoimino-4-benzyl-2-imidazolidin-5-one 263

A solution of O-phenylisourea **246** (0.55 g, 1.38 mmol), 4-hydoxymethylcyclopent-2-enylamine hydrochloride **252** (0.24 g, 1.61 mmol) and triethylamine (0.20 g, 1.98 mmol) in propan-2-ol (20 ml) was heated to reflux for 72 h. The solvent was removed by evaporation *in vacuo* and the resulting oil purified by flash chromatography, eluting with ethyl acetate:cyclohexane (4:1), to give the title compound (0.05 g, 12%).

M.pt: 145-147 °C.

M.S. *m/e* : 311.1519 ($C_{17}H_{19}N_4O_2$ requires 311.1508)
311 (MH^+), 310 (M^+), 280 (M^+-30), 91 (M^+-219).

^1H n.m.r. (C), δ: 9.07 (s, NH), 7.34-7.10 (m, Ph), 5.86-5.84 (m, **CH**CHNH), 5.26-5.24 (m, CH_2CH**CH**), 5.03-4.98 (m, CHN), 4.39 dd, **CH**CH_2Ph, J_{H-H}=4.92 Hz, J_{H-H}=4.48 Hz), 3.73 (dd, CH'OH, $J_{H'-H''}$=10.60 Hz, $J_{H'-H}$=4.60 Hz), 3,63 (dd, CH"OH, $J_{H''-H'}$=10.60 Hz, $J_{H''-H}$=4.28 Hz), 3.17 (dd, CH'Ph, $J_{H'-H''}$=14 10 Hz, $J_{H'-H}$=4.48 Hz), 3.11 (dd, CH"Ph, $J_{H''-H'}$=14.10 Hz, $J_{H''-H}$=4.92 Hz), 2.93-2.88 (m, **CH**CH_2OH), 2.27-2.19 (m, CH'), 1.65 (bs, OH), 1.56-1.49 (m, CH").

^{13}C n.m.r. (C), δ: 172.98, 162.33, 135.79, 133.20, 129.90, 129.45, 128.64, 127.66, 115.26, 64.99, 58.98, 57.69, 47.30, 36.70, 29.20.

I.R.($CHCl_3$): 3942, 2189, 1752, 1727, 1635 cm^{-1}.

8.40 Preparation of 1-(3'-methoxycarbonylcyclopentyl)-2-cyanoimino-4-methyloxycarbonyl-methyl-2-imidazolidin-5-one 264

To a solution of 13-methoxycarbonylcyclopentylamine hydrochloride **251** (0.20 g, 1.14 mmol) and O-phenylisourea **127** (0.34 g, 1.11 mmol) in propan-2-ol (20 ml) was added triethylamine (0.14 g, 1.38 mmol) and the resulting solution was heated to reflux for 48 h. The solvent was removed by evaporation *in vacuo* and the residue was purified by flash chromatography, eluting with chloroform:methanol (99:1), to give the title compound (0.05 g, 13.6 %) as a pale yellow oil.

M.S. *m/e* : 323.1369 ($C_{14}H_{17}N_4O_5$ requires 323.1355)
322 (M^+), 291 (M^+-31), 263 (M^+-59), 165 (M^+-167).

^1H n.m.r. (C), δ: 8.25 (bs, NH), 4.49 (m, NCH), 4.30 (m, NH**CH**), 3.71 (s, OCH_3), 3.68 (s, OCH_3), 2.96 (dd, CH'CO_2, J_{H-H}=3.76 Hz, J_{H-H}=17.56 Hz), 2.82 (dd, CH"CO_2, J_{H-H}=6.44 Hz, J_{H-H}=17.56 Hz), 2.80-2.74 (m, $CHCO_2$), 2.51-2.41 (m, 1H, CH_2), 2.27-2.09 (m, 3H, CH_2), 1.92-1.82 (m, 2h, CH_2).

^{13}C n.m.r. (C), δ: 174.92, 172.40, 169.50, 162.65, 117.98, 54.49, 52.38, 52.35, 51.95, 42.76, 42.67, 35.01, 31.85, 31.62, 27.65, 27.58, 27.30.

I.R.($CHCl_3$): 3418, 2195, 1758, 1730, 1635 cm^{-1}.

8.41 Preparation of N-benzyl-N-methyl-N'-cyano-N''-(1-benzyloxycarbonyl-2-phenylethyl) guanidine 284

N-methyl-benzylamine (10 ml) was added to O-phenylisourea **246** (0.30 g, 7.51 mmol) and the resulting solution stirred at room temperature for 8 h. Chloroform (30 ml) was added and the chloroform extracted with 5% citric acid solution (2x15 ml), dried ($MgSO_4$), and the solvent removed by evaporation *in vacuo*. The residue was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (2:1), to give the title compound (0.18 g, 56%).

M.S. *m/e* : 426.2087 ($C_{26}H_{26}N_4O_2$ requires 426.4916)
426 (M^+), 335 (M^+-91), 291 (M^+-135), 91 (M^+-335).

^1H n.m.r (C), δ: 7.39-7.08 (m, 13H, Ph), 6.84 (d, 2H, Ph), 5.20 (d, PhCH', $J_{H'-H''}$=11.90 Hz), 5.21-5.18 (m, NH**CH**), 5.12 (d, PhCH'', $J_{H''-H'}$=11.90 Hz), 5.08 (d, NH, J_{NH-H}=7.87 Hz), 4.49 (s, $PhCH_2$), 3.23 (dd, PhCH', $J_{H'-H''}$=14.04 Hz, $J_{H'-H}$=5.89 Hz), 3.18 (dd, PhCH'', $J_{H''-H'}$=14.04 Hz, $J_{H''-H}$=4.93 Hz), 2.88 (s, NCH_3).

^{13}C n.m.r. (C), δ: 171.25, 158.23, 135.14, 134.75, 134.64, 129.18, 128.98, 128.70, 128.66, 128.59, 128.01, 127.22, 127.02, 116.88, 67.75, 55.61, 54.39, 37.81, 36.51.

I.R: 3399, 2171, 1735, 1668, 1638 cm^{-1}.

8.42 Preparation of 2-(N-methylbenzylamine)-4-benzyl--imidazolidin-5-one 287

To a solution of guanidine **284** (0.15 g, 0.35 mmol) in degassed ethanol (10 ml) was added Pd/C (0.10 g, 5%) and the resulting suspension was stirred under an atmosphere of hydrogen (1 atm) for 48 h. The solution was filtered through celite, the solvent was removed by evaporation *in vacuo* and the residue was purified by flash chromatography, eluting with chloroform:methanol, (12.5:1) to give the title compound (0.08 g, 78%).

M.pt: 172-174 °C.

M.S. *m/e* : 293 (M^+), 278 (M^+-15), 202 (M^+-91), 91 (M^+-202).

^1H n.m.r. (D), δ: 8.28 (bs, 0.3H, NH), 8.14 (bs, 0.7H, NH), 7.25-7.15 (m, 8H, Ph), 7.00-6.80 (m, 2H, Ph), 4.81 (bd, 0.7H, PhCH'), 4.65 (bd, 0.3H, PhCH'), 4.30

(bd, PhCH"), 4.24 (t, NH**CH**, J_{H-H}=4.83 Hz), 3.38-2.98 (m, 1H, PhCH'), 2.92-2.88 (m, 4H, PhCH" and NCH_3).

^{1}H n.m.r. (D, 140°C), δ: 7.68 (bs, NH), 7.30-7.16 (m, 8H, Ph), 7.07 (d, 2H, Ph), 4.57 (d, PhCH', $J_{H'-H"}$=15.37 Hz), 4.50 (d, PhCH", $J_{H"-H'}$=15.37 Hz), 4.06 (dd, NH**CH**, $J_{H-H"}$=5.97 Hz, J_{H-NH}=4.78 Hz), 3.03 (dd, PhCH', $J_{H'-H"}$=14.11 Hz, $J_{H'-H}$=4.78 Hz), 2.86 (dd, PhCH", $J_{H"-H'}$=14.11 Hz, $J_{H"-H}$=5.97 Hz), 2.84 (s, NCH_3).

^{13}C n.m.r. (D), δ: 187.96, 171.58, 137.26, 137.02, 130.14, 128.92, 128.30, 127.54, 126.71, 62.34, 53.10, 51.50, 37.23, 33.83.

I.R.($CHCl_3$): 3500, 2925, 1715, 1595, 1578, 1458 cm^{-1}.

Analysis: Calculated for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.25; N, 14.32.
Found: C, 73.31; H, 6.58; N, 14.38.

8.43 Alternative preparation of 287

To potassium t-butoxide (0.55 g, 4.95 mmol) in dry ether (10 ml) cooled to 0 °C was added water (0.02 g, 1.28 mmol) and the suspension was stirred for 5 min. Guanidine **291** (0.20 g, 0.57 mmol) was added and the suspension stirred at room temperature for 2 h. Iced water (30 ml) was added to dissolve all the solid, the solution was acidified to pH 1.0 with 2M hydrochloric acid solution, extracted with ether (3x20 ml), and dried ($MgSO_4$). The solvent was removed by evaporation *in vacuo* to give a white foam. This was dissolved in ethyl acetate:methanol (19:1, 5 ml) and cooled to 4 °C for 6 h. The white crystalline product was filtered, washed with ether and dried to give the title compound (0.07 g, 44%), that was identical in all respects to imidazolidin-5-one **287** .

8.44 Preparation of N-cyano-N'-(1-carboxy-2-phenylethyl)-O-phenylisourea 288

To a solution of O-phenylisourea **246** (0.70 g, 1.75 mmol) in degassed ethanol (30 ml) was added Pd/C (10%, 0.10 g) and the resulting suspension stirred under an atmosphere of hydrogen (1 atm) for 8 h. The Pd/C was removed by filtration through celite and the solvent was removed by evaporation *in vacuo*. The residue was purified by flash chromatography, eluting with chloroform:methanol (9:1), to give the title compound (0.40 g, 74%).

M.S. *m.e* : 264.1146 (M^+-CO_2H, $C_{16}H_{14}N_3O$ requires 264.2897)
264 (M^+-45), 215 (M^+-94), 149 (M^+-160), 94 (M^+-215).

^{1}H n.m.r. (M), δ: 7.35-7.17 (m, Ph), 6.90 (d, 1H, Ph), 6.62 (d, 1H, Ph), 4.63 (m, 0.5 H, $CHCO_2$), 4.49 (m, 0.5 H, $CHCO_2$), 3.47-3.39 (m, CH'Ph), 3.06-3.00 (m, CH"Ph).

^{13}C n.m.r. (M), δ: 177.77, 164.10, 161.03, 152.49, 152.38, 139.26, 138.67, 131.41, 130.73, 130.56, 130.32, 129.67, 129.60, 129.47, 127.82, 127.73, 127.49, 127.43, 122.48, 121.34, 116.28, 115.90, 60.26, 59.80, 40.35, 38.01.

I.R: 3627, 2189, 1715, 1614 cm^{-1}.

8.45 Preparation of benzylamine salt of O-phenylisourea 288

Benzylamine (10 ml) was added to O-phenylisourea **288** (0.50 g, 1.62 mmol) and the resulting solution stirred at room temperature for 12 h. Chloroform (20 ml) was added and the reaction mixture was extracted with 5% citric acid solution (2x10 ml). The organic layer was dried ($MgSO_4$) and reduced to half its original volume by evaporation *in vacuo*. On cooling to 4 °C for 12 h the product **289** crystallised from solution (0.50 g, 74%).

^{1}H n.m.r. (D), δ: 7.80 (bs, NH), 7.44-7.04 (m, 15H, Ph), 4.30 (dd, PhCH', $J_{H'-H"}$=15.84 Hz, $J_{H'-H}$=6.18 Hz), 4.28 (dd, PhCH", $J_{H"-H'}$=15.84 Hz, $J_{H"-H}$=5.80 Hz), 4.10 (m, NH**CH**), 3.06 (dd, PhCH', $J_{H'-H"}$=13.57 Hz, $J_{H'-H}$=5.18 Hz), 3.00 (dd, PhCH", $J_{H"-H'}$=13.57 Hz, $J_{H"-H}$=5.40 Hz).

^{13}C n.m.r. (D), δ: 172.01, 158.54, 138.50, 138.07, 135.74, 129.58, 128.59, 128.50, 128.27, 128.01, 127.90, 126.98, 126.82, 118.05, 56.47, 56.44, 44.25, 42.53, 39.09, 38.88.

I.R: 3364, 3229, 2170, 1602, 1553 cm^{-1}.

8.46 Reaction of benzylamine salt of O-phenylisourea 288 with benzylamine

Benzylamine (10 ml) was added to the benzylamine salt **289** (0.50 g, 1.20 mmol) and the resulting solution was heated to 100 °C for 48 h. Chloroform (30 ml) was added and the mixture was extracted with 5% citric acid solution (3x20 ml). The chloroform layer was dried ($MgSO_4$), the solvent removed by evaporation *in vacuo* and the residue purified by flash chromatography, eluting with chloroform:methanol (9:1), to give **290** (0.31 g, 63%).

M.S. *m/e* : 412 (M^+), 320 (M^+-92), 277 (M^+-135), 91 (M^+-321).

^{1}H n.m.r. (C), δ: 7.32-7.21 (m, 3H, Ph), 7.19-7.12 (m, 10H, Ph), 6.94-6.92 (m, 2H, Ph), 4.60 (d, PhCH', $J_{H'-H''}$=14.88 Hz), 4.52 (d, PhCH'', $J_{H''-H'}$=14.88 Hz), 4.36 (dd, N**CH**, $J_{H-H'}$=4.56 Hz, $J_{H-H''}$=6.50 Hz), 4.30 (s, Ph**CH$_2$**), 3.22 (dd, PhCH', $J_{H'-H''}$=13.68 Hz, $J_{H'-H}$=4,56 Hz), 2.98 (dd, PhCH'', $J_{H''-H'}$=13.68 Hz, $J_{H''-H}$=6.50 Hz).

^{13}C n.m.r. (C), δ: 174.80, 160.01, 159.35, 137.80, 136.80, 136.63, 129.72, 128.75, 128.27, 128.06, 127.60, 127.35, 127.09, 126.96, 126.49, 65.32, 45.23, 42.70, 37.51.

I.R: 3437, 1755, 1712, 1620, 1586 cm^{-1}.

8.47 Preparation of N-cyano-N'-(1-benzyloxycarbonylpropyl)-O-phenylisourea 293

To diphenyl cyanocarbonimidate **53** (1.89 g, 7.98 mmol) in propan-2-ol (40 ml) was added 2-aminobutyric acid benzyl ester **292** (1.54 g, 7.98 mmol) and the resulting solution was stirred at room temperature for 3 h. The solvent was reduced to half by evaporation *in vacuo*, and the reaction mixture was cooled to 4 °C for 2 h. The product that crystallised from solution was filtered, washed with ether and dried to give the title compound (2.10 g, 78%).

M.pt: 95-96 °C.

M.S. *m/e* : 337.1437 ($C_{19}H_{19}N_3O_3$ requires 337.1426)
337 (M^+), 214 (M^+-123), 145 (M^+-192), 91 (M^+-246).

^{1}H n.m.r. (C, -20 °C), δ: 7.47-7.08 (m, 8H, Ph), 6.90 (d, 2H, Ph), 5.21 (s, Ph**CH$_2$**), 5.15 (d, PhCH', $J_{H'-H''}$=11.60 Hz)*, 5.10 (d, PhCH'', $J_{H'-H''}$=11.60 Hz)*, 4.50-4.23 (m, NH**CH**), 2.04-1.85 (m, 1.5H, **CH$_2$**CH$_3$), 1.73-1.69 (m, 0.5H, **CH$_2$**CH$_3$)*, 1.02 (t, CH_3, J_{H-H}=7.20 Hz), 0.75 (t, CH_3, J_{H-H}=7.20 Hz)*.

^{13}C n.m.r. (C, -20 °C), δ:170.75*, 170.59, 163.19, 161.24*, 150.39, 149.49*, 134.69, 134.35, 130.71, 129.95, 129.49, 128.69, 128.58, 128.48, 128.30, 127.85, 127.52, 127.46, 126.42, 121.99, 120.96, 120.58, 114.49, 114.14, 67.70*, 67.43, 56.78, 56.23*, 24.75, 24.35*, 10.15, 9.01*.

*Peaks of minor stereoisomer present.

I.R: 3180, 3045, 2195, 1733, 1635 cm^{-1}.

8.48 Preparation of N-benzyl-N-methyl-N'-cyano-N''-(1-carboxybenzylpropyl) guanidine 294

N-methyl benzylamine (7 ml) was added to O-phenylisourea **293** (0.63 g, 1.87 mmol) and the resulting solution stirred at room temperature for 12 h. Chloroform (30 ml) was added and the reaction mixture extracted with 5% citric acid solution (2x20 ml). The chloroform layer was dried ($MgSO_4$), the solvent removed by evaporation *in vacuo*, and the product purified by flash chromatography, eluting with ethyl acetate:cyclohexane (2:1), to give the title compound (0.41 g, 60%).

M.S. *m/e* : 364 (M^+), 273 (M^+-91), 229 (M^+-135), 91 (M^+-273).

^1H n.m.r. (C), δ: 7.37-7.29 (m, 8H, Ph), 7.21-7.20 (m, 2H, Ph), 5.31 (bd, NH, J_{NH-H}=7.68 Hz), 5.18 (d, PhCH', $J_{H'-H''}$=12.20 Hz), 5.13 (d, PhCH'', $J_{H''-H'}$=12.20 Hz), 4.87 (dt, NH**CH**, J_{H-NH}=7.68 Hz, J_{H-H}=11.30 Hz), 4.64 (d, PhCH', $J_{H'-H''}$=16.00 Hz), 4.57 (d, PhCH'', $J_{H''-H'}$=16.00 Hz), 3.05 (s, NCH_3), 2.02-1.91 (m, **CH'**CH_3), 1.84-1.74 (m, **CH''**CH_3), 0.78 (t, CH_3, J_{H-H}=7.44 Hz).

^{13}C n.m.r. (C), δ: 172.13, 158.41, 135.26, 134.88, 129.02, 128.60, 128.54, 128.25, 128.05, 127.04, 116.82, 67.51, 56.05, 54.58, 36.81, 25.66, 8.73.

I.R: 3406, 2992, 2171, 1731, 1578 cm^{-1}.

8.49 Preparation of 2-(N-methylbenzylamine)-4-ethyl-imidazolidin-5-one 295

To a solution of guanidine **294** (0.40 g, 1.10 mmol) in degassed ethanol (30 ml) was added Pd/C (0.10 g, 10%) and the resulting suspension was stirred under an atmosphere of hydrogen (1 atm) for 12 h. The solution was filtered through celite, the solvent was removed by evaporation *in vacuo* and the residue was purified by flash chromatography, eluting with chloroform:methanol (9:1), to give the title compound (0.20 g, 79%).

M.pt: 124-126 °C.

M.S. *m/e* : 231.1365 ($C_{13}H_{17}N_3O$ requires 231.1372)
231 (M^+), 216 (M^+-15), 202 (M^+-29), 91 (M^+-140).

^1H n.m.r. (C), δ: 8.19 (bs, NH), 7.27-7.21 (m, 3H, Ph), 7.16-7.14 (m, 2H, Ph), 4.62 (bs, $PhCH_2$), 3.95 (bs, NH**CH**), 3.00 (bs, NCH_3), 2.93 (bs, NCH_3), 1.90-1.72 (m, **CH'**CH_3), 1.70-1.66 (m, **CH''**CH_3), 0.85 (bs, CH_3).

^{13}C n.m.r. (C), δ: 190.41, 171.14, 136.12, 128.96, 128.54, 127.63, 127.10, 63.71, 54.05, 52.65, 36.37, 33.93, 24.64, 8.72.

I.R: 3284, 2978, 1702, 1592, 1451 cm^{-1}.

8.50 Preparation of N-trifluoroaceto-N'-benzyl-O-phenylisourea 297 and N-trifluoroacetoxy-N'-benzyl-O-phenylisourea 298

A solution of O-phenylisourea **296** (0.40 g, 1.59 mmol) and trifluoroacetic acid (1.11 g, 9.74 mmol) in THF (20 ml) was heated to reflux for 8 h. The solvent was removed by evaporation *in vacuo* and the resulting oil purified by flash chromatography, eluting with chloroform:methanol (9:1) to give the O-phenylisourea **297** (0.20 g, 39%) and O-phenylisourea **298** (0.12 g, 22%). A sample of each was recrystallised from cyclohexane for analytical purposes.

O-phenylisourea 297

M.pt: 94-96 °C.

M.S. *m/e* : 189 (M^+-133), 94 (M^+-228), 91 (M^+-231).

^1H n.m.r. (C), δ: 10.00 (bs, NH), 7.47-7.37 (m, 6H, Ph), 7.32-7.28 (m, 2H, Ph), 7.13 (d, 2H, PhO, J_{H-H}=1.2 Hz), 4.76 (d, Ph**CH_2**, J_{H-NH}=5.6 Hz).

^{13}C n.m.r. (C), δ: 168.44 (q, **C**OCF_3, J_{C-F}=36.92 Hz), 163.87, 150.89, 135.58, 129.25, 129.09, 128.33, 127.62, 126.30, 121.48, 116.13 (q, CO**CF_3**, J_{C-F}=284.55 Hz), 42.04.

I.R: 3419, 1657, 1608, 1427 cm^{-1}.

Analysis: Calculated for $C_{16}H_{13}N_2O_2F_3$: C, 59.62; H, 4.03; N, 8.69; F, 17.69.
Found: C, 59.24; H, 3.88; N, 8.58; F, 16.90.

O-phenylisourea 298

M.pt: 110-112 °C.

M.S. *m/e* : 225 (M^+-113), 133 (M^+-205), 91 (M^+-245).

^{1}H n.m.r. (C), δ: 7.46-7.32 (m, 8H, Ph), 7.01 (d, 2H, PhO, J_{H-H}=7.6 Hz), 6.00 (bs, NH), 4.58 (s, Ph**CH_2**).

^{13}C n.m.r. (C), δ: 163.19 (q, **C**OCF_3, J_{C-F}=35.07 Hz), 160.05, 148.61, 136.25, 130.86, 128.80, 128.44, 127.94, 127.48, 120.79, 116.34 (q, CO**CF_3**, J_{C-F}=290.46 Hz), 44.95.

I.R: 3336, 1684, 1531, 1440 cm^{-1}.

Analysis: Calculated for $C_{16}H_{13}N_2O_3F_3$: C, 56.80; H, 3.85; N, 8.28; F, 16.20.
Found: C, 56.51; H, 4.15; N, 8.26; F, 16.80.

8.51 Preparation of N-benzyl-N'-benzyl-N"-trifluoroacetyl guanidine 300

A solution of guanidine **299** (0.50 g, 1.89 mmol) and trifluoroacetic acid (1.32 g, 11.60 mmol) in THF (20 ml) was stirred at room temperature for 8 h. The solvent was removed by evaporation *in vacuo* and the resulting oil purified by flash chromatography, eluting with chloroform:methanol (49:1), to give the guanidine **300** (0.41 g, 65%). A sample was recrystallised from cyclohexane for analytical purposes.

M.pt: 135-137°C.

M.S. *m/e* : 267 (M^+-68), 266 (M^+-69), 244 (M^+-91), 91 (M^+-244).

^{1}H n.m.r. (C, 0°C), δ: 10.06 (bs, NH), 7.37-7.27 (m, 8H, Ph), 7.12 (bs, 2H, Ph), 5.08 (bs, NH), 4.61 (bs, 2H, Ph**CH_2**), 4.39 (bs, 2H, Ph**CH_2**).

^{13}C n.m.r. (C, 45°C), δ: 167.38 (q, **C**OCF_3, J_{C-F}=35.23 Hz), 160.89, 129.09, 128.12, 127.37, 116.93 (q, $COCF_3$, J_{C-F}=285.15 Hz), 45.54.

I.R: 3321, 1608, 1568, 1436 cm^{-1}.

Analysis: Calculated for $C_{17}H_{16}N_3OF_3$: C, 60.89; H, 4.81; N, 12.53.
Found: C, 61.04; H, 4.75; N, 12.39.

8.52 Preparation of N-aceto-N'-benzyl-O-phenylisourea 301 and isourea 302

A solution of O-phenylisourea **296** (0.40 g, 1.59 mmol) and glacial acetic acid (0.57 g, 9.56 mmol) in THF (20 ml) was heated to reflux for 48 h. The solvent was removed by evaporation *in vacuo* and the resulting oil purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:3), to give the O-phenylisourea **301** (0.12 g, 26%) as an oil, and the isourea **302** (0.08 g, 26%).

O-phenyisourea 301

M.S. *m/e* : 268.1211 ($C_{16}H_{16}N_2O_2$ requires 268.1212)
268 (M^+), 253 (M^+-15), 226 (M^+-42), 191 (M^+-77).

^{1}H n.m.r. (C), δ: 7.36-7.18 (m, 8H, Ph), 7.05-7.03 (m, 2H, Ph), 4.63 (bs, Ph**CH$_2$**), 1.99 (s, OCH_3).

^{13}C n.m.r. (C), δ: 185.80, 161.57, 151.48, 137.13, 129.09, 128.80, 127.72, 127.40, 125.52, 121.78, 45.33, 28.18.

I.R: 3217, 1703, 1623, 1596 cm^{-1}.

Isourea 302

M.pt: 125-127 °C.

M.S. *m/e* : 192.0894 ($C_{10}H_{12}N_2O_2$ requires 192.0899)
192 (M^+), 149 (M^+-43), 133 (M^+-59), 91 (M^+-101).

^{1}H n.m.r. (C), δ: 9.96 (bs, OH), 8.85 (bt, NH), 7.40-7.21 (m, Ph), 4.64 (d, $PhCH_2$ J_{H-H}=6.00 Hz), 4.46 (d, $PhCH_2$, J_{H-H}=6.00 Hz), 2.26 (s, OCH_3), 2.07 (s, OCH_3).

^{13}C n.m.r. (C), δ: 172.36, 162.52, 160.80, 154.78, 151.22, 137.99, 136.81, 129.22, 128.89, 128.60, 127.91, 127.47, 127.42, 127.39, 125.95, 121.83, 45.65, 43.51, 24.23, 23.91.

I.R: 3302, 1730, 1693, 1666 cm^{-1}.

8.53 Preparation of N-benzyl-N'-benzyl-N''-acetyl guanidine 304

A solution of guanidine **299** (0.79 g, 2.99 mmol) and glacial acetic acid (1.07 g, 17.83 mmol) in THF (30 ml) was heated to reflux for 72 h. The solvent was removed by evaporation *in vacuo* and the resulting oil purified by flash chromatography, eluting with dichloromethane:ethyl acetate (1:1), to give the guanidine **304** (0.45 g, 54%).

M.pt: 75-76 °C.

M.S. *m/e* : 281.1537 ($C_{17}H_{19}N_3O$ requires 281.1528)
281 (M^+), 266 (M^+-15), 222 (M^+-59), 91 (M^+-190).

^{1}H n.m.r. (C), δ: 7.30-7.24 (m, 6H, Ph), 7.17 (bs, 4H, Ph), 4.42 (bs, $PhCH_2$), 2.10 (s, OCH_3).

^{13}C n.m.r. (C), δ: 181.50, 159.60, 128.80, 127.65, 127.06, 44.88, 28.36.

I.R: 3327, 3217, 1596, 1565 cm^{-1}.

8.54 Preparation of 1-amino-2-cyanoimino-4-ethylimidazolidin-5-one 305

A solution of O-phenylisourea **403** (0.22 g, 0.84 mmol) and hydrazine (0.035 g, 1.10 mmol) in propan-2-ol (7 ml) was stirred at room temperature for 75 min. The resulting precipitate was collected by filtration, washed with ether and dried to give imidazolidin-5-one **305** (120 mg, 85 %).

M.pt: 137-139 °C.

M.S. *m/e*: 168.0892 ($C_6H_{10}N_5O$ requires 168.0885)
167 (M^+), 139 (M^+-28), 124 (M^+-43), 110 (M^+-47).

^{1}H n.m.r. (D), δ: 9.67 (bs, NH), 4.94 (s, NH_2), 4.18 (t, NH**CH**, $J_{H\text{-}NH}$=5.84 Hz), 1.77-1.61 (m, $\mathbf{CH_2}CH_3$), 0.84 (t, CH_3, $J_{H\text{-}H}$=7.52 Hz).

^{13}C n.m.r. (D), δ: 172.59, 162.01, 115.51, 57.22, 28.82, 8.42.

I.R: 3413, 2187, 1761, 1752, 1654 cm^{-1}.

8.55 Preparation of urea 306

A solution of imidazolidin-5-one **166**[83] (0.38 g, 1.25 mmol), trifluoroacetic acid (0.86 g, 7.54 mmol) and water (0.14 g, 7.54 mmol) in THF (10 ml) was heated to reflux for 6 h. The solvent was removed by evaporation *in vacuo* and the resulting oil triturated with ether to give the title compound as white crystals (0.25 g, 76 %).

M.pt: 107-109 °C.

M.S. *m/e* : 322.1431 ($C_{18}H_{18}N_4O_2$ requires 322.1430)
322 (M^+), 305 (M^+-17), 231 (M^+-91), 91 (M^+-231).

^{1}H n.m.r. (C), δ: 9.40 (bs, NH), 7.29-7.20 (m, 6H, Ph), 7.13-7.10 (m, 2H, Ph), 7.02-6.99 (m, 2H, Ph), 5.75 (bs, NH), 4.84 (d, PhCH', $J_{H'-H''}$=15.40 Hz), 4.82 (d, PhCH", $J_{H''-H'}$=15.40 Hz), 4.45 (dd, **C**HCH_2, $J_{H-H'}$=4.48 Hz, $J_{H-H''}$=6.72 Hz), 3.26 (dd, PhCH', $J_{H'-H''}$=14.32 Hz, $J_{H'-H}$=4.48 Hz), 3.05 (dd, PhCH", $J_{H''-H'}$=14.32 Hz, $J_{H''-H}$=6.72 Hz).

^{13}C n.m.r. (C), δ: 171.74, 160.69, 158.64, 133.96, 133.23, 129.33, 129.05, 128.71, 128.06, 127.91, 127.58, 59.13, 42.86, 36.87.

I.R: 3266, 1788, 1755, 1740, 1693 cm^{-1}.

8.56 Preparation of urea 307

A solution of imidazolidin-5-one **128** (0.41 g, 1.43 mmol), trifluoroacetic acid (0.98 g, 8.60 mmol) and water (0.15 g, 8.60 mmol) in THF (10 ml) was heated to reflux for 3 h. The solvent was removed *in vacuo* and the resulting oil purified by flash chromatography, eluting with chloroform:methanol (49:1), to give the urea **307** (0.30 g, 69%).

M.pt: 106-108 °C.

M.S. *m/e* : 304.1176 ($C_{14}H_{16}N_4O_4$ requires 304.1171)
304 (M^+), 287 (M^+-17), 261 (M^+-43), 91 (M^+-213).

^{1}H n.m.r. (C), δ: 9.50 (bs, NH_2), 7.39-7.26 (m, Ph), 6.06 (bs, NH), 4.95 (d, PhCH', $J_{H'-H''}$=15.00 Hz), 4.91 (d, PhCH", $J_{H''-H'}$=15.00 Hz), 4.45 (dd, **C**HCH_2, $J_{H-H'}$=3.62 Hz, $J_{H-H''}$=7.90 Hz), 3.66 (s, OCH_3), 3.04 (dd, CH'CO_2,

$J_{H'-H''}$=17.68 Hz, $J_{H'-H}$=3.62 Hz), 2.80 (dd, CH"CO_2, $J_{H''-H'}$=17.68 Hz, $J_{H''-H}$=7.90 Hz).

^{13}C n.m.r. (C), δ: 171.71, 169.55, 161.42, 158.96, 134.37, 128.80, 128.39, 128.32, 54.27, 52.60, 43.26, 35.09.

I.R: 3315, 1785, 1742, 1684 cm^{-1}.

8.57 Preparation of urea 308

A solution of imidazolidin-5-one **247** (0.12 g, 0.45 mmol), trifluoroacetic acid (0.28 g, 2.46 mmol) and water (0.04 g, 2.46 mmol) in THF (6 ml) was heated to reflux for 3 h. The solvent was removed by evaporation *in vacuo* and the product purified by flash chromatography, eluting with ethyl acetate:cyclohexane (4:1), to give the urea **308** (0.10 g, 74%).

M.pt: 100-102 °C.

M.S. *m/e* : 301.1675 ($C_{16}H_{21}N_4O_2$ requires 301.1664)
300 (M^+), 283 (M^+-17), 233 (M^+-67), 91 (M^+-209).

^{1}H n.m.r. (C), δ: 8.83 (bs, NH), 7.28-7.15 (m, Ph), 5.02 (bs, NH_2), 4.38 (m, CHN), 4.18 (dd, **C**HCH_2, $J_{H-H'}$=3.92 Hz, $J_{H-H''}$=7.32 Hz), 3.14 (dd, PhCH', $J_{H'-H}$=3.92 Hz, $J_{H'-H''}$=14.04 Hz), 2.90 (dd, PhCH", $J_{H''-H}$=7.32 Hz, $J_{H''-H'}$=14.04 Hz), 1.98-1.04 (m, 8H, CH_2).

^{13}C n.m.r. (C), δ: 173.07, 165.87, 159.77, 134.66, 129.35, 128.66, 127.29, 58.47, 51.98, 37.82, 28.40, 28.19, 24.90.

I.R: 3541, 1739, 1647, 1617 cm^{-1}.

8.58 Preparation of 5,6-dihydro-4(3H)-pyrimidinone 309

A solution of imidazolidin-5-one **307** (0.127 g, 0.42 mmol) in 2 M sodium hydroxide solution (2 ml) was stirred at room temperature for 6 min. The solution was acidified to pH 1.0 with concentrated hydrochloric acid and the solvent volume reduced to one half by evaporation *in vacuo* when the product precipitated from solution. The product was collected by filtration and dried to give the title compound (0.090 g, 74%).

M.pt: 188-190 °C.

M.S. *m/e* : 290 (M^+), 261 (M^+-29), 227 (M^+-63), 91 (M^+-199).

^{1}H n.m.r. (D), δ: 8.93 (bs, CO_2H), 7.34-7.22 (m, Ph), 6.50 (bs, NH), 6.24 (bs, NH), 4.66 (d, PhCH', $J_{H'-H''}$=15.36 Hz), 4.61 (d, PhCH", $J_{H''-H'}$=15.36 Hz), 4.38 (m, $CHCO_2$), 2.85 (dd, CH**CH'**, $J_{H'-H}$=4.64 Hz, $J_{H'-H''}$=17.36 Hz), 2.77 (dd, CH**CH"**, $J_{H''-H}$=5.46 Hz, $J_{H''-H'}$=17.36 Hz).

^{13}C n.m.r. (D), δ: 173.52, 171.15, 164.74, 157.99, 136.60, 128.26, 127.40, 127.33, 127.27, 54.00, 53.83, 41.66, 34.69.

I.R: 3480, 1746, 1700, 1632 cm^{-1}.

8.59 Preparation of urea 310

A solution of imidazolidin-5-one **305** (0.088 g, 0.52 mmol), trifluoroacetic acid (0.36 g, 3.15 mmol) and water (0.06 g, 3.15 mmol) in THF (10 ml) was heated to reflux for 2 h. The solvent was removed by evaporation *in vacuo* and ether (6 ml) added. The resulting solution was cooled to 4°C for 8 h during which the product crystallised from solution.The product was collected by filtration and recrystallised from methanol/ether to give the title compound (0.060 g, 62%).

M.pt: 215-217 °C.

M.S. *m/e* : 185.0918 ($C_6H_{11}N_5O_2$ requires 185.0913)
185 (M^+), 167 (M^+-18), 139 (M^+-46), 96 (M^+-89).

^{1}H n.m.r. (D), δ: 8.59 (bs, NH), 6.17 (bs, NH_2), 4.33 (dt, **CH**CH_2,J_{H-H}=5.48 Hz, J_{H-NH}=1.56 Hz), 3.40 (bs, NH_2), 1.84-1.77 (m, **CH'**CH_3), 1.70-1.59 (m, **CH"**CH_3), 0.87 (t, CH_3, J_{H-H}=7.20 Hz).

^{13}C n.m.r. (D), δ: 170.62, 165.49, 163.72, 65.76, 24.26, 8.93.

I.R: 3339, 1739, 1653, 1565 cm^{-1}.

8.60 Preparation of urea 311

A solution of guanidine **299** (0.50 g, 1.89 mmol), trifluoroacetic acid (1.32 g, 11.60 mmol) and water (0.20 g, 11.60 mmol) in THF (12 ml) was heated to reflux for 4 h. The solvent was removed by evaporation *in vacuo* and the resulting oil purified by flash chromatography, eluting with chloroform:methanol (19:1) to give the urea **311** (0.40 g, 75 %). A sample was recrystallised from chloroform/cyclohexane for analytical purposes.

M.pt: 111-113 °C.

M.S. *m/e*: 282.1489 ($C_{16}H_{18}N_4O$ requires 282.1481)
282 (M^+), 239 (M^+-43), 169 (M^+-113), 91 (M^+-191).

^{1}H n.m.r. (C), δ: 10.02 (bs, NH), 7.26-7.16 (m, Ph), 4.86 (bs, NH and NH_2), 4.36 (bs, Ph**C**H_2).

^{13}C n.m.r. (C), δ: 167.11 159.23, 139.00, 128.61, 127.34, 126.88, 44.69.

I.R: 3474, 1724, 1629, 1565 cm^{-1}.

8.61 Preparation of urea 312

A solution of O-phenylisourea **296** (0.60 g, 2.39 mmol) and trifluoroacetic acid (1.63 g, 14.29 mmol) in THF (20 ml) was stirred at room temperature for 13 days. The solvent was removed by evaporation *in vacuo* and the resulting oil purified by flash chromatography, eluting with ethyl acetate:cyclohexane (2:3), to give the title compound (0.40 g, 62%).

M.pt: 138-140 °C.

M.S. *m/e*: 269.1179 ($C_{15}H_{15}N_3O_2$ requires 269.1164)
269 (M^+), 253 (M^+-16), 226 (M^+-43), 91 (M^+-178).

^{1}H n.m.r. (C), δ: 9.90 (bs, NH), 7.78-7.19 (m, 8H, Ph), 7.01 (d, 2H, PhO, J_{H-H}=7.60 Hz), 5.80 (bs, NH), 4.85 (bs, NH), 4.61 (s, PhCH_2).

^{13}C n.m.r. (C), δ: 163.99, 160.88, 151.26, 137.09, 129.39, 128.81, 127.75, 127.34, 125.99, 121.56, 45.47.

I.R: 3474, 1739, 1641, 1617 cm^{-1}.

8.62 Preparation of N-cyano-N'-benzyl-N'-methyl-O-phenylisourea 313

To a solution of diphenyl cyanocarbonimidate **53** (0.11 g, 0.46 mmol) in propan-2-ol (10 ml) was added N-methyl benzylamine (0.07 g, 0.58 mmol) and the resulting solution was stirred at room temperature for 2 h. The solvent volume was reduced to one half by evaporation *in vacuo* and the reaction mixture cooled to 4 °C for 2 h. The crystalline product was filtered, washed with ether and dried to give the title compound (0.10 g, 85%).

M.pt: 122-124 °C.

M.S. *m/e* : 265.1240 ($C_{16}H_{15}N_3O$ requires 265.1215)
265 (M^+), 250 (M^+-15), 208 (M^+-57), 91 (M^+-174).

^{1}H n.m.r. (C), δ: 7.45-7.25 (m, 8H, Ph). 7.12 (d, 2H, Ph), 4.69 (bs, CH_2), 3.12 (bs, CH_3).

^{13}C n.m.r. (C), δ: 157.99, 157.80, 134.79, 129.95, 128.87, 128.19, 127.71, 127.63, 125.86, 118.80, 54.15, 36.64, 34.19.

I.R: 2990, 2187, 1617, 1476 cm^{-1}.

8.63 Preparation of N-trifluoroaceto-N'-benzyl-N'-methyl-O-phenylisourea 314

A solution of O-phenylisourea **313** (0.34 g, 1.28 mmol) and trifluoroacetic acid (0.88 g, 7.69 mmol) in THF (15 ml) was stirred for 12 h at room temperature. The solvent was removed by evporation *in vacuo* and the resulting oil purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:1) to give the O-phenylisourea **314** (0.25 g, 58%). A sample was recrystallised from cyclohexane for analytical purposes.

M.pt: 60-62 °C.

M.S *m/e*: 279 (M^+-57), 267 (M^+-69), 243 (M^+-93), 91 (M^+-245).

^{1}H n.m.r. (C),δ: 7.33-7.24 (m, 7H, Ph), 7.16-7.12 (m, 1H, Ph), 7.06-7.05 (m, 2H, Ph), 4.71 (bs, 1.3H, CH_2), 4.62 (bs, 0.7H, CH_2), 3.06 (bs, 3H, CH_3), 3.02 (bs, 1.7H, CH_3).

^{13}C n.m.r. (C),δ: 163.96, 159.57 (q, J_{C-F}=35.91 Hz), 159.51 (q, J_{C-F}=38.09 Hz), 151.81, 151.71, 133.95, 129.41, 129.08, 128.41, 127.46, 126.31, 120.15, 119.97, 116.36 (q, J_{C-F}=285.60 Hz), 55.22, 54.26, 37.24, 34.84.

I.R: 2953, 1721, 1657, 1589 cm^{-1}.

8.64 Preparation of N-benzyl-N-methyl-N'-cyano-N"-(methyl propionate)-guanidine 326

To a solution of O-phenylisourea **63**[83] (0.40 g, 1.62 mmol) in propan-2-ol (25 ml) was added N-methyl-benzylamine (1.95 g, 16.12 mmol) and the solution was stirred for 12 h. The solvent was removed by evaporation *in vacuo* and the residue redissolved in chloroform (20 ml).

The chloroform was extracted with 5% citric acid solution (2x10 ml), dried ($MgSO_4$) and the solvent removed by evaporation *in vacuo*. The residue was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:1) to give the title compound (0.40 g, 90 %) as an oil.

M.S. *m/e* : 274 (M^+), 259 (M^+-15), 215 (M^+-59), 91 (M^+-183).

^1H .n.m.r. (C), δ: 7.34-7.00 (m, Ph), 5.77 (bs, NH), 4.57 (s, PH**CH_2**), 3.76 (dt, CH_2N, J_{H-H}=6.04 HZ, J_{H-H}=5.88 Hz), 3.62 (s, OCH_3), 2.95 (s, NCH_3), 2.62 (t, CH_2, J_{H-H}=5.88 Hz).

^{13}C n.m.r. (C), δ: 173.06, 158.89, 135.60, 128.87, 127.87, 127.14, 117.42, 54.35, 51.88, 38.62, 36.41, 33.89.

I.R: 3217, 2164, 1739, 1544 cm^{-1}.

8.65 Preparation of N-benzyl-N-methyl-N'-cyano-N''-(2-carboxyethyl)-guanidine 327

To guanidine **326** (0.20 g, 0.73 mmol) in methanol (10 ml) was added sodium hydroxide solution (0.36 ml, 2M, 0.73 mmol) and the solution was stirred for 3 h. The solvent was removed by evaporation *in vacuo* and the residue was purified by flash chromatography, initially eluting with chloroform:methanol (9:1) and increasing the polarity to a final value of 6:4. Fractions containing the product were pooled to give the title compound as a white foam (0.15 g, 79 %). A sample was recrystallised from methanol for analytical purposes.

M.pt: 116-118 °C.

M.S. *m/e* : 188 (M^+-72), 173 (M^+-83), 91 (M^+-169).

^1H n.m.r. (C), δ: 7.60 (bs, NH), 7.35-7.20 (m, Ph), 4.58 (s, Ph**CH_2**), 3.55 (m, NCH_2), 2.84 (s, NCH_3), 2.25 (t, CH_2, J_{H-H}=6.67 Hz).

^{13}C n.m.r. (C), δ: 177.09, 158.82, 137.17, 128.58, 127.25, 117.45, 53.23, 39.75, 36.72, 36.03.

I.R: 3315, 2164, 1708, 1562 cm^{-1}.

8.66 Preparation of 3-amino-5-phenoxy-s-triazole 390

A solution of diphenyl cyanocarbonimidate **53** (0.50 g, 2.10 mmol) and hydrazine (0.08 g, 2.50 mmol) in propan-2-ol (15 ml) was heated to reflux for 3 h. The volume of the solvent was reduced to half by evaporation *in vacuo* and cooled to 4 °C. The resulting precipitate was removed by filtration to give s-triazole **390** (0.22 g, 59%).

M.pt: 128-130 °C.

M.S. *m/e* : 176.0704 ($C_8H_8N_4O$ requires 176.0698)
176 (MH^+), 148 (M^+-27), 119 (M^+-56), 77 (M^+-98).

^1H n.m.r. (D), δ: 11.49 (bs, NH), 7.35-7.31 (m, 2H, Ph), 7.11-7.07 (m, 3H, Ph), 6.09 (bs, NH_2).

^{13}C n.m.r. (D), δ: 163.59, 156.08, 155.39, 129.39, 123.44, 118.37.

I.R: 3437, 3149, 1651, 1590 cm^{-1}.

Analysis: Calculated for $C_8H_8N_4O$: C, 54.55; H, 4.54; N, 31.82.
Found: C, 53.88; H, 4.38; N, 32.21.

8.67 Preparation of 1-methyl-3-amino-5-phenoxy-s-triazole 391

A solution of diphenyl cyanocarbonimidate **53** (0.50 g, 2.1 mmol) and methylhydrazine (0.13 g, 2.8 mmol) in propan-2-ol (15 ml) was stirred at room temperature for 2 h. The solvent was removed by evaporation *in vacuo* and the resulting oil purified by flash chromatography, eluting with chloroform:methanol (49:1). Product fractions were collected and reduced to a small volume. Cyclohexane was added until the solution became cloudy and the mixture was cooled to 4 °C when precipitation occured. The crystalline product was removed by filtration and dried to give s-trazole **391** (0.22 g, 63%).

M.pt: 109-110 °C.

M.S. *m/e* : 190.0855 ($C_9H_{10}N_4O$ requires 190.0855)
190 (M^+), 119 (M^+-71), 91 (M^+-99), 77 (M^+-113).

^1H n.m.r. (D), δ: 7.43-7.41 (m, 2H, Ph), 7.39-7.20 (m, 3H, Ph), 5.23 (bs, NH_2), 3.47 (s, NCH_3).

^{13}C n.m.r. (D), δ: 159.73, 154.64, 154.03, 129.74, 125.06, 119.24, 32.39.

I.R: 3364, 1641, 1580, 1516 cm^{-1}.

Analysis: Calculated for $C_9H_{10}N_4O$: C, 56.54; H, 5.26; N, 29.47.
Found: C, 56.73; H, 5.13; N, 28.88.

8.68 Preparation of 1-phenyl-3-amino-5-phenoxy-s-triazole 392

A solution of diphenyl cyanocarbonimidate **53** (0.30 g, 1.26 mmol) and phenylhydrazine (0.10 g, 1.51 mmol) in propan-2-ol (15 ml) was heated to reflux for 6 h. The solution was cooled and the resulting precipitate removed by filtration to give s-triazole **392** (0.20 g, 63%).

M.pt: 165-167 °C.

M.S. *m/e* : 252.1021 ($C_{14}H_{12}N_4O$ requires 252.1011)
252 (M^+), 235 (M^+-17), 134 (M^+-118), 91 (M^+-161).

^1H n.m.r. (D), δ: 7.50-7.45 (m, 4H, Ph), 7.40-7.30 (m, 2H, Ph), 7.23-7.10 (m, 2H, Ph), 6.62 (bs, NH_2).

^{13}C n.m.r. (D), δ: 163.85, 154.65, 154.03, 136.97, 129.52, 129.37, 126.73, 124.09, 122.52, 119.14.

I.R: 3382, 3119, 1641, 1562 cm^{-1}.

8.69 Preparation of methyl 2-(5-amino-(3-amino-s-triazole))ethanoate 396

A solution of O-phenylisourea **395** (0.25 g, 1.07 mmol) and hydrazine (0.04 g, 1.25 mmol) in propan-2-ol (20 ml) was heated to reflux for 8 h. The solution was then reduced to half volume by evaporation *in vacuo*, cooled to 4° C and the resulting precipitate collected by filtration. The precipitate was washed with ether to give s-triazole **396** (0.14 g, 95%).

M.pt: 162-163° C.

M.S. *m/e* : 171 (M^+), 139 (M^+-32), 119 (M^+-52), 112 (M^+-59).

^1H n.m.r. (D), δ: 10.75 (bs, NH), 5.65 (bs, NH_2), 3.76 (d, NH**CH**, $J_{H\text{-}NH}$=6.0 Hz), 3.59 (s,OCH_3).

^{13}C n.m.r. (D), δ: 172.07, 161.67, 156.08, 51.36, 44.33.

I.R: 3406, 1724, 1654, 1571 cm^{-1}.

Analysis: Calculated for $C_5H_9N_5O_2$: C, 35.08; H, 5.26; N, 40.94.
Found: C, 34.90; H, 5.29; N, 42.46.

8.70 Preparation of methyl 3-(5-amino-(3-amino-s-triazole))propionate 397

A solution of O-phenylisourea **63** (0.42 g, 1.70 mmol) and hydrazine (0.07 g, 2.20 mmol) in propan-2-ol (10 ml) was stirred at room temperature for 6 h. The solvent volume was reduced to one half by evaporation *in vacuo* and ether added. On cooling to 4 °C the product crystallised from solution and was collected by filtration to give the s-triazole **397** (0.29 g, 93%).

M.pt: 135-137 °C.

M.S. *m/e* : 185.0911 ($C_6H_{11}N_5O_2$ requires 185.0913)
185 (M^+), 153 (M^+-32), 126 (M^+-59), 112 (M^+-73).

^1H n.m.r. (D), δ: 10.70 (bs, NH), 5.40 (bs, NH_2), 3.57 (s, OCH_3), 3.22 (q, NH**CH_2**, $J_{H\text{-}NH}$=6.80 Hz, $J_{H\text{-}H}$=6.96 Hz), 2.52 (t, **CH_2**CO_2Me, $J_{H\text{-}H}$=6.96 Hz).

^{13}C n.m.r. (D), δ: 172.23, 161.90, 158.50, 51.27, 38.84, 34.05.

I.R: 3443, 1718, 1608, 1565 cm^{-1}.

Analysis: Calculated for $C_6H_{11}N_5O_2$: C, 38.92; H, 5.94; N, 37.84.
Found: C, 39.08; H, 5.99; N, 37.91.

8.71 Preparation of methyl 4-(5-methylamino-(3-amino-s-triazole))butanoate 399

A solution of O-phenylisourea **398**[83] (0.82 g, 2.98 mmol) and hydrazine (0.11 g, 3.43 mmol) in propan-2-ol (40 ml) was heated to reflux for 7 h. Cyclohexane was then added until the solution just became cloudy and the mixture was kept at 15° C for 8 h. The precipitated crystalline material was collected by filtration, washed with ether and dried to give s-triazole **399** (0.60 g, 94%).

M.pt: 76-78 °C.

M.S. *m/e* : 213.1226 ($C_8H_{15}N_5O_2$ requires 213.1219)
213 (M^+), 181 (M^+-32), 140 (M^+-73), 126 (M^+-87).

^{1}H n.m.r. (D), δ: 10.83 (bs, NH), 5.48 (bs, NH_2), 3.56 (s, OCH_3), 3.18 (t, N(Me)**CH_2**, J_{H-H}=7.10 Hz), 2.75 (s, NCH_3), 2.25 (t, CH_2CO_2Me, J_{H-H}=7.58 Hz), 1.72 (tt, CH_2**CH_2**CH_2, J_{H-H}=7.1 Hz, J_{H-H}=7.58 Hz).

^{13}C n.m.r. (D), δ: 173.21, 161.20, 157.40, 51.30, 49.51, 35.56, 30.80, 22.15.

I.R: 3406, 1721, 1654, 1605 cm^{-1}.

Analysis: Calculated for $C_8H_{15}N_5O_2$: C, 45.07; H, 7.04; N, 32.86.
Found: C, 45.26; H, 7.19; N, 32.93.

8.72 Preparation of 3-amino-7-benzyl-1,2,4,6-tetraazabicyclo[3.3.0] octan-8-one 400

A solution of O-phenylisourea **246** (0.26 g, 0.65 mmol) and hydrazine (0.025 g, 0.78 mmol) in propan-2-ol (20ml) was stirred at 40 °C for 1 h. The solution was cooled to 4 °C and the precipitate collected by filtration and dried to give the octan-8-one **400** (0.10 g, 67%).

M.pt: 152-154 °C.

M.S. *m/e* : 229.0975 ($C_{11}H_{11}N_5O$ requires 229.0964)
229 (M^+), 170 (M^+-59), 110 (M^+-119), 91 (M^+-138).

^{1}H n.m.r. (D), δ: 10.69 (bs, NH), 9.04 (bs, NH), 7.26-7.22 (m, 4H, Ph), 7.16-7.14 (m, 1H, Ph), 4.17-4.11 (m, NH_2 and **CH**CH_2), 2.89 (dd, PhCH', $J_{H'-H''}$=13.72 Hz, $J_{H'-H}$=4.68 Hz), 2.79 (dd, PhCH", $J_{H''-H'}$=13.72 Hz, $J_{H''-H}$=9.24 Hz).

^{13}C n.m.r. (D), δ: 172.11, 161.01, 156.00, 138.61, 129.24, 127.98, 126.08, 56.70, 38.88.

I.R: 3314, 1641, 1565, 1534 cm^{-1}.

8.73 Preparation of 3-amino-7-methoxycarbonylmethyl-1,2,4,6-tetraazabicyclo[3.3.0]octan-8-one 401

A solution of O-phenylisourea **127** (0.30 g, 0.98 mmol) and hydrazine (0.039 g, 1.22 mmol) in propan-2-ol (25 ml) was heated to 60 °C for 2 h. The volume of the solution was reduced

to one half by evaporation *in vacuo* and ether was added. On cooling to 4 °C the product precipitated from solution and was collected by filtration, washed with ether and dried to give octan-8-one **401** (0.090 g, 43%).

M.pt: 117-119 °C.

M.S. *m/e* : 211.0700 ($C_7H_9N_5O_3$ requires 211.0705)
211 (M^+), 184 (M^+-27), 152 (M^+-59), 124 (M^+-87).

^{1}H n.m.r. (D), δ: 10.78 (bs, NH), 5.55 (bs, NH_2), 4.46-4.27 (m, **CH**CH_2), 3.58 (s, OCH_3), 2.82-2.73 (m, CH_2).

^{13}C n.m.r. (D), δ: 173.09, 170.87, 159.90, 156.50, 51.90, 51.04, 36.49.

I.R: 3449, 3370, 1736, 1565 cm^{-1}.

8.74 Preparation of N-cyano-N'-(methyl 2-propionate)-O-phenylisourea 402

Triethylamine (0.86 g, 8.85 mmol) was added to a stirred suspension of S-alanine-methyl ester hydrochloride (1.0 g, 7.17 mmol) and diphenyl cyanocarbonimidate **53** (1.71 g, 7.17 mmol) in propan-2-ol (40 ml) and the resulting solution heated to reflux for 3 h. The solvent was removed by evaporation *in vacuo* and the residue dissolved in chloroform (30 ml) and washed with saturated sodium bicarbonate (2x20 ml). The organic layer was dried ($MgSO_4$) and the solvent removed by evaporation *in vacuo*. The residue was redissolved in propan-2-ol (20 ml) and cooled to 4° C for 4 h. The resulting crystalline product was collected by filtration to give the O-phenylisourea **402** (1.0 g, 56%).

M.pt: 108-110 °C.

M.S. *m/e* : 188 (M^+-59), 153 (M^+-94), 126 (M^+-121), 118 (M^+-129).

^{1}H n.m.r. (C), δ: 7.45-7.02 (m, PhO), 5.70 (bs, NH), 4.53 (m, NH**CH**), 3.78 (bs, OCH_3), 1.55 (bd, CH_3, J_{H-H}=6.8 Hz), 1.42 (bs, CH_3).

^{13}C n.m.r. (C), δ: 171.60, 163.07, 150.79, 130.63, 129.53, 127.70, 126.73, 121.30, 121.00, 114.49, 52.89, 51.20, 17.62.

I.R: 3437, 2189, 1730, 1635 cm^{-1}.

Analysis: Calculated for $C_{12}H_{13}N_3O_3$: C, 58.20; H, 5.26; N, 17.00.
Found: C, 58.42; H, 5.26; N, 16.84.

8.75 Preparation of N-cyano-N'-(methyl 2-butanoate)-O-phenylisourea 403

Triethylamine (1.75 g, 17 mmol) was added to methyl 2-amino-butanoate hydrochloride (2.05 g, 13 mmol) in benzene (20 ml), with stirring. Dry ether was added and the resulting precipitate of triethylamine hydrochloride was removed by filtration. The solvent was removed from the filtrate to give methyl 2-amino-butanoate **404** as a yellow oil (0.46 g, 3.93 mmol). N-cyanocarbonimidate **53** (0.94 g, 3.93 mmol) was added to a solution of **404** (0.46 g, 3.93 mmol) in propan-2-ol (20 ml) and the mixture stirred at room temperature for 8 h. The resulting white precipitate was removed by filtration and a second crop was obtained by a similar method (2.1 g, 62%).

M.S. *m/e*: 262.1189 ($C_{13}H_{15}N_3O_3$ requires 262.1191)
261 (M^+), 202 (M^+-59), 140 (M^+-120), 94 (M^+-167).

^{1}H n.m.r. (C), δ: 7.47-7.04 (m, Ph), 6.77 (bs, NH), 4.46 (m, NH**CH**), 3.79 (s, OCH_3), 3.73 (s, OCH_3), 2.04-1.70 (m, **CH_2**CH_3), 1.04 (t, CH_3, $J_{H\text{-}H}$=7.30 Hz), 0.82 (t, CH_3, $J_{H\text{-}H}$=7.30 Hz).

^{13}C n.m.r. (C), δ: 170.95, 163.23, 150.76, 130.70, 129.56, 127.78, 126.79, 121.98, 121.17, 114.41, 113.67, 56.72, 56.61, 52.86, 52.75, 25.31, 24.63, 9.93, 9.06.

I.R: 3443, 2200, 1730, 1645 cm^{-1}.

Analysis: Calculated for $C_{13}H_{15}N_3O_3$: C, 59.77; H, 5.75; N, 16.09.
Found: C, 60.01; H, 5.71; N, 15.99.

8.76 Preparation of methyl 2-(5-amino-(3-amino-s-triazole))propionate 404

A solution of O-phenylisourea **402** (0.140 g, 0.57 mmol) and hydrazine (0.023 g, 0.70 mmol) in propan-2-ol (6 ml) was heated to reflux for 20 min. Cyclohexane was added and the mixture cooled to 4° when precipitation occured. The precipitate was collected by filtration, washed with ether and dried to give the s-triazole **404** (0.075 g, 71%).

M.pt: 189-191 °C.

M.S. *m/e* : 186.0996 ($C_6H_{11}N_5O_2$ requires 186.0991)
186 (MH^+), 185 (M^+), 126 (M^+-59).

^1H n.m.r. (D), δ: 10.73 (bs, NH), 5.84 (bs, NH), 5.53 (bs, NH_2), 4.01 (m, NH**CH**), 3.57 (s, OCH_3), 1.27 (d, CH_3, J_{H-H}=7.6 Hz).

^{13}C n.m.r. (D), δ: 175.05, 160.01, 157.30, 50.84, 50.71, 18.12.

I.R: 3437, 1724, 1654, 1568 cm^{-1}.

8.77 Preparation of methyl 2-(5-amino-(3-amino-s-triazole))butanoate 405

A solution of O-phenylisourea **403** (0.28 g, 1.07 mmol) and hydrazine (0.040 g, 1.25 mmol) in propan-2-ol (20 ml) was heated to reflux for 3.5 h. The solvent volume was reduced to half *in vacuo* , ether was added and mixture was cooled to 4 °C. The resulting precipitate was collected by filtration and washed with ether to give the s-triazole **405** (0.15 g, 70%).

M.pt: 169-171 °C.

M.S. *m/e* : 199.1076 ($C_7H_{13}N_5O_2$ requires 199.1069)
199 (M^+), 170 (M^+-29), 140 (M^+-59).

^1H n.m.r. (D), δ: 10.71 (bs, NH), 5.65 (bs, NH_2), 3.91-3.89 (m, NH**CH**), 3.57 (s, OCH_3), 1.70 -1.60 (m, $\mathbf{CH_2}CH_3$), 0.89 (t, CH_3, J_{H-H}=7.60 Hz).

^{13}C n.m.r. (D), δ: 172.45, 159.50, 154.01, 54.90, 49.32, 22.99, 8.51.

I.R: 3425, 1721, 1651, 1568 cm^{-1}.

8.78 Preparation of 3-amino-7-ethyl-1,2,4,6-tetraazabicyclo[3.3.0]octan-8 one 407

To a solution of O-phenylisourea **293** (1.00 g, 2.97 mmol) in propan-2-ol (40 ml) was added hydrazine (0.11 g, 3.56 mmol) and the resulting solution stirred at room temperature for 2 h. The solvent volume was reduced to one half by evaporation *in vacuo* and the resulting solution cooled to -10 °C for 2 h. The precipitated solid was collected by filtration, washed with ether and recrystallised from a large volume of propan-2-ol to give title compound (0.35 g, 71%).

M.pt: 200-202 °C.

M.S. *m/e* : 168.0881 ($C_6H_9N_5O$ requires 167.0807)
168 (M^+), 140 (M^+-28), 126 (M^+-42), 99 (M^+-69).

^1H n.m.r. (D), δ: 8.95 (bs, NH), 5.50 (bs, NH_2), 3.79 (dd, **CH**CH_2, J=7.28 Hz, J=15.04 Hz), 1.66-1.48 (m, CH_2), 0.83 (t, CH_3, J=7.60 Hz).

^{13}C n.m.r. (D), δ: 172.36, 56.56, 25.97, 10.35.

I.R: 3394, 1620, 1596, 1546 cm^{-1}.

8.79 Preparation of 1-amino-2-cyanoimino-4-methyl-2-imidazolidin-5-one 408

A solution of O-phenylisourea **402** (0.23 g, 0.93 mmol) and hydrazine (0.09 g, 1.25 mmol) in propan-2-ol (15 ml) was stirred at room temperature for 3 h. A precipitate formed which, at the end of this period, was collected by filtration, washed with ether and dried to give the imidazol-5-one **408** (0.11 g, 77%).

M.pt: 155-157° C.

M.S. *m/e* : 153.0658 ($C_5H_7N_5O$ requires 153.0651)
153 (M^+), 125 (M^+-28), 94 (M^+-59), 69 (M^+-84).

^1H n.m.r. (D), δ: 9.55 (bs, NH), 4.87 (s, NH_2), 4.22 (q, **CH**CH_3, J_{H-H}=7.0 Hz), 1.27 (d, CH_3, J_{H-H}=7.0 Hz).

^{13}C n.m.r. (D), δ: 173.25, 161.66, 115.49, 52.48, 52.31, 16.35.

I.R: 3333, 2189, 1767, 1663 cm^{-1}.

Analysis: Calculated for $C_5H_7N_5O$: C, 39.22; H, 4.58; N, 45.75.
Found: C, 39.54; H, 4.85; N, 44.35.

8.80 Preparation of methyl 2-(5-amino-(3-amino-1-methyl-s-triazole))butanoate 410

A solution of O-phenylisourea **403** (0.26 g, 1.0 mmol) and methylhydrazine (0.059 g, 1.2 mmol) in propan-2-ol (20 ml) was heated to reflux for 6 h. After removal of the solvent by evaporation *in vacuo* the residue was purified by flash chromatography, eluting with chloroform:methanol (9:1), to give the s-trazole **410** as an oil (0.155 g, 73%).

M.S. *m/e* : 214.1305 ($C_8H_{15}N_5O_2$ requires 214.1304)
214 (MH^+), 213 (M^+), 154 (M^+-59).

^1H n.m.r. (C), δ: 4.75 (d, NH, J_{NH-H}=8.40 Hz), 4.32 (ddd, **CH**CH_2, J_{H-NH}=8.40 Hz, $J_{H-H'}$=6.92 Hz, $J_{H-H''}$=6.22 Hz), 3.91 (bs, NH_2), 3.69 (s, OCH_3), 3.37 (s, NCH_3), 1.92-1.83 (m, CH'CH_3), 1.78-1.67 (m, CH''CH_3), 0.91 (t, CH_3, J_{H-H}=7.56 Hz).

^{13}C n.m.r. (C), δ: 174.11, 159.64, 153.66, 57.49, 52.33, 32.61, 25.73, 9.57.

I.R: 3363, 1733, 1608, 1543 cm^{-1}.

8.81 Reaction of O-phenylisourea 246 with methylhydrazine

A solution of O-phenylisourea **246** (0.38 g, 0.95 mmol) and methylhydrazine (0.048 g, 1.14 mmol) in propan-2-ol (30 ml) was heated to reflux for 6 h. The solvent was removed by evaporation *in vacuo* and the residue was purified by chromatography, eluting with chloroform:methanol (19:1), to give 2-methyl-s-triazole **409** (0.110 g, 32%) and 1-methyl-s-triazole **411** (0.120 g, 35%).

2-Methyl-s-triazole 409

M.S. *m/e* : 351.1671 ($C_{19}H_{21}N_5O_2$ requires 351.1695)
351 (M^+), 260 (M^+-91), 216 (M^+-135), 91 (M^+-260).

^1H n.m.r. (C), δ: 7.34-7.17 (m, 8H, Ph), 6.99-6.97 (m, 2H, Ph), 5.13 (d, PhCH', $J_{H'-H''}$=12.12 Hz), 5.08 (d, PhCH'', $J_{H''-H'}$=12.12 Hz), 4.78 (d, NH, J_{NH-H}=8.72 Hz), 4.74-4.69 (m, $CHCO_2$), 3.75 (bs, NH_2), 3.23 (s, NCH_3), 3.16 (dd, PhCH'', $J_{H'-H''}$=13.80 Hz, $J_{H'-H}$=5.84 Hz), 3.09 (dd, PhCH'', $J_{H''-H'}$=13.80 Hz, $J_{H''-H}$=5.68 Hz).

^{13}C n.m.r. (C), δ: 172.53, 159.66, 153.12, 135.62, 134.92, 129.16, 128.43, 128.34, 126.88, 67.14, 57.12, 37.80, 32.40.

I.R: 3400, 1733, 1617, 1589 cm^{-1}.

1-Methyl-s-triazole 411

M.pt: 124-126 °C.

M.S. *m/e*: 351.1678 ($C_{19}H_{21}N_5O_2$ requires 351.1695)
351 (M^+), 260 (M^+-91), 216 (M^+-135), 91 (M^+-260).

^{1}H n.m.r. (C), δ: 7.30-7.05 (m, Ph), 5.07 (d, PhCH', $J_{H'-H''}$=12.36 Hz), 5.05 (d, PhCH'', $J_{H''-H'}$=12.36 Hz), 4.70 (bs, NH_2), 4.54 (m, $CHCO_2$,), 3.25 (s, NCH_3), 3.10 (dd, PhCH', $J_{H'-H''}$=13.12 Hz, $J_{H'-H}$=6.10 Hz), 3.06 (dd, PhCH'', $J_{H''-H'}$=13.12 Hz, $J_{H''-H}$=6.40 Hz).

^{13}C n.m.r. (C), δ: 173.22, 159.58, 153.58, 136.30, 135.50, 129.30, 129.23, 128.29, 128.09, 126.66, 66.55, 56.89, 38.39, 32.82.

I.R: 3406, 1721, 1635, 1599 cm^{-1}.

8.82 Preparation of methyl 4-(5-methylamino-(3-amino-1-methyl-s-triazole))butanoate 412 and methyl 4-(5-methylamino-(3-amino-2-methyl-s-triazole))butanoate 413

A solution of O-phenylisourea **398** (1.16 g, 4.22 mmol) and methylhydrazine (0.30 g, 6.52 mmol) in propan-2-ol (50 ml) was heated to reflux for 6 h. The solvent was removed by evaporation *in vacuo* and the residue was purified by flash chromatography eluting with chloroform:methanol (99:1), to give **412** (0.35 g, 1.54 mmol) and **413** (0.30 g, 1.32 mmol). Each product was recrystallised from chloroform:cyclohexane for analytical purposes.

1-methyl-s-triazole 412

M.pt: 112-114 °C.

M.S. *m/e*: 227.1319 ($C_9H_{17}N_5O_2$ requires 227.1382)
227 (M^+), 196 (M^+-30), 154 (M^+-73), 140 (M^+-87).

^{1}H n.m.r. (C), δ: 4.99 (bs, NH_2), 3.64 (s, OCH_3), 3.43 (s, NCH_3), 3.28 (t, NCH_2, J_{H-H}=7.25 Hz), 2.86 (s, NCH_3), 2.32 (t, CH_2CO_2, J_{H-H}=7.42 Hz), 1.87 (tt, CH_2, J_{H-H}=7.25 Hz, J_{H-H}=7.42 Hz).

^{13}C n.m.r. (C), δ: 174.05, 162.57, 153.71, 51.46, 49.84, 35.49, 32.93, 31.30, 22.65.

I.R: 3406, 3125, 1733, 1663, 1608, 1454 cm^{-1}.

2-methyl-s-triazole 413

M.pt: 78-80 °C.

M.S. *m/e*: 227.1382 ($C_9H_{17}N_5O_2$ requires 227.1382)
227 (M^+), 196 (M^+-30), 154 (M^+-73), 140 (M^+-87).

^{1}H n.m.r. (C), δ: 3.86 (bs, NH_2), 3.64 (s, OCH_3), 3.49 (s, NCH_3), 3.10 (t, NCH_2, J_{H-H}=7.21 Hz), 2.78 (s, NCH_3), 2.32 (t, CH_2CO_2, J_{H-H}=7.30 Hz), 1.87 (tt, CH_2, J_{H-H}=7.30 Hz, J_{H-H}=7.21 Hz).

^{13}C n.m.r. (C), δ: 173.44, 159.88, 158.65, 53.36, 51.57, 39.60, 34.62, 31.11, 22.69.

I.R: 3333, 3186, 1733, 1635, 1586, 1541 cm^{-1}.

Analysis: Calculated for $C_9H_{17}N_5O_2$: C, 47.56; H, 7.54; N, 30.82.
Found: C, 47.53; H, 7.50; N, 30.84.

8.83 Preparation of N-(methyl butanoate)-N-benzyloxcarbonyl-N'-cyano-O-phenylisourea 432

To a solution of O-phenylisourea **431**[83] (0.500 g, 1.92 mmol) and benzyloxycarbonyl chloride (0.530 g, 3.12 mmol) in dry THF (30 ml) was added sodium hydride (0.058 g, 1.92 mmol, 80%) and the resulting suspension was stirred at room temperature for 1.5 h. Chloroform (30 ml) was added and the reaction mixture was washed with water (2x20 ml). The organic layer was dried ($MgSO_4$), the solvent removed by evaporation *in vacuo* and the residue purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:8), to give the title compound as a colourless oil (0.37 g, 56%).

M.S. *m/e*: 396.1526 ($C_{21}H_{22}N_3O_5$ requires 396.1559)
396 (MH^+), 352 (M^+-43), 320 (M^+-75), 302 (M^+-93).

^{1}H n.m.r. (C), δ: 7.42-7.20 (m, 8H, Ph), 7.12-7.02 (m, 2H, Ph), 5.30 (s, $PhCH_2$), 3.92 (t, NCH_2, J_{H-H}=6.80 Hz), 3.62 (s, OCH_3), 2.41 (t, CH_2CO_2, J_{H-H}=7.20 Hz), 2.04 (tt, CH_2, J_{H-H}=6.80 Hz, J_{H-H}=7.20 Hz).

^{13}C n.m.r. (C), δ: 172.92, 161.03, 152.22, 151.40, 134.13, 129.84, 128.88, 128.64, 120.35, 119.58, 69.99, 47.83, 30.28, 26.55, 23.47.

I.R.($CHCl_3$): 2996, 2947, 2207, 1736, 1626 cm^{-1}.

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