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Preparation of Imidazolones from N-cyano-N'-methylcarboxyguanidines. An Unusual C-N Bond Formation in the Hydrogenolysis of a Benzyl Ester in an Attempted Synthesis of an Inhibitor of Carboxypeptidase A

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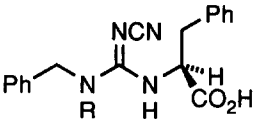
Abstract: Hydrogenolysis of the benzyl ester **5** gave the imidazolone **6** rather than the desired acid **1**, and the related benzyl ester **11** also hydrogenolysed to the imidazolone **12**. Examination of the hydrolysis of simpler guanidine derivatives with trifluoroacetic acid suggested a unified mechanism for these processes which, in the case of the imidazolones, involves the intramolecular formation of a 7-membered ring intermediate The hydrolytic reactions provide useful, high yield methods for transforming the N-cyanoimine group into other functional groups.

Introduction

Carboxypeptidase A is a zinc-containing proteolytic enzyme which cleaves the C-terminal amino acid from peptides. For the reaction to occur, the peptide must have a free terminal carboxyl group and the rate of hydrolysis is enhanced when the terminal residue has a benzylic or branched aliphatic α-substituent.[1] The terminal carboxy-residue must have the L-configuration and substitution of the amide nitrogen prohibits or greatly reduces the rate of hydrolysis. In the case of dipeptides, hydrolysis is much faster if the N-terminal amino acid is acylated on nitrogen. The actual mechanism of action remains controversial, although a number of issues have been resolved. Binding of the substrate is believed to involve charge pairing of the terminal carboxylate group with the guanidinium moiety of an arginine residue (Arg^{145}) allowing the carbonyl oxygen to ligand the active site zinc atom.[2] This polarizes the carbonyl group and facilitates nucleophilic mediated hydrolysis. Whether the general acid catalysis occurs directly through the carboxyl anion of glutamine (Glu^{270}) or via a water molecule is not known.[3] Particular substrates appear to have different mechanistic variations, although this has been disputed.[4,5] The enzyme catalyses other processes[6,7] and so there may not be a general mechanism for all substrates. We have attempted to design a substrate that would incorporate the N-cyanoimine function as an isostere for the carbonyl group,[8,9] on the premise that such a compound would bind to the enzyme but would not be hydrolysed. The target compounds for our

study had the general features shown in **1** in which all the binding requirements of the enzyme would be met.

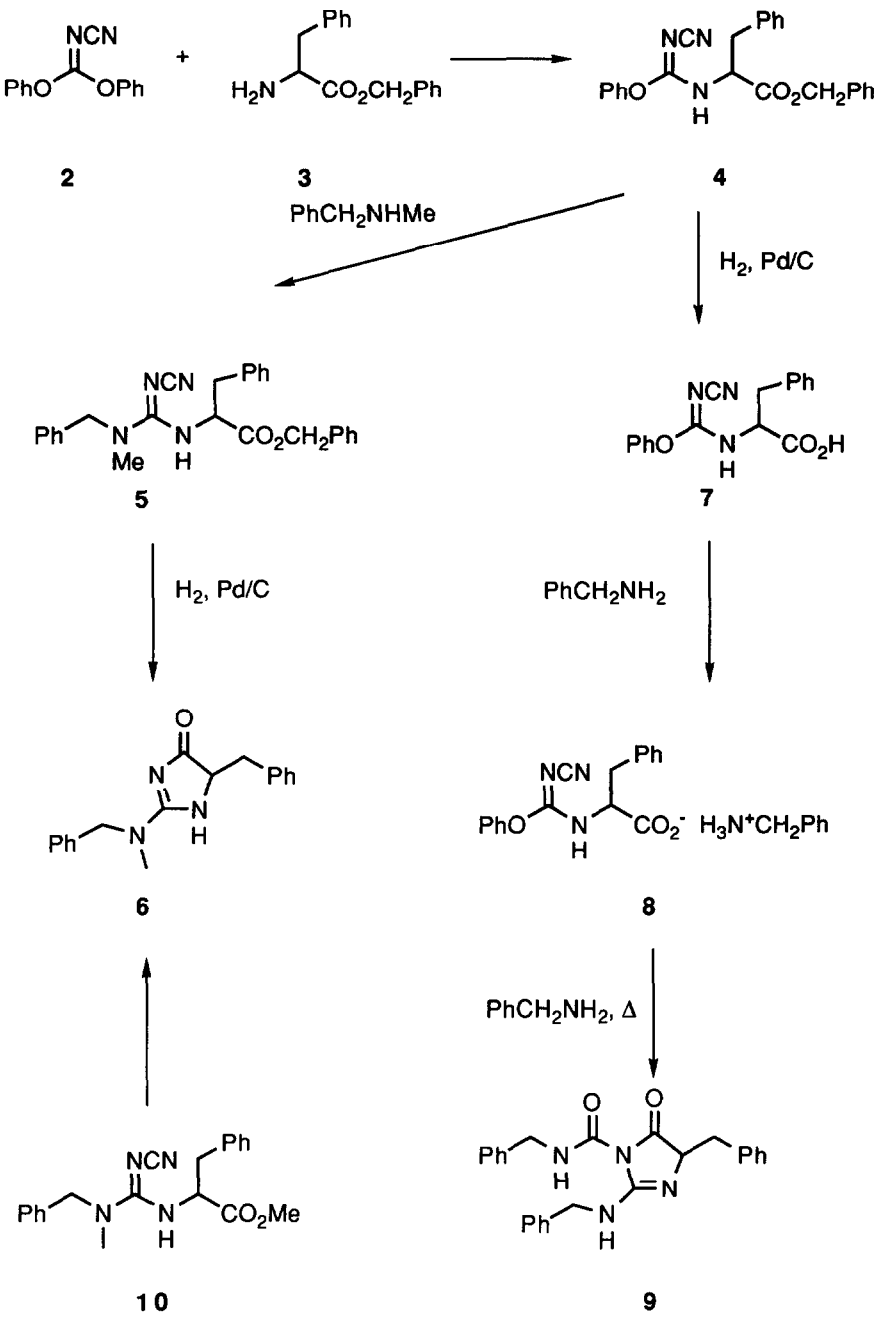


1

The synthesis of this compound appeared to be relatively straightforward using chemistry that we have developed for the synthesis of hexahydropyrimidines.[10,11] Reaction of diphenyl N-cyanocarbonimidate with a suitably carboxyl-protected phenylalanine followed by N-substituted benzylamine should give the desired carboxyl-protected derivative of **1** which could then be deprotected. While the synthesis of carboxyl-protected derivatives of **1** proved unexceptional our attempts to deprotect these compounds led not to **1** but to imidazolone derivatives.

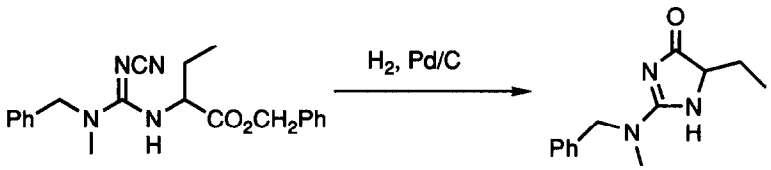
Results and Discussion

Treatment of diphenyl N-cyanocarbonimidate (**2**) with L-phenylalanine benzyl ester (**3**) gave the expected O-phenylisourea **4**. Treatment of **4** with N-methylbenzylamine then gave the guanidine **5** in 56% yield. This yield is lower than that usually observed in this type of reaction and was attributed to the greater steric requirements of this secondary amine over the primary amines that we have mainly investigated. The preparation of **1** then merely required the removal of the benzyl protecting group. Treatment of **5** with hydrogen over palladium charcoal gave, however, not the desired carboxylic acid but the imidazole derivative **6**, mp 172-174 °C in 78% yield. The mass spectrum showed the molecular ion at 293, the ^{13}C NMR spectrum showed the presence of 14 magnetically different carbon atoms, the resonance signals at δ 188.0 and 171.6 being assigned to the carbonyl carbon and the guanidine carbon, respectively. The ^{1}H NMR spectrum is temperature dependant, reflecting restricted rotation around the secondary nitrogen side chain. The direct route having been frustrated, we therefore investigated the prior cleavage of the benzyl group and treated **4** with H_2 over Pd when the acid **7** was formed in good yield. Treatment of **7** with benzylamine at room temperature gave the salt **8**. Heating **8** with benzylamine gave the imidazole derivative **9**. The mass and ^{13}C NMR spectra were consistent with the assigned structure. When the methyl ester **10** was hydrolysed with potassium t-butoxide in water[12] the imidazole **6** was again obtained. The methyl ester **10** could also be cleaved with trifluoroacetic acid in water or with chymotrypsin in tris buffer, but in both cases **6** was again obtained, although there was some evidence from TLC to suggest that a more polar product, possibly the desired acid, was also produced, but all attempts to separate this led to **6**. No inhibition of chymotrypsin was observed and its effectiveness in the hydrolysis of **10** could be expected since the latter resembles a dipeptide having a phenylalanine as the C-terminal residue.[13]



Hydrogenolysis of the benzyl ester **11**, prepared from methyl 2-aminobutanoate by a similar route to that used for **5**, also gave an imidazole derivative, in this case **12**, mp

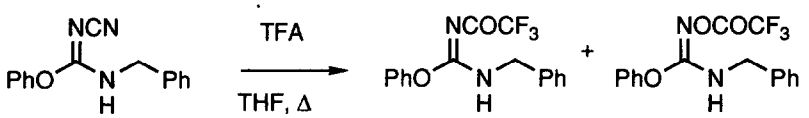
124-125 °C. The mass and ^{13}C NMR spectra were both consistent with the assigned structure, the latter showing signals at δ 190.4 and 171.1 for the carbonyl and guanidine carbon, respectively.



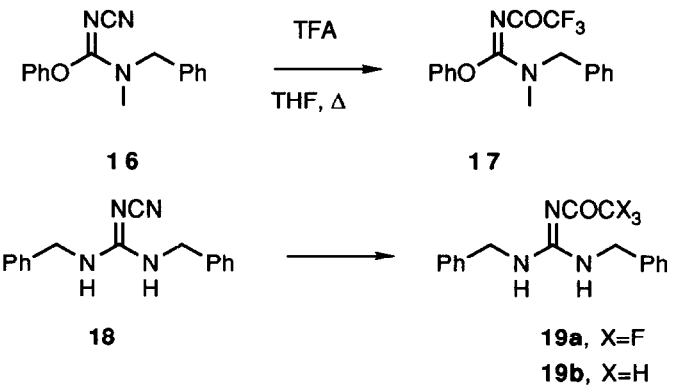
11 **12**

In all of these reactions forming imidazoles, it appears that liberation of the acid leads to rapid cyclisation onto the imine nitrogen of the N-cyanoimine. In order to better understand this process, we examined the reaction of a series of simpler N-cyanoimines with trifluoroacetic acid. The O-phenylisourea **13** was treated with 6 equivalents of TFA in boiling THF to give two products, the trifluoroacetyl derivative **14**, mp 94-96 °C, in 39% yield and the trifluoroacetoxy derivative **15**, mp 110-112 °C in 22% yield. In terms of the molecular formula, the latter compound represents the exchange of the cyanide group by trifluoroacetate, an unexpected process. The structure was deduced from the elemental analysis and the spectral properties. The ^1H NMR spectrum shows 10 aromatic protons, a broad singlet assigned to the NH proton, and a two proton singlet assigned to the benzylic protons. The ^{13}C NMR spectrum clearly shows the presence of the CF_3CO group with the appropriate C-F coupling constants, and the mass spectrum shows no molecular ion but signals at *m/e* 225, corresponding to the loss of CF_3CO_2, and at *m/e* 133, corresponding to the loss of CF_3CO_2 and C_6H_5O

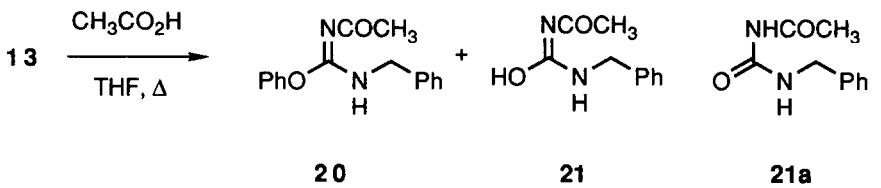
Treatment of the the O-phenylisourea **16** under the same conditions gave only the trifluoroacetyl compound **17**, mp 60-62 °C, in 58% yield, and the guanidine derivative **18** also gave only the corresponding trifluoroacetyl derivative **19a**, mp 135-137 °C, in 65% yield.



13 **14** **15**



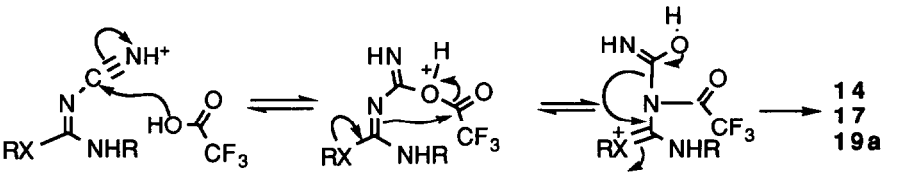
Similar products were obtained when glacial acetic acid was substituted for TFA but the times required for completion of the reaction were considerably greater. Treatment of **13** with glacial acetic in boiling THF gave **20**, corresponding to the trifluoroacetate **14**, and **21**, in which the phenoxy group has been hydrolysed, probably due to the intrusion of water with the longer reaction time. Compound **21** appears from its spectral properties to be in the enolic form shown, rather than the tautomeric urea structure **21a**, and to exist as a mixture of rotomers at room temperature. Treatment of **18** with glacial acetic acid in THF gave **19b**, analogous to the trifluoroacetate derivative **19a**.



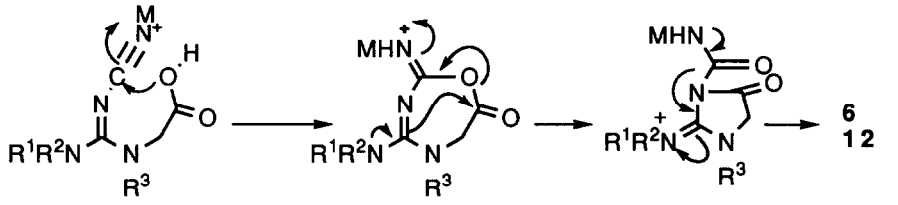
The trifluoroacetyl derivatives would appear to be derived by protonation on the cyanide nitrogen which facilitates nucleophilic addition of the trifluoroacetyl group to the cyanide carbon [Scheme (a)]. This intermediate then undergoes rearrangement, either as shown or possibly through a charged pair mechanism, to the product. Application of this intermolecular process to the formation of the imidazolone [Scheme (b)] requires the intramolecular formation of a seven-membered ring but this, once formed, should facilitate subsequent bond formation as a transannular process. The palladium may play a similar role in the conversion of the benzyl ester to the imidazolone, activating the nitrile group, as that suggested for the proton in the acid catalysed reactions.

Scheme

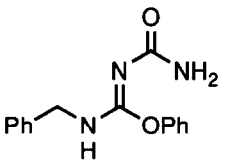
(a)



(b)



When **13** was treated with TFA at room temperature over a prolonged period the urea **22**, mp 138-140 °C, was obtained, and treatment of **18** with TFA and water in boiling THF gave the urea **23**, mp 111-113 °C. Nucleophilic attack by water on the carbonyl group of the initial intermediate shown in Scheme (a) would provide the urea, this mode of fragmentation not appearing to occur in the absence of added nucleophiles. This appears to be a general reaction and a number of cyanoimino substituted imidazoles (**24a-d**) were converted to the corresponding ureas by this method (**25a-d**) This reaction has also been reported to occur when gonadotrophin-releasing hormone antagonists containing modified N^{ω}-cyano-$N^{\omega'}$-alkyl or arylguanidino groups on homoarginine are stored in the lyophilized state as the trifluoroacetate salt. [14]



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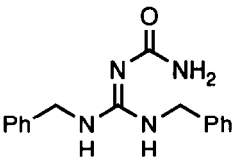

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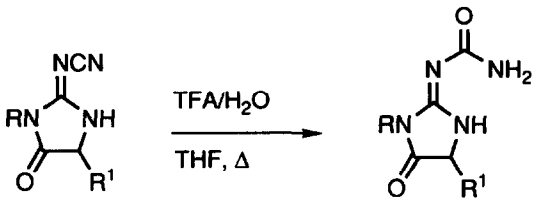
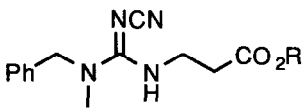
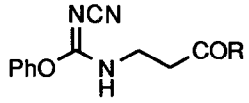


24a, R=R^1=CH_2Ph **25a**
24b, R=CH_2Ph, R^1=CH_2CO_2Me **25b**
24c, R=cyclopentyl, R^1=CH_2Ph **25c**
24d, R=NH_2, R^1=Et **25d**





26a R = Me
26b R = H

27a R = OCH_2Ph
27b R = $NMeCH_2Ph$

In keeping with the general observation in this area, the corresponding hexahydropyrimidines were not available directly by this route.[10,15] Thus saponification of the methyl ester **26a** proceeded smoothly to the corresponding acid **26b**. Spontaneous cyclization to the dihydropyrimidine, which would involve an 8-membered ring intermediate, clearly does not occur in these systems. The benzylic ester corresponding to **26a** could not be prepared by our general route since treatment of the benzylic ester **27a** with N-methylbenzylamine led to displacement of the benzyl ester rather than the phenoxy group to give **27b**. Hexahydropyrimidines can, however, be prepared from suitably substituted imidazolones, such as **25b**, as we have previously reported.[16]

Experimental

Melting points were determined on a Reichert Hot-stage microscope and are uncorrected ^1H NMR spectra were obtained on either a Varian Gemini 200 spectrometer at 200 MHz or a VXR 400 spectrometer at 400 MHz as solutions in $CDCl_3$ unless stated otherwise, with Me_4Si as internal standard ^{13}C NMR spectra were obtained on a Varian VXR 400 spectrometer at 100 MHz as solutions in $CDCl_3$ unless stated otherwise, with Me_4Si as internal standard IR spectra were obtained on a Perkin Elmer PE983 spectrometer as KBr pellets. Chromatography was carried out on Kieselgel 60 silica (200-400 mμ). Solvents were purified and dried by standard methods Tris buffer was 10 mM aqueous tris(hydroxymethyl)aminomethane, 20 mM aqueous $CaCl_2$

Preparation of N-cyano-N'-(S)-(1-benzyloxycarbonyl-2-phenylethyl)-O-phenylisourea (4).

A solution of (S)-phenylalanine benzyl ester 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 precipitate of diethylamine hydrochloride removed by filtration. The filtrate was evaporated under vacuo to give (S)-phenylalanine benzyl ester (3) (0.52 g, 99%) as a colourless oil The oil was dissolved in propan-2-ol (20 mL) and diphenyl cyanocarbonimidate (2) (0 48 g, 2.05 mmol) was added The resulting solution was heated at 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 4 as a colourless oil, 0 75 g, 75%, MS, *m/e*, 399, 354, 308,91; ^{1}H NMR, δ, 7.40-7.10 (m, 12H), 6 98-6.80 (m, 2H), 6 75-6.60 (m, 2H), 5.58 (bd, 1H), 5 23 (bs, 1H), 5.15 (bd, 1H), 4.85-4.78 (m, 1H), 3 40-3.00 (m,2H); ^{13}C NMR, δ, 170 6, 163.75, 151 4, 136 3, 131.1, 130 3, 129.95, 129 3, 128 95, 128.2, 127 6, 127 2, 121.8, 121 2, 116.0, 68.1, 57 4, 56 5, 38 1, 38.0, 27 2.

IR ($CHCl_3$), 3680, 2197, 1745, 1621 cm^{-1}

$C_{24}H_{21}O_3N$ requires C, 72 16, H, 5.30, N, 10 52 Found. C, 71 43; H, 5 54, N, 10 23

Preparation of N-benzyl-N-methyl-N'-cyano-N"-(1-benzyloxycarbonyl-2-phenylethyl)guanidine (5).

N-methylbenzylamine (10 mL) was added to the O-phenylisourea 4 (0 36 g, 7 51 mmol) and the resulting solution was stirred at room temperature for 8h Chloroform (30 mL) was added and the mixture extracted with 5% aqueous citric acid (2x15 mL) and dried ($MgSO_4$) The solvent was removed by evaporation under vacuo and the residue was purified by flash chromatography eluting with ethyl acetate.cyclohexane (2.1) to give 5, 0 18 g, 56%, MS, *m/e*, 426, 335, 291, 91, ^{1}H NMR, δ, 7 39-7 08 (m, 13H), 6.84 (d, 2H), 5.20 (d, 1H, J = 11 9 Hz) 5 21-5 18 (m, 1H), 5 12 (d, 1H, J = 11 9 Hz), 5 08 (d, J = 7.9 Hz), 4 49 (s, 2H), 3 23 (dd, 1H, J = 14.0, 5.9 Hz), 3 18 (dd, 1H, J = 14.0, 4 9 Hz), 2 88 (s, 3H), ^{13}C NMR, δ, 171 3, 158 2, 135 1, 134 8, 134 6, 129 2, 129 0, 128 7, 128 65, 128 6, 128 0, 127 2, 127 0, 116 9, 67 75, 55 6, 54 4, 37 8, 36.5, IR, 3399, 2171, 1735, 1668,1638 cm^{-1}

$C_{26}H_{26}N_4O_2$ requires 426 4916 Found 426 2087

Hydrogenolysis of 5. Preparation of 2-(N-methylbenzylamine)-4-benzylimidazolidin-5-one (6).

Palladium on charcoal (0.10 g, 5%) was added to a degassed solution of 5 (0 15 g, 0 53 mmol) in ethanol (10 mL) and the resulting suspension was stirred under an atmosphere of hydrogen (1 atm) for 48 h The mixture was filtered through Celite and the solvent was removed from the filtrate under vacuo The residue was purified by flash chromatography, eluting with chloroform methanol (12 5 1) to give 6, 0 080 g, 78%, mp 172-174 °C, MS, *m/e*, 293, 278, 202, 91, ^{1}H NMR, δ, DMSO, 8 28 (bs, 0 3H), 8 14 (bs, 0 7H), 7 25-7 15 (m, 8H), 7 00-6 80 (m, 2H), 4 81 (bd, 0.7H), 4 65 (bd, 0 3H), 4 30 (bd, 1H), 4 24 (t, 1H, J = 4 8 Hz), 3 38-2 98 (m, 1H), 2,92-2 88 (m, 4H), ^{13}C NMR , δ, DMSO, 188 0, 171 6, 137 3, 137 0, 130 1, 128 9, 128 3, 127 5, 126 7, 62 3, 53 1, 51 5, 37 2, 33 8; IR, $CHCl_3$, 3500, 2925, 1715, 1595, 1578, 1458 cm^{-1}

$C_{18}H_{19}N_3O$ requires C, 73 69, H, 6 25, N, 14 32 Found C, 73 31,, H, 6 58, N, 14 38

Hydrolysis of methyl ester 10.

(1) With potassium t-butoxide Water (0 020 g, 1 3 mmol) was added to an ice-cold mixture of KO-tBu (0 55 g, 5 0 mmol) in dry ether (10 mL) and the suspension stirred for 10 min The ester 10 (0 20 g, 0 6 mmol) was then added

and stirring continued at room temperature for 2 h Iced water (30 mL) was added, when all the solid dissolved, and the solution was then acidified to *ca* pH 1 with 2M HCl and extracted with ether (3x20 mL). The ethereal extracts were dried ($MgSO_4$) and the solvent removed under vacuo The residue was dissolved in EtOAc MeOH (19.1, 5 mL) and the solution cooled at 4 °C for 6 h The resulting crystals were collected by filtration, washed with ether and dried as **6** (0 070g, 44%), identical in all observed respects to the above sample

(2) With chymotrypsin. The ester **10** (0 70 g, 2.0 mmol) was dissolved in a mixture of MeCN (7 mL) and Tris buffer (60 mL, pH 7 8, Ca^{2+} 20mM) and a solution of chymotrypsin (30 mg) in a mixture of HCl (0 1 M, 9 mL) and Tris buffer (12 mL) was added The mixture was stirred overnight , the volume reduced to one half by evaporation under vacuo The remaining mixture containing some precipitate was cooled to 4 °C overnight and the precipitate collected by filtration Tlc and ^1H NMR spectroscopy indicated that it was a mixture of products The mixture was extracted with NaOH (2M) but the great majority of the material was insoluble in base The residue was recrystallised as above and identified as **6**

(3) with TFA The ester **10** (0 45 g, 1 3 mmol) , TFA (0.88 g, 6 eq), and water (0 14 g, 6 eq) were added to dry THF and the solution stirred at rt for 48 h. Tlc showed two components and the solvent was removed under vacuo and the residue chromatographed on silica, eluting with EtOAc MeOH (98 2) Only one product was obtained, identified as **6.**

Hydrogenolysis of 4. Preparation on N-cyano-N'-(1-carboxy-2-phenylethyl)-O-phenylisourea (7). Palladium on charcoal (0 10 g, 10%) was added to a degassed solution of **4**(0 70 g, 1 75 mmol) in ethanol (30 mL) and the resulting suspension stirred under an atmosphere of hydrogen (1 atm) for 8 h. The mixture was filtered through Celite and the solvent removed from the filtrate by evaporation under vacuo. The residue was purified by flash chromatography eluting with chloroform. methanol (9 1) to give **7**, 0.40 g, 74%, MS, *m/e*, 264 (M^+ - CO_2,H requires 264.2897, Found 264 1146), 215, 149, 94, ^1H NMR, δ, CD_3OD, 7 35-7 17 (m, 8H), 6.90 (d, 1H), 6.62 (d, 1H), 4 63 (m, 0 5H), 4 49 (m, 0 5H), 3 47-3 39 (m, 1H), 3 06-3 00 (m, 1H), ^{13}C NMR, δ, CD_3OD, 177 8, 164 1, 161.0, 152 5, 152 4, 139 3, 138 7, 131 4, 130 7, 130 6, 130 3, 129 7, 127 8, 127 7, 127 5, 127 4, 122 5, 121 3, 116 3, 115 9, 60 3, 59 8, 40 35, 38 0, IR, 3627, 2189, 1715, 1614 cm^{-1}

Formation of the salt 8.

Benzylamine (10 mL) was added to **7** (0 50 g, 1.62 mmol) and the resulting solution stirred at room temperature for 12h Chloroform (20 mL) was added and the mixture extracted with 5% aqueous citric acid solution (2x10 mL). The organic layer was dried ($MgSO_4$) and reduced to half volume by evaporation under vacuo The solution was cooled to 4 °C for 12h and the resulting crystals collected by filtration as **8**, 0 50 g, 74%, ^1H NMR, δ, DMSO, 7.80 (bs, 1H), 7 44-7 04 (m, 15H), 4 30 (dd, 1H, J = 15 8, 6 2 Hz), 4 28 (dd, J = 15 8, 5 8), 4 10 (m, 1H), 3 06 (dd, 1H, J = 13.6, 5 2 Hz), 3 00 (dd, 1H, J = 13 6, 5 4 Hz), ^{13}C NMR, δ, DMSO, 172 0,158 5, 138 5, 138 1, 135 7, 129 6, 128.6, 128.5, 128.3, 128 0, 127 9, 127 0, 126 8, 118.05, 56 5, 56 4, 44 25, 42.5, 39 1, 38 9, IR, 3364, 3229, 2170, 1602, 1553 cm^{-1}

Reaction of 8 with benzylamine. Preparation of 9.

Benzylamine (10 mL) was added to the salt **8** (0 50 g, 1 20 mmol) and the resulting solution heated at 100 C for 48h. Chloroform (30 mL) was added and the mixture was extracted with 5% aqueous citric acid solution (3x20 mL) The organic layer was dried ($MgSO_4$) and the solvent removed by evaporation in vacuo The residue was purified by flash chromatography eluting with chloroform methanol (9:1) to give **9**, 0.31 g, 63%, MS, *m/e*, 412, 320, 277, 91; ^1H NMR, δ, 7 32-7 21 (m, 3H), 7 19-7 12 (m, 10H), 6 94-6.92 (m, 2H), 4.60 (d, 1H, J = 14 9 Hz), 4 52 (d, 1H, J = 14.9 Hz), 4 36

(dd, 1H, J = 4 6, 6.5 Hz), 4 30 (s, 2H), 3.22 (dd, 1H, J = 13 7, 4 6 Hz), 2 98 (dd, 1H, J = 13 7, 6.5 Hz); ^{13}C NMR, δ, 174.8, 160 0, 159.35, 137 8, 136 6, 129 7, 128.75, 128.3, 128.1, 127 6, 127 35, 127 1, 127.0, 126 5, 65.3, 45 2, 42 7, 37 5; IR, 3437, 1755, 1712, 1629, 1586 cm^{-1}

Preparation of N-benzyl-N-methyl-N'-cyano-N'-(S)-(1-carboxybenzylpropyl)guanidine (11).

N-methylbenzylamine (7 mL) was added to N-cyano-N'-(S)-(1-benzyloxycarbonylpropyl)-O-phenylisourea (0 63 g, 1 87 mmol) and the resulting solution was stirred at room temperature for 12 h. Chloroform (30 mL) was added and the reaction mixture extracted with 5% aqueous citric acid solution (2x20 mL) The organic layer was dried ($MgSO_4$) and the solvent removed by evaporation under vacuo The residue was purified by flash chromatography eluting with ethyl acetate cyclohexane (2.1) to give **11**, 0 41 g, 60%, MS, *m/e*, 364, 273, 229, 91, ^1H NMR, δ, 7.37 7 29 (m,8H), 7 21-7.20 (m, 2H), 5 31 (bd, 1H, J = 7 7 Hz), 5.18 (d, 1H, J = 12.2 Hz), 4.87 (dt, 1H, J = 11.3, 7 7 Hz), 4 64 (d, 1H, J = 16 0 Hz), 4.57 (d, 1H, J = 16 0 Hz), 3 05 (s, 3H), 2 02-1 91 (m, 1H), 1 84-1 74 (m, 1H), 0 78 (t, 3H, J = 7 5 Hz); ^{13}C NMR, δ, 172 1, 158 4, 135.3, 134 9, 129 0, 128 6, 128 5, 128 25, 128.05, 127 0, 116.8, 67 5, 56 05, 54 6, 36.8, 25 7, 8 7, IR, 3406, 2992, 2171, 1731, 1578 cm^{-1}

Hydrogenolysis of 11. Preparation of 2-(N-methylbenzylamine)-4-ethylimidazolid-5-one (12).

Palladium on charcoal (0 10 g, 10%) was added to a degassed solution of **11** (0 40 g, 1 10 mmol) in ethanol (30 mL) and the resulting suspension was stirred under an atmosphere of hydrogen (1 atm) for 12h The mixture was filtered through Celite and the solvent removed from the filtrate by evaporation under vacuo The residue was purified by flash chromatography eluting with chloroform methanol (9 1) to give **12**, 0.20 g, 79%, mp 124-126 °C, MS, *m/e*, 231, 216, 202, 91, ^1H NMR, δ, 8 19 (bs, 1H), 7 27-7 21 (m, 3H), 7 16-7.14 (m, 2H), 4 62 (bs, 2H), 3 95 (bs, 1H), 3 00 (bs, 3H), 2 93 (bs, 3H), 1.90-1 72 (m, 1H), 1 70-1 66 (m, 1H), 0.85 (bs, 3H), ^{13}C NMR,δ, 190 4, 171 1, 136.1, 129.0, 128 5, 127 6, 127 1, 63 7, 54 05, 52 65, 36 4, 33 9, 24 6, 8 7, IR, 3284, 2978, 1702, 1592, 1451 cm^{-1}

$C_{13}H_{17}N_3O$ requires 231 1372 Found 231 1365

Reaction of 13 with Trifluoroacetic acid. Preparation of N-trifluoroacetyl-N'-benzyl-O-phenylisourea (14) and N-trifluoroacetoxy-N'-benzyl-O-phenylisourea (15).

A solution of **13** (0 40 g, 1 59 mmol) and TFA (1 11 g, 9 74 mmol) in THF (20 mL) was heated to reflux for 8 h The solvent was removed by evaporation under vacuo and the resulting oil purified by flash chromatography eluting with chloroform·methanol (9:1) to give **14**, 0 20 g, 39%, mp 94-96 °C, and **15**, 0 12 g, 22%, mp 110-112 °C

Compound **14** MS, *m/e*, 189, 94, 91, ^1H NMR, δ, 10 00 (bs, 1H), 7.47-7 37 (m, 2H), 7 13 (d, 2H, J = 1 2 Hz), 4 76 (d, 2H, J = 5 6, ^{13}C NMR, δ, 168.4, q, J = 36 9), 163 9, 150 9, 135 6, 129 25, 129 1, 128 3, 127 6, 126 3, 121 5, 116 1 (q, J = 284 6 Hz), 42 0, IR, 3419, 1657, 1608, 1427 cm^{-1}

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

Compound **15** MS, *m/e*, 225, 133, 91, ^1H NMR, δ, 7 46-7.32 (m, 8H), 7 01 (d, 2H, J = 7 6 Hz), 6 00 (bs, 1H), 4 58 (s, 2H); ^{13}C NMR, δ, 163.2 (q, J = 35 1 Hz), 160.05, 148 6, 136 25, 130 9, 128.8, 128 4, 127.9, 127.5, 120 8, 116.3 (q, J = 290 5 Hz), 44 95, IR, 3336, 1684, 1531, 1440 cm^{-1}

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

Preparation of N-cyano-N'-benzyl-N'-methyl-O-phenylisourea (16).

N-methylbenzylamine (0.07 g, 0.58 mmol) was added to a solution of **2** (0.11 g, 0.46 mmol) in propan-2-ol (10 mL) and the resulting solution was stirred for 2 h The solvent was reduced to one half by evaporation under reduced pressure and was then cooled to 4 °C for 2 h The resulting crystalline product was removed by filtration, washed with ether and dried to give **16**, 0 10 g, 85%, mp 122-124 °C, MS, *m/e*, 265, 250, 208, 91, ^{1}H NMR, δ, 7 45-7.25 (m, 8H), 7 12 (d, 2H), 4 69 (bs, 2H), 3 12 (bs, 3H), ^{13}C NMR, δ, 158 0, 157.8, 134 8, 129 95, 128 9, 127 7, 127 6, 125 9, 118 0, 54 15, 36.6, 34.2 IR, 2990, 2187, 1617, 1476 cm^{-1}

$C_{16}H_{15}N_3O$ requires 265 1215 Found 265 1240

Preparation of N-trifluoroaceto-N'-benzyl-N'-methyl-O-phenylisourea (17).

A solution of **14** (0.34 g, 1 28 mmol) and trifluoroacetic acid (0 88 g, 7 69 mmol) in THF (15 mL) was stirred at room temperature for 12 h. The solvent was removed by evaporation under vacuo and the resulting oil purified by flash chromatography eluting with ethyl acetate cyclohexane (1 1) to give **17** (0 24 g, 58%) A sample was recrystallised from cyclohexane for analytical purposes, mp 60-62 °C, MS, *m/e*, 279, 267, 243, 91, ^{1}H NMR, 7.33-7.24 (m, 7H), 7 16-7.12 (m, 1H), 7 06-7 05 (m, 2H), 4 71 (bs, 1.3H), 4 62 (bs, 0 7H), 3 06 (bs, 1.3H), 3.02 (bs, 1 7H); ^{13}C NMR, δ, 163 9, 159 6 (J = 35.9 Hz), 159 5 (q, J = 38 1 Hz), 151 8, 151 7, 133 95, 129.4, 129.1, 128 4, 127.5, 126 3, 120 15, 120 0, 116 4,(q, J = 285 6 Hz), 55 2, 54 3, 37 2, 34 8, IR, 2953, 1721, 1657, 1589 cm^{-1}

Preparation of N,N'-dibenzyl-N"-trifluoroacetyl guanidine (19a).

A solution of **18** (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 under vacuo and the resulting oil was purified by flash chromatography eluting with chloroform methanol (49 1) to give **19a**, 0 41 g, 65% A sample was recrystallised from cyclohexane for analytical purposes, mp 135-137 °C, MS, *m/e*, 267, 266, 244, 91, ^{1}H NMR, δ, 0 °C, 10 06 (bs, 1H), 7 37-7 27 (m, 8H), 7 12 (bs, 2H), 5 08 (bs, 1H), 4 61 (bs, 2H), 4 39 (bs, 2H), ^{13}C NMR, δ, 45 °C, 167 4(q, J = 35 23 Hz), 160 9, 129 1, 128 1, 127 4, 116 9 (q, J = 285 2 Hz), 45 5, IR, 3321, 1608, 1568, 1436 cm^{-1}

$C_{17}H_{16}N_3OF_3$ requires C, 60 89, H, 4 81, N, 12 53 Found C, 61 04, H, 4 75, N, 12 39

Preparation of N-acetyl-N',N"-dibenzylguanidine (19b).

A solution of **18** (0 79 g, 3 0 mol) and glacial acetic acid (1 07 g, 17 8 mmol) in THF (30 mL) was heated to reflux for 72h The solvent was removed by evaporation under vacuo and the resulting oil purified by flash chromatography eluting with dichloromethane ethyl acetate (1 1) to give **19b**, 0 45 g, 54%, mp 75-76 °C, MS, *m/e*, 281, 266, 222, 91, ^{1}H NMR, δ, 7 30-7 24 (m, 6H), 7 17 (bs, 4H), 4 42 (bs, 2H), 2 10 (s, 3H), ^{13}C NMR, δ, 181 5, 159 6, 128 8, 127 65, 44 9, 28 4, IR, 3327, 3217, 1596, 1565 cm^{-1}

$C_{17}H_{19}N_3O$ requires 281 1528 Found 281 1537

Preparation of N-acetyl-N'-benzyl-O-phenylisourea (20) and N-acetyl-N'-benzylisourea (21).

A solution of **13** (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 48h. The solvent was removed by evaporation under vacuo and the resulting oil was purified by flash chromatography eluting with ethyl acetate cyclohexane (1:3) to give **20**, 0 12 g, 26%, as an oil and **21**, 0.08g, 26%, mp 125-127 °C.

Compound **20**, MS, *m/e*, 268, 253, 226, 191; ^{1}H NMR, δ, 7 36-7 18 (m, 8H), 7.05-7 03 (m, 2H), 4.63 (bs, 2H), 1.99 (s, 3H), ^{13}C NMR, δ, 185.8, 161.6, 151 5, 137.1, 129.1, 128.8, 127 7, 127 4, 125 5, 121 8, 45.3, 28.2; IR, 3217, 1703, 1623, 1596 cm^{-1}

$C_{16}H_{16}N_2O_2$ requires 268 1212 Found: 268.1211

Compound **21**, MS, *m/e*, 192, 149, 133, 91, ^{1}H NMR, δ, 9.96 (bs, 1H), 8,85 (bt, 1H), 7.40-7.21 (m, 5H), 4 64 (d, J = 6 0 Hz), 4 46 (d, J = 6 0 Hz), 2.26 (s), 2 07 (s); ^{13}C NMR, δ, 172.4, 162.5, 160 8, 154 8, 151 2, 138.0, 136.8, 129 2, 128 9, 128 6, 127.9, 127 5, 127 4, 125 95, 121 8, 45.7,43.5, 24.23, 23 9; IR, 3302, 1730, 1693, 1666 cm^{-1}

$C_{10}H_{12}N_2O_2$ requires 192.0899 Found. 192 0894

Preparation of N-amido-N'-benzyl-O-phenylisourea (22).

A solution of **13** (0.60 g, 2 4 mmol) and trifluoroacetic acid (1 63 g, 14 3 mmol) in THF (20 mL) was stirred at room temperature for 13 days The solvent was removed by evaporation under vacuo and the resulting oil purified by flash chromatography eluting with ethyl acetate cyclohexane (2.3) to give **22**, 0 40 g, 62%, mp 138-140 °C, MS, *m/e*, 269, 253, 226, 91, ^{1}H NMR, δ, 9 90 (bs, 1H), 7 78-7 19 (m, 8H), 7 01 (d, 2H, J = 7 6 Hz), 5,80 (bs, 1H), 4 85 (bs, 1H), 4 61 (s, 2H), ^{13}C NMR, δ, 164 0, 160 9, 151 3, 137 1, 129 4, 128 8, 127 75, 127 3, 126 0, 121 6, 45 5 IR, 3474, 1739, 1641, 1617 cm^{-1}

$C_{15}N_{15}N_3O_2$ requires 269 1164 Found 269 1179

Preparation of N-amido-N',N''-dibenzylguanidine (23).

A solution of **18** (0 5 g, 1.9 mmol) , trifluoroacetic acid (1 32 g, 11 6 mmol) and water (0 20 g, 11 6 mmol) in THF (12 mL) was heated to reflux for 4 h The solvent was removed by evaporation under vacuo and the resulting oil purified by flash chromatography eluting with chloroform methanol (19 1) to give **23**, 0 40 g, 75% A sample was recrystallised from chloroform/cyclohexane for analytical purposes, mp 111-113 °C, MS, *m/e*, 282, 239, 169, 91, ^{1}H NMR, δ, 10 02 (bs, 1H), 7 26-7 16 (m, 10H), 4 86 (bm, 3H), 4 36 (bs, 2H), ^{13}C NMR, δ, 167 1, 159 2, 139 0, 128 6, 127.3, 126 9, 44 7, IR, 3474, 1724, 1629, 1565 cm^{-1}

$C_{16}H_{18}N_4O$ requires 282 1481 Found 282 1489

Preparation of ureas 25a-d.

These compounds were prepared from the corresponding imidazolidin-5-ones **24a-d** [15,16] by essentially the same procedure as used for **23** Compound **25a** could be isolated without chromatography

Compound **25a**, 76%, mp 107-109 °C, MS, *m/e*, 322, 305, 231, 91, ^{1}H NMR, δ, 9 40 (bs, 1H), 7 29-7 20 (m, 6H), 7 13-7 10 (m, 2H), 7 02-6 99 (m, 2H), 5 75 (bs, 1H), 4 84 (d, 1H, J = 15 4 Hz), 4 82 (d, 1H, J = 15 4 Hz), 4.45 (dd, 1H, J = 4 5, 6 7 Hz), 3 26 (dd, 1H, J = 14 3, 4 5 Hz), 3 05 (dd, 1H, J = 14 3, 6 7 Hz), ^{13}C NMR, δ, 171 7, 160 7, 158 6, 134 0, 133 2, 129 3, 129 05, 128 7, 128 1, 127 9, 127.6, 59 1, 42 9, 36 9, IR, 3266, 1788, 1755, 1740, 1693 cm^{-1}

$C_{18}H_{18}N_4O_2$ requires 322 1430 Found 322 1431

Compound **25b**, 69%, mp 106-108 °C, MS, *m/e*, 304, 287, 261, 91, ^{1}H NMR, δ, 9 50 (bs, 2H), 7 39-7 26 (m, 5H), 6 06 (bs, 1H), 4 95 (d, 1H, J = 15 0 Hz), 4 91 (d, 1H, J = 15 0 Hz), 4 45 (dd, 1H, J = 3.6, 7 9 Hz), 3 66 (s, 3H), 3 04 (dd, 1H, J = 17 7, 3 6 Hz), 2 80 (dd, J = 17 7, 7 9 Hz), ^{13}C NMR, δ, 171 7, 169 55, 161 4, 159 0, 134 4, 128 8, 128 4, 54 3, 52 6, 43 3, 35 1; IR, 3315, 1785, 1742, 1684 cm^{-1}

$C_{14}H_{16}N_4O_4$ requires 304 1171 Found 304 1176

Compound **25c**, 74%, mp 100-102 °C, MS, *m/e*, 301, 300, 283, 233, 91, ^{1}H NMR, δ, 8 83 (bs, 1H), 7 28-7 15 (m, 5H), 5 02 (bs, 2H), 4 38 (m, 1H), 4 18 (dd, 1H, J = 3 9, 7 3 Hz),3 14 (dd, 1H, J = 3 9, 14 0 Hz), 2 90 (dd, 1H, J = 7 3, 14 0 Hz), 1 98-1 04 (m, 8H), ^{13}C NMR, 173 1, 165 9, 159 8, 134 7, 129 35, 128 7, 127 3, 58 5, 52 0, 37 8, 28 4, 28 2, 24 9, IR, 3541, 1739, 1647, 1617 cm^{-1}

$C_{16}H_{21}N_4O_2$ (M^+ + 1) requires 301 1664 Found 301 1675

Compound **25d**, 62%, mp 215-217 °C,, MS, 185, 167, 139, 96, ^{1}H NMR, δ, DMSO, 8 59 (bs, NH), 6 17 (bs, 2H) 4 33 (dt, 1H, J = 5 5, 1 6 Hz), 3 40 (bs, 2H), 1 84-1 77 (m, 1H), 1 70-1 59 (m, 1H), 0 87 (t, 3H, J = 7 2 Hz), ^{13}C NMR, δ, 170 6, 165 5, 163 7, 65 8, 24 3, 8 9, IR, 3339, 1739, 1653, 1565 cm^{-1}

$C_6H_{11}N_5O_2$ requires 185 0913 Found 185 0918

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