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Synthesis of 1,2,4-Triazoles and 1,2,4,6-Tetraazabicyclo[3.3.0]octanes from Diphenyl Cyanocarbonimidate. Competition between Addition of Hydrazines to Esters or Nitriles

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Abstract: The reaction of hydrazine with suitably substituted isoureas gives tetraazabicyclo[3.3.0]octanes. The products obtained in this reaction are extremely susceptible to the nature of the substrate and the reaction conditions, but a suitable combination of these can usually be found in order to form the bicyclooctane. In cases where the bicyclic system is not formed 1,2,4-triazoles are usually obtained but, occasionally, the imidazolone is the reaction product. A mechanistic sequence is proposed based on the variation and interconversion of the products formed in these latter reactions The preference for addition of methylhydrazine at the substituted nitrogen is significantly reduced by the introduction of steric factors

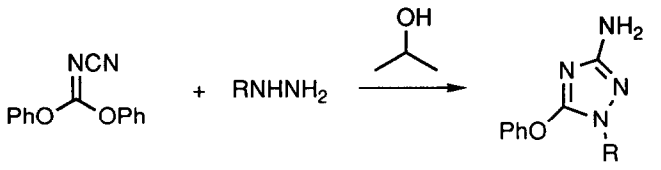
Triazoles have found considerable importance as components of therapeutically important compounds, including virazole[1,2,3] and a number of potential antidepressants,[4] the triazole nucleus resembling the pyrimidine ring of the natural pyrimidine systems. Webb and coworkers have prepared a potent H_2 antagonist using a triazole synthesis which they developed from the reaction of diphenyl cyanocarbonimidate with amines and hydrazines.[5,6] Our interest in the alternative modes of cyclisation of the initial reaction products of diphenyl cyanocarbonimidate with aminoacid derivatives[7] caused us to examine this reaction We were particularly intrigued as to whether cyclisation onto an ester function to give the imidazole would be competitive with cyclisation onto the cyanoimine to give the triazole, and if, with suitably chosen nucleophiles, bicyclic systems incorporating the triazole ring could be prepared

Results and Discussion

It was known from the work of Webb and co-workers [5,6] that the reaction of derivatives of diphenyl cyanocarbonimidate (**1**) with hydrazine gave triazoles by reaction of the cyanoimine group. The first route we envisaged was to follow their method by reacting **1** with hydrazines and then replacing the remaining phenoxy group with an amine.

Dedicated to Professor Charles Rees on the occasion of his 65th birthday.

Treatment of **1** with hydrazine gave 3-amino-5-phenoxy-s-triazole (**2a**) in 59.5% yield and similar treatment of **1** with methylhydrazine gave **2b** in 63% yield. The orientation of the substituents in **2b** is based on n.O.e experiments on the ^1H NMR spectra,[8] irradiation at the position of the methyl signal showing an enhancement of the O-phenyl resonance, whereas irradiation of the NH_2 signal showed no enhancement of the methyl signal. This is consistent with the substituted nitrogen of the hydrazine being most nucleophilic.Treatment of **1** with phenylhydrazine gave **2c** again in 63% yield, but the orientation of the substituent could not be determined. Attempts to replace the phenoxy group in **2a** with an amine by treatment in propan-2-ol at room temperature or under reflux were unsuccessful and an alternative pathway to bicyclic systems was investigated.

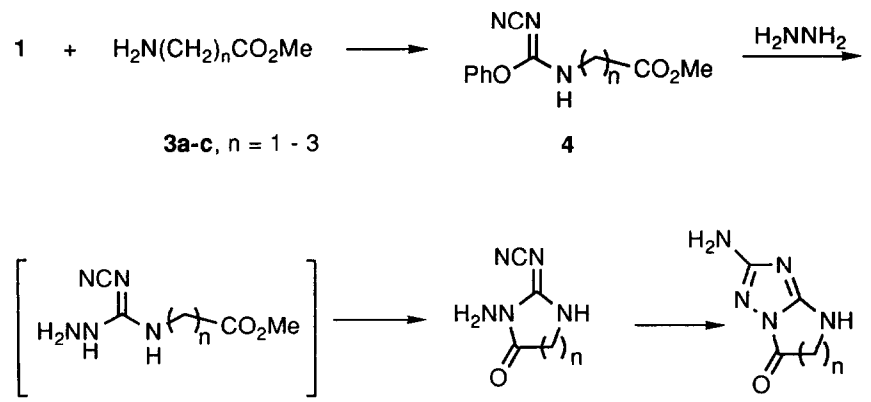


1

2a R = H
b R = Me

Reaction of **1** with an ω-aminoester **3** should give the monosubstituted compounds **4** which, on treatment with hydrazine should give N-cyanoguanidines that could, in principle, cyclise twice (Scheme 1).

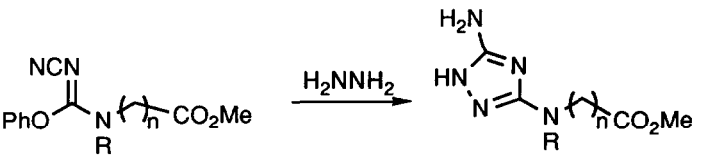
Scheme 1



The ester **4a**, obtained from reaction of **1** with methyl glycine (**3a**), was treated with hydrazine in propan-2-ol at reflux when the triazole **5a** was obtained in 97% yield The reaction

has proceeded as expected, the triazole ring presumably forming first, but the second cyclisation has not occurred.

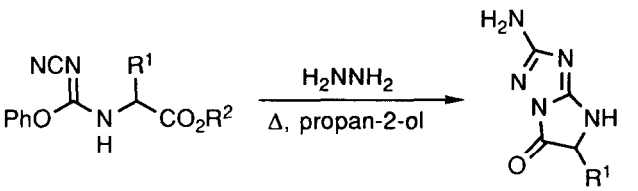
Similarly, the treatment of **4b** and **4c** with hydrazine also gave only the monocyclic products **5b** and **5c** respectively. Compound **5c** may not have been expected to cyclise further as this requires formation of a 7-membered ring,[9] but the failure to form the 5- and 6-membered rings in **5a** and **5b** suggests that the nitrogen in the triazole ring is less nucleophilic than the amines used previously.



4a n = 1, R = H
b n = 2, R = H
c n = 3, R = Me

5a n = 1, R = H
b n = 2, R = H
c n = 3, R = Me

Turning to the the reaction of the derivative **6a**, prepared from **1** and the benzyl ester of phenylalanine, indicated, however, that this was not the sole influence on the reaction. Treatment of **6a** with hydrazine in propan-2-ol at reflux gave the bicyclic product **7a** in 67% yield The spectral properties of **7a** clearly illustrate the loss of both the phenoxy and benzyl groups from the precursor **6a.**



6a, $R^1 = R^2 = CH_2Ph$
b, $R^1 = CH_2CO_2Me$, R^2 = Me

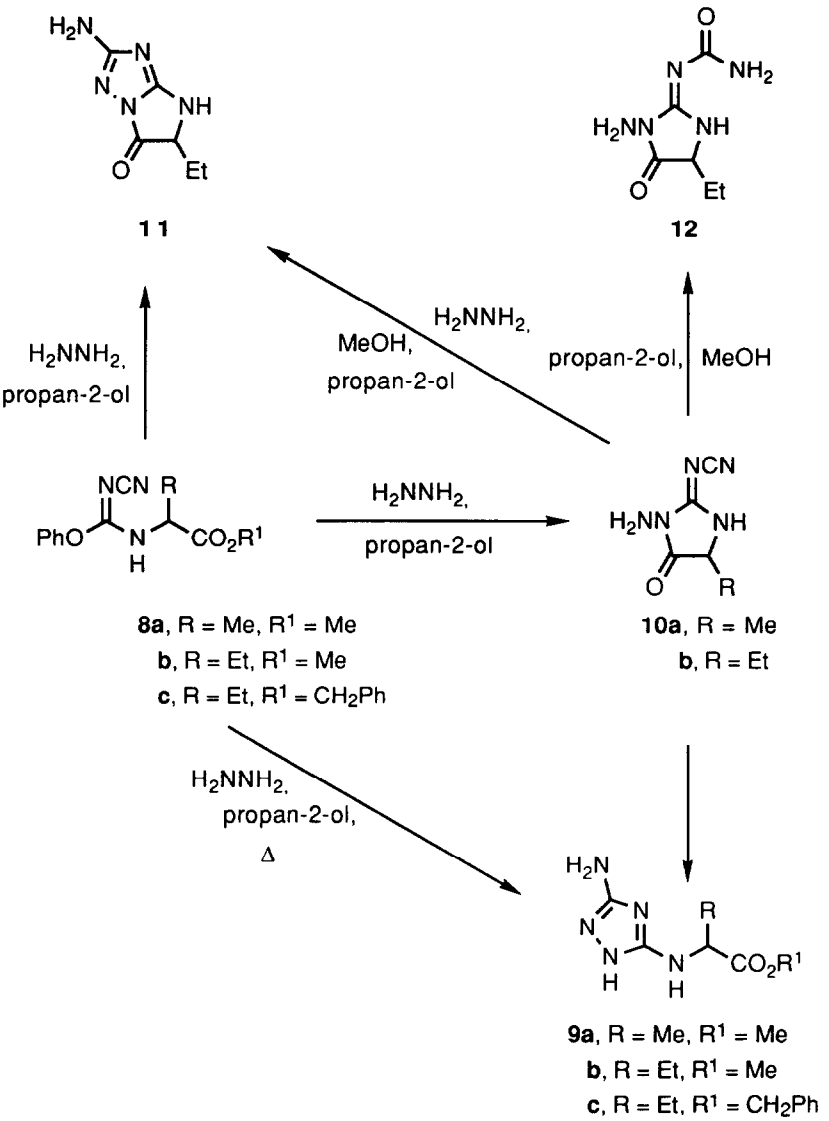
7a, $R^1 = CH_2Ph$
b, $R^1 = CH_2CO_2Me$

Similarly, **6b**, obtained from **1** and dimethyl aspartate, on treatment with hydrazine in propan-2-ol at 60 °C gave **7b** in 73% yield. In this case, if the reaction was carried at reflux, some ester exchange occurred and a mixture of the methyl and 2-propyl esters was formed

Presumably with both **6a** and **6b** the conformation required for ring closure is less disfavoured than in the case of **5a** and **5b** because of the substituent R^1 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 systems 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.

Scheme 2



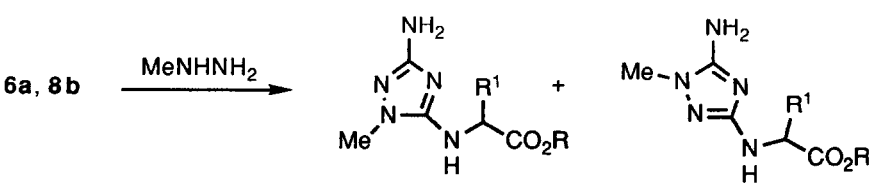
Treatment of **8a**, prepared from **1** and L-alanine methyl ester, with hydrazine in propan-2-ol at reflux gave the triazole **9a** (71 5%), apparently reproducing the behaviour of the nonsubstituted derivative **4a** Treatment of **8b**, prepared from **1** and methyl 2-aminobutanoate, gave a 9.1 mixture of **9b** and **11**, from which **9b** could be isolated in 70% yield (Scheme 2) When the reactions were carried out at 0 °C, however, the imidazoles **10a** and **10b** were obtained in 77% and 85% yields, respectively In further experiments, after **10b** had been formed at 0 °C, the reaction mixtures

were heated to reflux and monitored by TLC. The imidazolone slowly decreased in concentration with time and new compounds were observed. After 5h, the reaction mixtures showed the imidazolone was no longer present and the ^{1}H NMR spectrum of the product showed that it was a mixture of **9b** and **11**. Thus, although propan-2-ol is in vast excess it does not appear to react with **10b** and in none of these or the subsequently described reactions did we observe ester exchange, although we have observed such exchange in closely related systems.

These reactions are clearly delicately balanced and we therefore prepared **8c**, supposing that the leaving propensities of the benzyl group might encourage the formation of **11**. Treatment of **8c** with hydrazine in boiling propan-2-ol gave a 1:1.2 mixture of **9c** and **11**, which was transformed into a 1:9 mixture, from which **11** could be isolated in 71% 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 **10b** Treatment of **10b** with hydrazine and methanol in propan-2-ol at 80 °C gave the bicyclic tetraazaoctane **11** whereas a similar treatment without hydrazine gave the urea **12**. Each of these reactions, and that in which the reaction mixture containing **10b** is converted to **9c**, differ 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 **8b** contains a mole equivalent of phenol and 0 2 moles of hydrazine and is presumably acidic, whereas the direct reaction from **10b** contains a mole equivalent of hydrazine and is basic while the reaction mixture leading to **12** is approximately neutral. 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 bicyclic tetraazaoctane **11** was heated to reflux in benzyl alcohol and in propan-2-ol containing methanol, **11** being recovered unchanged in both experiments. It thus appears that in these examples the monocyclic triazole arises from ring opening of the imidazolone and reclosure to the thermodynamically more stable triazole ring system.

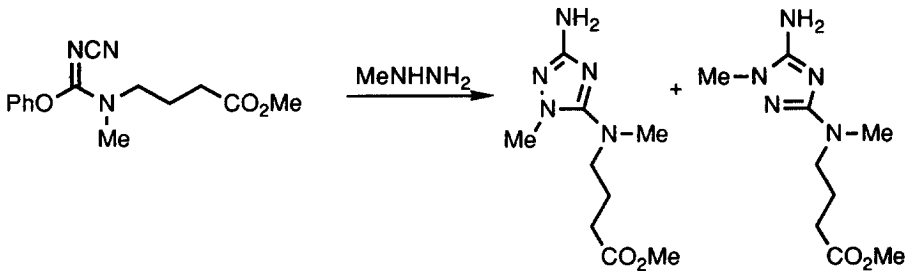
Treatment of **6a** with methylhydrazine gave two products, neither of them bicyclic. One compound was the expected triazole **13a** while the other was identified as the isomer **14** in which the nonsubstituted nitrogen of methylhydrazine has acted as the initial nucleophile. The structures of **13a** and **14** were determined by n O.e experiments. Irradiation of the Me group protons in **13a** caused enhancement of the NH, CH_2 and aromatic protons whereas irradiation of the Me group in **14** gave only enhancement of the NH_2 protons. These observations were supported by other n.O.e experiments irradiating the NH resonance signals. Treatment of **8b** with methylhydrazine gave only the triazole **13b**



13a, R = R^1 = $PhCH_2$ **14**, R = R^1 = $PhCH_2$

b, R = Me, R^1 = Et

The formation **2b, c** and **13a, b** 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. 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-methylsubstituted derivative **15**, however, on treatment with methyl hydrazine gives an ca. 50:50 mixture of **16** and **17**, the former arising from initial nucleophilic addition from the N-methyl group and the latter from the N-H group, a similar ratio to that found for reaction of **6a** with methylhydrazine. The triazoles **16** and **17** were again distinguished by n.O.e experiments, irradiation of the exocyclic N-Me group causing enhancement of the ring N-Me signal in **16** 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 **17** gave only enhancement of the acyclic methylene signals and irradiation of the ring N-Me gave enhancement only of the NH_2 signals.



15 **16** **17**

The reaction of hydrazines with pseudoureas of type **4** is clearly influenced by both the exact nature of **4** and 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 those cases examined in which there will be a substituent at C-7 in the tetraazabicyclooctane. 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.

Experimental

Melting points were determine 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 DMSO, unless stated otherwise, with Me_4Si as internal standard ^{13}C NMR spectra were obtained on a Varian VXR 400 spectrometer at 100 MHz in DMSO 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

Preparation of 3-Amino-5-phenoxy-s-triazole (2a)

A solution of diphenyl N-cyanocarbonimidate (1) (0.50g, 2 1 mmol) and hydrazine (0 08g, 2 5 mmol) in propan-2-ol (15 mL) was heated to reflux for 3 h. The volume of solution was reduced to half by evaporation under vacuo and cooled to 4 °C The resulting precipitate was removed by filtration as **2a**, 0 22g, 59 5%,mp 128 -130 °C, MS, *m/e* 176, 175, 148, 134, 119,104, 91, 77, ^{1}H NMR, δ, 11 49 (bs, 1H), 7 35-7 31 (m, 2H), 7 11 - 7 07 (m, 3H), 6 09 (bs, 3H), ^{13}C NMR, δ , 163 6, 156 1, 129.4, 123.4, 118.4, IR, 3437, 3149, 3100, 2923, 2801, 1651, 1590, 1547, 1403, 1213 cm^{-1}

$C_8H_8N_4O$ requires 176.0698. Found: 176 0704.

Preparation of 3-Amino-1-methyl-5-phenoxy-s-triazole (2b)

A solution of 1(0 50g, 2.1 mmol) and N-methylhydrazine (0 13g, 2.8 mmol) in propan-2-ol (15 mL) was stirred at RT for 2 h The solvent was removed under vacuo and the residue chromatographed on silica, eluting with $CHCl_3$, 2% methanol Product fractions were collected, reduced to small volume , cyclohexane added until the solution clouded and the mixture than cooled to 4 °C when precipitation occurred The crystalline precipitate was removed by filtration as **2b**, 0 22g, 63%, mp 109 - 110 °C, MS, *m/e* 191, 190, 189, 119, 113, 91,77; ^{1}H NMR, δ, 7 43-7 41 (m, 2H), 7 39 - 7 20 (m, 3H), 5 23 (bs, 2H), 3 47 (s, 3H), ^{13}C NMR, δ, 159 7, 154 6, 154 0, 129.7, 125.1, 119 2, 32 9; IR, 3369, 3321, 3198, 2923, 1641, 1580, 1516, 1482, 1412, 1394, 1219 cm^{-1}

$C_9H_{10}N_4O$ requires C, 56 54, H, 5 26, N, 29 97 Found C, 56 73, H, 5 13, N, 28 88

Preparation of (2c)

A solution of **1** (0 30 g, 1 26 mmol) and phenylhydrazine (0 10 g, 1 51 mmol) in propan-2-ol (10 mL) was heated to reflux for 6 h The solution was cooled and the resulting precipitate removed as **2c**, 0 20g, 63%, mp 165 - 167 °C, MS, *m/e* 253, 252, 235, 134, 119, 105, 91, 77, ^{1}H NMR, δ, 7 50 - 7 45 (m, 4H), 7 40 -7 30 (m, 2H), 7.23 - 7 10 (m, 2H), 6 62 (bs, 2H), ^{13}C NMR, 163 85, 154 65, 154 0, 137 0, 129 5, 129 4, 126 7, 124 1, 122 5, 119 1, IR, 3382, 3119, 1641, 1562, 1485, 1427, 1391 cm^{-1}

$C_{14}H_{12}N_4O$ requires 252 1011 Found 252 1021

Preparation of Methyl 2-(3-amino-(5-amino-s-triazole)ethanoate (5a) and Methyl 3-(3-amino-(5-amino-s-triazole)propionate (5b)

A solution of **4a** (0 25 g, 1 07 mmol) and hydrazine (0 040g, 1 25 mmol) in propan-2-ol (20 mL) was heated to reflux for 8 h The solution was then reduced to half volume under vacuo, cooled to 4 °C and the resulting precipitate collected by filtration The precipitate was washed with ether and dried to give **5a** (0.145 g 97%), mp 162 - 163 °C, MS, *m/e*, 172, 171, 139, 131, 119 112, ^{1}H NMR, δ, 10 75 (bs, 1H), 5 65 (b, 2H), 3 76 (d, 2H, J = 6 0 Hz), 3 59 (s, 3H), ^{13}C NMR, δ, 172 1, 161 7, 156 1, 51 4, 44 3, IR, 3406, 3339, 3308, 3094, 1724, 1654, 1571, 1397, 1225 cm^{-1}

$C_5H_9N_5O_2$ requires C, 35 08, H, 5 26, N, 40 94 Found C, 34 90, H, 5.29, N, 42 46

Compound **5b** was prepared from **4b** (0 42 g, 1 70 mmol) in the same manner (0 29g, 93%), mp 135 - 137 °C, MS, *m/e* 186, 185, 153, 126, 112, 99, ^{1}H NMR, δ, 10 70 (bs, 1H), 5 40 (b, 2H), 3 57 (s, 3H), 3 33 (dd, 2H, J = 6 96, 6 80 Hz), 2 52 (t, 2H, J = 6 80 Hz), ^{13}C NMR, δ, 172 2, 161 9, 158 5, 51 3, 38 8, 34 05, IR, 3443, 3370, 3223, 3174, 1718, 1608, 1565, 1443, 1375, 1216 cm^{-1}

$C_6H_{11}N_5O_2$ requires C, 38 92, H, 5 94, N, 37 84 Found C, 39 08, H, 5 99, N, 37 91

Preparation of Methyl 4-(3-methylamino-(5-amino-s-triazole)butanoate (5c)

A solution of **4c** (0.82 g, 2.98 mmol) and hydrazine (0.11 g, 3 43 mmol) in propan-2-ol (30 mL) was heated to reflux for 7 h Cyclohexane was then added until the solution just became cloudy and the mixture was then kept at 15 °C for 8 h The precipitated crystalline material was collected by filtration, washed with ether and dried as **5c**, 0.60g, 94% , mp 76 - 78 °C; MS *m/e* 214, 213, 181, 153, 140, 126, 113, ^{1}H NMR, δ, 10 83 (bs, 1H), 5.48 (bs, 2H), 3 56 (s, 3H), 3 58 (t, 2H, J = 7 1 Hz), 2 75 (s, 3H), 2.25, t, 2H, J = 7.6 Hz), 1 72 (dd, 2H, J = 7 1, 7.6 Hz); ^{13}C NMR, δ, 173.2, 161.2, 157 4, 51 3, 49.5, 35.5, 30.8, 22.15; IR 3406, 3327, 3156, 2947, 1721, 1654, 1605, 1562, 1507, 1436, 1409, 1210 cm^{-1}

$C_8H_{15}N_5O_2$ requires C, 45.07; H, 7 04, N, 32.86 Found· C, 45 26; H, 7 19; N, 32.93

Preparation of 3-Amino-7-benzyl-1,2,4,6-tetraazabicyclo[3.3.0]octan-8-one (7a)

A solution of **6a** (0.26 g, 0.65 mmol) and hydrazine (0 025g, 0.78 mmol) in propan-2-ol (20 mL) was stirred at 40 °C for 1 h. The solution was cooled to 4 °C and the precipitate collected by filtration and dried as **7a**, 0 100g, 67%, mp 152 - 154 °C; MS *m/e* 230, 229, 202, 170, 142, 110, 99, 91, 77, ^{1}H NMR, δ, 10.69 (bs, 1H), 9.04 (bs, 1H), 7 26 - 7 22 (m, 4H), 7 16 - 7 14 (m, 1H), 4.17 - 4 11 (m, 3H), 2 89 (dd, 1H, J = 13 7 and 4 7 Hz), 2 79 (dd, 1H, J = 13.7 and 9.2 Hz); ^{13}C NMR, δ, 172 1, 161 0, 156.0, 138 6, 129 2, 128.0, 126 1, 56 7, 38 9, IR, 3314, 2972, 2923, 1641, 1534, 1449 cm^{-1}

$C_{11}H_{11}N_5O$ requires 229.0964 Found 229 0975

Preparation of 3-Amino-7-methylcarboxymethyl-1,2,4,6-tetraazabicyclo[3.3.0]octan-8-one (7b)

A solution of **6b** (0 30 g, 0 98 mmol) and hydrazine (0 039 g, 1 22 mmol) in propan-2-ol (20 mL) was heated to reflux for 2 h The volume of the solution was then reduced to one half by evaporation under vacuo and ether was then added until the solution became cloudy On cooling to 4 °C the product precipitated from solution and was collected by filtration, washed with ether and dried as **7b**, 0 090g, 43%, mp 117 - 119 °C, MS *m/e* 212, 211, 184, 152, 124, 110; ^{1}H NMR, δ, 10 78 (bs, 1H), 5 55 (bs, 2H), 4.46 -4.27 (m, 1H), 3.58 (s, 3H), 2 82 - 2 73 (m, 2H), ^{13}C NMR, δ, 173 1, 170 9, 159 9, 156 5, 51 9, 51 1,36 5, IR, 3449, 3370, 3290, 1736, 1565, 1423, 1216 cm^{-1}

$C_7H_9N_5O_3$ requires 211 0705 Found 211 0700

Preparation of N-cyano-N'-(1-methoxycarbonylethyl)-O-phenylisourea (8a)

Triethylamine (o 86 g, 8 85 mmol) was added to a stirred suspension of S-alanine-methyl ester (1 0g, 7 17 mol) and diphenyl cyanocarbonimidate (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 under vacuo and the residue dissolved in $CHCl_3$ (30 mL) and washed with saturated sodium bicarbonate solution (2 x 20mL) The organic layer was dried ($MgSO_4$) and the solvent removed under vacuo The residue was dissolved in propan-2-ol (20 mL) and cooled to 4 °C for 4h. The resuting crystalline product was collected by filtration to give **8a** , 1 0 g, 56%, mp 108-110 °C, MS *m/e* 188,153,126,118, ^{1}H NMR, δ, 7 45-7 02 (m, 5H), 5 70 (bs, 1H), 4 53 (m, 1H), 3 78 (bs, 3H), 1 55 (bd, 3H), 1 42 (bs, 3H), ^{13}C NMR, δ, 171 6,163 1, 150 8, 130.6, 129.5, 127 7, 126.7, 121.3, 121 0, 114 5, 52.9, 51 2, 17 6, IR 3437 2189, 1730, 1635 cm^{-1}

$C_{12}H_{13}N_3O_3$ requires C, 58 20, H, 5 26, N, 17 00 Found C, 58 42, H, 5 26, N, 16 84

Preparation of N-cyano-N'-(1-methoxycarbonylpropyl)-O-phenylisourea (8b)

Diphenyl cyanocarbonimidate (0 94 g, 3 93 mmol) was added to a solution of methyl 2-aminobutanoate (prepared from the hydrochloride with triethylamine) (0 46 g, 3 93 mmol) in propan-2-ol (20 mL) and the mixture stirred at RT for 8h The resulting white precipitate was removed by filtration and a second crop collected by reducing the solvent volume as **8b**, 2 10g, 62%, MS *m/e* 261, 202, 140, 94, ^{1}H NMR, δ, 7 47 -7 04 (m, 5H), 6 67 (bs, 1H), 4 46 (m, 1H), 3 79 (s, 3H), 3 73 (s,

3H), 2 04-1 70 (m, 2H), 1.04 (t, 3H), o.82 (t, 3H); ^{13}C NMR, δ, 171 0, 163.2, 150.8, 130.7, 129 6, 127.8, 126.8, 122.0, 121 2, 114.4, 113.7, 56.7, 56.6, 52.9, 52.8, 25.3, 24.6, 9.9, 9.1; IR 3443, 2200, 1730, 1645 cm^{-1}.

$C_{13}H_{15}N_3O_3$ requires 262 1191; C, 59 77; H, 5.75, N, 16.09 Found 262.1189, C, 60 01, H, 5.71, N, 15 99.

Preparation of N-cyano-N'-(1-benzyloxycarbonylpropyl)-O-phenylisourea (8c)

Benzyl 2-aminobutanoate (1.54 g, 7.98 mmol) was added to **1** (1.89 g, 7.98 mmol) in propan-2-ol (40 mL) and the resulting solution stirred at RT for 3H The solvent was removed by evaporation under vacuo and the residue cooled to 4 °C for 12 h The precipitated product was removed by filtration, washed with ether and dried to give **6c**, 2.10 g (78%), mp 95-6 °C, MS *m/e* 337, 214, 145, 91, ^1H NMR, δ, - 20 °C, 7 47 - 7 08 (m, 8H), 6 90 (d, 2H), 5.21 (s) 5.15 (d, J = 11 60 Hz), 5 10 (d, J = 11.60), 4 50 - 4.23 (m), 2.04 - 1.85 (m), 1.73 - 1 69 (m), 1.02 (t, J = 7.20 Hz), 0.75 (t, J = 7 20 Hz), ^{13}C NMR, δ, -20 °C, 170.75, 170.6, 163.2, 161 2, 150 4, 149.5, 134.7, 134.35, 130.7, 129.95, 129 5, 128 7, 128 6, 128 5. 128 3 127 85. 127.5 127 45. 126.4 122.0. 121 0. 120.6, 114.5, 67.7, 67.4 56.8, 56.2, 24 75, 24 35, 10.15, 9.0; IR 3180, 3045, 2195, 1635 cm^{-1}

$C_{19}H_{19}N_3O_3$ requires 337 1426 Found 337 1437

Preparation of Methyl 2-(5-amino(3-amino-s-triazole)propionate (9a)

A solution of **8a** (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° C when precipitation occurred The precipitate was collected by filtration, washed and dried as **9a**, 0 075g, 71 5%, mp 189 - 191 °C, MS, *m/e* 186, 126, ^1H NMR, δ, 10 73 (bs, 1H), 5 84 (bs, 1H), 5 53 (bs, 2H), 4 01 (m, 1H), 3 57 (s, 3H), 1 27 (d, 3H, J = 7 6 Hz), ^{13}C NMR, δ, 175 05, 160 0, 157 3, 50 8, 50 7, 18 1, IR 3437, 3350, 3284, 3088, 1724, 1654, 1635, 1568, 1544, 1397, 125 cm^{-1}

$C_6H_{12}N_5O_2$ requires 186 0991 Found 186 0996

Preparation of 3-Amino-2-cyanoimino-5-methyltetrahydroimidazol-4-one (10a)

A solution of **8a** (0 23 g, 0 93 mmol) and hydrazine (0 09g, 1 25 mmol) in propan-2-ol (5 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 as **10a**, 0 110g, 77%, mp 155 - 157 °C, MS *m/e* 154, 153, 125, 110, 94, 69, ^1H NMR, δ, 9 55 (bs, 1H), 4 87 (s, 2H), 4 22 (q, 1H, J = 7 2 Hz), 1 27 (d, 3H, J = Hz), ^{13}C NMR, δ, 173 25, 161 7, 115 5, 52 5, 52 3, 16 35, IR 3333, 3295, 3174, 2189, 1767, 1663, 1480 cm^{-1}

$C_5H_7N_5O$ requires 153 0651, C, 39 22, H, 4 58, N, 45 7, Found 153 0658, C, 39 54, H, 4 85, N, 44 35

Preparation of Methyl 2-(5-amino-(3-amino-s-triazole)butanoate (9b)

A solution of **8b** (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 volume of solvent was reduced to half under vacuo, ether was added and the mixture cooled to 4 °C The resulting precipitate was collected by filtration and washed with ether as **9b**, 0 150g, 70%, mp 169 - 171 °C; MS *m/e* 200, 199, 170, 140, ^1H NMR, δ, 10.71 (bs, 1H), 5 65 (bs, 2H), 3 91 - 3 89 (m, 1H), 3 57 (s, 3H), 1 70 -1 8 (m, 2H), 0 89 (t, 3H, J = 7 6 Hz), ^{13}C NMR, δ, 172 45, 159 5, 154 0, 54 9, 49 3, 23 0, 8 5, IR 3425, 3345, 3278, 3088, 1721, 1651, 1568, 1219 cm^{-1}

$C_7H_{13}N_5O_2$ requires 199 1069 Found 199 1076

Preparation of 3-Amino-2-cyanoimino-5-ethyltetrahydroimidazol-4-one (10b)

A solution of **8b** (0.22g, 0.84 mmol) and hydrazine (0.035 g, 1.10 mmol) in propan-2-ol (7 mL) was stirred at RT for 75 min. The resulting precipitate was collected by filtration, washed with ether and dried as **10b**, 0.120g, 85%, mp 137 - 139 °C; MS *m/e* 168, 167, 140, 139, 124, 110; ^{1}H NMR, δ, 9.67 (bs, 1H), 4.94 (s, 2H), 4.18 (t, 1H, J = 5.8 Hz), 1.77 - 1.61 (m, 2H), 0.84 (t, 3H, J = 7.5 Hz); ^{13}C NMR, δ, 172.6, 162.0, 115.5, 57.2, 28.8, 8.4; IR 3413, 3162, 3045, 2187.
$C_6H_{10}N_5O$ (M +H) requires 168.0885. Found 168.0892.

Preparation of 3-amino-7-ethyl-1,2,4,6-tetraazabicyclo[3.3.0]octan-8-one (11)

Hydrazine (0.11 g, 3.56 mmol) was added to a solution of **8c** (1.00g, 2.97 mmol) in propan-2-ol (40 mL) and the resulting solution was stirred at 25 °C for 2h. The volume was reduced to one half by evaporation under vacuo and the resulting solution cooled to - 10 °C for 2h. The precipitated solid was collected by filtration, washed with ether and recrystallised from a large volume of propan-2-ol to give **11**, 0.35g (71%), mp 200-202 °C; ^{1}H NMR, δ, 8.95 (bs, 1H), 5.50 (bs, 2H), 3.79 (m, 1H), 1.66-1.48 (m, 2H,), 0.83 (t, 3H, J = 7.6 Hz); ^{13}C NMR, δ, 172.4, 56.6, 26.0, 10.35; IR 3394, 1620, 1596, 1546 cm^{-1}.
$C_6H_9N_5O$ requires 167.0881. Found 167.0807.

Treatment of 8b with hydrazine at different temperatures.

Hydrazine (0.06 g, 1.9 mmol) and **8b** (0.40g, 1.53 mmol) were dissolved in propan-2-ol (10 mL) and stirred at room temperature, monitoring the reaction at intervals by TLC. After 6h the TLC showed the absence of **8b** and the presence of phenol and **10b**. The reaction mixture was now heated to reflux for 2 h during which time TLC showed the disappearance of **10b** and the appearance of a new spot of lower Rf. The mixture was cooled to room temperature and then to 4 °C when the product began to crystallize. Removal of the solvent and examination of the ^{1}H NMR spectrum showed it to be a mixture of **9b** and **11**.

Preparation of 3-amino-2-ureido-5-ethyltetrahydroimidazol-4-one (12)

A solution of **10b** (0.089 g, 0.53 mmol) and methanol (0.2 mL, 4.94 mmol) in propan-2-ol (10 mL) was heated to reflux for 6 h. The volume was reduced to one half by evaporation under vacuo and the resulting solution cooled to -10 °C for 6 h. The resulting precipitate was collected by filtration, washed with ether and dried to give **12**, 0.09 g (91%), mp 215-217 °C; MS *m/e* 185, 167, 139, 96; ^{1}H NMR, δ, 8.59 (bs, 1H), 6.17 (bs, 2H), 4.33 (dt, 1H, J = 5.5 and 1.6 Hz), 3.40 (bs, 1H), 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, 24.3, 8.9; IR 3339, 1739, 1653, 1565 cm^{-1}.
$C_6H_{11}N_5O_2$ requires 185.0913. Found: 185.0918.

Reaction of 6a with Methylhydrazine

A solution of **6a** (0.38 g, 0.95 mmol) and N-methylhydrazine (0.048 g, 1.14 mmol) in propan-2-ol was heated to reflux for 6 h. The solvent was removed by evaporation and the residue chromatographed on silica, eluting with $CHCl_3$, 5% MeOH, to give **13a** as an oil, 0.110g, 32%; MS, *m/e* 352, 351, 260, 216, 91; ^{1}H NMR, δ, 7.34 -7.17 (m, 8H), 6.99 -6.97 (m, 2H), 5.13 (d, 1H, J = 12.1 Hz), 5.08 (d, 1H, J = 12.1 Hz), 4.78 (d,1H), 4.74 - 4.69 (m, 1H), 3.75 (bs, 2H), 3.23 (s, 3H), 3.16 (dd, 1H, J = 5.8, 13.8 Hz), 3.09 (dd, 1H, J = 5.68 , 13.8 Hz); ^{13}C NMR 172.5, 159.7, 153.1, 135.6, 134.9, 129.2, 128.4, 128.3, 67.1, 57.1, 37.8, 31.4; IR 3400,2978, 1733, 1617, 1546, 1495, 1418, 1271, 1186 cm^{-1}.
$C_{19}H_{21}N_5O_2$ requires 351.1695. Found: 351.1671.

and **14**, 0 120g, 35%, mp 124 - 126 °C, MS, *m/e* 352, 351, 260, 216, 91; ^{1}H NMR, δ, 7.30 - 7 05 (m, 10H), 5 07 (d, 1H, J = 12.4 Hz), 5.05 (d, 1H, 12.4 Hz), 4 70 (bs, 2H), 4 54 (m, 1H), 3 25 (s, 3H), 3.10 (dd, 1H, J = 6 1, 13.1 Hz), 3.06 (dd, 1H, J = 6 4, 13 1 Hz), ^{13}C NMR, δ, 173,2, 159.6, 153.6, 136 3, 135.5, 129.3, 129.2, 128.3, 128.15, 128 1, 126.7, 66.55, 56 9, 38 4, 32 8; IR, 3406, 3167, 1721, 1635, 1599, 1544, 1519, 1179 cm^{-1}

$C_{19}H_{21}N_5O_2$ requires 351.1695 Found. 351 1678

Preparation of Methyl 2-(5-amino-(3-amino-1-methyl-s-triazole)butanoate (13b)

A solution of **8b** (0 26 g, 1.0 mmol) and N-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 the residue was chromatographed on silica, eluting with $CHCl_3$, 10% methanol to give **11b** as an oil, 0 155g, 73%; MS *m/e* 214, 213, 154, ^{1}H NMR, δ, 4 75 (d, 1H), 4 32 (dd, J = 8 4, 6 9, 6 2 Hz), 3 91 (bs, 2H), 3 69 (s, 3H), 3.37 (s, 3H), 1 92 1 83 (m, 1H), 1 78 -1 67 (m, 1H), 0 91 (t, 3H, J = 7 6 Hz), ^{13}C NMR, δ, 174 1, 159 6, 153 7, 57 5, 52 3, 32 6, 25.7, 9.6, IR 3363, 2960, 1733, 1608, 1543, 1424, 1204 cm^{-1}

$C_8H_{15}N_5O_2$ requires 214 1304 Found 214 1305

Preparation of Methyl 4-(5-methylamino-(3-amino-1-methyl-s-triazole)butanoate (16) and Methyl 4-(3-methylamino-(5-amino-1-methyl-s-triazole)butanoate (17)

A solution of the isourea **15** (1 16g, 4 22 mmol) and methylhydrazine (0 30g, 6 52 mmol) in propan-2-ol (30 mL) was heated to reflux for 6 h The solvent was removed by evaporation under reduced pressure and the residue chromatographed on silica, eluting with $CHCl_3$ 1% MeOH to give **16** (0 35g, 1 54 mmol) and **17** (0 30g, 1 32 mmol) Each product was recrystallised from $CHCl_3$ cyclohexane for analytical purposes

16, mp 112 - 114 °C, MS, *m/e* 227, 196, 154, 140, ^{1}H NMR, δ, $CHCl_3$, 4 99 (bs, 2H, NH_2), 3.43 (s, 3H), 3 28 (t, 2H, J = 7 25Hz), 2 86 (s, 3H)2 32 (t, 2H, J = 7 4Hz), 1 87 (m, 2H, J = 7 25, 7 4 Hz), ^{13}C NMR, δ, 174 05, 162 5, 153 7, 51 5, 49 8, 35 5, 32 9, 31.3, 22.65, IR 3406, 3125, 1733, 1663, 1608, 1454 cm^{-1}

$C_9H_{17}N_5O_2$ requires 227 1382 Found 227 1319

17, mp 78 - 80 °C, MS, *m/e*, 227, 196, 154, 140, ^{1}H NMR, δ, $CHCl_3$, 3.86 (bs, 2H, NH_2), 3 64 (s, OCH_3), 3.49 (s, 3H), 3 10 (t, 2H, J = 7 2 Hz), 2 32 (t, 2H, J = 7 3Hz), 1 87 (m, 2H, J = 7 3, 7 2Hz), ^{13}C NMR, δ, 173 4, 159 9, 158 65, 53 4, 51 6, 39 6, 34 6, 31 1, 22 7, IR, 3333, 3186, 1733, 1635, 1586, 1541 cm^{-1}

$C_9H_{17}N_5O_2$ requires 227 1382, C, 47 56, H, 7 54, N, 30 82 Found 227 1382, C, 47 53, H, 7 50, N, 30 84

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