Preparation, Structure and Addition Reactions of 4- and 5-Aminoimidazoles

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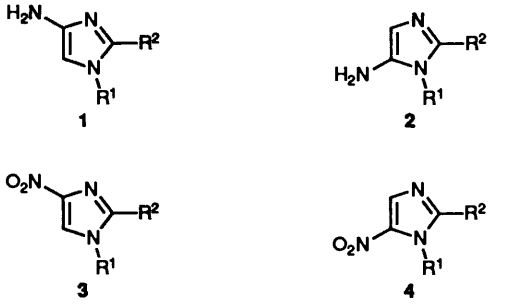
Catalytic reduction of 5-nitroimidazoles **4** in dioxane solution gives 5-aminoimidazoles **2** in good yield. The derivatives **2d–f** were isolated as stable, crystalline compounds which undergo slow decomposition on exposure to air. In a similar manner, solutions of 4-aminoimidazoles **1** were generated from the corresponding 4-nitroimidazoles **3** but attempts to isolate the amines were unsuccessful. The amines **1** and **2** are conveniently generated *in situ* and are used preparatively without isolation. With aryl isocyanates, aryl isothiocyanates, and diketene, 4- and 5-aminoimidazoles, **1** and **2**, give *N*-addition products whereas with dimethyl acetylenedicarboxylate, the *C*-addition products **11** and **15** are obtained. Thermal cyclisation of these adducts **11** and **15** gives imidazo[4,5-*b*]pyridin-5(4*H*)-one derivatives **12** and **16**. AM1 calculations for simple 4- and 5-aminoimidazoles, **1** and **2**, and 4- and 5-nitroimidazoles, **3** and **4** are reported. Molecular geometries, enthalpies of formation, dipole moments, and ionisation potentials are analysed and compared with experimental values. A Frontier Orbital Analysis of electrophilic addition reactions of 5-aminoimidazoles **2** is described and used to rationalise the preference of reagents for *N*- or *C*-addition.

Although 4- and 5-aminoimidazoles **1** and **2** are derivatives of a fundamental heterocyclic system, the literature on these compounds is limited.[1–5] This is surprising because 5-aminoimidazole ribonucleotide (AIR) **2a** is an essential intermediate in the *de novo* biosynthesis of purine ribonucleotides and thiamin.[6–13] Throughout the literature the derivatives **1** and **2** are described as unstable compounds which undergo rapid decomposition.[1a,2,14–16] We now report the results of our studies which demonstrate that 4- and 5-aminoimidazoles **1** and **2**, can be conveniently generated and used on a preparative scale. Here we describe preparative procedures, including the full characterisation of some 5-aminoimidazoles **2** as crystalline compounds, the participation of simple 4- and 5-aminoimidazoles **1** and **2** in addition reactions and the results of a molecular orbital study of their structure and reactivity. Novel syntheses of heterocyclic systems based upon addition–elimination reactions of the amines **1** and **2** are discussed in the following paper.[59]

4- and 5-Aminoimidazoles substituted with electron-withdrawing groups (*e.g.* CO_2H, $CONH_2$, CN, *etc.*) at the 5- and 4-positions, respectively, are well known and methods of preparation are documented.[17–24] Substituents *ortho* to the amino function stabilise these derivatives and they have been widely used in heterocyclic synthesis. Synthesis of the unsubstituted systems **1** and **2** is not so well explored but a number of approaches have been successful. These can be summarised as follows: i, decarboxylation of 4- or 5-aminoimidazolecarboxylic acids;[25–29] ii, hydrolysis of imidazole carbamates;[30] iii, ring transformations of other amino heterocycles;[31] iv, cyclisation of acyclic intermediates;[6,32–41] v, reduction of 4- or 5-nitroimidazoles.[42–50] The scope and yields of these approaches vary and, apart from characterisation as simple derivatives such as salts, the physical and chemical properties of the free bases have not been systematically investigated. A notable exception is the work of Shaw and co-workers who have demonstrated that carboxylation of 5-aminoimidazoles **2** using aqueous potassium hydrogen carbonate (70 °C) can be achieved *in vitro* without enzymic assistance.[27,37] However, the reactants and products were usually characterised in solution and the method has not been developed into a preparative procedure.



In formulae **1–4**,

a R^1 = 1-ribofuranosyl-5-phosphate, R^2 = H	**l** R^1 = H, R^2 = Et
b R^1 = R^2 = H	**m** R^1 = H, R^2 = Pr^i
c R^1 = H, R^2 = Me	**n** R^1 = CO_2Ph, R^2 = Me
d R^1 = R^2 = Me	**o** R^1 = CO_2Me, R^2 = Me
e R^1 = Me, R^2 = H	**p** R^1 = CO_2Et, R^2 = Me
f R^1 = CH_2CH_2OH, R^2 = Me	**q** R^1 = Me, R^2 = CH=CHPh
g R^1 = Me, R^2 = Pr^i	**r** R^1 = Me, R^2 = CH_2CH_2Ph
h R^1 = Me, R^2 = COPh	**s** R^1 = *p*-$NO_2C_6H_4$, R^2 = Me
i R^1 = Me, R^2 = SO_2Me	**t** R^1 = *p*-$NH_2C_6H_4$, R^2 = Me
j R^1 = CH_2OAc, R^2 = H	**u** R^1 = CH_2Ph, R^2 = H
k R^1 = CH_2OAc, R^2 = Me	**v** R^1 = CH_2Ph, R^2 = Me
	w R^1 = SO_2NMe_2, R^2 = H

Our own studies of aminoimidazoles have focused on their preparation by catalytic reduction of nitroimidazoles.[51] A number of 5-nitroimidazoles **4** are important therapeutic agents[52–55] and a range of 4- and 5-nitroimidazoles **3** and **4** are available on an industrial scale. This makes them attractive starting points for synthetic investigations.

The reduction of 4- and 5-nitroimidazoles **3** and **4** to the 4- and 5-aminoimidazoles **1** and **2** by chemical reagents or by catalytic hydrogenation has been described by several groups. Chemical reductions of 4- and 5-nitroimidazoles **3** and **4** have been achieved using sodium amalgam[43,44] stannous chloride[44] or zinc dust in either 50% tetrafluoroboric acid[46] or acetic acid.[50] The free bases **1** and **2** were not isolated and the products were obtained as salts or were converted into stable

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derivatives, *e.g.* amide or urea before isolation. In general, the yields from these approaches are low and these methods are not reliable synthetic procedures. Catalytic hydrogenation is a more attractive route and has been described using the following catalysts: 5–10% Pd–C with various solvents,[25,42,45,49,51] PtO_2 in MeOH,[48] and Raney Ni in ethyl acetate.[49] In addition, catalytic transfer hydrogenation of 2-methyl-4(5)-nitroimidazole **3c** using ammonium formate with 10% Pd–C in MeOH[56] or formic acid with 10% Pd–C[57] has been mentioned briefly but without experimental details. We now describe our own studies using 5% Pd–C as hydrogenation catalyst.

1,2-Dimethyl-5-nitroimidazole **4d** in 1,4-dioxane solution was reduced under 1 atm of hydrogen using 5% Pd–C catalyst; 3 mol equiv. of hydrogen were consumed and the reaction then ceased. Removal of the catalyst gave a pale yellow solution which upon concentration gave crystalline 5-amino-1,2-dimethylimidazole **2d** (74%). Using this method, the 5-aminoimidazoles **2e** (53%) and **2f** (58%) were also prepared as crystalline compounds and compound **2g** was obtained as a crude oil which did not crystallise. The amine **2d** gave the picrate [m.p. 196 °C (decomp.); lit.,[39] m.p. 193 °C (decomp.)]. No special precautions were necessary for handling the solid amines **2d–f** but they are unstable in air at ambient temperature and become brown amorphous solids after a few days. However, if thoroughly dried and stored *in vacuo* (with silica gel) at 0 °C they remain unchanged for several months.

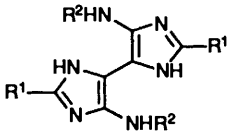
The amines **2d–f** were fully characterised by analytical and spectroscopic methods. The ^{1}H NMR spectra of the 5-aminoimidazoles **2** show an NH_2 signal (δ 3.75 ± 0.75) and a 4-H signal (δ 6.1 ± 0.3) demonstrating that these molecules exist as the amino tautomer in solution. For 5-aminoimidazoles **2** the aromatic 4-H signal was *ca.* 2 ppm upfield with respect to the aromatic 4-H signal in the corresponding 5-nitroimidazoles **4**.[58] This shift is in agreement with the expected difference in the electronic character of the two ring systems. Similar differences in chemical shifts were observed in the ^{13}C NMR spectra.[58] The IR spectra of compounds **2d–f** show absorptions in the region 3350–3400 cm^{-1} which can be attributed to primary NH stretching vibrations.

The compounds **2d–f** are the first examples of simple alkyl derivatives of 5-aminoimidazoles **2** to be obtained in a crystalline pure state. Nagarajan and co-workers[49] have reported the isolation of the stabilised 2-benzoyl derivative **2h** (m.p. 197–199 °C) and the 2-methylsulfonyl derivative **2i** (m.p. 123 °C).

Although our initial studies of reduction of nitroimidazoles were carried out in ethanol solution, we have subsequently found 1,4-dioxane to be a superior solvent. Reductions carried out in ethanol were associated with the formation of minor by-products (detected by TLC) and we were never able to obtain crystalline products using this solvent. The use of 1,4-dioxane frequently gave crystalline products in higher yield. Tetrahydrofuran also gives superior results to ethanol and is a useful alternative solvent. The generation of clean relatively stable 1,4-dioxane solutions of 5-aminoimidazoles **2** on a preparative scale provided the opportunity of exploring their potential as synthetic intermediates. In most of our studies it has been found unnecessary to isolate the amines **2d–g** and we have either carried out reductions in the presence of the desired reagent or have added the reagents to the amine solution after removal of the catalyst. In this manner the amine **2r** was also generated *in situ* by reduction of the 5-nitroimidazole **4q**.

The reduction of 4-nitroimidazoles **3** in 1,4-dioxane solution proceeded in a similar manner giving clean solutions of 4-aminoimidazoles **1**. Solutions of the amines **1 b, d, g, j, k, t–w** were generated in this way. The precursor of the diamine **1t** was the *p*-nitrophenyl derivative **3s**. All attempts to isolate crystalline samples of the amines **1** resulted in gross decomposition. The only crystalline 4-aminoimidazoles **1** which have been described are three *N*-glycoside derivatives.[48]

Although reduction of 4(5)-nitroimidazole **3b** gives the expected aminoimidazole **1b** as the sole product, an interesting and unexpected result was obtained when the 2-alkyl-4(5)-



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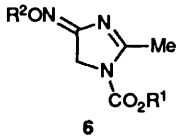

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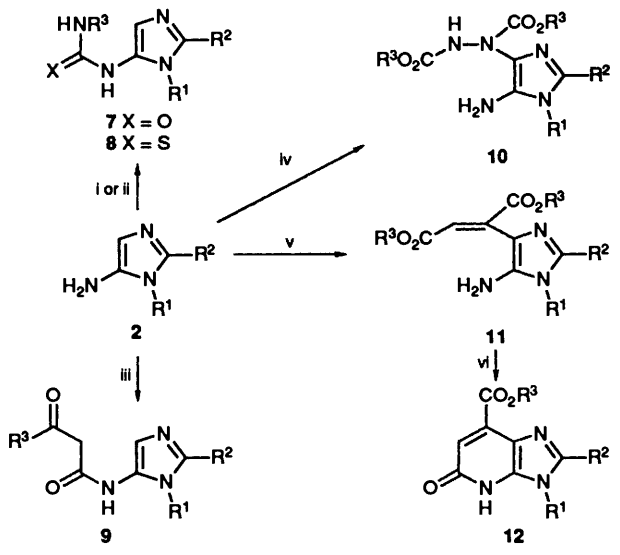
nitroimidazoles **3c, l, m** were reduced in the presence of trapping agents. In addition to products obtained directly from the amines **1c, l, m**, 5,5′-diimidazole derivatives **5** were also isolated. These results are discussed in detail in the following paper.[59] Here we restrict the discussion to reporting that the reduction of 2-methyl-4-nitroimidazole **3c** in a solution of acetic anhydride and acetic acid gives a mixture of 4,4′-diacetamido-2,2′-dimethyl-5,5′-biimidazole **5** (R^1 = Me, R^2 = Ac) (10%) and 4-acetamido-1-acetyl-2-methylimidazole (28%). Under similar conditions, 1,2-dimethyl-4-nitroimidazole **3d** gave only 4-acetamido-1,2-dimethylimidazole with no evidence of formation of a diimidazole product.

Reduction of 2-methyl-4-nitro-1-phenoxycarbonylimidazole **3n** also led to an unexpected product. Reduction stopped when 2 equiv. of hydrogen had been absorbed and the oxime **6**; (R^1 = Ph, R^2 = H) (62%) was isolated. The oxime structure **6** was confirmed by its ^{1}H NMR spectrum which showed a two-proton singlet at δ 4.68 corresponding to the methylene protons at position 5 of the ring. The oxime proton was observed at δ 10.8. In a similar manner the oximes **6** (R^1 = Me, Et, R^2 = H) were obtained by the reduction of the 4-nitroimidazoles **3o** and **3p**. The oximes **6** have novel structures but the reason why the ester substituents at position **1** lead to inhibition of further catalytic reduction is not clear. Treatment of the derivative **6** (R^1 = Et, R^2 = H) with 3,4-dichlorophenyl isocyanate gave the adduct **6** (R^1 = Et, R^2 = 3,4-$Cl_2C_6H_3NHCO$) (88%).

The structures of the 5-aminoimidazoles **2** are fully supported by their chemical reactions but we have observed two different modes of addition, either *N*-addition or *C*-addition (Scheme 1). With aryl isocyanates, aryl isothiocyanates and diketene, *N*-addition occurs in a manner analogous to reactions with most aromatic primary amines. Reaction of 5-amino-1,2-dimethylimidazole **2d** with 3,4-dichlorophenyl isocyanate gave the urea **7a**. In a similar manner the ureas **7b–g** were prepared and analogous reactions using phenyl isothiocyanate gave the thioureas **8h** and **8i**. *N*-Addition of compound **2d** with diketene gave the amide **9** (R^1 = R^2 = Me). The structures of the ureas **7**, thioureas **8** and amide **9** are fully supported by their spectroscopic properties: their ^{1}H NMR spectra are all associated with an imidazole 4-H signal in the region δ 6.75 ± 0.15.

When dimethyl acetylenedicarboxylate (DMAD) was added to a solution of 5-amino-1,2-dimethylimidazole **2d** in acetonitrile at ambient temperature a mildly exothermic reaction occurred yielding the *C*-adduct **11j** (44%). In a similar manner, the *C*-adducts **11k** (36%), **11l** (45%) and **11m** (35%) were prepared. Reaction of the amine **2d** with diethyl azodicarboxylate gave the adduct **10** (R^1 = R^2 = Me) (23%). The ^{1}H NMR spectra of these adducts, **10** and **11**, revealed the absence of imidazole 4-H signals and the presence of primary amine (NH_2) signals (δ 5.0 ± 0.6). This established that *C*-addition of the 4-positions of the imidazole rings had occurred. In these *C*-additions, **2**→**10** or **11**, the aminoimidazoles **2** are reacting like enamines: this functionalisation of the 4-position of the imidazole ring is comparable to the carboxylation of 5-aminoimidazole ribonucleotide **2a** in purine biosynthesis.[10]



Scheme 1 *Reagents and conditions:* i, R^3NCO, dioxane, RT, 0.5 h; ii, R^3NCS, dioxane, RT, 0.5 h; iii, Diketene, dioxane, RT, 2 h; iv, DEAZD, MeCN, RT, 1 h; v, $R^3O_2CC{\equiv}CCO_2R^3$, MeCN, RT, 1 h; vi, 190 °C, 1 min

In formulae 7, 8, 11 and 12

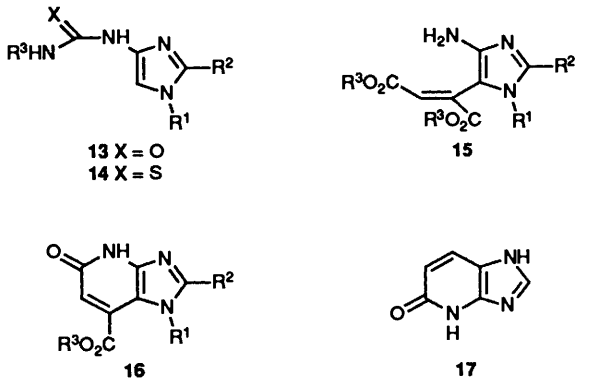
a $R^1 = R^2 = Me$, $R^3 = 3,4\text{-}Cl_2C_6H_3$
b $R^1 = R^2 = Me$, $R^3 = 3\text{-}Cl, 4\text{-}MeC_6H_3$
c $R^1 = Me$, $R^2 = Pr^i$, $R^3 = 3,4\text{-}Cl_2C_6H_3$
d $R^1 = Me$, $R^2 = Pr^i$, $R^3 = 3\text{-}Cl, 4\text{-}MeC_6H_3$
e $R^1 = Me$, $R^2 = Pr^i$, $R^3 = 4\text{-}MeC_6H_4SO_2$
f $R^1 = CH_2CH_2OCONH(3,4\text{-}Cl_2C_6H_3)$, $R^2 = Me$, $R^3 = 3,4\text{-}Cl_2C_6H_3$
g $R^1 = CH_2CH_2OH$, $R^2 = Me$, $R^3 = 3,4\text{-}Cl_2C_6H_3$
h $R^1 = R^2 = Me$, $R^3 = Ph$
i $R^1 = Me$, $R^2 = Pr^i$, $R^3 = Ph$
j $R^1 = R^2 = R^3 = Me$
k $R^1 = CH_2CH_2OH$, $R^2 = R^3 = Me$
l $R^1 = R^3 = Me$, $R^2 = Pr^i$
m $R^1 = R^2 = Me$, $R^3 = Et$

When 5-aminoimidazoles **2** were treated with ethyl propiolate or dimethyl maleate no reaction, other than decomposition of the amine, was observed, even under reflux conditions.

The reaction of DMAD at the carbon atom at position 4 of the 5-aminoimidazole ring **2** rather than at the amine nitrogen was not anticipated. Huisgen and co-workers have shown that DMAD adds to primary amines, including aniline, giving aminofumarates.[60] By analogy, we expected to observe the formation of similar products with aminoimidazoles but we have not detected either aminofumarates or aminomaleates in our studies. We are not able to assign the stereochemistry of the olefinic fragment in the products **11** but we have assumed that these are fumarate derivatives **11**. The derivative **11j** underwent thermal cyclisation when heated at 190 °C (1 min) giving the imidazo[4,5-*b*]pyridin-5(4*H*)-one **12j** (36%).

We have also investigated the additions of 4-aminoimidazoles **1** and have shown that they behave in a manner similar to the 5-amino isomers **2**. Reaction of 4(5)-aminoimidazole **1b** with phenyl isocyanate gave the urea **13a** and with phenyl isothiocyanate the thiourea **14a** was obtained. When 4-amino-1,2-dimethylimidazole **1d** was treated with DMAD, the C_5-adduct **15b** (50%) was isolated and fully characterised. Thermal cyclisation of compound **15b** gave the novel imidazo[4,5-*b*]pyridin-5(4*H*)-one **16b** (65%).

The preparation of derivatives **12j** and **16b** of imidazo[4,5-*b*]pyridin-5(4*H*)-one **17** in three steps from 4- or 5-nitroimidazoles **3** or **4** demonstrates the potential value of 4- and 5-



In formulae **13**–**16**:
a $R^1 = R^2 = H$, $R^3 = Ph$ **b** $R^1 = R^2 = R^3 = Me$

aminoimidazoles, **1** and **2**, as intermediates for the synthesis of heterocyclic systems which may not be easily accessible by other methods. We have not optimised the yields in the reactions **1**→**15**→**16** and **2**→**11**→**12** but our results form the basis of a good synthesis of derivatives of the relatively unexplored imidazo[4,5-*b*]pyridine ring system **17**.[61] Further examples of the use of aminoimidazoles as synthetic intermediates are described in the following paper.[59]

The unexpected *C*-addition of DMAD to the 4- and 5-aminoimidazoles **1** and **2** has led us to carry out a semi-empirical molecular orbital study of these amines. We now report the results of AM1 calculations[62] which form the basis of a frontier molecular orbital study (FMO) which is used here and in the following paper[59] to rationalise the preference for either *N*-addition or *C*-addition of electrophilic reagents to aminoimidazoles. Because of the possibility that in some of the reactions which we describe aminoimidazoles might be reacting with their nitroimidazole precursors, we have also carried out AM1 calculations for 4- and 5-nitroimidazoles. Only very limited molecular orbital studies of aminoimidazoles have been previously described.[63] As a result of their interesting biological properties,[64] theoretical studies of the structure and bonding of nitroimidazoles have attracted greater attention.[65–69] To our knowledge no calculations on both classes of imidazole derivative using the same molecular orbital method have been published.

We have carried out AM1 calculations on the amino-imidazole structures **1b**, **d** and **2b**, **d** and the nitroimidazole structures **3b**–**d** and **4b**, **d**. Tables of calculated bond lengths, bond angles, and dihedral angles for the molecules **1b**, **d**, **2b**, **d**, **3b**–**d** and **4b**, **d** have been deposited as a Supplementary Publication [Supp. No. 568964 (4 pp.)].* Table 1 compares the average values of the calculated imidazole bond lengths with measured imidazole values taken from the Cambridge Structural Database.[70] AM1 appears to overestimate the length of the ring bond-lengths in these imidazoles by *ca.* 0.02–0.06 Å. For comparison we have calculated the structure of imidazole ($C_3H_4N_2$) and this molecule also has calculated bond lengths greater than observed (Table 1).[71] This appears to be a systematic trend of the AM1 method when applied to imidazoles. The calculated lengths of the exocyclic CN bonds are also significantly longer than those determined experimentally and it may well be that AM1 overestimates the core-repulsion energies for multi-nitrogen heterocycles. The amino groups of the amines **1** and **2** are calculated to be pyramidal and, in agreement with experiment,[72–76] the nitro groups of the

* For details of the deposition scheme see: Instructions for Authors in *J. Chem. Soc. Perkin Trans. 1*, 1992, issue 1.

Table 1 Comparison of observed and calculated imidazole bond lengths

	Measured bond lengths (Å)		Calculated (AM1) bond lengths (Å)		
Bond[a]	Mean[b]	Imidazole[c]	Imidazole	Aminoimidazoles[d]	Nitroimidazoles[e]
N(1)–C(2)	1.349	1.349	1.400	1.406	1.407
N(1)–C(5)	1.370	1.369	1.395	1.405	1.393
N(3)–C(4)	1.377	1.378	1.394	1.403	1.396
N(3)–C(2)	1.314	1.326	1.351	1.352	1.358
C(4)–C(5)	1.361	1358	1.401	1.421	1.422
C–NH_2	—	—	—	1.403	—
C–NO_2	1.411[f]	—	—	—	1.463

[a] Atom numbering shown in Figs. 1 and 2. [b] Median values for structures in the Cambridge Structural Database and described in ref 70. [c] Taken from ref. 71. [d] Average values for the molecules **1b**, **d** and **2b**, **d**. [e] Average values for the molecules **3b–d** and **4b**, **d**. [f] Average value for the nitroimidazoles described in refs. 72–76.

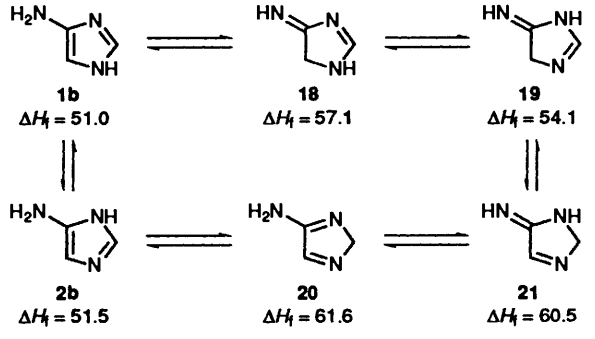
Table 2 AM1 Calculated properties of 4- and 5-nitro-imidazoles

	4-Nitroimidazoles			5-Nitroimidazoles		
Property	Compd.	Calc.	Obsd.	Compd.	Calc.	Obsd.
Enthalpy of formation	**3b**	56.9	—	**4b**	55.5	—
(kcal mol^{-1})	**3d**	53.3	—	**4d**	52.3	—
Dipole moment (D)	**3b**	7.79	7.38[65]	**4b**	4.15	—
	3d	8.55	—	**4d**	5.16	—
	3e	8.40	7.36[65]	**4e**	4.53	4.07[65]
Ionisation potential	**3b**	10.31	9.85[65]	**4b**	10.36	—
(eV)	**3d**	9.87	—	**4d**	9.88	—
	3e	10.17	9.40[65]	**4e**	10.20	9.55[65]

nitroimidazoles **3** and **4** are calculated to be essentially coplanar with the imidazole rings.

The calculated enthalpies of formation of the tautomers **1b** and **2b** are shown in Scheme 2. In the gas phase these isomers are calculated to be of comparable energy, with the 4-amino structure **1b** being slightly more stable. Both these isomers are calculated to be significantly more stable than the tautomeric imine structures **18**, **19** and **21** or the diazacyclopentadiene **20**. These results are in agreement with earlier calculations by Dewar, Bodor and Harget[63] who used a semi-empirical SCF MO π method to calculate a small predominance of the 4-amino tautomer **1b** in the equilibrium **1b** ⇌ **2b**. The ^1H and ^{13}C NMR spectra of simple 5-aminoimidazoles **2** are entirely consistent with the 5-amino structure and we have found no evidence of any equilibrium with imino tautomers.

In agreement with other theoretical studies,[65,67] the calculated enthalpies of formation of the isomers **3** and **4** are similar (Table 2) with the 5-nitro isomers calculated to be slightly more stable (*ca.* 1–1.5 kcal mol^{-1}) in the gas phase. In



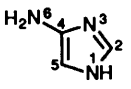
Scheme 2 Calculated enthalpies of formation of 4- and 5-aminoimidazole **1b** and **2b** and prototropic tautomers **18–21**

solution 4(5)-nitroimidazoles **3** or **4** (R^1 = H) are found to occur predominantly as the 4-nitro tautomers **3** (R^1 = H)[65,77] and this has been interpreted as being due to greater solvation of the more polar 4-nitro isomers **3**.[65,67] In agreement with other calculations,[65,67] dipole moment calculations by the AM1 method suggest that the 4-nitro isomers are significantly more polar than the 5-nitro isomers and the calculated dipole moments are in reasonably good agreement with experimental values[65] (Table 2).

The calculated dipole moments of the isomeric aminoimidazoles **1** and **2** are in the range 3.2–4.1 D (Fig. 1). Unlike the nitroimidazoles **3** and **4** (Table 2), there is not a large polarity difference between the isomers **1** and **2**. If the degree of solvent stabilisation is related to the size of the dipole moment, as has been suggested for nitroimidazoles,[65,67] the solvent stabilisation of isomeric aminoimidazoles **1** and **2** in solution can be expected to be similar. Since the isomers **1** and **2** are calculated to be similar in energy in the gas phase, both tautomers of the 1-unsubstituted derivatives **1** and **2**; (R^1 = H) can be predicted to be present in solution, **1** ⇌ **2** (R^1 = H).

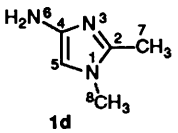
Fig. 1 shows the frontier orbital energies and coefficients for the amines **1b**, **d** and **2b**, **d** together with atomic charges. For both classes the calculated energies of the highest occupied molecular orbitals (HOMO) are relatively high and in the range −8.15 to −8.40 eV. Methyl substitution slightly increases the HOMO energies. The calculated ionisation potentials (Koopmans' theorem[78]) are compared with experimental[62,65,79] and calculated values (AM1) for aniline, pyrrole, imidazole, 1-methylimidazole and nitroimidazoles in Table 3. The average error (0.55 eV) is comparable to the average error (0.61 eV) for 256 compounds which has been described by Stewart.[80,81]

The first ionisation energies of the nitroimidazoles **3** and **4** estimated from the HOMO energies using Koopmans' theorem,



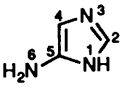
1b

	e/au	HOMO	LUMO
E/eV	—	−8.38	1.02
N-1	−0.21	−0.25	−0.44
C-2	−0.09	−0.38	0.54
N-3	−0.17	0.06	−0.22
C-4	−0.04	0.45	−0.35
C-5	−0.21	0.57	0.57
N-6	−0.27	−0.42	0.07
	$\mu_{calc.}$ 3.22D		



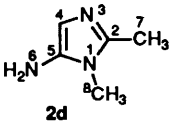
1d

	e/au	HOMO	LUMO
E/eV	—	−8.16	0.99
N-1	−0.15	−0.28	−0.42
C-2	−0.03	−0.40	0.55
N-3	−0.17	0.03	−0.26
C-4	−0.04	0.45	−0.30
C-5	−0.20	0.56	0.53
N-6	−0.27	−0.39	0.06
	$\mu_{calc.}$ 3.52D		



2b

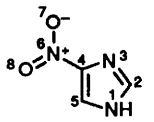
	e/au	HOMO	LUMO
E/eV	—	−8.38	0.92
N-1	−0.23	−0.01	0.40
C-2	−0.11	−0.49	−0.49
N-3	−0.12	−0.18	0.20
C-4	−0.22	0.53	0.34
C-5	−0.02	0.48	−0.60
N-6	−0.28	−0.40	0.13
	$\mu_{calc.}$ 4.02D		



2d

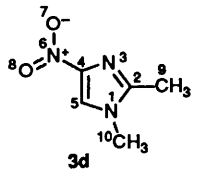
	e/au	HOMO	LUMO
E/eV	—	−8.15	0.88
N-1	−0.18	0.03	0.38
C-2	−0.06	0.49	−0.49
N-3	−0.12	0.21	0.22
C-4	−0.22	−0.51	0.30
C-5	−0.02	−0.48	−0.57
N-6	−0.27	0.37	0.13
	$\mu_{calc.}$ 4.09D		

Fig. 1 Calculated charge distribution and frontier orbital energies and coefficients for 4- and 5-aminoimidazoles



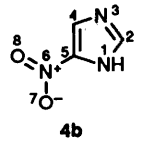
3b

	e/au	HOMO	LUMO
E/eV	—	−10.31	−0.65
N-1	−0.20	−0.17	−0.31
C-2	−0.03	−0.53	0.11
N-3	−0.07	−0.19	0.15
C-4	−0.20	0.56	−0.36
C-5	−0.06	0.55	0.59
N-6	0.61	−0.01	−0.42
O-7	−0.32	−0.14	0.34
O-8	−0.38	−0.13	0.32
	$\mu_{calc.}$ 7.79D		



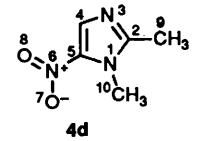
3d

	e/au	HOMO	LUMO
E/eV	—	−9.87	−0.51
N-1	−0.15	−0.20	−0.31
C-2	−0.03	−0.52	0.12
N-3	−0.07	−0.23	0.14
C-4	−0.20	0.53	−0.34
C-5	−0.06	0.51	0.59
N-6	0.61	0.01	−0.42
O-7	−0.32	−0.13	0.34
O-8	−0.38	−0.12	0.32
	$\mu_{calc.}$ 8.55D		



4b

	e/au	HOMO	LUMO
E/eV	—	−10.36	−1.10
N-1	−0.16	−0.17	−0.34
C-2	−0.04	−0.51	0.39
N-3	−0.14	−0.19	−0.01
C-4	−0.04	0.44	−0.43
C-5	−0.22	0.65	0.33
N-6	0.61	0.01	0.44
O-7	−0.34	−0.17	−0.35
O-8	−0.37	−0.16	−0.34
	$\mu_{calc.}$ 4.15D		



4d

	e/au	HOMO	LUMO
E/eV	—	−9.88	−0.96
N-1	−0.11	−0.22	−0.34
C-2	0.01	−0.50	0.41
N-3	−0.15	−0.20	−0.02
C-4	−0.04	0.41	−0.42
C-5	−0.23	0.61	0.32
N-6	0.62	0.02	0.43
O-7	−0.34	−0.16	−0.34
O-8	−0.38	−0.15	−0.33
	$\mu_{calc.}$ 5.16D		

Fig. 2 Calculated charge distribution and frontier orbital energies and coefficients for 4- and 5-nitroimidazoles

Table 3 Experimental (vertical) and calculated first ionisation potentials (IP) eV

Molecule	IP Obsd.	IP AM1	IP Difference
Aniline	7.70[79]	8.53	0.83
Pyrrole	8.22[62]	8.66[62]	0.44
Imidazole	9.00[65]	9.16	0.16
1-Methylimidazole	8.75[65]	—	—
1-Methyl-4-nitroimidazole **3e**	9.40[65]	10.17	0.67
5-Nitro-1-methylimidazole **4e**	9.55[65]	10.20	0.65
4-Amino-1-methylimidazole **1e**	—	8.29	—
5-Amino-1-methylimidazole **2e**	—	8.33	—

and vertical ionisation potentials derived experimentally using photoelectron spectroscopy for the derivatives **3b, e** and **4e** are in reasonable agreement (Table 2).

It is interesting to note that although the 4- and 5-nitroimidazoles **3** and **4** have HOMO energies of similar magnitude, there is a significant difference between their LUMO energies (Fig. 2). The 5-nitro imidazoles **4** have much lower LUMO energies (*ca.* −1.0 eV) than the 4-nitro isomers **3** (*ca.* −0.55 eV). The antibacterial, radiosensitisation and hypoxic cytotoxic properties of nitroimidazoles are believed to be related mechanistically to their one-electron reduction potentials,[64,82] which are closely related to the LUMO energies. This relationship between electronic structure and biological activity has been discussed by other investigators,[67] and the AM1 calculations described here are fully consistent with earlier calculations and conclusions.[65,67] The possibility that the magnitude of the LUMO energy of nitroimidazoles may critically influence their reaction with aminoimidazoles is discussed in the following paper.[59]

Frontier molecular orbital theory (FMO) assumes that favourable orbital interactions during the early stages of a bimolecular reaction result in transition-state stabilisation.[83] This is a reasonable assumption for exothermic reactions in which, according to Hammond's Postulate, the transition state occurs early in the reaction. The FMO approach has been successfully applied to many electrophilic substitution reactions[83] and we now describe an analysis of the reactions of aminoimidazoles with electrophilic reagents. Implicit in this analysis is the assumption that products are formed under kinetic control.

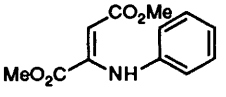
The aminoimidazoles **1** and **2** are *N,C*-ambident nucleophiles:[84] they can be regarded as heterocyclic enamines and reactions on either carbon (ring) or on nitrogen (exocyclic amino) are both observed. FMO theory is not suitable for describing absolute reactivities at alternative reaction centres: this depends upon the competing transition state structures which often differ significantly, especially for *N,C*-ambident nucleophiles. FMO theory can be useful for discussing variations in relative reactivity at alternative centres with respect to modifications of one of the reactants (*e.g.* the electrophile). This approach forms the basis of our FMO analysis of the variation of the reactivity and position of reaction of aminoimidazoles with a range of electrophilic reagents.

Two types of reaction of 5-aminoimidazoles **2** with electrophilic reagents have been investigated in our studies. The first type is a simple addition where the nucleophile adds to a double or triple bond followed by protonation of the resulting anionic centre. This mode of reaction can be classified as addition–protonation. The second type of reaction involves addition of the amine **2** to an electrophilic double bond followed by

elimination of a simple anion, and can be classified as an addition–elimination. Addition–eliminations of aminoimidazoles are described in the following paper.[59] Both modes of reaction (addition–protonation or addition–elimination) can occur on either *N* or *C* centres of the 5-aminoimidazole **2** and the first stage of each process is identical for the purposes of FMO analysis.

Inspection of the frontier π-orbitals of both the 4- and 5-aminoimidazoles **1** and **2** (Fig. 1) shows that for each molecule the largest coefficient of the highest occupied molecular orbital (HOMO) is i, on carbon and ii, significantly larger than the coefficient on the exocyclic nitrogen atom. The calculated HOMO energies of both aminoimidazole systems **1** and **2** (−8.15 to −8.40 eV) are moderately high and comparable to aniline (−8.53 eV) (Table 3). Accordingly, we classify them as borderline nucleophiles (*i.e.* intermediate between hard and soft).[83] Of the two reaction centres, the nitrogen atom which is more electronegative and has the larger calculated charge but smaller orbital coefficient can be expected to be more reactive towards hard electrophiles. The ring carbon atom (larger HOMO coefficient) can be expected to be more reactive towards soft electrophiles (low LUMO). This is precisely what we observe experimentally. Both 4-amino- and 5-amino-1,2-dimethylimidazole **1d** and **2d** react with dimethyl acetylenedicarboxylate (DMAD), which is a soft electrophile (low LUMO), to give *C*-addition products.

It is interesting to compare these results with the reactivity of aniline **22** and 6-aminouracil **23** towards DMAD.[85–87] For reasons discussed earlier, it is not possible to comment on the absolute reactivities of different molecules but it is informative



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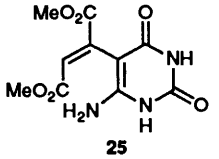
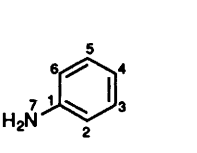
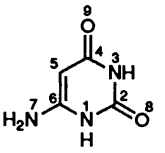


25

to compare parameters which may contribute to regioselectivity. Aniline **22** reacts exclusively at the nitrogen atom giving the anilinofumarate **24**[85] whereas 6-aminouracil **23** reacts exclusively at the carbon atom at position 5 giving the *C*-adduct **25**.[86,87] Calculated properties for the amines **22** and **23** using AM1 are shown in Fig. 3. Inspection of the results for aniline shows that the nitrogen atom has both a high negative charge and a large HOMO coefficient. Both coulombic (hard) and orbital (soft) interactions are therefore favourable for aniline to react on nitrogen. The 6-aminouracil molecule **23** has large but comparable negative charges on both C-5 and N-7 (Fig. 3) but the calculated HOMO coefficient is much greater at C-5. Soft interactions therefore favour reaction at C-5 and the resulting stabilisation of the transition state relative to that for reaction at N-7 may contribute to the outcome of the reaction. This situation is analogous to that for the aminoimidazoles (Fig. 1) where the calculated charges on carbon and nitrogen are similar but soft interactions can be expected to favour reaction on carbon. Of course, many other factors contribute to the relative energies of transition states but it is interesting to further explore the influence of coulombic and orbital interactions on the reactions of 5-aminoimidazoles **2** by studying their behaviour towards a range of electrophilic reagents. The results of this study are reported in the following paper.[59]



22



23

	e/au	HOMO	LUMO		*e*/au	HOMO	LUMO
E/eV	—	−8.53	0.64	*E*/eV	—	−9.44	−0.14
C-1	0.05	0.40	−0.04	N-1	−0.33	0.32	−0.21
C-2	−0.19	0.36	−0.47	C-2	0.40	0.06	−0.11
C-3	−0.09	−0.17	0.53	N-3	−0.37	0.04	0.19
C-4	−0.17	−0.48	−0.03	C-4	0.37	−0.04	−0.33
C-5	−0.09	−0.17	−0.49	C-5	−0.39	−0.72	−0.42
C-6	−0.19	0.36	0.51	C-6	0.23	−0.31	0.69
N-7	−0.33	−0.49	0.01	N-7	−0.35	0.36	−0.22
				O-8	−0.37	−0.18	0.08
				O-9	−0.34	0.30	0.26

Fig. 3 Calculated charge distribution and frontier orbital energies and coefficients for aniline and 6-aminouracil

Experimental

NMR spectra were recorded at ambient temperatures on either a Varian CFT-20 spectrometer at 80 MHz or a Varian XL-200 spectrometer at 200 MHz. IR spectra were obtained on a Pye-Unicam SP3-200 spectrometer. Unless otherwise stated IR spectra were measured using KBr discs and NMR spectra in hexadeuteriodimethyl sulfoxide (tetramethylsilane as internal reference). Only significant bands from IR spectra are quoted.

Elemental analyses were determined using a Carlo-Erba elemental analyser model 1106. UV spectra were recorded on a Pye-Unicam SP8-500 spectrophotometer and mass spectra on either a VG Micromass 6F or a VG 7070E spectrometer. An ionising potential of 70 eV was used with a source temperature of 250 °C.

Separations by column chromatography were carried out using Merck Kieselgel 60 (230–400 mesh). Concentration and evaporation refer to the removal of volatile materials under reduced pressure (10–15 mmHg at 25–70 °C) on a Buchi Rotovapor. Substances stated to be identical were so with respect to m.p.s, mixed m.p.s and IR spectra. M.p.s were determined using an Electrothermal melting point apparatus and are uncorrected.

Calculations were carried out using the AM1 semi-empirical method[62] and the geometry of each molecule studied was found by minimising the energy with respect to all geometrical variables.

Preparation of 5-Aminoimidazoles **2**.—A solution of 1,2-dimethyl-5-nitroimidazole[88] **4d** (14.1 g, 0.1 mol) in 1,4-dioxane (250 cm^3) and 5% Pd/C (40% w/w; 5.64g) were vigorously shaken under an atmosphere of H_2 until uptake of gas ceased (uptake corresponded to 3 mol equiv.). The catalyst was filtered off and the pale yellow solution was concentrated (*ca.* 60 cm^3). The solid which separated was collected and washed with dioxane (1 × 30 cm^3) and then ether (2 × 40 cm^3) to give 5-*amino*-1,2-*dimethylimidazole* **2d** (8.2 g, 74%) as a buff powder, m.p. 120–140 °C (softening) (Found: C, 53.8; H, 8.0; N, 37.5. $C_5H_9N_3$ requires C, 54.0; H, 8.1; N, 37.8%); λ_{max}(EtOH)/nm 221 (ε 2440); ν_{max}/cm^{-1} 1235, 1300, 1370, 1390, 1450, 1530, 1590, 1650, 3100 and 3380; δ_H 2.10 (s, CCH_3), 3.20 (s, NCH_3), 4.15 (br s, NH_2) and 5.8 (s, CH); δ_C(deuteriopyridine) 13.52 (C-CH_3), 28.36 (NCH_3), 112.50 (C-4), 136.52 (C-2 or C-5) and 139.09 (C-2 or C-5); *m*/*z* 111 ($M^{\cdot+}$).

The following compounds were similarly prepared from 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole[89] **4f**, 1-methyl-5-nitroimidazole[90] **4e** and 2-isopropyl-1-methyl-5-nitroimidazole[91] **4g** respectively: 5-*amino*-1-(2-*hydroxyethyl*)-2-*methylimidazole* **2f** (58%) as a buff powder, m.p. 118–122 °C. (Found: C, 51.3; H, 7.8; N, 30.0. $C_6H_{11}N_3O$ requires C, 51.1; H, 7.85,

29.8%); λ_{max}(EtOH)/nm 221 (ε 5550); ν_{max}/cm^{-1} 1370, 1400, 1430, 1520, 1615, 2700, 3090 and 3400; δ_H 2.17 (s, CCH_3), 3.58 (t, *J* 5, OCH_2), 3.79 (t, *J* 5, NCH_2), 4.06 (br s, NH_2), 4.90 (br s, OH) and 5.95 (s, CH); δ_C(deuteriopyridine) 13.52 (CCH_3), 45.48 (NCH_2), 61.51 (OCH_2), 111.07 (C-4), 137.25 (C-2 or C-5) and 139.22 (C-2 or C-5); *m/z* 141 ($M^{\bullet+}$); 5-*amino*-1-*methylimidazole* **2e** (53%) as a purple solid, m.p. 107–109 °C (Found: C, 49.8; H, 7.2; N, 43.7. $C_4H_7N_3$ requires C, 49.5; H, 7.3; N, 43.3%); ν_{max}/cm^{-1} 1220, 1430, 1510, 1590, 3140, 3300 and 3360; δ_H 3.45 (s, NCH_3), 4.50 (br s, NH_2), 6.20 (d, *J* 1, 4-H) and 7.20 (d, *J* 1, 2-H); *m/z* 97 ($M^{\bullet+}$); 5-amino-2-isopropyl-1-methylimidazole **2g** (crude yield >90%), obtained as an orange oil which did not crystallise and which was used without further purification.

Where 5-aminoimidazoles **2** were used *in situ* without isolation, the above procedure was followed but after filtration the yellow solution was used immediately. Using this procedure solutions of the amines (**2d–g, r**) were satisfactorily obtained.

Reductions were often accompanied by a moderate exotherm (temperatures rising to as high as 60 °C), but this had little effect on yields and cooling was found to be unnecessary.

5-*Amino*-1,2-*dimethylimidazolium Picrate*.—A solution of compound **2d** (0.56 g, 5 mmol) in ethanol (5 cm^3) was added to a stirred solution of picric acid (2.0 g, 8.7 mmol) in ethanol (65 cm^3) at ambient temperature. The yellow precipitate was collected, washed with ethanol (3 × 20 cm^3) and ether (2 × 25 cm^3) and dried (1.3 g, 77%). A small sample was recrystallised from ethanol giving the picrate salt as small yellow needles, m.p. 196 °C (decomp.) [lit.,[39] 193 °C (decomp.)] (Found: C, 38.7; H, 3.3; N, 24.3. Calc. for $C_{11}H_{12}N_6O_7$: C, 38.8; H, 3.6; N, 24.7%); ν_{max}/cm^{-1} 1280, 1330, 1365, 1435, 1560, 1630, 3360 and 3440; δ_H 2.25 (s, CCH_3), 3.47 (s, NCH_3), 5.32 (br s, NH_2), 6.47 (s, CH), 8.57 (s, 2 ArH) and 13.1 (br s, OH).

Additions of 5-*Aminoimidazoles* **2**.—(a) *With aryl isocyanates*. A solution of compound **2d** in 1,4-dioxane (190 cm^3) was generated *in situ* from 1,2-dimethyl-5-nitroimidazole[88] (15.0 g, 106 mmol) according to the general procedure described above. 3,4-Dichlorophenyl isocyanate (20 g, 106 mmol) was added immediately, with stirring, and after 10 min at room temperature, the solution was evaporated to give an oil. Trituration with ethanol (50 cm^3) gave a solid which was recrystallised from ethanol giving N-(3,4-*dichlorophenyl*-N^1-(1,2-*dimethylimidazol*-5-*yl*)*urea* **7a** (15 g, 47%), white powder, m.p. 169–170 °C (Found: C, 48.0; H, 3.9; Cl, 23.4; N, 18.8. $C_{12}H_{12}Cl_2N_4O$ requires C, 48.2; H, 4.0; Cl, 23.7; N, 18.7%); ν_{max}/cm^{-1} 1473, 1550, 1589, 1637 and 3295; δ_H 2.26 (s, CCH_3), 3.32 (s, NCH_3), 6.60 (s, CH), 7.33 (dd, *J* 2 and 8, 1 Ar*H*), 7.52 (d, *J* 8, 1 ArH), 7.87 (d, *J* 2, 1 ArH), 8.16 (br s, 1 exchangeable NH) and 9.16 (br s, 1 exchangeable NH).

In a similar manner, the following ureas were obtained from the appropriate solutions of 5-aminoimidazoles **2**: N-(3-*chloro*-4-*tolyl*-N^1-(1,2-*dimethylimidazol*-5-*yl*)*urea* **7b** (3.2 g, 38%) as a buff powder, m.p. 199–200 °C (Found: C, 56.1; H, 5.4; Cl, 13.0; N, 19.6. $C_{13}H_{15}ClN_4O$ requires C, 56.0; H, 5.4; Cl, 12.7; N, 20.1%); ν_{max}/cm^{-1} 1200, 1224, 1307, 1498, 1530, 1596 and 1708; δ_H 2.25 (s, 2 CCH_3), 3.30 (s, NCH_3), 6.57 (s, imidazole CH), 7.22 (d, *J* 1, 2 ArH), 7.67 (s, 1 ArH), 8.03 (br s, exchangeable NH) and 8.90 (br s, exchangeable NH); N-(3,4-*dichlorophenyl*)-N^1-(2-*isopropyl*-1-*methylimidazol*-5-*yl*)*urea* **7c** (19.5 g, 51%) as a white powder, m.p. 111–112 °C (Found: C, 51.2; H, 4.9; Cl, 21.6; N, 17.1. $C_{14}H_{16}Cl_2N_4O$ requires C, 51.4; H, 4.9; Cl, 21.7; N, 17.1%); ν_{max}/cm^{-1} 1220, 1305, 1383, 1479, 1534, 1591 and 2975; δ_H 1.2 [d, *J* 7, $CH(CH_3)_2$], 2.95 [sept, *J* 7, $CH(CH_3)_2$], 3.30 (s, NCH_3), 6.60 (s, imidazole CH), 7.27 (dd, *J* 2 and 8, 1 ArH), 7.43 (d, *J* 8, 1 ArH), 7.80 (d, *J* 2, 1 ArH), 8.06 (br s, exchangeable NH) and 9.13 (br s, exchangeable NH); N-(3-*chloro*-4-*tolyl*)-N^1-(2-*isopropyl*-1-*methylimidazol*-5-*yl*)*urea* **7d** (3.4 g, 37%) as a white solid, m.p. 202–203 °C (Found: C, 58.3; H, 6.1; Cl, 11.7; N, 18.2. $C_{15}H_{19}ClN_4O$ requires C, 58.7; H, 6.2; Cl, 11.6, N, 18.3%); ν_{max}/cm^{-1} 1218, 1305, 1450, 1497, 1534, 1600, 1709, 2965 and 3340; δ_H 1.19 [d, *J* 7, $CH(CH_3)_2$], 2.24 (s, CCH_3), 3.00 [sept, *J* 7, $CH(CH_3)_2$], 3.35 (s, NCH_3), 6.60 (s, imidazole CH), 7.2 (d, *J* 1, 2 ArH), 7.66 (s, 1 ArH), 7.98 (br s, exchangeable NH) and 8.95 (br s, exchangeable NH); N-(2-*isopropyl*-1-*methylimidazol*-5-*yl*)-N^1-(4-*tolylsulfonyl*)*urea* **7e** (1.5 g, 14.9%) as a white powder, m.p. 168–170 °C (Found: C, 53.8; H, 6.2; N, 17.0; S, 9.1. $C_{15}H_{20}N_4O_3S$ requires C, 53.6; H, 6.0; N, 16.7; S, 9.5%); ν_{max}/cm^{-1} 1270, 1290, 1325, 1493, 1600 and 1650; δ_H 1.22 [d, *J* 7, $CH(CH_3)_2$], 2.32 (s, CCH_3), 3.22 [sept, *J* 7, $CH(CH_3)_2$], 3.45 (s, NCH_3), 5.0–8.0 (vbr s, 2 exchangeable NH), 6.92 (s, imidazole CH), 7.20 (d, *J* 8, 2 × ArH) and 7.67 (d, *J* 8, 2 ArH).

Reaction of compound **2f** with dichlorophenyl isocyanate gave an oil which was shown to be a mixture of two products. This mixture was separated by MPLC [CH_2Cl_2–CH_3OH (9:1) as eluent]. The first component was identified as N-(3,4-*dichlorophenyl*)-N^1-{1-[2-(3,4-*dichloroanilinocarbonyloxy*)-*ethyl*]-2-*methylimidazol*-5-*yl*}*urea* **7f** (4.2 g, 8%) (R_f 0.4) as a white powder, m.p. 185–186 °C (Found: C, 46.3; H, 3.3; Cl, 27.5; N, 13.5. $C_{20}H_{17}Cl_4N_5O_3$ requires C, 46.4; H, 3.3; Cl, 27.4; N, 13.5%); ν_{max}/cm^{-1} 1228, 1387, 1418, 1480, 1525, 1596, 1643, 1740 and 3325; δ_H 2.30 (s, CCH_3), 3.9–4.4 (m, CH_2CH_2), 6.60 (s, imidazole CH), 7.15–7.55 (m, 4 ArH), 7.6–7.8 (m, 2 ArH), 8.05 (br s, 1 exchangeable NH) and 9.05 (br s, 1 exchangeable NH).

The second component was identified as N-(3,4-*dichlorophenyl*)-N-[1-(2-*hydroxyethyl*)-2-*methylimidazol*-5-*yl*]*urea* **7g** (1.0 g, 3%) (R_f 0.2) as colourless needles, m.p. 206–207 °C (Found: C, 47.4; H, 4.4; Cl, 21.9; N, 17.0. $C_{13}H_{14}Cl_2N_4O_2$ requires C, 47.4; H, 4.3; Cl, 21.5; N, 17.0%); ν_{max}/cm^{-1} 1233, 1380, 1478, 1535, 1598, 1640, 3180 and 3295; δ_H 2.30 (s, CCH_3), 3.45–3.85 (m, CH_2CH_2), 4.34 (s, 2 exchangeable H), 6.60 (s, imidazole CH), 7.23 (dd, *J* 2 and 8, 1 ArH), 7.45 (d, *J* 8, 1 ArH), 7.77 (d, *J* 2, 1 ArH) and 9.17 (br s, 1 exchangeable NH).

(b) *With phenyl isothiocyanate*. A solution of compound **2d** in 1,4-dioxane (200 cm^3) was generated *in situ* according to the method described above. Phenyl isothiocyanate (13.5 g, 100 mmol) was added with stirring. After 30 min the solid product was collected and identified as N-(1,2-*dimethylimidazol*-5-*yl*)-N-*phenylthiourea* **8h** (13.4 g, 55%) as a buff powder, m.p. 190–191 °C (Found: C, 58.1; H, 5.8; N, 22.7; S, 13.0. $C_{12}H_{14}N_4S$ requires C, 58.5; H, 5.7; N, 22.8; S, 13.0%); ν_{max}/cm^{-1} 1200, 1225, 1278, 1350, 1448, 1491, 1530, 1594, 2960 and 3140; δ_H 2.27 (s, CCH_3), 3.35 (s, NCH_3), 6.70 (s, imidazole CH), 7.0–7.6 (m, 5 ArH), 7.5–7.9 (vbr s, 1 exchangeable NH) and 9.70 (br s, 1 exchangeable NH).

In a similar manner, the following compound was obtained from 5-amino-2-isopropyl-1-methylimidazole **2g**: N-(2-*isopropyl*-1-*methylimidazol*-5-*yl*)-N-*phenylthiourea* **8i** (7.8 g, 24%) as a white powder, m.p. 167–168 °C (decomp.) (Found: C, 61.4; H, 6.88; N, 20.4; S, 11.4. $C_{14}H_{18}N_4S$ requires C, 61.3; H, 6.61; N, 20.4; S, 11.7%); ν_{max}/cm^{-1} 1317, 1471, 1513, 1597 and 2965; δ_H($CDCl_3$ + [$^2H_6$]-DMSO) 1.32 [d, *J* 7, $CH(CH_3)_2$], 3.30 [sept, *J* 7, $CH(CH_3)_2$], 3.50 (s, N-CH_3), 6.90 (s, imidazole CH), 7.15–7.6 (m, 5 ArH) and 8.0–9.5 (vbr s, 2 exchangeable NH).

(c) *With dialkyl acetylenedicarboxylates*. Dimethyl acetylenedicarboxylate (2.84 g, 20 mmol) was added to a stirred solution of 5-amino-1,2-dimethylimidazole **2d** (2.22 g, 20 mmol) in acetonitrile (150 cm^3) at room temperature. After further stirring (1 h), the red–brown solution was evaporated and the residual product purified by MPLC (9:1, $CHCl_3$–MeOH as eluent). The major component (R_f 0.2) was collected, washed with Et_2O (3 × 15 cm^3) and identified as *dimethyl* 1-(5-*amino*-

1,2-*dimethylimidazol*-4-*yl*)*ethylene*-1,2-*dicarboxylate* **11j** (2.24 g, 44%) as a yellow powder, m.p. 148–149 °C (Found: C, 51.9; H, 5.92; N, 16.3. $C_{11}H_{15}N_3O_4$ requires C, 52.2; H, 5.97; N, 16.6%); ν_{max}/cm^{-1} 1240, 1310, 1380, 1445, 1540, 1570, 1620, 1695, 1720, 2980, 3340 and 3470; δ_H 2.10 (s, CCH_3), 3.30 (s, NCH_3), 3.60 (s, OCH_3), 3.75 (s, OCH_3), 5.55 (br s, NH_2) and 5.80 (s, olefinic CH); *m*/*z* 253 ($M^{\bullet+}$).

In a similar manner, the following compounds were obtained starting from the appropriate 5-aminoimidazole **2** and either dimethyl or diethyl acetylenedicarboxylate: *dimethyl* 1-[5-*amino*-1-(2-*hydroxyethyl*)-2-*methylimidazol*-4-*yl*]*ethylene*-1,2-*dicarboxylate* **11k** (1.03 g, 36%) as tiny yellow prisms, m.p. 154–155 °C (Found: C, 51.0; H, 6.0; N, 14.4. $C_{12}H_{17}N_3O_5$ requires C, 50.9; H, 6.05; N, 14.8%); ν_{max}/cm^{-1} 1235, 1260, 1340, 1430, 1540, 1570, 1700, 1730, 2960 and 3300; δ_H 2.18 (s, CCH_3), 3.60 (m, OCH_2 and OCH_3), 3.74 (s, OCH_3), 3.82 (t, *J* 5, NCH_2), 5.02 (br t, *J* 5, OH), 5.54 (br s, NH_2) and 5.82 (s, olefinic CH); *m*/*z* 283 ($M^{\bullet+}$); *dimethyl* 1-(5-*amino*-1-*methyl*-2-*isopropylimidazol*-4-*yl*)*ethylene*-1,2-*dicarboxylate* **11l** (2.5 g, 45%) as a yellow powder, m.p. 152–154 °C (Found: C, 55.8; H, 6.98; N, 15.1. $C_{13}H_{19}N_3O_4$ requires C, 55.5; H, 6.81; N, 14.9%); ν_{max}/cm^{-1} 1250, 1290, 1340, 1425, 1440, 1550, 1635, 1700, 1730, 2960, 2990, 3370 and 3430; δ_H 1.15 [d, *J* 7, $CH(CH_3)_2$], 2.90 [sept, *J* 7, $CH(CH_3)_2$], 3.35 (s, NCH_3), 3.60 (s, OCH_3) 3.75 (s, OCH_3), 5.52 (br s, NH_2) and 5.85 (s, olefinic CH); *m*/*z* 281 ($M^{\bullet+}$); *diethyl* 1-(5-*amino*-1,2-*dimethylimidazol*-4-*yl*)*ethylene*-1,2-*dicarboxylate* **11m** (1.95 g, 35%) as tiny yellow prisms, m.p. 130–132 °C (Found: C, 55.6; H, 6.85; N, 14.8. $C_{13}H_{19}N_3O_4$ requires C, 55.5; H, 6.81; N, 14.9%); ν_{max}/cm^{-1} 1245, 1315, 1360, 1435, 1540, 1565, 1625, 1700, 1730, 2960, 3210, 3310, 3415 and 3560; δ_H 1.20 (t, *J* 8, CH_2CH_3), 1.24 (t, *J* 8, CH_2CH_3), 2.16 (s, CCH_3), 3.30 (s, NCH_3), 4.06 (q, *J* 8, CH_2CH_3), 4.23 (q, *J* 8, CH_2CH_3), 5.57 (br s, NH_2) and 5.80 (s, olefinic CH); *m*/*z* 281 ($M^{\bullet+}$).

(d) *With diethyl azodicarboxylate.* Diethyl azodicarboxylate (4.36 g, 25 mmol) was added to a stirred solution of compound **2d** (2.8 g, 25 mmol) in acetonitrile (90 cm^3) at room temperature. After further stirring (1 h), evaporation of the mixture gave a residue which was purified by MPLC (9:1, $CHCl_3$–MeOH as eluent). The major component (R_f 0.37) was collected and identified as *diethyl* 1-(5-*amino*-1,2-*dimethylimidazol*-4-*yl*)-*hydrazine*-1,2-*dicarboxylate* **10m** (1.65 g, 23%), white powder, m.p. 186–188 °C (decomp.) (Found: C, 46.5; H, 6.90; N, 24.6. $C_{11}H_{19}N_5O_4$ requires C, 46.3; H, 6.71; N, 24.5%); ν_{max}/cm^{-1} 1260, 1330, 1370, 1400, 1465, 1640, 1705, 1735, 2900, 3160, 3340 and 3410; δ_H 1.17 (t, *J* 7, 2 × CH_2CH_3), 2.13 (s, CCH_3), 3.26 (s, NCH_3), 4.06 (q, *J* 7, 2 × CH_2CH_3), 4.40 (br s, NH_2) and 9.92 (br s, hydrazine NH); *m*/*z* 285 ($M^{\bullet+}$).

(e) *With diketene.* Diketene (2.25 g, 27 mmol) was added to a stirred solution of compound **2d** (2.97 g, 27 mmol) in dioxane (50 cm^3) at room temperature, and stirring was continued (2 h). After evaporation, the solution gave an orange oil which was purified by MPLC (9:1, $CHCl_3$–MeOH as eluent). The major component (R_f 0.14) was collected and identified as N-(1,2-*dimethylimidazol*-5-*yl*)-3-*oxobutanocarboxamide* **9j** (2.45 g, 47%) as a white powder, m.p. 97–99 °C (Found: C, 55.0; H, 6.75; N, 21.4. $C_9H_{13}N_3O_2$ requires C, 55.4; H, 6.71; N, 21.5%); ν_{max}/cm^{-1} 1310, 1365, 1410, 1550, 1680, 1700, 2950 and 3160; δ_H 2.22 (s, CCH_3 or $COCH_3$), 2.25 (s, CCH_3 or $COCH_3$), 3.32 (s, NCH_3), 3.35 (s, CH_2), 6.56 (s, imidazole CH) and 9.64 (br s, exchangeable NH); *m*/*z* 195 ($M^{\bullet+}$).

In situ *Preparation of* 4-*Aminoimidazoles* **1**.—The appropriate 4-nitroimidazole **3** (0.1 mol) in 1,4-dioxane (250 cm^3) and 5% Pd/C (40% w/w) were shaken vigorously under an atmosphere of H_2 until reduction was complete. The catalyst was filtered off and the appropriate reagent was then added with stirring to the filtrate. Using this procedure solutions of the amines (**1b**, **d**, **g**, **j**, **k**, **t**–**w**) were satisfactorily obtained.

Reduction of 4-*Nitroimidazoles* **3** *in Acetic Anhydride Solution.*—A mixture of 2-methyl-4-nitroimidazole[14] **3c** (31.8 g), 5% Pd/C (10.0 g), acetic acid (500 cm^3) and acetic anhydride (350 cm^3) was vigorously shaken under an atmosphere of hydrogen until 3 mol equiv. had been consumed. After filtration to remove the catalyst, the filtrate was concentrated (*ca.* 100 cm^3) and ethyl acetate (200 cm^3) was added. After further concentration (*ca.* 150 cm^3) the mixture was kept at 0 °C (18 h). The solid which separated was collected, washed with ethyl acetate and identified as 4,4′-*diacetamido*-2,2′-*dimethyl*-5,5′-*biimidazole* **5** (R^1 = Me, R^2 = Ac) (7.2 g, 10%) as a crystalline solid, m.p. > 360 °C (Found: C, 51.8; H, 5.78; N, 30.4. $C_{12}H_{16}N_6O_2$ requires C, 52.2; H, 5.84; N, 30.4%); ν_{max}/cm^{-1} 1204, 1267, 1430, 1520, 1624, 1650 and 3300; δ_H 1.97 (s, 2 $COCH_3$), 2.26 (s, 2 CCH_3), 8.65 (vbr s, 2 NH) and 11.20 (vbr s, 2 NH); *m*/*z* 277 (MH^+).

The mother liquor was evaporated and the residue triturated with water. The resulting solid was collected, washed with ethanol and then ether and identified as 4-*acetamido*-1-*acetyl*-2-*methylimidazole* (12.5 g, 28%) as a crystalline solid, m.p. 245–247 °C (Found: C, 53.0; H, 6.36; N, 23.2. $C_8H_{11}N_3O_2$ requires C, 53.0; H, 6.12; N, 23.2%); ν_{max}/cm^{-1} 1230, 1270, 1350, 1386, 1525, 1580, 1650, 1740, 3060 and 3220; δ_H 2.01 (s, CCH_3), 2.50 (s, $COCH_3$), 2.54 (s, $COCH_3$), 7.47 (s, CH) and 10.20 (br s, NH); δ_C 16.79 (CCH_3), 22.65 ($COCH_3$), 24.11 ($COCH_3$), 103.91 (5-C), 136.78 (4-C), 143.99 (2-C), 167.48 (CO) and 168.74 (CO); *m*/*z* 182 ($M^{\bullet+}$).

Using a similar procedure 1,2-dimethyl-4-nitroimidazole[89] **3d** (18.5 g) gave 4-*acetamido*-1,2-*dimethylimidazole* (5.95 g, 30%) as a crystalline solid, m.p. 228–230 °C (Found: C, 54.7; H, 7.30; N, 27.3. $C_7H_{11}N_3O$ requires C, 54.9; H, 7.24; N, 27.4%); ν_{max}/cm^{-1} 1265, 1368, 1411, 1494, 1550, 1670, 3020 and 3180; δ_H([$^2H_6$]-DMSO) 1.93 (s, $COCH_3$), 2.19 (s, C-CH_3), 3.48 (s, N-CH_3), 7.02 (s, CH) and 10.05 (vbr s, NH).

Preparation of Imidazol-4(5H)-*one Oximes* **6**.—A mixture of 2-methyl-4-nitro-1-phenoxycarbonylimidazole **3n** (8.0 g, 32.3 mmol) and 5% Pd/C (3.0 g) in 1,4-dioxane (300 cm^3) was shaken under an atmosphere of hydrogen until uptake ceased (*ca.* 2 mol equiv.). The catalyst was filtered off and the filtrate evaporated. The residue was dissolved in *N*,*N*-dimethylformamide (100 cm^3) and treated with activated charcoal. The mixture was then filtered and the filtrate diluted with water until precipitation was complete. The precipitate was collected and dried to give *phenyl* 2-*methyl*-4-*oxo*-4,5-*dihydroimidazole*-1-*carboxylate* **6** (R^1 = Ph, R^2 = H) (4.7 g, 62%) as an off-white solid, m.p. 172–173 °C (Found: C, 56.9; H, 4.80; N, 17.8. $C_{11}H_{11}N_3O_3$ requires C, 56.65; H, 4.72; N, 18.0%); ν_{max}/cm^{-1} 1283, 1364, 1587, 1760, 2940, 3140 and 3250; δ_H 2.5 (s, CH_3), 4.68 (s, CH_2), 7.15–7.75 (m, 5 ArH) and 10.8 (s, NOH).

In a similar manner, the following compounds were obtained from ethyl 2-methyl-4-nitroimidazole-1-carboxylate **3p**[58] and methyl 2-methyl-4-nitroimidazole-1-carboxylate **3o**: *ethyl* 2-*methyl*-4-*oxo*-4,5-*dihydroimidazole*-1-*carboxylate* **6** (R^1 = Et, R^2 = H) (4.4 g, 36%) as a buff solid, m.p. 130 °C (decomp.) (Found: C, 45.4; H, 6.0; N, 23.0. $C_7H_{11}N_3O_3$ requires C, 45.5; H, 6.0; N, 22.7%); ν_{max}/cm^{-1} 1230, 1270, 1358, 1373, 1390, 1590, 1735, 2890, 3120 and 3210; δ_H([$^2H_6$]-DMSO + $CDCl_3$) 1.33 (t, *J* 7, CH_2CH_3), 2.48 (s, CCH_3), 4.26 (q, *J* 7, CH_2CH_3), 4.48 (s, CH_2) and 10.46 (vbr s, NOH); *methyl* 2-*methyl*-4-*oxo*-4,5-*dihydroimidazole*-1-*carboxylate* **6** (R^1 = Me, R^2 = H) (2.76 g, 34%) as an off-white solid, m.p. 157–159 °C (decomp.) (Found: C, 42.1; H, 5.40; N, 24.9. $C_6H_9N_3O_3$ requires C, 42.1; H, 5.26; N, 24.6%).

Ethyl 4-(3,4-*Dichlorophenylcarbamoyloxyimino*)-2-*methyl*-4,5-*dihydroimidazole*-1-*carboxylate* **6** (R^1 = Et, R^2 = 3,4-Cl_2C_6-

H_3).—Compound **6** (R^1 = Et, R^2 = H) (22.9 g, 125 mmol) was added to a stirred solution of 3,4-dichlorophenyl isocyanate (22.7 g, 121 mmol) in *N,N*-dimethylformamide (90 cm^3) at ambient temperature. A moderate exotherm (to 56 °C) was observed and the mixture was then maintained at 100 °C (2 h). The hot mixture was filtered, diluted with water until a slight cloudiness was observed and, after being allowed to cool was filtered again, the collected solid was identified as *ethyl* 4-(3,4-*dichlorophenylcarbamoyloxyimino*)-2-*methyl*-4,5-*dihydro*-*imidazole*-1-*carboxylate* **6** (R^1 = Et, R^2 = 3,4-$Cl_2C_6H_3$) (41 g, 88%) as a buff solid. Using MPLC (9:1, chloroform–methanol as eluent) an analytical sample was obtained as a colourless solid, m.p. 139 °C (decomp.) (Found: C, 44.7; H, 3.70; N, 15.0. $C_{14}H_{14}Cl_2N_4O_4$ requires C, 45.0; H, 3.75; N, 15.1%); ν_{max}/cm^{-1} 1240, 1377, 1390, 1510, 3305 and 3365; δ_H 1.37 (t, *J* 7, OCH_2CH_3), 2.66 (s, 2-CH_3), 4.32 (q, *J* 7, OCH_2CH_3), 4.76 (s, CH_2), 7.2–7.45 (m, 2 ArH), 7.77 (d, *J* 1, 1 ArH) and 8.55 (br s, NH).

Additions of 4-*Aminoimidazoles* **1**.—(a) *With phenyl isocyanate*. A solution of 4-aminoimidazole **1b** was generated from 4-nitroimidazole **3b** (4.24, 37.5 mmol). Phenyl isocyanate (4.47 g, 37.5 mmol) was added and after 2 h evaporation gave a residue which was purified by MPLC (9:1, $CHCl_3$–MeOH as eluent). The major component (R_f 0.1) was collected and trituration with Et_2O to give a crystalline solid which was identified as N-*imidazol*-4-*yl*-N-*phenylurea* **13a** (2.45 g, 32%) as a white powder, m.p. 183–184 °C (Found: C, 59.9; H, 5.14; N, 27.8. $C_{10}H_{10}N_4O$ requires C, 59.4; H, 4.98; N, 27.7%); ν_{max}/cm^{-1} 1230, 1330, 1500 and 1700; δ_H 6.86–7.02 (m, *p*-C_6H_5 + imidazole 5-H), 7.22–7.38 (m, *m*-C_6H_5), 7.40–7.56 (m, *o*-C_6H_5 + imidazole 2-H), 8.65 (br s, NH), 8.95 (br s, NH) and 11.82 (br s, imidazole NH); *m/z* 202 ($M^{\bullet+}$).

(b) *With phenyl isothiocyanate*. In the manner described for phenyl isocyanate, 4-aminoimidazole **1b** (3.11 g, 37.5 mmol) was treated with phenyl isothiocyanate (5.07 g, 37.5 mmol). The product obtained by evaporation was recrystallised from ethanol and identified as N-*imidazol*-4-*yl*-N-*phenylthiourea* **14a** (1.7 g, 21%) as pink needles m.p. 194–196 °C (Found: C, 54.8; H, 4.59; N, 25.3; S, 15.0. $C_{10}H_{10}N_4S$ requires C, 55.0; H, 4.62; N, 25.7; S, 14.7%); ν_{max}/cm^{-1} 1200, 1270, 1340, 1455, 1495, 1575, 1600 and 3230; δ_H 6.90 (br s, imidazole 5-H), 7.10–7.20 (m, *p*-C_6H_5), 7.28–7.40 (m, *m*-C_6H_5), 7.58–7.70 (m, *o*-C_6H_5 + imidazole 2-H), 10.2 (br s, NH) and 12.05 (br s, NH + imidazole NH); *m/z* 218 ($M^{\bullet+}$).

(c) *With dimethyl acetylenedicarboxylate*. A solution of compound **1d** in dioxane (125 cm^3) was prepared from 1,2-dimethyl-4-nitroimidazole[89] **3d** (7.05 g, 50 mmol) using the procedure described above. Dimethyl acetylenedicarboxylate (7.1 g, 50 mmol) was added, with stirring, to the pale yellow solution and, after further stirring (30 min), the solution was evaporated. The residue was purified by MPLC (9:1, $CHCl_3$–MeOH as eluent). The major fraction (R_f 0.3) was triturated with Et_2O to give a crystalline product which was identified as *dimethyl* 1-(4-*amino*-1,2-*dimethylimidazol*-5-*yl*)*ethylene*-1,2-*dicarboxylate* **15b** (6.3 g, 50%) as tiny orange prisms, m.p. 163–164 °C (Found: C, 52.0; H, 5.98; N, 16.4. $C_{11}H_{15}N_3O_4$ requires C, 52.2; H, 5.97; N, 16.6%); ν_{max}/cm^{-1} 1240, 1340, 1430, 1485, 1525, 1570, 1640, 1690, 1730, 3130, 3300 and 3430; δ_H 2.25 (s, CCH_3), 3.40 (s, NCH_3), 3.70 (s, OCH_3), 3.90 (s, OCH_3), 5.25 (br s, NH_2) and 5.85 (s, olefinic CH); *m/z* 253 ($M^{\bullet+}$).

Methyl 2,3-*Dimethyl*-5-*oxo*-4,5-*dihydro*-3H-*imidazo*[4,5-b]-*pyridine*-7-*carboxylate* **12j**.—Compound **11j** (3.16 g, 12.5 mmol) was heated at 190 °C (1 min) and the melt was then cooled. The solid product was powdered and recrystallisation from ethanol gave the *title compound* **12j** (1.0 g, 36%) as a buff powder, m.p. 250–252 °C (Found: C, 54.4; H, 5.12; N, 18.7. $C_{10}H_{11}N_3O_3$ requires C, 54.3; H, 5.01; N, 19.0%); ν_{max}/cm^{-1} 1265, 1370, 1440, 1500, 1595, 1720 and 2960; δ_H 2.55 (s, CCH_3), 3.7 (s, NCH_3), 3.95 (s, CO_2CH_3), 6.85 (s, 6-H) and 10.0 (br s, NH); *m/z* 221 ($M^{\bullet+}$).

Methyl 1,2-*Dimethyl*-5-*oxo*-4,5-*dihydro*-1H-*imidazo*[4,5-b]-*pyridine*-7-*carboxylate* **16b**.—Compound **15b** (0.76 g, 3 mmol) was heated at 190 °C (1 min) and the melt was then cooled. The solid product was powdered and recrystallisation from ethanol gave *methyl* 1,2-*dimethyl*-5-*oxo*-4,5-*dihydro*-1H-*imidazo*[4,5-b]*pyridine*-7-*carboxylate* **16b** (0.43 g, 65%) as a yellow powder, m.p. 237–238 °C (Found: C, 53.9; H, 5.00; N, 18.8. $C_{10}H_{11}N_3O_3$ requires C, 54.3; H, 5.01; N, 19.0%); ν_{max}/cm^{-1} 1255, 1325, 1580, 1660, 1725, 2770 and 2890; δ_H 2.47 (s, CCH_3), 3.70 (s, NCH_3), 3.92 (s, CO_2CH_3), 6.56 (s, 6-H) and 11.2 (br s, NH); *m/z* 221 ($M^{\bullet+}$).

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