Synthesis of 1*H*-Imidazoles by the Simple Ring Transformation of 5-Acylaminouracils and 5-Acylaminopyrimidin-4(3*H*)-ones[1]

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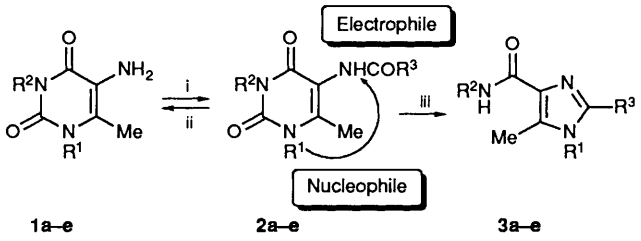
1,2-Disubstituted 4-alkylcarbamoyl-5-methyl-1*H*-imidazoles and 2-substituted 5-methyl-4-phenylcarbamoyl-1*H*-imidazoles were synthesized from 5-acylamino-6-methyluracils and 5-acylamino-6-methyl-3-phenylpyrimidin-4(3*H*)ones by treatment with sodium hydroxide in ethanol. In the case of 5-acylaminopyrimidinones which possess an olefinic group in the acylamino group, 2-ethoxyethyl (or 2-ethoxypropyl)-5-methyl-4-phenylcarbamoyl-1*H*-imidazoles were prepared as major products and the corresponding 2-alkenyl-1*H*-imidazoles were only minor products. Compounds which contain an aryl function in their acylamino group gave glycine anilides as by-products.

Various studies on the synthesis and reactivity of pyrimidines or pyrimidinones which have potential biological activity have been reported.[2] However, the reactivity of pyrimidin-4(3*H*)-ones is little known. In the course of medicinal and chemical studies of pyrimidinones in our laboratory, we discovered the ring transformation of 5-amino-pyrimidin-4(3*H*)-ones into imidazoles by reaction with nitrous acid.[3] Ring transformations of uracils or pyrimidinones have intrigued many organic chemists.[4] During our investigation of the reactivity of uracils and pyrimidinones, we have encountered an interesting ring transformation of 5-acylaminouracils and 5-acylamino-pyrimidin-4(3*H*)-ones into 1*H*-imidazoles in the presence of alkali in ethanol. Such a ring transformation seems useful for the syntheses of various 1*H*-imidazoles.

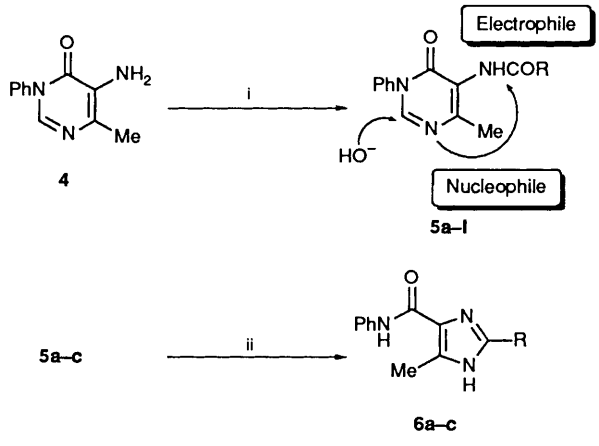
In this paper we describe the synthesis of 1,2-disubstituted 4-alkylcarbamoyl-5-methyl-1*H*-imidazoles and 2-substituted 5-methyl-4-phenylcarbamoyl-1*H*-imidazoles by the simple ring transformation of 1,3-disubstituted 5-acylamino-6-methyluracils and 5-acylamino-6-methyl-3-phenylpyrimidin-4(3*H*)-ones.

Results and Discussion

An examination of the stability of acyl derivatives of pyrimidinones in acid or alkaline medium was carried out first. The reaction of 1,3-disubstituted 5-acylamino-6-methyluracils **2** with 5% hydrochloric acid in ethanol gave deacylated products **1**[5] as expected, while attempted deacylation with 5% aq. sodium hydroxide in ethanol led to ring-transformed products, the 2-substituted imidazoles **3** (Scheme 1). For instance, 5-acetamido-3,6-dimethyl-1-phenyluracil **2a** gave 2,5-dimethyl-4-methylcarbamoyl-1-phenyl-1*H*-imidazole **3a** in 81% yield. In the ^{1}H NMR spectrum of compound **3a**, two methyl signals (δ 2.20 and 2.36) appeared at low field compared with the signals of the C-6 methyl group and acetamide group (δ 1.18 and 2.20) of compound **2a**. The MS spectrum gave the molecular ion peak at *m/z* 229, and the IR spectrum showed an absorption for a secondary amide at 3350 cm^{-1}. We concluded that the structure of compound **3a** was 2,5-dimethyl-4-methylcarbamoyl-1-phenyl-1*H*-imidazole. Elemental analysis gave results consistent with the assigned structure. Final confirmation was carried out by X-ray crystallographic analysis, which was reported in an earlier communication.[1]



Scheme 1 *Reagents:* i, Ac_2O or benzoyl chloride; ii, 5% HCl, EtOH; iii, 5% NaOH, EtOH **a**; R^1 = Ph, R^2 = R^3 = Me, **b**; R^1 = R^3 = Me, R^2 = Ph, **c**; R^1 = Me, R^2 = R^3 = Ph, **d**; R^1 = R^2 = R^3 = Me, **e**; R^1 = R^3 = Ph, R^2 = Me.



Scheme 2 *Reagents:* i, Ac_2O, propionyl chloride, butyryl chloride, formic acid, acryloyl chloride, crotonyl chloride, benzoyl chloride, *p*-toluoyl chloride, *p*-anisoyl chloride, *p*-nitrobenzoyl chloride, or chloroacetyl chloride ii, 5% NaOH, EtOH. **a**; R = Me.[6] **b**; R = Et, **c**; R = Pr, **d**; R = H, **e**; R = CH=CH$_2$, **f**; R = CH=CHMe, **g**; R = Ph, **h**; R = *p*-MeC$_6$H$_4$, **i**; R = *p*-MeOC$_6$H$_4$, **j** R = *p*-NO$_2$C$_6$H$_4$, **k**; R = CH$_2$Cl,[6] **l**; R = CH$_2$N(Me)$_2$[6]

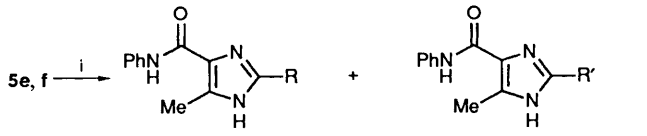
Our next interest was the examination of the similar transformation on 5-acylamino-6-methyl-3-phenylpyrimidin-4(3*H*)-ones **5**.† Treatment of compounds **5a–c** with 5% aq. sodium hydroxide in ethanol gave the corresponding 2-substituted 5-methyl-4-phenylcarbamoyl-1*H*-imidazoles **6a–c**, as expected (Scheme 2). Spectral and microanalytical data were consistent with the assigned structures. Treatment of 5-formamido-6-methyl-3-phenylpyrimidin-4(3*H*)one **5d** with 5% aq. sodium hydroxide resulted in deacylation. Hydrolysis of the

† Synthesis of compounds **5a**, **5k** and **5l** was previously reported (ref. 6).

Table 1 Yields of compounds **6e**, **6f**, **7a**, **7b** and **7c** under several alkaline conditions.

Starting compound	Conditions	Products (yield)	
5e	5% aq. NaOH, EtOH	**6e** (9%)	**7a** (46%)
5f	5% aq. NaOH, EtOH	**6f** (10%)	**7b** (35%)
5e	20% aq. NaOH, EtOH	**6e** (6%)	**7a** (54%)
5f	20% aq. NaOH, EtOH	**6f** (11%)	**7b** (35%)
5e	20% aq. NaOH, Pr^{i}OH	**6e** (10%)	**7c** (38%)
5e	20% aq. NaOH, Bu^{t}OH	**6e** (11%)	
5e	10% ethanolic KOH	**6e** (5%)	**7a** (67%)
5f	10% ethanolic KOH	**6f** (13%)	**7b** (69%)

formyl group seems to be faster than the nucleophilic attack on C-2. Compounds **5e** and **f**, which contain a double bond in the acyl group, were similarly treated with 5% aq. sodium hydroxide in ethanol. However, the expected products 5-methyl-3-phenylcarbamoyl-2-vinyl-1*H*-imidazole **6e** and 5-methyl-3-phenylcarbamoyl-2-(prop-1-enyl)-1*H*-imidazole **6f** were obtained in only poor yield (5–13%), and 2-(2-ethoxyethyl)-5-methyl-4-phenylcarbamoyl-1*H*-imidazole **7a** and 2-(2-ethoxypropyl)-5-methyl-4-phenylcarbamoyl-1*H*-imidazole **7b** were major products (Scheme 3). We reasoned that if bulky



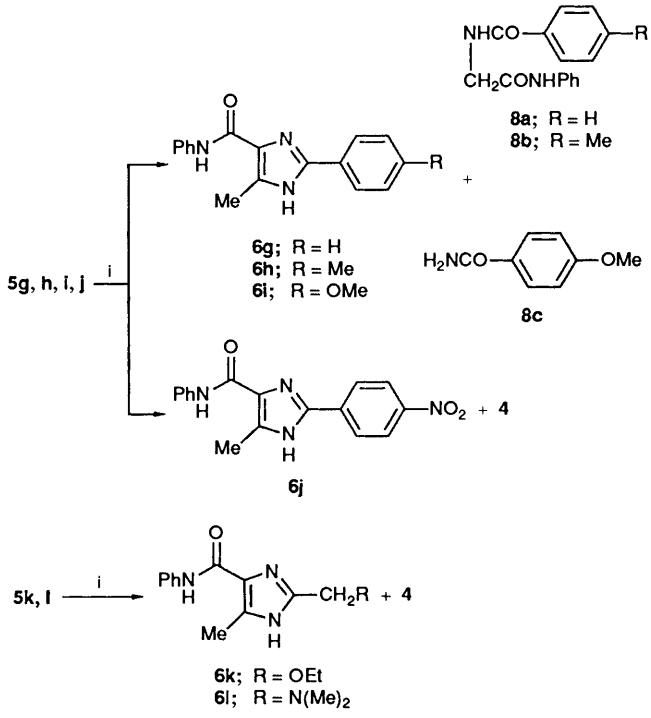
6e; R = CH=CH$_2$
6f; R = CH=CHMe

7a; R' = CH$_2$CH$_2$OEt
7b; R' = CH$_2$CH(OEt)Me
7c; R' = CH$_2$CH$_2$OCH(CH$_3$)$_2$

Scheme 3 *Reagent:* i, alkali

alcohols such as propan-2-ol or *t*-butyl alcohol were used as the solvent instead of ethanol, Michael-type addition to the double bond might be suppressed and our hoped for products **6e**, **f** would be obtained in much better yield. However, yields of compounds **6e** and **f** were not improved as shown in Table 1. Even with propan-2-ol as solvent the reaction of compound **5e** with 20% sodium hydroxide gave 2-(2-isopropoxyethyl)-5-methyl-4-phenylcarbamoyl-1*H*-imidazole **7c** as the major product. In the case of *t*-butyl alcohol the reaction of compound **5e** with 20% sodium hydroxide gave only compound **6e** in 11% yield. When an ethanolic solution of potassium hydroxide was used instead of aq. sodium hydroxide in ethanol, the yields of compounds **7a** and **7b** were improved to 67 and 69%, respectively.

We further examined this transformation on compounds **5g–j** with aromatic acyl substituents. Treatment of compounds **5g** and **5h** with 10% ethanolic potassium hydroxide gave imidazoles **6g** (62%) and **6h** (48%) accompanied by small amounts of by-products, *N*-benzoylglycine anilide **8a** and *N*-(*p*-toluoyl)glycine anilide **8b**, respectively. The ^{1}H NMR spectrum of compound **8a** showed methylene protons at δ 4.41 and 10 aromatic protons at 7.08–7.90. Its MS spectrum revealed peaks at *m/z* 254 (M^+), 105 ($M^+ - NHCH_2CONHPh$) and 93 ($M^+ - COCH_2NHCOPh$). Furthermore, compound **8a** was identical with an authentic sample which was synthesized by the reaction of glycine anilide[7] and benzoyl chloride. Reaction of compound **5i** with 10% ethanolic potassium hydroxide afforded compound **6i** (39%) and trace amounts of *p*-anisamide.* In the case of compound **5j** the reaction gave compound **4** as the major product and the yield of the imidazole **6j** was 25%. It seems that, because of the electron-withdrawing effect of the nitro group of compound **5j**, the acyl carbonyl function is attacked much faster than the C-2 position to give compound **4**. In the reaction of 5-(chloroacetamido)-6-methyl-3-phenylpyrimidin-4(3*H*)-one **5k**[6] with ethanolic potassium hydroxide, the chloro function was replaced with ethoxide anion to afford 2-(ethoxymethyl)-5-methyl-4-phenylcarbamoyl-1*H*-imidazole **6k** in 39% yield and compound **4** (33%). The expected 2-chloromethyl-5-methyl-4-phenylcarbamoyl-1*H*-imidazole was not obtained. Transformation of 5-[(dimethylamino)acetamido]-6-methyl-3-phenylpyrimidin-4(3*H*)-one **5l**[6] proceeded successfully to give 2-(dimethylaminomethyl)-5-methyl-4-phenylcarbamoyl-1*H*-imidazole **6l** in 91% yield (Scheme 4).



Scheme 4 *Reagent:* i, 10% KOH, EtOH

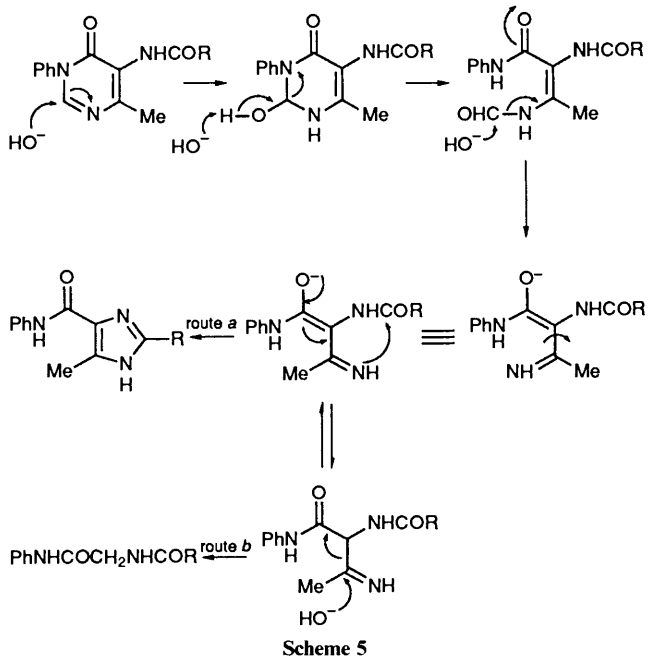
A possible reaction mechanism for the transformation of 5-acylaminopyrimidinones into imidazoles is given in Scheme 5. Initial nucleophilic attack of hydroxide ion at C-2 of pyrimidinones and the succeeding decarboxylation will give a ring-opened intermediate. Recyclization between the resulting imino group and the acylcarbonyl group *via* route *a* will give 1*H*-imidazoles. If the acylcarbonyl group is bulky and not electrophilic enough, *e.g.* benzoyl, *p*-toluoyl or *p*-methoxybenzoyl, glycine anilides will be formed *via* route *b*. The presence of electron-withdrawing groups in the acyl group gives rise to preferential deacylation.

Therefore the ring transformation described affords a new method for the preparation of 1*H*-imidazoles from 5-acylaminouracils or 5-acylaminopyrimidin-4-(3*H*)-ones in one step.

Experimental

M.p.s were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured with an IR-810 machine from Nihon Bunko Spectroscopic Co. Ltd. Mass spectra were measured with a JEOL JMS-DX 300 mass spectrometer. ^{1}H NMR spectra were recorded with a JEOL JNM-MH-100, JNM-FX-100 or JNM-EX-270 spectrometer using tetramethylsilane as internal standard. *J*-Values are given

* M.p. and NMR spectrum were coincident with those written in the Aldrich catalogue (1990 1991) and The Aldrich Library of NMR Spectra Edition II, vol. 2, 348D.



Scheme 5

in Hz. UV spectra were recorded on a Hitachi spectrophotometer.

5-*Acetamido*-3,6-*dimethyl*-1-*phenyluracil* **2a**.—5-Amino-3,6-dimethyl-1-phenyluracil **1a**[5a] (1 g, 4.33 mmol) was dissolved in acetic anhydride (10 cm^3) and the mixture was stirred at room temperature for 3 h. Cold water was added to the reaction mixture, which was extracted with chloroform. The extract was washed with brine and dried over anhydrous magnesium sulphate. The solvent was distilled off and the residue was purified by recrystallization to give *compound* **2a** (1.146 g, 97%), m.p. 251–253 °C (from benzene) (Found: C, 61.6; H, 5.5; N, 15.5. $C_{14}H_{15}N_3O_3$ requires C, 61.53; H, 5.53; N, 15.38%); ν_{max}(KBr)/cm^{-1} 3250 (NH), 1710 and 1640 (C=O); δ_H(100 MHz; $CDCl_3$) 1.88 (3 H, s, 6-Me), 2.20 (3 H, s, COMe), 3.43 (3 H, s, NMe) and 7.24–7.70 (6 H, m, Ph, NH); *m/z* 273 (M^+) and 231 ($M^+ - COCH_3$).

5-*Acetamido*-1,6-*dimethyl*-3-*phenyluracil* **2b**.—5-Amino-1,6-dimethyl-3-phenyluracil **1b**[5a] (1 g, 4.33 mmol) was treated by the same procedure as described for compound **2a** to give the *isomer* **2b** (1.158 g, 98%), m.p. 188–190 °C (Found: C, 61.6; H, 5.3; N, 15.4%); ν_{max}(KBr)/cm^{-1} 3350 (NH) and 1630 (C=O); δ_H(100 MHz; $CDCl_3$) 2.12 (3 H, s, 6-Me), 2.28 (3 H, s, COMe), 3.52 (3 H, s, NMe) and 7.16–7.68 (6 H, m, Ph, NH); *m/z* 273 (M^+).

5-*Benzamido*-1,6-*dimethyl*-3-*phenyluracil* **2c**.—To a solution of 5-amino-1,6-dimethyl-3-phenyluracil **1c** (≡ **1b**)[5a] (1 g, 4.33 mmol) in chloroform (100 cm^3) were added potassium carbonate (1.236 g, 8.96 mmol) and benzoyl chloride (547 mg, 3.89 mmol). The mixture was stirred at room temperature for 2 h, poured into ice–water, and extracted with EtOAc. The extract was washed with brine and dried over anhydrous magnesium sulphate. The solvent was distilled off and the residue was purified by recrystallization to give compound **2c** (1.45 g, 93%), m.p. 281–283 °C (Found: C, 67.8; H, 5.1; N, 12.5. $C_{19}H_{17}N_3O_3$ requires C, 68.05; H, 5.11; N, 12.53%); ν_{max}(KBr)/cm^{-1} 3340 (NH), 1700 and 1650 (C=O); δ_H(100 MHz; $CDCl_3$) 2.32 (3 H, s, 6-Me), 3.56 (3 H, s, NMe) and 7.10–7.96 (11 H, m, Ph, NH); *m/z* 335 (M^+).

5-*Acetamido*-1,3,6-*trimethyluracil* **2d**.—5-Amino-1,3,6-trimethyluracil **1d**[5b] (1 g, 5.92 mmol) was treated by the same procedure as described for **2a** to give the *amide* **2d** (1.248 g, 96%), m.p. 101–103 °C (Found: C, 51.4; H, 6.0; N, 19.9. $C_9H_{13}N_3O_3$ requires C, 51.18; H, 6.20; N, 19.89%); ν_{max}(KBr)/cm^{-1} 3280 (NH), 1700 and 1650 (C=O); δ_H(100 MHz; $CDCl_3$) 2.17 (3 H, s, NMe), 2.21 (3 H, s, 6-Me), 3.36 (3 H, s, NMe), 3.47 (3 H, s, NMe) and 7.28 (1 H, br s, NH); *m/z* 211 (M^+).

5-*Benzamido*-3,6-*dimethyl*-1-*phenyluracil* **2e**.—5-Amino-3,6-dimethyl-1-phenyluracil **1e** (≡ **1a**)[5a] (1 g, 4.33 mmol) was treated by the same procedure as described for compound **2c** to give the benzamide **2e** (1.349 g, 93%), m.p. 199–201 °C (Found: C, 67.8; H, 5.2; N, 12.3. $C_{19}H_{17}N_3O_3$ requires C, 68.05; H, 5.11; N, 12.53%); ν_{max}(KBr)/cm^{-1} 3350 (NH), 1690 and 1650 (C=O); δ_H(100 MHz; $CDCl_3$) 1.85 (3 H, s, 6-Me), 3.36 (3 H, s, NMe) and 7.16–7.92 (11 H, m, Ph, NH); *m/z* 335 (M^+) and 230 ($M^+ -$ COPh).

N′,2,5-*Trimethyl*-1-*phenyl*-1H-*imidazole*-4-*carboxamide* **3a**.—A mixture of compound **2a** (500 mg, 1.83 mmol), 5% aq. sodium hydroxide (5 cm^3) and ethanol (30 cm^3) was refluxed for 3 h. After cooling, the reaction mixture was neutralized with 5% aq. hydrochloric acid and extracted with chloroform. The extract was dried over anhydrous magnesium sulphate and the solvent was distilled off. The residue was purified by recrystallization to give compound **3a** (339 mg, 81%), m.p. 154–156 °C (from benzene) (Found: C, 68.15; H, 6.6; N, 18.2. $C_{13}H_{15}N_3O$ requires C, 68.10; H, 6.59; N, 18.33%); ν_{max}(KBr)/cm^{-1} 3350 (NH) and 1630 (C=O); λ_{max}(EtOH)/nm 243 (ε 12 400); δ_H(100 MHz; $CDCl_3$) 2.20 (3 H, s, 5-Me), 2.36 (3 H, s, 2-Me), 2.95 (3 H, s, NMe) and 6.90–7.78 (6 H, m, Ph, NH); *m/z* 229 (M^+).

1,2,5-*Trimethyl*-N′-*phenyl*-1H-*imidazole*-4-*carboxamide* **3b**.—Compound **2b** (500 mg, 1.83 mmol) was treated by the same procedure as described for compound **3a** to give the *amide* **3b** (294 mg, 70%), m.p. 171–173 °C (Found: 68.3; H, 6.5; N, 18.1%); ν_{max}(KBr)/cm^{-1} 3290 (NH) and 1660 (C=O); λ_{max}(EtOH)/nm 270 (ε 24 300); δ_H(100 MHz; $CDCl_3$) 2.36 (3 H, s, 2-Me), 2.56 (3 H, s, 5-Me), 3.43 (3 H, s, NMe), 6.96–7.80 (5 H, m, Ph) and 9.02 (1 H, br s, NH); *m/z* 229 (M^+) and 137 ($M^+ -$ NHPh).

1,5-*Dimethyl*-2,N′-*diphenyl*-1H-*imidazole*-4-*carboxamide* **3c**.—Compound **2c** (500 mg, 1.49 mmol) was treated by the same procedure as described for compound **3a** to give the amide **3c** (317 mg, 73%), m.p. 164–166 °C (Found: C, 74.4; H, 5.8; N, 14.4. $C_{18}H_{17}N_3O$ requires C, 74.21; H, 5.88; N, 14.42%); ν_{max}(KBr)/cm^{-1} 3350 (NH) and 1680 (C=O); λ_{max}(EtOH)/nm 272 (ε 30 400); δ_H(100 MHz; $CDCl_3$) 2.67 (3 H, s, 5-Me), 3.56 (3 H, s, NMe), 6.92–7.08 (10 H, m, Ph) and 9.08 (1 H, br s, NH); *m/z* 291 (M^+) and 199 ($M^+ -$ NHPh).

N′,1,2,5-*Tetramethyl*-1H-*imidazole*-4-*carboxamide* **3d**.—Compound **2d** (500 mg, 2.37 mmol) was treated by the same procedure as described for compound **3a** to give *compound* **3d** (174 mg, 44%), m.p. 169–170 °C (Found: C, 57.6; H, 7.78; N, 25.1. $C_8H_{13}N_3O$ requires C, 57.46; H, 7.84; N, 25.13%); ν_{max}(KBr)/cm^{-1} 3360 (NH) and 1640 (C=O); λ_{max}(EtOH)/nm 244 (ε 10 800); δ_H(100 MHz; $CDCl_3$) 2.34 (3 H, s, 5-Me), 2.54 (3 H, s, 2-Me), 2.92 (3 H, d, *J* 5, NH*Me*), 3.43 (3 H, s, NMe) and 7.01 (1 H, br s, NH); *m/z* 211 (M^+).

N′,5-*Dimethyl*-1,2-*diphenyl*-1H-*imidazole*-4-*carboxamide* **3e**.—Compound **2e** (500 mg, 1.49 mmol) was treated by the same procedure as described for compound **3a** to give the *amide*

3e (148 mg, 34%), m.p. 220–221 °C (Found: C, 74.0; H, 5.9; N, 14.4. $C_{18}H_{17}N_3O$ requires C, 74.21; H, 5.88; N, 14.42%); ν_{max}(KBr)/cm^{-1} 3350 (NH) and 1650 (C=O); λ_{max}(EtOH)/nm 255 (ε 14 100); δ_H(270 MHz; $CDCl_3$) 2.45 (3 H, s, 5-Me), 3.00 (3 H, d, *J* 5.3, NH*Me*) and 7.17–7.83 (11 H, m, Ph, NH); *m/z* 291 (M^+).

6-*Methyl*-3-*phenyl*-5-*propionamidopyrimidin*-4(3H)-*one* **5b**.—Potassium carbonate (1.854 g, 13.43 mmol) and propionyl chloride (622 mg, 6.72 mmol) were added to a solution of compound **4** (900 mg, 4.48 mmol) in chloroform. The mixture was stirred at room temperature for 5 h, poured into cold water, and extracted with chloroform (30 cm^3). The extract was washed with saturated aq. sodium hydrogen carbonate and dried over anhydrous magnesium sulphate. The solvent was distilled off and the residue was purified by silica gel column chromatography and elution with ethyl acetate to give *compound* **5b** (1.047 g, 91%), m.p. 143–145 °C (from EtOH) (Found: C, 65.7; H, 6.0; N, 16.45. $C_{14}H_{15}N_3O_2$ requires C, 65.36; H, 5.58; N, 16.33%); ν_{max}(KBr)/cm^{-1} 3450 (NH), 1680 and 1655 (C=O); δ_H (270 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7.5, CH_2Me), 2.33 (3 H, s, 6-Me), 2.43 (2 H, q, *J* 7.5, CH_2Me), 7.33–7.57 (6 H, m, Ph, NH) and 8.01 (1 H, s, 2-H); *m/z* 257 (M^+) and 201 ($M^+ - COCH_2CH_3$).

5-*Butyramido*-6-*methyl*-3-*phenylpyrimidin*-4(3H)-*one* **5c**.—Compound **4** (900 mg, 4.48 mmol) and butyryl chloride were treated by the same procedure as described for compound **5b** to give the *amide* **5c** (1.128 g, 93%), m.p. 142–144 °C (Found: C, 66.65; H, 6.2; N, 15.5. $C_{15}H_{17}N_3O_2$ requires C, 66.40; H, 6.32; N, 15.49%); ν_{max}(KBr)/cm^{-1} 3430 (NH), 1680 and 1655 (C=O); δ_H(270 MHz; $CDCl_3$) 1.02 (3 H, t, *J* 7.5, CH_2CH_2Me), 1.76 (2 H, m, CH_2CH_2Me), 2.33 (3 H, s, 6-Me), 2.40 (2 H, t, *J* 7.5, $COCH_2CH_2$Me), 7.33 (1 H, br s, NH), 7.36–7.57 (5 H, m, Ph) and 8.04 (1 H, s, 2-H); *m/z* 271 (M^+) and 201 ($M^+ - COCH_2CH_2CH_3$).

5-*Formamido*-6-*methyl*-3-*phenylpyrimidin*-4(3H)-*one* **5d**.—A mixture of compound **4** (600 mg, 2.99 mmol) and formic acid (7 cm^3) was stirred at room temperature for 1.5 h. Excess of formic acid was distilled off. The residue was purified by silica gel column chromatography and elution with ethyl acetate to give *compound* **5d** (417 mg, 61%), m.p. 150–152 °C (Found: C, 62.6; H, 4.7; N, 18.2. $C_{12}H_{11}N_3O_2$ requires C, 62.88; H, 4.84; N, 18.33%); ν_{max}(KBr)/cm^{-1} 3440 (NH) and 1660 (C=O); δ_H (270 MHz; $CDCl_3$) 2.37 (3 H, s, 6-Me), 7.34–7.55 (5 H, m, Ph), 7.71 (1 H, s, NH), 8.04 (1 H, s, 2-H) and 8.36 (1 H, s, CHO); *m/z* 229 (M^+) and 201 ($M^+ - CHO$).

5-*Acrylamido*-6-*methyl*-3-*phenylpyrimidin*-4(3H)-*one* **5e**.—Compound **4** (600 mg, 2.99 mmol) and acryloyl chloride were treated by the same procedure as described for compound **5b** to give the *amide* **5e** (738 mg, 97%), m.p. 170–172 °C (Found: C, 65.7; H, 5.1; N, 16.5. $C_{14}H_{13}N_3O_2$ requires C, 65.87; H, 5.13; N, 16.46%); ν_{max}(KBr)/cm^{-1} 3425 (NH), 1680 and 1655 (C=O); δ_H(100 MHz; $CDCl_3$) 2.33 (3 H, s, 6-Me), 5.68 (1 H, dd, *J* 3.9, 8.3, C*H*=CH_2), 6.30 and 6.33 (each 1 H, each d, *J* 8.3 and 3.9, CH=CH_2), 7.26–7.56 (5 H, m, Ph), 8.04 (1 H, s, 2-H) and 8.17 (1 H, br s, NH); *m/z* 255 (M^+).

5-*Crotonamido*-6-*methyl*-3-*phenylpyrimidin*-4(3H)-*one* **5f**.—Compound **4** (650 mg, 3.23 mmol) and crotonyl chloride were treated by the same procedure as described for compound **5b** to give the *amide* **5f** (844 mg, 97%), m.p. 150–152 °C (Found: C, 67.0; H, 5.3; H, 5.3; N, 15.7. $C_{15}H_{15}N_3O_2$ requires C, 66.90; H, 5.61; N, 15.60%); ν_{max}(KBr)/cm^{-1} 3440 (NH), 1680 and 1650 (C=O); δ_H(100 MHz; $CDCl_3$) 1.90 (3 H, d, *J* 7, CH=CH*Me*), 2.35 (3 H, s, 6-Me), 6.02 (1 H, d, *J* 15, C*H*=CHMe), 6.91 (1 H, m, CH=C*H*Me), 7.29–7.56 (6 H, m, Ph, NH) and 8.01 (1 H, s, 2-H); *m/z* 269 (M^+).

5-*Benzamido*-6-*methyl*-3-*phenylpyrimidin*-4(3H)-*one* **5g**.—Compound **4** (650 mg, 3.23 mmol) and benzoyl chloride were treated by the same procedure as described for compound **5b** to give the *amide* **5g** (906 mg, 98%), m.p. 123–124 °C; (Found: C, 70.6; H, 4.9; N, 13.9. $C_{18}H_{15}N_3O_2$ requires C, 70.81; H, 4.95; N, 13.76%) ν_{max}(KBr)/cm^{-1} 3425 (NH), 1660 and 1650 (C=O); δ_H(100 MHz; $CDCl_3$) 2.43 (3 H, s, 6-Me), 7.26–7.98 (11 H, m, Ph, NH) and 8.06 (1 H, s, 2-H); *m/z* 305 (M^+).

6-*Methyl*-3-*phenyl*-5-(p-*toluamido*)*pyrimidin*-4(3H)-*one* **5h**.—Compound **4** (600 mg, 2.99 mmol) and *p*-toluoyl chloride were treated by the same procedure as described for compound **5b** to give the *amide* **5h** (914 mg, 96%), m.p. 126–128 °C (Found: C, 71.5; H, 5.2; N, 13.1. $C_{19}H_{17}N_3O_2$ requires C, 71.46; H, 5.37; N, 13.16%); ν_{max}(KBr)/cm^{-1} 3470 (NH), 1660 and 1650 (C=O); δ_H(100 MHz; $CDCl_3$) 2.42 (6 H, s, 6-Me and C_6H_4Me), 7.26–7.87 (10 H, m, ArH, NH) and 8.05 (1 H, s, 2-H); *m/z* 319 (M^+).

5-(p-*Anisamido*)-6-*methyl*-3-*phenylpyrimidin*-4(3H)-*one* **5i**.—Compound **4** (600 mg, 2.99 mmol) and *p*-anisoyl chloride were treated by the same procedure as described for compound **5b** to give the *amide* **5i** (950 mg, 95%), m.p. 122–124 °C (Found: C, 67.8; H, 5.0; N, 12.45. $C_{19}H_{17}N_3O_3$ requires C, 68.05; H, 5.11; N, 12.53%); ν_{max}(KBr)/cm^{-1} 3450 (NH), 1660 and 1650 (C=O); δ_H(100 MHz; $CDCl_3$) 2.41 (3 H, s, 6-Me), 3.87 (3 H, s, OMe), 6.92–7.94 (10 H, m, ArH, NH) and 8.04 (1 H, s, 2-H); *m/z* 335 (M^+).

6-*Methyl*-5-(p-*nitrobenzamido*)-3-*phenylpyrimidin*-4(3H)-*one* **5j**.—Compound **4** (500 mg, 2.49 mmol) and *p*-nitrobenzoyl chloride were treated by the same procedure as described for compound **5b** to give the *amide* **5j** (827 mg, 92%), m.p. 131–133 °C (Found: C, 61.5; H, 4.2; N, 15.8. $C_{18}H_{14}N_4O_4$ requires C, 61.71; H, 4.03; N, 15.99%); ν_{max}(KBr)/cm^{-1} 3440 (NH), 1670 and 1650 (C=O); δ_H(270 MHz; $CDCl_3$) 2.42 (3 H, s, 6-Me), 7.37–7.57 (5 H, m, Ph) and 8.05–8.32 (6 H, m, *p*-$NO_2C_6H_4$, 2-H, NH); *m/z* 350 (M^+) and 200 ($M^+ - COPh - NO_2$).

2,5-*Dimethyl*-N′-*phenyl*-1H-*imidazole*-4-*carboxamide* **6a**.—5-Acetamido-6-methyl-3-phenylpyrimidin-4-(3*H*)-one **5a**[6] (350 mg, 1.44 mmol) was treated by the same procedure as described for compound **3a** to give the *amide* **6a** (247 mg, 81%), m.p. 152–154 °C (from hexane–EtOAc) (Found: C, 66.9; H, 6.1; N, 19.2. $C_{12}H_{13}N_3O$ requires C, 66.95; H, 6.09; N, 19.52%); ν_{max}(KBr)/cm^{-1} 3350 (NH) and 1645 (C=O); λ_{max}(EtOH)/nm 269 (ε 23 800); δ_H(100 MHz; $CDCl_3$) 2.38 (3 H, s, 2-Me), 2.58 (3 H, s, 5-Me), 7.07–7.71 (5 H, m, Ph), 8.74 (1 H, br s, NH) and 8.96 (1 H, br s, NH); *m/z* 215 (M^+).

2-*Ethyl*-5-*methyl*-N′-*phenyl*-1H-*imidazole*-4-*carboxamide* **6b**.—Compound **5b** (300 mg, 1.17 mmol) was treated by the same procedure as described for compound **3a** to give the *amide* **6b** (201 mg, 75%), m.p. 150–151 °C (Found: C, 67.9; H, 6.6; N, 18.3. $C_{13}H_{15}N_3O$ requires C, 68.10; H, 6.59; N, 18.33%); ν_{max}(KBr)/cm^{-1} 3375 (NH) and 1650 (C=O); λ_{max}(EtOH)/nm 270 (ε 22 200); δ_H(100 MHz; $CDCl_3$) 1.32 (3 H, t, *J* 8, CH_2Me), 2.57 (3 H, s, 5-Me), 2.70 (2 H, q, *J* 8, CH_2Me), 7.06–7.71 (5 H, m, Ph), 9.02 (1 H, br s, NH) and 9.25 (1 H, br s, NH); *m/z* 229 (M^+) and 137 ($M^+ - NHPh$).

5-*Methyl*-N′-*phenyl*-2-*propyl*-1H-*imidazole*-4-*carboxamide* **6c**.—Compound **5c** (350 mg, 1.29 mmol) was treated by the same procedure as described for compound **3a** to give the *amide* **6c** (223 mg, 71%), m.p. 179–180 °C (from hexane–EtOAc); (Found: C, 68.8; H, 7.2; N, 17.0. $C_{14}H_{17}N_3O$ requires C, 69.11;

H, 7.04; N, 17.27%); ν_{max}(KBr)/cm^{-1} 3360 (NH) and 1645 (C=O); λ_{max}(EtOH)/nm 271 (ε 23 600); δ_H(100 MHz; $CDCl_3$) 1.01 (3 H, t, *J* 6, CH_2CH_2*Me*), 1.77 (2 H, m, CH_2CH_2Me), 2.59 (3 H, s, 5-Me), 2.66 (2 H, t, *J* 8, CH_2CH_2Me), 7.08–7.72 (5 H, m, Ph), 9.04 (1 H, br s, NH) and 9.36 (1 H, br s, NH); *m*/*z* 243 (M^+) and 151 (M^+ – NHPh).

5-Methyl-N′-phenyl-2-vinyl-1H-imidazole-4-carboxamide **6e** *and* *2-(2-Ethoxyethyl)-5-methyl-N′-phenyl-1H-imidazole-4-carboxamide* **7a**.—A solution of compound **5e** (200 mg, 0.78 mmol) in 10% ethanolic potassium hydroxide (20 cm^3) was refluxed for 4.5 h. After cooling, the reaction mixture was neutralized with 5% aq. hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous magnesium sulphate. Solvent was distilled off and the residue was subjected to column chromatography on silica gel and elution with hexane–ethyl acetate (1:2) to give the title *amides* **6e** and **7a**.

Compound **6e:** (9 mg, 5%), m.p. 118–119 °C (from hexane–EtOAc) (Found: M^+, 227.1058. $C_{13}H_{13}N_3O$ requires M, 227.1058); ν_{max}(KBr)/cm^{-1} 3430 and 3395 (NH), and 1655 (C=O); λ_{max}(EtOH)/nm 281 (ε 23 600); δ_H(100 MHz; $CDCl_3$) 2.63 (3 H, s, 5-Me), 5.45 and 5.85 (each 1 H, each d, *J* 11 and 18, CH=CH_2), 6.57 (1 H, dd, *J* 11 and 18, C*H*=CH_2), 7.08–7.72 (5 H, m, Ph), 9.03 (1 H, br s, NH) and 9.35 (1 H, br s, NH); *m*/*z* 227 (M^+) and 135 (M^+ – NHPh).

Compound **7a:** (143 mg, 67%), glutinous oil (Found: M^+, 273.1479. $C_{15}H_{19}N_3O_2$ requires M, 273.1478); ν_{max}($CHCl_3$)/cm^{-1} 3400 (NH) and 1655 (C=O); λ_{max}(EtOH)/nm 270 (ε 21 300); δ_H(100 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7, OCH_2*Me*), 2.57 (3 H, s, 5-Me), 2.93 (2 H, t, *J* 5.5, C$H_2$$CH_2$OEt), 3.53 (2 H, q, *J* 7, OCH_2Me), 3.69 (2 H, t, *J* 5.5, CH_2CH_2OEt), 7.36 (5 H, m, Ph), 8.97 (1 H, br s, NH) and 9.72 (1 H, br s, NH); *m*/*z* 273 (M^+) and 181 (M^+ – NHPh).

5-Methyl-N′-phenyl-2-(prop-1-enyl)-1H-imidazole-4-carboxamide **6f** *and* *2-(2-Ethoxypropyl)-5-methyl-N′-phenyl-1H-imidazole-4-carboxamide* **7b**.—A solution of compound **5f** (250 mg, 0.93 mmol) in 10% ethanolic potassium hydroxide (20 cm^3) was treated by the same procedure as described above to give the title compounds **6f** and **7b**.

Compound **6f:** (29 mg, 13%), m.p. 125–127 °C (from hexane–EtOAc) (Found: M^+, 241.1217. $C_{14}H_{15}N_3O$ requires M, 241.1215); ν_{max}(KBr)/cm^{-1} 3440 and 3370 (NH) and 1645 (C=O); λ_{max}(EtOH)/nm 283 (ε 28 300); δ_H(100 MHz; $CDCl_3$) 1.92 (3 H, d, *J* 5, CH=CH*Me*), 2.61 (3 H, s, 5-Me), 6.28 (1 H, m, CH=C*H*Me), 6.92–7.84 (6 H, m, Ph and C*H*=CHMe), 9.04 (1 H, br s, NH) and 9.30 (1 H, br s, NH); *m*/*z* 241 (M^+) and 149 (M^+ – NHPh).

Compound **7b**: (184 mg, 69%), glutinous oil (Found: M^+, 287.1636. $C_{16}H_{21}N_3O_2$ requires M, 287.1634); ν_{max}(KBr)/ cm^{-1} 3400 (NH), and 1600 (C=O); λ_{max}(EtOH)/nm 270 (ε 29 400); δ_H(100 MHz; $CDCl_3$) 1.20 (3 H, d, *J* 6.5, CH*Me*), 1.23 (3 H, t, *J* 7, OCH_2*Me*), 2.59 (3 H, s, 5-Me), 2.84 [2 H, d, *J* 7, CH_2CH(OEt)Me], 3.55 (2 H, m, OCH_2Me), 3.60 [1 H, m, OCH_2C*H*(OEt)Me], 7.05–7.73 (5 H, m, Ph), 8.94 (1 H, br s, NH) and 9.61 (1 H, br s, NH); *m*/*z* 287 (M^+) and 195 (M^+ – NHPh).

2-(2-Isopropoxyethyl)-5-methyl-N′-phenyl-1H-imidazole-4-carboxamide **7c**.—A mixture of compound **5e** (250 mg, 0.98 mmol), 20% aq. sodium hydroxide (5 cm^3) and propan-2-ol (25 cm^3) was refluxed for 5 h and treated by the same procedure as described for compound **7a** to give the *amide* **7c** (107 mg, 38%) as a glutinous oil (Found: M^+, 287.1637. $C_{16}H_{21}N_3O_2$ requires M, 287.1634); ν_{max}($CHCl_3$)/cm^{-1} 3390 (NH) and 1660 (C=O); λ_{max}(EtOH)/nm 270 (ε 24 300); δ_H(100 MHz; $CDCl_3$) 1.18 (6 H, d, *J* 6.4, CHMe_2), 2.56 (3 H, s, 5-Me), 2.90 (2 H, t, *J* 5.9, CH_2CH_2O), 3.60 (1 H, m, C*H*Me_2), 3.70 (2 H, t, *J* 5.9, CH_2CH_2O), 7.71–7.05 (5 H, m, Ph), 9.03 (1 H, br s, NH) and 9.90 (1 H, br s, NH); *m*/*z* 287 (M^+) and 195 (M^+ – NHPh).

5-Methyl-N′,2-diphenyl-1H-imidazole-4-carboxamide **6g** *and* *N-Benzoylglycine Anilide* **8a**.—A mixture of compound **5g** (200 mg, 0.66 mmol) and 10% ethanolic potassium hydroxide (15 cm^3) was refluxed for 8 h. After cooling, the reaction mixture was neutralized with 5% HCl and extracted with ethyl acetate. The extract was washed with brine and dried. Solvent was distilled off and the residue was subjected to column chromatography on silica gel and elution with hexane–ethyl acetate (1:1) to give the title compounds **6g** and **8a**.

Compound **6g:** (113 mg, 62%), m.p. 244–246 °C (from hexane–EtOAc) (Found: C, 73.5; H, 5.2; N, 15.3. $C_{17}H_{15}N_3O$ requires C, 73.63; H, 5.45; N, 15.15%); ν_{max}(KBr)/cm^{-1} 3345 (NH), 1660 and 1645 (C=O); λ_{max}(EtOH)/nm 288 (ε_H 23 000); δ_H(270 MHz; $CDCl_3$) 2.68 (3 H, s, 5-Me), 7.07–8.12 (10 H, m, Ph), 9.18 (1 H, s, NH) and 9.60 (1 H, br s, NH); *m*/*z* 277 (M^+) and 185 (M^+ – NHPh).

Compound **8a:** (18 mg, 11%), m.p. 217–219 °C (from EtOAc) (Found: C, 70.8; H, 5.2; N, 10.9. $C_{15}H_{14}N_2O_2$ requires C, 70.85; H, 5.55; N, 11.02%); ν_{max}(KBr)/cm^{-1} 3310 (NH), 1680 and 1640 (amide C=O); δ_H(100 MHz; $CDCl_3$) 4.41 (2 H, d, *J* 5, CH_2NH), 7.08–7.90 (11 H, m, Ph, NH) and 9.08 (1 H, s, NH); *m*/*z* 254 (M^+), 105 (M^+ – $NHCH_2CONHPh$) and 93 (M^+ – $COCH_2NHCOPh$). This compound was identical with an authentic sample described below.

Synthesis of Authentic Sample **8a**.—Potassium carbonate (879 mg, 6.37 mmol) and benzoyl chloride (449 mg, 3.20 mmol) were added to a solution of glycine anilide[7] (318 mg, 2.12 mmol) in chloroform (30 cm^3). The mixture was stirred for 4 h, poured into ice–water, and extracted with chloroform. The extract was washed with brine and dried over anhydrous magnesium sulphate. Solvent was distilled off and the residue was purified by column chromatography on silica gel, with hexane–EtOAc (1:1) as solvent to give compound **8a** (512 mg, 95%).

5-Methyl-N′-phenyl-2-(p-tolyl)-1H-imidazole-4-carboxamide **6h** *and* *N-(p-Toluoyl)glycine Anilide* **8b**.—A mixture of compound **5h** (200 mg, 0.63 mmol) and 10% ethanolic potassium hydroxide (12 cm^3) was treated by the same procedure as described for compounds **6g** and **8a** to give the title compounds **6h** and **8b**.

Compound **6h**: (88 mg, 48%), m.p. 250–251 °C (from hexane–EtOAc) (Found: C, 73.95; H, 5.9; N, 14.5. $C_{18}H_{17}N_3O$ requires C, 74.21; H, 5.88; N, 14.42%); ν_{max}(KBr)/cm^{-1} 3350 (NH), 1665 and 1645 (C=O); λ_{max}(EtOH)/nm 287 (ε 31 100); δ_H(100 MHz; $CDCl_3$) 2.38 (3 H, s, *Me*C_6H_4), 2.65 (3 H, s, 5-Me), 7.03–7.77 (9 H, m, ArH), 9.15 (1 H, br s, NH) and 9.50 (1 H, br s, NH); *m*/*z* 291 (M^+), and 199 (M^+ – MePh).

Compound **8b**: (54 mg, 32%), m.p. 226–227 °C (from EtOAc) (Found: C, 71.4; H, 6.0; N, 10.2. $C_{16}H_{16}N_2O_2$ requires C, 71.62; H, 6.01; N, 10.44%); ν_{max}(KBr)/cm^{-1} 3260 (NH), 1675 and 1635 (C=O); δ_H(270 MHz; $CDCl_3$) 2.42 (3 H, s, *Me*C_6H_4), 4.38 (2 H, d, *J* 5.3, CH_2NH), 7.09–7.79 (10 H, m, ArH, NH) and 8.95 (1 H, s, NH); *m*/*z* 268 (M^+), 148 (M^+ – CONHPh) and 119 (M^+ – $NHCH_2CONHPh$).

2-(p-Methoxyphenyl)-5-methyl-N′-phenyl-1H-imidazole-4-carboxamide **6i**.—A mixture of compound **5i** (250 mg, 0.75 mmol) and 10% ethanolic potassium hydroxide (15 cm^3) was treated by the same procedure as described for compound **6g** to give the *amide* **6i** (89 mg, 39%), m.p. 218–220 °C (from benzene) (Found: C, 70.2; H, 5.3; N, 13.7. $C_{18}H_{17}N_3O_2$ requires C, 70.34; H, 5.57; N, 13.67%); ν_{max}(KBr)/cm^{-1} 3320 (NH) and 1650 (C=O); λ_{max}(EtOH)/nm 287 (ε 32 900); δ_H(100 MHz;

$CDCl_3$) 2.60 (3 H, s, 5-Me), 3.84 (3 H, s, OMe), 6.90–7.85 (9 H, m, ArH), 9.19 (1 H, s, NH) and 10.03 (1 H, br s, NH); *m/z* 307 (M^+) and 215 (M^+ – NHPh). A trace amount of *p*-anisamide **8c*** was separated, m.p. 165–167 °C (lit.,* 165–167 °C); ν_{max}(KBr)/cm^{-1} 3500, 3380 (NH), and 1680 (C=O); δ_H(100 MHz; $CDCl_3$)* 3.86 (3 H, s, OMe), 5.95 (2 H, s, NH_2) and 7.26–7.83 (4 H, m, ArH); *m/z* 151 (M^+) and 135 (M^+ – NH_2).

5-*Methyl*-2-(p-*nitrophenyl*)-N′-*phenyl*-1H-*imidazole*-4-*carboxamide* **6j**.—A mixture of compound **5j** (200 mg, 0.57 mmol) and 10% ethanolic potassium hydroxide (15 cm^3) was treated by the same procedure as described for compound **6g** to give compounds **6j** and **4**.

Compound **6j**: (46 mg, 25%), m.p. >300 °C (Found: C, 63.4; H, 4.3; N, 17.35. $C_{17}H_{14}N_4O_3$ requires C, 63.35; H, 4.38; N, 17.38%); ν_{max}(KBr)/cm^{-1} 3450 (NH) and 1650 (C=O); λ_{max}(EtOH)/nm 271 (ε 18 400) and 353 (ε 17 200); δ_H [100 MHz; $(CD_3)_2SO$] 2.61 (3 H, s, 5-Me), 7.08–7.78 (5 H, m, ArH), 8.20–8.42 (5 H, m, ArH, NH) and 9.68 (1 H, s, NH); *m/z* 322 (M^+).

Compound **4**: (78 mg, 65%).

2-*Ethoxymethyl*-5-*methyl*-N′-*phenyl*-1H-*imidazole*-4-*carboxamide*.—A mixture of compound **5k** (250 mg, 0.90 mmol) and 10% ethanolic potassium hydroxide (15 cm^3) was treated by the same procedure as described for compound **6g** to give compounds **6k** and **4**.

Compound **6k**: (91 mg, 39%) as a glutinous oil (Found: 259.1319. M^+, $C_{14}H_{17}N_3O_2$ requires M, 259.1320); ν_{max}(CHCl$_3$)/cm^{-1} 3360 (NH) and 1640 (C=O); λ_{max}(EtOH)/nm 269 (ε 23 100); δ_H(270 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7, CH_2*Me*), 2.63 (3 H, s, 5-Me), 3.62 (2 H, q, *J* 7, CH_2Me), 4.55 (2 H, s, CH_2O), 7.05–7.69 (5 H, m, Ph), 8.95 (1 H, s, NH) and 9.38 (1 H, br s, NH); *m/z* 259 (M^+) and 167 (M^+ – NHPh). **4**: (60 mg, 33%).

2-*Dimethylaminomethyl*-5-*methyl*-N′-*phenyl*-1H-*imidazole*-4-*carboxylate* **6l**.—A mixture of compound **5l** (250 mg, 0.87 mmol) and 10% ethanolic potassium hydroxide (12 cm^3) was treated by the same procedure as described for compound **6g** to give the *amide* **6l** (205 mg, 91%), m.p. 175–177 °C (Found: C, 64.9; H, 7.1; N, 21.65. $C_{14}H_{18}N_4O$ requires C, 65.09; H, 7.02; N, 21.69%); ν_{max}(KBr)/cm^{-1} 3350 (NH) and 1675 (C=O); λ_{max}(EtOH)/nm 269 (ε 20 700); δ_H(100 MHz; $CDCl_3$) 2.30 (6 H, s, NMe_2), 2.61 (3 H, s, 5-Me), 3.52 (2 H, s, CH_2N), 7.05–7.70 (5 H, m, Ph), 8.98 (1 H, br s, NH) and 9.75 (1 H, br s, NH); *m/z* 258 (M^+), 215 (M^+ – NMe_2) and 166 (M^+ – NHPh).

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