Synthesis of 5-substituted imidazo[4,5-*b*]pyridinones by annelation of 4-amino-5-ethoxalyl-1*H*-imidazole derivatives with active methylene compounds

George Tennant,*[a] Christopher J. Wallis[b] and George W. Weaver †[a]

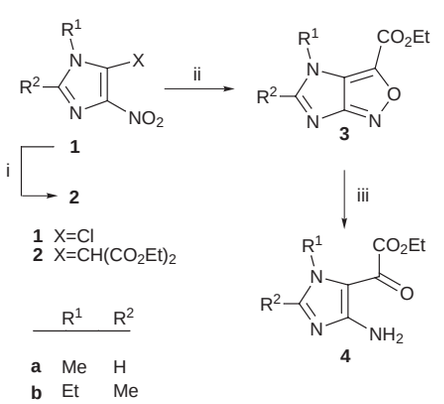
[a] *Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh, UK EH9 3JJ*
[b] *GlaxoWellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, UK SG1 2NY*

Received (in Cambridge) 26th October 1998, Accepted 12th February 1999

A new synthetic route to imidazo[4,5-*b*]pyridinones with a range of substituents at the 6-position has been developed. These compounds can be prepared in four steps from readily available 5-chloro-4-nitroimidazoles. The key step involves construction of the pyridine ring by annelation of 4-amino-5-ethoxalylimidazoles with active methylene compounds under dehydrating conditions or by acylation with substituted acetyl chlorides followed by spontaneous cyclisation. An exception is the reaction in which cyclisation of a phenylacetyl derivative occurs to give a seven-membered ring, forming an imidazo[4,5-*b*]azepinedione.

Introduction

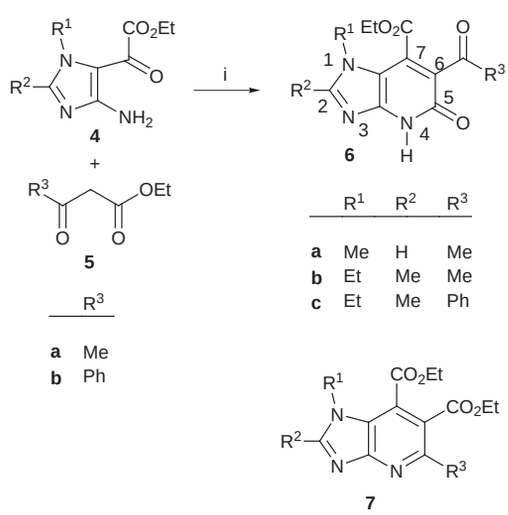
Imidazo[4,5-*b*]pyridines can be considered as 1-deazapurines and as such are of interest for their biological activity.[1] We have been interested in the synthesis of imidazo[4,5-*b*]pyridinones as potential adenosine receptor antagonists and have recently reported[2] a new route to 5-substituted-4-hydroxyimidazo-[4,5-*b*]pyridin-7(4*H*)-ones based on reductive cyclisation of 4-nitroimidazol-5-yl di- and tri-carbonyl compounds. In this paper we describe a new route to 6-substituted imidazo-[4,5-*b*]pyridin-5(4*H*)-ones starting from 4-amino-5-ethoxalylimidazole precursors and forming the pyridine ring in the key annelation step. The majority of imidazo[4,5-*b*]pyridine syntheses start with a substituted pyridine and involve construction of the imidazole ring.[3] There are fewer examples of syntheses beginning from imidazole precursors and building up the pyridine ring. Recently Perandones and Soto[4] have described how 4-aminoimidazole-5-carboxaldehydes can be converted into imidazo[4,5-*b*]pyridines by reaction with active methylene compounds in glacial acetic acid. Their results have prompted us to report our findings in this area. We wished to exploit our discovery that 4-amino-5-ethoxalylimidazoles **4** (Scheme 1) can easily be formed by reductive ring opening of imidazo[4,5-*c*]isoxazoles **3**. We have recently reported[5] the first synthesis of substituted imidazo[4,5-*c*]isoxazoles **3** by thermolysis of 4-nitroimidazol-5-yl acetate and malonate derivatives **2**. Reductive opening of the strained isoxazole ring in the imidazo[4,5-*c*]isoxazole allows easy access to 4-amino-5-ethoxalylimidazoles **4**. In our studies of the reactivity of these compounds we have now developed a general method for their annelation with active methylene compounds to generate imidazo[4,5-*b*]pyridin-5(4*H*)-ones with a variety of substituents at the 6-position. This approach thus complements our alternative route[2] which allows variation of the substituent at the 5-position of the imidazopyridine ring.



Scheme 1 *Reagents and conditions:* i, NaH, diethyl malonate, DMF, 100 °C; ii, xylene, heat; iii, H_2, Pd–C, EtOH.

Results and discussion

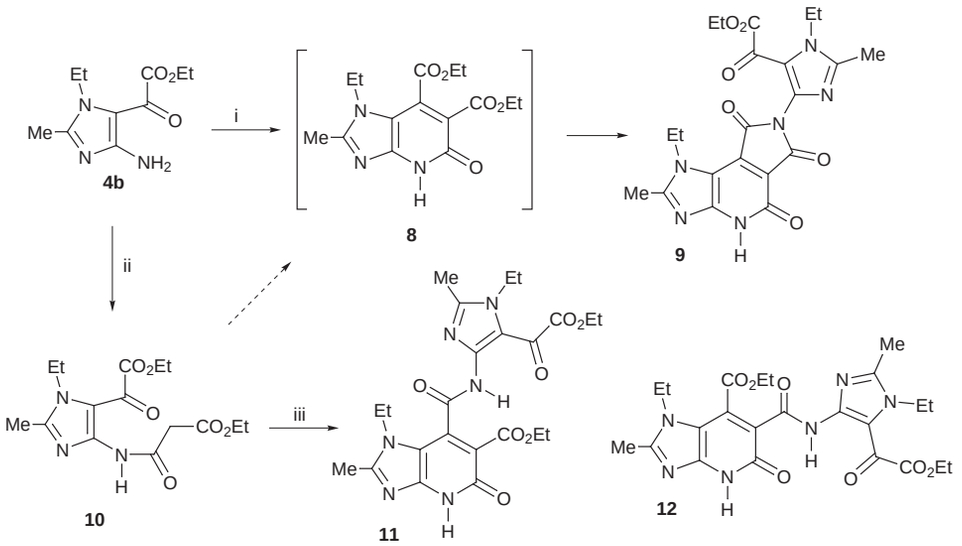
Our initial investigation was into the reaction of the amino ketones **4a** and **4b** with β-keto esters (Scheme 2). We found that



Scheme 2 *Reagents and conditions:* i, xylene, heat.

heating **4a** with ethyl acetoacetate in xylene with provision for the removal of ethanol by slow distillation afforded a very good yield (83%) of an orange crystalline solid. This was identified as the imidazo[4,5-*b*]pyridinone **6a** on the basis of elemental analysis and the compound's NMR and mass spectrometric

† Present address: Department of Chemistry, Loughborough University, Loughborough, UK LE11 3TU.

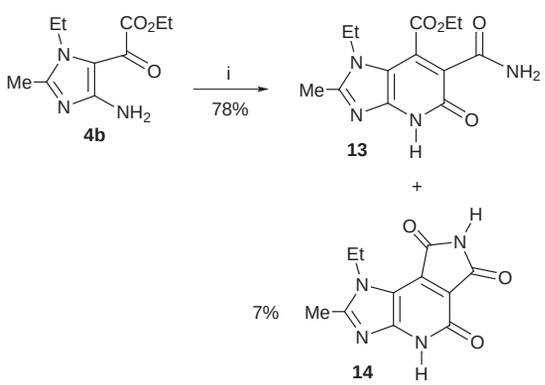


Scheme 3 *Reagents and conditions:* i, xylene, heat, ii, ethyl malonyl chloride, PhH, reflux; iii, PhMe, TsOH, reflux.

properties. This product is formed by preferential condensation of the amino and ethoxalyl substituents in the imidazole derivative **4a** with the ester and methylene moieties respectively in ethyl acetoacetate. There was no evidence for the formation of the alternative product **7a**, which could arise by condensation of the aminoimidazole **4a** with ethyl acetoacetate. The amino ketone **4b** likewise reacted with one equivalent of ethyl acetoacetate to give the corresponding imidazopyridinone **6b** in moderate 46% yield although in this case starting material **4b** was also recovered. Ethyl benzoylacetate was also successful as a substrate and reacted with **4b** to give the 6-benzoyl imidazopyridinone **6c** in 56% yield, the starting amine **4b** again being recovered (14%). The reason for the low efficiency of the condensation reactions of the aminoimidazole **4b** with ethyl acetoacetate and ethyl benzoylacetate is not obvious but recovery of unreacted amine **4b** indicates that the use of an excess of the active methylene compound might lead to improved yields of the imidazopyridinone derivatives.

We next investigated the reaction of **4b** with diethyl malonate (Scheme 3) with the intention of forming the imidazo[4,5-*b*]-pyridinone-6,7-diester **8**. Heating the amine **4b** with one equivalent of diethyl malonate in xylene for 9 hours gave a very good yield of an orange crystalline solid which was shown by a combination of ^{1}H and ^{13}C NMR spectroscopy and elemental analysis to be the 1,4,5,6,7,8-hexahydroimidazo[4,5-*b*]pyrrolo-[3,4-*d*]pyridine-5,6,8-trione **9** rather than the expected diester **8**. This compound was isolated in 93% yield and most probably arises by reaction of the initially formed imidazopyridinone **8** with a second molecule of the amine **4b** which reacts with the two adjacent ester groups through its 4-amino substituent to give the imide. Surprisingly, attempts to modify the reaction conditions to promote formation of the diester **8** were unsuccessful, even using a stepwise approach involving acylation of the aminoimidazole **4b** with ethyl malonyl chloride. This afforded the amide ester **10** in good yield but when this compound was heated in toluene with a catalytic amount of toluene-*p*-sulfonic acid, only the amide **11** (or the isomeric structure **12**) was isolated. It was not possible to distinguish between the two possible isomers **11** and **12**, but the formation of this product is remarkable as it indicates that the amide ester **10** can revert to the amino ketone **4b** under the reaction conditions. This must then react, in turn, with the imidazopyridine diester **8** formed in the expected fashion. None of the presumed diester intermediate **8** could be detected in the reaction mixture.

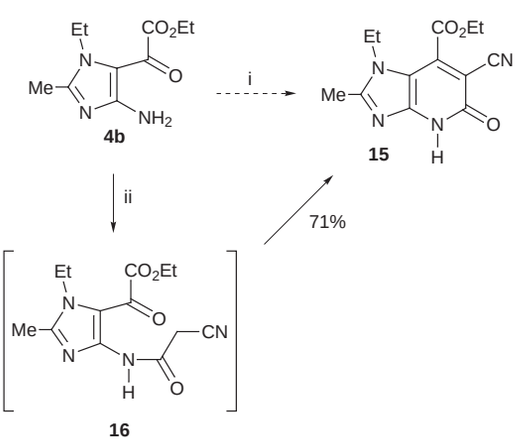
Employing the 'half' amide, ethyl malonate monoamide monoester (Scheme 4) in place of diethyl malonate afforded the expected oxoimidazopyridinone-6-carboxamide **13** in 78% yield together with a 7% yield of the corresponding imide **14** formed



Scheme 4 *Reagents and conditions:* i, ethyl malonamide, xylene, heat.

by elimination of ethanol from **13**. In this case no products derived by further reaction of the primary condensates with the imidazole amine **4b** were detected.

We then embarked on the study of the condensation of the amine **4b** with other activated methylene compounds in order to prepare a range of 6-substituted imidazo[4,5-*b*]pyridinones as potential adenosine antagonists. Disappointingly however (Scheme 5) heating amine **4b** with ethyl cyanoacetate in xylene

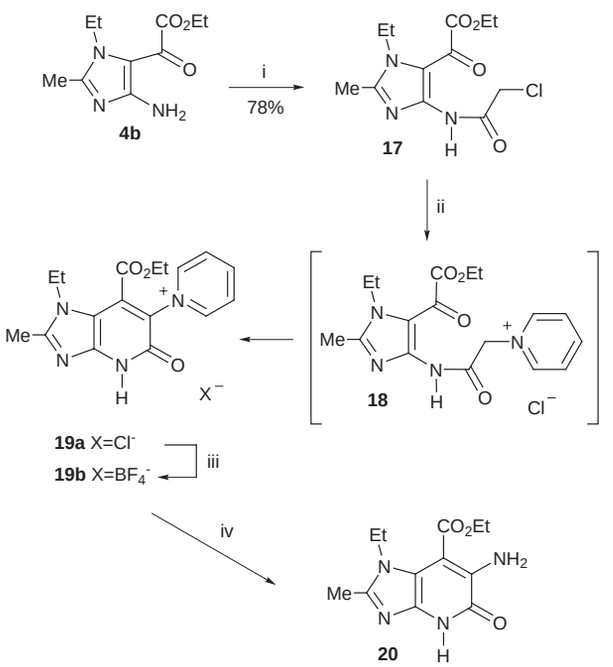


Scheme 5 *Reagents and conditions:* i, ethyl cyanoacetate, heat; ii, cyanoacetyl chloride, PhH, reflux.

failed to give the expected 6-cyanoimidazopyridinone **15**. The amine **4b** was recovered unchanged in essentially quantitative yield. Ethyl cyanoacetate is predictably more reactive than diethyl malonate as well as less sterically demanding and the

reason for its failure to participate in the annelation reaction is not clear, particularly in the light of the work of Perandones and Soto,[4] who have described the successful condensation of 4-amino-1,2-dimethylimidazole-5-carboxaldehyde with ethyl cyanoacetate to give a 5-aminoimidazo[4,5-*b*]pyridine ester. The amine **4b** also failed to react with acetylacetone, ethyl phenylsulfinylacetate or ethyl nitroacetate to give imidazopyridinone products. However treating **4b** with cyanoacetyl chloride in benzene with the intention of forming the cyanoamide **16** which could be cyclised to **15** in a separate step under dehydrating conditions, gave a good yield (71%) of a high melting solid (mp 224 °C) shown to be the desired cyanoimidazopyridinone **15**. Presumably the enhanced acidity of the methylene protons of the cyanoacetamide side chain in **16** together with the high electrophilicity of the ethoxalyl ketone allow spontaneous cyclisation and loss of water to occur even in the absence of any dehydrating agent.

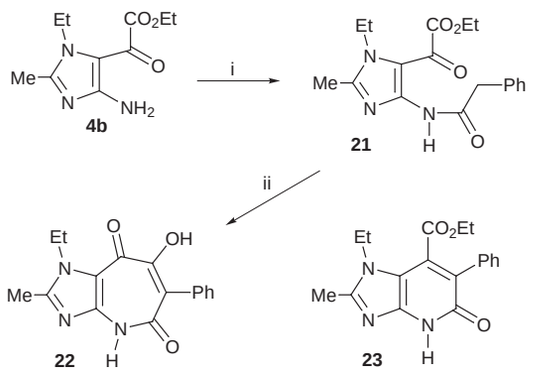
The success of the reaction with cyanoacetyl chloride prompted us to investigate the treatment of amine **4b** with chloroacetyl chloride (Scheme 6), as access to the chloro-



Scheme 6 *Reagents and conditions:* i, chloroacetyl chloride, PhMe, reflux; ii, pyridine, 100 °C; iii, HBF_4 (aq.), MeOH; iv, piperidine, MeOH, reflux.

acetamide **17** would allow introduction of a wide range of substituents into the 6-position of the imidazopyridinone by nucleophilic displacement of the chloro substituent in **17** followed by cyclisation. We were pleased to find **17** was formed as a bright yellow crystalline solid in quantitative yield on treatment of **4b** with chloroacetyl chloride in toluene. A first attempt to use this compound for the strategy described was frustrated however, when treatment of **17** with either potassium cyanide in ethanol or tetrabutylammonium cyanide[6] in acetonitrile failed to give either cyanoamide **16** or the 6-cyanoimidazopyridinone **15** which had already been obtained by the direct use of cyanoacetyl chloride as described before. However heating **17** in pyridine led to the successful displacement of chloride ion and formation of the pyridinium salt **18**. Again the high reactivity of the intermediate **18** precluded its isolation and resulted in its spontaneous cyclisation to the imidazopyridinone **19a**. The imidazopyridinone pyridinium salt **19a** was formed in essentially quantitative yield. The chloride salt **19a** proved somewhat unstable and was converted to the tetrafluoroborate salt **19b** for characterisation and storage. We were pleased to find that the pyridinium salt **19b** could be hydrolysed[7] under relatively mild conditions by heating with piperidine in methanol to give the 6-aminoimidazo[4,5-*b*]pyridinone **20**. The reaction sequence **4b**→**17**→**19b**→**20** therefore allows the introduction of a 6-amino substituent which would be difficult by other means and provides access to 6-aminoimidazopyridinone derivatives of value as intermediates for futher annelation reactions.

We next investigated the acylation of the imidazole amine **4b** with phenylacetyl chloride with the intention of forming the condensate **21** which, it was hoped as before, would undergo facile cyclisation to the 6-phenyl imidazopyridinone **23** thus extending further the scope of this method and allowing the introduction of aromatic ring substituents at the 6-position (Scheme 7). In practice, treatment of **4b** with phenylacetyl



Scheme 7 *Reagents and conditions:* i, phenylacetyl chloride, PhH, reflux; ii, NaOEt, EtOH, reflux.

chloride in benzene gave the expected phenylacetamide **21** in only moderate yield (65%).

Treating **4b** with phenylacetyl chloride in dioxane in the presence of triethylamine however failed to improve the yield of **21**. The reaction of **21** with base was then investigated with the intention of inducing cyclisation but this took an unexpected course. On treating the phenylacetamide with sodium ethoxide in ethanol, the imidazo[4,5-*b*]azepinedione **22** was formed rather than the imidazopyridinone **23**. In this case therefore, cyclisation involves the ester group of the ethoxalyl substituent in contrast to all of the previous examples described which follow the more favourable 6-*exo*-*trig* pathway. The structure of the seven membered ring product **22** was clearly demonstrated by its spectroscopic properties and elemental composition. It is not clear why the seven membered ring has formed in this case and whether this would be common for other aromatic substituents. The reason for the difference cannot be steric since the pyridinium salt **18** cyclised to give the orthodox imidazopyridinone ring **19a** and yet is isosteric with the phenylacetamide **21**. The reaction was carried out in the more polar solvent ethanol and differences in solvation of the enolate ion may be responsible for the change in reactivity. Further work is in hand to establish the scope and mechanism of the novel transformation **21**→**22** which may exemplify a concise general synthesis of usefully functionalised derivatives of the elusive[8] imidazo[4,5-*b*]azepine ring system.

In some final experiments to construct imidazopyridinones bearing other substituent patterns from the aminoimidazole **4b**, the amine was heated with diethyl acetylenedicarboxylate in the hope of forming the 5,6,7-triester substituted pyridine ring, and with nitroketene dimethyl dithioacetal[9] with the aim of generating a 5-methylthio-6-nitroimidazopyridine derivative. However neither of these reaction conditions led to the isolation of imidazopyridine products. The yields of 6-substituted imidazo-[4,5-*b*]pyridinones prepared are given in Table 1.

In conclusion we have developed a new and general synthetic route to 6-substituted imidazo[4,5-*b*]pyridin-5(4*H*)-ones with a range of substituents (notably ester, ketone, nitrile, amide and amine). The imidazopyridinones are formed in only four steps

Table 1 Imidazo[4,5-*b*]pyridinone derivatives prepared from **4a** or **b**

	R^1	R^2	R^3	Yield (%)
6a	Me	H	Me	83
6b	Et	Me	Me	46
6c	Et	Me	Ph	56[a]
13	Et	Me	$CONH_2$	85
15	Et	Me	CN	71
19b	Et	Me	pyridin-1-ium	79
20	Et	Me	NH_2	55

[a] Starting material **4b** recovered (14%).

from readily available 5-chloro-4-nitroimidazoles, thus providing a general synthetic approach to deazapurine analogues with potential applications in biology and medicine.

Experimental

Infra-red spectra were recorded using a Perkin Elmer 781 spectrophotometer as Nujol mulls or liquid films. ^{1}H NMR spectra were recorded at 80 or 200 MHz on Bruker WP80–SY and WP200-SY instruments. ^{13}C NMR spectra were recorded at 50 MHz on a Bruker WP200-SY instrument. Mass spectra were recorded at 70 eV on an AEI MS-902 instrument for EI spectra and on a Kratos MS-50TC instrument for FAB spectra. Microanalyses were carried out using a Carlo-Erba Strumentazione 1106 elemental analyser. Mps were determined using a Kofler hot-stage microscope and are uncorrected. All reagents were laboratory grade unless specified. Solvents were of technical grade unless otherwise stated. Organic extracts were dried over anhydrous sodium or magnesium sulfate prior to filtration and evaporation under reduced pressure. All yields are based on unrecovered starting material. Flash chromatography was carried out over silica gel (Merck 9385) and dry column flash chromatography over silica (Merck 7736). Thin layer chromatography was carried out on Polygram SIL G/UV_{254} precoated plastic sheets.

4-Amino-5-ethoxalyl-1*H*-imidazoles 4a and 4b

4-Amino-5-ethoxalyl-1*H*-imidazoles **4a**,**4b** were prepared by catalytic reduction of ethyl 4-ethyl-5-methyl-4*H*-imidazo-[4,5-*c*]isoxazole-3-carboxylate **3b** or ethyl 4-methyl-4*H*-imidazo[4,5-*c*]isoxazole-3-carboxylate **3a** as described by Tennant *et al*.[5]

Thermal condensation reactions of ethyl 2-(4-amino-1*H*-imidazol-5-yl)-2-oxoethanoates 4 with active methylene compounds

A solution of the corresponding amino keto ester **4a** or **4b** (0.002 mol) and the respective active methylene compound (0.002 mol) in anhydrous xylene (10–20 ml) was stirred and heated under reflux with provision for the removal of ethanol for the indicated time, then worked-up as described for the individual reactions below.

(a) The mixture from the amino keto ester **4b** and ethyl acetoacetate **5a** was heated under reflux for 16 h then evaporated and the residue triturated with ethanol to give a solid (0.4 g) which was extracted with boiling ethanol and hot filtered to remove some insoluble material.

On cooling, the ethanolic filtrate deposited *ethyl 6-acetyl-1-ethyl-2-methyl-5-oxo-4,5-dihydro-1*H-*imidazo[4,5*-b*]pyridine-7-carboxylate* **6b** (0.27 g, 46%) as yellow brown needles, mp 160–161 °C (from ethanol) (Found: C, 57.4; H, 5.8; N, 14.4%; *m*/*z* (EIMS) 291 (M^+), $C_{14}H_{17}N_3O_4$ requires: C, 57.7; H, 5.9; N, 14.4%; M, 291); ν_{max}/cm^{-1} 3200–2500 br (NH, OH) and 1730 and 1645 (CO); δ_H [$(CD_3)_2SO$] 12.69 (1H, s, NH) (exch.), 4.35 (2H, q, *J* 7, CH_2), 3.97 (2H, q, *J* 7, CH_2), 2.53 (3H, s, CH_3), 2.51 (3H, s, CH_3), 1.30 (3H, t, *J* 7, CH_3) and 1.20 (3H, t, *J* 7, CH_3).

(b) The mixture from the amino keto ester **4a** and ethyl acetoacetate **5a** was heated under reflux for 10 h then cooled and the precipitated solid collected to give *ethyl 6-acetyl-1-methyl-5-oxo-4,5-dihydro-1*H-*imidazo[4,5*-b*]pyridine-7-carboxylate* **6a** (0.44 g, 83%) which formed pale orange brown plates, mp 195–196 °C (from ethanol–water) (Found: C, 54.6; H, 5.0; N, 15.9%; *m*/*z* (EIMS) 263 (M^+), $C_{13}H_{13}N_3O_4$ requires: C, 54.8; H, 5.0; N, 16.0%; M, 263); ν_{max}/cm^{-1} (CO); δ_H [$(CD_3)_2SO$] 12.73 (1H, br s, NH) (exch.), 8.23 (1H, s, H-2), 4.36 (2H, q, *J* 7, CH_2), 3.66 (3H, s, CH_3), 2.54 (3H, s, CH_3) and 1.31 (3H, t, *J* 7, CH_3).

(c) The mixture from the amino keto ester **4b** and ethyl benzoylacetate **5b** was heated under reflux for 23 h then filtered to afford *ethyl 6-benzoyl-1-ethyl-2-methyl-5-oxo-4,5-dihydro-1*H-*imidazo[4,5*-b*]pyridine-7-carboxylate* **6c** (0.39 g, 56%) which formed yellow spars, mp 242–243 °C (from ethanol–water) (Found: C, 64.1; H, 5.4; N, 11.8%; *m*/*z* (EIMS) 353 (M^+), $C_{19}H_{10}N_3O$ requires: C, 64.6; H, 5.4; N, 11.9%; M, 353); ν_{max}/cm^{-1} 3160–2300 br (NH, OH) and 1730 and 1640 (CO); δ_H [$(CD_3)_2SO$] 12.38–12.00 (1H, br s, NH) (exch.), 7.82–7.39 (5H, m ArH), 4.14 (2H, q, *J* 7, CH_2), 4.08 (2H, q, *J* 7, CH_2), 2.55 (3H, s, CH_3), 1.21 (3H, t, *J* 7, CH_3) and 0.98 (3H, t, *J* 7, CH_3).

Evaporation of the xylene mother liquor gave a yellow green gum (0.29 g) which was triturated with ethanol to give unchanged amino keto ester **4b** (0.07 g, 14%), mp 128–129 °C, identified by comparison with an authentic sample.

(d) The mixture from the amino keto ester **4b** and diethyl malonate was heated under reflux for 9 h then cooled and filtered to afford *1-ethyl-7-(1-ethyl-5-ethoxalyl-2-methyl-1*H-*imidazol-4-yl)-2-methyl-1,4,5,6,7,8-hexahydroimidazo[4,5*-b*]-pyrrolo[3,4*-d*]pyridine-5,6,8-trione* **9** (0.42 g, 93%), which formed yellow orange needles, mp 247–248 °C (from ethanol–water) (Found: C, 55.5; H, 5.1; N, 18.2%; *m*/*z* (EIMS) 410 ($M^+ - CO_2$), $C_{21}H_{22}N_6O_6$ requires: C, 55.5; H, 4.8; N, 18.5%; M, 454); ν_{max}/cm^{-1} 3100–2300 br (NH, OH) and 1780, 1740 and 1655 (CO); δ_H [$(CD_3)_2SO$] 12.90 (1H, br s, NH) (exch.), 4.55–4.28 (4H, m, 2 × CH_2), 3.88 (2H, q, *J* 7, CH_2), 2.61 (3H, s, CH_3), 2.51 (3H, s, CH_3), 1.35 (3H, t, *J* 7, CH_3), 1.33 (3H, t, *J* 7, CH_3) and 1.06 (3H, t, *J* 7, CH_3); δ_C [$(CD_3)_2SO$] 174.8 (quat.), 164.4 (quat.), 164.0 (quat.), 162.6 (quat.), 160.0 (quat.), 156.2 (quat.), 155.9 (quat.), 151.7 (quat.), 138.3 (quat.), 129.0 (quat.), 121.6 (quat.), 105.0 (quat.), 62.5 (CH_2), 41.8 (CH_2), 41.1 (CH_2), 15.4 (CH_3), 15.0 (CH_3), 13.8 (CH_3), 13.3 (CH_3) and 12.8 (CH_3).

(e) The mixture from the amino keto ester **4b** and ethyl malonamide was heated under reflux for 7 h then cooled and filtered to afford a yellow solid which was combined with further material obtained by evaporating the filtrate and triturating the residue with ethanol to give *ethyl 6-carbamoyl-1-ethyl-2-methyl-5-oxo-4,5-dihydro-1*H-*imidazo[4,5*-b*]pyridine-7-carboxylate* **13** (total 0.44 g, 85%) which formed yellow spars, mp >330 °C (from ethanol–water) (Found: C, 53.5; H, 5.3; N, 19.0%; *m*/*z* (EIMS) 292 (M^+), $C_{13}H_{16}N_4O_4$ requires: C, 53.4; H, 5.5; N, 19.2%; M, 292); ν_{max}/cm^{-1} 3600–2500 br (NH, OH) and 1730 and 1675 (CO); δ_H [$(CD_3)_2SO$] 13.13 (1H, s, NH) (exch.), 9.35 (1H, d, *J* 1, NH) (exch.), 7.43 (1H, d, *J* 1, NH) (exch.), 4.34 (2H, q, *J* 7, CH_2), 3.97 (2H, q, *J* 7, CH_2), 2.51 (3H, s, CH_3), 1.31 (3H, t, *J* 7, CH_3) and 1.22 (3H, t, *J* 7, CH_3).

On heating, the carboxamide **13** was converted into *1-ethyl-2-methyl-1,4,5,6,7,8-hexahydroimidazo[4,5*-b*]pyrrolo[3,4*-d*]-pyridine-5,6,8-trione* **14**, which formed orange needles, mp 317–319 °C (sublimes) (Found: C, 53.1; H, 3.8; N, 21.9%; *m*/*z* (HRMS) 246.0755 (M^+), $C_{11}H_{10}N_4O_3$ requires: C, 53.7; H, 4.1; N, 22.8%; M, 246.0735); ν_{max}/cm^{-1} 3400–2500 br (NH, OH) and 1770 and 1725 (CO); δ_H [$(CD_3)_2SO$] 12.75–12.13 (1H, br s, NH) (exch.), 11.38–10.88 (1H, br s, NH) (exch.), 4.52 (2H, q, *J* 7, CH_2), 2.57 (3H, s, CH_3), 1.30 (3H, t, *J* 7, CH_3).

Ethyl 2-[*N*-(5-ethoxalyl-1-ethyl-2-methyl-1*H*-imidazol-4-yl)-carbamoyl]ethanoate 10

A solution of the amino keto ester **4b** (1.4 g, 0.006 mol) in

anhydrous benzene (15.0 ml) was treated dropwise at room temperature with a solution of ethyl malonyl chloride (0.90 g, 0.006 mol) in anhydrous benzene (15.0 ml) and the resulting solution was heated under reflux for 2 h.

The mixture was evaporated to give a golden brown oil (2.6 g) which was dry column flash-chromatographed over silica.

Elution with dichloromethane–ethyl acetate (1:1) gave a yellow gum (1.8 g) which solidified on rubbing with ether–light petroleum (bp 40–60 °C) to afford *ethyl 2-[*N-*(5-ethoxalyl-1-ethyl-2-methyl-1*H-*imidazol-4-yl)carbamoyl]ethanoate* **10** (1.5 g, 72%) as a pale yellow waxy solid, mp 69–71 °C (from benzene–light petroleum) (Found: C, 53.4; H, 6.3; N, 12.3%; *m/z* (EIMS) 339 (M^+), $C_{15}H_{21}N_3O_6$ requires: C, 53.1; H, 6.2; N, 12.4%; M, 339); ν_{max}/cm^{-1} 3210 and 3150 (NH) and 1760, 1690 and 1670 (CO); δ_H ($CDCl_3$) 10.00–9.63 (1H, br s, NH), 4.33 (2H, q, *J* 7, CH_2), 4.19 (4H, q, *J* 7, CH_2), 3.49 (2H, s, CH_2), 2.40 (3H, s, CH_3), 1.36 (3H, t, *J* 7, CH_3), 1.30 (3H, t, *J* 7, CH_3) and 1.24 (3H, t, *J* 7, CH_3).

Ethyl 7(6)-[*N*-(5-ethoxalyl-1-ethyl-2-methyl-1*H*-imidazol-4-yl)-carbamoyl]-1-ethyl-2-methyl-5-oxo-4,5-dihydro-1*H*-imidazo-[4,5-*b*]pyridine-6(7)-carboxylate 11

A solution of the amide **10** (0.68 g, 0.002 mol) in anhydrous toluene (25 ml) was treated with toluene-*p*-sulfonic acid (0.01 g) and the mixture was heated under reflux for 23.5 h using a Dean–Stark trap to remove any water formed.

The mixture was cooled and the insoluble solid was collected and combined with further solid material obtained by evaporating the toluene filtrate and triturating the resulting orange oil with ethyl acetate-ethanol to give *ethyl 7(6)-[*N-*5-ethoxalyl-1-ethyl-2-methyl-1*H-*imidazol-4-yl)carbamoyl]-1-ethyl-2-methyl-5-oxo-4,5-dihydro-1*H-*imidazo[4,5-*b*]pyridine-6(7)-carboxylate* **11** (0.41 g, 82%), which formed yellow microcrystals, mp 216–217 °C (from ethanol–acetic acid) (Found: C, 55.3; H, 5.8; N, 16.8%; *m/z* (EIMS) 380 (M^+), $C_{23}H_{28}N_6O_7$ requires: C, 55.2; H, 5.6; N, 16.8%; M, 500); ν_{max}/cm^{-1} 3100–2500 br (NH, OH) and 1740, 1720 and 1660 br (CO); δ_H [$(CD_3)_2SO$] 13.50 (1H, br s, NH) (exch.), 12.78 (1H, br s, NH) (exch.), 4.35 (2H, q, *J* 7, CH_2), 4.05 (6H, q, *J* 7, 3 × CH_2), 2.53 (3H, s, CH_3), 2.37 (3H, s, CH_3) and 1.41–1.05 (12H, m, 4 × CH_3).

Ethyl 6-cyano-1-ethyl-2-methyl-5-oxo-4,5-dihydro-1*H*-imidazo-[4,5-*b*]pyridine-7-carboxylate 15

A solution of the amino keto ester **4b** (0.45 g, 0.002 mol) in anhydrous benzene (5.0 ml) was stirred and treated dropwise at room temperature with a solution of cyanoacetyl chloride (0.21 g, 0.002 mol) in anhydrous benzene (5.0 ml). The mixture was then heated under reflux for 2 h during which time a yellow solid was deposited.

The solid was collected and combined with further material obtained by evaporating the benzene filtrate and triturating the resulting gum with ethanol to give *ethyl 6-cyano-1-ethyl-2-methyl-5-oxo-4,5-dihydro-1*H-*imidazo[4,5-*b*]pyridine-7-carboxylate* **15** (total 0.39 g, 71%) which formed yellow rhombic plates, mp 224–225 °C (from ethanol–water) (Found: C, 56.6; H, 5.2; N, 20.4%; *m/z* (EIMS) 274 (M^+), $C_{13}H_{14}N_4O_3$ requires: C, 56.9; N, 5.1; H, 20.4%; M, 274); ν_{max}/cm^{-1} 3200–2300 br (NH, OH), 2200 (CN) and 1730 and 1665 (CO); δ_H [$(CD_3)_2SO$] 13.50–12.75 (1H, br s, NH) (exch.), 4.52 (2H, q, *J* 7, CH_2), 4.01 (2H, q, *J* 7, CH_2), 2.54 (3H, s, CH_3), 1.37 (3H, t, *J* 7, CH_3) and 1.21 (3H, t, *J* 7, CH_3).

Ethyl 2-(4-chloroacetamido-1-ethyl-2-methyl-1*H*-imidazol-5-yl)-2-oxoethanoate 17

A stirred solution of the amino keto ester **4b** (2.3 g, 0.01 mol) in anhydrous toluene (25 ml) was treated dropwise at room temperature with a solution of 2-chloroacetyl chloride (1.1 g, 0.01 mol) in anhydrous toluene (25 ml) and the yellow solution was heated under reflux for 2 h.

Evaporation of the mixture gave a yellow oil which crystallised on rubbing to give *ethyl 2-(4-chloroacetamido-1-ethyl-2-methyl-1*H-*imidazol-5-yl)-2-oxoethanoate* **17** (3.0 g, 100%), which formed bright yellow rectangular prisms, mp 113–114 °C (from ethanol) (Found: C, 47.5; H, 5.4; N, 13.9%; *m/z* (EIMS) 301 and 303 (M^+), $C_{12}H_{16}ClN_3O_4$ requires: C, 47.8; H, 5.3; N, 13.9%; M, 301.5); ν_{max}/cm^{-1} 3330 (NH) and 1735 and 1715 (CO); δ_H ($CDCl_3$) 9.90–9.50 (1H, br s, NH) (exch.), 4.34 (2H, q, *J* 7, CH_2), 4.18 (2H, q, *J* 7, CH_2), 4.15 (2H, s, CH_2), 2.42 (3H, s, CH_3), 1.36 (3H, t, *J* 7, CH_3) and 1.29 (3H, t, *J* 7, CH_3).

The reaction of ethyl 2-chloroacetamido-1-ethyl-2-methyl-1*H*-imidazol-5-yl)-2-oxoethanoate 17 with pyridine

A solution of the chloroacetamide **17** (0.91 g, 0.003 mol) in pyridine (7.5 ml) was heated at 100 °C for 0.5 h.

The excess of pyridine was evaporated and the residue was triturated with anhydrous ether to give the unstable N-*(7-ethoxycarbonyl-1-ethyl-2-methyl-5-oxo-4,5-dihydro-1*H-*imidazo[4,5-*b*]pyridin-6-yl)pyridinium chloride* **19a** (1.1 g, 100%) (Found: *m/z* (EIMS) 327 (M^+ − Cl), $C_{17}H_{19}ClN_4O_3$ requires: M, 362.5); ν_{max}/cm^{-1} 3700–2300 (NH, OH) and 1720 (CO); δ_H [$(CD_3)_2SO$] 9.27–7.41 (5H, m, ArH), 4.17 (2H, q, *J* 7, CH_2), 4.04 (2H, q, *J* 7, CH_2), 2.61 (3H, s, CH_3), 1.24 (3H, t, *J* 7, CH_3) and 0.96 (3H, t, *J* 7, CH_3).

A sample of the pyridinium chloride **19a** (0.09 g, 0.00025 mol) was dissolved in methanol (0.1 ml) and the solution treated with 40% aqueous fluoroboric acid (0.06 g, 0.00025 mol). Addition of ether (1.0 ml) precipitated *N-(7-ethoxycarbonyl-1-ethyl-2-methyl-5-oxo-4,5-dihydro-1*H-*imidazo[4,5-*b*]pyridin-6-yl)pyridinium tetrafluoroborate* **19b** (0.08 g, 79%) which formed light brown needles, mp 203–204 °C (from ethanol–water) (Found: C, 49.1; H, 4.7; N, 13.6%; *m/z* (EIMS) 327 (M^+ − BF_4), $C_{17}H_{19}BF_4N_4O_3$ requires: C, 49.3; H, 4.6; N, 13.5%; M, 414); ν_{max}/cm^{-1} 1730 and 1660 (CO); δ_H [$(CD_3)_2SO$] 13.75–13.00 (1H, br s, NH) (exch.), 9.21 (2H, dd, *J* 1.5 and 5, ArH), 8.87 (1H, tt, *J* 1.5 and 5, ArH), 8.36 (2H, dd, *J* 6 and 8, ArH), 4.17 (2H, q, *J* 7, CH_2), 4.09 (2H, q, *J* 7, CH_2), 2.60 (3H, s, CH_3), 1.24 (3H, t, *J* 7, CH_3) and 0.96 (3H, t, *J* 7, CH_3).

Ethyl 6-amino-1-ethyl-2-methyl-5-oxo-4,5-dihydro-1*H*-imidazo-[4,5-*b*]pyridine-7-carboxylate 20

A stirred solution of the pyridinium chloride **19a** (0.36 g, 0.001 mol) in methanol (0.5 ml) was treated with piperidine (0.5 ml) and the mixture was heated under reflux for 3 h.

The mixture was evaporated and the residue was triturated with ethyl acetate–methanol to afford *ethyl 6-amino-1-ethyl-2-methyl-5-oxo-4,5-dihydro-1*H-*imidazo[4,5-*b*]pyridine-7-carboxylate* **20** (0.15 g, 55%) which formed yellow needles, mp 227–228 °C (from ethanol–water) (Found: C, 54.4; H, 6.2; N, 20.9%; *m/z* (EIMS) 264 (M^+), $C_{12}H_{16}N_4O_3$ requires: C, 54.5; H, 6.1; N, 21.2%; M, 264); ν_{max}/cm^{-1} 3435 and 3300 (NH), 3200–2500 br (NH, OH) and 1620 (CO); δ_H [$(CD_3)_2SO$] 12.32 (1H, s, NH) (exch.), 6.00 (2H, s, NH_2) (exch.), 4.40 (2H, q, *J* 7, CH_2), 4.10 (2H, q, *J* 7, CH_2), 2.39 (3H, s, CH_3), 1.34 (3H, t, *J* 7, CH_3) and 1.14 (3H, t, *J* 7, CH_3).

Ethyl 2-(1-ethyl-2-methyl-4-phenylacetamido-1*H*-imidazol-5-yl)-2-oxoethanoate 21

(a) A solution of the amino keto ester **4b** (0.45 g, 0.002 mol) in anhydrous benzene (5.0 ml) was stirred and treated dropwise at room temperature with a solution of 2-phenylacetyl chloride (0.31 g, 0.002 mol) in anhydrous benzene (5.0 ml). The resulting solution was then heated under reflux for 2 h.

Evaporation of the mixture and trituration of the residue with ethanol afforded *ethyl 2-(1-ethyl-2-methyl-4-phenylacetamido-1*H-*imidazol-5-yl)-2-oxoethanoate* **21** (0.44 g, 65%) which formed large yellow spars, mp 126–127 °C (from ethanol) (Found: C, 63.0; H, 6.3; N, 12.0%; *m/z* (EIMS) 343 (M^+),

$C_{18}H_{21}N_3O_4$ requires: C, 63.0; H, 6.2; N, 12.2%; M, 343); ν_{max}/cm^{-1} 3300 and 3250 (NH) and 1730, 1695 and 1630 (CO); δ_H ($CDCl_3$) 9.03 (1H, s, NH) (exch.), 7.28 (5H, s, ArH), 4.15 (4H, q, *J* 7, CH_2), 3.68 (2H, s, CH_2), 2.38 (3H, s, CH_3), 1.29 (3H, t, *J* 7, CH_3) and 1.27 (3H, t, *J* 7, CH_3).

(b) A solution of the amino keto ester **4b** (0.45 g, 0.002 mol) in anhydrous 1,4-dioxane (5.0 ml) was stirred and treated dropwise at room temperature with a solution of triethylamine (0.20 g, 0.002 mol) in anhydrous 1,4-dioxane (2.5 ml) and then dropwise with a solution of 2-phenylacetyl chloride (0.31 g, 0.002 mol) in anhydrous 1,4-dioxane (2.5 ml). The resulting suspension was stirred at room temperature for 24 h and then filtered to remove triethylammonium chloride. The filtrate was evaporated to give a yellow gum (1.1 g). This was treated with water (5.0 ml) and extracted with dichloromethane to give a gum (0.94 g) which was triturated with ether–methanol to afford ethyl 2-(1-ethyl-2-methyl-4-phenylacetamido-1*H*-imidazol-5-yl)-2-oxoethanoate **21** (0.16 g, 24%), mp 123–124 °C, identified by comparison with a sample prepared previously.

1-Ethyl-7-hydroxy-2-methyl-6-phenyl-1,4,5,8-tetrahydroimidazo[4,5-*b*]azepine-5,8-dione 22

A solution of the phenylacetamide **21** (0.69 g, 0.002 mol) in anhydrous ethanol (5.0 ml) was treated with a solution of sodium (0.18 g, 0.008 mol) in anhydrous ethanol (5.0 ml) and the yellow mixture was heated under reflux for 1 h.

The mixture was evaporated and the residue was dissolved in water (5.0 ml) and the solution neutralised with 2 M aqueous hydrochloric acid and sodium acetate to precipitate a colourless solid which was collected to give *1-ethyl-7-hydroxy-2-methyl-6-phenyl-1,4,5,8-tetrahydroimidazo[4,5-*b*]azepine-5,8-dione* **22** (0.57 g, 86%) as a colourless powder, mp 206–207 °C (from glacial acetic acid) (Found: C, 58.7; H, 5.6; N, 12.3%, *m*/*z* (HRMS) 297.1115 (M^+), $C_{16}H_{15}N_3O_3$ requires: C, 57.7; H, 5.8; N, 12.6%; M, 297.1113); ν_{max}/cm^{-1} 3500–2200 br (NH, OH) and 1725 (CO); δ_H [$(CD_3)_2SO$] 7.33 (5H, s, ArH), 4.07 (2H, q, *J* 7, CH_2), 2.50 (3H, s, CH_3), 1.91 (1H, s, H-6) and 1.24 (3H, q, *J* 7, CH_3).

Acknowledgements

This work was supported by the Science and Engineering Research Council. G. W. W. thanks Glaxo Group Research (Ware) for a CASE award.

References

1 (*a*) G. Cristalli, S. Vittori, A. Eleuteri, R. Volpini, E. Camaioni, G. Lupidi, N. Mahmood, F. Bevilacqua and G. Palu, *J. Med. Chem.*, 1995, **38**, 4019; (*b*) G. Cristalli, A. Eleuteri, S. Vittori, R. Volpini, M. J. Lohse and K.-N. Kotz, *J. Med. Chem.*, 1992, **35**, 2363; (*c*) G. Cristalli, P. Franchetti, M. Grifantini, S. Vittori, T. Bordoni and C. Geroni *J. Med. Chem.*, 1987, **30**, 1686; (*d*) G. Cristalli, P. Franchetti, M, Grifantini, S. Vittori, K.-N. Klotz and M. J. Lohse, *J. Med. Chem.*, 1988, **31**, 1179.

2 G. Tennant, C. J. Wallis and G. W. Weaver, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 629.

3 For a discussion of various synthetic approaches to imidazo[4,5-*b*]-pyridine derivatives see: (*a*) J. A. Montgomory and J. A. Secrist, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 5, section 4.10.4.3; (*b*) P. C. Srivastava, R. K. Robins and R. B. Myer, in *Chemistry of Nucleosides and Nucleotides*, ed. L. B. Townsend, vol. 1, ch. 2, Plenum Press, New York, 1988.

4 F. Perandones and J. L. Soto, *J. Heterocycl. Chem.*, 1997, **34**, 107.

5 G. Tennant, C. J. Wallis and G. W. Weaver, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 817.

6 (*a*) F. L. Merchan, P. Merino and T. Tomas, *Tetrahedron Lett.*, 1995, **38**, 6949; (*b*) E. V. Dehmlow and E. Kunesch, *Liebigs Ann. Chem.*, 1985, 1904.

7 G. Tennant, *J. Chem. Soc.*, 1963, 2428.

8 D. Macleod and G. R. Proctor, *J. Chem. Res.* (*S*), 1990, 88.

9 H. Schaefer, K. Gewald and M. Seifert, *J. Prakt. Chem.*, 1976, **318**, 39.

Paper 8/08294D