Synthesis of the first examples of the imidazo[4,5-*c*]isoxazole ring system

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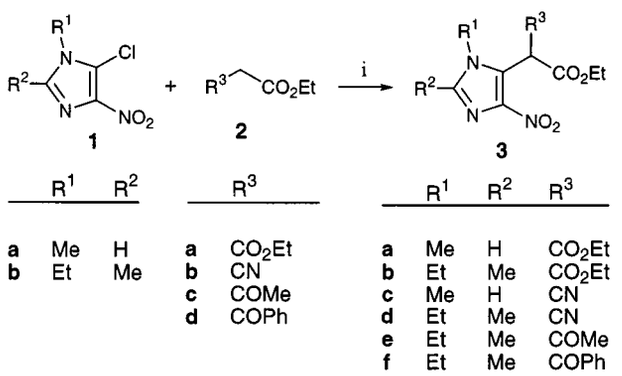
The synthesis of the first examples of the 4*H*-imidazo[4,5-*c*]isoxazole ring system are reported. These compounds are obtained in good yield by thermolysis of 2-(4-nitro-1*H*-imidazol-5-yl) acetate and malonate derivatives, in turn readily available from reaction of 5-chloro-4-nitro-1*H*-imidazoles with active methylene compounds. The X-ray crystal structure of an imidazo[4,5-*c*][1,2]oxazine derived from a proposed intermediate has been obtained and a mechanism for the reaction is discussed.

Introduction

As part of an investigation into the synthesis of imidazo[4,5-*b*]-pyridinones[1] as potential adenosine receptor antagonists,[2] we have investigated the displacement of chloride from substituted 5-chloro-4-nitroimidazoles[3] **1** (Scheme 1) by stabilised carb-



	R^1	R^2
a	Me	H
b	Et	Me

	R^3
a	CO_2Et
b	CN
c	COMe
d	COPh

	R^1	R^2	R^3
a	Me	H	CO_2Et
b	Et	Me	CO_2Et
c	Me	H	CN
d	Et	Me	CN
e	Et	Me	COMe
f	Et	Me	COPh

Scheme 1 *Reagents and conditions:* i, NaH, DMF, 100 °C.

anions derived from active methylene compounds **2** to generate synthetically useful, side chain functionalised imidazole derivatives **3**. On studying the reactivity of these compounds we found that heating in toluene or xylene led to their smooth conversion into imidazo[4,5-*c*]isoxazole derivatives **4** in high yield (Scheme 2). We believe these products to be the first examples of the 4*H*-imidazo[4,5-*c*]isoxazole ring system shown below. We further show that these compounds can undergo ring opening of either the isoxazole ring or the imidazole ring to generate 4-amino-5-acylimidazoles **22** and 3,4-diaminoisoxazoles **25** (Scheme 7) which are useful intermediates for the construction of other heterocycles.

Results and discussion

Our initial investigation involved studying the reaction of the chloronitroimidazole **1b** with diethyl malonate. The nitroimidazoles **1** are readily prepared by nitration[4] of substituted 5-chloro-1*H*-imidazoles available[5] from dialkyl oxamides. On treating **1b** with the anion of diethyl malonate generated by reaction with sodium hydride in DMF at room temperature, a bright orange solution was formed from which the 4-nitroimidazol-5-yl malonate ester **3b** was isolated in low yield after evaporation of the solvent and acidification. This was accompanied by recovered chloroimidazole **1b** and it was found that the yield of product **3b** could be substantially increased by employing two equivalents of sodiomalonate and heating the reaction mixture at 100 °C for 1 h. Thus the malonate derivative **3b** was now isolated in 88% yield. Using two equivalents of sodium hydride and one of diethyl malonate was not as successful in avoiding quenching of the malonate ion by the more acidic product. The 1-methyl-5-chloro-4-nitroimidazole **1a** reacted similarly with diethyl sodiomalonate in DMF to afford the known[6] diester **3a** in 92% yield. This compound has previously been prepared by reaction of **1a** with diethyl malonate in ethanol in the presence of sodium ethoxide. The reaction was then successfully extended to a range of other active methylene compounds shown in Scheme 1. Both cyano- and keto-esters reacted smoothly to afford adducts **3c**–**f** and chloride could also be displaced by phenylacetate and 4-nitrophenylacetate anions to give **13a** and **13b** (see Scheme 5). The yields of these compounds are given in Table 1.

Table 1 4-Nitroimidazol-5-yl carbonyl compounds **3a**–**f** and **13a**–**b** prepared from **1a**–**b**

	R^1	R^2	R^3	Yield (%)
3a	Me	H	CO_2Et	92
3b	Et	Me	CO_2Et	88
3c	Me	H	CN	59
3d	Et	Me	CN	91
3e	Et	Me	COMe	53
3f	Et	Me	COPh	17
13a	Et	Me	Ph	89
13b	Et	Me	$4\text{-}O_2NC_6H_4$	84

As part of a study into the chemistry of the substituted imidazoles **3**, we investigated their behaviour towards thermolysis and were pleased to find that the compounds were converted in good to excellent yield into imidazo[4,5-*c*]isoxazoles **4** (Scheme 2) on heating in toluene or xylene. Thus heating the malonate derivative **3b** in refluxing toluene led to complete consumption of starting material and formation of **4b** in 92% yield after heating for 23 h. Likewise the other substituted imidazoles reacted smoothly to give imidazo[4,5-*c*]isoxazoles **4** as the major products. Toluene was found to be the best solvent although dioxane could be employed effectively and the higher boiling xylene was preferred for large scale reactions to avoid

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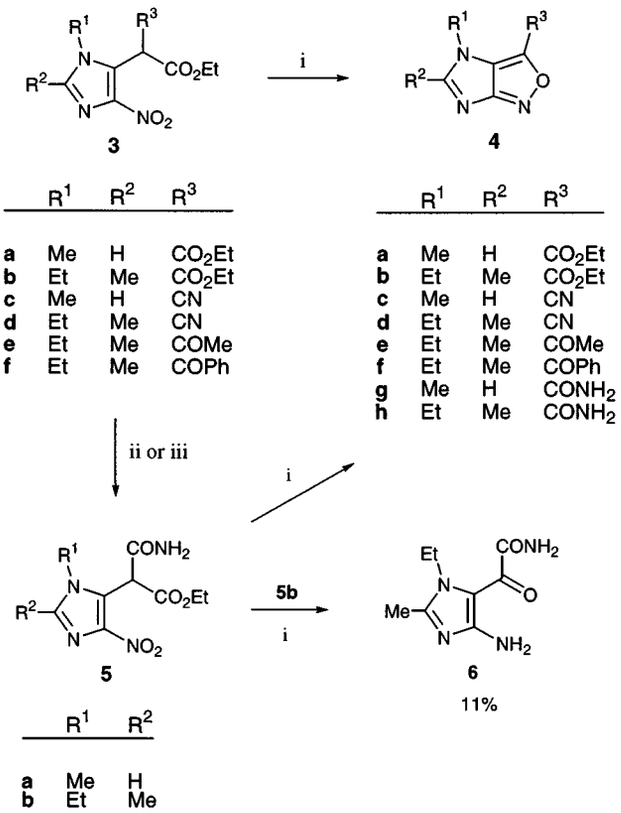


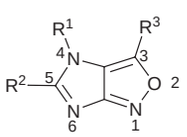
	R^1	R^2	R^3
a	Me	H	CO_2Et
b	Et	Me	CO_2Et
c	Me	H	CN
d	Et	Me	CN
e	Et	Me	COMe
f	Et	Me	COPh

	R^1	R^2	R^3
a	Me	H	CO_2Et
b	Et	Me	CO_2Et
c	Me	H	CN
d	Et	Me	CN
e	Et	Me	COMe
f	Et	Me	COPh
g	Me	H	$CONH_2$
h	Et	Me	$CONH_2$

	R^1	R^2
a	Me	H
b	Et	Me

Scheme 2 *Reagents and conditions:* i, toluene or xylene, reflux; ii, P_2O_5, H_3PO_4, 80 °C; iii, conc. H_2SO_4, room temp.

Table 2 Imidazo[4,5-*c*]isoxazoles **4a**–**f** and **14** prepared



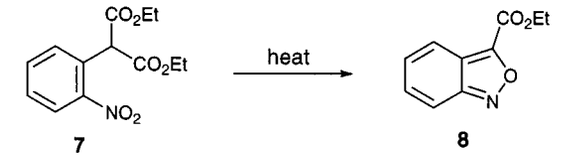
The imidazo[4,5-*c*]isoxazole ring system with numbering

	R^1	R^2	R^3	Yield (%)
4a	Me	H	CO_2Et	70
4b	Et	Me	CO_2Et	92
4e	Et	Me	COMe	94
4f	Et	Me	COPh	88
4h	Et	Me	$CONH_2$	51[a]
14b	Et	Me	4-$O_2NCH_6H_4$	48[b]

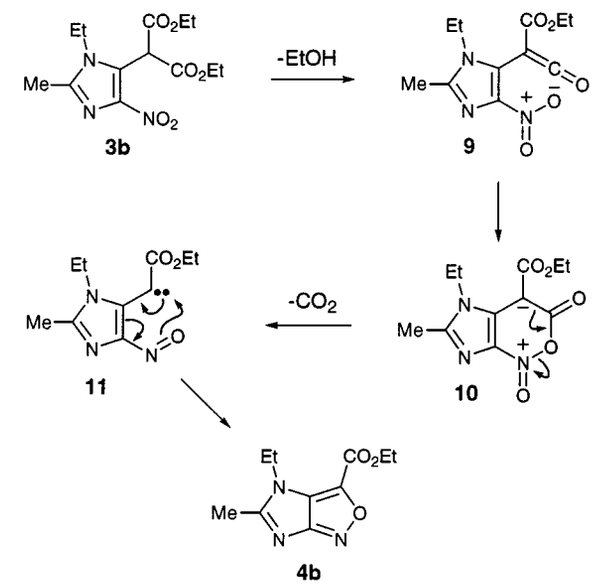
[a] Accompanied by a 22% yield of **4b**. [b] 41% starting material **13b** recovered.

excessively long heating times. Thus 3-substituted imidazo-[4,5-*c*]isoxazoles bearing ester, keto and amide groups can be efficiently prepared by this method. Yields are reported in Table 2. Attempts to prepare the 3-cyano derivatives **4c** and **4d** were unsuccessful with extensive decomposition of the substrates occurring. The structures of the imidazo[4,5-*c*]isoxazoles **4** were assigned on the basis of their analytical and spectroscopic properties and by their chemical conversion into both 4-amino-5-ethoxalyl-1*H*-imidazoles **22** and 3,4-diaminoisoxazole derivatives **23**–**26** (see Scheme 7). The ester groups in **4a** and **4b** could be hydrolysed under alkaline conditions to the corresponding carboxylic acids but attempts to decarboxylate these compounds to give 3-unsubstituted imidazo[4,5-*c*]isoxazoles were unsuccessful.

We believe the cyclisation reaction involves participation[7] of the 4-nitro substituent, as shown in the work[8] of Grob and Weissbach who demonstrated that benzisoxazole **8** (Scheme 3) is



Scheme 3

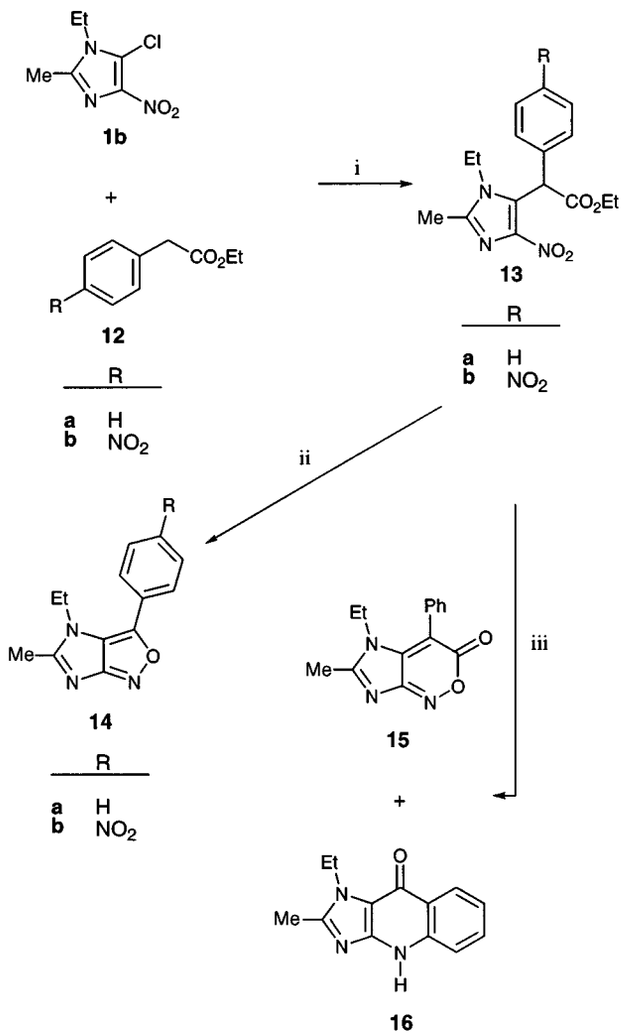


Scheme 4

formed by thermolysis of 2-(2-nitrophenyl) malonate derivative **7**. More recently Duffy and Tennant[9] have extended this reaction and prepared isoxazolo[3,4-*b*]pyridines and isoxazolo-[3,4-*d*]pyrimidines by employing molecular sieves to displace the reaction equilibrium in favour of the isoxazole product. Our proposed mechanism[10] for this transformation is outlined in Scheme 4 for the malonate derivative **3b** and follows a similar course to that described for the formation of six-membered ring fused isoxazoles.[9] Elimination of ethanol is thought to generate a reactive ketene intermediate **9** which undergoes cyclisation by attack of the adjacent nitro group to form an intermediate oxoimidazo[4,5-*c*]-1,2-oxazin-*N*-oxide **10**. Loss of carbon dioxide would then generate a nitroso carbene **11** which could undergo electrocyclic ring closure to form the isoxazole ring of the product.

Evidence for the intermediate oxazine **10** comes from a study of the thermolysis of the 4-nitroimidazol-5-yl(phenyl)acetates **13a** and **13b** (Scheme 5). These compounds were prepared in good yield from the 5-chloro-4-nitroimidazole **1b** and the appropriate phenylacetate **12**. Thermolysis of the 4-nitro-imidazol-5-yl(phenyl)acetate **13a** did not proceed as expected and none of the imidazo[4,5-*c*]isoxazole **14a** could be obtained. The compound **13a** was inert in boiling toluene but thermolysis in hot diglyme led to consumption of the imidazole and two crystalline products were isolated in low yield. These were shown to be the imidazo[4,5-*c*][1,2]oxazin-6-one **15** and the imidazo[4,5-*b*]quinolin-9(4*H*)-one **16** and their structures lend support to the reaction mechanism described above (Scheme 4).

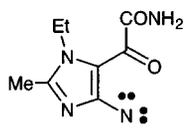
The imidazo[4,5-*c*][1,2]oxazin-6-one **15** which was isolated in 14% yield is thought to arise from reduction of the putative *N*-oxide **19** (Scheme 6) although the exact nature of this transformation is not clear. The structure of this compound was assigned on the basis of its analytical and spectroscopic properties and was firmly established by X-ray crystallography as shown in Fig. 1. This compound is to the best of our knowledge the first example of an imidazo[4,5-*c*][1,2]oxazine. The X-ray structure shows the almost planar nature of the oxazinone ring



Scheme 5 *Reagents and conditions:* i, NaH, DMF, 100 °C; ii, toluene or xylene, reflux; iii, diglyme, heat.

with the 7-phenyl substituent twisted out of the plane by 69°; the torsion angle for N4–O5–C6–C7 is only 1.7°. Key bond lengths in the oxazine ring are 1.422 ± 5 Å for the N4–O5 bond and 1.382 ± 6 Å for the O5–C6 bond, while the carbonyl bond is short at 1.205 ± 7 Å. The second product isolated in 4% yield was identified as the imidazo[4,5-*b*]quinolin-9(4*H*)-one **16**. This is believed to arise from decomposition of the imidazo-[4,5-*c*]isoxazoles **14a** as shown in Scheme 6. Under the more forcing reaction conditions needed to induce reaction of **13a**, the initially formed imidazo[4,5-*c*]isoxazoles **14a** can decompose by opening of the strained isoxazole ring to generate a nitrene **21** which can then insert into the benzene ring to produce the fused pyridinone **16**. The process (**14a**→**21**) finds analogy in the known[11] thermal rearrangement of 3-aryl-2,1-benzisoxazoles to acridones. The higher temperature required to initiate reaction of **13a** may be associated with the lower acidity of the methine C–H in this compound and the consequent reluctance of the compound to eliminate ethanol. To test this hypothesis we investigated the behaviour of the corresponding 4-nitrophenylacetate derivative **13b**. This compound did undergo slow conversion to the expected imidazo[4,5-*c*]isoxazole **14b** on heating in toluene suggesting that the acidity of the methine proton is crucial to successful cyclisation. The imidazoisoxazole **14b** was isolated in 48% yield together with a 41% recovery of the starting ester **13b** after heating for 80 h.

Thermolysis of the imidazolyl acetamide derivative **5b** (Scheme 2) was expected to follow a similar course and lead to imidazoisoxazole **4h**. This compound was formed in 51% yield after heating in toluene but was accompanied by the corresponding ester **4b** (22%) demonstrating that loss of ammonia to generate the ketene intermediate **9** is a competing reaction pathway. Also formed in 11% was the keto amide **6**. By analogy with the process (Scheme 6) suggested for the formation of the imidazoquinolinone **16**, the keto amide **6** may be the result of hydrogen abstraction by the nitrene intermediate (shown below) derived by thermal ring-opening of the imidazoisoxazole carboxamide **4h**. This idea is supported by the observation that heating the imidazoisoxazole **4b** at high temperature in diglyme afforded the ring opened product **22b** (Scheme 7) in moderate yield (63%) as the sole identifiable product.

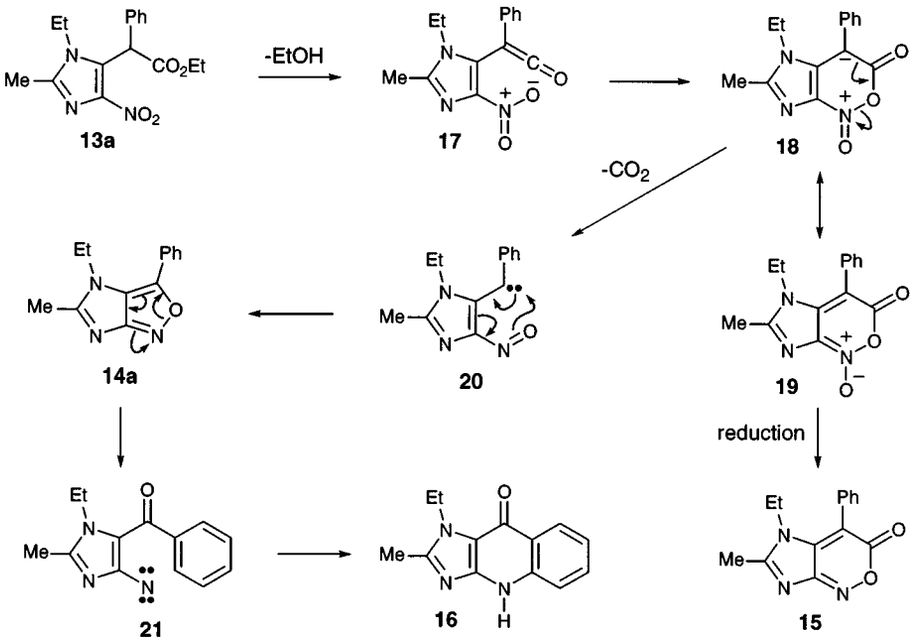


The strained nature of the imidazo[4,5-*c*]isoxazole ring system was demonstrated by the easy reductive opening of the isoxazoles **4** (Scheme 7). Hydrogenation over Pd–C led to rapid conversion to the yellow 4-amino-5-acyl imidazoles **22a** and **22b** in essentially quantitative yield. More surprising was the discovery that the imidazole ring in these compounds could be hydrolytically opened under relatively mild acidic conditions to give the 3,4-diaminoisoxazoles **25a** and **25b** in 66 and 71% yields respectively. Depending on the reaction conditions the intermediate amides **23** and **24** could also be isolated but hydrolysis was usually complete after heating in 2 M hydrochloric acid for only 1 h. The carboxylic acid **26** was also isolated in 12% yield in a large scale experiment employing **4b**. That these compounds could not be ring closed back to the imidazo[4,5-*c*]isoxazoles **4** under a variety of dehydrating conditions and that the N–O bond in the isoxazole **25** could not be reductively cleaved indicates the strain present in the imidazo[4,5-*c*]isoxazole ring system and shows the potential of the imidazoisoxazoles **4** to undergo further synthetically useful reactions. The use of the amino acyl imidazoles **22** and the diaminoisoxazoles **25** as building blocks for the construction of other heterocycles will be described elsewhere.

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. X-ray diffraction data were collected using a Stoe-Stadi-4 four circle diffractometer. 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. 5-Chloro-1-methyl-4-nitroimidazole **1a** and 5-chloro-1-ethyl-2-methyl-4-nitroimidazole **1b** were prepared according to literature methods.[4,5] Sodium hydride was used as a 60% dispersion in mineral oil and was washed with light petroleum, bp 40–60 °C before use. Solvents were of technical grade unless otherwise stated. Dimethylformamide was purified by distillation and stored over molecular sieves. 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.



Scheme 6

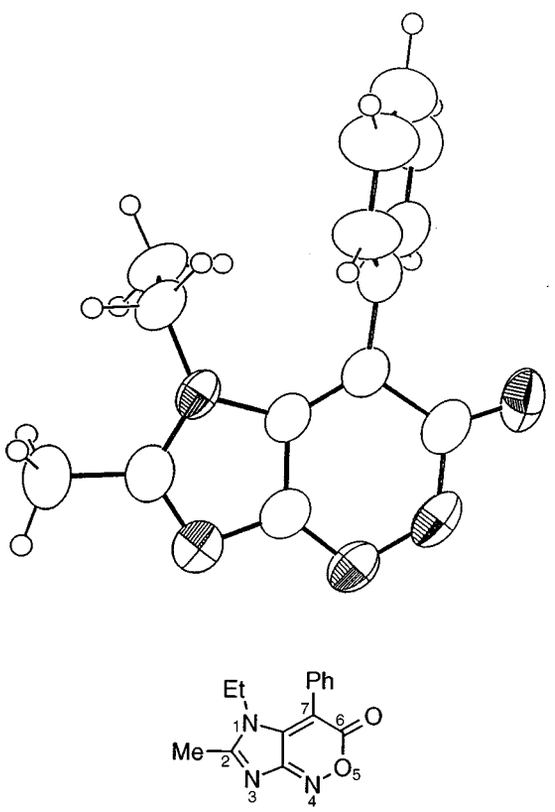
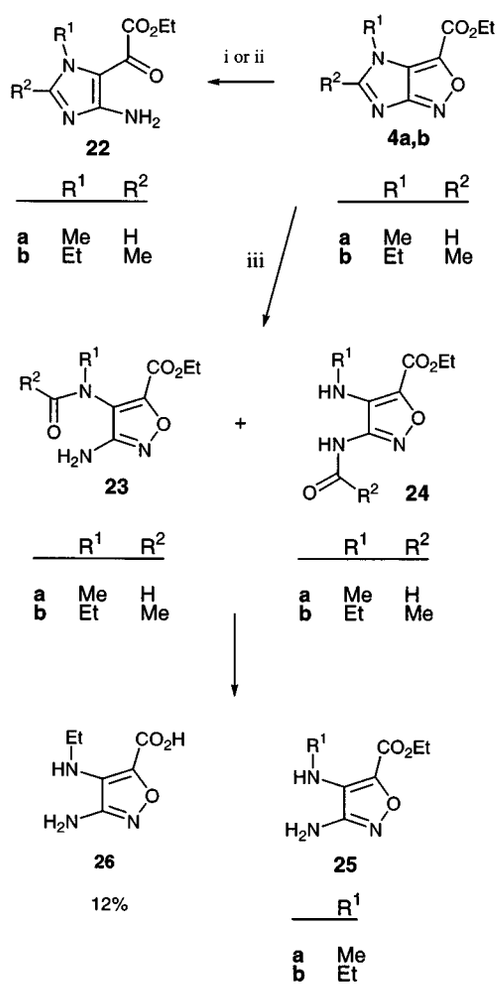


Fig. 1 X-ray crystal structure of imidazo[4,5-*c*][1,2]oxazine **15**.



Scheme 7 *Reagents and conditions:* i, H_2, 10% Pd–C, EtOH; ii, diglyme, heat; iii, HCl(aq.), EtOH, heat.

Diethyl 2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)propane-1,3-dioate 3a

A suspension of sodium hydride (2.1 g, 0.088 mol) in anhydrous DMF (40 ml) was stirred and treated dropwise at room temperature with a solution of diethyl malonate (14.1 g, 0.088 mol) in anhydrous DMF (20 ml). After 10 min, when gas evolution had ceased, the mixture was treated dropwise with a solution of the chloronitroimidazole **1a** (6.6 g, 0.04 mol) in anhydrous DMF (40 ml). The mixture turned orange and was stirred and heated at 100 °C for 1 h.

The mixture was evaporated and the residue was treated with water (10 ml) and dichloromethane (30 ml) and filtered to afford an orange solid (11.6 g), mp 295–296 °C (decomp.); ν_{max} 3700–2700 br and 1600 cm^{-1}. The solid was treated with 2 M aqueous hydrochloric acid (20 ml) and the resulting suspension was extracted with dichloromethane to give an oil which crys-

tallised to afford the *imidazole ester* **3a** (10.5 g, 92%) as soft waxy needles, mp 64–65 °C (lit.,[6] 67 °C) (Found: C, 46.4; H, 5.4; N, 14.6%; M^+, 285. $C_{11}H_{15}N_3O_6$ requires: C, 46.3; H, 5.3; N, 14.7%; M, 285); ν_{max}/cm^{-1} 1770 (CO) and 1500 and 1355 (NO_2); δ_H ($CDCl_3$) 7.40 (1H, s, H-2), 6.11 (1H, s, CH), 4.25 (4H, q, *J* 7, CH_2), 3.73 (3H, s, CH_3) and 1.27 (6H, t, *J* 7, CH_3).

Diethyl 2-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)propane-1,3-dioate 3b

(i) A suspension of sodium hydride (0.27 g, 0.011 mol) in anhydrous DMF (5.0 ml) was stirred and treated dropwise at room temperature with a solution of diethyl malonate (1.8 g, 0.011 mol) in anhydrous DMF (2.5 ml). After 10 min gas evolution had ceased and the mixture was treated dropwise with a solution of the chloronitroimidazole **1b** (1.9 g, 0.01 mol) in anhydrous DMF (5.0 ml). The mixture turned orange red in colour and was stirred at room temperature for 14 h.

The mixture was evaporated and the residue was treated with water (10 ml). The resulting red alkaline solution was extracted with dichloromethane to give a brown oil (2.3 g). This was triturated with ether to give unchanged chloronitroimidazole **1b** (0.46 g, 24%), mp 87–89 °C.

The aqueous mother liquor was neutralised with 2 M aqueous hydrochloric acid (2.8 ml) and sodium acetate and extracted with dichloromethane to give an orange oil (1.1 g). Trituration of the oil with ether followed by ether–ethyl acetate gave *diethyl 2-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)propane-1,3-dioate* **3b** (0.71 g, 23%) which formed colourless blades, mp 98–99 °C (from ethyl acetate) (Found: C, 49.7; H, 6.1; N, 13.4%; *m/z* (EIMS) 313 (M^+), $C_{13}H_{19}N_3O_6$ requires: C, 49.8; H, 6.1; N, 13.4%, M, 313); ν_{max}/cm^{-1} 1750 and 1735 (CO) and 1505 and 1315 (NO_2); δ_H ($CDCl_3$) 5.86 (1H, s, CH), 4.24 (2H, q, *J* 7, CH_2), 4.23 (2H, q, *J* 7, CH_2), 3.99 (2H, q, *J* 7, CH_2), 2.44 (3H, s, CH_3), 1.29 (3H, t, *J* 7, CH_3) and 1.26 (6H, t, *J* 7, CH_3).

(ii) Repetition of the reaction as described in (i) but heating the mixture at 100 °C for 1 h increased the yield of the product **3b** to 45% with no unreacted chloronitroimidazole **1b** being recovered.

(iii) Repetition of the reaction as described in (i) but using 2.2 molar equivalents of sodium hydride and 2.2 molar equivalents of diethyl malonate and heating the mixture at 100 °C for 1 h gave, after evaporation of the mixture and treatment with water and dichloromethane, a three phase mixture. Filtration gave an orange solid which was treated with 2 M aqueous hydrochloric acid and extracted with dichloromethane to afford the diester **3b** in an improved yield of 88%.

Ethyl 2-cyano-2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)ethanoate 3c

A suspension of sodium hydride (0.26 g, 0.011 mol) in anhydrous DMF (10 ml) was stirred and treated dropwise at room temperature with a solution of ethyl cyanoacetate (1.2 g, 0.011 mol) in anhydrous DMF (5.0 ml). After 10 min, gas evolution had ceased and the mixture was treated dropwise with a solution of the chloronitroimidazole **1a** (1.6 g, 0.01 mol) in anhydrous DMF (5.0 ml). The mixture turned bright red in colour and was stirred at room temperature for 16 h.

The mixture was evaporated and the residue was treated with water (10 ml) to give an insoluble solid which was collected and combined with further material obtained by extracting the aqueous mother liquor with dichloromethane and triturating the oil obtained on evaporation, with ether to give unchanged chloronitroimidazole **1a** (total 0.36 g, 22%), mp 145–146 °C. The aqueous mother liquor was neutralised with 2 M aqueous hydrochloric acid and sodium acetate and extracted with dichloromethane to give an oil (2.5 g) which was dry column flash-chromatographed over silica.

Elution with dichloromethane–ethyl acetate (2:1) afforded the *nitrile* **3c** (1.2 g, 59%) as a clear orange gum which could not be induced to crystallise (Found: C, 44.8; H, 4.4; N, 23.1%; *m/z* (EIMS) 195. $C_9H_{10}N_4O_4$ requires: C, 45.4; H, 4.2; N, 23.5%, M, 238); ν_{max}/cm^{-1} 2265 (CN), 1750 (CO) and 1510 and 1360 (NO_2); δ_H ($CDCl_3$) 7.53 (1H, s, H-2), 6.20 (1H, s, CH), 4.33 (2H, q, *J* 7, CH_2), 3.84 (3H, s, CH_3) and 1.32 (3H, t, *J* 7, CH_3).

Ethyl 2-cyano-2-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)-ethanoate 3d

(i) A suspension of sodium hydride (0.27 g, 0.011 mol) in anhydrous DMF (5.0 ml) was stirred and treated dropwise with a solution of ethyl cyanoacetate (1.2 g, 0.011 mol) in anhydrous DMF (5.0 ml). Gas evolution occurred and after stirring at room temperature for 10 min the mixture was treated dropwise with stirring with a solution of the chloronitroimidazole **1b** (1.9 g, 0.01 mol) in anhydrous DMF (5.0 ml). The mixture turned bright orange in colour and was stirred at room temperature for 15 h.

The mixture was evaporated and the residue was treated with water (10 ml) and filtered to afford unchanged starting material **1b** (0.20 g, 10%), mp 79–84 °C.

The alkaline aqueous mother liquor was extracted with dichloromethane and then acidified with concentrated hydrochloric acid. This discharged the red colour and precipitated an oil which solidified on rubbing. The solid was collected and combined with further material obtained by extracting the aqueous phase with dichloromethane and triturating the resulting oil with ether–methanol to give the *imidazole* **3d** (total 1.5 g, 55%) which formed colourless blades, mp 139–140 °C (from ethyl acetate) (Found: C, 49.4; H, 5.3; N, 21.1%; *m/z* (EIMS) 266 (M^+), $C_{11}H_{14}N_4O_4$ requires: C, 49.6; H, 5.3; N, 21.0%; M, 266); ν_{max}/cm^{-1} 2225 (CN), 1755 (CO) and 1510 and 1310 (NO_2); δ_H ($CDCl_3$) 4.57–4.06 (4H, m, 2 × CH_2), 2.54–2.33 (3H, m, CH_3) and 1.55–1.24 (6H, m, 2 × CH_3).

(ii) Repetition of the reaction as described in (i) but using 2.2 molar equivalents of sodium hydride and 2.2 molar equivalents of ethyl cyanoacetate and heating the mixture at 100 °C for 1 h increased the yield of product **3d** to 91%.

Ethyl 2-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)-3-oxobutanoate 3e

A suspension of sodium hydride (0.26 g, 0.011 mol) in anhydrous DMF (5.0 ml) was stirred and treated dropwise at room temperature with a solution of ethyl acetoacetate (1.4 g, 0.011 mol) in anhydrous DMF (2.5 ml). After 10 min, gas evolution had ceased and the mixture was treated dropwise with a solution of the chloronitroimidazole **1b** (0.95 g, 0.005 mol) in anhydrous DMF (2.5 ml) and then heated at 100 °C for 1 h.

The mixture was evaporated and the residue was treated with water (10 ml) and extracted with dichloromethane. The aqueous layer was neutralised with 2 M aqueous hydrochloric acid and sodium acetate and extracted with dichloromethane to give an orange oil (2.0 g) which was triturated with ether to afford the *ketoester* **3e** (0.74 g, 53%) which formed colourless spars, mp 129–130 °C (from ethyl acetate) (Found: C, 50.9; H, 6.1; N, 15.0%; *m/z* (EIMS) 283 (M^+), $C_{12}H_{17}N_3O_5$ requires: C, 50.9; H, 6.1; N, 14.8%; M, 283); ν_{max}/cm^{-1} 3200–2500 br (OH), 1645 (CO) and 1500 and 1345 (NO_2); δ_H ($CDCl_3$) 13.38 (1H, s, OH) (exch.), 4.16 (2H, q, *J* 7, CH_2), 3.76 (2H, q, *J* 7, CH_2), 2.45 (3H, s, CH_3), 1.83 (3H, d, *J* 0.5, CH_3), 1.23 (3H, t, *J* 7, CH_3) and 1.13 (3H, t, *J* 7, CH_3).

Ethyl 2-(1-ethyl-2-methyl-1*H*-imidazol-5-yl)-3-oxo-3-phenylpropanoate 3f

A suspension of sodium hydride (0.26 g, 0.011 mol) in anhydrous DMF (5.0 ml) was stirred and treated dropwise at room temperature with a solution of ethyl benzoylacetate (2.1

g, 0.011 mol) in anhydrous DMF (2.5 ml). After 10 min, gas evolution had ceased and the mixture was treated dropwise with a solution of the chloronitroimidazole **1b** (0.45 g, 0.005 mol) in anhydrous DMF (2.5 ml). The mixture turned red in colour and was heated at 100 °C for 1 h.

The mixture was evaporated and the residue was treated with water (10 ml) and extracted with dichloromethane. The aqueous layer was neutralised with 2 M aqueous hydrochloric acid and sodium acetate and extracted with dichloromethane to give a brown oil which was flash chromatographed over silica.

Elution with dichloromethane gave a gummy semi-solid (0.47 g) which was triturated with ether to give the *imidazole* **3f** (0.30 g, 17%) which formed colourless spars, mp 129–130 °C (from ethanol) (Found: C, 59.2; H, 5.6; N, 12.4%; *m*/*z* (EIMS) 345 (M^+), $C_{17}H_{19}N_3O_5$ requires: C, 59.1; H, 5.6; N, 12.2%; M, 345); ν_{max}/cm^{-1} 3200–2500 br (OH), 1640 and 1615 (CO) and 1490 and 1330 (NO_2); δ_H ($CDCl_3$) 13.92 (1H, s, OH) (exch.), 7.92–7.22 (5H, m, ArH), 4.28–4.16 (2H, m, CH_2), 3.47 (2H, q, *J* 7, CH_2), 2.34 (3H, s, CH_3), 1.15 (3H, t, *J* 7, CH_3) and 0.98 (3H, t, *J* 7, CH_3); δ_C ($CDCl_3$) 173.9 (quat.), 171.4 (quat.), 144.5 (quat.), 143.2 (quat.), 133.1 (quat.), 131.0 (CH), 128.2 (CH), 127.3 (CH), 126.2 (quat.), 90.4 (quat.), 61.5 (CH_2), 39.1 (CH_2), 14.1 (CH_3), 13.8 (CH_3) and 13.2 (CH_3).

Ethyl 2-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)-2-phenylethanoate 13a

A suspension of sodium hydride (1.1 g, 0.044 mol) in anhydrous DMF (20 ml) was stirred and treated dropwise at room temperature with a solution of ethyl 2-phenylethanoate (7.2 g, 0.0044 mol) in anhydrous DMF (10 ml). After 20 min gas evolution had ceased and the mixture was treated dropwise with a solution of the chloronitroimidazole **1b** (3.8 g, 0.02 mol) in anhydrous DMF (10 ml). The mixture turned blue in colour and was heated at 100 °C for 1 h.

The mixture was evaporated and the residue was treated with water (20 ml). The blue colour was discharged and the precipitated brown solid was collected and washed with ethanol to give the *imidazole ester* **13a** (5.7 g, 89%) as pale brown rectangular spars, mp 172–173 °C (from ethanol) (Found: C, 60.3; H, 6.1; N, 13.2%; *m*/*z* (EIMS) 317 (M^+), $C_{16}H_{19}N_3O_4$ requires: C, 60.6; H, 6.0; N, 13.2%; M, 317); ν_{max}/cm^{-1} 1730 (CO) and 1540 and 1335 (NO_2); δ_H ($CDCl_3$) 7.38–7.14 (5H, m, ArH), 6.08 (1H, s, CH), 4.24 (2H, q, *J* 7, CH_2), 4.11–3.66 (2H, m, CH_2), 2.38 (3H, s, CH_3), 1.33 (3H, t, *J* 7, CH_3) and 0.79 (3H, t, *J* 7, CH_3).

Ethyl 2-(4-nitrophenyl)ethanoate 12b

Ethyl 2-(4-nitrophenyl)ethanoate **12b** was prepared by the esterification of 4-nitrophenylacetic acid with ethanol in the presence of concentrated sulfuric acid under standard conditions, yield 99%, mp 59–60 °C (lit.,[11] 64 °C).

Ethyl 2-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)-2-(4-nitrophenyl)ethanoate 13b

A suspension of sodium hydride (0.26 g, 0.011 mol) in anhydrous DMF (5.0 ml) was stirred and treated dropwise at room temperature with a solution of ethyl 2-(4-nitrophenyl)-ethanoate **12b** (2.3 g, 0.011 mol) in anhydrous DMF (2.5 ml). The mixture turned purple in colour and gas was evolved. After 10 min a solution of the chloronitroimidazole **1b** (0.95 g, 0.01 mol) in anhydrous DMF (2.5 ml) was added dropwise with stirring and the mixture was stirred and heated at 100 °C for 1 h.

The mixture was evaporated and the residue was treated with water (20 ml) and extracted with dichloromethane to give a brown oil (4.3 g) which was triturated with ether to afford the *nitrophenylacetate* **13b** (1.5 g, 84%) which formed colourless rectangular spars of an ethanol solvate, mp 115–117 °C (from ethanol) (Found: C, 52.6; H, 5.9; N, 13.7%; *m*/*z* (EIMS) 362 (M^+), $C_{16}H_{18}N_4O_6$. CH_3CH_2OH requires: C, 52.9; H, 5.9; N, 13.7%; M, 362); ν_{max}/cm^{-1} 3520 (OH), 1740 (CO) and 1535, and 1345 (NO_2); δ_H [$(CD_3)_2SO$] 8.21 (2H, d, *J* 9, ArH), 7.58 (2H, d, *J* 9, ArH), 6.03 (1H, s, CH), 4.32–3.87 (4H, m, 2 × CH_2), 3.49–3.24 (2H, m, CH_2), 2.41 (3H, s, CH_3), 1.07 (3H, t, *J* 7, CH_3), 1.05 (3H, t, *J* 7, CH_3) and 0.97 (3H, t, *J* 7, CH_3).

Ethyl 2-carbamoyl-2-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-ethanoate 5a

The nitrile **3c** (0.87 g, 0.004 mol) was cooled (ice bath) and treated cautiously with 98% w/w aqueous sulfuric acid (2.4 ml). The resulting orange solution was stirred at room temperature for 20 h and then treated with ice (15 g).

The mixture was neutralised with 6 M aqueous sodium hydroxide and glacial acetic acid and extracted with dichloromethane to give a yellow gum (1.0 g) which was triturated with ether to afford the *amide* **5a** (0.82 g, 87%) which formed colourless spars, mp 157–158 °C (from ethanol) (Found: C, 42.3; H, 4.8; N, 22.1%; *m*/*z* (EIMS) 213. $C_9H_{12}N_4O_5$ requires: C, 42.2; H, 4.7; N, 21.9%; M, 256); ν_{max}/cm^{-1} 3330, 3240 and 3185 (NH_2), 1730 and 1695 (CO) and 1510 and 1340 (NO_2); δ_H [$(CD_3)_2SO$] 7.84 (1H, s, H-2), 7.78 (1H, s, NH), 7.57 (1H, s, NH), 5.69 (1H, s, CH), 4.17 (2H, q, *J* 7, CH_2), 3.69 (3H, s, CH_3) and 1.16 (3H, t, *J* 7, CH_3).

Ethyl 2-carbamoyl-2-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)ethanoate 5b

(a) The nitrile **3d** (0.53 g, 0.002 mol) was treated with polyphosphoric acid (14.5 g) and the resulting paste was stirred and heated at 100 °C for 10 min. Water (10 ml) was added and the resulting solution was washed with dichloromethane. The aqueous acidic mother liquor was neutralised with 50% w/w aqueous sodium hydroxide and glacial acetic acid and extracted with dichloromethane to give the *amide* **5b** (0.22 g, 38%) which formed yellow plates, mp 163–164 °C (from ethyl acetate) (Found: C, 46.2; H, 5.7; N, 19.7%; *m*/*z* (EIMS) 284 (M^+), $C_{11}H_{16}N_4O_5$ requires: C, 46.5; H, 5.7; N, 19.7%; M, 284); ν_{max}/cm^{-1} 3340 and 3175 (NH), 1745 and 1705 (CO) and 1505 and 1340 (NO_2); δ_H [$(CD_3)_3SO$] 7.83–7.63 (1H, br s, NH), 7.63–7.50 (1H, br s, NH), 5.54 (1H, s, CH), 4.15 (2H, q, *J* 7, CH_2), 4.09 (2H, q, *J* 7, CH_2), 2.43 (3H, s, CH_3), 1.23 (3H, t, *J* 7, CH_3) and 1.14 (3H, t, *J* 7, CH_3).

(b) The nitroimidazole derivative **3d** (2.7 g, 0.01 mol) was added in portions with stirring to concentrated sulfuric acid (11.0 g) and the resulting orange solution was stirred at room temperature for 16 h.

The mixture was then treated with ice (50 g) and neutralised with 8 M aqueous sodium hydroxide and glacial acetic acid. The precipitated solid was collected and combined with further material obtained by extracting the aqueous mother liquor with dichloromethane and triturating the resulting gum (0.28 g) with ethyl acetate to give **5b** (total 2.7 g, 95%).

Ethyl 4-methyl-4*H*-imidazo[4,5-*c*]isoxazole-3-carboxylate 4a

A solution of the diester **3a** (1.1 g, 0.004 mol) in anhydrous toluene (25 ml) was heated under reflux for 56 h. The mixture was evaporated to give a brown semi-solid (0.79 g). This was triturated with ethyl acetate to afford a solid which was combined with further material obtained by evaporating the ethyl acetate mother liquor and retriturating the residue with ether–ethanol to give the *imidazoisoxazole* **4a** (total 0.55 g, 70%) which formed light brown blades, mp 140–142 °C (from ethanol) (Found: C, 49.2; H, 4.6; N, 21.4%; *m*/*z* (EIMS) 195 (M^+), $C_8H_9N_3O_3$ requires: C, 49.2; H, 4.7; N, 21.4%; M, 195); ν_{max}/cm^{-1} 1730 (CO); δ_H ($CDCl_3$) 7.86 (1H, s, H-5), 4.46 (2H, q, *J* 7, CH_2), 3.89 (3H, s, CH_3) and 1.41 (3H, t, *J* 7, CH_3).

Ethyl 4-ethyl-5-methyl-4*H*-imidazo[4,5-*c*]isoxazole-3-carboxylate 4b

A solution of the diester **3b** (3.1 g, 0.01 mol) in anhydrous toluene (20 ml) was heated under reflux for 23 h. The mixture was evaporated and the residue was triturated with ether–ethyl acetate to give the *imidazoisoxazole* **4b** (2.1 g, 92%) which formed colourless spars, mp 113–114 °C (from ethyl acetate) (Found: C, 53.9; H, 5.9; N, 18.9%; *m*/*z* (EIMS) 223 (M^+), $C_{10}N_{13}N_3O_3$ requires: C, 53.8; H, 5.9; N, 18.8%; M, 223); ν_{max}/cm^{-1} 1725 (CO); δ_H ($CDCl_3$) 4.44 (2H, q, *J* 7, CH_2), 4.20 (2H, q, *J* 7, CH_2), 2.55 (3H, s, CH_3), 1.42 (3H, t, *J* 7, CH_3) and 1.37 (3H, t, *J* 7, CH_3).

3-Acetyl-4-ethyl-5-methyl-4*H*-imidazo[4,5-*c*]isoxazole 4e

A solution of the keto ester **3e** (0.57 g, 0.002 mol) in anhydrous toluene (5.0 ml) was heated under reflux for 23 h. The mixture was evaporated and the residue was triturated with ether–light petroleum (bp 40–60 °C) to give the *imidazo[4,5-c]isoxazole* **4e** (0.37 g, 94%) which formed pale brown needles, mp 116–117 °C (from toluene) (Found: C, 55.7; H, 5.7; N, 21.6%; *m*/*z* (EIMS) 193 (M^+), $C_9H_{11}N_3O_2$ requires: C, 56.0; H, 5.7; N, 21.8%; M, 193); ν_{max}/cm^{-1} 1695 (CO); δ_H ($CDCl_3$) 4.21 (2H, q, *J* 7, CH_2), 2.62 (3H, s, CH_3), 2.53 (3H, s, CH_3) and 1.36 (3H, t, *J* 7, CH_3).

3-Benzoyl-4-ethyl-5-methyl-4*H*-imidazo[4,5-*c*]isoxazole 4f

A solution of the keto ester **3f** (0.35 g, 0.001 mol) in anhydrous toluene (2.5 ml) was heated under reflux for 39 h. The mixture was evaporated and the residue was triturated with ether to give a solid which was combined with further material obtained by evaporating the ethereal washings and triturating the resulting gummy semi-solid with ethanol to give the *imidazo[4,5-c]-isoxazole* **4f** (total 0.22 g, 88%) which formed pale brown needles, mp 106–107 °C (from ethanol) (Found: C, 65.7; H, 5.1; N, 16.4%; *m*/*z* (EIMS) 255 (M^+), $C_{14}H_{13}N_3O_2$ requires: C, 65.9; H, 5.1; N, 16.5%; M, 255); ν_{max}/cm^{-1} 1670 (CO); δ_H ($CDCl_3$) 8.33–8.19 (2H, m, ArH), 7.65–7.43 (3H, m, ArH), 4.34 (2H, q, *J* 7, CH_2), 2.57 (3H, s, CH_3) and 1.38 (3H, t, *J* 7, CH_3).

Thermolysis reactions of ethyl 2-carbamoyl-2-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)ethanoate 5b

A solution of the amide **5b** (0.57 g, 0.002 mol) in toluene (50 ml) was heated under reflux for 24 h. The mixture was evaporated and the residue triturated with ethanol to give the *imidazo[4,5-c]isoxazole-3-carboxamide* **4h** (0.20 g, 51%) which formed colourless plates, mp 193–194 °C (decomp.) (from ethanol) (Found: C, 49.3; H, 5.2; N, 28.9%; *m*/*z* (EIMS) 194 (M^+), $C_8H_{10}N_4O_2$ requires: C, 49.5; H, 5.2; N, 28.9%; M^+, 194); ν_{max}/cm^{-1} 3420, 3330 and 3160 (NH) and 1695 (CO); δ_H [$(CD_3)_2SO$] 8.40–8.05 (1H, br s, NH) (exch.), 8.05–7.75 (1H, br s, NH) (exch.), 4.21 (2H, q, *J* 7, CH_2), 2.52 (3H, s, CH_3) and 1.27 (3H, t, *J* 7, CH_3).

The ethanolic mother liquor was evaporated and the residue was flash chromatograped over silica.

Elution with dichloromethane–ethyl acetate (5:1) yielded *ethyl 4-ethyl-5-methyl-4H-imidazo[4,5-c]isoxazole-3-carboxylate* **4b** (0.10 g, 22%), mp 107–108 °C.

Further elution with ethyl acetate afforded *2-(4-amino-1-ethyl-2-methyl-1H-imidazol-5-yl)-2-oxoethanamide* **6** (0.04 g, 11%) which formed orange plates, mp 202–203 °C (from ethanol) (Found: C, 49.1; H, 6.3; N, 28.5%; *m*/*z* (EIMS) 196 (M^+), $C_8H_{12}N_4O_2$ requires: C, 49.0; H, 6.2; N, 28.6%; M, 196); ν_{max}/cm^{-1} 3480 and 3380 (NH) and 1695, 1690 and 1660 (CO); δ_H [$(CD_3)_2SO$] 8.25–7.93 (1H, br s, NH), 7.93–7.63 (1H, br s, NH), 7.25–7.00 (2H, br s, NH_2) (exch.), 4.14 (2H, q, *J* 7, CH_2), 2.23 (3H, s, CH_3) and 1.15 (3H, t, *J* 7, CH_3).

Thermolysis of ethyl 2-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)-2-phenylethanoate 13a in diglyme

A solution of ethyl 2-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)-2-phenylethanoate **13a** (0.64 g, 0.002 mol) in anhydrous diglyme (10 ml) was heated at 150 °C for 18 h. The mixture was evaporated and the residue triturated with ethyl acetate to give a colourless solid which was flash chromatographed over silica. Elution with dichloromethane–ethyl acetate (5:1) afforded *1-ethyl-2-methyl-7-phenyl-1H-imidazo[4,5-c][1,2]oxazin-6-one* **15** (0.06 g, 14%) which formed yellow needles, mp 233–234 °C (from ethanol) (Found: C, 65.6; H, 5.1; N, 16.3; *m*/*z* (EIMS) 255 (M^+), $C_{14}H_{13}N_3O_2$ requires C, 65.9; H, 5.1; N, 16.5%; M, 255); ν_{max}/cm^{-1} 1700 (CO) and 1660 (C=N); δ_H [$(CD_3)_2SO$] 7.49 (5H, s, ArH), 3.46 (2H, q, *J* 7, CH_2), 2.49 (3H, s, CH_3) and 0.76 (3H, t, *J* 7, CH_3).

Evaporation of the mother liquor and further trituration with ethyl acetate gave *1-ethyl-2-methyl-1H-imidazo[4,5-b]-quinolin-9(4H)-one* **16** (0.02 g, 4%) as pale orange needles, mp 279 °C (sublimes) (Found: C, 68.6; H, 5.8; N, 18.1; *m*/*z* (EIMS) 227 (M^+), $C_{13}H_{13}N_3O$ requires C, 68.7; H, 5.9; N, 18.5%; M, 227); ν_{max}/cm^{-1} 3200–2500 br (NH, OH) and 1635 (CO); δ_H [$(CD_3)_2SO$] 12.13 (1H, s, NH) (exch.), 8.28–8.17 (1H, m, ArH), 7.71–7.47 (2H, m, ArH), 7.31–7.10 (1H, m, ArH), 4.48 (2H, q, *J* 7, CH_2), 2.49 (3H, s, CH_3) and 1.35 (3H, t, *J* 7, CH_3).

4-Ethyl-5-methyl-3-(4-nitrophenyl)-4*H*-imidazo[4,5-*c*]isoxazole 14b

A solution of the ester **13b** (0.73 g, 0.002 mol) in anhydrous toluene (10 ml) was heated under reflux for 80 h. On cooling a solid crystallised from the mixture and was collected by filtration to give *4-ethyl-5-methyl-3-(4-nitrophenyl)-4H-imidazo-[4,5-c]isoxazole* **14b** (0.26 g, 48%) as yellow needles, mp 224–225 °C (from glacial acetic acid) (Found: C, 57.8; H, 4.5; N, 20.6%; *m*/*z* (EIMS) 255 ($M^+ - OH$), $C_{13}H_{12}N_4O_3$ requires: C, 57.4; H, 4.4; N, 20.6%; M, 272); ν_{max}/cm^{-1} 1510 and 1340 (NO_2); δ_H [$(CD_3)_2SO$] 8.40 (2H, d, *J* 9, ArH), 8.00 (2H, d, *J* 9, ArH), 4.26 (2H, q, *J* 7, CH_2), 2.57 (3H, s, CH_3) and 1.22 (3H, t, *J* 7, CH_3).

Evaporation of the toluene filtrate gave a gummy orange solid which was triturated with ether to give unchanged starting material **13b** (0.30 g, 41%), mp 114–115 °C.

Ethyl 2-(4-amino-1-methyl-1*H*-imidazol-5-yl)-2-oxoethanoate 22a

A solution of the imidazo[4,5-*c*]isoxazole **4a** (0.78 g, 0.004 mol) in ethanol (125 ml) was hydrogenated over 5% palladium on charcoal (0.56 g) at room temperature for 2.5 h.

The mixture was filtered through Celite and the filtrate evaporated to give the *amino keto ester* **22a** (0.78 g, 99%) which formed yellow spars, mp 97–98 °C (from ethanol) (Found: C, 48.4; H, 5.5; N, 21.3%; *m*/*z* (EIMS) 197 (M^+), $C_8H_{11}N_3O_3$ requires: C, 48.7; H, 5.6; N, 21.3%; M, 197); ν_{max}/cm^{-1} 3420, 3280 and 3120 (NH), and 1730 (CO); δ_H [$(CD_3)_2SO$] 7.61 (1H, s, H-2), 6.72 (2H, br s, NH_2) (exch.), 4.33 (2H, q, *J* 7, CH_2), 3.56 (3H, s, CH_3) and 1.30 (3H, t, *J* 7, CH_3).

Ethyl 2-(4-amino-1-ethyl-2-methyl-1*H*-imidazol-5-yl)-2-oxoethanoate 22b

A solution of the imidazo[4,5-*c*]isoxazole **4b** (5.6 g, 0.025 mol) in ethanol (400 ml) was hydrogenated over 5% palladium on charcoal (0.56 g) at room temperature for 2 h.

The mixture was filtered through Celite and the filtrate evaporated to give the *amino keto ester* **22b** (5.6 g, 99%) which formed yellow spars, mp 135–136 °C (from ethyl acetate) (Found: C, 53.5; H, 6.8; N, 18.6%; *m*/*z* (EIMS) 225 (M^+), $C_{10}H_{15}N_3O_3$ requires: C, 53.3; H, 6.7; N, 18.7%; M, 225); ν_{max}/cm^{-1} 3410 and 3300 (NH), and 1735 and 1630 (CO); δ_H ($CDCl_3$)

6.95–6.50 (2H, br s, NH_2) (exch.), 4.34 (2H, q, *J* 7, CH_2), 4.07 (2H, q, *J* 7, CH_2), 2.37 (3H, s, CH_3), 1.40 (3H, t, *J* 7, CH_3) and 1.30 (3H, t, *J* 7, CH_3).

The thermal ring opening of ethyl 4-ethyl-5-methyl-4*H*-imidazo[4,5-*c*]isoxazole-3-carboxylate 4b

A solution of ethyl 4-ethyl-5-methyl-4*H*-imidazo[4,5-*c*]isoxazole-3-carboxylate **4b** (0.45 g, 0.002 mol) in anhydrous diglyme (10 ml) was heated under reflux for 23 h. The mixture was evaporated and the residue flash chromatographed. Elution with ethyl acetate afforded the *amino keto ester* **22b** (0.29 g, 63%), mp 128–130 °C, identified by comparison (IR spectrum) with an authentic sample prepared before.

Ethyl 3-amino-4-(methylamino)isoxazole-5-carboxylate 25a

A solution of the imidazo[4,5-*c*]isoxazole **4a** (0.78 g, 0.004 mol) in ethanol (5.0 ml) and 2 M aqueous hydrochloric acid (5.0 ml) was heated under reflux for 1 h.

The mixture was evaporated, the residue was dissolved in water (2.0 ml) and the solution was neutralised with 2 M aqueous sodium hydroxide and glacial acetic acid. The precipitated pink solid was collected and combined with further material obtained by extracting the aqueous mother liquor with dichloromethane to give the *aminoisoxazole* (**25a**) (total 0.49 g, 66%), which formed pale pink plates, mp 99–100 °C (from ethanol) (Found: C, 45.4; H, 6.1; N, 22.8%, *m*/*z* (EIMS) 185 (M^+), $C_7H_{11}N_3O_3$ requires: C, 45.4; H, 6.0; N, 22.7%, M, 185); ν_{max}/cm^{-1} 3450, 3360, 3320 (NH) and 1680 (CO); δ_H ($CDCl_3$) 4.35 (2H, q, *J* 7, CH_2), 3.99 (2H, s, NH_2) (exch.), 2.93 (3H, s, CH_3) and 1.36 (3H, t, *J* 7, CH_3).

Ethyl 3-amino-4-(ethylamino)isoxazole-5-carboxylate 25b hydrochloride

A solution of the imidazo[4,5-*c*]isoxazole **4b** (0.45 g, 0.002 mol) in ethanol (5.0 ml) was treated with 2 M aqueous hydrochloric acid (5.0 ml) and the mixture was heated under reflux for 1 h.

The mixture was evaporated and the residue co-evaporated with ethanol and then triturated with ether–ethanol to give the *diaminoisoxazole-5-carboxylate* **25a** hydrochloride (0.33 g, 70%) which formed colourless needles, mp 127–130 °C (from ethanol) (Found: C, 41.1; H, 6.1; N, 18.0%; *m*/*z* (EIMS) 199 (M^+ − HCl), $C_8H_{14}ClN_3O_3$ requires: C, 40.8; H, 6.0; N, 17.8%; M, 234.5); ν_{max}/cm^{-1} 3400 and 3305 (NH), 3000–2000 br (NH) and 1720 (CO); δ_H [$(CD_3)_2SO$] 7.52 (4H, s, NH), 4.25 (2H, q, *J* 7, CH_2), 3.22 (2H, q, *J* 7, CH_2), 1.26 (3H, t, *J* 7, CH_3) and 1.11 (3H, t, *J* 7, CH_3).

Evaporation of the ether–ethanol mother liquor gave a gum (0.15 g) which was triturated with ethanol to afford *ethyl 3-amino-4-(N-ethylacetamido)isoxazole-5-carboxylate* **23b** (0.01 g, 2%) which formed colourless spars, mp 208–209 °C (from ethanol) (Found: C, 47.7; H, 6.3; N, 17.4%; *m*/*z* (EIMS) 241 (M^+), $C_{10}H_{15}ClN_3O_4$ requires: C, 47.8; H, 6.3; N, 17.4%; M, 241); ν_{max}/cm^{-1} 3390, 3330 and 3220 (NH), and 1745, 1665 and 1620 (CO); δ_H [$(CD_3)_2SO$] 6.14 (2H, s, NH_2), 4.30 (2H, q, *J* 7, CH_2), 3.78–3.24 (2H, m, CH_2), 1.78 (3H, s, CH_3), 1.25 (3H, t, *J* 7, CH_3) and 0.94 (3H, t, *J* 7, CH_3).

Ethyl 3-amino-4-ethylaminoisoxazole-5-carboxylate 25b

(i) A solution of the imidazo[4,5-*c*]isoxazole **4b** (2.2 g, 0.01 mol) in ethanol (25 ml) was treated with 2 M aqueous hydrochloric acid (25 ml) and the resulting solution was heated under reflux for 1 h.

The mixture was evaporated to give a yellow solid which was treated with 2 M aqueous sodium hydroxide until just alkaline and the mixture then neutralised with glacial acetic acid and filtered to afford *ethyl 3-amino-4-ethylaminoisoxazole-5-carboxylate* **25b** (1.4 g, 71%) which formed colourless spars, mp 74–75 °C (from ethanol) (Found: C, 48.2; H, 6.7; N, 21.2%; *m*/*z* (EIMS) 199 (M^+, 199), $C_8H_{13}N_3O_3$ requires: C, 48.2; H, 6.6; N, 21.1%; M, 199); ν_{max}/cm^{-1} 3330 and 3190 (NH) and 1695 (CO); δ_H ($CDCl_3$) 4.45 (2H, q, *J* 7, CH_2), 4.18–3.58 (3H, br s, NH) (exch.), 3.23 (2H, q, *J* 7, CH_2), 1.37 (3H, t, *J* 7, CH_3) and 1.17 (3H, t, *J* 7, CH_3).

(ii) The reaction described in (i) was repeated on a larger scale (0.02 mol). Evaporation of the mixture gave a yellow solid which was treated with 2 M aqueous sodium hydroxide and then neutralised with glacial acetic acid. The pink solid obtained (3.2 g) was collected and heated under reflux in ethanol. Hot filtration removed an insoluble solid and the ethanolic filtrate was evaporated to give a solid which was combined with further material obtained by extracting the aqueous mother liquor with dichloromethane and triturating the resulting oil with ether–ethanol to give ethyl 3-amino-4-ethylaminoisoxazole-5-carboxylate **25b**, (2.3 g total, 57%), mp 73–75 °C.

The ethanol-insoluble material (0.46 g) was dissolved in hot water and the pH of the solution adjusted to 6 with glacial acetic acid. After cooling, filtration afforded *3-amino-4-ethylaminoisoxazole-5-carboxylic acid* **26** (0.41 g, 12%) which formed pink spars, mp 167–168 °C (from ethanol–water) (Found: C, 41.5; H, 5.3; N, 24.1%, *m*/*z* (HRMS) 171.0641 (M^+), $C_6H_9N_3O_3$ requires: C, 42.1; H, 5.3; N, 24.6%; M, 171.0644); ν_{max}/cm^{-1} 3400–2000 br (OH), 3290 and 3160 (NH), and 1665 and 1630 (CO); δ_H [$(CD_3)_2SO$] 5.75–5.38 (2H, br s, NH) (exch.), 5.38–4.50 (2H, br s, NH and OH), 3.28 (2H, q, *J* 7, CH_2) and 1.05 (3H, t, *J* 7, CH_3).

(iii) Repetition of the reaction described in (i) but using only 2.5 molar equivalents of hydrochloric acid gave a 68% yield of the *diaminoisoxazole* **25b** together with a 2% yield of *ethyl 3-acetylamino-4-ethylaminoisoxazole-5-carboxylate* **24b**, which formed pale pink plates, mp 125–126 °C (from ethanol) (Found: C, 49.8; H, 6.3; N, 17.4%; *m*/*z* (EIMS) 241 (M^+), $C_{10}H_{15}N_3O_4$ requires: C, 49.8; H, 6.3; N, 7.3%; M, 241); ν_{max}/cm^{-1} 3460, 3380, 3340, 3110 and 3070 (NH) and 1710 and 1675 (CO); δ_H [$(CD_3)_2SO$] 10.19 (1H, s, NH) (exch.), 5.24 (1H, t, *J* 6, NH), 4.30 (2H, q, *J* 7, CH_2), 3.28 (2H, dq, *J* 7 and 7, CH_2), 2.07 (3H, s, CH_3), 1.29 (3H, t, *J* 7, CH_3) and 1.05 (3H, t, *J* 7, CH_3).

Crystal structure determination of *imidazo[4,5-c][1,2]oxazin-6-one* 15‡

A lath shaped crystal of compound **15** of dimensions 0.83 × 0.13 × 0.04 mm was mounted on a glass fibre and measured on a Stoe-Stadi-4 four-circle diffractometer using graphite monochromated Cu-Kα radiation (λ = 1.5418 Å). *Crystal data:* $C_{14}H_{13}N_3O_2$, *M* = 255.3, monoclinic, *a* = 12.1835(11), *b* = 6.45.06(5), *c* = 16.8724 Å, β = 105.046(7)°, *U* = 1280.6(2) $Å^3$, space group $P2_1/n$ (No. 14), *Z* = 4, D_x = 1.324 g cm^{-3}. 2491 Reflections were measured at 298 K ($5 \leqslant 2\theta \leqslant 120°$) with 1875 unique (merging *R* = 0.052), of which 971 had $F \geqslant 4\sigma(F)$ and 1875 were used in all calculations. The structure was solved by automatic direct methods (all non-H atoms) using SHELXS-86 and refined by full-matrix least-squares refinement with all non-H atoms anisotropic; hydrogen atoms were located from a Δ*F* synthesis refined riding on their parent atoms. Final *R*[1] [$F \geqslant 4\sigma(F)$] = 0.0564, $\omega R2$ = 0.161, S[*F*2] = 0.942 for 174 parameters. The final Δ*F* synthesis showed no peaks above +0.39 e $Å^3$.

‡ Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/306. See http://www.rsc.org/suppdata/p1/1999/817/ for crystallographic files in .cif format.

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