Pergamon

Tetrahedron, Vol. 53, No. 34, pp. 11781-11790, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00752-7

Alkylation of an Imidazolidine Enaminoester: A New Sequence for the C^{α}-Alkylation of 4,5-Dihydroimidazoles

Raymond C. F. Jones* and Pravin Patel

Chemistry Department, The Open University, Walton Hall, Milton Keynes MK7 6AA, U.K.

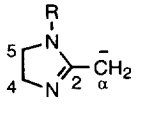
Simon C. Hirst and Ian Turner

Chemistry Department, University of Nottingham, Nottingham, NG7 2RD, U.K.

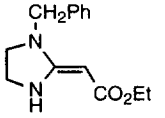
Abstract: 1-Benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole undergoes preferred *C*-alkylation with halogenoalkanes, dihalogenoalkanes and epoxides; subsequent removal of of the ethoxycarbonyl group provides a new route to 2-alkyl-4.5-dihydroimidazoles. 1,3-Dihalogenoalkanes afford imidazo[1,2-*a*]pyridines *via* *C,N*-dialkylation. © 1997 Elsevier Science Ltd.

INTRODUCTION

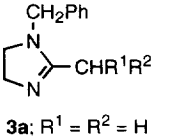
Generation of nucleophilic reactivity at the α-carbon atom (as in **1**) has been an important part of our studies of the 4,5-dihydromidazole (2-imidazoline) heterocycle,[1] a moiety that occurs in a number of pharmacologically active molecules[2] and is involved as N^5, N^{10}-methenyltetrahydrofolate in biological C_1-transfers.[3] As an alternative to lateral metallation of 1-benzyl-2-methyl-4,5-dihydroimidazole **3a** to produce anion **1** directly, we were attracted to the nucleophilic potential of the readily available crystalline enaminoester (heterocyclic ketene aminal) **2**.[1a] We report herein details of the realisation of this objective in *C*-alkylation of enaminoester **2**,[4] and the demonstration of the synthetic equivalence of **2** and anion **1**.[5]



1



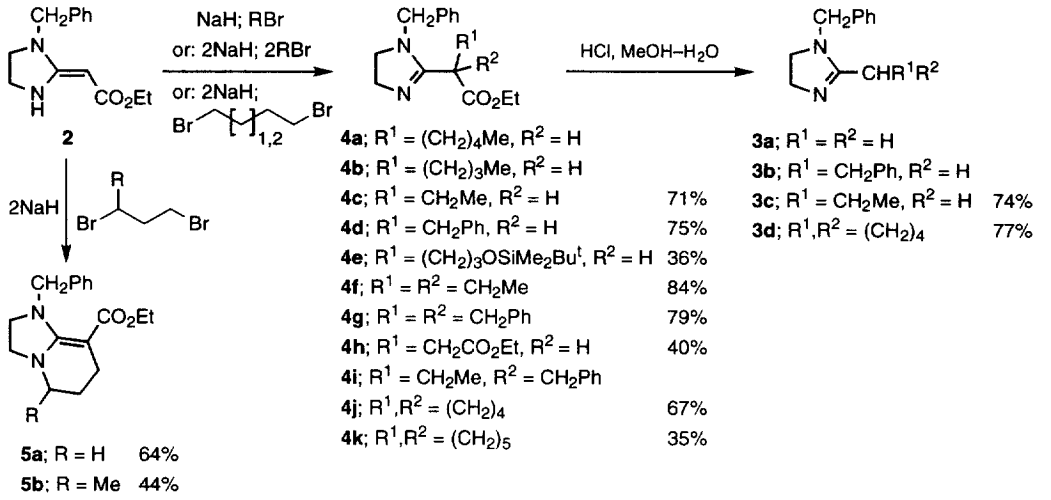
2



3a; $R^1 = R^2 = H$

RESULTS AND DISCUSSION

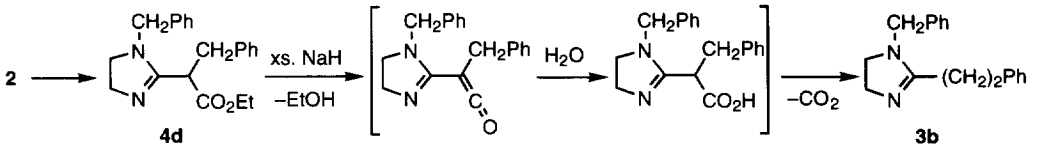
Initial studies were aimed at exploiting the enamine character of **2** that we have reported in conjugate additions.[6] Enaminoester **2** was thus treated with 1-bromopentane (1 mol equiv.) in ethanol [reflux; Et_3N (2 mol equiv.)] for 18 h. The *C*-alkylated material **4a** was indeed produced but in only 38% yield, along with substantial recovery of starting material and some polar material presumed to be quaternised compounds. Heating of **2** with 1-iodobutane in DMF (110°C, 24 h) gave the *C*-butyl dihydroimidazole **4b** in a much



Scheme 1

improved 67% yield with no added base, whereas use of DMSO as solvent at 130°C led to an inseparable mixture. It did not, however, prove possible to generalise the DMF protocol. A more generally useful procedure, that overcame the problem of competing quaternisation, was developed involving the initial stoichiometric deprotonation of enaminoester **2** with sodium hydride (1 mol equiv., THF, 30 min at reflux, or 30 min at 0°C then 1 h at 20°C) before addition of the alkylating agent with carefully controlled stoichiometry (1 mol equiv.) and either heating at reflux for 4 h, or stirring at 20°C overnight. In this way the *C*-alkylated dihydroimidazoles **4c-e** were prepared from iodoethane, benzyl bromide and 3-(*tert*-butyldimethylsilyloxy)-1-bromopropane (Scheme 1). Interestingly, all of the monoalkylated products **4a-e** were found to exist as the illustrated imine tautomer rather than the enamine seen in the starting ketene aminal **2**.[6b] This was supported by an IR absorption at approx. 1735 cm^{-1} (unconjugated ester C=O) and a ^1H NMR signal, typically δ 3.3–3.7, assigned to the α-CH resonance. The symmetrically *C*-dialkylated dihydromidazoles **4f** and **4g** were readily obtained by using enaminoester **2** with 2.5 mol equiv. each of sodium hydride and the haloalkane, iodoethane or benzyl bromide, respectively. The α-haloester, ethyl bromoacetate, with two differentiated electrophilic sites, reacted by *C*-alkylation rather than acylation,[7] to afford **4h** along with some recovered enaminoester **2**.

Attempts to prepare unsymmetrically dialkylated materials **4** ($R^1 \neq R^2 \neq H$) by a second separate *C*-alkylation of the monoalkylated materials, using the same sodium hydride protocol, were not successful. Thus attempted benzylation of *C*-ethyl dihydroimidazole **4c**, or ethylation of the *C*-benzyl compound **4d** led to good recoveries of the starting materials **4c** and **4d**, respectively. A 'one-pot' procedure, involving successive additions to **2** of one mol equiv. sodium hydride, 1 mol equiv. iodethane, a further portion of base and finally 1 mol equiv. of benzyl bromide, led to a multi-component mixture. Alternatively, ketene aminal **2** was treated with 2 mol equiv. sodium hydride followed after 1 h by iodoethane and benzyl bromide together (each 1 mol equiv.), in the expectation of producing a mixture of the two symmetrically dialkylated materials **4f,g** along with the sought-after unsymmetrically dialkylated compound **4i**. On work-up, we were surprised to find the products to be the *C*-benzylated material **3b** (49%), lacking an ethoxycarbonyl group, and recovered starting material **2** (32%). One possible rationale for this finding is shown in Scheme 2. Excess base could promote

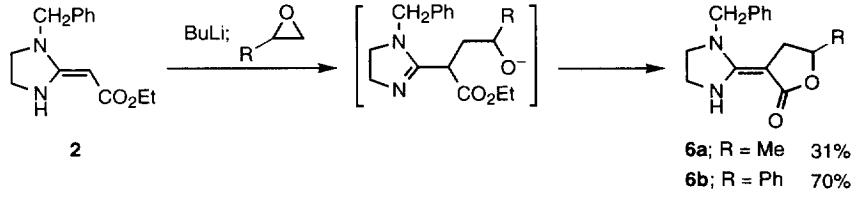


Scheme 2

elimination of ethanol from a monoalkyl intermediate **4d**, and addition of water on work-up, followed by easy decarboxylation of the β-iminoacid formed could afford **3b**. Attempts to further exploit this process were not fruitful; treatment of **2** with 2 mol equiv. sodium hydride and iodoethane (1 mol equiv.) led only to the conventional *C*-ethylation product **4c**. A related dealkoxycarboxylation was, however, observed during the attempted transesterification of enaminoester **2** (KO^{t}Bu, EtOH, 25°C, 7 days), resulting in the quantitative recovery of the 2-methyl-4,5-dihydroimidazole **3a**.

Interesting results were obtained using dihaloalkanes as electrophiles under the standard protocol. Thus enaminoester **2** with sodium hydride (2.2 mol equiv.) followed by 1,4-dibromobutane or 1,5-dibromopentane afforded the cyclic *C*-dialkylated dihydroimidazoles **4j** and **4k**, respectively (Scheme 1). In contrast, the 1,3-dihalides, 1,3-dibromopropane and 1,3-dibromobutane led, *via* *C,N*-dialkylation, to the hexahydroimidazo-[1,2-*a*]pyridines **5a** and **5b**, respectively, the products of six-membered ring annulation. The regiochemistry of **5b** indicates that the initial alkylation (at the primary centre) remains a *C*-alkylation. Under the same conditions 1,2-dibromoethane gave only recovered starting material **2**.

The use of epoxides as electrophiles was briefly examined. Attempts to open methyloxirane by direct attack of **2** in acetonitrile at reflux, with or without addition of boron trifluoride etherate as Lewis-acid catalyst, led only to recovered starting materials. The sodium hydride deprotonation protocol was similarly unproductive. In contrast, reaction of ketene aminal **2** with methyloxirane in the presence of base [BuLi (1 mol equiv.), THF 0°C → reflux, 2 h] did give *C*-alkylation, which was followed by *in situ* transesterification to produce the lactone **6a** (Scheme 3).[8] A similar reaction with phenyloxirane (using LiNPr$^i_2$ as base) led to lactone **6b** in better yield. The illustrated regiochemistry and tautomerism of lactones **6** is supported by signals for CHO and NH in the ^{1}H and ^{13}C NMR spectra, and for NH in the IR spectra. Attack has taken place in each case at the least hindered epoxide carbon atom.



Scheme 3

The equivalence of the enaminester **2** to the α-deprotonated dihydroimidazole **1**, was confirmed by removal of the ethoxycarbonyl group from some of the alkylation products **4**. Thus, hydrolysis and decarboxylation of the monoethyl compound **4c** (approx. 3% HCl in methanol–water, reflux, 3 d) afforded the 2-propyl-4,5-dihydroimidazole **3c** in good yield (Scheme 1). More vigorous conditions (2M aq. HCl, reflux 10 d) were required for an α,α-dialkylated derivative, to prepare 2-cyclopentyl-4,5-dihydroimidazole **3d** from **4j**. Cyclic compounds of this type are not accessible by the lateral metallation route.[1b]

We have therefore demonstrated the successful *C*-alkylation of enaminoester **2** and its use as an alternative route to α-alkylated 4,5-dihydroimidazoles (and hence potentially to alkanoic acids[1b] and to ketones[9]), and in a simple new route to imidazo[1,2-*a*]pyridines.[10]

EXPERIMENTAL

General: Melting points were measured on a Kofler hot-stage and are uncorrected. IR spectra were recorded on Perkin-Elmer 1600, Pye-Unicam SP3-100 or Philips PU 9706 spectrometers, in chloroform unless otherwise stated. ^{1}H NMR spectra were recorded in deuteriochloroform (TMS as internal standard) at 90 MHz using a Perkin-Elmer R32 spectrometer, unless otherwise stated; spectra at 250 MHz and 400 MHz were determined using Bruker WM250 and JEOL EX400 spectrometers, respectively. ^{13}C NMR spectra were recorded on a Jeol FX90Q instrument at 22.5 MHz unless otherwise stated; spectra at 100 MHz were recorded on a JEOL EX400 spectrometer. Multiplicities in ^{13}C NMR spectra were determined by use of DEPT sequences.[11] Mass spectra were obtained using AEI MS902 or MM7070E spectrometers, in EI-positive mode. Butyl-lithium solutions were standardised by the diphenylacetic acid method.[12] Ether refers to diethyl ether. Solvents were dried, and distilled before use; tetrahydrofuran (THF) distilled from K immediately before use, dimethylformamide (DMF), chloroform and dichloromethane distilled from CaH_2, ethanol distilled from magnesium ethoxide and stored over activated 4A molecular sieves. Aq. NH_3 refers to ammonia solution, *d* 0.88. Column chromatography was carried out under medium pressure using Merck Kieselgel 60 (Art. 7729); flash column chromatography refers to chromatography using Merck Kieselgel 60 (Art. 9328). Organic extracts were dried over anhydrous magnesium sulphate for 10 min.

***1-Benzyl-2-(1-ethoxycarbonylhexyl)-4,5-dihydroimidazole* 4a**. 1-Benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (1.50 g, 6.1 mmol), triethylamine (1.7 cm^3, 12.2 mmol) and 1-bromopentane (1.1023 g, 7.3 mmol) were heated at reflux in ethanol (50 cm^3) for 18 h under nitrogen. Removal of the solvent under reduced pressure and flash column chromatography (gradient elution, hexane → EtOAc) gave the title compound (0.73 g, 38%) as a yellow oil (Found: MH^+ 317.2229. $C_{19}H_{28}N_2O_2$ requires *MH* 317.2229); ν_{max} ($CHBr_3$) 2920, 2860, 1730 (C=O), 1605 (C=N), 1490, 1450, 1030 cm^{-1}; δ_H (400 MHz) 0.85 (3H, t, *J* 8 Hz, $CH_2CH_2CH_3$), 1.25 (3H, t, *J* 7 Hz, OCH_2CH_3), 1.30 (6H, m, $CH_2CH_2CH_2CH_3$), 1.90 and 2.05 (each 1H, m, $CHCH_2$), 3.20 and 3.70 (each 2H, t, NCH_2CH_2N,) 3.40 (1H, t, CH), 4.20 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 4.30 (2H, s, CH_2Ph), 7.2-7.35 (5H, m, Ar-H); δ_C (100 MHz) 13.8, 14.0, 22.2, 27.1, 29.8, 31.5, 44.6, 50.4, 50.8, 52.2, 61.0 (OCH_2), 127.3, 127.4 and 128.5 (ArCH), 137.4 (ArC), 163.8 (C=O), 170.8 (C-2); *m/z* 317 (MH^+, 7%), 301 (M^+–Me, 3), 271 (7), 259 (22), 246 (50), 245 (25), 243 (M^+–CO_2Et, 15), 187 (18), 174 (17), 173 (25), 91 (100).

***1-Benzyl-2-(1-ethoxycarbonylpentyl)-4,5-dihydroimidazole* 4b**. 1-Benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (0.50 g, 2.0 mmol) and 1-iodobutane (0.28 cm^3, 2.4 mmol) were heated to 110°C in dry DMF (25 cm^3) for 14 h, and the reaction mixture poured into water (25 cm^3). The solution was extracted with ethyl acetate (3 x 50 cm^3), the extracts were dried and the solvents removed under reduced pressure to give a brown oil which was purified by flash column chromatography (dichloromethane: ethanol:aq. NH_3, 250:8:1 v/v/v) to afford the *title compound* (0.41 g, 67%) as a brown oil (Found: M^+

302.2004. $C_{18}H_{26}N_2O_2$ requires *M* 302.1992); ν_{max} (film) 3060, 3000, 2970, 2810, 1735 (C=O), 1640, 1605, 1455, 1200, 740, 705 cm^{-1}; δ_H 0.90 (3H, t, *J* 6 Hz, $CH_2CH_2CH_3$), 1.25 (3H, t, *J* 7 Hz, OCH_2CH_3), 1.30 (4H, m, $CH_2CH_2CH_3$), 2.00 (2H, m, $CHCH_2$), 3.40 (2H, m, NCH_2CH_2N), 3.70 (3H, m, NCH_2CH_2N and CH), 4.20 (2H, q, *J* 7 Hz, OCH_2CH_3), 4.50 (2H, s, CH_2Ph), 7.35 (5H, m, Ar-H); *m/z* 302 (M^+, 2%), 274 (9), 246 (M^+, 13), 218 (20), 133 (22), 120 (53), 106 (54) , 91 (100).

***1-Benzyl-2-(1-ethoxycarbonylpropyl)-4,5-dihydroimidazole* 4c**. 1-Benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (0.25 g, 1.0 mmol) in tetrahydrofuran (25 cm^3) was treated with sodium hydride (0.041 g of a 60% dispersion in oil, 1.0 mmol) and the mixture heated at reflux for 30 min. Iodoethane (0.081 cm^3, 1.0 mmol) was added and the mixture was heated at reflux for 4 h, poured into saturated aqueous sodium hydrogencarbonate (30 cm^3), and the solution extracted with dichloromethane (3 x 20 cm^3). Removal of the solvents under reduced pressure gave a yellow oil which was purified by column chromatography (dichloromethane:ethanol:aq. NH_3, 300:8:1 v/v/v) to give the *title compound* (0.198 g, 71%) as a yellow oil (Found: M^+ 274.1663. $C_{16}H_{22}N_2O_2$ requires *M* 274.1645); ν_{max} (film) 3040, 2990, 2940, 2880, 1740 (C=O), 1645 (C=N), 1605, 1370, 1225, 740, 700 cm^{-1}; δ_H 1.00 (3H, t, *J* 7 Hz, $CHCH_2CH_3$), 1.25 (3H, t, *J* 7 Hz, OCH_2CH_3), 2.05 (2H, dq, *J* 3 and 7 Hz, $CHCH_2CH_3$), 3.30 (3H, m, NCH_2CH_2N and CH), 3.75 (2H, m, NCH_2CH_2N), 4.20 (2H, q, *J* 7 Hz, OCH_2CH_3), 4.40 (2H, s, CH_2Ph), 7.35 (5H, m, Ar-H); δ_C 11.9, 13.9, 23.1, 46.0, 50.3, 50.8, 51.7, 60.8 (OCH_2), 127.0, 127.2 and 128.3 (ArCH), 137.1 (ArC), 163.6 (C=O), 171.3 (C-2); *m/z* 274 (M^+, 2%), 259 (M^+–Me, 2), 246 (24), 133 (10), 120 (37), 106 (22) , 91 (100).

***1-Benzyl-2-(1-ethoxycarbonyl-2-phenylethyl)-4,5-dihydromidazole* 4d** was prepared by the method described for **4c**, using 1-benzyl-2-(ethoxycarbonymethylene)-2,3,4,5-tetrahydroimidazole **2** (0.25 g, 1.0 mmol), sodium hydride (0.041 g of a 60% dispersion in oil, 1.0 mmol) and benzyl bromide (0.121 cm^3, 1.0 mmol). Work-up and column chromatography gave the *title compound* (0.253 g, 75%) as a waxy yellow solid, m.p. 56-58°C (Found: M^+ 336.1823. $C_{21}H_{24}N_2O_2$ requires *M* 336.1809); ν_{max} 2950, 2880, 1740 (C=O), 1605, 1440, 1380, 1100, 1030 cm^{-1}; δ_H 1.20 (3H, t, *J* 7 Hz, CH_2CH_3), 3.30 (4H, m, NCH_2CH_2N and $CHCH_2Ph$), 3.70 (3H, m, NCH_2CH_2N and CH), 4.15 (2H, q, *J* 7 Hz, CH_2CH_3), 4.25 (2H, s, NCH_2Ph), 7.30 (10H, m, Ar-H); *m/z* 336 (M^+, 20%), 335 (22), 264 (20), 263 (M^+–CO_2Et, 96), 261 (11), 105 (12), 91 (100).

***1-Benzyl-2-(1-ethoxycarbonyl-4-*tert*-butyldimethylsilyloxybutyl)-4,5-dihydroimidazole* 4e** was prepared by the method described for **4c**, using 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (0.30 g, 1.2 mmol), sodium hydride (0.049 g of a 60% dispersion in oil, 1.2 mmol) and 3-bromo-1-*tert*-butyldimethylsilyloxypropane (0.31 g, 1.2 mmol). Work-up and column chromatography gave the *title compound* (0.183 g, 36%) as a colourless oil (Found: M^+ 418.2629. $C_{23}H_{38}N_2O_3Si$ requires *M* 418.2652); ν_{max} (film) 2980, 2960, 2860, 1735 (C=O), 1605, 1255 (Si–C), 1100 (Si–O), 840 (Si–C), 975 cm^{-1}; δ_H 0.10 (6H, s, 2 x $SiCH_3$), 0.95 (9H, s, $SiC(CH_3)_3$), 1.30 (3H, t, *J* 7 Hz, CH_2CH_3), 1.70 (2H, m, $CHCH_2$), 2.10 (2H, m, CH_2CH_2OSi), 3.30 (2H, m, NCH_2CH_2N), 3.70 (5H, m, NCH_2CH_2N, CH_2OSi, and CH), 4.25 (2H, q, *J* 7 Hz, CH_2CH_3), 4.40 (2H, s, CH_2Ph), 7.35 (5H, m, Ar-H); δ_C –5.3 & 0.2 ($SiCH_3$), 14.2, 19.1 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 26.7, 30.7, 44.5, 50.7, 51.2, 52.5, 61.2 (CH_2OSi), 62.8 (CH_2CO_2), 127.3, and 128.7 (ArCH), 137.7 (ArC), 163.9 (C=O),170.9 (C-2); *m/z* 418 (M^+, 18%), 361 (M^+–Bu^t, 45), 260 (20), 259 (34), 246 (37), 187 (42), 91 (100).

***1-Benzyl-2-(1-ethoxycarbonyl-1-ethylpropyl)-4,5-dihydroimidazole* 4 f** was prepared by the method described for **4c**, using 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (0.25 g, 1.0 mmol), sodium hydride (0.102 g of a 60% dispersion in oil, 2.5 mmol) and iodoethane (0.202 cm^3, 2.5 mmol). Work-up and column chromatography gave the *title compound* (0.257 g, 84%) as a colourless oil (Found: M^+ 302.1981. $C_{18}H_{26}N_2O_2$ requires M 302.1967); ν_{max} (film) 3040, 2980, 2880, 1725 (C=O), 1605 (C=N), 1230, 1135, 1040, 745, 710 cm^{-1}; δ_H 0.90 (6H, t, J 7 Hz, 2 x CCH_2CH_3), 1.25 (3H, t, J 7 Hz, OCH_2CH_3), 2.00 (4H, q, J 7 Hz, 2 x CCH_2CH_3), 3.10 and 3.65 (each 2H, m, NCH_2CH_2N), 4.10 (2H, s, CH_2Ph), 4.20 (2H, q, J 7 Hz, OCH_2CH_3), 7.25 (5H, m, Ar-H); *m/z* 302 (M^+, 10%), 274 (25), 273 (M^+–Et, 16), 259 (40), 229 (38), 201 (52), 91 (100).

***1-Benzyl-2-(1-benzyl-1-ethoxycarbonyl-2-phenylethyl)-4,5-dihydroimidazole* 4g** was prepared by the method described for **4c**, using 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (0.35 g, 1.4 mmol), sodium hydride (0.142 g of a 60% dispersion in oil, 3.6 mmol) and benzyl bromide (0.42 cm^3, 3.6 mmol). Work-up and column chromatography gave the *title compound* (0.471 g, 79%) as a yellow oil (Found: M^+ 426.2290. $C_{28}H_{30}N_2O_2$ requires M 426.2273); ν_{max} (film) 3070, 3040, 2860, 1725 (C=O), 1600, 1495, 1090, 1000, 740, 710 cm^{-1}; δ_H 1.10 (3H, t, J 7 Hz, CH_2CH_3), 3.25 & 3.70 (each 2H, m, NCH_2CH_2N), 3.55 (4H, s, 2 x CCH_2Ph), 3.80 (2H, s, NCH_2Ph), 4.00 (2H, q, J 7 Hz, CH_2CH_3), 7.25 (15H, m, Ar-H); *m/z* 426 (M^+, 19%), 354 (11), 353 (M^+–CO_2Et, 37), 266 (14), 175 (17), 92 (10), 91 (100).

***1-Benzyl-2-(1,2-diethoxycarbonylethyl)-4,5-dihydroimidazole* 4h** (with RACHEL H. LLOYD and JEFFREY W. HOBBS) was prepared by the method described for **4c**, using 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (2.0 g, 8.1 mmol), sodium hydride (0.33 g of a 60% dispersion in oil, 8.1 mmol) and ethyl bromoacetate (1.78 cm^3, 16 mmol). Work-up and column chromatography (dichloromethane: ethanol, 300:8 v/v) gave recovered starting material **2** (0.82 g, 41%), followed by the title compound (1.08 g, 40%) (Found: M^+ 332.1736. $C_{18}H_{24}N_2O_4$ requires M 332.1736); ν_{max} (film) 2982, 2937, 1738 (C=O), 1609 (C=N), 1454, 1371, 1266, 1215, 1097, 733 cm^{-1}; δ_H 1.4 (6H, 2 x t, J 7 Hz, 2 x CH_2CH_3), 3.55 (2H, d, $CHCH_2$), 3.6-4.1 (7H, m, NCH_2CH_2N, CH_2Ph, and CH), 4.4 (4H, 2 x q, J 7 Hz, 2 x CH_2CH_3), 7.5 (5H, br s, Ar-H); *m/z* 332 (M^+, 2%), 317 (M–Me, 1), 287 (2), 259 (M^+–CO_2Et, 15), 218 (10), 133 (18), 120 (42), 106 (30), 91 (100).

***1-Benzyl-2-phenylethyl-4,5-dihydroimidazole* 3b**. Sodium hydride (80 mg of a 60% dispersion in oil, 2.0 mmol) was added to 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (0.25 g, 1.0 mmol) in dry THF (5 cm^3) stirred at 0°C under nitrogen. The mixture was stirred at 0°C for 30 min, then at room temperature for 1 h, before benzyl bromide (0.17 g, 1.0 mmol) and iodoethane (0.16 g, 1.0 mmol) were added simultaneously dropwise. The solution was stirred at room temperature under nitrogen overnight, and the resulting mixture poured into saturated aqueous sodium hydrogencarbonate (20 cm^3) then extracted with dichloromethane (3 x 25 cm^3). The combined dichloromethane extracts were dried, filtered and evaporated under reduced pressure to leave an oil, from which flash column chromatography (ethyl acetate:hexane: triethylamine, 15:4:1 v/v/v) gave recovered starting material **2** (0.078 g, 32%), followed by the title compound (0.13 g, 49%) as a colourless oil (Found: M^+ 264.1617. $C_{18}H_{20}N_2$ requires M 264.1626); ν_{max} (film) 3000, 2900, 2810, 1610 (C=N), 1500, 1420, 1105, 1010, 745, 700 cm^{-1}; δ_H 2.55-2.75 and 2.90-3.10 (each 2H, m,

PhC*H*$_2$C*H*$_2$), 3.15-3.35 and 3.55-3.75 (each 2H, m, NCH$_2$CH$_2$N), 4.25 (2H, s, NC*H*$_2$Ph), 7.10-7.40 (10H, m, Ar-H), identical to an authentic sample.[1b]

***Attempted Transesterification of 1-Benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole* 2.** Potassium t-butoxide (11 mg, 0.1 mmol) was added to 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (0.15 g, 0.6 mmol) in dry ethanol (25 cm^3) and the mixture stirred at 25°C for 7 d. Removal of solvent under reduced pressure, and chromatography of the residue (ethyl acetate:triethylamine, 99:1 v/v) gave 1-benzyl-2-methyl-4,5-dihydroimidazole **3a** (0.11 g, 100%) (Found: *M*$^+$ 174.1174. $C_{11}H_{14}N_2$ requires *M*, 174.1157); δ_H 2.05 (3H, s, CH$_3$), 3.25 and 3.75 (each 3H, t, *J* 9 Hz, NCH$_2$CH$_2$N), 4.35 (2H, s, NC*H*$_2$Ph), 7.35 (5H, m, Ar-H), identical with an authentic sample.[1b]

***Ethyl 1-(1-benzyl-4,5-dihydromidazol-2-yl)cyclopentanecarboxylate* 4j.** Sodium hydride (0.18 g of a 60% dispersion in oil, 4.4 mmol) was added to 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (0.49 g, 2 mmol) in dry THF (10 cm^3) stirred at 0°C under nitrogen. The mixture was stirred at 0°C for 30 min, then at room temperature for 1 h, before 1,4-dibromobutane (0.43 g, 2 mmol) was added dropwise. Stirring was continued at room temperature under nitrogen for 3 d, then water (10 cm^3) was added and the solution extracted with ethyl acetate (3 x 25 cm^3). The combined organic extracts were dried, filtered and evaporated under reduced pressure to leave an oily solid, from which flash column chromatography (ethyl acetate:triethylamine, 20:1 v/v) gave the *title compound* (0.40 g, 67%) as a yellow solid, m.p. 84°C (Found: C, 72.1; H, 8.35; N, 9.55%; *M*$^+$ 300.1834. $C_{18}H_{24}N_2O_2$ requires C, 71.95; H, 8.05; N, 9.35%; *M*, 300.1838); ν_{max} 3040, 2985, 2880, 1730 (C=O), 1600 (C=N), 1235, 1160, 1130, 1040, 745, 710 cm^{-1}; δ_H 1.30 (3H, t, *J* 7 Hz, CH$_2$C*H*$_3$), 1.60-1.90 (4H, m, CH$_2$C*H*$_2$C*H*$_2$CH$_2$), 2.20-2.60 (4H, m, C*H*$_2$CH$_2$CH$_2$C*H*$_2$), 3.20 and 3.80 (each 2H, m, NCH$_2$CH$_2$N), 4.20 (2H, s, NC*H*$_2$Ph), 4.25 (2H, q, *J* 7 Hz, C*H*$_2$CH$_3$) , 7.20-7.50 (5H, m, Ar-H); *m/z* 300 (*M*$^+$, 8%), 260 (5), 259 (30), 255 (6), 228 (19), 227 (100), 225 (8), 135 (6), 92 (7), 91 (75).

***Ethyl 1-(1-benzyl-4,5-dihydromidazol-2-yl)cyclohexanecarboxylate* 4k** was prepared by the method described for **4j**, using 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (0.25 g, 1 mmol) in dry THF (10 cm^3), sodium hydride (0.09 g of a 60% dispersion in oil, 2.2 mmol) and 1,5-dibromopentane (0.23 g 1 mmol). Work-up and flash column chromatography (ethyl acetate:triethylamine, 20:1 v/v) gave the *title compound* (0.11 g, 35%) as a yellow oil (Found: *M*$^+$ 314.1988. $C_{19}H_{26}N_2O_2$ requires *M* 314.1994); ν_{max} 3060, 2980, 2880, 1735 (C=O), 1610 (C=N), 1240, 1165, 1120, 1040, 745, 710 cm^{-1}; δ_H 1.30 (3H, t, *J* 7 Hz, CH$_2$C*H*$_3$), 1.40-1.90 (6H, m, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$), 3.20 and 3.80 (each 2H, m, NCH$_2$CH$_2$N), 3.45 (4H, m, C*H*$_2$CC*H*$_2$), 4.20 (2H, q, *J* 7 Hz, C*H*$_2$CH$_3$), 4.25 (2H, s, NC*H*$_2$Ph), 7.20-7.50 (5H, m, Ar-H); *m/z* 314 (*M*$^+$, 8%), 260 (10), 259 (46), 242 (20), 241 (100), 239 (8), 187 (9), 135 (6), 92 (7), 91 (84).

***Ethyl 1-benzyl-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-8-carboxylate* 5a** was prepared by the method described for **4j**, using 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (1.48 g, 6 mmol) in dry THF (30 cm^3), sodium hydride (0.53 g of a 60% dispersion in oil, 13 mmol) and 1,3-dibromopropane (1.21 g, 6 mmol). Work-up and flash column chromatography (ethyl acetate:triethylamine, 20:1 v/v) gave the *title compound* (1.25 g, 73%) as a yellow crystalline solid, m.p. 71-73°C (Found: C, 71.15; H, 8.1; N, 9.95%; *M*$^+$ 286.1653. $C_{17}H_{22}N_2O_2$ requires C, 71.3; H, 7.75; N, 9.8%; *M*$^+$ 286.1681); ν_{max} (nujol)

3023, 2928, 2855, 1655 (C=O), 1602, 1548, 1492, 1467, 1454, 1443, 1362, 1352, 1288, 1253, 1198, 1183, 1171, 1141, 1099, 1074, 1051, 1008, 959, 911, 855, 754, 707, 699 cm^{-1}; δ_H 1.15 (3H, t, *J* 7Hz, CH_2CH_3), 1.90 (2H, m, $CH_2CH_2CH_2$), 2.45 (2H, t, *J* 7 Hz, CH_2CH_2C), 3.00 (2H, t, *J* 6 Hz, CH_2CH_2N), 3.20 (4H, s, NCH_2CH_2N), 4.10 (2H, q, *J* 7 Hz, CH_2CH_3), 4.65 (2H, s, NCH_2Ph), 7.20-7.60 (5H, m, Ar-H); δ_C 14.4 (CH_3), 22.2 and 22.9 (CH_2CH_2C), 45.1, 47.6 and 48.2 (NCH_2), 55.7 (OCH_2), 57.3 (NCH_2Ph), 73.1 (CCO_2Et), 126.5 and 127.7 (ArC), 161.3 (NCN), 166.6 (C=O).

Ethyl 1-benzyl-5-methyl-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-8-carboxylate **5b** was prepared by the method described for **4j**, using 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (0.49 g, 2 mmol) in dry THF (10 cm^3), sodium hydride (0.18 g of a 60% dispersion in oil,4.4 mmol) and 1,3-dibromobutane (0.43 g, 2 mmol). Work-up and flash column chromatography (ethyl acetate:triethylamine, 20:1 v/v) gave the *title compound* (0.26 g, 44%) as a yellow oil (Found: C, 71.85; H, 8.3; N, 9.55%; M^+ 300.1835. $C_{18}H_{24}N_2O_2$ requires C, 72.0; H, 8.0; N, 9.3%; *M* 300.1838); ν_{max} (film) 3020, 2990, 2950, 2870, 1740, 1645 (C=O), 1555, 1485, 1460, 1375, 1345, 1295, 1270, 1230, 1210, 1180, 1170, 1120, 1095, 1060, 1040, 980, 745, 710 cm^{-1}; δ_H 1.10 (3H, d, *J* 6 Hz, $CHCH_3$), 1.15 (3H, t, *J* 7 Hz, CH_2CH_3), 1.40-2.00 (2H, m, $CHCH_2CH_2$), 2.50 (2H, t, *J* 7 Hz, CH_2CH_2C), 2.90-3.50 (5H, m, $CHCH_3$ and NCH_2CH_2N), 4.10 (2H, q, *J* 7 Hz, CH_2CH_3), 4.44 and 4.80 (each 1H, d, *J* 15 Hz, NCH_2Ph), 7.20-7.60 (5H, m, Ar-H); *m/z* 300 (M^+, 1%), 227 (5), 186 (7), 133 (39), 132 (10, 120 (42), 106 (7), 92 (9), 91 (100).

1-Benzyl-2-(5-methyl-2-oxotetrahydrofuran-3-ylidene)-2,3,4,5-tetrahydroimidazole **6a**. To 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (0.30 g, 1.2 mmol) in dry THF (25 cm^3) at 0°C under nitrogen, was added n-butyl-lithium (0.95 $cm^3$of a 1.4M solution in hexanes, 1.4 mmol). After 30 min methyloxirane (0.091 cm^3, 1.3 mmol) was added and after a further 1 h the solution was first allowed to warm to room temperature, and then heated at reflux for 2 h before the reaction was quenched with ethanol (1 cm^3). Removal of the solvent under reduced pressure and purification by column chromatography (ethyl acetate: triethylamine, 98:2 v/v) gave the *title compound* (0.096 g, 31%) as a yellow oil (Found: M^+ 258.1374. $C_{15}H_{18}N_2O_2$ requires *M* 258.1380); ν_{max} 3300 (NH), 3020, 2960, 2880, 1710 (C=O), 1670, 1605, 1430, 1270, 1310, 1120 cm^{-1}; δ_H 1.35 (3H, d, *J* 6 Hz, $CHCH_3$), 2.60 (1H, dd, *J* 12 and 6 Hz, CH_aH_bCH), 3.20 (1H, dd, *J* 12 and 8 Hz, CH_aH_bCH), 3.50 (5H, m, $CHCH_3$ and NCH_2CH_2N), 4.55 (2H, s, NCH_2Ph), 7.40 (5H, m, Ar-H), 7.90 (1H, br s, NH); δ_C 22.4 (Me), 34.0 (CH_2CHO), 42.0, 49.1 and 50.2 (CH_2N), 65.3 (CHO), 72.6 (CC=O), 126.9, 127.7 and 128.9 (ArCH), 137.2 (ArC), 160.1 (C=O), 175.4 (C-2); *m/z* 258 (M^+, 50%), 201 (27), 187 (34), 185 (35), 104 (20), 91 (100).

1-Benzyl-2-(5-phenyl-2-oxotetrahydrofuran-3-ylidene)-2,3,4,5-tetrahydroimidazole **6b** was prepared by a similar procedure to that described above for **6a**, using 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **2** (2.25 g, 9.2 mmol) in dry THF (150 cm^3), but with lithium diisopropylamide (4.6 cm^3 of a 2M solution in heptane–THF–ethylbenzene, 9.2 mmol) as the base, and phenyloxirane (1.1 g, 9.2 mmol). The reaction mixture was quenched with water (5 cm^3), the solvents were removed under reduced pressure, and the residue was taken up in ethyl acetate (100 cm^3) and washed with water (2 x 20 cm^3). The organic layer was dried, filtered and evaporated to leave a yellow oil that was purified by column chromatography (gradient elution, hexane → ethyl acetate) to give the *title compound* (2.1 g, 70%) as a white crystalline solid, m.p.

104.5-106°C (Found: M^+ 350.1525. $C_{20}H_{20}N_2O_2$ requires M^+ 320.1525); ν_{max} 3320 (NH), 3000, 2920, 2840, 1715, 1670, 1595, 1540, 1450, 1100 cm^{-1}; δ_H (400 MHz) 2.95 (1H, dd, *J* 12 and 6.5 Hz, CH_aH_bCH), 3.40 (3H, m, CH_aH_bCH and NCH_2CH_2N), 3.55 (2H, t, NCH_2CH_2N), 4.40 and 4.55 (each 1H, d, *J* 16 Hz, NCH_2Ph), 5.40 (1H, dd, *J* 9 and 6.5 Hz, *CH*Ph), 7.2-7.35 (10H, m, Ar-H) , 7.90 (1H, s, NH); δ_C (100 MHz) 35.3 (CH_2CHO), 41.9, 48.9, 50.0 (CH_2N), 64.6 (CHO), 77.0 (*C*C=O), 125.4, 126.8, 127.6, 127.8, 128.7 and 129.0 (ArCH), 136.8 and 142.6 (ArC), 160.0 (C=O), 175.4 (C-2); *m/z* 320 (M^+, 23%), 276 (10), 201 (22), 187 (24), 185 (52), 91 (100).

1-Benzyl-2-propyl-4,5-dihydroimidazole **3c**. 1-Benzyl-2-(1-ethoxycarbonylpropyl)-4,5-dihydroimidazole **4c** (0.11 g, 0.4 mmol) was heated at reflux for 3 d in a mixture of 2M hydrochloric acid (4 cm^3) and methanol (6 cm^3). The cooled reaction mixture was basified to pH 9 using saturated aqueous sodium hydrogencarbonate and extracted with dichloromethane (3 x 25 cm^3). The combined dichloromethane extracts were dried, filtered and evaporated under reduced pressure to leave a yellow oil, from which flash column chromatography (ethyl acetate:hexane:triethylamine, 15:4:1 v/v/v) gave the title compound (0.060g, 74%) as a colourless oil (Found: M^+ 202.150. $C_{13}H_{18}N_2$ requires M^+ 202.147); ν_{max} 2900, 2800, 1610 (C=N), 1500, 1450, 1240, 745, 700 cm^{-1}; δ_H 1.10 (3H, t, *J* 7 Hz, CH_2CH_3), 1.50-1.90 (2H, m, $CH_2CH_2CH_3$), 2.35 (2H, t, *J* 7 Hz, $CH_2CH_2CH_3$), 3.10-3.80 (4H, m, NCH_2CH_2N), 4.25 (2H, s, NCH_2Ph) , 7.25-7.35 (5H, m, Ar-H), identical to an authentic sample.[1b]

1-Benzyl-2-cyclopentyl-4,5-dihydroimidazole **3 d**. Ethyl 1-(1-benzyl-4,5-dihydromidazol-2-yl)cyclopentanecarboxylate **4j** (0.27 g, 0.9 mmol) in 2M hydrochloric acid (5 cm^3) was heated at reflux with stirring for 10 d. Work-up as described for **3c** above, and flash column chromatography (ethyl acetate:triethylamine, 19:1 v/v) gave the *title compound* (0.044g, 77%) as a colourless oil (Found: C, 78.6; H, 8.9; N, 12.55%. $C_{15}H_{20}N_2$ requires C, 78.95; H, 8.75; N, 12.3%); ν_{max} 2952, 2867, 1644 (C=N), 1548, 1452, 1239, 745, 698 cm^{-1}; δ_H 1.40-2.10 (8H, m, $CH_2CH_2CH_2CH_2$), 2.75 (1H, m, CH), 3.10-3.90 (4H, m, NCH_2CH_2N), 4.38 (2H, s, NCH_2Ph), 7.25-7.55 (5H, m, Ar-H); δ_C 25.7 ($CH_2CH_2CH_2CH_2$), 31.0 (CH_2CHCH_2), 37.2 (CH), 50.6, 50.8 and 52.2 (CH_2N), 127.2 and 128.6 (ArCH), 138.1 (Ar-C), 170.4 (C=N).

ACKNOWLEDGEMENTS

We thank Drs. Eric W. Collington & Peter Hallett for helpful discussions, Rachel H. Lloyd & Jeffrey W. Hobbs for the preparation of compound **4h**, SERC and Glaxo Group Research for a CASE studentship (S.C.H.), SERC for a studentship and Glaxo Group Research for financial support (I.T.), and the EPSRC National Mass Spectrometry Service Centre, Swansea, for some MS data.

REFERENCES AND FOOTNOTES

1. (a) Anderson, M. W.; Begley, M. J.; Jones, R. C. F.; Saunders, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2599-2602;
(b) Anderson, M. W.; Jones, R. C. F.; Saunders, J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 205-209;
(c) Jones, R. C. F.; Anderson, M. W.; Smallridge, M. J. *Tetrahedron Lett.* **1988**, *29*, 5001-5004;

(d) Jones, R. C. F.; Schofield, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 375-383;
(e) Jones, R. C. F.; Smallridge, M. J.; Chapleo, C. B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 385-391.

2. See, for example: Grout, R. J. in *The Chemistry of Amidines and Imidates*; Patai, S. Ed.; Wiley. London, 1975, p. 255 *et seq.*; Chapleo, C. B. *Chem. Br.* **1986**, 313-314.
3. See, for example: Saier, M. H. *Enzymes in Metabolic Pathways*; Harper & Row: New York, 1990; pp.83-85.
4. For other studies with heterocyclic ketene aminals, see: Yu, C.-Y.; Wang, L.-B.; Li, W.-Y.; Huang, Z.-T. *Synthesis* **1996**, 959-962, and refs. therein.
5. For a preliminary report of this work, see: Jones, R. C. F.; Hirst, S. C.; Turner, I. *J. Chem. Soc., Perkin Trans. 1* **1991**, 953-954.
6. (a) Jones, R. C. F.; Anderson, M. W.; Smallridge, M. J. *Tetrahedron Lett.* **1988**, *29*, 5001-5004;
(b) Jones, R. C. F.; Hirst, S. C. *Tetrahedron Lett.* **1989**, *30*, 5361-5364.
7. *Cf.* Wang, L.-B.; Yu, C.-Y.; Huang, Z.-T. *Synthesis* **1994**, 1441-1444. These authors report *N*-alkylation of N-*unsubstituted* ketene aminals with ethyl bromoacetate using a different solvent (DMF *vs.* THF), but make a comment on the importance of the reaction medium; retention of the H-bonded enaminocarbonyl tautomer is observed, in contrast to the β-iminocarbonyl tautomer found in our *N*-benzyl example .
8. For related lactones, see: Jones, R. C. F.; Hirst, S. C. *Tetrahedron Lett.* **1989**, *30*, 5365-5368.
9. Anderson, M. W.; Jones, R. C. F.; Saunders, J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1995-1998.
10. *Cf.* Jones, R. C. F.; Turner, I.; Howard, K. J. *Tetrahedron Lett.* **1993**, *34*, 6329-6332.
11. See, for example: Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon: Oxford, 1987; pp.143-151.
12. Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879-1880.

(*Received in UK* 20 *November* 1996; *revised* 30 *June* 1997; *accepted* 3 *July* 1997)