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Annulation of Imidazolines with bis-Electrophiles: Synthesis of Imidazo[1,2-*a*]pyridines

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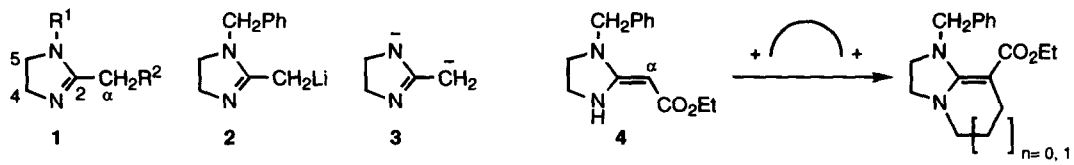
Abstract: 1-Benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole undergoes annulation with a variety of 1,3-bis-electrophiles (α,β-unsaturated acid derivatives, β-ketoesters, α,β-unsaturated aldehydes) to form imidazo[1,2-*a*]pyridines.

INTRODUCTION

A theme of our studies with the 2-imidazoline (4,5-dihydroimidazole) heterocycle **1** has been the generation and utilisation of nucleophilic reactivity at the α-carbon atom.[1] Indeed, we have reported extensively on the reactivity of lithio-derivatives **2**, including the realisation of the doubly nucleophilic synthon **3** by successive reactions at N(1) and C(α).[1d,2] An alternative readily available source of nucleophilic properties at C(α) is found in the enaminoester **4**.[1a] Prompted by the biological activity shown by many imidazolines,[3] and by the opportunity to access aza-analogues of the bicyclic indolizidine system (which is found in a number of bioactive natural products[4]), we have explored the annulation of the heterocyclic ketene-aminal **4** in reaction with bis-electrophiles according to the general Scheme 1. We report herein details of successful imidazo[1,2-*a*]pyridone formation with a variety of carbonyl 1,3-bis-electrophiles, namely α,β-unsaturated carbonyl compounds (acid derivatives, aldehydes), β-ketoesters and derivatives.[5] α,β-Unsaturated ketones show a distinctive behaviour[5b] that will be reported separately, and we have already reported on annulation with dihaloalkane electrophiles.[6] Brief trials with some carbonyl 1,2-bis-electrophiles are also described. Related annulation studies have been reported elsewhere.[7]



1 2 3 4

Scheme 1

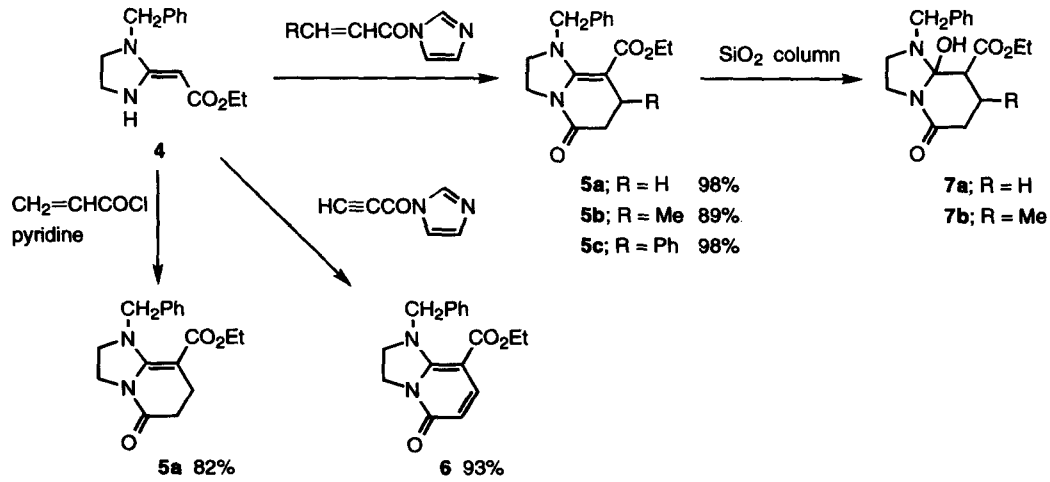
PII: S0040-4020(98)00312-3

RESULTS AND DISCUSSION

The enaminoester **4** is easily prepared from *C*-acylation of lithio-imidazoline **2** with diethyl carbonate, or (more conveniently on a preparative scale) directly from N-benzyl-1,2-diaminoethane and the imidate obtained from ethyl cyanoacetate (EtOH, HCl).[1a]

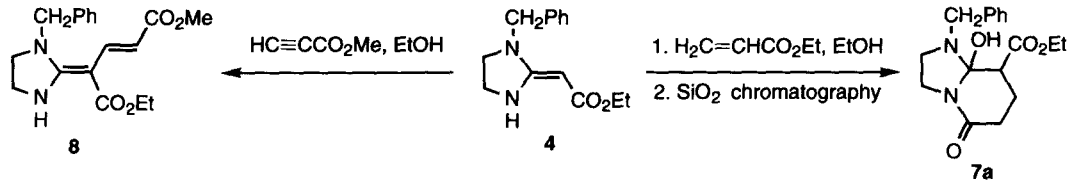
Our intention when using α,β-unsaturated acid derivatives as 1,3-bis-electrophiles was to sufficiently activate the acid function to promote initial *N*-acylation with subsequent conjugate *C*-addition; this sequence has been observed with related cyclic enaminoesters.[8] Thus reaction of **4** with propenoyl chloride (pyridine, toluene at reflux) led to the hexahydroimidazo[1,2-*a*]pyridone **5a** in good yield. A more convenient protocol, however, was developed based on *in situ* formation of α,β-unsaturated acyl imidazolides. Thus the α,β-unsaturated acid (propenoic, 2-butenoic, 3-phenylpropenoic, propynoic) was treated with 1,1'-carbonyldiimidazole (THF, 25°C, 3h) before addition of the ketene aminal **4** and heating at reflux for 24h. Simple basic work-up by partition of the reaction mixture between chloroform and aqueous sodium hydrogencarbonate afforded the imidazopyridones **5a-c** and **6**, respectively, in excellent yields (Scheme 2). The acid component was used in excess. Interestingly, when chromatographed on silica, the imidazopyridones **5a** and **5b** underwent hydration to afford the cyclols **7a** and **7b**, respectively; the former was obtained as a mixture with **5a** from which pure cyclol **7a** could be isolated in low yield by further chromatography, whilst **7b** was obtained in good yield but could not be fully characterized. In contrast, the imidazopyridones **5c** and **6** were stable towards chromatography. It is known that acylamidines undergo hydration to form cyclols more readily than unsubstituted amidines,[9] and we have observed a related cyclol formation in other work.[1c] The cyclols **7** show the expected extra peaks in the ^{1}H NMR spectra for OH and C*H*CO$_2$Et, and also exhibit an upfield shift of the benzylic protons of approx. 1 ppm relative to the corresponding imidazopyridines **5**; the signals from the methylene protons at C-4 and C-5 of the imidazoline ring of cyclols **7** also show a much greater chemical shift separation (1-1.2 ppm) than the corresponding signals for imidazopyridones **5**.

α,β-Unsaturated esters were briefly examined as cyclocondensation partners. Treatment of enaminoester **4** with ethyl propenoate (ethanol at reflux), followed by chromatography on silica gave the expected cyclol **7a**



Scheme 2

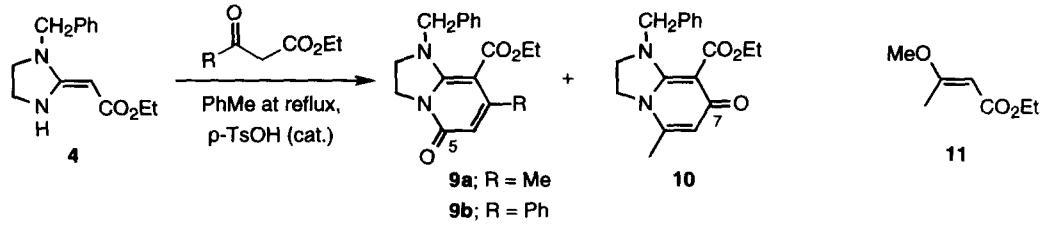
(Scheme 3). Reaction of **4** with methyl propynoate (ethanol, reflux) afforded the *trans* (*J* 16 Hz) *C*-addition product **8** (95%); the illustrated enamine geometry is proposed based on spectroscopic similarities between **8** and starting material **4**.[10] Isolation of this *C*-addition product implies, in line with the work of others,[10,11] that annulation with conjugated esters proceeds *via* an initial *C*-addition, whereas we suggest (see above) that the more reactive conjugated acyl imidazolides proceed *via* initial *N*-acylation. It has been shown that the reaction of secondary enamines such as **4** with propynoate esters in non-protic solvents proceeds *via* an aza-ene pathway,[10] which can be viewed as a conjugate addition with concerted intramolecular proton transfer.



Scheme 3

Using 1,3-bis-electrophiles at a higher oxidation level, enaminoester **4** was found to react with β-keto-esters, Scheme 4. Reflux in toluene with ethyl acetoacetate afforded an excellent yield of a separable mixture of the regioisomeric imidazopyridin-5-one **9a** (79%) and imidazopyridin-7-one **10** (21%), arising from competing acylation at N(3) or at the enamine C(α). The regiochemical assignment of **9a** and **10** was based on n.O.e experiments; irradiation of the alkenyl-CH_3 at δ2.21 in the 5-oxo isomer **9a** gave enhancement only of the alkenyl-H (δ 5.80), whereas irradiation of the corresponding signal in the 7-oxo isomer **10** produced enhancements of both the alkenyl-H and an imidazoline ring methylene signal. The 5-oxo isomer also exhibits more extended conjugation than the 7-oxo compound in the UV spectrum. When ethyl benzoyl-acetate was used as bis-electrophile, only the 5-oxo isomer **9b** was obtained (72%). The enol ether, ethyl 3-methoxy-2-butenoate **11**, led to the 5-oxo compound **9a** as the only imidazopyridone component of a complex reaction mixture. The related annulation of 2-benzyl-2-imidazoline with ethyl acetoacetate has been reported to afford an imidazopyridin-7-one,[12] presumably *via* enamine formation with cyclisation by *C*-acylation.

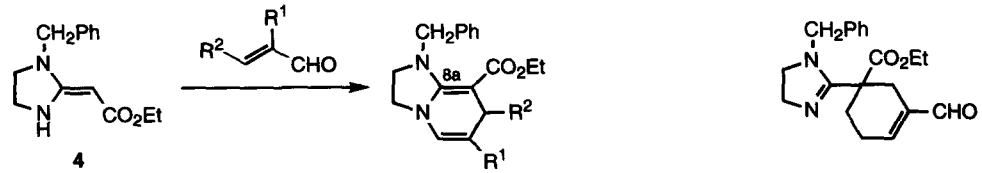
No reaction was observed between the ketene aminal **4** and pentan-2,4-dione or diethyl malonate under a variety of conditions: toluene at reflux, with or without catalytic toluene-4-sulphonic acid; THF at reflux, sodium hydride. Starting materials were recovered in all cases.



Scheme 4

Next we examined α,β-unsaturated aldehydes as 1,3-bis-electrophiles. Treatment of enaminoester **4** with enals in refluxing solvent (2-butenal in acetonitrile; 2-methyl-2-butenal, 2-methylpropenal, 3-phenylpropenal in dioxan) gave annulation products **12a-d**, Scheme 5. The isolated yields of tetrahydroimidazopyridines **12**

were only moderate after chromatography; presumably water addition at C-8a to produce polar cyclols is intervening to lower recoveries. In the case of **12a** a higher yield was secured by distillation rather than chromatography (62 vs. 53%), but this did not prove possible with **12b-d**. We suggest that this annulation proceeds *via* initial conjugate *C*-addition followed by cyclocondensation to form the enamine function. This sequence is supported by the observation that no enamine formation takes place with simple aldehydes. In addition, the reaction of enaminoester **4** with propenal unexpectedly afforded the imidazoline-substituted cyclohexene **13** (60% based on **4**, with 1.2 mol equiv. of propenal, i.e. quantitative based on the aldehyde). This structure is supported by ^1H–^1H and ^1H–^{13}C correlation spectroscopy, and rationalized by conjugate *C*-addition of enaminoester **4** to two molecules of aldehyde followed by intramolecular aldol condensation.



Scheme 5

When α,β-unsaturated ketones and lactones are reacted with ketene aminal **4**, the initial Michael adducts are isolated and cyclocondensation does not occur.[5b] These conjugate additions, and the further chemistry of the Michael adducts that leads *inter alia* to a novel piperidine synthesis,[13] will be reported separately.

The above findings suggest that the enaminoester **4** shows a preference for conjugation addition of C(α) onto α,β-unsaturated carbonyl systems, shown schematically in **Fig. 1**. We speculate that the reactions with β-dicarbonyl compounds usually follow a similar pathway *via* conjugate addition onto their enol forms (**Fig. 1**; R^3 = OX). This would account for the preferred regiochemistry of β-ketoester annulation and the reaction with enol derivative **11**. The lack of reaction with β-diesters may be related to their lower enol content (e.g. diethyl malonate 7.7 x 10^{-3}% vs. ethyl acetoacetate 8.0% in pure compound). β-Diketones have much higher enol content (pentane-2,4-dione 76.4%) and we propose that they may undergo ready conjugate addition (Scheme 6) but that the primary adduct **14** will resist cyclocondensation (*cf.* the results with α,β-unsaturated ketones[5b]), and our experience with 2-(2-hydroxyalkyl)-2-imidazolines suggests they will undergo 'retro-aldol' fragmentation under the reaction conditions,[1c] thus returning starting materials.

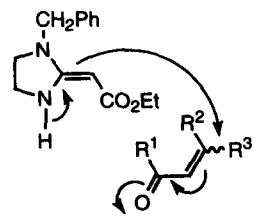
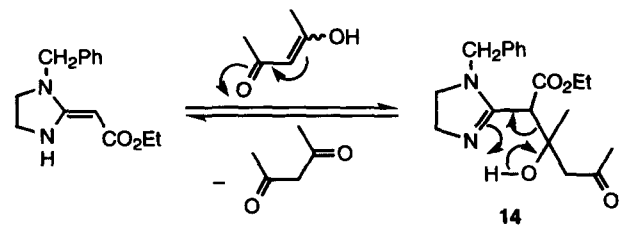
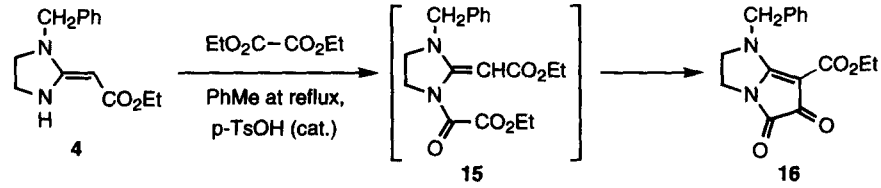


Fig. 1



Scheme 6

As a representative of carbonyl 1,2-bis-electrophiles, we observed annulation of ketene aminal **4** with the α-diester diethyl oxalate. Under neutral (toluene, reflux) or basic conditions (THF, reflux, sodium hydride) starting materials were recovered, whilst under acidic conditions (toluene, catalytic toluene-4-sulphonic acid, reflux 24 h) the dioxopyrrolo[1,2-*a*]imidazole **16** was isolated (50%). When the reaction was interrupted after 12 h, it was possible to obtain a low yield (28%) of *N*-acylation product **15** (Scheme 7); δ 5.5 (CH), no NH absorption in the IR spectrum, that was not fully characterised. These findings are consistent with a recent report on the reaction of oxalate esters with *N*-unsubstituted heterocyclic ketene aminals.[7]



Scheme 7

We have thus shown that the enaminoester **4** is a synthetically useful 1,3-(C,N)-bis-nucleophile in annulation with a range of carbonyl 1,3-bis-electrophiles to form imidazo[1,2-*a*]pyridines, and with a 1,2-diester to form a pyrrolo[1,2-*a*]imidazole.

EXPERIMENTAL

General: Melting points were measured on a Kofler hot-stage and are uncorrected. IR spectra were recorded on Perkin-Elmer 710B, 1710 FT-IR, Pye-Unicam SP3-100 or Philips PU 9706 spectrometers in chloroform unless otherwise stated. UV spectra were recorded in ethanol using a Pye-Unicam SP800 spectrometer. ^{1}H NMR spectra were recorded in deuteriochloroform (internal standard TMS) at 90 MHz on a Perkin-Elmer R32 spectrometer, unless otherwise stated; spectra at 250 and 400 MHz were recorded on Bruker WM250 and JEOL EX400 spectrometers, respectively. ^{13}C NMR spectra were measured on Jeol FX90Q or Bruker FX90 instruments at 22.5 MHz unless otherwise stated; spectra at 100 MHz were recorded on a JEOL EX400 spectrometer. Mass spectra were obtained using AEI MS902 or MM7070E spectrometers in EI-positive mode. Solvents were dried and distilled before use: acetonitrile distilled from P_2O_5 and stored over activated 4Å molecular sieves; chloroform and dichloromethane distilled from CaH_2; dioxan (referring to 1,4-dioxan) dried over activated 4Å molecular sieves and distilled; ethanol distilled from magnesium ethoxide and stored over activated 4Å molecular sieves; tetrahydrofuran (THF) distilled from K immediately before use; toluene dried over sodium and distilled. Aqueous ammonia 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-8-ethoxycarbonyl-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridin-5-one* 5a**. Method A: Propenoic acid (0.14 g, 1.94 mmol) and 1,1'-carbonyldiimidazole (0.36 g, 2.2 mmol), were stirred together in THF (12 cm^3) for 3 h at 20°C before addition of 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydro-

imidazole **4** (0.10 g, 0.41 mmol). The solution was heated at reflux for 24 h, allowed to cool and the solvent removed under reduced pressure. The residue was dissolved in chloroform and washed repeatedly with saturated sodium hydrogen carbonate solution to remove imidazole. The chloroform solution was dried, filtered and concentrated under reduced pressure to afford the *title compound* (0.12 g, 98%) as an oil (Found: M^+ 300.1469. $C_{17}H_{20}N_2O_3$ requires *M* 300.1474); δ_H 1.2 (3H, t, *J* 7 Hz, CH_3), 2.4-2.8 (4H, m, CH_2CH_2CO), 3.3-3.9 (4H, m, NCH_2CH_2N), 4.15 (2H, q, *J* 7 Hz, CH_2CH_3), 4.8 (2H, s, CH_2Ph), 7.4 (5H, m, Ar-H); *m/z* 301 (MH^+, 8%), 300 (M^+, 33), 299 (14), 255 (13), 228 (12), 227 (52), 120 (11), 106 (12), 92 (10), 91 (100).

Method B: To 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **4** (0.25 g, 1.02 mmol) and pyridine (0.1 g, 1.26 mmol) in toluene (5 cm^3) heated under reflux was added propenoyl chloride (0.09 cm^3, 1.11 mmol) in toluene (1 cm^3). After 3 h the solution was cooled, poured into sodium hydroxide solution (5% w/v), and extracted into chloroform. The combined chloroform extracts were dried, filtered and concentrated under reduced pressure to give the title compound as an oil (0.25 g, 82%), identical with material prepared by method A.

Column chromatography of a sample of the imidazo[1,2-*a*]pyridine **5a** (0.59 g, 1.97 mmol), prepared by Method A, on silica gel eluting with chloroform–ethanol (99.5:0.5 v/v) gave a 45:65 mixture (estimated by ^1H NMR spectroscopy) of **5a** and the cyclol **7a** (0.46 g). This mixture was re-chromatographed over silica gel eluting with chloroform to give ***1-benzyl-8-ethoxycarbonyl-8a-hydroxy-1,2,3,5,6,7,8,8a-octahydroimidazo-[1,2-a]pyridin-5-one* 7a** (0.094 g, 15%) as an oil (Found: M^+ 318.1591. $C_{17}H_{22}N_2O_4$ requires *M* 318.1580); δ_H 1.3 (3H, t, *J* 7 Hz, CH_3), 1.9 (1H, br s, OH), 2.1-3.0 (6H, m, CH_2CH_2CO, NCH_2CH_2NCO), 3.7 (1H, t, *J* 7 Hz, CHCO), 3.85 (2H, s, CH_2Ph), 4.0 (2H, t, NCH_2CH_2NCO), 4.3 (2H, q, *J* 7 Hz, CH_2CH_3), 7.4 (5H, m, Ar-H); *m/z* 318 (M^+, 1%), 317 (2), 301 (8), 300 (M^+–H_2O, 40), 299 (17): the rest of the fragmentation pattern was the same as for **5a**. No further material was isolated, indicating that these compounds decompose after prolonged exposure to silica during column chromatography.

Compound **7a** was also prepared by treatment of 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **4** (0.15 g, 0.6 mmol) with ethyl propenoate (0.067 cm^3 g, 0.67 mmol) in ethanol (25 cm^3) at reflux for 24 h. Removal of the solvent under reduced pressure and chromatography of the residue on silica gel eluting with ethyl acetate–triethylamine (99:1 v/v) afforded cyclol **7a** (0.135 g, 70%), identical with material described above. (Yields were variable depending on the length of exposure to silica gel.)

***1-Benzyl-8-ethoxycarbonyl-7-methyl-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridin-5-one* 5b**: prepared by the method A described for **5a**, using (*E*)-2-butenoic acid (0.17 g, 2.0 mmol) and 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **4** (0.46 g, 1.9 mmol). Work-up afforded the *title compound* (0.52 g, 89%) as an oil (Found: M^+ 314.1615. $C_{18}H_{22}N_2O_3$ requires *M* 314.1630); ν_{max}/cm^{-1} (film) 2970, 1660 (C=O), 1580; δ_H 1.05 (3H, d, *J* 8 Hz, $CHCH_3$), 1.2 (3H, t, *J* 7 Hz, CH_2CH_3), 2.4-2.6 (2H, m, CH_2CO), 3.1-3.8 (5H, m, NCH_2CH_2N, $CHCH_3$), 4.1 (2H, q, *J* 7 Hz, CH_2CH_3), 4.7 (2H, 2 x d, CH_2Ph), 7.3 (5H, br s, Ar-H); *m/z* 315 (MH^+, 3%), 314 (M^+, 21), 299 (35), 269 (10), 241 (34), 120 (30), 106 (15), 92 (13), 91 (100).

Column chromatography of the imidazo[1,2-*a*]pyridine **5b** on silica gel eluting with hexane–ethyl acetate (4:6 v/v) afforded 1-benzyl-8-ethoxycarbonyl-8a-hydroxy-7-methyl-1,2,3,5,6,7,8,8a-octahydroimidazo[1,2-*a*]pyridin-5-one **7b** (0.45g, 73%) as an unstable oil that could not be fully characterized; ν_{max}/cm^{-1} (film) 3320, 1725, 1665; δ_H 1.1 (3H, d, *J* 8 Hz, $CHCH_3$), 1.3 (3H, t, *J* 7 Hz, CH_2CH_3), 1.55 (1H, s, OH), 2.3-3.0 (5H, m, NCH_2CH_2NCO, CH_2CO, $CHCH_3$), 3.35 (1H, d, *J* 7 Hz, CHCO), 3.8 (2H, s, CH_2Ph) 4.0 (2H, t, NCH_2CH_2NCO), 4.3 (2H, q, *J* 7 Hz, CH_2CH_3), 7.35 (5H, s, Ar-H); *m/z* 332 (M^+, 1%), 331 (2), 314 (M^+–

H_2O, 12): the rest of the fragmentation pattern was the same as for **5b**.

1-Benzyl-8-ethoxycarbonyl-7-phenyl-1,2,3,5,6,7-hexahydroimidazo[1,2-a]-pyridin-5-one **5c**: prepared by the method A described for **5a**, using 3-phenylpropenoic acid (0.30g, 2.02 mmol) and 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **4** (0.50 g, 2.03 mmol). Work-up afforded the *title compound* (0.75 g, 98%) as an oil (Found: M^+ 376.1775. $C_{23}H_{24}N_2O_3$ requires *M* 376.1787); ν_{max}/cm^{-1} (film) 2980, 1665, 1585, 1380, 1110, 750, 700; δ_H 1.15 (3H, t, *J* 7 Hz, CH_3), 2.95 (2H, d, *J* 8 Hz, CH_2CO), 3.35-3.75 (4H, m, NCH_2CH_2N), 4.15 (2H, q, *J* 7 Hz, CH_2CH_3), 4.45 (1H, t, *J* 8 Hz, CHPh), 4.85 (2H, 2 x d, CH_2Ph), 7.15-7.45 (10H, m, Ar-H); δ_C 14.4, 37.4, 38.0, 40.8, 48.0, 54.3, 59.2, 80.7, 126.1, 126.4, 127.8, 128.2, 128.5, 136.6, 143.0, 152.9, 166.5, 168.5 (one coincidence of signals); *m/z* 376 (M^+, 27%), 304 (16), 303 (67), 299 (5), 285 (7), 105 (8), 92 (9), 91 (100).

1-Benzyl-8-ethoxycarbonyl-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-5-one **6**: prepared by the method A described for **5a**, using propynoic acid (0.142 g, 2.03 mmol) and 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **4** (0.46 g, 1.9 mmol). Work-up afforded a residue that was chromatographed over silica gel eluting with chloroform to afford the *title compound* (0.52 g, 93%) as an oil (Found: M^+ 298.1303. $C_{17}H_{18}N_2O_3$ requires *M* 298.1317); ν_{max}/cm^{-1} (film) 1655, 1535, 1495; δ_H 1.2 (3H, t, *J* 7 Hz, CH_3), 3.5-3.7 (2H, m, NCH_2CH_2N), 3.95-4.3 (4H, m, CH_2CH_3, NCH_2CH_2N), 4.8 (2H, s, CH_2Ph), 5.85 (1H, d, *J* 10 Hz, CH=CHCO), 7.3 (5H, s, Ar-H), 7.85 (1H, d, *J* 10 Hz, CH=CHCO); δ_C 14.3, 42.6, 48.8, 54.2, 60.5, 91.1, 106.7, 127.8, 128.8, 136.0, 143.8, 154.5, 161.8, 164.8 (one coincidence of signals); *m/z* 298 (M^+, 28%), 246 (9), 92 (8), 91 (100).

1-Benzyl-2-(1-ethoxycarbonyl-3-methoxycarbonylprop-2-enylidene)-2,3,4,5-tetrahydroimidazole **8**: A solution of 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **4** (0.40 g, 1.63 mmol) and methyl propynoate (0.145 cm^3, 1.63 mmol) in ethanol (20 cm^3) was stirred at 20°C for 48 h. The solvent was removed under reduced pressure to afford an oil (0.54 g, 100%) which was suspended in hot hexane and chloroform added until solution. On cooling the *title compound* was collected as crystals (0.5 g, 95%), m.p. 101-103°C (Found: M^+ 330.1580. $C_{18}H_{22}N_2O_4$ requires *M* 330.1580); ν_{max}/cm^{-1} (nujol) 2927, 1701, 1663, 1651, 1605, 1589, 1549, 1497; δ_H (400 MHz) 1.28 (3H, t, *J* 6 Hz, CH_2CH_3), 3.4-3.55 (4H, m, NCH_2CH_2N), 3.50 (3H, s, OCH_3), 4.14 (2H, q, *J* 6 Hz, CH_2CH_3), 4.47 (2H, s, CH_2Ph), 5.78 (1H, d, *J* 16 Hz, CH=CHCO), 7.2-7.3 (5H, m, Ar-H), 7.68 (1H, d, *J* 16 Hz, CH=CHCO), 8.46 (1H, br s, NH); δ_C (100 MHz) 14.6, 42.0, 49.0, 50.6, 55.1, 59.5, 78.5, 105.1, 127.5, 127.9, 128.8, 136.2, 141.1, 167.9, 141.0, 141.1; *m/z* 330 (M^+, 1%), 246 (M^+–$C_4H_4O_2$, 47), 201 (22), 173 (37), 91 (100).

1-Benzyl-8-ethoxycarbonyl--7-methyl-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-5-one **9a** **and** ***1-Benzyl-8-ethoxycarbonyl-5-methyl-1,2,3,7-tetrahydroimidazo[1,2-a]pyridin-7-one*** **10**: To 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **4** (2.0 g, 8.1 mmol) in toluene (100 cm^3) were added toluene-4-sulphonic acid (0.2 g, catalytic) and ethyl acetoacetate (1.05 cm^3, 8.24 mmol). The solution was heated at reflux under a Dean and Stark separator for 12 h and the solvent removed under reduced pressure. The residual oil was purified by flash column chromatography on silica gel eluting with dichloromethane–ethanol–aqueous ammonia (300:8:1 v/v/v) to give the *imidazopyridin-7-one* **10** as a white crystalline solid (0.52 g, 21%), m.p. 96-97°C (Found: C, 65.70; H, 6.91; N, 8.56%; M^+ 312.1482. $C_{18}H_{20}N_2O_3.H_2O$ requires C, 65.44; H, 6.71; N, 8.48%; $C_{18}H_{20}N_2O_3$ requires *M* 312.1474); ν_{max}/cm^{-1} 2940, 2880, 1710 (ester C=O), 1640 (NC=O), 1540, 1360, 1225, 1100, 890; λ_{max}/nm 230 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 25 x 10^4); δ_H (250 MHz) 1.14 (3H, t, *J* 7.1 Hz, CH_2CH_3), 2.19 (3H, s, CH_3C=C), 3.55 & 4.03 (4H, 2 x m, NCH_2CH_2N), 4.15 (2H, q, *J* 7.1

Hz, CH_2CH_3), 4.39 (2H, s, CH_2Ph), 5.89 (1H, s, CH), 7.37 (5H, m, Ar-H); δ_C 13.4, 44.3, 47.8, 51.3, 57.1, 60.7, 100.1 (C=CCO_2), 111.4 (CH), 127.2, 127.4 and 128.3 (ArCH), 135.2 (ArC), 143.7, 151.5, 166.7 (CO_2Et), 176.8 (CO keto); *m/z* 312 (M^+, 39%), 267 (M^+–OEt, 33), 266 (26), 239 (94), 119 (21), 91 (100). Further elution gave the *imidazopyridin-5-one* **9a** as a pale yellow solid (2.0 g, 79%), m.p. 70-72°C (Found: M^+ 312.1486. $C_{18}H_{20}N_2O_3$ requires *M* 312.1474); ν_{max}/cm^{-1} 2940, 2880, 1710 (ester C=O), 1645 (NC=O), 1590, 1510, 1370, 1300; λ_{max}/nm 284 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 4.8 x 10^4), 324 (7.2 x 10^4); δ_H 1.15 (3H, t, *J* 7.2 Hz, CH_2CH_3), 2.21 (3H, s, CH_3C=C), 3.60 and 4.15 (each 2H, m, NCH_2), 4.25 (2H, q, *J* 7.2 Hz, CH_2CH_3), 4.43 (2H, s, CH_2Ph), 5.80 (1H, s, CH), 7.35 (5H, m, Ar-H); δ_C 13.6, 41.8, 48.4, 52.5, 57.2, 60.4, 92.6 (C=CCO_2), 107.2 (CH), 126.9, 127.4 and 128.3 (ArCH), 135.1 (ArC), 151.0, 151.5, 160.0 (NCO), 166.3 (CO_2Et); *m/z* 312 (M^+, 14%), 246 (20), 201 (8), 173 (11), 92 (8), 91 (100).

The imidazopyridin-5-one **9a** was also observed using the method described above, using ethyl 3-methoxy-2-butenoate **11** (1.2 g, 8.0 mmol) instead of ethyl acetoacetate, and heating at reflux for 24 h. Purification of the residual oil by column chromatography on silica gel eluting with chloroform–ethanol (50:1 v/v) gave compound **9a** in a mixed fraction with unchanged enaminoester **4**, that was not further separated.

***1-Benzyl-8-ethoxycarbonyl-7-phenyl-1,2,3,5-tetrahydroimidazol[1,2-a]pyridin-5-one* 9b**: To 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **4** (2.03 g, 8.1 mmol) in toluene (100 cm^3) was added toluene-4-sulphonic acid (0.2 g, catalytic) and ethyl benzoylacetate (1.4 cm^3, 8.1 mmol). The solution was heated at reflux under a Dean and Stark separator for 12 h and the solvent was removed under reduced pressure. The residual oil (4.3 g) was purified by flash chromatography eluting with chloroform to give the *title compound* as a clear oil (2.2 g, 72%) (Found: M^+ 374.1630. $C_{23}H_{22}N_2O_3$ requires *M* 374.1630); ν_{max}/cm^{-1} (film) 3061, 2983, 1704 (C=O ester), 1652 (NC=O), 1587, 1572, 1531, 1497; λ_{max}/nm (CH_3CN) 284 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 6.8 x 10^3), 335 (8.1 x 10^3); δ_H (400 MHz) 0.55 (3H, t, *J* 8 Hz, CH_3), 3.55 (2H, q, *J* 8 Hz, CH_2CH_3), 3.60 and 4.10 (each 2H, t, *J* 9 Hz, NCH_2), 4.48 (2H, s, CH_2Ph), 5.78 (1H, s, CH), 7.15-7.3 (10H, br s, Ar-H); δ_C (100 MHz) 13.1, 42.2, 48.9, 52.2, 61.0, 93.2 (C=CCO_2), 107.9 (CH), 126.9, 127.5, 127.9, 128.0, 128.1 and 128.8 (ArCH), 135.4 and 140.1 (ArC), 150.4, 155.4, 160.3 (NCO), 167.0 (CO_2Et); *m/z* 374 (M^+, 36%), 329 (5), 301 (9), 92 (10), 91 (100).

***1-Benzyl-8-ethoxycarbonyl-7-methyl-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine* 12a**: 1-Benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **4** (0.30 g, 1.2 mmol) and (*E*)-2-butenal (0.12 cm^3, 1.4 mmol) were heated together in acetonitrile (25 cm^3) at reflux for 24 h. After cooling, the solvent was removed under reduced pressure and the dark yellow oil purified by flash colum chromatography eluting with dichloromethane–ethanol–aqueous ammonia (300:8:1 v/v/v) to give the *title compound* (0.19 g, 53%). Purification by kugelrohr distillation (bulb temperatue 250°C, 2 mmHg) instead of chromatography increased the yield to 62% (Found: M^+–Me 283.1440. $C_{18}H_{22}N_2O_2$ requires *M*–Me 283.1447); ν_{max}/cm^{-1} 2900, 2850, 1665 (C=O), 1640 (NC=C), 1535, 1425, 1270, 1175, 1110; δ_H 1.00 (3H, d, *J* 8 Hz, $CHCH_3$), 1.20 (3H, t, *J* 7 Hz, CH_2CH_3), 3.3-3.8 (5H, m, NCH_2CH_2N and $CHCH_3$), 4.15 (2H, q, *J* 7 Hz, CH_2CH_3), 4.65 and 4.80 (each 1H, d, *J* 16 Hz, CH_aH_bPh), 5.15 (1H, t, *J* 8 Hz, NCH=C*H*), 6.0 (1H, d, *J* 8 Hz, NC*H*=CH), 7.45 (5H, m, Ar-H); δ_C 14.5, 23.4, 28.7, 46.2, 48.3, 55.1, 58.4, 77.5, 111.2, 124.1, 127.0, 128.0, 128.2, 137.6, 157.6, 166.7; *m/z* (M^+ not observed) 284 (3%), 283 (M^+–Me, 13), 136 (65), 119 (59), 92 (18), 91 (100).

***1-Benzyl-8-ethoxycarbonyl-6,7-dimethyl-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine* 12b**: prepared by the method described for **12a**, using 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **4** (0.50 g, 2.0 mmol), (*E*)-2-methyl-2-butenal (0.14 cm^3, 2.4 mmol) and heating in dioxan (25 cm^3) at reflux for

24 h, to afford the *title compound* (0.20 g, 32%) as a yellow oil (Found: M^+ 312.1840. $C_{19}H_{24}N_2O_2$ requires *M* 312.1838); ν_{max}/cm^{-1} 2940, 2860, 1660 (br, C=O and NC=C), 1550, 1430, 1285, 1110; δ_H 1.00 (3H, d, *J* 6 Hz, $CHCH_3$), 1.20 (3H, t, *J* 7 Hz, CH_2CH_3), 1.80 (3H, s, $C=CCH_3$), 3.3-3.8 (5H, m, NCH_2CH_2N and $CHCH_3$), 4.15 (2H, q, *J* 7 Hz, CH_2CH_3), 4.60 and 4.80 (each 1H, d, *J* 13 Hz, CH_aH_bPh), 5.80 (1H, s, C=CH), 7.40 (5H, m, Ar-H); δ_C 14.5, 17.8, 20.4, 34.1, 46.2, 48.5, 55.1, 58.3, 76.2, 119.4, 120.1, 126.9, 127.9, 128.0, 137.7, 157.6, 166.6; *m/z* 312 (M^+, 7%), 298 (31), 297 (M^+–Me, 100), 267 (12), 134 (23), 91 (54).

***1-Benzyl-8-ethoxycarbonyl-6-methyl-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine* 12c**: prepared by the method described for **12a**, using 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **4** (0.50 g, 2.0 mmol), 2-methylpropenal (0.17 cm^3, 2.0 mmol) and heating in dioxan (25 cm^3) at reflux for 96 h, to afford the *title compound* (0.19 g, 32%) as a yellow oil (Found: M^+ 298.1666. $C_{18}H_{22}N_2O_2$ requires *M* 298.1681); ν_{max}/cm^{-1} 2940, 2880, 1665 (C=O), 1645 (NC=C), 1540, 1450, 1180, 1110; δ_H 1.20 (3H, t, *J* 7 Hz, CH_2CH_3), 1.75 (3H, s, $C=CCH_3$), 3.2-3.45 (4H, m, NCH_2CH_2N), 3.7 (2H, s, $C=CCH_2$), 4.15 (2H, q, *J* 7 Hz, CH_2CH_3), 4.80 (2H, s, CH_2Ph), 6.45 (1H, s, C=CH), 7.40 (5H, m, Ar-H); *m/z* 298 (M^+, 35%), 297 (47), 269 (14), 253 (15), 176 (17), 134 (16), 133 (18), 132 (38), 125 (12), 120 (15), 92 (20), 91 (100).

***1-Benzyl-8-ethoxycarbonyl-7-phenyl-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine* 12d**: To 1-benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **4** (0.50 g, 2.0 mmol) and (*E*)-3-phenylpropenal (0.30 cm^3, 2.4 mmol) in dioxane (25 cm^3) were added powdered 4Å molecular sieves (1 g, activated at 180°C for 72 h) and the mixture was heated at reflux for 72 h. Removal of the solvent under reduced pressure gave a dark oil which was purified by flash column chromatography eluting with dichloromethane–ethanol–aqueous ammonia (300:8:1 v/v/v) to give the *title compound* (0.20 g, 27%) as a brown oil (Found: M^+ 360.1832. $C_{23}H_{24}N_2O_2$ requires *M* 360.1838); ν_{max}/cm^{-1} 2940, 2860, 1665 (C=O), 1640 (NC=C), 1530, 1090; δ_H 1.20 (3H, t, *J* 7 Hz, CH_2CH_3), 3.50 (4H, m, NCH_2CH_2N), 4.15 (2H, q, *J* 7 Hz, CH_2CH_3), 4.70 (1H, d, *J* 8 Hz, CHPh), 4.75 (2H, s, CH_2Ph), 5.35 (1H, t, *J* 8 Hz, NCH=CH), 6.15 (1H, d, *J* 8 Hz, NCH=CH), 7.40 (10H, m, Ar-H); δ_C 14.6, 39.5, 46.4, 48.2, 55.2, 58.8, 76.6, 109.4, 124.9, 125.7, 127.2, 128.0, 128.3, 137.5, 148.0, 157.6, 166.8; *m/z* 360 (M^+, 11%), 287 (M^+-CO_2Et), 283 (M^+-Ph, 100), 269 (M^+-CH_2Ph, 29), 195 (16), 147 (7), 120 (15), 91 (77).

***1-Benzyl-2-[4-ethoxycarbonyl-2-formylcyclohexen-4-yl]-4,5-dihydroimidazole* 13**: 1-Benzyl-2-(ethoxycarbonylmethylene)-2,3,4,5-tetrahydroimidazole **4** (0.50 g, 2.0 mmol) and propenal (0.163 cm^3, 2.4 mmol) were heated together in acetonitrile at reflux for 4 h. After removal of the solvent under reduced pressure the residual oil was purified by flash column chromatography eluting with dichloromethane–ethanol–aqueous ammonia (300:8:1 v/v/v) to give the *title compound* (0.41 g, 60% based on **4**) as a colourless oil (Found: M^+ 340.1783. $C_{20}H_{24}N_2O_3$ requires *M* 340.1787); ν_{max}/cm^{-1} 2950, 2880, 2850, 1730 (ester C=O), 1680 (C=O), 1600, 1390, 1170, 920; δ_H (250 MHz) 1.27 (3H, t, *J* 7.1 Hz, CH_2CH_3), 2.32 (3H, m, CH_2CCO_2 and $CH_aH_bCH_2CH$=C), 2.62 (1H, m, $CH_aH_bCH_2CH$=C), 2.80 (2H, m, CH_2CH=C), 3.14 and 3.72 (each 2H, m, NCH_2CH_2N), 4.22 (2H, q, *J* 7.1 Hz, CH_2CH_3), 4.25 (2H, s, CH_2Ph), 6.81 (1H, dd, *J* 5.7, 3.5 Hz, CH=C), 7.30 (5H, m, Ar-H), 9.48 (1H, s, CH=O); δ_C 13.5, 17.8, 23.3, 28.2, 28.5, 45.7, 50.9, 51.5, 51.6, 56.8, 61.0, 126.6, 126.8, 128.0, 136.9, 138.2, 148.3, 164.7, 172.5, 192.2 (C=O); *m/z* 340 (M^+, 15%), 311 (M^+–CHO, 15%), 312 (12), 311 (M^+-Et, 32), 268 (14), 267 (69), and 91 (100). The NMR assignments were confirmed by ^1H–^1H and ^1H–^{13}C correlation spectroscopy.

***1-Benzyl-7-ethoxycarbonyl-1,2,3,6-tetrahydro-5H-pyrrolo[1,2-a]imidazole-5,6-dione* 16**: Diethyl oxalate (1.1 cm^3, 8.1 mmol) and toluene-4-sulphonic acid (10 mg, catalytic) were added to 1-benzyl-2-

(ethoxycarbonylmethylene)-2,3,4,5-tetrahydromidazole **4** (2.0 g, 8.1 mmol) in toluene (100 cm^3) and the solution was heated at reflux under a Dean and Stark separator for 24 h. The solvent was removed under reduced pressure and the residual oil purified by flash column chromatography on silica gel eluting with chloroform → chloroform–ethanol (300:8 v/v) to give the *title compound* as a yellow solid (1.5 g, 50%), m.p. 154-156°C (decomp.) (Found: C, 63.95; H, 5.75; N, 9.22%. $C_{16}H_{16}N_2O_4$ requires C, 63.99; H, 5.37; N, 9.33%); ν_{max}/cm^{-1} (nujol) 1751 and 1675 (C=O), 1617, 1483, 1456, 1409, 1377; λ_{max}/nm 248 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 1.86 x 10^4), 348 (4.0 x 10^3); δ_H (400 MHz) 1.24 (3H, t, CH_2CH_3), 3.82 and 3.93 (each 2H, m, CH_2N), 4.20 (2H, q, CH_2CH_3), 5.40 (2H, s, CH_2Ph), 7.2-7.35 (5H, m, Ar-H); δ_C (100 MHz) 14.1, 37.8, 52.0, 53.3, 59.7, 86.5, 128.0, 128.4, 128.9, 133.6, 157.9, 162.4, 165.4, 177.0; *m/z* 300 (M^+, 4%), 272 (M^+–CO, 4), 254 (M^+–CO–CO, 6), and 91 (100). When the reaction was interrupted after 12 h, a yellow oil was isolated (0.8 g, 28%) and partially identified as 1-benzyl-2-(ethoxycarbonylmethylene)-3-ethoxycarbonyloxy-2,3,4,5-tetrahydroimidazole **15**; ν_{max}/cm^{-1} (film) 2936, 1761 and 1673 (C=O), 1608, 1456, 1355, 1115; λ_{max}/nm 244 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 1.06 x 10^4), 270 (1.05 x 10^4), 348 (1.5 x 10^3); δ_H (250 MHz) 1.3 (6H, m, 2 x CH_2CH_3), 3.45 and 4.15 (10H, m, 2 x CH_2N, 2 x OCH_2CH_3, CH_2Ph), 5.5 (1H, s, C=CH), 7.30 (5H, s, Ar-H).

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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 For an alternative solution in 2-benzylic cases: Dalko, P. I.; Langlois, Y. *Chem. Commun.* **1988**, 331-332.

3 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.

4 See, for example: Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 619-636, & refs. therein.

5 For preliminary reports of part of this work, see: (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.

6 Jones, R. C. F.; Patel, P.; Hirst, S. C.; Turner, I. *Tetrahedron* **1997**, *53*, 11781-11790.

7 Yu, C.-L.; Wang, L.-B.; Li, W.-Y.; Huang, Z.-T. *Synthesis* **1996**, 959-962, & refs. therein.

8 Brunerie, P.; Célérier, J.; Huché, M.; Lhommet, G. *Synthesis* **1985**, 735-738.

9 Shemyakin, M. M.; Antonov, V. K.; Shkrob, A. M.; Shchelokov, V. I.; Agadzhanyan, Z. E. *Tetrahedron* **1965**, *21*, 3537-3572.

10 Huang, Z.-T.; Wang, M.-X. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1085-1090.

11 Huang, Z.-T.; Tzai, L.-H. *Chem. Ber.* **1986**, *119*, 2208-2219.

12 Magatti, C. V.; Villani, F. J. *J. Heterocyclic Chem.* **1978**, *15*, 1021-1023.

13 Jones, R. C. F.; Hirst, S. C. *Tetrahedron Lett.* **1989**, *30*, 5365-5368; Jones, R. C. F.; Turner, I.; Howard, K. J. *Tetrahedron Lett.* **1993**, *39*, 6329-6332.