Aza-annulation of enaminones with itaconic anhydride: kinetic preference for exocyclic enamide products

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Enaminones react with itaconic anhydride in methylene chloride at room temperature to give exocyclic enamides as the major products. These can be readily equilibrated to the thermodynamically more stable endocyclic enamides. In substrates where the exocyclic isomer could not be formed only intractable materials were produced from this reaction. An intermediate in this two step process was detected and identified by proton and ^{13}C NMR spectroscopy. In two cases chiral enaminones were employed and the relative stereochemistry at the new chiral centre in the product was established by a crystal structure of compound **27**.

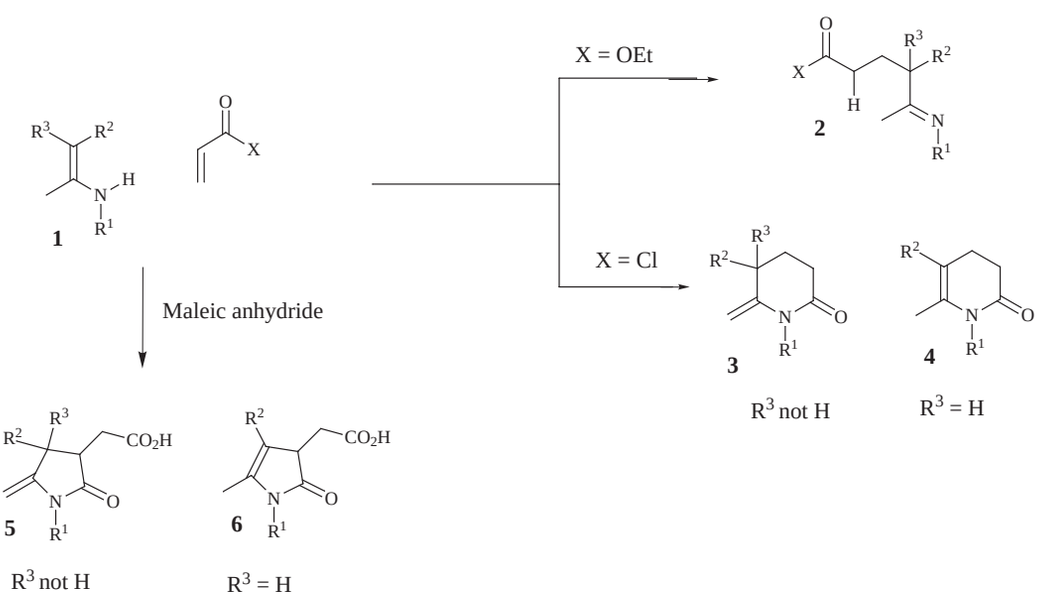
Introduction

There has recently been intense interest in the reaction of enaminones with acrylates for the construction of quaternary chiral centres[1] **1**→**2** (X = OEt) and with activated acrylates (X = halide, azide, acetate) for the synthesis of polyalkyl substituted piperidinones[2] (**1**→**3** or **4** Scheme 1). It is now certain that the formal 1,2-addition reaction **1**→**2** is proceeding *via* an aza-ene-type mechanism where the new carbon–carbon and carbon–hydrogen bonds are formed in a concerted process.[3] This opens possibilities for the control of relative stereochemistry in the proton transfer. There has been debate as to whether or not aza-annulation (**1**→**4**, Scheme 1) is simply an extension of 1,2-addition, with imine **2** being the key intermediate in the formation of piperidinones **3** and **4**. In general, this simple view does not explain a number of factors observed in the aza-annulation reaction **1**→**4**,[4] and other mechanisms based on Diels–Alder cycloaddition[5] and 3-aza-Cope rearrangement[6] have been proposed.

Endocyclic α,β-unsaturated cyclic anhydrides have also proved to be useful partners for aza-annulation[7] (**1**→**5** or **6**, Scheme 1), with asymmetric examples recently being reported.[8] With the exception of pyrrolidin-2-ylideneacetates, the reaction of enaminones with exocyclic α,β-unsaturated anhydrides has been an underdeveloped area.[9]

Results and discussion

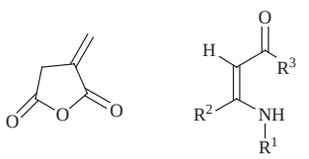
We now report our findings on the reaction of simple acyclic enaminones **7**–**13** with itaconic anhydride (2-methylene-succinic anhydride) which gave the unprecedented β,γ-unsaturated carbonyl compounds **14** –**16** as the kinetic products (Scheme 2, Table 1). Enaminones **7**–**11** were readily available by condensation of primary amines with the corresponding 1,3-dicarbonyl compounds. Enaminones **12** and **13** were prepared by reaction of benzylamine with methyl propiolate and 4-methoxybut-3-en-2-one, respectively. Due to intramolecular hydrogen-bonding between the carbonyl and NH groups the stereochemistry of the enaminones is predominantly *cis*. Reaction of enaminone **7** with itaconic anhydride proceeded smoothly at 25 °C in methylene chloride and gave after 40 min a 5 : 1 mixture of cyclic compounds **14** and **19**. The most remarkable aspect of this reaction is that the major isomer is the thermodynamically less stable β,γ-unsaturated carbonyl compound with the double bond outside the ring. The absence of a methyl signal and the presence of an olefinic methylene group



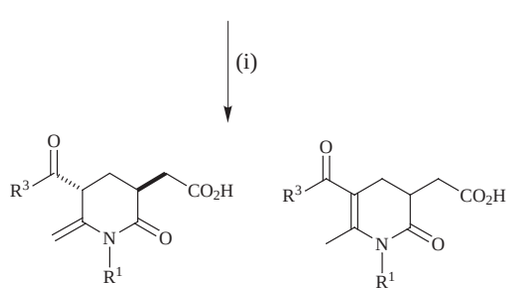
Scheme 1

Table 1 Reaction of **7**–**13** with itaconic anhydride

Substrate	R^1	R^2	R^3	*t*/h	Ratio *endo*:*exo*	Yield (%)
7	Bn	Me	OEt	0.75	5:1	60
8	$BnCH_2$	Me	OEt	0.75	5:1	67
9	Bu	Me	OEt	0.75	5:1	73
10	Bn	Me	Me	10	2:1	57
11	Bn	Me	Ph	10	1:0	82
12	Bn	H	OEt	10	—	0
13	Bn	H	Me	10	—	0



7 R^1 = Bn, R^2 = Me, R^3 = OEt
8 R^1 = $BnCH_2$, R^2 = Me, R^3 = OEt
9 R^1 = Bu, R^2 = Me, R^3 = OEt
10 R^1 = Bn, R^2 = Me, R^3 = Me
11 R^1 = Bn, R^2 = Me, R^3 = Ph
12 R^1 = Bn, R^2 = H, R^3 = OEt
13 R^1 = Bn, R^2 = H, R^3 = Me



14 R^1 = Bn, R^3 = OEt
15 R^1 = $BnCH_2$, R^3 = OEt
16 R^1 = Bu, R^3 = OEt
17 R^1 = Bn, R^3 = Me
18 R^1 = Bn, R^3 = Ph

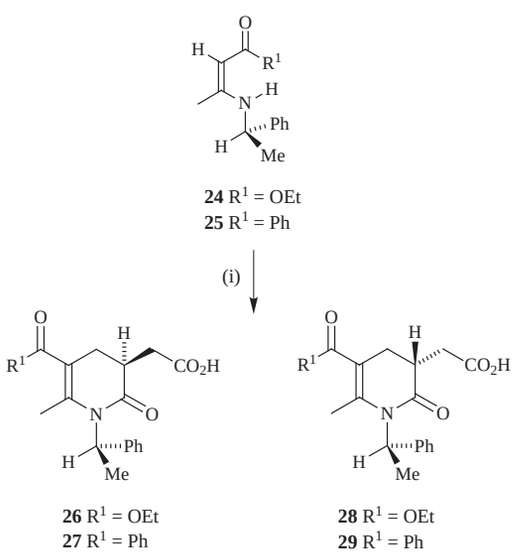
19 R^1 = Bn, R^3 = OEt
20 R^1 = $BnCH_2$, R^3 = OEt
21 R^1 = Bu, R^3 = OEt
22 R^1 = Bn, R^3 = Me
23 R^1 = Bn, R^3 = Ph

Scheme 2 *Reagents and conditions*: (i) methylene chloride, room temperature.

at δ 4.32 and 4.45 in the ^{1}H NMR spectrum was a key feature in assigning the structure **14**. This appears to be the first example of an aza-annulation reaction on an enaminone bearing a hydrogen atom α to the electron withdrawing group in which the β,γ-unsaturated isomer is observed as the major isomer. Careful analysis of the proton NMR spectrum of **14**, particularly the coupling constants, revealed that this was exclusively the *trans* diastereoisomer as shown. The coupling constants J_{ax}, J_{bx} and J_{ay}, J_{by} for $EtCO_2CH^xCH^aH^bCH^y$ were 5.8, 2.2, 13.2 and 5.0 Hz respectively. These coupling constants were readily extracted from multiplets H^a and H^b and confirmed by decoupling protons H^x and H^y. This confirmed that H^y was axial and H^x was equatorial, with the ethoxycarbonyl group occupying the axial position. Allylic 1,3-strain from the hydrogens on the adjacent alkene to the ethoxycarbonyl group is minimised when the ethoxycarbonyl group is axial, so the *trans*-diastereoisomer is probably thermodynamically more stable than the *cis*-diastereoisomer in this case.[10]

It proved impossible to separate exocyclic isomers **14**–**16** from **19**–**21** by flash chromatography. In order to fully characterise these compounds, derivatives were sought. Ozonolysis gave the corresponding cyclic imides but unfortunately 1:1 mixtures of *cis* and *trans* diastereoisomers resulted and this was not pursued further. The exocyclic isomers **14**–**16** are stable at room temperature but thermally isomerise to the thermodynamically more stable endocyclic α,β-unsaturated esters **19**–**21** after refluxing in toluene for 30 min. All new compounds were fully characterised as the endocyclic isomers **19**–**23** after thermal equilibration. With ketone substrate **10** the products **17** and **22** are much more prone to equilibrate at room temperature, hence the poorer ratio of exo- to endo-cyclic isomers. This reflects the greater acidity of ketones relative to esters. Phenyl ketone substrate **11** gave only the endocyclic isomer **23** on completion of the reaction. However, when the reaction was monitored by proton NMR spectroscopy it was revealed that after 10% consumption of starting enaminone **11** the ratio of **18**:**23** was 4:1, clearly showing that **18** is the kinetic product of this reaction. With enaminone substrates **12** and **13**, where it was not possible to get exocyclic enamide products; reaction with itaconic anhydride gave only intractable products after 2 h at room temperature.

Reaction of chiral enaminone **24**, derived from (*R*)-(+)-α-methylbenzylamine, with itaconic anhydride proceeded over 24 h at 25 °C (Scheme 3) and gave a complex mixture of products.



24 R^1 = OEt
25 R^1 = Ph

26 R^1 = OEt
27 R^1 = Ph

28 R^1 = OEt
29 R^1 = Ph

Scheme 3 *Reagents and conditions*: (i) itaconic anhydride, methylene chloride, room temperature.

Thermal isomerisation of this mixture by boiling in toluene gave a 4.9:1 inseparable mixture of diastereoisomers **26**:**28** in 81% overall yield. In the case of substrate **25,** a 5.6:1 mixture of diastereoisomers **27**:**29** resulted, but this time the major isomer **27** was separated and purified by a single crystallisation in 48% yield. The relative configuration of the major diasteroisomer **27** was determined by X-ray crystallography (Fig. 1) and was found to be (7*R*,3*S*) using the numbering from Fig. 1. Although chiral enaminones are well known to participate in face selective reactions,[1] in this case the new chiral centre was created in the proton transfer step. The reasonable levels of 1,4-asymmetric induction observed in this reaction (formally 1,6-asymmetric induction) is further evidence of a highly ordered

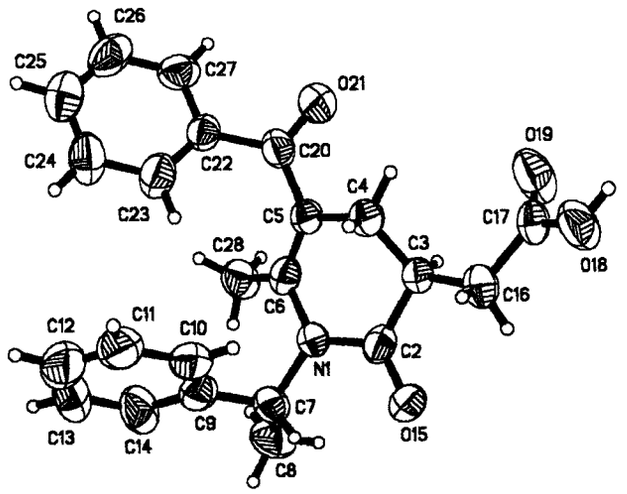
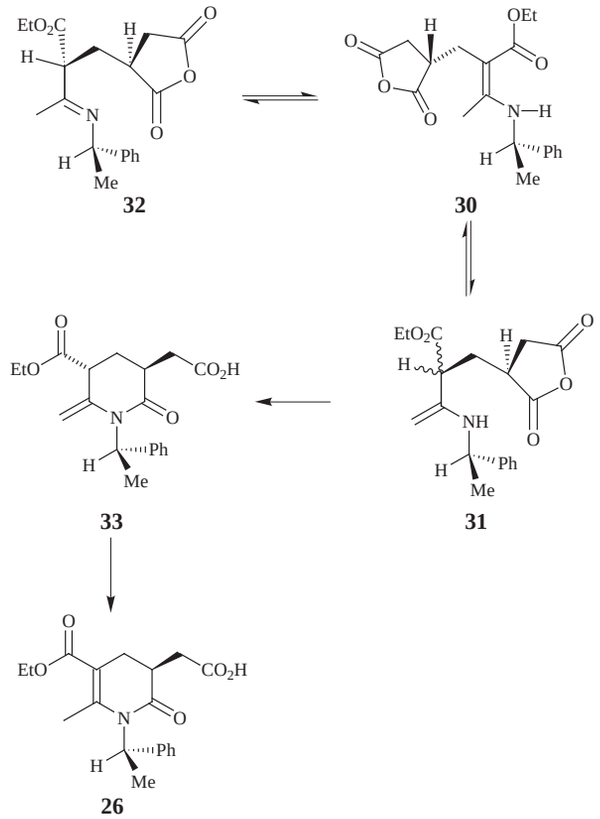


Fig. 1 X-Ray crystal structure of major diastereoisomer **27** depicting absolute stereochemistry at C7 and C3.

transition state for this step. The absolute stereochemistry at C3 is consistent with approach of the anhydride to the top face of enaminone **25** (shielded by the methyl group in the conformation depicted), with the nitrogen and conjugated carbonyl group of the anhydride *syn*, with concerted transfer of the hydrogen from the nitrogen to C3, *i.e.* d'Angelo's model for 1,2 addition.[11]

In order to gain further insight, the reaction of enaminone **7** with itaconic anhydride was conducted in deuteriochloroform at room temperature and monitored by proton NMR spectroscopy. After 10 min products **14** and **19** were detected (10% conversion, ratio 5 : 1), along with an intermediate. The concentration of the intermediate reached a steady-state of 15% and after 40 min it had been totally consumed. Due to the low concentration of this compound, and the extensive overlap in the proton NMR spectrum, it was not possible to unambiguously identify this compound. However, it did establish that the cyclisation reaction was slower that the initial addition reaction. When the same reaction was carried out with the more sterically hindered enaminone **24**, after 1 h, all the starting material was consumed and an intermediate compound had built up to 85%. This intermediate was readily assigned structure **30** from its proton and ^{13}C NMR spectra (Scheme 4) *i.e.* the formal product of 1,2-addition **32** followed by tautomerisation. Only one set of signals is observed in the ^{13}C NMR spectrum of intermediate **30**. This compound is definitely a single stereoisomer with respect to double bond stereochemistry, but must be a 4.9 : 1 mixture of diastereoisomers with respect to the two chiral centres present. The most likely explanation for this is that the chemical shifts for the two diastereoisomers are coincident, due to the distance between the two chiral centres. The high chemical shift value of the proton attached to the nitrogen atom, δ 10.0, is consistent with a strong intramolecular hydrogen bond to the ester carbonyl group, supporting (*E*)-stereochemistry of the enaminone **30**. This stereochemistry is incorrect for the subsequent lactamisation. Either tautomeric forms **31** or **32** is capable of interconverting *E* to *Z* stereochemistry of the enaminone **30**, or themselves cyclising onto the anhydride carbonyl group. Since these reactions only proceed when there is an alkyl group attached to the carbon next to the nitrogen, and due to the exocyclic alkene nature of products, it seems likely that diastereoisomeric enamine tautomers **31** (not observed by NMR spectroscopy) are likely intermediates in these reactions.

In conclusion, the direct spectroscopic observation of intermediate enaminone **30** and the good correlation of relative stereochemistry of aza-annulation with 1,2-addition, confirms that the first stage of aza-annulation with itaconic anhydride involves formal 1,2-addition. Itaconic anhydride as a heterodiene is locked in an s-*cis* conformation and as such is ideally



Scheme 4

predisposed to Diels–Alder chemistry. If a Diels–Alder-type mechanism is not operating in this case, it seems it would be even less likely to operate with an acyclic s-*trans*-anhydride.

Experimental

General

Melting points were recorded using a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 983G instrument coupled to a Perkin-Elmer 3700 Data Station as potassium bromide (KBr) disks, or films (liquids). ^{1}H nuclear magnetic resonance (NMR) spectra were recorded at 300 and 500 MHz using General Electric QE 300, Bruker DPX 300 and DRX 500 NMR spectrometers. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard, and coupling constants (J) are given in Hz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Mass spectra were recorded using a Double Focusing Triple Sector VG Auto Spec and accurate molecular masses were determined by the peak matching method using perfluorokerosene as standard reference and were accurate to within ±0.006 amu. Microanalyses were obtained using a Perkin-Elmer 2400 CHN elemental analyser. Optical rotations were determined on a Perkin-Elmer precision polarimeter Model 241, using specified solvent and concentration at the sodium D-line (589 nm) and at ambient temperature.

Analytical TLC was carried out on Merck Kieselgel 60_{254} plates and the spots visualised using a Hanovia Chromatolite UV lamp. Flash chromatography was effected using Merck Kieselgel 60 (230–400 mesh). Enaminones **7**–**11** and **24**–**25** were made by the literature methods[1] by condensing a 1,3-dicarbonyl compound with a primary amine with azeotropic removal of water. Enaminones **12**–**13** were made by adding benzylamine to solutions of methyl propiolate and 4-methoxybut-3-en-2-one respectively in methylene chloride at room temperature.

Aza-annulation general procedures

Procedure A. Itaconic anhydride (0.5 g, 4.5 mmol) was added to a solution of enaminone (4.5 mmol) in methylene chloride (25 ml) and this was stirred at room temperature for the time indicated in Table 1. Concentration, followed by flash chromatography, gave the desired compounds. Proton NMR data only is given for the exocyclic enamide products, which could not be separated from the corresponding endocyclic isomer.

Procedure B. Repetition of the above procedure with refluxing of the crude product in boiling toluene (20 ml) for 30 min, followed by concentration and flash chromatography, gave endocyclic products only.

With both procedures, the solvents for which the R_f values are quoted are those that were used for the flash chromatography.

1-Benzyl-5-carboxymethyl-2-methylene-6-oxopiperidine-3-carboxylic acid ethyl ester 14

General procedure A with enaminone **7** gave the titled compound **14** (0.88 g, 60%) as a colourless oil, R_f 0.66 (ethyl acetate), δ_H($CDCl_3$, 500 MHz) 1.23 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 2.0 (1H, td, *J* 13.2, 5.0, NCOCHCH*H*), 2.31 (1H, ddd, *J* 13.2, 5.1, 2.2, NCOCHC*H*HC), 2.78 (1H, dd, *J* 17.1, 5.8, CHC*H*HCO$_2$H), 2.85 (1H, dd, *J* 17.1, 6.2, CHCH*H*CO$_2$H), 3.10 (1H, m, C*H*CH$_2$CO$_2$H), 3.59 (1H, m, C*H*CO$_2$Et), 4.17 (2H, q, *J* 7.1, CH$_3$C*H*$_2$O), 4.32 (1H, d, *J* 1.4, =C*H*H), 4.45 (1H, d, *J* 1.4, =CH*H*), 4.89 (1H, d, *J* 16, PhC*H*H), 5.08 (1H, d, *J* 16, PhCH*H*), 7.20 (5H, m, Ar*H*).

1-Benzyl-5-carboxymethyl-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester 19

General procedure B gave titled compound **19** (0.95 g, 64%) as a white solid, R_f 0.66 (ethyl acetate), mp 93.0–94.5 °C (from EtOH) (Found C, 65.2; H, 6.5; N, 4.4; $C_{18}H_{21}NO_5$ requires C, 65.2; H, 6.4; N, 4.2%); ν_{max}(KBr)/cm^{-1} 1704.8, 1678.5, 1625.5; δ_H($CDCl_3$, 500 MHz) 1.20 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 2.28 (3H, s, C*H*$_3$C=), 2.34 (1H, t, *J* 16.5, =CC*H*HCH), 2.47 (1H, dd, *J* 16.5, 5.8, =CCH*H*CH), 2.81 (1H, dd, *J* 16.0, 6.0, CHC*H*HCO$_2$H), 2.84–2.96 (2 × 1H, m, C*H*CH*H*CO$_2$H), 4.10 (2H, q, *J* 7.1, CH$_3$C*H*$_2$O), 4.69 (1H, d, *J* 16.4, PhC*H*H), 5.16 (1H, d, *J* 16.4, PhCH*H*), 7.03–7.20 (5H, m, Ar*H*); δ_C($CDCl_3$, 125.758 MHz) 13.25 (*C*H$_3$CH$_2$), 15.41 (*C*H$_3$C6), 24.82 (*C*4), 32.71 (*C*H$_2$CO$_2$H), 35.82 (*C*5), 44.48 (N*C*H$_2$Ph), 59.49 (*C*H$_2$O), 108.09 (*C*3), 125.31, 126.66, 127.82 (*C*H$_{ar}$), 136.26 (*C*$_{ar}$), 147.13 (*C*2), 166.19 (*C*O$_2$Et), 171.26 (N*C*O), 176.12 (*C*O$_2$H); *m*/*z* 331 (M$^+$, 55%), 272 (12), 91 (100).

5-Carboxymethyl-2-methylene-6-oxo-1-phenethylpiperidine-3-carboxylic acid ethyl ester 15

General procedure A with enaminone **8** gave the titled compound (1.03 g, 67%) as a colourless oil, R_f 0.63 (ethyl acetate), δ_H($CDCl_3$, 300 MHz) 1.30 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 1.93 (1H, dt, *J* 13.1, 4.9, CHC*H*HCH), 2.32 (1H, ddd, *J* 13.1, 5.7, 2.9, CHCH*H*CH), 2.62 (1H, dd, *J* 16.7, 6.0, C*H*HCO$_2$H), 2.75–3.05 (4 × 1H, 4 × m, C*H*CH*H*CO$_2$H, PhC*H*$_2$CH$_2$), 3.58 (1H, dd, *J* 4.9, 2.9, EtO$_2$CC*H*CH$_2$), 3.94 (2H, m, PhCH$_2$C*H*$_2$N), 4.18 (2H, q, *J* 7.1, CH$_3$C*H*$_2$O), 4.42 (1H, d, *J* 1.5, =C*H*H), 4.62 (1H, d, *J* 1.5, =CH*H*), 7.09–7.24 (5H, m, Ar*H*).

5-Carboxymethyl-2-methyl-6-oxo-1-phenethyl-1,4,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester 20

General procedure B with enaminone **8** gave the titled compound (1.2 g, 78%) as a yellow solid, R_f 0.66 (ethyl acetate), mp 134–135 °C (from EtOH) (Found: C, 65.8, H; 6.6; N, 4.1. $C_{19}H_{23}NO_5$ requires C, 66.1; H, 6.7; N, 4.1%); ν_{max}(KBr)/cm^{-1} 1712.1, 1694.6, 1674.6, 1613.4; δ_H($CDCl_3$, 300 MHz) 1.20 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 2.12 (1H, t, *J* 15.4, C*H*HCH), 2.31 (4H, m, C*H*$_3$C=, CH*H*CH), 2.67–2.84 (5H, m, C*H*CH$_2$CO$_2$H, PhC*H*$_2$), 3.66 (1H, ddd, *J* 14.2, 9.3, 6.5, C*H*HN), 4.03 (1H, ddd, *J* 14.2, 9.0, 5.9, CH*H*N), 4.1 (2H, q, *J* 7.1, CH$_3$C*H*$_2$O), 7.09–7.24 (5H, m, Ar*H*), 9.9 (1H, br, CO$_2$*H*); δ_C($CDCl_3$, 125.758 MHz) 13.29 (*C*H$_3$CH$_2$O), 15.20 (*C*H$_3$C2), 26.12 (*C*4), 33.94 (*C*H$_2$CO$_2$H), 34.39 (*C*5), 35.71 (Ph*C*H$_2$), 42.94 (N*C*H$_2$), 59.45 (*C*H$_2$O), 108.1 (*C*3), 125.84, 127.54, 127.82 (*C*H$_{Ar}$), 137.11 (*C*$_{Ar}$), 146.67 (*C*2), 166.20 (*C*O$_2$Et), 170.82 (N*C*O), 176.25 (*C*O$_2$H); *m*/*z* 345 (M$^+$, 26%), 286 (67), 105 (100), 91 (96).

1-Butyl-5-carboxymethyl-2-methylene-6-oxopiperidine-3-carboxylic acid ethyl ester 16

General procedure A with enaminone **9** gave the titled compound **16** (0.97 g, 73%) as a colourless oil, R_f 0.6 (ethyl acetate), δ_H($CDCl_3$, 300 MHz) 0.95 (3H, m, C*H*$_3$CH$_2$CH$_2$), 1.26 (5H, m, CH$_3$C*H*$_2$CH$_2$, C*H*$_3$CH$_2$O), 1.55 (2H, m, C*H*$_2$CH$_2$N), 1.93 (1H, dt, *J* 13.1, 4.9, CHC*H*HCH), 2.32 (1H, ddd, *J* 13.1, 5.8, 2.1, CHCH*H*CH), 2.58 (1H, dd, *J* 16.8, 5.5, C*H*HCO$_2$H), 2.84 (1H, dd, *J* 16.8, 6.3, CH*H*CO$_2$H), 2.97 (1H, m, C*H*CH$_2$CO$_2$H), 3.50 (1H, m, C*H*HN), 3.55 (1H, dd, *J* 4.9, 2.9, C*H*CO$_2$Et), 3.80 (1H, m, CH*H*N), 4.16 (2H, q, *J* 7.1, CH$_3$C*H*$_2$O), 4.37 (1H, d, *J* 1.5, =C*H*H), 4.55 (1H, d, *J* 1.5, =CH*H*), 9.3 (1H, br, CO$_2$*H*).

1-Butyl-5-carboxymethyl-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester 21

General procedure B with enaminone **9** gave the titled compound **21** (0.85 g, 64%) as a yellow oil, R_f 0.6 (ethyl acetate) ($C_{15}H_{23}NO_5$ requires M$^+$ 297.1576. Found 297.1576); ν_{max}(KBr)/cm^{-1} 1738.1, 1708.3, 1681.1, 1623.2; δ_H($CDCl_3$, 500 MHz) 0.93 (3H, t, *J* 7.4, C*H*$_3$CH$_2$CH$_2$), 1.31 (5H, m, CH$_3$C*H*$_2$CH$_2$, C*H*$_3$CH$_2$O), 1.48 (2H, m, CH$_3$CH$_2$C*H*$_2$) 2.28 (1H, t, *J* 15.4, C*H*HC), 2.44 (4H, s overlapping with m, C*H*$_3$-C=, =CCH-*H*CH), 2.85 (3H, 3 × m, C*H*CH$_2$CO$_2$H), 3.52 (1H, ddd, *J* 14.3, 9.2, 5.3, NC*H*HCH$_2$), 3.90 (1H, ddd, *J* 14.3, 9.4, 6.3, NCH*H*-CH$_2$), 4.21 (2H, q, *J* 7.4, CH$_3$C*H*$_2$O), 9.1 (1H, br, CO$_2$*H*); δ_C($CDCl_3$, 125.758 MHz) 12.73 (*C*H$_3$CH$_2$), 13.29 (*C*H$_3$CH$_2$O), 15.14 (*C*H$_3$C2), 19.01 (CH$_3$*C*H$_2$), 25.87 (*C*4), 30.35 (NCH$_2$-*C*H$_2$), 33.70 (*C*H$_2$CO$_2$H), 35.78 (*C*5), 41.32 (N*C*H$_2$), 59.43 (*C*H$_2$O), 108.25 (*C*3), 146.99 (*C*4), 166.30 (*C*O$_2$Et), 170.60 (N*C*O), 176.04 (*C*O$_2$H); *m*/*z* 297 (M$^+$, 52%), 238 (100), 57 (17), 43 (26), 29 (61).

(5-Acetyl-1-benzyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyridin-3-yl)acetic acid 22

General procedure B with enaminone **10** gave the titled compound **22** (0.65 g, 48%) as a yellow solid, mp 149–150 °C (from EtOH) ($C_{17}H_{19}NO_4$ requires M$^+$ 302.1392. Found 301.1397); ν_{max}(KBr)/cm^{-1} 1729.5, 1687.4, 1668.1, 1602.6; δ_H($CDCl_3$, 300 MHz) 2.20 (2 × 3H, 2 × s, C*H*$_3$C=O, C*H*$_3$C=C), 2.48 (2 × 1H, 2 × m, =CC*H*HCH), 2.66 (1H, dd, *J* 15.6, 5.6, CH*H*CO$_2$H), 2.90–2.98 (2 × 1H, 2 × m, C*H*CH*H*CO$_2$H), 4.71 (1H, d, *J* 16.4, PhCH*H*N), 5.13 (1H, d, *J* 16.4, PhC*H*HN), 7.0–7.16 (5H, m, Ar*H*), 8.5 (1H, br, CO$_2$*H*); δ_C($CDCl_3$, 125.758 MHz) 15.29 (*C*H$_3$C3), 26.86 (*C*4), 28.88 (*C*H$_3$CO), 33.52 (*C*H$_2$CO$_2$H), 35.90 (*C*5), 44.39 (N*C*H$_2$), 116.14 (*C*3), 125,13, 126.33, 127.85 (*C*H$_{Ar}$), 136.11 (*C*$_{Ar}$), 145.17 (*C*2), 170.87 (N*C*O), 175.67 (*C*O$_2$H), 197.88 (CH$_3$*C*O); *m*/*z* 301 (M$^+$, 70%), 286 (31), 283 (50), 259 (76), 91 (100), 43 (52).

(5-Benzoyl-1-benzyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyridin-3-yl)acetic acid 23

General procedure A with enaminone **11** gave the titled compound **23** (1.33 g, 82%) as a white solid, mp 124–125 °C (from EtOH) ($C_{22}H_{21}NO_4$ requires M$^+$ 363.1470. Found 363.1471); ν_{max}(KBr)/cm^{-1} 1734.5, 1684.5, 1653.9, 1636.5; δ_H($CDCl_3$, 300 MHz) 1.83 (3H, s, C*H*$_3$C=), 2.46 (1H, dd, *J* 16.9, 6.5, CHC*H*-HCO$_2$H), 2.54 (2 × 1H, 2 × m, =CC*H*HCH), 2.88 (1H, dd, *J* 16.9, 6.5, CHCH*H*CO$_2$H), 3.05 (1H, m, CH$_2$C*H*CH$_2$CO$_2$H), 4.59 (1H, d, *J* 16.4, PhC*H*HN), 5.25 (1H, d, *J* 16.4, PhCH*H*N),

7.04–7.6 (10H, m, *H*ArCH$_2$, *H*ArC=O), 8.9 (1H, br, CO$_2$*H*); δ_C(CDCl$_3$, 125.758 MHz) 16.39 (*C*H$_3$C2), 28.02 (*C*4), 33.51 (*C*H$_2$CO$_2$H), 36.23 (*C*5), 44.29 (N*C*H$_2$), 116.57 (*C*3), 125.23, 126.35, 127.65, 127.68, 127.87, 131.82 (*C*H$_{Ar}$), 136.29, 137.28 (*C*$_{Ar}$), 141.90 (*C*2), 170.91 (N*C*O), 175.91 (*C*O$_2$H), 195.87 (Ph*C*O); *m*/*z* 363 (M$^+$, 25%), 304 (98), 105 (38), 91 (100), 77 (30).

5-Carboxymethyl-2-methyl-6-oxo-1-(1-phenylethyl)-1,4,5,6-tetrahydropyridine-3-carboxylic acid ethyl esters 26 and 28

General procedure B with (*R*)-enaminone **24** over 24 h gave diastereoisomers **26**:**28**, ratio 4.9:1 after flash chromatography, R_f 0.63 (ethyl acetate) as a white solid (1.2 g, 81%), mp 134–140 °C (from EtOH). Recrystallisation changed the ratio of diastereoisomers **26**:**28** to 10:1 ($C_{19}H_{23}NO_5$ requires M$^+$ 345.1576. Found 345.1578); $[\alpha]_D^{20}$ +196.6 (*c* 6.5 in CHCl$_3$); ν_{max}(KBr)/cm^{-1} 1736.6, 1708.5, 1679.4, 1624.2; δ_H(CDCl$_3$, 300 MHz) 1.21 (3H, t, *J* 7.2, C*H*$_3$CH$_2$O), 1.73 (3H, d, *J* 7.1, C*H*$_3$CHN), 2.07 (3H, s, C*H*$_3$C=), 2.35 (1H, t, *J* 14.9, C*H*HCHCO), 2.45 (1H, dd, *J* 14.9, 4.5, CH*H*CHCO), 2.84 (3H, 3 × m, C*H*C*H*$_2$CO$_2$H), 4.1 (2H, q, *J* 7.0, CH$_3$C*H*$_2$O), 5.8 (1H, q, *J* 7.2, CH$_3$C*H*), 7.1–7.37 (5H, m, Ar*H*); δ_C(CDCl$_3$, 125.758 MHz) 13.25 (*C*H$_3$CH$_2$O), 16.61 (*C*H$_3$CHN), 17.55 (*C*H$_3$C2), 25.80 (*C*4), 33.69 (*C*H$_2$CO$_2$H), 36.78 (*C*5), 51.32 (*C*HN), 59.46 (*C*H$_2$O), 109.99 (*C*3), 124.69, 125.86, 127.65 (*C*H$_{Ar}$), 139.67 (*C*$_{Ar}$), 147.90 (*C*2), 166.05 (*C*O$_2$Et), 171.58 (N*C*O), 175.55 (*C*O$_2$H); *m*/*z* 345 (M$^+$, 37%), 300 (16), 182 (82), 105 (100).

When this reaction was performed in deuteriochloroform and monitored by NMR spectroscopy, after one hour, an intermediate **30** was observed, which had the following NMR spectra: δ_H(CDCl$_3$, 300 MHz) 1.30 (3H, t, *J* 7.1, CH$_3$C*H*$_2$O), 1.52 (3H, d, *J* 6.9, C*H*$_3$CHN), 1.84 (3H, s, C*H*$_3$C=), 2.70 (1H, dd, *J* 15.3, 8.7, C*H*HCHCO$_2$Et), 2.77 (2H, 2 × m, CH*H*CH-CH*H*C=O), 2.93 (1H, dd, *J* 18.8, 9.7, C*H*HCO$_2$), 3.15 (1H, m, COC*H*CH$_2$), 4.16 (2H, m, CH$_3$C*H*$_2$O), 4.63 (1H, m, NC*H*), 7.15 (5H, m, Ar*H*), 10.0 (1H, d, *J* 6.8, N*H*CH); δ_C(CDCl$_3$, 75.45 MHz) 14.97 (*C*H$_3$CH$_2$O), 16.19 (*C*H$_3$CHN), 25.48 (=C*C*H$_2$), 29.23 (*C*H$_3$C=), 34.025 (*C*H$_2$CO), 42.16 (*C*HCO), 53.87 (*C*HN), 59.68 (*C*H$_2$O), 88.34 (NC=*C*), 125.78, 127.65, 129.07 (*C*H$_{Ar}$), 145.28 (*C*$_{Ar}$) 161.47 (N*C*=), 170.69 (*C*O$_2$Et), 171.19 (*C*O), 174.15 (*C*O).

After one day all these signals were replaced with those of the products.

(7*R*,3*S*)-[5-Benzoyl-6-methyl-2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydropyridin-3-yl]acetic acid 27

General procedure B with (*R*)-enaminone **25** over 24 h gave diastereoisomers **27**:**29** (1.1 g, 61%) as a 5.6:1 mixture of diastereoisomers after flash chromatography, R_f 0.68 (ethyl acetate). Recrystallisation gave pure **27** (0.78 g, 48%) as prisms, mp 154–155 °C (from EtOH) ($C_{23}H_{23}NO_4$ requires M$^+$ 377.1627. Found 377.1627); $[\alpha]_D^{20}$ +276.6 (*c* 6.1 in CHCl$_3$); ν_{max}(KBr)/cm^{-1} 1735.0, 1653.7, 1627.5; δ_H(CDCl$_3$, 300 MHz) 1.60 (3H, d, *J* 1.5, C*H*$_3$C=), 1.71 (3H, d, *J* 7.1, C*H*$_3$CHN), 2.48 (3H, 3 × m, C*HH*CHC*H*HCO$_2$H), 2.87 (1H, dd, *J* 16.7, 6.6, CH*H*CO$_2$H), 2.97 (1H, m, CH$_2$C*H*CH$_2$CO$_2$H), 6.0 (1H, q, *J* 7.0, CH$_3$C*H*N), 7.18–7.55 (10H, m, *H*ArC=O, *H*ArCH); δ_C(CDCl$_3$, 75.437 MHz) 17.32 (C3*C*H$_3$), 17.52 (*C*H$_3$CHN), 27.79 (*C*4), 33.65 (*C*H$_2$CO$_2$H), 37.12 (*C*5), 50.45 (N*C*H), 119.24 (*C*3), 124.84, 126.03, 127.52, 127.63, 127.93, 131.85 (*C*H$_{Ar}$), 137.07, 139.63 (*C*$_{Ar}$), 141.97 (*C*2), 171.25 (N*C*O), 175.87 (*C*O$_2$H), 195.71 (Ph*C*O); *m*/*z* 377 (M$^+$, 35%), 359 (23), 272 (55), 105 (100), 77 (41).

Crystal data for [$C_{23}H_{23}O_4N$]. M = 377.42, monoclinic, space group $P2_1$, a = 9.737(6), b = 10.496(6), c = 10.159(7) Å, β = 107.53°, U = 990(1) Å^{-3}, Z = 2, D_c = 1.266 Mg m^{-3}, F(000) = 400, μ = 0.701 mm^{-1}, crystal dimensions = 0.54 × 0.36 × 0.24 mm. A total of 4982 reflections were measured for $5 < 2\theta < 110°$ and 2511 unique reflections were used in the refinement. The final parameters were $wR2 = 0.1589$ and $R1 = 0.0564$ [$I > 2\sigma(I)$], S = 1.062, 254 parameters, $(\Delta/\sigma)_{max} < 0.001$, $(\Delta\rho)_{max,min}$ = 0.207, −0.199 e Å^{-3}.

Data were collected using a Siemens P3 four circle diffractometer with graphite monochromated Cu-Kα radiation. The crystal's stability was monitored every 100 reflections and there were no significant variations (±1%). Cell parameters were obtained from 25 accurately centred reflections in the 2θ range 5–30°. Data were collected at room temperature and ω scans were employed for data collection. Lorentz and polarisation corrections were applied.

The structure was solved by direct methods and the non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atom positions were added at idealised positions and a riding model with fixed thermal parameters [U_{iso}(eq) = 1.2 U_{ij}(eq), 1.5 U_{ij}(eq) for methyl and hydroxy groups] was used for subsequent refinement. The function minimised for *wR*2 was $\Sigma[w(|F_o|^2 - |F_c|^2)]$ with reflection weights $w^{-1} = [\sigma^2 |F_o|^2 + (g_1P)^2 + g_2P]$, where $P = [\max |F_o|^2 + 2|F_c|^2]/3$ for all F^2, and the function minimised for *R*1 was $\Sigma[w(|F_o| - |F_c|)]$. The SHELXTL PC and SHELXL-93 packages were used for data collection, reduction, structure solution and refinement.

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 207/257.

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