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Aza-annulation of Enaminones with Crotonyl chloride - Formal Reversal of Regioselectivity.

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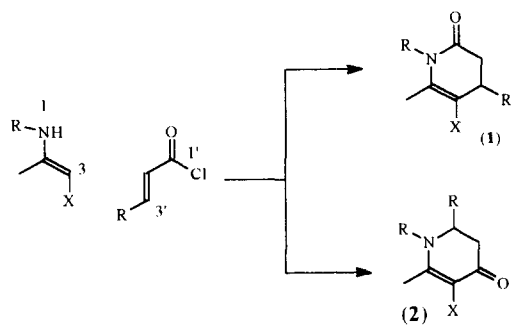
Abstract. The regiochemistry of aza-annulation of enaminones with α,β-unsaturated acid chlorides bearing hydrogen atoms on the γ-carbon is reversed when triethylamine is used as mediator. When the reaction was carried out at lower temperatures a 3-acyl β,γ-unsaturated compound could be isolated which cyclised to the desired product under thermal or basic conditions. The nature of this intermediate strongly suggests that a vinyl ketene is the active acylating agent. © 1997 Elsevier Science Ltd.

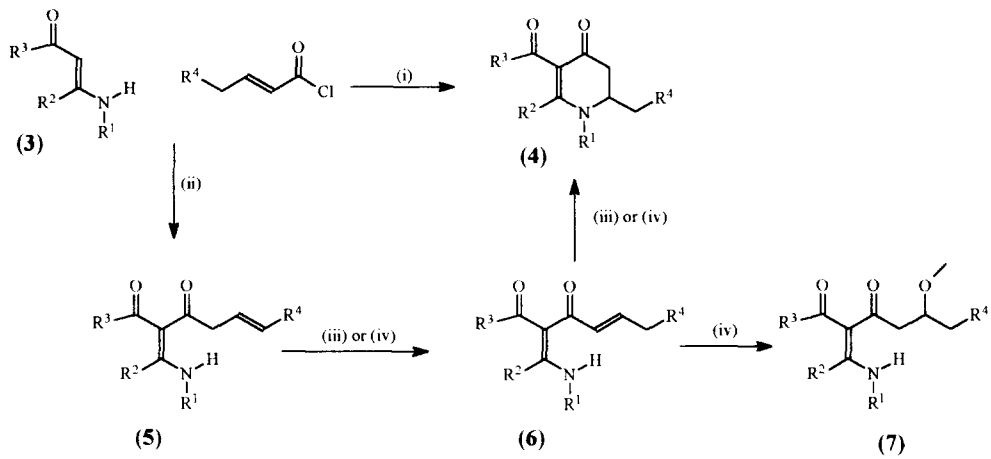
Piperidines form the key structural elements of many biologically interesting alkaloids[1] and versatile flexible regioselective approaches to this moiety are in demand. Recent approaches to piperidines and piperidinones include radical cyclisation[2], iminium ion cyclisation[3] and aldol type cyclisation[4]. One of the simplest methods for forming 2-piperidinones (**1**), originally introduced by Hickmott[5], consists of treating an enamine with an α,β-unsaturated acid chloride. This reaction works best when there are electron withdrawing groups on the carbon β to the nitrogen on the enamine (**Scheme 1**, X = electron withdrawing group). Strictly speaking these substrates are no longer simple enamines but are now enaminones, the chemistry of which is extensive and has been the subject of a review[6]. Stille[7], Danishefsky[8] and Kadouri-Puchot[9] have independently harnessed this additional reactivity of enaminones, in aza-annulation reactions, in a number of elegant syntheses of biologically important piperidines via 2-piperidinones of the type (**1**).



Scheme 1

The aza-annulation of enaminones is mechanistically interesting in that the enaminone is an ambident nucleophile, which can react at position **1** or **3** and the α,β-unsaturated acid chloride is an ambident electrophile which can react at positions **1'** or **3'**, **Scheme 1**. In principle, two cyclic regio-isomeric products (**1**) and (**2**) could result from this reaction and to date 2-piperidinones (**1**) have been the only reported cyclic products. Acyclic N-acylation products predominate when pyridine is used as base.

We now report the first examples of regio-reversed aza-annulation of enaminones with crotonyl and 2-hexenoyl chloride to give 4-piperidinones (**4**) **Scheme 2**. This was achieved simply by adding triethylamine to the reaction mixture and using a high boiling solvent, xylene. The secondary enaminones (**3a-i**) were prepared by a number of methods in excellent yield. When R^2 = H, 1,4-addition of a primary amine to a terminal acetylenic ketone, or by reaction with 4-methoxy-3-buten-2-one gave a quantitative yield of the enaminones (**3a-c, h-i**). Condensation of a primary amine with β-keto esters or ketones was employed when R^2 was alkyl (**3d-g**). Hence treatment of enaminones (**3a-i**) with an acyl chloride and triethylamine in boiling xylene gave the 4-piperidinones (**4a-i**), **Table 1**.



Reagents: (i) Triethylamine/ xylene 143°C. (ii) Triethylamine THF 66°C. (iii) Xylene 143°C. (iv) Sodium methoxide, methanol 64°C.

Scheme 2

Table 1

Compound 4	R^1	R^2	R^3	R^4	Time hr	Yield %
a	**Bn**	**H**	**COMe**	**H**	**2**	**46**
b	**$BnCH_2$**	**H**	**COMe**	**H**	**2**	**52**
c	**Bu^n**	**H**	**COMe**	**H**	**2**	**52**
d	**Bn**	**Me**	**CO_2Et**	**H**	**8**	**22**
e	**$BnCH_2$**	**Me**	**CO_2Et**	**H**	**8**	**26**
f	**Bu^n**	**Me**	**CO_2Et**	**H**	**8**	**14**
g	**Bu^n**	**Me**	**COPh**	**H**	**2**	**49**
h	**Bn**	**H**	**COMe**	**Et**	**2**	**51**
i	**PhCHMe**	**H**	**COMe**	**H**	**8**	**42**

Although the yields are poor to moderate, the ready availability of the starting materials and the convenience of the procedure make this method attractive. The regiochemistry of the cyclisation was confirmed by ^{13}C NMR spectroscopy. The endocyclic carbonyl signals in (**4**) were unambiguously assigned using reverse

detected long range proton carbon 2D shift correlation (HMBC) and are in the range 185.5-190.1ppm. Lactams of the type (**1**) typically have amide carbonyl signals in the region of 170ppm in the ^{13}C spectrum.

One example of a chiral enaminone was investigated **Table 1 entry i**. Although the d.e. for this reaction was very low one of the diastereoisomers separated on flash chromatography, hence the auxiliary is providing a handle for resolution of these compounds.When the reaction of enaminone (**3a**) with crotonyl chloride and triethylamine was carried out at lower temperature, in THF at 66°C, the 3-butenoyl enaminone (**5a**) was isolated in 59% yield as a 1.5:1 mixture of Z:E diasteroisomers, stereochemistry not assigned. Subsequent heating of purified (**5a**) in xylene at b.p. 143°C, resulted in cyclisation to (**4a**), in quantitative yield, strongly indicating that (**5a**) was an intermediate in the formation of (**4a**). The cyclisation probably involves thermal isomerisation of the β,γ-unsaturated compound (**5a**) to the α,β–unsaturated compound (**6a**) followed by cyclisation via intramolecular 1,4-addition. In an attempt to carry out the isomerisation, cyclisation at lower temperatures the reaction was carried out in boiling methanol containing sodium methoxide since this should facilitate both steps. This protocol did indeed lead to cyclic product (**4a**, 20%) but unfortunately the major product (**7a**, 62%) was that resulting from isomerisation of the β,γ-unsaturated ketone to the α,β-unsaturated ketone followed by 1,4-addition of the methoxide to this moiety. The 1,4-addition product was a 1.5:1 mixture of alkene diastereoisomers, stereochemistry not assigned. The key to success in reversing of the regiochemistry of aza-annulation is therefore selective **C-3** acylation of the enaminone (**3**) and triethylamine is facilitating this. The nature of the β,γ-unsaturated acyl intermediate (**5a**), and the fact that α,β-unsaturated acyl chlorides, with hydrogen atoms on the γ-carbon, and tertiary amines are precursors to vinyl ketenes[10], strongly indicates that a vinyl ketene is the active acylating agent in this sequence. This is further supported by the Merck group observation[11] that selective **C3**-acylation of secondary enaminones can be readily achieved using ketene. However it should be noted that **C3** acylation of enaminones has been reported with aromatic acyl chlorides and triethylamine in cases were there is no possibility of ketene formation[12]. When acid chlorides bearing no γ-hydrogen atoms were employed, cinnamoyl and acryloyl chloride, complex product mixtures resulted.

Experimental.

General

Melting points were recorded using a Kofler hot stage apparatus and are uncorrected. I.R 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). ^1H nuclear magnetic resonance (nmr) spectra were recorded at 300MHz and 500MHz using General Electric QE and Bruker DRX 500 spectrometers respectively. Chemical shifts are given in parts per million (δ) down field from tetramethylsilane as internal standard and coupling constants are given in Hertz. Unless otherwise stated, deuteriochloroform was used as solvent. The following abbreviations are used:- s = singlet, d=doublet, t=triplet, q=quartet, qi=quintet, m=multiplet and br=broad. Mass spectra were recorded using Double Focusing Triple Sector VG Auto Spec and accurate molecular masses were determined by computer using the peak matching method using perfluorokerosene as standard reference and were accurate to within +/-0.006 a.m.u. Microanalyses were obtained using a Perkin Elmer 2400 CHN elemental analyser. Analytical tlc was carried out on Merck Kielselgel 60_{254} plates and the spots visualised using a Hanovia Chromatolite uv lamp. Flash chromatography was effected using Merck Kielselgel 60 (230-400 mesh).

Enaminones (3a-i).

Enaminones (**3a-c, i**) were prepared by treating 4-methoxy-3-buten-2one with the corresponding primary amine in methylene chloride at room temperature for 3h. Enaminones (**3d-g**) were prepared by treating the corresponding1,3-dicarbonyl compound with the appropriate primary amine in benzene containing a catalytic amount of *p*-toluenesulfonic acid with azeotropic removal of water. In both cases the enaminones were used crude for subsequent stages.

General Aza-annulation Procedure.

A solution of enaminone (9mmol) and triethylamine (20mmol) in xylene (40ml) was brought to reflux. Crotonyl chloride (18mmol) was added over ten minutes and the mixture allowed to reflux for the time indicated in **Table 1**. The xylene was removed under reduced pressure and the residue was dissolved in dichloromethane (30ml), washed with water (2 x 20ml), dried over magnesium sulphate and concentrated. Products were purified by flash chromatography. In cases where the R_f <0.1 the solvent quoted was used to remove high R_f material and then methanol /solvent, ratio 1:4 was used to remove the desired compound from the column.

5-Acetyl-1-benzyl-2-methyl-2,3-dihydro-*1H*-pyridin-4-one (4a). Enaminone (**3a,** 1.6g 9mmol) triethylamine amine and crotonyl chloride reacted according to general procedure to give the titled compound as an orange oil (1.0g 46%) R_f=0.38 ethyl acetate. δ_H ($CDCl_3$, 300MHz) 1.18(3H, d, J=6.7Hz, CH(C<u>H</u>$_3$), 2.13(1H, dd, J=16.0Hz, 2.8Hz, -(C=O)-C<u>H</u>(H)-CH(CH_3)), 2.43(3H, s, C<u>H</u>$_3$-C=O), 2.62(1H, dd, J=16.0Hz, 7.0Hz, -(C=O)-CH(<u>H</u>)-CH(CH_3)), 3.59(1H, m, C<u>H</u>(CH_3)), 4.50(2H, 2xd, J=15.0Hz, PhC<u>H</u>$_2$N-), 7.28(5H, m, <u>Ph</u>CH_2N-), 8.27(1H, s, N-C<u>H</u>=C). $\delta_{C\text{-}13}$ ($CDCl_3$, 75MHz) 16.09, 30.79, 43.11, 52.61, 59.32, 109.71, 128.05, 129.29, 129.69, 134.91, 158.16, 188.07, 195.40. m/z (%) 243(M+, 27), 228(M-15$^+$, 34), 91(M-152$^+$, 100), 65(M-178$^+$, 11), 43(M-200$^+$, 13). $\nu_{max.}$ (KBr) 2973, 2927, 1632, 1574, 1384, 1360, 1326, 1306, 1151 cm^{-1}. Found: M^+ =243.1258. $C_{15}H_{17}NO_2$ requires M^+ = 243.1259.

5-Acetyl-2-methyl-1-phenethyl-2,3-dihydro-*1H*-pyridin-4-one (4b). Enaminone (**3b,** 1.4g, 7.4mmol) triethylamine amine and crotonyl chloride reacted according to general procedure to give the titled compound as white crystals mp129-130 (0.99g, 52%), R_f =0.05 ether,. δ_H ($CDCl_3$, 300MHz) 1.20(3H, d, J=6.7Hz, -C(H)(C<u>H</u>$_3$)), 2.18(1H, dd, J=15.9Hz, 2.7Hz, (C=O)-C<u>H</u>(H)CH(CH_3)), 2.48(3H, s, C<u>H</u>$_3$-C=O), 2.67(1H, dd, J=15.9Hz, 6.7Hz, (C=O)-CH(<u>H</u>)CH(CH_3)), 2.97(2H, t, J=7.0Hz, PhC<u>H</u>$_2$$CH_2$, 3.49-3.68(3H, 2x overlapping m, $PhCH_2$C<u>H</u>$_2$, C<u>H</u>(CH_3), 7.17-7.37(5H, m, <u>Ph</u>CH_2-), 8.09(1H, s, N-C<u>H</u>=C). $\delta_{C\text{-}13}$ ($CDCl_3$, 75MHz) 14.48, 28.82, 34.72, 41.04, 52.01, 54.80, 107.74, 125.82, 127.12, 127.50, 135.16, 155.75, 185.99, 193.36. m/z (%) 257(M$^+$, 43), 166(M-91$^+$, 100), 124(M-133$^+$, 38), 105(M-152$^+$, 23), 82(M-175$^+$, 21). $\nu_{max.}$ (KBr) 3029, 2970, 1654, 1631, 1548, 1384, 1376, 1361, 1158 cm^{-1}. Found: M^+ =257.1424. $C_{16}H_{19}NO_2$ requires M^+ =257.1416.

5-Acetyl-1-butyl-2-methyl-2,3-dihydro-*1H*-pyridin-4-one (4c). Enaminone (**3c**, 1.3g, 9mmol) reacted according to general procedure to give the titled compound as a light brown oil (0.98g, 52%), R_f=0.70 diethyl ether. δ_H ($CDCl_3$, 300MHz) 0.98(3H, t, J=7.3Hz, C<u>H</u>$_3$$CH_2$$CH_2$-), 1.25(3H, d, J=6.7Hz, C<u>H</u>$_3$-CH), 1.41(2H, m, CH_3C<u>H</u>$_2$$CH_2$-), 1.69(2H, qi, J=7.3Hz, $CH_3$$CH_2$C<u>H</u>$_2$$CH_2$-), 2.28(1H, dd, J=15.9Hz, 2.7Hz, (C=O)-C<u>H</u>(H)CH(CH_3)), 2.49(3H, s, C<u>H</u>$_3$-C=O), 2.80(1H, dd, J=15.9Hz, 6.7Hz, (C=O)-CH(<u>H</u>)CH(CH_3)), 3.40(2H, t,

J=7.3Hz, N-C$\underline{H}_2$-CH_2-), 3.75(1H, m, -C($\underline{H}$)(CH_3)), 8.17(1H, s, N-C$\underline{H}$=C). δ_{C-13} ($CDCl_3$, 75MHz) 16.21, 18.63, 22.27, 32.89, 33.80, 45.37, 55.53, 57.45, 111.56, 159.94, 190.11, 197.43. m/z (%) 209(M^+, 47), 194(M-15$^+$, 100), 166(M-43$^+$, 42), 69(M-140$^+$, 72), 41(M-168$^+$, 40). $\nu_{max.}$ (KBr) 2933, 2346, 1632, 1581, 1385, 1324, 1155 cm^{-1}. Found: M^+ =209.1415. $C_{12}H_{19}NO_2$ requires M^+ =209.1416.

1-Benzyl-2,6-dimethyl-4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester (4d). Enaminone (**3d,** 1.97g, 9mmol) reacted according to general procedure to give the titled compound as a yellow oil (0.57g, 22%), R_f=0.77 diethyl ether. δ_H ($CDCl_3$, 300MHz) 1.27(3H, d, J=6.7Hz, C$\underline{H}_3$-CH), 1.27(3H, t, J=7.1Hz, C$\underline{H}_3CH_2OC$=O), 2.22(1H, d, J=2.0Hz, (C=O)-C$\underline{H}_2CH(CH_3)$), 2.28(3H, s, N-C(C$\underline{H}_3$)=C), 2.85(1H, dd, J=15.8Hz, 6.8Hz, (C=O)-CH($\underline{H}$)$CH_2(CH_3)$), 3.66(1H, m, C$\underline{H}(CH_3)$), 4.29(2H, q, J=7.1Hz, $CH_3C\underline{H}_2OC$=O), 4.31-4.93(2H, 2xd, J=16.6Hz, PhC$\underline{H}_2$N), 7.33(5H, m, $\underline{Ph}CH_2N$). δ_{C-13} ($CDCl_3$, 300MHz) 16.42, 17.29, 20.93, 43.77, 55.30, 55.93, 62.49, 107.56, 128.11, 130.19, 131.28, 137.94, 164.21, 170.04, 188.60. m/z (%) 287(M^+, 25), 242(M-45$^+$, 17), 215(M-72+, 12), 91(M-196$^+$, 100), 69(M-218$^+$, 170). $\nu_{max.}$ (KBr) 2977, 1682, 1636, 1544, 1449, 1195, 1152, 1134 cm^{-1}. Found: M^+ =287.1514. $C_{17}H_{21}NO_3$ requires M^+ =287.1521.

2,6-Dimethyl-4-oxo-1-phenethyl-1,4,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester (4e). Enaminone (**3e**, 4.0g, 17.2mmol) reacted according to general procedure to give the titled compound as an orange oil (1.35g, 26%), R_f=0 ethyl acetate. δ_H ($CDCl_3$, 300MHz) 1.24(3H, d, J=6.7Hz, C$\underline{H}_3$-CH), 1.30(3H, t, J=7.1Hz, C$\underline{H}_3CH_2OC$=O), 2.10(1H, dd, J=15.6Hz, J=2.8Hz, (C=O)-C$\underline{H}$(H)CH(CH_3)), 2.15(3H, s, N-C(C$\underline{H}_3$)=C), 2.66(1H, dd, J=15.8Hz, J= 6.6Hz, (C=O)-CH($\underline{H}$)CH(CH_3)), 2.90(2H, m, PhC$\underline{H}_2CH_2$), 3.48(1H, dt, J=14.6Hz, 7.3Hz, $PhCH_2CH(\underline{H})$), 3.49(1H, m, C$\underline{H}(CH_3)$), 3.89(1H, ddd, J=14.6Hz, 7.3Hz, 6.5Hz, PhCH(H)C$\underline{H}$(H)), 4.23(2H, q, J=7.1Hz, $CH_3C\underline{H}_2OC$=O), 7.19-7.25(5H, m, $\underline{Ph}$-CH_2-). δ_{C-13} ($CDCl_3$, 75MHz) 14.73, 15.48, 18.73, 36.38, 41.90, 50.88, 52.49, 54.60, 60.67, 105.35, 127.57, 129.12, 129.33, 137.68, 162.55, 168.34, 186.97. m/z (%) 301(M^+, 19), 256(M-45$^+$, 23), 210(M-91$^+$, 100), 168(M-133$^+$, 53), 105(M-196$^+$, 38), 91(M-210$^+$, 22), 67(M-234$^+$, 31). $\nu_{max.}$ (KBr) 2977, 2934, 2902, 1714, 1684, 1634, 1497, 1382, 1226, 1152 cm^{-1}. Found: M^+ =301.1682. $C_{18}H_{23}NO_3$ requires M^+ =301.1678.

1-Butyl-2,6-dimethyl-4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester (4f). Enaminone (**3f,** 4.0g, 21.6mmol) reacted according to general procedure to give the titled compound as an orange oil (0.77g, 14%), R_f=0.03 diethyl ether. δ_H ($CDCl_3$, 300MHz) 0.98(3H, t, J=7.3Hz, C$\underline{H}_3CH_2CH_2$-), 1.24(3H, d, J=6.7Hz, C$\underline{H}_3$-CH), 1.32(3H, t, J=7.0Hz, C$\underline{H}_3CH_2OC$=O), 1.39(2H, m, $CH_3C\underline{H}_2CH_2$-), 1.65(2H, m, $CH_3CH_2C\underline{H}_2CH_2$-), 2.35(1H, dd, J=15.6Hz, 1.8Hz, (C=O)-C$\underline{H}$(H)CH(CH_3)), 2.23(3H, s, N-C(C$\underline{H}_3$)=C), 2.77(1H, dd, J=15.8Hz, 6.6Hz, (C=O)-CH($\underline{H}$)CH(CH_3)), 3.08(1H, dt, J=14.8Hz, 7.4Hz, N-CH($\underline{H}$)-CH_2), 3.60(2H, dt overlapping with m, N-C$\underline{H}$(H)-CH_2, and C$\underline{H}(CH_3)$), 4.25(2H, q, J=7.05Hz, $CH_3C\underline{H}_2OC$=O). δ_{C-13} ($CDCl_3$, 75MHz) 12.79, 13.37, 14.25, 17.50, 19.01, 30.61, 40.77, 49.40, 52.91, 59.30, 103.61, 161.28, 167.10, 185.46. m/z (%) 253(M^+, 50), 208(M-45$^+$, 100), 181(M-72$^+$, 46), 168(M-85$^+$, 31), 69(M-184$^+$, 63), 41(M-212$^+$, 66). $\nu_{max.}$ (KBr) 2934, 1684, 1635, 1549, 1465, 1448, 1417, 1148 cm^{-1}. Found: M^+ =253.1682. $C_{14}H_{23}NO_3$ requires M^+ =253.1678.

5-Benzoyl-1-butyl-2,6-dimethyl-2,3-dihydro-*1H*-pyridin-4-one (4g). Enaminoketone (**3g**, 3.0g, 13.8mmol) reacted according to general procedure to give the titled compound as a brown oil (1.92g, 49%),

R_f=0 ethyl acetate. δ_H ($CDCl_3$, 300MHz) 1.00(3H, t, J=7.2Hz, C<u>H</u>$_3$CH$_2$CH$_2$-), 1.31(3H, d, J=6.7Hz, C<u>H</u>$_3$-CH), 1.40(2H, m, CH$_3$C<u>H</u>$_2$CH$_2$-), 1.68(2H, m, CH$_3$CH$_2$C<u>H</u>$_2$CH$_2$-), 2.16(3H, s, N-C(C<u>H</u>$_3$)=C), 2.23(1H, dd, J=15.7Hz, 1.6Hz, (C=O)-C<u>H</u>(H)CH(CH$_3$)), 2.90(1H, dd, J=15.6Hz, 6.6Hz, (C=O)-CH(<u>H</u>)CH$_2$(CH$_3$)), 3.12(1H, dt, J=14.7Hz, J= 7.4Hz, -CH$_2$CH(<u>H</u>)-N), 3.64(1H, dt, J=14.7Hz, J= 7.4Hz, -CH$_2$C(<u>H</u>)H-N), 3.75(1H, m, -C(<u>H</u>)(CH$_3$)), 7.28-7.73(5H, m, <u>Ph</u>-C=O). δ_{C-13} ($CDCl_3$, 75MHz) 14.83, 16.66, 21.04, 32.48, 42.65, 51.60, 55.15, 112.36, 129.10, 129.84, 132.80, 141.72, 164.47, 188.88, 197.55. m/z (%) 285(M^+, 64), 256(M-29$^+$, 31), 242(M-43$^+$, 23), 105(M-180+, 100), 86(M-199$^+$, 33), 77(M-208+, 63), 69(M-216$^+$, 50), 41(M-244$^+$, 59). $\nu_{max.}$ (KBr) 2960, 2928, 1642, 1618, 1542, 1382, 1189 cm^{-1}. Found: M^+ =285.1729. $C_{18}H_{23}NO_2$ requires M^+ =285.1729.

5-Acetyl-1-benzyl-2-propyl-2,3-dihydro-*1H*-pyridin-4-one (4h). Enaminone (**3a**, 0.88g, 5.0mmol) and 2-hexenoyl chloride reacted according to general procedure to give the titled compound as a yellow oil (0.6g, 51%), R_f=61 ethyl acetate. δ_H ($CDCl_3$, 300MHz) 0.98(3H, t, J=6.8Hz, C<u>H</u>$_3$CH$_2$CH$_2$), 1.18(1H, m, CH$_3$C<u>H</u>(H)CH$_2$), 1.33(1H, m, CH$_3$CH(<u>H</u>)CH$_2$), 1.56(2H, m, CH$_3$CH(H)C<u>H</u>$_2$), 2.25(1H, d, J=16.0Hz, -(C=O)-C<u>H</u>(H)-CH), 2.41(3H, s, C<u>H</u>$_3$C=O), 2.56(1H, dd, J=16.0Hz, 6.8Hz, -(C=O)-C(H)<u>H</u>-CH), 3.42(1H, m, CH$_2$C(<u>H</u>), 4.50(2H, 2xd, J=14.8Hz, PhC<u>H</u>$_2$N), 7.27(5H, m, <u>Ph</u>CH$_2$N), 8.28(1H, s, N-C<u>H</u>=). δ_{C-13} ($CDCl_3$, 75MHz) 13.73, 18.65, 30.24, 31.41, 39.91, 56.26, 59.40, 109.44, 127.60, 128.82, 129.22, 134.67, 157.96, 187.61, 194.70. m/z (%) 271(M^+, 19), 256(M-15$^+$, 14), 228(M-43$^+$, 14), 91(M-180$^+$, 100), 43(M-228$^+$, 45). $\nu_{max.}$ (KBr) 3031, 1633,1569, 1385, 1360, 1328, 1306, 1149, cm^{-1}. Found: M^+ =271.1580. $C_{17}H_{21}NO_2$ requires M^+ =271.1572.

5-Acetyl-2-methyl-1-(1-phenyl-ethyl)-2,3-dihydro-*1H*-pyridin-4-one (4i). Enaminone (**3i**, 1.5g, 7.9mmol) reacted according to general procedure to give the titled compound as a yellow oil in (0.85g, 42%), R_f=0.42 ethyl acetate as a 1:1 mixture of diastereoisomers. A small sample of one diastereoisomer was obtained pure by the flash chromatography which gave the following spectroscopic data. δ_H ($CDCl_3$, 300MHz) 1.11(3H, d, J=6.7Hz, (C=O)CH$_2$CH(C<u>H</u>$_3$)), 1.68(3H, d, J=7.1Hz, PhCH(C<u>H</u>$_3$)(N)), 2.05(1H, dd, J= 15.7Hz, 1.9Hz, (C=O)-C<u>H</u>(H)-CH), 2.42(3H, s, C<u>H</u>$_3$C=O), 2.75(1H, dd, J= 15.8Hz, 6.4Hz, (C=O)-C(H)<u>H</u>-CH), 3.68(1H, m, (C=O)CH$_2$C<u>H</u>(CH$_3$)), 4.71(1H, q, J=7.0Hz, PhC<u>H</u>(CH$_3$)(N)), 7.35(5H, m, <u>Ph</u>CH(CH$_3$)), 8.37(1H, s, N-C<u>H</u>=). δ_{C-13}($CDCl_3$, 75MHz) 17.08, 19.20, 30.09, 42.88, 51.91, 64.25, 109.25, 126.55, 128.62, 128.97, 138.36, 155.43, 187.64, 194.73. m/z (%) 257(M^+, 20), 126(M-131$^+$, 14), 105(M-152$^+$, 100), 84(M-173$^+$, 24), 69(M-188+, 41), 43(M-214$^+$, 27). $\nu_{max.}$ (KBr) 2977, 1631, 1570, 1454, 1378, 1289, 1053, 966, 732 cm^{-1}. Found: M^+ =257.1419. $C_{16}H_{19}NO_2$ requires M^+ =257.1416.

3-(Benzylamino-methylene)-hept-6-ene-2,4-dione (5a). Enaminoketone (**3a**, 1.6g, 9mmol) triethyl amine and crotonyl chloride reacted according to general procedure except that xylene was substituted for THF to give the titled compound as an orange oil (1.29g, 59%), R_f=0.6 ether as a 60:40 mixture of alkene diastereoisomers. δ_H ($CDCl_3$, 500MHz) 2.16(3H, s, C<u>H</u>$_3$-C=O), 2.50 (3H, s, C<u>H</u>$_3$-C=O), 3.22(2H, d, J=6.6Hz, (C=O)-C<u>H</u>$_2$-CH=), 3.64(2H, d, J=7.0Hz, (C=O)-C<u>H</u>$_2$-CH=), 4.45(2H, d, J=5.8Hz, Ph-C<u>H</u>$_2$-NH-), 4.83-5.06(2H, m, (C=O)-CH$_2$-CH=CH<u>$_2$</u>), 5.83-6.67 (1H, m, (C=O)-CH$_2$-C<u>H</u>=CH$_2$), 7.16-7.32(5H, m, <u>Ph</u>-CH$_2$-), 7.73-7.76(1H, 2 overlapping d, J=13.1Hz, 12.9Hz, -CH$_2$-NH-C<u>H</u>=), 11.25(1H, 2 overlapping br, -N<u>H</u>-). δ_{C-13} ($CDCl_3$, 75MHz) 28.12, 31.33, 44.40, 41.46, 53.89, 53.99, 111.07, 111.25, 117.47, 118.00, 127.94, 128.59, 129.25, 133.17, 133.40, 160.17, 160.81, 194.63, 194.68, 200.48, 200.79. m/z (%) 243(M^+, 8), 202(M-41$^+$, 47), 160(M-83$^+$, 14),

91(M-152$^+$, 100), 85(M-158$^+$,16). $\nu_{max.}$ (KBr) 3250, 2928, 1655, 1390, 1316, 1230, 1174, 990, cm^{-1}. Found: M$^+$=243.1262. $C_{15}H_{17}NO_2$ requires M$^+$ = 243.1259.

3-(Benzylamino-methylene)-6-methoxy-heptane-2,4-dione (7a). A solution of 3-(benzylamino-methylene)-hept-6-ene-2,4-dione (**5a**, .49g, 2mmol) in 0.5M sodium methoxide in methanol (15ml) was boiled under reflux for 3.5h. Methanol was removed under reduced pressure, water added and this was extracted with methylene chloride (2x10ml), dried over magnesium sulphate and concentrated. Flash chromatography gave the titled compound (0.34g, 62%) as a yellow low melting solid, as a 1.5:1 mixture of diastereoisomers, R_f=0.68 ethyl acetate. δ_H ($CDCl_3$, 500MHz) 1.11(6H, 2 overlapping d, J=6.2Hz, 6.1Hz, CH(C$\underline{H}_3$)(OCH$_3$), 2.16(3H, s, C$\underline{H}_3$C=O), 2.34(1H, dd, J=14.7Hz, 5.1Hz (C=O)-C$\underline{H}$(H)CH), 2.41(3H, s, C$\underline{H}_3$C=O), 2.78(1H, dd, J=14.7Hz, 7.1Hz (C=O)-CH($\underline{H}$)CH), 2.86(1H, dd, J=15.7Hz, 5.2Hz (C=O)-C$\underline{H}$(H)CH), 3.16(1H, dd, J=15.8Hz, 7.1Hz (C=O)-CH($\underline{H}$)CH), 3.21(3H, s, CH(CH$_3$)(OC$\underline{H}_3$), 3.24(3H, s, CH(CH$_3$)(OC$\underline{H}_3$), 3.77(2H, m, C$\underline{H}$(CH$_3$)(OCH$_3$), 4.44(4H, m, PhC$\underline{H}_2$NH), 7.23(10H, m, $\underline{Ph}$CH$_2$NH), 7.72(1H, d, J=13.1Hz, NH-C$\underline{H}$=), 7.82(1H, d, J=13.1Hz, NH-C$\underline{H}$=), 11.23(2H, br, N$\underline{H}$-C=). δ_{C-13} ($CDCl_3$, 75MHz) 18.45, 26.27, 28.66, 30.72, 45.05, 48.63, 52.66, 54.99, 55.41, 72.47, 73.52, 110.75, 111.14, 126.30,127.30, 128.05, 134.89, 135.09, 159.10, 193.28, 194.38, 199.49. m/z (%) 275(M$^+$, 2), 228(M-47$^+$, 15), 202(M-73$^+$, 66), 184(M-91$^+$, 72), 175(M-100$^+$, 25), 91(M-184$^+$, 100). $\nu_{max.}$ (KBr) 3200, 2930, 2822, 1622, 1580, 1393, 1227, 1084, 936cm^{-1}.

The lower R_f fraction was 5-acetyl-1-benzyl-2-methyl-2,3-dihydro-1H-pyridin-4-one (**4a**, 0.1g 20%), data already given.

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