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SYNTHESIS AND X-RAY CRYSTAL STRUCTURE DETERMINATIONS OF PYRROLIDINE-2,4-DIONES, 2-IMINOPYRROLIDIN-5-ONES AND 1,3-OXAZINE-2,4-DIONES DERIVED FROM ACETOACETANILIDES

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Abstract – Commercially available acetoacetanilides may, after initial alkylation, be cyclized to pyrrolidine-2,5-diones by reaction with ethyl bromoacetate or cyclized to 5-iminopyrrolidin-2-ones with chloroacetonitrile. Reaction with ethyl chloroformate gives 1,3-oxazine-2,4-diones. Several examples of these reactions using different alkyl groups are described. The structures of the products were confirmed by X-Ray crystallography.

INTRODUCTION

There remains considerable ongoing research into the area of small heterocycle synthesis from readily available starting materials. The use of alkylated acetoacetanilides as precursors to substituted β-lactams has previously been reported by this group.[1] Herein, the preparation of three heterocycles, namely pyrrolidine-2,5-diones (succinimides), 2-iminopyrrolidin-5-ones and 1,3-oxazine-2,4-diones are described. Succinimides have attracted attention for a wide range of potential applications including enzyme inhibitors,[2] anti convulsants,[3-5] Tat HIV-1 inhibitors,[6a] irreversible protease inhibitors[6b] and 5-HT_{1A} receptor ligands.[7] Succinimides have previously been prepared by numerous methods including the condensation of amines with derivatives of succinic anhydride, Diels-Alder and ene reactions of maleimides and Stobbe type condensations. More recently new derivatives have been

prepared from three component Ugi type reaction of alkyl isocyanates and isopropylidene Meldrum's acid in the presence of either pyrrole, indoles or phenols.[8-9] An unsual reaction was discovered by Furukawa[10] involving the solvent free reaction of α-oxoketene *O,N*-acetals with maleic anhydride and allows the introduction of a carbonyl functionality at C3.

Literature reports for the synthesis of 2-iminopyrrolidin-5-ones are much scarcer than their succinimide counterparts. A few papers describe their preparation[11-13] by alkoxide catalysed ring opening of 3-cyanosuccinimides to give an open chain intermediate which spontaneously ring closes by reaction at the cyano group. As a class of compounds 1,3-oxazine-2,4-diones have received less attention though some have been reported. The methods used in their preparation included rearrangement of a 2-hydroxy-2-phenylazo-γ-butyrolactone using BF_3Et_2O,[14] or by rearrangement of an 1,3-oxazine-2-one using excess Bu_2BOTf,[15] by reaction of diketene with urethane followed by cyclization with conc H_2SO_4,[16] or from ethyl acetoacetate by reaction with *N,N*-dialkyl-ureas in $AcOH/(Ac)_2O$.[17] They were also prepared by reaction of diketene with nitrourea in pyridine,[18] by reaction of malonyl dichlorides with isocyanates[19] or by the cyclization of α,α-disubstituted β-carbamoyloxypropionic acids with $SOCl_2$/pyridine.[20] None of these three classes of compounds have been prepared according to the methods described below.

RESULTS AND DISCUSSION

When **1, (Y = H, Cl Scheme 1)** was alkylated with simple alkyl halides such as ethyl or methyl iodide, the only products isolated were the C3-alkylated mono- or disubstituted acetoacetanilides (**6)** according as one or two moles of the reagents were used The introduction of an ethoxycarbonylmethyl group at the C3 position was achieved by reaction of **1** with ethyl bromoacetate to give the desired product (**5)**. However, stepwise alklations at the C3 position using firstly methyl iodide for example, followed by ethyl bromoacetate lead to the isolation of pyrrolidine-2,5-diones (succinimides) (**3)** in moderate yield. When ethyl cloroformate was used in the alkylation step the six membered 1,3-oxazine-2,4-dione ring system (**4)** was formed (**Figure 1**). These are stepwise alkylation/cyclizations with the final product depending on the alkylating reagent used. The mechanisms for the formation of products (**3** and **4**) from monosubstituted acetoacetanilides differ with respect to the initial site of alkylation with the consequential cyclizations being similar in both cases. In the case of **3** the mechanism involves the alkylation of an enol oxygen followed by intramolecular cyclisation. The formation of **4** involves alkylation on carbon followed by cyclisation. Another variation of this reaction involves the use of bromoacetonitrile as the alkylating reagent. Thus when **6 (R =H, Y = H)** was treated with bromoacetonitrile and base there was formed 2-iminopyrrolidin-5-one (**7)**. Reversal of the

alkylation sequence where ethyl bromoacetate was first used to obtain **5**, followed by alkylation with propyl iodide, also gave **3** as in the conversion of **5A** to **3B**. Crystal structures have been obtained for each of the three classes of compound prepared and are shown in **Figure 2**. The data analysis for the crystal structure of **7** indicates that the methyl group at C10 is disordered.

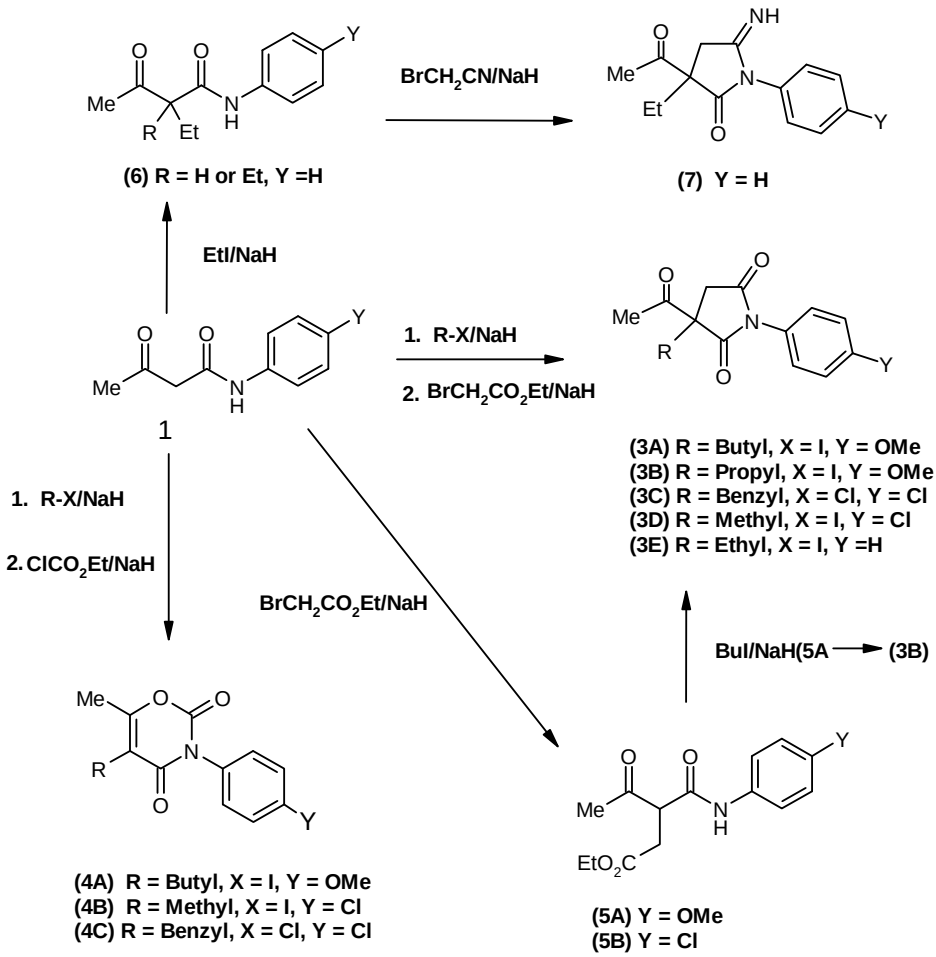
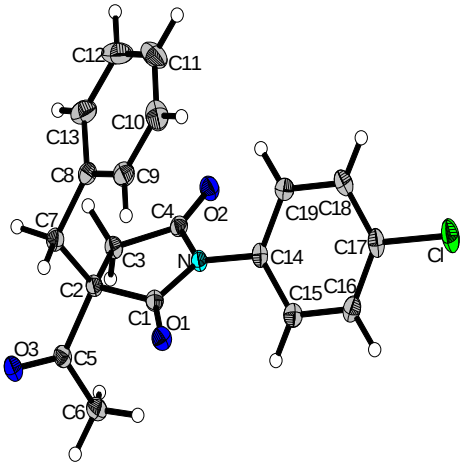
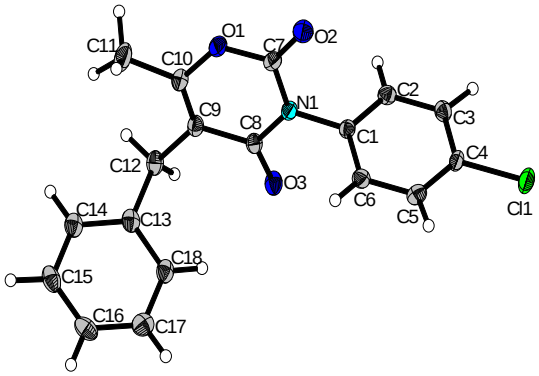


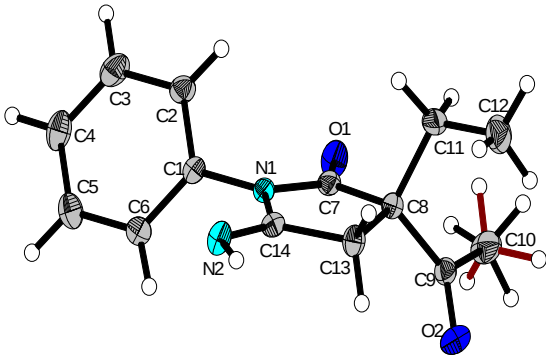
FIGURE 1



(3C)



(4C)



(7)

FIGURE 2

EXPERIMENTAL

Acetoacetanisidine, 4-chloroacetoacetanilide, ethyl bromoacetate, ethyl chloroformate and all alkyl halides were purchased from Sigma Aldrich and used as received. Acetone was dried and distilled before use. Melting points were determined using a Griffin melting point apparatus and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer 2000FT-IR spectrometer. NMR spectra were recorded on a Bruker AC 400 NMR spectrophotometer operating at 400 MHz for ^{1}H NMR and at 100 MHz for ^{13}C NMR. The ^{1}H and ^{13}C NMR chemical shifts (ppm) are relative to TMS and all coupling constants (*J)* are in Hertz (Hz). The electrospray m/s spectral data were aquired using a Bruker LCQ Esquire, the samples being introduced as solutions in MeOH or MeCN.

X-Ray crystallographic data

"CCDC 269713 (**3C)**, CCDC 272231 (**4C)** and CCDC 272233 (**7)** contains the supplementary crystallographic data for this paper. These can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk)".

Preparation of alpha substituted acetoacetanilides and acetoacetanisidines .

These compounds were prepared according to a general procedure as follows.

A solution of acetoacetanisidine or 4-chloroacetoacetanilide (0.02 mol) was heated under reflux in acetone (200 mL) containing anhydrous K_2CO_3 (2.76 g, 0.02 mol). To this was added the appropriate alkyl halide (0.02 mole) **(Figure 1)** and the reaction was heated under reflux overnight. After removal of the solid potassium carbonate, the filtrate was concentrated to an oil. The oil was purified by column chromatography using SiO_2 and a mixture of EtOAc and hexane as eluant (50%:50% by volume). The monosubstituted products were obtained in yields of 50–70% along with small quantities of disubstituted products and unreacted starting materials. Compound (**5A)** was prepared according to the literature procedure.[21]

General procedure for the preparation of 1,3-oxazine-2,4-diones (**4**)

A solution of the monosubstituted acetoacetanilide (4 mmol) in acetone (80 mL) was treated with NaH (60 % dispersion in oil, 200 mg, 5 mmol), followed by ethyl chloroformate (0.5 mL, 5 mmol). The reaction mixture was heated under reflux overnight, concentrated to an oil and subjected to column chromatography using SiO_2 and a mixture of EtOAc and hexane as eluant (50%:50% by volume) to give the cyclized products.

Synthesis of 5-Butyl-3-(4-methoxyphenyl)-6-methyl[1,3]oxazine-2,4-dione **(4A)**

Following column chromatography using SiO_2 and a mixture of EtOAc and hexane as eluant (50%:50% by volume) the major component was isolated as a white crystalline solid (750 mg, 69%). mp 98-100^{0}C (EtOH). IR (KBr) 1773, 1683, 1517, 1401, 1256, 1026, 841 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 0.95 (3H, t, CH_3, J

= 7.2), 1.40 (2H, m, CH_2, J = 7.2), 1.47 (2H, m, CH_2, J = 7.0), 2.30 (3H, s, CH_3), 2.40 (2H, m, CH_2, J = 7.6), 3.80 (3H, s, OCH_3), 7.00 (2H, d, 2 x Ar CH, J = 6.8), 7.20 (2H, d, 2 x Ar CH, J = 6.6). ^{13}C NMR ($CDCl_3$) δ 14.2, 17.3, 55.9 (3 x CH_3), 22.9, 25.3, 31.2 (3 x CH_2), 115.2, 129.4 (2 x Ar CH), 113.0 127.0, 149.4, 160.2, 160.5, 162.9 (6 x qC). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.43; H; 6.6, N; 4.84, Found: C, 66.3; H, 6.58; N, 4.76. ESMS (MeOH CV +40 V) *m/z* 312 ([M + Na^+]$^+$, 100%).

Synthesis of 5,6-Dimethyl-3-(4-chlorophenyl)[1,3]oxazine-2,4-dione **(4B)**

Following chromatography using SiO_2 and a mixture of EtOAc and hexane as eluant (50%:50% by volume) the major component was isolated as a white solid (120 mg, 27%). mp 155-157^{o}C (EtOH). IR (KBr) 1765, 1690, 1585, 1420, 1230, 998, 832 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 2.0 (3H, s, CH_3), 2.30 (3H, s, CH_3), 7.20 (2H, d, 2 x Ar CH, J = 6.8), 7.50 (2H, d, 2 x Ar CH, J = 6.8). ^{13}C NMR ($CDCl_3$) δ 10.7 (CH_3), 17.5 (CH_3), 129.8, 130.2 (2 x Ar CH), 108.5, 133.0, 135.5, 148.8, 160.5, 162.7 (6 x qC). Anal. Calcd for $C_{12}H_{10}NO_3Cl$: C, 57.3; H, 3.98; N, 5.56. Found: C, 56.82; H, 3.94; N, 5.49. ESMS (MeOH CV +20 V) *m/z* 274 ([M + Na^+]$^+$, 100%).

Synthesis of 5-Methyl-3-(4-chlorophenyl)-6-benzyl-[1,3]oxazine-2,4-dione **(4C)**

The oil was diluted with 10 mL of ethyl acetate and then with 200 mL of hexane and chilled in a freezer overnight. A white crystalline product was filtered. (520 mg, 24%) mp 148-150^{0}C (EtOH). IR (KBr) 1761, 1681, 1492, 1404, 1231, 1091, 752 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 2.25 (3H, s, CH_3), 3.70 (2H, s, CH_2), 7.0-7.2 (7H, m, 7 x Ar CH), 7.40 (2H, d, 2 x Ar CH, J = 6.6). ^{13}C NMR ($CDCl_3$) δ 17.9 (CH_3), 31.0 (CH_2), 127.2, 128.8, 129.2, 129.8, 130.2 (5 x Ar CH), 112.4, 132.8, 135.6, 138.5, 148.5, 162.2, 162.5 (7 x qC). Anal. Calcd for $C_{18}H_{14}NO_3Cl$: C, 65.95; H, 4.27; N, 4.27. Found: C; 65.76, H; 4.23, N; 4.10. ESMS (MeCN CV +36 V) *m/z* 350 ([M + Na^+]$^+$, 100%).

General procedure for the preparation of pyrolidine-2,5-diones **(3)**

A solution of the monosubstituted acetoacetanilide (6 mmol) in acetone (80 mL) was treated with NaH (60 % dispersion in oil, 400 mg, 10 mmol), followed by ethylbromoacetate (1.1 mL, 10 mmol). The reaction mixture was heated under reflux overnight, concentrated to an oil which was subjected to column chromatography (see individual entries) to give the cyclised products.

Synthesis of 3-Acetyl-3-butyl-1-(4-methoxyphenyl)-pyrolidine-2,5-dione **(3A)**

Following column chromatography using SiO_2 and a mixture of EtOAc and hexane as eluant (50%:50% by volume) the product eluted as the fastest eluting component. **3A** was obtained as a white crystalline solid (500 mg, 28%). mp 78-80^{o}C (EtOH). IR (KBr) 2960,1701, 1520, 1394, 1248, 1184, 1031, 818 cm^{-1}.

^{1}H NMR (DMSO-d_6), δ 0.90 (3H, t, CH_3, J = 7.2), 1.20 (2H, m, CH_2, J = 6.8), 1.30 (2H, m, CH_2, J = 7.0), 2.00 (2H, m, CH_2, J = 6.0), 2.30 (3H, s, CH_3), 2.70 (1H, d, CH_2, J = 18.4), 3.32 (1H, d, CH_2, J = 18.4), 3.80 (3H, s, OCH_3), 7.0 (2H, d, 2 x Ar CH, J = 6.5), 7.20 (2H, d, 2 x Ar CH, J = 6.8). ^{13}C NMR (DMSO-d_6), δ 14.0, 26.4, 55.7 (3 x CH_3), 22.6, 26.3, 34.5, 35.5 (4 x CH_2), 114.5, 128.8 (2 x Ar CH), 61.8, 125.0, 160.0, 175.0, 176.2, 203.3 (6 x qC). Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.32; H, 6.93; N, 4.62. Found: C, 67.29; H, 6.97; N, 4.56. ESMS (MeOH CV +40 V) *m/z* 326 ([M + Na^+]$^+$, 100%).

Synthesis of 3-Acetyl-3-propyl-1-(4-methoxyphenyl)pyrolidine-2,5-dione (**3B**)

Method A

3-Ethoxycarbonylmethylacetoacetanisidine (**5**) (1.5 g, 5 mmol) was heated under reflux in acetone (100 mL) with K_2CO_3 (690 mg, 5 mmol) and iodopropane (850 mg, 5 mmol) for 2 days. The usual work up followed by column chromatography using SiO_2 and a mixture of EtOAc and hexane as eluant (50%:50% by volume) gave the product (the faster eluting component) as a pale yellow solid (300 mg, 21%.)

Method B

3-Propylacetoacetanisidine (5.1 g, 0.02 mol) was heated overnight under reflux in acetone (250 mL) with K_2CO_3 (2.8 g, 0.02 mol) and ethyl bromoacetate (2.2 mL, 0.02 mol). Work up gave an oil which was purified by chromatography using SiO_2 and a mixture of EtOAc and hexane as eluant (50%:50% by volume) as the second fastest component, yielding a white solid (2.5 g, 43%) mp 96-98^{0}C (EtOH). IR (KBr) 2967, 1703, 1520, 1387, 1253, 1188, 1027, 850 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.90 (3H, t, CH_3, J = 7.2), 1.30 (2H, m, CH_2, J = 7.6), 2.00 (2H, m, CH_2, J = 7.6), 2.30 (3H, s, CH_3), 2.70 (1H, d, CH_2, J = 18.4), 3.32 (1H, d, CH_2, J = 18.4), 3.80 (3H, s, OCH_3), 7.00 (2H, d, 2 x Ar CH, J = 6.8), 7.20 (2H, d, 2 x Ar CH, J = 7.0). ^{13}C NMR (DMSO-d_6): δ 14.0, 26.4, 55.7 (3 x CH_3), 17.7, 35.5, 36.8 (3 x CH_2), 114.5, 128.8 (2 x Ar CH), 61.8, 125.0, 159.4, 175.0, 176.2, 203.3 (6 x qC). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.43; H, 6.57; N, 4.84. Found: C, 66.31; H, 6.57; N, 4.76. ESMS (MeCN CV +33 V) *m/z* 312 ([M + Na^+]$^+$, 100%).

Synthesis of 3-Acetyl-3-benzyl-1-(4-chlorophenyl)pyrolidine-2,5-dione **(3C)**

The oil was purified by column chromatography using SiO_2 and a mixture of EtOAc and hexane as eluant (50%:50% by volume) to give the product as the faster eluting component yielding a white solid (900 mg 13%). mp 105-108^{0}C (EtOH). IR (KBr) 3021, 1717, 1493, 1387, 1177, 1091, 829 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.60 (3H, s, CH_3), 2.70 (1H, d, CH_2, J = 18.4), 3.50 (1H, d, CH_2, J = 18.4), 3.00 (1H, d, CH_2, J = 18.4), 3.76 (1H, d, CH_2, J = 18.4), 6.95 (2H, d, 2 x Ar CH, J = 6.8), 7.25 (2H, d, 2 x Ar CH, J = 6.5), 7.30-7.40 (5H, m, 5 x Ar CH). ^{13}C NMR ($CDCl_3$): δ 27.0 (CH_3), 34.7 (CH_2), 40.5 (CH_2), 128.0, 128.5,

129.5, 129.8, 130.2 (5 x Ar CH), 63.2, 130.2, 134.4, 135.2, 173.7, 175.3, 202.3 (7 x qC). Anal. Calcd for $C_{19}H_{16}NO_3Cl$: C, 66.76; H, 4.68; N, 4.10. Found: C, 66.65, H, 4.63, N, 4.0. ESMS (MeCN CV +36 V) *m/z* 364 ([M + Na^+]$^+$, 100%).

Synthesis of 3-Acetyl-3-methyl-1-(4-chlorophenyl)pyrolidin-2,5-dione **(3D)**

The oil purified by column chromatography using SiO_2 and a mixture of EtOAc and hexane as eluant (50%:50% by volume) to give the product as the faster eluting component as a white solid (300 mg, 20%) mp 102-105^{0}C (EtOH). IR (KBr) 2986, 1706, 1495, 1397, 1200, 1091, 875 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.73 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.53 (1H, d, CH_2, J = 18.4), 3.60 (1H, d, CH_2, J = 18.4), 7.20 (2H, m, 2 x Ar CH), 7.43 (2H, m, 2 x Ar CH). ^{13}C NMR ($CDCl_3$): δ 22.3 (CH_3), 26.5 (CH_3), 38.7 (CH_2), 57.9, 130.4, 135.0, 174.0, 176.0, 203.0 (6 x qC), 128.0, 130.0 (2 x Ar CH). Anal. Calcd for $C_{13}H_{12}NO_3Cl$: C, 58.75; H, 4.52; N, 5.27. Found: C, 58.60; H, 4.50; N, 5.15 ESMS (MeOH CV +20 V) *m/z* 274 ([M + Na^+]$^+$, 100%).

Synthesis of 3-Acetyl-3-ethyl-1-(phenyl)pyrolidine-2,5-dione **(3E)**

White solid (800 mg, 19%) mp 82-85^{0}C (EtOH). IR (KBr) 2984, 1707, 1488, 1395, 1187, 1103, 971, 864 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.00 (3H, t, CH_3, J = 7.2), 2.20 (2H, m, CH_2), 2.50 (3H, s, CH_3, J = 6.8), 2.60 (1H, d, CH_2, J = 18.8), 3.70 (1H, d, CH_2, J = 18.8), 7.20 (2H, m, 2 x Ar CH), 7.40-7.45 (3H, m, 3 x Ar CH). ^{13}C NMR ($CDCl_3$): δ 9.30, 26.5 (2 x CH_3), 29.0, 35.0 (2 x CH_2), 63.2, 132.0, 174.5, 175.7, 203.0 (5 x qC), 126.8,129.2, 129.6 (3 x Ar CH)). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 68.57; H, 6.12; N, 5.71, Found: C, 68.56; H, 6.17; N, 5.71. ESMS (MeCN CV +30 V) *m/z* 268 ([M + Na^+]$^+$, 100%).

Synthesis of α-Ethoxycarbonylmethyl-4-chloroacetoacetanilide **(5B) Y = Cl**

Procedure as for **5A**[21]. White solid (2g, 40%), mp 90-92^{0}C. (EtOH). IR (KBr) 3306, 2987, 1708, 1602, 1539, 1400, 1338, 1202, 1089, 833 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.27 (3H, m, CH_3, J = 7.4), 2.30 (3H, s, CH_3), 3.00 (2H, m, CH_2, J = 8.0), 3.90 (1H, t, CH, J = 6.8), 4.15 (2H, q, CH_2, J = 7.2), 7.25 (2H, d, 2 x Ar CH, J = 7.0), 7.44 (2H, d, 2 x Ar CH, J = 6.8), 8.71 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 14.5, 29.3, (2 x CH_3), 33.5, 62,0 (2 x CH_2), 57.7 (CH), 121.6, 129.4 (2 x Ar CH), 130.2, 136.5, 166.0, 172.5, 204.8 (5 x qC). Anal. Calcd for $C_{14}H_{16}NO_4Cl$: C, 56.47; H, 5.38; N, 4.70, Found: C, 56.50; H, 5.25; N, 4.61. ESMS (MeCN CV +30 V) *m/z* 320 ([M + Na^+]$^+$, 100%).

Synthesis of 3-Acetyl-3-ethyl-5-imino-1-phenyl-pyrrolidin-2-one ***(7)***

3-Ethylacetoacetanilide (**6**) (3.5 g, 17 mmol) was heated under reflux in acetone (150 mL) with NaH (60% dispersion, 1g, 25 mmol) and chloroacetonitrile (1.6 mL, 25 mmol) for 16 h. The reaction was

filtered and the filtrate was then concentrated to an oil and purified by column chromatography using SiO_2 and a mixture of EtOAc and hexane as eluant (50%:50% by volume) to give the product as the slowest running component along with unreacted material. **7** (920 mg, 22%). mp 100-115^{0}C.(EtOH). IR (KBr) 3292 (s), 2974, 1706, 1653, 1498, 1416, 1208 1132 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.1 (3H, t, CH_3, J = 7.2), 2.20 (2H, m, CH_2, J = 7.2), 2.50 (3H, s, CH_3), 2.6 (1H, d, CH_2, J = 18.8), 3.7 (1H, d, CH_2, J = 18.8), 7.2 (2H, m, 2 x Ar CH), 7.4-7.45 (3H, m, 3 x Ar CH). ^{13}C NMR ($CDCl_3$): δ 9.30, 26.5 (2 x CH_3), 29.0, 33.6 (2 x CH_2), 63.3, 126.8, 132.0, 132.6, 174.5, 203.7 (5 x qC), 127.8,129.5, 130.1 (3 x Ar CH). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 68.85; H, 6.55; N, 11.47, Found: C; 68.69, H; 6.61, N; 10.71. ESMS (MeCN CV +30 V) *m/z* 267 ([M + Na^+]$^+$, 100%).

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