

An Efficient Synthesis of Achiral and Chiral Cyclic Dehydro- α -Amino Acid Derivatives Through Nucleophilic Addition of Amines to β,γ -Unsaturated α -Keto Esters

Francisco Palacios,^{*,[a]} Javier Vicario,^[a] and Domitila Aparicio^[a]

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A very simple and efficient synthesis of 3-amino-1,5-dihydro-2H-pyrrol-2-ones is reported. These cyclic dehydro-amino acid derivatives with a stereogenic center at the 5-position were obtained by the addition of two equivalents of amine to β,γ -unsaturated keto esters. These cyclic enamines can

also be obtained by the three-component reaction of ethyl pyruvate, amines and aldehydes.

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1,5-Dihydro-2H-pyrrol-2-ones are an appealing family of lactams found as substructures in many natural products with interesting pharmacological properties, such as the lipopeptides microcolin A and B.^[1] When an amino substituent is present at the 3-position, these heterocycles are also enamines, substrates that have attracted a great deal of attention in recent years because of their range of applications.^[2,3] In addition, these cyclic enamines are not only susceptible to being further functionalized,^[4] but they are also an important family of compounds in organic and medicinal chemistry, for example, the cyclic dehydro- α -amino acid derivatives^[5] and, therefore, α -amino acid sources with an additional stereogenic center at the γ position.

In this context, we are interested in the preparation of three-,^[6] five-^[7] and six-membered^[8] nitrogen heterocycles, as well as in the synthesis of acyclic enamines or dehydro- β -amino phosphorus derivatives^[9] and their synthetic use in the preparation of functionalized acyclic compounds^[10,11] and heterocycles.^[12] As a continuation of our work on the synthesis and reactivity of 1-azabutadienes^[13] and enamines,^[11] we report herein a very simple and efficient synthesis of 3-amino-1,5-dihydro-2H-pyrrol-2-ones through

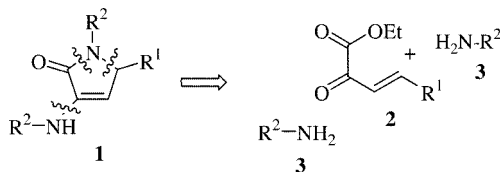
the conjugate addition of amines to β,γ -unsaturated α -keto esters (Scheme 1).

Results and Discussions

Reaction of β,γ -Unsaturated α -Keto Esters **2** with Amines **3**

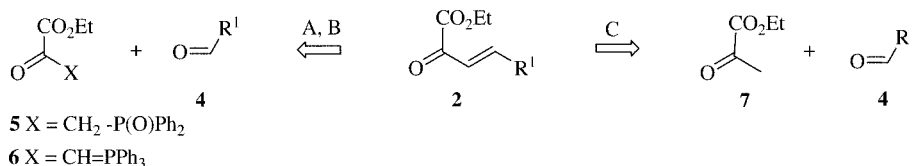
The required β,γ -unsaturated α -keto esters **2** were prepared by using strategies outlined in Scheme 2. Olefination with aldehydes **4** was performed either by the Wittig–Horner reaction starting from the phosphorylated α -keto ester **5** derived from phosphane oxide^[14] (Scheme 2, route A) or by the Wittig reaction of the conjugated phosphorus ylide **6** using Le Corre's method^[15] (Scheme 2, route B). The acid-catalyzed aldolic condensation of ethyl pyruvate **7** and aldehydes **4**^[16] was also used to prepare α -keto esters **2** (Scheme 2, route C).

The acid-catalyzed aldol reaction (route C, Scheme 2) is the best choice when an aromatic aldehyde (*p*-nitrobenzaldehyde) is used, since lower yields were obtained with the other two olefination approaches (Table 1, entry 1). The yield dropped considerably in the case of a conjugated aldehyde (Table 1, entry 5) and dramatically when a heteroaromatic aldehyde (Table 1, entry 4) was used. No unsaturated ketones **2** were observed when aliphatic aldehydes were used. Attempts to improve the reactivity by addition of trimethyl orthoformate as a co-solvent to promote the dehydration process were unsuccessful. Direct use of the conjugated phosphorus ylide **6** with aldehydes **4** improved the yield (Scheme 2, route B) when 2-furylaldehyde was used (Table 1, entry 4) and good yields were obtained in the Wittig reaction with ethyl glyoxalate or acetaldehyde (Table 1, entries 2 and 3). Note that by using any of the proposed approaches only the (*E*)-alkene was obtained.



Scheme 1. Retrosynthesis of 3-amino-1,5-dihydro-2H-pyrrol-2-ones (**1**).

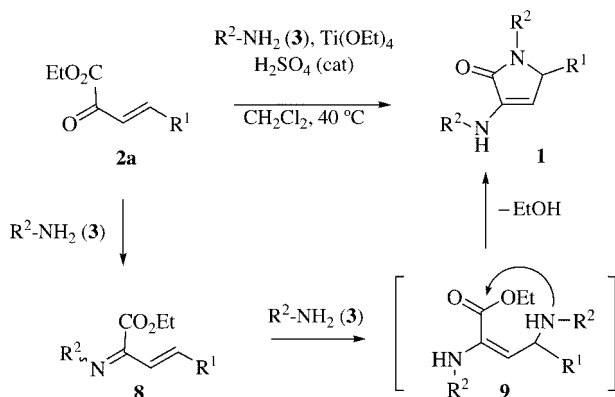
[a] Departamento de Química Orgánica I, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080 Vitoria-Gasteiz, Spain
E-mail: qoppagaf@vc.ehu.es

Scheme 2. Synthetic strategies used for the synthesis of β,γ -unsaturated α -keto esters **2**.Table 1. Yields of the β,γ -unsaturated α -keto esters **2** prepared by the three approaches.

Entry	Compd.	R ¹	Yield [%] ^[a]
1	2a	<i>p</i> -NO ₂ -Ph	35, ^[b] 49, ^[c] 72 ^[d]
2	2b	CO ₂ Et	77 ^[c]
3	2c	Me	61 ^[c]
4	2d	2-furyl	55, ^[c] 10 ^[d]
5	2e	(<i>E</i>)-CH ₂ =CH-Ph	42 ^[d]

[a] Isolated yield. [b] Method A. [c] Method B. [d] Method C.

In the course of our studies on the preparation of 1-azadienes,^[13] the condensation of β,γ -unsaturated α -keto esters **2** with amines **3** was explored. *p*-Toluidine (**3a**) (R¹ = *p*-Me-Ph) did not react with unsaturated carbonyl compounds **2** using Dean–Stark apparatus or with a dehydrating agent or in the presence of Lewis acids [Yb(OTf)₃, BF₃, Ti(OEt)₄] and starting compounds were recovered. However, when β,γ -unsaturated α -keto ester **2a** (R¹ = *p*-NO₂-Ph) was treated with one equivalent of *p*-toluidine (**3a**) (R² = *p*-Me-Ph) in the presence of an equimolecular amount of Ti(OEt)₄ and a catalytic amount of H₂SO₄, not only was the 1-azadiene derived from α -amino ester **8aa** (18%, R¹ = *p*-NO₂-Ph, R² = *p*-Me-Ph) obtained as an *anti*/*syn* mixture of imines (60:40), but also a cyclic enamine **1aa** (36%, R¹ = *p*-NO₂-Ph, R² = *p*-Me-Ph) containing two amino groups (Scheme 3).

Scheme 3. Synthesis of 1-azadiene **8** and cyclic amines **1**.

Heterodiene **8aa** and enamine **1aa** were fully characterized by ¹H and ¹³C NMR, MS and IR spectroscopy. Characteristic signals of **8aa** in the ¹H NMR spectrum are the two doublets observed at δ = 7.47 and 6.76 ppm, with a coupling constant ³J_{H,H} = 16.2 Hz, corresponding to the *anti* isomer, as well as another two doublets at δ = 7.02 and 7.29 ppm, with a coupling constant ³J_{H,H} = 16.3 Hz, which correspond to the *syn* isomer. Both coupling constants are

consistent with an (*E*) configuration of the double bond. On the other hand, characteristic signals of **1aa** in the ¹H NMR spectrum are the two doublets at δ = 5.75 and 5.96 ppm, with a coupling constant ³J_{H,H} = 2.4 Hz, corresponding to the protons at the stereogenic center and the double bond, respectively, whereas the ¹³C NMR spectrum shows characteristic signals at δ = 63.7 ppm for C-5, 105.5 and 138.6 ppm for the C-4 and C-3 enamine carbon atoms, respectively, and 167.1 ppm for the amide C=O. The formation of both products can be explained by an initial amine/carbonyl condensation to give 1-azadiene **8**, which undergoes conjugate addition of a second molecule of amine to yield a γ -amino α -enamino ester **9**. The enamine is expected to have an (*E*) configuration if the α,β -unsaturated imine is in its more stable pseudo-*trans* conformation during the addition of the amine. The 3-amino-1,5-dihydro-2*H*-pyrrol-2-one (**1aa**) is obtained after the loss of ethanol (Scheme 3). The participation of the functionalized azadiene **8** in the formation of cyclic enamine **1** was also tested. Reaction of 1-azadiene **8aa** with one equivalent of *p*-toluidine (**3a**) (R² = *p*-Me-Ph) in the presence of Ti(OEt)₄ and H₂SO₄ also gave cyclic enamine **1aa** (R¹ = *p*-NO₂-Ph, R² = *p*-Me-Ph) (Table 2, entry 1).

Table 2. 3-Amino-1,5-dihydro-2*H*-pyrrol-2-ones **1** obtained in this work.

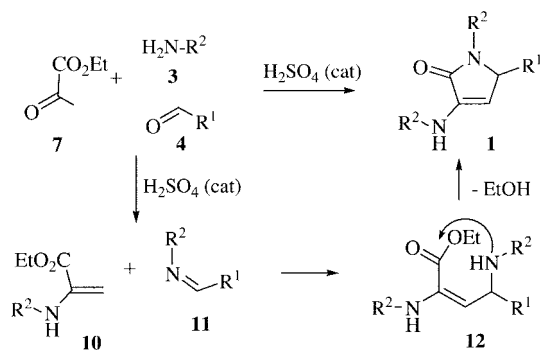
Entry	Starting compounds	Compd. obtained	R ¹	R ²	Yield (%) ^[a]
1	2a 3a	1aa	<i>p</i> -NO ₂ -Ph	<i>p</i> -Me-Ph	76, ^[b] 79, ^[c] 80 ^[d]
2	2b 3a	1ba	CO ₂ Et	<i>p</i> -Me-Ph	71 ^[b] , 77 ^[d]
3	2b 3b	1bb	CO ₂ Et	<i>p</i> -MeO-Ph	85 ^[b]
4	2b 3c	1bc	CO ₂ Et	<i>p</i> -Cl-Ph	88 ^[b]
5	2c 3a	1ca	Me	<i>p</i> -Me-Ph	80 ^[b] , 78 ^[d]
6	2c 3b	1cb	Me	<i>p</i> -MeO-Ph	83 ^[b]
7	2d 3a	1da	2-furyl	<i>p</i> -Me-Ph	69 ^[b] , 73 ^[d]
8	2a 3d	13/14	<i>p</i> -NO ₂ -Ph		82 ^[b]

[a] Isolated yield. [b] Yield obtained by the reaction of amines **3** with β,γ -unsaturated α -keto ester **2**. [c] Yield obtained by the reaction of amine **3** with 1-azadiene **8**. [d] Yield obtained by the three-component reaction.

Next, we tried to extend this process to the regioselective preparation of cyclic enamines^[17,18] **1** by using an excess of amine. Thus, when the reaction of β,γ -unsaturated α -keto ester **2a** (R¹ = *p*-NO₂-Ph) was performed with two equivalents of *p*-toluidine (**3a**) (R² = *p*-Me-Ph) in the presence of Ti(OEt)₄ and H₂SO₄ and in refluxing CH₂Cl₂ only cyclic

enamine **1aa** (76%, $R^1 = p\text{-NO}_2\text{-Ph}$, $R^2 = p\text{-Me-Ph}$) was obtained (Scheme 3, Table 2, entry 1). By following a similar procedure, a wide variety of cyclic α -dehydro-amino acid derivatives **1** were prepared. Good yields were obtained when the substituent at the 5-position was an ester (Table 2, entries 2-4), a methyl (Table 2, entry 5 and 6) or a furyl group (Table 2, entry 7).

Taking into account the fact that β,γ -unsaturated α -keto ester **2a** was obtained from ethyl pyruvate **7** and *p*-nitrobenzaldehyde (see Scheme 2, vide supra), we next tried to explore if dehydro-amino acid derivatives **1** could also be prepared by a three-component reaction involving ethyl pyruvate **7**, aldehydes **4** and amines **3**. Reaction of a mixture of ethyl pyruvate **7**, aldehyde **4** and two equivalents of amine **3** in CH_2Cl_2 at room temperature and with a catalytic amount of H_2SO_4 yielded dehydro- α -amino acid derivatives **1aa**, **1ba**, **1ca** and **1da** in excellent yields (Scheme 4, Table 2, entries 1, 2, 5 and 7). The three-component reaction was monitored by ^1H NMR spectroscopy when *p*-toluidine (**3a**) ($R^2 = p\text{-Me-Ph}$) and *p*-nitrobenzaldehyde (**4a**) ($R^1 = p\text{-NO}_2\text{-Ph}$) were used, and enamine **10** and imine **11** were detected as intermediates. Therefore in this three-component process, the formation of cyclic enamines **1** can be explained by the initial formation of enamine **10** by condensation of ethyl pyruvate **7** and amine **3** and subsequent imine–enamine tautomerization (Scheme 4). The enamines **10** then reacted with imines **11** generated by condensation of aldehydes **4** and amines **3**, followed by intramolecular cyclocondensation of functionalized enamine **12** and the loss of ethanol. The formation of enamines **10** and imines **11** is favored by the presence of a catalytic amount of acid.

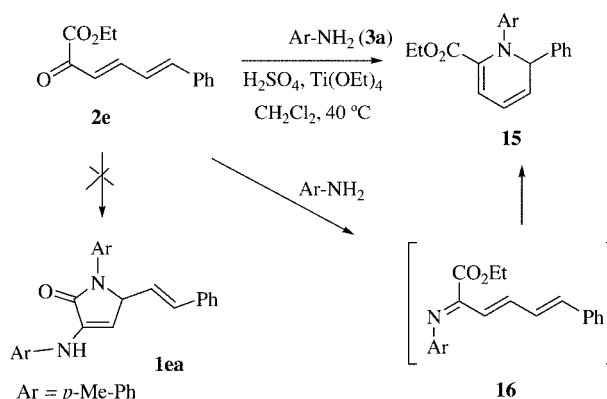


Scheme 4. Proposed mechanism for the three-component reaction.

The process can also be extended to the formation of optically pure dehydro- α -amino acid derivatives when chiral amines are used. The reaction of β,γ -unsaturated α -keto ester **2a** ($R^1 = p\text{-NO}_2\text{-Ph}$) with enantiopure (*R*)- α -methylben-

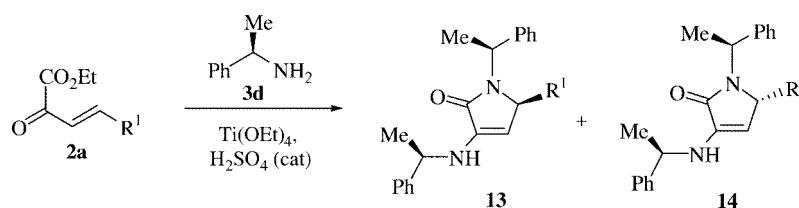
zylamine (**3d**) in toluene at 110°C and in the presence of $\text{Ti}(\text{OEt})_4$ and H_2SO_4 gave a 1:1 mixture of the two diastereoisomers **13** and **14** with three stereogenic centers (Scheme 5, Table 2, entry 8). Separation and isolation of the two optically pure isomeric cyclic enamines **13** and **14** were carried out by simple chromatography (see Expt. Sect.).

Different behavior was observed when α -keto ester **2e** containing two conjugated double bonds was used. The reaction of the conjugate α -keto ester **2e** with *p*-toluidine (**3a**) ($\text{Ar} = p\text{-Me-Ph}$) under the same conditions as described above did not give cyclic enamine **1ea** (Scheme 6); instead 1,2-dihydropyridine **15** derived from an α -amino ester was obtained (81%). The formation of this heterocycle **15** can be explained through the generation of the nonisolable 1-azatriene **16** followed by a 6π -azaelectrocyclization.



Scheme 6. Synthesis of 1,2-dihydropyridine **15**.

The thermal cyclization of 1-azatrienes into 1,2-dihydropyridines (6π -azaelectrocyclization) is a well-known concerted pericyclic reaction.^[19] The synthesis of 1,2-dihydropyridines from primary amines and diunsaturated carbonyl compounds usually requires high temperatures and the isolation of 1-azatriene intermediates involved is uncommon. Not many 6π -azaelectrocyclization reactions carried out under mild conditions are described in the literature and it has been established that the orbital interaction between the HOMO (C5–C6) and the LUMO (C1–C4) can be improved if C6-phenyl or -alkenyl and C4- or C3-carbonylic substituents are present.^[20] In our case the combined effect of an electron-withdrawing group in the 2-position and a phenyl terminal substituent seems to activate the intramolecular 6π -azaelectrocyclization reaction with the process favoring the electrocyclization of 2-azatrienes^[21] and 3-azatrienes.^[22]



Scheme 5. Synthesis of the optically pure 1,5-dihydro-2*H*-pyrrol-2-ones **13** and **14**.

In conclusion, we have described herein an easy and efficient synthesis of 3-amino-1,5-dihydro-2*H*-pyrrol-2-ones either through double nucleophilic addition of amines to β,γ -unsaturated α -keto esters or by the three-component reaction of ethyl pyruvate, aldehydes and amines. We have shown that in the addition of amines to conjugated α -keto esters, a 1-azadiene could be involved in the reaction and that the mechanism of the reaction could involve sequential 1,2 addition of the amine to β,γ -unsaturated α -keto esters and conjugate addition of the amine to the 1-azadiene followed by spontaneous intramolecular cyclization. An example of a 6π -azaelectrocyclization reaction of a functionalized 1-azatriene under mild conditions has also been reported. Note that pyridine compounds derived from α -amino acids are useful heterocycles not only for their biological activity^[23] but also because the pyridine nucleus is a structural unit that appears in many natural products.^[24]

Experimental Section

General: Chemicals were purchased from Aldrich or Acros. Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under dry nitrogen. Analytical TLC was performed with Merck silica gel 60 F₂₅₄ plates. Visualization was accomplished using UV light. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. NMR spectra were obtained using a Varian VXR 300 MHz spectrometer operating at 300 and 80 MHz for ¹H and ¹³C nuclei, respectively. Chemical shifts are reported in δ units (ppm) relative to the residual deuterated solvent signals of CDCl₃ (¹H NMR: δ = 7.26 ppm; ¹³C NMR: δ = 77.0 ppm) and coupling constants (*J*) are reported in Hertz. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EI-MS) with a Hewlett-Packard 5971 or 5973 spectrometer and by chemical ionization (CI) (N₂) on a Hewlett-Packard 1100MSD instrument. Data are reported in the form *m/z* (intensity relative to base $\times$ 100). Infrared spectra (IR) were recorded with a Nicolet IRFT Magna 550 spectrometer as solids in KBr or as neat oils. Peaks are reported in cm⁻¹. Elemental analyses were performed with a LECO CHNS-932 apparatus.

General Procedure for the Synthesis of β,γ -Unsaturated α -Keto Esters 2

Procedure A: Wittig–Horner reaction of β -ketophosphane oxide **5**. Following a literature procedure,^[14] a solution of ethyl 3-(diphenylphosphino)-2-oxopropionate (**5**, 15.8 g, 50 mmol) in THF (100 mL) was added to a suspension of NaH (1.24 g, 50 mmol) in THF (100 mL) at 0 °C. The mixture was stirred at this temperature for 1 h and then a solution of the corresponding aldehyde (50 mmol) in THF (50 mL) was added. After allowing the mixture to warm to room temp., the reaction was stirred overnight. The mixture was then diluted with water (200 mL) and extracted with CH₂Cl₂ (3 $\times$ 100 mL). The combined organic layers were washed with water, dried with MgSO₄ and concentrated under reduced pressure. The crude residue was purified by chromatography (SiO₂, AcOEt/hexanes, 1:4).

Procedure B: Wittig reaction of phosphorus ylide **6**. Following a literature procedure,^[15] a solution of ethyl 2-oxo-3-(triphenyl- λ^5 -

phosphanylidene)propionate **6** (18.8 g, 50 mmol) and the corresponding aldehyde (50 mmol) was refluxed in xylene (150 mL) or stirred at room temp. in benzene (150 mL) for 3 h. The solvent was evaporated under reduced pressure and the crude residue was purified as indicated.

Procedure C: Acid-catalyzed aldol condensation of ethyl pyruvate **7**. Following a literature procedure,^[16] a solution of ethyl pyruvate **7** (8.33 mL, 75 mmol), aldehyde (50 mmol) and Cu(OTf)₂ (1.81 g, 5 mmol) in CHCl₃ (150 mL) was stirred and refluxed for 7 d. The resulting mixture was cooled to room temp. and filtered through basic alumina and the homogeneous solution was evaporated under reduced pressure. The crude residue was purified by crystallization from EtOH.

Ethyl (E)-4-(*p*-Nitrophenyl)-2-oxobut-3-enoate (2a**):** Synthesized according to general procedure A with *p*-nitrobenzaldehyde (7.56 g, 50 mmol), affording 4.35 g (35%) of **2a** as a yellow solid. Synthesized according to general procedure B with *p*-nitrobenzaldehyde (7.56 g, 50 mmol) in xylene at 140 °C. The crude residue was purified by crystallization from EtOH, affording 6.10 g (49%) of **2a** as a yellow solid. Synthesized according to general procedure C with *p*-nitrobenzaldehyde (7.56 g, 50 mmol), affording 8.96 g (72%) of **2a** as a yellow solid. Physical and spectroscopic data are in agreement with published data.^[15]

Ethyl (E)-4-Oxo-pent-2-enedioate (2b**):** Synthesized according to general procedure B with ethyl glyoxalate (5.10 g, 50 mmol) in benzene at room temp. The crude residue was purified by distillation (86–88 °C, 10⁻³ Torr), affording 7.74 g (77%) of **2b** as a yellow oil. ¹H NMR (300 MHz, CDCl₃, 30 °C): δ = 7.56 (d, ³*J*_{H,H} = 6.0 Hz, 1 H, CH=), 6.92 (d, ³*J*_{H,H} = 6.0 Hz, 1 H, CH=), 4.36 (d, ³*J*_{H,H} = 7.2 Hz, 2 H, CH₂-O), 4.26 (d, ³*J*_{H,H} = 7.2 Hz, 2 H, CH₂-O), 1.37 (t, ³*J*_{H,H} = 7.2 Hz, 3 H, CH₃), 1.30 (t, ³*J*_{H,H} = 7.2 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃, 30 °C): δ = 182.2 (C=O), 164.2 (C=O), 160.3 (C=O), 135.0 (CH), 133.7 (CH), 62.4 (CH₂-O), 61.2 (CH₂-O), 13.5 (CH₃), 13.4 (CH₃) ppm. IR (KBr): $\tilde{\nu}_{\text{max}}$ = 1738 (br s, C=O ester + ketone) cm⁻¹. EI-MS: *m/z* = 200 (10) [M]⁺, 127 (100) [M - CO₂Et]⁺. C₉H₁₂O₅ (200.1): calcd. C 54.00, H 6.04; found: C 53.95, H 6.08.

Ethyl (E)-2-Oxopent-3-enoate (2c**):** Synthesized according to general procedure B with acetaldehyde (2.81 mL, 50 mmol) in xylene at 140 °C. The crude residue was purified by distillation (42–45 °C, 10⁻³ Torr), affording 5.34 g (61%) of **2c** as a pale yellow oil. Physical and spectroscopic data are in agreement with published data.^[25]

Ethyl (E)-4-(Furan-2-yl)-2-oxobut-3-enoate (2d**):** Synthesized according to general procedure B with 2-furfural (4.14 mL, 50 mmol) in xylene at 140 °C. The crude residue was purified by crystallization from EtOH, affording 5.34 g (55%) of **2d** as a pale brown solid. Synthesized according to general procedure C with 2-furfural (4.14 mL, 50 mmol), affording 0.91 g (10%) of **2d** as a yellow solid. Physical and spectroscopic data are in agreement with published data.^[26]

Ethyl (E,E)-2-Oxo-6-phenylhexa-3,5-dienoate (2e**):** Synthesized according to general procedure C with *trans*-cinnamaldehyde (6.29 mL, 50 mmol), affording 4.83 g (42%) of **2e** as a pale yellow solid. M.p. 81–82 °C (EtOH). ¹H NMR (300 MHz, CDCl₃, 30 °C): δ = 7.64 (dd, ³*J*_{H,H} = 13.9, ³*J*_{H,H} = 15.4 Hz, 1 H, CH=), 7.51–7.47 (m, 2 H, 2 CH Ph), 7.39–7.35 (m, 3 H, 3 CH Ph), 7.11–6.95 (m, 2 H, 2 CH=), 6.87 (d, ³*J*_{H,H} = 15.4 Hz, 1 H, CH=), 4.38 (q, ³*J*_{H,H} = 7.2 Hz, 2 H, CH₂O), 1.37 (t, ³*J*_{H,H} = 7.2 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃, 30 °C): δ = 182.6 (C=O), 162.0 (C=O), 148.1 (CH), 144.3 (CH), 135.4 (C_{quat}), 129.7 (CH), 128.7 (2 CH), 127.5 (2 CH), 126.4 (CH), 123.9 (CH), 62.2 (CH₂O), 13.9

(CH₃) ppm. IR (KBr): $\tilde{\nu}_{\max}$ = 729 (s, C=O ester), 1679 (s, C=O ketone) cm⁻¹. EI-MS: m/z = 230 (10) [M]⁺, 157 (100) [M – CO₂Et]⁺. C₁₄H₁₄O₃ (230.1): C 73.03, H 6.13; found: C 72.95, H 6.17.

General Procedure for the Synthesis of 3-Amino-1,5-dihydro-2H-pyrrol-2-ones 1

Procedure A: Reaction of amines with β,γ -unsaturated α -keto esters 2. A solution of β,γ -unsaturated α -keto ester 2 (5 mmol), the corresponding amine (10 mmol), Ti(OEt)₄ (2.10 mL, 10 mmol) and a drop of H₂SO₄ in CH₂Cl₂ (15 mL) was stirred and refluxed for 2 h. The reaction was warmed to room temp. and a solution of aqueous saturated NaHCO₃ (20 mL) was then added. The mixture was filtered through Celite, washed with H₂O (50 mL) and extracted with CH₂Cl₂ (3 $\times$ 25 mL). The organic layer was dried with MgSO₄ and concentrated under reduced pressure and the crude residue purified by crystallization from Et₂O.

Procedure B: Reaction of amines 3 with 1-azadiene 8. A solution of 1-azadiene 8 (1 mmol), the corresponding amine (1 mmol), Ti(OEt)₄ (0.42 mL, 2 mmol) and a drop of H₂SO₄ in CH₂Cl₂ (5 mL) was stirred and refluxed for 2 h. The reaction was warmed to room temp. and a solution of aqueous saturated NaHCO₃ (10 mL) was then added. The mixture was filtered through Celite, washed with H₂O (20 mL) and extracted with CH₂Cl₂ (3 $\times$ 15 mL). The organic layers were dried with MgSO₄ and concentrated under reduced pressure and the crude residue purified by crystallization from Et₂O.

Procedure C: The three-component reaction. A solution of ethyl pyruvate 7 (0.55 mL, 5 mmol), aldehyde 4 (5 mmol) and amine 3 (10 mmol) in CH₂Cl₂ was stirred for 48 h at room temp. The solution was then dried with MgSO₄ and concentrated under reduced pressure and the crude residue purified by crystallization from Et₂O.

5-(*p*-Nitrophenyl)-1-(*p*-tolyl)-3-(*p*-tolylamino)-1,5-dihydro-2H-pyrrol-2-one (1aa): Synthesized according to general procedure A with ethyl (*E*)-4-(*p*-nitrophenyl)-2-oxobut-3-enoate (2a) (1.25 g, 5 mmol) and *p*-toluidine (3a) (1.07 g, 10 mmol), affording 1.52 g (76%) of 1aa as a yellow solid. Synthesized according to general procedure B with ethyl (*E*)-4-(*p*-nitrophenyl)-2-(*p*-tolylimino)but-3-enoate (8aa) (0.34 g, 1 mmol) and *p*-toluidine (3a) (0.11 g, 1 mmol), affording 0.32 g (79%) of 1aa as a yellow solid. Synthesized according to general procedure C with ethyl glyoxalate (0.51 g, 5 mmol) and *p*-toluidine (3a) (1.07 g, 10 mmol), affording 1.59 g (80%) of 1aa as a yellow solid. M.p. 142–145 °C (decomp.) (Et₂O). ¹H NMR (300 MHz, CDCl₃, 30 °C): δ = 8.13 (d, ³*J*_{H,H} = 8.6 Hz, 2 H, 2 CH ar), 7.38 (d, ³*J*_{H,H} = 8.6 Hz, 2 H, 2 CH ar), 7.35 (d, ³*J*_{H,H} = 8.1 Hz, 2 H, 2 CH ar), 7.12 (d, ³*J*_{H,H} = 7.6 Hz, 2 H, 2 CH ar), 7.09 (d, ³*J*_{H,H} = 7.6 Hz, 2 H, 2 CH ar), 6.98 (d, ³*J*_{H,H} = 8.1 Hz, 2 H, 2 CH ar), 6.61 (s, 1 H, NH), 5.96 (d, ³*J*_{H,H} = 2.4 Hz, 1 H, CH=), 5.75 (d, ³*J*_{H,H} = 2.4 Hz, 1 H, CH–N), 2.30 (s, 3 H, CH₃ tol), 2.27 (s, 3 H, CH₃ tol) ppm. ¹³C NMR (75 MHz, CDCl₃, 30 °C): δ = 167.1 (C=O), 147.9 (C_{quat}), 145.8 (C_{quat}), 138.6 (C_{quat}), 135.5 (C_{quat}), 134.4 (C_{quat}), 133.5 (C_{quat}), 131.5 (C_{quat}), 130.2 (2 CH), 130.0 (2 CH), 127.9 (2 CH), 124.5 (2 CH), 121.8 (2 CH), 117.3 (2 CH), 105.5 (CH=), 63.7 (CH–N), 21.1 (CH₃), 20.9 (CH₃) ppm. IR (KBr): $\tilde{\nu}_{\max}$ = 3307 (s, N–H enamine), 1684 (s, C=O amide) cm⁻¹. EI-MS: m/z = 399 (100) [M]⁺, 277 (55) [M – *p*-NO₂-Ph]⁺. C₂₄H₂₁N₃O₃ (399.2): C 72.16, H 5.30, N 10.52; found: C 72.16, H 5.30, N 10.52.

5-(Ethoxycarbonyl)-1-(*p*-tolyl)-3-(*p*-tolylamino)-1,5-dihydro-2H-pyrrol-2-one (1ba): Synthesized according to general procedure A with ethyl (*E*)-4-(ethoxycarbonyl)-2-oxobut-3-enoate (2b) (1.00 g, 5 mmol) and *p*-toluidine (3a) (1.07 g, 10 mmol), affording 1.24 g

(71%) of 1ba as a white solid. Synthesized according to general procedure C with ethyl glyoxalate (0.51 g, 5 mmol) and *p*-toluidine (3a) (1.07 g, 10 mmol), affording 1.35 g (77%) of 1ba as a white solid. M.p. 159–160 °C (Et₂O). ¹H NMR (300 MHz, CDCl₃, 30 °C): δ = 7.49 (d, ³*J*_{H,H} = 8.4 Hz, 2 H, 2 CH tol), 7.21 (d, ³*J*_{H,H} = 8.6 Hz, 2 H, 2 CH tol), 7.14 (d, ³*J*_{H,H} = 8.4 Hz, 2 H, 2 CH tol), 7.00 (d, ³*J*_{H,H} = 8.6 Hz, 2 H, 2 CH tol), 6.66 (s, 1 H, NH), 5.93 (d, ³*J*_{H,H} = 2.9 Hz, 1 H, CH=), 5.26 (d, ³*J*_{H,H} = 2.9 Hz, 1 H, CH–N), 4.20–4.08 (m, 2 H, CH₂–O diastereotopic), 2.35 (s, 3 H, CH₃ tol), 2.32 (s, 3 H, CH₃ tol), 1.17 (t, ³*J*_{H,H} = 7.6 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃, 30 °C): δ = 168.7 (C=O), 166.5 (C=O), 138.3 (C_{quat}), 135.1 (C_{quat}), 134.9 (C_{quat}), 134.7 (C_{quat}), 130.9 (C_{quat}), 129.7 (2 CH), 129.5 (2 CH), 120.4 (2 CH), 117.0 (2 CH), 97.9 (CH=), 62.5 (CH–N), 61.7 (CH₂–O), 20.7 (CH₃), 20.5 (CH₃), 13.8 (CH₃) ppm. IR (KBr): $\tilde{\nu}_{\max}$ = 3350 (s, N–H enamine), 1759 (s, C=O ester), 1666 (s, C=O amide) cm⁻¹. EI-MS: m/z = 350 (41) [M]⁺, 277 (100) [M – CO₂Et]⁺. C₂₁H₂₂N₂O₃ (350.2): C 71.98, H 6.33, N 7.99; found: C 72.01, H 6.33, N 7.96.

5-(Ethoxycarbonyl)-1-(*p*-methoxyphenyl)-3-(*p*-methoxyphenyl-amino)-1,5-dihydro-2H-pyrrol-2-one (1bb): Synthesized according to general procedure A with ethyl 4-(ethoxycarbonyl)-2-oxobut-3-enoate (2b) (1.00 g, 5 mmol) and *p*-anisidine (3b) (1.23 g, 10 mmol), affording 1.62 g (85%) of 1bb as a white solid. M.p. 170–171 °C (Et₂O). ¹H NMR (300 MHz, CDCl₃, 30 °C): δ = 7.47 (d, ³*J*_{H,H} = 8.7 Hz, 2 H, 2 CH ar), 7.05 (d, ³*J*_{H,H} = 8.7 Hz, 2 H, 2 CH ar), 6.93 (d, ³*J*_{H,H} = 9.2 Hz, 2 H, 2 CH ar), 6.89 (d, ³*J*_{H,H} = 9.2 Hz, 2 H, 2 CH ar), 6.51 (s, 1 H, NH), 5.83 (d, ³*J*_{H,H} = 2.7 Hz, 1 H, CH=), 5.20 (d, ³*J*_{H,H} = 2.7 Hz, 1 H, CH–N), 4.21–4.03 (m, 2 H, CH₂–O diastereotopic), 3.81 (s, 3 H, CH₃), 3.79 (s, 3 H, CH₃), 1.16 (t, ³*J*_{H,H} = 7.0 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃, 30 °C): δ = 168.8 (C=O), 166.6 (C=O), 157.2 (C_{quat}), 154.6 (C_{quat}), 135.5 (C_{quat}), 134.3 (C_{quat}), 130.6 (C_{quat}), 122.8 (2 CH), 118.7 (2 CH), 114.5 (2 CH), 114.2 (2 CH), 96.9 (CH=), 62.9 (CH–N), 61.7 (CH₂–O), 55.4 (CH₃O), 55.3 (CH₃O), 13.8 (CH₃) ppm. IR (KBr): $\tilde{\nu}_{\max}$ = 3303 (s, N–H enamine), 1739 (s, C=O ester), 1686 (s, C=O amide) cm⁻¹. EI-MS: m/z (%) = 382 (16) [M]⁺, 309 (100) [M – CO₂Et]⁺. C₂₁H₂₂N₂O₅ (382.2): C 65.96, H 5.80, N 7.33; found: C 65.90, H 5.77, N 7.35.

1,3-Bis(*p*-Chlorophenyl)-5-(ethoxycarbonyl)-1,5-dihydro-2H-pyrrol-2-one (1bc): Synthesized according to general procedure A with ethyl 4-(ethoxycarbonyl)-2-oxobut-3-enoate (2b) (1.00 g, 5 mmol) and *p*-chlorophenylamine (3c) (1.28 g, 10 mmol), affording 1.71 g (88%) of 1bc as a white solid. M.p. 200–201 °C (Et₂O). ¹H NMR (300 MHz, CDCl₃, 30 °C): δ = 7.56 (d, ³*J*_{H,H} = 8.1 Hz, 2 H, 2 CH ar), 7.36 (d, ³*J*_{H,H} = 8.6 Hz, 2 H, 2 CH ar), 7.25 (d, ³*J*_{H,H} = 8.1 Hz, 2 H, 2 CH ar), 7.01 (d, ³*J*_{H,H} = 8.6 Hz, 2 H, 2 CH ar), 6.70 (s, 1 H, NH), 5.96 (d, ³*J*_{H,H} = 2.9 Hz, 1 H, CH=), 5.26 (d, ³*J*_{H,H} = 2.9 Hz, 1 H, CH–N), 4.22–4.10 (m, 2 H, CH₂O diastereotopic), 1.18 (t, ³*J*_{H,H} = 7.2 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃, 30 °C): δ = 168.3 (C=O), 166.3 (C=O), 139.2 (C_{quat}), 136.2 (C_{quat}), 134.5 (C_{quat}), 130.7 (C_{quat}), 129.4 (C_{quat}), 129.3 (2 CH), 126.8 (2 CH), 121.4 (2 CH), 118.2 (2 CH), 99.4 (CH=), 62.5 (CH–N), 62.3 (CH₂O), 14.0 (CH₃) ppm. IR (KBr): $\tilde{\nu}_{\max}$ = 3317 (s, N–H enamine), 1739 (s, C=O ester), 1692 (s, C=O amide) cm⁻¹. EI-MS: m/z (%) = 390 (39) [M]⁺, 287 (100) [M – CO₂Et]⁺. C₁₉H₁₆Cl₂N₂O₃ (390.1): C 58.33, H 4.12, N 7.16; found: C 58.26, H 4.09, N 7.14.

5-Methyl-1-(*p*-tolyl)-3-(*p*-tolylamino)-1,5-dihydro-2H-pyrrol-2-one (1ca): Synthesized according to general procedure A with ethyl (*E*)-2-oxopent-3-enoate (2c) (1.24 g, 5 mmol) and *p*-toluidine (3a) (1.07 g, 10 mmol), affording 1.17 g (80%) of 1ca as a white solid. Synthesized according to general procedure C with acetaldehyde (0.21 mL, 5 mmol) and *p*-toluidine (3a) (1.07 g, 10 mmol), afford-

ing 1.14 g (78 %) of **1ca** as a white solid. M.p. 121–122 °C (Et₂O). ¹H NMR (300 MHz, CDCl₃, 30 °C): δ = 7.40 (d, ³J_{H,H} = 7.8 Hz, 2 H, 2 CH tol), 7.23 (d, ³J_{H,H} = 8.2 Hz, 2 H, 2 CH tol), 7.13 (d, ³J_{H,H} = 8.2 Hz, 2 H, 2 CH tol), 7.00 (d, ³J_{H,H} = 7.8 Hz, 2 H, 2 CH tol), 6.49 (s, 1 H, NH), 6.00 (d, ³J_{H,H} = 2.4 Hz, 1 H, =CH), 4.73 (dq, ³J_{H,H} = 2.4, ³J_{H,H} = 6.6 Hz, 1 H, CH–N), 2.37 (s, 3 H, CH₃ tol), 2.31 (s, 3 H, CH₃ tol), 1.27 (d, ³J_{H,H} = 6.6 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃, 30 °C): δ = 166.0 (C=O), 139.1 (C_{quat}), 134.9 (C_{quat}), 134.1 (C_{quat}), 132.9 (C_{quat}), 130.3 (C_{quat}), 129.8 (2 CH), 129.6 (2 CH), 122.5 (2 CH), 116.6 (2 CH), 107.3 (CH), 55.6 (CH–N), 20.8 (CH₃), 20.6 (CH₃), 18.7 (CH₃) ppm. IR (KBr): ν_{max} = 3312 (s, N–H enamine), 1676 (s, C=O amide) cm^{−1}. EI-MS: *m/z* (%) = 292 (100) [M]⁺, 277 (51) [M – CH₃]. C₁₉H₂₀N₂O (292.2): C 78.05, H 6.89, N 9.58; found C 77.98, H 6.93, N 9.63.

1-(*p*-Methoxyphenyl)-3-(*p*-methoxyphenylamino)-5-methyl-1,5-dihydro-2H-pyrrol-2-one (1cb): Synthesized according to general procedure A with ethyl (*E*)-2-oxopent-3-enoate (**2c**) (1.24 g, 5 mmol) and *p*-anisidine (**3b**) (1.23 g, 10 mmol), affording 1.35 g (83 %) of **1cb** as a white solid. M.p. 151–152 °C (Et₂O). ¹H NMR (300 MHz, CDCl₃, 30 °C): δ = 7.38 (d, ³J_{H,H} = 9.1 Hz, 2 H, 2 CH ar), 7.05 (d, ³J_{H,H} = 9.0 Hz, 2 H, 2 CH ar), 6.96 (d, ³J_{H,H} = 9.1 Hz, 2 H, 2 CH ar), 6.89 (d, ³J_{H,H} = 9.0 Hz, 2 H, 2 CH ar), 6.40 (s, 1 H, NH), 5.92 (d, ³J_{H,H} = 2.4 Hz, 1 H, CH–N), 4.65 (dq, ³J_{H,H} = 2.4, ³J_{H,H} = 6.6 Hz, 1 H, CH–N), 3.82 (s, 3 H, CH₃), 3.89 (m, 3 H, CH₃), 1.23 (d, ³J_{H,H} = 6.6 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃, 30 °C): δ = 166.1 (C=O), 157.3 (C_{quat}), 154.3 (C_{quat}), 135.1 (C_{quat}), 133.5 (C_{quat}), 129.6 (C_{quat}), 124.6 (2 CH), 118.3 (2 CH), 114.7 (2 CH), 114.3 (2 CH), 106.2 (CH=), 56.1 (CH₂O), 55.6 (CH–N), 55.5 (CH₂O), 18.8 (CH₃) ppm. IR (KBr): ν_{max} = 3330 (s, N–H enamine), 1679 (s, C=O amide) cm^{−1}. EI-MS: *m/z* (%) = 324 (100) [M]⁺, 309 (25) [M – CH₃]⁺. C₁₉H₂₀N₂O₃ (292.2): C 70.35, H 6.21, N 8.64; found: C 70.29, H 6.18, N 8.63.

5-(Furan-2-yl)-1-(*p*-tolyl)-3-(*p*-tolylamino)-1,5-dihydro-2H-pyrrol-2-one (1da): Synthesized according to general procedure A with ethyl (*E*)-4-furan-2-yl-2-oxobut-3-enoate (**2d**) (0.97 g, 5 mmol) and *p*-toluidine (**3a**) (1.07 g, 10 mmol), affording 1.19 g (69 %) of **1da** as a white solid. Synthesized according to general procedure C with 2-furfural (0.47 mL, 5 mmol) and *p*-toluidine (**3a**) (1.07 g, 10 mmol), affording 1.26 g (73 %) of **1ca** as a white solid. M.p. 151–152 °C (Et₂O). ¹H NMR (300 MHz, CDCl₃, 30 °C): δ = 7.36 (d, ³J_{H,H} = 8.5 Hz, 2 H, 2 CH tol), 7.33 (d, ³J_{H,H} = 1.8 Hz, 1 H, CH fur), 7.17 (d, ³J_{H,H} = 8.1 Hz, 2 H, 2 CH tol), 7.14 (d, ³J_{H,H} = 8.1 Hz, 2 H, 2 CH tol), 7.03 (d, ³J_{H,H} = 8.5 Hz, 2 H, 2 CH tol), 6.61 (s, 1 H, NH), 6.28 (dd, ³J_{H,H} = 1.8, ³J_{H,H} = 3.1 Hz, 1 H, CH fur), 6.19 (d, ³J_{H,H} = 3.1 Hz, 1 H, CH fur), 6.03 (d, ³J_{H,H} = 2.6 Hz, 1 H, =CH), 5.76 (d, ³J_{H,H} = 2.6 Hz, 1 H, CH–N), 2.34 (s, 6 H, 2 CH₃ tol) ppm. ¹³C NMR (75 MHz, CDCl₃, 30 °C): δ = 166.6 (C=O), 150.1 (C_{quat}), 142.5 (CH), 138.8 (C_{quat}), 135.3 (C_{quat}), 134.4 (C_{quat}), 133.5 (C_{quat}), 130.7 (C_{quat}), 129.8 (2 CH), 129.4 (2 CH), 122.5 (2 CH), 116.9 (2 CH), 110.4 (CH), 108.3 (CH), 102.8 (CH), 58.8 (CH–N), 20.9 (CH₃), 20.6 (CH₃) ppm. IR (KBr): ν_{max} = 3321 (s, N–H enamine), 1674 (C=O amide) cm^{−1}. EI-MS: *m/z* (%) = 344 (36) [M]⁺, 277 (100) [M – fur]⁺. C₂₂H₂₀N₂O₂ (344.2): C 76.72, H 5.85, N 8.13; found: C 76.67, H 5.81, N 8.09.

1-[(*R*)-α-Methylbenzyl]-3-[(*R*)-α-methylbenzylamino]-5-(*p*-nitrophenyl)-1,5-dihydro-2H-pyrrol-2-one (13/14): Synthesized according to general procedure A with ethyl (*E*)-4-(*p*-nitrophenyl)-2-oxobut-3-enoate (**2a**) (1.25 g, 5 mmol) and (*R*)-α-methylbenzylamine (1.10 mL, 10 mmol) using xylene as solvent at 140 °C. The mixture of diastereoisomers was purified by chromatography (SiO₂, AcOEt/hexanes, 1:4), affording 0.87 g (41 %) of the diastereoisomer **13** and

0.88 g of the diastereoisomer **14** (41 %) as pale yellow solids. M.p. **13**: 137–138 °C (Et₂O); **14**: 143–144 °C (Et₂O). **13**: [α]_D²⁰ = +81.2 (*c* = 1.01, CH₂Cl₂). **14**: [α]_D²⁰ = +71.2 (*c* = 0.91, CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃, 30 °C): **13**: δ = 8.10 (d, ³J_{H,H} = 8.9 Hz, 2 H, 2 CH ar), 7.28–7.23 (m, 8 H, 8 CH Ph), 7.12 (d, ³J_{H,H} = 8.9 Hz, 2 H, 2 CH ar), 7.08–7.02 (m, 2 H, 2 CH Ph), 5.56 (q, ³J_{H,H} = 7.3 Hz, 1 H, CH–N), 4.70 (d, ³J_{H,H} = 2.3 Hz, 1 H, CH=), 4.65 (s, 1 H, NH), 4.54 (d, ³J_{H,H} = 2.3 Hz, 1 H, CH–N), 4.22 (q, ³J_{H,H} = 6.7 Hz, 1 H, CH–N), 1.50 (d, ³J_{H,H} = 6.7 Hz, 3 H, CH₃), 1.20 (d, ³J_{H,H} = 7.3 Hz, 3 H, CH₃) ppm; **14**: δ = 7.80 (d, ³J_{H,H} = 8.9 Hz, 2 H, 2 CH ar), 7.26 (s, 5 H, 5 CH Ph), 7.06 (s, 5 H, 5 CH Ph), 6.83 (d, ³J_{H,H} = 8.9 Hz, 2 H, 2 CH ar), 5.01 (q, ³J_{H,H} = 7.2 Hz, 1 H, CH–N), 4.88 (d, ³J_{H,H} = 2.4 Hz, 1 H, CH=), 4.72 (d, ³J_{H,H} = 2.4 Hz, 1 H, CH–N), 4.65 (s, 1 H, NH), 4.24 (q, ³J_{H,H} = 6.7 Hz, 1 H, CH–N), 1.68 (d, ³J_{H,H} = 7.3 Hz, 3 H, CH₃), 1.52 (d, ³J_{H,H} = 6.7 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃, 30 °C): **13**: δ = 168.6 (C=O), 147.5 (C_{quat}), 147.2 (C_{quat}), 143.5 (C_{quat}), 139.9 (C_{quat}), 137.6 (C_{quat}), 128.5 (2 CH), 128.4 (2 CH), 128.2 (2 CH), 127.6 (CH), 127.3 (2 CH), 127.0 (CH), 125.8 (2 CH), 123.6 (2 CH), 104.8, 61.2 (CH–N), 54.3 (CH–N), 51.7 (CH–N), 24.1 (CH₃), 18.1 (CH₃) ppm; **14**: δ = 168.4 (C=O), 147.0 (C_{quat}), 145.8 (C_{quat}), 143.4 (C_{quat}), 140.4 (C_{quat}), 138.3 (C_{quat}), 128.4 (CH), 128.1 (2 CH), 128.0 (CH), 127.2 (2 CH), 127.1 (2 CH), 127.0 (2 CH), 125.7 (2 CH), 123.1 (2 CH), 104.6 (CH=), 61.6 (CH–N), 54.3 (CH–N), 51.9 (CH–N), 23.9 (CH₃), 17.9 (CH₃) ppm. IR (KBr): **13**: ν_{max} = 3329 (s, N–H enamine), 1692 (s, C=O amide) cm^{−1}; **14**: ν_{max} = 3329 (s, N–H enamine), 1679 (s, C=O amide) cm^{−1}. CI-MS: **13**: *m/z* (%) = 428 (100) [M + 1]⁺, 306 (64) [M – *p*-NO₂-Ph]⁺; **14**: *m/z* (%) = 429 (100) [M + 1]⁺, 306 (92) [M – *p*-NO₂-Ph]⁺. C₂₆H₂₅N₃O₃ (427.2): C 73.05, H 5.89, N 9.83; found: **13**: C 73.01, H 5.93, N 9.80; **14**: C 73.09, H 5.84, N 9.79.

Procedure for the Synthesis and Isolation of *syn* and *anti* Ethyl (*E*)-4-(*p*-Nitrophenyl)-2-(*p*-tolylimino)but-3-enoate (8aa): A solution of β,γ-unsaturated α-keto ester **2a** (1.25 g, 5 mmol), *p*-toluidine (**3a**) (0.54 g, 5 mmol), Ti(OEt)₄ (2.10 mL, 10 mmol) and a drop of H₂SO₄ in CH₂Cl₂ (15 mL) was stirred and refluxed for 2 h. The reaction mixture was warmed to room temp. and a solution of aqueous saturated NaHCO₃ (20 mL) was then added. The mixture was filtered through Celite, washed with H₂O (50 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The organic layers were dried with MgSO₄ and concentrated under reduced pressure. The crude residue was purified by chromatography (SiO₂, AcOEt/hexanes, 1:4), affording 0.30 g (18 %) of **8aa** as a yellow solid (*syn/anti* = 40:60). M.p. 98–99 °C (Et₂O). ¹H NMR (300 MHz, CDCl₃, 30 °C): δ = 8.19 and 8.12 (d, ³J_{H,H} = 8.8 Hz and d, ³J_{H,H} = 8.7 Hz, 2 H, 2 CH ar *anti* and 2 CH ar *syn*), 7.61 and 7.41 (d, ³J_{H,H} = 8.8 Hz and d, ³J_{H,H} = 8.7 Hz, 2 H, 2 CH ar *anti* and 2 CH ar *syn*), 7.47 and 7.02 (d, ³J_{H,H} = 16.2 Hz and d ³J_{H,H} = 16.3 Hz, 1 H, CH = *anti* and CH = *syn*), 7.29 and 6.76 (d, ³J_{H,H} = 16.3 Hz and d ³J_{H,H} = 16.2 Hz, 1 H, CH = *syn* and CH = *anti*), 7.17 (d, ³J_{H,H} = 8.1 Hz, 2 H, CH ar *syn* + *anti*), 6.74 (d, ³J_{H,H} = 8.1 Hz, 2 H, CH ar *syn* + *anti*), 4.43 and 4.09 (q, ³J_{H,H} = 7.1 Hz and q, ³J_{H,H} = 7.2 Hz, 2 H, CH₂O *anti* and CH₂O *syn*), 2.33 and 2.28 (s, 3 H, CH₃ *syn* and CH₃ *anti*), 1.42 and 0.98 (t, ³J_{H,H} = 7.1 Hz and t, ³J_{H,H} = 7.2 Hz, 3 H, CH₃ *syn* and CH₃ *anti*) ppm. ¹³C NMR (75 MHz, CDCl₃, 30 °C): δ = 164.3 and 164.0 (C=O *syn* and *anti*), 159.5 and 157.4 (C=N *anti* and *syn*), 147.7 (C_{quat} *syn* + *anti*), 146.5 and 145.0 (C_{quat} *anti* and *syn*), 141.3 and 141.1 (C_{quat} *syn* and *anti*), 139.0 and 137.9 (CH *syn* and *anti*), 135.4 and 135.3 (C_{quat} *syn* and *anti*), 129.4 and 129.1 (2 CH *syn* and *anti*), 128.0 and 127.9 (2 CH *syn* and *anti*), 123.8 and 123.7 (2 CH *anti* and *syn*), 121.6 and 120.6 (2 CH *anti* and *syn*), 120.2 and 119.4 (CH *syn* and *anti*), 62.2 and 61.5 (CH₂O *syn* and *anti*), 20.5 and 20.4 (CH₃ *syn* and *anti*), 13.7 and 13.4 (CH₃

syn and *anti*) ppm. IR (KBr): $\tilde{\nu}_{\max}$ = 1732 (s, C=O ester), 1599 (s, C=N imine) cm^{-1} . EI-MS: m/z (%) = 338 (20) $[\text{M}]^+$, 265 (100) $[\text{M} - \text{CO}_2\text{Et}]^+$, 216 (92) $[\text{M} - p\text{-NO}_2\text{-Ph}]^+$. $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_4$ (338.1): C 67.44, H 5.36, N 8.28; found: C 67.51, H 5.40, N 8.23.

Procedure for the Synthesis of 6-(Ethoxycarbonyl)-2-phenyl-1-(*p*-tolyl)-1,2-dihydropyridine (15): A solution of ethyl (*E,E*)-2-oxo-6-phenylhexa-3,5-dienoate (**2e**) (0.32 g, 1 mmol), *p*-toluidine (**3a**) (0.11 g, 1 mmol), $\text{Ti}(\text{OEt})_4$ (0.32 g, 1.5 mmol) and a drop of H_2SO_4 in CH_2Cl_2 (6 mL) was stirred and refluxed for 3 h. The reaction was warmed to room temp. and an aqueous saturated solution of NaHCO_3 was then added. The mixture was filtered through Celite and the organic layer was washed with H_2O , dried with MgSO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with AcOEt /hexanes (1:2), affording 0.26 g (81%) of **15** as a white solid. M.p. 197–199 °C (decomp.) (Et_2O). ^1H NMR (300 MHz, CDCl_3 , 30 °C): δ = 7.47–7.51 (m, 2 H, 2 CH Ph), 7.37–7.21 (m, 3 H, 3 CH Ph), 7.04 (d, $^3J_{\text{H,H}}$ = 8.1 Hz, 2 H, 2 CH tol), 6.86 (d, $^3J_{\text{H,H}}$ = 8.1 Hz, 2 H, 2 CH tol), 6.43 (d, $^3J_{\text{H,H}}$ = 4.9 Hz, 1 H, CH=), 6.17 (dd, $^3J_{\text{H,H}}$ = 4.9, $^3J_{\text{H,H}}$ = 8.7 Hz, 1 H, CH=), 5.96 (dd, $^3J_{\text{H,H}}$ = 6.6, $^3J_{\text{H,H}}$ = 8.7 Hz, 1 H, CH=), 5.41 (d, $^3J_{\text{H,H}}$ = 6.6 Hz, 1 H, CH-N), 4.12 (q, $^3J_{\text{H,H}}$ = 7.2 Hz, 2 H, CH_2O), 2.29 (s, 3 H, CH_3 tol), 1.10 (t, $^3J_{\text{H,H}}$ = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, CDCl_3 , 30 °C): δ = 164.4 (C=O), 145.3 (C_{quat}), 142.7 (C_{quat}), 131.8 (C_{quat}), 131.5 (C_{quat}), 129.0 (2 CH), 128.3 (2 CH), 126.7 (CH), 124.8 (2 CH), 122.6 (CH), 120.9 (CH), 119.5 (2 CH), 115.4 (CH), 62.0 (CH-N), 62.3 (CH_2O), 20.3 (CH_3), 13.5 (CH_3) ppm. IR (KBr): $\tilde{\nu}_{\max}$ = 1753 (s, C=O ester) cm^{-1} . EI-MS: m/z (%) = 319 (36) $[\text{M}]^+$, 246 (100) $[\text{M} - \text{CO}_2\text{Et}]^+$, 214 (44) $[\text{M} - p\text{-Me-Ph-N}]^+$. $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_4$ (319.2): C 67.44, H 5.36, N 8.28; found: C 67.51, H 5.40, N 8.23.

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