Synthesis S. P. Chavan et al. Paper

Scalable Synthesis of 3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one: An Important Building Block of the Antidiabetic Drug Glimepiride

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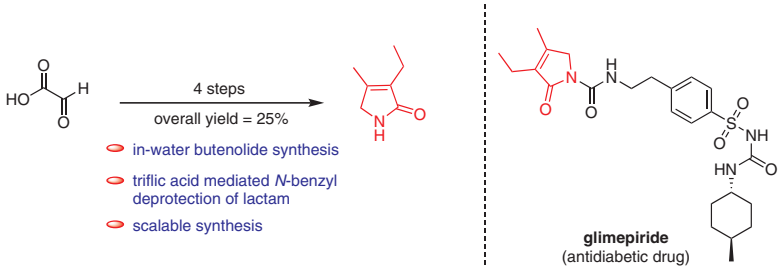

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Abstract A four-step, practical, and easily scalable synthesis of 3-ethyl-4-methyl-1,5-dihydro-2H-pyrrol-2-one, an important building block of the antidiabetic drug glimepiride, has been accomplished. Key features are the synthesis of 3-methyl-4-hydroxy-2-butenolide in water and triflic acid mediated N-benzyl lactam N-deprotection. The main advantages of this process are the scalable synthetic route and decreased number of reaction steps, which paves the way for the industrial-scale synthesis of 3-ethyl-4-methyl-1,5-dihydro-2H-pyrrol-2-one.

Key words glimepiride, antidiabetic drug, scalable synthesis, lactams, butenolide

The rapidly rising prevalence of diabetes, especially among the middle- and low-income countries, has caused growing concern among the scientific community. In 2016, diabetes alone was responsible for the deaths of an estimated 1.6 million people. Also, another 2.2 million deaths were attributable to high blood sugar in 2012. Almost half of all deaths due to high blood glucose occur before the age of 70 years. WHO estimates that diabetes was the seventh leading cause of death in 2016.[1]

Currently, many drugs are available in the market for the treatment of diabetes. In that context, in 2003, Gurjar et al. reported the synthesis of *trans*-hydroxyglimepiride, a metabolite of the antidiabetic drug glimepiride (**1**).[2] Glimepiride is a third-generation sulfonylurea approved in 1995 for the treatment of type 2 diabetes mellitus. It is used in medication as a monotherapy or in combination with metformin or insulin, and is currently used in more than 60 countries worldwide. Glimepiride reduces the blood sugar by stimulating the release of insulin by the pancreas and induces increased activity of intracellular insulin receptors.[3] The antidiabetic drug glimepiride (**1**) consists of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) as an essential heterocyclic building block. Pyrrolinone **3** is also present as the main precursor in bile pigments, and is in the blue protein C-phycocyanin[4] (**2**) (Figure 1).

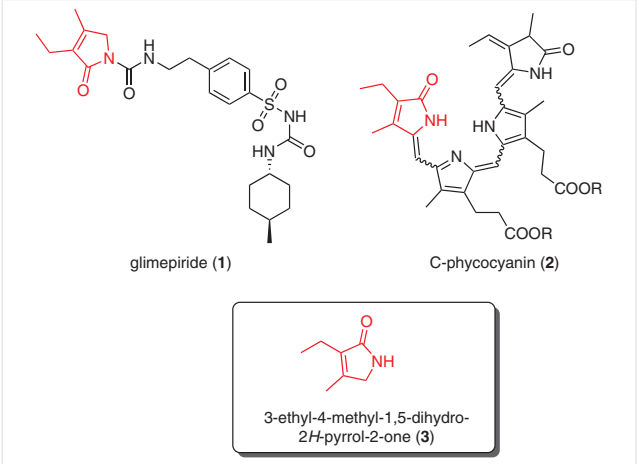

Figure 1 Glimepiride (**1**) and C-phycocyanin (**2**) consist of the scaffold 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**)

The importance in medicinal chemistry and the challenging structural features of pyrrolinone **3** have attracted synthetic chemists for its short and industrially scalable synthesis.[5,6] The reported synthetic routes involve the use of toxic reagents such as NaCN and $Pb(OAc)_4$, and expensive transition-metal catalysts such as $PdCl_2$ and Grubbs' catalyst (Figure 2). So, there is a long-standing need to develop a short, high yielding, and industrially scalable method using simple and easily accessible reagents. In continuation of our research towards the synthesis of biologically active natural products and medicinally important drug molecules, development of a scalable process for the synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) was initiated.

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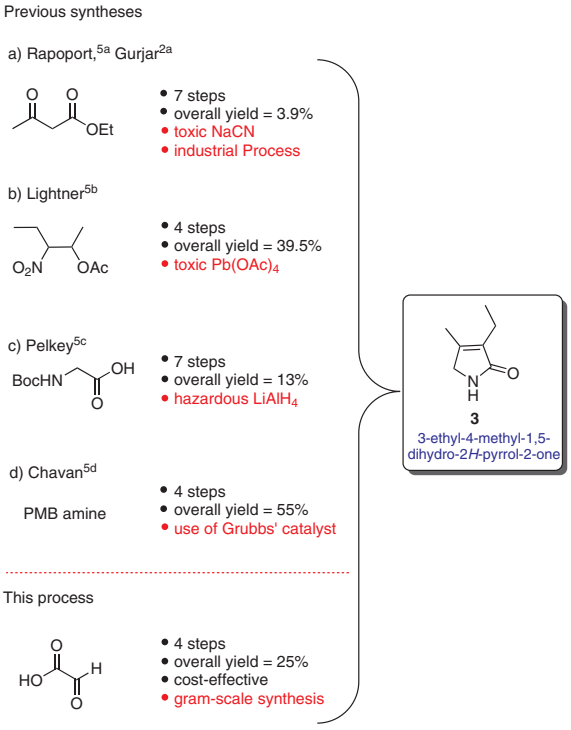
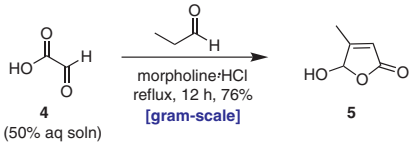


Figure 2 Synthetic approaches to 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**)

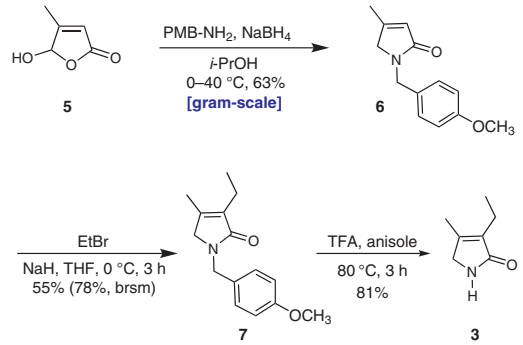
Our synthesis commenced with the preparation of 3-methyl-4-hydroxy-2-butenolide (**5**) using glyoxylic acid (**4**) as starting material (Scheme 1). Synthesis of butenolide **5** from acid **4** and propanal in dioxane as solvent has been reported by Bourguignon and Wermuth.[7] For the large-scale synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**), the cost of the solvent dioxane would contribute significantly to the total cost of compound **3**. So, we decided to develop a process using either water as the solvent, which is considered to be a green solvent, or a solvent-free process. Towards this, when the reaction of glyoxylic acid (50% aqueous solution) with propanal in the presence of morpholine hydrochloride was carried out at reflux temperature, to our delight the formation of 3-methyl-4-hydroxy-2-butenolide (**5**) was observed in 55% yield in 24 hours. After slight optimization of the time, butenolide **5** was isolated in 76% yield in 12 hours. It was observed that longer reaction time (24 h) reduces the yield of the reaction mainly due to decomposition of the product formed. It is noteworthy that morpholine hydrochloride was prepared from morpholine and 35% HCl and used as such without isolation.

Thus, 3-methyl-4-hydroxy-2-butenolide (**5**) was successfully synthesized on a multigram scale using water as solvent, which makes this process green, cost-effective, and industrially applicable.



Scheme 1 Synthesis of 3-methyl-4-hydroxy-2-butenolide (**5**) in water

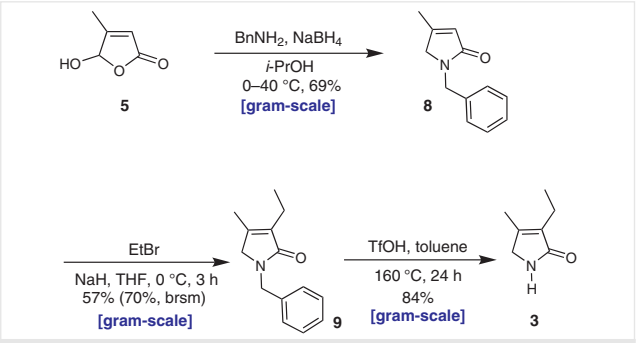
The next crucial step was the synthesis of lactam **6** from butenolide **5**. To this end, when 3-methyl-4-hydroxy-2-butenolide (**5**) was treated with *p*-methoxybenzylamine (PMB amine) in isopropyl alcohol, followed by treatment with $NaBH_4$ under basic conditions, lactam **6** was furnished in 63% yield (Scheme 2). Initially, isolation of hydroxy lactam was attempted, and then it was subjected to reduction using $NaBH_4$, but the yield of lactam was severely reduced to ~20% mainly due to instability of the hydroxy lactam on silica gel purification. For the required substitution on the olefin moiety, lactam **6** was treated with ethyl bromide and NaH at 0 °C to obtain compound **7** in 55% yield (78% brsm).[5d] Here, it was observed that starting material remained even after stirring the reaction mixture for a longer time under a range of temperature conditions. All our efforts to obtain 100% conversion failed in this case. The final step, *N*-PMB deprotection of the lactam, was carried out using CAN, as earlier reported by us.[5d] CAN, a well-known one-electron oxidant, has several disadvantages, one of which is its requirement for excess addition (2 equivalents or more) owing to its high molecular weight. This not only adds to the cost, but also raises disposal and environmental issues. These issues have led to the development of a simple and more convenient method which could be utilized on a large scale. Towards this, *N*-PMB deprotection of lactam **7** was carried out using TFA in anisole at 80 °C under microwave conditions to obtain 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) in 81% yield.[8] The same reaction was reproduced using conventional heating conditions for the synthesis of pyrrolinone **3**.



Scheme 2 First-generation approach for the synthesis of **3**

Though we achieved a good overall yield for this process (21%) in a decreased number of steps and the process was scalable at large scale, our main goal was to develop a cost-effective and scalable process for the synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**). It was realized that PMB amine, TFA, and anisole contributed largely to the overall cost of the process. This led us to explore commercially, readily available and inexpensive benzylamine and the development of a cost-effective and practical method for the N-debenzylation of lactam.

Accordingly, following a similar reaction sequence, *N*-benzyl lactam **9** was synthesized from **4** in three steps in 30% yield (Scheme 3). To achieve the last step, the *N*-benzyl deprotection of lactam **9**, known reaction conditions were screened. When *N*-benzyl lactam **9** was treated with TFA in anisole, starting material was recovered after 48 hours and product formation was not observed. But, when *N*-benzyl lactam **9** was subjected to microwave-mediated *N*-benzyl deprotection using triflic acid in toluene, product formation was observed in 86% yield.[9] To avoid the microwave conditions, when the same reaction was carried out using conventional heating with triflic acid in toluene, to our delight the formation of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) was observed in 84% yield, which meets our requirements of a scalable process. The spectroscopic and analytical data of pyrrolinone **3** were in complete agreement with the reported data.[5d]



Scheme 3 Second-generation approach for the synthesis of **3**

In conclusion, a short, cost-effective, and scalable synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) has been developed. Key features are the synthesis of 3-methyl-4-hydroxy-2-butenolide in water, one-pot opening–reductive cyclization of the butenolide for the synthesis of five-membered lactams, and triflic acid mediated *N*-benzyl deprotection of lactam **9**. As the synthesis of pyrrolinone **3** was achieved in four steps in 25% overall yield, we believe that this short, cost-effective, and scalable synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one, a key building block of the antidiabetic drug glimepiride, paves the way for its industrial-scale synthesis.

All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen, unless otherwise mentioned, with magnetic stirring. Air-sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by TLC with 0.25 mm precoated silica gel plates (60 F254). Visualization was accomplished with either UV light, iodine adsorbed on silica gel, or by immersion in an ethanolic solution of phosphomolybdic acid, *p*-anisaldehyde, 2,4-DNP, $KMnO_4$, or ninhydrin followed by heating with a heat gun for ~15 sec. Melting points are uncorrected. ^{1}H NMR spectra were recorded on Bruker AV 200, 400, and 500 MHz NMR spectrometers (^{13}C NMR spectra at 50, 100, and 125 MHz, respectively) using solvent residue signal as an internal standard ($CDCl_3$, ^{1}H NMR: 7.27 ppm, ^{13}C NMR: 77.00 ppm). HRMS (ESI) were taken on an Orbitrap (quadrupole plus ion trap) TOF mass analyzer. IR spectra were recorded on a Bruker FT-IR spectrophotometer. Column chromatographic separations were carried out on silica gel (230–400 mesh).

5-Hydroxy-4-methylfuran-2(5*H*)-one (5)[7]

To a stirred, ice-cold (0 °C) solution of morpholine (58.2 mL, 675 mmol, 1 equiv), concd HCl (70.4 mL, 675 mmol, 1 equiv) was added dropwise over a 15-min period. The reaction mixture was then stirred for 2 h. To this, glyoxylic acid (100 mL, 50% aqueous solution, 675 mmol, 1 equiv) was added followed by propanal (50.7 mL, 708 mmol, 1.05 equiv), and the reaction mixture was further stirred at rt for 1 h and then refluxed for 12 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated to dryness and the residue was extracted with EtOAc (3 × 500 mL). The combined organic layer was washed with brine (200 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 30:70) afforded pure **5** as a yellow oil; yield: 58.5 g (76%).

R_f = 0.3 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 3407, 1760, 1216, 766 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00 (s, 1 H), 5.85 (q, *J* = 1.5 Hz, 1 H), 5.41 (br s, 1 H), 2.10 (d, *J* = 1.5 Hz, 3 H).

Spectroscopic data were consistent with the earlier reported analytical information.

1-(4-Methoxybenzyl)-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (6)[5d]

To a stirred solution of *p*-methoxybenzylamine (6.52 mL 49.9 mmol, 1.14 equiv) in isopropyl alcohol (40 mL), compound **5** (5 g, 43.8 mmol, 1 equiv) was added at rt. The reaction mixture was stirred at 40 °C for 1 h, then cooled to 0 °C and treated with a freshly prepared solution of $NaBH_4$ (1.06 g, 28 mmol, 0.64 equiv) in water (15 mL) containing NaOH (1 mL, 50% w/w in water) while maintaining the internal temperature below 25 °C. The reaction mixture was stirred for 1.5 h at that temperature. Excess $NaBH_4$ was quenched by addition of acetone to the reaction mixture while maintaining the internal temperature below 30 °C. The mixture was filtered and AcOH (1 mL) was added to the filtrate to adjust the pH between 7–8 and the reaction mixture was heated to 50 °C for 16 h. The mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The obtained residue was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by

purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 40:60) afforded pure **6** as a pale yellow solid; yield: 6.0 g (63%).

Mp 121 °C (Lit.[5d] 122 °C); R_f = 0.2 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 1674, 1222, 760 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 5.86 (d, *J* = 1.1 Hz, 1 H), 4.52 (s, 2 H), 3.79 (s, 3 H), 3.69 (s, 2 H), 2.00 (d, *J* = 1.1 Hz, 3 H).

Spectroscopic data were consistent with the earlier reported analytical information.

3-Ethyl-1-(4-methoxybenzyl)-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (7)[5d]

To a stirred solution of compound **6** (1 g, 4.6 mmol, 1 equiv) in anhydrous THF (25 mL), NaH (0.121 g, 5.06 mmol, 1.1 equiv) was added slowly at 0 °C. The reaction mixture was stirred for 15 min, ethyl bromide (0.41 mL, 5.52 mmol, 1.2 equiv) in anhydrous THF (5 mL) was added dropwise at 0 °C, and stirring was continued for 3 h at that temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated NH_4Cl solution and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 20:80) afforded pure **7** as a yellow solid [yield: 0.62 g (55%)] along with recovery of the starting material (0.3 g).

Mp 128 °C (Lit.[5d] 127–131 °C); R_f = 0.6 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 1674, 1216, 762 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 4.54 (s, 2 H), 3.79 (s, 3 H), 3.58 (s, 2 H), 2.29 (q, *J* = 7.5 Hz, 2 H), 1.91 (s, 3 H), 1.08 (t, *J* = 7.5 Hz, 3 H).

Spectroscopic data were consistent with the earlier reported analytical information.

3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (3)[5d]

To a stirred solution of compound **7** (0.2 g, 0.816 mmol, 1 equiv) in anisole (2 mL), TFA (2 mL) was added and the reaction mixture was heated at 80 °C for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to rt, quenched with saturated $NaHCO_3$ solution (4 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **3** as a pale yellow solid; yield: 82 mg (81%).

Mp 103 °C (Lit.[5d] 102 °C); R_f = 0.3 (EtOAc–PE, 70:30).

IR ($CHCl_3$): 3440, 1722, 1216, 765 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (br s, 1 H), 3.77 (s, 2 H), 2.24 (q, *J* = 7.5 Hz, 2 H), 1.96 (s, 3 H), 1.04 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 148.6, 133.9, 50.0, 16.5, 13.1, 12.9.

HRMS (ESI): *m*/*z* calcd for $C_7H_{12}NO$ $[M + H]^+$: 126.0913; found: 126.0910.

1-Benzyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (8)

To a stirred solution of benzylamine (5.45 mL, 50 mmol, 1.14 equiv) in isopropyl alcohol (45 mL), compound **5** (5 g, 43.8 mmol, 1 equiv) was added at rt. The reaction mixture was stirred at 40 °C for 1 h, then cooled to 0 °C and treated with a freshly prepared solution of $NaBH_4$ (1.06 g, 28 mmol, 0.64 equiv) in water (15 mL) containing NaOH (1 mL, 50% w/w in water) while maintaining the internal temperature below 25 °C. The reaction mixture was stirred for 1.5 h at that temperature. Excess $NaBH_4$ was quenched by addition of acetone to the reaction mixture while maintaining the internal temperature below 30 °C. The mixture was filtered and AcOH (1 mL) was added to the filtrate to adjust the pH between 7–8 and the reaction mixture was heated to 50 °C for 16 h. The mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The obtained residue was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **8** as a yellow solid; yield: 5.65 g (69%).

Mp 96–98 °C; R_f = 0.3 (EtOAc–PE, 30:70).

IR ($CHCl_3$): 1674, 1217, 763 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.32–7.09 (m, 5 H), 5.82 (q, *J* = 1.4 Hz, 1 H), 4.53 (s, 2 H), 3.65 (s, 2 H), 1.95 (d, *J* = 1.4 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.9, 155.2, 137.3, 128.5 (2 C), 127.8 (C), 127.3, 122.5, 54.9, 45.6, 15.1.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{14}NO$ $[M + H]^+$: 188.1070; found: 188.1062.

1-Benzyl-3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (9)

To a stirred solution of compound **8** (8 g, 42.7 mmol, 1 equiv) in anhydrous THF (200 mL), NaH (1.13 g, 47.0 mmol, 1.1 equiv) was added slowly at 0 °C. The reaction mixture was stirred for 15 min, ethyl bromide (3.83 mL, 51.3 mmol, 1.2 equiv) in anhydrous THF (40 mL) was added dropwise at 0 °C, and stirring was continued for 3 h at that temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated NH_4Cl solution and extracted with EtOAc (3 × 200 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 35:65) afforded pure **9** as a sticky yellow solid [yield: 5.25 g (57%)] along with recovery of the starting material (1.5 g).

R_f = 0.26 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 1703, 1216, 765 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.15 (m, 5 H), 4.60 (s, 2 H), 3.60 (s, 2 H), 2.31 (q, *J* = 7.5 Hz, 2 H), 1.62 (s, 3 H), 1.09 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 145.4, 137.6, 134.1, 128.6 (2 C), 128.0 (2 C), 127.3, 53.5, 45.9, 17.0, 13.1, 12.7.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}NO$ $[M + H]^+$: 216.1383; found: 216.1379.

3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (3) by *N*-Debenzylation of Lactam 9

Method A: Microwave Assisted

To a glass vial, equipped with a Teflon cap, compound **9** (0.2 g, 0.93 mmol, 1 equiv) in toluene (2 mL) followed by triflic acid (0.328 mL, 3.72 mmol, 4 equiv) was added. The reaction mixture was kept for 45 min in a microwave reactor (Anton Paar, Monowave 300 microwave synthesis reactor) at 800 W (150 °C). The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to rt, quenched with saturated $NaHCO_3$ solution (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **3** as a pale yellow solid; yield: 0.1 g (86%).

Method B: By Heating

To a stirred solution of compound **9** (3 g, 13.9 mmol, 1 equiv) in toluene (30 mL) was added triflic acid (4.94 mL 55.8 mmol, 4 equiv). The reaction mixture was heated at 160 °C for 24 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to rt, quenched with saturated $NaHCO_3$ solution (20 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **3** as a pale yellow solid; yield: 1.47 g (84%).

Mp 103 °C (Lit.[5d] 102 °C); R_f = 0.3 (EtOAc–PE, 70:30).

IR ($CHCl_3$): 3440, 1722, 1216, 765 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (br s, 1 H), 3.77 (s, 2 H), 2.24 (q, *J* = 7.5 Hz, 2 H), 1.96 (s, 3 H), 1.04 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 148.6, 133.9, 50.0, 16.5, 13.1, 12.9.

HRMS (ESI): *m*/*z* calcd for $C_7H_{12}NO$ $[M + H]^+$: 126.0913; found: 126.0910.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707344.

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