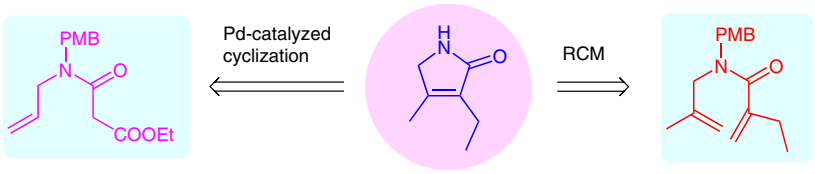
Synthesis S. P. Chavan et al. Paper

Synthesis of 3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one by Novel Palladium(II)-Catalyzed Cyclization and Ring-Closing Metathesis

Subhash P. Chavan*
Ashok B. Pathak
Kailash P. Pawar

Organic Chemistry Division, CSIR-NCL (National Chemical Laboratory), Dr. Homi Bhabha Road, Pune 411008, Maharashtra, India
sp.chavan@ncl.res.in



Received: 30.09.2014
Accepted after revision: 18.12.2014
Published online: 17.02.2015
DOI: 10.1055/s-0034-1379985; Art ID: ss-2014-z0602-op

Abstract Synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one is described starting from commercially available allylamine and 4-methoxybenzylamine employing palladium-catalyzed cyclization or ring-closing metathesis as the key steps.

Key words pyrrolinone, glimepiride, antidiabetic, metabolite, lactams, ring-closing metathesis, cyclization

Five- and six-membered lactones and lactams are widely present as key building blocks in several natural products showing promising biological activity. 3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**1**) is an important heterocyclic building block of antidiabetes drug glimepiride (**2**)[1] and its derivatives that are sulfonylurea drugs and show potent activity against diabetic diseases.[1b] The synthesis of *trans*-hydroxyglimepiride, a metabolite of the drug glimepiride was reported by Gurjar et al.[1a] Pyrrolinone **1** is also present as main precursor in bile pigments; the blue protein C-phycocyanin **3** (Figure 1) was isolated from the blue-green alga *Synechococcus sp.* 6301.[2] Bile pigments take part in photosynthesis.

Scrutiny of the literature reveals that several syntheses of **1** and its derivatives have been reported.[1–3] Structurally, **1** is a five-membered α,β-unsaturated lactam bearing substituents at positions 3 and 4. Though it appears to be a simple structure, its formation is difficult due to steric crowding of the substituents present on the olefin and ring strain. Due to its utility in the field of medicinal chemistry and biology, devising an efficient and practical route has attracted the attention of synthetic chemists. The literature reports reveal that there are very few practical synthetic routes reported for **1**. The reported syntheses employ very toxic reagents such as sodium cyanide and drastic reaction conditions like high temperature and pressure with very poor overall yields in the range of 7–8%.[1,2]

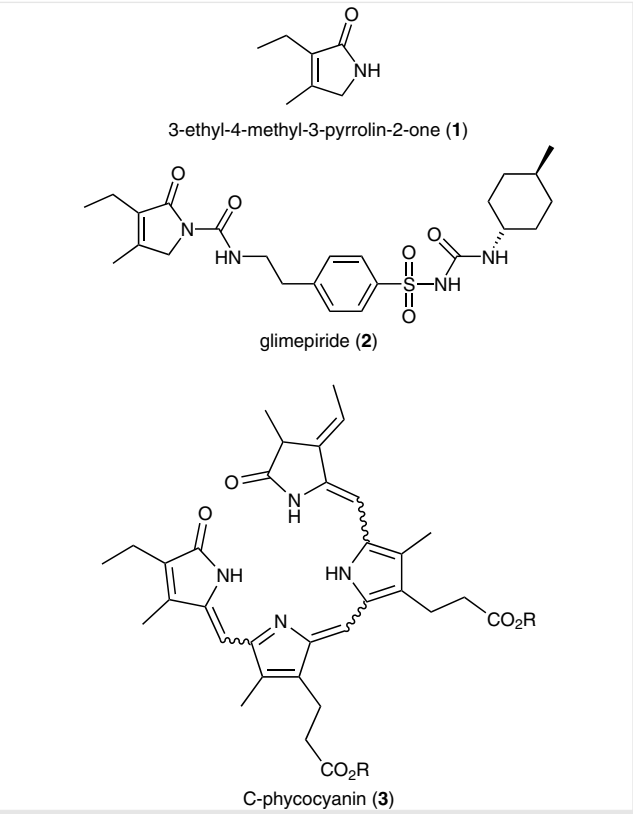


Figure 1 Structures of 3-ethyl-4-methyl-3-pyrrolin-2-one, glimepiride and C-phycocyanin

Palladium plays a very important role in organic synthesis. Palladium in its different oxidation states is a very useful catalyst in effecting critical C–C, C=C, and C–X bond-

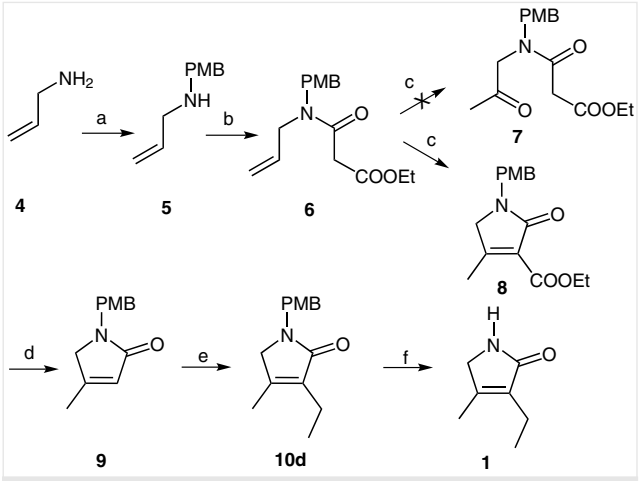
forming reactions and it is utilized in different coupling reactions while palladium(II) catalyst finds use in the Wacker oxidation and in different types of cyclization reactions.[4]

We have previously described a novel C=C bond-forming annulation strategy as the key step for the synthesis of six-membered lactams (D ring of camptothecin) under Wacker oxidation conditions and exploited it for the synthesis of (+)-camptothecin.[5] Ring-closing metathesis has also become a powerful and almost indispensable tool for the construction of small-to-large rings in various natural products due to its efficiency and versatility. Our group has initiated a programme on the utility of ring-closing metathesis in the synthesis of different natural products.[6] In continuation of our ongoing studies, we herein report the synthesis of **1** by two different methods employing novel palladium-catalyzed cyclization or ring-closing metathesis as the key reactions for the formation of the carbon–carbon double bond.

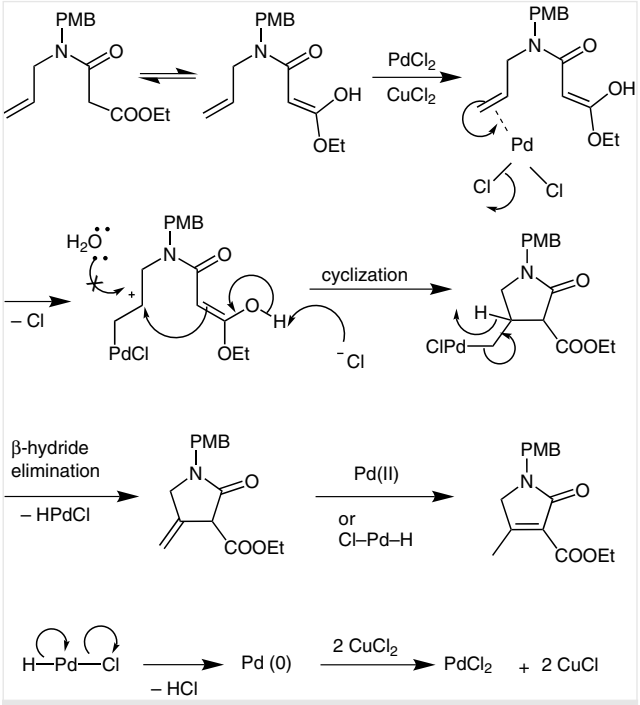
The synthesis commenced from inexpensive and commercially available allylamine (**4**), which was converted into secondary amine **5** in excellent yield (97%) by reductive amination using *p*-anisaldehyde and sodium borohydride (Scheme 1). Amine **5** was treated with ethyl malonyl chloride using potassium carbonate as the base to furnish amide **6** in 86% yield. When **6** was treated with palladium(II) chloride (10 mol%) and copper(II) chloride (2.1 equiv) as a co-oxidant in *N*,*N*-dimethylformamide–water (3:1) at 95 °C for six to eight hours surprisingly the cyclized product **8** was obtained in 62% yield instead of the anticipated ketone **7**.[7] This observation is consistent with our earlier study of the formation of six-membered rings.[5] Compound **8** underwent facile Krapcho's decarboxylation to afford compound **9** in 87% yield.[8]

Regioselective ethylation at the α carbon was accomplished on α,β-unsaturated lactam **9** using sodium hydride as the base and ethyl iodide as the electrophile in tetrahydrofuran, which resulted in the formation of compound **10d** in good yield (71%).[9] PMB deprotection of lactam **10d** employing ammonium cerium(IV) nitrate as the reagent in acetonitrile–water (5:1) at ambient temperature, furnished the desired lactam **1** in 80% yield.[10] The formation of compound **8**[11] can be explained by the probable mechanism shown in Scheme 2.

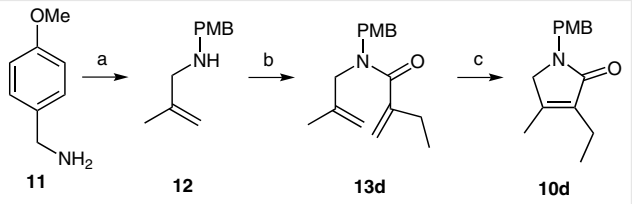
After the successful synthesis of **1** employing palladium(II)-assisted cyclization (Scheme 1), we felt that **1** could also be synthesized by employing a ring-closing-metathesis strategy, which is outlined in Scheme 3. This strategy involved use of commercially available 4-methoxybenzylamine (**11**) as the starting material which was then alkylated with methallyl chloride using potassium carbonate as the base and potassium iodide in catalytic quantities to furnish the secondary amine **12** in 84% yield (based on the recovered of starting material **11**). N-Acylation of amine **12** with ethacryloyl chloride, which in turn was prepared from butyraldehyde by a reported procedure,[12,13] using potassium carbonate as the base afforded tertiary amide **13d** in excellent yield (91%).



Scheme 1 *Reagents and conditions*: (a) (i) *p*-anisaldehyde (1.1 equiv), MeOH, 0 °C, 1 h; (ii) $NaBH_4$ (1.0 equiv), MeOH, 0 °C, 1 h, 97%; (b) K_2CO_3 (1.2 equiv), ethyl malonyl chloride (1.2 equiv), CH_2Cl_2, 0 °C, 1 h, 86%; (c) $PdCl_2$ (10 mol%), $CuCl_2$ (2.1 equiv), DMF–H_2O (3:1), 95 °C, 6–8 h, 62%; (d) NaCl (4.0 equiv), DMSO–H_2O (3:1), 120–130 °C, 12 h, 87%; (e) NaH (1.2 equiv), EtI (1.2 equiv), anhyd THF, 0 °C to r.t., 3 h, 71%; (f) CAN (2.5 equiv), MeCN–H_2O (5:1), r.t., 2 h, 80%.



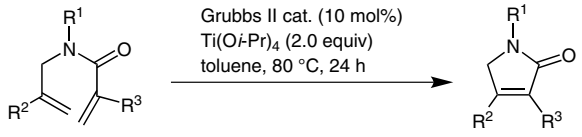
Scheme 2 Probable mechanism



Scheme 3 *Reagents and conditions*: (a) methallyl chloride (0.33 equiv), K_2CO_3 (1.2 equiv), KI (cat.), anhyd CH_2Cl_2, 0 °C to r.t., 12 h, 84%; (b) K_2CO_3 (1.2 equiv), ethacryloyl chloride (1.2 equiv), anhyd CH_2Cl_2, 0 °C to r.t., 3 h, 91%; (c) Grubbs II catalyst (10 mol%), Ti(O*i*-Pr)$_4$ (2.0 equiv), anhyd toluene, 80 °C, 12 h (90% based recovered **13d**).

After obtaining the requisite amide **13d**, we focused our attention on the ring-closing metathesis reaction as the key step. Although a number of syntheses of five- and six-membered α,β-unsaturated lactones and lactams by ring-closing metathesis have been reported in the literature,[14] very few reports are available for the construction of five- and six-membered rings containing tetrasubstituted olefins,[15] due to the difficulties encountered in their formation, which may be attributed to steric hindrance encountered by the substituents, electronic features of acrylamide, and ring strain of the resulting five-membered ring. Hence the construction of tetrasubstituted α,β-unsaturated lactones or lactams by the ring-closing-metathesis strategy is a challenging task. In the present study the ring-closing-metathesis reaction was studied and generalized. The substituent effect was studied by performing ring-closing-metathesis reactions on differently substituted acrylamides and the results are given in Table 1.

Table 1 RCM Reactions of Allyl Acrylamides in Toluene at 80 °C



13a–g 10a–g

Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)
1	**13a**[16a]	PMB	H	H	**10a**[16b,c]	98
2	**13b**	PMB	Me	H	**10b** (= **9**)	45
3	**13c**	PMB	Me	Me	**10c**	44
4	**13d**	PMB	Me	Et	**10d**	40
5	**13e**[16d]	Bn	Me	Me	**10e**[16e]	45
6	**13f**	Bn	Me	Et	**10f**	43
7	**13g**	Boc	Me	H	**10g**	37

From the results in Table 1, it is observed that the substituent present on the allyl moiety (electron-rich olefin) has a profound influence on the rate of reaction as well as the yield while the substituent present on the acrylamide (electron-deficient olefin) does not have a detrimental effect. The compound **13d** was subjected to ring-closing metathesis reactions employing Grubbs' 2nd generation catalyst (10 mol%) in anhydrous toluene at 80 °C for 24 hours, to deliver the α,β-unsaturated lactam **10d** in 40% yield (90% yield based on the recovered starting material). The lactam **10d**[15] was transformed into the desired intermediate **1** as shown in Scheme 1.

In conclusion, we have described novel synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**1**) employing two metal-catalyzed protocols viz. palladium-catalyzed cyclization in six steps in 25% overall yield and ring-closing metathesis in four steps in 55% overall yield that are superior to the reported syntheses.

All reagents and solvents were used as received from the manufacturers. Melting points are recorded using Buchi B-540 melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on Perkin-Elmer Model 68B or 1615 FT infrared spectrophotometer. ^{1}H (200 and 300 MHz) and ^{13}C (50 and 75 MHz) NMR spectra were recorded on Bruker and Bruker Advance 300 spectrometers, using $CDCl_3$–CCl_4 (2:1) as the solvent with reference to residual $CHCl_3$ (δ = 7.26) for ^{1}H NMR or the central line of $CDCl_3$ (δ = 77.0) for ^{13}C NMR. In the ^{13}C NMR spectra, the natures of the carbons (C, CH, CH_2, or CH_3) were determined by recording the DEPT-135 spectra. The reaction progress was monitored by the TLC analysis using precoated with silica gel 60 F_{254} (Merck) and visualized by fluorescence quenching or I_2 or by charring after treatment with *p*-anisaldehyde and also 2,4-DNP. Merck flash silica gel (230–400 mesh) was used for column chromatography.

N-(4-Methoxybenzyl)prop-2-en-1-amine (5)

To the stirred solution of allylamine (**4**, 1.0 g, 1.3 mL, 17.5 mmol) in dry MeOH (20 mL) was added *p*-anisaldehyde (2.62 g, 2.34 mL, 19.25 mmol) at 0 °C and the mixture was stirred for 1 h. After disappearance of the starting material (TLC), $NaBH_4$ (0.66 g, 17.5 mmol) was added portionwise at 0 °C and the mixture was stirred for a further 0.5 h. After completion of the reaction (TLC), the mixture was concentrated in vacuo and residue was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (anhyd Na_2SO_4), and filtered, and solvent was evaporated on rotary evaporator under reduced pressure. The resultant residue was purified by flash column chromatography (silica gel, EtOAc–petroleum ether, 4:6) to furnish **5** (3.0 g, 97%) as pale yellow liquid.

IR ($CHCl_3$): 3393, 3019, 1613, 1215, 758 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ = 1.94 (s, 1 H), 3.28 (d, *J* = 4.0 Hz, 2 H), 3.78 (s, 3 H), 4.65 (s, 2 H), 5.14–5.28 (m, 2 H), 5.91 (m, 1 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 7.26 (d, *J* = 9.0 Hz, 2 H).

MS (ESI): *m*/*z* = 178 (M + H)$^+$.

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.59; H, 8.47; N, 7.87.

Ethyl 3-[Allyl(4-methoxybenzyl)amino]-3-oxopropanoate (6)

To the stirred solution of **5** (1.0 g, 5.6 mmol) in anhyd CH_2Cl_2 (10 mL) was added K_2CO_3 (2.3 g, 16.8 mmol) at 0 °C and the mixture was stirred for 15 min. Then ethyl malonyl chloride (1.0 g, 0.84 mL, 6.72 mmol) was added dropwise at 0 °C and the mixture was stirred at

0 °C under N_2 atmosphere until completion of reaction (1 h, TLC). The mixture was filtered and the residue was washed with CH_2Cl_2 (3 × 15 mL), the filtrate was concentrated in vacuo and the residue obtained was purified by flash column chromatography (silica gel, EtOAc–petroleum ether, 1:4) to furnish **6** (1.41 g, 86%) as a colorless syrup.

IR ($CHCl_3$): 3458, 2982, 2936, 1735, 1654, 1513, 1248, 1032 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ = 1.28 (t, *J* = 7.2 Hz, 3 H), 3.46 (s, 2 H), 3.78 (s, 3 H), 3.75–3.97 (m, 2 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 4.43–4.50 (m, 2 H), 5.12–5.25 (m, 2 H), 5.59–5.58 (m, 1 H), 6.85 (d, *J* = 9.0 Hz, 2 H), 7.16 (d, *J* = 9.0 Hz, 2 H) (mixture of rotamers).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ = 14.0, 41.0, 41.1, 47.6, 49.25, 50.1, 55.0, 61.1, 113.8, 114.2, 116.95, 117.40, 127.6, 127.8, 128.9, 129.3, 132.3, 158.9, 159.1, 166.0, 166.2, 167.4 (mixture of rotamers).

MS (ESI): *m*/*z* = 292 $(M)^+$.

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.09; H, 7.19; N, 4.77.

Ethyl 1-(4-Methoxybenzyl)-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (8)

To a stirred solution of olefinic ester **6** (0.2 g, 0.68 mmol) in DMF–H_2O (3:1, 12 mL), $PdCl_2$ (0.011 g, 0.068 mmol), and $CuCl_2{\cdot}2H_2O$ (0.24 g, 1.4 mmol) were added and the resultant solution was heated to 95 °C (TLC monitoring) for 8 h. The mixture was cooled to r.t. and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried (anhyd Na_2SO_4) and filtered and the solvent was removed on a rotary evaporator under reduced pressure and the residue obtained was purified by flash column chromatography (silica gel, EtOAc–petroleum ether, 2:3) to furnish **8** (0.122 g, 62%) as a pale yellow syrup.

IR ($CHCl_3$): 1721, 1687, 1214, 757 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 1.38 (t, *J* = 7.1 Hz, 3 H), 2.29 (s, 3 H), 3.74 (s, 2 H), 3.78 (s, 3 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 4.52 (s, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 7.15 (d, *J* = 8.8 Hz, 2 H).

MS (ESI): *m*/*z* = 290 $(M + H)^+$, 312 $(M + Na)^+$.

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.56; H, 6.45; N, 4.77.

1-(4-Methoxybenzyl)-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (9)

To a stirred solution of **8** (0.5 g, 1.7 mmol) in DMSO–H_2O (3:1, 20 mL), NaCl (0.4 g, 6.8 mmol) was added and resultant mixture was heated at 120–130 °C for 12 h. After disappearance of the starting material (TLC monitoring), the mixture was allowed to cool to r.t., diluted with water (25 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography (silica gel, EtOAc–petroleum ether, 4:6) to give **9** (0.326 g, 87%) as a pale yellow solid; mp 122 °C.

IR ($CHCl_3$): 3347, 1672, 1513, 1247, 1216, 756 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 2.01 (s, 3 H), 3.68 (s, 2 H), 3.78 (s, 3 H), 4.50 (s, 2 H), 5.85 (s, 1 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 7.14 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 15.05, 45.05, 54.7, 55.0, 114.0, 122.7, 129.1, 129.5, 154.9, 159.0, 171.6.

MS (ESI): *m*/*z* = 218 $(M + H)^+$, 240 $(M + Na)^+$.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.61; H, 6.98; N, 6.69.

3-Ethyl-1-(4-methoxybenzyl)-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (10d)

To 60% NaH (0.044 g, 1.08 mmol), prewashed with anhyd petroleum ether (3 × 10 mL), was added **9** (0.2 g, 0.9 mmol) in anhyd THF (10 mL) slowly at 0 °C. The mixture was stirred for 15 min and the EtI (0.158 g, 0.081 mL, 0.99 mmol) in anhyd THF (5 mL) was added dropwise and the mixture was stirred for 3 h at this temperature (TLC monitoring). The reaction was quenched by the addition of sat. NH_4Cl solution and the organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (anhyd Na_2SO_4), and filtered, the solvent was evaporated in vacuo, and the resultant residue was purified by flash column chromatography (silica gel, EtOAc–petroleum ether, 1:4) to furnish **10d** (0.160 g, 71%) as a yellow solid; mp 127–131 °C.

IR ($CHCl_3$): 1671, 1515, 1248, 1212, 757 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ = 1.07 (t, *J* = 7.6 Hz, 3 H), 1.91 (s, 3 H), 2.28 (q, *J* = 7.6 Hz, 2 H), 3.56 (s, 2 H), 3.77 (s, 3 H), 4.51 (s, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 7.14 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ = 12.9, 12.95, 18.9, 46.1, 53.2, 54.3, 113.8, 128.1, 128.6, 135.0, 144.95, 158.7, 171.7.

MS (ESI): *m*/*z* = 246 $(M + H)^+$, 268 $(M + Na)^+$.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.47; H, 7.78; N, 5.76.

N-(4-Methoxybenzyl)-2-methylprop-2-en-1-amine (12)

To the stirred solution of 4-methoxybenzylamine (**11**, 1.0 g, 7.2 mmol) in anhyd CH_2Cl_2 (10 mL), K_2CO_3 (3.03 g, 21.6 mmol) was added at 0 °C and the mixture was stirred for 30 min. A solution of methallyl chloride (0.217 g, 0.234 mL, 2.37 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 10 min at 0 °C followed by cat. KI (0.1 equiv) under N_2 atmosphere. The mixture was stirred for 3 h (TLC monitoring). When the reaction was complete, the mixture was quenched by the addition of sat. NH_4Cl solution and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (anhyd Na_2SO_4), filtered, and concentrated in vacuo and the residue obtained was purified by flash column chromatography (silica gel, EtOAc–petroleum ether, 2:3) to furnish **12** (0.384 g, 84%, based on the recovery of starting material) as a colorless oil; 0.670 g starting material was recovered.

IR ($CHCl_3$): 1611, 1512, 1216, 757 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ = 1.78 (s, 3 H), 1.85 (s, 1 H), 3.18 (s, 2 H), 3.70 (s, 2 H), 3.80 (s, 3 H), 4.86 (s, 1 H), 4.90 (s, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 7.25 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ = 20.5, 52.1, 54.5, 54.6, 110.6, 113.3, 128.9, 132.1, 143.4, 158.3.

MS (ESI): *m*/*z* = 192 $(M + H)^+$.

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.23; H, 9.07; N, 7.27.

N-(4-Methoxybenzyl)-*N*-(2-methylallyl)-2-methylenebutanamide (13d); Typical Procedure

To the stirred solution of amine **12** (0.25 g, 1.3 mmol) in anhyd CH_2Cl_2 (10 mL), K_2CO_3 (0.545 g, 3.9 mmol) was added at 0 °C under N_2 atmosphere followed by dropwise addition of ethacryloyl chloride (0.186 g, 1.56 mmol) at 0 °C and the mixture was stirred for 3 h (TLC monitoring). When the reaction was complete, the mixture was filtered and the residue washed with CH_2Cl_2 (3 × 10 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, EtOAc–petroleum ether, 1:4) to afford **13d** (0.325 g, 91%) as a thick colorless oil.

IR ($CHCl_3$): 3081, 1970, 1644, 1614, 1512, 1247, 755 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ = 1.08 (t, *J* = 7.5 Hz, 3 H), 1.65 (s, 3 H), 2.33 (q, *J* = 7.5 Hz, 2 H), 3.77–3.87 (m, 5 H), 4.51 (s, 2 H), 4.67–4.95 (m, 2 H), 5.10 (s, 2 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 7.17 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ = 11.4, 19.65, 26.9, 45.2, 47.6, 49.8, 52.3, 54.6, 111.9, 112.2, 113.3, 113.6, 127.9, 129.1, 139.9, 146.0, 158.65, 172.3 (mixture of rotamers).

MS (ESI): *m*/*z* = 274 $(M + H)^+$.

Anal. Calcd for $C_{17}H_{23}NO$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.63; H, 8.37; N, 5.23.

N-(4-Methoxybenzyl)-*N*-(2-methylallyl)acrylamide (13b)

Yield: 205 mg (80%); colorless liquid.

IR ($CHCl_3$): 2935, 1646, 1612, 1512 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.62–1.79 (m, 3 H), 3.64–4.11 (m, 5 H), 4.43–4.65 (m, 2 H), 4.71–5.05 (m, 2 H), 5.61–5.78 (m, 1 H), 6.33–6.70 (m, 2 H), 6.76–6.96 (m, 2 H), 7.03–7.25 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 48.0 (49.0), 50.5, (51.8), 55.2, 111.7 (112.4), 113.8 (114.2), 127.6, 127.7, 128.3 (128.5), 128.8, 129.5, 129.7, 139.8 (140.4), 158.9 (159.0), 166.7 (166.9).

HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{19}NO_2$ $[M + H]^+$: 246.1494; found: 246.1498.

N-(4-Methoxybenzyl)-*N*-(2-methylallyl)methacrylamide (13c)

Yield: 200 mg (73%); colorless liquid.

IR ($CHCl_3$): 2930, 1648, 1614, 1465 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.54–1.76 (m, 3 H), 1.98 (br s, 3 H), 3.66–4.02 (m, 5 H), 4.40–4.59 (m, 2 H), 4.63–5.02 (m, 2 H), 5.04–5.34 (m, 2 H), 6.85–6.89 (m, 2 H), 6.99–7.25 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 20.6 (20.8), 45.6 (48.0), 50.1 (52.8), 55.1, 112.4, 113.9, 114.7, 114.9, 128.1, 128.5, 129.2 129.5, 139.9 (140.2), 140.5 (140.7), 158.9, 173.0.

HRMS (ESI+): *m*/*z* calcd for $C_{16}H_{21}NO_2$ $[M + H]^+$: 260.1650; found: 260.1650.

N-Benzyl-*N*-(2-methylallyl)-2-methylenebutanamide (13f)

Yield: 303 mg (67%); colorless liquid.

IR ($CHCl_3$): 3020, 1648, 1617, 1421 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.03–1.21 (m, 3 H), 1.58–1.80 (m, 3 H), 2.26–2.46 (m, 2 H), 3.69–4.07 (m, 2 H), 4.48–4.67 (m, 2 H), 4.67–5.06 (m, 2 H), 5.14 (s, 2 H), 7.06–7.44 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.6, 20.0, 27.1, 46.3 (48.3), 50.7 (52.9), 112.5, 124.5, 126.8, 127.3 (127.4), 128.2, 128.5, 128.7, 136.7 (137.2), 139.9 (140.2), 146.1 (146.3), 173.2.

HRMS (ESI+): *m*/*z* calcd for $C_{16}H_{21}NO$ $[M + H]^+$: 244.1701; found: 244.1699.

tert-Butyl Acryloyl(2-methylallyl)carbamate (13g)

Yield: 320 mg (59%); thick colorless oil.

IR ($CHCl_3$): 3364, 2979, 2937, 1734, 1687, 1619, 1404 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ = 1.48 (s, 9 H), 1.72 (s, 3 H), 4.23 (s, 3 H), 4.67–4.80 (2 s, 2 H), 5.69 (dd, *J* = 10.4, 1.9 Hz, 1 H), 6.32 (dd, *J* = 16.8, 1.9 Hz, 1 H), 7.04 (dd, *J* = 16.8, 10.4 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ = 20.6, 28.1, 49.5, 83.2, 110.1, 128.1, 131.3, 141.0, 153.2, 168.25.

MS (ESI): *m*/*z* = 226 $(M + H)^+$.

3-Ethyl-1-(4-methoxybenzyl)-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (10d); Typical Procedure

To a degassed homogeneous solution of **13d** (0.2 g, 0.7 mmol) in anhyd toluene (20 mL), Grubbs' 2nd generation catalyst (0.062 g, 10 mol%) and $Ti(Oi\text{-}Pr)_4$ (2 equiv) were added under an argon atmosphere; the resultant mixture was heated at 80 °C for 12 h. When the reaction was complete (TLC), the solvent was removed on a rotary evaporator under reduced pressure and residue obtained was purified by flash column chromatography (silica gel, EtOAc–petroleum ether, 1:4) to provide lactam **10d** (0.072 g, 40%) as a yellow solid and 0.11 g of starting material was recovered; mp 127–131 °C.

IR ($CHCl_3$): 1671, 1515, 1248, 1212, 757 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ = 1.07 (t, *J* = 7.6 Hz, 3 H), 1.91 (s, 3 H), 2.28 (q, *J* = 7.6 Hz, 2 H), 3.56 (s, 2 H), 3.77 (s, 3 H), 4.51 (s, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 7.14 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ = 12.9, 12.95, 18.9, 46.1, 53.2, 54.3, 113.8, 128.1, 128.6, 135.0, 144.95, 158.7, 171.7.

MS (ESI): *m*/*z* = 246 $(M + H)^+$, 268 $(M + Na)^+$.

Anal. Calcd for $C_{15}H_{19}NO$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.47; H, 7.78; N, 5.76.

1-(4-Methoxybenzyl)-3,4-dimethyl-1*H*-pyrrol-2(5*H*)-one (10c)

Yield: 39 mg (44%); pale yellowish liquid.

IR ($CHCl_3$): 2940, 1666, 1513, 1460 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 3 H), 1.92 (s, 3 H), 3.61 (s, 2 H), 3.81 (s, 3 H), 4.56 (s, 2 H), 6.86 (d, *J* = 8.80 Hz, 2 H), 7.19 (d, *J* = 8.56 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.7, 12.9, 45.4, 53.5, 55.2, 114.0, 128.6, 129.3, 129.8, 145.7, 158.9, 172.6.

HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{17}NO_2$ $[M + H]^+$: 232.1337; found: 232.1337.

1-Benzyl-3-ethyl-4-methyl-1*H*-pyrrol-2(5*H*)-one (10f)

Yield: 38 mg (43%); colorless viscous liquid.

IR ($CHCl_3$): 2925, 1671, 1656, 1458 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 7.5 Hz, 3 H), 1.95 (s, 3 H), 2.34 (q, *J* = 7.5 Hz, 2 H), 3.63 (s, 2 H), 4.64 (s, 2 H), 7.21–7.42 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 13.1, 17.0, 46.0, 53.6, 127.3, 128.0, 128.6, 134.2, 137.7, 145.4, 172.2.

HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{17}NO$ $[M + H]^+$: 216.1388; found: 216.1390.

tert-Butyl 4-Methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (10g)[6e,h]

Yield: 28 mg (37%); thick colorless oil.

IR ($CHCl_3$): 3448, 2980, 1778, 1739, 1712, 1643, 1447, 1293, 1164, 843, 755 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ = 1.52 (s, 9 H), 2.07 (s, 3 H), 4.17 (s, 2 H), 5.80 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ = 15.3, 27.9, 54.1, 82.1, 122.6, 149.1, 157.8, 169.0.

MS (ESI): *m*/*z* = 198 $(M + H)^+$.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.26; H, 8.06; N, 6.75.

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

To a stirred solution of lactam **10d** (0.1 g, 0.40 mmol) in MeCN (10 mL) and H_2O (2 mL), CAN (0.447 g, 0.80 mmol) was added. The mixture was stirred at r.t. until completion of the reaction (TLC monitoring, 2 h). The solvent was removed on a rotary evaporator under reduced pressure, the resultant residue was diluted with H_2O (40 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (anhyd Na_2SO_4), filtered, and concentrated in vacuo and the residue obtained was purified by flash column chromatography (silica gel, EtOAc–petroleum ether, 1:2) to furnish target **1** (0.036 g, 80%) as a pale yellow solid; mp 102 °C.

IR ($CHCl_3$): 3326, 2974, 1681, 1451, 1216 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.4 Hz, 3 H), 1.95 (s, 3 H), 2.22 (q, *J* = 7.4 Hz, 2 H), 3.76 (s, 2 H), 8.04 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.3, 12.5, 16.0, 49.7, 133.4, 148.2, 175.9.

MS (ESI): *m*/*z* = 125 $(M)^+$.

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.93; H, 9.11; N, 11.38.

Acknowledgement

A.B.P. and K.P.P. thank CSIR, New Delhi, India, for fellowships. The authors thank Dr. K. Pasupathy, Dr. H. B. Borate, and Dr. U. R. Kalkote for helpful discussions and Dr. P. R. Rajamohanan for NMR facility, and CSIR, New Delhi, India, for financial support as part of the XIIth Five Year plan programme under title ACT (CSC-0301).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379985.

References

(1) (a) Gurjar, M. K.; Joshi, R. A.; Chaudhuri, S. R.; Joshi, S. V.; Barde, A. R.; Gediya, L. K.; Ranade, P. V.; Kadam, S. M.; Naik, S. J. *Tetrahedron Lett.* **2003**, *44*, 4853. (b) Zhang, H.; Huang, H.; Zhou, J.; Zhao, S.; Huang, W. *Zhongguo Yaoke Daxue Xuebao* **1999**, *30*, 163.

(2) (a) Bishop, J. E.; Nagy, J. O.; O'Connell, J. F.; Rapoport, H. *J. Am. Chem. Soc.* **1991**, *113*, 8024. (b) Sabido, P. M. G.; Lightner, D. A. *Monatsh. Chem.* **2014**, *145*, 775.

(3) (a) Deng, Y.; Zhong, Y. *Huaxi Yaoxue Zazhi* **2000**, *15*, 289. (b) Deng, Y.; Zhong, Y.; Tang, W.; Zhong, Z. *Zhongguo Yaowu Huaxue Zazhi* **2000**, *10*, 134. (c) Coffin, A. R.; Roussell, M. A.; Tserlin, E.; Pelkey, E. T. *J. Org. Chem.* **2006**, *71*, 6678; and references cited therein.

(4) Hayashi, T.; Hegedus, L. S. *J. Am. Chem. Soc.* **1977**, *99*, 7093.

(5) Chavan, S. P.; Pathak, A. B.; Kalkote, U. R. *Synlett* **2007**, 2635.

(6) (a) Chavan, S. P.; Pasupathy, K.; Venkatraman, M. S.; Kale, R. R. *Tetrahedron Lett.* **2004**, *45*, 6879. (b) Chavan, S. P.; Praveen, C. *Tetrahedron Lett.* **2005**, *46*, 1939. (c) Chavan, S. P.; Thakkar, M.; Jogadand, G. F. *J. Org. Chem.* **2006**, *71*, 8986. (d) Chavan, S. P.; Sharma, P. S.; Sivappa, R.; Kalkote, U. R. *Tetrahedron Lett.* **2006**, *47*, 9301. (e) Chavan, S. P.; Pathak, A. B.; Dhawane, A. N.; Kalkote, U. R. *Synth. Commun.* **2007**, *37*, 1503. (f) Chavan, S. P.; Dhawane, A. N.; Kalkote, U. R. *Tetrahedron Lett.* **2007**, *48*, 965. (g) Chavan, S. P.; Pathak, A. B.; Pandey, A.; Kalkote, U. R. *Synth. Commun.* **2007**, *37*, 3143. (h) Li, W.-R.; Lin, S. T.; Hsu, N.-M.; Chern, M.-S. *J. Org. Chem.* **2002**, *67*, 4702.

(7) Aggarwal, V. K.; Astle, C. J.; Rogers-Evans, M. *Org. Lett.* **2004**, *6*, 1469.

(8) Giles, M.; Hadley, M. S.; Gallagher, T. *Chem. Commun.* **1990**, 1047.

(9) Lee, R. A.; McAndrews, C.; Patel, K. M.; Ruesch, W. *Tetrahedron Lett.* **1973**, 965.

(10) Bryans, J. S.; Chessums, E. A. N.; Nathalie, H.; Parsons, A. F.; Ghelfi, F. *Tetrahedron* **2003**, *59*, 6221.

(11) For Pd(II)-mediated isomerization of olefins please see: (a) Sen, A.; Lai, T.-W. *Inorg. Chem.* **1981**, *20*, 4036. (b) Sen, A.; Lai, T.-W. *Inorg. Chem.* **1984**, *23*, 3257. For palladium hydride mediated isomerization of olefins see: (c) Borszeky, K.; Mallat, T.; Baiker, A. *Catal. Lett.* **1999**, *59*, 95. (d) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*; Wiley: New York, **1988**, 188. (e) Bartok, M.; Czombos, J.; Felfoldi, K.; Gera, L.; Gondos, G.; Molnar, A.; Notheisz, F.; Palinko, I.; Wittmann, G.; Zsigmond, A. G. *Stereochemistry of Heterogeneous Metal Catalysis*; Wiley: New York, **1985**.

(12) Pikh, Z. G.; Fedevich, M. D.; Yatchishin, I. I. *Zh. Org. Khim.* **1978**, *1*, 60.

(13) Hon, Y.-S.; Lin, W.-C. *Tetrahedron Lett.* **1995**, *36*, 7693.

(14) (a) Furstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.; Nolan, P. S. *J. Org. Chem.* **2000**, *65*, 2204. (b) Rodriguez, S.; Castillo, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 1185. (c) Ackermann, L.; Ftirstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787.

(15) (a) Andreana, P. R.; McLellan, J. S.; Chen, Y.; Wang, P. G. *Org. Lett.* **2002**, *4*, 3875. (b) D'Annibale, A.; Ciaralli, L.; Bassetti, M.; Pasquini, C. *J. Org. Chem.* **2007**, *72*, 6067.

(16) (a) Compound **13a**: Riggi, I. D.; Gastaldi, S.; Surzur, J.-M.; Bertrand, M. P. *J. Org. Chem.* **1992**, *57*, 6118. (b) Compound **10a**: Curti, C.; Ranieri, B.; Battistini, L.; Rassu, G.; Zambrano, V.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2010**, *352*, 2011. (c) Shao, C.; Yu, H.-J.; Wu, N.-Y.; Tian, P.; Wang, R.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2011**, *13*, 788. (d) Compound **13e**: Kitagawa, O.; Aoki, K.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 593. (e) Compound **10e**: Mathew, J.; Alink, B. *J. Org. Chem.* **1990**, *55*, 3880.