Beckmann rearrangement for the synthesis of derivatives of *β*- and *γ*-carbolinones, dihydropyrrolopyridinone and tetrahydroisoquinolinone

Prajakta N. Naik, Nabil A. H. Alkobati, and Radhika S. Kusurkar*

Department of Chemistry, Savitribai Phule Pune University (former University of Pune), Pune - 411 007, India
E-mail: rsk@chem.unipune.ac.in

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Abstract
Beckmann rearrangement was used as a key step to synthesize six-membered lactams fused to a heteroaromatic or aromatic system. Derivatives of biologically active scaffolds like *β*- and *γ*-carbolinone, dihydropyrrolopyridinone and tetrahydroisoquinolinone were synthesized using this strategy.

Keywords: Beckmann rearrangement, *β*-carbolinone, *γ*-carbolinone, dihydropyrrolopyridinone, tetrahydroisoquinolinone

Introduction

Since the discovery of this Beckmann rearrangement (BR) in 1896, successive investigations have been largely carried out and applied in many ways. BR is a skeletal rearrangement, which accomplishes both, the cleavage of C-C bond and formation of C-*N* bond. It has become a very useful and efficient method for incorporation of nitrogen atom in both cyclic and acyclic systems and also for the synthesis of various alkaloids. Several catalyst have been used for this rearrangement like zeolites[1], metal catalysts[2,3], $FeCl_3/AgSbF_6$[4], etc.

Though BR is a very well-known and old reaction,[5-7] there are very few reports for its use to rearrange cyclic oximes fused with heterocyclic ring systems.[8-10] It was thus envisaged to use BR for the synthesis of cyclic lactams fused to indole, pyrrole and benzene ring.

Dihydropyrrolopyridinones are compounds in which, a dihydropyridinone ring is fused to the pyrrole ring. It is reported[11] that substituted pyrrolopyridinones act as Cdc7 kinase inhibitors and are also known to be potential antitumor agents. This moiety is a part of the *β*-carbolinone unit which is of interest in medicine and in recent years, many of these derivatives have been patented and described as useful central nervous system depressant and antitumor agents.[12-14]

They have been isolated from various natural sources and show variety of activities like antileukemic,[15] serotonin regulating activity,[16,17] etc.

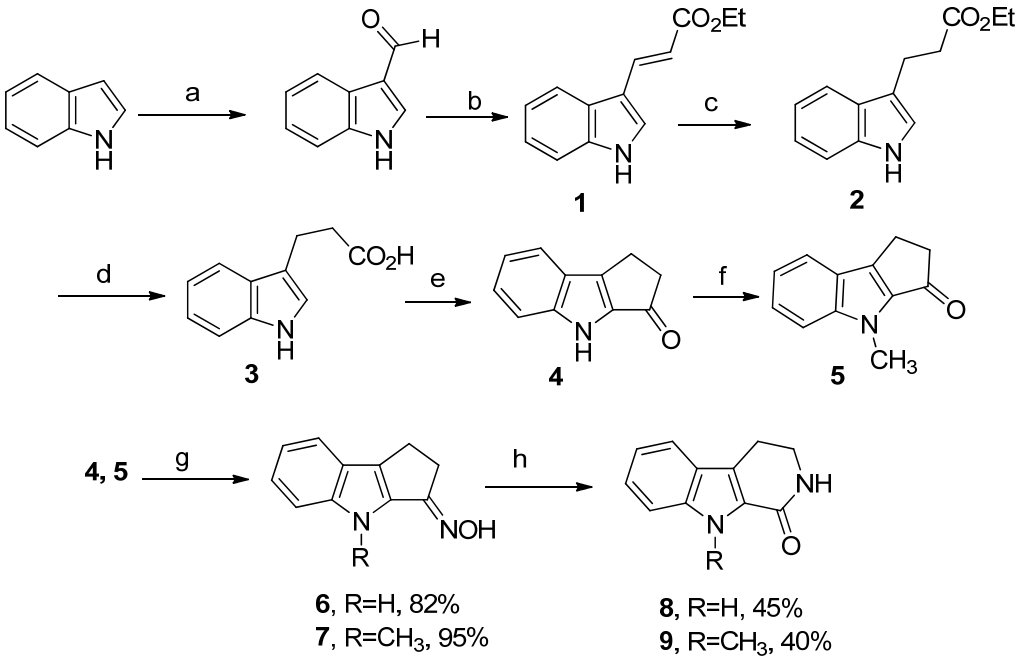
Tetrahydroisoquinolinones are part of biologically important molecules and have been used as intermediates in the synthesis of various scaffolds. Grunewald et al[18] have demonstrated the use of tetrahydroisoquinolinones as substrates exhibiting PNMT inhibitory activity and these derivatives have been synthesized[19-22] in the past using strategies like Bischler-Napieralski cyclization and amide formation reactions.

We are herewith reporting the successful use of BR for the synthesis of derivatives of *β*- and *γ*-carbolinones, dihydropyrrolopyridinone and tetrahydroisoquinolinone scaffolds.

Results and Discussion

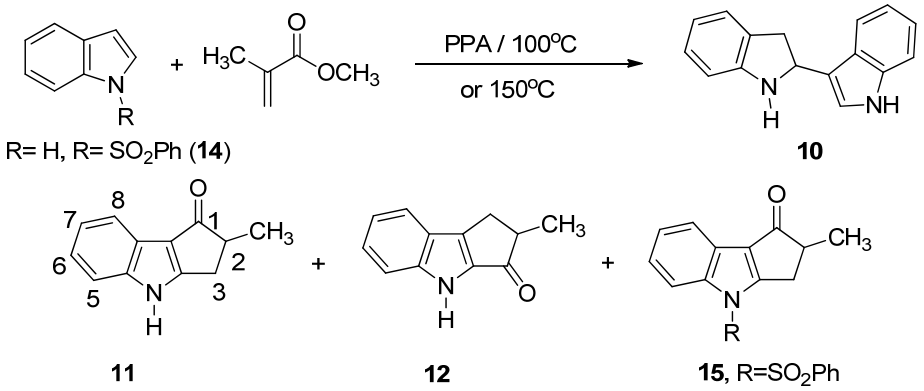
The work started with the synthesis of *β*- and *γ*-carbolinones. Thus, indole was formylated (Scheme 1) to get 3-formyl indole followed by Wittig reaction to furnish *E* isomer of 3-(*β*-carboethoxyvinyl)indole, **1**. Further reduction and hydrolysis furnished acid **3**. PPA (polyphosphoric acid) cyclization of acid **3** resulted in formation of cyclic ketone **4**, which was converted to oxime **6**. [23,24] Ketone **4** was also *N*-methylated using dimsyl anion and methyl iodide to get ketone **5**, which was converted to oxime **7**.[24,25] Oxime **6** was obtained as a mixture of geometrical isomers in the ratio 4:1 and oxime **7** as a single isomer as seen from the spectral data. However, geometry could not be assigned to the oximes at this stage.

Oximes **6** and **7** were further separately treated with $POCl_3$ to furnish selectively only one BR product in each reaction as *β*-carboline-1-one (**8**) and *N*-methyl-*β*-carboline-1-one (**9**) respectively. Both the structures were confirmed by comparing the NMR values with the reported[26-28] data. Though the starting oxime **6** was a mixture of isomers, selectively a single product was obtained. This could be explained by the conversion of *anti* isomer of oxime to its *syn* isomer during the reaction course followed by BR to furnish the product **8**. The conversion of one isomer to the other was also observed on keeping the mixture of oximes at room temperature for a long time. Thus, use of BR was demonstrated for the synthesis of *β*-carbolinones **8** and **9** (Scheme 1).



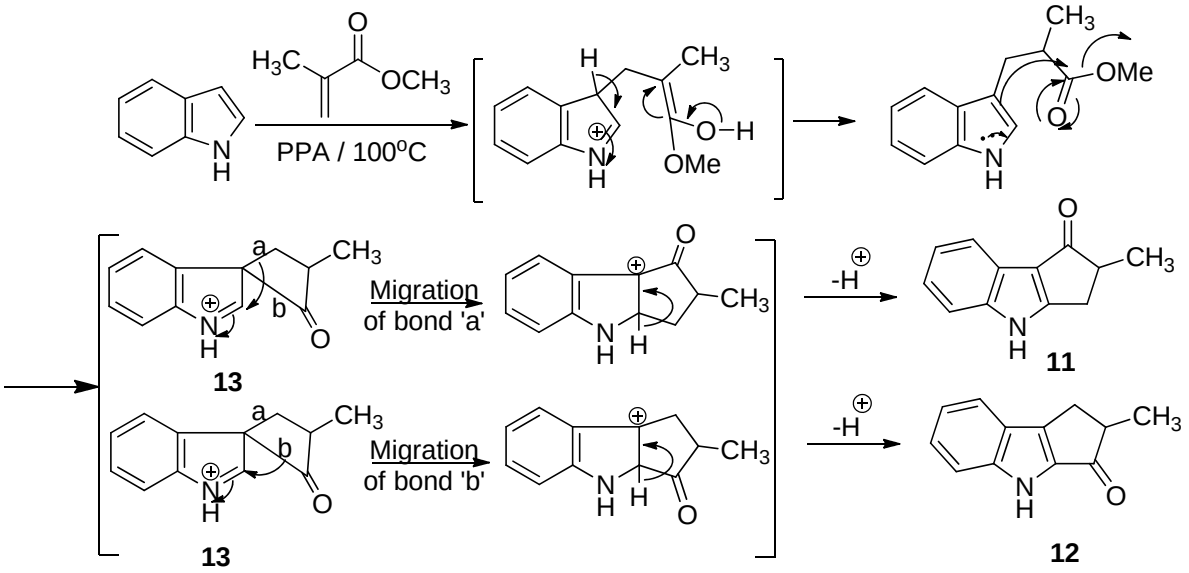
Scheme 1. Reagents and Conditions: a) DMF, $POCl_3$, RT, 5 h, 95%; b) $PPh_3CHCOOEt$, toluene, reflux, 6 h, 92%; c) Pd/C, MeOH/ H_2, RT, 1 h, 94%; d) NaOH, reflux, 1 h, 90%; e) PPA, toluene, 110 °C, 4 h, 76%; f) DMSO, KOH, MeI, 2 h, 92%; g) NH_2OH. HCl, pyridine, EtOH, 70 °C, 6 h; h) $POCl_3$, THF, 60 °C, 2 h.

Subsequently, BR was planned using two more oximes **18** and **22**, having oximino group at C_1. A new method was attempted for the synthesis of ketone **11**[29] which was the starting material for above oximes. Thus, Michael addition of indole (Scheme 2) was carried out on methylmethacrylate at 100 ºC in PPA. Unexpectedly, a dimer[30] **10** was obtained as a major compound in 40% yield along with two ketones **11** and **12** in 7% and 3% yield respectively.



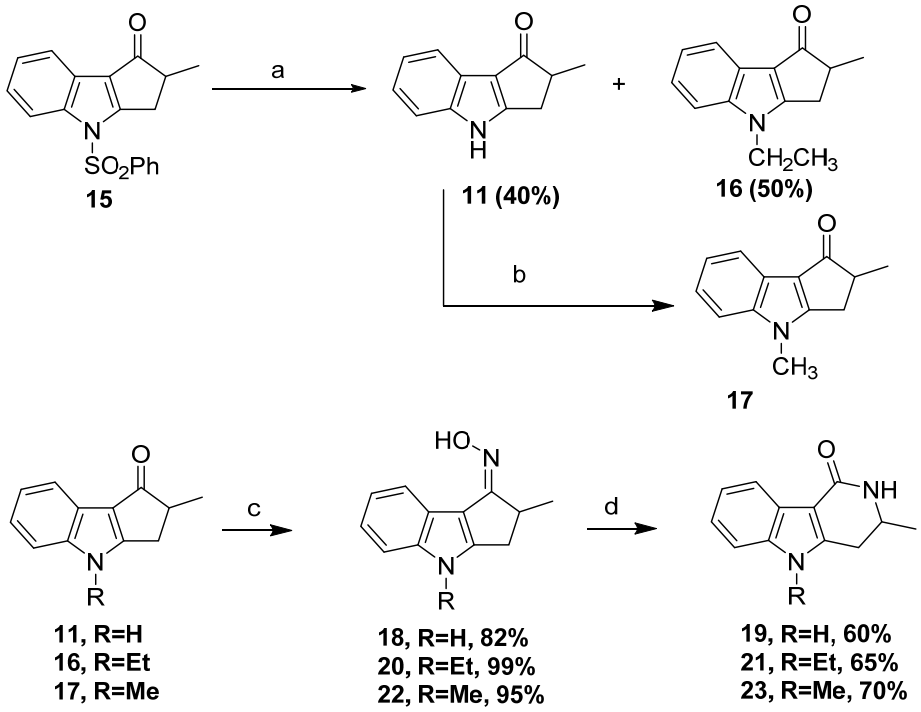
Scheme 2. One pot reaction for synthesis of cyclic ketone **11.**

The formation of two ketones can be explained by migration of two bonds, one at a time from the possible *spiro* intermediate **13** as shown in Scheme 3. The structure of compound **11** was assigned and confirmed from the downfield position of the doublet at δ 7.9 for C_8H due to its *peri* position with respect to carbonyl group.



Scheme 3. Mechanism for migration of bond.

Formation of unwanted dimer **10** in major amount can be attributed to the presence of free NH group. To get the required ketone **11** as a major compound, *N*-benzenesulphonyl indole (**14**) was used for the reaction. It was expected that the -SO_2Ph group would decrease the reactivity of indole ring and would give selectively the required product. The reaction of *N*-benzenesulphonyl indole with methylmethacrylate at 150 °C using PPA (Scheme 2) furnished two products, **11** (15%) and **15 (**70%).



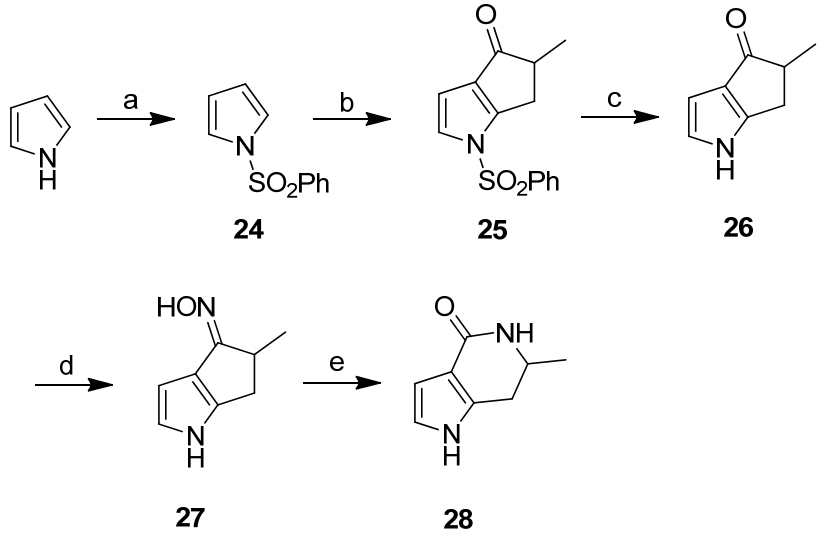
Scheme 4. Reagents and conditions: a) CH_3CH_2ONa, ethanol, reflux, 1 h; b) DMSO, KOH, MeI, 2 h, 90%; c) $NH_2OH.HCl$, Pyridine, ethanol, reflux, 10 h; d) $POCl_3$, Ethyl acetate, 70 °C, 5 min for **19** and 2 h for **21** and **23**.

Ketone **15** was then deprotected using sodium ethoxide to get desired ketone **11** in 40% yield. In this reaction, a new compound was isolated in 50% yield along with **11**, which was shown to be *N*-ethylketone **16** (Scheme 4). The ketone **11** was *N*-methylated using dimsyl anion and methyliodide to get the *N*-methyl ketone **17**.

Having the ketones **11**, **16** and **17** in hand, they were further converted to single isomer of oximes **18, 20** and **22** respectively. BR of oximes **18**, **20** and **22** using $POCl_3$ furnished selectively unreported γ-carboline-4-ones **19**, **21** and **23** respectively (Scheme 4). The structures of these compounds were confirmed using spectral and analytical data. ^{1}H NMR showed the down field position of proton adjacent to nitrogen [for **19** at δ 3.94–4.1 (m), for **21** at δ 3.93–4.07 (m) and for **23** at δ 3.99 (m)] as compared to its position in the corresponding ketones [for **11** at δ 3.1 (m), for **16** at δ 3.08 (m) and for **17** at δ 3.0–3.12 (m)], which confirmed the structures as γ-carbolinones and not δ-carbolinones.

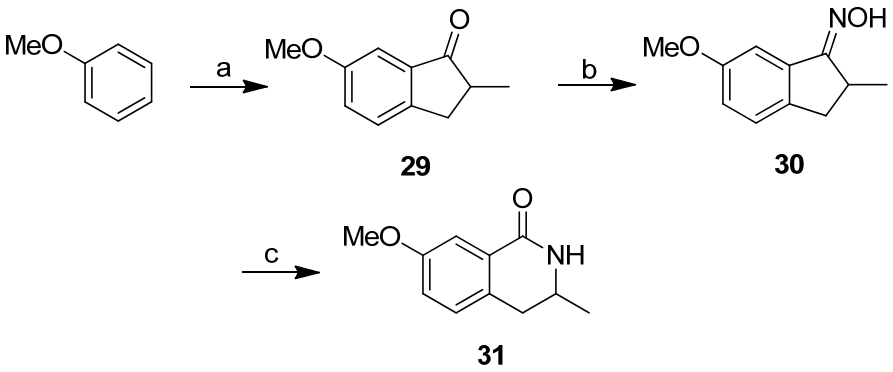
With this successful synthesis of β- and γ-carbolinones using BR, pyrrolopyridinone was the next synthetic target. The synthesis towards dihydropyrrolopyridinone started with protection of pyrrole with benzenesulphonyl chloride to get the *N*-protected pyrrole **24** (Scheme 5). The protected pyrrole was further treated with methyl methacrylate in PPA at 140 °C to get the cyclic ketone **25**. Subsequently, one pot deprotection and oxime formation was attempted by treatment of ketone **25** with hydroxyl amine hydrochloride and sodium hydroxide in methanol. However,

the spectral analysis of the isolated product indicated that only deprotection had occurred to give compound **26**. Even after continuation of reaction for longer time and refluxing the reaction mixture did not furnish the required oxime. Further, reaction of deprotected ketone **26** with hydroxylamine hydrochloride in presence of pyridine as a base, furnished the oxime **27** in 95% yield after refluxing the contents at 80 °C for 5 hours. The Beckmann reaction of this oxime using $POCl_3$ at lower temperature, furnished the desired unreported dihydropyrrolopyridinone **28** in good yield.



Scheme 5. Reagents and Conditions: a) KOH, DMSO, $PhSO_2Cl$, rt, 5 h, 95%; b) Methyl methacrylate, PPA, 140 °C, 10 h, 85%; c) NaOH, MeOH, rt, 1 h, 98%; d) $NH_2OH.HCl$, Pyridine, MeOH, 80 °C, 5 h, 95%; e) $POCl_3$, EtOAc, 0 °C, 30 min, 80%.

In order to check the BR strategy for non-heterocyclic oxime, tetrahydroisoquinolinone **31,** was identified as the target. Thus, as shown in Scheme 6, anisole was treated with methyl methacrylate in PPA at 140 °C for 10 hours to afford the ketone **29**. This ketone was subsequently treated with hydroxyl amine hydrochloride and sodium hydroxide in methanol giving the required oxime **30** after one hour of stirring at room temperature. Oxime **30** was obtained as an inseparable mixture of *syn* and *anti* products (1:1 ratio) which was clear from the NMR spectra. The mixture of oximes was treated as such with $POCl_3$ in ethyl acetate to afford the BR product[31] **31** in 87% yield. In this case also, though the starting oxime was a mixture of isomers, selectively a single product was obtained, indicating the possibility of conversion of one isomer of oxime to the other during the reaction course followed by BR. This method thus gives a better result than a similar report in literature which uses PPA/BIT as a reagent for the rearrangement.[32]



Scheme 6. Reagents and Conditions: a) Methyl methacrylate, PPA, 140 °C, 10 h, 80%; b) $NH_2OH.HCl$, NaOH, MeOH, rt, 1 h, 98%; c) $POCl_3$, EtOAc, 60 °C, 1 h, 87%.

Conclusions

In this work, Beckmann rearrangement was successfully used to synthesize derivatives of biologically active scaffolds. The synthesis of two β-carbolinone, three new γ-carbolinone, new pyrrolopyridinone and tetrahydroisoquinolinone derivatives was achieved in good to moderate yields.

Experimental Section

General. All reactions were carried out under an inert atmosphere with dry solvents, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (Kieselgel 60 F254, Merck). Visualization of the spots on TLC plates was achieved either by UV light or by staining the plates in 2, 4-dinitrophenylhydrazine/anisaldehyde and charring on hot plate. All products were characterized by ^{1}H NMR and ^{13}C NMR, IR and HRMS/elemental analysis. ^{1}H NMR and ^{13}C NMR were recorded on Varian Mercury 300 MHz and 75 MHz instrument respectively. Chemical shifts are expressed in parts per million values and ^{1}H NMR spectra are referenced to 0.00 ppm for Me_4Si (TMS) and ^{13}C NMR spectra are referenced to 77.00 ppm for $CDCl_3$. Peak multiplicities are designated by the following abbreviations: s, singlet; brs, broad singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; exch, D_2O exchangeable; J, coupling constant in Hertz. IR spectra were recorded on Bruker instrument as ATR and PerkineElmer 1600 instrument as KBr. Mass spectra were recorded on a Shimadzu QP 5050. HRMS spectra were obtained on a Micromass Q-TOF apparatus. Elemental analyses were recorded on Flash EA1112 Thermo instrument. Melting points recorded are uncorrected. Column chromatography on silica gel (100-200 mesh) was performed with reagent grade ethyl acetate and hexane as an eluent.

(*E*)-Ethyl 3-(1*H*-indol-3-yl)acrylate (1). Prepared according to literature[33] procedure (mp 117-119 °C).

Ethyl 3-(1*H*-indol-3-yl)propanoate (2). Prepared according to literature[34] procedure (mp 44-45 °C).

3-(1*H*-Indol-3-yl)propanoic acid (3). Prepared according to literature[35] procedure (mp 132- 135 °C).

1,2-Dihydrocyclopenta[*b*]indol-3(4*H*)-one[36] (4). 3-(1*H*-Indol-3-yl)propanoic acid (**3**, 2.08 g, 0.011 mol) was added to a solution of polyphosphoric acid (PPA, 10 g) in toluene (30 mL). The mixture was stirred at 110 °C for 4h, and then ice water (100 mL) was added to it. The aqueous layer was extracted three times with heated ethyl acetate. The combined organic phases were dried with sodium sulphate, and the solvent was evaporated. The residue was purified by column chromatography to get the compound **4** in 76% yield; mp 241- 243 °C.

4-Methyl-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-one[37] (5). Prepared according to literature procedure (mp 135 -136 °C).

1,2-Dihydrocyclopenta[*b*]indol-3(4*H*)-one oxime[38] (6). Prepared according to literature procedure (mp 168- 170 °C).

4-Methyl-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-one oxime[24,25] (7). To a solution of 4- methyl-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-one (0.64 g, 0.0032 mol) in methanol (20 mL), hydroxylamine hydrochloride (0.9 g, 0.013 mol) and (1.0 mL, 0.013 mol) of pyridine were added, the reaction mixture was heated on water bath for 10 hours. The reaction was monitored by tlc. After confirming the absence of starting compound, the reaction mixture was kept to cool when pale yellow crystals separated out. Methanol was removed on rota evaporator, crushed ice was added, and the solid was filtered off as a pale yellow crystalline compound **7** in 95% yield. mp 194-196 °C; FTIR (KBr cm^{-1}) 3263, 1659; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (1H, brs, exch., -O*H*), 7.52 (1H, d, *J* 7.7 Hz, Ar*H*), 7.25 (2H, bd, *J* 7.2 Hz, Ar*H*), 7.1 (1H d, *J* 7.2 Hz, Ar*H*), 3.87 (3H, s, -NCH_3), 3.3 (2H,d, *J* 4.4 Hz, -CH_2), 2.97 (2H,d, *J* 4.4 Hz, -CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.4, 143.7, 137.6, 131.5, 123.6, 120.0, 119.5, 110.0, 31.6, 31.2, 21.6; HRMS (ESI) (M+H): 201.1022; Calculated for $C_{12}H_{13}N_2O$ 201.1028.

2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one[27] (8). To a solution of 1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-one oxime, **6** (0.47 g, 0.0025 mol) in dry THF, phosphorous oxychloride (0.5 mL, 0.005 mol) was added and the reaction mixture was heated on water bath at 60 °C for two hours. The reaction was monitored by tlc. During the course of the reaction, it was observed that the reaction was not going to completion. The reaction mixture was cooled and cold water was added drop wise. It was extracted with ethyl acetate, dried over sodium sulphate and concentrated by vacuum distillation. The crude product obtained was column chromatographed on alumina using hexane and ethyl acetate (50%) as an eluent yielding pure compound as a pale yellow crystalline compound in 45% yield; mp 183-185 °C.

9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one[28] (9). Prepared according to procedure for compound **8**. (Yield 40%; mp 198-199 °C).

Reaction of indole and methyl methacrylate. Polyphosphoric acid (5 g) was added to a mixture of indole (0.5 g, 0.0043 mol) and methyl methacrylate (15 mL). The reaction mixture was heated on oil bath at 100 °C for 5 min. Crushed ice was poured into the cooled reaction mixture with stirring and the reaction mixture was extracted with hot ethyl acetate. The organic layer was treated with saturated sodium bicarbonate, dried over sodium sulphate and concentrated by vacuum distillation. Crude product was thick brown liquid which was column chromatographed on silica using hexane and ethyl acetate as an eluent yielding dimer **10** of indole[30] as a white powder (40%), a pale yellow crystalline compound **11** (7%) and a white crystalline compound **12** (3%) which decomposed at 220 °C before melting.

2-Methyl-2,3-dihydrocyclopenta[*b*]indol-1(4*H*)-one[29] (11). mp 210- 212 °C; FTIR (KBr cm^{-1}) 3150, 1651; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.18 (1H, brs, exch., -N*H*), 7.9 (1H, d, *J* 3.0 Hz, Ar*H*), 7.4 (1H, dd, *J* 1.9 Hz, 6.0 Hz, Ar*H*), 7.2-7.34 (2H, m, Ar*H*), 3.3 (1H, dd, *J* 7.4 Hz, 17.4 Hz, –CH-*H*), 3.1 (1H, m, -C*H*), 2.7 (1H, brd, *J* 17.4 Hz, –CH-*H*), 1.4 (3H, d, *J* 7.4 Hz, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 196.6, 164.4, 141.2, 121.6, 120.1, 118.6, 117.0, 111.1, 45.6, 28.8, 16.1; HRMS (ESI) (M+H): 186.0913; Calculated for $C_{12}H_{12}NO$ 186.0919.

2-Methyl-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-one (12). mp 220 °C, decomp.; MS: m/z 185 M+, 170, 157, 129, 115, 85, 79, 63, and 51; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.28 (1H, brs, exch., -N*H*), 7.68 (1H, d, *J* 7.2 Hz, Ar*H*), 7.5 (1H, d, *J* 7.2 Hz, Ar*H*), 7.38 (1H d, *J* 7.2 Hz, Ar*H*), 7.17 (1H d, *J* 7.2 Hz, Ar*H*), 3.4 (1H,, dd, *J* 7.7 Hz, 16.8 Hz, –CH-*H*), 3.1 (1H, m, -C*H*), 2.7 (1H dd, *J* 1.9 Hz, 16.8 Hz –CH-*H*), 1.4 (3H, d, *J* 7.7 Hz, -CH_3); HRMS (ESI) (M+H): 186.0913; Calculated for $C_{12}H_{12}NO$ 186.0919.

2-Methyl-4-(phenylsulfonyl)-2,3-dihydrocyclopenta[*b*]indol-1(4*H*)-one (15). Prepared according to procedure for compound **11** using *N*-protected indole **14** in place of indole. Yield 70%; mp 156-157 °C; FTIR (KBr cm^{-1}) 1697; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97-8.04 (1H, m, Ar*H*), 7.9-7.97 (1H, m, Ar*H*), 7.84 (2H, dd, *J* 1.1 Hz, 8.2 Hz, Ar*H*), 7.58-7.66 (1H, m, Ar*H*), 7.46-7.56 (2H, m, Ar*H*), 7.26-7.4 (2H, m, Ar*H*), 3.58-3.72 (1H, dd, *J* 6.3 Hz, 18.4 Hz, –CH-*H*), 2.94-3.1 (2H, m, -C*H*, –CH-*H*), 1.38 (3H, d, *J* 7.4 Hz, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.8, 164.7, 140.3, 137.7, 134.5, 129.6, 126.7, 125.4, 124.7, 124.4, 122.4, 121.0, 113.8, 46.6, 32.6, 16.8; HRMS (ESI) (M+H): 326.0860; Calculated for $C_{18}H_{16}NO_3S$ 326.0851.

Deprotection of 2-methyl-4-(phenylsulfonyl)-2,3-dihydrocyclopenta[b]indol-1(4*H*)-one (15). Sodium ethoxide was prepared by adding sodium metal (0.23 g, 0.01 mol) in dry ethanol (30 mL), which was added immediately to a solution of **15** (3.52 g, 0.01 mol.), in dry ethanol. Then the reaction mixture was refluxed for 1h. The reaction was monitored by tlc, after completion of the reaction, ethanol was removed on rota evaporator, water was added to the residue. It was treated with dilute HCl and extracted with ethyl acetate; the solid obtained was a mixture of two compounds. Chromatographic separation on silica gel using hexane and ethyl acetate as an eluent furnished two compounds, **11** (40%) and **16** (50%).

4-Ethyl-2-methyl-2,3-dihydrocyclopenta[b]indol-1(4*H*)-one (16). mp 108–110 °C; FTIR (KBr cm^{-1}) 1674; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (1H, d, *J* 0.8 Hz, Ar*H*), 7.2-7.4 (3H, m, Ar*H*), 4.16 (2H, q, *J* 7.4 Hz, -CH_2CH$_3$), 3.3 (1H, dd, *J* 1.4 Hz, 6.9 Hz, –CH-*H*), 3.08 (1H, m, -C*H*),

2.61 (1H, dd, *J* 2.54 Hz, 17.1 Hz, –CH-*H*), 1.5 (3H, t, *J* 7.4 Hz, -CH_2CH_3), 1.4 (3H, d, *J* 7.4 Hz, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.7, 165.4, 141.9, 123.0, 121.9, 121.7, 120.9, 118.1, 110.0, 46.6, 39.4, 29.3, 17.4, 15.0; HRMS (ESI) (M+H): 214.1238; Calculated for $C_{14}H_{16}NO$ 214.1232.

2,4-Dimethyl-2,3-dihydrocyclopenta[*b*]indol-1(4*H*)-one[39] **(17).** Prepared according to literature procedure (mp 137-138 °C).

Preparation of oximes 18, 20 and 22. The oximes **18**, **20** and **22** were prepared according to procedure for compound **7**.

(*Z*)-2-Methyl-2,3-dihydrocyclopenta[b]indol-1(4*H*)-one oxime (18). Yield 82%; mp 168-170 °C; FTIR (KBr cm^{-1}) 3157, 1651; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.1 (1H, brs, exch., -N*H*), 9.8 (1H, brs, exch., -O*H*), 8.02 (1H, d, *J* 7.4 Hz, Ar*H*), 7.3 (1H, d, *J* 7.7 Hz, Ar*H*), 7.02-7.34 (2H, m, Ar*H*), 3.4 (1H, bm, -C*H*), 3.23 (1H, dd, *J* 7.4 Hz, 16.8 Hz, –CH-*H*), 2.6 (1H, bd, *J* 16.8 Hz, –CH-*H*), 1.35 (3H, d, *J* 6.8 Hz, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.2, 151.3, 140.4, 122.0, 121.3, 120.3, 118.6, 113.4, 110.4, 38.6, 30.6, 19.7; HRMS (ESI) (M+H): 201.1019; Calculated for $C_{12}H_{13}N_2O$ 201.1028.

(*Z*)-4-Ethyl-2-methyl-2,3-dihydrocyclopenta[*b*]indol-1(4*H*)-one oxime (20). Yield 99%; mp 202- 203 °C; FTIR (KBr cm^{-1}) 3271, 1670; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18 (1H, d, *J* 7.2 Hz, Ar*H*), 7.1-7.36 (3H, m, Ar*H*), 4.1 (2H, q, *J* 7.2 Hz, -CH_2CH_3), 3.52 (1H, m, -C*H*), 3.28 (1H, dd, *J* 3.0 Hz, 16.5 Hz, –CH-*H*), 2.6 (1H, dd, *J* 3.0 Hz, 16.5 Hz, –CH-*H*), 1.45 (1H, brs, exch., -O*H*), 1.38-1.45 (6H, m, 2 × -CH_3); HRMS (ESI) (M+H): 229.1335; Calculated for $C_{14}H_{17}N_2O$ 229.1341.

(*Z*)-2,4-Dimethyl-2,3-dihydrocyclopenta[*b*]indol-1(4*H*)-one oxime (22). Yield 95%; mp 218-220 °C; FTIR (KBr cm^{-1}) 2941(broad), 1657; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05 (1H, brs, Ar*H*), 7.14-7.5 (3H, m, Ar*H*), 4.40 (1H, brs, exch., -O*H*),3.8 (3H, s, -NCH_3), 3.28 (1H, bd, *J* 16.5 Hz, –CH-*H*), 2.8 (1H, bd, *J* 17.1 Hz, –CH-*H*), 2.58 (1H, bs, -C*H*), 1.3 (3H, d, *J* 6.6 Hz, -CH_3); HRMS (ESI) (M+H): 215.1176; Calculated for $C_{13}H_{15}N_2O$ 215.1184.

BR of oximes 18, 20 and 22 to give cyclic lactams 19, 21 and 23 respectively. The compounds **19**, **21** and **23** were prepared according to the procedure for compound **8**.

3-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-1-one (19). Yield 60%; mp 203- 205 °C; $C_{12}H_{12}N_2O$ requires: C, 71.98%; H, 6.04%, found: C, 72.40; H, 5.60; FTIR (KBr cm^{-1}) 3531, 3396, 1611; MS *m/z* 200 (M^+), 185, 171, 157, 129, 115; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.4 (1H, brs, exch., -N*H*), 8.18 (1H, d, *J* 8.3 Hz, Ar*H*), 7.2-7.8 (3H, m, Ar*H*), 5.2 (1H, brs, exch., -N*H*CO)**,** 3.94-4.1 (1H, m, -C*H*), 2.7-3.0 (2H, m, -CH_2**),** 1.4 (3H, d, *J* 6.3 Hz, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.6, 142.6, 134.9, 124.0, 120.4, 119.5, 118.7, 110.2, 103.8, 46.8, 29.4, 20.1.

5-Ethyl-3-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-1-one (21). Yield 65%; mp 220-221 °C; $C_{14}H_{16}N_2O$ requires: C, 73.66%; H, 7.06%, found: C, 74.15%; H, 7.60%; FTIR (KBr cm^{-1}) 3202, 1655; MS *m/z* 228 M^+, 213, 185, 157, 129, 115, 101, 77; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.2-8.3 (1H, m, Ar*H*), 7.27-7.36 (1H, m, Ar*H*), 7.18-7.27(2H, m, Ar*H*), 5.38 (1H, brs, exch., -N*H*), 4.12 (2H, q, *J* 9.4 Hz, -CH_2CH_3), 3.93-4.07 (1H, m, -C*H*), 2.98 (1H, dd, *J* 5.0 Hz, 16.0 Hz,

–CH-*H*), 2.75 (1H, dd, *J* 11.0 Hz, 16.0 Hz, –CH-*H*), 1.34-1.46 (6H, m, 2 × -C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.6, 143.5, 136.2, 125.3, 122.0, 121.5, 120.8, 109.2, 105.0, 47.9, 38.3, 29.4, 21.4, 15.3.

3,5-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-1-one (23). Yield 70%; mp 237-240 °C; $C_{13}H_{14}N_2O$ requires: C, 72.87%; H, 6.59%, found: C, 72.48%; H, 6.98%; FTIR (KBr cm^{-1}) 3402, 1649; MS *m/z* 214 M^+, 199, 185, 171, 156, 143, 128, 115; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13 (1H, dd, *J* 5.8 Hz, 3.3 Hz, Ar*H*), 7.14-7.3 (3H, m, Ar*H*), 5.29 (1H, brs, exch., -N*H*), 3.99 (1H, m, -C*H*), 3.65 (3H, s, -NC*H*$_3$), 2.97 (1H, dd, *J* 16 Hz, 5.0 Hz, -CH-*H*), 2.7 (1H, dd, *J* 11.3 Hz, 15.9 Hz, -CH-*H*), 1.4 (3H, d , *J* 6.3 Hz, -C*H*$_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.4, 144.9, 136.9, 124.6, 121.2, 120.7, 119.4, 109.9, 104.1, 47.2, 29.6, 28.6, 21.0.

1-(Phenylsulfonyl)-1*H*-pyrrole (24). Prepared according to literature procedure (mp[40] 89-90 °C).

5-Methyl-1-(phenylsulfonyl)-5,6-dihydrocyclopenta[*b*]pyrrol-4(1*H*)-one (25). In a round bottom flask equipped with a reflux condenser, were taken 1-(phenylsulfonyl)-1*H*-pyrrole (**24**) (5 g, 24 mmol), methyl methacrylate (excess, ~ 15-20 mL) and PPA (~ 10 g). The contents were refluxed for 10h and the reaction was followed by TLC. After completion of reaction, the reaction mixture was quenched by addition of ice cold water and extracted with hot ethyl acetate. Evaporation of the solvent under reduced pressure followed by column chromatography gave compound **25** as a white solid in 85% yield. mp 93-94°C; FTIR (ATR cm^{-1}) 2968, 1690, 1580, 1369, 1175, 773; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18-8.21 (2H, m, Ar*H*), 7.50-7.66 (4H, m, Ar*H*), 6.24 (1H, d, *J* 2.8 Hz, Ar*H*), 3.02 (1H, dd, *J* 6.7 Hz, 17.2 Hz, ArC*H*-H), 2.86-2.94 (1H, m, -C*H*), 2.38 (1H, dd, *J* 2.4 Hz, 17.2 Hz, ArC*H*-H), 1.25 (3H, d, *J* 7.1 Hz, -C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.6, 157.2, 137.8, 134.3, 133.6, 132.8, 129.2, 128.2, 108.9, 47.4, 29.3, 16.7; HRMS (ESI) (M+Na) 298.0506; Calculated for $C_{14}H_{13}NO_3SNa$ 298.0508.

5-Methyl-5,6-dihydrocyclopenta[*b*]pyrrol-4(1*H*)-one (26). To a solution of 5-methyl-1-(phenylsulfonyl)-5,6-dihydrocyclopenta[*b*]pyrrol-4(1*H*)-one (**25**) (0.2 g, 0.7 mmol) in methanol (10 mL), was added sodium hydroxide (0.06 g, 1.4 mmol) and the mixture was stirred at room temperature for 1h. After the completion of reaction, methanol was evaporated under reduced pressure to get a white solid of compound **26** in 98% yield. mp 116-117 °C; FTIR (ATR cm^{-1}) 3218 (br), 2958, 1654, 1489, 1455, 736; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.22 (1H, brs, (exch.) -N*H*), 7.36 (1H, t, *J* 2.3 Hz, Ar*H*), 6.12 (1H, d, *J* 1.7 Hz, Ar*H*), 3.13 (1H, dd, *J* 6.4, 17 Hz, ArC*H*-H), 2.99-3.1 (1H, m, C*H*), 2.47 (1H, dd, *J* 2.4 Hz, 17 Hz ArC*H*-H), 1.33 (3H, d, *J* 7.1 Hz C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 195.3, 152.3, 133.4, 133.1, 105.8, 47.6, 29.7, 17.2; HRMS (ESI) (M+H) 136.0758; Calculated for $C_8H_{10}NO$ 130.0757;

5-Methyl-5,6-dihydrocyclopenta[*b*]pyrrol-4(1*H*)-one oxime (27). In a round bottom flask, hydroxyl amine hydrochloride (0.5 g, 7.4 mmol) and pyridine (0.6 mL, 7.4 mmol) were added to a solution of 5-methyl-5,6-dihydrocyclopenta[*b*]pyrrol-4(1*H*)-one (**26**) (0.5 g, 3.7 mmol) in methanol under inert atmosphere. The reaction mixture was refluxed for 5h at 80 °C. After the completion of reaction, methanol was evaporated under reduced pressure and the residue was extracted with ethyl acetate. Evaporation of the solvent under reduced pressure gave compound

27 as a white solid in 95% yield. mp 150-152 °C; FTIR (ATR cm^{-1}) 3046 (br), 2923, 1653, 1442, 809; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.07 (1H, brs, (exch.) -N*H*), 6.98 (1H, t, *J* 2.6 Hz, Ar*H*), 6.04 (1H, s, ArH), 3.36-3.42 (1H, m, CH), 3.07 (1H, dd, J 7.5 Hz, 15.8 Hz, ArC*H*-H), 2.40 (1H, dd, *J* 3.7 Hz, 15.8 Hz, ArC*H*-H), 1.34 (3H, d, *J* 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.1, 149.6, 137.8, 136.1, 104.6, 40.7, 32.3, 20.1; HRMS (ESI) (M+H) 151.0866; Calculated for $C_8H_{11}N_2O$ 151.0866;

6-Methyl-6,7-dihydro-1*H*-pyrrolo[3,2-c]pyridin-4(5*H*)-one (28). To a solution of 5-methyl-5,6-dihydrocyclopenta[*b*]pyrrol-4(1*H*)-one oxime (**27**) (0.4 g, 2 mmol) in ethyl acetate, was added phosphorus oxychloride (0.5 mL, 5 mmol) dropwise under inert atmosphere at 0 °C. The reaction mixture was stirred for 30 min and then cold water was added slowly to the mixture followed by extraction with ethyl acetate. Evaporation of the solvent under reduced pressure followed by column chromatography gave compound **28** as a white solid in 80% yield. mp 200 °C (decomp.); FTIR (ATR cm^{-1}) 3206 (br), 1633, 1557, 1429, 1137, 733; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.23 (1H, brs, (exch.) –N*H*), 6.89 (1H, t, *J* 2.4 Hz, Ar*H*), 6.07 (1H, bs, Ar*H*), 5.12 (1H, brs, (exch.) –N*H*), 3.89-3.97 (1H, m, NC*H*), 2.80 (1H, dd, *J* 4.8 Hz, 15.3 Hz, ArC*H*-H), 2.60 (1H, dd, *J* 11.4 Hz, 15.7 Hz, ArC*H*-H), 1.33 (3H, d, *J* 6.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.8, 124.2, 124.0, 107.4, 105.2, 50.9, 36.0, 29.6; HRMS (ESI) (M+Na) 173.0686; Calculated for $C_8H_{10}N_2ONa$ 173.0685;

6-Methoxy-2-methyl-2,3-dihydro-1*H*-inden-1-one (29). Prepared according to procedure for compound **25**. Obtained as viscous oil.[41]

6-Methoxy-2-methyl-2,3-dihydro-1*H*-inden-1-one oxime (30). In a round bottom flask, hydroxyl amine hydrochloride (0.7 g, 10.2 mmol) and sodium hydroxide (0.4 g, 10.2 mmol) were added to a solution of 6-methoxy-2-methyl-2,3-dihydro-1*H*-inden-1-one (**29**) (0.9 g, 5.1 mmol) in methanol. The reaction mixture was stirred at room temperature for 1h. After the completion of reaction, methanol was evaporated under reduced pressure and the residue was extracted with ethyl acetate. Evaporation of the solvent under reduced pressure followed by column chromatography gave yellow solid of compound **30** as a mixture of *syn* and *anti* isomers (1:1) in 98% yield. mp 86-88 °C; FTIR (ATR cm^{-1}) 3154 (br), 2925, 1602, 1440, 1248, 943, 817; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.36 (1H, d, *J* 8.4 Hz, Ar*H*), 7.56 (1H, d, *J* 8.3 Hz, Ar*H*), 6.79-6.85 (4H, m, Ar*H*), 3.83 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.55 (1H, m, CH_2 / C*H*), 3.09-3.30 (3H, 2 × m, CH_2 / C*H*), 2.53-2.66 (2H, m, CH_2 / C*H*), 1.33 (6H, 2 × d, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.3, 162.9, 161.9, 161.9, 149.9, 148.9, 130.9, 129.9, 127.7, 126.2, 122.9, 114.3, 113.3, 109.7, 55.4, 55.3, 38.2, 38.1, 36.5, 34.4, 19.8, 18.3; HRMS (ESI) (M+Na) 192.1020; Calculated for $C_{11}H_{14}O_2N$: 192.1019;

7-Methoxy-3-methyl-3,4-dihydroisoquinolin-1(2*H*)-one[31] **(31).** Prepared according to procedure for compound **8**. (mp 150-151 °C).

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