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A rapid method toward the synthesis of new substituted tetrahydro α-carbolines and α-carbolines

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ABSTRACT

A rapid and efficient method for stereoselective synthesis of new substituted tetrahydro-α-carbolines using Diels–Alder reaction under microwave irradiation has been developed. Further, dehydrogenation of these adducts resulted in synthesis of new substituted α-carbolines.

1. Introduction

Pyrido[2,3-*b*]indole (α-carbolines) scaffold is prevalent in a variety of naturally occurring and synthetic molecules displaying various biological properties. This skeleton is found in several alkaloids[1] and carcinogenic metabolites.[2] Moreover, some α-carboline derivatives, which are anxiolytic or neuroprotectant agents,[3] also exhibit antiviral and antitumor activities.[4] It is reported that replacement of a carbon atom by a nitrogen atom in the carbazole unit could increase the affinity for the binding site on the target enzyme(s) and also modify the electronic distribution of the aromatic framework and the lipophilicity of the molecule.[5] Consequently, the development of efficient ways to synthesize this class of compounds continues to be an active area of research.

In our earlier work[6] substituted carbazoles have been prepared regio- and stereoselectively using Diels–Alder reactions from 3-vinyl indoles. In continuation of this work we have extended this strategy of Diels–Alder reactions using 3-vinyl azaindole toward the synthesis of substituted α-carbolines.

Microwave irradiation is used to achieve fast, clean and high-yielding transformations. There are various reviews[7] in literature, which reveals efficient use of microwave in organic synthesis. We herein report the use of same technique for facile synthesis of substituted tetrahydro-α-carbolines. The choice of *N*-substituted maleimides as dienophile was based on the importance of imido substituted α-carbolines in displaying anticarcinogenic activity.[4]

2. Result and discussion

Formylation of 7-azaindole (**1**) using Vilsmeier Haack reaction[8] at 85 °C followed by protection using benzenesulphonylchloride in presence of NaH furnished protected aldehyde **3** (Scheme 1). Olefination of aldehyde by Wittig reaction afforded diene **4** in 68% yield. The Diels–Alder reaction of diene **4** with *N*-phenyl maleimide (**5a**) was carried out by adsorbing them on silica gel and irradiating under microwave (700 watts) at 75 °C 10 min to afford compound **6a** in 88% yield. Elemental analysis and spectral data of purified product revealed that Diels–Alder reaction has occurred with high stereoselectivity furnishing *endo* product **6a** and no traces of other diasteromer (*exo*) was observed.

2.1. Sterochemistry of the Diels–Alder adduct 6a

As Diels–Alder reaction involves *supra–supra* interaction, the geometry at C_7 and C_8 must be *cis*. The only newly generated stereocentre that needs to be established is C_9. One isomer (*endo*) will have H_7, H_8, and H_9 all *cis* while the other isomer (*exo*) will have H_8 and H_9 *trans*. The isomer **6a** (Fig. 1) corresponds to *endo* geometry, which is the one usually observed in Diels–Alder reaction due to secondary orbital overlap. The value of J_{H8-H9} observed in

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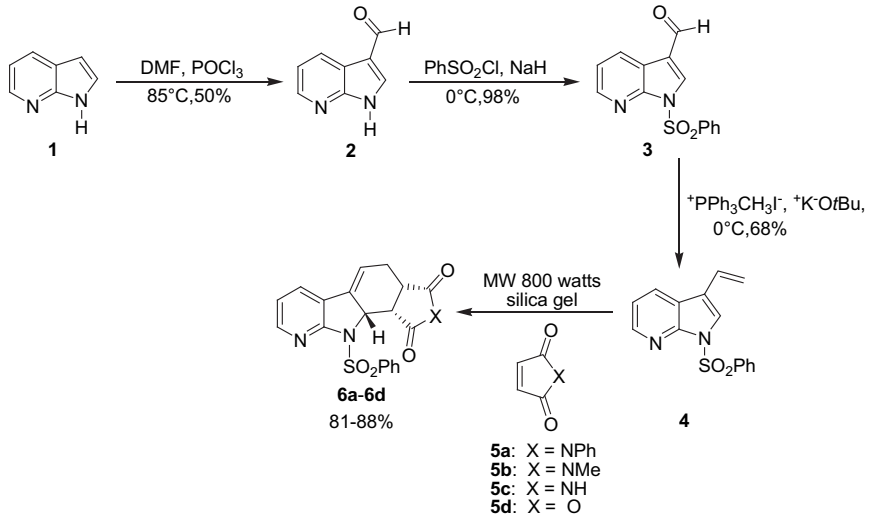


Scheme 1.

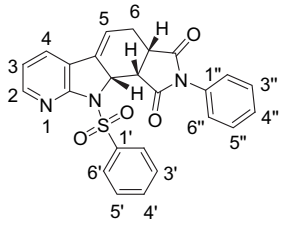


Figure 1.

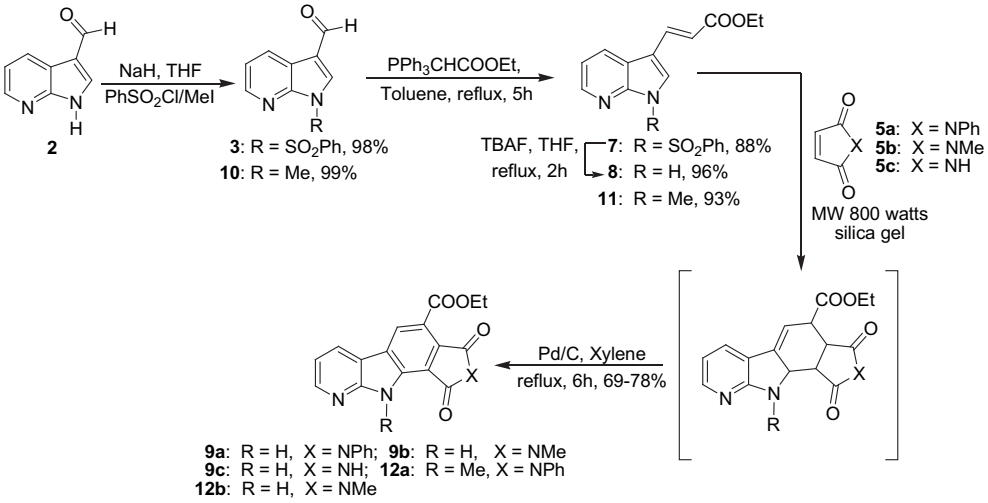
^{1}H NMR was 6.8, which corroborates with the *endo* stereo structure of **6a**. In keeping with this structure J_{H7-H8}=9 Hz is consistent with a dihedral angle ~0°. Earlier Pfeuffer and Pindur[9] using 3-vinyl indole as diene also assigned *endo* geometry for a similar type Diels–Alder adduct. The ^{1}H NMR values and coupling constants are consistent with those obtained by us.

Other dienophiles such as **5b**–**d** were also used for the above Diels–Alder reaction furnishing cycloadducts **6b**–**d** in 81, 88, and 85% yields, respectively. All these cycloadducts showed spectral data similar to **6a** indicating the formation of *endo* adduct in all the cases.

Next, dehydrogenation of **6a** was attempted using DDQ in xylene, but without success. This could be attributed to the presence bulky protecting group in the substrate. We modified the strategy by carrying out deprotection at the first step followed by dehydrogenation. Various reagents like Na–MeOH, TBAF–THF, and NaOH–MeOH were screened for the removal of phenylsulphonyl group, but all remain unsuccessful and starting was recovered. Similar results were observed during our previous work on the synthesis of carbazole derivatives. This may be explained by the steric hindrance of *endo* five membered ring for the approach of the base.

Further, it was thought to use deprotected diene **8** for the Diels–Alder reaction. Thus Wittig–Horner reaction of aldehyde **3** with carbethoxymethylenetriphenyl phosphorane afforded the diene **7**. Deprotection of compound **7** with tetrabutylammonium fluoride in dry THF furnished diene **8** in 99% yield. To our surprise Diels–Alder reaction of diene **8** with dienophiles **5a** resulted in the formation of cycloadduct, which was a mixture of diastereomers as detected in TLC. It was directly utilized for dehydrogenation without purification using 10% Pd/C to furnish α-carbolines **9a**. Similarly Diels–Alder reaction of **8** with other dienophiles **5b** and **5c** resulted in the formation of α-carbolines **9b** and **9c** (Scheme 2).

After establishing an efficient new route toward α-carbolines, we desired to extend our sequence of cycloaddition and dehydrogenation to achieve the synthesis of *N*-methyl α-carbolines. Thus aldehyde **2** was protected to obtain *N*-methyl aldehyde **10**, which intern was



Scheme 2.

converted to diene **11**. Diels–Alder reaction of diene **11** with **5a** and **5b** resulted in the formation of cycloadducts, which were dehydrogenated to *N*-methyl α-carbolines **12a** and **12b** (Scheme 2).

3. Conclusion

In conclusion a rapid and efficient method was established for synthesis of tetrahydro-α-carbolines via Diels–Alder reaction under microwave irradiation. Similar report[10] on Diels–alder reactions using other dienophiles under conventional heating required longer time and resulted in less yield (40–50%). During the present study nine new substituted tetrahydro-α-carbolines were synthesized, amongst those four compounds obtained stereoselectively, were isolated and fully characterized. Other five were dehydrogenated to the new substituted α-carbolines.

4. Experimental

4.1. General

Melting points determined are uncorrected. All solvents were of reagent grade and, when necessary, were purified and dried by standard methods. Reactions and products were routinely monitored by thin layer chromatography (TLC) on silica gel (Kieselgel 60 F_{254}, Merck). Column chromatographic purifications were performed using 100–200 mesh silica gel.

IR spectra were recorded on Shimadzu 8400 instrument. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Varian Mercury instrument using TMS as internal standard. ^{1}H NMR peaks expressed as s, br s, d, t, m correspond to singlet, broad-singlet, doublet, triplet, and multiplet, respectively. Mass spectra were recorded on Shimadzu QP 5050. Elemental analysis was recorded on Flash E. A. 1112 Thermo instrument. Microwave activated reactions were carried out in Raga electromagnetic system with IR sensor at 700 watt. All the analysis was carried out at Department of Chemistry, University of Pune, Pune, India.

4.2. Preparation of protected 1-[*H*]-pyrrolo[2,3-*b*]–pyridine-3-carbaldehyde (3 and 10)

To a cooled (0 °C) suspension of sodium hydride (0.40 g, 0.01 mol) in dry THF (30 ml), aldehyde **2** (1.46 g, 0.01 mol) was added and stirred at rt for 15–20 min. To this, alkyl halide (benzenesulphonylchloride/methyl iodide 0.015 mol) was added dropwise. The solution was stirred for two hours and progress of the reaction was monitored by TLC. After completion of the reaction, it was quenched with water and THF was removed under vacuo. The reaction mixture was then extracted with DCM, washed with brine and dried. The solvent was removed and the residue thus obtained was chromatographed on silica gel using 20% hexane–ethyl acetate as an eluent to afford the product as colorless solid.

4.2.1. Compound ***3***. Yield: 2.80 g, 98%; colorless solid, mp; 152–153 °C; R_f (30% Hexane/Ethyl Acetate) 0.42, IR ($CHCl_3$): 3066, 1658, 1543 cm^{-1}; ^{1}H NMR (DMSO-d_6): 7.42 (dd, 1H, *J*=4.6, 7.7 Hz, Ar*H*), 7.63–7.68 (m, 2H, Ar*H*), 7.41–7.52 (t, 1H, *J*=7.4 Hz, C_4H), 8.22 (d, 2H, *J*=7.7 Hz, Ar*H*), 8.40–8.47 (m, 2H, Ar*H*), 8.99 (s, 1H, C_2H), 10.06 (s, 1H, C*HO*); ^{13}C NMR (DMSO-d_6): 118.24, 118.74, 120.99, 128.02, 129.71, 130.63, 135.34, 136.45, 137.74, 146.26, 146.59, 186.73; *m*/*z* 286 (M^+).

4.2.2. Compound ***10***. Yield: 1.58 g, 99%; Elemental analysis for $C_9H_8N_2O$: requires: C, 67.46; H, 5.03; N, 17.49; found: C, 67.42; H, 4.98; N, 17.54; R_f (30% Hexane/Ethyl Acetate) 0.35, IR ($CHCl_3$): 2247, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$): 3.92 (s, 3H, NCH_3), 7.21 (t, 1H, *J*=2.7, 7.4 Hz, C_5H), 7.80 (s, 1H, C_2H), 8.38 (d, 1H, *J*=3.0 Hz, C_4H), 8.48 (d, 1H, *J*=6.6 Hz, C_6H), 9.89 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): 31.93, 115.85, 117.20, 118.56, 130.12, 138.85, 144.77, 148.28, 184.10; *m*/*z* 160 (M^+).

4.3. Preparation of phenylsulfonyl-3-vinyl-1*H*-pyrrolo[2,3-*b*] pyridine (4)

Potassium-*tert*-butoxide was freshly prepared from potassium (0.46 g, 0.012 mol) and anhydrous *tert*-butanol (5 ml) in nitrogen atmosphere. In 100 ml three necked flask provided with a nitrogen inlet and a dropping funnel was placed, the suspension of methyltriphenyl phosphonium iodide (4.8 g, 0.012 mol) in freshly distilled anhydrous THF (20 ml). The apparatus was swept with dry nitrogen at rt. To the stirred suspension of the salt, potassium-*tert*-butoxide in dry THF (5 ml) was added dropwise for 10 min. The resulting dark yellow colored phosphorane was kept stirring for 20 min. Protected 1-[*H*]-pyrrolo[2,3-*b*]–pyridine-3-carbaldehyde (**3**) (1.7 g, 0.006 mol) in dry THF (5 ml) was added dropwise. After complete addition of aldehyde, the color of reaction mixture turned brown. Stirring was continued for two hours and it was decomposed with water. THF was distilled out and then extracted with DCM. The DCM layer was dried over sodium sulfate and evaporated. The residue was chromatographed on silica using 20% hexane–ethyl acetate to give brown solid.

4.3.1. Compound ***4***. Yield: 1.14 g, 68%; mp: 114–116 °C; Elemental analysis for $C_{15}H_{12}N_2O_2S$: requires: C, 63.36; H, 4.25; N, 9.85; found: C, 63.39; H, 4.29; N, 9.81; R_f (30% Hexane/Ethyl Acetate) 0.39, IR ($CHCl_3$): 3075, 1628, 1342, 1145 cm^{-1}; ^{1}H NMR ($CDCl_3$): 5.37 (d, 1H, *J*=11.2 Hz, CH_2), 5.77 (d, 1H, *J*=17.6 Hz, CH_2), 6.74 (dd, 1H *J*=11.2, 17.8 Hz, C*H*), 7.22 (dd, 1H, *J*=3.3, 7.9 Hz, Ar*H*), 7.45–7.5 (m, 3H, Ar*H*), 7.74 (s, 1H, Ar*H*), 8.07 (d, 1H, *J*=7.9 Hz, C_4H), 8.19 (m, 2H, Ar*H*), 8.44 (d, 1H, *J*=4.6 Hz, C_6H); ^{13}C NMR ($CDCl_3$): 115.18, 117.41, 118.81, 120.77, 123.80, 127.07, 127.54, 128.66, 128.74, 133.75, 137.67, 144.74, 147.17; *m*/*z* 284 (M^+).

4.4. Cycloaddition reaction of 1-phenylsulfonyl-3-vinyl-1*H*-pyrrolo[2,3-*b*]pyridine with maleic anhydride and different maleimides in microwave (6(a–d))

1-Phenylsulfonyl-3-vinyl-1H-pyrrolo[2,3-*b*]pyridine (0.0003 mol) and the dienophile (**5a**/**5b**/**5c**/**5d**) (0.0003 mol) were adsorbed on 0.3 g silica (100–200 mesh) and irradiated in a microwave oven (700 watts) at 75 °C for 8–10 min. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was directly loaded on a silica gel column and eluted with hexane–ethyl acetate to afford the products given below.

4.4.1. Compound ***6a***. Yield: 0.016 g, 88%; mp: 185–186 °C; Elemental analysis for $C_{25}H_{19}N_3O_4S$: requires: C, 65.63; H, 4.19; N, 9.18; found: C, 65.59; H, 4.12; N, 9.11; R_f (2% CH_2Cl_2/MeOH) 0.66; IR (KBr): 3441, 2332, 1635 cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.32–2.40 (m, 1H, C_6H), 3.14 (dd, 1H, *J*=7.4, 15.6 Hz, C_6H), 3.41 (t, 1H, *J*=7.7 Hz, C_7H), 4.31 (dd, 1H, *J*=6.8, 9.0 Hz, C_8H), 5.06–5.10 (m, 1H, C_9H), 6.27–6.32 (m, 1H, C_5H), 6.86 (dd, 1H, *J*=5.0, 7.4 Hz, C_3H), 7.02–7.05 (m, 2H, ArH), 7.27–7.36 (m, 3H, ArH), 7.46–7.59 (m, 4H, ArH), 8.15 (t, 1H, *J*=3.5 Hz, C_2H), 8.30 (m, 2H, $C_{2''}H$, $C_{6''}H$); ^{13}C NMR (DMSO-d_6): 25.78, 37.42, 42.55, 59.97, 115.70, 118.44, 119.25, 126.16, 128.47, 128.53, 128.63, 128.85, 131.33, 133.30, 135.03, 138.89, 149.07, 157.63, 172.94, 177.50; *m*/*z* 457(M^+).

4.4.2. Compound ***6b***. Yield: 0.013 g, 81%; mp: oil; Elemental analysis for $C_{20}H_{17}N_3O_4S$: requires: C, 60.75; H, 4.33; N, 10.63; found: C, 60.68; H, 4.29; N, 10.58; R_f (2% CH_2Cl_2/MeOH) 0.44; IR (KBr): 3446, 2958, 1695 cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.66–2.78 (m, 4H, CH_3, C_6H), 3.30–3.37 (m, 2H, C_6H, C_7H), 4.03 (t, 1H, *J*=7.7 Hz, C_8H), 5.12 (t, 1H, *J*=3.3 Hz, C_9H), 6.39 (t, 1H, *J*=3.3 Hz, C_5H), 6.95 (t, 1H, *J*=7.4 Hz,

$C_{4'}H$), 7.55(m, 2H, $C_{3'}H$, $C_{5'}H$), 7.65 (t, 1H, J=6.8 Hz, C_4H), 7.79 (d, 1H, J=7.7 Hz, C_3H), 8.06 (d, 1H, J=4.4 Hz, C_2H), 8.12 (m, 2H, $C_{2'}H$, $C_{6'}H$); ^{13}C NMR (DMSO-d_6): 24.49, 36.99, 43.02, 48.84, 59.88, 117.55, 118.64, 119.36, 127.75, 128.69, 129.25, 133.38, 133.44, 138.19, 147.89, 156.56, 174.61, 178.69; m/z 395 (M^+).

4.4.3. Compound ***6c***. Yield: 0.013 g, 88%; mp: oil; Elemental analysis for $C_{19}H_{15}N_3O_4S$: requires: C, 59.83; H, 3.96; N, 11.02; found: C, 59.72; H, 3.91; N, 10.93; R_f (2% CH_2Cl_2/MeOH) 0.42; IR (KBr): 3362, 1665, 1358, 1156 cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.31–2.49 (m, 1H, C_6H), 2.71 (dd, 1H, J=6.8, 14.5 Hz, C_6H), 3.25 (t, 1H, J=7.9 Hz, C_7H), 3.98 (t, 1H, J=7.1 Hz, C_8H), 5.06–5.08 (m, 1H, C_9H), 6.45 (t, 1H, J=3.5 Hz, C_5H), 6.98 (dd, 2H, J=5.2, 7.4 Hz, $C_{3'}H$, $C_{5'}H$), 7.53–7.65 (m, 1H, C_4H), 7.82 (d, 2H, J=7.4 Hz, C_3H, $C_{4'}$H), 8.07–8.13 (m, 3H, $C_{2'}H$, $C_{3'}H$, C_2H), 11.11 (s, 1H, NH);^{13}C NMR (DMSO-d_6): 24.60, 31.12, 43.99, 59.94, 117.86, 118.77, 119.63, 127.89, 128.85, 129.36, 133.62, 138.35, 148.08, 156.77, 176.19, 180.28; m/z 381 (M^+).

4.4.4. Compound ***6d***. Yield: 0.013 g, 85%; mp: 224–225 °C; Elemental analysis for $C_{19}H_{14}N_2O_5S$: requires: C, 59.68; H, 3.69; N, 7.33; found: C, 59.62; H, 3.65; N, 7.28; R_f (2% CH_2Cl_2/MeOH) 0.46; IR (KBr): 3015, 1673, 1343, 1168 cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.78 (dd, 1H, J=7.1, 15.4 Hz, C_6H), 3.70 (dd, 1H, J=7.7, 9.0 Hz, C_6H), 4.38 (dd, 1H, J=7.1, 9.3 Hz, C_7H), 5.17 (dd, 1H, J=3.3, 6.8 Hz, C_8H), 6.52 (dd, 1H, J=3.8, 7.1 Hz, C_9H), 7.01(m, 1H, C_5H), 7.53–7.68 (m, 4H, ArH), 7.86 (dd, 1H, J=1.3, 7.4 Hz, C_2H), 8.10 (m, 3H, ArH); m/z 216 (M^+).

4.5. Preparation of 1-alkyl-3-(2-carbethoxyvinyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7 and 11)

To the solution of protected aldehyde **3** or **10** (0.006 mol) in dry toluene (20 ml), carbethoxymethylenetriphenyl phosphorane (4.1 g, 0.012 mol) was added and the reaction mixture was refluxed for 4–5 h. The progress of the reaction was monitored by TLC till the aldehyde was consumed. After completion, the reaction mixture was concentrated and directly loaded on a silica gel column and eluted with hexane–ethyl acetate to afford the product.

4.5.1. Compound ***7***. Yield: 88%; mp: 166–167 °C; Elemental analysis for $C_{18}H_{16}N_2O_4S$: requires: C, 60.66; H, 4.53; N, 7.86; found: C, 60.62, H, 4.49, N, 7.90; R_f (30% Hexane/Ethyl Acetate) 0.42, IR ($CHCl_3$): 2345, 1608, 1030, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.34 (t, 3H, J=6.7 Hz, CH_3), 4.27 (q, 2H, J=6.8 Hz, CH_2), 6.45 (d, 1H, J=15.9 Hz, olefinic proton), 7.25 (dd, 2H, J=4.4, 7.9 Hz, ArH), 7.46–7.58 (m, 2H, ArH), 7.72 (d, 1H, J=15.9 Hz, olefinic proton), 7.97 (s, 1H, C_2H), 8.11 (dd, 1H, J=1.3, 7.8 Hz, C_4H), 8.19 (t, 2H, J=1.3, 8.8 Hz, ArH), 8.46 (dd, 1H, J=1.3, 4.6 Hz, C_6H); ^{13}C NMR ($CDCl_3$): 14.42, 60.63, 114.97, 118.47, 119.50, 120.34, 128.12, 129.02, 129.19, 134.29, 135.23, 137.56, 142.19, 145.62, 166.63, 172.48; m/z 356 (M^+).

4.5.2. Compound ***11***. Yield: 93%; mp: 75–77 °C; Elemental analysis for $C_{13}H_{14}N_2O_2$: requires: C, 67.81; H, 6.13; N, 12.17; found: C, 67.84, H, 6.17, N, 12.22; R_f (50% Hexane/Ethyl Acetate) 0.32, IR ($CHCl_3$): 3054, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.34 (t, 3H, J=7.1 Hz, CH_3, CH_2), 3.89 (s, 3H, NCH_3), 4.25 (q, 2H, J=6.8 Hz, CH_2), 6.35 (d, 1H, J=15.9 Hz, olefinic proton), 7.16 (dd, 1H, J=4.9, 7.7 Hz, C_4H), 7.45 (s, 1H, C_2H), 7.78 (d, 1H, J=15.9 Hz, olefinic proton), 8.16 (d, 1H, J=7.7 Hz, C_6H), 8.36 (d, 1H, J=4.1 Hz, C_5H); ^{13}C NMR ($CDCl_3$): 14.47, 31.55, 60.10, 110.28, 113.42, 116.86, 118.20, 128.68, 132.75, 137.23, 143.65, 148.40, 167.64; m/z 230 (M^+).

4.6. Preparation of (*E*)-ethyl 3-(1*H*-pyrrolo[2,3-*b*] pyridine-3-yl) acrylate (8)

To the solution of compound **7** (0.36 g, 0.001 mol) in dry THF (30 ml), TBAF (0.5 ml) was added and the mixture was refluxed under nitrogen atmosphere for 2 h. The completion of reaction was confirmed by TLC. After workup and chromatographic separation on silica gel column with hexane–ethyl acetate afforded product.

Yield: 0.21 g, 96%; mp: 108–110 °C; Elemental analysis for $C_{12}H_{12}N_2O_2$: requires: C, 66.65; H, 5.59; N, 12.96; found: C, 66.69, H, 5.64, N, 13.01; R_f (50% Hexane/Ethyl Acetate) 0.39 IR (KBr): 3441, 2332, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.35 (t, 3H, J=6.8 Hz, CH_3), 4.29 (q, 2H, J=7.1 Hz, CH_2), 6.40 (d, 1H, J=15.9 Hz, olefinic proton), 7.25 (m, 1H, C_5H), 7.69 (s, 1H, C_2H), 7.85 (d, 1H, J=15.9 Hz, olefinic proton), 8.30 (d, 2H, J=7.9 Hz, C_4H, NH), 8.38 (d, 1H, J=4.4 Hz, C_6H); ^{13}C NMR ($CDCl_3$): 14.46, 60.23, 111.57, 114.00, 116.82, 118.60, 129.55, 129.87, 137.48, 137.48, 149.05, 167.65; m/z 216 (M^+).

4.7. Cycloaddition reaction of (*E*)-ethyl 3-(1*H*-pyrrolo[2,3-*b*]-pyridine-3-yl)acrylate with different maleimides in microwave (9(a–c))

(*E*)-Ethyl 3-(1*H*-pyrrolo[2,3-*b*]pyridine-3-yl)acrylate (0.050 g, 0.0002 mol) and maleimides (0.0002 mol) were adsorbed on 0.3 g silica (100–200 mesh) and irradiated in microwave (700 watts) at 75 °C for 8–10 min. Reaction was monitored by TLC. The reaction mixture was washed with acetone and filtrate was concentrated and used for next step. Then Pd/C (5%) in xylene was added followed by reflux for 24 h. The reaction was monitored by TLC and xylene was distilled out. The residue was passed through Celite bed and washed with methanol. The compound was purified by column chromatography in hexane/ethyl acetate.

4.7.1. Compound ***9a***. Yield: 0.069 g, 78%; mp: 196–197 °C; Elemental analysis $C_{22}H_{15}N_3O_4$: requires: C, 68.57; H, 3.92; N, 10.90; found: C, 68.51; H, 3.86, N, 10.87; R_f (5%CH_2Cl_2/MeOH) 0.51; IR (KBr): 3428, 3065, 1712 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.39 (t, 3H, J=7.1 Hz, CH_3), 4.30 (q, 2H, J=7.4 Hz, CH_2), 7.00 (m, 2H, $C_{3'}H$, $C_{5'}H$), 7.23 (m, 3H,C_3H, C_4H, $C_{4'}H$), 7.56 (d, 2H, J=7.7 Hz, $C_{2'}H$, $C_{6'}H$), 8.17 (m, 1H, C_2H), 8.38 (s, 1H, C_5H), 9.57 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 13.87, 61.45, 107.77, 118.94, 122.62, 127.40, 127.89, 129.53, 138.44, 142.17, 162.50, 168.13; m/z 385 (M^+).

4.7.2. Compound ***9b***. Yield: 0.051 g, 69%; mp: 183–185 °C; Elemental analysis for $C_{17}H_{13}N_3O_4$: requires: C, 63.16; H, 4.05; N, 13.00; found: C, 63.19, H, 4.09, N, 12.96; R_f (5%CH_2Cl_2/MeOH) 0.51; IR (KBr): 3294, 1680, 1653 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.40 (t, 3H, J=7.2 Hz, CH_3), 3.21 (s, 3H, NCH_3), 4.32 (q, 2H, J=7.2 Hz, CH_2), 7.11–7.15 (m, 1H, C_3H), 8.03–8.06 (m, 1H, C_4H), 8.34–8.38 (m, 2H, C_2H, C_5H), 9.23 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): 13.93, 28.54, 62.09, 105.68, 114.64, 114.89, 116.62, 124.78, 125.42, 127.63, 129.42, 140.84, 145.13, 162.09, 171.96; m/z 323 (M^+).

4.7.3. Compound ***9c***. Yield: 0.052 g, 74%; mp: 189–190 °C; Elemental analysis for $C_{16}H_{11}N_3O_4$: requires: C, 62.14; H, 3.58; N, 13.59; found: C, 62.09, H, 3.54, N, 13.55; R_f (2%CH_2Cl_2/MeOH) 0.40; IR (KBr): 3412, 1740, 1705 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.39 (t, 3H, J=7.1 Hz, CH_3), 4.31 (q, 2H, J=7.1 Hz, CH_2), 7.02–7.05 (m, 1H, C_3H), 8.13–8.16 (m, 2H, C_4H, NH), 8.36–8.39 (m, 2H, C_2H, C_5H), 12.37 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): 13.8, 61.35, 107.55, 116.31, 116.62, 119.45, 126.50, 127.65, 129.49, 142.82, 147.09, 162.41, 172.5; m/z 309 (M^+).

4.8. Cycloaddition reaction of *N*-methyl(*E*)-ethyl 3-(1*H*-pyrrolo[2,3-*b*]pyridine-3-yl)acrylate with different maleimides in microwave (12a and 12b)

Same procedure was followed as mentioned above.

4.8.1. Compound ***12a***. Yield: 0.065 g, 76 %; mp: oil; Elemental analysis for $C_{23}H_{17}N_3O_4$: requires: C, 69.17; H, 4.29; N, 10.52; found: C, 69.13; H, 4.34; N, 10.47; R_f (5% CH_2Cl_2/MeOH) 0.78; IR (neat):

1699, 1651 cm^{-1}; ^1H NMR (DMSO-d_6): 1.35 (t, 3H, J=7.1 Hz, CH_3), 4.37–4.43 (m, 5H, CH_2, NCH_3), 7.18–7.23 (m, 1H, ArH), 7.41–7.49 (m, 5H, ArH), 8.66 (d, 1H, J=4.6 Hz, ArH), 8.78 (d, 1H, J=7.7 Hz, ArH), 8.85 (d, 1H, J=1.6 Hz, ArH); ^{13}C NMR (DMSO-d_6): 14.66, 48.03, 60.88, 108.51, 115.64, 116.08, 119.92, 122.05, 123.17, 128.22, 142.17, 146.14, 152.00, 166.94, 173.98; m/z 399 (M^+).

4.8.2. Compound ***12b****.* 0.52 g, Yield: 71%; mp: oil; Elemental analysis for$C_{18}H_{15}N_3O_4$: requires: C, 64.09; H, 4.48; N, 12.46; found: C, 64.04; H, 4.53; N, 12.50; R_f (2% CH_2Cl_2/MeOH) 0.63; IR (neat): 3019, 1704, 1683 cm^{-1}; ^1H NMR (DMSO-d_6): 1.36 (t, 3H, J=7.2 Hz, CH_3), 3.04 (s, 3H, NCH_3), 4.32–4.41 (m, 5H, NCH_3, CH_2), 7.36–7.41 (m, 1H, C_3H), 7.65–7.68 (m, 1H, C_4H), 8.61–8.63 (m, 1H, C_2H), 8.73 (s, 1H, C_5H); ^{13}C NMR (DMSO-d_6): 14.48, 30.89, 42.18, 60.96, 107.18, 117.37, 126.48, 129.43, 132.55, 143.97, 148.85, 149.52, 166.32, 174.75; m/z 337 (M^+).

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