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NOTE

Decarboxylative Aromatization of β-Carbolines by Using Metal Free Catalysis and Efficient Synthesis of β-Carboline Derivatives

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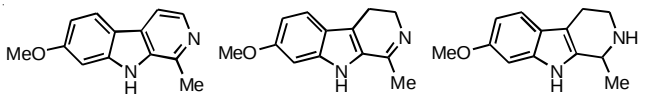
A new novel metal-free decarboxylative and aromatized β-carboline (**5a-j**) derivatives were synthesized by one-pot reaction. In all cases, resulting β-carboline derivatives with above 90 % yield.

Keywords: Harmine, Harmaline, Tetrahydroharmine, β-Carbolines.

Nitrogen atom contains polycyclic indolic compounds have attracted a great deal of interest amongst synthetic chemists over the years, partially because of their diverse biological activities demonstrated[1]. Alkaloids are a group of some 10,000 compounds that was originally defined by Carl Friedrich Wilhelm Meissner in 1819 as natural compounds similar in behaviour to alkalis and basic compounds[2]. The β-carboline alkaloids, also known as harmala's alkaloids, because they were first isolated from *Peganum harmala*, are natural products widely distributed in plants. Synthetic and naturally occurring compounds containing the β-carboline nucleus possess a large spectrum of important pharmacological properties, including potent antitumor activity. Harmine (**1**), harmaline (**2**) and tetrahydroharmine (**3**) alkaloids exist in eight plant families and there are 64 different kinds of such alkaloids have been separated and found to exhibit a variety of biological activities[3-8]. The reported biological effects of this class of compounds include antithrombotic[9], sedative[10], DNA-targeting properties[11], anti-HIV[12], and as well as suppression of CDK[13,14], DNA topoisomerase[15] and IrK[16].



Harmine **(1)** Harmaline **(2)** Tetrahydroharmine **(3)**

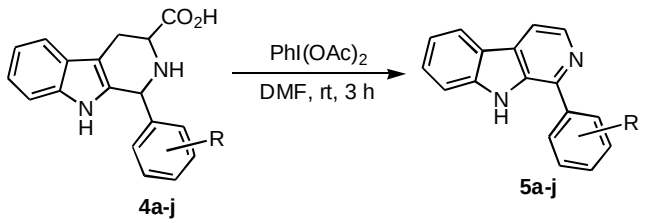
Structures of alkaloids

Because of their importance, previously a number of methods have been developed for the synthesis of β-carbolines, which involved aromatization, oxidation and decarboxylation in a single step. This reaction is catalyzed by potassium dichromate[17], sulfur[18], selenium dioxide[19], TsOH[20], $CuCl_2$[21], $(NH_4)_2S_2O_8$[22] and H_2O_2-peroxidase[23]. Based on the above literature, in this paper, we have report the synthesis of novel β-carboline derivatives employing $PhI(OAc)_2$ as the catalyst.

All chemicals and reagents were obtained from Aldrich (Sigma-Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glassplates containing 60 F-254 and visualization on TLC was achieved by UV light or iodine indicator. ^1H and ^{13}C NMR spectra were recorded on Gemini Varian-VXR-unity (300 MHz) or Bruker UXNMR/XWIN-NMR (300 MHz) instruments. Chemical shifts (δ) are reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an electrothermal melting point apparatus and are uncorrected.

General procedure for synthesis of β-carboline derivatives (5a-j): To a solution of substituted 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indole-3-carboxylic acids (1 mmol) in DMF was added catalytic amount of $PhI(OAc)_2$ (150 mg) and the reaction mixture stirred at room temperature for 3 h under N_2

atmosphere. After completion of reaction and extracted with ethyl acetate (3 × 10 mL). Combined organic layer washed with brine (10 mL) and dried over Na_2SO_4 and concentration in vacuum and purified by column chromatography to afforded respective compounds (**5a-j**) (**Scheme-I**).



4a-j **5a-j**

4a; R = H
4b; R = 3,4,5-trimethoxy
4c; R = 4-methoxy
4d; R = 3-methoxy
4e; R = 4-fluoro
4f; R = 4-chloro
4g; R = 4-nitro
4h; R= 4-trifluoromethyl
4i; R = 3,5-dimethoxy
4j; R = 4-bromo

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5b; R = 3,4,5-trimethoxy
5c; R = 4-methoxy
5d; R = 3-methoxy
5e; R = 4-fluoro
5f; R = 4-chloro
5g; R = 4-nitro
5h; R= 4-trifluoromethyl
5i; R = 3,5-dimethoxy
5j; R = 4-bromo

Scheme-I

1-Phenyl-9*H*-pyrido[3,4-b]indole: m.p.: 234-236 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.5 (s, 1H), 8.56 (d, *J* = 5.10 Hz, 1H), 8.15 (d, *J* = 8.10 Hz, 1H), 7.94 (m, 2H), 7.52 (m, 5H), 7.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.10, 140.02, 138.32, 132.92, 129.07, 128.65, 128.45, 128.316, 128.07, 121.49, 120.14, 119.42, 113.79, 112.36; m.f.: $C_{17}H_{12}N_2$(244), *m/z* (%): 244 (M+, 100), 215 (8), 189(5), 140 (8), 122(15), 89(5).

1-*p*-Tolyl-9*H*-pyrido[3,4-b]indole: m.p.: 190-191 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.3 (s, 1H), 8.50 (d, *J* = 5.10 Hz, 1H), 8.11 (d, *J* = 7.80 Hz, 1H), 7.87 (d, *J* = 5.40 Hz, 1H), 7.78 (d, *J* = 8.10 Hz, 2H), 7.45 (m, 2H), 7.26 (m, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1, 140.3, 139.1, 138.5, 135.5, 133.4, 129.6, 129.5, 128.2, 127.9, 121.7, 121.6, 120.0, 113.4, 111.5, 21.2; m.f.: $C_{18}H_{14}N_2$ (258), *m/z* (%): 258 (M+, 100), 243 (10), 228 (3), 214 (3), 188 (3), 140 (2) 128 (5).

1-(4-Fluorophenyl)-9*H*-pyrido[3,4-b]indole: m.p.: 203.1-205 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.96 (s, 1H), 8.46 (d, *J* = 5.10 Hz, 1H), 8.23 (d, *J* = 7.80 Hz, 1H), 8.05 (m, 3H), 7.64 (d, *J* = 8.40 Hz, 1H), 7.53 (dt, *J* = 6.90, 1.20 Hz, 1H), 7.30 (m, 3H); ^{13}C NMR (75.474 MHz, $CDCl_3$): δ 166.7, 138.8, 130.5, 130.4, 128.3, 127.4, 126.9, 125.1, 121.5, 119.8, 115.6, 115.3, 113.7, 112.2, 112.1; ^{19}F NMR (282.40 MHz, $CDCl_3$): δ 107.38 m.f.: $C_{17}H_{11}N_2F$ (262), *m/z* (%): 262 (M+, 100), 243 (5), 233(3), 207 (3), 140(5), 131(3) 107(2).

1-(3,4,5-Trimethoxyphenyl)-9*H*-pyrido[3,4-b]indole: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.8 (s, 1H), 8.7 (d, *J* = 5.10 Hz, 1H), 8.20 (d, *J* = 8.10 Hz, 1H), 7.9 (m, 1H), 7.6 (m, 2H), 7.28 (m, 1H), 7.1 (m, 2H), 3.9 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5, 143.07, 140.5, 139.0, 138.19, 138.27, 134.0, 133.5, 129.7, 128.5, 121.7, 121.6, 120.0, 113.6, 111.6, 10.2, 60.7, 56.1; m.f.: $C_{20}H_{19}O_3N_2$ (334).

1-(4-Nitrophenyl)-9*H*-pyrido[3,4-b]indole: ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.1 (s, 1H), 8.59 (d, *J* = 5.10 Hz, 1H), 8.42 (d, *J* = 8.10 Hz, 2H), 8.30 (m, 2H), 8.11 (m, 1H), 7.61 (m, 2H). 7.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.5, 144.2, 140.7, 138.9, 137.8, 129.5, 128.6, 127.1, 122.8, 120.5, 120.1, 119.1, 114.0, 111.4; m.f.: $C_{17}H_{12}O_2N_3$ (289).

1-(4-Methoxyphenyl)-9*H*-pyrido[3,4-b]indole: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.7 (s, 1H), 8.6 (d, *J* = 5.10 Hz, 1H), 8.3 (d, *J* = 8.10 Hz, 1H), 7.8 (m, 3H), 7.5 (m, 2H), 7.3 (m, 1H), 7.1 (d, *J* = 5.1 Hz, 2H), 3.9 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 141.5, 140.2, 137.3, 132.3, 130.0, 128.6, 128.1, 126.7, 120.0, 118.2, 113.0, 112.0, 111.2, 54.19; m.f.: $C_{18}H_{15}ON_2$ (275).

The synthesis of these different substituted β-carboline (**5a-j**) derivatives was conducted by the substituted β-carboline-3-carboxylic acids in DMF solvent and $PhI(OAc)_2$ at room temperature for 3 h (**Scheme-I**). Some of the compounds (**5a-i**) were previously reported[13]. In all cases, resulting β-carboline derivatives with above 90 % yield.

In conclusion, a new novel metal-free decarboxylative and aromatized β-carboline derivatives were synthesized by one-pot reaction. In all cases, resulting β-carboline derivatives with > 90 % yield.

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