



## NOTE

### Decarboxylative Aromatization of $\beta$ -Carbolines by Using Metal Free Catalysis and Efficient Synthesis of $\beta$ -Carboline Derivatives

CHUNDURU SRINIVASA RAO<sup>1,\*</sup>, Ch. VENKATA RAMANA REDDY<sup>1</sup>, B. RAMA DEVI<sup>1</sup>,  
JYOTHI VANTIKOMMU<sup>1</sup>, JYOTNA CHERUKURI<sup>2</sup> and SHAKIL S. SAIT<sup>3</sup>

<sup>1</sup>Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad-500 085, India

<sup>2</sup>Department of Chemistry, VNR Engineering College, Bachupally, Hyderabad-500 090, India

<sup>3</sup>Dr. Reddy's Laboratories Limited, Bachupally, Hyderabad-500 090, India

\*Corresponding author: E-mail: chemistrycsr@gmail.com

Received: 20 April 2015;

Accepted: 26 May 2015;

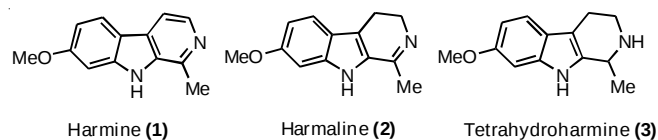
Published online: 29 August 2015;

AJC-17533

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

**Keywords:** Harmine, Harmaline, Tetrahydroharmine,  $\beta$ -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<sup>1</sup>. 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<sup>2</sup>. The  $\beta$ -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  $\beta$ -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<sup>3-8</sup>. The reported biological effects of this class of compounds include antithrombotic<sup>9</sup>, sedative<sup>10</sup>, DNA-targeting properties<sup>11</sup>, anti-HIV<sup>12</sup>, and as well as suppression of CDK<sup>13,14</sup>, DNA topoisomerase<sup>15</sup> and IrK<sup>16</sup>.



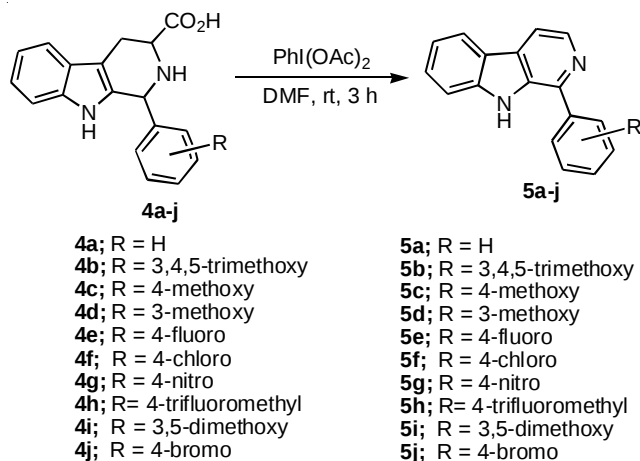
Structures of alkaloids

Because of their importance, previously a number of methods have been developed for the synthesis of  $\beta$ -carbolines, which involved aromatization, oxidation and decarboxylation in a single step. This reaction is catalyzed by potassium dichromate<sup>17</sup>, sulfur<sup>18</sup>, selenium dioxide<sup>19</sup>, TsOH<sup>20</sup>, CuCl<sub>2</sub><sup>21</sup>, (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub><sup>22</sup> and H<sub>2</sub>O<sub>2</sub>-peroxidase<sup>23</sup>. Based on the above literature, in this paper, we have report the synthesis of novel  $\beta$ -carboline derivatives employing PhI(OAc)<sub>2</sub> 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. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Gemini Varian-VXR-unity (300 MHz) or Bruker UXNMR/XWIN-NMR (300 MHz) instruments. Chemical shifts ( $\delta$ ) 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  $\beta$ -carboline derivatives (**5a-j**):** To a solution of substituted 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acids (1 mmol) in DMF was added catalytic amount of PhI(OAc)<sub>2</sub> (150 mg) and the reaction mixture stirred at room temperature for 3 h under N<sub>2</sub>

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<sub>2</sub>SO<sub>4</sub> and concentration in vacuum and purified by column chromatography to afforded respective compounds (**5a-j**) (**Scheme-I**).



Scheme-I

**1-Phenyl-9H-pyrido[3,4-b]indole**: m.p.: 234-236 °C <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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<sub>17</sub>H<sub>12</sub>N<sub>2</sub> (244), *m/z* (%): 244 (M<sup>+</sup>, 100), 215 (8), 189(5), 140 (8), 122(15), 89(5).

**1-*p*-Tolyl-9H-pyrido[3,4-b]indole**: m.p.: 190-191 °C, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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<sub>18</sub>H<sub>14</sub>N<sub>2</sub> (258), *m/z* (%): 258 (M<sup>+</sup>, 100), 243 (10), 228 (3), 214 (3), 188 (3), 140 (2) 128 (5).

**1-(4-Fluorophenyl)-9H-pyrido[3,4-b]indole**: m.p.: 203.1-205 °C <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C NMR (75.474 MHz, CDCl<sub>3</sub>): 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; <sup>19</sup>F NMR (282.40 MHz, CDCl<sub>3</sub>): δ 107.38 m.f.: C<sub>17</sub>H<sub>11</sub>N<sub>2</sub>F (262), *m/z* (%): 262 (M<sup>+</sup>, 100), 243 (5), 233(3), 207 (3), 140(5), 131(3) 107(2).

**1-(3,4,5-Trimethoxyphenyl)-9H-pyrido[3,4-b]indole**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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<sub>20</sub>H<sub>19</sub>O<sub>3</sub>N<sub>2</sub> (334).

**1-(4-Nitrophenyl)-9H-pyrido[3,4-b]indole**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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<sub>17</sub>H<sub>12</sub>O<sub>2</sub>N<sub>3</sub> (289).

**1-(4-Methoxyphenyl)-9H-pyrido[3,4-b]indole**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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<sub>18</sub>H<sub>15</sub>ON<sub>2</sub> (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)<sub>2</sub> at room temperature for 3 h (**Scheme-I**). Some of the compounds (**5a-i**) were previously reported<sup>13</sup>. 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.

## REFERENCES

- P.D. Bailey, P.J. Cochrane, A.H. Förster, K.M. Morgan and D.P.J. Pearson, *Tetrahedron Lett.*, **40**, 4597 (1999).
- W. Meissner, *J. Chem. Phys.*, **25**, 377 (1919).
- E.J. Massaro, *Handbook of Neurotoxicology*; Humana Press: Totowa, NJ, USA, p. 237 (2002).
- J.C. Callaway, D.J. McKenna, C.S. Grob, G.S. Brito, L.P. Raymon, R.E. Poland, E.N. Andrade, E.O. Andrade and D.C. Mash, *J. Ethnopharmacol.*, **65**, 243 (1999).
- J. Reniers, S. Robert, R. Frederick, B. Masereel, S. Vincent and J. Wouters, *Bioorg. Med. Chem.*, **19**, 134 (2011).
- S.K. Srivastava, A. Agarwal, P.M.S. Chauhan, S.K. Agarwal, A.P. Bhaduri, S.N. Singh, N. Fatima and R.K. Chatterjee, *J. Med. Chem.*, **42**, 1667 (1999).
- J.G. Tang, Y.H. Wang, R.R. Wang, Z.J. Dong, L.M. Yang, Y.T. Zheng and J.K. Liu, *Chem. Biodivers.*, **5**, 447 (2008).
- J.F. Miller, E.M. Turner, R.G. Sherrill, K. Gudmundsson, A. Spaltenstein, P. Sethna, K.W. Brown, R. Harvey, K.R. Romines and P. Golden, *Bioorg. Med. Chem. Lett.*, **20**, 256 (2010).
- N. Lin, M. Zhao, C. Wang and S. Peng, *Bioorg. Med. Chem. Lett.*, **12**, 585 (2002).
- A. Batch and R.H. Dodd, *J. Org. Chem.*, **63**, 872 (1998).
- H. Guan, H. Chen, W. Peng, Y. Ma, R. Cao, X. Liu and A. Xu, *Eur. J. Med. Chem.*, **41**, 1167 (2006).
- J. Ishida, H.K. Wang, M. Oyama, M.L. Cosentino, C.Q. Hu and K.H. Lee, *J. Nat. Prod.*, **64**, 958 (2001).
- Y. Song, J. Wang, S.F. Teng, D. Kesuma, Y. Deng, J. Duan, J.H. Wang, R.Z. Qi and M.M. Sim, *Bioorg. Med. Chem. Lett.*, **12**, 1129 (2002).
- Y. Song, D. Kesuma, J. Wang, Y. Deng, J. Duan, J.H. Wang and R.Z. Qi, *Biochem. Biophys. Res. Commun.*, **317**, 128 (2004).
- A.M. Deveau, M.A. Labroli, C.M. Dieckhaus, M.T. Barthen, K.S. Smith and T.L. MacDonald, *Bioorg. Med. Chem. Lett.*, **11**, 1251 (2001).
- A.C. Castro, L.C. Dang, F. Soucy, L. Grenier, H. Mazdiyasn, M. Hottelet, L. Parent, C. Pien, V. Palombella and J. Adams, *Bioorg. Med. Chem. Lett.*, **13**, 2419 (2003).
- D.G. Harvey and W. Robson, *J. Chem. Soc.*, 97 (1938).
- Q. Wu, R. Cao, M. Feng, X. Guan, C. Ma, J. Liu, H. Song and W. Peng, *Eur. J. Med. Chem.*, **44**, 533 (2009).
- B. Xin, W. Tang, Y. Wang, G. Lin, H. Liu, Y. Jiao, Y. Zhu, H. Yuan, Y. Chen and T. Lu, *Bioorg. Med. Chem. Lett.*, **22**, 4783 (2012).
- M.-L. Yang, P.-C. Kuo, T.-L. Hwang, W.-F. Chiou, K. Qian, C.-Y. Lai, K.-H. Lee and T.-S. Wu, *Bioorg. Med. Chem.*, **19**, 1674 (2011).
- R. Meesala, M. Ezzat, M. Mordi and S. Mansor, *Synlett*, **25**, 2176 (2014).
- W. Huang, J. Li and L. Ou, *Synth. Commun.*, **37**, 2137 (2007).
- T.H. Tomico, J.G. Ochaita and C.C. Ronda, Preparation of β-Carboline from Natural Products and Foods having Monoaminoxidase Inhibiting Activity, PCT Int. Appl., 2007085679 (2007).