

# Copper-Catalyzed Protodecarboxylation and Aromatization of Tetrahydro- $\beta$ -Carboline-3-Carboxylic Acids

Ramu Meesala, Mohd Nizam Mordi,\* Sharif Mahsufi Mansor

Centre For Drug Research, Universiti Sains Malaysia, Minden, 11800 USM, Penang, Malaysia  
Fax +60(4)6568669; E-mail: mnizam@usm.my

Received: 03.09.2013; Accepted after revision: 30.09.2013

**Abstract:** An efficient synthetic methodology has been developed to construct aromatic  $\beta$ -carbolines from tetrahydro- $\beta$ -carboline-3-carboxylic acids by copper-promoted sequential decarboxylation and oxidative aromatization.

**Key words:** tetrahydro- $\beta$ -carboline-3-carboxylic acids, decarboxylation, aromatization, copper, aromatic  $\beta$ -carboline

The aromatic  $\beta$ -carboline moiety is found in a wide variety of natural products and synthetic congeners.<sup>1</sup> Compounds containing this fragment display a wide range of biological properties including antimalarial,<sup>2</sup> antitumor,<sup>3</sup> and anti-HIV activities.<sup>4</sup>  $\beta$ -Carbolines also exhibit potent binding affinities toward benzodiazepine receptors in the central nervous system, thereby acting as diazepam antagonists.<sup>5</sup> As a result of their significant potential as therapeutics, interest has grown in the development of methods for the efficient and rapid synthesis of  $\beta$ -carboline derivatives. A general synthetic method for its preparation is the dehydrogenation of a suitable tetrahydro- $\beta$ -carboline precursor. Typical reported methods<sup>6</sup> involve heating the substrate with palladium on carbon,<sup>6a–c</sup> sulfur,<sup>7</sup> and  $\text{SeO}_2$ <sup>8</sup> for extended reaction times.

Decarboxylation of aromatic carboxylic acids by copper has been widely investigated since the 1960s by Sheppard,<sup>9</sup> Cohen,<sup>10</sup> Nilsson,<sup>11</sup> and others.<sup>12</sup> Sheppard et al. reported that cuprous arylcarboxylates readily decarboxylate on heating. Myers developed a palladium-catalyzed decarboxylative Heck-type reaction in 2002.<sup>13</sup> Gooßen reported a practical and an efficient large-scale synthesis of biaryls by using decarboxylative coupling.<sup>14</sup> Carboxylic acids have many advantages as surrogates of organometallic nucleophiles. They are stable, easy to make and store, and readily available. In addition, they generate carbon dioxide as a byproduct in the decarboxylation process instead of producing metal waste. A variety of decarboxylative coupling reactions of carboxylic acids have been developed over the past few decades.<sup>15</sup>

In this Letter, we describe a simple method for the synthesis of aromatic  $\beta$ -carbolines by sequential decarboxylation and aromatization of tetrahydro- $\beta$ -carboline-3-carboxylic acids by employing 10 mol% of  $\text{CuCl}_2$  without any ligand. We initiated our studies by examining the re-

action of tetrahydro- $\beta$ -carboline-3-carboxylic acid in the presence of a catalytic amount (10 mol%) of copper salts, without any ligand, in DMF at 130 °C as shown in Table 1. After examining various copper salts, the best outcome was obtained by using 10 mol% of  $\text{CuCl}_2$  (Table 1, entry 4).  $\text{Cu(OAc)}_2$  also catalyzed the reaction similarly (Table 1, entry 5). Copper(I) salts can also perform the reaction but with less efficiency (Table 1, entry 1–3).

**Table 1** Screening of Reaction Conditions

Entry	Cu salt (mol%)	Time (h)	Yield (%) <sup>a</sup>
1	$\text{CuI}$ (10)	6	76
2	$\text{CuBr}$ (10)	6	72
3	$\text{CuCl}$ (10)	6	74
4	$\text{CuCl}_2$ (10)	1	81
5	$\text{Cu(OAc)}_2$ (10)	3	75

<sup>a</sup> Isolated yields.

After having optimized reaction conditions, we attempted the decarboxylation–aromatization of various tetrahydro- $\beta$ -carboline-3-carboxylic acid derivatives, obtained by Pictet–Spengler condensation of L-tryptophan with the appropriate aldehyde,<sup>16</sup> to explore the scope and generality of the reaction. The outcomes of the reactions<sup>17</sup> are presented in Table 2. Yields were generally good and were observed to be dependent on the electronic characteristics of the substituent at C(1); substrates containing electron-donating groups (Table 2, entries 2 and 4) affording higher yields than those with electron-withdrawing groups (Table 2, entry 5). Finally, the conditions proved to be tolerant of aromatic functional groups.

Based on previous reports,<sup>18</sup> a possible mechanism is outlined in Scheme 1. Initially, the copper catalyst inserts into the carboxylate bond to give intermediate **4** which undergoes oxidative addition to provide intermediate **5**. Finally, a rapid reductive elimination provides the decarboxylation to produce intermediate **6**. On protonolysis, the intermediate **6** is converted into tetrahydro- $\beta$ -carbo-

**Table 2** Cu-Mediated Decarboxylation and Aromatization of Tetrahydro- $\beta$ -Carboline-3-Carboxylic Acids

Entry	Substrate	Product	Yield (%) <sup>a</sup>
1			81
2			84
3			77
4			87
5			63

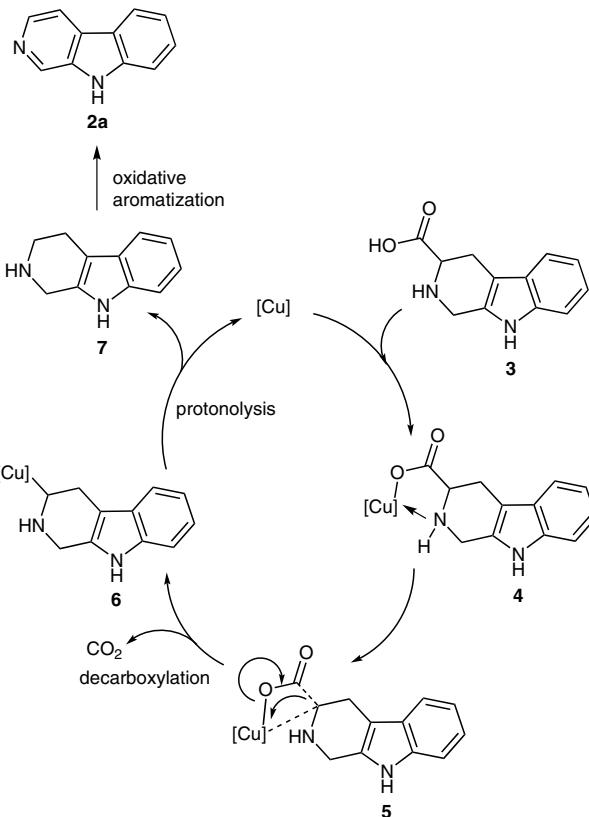
<sup>a</sup> Isolated yields.

line **7** which then transforms into the aromatic  $\beta$ -carboline by oxidative aromatization.

In summary, we have developed a convenient protocol for the synthesis of aromatic  $\beta$ -carbolines via copper(II)-mediated decarboxylation and subsequent aromatization of tetrahydro- $\beta$ -carboline-3-carboxylic acid precursors in the absence of a ligand.

### Acknowledgement

Financial support of this research provided by the Research University Grant Scheme of Universiti Sains Malaysia (RUT-USM) is gratefully acknowledged by the authors.



**Scheme 1** Proposed mechanism for copper-mediated decarboxylation and aromatization of tetrahydro- $\beta$ -carboline-3-carboxylic acids

**Supporting Information** for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

### References and Notes

- (a) Love, B. E. *Org. Prep. Proced. Int.* **1996**, *28*, 3. (b) Cao, R.; Peng, W.; Wang, Z.; Xu, A. *Curr. Med. Chem.* **2007**, *14*, 479.
- (a) Shilabin, A. G.; Kasanah, N.; Tekwani, B. L.; Hamann, M. T. *J. Nat. Prod.* **2008**, *71*, 1218. (b) Winkler, J. D.; Londregan, A. T.; Hamann, M. T. *Org. Lett.* **2006**, *8*, 2591. (c) Bourcereau, Y.; Coldham, I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5841.
- (a) Guan, H.; Chen, H.; Peng, W.; Ma, Y.; Cao, R.; Liu, X.; Xu, A. *Eur. J. Med. Chem.* **2006**, *1167*. (b) Rashid, M. A.; Gustafson, K. R.; Boyd, M. R. *J. Nat. Prod.* **2001**, *64*, 1454. (c) Prinsep, M. R.; Blunt, J. W.; Munro, M. H. G. *J. Nat. Prod.* **1991**, *54*, 1068.
- (a) Tang, J. G.; Wang, Y. H.; Wang, R. R.; Dong, Z. J.; Yang, L. M.; Zheng, Y. T.; Liu, J. K. *Chem. Biodiversity* **2008**, *5*, 447. (b) Wang, Y. H.; Tang, J. G.; Wang, R. R.; Yang, L. M.; Dong, Z. J.; Du, L.; Shen, X.; Liu, J. K.; Zheng, Y. T. *Biochem. Biophys. Res. Commun.* **2007**, *355*, 1091. (c) Yu, X.; Lin, W.; Li, J.; Yang, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3127.
- (a) Hagen, T. J.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1987**, *30*, 750. (b) Hagen, T. J.; Guzman, F.; Schultz, C.; Cook, J. M.; Skolnick, P.; Shannon, H. E. *Heterocycles* **1986**, *10*, 2845. (c) Müller, W. E.; Fehske, K. J.; Borbe, H.

- O.; Wollert, U.; Nanz, C.; Rommelspacher, H. *Pharmacol., Biochem. Behav.* **1981**, *14*, 693.
- (6) (a) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535. (b) Hibino, S.; Miko, O.; Masataka, I.; Kohichi, S.; Takashi, I. *Heterocycles* **1985**, *23*, 261. (c) Coutts, R. T.; Micetich, R. G.; Baker, G. B.; Benderly, A.; Dewhurst, T.; Hall, T. W.; Locock, A. R.; Pyrozko, J. *Heterocycles* **1984**, *22*, 131. (d) Hagen, T. J.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1987**, *30*, 750. (e) Huang, W.; Li, J.; Ou, L. *Synth. Commun.* **2007**, *37*, 2137. (f) Agarwal, S. K.; Saxena, A. K.; Jain, P. C.; Malviya, B.; Chandra, H.; Anand, N. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1987**, *26*, 757.
- (7) (a) Cain, M.; Weber, R. W.; Guzman, F.; Cook, J. M.; Barker, S. A.; Rice, K. C.; Crawley, J. N.; Paul, S. M.; Skolnick, P. *J. Med. Chem.* **1982**, *25*, 1081. (b) Still, I. J. W.; McNulty, J. *Heterocycles* **1989**, *29*, 2057. (c) Qifeng, W.; Rihui, C.; Manxiu, F.; Xiangdong, G.; Chunming, M.; Jinbing, L.; Huacan, S.; Wenlie, P. *Eur. J. Med. Chem.* **2009**, *44*, 533.
- (8) (a) Gatta, F.; Misiti, D. *J. Heterocycl. Chem.* **1987**, *24*, 1183. (b) Cain, M.; Campos, O.; Guzman, F.; Cook, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 907. (c) Campos, O.; DiPierro, M.; Cain, M.; Mantei, R.; Gawish, A.; Cook, J. M. *Heterocycles* **1980**, *14*, 975.
- (9) Cairncross, A.; Roland, J. R.; Henderson, R. M.; Sheppard, W. A. *J. Am. Chem. Soc.* **1970**, *92*, 3187.
- (10) (a) Cohen, T.; Schambach, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 3189. (b) Cohen, T.; Berninger, R. W.; Wood, J. T. *J. Org. Chem.* **1978**, *43*, 837.
- (11) (a) Nilsson, M. *Acta Chem. Scand.* **1966**, *20*, 423. (b) Björklung, C.; Nilsson, M. *Acta Chem. Scand.* **1968**, *22*, 2585. (c) Chodowska-Palicka, J.; Nilsson, M. *Acta Chem. Scand.* **1970**, *24*, 3353. (d) Nilsson, M.; Ullenius, C. *Acta Chem. Scand.* **1971**, *25*, 2428. (e) Chodowska-Palicka, J.; Nilsson, M. *Acta Chem. Scand.* **1971**, *25*, 3451.
- (12) (a) Shepard, A. F.; Winslow, N. R.; Johnson, J. R. *J. Am. Chem. Soc.* **1930**, *52*, 2083. (b) Shang, R.; Liu, L. *Sci. China Chem.* **2011**, *54*, 1670. (c) Gooßen, L. J.; Rodriguez, N.; Gooßen, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3100; *Angew. Chem.* **2008**, *120*, 3144. (d) Gooßen, L. J.; Gooßen, K.; Rodriguez, N.; Blanchot, M.; Linder, C.; Zimmermann, B. *Pure Appl. Chem.* **2008**, *80*, 1725.
- (13) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250.
- (14) Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662.
- (15) (a) Gooßen, L. J.; Knauber, T. *J. Org. Chem.* **2008**, *73*, 8631. (b) Fu, Z.; Huang, S.; Su, W.; Hong, M. *Org. Lett.* **2010**, *12*, 4992. (c) Shang, R.; Yang, Z.; Zhang, S.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 14391. (d) Rodríguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030. (e) Chou, C.-M.; Chatterjee, I.; Studer, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8614.
- (16) Cao, R.; Peng, W.; Chen, H.; Hou, X.; Guan, H.; Chen, Q.; Ma, Y.; Xu, A. E. *Eur. J. Med. Chem.* **2005**, *40*, 249.
- (17) **General Procedure**  
To 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (1 mmol) in DMF (10 mL) was added CuCl<sub>2</sub> (10 mol%) and stirred for 1 h at 130 °C. On completion of the reaction (TLC), H<sub>2</sub>O (5 mL) was added to the reaction, and the mixture was basified to pH 9 with 1 M NaOH. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL), and the combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The CH<sub>2</sub>Cl<sub>2</sub> was evaporated, and the residue was purified by chromatography which afforded pure 9*H*-pyrido[3,4-*b*]indole (**2a**) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ = 11.63 (1 H, s), 8.89 (d, *J* = 0.5 Hz, 1 H), 8.31 (d, *J* = 5.5 Hz, 1 H), 8.2 (d, *J* = 7.0 Hz, 1 H), 8.09 (dd, *J*<sub>1</sub> = 0.5 Hz, *J*<sub>2</sub> = 1.0 Hz, 1 H), 7.60 (d, *J* = 10.0 Hz, 1 H), 7.55–7.53 (m, 1 H), 7.24–7.21 (m, 1 H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>): δ = 140.5, 137.9, 135.9, 133.7, 128.5, 127.6, 121.7, 120.4, 119.4, 114.7, 112.1. GC-MS: 168 [M<sup>+</sup>].
- (18) (a) Cohen, T.; Schambach, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 3189. (b) Goossen, L. J.; Thiel, W. R.; Rodríguez, N.; Linder, C.; Melzer, B. *Adv. Synth. Catal.* **2007**, *349*, 2241.