# Copper-Catalyzed Protodecarboxylation and Aromatization of Tetrahydro-β-Carboline-3-Carboxylic Acids

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

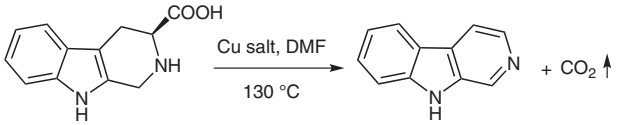
**Key words:** tetrahydro-β-carboline-3-carboxylic acids, decarboxylation, aromatization, copper, aromatic β-carboline

The aromatic β-carboline moiety is found in a wide variety of natural products and synthetic congeners.[1] Compounds containing this fragment display a wide range of biological properties including antimalarial,[2] antitumor,[3] and anti-HIV activities.[4] β-Carbolines also exhibit potent binding affinities toward benzodiazepine receptors in the central nervous system, thereby acting as diazepam antagonists.[5] As a result of their significant potential as therapeutics, interest has grown in the development of methods for the efficient and rapid synthesis of β-carboline derivatives. A general synthetic method for its preparation is the dehydrogenation of a suitable tetrahydro-β-carboline precursor. Typical reported methods[6] involve heating the substrate with palladium on carbon,[6a–c] sulfur,[7] and $SeO_2$[8] for extended reaction times.

Decarboxylation of aromatic carboxylic acids by copper has been widely investigated since the 1960s by Sheppard,[9] Cohen,[10] Nilsson,[11] and others.[12] Sheppard et al. reported that cuprous arylcarboxylates readily decarboxylate on heating. Myers developed a palladium-catalyzed decarboxylative Heck-type reaction in 2002.[13] Gooßen reported a practical and an efficient large-scale synthesis of biaryls by using decarboxylative coupling.[14] 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.[15]

In this Letter, we describe a simple method for the synthesis of aromatic β-carbolines by sequential decarboxylation and aromatization of tetrahydro-β-carboline-3-carboxylic acids by employing 10 mol% of $CuCl_2$ without any ligand. We initiated our studies by examining the reaction of tetrahydro-β-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 $CuCl_2$ (Table 1, entry 4). $Cu(OAc)_2$ 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 (%)[a] |
|---|---|---|---|
| 1 | CuI (10) | 6 | 76 |
| 2 | CuBr (10) | 6 | 72 |
| 3 | CuCl (10) | 6 | 74 |
| 4 | $CuCl_2$ (10) | 1 | 81 |
| 5 | $Cu(OAc)_2$ (10) | 3 | 75 |

[a] Isolated yields.

After having optimized reaction conditions, we attempted the decarboxylation–aromatization of various tetrahydro-β-carboline-3-carboxylic acid derivatives, obtained by Pictet–Spengler condensation of L-tryptophan with the appropriate aldehyde,[16] to explore the scope and generality of the reaction. The outcomes of the reactions[17] 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,[18] 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-β-carbo-

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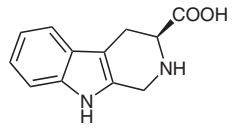
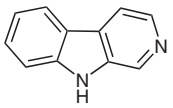
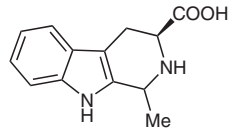
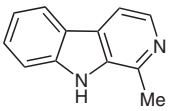
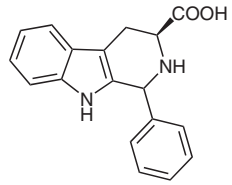
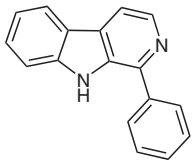
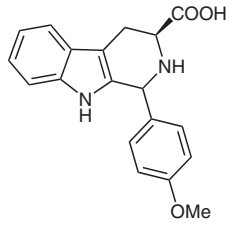
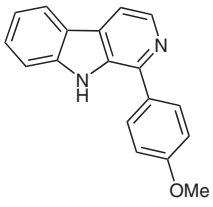
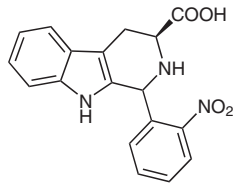
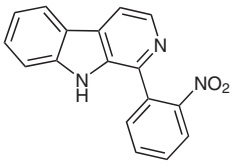
**Table 2** Cu-Mediated Decarboxylation and Aromatization of Tetrahydro-β-Carboline-3-Carboxylic Acids

| Entry | Substrate | Product | Yield (%)[a] |
|---|---|---|---|
| 1 |  **1a** |  **2a** | 81 |
| 2 |  **1b** |  **2b** | 84 |
| 3 |  **1c** |  **2c** | 77 |
| 4 |  **1d** |  **2d** | 87 |
| 5 |  **1e** |  **2e** | 63 |

[a] Isolated yields.

line **7** which then transforms into the aromatic β-carboline by oxidative aromatization.

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

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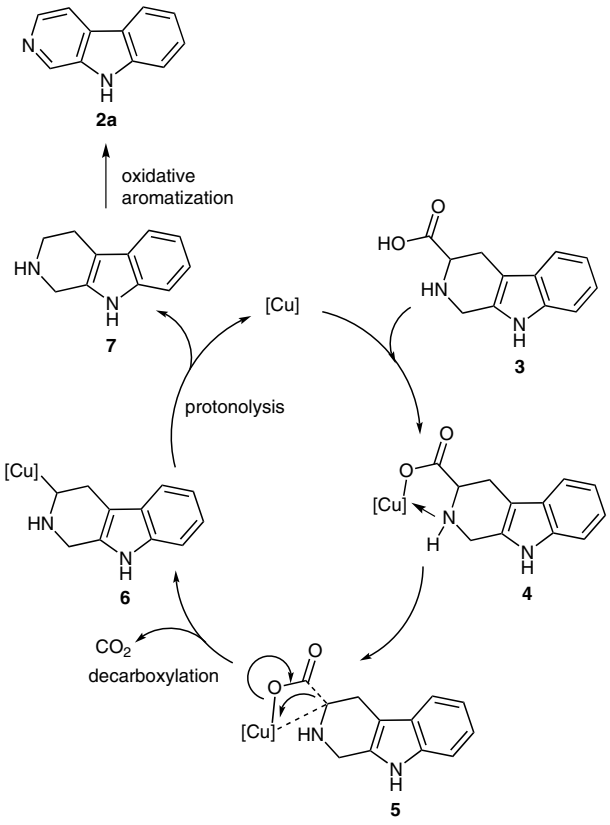


**Scheme 1** Proposed mechanism for copper-mediated decarboxylation and aromatization of tetrahydro-β-carboline-3-carboxylic acids

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

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(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 $CuCl_2$ (10 mol%) and stirred for 1 h at 130 °C. On completion of the reaction (TLC), $H_2O$ (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 $CH_2Cl_2$ (3 × 20 mL), and the combined organic layers were dried over anhydrous $Na_2SO_4$. The $CH_2Cl_2$ was evaporated, and the residue was purified by chromatography which afforded pure 9*H*-pyrido[3,4-*b*]indole (**2a**) as a white solid. $^1$H NMR (500 MHz, DMSO-$d_6$): 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, $J_1$ = 0.5 Hz, $J_2$ = 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). $^{13}$C NMR (125 MHz, DMSO-$d_6$): 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 [$M^+$].

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