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

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Received: 03.09.2013; Accepted after revision: 30.09.2013

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 methods⁶ involve heating the substrate with palladium on carbon,^{6a-c} sulfur,⁷ and SeO₂⁸ 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 CuCl₂ without any ligand. We initiated our studies by examining the re-

action 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 CuCl₂ (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 reactions¹⁷ 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-

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

Entry	Substrate	Product	Yield (%) ^a
1			81
2			84
3			77
4			87
5			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.

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- 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 CuCl₂ (10 mol%) and stirred for 1 h at 130 °C. On completion of the reaction (TLC), H₂O (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 CH₂Cl₂ (3 × 20 mL), and the combined organic layers were dried over anhydrous Na₂SO₄. The CH₂Cl₂ was evaporated, and the residue was purified by chromatography which afforded pure 9*H*-pyrido[3,4-*b*]indole (**2a**) as a white solid. ¹H 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). ¹³C 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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