Copper-Catalyzed Protodecarboxylation and Aromatization of Tetrahydro-β-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 β-carboline 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-Carboline 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 our 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 Shepard,9 Cohen,10 Nilsson,11 and others.12 Sheppard et al. reported that cuprous arylcarboxylates readily decarboxylate on heating. Myers developed a palladium-catalyzed dehydroacetylation Heck-type reaction in 2002.13 Gooßen reported a practical and an efficient large-scale synthesis of biaryl by using dehydroacetylation 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 dehydroacetylation 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-carboline 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 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 observed 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**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu salt (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuI (10)</td>
<td>6</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>CuBr (10)</td>
<td>6</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>CuCl (10)</td>
<td>6</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>CuCl2 (10)</td>
<td>1</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)2 (10)</td>
<td>3</td>
<td>75</td>
</tr>
</tbody>
</table>

<sup>a</sup> 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-carboline.

SYNLETT 2014, 25, 0120–0122
Advanced online publication: 12.11.2013
© Georg Thieme Verlag Stuttgart · New York
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.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2b</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2c</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2d</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>2e</td>
<td>63</td>
</tr>
</tbody>
</table>

a Isolated yields.

References and Notes


(5) (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.
11.63 (1 H, s), 8.89 (d, J = 7.24–7.21 (m, 1 H). 13C NMR (125 MHz, DMSO-
662.
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+].

The CH2Cl2 was evaporated, and the residue was purified by chromatography which afforded pure 9
H2a
H
d
J= 7.0 Hz, 1 H), 7.55–7.53 (m, 1 H), 7.24–7.21 (m, 1 H). 13C NMR (125 MHz, DMSO-d6): 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+].

General Procedure
To 2,3,4,9-tetrahydro-1H-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.


11.63 (1 H, s), 8.89 (d, J = 7.24–7.21 (m, 1 H). 13C NMR (125 MHz, DMSO-
662.
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+].

The CH2Cl2 was evaporated, and the residue was purified by chromatography which afforded pure 9H-pyrido[3,4-b]indole (2a) as a white solid. 1H NMR (500 MHz, DMSO-d6): δ = 11.63 (1 H, s), 8.89 (d, J = 7.0 Hz, 1 H), 8.31 (d, J = 5.5 Hz, 1 H), 8.2 (d, J = 7.0 Hz, 1 H), 8.09 (dd, J1 = 0.5 Hz, J2 = 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-d6): 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+].


General Procedure
To 2,3,4,9-tetrahydro-1H-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.

1H NMR (500 MHz, DMSO-d6): δ = 11.63 (1 H, s), 8.89 (d, J = 7.0 Hz, 1 H), 8.31 (d, J = 5.5 Hz, 1 H), 8.2 (d, J = 7.0 Hz, 1 H), 8.09 (dd, J1 = 0.5 Hz, J2 = 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-d6): 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+].

