Supplementary Information for

Constructions of Tetrahydro-γ-carboline Skeletons via Intramolecular Oxidative Carbon-Carbon Bond Formation of Enamines

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Supplementary Material

<table>
<thead>
<tr>
<th>I</th>
<th>General Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Experimental section</td>
</tr>
<tr>
<td>III</td>
<td>References</td>
</tr>
<tr>
<td>IV</td>
<td>$^1$H and $^{13}$C NMR spectra</td>
</tr>
</tbody>
</table>

Page
S2
S3-S8
S9
S10-S20
**General Information**

$^1$H and $^{13}$C NMR spectra were recorded on a 400 MHz spectrometer at 25 °C. Chemical shifts values are given in ppm and referred as the internal standard to TMS: 0.00 ppm. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; br, broad and dd, doublet of doublets. The coupling constants $J$, are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were obtained on a Q-TOF micro spectroMeter. Melting points were determined with a national micromelting point apparatus without corrections. TLC plates were visualized by exposure to ultraviolet light. Dichloromethane was dried by CaH$_2$ before use, other reagents and solvents were purchased as reagent grade and were used without further purification. Flash column chromatography was performed over silica gel 200-300 m and the eluent was a mixture of ethyl acetate (EA) and petroleum ether (PE), or a mixture of methanol (M) and dichloromethane (D).
Experimental section

Methyl 3-(methylamino)propanoate (2)

\[
\begin{array}{c}
\text{Me} \quad \text{O} \\
\text{N} \quad \text{Me} \\
\text{O} \quad \text{Me}
\end{array}
\quad \text{MeNHNMe, EtOH, -10 °C} \\
\begin{array}{c}
\text{Me} \quad \text{O} \\
\text{N} \quad \text{Me} \\
\text{O} \quad \text{Me}
\end{array}
\]

Compound 2 was obtained according to published procedure.\(^1\) Yield: 86%, colorless oil.

Methyl 3-[(tert-butoxycarbonyl)(methyl)amino]propanoate (3)\(^2\)

\[
\begin{array}{c}
\text{Me} \quad \text{O} \\
\text{N} \quad \text{Me} \\
\text{O} \quad \text{Me}
\end{array}
\quad \text{(Boc)2O, TEA, CH2Cl2} \\
\begin{array}{c}
\text{Me} \quad \text{O} \\
\text{N} \quad \text{Boc} \\
\text{O} \quad \text{Me}
\end{array}
\]

To a stirred solution of 2 (9.4 g, 80 mmol) in dry CH₂Cl₂ (200 mL), Boc₂O (19.0 g, 88 mmol) and Et₃N (22 mL, 160 mmol) were added. The resulted mixture was stirred at rt until TLC indicated the total consumption of 2. To the reaction mixture was added saturated aq. NH₄Cl solution (100 mL) and stirred for another 30 min, CH₂Cl₂ was used to extract the mixture. The organic phase, after dried with anhydrous Na₂SO₄, was evaporated to remove the solvent, and the residue was purified by chromatography to afford the desired product 3 (17.4 g, 75 mmol). Yield: 94%, colorless oil.\(^1\)H NMR (400 MHz, CDCl₃): δ 3.69 (s, 3H), 3.51 (t, J = 6.8 Hz, 2H), 2.87 (s, 3H), 2.55 (t, J = 6.8 Hz, 2H), 1.46(s, 9H). \(^1^3\)C NMR (101 MHz, CDCl₃): δ 171.9, 155.2, 79.3, 51.4, 44.9, 34.5, 32.9, 28.2.

3-[(tert-Butoxycarbonyl)(methyl)amino]propanoic acid (4)\(^3\)

\[
\begin{array}{c}
\text{Me} \quad \text{N} \\
\text{Boc} \\
\text{O} \quad \text{Me}
\end{array}
\quad \text{NaOH, EtOH/H₂O} \\
\begin{array}{c}
\text{Me} \quad \text{N} \\
\text{Boc} \\
\text{O} \quad \text{Me}
\end{array}
\]

To a stirred solution of 3 (6.5 g, 30 mmol) in alcohol (150 mL) was added 50 mL aq. NaOH (1.8 g, 45 mmol) solution dropwise, the resulted mixture was stirred at rt until TLC indicated the total consumption of 3. The mixture was evaporated to remove the alcohol, and the resulted solution was carefully acidified by aq. HCl (2 N) until the pH reached 3. EA was used to extract the mixture. The combined organic phase, after dried with anhydrous Na₂SO₄, was evaporated to
remove the solvent under vacuum and the residue was purified by chromatography to give the desired product 4 (5.8 g, 28 mmol). Yield: 95%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.53 (t, $J$ = 6.9 Hz, 2H), 2.89 (s, 3H), 2.61 (t, $J$ = 6.8 Hz, 2H), 1.47 (s, 9H).

**Ethyl 5-[methyl(tert-butoxycarbonyl)amino]-3-oxopentanoate (5)**

Under $N_2$, CDI (4.2 g, 26 mmol) was added to a stirred solution of 4 (4.9 g, 24 mmol) in anhydrous MeCN (120 mL) and the mixture was stirred at rt for 2 h. A solid mixture of anhydrous MgCl$_2$ (3.0 g, 31 mmol) and potassium monomethyl malonate (6.2 g, 36 mmol) was added, the mixture was stirred under $N_2$ at 40 $^\circ$C until TLC indicated the total consumption of starting material. To the reaction mixture was added aq. HCl (2 N) dropwise until the pH reached 3. EA was used to extract the mixture. The combined organic phase, after dried with anhydrous Na$_2$SO$_4$, was evaporated to remove the solvent under vacuum and the residue was purified by column chromatography to afford the desired product 5 (6.0 g, 22 mmol). Yield: 92%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.26-4.11 (m, 2H), 3.46 (m, 4H), 2.85-2.82 (m, 5H), 1.43 (s, 9H), 1.32-1.20 (m, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 166.93, 155.48, 79.62, 61.36, 59.99, 49.45, 43.88, 41.48, 34.86, 28.36, 14.04.

**General procedure for the preparation of 7a and 7b**

A mixture of compound 5 (23 mmol), substituted aniline 6 (25 mmol) and acetic acid (25 mmol) were stirred at room temperature for 18 h. After the completion of the reaction, EtOH (50 mL) was added. The solution was dried with anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give the desired products 7a-7b, which were characterized as follows:
Ethyl 5-[(tert-butoxycarbonyl)(methyl)amino]-3-(p-tolylamino)pent-2-enoate (7a)

Following the general procedure, 7a was obtained. Yield: 94%, white solid, mp 94-96 °C. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 10.16 (s, 1H), 7.17-7.11 (d, 2H), 7.07-6.96 (d, 2H), $\delta$ 4.14 (q, $J = 7.0$ Hz, 2H), 3.24 (t, $J = 6.9$ Hz, 2H), 2.65 (s, 3H), 2.47 (d, $J = 6.8$ Hz, 2H), 2.33 (s, 3H), 1.39 (s, 9H), 1.28 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 170.50, 160.49, 154.97, 136.33, 135.65, 129.81, 125.63, 85.71, 79.56, 58.79, 48.08, 34.11, 30.76, 28.41, 20.89, 14.56. HRMS (ESI) $m/z$ calcd for C$_{20}$H$_{31}$N$_2$O$_4^+$ [M + H$^+$] 363.2278, found 363.2280.

Ethyl 5-[(tert-butoxycarbonyl)(methyl)amino]-3-(4-methoxyphenyl)amino)pent-2-enoate (7b)

Following the general procedure, 7b was obtained. Yield: 91%, white solid, mp 78-79 °C. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 10.06 (s, 1H), 7.18-6.97 (m, 2H), 6.86 (d, $J = 18.3$, 8.8 Hz, 2H), 4.14 (q, $J = 7.0$ Hz, 2H), 3.80 (s, 3H), 3.23 (s, 2H), 2.64 (s, 3H), 2.41 (s, 2H), 1.40 (s, 9H), 1.31-1.24 (m, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 170.53, 160.96, 157.86, 155.30, 131.71, 127.57, 114.38, 85.20, 79.55, 58.74, 55.43, 48.07, 34.09, 30.73, 28.35, 14.56. HRMS (ESI) $m/z$ calcd for C$_{20}$H$_{31}$N$_2$O$_5^+$ [M + H$^+$] 379.2228, found 379.2228.

General procedure for the preparation of 8a and 8b

7 (5 mmol) was stirred with Pd(OAc)$_2$ (0.5 mmol), Cu(OAc)$_2$ (15 mmol), K$_2$CO$_3$ (15 mmol) and DMF (50 mL) under N$_2$ in a preheated oil bath at 80 °C for 4 h until TLC indicated the total consumption of starting material. The reaction mixture was diluted with EA (150 mL) and filtered through a short pad of silica. The solid was washed with EA (50 mL), and the combined filtrates were evaporated to dryness. The residue was purified by flash column chromatography on silica gel to give the desired products 8a-8b, which were characterized as follows:
Ethyl 2-[(tert-butoxycarbonyl)(methyl)amino]ethyl]-5-methyl-1H-indole-3-carboxylate (8a)

Following the general procedure, 8a was obtained. Yield: 89%, light brown solid, mp 99-102 °C. ¹H NMR (600 MHz, CDCl₃): δ 10.48 (s, 1H), 7.87 (s, 1H), 7.21 (d, J = 6.4 Hz, 1H), 7.00 (d, J = 9.2 Hz, 1H), 4.44-4.37 (q, J = 7.0 Hz, 2H), 3.74 (m, 2H), 3.47 (m, 2H), 2.86 (s, 3H), 2.46 (s, 3H), 1.56-1.32 (m, 12H).

¹³C NMR (151 MHz, CDCl₃): δ 166.24, 157.06, 145.17, 133.28, 130.88, 127.40, 123.67, 120.91, 110.84, 103.60, 80.58, 59.32, 45.91, 34.05, 28.38, 26.97, 21.73, 14.72. HRMS (ESI) m/z calcld for C₂₀H₂₈N₂NaO₄⁺ [M + Na⁺] 383.1941, found 383.1942.

Ethyl 2-[(tert-butoxycarbonyl)(methyl)amino]ethyl]-5-methoxy-1H-indole-3-carboxylate (8b)

Following the general procedure, 8b was obtained. Yield: 90%, light brown solid, mp 82-86 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.54 (s, 1H), 7.63 (s, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 4.42 (q, J = 7.1 Hz, 2H), 3.89 (s, 3H), 3.75 (m, 2H), 3.49 (m, 2H), 2.88 (s, 3H), 1.59-1.28 (m, 12H). ¹³C NMR (101 MHz, CDCl₃): δ 166.06, 157.07, 155.52, 145.45, 129.99, 128.03, 112.01, 111.81, 103.90, 103.49, 80.45, 59.29, 55.71, 46.01, 34.08, 28.32, 27.04, 14.65. RMS (ESI) m/z calcld for C₂₀H₂₈N₂NaO₅⁺ [M + Na⁺] 399.1890, found 399.1894.

General procedure for the preparation of 9a and 9b

To a stirred solution of 8 (5 mmol) in CH₂Cl₂ (100 mL) was added TFA (25 mL) dropwise at 0 °C under N₂. The mixture was stirred at rt until TLC indicated the total consumption of starting material. The mixture was evaporated to remove the solvent and excess TFA. Then saturated NaHCO₃ (60 mL) was added and CH₂Cl₂ was used to extract the mixture. The combined organic
phase, after dried with anhydrous Na$_2$SO$_4$, was evaporated to remove the solvent. The residue was redissolved in MeOH (100 mL), NaOH (6 mmol) was added, the resulted mixture was refluxed for 5 h. After the completion of the reaction, the mixture was evaporated to remove the solvent. The residue was purified by flash column chromatography on silica gel to give the desired products 9a-9b, which were characterized as follows:

2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one (9a)

Following the general procedure, 9a was obtained. Yield: 91%, white solid, mp > 300 °C. $^1$H NMR (600 MHz, DMSO): δ 11.44 (s, 1H), 7.70 (s, 1H), 7.25 (s, 1H), 6.93 (s, 1H), 3.58 (t, 2H), 3.03 (t, 2H), 2.93 (s, 3H), 2.37 (s, 3H). $^{13}$C NMR (151 MHz, DMSO): δ 164.83, 143.40, 134.28, 129.10, 125.61, 122.81, 119.38, 111.07, 104.87, 48.07, 33.17, 22.29, 21.24. HRMS (ESI) m/z calcd for C$_{13}$H$_{15}$N$_2$O $[^{1+}] + [M + H]^+$ 215.1179, found 215.1184.

8-Methoxy-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one (9b)

Following the general procedure, 9b was obtained. Yield: 92%, white solid, mp 294-296 °C. $^1$H NMR (600 MHz, DMSO): δ 7.37 (s, 1H), 7.29 (d, $J = 6.3$ Hz, 1H), 6.75-6.70 (m, 1H), 3.75 (s, 3H), 3.56 (t, $J = 6.9$ Hz, 2H), 3.04 (t, $J = 6.7$ Hz, 2H), 2.93 (s, 3H). $^{13}$C NMR (151 MHz, DMSO): δ 164.91, 154.42, 143.80, 130.86, 126.01, 112.26, 110.88, 105.09, 101.63, 55.16, 48.07, 33.12, 22.41. HRMS (ESI) m/z calcd for C$_{13}$H$_{16}$N$_2$O$_2$ $[^{1+}] + [M + H]^+$ 231.128, found 231.1130.

General procedure for the preparation of 10a and 10b

To a suspension of LiAlH$_4$ (6 mmol) in anhydrous THF (20 mL) was added 9 (2 mmol) at 0°C. The resulted mixture was stirred at reflux temperature for 4 h. The reaction mixture was cooled to 0 °C before water (5 mL) was added dropwise. CH$_2$Cl$_2$ was used to extract the mixture. The organic phase, after dried with anhydrous Na$_2$SO$_4$, was evaporated to remove the solvent under vacuum.
The residue was purified by flash column chromatography on silica gel to give the desired products 10a-10b, which were characterized as follows:

**2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (10a)**

Following the general procedure, 10a was obtained. Yield: 85%, white solid, mp 97-99 °C. $^1$H NMR (400 MHz, DMSO): $\delta$ 10.75 (s, 1H), 7.15 (d, $J = 8.4$ Hz, 1H), 7.11 (s, 1H), 6.84 (d, $J = 8.4$ Hz, 2H), 3.72 (s, 2H), 2.91-2.93 (m, 2H), 2.85-2.86 (m, 2H), 2.51 (s, 3H), 2.35 (s, 3 H). HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{17}\text{N}_2^+$ [M + H$^+$] 201.1386, found 201.1388.

**8-Methoxy-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (10b)**

Following the general procedure, 10b was obtained. Yield: 88%, white solid, mp 149-151 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.29 (s, 1H), 7.13 (d, $J = 8.7$ Hz, 1H), 6.87 (s, 1H), 6.77 (d, $J = 8.7$ Hz, 1H), 3.86 (s, 3H), 3.70 (s, 2H), 2.84 (t, $J = 5.6$ Hz, 2H), 2.80 (t, $J = 5.5$ Hz, 2H), 2.60 (s, 3H). HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}^+$ [M + H$^+$] 217.1335, found 217.1338.

**1-Methyl-4-(p-tolylamino)-5,6-dihydropyridin-2(1H)-one (15)**

1-Methylpiperidine-2,4-dione 14 was prepared by the known method. $^8$ 14 (2.9 g, 23 mmol), p-toluidine (2.7 g, 25 mmol) and acetic acid (150 mg, 25 mmol) were stirred at rt for 18 h. After the completion of the reaction, EtOH (50 mL) was added, the solution was dried with anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to afford the pure product 15 (4.5 g, 21 mmol). Yield: 92%, white solid, mp 179-180 °C. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.06 (d, $J = 12$ Hz, 2H), 7.01 (d, $J = 6$ Hz, 2H), 5.25 (s, 1H), 3.34 (t, $J = 6$ Hz, 2H), 2.92 (s, 3H), 2.54 (t, $J = 6$ Hz, 2H), 2.29 (s, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 169.18, 152.56, 136.83, 133.83, 129.71, 122.44, 90.74, 46.82, 34.21, 28.70, 20.85. HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}^+$ [M + H$^+$] 217.1335, found 217.1335.
References:


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