Synthesis of 6,7-Dihydro-5H-cyclopenta[b]pyridin-5-one analogues through Manganese-Catalyzed Oxidation of the CH₂ Adjacent to Pyridine Moiety in Water

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General
1. Reaction parameter optimization for the oxidation of 2,3-Cyclopentenopyridine 1a
2. The oxidation reactions
3. The synthesis of some substrates
4. Crystal data and structure refinement for 2a
5. ¹H and ¹³C NMR spectra
**General:** Unless otherwise stated, all reactions were carried out under air atmosphere in oven-dried and/or flame-dried glassware with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agent prior to use. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Reactions were monitored by thin layer chromatography using 0.25 mm E. Merck silica gel precoated glass plates (0.25 mm thickness, 60F-254, E. Merck) using UV light to visualize the course of reaction. $^1$H NMR and $^{13}$C NMR spectra were recorded at room temperature in CDCl$_3$ on 400 MHz instrument with tetramethylsilane (TMS) as internal standard. Flash column chromatography was performed on silica gel (200-300 mesh). Mass spectra (EI) were recorded on a Finnigan MAT 8200 at 70 eV in the EI mode. High resolution mass spectra were determined on a Thermo Scientific Orbitrap Elite, and amoles were dissolved in CH$_3$OH. The Mn(OTf)$_2$ was bought from Sigma-Aldrich. The possible metallic impurities in Mn(OTf)$_2$ were tested using ICP. Co content is 4.82 ppm. Fe content is 6.05 ppm, and Pd content is only 0.96 ppm. Cu was not detected.

1. **Reaction parameter optimization for the oxidation of 2,3-Cyclopentenopyridine 1a**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Temp. [°C]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mn(OTf)$_2$</td>
<td>H$_2$O$_2$</td>
<td>MeCN</td>
<td>25(24h)</td>
<td>n.d</td>
</tr>
<tr>
<td>2</td>
<td>Mn(OTf)$_2$</td>
<td>O$_2$</td>
<td>MeCN</td>
<td>25(24h)</td>
<td>n.d</td>
</tr>
<tr>
<td>3</td>
<td>Mn(OTf)$_2$</td>
<td>AcOOH</td>
<td>MeCN</td>
<td>25(24h)</td>
<td>2,3-cyclopentenopyridine N-Oxide</td>
</tr>
<tr>
<td>4</td>
<td>Mn(OTf)$_2$</td>
<td>M-CPBA</td>
<td>MeCN</td>
<td>25(24h)</td>
<td>2,3-cyclopentenopyridine N-Oxide</td>
</tr>
<tr>
<td>5</td>
<td>Mn(OTf)$_2$</td>
<td>t-BuOOH</td>
<td>Methanol</td>
<td>25(24h)</td>
<td>n.d</td>
</tr>
<tr>
<td>6</td>
<td>Mn(OTf)$_2$</td>
<td>t-BuOOH</td>
<td>Alcohol</td>
<td>25(24h)</td>
<td>n.d</td>
</tr>
<tr>
<td>7</td>
<td>Mn(OTf)$_2$</td>
<td>t-BuOOH</td>
<td>Isobutanol</td>
<td>25(24h)</td>
<td>n.d</td>
</tr>
</tbody>
</table>

nd: no detected

2,3-cyclopentenopyridine N-Oxide:

2. **The oxidation reactions**

General Oxidation Procedure A

6,7-dihydro-5H-cyclopenta[b]pyridin-5-one 2a:
A 25 mL round-bottom flask was subsequently charged with 2,3-Cyclopenteno pyridine (0.50 mmol), Mn(OTf)₂ (0.0025 mmol), t-BuOOH (65% in H₂O, 2.5 mmol), H₂O (2.5 mL) and then stirred at 25°C for 24h. The reaction was then extracted with ethyl acetate (3×10 mL). Organic layer was dried over anhydrous Na₂SO₄, and evaporated in vacuo. The resulting residue was finally purified by flash column chromatography (Ethyl acetate/Petroleum ether = from 1:5 to 1:1). This gave the title compound in 88% yield. Off-white solid; mp: 62-63°C; ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.82-8.77 (m, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.34-7.28 (m, 1H), 3.27 (dd, J = 8.0, 4.0 Hz, 2H), 2.81-2.74 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ ppm: 204.88, 174.36, 155.72, 131.91, 130.33, 122.47, 35.78, 28.73. HRMS (ESI) for C₈H₈NO [M+H]+, calcd: 134.0606, found: 134.0598.

The processing method of the large experiment in detail
A 500 mL round-bottom flask was subsequently charged with 2,3-cyclopenteno pyridine (25 mmol), Mn(OTf)₂ (0.125 mmol), t-BuOOH (65% in H₂O, 125 mmol), H₂O (125 mL) and then stirred at 25°C for 72h. The saturation sodium thiosulfate aqueous solution was added to the reaction system until the KI-starch test paper did not change its color. The reaction was then extracted with ethyl acetate (3×100 mL). Organic layer was dried over anhydrous Na₂SO₄, and evaporated in vacuo. The resulting residue was finally purified by flash column chromatography (Ethyl acetate/Petroleum ether = from 1:5 to 1:1). This gave the title compound in 68% yield.

General Oxidation Procedure B
2-Benzoylpyridine 2h:

A 25 mL round-bottom flask was subsequently charged with 2-Benzylpyridine (0.5 mmol), Mn(OTf)₂ (0.0025 mmol), t-BuOOH (65% in H₂O, 2.5 mmol), tert-butanol (2.5 mL) and then stirred at 50°C for 48h. The reaction mixture was evaporated in vacuo. The resulting residue was purified by flash column chromatography (Ethyl acetate/Petroleum ether = 1:5). This gave the title compound in 87% yield. Colorless solid; mp: 41-43°C; ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.60 (d, J = 4.7 Hz, 1H), 8.01-7.93 (m, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.47 (s, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.34 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ ppm: 193.84, 155.16, 148.56, 137.03, 136.32, 132.90, 130.99, 128.15, 126.13, 124.60. HRMS (ESI) for C₁₂H₁₀NO [M+H]+, calcd: 184.0762, found: 184.0758.

The compounds 2b, 2d, 2e, 2f, 2g were prepared according to general oxidation procedure A.

7,8-dihydroquinolin-5(6H)-one 2b

Compound 2b was isolated in 77% yield. Colorless solid; mp: 208-212°C; ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.61 (dd, J = 4.8, 1.8 Hz, 1H), 8.21 (dd, J = 7.9, 1.8 Hz, 1H), 7.24-7.20 (m, 1H), 6.10 (t, J = 6.2 Hz, 2H), 2.66-2.60 (m, 2H), 2.18-2.10 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ ppm: 196.91, 162.68, 152.49, 134.02, 127.18, 121.24, 37.55, 31.54, 20.85. HRMS (ESI) for C₁₂H₁₀NO [M+H]+, calcd: 184.0762, found: 184.0759.

4-methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-5-one 2d
Compound 2d was isolated in 83% yield. White solid; mp: 103-105°C; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 8.54 (dd, $J = 5.8$, 3.0 Hz, 1H), 6.72-6.64 (m, 1H), 3.95 (d, $J = 2.5$, 3H), 3.12 (td, $J = 6.0$, 3.0 Hz, 2H), 2.66 (td, $J = 6.1$, 3.3 Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm: 202.89, 177.01, 164.18, 157.24, 119.53, 105.26, 56.10, 35.89, 28.59. HRMS (ESI) for C$_9$H$_{10}$NO$_2$ [M+H]$^+$, calcd: 164.0712, found: 164.0703.

4-ethoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-5-one 2e

Compound 2e was isolated in 82% yield. Colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 8.55 (d, $J = 5.9$ Hz, 1H), 6.70 (d, $J = 5.9$ Hz, 1H), 4.26 (q, $J = 7.0$ Hz, 2H), 3.21-3.12 (m, 2H), 2.74-2.66 (m, 2H), 1.51 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm: 202.67, 177.13, 163.55, 157.02, 119.64, 105.86, 64.81, 35.92, 28.59, 14.18. HRMS (ESI) for C$_{10}$H$_{12}$NO$_2$ [M+H]$^+$, calcd: 178.0868, found: 178.0867.

4-propoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-5-one 2f

Compound 2f was isolated in 81% yield. White solid; mp: 161-162°C; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 8.53 (d, $J = 5.9$ Hz, 1H), 6.69 (d, $J = 5.9$ Hz, 1H), 4.15 (t, $J = 6.7$ Hz, 2H), 3.19-3.09 (m, 2H), 2.72-2.63 (m, 2H), 1.90-1.79 (m, 2H), 1.55-1.44 (m, 2H), 0.96 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm: 203.0, 177.53, 164.24, 157.43, 120.17, 106.42, 71.00, 36.39, 29.06, 22.46, 10.70. HRMS (ESI) for C$_{11}$H$_{14}$NO$_2$ [M+H]$^+$, calcd: 192.1025, found: 192.1032.

4-butoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-5-one 2g

Compound 2g was isolated in 73% yield. Colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 8.53 (d, $J = 5.9$ Hz, 1H), 6.69 (d, $J = 5.9$ Hz, 1H), 4.15 (t, $J = 6.7$ Hz, 2H), 3.19-3.09 (m, 2H), 2.72-2.63 (m, 2H), 1.90-1.79 (m, 2H), 1.55-1.44 (m, 2H), 0.96 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm: 202.50, 177.02, 163.75, 156.92, 119.67, 105.93, 68.86, 35.90, 30.54, 28.55, 18.99, 13.70. HRMS (ESI) for C$_{12}$H$_{16}$NO$_2$ [M+H]$^+$, calcd: 206.1181, found: 206.1171.

The compounds 2i, 2j, 2k, 2l, 2m, 2n, 2o were prepared according to general oxidation procedure B.

(4-chlorophenyl)(pyridin-2-yl)methanone 2i
Compound 2i was isolated in 86% yield. White solid; mp: 65-66°C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 8.68 (d, \(J = 4.4\) Hz, 1H), 8.09-8.00 (m, 3H), 7.87 (td, \(J = 7.7, 1.7\) Hz, 1H), 7.49-7.39 (m, 3H); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm: 192.29, 154.68, 148.49, 139.34, 137.16, 134.61, 132.50, 128.43, 126.39, 124.63. HRMS (ESI) for C\(_{12}\)H\(_9\)ClNO [M+H]\(^+\), calcd: 218.0373, found: 218.0364.

(2,4-dinitrophenyl)(pyridin-2-yl)methanone 2j

Compound 2j was isolated in 31% yield. White solid; mp: 146-147°C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 9.02 (s, 1H), 8.61 (d, \(J = 8.3\) Hz, 1H), 8.48 (d, \(J = 4.6\) Hz, 1H), 8.29 (d, \(J = 7.8\) Hz, 1H), 7.94 (t, \(J = 7.7\) Hz, 1H), 7.77 (d, \(J = 8.3\) Hz, 1H), 7.48 (dd, \(J = 7.4, 4.9\) Hz, 1H); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm: 191.53, 151.81, 149.31, 148.50, 143.79, 136.99, 133.66, 131.15, 128.90, 126.00, 124.52, 21.73. HRMS (ESI) for C\(_{12}\)H\(_8\)N\(_3\)O\(_5\) [M+H]\(^+\), calcd: 274.0464, found: 274.0460.

Pyridin-2-yl(p-tolyl)methanone 2k

Compound 2k was isolated in 80% yield. Yellow oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 8.74-8.67 (m, 1H), 8.03-7.95 (m, 3H), 7.90-7.82 (m, 1H), 7.45 (td, \(J = 4.8, 2.4, 1.2\) Hz, 1H), 7.28 (d, \(J = 7.5\) Hz, 2H), 2.41 (d, \(J = 1.6\) Hz, 3H); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm: 193.56, 155.42, 148.50, 143.79, 136.99, 133.66, 131.15, 128.90, 126.00, 124.52, 21.73. HRMS (ESI) for C\(_{13}\)H\(_8\)N\(_3\)O\(_5\) [M+H]\(^+\), calcd: 198.0919, found: 198.0919.

(4-ethylphenyl)(pyridin-2-yl)methanone 2l

Compound 2l was isolated in 81% yield. Yellow oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 8.73-8.65 (m, 1H), 7.99 (d, \(J = 8.1\) Hz, 2H), 7.85 (dd, \(J = 11.3, 4.2\) Hz, 1H), 7.43 (dd, \(J = 6.8, 5.6\) Hz, 1H), 7.29 (d, \(J = 7.9\) Hz, 2H), 2.69 (q, \(J = 7.6\) Hz, 2H), 1.24 (td, \(J = 7.6, 0.8\) Hz, 3H); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm: 193.56, 155.41, 149.94, 148.50, 137.01, 133.85, 131.26, 127.76, 126.01, 124.54, 29.05, 15.24. HRMS (ESI) for C\(_{14}\)H\(_{14}\)NO [M+H]\(^+\), calcd: 212.1075, found: 212.1079.

4-Benzoylpyridine 2m

Compound 2k was isolated in 72% yield. White solid; mp: 68-70°C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 8.77 (d, \(J = 5.7\) Hz, 2H), 7.78 (d, \(J = 7.5\) Hz, 2H), 7.60 (t, \(J = 7.4\) Hz, 1H), 7.54 (d, \(J = 5.7\) Hz, 2H), 7.47 (t, \(J = 7.6\) Hz, 2H); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm: 195.49, 150.75, 144.78, 136.32, 133.91, 130.52, 129.05, 123.25. HRMS (ESI) for C\(_{12}\)H\(_{10}\)NO [M+H]\(^+\), calcd: 184.0762, found: 184.0759.
(4-nitrophenyl)(pyridin-4-yl)methanone 2n

\[
\text{N} \quad \text{NO}_2
\]

Compound 2n was isolated in 70% yield. White solid; mp: 121-123°C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 8.84 (d, \(J = 4.2\) Hz, 2H), 8.34 (d, \(J = 7.9\) Hz, 2H), 7.96 (d, \(J = 8.5\) Hz, 2H), 7.60-7.54 (m, 2H); \(^1^3\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm: 193.92, 151.24, 150.91, 143.29, 141.27, 131.36, 124.32, 123.09. HRMS (ESI) for C\(_{12}\)H\(_9\)N\(_2\)O\(_3\) [M+H]\(^+\), calcd: 229.0613, found: 229.0618.

(4-chlorophenyl)(pyridin-4-yl)methanone 2o

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\text{Cl}
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Compound 2o was isolated in 70% yield. White solid; mp: 108-110°C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 8.80 (d, \(J = 4.3\) Hz, 2H), 7.75 (d, \(J = 8.2\) Hz, 2H), 7.53 (d, \(J = 4.5\) Hz, 2H), 7.47 (d, \(J = 8.2\) Hz, 2H); \(^1^3\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm: 193.85, 150.48, 143.99, 140.17, 134.22, 131.46, 129.04, 122.65. HRMS (ESI) for C\(_{12}\)H\(_9\)ClNO [M+H]\(^+\), calcd: 218.0373, found: 218.0368.

The oxidation procedure of 1c forming compound 2c.

A 25 mL round-bottom flask was subsequently charged with 2,3-cycloheptenopyridine (0.5 mmol), Mn(OTf)\(_2\) (0.0025 mmol), \(t\)-BuOOH (65% in H\(_2\)O, 2.5 mmol), \(t\)-butanol (2.5 mL) and then stirred at 50°C for 24 h. The reaction mixture was evaporated in vacuo. The resulting residue was purified by flash column chromatography (Ethyl acetate/Petroleum ether = 1:5). This gave the title compound in 41% yield. Colorless oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 8.55 (dd, \(J = 4.8, 1.8\) Hz, 1H), 7.96 (dd, \(J = 7.8, 1.8\) Hz, 1H), 7.20 (d, \(J = 4.9\) Hz, 1H), 7.18 (s, 1H), 3.16-3.10 (m, 2H), 2.74 (dd, \(J = 7.2, 5.3\) Hz, 2H), 1.95-1.87 (m, 2H), 1.87-1.79 (m, 2H); \(^1^3\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm: 203.35, 160.18, 150.78, 135.66, 132.94, 120.84, 39.87, 34.87, 23.05, 20.43. HRMS (ESI) for C\(_{10}\)H\(_{12}\)NO [M+H]\(^+\), calcd: 162.0919, found: 162.0928.

The oxidation reaction of 1a with BHT

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\begin{array}{c}
1a \\
\text{Mn(OTf)}_2 (0.5\text{ mol\%}) \\
\text{t-BuOOH (0.5\%, 65\% in H}_2\text{O)} \\
\text{H}_2\text{O (2.5 mL), BHT (2 equiv.)} \\
2a \\
\text{Not Detected}
\end{array}
\]

A 25 mL round-bottom flask was subsequently charged with 2,3-Cyclopentenopyridine 1a (0.50 mmol), Mn(OTf)\(_2\) (0.0025 mmol), BHT (1 mmol), H\(_2\)O (2.5 mL) and then added \(t\)-BuOOH (65% in H\(_2\)O, 2.5mmol), stirred at 25°C for 24h.

3. The synthesis of some substrates

The synthesis of 2,3-Cyclopentenopyridine N-Oxide
Under air, CH₃COOOH (126 mmol, 30% in H₂O) was added slowly to a 25 °C solution of 2,3-cycloheptenopyridine (1c, 42 mmol) in 100 mL CH₂Cl₂ in a 250 mL 2-L flask, and then stirred for 48 h. 100 mL H₂O was added to the reaction mixture. Then anhydrous K₂CO₃ was slowly added to the reaction mixture until no bubbles up. The mixture was then extracted with CH₂Cl₂ (5×100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated on a rotary evaporator. This gave the title compound in 98% yield. White solid; mp 120-122 °C. ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.11 (d, J = 3.8 Hz, 1H), 7.15 (dd, J = 23.3, 5.8 Hz, 2H), 3.22 (s, 2H), 3.04 (t, J = 7.0 Hz, 2H), 2.35-2.11 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ ppm: 153.08, 142.22, 137.18, 123.80, 122.75, 77.51, 77.20, 76.88, 31.49, 29.45, 21.94. GC-MS: 135.0, 118.0, 104.0, 91.0, 77.0, 63.0, 51.0, 39.0, 27.1, 15.1.

The synthesis of 4-Chloro-6,7-dihydro-5H-cyclopenta[b]pyridine

Under argon, POCl₃ (81.4 mmol) was added slowly to a 25 °C solution of 2,3-Cyclopentenopyridine N-Oxide (40.7 mmol) in anhydrous 1,2-dichloroethane (100 mL) in a 250 mL 2-L flask that was placed in an ice bath. The reaction mixture was stirred for 20 min at room temperature. The reaction vessel was then fitted with a condenser and heat to reflux for 5 h. Next, the reaction mixture was allowed to room temperature and poured into a mixture of ice and water slowly. Then, anhydrous K₂CO₃ was slowly added to the reaction mixture until no bubbles up. The mixture was then extracted with CH₂Cl₂ (3×150 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated on a rotary evaporator. The resulting residue was purified by flash column chromatography (Ethyl acetate/Petroleum ethene = 1:5). This gave the title compound in 85% yield. Yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.15 (d, J = 5.0 Hz, 1H), 6.96 (d, J = 4.8 Hz, 1H), 3.01 (t, J = 7.7 Hz, 2H), 2.92 (t, J = 7.5 Hz, 2H), 2.08 (dd, J = 15.4, 7.7 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ ppm: 167.17, 148.44, 140.59, 135.68, 121.30, 34.95, 29.86, 21.92. HRMS (ESI) for C₈H₉ClN [M+H]+, calcd: 154.0424, found: 154.0422.


The synthesis of 4-Methoxy-6,7-dihydro-5H-cyclopenta[b]pyridine

A 150 mL thick wall pressure bottle was charged with 20 mL CH₃OH and Na (7.5 mmol) was added. After the Na reacted completely, the 4-chloro-6,7-dihydro-5H-cyclopenta[b]pyridine (1.5 mmol) was added, and screwed on the sieve, and then stirred at 100°C for 24 h. The reaction mixture was evaporated in vacuo. 20 mL H₂O was added to the resulting residue and the mixture was then extracted with CH₂Cl₂ (3×100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated on a rotary evaporator and purified by flash column chromatography (Ethyl acetate/Petroleum ethene= 1:3). This gave the title compound in 91% yield. Yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.20 (d, J = 5.7 Hz, 1H), 6.51 (d, J = 5.8 Hz, 1H), 3.79 (s, 3H), 2.94 (t, J = 7.7 Hz, 2H), 2.81 (t, J = 7.5 Hz, 2H), 2.09-1.99 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ ppm: 166.83, 162.30, 149.77, 124.23, 103.86, 77.42, 77.10, 76.78, 54.98, 34.50, 27.32, 22.48. HRMS (ESI) for C₉H₁₂NO [M+H]+, calcd: 150.0919, found: 150.0937.
4-Ethoxy-6,7-dihydro-5H-cyclopenta[b]pyridine

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\text{H}_3\text{C} - \text{O} - \text{N}
\]

Compound 1f was isolated in 89% yield. Colourless oil. \(^{1}\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 8.14 (d, \(J = 5.8\) Hz, 1H), 6.44 (d, \(J = 5.8\) Hz, 1H), 3.99 (q, \(J = 7.0\) Hz, 2H), 2.90 (t, \(J = 7.7\) Hz, 2H), 2.78 (t, \(J = 7.4\) Hz, 2H), 2.01 (dd, \(J = 15.2, 7.6\) Hz, 2H), 1.33 (t, \(J = 7.0\) Hz, 3H); \(^{13}\text{C}\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm: 166.77, 161.62, 149.56, 124.31, 104.51, 63.27, 34.51, 27.37, 22.45, 14.51. HRMS (ESI) for C\(_{10}\)H\(_{14}\)NO \([M+H]^+\), calcd: 164.1075, found: 164.1079.

4-Propoxy-6,7-dihydro-5H-cyclopenta[b]pyridine

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\text{H}_3\text{C} - \text{O} - \text{N}
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Compound 1g was isolated in 92% yield. Yellow oil. \(^{1}\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 8.15 (d, \(J = 5.7\) Hz, 1H), 6.47 (d, \(J = 5.8\) Hz, 1H), 3.90 (t, \(J = 6.5\) Hz, 2H), 2.92 (t, \(J = 7.7\) Hz, 2H), 2.80 (t, \(J = 7.4\) Hz, 2H), 2.02 (p, \(J = 7.6\) Hz, 2H), 1.82-1.68 (m, 2H), 0.97 (t, \(J = 7.4\) Hz, 3H); \(^{13}\text{C}\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm: 166.74, 161.81, 149.54, 124.39, 104.60, 69.17, 34.49, 27.33, 22.38 (d, \(J = 15.4\) Hz), 10.32. HRMS (ESI) for C\(_{11}\)H\(_{16}\)NO \([M+H]^+\), calcd: 178.1232, found: 178.1221.

4-Butoxy-6,7-dihydro-5H-cyclopenta[b]pyridine

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\text{H}_3\text{C} - \text{O} - \text{N}
\]

Compound 1h was isolated in 90% yield. Yellow oil. \(^{1}\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 8.13 (d, \(J = 4.9\) Hz, 1H), 6.45 (d, \(J = 5.2\) Hz, 1H), 3.92 (t, \(J = 5.9\) Hz, 2H), 2.90 (t, \(J = 7.6\) Hz, 2H), 2.78 (t, \(J = 7.2\) Hz, 2H), 2.00 (dd, \(J = 9.9, 5.0\) Hz, 2H), 1.77-1.62 (m, 2H), 1.49-1.32 (m, 2H), 0.90 (dt, \(J = 11.5, 5.6\) Hz, 3H); \(^{13}\text{C}\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm: 166.69, 161.79, 149.53, 124.36, 104.55, 67.42, 34.47, 30.96, 27.33, 22.43, 19.10, 13.70. HRMS (ESI) for C\(_{12}\)H\(_{18}\)NO \([M+H]^+\), calcd: 192.1388, found: 192.1365.

2,4-Dimethyl-3-(2-pyridinylmethyl)pentan-3-ol

To a stirred solution of 2-methylpyridine (8 mL, 80.8 mmol) in dry THF (120 mL), under Ar-atmosphere was added BuLi (34 mL, 2.5 M in hexanes, 85mmol) dropwise at -78 °C. After 1 h stirring at -78 °C/-50 °C, diisopropylketone (13 mL, 91.4 mmol) was added and the mixture was stirred further at -50 °C for 2 h. The reaction was then quenched with water (50 mL) and extracted three times with ethyl acetate (3 × 100mL). The combined organic fractions were dried over MgSO\(_4\) and filtered over a pad of Celite. The solvent was removed under reduced pressure and the resulting residue was finally purified via column chromatography (Ethyl acetate/Petroleum ether= 1:10).

2,4-Dimethyl-3-(2-pyridinylmethyl)pentan-3-ol was isolated in 91% yield. Colourless oil; \(^{1}\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm: 8.35 (d, \(J = 4.6\) Hz, 1H), 7.52 (tt, \(J = 7.7, 2.4\) Hz, 1H), 7.10 (d, \(J = 6.9\) Hz, 1H), 7.06-6.98 (m, 1H), 6.23 (d, \(J = 1.0\) Hz, 1H), 2.83 (d, \(J = 2.0\) Hz, 2H), 1.92-1.77 (m, 2H), 0.83 (td, \(J
= 6.7, 2.1 Hz, 12H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm: 161.74, 147.76, 136.74, 124.52, 120.98, 78.02, 38.11, 35.14, 18.12, 17.88.

2-(4-methylbenzyl)pyridine

A 50 mL RBF was subsequently charged with palladium(II) trifluoroacetate (42mg, 0.125 mmol), 1-bromo-4-methylbenzene (0.43, 2.5 mmol), 2,4-dimethyl-3-(2-pyridylmethyl)pentan-3-ol (0.621 g, 3 mmol), Cs$_2$CO$_3$ (1.22 g, 3.75 mmol), o-xylene (6 mL) and tricyclohexylphosphine (70mg, 0.25 mmol). The resulting mixture was replaced with Ar for 3 times and stirred at reflux under a Ar-atmosphere for 6 h. After cooling down to room temperature, the mixture was filtered over a pad of Celite. The solvent was removed under reduced pressure and the crude residue was finally purified via column chromatography (Ethyl acetate/Petroleum ethe= 1:5).

2-(4-methylbenzyl)pyridine was isolated in 85% yield. Colourless oil; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 8.52-8.47 (m, 1H), 7.50 -7.40 (m, 1H), 7.13 (d, J = 7.9 Hz, 2H), 7.10-6.96 (m, 4H), 4.08 (s, 2H), 2.27 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm: 161.33, 149.34, 136.50 (d, J = 6.2 Hz), 135.84, 129.33, 129.05, 123.03, 121.17, 44.39, 21.09. HRMS (ESI) for C$_{13}$H$_{14}$N [M+H]$^+$, calcd: 184.1126, found: 184.1129.

2-(4-ethylbenzyl)pyridine

2-(4-ethylbenzyl)pyridine was isolated in 87% yield. Colourless oil; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 8.54-8.47 (m, 1H), 7.50-7.41 (m, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 7.8 Hz, 1H), 7.02-6.96 (m, 1H), 4.10 (s, 2H), 2.58 (q, J = 7.6 Hz, 2H), 1.18 (t, J = 7.6 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm: 161.31, 149.35, 142.24, 136.77, 136.45, 129.09, 128.12, 123.07, 121.16, 44.43, 28.52, 15.67. HRMS (ESI) for C$_{14}$H$_{16}$N [M+H]$^+$, calcd: 198.1283, found: 198.1290.

Table 2 Crystal data and structure refinement for 2a

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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<tbody>
<tr>
<td>Empirical formula</td>
<td>C8 H7 N O</td>
</tr>
<tr>
<td>Formula weight</td>
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</tr>
<tr>
<td>Temperature</td>
<td>293(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
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</tr>
<tr>
<td>Space group</td>
<td>P b c a</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 7.5044(13) Å, α= 90°</td>
</tr>
</tbody>
</table>
b = 11.9291(19) Å

\[ \beta = 90^\circ. \]

c = 14.8473(19) Å

\[ \gamma = 90^\circ. \]

Volume

1329.1(4) Å³

Z

8

Density (calculated)

1.331 Mg/m³

Absorption coefficient

0.089 mm⁻¹

F(000)

560

Crystal size

0.211 x 0.165 x 0.123 mm³

Theta range for data collection

3.416 to 25.492°.

Index ranges

-7 \leq h \leq 9, -9 \leq k \leq 14, -17 \leq l \leq 17

Reflections collected

4238

Independent reflections

1228 [R(int) = 0.0483]

Completeness to theta = 25.242°

99.7 %

Absorption correction

Semi-empirical from equivalents

Max. and min. transmission

1.00000 and 0.63215

Refinement method

Full-matrix least-squares on F²

Data / restraints / parameters

1228 / 0 / 92

Goodness-of-fit on F²

1.085

Final R indices [I>2sigma(I)]

R1 = 0.0552, wR2 = 0.1269

R indices (all data)

R1 = 0.0693, wR2 = 0.1383

Extinction coefficient

0.26(2)

Largest diff. peak and hole

0.269 and -0.316 e.Å⁻³

5. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra