Supporting Information

Efficient synthesis of anthranilic esters via Pd-catalyzed
dehydrogenative/decarbonylative coupling of anilides and glyoxylates

Sizhuo Wang, Zhiyong Yang, Jidan Liu, Kai Xie, Anwei Wang,
Xiang chen, Ze Tan,*

State Key Laboratory of Chemo/Biosensing and Chemometrics, College of
Chemistry and Chemical Engineering, Hunan University, Changsha
410082, P.R. China. Tel: +86-731 88822400;
E-mail: ztanze@gmail.com

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I. General Information

All the solvents and commercially available reagents were purchased from commercial sources and used directly. $^1$H NMR and $^{13}$C NMR were recorded in CDCl$_3$ at room temperature on the Varian INOVA-400 spectrometer (400 MHz $^1$H). The chemical-shifts scale is based on internal TMS. The coupling constants, $J$, are reported in Hertz (Hz). Products were purified by flash column chromatography on 200-300 mesh silica gel, SiO$_2$.

II. Representative Procedure and Selected Compounds Data

2-Acetylamino-benzoic acid ethyl ester

\[
\begin{align*}
\text{NHAc} & \quad + \quad \text{OEt} \quad \text{Pd(TFA)$_2$, TBHP} \\
\text{HOC} & \quad \text{Dppp, Toluene} \\
\text{COOEt} & \quad \text{NHAc}
\end{align*}
\]

A 25 mL tube was charged with acetonilide (67.5mg, 0.5mmol), glyoxylate (204mg, 1.0mmol), TBHP (0.36mL, 2.0mmol), dppp (20.7mg, 0.05mmol), Pd(TFA)$_2$ (13.9mg, 0.05 mmol) and toluene (1mL). The reaction tube was then capped under N$_2$ and stirred at 120°C for 16-24h. Upon completion of the reaction, the reaction tube was allowed to cool room temperature and quenched with brine and diluted with DMC. The organic layer was separated and the aqueous layer was washed with DMC. The filtrate was concentrated under reduced pressure. The crude products were purified with flash column chromatography on silica gel (petroleum ether/ethyl acetate, 8/1) to afford 56.9 mg of the desired 2-Acetylamino–benzoic acid ethyl ester in 55% yield. Better yield (66%) can be obtained if the reaction was stopped at 12h, and another batch of Pd(TFA)$_2$ (5mol%) was added.
Analytical data of Acetylamino-benzoic acid ethyl ester

2-Acetylamino-benzoic acid ethyl ester \(^{1-4}\)

\[
\text{COOEt} \quad \text{NHAc}
\]

TLC: R\(_f\) = 0.60 (petroleum ether/ethyl acetate, 4/1); Yield 66%;

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 11.14 (s, 1H), 8.70 (d, \(J = 8.4\) Hz, 1H), 8.04-8.06 (m, 1H), 7.52-7.56 (m, 1H), 7.07-7.10 (m, 1H), 4.38 (q, \(J = 7.2\) Hz, 2H), 2.25 (s, 3H), 1.42 (t, \(J = 7.2\) Hz, 3H);

\(^13\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 169.22, 168.29, 141.46, 134.54, 130.73, 122.38, 120.23, 114.98, 61.38, 25.48, 14.15;

HRMS: calcd for C\(_{11}\)H\(_{13}\)NO\(_3\) : 207.0895 , found: 207.0893;

2-Acetylamino-5-methyl-benzoic acid ethyl ester

\[
\text{COOEt} \quad \text{NHAc}
\]

TLC: R\(_f\) = 0.6 (petroleum ether/ethyl acetate, 4/1); Yield 60%;

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 11.00 (s, 1H), 8.58 (d, \(J = 8.8\) Hz, 1H), 7.83 (s, 1H), 7.35 (dd, \(J = 8.8\) Hz, 2Hz, 1H), 4.37 (dd, \(J = 14.4\) Hz, 6.4Hz, 2H), 2.33 (s, 3H), 2.24 (s, 3H), 1.43 (t, \(J = 7.2\) Hz, 3H);

\(^13\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 168.89, 168.32, 139.12, 135.22, 131.84, 130.74, 120.19, 114.85, 61.28, 25.44, 20.65, 14.17;

LRMS: m/z calcd for C\(_{12}\)H\(_{15}\)NO\(_3\) : 221, found: 221;

IR.(KBr)/cm\(^{-1}\): 3268, 2925, 1694, 1239;

2-Acetylamino-5-fluoro-benzoic acid ethyl ester

\[
\text{COOEt} \quad \text{NHAc}
\]

TLC: R\(_f\) = 0.45 (petroleum ether/ethyl acetate, 4/1); Yield 40%;

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.97 (s, 1H), 8.71 (dd, \(J = 9.6\) Hz, 5.2 Hz, 1H), 7.72 (dd, \(J = 9.2\) Hz, 3.2 Hz, 1H), 7.29-7.24 (m, 1H), 4.39 (dd, \(J = 14.4\) Hz, 7.6 Hz, 2H), 2.24 (s, 3H), 1.43 (t, \(J = 7.2\) Hz, 3H);

\(^13\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 168.93, 167.23, 157.15 (d, \(J_{C-F} = 241\) Hz), 137.92, 122.07 (d, \(J_{C-F} = 7.6\) Hz ), 121.53 (d, \(J_{C-F} = 21.3\) Hz), 116.72 (d, \(J_{C-F} = 24.4\) Hz)
Hz), 116.24 (d, J_C-F = 6.8 Hz), 61.80, 25.38, 14.10;

HRMS: m/z calcd for C_{11}H_{12}FNO_3: 225.0801, found: 225.0804;
IR.(KBr)/cm^{-1}: 3281, 2987, 1701, 1236;

2-Acetylamino-5-chloro-benzoic acid ethyl ester

TLC: R_f = 0.45 (petroleum ether/ethyl acetate, 4/1); Yield 41%;

^1H NMR (400 MHz, CDCl_3): δ 11.05 (s, 1H), 8.69 (d, J = 9.2 Hz, 1H), 7.99 (s, 1H), 7.48 (dd, J = 9.2 Hz, 2.8 Hz, 1H), 4.18-4.36 (m, 2H), 2.24 (s, 3H), 1.43 (t, J = 6.8 Hz, 3H);

^13C NMR (100 MHz, CDCl_3): δ 169.09, 167.22, 140.08, 134.32, 130.27, 127.33, 121.64, 116.18, 61.80, 25.46, 14.12.

HRMS: m/z calcd for C_{11}H_{12}ClNO_3: 241.0506, found: 241.0510;
IR.(KBr)/cm^{-1}: 3265, 2961, 1703, 1235;

2-Acetylamino-4-methoxy-benzoic acid ethyl ester

TLC: R_f = 0.56 (petroleum ether/ethyl acetate, 4/1); Yield 51%;

^1H NMR (400 MHz, CDCl_3): δ 11.34 (s, 1H), 8.38 (d, J = 2.4 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 6.60 (dd, J = 12 Hz, 2.8 Hz, 1H), 4.37-4.32 (m, 2H), 3.87 (s, 3H), 2.24 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H);

^13C NMR (100 MHz, CDCl_3): δ 169.33, 168.19, 164.35, 143.73, 132.31, 109.62, 107.41, 103.72, 60.94, 55.49, 25.46, 14.21;

HRMS: m/z calcd for C_{12}H_{13}ClNO_3: 241.0506, found: 241.0510;
IR.(KBr)/cm^{-1}: 3265, 2961, 1703, 1235;

2-Acetylamino-5-propoxy-benzoic acid ethyl ester

TLC: R_f = 0.58 (petroleum ether/ethyl acetate, 4/1); Yield 58%;

^1H NMR (400 MHz, CDCl_3): δ 10.84 (s, 1H), 8.60 (d, J = 9.2 Hz, 1H), 7.53 (s, 1H), 7.11 (dd, J = 9.2 Hz, 3.2 Hz, 1H), 4.40-4.35 (m, 2H), 3.92 (t, J = 6.8 Hz, 2H), 2.22 (s, 3H), 1.84-1.79 (m, 2H), 1.42 (t, J = 7.2 Hz, 3H), 1.05 (t, J = 7.6 Hz, 3H);

^13C NMR (100 MHz, CDCl_3): δ 168.64, 167.94, 153.81, 134.96, 121.72, 120.85, 116.08, 115.59, 69.82, 61.41, 25.32, 22.48, 14.15, 10.46;

HRMS: m/z calcd for C_{14}H_{19}NO_4: 265.1314, found: 265.1318;

S4
2-Acetylamino-4-chloro-benzoic acid ethyl ester

TLC: Rₜ = 0.45 (petroleum ether/ethyl acetate, 4/1); Yield 49%

¹H NMR (400 MHz, CDCl₃): δ 11.19 (s, 1H), 8.80 (d, J = 2Hz, 1H), 7.97 (d, J = 8.8Hz, 1H), 7.05 (dd, J = 8.4Hz, 2.4Hz, 1H), 4.38 (dd, J = 14.4Hz, 7.6Hz, 2H), 2.25 (s, 3H), 1.42 (t, J = 6.8Hz, 3H);

¹³C NMR (100MHz, CDCl₃): δ 169.29, 167.71, 142.30, 140.81, 131.80, 128.79, 122.64, 120.80, 113.13, 16.64, 25.47, 14.12;

LRMS: m/z calcd for C₁₁H₁₂ClNO₃: 241, found: 241

Anal. Calcd for C₁₁H₁₂ClNO₃: C, 54.67; H, 5.00; N, 5.80; Found: C, 54.60; H, 4.95; N, 5.74;

2-Acetylamino-5-butoxy-benzoic acid ethyl ester

TLC: Rₜ = 0.60 (petroleum ether/ethyl acetate, 4/1); Yield 54%

¹H NMR (400 MHz, CDCl₃): δ 10.83 (s, 1H), 8.60 (d, J = 9.2Hz, 1H), 7.52 (s, 1H), 7.11 (d, J = 9.2Hz, 1H), 4.04 (t, J = 7.6Hz, 2H), 3.96 (t, J = 6.8Hz, 2H), 2.22 (s, 3H), 1.79-1.75 (m, 2H), 1.53-1.47 (m, 2H), 1.44-1.40 (m, 3H), 0.98 (t, J = 14.8Hz, 3H);

¹³C NMR (100MHz, CDCl₃): δ 168.66, 167.96, 153.84, 134.98, 121.74, 120.85, 116.10, 115.60, 68.02, 61.43, 31.20, 25.34, 19.17, 14.17, 13.83;

HRMS: m/z calcd for C₁₅H₂₁NO₄: 279.1471, found: 279.1474;

2-Acetylamino-5-methoxy-benzoic acid ethyl ester

TLC: Rₜ = 0.55 (petroleum ether/ethyl acetate, 4/1); Yield 63%

¹H NMR (400 MHz, CDCl₃): δ 10.82 (s, 1H), 8.61 (d, J = 9.2Hz, 1H), 7.52 (s, 1H), 7.11 (dd, J = 9.6Hz, 3.6Hz, 1H), 4.38 (dd, J = 14.8Hz, 7.6Hz, 2H), 3.82 (s, 3H), 2.21 (s, 3H), 1.41 (t, J = 6.8Hz, 3H);

¹³C NMR (100MHz, CDCl₃): δ 168.66, 167.90, 154.23, 135.19, 121.81, 120.47, 116.09, 114.75, 61.47, 55.56, 25.35, 14.16;

LRMS: m/z calcd for C₁₂H₁₅NO₄: 237.1001, found: 237.0944;

Anal. Calcd for C₁₂H₁₅NO₄: C, 60.75; H, 6.37; N, 5.90; Found: C, 60.97; H, 6.10;
N, 5.63;

IR (KBr/cm\(^{-1}\)): 3267, 2982, 1680, 1240;

2-Acetylamino-4-fluoro-benzoic acid ethyl ester

\[
\text{COOEt} \quad \text{NHAc}
\]

TLC: \( R_f = 0.45 \) (petroleum ether/ethyl acetate, 4:1); Yield 41%;

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 11.29 (s, 1H), 8.53 (dd, \( J = 12.4 \text{Hz}, 2.8 \text{Hz}, 1H \)), 8.06 (dd, \( J = 7.2 \text{Hz}, 1H \)), 6.79-6.74 (m, 1H), 4.38 (dd, \( J = 14.8 \text{Hz}, 7.2 \text{Hz}, 2H \)), 2.25 (s, 3H), 1.42 (t, \( J = 7.2 \text{Hz}, 3H \));

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 169.36, 167.65, 166.19 (d, \( J_{C-F} = 251 \text{ Hz} \)), 143.65 (d, \( J_{C-F} = 13 \text{ Hz} \)), 132.54 (d, \( J_{C-F} = 10.7 \text{ Hz} \)), 111.10, 109.69 (d, \( J_{C-F} = 22.9 \text{ Hz} \)), 107.32 (d, \( J_{C-F} = 27.5 \text{ Hz} \)), 61.48, 25.48, 14.17;

LRMS: m/z calcd for C\(_{11}\)H\(_{12}\)FNO\(_3\): 225, found: 225;

Anal. Calcd for C\(_{11}\)H\(_{12}\)FNO\(_3\): C, 58.66; H, 5.37; N, 6.22; Found: C, 58.89; H, 5.18; N, 6.02.

2-Acetylamino-5-ethoxy-benzoic acid ethyl ester

\[
\text{COOEt} \quad \text{NHAc}
\]

TLC: \( R_f = 0.57 \) (petroleum ether/ethyl acetate, 4:1); Yield 62%;

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 10.84(s, 1H), 8.61 (d, \( J = 9.2 \text{Hz}, 1H \)), 7.53(s, 1H), 7.10 (dd, \( J = 9.2 \text{Hz}, 2.8 \text{Hz}, 1H \)), 4.37 (dd, \( J = 14 \text{Hz}, 6.8 \text{Hz}, 2H \)), 4.04 (dd, \( J = 14 \text{Hz}, 7.2 \text{Hz}, 2H \)), 2.22 (s, 3H), 1.44-1.40 (m, 6H);

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 167.71, 166.95, 152.64, 134.04, 120.77, 119.86, 115.13, 114.62, 62.84, 60.45, 24.34, 13.75, 13.17;

HRMS: m/z calcd for C\(_{13}\)H\(_{17}\)NO\(_4\): 251.1158, found: 251.1156;

2-Acetylamino-5-ethyl-benzoic acid ethyl ester

\[
\text{COOEt} \quad \text{NHAc}
\]

TLC: \( R_f = 0.58 \) (petroleum ether/ethyl acetate, 4:1); Yield 61%;

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 11.00 (s, 1H), 8.59 (d, \( J = 8.8 \text{Hz}, 1H \)), 7.85 (s, 1H), 7.38 (dd, \( J = 8.4 \text{Hz}, 2Hz, 1H \)), 4.40 (dd, \( J = 14 \text{Hz}, 7.2 \text{Hz}, 2H \)), 2.63 (dd, \( J = 15.2 \text{Hz}, 7.6 \text{Hz}, 2H \)), 2.23 (s, 3H), 1.43 (t, \( J = 7.2 \text{Hz}, 3H \)), 1.23 (t, \( J = 7.6 \text{Hz}, 3H \));

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 168.91, 168.37, 139.31, 138.28, 134.13, 129.66, 120.35, 114.95, 61.29, 28.10, 25.46, 15.59, 14.20;

LRMS: m/z calcd for C\(_{13}\)H\(_{17}\)NO\(_3\): 235, found: 235;
2-Acetylamino-5-isopropyl-benzoic acid ethyl ester

TLC: R_{f} = 0.56 (petroleum ether/ethyl acetate, 4/1); Yield 62%;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 11.00 (s, 1H), 8.60 (d, $J = 8.8$ Hz, 1H), 7.83 (s, 1H), 7.42 (dd, $J = 8.8$ Hz, 2.4 Hz, 1H), 4.39 (dd, $J = 14.8$ Hz, 5.6 Hz, 2H), 2.94-2.87 (m, 1H), 2.23 (s, 3H), 1.43 (t, $J = 6.8$ Hz, 3H), 1.25-1.24 (m, 6H);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 168.91, 168.39, 142.88, 139.37, 132.65, 128.29, 120.41, 114.95, 61.30, 33.44, 25.44, 23.85, 14.21;

LRMS: m/z calcd for C$_{14}$H$_{10}$NO$_3$: 249 , found: 249;

Anal. Calcd for C$_{14}$H$_{19}$NO$_3$ : C, 67.45; H, 7.68; N, 5.62; Found: C, 67.11; H, 7.74; N, 5.49;

2-Propionylamino-5-methyl-benzoic acid ethyl ester

TLC: R_{f} = 0.49 (petroleum ether/ethyl acetate, 4/1); Yield 47%;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 11.02 (s, 1H), 8.62 (d, $J = 8.8$ Hz, 1H), 7.83 (s, 1H), 7.35 (dd, $J = 8.8$ Hz, 2 Hz, 1H), 4.37 (dd, $J = 14$ Hz, 6.8 Hz, 2H), 2.47 (dd, $J = 14.8$ Hz, 7.2 Hz, 2H), 2.33 (s, 3H), 1.42 (t, $J = 7.6$ Hz, 3H), 1.27 (t, $J = 7.6$ Hz, 3H);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.69, 168.35, 139.26, 135.25, 131.69, 130.76, 120.23, 114.83, 61.25, 31.61, 20.65, 14.19, 9.63;

HRMS: m/z calcd for C$_{14}$H$_{19}$NO$_3$: 235.1208 , found: 235.1210;

IR.(KBr)/cm$^{-1}$: 3262, 2938, 1689, 1235;

2-Propionylamino-5- methoxy-benzoic acid ethyl ester

TLC: R_{f} = 0.46 (petroleum ether/ethyl acetate, 4/1); Yield 45%;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.87 (s, 1H), 8.66 (d, $J = 9.6$ Hz, 1H), 7.53 (d, $J = 2.8$ Hz, 1H), 7.12 (dd, $J = 9.2$ Hz, 2.8 Hz, 1H), 4.38 (dd, $J = 14.4$ Hz, 7.2 Hz, 2H), 3.82 (s, 3H), 2.46 (dd, $J = 15.2$ Hz, 7.6 Hz, 2H), 1.42 (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.6$ Hz, 3H);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.45, 167.91, 154.15, 135.32, 121.82, 120.48, 116.06, 114.78, 61.43, 55.56, 31.52, 14.16, 9.66;
HRMS: m/z calcd for C$_{13}$H$_{17}$NO$_4$: 251.1158, found: 251.1160;

III. References and notes


IV. $^1$H and $^{13}$C NMR Spectra