Iron-Catalyzed Oxidative Coupling Reaction of \(N\)-Acyl Glycine Esters and Malonates

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Supporting Information

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(A) General Methods

Commercially available reagents were used as received without further purification unless otherwise indicated. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using Silica Gel 60 F254 plates and were visualized by fluorescence quenching at 254 nm. For chromatographic purifications, analytically pure solvents were used and the silica gel 300-400 mesh was used as the solid support. $^1$H NMR and $^{13}$C NMR chemical shifts were reported in $\delta$ units, parts per million (ppm) relative to the chemical shift of residual solvent. Reference peaks for chloroform in 1H NMR and 13C NMR spectra were set at 7.26 ppm and 77.0 ppm, respectively.

(B) Analytical data for the products

Typical experimental procedure for the synthesis of product 3a-3n

To a mixture of FeCl$_3$·6H$_2$O (0.04 mmol, 20mol %), [(Pyridine-2-carbonyl)-amino]-acetic acid ester (0.2 mmol, 1.0 equiv), Cs$_2$CO$_3$ (0.10 mmol, 50mol%) in DCE (1.5 mL) were added Malonic acid diethyl ester (0.40 mmol, 2.0 equiv) and DTBP (0.40 mmol, 2.0 equiv). The reaction vessel was capped and allowed to stir at 95°C overnight. The volatiles were removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain the product. All products were identified by full spectroscopic characterization and comparison with literature or analogous literature data.

2-ethoxycarbonyl-3-[(pyridine-2-carbonyl)-amino]-2-enedioic acid diethyl ester (3a)

Yellow liquid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ =12.77 (s, 1H), 8.74 (s, 1H), 8.19 (d, $J$ = 7.8 Hz, 1H), 7.91 (td, $J$ = 7.7, 1.5 Hz, 1H), 7.54 (ddd, $J$ = 7.5, 4.8, 0.8 Hz, 1H), 4.43 (q, $J$ = 7.2 Hz, 2H), 4.37 (q, $J$ = 7.1 Hz, 2H), 4.28 (q, $J$ = 7.1 Hz, 2H), 1.40 (d, $J$ = 7.2 Hz, 3H), 1.35 (d, $J$ = 6.7 Hz, 3H), 1.32 (d, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ =165.70, 164.20, 162.72, 162.28, 148.89, 147.87, 145.07, 137.53, 127.40,
2-Ethoxycarbonyl-3-((pyridine-2-carbonyl)-amino)-2-enedioic acid 1-ethyl ester 4-methyl ester (3b)

Yellow liquid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta =$12.78 (s, 1H), 8.75 (d, $J = 4.7$ Hz, 1H), 8.19 (d, $J = 7.8$ Hz, 1H), 7.91 (t, $J = 8.5$ Hz, 1H), 7.58 – 7.51 (m, 1H), 4.37 (q, $J = 7.1$ Hz, 2H), 4.27 (q, $J = 7.1$ Hz, 2H), 3.96 (s, 3H), 1.36 (t, $J = 7.2$ Hz, 3H), 1.32 (t, $J =$ 7.2 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$165.71, 164.15, 163.35, 162.37, 148.93, 147.80, 144.91, 137.57, 127.48, 123.40, 61.85, 61.76, 53.07, 14.01, 13.90. HRMS (ESI): m/z =373.1012 [M + Na]$^+$, calcd for C$_{16}$H$_{18}$N$_2$NaO$_7$ 373.1009.

2-Ethoxycarbonyl-3-((pyridine-2-carbonyl)-amino)-2-enedioic acid 4-benzyl ester 1-ethyl ester (3c)

Yellow liquid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta =$12.77 (s, 1H), 8.73 (d, $J = 4.3$ Hz, 1H), 8.19 (d, $J = 7.8$ Hz, 1H), 7.89 (t, $J = 8.5$ Hz, 1H), 7.57 – 7.50 (m, 1H), 7.45 (d, $J = 6.6$ Hz, 2H), 7.39 – 7.32 (m, 3H), 5.38 (s, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 4.14 (q, $J =$ 7.1 Hz, 2H), 1.35 (t, $J = 7.1$ Hz, 3H), 1.23 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$165.63, 164.04, 162.65, 162.30, 148.88, 147.79, 144.70, 137.52, 134.62, 128.62, 128.43, 128.39, 127.42, 123.35, 107.28, 68.28, 61.78, 61.65, 13.98, 13.83. HRMS (ESI): m/z =449.1325 [M + Na]$^+$, calcd for C$_{22}$H$_{22}$N$_2$NaO$_7$ 449.1327.

2-Ethoxycarbonyl-3-((pyridine-2-carbonyl)-amino)2-enedioic acid 4-butyl ester 1-ethyl ester (3d)
2-Methoxycarbonyl-3-[(pyridine-2-carbonyl)-amino]-2-enedioic acid 4-ethyl ester 1-methyl ester (3e)

Yellow liquid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ =12.76 (s, 1H), 8.74 (d, $J$ = 4.6 Hz, 1H), 8.19 (d, $J$ = 7.8 Hz, 1H), 7.90 (t, $J$ = 8.5 Hz, 1H), 7.53 (dd, $J$ = 7.5, 4.8 Hz, 1H), 4.40 – 4.33 (m, 4H), 4.27 (q, $J$ = 7.1 Hz, 2H), 1.80 – 1.68 (m, 2H), 1.43 (dd, $J$ = 15.0, 7.5 Hz, 2H), 1.34 (dt, $J$ = 14.3, 7.1 Hz, 6H), 0.95 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ =165.77, 164.23, 162.87, 162.29, 148.93, 147.96, 145.14, 137.54, 127.40, 123.39, 107.12, 66.48, 61.79, 61.71, 30.12, 19.07, 14.05, 13.94, 13.64. HRMS (ESI): m/z =415.1481 [M + Na]$^+$, calcd for C$_{19}$H$_{24}$N$_2$NaO$_7$ 415.1483.

2-Methoxycarbonyl-3-[(pyridine-2-carbonyl)-amino]-2-enedioic acid dimethyl ester (3f)

Yellow liquid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.91 (s, 1H), 8.78 (d, $J$ = 4.6 Hz, 1H), 8.22 (d, $J$ = 7.8 Hz, 1H), 7.93 (t, $J$ = 8.5 Hz, 1H), 7.57 (dd, $J$ = 7.1, 5.3 Hz, 1H), 4.45 (q, $J$ = 7.2 Hz, 2H), 3.93 (s, 3H), 3.83 (s, 3H), 1.42 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$= 166.35, 164.58, 162.75, 162.38, 148.88, 147.83, 145.99, 137.60, 127.52, 123.37, 106.15, 62.68, 52.80, 52.68, 13.82. HRMS (ESI): m/z =359.0855 [M + Na]$^+$, calcd for C$_{15}$H$_{16}$N$_2$NaO$_7$ 359.0859.

2-Isopropoxycarbonyl-3-[(pyridine-2-carbonyl)-amino]-2-enedioic acid 4-ethyl ester 1-isopropyl ester (3g)

Yellow liquid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.90 (s, 1H), 8.76 (d, $J$ = 4.5 Hz, 1H), 8.19 (d, $J$ = 7.8 Hz, 1H), 7.91 (t, $J$ = 7.7 Hz, 1H), 7.55 (dd, $J$ = 7.1, 5.3 Hz, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.81 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.30, 164.51, 163.33, 162.41, 149.00, 147.70, 145.84, 137.62, 127.58, 123.47, 106.10, 53.22, 52.82, 52.76. HRMS (ESI): m/z =345.0699 [M + Na]$^+$, calcd for C$_{14}$H$_{14}$N$_2$NaO$_7$ 345.0711.
2-Isopropoxycarbonyl-3-[(pyridine-2-carbonyl)-amino]-2-enedioic acid 1-isopropyl ester 4-methyl ester (3h)

Yellow liquid; $^1$H NMR (400 MHz, CDCl$_3$) δ 12.68 (s, 1H), 8.74 (d, $J = 4.7$ Hz, 1H), 8.19 (d, $J = 7.8$ Hz, 1H), 7.90 (t, $J = 8.5$ Hz, 1H), 7.58 – 7.48 (m, 1H), 5.26 (dt, $J = 12.5$, 6.2 Hz, 1H), 5.14 (dt, $J = 12.5$, 6.3 Hz, 1H), 4.42 (q, $J = 7.2$ Hz, 2H), 1.39 (t, $J = 7.2$ Hz, 3H), 1.32 (dd, $J = 7.5$, 6.4 Hz, 12H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ =165.16, 163.98, 162.79, 162.29, 148.89, 147.98, 144.27, 137.50, 127.34, 123.33, 108.21, 21.74, 21.54, 13.72. HRMS (ESI): m/z =415.1481 [M + Na]$^+$, calcd for C$_{19}$H$_{24}$N$_2$NaO$_7$ 415.1477.

2-(Amino-benzylcarbamoyl-methylene)-malonic acid diethyl ester (5c)

Yellow solid; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.39 (dd, $J = 7.3$, 1.8 Hz, 2H), 7.33 – 7.28 (m, 3H), 4.73 (s, 2H), 4.43 (q, $J = 7.1$ Hz, 2H), 4.30 (q, $J = 7.1$ Hz, 2H), 3.73 (s, 2H), 1.37 (t, $J = 7.1$ Hz, 3H), 1.32 (t, $J = 7.1$ Hz, 3H).$^{13}$C NMR (101 MHz, CDCl$_3$) δ 188.85, 169.32, 164.55, 149.14, 148.17, 137.21, 131.43, 126.33, 122.20, 118.79, 65.90, 58.18, 41.24, 18.29. HRMS (ESI): m/z = 343.1266 [M + Na]$^+$, calcd for C$_{16}$H$_{20}$N$_2$NaO$_7$ 343.1270.
(C) Spectra

$^1$H NMR (3a)

$^{13}$C NMR (3a)
$^1$H NMR (3b)

$^{13}$C NMR (3b)
$^1$H NMR (3c)

$^{13}$C NMR (3c)
$^1$H NMR (3d)

$^{13}$CNMR (3d)
$^1$H NMR (3f)

$^{13}$C NMR (3f)
$^1$H NMR (3g)

$^{13}$C NMR (3g)
$^1$H NMR (3h)

$^{13}$C NMR (3h)
$^1$H NMR (5c)

$^{13}$C NMR (5c)