Direct, rapid, solvent-free conversion of unactivated esters to amides using lithium hydroxide as a catalyst

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Supporting Information: Experimental Studies

Key to Abbreviated Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CDCl\textsubscript{3}</td>
<td>deuterated chloroform</td>
<td></td>
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<tr>
<td>DCM</td>
<td>dichloromethane</td>
<td></td>
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<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
<td></td>
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<tr>
<td>Hex</td>
<td>hexanes</td>
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S1

General Considerations
Comments regarding origins of commercial starting materials, purification of solvents, and our spectroscopic techniques.

Synthesis of Substrates
Procedures for the synthesis of amides and spectral characterization information

\textsuperscript{1}H-NMR Spectra of Synthesized Compounds

\textsuperscript{13}C-NMR Spectra of Synthesized Compounds

Key to Abbreviated Terms:
General Considerations:

General:
Reactions were performed using a CEM Discover microwave unit. NMR Spectra (1H, 13C) were performed at 298 K on either a Bruker Avance Ultra Shield 300 MHz NMR, Bruker DRX-400 400 MHz NMR, or Bruker Avance 500 MHz NMR. $^1$H-NMR Spectra obtained in CDCl$_3$ were referenced to residual non-deuterated chloroform (7.26 ppm) in the deuterated solvent. $^{13}$C- NMR Spectra obtained in CDCl$_3$ were referenced to chloroform (77.3 ppm). Flash chromatography and silica plugs utilized Dynamic Adsorbents Inc. Flash Silica Gel (60Å porosity, 32-63 µm).

Chemicals:
Deuterated chloroform was purchased from Cambridge Isotope Laboratories and stored over 4Å molecular sieves. Ethyl benzoate, benzylamine, pyrrolidine, and cyclohexylamine were purchased from Sigma-Aldrich. Lithium hydroxide and 1,2,3,4-tetrahydroisoquinoline were purchased from Acros Organic. Ethyl-$p$-nitrobenzoate, ethyl-$4$-bromobenzoate, $n$-octylamine, and $\delta$-valerolactone were purchased from Alfa Aesar. Aniline was purchased from Fisher Scientific. Ethyl-$4$-(trifluoromethyl)benzoate and 4-methoxybenzylamine were purchased from Oakwood Chemicals. Ethyl hexanoate and benzyl benzoate were purchased from Chem Service.
Synthesis of Amides

TYPICAL PROCEDURE

N-Benzylbenzamide (3a)

To a 10-mL capacity glass microwave tube equipped with a stir bar was added ethyl benzoate (0.75 g, 5 mmol, 1 equiv), benzylamine (0.80 g, 7.5 mmol, 1.5 equiv), and lithium hydroxide (0.009 g, 0.375 mmol, 0.075 equiv). The tube was sealed with a septum and placed into the microwave cavity. The reaction mixture was heating to 200 °C using an initial microwave power of 200 W and setting a pressure cut-off of 250 psi for safety purposes. Once at temperature, the contents of the tube were maintained at 200 °C for 30 min. After completion of the heating time, the reaction vessel was cooled to 50 °C before removing from the microwave unit. Product conversion was then determined by $^1$H NMR. To isolate the product, the contents of the tube were triturated with hexanes, filtered through a fritted funnel, and washed with more hexanes. The solid precipitate was dissolved in EtOAc and filtered through a pad of Celite. The ethyl acetate was removed in vacuo by rotary evaporation to afford the pure amide product, N-benzyl benzamide as a white solid (0.823 g, 78%).$^{1,6}$

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 4.56 (d, $J$=5.84 Hz, 2 H) 7.26 - 7.32 (m, 5 H) 7.35 (t, $J$=7.59 Hz, 2 H) 7.46 (t, $J$=1.00 Hz, 1 H) 7.81 (d, $J$=7.79 Hz, 2 H)

$^1^3$C NMR (CDCl$_3$, 100 MHz) δ ppm 43.55 (CH$_2$) 115.61 - 115.96 (d, $J$=1.00 Hz, C-$H$) 127.24 (CH) 127.45 (CH) 127.82 (CH) 128.56 (CH) 128.72 (CH) 131.52 (CH) 134.48 (C) 138.56 (C) 167.73 (C)

N-(4-Fluorobenzyl) benzamide (3b) (0.915 g, 80%) was prepared from 4-fluorobenzylamine and ethyl benzoate using the typical procedure. The crude compound was filtered through a silica plug with a gradient of 9:1 Hex: EtOAc then 1:1 Hex: EtOAc basified with 10% triethylamine as the eluent to afford the product as a brown solid.$^{5}$

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 4.56 (d, $J$=5.76 Hz, 2 H) 6.77 (br. s., 1 H) 6.99 (tt, $J$=1.00 Hz, 2 H) 7.26 - 7.33 (m, 2 H) 7.35 - 7.44 (m, 2 H) 7.49 (tt, $J$=1.00 Hz, 1 H) 7.74 - 7.82 (m, 2 H)

$^1^3$C NMR (CDCl$_3$, 100 MHz) δ ppm 43.55 (CH$_2$) 115.61 - 115.96 (d, $J$=1.00 Hz, CH) 127.24 (CH) 128.82 (CH) 129.74 (d, $J$=8.09 Hz, CH) 131.85 (CH) 134.36 (d, $J$=8.09 Hz, C) 134.49 (C) 161.15 - 163.70 (d, $J$=1.00 Hz, C) 167.69 (C)
**N-(4-Methoxybenzyl)-benzoylamide (3c)** (0.974 g, 81%) was prepared from 4-methoxybenzylamine and ethyl benzoate using the typical procedure. The crude compound was filtered through a silica plug with a gradient of 9:1 Hex: EtOAc then 1:1 Hex: EtOAc basified with 10% triethylamine as the eluent to afford the product as a white solid.\(^5\)

\(^{1}\text{H NMR}\) (400 MHz, CDCl\(_3\)) δ ppm 3.79 (s, 3 H) 4.56 (d, \(J=5.21\) Hz, 2 H) 6.75 (br. s., 1 H) 6.87 (d, \(J=8.42\) Hz, 2 H) 7.27 (d, \(J=8.27\) Hz, 2 H) 7.40 (t, \(J=1.00\) Hz, 2 H) 7.49 (t, \(J=1.00\) Hz, 1 H) 7.79 (q, \(J=1.00\) Hz, 1 H)

\(^{13}\text{C NMR}\) (CDCl\(_3\), 100 MHz) δ ppm 43.71 (CH\(_2\)) 55.41 (CH\(_3\)) 114.26 (2 x CH) 127.17 (CH) 128.67 (CH) 129.39 (CH) 130.53 (C) 131.60 (CH) 134.59 (C) 159.20 (C) 167.55 (C)

**N-Octylbenzamide (3d)** (0.949 g, 81%) was prepared from n-octylamine and ethyl benzoate using the typical procedure. The crude compound was filtered through a silica plug with a gradient of 95:5 Hex: EtOAc then 1:1 Hex: EtOAc basified with 1% triethylamine as the eluent to afford the product as a white solid.\(^7\)

\(^{1}\text{H NMR}\) (400 MHz, CDCl\(_3\)) δ ppm 0.79 - 0.94 (m, 3 H) 1.14 - 1.43 (m, 10 H) 1.52 - 1.66 (m, 2 H) 3.36 - 3.48 (m, 2 H) 6.34 (br. s., 1 H) 7.31 - 7.51 (m, 3 H) 7.69 - 7.82 (m, 2 H)

\(^{13}\text{C NMR}\) (CDCl\(_3\), 100 MHz) δ ppm 14.22 (CH\(_3\)) 22.78 (CH\(_2\)) 27.19 (CH\(_2\)) 29.37 (CH\(_2\)) 29.46 (CH\(_2\)) 31.94 (CH\(_2\)) 40.31 (CH\(_2\)) 127.13 (CH) 128.52 (CH) 131.29 (CH) 135.03 (C) 167.78 (C)

**2-Benzoyl-1,2,3,4-tetrahydroisoquinoline (3e)** (0.693 g, 58%) was prepared was prepared from 1,2,3,4-tetrahydroisoquinoline and ethyl benzoate using the typical procedure. The crude product was triturated with a 3:1 hex: EtOAc mixture, filtered through a fritted funnel, and washed with more hexanes. The solid precipitate was dissolved in EtOAc and filtered through a pad of Celite. The ethyl acetate was removed \(\text{in vacuo}\) by rotary evaporation to afford the pure amide product to afford 2-benzoyl-1,2,3,4-tetrahydro-isoquinoline as a white solid.\(^2\)

\(^{1}\text{H NMR}\) (400 MHz, CDCl\(_3\)) δ ppm 3.05 (br. s., 2 H) 3.44 (br. s., 2 H) 4.34 (br. s., 2 H) 7.02 - 7.45 (m, 7 H) 7.84 (d, \(J=5.50\) Hz, 2 H)

\(^{13}\text{C NMR}\) (CDCl\(_3\), 100 MHz) δ ppm 26.23 (CH\(_2\)) 41.51 (CH\(_2\)) 44.75 (CH\(_2\)) 126.96 (CH) 127.63 (CH) 127.96 (CH) 129.23 (CH) 129.48 (CH) 129.91 (CH) 130.85 (C) 132.57 (C) 136.26 (1 C) 173.92 (C)
**N-Benzoylpyrrolidine (3f)** (0.607 g, 70%) was prepared from pyrrolidine and ethyl benzoate using the typical procedure. The crude compound was filtered through a silica plug with a gradient of 9:1 Hex: EtOAc then 1:1 Hex: EtOAc basified with 10% triethylamine as the eluent to afford the product as a brown oil.²

\[ ^1H \text{NMR} (400 \text{ MHz, CDCl}_3) \delta \text{ ppm } 1.72 \text{ (q, } J=1.00 \text{ Hz, } 2 \text{ H) } 1.81 \text{ (q, } J=1.00 \text{ Hz, } 2 \text{ H) } 3.28 \text{ (t, } J=6.59 \text{ Hz, } 2 \text{ H) } 7.26 - 7.31 \text{ (m, } 3 \text{ H) } 7.38 - 7.44 \text{ (m, } 2 \text{ H) } 7.82\]

**Benzoylaminobenzene (3g)** (0.067 g, 7%) was prepared from aniline and ethyl benzoate using the typical procedure. The crude compound was triturated with hexanes, filtered through a fritted funnel, and washed with more hexanes. The solid precipitate was dissolved in EtOAc and filtered through a pad of Celite. The solvent was removed \textit{in vacuo} by rotary evaporation to afford the product as a white solid.⁷

\[ ^1H \text{NMR} (400 \text{ MHz, CDCl}_3) \delta \text{ ppm } 7.11 - 7.20 \text{ (m, } 1 \text{ H) } 7.38 \text{ (t, } J=7.90 \text{ Hz, } 2 \text{ H) } 7.45 - 7.60 \text{ (m, } 3 \text{ H) } 7.65 \text{ (d, } J=7.74 \text{ Hz, } 2 \text{ H) } 7.82 \text{ (br. s., } 1 \text{ H) } 7.84 - 7.92 \text{ (m, } 2 \text{ H) } 120.51 \text{ (CH) } 124.84 \text{ (CH) } 129.05 \text{ (CH) } 129.36 \text{ (CH) } 132.10 \text{ (CH) } 135.29 \text{ (C) } 138.22 \text{ (C) } 166.05 \text{ (C) }\]

**N-Cyclohexylbenzamide (3h)** (24% by \(^1H\) NMR) was prepared from cyclohexylamine and ethyl benzoate using the typical procedure. The crude compound was triturated with hexanes, filtered through a fritted funnel, and washed with more hexanes. The solid precipitate was dissolved in EtOAc and filtered through a pad of Celite. The solvent was removed \textit{in vacuo} by rotary evaporation to afford the product as a tan solid.⁷

\[ ^1H \text{NMR} (400 \text{ MHz, CDCl}_3) \delta \text{ ppm } 1.14 - 1.31 \text{ (m, } 3 \text{ H) } 1.36 - 1.50 \text{ (m, } 2 \text{ H) } 1.65 \text{ (d, } J=12.94, 3.80 \text{ Hz, } 1 \text{ H) } 1.75 \text{ (dt, } J=13.66, 3.73 \text{ Hz, } 2 \text{ H) } 1.99 - 2.09 \text{ (m, } 2 \text{ H) } 3.91 - 4.04 \text{ (m, } 1 \text{ H) } 5.97 \text{ (br. s., } 1 \text{ H) } 7.33 - 7.52 \text{ (m, } 3 \text{ H) } 7.69 - 7.79 \text{ (m, } 2 \text{ H) } 123.90 \text{ (CH) } 131.40 \text{ (CH) } 135.34 \text{ (C) } 166.87 \text{ (C) }\]

**N-Benzyl-4-bromo benzamide (3j)** (0.906 g, 62%) was prepared from benzylamine and ethyl-4-bromobenzoate using the typical procedure. The crude compound was filtered through a silica plug with a gradient of 9:1 then 6:4 Hex: EtOAc as the eluent to afford the product as a white solid.⁵

\[ ^1H \text{NMR} (400 \text{ MHz, CDCl}_3) \delta \text{ ppm } 4.60 \text{ (d, } J=5.35 \text{ Hz, } 2 \text{ H) } 6.59 \text{ (br. s., } 1 \text{ H) } 7.29 - 7.40 \text{ (m, } 5 \text{ H) } 7.53 \text{ (d, } J=8.08 \text{ Hz, } 2 \text{ H) } 7.65 \text{ (d, } J=8.08 \text{ Hz, } 2 \text{ H) } 127.96 \text{ (C) } 128.17 \text{ (CH) } 128.89 \text{ (CH) } 129.07 \text{ (CH) } 132.05 \text{ (CH) } 133.45 \text{ (C) } 138.21 \text{ (C) } 166.70 \text{ (C) }\]
**N-benzyl-4-(trifluoromethyl) benzamide** (3k) (1.082 g, 78%) was prepared from was prepared from benzylamine and ethyl-4-trifluoromethylbenzoate using the typical procedure. The crude compound was triturated with hexanes, filtered through a fritted funnel, and washed with more hexanes. The solid precipitate was dissolved in EtOAc and filtered through a pad of Celite. The solvent was removed in vacuo by rotary evaporation to afford the product as a white solid.\(^5\)

**\(^1\text{H NMR}\)** (400 MHz, CDCl\(_3\)) \(\delta\) ppm 4.63 (d, \(J=5.69\) Hz, 2 H) 6.64 (br. s., 1 H) 7.29 - 7.38 (m, 5 H) 7.66 (d, \(J=8.17\) Hz, 2 H) 7.88 (d, \(J=8.08\) Hz, 2 H)

**\(^{13}\text{C NMR}\)** (CDCl\(_3\), 100 MHz) \(\delta\) ppm 44.58 (CH\(_2\)) 125.91 (q, \(J=3.70\) Hz, 1 CF\(_3\)) 127.74 (CH) 128.09 (CH) 128.21 (CH) 129.15 (CH) 133.57 (d, \(J_{C-C-F}=1.00\) Hz) 137.91 (C) 138.01 (C) 166.38 (C)

**N-Benzylhexanamide** (3l) (0.593 g, 58%) was prepared from benzylamine and ethyl hexanoate using the typical procedure. The crude compound was filtered through a silica plug with a gradient of 9:1 Hex: EtOAc then 1:1 Hex: EtOAc basified with 1% triethylamine as the eluent to afford the product as a white solid.\(^6\)

**\(^1\text{H NMR}\)** (400 MHz, CDCl\(_3\)) \(\delta\) ppm 0.89 (t, \(J=6.69\) Hz, 3 H) 1.23 - 1.37 (m, 4 H) 1.64 (quin, \(J=7.32\) Hz, 2 H) 2.18 (t, \(J=7.61\) Hz, 2 H) 4.40 (d, \(J=5.74\) Hz, 2 H) 6.11 (br. s., 1 H) 7.24 (br. s., 1 H) 7.26 - 7.28 (m, 1 H) 7.28 - 7.35 (m, 2 H)

**\(^{13}\text{C NMR}\)** (CDCl\(_3\), 100 MHz) \(\delta\) ppm 14.14 (CH\(_3\)) 22.60 (CH\(_2\)) 25.67 (CH\(_2\)) 31.69 (CH\(_2\)) 36.89 (CH\(_2\)) 43.69 (CH\(_2\)) 127.59 (CH) 127.95 (CH) 128.84 (CH) 138.74 (C) 173.33 (C)

**N-(2-(benzylamino)-2-oxoethyl)benzamide** (3o) (0.450 g, 76%) was prepared from the benzyl ester of benzoyl glycine and benzylamine using the typical procedure, but with modified conditions of 90 °C with 50 W for 30 min. The crude compound was triturated with chilled hexanes, filtered through a fritted funnel, and washed with more chilled hexanes. The solid precipitate was dissolved in DCM and filtered through a pad of Celite. The solvent was removed in vacuo by rotary evaporation to afford the product as a white solid.\(^8\)

**\(^1\text{H NMR}\)** (400 MHz, CDCl\(_3\)) \(\delta\) ppm 4.17 (d, \(J=5.06\) Hz, 2 H) 4.43 (d, \(J=5.69\) Hz, 2 H) 7.20 - 7.31 (m, 5 H) 7.38 (t, \(J=7.61\) Hz, 3 H) 7.48 (t, \(J=7.37\) Hz, 2 H) 7.75 (d, \(J=7.30\) Hz, 2 H)

**\(^{13}\text{C NMR}\)** (CDCl\(_3\), 100 MHz) \(\delta\) ppm 39.00 (CH\(_2\)) 44.13 (CH\(_2\)) 127.43 (CH) 127.77 (CH) 127.99 (CH) 128.84 (CH) 128.94 (CH) 132.12 (CH) 133.63 (C) 138.09 (C) 168.16 (C) 169.32 (C)
5-Hydroxy-N-(phenylmethyl)pentanamide (3o) (5.404 g, 87%) was prepared from benzylamine and δ-valerolactone using the typical procedure. The crude compound was triturated with hexanes, filtered through a fritted funnel, and washed with more hexanes. The solid precipitate was dissolved in EtOAc and filtered through a pad of Celite. The solvent was removed in vacuo by rotary evaporation to afford the product as a white solid.\(^8\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 1.52 - 1.64 (m, 2 H) 1.69 - 1.81 (m, 2 H) 2.25 (t, \(J=7.20\) Hz, 2 H) 3.62 (t, \(J=6.14\) Hz, 2 H) 4.42 (d, \(J=5.70\) Hz, 2 H) 6.02 (br. s., 1 H) 7.21 - 7.37 (m, 5 H)
\(^13\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 21.96 (CH\(_2\)) 32.26 (CH\(_2\)) 36.27 (CH\(_2\)) 43.88 (CH\(_2\)) 62.28 (CH\(_2\)) 127.78 (CH) 128.07 (CH) 128.97 (CH) 138.56 (C) 173.28 (C)
References


N-Benzyl benzamide
400 MHz, CDCl3
N-(4-Methoxybenzyl)-benzoylamide
400 MHz, CDCl₃

[Chemical Structure]

[Graphical Representation]
N-Octylbenzamide
400 MHz, CDCl3
2-Benzoyl-1,2,3,4-tetrahydroisoquinoline
400 MHz, CDCl3
N-Benzoylpyrrolidine
400 MHz, CDCl3
Benzoylaminobenzene
400 MHz, CDCl3
N-Cyclohexylbenzamide
400 MHz, CDCl3
N-Benzyl-4-bromo-benzamide
400 MHz, CDCl3
N-Benzyl-4-(trifluoromethyl) benzamide
400 MHz, CDCl3
N-Benzylhexanamide
400 MHz, CDCl3
N-(2-(benzylamino)-2-oxoethyl)benzamide
400MHz, CDCl3
5-Hydroxy-N-(phenylmethyl)pentanamide
400 MHz, CDCl3
N-Benzyl benzamide
100 MHz, CDCl3
N-(4-Fluorobenzyl) benzamide
100 MHz, CDCl₃
N-(4-Methoxybenzyl)-benzamide
100 MHz, CDCl3
N-Octylbenzamide
100 MHz, CDCl3
2-Benzoyl-1,2,3,4-tetrahydroisoquinoline
100 MHz, CDCl3
N-Benzylopyrrolidine
100 MHz, CDCl3
Benzoylaminobenzene
100 MHz, CDCl3
N-Cyclohexylbenzamide
100MHz, CDCl3
N-Benzyl-4-bromo-benzamide
100 MHz, CDCl3
N-Benzy]-4-(trifluoromethyl)benzamide
100 MHz, CDCl3
N-Benzylhexanamide
100 MHz, CDCl3
N-(2-(benzylamino)-2-oxoethyl)benzamide

100 MHz, CDCl3
5-Hydroxy-N-(phenylmethyl)pentanamide
100 MHz, CDCl3