Clean, Reusable and Low Cost Heterogeneous Catalyst for Amide Synthesis


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SUPPORTING INFORMATION

Contents

General Information 1
Experimental 2
Amide Analytical Data 2-6
Green Metrics

<table>
<thead>
<tr>
<th>Metric</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thionyl Chloride</td>
<td>7</td>
</tr>
<tr>
<td>DCC</td>
<td>8</td>
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<tr>
<td>IBA</td>
<td>9</td>
</tr>
<tr>
<td>K60</td>
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</table>

General Information: Amides were synthesized in refluxing toluene under an air atmosphere using a Teflon coated stirrer bar. The typical quantities used were 12mmols of acid, 12mmols of amine, 20ml of toluene and varying quantities of K60 catalyst. NMR spectra were obtained on a 270MHz JEOL spectrometer using CDCl3 solvent. Where needed, kugelrohr distillation apparatus was used with a pressure of <0.5mbar.
Experimental Section

General Procedure for Amide Synthesis - 4, N-diphenylbutyramide (Entry 1)

4-Phenylbutyric acid (1.968g, 12mmol), activated K60 (0.62g) and 20ml of toluene were heated to reflux (110°C) in a two-necked round bottom flask equipped with a condenser and suba-seal. Once reflux was reached, aniline (1.12g, 12mmols) was injected. After 24 hours the hot reaction mixture was filtered through a sintered glass funnel and the catalyst washed with 10ml of hot toluene and left to crystallize. Yield obtained for 4,N-diphenylbutyramide; 2.13g (74.3%); Literature m.p. 118°C; m.p. 116-118°C; 1H NMR (270MHz, CDCl3): δ = 7.73 (br s, 1H; NH), 7.53 (d, J=8.2, 2H; Ar), 7.32-7.07 (m, 8H; Ar), 2.67 (t, J=7.1Hz, 2H), 2.33 (t, J=7.1Hz, 2H), 2.03 (m, 2H); 13C NMR (270MHz, CDCl3): δ = 171.36, 141.32, 137.95, 128.90, 128.46, 128.40, 125.98, 124.20, 119.99, 36.67, 35.05, 26.91; IR: ν˜ = 3324 (NH), 1662 cm⁻¹ (C=O).

Amide Analytical Data

Entry 2) 2,N-Diphenylacetamide

\[
\text{\begin{figure}
\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}
\end{figure}}
\]

Literature m.p. 118 oC; m.p. 118-119oC; 1H NMR (270MHz, CDCl3): δ = 7.25-7.39 (m, 10H; Ar), 3.49 (s, 2H); 13C NMR (270MHz, CDCl3): δ = 169.12, 137.85, 134.41, 129.47, 129.16, 128.9, 127.61, 124.41, 119.81, 44.76; IR: ν˜ = 3254 (NH), 1655 cm⁻¹ (C=O).
Entry 3) N-Phenyl-2-phenylpropionamide

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{entry3}
\end{center}}
\]

Literature m.p. 134oC; m.p. 132-134oC; 1H NMR (270MHz, CDCl3): \(\delta = 7.47\) (br s, 1H; NH), 7.26-7.42 (m, 10H; Ar), 3.71 (m, 1H), 1.60 (d, \(J=7.4\)Hz, 3H); 13C NMR (270MHz, CDCl3): \(\delta = 172.30, 140.87, 137.80, 129.69, 129.01, 128.87, 127.55, 124.21, 119.68, 48.08, 18.52\); IR: \(\tilde{\nu} = 3360\) (NH), 1660cm\(^{-1}\) (C=O).

Entry 4) N-Phenylbenzamide

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{entry4}
\end{center}}
\]

Literature m.p. 166oC; m.p. 165-166oC; 1H NMR (270MHz, CDCl3): \(\delta = 7.13 - 7.86\) (m, 10H; Ar); 13C NMR (270MHz, CDCl3): \(\delta = 165.79, 137.88, 134.95, 131.79, 129.05, 128.73, 127.00, 124.53, 120.20\); IR: \(\tilde{\nu} = 3343\) (NH), 1653cm\(^{-1}\) (C=O).

Entry 5) N-Phenylpropionamide

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{entry5}
\end{center}}
\]

Literature m.p. 106oC; m.p. 105-107oC; 1H NMR (270MHz, CDCl3): \(\delta = 7.77\) (br s, 1H; NH), 7.49 (d, \(J=7.8\)Hz, 2H; Ar), 7.27 (t, \(J=7.8\)Hz, 2H; Ar), 7.07 (t, \(J=7.4\)Hz, 1H; Ar), 2.34 (m, 2H), 1.20 (t, \(J=7.8\)Hz, 3H); 13C NMR (270MHz, CDCl3): \(\delta = 172.42, 138.01, 128.82, 124.05, 119.91, 30.56, 9.66\); IR: \(\tilde{\nu} = 3256\) (NH), 1665cm\(^{-1}\) (C=O).
Entry 6) 2-Chloro-N-phenyl-propionamide

\[
\text{\includegraphics[width=1.5cm]{molecule1.png}}
\]

Literature m.p. 92°C; m.p. 92-93°C; 1H NMR (270MHz, CDCl3): \(\delta = 8.31\) (br s, 1H; NH), 7.55 (d, J=7.4Hz, 2H; Ar), 7.34 (t, J=7.4Hz, 2H; Ar), 7.15 (t, J=7.4Hz, 1H; Ar), 4.55 (m, 1H), 1.79 (d, J=8.1Hz, 3H); 13C NMR (270MHz, CDCl3): \(\delta = 167.28, 136.88, 129.10, 125.08, 120.07, 56.18, 22.68\); IR: \(\tilde{\nu} = 3297\) (NH), 1672cm\(^{-1}\) (C=O).

Entry 7) 2-(4-Chloro-phenoxy)-N-phenyl-acetamide

\[
\text{\includegraphics[width=1.5cm]{molecule2.png}}
\]

Literature m.p. 129°C; m.p. 128-129°C; 1H NMR (270MHz, CDCl3): \(\delta = 8.2\) (br s, 1H; NH), 7.58 (d, J=8.9Hz, 2H; Ar), 7.35 - 7.28 (m, 4H; Ar), 7.15 (t, J=7.4Hz, 1H; Ar), 6.93 (d, J=8.9Hz, 2H; Ar), 4.56 (s, 2H); 13C NMR (270MHz, CDCl3): \(\delta = 165.73, 155.51, 136.62, 129.81, 129.10, 127.50, 124.97, 120.10, 116.12, 67.82\); IR: \(\tilde{\nu} = 3188\) (NH), 1690cm\(^{-1}\) (C=O).

Entry 8) N-(2-Chloro-phenyl)phenyl-acetamide

\[
\text{\includegraphics[width=1.5cm]{molecule3.png}}
\]

Literature m.p. 129°C; m.p. 128-129°C; 1H NMR (270MHz, CDCl3): \(\delta = 7.66\) (br s, 1H; NH), 7.41 - 7.25 (m, 7H; Ar), 7.27 (d, J=8.0Hz, 1H; Ar), 6.99 (t, J=8.0Hz, 1H; Ar), 3.78 (s, 2H); 13C NMR (270MHz, CDCl3): \(\delta = 169.05, 134.21, 129.62, 129.27, 128.83, 127.81, 127.59, 124.60, 122.30, 121.65, 121.16, 45.05\); IR: \(\tilde{\nu} = 3258\) (NH), 1659cm\(^{-1}\) (C=O).
 Entry 9) \(N-(2,6\text{-Dimethyl-phenyl})\text{phenyl-acetamide}\)

![Structure of \(N-(2,6\text{-Dimethyl-phenyl})\text{phenyl-acetamide}\)]

Literature m.p. 147°C; m.p. 146-147°C; 1H NMR (270MHz, CDCl3): \(\delta = 7.43 - 7.01\) (m, 8H; Ar), 6.64 (br. s, 1H; NH), 3.76 (s, 2H), 2.12 (s, 6H; 2(CH3)); 13C NMR (270MHz, CDCl3): \(\delta = 169.41, 135.30, 133.61, 129.53, 129.27, 128.32, 128.15, 127.68, 127.37, 44.08, 18.26\); IR: \(\tilde{\nu} = 3248\) (NH), 1642 cm\(^{-1}\) (C=O).

 Entry 10) Phenylacetyl-pyrrolidine

![Structure of Phenylacetyl-pyrrolidine)]

Literature m.p. 48°C; m.p. 47-48°C; 1H NMR (270MHz, CDCl3): \(\delta = 7.19 - 7.11\) (m, 5H; Ar), 3.52 (s, 2H; CH2), 3.4-3.26 (m, 4H; 2x N-CH2-CH2), 1.66-1.79 (m, 4H; 2x N-CH2-CH2); 13C NMR (270MHz, CDCl3): \(\delta = 169.59, 135.28, 129.30, 128.52, 126.65, 45.92, 42.11, 24.19\); IR: \(\tilde{\nu} = 1625\) cm\(^{-1}\) (C=O).
Entry 11) N-Butyl-benzamide

![Structure of N-Butyl-benzamide](image)

Oil; 1H NMR (270MHz, CDCl3): $\delta = 8.66$ (br s, 1H; NH), 7.97 (d, $J=7.0$Hz, 2H; Ar), 7.44-7.30 (m, 3H; Ar), 2.83 (t, $J=7.4$Hz, 2H), 1.54 (dt, $J=7.8$ Hz, $J=7.4$ Hz, 2H), 1.22 (dq, $J=7.4$Hz, $J=7.4$Hz, 2H), 0.72 (t, $J=7.4$ Hz, 3H); 13C NMR (270MHz, CDCl3): $\delta = 173.49, 136.19, 130.74, 129.17, 127.74, 39.24, 29.71, 19.56, 13.25$; IR: $\tilde{\nu}=3259$ (NH), 1643 cm$^{-1}$ (C=O).

Entry 12) N-Butyl-propionamide

Oil; 1H NMR (270MHz, CDCl3): $\delta = 6.31$ (br s, 1H; NH), 3.07 (m, 2H), 2.05 (m, 2H), 1.32 (t, $J=6.7$ Hz, 2H) 1.19 (m, 2H), 0.98 (t, $J=7.4$ Hz, 3H), 0.75 (t, $J=7.4$ Hz, 3H); 13C NMR (270MHz, CDCl3): $\delta = 174.56, 39.32, 31.69, 29.63, 20.15, 13.80, 10.12$; IR: $\tilde{\nu}=3296$ (NH), 1663 cm$^{-1}$ (C=O).
Green Metrics


\[
\text{\begin{array}{c}
\text{4-Phenylbutyric acid} & 1.97g \\
\text{Aniline} & 1.12g \\
\text{Toluene} & 69.4g (80ml) \\
\text{NaOH 10\% (aq)} & 20g \\
\text{CH2Cl2} & 106.1g (80ml) \\
\text{Total} & 199.5g \\
\end{array}}
\]

\[
\text{\begin{array}{c}
\text{Crude 4,N-diphenylbutyramide} & 2.78g \\
\text{Aqueous waste} & 20g \\
\text{Organic solvent waste (assuming 90\% recovery)} & 17.6g \\
\text{Total waste} & 37.6g \\
\end{array}}
\]

\[
\text{E-factor, } \frac{37.6\text{g of waste}}{2.78\text{g of crude product}} = 13.5
\]

\[
\text{Mass Intensity, } \frac{199.5\text{g of raw materials used}}{2.78\text{g of crude product}} = 71.8
\]

\[
\text{Atom Economy, } \frac{239}{182 + 93} \times 100 = 86.9\%
\]

Assumptions

- 90\% of organic solvents are recovered.
- The formation of acyl chloride and use of thionyl chloride is not accounted for in calculations.

![Chemical structure of 4,N-diphenylbutyramide synthesis](image)

<table>
<thead>
<tr>
<th>Input</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Phenylbutyric acid</td>
<td>1.97g</td>
</tr>
<tr>
<td>Aniline</td>
<td>1.12g</td>
</tr>
<tr>
<td>DCC</td>
<td>2.72g</td>
</tr>
<tr>
<td>CH2Cl2</td>
<td>106.1g (80ml)</td>
</tr>
<tr>
<td>HCl(aq) 0.5 mol-1</td>
<td>20g</td>
</tr>
<tr>
<td>KHCO3 (aq) 1 mol-1</td>
<td>20g</td>
</tr>
<tr>
<td>Total</td>
<td>151.9g</td>
</tr>
<tr>
<td>Crude 4,N-diphenylbutyramide</td>
<td>2.73g</td>
</tr>
<tr>
<td>Aqueous waste</td>
<td>40g</td>
</tr>
<tr>
<td>Organic solvent waste</td>
<td>13.3g (assuming 90% recovery)</td>
</tr>
<tr>
<td>Total waste</td>
<td>53.3g</td>
</tr>
</tbody>
</table>

E-Factor,
\[
\frac{53.3 \text{g of waste}}{2.73 \text{g of crude product}} = 19.5
\]

Mass intensity,
\[
\frac{151.9 \text{g of raw materials used}}{2.73 \text{g of crude product}} = 55.6
\]

Atom economy,
\[
\frac{239}{370 + 93} \times 100 = 51.6\%
\]

Assumptions

- 90% of organic solvents were recovered,
- Calculations did not take into account recrystallization of the product,
- Calculations did not account for the synthesis of DCC.

\[
\begin{align*}
\text{4-Phenylbutyric acid} & \quad 0.164\text{g} \quad (1 \text{ mmol}) \\
\text{Aniline} & \quad 0.093\text{g} \quad (1 \text{ mmol}) \\
\text{Crude 4,N-diphenylbutyramide} & \quad 0.11\text{g} \\
\text{ortho-N,N-Di-isopropylbenzylaminoboronic acid} & \quad 0.0235\text{g} \quad (1 \text{ mol %}) \\
\text{Toluene} & \quad 8.67\text{g} \quad (10\text{ml}) \\
\text{Methyl-tert-butyl ether (MTBE)} & \quad 7.40\text{g} \quad (10\text{ml}) \\
\text{HCl 5\%w/v (aq)} & \quad 10\text{g} \\
\text{Brine (aq)} & \quad 10\text{g} \\
\text{NaOH 5\%w/v (aq)} & \quad 10\text{g} \\
\text{Brine (aq)} & \quad 10\text{g} \\
\text{Total} & \quad 56.4\text{g} \\
\text{Total waste} & \quad 41.6\text{g}
\end{align*}
\]

E-Factor - Synthesis of amide

\[
\left(\frac{41.6\text{g of waste}}{0.11\text{g of product}}\right) = 378.2
\]

Mass intensity - Synthesis of amide

\[
\left(\frac{56.4\text{g of raw materials used}}{0.11\text{g of crude product}}\right) = 512.7
\]

Atom economy - Synthesis of amide

\[
\left(\frac{239}{164 + 93}\right) \times 100 = 93\%
\]

Assumptions

- Calculations did not account for the synthesis of the catalyst
- 90% recovery of organic solvents
4) Calculations for the synthesis of 4,N-diphenylbutyramide using activated K60 silica gel

\[
\text{OH} \quad + \quad \text{H}_2\text{N} \quad \text{O} \quad \text{H} \quad \text{N} \quad \text{O} \\
\text{4-Phenylbutyric acid} \quad 1.968\text{g (12mmols)} \quad 4,N^{-}\text{diphenylbutyramide} \quad 2.12\text{g}
\]

<table>
<thead>
<tr>
<th>Input</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Phenylbutyric acid</td>
<td>4,N-diphenylbutyramide</td>
</tr>
<tr>
<td>1.968g (12mmols)</td>
<td>2.12g</td>
</tr>
<tr>
<td>Aniline</td>
<td>Organic solvent waste</td>
</tr>
<tr>
<td>1.12g (12mmols)</td>
<td>(90% recovery)</td>
</tr>
<tr>
<td>Toluene</td>
<td>1.73g</td>
</tr>
<tr>
<td>17.34g (20ml)</td>
<td>K60 catalyst</td>
</tr>
<tr>
<td>K60</td>
<td>0.62g (20% wt)</td>
</tr>
<tr>
<td>0.62g (20% wt)</td>
<td>Total waste</td>
</tr>
<tr>
<td>Total</td>
<td>21.05g</td>
</tr>
<tr>
<td>2.35g of waste</td>
<td>Total waste</td>
</tr>
<tr>
<td>2.12g of product</td>
<td>2.35g</td>
</tr>
</tbody>
</table>

E-Factor - Synthesis of amide

\[
\left( \frac{2.35\text{g of waste}}{2.12\text{g of product}} \right) = 1.11 \quad \left( \frac{1.73\text{g of waste}}{2.00\text{g of product}} \right) = 0.87
\]

Mass intensity - Synthesis of amide

\[
\left( \frac{21.05\text{g of raw materials used}}{2.12\text{g of crude product}} \right) = 9.93
\]

Atom economy - Synthesis of amide

\[
\left( \frac{239}{164 + 93} \right) \times 100 = 93\%
\]

Assumptions

- 90\% recovery of organic solvents
- 4th use of K60 - calculated according to loss of the catalysts activity (~4\% yield lower) after four reactions and subsequent re-activations at 700oC.