Sulfated Tungstate : A New Solid Heterogeneous Catalyst For Amide Synthesis

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A) Experimental

a) Regents:

Na$_2$WO$_4$.2H$_2$O was purchased from West Coast Laboratories, India. Other chemicals were purchased from Spectrochem Pvt. Ltd. India and were used without further purification.

b) Catalyst preparation:

The catalyst was prepared by adding anhydrous sodium tungstate (0.1 mol) gradually to a stirred solution of chlorosulfonic acid (0.2 mol) in chloroform (150ml) contained in a 250ml round bottom flask placed in an ice bath. After completion of addition the mixture was stirred further for 1 h. A yellowish-white solid was obtained. It was filtered and repeatedly washed with deionized water until a neutral filtrate was obtained. The absence of chlorine ion was detected by AgNO$_3$ test. Then catalyst was dried in an oven for 2 h at 100 °C.

c) General procedure for amide synthesis:

To a solution of benzoic acid (2g, 16.39 mmol) in toluene (20ml) was added the catalyst (0.64g, 18 % (w/w)). To this mixture was added benzylamine (1.59g, 14.9 mmol) in one portion. The reaction mixture was refluxed for 12 hour and water was collected azeotropically in the Dean-Stark trap. After 12 hour the reaction mixture was allowed to cool at about 50-60 °C and filtered through a Buchner funnel and catalyst was recovered by washing with acetone and water. The filtrate was distilled off under reduced pressure to remove toluene. The residue obtained was dissolved in ethyl acetate (30ml) and wash with 10% (w/v) NaHCO$_3$ (10ml) and 5% (w/v) HCl (10ml). The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure to afford amide as a white solid with purity of 98% (HPLC)
B) Characterization data of Catalyst:

1. IR of Catalyst of the catalyst :
3) Elemental Analysis the catalyst:
Title: SAIF-IIT, Powai, Mumbai

Operator ID: SMD
Company name: ThermoFinnigan
Method filename: C:\Eager 300 for EA1112\data\Sys_data_example\chsn-2009-149-09-2009-CHN8.mth
Method name: NCHS
Analysed: 09/14/2009 19:04
Printed: 09-16-2009 11:16
Elemental Analyser method: Sampler method:
Sample ID: 14-09-2009-035-P-12-CHN-97 (#35)
Analysis type: Unknown
Chromatogram filename: 14-09-2009-035-P-12-CHN-97.dat
Calibration method: K Factors
Sample weight: 2.281
Protein factor: 6.25

<table>
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<tr>
<th>Peak Number (#)</th>
<th>Retention Time (min)</th>
<th>Area (**uV*sec)</th>
<th>Element %</th>
<th>Component</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1.017</td>
<td>73336</td>
<td>0.000</td>
<td>Carbon</td>
</tr>
<tr>
<td>2</td>
<td>1.409</td>
<td>3723</td>
<td>0.000</td>
<td>Hydrogen</td>
</tr>
<tr>
<td>3</td>
<td>3.800</td>
<td>335642</td>
<td>0.825</td>
<td>Sulfur</td>
</tr>
<tr>
<td>4</td>
<td>8.250</td>
<td>11806</td>
<td>0.294</td>
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<td>424507</td>
<td>1.119</td>
<td></td>
</tr>
</tbody>
</table>
4) EDAX Report of the catalyst

```
EDAX EAF Quantification (Standardless)
Element Normalized

| Element | Wt % | At % | K-Ratio | Z | A | F | P
|---------|------|------|---------|---|---|---|---
| O K     | 30.55| 83.19| 0.0708  | 1.1688| 0.1983| 1.0000|
| S K     | 0.31 | 0.43 | 0.0009  | 1.1173| 0.2626| 1.0000|
| W L     | 69.13| 16.38| 0.6245  | 0.6474| 1.0415| 1.0000|
| Total   | 100.00| 100.00|

Element | Net Inte. | Ekpg Inte. | Inte. Error | P/B
|---------|-----------|------------|-------------|----
| O K     | 34.60     | 3.50       | 2.64        | 9.89|
| S K     | 8.88      | 7.32       | 43.31       | 0.24|
| W L     | 78.00     | 6.08       | 1.72        | 12.83|
```
5) Particle size analysis report
Size Statistics Report by Intensity

Sample Details

Sample Name: Sawant Sr 1
File Name: AAVTV_Nanosuspension fine tuned.dts
SOP Name: Atovaquone Nanosuspension sop
Measurement Date and Time: Friday, September 18, 2009 3:39:24 PM

Z-Average (nm): 1428.832
Derived Count Rate (kcps): 2663791.63214...
Standard Deviation: 0
%Std Deviation: 0
Variance: 0
%Variance: 0

Statistics Graph (1 measurement)
Size Distribution Report by Intensity

Sample Details

Sample Name: Sawant Sr 1
SOP Name: Atovaquone Nanosuspension sop
General Notes:

File Name: AATV_Nanosuspension.f...
Record Number: 2895
Material RI: 1.53
Material Absorption: 0.01

Dispersant Name: Water
Dispersant RI: 1.330
Viscosity (cP): 0.8872
Measurement Date and Time: Friday, September 18, 2009 3:...

System

Temperature (°C): 25.0
Count Rate (kcps): 328.4
Cell Description: Disposable sizing cuvette
Attenuator: 3
Duration Used (s): 50
Measurement Position (mm): 0.65

Results

<table>
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<tr>
<th>Diam. (nm)</th>
<th>% Intensity</th>
<th>Width (nm)</th>
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</thead>
<tbody>
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<td>1429</td>
<td>1396</td>
<td>376.4</td>
</tr>
<tr>
<td>677</td>
<td>424.4</td>
<td>116.5</td>
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<tr>
<td>807</td>
<td>116.8</td>
<td>16.24</td>
</tr>
</tbody>
</table>

Result quality: Refer to quality report

Size Distribution by Intensity

Record 2895: Sawant Sr 1
C) Amide Analytical Data

**Entry 1) N-Benzylbenzamide**

\[ \begin{align*}
\text{m.p. } & 129-130 ^\circ \text{C (lit.,} ^1 128-130 ^\circ \text{C); } \\
\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1} & 3445 (\text{NH}), 1655 (\text{C}=\text{O}); \\
\delta_{\text{H}}(300 \text{ MHz; CDCl}_3; \text{Me}_4\text{Si}) & 4.65 (2 \text{ H, d, } J=6), 6.42 (1 \text{ H, br s}), 7.25-7.56 (8 \text{ H, m}) \text{ and } 7.79 (2 \text{ H, m}); \\
\delta_{\text{C}}(75 \text{ MHz; CDCl}_3; \text{Me}_4\text{Si}) & 44.0, 127.1, 127.5, 127.6, 127.8, 128.5, 128.6, 134.3, 138.1 \text{ and } 167.3.
\end{align*} \]

**Entry 2) N-Phenylbenzamide**

\[ \begin{align*}
\text{m.p. } & 165-166 ^\circ \text{C (lit.,} ^2 162 ^\circ \text{C); } \\
\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1} & 3343 (\text{NH}) \text{ and } 1653 (\text{C}=\text{O}); \\
\delta_{\text{H}}(300 \text{ MHz; CDCl}_3; \text{Me}_4\text{Si}) & 7.13-7.86 (10 \text{ H, m}); \\
\delta_{\text{C}}(75 \text{ MHz; CDCl}_3; \text{Me}_4\text{Si}) & 165.79, 137.88, 134.95, 131.79, 129.05, 128.73, 127.00, 124.53 \text{ and } 120.20.
\end{align*} \]

**Entry 3) Morpholino (phenyl)methanone**

\[ \begin{align*}
\text{m.p. } & 72 ^\circ \text{C (lit.,} ^3 72-74 ^\circ \text{C); } \\
\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1} & 1660 (\text{C}=\text{O}); \\
\delta_{\text{H}}(300 \text{ MHz; CDCl}_3; \text{Me}_4\text{Si}) & 3.34 (4 \text{ H, t}), 1.5 (6 \text{ H, m}), 7.95 (2 \text{ H, m}), 7.44 (2 \text{ H, m}) \text{ and } 7.51 (1 \text{ H, m}); \\
\delta_{\text{C}}(75 \text{ MHz; CDCl}_3; \text{Me}_4\text{Si}) & 46.1, 66.8, 127.2, 128.6, 129.2, 135.5 \text{ and } 168.9.
\end{align*} \]

**Entry 4) N-Benzyl-2-phenylacetamide**
Entry 5) 2,N-Diphenylacetamide

Entry 6) 4-(phenylacetyl)morpholine

Entry 7) N-Cyclohexyl-2-phenylacetamide

Entry 8) N-Benzyl-2-(4-isobutylphenyl)propanamide
m.p. Yellow Oil (lit., Yellow Oil); \( \nu_{\text{max}} \text{(Neat)}/\text{cm}^{-1} 3280 \) (NH) and 1646 (C=O); \( \delta_{\text{H}} \) (300 MHz; CDCl\(_3\); Me\(_4\)Si) 0.89 (6 H, d, \( J=6\text{Hz} \)), 1.53 (3 H, d, \( J=6\text{Hz} \)), 1.84 (1 H, m), 2.5 (3 H, d, \( J=8\text{Hz} \)), 3.64 (1 H, quartet, \( J=8\text{Hz} \)), 4.34 (2 H, d, \( J=6\text{Hz} \)), 6.4 (1 H, br s) and 7.05-7.4 (9 H, m); \( \delta_{\text{C}} \) (75 MHz; CDCl\(_3\); Me\(_4\)Si) 18.27, 22.24, 30.01, 43.26, 44.86, 46.61, 127.28, 127.4, 127.43, 128.59, 129.64, 138.54, 140.69 and 174.77.

**Entry 9)** \( N \)-Benzyl-2-hydroxy-2-phenylethanamide

![Structural formula of Entry 9](image)

m.p. 96-99 °C (lit., 96 °C); \( \nu_{\text{max}} \text{(KBr)}/\text{cm}^{-1} 3250 \) (NH), 1641 (C=O); \( \delta_{\text{H}} \) (300 MHz; CDCl\(_3\); Me\(_4\)Si) 3.6-3.65 (1 H, br s, OH exchangeable with D\(_2\)O), 4.43 (2 H, d, \( J=5.78 \)), 5.07 (1 H, d, \( J=3.49 \)), 6.52 (1 H, br s) and 7.16-7.43 (10 H, m); \( \delta_{\text{C}} \) (75 MHz; CDCl\(_3\); Me\(_4\)Si) 43.06, 43.14, 73.93, 74.0, 126.59, 127.44, 127.48, 128.33, 128.55, 128.59, 137.63, 139.52 and 172.54.

**Entry 10)** (\( E \))-\( N \)-Benzylcinnamamide

![Structural formula of Entry 10](image)

m.p. 106-108 °C (lit., 108 °C); \( \nu_{\text{max}} \text{(KBr)}/\text{cm}^{-1} 3263 \) (NH), 1652 (C=O) and 1615 (C=C); \( \delta_{\text{H}} \) (300 MHz; CDCl\(_3\); Me\(_4\)Si) 7.67 (1 H, d, \( J=15.3 \)), 7.47 (2 H, m), 7.32 (8 H, m), 6.44 (1 H, d, \( J=15.3 \)), 6.21 (1 H, s) and 4.54 (2 H, d, \( J=4.8 \)); \( \delta_{\text{C}} \) (75 MHz; CDCl\(_3\); Me\(_4\)Si) 165.8, 141.3, 138.2, 134.7, 129.6, 128.7, 128.6, 127.9, 127.8, 127.5, 120.4 and 43.8.

**Entry 11)** (\( E \))-3-phenyl-1-(piperidine-1-yl)prop-2-en-1-one

![Structural formula of Entry 11](image)

m.p. 110-112 °C (lit., 114 °C); \( \nu_{\text{max}} \text{(KBr)}/\text{cm}^{-1} 1620 \) (C=C), 1645 (C=O); \( \delta_{\text{H}} \) (300 MHz; CDCl\(_3\); Me\(_4\)Si) 1.30-1.78 (6 H, m), 3.32-3.65 (4 H, m), 6.74 (1 H, d, \( J=16 \)), 7.01-7.45 (5 H, m) and 7.48 (1 H, d, \( J=16 \)); \( \delta_{\text{C}} \) (75 MHz; CDCl\(_3\); Me\(_4\)Si) 44.8, 25.4, 25.6, 166.4, 144, 118.9, 135.2, 126.4, 128.7 and 128.
Entry 12) \( N \)-Benzyl laurylamide

\[
\text{C}_{11}\text{H}_{23}\overset{\text{O}}{\text{N}}\text{H}
\]

m.p. 82-83 °C (lit.,\(^{12}\) 84 °C); \( \nu_{\text{max}}(\text{KBr})/\text{cm}^{-1} \) 3250 (NH), 1641 (C=O); \( \delta_{\text{H}}(300 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si}) \) 0.88 (3 H, t), 1.51 (2 H, sextet), 1.21 (16 H, m), 1.41 (2 H, t), 3.85 (2 H, d) and 7.15-7.33 (5 H, m); \( \delta_{\text{C}}(75 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si}) \) 14.13, 22.69, 25.78, 29.24, 29.62, 25.9, 35.8, 175.0, 57.4, 142.10, 128.2, 128.3 and 126.7.
D) Green Metrics

1) Calculations for the synthesis of N-Benzylbenzamide via thionyl chloride, producing an acid chloride.\textsuperscript{13}

\[
\text{Benzoyl Chloride} + \text{Benzyl amine} \rightarrow \text{Crude N-benzylbenzamide} + \text{HCl}
\]

<table>
<thead>
<tr>
<th>Input</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoyl Chloride</td>
<td>3.5g</td>
</tr>
<tr>
<td>Benzyl amine</td>
<td>2.7g</td>
</tr>
<tr>
<td>Acetone</td>
<td>26.4 (33ml)</td>
</tr>
<tr>
<td>NaHCO\textsubscript{3} (aq)</td>
<td>12g</td>
</tr>
<tr>
<td>Brine (aq)</td>
<td>50g</td>
</tr>
<tr>
<td>Total</td>
<td>94.6g</td>
</tr>
<tr>
<td>Crude N-benzylbenzamide</td>
<td>3.8g</td>
</tr>
<tr>
<td>Aqueous waste</td>
<td>62g</td>
</tr>
<tr>
<td>Organic Solvent Waste</td>
<td>2.7g</td>
</tr>
<tr>
<td>Total</td>
<td>64.7</td>
</tr>
</tbody>
</table>
E-Factor, \[
\frac{64.7 \text{g of waste produced}}{3.8 \text{g of crude product}} = 17
\]

Mass Intensity, \[
\frac{94.6 \text{g of raw material used}}{3.8 \text{g of crude product}} = 25
\]

Atom Economy, \[
\frac{211}{140.5 + 107} \times 100 = 85.2\%
\]

Assumptions
1. 90% of organic solvents are recovered.
2. The formation of acyl chloride and use of thionyl chloride is not accounted for in calculations.

2) Calculations for the synthesis of \(N\)-Benzylbenzamide using DCC as activating agent.\(^{14}\)

\[
\text{C}_{(\text{OH})} + \text{C}_{(\text{H}_2\text{N})\text{C}_6\text{H}_5} \rightarrow \text{C}_{(\text{N})\text{C}_6\text{H}_5\text{CH}_2} + \text{C}_{\text{H}_2\text{N}\text{C}_6\text{H}_5\text{CO}_2}\] 82%

<table>
<thead>
<tr>
<th>Input</th>
<th>Output</th>
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<tbody>
<tr>
<td>Benzoic acid</td>
<td>1.5g Crude (N)-benzylbenzamide 2g</td>
</tr>
<tr>
<td>Benzylic amine</td>
<td>1.3g</td>
</tr>
<tr>
<td>DCC</td>
<td>2.7g</td>
</tr>
<tr>
<td>DCM</td>
<td>92.7g (70ml)</td>
</tr>
<tr>
<td>HCl (aq)</td>
<td>18g</td>
</tr>
<tr>
<td>KHCO(_3) (aq)</td>
<td>18g</td>
</tr>
<tr>
<td></td>
<td>Aqueous waste 36g</td>
</tr>
<tr>
<td></td>
<td>Organic Solvent Waste 9.3g</td>
</tr>
</tbody>
</table>
45.3g of waste produced

2g of crude product

E-Factor, \( \left( \frac{45.3g \text{ of waste produced}}{2g \text{ of crude product}} \right) \) = 22.6

Mass Intensity, \( \left( \frac{134.2g \text{ of raw material used}}{2g \text{ of crude product}} \right) \) = 67

Atom Economy, \( \left( \frac{211}{206 + 107 + 122} \right) \times 100 \) = 48.5

Assumptions

1. 90% of organic solvents were recovered.
2. Calculations did not take into account of recrystallisation of the product.
3. Calculations did not account for the synthesis of DCC.

3) Calculation for the synthesis of \( N \)-Benzylbenzamide using ortho-\( N,N \)-Di-isopropylbenzylaminoboronic acid (IBA).\(^{15}\)

\[
\begin{array}{c}
\text{Benzoic acid} \quad 0.6g \\
\text{Benzyl amine} \quad 0.54g \\
\text{IBA} \quad 0.12g \\
\text{Flurobenzene} \quad 51.2g \ (50ml)
\end{array}
\]

<table>
<thead>
<tr>
<th>Input</th>
<th>Output</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic acid</td>
<td>0.6g</td>
<td>Crude ( N )-benzylbenzamide</td>
</tr>
<tr>
<td>Benzyl amine</td>
<td>0.54g</td>
<td></td>
</tr>
<tr>
<td>IBA</td>
<td>0.12g</td>
<td></td>
</tr>
<tr>
<td>Flurobenzene</td>
<td>51.2g (50ml)</td>
<td></td>
</tr>
</tbody>
</table>
DCM 33.1g (25ml) Aqueous waste 125g
Brine (aq) 25g
HCl (aq) 25g
Brine (aq) 25g
NaOH (aq) 25g Organic Solvent Waste 8.4g
Brine (aq) 25g
Total 210.6g Total 133.4g

E-Factor, \( \frac{133.4\text{g of waste produced}}{0.5\text{g of crude product}} \) = 251.7

Mass Intensity, \( \frac{210.5\text{g of raw material used}}{0.53\text{g of crude product}} \) = 397.3

Atom Economy, \( \frac{211}{107 + 122} \times 100 \) = 92.13%

1. Calculations did not account for the synthesis of catalyst.
2. 90% recovery of organic solvents.
4) Calculations for the synthesis of \( N \)-Benzylbenzamide using \( N,N' \)-Carbonyldiimidazole as an activating agent.\(^{16}\)

\[
\text{Input} \quad \text{Output} \\
\text{Benzoic acid} \quad 1.2\text{g} \quad \text{Crude \( N \)-} \quad 1.9\text{g}
\]
Benzyl amine 1g
THF 17.7g (20ml)
CDI 1.62g
NaOH (aq) 10g
HCl (aq) 50g
Total 63.9g

<table>
<thead>
<tr>
<th>Material</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous waste</td>
<td>60g</td>
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<tr>
<td>Organic Solvent Waste</td>
<td>1.7g</td>
</tr>
<tr>
<td>NaOH (aq)</td>
<td>10g</td>
</tr>
<tr>
<td>HCl (aq)</td>
<td>50g</td>
</tr>
<tr>
<td>Total</td>
<td>61.7g</td>
</tr>
</tbody>
</table>

E-Factor, \[ \left( \frac{61.7 \text{g of waste produced}}{1.9 \text{g of crude product}} \right) = 31.8 \]

Mass Intensity, \[ \left( \frac{63.9 \text{g of raw material used}}{1.9 \text{g of crude product}} \right) = 32.9 \]

Atom Economy, \[ \left( \frac{211}{122 + 107 + 162} \right) \times 100 = 53.9\% \]

Assumptions

1. 90% of organic solvents were recovered.
2. Calculations did not take into account of recrystallisation of the product.
3. Calculations did not account for the synthesis of CDI.
4. Calculations for the synthesis of N-Benzylbenzamide using Sulfated Tungstate (Catalyst).

\[
\begin{align*}
\text{Benzoic acid} & \quad + \quad \text{H}_2\text{NCH}_2\text{C}_6\text{H}_4\text{OH} & \quad \rightarrow \quad \text{N-Benzylbenzamide} & \quad + \quad \text{H}_2\text{O} \\
\text{Input} & \quad 2\text{g} & \quad \text{Output} & \quad 2.8\text{g}
\end{align*}
\]
Benzyl amine 1.7g benzylbenzamide
Catalyst 0.64g Aqueous waste 4.4g
Toluene 17.2g (20ml)
EtOAc 27g (30ml) Organic Solvent Waste 20
NaHCO₃ (aq) 10g
HCl (aq) 10g
Total 68.5g Total 24.4g

E-Factor,
\[
\frac{24.4 \text{g of waste produced}}{2.8 \text{g of crude product}} = 8.7
\]

Mass Intensity,
\[
\frac{68.5 \text{g of raw material used}}{2.8 \text{g of crude product}} = 24.4
\]

Atom Economy,
\[
\frac{211}{122 + 107} \times 100 = 92.13\%
\]

Assumptions
1. 90% recovery of organic solvents.
2. Calculations did not account for the synthesis of the catalyst.

E) References:


