Supplementary Material (ESI) for Chemical Communications

Clean, Reusable and Low Cost Heterogeneous Catalyst for Amide Synthesis

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SUPPORTING INFORMATION

Contents

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.

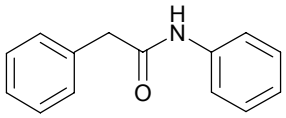
Experimental Section

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 (110oC) 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. 118oC ; m.p. 116-118oC; 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), 1662cm-l (C=O).

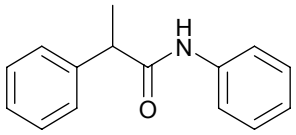
Amide Analytical Data

Entry 2) 2,*N*-Diphenylacetamide



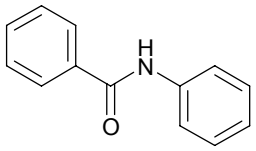
Literature m.p. 118 oC; m.p. 118-119oC; 1H NMR (270MHz, CDCl3): δ = 7.25-7.39 (m, 10H; Ar), 3.49 (s, 2H); 13C NMR (270MHz, CDCl3): δ = 169.12, 137.85, 134.41, 129.47, 129.16, 128.89, 127.61, 124.41, 119.81, 44.76; IR: ν˜= 3254 (NH), 1655cm-l (C=O).

Entry 3) N-Phenyl-2-phenylpropionamide



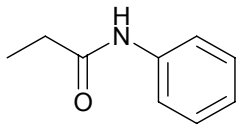
Literature m.p. 134oC; m.p. 132-134oC; 1H NMR (270MHz, CDCl3): δ = 7.47 (br s, 1H; NH), 7.26-7.42 (m, 10H; Ar), 3.71 (m, 1H), 1.60 (d, J=7.4Hz, 3H); 13C NMR (270MHz, CDCl3): δ = 172.30, 140.87, 137.80, 129.69, 129.01, 128.87, 127.55, 124.21, 119.68, 48.08, 18.52; IR: ν˜= 3360 (NH), 1660cm-l (C=O).

Entry 4) N-Phenylbenzamide



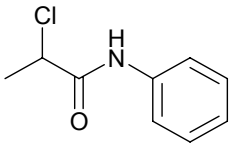
Literature m.p. 166oC; m.p. 165-166oC; 1H NMR (270MHz, CDCl3): δ = 7.13 - 7.86 (m, 10H; Ar); 13C NMR (270MHz, CDCl3): δ = 165.79, 137.88, 134.95, 131.79, 129.05, 128.73, 127.00, 124.53, 120.20; IR: ν˜= 3343 (NH), 1653cm-l (C=O).

Entry 5) N-Phenylpropionamide



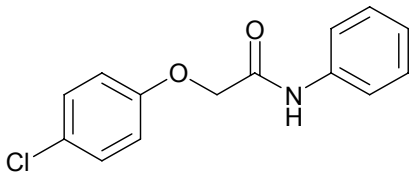
Literature m.p. 106oC; m.p. 105-107oC; 1H NMR (270MHz, CDCl3): δ = 7.77 (br s, 1H; NH), 7.49 (d, J=7.8Hz, 2H; Ar), 7.27 (t, J=7.8Hz, 2H; Ar), 7.07 (t, J=7.4Hz, 1H; Ar), 2.34 (m, 2H), 1.20 (t, J=7.8Hz, 3H); 13C NMR (270MHz, CDCl3): δ = 172.42, 138.01, 128.82, 124.05, 119.91, 30.56, 9.66; IR: ν˜= 3256 (NH), 1665cm-l (C=O).

Entry 6) 2-Chloro-*N*-phenyl-propionamide



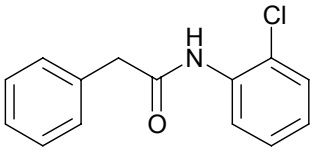
Literature m.p. 92oC; m.p. 92-93oC; 1H NMR (270MHz, CDCl3): δ = 8.31 (br s, 1H; NH), 7.55 (d, J=7.4Hz, 2H; Ar), 7.34 (t, J=7.4Hz, 2H; Ar), 7.15 (t, J=7.4Hz, 1H; Ar), 4.55 (m, 1H), 1.79 (d, J=8.1Hz, 3H); 13C NMR (270MHz, CDCl3): δ = 167.28, 136.88, 129.10, 125.08, 120.07, 56.18, 22.68; IR: ν˜= 3297 (NH), 1672cm-l (C=O).

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



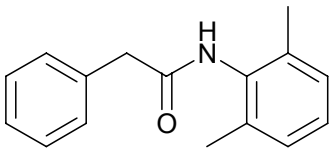
Literature m.p. 129oC; m.p. 128-129oC; 1H NMR (270MHz, CDCl3): δ = 8.2 (br s, 1H; NH), 7.58 (d, J=8.9Hz, 2H; Ar), 7.35 - 7.28 (m, 4H; Ar), 7.15 (t, J=7.4Hz, 1H; Ar), 6.93 (d, J=8.9Hz, 2H; Ar), 4.56 (s, 2H); 13C NMR (270MHz, CDCl3): δ = 165.73, 155.51, 136.62, 129.81, 129.10, 127.50, 124.97, 120.10, 116.12,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

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



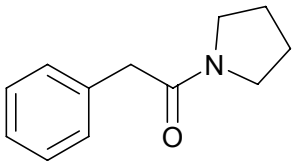
Literature m.p. 129oC; m.p. 128-129oC; 1H NMR (270MHz, CDCl3): δ = 7.66 (br. s, 1H; NH), 7.41 - 7.25 (m, 7H; Ar), 7.27 (d, J=8.0Hz, 1H; Ar), 6.99 (t, J=8.0Hz, 1H; Ar), 3.78 (s, 2H); 13C NMR (270MHz, CDCl3): δ = 169.05, 134.21, 129.62, 129.27, 128.83, 127.81, 127.59, 124.60, 122.30, 121.65, 121.16, 45.05; IR: ν˜= 3258 (NH), 1659cm-l (C=O).

Entry 9) N-(2,6-Dimethyl-phenyl)phenyl-acetamide



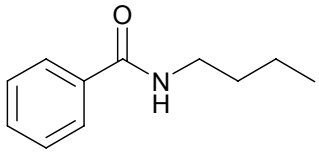
Literature m.p. 147oC; m.p. 146-147oC; 1H NMR (270MHz, CDCl3): δ = 7.43 - 7.01 (m, 8H; Ar), 6.64 (br. s, 1H; NH), 3.76 (s, 2H), 2.12 (s, 6H; 2(CH3)); 13C NMR (270MHz, CDCl3): δ = 169.41, 135.30, 133.61, 129.53, 129.27, 128.32, 128.15, 127.68, 127.37, 44.08, 18.26; IR: ν˜= 3248 (NH), 1642cm-l (C=O).

Entry 10) Phenylacetyl-pyrrolidine



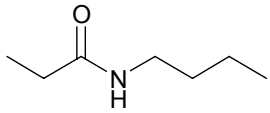
Literature m.p. 48oC; m.p. 47-48oC; 1H NMR (270MHz, CDCl3): δ = 7.19-7.11 (m, 5H; Ar), 3.52 (s, 2H; CH2), 3.4-3.26 (m, 4H; 2x N-CH2-CH2), 1.66-1.79 (m, 4H; 2x N-CH2-CH2); 13C NMR (270MHz, CDCl3): δ = 169.59, 135.28, 129.30, 128.52, 126.65, 45.92, 42.11, 24.19; IR: ν˜=1625cm-l (C=O).

Entry 11) N-Butyl-benzamide



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

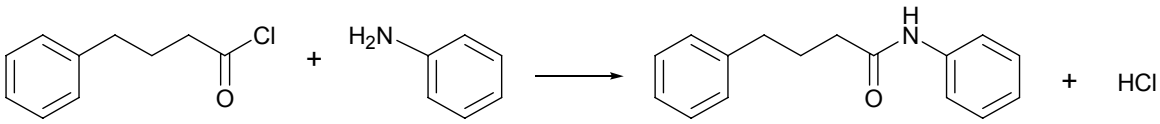
Entry 12) N-Butyl-propionamide



Oil; 1H NMR (270MHz, CDCl3): δ = 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): δ = 174.56, 39.32, 31.69, 29.63, 20.15, 13.80, 10.12; IR: ν˜=3296 (NH), 1663 cm-l (C=O).

Green Metrics

1) Calculations for the synthesis of 4,*N*-diphenylbutyramide via thionyl chloride, producing an acid chloride, (A. J. Pearson, W. R. Roush, *Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups*, Wiley, New York, 1999, p370 - 373.)



97% yield

Input		Output	
4-Phenylbutyric acid	1.97g	Crude 4,*N*-diphenylbutyramide	2.78g
Aniline	1.12g	Aqueous waste	20g
Toluene	69.4g (80ml)		
NaOH 10% (aq)	20g	Organic solvent waste (assuming 90% recovery)	17.6g
CH2Cl2	106.1g (80ml)		
Total	199.5g	Total waste	37.6g

E-factor, $\left(\frac{\text{37.6g of waste}}{\text{2.78g of crude product}} \right) = 13.5$

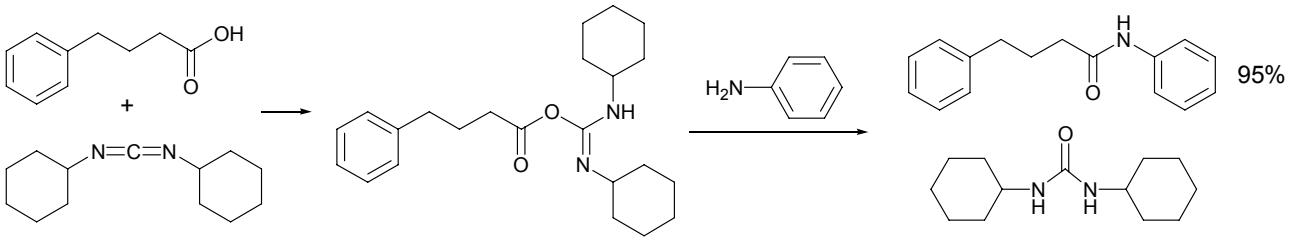
Mass Intensity, $\left(\frac{\text{199.5g of raw materials used}}{\text{2.78g of crude product}} \right) = 71.8$

Atom Economy, $\left(\frac{239}{182 + 93} \right) \times 100 = 86.9\%$

Assumptions

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

2) Calculations for the synthesis of 4,*N*-diphenylbutyramide using dicyclohexylcarbodiimide (DCC) as an activating agent, (J. C. Sheehan, P. G. Hess, J. Am. Chem. Soc. 1955, 77, 1067.)



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

E-Factor, $\left(\frac{\text{53.3g of waste}}{\text{2.73g of crude product}} \right) = 19.5$

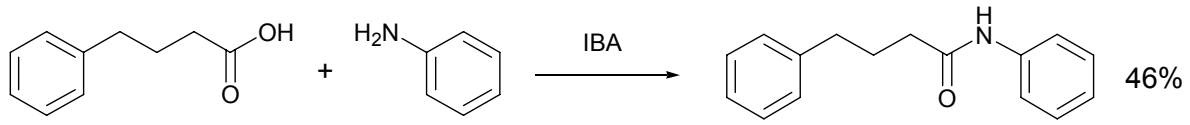
Mass intensity, $\left(\frac{\text{151.9g of raw materials used}}{\text{2.73g of crude product}} \right) = 55.6$

Atom economy, $\left(\frac{239}{370 + 93} \right) \times 100 = 51.6\%$

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.

3) Calculations for the synthesis of 4,*N*-diphenylbutyramide using ortho-*N,N*-Di-isopropylbenzylaminoboronic acid, (IBA), (K. Arnold, A. S. Batsanov, B. Daves and A. Whiting, Green Chem. 2008, 10, 124-134).



Input		**Output**	
4-Phenylbutyric acid	0.164g (1 mmol)	Crude 4,*N*-diphenylbutyramide	0.11g
Aniline	0.093g (1 mmol)		
ortho-N,N-Di-isopropylbenzylaminoboronic acid	0.0235g (1 mol %)	Aqueous waste	40g
Toluene	8.67g (10ml)		
Methyl-tert-butyl ether (MTBE)	7.40g (10ml)		
HCl 5%w/v (aq)	10g	Organic waste solvent (assuming 90% recovery)	1.6g
Brine (aq)	10g		
NaOH 5%w/v (aq)	10g		
Brine (aq)	10g		
Total	56.4g	Total waste	41.6g

E-Factor - Synthesis of amide

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

Mass intensity - Synthesis of amide

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

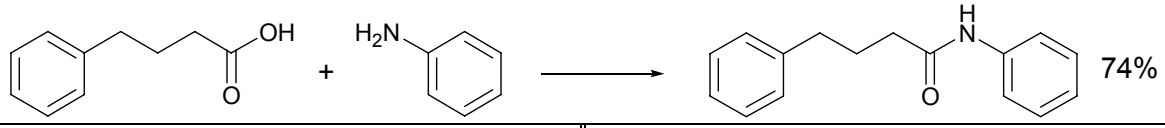
Atom economy - Synthesis of amide

$$\left(\frac{239}{164 + 93} \right) \text{x } 100 = 93\%$$

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



Input		Output	
4-Phenylbutyric acid	1.968g (12mmols)	4,*N*-diphenylbutyramide	2.12g
Aniline	1.12g (12mmols)	Organic solvent waste (90% recovery)	1.73g
Toluene	17.34g (20ml)		
K60	0.62g (20% wt)	K60 catalyst	0.62g
Total	21.05g	Total waste	2.35g

E-Factor - Synthesis of amide

Without reusing catalyst

$$\left(\frac{\text{2.35g of waste}}{\text{2.12g of product}} \right) = 1.11$$

4th reuse of K60

$$\left(\frac{\text{1.73g of waste}}{\text{2.00g of product}} \right) = 0.87$$

Mass intensity - Synthesis of amide

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

Atom economy - Synthesis of amide

$$\left(\frac{239}{164 + 93} \right) \text{x } 100 = 93\%$$

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.