

Facile and Efficient KOH-Catalysed Reduction of Esters and Tertiary Amides

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GENERAL CONSIDERATIONS:

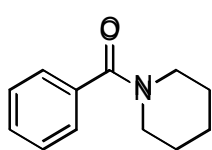
Esters (**1a-1l**) and amides **3a**, **3f**, **3h** and **3i** were purchased from Sigma Aldrich and used as received. THF and DCM were dispensed from a solvent purification system from Innovative Technology. ^1H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance 300 or Bruker Avance II 400 Ultrashield NMR spectrometers. Mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre at Swansea University, Grove building, Singleton Park, Swansea, SA2 8PP, Wales, UK.

EXPERIMENTAL PROCEDURES AND CHARACTERIZATION:

General procedure for the preparation of amides:¹

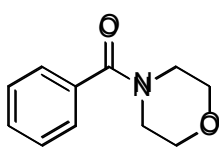
To the corresponding carboxylic acid (10 mmol) was added thionyl chloride (15 mmol). The mixture was stirred for 3-4 h at 55°C, and then the excess of thionyl chloride was removed under vacuum. Then, the acyl chloride was added in one portion to a solution of the amine (11 mmol), NEt_3 (12.5 mmol) and dichloromethane (20 mL) at room temperature, resulting rapidly in a boiling solution. The reaction mixture was stirred for 1h at room temperature and then was diluted with dichloromethane (30 mL). The solution was transferred to a separation funnel and was washed with 1N HCl (20 mL). The combined fractions were concentrated under reduced pressure. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 3:1).

1-Benzoylpiperidine (**3b**):²



^1H NMR (300 MHz, CDCl_3): δ 7.38 (s, 5H), 3.71 (br s, 2H), 3.33 (br s, 2H), 1.67 (br s, 4H), 1.51 (br s, 2H).

1-Benzoylmorpholine (**3c**):²

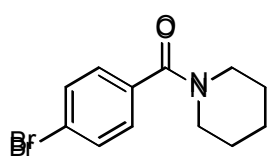


^1H NMR (300 MHz, CDCl_3): δ 7.41 (s, 5H), 3.90-3.30 (m, 8H).

¹ Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 18.

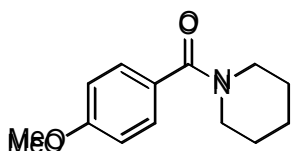
² Li, J.; Xu, F.; Zhang, Y.; Shen, Q. *J. Org. Chem.*, **2009**, *74*, 2575.

***N*-(4-Bromobenzoyl)piperidine (3d):³**



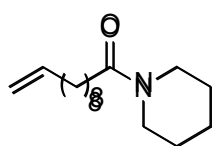
¹H NMR (300 MHz, CDCl₃): δ 7.56-7.54 (m, 2H), 7.29-7.27 (m, 2H), 3.68 (s, 2H), 3.32 (br s, 2H), 1.68 (br s, 4H), 1.56 (br s, 2H).

***N*-(4-Methoxybenzoyl)piperidine (3e):²**



¹H NMR (300 MHz, CDCl₃): δ 7.39-7.34 (m, 2H), 6.92-6.87 (m, 2H), 3.82 (s, 3H), 3.52 (br s, 4H), 1.70-1.65 (m, 3H), 1.58 (br s, 3H).

1-(Piperidin-1-yl)undec-10-en-1-one (3g):

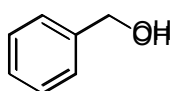


¹H NMR (300 MHz, CDCl₃): δ 5.84 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.06-4.93 (m, 2H), 3.61-3.54 (m, 2H), 3.45-3.39 (m, 2H), 2.38-2.29 (m, 2H), 2.07 (q, *J* = 6.8 Hz, 2H), 1.74-1.52 (m, 9H), 1.42-1.27 (m, 10). ¹³C NMR (100 MHz, CDCl₃): δ 171.5, 139.2, 114.1, 46.7, 42.6, 33.8, 33.5, 29.5, 29.4, 29.3, 29.1, 28.9, 26.6, 25.6, 25.5, 24.6. **MS** (NSI): *m/z* 252 (M+1)⁺; **HRMS** (NSI, *m/z*) calcd. for C₁₆H₃₀NO, 252.2322; found 252.2321.

General procedure for hydrosilylation of esters:

To KOH (0.04 mmol) were added the corresponding ester (**1**) (1 mmol) and PhSiH₃ (1.1 mmol). The resulting mixture was stirred at r.t. After the indicated time (Table 2), the reaction was hydrolyzed with aqueous HCl (1 mL, 1M) in THF (0,5 mL) at r.t. for 1h. Then, the aqueous phase was extracted with Et₂O (3x5mL). The organic layer was washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel. The eluent is indicated below.

Benzyl alcohol (2a):⁴

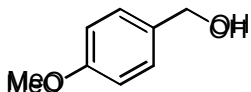


Chromatography: pentane/Et₂O, 9:1. ¹H NMR (300 MHz, CDCl₃): δ 7.36 (s, 5H), 4.66 (s, 2H).

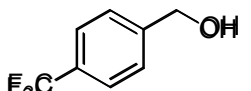
³ Takahata, H.; Yamazaki, T. *J. Org. Chem.* **1985**, *50*, 4648.

⁴ Jiang, F.; Bezier, D.; Sortais, J. -B.; Darcel, C. *Adv. Synth. Catal.* **2011**, *353*, 239.

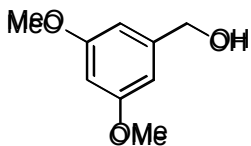
(4-Methoxyphenyl)methanol (2b):⁵

 Chromatography: pentane/Et₂O, 8:1. Yield: 81%. ¹H NMR (300 MHz, CDCl₃): δ 7.31 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 2H), 4.62 (s, 2H), 3.84 (s, 3H).

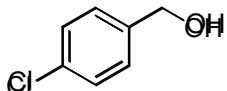
[4-(Trifluoromethyl)phenyl]methanol (2c):⁶

 Chromatography: pentane/Et₂O, 7:1. Yield: 96%. ¹H NMR (300 MHz, CDCl₃): δ 7.58-7.55 (m, 2H), 7.40-7.38 (m, 2H), 4.66 (s, 2H).

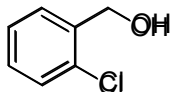
(3,5-Dimethoxyphenyl)methanol (2d):⁷

 Chromatography: pentane/Et₂O, 6:1. Yield: 80%. ¹H NMR (300 MHz, CDCl₃): δ 6.51 (d, *J* = 2.3 Hz, 2H), 6.38 (t, *J* = 2.3 Hz, 1H), 4.62 (m, 2H), 3.78 (s, 6H).

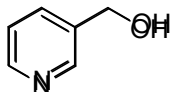
(4-Chlorophenyl)methanol (2e):⁷

 Chromatography: pentane/Et₂O, 3:1. Yield: 96%. ¹H NMR (300 MHz, CDCl₃): δ 7.24-7.16 (m, 4H), 4.53 (s, 2H).

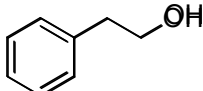
(2-Chlorophenyl)methanol (2f):⁸

 Chromatography: pentane/Et₂O, 3:1. Yield: 86%. ¹H NMR (300 MHz, CDCl₃): δ 7.52-7.47 (m, 1H), 7.38 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.33-7.22 (m, 2H), 4.79 (s, 2H).

Pyridin-3-ylmethanol (2g):⁷

 Chromatography: pentane/Et₂O, 3:1. Yield: 85%. ¹H NMR (300 MHz, CDCl₃): δ 8.53 (d, *J* = 4.9 Hz, 1H), 7.67 (td, *J* = 7.7, 1.7 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.21-7.16 (m, 1H), 4.75 (s, 2H).

2-Phenylethanol (2h):⁹

 Chromatography: pentane/Et₂O, 4:1. Yield: 83%. ¹H NMR (300 MHz, CDCl₃): δ 7.38-7.33 (m, 2H), 7.29-7.25 (m, 3H), 3.88 (t, *J* = 6.6 Hz, 1H), 2.90 (t, *J* = 6.6 Hz, 1H).

⁵ Buitrago, E.; Tinnis, F.; Adolfsson, H. *Adv. Synth. Catal.* **2012**, *354*, 217.

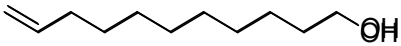
⁶ Wei, Y.; Xue, D.; Lei, Q.; Wang, C.; Xiao, J. *Green Chemistry*, **2013**, *15*, 629.

⁷ Murai, N.; Yonaga, M.; Tanaka, K. *Org. Lett.*, **2012**, *14*, 1278.

⁸ Shaikh, N. S.; Junge, K.; Beller, M. *Org. Lett.*, **2007**, *9*, 5429.

⁹ Dieskau, A. P.; Plietker, B. *Org. Lett.*, **2011**, *13*, 5544.

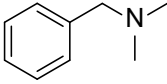
Undec-10-en-1-ol (**2i**):⁴

 Chromatography: pentane/Et₂O, 4:1. Yield: 80%. ¹H NMR (300 MHz, CDCl₃): δ 5.87 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.10-4.95 (m, 2H), 3.69 (t, *J* = 6.6 Hz, 2H), 2.14-2.05 (m, 2H), 1.70-1.56 (m, 3H), 1.49-1.29 (m, 13H).

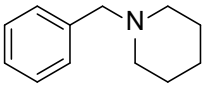
General procedure for the hydrosilylation of amides:

To KOH (0.04 mmol) were added the corresponding amide (**3**) (1 mmol) and PhSiH₃ (1.1 mmol). The resulting mixture was stirred at r.t. After the indicated time (Table 3), the reaction was diluted with DCM (0.5 mL) and SiO₂ was added. The residue was directly purified by flash chromatography on silica gel (*n*-hexane:EtOAc; 2:1).

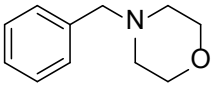
N,N-Dimethyl-1-phenylmethanamine (**4a**):¹⁰

 Yield: 90%. ¹H NMR (300 MHz, CDCl₃): δ 7.23 (s, 5H), 3.35 (s, 2H), 2.17 (s, 6).

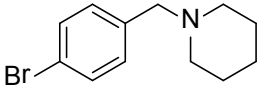
1-Benzylpiperidine (**4b**):¹¹

 Yield: 91%. ¹H NMR (300 MHz, CDCl₃): δ 7.32-7.31 (m, 5H), 3.47 (s, 2H), 2.38 (br s, 4H), 1.61-1.54 (m, 4H), 1.46-1.39 (m, 2H).

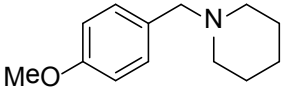
1-Benzylmorpholine (**4c**):¹²

 Yield: 75%. ¹H NMR (300 MHz, CDCl₃): δ 7.36-7.34 (m, 5H), 3.76-3.70 (m, 4H), 3.53 (s, 2H), 2.50-2.44 (m, 4H).

1-(4-Bromobenzyl)morpholine (**4c**):

 Amine **4c** was synthesized following the general procedure using THF as a solvent (1.25 M). Yield: 81%. ¹H NMR (300 MHz, CDCl₃): δ 7.44-7.40 (m, 2H), 7.21-7.18 (m, 2H), 3.41 (s, 2H), 2.35 (br s, 4H), 1.60-1.53 (m, 4H), 1.46-1.40 (m, 2H).

1-(4-Methoxybenzyl)morpholine (**4d**):

 Amine **4d** was synthesized following the general procedure at 60°C. Yield: 88%. ¹H NMR (300 MHz, CDCl₃): δ 7.22 (d, *J*

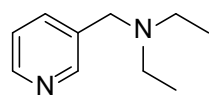
¹⁰ Reeves, J. T.; Tan, Z.; Marsini, M. A.; Han, Z. S.; Xu, Y.; Reeves, D. C.; Lee, H.; Lu, B. Z.; Senanayake, C. H. *Adv. Synth. Catal.*, **2013**, 355, 47.

¹¹ Xiao, K.-J.; Wang, Y.; Ye, K.-Y.; Huang, P.-Q. *Chem. Eur. J.*, **2010**, 16, 12792.

¹² Das, S.; Addis, D.; Zhou, S.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2010**, 132, 1770.

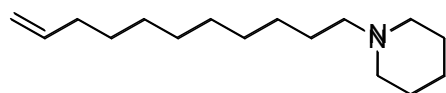
= 8.3 Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 3.80 (s, 3H), 3.41 (s, 2H), 2.35 (br s, 4H), 1.60-1.53 (m, 4H), 1.45-1.41 (m, 2H).

N-Ethyl-N-(pyridin-3-ylmethyl)ethanamine (4e):¹³



Yield: 80%. ¹H NMR (300 MHz, CDCl₃): δ 8.53 (d, $J = 1.6$ Hz, 1H), 8.47 (dd, $J = 4.8, 1.6$ Hz, 1H), 7.71-7.63 (m, 1H), 7.23 (dd, $J = 7.8, 4.8$ Hz, 1H), 3.56 (s, 2H), 2.51 (q, $J = 7.1$ Hz, 4H), 1.03 (t, $J = 7.1$ Hz, 6H).

1-(Undec-10-en-1-yl)piperidine (4f):



Amine **4f** was synthesized following the general procedure at 60°C. Yield: 86%. ¹H NMR (300 MHz, CDCl₃): δ 5.81 (ddt, $J = 16.9, 10.1, 6.7$ Hz, 1H), 5.02-4.89 (m, 2H), 2.37 (br s, 3H), 2.29-2.24 (m, 2H), 2.07-1.98 (m, 2H), 1.64-1.55 (m, 4H), 1.51-1.34 (m, 6H), 1.32-1.23 (m, 11). ¹³C NMR (100 MHz, CDCl₃): δ 139.2, 114.1, 59.7, 54.6, 33.8, 29.6, 29.5, 29.5, 29.1, 28.9, 27.8, 26.9, 25.9, 24.5. **MS** (NSI): m/z 238 (M+H)⁺; **HRMS** (NSI, m/z) calcd. for C₁₆H₃₂N, 238.2529; found 238.2529.

¹³ Raushel, J.; Sandrock, D. L.; Molander, G. A.; Josyula, K. V.; Pakyz, D. *J. Org. Chem.* **2011**, *76*, 2762.

NMR SPECTRA:

