‘Evaluation of Alternative Solvents in Common Amide Coupling Reactions: Replacement of Dichloromethane and N,N-Dimethylformamide’

Donna S. MacMillan,a Jane Murray,b Helen F. Sneddon,c Craig Jamieson,a and Allan J. B. Watson*a

aDepartment of Pure and Applied Chemistry, WestCHEM, University of Strathclyde, Thomas Graham Building, 295 Cathedral Street, Glasgow, G1 1XL, UK. Fax: +44 (0)141 548 4822; Tel: +44 (0)141 548 2439; E-mail: allan.watson.100@strath.ac.uk.
bSigma-Aldrich, The Old Brickyard, New Road, Gillingham, Dorset, SP8 4XT, UK.
cGlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK.

Supporting Information

1. General

1.1. Reagents
All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated.

1.2 Experimental Details
All reactions were carried out using conventional glassware at room temperature (generally approx. 18 °C) under an air atmosphere and with no special attention given to the exclusion of moisture.

1.3 Purification of Products
i) Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analysed under 254 nm UV light or developed using potassium permanganate or vanillin solution.
ii) Flash chromatography was carried out using ZEOprep 60 HYD 40-63µm silica gel or IST Isolute Flash silica cartridges.

1.4 Analysis of Products
i) Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine.
ii) 1H and 13C NMR spectra were obtained on a Bruker AV 400 at 400 MHz and 100 MHz respectively, or a Bruker DRX 500 at 500 MHz and 125 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with CDCl3 referenced at 7.27 (1H) and 77.0 ppm (13C), respectively, and DMSO-d6 referenced at 2.52 (1H) and 39.5 ppm (13C), respectively.
iii) High-resolution mass spectra were obtained through analysis at the EPSRC National Mass Spectrometry Facility, University of Swansea.
iv) HPLC analysis was carried out on an Agilent Technologies 1200 Series Analytical HPLC using a Phenomenex or Macherey-Nagel C18 5 µM 4.6 x 50 mm column using MeCN/H2O as the the mobile phase with the following gradient:
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Conversions were obtained using an internal standard which were either dibenzyl ether (A), benzamide (B), bromobenzene (C), or ethyl 2-pyridylacetate (D).

2. Experimental Procedures

2.1 Representative Reactions

2.2 General Experimental Procedure

A solution of acid (1 equiv, 0.2 mmol), standard A, B, C, or D and coupling agent (1.2 equiv, 0.24 mmol) were stirred in solvent (1 mL, 0.2 M) at room temperature. DIPEA (2 equiv, 0.4 mmol) was added and the mixture was stirred for 5 minutes before addition of the amine (1.1 equiv, 0.22 mmol). The reaction was then followed by HPLC at 0 h (approx. 5 min), 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, and 24 h by removal of an aliquot (10 µL) which was diluted to 1 mL in MeCN before injection.
3. Experimental Data

3.1 Conversion vs. Time Data for Reactions 1-4 Using Specific Coupling Agents in the Range of Solvents

The internal standard used for each dataset is indicated in superscript at the header of each column.

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**Electronic Supplementary Material (ESI) for Green Chemistry**
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## Reaction 2: EtOAc

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### Graph

*Graph showing % conversion vs. Time (h) for different coupling agents: COMU, DIC/HOBt, HATU, PyBOP, T3P.*

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Electronic Supplementary Material (ESI) for Green Chemistry
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**Reaction 2: IPA**

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3.3 Compound Library – PCA Contributors

Physicochemical parameters were computed using KNIME version 2.6.0. Briefly, an sdf file representing the compound library was generated from ChemDraw. This was loaded into KNIME and a workflow was subsequently generated using the Chemistry Development Kit (CDK) community node to calculate PSA, HBA, HBD, MW, and rotatable bonds. XLogP was determined separately and combined with the other descriptors. The outputs for compounds 5-14 are given below.

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3.4 Charaterisation Data for Amide Products

**Compound 1: 4-Methyl-N-phenylbenzamide**

Appearance: White solid.

$\nu_{\text{max}}$ (neat): 3348, 2918, 2852, 1649, 825 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 2.41 (s, 3H), 7.14 (t, 1H, $J = 7.6$ Hz), 7.24 (d, 2H, $J = 8.0$ Hz), 7.35 (t, 2H, $J = 8.8$ Hz), 7.65 (dd, 2H, $J = 7.6$, 2.8 Hz), 7.76 (d, 2H, $J = 8.4$ Hz), 8.05 (br s, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 21.4, 120.3, 124.3, 127.0, 128.9, 129.3, 132.0, 138.0, 142.2, 165.9.

HRMS (C$_{16}$H$_{13}$NO) [M+H$^+$] requires 212.1070, found [M+H$^+$] 212.1069.

**Compound 2: N-(4-Methoxybenzyl)-4-methylbenzamide**

Appearance: Pale yellow crystalline solid.

$\nu_{\text{max}}$ (neat): 3246, 2918, 2833, 1033, 1633, 839 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 2.37 (s, 3H), 3.77 (s, 3H), 4.52 (d, 2H, $J = 4.4$ Hz), 6.78 (br s, 1H), 6.84 (d, 2H, $J = 8.8$ Hz), 7.18 (d, 2H, $J = 8.0$ Hz), 7.24 (d, 2H, $J = 8.8$ Hz), 7.68 (d, 2H, $J = 8.4$ Hz).
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 21.3, 43.4, 55.2, 114.0, 126.9, 129.0, 129.1, 130.3, 131.4, 141.7, 158.9, 167.4.

HRMS (C$_{18}$H$_{17}$NO$_2$) [M+H$^+$] requires 256.1332, found [M+H$^+$] 256.1334.

**Compound 3: N$_2$Diphenylacетamide**

Appearance: White solid.

$\nu$ max (neat): 3254, 2920, 2850, 1656, 1440, 1159 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 3.74 (s, 2H), 7.09 (t, 1H, $J = 7.6$ Hz), 7.24 (br s, 1H), 7.29 (t, 2H, $J = 8.4$ Hz), 7.34-7.44 (m, 7H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 44.8, 119.9, 124.5, 127.6, 128.9, 129.2, 129.5, 134.4, 137.6, 169.2.

HRMS (C$_{14}$H$_{13}$NO) [M+H$^+$] requires 212.1070, found [M+H$^+$] 212.1070.

**Compound 4: N-(4-Methoxybenzyl)-2-phenylacetamide**

Appearance: White solid.

$\nu$ max (neat): 3238, 2920, 2850, 1649, 1026, 815 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 3.62 (s, 2H), 3.79 (s, 3H), 4.36 (d, 2H, $J = 5.5$ Hz), 5.62 (br s, 1H), 6.83 (d, 2H, $J = 8.4$ Hz), 7.11 (d, 2H, $J = 8.4$ Hz), 7.26-7.31 (m, 4H), 7.33-7.37 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 29.7, 43.0, 43.8, 114.0, 127.3, 128.8, 129.0, 129.4, 130.1, 134.8, 158.9, 170.8.

HRMS (C$_{16}$H$_{17}$NO$_2$) [M+H$^+$] requires 256.1332, found [M+H$^+$] 256.1334.

**Compound 5: 2-Chloro-N-(2-Methoxybenzyl)nicotinamide**

Appearance: White solid.

$\nu$ max (neat): 3248, 2916, 2833, 1633, 1244, 746 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 3.76 (s, 3H), 4.51 (d, 2H, $J = 5.5$ Hz), 5.61 (d, 2H, $J = 8.5$ Hz), 6.84 (d, 2H, $J = 8.5$ Hz), 7.01 (br s, 1H), 7.23-7.27 (m, 3H), 7.94 (dd, 1H, $J = 7.5$, 2.0 Hz), 8.34 (dd, 1H, $J = 7.5$, 2.0 Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 43.6, 55.2, 114.0, 122.6, 129.1, 129.3, 131.4, 139.3, 147.0, 150.6, 159.0, 164.6.

HRMS (C$_{16}$H$_{13}$CIN$_2$O$_2$) [M+H$^+$] requires 277.0738, found [M+H$^+$] 277.0741.
**Compound 6: N-(4-[(Trifluoromethyl)phenyl]pyrazine-2-carboxamide**

![Chemical Structure of Compound 6](image)

*Appearance:* Pale yellow solid.

$\nu_{\text{max}}$ (neat): 3253, 2920, 2850, 1633, 1244 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.66 (d, 2H, $J = 8.8$ Hz), 7.90 (d, 2H, $J = 8.8$ Hz), 8.62 (dd, 1H, $J = 4.0, 1.6$ Hz), 8.85 (d, 1H, $J = 6.0$ Hz), 9.53 (d, 1H, $J = 1.6$ Hz), 9.84 (br s, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 119.0, 123.5 ($^1J = 270$ Hz), 126.0, ($^2J = 4$ Hz), 126.4 ($^2J = 24$ Hz), 139.7, 141.9, 143.4, 144.3, 147.4, 160.5.

HRMS (C$_{12}$H$_{8}$N$_3$O) [M+H$^+$] requires 268.0692, found [M+H$^+$] 268.0697.

**Compound 7: N-(2-Methoxybenzyl)furan-3-carboxamide**

![Chemical Structure of Compound 7](image)

*Appearance:* Yellow-orange solid.

$\nu_{\text{max}}$ (neat): 3242, 2918, 2833, 1633, 1244, 1033 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 3.89 (s, 3H), 4.62 (d, 2H, $J = 6.0$ Hz), 6.48 (dd, 1H, $J = 2.0, 1.6$ Hz), 6.89-6.96 (m, 3H), 7.11 (dd, 1H, $J = 2.4, 0.8$ Hz), 7.28 (dt, 1H, $J = 7.6, 1.6$ Hz), 7.34 (dd, 1H, $J = 7.2, 1.6$ Hz), 7.42 (dd, 1H, $J = 1.6, 0.8$ Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 38.9, 55.3, 110.3, 112.0, 114.1, 120.7, 125.9, 129.8, 143.7, 148.1, 157.6, 158.1.

HRMS (C$_{13}$H$_{12}$NO$_3$) [M+H$^+$] requires 232.0968, found [M+H$^+$] 232.0969.

**Compound 8: 2-(2-(4-Bromophenyl)acetamido)benzamide**

![Chemical Structure of Compound 8](image)

*Appearance:* White solid.

$\nu_{\text{max}}$ (neat): 3259, 3061, 3001, 2918, 2833, 1631, 1610, 1236, 1174, 1033 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 3.69 (s, 2H), 5.89 (br s, 1H), 6.10 (br s, 1H), 7.08 (dt, 1H, $J = 7.5, 1.5$ Hz), 7.26 (d, 2H, $J = 8.5$), 7.48-7.51 (m, 4H), 8.63 (d, 1H), 11.3 (br s, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 45.0, 118.5, 121.3, 121.5, 122.9, 127.2, 131.2, 131.9, 133.4, 133.5, 140.1, 169.3, 171.2.

HRMS (C$_{15}$H$_{13}$BrN$_2$O$_2$) [M+H$^+$] requires 333.0233, found [M+H$^+$] 333.0237.
**Compound 9: Methyl 4-(furan-2-carboxamido)benzoate**

Appearance: White solid.

$\nu_{max}$ (neat): 3246, 2918, 2833, 1633, 1610, 1244, 748 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 3.90 (s, 3H), 6.57 (dd, 1H, $J = 3.5, 2.0$ Hz), 7.27 (d, 1H, $J = 7.0$ Hz), 7.51 (dd, 1H, $J = 2.0, 0.5$), 7.75 (d, 2H, $J = 8.5$ Hz), 8.04 (d, 2H, $J = 8.5$ Hz), 8.30 (br s, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 52.0, 112.8, 115.9, 119.0, 125.8, 130.9, 141.6, 144.5, 147.4, 156.0, 166.5.

HRMS (C$_{13}$H$_{11}$NO$_4$) [M+H$^+$] requires 246.0761, found [M+H$^+$] 246.0763.

**Compound 10: 2-(4-Bromophenyl)-1-(3,4-dihydroisoquinolin-2(1H)-yl)ethanone**

Appearance: White solid.

$\nu_{max}$ (neat): 2918, 2833, 1633, 1244, 746 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-d$_6$, 80 °C) $\delta$: 2.80 (t, 2H, $J = 6.0$ Hz), 3.72 (t, 2H, $J = 6.0$ Hz), 3.79 (s, 2H), 4.65 (br s, 2H), 7.16 (br s, 4H), 7.22 (d, 2H, $J = 8.0$ Hz), 7.47 (t, 2H, $J = 8.0$ Hz).

$^{13}$C NMR (125 MHz, CDCl$_3$, 77 °C) $\delta$: 27.9, 28.6, 42.9, 43.7, 46.7, 119.4, 119.5, 126.1, 126.11 126.2, 126.3, 126.4, 126.5, 128.3, 128.5, 131.0, 131.0, 131.5, 131.6, 133.2, 133.5, 134.4, 134.7, 135.3, 135.4. Variable temperature $^{13}$C NMR up to 90 °C failed to resolve the rotameric carbons.

HRMS (C$_{17}$H$_{16}$BrNO) [M+H$^+$] requires 330.0488, found [M+H$^+$] 330.0492.

**Compound 11: Furan-3-yl(4-phenylpiperazin-1-yl)methanone**

Appearance: Red-brown gummy solid.

$\nu_{max}$ (neat): 2916, 2848, 1633, 1236, 1010, 750 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 3.26 (t, 4H, $J = 5.0$ Hz), 3.99 (br s, 4H), 6.51 (dd, 1H, $J = 5.0, 1.5$ Hz), 6.93 (t, 1H, $J = 7.5$ Hz), 6.97 (d, 2H, $J = 8.0$ Hz), 7.07 (d, 1H, $J = 3.5$ Hz), 7.30 (dt, 2H, $J = 8.0, 1.0$ Hz), 7.51 (d, 1H, $J = 1.0$ Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 29.7, 31.9, 49.7, 111.4, 116.6, 116.7, 120.6, 129.3, 143.8, 147.9, 150.9, 159.1.

HRMS (C$_{15}$H$_{16}$N$_2$O$_2$) [M+H$^+$] requires 257.1290, found [M+H$^+$] 257.1287.
**Compound 12: Ethyl 3-((tert-butoxycarbonyl)amino)acetamido)benzoate**

Appearance: Opaque oil.

$\nu_{\text{max}}$ (neat): 3323, 2978, 2933, 1710, 1681, 1284, 1161 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.34 (t, 3H, $J = 7.2$ Hz), 1.44 (s, 9H), 4.00 (d, 2H, $J = 4.4$ Hz), 4.33 (q, 2H, $J = 7.2$ Hz), 5.74 (br s, 1H), 7.33 (t, 1H, $J = 8.0$ Hz), 7.74 (d, 1H, $J = 8.0$ Hz), 7.85 (d, 1H, $J = 8.0$ Hz), 8.05 (s, 1H), 8.93 (br s, 1H, NH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 14.1, 28.2, 45.0, 61.1, 80.4, 120.8, 124.4, 125.3, 128.9, 131.0, 137.8, 156.5, 166.2, 168.3.

HRMS (C$_{16}$H$_{22}$N$_2$O$_5$) [M+H$^+$] requires 323.1601, found [M+H$^+$] 323.1606.

**Compound 13: tert-Butyl 4-benzamidopiperidine-1-carboxylate**

Appearance: Off-white solid.

$\nu_{\text{max}}$ (neat): 3261, 2918, 2833, 1631, 839 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.36-1.46 (m, 11H), 2.01 (dd, 2H, $J = 12.4$, 2.8 Hz), 2.90 (dt, 2H, $J = 12.0$, 2.4 Hz), 4.07-4.17 (m, 3H), 6.17 (d, 1H, $J = 7.6$ Hz), 7.39-7.43 (m, 2H), 7.47-7.51 (m, 1H), 7.75-7.78 dd, 2H, $J = 7.2$, 1.6 Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 28.4, 32.1, 42.7, 47.2, 79.7, 126.9, 128.5, 131.5, 134.5, 154.7, 166.9.

HRMS (C$_{17}$H$_{24}$N$_2$O$_3$) [M+H$^+$] requires 305.1860, found [M+H$^+$] 305.1862.

**Compound 14: N-(2-Bromophenyl)-6-methylpicolinamide**

Appearance: White solid.

$\nu_{\text{max}}$ (neat): 3253, 2918, 2852, 1633, 839 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 2.66 (s, 3H), 7.01 (dt, 1H, ArH, $J = 8.0$, 1.6 Hz), 7.34-7.40 (m, 2H), 7.60 (dd, 1H, $J = 8.0$, 1.6 Hz), 7.79 (t, 1H, $J = 7.6$ Hz), 8.09 (d, 1H, $J = 7.6$ Hz), 8.66 (dd, 1H, $J = 8.0$, 1.6 Hz), 10.86 (br s, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 24.3, 113.8, 119.4, 121.1, 124.9, 126.3, 128.3, 132.4, 136.0, 137.7, 148.9, 157.3, 162.4.

HRMS (C$_{13}$H$_1$BrN$_2$O) [M+H$^+$] requires 291.0128, found [M+H$^+$] 291.0132.
3.5 IR, $^1$H NMR, $^{13}$C NMR, HRMS, and HPLC Spectra for Compounds 1-14

Compound 1: 4-Methyl-N-phenylbenzamide

$^1$H NMR:

$^{13}$C NMR:
FTIR:

HRMS:
DM93 MW=2117
(MeOH)MeOH + NH4Ac
EPSRC National Centre Swansea
LTQ Orbitrap XL
Donna MacMillan
31/10/2012 15:37:31

Observed Data

Theoretical Isotope Model: [M + H]^+

NL:
9.56E7
STRWAT014-OJ-HNESP-2#30-50 RT: 0.75-1.28 AV: 20 T:
FTMS + p NSI Full ms [120.00-2000.00]

NL:
2.00E4
C_{14}H_{13}NOH:
C_{14}H_{14}N_1O_3
p (gss, s /p:40) Chrg 1
R: 100000 Res. Pwr. @FWHM
HPLC assay:

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<td>Aniline</td>
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<td>Dibenzyl ether (standard)</td>
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<td>Bromobenzene (standard)</td>
<td>3.18</td>
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Compound 2: N-(4-Methoxybenzyl)-4-methylbenzamide

$^1$H NMR:

$^{13}$C NMR:
**FTIR:**

![FTIR spectrum](image)

**HRMS:**

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SM: 7G

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Observed Data

Theoretical Isotope Model: [M + H]+

NL: 3.68E6
STRWAT013-OJ-HNESP#29-44 RT: 0.88-1.29 AV: 15 T:
FTMS + p NSI Full ms [120.00-2000.00]

NL: 1.95E4
C_{16}H_{17}NO_2 H:
C_{16}H_{18}N_2O_3
p (gss, s /p-40) Chg 1
R: 100000 Res . Pwr . @FWHM
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Electronic Supplementary Material (ESI) for Green Chemistry
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HPLC assay:

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<th>Substrate</th>
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<tr>
<td>p-Methoxybenzylamine</td>
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<td>Compound 2: N-(4-Methoxybenzyl)-4-methylbenzamide</td>
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<td>Bromobenzene (standard)</td>
<td>3.17</td>
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Compound 3: \( N,2 \)-Diphenylacetamide

\(^1\)H NMR:

\[^{13}\text{C}\] NMR:
FTIR:

HRMS:

DM92  MW=2127
(MeOH)/MeOH + NH4OAc

(£PSRC National Centre Swansea
LTQ Orbitrap XL
Donna MacMillan
29/10/2012 21:47:11

Observed Data

Theoretical Isotope Model: [M + H]+

NL:
2.80E7
STRWAT016-OJ-HNESP#30-45 RT: 0.92-1.27 AV: 13 T:
FTMS + p NSI Full ms
[120.00-2000.00]

NL:
2.00E4
C_{14}H_{13}NOH:
C_{14}H_{12}N_{1}O_{4}
p (g8, s/p:40) Chrg 1
R: 100000 Res .Pwr . @FWHM
HPLC assay:

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<td>Compound 3: N₂-Diphenylacetamide</td>
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<td>Dibenzyl ether (standard)</td>
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<tr>
<td>Bromobenzene (standard)</td>
<td>3.18</td>
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</table>
Compound 4: N-(4-Methoxybenzyl)-2-phenylacetamide

$^1$H NMR:

$^{13}$C NMR:
HPLC assay:

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Compound 5: 2-Chloro-N-(2-Methoxybenzyl)nicotinamide

$^1$H NMR:

$^{13}$C NMR:
**HPLC assay:**

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<td>Compound 5: 2-Chloro-N-(2-Methoxybenzyl)nicotinamide</td>
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<td>Bromobenzene (standard)</td>
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</table>
Compound 6: \( N-(4\text{-}(\text{Trifluoromethyl})\text{phenyl})\text{pyrazine-2-carboxamide} \)

\( ^1H \text{NMR:} \)

\( ^{13}C \text{NMR:} \)
FTIR:

HRMS:

DM1024  MW=267?
ASAP (MeOH)
EPSRC National Centre Swansea
LTQ Orbitrap XL
MacMillan
09/11/2012 08:41:05

STRWAT007 P-G HAP #16-19  RT: 0.47 0.55  AV: 4  SM: 7G  NL: 8.01E6
T: FTMS + p APCI corona Full ms [100.00-800.00]
**HPLC assay:**

![HPLC assay graph]

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<tbody>
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<td>4-Trifluoromethyl aniline</td>
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<tr>
<td>2-Pyrazine carboxylic acid</td>
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<tr>
<td>Compound 6: N-(4-(Trifluoromethyl)phenyl)pyrazine-2-carboxamide</td>
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<td>Bromobenzene (standard)</td>
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</tr>
</tbody>
</table>
Compound 7: N-(2-Methoxybenzyl)furan-3-carboxamide

\[ \text{H NMR:} \]

\[ \text{C NMR:} \]

Electronic Supplementary Material (ESI) for Green Chemistry
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### HPLC assay:

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<td>2-Furoic acid</td>
<td>1.28</td>
</tr>
<tr>
<td>2-Methoxybenzylamine</td>
<td>0.4, 1.87</td>
</tr>
<tr>
<td>Compound 7: N-(2-Methoxybenzyl)furan-3-carboxamide</td>
<td>1.90</td>
</tr>
<tr>
<td>Bromobenzene (standard)</td>
<td>3.18</td>
</tr>
</tbody>
</table>
Compound 8: 2-(2-(4-Bromophenyl)acetamido)benzamide

$^1$H NMR:

$^{13}$C NMR:
FTIR:

HRMS:

DM1029 MW=3327
(MeOH)/MeOH + NH4OAc
EPSRC National Centre Swansea
LTQ Orbitrap XL
Donna MacMillan
29/10/2012 21:43:44

STRWAT010-OJ-HNESD #2B-45 RT: 0.84-1.30 AV: 17 SM: 7G NL: 1.02E7
T: FTMS + p NSI Full ms [120.00-2000.00]
**HPLC assay:**

<table>
<thead>
<tr>
<th>Component</th>
<th>Rt (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Bromophenyl acetic acid</td>
<td>1.92</td>
</tr>
<tr>
<td>2-Aminobenzamide</td>
<td>1.14</td>
</tr>
<tr>
<td>Compound 8: 2-(2-(4-Bromophenyl)acetamido)benzamide</td>
<td>2.13</td>
</tr>
<tr>
<td>Bromobenzene (standard)</td>
<td>3.18</td>
</tr>
</tbody>
</table>
Compound 9: Methyl 4-(furan-2-carboxamido)benzoate

$^1$H NMR:

$^{13}$C NMR:
<table>
<thead>
<tr>
<th>Component</th>
<th>R&lt;sub&gt;t&lt;/sub&gt; (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Furoic acid</td>
<td>1.34</td>
</tr>
<tr>
<td>Methyl 4-aminobenzoate</td>
<td>1.61</td>
</tr>
<tr>
<td>Compound 9: Methyl 4-(furan-2-carboxamido)benzoate</td>
<td>1.94</td>
</tr>
<tr>
<td>Bromobenzene (standard)</td>
<td>3.18</td>
</tr>
</tbody>
</table>
Compound 10: 2-(4-Bromophenyl)-1-(3,4-dihydroisoquinolin-2(1H)-yl)ethanone

$^1$H NMR:

$^{13}$C NMR:
FTIR:

HRMS:

DM1035-2  MW=329?
(MeOH)/MeOH + NH4OAc
EPSRC National Centre Swansea
LTO/Orbitrap XL
Donna MacMillan
29/10/2012 21:33:27

STRWAT012-OJ-HNESp #31-43 RT: 0.96-1.27 AV: 12 SM: 7G NL: 1.84E6
T: FTMS + p NSI Full ms [120.00-2000.00]

Relative Abundance

328.0338  336.9863  340.9376  344.9849  348.9735  352.0310  362.0390
364.9682  371.1016  376.9748  386.0188  388.1281

m/z

0 10 20 30 40 50 60 70 80 90 100

320 330 340 350 360 370 380 390
### HPLC assay:

<table>
<thead>
<tr>
<th>Component</th>
<th>R&lt;sub&gt;t&lt;/sub&gt; (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Bromo phenyl acetic acid</td>
<td>1.92</td>
</tr>
<tr>
<td>1,2,3,4-Tetrahydroisoquinoline</td>
<td>0.42, 0.95</td>
</tr>
<tr>
<td>Compound10: 2-(4-Bromophenyl)-1-(3,4-dihydroisoquinolin-2(1H)-yl)ethanone</td>
<td>3.41</td>
</tr>
<tr>
<td>Bromobenzene (standard)</td>
<td>3.18</td>
</tr>
</tbody>
</table>
Compound 11: Furan-3-yl(4-phenylpiperazin-1-yl)methanone

$^1$H NMR:

$^{13}$C NMR:
Electronic Supplementary Material (ESI) for Green Chemistry
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### HPLC assay:

<table>
<thead>
<tr>
<th>Component</th>
<th>$R_t$ (min)</th>
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</thead>
<tbody>
<tr>
<td>2-Furoic acid</td>
<td>1.30</td>
</tr>
<tr>
<td>1-Phenyl piperazine</td>
<td>0.30, 0.44, 1.65</td>
</tr>
<tr>
<td>Compound 11: Furan-3-yl(4-phenylpiperazin-1-y1)methanone</td>
<td>2.11</td>
</tr>
<tr>
<td>Bromobenzene (standard)</td>
<td>3.18</td>
</tr>
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</table>
Compound 12: Ethyl 3-((2-tert-butoxycarbonyl)amino)acetamido)benzoate

$^1$H NMR:

$^{13}$C NMR:
## HPLC assay:

<table>
<thead>
<tr>
<th>Component</th>
<th>$R_t$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl 3-aminobenzoate</td>
<td>1.76</td>
</tr>
<tr>
<td>Compound 12: Ethyl 3-((tert-butoxycarbonyl)amino)acetamido)benzoate</td>
<td>2.27</td>
</tr>
<tr>
<td>Bromobenzene (standard)</td>
<td>3.18</td>
</tr>
</tbody>
</table>
Compound 13: tert-Butyl 4-benzamidopiperidine-1-carboxylate

$^1$H NMR:

$^{13}$C NMR:
FTIR:

HRMS:

DM1065  MW=3047  EPSRC National Centre Swansea  Donna MacMillan
(MeOH)/MeOH + NH4OAc  LTQ Orbitrap XL  29/10/2012 21:30:00
T: FTMS + p NSI Full ms [200.00-4000.00]
### HPLC assay:

<table>
<thead>
<tr>
<th>Component</th>
<th>( R_t ) (min)</th>
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</thead>
<tbody>
<tr>
<td>Benzoic acid</td>
<td>1.61</td>
</tr>
<tr>
<td>Compound 13: ( \text{tert-Butyl 4-} )benzamidopiperidine-1-carboxylate</td>
<td>2.24</td>
</tr>
<tr>
<td>Bromobenzene (standard)</td>
<td>3.18</td>
</tr>
</tbody>
</table>
Compound 14: N-(2-Bromophenyl)-6-methylpicolinamide

$^1$H NMR:

$^{13}$C NMR:
<table>
<thead>
<tr>
<th>Component</th>
<th>R_t (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Methyl picolinic acid</td>
<td>0.29, 0.42</td>
</tr>
<tr>
<td>2-Bromo aniline</td>
<td>2.07</td>
</tr>
<tr>
<td>Compound 14: N-(2-Bromophenyl)-6-methylpicolinamide</td>
<td>4.44</td>
</tr>
<tr>
<td>Bromobenzene (standard)</td>
<td>3.18</td>
</tr>
</tbody>
</table>
4. References