Identification of 1,5,7-triazabicyclododecene and polystyrene supported superbases as efficient hydroxylaminolysis agent of sterically hindered and epimerizable esters

Romain Pierre, Grégoire Mouis, Frédéric Gaigne, Ghizlane El-Bazbouz, Gilles Ouvry, Craig S. Harris,* Loic Tomas*

General Methods

$^1$H NMR spectra were recorded on a BRUKER Biospin AVANCE 400 spectrometer. Chemical shifts are reported as $\delta$ values downfield from internal TMS in appropriate organic solutions. The purity and the structures of the products were confirmed by LCMS (254 nm) on a Waters 2690 photodiode array detector system using the following conditions: Column, Symmetry C-18; Solvent A, water 0.1% formic acid; Solvent B, CH$_3$CN; flow rate, 2.5 mL/min; run time, 2.5 min; gradient, from 0 to 100%; mass detector, micro mass ZMD. Preparative LCMS was carried out using Waters 600. Pumps linked to a Waters 2700 Sample Manager and a Waters micromass ZMD mass detector. Samples are routinely filtered at concentrations of around 50 mg of expected product per mL of methanol.

General procedure

To a stirred solution of 50 wt. % hydroxylamine (10 eq) and organobase (3 eq) (supported or in solution) in MeOH (10 vols) at r.t., was added the ester substrate (1 eq) either all at once or by use of a syringe pump over the specified time. The crude reaction mixtures were purified as follows:

a) If free base was used, the crude reaction mixtures were purified directly by mass-triggered Prep LCMS (using formic acid buffer).

b) If polymer-supported bases were used, acetic acid (5 eq) was added when the reaction was complete and the reaction mixture was filtered and the filtrate was concentrated to dryness and triturated with ether to afford the desired hydroxamic acids without the need for chromatography. The polymer-supported base was regenerated using 7N NH$_3$ in MeOH under slow agitation followed by MeOH washing.
**Preparation of** \((S)-N-(1-\text{hydroxyamino})-1-\text{oxo}-3-\text{phenylpropan-2-yl})\text{benzamide (5)}\) and the racemate

**Methyl benzoyl-L-phenylalaninate (4)**

![Methyl benzoyl-L-phenylalaninate](image)

To a stirred suspension of L-phenylalanine methyl ester hydrochloride (1.00 g, 4.64 mmol) in THF (10.0 mL) was added triethylamine (1.93 mL, 13.91 mmol) à 0°C followed by benzoyl chloride (0.98 g, 6.95 mmol) and the reaction mixture was stirred for 1 h at r.t. The resulting solution was diluted with EtOAc (30 mL) and washed with a saturated aqueous solution of ammonium chloride (20 mL), a saturated solution of sodium hydrogen carbonate (20 mL), water (20 mL), dried (MgSO₄) and concentrated to dryness. The residue was purified by flash chromatography (silica gel, eluting with heptane/EtOAc 0-40%) to afford methyl benzoyl-L-phenylalaninate (4, 1.15 g, 87.5%) as a white solid:

LCMS \((t_R = 1.09 \text{ min.}, \text{ purity} = 100%)\);

\(^1\)H NMR (400 MHz, DMSO-\text{d6}) δ 8.86 (d, \(J = 7.8 \text{ Hz}, 1\text{H})\), 7.89 – 7.70 (m, 2H), 7.60 – 7.41 (m, 3H), 7.37 – 7.12 (m, 5H), 4.67 (ddd, \(J = 10.2, 7.8, 5.3 \text{ Hz}, 1\text{H})\), 3.24 – 2.99 (m, 2H).

\((S)-N-(1-\text{hydroxyamino})-1-\text{oxo}-3-\text{phenylpropan-2-yl})\text{benzamide (5)}\)

![S-(1-Hydroxyamino)-1-oxo-3-phenylpropan-2-yl]benzamide](image)

To a stirred solution of 50 wt. % NH₂OH (aq) (216 μl, 3.53 mmol, 10 eq) and 1,8-diazabicyclo[5.4.0]undec-7-ene (158 μl, 1.06 mmol, 3.00 eq.) was added methyl benzoyl-L-phenylalaninate (100 mg, 0.35 mmol, 1 eq) and the reaction mixture was stirred at r.t. for 20 minutes and purified directly by mass-triggered preparative LCMS to afford \((S)-N-(1-\text{hydroxyamino})-1-\text{oxo}-3-\text{phenylpropan-2-yl})\text{benzamide (5, 90 mg, 90%)}\) as a beige solid:

LCMS \((t_R = 1.01 \text{ min.}, \text{ purity} = 100\%\), MS ES\(^+\) \text{m/z} 285.04 (M+H)\); \(^1\)H NMR (DMSO-d6, 400 MHz): δ (ppm) 10.78 (s, 1H), 8.89 (s, 1H), 8.61 (d, \(J = 8.5 \text{ Hz}, 1\text{H})\), 7.87 – 7.75 (m, 2H), 7.55 – 7.48 (m, 1H), 7.43 (dd, \(J = 8.2, 6.5 \text{ Hz}, 2\text{H})\), 7.36 – 7.30 (m, 2H), 7.26 (t, \(J = 7.5 \text{ Hz}, 2\text{H})\), 7.20 – 7.14 (m, 1H), 4.61 (td, \(J = 8.6, 6.3 \text{ Hz}, 1\text{H})\), 3.07 – 2.95 (m, 2H).
An identical protocol was followed to prepare \((\text{rac})-N-(2-\text{(hydroxyamino)}-2\text{-oxo-1-phenylpropan-2-yl)}\text{benzamide}\) starting from D/L-phenylglycine methyl ester hydrochloride.

Table 3: Study of epimerization study using methyl benzoyl-L-phenylalaninate (4)

| Entry 2 | NaOH (3 eq) (r.t., 30 min) \(S/R = 99/1\) | \(S/R = 99/1\) |
Entry 3 – DBU (3 eq) (r.t., 30 min) $S/R = 99/1$

Entry 5 – MTBD (3 eq) (r.t., 30 min) $S/R = 99/1$
Entry 6 – PS-DBU (3 eq) (r.t., 30 min) $S/R = 99/1$

Entry 7 – PS-TBD (3 eq) (r.t., 30 min) $S/R = 99/1$
Preparation of (S)-N-(2-(hydroxyamino)-2-oxo-1-phenylethyl)benzamide and the racemate

Methyl (S)-2-benzamido-2-phenylacetate (6)

To a stirred solution of (S)-(+)2-phenylglycine methyl ester hydrochloride (10.0 g, 0.05 mol) in THF (100 mL) was added triethylamine (20.6 mL, 0.15 mol) at 0 °C, followed by benzoyl chloride (8.63 mL, 0.07 mol) and the reaction mixture was stirred at room temperature for 1 h. The resulting solution was diluted with EtOAc (30 mL) and washed with a saturated aqueous solution of ammonium chloride (20 mL), a saturated solution of sodium hydrogen carbonate (20 mL), water (20 mL), dried (MgSO$_4$) and concentrated to dryness. The residue was purified by flash chromatography (silica gel, eluting with heptane/EtOAc 0-40%) to afford methyl (S)-2-benzamido-2-phenylacetate (6, 10.8 g, 81.2% yield) as a white solid: LCMS ($t_{r} = 1.34$ min., purity = 100%, MS ES$^+$ m/z 270.86 (M+H)$^+$; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.18 (d, $J = 7.2$ Hz, 1H), 8.00 – 7.83 (m, 2H), 7.62 – 7.26 (m, 8H), 5.70 (d, $J = 7.2$ Hz, 1H), 3.67 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 171.12, 166.57, 136.29, 133.57, 131.62, 128.58, 128.30, 128.26, 128.23, 127.80, 56.93, 52.31; Chiral HPLC shows a starting R/S ratio of 97.7/2.3
An identical protocol was followed to prepare (rac)-N-(2-(hydroxyamino)-2-oxo-1-phenylethyl)benzamide starting from D/L-phenylglycine methyl ester hydrochloride.
**N-(2-(Hydroxyamino)-2-oxo-1-phenylethyl)benzamide (7)**

To a stirred solution of 50 wt. % NH₂OH (aq) (216 µl, 3.53 mmol, 10 eq) and the base (see Table 4) was added methyl benzoyl-D/L-phenylalaninate (100 mg, 0.35 mmol, 1 eq) and the reaction mixture was stirred at r.t. for the time recorded in Table 4 and purified directly by mass-triggered preparative LCMS to afford \(N-(2-( hydroxyamino)-2-oxo-1-phenylethyl)benzamide\) (7, 90 mg, 90%) as a beige solid: LCMS (\(t_R = 1.01\) min., purity = 100%, MS ES⁺ m/z 285.04 (M+H)⁺); \(^1\)H NMR (400 MHz, DMSO-d₆) δ 11.02 (s, 1H), 9.01 (s, 1H), 8.85 (d, J = 8.1 Hz, 1H), 8.06 – 7.79 (m, 2H), 7.62 – 7.20 (m, 9H), 5.62 (d, J = 8.2 Hz, 1H); \(^{13}\)C NMR (101 MHz, DMSO) δ 166.74, 166.27, 138.50, 133.91, 131.47, 128.30, 128.21, 127.79, 127.66, 127.45, 54.68.

An identical protocol was followed to prepare \((rac)-N-(1-(hydroxyamino)-1-oxo-3-phenylpropan-2-yl)benzamide\) starting from D/L-phenylalanine methyl ester hydrochloride.

**Table 4: Epimerization study using methyl benzoyl-L-phenylglycinate (6)**

| Entry | No base (r.t., 12 h) S/R = 84.8/15.2 / effective erosion = 12.9% |

<table>
<thead>
<tr>
<th>Name</th>
<th>RT</th>
<th>Area</th>
<th>Height</th>
<th>Amount</th>
<th>Units</th>
<th>% Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.777</td>
<td>571649</td>
<td>1298813</td>
<td>84.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.001</td>
<td>1022300</td>
<td>129802</td>
<td>15.17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Entry 6 - 3 eq PS-TBD (r.t., 30 min.) $S/R = 78.0 / 22.0$ – effective erosion = 19.7%

![Auto-Scaled Chromatogram](image1)

<table>
<thead>
<tr>
<th>Peak Results</th>
<th>Name</th>
<th>RT</th>
<th>Area</th>
<th>Height</th>
<th>Amount</th>
<th>Units</th>
<th>% Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>2.780</td>
<td>3410401</td>
<td>742927</td>
<td></td>
<td></td>
<td>77.97</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>3.996</td>
<td>963311</td>
<td>124340</td>
<td></td>
<td></td>
<td>22.03</td>
</tr>
</tbody>
</table>

Entry 7 – 1 eq of PS-TBD (r.t., 1 h) $S/R = 81.1 / 18.9$ – effective erosion = 16.6%

![Auto-Scaled Chromatogram](image2)

<table>
<thead>
<tr>
<th>Peak Results</th>
<th>Name</th>
<th>RT</th>
<th>Area</th>
<th>Height</th>
<th>Amount</th>
<th>Units</th>
<th>% Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>2.703</td>
<td>4253150</td>
<td>949331</td>
<td></td>
<td></td>
<td>81.11</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>3.070</td>
<td>902732</td>
<td>130571</td>
<td></td>
<td></td>
<td>18.89</td>
</tr>
</tbody>
</table>

Entry 8 – 0.5 eq TBD (r.t., 4 h) – $S/R = 82.1 / 17.9$ – effective erosion = 15.6%

![Auto-Scaled Chromatogram](image3)
Entry 9 – 3 eq of PS-DBU (r.t., 30 min.) $S/R = 78.3 / 21.7$ – effective erosion = 19.4%
Entry 10 – 1 eq of PS-DBU (r.t., 2 h) \( S/R = 81.1 / 18.9 \) – effective erosion = 16.6%

Entry 11 - 0.5 eq PS-DBU (r.t., 4 h) \( S/R = 89.1 / 10.9 \) – effective erosion = 8.6%
Entry 12 – Reverse addition of 6 (r.t., 2 min then 20 min.) $S/R = 85/15$ – effective erosion = 12.7%

Entry 13 – Reverse addition at 0 °C (1 h) – $S/R = 93.8 / 6.2$ – effective erosion = 3.9%

Table 5: Study of effect of TBD as an acylation catalyst with other nucleophiles
General procedure

To a stirred solution of nucleophile (10 eq) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (3 eq) (supported or in solution) in MeOH (4 vols) at r.t., was added the ester substrate (50 mg, 0.18 mmol, 1 eq) and the crude reaction mixtures were stirred for 1-24 h and purified directly by mass-trigger Prep LCMS.

(S)-N-(1-Hydrazineyl-1-oxo-3-phenylpropan-2-yl)benzamide (40 mg, 78% yield)

![Chemical Structure](image)

LCMS (t<sub>R</sub> = 0.87 min., purity = 100%, MS ES<sup>+</sup> m/z 284.02 (M+H)<sup>+</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ (ppm) 9.30 (s, 1H), 8.56 (d, J = 8.5 Hz, 1H), 7.85 – 7.72 (m, 2H), 7.56 – 7.47 (m, 1H), 7.47 – 7.39 (m, 2H), 7.39 – 7.30 (m, 2H), 7.26 (dd, J = 8.3, 6.7 Hz, 2H), 7.20 – 7.11 (m, 1H), 4.67 (td, J = 8.7, 6.0 Hz, 1H), 3.07 – 2.98 (m, 2H).
(S)-N-(1-Oxo-3-phenyl-1-(piperidin-1-yl)propan-2-yl)benzamide (21 mg, 35% yield)

LCMS (t_R = 1.16 min., purity = 100%, MS ES^+ m/z 337.12 (M+H)^+); ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm) 8.75 (d, J = 8.2 Hz, 1H), 7.78 – 7.87 (m, 2H), 7.47 – 7.58 (m, 1H), 7.21 – 7.34 (m, 4H), 7.13 – 7.21 (m, 1H), 5.12 (td, J = 8.3, 6.4 Hz, 1H), 3.43 (dd, J = 6.8, 4.4 Hz, 4H), 2.89 – 3.13 (m, 2H), 1.13 – 1.63 (m, 6H).

(S)-N-(1-((Benzyloxy)amino)-1-oxo-3-phenylpropan-2-yl)benzamide (15 mg, 23% yield)

LCMS (t_R = 1.13 min., purity = 100%, MS ES^+ m/z 375.10 (M+H)^+); ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm) 11.41 (s, 1H), 8.68 (d, J = 8.2 Hz, 1H), 7.73 – 7.96 (m, 2H), 7.07 – 7.62 (m, 14H), 4.67 – 4.83 (m, 2H), 4.56 (td, J = 8.7, 6.2 Hz, 1H), 2.93 – 3.09 (m, 2H).

(S)-N-(1-Amino-1-oxo-3-phenylpropan-2-yl)benzamide (15 mg, 31% yield)

LCMS (t_R = 0.91 min., purity = 100%, MS ES^+ m/z 269.05 (M+H)^+); ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm) 8.49 (d, J = 8.5 Hz, 1H), 7.74 – 7.83 (m, 2H), 7.48 – 7.61 (m, 2H), 7.40 – 7.47 (m, 2H), 7.34 (d, J = 7.2 Hz, 2H), 7.25 (t, J = 8.5 Hz, 1H), 7.13 – 7.20 (m, 1H), 7.11 (s, 1H), 4.64 (dd, J = 8.5, 4.1 Hz, 1H), 2.90 – 3.20 (m, 2H).