Supporting Information

Benzoyl shift: a new approach to reverse regioselectivity in the monoprotection of \textit{vic}-diols

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Table of Contents

1. General information \hspace{1cm} S2

2. Experimental procedure and characterization data \hspace{1cm} S2

3. Kinetic monitoring of the benzoyl shift \hspace{1cm} S6

4. $^1$H and $^{13}$C NMR spectra \hspace{1cm} S7
1. General Information

All reactions requiring anhydrous conditions were conducted in oven-dried glassware (120°C), syringes and needles with magnetic stirring under nitrogen unless mentioned otherwise. Anhydrous THF and Et₂O were obtained from the Innovative Technology PS-Micro solvent purification system. Other solvents and reagents were used as obtained from the supplier unless otherwise noted. Reactions were monitored by TLC using plates precoated with silica gel 60 (Merck). Reaction components were visualized by using a 254 nm UV lamp, treatment with acidic p-anisaldehyde stain followed by gentle heating. Organic layers were dried with MgSO₄ unless otherwise stated. Column chromatography was performed by using silica gel 40–63 μm. Infrared data are reported as wavenumbers (cm⁻¹). ES-MS data were obtained by positive electrospray ionization methods. ¹H NMR spectra were obtained at 300 or 500 MHz on Bruker spectrometers. The spectra were recorded in CDCl₃ (internal reference at δ = 7.26 ppm) unless otherwise noted. The ¹H NMR spectra are reported as follows: chemical shift in ppm [multiplicity, coupling constant(s) J in Hz, relative integral]. The multiplicities are defined as follows: br. = broad, m = multiplet, s = singlet, d = doublet, t = triplet, or combinations thereof. Selected ¹³C NMR spectra were recorded by using a J-modulated sequence, reported as follows: CH₃, CH₂, CH, and Cq (for quaternary carbon atoms), and the central peak of the CDCl₃ triplet was used as the internal reference (δ = 77.16 ppm).

2. Experimental procedure and characterization data

The following procedure stands for all monoprotections: to a 0°C solution of diol (1 mmol) in DCM (4 mL) were added Et₃N (2.2 mmol), DMAP (0.05 mmol), then slowly BzCl (1.1 mmol) and the reaction was allowed to warm to r.t. for 3h. The reaction was quenched by addition of aqueous HCl (0.1 M, ca. 3 mL), the organic phases separated and the aqueous phases extracted with EtOAc (3 x 2 mL). The joined organic phases were dried over MgSO₄ and concentrated under vacuum. The crude product was dissolved in 4 mL MeOH/H₂O (9/1: v/v), solid NaHCO₃ (5 mmol) was added to the solution and the reaction was stirred 90 min. at r.t. Water was added (ca. 4 mL), then EtOAc followed by extraction of the aqueous phase (3 times all together). The joined organic phases were dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography.

4-ethoxy-3-hydroxy-4-oxobutan-2-yl benzoate

Rf= 0.52 (50% EtOAc/cyclohexane).

¹H NMR (500 MHz, CDCl₃) δ = 7.98 (d, J=8.4, 2H), 7.53 (t, J=7.4, 1H), 7.40 (t, J=7.8, 2H), 5.46 (qd, J=6.5, 2.4, 1H), 4.35 – 4.05 (m, 3H), 3.15 (br s., 1H), 1.48 (d, J=6.5, 3H), 1.17 (t, J=7.1, 3H).
\(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \(\delta = 168.6\) (Cq), 166.0 (Cq), 133.7 (CH), 130.0 (2C, CH), 129.3 (Cq), 128.7 (2C, CH), 76.4 (CH), 67.8 (CH), 61.9 (CH\(_2\)), 19.5 (CH\(_3\)), 14.3 (CH\(_3\)).


HRMS (ESI+) calculated for C\(_{13}\)H\(_{16}\)O\(_5\)Na [M+Na]^+ 275.0895, found 275.0895.

\(\nu_{\text{max}}\) cm\(^{-1}\) 3496, 2985, 2939, 1717, 1602, 1585, 1451, 1357, 1316, 1268, 1208, 1177, 1147, 1109, 1070, 1054, 1025, 1009, 907, 862, 888, 806, 767, 710, 687.

1-ethoxy-3-hydroxy-3-methyl-1-oxobutan-2-yl benzoate

Rf= 0.53 (50% EtOAc/cyclohexane).

\(^1\text{H}\) NMR (500 MHz, CDCl\(_3\)) \(\delta = 8.04\) (dd, \(J=8.4, 1.3, 2H\)), 7.53 (t, \(J=7.4, 1H\)), 7.41 (t, \(J=7.8, 2H\)), 5.04 (s, 1H), 4.21 (qd, \(J=7.1, 1.9, 2H\)), 3.10 (br. s, 1H), 1.36 (d, \(J=2.8, 6H\)), 1.22 (t, \(J=7.2, 3H\)).

\(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \(\delta = 168.7\) (Cq), 165.8 (Cq), 133.5 (CH), 129.8 (2C, CH), 129.2 (Cq), 128.5 (2C, CH), 78.8 (CH), 71.2 (Cq), 61.6 (CH\(_2\)), 26.2 (CH\(_3\)), 25.9 (CH\(_3\)), 14.0 (CH\(_3\)).


HRMS (ESI+) calculated for C\(_{14}\)H\(_{18}\)O\(_5\)Na [M+Na]^+ 289.1052, found 289.1052.

\(\nu_{\text{max}}\) cm\(^{-1}\) 3490, 2983, 1721, 1602, 1585, 1452, 1375, 1348, 1316, 1262, 1207, 1177, 1109, 1071, 1046, 1027, 977, 916, 859, 805, 777, 748, 710, 687.

1-ethoxy-4,4,4-trifluoro-3-hydroxy-1-oxobutan-2-yl benzoate

Rf= 0.5 (30% EtOAc/cyclohexane).

\(^1\text{H}\) NMR (500 MHz, CDCl\(_3\)) \(\delta = 8.09\) (dd, \(J=8.5, 1.3, 2H\)), 7.60 (t, \(J=7.5, 1H\)), 7.46 (t, \(J=7.8, 2H\)), 5.66 (d, \(J=2.1, 1H\)), 4.70 – 4.62 (m, 1H), 4.28 (q, \(J=7.1, 2H\)), 3.81 (br. s, 1H), 1.28 (t, \(J=7.1, 3H\)).

\(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \(\delta = 166.8\) (Cq), 165.3 (Cq), 134.0 (CH), 130.2 (2C, CH), 128.7 (2C, CH), 124.8 (Cq), 123.7 (q, \(J=282, Cq\)), 70.4 (CH), 70.1 (q, \(J=32.1, CH\)), 62.8 (CH\(_2\)), 14.1 (CH\(_3\)).


HRMS (ESI+) calculated for C\(_{13}\)H\(_{13}\)O\(_3\)NaF\(_3\) [M+Na]^+ 329.0613, found 329.0612.

\(\nu_{\text{max}}\) cm\(^{-1}\) 3463, 2981, 1729, 163, 1586, 1453, 1373, 1349, 1262, 1219, 1173, 1136, 1095, 1072, 1056, 1025, 978, 906, 884, 862, 804, 747, 710, 685.

1-cyano-2-hydroxypropyl benzoate

This compound was obtained from a mixture of diastereoisomers of the diol. The doubled signals in \(^{13}\text{C}\) NMR are noted as “epi”.

Rf= 0.4 (30% EtOAc/cyclohexane).
$^1$H NMR (500 MHz, CDCl$_3$) $\delta = 8.12 – 7.94$ (m, 2H), $7.67 – 7.51$ (m, 1H), $7.51 – 7.35$ (m, 2H), $5.41 – 5.20$ (m, 1H), $4.68$ (dd, $J=36.0$, $4.5$, 1H), $1.49$ (dd, $J=23.5$, $6.5$, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 166.4$ (Cq), $166.1$ (Cq, epi), $133.8$ (CH), $129.9$ (2C, CH), $129.1$ (Cq), $128.6$ (2C, CH), $117.8$ (Cq), $117.4$ (Cq, epi), $71.5$ (CH), $70.5$ (CH, epi), $64.9$ (CH), $63.9$ (CH, epi), $15.9$ (CH$_3$), $15.0$ (CH$_3$, epi).


HRMS (ESI+) calculated for C$_{11}$H$_{12}$NO$_3$ [M+H]$^+$ 206.0817, found 206.0816.

$\nu_{\text{max}}$ cm$^{-1}$ 3419, 2988, 1719, 1700, 1602, 1585, 1492, 1452, 1385, 1340, 1317, 1266, 1178, 1109, 1069, 1026, 1002, 942, 889, 865, 805, 708, 686.

2-cyano-2-hydroxy-1-phenylethyl benzoate

This compound was obtained from a mixture of diastereoisomers of the diol. The doubled signals in $^{13}$C NMR are noted as “epi”.

Rf= 0.33 (30% EtOAc/cyclohexane).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta = 8.13$ (dd, $J=16.3$, 7.5, 2H), $7.61 – 7.37$ (m, 8H), $6.19$ (dd, $J=36.5$, 4.9, 1H), $4.82$ (dd, $J=61.0$, 4.9, 1H), $4.44$ (br. d, $J=133.4$, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 165.7$ (Cq), $165.5$ (Cq, epi), $134.2$ (Cq), $133.8$ (CH), $130.0$ (2C, CH), $129.6$ (CH), $129.4$ (CH, epi), $129.0$ (CH), $128.9$ (Cq), $128.8$ (CH), $128.6$ (2C, CH), $127.5$ (CH), $126.8$ (CH), $117.3$ (Cq), $117.1$ (Cq, epi), $76.3$ (CH), $75.2$ (CH, epi), $65.8$ (CH), $64.4$ (CH, epi).


HRMS (ESI+) calculated for C$_{16}$H$_{14}$NO$_3$ [M+H]$^+$ 268.0974, found 268.0975.

$\nu_{\text{max}}$ cm$^{-1}$ 3414, 3065, 1725, 1707, 1601, 1585, 1497, 1452, 1375, 1316, 1262, 1198, 1178, 1094, 1069, 1046, 1026, 993, 936, 849, 804, 760, 707.

2-hydroxy-3-methoxy-3-oxo-1-phenylpropyl benzoate

Rf= 0.42 (30% EtOAc/cyclohexane).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta = 8.11 – 8.03$ (m, 2H), $7.72 – 7.12$ (m, 8H), $6.33$ (d, $J=2.4$, 0.73H), $5.49$ (d, $J=3.7$, 0.27H), $5.37$ (d, $J=3.3$, 0.27H), $4.56$ (s, 0.73H), $3.77 – 3.73$ (m, 3H), $3.29$ (s, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 172.5$ (1C, major regio, Cq), $168.8$ (1C, minor regio, Cq), $165.8$ (1C, minor regio, Cq), $165.3$ (1C, major regio, Cq), $139.0$ (1C, minor regio, Cq), $136.3$ (1C, major regio, Cq), $133.5$ (CH), $129.9$ (2C, CH), $129.5$ (1C, major regio, Cq), $129.0$ (1C, minor regio, Cq), $128.5$ (5C, CH), $126.8$ (2C, major regio, CH), $126.3$ (2C, minor regio, CH), $76.5$ (1C, minor regio, CH), $76.2$ (1C, major regio, CH), $73.7$ (1C, major regio, CH), $73.5$ (1C, minor regio, CH), $53.1$ (1C, major regio, CH), $52.7$ (1C, minor regio, CH).

HRMS (ESI+) calculated for C_{17}H_{16}O_{5}Na [M+Na]^+ 323.0895, found 323.0894.

_{\nu max} \text{ cm}^{-1} 3518, 2956, 1737, 1704, 1601, 1585, 1496, 1451, 1438, 1395, 1369, 1316, 1264, 1211, 1176, 1098, 1069, 1027, 1006, 998, 972, 938, 923, 899, 853, 806, 758, 698, 685, 673.

2-hydroxy-3-phenylpropyl benzoate

Rf= 0.5 (30% EtOAc/cyclohexane).

_{1}H \text{ NMR (500 MHz, CDCl}_3\text{)} \delta = 8.15 – 7.98 (m, 2H), 7.68 – 7.53 (m, 1H), 7.53 – 7.40 (m, 2H), 7.38 – 7.30 (m, 2H), 7.30 – 7.22 (m, 3H), 4.41 (dd, J=11.3, 3.5, 1H), 4.29 (dd, J=11.3, 6.5, 1H), 4.26 – 4.20 (m, 1H), 2.92 (qd, J=13.7, 6.6, 2H), 2.57 (s, 1H).

_{13}C \text{ NMR (125 MHz, CDCl}_3\text{)} \delta = 166.7 (Cq), 137.4 (Cq), 133.1 (CH), 129.8 (Cq), 129.7 (2C, CH), 129.4 (2C, CH), 128.6 (2C, CH), 128.4 (2C, CH), 126.6 (CH), 70.8 (CH), 68.1 (CH$_2$), 40.1 (CH$_3$).


HRMS (ESI+) calculated for C_{16}H_{16}O_{3}Na [M+Na]^+ 279.0997, found 279.0996.

_{\nu max} \text{ cm}^{-1} 3447, 3063, 3029, 2948, 1715, 1602, 1584, 1496, 1452, 1378, 1315, 1269, 1177, 1118, 1096, 1070, 1026, 978, 939, 910, 846, 806, 746, 709, 699.

dimethyl 2-(benzoyloxy)-3-hydroxypentanedioate

Rf= 0.37 (50% EtOAc/cyclohexane).

_{1}H \text{ NMR (500 MHz, CDCl}_3\text{)} \delta = 8.09 (d, J=7.8, 2H), 7.58 (t, J=7.2, 1H), 7.45 (t, J=7.5, 2H), 5.37 – 5.33 (m, 1H), 4.82 – 4.63 (m, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 2.74 – 2.64 (m, 2H).

_{13}C \text{ NMR (125 MHz, CDCl}_3\text{)} \delta = 172.1 (Cq), 168.4 (Cq), 165.8 (Cq), 133.8 (CH), 130.1 (2C, CH), 128.9 (Cq), 128.6 (2C, CH), 74.7 (CH), 67.8 (CH$_2$), 52.8 (CH$_3$), 52.2 (CH$_3$), 37.4 (CH$_2$).


HRMS (ESI+) calculated for C_{14}H_{17}O_{7} [M+H]^+ 297.0974, found 297.0972.

_{\nu max} \text{ cm}^{-1} 3484, 2956, 1720, 1602, 1585, 1493, 1452, 1438, 1362, 1316, 1250, 1213, 1176, 1116, 1096, 1071, 1052, 1025, 1002, 939, 903, 851, 791, 748, 710, 687.

3. Kinetic monitoring of the benzoyl shift

In order to monitor the benzoyl shift, the following experiment was performed:
To a 0°C solution of diol 6a (1 mmol) in DCM (4 mL) were added Et$_3$N (2.2 mmol), DMAP (0.05 mmol), then slowly BzCl (1.1 mmol) and the reaction was allowed to warm to r.t. for 3h. The reaction was quenched by addition of aqueous HCl (0.1 M, ca. 3 mL), the organic phases separated and the aqueous phases extracted with EtOAc (3 x 2 mL). The joined organic phases were dried over MgSO$_4$ and concentrated under vacuum. The crude product was dissolved in 4 mL CD$_3$OD/D$_2$O (9/1: v/v), solid NaHCO$_3$ (5 mmol) was added to the solution and the reaction was stirred at r.t. The reaction mixture was monitored by NMR at t = 0 min (before addition of the solid NaHCO$_3$), 5 min, 20 min, 60 min, 120 min. Results are reported in Table 1. See NMR monitoring at the end of the document.

<table>
<thead>
<tr>
<th>Reaction time (min)</th>
<th>0</th>
<th>5</th>
<th>20</th>
<th>60</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio (7a : 8a : 9a)</td>
<td>1.8 : 10.2 : 1</td>
<td>2.3 : 9.7 : 1</td>
<td>4.7 : 7.3 : 1</td>
<td>9.2 : 2.8 : 1</td>
<td>9.8 : 2.2 : 1</td>
</tr>
</tbody>
</table>

Table 1. Kinetic monitoring of the benzoyl shift.
4. $^1$H and $^{13}$C NMR spectra
NMR monitoring (spectrums of part 3)