Supporting Information

A general method for the α-acyloxylation of carbonyl compounds

Cory S. Beshara,† Adrian Hall,‡ Robert L. Jenkins,† Kerri L. Jones,† Teyrnon C. Jones,† Niall M. Killeen,† Paul H. Taylor,† Stephen P. Thomas† and Nicholas C. O. Tomkinson†,*

†School of Chemistry, Main Building, Cardiff University, Park Place, Cardiff, CF10 3AT, U.K., and
‡Neurology & GI Centre of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, U.K.
tomkinsonnc@cardiff.ac.uk

CONTENTS.

S1 General Procedures.
S2 Preparation of N-methyl-O-benzoyl hydroxylamine hydrochloride (10).
S3 Typical experimental procedure for the reaction of cyclic ketones.
S4 Typical experimental procedure for the reaction of acyclic ketones.
S4 Typical experimental procedure for the reaction of aldehydes.
S6-14 1H and 13C NMR data for reagents 9-12.
S15-16 1H NMR of crude reaction mixtures for reaction of 10 with cyclohexanone in a variety of solvents.
S17-39 1H and 13C NMR data of all α-functionalised products.

General Procedures. Commercially available solvents and reagents were used without further purification. Light petroleum refers to the fraction with bp 40-60 °C and ether refers to diethyl ether. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF254 that were visualised under UV light (at 254 and/or 360 nm). Infra-red (IR) spectra were recorded in the range 4000-600 cm⁻¹ using KBr disks for solid samples and thin films between NaCl plates for liquid samples or as a nujol mull and are reported in cm⁻¹. Nuclear magnetic resonance (NMR) spectra were recorded in CDCl₃ at 18 °C unless stated otherwise and were reported in ppm; J values were recorded in Hz and multiplicities were expressed by the usual conventions. Low-resolution mass spectra (MS) were determined using atmospheric pressure chemical ionization (APCI) unless
otherwise stated. ES refers to electrospray ionization, CI refers to chemical ionization (amphetamine) and EI refers to electron ionization. High-resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service at University College of Wales, Swansea, UK using the ionization methods specified. In vacuo refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump.

**Preparation of N-methyl-O-benzoyl hydroxylamine hydrochloride**

*N-Methyl-N-Boc hydroxylamine¹ (4)*

Potassium carbonate (14.5 g, 0.1 mol) was added to an ice-cold solution of N-methyl hydroxylamine hydrochloride (30 g, 0.2 mol) in a 1:1 mixture of tetrahydrofuran and water (80 ml). A solution of di-tert-butyl dicarbonate (48 g, 0.22 mol) in tetrahydrofuran (60 ml) was then added dropwise to the mixture and stirring was continued for 2 hours at 0 °C and then at room temperature for 3 hours. After this period, the solution was concentrated in vacuo and the residue dissolved in dichloromethane (100 ml) before washing with water (3 × 40 ml) and brine (50 ml). The organic fraction was collected, dried and reduced in vacuo to yield an orange oil (29.3 g). The crude product was purified by distillation (< 1 mbar, 84-87 °C) to yield N-Boc-N-methylhydroxylamine as a colourless oil (28.5 g, 97%); IR (neat) 3257, 1699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.05 (brs, 1H), 3.31 (s, 3H), 1.63 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 157.4 (s), 80.6 (s), 37.5 (q), 27.5 (q). MS (ES) m/z 148.2 [M+H]+; HRMS calculated for C₆H₁₃NO₃ 148.0973 [M+H]+, found 148.0974.

*N-Methyl-N-Boc-O-benzoyl hydroxylamine² (6)*

A solution of N-Boc-N-methyl hydroxylamine (25 g, 0.17 mol), dimethylaminopyridine (2 mol %) and triethylamine (17.2 g, 23.7 ml, 0.17 mmol) in dichloromethane (300 ml) was cooled to 0 °C prior to slow addition of benzoyl chloride (23.89 g, 19.7 ml, 0.17). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Evaporation of the solvent under reduced pressure

---

gave a yellow solid, which was triturated with light petroleum, filtered, diluted with
dichloromethane (200 ml), washed with saturated sodium hydrogen carbonate
solution (2 x 60 ml), water (60 ml) and brine (60 ml). The organics were dried over
MgSO₄ and concentrated to give the title compound as a colourless liquid (40.58 g,
95%) which can be purified if necessary by vacuum distillation (1 mbar, 122-124 °C);
IR (thin film) 1763, 1721 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, J = 8.5 Hz,
2H), 7.61 (t, J = 7.05 Hz, 1H), 7.46 (dd, J = 8.5 7.05 Hz, 2H), 3.34 (s, 3H), 1.46 (s,
9H); ¹³C NMR (125 MHz, CDCl₃) δ 164.74, 155.38, 133.86, 129.89, 128.62, 127.64,
82.40, 38.00, 28.13; MS (APCI) m/z 252 [M+H]⁺; HRMS calculated for C₁₃H₁₇NO₄
252.1236 [M+H]⁺, found 252.1236.

N-Methyl-O-benzoyl hydroxylamine hydrochloride³ (10)

Gaseous hydrogen chloride, generated from the slow addition of concentrated sulfuric
acid (ca. 50 ml) to ammonium chloride (ca. 50 g) was bubbled through a solution of
N-Boc-N-methyl-O-benzoyl hydroxylamine (25 g, 0.1 mol) in 1,4-dioxane for 2
hours. The resulting white precipitate was filtered and washed with cold ether and
dried under high vacuum to give the title compound (17.83 g, 95%) as a colourless
solid; Mp 129-129.5 °C; IR (thin film) 3458, 3056, 1712, 1600, 1550, 1422, 1264 cm⁻¹;
¹H NMR (400 MHz, DMSO-d₆) δ 11.95 (brs, 2H), 7.95 (d, J = 7.0 Hz, 2H), 7.73
(t, J = 7.5 Hz, 1H), 7.57 (dd, J = 7.0 7.5 Hz, 2H), 2.93 (3H, s); ¹³C NMR (100 MHz,
DMSO-d₆) δ 164.33, 134.86, 129.69, 129.60, 127.15, 37.49; MS (APCI) m/z 152
[M+H]⁺; HRMS calculated for C₈H₉NO₂ 152.0711 [M+H]⁺, found 152.0712.

Typical experimental procedure for cyclic ketones

1,4-Cyclohexanedione mono-ethylene ketal (100 mg, 0.64 mmol) and N-Methyl-O-
benzoyl hydroxylamine hydrochloride (111 mg, 0.64 mmol) were dissolved in
dimethylsulfoxide (1.5 ml) and the resultant mixture allowed to stir at room
temperature for two hours, after which time TLC analysis showed the reaction to be
complete. The solution was subsequently diluted with ethyl acetate (50 ml) and
washed repeatedly with saturated aqueous brine to remove the reaction solvent (5 ×

50 ml). The organic fraction was dried (magnesium sulfate), concentrated in vacuo, and the crude product purified by flash column chromatography (4:1 light petroleum/ethyl acetate) to yield benzoic acid 8-oxo-1,4-dioxa-spiro[4.5]dec-7-yl ester as colourless microcrystals (122 mg, 70%); Mp 114-116 °C; IR (dichloromethane) 2915, 1714, 1448, 1260, 1101, 1036 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.01 (d, $J = 8$ Hz, 2H), 7.51 (t, $J = 8$ Hz, 1H), 7.38 (t, $J = 8$ Hz, 2H), 5.57–5.69 (m, 1H), 3.95–4.11 (m, 4H), 2.66–2.80 (m, 1H), 2.35–2.49 (m, 2H), 2.20 (t, $J = 13$ Hz, 1H), 1.90–2.09 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 203.4 (s), 165.4 (s), 133.3 (d), 129.9 (d), 129.4 (s), 128.4 (d), 107.3 (s), 73.7 (d), 65.0 (t), 64.9 (t), 40.3 (t), 35.6 (t), 34.6 (t); MS (APci) $m/z$ 277 [M+H]$^+$; HRMS calculated for C$_{15}$H$_{16}$O$_5$ [M+H]$^+$ 277.1071, found 277.1073.

Typical experimental procedure for acyclic ketones

Pentan-3-one (60 µl, 0.57 mmol) and N-Methyl-O-benzoyl hydroxylamine hydrochloride (100 mg, 0.57 mmol) were dissolved in dimethylsulfoxide (1 ml) and the resultant mixture allowed to stir at 50 °C for sixteen hours. After this period the solution was diluted with ethyl acetate (50 ml) and washed repeatedly with saturated aqueous brine (5 × 50 ml). The organic fraction was dried (magnesium sulfate) and concentrated in vacuo, and the crude product purified by flash chromatography (dichloromethane) to yield benzoic acid 1-methyl-2-oxo-butyl ester$^4$ as a pale yellow oil (81 mg, 74%); IR (dichloromethane) 2353, 1719, 1262, 1097 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, $J = 8$ Hz, 2H), 7.53 (t, $J = 8$ Hz, 1H), 7.40 (t, $J = 8$ Hz, 2H), 5.29 (q, $J = 7$ Hz, 2H), 2.39-2.66 (m, 2H), 1.47 (d, $J = 7$ Hz, 3H), 1.03 (t, $J = 8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 208.6 (s), 165.96 (s), 133.4 (d), 129.8 (d), 129.5 (s), 128.5 (d), 75.2 (d), 31.5 (t), 16.5 (q), 7.3 (q); MS (APci) $m/z$ 207 [M+H]$^+$; HRMS calculated for C$_{13}$H$_{16}$O$_3$ [M+H]$^+$ 207.1016, found 207.1016.

Typical experimental procedure for aldehydes

1-Heptanal (79 µl, 0.57 mmol) and N-Methyl-O-benzoyl hydroxylamine hydrochloride (100 mg, 0.57 mmol) were dissolved in dimethylsulfoxide (1 ml) and

the resultant mixture allowed to stir at 50 °C for sixteen hours. After this period the solution was diluted with ethyl acetate (50 ml) and washed repeatedly with saturated aqueous brine (5 × 50 ml). The organic fraction was dried (magnesium sulfate) and concentrated in vacuo, and the crude product subjected to flash chromatography (1:1 dichloromethane/light petroleum) to furnish benzoic acid 1-formyl-hexyl ester\(^5\) as a colourless oil (110 mg, 83%); IR (neat) 2910, 1715, 1250, 1030 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.53 (s, 1H), 7.99 (d, \(J = 8\) Hz, 2H), 7.50 (t, \(J = 8\) Hz, 1H), 7.37 (t, \(J = 8\) Hz, 2H), 5.07–5.14 (m, 1H), 1.71–1.90 (m, 2H), 1.35–1.46 (m, 2H), 1.17–1.29 (m, 4H), 0.79 (t, \(J = 8\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 198.6 (s), 166.2 (s), 133.6 (d), 129.9 (d), 129.2 (s), 128.6 (d), 78.8 (d), 31.5 (t), 28.9 (t), 24.7 (t), 22.4 (t), 14.0 (q); MS (APCI) \(m/z\) 235 [M+H]\(^+\); HRMS calculated for C\(_{14}\)H\(_{19}\)O\(_3\) [M+H]\(^+\) 235.1329, found 235.1329.

N-Methyl-N-Boc hydroxylamine\textsuperscript{1} (4)
N-Methyl-N-Boc-O-acyl hydroxylamine\(^6\) (5)

\[ \text{Diagram of N-Methyl-N-Boc-O-acyl hydroxylamine} \]

N-Methyl-N-Boc-O-benzoyl hydroxylamine² (6)
$N$-Methyl-$N$-Boc-$O$-(4-methoxybenzoyl) hydroxylamine (7)
N-Methyl-N-Boc-O-pivaloyl hydroxylamine (8)
N-Methyl-O-acyl hydroxylamine hydrochloride

\[ \text{N-Me-\text{O-acyl hydroxylamine HCl}} \] (9)
N-Methyl-O-benzoyl hydroxylamine hydrochloride (10)
N-Methyl-\textit{O}-(4-methoxybenzoyl) hydroxylamine hydrochloride (11)
$N$-Methyl-$O$-pivaloyl hydroxylamine hydrochloride$^7$ (12)

$^1$H NMR of crude reaction mixture between 10 and cyclohexanone in CHCl₃, THF, DMSO, THF/H₂O.

CHCl₃:

THF:
DMSO:

THF/H₂O (9/1):
2-(Benzoyloxy)cyclopentanone$^8$ (Table 1 entry 1)

2-(Benzoyloxy)cyclohexanone\(^8\) (14)
2-(Benzoyloxy)cycloheptanone (Table 1 entry 3)
2-(Benzoyloxy)pentan-3-one (Table 1 entry 4)
3-(Benzoyloxy)heptan-4-one (Table 1 entry 5)
2-(Benzoyloxy)isovaleraldehyde\textsuperscript{9} (Table 1 entry 6)

2-(Benzoyloxy)heptanal

\[ \text{O} \text{Bz} \]

\[ \text{H} \]

\[ \text{O} \]
Benzoyloxy cyclohexanecarboxaldehyde$^{10}$ (Table 1 entry 7)

3-(Benzyloxy)tetrahydro-4H-pyran-4-one\textsuperscript{8} (Table 1 entry 8)
3-(Benzoyloxy)tetrahydro-4H-thiopyran-4-one (Table 1 entry 9)
2-(Benzoyloxy)cyclohexane-1,4-dione monoethylene ketal (Table 1 entry 10)
N-Benzoyl-3-(benzoyloxy)piperidin-4-one (Table 1 entry 11)
$N$-$p$-toluenesulfonyl-$3$-(benzoyloxy)piperidin-4-one (Table 1 entry 12)
Ethyl 2-(benzoyloxy)-4-oxocyclohexanecarboxylate (Table 1 entry 13)
2-(Benzoyloxy)-4-methylcyclohexanone\textsuperscript{11} (Table 1 entry 14)

2-(Benzoyloxy)-4-tertbutylcyclohexanone (Table 1 entry 15)
2-(Benzoyloxy)propiophenone\textsuperscript{12} (Table 1 entry 16)

1-(4-Methoxyphenyl)-2-(benzoyloxy)propan-1-one\textsuperscript{13} (Table 1 entry 17)

1-(4-Bromophenyl)-2-(benzoyloxy)propan-1-one (Table 1 entry 18)
1-(4-Hydroxyphenyl)-2-(benzoyloxy)propan-1-one (Table 1 entry 19)
4-Methyl-3-benzoyloxypentan-2-one (Table 2 entry 1)
5-Hexen-3-benzoyloxy-2-one (Table 2 entry 2)
1-(4-Hydroxyphenyl)-3-oxobutan-2-yl benzoate (Table 2 entry 3)
1-(4-Methoxyphenyl)-3-oxobutan-2-yl benzoate (Table 2 entry 4)