Oxonitriles: A Grignard Addition-Acylation Route to Enamides

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General Grignard Addition-Acylation procedure: A THF solution of MeMgCl (1.05-1.1 equiv) was added to a -15 °C THF solution (0.1M) of oxonitrile **1**. After 2 h a THF solution of a second Grignard reagent (1.5 equiv) was added and then the reaction solution was allowed to warm to room temperature. After 2 h, the solution was cooled to 0 °C followed by the sequential addition of a THF solution of the third Grignard reagent (4.0 equiv) and pivaloyl chloride (6.0 equiv). After 2 h, subsequent addition of saturated NH₄Cl and extraction with EtOAc afforded a crude product that was washed with brine and dried (MgSO₄), concentrated and purified by radial chromatography to afford the pure nitrile.

Dimethyl 1-[(2*R*,3*S*)-3-[(methoxycarbonyl)oxy]-2,3-dimethylcyclohexylidene]ethylimido-dicarbonate (7): The standard procedure was employed with oxonitrile **1** (15 mg, 0.12 mmol) with the MeMgCl (1.6 M, 0.3 mmol) being added in one portion followed, after 2 h at room temperature by cooling to -78 °C and addition of methyl chloroformate (28 mg, 0.3 mmol). After 1 h at -78 °C, the reaction was allowed to warm to room temperature and after 1 h, saturated, aqueous NH₄Cl was added to afford, after radial chromatography (stepped gradient 1:9, 1:4, 1:3 EtOAc/hexanes), 15 mg (37%) of **7** as a white solid (m.p.143-135 °C). IR (film): 1787, 1745, 1711 cm⁻¹; ¹H NMR: δ 0.97 (d, *J* = 3.2 Hz, 3H), 1.41 (s, 3H), 1.87 (s, 3H), 1.75-2.05 (m, 5H), 2.40 (br d, *J* = 14.7 Hz, 1H), 3.15 (q, *J* = 6.9 Hz, 1H), 3.70 (s, 3H), 3.79 (s, 6H); ¹³C NMR: δ 13.1, 17.7, 22.3, 22.7, 23.9, 30.5, 40.4, 53.5, 53.6, 54.0, 85.8, 125.9, 137.9, 152.9, 152.9, 153.6; HRMS(EI) calcd for (M⁺), C₁₆H₂₅NO₇Na⁺ 366.1523, found 366.1534.

***N*-{1-[(2*R*,3*S*)-3-hydroxy-2,3-dimethylcyclohexylidene]ethyl}-2,2-dimethylpropanamidem (8a):** The standard procedure was employed with oxonitrile **1** (20 mg, 0.017 mmol) with the MeMgCl (1.5 M, 0.6 mmol) being added in one portion followed, after 2 h at room temperature, by pivaloyl chloride (41 mg, 0.34 mmol) at room temperature. The reaction was left at room temperature for 16 h to afford, after radial chromatography (stepped gradient 1:4, 2:3, 1:1 EtOAc/hexanes), 24 mg (57%) of **8a** as a light brown oil. IR (film): 3450, 1666, 1650 cm⁻¹; ¹H NMR: δ 1.06 (d, *J* = 7.3 Hz, 3H), 1.16 (s, 3 H), 1.23 (s, 9H), 1.90 (s, 3H), 0.95 – 2.11 (m, 6H), 2.35 (br d, *J* = 14.0 Hz, 1H), 2.63 (q, *J* = 6.9 Hz, 1H), 6.51 (s, 1H); ¹³C NMR: δ 13.3, 17.4, 23.3, 23.5, 27.6, 34.4, 38.9, 42.9, 73.0, 123.5, 134.9, 176.8; HRMS(EI) calcd for (M⁺), C₁₅H₂₇NO₂Na⁺ 276.1934, found 276.1959.

N-((Z)-1-((2R, 3S)-3-hydroxy-3-methyl-2-phenylcyclohexylidene)ethyl)pivalamide (8b): The standard procedure was employed with oxonitrile **1** (30.3 mg, 0.25 mmol), MeMgCl (2.65 M, 0.1 mL), PhMgBr (1.0M, 0.37 mL), MeMgCl (2.65 M, 0.38 mL), and pivaloyl chloride (0.18 mL) to afford, after radial chromatography with 1:2 EtOAc/Hexanes, **8b** in 73% yield as a white solid (mp 133-134 °C) whose structure was determined by x-ray crystallography. IR (film): 3417, 2239, 1654 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 1.12 (s, 9H), 1.28 (s, 3H), 1.57-1.79 (m, 5H), 1.95 (s, 3H), 2.39-2.49 (m, 1H), 2.64-2.71 (m, 1H), 3.63 (s, 1H), 6.32 (s, 1H), 7.20-7.45 (m, 5H); ^{13}C NMR (300 MHz, CDCl_3): δ 17.0, 21.2, 25.1, 27.5, 28.7, 34.9, 38.9, 54.8, 71.9, 127.2, 127.3, 128.6, 129.9, 130.4, 140.2, 176.5; HRMS (ESI), m/z calculated for $(\text{M}+\text{Na})^+$ ($\text{C}_{20}\text{H}_{29}\text{NO}_2\text{Na}^+$): 338.2090, found 338.2089.

N-((Z)-5-Chloro-1-((2R, 3S)-3-hydroxy-3-methyl-2-phenylcyclohexylidene)pentyl)-pivalamide (8c): The standard procedure was employed with oxonitrile **1** (30.3 mg, 0.25 mmol), MeMgCl (2.65 M, 0.1 mL), PhMgBr (1.0 M, 0.37 mL), $\text{Cl}(\text{CH}_2)_4\text{MgBr}$ [1.0M, 1.0 mL, prepared from $\text{Cl}(\text{CH}_2)_4\text{Br}$ (0.12 mL) and Mg (33 mg) at 0 °C],³ and pivaloyl chloride (0.18 mL) to afford, after radial chromatography with 2:3 EtOAc/Hexanes, **8c** in 40% yield. IR (film): 3415, 2240, 1665 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 1.12 (s, 9H), 1.28 (s, 3H), 1.40-1.98 (m, 9H), 2.35-2.75 (m, 4H), 3.46-3.50 (m, 2H), 3.61 (s, 1H), 6.18 (s, 1H), 7.20-7.46 (m, 5H); ^{13}C NMR (300 MHz, CDCl_3): δ 21.2, 25.0, 25.1, 27.6, 28.1, 28.4, 28.9, 32.0, 34.7, 39.0, 44.8, 54.7, 72.0, 127.2, 128.6, 129.9, 131.2, 131.9, 140.0, 176.7; HRMS (ESI) m/z calculated for $(\text{M}+\text{Na})^+$ ($\text{C}_{23}\text{H}_{34}\text{ClNO}_2\text{Na}^+$): 414.2170, found 414.2153.

N-((Z)-1-((2R, 3S)-3-Hydroxy-3-methyl-2-vinylcyclohexylidene)ethyl)pivalamide (8d): The standard procedure was employed with oxonitrile **1** (30.3 mg, 0.25 mmol), MeMgCl (2.65 M, 0.1

mL), CH₂=CHMgBr (0.7 M, 0.55 mL), MeMgCl (2.65 M, 0.38 mL), and pivaloyl chloride (0.18 mL) to afford, after radial chromatography with 2:5 EtOAc/Hexanes, **8d** in 69% yield. IR (film): 3341, 3075, 1651 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.19 (s, 3H), 1.24 (s, 9H), 1.30-1.85 (m, 6H), 1.96 (s, 3H), 2.40-2.55 (m, 1H), 3.15 (d, *J* = 8.8 Hz, 1H), 5.08-5.29 (m, 2H), 5.92-6.07 (m, 1H), 6.59 (br s, 1H); ¹³C NMR (300 MHz, CDCl₃): δ 17.1, 23.0, 24.5, 26.8, 27.6, 36.2, 39.0, 54.5, 72.0, 118.4, 126.1, 130.6, 135.6, 176.8; MS (EI) *m/z* 266 (M+1)⁺.

N-((Z)-1-((2R, 3S)-2-(2-(1, 3-Dioxan-2-yl)ethyl)-3-hydroxy-3-methylcyclohexylidene)ethyl)-pivalamide (8e): The standard procedure was employed with oxonitrile **1** (30.3 mg, 0.25 mmol), MeMgCl (2.65 M, 0.1 mL), (1, 3-dioxan-2-ylethyl)magnesium bromide (0.5 M, 0.77 mL), MeMgCl (2.65 M, 0.38 mL), and pivaloyl chloride (0.18 mL) to afford, after radial chromatography with 4:5 EtOAc/Hexanes, **8e** in 69% yield. IR (film): 3460, 3384, 1655 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.17 (s, 3H), 1.22 (s, 9H), 1.31-1.42 (m, 3H), 1.43-1.57 (m, 3H), 1.66-1.91 (m, 5H), 1.94 (s, 3H), 2.01-2.13 (m, 1H), 2.32-2.38 (m, 1H), 2.53 (dd, *J* = 10.7, 3.4 Hz, 1H), 3.71-3.80 (m, 2H), 4.06-4.14 (m, 2H), 4.50-4.54 (m, 1H), 6.74 (s, 1H); ¹³C NMR (500 MHz, CDCl₃): δ 17.3, 21.1, 23.4, 25.7, 27.7, 28.0, 33.0, 34.9, 38.9, 48.6, 66.9, 67.0, 73.4, 102.9, 102.9, 126.2, 131.6, 176.7.

N-((Z)-1-((2R, 3S)-3-Hydroxy-2, 3-dimethylcyclohexylidene)-3-phenylprop-2-ynyl)-pivalamide (8f): The standard procedure was employed with oxonitrile **1** (30.3 mg, 0.25 mmol), MeMgCl (2.65 M, 0.24 mL), PhC≡CMgCl [prepared by deprotonating a THF solution (1.0 mL) of PhC≡CH (0.11 mL) with MeMgCl (2.65 M, 0.42 mL) at reflux for 0.5 h), and pivaloyl chloride (0.18 mL) to afford, after radial chromatography with 1:3 EtOAc/Hexanes, **8f** in 50%

yield. IR (film): 3588, 3448, 3292, 2202, 1652, 1596, 1505 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 1.15 (d, $J = 7.3$ Hz, 3H), 1.20 (s, 3H), 1.28 (s, 9H), 1.40-1.58 (m, 3H), 1.76-1.84 (m, 2H), 2.17-2.25 (m, 1H), 2.71 (q, $J = 7.3$ Hz, 1H), 2.87-2.94 (m, 1H), 6.48 (s, 1H), 7.28-7.32 (m, 3H), 7.41-7.44 (m, 2H); ^{13}C NMR (500 MHz, CDCl_3): δ 13.3, 23.2, 26.5, 27.6, 27.7, 34.3, 39.03, 43.5, 73.4, 85.9, 90.9, 110.6, 123.1, 128.1, 128.2, 131.4, 150.7, 176.8; MS (EI) m/z 339 (M^+).

N-((Z)-1-((2R, 3S)-3-Hydroxy-3-methyl-2-phenylcyclohexylidene)(phenyl)methyl)-pivalamide (8g): The standard procedure was employed with oxonitrile **1** (30.3 mg, 0.25 mmol), MeMgCl (2.65 M, 0.1 mL), PhMgBr (1.0M, 1.37 mL), and pivaloyl chloride (0.18 mL). The latter two reagents were added as follows: an initial addition of PhMgBr (1.0 M, 1.2 equiv), and pivaloyl chloride (2.3 equiv) followed after 10 min by pivaloyl chloride (2.0 equiv), followed after 15 min by PhMgBr (1.4 equiv), followed 20 min later by pivaloyl chloride (2.0 equiv), followed 15 min later by PhMgBr (1.4 equiv), followed 3 h later by PhMgBr (1 equiv), and the reaction was then left for 1 h before the addition of NH_4Cl . The modified procedure afforded, after radial chromatography with 1:5 EtOAc/Hexanes, **8g** in 47% yield as a white solid (mp 125-126.5 $^\circ\text{C}$) whose structure was determined by x-ray crystallography. IR (film): 3548, 3422, 3081, 3056, 3024, 1676, 1599 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 1.09 (s, 9H), 1.26 (br s, 1H), 1.35 (s, 3H), 1.62-1.74 (m, 2H), 1.83-1.94 (m, 2H), 2.50-2.68 (m, 2H), 3.75 (s, 1H), 6.52 (s, 1H), 7.15-7.43 (m, 10H); ^{13}C NMR (500 MHz, CDCl_3): δ 21.5, 26.2, 27.4, 29.2, 34.9, 38.8, 55.2, 72.3, 127.2, 127.2, 127.9, 128.7, 128.7, 129.9, 130.9, 134.6, 138.2, 140.0, 176.2; MS (EI) m/z 378 ($\text{M}+1$) $^+$.

N-((Z)-1-((2R, 3S)-3-Hydroxy-2, 3-dimethylcyclohexylidene)allyl)pivalamide (8h): The standard procedure was employed with oxonitrile **1** (30.3 mg, 0.25 mmol), MeMgCl (2.65 M, 0.24 mL), CH₂=CHMgBr (0.7 M, 1.43 mL), and pivaloyl chloride (0.18 mL) to afford, after radial chromatography with 1:5 EtOAc/Hexanes, **8h** in 59% yield. IR (film): 3442, 3336, 3094, 1655, 1500 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.12 (d, *J* = 6.9 Hz, 3H), 1.17 (s, 3H), 1.21-1.28 (m, 1H), 1.30 (s, 9H), 1.34-1.44 (m, 1H), 1.50-1.54 (m, 1H), 1.73-1.82 (m, 2H), 2.05-2.13 (m, 1H), 2.62-2.68 (m, 1H), 2.72 (q, *J* = 6.9 Hz, 1H), 5.04-5.13 (m, 2H), 6.30 (s, 1H), 6.73 (dd, *J* = 16.6, 10.8 Hz, 1H); ¹³C NMR (500 MHz, CDCl₃): δ 13.3, 23.3, 23.6, 27.84, 34.4, 39.1, 44.3, 73.3, 113.1, 125.8, 130.7, 143.7, 176.9; MS (EI) *m/z* 265 (M⁺).

N-((Z)-1-((2R, 3S)-3-Hydroxy-3-methyl-2-vinylcyclohexylidene)allyl)pivalamide (8i): The standard procedure was employed with oxonitrile **1** (30.3 mg, 0.25 mmol), MeMgCl (2.65 M, 0.1 mL), CH₂=CHMgBr (0.7 M, 1.98 mL), and pivaloyl chloride (0.18 mL). The latter two reagents were added as follows: an initial addition of PhMgBr (1.0 M, 1.2 equiv), and pivaloyl chloride (2.3 equiv) followed after 10 min by pivaloyl chloride (2.0 equiv), followed after 15 min by PhMgBr (1.4 equiv), followed 20 min later by pivaloyl chloride (2.0 equiv), followed 15 min later by PhMgBr (1.4 equiv), followed 3 h later by PhMgBr (1 equiv), and the reaction was then left for 1 h before the addition of NH₄Cl. The modified procedure afforded, after radial chromatography with 1:4 EtOAc/Hexanes, **8i** in 40% yield. IR (film): 3549, 3456, 3298, 3093, 3010, 1654, 1631, 1506 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.19 (s, 3H), 1.30 (s, 9H), 1.40-1.53 (m, 1H), 1.60-1.67 (m, 2H), 1.76-1.85 (m, 1H), 1.93 (br s, 1H), 2.05-2.14 (m, 1H), 2.70-2.77 (m, 1H), 3.26 (d, *J* = 8.8 Hz, 1H), 5.08-5.17 (m, 3H), 5.21-5.25 (m, 1H), 5.95-6.04 (m, 1H), 6.34 (s, 1H), 6.73 (dd, *J* = 17.1, 10.8 Hz, 1H); ¹³C NMR (500 MHz, CDCl₃): δ 23.1, 24.6, 26.9,

27.8, 36.2, 39.0, 55.4, 72.4, 113.9, 119.1, 127.8, 130.1, 135.2, 139.6, 176.6; MS (EI) m/z 278 ($M+1$)⁺; HRMS (ESI), m/z calculated for ($M+Na$)⁺ ($C_{17}H_{27}NO_2Na^+$): 300.1940, found 300.1926.

N-((Z)-1-((2R, 3S)-3-Hydroxy-2, 3-dimethylcyclohexylidene)propyl)pivalamide (8j): The standard procedure was employed with oxonitrile **1** (30.3 mg, 0.25 mmol), MeMgCl (2.65 M, 0.24 mL), $(CH_3)_3SiCH_2(Et_2)ZnLi$ [prepared from $(CH_3)_3SiCH_2Li$ (0.82 M, 1.2 mL) and Et_2Zn (15% w/w in hexane, 1.2 mL)], and pivaloyl chloride (0.18 mL). The latter two reagents were added as follows: an initial addition of $(CH_3)_3SiCH_2(Et_2)ZnLi$ (1.0 M, 1.2 equiv), and pivaloyl chloride (2.3 equiv) followed after 10 min by pivaloyl chloride (2.0 equiv), followed after 15 min by $(CH_3)_3SiCH_2(Et_2)ZnLi$ (1.4 equiv), followed 20 min later by pivaloyl chloride (2.0 equiv), followed 15 min later by $(CH_3)_3SiCH_2(Et_2)ZnLi$ (1.4 equiv), followed 3 h later by $(CH_3)_3SiCH_2(Et_2)ZnLi$ (1 equiv), and the reaction was then left for 1 h before the addition of NH_4Cl . The modified procedure afforded, after radial chromatography with 1:3 EtOAc/Hexanes, **8j** in 63% yield. IR (film): 3341, 2235, 1646 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$): δ 0.96 (t, $J = 7.4$ Hz, 3H), 1.07 (d, $J = 7.3$ Hz, 3H), 1.17 (s, 3H), 1.25 (s, 9H), 1.44-1.53 (m, 2H), 1.70-1.79 (m, 3H), 1.89-2.02 (m, 1H), 2.30-2.42 (m, 3H), 2.62 (q, $J = 6.9$ Hz, 1H), 6.45 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 12.8, 13.3, 23.2, 23.7, 23.7, 27.6, 27.7, 34.5, 39.0, 43.1, 73.1, 129.3, 135.0, 176.9; MS (EI) m/z 268 ($M+1$)⁺.

FFZY069.002
DATE 4-6-2

SF	300.133
SY	210.0
O1	4800.000
SI	8192
TD	8192
SW	4504.505
HZ/PT	1.100
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AG	4.909
RG	4
NS	8
TE	297
FW	5700
O2	5684.205
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LB	0.0
GB	0.0
CX	25.00
CY	10.00
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F2	-1.98P
HZ/CM	122.422
PPM/CM	.408
SR	3367.05

FFZY085.001
DATE 12-6-2

SF	300.133
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SI	8192
TD	8192
SW	6024.096
HZ/PT	1.471
PW	5.0
RD	2.500
AG	4.680
RG	4
NS	8
TE	297
FW	7600
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GB	0.0
CX	25.00
CY	10.00
F1	10.003P
F2	194P
HZ/CM	122.423
PPM/CM	408
SR	3367.05

Two of the conformers showing the axial and equatorial orientations of the phenyl group on the cyclohexane ring.

References

¹ For general experimental procedures see: Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305. The high-resolution mass spectra were recorded at Duquesne University on an Agilent 1100 TOF MS system with electrospray.

² The authors have deposited the crystallographic data for **8b** and **8g** with the Cambridge Crystallographic Data Center (CCDC 605398 and 605397, respectively). The supplementary crystallographic data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44 1223 336033; or deposit@ccdc.cam.ac.uk.).

³ Bernady, K. F.; Poletto, J. F.; Nocera, J.; Mirando, P.; Schaub, R. E.; Weiss, M. J. *J. Org. Chem.* **1980**, *45*, 4702.