Reactions Between Weinreb Amides and 2-Magnesiated Oxazoles—A Simple and Efficient Preparation of 2-Acyl Oxazoles

Daniel J. Pippel, Christopher M. Mapes, Neelakandha Mani

Supporting Information

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General Experimental Chemical Procedures. Nuclear magnetic resonance (^1H NMR, ^{13}C NMR) spectra were recorded on a 400, 500, or 600 MHz spectrometer. Differential scanning calorimetry (DSC) was performed with either a 5 or 10 $^{\circ}\text{C}$ / min ramp. High resolution mass spectra were taken on a MicroTOF apparatus. Flash chromatography was performed on an automated system, typically utilizing 40 g pre-packed columns for separations on 2.5 mmol scale. Filtrations through silica gel plugs were performed using Merck silica gel 60. HPLC analysis was performed on a Hewlett Packard 1100 (Agilent ZORBAX® Eclipse XDB-C8, 5 μm , 4.6x150 mm, Flow rate 1 mL/min, Gradient (acetonitrile/water with 0.05% trifluoroacetic acid): 1% acetonitrile/99% water to 99% acetonitrile/1% water ramp over 8 min, then hold at 99% acetonitrile/1% water). All reagents were used as received from commercial sources. All solvents utilized were purchased in anhydrous form and passed through two columns of neutral alumina (DCE, THF, MTBE, MeOH) or one column of neutral alumina and one column of Q5 oxygen scavenger (toluene). *N*-(*tert*-butoxycarbonyl)glycine *N'*-methoxy-*N'*-methyl-amide is commercially available and was used directly. EA is utilized below as an abbreviation for ethyl acetate.

***N*-Methoxy-*N*-methyl-3-phenyl-propionamide (S1).**^{1,2} A slurry of ethyl hydrocinnamate (15 g, 84.2 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (12.73 g, 130.51 mmol) in THF (170 mL) was cooled to $-20\text{ }^{\circ}\text{C}$ under a $\text{N}_{2(g)}$ atmosphere. Over 35 min, *i*-PrMgCl (2 M in THF, 126.3 mL, 252.6 mmol) was added such that the temperature was maintained below $0\text{ }^{\circ}\text{C}$. The mixture was aged for 20 min at $-10\text{ }^{\circ}\text{C}$ and then quenched with $\text{NH}_4\text{Cl}_{(aq)}$ (13% w/w, 170 mL). After vigorous mixing, the layers were separated, and the aqueous layer was further extracted with MTBE (170 mL). The combined organics were dried (MgSO_4), filtered, and concentrated to afford **S1** as a clear oil (15.63 g, 96%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.32-7.17 (m, 5H), 3.60 (s, 3H), 3.18 (s, 3H), 2.96 (t, $J = 8.0$, 2H), 2.74 (t, $J = 7.8$, 2H).

***N*-Methoxy-*N*-methyl-propionamide (S2).**³ A slurry of *N,O*-dimethylhydroxylamine hydrochloride (4.88 g, 50 mmol) in dichloromethane (100 mL) under a $\text{N}_{2(g)}$ atmosphere was cooled to $0\text{ }^{\circ}\text{C}$. Triethylamine (14.6 mL, 105 mmol) was added, and an exotherm of $10\text{ }^{\circ}\text{C}$ was noted. When the mixture had returned to $0\text{ }^{\circ}\text{C}$, propionyl chloride (4.34 mL, 50 mmol) was added slowly, maintaining an internal temperature of $< 7\text{ }^{\circ}\text{C}$. After stirring for 65 h at room temperature, water (100 mL) was added, and the layers were

mixed and then separated. The organic layer was dried (MgSO₄), filtered, and concentrated to provide **S2** as a clear oil (4.96 g, 85%). ¹H NMR (CDCl₃, 400 MHz) δ 3.69 (s, 3H), 3.18 (s, 3H), 2.45 (q, *J* = 7.5, 2H), 1.14 (t, *J* = 7.6, 3H). HRMS: (M+H) calculated for C₅H₁₂NO₂: 118.0863; found 118.0854.

4-[3-(Methoxy-methyl-carbamoyl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester (S3). Step 1. To a 5 L, jacketed reactor affixed with an overhead mechanical stirrer, N_{2(g)} inlet, and thermocouple were added ethanol (1.4 L) and then acetyl chloride (6.95 mL, 97.7 mmol). After stirring for 5 min, piperidine butyric acid•HCl (70.3 g, 337 mmol) was added, and the mixture was warmed to reflux for 2.5 h. The reaction mixture was then cooled to 40 °C, and solid sodium bicarbonate (70.8 g, 842 mmol) was added. Upon additional cooling to 23 °C, di-*tert*-butyl dicarbonate (73.5 mL, 320 mmol) was added followed by water (980 mL). The mixture was stirred overnight and then concentrated to 1,075 g. The concentrate was slurried with dichloromethane (1.5 L) and then 1 N HCl (450 mL) was slowly added to pH ~3. The layers were quickly mixed and separated and then the aqueous was extracted a second time with dichloromethane. The combined organics were dried (MgSO₄), filtered, and concentrated to provide 4-(3-ethoxycarbonyl-propyl)-piperidine-1-carboxylic acid tert-butyl ester as a slightly off-color, clear oil (94.7 g, 97%). ¹H NMR (CDCl₃) δ 4.13 (q, *J* = 7.2, 2H), 4.07 (br s, 2H), 2.67 (br t, *J* = 12.2, 2H), 2.28 (t, *J* = 7.3, 2H), 1.69-1.60 (m, 4H), 1.45 (s, 9H), 1.42-1.32 (m, 1H), 1.26 (t, *J* = 7.2, 3H), 1.30-1.22 (m, 2H), 1.15-1.01 (m, 2H). Step 2. In a 5 L reactor, equipped as in step 1, were slurried the product of step 1 (94.64 g, 316 mmol) and *N,O*-dimethylhydroxylamine•HCl (47.79 g, 490 mmol) in THF (1.05 L). To this slurry was added *i*-PrMgCl (2.0 M in Et₂O, 474 mL, 948 mmol) over 1.5 h such that the internal temperature remained below -5 °C. After dosing was complete, the mixture was stirred for 40 min, and then 13% NH₄Cl_(aq) (1.5 L) was added. After stirring an additional 15 min and warming to room temperature, the layers were separated. The aqueous was extracted with MTBE (1.5 L). The combined organics were dried (MgSO₄), filtered, and concentrated to a slightly yellow oil (97.2 g, 98%). ¹H NMR (CDCl₃, 600 MHz) δ 4.20-3.90 (br s, 2H), 3.68 (s, 3H), 3.18 (s, 3H), 2.77-2.57 (br s, 2H), 2.41 (bt, *J* = 7.1, 2H), 1.71-1.60 (m, 4H), 1.45 (s, 9H), 1.45-1.34 (m, 1H), 1.31-1.25 (m, 2H), 1.14-1.03 (m, 2H). ¹³C NMR (CDCl₃, 151 MHz): 174.5, 154.9, 79.1, 61.2, 36.2, 35.9, 32.1, 32.0, 28.4, 21.7. HRMS: (M+2H-Boc) calculated for C₁₁H₂₃N₂O₂: 215.1754; found 215.1753.

Cyclohexanecarboxylic acid methoxy-methyl-amide (S4).⁴ The compound was prepared in 95% yield according to the method detailed for **S2**. ¹H NMR (CDCl₃, 400 MHz) δ 3.70 (s, 3H), 3.18 (s, 3H), 2.68 (t, *J* = 11.1, 1H), 1.84-1.64 (m, 5H), 1.55-1.42 (m, 2H), 1.36-1.18 (m, 3H). ¹³C NMR (CDCl₃, 151 MHz): 61.5, 39.9, 29.0, 25.8, 25.8. HRMS: (M+H) calculated for C₉H₁₈NO₂: 172.1332; found 172.1346.

2-Benzyloxy-N-methoxy-N-methyl-acetamide (S5).⁵ The compound was prepared in 71% yield after flash chromatography (10% to 60% ramp, EtOAc in Hexanes) according to the method detailed for **S2**. ¹H NMR (CDCl₃, 600 MHz) δ 7.41-7.38 (m, 2H), 7.37-7.33 (m, 2H), 7.31-7.28 (m, 1H), 4.67 (s, 2H), 4.28 (s, 2H), 3.62 (s, 3H), 3.19 (s, 3H). ¹³C NMR (CDCl₃, 151 MHz): 137.5, 128.4, 128.1, 127.9, 73.2, 67.0, 61.4, 32.2. HRMS: (M+H) calculated for C₁₁H₁₆NO₃: 210.1125; found 210.1122.

N-Methoxy-N-methyl-3-phenyl-acrylamide (S6).^{6,7} To a mixture of *trans*-cinnamic acid (3.70 g, 25 mmol), *N,O*-dimethylhydroxylamine•HCl (3.66g, 37.5 mmol), and *N*-methyl-morpholine (5.5 mL, 50 mmol) in methanol (200 mL) was added 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (8.30 g, 30 mmol) at room temperature. The mixture was allowed to stir overnight. After concentration, the remaining residue was partitioned between ethyl acetate (100 mL) and saturated NaHCO_{3(aq)} (100 mL). The organic layer was then washed with 1 M HCl_(aq), water and brine. After drying over MgSO₄ and filtering, the resulting solution was

concentrated to a clear oil (4.96 g, quant.). ^1H NMR (CDCl_3 , 400 MHz) δ 7.74 (d, J = 15.6, 1H), 7.60-7.55 (m, 2H) 7.42-7.33 (m, 3H), 7.04 (d, J = 15.6, 1H), 3.77 (s, 3H), 3.32 (s, 3H). HRMS: (M+H) calculated for $\text{C}_{11}\text{H}_{14}\text{NO}_2$: 192.1019; found 192.1022.

4-Fluoro-*N*-methoxy-*N*-methyl-benzamide (S7).⁷ The compound was prepared in 98% yield according to the method detailed for **S2**. ^1H NMR (CDCl_3 , 400 MHz) δ 7.77-7.71 (m, 2H), 7.12-7.05 (m, 2H), 3.54 (s, 3H), 3.36 (s, 3H). HRMS: (M+H) calculated for $\text{C}_9\text{H}_{11}\text{NO}_2\text{F}$: 184.0768; found 184.0768.

7-Phenyl-heptanoic acid methoxy-methyl-amide (S8). To an aqueous solution of KOH (18.37 g in 92 mL water) was added 2-benzoylcyclohexanone (22.64 g, 112 mmol). The heterogeneous mixture was warmed until homogeneous (68 °C) and then cooled in an ice bath. Concentrated $\text{HCl}_{(aq)}$ was added to pH = 0 (28 mL) and then additional water (100 mL) and dichloromethane (200 mL) were added. The layers were mixed and then separated. The aqueous was extracted with additional dichloromethane (200 mL) and the combined organics were then dried over MgSO_4 , filtered, and concentrated. Recrystallization of the resulting residue in diisopropyl ether (100 mL) provided 7-oxo-7-phenyl-heptanoic acid (13.04 g, 53% yield) as a crystalline solid. A solution of 7-oxo-7-phenyl-heptanoic acid (46.56 g, 211.4 mmol) in EtOH (500 mL) was poured over 10% Pd/C (4.86 g) and then submitted to an atmospheric pressure of $\text{H}_{2(g)}$ at 65 °C. After 24 h, the reaction system was thoroughly purged with $\text{N}_{2(g)}$ and filtered. Concentration of the supernatant provided 7-phenyl heptanoic acid (43.29 g, 99%) as a clear oil. To a solution of 7-phenyl heptanoic acid (93.66 g, 454 mmol) in ethanol (600 mL) was slowly added acetyl chloride (10.7 g, 136 mmol, 0.3 equiv). The mixture became cloudy and heterogeneous. After heating at reflux overnight, the mixture was concentrated to provide 7-phenyl heptanoic acid ethyl ester. This concentrate containing 7-phenyl heptanoic acid ethyl ester was slurried in THF (1.4 L) with *N,O*-dimethylhydroxylamine•HCl and cooled to -5 °C and *i*-PrMgCl (2.0 M in THF, 633 mL, 1.27 mol, 3 equiv) was added at such a rate as to maintain an internal temperature of < -5 °C. The reaction was then aged for 35 min prior to the slow addition of $\text{NH}_4\text{Cl}_{(aq)}$ (13.5% w/w, 2L). The biphasic mixture was stirred vigorously for 2 h and then the layers were partitioned. The aqueous layer was extracted once with MTBE (1.5 L), and the combined

organics were dried (MgSO_4), filtered, and concentrated to 7-phenyl-heptanoic acid methoxy-methyl-amide (105.71 g, 93% for two steps) as a clear oil. ^1H NMR (CDCl_3 , 600 MHz) δ 7.28-7.24 (m, 2H), 7.18-7.14 (m, 3H), 3.67 and 3.66 (s, 3H), 3.17 (s, 3H), 3.62-2.58 (m, 2H), 2.40 (bt, $J = 6.9$, 2H), 1.66-1.59 (m, 4H), 1.39-1.35 (m, 4H). ^{13}C NMR (CDCl_3 , 151 MHz): 142.8, 128.4, 128.2, 125.6, 61.2, 35.9, 32.1, 31.8, 31.4, 29.3, 29.1, 24.6. HRMS: ($\text{M}+\text{H}$) calculated for $\text{C}_{15}\text{H}_{24}\text{NO}_2$: 250.1802; found 250.1803.

Preparation of 5-aryl oxazoles. 5-aryl oxazoles were prepared according to the standard literature procedure and used without purification unless otherwise indicated.^{8,9} The following preparation is illustrative:

4-Oxazol-5-yl-pyridine (S14). To a slurry of *p*-toluenesulfonylmethyl isocyanide (14.64 g, 75 mmol) and K_2CO_3 (10.37g, 75 mmol) in methanol (150 mL) was added 4-pyridine carboxaldehyde (8.03 g, 75 mmol). The reaction mixture was held at reflux for 2 h and then cooled, concentrated, and partitioned between MTBE and water. After separation of the layers, the aqueous layer was extracted once with additional MTBE. The combined organics were dried (MgSO_4), filtered and concentrated to provide 4-oxazol-5-yl-pyridine as a yellow solid (9.34 g, 85%) that was used directly.

Entry	Structure	Yield	Purification, Purity estimate	Analytical Data
S9⁸		63%	Flash Chromatography (1-20% EA/Hex) >95%	¹ H NMR (CDCl ₃ , 400 MHz) δ 7.92 (s, 1H), 7.66 (m, 2H), 7.43 (m, 2H), 7.36 (s, 1H), 7.34 (m, 1H). HRMS: (M+H) calculated for C ₉ H ₈ NO: 146.0600; found 146.0608.
S10⁸		59%	Flash Chromatography (1-20% EA/Hex) >99%	¹ H NMR (CDCl ₃ , 400 MHz) δ 7.92 (s, 1H), 7.60 (m, 2H), 7.41 (m, 2H), 7.35 (s, 1H). HRMS: (M+H) calculated for C ₉ H ₇ NOCl: 180.0211; found 180.0208.
S11⁸		63%	Filtration of ppt during aqueous work-up >99%	¹ H NMR (CDCl ₃ , 400 MHz) δ 8.31 (m, 2H), 8.03 (s, 1H), 7.83 (m, 2H), 7.58 (s, 1H). HRMS: (M+H) calculated for C ₉ H ₇ N ₂ O ₃ : 191.0451; found 191.0454.
S12⁹		47%	Flash Chromatography (1-20% EA/Hex) >95%	¹ H NMR (CDCl ₃ , 400 MHz) δ 7.86 (s, 1H), 7.34 (dd, <i>J</i> = 5.0, 1.1, 1H), 7.33 (dd, <i>J</i> = 3.7, 1.1, 1H), 7.22 (s, 1H), 7.09 (dd, <i>J</i> = 5.0, 3.6, 1H). HRMS: (M+H) calculated for C ₇ H ₆ NOS: 152.0165; found 152.0178.
S13⁹		26%	Flash Chromatography (1-20% EA/Hex) >95%	¹ H NMR (CDCl ₃ , 400 MHz) δ 7.86 (s, 1H), 7.48 (dd, <i>J</i> = 1.8, 0.6, 1H), 7.27 (s, 1H), 6.65 (d, <i>J</i> = 3.4, 1H), 6.50 (dd, <i>J</i> = 3.4, 1.8, 1H). HRMS: (M+H) calculated for C ₇ H ₆ NO ₂ : 136.0393; found 136.0387.
S14⁹		85%	No Purification >95%	¹ H NMR (CDCl ₃ , 400 MHz) δ 8.68 (dd, <i>J</i> = 4.6, 1.6, 2H), 8.02 (s, 1H), 7.58 (s, 1H), 7.53 (dd, <i>J</i> = 4.5, 1.6, 2H). HRMS: (M+H) calculated for C ₈ H ₇ N ₂ O: 147.0553; found 147.0547.
S15⁹		91%	No Purification >95%	¹ H NMR (CDCl ₃ , 400 MHz) δ 8.94 (dd, <i>J</i> = 2.2, 0.6, 1H), 8.59 (dd, <i>J</i> = 4.8, 1.6, 1H), 7.99 (s, 1H), 7.94 (dt, <i>J</i> = 7.9, 2.0, 1H), 7.46 (s, 1H), 7.38 (ddd, <i>J</i> = 8.0, 4.8, 0.8 Hz, 1H). HRMS: (M+H) calculated for C ₈ H ₇ N ₂ O: 147.0553; found 147.0546.
S16⁹		95%	No Purification >98%	¹ H NMR (CDCl ₃ , 500 MHz) δ 8.65 (ddd, <i>J</i> = 4.8, 1.6, 0.9, 1H), 7.98 (s, 1H), 7.78 (td, <i>J</i> = 7.7, 1.8, 1H), 7.71 (s, 1H), 7.68 (dt, <i>J</i> = 8.0, 1.0, 1H), 7.25 (ddd, <i>J</i> = 7.6, 4.9, 1.2 Hz, 1H). HRMS: (M+H) calculated for C ₈ H ₇ N ₂ O: 147.0553; found 147.0549.

General Procedure for the Synthesis of 2-Acyl Oxazoles from Oxazoles and Weinreb amides.

1c
 $C_{17}H_{26}N_2O_4$
Exact Mass: 322.1893
Mol. Wt.: 322.3994
C, 63.33; H, 8.13; N, 8.69; O, 19.85

4-(4-Oxazol-2-yl-4-oxo-butyl)-piperidine-1-carboxylic acid tert-butyl ester (1c). To a 5 L jacketed reactor equipped with an overhead mechanical stirrer, a thermocouple probe, and a J-Kem dose controller, THF (1.46 L) was added under $N_{2(g)}$. After cooling to an internal temperature of $-15\text{ }^{\circ}\text{C}$, oxazole (25.60 g, 371 mmol, 1.2 equiv) was added and the dose controller was utilized to meter in *i*-PrMgCl (2 M in THF, 186 mL, 371 mmol, 1.2 equiv) over 20 min, maintaining an internal temperature of $<-10\text{ }^{\circ}\text{C}$. The homogeneous solution was then stirred for 40 min. After this aging period, 4-[3-(Methoxy-methyl-carbamoyl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester (**S3**) (97.25 g, 309 mmol, 1.0 equiv) was added in 550 mL of THF over 8 min maintaining an internal temperature below $-14\text{ }^{\circ}\text{C}$. The reaction was then warmed to a jacket temperature of $28\text{ }^{\circ}\text{C}$ and stirred for 13 h. After this hold time, the reaction was quenched by addition of 13.5% $NH_4Cl_{(aq)}$ w/w (2 L). The layers were mixed and then separated and the aqueous layer was extracted once with MTBE (1.5 L). The combined organics were dried over $MgSO_4$, filtered and concentrated to a crude mass of 110.74 g. The material was purified through filtration through a plug of silica gel with 25% EA/Hexanes to provide the desired product **1c** as a white solid (76.91 g, 77%).

Data:

1H NMR ($CDCl_3$, 600 MHz): 7.84 (s, 1H), 7.34 (s, 1H), 4.25-3.90 (bs, 2H), 3.07 (t, $J = 7.4$, 2H), 2.81-2.55 (bs, 2H), 1.81-1.75 (m, 2H), 1.67 (bd, $J = 12.7$, 2H), 1.47-1.39 (m, 1H), 1.45 (bs, 9H), 1.36-1.30 (m, 2H), 1.09 (qd, $J = 12.6$, 4.1, 2H).

^{13}C NMR ($CDCl_3$, 151 MHz): 188.3, 158.0, 154.8, 141.6, 129.0, 79.2, 39.2, 35.85, 35.78, 32.0, 28.4, 20.9

TLC $R_f = 0.12$ in 20% ethyl acetate / 80% hexanes

HPLC Retention Time = 9.92 min

Microanalysis: Anal. calcd. for $C_{17}H_{26}N_2O_4$: C 63.33, H 8.13, N 8.69; Found C 63.43, H 7.83, N 8.91.

m.p. (from DSC)

64.6 °C onset, 68.9 °C max; 88.4 J/g (pentane)

$C_{12}H_{11}NO_2$
Exact Mass: 201.0790

Mol. Wt.: 201.2213
C, 71.63; H, 5.51; N, 6.96; O, 15.90

1-Oxazol-2-yl-3-phenyl-propan-1-one (1a). The compound was synthesized according to the general procedure outlined for **1c**. Purification was performed through flash chromatography (1-10% EA/Hexanes) to provide **1a** as a clear oil in 76% (2.5 mmol scale).

Data:

1H NMR ($CDCl_3$, 600 MHz): 7.80 (d, J = 0.6, 1H), 7.30 (d, J = 0.6, 1H), 7.30-7.23 (m, 4H), 7.21-7.17 (m, 1H), 3.43-3.40 (m, 2H), 3.09-3.06 (m, 2H).

^{13}C NMR ($CDCl_3$, 151 MHz): 187.3, 157.9, 141.6, 140.3, 129.1, 128.5, 128.4, 126.3, 40.7, 29.5

TLC R_f = 0.10 in 10% ethyl acetate / 90% hexanes

HPLC Retention Time = 8.85 min

HRMS: (M+H) calculated for $C_{12}H_{12}NO_2$: 202.0863; found 202.0853

$C_6H_7NO_2$
Exact Mass: 125.0477

Mol. Wt.: 125.1253
C, 57.59; H, 5.64; N, 11.19; O, 25.57

1-Oxazol-2-yl-propan-1-one (1b). The compound was synthesized according to the general procedure outlined for **1c**. Purification was performed through flash chromatography (1-20% EA/Hexanes). Due to concerns related to the volatility of the product, **1b** was isolated as a clear oil (52% product/48% ethyl acetate mixture by weight). Subtracting the mass contributions of residual solvent the yield was calculated to be 80% (2.5 mmol scale).

Data:

^1H NMR (CDCl_3 , 600 MHz): 7.87 (s, 1H), 7.34 (s, 1H), 3.12 (q, $J = 7.3$, 2H), 1.24 (t, $J = 7.2$, 3H).

^{13}C NMR (CDCl_3 , 151 MHz): 188.8, 157.9, 141.4, 128.9, 32.4, 7.5

TLC $R_f = 0.34$ in 20% ethyl acetate / 80% hexanes

HPLC Retention Time = 6.94 min

HRMS: (M+H) calculated for $\text{C}_6\text{H}_8\text{NO}_2$: 126.0550; found 126.0560

$\text{C}_{10}\text{H}_{13}\text{NO}_2$
Exact Mass: 179.0946
Mol. Wt.: 179.2158

C, 67.02; H, 7.31; N, 7.82; O, 17.85

Cyclohexyl-oxazol-2-yl-methanone (1d). The compound was synthesized according to the general procedure outlined for **1c**. Purification was performed through flash chromatography (1-20% EA/Hexanes). The product was isolated as a clear oil in a yield of 75% (2.5 mmol scale).

Data:

^1H NMR (CDCl_3 , 600 MHz): 7.83 (s, 1H), 7.34 (s, 1H), 3.44 (tt, $J = 11.6$, 3.4, 1H), 2.02-1.95 (m, 2H), 1.89-1.81 (m, 2H), 1.78-1.70 (m, 1H), 1.56-1.35 (m, 4H), 1.32-1.20 (m, 1H)

^{13}C NMR (CDCl_3 , 151 MHz): 191.5, 157.6, 141.5, 128.9, 46.7, 28.6, 25.7, 25.5

TLC $R_f = 0.49$ in 20% ethyl acetate / 80% hexanes

HPLC Retention Time = 9.21 min

HRMS: (M+H) calculated for $\text{C}_{10}\text{H}_{14}\text{NO}_2$: 180.1019; found 180.1020

C₁₂H₁₁NO₃
 Exact Mass: 217.0739
 Mol. Wt.: 217.2207
 C, 66.35; H, 5.10; N, 6.45; O, 22.10

2-Benzyloxy-1-oxazol-2-yl-ethanone (1e). The compound was synthesized according to the general procedure outlined for **1c**. Purification was performed through flash chromatography (5-25% EA/Hexanes). The product was isolated as a clear oil in a yield of 52% (2.5 mmol scale).

Data:

¹H NMR (CDCl₃, 400 MHz): 7.85 (s, 1H), 7.44-7.29 (m, 5H), 7.31 (s, 1H), 4.88 (s, 2H), 4.72 (s, 2H).

¹³C NMR (CDCl₃, 151 MHz): 184.2, 156.1, 141.8, 137.0, 130.0, 129.0, 128.6, 128.1, 73.6, 72.0

TLC R_f = 0.18 in 20% ethyl acetate / 80% hexanes

HPLC Retention Time = 8.49 min

HRMS: (M+H) calculated for C₁₂H₁₂NO₃: 218.0812; found 218.0813

C₁₂H₉NO₂
 Exact Mass: 199.0633
 Mol. Wt.: 199.2054
 C, 72.35; H, 4.55; N, 7.03; O, 16.06

1-Oxazol-2-yl-3-phenyl-propenone (1f). The compound was synthesized according to the general procedure outlined for **1c**. Purification was performed through flash chromatography (1-10% EA/Hexanes). The product was isolated as a yellow solid in a yield of 74% (2.5 mmol scale).

Data:

¹H NMR (CDCl₃, 600 MHz): 8.05 (d, *J* = 16.0, 1H), 7.88 (s, 1H), 7.79 (d, *J* = 16.0, 1H), 7.72-7.67 (m, 2H), 7.47-7.42 (m, 3H), 7.40 (s, 1H)

^{13}C NMR (CDCl_3 , 151 MHz):	176.4, 159.1, 146.4, 141.9, 134.3, 131.3, 129.2, 129.0, 129.0, 121.1
TLC	$R_f = 0.35$ in 20% ethyl acetate / 80% hexanes
HPLC	Retention Time = 8.78 min
m.p. (from DSC)	67.1 °C onset, 75.0 °C max; 96.6 J/g (dichloromethane)
HRMS:	(M+H) calculated for $\text{C}_{12}\text{H}_{10}\text{NO}_2$: 200.0706; found 200.0708

$\text{C}_{10}\text{H}_6\text{FNO}_2$
 Exact Mass: 191.0383
 Mol. Wt.: 191.1586
 C, 62.83; H, 3.16; F, 9.94; N, 7.33; O, 16.74

(4-Fluoro-phenyl)-oxazol-2-yl-methanone (1g). The compound was synthesized according to the general procedure outlined for **1c**. Purification was performed through flash chromatography (1-20% EA/Hexanes). The product was isolated as a white solid in a yield of 71% (2.5 mmol scale).

Data:

^1H NMR (CDCl_3 , 400 MHz):	8.63-8.56 (m, 2H), 7.92 (s, 1H), 7.44 (s, 1H), 7.24-7.17 (m, 2H)
^{13}C NMR (CDCl_3 , 126 MHz):	177.1, 166.4 (d, $J_{\text{C-F}} = 255.4$), 157.7, 141.6, 133.8 (d, $J_{\text{C-F}} = 9.6$), 131.3 (d, $J_{\text{C-F}} = 2.9$), 129.0, 115.7 (d, $J_{\text{C-F}} = 22.0$)
TLC	$R_f = 0.41$ in 20% ethyl acetate / 80% hexanes
HPLC	Retention Time = 8.72 min
Microanalysis:	Anal. calcd. for $\text{C}_{10}\text{H}_6\text{FNO}_2$: C 62.83, H 3.16, N 7.33; Found C 62.67, H 3.51, N 7.43

m.p. (from DSC)

118.9 °C onset, 124.1 °C max; 134.6 J/g (ethyl acetate/hexanes)

C₁₀H₁₄N₂O₄

Exact Mass: 226.0954

Mol. Wt.: 226.2292

C, 53.09; H, 6.24; N, 12.38; O, 28.29

(2-Oxazol-2-yl-2-oxo-ethyl)-carbamic acid tert-butyl ester (1h). The compound was synthesized according to the general procedure outlined for **1c**, with the caveat that the Weinreb amide was pretreated with 1 equiv of *i*-PrMgCl. Purification was performed through flash chromatography (10-30% EA/Hexanes). The product was isolated in a as a white solid in a yield of 25% (2.5 mmol scale).

Data:

¹H NMR (acetone, 600 MHz): 8.24 (s, 1H), 7.48 (s, 1H), 6.35 (bs, 0.85H) and minor rotamer 5.94 (bs, 0.15H), 4.61 (d, *J* = 5.9, 2H), 1.43(bs, 8H) and minor rotamer 1.37 (bs, 1H).

¹³C NMR (acetone, 151 MHz): 184.6, 157.8, 156.9, 143.6, 1230.0, 79.4, 48.2 (+ minor peak at 48.1 attributed to rotamer), 28.6 (+ minor peak at 28.3 attributed to rotamer)

TLC R_f = 0.27 in 30% ethyl acetate / 70% hexanes

HPLC Retention Time = 7.83 min

HRMS: (M+2H-Boc) calculated for C₅H₇N₂O₂: 127.0502; found 127.0501

m.p. (from DSC)

92.0 °C onset, 103.0 °C max; 109.0 J/g (ethyl acetate/hexanes)

$C_{18}H_{15}NO_2$
 Exact Mass: 277.1103
 Mol. Wt.: 277.3172
 C, 77.96; H, 5.45; N, 5.05; O, 11.54

3-Phenyl-1-(5-phenyl-oxazol-2-yl)-propan-1-one (2a). The compound was synthesized according to the general procedure outlined for **1c**. Purification was performed through flash chromatography (5-15% EA/Hexanes). The product was isolated as a white solid in a yield of 48% (2.5 mmol scale).

Data:

1H NMR ($CDCl_3$, 400 MHz): 7.79-7.74 (m, 2H), 7.50 (s, 1H), 7.49-7.39 (m, 3H), 7.34-7.24 (m, 4H), 7.23-7.18 (m, 1H), 3.44 (t, J = 7.6, 2H), 3.11 (t, J = 7.6, 2H)

^{13}C NMR ($CDCl_3$, 126 MHz): 187.1, 157.0, 154.3, 140.5, 130.0, 129.1, 128.5, 128.5, 126.7, 126.3, 125.3, 123.8, 40.6, 29.8

TLC R_f = 0.42 in 20% ethyl acetate / 80% hexanes

HPLC Retention Time = 10.23 min

Microanalysis: Anal. calcd. for $C_{18}H_{15}NO_2$: C 77.96, H 5.45, N 5.05; Found C 77.73, H 5.43, N 5.20

m.p. (from DSC) 88.2 °C onset, 96.8 °C max; 100.0 J/g (ethyl acetate/hexanes)

$C_{18}H_{14}ClNO_2$
 Exact Mass: 311.0713
 Mol. Wt.: 311.7620
 C, 69.35; H, 4.53; Cl, 11.37; N, 4.49; O, 10.26

1-[5-(4-Chloro-phenyl)-oxazol-2-yl]-3-phenyl-propan-1-one (2b). The compound was synthesized according to the general procedure outlined for **1c**. Purification was

performed through flash chromatography. A portion of the product was isolated as a yellow solid in pure form, while another portion was isolated as a mixture containing a small amount of the oxazole starting material. The calculated total yield was 54% (2.5 mmol scale).

Data:

¹H NMR (CDCl₃, 400 MHz): 7.73-7.68 (m, 2H), 7.49 (s, 1H), 7.47-7.41 (m, 2H), 7.32-7.23 (m, 4H), 7.23-7.18 (m, 1H), 3.43 (t, *J* = 7.7, 2H), 3.10 (t, *J* = 7.7, 2H)

¹³C NMR (CDCl₃, 126 MHz): 187.1, 157.1, 153.2, 140.4, 136.0, 129.5, 128.54, 128.46, 126.5, 126.3, 125.2, 124.1, 40.6, 29.8

TLC *R*_f = 0.39 in 20% ethyl acetate / 80% hexanes

HPLC Retention Time = 10.59 min

Microanalysis: Anal. calcd. for C₁₈H₁₄ClNO₂: C 69.35, H 4.53, N 4.49; Found C 69.06, H 4.91, N 4.71

m.p. (from DSC) 103.6 °C onset, 115.9 °C max; 75.2 J/g (ethyl acetate/hexanes)

C₁₆H₁₃NO₂S
Exact Mass: 283.0667
Mol. Wt.: 283.3460
C, 67.82; H, 4.62; N, 4.94; O, 11.29; S, 11.32

3-Phenyl-1-(5-thiophen-2-yl-oxazol-2-yl)propan-1-one (2d). The compound was synthesized according to the general procedure outlined for **1c**. Purification was performed through flash chromatography (5-10% EA/Hexanes). A portion of the product was isolated as a yellow oil in moderately pure form, while another portion was isolated as a mixture with the oxazole starting material. The calculated total yield was 40% (2.5 mmol scale).

Data:

¹H NMR (CDCl₃, 400 MHz): 7.50 (dd, *J* = 3.6, 1.2, 1H), 7.44 (dd, *J* = 5.2, 1.2, 1H), 7.34 (s, 1H), 7.32-7.23 (m, 4H), 7.22-7.17 (m, 1H), 7.12 (dd, *J* = 4.8, 3.6, 1H), 3.42 (t, *J* =

7.6, 2H), 3.09 (t, $J = 7.6$, 2H)

^{13}C NMR (CDCl_3 , 150 MHz): 186.9, 156.3, 149.8, 140.5, 128.53, 128.47, 128.4, 128.2, 127.9, 126.8, 126.3, 123.3, 40.5, 29.8

TLC $R_f = 0.43$ in 20% ethyl acetate / 80% hexanes

HPLC Retention Time = 10.07 min

HRMS: (M+H) calculated for $\text{C}_{16}\text{H}_{14}\text{NO}_2\text{S}$: 284.0740; found 284.0744

$\text{C}_{16}\text{H}_{13}\text{NO}_3$
Exact Mass: 267.0895
Mol. Wt.: 267.2794
C, 71.90; H, 4.90; N, 5.24; O, 17.96

1-(5-Furan-2-yl-oxazol-2-yl)-3-phenyl-propan-1-one (2e). The compound was synthesized according to the general procedure outlined for **1c**. Purification was performed through flash chromatography (5-10% EA/Hexanes). A portion of the product was isolated as a tan solid in pure form, while another portion was isolated as a mixture containing a small amount of the oxazole starting material. The calculated total yield was 60% (2.5 mmol scale).

Data:

^1H NMR (CDCl_3 , 400 MHz): 7.53 (d, $J = 1.2$, 1H), 7.40 (s, 1H), 7.33-7.22 (m, 4H), 7.22-7.17 (m, 1H), 6.89 (d, $J = 3.6$, 1H), 6.54 (dd, $J = 3.6$, 1.6, 1H), 3.42 (t, $J = 7.8$, 2H), 3.09 (t, $J = 7.6$, 2H)

^{13}C NMR (CDCl_3 , 150 MHz): 186.9, 156.3, 146.4, 144.3, 142.5, 140.4, 128.54, 128.46, 126.3, 123.4, 112.1, 110.4, 40.6, 29.8

TLC $R_f = 0.38$ in 20% ethyl acetate / 80% hexanes

HPLC Retention Time = 9.88 min

Microanalysis: Anal. calcd. for $\text{C}_{16}\text{H}_{13}\text{NO}_3$: C 71.90, H 4.90, N 5.24; Found C 71.53, H 5.25, N 5.33

m.p. (from DSC)

60.0 °C onset, 68.2 °C max; 70.6 J/g (ethyl acetate/hexanes)

$C_{17}H_{14}N_2O_2$

Exact Mass: 278.1055

Mol. Wt.: 278.3053

C, 73.37; H, 5.07; N, 10.07; O, 11.50

3-Phenyl-1-(5-pyridin-4-yl-oxazol-2-yl)-propan-1-one (2f). The compound was synthesized according to the general procedure outlined for **1c**. Purification was performed through flash chromatography. A portion of the product was isolated as a white solid in pure form, while another small portion was isolated as a mixture containing a small amount of the oxazole starting material. The calculated total yield was 79% (2.5 mmol scale).

Data:

^1H NMR (CDCl_3 , 400 MHz): 8.74-8.72 (m, 2H), 7.69 (s, 1H), 7.64-7.61 (m, 2H), 7.35-7.25 (m, 4H), 7.25-7.17 (m, 1H), 3.46 (t, $J = 7.6$, 2H), 3.11 (t, $J = 7.6$, 2H)

^{13}C NMR (CDCl_3 , 150 MHz): 187.2, 157.7, 151.5, 150.8, 140.3, 133.6, 128.6, 128.4, 126.6, 126.4, 118.9, 40.7, 29.7

TLC $R_f = 0.29$ in 50% ethyl acetate / 50% hexanes

HPLC Retention Time = 7.49 min

Microanalysis: Anal. calcd. for $C_{17}H_{14}N_2O_2$: C 73.37, H 5.07, N 10.07; Found C 73.25, H 5.54, N 10.21

m.p. (from DSC)

122.9 °C onset, 129.3 °C max; 107.3 J/g (ethyl acetate/hexanes)

2g
 $C_{17}H_{14}N_2O_2$
 Exact Mass: 278.1055
 Mol. Wt.: 278.3053
 C, 73.37; H, 5.07; N, 10.07; O, 11.50

3-Phenyl-1-(5-pyridin-3-yl-oxazol-2-yl)-propan-1-one (2g). The compound was synthesized according to the general procedure outlined for **1c**. Purification was performed through flash chromatography. A portion of the product was isolated as a white solid in pure form, while another small portion was isolated as a mixture containing a small amount of the oxazole starting material. The calculated total yield was 54% (2.5 mmol scale).

Data:

1H NMR ($CDCl_3$, 400 MHz): 9.02 (d, $J = 1.6$, 1H), 8.65 (dd, $J = 4.8$, 1.6, 1H), 8.06 (dt, $J = 8.0$, 1.8, 1H), 7.60 (s, 1H), 7.41 (dd, $J = 7.6$, 5.2, 2H), 7.32-7.23 (m, 4H), 7.23-7.18 (m, 1H), 3.45 (t, $J = 7.6$, 2H), 3.11 (t, $J = 7.6$, 2H)

^{13}C NMR ($CDCl_3$, 125 MHz): 187.1, 157.5, 151.4, 150.7, 146.5, 140.4, 132.4, 128.6, 128.4, 126.3, 124.8, 123.8, 123.1, 40.6, 29.7

TLC $R_f = 0.32$ in 50% ethyl acetate / 50% hexanes

HPLC Retention Time = 8.11 min

Microanalysis: Anal. calcd. for $C_{17}H_{14}N_2O_2$: C 73.37, H 5.07, N 10.07; Found C 73.46, H 5.44, N 10.33

m.p. (from DSC) 92.2 °C onset, 96.2 °C max and 97.2 onset, 100.6 max; 97.8 J/g (ethyl acetate/hexanes)

3
 $C_{21}H_{22}N_2O_2$
 Exact Mass: 334.1681
 Mol. Wt.: 334.4117
 C, 75.42; H, 6.63; N, 8.38; O, 9.57

7-Phenyl-1-(5-pyridin-2-yl-oxazol-2-yl)-heptan-1-one (3). A 5 L jacketed reactor was equipped with an overhead mechanical stirrer and an internal thermocouple probe and purged with N_{2(g)}. Pyridyl oxazole **S16** (90 g, 616 mmol, 2.2 equiv) in anhydrous diglyme (900 mL) was added and the reactor contents were cooled to -10 °C. Maintaining a temperature of <0 °C, *i*-PrMgCl (2 M in THF, 308 mL, 616 mmol, 2.2 equiv) was added over ~45 min. The solution was aged at -5 °C for 50 min and then Weinreb amide **S8** (69.82 g, 280 mmol, 1 equiv) was added in 200 mL of diglyme. The reaction was warmed to 82 °C and held at that temperature for 20 h. The reaction was then carefully quenched with water (25 mL) and concentrated to near dryness. The concentrate was taken up in 13.5% NH₄Cl_(aq) w/w (1.5 L) and ethyl acetate (1.5 L). The layers were filtered through 1L of sand to remove suspended black solids and then separated. The aqueous layer was extracted 2X with ethyl acetate and the combined organics were dried with MgSO₄, filtered, and concentrated to 167.08 g of a black oil. The oil was purified through flash chromatography (15-35% EA/Hexanes). The resulting solid was recrystallized in boiling heptane to provide **3** as a white solid (40.65 g, 43%).

Data:

¹ H NMR (CDCl ₃ , 400 MHz):	8.67 (ddd, <i>J</i> = 4.8, 1.6, 0.97, 1H), 7.88 (s, 1H), 7.87 (partially obscured dt, <i>J</i> = 8.1, 1.1, 1H), 7.81 (td, <i>J</i> = 7.8, 1.7, 1H), 7.32 (ddd, <i>J</i> = 7.5, 4.8, 1.3, 1H), 7.29-7.24 (m, 2H), 7.19-7.14 (m, 3H), 3.11 (t, <i>J</i> = 7.4, 2H), 2.61 (t, <i>J</i> = 7.7, 2H), 1.78 (m, 2H), 1.64 (m, 2H), 1.50-1.35 (m, 4H).
¹³ C NMR (CDCl ₃ , 150 MHz):	188.5, 157.4, 153.3, 150.2, 146.3, 142.7, 137.1, 128.4, 128.3, 126.9, 125.6, 124.1, 120.4, 39.1, 35.9, 31.3, 29.0, 23.9
TLC	R _f = 0.17 in 20% ethyl acetate / 80% hexanes
HPLC	Retention Time = 10.84 min
Microanalysis:	Anal. calcd. for C ₂₁ H ₂₂ N ₂ O ₂ : C 75.42, H 6.63, N 8.38; Found C 75.45, H 7.03, N 8.62
m.p. (from DSC)	69.5 °C onset, 73.2 °C max; 121.6 J/g (heptane)

1b

(With residual EtOAc
to prevent loss of
volatile product)

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- ¹ This general approach to Weinreb amides has been previously documented: Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
- ² Compound **S1** has been previously characterized: Satyamurthi, N.; Singh, J.; Aidhen, I. S. *Synthesis*, **2000**, 375.
- ³ Compound **S2** has been previously characterized: Wolberg, M.; Hummel, W.; Müller, M. *Chem. Eur. J.* **2001**, *7*, 4562.
- ⁴ Compound **S4** has been previously reported and partially characterized: Buswell, M.; Fleming, I.; Ghosh, U.; Mack, S.; Russell, M.; Clark, B. P. *Org. Biomol. Chem.* **2004**, *2*, 3006.
- ⁵ Compound **S5** has been previously prepared and partially characterized: Williams, R. M.; Ehrlich, P. P.; Zhai, W.; Hendrix, J. J. *Org. Chem.* **1987**, *52*, 2615.
- ⁶ The DMT-MM method for preparation of Weinreb amides: Hioki, K.; Kobayashi, H.; Ohkikara, R.; Tani, S.; Kunishima, M. *Chem. Pharm. Bull.* **2004**, *52*, 470.
- ⁷ Compounds **S6** and **S7** have been previously characterized: Murphy, J. A.; Commeureuc, A. G. J.; Snaddon, T. N.; McGuire, T. M.; Khan, T. A.; Hisler, K.; Dewis, M. L.; Carling, R. *Org. Lett.* **2005**, *7*, 1427.
- ⁸ **S9**, **S10**, and **S11** were all reported in the original reference for the synthesis of oxazoles from tosylmethylisocyanide and carbonyl compounds. van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, *13*, 2369.
- ⁹ **S12-S16** are all known in the literature. Saikachi, H.; Kitagawa, T.; Sasaki, H.; van Leusen, A. M. *Chem. Pharm. Bull.* **1979**, *27*, 793.