Construction of 5,6-Fused 2-Pyridones: An Effective Annulation Tactic Achieved in Water

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Materials and Methods

All non-aqueous reactions were carried out in oven or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents were reagent grade. Except as indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 0.25-mm E. Merck pre-coated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 230 - 400 mesh) supplied by E. Merck. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated.

Melting points were determined on a Bristoline heated-stage microscope or Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 283B, a Perkin-Elmer Model 1600 FTIR, or a Jasco FTIR-480 plus spectrometer with polystyrene as an external standard, and are reported in cm\(^{-1}\) (abs). Proton NMR spectra were recorded on a Bruker AM-500 spectrometer. Carbon-13 NMR spectra were recorded on a Bruker AM-500. Chemical shifts are reported in ppm with the solvent resonance as the internal standard relative to either chloroform (δ 7.26) for \(^1\)H or chloroform (δ 77.0) for \(^13\)C. Optical rotations were obtained with a Perkin-Elmer model 241 polarimeter with a sodium lamp, and are reported as follows: [α]_D^20 , [c (g/100 mL), solvent]. High resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Center on a VG Micromass 70/70H or VG ZAB-E spectrometer.

Representative Procedure for Michael Addition : Preparation of 6

\[ \text{To a solution of propiolamide (325 mg, 4.70 mmol) and sodium carbonate (270 mg, 2.75 mmol) in water (5 mL) at 0 }^\circ C \text{ methyl-2-oxocyclopentanecarboxylate (5) (390 mg, 2.75 mmol) was added dropwise. The reaction mixture was warmed to room temperature over 2 h and then extracted with CH}_2\text{Cl}_2 (3x20 mL). The combined organic layers were dried over MgSO}_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (eluent 1:1 ethyl acetate/hexanes r.f. 0.2) afforded 6 as a white solid (511 mg , 88% yield). Melting point: 210-214 }^\circ C; \text{ IR (NaCl plate, thin film, CH}_2\text{Cl}_2): 3299 (br,s), 3077(m), 2956 (s), 2956 (s), 2927 (m), 1647 (s), 1557 (s), 1456} \]
(m), 1067 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.58 (d, J = 10.0 Hz, 1H), 6.12 (s, 1H), 5.95 (dd, J = 9.9, 1.4 Hz, 1H), 4.86 (s, 1H), 3.77 (s, 3H), 2.48 (ddd, J = 13.5, 9.4, 7.4 Hz, 1H), 2.25 (ddd, J = 13.6, 9.1, 7.1 Hz, 1H), 2.13 – 1.85 (m, 1H), 1.79 – 1.48 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 173.5, 164.1, 143.1, 123.3, 92.4, 55.7, 53.0, 40.4, 36.5, 20.7. high resolution mass spectrum (ES⁺) m/z 250.0689 [(M+Na)⁺; calculated for C₁₀H₁₃NNaO₅: 250.0691].

Alternative Protocol for Michael Addition: Preparation of 6
To a solution of propiolic acid (305 mg, 4.41 mmol) and potassium carbonate (357 mg, 2.58 mmol) in acetone (10 mL), methyl-2-oxocyclopentanecarboxylate (5) (356 mg, 2.58 mmol) was added and the solution was heated at 50 ºC for 1 h. The reaction mixture was cooled to room temperature and than 10 ml water was added. The resulted solution was extracted with CH₂Cl₂ (3x40 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (eluent 1:1 ethyl acetate/hexanes r.f. 0.2) afforded 6 as a white solid (445.51 mg, 76% yield).

Representative Procedure for Annulation: Preparation of 8

A thick walled tube containing a stir bar and methyl 1-(3-amino-3 oxoprop-1-enyl)2-oxocyclopentanecarboxylate (154.1 mg, 0.730 mmol) (6) was dissolved in concentrated HCl (2 mL). The tube was sealed tightly and heated to 130 ºC in an oil bath. After 6h the reaction mixture was allowed to cool to room temperature, the tube carefully opened and the reaction mixture poured onto ice (5g). The pH was adjusted to 7 by dropwise addition of saturated aqueous NaHCO₃ and then the mixture extracted with ethyl acetate. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to furnish a white solid. Purification through a short pad of silica gel (eluent 100% ethyl acetate) afforded 8 as a white amorphous solid (97.4 mg, 99% yield). Melting point: 202-204 ºC; IR (NaCl plate, thin film, CH₂Cl₂): 3277 (br), 3077(m), 2929 (s), 2857 (s), 1729 (s), 1369 (m), 1255(m), 1159 (m), 1090 (m), 1005(m), 914 (m), 837 (m), 809 (w), 778 (m), 759 (w), 663 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.35 (d, J = 9.0 Hz, 1H), 6.38 (d, J = 9.0 Hz, 1H), 2.97 – 2.81 (m, 2H), 2.75 – 2.63 (m, 2H), 2.21 – 2.01 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 166.3, 149.8, 139.7, 120.2, 116.8, 31.4, 29.9, 23.3. high resolution mass spectrum (ES⁺) m/z 136.0759 [(M+H)⁺; calculated for C₈H₁₀NO: 136.0762].
Melting point: 202-204 °C: IR (NaCl plate, thin film, CH₂Cl₂): 3273 (b), 2923 (m), 2871 (m), 1654 (s), 1609 (m), 1552 (m), 1456 (w), 1260 (w), 1118 (w), 840 (w), 756 (w) cm⁻¹;¹HNMR (500 MHz, CDCl₃) δ 1.7-1.83 (m, 4H), 2.47 (t, J = 6.0, 2H), 2.67 (t, J = 5.6, 2H), 6.38 (d, J = 9.0 Hz, 1H), 7.18 (d, J = 9.0 Hz, 1H).¹³CNMR (125 MHz, CDCl₃) δ 165.2, 144.1, 143.2, 116.8, 114.9, 26.8, 26.2, 22.6, 21.7; high resolution mass spectrum (ES+) m/z 150.0921 [(M+H)+; calculated for C₆H₁₂NO: 150.0919].

Melting point: 205-208 °C: IR (NaCl plate, thin film, CH₂Cl₂): 2921 (m), 2861 (m), 1650 (s), 1608 (m), 1558 (m), 1459 (m), 1415 (w), 1372 (w), 1193 (w), 1144 (w), 1107 (w), 972 (w), 829 (w), 721 (w), 668 (w) cm⁻¹;¹HNMR (500 MHz, CDCl₃) δ 6.70 (d, J = 7.4 Hz, 1H), 6.25 (d, J = 7.2 Hz, 1H), 2.33 (d, J = 8.1 Hz, 4H), 1.90 – 1.51 (m, 6H).¹³CNMR (125 MHz, CDCl₃) δ 166.2, 151.1, 142.7, 127.3, 124.3, 35.1, 31.4, 28.7, 28.3, 27.1; high resolution mass spectrum (ES+) m/z 186.0899 [(M+Na)+; calculated for C₁₀H₁₃NNaO: 186.0895].

Melting point: 207-220 °C: IR (NaCl plate, thin film, CH₂Cl₂): 3473 (br), 2920 (s), 2851 (m), 1648 (s), 1615 (m), 1550 (m), 1473 (m), 1447 (w), 1410 (w), 1262 (w), 1118 (w), 831 (w), 801 (w), 722 (w) cm⁻¹;¹HNMR (500 MHz, ) δ 7.22 (d, J = 10.4 Hz, 1H), 6.38 (d, J = 7.2 Hz, 1H), 2.72 (dt, J = 3.9, 8.4 Hz, 2H), 2.49 (dt, J = 3.8, 8.5 Hz, 2H), 1.76 (m, 2H), 1.60 (m, 2H), 1.39 (m, 4H), 1.29 (br s, 1H).¹³CNMR (125 MHz, CDCl₃) δ 165.5, 146.9, 144.4, 118.6, 117.0, 31.6, 30.0, 29.8, 29.8, 26.1, 25.8; high resolution mass spectrum (ES+) m/z 178.1229 [(M+H)+; calculated for C₁₁H₁₆NO: 178.1232].

Melting point: 205-208 °C IR (NaCl plate, thin film, CH₂Cl₂): 3256 (b), 2930 (m), 2875 (m), 1652 (s), 1615 (m), 1560 (m), 1453 (w), 1268 (w), cm⁻¹;¹HNMR (500 MHz, ) δ 6.75 (d, J = 10.9 Hz, 1H), 6.19 (d, J = 10.8 Hz, 1H), 2.50 (t, J = 5.9 Hz, 2H), 2.12 (ddd, J = 5.1, 5.4, 6.3 Hz, 1H), 1.98 (ddd, J = 5.1, 5.4, 6.4 Hz, 1H), 1.84 (ddd, J = 4.3, 4.4, 5.4
Hz, 1H), 1.77 (ddd, J = 4.8, 4.4, 5.4 Hz, 1H), 1.35 (ddd, J = 4.9 Hz, 3H), 1.46-1.37 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 165.7, 145.8, 137.8, 129.4, 111.8, 32.1, 29.7, 29.1, 22.3, 20.3; high resolution mass spectrum (ES+) m/z 164.1077 [(M+H)+; calculated for C10H14NO: 164.1075].

Melting point: 205-208 °C: IR (NaCl plate, thin film, CH2Cl2): 2921 (m), 2861 (m), 1650 (s), 1608 (m), 1558 (m), 1459 (m), 1415 (w), 1372 (w), 1193 (w), 1144 (w), 1107 (w), 972 (w), 829 (w), 721 (w), 668 (w) cm⁻¹; 1H NMR (500 MHz, CDCl3) δ 6.73 (d, J = 8.7 Hz, 1H), 6.20 (d, J = 8.8 Hz, 1H), 5.10 (t, J = 6.4 Hz, 1H), 2.63 – 2.45 (m, 3H), 2.21 (dq, J = 6.3, 4.1 Hz, 1H), 2.03 – 1.62 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 163.7, 141.1, 134.5, 128.6, 110.6, 49.9, 33.5, 29.1, 22.9; high resolution mass spectrum (ES+) m/z 228.0028 [(M+H)+; calculated for C9H11BrNO: 228.0024].

Melting point: 207-209 °C: IR (NaCl plate, thin film, CH2Cl2): 2921 (m), 2861 (m), 1650 (s), 1608 (m), 1558 (m), 1459 (m), 1415 (w), 1372 (w), 1193 (w), 1144 (w), 1107 (w), 972 (w), 829 (w), 721 (w), 668 (w) cm⁻¹; 1H NMR (500 MHz, CDCl3) δ 6.77 (d, J = 8.5 Hz, 1H), 6.11 (d, J = 8.7 Hz, 1H), 3.76 (t, J = 6.1 Hz, 1H), 3.43 (s, 3H), 2.55 (t, J = 4.6 Hz, 2H), 2.02 – 1.58 (m, 4H); 13C NMR (125 MHz, CDCl3) δ 166.5, 142.5, 138.4, 129.39, 116.9, 74.5, 56.8, 30.5, 29.1, 21.6; high resolution mass spectrum (ES+) m/z 180.1027 [(M+H)+; calculated for C10H14NO2: 180.1025].

Melting point: 215-218 °C: IR (NaCl plate, thin film, CH2Cl2): 3518(br), 3057(m), 3027(s), 2930 (s), 2849 (m), 2792 (w), 1652 (s), 1610(s), 1349 (m), 1266 (m), 1201 (m), 1153 (m), 1084 (m), 1028 (m), 924 (m), 831 (w), 734 (m) cm⁻¹; 1H NMR (500 MHz, CDCl3) δ 7.54 – 7.16 (m, 4H), 6.79 (d, J = 8.5 Hz, 1H), 6.33 (d, J = 8.8 Hz, 1H), 3.71 (s, 2H); 13C NMR (125 MHz, CDCl3) δ 164.7, 142.8, 140.9, 139.8, 136.3, 126.4, 126.0, 125.1, 118.9, 118.5, 116.4, 40.5; high resolution mass spectrum (ES+) m/z 184.0759 [(M+H)+; calculated for C12H10NO: 184.0762].
Melting point: 211-213 °C: IR (NaCl plate, thin film, CH₂Cl₂): 3413 (br), 2923 (s), 2853 (m), 1652 (s), 1464 (m), 1378 (w), 1260 (w), 668 (w) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.67 (d, J = 8.5 Hz, 1H), 6.17 (d, J = 8.5 Hz, 1H), 2.18 (t, J = 2.8 Hz, 2H) 2.16 (dd, J = 14.9, 6.3 Hz, 2H), 1.77 – 1.47 (m, 4H). ¹³C NMR (125 MHz, CDCl₃) δ 164.4, 142.4, 135.1, 126.1, 124.2, 43.9, 43.7, 42.7, 27.0, 25.0. ; high resolution mass spectrum (ES⁺) m/z 162.0917 [(M+H)⁺; calculated for C₁₀H₁₂NO: 162.0919].

β-Keto Ester 33: The ketone (55 mg, 0.37 mmol) was dissolved in tetrahydrofuran (5 mL) and cooled to -78 °C. Lithium hexamethyldisilazide (0.27 mL, 1.33M solution in toluene, 0.37 mmol, 1 equiv) was added dropwise and the mixture was stirred at -78 °C for 40 minutes. Methyl cyanoformate (35 μL, 0.44 mmol, 1.2 equiv) was added and the reaction mixture was stirred for an additional 15 minutes at -78 °C, treated with ammonium chloride (10 mL, aqueous saturated) and then warmed to ambient temperature. The mixture was poured into water (20 mL), extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried with sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel gradient chromatography (100:0 to 84:16; hexanes:ethyl acetate), providing an inseparable mixture of the β-keto ester diastereomers 33 (38.5 mg, 50% yield); ¹H NMR (500 MHz, CDCl₃) δ 3.74 (s), 3.64 (m), 3.25 (d, J = 6.3 Hz), 2.84-2.80 (m), 2.73-2.69 (m), 2.62-2.52 (m), 2.51-2.43 (m), 2.33 (br s), 2.18 (d, J = 13.8 Hz), 2.07-2.02 (m), 1.99-1.88 (m), 1.84-1.62 (m), 1.56-1.52 (m) ppm; high resolution mass spectrum (CI⁺) m/z 209.1183 [(M+H)⁺; calculated for C₁₂H₁₇O₃: 209.1178].

The β-keto esters 33 (93 mg, 0.45 mmol) were dissolved in acetone (10 mL) and transferred to a sealed tube that was charged with potassium carbonate (0.50g, 4.5 mmol, 10 equiv) and propiolamide (62 mg, 0.89 mmol, 2 equiv). The vessel was sealed and placed into an oil bath preheated to 65 °C for 48 hours. The mixture was cooled to ambient temperature, poured into water (50 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic extracts were dried with sodium sulfate, filtered and concentrated in vacuo and the residue was purified by silica gel gradient chromatography (100:0 to 95:5; dichloromethane:methanol), providing the unsaturated amide 34 (51 mg, 41% yield): ¹H-NMR (500 MHz, CD₃OD) δ 6.85 (d, J = 16.4 Hz, 1H), 6.20 (d, J = 15.6 Hz, 1H), 3.74 (s, 3H), 2.86 (t, J = 9.1 Hz, 1H), 2.58 (br m, 1H), 2.52 (br m, 1H), 2.31 (br m, 1H), 2.06 (d, J = 13.0 Hz, 1H), 2.00 (d, J= 14.9 Hz, 1H), 1.91 (t, J= 11.7 Hz, 1H),
1.82-1.64 (m, 5H); $^{13}$C-NMR (125 MHz, CD$_3$OD) δ 210.2, 172.3, 144.5, 127.3, 65.8, 53.3, 52.5, 42.8, 39.8, 38.2, 37.5, 36.8, 35.0, 32.6 ppm; high resolution mass spectrum (ES+) m/z 300.1217 [(M+Na)$^+$; calculated for C$_{16}$H$_{19}$NaNO$_4$: 300.1212].

**Pyridinone 35:**

**Basic Conditions**: The unsaturated amide 34 (24 mg, 0.086 mmol) was dissolved in dimethylsulfoxide (3 mL) and transferred to a screw capped vial and treated with sodium hydroxide (0.22 mL, 1M aqueous, 0.22 mmol, 2.5 equiv). The vial was sealed and placed into an oil bath preheated to 150 °C for 18 h. The mixture was cooled to ambient temperature, poured into water (20 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic extracts were dried with sodium sulfate, filtered and concentrated in vacuo and the residue was purified twice by silica gel chromatography (100:0 to 94:6; dichloromethane:methanol), providing the pyridinone 35 (10 mg, 59% yield).

**Neutral Conditions**: The unsaturated amide 34 (25 mg, 0.088 mmol) was dissolved in anhydrous acetonitrile (3 mL) and transferred to a screw capped vial. Tetramethylammonium acetate(15 mg, 0.88 mmol, 10 equiv) was added and the vial was sealed and placed into an oil bath preheated to 135 °C for 18 hours. The mixture was cooled to ambient temperature, poured into sodium bicarbonate (50 mL, aqueous saturated) and extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried with sodium sulfate, filtered and concentrated in vacuo and the residue was purified twice by silica gel chromatography (100:0 to 94:6; dichloromethane:methanol), providing the σ-pyridinone 35 (7.4 mg, 42% yield).

Melting point: 220-225 °C: IR (NaCl plate, thin film, CH$_2$Cl$_2$): 2921 (m), 2861 (m), 1650 (s), 1608 (m), 1558 (m), 1459 (m), 1415 (w), 1372 (w), 1193 (w), 1144 (w), 1107 (w), 972 (w), 829 (w), 721 (w), 668 (w) cm$^{-1}$; $^1$H-NMR (500 MHz, CDCl$_3$) δ 7.25 (d, $J=8.9$ Hz, 1H), 6.29 (d, $J=8.9$ Hz, 1H), 3.72 (s, 3H), 3.29 (dd, $J=9.1$, 7.6 Hz, 1H), 2.79 (br m, 1H), 2.69 (q, $J=6.2$ Hz, 1H), 2.36 (br m, 1H), 2.11-2.06 (m, 1H), 1.92 (dd, $J=12.1$, 3.5 Hz, 1H), 1.85-1.79 (m, 2H), 1.72 (dd, $J=11.0$, 2.8 Hz, 1H), 1.58 (d, $J=13.4$ Hz, 1H), 1.54 (dd, $J=12.1$, 2.8 Hz, 1H), 1.51-1.47 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$) 165.3, 153.8, 141.2, 124.5, 114.0, 43.0, 42.4, 39.5, 38.5, 35.8, 34.7, 33.4, 29.9; high resolution mass spectrum (Cl+) m/z 201.1150 [(M+Na)$^+$; calculated for C$_{13}$H$_{19}$NaNO$_4$: 201.1154].