Intramolecular Baylis-Hillman and Morita Reactions Using Unsaturated Thiol Ester Substrates Containing Enolizable Aldehydes

Gary E. Keck* and Dennie S. Welch

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112-0850

keck@chemistry.utah.edu

Supplemental Information

General Experimental

Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon: Oxford, U.K., 1966). All other reagents were purchased and used without further purification. Yields were calculated for material judged homogeneous by thin-layer chromatography and NMR. Thin layer chromatography was performed on Merck Kieselgel 60 F₂₅₄ plates, eluting with the solvents indicated. Visualization was accomplished by a 254 nm UV lamp and staining with an ethanolic solution of phosphomolybdic acid. Nuclear magnetic resonance spectra were acquired at 500 or 300 MHz for ¹H, and at 125 or 75 MHz for ¹³C (as specified below). Chemical shifts for ¹H and ¹³C NMR spectra are reported in ppm relative to the singlet at 7.27 and the center line of the triplet at 77.23 ppm, respectively. Infrared spectra were recorded on a Mattson 3000 FT-IR instrument. Column chromatography was performed with glass columns slurry-packed with Silicycle silica gel (230-400 mesh). The abbreviations s, d, t, br s, br d, m, and dd, stand for the resonance multiplicities singlet, doublet, triplet, broad single, broad doublet, doublet of doublets, respectively. Melting points were obtained on an Electro thermal melting point apparatus and are uncorrected. Analytical C & H combustion analyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. Glassware for all reactions was oven dried at 125 °C and cooled in a desiccator prior to use.

Preparation of 4-(1,1,2,2-tetramethyl-1-silapropoxy)butan-1-ol (10).¹ To a stirring solution of butane-1,4-diol (9.88 mL, 111.0 mmol) in 800 mL of THF at $-78\text{ }^{\circ}\text{C}$ was added *n*-BuLi (46.6 mL, 116.5 mmol, 2.50 M in hexane) dropwise, *via* syringe, slowly down the side of the flask. After the solution was allowed to stir for 30 min TBS-Cl (17.60 g, 116.5) was added in four equal portions, each separated by 30 minutes. The reaction mixture was allowed to slowly warm to rt. After 12 h the mixture was concentrated under reduced pressure, diluted with 300 mL of 60% EtOAc/hexanes, washed with H_2O ($2 \times 100\text{ mL}$), 100 mL of brine, dried over Na_2SO_4 , filtered, and then concentrated under reduced pressure to give 24.0 g of a crude yellow oil. Purification was accomplished by MPLC on a $5.7 \times 68\text{ cm}$ column eluting with 50% EtOAc/hexanes, collecting 25 mL fractions after 900 mL of solvent elution. The product containing fractions (13-43) were combined and concentrated under reduced pressure to give alcohol **10** (18.47 g, 81%) as a colorless oil: R_f 0.53 (50% EtOAc/hexanes); 300 MHz ^1H NMR (CDCl_3) δ 3.70-3.66 (m, 4H), 2.54 (br s, 1H), 1.69-1.60 (m, 4H), 0.91 (s, 9H), 0.08 (s, 6H); 75 MHz ^{13}C NMR (CDCl_3) δ 63.6, 63.0, 30.5, 30.1, 26.1, 18.5, -5.2; IR (neat) 3349 (br), 2932, 2859, 1469, 1254, 1102 cm^{-1} .

Preparation of 4-(1,1,2,2-tetramethyl-1-silapropoxy)butanal (11).² To a stirring solution of oxalyl chloride (2.55 mL, 29.21 mmol) in 200 mL of CH_2Cl_2 at $-78\text{ }^{\circ}\text{C}$ was slowly added DMSO (4.15 mL, 58.42), *via* syringe. After 10 min, alcohol **10** (4.00 g, 19.47 mmol) in 20 mL of CH_2Cl_2 was added *via* cannula. An additional 10 mL of CH_2Cl_2 was used to rinse, *via* cannula, the alcohol from the 25 mL flask to the reaction mixture. After the solution was stirred for 45 min at $-78\text{ }^{\circ}\text{C}$, Et_3N (13.0 mL, 93.4 mmol) was added, *via* syringe, down the side of the flask. After 1 h, the reaction mixture was allowed to slowly warm to $0\text{ }^{\circ}\text{C}$. After 30 min at $0\text{ }^{\circ}\text{C}$ TLC analysis indicated complete consumption of starting material. The reaction was quenched by addition of 50 mL of saturated aqueous NaHCO_3 solution and diluted with 500 mL of 20% EtOAc/hexanes. The layers were separated, and the organic layer was washed with H_2O ($4 \times 50\text{ mL}$) and 100 mL of brine. The organic layer was dried over MgSO_4 , filtered, and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a $4.6 \times 25\text{ cm}$ column eluting with 20% EtOAc/hexanes, collecting 8 mL fractions. The product containing fractions (40-73) were combined and concentrated under reduced pressure to give aldehyde **11** (3.13 g, 79% yield) as a colorless oil: R_f 0.50 (20% EtOAc/hexanes); 300 MHz ^1H NMR (CDCl_3) δ 9.80 (t, $J = 1.7$

¹ McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, 51, 3388.

² Danishefsky, S. J.; Pearson, W. H. *J. Org. Chem.* **1983**, 48, 3865.

Hz, 1H), 3.66 (t, $J = 6.1$ Hz, 2H), 2.51 (dt, $J = 7.1, 1.7$ Hz, 2H), 1.86 (tt, $J = 7.1, 6.1$ Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H); 75 MHz ^{13}C NMR δ 202.9, 62.3, 41.0, 26.1, 25.7, 18.5, -5.2; IR (neat) 2955, 1737, 1255, 1100 cm^{-1} .

Preparation of (2E)-1-ethylthio-6-(1,1,2,2-tetramethyl-1-sila-propoxy)hex-2-en-1-one (12). To a stirring solution of aldehyde **11** (5.45 g, 26.92 mmol) in 225 mL of CHCl_3 was added 1-ethylthio-2-(triphenylylidene)ethan-1-one (11.77 g, 32.31 mmol). After 24 h at reflux the mixture was concentrated under reduced pressure, diluted with 100 mL of 20% EtOAc/hexanes, and filtered. The filtrate was dried over Na_2SO_4 , filtered, diluted with 100 mL of 5% EtOAc/hexanes, filtered over a plug of Celite, and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 4.6×23 cm column eluting with 3% EtOAc/hexanes, collecting 8 mL fractions. The product containing fractions (30-78) were combined to give α,β -unsaturated thioester **12** (5.66 g, 73%) as the major product (15:1) as a colorless oil: thioester **12** R_f 0.36 (10% EtOAc/hexanes); 300 MHz ^1H NMR (CDCl_3) δ 6.91 (dt, $J = 15.6, 6.9$ Hz, 1H), 6.12 (dt, $J = 15.6, 1.3$ Hz, 1H), 3.63 (t, $J = 6.1$ Hz, 2H), 2.94 (q, $J = 7.4$ Hz, 2H), 2.31-2.24 (m, 2H), 1.72-1.63 (m, 2H), 1.28 (t, $J = 7.4$ Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H); 75 MHz ^{13}C NMR (CDCl_3) δ 190.3, 145.2, 129.1, 62.3, 31.2, 28.8, 26.1, 23.3, 18.5, 15.0, -5.1; IR (neat) 2954, 2857, 1674, 1634, 1471, 1254, 1104, 837 cm^{-1} ; Anal. Calcd for $\text{C}_{14}\text{H}_{28}\text{O}_2\text{SSi}$: C, 58.28; H, 9.78. Found: C, 58.11; H, 10.07.

Preparation of (2E)-1-ethylthio-6-hydroxyhex-2-en-1-one (13). To stirring thioester **12** (430.0 mg, 1.49 mmol) at rt was added 25 mL of a 90:10:1 (by volume) solution of MeOH/ H_2O /HCl. After 15 min TLC analysis indicated complete consumption of starting material. The solution was neutralized by the addition of saturated aqueous NaHCO_3 solution, then concentrated under reduced pressure and diluted with 35 mL of EtOAc and 10 mL of H_2O . The layers were separated, and the aqueous layer was extracted with 10 mL of EtOAc. The combined organic layers were washed with 10 mL of H_2O , dried over NaSO_4 ,

filtered, and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2.5×20 cm column eluting with 50% EtOAc/hexanes, collecting 8 mL fractions. The product containing fractions (33-52) were combined and concentrated under reduced pressure to give alcohol **13** (260 mg, quant. yield) as a colorless oil: R_f 0.50 (50% EtOAc/hexanes); 300 MHz ^1H NMR (CDCl_3) δ 6.91 (dt, $J = 15.6, 7.1$ Hz, 1H), 6.14 (td, $J = 15.6, 1.5$ Hz, 1H), 3.69 (t, $J = 6.4$ Hz, 2H), 2.95 (q, $J = 7.3$ Hz, 2H), 2.31 (dq, $J = 7.1, 6.4$ Hz, 2H), 1.36 (bs, 1H), 1.28 (t, $J = 7.3$ Hz, 3H); 75 MHz ^{13}C NMR (CDCl_3) δ 190.4, 144.5, 129.3, 62.2, 31.1, 28.7, 23.3, 15.0; IR (neat) 3406 (br), 2932, 2874, 1666, 1631, 1451, 1061 cm^{-1} ; HRMS m/z (CI) calcd $\text{C}_8\text{H}_{14}\text{O}_2\text{S}$ 174.07145, obsd 174.07054.

Preparation of (4E)-6-ethylthio-6-oxohex-4-enal (3). To a stirring solution of oxalyl chloride (0.30 mL, 3.42 mmol) in 20 mL of CH_2Cl_2 at -78°C was slowly added, *via* syringe, DMSO (0.49 mL, 6.84 mmol) down the side of the flask. After stirring for 10 min the alcohol **13** (397.0 mg, 2.28 mmol) in 5 mL of CH_2Cl_2 was added, *via* cannula, to the reaction mixture. An additional 5 mL of CH_2Cl_2 was used to rinse, *via* cannula, the alcohol from the flask to the reaction mixture. After the solution was stirred for 45 min at -78°C , Et_3N (1.59 mL, 11.4 mmol) was added, *via* syringe, down the side of the flask. After 30 min TLC analysis indicated complete consumption of the starting material. The reaction was quenched at -78°C by the addition of 10 mL of saturated aqueous NaHCO_3 solution and then diluted with 400 mL of 33% EtOAc/hexanes. The layers were separated, and the organic layer was washed with H_2O (4×50 mL), 50 mL of brine, dried over MgSO_4 , filtered, and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2.5×18 cm column eluting with 25% EtOAc/hexanes, collecting 4 mL fractions. The product containing fractions (24-38) were combined and concentrated under reduced pressure to give aldehyde **3** (357.1 mg, 91% yield) as a colorless oil: R_f 0.66 (50% EtOAc/hexanes); 300 MHz ^1H NMR (CDCl_3) δ 9.79 (s, 1H), 6.85 (dt, $J = 15.5, 6.7$ Hz, 1H), 6.12 (dt, $J = 15.5, 1.5$ Hz, 1H), 2.93 (q, $J = 7.4$, 2H), 2.68-2.63 (m, 2H), 2.56-2.48 (m, 1H), 1.27 (t, $J = 7.4$ Hz, 3H); 75 MHz ^{13}C NMR (CDCl_3) δ 200.4, 190.0, 142.3, 129.7, 42.0, 24.5, 23.3, 14.9; IR (neat) 2918, 2849, 1725, 1670, 1632, 1453, 1266, 1147, 1062 cm^{-1} ; HRMS m/z (CI) calcd $\text{C}_8\text{H}_{12}\text{O}_2\text{S}$ 174.05580, obsd 174.05383.

Representative Procedure for the Syntheses of Baylis-Hillman Adducts using the DMAP, DMAP·HCl protocol. Preparation of ethylthio 2-hydroxycyclopent-1(5)-enyl ketone (4). To a stirring solution of aldehyde **3** (30.0 mg, 0.174 mmol) in 1.74 mL of EtOH (absolute) in a 4 mL vial was added 4-(dimethylamino)pyridine (21.3 mg, 0.174 mmol) and 4-(dimethylamino)pyridine hydrochloride (7.0 mg, 0.044 mmol). The reaction mixture was heated at 78 °C for 1 h, after which time TLC analysis indicated complete consumption of starting material. The mixture was diluted with 100 mL of CH₂Cl₂, washed with H₂O (2 × 10 mL), brine (2 × 15 mL), dried over NaSO₄, filtered, and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 1.5 × 23 cm column eluting with 20% EtOAc/hexanes, collecting 4 mL fractions. The product containing fractions (36-45) were combined and concentrated under reduced pressure to give Baylis-Hillman adduct (**4**) (26.0 mg, 87% yield) as a colorless oil.

Representative Procedure for the Syntheses of Baylis-Hillman Adducts using PMe₃. Preparation of ethylthio 2-hydroxycyclopent-1(5)-enyl ketone (4). To a stirring solution of aldehyde **3** (34.0 mg, 0.197 mmol) in 10 mL of CH₂Cl₂ in a 15 mL round bottom flask was added trimethylphosphine (2.0 μL, 0.02 mmol). The reaction mixture was stirred at rt for 15 h after which time TLC analysis indicated complete consumption of starting material. The mixture was concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 1.75 × 20 cm column eluting with 5% EtOAc/hexanes collecting 4 mL fraction. The product containing fractions were combined and concentrated under reduced pressure to give Baylis-Hillman adduct (**4**) (28.0 mg, 82% yield) as a colorless oil.

Analytical Data for ethylthio 2-hydroxycyclopent-1(5)-enyl ketone (4). *R_f* 0.48 (50% EtOAc/hexanes); 300 MHz ¹H NMR (CDCl₃) δ 6.93 (t, *J* = 2.5 Hz, 1H), 5.22-5.10 (m, 1H), 3.05-2.88 (m, 2H), 2.80 (br d, *J* = 2.0 Hz, 1H), 2.76-2.59 (m, 1H), 2.52-2.27 (m, 2H),

1.96-1.80 (m, 1H), 1.30 (t, $J = 7.3$ Hz, 3H); 75 MHz ^{13}C NMR (CDCl_3) δ 190.4, 145.3, 144.9, 76.0, 32.0, 31.3, 23.1, 15.0; IR (neat) 3424 (br), 2966, 2929, 1656, 1615, 1266, 1163, 1056 cm^{-1} ; Anal. Calcd for $\text{C}_8\text{H}_{14}\text{O}_2\text{S}$: C, 55.78; H, 7.02; S, 18.62. Found C, 55.49; H, 6.89; S, 18.40.

Preparation of ethyl 2-hydroxy-3,3-dimethylcyclopent-1(5)-enyl ketone (6). This material was prepared according to the general DMAP, DMAP·HCl protocol using 35.0 mg (0.175 mmol) of aldehyde substrate, DMAP (1 eq.), and DMAP·HCl (0.25 eq.) in EtOH (1.74 mL, 0.1 M substrate solution) at 78 °C for 1.75 h, to give 30.7 mg of **6** (88%) after purification by flash column chromatography. This material was also prepared using 34.9 mg (0.174 mmol) of aldehyde substrate, PMe_3 (1 eq.), in CH_2Cl_2 (8.70 mL, 0.02 M substrate solution) at rt for 1 h, to give 28.9 mg of **6** (83%) after purification by flash column chromatography.

Analytical Data for ethyl 2-hydroxy-3,3-dimethylcyclopent-1(5)-enyl ketone (6). R_f 0.41 (30% EtOAc/hexanes); 300 MHz ^1H NMR (CDCl_3) δ 6.86 (t, $J = 2.7$ Hz, 1H), 4.52 (s, 1H), 3.04-2.83 (m, 2H), 2.55 (br s, 1H), 2.49-2.38 (m, 1H), 2.29-2.18 (m, 1H), 1.29 (t, $J = 7.4$ Hz, 3H), 1.10 (s, 3H); 1.09 (s, 3H); 75 MHz ^{13}C NMR (CDCl_3) δ 190.5, 144.5, 143.9, 82.4, 46.4, 42.5, 28.3, 23.0, 22.3, 15.0; IR (neat) 3415 (br), 2957, 2928, 1652, 1614, 1153, 1057, cm^{-1} ; Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2\text{S}$: C, 59.96; H, 8.05. Found C, 59.77; H, 8.10; HRMS m/z (CI) calcd $\text{C}_{10}\text{H}_{17}\text{O}_2\text{S}$ 201.09493, obsd 201.09414.

Preparation of ethylthio 2-hydroxy-4,4-dimethylcyclopent-1(5)-enyl ketone (7). This material was prepared according to the general DMAP, DMAP·HCl protocol using 30.3 mg (0.151 mmol) of aldehyde substrate, DMAP (1 eq.), DMAP·HCl (0.25 eq.), in EtOH (1.51 mL, 0.1 M substrate solution) at 78 °C for 3.5 h, to give 12.7 mg of **7** (41%) after purification by flash column chromatography. This material was also prepared using 34.8 mg (0.174 mmol) of aldehyde substrate, PMe_3 (1 eq.), in CH_2Cl_2 (8.70 mL, 0.02 M substrate solution) at rt for 1 h, to give 27.8 mg of **7** (83%) after purification by flash column chromatography.

Analytical Data for ethylthio 2-hydroxy-4,4-dimethylcyclopent-1(5)-enyl ketone (7). R_f 0.62 (30% EtOAc/hexanes); 300 MHz ^1H NMR (CDCl_3) δ 6.64 (s, 1H), 5.11 (dd, $J = 7.1, 4.7$ Hz, 1H), 3.00-2.83 (m, 2H), 2.80 (br s, 1H), 2.12 (dd, $J = 13.6, 7.4$ Hz, 1H), 1.68 (dd, $J = 13.6, 4.4$ Hz, 1H), 1.25 (t, $J = 7.3$ Hz, 3H), 1.20 (s, 3H); 1.09 (s, 3H); 75 MHz ^{13}C NMR (CDCl_3) δ 190.9, 153.6, 142.2, 75.7, 47.3, 44.6, 29.1, 28.4, 23.1, 15.0; IR (neat) 3461 (br), 2959, 2930, 1651, 1618, 1261, 1145, 813 cm^{-1} ; Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2\text{S}$: C, 59.96; H, 8.05. Found C, 59.88; H, 8.10.

Preparation of ethylthio 2-hydroxycyclohex-1(6)-enyl ketone (8). This material was prepared according to the general DMAP, DMAP·HCl protocol using 30.0 mg (0.151 mmol) of aldehyde substrate, DMAP (1 eq.), DMAP·HCl (0.25 eq.), in EtOH (1.75 mL, 0.1 M substrate solution) at 78 °C for 24 h, to give 8.7 mg of **8** (29%) after purification by flash column chromatography. This material was also prepared using 33.1 mg (0.174 mmol) of aldehyde substrate, PMe₃ (0.25 eq.), in CH₂Cl₂ (8.70 mL, 0.02 M substrate solution) at rt for 2 h, to give 24.8 mg of **8** (75%) after purification by flash column chromatography.

Analytical Data for ethylthio 2-hydroxycyclohex-1(6)-enyl ketone (8). *R_f* 0.60 (50% EtOAc/hexanes); 300 MHz ¹H NMR (CDCl₃) δ 7.10 (t, *J* = 4.0 Hz, 1H), 4.60 (br d, *J* = 1.8 Hz, 1H), 3.05-2.85 (m, 3H), 2.40- 2.25 (m, 1H), 2.24-2.09 (m, 1H), 1.93-1.53 (m, 4H), 1.28 (t, *J* = 7.4 Hz, 3H); 75 MHz ¹³C NMR (CDCl₃) δ 194.7, 141.9, 140.6, 63.7, 30.0, 26.4, 23.2, 17.5, 15.0; IR (neat) 3426 (br), 2933, 2871, 1651, 1454, 1418, 1167 cm⁻¹; Anal. Calcd for C₉H₁₄O₂S: C, 58.03; H, 7.58. Found C, 57.92; H, 7.61.

Preparation of ethyl 5-hydroxycyclopent-1-enecarboxylate (2)³. This material was prepared according to the general DMAP, DMAP·HCl protocol using 20.7 mg (0.128 mmol) of aldehyde substrate, DMAP (1 eq.), DMAP·HCl (0.25 eq.), in EtOH (1.30 mL, 0.1 M substrate solution) at 78 °C for 48 h, to give 8.2 mg of **2** (40%) after purification by flash column chromatography. This material was also prepared using 50.0 mg (0.31 mmol) of aldehyde substrate, PMe₃ (1 eq.), in CH₂Cl₂ (15.5 mL, 0.02 M substrate solution) at rt for 5.5 h, to give 16.5 mg of **2** (33%) after purification by flash column chromatography.

Analytical Data for ethyl 5-hydroxycyclopent-1-enecarboxylate (2). *R_f* 0.35 (50% EtOAc/hexanes); 300 MHz ¹H NMR (CDCl₃) δ 6.93-6.88 (m, 1H), 5.14-5.03 (m, 1H), 4.24 (q, *J* = 7.3 Hz, 2H), 2.88 (br s, 1H), 2.72-2.57 (m, 1H), 2.48-2.26 (m, 2H), 1.95-1.80 (m, 1H), 1.31 (t, *J* = 7.3 Hz, 3H); 75 MHz ¹³C NMR (CDCl₃) δ 165.3, 146.5, 138.2, 75.8, 60.7, 32.0, 31.0, 14.5; IR (neat) 3365 (br), 2918, 2850, 1734, 1652, 1161, 1062 cm⁻¹.

³ Richards, E. J.; Murphy, P. J.; Dinon, F.; Fratucello, S.; Brown, P. M.; Gelbrich, T.; Hursthouse, M. B. *Tetrahedron*, **2001**, 57, 7771.