Unexpected Facile Sequential Halolactamization-Hydroxylation of 2,3-Allenamides with CuX_2 for the Efficient Synthesis of 4-Halo-5-hydroxypyrrol-2(5H)-ones

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Supplemental Material

Experimental Section

General procedure. A solution of allenic amide (**1a~e)** (0.5 mmol) and CuX_2 (1.1~4 equiv) in THF/H_2O (1:1) (or enthanol/H_2O (3:2)) (8 mL) was stirred at 50°C. When the reaction was complete, the mixture was then quenched with saturated NH_4Cl and extracted five times with chloroform. The combined organic layer was combined and dried over Na_2SO_4. After evaporation, the residue was purified via flash chromatography on silica gel to afford **2a~2i.** All of the solid products were recrystallized from petroleum ether.

(1) 4-Bromo-1-benzyl-5-*n*-hexyl-5-hydroxy-3-methylpyrrol-2(5H)-one (2a): starting from **1a** (75 mg, 0.28 mmol) and $CuBr_2$ (68 mg, 0.30 mmol) in THF (4 mL) and H_2O (4 mL) at 50 ^oC for 18.5 h to afford 73 mg (72% yield) of **2a**; white solid, m.p. 119-119.5^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.35 (m, 2H), 7.35-7.25 (m, 3 H), 4.65 (d, *J* = 15.00 Hz, 1 H), 4.42 (d, *J* = 15.00 Hz, 1 H), 2.98 (s, 1 H), 1.92 (s, 3

H), 2.10-1.59 (m, 2 H), 1.12-0.45 (m, 8 H), 0.79 (t, *J* = 7.14 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.8, 139.2, 137.9, 134.1, 128.8, 128.5, 127.5, 92.5, 42.7, 34.3, 31.4, 28.5, 22.6, 22.4, 14.0, 10.5; MS (m/e) 368 ($M^+(^{81}Br)$+1, 22.17), 366 ($M^+(^{79}Br)$+1, 23.76), 91 (100); IR (KBr) 3303, 1677, 1072, 1026 cm^{-1}; Anal. Calcd for $C_{18}H_{24}BrNO_2$: C 59.02, H 6.60, N 3.82. Found: C 59.15, H 6.74, N 3.82.

(2) 1-Benzyl-4-chloro-5-*n*-hexyl-5-hydroxy-3-methylpyrrol-2(5H)-one (2b): starting from **1a** (91 mg, 0.34 mmol) and $CuCl_2 \cdot 2H_2O$ (63 mg, 0.37 mmol) in THF (5 mL) and H_2O (5 mL) at reflux for 21 h to afford 61 mg (57% yield) of **2b**; white solid, m.p. 101-102^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.39 (m, 2 H), 7.38-7.25 (m, 3 H), 4.65 (d, *J* = 15 Hz, 1 H), 4.43 (d, *J* = 15 Hz, 1 H), 2.81 (s, 1 H), 1.90 (s, 3 H), 1.97-1.68 (m, 2 H), 1.13-0.50 (m, 8 H), 0.79 (t, *J* = 7.15 Hz, 3 H); MS (m/e) 324 ($M^+(^{37}Cl)$+1, 0.48), 322 ($M^+(^{35}Cl)$+1, 1.46), 91 (100); IR (KBr) 3310, 1673, 1092, 1031 cm^{-1}; Anal. Calcd for $C_{18}H_{24}ClNO_2$: C 67.17, H 7.52, N 4.35. Found: C 67.13, H 7.65, N 4.19.

(3) 1-Benzyl-4-bromo-5-hydroxy-3-methylpyrrol-2(5H)-one (2c): starting from **1b** (87 mg, 0.47 mmol) and $CuBr_2$ (208 mg, 0.93 mmol) in ethanol (3 mL) and H_2O (2 mL) at 50 ^{o}C for 19 h to afford 102 mg (78% yield) of **2c**; white solid, m.p. 113-114^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.28 (m, 5 H), 5.07 (d, *J* = 10.26 Hz, 1 H), 4.97 (d, *J* = 14.84 Hz, 1 H), 4.25 (d, *J* = 14.84 Hz, 1 H), 4.09 (d, *J* = 10.26 Hz, 1 H), 1.86 (s, 3 H); MS (m/e) 283 ($M^+(^{81}Br)$, 2.09), 281 ($M^+(^{79}Br)$, 2.30), 106 (100); IR (KBr) 3294, 1665, 1065, 1023 cm^{-1}; Anal. Calcd for $C_{12}H_{12}BrNO_2$: C 51.09, H 4.29, N 4.96.

Found: C 50.75, H 4.03, N 4.85.

(4) 1-Benzyl-4-chloro-5-hydroxy-3-methylpyrrol-2(5H)-one (2d): starting from **1b** (97 mg, 0.52 mmol) and $CuCl_2 \cdot 2H_2O$ (177 mg, 1.04 mmol) in ethanol (3 mL) and H_2O (2 mL) at 50 ^oC for 22 h to afford 74 mg (60% yield) of **2d**; white solid, m.p. 99-100.5^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.25 (m, 5 H), 5.03-4.93 (m, 2 H), 4.23 (d, *J* = 14.88 Hz, 1 H), 3.23 (d, *J* = 10.37 Hz, 1 H), 1.86 (s, 3 H); MS (m/e) 239 ($M^+(^{37}Cl)$, 1.37), 237 ($M^+(^{35}Cl)$, 4.04), 106 (100); IR (KBr) 3418, 1670, 1079, 1044 cm^{-1}; Anal. Calcd for $C_{12}H_{12}ClNO_2$: C 60.64, H 5.09, N 5.89. Found: C 60.59, H 5.07, N 5.81.

(5) 4-Bromo-1-(*n*-butyl)-5-hydroxy-3-methyl-5-phenylpyrrol-2(5H)-one (2e): starting from **1c** (33 mg, 0.14 mmol) and $CuBr_2$ (65 mg, 0.29 mmol) in THF (2 mL) and H_2O (2 mL) at reflux for 24 h to afford 44 mg (94% yield) of **2e**; yellow solid, m.p. 99-100^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 5 H), 3.46 (s, 1 H), 3.41-3.31 (m, 1 H), 2.98-2.88 (m, 1 H), 1.91 (s, 3 H), 1.44-1.13 (m, 4 H), 0.77 (t, *J* = 7.24 Hz, 3 H); MS (m/e) 325 ($M^+(^{81}Br)$, 26.02), 323 ($M^+(^{79}Br)$, 25.86), 253 (100); IR (KBr) 3283, 1638, 1069, 1027 cm^{-1}; Anal. Calcd for $C_{15}H_{18}BrNO_2$: C 55.57, H 5.60, N 4.32. Found: C 55.55, H 5.60, N 4.31.

(6) 1-(*n*-Butyl)-4-chloro-5-hydroxy-3-methyl-5-phenylpyrrol-2(5H)-one (2f): starting from **1c** (70 mg, 0.31 mmol) and $CuCl_2 \cdot 2H_2O$ (208 mg, 1.22 mmol) in THF (4 mL) and H_2O (4 mL) at reflux for 5 d to afford 61 mg (71% yield) of **2f**; yellow solid, m.p. 89-90^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.39 (m, 5 H), 3.40 (s, 1 H),

3.43-3.36 (m, 1 H), 3.01-2.96 (m, 1 H), 1.96 (s, 3 H), 1.54-1.18 (m, 4 H), 0.82 (t, *J* = 7.25 Hz, 3 H); MS (m/e) 281 ($M^+(^{37}Cl)$, 7.89), 279 ($M^+(^{35}Cl)$, 21.94), 207 (100); IR (KBr) 3294, 1683, 1073, 1037 cm^{-1}; Anal. Calcd for $C_{15}H_{18}ClNO_2$: C 64.40, H 6.48, N 5.01. Found: C 64.47, H 6.44, N 4.93.

(7) 4-Bromo-5-(*n*-heptyl)-5-hydroxypyrrol-2(5H)-one (2g): starting from **1d** (72 mg, 0.40 mmol) and $CuBr_2$ (98 mg, 0.44 mmol) in THF (6 mL) and H_2O (6 mL) at 50°C for 22 h to afford 76 mg (69% yield) of **2g**; white solid, m.p. 89-90°C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (s, 1 H), 6.17 (s, 1 H), 4.05 (s, 1 H), 1.87-1.82 (m, 2 H), 1.26-1.14 (m, 10 H), 0.87 (t, *J* = 5.23 Hz, 3 H); MS (m/e) 278 ($M^+(^{81}Br)$+1, 8.77), 276 ($M^+(^{79}Br)$+1, 9.16), 258 (100); IR (KBr) 3258, 1687, 1093, 1039 cm^{-1}; Anal. Calcd for $C_{11}H_{18}BrNO_2$: C 47.84, H 6.57, N 5.07. Found: C 47.78, H 6.34, N 4.94.

(8) 1-Benzyl-4-bromo-5-(*n*-heptyl)-5-hydroxypyrrol-2(5H)-one (2h): starting from **1e** (62 mg, 0.23 mmol) and $CuBr_2$ (57 mg, 0.26 mmol) in THF (5 mL) and H_2O (5 mL) at 50°C for 32 h to afford 65 mg (78% yield) of **2h**; white solid, m.p. 120.5-122.5°C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.27 (m, 5 H), 6.33 (s, 1 H), 4.64 (d, *J* = 15.11Hz, 1 H), 4. 46 (d, *J* = 15.14 Hz, 1 H), 2.91 (s, 1 H), 1.88-1.67 (m, 2 H), 1.26-0.53 (m, 10 H), 0.86 (t, *J* = 7.13 Hz, 3 H); MS (m/e) 368 ($M^+(^{81}Br)$+1, 2.15), 366 ($M^+(^{79}Br)$+1, 2.33), 106 (100); IR (KBr) 3258, 1673, 1095, 1036 cm^{-1}; Anal. Calcd for $C_{18}H_{24}BrNO_2$: C 59.02, H 6.60, N 3.82. Found: C 58.94, H 6.44, N 3.90.

(9) 1-benzyl-4-chloro-5-(*n*-heptyl)-5-hydroxypyrrol-2(5H)-one (2i): starting from **1f** (63 mg, 0.23 mmol) and $CuCl_2 \cdot 2H_2O$ (79 mg, 0.46 mmol) in THF (5 mL) and H_2O

(5 mL) at 50°C for 3 d to afford 58 mg (78% yield) of **2j**; white solid, m.p. 120-120.5°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.23 (m, 5 H), 6.05 (s, 1 H), 4.62 (d, *J* = 15.10 Hz, 1 H), 4. 36 (d, *J* = 15.10 Hz, 1 H), 3.41 (bs, 1 H), 1.86-1.69 (m, 2 H), 1.19-0.53 (m, 10 H), 0.82 (t, *J* = 7.09 Hz, 3 H); MS (m/e) 324 ($M^+(^{37}Cl)$+1, 0.78), 322 ($M^+(^{35}Cl)$+1, 2.19), 106 (100); IR (KBr) 3264, 1674, 1096, 1035 cm^{-1}; Anal. Calcd for $C_{18}H_{24}ClNO_2$: C 67.17, H 7.52, N 4.35. Found: C 67.23, H 7.49, N 4.28.

Halolactamization of N-benzyl 2-benzyl-4-methyl-2,3-pentadienamide (1f).

(1) 4-Bromo-1, 3-dibenzyl-5, 5-dimethylpyrrol-2(5H)-one (3b): starting from **1f** (62 mg, 0.21 mmol) and $CuBr_2$ (195 mg, 0.87 mmol) in THF (4 mL) and H_2O (4 mL) at rt for 1 h to afford 70 mg (89% yield) of **3b**; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.22 (m, 10 H), 4.51 (s, 2 H), 3.70 (s, 2 H), 1.48 (s, 6 H); MS (m/e) 371 ($M^+(^{81}Br)$, 52.32), 369 ($M^+(^{79}Br)$, 54.98), 91 (100); IR (neat) 1682 cm^{-1}; Anal. Calcd for $C_{20}H_{20}BrNO$: C 64.87, H 5.44, N 3.78. Found: C 64.75, H 5.50, N 3.97.

(2) 4-Chloro-1,3-dibenzyl-5,5-dimethylpyrrol-2(5H)-one (3c): starting from **1f** (84 mg, 0.29 mmol) and $CuCl_2 \cdot 2H_2O$ (197 mg, 1.16 mmol) in THF (4 mL) and H_2O (4 mL) at rt for 3.5 h to afford 75 mg (80% yield) of **3c**; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.24 (m, 10 H), 4.64 (s, 2 H), 3.75 (s, 2 H), 1.53 (s, 6 H); MS (m/e) 327 ($M^+(^{37}Cl)$, 36.93), 325 ($M^+(^{35}Cl)$, 84.57), 91 (100); IR (neat) 1683 cm^{-1}; Anal. Calcd for $C_{20}H_{20}ClNO$: C 73.72, H 6.19, N 4.30. Found: C 73.36, H 6.09, N 4.20.