Facile 5-Endo Amidyl Radical Cyclization Promoted by Vinylic Iodine Substitution

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Supporting Information

NMR spectra were recorded in CDCl₃ (¹H at 300 MHz and ¹³C at 75.47 MHz) using TMS as the internal standard. The melting points were uncorrected. All the products were purified by column chromatography on silica gel with ethyl acetate-hexane in an appropriate ratio as the eluent. Dichloromethane was dried over CaH₂ and freshly distilled prior to use. Triethylborane (1 M solution in hexane) was commercially available and used without further purification. Boron trifluoride etherate was distilled prior to use.

N-Phenyl-4-iodo-3-octenoamide (3e). Typical procedure. Boron trifluoride etherate (2.1 mL, 17 mmol) was added to a dichloromethane (55 mL) solution of 1-hexyne (1.9 mL, 17 mmol) and N-Phenyl-iodoacetamide (2.2 g, 8.3 mmol). Triethylborane (2.0 mL, 2.0 mmol, 1.0 M solution in hexane) was added in portions. The mixture was stirred in the dark at room temperature. The reaction was monitored by TLC. After the substrate amide was consumed (20 h), the resulting mixture was poured into saturated NaHCO₃ solution (50 mL) and then extracted with dichloromethane (20 mL × 3). The combined organic layer was washed with brine, dried (Na₂SO₄) and then concentrated. The crude product was purified by flash chromatography on silica gel with hexane – ethyl acetate (4 : 1, v : v) as the eluent to afford the pure product **3e** as a white solid as a mixture of two stereoisomers (Z / E = 5 / 1, determined by ¹H NMR). Yield: 2.2 g (78%). R_f = 0.7 (hexane/ethyl acetate = 4/1). ¹H NMR (300 MHz, CDCl₃) δ 0.94 (3H, t, J = 7.2 Hz), 1.27-1.40 (2H, m), 1.51-1.61 (2H, m), 2.46/2.58 (2H, 2t, J = 7.2 Hz), 3.16/3.27 (2H, 2d, J = 8.1 Hz), 5.89/6.46 (1H, 2t, J = 7.5 Hz), 7.08-7.51 (6H, m). IR (KBr): ν (cm⁻¹) 3240, 3190, 3133, 1659, 1598, 1548. EIMS: m/z (rel intensity) 343 (M⁺, 2), 250 (1), 216 (100), 174 (3), 120 (25), 93 (32), 77 (17), 55 (18). Anal. calcd for C₁₄H₁₈NOI: C, 48.99; H, 5.29; N, 4.08. Found: C, 48.73; H, 5.12; N, 3.85.

4-Iodo-3-octenoamide (3a): White solid. R_f = 0.5 (hexane/ethyl acetate = 1/1). Yield: 68%. (Z / E

= 10 / 1, determined by ^1H NMR). ^1H NMR (300 MHz, CDCl_3) δ 0.90-0.96 (3H, m), 1.28-1.38 (2H, m), 1.49-1.59 (2H, m), 2.42/2.55 (2H, 2t, J = 7.5 Hz), 3.02/3.13 (2H, 2d, J = 7.8/6.9 Hz), 5.67 (2H, br), 5.82/6.39 (1H, 2t, J = 6.9 Hz); IR (KBr): ν (cm^{-1}) 3354, 3182, 1666, 1627. EIMS: m/z (rel intensity) 268 ($\text{M}^+ + 1$, 1), 181 (2), 167 (1), 140 (100), 123 (4), 95 (13), 81 (17), 55 (53). Anal. calcd for $\text{C}_8\text{H}_{14}\text{INO}$: C, 35.97; H, 5.28; N, 5.24. Found: C, 35.87; H, 5.11; N, 5.10.

4-Iodo-5-phenyl-3-pentenoamide (3b): White solid. R_f = 0.45 (hexane/ethyl acetate = 1/1). Yield: 64%. (Z / E = 10 / 1, determined by ^1H NMR). ^1H NMR (300 MHz, CDCl_3) δ 3.16 (2H, dd, J = 6.9, 1.0 Hz), 3.85/3.91 (2H, 2s), 5.67 (2H, br), 5.92-5.98/6.54-6.59 (1H, 2m), 7.19-7.36 (5H, m). IR (KBr): ν (cm^{-1}) 3393, 3202, 3060, 1654, 1623. EIMS: m/z (rel intensity) 174 (100), 157 (4), 129 (34), 115 (24), 91 (47), 77 (8), 53 (13), 44 (23). Anal. calcd for $\text{C}_{11}\text{H}_{12}\text{INO}$: C, 43.87; H, 4.02; N, 4.65. Found: C, 43.76; H, 4.23; N, 4.42.

5-Ethoxycarbonyl-4-iodo-3-pentenoamide (3c): White solid. R_f = 0.4 (hexane/ethyl acetate = 1/1). Yield: 69%. ($Z:E$ = 5:1, determined by ^1H NMR). ^1H NMR (300 MHz, CDCl_3) δ 1.27-1.36 (3H, m), 3.02/3.18 (2H, 2d, J = 8.1/7.2 Hz), 3.71/3.73 (2H, 2s), 4.22 (2H, q, J = 6.3 Hz), 5.52 (1H, br), 6.00/6.62 (1H, 2t, J = 7.2 Hz), 6.05 (1H, br). EIMS: m/z (rel intensity) 252 (3), 224 (3), 197 (2), 170 (100), 124 (23), 96 (27), 53(42), 44 (30). Anal. calcd for $\text{C}_8\text{H}_{12}\text{INO}_3$: C, 32.24; H, 4.07; N, 4.71. Found: C, 32.32; H, 3.96; N, 4.57.

4-Iodo-2-methyl-3-octenoamide (3d): R_f = 0.6 (hexane/ethyl acetate = 1/1). Yield: 89%. (Z / E = 10 / 1 determined by ^1H NMR). ^1H NMR (300 MHz, CDCl_3) δ 0.89-0.95 (3H, m), 1.26-1.34 (5H, m), 1.50-1.55 (2H, m), 2.51 (2H, t, J = 7.5 Hz), 3.21-3.34 (1H, m), 5.44 (1H, br), 5.57 (1H, d, J = 9.0 Hz), 5.62 (1H, br). EIMS: m/z (rel intensity) 282 ($\text{M}^+ + 1$, 1), 237 (1), 195 (3), 169 (1), 154 (100), 110 (11), 81 (15), 69 (17), 55 (15). Anal. calcd for $\text{C}_9\text{H}_{16}\text{INO}$: C, 38.45; H, 5.74; N, 4.98. Found: C, 38.41; H, 5.73; N, 4.80.

N-Phenyl-4-iodo-2-methyl-3-octenoamide (3f): White solid. R_f = 0.6 (hexane/ethyl acetate = 4/1). Yield: 90%. (Z / E = 2.5 / 1 determined by ^1H NMR). ^1H NMR (300 MHz, CDCl_3) δ 0.91-0.95 (3H, m), 1.26-1.38 (5H, m), 1.53-1.60 (2H, m), 2.43-2.54 (2H, m), 3.32-3.48 (1H, m), 5.64/6.35 (1H, 2d, J = 9.9/10.8 Hz), 7.27-7.53 (6H, m). EIMS: m/z (rel intensity) 357 (M^+ , 3), 230 (100), 186 (2), 172 (3), 120 (26), 93 (13), 77 (14), 55 (11). Anal. calcd for $\text{C}_{15}\text{H}_{20}\text{INO}$: C, 50.43; H, 5.64; N, 3.92. Found: C, 50.39; H, 5.80; N, 3.74.

N-Methyl-4-iodo-3-octenoamide (3g): Colorless oil. R_f = 0.4 (hexane/ethyl acetate = 4/1). Yield: 72%. (Z / E = 6 / 1 determined by ^1H NMR). ^1H NMR (300 MHz, CDCl_3) δ 0.92 (3H, t, J = 7.2 Hz), 1.25-1.37 (2H, m), 1.43-1.58 (2H, m), 2.40/2.53 (2H, 2t, J = 7.2 Hz), 2.81/2.83 (3H, 2s), 3.11 (2H, d,

$J = 6.9$ Hz), 5.62 (1H, br), 5.78/6.34 (1H, 2t, $J = 6.9/7.8$ Hz). IR (KBr): ν (cm^{-1}) 3298, 3095, 1652, 1563. EIMS: m/z (rel intensity) 282 ($M^+ + 1$, 1), 223 (1), 182 (2), 154 (100), 112 (3), 95 (7), 81 (6), 58 (71), 55 (37). Anal. calcd for $\text{C}_9\text{H}_{16}\text{INO}$: C, 38.45; H, 5.74; N, 4.98. Found: C, 38.65; H, 5.72; N, 4.73.

5-Butylidene-1-phenyl-1,5-dihydropyrrol-2-one (8e). **Typical procedure.** *tert*-Butyl hypochlorite (0.043 mL, 0.38 mmol) was added to a dichloromethane (5 mL) solution of iodine (97 mg, 0.38 mmol) and *N*-phenyl-4-iodo-3-octenoamide (**3e**) (87 mg, 0.25 mmol) and the mixture was stirred under nitrogen in the dark at room temperature. The reaction was monitored by TLC. After the substrate amide disappeared (10 h), the mixture was treated with an excess of aqueous sodium thiosulfate and then extracted with dichloromethane (10 mL $\times$ 3). The combined organic layer was washed with brine, dried (Na_2SO_4) and then concentrated. The crude product was purified by flash chromatography on silica gel with hexane – ethyl acetate (4 : 1, v : v) as the eluent to afford the pure product **8e** as a yellowish oil. Yield: 34 mg (63%). $R_f = 0.5$ (hexane/ethyl acetate = 4/1). ^1H NMR (300 MHz, CDCl_3) δ 0.91 (3H, t, $J = 7.5$ Hz), 1.39-1.51 (2H, m), 2.31 (2H, q, $J = 7.5$ Hz), 5.37 (1H, td, $J = 8.7, 1.2$ Hz), 6.29 (1H, dd, $J = 6.0, 1.5$ Hz), 7.26-7.50 (6H, m). ^{13}C NMR (CDCl_3) δ 169.7, 141.0, 134.4, 132.6, 129.2, 128.2, 127.7, 123.7, 117.1, 29.5, 23.1, 13.6. IR (KBr): ν (cm^{-1}) 3060, 1699, 1598, 1500. EIMS: m/z (rel intensity) 213 (M^+ , 100), 184 (99), 156 (58), 146 (52), 128 (25), 93 (77), 77 (45), 55 (38). HRMS calcd for $\text{C}_{14}\text{H}_{15}\text{NO}$: 213.1154, Found: 213.1171.

5-Butyl-4-iodo-3,4-dihydropyrrol-2-one (8a): Yellowish oil. $R_f = 0.4$ (hexane/ethyl acetate = 8/1). ^1H NMR (300 MHz, CDCl_3) δ 0.93 (3H, t, $J = 7.2$ Hz), 1.30-1.40 (2H, m), 1.60-1.70 (2H, m), 2.60 (1H, dt, $J = 16.8, 6.9$ Hz), 2.95-3.06 (2H, m), 3.19 (1H, dd, $J = 17.1, 6.9$ Hz), 4.69-4.74 (1H, m). ^{13}C NMR (CDCl_3) δ 202.2, 117.5, 38.7, 26.2, 23.7, 22.0, 19.8, 13.7. IR (KBr): ν (cm^{-1}) 1710, 1672. EIMS: m/z (rel intensity) 265 (M^+ , 1), 208 (1), 180 (6), 138 (5), 111 (9), 96 (5), 85 (100), 57 (68). HRMS calcd for $\text{C}_8\text{H}_{12}\text{INO}$: 264.9964, Found: 264.9997.

5-Benzyl-4-iodo-3,4-dihydropyrrol-2-one (8b): Yellowish oil. $R_f = 0.2$ (hexane/ethyl acetate = 8/1). ^1H NMR (300 MHz, CDCl_3) δ 3.00 (1H, dd, $J = 7.2, 17.1$ Hz), 3.13 (1H, dd, $J = 6.6, 17.1$ Hz), 4.09 (2H, AB, $J = 15.3$ Hz), 4.73-4.78 (1H, m), 7.23-7.40 (5H, m). ^{13}C NMR (CDCl_3) δ 199.5, 132.8, 129.3, 129.1, 127.7, 117.3, 45.7, 23.8, 18.5. EIMS: m/z (rel intensity) 299 (M^+ , 13), 208 (1), 180 (2), 172 (2), 119 (15), 91 (100), 65 (17), 52 (4). HRMS calcd for $\text{C}_{11}\text{H}_{10}\text{INO}$: 298.9807, Found: 298.9807.

5-Ethoxycarbonylmethyl-4-iodo-3,4-dihydropyrrol-2-one (8c): Yellowish oil. $R_f = 0.5$ (hexane/ethyl acetate = 4/1). ^1H NMR (300 MHz, CDCl_3) δ 1.26-1.33 (3H, m), 3.08 (1H, dd, $J = 17.4, 8.1$ Hz), 3.22 (1H, dd, $J = 6.0, 17.4$ Hz), 3.62 (1H, dd, $J = 16.2, 2.4$ Hz), 3.99 (1H, d, $J = 16.2$ Hz),

4.19-4.26 (2H, m), 5.05-5.10 (1H, m). ^{13}C NMR (300 MHz, CDCl_3) δ 194.6, 166.7, 117.1, 62.1, 44.9, 23.6, 20.0, 14.0. EIMS: m/z (rel intensity) 295 (M^+ , 8), 250 (19), 208 (20), 168 (43), 115 (85), 85 (74), 71 (86), 57 (100), 43 (90). HRMS calcd for $\text{C}_8\text{H}_{10}\text{INO}_3$: 294.9705, Found: 294.9692.

5-Butyl-4-iodo-3-methyl-3,4-dihydropyrrol-2-one (8d): The mixture of two stereoisomers in about 6 to 1 (trans to cis) ratio determined by ^1H NMR. Yellowish oil. R_f = 0.5 (hexane/ethyl acetate = 8/1).

^1H NMR (300 MHz, CDCl_3) δ 0.93 (3H, t, J = 7.2 Hz), 1.26-1.40 (2H, m), 1.51 (3H, d, J = 7.2 Hz), 1.60-1.68 (2H, m), 2.52-2.68 (1H, m), 2.89-3.01 (1H, m), 3.08-3.18 (1H, m), 4.55/4.61 (1H, 2d, J = 8.1 Hz). ^{13}C NMR (CDCl_3) δ 202.3/202.0, 118.9/120.8, 39.2/39.4, 30.4, 28.7/29.7, 26.1/26.2, 22.0/21.9, 18.5/17.7, 13.7. EIMS: m/z (rel intensity) 279 (M^+ , 1), 222 (1), 194 (2), 168 (2), 125 (7), 85 (100), 57 (68), 41 (24). HRMS calcd for $\text{C}_9\text{H}_{14}\text{INONa}$ ($\text{M} + \text{Na}$): 302.0039, Found: 302.0023.

(E)-5-Butylidene-3-methyl-1-phenyl-1,5-dihydropyrrol-2-one (8f): Yellowish oil. R_f = 0.3 (hexane/ethyl acetate = 8/1). ^1H NMR (300 MHz, CDCl_3) δ 0.97-0.86 (3H, m), 1.22-1.51 (2H, m), 2.06 (3H, s), 2.23-2.34 (2H, m), 5.21-5.26 (1H, m), 7.08-7.50 (6H, m). ^{13}C NMR (CDCl_3) δ 170.0, 139.7, 134.9, 132.9, 129.1, 128.1, 127.4, 127.0, 114.2, 29.6, 29.3, 23.2, 13.6, 11.1. EIMS: m/z (rel intensity) 227 (M^+ , 62), 198 (100), 187 (28), 170 (19), 156 (14), 130 (8), 77 (25), 55 (23). HRMS calcd for $\text{C}_{15}\text{H}_{18}\text{NO}$ ($\text{M} + \text{H}$): 228.1398, Found: 228.1383.

(E)-5-Butylidene-1-(4-iodophenyl)-1,5-dihydropyrrol-2-one (9): ^1H NMR (300 MHz, CDCl_3) δ 0.92 (3H, t, J = 7.5 Hz), 1.40-1.52 (2H, m), 2.27-2.35 (2H, m), 5.36 (1H, td, J = 8.4, 1.2 Hz), 6.28 (1H, dd, J = 6.0, 1.5 Hz), 7.20-7.27 (2H, m), 7.44 (1H, d, J = 6.0 Hz), 7.75-7.82 (2H, m); EIMS: m/z (rel intensity) 339 (M^+ , 4), 310 (1), 213 (66), 184 (100), 156 (49), 128 (18), 77 (40), 51 (17); Anal. calcd for $\text{C}_{14}\text{H}_{14}\text{INO}$: C, 49.58; H, 4.16; N, 4.13. Found: C, 49.54; H, 4.05; N, 4.02. The structure was further confirmed by its X-ray diffraction analysis.

(E)-N-Phenyl-3-octenoamide (10): ^1H NMR (300 MHz, CDCl_3) δ 0.84 (3H, t, J = 6.9 Hz), 1.18-1.36 (4H, m), 1.99-2.06 (2H, m), 3.03 (2H, d, J = 6.9 Hz), 5.54-5.65 (2H, m), 7.02 (1H, t, J = 7.8 Hz), 7.24 (2H, t, J = 8.1 Hz), 7.43 (2H, d, J = 8.4 Hz), 7.50 (1H, br). IR (KBr): ν (cm^{-1}) 3294, 1662, 1598, 1531. EIMS: m/z (rel intensity) 217 (M^+ , 24), 188 (4), 175 (4), 135 (10), 120 (21), 93 (100), 77 (19), 55 (23). Anal. calcd for $\text{C}_{14}\text{H}_{19}\text{NO}$: C, 77.83; H, 8.81; N, 6.45. Found: C, 77.42; H, 9.09; N, 6.21.

(Z)-5-Ethoxycarbonylmethylene-1,5-dihydropyrrol-2-one (15): R_f = 0.8 (hexane/ethyl acetate = 4/1). ^1H NMR (300 MHz, CDCl_3) δ 1.18-1.27 (3H, m), 4.19 (2H, q, J = 6.3 Hz), 5.21 (1H, s), 6.14 (1H, d, J = 16.2 Hz), 6.63 (1H, d, J = 16.5 Hz), 11.62 (1H, s). ^{13}C NMR (CDCl_3) δ 171.6, 163.8,

143.0, 116.6, 104.4, 97.2, 61.1, 14.1. EIMS: m/z (rel intensity) 167 (M^+ , 51), 139 (29), 122 (95), 93 (100), 80 (94), 69 (25), 52 (30). HRMS calcd for $C_8H_9NO_3$: 167.0582. Found: 167.0580.

References for known compounds:

8g: *J. Org. Chem.* **1984**, 49, 551.

11: *J. Org. Chem.* **1994**, 59, 284.

Figure 1. ORTEP representation of compound **9**.