Synthesis of Lactams via Copper-Catalyzed Intramolecular Vinylation of Amides

Tianshun Hu and Chaozhong Li*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354
Fenglin Road, Shanghai 200032, P. R. China

clig@mail.sioc.ac.cn

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Copper (I) iodide (98%) was purified by refluxing in THF at soxhlet. Cesium carbonate was purchased and used without further purification. *N,N'*-dimethylethylenediamine was synthesized according to the literature method.^[1] Dioxane was dried over Na and freshly distilled prior to use. The iodoenamides **1a-k** and **12** were prepared according to the literature methods.^[2-7] Flash column chromatography was performed on silica gel (300-400 mesh) with ethyl acetate-hexane (or acetone-hexane) in an appropriate ratio as the eluent. ¹H NMR and ¹³C NMR spectra were recorded on a 300 MHz NMR spectrometer with TMS as the internal standard.

(Z)-5-Iodo-N-phenylpent-4-enamide (1a). White solid. Yield: 72%. ¹H NMR (300 MHz, CDCl₃) δ 2.46-2.51 (2H, m), 2.54-2.60 (2H, m), 6.26-6.33 (2H, m), 7.11 (1H, t, *J* = 7.5 Hz), 7.26-7.34 (2H, t, *J* = 7.5 Hz), 7.38 (1H, br), 7.51 (2H, d, *J* = 7.2 Hz). ¹³C NMR (CDCl₃) δ 32.7, 37.3, 86.0, 122.3, 126.3, 130.9, 139.8, 141.3, 172.5. EIMS: *m/z* (rel intensity) 301 (*M*⁺, 1), 209 (1), 181 (8), 174 (92), 167 (7), 120 (9), 93 (100), 77 (13). HRMS calcd for C₁₁H₁₃INO (*M*⁺+1): 302.0042. Found: 302.0037. Anal. calcd for C₁₁H₁₂INO: C, 43.87; H, 4.02; N, 4.65. Found: C, 43.63; H, 4.18; N, 4.41.

(Z)-6-Iodo-N-phenylhex-5-enamide (1b). White solid. Yield: 54%. ¹H NMR (300 MHz, CDCl₃) δ 1.82-1.92 (2H, m), 2.19-2.26 (2H, m), 2.32-2.40 (2H, m), 6.12-6.25 (2H, m), 7.09 (1H, t, *J* = 8.4 Hz), 7.26-7.33 (2H, m), 7.52 (2H, d, *J* = 8.7 Hz), 7.67 (1H, br). ¹³C NMR (CDCl₃) δ 23.7, 34.1, 36.6, 83.5, 119.9, 124.2, 128.9, 137.8, 140.3, 170.9. EIMS: *m/z* (rel intensity) 315 (*M*⁺, 2), 188 (54), 163 (10), 135 (27), 120 (4), 93 (100), 77 (9), 65 (12). HRMS calcd for C₁₂H₁₅INO (*M*⁺+1): 316.0198. Found: 316.0194.

(Z)-6-Iodo-N-phenylhex-5-enamide (1c). White solid. Yield: 69%. ¹H NMR (300 MHz, CDCl₃) δ 1.75-2.09 (2H, m), 2.18-2.29 (4H, m), 5.70 (1H, br), 5.98 (1H, br), 6.14-6.27 (2H, m). ¹³C NMR (CDCl₃) δ 23.6, 34.0, 34.9, 83.4, 140.2, 175.0. EIMS: *m/z* (rel intensity) 240 (*M*⁺+1, 1), 181 (0.2), 167 (3), 127 (1), 112 (59), 86 (7), 72 (13), 59 (100). Anal. calcd for C₆H₁₀INO: C, 30.15; H, 4.22; N, 5.86. Found: C, 30.47; H, 4.44; N, 5.94.

(Z)-6-Iodo-N-methylhex-5-enamide (1d). Yellow oil. Yield: 66%. ¹H NMR (300 MHz, CDCl₃) δ 1.76-1.86 (2H, m), 2.16-2.23 (4H, m), 2.811 (3H, d, *J* = 5.1 Hz), 5.99 (1H, br), 6.13-6.26 (2H, m). ¹³C NMR (CDCl₃) δ 23.9, 26.3, 34.1, 35.7, 83.3, 140.4, 173.1. EIMS: *m/z* (rel intensity) 254 (*M*⁺+1, 1), 167 (7), 126 (96), 116 (3), 86 (4), 73 (100), 58 (69), 39 (18). HRMS calcd for C₇H₁₃INO (*M*⁺+1): 254.0042. Found: 254.0043.

4-Iodo-N-phenylpent-4-enamide (1e): White solid. Yield: 64%. ¹H NMR (300 MHz, CDCl₃) δ 2.58 (2H, t, *J* = 7.5 Hz), 2.82 (2H, t, *J* = 7.5 Hz), 5.75 (1H, d, *J* = 1.2 Hz), 6.16 (1H, d, *J* = 1.2 Hz),

7.12 (1H, t, $J = 7.8$ Hz), 7.23 (1H, br), 7.33 (2H, t, $J = 7.5$ Hz), 7.50 (1H, d, $J = 7.5$ Hz). ^{13}C NMR (CDCl_3) δ 39.1, 42.9, 111.5, 122.0, 126.4, 129.1, 130.9, 139.8, 171.4. EIMS: m/z (rel intensity) 301 (M^+ , 1), 174 (100), 167 (1), 120 (9), 106 (2), 93 (38), 77 (8), 65 (8). HRMS calcd for $\text{C}_{11}\text{H}_{12}\text{INO}$ (M^+): 300.9964. Found: 300.9943. Anal. calcd for $\text{C}_{11}\text{H}_{12}\text{INO}$: C, 43.87; H, 4.02; N, 4.65. Found: C, 43.96; H, 4.01; N, 4.61.

5-Iodo-*N*-phenylhex-5-enamide (1f). Yellow oil. Yield: 61%. ^1H NMR (300 MHz, CDCl_3) δ 1.80-2.01 (2H, m), 2.36 (2H, t, $J = 7.5$ Hz), 2.46-2.52 (2H, m), 5.76 (1H, s), 6.09 (1H, s), 7.11 (1H, t, $J = 7.8$ Hz), 7.18 (1H, br), 7.33 (2H, t, $J = 7.8$ Hz), 7.51 (2H, d, $J = 8.1$ Hz). ^{13}C NMR (CDCl_3) δ 24.6, 35.4, 44.1, 111.1, 119.9, 124.3, 126.4, 128.9, 137.8, 170.6. EIMS: m/z (rel intensity) 315 (M^+ , 1), 237 (4), 223 (2), 194 (42), 188 (100), 167 (1), 112 (8), 93 (30). Anal. calcd for $\text{C}_{12}\text{H}_{14}\text{INO}$: C, 45.73; H, 4.48; N, 4.44. Found: C, 45.89; H, 4.32; N, 4.37.

5-Iodohept-5-enamide (1g). White solid. Yield: 60%. ^1H NMR (300 MHz, CDCl_3) δ 1.81-1.93 (2H, m), 2.23 (2H, t, $J = 7.5$ Hz), 2.46 (2H, t, $J = 7.2$ Hz), 5.42 (2H, br), 5.75 (1H, t, $J = 0.6$ Hz), 6.07-6.08 (1H, m). ^{13}C NMR (CDCl_3) δ 24.4, 33.7, 44.1, 111.0, 126.2, 175.4. EIMS: m/z (rel intensity) 240 ($\text{M}^+ + 1$, 1), 167 (1), 127 (4), 112 (97), 95 (5), 69 (58), 59 (14), 44 (100). Anal. calcd for $\text{C}_6\text{H}_{10}\text{INO}$: C, 30.15; H, 4.22; N, 5.86. Found: C, 30.52; H, 4.35; N, 6.01.

6-Iodo-*N*-phenylhept-6-enamide (1h). White solid. Yield: 58%. ^1H NMR (300 MHz, CDCl_3) δ 1.54-1.59 (2H, m), 1.66-1.74 (2H, m), 2.34-2.42 (4H, m), 5.69 (1H, s), 6.01 (1H, d, $J = 1.2$ Hz), 7.09 (1H, t, $J = 7.5$ Hz), 7.26-7.33 (2H, m), 7.52 (2H, d, $J = 7.5$ Hz), 7.67 (1H, br). ^{13}C NMR (CDCl_3) δ 24.0, 28.5, 37.3, 44.9, 111.7, 119.8, 124.2, 125.8, 128.9, 137.8, 171.0. EIMS: m/z (rel intensity) 329 (M^+ , 2), 202 (100), 160 (4), 135 (5), 120 (15), 93 (98), 81 (16), 65 (12). HRMS calcd for $\text{C}_{13}\text{H}_{17}\text{INO}$ ($\text{M}^+ + 1$): 330.0355. Found: 330.0358.

6-Iodohept-6-enamide (1i). White solid. Yield: 71%. ^1H NMR (300 MHz, CDCl_3) δ 1.56-1.68 (4H, m), 2.26 (2H, t, $J = 7.2$ Hz), 2.39-2.44 (2H, m), 5.52 (2H, br), 5.70 (1H, t, $J = 0.9$ Hz), 6.03-6.05 (1H, m). ^{13}C NMR (CDCl_3) δ 23.9, 28.5, 35.5, 44.9, 111.8, 125.8, 175.0. EIMS: m/z (rel intensity) 254 ($\text{M}^+ + 1$, 28), 237 (1), 167 (3), 126 (100), 109 (8), 84 (11), 67 (6), 55 (17). HRMS calcd for $\text{C}_7\text{H}_{13}\text{INO}$ ($\text{M}^+ + 1$): 254.0042. Found: 254.0046.

4-(2-Iodocyclohexen-3-yl)-*N*-phenylbutanamide (1j). Yellowish Solid. Yield: 63%. ^1H NMR (300 MHz, CDCl_3) δ 1.58-1.72 (4H, m), 1.79-1.95 (4H, m), 2.04-2.06 (2H, m), 2.32-2.43 (3H, m), 6.37-6.40 (1H, m), 7.10 (1H, t, $J = 7.2$ Hz), 7.27 (2H, t, $J = 7.5$ Hz), 7.40 (1H, br), 7.53 (2H, d, $J = 8.1$ Hz). ^{13}C NMR (CDCl_3) δ 18.4, 22.7, 27.9, 29.5, 34.2, 37.6, 44.6, 106.2, 119.8, 124.2, 128.9,

138.0, 138.9, 171.1. EIMS: m/z (rel intensity) 242 (M^+ -127, 1), 167 (2), 127 (3), 112 (100), 95 (5), 69 (37), 59 (7), 44 (31). Anal. calcd for $C_{16}H_{20}INO$: C, 52.04; H, 5.46; N, 3.79. Found: C, 52.38; H, 5.74; N, 3.90.

4-(2-Iodocyclohexen-3-yl)butanamide (1k). White solid. Yield: 48%. 1H NMR (300 MHz, $CDCl_3$) δ 1.59-1.86 (8H, m), 2.03-2.08 (2H, m), 2.22-2.32 (3H, m), 5.55 (1H, br), 5.73 (1H, br), 6.38-6.40 (1H, m). ^{13}C NMR ($CDCl_3$) δ 18.4, 22.6, 27.9, 29.5, 34.2, 35.8, 44.6, 106.2, 138.9, 175.4. EIMS: m/z (rel intensity) 294 (M^+ , 1), 242 (100), 227 (3), 213 (9), 148 (11), 131 (10), 107 (19), 93 (66). Anal. calcd for $C_{10}H_{16}INO$: C, 40.97; H, 5.50; N, 4.78. Found: C, 41.15; H, 5.43; N, 4.69.

3-(2-Iodoallyloxy)propanamide (12). White solid. Yield: 56%. 1H NMR (300 MHz, $CDCl_3$) δ 2.55 (2H, t, $J = 5.4$ Hz), 3.70-3.74 (2H, m), 4.09 (2H, d, $J = 1.2$ Hz), 5.93- 5.96 (1H, m), 5.53 (1H, br), 5.94 (1H, d, $J = 0.9$ Hz), 6.23 (1H, br), 6.38 (1H, d, $J = 1.5$ Hz). ^{13}C NMR ($CDCl_3$) δ 36.4, 65.9, 78.5, 106.5, 127.0, 173.7. EIMS: m/z (rel intensity) 256 (M^++1 , 1), 167 (12), 153 (1), 128 (12), 111 (1), 88 (8), 72 (100), 7 (8). HRMS calcd for $C_6H_{11}INO_2$ (M^++1): 255.9834. Found: 255.9835. Anal. calcd for $C_6H_{10}INO_2$: C, 28.25; H, 3.95; N, 5.49. Found: C, 27.96; H, 3.93; N, 5.44.

Typical procedure for the intramolecular vinylation of iodoenamides.

CuI (7.6 mg, 0.04 mmol), iodoenamide (0.2 mmol) and Cs_2CO_3 (130 mg, 0.4 mmol) were added to a round flask under nitrogen. N,N' -Dimethylethylenediamine (8.6 μ L, 0.08 mmol) and dioxane (6.7 mL) was then added under nitrogen. The reaction mixture was stirred at refluxing temperature for 20 h and then cooled down to room temperature. Ethyl acetate (20 mL) was added and the mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was then purified by column chromatography on silica gel.

1-Phenyl-3,4-dihydro-pyridin-2-one (2a). White solid. 1H NMR (300 MHz, $CDCl_3$) δ 2.41-2.48 (2H, m), 2.68-2.73 (2H, t, $J = 7.5$ Hz), 5.25-5.30 (1H, m), 6.25-6.29 (1H, m), 7.25-7.30 (3H, m), 7.37-7.43 (2H, m). ^{13}C NMR ($CDCl_3$) δ 23.1, 34.9, 109.4, 128.8, 129.7, 131.8, 133.7, 143.0, 171.8. EIMS: m/z (rel intensity) 173 (M^+ , 100), 144 (21), 130 (52), 118 (8), 104 (20), 93 (6), 77 (31), 51 (10). HRMS calcd for $C_{11}H_{12}NO$ (M^++1): 174.0919. Found: 174.0916. Anal. calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.05; H, 6.42; N, 7.76.

1-Phenyl-2,3,4,5-tetrahydro-1H-azepin-2-one (2b). Yellowish oil. 1H NMR (300 MHz, $CDCl_3$) δ 2.10-2.18 (2H, m), 2.22-2.29 (2H, m), 2.61-2.65 (2H, m), 5.54-5.61 (1H, m), 5.99-6.02 (1H, m), 7.17-7.22 (3H, m), 7.27-7.33 (2H, m). ^{13}C NMR ($CDCl_3$) δ 24.7, 28.4, 35.9, 119.5, 126.0, 126.6, 128.8, 130.9, 140.8, 174.2. EIMS: m/z (rel intensity) 187 (M^+ , 37), 132 (100), 116 (16), 68 (3), 105

(30), 93 (5), 77 (50), 51 (21). HRMS calcd for $C_{12}H_{14}NO$ ($M^+ + 1$): 188.1075. Found: 188.1081. Anal. calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.84; H, 7.11; N, 7.35.

6-Methylene-1-phenylpiperidin-2-one (2f). White solid. 1H NMR (300 MHz, $CDCl_3$) δ 1.83-1.91 (2H, m), 2.55- 2.63 (4H, m), 3.52 (1H, d, $J = 6.0$ Hz), 4.01 (1H, d, $J = 5.7$ Hz), 7.04-7.09 (2H, m), 7.26-7.31 (1H, m), 7.33-7.41 (2H, m). ^{13}C NMR ($CDCl_3$) δ 19.6, 20.2, 32.0, 104.7, 127.7, 128.8, 129.0, 136.7, 138.5, 170.9. EIMS: m/z (rel intensity) 187 (M^+ , 100), 172 (6), 158 (35), 144 (47), 130 (45), 118 (46), 104 (4), 77 (68). HRMS calcd for $C_{12}H_{13}NO$ (M^+): 187.0997. Found: 187.0980.

7-Methylene-1-phenyl-2,3,4,5,6,7-hexahydro-1H-azepin-2-one (2h). Colorless oil. 1H NMR (300 MHz, $CDCl_3$) δ 1.83-1.91 (4H, m), 2.54 (2H, t, $J = 6.3$ Hz), 2.67 (2H, t, $J = 6.6$ Hz), 4.80 (1H, s), 5.05 (1H, s), 7.19-7.26 (3H, m), 7.32-7.38 (2H, m). ^{13}C NMR ($CDCl_3$) δ 22.9, 29.6, 35.6, 37.2, 113.0, 126.1, 126.2, 128.9, 143.5, 150.8, 173.5. EIMS: m/z (rel intensity) 201 (M^+ , 96), 172 (100), 158 (27), 144 (94), 130 (46), 117 (29), 93 (31), 77 (86). HRMS calcd for $C_{13}H_{15}NO$ ($M^+ + 1$): 202.1232. Found: 202.1230.

7-Methyl-2,3,4,5-tetrahydro-1H-azepin-2-one (2i). Yellowish oil. 1H NMR (300 MHz, $CDCl_3$) δ 1.82 (3H, d, $J = 1.2$ Hz), 1.94-2.03 (2H, m), 2.17-2.24 (2H, m), 2.50-2.54 (2H, m), 5.04-5.08 (1H, m), 6.64 (1H, br). ^{13}C NMR ($CDCl_3$) δ 23.0, 24.7, 27.1, 36.0, 111.5, 131.2, 175.7. EIMS: m/z (rel intensity) 125 (M^+ , 33), 110 (7), 105 (2), 97 (10), 82 (10), 70 (100), 59 (13), 43 (9). HRMS calcd for C_7H_9NO (M^+): 125.0841. Found: 125.0846.

1-Phenyl-2,3,4,5,5a,6,7,8-octahydro-1(1H)-benzazepin-2-one (2j). Yellowish oil. 1H NMR (300 MHz, $CDCl_3$) δ 1.63-1.88 (8H, m), 1.93-2.02 (1H, m), 2.04-2.22 (1H, m), 2.35-2.41 (1H, m), 2.50-2.57 (1H, m), 2.64-2.73 (1H, m), 5.64 (1H, t, $J = 3.6$ Hz), 7.15-7.35 (5H, m). ^{13}C NMR ($CDCl_3$) δ 17.6, 22.5, 25.0, 29.3, 35.2, 36.9, 38.1, 125.4, 125.7, 127.9, 128.7, 143.8, 144.0, 173.8. EIMS: m/z (rel intensity) 241 (M^+ , 100), 212 (8), 184 (42), 171 (61), 158 (16), 144 (18), 120 (29), 93 (49). HRMS calcd for $C_{16}H_{20}NO$ ($M^+ + 1$): 242.1545. Found: 242.1544.

2,3,4,5,5a,6,7,8-octahydro-1(1H)-benzazepin-2-one (2k). White solid. 1H NMR (300 MHz, $CDCl_3$) δ 1.52-1.86 (8H, m), 2.06-2.08 (2H, m), 2.27-2.31 (1H, m), 2.39-2.57 (2H, m), 5.34 (1H, t, $J = 3.6$ Hz), 7.17 (1H, br). ^{13}C NMR ($CDCl_3$) δ 18.6, 22.3, 24.6, 29.9, 34.5, 35.6, 36.2, 116.3, 137.0, 175.3. EIMS: m/z (rel intensity) 165 (M^+ , 67), 149 (2), 137 (14), 122 (8), 108 (100), 94 (66), 82 (80), 68 (26). HRMS calcd for $C_{10}H_{16}NO$ ($M^+ + 1$): 166.1232. Found: 166.1223.

Compound 9. White solid. 1H NMR (300 MHz, $CDCl_3$) δ 1.72-1.79 (4H, m), 2.02-2.12 (4H, m),

2.21-2.31 (4H, m), 4.77 (2H, q, $J = 16.8$ Hz), 6.57 (2H, t, $J = 9.0$ Hz), 9.30 (1H, br), 9.33 (1H, br). ^{13}C NMR (CDCl_3) δ 23.5, 24.3, 33.4, 110.0, 123.0, 171.2. ESIMS: m/z (rel intensity) 223 ($\text{M}^+ + 1$), 245 ($\text{M}^+ + \text{Na}$). ESI-HRMS calcd for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{NaO}_4$ ($\text{M}^+ + \text{Na}$): 245.1266. Found: 245.1264. The structure was further confirmed by its X-ray diffraction analysis.

Compound 13. Yellow solid. ^1H NMR (300 MHz, CDCl_3) δ 2.65 (4H, t, $J = 6.0$ Hz), 3.67 (4H, t, $J = 5.1$ Hz), 4.04 (4H, s), 4.72 (2H, s), 5.94 (2H, s), 8.09 (2H, br). ^{13}C NMR (CDCl_3) δ 38.1, 65.7, 74.2, 101.9, 135.8, 170.4. ESI-MS: m/z (rel intensity) 255 ($\text{M}^+ + 1$), 277 ($\text{M}^+ + \text{Na}$). ESI-HRMS calcd for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{NaO}_4$ ($\text{M}^+ + \text{Na}$): 277.1164. Found: 277.1157. The structure was further confirmed by its X-ray diffraction analysis.

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2c	Doumaux, A. R.; Trecker, D. J. <i>J. Org. Chem.</i> 1970 , 35, 2121.
2d	Easton, C. J.; Peters, S. C.; Love, S. G. <i>Heterocycles</i> 1988 , 27, 2305.
2e	Cannizzo, L. F.; Grubbs, R. H. <i>J. Org. Chem.</i> 1985 , 50, 2316.
2g	Murahashi, S.; Sasao, S.; Saito, E.; Naota, T. <i>Tetrahedron</i> 1993 , 49, 8805.

Lech-4-71c
Pulse Sequence: zgpg30

LC2H-3-11C
Pulse Sequence: zgpg30

LCN-3-148
Pulse Sequence: szpu1