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A Highly Stereoselective Aza-[3,3]-Claisen Rearrangement of Vinylaziridines as a Novel Entry to Seven-Membered Lactams

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Supplementary Material

General. All infrared spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer and only the strongest/structurally most important peaks (ν, cm^{-1}) are listed. ^1H and ^{13}C NMR spectra were recorded on Varian XL-300 or Bruker DRX 400 spectrometers using $CDCl_3$ ($CHCl_3$, δ 7.26) as solvent. Chemical shifts are reported in the δ scale with multiplicity (b=broad, s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet), integration, and coupling constants (Hz). Optical rotations, $[\alpha]_D$, were measured on a Perkin-Elmer 141 polarimeter at the sodium D line and at ambient temperature. High resolution mass spectra were recorded on a JEOL SX-102 spectrometer. Analytical thin layer chromatography was performed on Merck silica gel 60 F_{254} plates and the plates were visualised with UV light and the phosphomolybdic acid/cerium sulphate staining reagent.[1] Flash chromatography employed Grace Amicon silica gel 60 (35 - 70 mm). All reactions were carried out in oven-dried, septum-capped flasks, and under an atmospheric pressure of nitrogen. All liquid reagents were transferred *via* oven dried syringes. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl immediately before use; dichloromethane was distilled from CaH_2. Lithium hexamethyldisilazide (LiHMDS) in hexanes was purchased from Aldrich and the exact concentration was determined by hydrolysing an aliquot of the base

[1] 25 g of phosphomolybdic acid/10 g of cerium sulphate/940 mL of water/60 mL of conc. sulfuric acid

(H_2O:EtOH 1:1) and titrating against camphorsulfonic acid (CSA), with phenolphthalein as indicator.

Representative experimental. Rearrangement of *N*-Acyl Vinylaziridine 4b into Tetrahydroazepinone 6b. To a solution of the vinylaziridine **3b** (9.2 mg, 0.053 mmol), NEt_3 (0.015 mL, 0.106 mmol) and one crystal of DMAP in CH_2Cl_2 (1 mL) was added Ac_2O (0.006 mL, 0.059 mmol) at -78 °C. After 10 min, the reaction was quenched with phosphate buffer (pH 7), diluted with Et_2O, and washed with water, sat. aq. $NaHCO_3$, and brine. Drying ($MgSO_4$) and concentration gave the crude N-acyl vinylaziridine, **4b**, which was taken on directly to the next step. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.24 (m, 5H), 5.45-5.35 (m, 1H), 5.30-5.20 (m, 2H), 2.77 (m, 3H), 2.51 (dt, J = 6.3, 2.7 Hz), 2.06 (s, 3H), 1.98 (m, 2H), 1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.7, 141.5, 134.6, 132.5, 128.9, 126.5, 120.5, 46.4, 43.9, 33.9, 33.7, 24.9; IR (neat) 3020, 2920, 2860, 1680 cm^{-1}.

The crude aziridine from above was dissolved in THF (0.5 mL) and added to a solution of LiHMDS (0.096 mL, 0.106 mmol, 1.10 M in hexanes) in THF (0.5 mL) at -78 °C. After 20 min the cooling bath was removed, and after 20 min at RT the reaction was quenched with phosphate buffer (pH 7). The mixture was diluted with Et_2O, washed with water, and then brine. Drying ($MgSO_4$), concentration, and flash chromatography (heptane:ethyl acetate 7:1, 3% $iPrNH_2$) of the residue gave **6b** (9.5 mg, 83% for two steps) as a low-melting solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.17 (m, 5H), 6.12 (br s, 1H), 5.73 (m, 1H), 5.58 (br dd, 1H, J = 11.7, 2.5 Hz), 4.15 (br m, 1H), 2.91 (m, 1H), 2.74 (m, 2H), 2.41 (m, 3H), 1.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 140.9, 130.8, 130.5, 129.1, 128.8, 126.7, 49.6, 37.9, 34.0, 32.3, 25.0; IR (KBr) 3210, 2910, 2860, 1670 cm^{-1}; $[\alpha]_D$ +236 (*c* 0.87, $CHCl_3$); HRMS (EI+) Exact mass Calc for $C_{14}H_{17}NO$ (M): 215.1310. Found: 215.1312.

***N*-Acyl Vinylaziridine 4a.** ^1H NMR (300 MHz, $CDCl_3$): δ 7.39-7.24 (m, 5H), 5.54-5.28 (m, 3H), 4.59 (s, 2H), 3.71 (dd, 1H, J = 10.9, 4.1 Hz), 3.67 (dd, 1H, J = 10.9, 4.6 Hz), 3.08 (dd, 1H, J = 7.6, 2.7 Hz), 2.75 (ddd, 1H, J = 4.5, 2.8, 2.7 Hz), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.5, 138.1, 134.3, 132.6, 132.5, 128.9, 128.3, 120.5, 73.4, 68.4, 43.3, 42.9, 24.7; IR (neat) 3400, 3060, 3030, 2980, 2920, 2860, 1680 cm^{-1}.

***N*-Acyl Vinylaziridine 4c.** ^1H NMR (400 MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H), 5.40 (m, 1H), 5.24 (m, 2H), 2.79 (m, 2H), 2.52 (dt, 1H, J = 6.3, 2.8 Hz), 2.40 (dq,

1H, J = 15.1, 7.5 Hz), 2.26 (dq, 1H, J = 16.5, 7.5 Hz), 1.97 (m, 1H), 1.75 (m, 1H), 1.15 (t, 3H, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.5, 141.6, 134.8, 129.0, 128.9, 126.5, 120.1, 46.4, 43.5, 33.9, 33.8, 31.1, 9.5; IR (neat) 3030, 2980, 2930, 2860, 1690 cm^{-1}.

***N*-Acyl Vinylaziridine 4d.** ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.28 (m, 7H), 7.20 (m, 3H), 5.40-5.35 (m, 1H), 5.31-5.21 (m, 2H), 4.65 (d, 1H, J = 11.8 Hz), 4.61 (d, 1H, J = 11.8 Hz), 4.14 (d, 1H, J = 16.2 Hz), 4.05 (d, 1H, J = 16.2 Hz), 2.85-2.73 (m, 3H), 2.61 (dt, 1H, J = 6.4, 3.0 Hz), 2.04 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.1, 141.4, 137.7, 134.2, 134.1, 132.6, 129.5, 129.0, 128.9, 128.4, 126.5, 120.6, 73.7, 70.8, 46.7, 43.5, 33.7, 33.6; IR (neat) 3050, 3020, 2920, 2850, 1750, 1690 cm^{-1}.

***N*-Acyl Vinylaziridine 4e.** ^1H NMR (400 MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H), 5.43 (dd, 1H, J = 16.0, 1.9 Hz), 5.27 (m, 2H), 5.13 (br s, 1H), 4.01 (dd, 1H, J = 18.2, 4.9 Hz), 3.85 (dd, 1H, J = 18.2, 5.4 Hz), 2.79 (m, 3H), 2.58 (dt, 1H, J = 6.3, 2.9 Hz), 2.01 (m, 1H), 1.76 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.2, 156.1, 141.3, 133.9, 129.1, 126.6, 126.2, 121.2, 46.8, 45.6, 43.8, 33.6, 28.8; IR (neat) 3340, 3060, 2970, 2920, 2850, 1690 cm^{-1}.

***N*-Acyl Vinylaziridine 4f.** ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.23 (m, 5H), 5.82 (ddq, 1H, J = 10.9, 7.0, 0.8 Hz), 4.90 (m, 1H), 4.54 (s, 2H), 3.66 (dd, 2H, J = 4.7, 1.4 Hz), 3.31 (dd, 1H, J = 9.5, 2.8 Hz), 2.73 (dt, 1H, J = 4.6, 2.9 Hz), 2.08 (s, 3H), 1.83 (dd, 3H, J = 7.1, 1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.8, 138.2, 132.6, 132.5, 132.4, 128.9, 128.2, 126.0, 73.4, 69.0, 43.2, 38.6, 24.8, 13.8; IR (neat) 3290, 3050, 3020, 2910, 2850, 1670 cm^{-1}.

***N*-Acyl Vinylaziridine 4g.** ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.29 (m, 5H), 6.04 (ddt, 1H, J = 15.5, 5.7, 0.4 Hz), 5.32 (ddt, 1H, J = 15.5, 8.6, 1.5 Hz), 4.52 (s, 2H), 4.03 (dd, 2H, J = 5.7, 1.5 Hz), 2.82 (dd, 1H, J = 8.6, 2.8 Hz), 2.55 (dq, 1H, J = 5.6, 2.8 Hz), 2.09 (s, 3H), 1.33 (d, 3H, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.7, 138.4, 132.6, 132.4, 132.2, 129.5, 129.0, 128.9, 128.2, 72.9, 70.1, 45.7, 40.4, 25.0, 17.1; IR (neat) 3360, 3050, 3020, 2960, 2920, 2850, 1660 cm^{-1}.

Tetrahydroazepinone 6a. ^1H NMR (400 MHz, $CDCl_3$): δ 7.40-7.29 (m, 5H), 6.14 (br s, 1H), 5.79(m, 1H), 5.42 (dd, 1H, J = 11.6, 2.4 Hz), 4.56 (s, 2H), 4.39 (br m, 1H), 3.52 (dd, 1H, J = 9.5, 4.4 Hz), 3.43 (dd, 1H, J = 9.5, 8.5 Hz), 2.90 (ddd,

1H, J = 5.1, 4.1, 3.1 Hz), 2.52-2.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 137.6, 131.9, 129.0, 128.5, 128.3, 126.6, 73.7, 72.2, 50.3, 34.3, 25.0; IR (neat) 3360, 2910, 2860, 1660 cm^{-1}; $[\alpha]_D$ -9.5 (*c* 1.31, $CHCl_3$); HRMS (CI+) Exact mass Calc for $C_{14}H_{18}NO_2$ (M+H): 232.1337. Found: 232.1335.

Tetrahydroazepinone 6c. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.17 (m, 5H), 5.82 (br s, 1H), 5.71 (m, 1H), 5.58 (ddd, J = 11.5, 6.8, 2.3 Hz), 4.26 (br m, 1H), 3.09 (m, 1H), 2.73 (m, 2H), 2.22 (m, 2H), 1.87 (m, 2H), 1.16 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3, 140.9, 131.1, 130.7, 129.1, 128.8, 126.8, 48.9, 37.7, 35.4, 34.2, 32.2, 16.9; IR (KBr) 3210, 2910, 2860, 1670 cm^{-1}; $[\alpha]_D$ +36.8 (*c* 1.26, $CHCl_3$); HRMS (EI+) Exact mass Calc for $C_{15}H_{19}NO$ (M): 229.1467. Found: 229.1468.

Tetrahydroazepinone 6d. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.16 (m, 10H), 6.03 (br d, 1H, J =4.5 Hz), 5.71 (m, 1H), 5.55 (ddd, 1H, J = 11.6, 7.2, 2.5 Hz), 4.90 (d, 1H, J = 12.0 Hz), 4.51, (t, 1H, 8.2 Hz), 4.47 (d, 1H, J = 12.0 Hz), 4.05 (br m, 1H), 2.73 (m, 2H), 2.54 (m, 2H), 1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 140.7, 138.1, 130.7, 129.1, 128.9, 128.8, 128.5, 128.2, 126.8, 73.2, 72.2, 48.7, 37.5, 32.7, 32.1; IR (KBr) 3210, 2910, 2860, 1670 cm^{-1}.; $[\alpha]_D$ -60.8 (*c* 1.01, $CHCl_3$); HRMS (CI+) Calc for $C_{21}H_{24}NO_2$ (M+H): 322.1807. Found: 322.1803.

Tetrahydroazepinone 6e. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.17 (m, 5H), 6.25 (br s, 1H), 5.77 (br d, 1H, J = 6.7 Hz), 5.72 (m, 1H), 5.58 (dd, 1H, J =11.5, 2.1 Hz), 4.82 (m, 1H), 4.27 (br m, 1H), 2.73 (m, 3H), 2.23 (m, 1H), 1.91 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 155.5, 140.7, 130.4, 129.6, 129.2, 128.8, 126.8, 80.1, 50.3, 49.4, 37.6, 33.4, 32.2, 28.8; IR (KBr) 3420, 3210, 2980, 2930, 1700, 1670 cm^{-1}; $[\alpha]_D$ +29.7 (*c* 0.99, $CHCl_3$); HRMS (CI+) Exact mass Calc for $C_{19}H_{27}N_2O_3$ (M+H): 331.2022. Found: 331.2015.

Tetrahydroazepinone 6f. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.27 (m, 5H), 6.06 (br s, 1H), 5.62 (ddd, 1H, J = 11.6, 6.6, 1.7 Hz), 5.35 (ddd, 1H, J = 11.6, 5.0, 0.8 Hz), 4.56 (m, 2H), 4.42 (m, 1H), 3.57 (dd, J = 9.5, 4.4 Hz), 3.42 (dd, 1H, J = 9.5, 8.5 Hz), 2.73 (t, 1H, J = 12.1 Hz), 2.67 (m, 1H), 2.37 (ddd, 1H, J = 12.1, 6.2, 1.7 Hz), 1.12 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 138.1, 137.6, 129.0, 128.5, 128.3, 125.3, 73.7, 72.1, 50.1, 42.2, 30.84, 23.2; IR (neat) 3360, 2910, 2860, 1660 cm^{-1}; HRMS (CI+) Exact mass Calc for $C_{15}H_{20}NO_2$ (M+H): 246.1494. Found: 246.1494.

Tetrahydroazepinone 6g. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.27 (m, 5H), 5.71 (m, 1H), 5.63-5.50 (m, 2H), 4.60 (d, 1H, J = 11.9 Hz), 4.52 (d, 1H, J = 11.9 Hz), 4.30 (m, 1H), 3.48 (d, 2H, J = 6.7 Hz), 3.00 (dd, 1H, J = 13.3, 4.0 Hz), 2.76 (m, 1H), 2.60 (ddt, 1H, J = 13.3, 5.4, 1.5 Hz), 1.30 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 138.7, 132.9, 132.6, 132.4, 131.6, 129.0, 128.8, 128.1, 128.0, 73.8, 73.4, 46.0, 36.4, 36.0, 22.6; IR (neat) 3390, 2920, 2860, 1660 cm^{-1}; HRMS (CI+) Exact mass Calc for $C_{15}H_{20}NO_2$ (M+H): 246.1494. Found: 246.1485.