A Formal [3+2] cycloaddition process with nonactivated aziridines to polysubstituted indolizidines

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Experimental

General procedure for reaction of aziridines 2 and iodides 1. A mixture of aziridine **1** (0.24 mmol), iodide **2** (0.20 mmol), anhydrous K₂CO₃ (0.24 mmol) in 3 mL of dry MeCN was stirred at the indicated temperature in tables until the starting material disappeared monitored by TLC. The cooled solution was concentrated and partitioned between brine and ether. The organic phase was concentrated and the residue was chromatographed eluting with 1:1 to 1:10 ethyl acetate/petroleum ether to afford desired product.

2-Phenyl-2,3,5,6,7,8-hexahydroindolizine-1-carboxylic acid ethyl ester 3a. IR (film) 2943, 1670, 1578 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.24-7.14 (m, 5H), 4.14 (dd, *J* = 11.1, 4.6 Hz, 1H), 4.01-3.88 (m, 2H), 3.72 (t, *J* = 10.6 Hz, 1H), 3.29 (dd, *J* = 10.3, 4.7 Hz, 1H), 3.19-3.06 (m, 2H), 2.96-2.87 (m, 1H), 2.80-2.69 (m, 1H), 1.87-1.74 (m, 3H), 1.67-1.57 (m, 1H), 1.02 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 166.6, 161.7, 146.4, 128.0, 127.0, 125.9, 100.3, 61.9, 58.0, 47.3, 44.8, 24.3, 23.1, 20.2, 14.3; EI-MS *m/z* 271 (M⁺); HRMS calcd. for C₁₇H₂₂NO₂ 272.1645 (M + H)⁺, found 272.1651.

3b

2-Naphthalen-2-yl-2,3,5,6,7,8-hexahydroindolizine-1-carboxylic acid ethyl ester 3b. IR (film) 2931, 1668, 1579 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.79-7.74 (m, 3H), 7.63 (br s, 1H), 7.45-7.35 (m, 3H), 4.33 (dd, $J = 11.3, 4.7$ Hz, 1H), 3.97-3.88 (m, 2H), 3.78 (t, $J = 10.9$ Hz, 1H), 3.34 (dd, $J = 10.4, 4.7$ Hz, 1H), 3.21-3.08 (m, 2H), 2.96-2.90 (m, 1H), 2.85-2.80 (m, 1H), 1.89-1.76 (m, 3H), 1.63-1.60 (m, 1H), 0.98 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.7, 162.0, 143.8, 133.5, 132.3, 127.9, 127.6, 127.5, 125.9, 125.6, 125.3, 125.0, 100.2, 61.9, 58.1, 47.5, 45.1, 24.5, 23.2, 20.3, 14.4; ESI-MS m/z 322 ($\text{M} + \text{H}^+$); HRMS calcd. for $\text{C}_{21}\text{H}_{24}\text{NO}_2$ 322.1802 ($\text{M} + \text{H}^+$), found 322.1802.

3c

2-p-Tolyl-2,3,5,6,7,8-hexahydroindolizine-1-carboxylic acid ethyl ester 3c. IR (film) 2930, 1670, 1585 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz)

δ 7.12 (m, 4H), 4.11 (dd, J = 11.1, 4.2 Hz, 1H), 4.02-3.90 (m, 2H), 3.70 (t, J = 10.8 Hz, 1H), 3.26 (dd, J = 10.4, 4.6 Hz, 1H), 3.17-3.05 (m, 2H), 2.94-2.86 (m, 1H), 2.79-2.71 (m, 1H), 2.30 (s, 3H), 1.85-1.73 (m, 3H), 1.63-1.56 (m, 1H), 1.06 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.7, 161.6, 143.5, 135.4, 128.8, 127.0, 100.5, 62.2, 58.1, 47.5, 44.5, 24.5, 23.2, 21.0, 20.4, 14.4; EI-MS m/z 285 (M^+); HRMS calcd. for $\text{C}_{18}\text{H}_{24}\text{NO}_2$ 286.1802 ($\text{M} + \text{H}^+$), found 286.1798.

2-(4-Chlorophenyl)-2,3,5,6,7,8-hexahydroindolizine-1-carboxylic acid ethyl ester 3d. IR (film) 1669, 1581, 1490 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.24-7.12 (m, 4H), 4.12 (dd, J = 11.2, 5.1 Hz, 1H), 4.02-3.89 (m, 2H), 3.71 (t, J = 10.9 Hz, 1H), 3.23 (dd, J = 10.4, 4.8 Hz, 1H), 3.18-3.05 (m, 2H), 2.96-2.87 (m, 1H), 2.78-2.67 (m, 1H), 1.86-1.74 (m, 3H), 1.61-1.56 (m, 1H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.5, 161.9, 145.1, 131.6, 128.128.2, 100.2, 61.8, 58.2, 47.4, 44.4, 24.4, 23.2, 20.3, 14.4; EI-MS m/z 305 (M^+); HRMS calcd. for $\text{C}_{17}\text{H}_{21}\text{NO}_2\text{Cl}$ 306.1255 ($\text{M} + \text{H}^+$), found 306.1267.

2-(4-Bromophenyl)-2,3,5,6,7,8-hexahydroindolizine-1-carboxylic acid ethyl ester 3e. IR (film) 2944, 1669, 1583, 1486 cm^{-1} ; ^1H NMR

(CDCl_3 , 300 MHz) δ 7.38-7.34 (m, 2H), 7.10-7.07 (m, 2H), 4.10 (dd, $J = 11.3, 4.7$ Hz, 1H), 4.01-3.90 (m, 2H), 3.71 (t, $J = 11.0$ Hz, 1H), 3.23 (dd, $J = 10.1, 4.7$ Hz, 1H), 3.18-3.05 (m, 2H), 2.95-2.89 (m, 1H), 2.78-2.70 (m, 1H), 1.86-1.76 (m, 3H), 1.63-1.58 (m, 1H), 1.05 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.4, 161.9, 145.6, 131.1, 128.9, 119.6, 100.1, 61.8, 58.2, 47.4, 44.5, 24.4, 23.1, 20.2, 14.4; ESI-MS m/z 350 ($\text{M} + \text{H}^+$); HRMS calcd. for $\text{C}_{17}\text{H}_{21}\text{NO}_2\text{Br}$ 350.0750 ($\text{M} + \text{H}^+$), found 350.0767.

2-(4-Nitrophenyl)-2,3,5,6,7,8-hexahydroindolizine-1-carboxylic acid ethyl ester 3f. IR (film) 2945, 1670, 1578, 1517, 1346 cm^{-1} ; ^1H

NMR (CDCl₃, 300 MHz) δ 8.15-8.11 (m, 2H), 7.40-7.35 (m, 2H), 4.26 (dd, J = 11.4, 5.2 Hz, 1H), 4.03-3.89 (m, 2H), 3.78 (t, J = 11.1 Hz, 1H), 3.28 (dd, J = 10.8, 4.5 Hz, 1H), 3.20-3.09 (m, 2H), 2.99-2.91 (m, 1H), 2.80-2.69 (m, 1H), 1.89-1.75 (m, 3H), 1.66-1.58 (m, 1H), 1.04 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 165.8, 162.0, 153.8, 146.0, 127.6, 123.2, 99.2, 60.9, 57.9, 47.0, 44.5, 24.1, 22.7, 19.7, 14.0; EI-MS m/z 316 (M⁺); HRMS calcd. for C₁₇H₂₁N₂O₄ 317.1496 (M + H)⁺, found 317.1493.

2-Styryl-2,3,5,6,7,8-hexahydroindolizine-1-carboxylic acid ethyl ester 3g. IR (film) 2930, 1706, 1236 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.36-7.15 (m, 5H), 6.40 (d, J = 15.9 Hz, 1H), 6.20 (dd, J = 15.9, 7.8 Hz, 1H), 4.16-4.00 (m, 2H), 3.81-3.73 (m, 1H), 3.51 (t, J = 10.2 Hz, 1H), 3.23 (dd, J = 10.2, 4.8 Hz, 1H), 3.15-3.06 (m, 2H), 2.93-2.85 (m, 1H), 2.69-2.65 (m, 1H), 1.85-1.71 (m, 2H), 1.62-1.52 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 166.8, 137.9, 132.4, 128.8, 128.4, 126.8, 126.2, 119.3, 91.7, 59.3, 58.3, 47.7, 42.4, 24.6, 23.2, 20.3, 14.7; ESI-MS m/z 298 (M + H)⁺; HRMS calcd. for C₁₉H₂₄NO₂ 298.1802 (M + H)⁺, found 298.1819.

(2-Phenyl-2,3,5,6,7,8-hexahydroindolizin-1-yl)phosphonic acid diethyl ester 3i. IR (film) 1664, 1600, 1574 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.27-7.18 (m, 5H), 3.94-3.85 (m, 3H), 3.71-3.59 (m, 2H), 3.36-3.28 (m, 2H), 3.09-2.98 (m, 2H), 2.86-2.78 (m, 1H), 2.60-2.53 (m, 1H), 1.87-1.70 (m, 3H), 1.60-1.53 (m, 1H), 1.25 (t, $J = 7.2$ Hz, 3H), 0.84 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 162.9, 145.8, 128.1, 127.4, 126.3, 94.7, 62.8, 60.4, 48.8, 47.3, 24.2, 23.7, 21.3, 16.3, 15.8; EI-MS m/z 335 (M^+); HRMS calcd. for $\text{C}_{18}\text{H}_{27}\text{NO}_3\text{P}$ 336.1723 ($\text{M} + \text{H}^+$), found 336.1718.

Phenyl (2-phenyl-2,3,5,6,7,8-hexahydroindolizin-1-yl)methanone 3j. IR (film) 2950, 1712, 1602, 1540 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.89-7.85 (m, 2H), 7.45-7.20 (m, 6H), 6.11-6.06 (m, 2H), 3.60 (t, $J = 6.2$ Hz, 2H), 3.29 (t, $J = 6.5$ Hz, 2H), 1.96-1.92 (m, 2H), 1.81-1.77 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 189.0, 161.7, 141.5, 136.7, 131.5, 131.0, 128.8, 128.2, 127.5, 126.6, 125.4, 113.0, 99.1, 47.9, 28.6, 23.0, 20.3; ESI-MS

m/z 304 ($M + H$)⁺; HRMS calcd. for C₂₁H₂₂NO 304.1696 ($M + H$)⁺, found 304.1695.

2-Phenyl-1-(toluene-4-sulfonyl)-2,3,5,6,7,8-hexahydroindolizine 3k. IR (film) 2945, 1558, 1294 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.38-6.92 (m, 9H), 4.24 (dd, J = 11.3, 5.2 Hz, 1H), 3.74 (t, J = 10.8 Hz, 1H), 3.29-3.14 (m, 2H), 3.08-3.01 (m, 1H), 2.96-2.88 (m, 1H), 2.64-2.54 (m, 1H), 2.29 (s, 3H), 1.85-1.62 (m, 4H); ¹³C NMR (CDCl₃, 75 MHz) δ 159.4, 143.2, 141.9, 141.3, 128.7, 128.2, 127.7, 126.4, 126.1, 105.9, 62.0, 47.6, 46.3, 23.3, 23.0, 21.3, 20.1; EI-MS m/z 353 (M^+); HRMS calcd. for C₂₁H₂₄NO₂S 354.1522 ($M + H$)⁺, found 354.1518.

3-Benzyloxymethyl-2-Phenyl-1-(toluene-4-sulfonyl)-2,3,5,6,7,8-hexahydroindolizine 5. IR (film) 1598, 1494, 1454 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.38-6.96 (m, 14H), 4.47 (m, 2H), 3.88 (d, J = 6.9 Hz, 1H), 3.58-3.37 (m, 4H), 3.17-3.08 (m, 1H), 2.89-2.85 (m, 1H), 2.76-2.70

(m, 1H), 2.31 (s, 3H), 1.84-1.77 (m, 3H), 1.58 (m, 1H); EI-MS m/z 474 ($M + H$)⁺; HRMS calcd. for C₂₉H₃₂NO₃S 474.2097 ($M + H$)⁺, found 474.2113.

2-Phenyl-2,5,6,7,8,9-hexahydro-3H-pyrrolo[1,2-*a*]azepine-1-carboxylic acid ethyl ester 8. IR (film) 2929, 1695, 1670, 1577 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.29-7.16 (m, 5H), 4.12 (dd, $J = 11.3, 4.6$ Hz, 1H), 3.99-3.86 (m, 3H), 3.36 (dd, $J = 11.3, 4.3$ Hz, 1H), 3.21-3.18 (m, 2H), 3.07 (br s, 2H), 1.73-1.59 (m, 6H), 0.99 (t, $J = 7.0$ Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.8, 167.0, 146.7, 128.1, 127.1, 126.0, 101.0, 62.2, 58.1, 48.8, 45.7, 30.9, 27.5, 26.2, 25.8, 14.3; EI-MS m/z 285 (M^+); HRMS calcd. for C₁₈H₂₄NO₂ 286.1802 ($M + H$)⁺, found 286.1806.

8-(2-Phenylaziridin-1-yl)oct-2-ynoic acid ethyl ester 9. IR (film) 2839, 2235, 1710, 1257 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.32-7.22 (m, 5H), 4.22 (q, $J = 7.2$ Hz, 2H), 2.51-2.44 (m, 1H), 2.39-2.28 (m, 4H), 1.90-1.88 (m, 1H), 1.67-1.46 (m, 7H), 1.28 (t, $J = 7.2$ Hz, 3H); EI-MS m/z

285 (M^+); HRMS calcd. for $C_{18}H_{24}NO_2$ 286.1802 ($M + H$)⁺, found 286.1801.

3-Benzyl-2-phenyl-2,3,5,6,7,8-hexahydroindolizine-1-carboxylic acid ethyl ester 5. IR (film) 1670, 1577, 1454 cm^{-1} ; 1H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.15 (m, 10H), 4.54 (s, 2H), 3.98-3.81 (m, 3H), 3.65-3.54 (m, 2H), 3.51-3.44 (m, 1H), 3.42-3.37 (m, 1H), 3.22 (dt, $J = 17.7$, 5.4 Hz, 1H), 2.96-2.88 (m, 1H), 2.73-2.62 (m, 1H), 1.87-1.73 (m, 3H), 1.66-1.60 (m, 1H), 0.96 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8, 161.2, 146.2, 138.0, 128.4, 128.1, 127.6, 127.5, 127.3, 126.0, 98.0, 73.2, 72.5, 71.8, 58.0, 49.2, 46.5, 24.7, 23.5, 20.2, 14.3; EI-MS m/z 391 (M^+); HRMS calcd. for $C_{25}H_{30}NO_3$ 392.2220 ($M + H$)⁺, found 392.2214.

(S)-2-Phenyl-2,3,5,6,7,8-hexahydroindolizine-1-carboxylic acid ethyl ester 3a. $[\alpha]_D^{27} +180.1$ (c 1.1, $CHCl_3$); IR (film) 2943, 1670, 1578

cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.24-7.14 (m, 5H), 4.14 (dd, *J* = 11.1, 4.6 Hz, 1H), 4.01-3.88 (m, 2H), 3.72 (t, *J* = 10.6 Hz, 1H), 3.29 (dd, *J* = 10.3, 4.7 Hz, 1H), 3.19-3.06 (m, 2H), 2.96-2.87 (m, 1H), 2.80-2.69 (m, 1H), 1.87-1.74 (m, 3H), 1.67-1.57 (m, 1H), 1.02 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 166.6, 161.7, 146.4, 128.0, 127.0, 125.9, 100.3, 61.9, 58.0, 47.3, 44.8, 24.3, 23.1, 20.2, 14.3; EI-MS *m/z* 271 (M⁺); HRMS calcd. for C₁₇H₂₂NO₂ 272.1645 (M + H)⁺, found 272.1651. (The ee value was determined by Chiralcel OD, 250 x 4.6 mm with 95/5 to 80/20 hexane/*i*-PrOH as eluent).

(*R*)-2-(4-Chlorophenyl)-2,3,5,6,7,8-hexahydroindolizine-1-carboxylic acid ethyl ester **3d**. IR (film) 1669, 1581, 1490 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.24-7.12 (m, 4H), 4.12 (dd, *J* = 11.2, 5.1 Hz, 1H), 4.02-3.89 (m, 2H), 3.71 (t, *J* = 10.9 Hz, 1H), 3.23 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.18-3.05 (m, 2H), 2.96-2.87 (m, 1H), 2.78-2.67 (m, 1H), 1.86-1.74 (m, 3H), 1.61-1.56 (m, 1H), 1.05 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 166.5, 161.9, 145.1, 131.6, 128.128.2, 100.2, 61.8, 58.2, 47.4, 44.4, 24.4, 23.2, 20.3, 14.4; EI-MS *m/z* 305 (M⁺); HRMS calcd. for C₁₇H₂₁NO₂Cl 306.1255 (M + H)⁺, found 306.1267. (The ee value was determined by Chiralcel OD, 250 x 4.6 mm with 95/5 to 80/20 hexane/*i*-PrOH as eluent).

3-Benzylloxymethyl-2-Phenyl-1-(toluene-4-sulfonyl)octahydroindolizine 6. A mixture of **5** (56 mg, 0.12 mmol) and 10 mg of 10% Pd/C in

5 mL of methanol was stirred at 50 °C under hydrogen atmosphere (100 atm) for 24 h. The suspension was filtered through celite, washed with methanol, and concentrated in vacuo. The residue was chromatographed eluting with 10:1 ethyl acetate/methanol to afford 47mg (84%) of **6**. IR (film) 2922, 2852, 1600, 1456 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.56-7.54 (m, 2H), 7.29-6.97 (m, 10H), 7.63-7.61 (m, 2H), 4.50-4.31 (m, 2H), 3.75-3.70 (m, 1H), 3.58-3.46 (m, 3H), 3.11-3.06 (m, 1H), 2.81-2.76 (m, 1H), 2.50-2.44 (m, 1H), 2.34 (s, 3H), 2.26-2.21 (m, 2H), 2.00-1.91 (m, 2H), 1.67-1.62 (m, 4H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 144.1, 140.7, 138.2, 136.5, 129.4, 128.4, 128.2, 128.1, 127.7, 127.4, 126.5, 73.4, 73.1, 72.3, 69.6, 68.1, 53.2, 49.0, 31.9, 29.6, 29.3, 27.5; ESI-MS m/z 476 ($\text{M} + \text{H}$) $^+$; HRMS calcd. for $\text{C}_{29}\text{H}_{34}\text{NO}_3\text{S}$ 476.2254($\text{M} + \text{H}$) $^+$, found 476.2247.