Unique Ionic Iodine Atom Transfer Cyclization: A New Route to Iodomethylated Pyrrolidine Derivatives from γ-Iodoolefin and Chloramine-T

Supporting Information

Satoshi Minakata, Daisuke Kano, Yoji Oderaotoshi, and Mitsuo Komatsu*
Department of Applied Chemistry, Graduate School of Engineering, Osaka University,
Yamadaoka 2-1, Suita, Osaka 565-0871, Japan

Experimental

General Methods.

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained on a Jasco FT/IR-410 infrared spectrophotometer. ^{1}H and ^{13}C-NMR spectra were recorded on a JEOL FT-NMR JNM EX 270 spectrometer (^{1}H-NMR, 270 MHz; ^{13}C-NMR, 68 MHz) using tetramethylsilane as the internal standard. Mass spectra were measured using a Shimadzu Model GCMS-QP5000 spectrometer. High-resolution mass spectral data were obtained on a JEOL DX-303 mass spectrometer. Elemental analyses were performed at the Analytical Center, Faculty of Engineering, Osaka University. The single-crystal X-ray data were collected on a Rigaku AFC-5R diffractometer with graphite-monochromatized Mo Kα radiation, and the structure solved by direct methods. Flash column chromatography (FCC) was performed using silica gel BW-300 (Fuji Silysia Chemical Co.). Preparative gel permeation liquid chromatography (GPLC) was performed on a JAI (Japan Analytical Industry) LC-908 instrument with JAIGEL 1H-2H columns and chloroform as an eluent. Analytical thin layer chromatography was performed using EM reagent 0.25 mm silica gel 60-F plates.

Visualization was accomplished with UV light and ethanolic phosphomolybdic acid followed by heating.

General Procedure for Preparation of Pyrrolidines from γ-Iodoolefins.

The γiodoolefins (1.0 mmol) were added to a suspension of Chloramine-T (2.0 mmol) in distilled MeCN (6.0 mL). The mixture was allowed to stir in the dark at room temperature for 48 hours under a nitrogen atmosphere. After the addition of Et_2O (40 mL), the organic layer was washed with H_2O (60 mL). The aqueous phase was extracted with Et_2O (20 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over K_2CO_3, and concentrated in vacuo. Purification by flash column chromatography (silica gel, 10% EtOAc in hexane) gave the pyrrolidines as white solids. Further purification was performed by recycling preparative HPLC (GPC column, chloroform), if necessary.

2-Iodomethyl-1-(*p*-toluenesulfonyl)pyrrolidine (2a). colorless crystalline solid; mp. 86-88 ˚C; TLC R_f 0.31 (hexane/EtOAc, 4:1); IR (KBr) 1346, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.50-1.59 (m, 1H), 1.80-1.86 (m, 3H), 2.44 (s, 3H), 3.14-3.21 (m, 2H), 3.45-3.53 (m, 1H), 3.62 (dd, 1H, *J* = 3.0, 9.6 Hz), 3.70-3.79 (m, 1H), 7.34 (d, 2H, *J* = 8.1 Hz), 7.73 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 11.5, 21.5, 23.8, 32.0, 50.1, 60.7, 127.5, 129.8, 134.2, 143.7; MS (CI, methane) *m/z* (relative intensity, %) 366 ($[M+1]^+$, 100), 238 (53); Anal. Calcd for $C_{12}H_{16}INO_2S$: C, 39.46; H, 4.42; N, 3.84. Found: C, 39.54; H, 4.28; N, 3.74.

***threo*-2-(1-Iodoethyl)-1-(*p*-toluenesulfonyl)pyrrolidine (2b)**. colorless crystalline solid; mp. 112.5-113.5 ˚C; TLC R_f 0.26 (hexane/EtOAc, 4:1); IR (KBr) 1341, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.33-1.48 (m, 1H), 1.68-1.99 (m, 6H), 2.44 (s, 3H), 3.32 (ddd, 1H, *J* = 5.4, 9.9, 12.0 Hz), 3.49 (ddd, 1H, *J* = 5.7, 9.9, 9.9 Hz), 3.99 (ddd, 1H, *J* = 4.0, 4.8, 8.1 Hz), 4.75 (dq, 1H, *J* = 4.0, 6.8 Hz), 7.34 (d, 2H, *J* = 8.3 Hz), 7.72 (d, 2H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 20.4, 21.6, 24.4, 28.5, 30.2, 51.4, 65.4, 127.6, 129.8, 133.7, 143.8; MS (CI, methane) *m/z* (relative intensity, %) 380 ($[M+1]^+$, 100), 252 (54), 224 (21), 155 (2); Anal. Calcd for $C_{13}H_{18}INO_2S$: C, 41.17; H, 4.78; N, 3.69. Found: C, 41.12; H, 4.59; N, 3.67.

***erythro*-2-(1-Iodoethyl)-1-(*p*-toluenesulfonyl)pyrrolidine (2c)**. colorless crystalline solid; mp. 122-125 ˚C; TLC R_f 0.31 (hexane/EtOAc, 4:1); IR (KBr) 1341, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.33-1.45 (m, 1H), 1.75-1.93 (m, 6H), 2.44 (s, 3H), 3.08-3.16 (m, 1H), 3.35-3.39 (m, 2H), 4.72-4.81 (m, 1H), 7.33 (d, 2H, *J* = 8.3 Hz), 7.75 (d, 2H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 21.5, 24.4, 25.1, 30.4, 36.8, 49.3, 65.5, 127.5, 129.7, 135.1, 143.6; MS (CI, methane) *m/z* (relative intensity, %) 380 ($[M+1]^+$, 100), 252 (31), 224 (14), 155 (5); Anal. Calcd for $C_{13}H_{18}INO_2S$: C, 41.17; H, 4.78; N, 3.69. Found: C, 41.26; H, 4.66; N, 3.66.

***cis*- and *trans*-2-(Iodomethyl)-3-methyl-1-(*p*-toluenesulfonyl)pyrrolidine (2d)**. colorless oil; TLC R_f 0.27 (hexane/EtOAc, 4:1); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.61 (d, $3H_{trans}$, *J* =

6.8 Hz), 1.09 (d, 3H$_{cis}$, J = 7.3 Hz), 1.22-1.34 (m, 1H$_{trans}$), 1.51-1.63 (m, 1H$_{cis}$) , 1.67-1.80 (m, 1H$_{cis}$), 1.94-2.07 (m, 1H$_{trans}$), 2.19 (ddt, 1H$_{cis}$, J = 7.2, 7.2, 7.3 Hz), 2.26-2.36 (m, 1H$_{trans}$), 2.44 (s, 3H$_{cis}$ and 3H$_{trans}$), 3.17-3.58 (m, 3H$_{cis}$ and 5H$_{trans}$), 3.63 (dd, 1H$_{cis}$, J = 2.7, 10.5 Hz), 3.74 (ddd, 1H$_{cis}$, J = 2.7, 7.2, 10.3 Hz), 7.34 (d, 2H$_{cis}$ and 2H$_{trans}$, J = 8.0 Hz), 7.73 (d, 2H$_{cis}$ and 2H$_{trans}$, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 5.9, 11.7, 13.6, 18.5, 21.6, 21.6, 31.0, 31.2, 37.0, 38.6, 48.2, 48.4, 62.8, 67.2, 127.4, 127.5, 129.6, 129.7, 133.9, 133.9, 143.6, 143.6. ***cis*-2d** was isolated by recrystallization from chloroform. ***cis*-2d**: colorless crystalline solid; mp. 97-100 ˚C; TLC R_f 0.27 (hexane/EtOAc, 4:1); IR (KBr) 1345, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.09 (d, 3H, J = 7.3 Hz), 1.51-1.63 (m, 1H) , 1.67-1.80 (m, 1H), 2.19 (ddt, 1H, J = 7.2, 7.2, 7.3 Hz), 2.44 (s, 3H), 3.20-3.30 (m, 2H), 3.51 (ddd, 1H, J = 2.2, 9.5, 10.0 Hz), 3.63 (dd, 1H, J = 2.7, 10.5 Hz), 3.74 (ddd, 1H, J = 2.7, 7.2, 10.3 Hz), 7.34 (d, 2H, J = 8.0 Hz), 7.73 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 5.9, 13.6, 21.6, 31.2, 37.0, 48.4, 62.8, 127.5, 129.7, 133.9, 143.6; MS (CI, methane) *m/z* (relative intensity, %) 380 ([M+1]$^+$, 100), 252 (10); Anal. Calcd for $C_{13}H_{18}INO_2S$: C, 41.17; H, 4.78; N, 3.69. Found: C, 41.21; H, 4.72; N, 3.70.

X-ray crystallographic data: $C_{13}H_{18}INO_2S$, MW = 379.26, colorless, prismatic, monoclinic, space group $P2_1/a$ (#14), a = 9.909(4) Å, b = 13.007(4) Å, c = 12.400(4) Å, β = 111.58(2)˚, V = 1486.3(8) Å^3, Z = 4, Dc 1.695 g/cm^3, F(000) = 752.00, μ(Mo Kα) = 22.90 cm^{-1}, graphite-monochromatized Mo Kα (λ = 0.71069 Å), T = 23 ˚C, Final discrepancy factor: R = 0.065 and R_w = 0.120, The structure was solved by direct method (SIR92).

6-Iodo-4-(*p*-toluenesulfonyl)-4-azabicyclo[3.3.0]octane (2e). colorless crystalline solid;

mp. 78-84 ˚C; TLC R_f 0.26 (hexane/EtOAc, 4:1); IR (KBr) 1344, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.44-1.56 (m, 2H), 1.66-1.78 (m, 1H), 1.98-2.24 (m, 3H), 2.45 (s, 3H), 2.74 (ddddd, 1H, *J* = 2.2, 7.1, 7.1, 7.1, 7.1 Hz), 3.00 (dt, 1H, *J* = 7.3, 10.1 Hz), 3.45 (dt, 1H, *J* = 6.1, 10.1 Hz), 4.03 (d, 1H, *J* = 7.1 Hz), 4.80 (d, 1H, *J* = 3.5 Hz), 7.35 (d, 2H, *J* = 8.0 Hz), 7.72 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 21.6, 30.7 (2C), 35.5, 35.6, 42.0, 50.1, 74.8, 127.8, 129.6, 132.6, 143.7; MS (EI) *m/z* (relative intensity, %) 391 (M^+, 14), 264 (100), 236 (58), 155 (49); Anal. Calcd for $C_{14}H_{18}INO_2S$: C, 42.98; H, 4.64; N, 3.58. Found: C, 42.87; H, 4.57; N, 3.57.

5-Iodo-7-(*p*-toluenesulfonyl)-7-azabicyclo[4.3.0]nonane (2f). white solid; mp. 96-98 ˚C; TLC R_f 0.30 (hexane/EtOAc, 4:1); IR (KBr) 1347, 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.18-1.78 (m, 6H), 1.90-1.96 (m, 2H), 2.40-2.45 (m, 1H), 2.45 (s, 3H), 3.44-3.60 (m, 2H), 3.65 (dd, 1H, *J* = 4.0, 4.0 Hz), 5.26 (dt, 1H, *J* = 4.0, 7.8 Hz), 7.36 (d, 2H, *J* = 8.2 Hz), 7.71 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 21.5, 21.7, 26.6, 28.6, 30.8, 33.5, 36.3, 48.8, 66.5, 127.7, 129.7, 133.0, 143.7; MS (EI) *m/z* (relative intensity, %) 405 (M^+, 9), 278 (11), 155 (36), 91 (100); Anal. Calcd for $C_{15}H_{20}INO_2S$: C, 44.45; H, 4.97; N, 3.46. Found: C, 44.20; H, 4.96; N, 3.36.

(1*SR*,6*RS*,7*RS*)-6-Iodo-8-(*p*-toluenesulfonyl)-8-azabicyclo[5.3.0]decane (2g). colorless crystalline solid; mp. 119-121 ˚C; TLC R_f 0.31 (hexane/EtOAc, 4:1); IR (KBr) 1340, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.21-1.84 (m, 7H), 1.90-1.96 (m, 2H), 2.12 (dt, 1H, *J* = 3.9, 10.8 Hz), 2.44 (s, 3H), 3.14 (dt, 1H, *J* = 7.6, 10.1 Hz), 3.51 (dt, 1H, *J* = 6.3, 10.1 Hz),

4.06 (dd, 1H, J = 4.1, 8.5 Hz), 5.21 (ddd, 1H, J = 4.1, 4.1, 4.1 Hz), 7.35 (d, 2H, J = 8.1 Hz), 7.73 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 21.6, 24.6, 28.9, 29.2, 30.5, 32.2, 39.0, 42.2, 48.9, 69.2, 128.0, 129.7, 133.0, 143.7; MS (CI, isobutane) *m/z* (relative intensity, %) 419 (M^+, 32), 292 (100), 264 (6), 155 (42); Anal. Calcd for $C_{16}H_{22}INO_2S$: C, 45.83; H, 5.29; N, 3.34. Found: C, 45.89; H, 4.96; N, 3.34.

X-ray crystallographic data: $C_{16}H_{22}INO_2S$, MW = 419.32, colorless, prismatic, orthorhombic, space group Pb_{ca} (#61), a = 12.053(3) Å, b = 24.678(6) Å, c = 11.482(3) Å, V = 3415(1) Å^3, Z = 8, Dc 1.631 g/cm^3, F(000) = 1680.00, μ(Mo Kα) = 20.02 cm^{-1}, graphite-monochromatized Mo Kα (λ = 0.71069 Å), T = 23 ˚C, Final discrepancy factor: R = 0.041 and R_w = 0.054, The structure was solved by direct method (SIR92).

2-Iodomethyl-1-(*p*-toluenesulfonyl)piperidine (4). colorless oil; TLC R_f 0.39 (hexane/EtOAc , 4:1); IR (neat) 1338, 1152cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.21-1.50 (m, 5H), 2.04-2.11 (m, 1H), 2.43 (s, 3H), 2.95 (dt, 1H, J = 2.3, 13.4 Hz), 3.23 (dd, 1H, J = 4.8, 10.0 Hz), 3.36 (dd, 1H, J = 10.0, 10.0 Hz), 3.71 (dd, 1H, J = 3.3, 13.4 Hz), 4.22-4.29 (m, 1H), 7.30 (d, 2H, J = 8.1 Hz), 7.72 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 4.0, 17.7, 21.5, 24.3, 26.2, 40.6, 53.8, 127.0, 129.8, 137.9, 143.3; MS (CI, methane) *m/z* (relative intensity, %) 380 ($[M+1]^+$, 100), 252 (90), 155 (3); Anal. Calcd for $C_{13}H_{18}INO_2S$: C, 41.17; H, 4.78; N, 3.69. Found: C, 41.30; H, 4.62; N, 3.59.

2-(4-*N*-(*p*-Toluenesulfonyl)aminobutyl)-1-(*p*-toluenesulfonyl)aziridine (3h) . white solid; mp. 75-80 ˚C; TLC R_f 0.06 (hexane/EtOAc, 4:1); IR (KBr) 3287, 1323, 1162 cm^{-1}; ^{1}H

NMR ($CDCl_3$, 270 MHz) δ 1.19-1.63 (m, 6H), 2.02 (d, 1H, *J* = 4.6 Hz), 2.43 (s, 3H), 2.45 (s, 3H), 2.57 (d, 1H, *J* = 6.9 Hz), 2.65-2.70 (m, 1H), 2.86 (dt, 2H, *J* = 5.3, 6.3 Hz), 4.52 (br, 1H), 7.31 (d, 2H, *J* = 7.8 Hz), 7.34 (d, 2H, *J* = 8.4 Hz), 7.73 (d, 2H, *J* = 8.4 Hz), 7.81 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 21.5, 21.6, 23.8, 28.6, 30.5, 33.9, 39.7, 42.8, 127.0, 128.0, 129.7, 134.9, 136.9, 143.4, 144.7; MS (CI, methane) *m/z* (relative intensity, %) 423 ($[M+1]^+$, 92), 269 (100), 267 (32), 252 (57); HRMS (CI, isobutane) *m/z* calcd for $C_{20}H_{27}N_2O_4S_2$ (M + H) 423.1412, found 423.1405.

2-(4-Iodobutyl)-1-(*p*-toluenesulfonyl)aziridine (3h'). colorless oil; TLC R_f 0.30 (hexane/EtOAc , 4:1); IR 1323, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.23-1.35 (m, 3H), 1.64-1.77 (m, 3H), 2.07 (d, 1H, *J* = 4.3 Hz), 2.45 (s, 3H), 2.63-2.73 (m, 2H), 3.06 (t, 2H, *J* = 6.8 Hz), 7.35 (d, 2H, *J* = 8.4 Hz), 7.83 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 6.1, 21.6, 27.7, 30.1, 32.5, 33.6, 39.9, 127.9, 129.7, 135.0, 144.5; MS (CI, methane) *m/z* (relative intensity, %) 380 ($[M+1]^+$, 100), 252 (53), 224 (9), 155 (15); Anal. Calcd for $C_{13}H_{18}INO_2S$: C, 41.17; H, 4.78; N, 3.69. Found: C, 41.04; H, 4.67; N, 3.72.