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Aza-Henry reaction with perfluoroalkylated cyclic ketimines

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Experimental

General Remarks. 1D NMR (^{1}H, ^{19}F, and ^{13}C) spectra were obtained with Bruker VRX-400 and Agilent 400-MR spectrometers. Chemical shifts for ^{1}H NMR spectroscopic data were referenced to internal tetramethylsilane (δ = 0.0 ppm); chemical shifts for ^{13}C NMR spectroscopic data were referenced to $CDCl_3$ (δ = 77.0 ppm); chemical shifts for ^{19}F NMR spectroscopic data were referenced to $PhCF_3$ (δ = –63.90 ppm) or $CFCl_3$ (δ = 0.0 ppm). TLC was carried out on precoated silica plates (Silufol UV-254), which were visualized with UV light and/or spraying with ninhydrin solution or aqueous $Ce(SO_4)_2$ solution with phosphomolybdic and sulfuric acids. Flash chromatography was carried out using MP Silica 60 (320–630 mesh) with the solvents indicated. All solvents and reagents for the reactions were of reagent grade, and were dried and distilled immediately before use. Compounds **1a-e** were synthesized according to procedure.**Error! Bookmark not defined.**

General procedure for the aza-Henry reaction: To a solution of cyclic imine (1 mmol) in nitroalkane (1 ml) anhydrous zinc chloride (0.5 mmol, 68 mg) and DBU (0.5 mmol, 75 μl) were added. The mixture was heated at 95°C (for **1a**) or kept at room temperature (for **1b-e**). The reaction was monitored by NMR ^{19}F. The mixture was cooled to room temperature, $ZnCl_2$ was filtered off, the filtrate was concentrated under reduced pressure, and the product was isolated by column chromatography (eluent: dichloromethane).

2-Nitromethyl-2-(trifluoromethyl)pyrrolidine (2a): Yellowish oil (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73-1.81 (1H, m, CH_2), 1.84-1.94 (1H, m, CH_2), 2.00-2.07 (1H, m, CH_2), 2.14-2.21 (1H, m, CH_2), 2.39 (1H, br. s, H-N), 3.05 (2H, t, $^{3}J_{HH}$ = 6.4 Hz, CH_2), 4.52 (1H, d, $^{2}J_{HH}$ = 11.5 Hz, CH_2-NO_2), 4.59 (1H, d, $^{2}J_{HH}$ = 11.5 Hz, CH_2-NO_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8 (CH_2), 30.3 (CH_2), 46.9 (CH_2), 66.7 (q, $^{2}J_{CF}$ = 27.9 Hz, C-CF_3), 77.4 (CH_2-NO_2), 126.1 (q, $^{1}J_{CF}$ = 284.3 Hz, CF_3). ^{19}F NMR (280 MHz, $CDCl_3$): δ -71.14 (CF_3). IR (KBr) ν = 1230 (CF) cm^{-1}. ESI-MS (m/z): $C_6H_{10}F_3N_2O_2$ $[M+H]^+$ 199.0650, found 199.0686.

2-Nitromethyl-2-(trifluoromethyl)piperidine (2b): Yellowish oil (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48-1.62 (3H, m, CH_2-CH_2), 1.68-1.78 (2H, m, CH_2), 1.89-1.96 (1H, m, CH_2), 2.31 (1H, br. s, H-N), 2.89-3.03 (2H, m, CH_2), 4.57 (1H, d, $^{2}J_{HH}$ = 11.6 Hz, CH_2-NO_2), 4.71 (1H, d, $^{2}J_{HH}$ = 11.6 Hz, CH_2-NO_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5 (CH_2), 24.0 (CH_2), 26.5 (CH_2), 40.7 (CH_2), 60.1 (q, $^{2}J_{CF}$ = 25.8 Hz, C-CF_3), 74.7 (CH_2-NO_2), 125.9 (q, $^{1}J_{CF}$ = 286.5 Hz, CF_3). ^{19}F NMR (280 MHz, $CDCl_3$): δ -75.62 (CF_3). IR (KBr) ν = 1230 (CF) cm^{-1}. ESI-MS (m/z): $C_7H_{12}F_3N_2O_2$ $[M+H]^+$ 213.0806, found 213.0840.

2-Nitromethyl-2-(trifluoromethyl)azepane (2c): Yellowish oil (78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39-1.61 (5H, m, CH_2- CH_2- CH_2), 1.75-1.81 (2H, m, CH_2), 1.92-1.99 (1H, m, CH_2), 2.27 (1H, br. s, H-N), 2.73-2.92 (2H, m, CH_2), 4.41 (1H, d, $^{2}J_{HH}$ = 11.4 Hz, CH_2-NO_2), 4.49 (1H, d, $^{2}J_{HH}$ = 11.4 Hz, CH_2-NO_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2 (CH_2), 30.2 (CH_2), 30.9 (CH_2), 32.6 (CH_2), 42.8 (CH_2), 60.1 (q, $^{2}J_{CF}$ = 25.5 Hz, C-CF_3), 77.7 (CH_2-NO_2), 126.6 (q, $^{1}J_{CF}$ = 287.8 Hz, CF_3). ^{19}F NMR (280 MHz, $CDCl_3$): δ -76.08 (CF_3). IR (KBr) ν = 1230 (CF) cm^{-1}. ESI-MS (m/z): $C_8H_{14}F_3N_2O_2$ $[M+H]^+$ 227.0963, found 227.1001.

2-Nitromethyl-2-(pentafluoroethyl)pyrrolidine (2d): Brown oil (27%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72-1.95 (4H, m, CH_2-CH_2), 2.62 (1H, br. s, H-N), 3.05-3.11 (2H, m, CH_2), 5.14 (1H, d, $^{2}J_{HH}$ = 12.8 Hz, CH_2-NO_2), 5.62 (1H, d, $^{2}J_{HH}$ = 12.8 Hz, CH_2-NO_2). ^{19}F NMR (280 MHz, $CDCl_3$): δ -78.56 (3F, s, CF_3), -120.40 (2F, q, $^{3}J_{FF}$ = 276.9 Hz, CF_2). IR (KBr) ν = 1220 (CF) cm^{-1}, 1227 (CF) cm^{-1}. ESI-MS (m/z): $C_7H_{10}F_5N_2O_2$ $[M+H]^+$ 249.0657, found 249.0640.

2-Nitromethyl-2-(pentafluoroethyl)piperidine (2e): Brown oil (16%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45-1.72 (4H, m, CH_2-CH_2), 1.78-1.82 (1H, m, CH_2), 1.95-2.02 (1H, m, CH_2), 2.35 (1H, br. s, H-N), 2.88-3.05 (2H, m, CH_2), 4.72 (2H, dd, J_1 = 2.6 Hz, J_2 = 12.3 Hz, CH_2-NO_2). ^{19}F NMR (280 MHz, $CDCl_3$): δ -77.23 (3F, s, CF_3), -120.52 (2F, q, $^{3}J_{FF}$ = 276.9 Hz, CF_2). IR (KBr) ν = 1220 (CF) cm^{-1}, 1227 (CF) cm^{-1}. ESI-MS (m/z): $C_8H_{12}F_5N_2O_2$ $[M+H]^+$ 263.0814, found 263.0810.

2-(1-Nitroethyl)-2-(trifluoromethyl)pyrrolidine (2f): Yellowish oil (60%), mixture of diastereomers (1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58-1.62 (6H, m, $2CH_3$), 1.72-1.79 (2H, m, CH_2), 1.82-1.88 (2H, m, CH_2), 2.04-2.25 (6H, m, 2NH-CH_2), 3.02-3.07 (4H, m, $2CH_2$), 4.80 (1H, q, $^{3}J_{HH}$ = 4.8 Hz, CH-NO_2), 4.84 (1H, q, $^{3}J_{HH}$ = 4.9 Hz, CH-NO_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.9 (CH_3), 15.3 (CH_3), 24.5 (CH_2), 25.3 (CH_2), 28.1 (CH_2), 28.8 (CH_2), 46.9 (CH_2), 47.2 (CH_2), 68.9 (q, $^{2}J_{CF}$ = 26.9 Hz, C-CF_3), 69.0 (q, $^{2}J_{CF}$ = 26.9 Hz, C-CF_3), 84.4 (CH-NO_2), 84.5 (CH-NO_2), 125.5 (q, $^{1}J_{CF}$ = 286.7 Hz, CF_3), 125.6 (q, $^{1}J_{CF}$ = 286.7 Hz, CF_3). ^{19}F NMR (280

MHz, $CDCl_3$): δ -76.20 (CF_3), δ -76.20 (CF_3). IR (KBr) ν = 1230 (CF) cm^{-1}. ESI-MS (m/z): $C_7H_{12}F_3N_2O_2$ $[M+H]^+$ 213.0846, found 213.0801.

2-(1-Nitroethyl)-2-(trifluoromethyl)piperidine (2g): Yellowish oil (60%), mixture of diastereomers (1:1). ^1H NMR (400 MHz, $CDCl_3$): δ 1.60-1.76 (14H, m, $2CH_3$+CH_2-CH_2), 2.10-2.21 (6H, m, 2NH-CH_2), 3.85-3.90 (2H, m, CH_2), 3.92-3.97 (2H, m, CH_2), 5.15 (1H, q, $^3J_{HH}$ = 6.7 Hz, *CH*-NO_2), 5.21 (1H, q, $^3J_{HH}$ = 7.1 Hz, *CH*-NO_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 14.1 (CH_3), 23.5 (CH_2), 23.6 (CH_2), 24.0 (CH_2), 25.4 (CH_2), 33.4 (CH_2), 34.4 (CH_2), 58.7 (CH_2), 59.0 (CH_2), 60.2 (q, $^2J_{CF}$ = 25.5 Hz, *C*-CF_3), 83.1 (*CH*-NO_2), 83.2 (*CH*-NO_2), 127.0 (q, $^1J_{CF}$ = 294.0 Hz, CF_3). ^{19}F NMR (280 MHz, $CDCl_3$): δ -72.91 (CF_3), δ -73.75 (CF_3). IR (KBr) ν = 1230 (CF) cm^{-1}. ESI-MS (m/z): $C_8H_{14}F_3N_2O_2$ $[M+H]^+$ 227.1002, found 226.9997.

2-(1-Nitropropyl)-2-(trifluoromethyl)pyrrolidine (2h): Brownish oil (38%), mixture of diastereomers (1:1). ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (3H, t, $^2J_{HH}$ = 7.3 Hz, CH_3), 0.95 (3H, t, $^2J_{HH}$ = 7.2 Hz, CH_3), 1.76-1.83 (3H, m, CH_2-NH), 1.84-1.93 (3H, m, CH_2-NH), 1.97-2.29 (8H, m, $4CH_2$), 3.03-3.06 (2H, m, CH_2), 4.57 (1H, dd, J_1 = 3.4 Hz, J_2 = 11.2 *CH*-NO_2), 4.66 (1H, dd, J_1 = 2.6 Hz, J_2 = 12.0 *CH*-NO_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.1 (CH_3), 10.2 (CH_3), 21.7 (CH_2), 22.2 (CH_2), 24.1 (CH_2), 25.1 (CH_2), 28.0 (CH_2), 28.4 (CH_2), 46.6 (CH_2), 46.7 (CH_2), 74.2 (q, $^2J_{CF}$ = 25.0 Hz, *C*-CF_3), 91.3 (*CH*-NO_2), 91.6 (*CH*-NO_2), 126.4 (q, $^1J_{CF}$ = 286.9 Hz, CF_3), 126.5 (q, $^1J_{CF}$ = 286.9 Hz, CF_3). ^{19}F NMR (280 MHz, $CDCl_3$): δ -76.49 (CF_3), δ -76.71 (CF_3). IR (KBr) ν = 1230 (CF) cm^{-1}. ESI-MS (m/z): $C_8H_{14}F_3N_2O_2$ $[M+H]^+$ 227.1002, found 227.1026.

General procedure for the reduction of nitro amines: Nitro amine **2a-c** (0.2 mmol) was dissolved in methanol (15 ml) and saturated aqueous ammonia (2 ml), and 10% palladium on carbon (50 mg) as catalyst was added. The suspension was stirred under hydrogen atmosphere (1 atm) for 28 h and then filtered through a Celite plug. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (dichloromethane/methanol, 10:1).

[2-(Trifluoromethyl)pyrrolidin-2-yl]methanamine (3a): Yellowish oil (48%): ^1H NMR (400 MHz, $CDCl_3$): δ 1.62-2.01 (7H, m, CH_2-CH_2+NH+NH_2), 2.68 (1H, d, *J* = 13.4 Hz, *CH*$_2$-NH_2), 2.94 (1H, d, *J* = 13.4 Hz, *CH*$_2$-NH_2), 2.98-3.08 (2H, m, *CH*$_2$-NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0 (CH_2), 30.1 (CH_2), 45.0 (CH_2), 47.4 (CH_2), 67.4 (q, $^2J_{CF}$ = 24.7 Hz, *C*-CF_3), 128.4 (q, $^1J_{CF}$ = 284.6 Hz, CF_3). ^{19}F NMR (280 MHz, $CDCl_3$): δ -78.20 (3F, s, CF_3). IR(KBr): 3300 (bs, NH), 1169 (CF), 1147 (CF) cm^{-1}. HRMS (ESI): calcd. for $C_6H_{12}F_3N_2$ $[M+H]^+$ 169.0948, found 169.0944.

[2-(Trifluoromethyl)piperidin-2-yl]methanamine (3b): Colourless oil (82 %): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41-1.64 (9H, m, CH_2-CH_2-CH_2+NH+NH_2), 2.65-2.68 (1H, m, *CH_2*-NH), 2.72 (2H, s, *CH_2*-NH_2), 2.81-2.82 (1H, m, *CH_2*-NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6 (CH_2), 24.6 (CH_2), 25.5 (CH_2), 40.7 (CH_2), 42.9 (CH_2), 58.0 (q, $^{2}J_{CF}$ = 22.4 Hz, *C*-CF_3), 128.1 (q, $^{1}J_{CF}$ = 288.0 Hz, CF_3). ^{19}F NMR (280 MHz, $CDCl_3$): δ -75.82 (3F, s, CF_3). IR(KBr): 3305 (bs, NH), 1159 (C-F), 1130 (C-F) cm^{-1}. HRMS (ESI): calcd. for $C_7H_{14}F_3N_2$ $[M+H]^+$ 183.1104, found 183.1108.

1-[2-(Trifluoromethyl)azepan-2-yl]methanamine (3c): Yellowish liquid (82 %): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26-1.50 (5H, m, CH_2-CH_2+NH), 1.61-1.77 (6H, m, CH_2-CH_2+NH_2), 2.58-2.62 (1H, m, *CH_2*-NH_2), 2.77-2.83 (3H, m, *CH_2*-NH_2+CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.7 (CH_2), 30.6 (CH_2), 31.0 (CH_2), 33.7 (CH_2), 43.2 (CH_2), 46.4 (CH_2), 61.6 (q, $^{2}J_{CF}$ = 22.4 Hz, **C**-CF_3), 129.0 (q, $^{1}J_{CF}$ = 290.0 Hz, CF_3). ^{19}F NMR (280 MHz, $CDCl_3$): δ -76.91 (3F, s, CF_3). IR(neat): 3340 (bs), 1155 cm^{-1}. HRMS (ESI): calcd. for $C_8H_{16}F_3N_2$ $[M+H]^+$ 197.1260, found 197.1268.