Electronic supplementary materials *Mendeleev Commun.*, 2018, **28**, 133–134

Aza-Henry reaction with trifluoropiruvate ketimines

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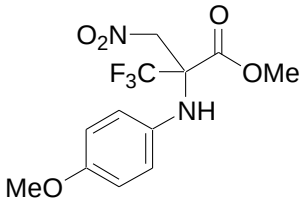
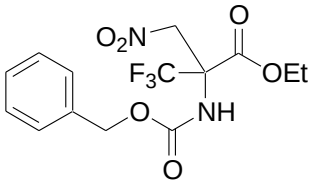
Experimental

General Remarks: 1D NMR (^{1}H, ^{19}F, and ^{13}C) spectra were recorded on 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) or DMSO-d_6 (δ = 39.5 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 staining 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 were of reagent grade, and were dried and distilled immediately before use. Compound **1a** was synthesized according to procedure[1] and compounds **1b-c** were synthesized according to procedure.[2]

General Procedure for aza-Henry reaction: To a solution of ketimine **1a-c** (1 mmol) in toluene (4 ml), nitroalkane (10 mmol, 0.535 ml of nitromethane, 0.500 ml of nitroethane or 0.890 ml of nitropropane) and DBU (1 mmol, 152 μl) were added. The mixture was kept at room temperature for 1 h (TLC control, eluent hexane – dichloromethane 3:1). The mixture was concentrated under reduced pressure, and the products **2a-g** were isolated by column chromatography using mixture of hexane and dichloromethane in ratio 1:1.

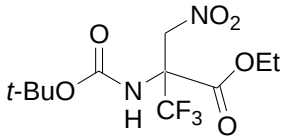


Methyl 3,3,3-trifluoro-2-(4-methoxyphenylamino)-2-(nitromethyl)-propanoate **2a**, 98%, brown oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (3H, s, CH_3-O), 3.99 (3H, s, CH_3-O), 4.83 (1H, bs, H-N), 5.01 (1H, d, $^2J_{HH}$ = 15.9, CH_2), 5.14 (1H, d, $^2J_{HH}$ = 15.9, CH_2), 6.80-6.81 (2H, m, Ar), 6.92-6.94 (2H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.0 (CH_3-O), 66.4 (q, $^2J_{CF}$ = 27.1 Hz, **C**-CF_3), 70.8 (**C**$\mathbf{H_2}$-NO_2), 114.1 (Ar), 122.2 (q, $^1J_{CF}$ = 289.0 Hz, CF_3), 125.3 (Ar), 133.0 (C_q, Ar), 114.1 (C_q, Ar), 156.3 (C=O). ^{19}F NMR (375 MHz, $CDCl_3$): δ -73.87 (CF_3). IR (ν, sm^{-1}) (neat): 3000 bs (NH), 1750 (CO). ESI-MS (m/z): calculated for $C_{12}H_{13}F_3N_2NaO_5$ $[M+Na]^+$ 345.0669, found 345.0666.

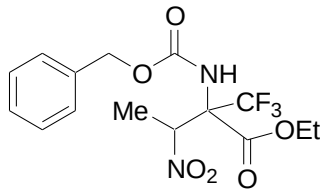


Ethyl 2-benzyloxycarbonylamino-3,3,3-trifluoro-2-(nitromethyl)propanoate **2b**, 85%, yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (3H, t, $^3J_{HH}$ = 7.3 Hz, $\mathbf{CH_3}$-CH_2), 4.43 (2H, q, $^3J_{HH}$ = 7.3 Hz, CH_3-$\mathbf{CH_2}$), 5.12 (2H, s, CH_2),

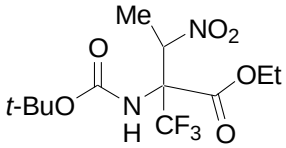
6.23 (2H, s, CH_2), 7.35-7.39 (5H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2 (**CH_3**-CH_2), 27.8 (CH_3-**CH_2**), 63.1 (q, $^2J_{CF}$ = 30.2 Hz, **C**-CF_3), 64.4 (CH_2), 67.3 (**CH_2**-NO_2), 117.9 (q, $^1J_{CF}$ = 283.5 Hz, **C**F_3), 127.8 (Ar), 128.2 (Ar), 132.2 (Ar), 134.8 (C_q, Ar), 153.5 (C=O), 163.1 (C=O). ^{19}F NMR (375 MHz, $CDCl_3$): δ -74.69 (CF_3). IR (ν, sm^{-1}) (neat): 3225 bs (NH), 1680 (CO), 1720 (CO). Calculated for $C_{14}H_{15}F_3N_2O_6$: C(46.16%), H(4.15%), N(7.69%); found C(46.36%), H(4.34%), N(7.88%).



Ethyl 2-tert-butoxycarbonylamino-3,3,3-trifluoro-2-(nitromethyl)propanoate **2c,** 91%, yellowish-brown oil: ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (3H, t, $^3J_{HH}$ = 7.3 Hz, **CH_3**-CH_2), 1.43 (9H, s, 3CH_3), 4.41 (2H, q, $^3J_{HH}$ = 7.3 Hz, CH_3-**CH_2**), 5.15-5.19 (2H, m, **CH_2**), 5.93 (1H, bs, H-N). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2 (CH_3), 27.6 (CH_3), 61.0 (q, $^2J_{CF}$ = 28.2 Hz, **C**-CF_3), 64.4 (CH_2-O), 70.0 (**C**-CH_3), 81.4 (**CH_2**-NO_2), 124.8 (q, $^1J_{CF}$ = 293.7 Hz, CF_3), 152.8 (C=O), 163.4 (C=O). ^{19}F NMR (375 MHz, $CDCl_3$): δ -74.71 (CF_3). IR (ν, sm^{-1}) (neat): 3345 bs (NH), 1780 (CO), 1670 (CO). Calculated for $C_{11}H_{17}F_3N_2O_6$: C(40.00%), H(5.19%), N(8.48%); found C(40.18%), H(5.23%), N(8.52%).

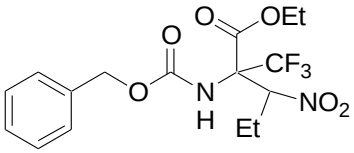


Ethyl 2-benzyloxycarbonylamino-3-nitro-2-(trifluoromethyl)butanoate **2d**, 55%, yellow oil (two diastereomers, 10:1): ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (0.3H, t, $^3J_{HH}$ =7.1 Hz, **CH_3**-CH_2), 1.35 (3H, t, $^3J_{HH}$ = 7.2 Hz, **CH_3**-CH_2), 1.77 (0.3H, dd, J_1 = 1.0 Hz, J_2 = 7.0 Hz, CH-**CH_3**), 1.94 (3H, d $^3J_{HH}$ =7.1 Hz, CH-**CH_3**), 4.24-4.30 (0.2H, m, CH_3-**CH_2**), 4.39-4.46 (2H, m, CH_3-**CH_2**), 5.10 (2H, s, **CH_2**-O), 5.49 (0.2H, s, **CH_2**-O), 6.24-6.29 (1H, m, **CH**-NO_2), 6.32 (1H, bs, NH), 7.31-7.40 (5.5H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 13.7 (CH_3), 14.5 (CH_3), 16.4 (CH_3), 63.5 (q, $^2J_{CF}$ = 24.8 Hz, **C**-CF_3), 64.2 (CH_2), 64.7 (CH_2), 67.6 (CH_2-O), 67.9 (CH_2-O), 80.9 (**CH**-NO_2), 82.6 (**CH**-NO_2), 122.5 (q, $^1J_{CF}$ = 287.2 Hz, CF_3), 122.7 (q, $^1J_{CF}$ = 287.2 Hz, CF_3), 127.5 (Ar), 128.1 (Ar), 128.3 (Ar), 128.4 (Ar), 128.5 (Ar), 128.6 (Ar), 135.3 (C_q), 135.7 (C_q), 153.7 (C=O), 153.9 (C=O), 163.1 (C=O), 163.3 (C=O). ^{19}F NMR (375 MHz, $CDCl_3$): δ -68.65 (CF_3), -80.66 (CF_3). IR (ν, sm^{-1}) (neat): 3405 bs (NH), 1780 (CO), 1775 (CO). ESI-MS (m/z): calculated for $C_{15}H_{18}F_3N_2O_6$ $[M+H]^+$ 345.1268, found 345.1246.

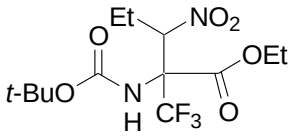


Ethyl 2-tert-butoxycarbonylamino-3-nitro-2-(trifluoromethyl)butanoate **2e**, 65%, yellowish oil (two diastereomers, 1:1): ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (3H, t, $^3J_{HH}$ = 7.1 Hz, **CH_3**-CH_2), 1.33 (3H, t, $^3J_{HH}$ = 7.1 Hz, **CH_3**-CH_2), 1.41 (9H, s, 3CH_3), 1.42 (9H, s, 3CH_3), 1.74 (3H, d, $^3J_{HH}$ = 7.0 Hz, **CH_3**-CH), 1.88 (3H, d, $^3J_{HH}$ = 7.0 Hz, **CH_3**-CH), 4.26-4.33 (2H, m, CH_3-**CH_2**), 4.36-4.41 (2H, m, CH_3-**CH_2**), 5.14-5.20 (1H, m, **CH**-NO_2), 5.29-5.34 (1H, m, **CH**-NO_2), 5.87 (1H, bs, NH), 5.99 (1H, bs, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2 (CH_3), 14.2 (CH_3), 15.8 (CH_3), 15.9 (CH_3), 27.5 (C-**CH_3**), 27.6 (C-**CH_3**), 63.3 (CH_2), 64.0 (CH_2), 80.7 (**CH**-NO_2), 81.4 (q, $^2J_{CF}$ = 27.2 Hz, **C**-CF_3), 82.4 (**CH**-NO_2), 122.2 (q, $^1J_{CF}$ = 289.5 Hz, CF_3), 122.4 (q, $^1J_{CF}$ = 289.5 Hz, CF_3), 152.6 (C=O), 152.8 (C=O), 163.1 (C=O), 163.2 (C=O).

^{19}F NMR (375 MHz, $CDCl_3$): δ -68.59 (CF_3), -83.16 (CF_3). IR (ν, sm^{-1}) (neat): 3385 bs (NH), 1745 (CO), 1675 (CO). ESI-MS (m/z): calculated for $C_{12}H_{20}F_3N_2O_6$ $[M+H]^+$ 379.1112, found 379.1109. Single diastereomer **3c**, yellowish oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (3H, t, $^3J_{HH}$ = 7.1 Hz, **CH₃**-CH_2), 1.43 (9H, s, $3CH_3$), 1.75 (3H, d $^3J_{HH}$ =7.0 Hz, CH-**CH₃**), 4.29-4.36 (2H, m, CH_3-**CH₂**), 5.32-5.34 (1H, m, **CH**-NO_2), 5.87 (1H, bs, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3 (CH_3), 14.2 (CH_3), 27.6 (C-**CH₃**), 63.4 (CH_2), 81.6 (q, $^2J_{CF}$ = 27.2 Hz, **C**-CF_3), 82.4 (**CH**-NO_2), 122.4 (q, $^1J_{CF}$ = 289.5 Hz, CF_3), 152.8 (C=O), 163.2 (C=O). ^{19}F NMR (375 MHz, $CDCl_3$): δ -83.16 (CF_3).

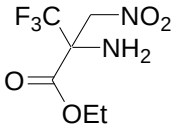


Ethyl 2-benzyloxycarbonylamino-3-nitro-2-(trifluoromethyl)pentanoate **2f**, 40%, yellow oil, (two diastereomers, 1:1): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, $^3J_{HH}$ = 7.2 Hz, **CH₃**-CH_2), 1.01 (3H, t, $^3J_{HH}$ = 7.6 Hz, **CH₃**-CH_2), 1.15-1.18 (3H, m, **CH₃**-CH_2), 1.24-1.38 (3H, m, **CH₃**-CH_2), 1.97-2.00 (1H, m, CH_3-**CH₂**), 2.33-2.36 (1H, m, CH_3-**CH₂**), 3.65-3.69 (1H, m, CH_3-**CH₂**), 3.69-3.71 (1H, m, CH_3-**CH₂**), 4.30-4.34 (2H, m., CH_2), 4.35-4.43 (2H, m, CH_2), 5.13-5.14 (1H, m, CH), 5.15-5.18 (1H, m, CH), 5.89 (2H, s, CH_2), 6.03 (2H, s, CH_2), 7.31-7.36 (5H, m, Ar). 7.37-7.39 (5H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6 (**CH₃**-CH_2), 10.7 (**CH₃**-CH_2), 13.2 (**CH₃**-CH_2), 13.4 (**CH₃**-CH_2), 21.7 (CH_3-**CH₂**), 22.7 (CH_3-**CH₂**), 29.3 (CH_3-**CH₂**), 30.5 (CH_3-**CH₂**), 67.3 (q, $^2J_{CF}$ = 27.4 Hz, **C**-CF_3), 88.0 (CH_2), 81.7 (CH_2), 88.3 (CH), 89.7 (CH), 122.0 (q, $^1J_{CF}$ = 301.5 Гц, CF_3), 127.8 (Ar), 127.9 (Ar), 128.0 (Ar), 128.1 (Ar), 128.2 (Ar), 128.3 (Ar), 134.9 (C_q, Ar), 135.0 (C_q, Ar), 153.3 (C=O), 153.7 (C=O), 163.0 (C=O), 163.4 (C=O). ^{19}F NMR (375 MHz, $CDCl_3$): δ -68.84 (CF_3), 78.79 (CF_3). IR (ν, sm^{-1}) (neat): 3340 bs (NH), 1670 (CO), 1700 (CO). ESI-MS (m/z): calculated for $C_{12}H_{13}F_3N_2NaO_5$ $[M+Na]^+$ 345.0669, found 345.0666. ESI-MS (m/z): calculated for $C_{16}H_{20}F_3N_2O_6^+$ $[M+H]^+$ 393.1268, found 393.1280.

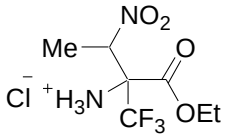


Ethyl 2-tert-butoxycarbonylamino-3-nitro-2-(trifluoromethyl)pentanoate **2g,** 44%, brown oil, (two diastereomers, 1:1): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, $^3J_{HH}$ = 7.1 Hz, **CH₃**-CH_2), 1.03 (3H, t, $^3J_{HH}$ = 7.1 Hz, **CH₃**-CH_2), 1.21-1.30 (3H, m, **CH₃**-CH_2), 1.32-1.39 (3H, m, **CH₃**-CH_2), 1.43 (9H, s, $3CH_3$), 1.46 (9H, s, $3CH_3$), 2.05-2.17 (1H, m, CH_3-**CH₂**), 2.26-2.37 (1H, m, CH_3-**CH₂**), 3.64-3.72 (1H, m, CH_3-**CH₂**), 3.74-3.82 (1H, m, CH_3-**CH₂**), 4.30-4.34 (2H, m, CH_2), 4.39-4.44 (2H, m, CH_2), 5.55-5.57 (1H, m, CH), 5.68-5.73 (1H, m, CH), 5.95 (1H, bs, H-N), 6.26 (1H, bs, H-N). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6 (**CH₃**-CH_2), 10.8 (**CH₃**-CH_2), 13.3 (**CH₃**-CH_2), 13.4 (**CH₃**-CH_2), 21.7 (CH_3-**CH₂**), 22.0 (CH_3-**CH₂**), 27.6 ($3CH_3$), 29.3 ($3CH_3$), 63.3 (CH_3-**CH₂**), 63.9 (CH_3-**CH₂**), 65.9 (q, $^2J_{CF}$ = 28.9 Hz, **C**-CF_3), 81.2 (**C**-CH_3), 81.7 (**C**-CH_3), 88.3 (CH), 89.7 (CH), 121.3 (q, $^1J_{CF}$ = 285.5 Hz, **C**F_3), 152.5 (C=O), 152.9 (C=O), 162.8 (C=O), 163.3 (C=O). ^{19}F NMR (375 MHz, $CDCl_3$): δ -69.75 (CF_3), 77.37 (CF_3). IR (ν, sm^{-1}) (neat): 3300 bs (NH), 1680 (CO), 1760 (CO). ESI-MS (m/z): calculated for $C_{13}H_{22}F_3N_2O_6^+$ $[M+H]^+$ 359.1425, found 359.1441.

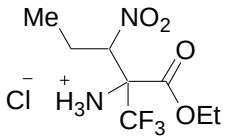
General Procedure for Boc-deprotection of amine group: A Boc-derivative of α-nitro amine **2c,e,g** (0.17 mmol) was dissolved in 5 M methanolic hydrogen chloride (1 ml). The solution was kept at room temperature for 2 h and then evaporated. The residues were pure hydrochlorides of compounds **3b** and **3c**, the yields were quantitative. Hydrochloride **3a** was treated with 1M KOH (5 ml), extracted with CH_2Cl_2 (10 ml) and evaporated *in vacuo* to give pure nitroamine.



Ethyl 2-amino-3,3,3-trifluoro-2-(nitromethyl)propanoate **3a**, 97%, yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (3H, t, $^3J_{HH}$ = 7.1 Hz, **CH₃**-CH_2), 4.39 (1H, bs, H-N), 4.46 (2H, q, $^3J_{HH}$ = 7.1 Hz, CH_3-**CH₂**), 4.80 (1H, d,$^2J_{HH}$ = 14.4 Hz, **CH₂**-NO_2), 5.08 (1H, d,$^2J_{HH}$ = 14.4 Hz, **CH₂**-NO_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7 (**CH₃**-CH_2), 65.1 (CH_3-**CH₂**), 74.6 (**CH₂**-NO_2), 75.1 (q, $^2J_{CF}$ = 29.3 Hz, **C**-CF_3), 121.8 (q, $^1J_{CF}$ = 285.5 Hz, **C**F_3), 166.3 (C=O). ^{19}F NMR (375 MHz, $CDCl_3$): δ -77.30 (CF_3). ESI-MS (m/z): calculated for $C_6H_{10}F_3N_2O_4^+$ $[M+H]^+$ 231.0588, found 231.0593.



Ethyl 2-amino-3-nitro-2-(trifluoromethyl)butanoate hydrochloride **3b**·HCl, 98%, yellowish oil, (two diastereomers 1:1): ^{1}H NMR (400 MHz, DMSO-d^6): δ 1.22-1.26 (6H, m, 2**CH₃**-CH_2), 1.53-1.55 (6H, m, 2**CH₃**-CH), 4.26-4.31 (4H, m, 2CH_3-**CH₂**), 5.23-5.28 (1H, m, **CH**-NO_2), 5.42-5.47 (1H, m, **CH**-NO_2). ^{13}C NMR (100 MHz, DMSO-d^6): δ 12.2 (CH_3), 12.5, (CH_3), 13.6 (CH_3), 14.3 (CH_3), 62.9 (CH_2), 63.4 (CH_2), 73.0 (q, $^2J_{CF}$ = 30.3 Hz, **C**-CF_3), 83.6 (**CH**-NO_2), 83.9 (**CH**-NO_2), 123.8 (q, $^1J_{CF}$ = 287.1 Hz, **C**F_3) 165.1 (C=O), 166.4 (C=O). ^{19}F NMR (375 MHz, $CDCl_3$): δ - 71.79 (CF_3), -72.78 (CF_3). ESI-MS (m/z): calculated for $C_7H_{12}F_3N_2O_4^+$ $[M+H]^+$ 245.0744, found 245.0748.



Ethyl 2-amino-3-nitro-2-(trifluoromethyl)pentanoate hydrochloride **5c**·HCl, 99%, yellowish oil, (mixture of two diastereomers 1:1): ^{1}H NMR (400 MHz, DMSO-d^6): δ 0.81-0.90 (3H, m, **CH₃**-CH_2), 1.17-1.22 (3H, m, **CH₃**-CH_2), 1.59-2.23 (2H, m, CH_3-**CH₂**), 4.18-4.31 (2H, m, CH_3-**CH₂**), 5.07-5.15 (1H, m, **CH**-NO_2), 5.71 (3H, bs, H-N). ^{13}C NMR (100 MHz, DMSO-d^6): δ 10.0 (CH_3), 10.3 (CH_3), 13.6 (CH_3), 13.7, (CH_3), 21.5 (CH_3), 22.2 (CH_3), 63.7 (CH_2), 64.2 (CH_2), 66.7 (q, $^2J_{CF}$ = 27.1 Hz, **C**-CF_3), 89.6 (**CH**-NO_2), 90.0 (**CH**-NO_2), 123.5 (q, $^1J_{CF}$ = 287.1 Hz, **C**F_3) 164.2 (C=O), 165.1 (C=O). ^{19}F NMR (375 MHz, $CDCl_3$): δ - 72.21 (CF_3), -73.53 (CF_3). ESI-MS (m/z): calculated for $C_8H_{14}F_3N_2O_4^+$ $[M+H]^+$ 259.0901, found 259.0910.

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[1] X. Han, H. Wu, W. Wang, C. Dong, P. Tien, S. Wu and H. Zhou, *Org. Biomol. Chem.*, 2014, **12**, 8308.

[2] L. Hill, B. Gherman, N. Aboelella, C. Cramer and W. Tolman, *Dalton Trans*., 2006, 4944.