Supplementary Material

An application of triflic anhydride as an acid activator: Synthesis of N^{α} protected amino hydroxamic acids

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Experimental section

All the chemicals were purchased from Sigma Aldrich Company, USA. All the solvents were freshly distilled and dried whenever required. TLC analysis was carried out using Merck aluminium TLC sheets (Silica gel 60 F254), the chromatograms were visualized by UV light and also by exposing in an iodine chamber. Column chromatography using mixtures of ethyl acetate and hexane as eluents through silica gel (100-200 mesh). HRMS spectra were recorded in a XEVO-G2-XS-Q-TOF mass spectrometer. ¹H and ¹³C NMR were determined in Brucker AV NMR (400 MHz, 100 MHz) spectrometer. The RP-HPLC analysis of epimers was carried out using an Agilent instrument (Model: 1260). Column chromatography was performed on silica gel (100-200 mesh) using ethyl acetate and hexane mixture as eluent.

General procedure for the synthesis of N^{α} -protected amino hydroxamic acid

To a solution of N^{α} -protected amino acid (100 mg, 0.447 mmol, 1 equiv.) in CH₂Cl₂, Triflic anhydride (1.5 equiv.) and Et₃N (1.5 equiv.) was added stirring at 0 °C for 15 min under an inert atmosphere. To the above activated carboxylic acid, methanolic solution of hydroxylamine hydrochloride (2.0 equiv.l) and Et₃N (3.0 equiv.) was added and stirred reaction mixture for 2.5 h at 0 °C to rt. After the completion of the reaction (observed in TLC), solvent was evaporated under vacuum and diluted with EtOAc, washed with 10% citric acid solution, water and brine solution. The organic phase was dried over anhydrous Na₂SO₄ and removed under reduced pressure. The crude residue was purified by column chromatography using hexane and ethyl acetate as eluents.

General procedure for the synthesis of aryl hydroxamic acid

To a solution of aryl acid (100 mg, 0.818 mmol, 1 equiv.) in CH₂Cl₂, Triflic anhydride (1.2 equiv.) and Et₃N (1.0 equiv.) was added stirring at 0 °C for 15 min under an inert atmosphere. To the above activated carboxylic acid, methanolic solution of hydroxylamine hydrochloride (2.0 equiv.) and Et₃N (3.0 equiv.) was added and stirred reaction mixture for 2.5 h at 0 °C to rt. After the completion of the reaction (observed in TLC), solvent was evaporated under vacuum and diluted with EtOAc, washed with 10% citric acid solution, water and brine solution. The organic phase was dried over anhydrous Na₂SO₄ and removed under reduced pressure. The crude residue was purified by column chromatography using hexane and ethyl acetate as eluents.

Characterization data



(S)-tert-butyl (1-(hydroxyamino)-1-oxo-3-phenylpropan-2-yl)carbamate (2.1a)

White solid; (96.1 mg, 0.342 mmol 91% yield); ¹H NMR (400 MHz, DMSO- d_6): δ 9.5 (s, 1H), 8.03 (s, 1H), 7.28-7.13 (m, 5H), 4.02 (dd, J = 16 Hz, 8 Hz, 1H), 2.96-2.84 (m, 2H), 1.34 (s, 9H); ¹³C NMR (100 MHz, DMSO- d_6): δ 171.1, 155.3, 137.6, 129, 128, 126.2, 80.3, 55.8, 36.5, 27.5; FT-IR (cm⁻¹) 3350, 3309, 2918, 2927, 1672, 1662, 1513; HRMS: calcd. For C₁₄H₂₀N₂O₄Na [M+Na]: 303.1321, found: 303.1322.



benzyl (2-(hydroxyamino)-2-oxoethyl)carbamate (2.1b)

White solid; (93.2 mg, 0.415 mmol 87% yield); ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.49 (s, 1H), 8.78 (s, 1H), 7.45-7.34 (m, 5H), 5.03 (s, 2H), 3.52 (d, *J* = 4 Hz, 2H); ¹³C NMR (100 MHz, DMSO*d*₆): δ 166, 156.3, 137, 128.2, 127.7, 127.6, 65.4, 41.3; FT-IR (cm⁻¹) 3318, 2943, 1705, 1672, 1536, 770, 697; HRMS: calcd. ForC₁₀H₁₂N₂NaO₄[M+Na]: 247.0694, found: 247.0696.



(S)-benzyl (1-(hydroxyamino)-4-methyl-1-oxopentan-2-yl)carbamate (2.1c)

White solid; (95.1 mg, 0.339 mmol 90% yield); ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.66 (s, 1H), 7.35 (t, *J* = 4 Hz, 5H), 7.07 (s, 1H), 5.01 (s, 2H), 4.03 (dd, *J* = 12 Hz, 8 Hz, 1H), 1.56 (dd, *J* = 16 Hz, 8 Hz, 3H), 0.85 (dd, *J* = 16 Hz, 4 Hz, 6H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 168.8, 155.7, 137, 128.3, 128.2, 127.7, 127.6, 127.3, 65.3, 50.8, 40.8, 24.1, 22.7, 21.6; FT-IR (cm⁻¹) 3301, 2956, 2461, 1642, 1612, 1535, 1425, 866, 693; HRMS: calcd. For C₁₄H₂₀N₂O₄Na [M+Na]: 303.1321, found: 303.1320.



(S)-benzyl (1-(hydroxyamino)-1-oxopropan-2-yl)carbamate(**2.1d**)

White solid; (100.3 mg, 0.421 mmol 94% yield); ¹H NMR (400 MHz, DMSO- d_6): δ 10.54 (s, 1H), 8.83 (s, 1H), 7.43-7.34 (m, 5H), 5.01 (s, 2H), 3.98-3.91 (m, 1H), 1.19 (d, J = 8 Hz, 3H); ¹³C NMR (100 MHz, DMSO- d_6): δ 169.2, 155.5, 137, 128.3, 127.7, 127.6, 65.3, 47.9, 18.2; FT-IR (cm⁻¹) 3426, 3306, 2925, 1685, 1618, 1533; HRMS: calcd. For C₁₁H₁₄N₂NaO₄ [M+Na]: 261.0851, found: 261.0846.



benzyl (S)-(1-(hydroxyamino)-1-oxo-3-phenylpropan-2-yl)carbamate (**2.1e**)

White solid; (98.7 mg, 0.314 mmol 92% yield); ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.66 (s, 1H), 7.58 (d, *J* = 8 Hz, 1H), 7.35-7.21 (m, 10H), 4.95 (s, 2H), 4.16-4.10 (m, 1H), 2.91 (dd, *J* = 16 Hz, 4 Hz, 1H), 2.80 (dd, *J* = 12 Hz, 12 Hz, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 168, 155.6, 137.9, 137, 129.1, 128.2, 128, 127.6, 127.4, 126.2, 65.1, 54, 37.6; FT-IR (cm⁻¹) 3350, 3309, 2918, 2927, 1672, 1662, 1513.



(9H-fluoren-9-yl)methyl ((2S,3S)-1-(hydroxyamino)-3-methyl-1-oxopentan-2-yl)carbamate

(2.1f)

White solid; (103.6 mg, 0.281 mmol 91% yield); ¹H NMR (400 MHz, DMSO- d_6): δ 10.63 (s, 1H), 8.84 (s, 1H), 7.89 (d, J = 8 Hz, 2H), 7.75 (d, J = 8 Hz, 2H), 7.41 (t, J = 8 Hz, 4H), 7.32 (dd, J = 4 Hz, 4 Hz, 2H), 4.27-4.19 (m, 4H), 1.75-1.69 (m, 1H), 1.50-1.42 (m, 2H), 1.24 (d, J = 12 Hz, 3H), 0.88 (d, J = 8 Hz, 3H); ¹³C NMR (100 MHz, DMSO- d_6): δ 167.8, 155.8, 143.7, 140.6, 127.6, 127, 125.3, 120, 65.6, 56.7, 46.6, 35.8, 24.5, 15.2, 10.5; FT-IR (cm⁻¹) 3308, 3162, 2971, 1695, 1641, 1541; HRMS: calcd. For C₂₁H₂₅N₂O₄ [M+H]: 369.1814, found: 369.1807.



(9H-fluoren-9-yl)methyl (S)-(1-(hydroxyamino)-3-methyl-1-oxobutan-2-yl)carbamate (2.1g)

White solid; (92.9 mg, 0.262 mmol 89% yield); ¹H NMR (400 MHz, DMSO- d_6): δ 10.62 (s, 1H), 7.90 (d, J = 8 Hz, 2H), 7.76 (dd, J = 4 Hz, 4 Hz, 2H), 7.51 (d, J = 8 Hz, 1H), 7.43 (t, J = 8 Hz, 2H), 7.36-7.31 (m, 2H), 4.28-4.21 (m, 3H), 3.64 (t, J = 8 Hz, 1H), 1.96-1.89 (m, 1H), 0.88 (dd, J = 12 Hz, 8 Hz, 6H); ¹³C NMR (100 MHz, DMSO- d_6): δ 167.8, 155.9, 143.8, 140.6, 127.6, 127, 125.3, 120, 65.7, 58.2, 46.6, 30, 19.1, 18.7; FT-IR (cm⁻¹) 3305, 3208, 2925, 2467, 1686, 1647, 1536; HRMS: calcd. For C₂₀H₂₃N₂O₄ [M+H]: 355.1658, found: 355.1655.



(9H-fluoren-9-yl)methyl (S)-(1-(hydroxyamino)-4-methyl-1-oxopentan-2-yl)carbamate (2.1h)

White solid; (103.6 mg, 0.281 mmol 91% yield); ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.66 (s, 1H), 7.90 (d, *J* = 8 Hz, 2H), 7.74 (d, *J* = 8 Hz, 2H), 7.52 (d, *J* = 12 Hz, 1H), 7.43 (t, *J* = 8 Hz, 2H), 7.36-7.31 (m, 2H), 4.29-4.22 (m, 3H), 3.97-3.92 (m, 1H), 1.60-1.49 (m, 2H), 1.42-1.35 (m, 1H), 0.90 (d, *J* = 8 Hz, 3H), 0.86 (d, *J* = 8 Hz, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 168.8, 155.7, 143.9, 140.6, 127.6, 127, 125.3, 120, 65.5, 50.7, 46.6, 40.8, 24.1, 22.7, 21.6; FT-IR (cm⁻¹) 3342, 3259, 2922, 1695, 1661, 1561, 1288, 737, 697.



(9H-fluoren-9-yl)methyl 2-(hydroxycarbamoyl)pyrrolidine-1-carboxylate (2.1i)

White solid; (88.7 mg, 0.251 mmol 85% yield); ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.58 (s, 1H), 7.90 (d, *J* = 8 Hz, 2H), 7.67 (t, *J* = 8 Hz, 2H), 7.42 (t, *J* = 8 Hz, 2H), 7.34 (d, *J* = 8 Hz, 2H), 4.20-4.02 (m, 4H), 3.50-3.45 (m, 2H), 1.90-1.81 (m, 4H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 168.6, 153.8, 143.9, 140.7, 139.4, 137.4, 128.9, 127.6, 127.2, 127.1, 125.1, 121.3, 120 (2C), 66.5, 57.9, 47, 46.6, 30, 23.9; FT-IR (cm⁻¹) 3324, 3098, 2981, 1682, 1647, 1545; HRMS: calcd. For C₂₀H₂₁N₂O₄ [M+H]: 353.1501, found: 353.1504.



(9H-fluoren-9-yl) methyltert-butyl (6-(hydroxyamino)-6-oxohexane-1,5-diyl) (S)-dicarbamate

(**2.1**j)

White solid; (89.0 mg, 0.201 mmol 86% yield); ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.89 (s, 1H), 7.90 (d, *J* = 8 Hz, 2H), 7.74 (d, *J* = 4 Hz, 2H), 7.49 (d, *J* = 8 Hz, 1H), 7.43 (t, *J* = 8 Hz, 2H), 7.36-7.32 (m, 2H), 6.76 (s, 1H), 4.27-4.22 (m, 3H), 3.85 (dd, *J* = 12 Hz, 8 Hz, 1H), 2.90 (d, *J* = 4 Hz, 2H), 1.56 (dd, *J* = 16 Hz, 4 Hz, 2H), 1.38 (s, 9H), 1.31-1.21 (m, 4H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 168.6, 155.7, 155.5, 143.8, 140.6, 127.6, 127, 125.3, 120, 77.3, 65.6, 52.3, 46.6, 31.6, 29.1, 28.2, 22.7; FT-IR (cm⁻¹) 3295, 3217, 2915, 2461, 1687, 1637, 1529; HRMS: calcd. For C₂₆H₃₄N₃O₆ [M+H]: 484.2447, found: 484.2443.



tert-butyl (S)-3-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(hydroxyamino)-3oxopropyl)-1H-indole-1-carboxylate (**2.1k**)

White solid; (85.3 mg, 0.157 mmol 83% yield); ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.84 (s, 1H), 8.04 (d, *J* = 8 Hz, 1H), 7.87 (d, *J* = 8 Hz, 2H), 7.79 (dd, *J* = 16 Hz, 8 Hz, 2H), 7.63 (dd, *J* = 20 Hz, 8 Hz, 3H), 7.41-7.27 (m, 6H), 4.28 (t, *J* = 8 Hz, 1H), 4.16 (dd, *J* = 4 Hz, 8 Hz, 2H), 4.04 (dd, *J* = 16 Hz, 8 Hz, 1H), 3.04-3.01 (m, 2H), 1.58 (s, 9H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 168, 155.7, 149, 143.7, 143.6, 140.6 (2C), 134.6, 130.1, 127.5, 126.9, 125.2, 124.2, 124, 122.4, 120, 119.4, 116.6, 114.6, 83.4, 65.7, 52.2, 46.5, 27.6, 27.4; FT-IR (cm⁻¹) 3299, 3198, 2931, 2461, 1682, 1642, 1530.



(9H-fluoren-9-yl)methyl (S)-(3-(4-(tert-butoxy)phenyl)-1-(hydroxyamino)-1-oxopropan-2yl)carbamate (**2.1l**)

White solid; (89.8 mg, 0.217 mmol 87% yield); ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.7 (s, 1H), 7.89 (d, *J* = 8 Hz, 2H), 7.69 (t, *J* = 4 Hz, 3H), 7.42 (t, *J* = 8 Hz, 2H), 7.32 (dd, *J* = 16 Hz, 8 Hz, 2H), 7.19 (d, *J* = 8 Hz, 2H), 6.82 (d, *J* = 8 Hz, 2H), 4.13-4.09 (m, 4H), 2.90-2.79 (m, 2H), 1.20 (s, 9H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ168.1, 155.6, 153.4, 143.7 (2C), 140.6 (2C), 132.5, 129.6, 127.5, 127, 125.3, 123.2, 120, 77.5, 65.7, 54, 46.5, 37.1, 28.4; FT-IR (cm⁻¹) 3312, 3212, 2937, 2462, 1697, 1612, 1525; HRMS: calcd. For C₂₈H₃₁N₂O₅ [M+H]: 475.2233, found: 475.2232.



(9H-fluoren-9-yl)methyl ((S)-1-(((S)-1-(hydroxyamino)-3-methyl-1-oxobutan-2-yl)amino)-1,5dioxo-5-(tritylamino)pentan-2-yl)carbamate (**2.1m**)

White solid; (86.7 mg, 0.119 mmol 85% yield); ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.58 (s, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 7.4 Hz, 2H), 7.48 – 7.38 (m, 3H), 7.35 – 7.16 (m, 18H), 4.31 – 4.15 (m, 4H), 4.10 - 4.04 (m, 1H), 2.46 – 2.35 (m, 1H), 2.34 – 2.25 (m, 1H), 2.08 – 1.98 (m, 1H), 1.86 – 1.79 (m, 1H), 1.72 – 1.64 (m, 1H), 0.85 (dd, *J* = 6.7, 4.4 Hz, 7H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.5, 172.4, 171.9, 156.3, 145.3, 144.2 (2), 141.1, 128.9, 128.1, 127.9, 127.5, 126.8, 125.7, 120.6, 69.6, 66.0, 57.7, 54.4, 47.1, 33.3, 30.3, 28.4, 19.3, 18.5; FT-IR (cm⁻¹) 3294, 3219, 2932, 1734, 1692, 1634, 1538, 736, 552.



N-hydroxybenzamide (4a)

White solid; (99.9 mg, 0.728 mmol 89% yield); ¹H NMR (400 MHz, DMSO- d_6): δ 9.03 (s, 1H), 7.75 (dd, J = 8 Hz, 3 Hz, 2H), 7.50-7.43 (m, 3H); ¹³C NMR (100 MHz, DMSO- d_6): δ 164.1, 131, 128.3, 127.4, 126.8; FT-IR (cm⁻¹) 3298, 3051, 2758, 1640, 1618, 1573; HRMS: calcd. For C₇H₈NO₂ [M+H]: 138.0555, found: 138.0553.



4-fluoro-N-hydroxybenzamide (**4b**)

White solid; (95.2 mg, 0.613 mmol 86% yield); ¹H NMR (400 MHz, DMSO- d_{\circ}): δ 11.23 (s, 1H),

7.85-7.80 (m, 2H), 7.32-7.27 (m, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 165.4, 163.7, 163,

129.9, 129.8, 115.9, 115.7; FT-IR (cm⁻¹) 3314, 3150, 2780, 1647, 1629, 1563.



N-hydroxy-4-methoxybenzamide (**4c**)

White solid; (101.0 mg, 0.604 mmol 92% yield); ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.89 (s, 1H), 7.74 (dd, J = 8 Hz, *J* = 1.0 Hz, 2H), 6.99 (dd, *J* = 4 Hz, 2H), 3.81 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 164, 161.4, 128.5, 124.9, 113.5, 55.2; FT-IR (cm⁻¹) 3201, 3071, 2754, 1641, 1621, 1568.



3-bromo-N-hydroxybenzamide (**4d**)

White solid; (97.7 mg, 0.452 mmol 91% yield); ¹H NMR (400 MHz, DMSO- d_6): δ 11.33 (s, 1H), 7.92 (t, J = 4 Hz, 1H), 7.78-7.73 (m, 2H), 7.44 (t, J = 8 Hz, 1H); ¹³C NMR (100 MHz, DMSO-

*d*₆): δ 162.5, 134.9, 133.8, 130.6, 129.5, 125.9, 121.6; FT-IR (cm⁻¹) 3260, 3015, 2769, 1661, 1619, 1499.



HRMS Spectrum of compound 2.1a



¹H NMR Spectrum of compound 2.1a



¹³C NMR Spectrum of compound 2.1a



HRMS Spectrum of compound 2.1b



¹H NMR Spectrum of compound 2.1b





¹³C NMR Spectrum of compound 2.1b



HRMS Spectrum of compound 2.1c



¹H NMR Spectrum of compound 2.1c





¹³C NMR Spectrum of compound 2.1c



HRMS Spectrum of compound 2.1d





Special Issue 'Synthetic and structural organic chemistry'







¹H NMR Spectrum of compound 2.1e



¹³C NMR Spectrum of compound 2.1e



HRMS Spectrum of compound 2.1f



¹H NMR Spectrum of compound 2.1f







HRMS Spectrum of compound 2.1g



¹H NMR Spectrum of compound 2.1g



¹³C NMR Spectrum of compound 2.1g



¹H NMR Spectrum of compound 2.1h



¹³C NMR Spectrum of compound 2.1h



HRMS Spectrum of compound 2.1i



¹H NMR Spectrum of compound 2.1i







HRMS Spectrum of compound 2.1j





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¹³C NMR Spectrum of compound 2.1j



¹H NMR Spectrum of compound 2.1k







HRMS Spectrum of compound 2.11







¹³C NMR Spectrum of compound 2.11



¹H NMR Spectrum of compound 2.1m



¹³C NMR Spectrum of compound 2.1m

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¹³C NMR Spectrum of compound 4a

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¹H NMR Spectrum of compound 4b





¹³C NMR Spectrum of compound 4b



¹H NMR Spectrum of compound 4c











¹³C NMR Spectrum of compound 4d



RP-HPLC Chromatogram of compound Fmoc-L-Val-NHOH

RP-HPLC profiles of **2.1g** (method: water-methanol (20-80%) in 40 min; VWD at $\lambda = 254$ nm; flow rate: 1.0 mL/min; column: phenominex made Lux, pore size-5 μ , Cellulose-1, diameter x length = 250 x 4.6 mm).



RP-HPLC Chromatogram of compound Fmoc-L&D-Val-NHOH

RP-HPLC profiles of racemic mixture of **2.1g** (method: water-methanol (20-80%) in 40 min; VWD at $\lambda = 254$ nm; flow rate: 1.0 mL/min; column: phenominex made Lux, pore size-5 μ , Cellulose-1, diameter x length = 250 x 4.6 mm).



RP-HPLC Chromatogram of compound Cbz-L-Phe-NHOH

RP-HPLC profiles of **2.1e** (method: water-methanol (40-60%) in 40 min; VWD at $\lambda = 254$ nm; flow rate: 1.0 mL/min; column: phenominex made Lux, pore size-5 μ , Cellulose-1, diameter x length = 250 x 4.6 mm).



RP-HPLC Chromatogram of compound Fmoc-L-Leu-NHOH

RP-HPLC profiles of **2.1h** (method: water-methanol (20-80%) in 40 min; VWD at $\lambda = 254$ nm; flow rate: 1.0 mL/min; column: phenominex made Lux, pore size-5 μ , Cellulose-1, diameter x length = 250 x 4.6 mm).



RP-HPLC Chromatogram of compound Fmoc-L-Lys(Boc)-NHOH

RP-HPLC profiles of **2.1j** (method: water-methanol (15-85%) in 40 min; VWD at $\lambda = 254$ nm; flow rate: 0.5 mL/min; column: phenominex made Lux, pore size-5 μ , Cellulose-1, diameter x length = 250 x 4.6 mm).



RP-HPLC Chromatogram of compound Fmoc-L-Try(Boc)-NHOH

RP-HPLC profiles of **2.11** (method: water-methanol (10-90%) in 40 min; VWD at $\lambda = 254$ nm; flow rate: 1.0 mL/min; column: phenominex made Lux, pore size-5 μ , Cellulose-1, diameter x length = 250 x 4.6 mm).