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

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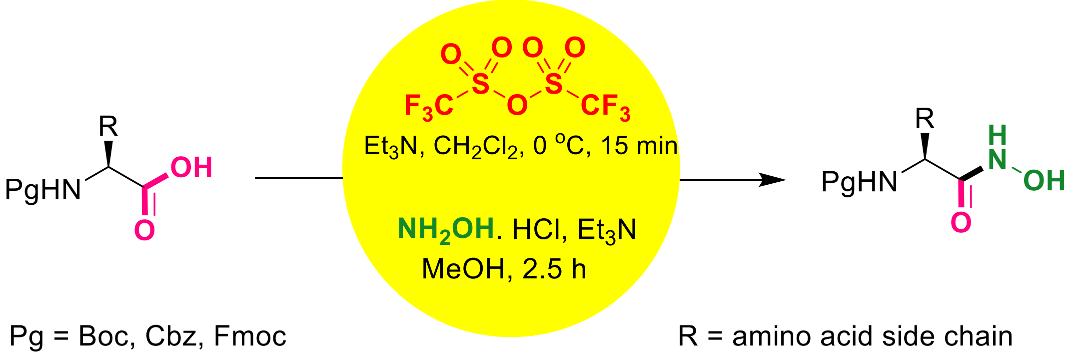
Abstract

A One-step synthesis of N^{α}-protected amino hydroxamic acids using triflic anhydride as an acid activator is demonstrated. The reaction can be executed under simple and mild conditions with good yields and purity. This method provides compatibility to Fmoc, Cbz and Boc protecting groups and the reaction is racemization-free which adds an advantage.



Keywords: Hydroxyl amine hydrochloride, N^{α}-protected amino hydroxamic acids, Triflic anhydride.

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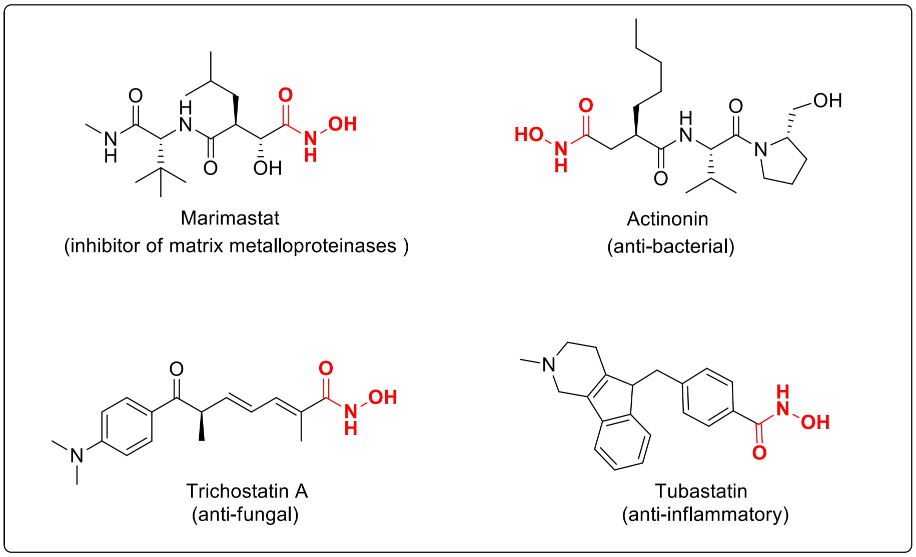
Introduction

Hydroxamic acid is an interesting functionality which has high relevance in the synthesis of drugs as well as the development of new pharmaceuticals.[1] The studies on the chelating ability of hydroxamic acids with Fe, Co, Ni, Cu and especially Zn(II) containing proteins has proven that these are strong metal ion chelators.[2, 3] Molecules with a NHOH moiety act as inhibitors of metalloproteins and histone deacetylase which are targets for anticancer therapy.[4] Due to their characteristics, hydroxamic acids are found in natural products as active functionality and are involved in a wide range of biological activities such as antibacterial, antihypertensive, antifungal and anticancer.[5, 6] Owing to their chelating ability towards metal ions, they are excellent inhibitors of histone deacetylases (HDAC)[5] and matrix metalloproteases (MMP),[6] which are associated with various afflictions including malaria, cancer, schizophrenia and arthritis (Figure 1). They also serve as plant regulators and found in natural products as active scaffold. Also, hydroxamic acids are recognized as key precursors in several synthetic protocols to obtain peptides, peptide hydroxamates and ureidopeptides which are being explored for new applications in medicinal chemistry.[7-9]


Marimastat
(inhibitor of matrix metalloproteinases)

Actinonin
(anti-bacterial)

Trichostatin A
(anti-fungal)

Tubastatin
(anti-inflammatory)

Figure 1. Drugs containing hydroxamic acid moiety.

Various approaches have been reported on the synthesis of hydroxamic acids. The widely employed method constitutes the coupling of O/N-protected hydroxyl amine such as N,O-bis (tert-butoxycarbonyl) hydroxylamine, N/O-bis(phenoxycarbonyl) hydroxylamine with activated carboxylic acid derivatives[10-12] such as acid fluorides and acid chlorides. Although, the acid chloride method furnishes good yields for Fmoc amino acids, however it is non-preferable in case of N-Boc/Cbz-protected amino acids. Also, active esters using KCN,[13] and ethyl chloroformate (ECF) activated carboxylic acid[14] were utilized for the synthesis of hydroxamic acids despite the fact that it is time consuming and involves moisture sensitive ECF, respectively. Interestingly, the transformation of carboxylic acid esters to hydoxamic acids using continuous flow reactor has been documented.[15] A number of coupling reagents viz. ethyl-2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate (NBsOXY),[16] 2,4,6-trichloro[1,3,5]triazine (TCT),[17] cyclic phosphonic anhydride (PPAA),[18, 19] tetramethylfluoroformamidiniumhexafluorophosphate (TFFH),[20] etc., are explored for the preparation of hydroxamic acids starting from the corresponding carboxylic acid. Aldehydes were also employed to yield hydroxamic acids using *N*-hydroxybenzenesulfonamide in the presence of strong base.[21] Kokotos' group reported an interesting one-pot synthesis of hydroxamic acids from aldehydes by photo-organocatalytic approach under metal-free conditions using visible light.[22] Alternatively, the oxidative reaction of an alcohol and its transformation to hydroxamic acid derivatives in the presence of (diacetoxyiodo)benzene ($PhI(OAc)_2$) and hydroxylamine has also been known;[23] however long reaction times, a two-step protocol and the necessity of catalysts makes this route cumbersome for amino acid chemistry.

Hydroxamic acids can also be prepared using a Lewis acid, samarium triflate as a promoter using *N*-acyloxazolidinones with hydroxylamine,[24] and esters under microwave conditions with the assistance of a base.[25] Additionally, there are reports on solid-phase synthesis of hydroxamic acids that generally involve the cleavage of resin-bound ester/thioester.[26] Our group has been involved in the synthesis of different precursors to achieve peptidomimetic molecules. With respect to this, we have reported the synthesis of hydroxamic acids using different reagents: COMU (1-cyano-2-ethoxy-2-oxoethylidenamiooxy)dimethylamino-morpholino-carbenium hexafluorophosphate)[27] and CPI-Cl (3,3-dichloro-1,2-diphenylcyclopropene).[28] However, the reagent CPI-Cl has to be prepared and the formed byproduct, 2,3-diphenylcyclopropenone, needs to be removed from the reaction mixture through chromatography. The aforementioned approaches, in spite of their routine use, present their own limitations which prompted us to look for an alternative strategy.

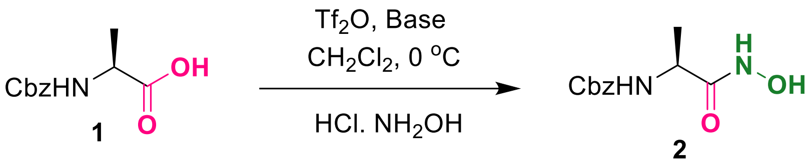
Triflic anhydride (Tf_2O) has been proven to exhibit broad applications in synthetic chemistry as an efficient electrophilic activator for carbonyl-type compounds, especially as excellent amide bond activator [28-31] which subsequently leads to various transformations like esters, thioamides, amidines, etc.,[32] when subjected to different nucleophiles. Despite of these inherent advantages, the application of Tf_2O to obtain hydroxamic acids from amino acids has not been explored.

Results and Discussion

Initially, Cbz-Ala-OH was chosen as a test substrate to convert to the corresponding hydroxamic acid. At first, Cbz-Ala-OH **1** was activated using triflic anhydride (Tf_2O) using Et_3N as base in DCM at 0 °C for 15 min. Then, the solution of preneutralized hydroxylamine in DCM was added to the activated acid and stirred at room temperature till the completion of the reaction. The corresponding hydroxamic acid **2** was found to be formed in 4 h in low yield. In our previous report on the synthesis of α-ureidopeptidomimetics, the *in situ* isocyanato ester was formed when the carbamate moiety of Cbz-Ala-OMe was made to react with Tf_2O.[33] To verify the possible formation of amino acid isocyanate under the present reaction conditions, the reaction mixture was subject to IR studies. Notably, no band appeared in the expected region which corresponds to the NCO functionality in the IR spectra. Therefore, this confirms that Tf_2O selectively reacts with the carboxylic acid when compared to the carbamate or Cbz group. The low yield of the hydroxamic acid [entry 1, table 1] was therefore attributed to the presence of the unreacted acid and the partial solubility of hydroxyl amine hydrochloride in DCM. Further, the composition of the reactants was slightly increased with a change in solvent i.e., DMF for the neutralization of the hydroxyl amine hydrochloride. Herein, a moderate yield of the product was obtained and it was also noticed that there was no presence of Cbz-Ala-OH residue (monitored by TLC) in the reaction mixture. The improved reactivity was caused by the change of solvent from DCM to DMF. This inferred the impact of choice of the solvent on the yield. Although the yield was moderate, it is also usually difficul to remove DMF from the reaction mixture. Further, we explored the reaction conditions of our previously reported hydroxamic acids preparation,[27] i.e. methanolic KOH for the neutralization [table 1 entry 4]. The reaction proceeded well with an acceptable 83% yield of hydroxamic acid **2** along with uncharacterized trace impurities (monitored by TLC). Instead of KOH, three equivalents of Et_3N were tested for neutralization which afforded a good yield of

94% in 2.5 h. The reaction went smoothly without any possible side products (isocyanate, methyl ester, or carboxylic acid). As shown in Table 1, entry 8 and 9, the commonly employed bases N,N-diisopropylethylamine (DIPEA) and N-methylmorpholine (NMM) were tested with a subtle increase in nucleophilic hydroxyl amine equivalents; however no significant improvement in yield was noticed. Hence, the optimized condition for the efficient conversion to the hydroxamic acid was chosen as a reaction of Cbz-Ala-OH (1.0 equiv.) with Tf_2O (1.5 equiv.) and Et_3N (1.5 equiv.), followed by neutralized hydroxyl amine in methanol at 0 °C to rt for 2.5 h (Table 1, entry 5). Further, a gram-scale synthesis was carried out to demonstrate the practical utility of the proposed protocol. Notably, the reaction proceeds smoothly and the desired product **2** was isolated in a 89% yield.

Table 1. Optimization of the reaction conditions for the synthesis of hydroxamic acids



S.No	Tf_2O (equiv.)	Base (equiv.)	Equiv of HCl.H_2NOH (base equiv for deprotonation)	Temp	Yield (%)*
1	1.2	Et_3N (1.2)	1.2 in DCM (1.2 equiv. of Et_3N)	rt	32
2	1.5	Et_3N (1.5)	1.5 in DMF (1.5 equiv. of Et_3N)	0 °C	61
3	1.5	Et_3N (1.5)	2.0 in DMF (2.0 equiv. of Et_3N)	0 °C	69
4	1.5	Et_3N (1.5)	2.0 in MeOH (3.0 equiv. of KOH)	0 °C	83
5	1.5	Et_3N (1.5)	2.0 in MeOH (3.0 equiv. of Et_3N)	0 °C	94
6	1.5	Et_3N (1.5)	2.0 in MeOH (3.0 equiv. of Et_3N)	-15 °C	91
7	1.5	Et_3N (1.5)	2.5 in MeOH (3.5 equiv. of Et_3N)	0 °C	87
8	1.5	DIPEA (1.5)	2.0 in MeOH (3.0 equiv. of DIPEA)	0 °C	81
9	1.5	NMM (1.5)	2.0 in MeOH (3.0 equiv. of NMM)	0 °C	79

Using the optimized conditions, various N^{α}-protected amino/aryl acid substrates were smoothly converted to the corresponding hydroxamic acids in good yields. The sterically hindered side chain protected amino acids were also converted and well tolerated under the reaction conditions and provided satisfactory yields up to 87% (**2.1j-2.1l**). Also, the protocol was applied to the peptide moiety and furnished the corresponding peptidyl hydroxamic acid (**2.1m**) in good yield. The infrared absorption bands of **2.1a** show a strong band at 1672 cm^{-1}

due to the (C=O) and 3350 cm^{-1} due to the (O-H) absorption. This preliminary result confirms the identity of compound **2.1a**. Similarly, all the amino acid derived hydroxamic acids synthesized (**2.1b-2.1m**) show infrared spectra with two major functional groups i.e., the carbonyl 1685-1615 cm^{-1} and the hydroxamic acid group (O-H) at 3350-3200 cm^{-1}. Further, infrared absorption bands of **4a** show a strong band at 1618 cm^{-1} due to the (C=O) and 3298 cm^{-1} due to the (O-H) function. All the corresponding aryl hydroxamic acids (**4b-4d**) also show two absorption bands (see SI).

Table 2. List of *N*$^{\alpha}$-Protected amino hydroxamic acids synthesized

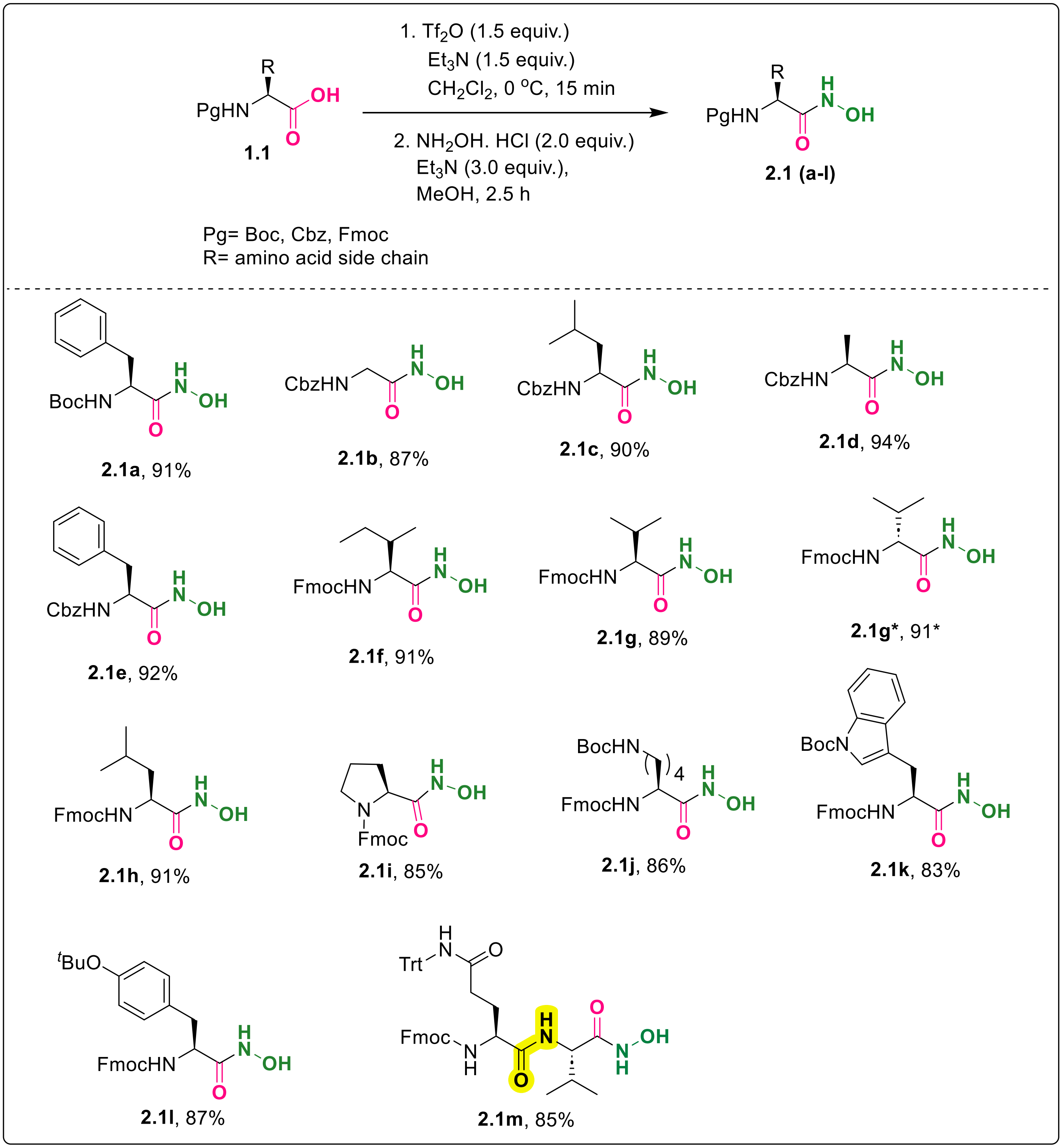
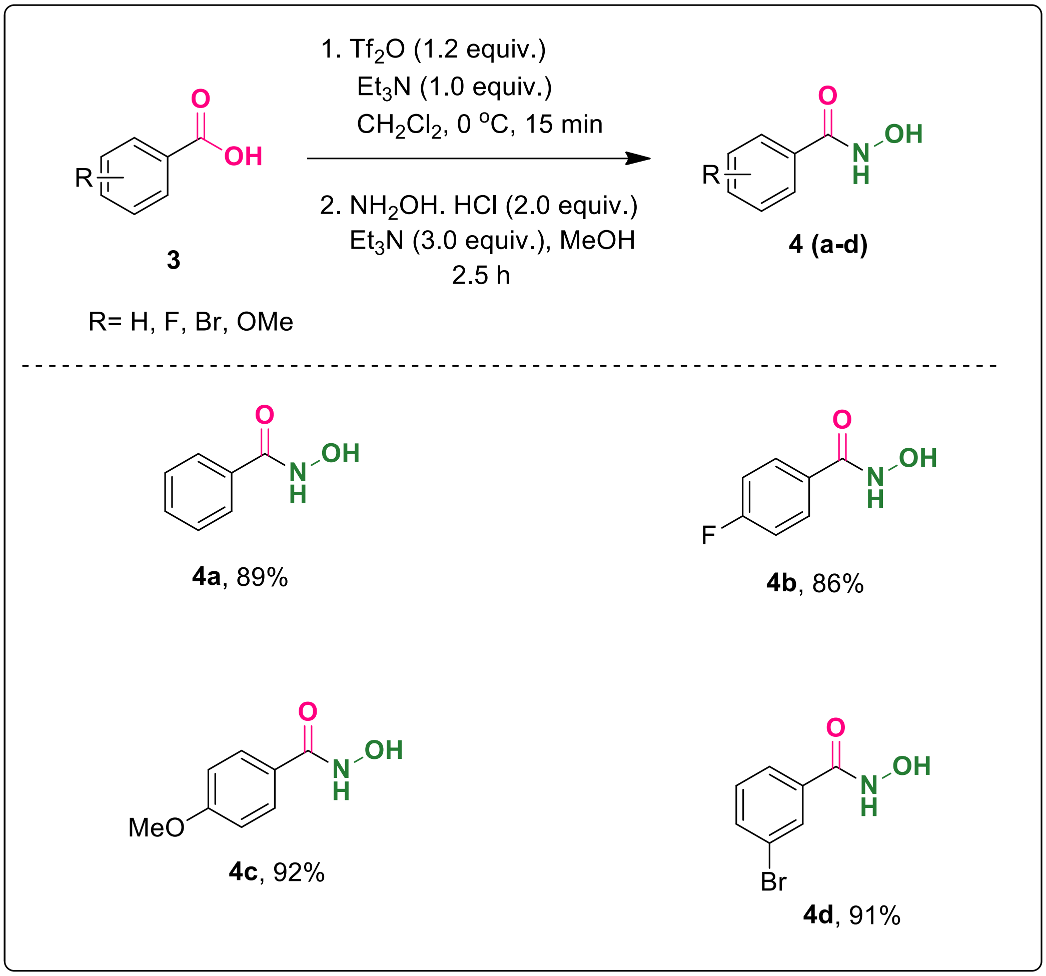
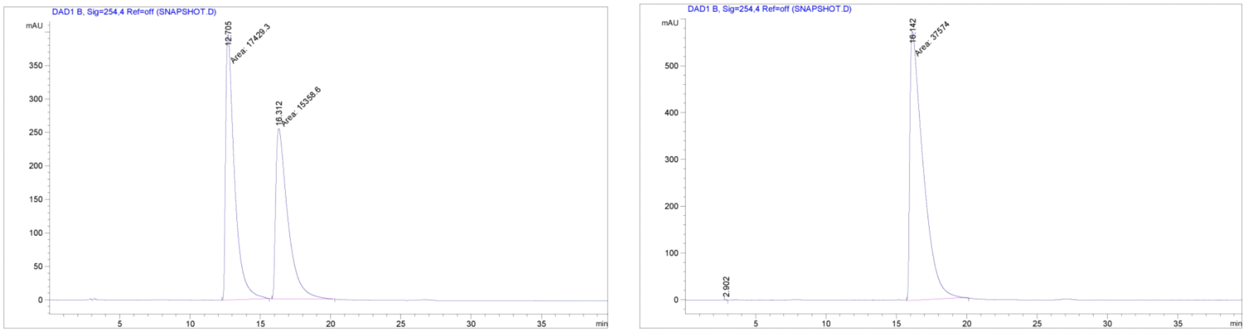


Table 3. List of aryl hydroxamic acids synthesized



To check the possible epimerization/racemization during the activation of the carboxylic acid and the subsequent coupling step, Fmoc-Val-OH was chosen as the model carboxyl component for the racemization study. The products **2.1g** and **2.1g*** were subjected to RP-HPLC analysis. The diastereomeric mixture of **2.1g** and **2.1g*** showed two distinct peaks at the retention times of 16.31 min and 12.70 min, respectively (i, Figure 2) and their enantiomeric pure compound **2.1g** showed a single peak at 16.14 min (ii, Figure 2). Therefore RP-HPLC analysis ensured that the reaction is free from detectable racemization.



i. RP-HPLC profile of racemic mixture of **2.1g** ii. RP-HPLC profile of compound **2.1g**

Figure 2. RP-HPLC Chromatograms of DL and L- Fmoc-Val-NHOH.

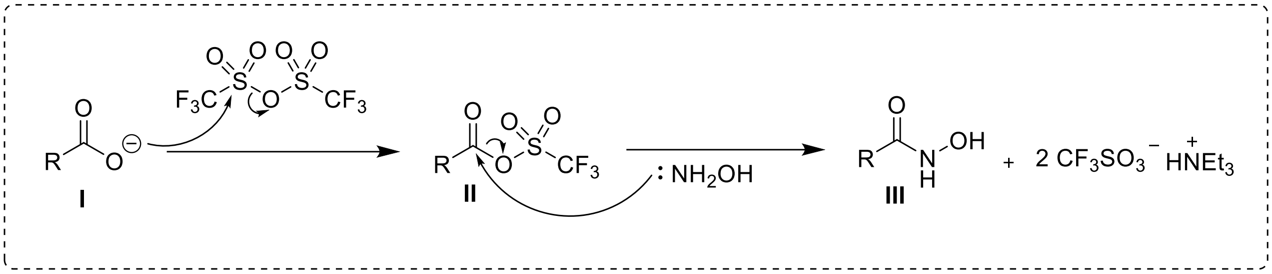


Figure 3. Plausible mechanism for the formation of the hydroxamic acid.

Owing to the chemoselectivity of triflic anhydride, it reacts preferably with acids over the carbamate group of Cbz amino acid. In the first step, nucleophilic attack of the carboxylate **I** on triflic anhydride leads to the mixed anhydride **II**, after which the pre-neutralized hydroxylamine hydrochloride displaces the triflate leading to the formation of the desired hydroxamic acid **III**. The elimination of triflate ions during the reaction was assisted by protonated triethylamine.

Conclusions

We have developed a simple and efficient protocol for the synthesis of N^α-protected amino hydroxamic acids involving Tf_2O as a carboxylic acid activator in amino acid chemistry. The friendly reaction conditions and the use of inexpensive reagents make this protocol a valid alternative to the existing ones. The reaction conditions do not effect the chirality of the amino acid derivatives. The protocol is compatible with commonly used urethanes namely Cbz, Boc and Fmoc. All the compounds were obtained in good yields and confirmed by HRMS, ^{1}H and ^{13}C NMR analysis.

Experimental Section

General. 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. ^{1}H and ^{13}C NMR were determined using a 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 (1 equiv.) in CH_2Cl_2, triflic anhydride (1.5 equiv.) and Et_3N (1.5 equiv.) was added while stirring at 0 °C for 15 min under an inert atmosphere. To the above activated carboxylic acid, a methanolic solution of hydroxylamine hydrochloride (2.0 equiv.l) and Et_3N (3.0 equiv.) was added and the reaction mixture was stirred for 2.5 h at 0 °C to rt. After the completion of the reaction (observed by TLC), the solvent was evaporated under vacuum and diluted with EtOAc, washed with a 10% citric acid solution, water and a brine solution. The organic phase was dried over anhydrous Na_2SO_4 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 (1 equiv.) in CH_2Cl_2, triflic anhydride (1.2 equiv.) and Et_3N (1.0 equiv.) was added while stirring at 0 °C for 15 min under an inert atmosphere. To the above activated carboxylic acid, a methanolic solution of hydroxylamine hydrochloride (2.0 equiv.l) and Et_3N (3.0 equiv.) was added and the reaction mixture was stirred for 2.5 h at 0 °C to rt. After the completion of the reaction (observed by TLC), the solvent was evaporated under vacuum and diluted with EtOAc, washed with a 10% citric acid solution, water and a brine solution. The organic phase was dried over anhydrous Na_2SO_4 and removed under reduced pressure. The crude residue was purified by column chromatography using hexane and ethyl acetate as eluents.

(S)-*tert*-Butyl (1-(hydroxyamino)-1-oxo-3-phenylpropan-2-yl)carbamate (2.1a). hite 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, *CCC* 16 Hz, 8 Hz, 1H), 2.96-2.84 (m, 2H), 1.34 (s, 9H); ^{13}C 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$C_{14}H_{20}N_2O_4Na$ [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); ^{13}C 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. For$C_{10}H_{12}N_2NaO_4$[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); ^{13}C 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 $C_{14}H_{20}N_2O_4Na$ [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); ^{13}C 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 $C_{11}H_{14}N_2NaO_4$ [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); ^{13}C 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.

(9*H*-Fluoren-9-yl)methyl ((2*S*,3*S*)-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); ^{13}C 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 $C_{21}H_{25}N_2O_4$ [M+H]: 369.1814, found: 369.1807.

(9*H*-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); ^{13}C 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 $C_{20}H_{23}N_2O_4$ [M+H]: 355.1658, found: 355.1655.

(9*H*-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); ^{1}H 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); ^{13}C 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); ^{1}H 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); ^{13}C 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 $C_{20}H_{21}N_2O_4$ [M+H]: 353.1501, found: 353.1504.

(9*H*-Fluoren-9-yl)methyltert-butyl (6-(hydroxyamino)-6-oxohexane-1,5-diyl)(*S*)-dicarbamate (2.1j). White solid; (89.0 mg, 0.201 mmol 86% yield); ^{1}H 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); ^{13}C 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 $C_{26}H_{34}N_3O_6$ [M+H]: 484.2447, found: 484.2443.

***tert*-Butyl (*S*)-3-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(hydroxyamino)-3-oxopropyl)-1*H*-indole-1-carboxylate (2.1k).** White solid; (85.3 mg, 0.157 mmol 83% yield); ^{1}H 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); ^{13}C 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.

(9*H*-Fluoren-9-yl)methyl (*S*)-(3-(4-(*tert*-butoxy)phenyl)-1-(hydroxyamino)-1-oxopropan-2-yl)carbamate (2.1l). White solid; (89.8 mg, 0.217 mmol 87% yield);^{1}H 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); ^{13}C 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 $C_{28}H_{31}N_2O_5$ [M+H]: 475.2233, found: 475.2232.

(9H-Fluoren-9-yl)methyl ((*S*)-1-(((*S*)-1-(hydroxyamino)-3-methyl-1-oxobutan-2-yl)amino)-1,5-dioxo-5-(tritylamino)pentan-2-yl)carbamate (2.1m). White solid; (86.7 mg, 0.119 mmol 85% yield); ^{1}H 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); ^{13}C 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); ^{1}H 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); ^{13}C 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 $C_7H_8NO_2$ [M+H]: 138.0555, found: 138.0553.

4-Fluoro-*N*-hydroxybenzamide (4b). White solid; (95.2 mg, 0.613 mmol 86% yield);^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 11.23 (s, 1H), 7.85-7.80 (m, 2H), 7.32-7.27 (m, 2H); ^{13}C 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); ^{1}H 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); ^{13}C 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); ^{1}H 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); ^{13}C 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.

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Supplementary Material

^{1}H NMR, ^{13}C NMR, Mass and RP-HPLC data for the title compounds.

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