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Convenient synthesis of a library of discrete hydroxamic acids using the hydroxythiophenol (Marshall) resin ☆

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Abstract

Several resins have reportedly been used to synthesize hydroxamic acids except for the hydroxythiophenol (Marshall) resin. Herein, we report the use of the Marshall resin to synthesize hydroxamic acids from carboxylic acids and its application to convert a library of 14 discrete aliphatic and aromatic carboxylic acids including N-protected amino acids to their corresponding hydroxamic acids in good yields.
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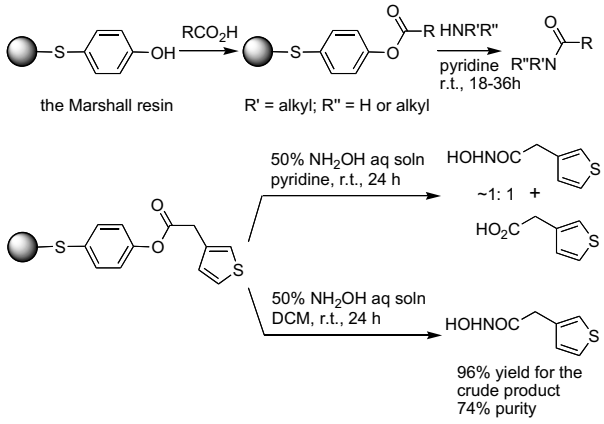
Hydroxamic acids are known as zinc coordinators that have been widely used as zinc protease inhibitors.[1–11] In the course of developing small-molecule inhibitors of the zinc endopeptidase of botulinum neurotoxin serotype A (BoNTA),[12,13] we needed a method to convert a library of discrete carboxylates immobilized on the hydroxythiophenol (Marshall) resin to hydroxamates to derivatize our hydroxamate-containing BoNTA inhibitors using split-and-pool combinatorial synthesis.[14,15] Several resins have reportedly been used for the syntheses of hydroxamic acids and these include (1) the thioester-attached resin,[16] (2) the O-immobilized-hydroxylamine-containing Wang resin,[17–22] (3) the oxime (Kaiser) resin,[23] (4) the *N*-hydroxybenzenesulfonamide-attached resin,[24] (5) the trityl resin,[25,26] (6) the chlorotrityl resin,[27] and (7) the HMBA-AM resin.[28] However, the Marshall resin has not been reported for its use in synthesizing hydroxamic acids.

The reports of facile cleavage of amides from the Marshall resin by primary or secondary amines using pyridine as a swelling solvent[29–38] prompted us to investigate the feasibility of obtaining hydroxamic acids from carboxylates immobilized on the Marshall resin using hydroxylamine as a cleavage agent (Scheme 1). On converting 2-(thiophen-3-yl)acetate immobilized on the Marshall resin to *N*-hydroxy-2-(thiophen-3-yl)acetamide (Scheme 1), we obtained the desired pure product when cleaving the acetate from the Marshall resin using 50% hydroxylamine aqueous solution in pyridine and using high-performance



Scheme 1. Syntheses of amides and hydroxamic acids using the Marshall resin.

☆ Author contributions: Conceived and designed the experiments: J.G.P. Performed the experiments: J.C. and J.G.P. Analyzed the data: J.C., J.G.P., and Y.P.P. Wrote the Letter: J.G.P., and Y.P.P.

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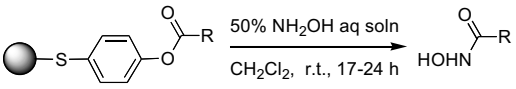
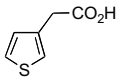
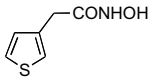
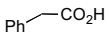
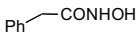
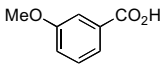
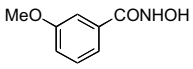
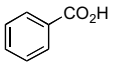
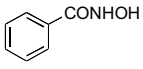
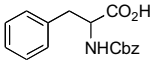
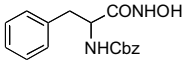
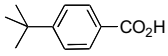
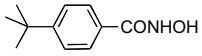
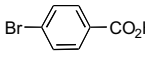
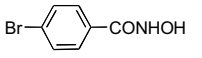
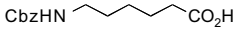
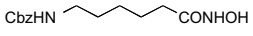
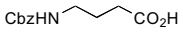
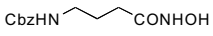
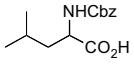
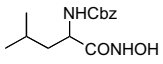
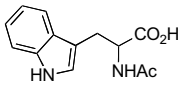
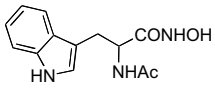
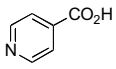
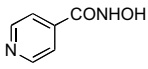
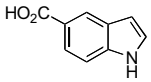
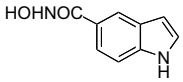
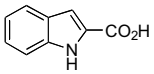
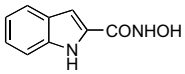


Scheme 2. Syntheses of hydroxamic acids using the Marshall resin.

liquid chromatography (HPLC) purification. However, the crude product was in a mixture (nearly 1:1 ratio) with the corresponding carboxylic acid that was generated presumably by water in the presence of pyridine during the cleavage. To avoid the formation of the carboxylic acid, we performed the cleavage by using 50% hydroxylamine aqueous solution in dichloromethane (DCM) or toluene and readily obtained the desired hydroxamic acid without contamination by the carboxylic acid according to the proton NMR spectrum of the crude hydroxamic acid.

Further studies showed that the new method of converting carboxylates to hydroxamates shown in Scheme 2[39] is applicable to both aromatic and aliphatic acids including N-protected amino acids. This method can be used for the synthesis of a library of discrete hydroxamic acids (Table 1). For the synthesis of a library of 14 discrete, representative hydroxamic acids listed in Table 1, only 1*H*-indole-5-carboxylic acid (entry 13) had a low yield of

Table 1
Syntheses of a library of discrete hydroxamic acids using the Marshall resin

Entry	Starting material	Product	Yield[a] (%)	Purity[b] (%)
1			96	74
2			63[c]	97
3			80	94
4			71	88
5			82	91
6			50	79
7			100	95
8			100	94
9			92	91
10			87	85
11			100	81
12			86	85[d]
13			33	92
14			67	93

[a] The yield for the crude product was calculated according to the capacity of the resin.

[b] Purity was estimated according to the integration (area %) of the HPLC chromatogram at 254 nm with correction of the methanol peak. The HPLC analysis condition: Zorbax SB C-18 4.6 × 250 mm, 1.0 mL/min, and linear gradient [the concentration of B in A was changed from 20% to 100% over 20 min, A = H_2O (0.1% TFA), B = CH_3CN/H_2O 9:1 (0.1% TFA)].

[c] The same amount of the product was obtained when toluene was used as a swelling solvent.

[d] Linear gradient: the concentration of B in A was changed from 0% to 2% over 20 min.

33% while others had yields of 50–100%. Purities of the products cleaved from the Marshall resin were 74–97% according to HPLC analysis. Liquid-chromatography–mass-spectrometry analyses of the 14 crude products listed in Table 1 showed that all products were free of starting materials except that hydroxamic acids of entries 8 and 12 were contaminated, respectively, by 2% and 15% of corresponding carboxylic acids that can be readily separated from the hydroxamic acids by HPLC.

The above results show that the Marshall resin is a useful solid-phase support for converting a wide range of carboxylic acids to hydroxamic acids by using split-and-pool combinatorial method.[14,15] The Marshall resin can yield directly a hydroxamic acid, unlike the thioester-attached resin that requires the use of NH_2OTMS and needs an extra step of deprotection after obtaining the O-protected hydroxamic acid. The convenient synthesis of a library of discrete hydroxamic acids using the Marshall resin demonstrated herein is useful to the syntheses of hydroxamate-containing inhibitors of metalloproteins involved in many diseases such as cancers,[5] cardiovascular diseases,[6–8] AIDS,[9,10] and Alzheimer's disease.[11]

Acknowledgments

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39. *Procedure*: the Marshall resin (1.6 mmol/g obtained from Aldrich Chem. Co., Milwaukee, WI, catalog number 554804-5G) was loaded into porous polypropylene containers, termed MicroKans (IRORI, San Diego, CA), using the dry resin filler from IRORI (~0.05 mmol, ~30 mg of the resin per MicroKan). The resin-containing MicroKans were shaken in DCM on an orbital shaker at room temperature for 10 min. Each member of a library of discrete carboxylic acids (3.0 equiv), *N*,*N*′-diisopropylcarbodiimide (26 μL, 3.2 equiv), and 4-di(methylamino)pyridine (6 mg, 0.9 equiv) were added to a labeled resin-containing MicroKan. [Note: addition of 1 mL of dimethylformamide (DMF) was necessary to dissolve carboxylic acids of entries 3, 4, 11, and 13.] The resulting MicroKans were shaken on an orbital shaker at room temperature for 20–30 h. The MicroKans were washed with DMF (2 × 3 mL/MicroKan), methanol (3 mL/MicroKan), and DCM (3 mL/MicroKan). The sequential washing with methanol and DCM was repeated two more times. The MicroKans were dried under high vacuum, and 100 μL of 50% hydroxylamine aqueous solution was then added to each MicroKan soaked separatedly in 3 mL of DCM. The resulting MicroKans were shaken on an orbital shaker at room temperature for 17–24 h. Afterwards the organic layer was separated from the aqueous layer by using a disposable pipette and concentrated under N_2 stream then further dried under high vaccum overnight to give the desired hydroxamic acid. ^{1}H NMR (400 MHz, DMSO-d_6) spectra of the products (purity: 74–97%) are as follows.
N-Hydroxy-2-(thiophen-3-yl)acetamide (entry 1): δ 10.61 (s, 1H), 8.81 (s, 1H), 7.44 (dd, $J = 4.9, 2.9$ Hz, 1H), 7.22 (m, 1H), 7.00 (d, $J = 4.9$ Hz, 1H), and 3.28 (s, 2H).
N-Hydroxy-2-phenylacetamide (entry 2): δ 10.64 (s, 1H), 8.81 (s, 1H), 7.22 (m, 5H), and 3.25 (s, 2H).

N-Hydroxy-3-methoxybenzamide (entry 3): δ 11.0 (br s, 1H), 9.1 (br s, 1H), 7.48–7.27 (m, 3H), 7.06 (m, 1H), and 3.77 (s, 3H).
N-Hydroxybenzamide (entry 4): δ 11.20 (s, 1H), 9.02 (s, 1H), 7.74–7.71 (m, 2H), and 7.52–7.41 (m, 3H).
Benzyl 1-(hydroxyamino)-1-oxo-3-phenylpropan-2-ylcarbamate (entry 5): δ 10.71 (s, 1H), 8.87 (s, 1H), 7.61 (d, $J = 8.8$ Hz, 1H), 7.34–7.13 (m, 10H), 4.95 (s, 2H), 4.09 (m, 1H), 2.87 (dd, $J = 13.6$, 4.9 Hz, 1H), and 2.76 (dd, $J = 13.6$, 3.5 Hz, 1H).
4-tert-Butyl-N-hydroxybenzamide (entry 6): δ 11.1 (br s, 1H), 8.9 (br s, 1H), 7.66 (d, $J = 8.2$ Hz, 2H), 7.44 (d, $J = 8.2$ Hz, 2H), and 1.27 (s, 9H).
4-Bromo-N-hydroxybenzamide (entry 7): δ 11.6 (br s, 1H), 9.32 (br s, 1H), 8.29 (d, $J = 8.8$ Hz, 2H), and 7.97 (d, $J = 8.8$ Hz, 2H).
Benzyl 6-(hydroxyamino)-6-oxohexylcarbamate (entry 8):δ 10.32 (s, 1H), 8.65 (s, 1H), 7.34 (m, 6H), 4.98 (s, 2H), 2.94 (m, 2H), 1.90 (t, $J = 7.2$ Hz, 2H), 1.45 (m, 2H), 1.36 (m, 2H), and 1.20 (m, 2H).
Benzyl 4-(hydroxyamino)-4-oxobutylcarbamate (entry 9): δ 10.34 (s, 1H), 8.75 (br s, 1H), 7.37–7.25 (m, 6H), 4.98 (s, 2H), 2.96 (m, 2H), 1.93 (t, $J = 7.5$ 2H), and 1.60 (m, 2H).
Benzyl 1-(hydroxyamino)-4-methyl-1-oxopentan-2-ylcarbamate (entry 10): δ 10.66 (s, 1H), 8.80 (br s, 1H), 7.43 (d, $J = 8.4$ Hz, 1H), 7.37–7.27 (m, 5H), 4.99 (s, 2H), 3.90 (m, 1H), 1.56–1.31 (m, 3H), 0.85 (d, $J = 6.6$ Hz, 3H), and 0.81 (d, $J = 6.6$ Hz, 3H).
2-Acetamido-N-hydroxy-3-(1H-indol-3-yl)propanamide (entry 11): δ 10.78 (s, 1H), 8.8 (br s, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 7.57 (d, $J = 7.8$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.09 (d, $J = 2.1$ Hz, 1H), 7.03 (m, 1H), 6.95 (m, 1H), 6.44 (br s, 1H), 4.40 (m, 1H), 3.02 (dd, $J = 14.4$, 5.9 Hz, 1H), 2.85 (dd, $J = 14.4$, 8.8 Hz, 1H), and 1.75 (s, 3H).
N-Hydroxyisonicotinamide (entry 12): δ 11.40 (s, 1H), 9.22 (br s, 1H), 8.90 (s, 1H), 8.69 (d, $J = 4.3$ Hz, 1H), 8.09 (d, $J = 8.0$ Hz, 1H), and 7.49 (dd, $J = 8.0$, 3.1 Hz, 1H).
N-Hydroxy-1H-indole-5-carboxamide (entry 13): δ 11.31 (s, 1H), 11.2 (s, 1H), 8.82 (br s, 1H), 7.99 (s, 1H), 7.50 (dd, $J = 8.6$, 1.6 Hz, 1H), 7.40 (m, 2H), and 6.49 (m, 1H).
N-Hydroxy-1H-indole-2-carboxamide (entry 14): δ 11.63 (s, 1H), 11.25 (br s, 1H), 9.1 (br s, 1H), 7.57 (d, $J = 8.0$ Hz, 1H), 7.40 (d, $J = 8.2$ Hz, 1H), 7.15 (m, 1H), 7.01 (m, 1H), and 6.96 (s, 1H).