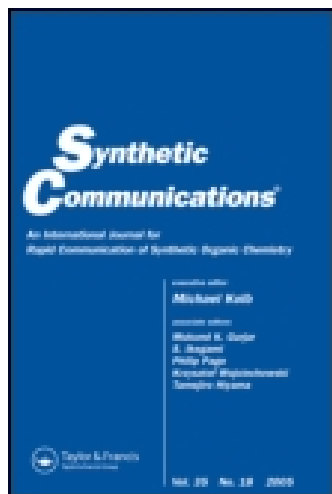


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### N-Linked Hydroxylamine Resin: Solid-Phase Synthesis of Hydroxamic Acids

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## ***N*-Linked Hydroxylamine Resin: Solid-Phase Synthesis of Hydroxamic Acids**

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**Abstract:** A novel hydroxylamine resin for solid-phase synthesis of hydroxamic acids is described. Its facile application is illustrated by the solid-phase synthesis of various hydroxamic acids. Cleavage is induced under acidic conditions by treatment with trifluoroacetic acid, providing hydroxamic acids in high purity and good yields.

**Keywords:** Hydroxamic acids, hydroxylamine resin, solid-phase synthesis

Hydroxamic acids, as effective ion chelators, are key structural components in the design of a wide spectrum of bioactive agents,<sup>[1]</sup> especially in the field of zinc metalloenzyme inhibitors such as MMP (matrix metalloprotease) inhibitors.<sup>[2]</sup> Recently, solid-phase synthesis has emerged as an important tool for the high-throughput synthesis of hydroxamic acids.<sup>[3]</sup> A variety of methods for the preparation of hydroxylamine resin via *O*-linkage have been reported.<sup>[4]</sup> However, the use of *O*-linked hydroxylamine resins for the multistep synthesis of hydroxamic acids may result in undesired by-products derived from side reactions of the NH group of the hydroxamate. Therefore, we were interested in the development of *N*-linked hydroxylamine resins in which the linker group serves not only as a cleavage site of attachment for the molecule to a solid support but also as a nitrogen-protecting group for the hydroxamate functionality. Here we present the preparation of a novel *N*-linked hydroxylamine resin derived from Merrifield resin and its application to the synthesis of various hydroxamic acids.

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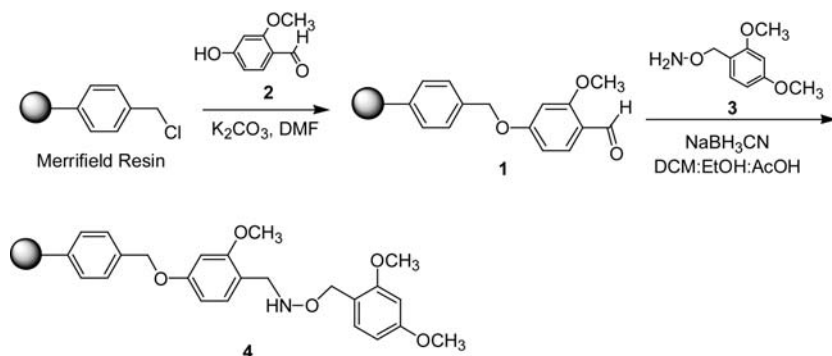
Address correspondence to Zheng Yin, Novartis Institute for Tropical Diseases, 10 Biopolis Road, #05-01 Chromos, Singapore 138670. Tel.: + 65-6777 7281; Fax: + 65-6777 7218; E-mail: zheng.yin@novartis.com

The synthesis of hydroxylamine resin **4** is summarized in Scheme 1. Merrifield resin was first converted to PS-MB-CHO resin **1** by loading with an acid labile aldehyde linker. The acid labile *O*-2,4-dimethoxybenzyl (DMB) protected hydroxylamine **3**<sup>[5]</sup> was easily attached to resin **1** using amino functionality via simple reductive amination in the presence of sodium cyanoborohydride to obtain *N*-linked hydroxylamine resin **4**. DMB was chosen as the protecting group for convenient simultaneous deprotection and cleavage of final hydroxamic acids from the solid support. In addition, the cation generated from DMB during deprotection by TFA was reported to polymerize,<sup>[5]</sup> which can be potentially removed by filtration to afford the hydroxamic acids with high purity.

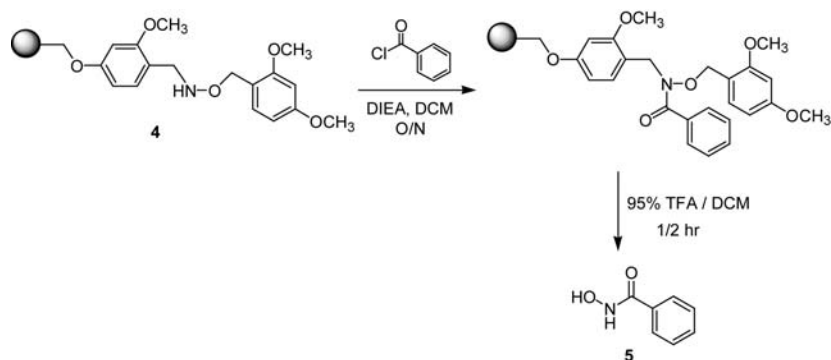
The formation of resin **4** was confirmed by the product of acylation with benzoyl chloride. Resin **4** was treated by benzoyl chloride in the presence of diisopropylethylamine. Cleavage of the product from the resin was readily achieved by 95% *v/v* TFA in dichloromethane for half an hour, providing the desired phenyl hydroxamic acid **5** in high purity (95%) and quantitative yield (Scheme 2).

To establish the utility of hydroxylamine resin **4**, the synthesis of hydroxamic acids via coupling with carboxylic acids was performed. Hydroxylamine resin **4** was coupled with carboxylic acids under standard carbodiimide coupling condition, followed by acidolysis cleavage, which provided the desired hydroxamic acids. Representative results are summarized in Table 1. Both coupling and cleavage reactions proceeded well to afford the hydroxamic acids in good to high purities.

In summary, we have developed a novel *N*-linked hydroxylamine resin for the generation of hydroxamic acids on solid support. Its simple and efficient production, effective acylation using standard solid-phase methodology, and compound cleavage (accomplished by acidolysis) make it invaluable for the solid-phase synthesis of hydroxamic acid based molecules by multiple and combinatorial approaches. Efforts to synthesize heterocyclic hydroxamic



**Scheme 1.**



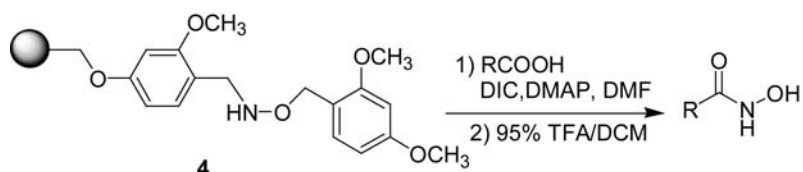
Scheme 2.

acids and apply of this resin to the production of a variety of combinatorial libraries for biological screening are underway.

## EXPERIMENTAL

### Synthesis of PS-MB-CHO Resin 1 (SASRIN Resin)

Into a 5-L dry three-neck round-bottom flask, K<sub>2</sub>CO<sub>3</sub> anhydrous (69 g, 500 mmol) and 4-hydroxy-2-methoxybenzaldehyde (76 g, 500 mmol) followed by *N*-methyl-2-pyrrolidone (2 L) were added under N<sub>2</sub> gas. Then, Merrifield resin (250 g, 1 mmol/g, 250 mmol) was added, and the reaction was allowed to shake at 120°C for 20 h. The resin was then washed through reverse filtration using the following washing cycle at 10-min intervals unless otherwise indicated: DMF (1 × 1 L), H<sub>2</sub>O (2 × 1 L), DMF (2 × 1 L), H<sub>2</sub>O (2 × 1 L), DMF (1 × 1 L), DMF (1 × 1 L, 16 h), CH<sub>2</sub>Cl<sub>2</sub> (1 × 1 L), AcOH (1 × 1 L), H<sub>2</sub>O (1 × 1 L), DMF (8 × 1 L), MeOH (1 × 1 L), CH<sub>2</sub>Cl<sub>2</sub> (1 × 1 L), and lastly dried *in vacuo*. The resin loading is estimated by analysis of the cleavage product of derivative: Sasrin resin 1 (500 mg) was added into a 20-mL scintillation vial followed by benzylamine (546 μL, 5 mmol) in TMOF. The reaction mixture was allowed to shake at room temperature for 18 h and the resin was then washed using CH<sub>2</sub>Cl<sub>2</sub>. Subsequently, BH<sub>3</sub>-pyridine complex in THF (8 M, 125 μL, 1 mmol) and MeOH:CH<sub>2</sub>Cl<sub>2</sub>:AcOH (2:2:1) (5 mL) was added to the washed resin, and the reaction mixture was shaken at room temperature for 18 h. The resin was then washed with the following cycle at 10-min intervals: DMF (2 × 50 mL), MeOH (2 × 50 mL), and CH<sub>2</sub>Cl<sub>2</sub> (2 × 50 mL). The resin was dried *in vacuo*. The dried resin was added to a solution of benzoyl chloride (500 μL, 0.43 mmol) and DIEA (1 mL, 5.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and shaken at room temperature for 18 h. The resin was then washed using the following

**Table 1.** Representative hydroxamic acids starting from resin **4**

Compound	R	Purity <sup>a</sup>	Yield <sup>b</sup>
6		98.8	81
7		95.5	69
8		85.7	90
9		62.5	95
10		93.0	80
11		91.3	90
12		98.0	83
13		98.2	80
14		89.5	76

<sup>a</sup>Purity determined from relative peak areas of reverse-phase HPLC chromatograms monitoring at 254 nm.

<sup>b</sup>Product yields determined using the loading level of the starting resin.

cycle at 10-min intervals: DMF (1 × 3 mL), H<sub>2</sub>O (1 × 3 mL), DMF (1 × 3 mL), H<sub>2</sub>O (1 × 3 mL), DMF (3 × 3 mL), MeOH (1 × 3 mL), CH<sub>2</sub>Cl<sub>2</sub> (1 × 3 mL), MeOH (1 × 3 mL), and CH<sub>2</sub>Cl<sub>2</sub> (1 × 3 mL). The dried resin was subjected to cleavage by treating with 95% TFA in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) for 3 h. Subsequently, the cleaved solution was filtered and dried to obtain *N*-benzyl benzamide. The loading of the SASRIN resin **1** was then calculated as 0.59 mmol/g.

### Synthesis of the Hydroxylamine Resin **4**

To a pot of SASRIN resin (5 g, 0.59 mmol/g, 2.95 mmol) was added DMB (5.5 g, 30 mmol) followed by DCM:EtOH:AcoH (2 : 2 : 1) (37.5 mL). Then, NaBH<sub>3</sub>CN was added (2.8 g, 45 mmol). The reaction mixture was allowed to shake at room temperature for 24 h. Resin was then washed via reverse filtration using the following cycle at 10-min intervals: DMF (2 × 50 mL), MeOH (2 × 50 mL), CH<sub>2</sub>Cl<sub>2</sub> (2 × 50 mL). The cycle was repeated twice, and the resin was dried *in vacuo*.

### General Procedure for the Solid-Phase Synthesis of Hydroxamic Acid (Compound **11**)

To a pot of resin **4** (25 mg, 0.025 mmol) was added trans-4-chloro-3-nitrocinamic acid (34 mg, 0.15 mmol) and DMAP (catalytic) followed by *N*-methyl-2-pyrrolidone (500 μL) and DIC (19.3 μL, 0.125 mmol). The reaction mixture was shaken at room temperature for 16 h. The resin was then washed using the following cycle at 5-min intervals: DMF (1 × 3 mL), H<sub>2</sub>O (1 × 3 mL), DMF (1 × 3 mL), H<sub>2</sub>O (1 × 3 mL), DMF (3 × 3 mL), MeOH (1 × 3 mL), CH<sub>2</sub>Cl<sub>2</sub> (1 × 3 mL), MeOH (1 × 3 mL), and CH<sub>2</sub>Cl<sub>2</sub> (1 × 3 mL). The resin was dried *in vacuo* and subsequently subject to acidolysis cleavage using 95% TFA in DCM (300 μL).

### Characterization of Novel Compounds

Compound (**10**): <sup>1</sup>H NMR (400 MHz, MeOD): δ 7.92 (dd, 1H, *J* = 9 Hz, 2 Hz), 8.13 (d, 1H, *J* = 9 Hz), 8.49 (s, 1H), 9.38 (s, 1H); <sup>13</sup>C NMR (400 MHz, MeOD): δ 122.8, 124.0, 126.2, 131.2, 135.3, 156.1, 159.7, 167.4; IR (neat): 3433, 3201, 1672 cm<sup>-1</sup>; HRMS (EI): calcd. for C<sub>8</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>S (M<sup>+</sup>): 194.0150; found: 194.0145.

Compound (**11**): <sup>1</sup>H NMR (400 MHz, DMSO): δ 6.61 (d, 1H, *J* = 16 Hz), 7.52 (d, 1H, *J* = 16 Hz), 7.80 (d, 1H, *J* = 8 Hz), 7.89 (dd, 1H, *J* = 8 Hz, 2 Hz), 8.29 (d, 1H); <sup>13</sup>C NMR (400 MHz, DMSO): δ 122.7, 124.0, 125.0, 132.0, 132.2,

135.0, 135.6, 150.0, 161.9; IR (neat): 3442, 3178, 1618, 1537, 1353, 1048  $\text{cm}^{-1}$ ; HRMS (EI): calcd. for  $\text{C}_9\text{H}_7\text{ClN}_2\text{O}_4$  ( $\text{M}^+$ ): 242.0094; found: 242.0086.

Compound (**13**):  $^1\text{H}$  NMR (400 MHz, MeOD):  $\delta$  7.08 (d, 1H,  $J = 4$  Hz), 7.20 (d, 1H,  $J = 3$  Hz), 7.63–7.64 (m, 2H), 8.05–8.09 (m, 1H), 8.20 (s, 1H);  $^{13}\text{C}$  NMR (400 MHz, MeOD):  $\delta$  107.4, 115.4, 120.2, 124.0, 127.0, 128.9, 129.9, 130.4, 130.7, 145.0, 153.7, 157.0; IR (neat): 3238, 1614, 1334  $\text{cm}^{-1}$ ; HRMS (EI): calcd. for  $\text{C}_{12}\text{H}_8\text{F}_3\text{NO}_3$  ( $\text{M}^+$ ); 271.0456, found: 271.0448.

Compound (**14**):  $^1\text{H}$  NMR (400 MHz, MeOD):  $\delta$  4.84 (s, 3H), 7.40–7.60 (m, 5H), 7.89 (s, 1H);  $^{13}\text{C}$  NMR (400 MHz, MeOD):  $\delta$  9.8, 112.2, 125.0, 128.1, 128.5, 137.5, 138.0, 141.8, 162.6; IR (neat): 3311, 3067, 2829, 1644  $\text{cm}^{-1}$ ; HRMS (EI): calcd. for  $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_2$  ( $\text{M}^+$ ): 217.0851; found: 217.0857.

## REFERENCES

1. For a review, see Muri, E. M. F.; Nieto, M. J.; Sindelar, R. D.; Williamson, J. S. Hydroxamic acids as pharmacological agents. *Curr. Medicinal Chem.* **2002**, *9*, 1631.
2. For a review, see Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. Design and therapeutic application of matrix metalloproteinase inhibitors. *Chem. Rev.* **1999**, *99*, 2735.
3. Yang, K.; Lou, B. Molecular diversity of hydroxamic acids: Part I. Solution- and solid-phase synthesis. *Mini. Rev. Med. Chem.* **2003**, *3*, 249.
4. (a) Richter, L. S.; Desai, M. A TFA-cleavable linkage for solid-phase synthesis of hydroxamic acids. *Tetrahedron Lett.* **1997**, *38*, 321; (b) Floyd, C. D.; Lewis, C. N.; Patel, S. R.; Whittaker, M. A method for the synthesis of hydroxamic acids on solid phase. *Tetrahedron Lett.* **1996**, *37*, 8045; (c) Bauer, U.; Ho, W.-B.; Koslunen, M. P. A novel linkage for the solid-phase synthesis of hydroxamic acids. *Tetrahedron Lett.* **1997**, *38*, 7233; (d) Mellor, S. L.; McGuire, C.; Chan, W. C. *Tetrahedron Lett.* **1997**, *38*, 3311; (e) Mellor, S. L.; Chan, W. B. 4-[2,4-dimethoxyphenyl (N-fluoren-9-ylmethoxycarbonyl-N-alkylaminoxy)-methyl]phenoxyethyl polystyrene: A multiple solid-phase approach to N-alkylhydroxamic acids. *Chem. Commun.* **1997**, *20*, 2005.
5. Barlaam, B.; Hamon, A.; Maudet, M. New hydroxylamines for the synthesis of hydroxamic acids. *Tetrahedron Lett.* **1998**, *39*, 7865.