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Solid Supported Synthesis of Hydroxamic Acids

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This work is in memory of our colleague and friend Hoang Do.

Abstract: A novel approach to the solid supported synthesis of hydroxamic acids was developed. It employs oxime resin and unlike all previously reported methods allows for the use of acid labile protecting groups. Cleavage is induced by treatment with *tert*-butyldimethylsilyl-*O*-hydroxylamine, followed by silyl group deprotection with trifluoroacetic acid.

Hydroxamic acids are an important class of organic molecules playing a key role in many biologically relevant interactions. Inhibition of matrix metalloproteinases[1] (MMPs) or a unique deacetylase of lipid A biosynthesis[2] testify to the significance of this class of compounds.

Synthesis on a solid support is a crucial technology for combinatorial chemistry efforts.[3] It allows for easy automation of the processes, convenient handling of polar molecules throughout the synthetic protocol, and it provides a reliable method for the preparation of mixtures of compounds (split-mix synthesis). The solid-supported synthesis of hydroxamic acids, based on Wang[4], Sasrin,[5] or the 2-chlorotrityl[6] *O*-hydroxylamine bound resin has recently been reported. The later resin is commercially available (Novabiochem). Another alternative synthetic approach, based on resin *N*-linked hydroxylamine was recently reported by Ngu and Patel.[7] The transformation of aspartic and glutamic acid side carboxylate moiety into a hydroxamate functional group was reported by Chen and Spatola.[8]

While preparing modified hydroxamic acids on the solid support, we noted two major limitations of the reported methods. First, using *O*-hydroxylamine bound resin leads frequently, during side chain modifications, to by-product formation derived from functionalization of the resin-ONHCOR hydroxamate nitrogen. Secondly, none of the known methods allows for application of acid labile protecting groups (e.g. Boc).

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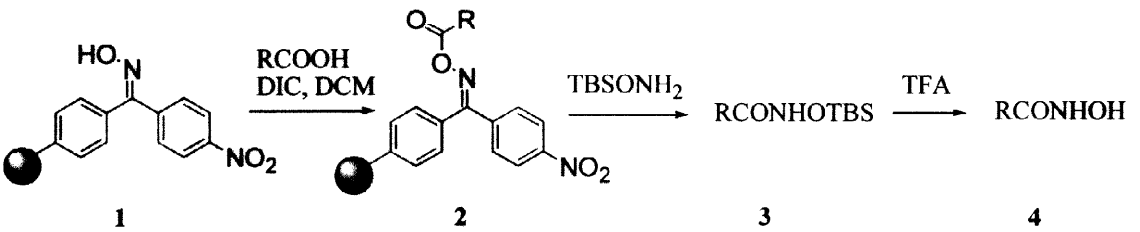
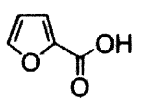
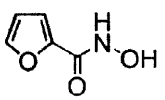
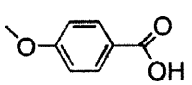
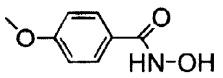
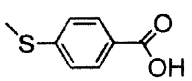
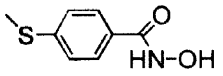
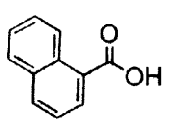
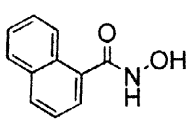
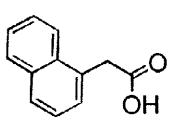
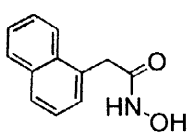
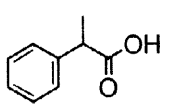
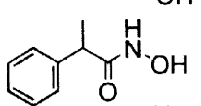
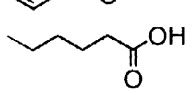
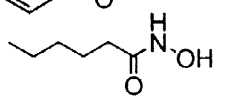
Scheme 1



1 2 3 4

Our synthetic route, which is outlined in Scheme 1, utilizes oxime (Kaiser) resin esters (**2**). After side chain modification, the product is cleaved as an *O*-protected hydroxamic acid (**3**), using *tert*-butyldimethylsilyl hydroxylamine (at this stage the crude product can be purified by silica gel chromatography). *O-tert*-Butyldimethylsilyl protected hydroxylamine was found to be optimal for this process, we also tested unprotected as well as *O*-benzyl, *O*-trimethylsilyl- and *O*-trityl blocked hydroxylamines under a variety of reaction conditions. Finally, the silyl group is removed with trifluoroacetic acid at room temperature to afford pure hydroxamic acid (**4**).

Table 1

Entry	Acid (R)	Hydroxamic acid (4)	% Yield (crude) Hydroxamic acid (4)[a]	HPLC Purity (%)[b]
a			72	97
b			36	89
c			34	65
d			27	96
e			89	95
f			74	94
g			68	95

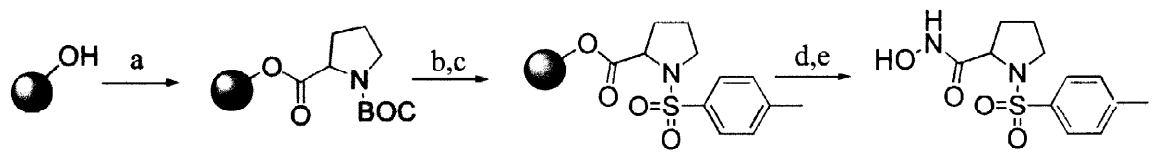
[a] Isolated yield of final products based on an initial loading of 1.17 mmol/g

[b] Reverse phase HPLC using an evaporative light scattering detector.

A small set of hydroxamic acids was prepared to test the scope and limitations of this process (Table 1). The loading and cleavage chemistry were not optimized. The results of this initial study show that heteroaromatic (2-furoic acid; entry a) or aliphatic acids with an aromatic ring in the side chain (entry e and f) as well as aliphatic acids (entry g) leads to final products in good yield. The presented synthetic protocol appears to be less suitable for aromatic hydroxamic acids (entry b-d).

To demonstrate the possibility of using acid labile protecting groups we prepared N-tosyl-proline hydroxamic acid (7) (Scheme 2).

Scheme 2[a]



1 5 6 7

Reagents and conditions: a) Boc-Pro-OH 5eq, DIC, DMAP, DCM; b) 25% TFA/DCM ; c) TsCl 6eq, DIPEA, DCM; d) $TBSONH_2$ (5eq), 1,2-DCE, 90°C, 20h; e) 95% TFA/H_2O, 16h.

Typical procedure: Oxime resin **1** (1.0 g, 1.17 mmol/g, 1.17 mmol; Novabiochem) was rinsed several times with dichloromethane and Boc-proline (5eq, 1.28 g, 5.85 mmol) in DCM (12 mL) was added, followed by 1,3-diisopropylcarbodiimide (DIC; 737 mg, 5.85 mmol) and a catalytic amount of DMAP (5 mg). The reaction mixture was shaken for 17 hours and the resin was filtered and washed (DCM, 2-propanol, DMF). Alternate washing with DCM and 2-propanol was repeated several times and finally resin was dried under vacuum for several hours at room temperature to give 1.188 g of loaded resin (**5**) (Yield 82%, new loading 0.78 mmol/g). Boc-Proline oxime resin ester (**5**) (158 mg, 0.123 mmol) was treated with 25% trifluoroacetic acid in DCM and shaken for 1h. The resin was filtered and washed several times with DCM and 10% DIPEA/DCM. 1,2-Dichloroethane (DCE) and *N,N*-diisopropylethylamine (DIPEA) were added (2:1, total 5 mL) followed by p-toluenesulfonyl chloride (140 mg, 0.730 mmol). The reaction mixture was shaken for 6 h, then filtered, washed (DCM, 2-propanol and again DCM several times) and vacuum dried (RT, 48h) to give **6**. The resin was swelled in DCE (10 mL) and tert-butyl dimethylsilyl-*O*-hydroxylamine (0.107 mg, 0.730 mmol) was added and the reaction mixture was refluxed for 20 h (ca. 90°C). The resin was filtered and washed (DCM and MeOH several times), filtrate collected and evaporated. The oily residue was vacuum dried and co-evaporated with chloroform several times to give 55 mg of oily product (49 mg = 100% theoretical yield) which was re-dissolved in trifluoroacetic acid/water (95:5) and stirred for 16 h, evaporated to yield compound **7** as a yellowish, waxy solid 34 mg (96% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 7.78(d, 2H, J = 8.1 Hz), 7.46 (d, 2H, J = 8.1 Hz), 4.06 (dd, 1H, J = 3.3 Hz), 3.55 (m, 1H), 3.24 (m, 1H), 2.46 (s, 3H), 1.55 - 2.09 (m, 4H). MS (ESI): m/z 285 $[M+H]^+$

The presented solid supported synthesis of hydroxamic acids opens the way to the automated preparation of this important class of compounds. The use of protected hydroxylamine at the end of the

synthesis avoids all side-processes related to the acidic NH proton of the hydroxamate intermediates encountered in previously reported methods. The proposed synthetic protocol allows the use of acid-labile protective group strategy as an alternative to existing literature procedures. The extension of this method toward the synthesis of more complex hydroxamic acids as well as other classes of products is currently under investigation.

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