A New and Efficient Solid Phase Synthesis of Hydroxamic Acids

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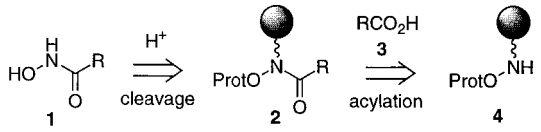
The hydroxamic acid functionality is a key structural constituent of a wide spectrum of bioactive agents including various antibacterial, antifungal, and anticancer agents.[1,2] Hydroxamates are very effective metal-ion chelators and have led to the rational design and discovery of novel and potent inhibitors of metalloenzymes such as thermolysin,[3] angiotensin-converting enzyme (ACE),[4] and the matrix metalloprotease (MMP) family of enzymes.[5] The growing importance of combinatorial chemistry as a modern drug discovery tool has created a need for developing new solid phase synthesis (SPS) methods for important classes of bioactive compounds.[6] Our interest in novel metalloenzyme inhibitors prompted us to explore the possibility of combinatorial, SPS of hydroxamic acids.

Since a hydroxamate moiety would be a common feature of all library members, a convergent and versatile strategy calls for immobilizing the hydroxylamine [$HONH_2$] group first, and then subjecting it to various synthetic transformations to prepare diverse sets of hydroxamate pharmacophore inhibitor libraries. Unlike solution phase synthesis, it then becomes necessary to have fully (both N- and O-) protected alkoxyamine **4** and hydroxamate intermediates **2** on solid support, to avoid undesired potential side reactions with synthetic reagents or intermediates encountered during subsequent transformations leading to the final products.[7] On the basis of these considerations, we decided to investigate the synthesis and potential applications of O-protected, N-immobilized hydroxamates **2**, wherein *the linker group, besides being a cleavable site of attachment for the molecule to a solid support, also serves as a nitrogen protecting group for the hydroxamate functionality.*

Scheme 1. Retrosynthesis for SPS of Hydroxamic Acids



The two critical aspects of this approach are the selection of a suitable O-protecting group and the N-linker group. After examining several alkoxyamines, we selected two complementary O-protecting groups—the acid stable allyl group and an acid labile tetrahydropyran (THP) group. Initial experimentation with our recently described bromo resin[8] derived from commercially available alcohol resins resulted only in modest recovery of desired hydroxamic acids.[9] These results suggested the need for a more acid labile linker to permit smooth cleavage of the desired hydroxamate products. The hypersensitive acid-labile (HAL) tris(alkoxy)benzyl ester linker **5** was thus chosen for our study.[10]

Since early stage synthetic steps involving the attachment of an alkoxyamine group on the linker do not contribute to chemical diversity, these reactions were conducted in solution to benefit from the convenience of scale-up, purification, and analytical characterization of intermediates (Scheme 2).[11] Thus, reductive amination of aldehyde **5**[10] with $NH_2OCH_2CH{=}CH_2$ **6** (Aldrich) or H_2N-OTHP **7**[12] gave the alkoxy-amine acids **8** (70%) and **9** (63%), respectively. The intermediate oximes are stable and require prolonged treatment for effective reduction ($NaBH_3CN$, AcOH, 18 h).[13] Compounds **8** and **9** are Fmoc protected[14] to give the fully protected alkoxyamines **10** (89%) and **11** (87%), respectively, suitable for immobilization on a wide variety of amine resins. In our case, we proceeded with acylation of Tentagel S NH_2 resin (RAPP Polymere) with acids **10** and **11** followed by Fmoc removal to obtain resins **12** and **13**, respectively.

N-Tethered, O-protected alkoxyamine resins **12** and **13** proved to be ideal starting materials for general SPS of various types of hydroxamic acids. Thus, allyloxy resin **12** was acylated with 3-phenylpropionyl chloride and treated with 50% TFA for 1 h followed by treatment with $Pd(PPh_3)_4/PPh_3$ in solution to furnish the desired hydroxamic acid **14** (84%). Cleavage of hydroxamate ether from this linker was cleaner and faster in comparison to the relatively less acid-labile linkers.[9] Analogous synthesis of **14** was also carried out with O-THP alkoxyamine resin **13** (Scheme 3). In this instance, the acylated intermediate was first treated with 2.5% aqueous TFA in CH_2Cl_2 for 1 h to remove the THP group, followed by treatment with 50% aqueous TFA in CH_2Cl_2 for 1 h to cleave **14** from the resin (88%). The convenience of simultaneously

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(7) We and others have recently independently published the SPS of hydroxamic acids commencing from O-linked hydroxylamine resins (Support-O-NH_2). While this method works well for simple examples, the acidic NH group (app $pK_a = 10$) of such hydroxamate intermediates is vulnerable to side reactions such as alkylations and cyclizations under basic and Mitsunobu type conditions, thus limiting the potential for further synthetic manipulations typically required for synthesizing nonpeptidic metalloenzyme inhibitors. For SPS of O-linked hydroxamic acids, see (a) Floyd, C. D.; Lewis, C. N.; Patel, S. R.; Whittaker, M. *Tetrahedron Lett.* **1996**, *37*, 8045. (b) Richter, L. S.; Desai, M. C. *Tetrahedron Lett.* **1997**, *38*, 321. (c) Gordeev, M. F.; Hui, H. C.; Gordon, E. M.; Patel, D. V. *Tetrahedron Lett.* **1997**, *38*, 1729. (d) Miller, S. L.; McGuire, C.; Chan, W. C. *Tetrahedron Lett.* **1997**, *38*, 3311.

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(9) Attempted cleavage of the product from the Wang resin gave the *p*-hydroxybenzyl-derived adduct derived from partial O-cleavage of the linker group.

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(11) Direct attachment of linker **5** to resin followed by oxime formation with alkoxyamines **6** and **7** and reduction on solid support to arrive at alkoxyamines **13** and **12**, respectively, was attempted but found to be less satisfactory compared to the current approach.

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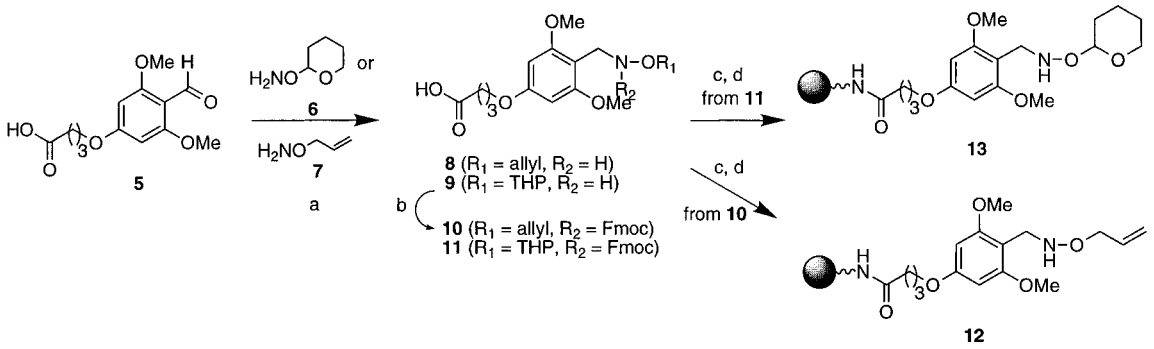
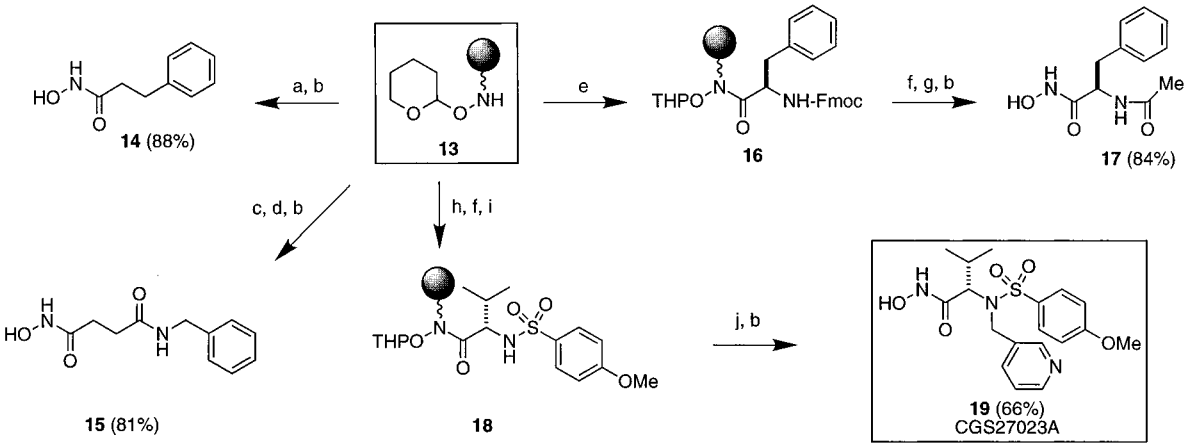
Scheme 2. Preparation of N-Tethered, Alkoxyamine Linker Resins 12 and 13



Reagents: a) $NaBH_3CN$, AcOH, 70% for **8**; 63% for **9** b) Fmoc-Cl, 89% for **10**; 87% for **11** c) TGS-NH_2, HATU, DIEA, DMF d) Piperidine

Scheme 3. Preparation of Hydroxamic Acids Using Alkoxyamine Resin 13



Reagents: a) $Ph(CH_2)_2COCl$, iPr_2NEt, CH_2Cl_2 b) i) 2.5% TFA and 1% H_2O in CH_2Cl_2, 1 h, followed by 50% TFA and 1% H_2O in CH_2Cl_2, 1 h c) succinic anhydride, DMF d) DIC (5.0 equiv.), $PhCH_2NH_2$ (10.0 equiv.), CH_2Cl_2 e) DIC (5.0 equiv.), Fmoc-L-Phe-OH (10.0 equiv.), DMF f) 20% Piperidine in DMF g) Ac_2O, pyridine h) DIC (5.0 equiv.), Fmoc-D-Val-OH (10.0 equiv.), DMF i) (p-OMe)Ph-SO_2Cl, NMM, CH_2Cl_2, 4h j) $Me_2N(O)CN{=}NC(O)NMe_2$, Bu_3P, 3-PyridylCH$_2$OH, THF, 18 h

removing the O-protecting THP group and effecting cleavage of final hydroxamic acids from the resin led us to pursue further studies with **13**. Succinic acid derived hydroxamates have received good attention as potent and selective matrix metalloprotease (MMP) inhibitors.[5] Synthesis of a simple succinyl analog is exemplified by **15**, prepared by acylation of **13** with succinic anydride followed by coupling with benzylamine and TFA cleavage (81%). Preparation of phenylalanine derived α-acetamido hydroxamate was also uneventful (**17**, 84%). Finally, we undertook the synthesis of hydroxamic acid CGS 27023A **19** recently described by the Ciba-Geigy group as a broad-spectrum MMP inhibitor (K_i = 43 nM against stromelysin) with good oral bioavailability in animals.[15] This synthesis requires several challenging synthetic transformations such as N-acylation with hindered amino acid (valine), N-sulfonylation of amine, and finally an N-alkylation of sulfonamide group on solid support. DIC-mediated coupling of Fmoc-D-valine to **13** was essentially quantitative, as judged by spectrophotometric estimation of the Fmoc group. Removal of the Fmoc group was followed by sulfonylation of liberated amine with *p*-MeO-$PhSO_2Cl$ (NMM, CH_2Cl_2, 4 h). A small aliquot was cleaved to characterize the intermediate and assure the fidelity of the synthesis up to this stage (>90%). The final N-alkylation of sulfonamide **18** was not straightforward. Attempts with 3-pyridyl-CH_2Cl and a variety of bases (K_2CO_2, DBU, LHMDS) were less rewarding, and model studies employing standard Mitsunobu reagents (DEAD/Ph_3P)[16a] were successful with simple alcohols, but not with 2-pyridylcarbinol. The desired transformation was finally accomplished by employing Tsunoda's modified redox system of tributylphosphine and 1,1'-azobis(*N*,*N*-dimethylformamide).[16b,17] Deprotection and cleavage from the resin by TFA treatment yielded the desired final product in good overall yield (66% from **13**).

In summary, a new and versatile method for SPS of hydroxamic acids proceeding through the intermediacy of N-tethered-O-protected alkoxyamine resin **4** is described. The current method should serve to facilitate the combinatorial synthesis of hydroxamic acid pharmacophore based molecules and accelerate the discovery of metalloenzyme inhibitor based pharmaceutical agents.

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Supporting Information Available: Procedures and characterization data for compounds **6**−**19** (8 pages).

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(17) Further applications of Tsunda's various modified Mitsunobu reagent systems for solid phase N-alkylation of sulfonamides are in progress and will be reported separately in the near future.