ORGANIC LETTERS

2005
Vol. 7, No. 17
3761−3763

Solid-Phase Synthesis of *N*-Formylhydroxylamines (Reverse/Retro-Hydroxamates)

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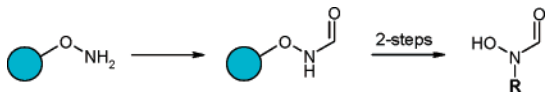
Received June 16, 2005

ABSTRACT



***N*-Formylhydroxylamines, also known as reverse- or retro-hydroxamates, have become of significant interest in the recent past as inhibitors of metalloenzymes. Although solution-phase synthetic routes to such compounds have been reported, these are often lengthy and involve purification at each stage. Herein, novel three-step solid-phase synthetic approaches are described that enable libraries of such compounds to be produced in a convergent and efficient manner using commercially available starting materials.**

Metalloenzymes have been identified as key regulators in a variety of homeostatic and pathological processes in the body. Inhibiting these enzymes in disease states is a well-documented way of providing useful therapeutics throughout the pharmaceutical industry.[1]

Metalloenzymes implicated in disease states use a transition metal atom, often either zinc[1−6] or iron,[7] to facilitate the processes that they catalyze. To date, most successful inhibitors contain a metal-chelating group that provides a significant decrease in entropy by binding to the metal atom either in a mono- or a bidentate fashion. Metal-chelating groups that medicinal chemists have used include hydroxamic acids, sulfamides, thiols, α-mercaptocarbonyls, and phosphates, all of which have demonstrated issues with respect to pharmacokinetic properties. Consequently, there has been a drive to find novel metal-chelating groups with more favorable pharmacodynamic and pharmacokinetic properties that, in addition, provide new intellectual property positions.

Recently, *N*-formylhydroxylamines, also known as reverse- or retro-hydroxamates, have emerged as an alternative class of bidentate metal-chelating group. This has provided inhibitors against a variety of metalloenzyme targets, including carboxy peptidase A (CPA),[2] tumor necrosis factor-α converting enzyme (TACE),[3] matrix metalloproteinases (MMPs),[4] thermolysin (TLN),[5] histone deacetylase (HDAC),[6] and peptide deformylase (PDF).[7]

So far, the reported literature syntheses of metalloenzyme inhibitors containing an *N*-formylhydroxylamine group have been limited to solution-phase chemistry.[2−7] However, the *N*-formylhydroxylamine group is incorporated into a target inhibitor over a number of synthetic steps, which generally include purification at each stage. An example is depicted in Scheme 1.[6]

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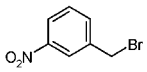
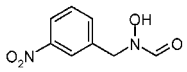
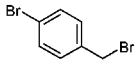
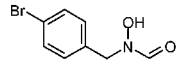
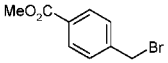
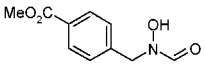
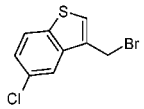
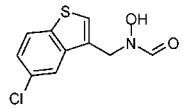
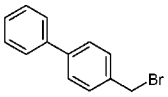
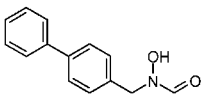
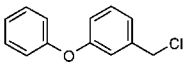
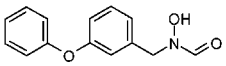
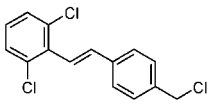
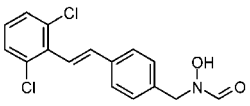
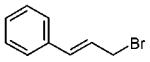
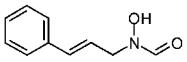
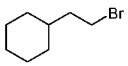
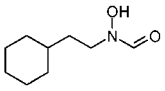
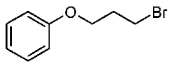
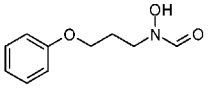
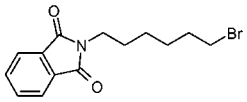
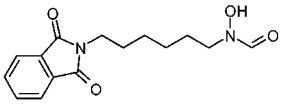
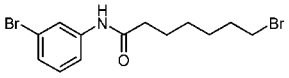
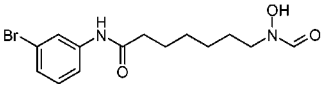
10.1021/ol0513995 CCC: $30.25
Published on Web 07/20/2005

Table 1. Alkylation of *N*-Formyl Wang-*O*-hydroxylamine Resin (**2**) and Subsequent Cleavage to Produce *N*-Formylhydroxylamines (**4**)[a]

entry	alkyl halide ($\mathbf{R^1}$X)	product of type **4**		isolated yield (%)	purity (%)[b]
1			**4a**	87	>95
2			**4b**	85	>95
3			**4c**	86	>95
4			**4d**	89	>95
5			**4e**	89	>95
6			**4f**	60	>95
7			**4g**	79	>95
8			**4h**	86	>95
9			**4i**	76	>95
10			**4j**	56	>75
11			**4k**	49	>95
12			**4l**	35	89

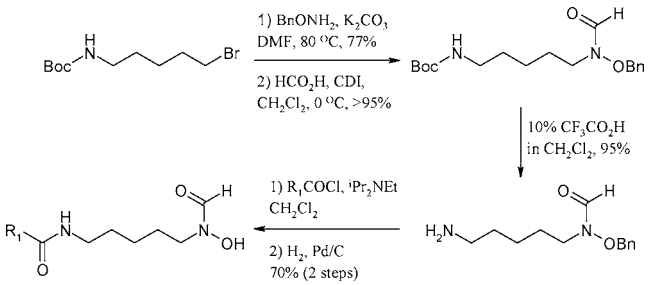
[a] General Procedure for the Alkylation of *N*-Formyl Wang-*O*-hydroxylamine Resin **2** and Subsequent Cleavage of *N*-Formylhydroxylamine **4**. To a mixture of *N*-formyl Wang-*O*-hydroxylamine resin **2** (50 mg, 1.0 mmol/g) and dry toluene (1 mL) in a sealed tube was added DBU (255 μmol, 5 equiv). The reaction was agitated at room temperature for 1 h before a solution of alkyl halide ($\mathbf{R^1}$X, 5 equiv) in toluene (1 mL) was added, and the resulting mixture was agitated for 16 h. The resin was filtered and then washed five times, each with MeOH followed by CH_2Cl_2, and Et_2O, before being dried at 40 °C to provide *N*-alkyl,*N*-formyl Wang-*O*-hydroxylamine resin **3** (50 mg). The resin **3** (50 mg) was then treated with TFA in CH_2Cl_2 (2 mL, 1:1, v/v) at room temperature for 45 min before being collected by filtration and washed three times with CH_2Cl_2 (2 mL). The combined organic filtrates were concentrated to provide the desired *N*-formylhydroxylamine **4**. [b] Purity was determined by LCMS.

Synthesizing libraries of *N*-formylhydroxylamines using current methodologies would be nonconvergent and extremely time-consuming, rendering this approach practically infeasible, from the pool of commercially available starting materials.

In search of a new, general, and synthetically convergent route to produce libraries of *N*-formylhydroxylamines that utilizes commercially available starting materials, we considered alternative approaches that would allow the introduction of diversity at the penultimate stage of any synthetic route (i.e., prior to liberation of the free *N*-formylhydroxylamine itself). To achieve this, we required the protected *N*-formylhydroxylamine functionality to be introduced as early as possible into the synthetic route with protecting groups that are easily removed.

The stringent requirements outlined above led us to investigate the reaction of electrophiles with the nitrogen atom of a suitably O-protected *N*-formylhydroxylamine. We decided to utilize a solid-phase O-protected *N*-formylhydroxylamine to increase further the ease of library synthesis, with cleavage from the resin constituting the final step. At the outset of this work, no literature reports had described the addition of an electrophile to the nitrogen atom of O-protected *N*-formylhydroxylamine. However, during the

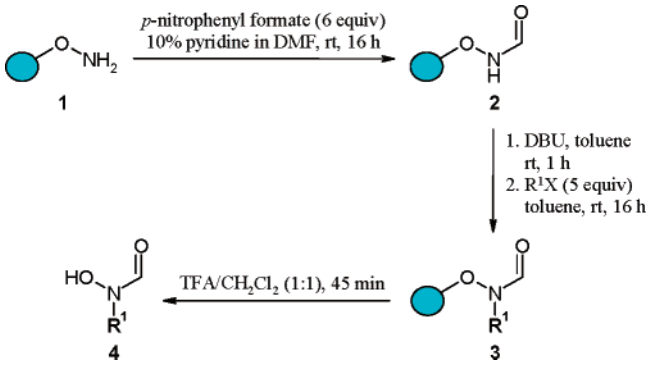
Scheme 1



preparation of this manuscript, the N-alkylation of an O-benzylated *N*-formylhydroxylamine was reported.[8]

Wang-*O*-hydroxylamine resin **1**[9] (1 equiv) was treated with *p*-nitrophenyl formate (6 equiv) and 10% pyridine in DMF at room temperature for 16 h to provide the desired *N*-formyl Wang-*O*-hydroxylamine resin **2**.[10] N-Alkylation was achieved by treating the *N*-formyl Wang-*O*-hydroxylamine resin **2** (1 equiv) with DBU (5 equiv), in toluene for 1 h, followed by addition of the appropriate alkyl halide (5 equiv) in toluene, and stirring for 16 h. The *N*-alkyl,*N*-formyl Wang-*O*-hydroxylamine resin **3** was subsequently treated with a solution of TFA and CH_2Cl_2 (1:1) to provide the desired *N*-formylhydroxylamines **4** as TFA salts in modest to good yield (Scheme 2, Table 1).

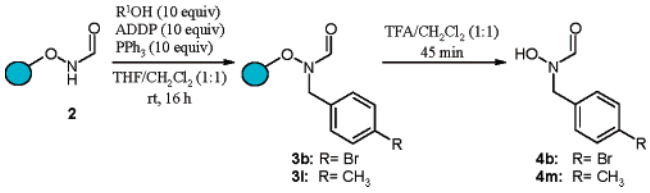
Scheme 2



A broad range of alkyl halides was selected for the N-alkylation reaction, which included activated alkyl halides such as benzyl bromides **4a**−**e**, benzyl chlorides **4f**−**g**, an allyl bromide **4h** and also included unactivated alkyl bromides **4i**−**l**. In addition, some of the alkyl halides contain functional groups that may be further functionalized or derivatized using known literature solid-phase reactions. This would produce additional sublibraries of molecules prior to cleavage from the resin. Some examples include the reduction of the aromatic nitro group in **4a** followed by acylation or reductive amination; metal-mediated cross-coupling reactions with aryl bromide **4b** (e.g., Suzuki, Buchwald) or saponification of the benzoic ester **4c** followed by amide bond formation.

To broaden further the range of commercially available starting materials that could be utilized to produce libraries of *N*-formylhydroxylamines, alcohols were investigated. The *N*-formylhydroxylamine resin **2** was subjected to Mitsunobu reaction conditions[11] separately with two substituted benzyl alcohols (10 equiv), triphenylphosphine (10 equiv), and 1,1′-(azodicarbonyl)dipiperidine (ADDP) (10 equiv) in THF and CH_2Cl_2 at room temperature for 16 h. Subsequent cleavage with a solution of TFA in CH_2Cl_2 (1:1) provided the desired *N*-formylhydroxylamines **4b** and **4m** in good yields, 58 and 66%, respectively (Scheme 3).[12]

Scheme 3



In summary, we have demonstrated a novel and highly convergent solid-phase synthetic method to produce libraries of *N*-formylhydroxylamines using commercially available alkyl halides. In addition, we have also shown that further synthetic routes may be accessible utilizing Mitsunobu chemistry and commercially available alcohols.

Acknowledgment. We thank the analytical department at Argenta Discovery for analysis of the final compounds.

Supporting Information Available: Experimental procedures and characterization for all new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0513995

(8) Watanabe, L. A.; Jose, B.; Kato, T.; Nishino, N.; Yoshida, M. *Tetrahedron Lett.* **2004**, *45*, 491−494.

(9) (a) Salvino, J. M.; Mervic, M.; Mason, H. J.; Kiesow, T.; Teager, D.; Airey, J.; Labaudiniere, R. *J. Org. Chem.* **1999**, *64*, 1823−1830. (b) Floyd, C. D.; Lewis, C. N.; Patel, S. R.; Whittaker, M. *Tetrahedron Lett.* **1996**, *37*, 8045−8048.

(10) **General Procedure for the Preparation of Wang-*O*-hydroxylamine Resin 2.** A solution of *para*-nitrophenylformate (51 mg, 0.31 mmol) and 10% pyridine in DMF (2 mL) was added to Wang-*O*-hydroxylamine resin **1** (50 mg, 1.0 mmol/g) in a sealed tube. After agitation for 16 h, the resin was washed five times, each with DMF followed by CH_2Cl_2, and then Et_2O, before being dried at 40 °C to provide *N*-formyl Wang-*O*-hydroxylamine resin **2**.

(11) Heinonen, P.; Lonnberg, H. *Tetrahedron Lett.* **1997**, *38*, 8569−8572.

(12) **General Procedure for Mitsunobu Reaction with *N*-Formyl Wang-*O*-hydroxylamine Resin 2 and Subsequent Cleavage of *N*-Formylhydroxylamine 4.** To a mixture of *N*-formyl Wang-*O*-hydroxylamine resin **2** (75 mg, 0.077 mmol), substituted benzyl alcohol (0.77 mmol, 10 equiv), and PPh_3 (0.77 mmol, 10 equiv) in THF and CH_2Cl_2 (1 mL, 1:1, v/v) was added ADDP (0.77 mmol, 10 equiv) in a sealed tube. The reaction mixture was agitated at room temperature for 16 h. The resin was then washed five times with MeOH followed by CH_2Cl_2 and then Et_2O, before being dried under vacuum overnight, to provide *N*-alkyl,*N*-formyl Wang-*O*-hydroxylamine resin **3b**. The resin **3b** (75 mg) was then treated with TFA in CH_2Cl_2 (3 mL, 1:1, v/v) at room temperature for 45 min before being collected by filtration and washed three times with CH_2Cl_2 (2 mL). The combined organic filtrates were concentrated to provide the desired *N*-formylhydroxylamine **4b**.