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Convenient Method for the Preparation of Some Polyhydroxamic Acids: Michael Addition of Amines to Acrylohydroxamic Acid Derivatives†

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Abstract: **Reagents 1, 2, and 3 are readily prepared by the reaction of the appropriate hydroxylamine derivatives with acryloyl chloride. They undergo Michael addition with a variety of amines to give the corresponding O-protected hydroxamate derivatives in moderate to good yields. Subsequent removal of the protecting group provides a convenient method for the preparation of a number of mono, di, tri and tetrahydroxamic acids.**

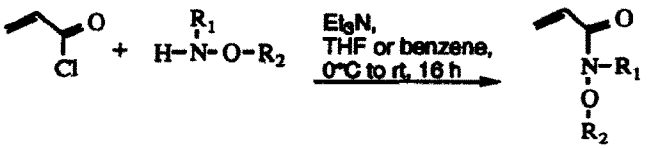
As part of a program for the design and synthesis of chelators for the specific binding of actinides,[1] we have been interested in the preparation of a number of potential chelators having multiple hydroxamic acid groups. The hydroxamate ligand is a negatively charged bidentate ligand which is known to bind hard Lewis acids such as iron(III) and tetravalent actinides strongly.[2] In fact many naturally occurring microbial siderophores have two or more hydroxamate functionalities in their structure, which allow them to complex a ferric iron strongly.[3] Also many hydroxamate chelators have been synthesized and examined as potential drugs to treat patients suffering from Cooley's anemia.[4] Patients suffering from this disease must receive blood transfusions all their lives and there is a need for new drugs to handle the resultant iron overload in the body. The use of hydroxamic acids as reagents for colorimetric and gravimetric analyses is also well documented.[5]

A variety of methods are known for the preparation of hydroxamic acids.[6] Perhaps the most common method involves the acylation of an acid derivative such as an ester or acid chloride with hydroxylamine and its derivatives.[7] Recently, the preparation of trishydroxamic acids from the corresponding triacids by water soluble carbodiimide coupling with hydroxylamines has been reported.[8] The isolation of polyhydroxamic acids from reactions can be complicated by the fact that they are frequently water soluble. They are also highly polar compounds that are difficult to purify by standard methods such as chromatography. In order to alleviate some of the isolation and purification problems encountered in the preparation of hydroxamic acids the use of protected derivatives of hydroxylamine such as N-BOC-O-THP and N-BOC-O-TBDMS[9] has been of interest.

In this paper, we would like to disclose the preparation and synthetic utility of three reagents **1**, **2** and **3** for the preparation of a number of primary and secondary (N-methyl) hydroxamic acids from readily available amines. The Michael additions of various amines with these acrylohydroxamate reagents lead to the expected

adducts which are organic soluble and amenable to purification by routine methods. Subsequently, it is possible to remove either the benzyl or the silyl protecting groups present in the Michael adducts under mild conditions[10] affording the target compounds in satisfactory purities and high yields directly.

Reagent **1** was prepared in moderate yield by the coupling of O-benzylhydroxylamine with acryloyl chloride in benzene. Reagents **2** and **3** were prepared by a two step procedure. The reaction of N-methyl hydroxylamine hydrochloride (1 equiv) with one equiv of either *t*-butyldiphenylsilylchloride (TBDPSCl) or *t*-butyldimethylsilylchloride (TBDMSCl) in the presence of Et_3N (2.5 equiv) in CH_2Cl_2 at room temperature gave the corresponding O-silylated derivatives. These protected hydroxylamines were subsequently coupled to acryloyl chloride in THF in the presence of Et_3N in good yields to give **2** and **3**, respectively (Scheme 1). Reagents **1** and **2** were purified by silica gel chromatography, while reagent **3** was purified by chromatography followed by vacuum distillation (61° C, 1 mm Hg).



1 $R_1 = H$; $R_2 = CH_2Ph$ 51% yield
2 $R_1 = CH_3$; $R_2 = Si(t\text{-}Bu)(Ph)_2$ 73% yield
3 $R_1 = CH_3$; $R_2 = Si(t\text{-}Bu)(Me)_2$ 65% yield

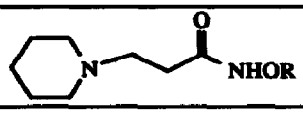
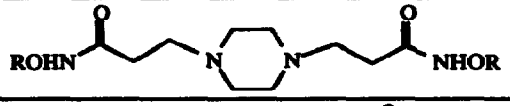
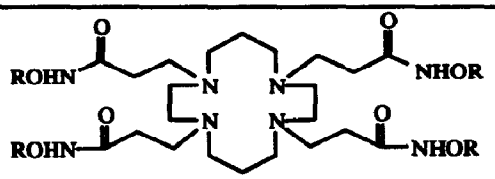
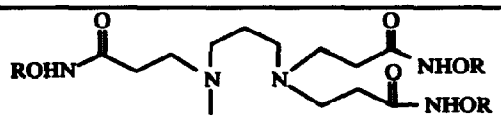
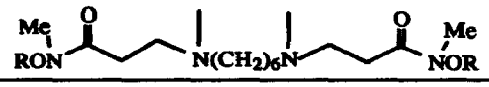
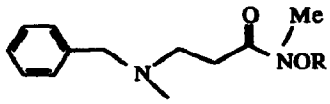
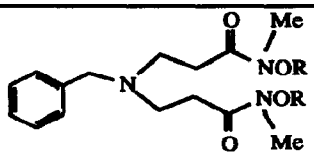
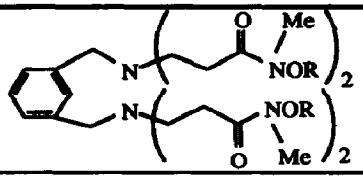
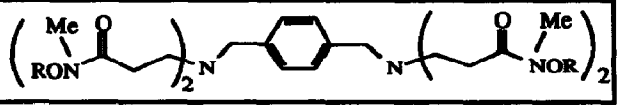
Scheme 1

The protected acrylohydroxamates **1**, **2** and **3** were reacted successfully with a number of amines to give the corresponding adducts in good to moderate yields. The Michael addition reactions were usually carried out by refluxing the amine with a slight excess of the reagent in THF for about 24 h. The Michael adducts derived from the reagents **1** and **2** were readily purified by chromatography on silica gel. Surprisingly, some of the corresponding adducts of **3** were somewhat unstable to purification by silica gel chromatography. For example, the di-TBDMS derivative **11c** underwent significant decomposition upon purification resulting in low isolated yields. The results of these addition reactions are summarized in Table 1.

Deprotection of the Michael adducts to the hydroxamic acids proceeded smoothly to give the desired products in high purities and satisfactory yields. As anticipated the benzyl group in **4a**, **5a**, **7a**, and **8a** could be removed by catalytic hydrogenation using 5% Pd on carbon in ethanol at room temperature and atmospheric pressure. An exception to this was the tetraadduct **6a** derived from cyclam and reagent **1**. Numerous attempts to debenzylate this material under a variety of hydrogenation conditions were all unsuccessful.

The TBDMS protecting group of **11c** could be removed using trifluoroacetic acid in methylene chloride at 0°C yielding the hydroxamic acid **11b** as its trifluoroacetate salt. Removal of the TBDPS protecting group could be accomplished using methanolic potassium hydroxide at 0°C and gave the potassium salts of the hydroxamic acids. However, the preferred reagent for this deprotection was 5% hydrochloric acid in isopropanol which led to the isolation of the hydroxamic acid products as their hydrochloride salts. The crude hydrochlorides were easily purified by washing with benzene or ether.[11, 12]

Table 1. Preparation of hydroxamic acids.

Amine	Reagent	Product (Yield)	
piperidine	1	**4a** (R=Bn, 99%) **4b**[a] (R=H, 94%)	
piperazine	1	**5a** (R=Bn, 85%) **5b**[a] (R=H, 79%)	
cyclam	1	**6a** (R=Bn, 66%)	
N-methyl propane diamine	1	**7a** (R=Bn, 89%) **7b**[a] (H=91%)	
N,N'-dimethyl hexane diamine	1	**8a** (R=Bn, 68%) **8b**[a] (R=H, 98%)	
	2	**9a** (R=TBDPS, 77%) **9b**[b] (R=H, 99%)	
N-methyl benzylamine	2	**10a** (R=TBDPS, 70%) **10b**[b](R=H, 84%)	
benzylamine	2	**11a** (R=TBDPS, 71%) **11b**[b] (R=H, 99%)	
	3	**11c** (R=TBDMS, 42%) **11b**[c] (R=H, 77%)	
m-xylylene diamine	2	**12a** (R=TBDPS, 56%) **12b**[b] (R=H, 85%)	
p-xylylene diamine	2	**13a** (R=TBDPS, 54%) **13b**[b](R=H, 94%)	

Deprotection conditions: a) H_2, 5% Pd/C, EtOH,rt b) 5% HCl/iPrOH, rt, 16 h c) CF_3CO_2H, 0°C

The Michael additions of amines with these acrylohydroxamate reagents lead to the desired adducts which are organic soluble and amenable to purification by routine methods. This is a major advantage particularly for the preparation of polyhydroxamic acids, where purification of the final products is often tedious. Reagent **1** is particularly useful for the preparation of primary hydroxamic acid derivatives of aliphatic amines while the acrylohydroxamate reagent **2** allows the preparation of N-methyl hydroxamate derivatives of both aliphatic and aromatic amines. The fact that the TBDMS Michael adducts are unstable to chromatographic purification, limits the synthetic utility of acrylohydroxamate **3**.

The methodology described here has the potential to be useful for the preparation of a wide variety of hydroxamic acids. The reactions of acrylohydroxamates **1** and **2** with other nucleophiles including carbanions is currently under investigation. Also, some of the polyhydroxamic acids prepared in this study are currently being evaluated for their metal binding properties.

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11. Spectroscopic and elemental analysis of all compounds are in agreement with their assigned structures.
12. Products **4b, 5b, 7b,** and **8b** were isolated as hydroxamic acids. Products **10b** and **11b** were isolated as HCl salts. Products **9b, 12b,** and **13b** were isolated as dihydrochloride salts.

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