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A Convenient Method for the Conversion of *N*-Acyloxazolidinones to Hydroxamic Acids

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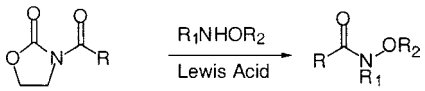
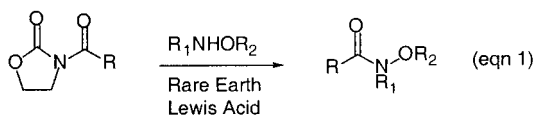
ABSTRACT



Treatment of *N*-acyloxazolidinones with hydroxylamines using samarium triflate as a Lewis acid provides the corresponding hydroxamic acids in 50–98% yields at room temperature. The conversion proceeds with high degree of chemoselectivity and without racemization of chiral centers α- to the acyl group.

Hydroxamic acids are key pharmacophores in many important chemotherapeutic agents. This is especially evident in the succinate-based matrix metalloproteinase inhibitors.[1] A variety of methods have been developed for the preparation of hydroxamic acids starting from carboxylic acids or their derivatives.[2] Although some of these methods are quite efficient for the preparation of substituted hydroxamic acids, the preparation of the parent compound is still a problem and yields are often quite unacceptable, in part due to the low solubility of the parent hydroxylamine hydrochloride in organic solvents. Given the importance of the functionality and the difficulties one often faces in their preparation, development of new methods for the efficient synthesis of hydroxamic acids from carboxylic acid derivatives is important. This letter reports an efficient and convenient method for the conversion of *N*-acyloxazolidinones **1** to hydroxamic acids and derivatives **2** (eq 1).[3,4] The reaction is chemoselective and proceeds without racemization when an α-substituent is present in the acyl group.



1 2 (eqn 1)

Oxazolidinone is a very versatile functional group. Chiral oxazolidinones, readily prepared from amino acids, are premiere auxiliaries with broad utility in synthetic chemistry.[5] Thus, the post-modification of this functionality to others is

(1) For a review, see: Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735.

(2) For a very recent report on the synthesis of hydroxamic acids from carboxylic acids, see: Bailén, M. A.; Chinchilla, R.; Dodsworth, D. J.; Nájera, C. *Tetrahedron Lett.* **2001**, *42*, 5013. Preparation of hydroxamic acids: from hydroxylamine and esters: (a) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; J. Wiley and Sons, Inc.: New York, 1967; Vol. 1, pp 478−479. (b) Hauser, C. R.; Renfrow, W. B., Jr. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, pp 67−68. Cleavage of an ester on a solid support: Dankwardt, S. M.; Billedeau, R. J.; Lawley, L. K.; Abbot, S. C.; Martin, R. L.; Chan, C. S.; Van Wart, H. E.; Walker, K. A. M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2513. From acid chloride and *O*-benzyl hydroxylamine: Lee, B. H.; Miller, M. J. *J. Org. Chem.* **1983**, *48*, 24. For selective debenzylation of the *O*-benzyl ethers: Nikam, S. S.; Kronberg, B. E.; Johnson, D. R.; Doherty, A. M. *Tetrahedron Lett.* **1995**, *36*, 197. From acid chloride and *N*,*N*,*O*-tristrimethylsilyl hydroxylamine: Ando. W.; Tsumaki, H. *Synth. Commun.* **1983**, *13*, 1053. From acid chloride and *N*-Boc-*O*-*tert*-butyldimethylsilyl hydroxylamine: Altenburger, J. M.; Mioskowski, C.; d'Orchymont, H.; Schirlin, D.; Schalk, C.; Tarnus, C. *Tetrahedron Lett.* **1992**, *33*, 5055. From acids and *O*-allyl hydroxylamine followed by deprotection. Fray, M. J.; Burslm, M. F.; Dickinson, R. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 567. From acid chloride and *N*,*O*-bistrimethylsilyl hydroxylamine: King, F. D.; Pike, S.; Walton, D. R. M. *J. Chem. Soc., Chem. Commun.* **1978**, 351. Pirrung, M. C.; Chang, J. H.-L. *J. Org. Chem.* **1995**, *60*, 8084. From carboxylic acids and amine using coupling reagents: Barlaam, B.; Hamon, A.; Maudet, M. *Tetrahedron Lett.* **1998**, *39*, 7865.

(3) For the conversion of acyl oxazolidinones to esters using LaI_3 see: Fukuzawa, S.-i.; Hongo, Y. *Tetrahedron Lett.* **1998**, *39*, 3521. For the use of magnesium Lewis acids, see: Evans, D. A.; Anderson, J. C.; Taylor, M. K. *Tetrahedron Lett.* **1993**, *34*, 5563. Also see: Yamada, S.; Katsumata, H. *J. Org. Chem.* **1999**, *64*, 9365. For the formation of amides from acyl oxazolidinones using titanocene dichloride, see: Yokomatsu, T.; Arakawa, A.; Shibuya, S. *J. Org. Chem.* **1994**, *59*, 3506.

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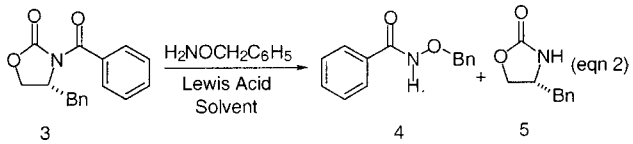
of interest to the synthetic community. The conversion of *N*-acyloxazolidinones to esters using rare earth Lewis acid has been recently reported by Otera and co-workers.[6] Similarly, the conversion of acyl oxazolidinones to *N*,*O*-dimethylhydroxamides (Weinreb amides)[7] using trimethylaluminum has also been noted in the literature.[8] The chemoselectivity, exo or endo attack, in these reactions are well controlled, and only the product arising from exo attack is observed.[9] In a program aimed at developing methods for the preparation of succinate based MMP inhibitors, we became interested in the efficient conversion of oxazolidinones to hydroxamic acids. This paper details one such process.

Our initial goal was to evaluate lanthanide triflates as catalysts for the conversion of acyloxazolidinones to hydroxamic acids. The catalyst choice was based on several unique properties of the rare earth Lewis acids: (1) ready availability, (2) a large number of triflates with varied Lewis acidity, (3) compatibility with amine nucleophiles, and (4) potential for reactions in aqueous medium. Our experiments began with the optimization of reaction conditions for the conversion of *N*-benzoyl-4-benzyl-2-oxazolidinone **3** to *O*-benzylbenzohydroxamic acid **4** (eq 2), and these results are shown in Table 1. Treatment of **3** with 2 equiv of *O*-benzylhydroxylamine in THF at room temperature gave the hydroxamic acid **4** in 90% isolated yield (entry 1). Ether or acetonitrile were equally efficient as a solvent in the amidation reaction (entries 2 and 3). Increasing the number of equivalents of the amine nucleophile to 5 led to moderate improvements in reaction time (2 h for entry 2 and 0.5 h for entry 4). However, the yield did not improve. Substoichiometric amounts of the catalyst (30 mol %) also gave **4** in high yields (Table 1, entry 6). Of the other rare earth Lewis acids evaluated (entries 7−12), europium and lanthanum triflates also showed good reactivity (entries 9, 10, and 12).

Having established that the amidation sequence was feasible, we turned our attention to examining the scope of the nucleophiles in these reactions, and these results are shown in Table 2 (eq 3). Treatment of the achiral oxazolidinone **6** with a variety of hydroxylamines gave **7** in moderate to good yields depending on the amine. As described previously, reaction with *O*-benzylhydroxylamine proceeds in high yield (entry 1). The reaction proceeds equally well with the amine hydrochloride salt with in situ neutralization (entry 2). Reaction with the parent hydroxylamine was less efficient (entry 3). Reactions with silylated hydroxylamines gave the hydroxamic acid directly in moderate yields (entries 4 and 5). The THP-protected hydroxylamine served as a better synthon for the parent hydroxy-

Table 1. Conversion of *N*-Benzoyloxazolidinone to *O*-Benzylhydroxamide[a]

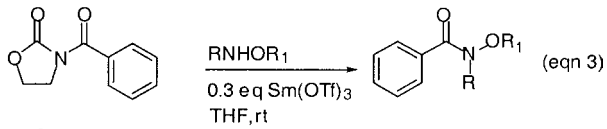


3 4 5

entry	Lewis acid (equiv)	amine (equiv)	solvent[b]	yield,[c] %
1	$Sm(OTf)_3$ (1.0)	2	THF	90
2	$Sm(OTf)_3$ (1.0)	2	ether	83
3	$Sm(OTf)_3$ (1.0)	2	CH_3CN	88
4	$Sm(OTf)_3$ (1.0)	5	THF	91
5	$Sm(OTf)_3$ (0.5)	2	THF	90
6	$Sm(OTf)_3$ (0.3)	2	THF	78
7	$Yb(OTf)_3$ (1.0)	2	THF	68
8	$Yb(OTf)_3$ (1.0)	2	ether	50
9	$Eu(OTf)_3$ (1.0)	2	THF	80
10	$Eu(OTf)_3$ (1.0)	2	ether	85
11	$La(OTf)_3$ (1.0)	2	THF	50
12	$La(OTf)_3$ (1.0)	2	ether	80

[a] Reactions were carried out at rt. [b] An average concentration of 0.1−0.2 M was employed. [c] Isolated yields for column purified materials.

Table 2. Evaluation of Different Hydroxylamines[a,b]



6 7

		product		
entry	amine (equiv)	R	R_1	yield,[c] %
1	$BnONH_2$ (2)	H	Bn	98
2	$BnONH_2$ (2)	H	Bn	98[d]
3	$HONH_2$	H	H	45[d]
4	$TMSONH_2$	H	H	39
5	TMSONHTMS	H	H	55
6	$THPONH_2$	H	H	70
7	$4\text{-}OMePhCH_2ONH_2$	H	4-MeOBn	75
8	MeONHMe	Me	Me	75[d]

[a] Reactions were carried out at room temperature. [b] An average concentration of 0.1−0.2 M was employed. [c] Isolated yields for column purified materials. [d] The reaction was carried out by in situ generation of the amine (4 equiv) from the corresponding hydrochloride using triethylamine (3.8 equiv).

(4) The direct conversion of acyl thiazolidine thiones to hydroxamic acid derivatives has been reported. (a) Jung, M.; Miller, M. J. *Tetrahedron Lett.* **1985**, *26*, 977. (b) Hsiao, C.-N.; Ashburn, S. P.; Miller, M. J. *Tetrahedron Lett.* **1985**, *26*, 4855. (c) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49.

(5) (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta* **1997**, *30*, 3. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (c) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23. (d) Sibi, M. P. *Aldrichim. Acta* **1999**, *32*, 93.

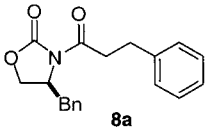
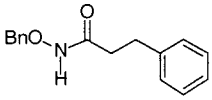
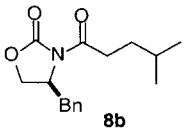
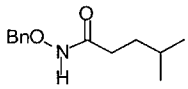
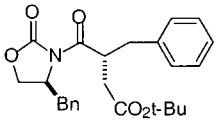
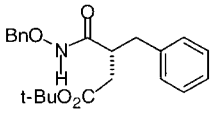
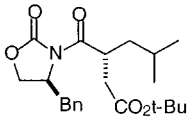
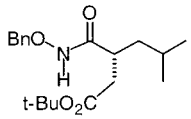
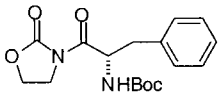
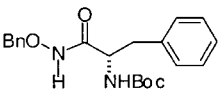
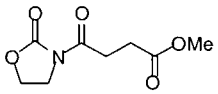
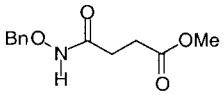
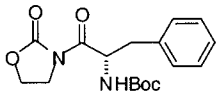
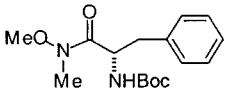
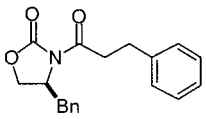
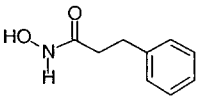
(6) Orita, A.; Nagano, Y.; Hirano, J.; Otera, J. *Synlett* **2001**, 637.

(7) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) For reviews on Weinreb amides, see: Sibi, M. P. *Org. Prep. Proced. Intl.* **1993**, *25*, 15. (b) Mentzel, M.; Hoffmann, H. M. R. *J. Prakt. Chem.* **1997**, *339*, 517.

(8) Conversion of *N*-acyl oxazolidinones to Weinreb amides. Evans, D. A.; Miller, S. J.; Ennis, M. D.; Ornstein, P. L. *J. Org. Chem.* **1992**, *57*, 1067. Convesrion of esters to Weinreb amides. Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461. Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1985**, *107*, 7790.

(9) *N*-Acyl oxazolidinones can be selectively cleaved either at the exo or at the endo site. Exo cleavage: Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123. Evans, D. A.; Sjogren, E. B.; Bartroli, J. Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957. Jacobi, P. A.; Zhang, W. *Tetrahedron Lett.* **1993**, *34*, 2585. Endo cleavage: Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 4185. Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151.

Table 3. Chemoselectivity and Scope of the Method[a]

Entry	Acyl Oxazolidinone	Substrate concentration M	Hydroxylamine	Time h	Product	Yield[b] %
1.	 **8a**	0.1	$BnONH_2$ (2)	5	 **9a**	70
2.	 **8b**	0.1	$BnONH_2$ (2)	5	 **9b**	87
3.	 **8c**	0.5	$BnONH_2$ (4)	5	 **9c**	70
4.	 **8d**	0.5	$BnONH_2$ (4)	5	 **9d**	84
5.	 **8e**	0.1	$BnONH_2$ (2)	1	 **9e**	98
6.	 **8f**	0.1	$BnONH_2$ (2)	1	 **9f**	90
7.	 **8e**	0.2	MeONHMe (4)[c]	72	 **9g**	75
8.	 **8a**	0.2	NH_2OH (4)[c]	72	 **9h**	60

[a] Reactions were carried out at room temperature using 0.3 equiv of $Sm(OTf)_3$ as catalyst. [b] Isolated yields for column purified materials. [c] The reaction was carried out by in situ generation of the amine (4 equiv) from the corresponding hydrochloride using triethylamine (3.8 equiv).

lamine. Reaction with this reagent proceeded smoothly to give the parent hydroxamic acid directly (entry 6) in good yield. In this case, the cleavage of the protecting group occurs during column chromatography. The *p*-methoxybenzyl protecting group offers the advantage of being more robust. However, it can be readily cleaved either under strongly acidic conditions or by DDQ.[10] Reactions with *p*-methoxybenzylhydroxylamine were facile, giving the acyl hydroxamate in good yield (entry 7). *N*-Methoxy-*N*-methylamide, the Weinreb amide, has found extensive utility as a carbonyl synthon. The preparation of these compounds from oxazolidinone is typically carried out using trimethylaluminum.[7] The Weinreb amide **7** can be readily prepared in high yield

(10) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

from **6** and *N*,*O*-dimethylhydroxylamine prepared *in situ* (entry 8) from the corresponding hydrochloride. Thus, the present methodology offers a convenient protocol for the synthesis of Weinreb amides.

The chemoselectivity of the amidation reactions has also been explored using a range of substrates containing ester and protected amino functional groups. The results from these experiments are shown in Table 3. The standard reaction conditions developed previously were used in all the experiments. Substrates **8a**,**b** show the facility of the amidation process with both aliphatic and aromatic compounds. The differentially protected succinates **8c**,**d** containing a *t*-Bu ester underwent chemoselective amidation using *O*-benzylhydroxylamine in good yields. Similarly, the *N*-Boc-protected amino acid derivative **8e** also reacted cleanly to give the product amides. These reactions proceed without affecting the amino functionality. Additionally, no racemization of the α-chiral center was observed.[11] Chemoselective amidation of the oxazolidinone in the presence of the methyl ester in reaction with **8f** clearly demonstrates the utility of the methodology. The preparation of the Weinreb amide **9g** proceeded smoothly in high yield. Thus, a variety of hydroxamic acids could be prepared in protected form in good yields from the corresponding *N*-acyloxazolidinones.

In conclusion, we have developed a simple and effective methodology for the conversion of *N*-acyloxazolidinones to hydroxamic acid derivatives. A variety of hydroxylamines can be used in the amidation process, and the reactions proceed with high chemoselectivity and without racemization. Application of the methodology in complex molecule synthesis is described in the next paper.[12]

Acknowledgment. This work was supported by a grant from the National Institutes of Health−National Center for Research Resources 1 P20 RR15566-01.

Supporting Information Available: Characterization data for compounds **1**−**9** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0263301

(11) The structure for **9a** was established by comparing its analytical and spectral characteristics with those reported in the literature. Takahashi, H.; Hitomi, Y.; Iwai, Y.; Ikegami, S. *J. Am. Chem. Soc.* **2000**, *122*, 2995. The optical purity of compound **9g** was verified by comparing its specific rotation to that reported in the literature. Tunoori, A. R.; White, J. M.; Georg, G. I. *Org. Lett.* **2000**, *2*, 4091.

(12) Sibi, M. P.; Hasegawa, H. *Org. Lett*. **2002**, *4*, 3347.