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One-Step Synthesis of *O*-Benzyl Hydroxamates from Unactivated Aliphatic and Aromatic Esters

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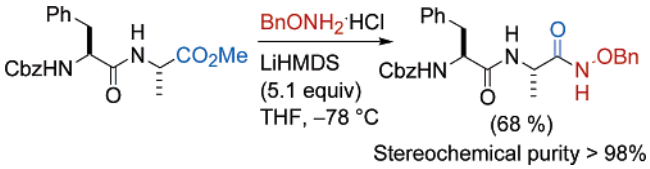

We have developed a simple and high yielding one-step method for the synthesis of hydroxamate derivatives directly from a broad range of unactivated esters and the anion of *O*-benzyl-hydroxylamine generated in situ. The reaction takes place in minutes at −78 °C. Very importantly, the method was successfully employed with enolizable esters, including chiral α-amino acid esters and peptides, with no trace of racemization/epimerization at the α carbon detected.

Hydroxamic acids are of utmost importance in the field of bioorganic and coordination chemistry. They indeed feature excellent bioavailability and count among the best ligands known for most biologically relevant metals. They are for instance found in the structure of numerous drugs that either trigger metal-dependent proteins or are involved in the regulation of intracellular concentrations of metals such as iron and others.[1] Their biological significance is further illustrated by the number of methods that have been and still are developed for their chemical synthesis.[2] These methods overwhelmingly make use of activated forms of carboxylic acids that are reacted with *O*-Bn hydroxylamine to give *O*-Bn hydroxamates, a conveniently protected form of free hydroxamic acids, each method differing in the activating group used. Hydrolysis is thus a prerequisite if very common precursors such as esters are to be converted into hydroxamates.[3] Besides, many carboxylic acids proved reluctant in the activation step resulting in poor yields in the coupling reaction.

A one-step conversion of esters into hydroxamates should therefore save both the hydrolysis and the potentially troublesome activation steps. In fact, esters have been successfully reacted with *O*-Bn hydroxylamine. To overcome the alleged poor electrophilicity of unactivated aliphatic esters, $AlMe_3$ is yet necessary, the reaction usually being carried out in THF or chlorinated solvents.[4] This method is quite limited in scope because of environmental concerns and poor functional group tolerance associated with the use of the hazardous and very reactive $AlMe_3$.

Within the frame of a research project dealing with the synthesis of fluorinated matrix metalloproteinases inhibitors,[5] we decided to explore the feasibility of a one-step protocol for the synthesis of hydroxamates directly from esters and *O*-Bn hydroxylamine. In this article we show that readily available methyl or ethyl esters themselves are excellent electrophiles in the reaction with the anion of *O*-Bn-hydroxylamine in the absence of any activator.[6] The reaction is operatively simple, takes place smoothly and efficiently at −78 °C in THF, and is very broad in scope.

In a first set of experiments, different organic bases were tested in the reaction of ethyl benzoate with *O*-Bn-hydroxylamine (Table 1). Thus, a mixture of *O*-Bn-hydroxylamine hydrochloride and ethyl benzoate (1 equiv) in dry THF was treated with the base (3.1 equiv).

In a control reaction with triethylamine as a base, neutral *O*-Bn hydroxylamine proved unreactive at room temperature (entry 1). Although no reaction was observed at −78 °C in the presence of the stronger KH base (entry 2), the desired *O*-Bn hydroxamate **1a** was obtained in a satisfactory 76% yield at room temperature (entry 3). At least 3 equiv of base are necessary for this transformation, the first to neutralize hydrochloric acid, the second to form the nucleophilic *N*-centered anion, and the third

(1) (a) Abbenante, G.; Fairlie, D. P. *Med. Chem.* **2005**, *1*, 71−104. (b) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735−2776. (c) Muri, E. M. F.; Nieto, M. J.; Sindelar, R. D.; Williamson, J. S. *Curr. Med. Chem.* **2002**, *9*, 1631−1653. (d) Marmion, C. J.; Griffith, D.; Nola, K. B. *Eur. J. Inorg. Chem.* **2004**, 3003−3016.

(2) For recent examples: (a) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534−2537. (b) Sibi, M. P.; Hasegawa, H.; Ghorpade, S. R. *Org. Lett.* **2002**, *4*, 3343−3346. (c) Giacomelli, G.; Porcheddu, A.; Salaris, M. *Org. Lett.* **2003**, *5*, 2715−2717 and references therein.

(3) (a) Moriyama, H.; Tsukida, T.; Inoue, Y.; Kondo, H.; Yoshino, K.; Nishimura, S. I. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2737−2740. (b) Cherney, R. J.; Duan, J. J. W.; Voss, M. E.; Chen, L.; Wang, L.; Meyer, D. T.; Wasserman, Z. R.; Hardman, K. D.; Liu, R. O.; Covington, M. B.; Qian, M.; Mandlekar, S.; Christ, D. D.; Trzaskos, J. M.; Newton, R. C.; Magolda, R. L.; Wexler, R. R.; Decicco, C. P. *J. Med. Chem.* **2003**, *46*, 1811−1823. (c) Fujisawa, T.; Igeta, K. Odake, S.; Morita, Y.; Yasuda, J.; Morikawa, T. *Bioorg. Med. Chem.* **2002**, *10*, 2569−2581, (d) Kamimura, A.; Morita, R.; Matsuura, K.; Omata, Y.; Shirai, M. *Tetrahedron Lett.* **2002**, *43*, 6189−6191. (e) Durham, B. T.; Miller, M. J. *Org. Lett.* **2002**, *4*, 135−138.

(4) See for instance: (a) Pirrung, M. C.; Chau, J. H. L. *J. Org. Chem.* **1995**, *60*, 8084−8085. (b) Durham, T. B.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 27−34. (c) Takahashi, H.; Hitomi, Y.; Iwai, Y.; Ikegami, S. *J. Am. Chem. Soc.* **2000**, *122*, 2995−3000. (d) Banfi, L.; Cascio, G.; Guanti, G.; Manghisi, E.; Narisano, E.; Riva, R. *Tetrahedron* **1994**, *50*, 11967−11982.

(5) Zanda, M. *New. J. Chem.* **2004**, *28*, 1401−1411.

(6) A classical protocol for the synthesis of Weinreb amides consists of the treatment of methyl or ethyl esters with the anion of *N*,*O*-dimethyl hydroxylamine. This concept is thus not new, but as we shall see later, the conditions employed for the synthesis of Weinreb amides are not suitable for the synthesis of *O*-Bn hydroxamates. For examples of synthesis of Weinreb amides directly from esters, see: (a) Davis, F. A.; Rao, A.; Carroll, P. J. *Org. Lett.* **2003**, *5*, 3855−3857 (b) Ducharme, Y.; Friesen, R. W.; Blouin, M.; Côté, B.; Dubé, D.; Ethier, D.; Frenette, R.; Laliberté, F.; Mancini, J. A.; Masson, P.; Styhler, A.; Young, R. N.; Girard, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1923−1926, (c) Papaioannou, N.; Blank, J. T.; Miller, S. J. *J. Org. Chem.* **2003**, *68*, 2728−2734, (d) Miller, A. K.; Banghart, M. R.; Beaudry, C. M.; Suh, J. M.; Trauner, D. *Tetrahedron* **2003**, *59*, 8919−8930, (e) Wender, P. A.; Koehler, M. F. T.; Sendzik, M. *Org. Lett.* **2003**, *5*, 4549−4552.

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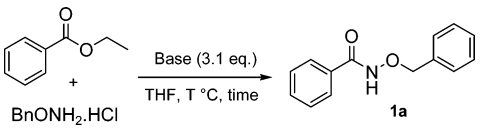
TABLE 1. Reaction of Ethyl Benzoate and *O*-Bn-Hydroxylamine with Different Bases



entry	base	*T* (°C)	time (min)	yield of **1a** (%)
1	TEA	25	360	0
2	KH	−78	240	0
3	KH	25	120	76
4	*n*-BuLi	−78	20	47 [a]
5	NaHMDS	−78	20	86
6	LiHMDS	−78	10	95

[a] Valerophenone was also obtained (40% yield) together with a minor uncharacterized impurity.

to deprotonate the acidic hydroxamate proton of the product. Commercially available solutions of strong organic bases were used in the following experiments (entries 4−6). Slow addition of *n*-BuLi at −78 °C to the mixture of ester and *O*-Bn hydroxylamine hydrochloride did produce **1a**, although in modest yield (entry 4). The attack of *n*-BuLi directly onto the carbonyl competes with the desired coupling reaction as evidenced by the formation of valerophenone in 40% yield.[7] We nevertheless found that side reactions are suppressed using sodium and lithium hexamethyldisilazide instead. Both afforded the desired **1a** in minutes and in excellent yield at −78 °C in THF (entries 5 and 6). The lithium salt of *O*-Bn hydroxylamine proved more reactive over the sodium derivative, perhaps due to its higher solubility in THF at low temperatures, and was therefore used to study the scope of the reaction (Table 2).

Electron-rich (R^1 = OMe) or -poor (R^1 = F) aromatics gave the desired products **1b** and **1c**, respectively, in good yields. Surprisingly, the nitro-substituted **1d** was obtained in 37% yield only from the highly activated 4-nitro methyl benzoate.[8] Heteroaromatic furyl and nicotinic esters gave **1e** and **1f** in very good yields. No aza-Michael addition of the nucleophile was observed with methyl cinnamate, the desired hydroxamate **1g** being obtained quantitatively. Quite surprisingly, enolizable substrates were also found very reactive provided that an additional equivalent of base and a different addition sequence were used.[9] For instance, ethyl hydrocinnamate reacted virtually instantaneously when added slowly to a mixture of *O*-Bn hydroxylamine and 4.1 equiv of LiHMDS at −78 °C in THF, affording the hydroxamate **1h** quantitatively. Cyclic enolizable esters such as α-methyl β-lactone and γ-lactone also reacted effectively affording the hydroxamates $HOCH_2CH(CH_3)CONHOBn$ (**1i**) and $HO(CH_2)_2$-$CH(CH_3)CONHOBn$ (**1j**). Interestingly, chiral *O*-Bn hydroxamate **1k** was obtained in good yields without noticeable epimerization of the α position (^1H and ^{13}C NMR analysis).

Given the significance of amino acid and peptide derived hydroxamates, the method was also probed with such derivatives such as *N*-Boc-Ala, *N*-Cbz-Glu, and *N*-Boc-Ser methyl esters.

These substrates proved very reactive at −78 °C—no protection of the free hydroxyl and carboxylic positions was required using an additional equivalent of base—affording the corresponding *O*-Bn hydroxamates **1l**, **1m**, and **1n**, respectively, in good to excellent yields.[10] Quite surprisingly, and to our delight, the stereochemistry of the α-amino acidic carbon was preserved.[11] The preservation of the stereochemical purity and the fact that 4.1 equiv of LiHMDS (or 5.1 in the case of Glu and Ser, which have two acidic protons) are sufficient to perform the reaction strongly suggest that deprotonation at the α-carbon does not take place.[12] The method could be extended to peptidic esters as well, as demonstrated by the formation of the *O*-Bn hydroxamate Cbz-Phe-Ala-NHOBn (**1p**) from the corresponding dipeptide methyl ester. In this case too, no trace of epimerization was detected despite the use of 5.1 equiv of base (^1H and ^{13}C NMR analysis).

In conclusion, we have disclosed a simple, straightforward, and high yielding method for the one-step synthesis of *O*-Bn hydroxamates from a broad range of unactivated esters. Very importantly, enolizable esters, α-amino acid esters, and peptide esters were also successfully reacted with no trace of racemization at the α carbon. In the optimized experimental protocol for non-enolizable esters, a mixture of *O*-Bn-hydroxylamine hydrochloride and ester in dry THF was treated at −78 °C with 3 equiv of LiHMDS delivering in few minutes the desired *O*-Bn hydroxamate. With enolizable esters or esters containing acidic protons (such as amino acid esters and peptide esters), addition of the ester to the mixture of *O*-Bn hydroxylamine hydrochloride and 3 + *n* equivalents of base (*n* is the number of acidic protons of the ester) in dry THF at −78 °C represents the optimized protocol. Good to excellent yields of *O*-Bn hydroxamates were generally obtained. Given its simplicity and efficiency, we hope this will become the method of choice for the preparation of hydroxamates and hydroxamic acids.

(7) Since *n*-BuLi is always present in excess to deprotonate the final hydroxamate, this side reaction is unavoidable even if the ester is added last to the anion of *O*-Bn-hydroxylamine (result not shown). In turn, this result shows that if the use of *n*-BuLi or Grignard reagents to deprotonate *N*,*O*-dimethylhydroxylamine constitutes a powerful method to synthesize Weinreb amides from esters, this strategy cannot be utilized with *O*-Bn-hydroxylamine (which has an additional proton) to form hydroxamic acid derivatives, as addition of the base to the ester will always compete with deprotonation.

(8) An intense red color was observed upon addition of the ester to the lithiated *O*-Bn hydroxylamine. This color might indicate the formation of a charge-transfer complex that perturbs the reaction. Unfortunately, an even poorer yield was obtained with KH at 20 °C instead of LiHMDS and no reaction was observed with TEA (5 equiv) in refluxing THF.

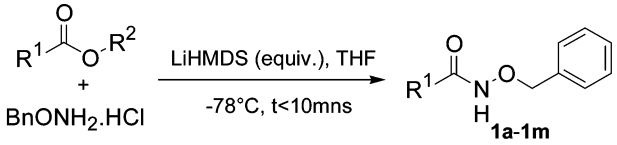
(9) Deprotonation α to the ester does take place as evidenced by the formation of the Claisen condensation product from ethyl hydrocinnamate when LiHMDS was slowly added to the mixture of ester and *O*-benzylhydroxylamine at −78 °C in THF (result not shown).

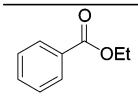
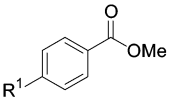
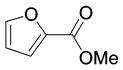
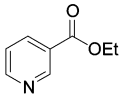
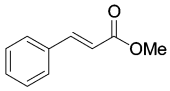
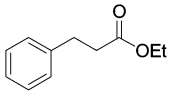
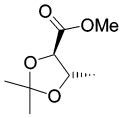
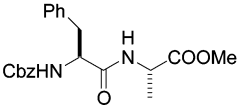
(10) As the hydroxamates are poorly soluble in many organic solvents, the flash chromatography was done using a $CHCl_3$/MeOH mixture as eluent.

(11) To assess the enantiomeric purity, **1n** was derivatized with (*S*)-α-methylphenylacetic acid affording the corresponding ester in de > 98% (95% yield). The enantiomeric purity of **1l** was assessed by polarimetric analysis, which showed an $[\alpha]_D$ identical to that reported in the literature for the enantiopure compound (see Supporting Information).

(12) Prior deprotonation of the NH-Cbz or NH-Boc groups may prevent the amino acid from undergoing additional deprotonation at the stereogenic center.

TABLE 2. Reaction of *O*-Bn-Hydroxylamine with Different Esters under Optimized Conditions



Ester		Eq. of base	Product	Yield [a](%)
		3.1	**1a**	95
	R^1 = OMe	3.1	**1b**	89
	R^1 = F	3.1	**1c**	85
	R^1 = NO_2	3.1	**1d**	37
		3.1	**1e**	87
		3.1	**1f**	89
		3.1	**1g**	>98
		4.1	**1h**	>98
		4.1	**1i**	83
		4.1	**1j**	72
		4.1	**1k**	70[c]
N-Boc-L-Ala-OMe		4.1	**1l**	95 [b]
N-Cbz-L-Glu-OMe		5.1	**1m**	94[b]
N-Boc-L-Ser-OMe		5.1	**1n**	68[b]
		5.1	**1p**	68[c]

[a] Isolated yield of pure product. All reactions carried out on a 1 mmol scale. [b] Enantiomerically pure product. [c] Diastereomerically pure product.

Experimental Section

General Procedure with Nonenolizable Esters (1a−g). A stirred suspension of *O*-Bn-hydroxylamine hydrochloride (1 equiv) and ester (1 equiv) in dry THF (10 mL) at −78 °C and under nitrogen atmosphere was treated with a 1 M solution of LiHMDS (3.1 equiv). After less than 10 min the reaction was quenched with a saturated aqueous solution of NH_4Cl, warmed to room temperature, and extracted with AcOEt. The collected organic layers were dried ($NaSO_4$), filtered, and concentrated under reduced pressure, and the crude purified by flash chromatography.

General Procedure with Enolizable Esters, Amino Acid, and Peptide-Derived Esters Containing *n* Acidic Protons (1h−p). A stirred suspension of *O*-Bn-hydroxylamine hydrochloride (1 equiv) in dry THF (10 mL) at −78 °C and under nitrogen atmosphere was treated with a 1 M solution of LiHMDS (3.1 + *n* equiv). After 10 min a solution of the ester (1 equiv) in a minimum amount of dry THF was added. After the total consumption of the starting material (TLC) the reaction was quenched with a saturated aqueous solution of NH_4Cl, warmed to room temperature, and extracted with AcOEt. The collected organic layers were dried ($NaSO_4$), filtered, and concentrated under reduced pressure, and the crude purified by flash chromatography.

As the hydroxamates are often poorly soluble in many organic solvents, the FC was done using a $CHCl_3$/MeOH mixture as eluent.

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Supporting Information Available: Spectroscopic characterization and copies of the NMR spectra of the hydroxamates **1a**−**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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