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Simple One-Flask Method for the Preparation of Hydroxamic Acids

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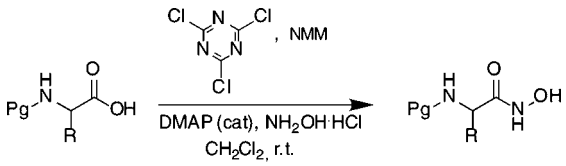
ABSTRACT



A one-step conversion of carboxylic acids to hydroxamic acids under very mild conditions is described. This simple and efficient method has been applied for the synthesis of enantiopure hydroxamate of α-amino acids and peptides.

Hydroxamic acids are strong metal ion chelators[1] and possess a wide spectrum of biological activities with antibacterial, antifungal, antiinflammatory, and anti-asthmatic properties, etc.[2] They also have been identified as potent inhibitors of matrix metalloproteinases.[3] O-Silylated hydroxamic acids have been used for generating nitrile oxides under mild conditions.[4] Therefore, several methods have been developed for the preparation of hydroxamic acids and have been well documented in the literature. Hydroxamic acids have generally been synthesized in solution from nitro compounds or through reaction of O/N-protected hydroxylamines such as NH_2-*O*-Bn, *N*-*t*-BOC-*O*-THP, *N*-*t*-BOC-*O*-TBDMS, *N*,*O*-bis(phenoxycarbonyl)hydroxylamine, *N*,*O*-bis(*tert*-butoxycarbonyl)hydroxylamine and *N*,*N*,*O*-tris(trimethylsilyl)hydroxylamine with activated carboxylic acids.[5] Recently, hydroxamic acids were obtained by treatment of *N*-acyloxazolidinones with hydroxylamines using samarium triflate as a Lewis acid.[6] Solid-phase synthesis also has become an important tool, and there have been several reports describing syntheses of hydroxamic acid derivatives.[7] However, these methods utilize highly expensive hydroxylamine reagents and some of them are not commercially available.

Thus, the economical way to obtain hydroxamic acid derivatives[8] remains the reaction of hydroxylamine with esters[9] or acid chlorides even if this last method cannot be applied to amino acids. In this context, a one-step approach was reported to use ethyl chloroformate as a carboxylic acid activator.[10] However, ethyl chloroformate is moisture sensi-

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(8) For a recent report on the synthesis of hydroxamic acids from carboxylic acids, see: Bailén, M. A.; Chinchilla, R.; Dodsworth, D. J.; Nàjera, C. *Tetrahedron Lett.* **2001**, *42*, 5013.

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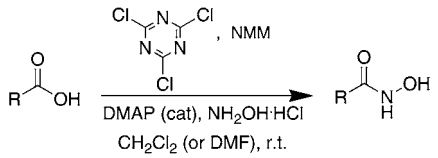
tive and its vapor is a powerful irritant, particularly to the respiratory system and to the eyes.

Following our interest in the use of [1,3,5]triazine derivatives in organic synthesis,[11] we wish to report here a new simple, mild, and high-yielding one-flask synthesis of hydroxamic acids from carboxylic acids and N-protected amino acids[12] that uses the very cheap 2,4,6-trichloro[1,3,5]-triazine (cyanuric chloride, TCT) as a coupling agent (Scheme 1).

Scheme 1



The method allows the preparation of hydroxamic acids in a single-step reaction. Thus, a carboxylic acid is treated with TCT (0.3 equiv), *N*-methylmorpholine (NMM) (1 equiv) in CH_2Cl_2, and dimethylamino pyridine (DMAP) as a catalyst (0.1 equiv), followed by hydroxylamine hydrochloride (1.1 equiv) in dichloromethane. Stirring is continued at room temperature until complete conversion of the carboxylic acid (monitored by TLC). The reaction mixture is filtered on Celite and washed with diluted HCl and brine.

The desired product is recovered in pure form and in high yields simply by concentration of the CH_2Cl_2 extracts at reduced pressure (Table 1). The triazine byproducts are easily removed by this simple aqueous workup. The reaction is not fast and requires from 6 to 12 h for completion in most cases. However, this method can be also successfully applied on a large scale.

The yields are high in all cases examined, and no O-acylated or di- and triacylated products were found in the reaction mixture. As shown from the results reported in Table 1, the method is compatible with the common N-protecting groups and no deprotection was noted even with the less stable Boc-N-protected amino acids. The reaction can be carried out in DMF as a solvent with the same results and comparable yields.

The data collected show that no significant racemization of the chiral center on the α-carbon atom occurred during the synthesis. In fact, a sample of (*S*)-*N*-Boc-phenylglycine, $[\alpha]^{25}_D$ +145 (*c* 1, ethanol) gave (*S*)-*N*-Boc-phenylglycine hydroxamate, **17**, $[\alpha]^{25}_D$ +46.1 (*c* 0.2, methanol), ee >99%.[13] Analogously, (*S*)-*N*-Boc-proline, $[\alpha]^{20}_D$ −61.1 (*c* 1, AcOH) gave (*S*)-*N*-Boc-proline hydroxamate, **9**, $[\alpha]^{25}_D$ −57.1 (*c* 1, methanol), according to literature data.[14]

Table 1. Conversion of Carboxylic Acids into the Corresponding Hydroxamic Acids

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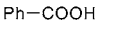
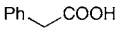
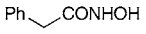
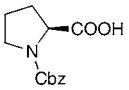
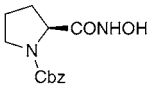
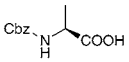
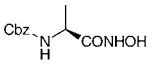
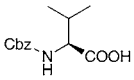
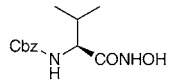
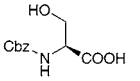
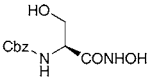
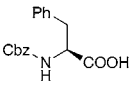
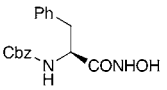
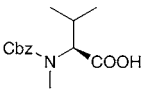
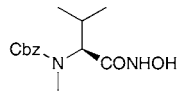
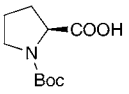
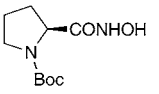
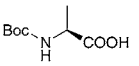
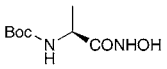
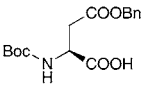
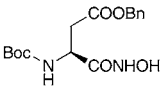
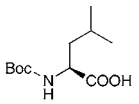
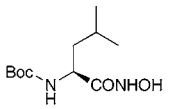
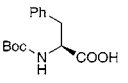
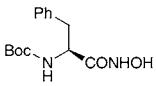
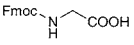
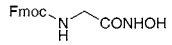
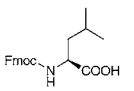
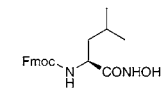
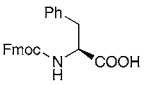
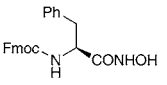
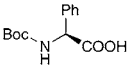
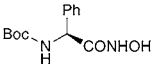
1			95
2			90
3			96
4			87
5			94
6			90
7			92
8			96
9			85
10			90
11			90
12			97
13			95
14			97
15			98
16			80
17			90

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(12) Reaction conducted on free amino acids produces the corresponding hydroxamate in very low yields (<10%), and the final products are not easily recovered from the reaction mixture.

(13) Determined by analysis of the ^{19}F NMR spectra of the corresponding MPTA derivatives [Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543] of both racemic and optically active Boc-phenylglycine hydroxamates. ^1H NMR analysis on the hydroxamates carried out in the presence of $Eufod_3$ gave analogous results.

(14) Thouin, E.; Lubell, W. D. *Tetrahedron Lett.* **2000**, *41*, 457.

Moreover, the method seems to be directly applicable to the synthesis of peptide hydroxamic acids, as demonstrated by the preparation of the model dipeptide hydroxamic acids of Figure 1.

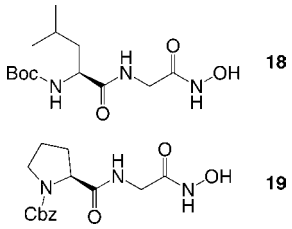

Figure 1.

Thus, compounds **18**[15] and **19** were prepared with 73 and 82% overall yields, respectively, and recovered without any further purification.

The procedure for the preparation of (*S*)-(*N*-benzyloxycarbonyl)proline hydroxamate, **3**, is representative for all cases. Cyanuric chloride (TCT, 0.5 g, 3.0 mmol) was added to a solution of (*S*)-(*N*-benzyloxycarbonyl)proline (2.24 g, 9.0 mmol), NMM (1.0 g, 1.1 mL, 9.9 mmol), and DMAP (0.01 g, 0.1 mmol) in CH_2Cl_2 (20 mL), containing hydroxylamine hydrochloride (0.68 g, 9.8 mmol), stirred, and maintained at 0 °C. After the addition, the mixture was warmed to room temperature, stirred for 12 h, and then filtered on Celite, and the organic phase was washed three times with 15 mL of 1 N HCl and then brine. The organic layers were dried (Na_2SO_4) and the solvent evaporated to yield compound **3** that was isolated without other purifications (2.3 g, 96%), $[\alpha]^{25}_D$ −46.1 (*c* 0.5, methanol):[14] ^{1}HNMR δ 8.06 (s, 1H), 7.26−7.36 (m, 5H), 5.34 (s, 2H), 4.29 (t, 1H), 3.35 (t, 2H), 2.17 (s, 1H), 1.60−1.83 (m, 4H); ^{13}CNMR δ 170.0, 155.8, 137.0, 128.4, 127.8, 127.5, 67.0, 60.2, 40.9, 23.7, 20.1.

In conclusion, we think that the one-flask method described here is one of the most simple and convenient for the preparation of hydroxamic acids, even in large scale, as it uses friendly reaction conditions and inexpensive reagents. The method can be used as a valid alternative to other ones, thereby avoiding the use of N-protected hydroxylamine[5] and consequently any tedious subsequent deprotection reaction or purification.

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Supporting Information Available: Physical and spectroscopic data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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