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New hydroxylamines for the synthesis of hydroxamic acids

Bernard Barlaam*, Annie Hamon, Mickaël Maudet

Zeneca Pharma, Centre de Recherches, Z.I. La Pompelle, BP1050, Chemin de Vrilly, 51689 Reims Cedex2, France

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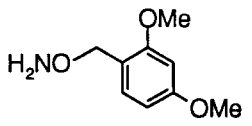
Abstract: O-2,4-Dimethoxybenzyl hydroxylamine and O-2,4-dimethoxybenzyl-N-2,4,6-trimethoxybenzyl hydroxylamine have been prepared and used for the preparation of hydroxamic acid based inhibitors of biological interest.

Keywords: hydroxylamines, hydroxamic acids, protecting groups.

Hydroxamic acids are very effective metal ion chelators. They have been extensively used as zinc binding ligand in the field of zinc metalloenzyme inhibitors, especially in matrix metalloprotease (MMP) inhibitors. This approach has led to pseudopeptide and non peptide hydroxamic acids which are potent MMP inhibitors: several of them have been advanced into human clinical trials for the treatment of cancer, arthritis and corneal ulceration.[1]

Common methods[2, 3] for the synthesis of hydroxamic acids are the direct acylation of hydroxylamine or protected hydroxylamines, including O-benzyl,[4] O-silyl and O-*t*-butyl,[2e] with acid chlorides or various activated esters. However we found that these methods are not suitable for multiple parallel synthesis (m.p.s.) of hydroxamic acids. They suffer from tedious purification and isolation steps or deprotection conditions (e.g. hydrogenolysis[4] for the benzyl group) which are often incompatible with m.p.s.

As part of our on-going interest in the design and synthesis of inhibitors of TNFα convertase[5], a zinc metalloenzyme, we have prepared two new hydroxylamines **1** and **2** for the synthesis of O-protected or N,O-bisprotected hydroxamic acids[6] that can be deprotected under mild acidic conditions (easily applicable to m.p.s.).



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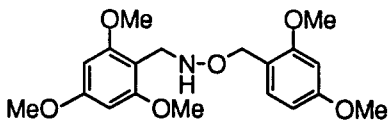

2

1[7] was prepared from 2,4-dimethoxybenzyl alcohol according to Grochowski and Jurczak's procedure.[8] Reacting **1** with 2,4,6-trimethoxybenzaldehyde and subsequent reduction[6a] of the oxime[9] with $NaBH_3CN$ at pH 3 afforded the crystalline N,O-bisprotected hydroxylamine **2** in good yield (Scheme 1). Both are stable at room temperature for months.

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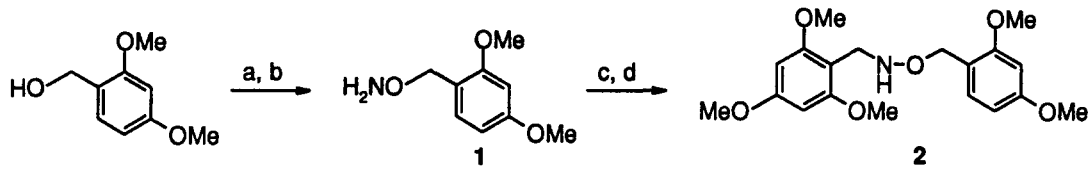
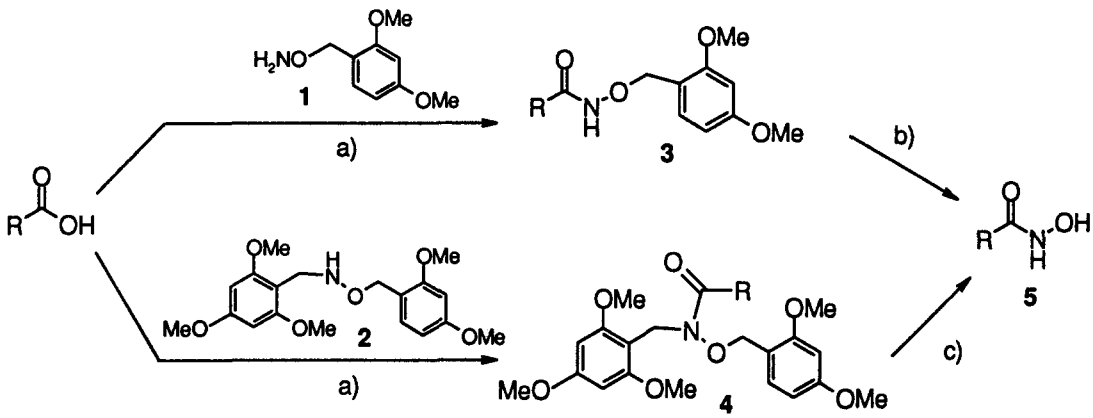


a) N-hydroxyphthalimide, PPh_3, DEAD; b) NH_2NH_2, MeOH; c) 2,4,6-trimethoxybenzaldehyde, CH_2Cl_2; d) $NaBH_3CN$, EtOH, pH= 3

Scheme 1

Coupling of the O-protected hydroxylamine **1** or N,O-bisprotected hydroxylamine **2** with a carboxylic acid was performed under standard conditions (e.g. carbodiimide coupling) to give the protected hydroxamates **3** and **4** in good yields (Scheme 2). Reaction of **1** or **2** with an acyl chloride worked equally well (see Table 1 examples 10 and 11).

The O-protected hydroxamate **3** was deprotected by 5% TFA in dichloromethane in a few minutes to give the corresponding unprotected hydroxamate **5** (even with 1% TFA, the hydroxamate **5** was detectable after a few seconds.). The N,O-bisprotected hydroxamate **4** is fully deprotected with 10% TFA in dichloromethane after 2 hours (Scheme 2). However it is possible to selectively deprotect the O-dimethoxybenzyl group by using 1% TFA without affecting the N-protection.[10] The crude hydroxamates can be either precipitated in ether or subjected to chromatography to obtain highly pure hydroxamates.



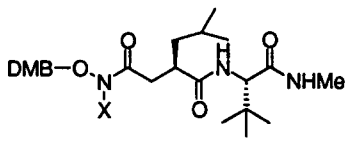
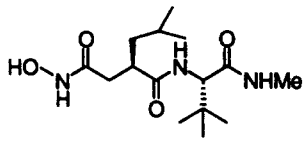
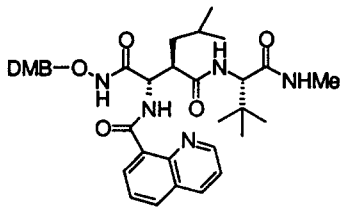
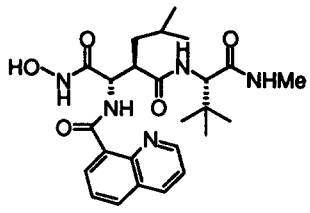
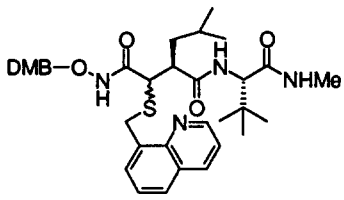
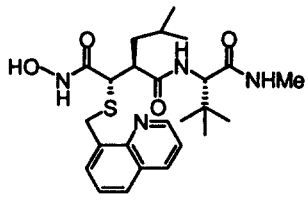
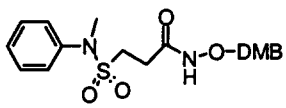
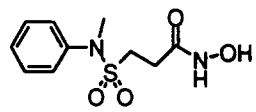
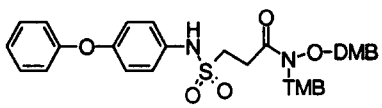
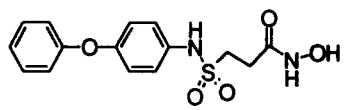
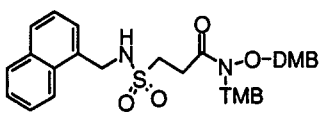
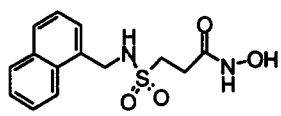
a) EDCI, HOBT, DMF; b) 5% CF_3COOH/ CH_2Cl_2, 15mn; c)10% CF_3COOH/ CH_2Cl_2, 2h

Scheme 2

Representative results[11] are summarized in Table 1. In Examples **9**, **10** and **11**, we used triethylsilane to trap the benzyl cations[12] formed during the deprotection step. Interestingly, deprotection of **10b** in the absence of triethysilane afforded a complex mixture resulting presumably from side reactions of the cations formed with electron rich aromatics like aniline.

In conclusion, the new hydroxylamine derivatives **1** and **2** are easily accessible and efficient reagents for the preparation of hydroxamic acids.

Table 1

Protected hydroxamates	Yield (%)	Unprotected hydroxamates	Yield (%)
	X= H; **6a**[a] (50%) X=TMB; **6b** (54%)		**6** (78%) **6** (65%)
	**7a**[b] (74%)		**7** (76%)
	**8a**[c]		**8** (36%)
	**9a** (84%)		**9**[e] (87%)
	**10b**[d] (50%)		**10**[e] (83%)
	**11b**[d] (60%)		**11**[e] (58%)

DMB= 2,4-dimethoxybenzyl; TMB= 2,4,6-trimethoxybenzyl; a) The carboxylic acid precursor was prepared according to European Patent EP497192 (Roche); b) The carboxylic acid precursor was prepared according to Patent WO9807742 (Zeneca); c) The carboxylic acid precursor was prepared according to Patent WO9742168 (Zeneca). **8a** was not isolated. Hydroxamate **8** was purified by C18 HPLC, the other epimer was not isolated; d) Prepared by slow addition of **2** (1 eq.) and diisopropylethylamine to 3-chlorosulfonylpropionyl chloride in CH_2Cl_2 at -78°C, stirring for 15mn at -78°C and reaction with the corresponding aniline or amine. e) Deprotection was performed in the presence of Et_3SiH (2 equivalents)

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References and Notes

1. a) Beckett, R.P.; Davidson, A.H.; Drummond, A.H.; Huxley, P.; Whittaker, M. *Drug Discovery Today* **1996**, *1*, 16 b) Beckett, R.P., Whittaker, M. *Exp. Opin. Ther. Patents* **1998**, *8*, 259 c) Hagmann, W.K.; Lak, M.W.; Becker, J.W. in Ann. Rep. Med. Chem, Bristol, J.A. (Ed) Academic Press Inc **1996**, Vol. 31, 231
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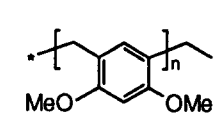
5. Isolation of TNFα convertase: a) Black, R.A. and al. *Nature* **1997**, *385*, 729 b) Moos, M.L. and al. *Nature* **1997**, *385*, 733
6. The acidic NH group (pKa about 10) of O-protected hydroxamates is vulnerable to side reactions like alkylation or acylation. For other N,O-bisprotection of hydroxamates: a) N,O-benzyl: Bashiardes, G.; Bodwell, G.J.; Davies, S.G. *J. Chem. Soc. Perkin Trans. 1* **1993**, 459 b) N-BOC-O-TBDMS or N-BOC-O-THP: Altenburger, J.M.; Mioskowski, C.; d'Orchymont, H.; Schirlin, D.; Schalk, C.; Tarnus, C. *Tetrahedron Lett.* **1992**, *33*, 5055 c) During that work, an independant communication disclosed the N-2,4,6-dimethoxybenzyl-O-THP or -O-allyl protection on solid phase: Gu, K.N.; Patel, D.V. *J. Org. Chem.* **1997**, *62*, 7088
7. Preparation of **1**: To a solution of 2,4-dimethoxybenzyl alcohol (27 g) in chloroform (1.2 l) under argon were added N-hydroxyphthalimide (35.2 g) and triphenylphosphine (56.6 g). Diethylazodicarboxylate (34 ml) was added and the solution stirred overnight at room temperature. The solvent was evaporated in vacuo and the residue purified by flash chromatography on silica using dichloromethane as eluant to give N-(2,4-dimethoxybenzyloxy)phthalimide (41.1 g, 82%) : ^{1}HNMR ($CDCl_3$): 3.72 (s, 3H), 3.79 (s, 3H), 5.22 (s, 2H), 6.40-6.45 (m, 2H), 7.30 (d, 1H, J= 8.1 Hz), 7.72 (m, 2H), 7.78 (m, 2H). A mixture of N-(2,4-dimethoxybenzyloxy)phthalimide (33.45 g) and hydrazine hydrate (51.3 ml) in ethanol (95 %, 400 ml) was heated under reflux for 15 minutes and then allowed to cool. The mixture was filtered and the residue washed with ethanol. The filtrate was evaporated to dryness in vacuo to give O-2,4-dimethoxybenzylhydroxylamine (18.4 g ; 95 %) as a colourless oil : ^{1}HNMR ($CDCl_3$): 3.81 (s, 3H), 3.82 (s, 3H), 4.68 (s, 2H), 5.30 (s br, 2H), 6.49 (m, 2H), 7.24 (d, 1H, J= 8.8 Hz). $C_9H_{13}NO_3$ calc. C 59.00, H 7.15, N 7.65 found C 58.10, H 7.10, N 7.35.
8. Grochowski, E.; Jurczak, J. *Synthesis*, **1976**, 682
9. This oxime can also be obtained by alkylation of the free oxime with 2,4-dimethoxybenzyl bromide (Ciba-Geigy, European Patent EP708085 A2) and NaH in THF. However, due to the instability of this bromide, we prefered the following route to **2**:
   A solution of 2,4,6-trimethoxybenzaldehyde (13.72 g, 70 mmol) and **1** (12.81 g, 70 mmol) in dichloromethane (70 ml) was stirred for 4 hours. The solvent was evaporated in vacuo. Crystallisation in ethanol afforded the oxime as white crystals (23.3 g, 92 %): ^{1}HNMR ($CDCl_3$): 3.80-3.82 (m, 15 H), 5.19 (s, 2H), 6.11 (s, 2H), 6.47 (m, 2H), 7.37 (d, 1H, J= 7.7 Hz), 8.47 (s, 1H). To a suspension of this oxime (38.11 g, 106 mmol) in ethanol (840 ml) was added sodium cyanoborohydride (19.9 g, 317 mmol) in four portions. A solution of aq. 12N HCl (27 ml) in 1300 ml EtOH was added dropwise to maintain pH = 3. The mixture was stirred for 1 hour. After evaporation of the solvent, the residue was dissolved in water and aqueous NaOH to pH = 8, extracted with CH_2Cl_2 and dried over $MgSO_4$. The residue was purified on silica chromatography (eluant : CH_2Cl_2 - diethylether (95/5)) to afford **2** (32.4 g, 85%) as white crystals after crystallisation in ethanol: ^{1}HNMR ($CDCl_3$): 3.78-3.81 (m, 15 H), 4.14 (s, 2H), 4.75 (s, 2H), 6.10 (s, 2H), 6.45 (m, 2H), 7.27 (m, 1H); m.p.: 72-74 °C.
10. When treated with 1% TFA-dichloromethane for 15 mn, the fully N,O-protected hydroxamate **6b** gave the corresponding N-protected-O-deprotected hydroxamate (not isolated, characterised by HPLC/MS) with only traces of the fully deprotected hydroxamic acid **6**.
11. Typical procedures for the preparation of the O- and N,O-protected hydroxamates and their deprotection are as follows:
    To the carboxylic acid precursor (0.5 mmol) in DMF (1.5 ml) was successively added 1-hydroxybenzotriazole (37 mg, 0.65 mmol), 2,4-dimethoxybenzyl hydroxylamine **1** (135 mg, 0.74 mmol), and dimethylaminopropylethylcarbodiimide hydrochloride (143 mg, 0.74 mmol). The mixture was stirred at room temperature for 18 hours. The mixture was diluted with EtOAc and washed with water, saturated sodium bicarbonate, brine and dried over $MgSO_4$. Purification by flash chromatography gave **6a** (116 mg , 50%). **6b** was prepared similarly.
    6a (25 mg) in 5% TFA-dichloromethane (1 ml) was stirred at room temperature. The reaction mixture turned deep purple. After 15 minutes, the mixture was evaporated in vacuo, diluted in MeOH and filtered to remove insoluble material.[12] Evaporation of the filtrate gave **6** which can be further purified with precipitation in ether (13 mg; 78%).
    6b (30 mg) in 10% TFA-dichloromethane (1 ml) was stirred at room temperature. The reaction mixture turned deep purple. After 2 hours, the mixture was evaporated in vacuo, diluted in MeOH and filtered to remove insoluble material.[12] Evaporation of the filtrate gave **6** which can be further purified by trituration in ether (10 mg; 65 %).
12. When the deprotection step is performed in the absence of a scavenger, the cation polymerises during work up. In the case of O-dimethoxybenzyl protection, the solid obtained is **12**: ^{1}HNMR ($CDCl_3$ + CF_3COOD) : 3.72 (s, 2H), 3.80 (s, 6H), 6.34 (s, 2H),^{13}CNMR: 155.9, 131.3, 118.5, 99.7, 57.4, 28.2; CHNS (Found: C, 69.5; H,: 6.60; N, 0; S, 0; Required for $C_9H_{10}O_2$ + 0.3 CF_3COOH: C: 69.48, H: 6.87).



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