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Effective synthesis of enantiopure hydroxamates by displacement of resin-bound esters with hydroxylamine

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Abstract

Enantiopure hydroxamic acids have been synthesized by nucleophilic displacement of carboxylates linked to oxime resin using hydroxylamine in a MeOH:$CHCl_3$ solution.

Keywords: solid phase synthesis; hydroxamic acids; amino acids; amino acid derivatives.

The hydroxamic acid functional group is an important constituent of many biologically relevant compounds,[1–3] such as specific matrix metalloprotease enzyme inhibitors.[4–6] Several strategies have thus emerged that employ solid-phase chemistry to synthesize hydroxamic acid libraries. For example, hydroxylamine, *O*-protected and *N*-tethered to MBHA[7] and Tentagel™ resin,[8] as well as *O*-tethered to Wang,[9,10] Sasrin[11,12] and trityl[13,14] resins, has served as the starting point for syntheses of various hydroxamates. Alternatively, direct nucleophilic displacement of support-bound carboxylates has been employed to synthesize hydroxamates with some limitations. For example, *O*-*tert*-butyldimethylsilyl-protected hydroxylamine displaced ordinary acids and *N*-(toluenesulfonyl)proline from oxime resin; however, an additional treatment with trifluoroacetic acid (TFA) was necessary to remove the silyl group to afford the hydroxamic acids in 27–89% yields.[15] Although 50% aqueous hydroxylamine in THF cleaved *N*-(Cbz)amino esters from ArgoGel-OH™ resin, 25 equivalents of hydroxylamine and a reaction time of 2 days were required to effect this transformation which gave *N*-(Cbz)proline hydroxamate in only 33% yield.[16]

We have effectively synthesized azacycloalkane amino acids that serve as conformationally rigid scaffolds.[17–19] Because proline-derived hydroxamates may act in constrained analogs of metalloprotease inhibitors,[15,16] we have sought a convenient technique for using related proline analogs to generate hydroxamate libraries by parallel synthesis. Perceiving that nucleophilic displacement with hydroxylamine could furnish hydroxamate of high purity without the need of protection nor resin alteration, we modified the original procedure for cleaving *N*-(acyl)amino acids from oxime resin[20–23] and have found that

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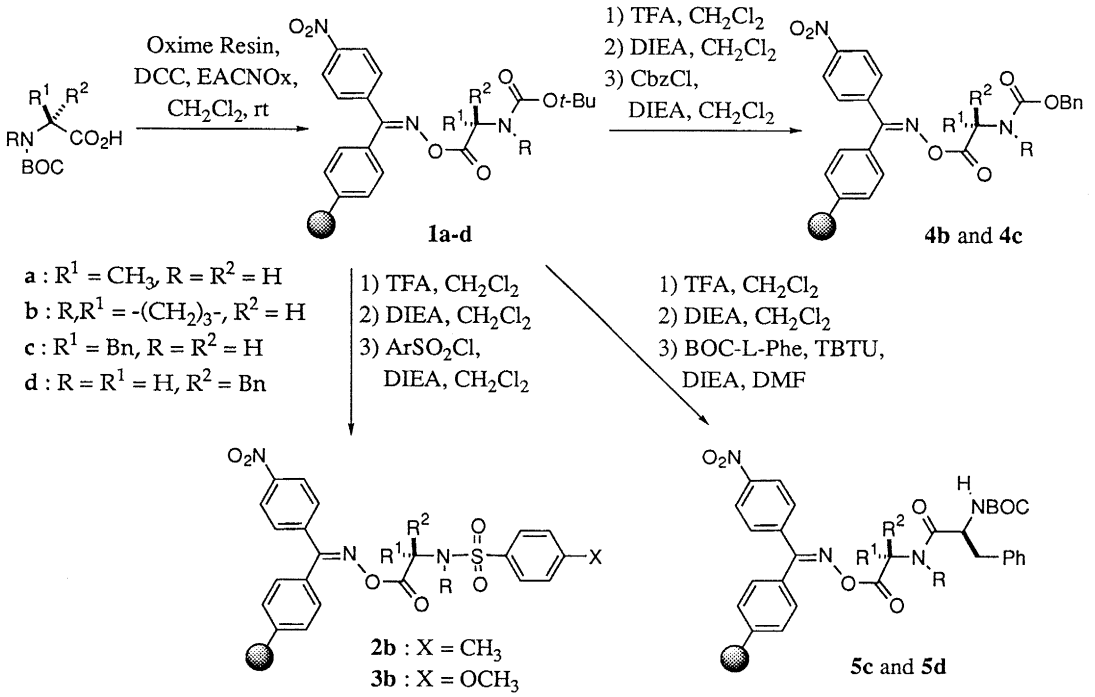
anhydrous hydroxylamine in a MeOH:$CHCl_3$ solution provides enantiopure hydroxamates possessing a variety of functional groups.

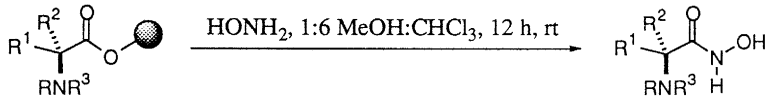
Three *N*-(BOC)amino acids, proline, phenylalanine and alanine, were anchored onto oxime resin using dicyclohexylcarbodiimide (DCC) and ethyl-2-(hydroxyimino)-2-cyanoacetate (EACNOx) in dichloromethane at room temperature (rt, Scheme 1),[24] and the loading of *N*-(BOC)amino esters **1a**–**d** was determined by weighing displaced amide from treatment of resin samples with *iso*-butylamine. The BOC group was then removed with TFA and the amines were free based with diisopropylethylamine (DIEA).



Scheme 1. Synthesis and modification of resin-bound esters **1**–**5**

Resin-bound L-proline was, respectively, acylated with 4-toluenesulfonyl chloride, 4-methoxyphenylsulfonyl chloride and benzyl chloroformate in the presence of DIEA in dichloromethane to furnish support-bound prolines **2b**–**4b**. Under similar conditions L-phenylalanine was reacted with benzyl chloroformate until a negative ninhydrin test[25] was observed and provided support-bound *N*-(Cbz)phenylalanine **4c**. Resin-linked L- and D-phenylalanine were also coupled to *N*-(BOC)-L-phenylalanine using benzotriazolyl-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU) with DIEA in DMF to yield dipeptides **5c** and **5d**, that were converted to their respective hydroxamates by cleavage under the standard conditions in order to examine if treatment with hydroxylamine would cause epimerization at the α-center of the active ester.

Nine different hydroxamates **6**–**14** were synthesized by exposing oxime resin-bound substrates **1**–**5** to solutions of hydroxylamine in 1:6 MeOH:$CHCl_3$ (Scheme 2, Table 1). Evaporation of the filtrate gave crude hydroxamates **6**–**14** of good purity as determined by ^{1}H NMR spectroscopy and reverse-phase HPLC analysis. Thin layer chromatography of the crude material and staining with a solution of $FeCl_3$ in aqueous HCl detected only a single hydroxamate spot in each case. Certain cases were further purified by column chromatography. Furthermore, analysis of L,D- and L,L-*N*-(BOC)phenylalanyl-phenylalanine hydroxamates **13** and **14** by HPLC and incremental additions of the minor isomer showed that the dipeptide hydroxamic acids were of a >99% diastereomeric ratio; hence, no epimerization at the α-center of the active ester occurred during the hydroxamate syntheses.



Scheme 2. Synthesis of hydroxamic acids **6–14**

Table 1
Recovery and purity of hydroxamic acid

Compound Number	Hydroxamate	Weight[a] (mg) Theoretical / Isolated	Percent Recovery (Purity)	HRMS Calcd / Found
6	*N*-Boc-L-Ala-NHOH	13.3 / 13.2[b]	99[b] (>90)[c]	$C_8H_{17}O_4N_2$ (MH^+) 205.1188 / 205.1194
7	*N*-Boc-L-Pro-NHOH	15.0 / 15.5[b]	103[b] (>90)[c]	$C_{10}H_{19}O_4N_2$ (MH^+) 231.1345 / 231.1338
8	*N*-Cbz-L-Pro-NHOH	16.8 / 8.0[b]	48[b] (95)[d]	$C_{13}H_{17}O_4N_2$ (MH^+) 265.1188 / 265.1197
9	*N*-*p*-Ts-L-Pro-NHOH	17.8 / 16.9	95 (79)[d]	$C_{12}H_{17}O_4N_2S$ (MH^+) 285.0909 / 285.0899
10	*N*-*p*-MeOPhSO$_2$-L-Pro-NHOH	18.7 / 13.5	72 (96)[d]	$C_{12}H_{17}O_5N_2S$ (MH^+) 301.0858 / 301.0849
11	*N*-Boc-L-Phe-NHOH	18.2 / 20.3	112 (64)[d]	$C_{14}H_{21}O_4N_2$ (MH^+) 281.1502 / 281.1489
12	*N*-Cbz-L-Phe-NHOH	20.0 / 22.4	112 (78)[d]	$C_{17}H_{19}O_4N_2$ (MH^+) 315.1345 / 315.1360
13	*N*-Boc-L-Phe-D-Phe-NHOH	25.3 / 24.6	97 (77)[d]	$C_{23}H_{30}O_5N_3$ (MH^+) 428.2185 / 428.2197
14	*N*-Boc-L-Phe-L-Phe-NHOH	25.3 / 24.9	98 (80)[d]	$C_{23}H_{30}O_5N_3$ (MH^+) 428.2185 / 428.2197

[a]Based on the loading of *N*-(BOC)amino acid resin. [b]Obtained after column chromatography. [c]Based on ^{1}H NMR analysis. [d]Based on reverse-phase HPLC analysis with detection at 254 nm.

General protocol for displacements with $HONH_2$: A stock hydroxylamine solution was prepared by dissolving $HONH_3Cl$ (0.695 g, 10 mmol) in dry MeOH (5 mL), cooling to 0°C, and adding 2 mL of MeONa in MeOH (25% wt/wt, 8.75 mmol). The precipitated NaCl was removed by filtration and the filtrate was diluted up to a volume of 50 mL with $CHCl_3$. Resino ester **1–5** (100 mg, 0.059–0.065 mmol) was suspended in $CHCl_3$ (0.5 mL) in a 10 mL borosilicate test tube, treated with 1.0 mL of the stock solution (0.175 mmol of $HONH_2$), shaken on a vortex-evaporator (Labconco™) for 12 h, filtered and washed with $CHCl_3$ (2×1 mL) and 1:1 $CHCl_3$:MeOH (2×1 mL). The combined filtrates were evaporated to crude hydroxamate **6–14** that was analyzed directly by ^{1}H NMR spectroscopy in $CDCl_3$ or by reverse-phase HPLC on a C-18 column using a flow rate of 1.5 mL/min and the detector centered at 254 nm. The majority of the compounds were analyzed with a gradient of 10–100% CH_3CN in H_2O containing 0.1% TFA over 30 min; **8** was analyzed with 15% CH_3CN and **12** was analyzed with 30% CH_3CN in H_2O containing 0.1% TFA.[26]

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26. (*S*)-*N*-(BOC)Alanine hydroxamate (**6**) was purified by column chromatography on silica gel using 0.5% AcOH in EtOAc: R_f=0.60 (3% AcOH in EtOAc); $[\alpha]_D^{20}$ −35 (*c* 0.8, MeOH), ^{1}H NMR: (CD_3OD, 400 MHz) δ 1.28 (d, 3H, *J*=7.1), 1.43 (s, 9H), 4.01 (q, 1H, *J*=7.0). (*S*)-*N*-(BOC)Proline hydroxamate (**7**) chromatographed on silica gel with 0.5% AcOH/EtOAc: R_f=0.45 (3% AcOH/EtOAc); $[\alpha]_D^{20}$ −57 (*c* 1.0, MeOH); ^{1}H NMR: (CD_3OD, 400 MHz) δ 1.4–1.47 (m, 9H), 1.80–2.00 (m, 3H), 2.10–2.25 (m, 1H), 3.35–3.51 (m, 2H), 4.00–4.13 (m, 1H). (*S*)-*N*-(Cbz)Proline hydroxamate (**8**) was purified on silica gel with 0.5% AcOH/EtOAc: R_f=0.43 (3% AcOH/EtOAc); $[\alpha]_D^{20}$ −45 (*c* 0.5, MeOH); ^{1}H NMR: (CD_3OD, 400 MHz) δ 1.83–2.05 (m, 3H), 2.10–2.27 (m, 1H), 3.43–3.60 (m, 2H), 4.20 (m, 1H), 5.10 (m, 2H), 7.25–7.40 (m, 5H). (*S*)-*N*-(*p*-Toluenesulfonyl)proline hydroxamate (**9**): R_f=0.53 (3% AcOH in EtOAc); ^{1}H NMR: (CD_3OD, 400 MHz) δ 1.50–1.62 (m, 1H), 1.70–1.97 (m, 3H), 2.44 (s, 3H), 3.20 (m, 1H), 3.50 (m, 1H), 4.00 (m, 1H), 7.43 (d, 2H, *J*=8.0), 7.75 (d, 2H, *J*=8.3). (*S*)-*N*-(*p*-Methoxybenzenesulfonyl)proline hydroxamate (**10**): R_f=0.43 (3% AcOH in EtOAc); ^{1}H NMR: (CD_3OD, 400 MHz) δ 1.53–1.63 (m, 1H), 1.70–1.97 (m, 3H), 3.20 (m, 1H), 3.50 (m, 1H), 3.88 (s, 3H), 4.00 (m, 1H), 7.12 (d, 2H, *J*=9.0), 7.81 (d, 2H, *J*=9.0). (*S*)-*N*-(BOC)Phenylalanine hydroxamate (**11**): R_f=0.76 (3% AcOH in EtOAc); ^{1}H NMR: (CD_3OD, 400 MHz) δ 1.36 (s, 9H), 2.83 (dd, 1H, *J*=6.6, 13.6), 3.03 (dd, 1H, *J*=8.4, 13.6), 4.17 (t, 1H, *J*=7.4), 7.15–7.30 (m, 5H). (*S*)-*N*-(Cbz)Phenylalanine hydroxamate (**12**) R_f=0.56 (EtOAc); ^{1}H NMR: (CD_3OD, 400 MHz) δ 2.87 (dd, 1H, *J*=8.7, 13.6), 3.06 (dd, 1H, *J*=6.3, 13.7), 4.25 (t, 1H, *J*=7.5), 5.00 (m, 2H), 7.15–7.35 (m, 10H). (*S*,*S*)-*N*-(BOC)Phenylalanyl-phenylalanine hydroxamate (**14**): R_f=0.56 (EtOAc); ^{1}H NMR: (CD_3OD, 400 MHz) δ 1.34 (s, 9H), 2.60–3.10 (m, 4H), 4.23 (dd, 1H, *J*=5.2, 9.2), 4.50 (t, 1H, J=7.3), 7.10–7.30 (m, 10H).