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Direct synthesis of Fmoc protected amino acid hydroxamates from acid chlorides mediated by magnesium oxide

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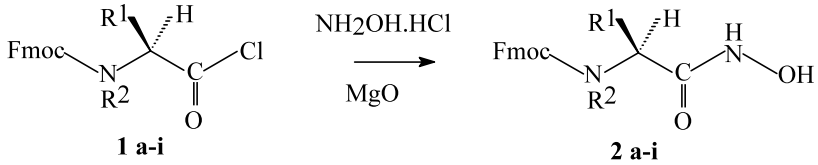
Abstract—The synthesis of Fmoc protected amino acid hydroxamates using Fmoc-amino acid chlorides and magnesium oxide is described. The method is simple and efficient, results in complete conversion, and gives good yields and satisfactory purity.

Amino acid hydroxamates are useful as building blocks for the synthesis of peptide hydroxamates which have received increased attention due to their variety of biological activities especially as antibacterial, anticancer, antiasthmatic, psychotropic, antifungal and insecticidal agents.[1] As the hydroxamic acid functionality is an effective metal ion chelator, compounds having this functionality serve as potent inhibitors of metalloproteases.[2] Hydroxamic acids have generally been synthesized in solution by the acylation of *O*-/*N*-protected hydroxylamines such as *O*-benzyl hydroxylamine, *N*,*N*^{1},*O*-(tristrimethylsilyl)-hydroxylamine, *N*-Boc-*O*-THP hydroxylamine, *N*-Boc-*O*-TBDMS-hydroxylamine and *O*-trimethylsilylhydroxylamine with activated carboxylic acids.[3] Direct acylation of hydroxylamine itself is well known to result in a mixture of *N*- and *O*-acylated as well as di- and tri-acylated products.[4] Alternatively, acylations using peptide coupling agents like PyBOP, TBTU, HATU, BOP, etc., need *O*-protected hydroxylamine derivatives and the reaction has to be carried out in the presence of an equimolar quantity of an organic base such as triethylamine (TEA), *N*-ethyldiisopropylamine (DIEA), 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), *N*-methylpyrrolidone (NMP), etc.[5] On the other hand, our group has demonstrated the advantages of base-free conditions for the coupling of Fmoc-amino acid chlorides in the synthesis of peptides containing adjacent Aib groups as well as for the introduction of the Fmoc group into amino acids.[6] Thus, the use of co-coupling agents like potassium salts of 1-hydroxybenzotriazole (KOBt) and 7-aza-1-hydroxybenzotriazole (KOAt), AgCN, zinc dust,



1 a-i **2 a-i**

a $R^1 = CH(CH_3)CH_2CH_3$, $R^2 = H$; **f** $R^1 = CH_3$, $R^2 = H$

b $R^1 = CH(CH_3)_2$, $R^2 = H$; **g** $R^1 = C_6H_5$, $R^2 = H$

c $R^1 = CH_2CH(CH_3)_2$, $R^2 = H$; **h** R^1- $R^2 = (CH_2)_3$

d $R^1 = R^2 = H$; **i** $R^1 = CH_2OCH_2C_6H_5$, $R^2 = H$

e $R^1 = CH_2C_6H_5$, $R^2 = H$

Scheme 1.

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etc., led us to carry out acylation reactions under non-Schotton–Baumann conditions which naturally circumvents the well identified side reactions.

Magnesium oxide (MgO) has gained some attention because of its novel surface catalytic properties.[7] Its use in the synthesis of pyrimidine from 2,4-dichloropyrimidine, in the hydrogenation of 1,3-butadiene to *cis*-2-butene, in the reduction of α,β-unsaturated ketones to allylic alcohols by the Meerwein–Ponndorf–Verley method, in the dehydrogenative coupling between hydrosilanes and mono substituted alkynes, and in the heterogeneous Wittig, Knoevenagel, and Wittig–Horner reactions is well documented.[8]

A selection of suitably *N*- as well as *O*-protected hydroxylamine derivatives and convenient methods for their deprotection after acylation have to be employed as key steps in the multistep synthesis of hydroxamic acids. In the present communication, the preparation of *O*-unacylated amino acid hydroxamates directly via a simple nucleophilic displacement is described. They were synthesized by reacting hydroxylamine hydrochloride with Fmoc-amino acid chlorides in the presence of MgO (Scheme 1). Hydroxylamine hydrochloride was deprotonated using an equivalent of MgO in methanol/water. The Fmoc-amino acid chloride, dissolved in THF and two equivalents of MgO were then added to the hydroxylamine solution and stirring was continued. The reaction, as monitored by TLC and IR was complete in about 20–30 min. The resulting amino acid hydroxamates were isolated as crystalline solids in good yield (Table 1). Their purity, as checked by analytical RP-HPLC, was satisfactory. All the amino acid hydroxamates were fully characterized by ^{1}H NMR and ES-MS. The spectroscopic analysis clearly revealed that no traces of *O*-acylated or *N*,*O*-bisacylated derivatives were present under the conditions employed.

In conclusion, Fmoc-amino acid hydroxamates can be synthesized by the acylation of hydroxylamine using Fmoc-amino acid chlorides in the presence of MgO. The route is simple, efficient and affords good to excellent yields of products. The ^{1}H NMR and MS data confirms that no *O*-acylation took place.

General procedure for the synthesis of Fmoc-amino acid hydroxamates

Hydroxylamine hydrochloride (0.084 g, 1.2 mmol) in methanol/water (3:2, 5 mL) was treated with MgO (0.040 g, 1 mmol), then a solution of Fmoc-amino acid chloride (1 mmol) in THF (8 mL), and MgO (0.080 g, 2 mmol) were added. The mixture was stirred at rt until completion of the reaction, then filtered and evaporated

Table 1. Physical constants and characterization data of Fmoc-amino acid hydroxamates*

Compd **2**	Yield (%)	Mp (°C)	R_f value	IR ($\nu_{max.}$, cm^{-1})	^{1}H NMR (δ, ppm)
a	86	178	0.34	1560, 1650 1690, 3300	0.9 (t, J=6.2 Hz, 3H), 0.98 (d, J=6.2 Hz, 3H), 1.3 (m, 2H), 1.9 (m, 1H), 3.2 (t, J=9.35 Hz, 1H), 4.25 (t, J=6.5 Hz, 1H), 4.32 (d, J=6.5 Hz, 2H), 7.2–7.8 (m, 9H), 8.7 (br, 1H) and 10.4 (br, 1H).
b	90	171	0.36	1540, 1650 1698, 3200	1.3 (d, J=7.4 Hz, 6H), 2.6 (m, 1H), 3.4 (t, J=9.3 Hz, 1H), 4.1 (t, J=6.5 Hz, 1H), 4.3 (d, J=6.5 Hz, 2H), 7.3–7.9 (m, 9H), 8.8 (s, 1H) and 10.6 (s, 1H).
c	86	182	0.31	1540, 1640 1690, 3200	0.96 (d, J=7.35 Hz, 6H), 1.65 (m, 3H), 3.8 (m, 1H), 4.18 (t, J=6.5 Hz, 1H), 4.45 (d, J=6.5 Hz, 2H), 7.2–7.8 (m, 9H), 8.6 (br, 1H) and 10.5 (br, 1H).
d	88	96	0.39	1550, 1650 1700, 3300	3.3 (t, J=6.5 Hz, 2H), 4.25 (t, J=6.5 Hz, 1H), 4.5 (d, J=6.5 Hz, 2H), 7.2–7.8 (m, 9H), 8.9 (br, 1H) and 10.9 (br, 1H).
e	96	195	0.45	1560, 1640 1698, 3300	2.52 (m, 2H), 3.1 (m, 1H), 4.1 (t, J=6.5 Hz, 1H), 4.25 (d, J=6.5 Hz, 2H), 7.3–7.8 (m, 14H), 8.6 (br, 1H) and 10.62 (br, 1H).
f	94	128	0.38	1540, 1660 1705, 3200	1.45 (d, J=7.1 Hz, 3H), 3.85 (m, 1H), 4.25 (t, J=6.5 Hz, 1H), 4.4 (d, J=6.5 Hz, 2H), 7.3–7.9 (m, 9H), 8.55 (br, 1H) and 10.62 (br, 1H).
g	84	132	0.43	1560, 1650 1703, 3300	3.2 (d, J=9.3 Hz, 1H), 4.1 (t, J=6.5 Hz, 1H), 4.45 (d, J=6.5 Hz, 2H), 7.2–7.8 (m, 14H), 8.7 (br, 1H) and 10.4 (br, 1H).
h	82	92	0.42	1540, 1660 1698, 3200	2.2 (m, 4H), 3.5 (m, 2H), 4.1 (t, J=6.5 Hz, 1H), 4.3 (d, J=6.5 Hz, 2H), 7.2–7.8 (m, 9H), 8.45 (br, 1H) and 10.52 (br, 1H).
i	85	164	0.48	1550, 1660 1690, 3300	3.3 (s, 2H), 3.6 (m, 2H), 4.25 (m, 3H), 4.5 (m, 1H), 7.2–7.8 (m, 14H), 8.9 (s, 1H) and 10.75 (s, 1H).

TLC analysis was carried out using the solvent system: chloroform:MeOH:acetic acid: 45:2:1, v/v/v.
* All the amino acid hydroxamates were characterized by ES-MS.

to dryness. The residue was dissolved in ethyl acetate (20 mL) washed with 5% HCl (3×10 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, evaporated in vacuo and trituration with pet. ether gave the product as a white crystalline solid.

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