

## Convenient Conversion of Amino Acids to Their *N*-Hydroxylated Derivatives on a Solid Support: Synthesis of Hydroxamate-Based Pseudo-Peptides

Yunpeng Ye and Garland R. Marshall

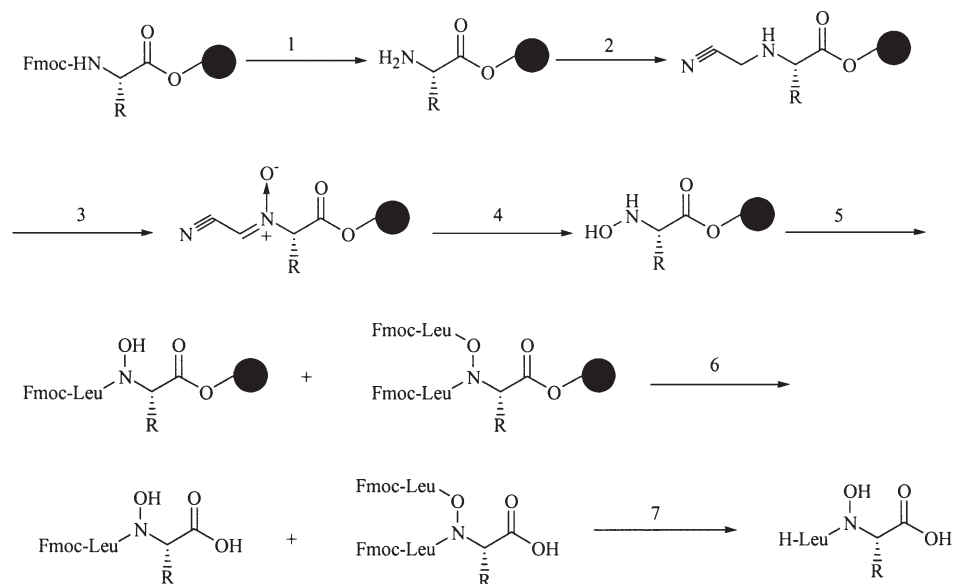
Biochemistry and Molecular Biophysics, Washington University School of Medicine,  
660 S. Euclid Avenue, St. Louis, MO 63110, USA

### Introduction

*N*-Hydroxyl-substituted amino acid derivatives are key building blocks for synthesis of hydroxamate-based pseudo-peptides. They have potentially important applications in the synthesis of peptidomimetics, enzyme inhibitors, natural products, and in combinatorial chemistry. Several methods for synthesis of *N*-hydroxylamino acid derivatives in solution have been reported. But no method has been reported to our knowledge for the direct conversion of amino acids to their *N*-hydroxyl-substituted derivatives on a solid support. In our continuing efforts to constructing a library of metal-binding, hydroxamate-based pseudo-peptide, we have been interested in developing a protocol for efficient conversion of amino acids to their corresponding *N*-hydroxylated derivatives on a solid support.

### Results and Discussion

The solid phase synthesis of *N*-hydroxyl amino acids was predicated on a reported solution phase method [1] that includes the following three major steps: 1. monocyanomethylation of a primary amine with  $\text{NCCH}_2\text{Br}$ ; 2. oxidation with *m*-CPBA; and 3.



1. Piperidine/DMF (20%); 2.  $\text{NCCH}_2\text{Br}$ /DIEA/DMF; 3. *m*-CPBA/DCM; 4.  $\text{NH}_2\text{OH}\cdot\text{HCl}$ /DMF, 60 °C;  
5. Fmoc-Leu-Cl/AgCN/Toluene; 6. TFA; 7. Piperidine/DMF (20%).

Fig. 1. Conversion of amino acids to their *N*-hydroxylated derivatives on Wang resin and their incorporation into peptides.

*Ye et al.*

hydroxylaminolysis with  $\text{NH}_2\text{OH}\cdot\text{HCl}$  at 60 °C. We have successfully adapted this method for the conversion of a series of amino acids including Glu, Phe, Lys, Gln, Leu, and Ser to their *N*-hydroxylated derivatives on Wang resin with a total yields of 60–70% (Figure 1). According to ESI-MS analysis, we deduced that some byproducts may result from *N,N*-dicyanomethylation.

The resin-bound *N*-hydroxylated amino acid derivatives were efficiently incorporated into peptides by reacting with Fmoc-AA-Cl/AgCN in toluene [2]. When 5 equiv. of Fmoc-Leu-Cl were used, the major product was found to be the mono-(Fmoc-Leu) substituted product Fmoc-Leu- $\Psi[\text{CON}(\text{OH})]\text{X}_{\text{AA}}\text{OH}$  (**1**) together with the minor *N,O*-bis(Fmoc-Leu) derivative Fmoc-Leu- $\Psi[\text{CON}(\text{O-Leu-Fmoc})]\text{X}_{\text{AA}}\text{OH}$  (**2**). **1** and **2** were deprotected with piperidine/DMF (20%) to afford the pseudo-peptide H-Leu- $\Psi[\text{CON}(\text{OH})]\text{X}_{\text{AA}}\text{OH}$ . As exemplified by the preparation of Fmoc-protected *N*-hydroxyl Glu(OH)-OH *via* a reaction with Fmoc-Cl, *N*-hydroxyl-amino acids can be changed into their Fmoc-protected derivatives **3**. Compounds **1**, **2**, and **3** can serve as building blocks in solid-phase synthesis. HO-Phe-Phe-NH<sub>2</sub>, Fmoc-Leu $\Psi$ (CONOH)-Phe-Phe-NH<sub>2</sub>, and H-Leu $\Psi$ (CONOH)-Phe-Phe-NH<sub>2</sub> were synthesized on Fmoc amide MBHA resin similarly, demonstrating that this protocol is also compatible with the amide resin.

Based on these results, site-specific *N*-hydroxylation of peptides and efficient solid-phase synthesis of a hydroxamate-based pseudo-peptide library appears feasible and is currently under investigation.

#### **Acknowledgments**

The authors acknowledge support for this research from NIH Grants EY12113 and GM53630. The Washington University Mass Spectroscopy Resource Center supported by NIH (RR00954) was utilized to characterize the peptides synthesized as part of this study.

#### **References**

1. Tokuyama, H., Kuboyama, T., Amano, A., Yamashita, T., Fukuyama, T.A. *Synthesis* 1299–1304 (2000).
2. Perlow, D.S., Erb, J.M., Gould, N.P., Tung, R.D., Freidinger, R.M., Williams, P.D., Veber, D.F. *J. Org. Chem.* **57**, 4394–4400 (1992).