



Efficient stereocontrolled synthesis of (S)-Fmoc-β-nitroalanine via oxidation of oxime

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ABSTRACT

Stereocontrolled synthesis of (S)-Fmoc-β-nitroalanine (**20**) was accomplished from (R)-Fmoc-Ser(^tBu)-OH (**14**) in a total of six steps via an oxime. The oxime (**17**) was obtained from (R)-Fmoc-Ser(^tBu)-H (**16**), which in turn was obtained by reduction of Weinreb amide (**15**). Oxidation of oxime was realized with peroxytrifluoroacetic acid at a neutral pH at 0 °C. After removal of the ^tBu protecting group with 90% TFA/H₂O, the hydroxyl group was oxidized with Jones reagent to afford (S)-Fmoc-β-nitroalanine (**20**) in overall good yield.

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1. Introduction

β-Nitroamino acids are a significant class of building blocks for the synthesis of a variety of important target molecules. For example, β-nitroamino acids are used as precursors for α,β-dehydroamino acids,^{1,2} which are commonly found in naturally occurring peptides.^{3–5} In addition, nitro group can be efficiently converted into other valuable functional groups, such as amines, aldehydes, or acid moieties, making it a versatile functional group for further modifications into a variety of other chemical structures.^{6,7} Furthermore, β-nitroamino acids are important as enzyme inhibitors^{8,9} and are also useful as modified enzyme substrates.^{10,11}

Among β-nitroamino acids, β-nitroalanine has been particularly useful in studying aspartate metabolism because it is an isostere of aspartic acid.^{10,12,13} However, the main reason for its biological activity is that it is isoelectronic with aspartic acid/aspartate (**1,2**) in its neutral (**3**) and nitronate (**4**) anionic states (Fig. 1).¹⁰

It is important to note that α,β-dehydroalanine can be synthesized by utilizing racemic β-nitroalanine as a surrogate amino acid derivative since the stereochemistry at the α-carbon is lost during dehydronitration (elimination of HNO₂). However, other chemical applications, such as peptide synthesis, require use of a single isomer of β-nitroalanine.

Stereoselective synthesis of β-nitroalanine is not reported in the literature. However, racemic β-nitroalanine has been synthesized by exploiting the following strategies as shown in Scheme 1. (a)

2-Chloro-3-nitropropionic acid (**5**) was treated with ammonium hydroxide in methanol.¹⁰ 3-Nitropropionic acid was prepared from acrylic acid and nitryl chloride, (b) protected bromoglycine (**6**) was reacted with methyl nitronate,² and (c) Easton's three-component coupling method.¹⁴ The latter procedure utilized dipotassium salt of nitroacetic acid (**8**), glyoxalic acid (**9**), and ammonia to produce β-nitroaspartate (**7**), which upon decarboxylation afforded β-nitroalanine. In this communication, we describe a stereocontrolled

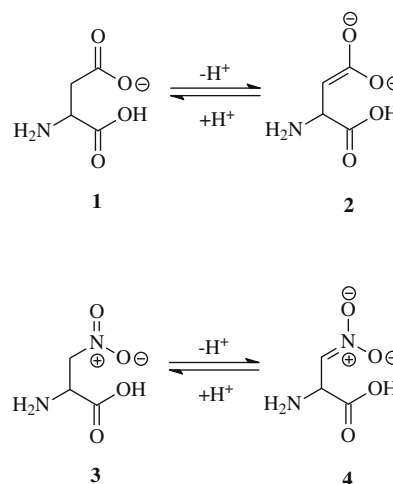
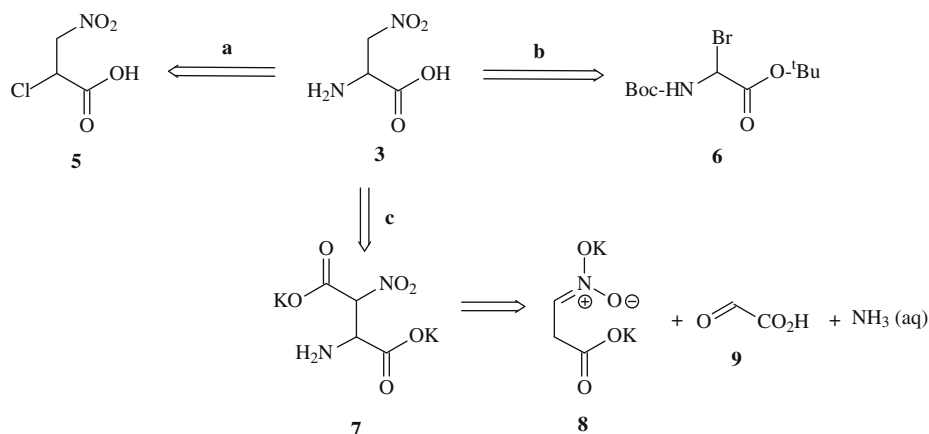


Figure 1. Anionic states of aspartic acid (**1, 2**) and β-nitroalanine (**3, 4**).

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Scheme 1.

synthetic strategy for the preparation of (S)-Fmoc- β -nitroalanine starting from (R)-Fmoc-Ser(^tBu)-OH.

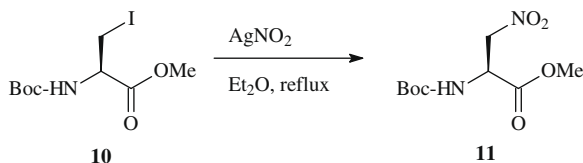
2. Results and discussion

β -Nitroalanine derivatives can be synthesized in various ways. However, two methods can be considered particularly useful: (1) displacement of a good nucleofuge with a nitrite anion^{15,16} and (2) oxidation of nitrogenous derivatives, such as amine,¹⁷ oxime,¹⁸ or isocyanate.¹⁹

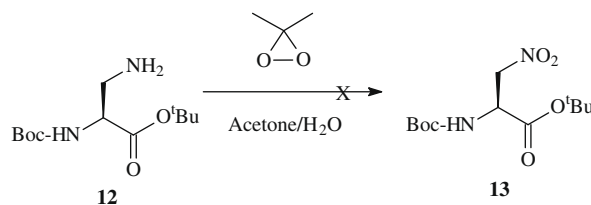
Based on above methodologies, we designed a short three-step synthesis of (S)-Fmoc- β -nitroalanine starting from protected forms of either (S)- β -iodoalanine or (S)-2,3-diaminopropionic acid (Dap) via substitution or oxidation, respectively. Cleavage of the protecting groups followed by Fmocylation should afford the target compound. An important aspect of this strategy was the choice of the protecting groups. Since the nitro group is reduced under catalytic hydrogenation conditions and also undergoes elimination under basic conditions, the protecting groups should be cleavable under acidic conditions.

In our first attempt, we utilized a commercially available Boc- β -iodo-Ala-OMe (**10**) since following the substitution reaction with silver nitrite both the Boc and methyl ester protecting groups can be removed by aqueous HCl hydrolysis yielding (S)- β -nitroalanine. Thus, the iodo compound (**10**) was refluxed with 5 equiv of silver nitrite in diethyl ether for 48 h as shown in Scheme 2.¹⁶ Boc- β -nitro-Ala-OMe (**11**) was isolated in 11% yield after silica gel column chromatography.²⁰ Longer reaction time and addition of excess silver nitrite did not improve the yield of the nitro compound (**11**). We also tried sodium nitrite in DMF at ambient temperature overnight, but the yield could not be improved.¹⁵ Since the substitution reaction gave a poor yield of nitro compound (**11**), we did not proceed further.

Oxidation of the side-chain NH₂ group of Boc-Dap-O^tBu (**12**; Scheme 3) followed by TFA treatment would also yield (S)- β -nitroalanine. However, oxidation of the compound (**12**) with dimethyldioxirane in wet acetone resulted in a complex mixture and



Scheme 2.



Scheme 3.

the desired nitro compound (**13**) could not be isolated as shown in Scheme 3.¹⁷ Dimethyldioxirane was freshly prepared from oxone (2KHSO₅·KHSO₄·K₂SO₄) in buffered aqueous acetone following a reported procedure.²¹ Therefore, we tried a different strategy that utilized oxidation of oxime. In this case, we started with (R)-Fmoc-Ser(^tBu)-OH (**14**) as the starting material.

As shown in Scheme 4, (R)-Fmoc-Ser(^tBu)-OH (**14**) was reacted with *N*,*O*-dimethylhydroxylamine hydrochloride using a mixed anhydride method with isobutyl chloroformate to afford Weinreb amide (**15**) in quantitative yield. The amide (**15**) was dissolved in anhydrous ether/THF (3:2) and was added to lithium aluminum hydride suspension in ether at -40 ± 5 °C dropwise. After stirring at the same temperature for 1 h, the reaction mixture was allowed to warm to 0 °C and the stirring was continued at that temperature for additional 2 h. The reaction was quenched with 1 N aq KHSO₄ and the aldehyde was extracted with ether. (R)-Fmoc-Ser(^tBu)-H (**16**) was obtained as a light yellow solid in 91.8% yield.²² The unpurified aldehyde (**16**) was treated with 5 equiv of hydroxylamine hydrochloride and 5 equiv of pyridine in refluxing ethanol for 30 min. Aldoxime (**17**) was obtained as white solid after work-up and trituration with hexane in 82% yield and showed two close spots on TLC (5% MeOH/DCM), perhaps due to *E/Z* isomers. Before proceeding further, the structure of aldoxime (**18**) was confirmed by spectroscopic methods and was consistent with the structure.²³

In the next step, oxime was oxidized into NO₂ function. For this purpose we utilized peroxytrifluoroacetic acid at a neutral pH. The peroxytrifluoroacetic acid was freshly generated from urea-hydrogen peroxide (UHP) complex and trifluoroacetic anhydride (TFAA) in acetonitrile at 0 °C. The reaction was complete within 2 h. The reaction mixture was washed with 5% aq Na₂SO₃ to decompose any residual peroxy acid/hydrogen peroxide.¹⁸ After silica gel column chromatography the nitro compound (**18**) was obtained in 68% yield as a viscous light yellow oil.²⁴

The nitro compound (**18**) was treated with TFA/H₂O (9:1) for 35 min to cleave the ^tBu protecting group. TFA was evaporated un-

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