Asymmetric synthesis of 3-azide-4-fluoro-L-phenylalanine

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The asymmetric synthesis of N-Fmoc-protected 3-azide-4-fluoro-L-phenylalanine as a photoactive phenylalanine analog has been achieved by Schöllkopf’s alkylation.

Key words: amino acid; asymmetric synthesis; photoaffinity labeling; Schöllkopf’s alkylation

In studies of molecular interaction, photoaffinity labeling has been widely used as a powerful and reliable approach because it can identify spatial interrelationships by photochemical labeling around interacting sites. Among successfully utilized photophores, fluorophenyl azide has been frequently employed due to the chemical stability of photoreactive azide group and easy preparation. Toward realizing our purpose by photoaffinity technology, azide-fluoro-l-phenylalanine, an unnatural L-amino acid, is one of a few candidates, since it could substitute one or more natural aromatic L-amino acid in protein through gene manipulation. In addition, the fluorine atom can make not only stabilizing the reactive nitrone intermediate but also enhancing the sensitivity for the mass spectrometric analysis in future proteomic method. In a series of studies on the asymmetric synthesis of non-proteinogenic \( \alpha \)-amino acids, Schöllkopf synthesis is one of the classical and versatile approaches, and the diastereoselective alkylation of bislactim ether auxiliary would be controlled via 1,4-asymmetric induction with high chemical yield and optical purity. In this study, we report the synthesis of N-Fmoc-protected 3-azide-4-fluoro-L-phenylalanine \( 1 \) as a photoactive unit by alkylation of azide- and fluoro-substituted benzyl halide \( 3 \) with Schöllkopf’s bislactim ether \( 2 \) (Scheme 1).

Synthesis of the azide- and fluoro-substituted benzyl bromide \( 7a \) is illustrated in Scheme 1. Nitration of 4-fluorobenzaldehyde with HNO\(_3\) and H\(_2\)SO\(_4\) gave 4-fluoro-3-nitrobenzaldehyde \( 5 \) in 67% yield. After reduction of the aldehyde of \( 5 \) with NaBH\(_4\), hydrogenolysis of the nitro group and subsequent azidation in AcOH/TFA/H\(_2\)O (10:1:1) afforded 3-azide-4-fluorobenzyl alcohol \( 6 \) in 68% yield over three steps. In this azidation, the combination of solvents was crucial to prevent formation of benzyl azide as a by-product. Finally, benzyl alcohol of \( 6 \) was brominated to give 3-azide-4-fluorobenzyl bromide \( 7a \).

We next examined Schöllkopf’s alkylation of the 3-azide-4-fluorobenzyl bromide \( 7a \) with bislactim ether \( 2 \), which was synthesized by reported procedures from D-valine. Treatment of \( 2 \) with \( n \)-BuLi at −78 °C was followed by the addition of \( 7a \) and gradual increase in the reaction temperature to provide a complex mixture of products (Table 1, entry 1). In the case of the reaction of benzyl bromide \( 7b \), the diastereoselective alkylation under the same conditions proceeded to afford the coupling product \( 8b \) in 83% yield as a single diastereomer (entry 2). These results clearly indicated that either a fluorine group at the para position or an azide group at the meta position on the benzene ring decreases the reactivity of benzyl bromide \( 7a \). To clarify the reasons, alkylations of the benzyl bromides \( 7c \) and \( 7d \) were examined (entries 3 and 4). When \( 7c \) was treated under the same conditions, the coupling product \( 8c \) was obtained in 17% yield and a considerable amount of starting material \( 7c \) was recovered (entry 3). Attempted alkylation of \( 7d \) gave a complex mixture of products (entry 4). A series of these studies revealed that both substituents decreased the reactivity.

Although Zhu and co-workers reported an improved alkylation methodology via transmetalated organocuprate of the bislactim ether \( 2 \), alkylation of benzyl bromide \( 7a \) failed under their conditions (Table 1, entry 5). In order to overcome the problematic reaction, alkylation conditions of 3-azidebenzyl bromide \( 7d \) using several additives were examined (entries 6–8). Treatment of \( 7d \) in the presence of HMPA gave a complex mixture of products (entry 6). When the reaction was conducted with 12-crown-4, a trace amount of coupling product \( 8d \) was obtained (entry 7). Further examinations of the reaction conditions led us to find that the addition of BF\(_3\)OEt\(_2\) (1.0 equiv) improved the yield of the alkylation (entries 8 and 9). Finally, based on the optimized condition, alkylation of 3-azide-4-fluorobenzyl iodide \( 7f \) (1.0 equiv) with bislactim ether \( 2 \) (1.25 equiv) in the presence of \( n \)-BuLi (1.25 equiv) and BF\(_3\)OEt\(_2\) (1.88 equiv) provided the desired coupling product \( 8a \) in 82% yield as a single diastereomer (entry 12).

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The bislactim ether 8a was hydrolyzed with 2N aqueous HCl to give the desired methyl ester 9 (Scheme 2). Alkaline hydrolysis and subsequent protection of the amino group with Fmoc-OSu provided N-Fmoc-protected 3-azide-4-fluoro-L-phenylalanine 1 in a high yield.

In conclusion, N-Fmoc-protected 3-azide-4-fluoro-L-phenylalanine was synthesized as a photoactive phenylalanine analog. Although several problems were encountered under the reported standard conditions of Schöllkopf’s alkylation, we found that addition of BF₃·OEt₂ was a crucial role in the alkylation of unreactive benzyl halides such as azide- and fluoro-substituted benzyl bromide.

**Supplemental material**

The supplemental material for this paper is available at [http://dx.doi.org/10.1080/09168451.2014.997185](http://dx.doi.org/10.1080/09168451.2014.997185).
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