Convenient Asymmetric Synthesis of Fmoc-(S)-6,6,6-Trifluoro-Norleucine

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Abstract: In this work we report a convenient asymmetric synthesis of Fmoc-(S)-6,6,6-trifluoro-norleucine via alkylation reaction of chiral glycine equivalent. The target amino acid of 99% enantiomeric purity was prepared with 82.4% total yield (three steps).

Keywords: fluorine; amino acids; alkylation; asymmetric synthesis; Ni(II) complexes

1. Introduction

Medicinal applications of new organic compounds have always been a major driving force behind the development of organic methodology. In this regard, one can notice two general trends in the design of modern pharmaceutical drugs: the introduction of fluorine-containing substituents and tailor-made amino acids (AAs) [1–10]. While the strategic fluorination usually leads to improved pharmacokinetics and greater oxidative metabolic stability [9,11,12], the presence of tailor-made amino AAs residues allows for more precise mimicking of the natural peptide–receptor interactions [1–8]. Subsequently, fluorine-containing α- [13–21] and β-AAs [22–24], featuring both structural traits, are currently an increasingly important class of compounds used in bio-medicinal studies and drug design [25–28]. For example, (S)-2-amino-6,6,6-trifluorohexanoic acid and 6,6,6-trifluoro-norleucine 1 (Scheme 1) and its derivatives were shown to possess interesting biological properties, such as antitumor [29], antimicrobial [30], and enzyme inhibitory activity [31,32]. However, the major interest in fluorinated AA 1 is related to its various applications in the therapeutic peptide engineering [33–36] and protein structural studies [37–39]. Over the last decade, various synthetic approaches for preparation of tailor-made fluorinated norleucine 1 have received due attention. One group of the methods is based on elaboration of functional groups in the already prearranged AA skeleton 2, such as additions of CF3 radical to the terminal C=C bond [40,41] or biomimetic transamination [42,43]. However, a more general approach for synthesis of AA 1 includes alkyl halide alkylation of properly protected glycine derivatives 3 [44–48]. These reactions can be conducted under homogeneous [45–48], as well as PTC conditions [44].
In this paper we describe a convenient asymmetric synthesis of Fmoc derivative 6,6,6-trifluoro-norleucine 1 via CF$_3$(CH$_2$)$_3$I alkylation of the recently rationally designed chiral equivalent of nucleophilic glycine 4. The method is operationally convenient, robust, scalable, and can be recommended for practical preparation of enantiomerically pure (~99% ee) derivative of this important tailor-made AA.

2. Materials and Methods

General Methods. All solvents and reagents were used as purchased without further purification. All reactions were conducted by magnetically stirring and detected by routine chromatography on TLC plates. Flash chromatography was carried out using the corresponding solvents on silica gel (0.064–0.210 mm). The reported yields are for isolated and chemically pure compounds. HPLC experiments were performed on a standard equipment using the Inertsil$^\text{TM}$ ODS-3 column (3 μm, 150 × 4.6 mm) ran at 1.0 mL/min, 30 °C; monitoring was set at 254 nm with a gradient of 10 mM aqueous HCOOH/NH$_3$ containing 0.1% HCOOH (elucent A) and MeCN (elucent B) from A: B = 95:5 to 20:80 and 20:80. $^1$H-, $^{19}$F-, and $^{13}$C-NMR data were recorded on Bruker AVANCE III-400 instrument. Chemical shifts are presented in ppm (δ), referenced to SiMe$_4$ (TMS). Optical rotations data were conducted on a DIP-370 instrument. Melting points were taken as usual.

Alkylation Reaction of Glycine Complex (S)-4 with CF$_3$(CH$_2$)$_3$I. The Ni–glycine complex (S)-4 (20.0 g, 33.2 mmol, 1.0 equiv.) and 1,1,1-trifluoro-4-iodobutane (7.90 g, 33.2 mmol, 1.0 equiv.) were stirred in deoxygenated N,N-dimethyl-formamide (DMF) (140 mL, 7 v/v) at room temperature under argon. Then, 10% NaOMe methanol solution (1.0 equiv.) was added into the above mixture. The resulting solution was stirred at room temperature for 2 h, and then was poured into water (46 mL) at same temperature to give the precipitate. After 0.5 h, the mixture was added water (24 mL), and was stirred for 15 h. After that, the precipitate was filtered, washed with DMF-H$_2$O (36 mL, 2:1 v/v), washed with water (40 mL) and dried in vacuo at 60 °C for 7 h to afford the crude Ni complex (20.8 g, 87.9%, a red solid) as a mixture of (S,2S)-6 and (S,2R)-7, the diastereomeric ratio was determined to be (98.7% $\pm$δe) by HPLC analysis, in which the major (S,2S)-6 was eluted at a retention time ($t_R$) of 20.3 min and the minor (S,2R)-7 at 21.5 min under the conditions described in the general methods. The mixture of 6 and 7 was purified by column to give the diastereomerically pure major product 6 in 87.5% yield (see Supplementary Materials).

(S,2S)-6 (major isomer): M.p. 229–231 °C. [α]$^{25}_D = +2616$ (c = 0.2, CH$_3$OH). $^1$H NMR (400 MHz, CDCl$_3$): δ = 8.89 (d, J = 1.6 Hz, 1H), 8.09 (d, J = 9.2 Hz, 1H), 7.77 (dd, J = 1.7, 8.1 Hz, 1H), 7.49–7.58 (m, 3H), 7.37 (d, J = 8.1 Hz, 1H), 7.29–7.30 (m, 1H), 7.11 (dd, J = 2.4, 9.2 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 6.59 (d, J = 2.4 Hz, 1H), 4.34 (d, J = 12.6 Hz, 1H), 3.87 (dd, J = 8.0, 3.4 Hz, 1H), 3.51–3.57 (m, 2H), 3.35–3.39 (m, 1H), 3.21 (d, J = 12.6 Hz, 1H), 2.59–2.71 (m, 2H), 2.35–2.37 (m, 1H), 2.24–2.25 (m, 1H).
1.3 equiv) and Fmoc-OSu (9.48 g, 1.0 equiv.) were added to the resulting mixture. The mixture was cooled to room temperature, and then was concentrated. To the residue was added ethyl acetate (100 mL) and HCl (6N, 20.0 mL), and the phases were separated. The aqueous layer was extracted with ethyl acetate (3 N, 46.8 mL, 5.0 equiv.), and the resulting mixture was heated at 50–60 ̊C for 2 h. Then, the reaction mixture was cooled to room temperature, and the reaction mixture was evaporated to remove DME. Water (400 mL) was added, and white precipitate (HCl salt) appeared. The precipitate was filtered, washed with water (20 mL × 2). The filtrate was total 80 mL.

Preparation of Fmoc-(S)-2-amino-6,6,6-trifluorohexanoic acid (S)-9. To a solution of Ni complex (S,2S)-2-amino-6,6,6-trifluorohexanoic acid (S)-9. To a solution of Ni complex of AA Schi 5 was developed by and commercially available from Hamari Chemicals. However, other methodological avenues of ligand bases of AA as a general methodology 5-AAs [70]. It was shown that the presence of strategically positioned chlorine atoms favorably influence the parallel displaced type of aromatic stacking interactions between the proline N-benzyl and o-amino-benzophenone ring [66]. The quality of these aromatic stacking has important synthetic consequences [67] enhancing the stereochemical preferences at the α-position of the amino acid residue. It should be mentioned that the strategically chlorinated ligand S was developed by and commercially available from Hamari Chemicals. However, other methodological avenues of ligand S applications for the asymmetric stacking interactions between the proline N-benzyl and o-amino-benzophenone ring [66].

1.80–2.00 (m, 2H), 1.64–1.77 (m, 2H).

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3. Results and Discussion

In line with our longstanding curiosity in synthesis of several types of tailor-made AAs, in particular trifluoromethyl- and phosphorus-containing [51,52], sterically constrained [53,54], and nonlinear optical properties of AA and their derivatives, such as self-disproportionation of enantiomers [55–57], we were contributing to the chemistry of Ni(II) complexes of Schiff bases of AA as a general methodology for synthesis of tailor-made AAs [58–60].

Over the last several years, we were focusing on the modular design [61,62] of chiral tridentate ligands used for preparation of the corresponding Ni(II) complexes of AA Schiff bases. Among other advances [63–65], recently we developed a strategically chlorinated ligand 5 (Scheme 2) [66,67], which showed excellent stereoccontrolling properties in the dynamic kinetic resolution of unprotected α- [68,69] and β-AAs [70]. It was shown that the presence of strategically positioned chlorine atoms favorably influence the parallel displaced type of aromatic stacking interactions between the proline N-benzyl and o-amino-benzophenone ring [66]. The quality of these aromatic stacking has important synthetic consequences [67] enhancing the stereochemical preferences at the α-position of the amino acid residue. It should be mentioned that the strategically chlorinated ligand S was developed by and commercially available from Hamari Chemicals. However, other methodological avenues of ligand S applications for the asymmetric
preparation of tailor-made AAs still remain unexplored [71]. Ligands (S)- or (R)-5 are commercially available and can be conveniently prepared [72] starting from (S)- or (R)-proline and transformed to the Ni(II) complexes of glycine Schiff base 4 [71,73]. As presented in Scheme 2, ligand 5 is reacting with glycine and Ni(II) ions in basic methanol solution to afford complex 4.

Scheme 2. Synthesis of chiral Ni(II) complex of glycine Schiff base 4.

Alkylation of the glycine moiety in complexes of type 4 with alkyl halide as alkyl precursor can be conducted under homogeneous [74] as well as phase-transfer catalysis (PTC) conditions [75]. The latter are usually preferred, due to the low byproducts formation, but can be realized only for activated alkyl halides. Thus, under standard PTC conditions [75], CF$_3$(CH$_2$)$_3$I was found to be totally inefficient for alkylation of complex (S)-4, resulting in noticeable decomposition of the alkylating reagent. In sharp contrast, under the homogeneous conditions (Scheme 3), by use of DMSO as a solvent and NaOH as a base (Table 1), the expected alkylation products were isolated and fully characterized.

Scheme 3. Alkylation of (S)-3 with CF$_3$(CH$_2$)$_3$I under homogeneous conditions.

HPLC analysis of the reaction mixture revealed rather low rate of the alkylation and disappointing diastereoselectivity. As shown in Table 1, in entries 1–3, after 4.5 h of the reaction time, over 43% of
starting complex 4 was still intact. Near-complete consumption of glycine complex 4 was observed after 24 h (entry 4) along with a large amount of various byproducts. One of the major byproducts was identified as previously described [73] compound 8 resulting from oxidative decomposition of stating glycine complex 4 [76,77].

Table 1. Reaction of complex (S)-4 with CF$_3$(CH$_2$)$_3$I in DMSO using solid NaOH as a base [a].

| Entry | Time (h) | 4 (%) | 6 (%) | 7 (%) | Dr (6:7) | 5 (%) | 8 + uk [b] (%) |
|-------|----------|-------|-------|-------|----------|-------|---------------|
| 1     | 1.5      | 63.9  | 21.7  | 4.0   | 84:16    | 0.7   | 3.0           |
| 2     | 3.0      | 54.5  | 25.7  | 4.7   | 85:15    | 0.4   | 5.1           |
| 3     | 4.5      | 43.6  | 27.8  | 5.3   | 84:16    | 0.6   | 8.9           |
| 4     | 24.0     | 0.7   | 37.9  | 2.1   | 95:5     | 5.1   | 42.5          |

[a] Reaction conditions: complex (S)-4, DMSO (20 v/w), NaOH (1.0 equiv), CF$_3$(CH$_2$)$_3$I (1.0 equiv). [b] unknown compounds.

One of the critical notes made in this series of experiment was the observation that solid NaOH is not the best choice of introducing the base into the reaction mixture. After a series of experiments focused on solvent/base issue, we found that combination of DMF as a reaction solvent and solution of NaOMe in MeOH as a base allows for a dramatically improved outcome. Thus, as presented in Table 2, the alkylation of (S)-4 with CF$_3$(CH$_2$)$_3$I performed in DMF and using NaOMe/MeOH (28% solution) proceeded with high rate providing for virtually complete (>99%) consumption of the starting materials within about 30 min (entry 1). Importantly, the amount of byproducts was also dramatically reduced, albeit the stereochemical outcome was rather marginal (90:10 dr). Interestingly, extension of the reaction time from 0.5 to 2.0 h did not result in any visible changes of the chemical or stereochemical outcome (entry 2).

Table 2. Reaction of complex (S)-4 with CF$_3$(CH$_2$)$_3$I in DMF using solid NaOMe (28% and 10% solution in MeOH) as a base [a].

| Entry | Time (h) | NaOMe (Concentration) | 4 (%) | 6 (%) | 7 (%) | Dr (6:7) | 5 (%) | 8 + uk [b] (%) |
|-------|----------|-----------------------|-------|-------|-------|----------|-------|---------------|
| 1     | 0.5      | 28%                   | 0.9   | 81.3  | 9.0   | 90:10    | 1.15  | 0.2           |
| 2     | 2.0      | 28%                   | <0.1  | 82.1  | 9.1   | 90:10    | 1.8   | 0.35          |
| 3     | 0.5      | 10%                   | 0.2   | 89.05 | 3.2   | 97.3     | 0.3   | 2.5           |
| 4     | 2.0      | 10%                   | 0.2   | 89.3  | 3.25  | 96.5:3.5 | 0.35  | 3.7           |

[a] Reaction conditions: complex (S)-4, DMF (7 v/w), NaOMe/MeOH (1.0 equiv), CF$_3$(CH$_2$)$_3$I (1.0 equiv). Isolated yield of 6 was 87.5%. [b] unknown compounds.

Additional experiments with combination of DMF/NaOMe indicated that the application of less concentrated solution of NaOMe, has some advantageous effect on the reaction outcome. As shown in Table 2 (entry 3), the use of 10% NaOMe solution in MeOH as a base resulted in almost complete alkylation of glycine complex (S)-4 with CF$_3$(CH$_2$)$_3$I in less than 30 min of the reaction time. Similar to the previous experiments (entries 1 and 2) the alkylation proceeded rather cleanly, but most notably with rather improved diastereoselectivity (97.3 dr). Also in this case, the extended reaction time has no detrimental effect on the overall outcome. Using these conditions we were able to isolate diastereomerically pure major product 6 with reasonably good chemical yield of 87.5%. Diastereomers (S,2S)-6 and (S,2R)-7 were purified by column and fully characterized. The major product (S,2S)-6 gave [\(\alpha\)]$^25_D = +2616$, indicating \(\alpha\)-(S) configuration of the CF$_3$-AA, while the minor diastereomer showed a negative sign of optical rotation ([\(\alpha\)]$^25_D = -1998$), confirming \(\alpha\)-(R) stereochemistry of the AA residue.
The obtained data are in agreement of general trends in optical rotation observed for diastereomeric Ni(II)-complexes of this type [1f,5i,20].

As presented in Scheme 4, the disassembly of purified diastereomERICally pure (>98% de) major product (S,2S)-6 was performed under the action of 3N aqueous HCl at 60 °C using dimethoxyethane (DME) as organic solvent. Virtually complete disappearance of complex (S,2S)-6 was observed within about 2 h of the reaction time. Upon cooling of the reaction mixture, the precipitate of salt of ligand (S)-5 was conveniently removed by filtration. The aqueous solution of the Ni(II) ions and free (S)-1, was concentrated, and treated with Fmoc-OSu in MeCN/H2O to provide the N-Fmoc protected amino acid (S)-9.

**Scheme 4.** Disassembly of diastereomERICally pure (S,2S)-6, recovery of chiral ligand (S)-5, and isolation of Fmoc-(S)-6,6,6-trifluoro-norleucine 9.

4. Conclusions

In summary, it was found that the application of new generation of chiral glycine equivalent (S)-4, prepared from commercially available ligand (S)-5, allows for convenient preparation of Fmoc-(S)-6,6,6-trifluoro-norleucine via alkylation reaction with CF3(CH2)3I. This protocol was consistently reproduced for synthesis of the target AA on ~10 g scale.

**Supplementary Materials:** The following are available online at http://www.mdpi.com/2073-8994/11/4/578/s1, Experimental procedures, full spectroscopic data for compounds 6, 7, and 9, and copies of 1H NMR, 13C, 19F NMR, and HPLC spectra (PDF).

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