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Operationally convenient asymmetric synthesis of (*S*)-2-amino-3,3-*bis*-(4-fluorophenyl)propanoic acid

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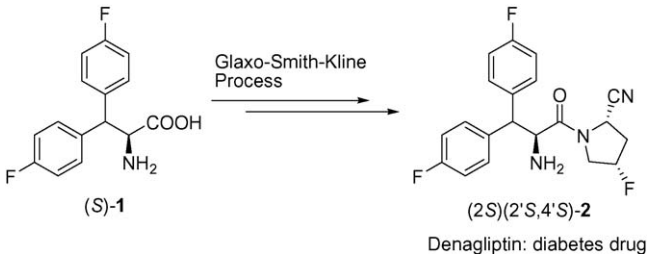
ABSTRACT

This study demonstrated that alkylation of chiral glycine Schiff base **3** with chloride **4** can be efficiently conducted in acetonitrile as a solvent using commercial-grade potassium *tert*-butoxide as a base. High reaction rate (1 h) chemical (>90%) and stereochemical (>95% de) outcomes of the alkylation step render this procedure reliable and operationally convenient for multi-gram synthesis of enantiomerically pure amino acid **1**. Due to the simplicity of experimental procedures and commercial availability all reagents involved, this procedure can be easily reproduced in regular biochemistry laboratories allowing for systematic biological studies and medicinal applications of compound **1**.

1. Introduction

In the recent decade, synthetic availability of tailor-made α-amino acids [1] possessing the designed structural and functional features has gained a significant importance in the development of new peptide-based pharmaceuticals and drugs [2]. Of general importance are sterically constrained α-amino with a substantially reduced number of possible conformations in the χ-(chi)-space [3]. Such amino acids are indispensable structural building block in the design and synthesis of peptides and peptidomimetics with a pre-supposed 3D structure [4]. In particular, among sterically constrained phenylalanine analogues, β,β-diphenylalanine has received quite an special attention. This amino acid has frequently been used as a replacement for phenylalanine in native peptides allowing to significantly increasing both efficacy and selectivity of their original biological activity [5]. Taking into account that introduction of fluorine in strategic position of organic molecules can significantly slowdown their metabolic degradation [6], fluorinated analog of β,β-diphenylalanine, (*S*)-2-amino-3,3-*bis*-(4-fluorophenyl)propanoic acid (**1**) (Scheme 1) has recently attracted a considerable interest. In particular, amino acid **1** is a key intermediate in the developed by Glaxo-Smith-Kline a type-2 diabetes drug Denagliptin, showing potent inhibitory activity against dipeptidyl peptidase IV [7].

First asymmetric synthesis of fluorinated derivative **1** was reported by Haffner et al. using Evans chiral oxazolidinone-controlled diastereoselective α-azidation procedure [7a]. Obvious complications associated with handling the intermediate alkyl azide and multiple synthetic steps render this methods rather unattractive. Patterson et al. have recently explored an asymmetric PTC approach for preparation of amino acid **1** based on alkylation of the corresponding *tert*-butyl glycinate-benzophenone Schiff base in the presence of cinchonidine-derived chiral catalyst [8]. The originally obtained alkylation product of 60% ee was purified via crystallization and isolated in 55% yield. Besides both low enantioselectivity of the alkylation step and chemical yield,



Scheme 1. (*S*)-2-Amino-3,3-*bis*-(4-ftuorophenyl)propanoic acid (1) and derived from it Denagliptin.

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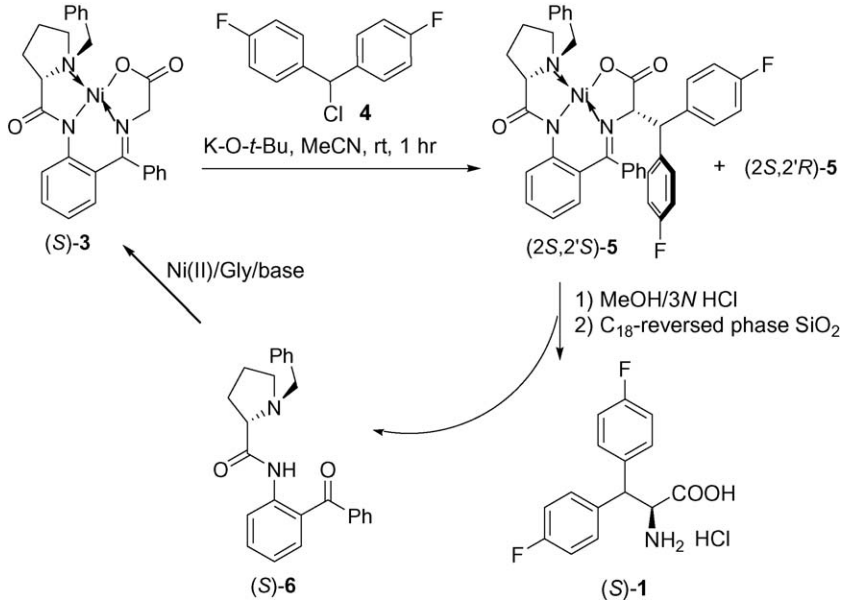

Scheme 2. Asymmetric synthesis of (*S*)-2-amino-3,3-*bis*-(4-fluorophenyl)propanoic acid (1).

general shortcomings of this approach [9] render it synthetically unappealing. When our present work was in preparation, Liu and co-workers have reported [10] asymmetric synthesis of amino acid **1** via alkylation of the Ni(II) complex of glycine Schiff base **3** (Scheme 2) [11,12]. Their optimized procedure included application of NaH (60% suspension in oil) as a base, DMF as a solvent and 2.5 h at minus 20 °C [10]. Here we describe, in our opinion, synthetically more attractive and operationally convenient [13] procedure for alkylation of Ni(II) complex of glycine Schiff base **3** and overall preparation of the target amino acid (*S*)-**1** in enantiomerically pure form.

Based on our extensive experience in the chemistry of Ni(II) complex of glycine Schiff base **3** as well as related chiral/achiral nucleophilic glycine equivalents [14–16], and drawing inspiration from Professor Belokon' work [17], we considered carefully all possible reaction parameters, including: solvent, base, nature of the alkyl halide, temperature and isolation of products, to develop practical, scalable and operationally convenient synthetic protocol (Scheme 2).

Considering the significant difference in availability and price of chloride **4** vs. the corresponding bromide, we concentrated our efforts on using compound **4**. We found that the key issue in the alkylation of (*S*)-**3** with chloride **4** is the nature of base used. Thus, application of NaOH, KOH and NaH, which produce heterogeneous suspensions in a solvent used (DMF, MeCN), leads to relatively slow reaction rates (>2 h) and formation of undesired byproducts. On the other hand application of commercial-grade potassium *tert*-butoxide, well-soluble in most of organic solvents was found to be most efficient form the stand point of reaction rate and yield of the alkylation product **5**. Formation of homogeneous solution of potassium *tert*-butoxide in DMF or acetonitrile resulted in a relatively fast generation of the corresponding enolate from **3** and allowed for the reaction to be completed in about 1 h at ambient temperature. Due to this high reaction rate, the application of inert (oxygen excluded) [18] atmosphere was not a mandatory condition. In agreement with the previously reported data on alkylation of complex **3** with bulky alkyl halides [14g,17], the kinetic diastereoselectivity of this reaction was poor. For instance, at about 10–15% conversion of the starting **3**, the ratio of diastereomers (2*S*,2′*S*)-**5** and (2*S*,2′*R*)-**5** was approximately 50/50 (judged by the size of colored spots on TLC). However, upon completion of the reaction the final termodinamic control strongly favored the major product (2*S*,2′*S*)-**5** (>95% de). Upon completion, the reaction mixture was poured into icy water-containing acetic acid to neutralize the base. Acetonitrile was found to be a superior, over DMF, solvent allowing precipitation of product (2*S*,2′*S*)-**5** as well-formed crystals and therefore facilitation their washing with water and filtration. Diastereomerically pure product (2*S*,2′*S*)-**5** was obtained by column chromatography and disassembled via standard procedure (heating **5** in MeOH/3N HCl) furnishing the target acid **1** as well as the chiral ligand **6**, which can be recovered and transformed back to glycine Schiff base complex **3**. Due to the specific physiochemical properties of amino acid **1**, the previous procedures (Dowex resin, precipitation with EDTA) developed for isolation of various α-amino acids, gave rather unsatisfactory results. In this regard, we are pleased to confirm that application of commercially available and reusable C_{18}-reversed phase (230–400) silica gel for isolation of amino acid **1** as the hydrochloric salt, suggested by Liu and co-workers [10] gave excellent result providing high isolated yield (>95%) and chemical purity of compound **1**.

In summary, we found that alkylation of chiral glycine Schiff base **3** with chloride **4** can be efficiently conducted in acetonitrile as a solvent using commercial-grade potassium *tert*-butoxide as a base. High reaction rate chemical and stereochemical outcomes render this procedure reliable and operationally convenient for multi-gram synthesis of enantiomerically pure amino acid **1**. Due to the simplicity of experimental procedures and commercial availability all reagents involved, this procedure can be easily reproduced in regular biochemistry laboratories rendering compound **1** readily available for systematic biological studies.

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Appendix A. Experimental Part

General Methods Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. All of the reactions were carried out under atmospheric conditions without any special caution to exclude air. Unless indicated ^{1}H and ^{13}C NMR spectra, were taken in $CDCl_3$ solutions at 299.95 and 75.42 MHz, respectively. Chemical shifts refer to TMS as the internal standard.

Yields refer to isolated yields of products of greater than 95% purity as estimated by ^{1}H and ^{13}C NMR spectrometry. All compounds were characterized by ^{1}H, and ^{13}C NMR, high-resolution mass spectrometry (HRMS-ESI), melting point, and optical rotation, when applicable.

Ni(II) complex of (*S*)-2-amino-3,3-*bis*-(4-fluorophenyl)propanoic acid Schiff base with (*S*)-**6** [(2*S*,2′*S*)-**5**]. To a mixture of 50 g (0.1 mole) of (*S*)-**3**, 22.0 mL (0.12 mole) of **4** in 125 mL of anhydrous (commercial-grade) 18 g (0.16 mole) of potassium *tert*-butoxide was added at ambient temperature with stirring. The reaction progress was monitored by TLC (chloroform/acetone, 5/1). After disappearance of starting glycine equivalent (*S*)-**3**, the reaction mixture was poured into a beaker under stirring containing 1 L ice water (12 mL of acetic acid). After the ice had melted the corresponding product, was washed with water, filtered and dried in an oven (40-45 °C) to afford the appropriate product (2*S*,2′*S*)-**5** in 96% chemical yields. M.p. 237–239 °C, $[\alpha]_D^{25}$ +2054 (*c* = 0.1, MeOH); $[\alpha]_D^{25}$ +1991.9 (*c* = 0.49, $CHCl_3$) [10]. ^{1}H and ^{13}C NMR ($CDCl_3$) data are similar to that reported in the literature [10].

(*S*)-2-amino-3,3-*bis*-(4-fluorophenyl)propanoic acid, hydrochloride (**1**). Was prepared via disassembling of (2*S*,2′*S*)-**5**, as previously described [10]. Yield 93%, m.p. 155–157 °C, $[\alpha]_D^{25}$ +55.7 (*c* = 0.1, MeOH); +55.1 [10], +56.3 [8]. ^{1}H and ^{13}C NMR (CD_3OD) data are similar to that reported in the literature [8,10].

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