Tetrahedron Letters,Vol.26,No.26,pp 3067-3070,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

A CONVENIENT SYNTHESIS OF **erythro-** AND **threo-**3-FLUOROPHENYLALANINE FROM A PROTECTED GLYCINE SYNTHON

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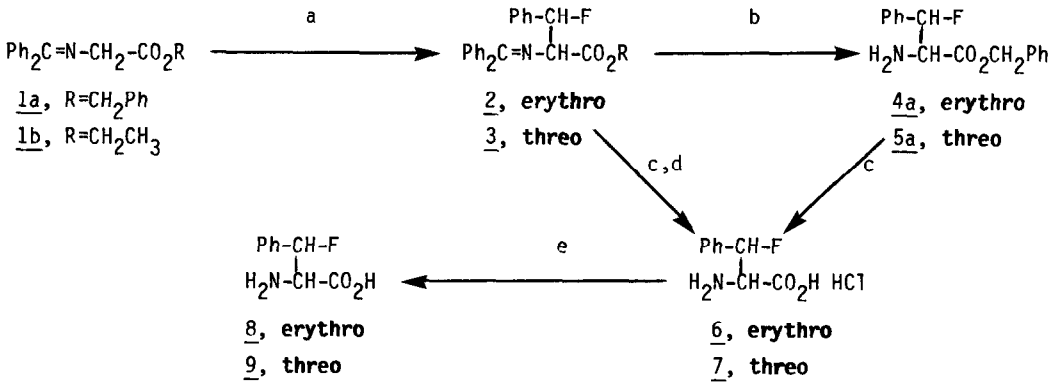
Abstract: A facile synthesis of the title compounds (8 and 9) is described; key steps include the mono-C-alkylation of the glycine Schiff base benzyl ester 1a with α-bromo-α-fluorotoluene, which provides the readily separable fluorinated diastereomers 2a and 3a, and the dealkylative hydrolysis of the benzyl esters 2a-5a without concomitant loss of the benzylic fluorine.

Convenient routes to β-fluorinated amino acids are important because of the potential for a number of these compounds to act as enzyme activated irreversible inhibitors.[2-4] 3-Fluorophenylalanine has attracted considerable recent attention,[5-11] in part because it represents a unique class of β-fluorinated aromatic amino acids.[8] Two chemical methods for the preparation of this amino acid as well as two routes to the corresponding isopropyl and methyl esters have been reported recently. Synthesis of the amino acid by fluorodehydroxylation provided the **threo** diastereomer 9 when SF_4-HF was utilized to introduce the benzylic fluorine,[5] but gave a mixture of 8 and 9 when diethylaminosulfur trifluoride (DAST) was the fluorinating agent.[6] Alternatively, fluorine gas was used in a sequence to the **erythro** diastereomer.[7,8] An aziridine ring opening reaction with HF-pyridine has been used to obtain the **threo** diastereomer 8 as its isopropyl ester.[9] Schöllkopf has developed an asymmetric synthesis of the methyl ester of **threo** amino acid 9.[10] Tsushima and co-workers[8] have, however, recently noted that there is no chemical method for the hydrolysis of an ester blocking group on 8 or 9 without concomitant loss of fluorine, and were only able to isolate the pure **threo** diastereomer by an inefficient enzymatic ester hydrolysis method or by the cellulose chromatographic separation of the diastereomers 8 and 9, obtained from the aforementioned DAST fluorination procedure.[6]

We wish to report a short and convenient route to the title compounds (8 and 9) which: (a) avoids the use of F_2, HF, or SF_4, (b) is amenable to a multigram scale, (c) makes novel use of α-bromo-α-fluorotoluene as an electrophile and (d) utilizes a method to deblock an ester without loss of benzylic fluorine.

The Schiff base benzyl ester (1a) and ethyl ester (1b) were monoalkylated under ion-pair extraction conditions.[12,13] Selective monoalkylation involving introduction of an acid-strengthening group is of particular interest because such systems often lead to extensive

Scheme



(a) PhCHBrF, $(n\text{-}Bu)_4N^+ HSO_4^-$, CH_2Cl_2, 10% NaOH, 5°C. (b) 1N HCl, ether, RT, 48 hrs, $NaHCO_3$ workup. (c) TMSI, $CHCl_3$, 60°C, 24 hrs, HCl workup. (d) 1N HCl, $CHCl_3$, RT, 48 hrs. (e) Propylene oxide, iPrOH, 6 hrs.

dialkylation.[13] It was possible, due to the increased stability of the benzophenone imines,[12] to separate the **erythro** and **threo** diastereomers at this stage using flash chromatography. Acid promoted hydrolysis of the Schiff bases 2a or 3a followed by a basic workup provided the amino esters 4a and 5a. The possible problem of attendant loss of fluorine during ester hydrolysis[8] was overcome by dealkylative hydrolysis with trimethylsilyl iodide (TMSI).[15] Although such hydrolyses of the ethyl esters (2b and 3b) were sluggish and led to incomplete reaction, the benzyl esters (2a and 3a) were cleanly converted, following acid hydrolysis, to the amino acids 6 and 7 using this method. Of concern was the potential for conversion of the benzylic fluoride to the corresponding iodide.[16] However, no evidence of this reaction was observed with either 2a or 3a. Alternatively, amino esters 4a or 5a smoothly underwent dealkylative hydrolysis with TMSI followed by treatment with 1N HCl to provide 6 and 7. Treatment of the hydrochloride salts with propylene oxide gave the free amino acids (8 and 9).

The following procedures leading to 8 are illustrative:

Preparation of 2 and 3: To a flask equipped with an overhead stirrer, thermometer and dropping funnel was added N-(diphenylmethylene)glycine benzyl ester (1a)[17] (57.0 g, 173 mmol), α-bromo-α-fluorotoluene[18] (39 g, 208 mmol), $n\text{-}Bu_4N^+HSO_4^-$ (70.5 g, 208 mmol) and CH_2Cl_2 (250 ml). The light yellow solution was stirred at 5°C[19] and 10% NaOH (220 ml, 606 mmol) was added dropwise. The progress of the reaction was followed by HPLC[20] and after 3.5 hrs. the organic layer was separated, washed with water and evaporated to a mixture of 2a and 3a (53 g, 71%). Flash chromatography on Kieselgel (Merck) with 5%

EtOAc/hexane as elutant gave 18.0 g (34%) of 2a as a light yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (1H,dd,J_{HF}=6.4Hz, J_{HH}=8.3Hz, C2-H), 5.23 (1H,d,J=12.5Hz,Ha of benzyl CH_2), 5.26 (1H,d,J=12.5Hz,Hb of benzyl CH_2), 6.09 (1H,dd,J_{HH}=8.3Hz,J_{HF}=45.4Hz,C3-H), 6.38-7.60 (20H,m); ^{19}F NMR (282.2 MHz, $CDCl_3$) δ(from $(CFCl_3)$-182.9 (dd,J_{FH2}=6.1 Hz,J_{FH3}=45.8Hz; high-resolution mass spectrum, obsd 417.1729, $C_{29}H_{23}NO_2$ requires 417.1730 (M-HF), obsd 302.1345, $C_{21}H_{17}FN$ requires 302.1346 (M-CO_2CH_2Ph). Further elution yielded 7.9 g (15%) of 3a as a white crystalline solid (EtOAc-Hexane); mp 88-90°C. Anal. Calcd for $C_{29}H_{24}FNO_2$: C, 79.61; H, 5.53; N, 3.22. Found: C, 79.66; H, 5.67; N, 2.99.[21,22]

Preparation of 6: A solution of 2a (4.0 g, 9.14 mmole) in $CHCl_3$ (10 mL) and TMSI (1.97 g, 10.1 mmole) was warmed at 60°C and the progress of the reaction was monitored by ^{1}H NMR. After 24 hours, the reaction was cooled to room temperature, treated with cold 1N HCl (10 mL) and stirred under a nitrogen atmosphere for 48 hours. The aqueous layer was washed with EtOAc (5 x 25 mL) and lyophilized to give 6 (1.4 g, 70%) as a white solid; mp 179-180°C (iPrOH/EtOAc).

Preparation of 8: A solution of 6 (45.7 mg, 0.249 mmole) in iPrOH (3 mL) was treated with propylene oxide (57.5 mg, 0.996 mmole) and stirred at room temperature for 6 hours. The resulting white solid was collected by filtration and dried to give 8 (27 mg, 59%), mp 170-171°C (inserted at 165°C) (Lit[7] mp 168-169°C). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 3.80 (1H, dd, J_{HF}=15.14 Hz, J_{HH}=3.91 Hz), 6.03 (1H, dd, J_{HF}=44.2 Hz, J_{HH}=3.91 Hz), 7.35 (5H, s); ^{19}F-NMR (74.8 MHz, D_2O) δ (From $CFCl_3$) - 186.9 (dd, J_{FH3}=43.9 Hz, J_{FH2}=16.1 Hz). Anal. Calcd for $C_9H_{10}FNO_2$: C, 59.01; H, 5.50; N, 7.65. Found: C, 58.72; H, 5.53; N, 7.33.

The ready availability of starting materials and facile reaction procedures, combined with the elimination of hazardous reagents makes this an attractive route to both diastereomers of 3-fluorophenylalanine. We are currently exploring the scope and further applications of the method outlined in this letter.

Acknowledgment: We thank the National Institutes of Health (GM 28193) for partial support of this research and Mr. Robert J. Barbuch, Mr. Edward W. Huber and Dr. Michael R. Whalon for spectral data. The support of Merrell Dow Pharmaceuticals, which made this collaborative effort possible, is also gratefully acknowledged.

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(19) The reaction should be kept at <10°C until workup, or product often was not isolated.
(20) Waters Associates Z-Module Radial C-18 column, CH3CN: 0.01M ammonium formate: formic acid:: 700:300:0.2.
(21) The assignment of the **threo** configuration to the slower moving band (3) eluted from the column was tentatively made based on the 1H NMR reported for the **threo** methyl ester. Confirmation of the **threo** (and **erythro**) assignments were made by the conversion of 2a and 3a to the parent amino acids 8 and 9 respectively.
(22) Satisfactory spectral data (1H NMR, 19F NMR, MS) have been obtained for all compounds reported in this communication. Elemental composition as determined by combustion analysis and/or high-resolution mass spectroscopy has been obtained for compounds 2a, 3a, 4a, 5a, 8 and 9. The following are spectral data and physical constants for some representative compounds:

3a: 1H-NMR (300 MHz, CDCl3) δ 4.47 (1H,dd,JHF=20.5Hz, JHH=5.38Hz), 5.09 (1H,d,J=12.4Hz), 5.15 (1H,d, J=12.4Hz), 6.06 (1H,dd, JHF=45.9Hz, JHH=5.38Hz), 6.58-7.64 (20H,m); 19F-NMR (282.2 MHz, CDCl3) δ (From CFCl3)-186.2 (dd, JFH3=45.8 Hz, JFH2=19.9Hz).

4a (HCl): (92%); mp 190-193°C (iPrOH/H2O); 1H-NMR (300 MHz, DMSO-d6) δ 4.81 (1H,dd,JHH= 2.7 Hz, JHF=26.6Hz), 5.06 (1H,d, J=12.2Hz), 5.12 (1H, d, J=12.2 Hz), 6.20 (1H, dd, JHH,=2.9 Hz, JHF=45.9 Hz), 7.11-7.39 (10H, m), 9.04 (3H, broad s); 19F-NMR (282.2 MHz, DMSO-d6) δ (From CFCl3) -132.0 (dd, JFH3= 45.8 Hz, JFH2=25.9 Hz); MS (CI) m/e 274 (M+1), 254 (M+1-HF).

5a (HCl): (89%); mp 162-164°C (iPrOH/H2O); 1H-NMR (300 MHz, DMSO-d6) δ 4.86 (1H, dd, JHF= 20.0 Hz, JHH=6.4 Hz), 5.11 (1H, d, J=12.45 Hz), 5.17 (1H, d, J=12.45 Hz), 6.01 (1H, dd, JHF=45.4 Hz, JHH=6.4 Hz), 7.19-7.46 (10H, m), 8.87 (3H, broad s); 19F-NMR (282.2 MHz, DMSO-d6) δ (From CFCl3)-187.6 (dd, JFH3=44.2 Hz, JFH2=20 Hz); MS (CI) m/e 274 (M+1), 254 (M+1-HF).

6: (62% from 4a).

7: (42% from 3a; 75% from 5a); mp 166-167°C (iPrOH/EtOAc).

9: (77%); mp 183-186°C (inserted at 175°C) (Lit (ref. 5) mp 173-174°C); 1H-NMR (300 MHz, DMSO-d6) δ 3.62 (1H, dd, JHF=27.35 Hz, JHH=3.91 Hz), 5.95 (1H, dd, JHF=44.9 Hz, JHH=3.91 Hz), 7.34-7.4 (5H, m); 19F-NMR (74.8 MHz, D2O) δ (From CFCl3)-191.3 (dd, JFH3=44.9 Hz, JFH2=27.4 Hz). Anal. Calcd for C9H10FNO2: C, 59.01; H, 5.50; N, 7.65. Found: C, 58.92; H, 5.45; N, 7.42.

(Received in USA 2 April 1985)