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Large-Scale Practical Process of Boc-Protected 4-Fluoro-L- Proline

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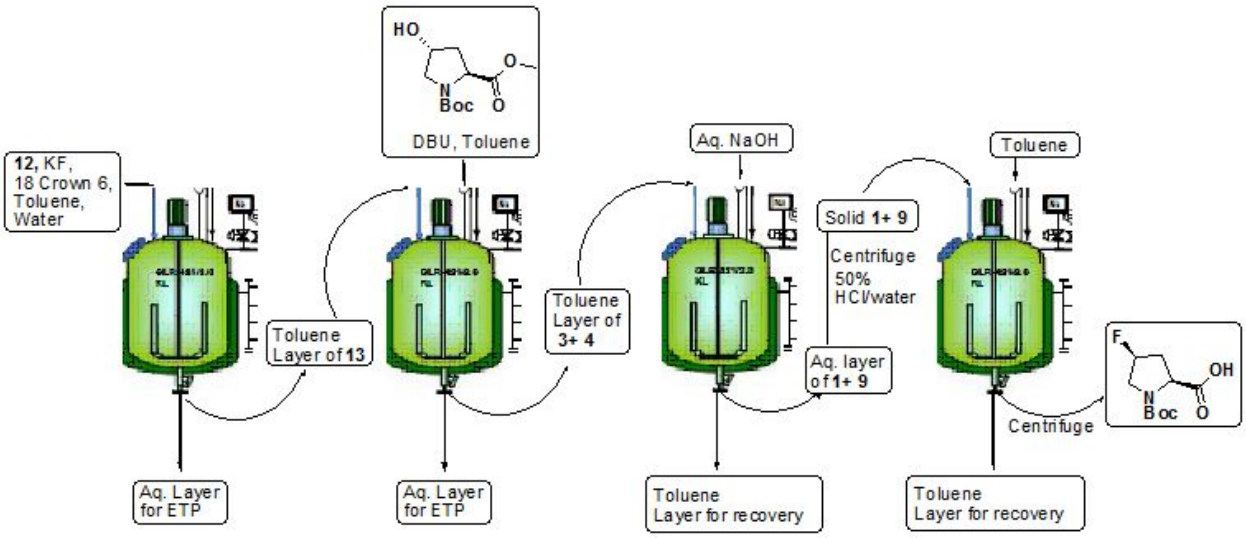


Abstract

A large-scale synthesis of N-Boc-4-Fluoro-L-Proline (**1**) from N-Boc-4-hydroxy-L-Proline methyl ester (**2**) using Nosyl fluoride (**13**) as deoxyfluorinating agent has been developed. Eco-friendly and large scale feasible process using single solvent was developed to afford excellent purity >99% by HPLC with moderate yield. Key feature of the optimization included chromatography free purification and isolation on kilogram scale at pilot plant scale is described.

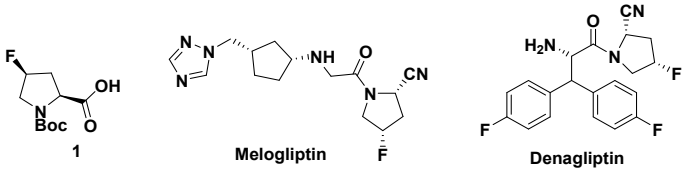
Key words

Deoxyfluorination, Nosyl fluoride, N-Boc-4-Fluoro-L-Proline, N-Boc-cis-4-fluoro-L-proline methyl ester, chromatography free

Introduction

The fluorine substituted natural amino acids have been used as a powerful tool in medicinal chemistry. Naturally occurring bioactive Proline and its 4-substituted derivatives are important amino acids and have been extensively used in the pharmaceutical industry. 4-Fluoroproline is tool for protein design and engineering.[1] N-Boc-4-Fluoro-L-Proline (**1**) is useful intermediate in the synthesis of several drug molecules, such as Dipeptidyl peptidase IV inhibitors[2a-d], Hepatitis C virus (HCV) inhibitors[3], HIV-1 protease inhibitors[4a,b], Anti-alzheimer agents[5], Anti-tumor agents[6], GABA uptake inhibitors[7], Thrombin inhibitors[8], Peptide deformylase (PDF) inhibitors[9], TNF-α production inhibitors[10], Pan-aurora kinase inhibitors[11], Inhibitors of ROS1 and NTRK kinase[12], GPR119 receptor agonists[13], VLA-4 inhibitors[14a,b], Fibroblast activation arotein (FAP) inhibitors.[15] Unfortunately methods reported in literature for preparation of N-Boc-4-Fluoro-L-Proline (**1**) are extremely expensive and very difficult to synthesize on

large scale. Short, chromatography-free and scale up suitable process is not reported. Herein, we report an efficient and scalable process of N-Boc-4-Fluoro-L-Proline (**1**).

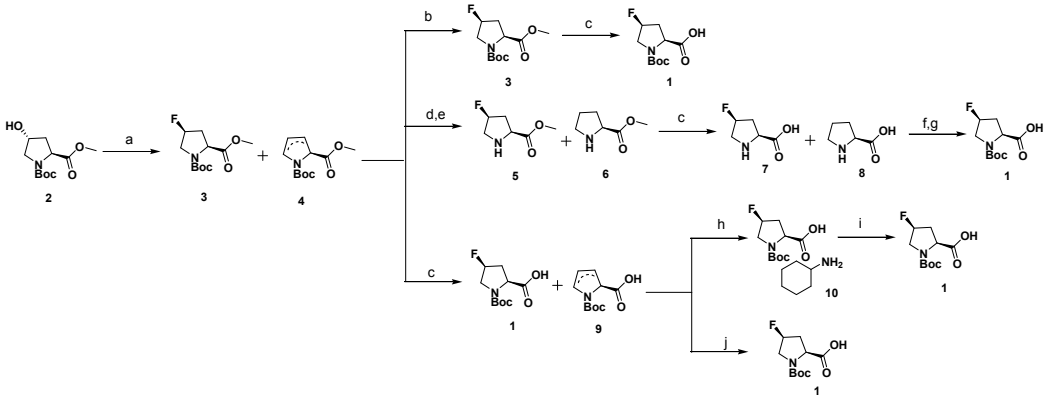


Results and Discussions

There are a number of drawbacks in the conventional synthesis of an optically active N-Boc-4-Fluoro-L-Proline (**1**). (Diethylamino)sulfur trifluoride {DAST}[2a,e] is most popular fluorinating agent utilized in small scale deoxyfluorination of N-Boc-4-hydroxy-L-Proline methyl ester (**2**). However DAST is not suitable for large scale due to low temperature reaction conditions and thermally unstable/potentially explosive.[16] Other deoxyfluorination agents such as Ishikawa reagent[17], Diethylaminosulfur trifluoride & Morpholinoaminosulfurtrifluoride[18a,b], Yarovenko reagent[19], 2,2-difluoro-1,3-dimethyl imidazolidine[20], Perfluoroalkanesulfonylfluoride/base[21], Sulfuryl fluoride[22] are expensive, highly reactive, involved complex work-up, racemisation and offer only marginal improvements in chemo-selectivity. Therefore, the use of conventional fluorinating agents in a large scale may result in severe handling (costs, time) and safety problems. Unfortunately, the majority of synthetic methods for fluorination have poor green chemistry metrics or lack practicality. Nucleophilic aliphatic substitution is more general method through the displacement of a leaving group with a simple fluoride source.[23] The present study describes the use of inexpensive Nosyl fluoride as a fluorinating agent[24a,b] which is safe, stable and easy to handle.

Conventional methods for synthesis of **1** suffer with substantial amount of elimination products. Hence the purification of optically active **1** from **4** (3,4 or 4,5-dehydro impurities) is the major challenge in large scale. As outlined in Scheme-1, literature synthesis of **1** is as follows

Scheme-1. Literature synthesis of 1



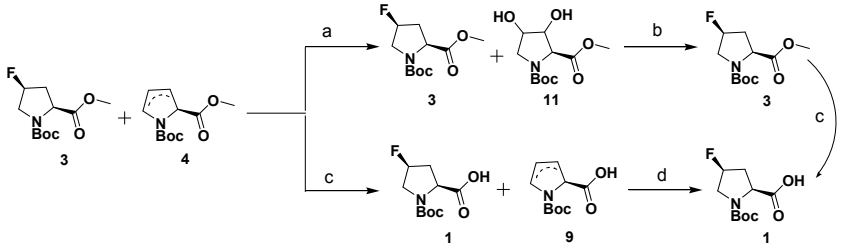
Reagents: (a) Fluorinating agent; (b) Column chromatography; (c) NaOH; (d) TFA;(e) Pd/C; (f) recrystalization; (g) Boc-anhydride; (h) cylcohexylamine & recrystalization; (i) HCl; (j) NaOCl

a) Column chromatography purification of N-Boc-cis-4-fluoro-L-proline methyl ester **(3)** followed by hydrolysis. b) Boc deprotection and reduction of double bond with Pd/C of **3** & **4**. Hydrolysis of **5** & **6** followed by hot ethanol/water treatment to get 4-Fluoro-L-Proline (**7**)[25] which on Boc protection affords **1**. c) Hydrolysis of **3** & **4** to get **1** & **9**. Obtained acid derivatives were converted to corresponding cyclohexylamine salts. Pure **10** was obtained by recrystallization followed by acidification with HCl affords **1**.[26] d) Hydrolysis of **3** & **4** to get **1** & **9** followed by oxidization affords **1**.[20] For the pilot-plant campaign, major issues need to address were economic synthesis, simple process and most importantly isolation without chromatography.

We postulate that the polar diol derivatives can be easily removed by polar solvents. As shown in Scheme 2, our initial approach was to prepare easily removable polar derivatives of **4**. Osmium tetroxide (OsO_4) & Potassium permanganate ($KMnO_4$)

were found to be best among different oxidizing agents investigated for oxidation of alkenes **4** to get corresponding diol **11**. Multiple solvents and mixture of solvents were tested to eliminate diol derivatives **11** while keeping product intact in Toluene. Gratifyingly, 50% methanol in water was achieved complete elimination of **11** from **1**.

Scheme-2. Initial approach for synthesis of 1



Reagents: (a) $KMnO_4$ or OsO_4; (b) washing with mixture of solvents; (c) NaOH; (d) hot toluene

However, these procedures were not taken forward for large scale as OsO_4 is highly toxic[27] and expensive whereas $KMnO_4$ reaction involved tedious work-up. Therefore, we examined alternate suitable conditions for large scale synthesis. Development of the crystallization of **1** was a major focus prior to the pilot-plant campaign because this offered an excellent point in the synthesis sequence to purge impurities and ensure that the final product **1** would be obtained with consistent purity.

We decided to do hydrolysis of **3** to utilize an aqueous workup to remove impurities. The decision to isolate the carboxylic acid **1** was further supported by physical properties and solubility studies. Crystalline **1** could be obtained from hot Toluene. Serendipitously, simple hydrolysis of **3** & **4** using sodium hydroxide afforded **1** & **9**, where pH and temperature played crucial role during isolation. Loss of yield has been observed in case of lower/higher pH with elevated temperature. A screening of solvents showed hot Toluene was the most effective solvent to isolate **1** selectively. Optimized

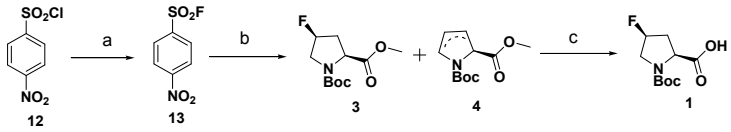
purification process was successfully applied to isolate **1** for popular reaction conditions using deoxyfluorination agents such as DAST and Triflic anhydride/TBAF (1M Tetrabutyl ammonium fluoride in THF).

We also developed large scale suitable economical process for Nosyl fluoride (**13)**. Economical, easily recoverable and re-usable solvent such as Toluene was used instead of Tetrahydrofuran[28], Acetonitrile[29] and Acetone[30]. Time of reaction was reduced by elevated temperature to 55 ^{o}C from RT. It was observed that Toluene layer retain pure product **13** whereas simple water work-up able to remove of associated impurities. During lab scale reactions, **13** was obtained as a solid by concentration of Toluene solution to dryness. In view of safety during pilot batch, a solution of **13** in Toluene layer directly used for next reaction instead of solid isolation. Etching on glass assembly was observed during lab reaction, it is highly recommended to wear appropriate personal protective equipment (PPE) and adhere to the standard operating procedure (SOP) while performing reaction.[31]

Ultimately, for the pilot-plant campaign, we chose to implement an inherently safer process in which Toluene layer with **13** was obtained from inexpensive commercially available Nosyl chloride (**12**) by treatment of Potassium fluoride (KF) in biphasic media such as Toluene and water using 18-crown-6 as phase transfer catalyst at 50-55^{o}C. Aqueous layer separated and Toluene layer with **13** was utilized for deoxyfluorination of **2** to afford **3** & **4** using 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) as base. After treatment with $KHSO_4$ solution and $NaHCO_3$ solution, Toluene layer was hydrolysed by NaOH. Acid derivatives **1** & **9** were then isolated by acidification of aqueous layer with 50% HCl in water till pH ~3-4 at 0 ^{o}C. Obtained solid was treated

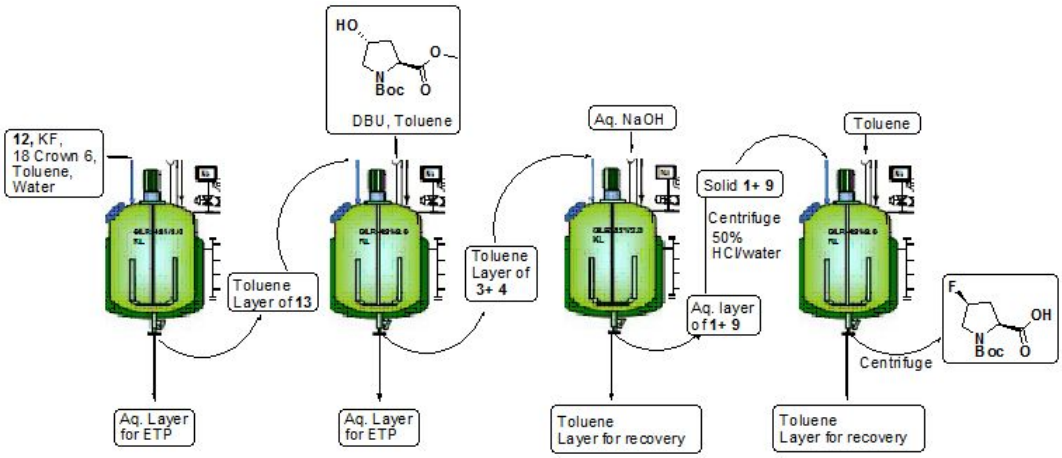
with Toluene at 80 °C. Pure **1** obtained by filtration (lab scale)/centrifugation (pilot scale) at RT as shown in Scheme-3 and Figure-1.

Scheme-3. Pilot-plant synthesis of 1



Reagents: (a) KF, 18-crown-6, Toluene; (b) N-Boc-4-hydroxy-L-Proline methyl ester, DBU, Toluene; (c) NaOH and hot Toluene

Figure-1. Flow diagram of 1



Use of single solvent was major advantage of developed process in case of recovery and re-use of solvent. Current process established on pilot scale; however it can be scaled up on commercial scale.

Conclusion

An economical process had been developed for the large scale synthesis of pure N-Boc-4-Fluoro-L-Proline with moderate yield. The new process involved minimum steps using plant feasible/re-usable single solvent and overcame purification problems related to the synthesis of **1**. In addition, cost-effective and safe process of Nosyl fluoride as deoxyfluorinating agent on large scale was identified.

Experimental Section

N-Boc-cis-4-fluoro-L-proline methyl ester (3).

Method-a (using DAST): To a stirred solution of **2** (200g, 0.812 mol) in DCM (2L), DAST (129mL, 0.978mol) [**Caution: highly toxic, extremely corrosive to skin and readily etches glass. Must be handled with appropriate precautions!**] was added drop-wise at below -15 ^{o}C, during the addition, a slight exotherm was observed and stirred for 4h at RT. After completion of the reaction, the reaction mixture allowed to cool to 0 ^{o}C and quenched with 1.5L of saturated $NaHCO_3$. Separated organic layer washed with 1L of brine. Organic layer concentrated under reduced pressure. The crude material (195g) dissolved in 4L acetone and water (1:1), $MgSO_4.7H_2O$ (100g, 0.406 mol) followed by addition of $KMnO_4$ (64.14g, 0.406mol) portion-wise at 10-20 °C and stirred at RT for 2-3h. 100g of celite was added and stirred for 30min. The resulting light brown suspension was filtered, washed with acetone (800mL); filtrate was concentrated under reduced pressure and diluted with 800mL Toluene. Toluene layer washed with 3x200mL of methanol: water (1:1) and concentrated under reduced pressure to afford **3** as thick oil (133g, 66%).

Method-b (using Nosyl Fluoride): To a stirred solution of **2** (1Kg, 4.08 mol) in Toluene (10 L), DBU (1.24Kg, 8.16mol) was added drop-wise and stirred for 30min at RT. Nosyl fluoride (1Kg, 4.89 mol) was added portion-wise and heated to 45 ^{o}C for 10h. After completion of the reaction, the reaction mixture allowed to cool to RT and washed with 5% aq. $KHSO_4$ solution (2L). Separated Toluene layer washed with saturated $NaHCO_3$ (2L) and concentrated under reduced pressure to get thick oily mass. The crude material

(1.1Kg) dissolved in 4L acetone and water (1:1), $MgSO_4.7H_2O$ (500g, 2.04mol) followed by addition of $KMnO_4$ (320g, 2.04 mol) portion-wise at 10-20 ^oC. Reaction mass allowed to warm to RT and stirred for 2-3h. After completion of reaction, 500g of celite was added and stirred for 10min. The resulting light brown suspension was filtered, washed with acetone (500mL); filtrate was concentrated under reduced pressure and diluted with 4L of Toluene. Toluene layer washed with 3x1L of methanol:water (1:1) and concentrated under reduced pressure to afford **3** as thick oil (524.3g, 52%). ^1H NMR (a mixture of rotamers, 400 MHz, $CDCl_3$) δ 1.43-1.49 (s, 9H), 2.29-2.52 (m, 2H), 3.61-3.69 (m, 1H), 3.75 (s, 3H), 3.79-3.86 (m, 1H), 4.42-4.44 (d, 0.5H), 4.54-4.56 (d, 0.5H), 5.15-5.25 (br d, 1H); $^{13}CNMR$ (125 MHz, $CDCl_3$) δ 28.2, 28.4, 36.5, 36.7, 37.4, 37.5, 52.2, 52.3, 52.8, 53.0, 53.1, 53.3, 57.2, 57.6, 60.4, 76.9, 77.1, 77.4, 80.4, 90.4, 91.5, 91.9, 92.9, 153.6, 154.0, 171.9, 172.3; Mass**:** 248 as $(M+1)^+$.

N-Boc-cis-4-fluoro-L-proline (1).

Method-a (using DAST): To a stirred solution of **2** (200g, 0.812 mol) in DCM (2L), DAST (129mL, 0.978mol) [**Caution: highly toxic, extremely corrosive to skin and readily etches glass. Must be handled with appropriate precautions!**] was added drop-wise at below -15 ^oC, during the addition, a slight exotherm was observed and stirred for 4h at RT. After completion of the reaction, the reaction mixture allowed to cool to 0 ^oC and quenched with 1.5L of saturated $NaHCO_3$. Separated organic layer washed with 1L of brine. Solution of NaOH (65.3g, 1.63mol) in water (650mL) was added to organic layer and heated to 40^oC for 3h. After completion of reaction, DCM layer was separated. Aqueous layer acidified with 50% HCl in water at 0^oC till pH ~3-4. Obtained solid was filtered, suspended in Toluene (600mL) and heated to 80 ^oC for 2h.

Reaction mass allowed to cool to RT, filtered, washed with Toluene (200mL), dried to afford **1** as white solid (137g, 72%)

Method-b (using triflic anhydride/TBAF): To a stirred mixture of **2** (50g, 0.204 mol) and Triethyl amine (41.3g, 0.408 mol) in THF (500mL), triflic anhydride (70.52g, 0.25mol) was added drop-wise at 0-5 ^{o}C and stirred for 4h at RT. After completion of reaction, 1M TBAF in THF (306mL) was added at 0-5 ^{o}C and stirred for 16h at RT. After completion of reaction, reaction mass diluted with ice-cold water and extracted with DCM. Solution of NaOH (16.2g, 2eq) in water (160mL) was added to DCM layer and heated to 40 ^{o}C for 3h. DCM layer was separated. Aqueous layer was acidified with 50% HCl in water at 0^{o}C till pH ~3-4. Obtained solid was filtered, suspended in Toluene (150mL) and heated to 80 ^{o}C for 2h. Reaction mass allowed to cool to RT, filtered, washed with Toluene (50mL), dried to afford **1** as white solid (26.1g, 55%)

Method-c (using Nosyl fluoride): To a stirred solution of 4-nitrobenzene-1-sulfonyl chloride (**11**) (8.89Kg, 40.11 mol) in Toluene (35L), solution of KF (11.55Kg, 199.1mol) in water (35L) followed by 18-crown-6 (0.115kg, 0.44mol) were added and heated to 55 ^{o}C for 6h. After completion of reaction, reaction mass cooled to RT, filtered through pressure nutsche filter (PNF) and washed with Toluene (5L). Separated Toluene layer was added to stirred mixture of **2** (7.0 Kg, 28.57mol) and DBU (8.7 Kg, 57.16mol) in Toluene (21L). Reaction mass heated to 50-55^{o}C for 10h. After completion of reaction, reaction mixture allowed to cool to RT and washed by 5% aq. $KHSO_4$ solution (21L). Separated Toluene layer was washed with saturated $NaHCO_3$ (21L). Solution of NaOH (2.4Kg, 60mol) in water (17L) was added to Toluene layer and heated to 45^{o}C for 3h. Toluene layer was separated and recovered. Aqueous layer acidified with 50% HCl (10L)

in water at 0 °C till pH ~3-4. Obtained solid was filtered, suspended in Toluene (21L) and heated to 80 °C for 2h. Reaction mass allowed to cool to RT, filtered, washed with Toluene (7L), dried to afford **1** as white solid (4.2Kg, 63%). ^{1}H NMR (a mixture of rotamers, 400 MHz, DMSO-d_6) δ 1.36 (s, 5H), 1.41 (s, 4H), 2.21-2.57 (m, 2H), 3.51-3.58 (m, 2H), 4.25-4.30 (m, 1H), 5.19-5.31 (br d, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 27.9, 28.1, 35.9, 36.0, 36.7, 36.8, 52.7, 52.9, 53.0, 53.1, 56.9, 57.2, 78.9, 79.0, 90.9, 92.0, 92.3, 93.4, 153.1, 153.2, 172.6, 172.8; Mass**:** 232 as $(M-1)^{+}$; HPLC: 99.29%; SOR [α] 22/D: −71.0 to -74.0 deg, c = 1 in chloroform; Melting point: 159-162 °C (D).

Supporting Information

Experimental procedures, copies of the NMR, Mass and HPLC spectra of all intermediates and the final product.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors are employees of Wockhardt Research Centre, Aurangabad, India and declare no competing financial interest.

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