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Synthesis of 1-Boc-3-fluoroazetidine-3-carboxylic Acid

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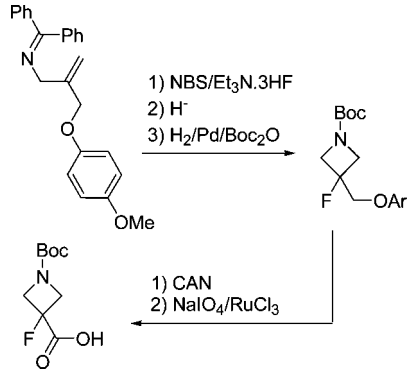

Synthetic strategies toward 3-fluoroazetidine-3-carboxylic acid, a new cyclic fluorinated β-amino acid with high potential as building block in medicinal chemistry, were evaluated. The successful pathway includes the bromofluorination of *N*-(diphenylmethylidene)-2-(4-methoxyphenoxymethyl)-2-propenylamine, yielding 1-diphenylmethyl-3-hydroxymethyl-3-fluoroazetidine after reduction of the imino bond, ring closure, and removal of the 4-methoxybenzyl group. Changing the *N*-protecting group to a Boc-group allows further oxidation to 1-Boc-3-fluoroazetidine-3-carboxylic acid, a new fluorinated heterocyclic amino acid.

The beneficial effects of fluorine as a substituent in organic compounds stimulated the intense research in organofluorine chemistry in the past decade. This is reflected by the numerous papers in this area in recent years and the commercial applications of organofluorine compounds in pharmaceutical chemistry and agrochemistry.[1−6] As a specific class of fluorine-containing biologically active compounds, fluorinated β-amino acids are recognized as exciting building blocks for the synthesis of β-peptides and antibiotics, as enzyme inhibitors, and as therapeutic agents.[7,8] Nevertheless, very little is known about the chemistry of their cyclic counterparts.[7] Only very recently, Fustero et al. reported the synthesis of various cyclic fluorinated β-amino acid derivatives, using a cross-metathesis reaction of suitable fluorinated imidoyl chlorides and acrylates as a key step.[9]

Furthermore, fluoroazetidines exhibit interesting biological activities, such as dipeptidyl peptidase IV inhibitors,[10] cannabinoid receptor modulators,[11] and antibiotics.[12] In addition, the patents concerning fluorinated azetidines emphasize the possibilities of these compounds as substituents to modulate the activity of different active compounds.[13] Since cyclic secondary amines can easily be incorporated in compounds of pharmaceutical interest, the synthesis of *N*-deprotected 3-fluoroazetidines is of concern. In continuation of our interest in fluorinated azetidines,[14] we herein describe an optimized procedure for the

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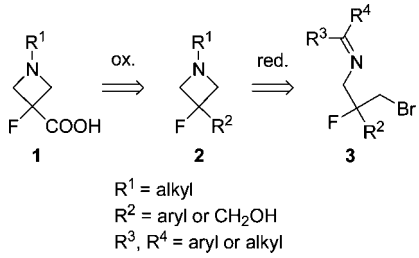
SCHEME 1. Retrosynthetic Analysis for the Synthesis of 1-Boc-3-fluoroazetidine 1

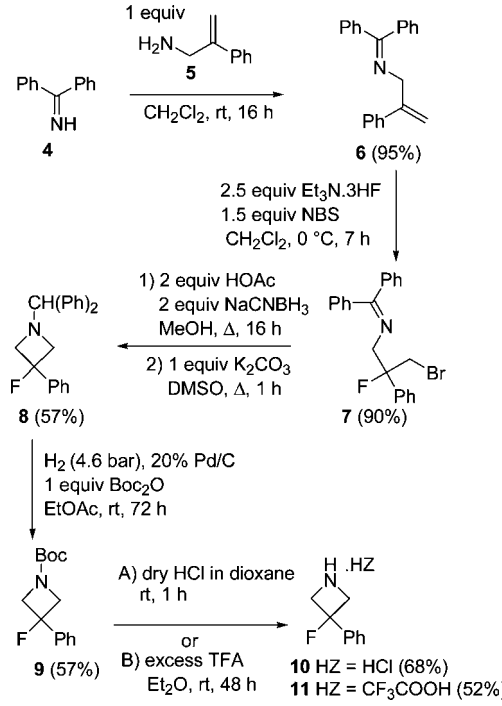


synthesis of 3-fluoro-3-phenylazetidines **2** (R^2 = Ph). In addition, the first synthesis of 1-Boc-3-fluoroazetidine-3-carboxylic acid **1** (R^1 = Boc), an interesting amino acid building block, is described (Scheme 1).

Because of the above-described importance of 3-fluoroazetidine-3-carboxylic acids, a synthetic strategy was designed for their synthesis via bromofluorination of suitable imines, followed by reductive ring closure (Scheme 1). In that respect, the synthesis of 3-aryl-3-fluoroazetidines (**2**, R^2 = aryl), which could be used as substrates for the synthesis of the corresponding fluorinated β-amino acids via oxidative cleavage of the aryl moiety, was envisaged. At first, attempts were directed toward synthesizing 1-alkyl-3-fluoro-3-phenylazetidines via our recently disclosed method that involves the bromofluorination of aldimines.[14] Unfortunately, this pathway proved unsuitable for the large scale preparation of the required fluoroazetidines **2** due to the unavoidable hydrolysis of the starting imines during the bromofluorination reaction. During this reaction, most probably a *N*-halogenation takes place causing rapid hydrolysis. It was reasoned that a more stable protecting group on the imine nitrogen was required. Toward this end, *N*-(diphenylmethylidene)amines **6** were considered, which were synthesized via transimination of benzophenone imine **4** with 2-phenyl-2-propenylamine **5** (Scheme 2).

This moist-stable *N*-(diphenylmethylidene)-2-phenyl-2-propenylamine **6** was very smoothly bromofluorinated with triethylamine trihydrofluoride and *N*-bromosuccinimide (NBS) in dichloromethane at 0 °C in high yield (90%). The resulting *N*-(diphenylmethylidene)-(3-bromo-2-fluoro-2-phenylpropyl)-amine **7**, which was pure enough to use without chromatographic purification, was reacted with sodium cyanoborohydride in methanol under reflux for 16 h. The resulting reaction mixture already contained the desired 3-fluoroazetidine **8** at this stage, together with equal amounts of the intermediate γ-bromoamine. After workup, this mixture was refluxed in DMSO in the presence of K_2CO_3 to complete the ring-closing reaction. In this way, 1-(diphenylmethyl)-3-fluoro-3-phenylazetidine **8** was obtained in 57% yield after chromatographic purification. *N*-Deprotection of the 3-fluoroazetidine **8** by hydrogenation over Pd/C afforded the corresponding 1-unsubstituted azetidine, which could not easily be isolated and purified. Therefore, this azetidine was *in situ* trapped with Boc_2O to yield the corresponding 1-Boc-azetidine **9**. It was found that 3-fluoro-3-phenylazetidine could easily be obtained as the hydrochloride or trifluoroacetate after reaction of azetidine **9** with the corresponding acid and subsequent precipitation of the formed ammonium salts from Et_2O (Scheme 2). Using the above-described optimized method, the new 3-fluoroazetidines **8** and **9** could be prepared on a gram scale, which makes these compounds of interest for use in medicinal chemistry. In order to establish a convenient route to the new 3-fluoroazetidine-3-

SCHEME 2. Synthesis of 1-Boc-3-fluoro-3-phenylazetidine 9 via Bromofluorination of *N*-(Diphenylmethylidene)allylamine 6



carboxylic acid, attempts were performed to transform the phenyl group of **9** into a carboxylic group via oxidative cleavage using $NaIO_4/RuCl_3 \cdot 3H_2O$. Unfortunately, these oxidation reactions failed to yield any fluorinated azetidine-3-carboxylic acid. In addition, experiments to synthesize 3-fluoroazetidines bearing a more electron-rich aromatic substituent at the 3-position revealed that this strategy is not suitable, due to the tedious synthesis of the necessary 2-(methoxyaryl)-2-propenylamines, as was experienced for 2-(3,4-dimethoxyphenyl)-2-propenylamines.[15]

Although the above-described method cleanly resulted in interesting new fluorinated azetidines **10** and **11**, these compounds proved unsuitable for the synthesis of the corresponding 3-fluoroazetidine-3-carboxylic acid, due to failure of the oxidative cleavage of the phenyl group into a carboxylic acid.

Therefore, the 4-methoxyphenoxymethyl group at C-3 was chosen as a latent hydroxymethyl and carboxylic acid function. In our strategy, the allylamine **14** was identified as a key intermediate. A large-scale preparation of allylamine **14** was performed via initial reaction of 3-chloro-2-chloromethylpropene **12** with 4-methoxyphenol (PMP-OH) in the presence of KOtBu in DMF at room temperature during 15 h, and subsequent reaction of the obtained 3-chloro-2-(4-methoxyphenoxymethyl)propene **13**with ammonia in methanol in a pressure vessel at 130 °C for 4 h. This procedure can be used to prepare 2-(4-methoxyphenoxymethyl)-2-propenylamine **14** on a 20 g scale without the need for chromatographic purification. Subsequent transimination of *N*-(diphenylmethylene)amine **4** with the obtained allylamine **14** afforded imine **15**, which was regioselectively bromofluorinated using triethylamine trihydrofluoride and NBS in dichloromethane.[16] It should be noted that it was necessary to purify NBS prior to use by recrystallization from benzene

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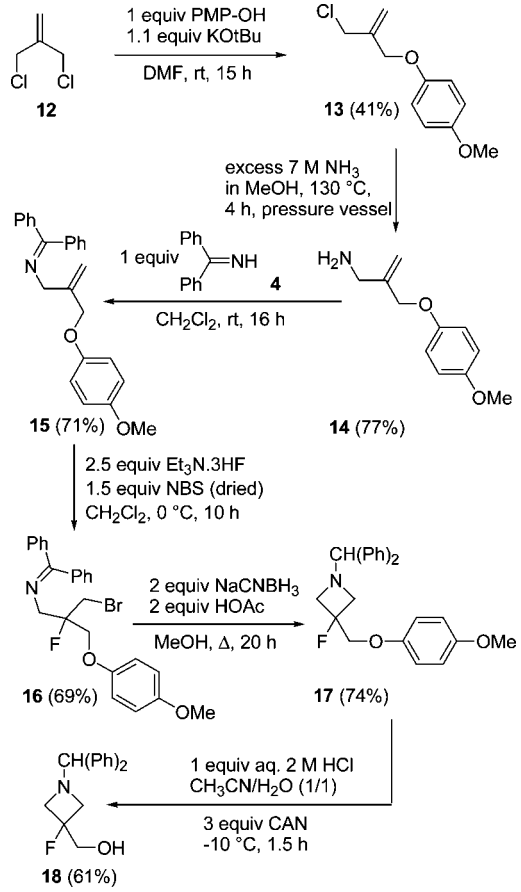
SCHEME 3. Synthesis of 1-Diphenylmethyl-3-fluoro-3-hydroxymethylazetidine 18

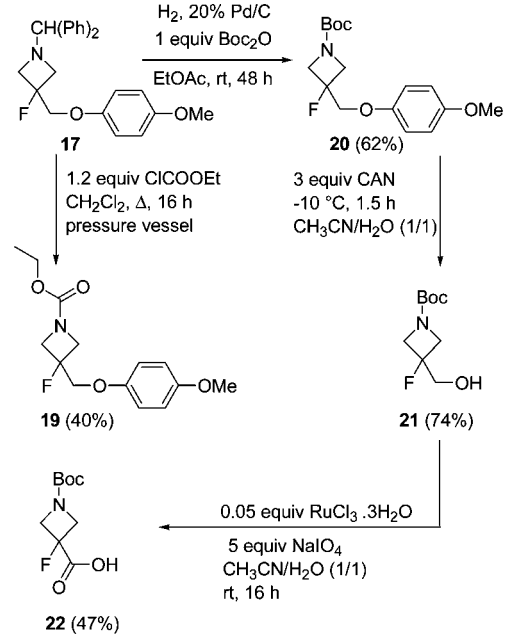


and drying over P_2O_5 to prevent hydrolysis of the imine during reaction. Reaction of the fluorinated imine **16** with 2 equiv of sodium cyanoborohydride in the presence of HOAc gave rise to pure 1-diphenylmethyl-3-fluoro-3-(4-methoxyphenoxymethyl)-azetidine **17** in 74% yield after recrystallization from diethyl ether and hexane (1:3). Subsequently, the *O*-protecting group was easily removed via oxidation with ceric ammonium nitrate (CAN), yielding 1-diphenylmethyl-3-fluoro-3-hydroxymethyl-azetidine **18** in 61% yield. This fluorinated 3-(hydroxymethyl)-azetidine **18** represents an unknown class of compounds with considerable potential as building blocks for pharmaceutical applications (Scheme 3).

Several attempts to oxidize the hydroxymethyl function of **18** to the corresponding carboxylic acid failed, probably due to the presence of the basic amino group in azetidine **18**. Therefore, the nitrogen atom of **18** was rendered less-basic by treatment of 1-diphenylmethyl-3-fluoro-3-(4-methoxyphenoxymethyl)-azetidine **17** with ethyl chloroformate in dichloromethane in a pressure vessel to give 1-ethoxycarbonylazetidine **19** as a suitable substrate for further oxidation reactions (Scheme 4). However, it was observed that a higher yield of *N*-alkoxycarbonylazetidine could be obtained by hydrogenolysis of the diphenylmethyl group and in situ protection of the free N−H using Boc_2O toward *N*-Boc-azetidine **20** in 62% yield.

Subsequently, 4-methoxyphenylether **20** was successfully cleaved with CAN in acetonitrile/water (1/1) at −10 °C yielding 3-fluoro-3-hydroxymethylazetidine **21** in 74% yield. Next, the oxidation with 5 equiv $NaIO_4$ in the presence of catalytic amounts of ruthenium(III) chloride trihydrate in acetonitrile/

SCHEME 4. Synthesis of 1-Boc-3-fluoroazetidine-3-carboxylic Acid 22 via Oxidation of the Corresponding Alcohol 21 with $NaIO_4/RuCl_3$



water[17] could be accomplished and resulted in the envisaged 1-Boc-3-fluoroazetidine-3-carboxylic acid **22** (Scheme 4).

It should be noted that an apparent direct route toward analogous 3-fluoroazetidines via deprotonation of the commercially available 1-diphenylmethyl-3-cyanoazetidine followed by electrophilic fluorination does not result in the corresponding 3-fluoroazetidine-3-carbonitrile. This reaction was evaluated using a range of bases (NaH, LiHMDS, LDA, *n*-BuLi, *t*-BuLi) in acetonitrile or THF followed by quenching with *N*-fluorodibenzenesulfonimide (NFSI) or 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor). Although deuteration experiments proved that deprotonation can be accomplished using LDA as a base in THF at 0 °C in 1 h, all fluorination reactions failed, yielding only starting material.

In conclusion, the first synthesis of 3-fluoroazetidine-3-carboxylic acid, a cyclic fluorinated β-amino acid derivative with high potential as building block in medicinal chemistry, is disclosed. The synthetic pathway includes the bromofluorination of *N*-(diphenylmethylidene)-2-(4-methoxyphenoxymethyl)prop-2-enylamine, yielding 1-diphenylmethyl-3-fluoro-3-hydroxymethylazetidine after reduction, ring closure, and cleavage of the *O*-(4-methoxyphenyl) group. After hydrogenolysis of the *N*-protecting group and reaction with Boc_2O, the successful oxidation of 1-Boc-3-fluoro-3-hydroxymethylazetidine using $NaIO_4/RuCl_3 \cdot 3H_2O$ toward 1-Boc-3-fluoroazetidine-3-carboxylic acid, a new fluorinated amino acid, was accomplished.

Experimental Section

1-Boc-3-fluoro-3-(4-methoxyphenoxymethyl)azetidine (20). The synthesis of azetidine **20** is given as a representative example for the synthesis of azetidine **9**. To a solution of 0.60 g (1.6 mmol) of 3-fluoroazetidine **17** and 0.35 g (1.6 mmol, 1 equiv) of Boc_2O in 2 mL of dry ethyl acetate was added 0.15 g of Pd/C (20% w/w). The solution was stirred at room temperature under hydrogen

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atmosphere (4 bar). After 48 h, the solution was filtered, and the solvent was evaporated yielding a clear oil. The obtained azetidine **20** was separated from diphenylmethane by flash chromatography on silicagel using hexane/EtOAc/Et_3N (90:9:1) as the solvent mixture, yielding 0.31 g of azetidine **20**. $R_f = 0.1$. White crystals. Yield: 62%. Mp. 53 °C. ^{1}H NMR ($CDCl_3$): δ 1.46 (9H, s, $C(CH_3)_3$); 3.77 (3H, s, CH_3O); 4.13 (4H, d, J = 19.0 Hz, $(CH_2)_2N$); 4.15 (2H, d, J = 19.0 Hz, CH_2O); 6.82−6.88 (4H, m, 4 × CH_{ar}). ^{19}F NMR ($CDCl_3$): δ −158.42 (septet, J = 18.9 Hz). ^{13}C NMR ($CDCl_3$): δ 28.5 (3 × CCH_3); 55.9 (CH_3O); 57.8 (d (br), J = 23.1 Hz, $(CH_2)_2N$); 70.0 (d, J = 27.7 Hz, CH_2O); 80.4 ($C(CH_3)_3$); 90.0 (d, J = 210.0 Hz, CF); 114.9 (2 × CH_{ar}); 116.0 (2 × CH_{ar}); 152.6 ($C_{q,ar}$); 154.7 ($C_{q,ar}$); 156.4 (d, J = 2.3 Hz, C═O). IR (ATR, cm^{-1}): ν = 2975; 1700 (C═O); 1508. GC−MS (EI): m/z 311 (M^+, 45); 255 (14); 211 (38); 124 (100); 109 (34); 57 (60). Anal. Calcd for $C_{16}H_{22}FNO_4$: C, 61.7; H, 7.1; N, 4.5. Found: C, 61.9; H, 7.0; N, 4.5.

1-Boc-3-fluoro-3-(hydroxymethyl)azetidine (21). A solution of 0.34 g (1.1 mmol) of azetidine **20** in 3 mL of CH_3CN was cooled to −10 °C. During stirring, a solution of 1.8 g (3.3 mmol, 3 equiv) of ceric ammonium nitrate (CAN) in 3 mL of destilled water was added during 5 min using a syringe. Stirring was continued at −10 °C. After 1.5 h, the reaction mixture was poured in 10 mL of water and extracted with EtOAc (3 × 10 mL). The obtained 3-hydroxymethylazetidine **21** was purified by flash chromatography on silica gel using hexane/EtOAc (80:20) as the solvent mixture, yielding 0.18 g of azetidine **21**. $R_f = 0.01$. The spots on silicagel are only visible for a short moment after treatment of the TLC plate with $KMnO_4$. Yellow oil. Yield = 74%. ^{1}H NMR ($CDCl_3$): δ 1.44 (9H, s, $C(CH_3)_3$); 2.89 (1H, s(br), OH); 3.84 (2H, d, J = 21.2 Hz, CH_2O); 3.95−4.10 (4H, m, $(CH_2)_2N$). ^{19}F NMR ($CDCl_3$): δ −161.15 (septet, J = 19.3 Hz). ^{13}C NMR ($CDCl_3$): δ 28.3 ($C(CH_3)$); 57.3 (d (br), J = 25.4 Hz, $(CH_2)_2N$); 64.4 (d, J = 26.5 Hz, CH_2OH); 80.4 ($C(CH_3)_3$); 91.2 (d, J = 208.8 Hz, CF); 156.4 (d, J = 3.5 Hz, $COOtBu$). IR (ATR, cm^{-1}): ν = 3408; 2977; 1678; 1407. MS (ES^+): m/z 150 ($M + H^+$-t-Bu, 100). Anal. Calcd for $C_9H_{16}FNO_3$: C, 52.7; H, 7.9; N, 6.8. Found: C, 52.4; H, 7.8; N, 6.9.

1-Boc-3-fluoroazetidine-3-carboxylic Acid (22). To a solution of 0.20 g (1.0 mmol) of azetidine **21** in 2 mL of CH_3CN/water (1/1) was added 13.1 mg (0.05 mmol, 0.05 equiv) of ruthenium(III) chloride trihydrate and 1.10 g (5 mmol, 5 equiv) of $NaIO_4$. After being stirred for 16 h at room temperature, the mixture was poured in 4 mL of 1 M HCl and extracted with dichloromethane (3 × 5 mL). After drying ($MgSO_4$), filtration, and evaporation of the solvent, 0.10 g of 1-Boc-3-fluoroazetidine-3-carboxylic acid **22** was obtained as a crystalline compound. White crystals. Yield 47%. Mp: 86 °C. ^{1}H NMR ($CDCl_3$): δ 1.46 (9H, s, $C(CH_3)_3$); 4.21 (2H, dd, J = 10.5 Hz, J = 21.1 Hz, $(C(H)H)_2N$); 4.43 (2H, dd, J = 10.5 Hz, J = 18.2 Hz, $(CH(H))_2N$); 8.99 (1H, s(br), COOH). ^{19}F NMR ($CDCl_3$): δ −163.19 (pentet, J = 19.5 Hz). ^{13}C NMR ($CDCl_3$): δ 28.5 ($C(CH_3)_3$); 59.3 (d (br), J = 24.2 Hz, $(CH_2)_2N$); 81.7 ($C(CH_3)_3$); 87.0 (d, J = 220.4 Hz, CF); 156.6 (d, J = 2.3 Hz, $COOtBu$); 170.8 (d, J = 28.8 Hz, COOH). IR (ATR, cm^{-1}): ν = 2979; 1753; 1636. MS (ES-): m/z 218 ($M - H^+$, 100). Anal. Calcd for $C_9H_{14}FNO_4$: C, 49.3; H, 6.4; N, 6.4. Found: C, 49.0; H, 6.1; N, 6.5.

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Supporting Information Available: General experimental conditions and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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