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Synthesis of (2*R*)-*N*-Boc-2-amino-4,4,4-trifluorobutanoic acid using trifluoromethylation of Garner's aldehyde

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Abstract

Synthesis of enantiomerically pure (2*R*)-*N*-Boc-2-amino-4,4,4-trifluorobutanoic acid (**1**) is described. The key step is trifluoromethylation of Garner's aldehyde.

Keywords: Trifluoromethylation; α-Amino acid; Garner's aldehyde

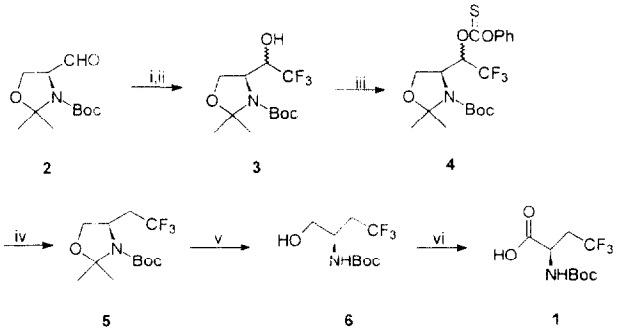
1. Introduction

Due to the electron-withdrawing effect caused by fluorine atoms without significant steric consequence, a series of fluorine-containing amino acids with unique biological properties have been prepared [1]. Among them, trifluoromethylated amino acids have received much attention not only because of their potential use in pharmaceuticals but also because of the challenge associated with their preparation in a stereoselective manner [2].

In 1991, Seebach and Burger [3] reported the preparation of optically active (2*S*)-2-amino-4,4,4-trifluorobutanoic acid. It was synthesized by catalytic hydrogenation of *t*-butyl (*R*)-5-(2,2,2-trifluoroethylidene)-2-*t*-butyl-3-methyl-4-oxo-1-imidazolidinecar-boxylate followed by hydrolysis of the corresponding imidazolidinone. Here, we describe a synthesis of (2*R*)-*N*-Boc-2-amino-4,4,4-trifluorobutanoic acid from the trifluoromethylation of Garner's aldehyde, which is a versatile intermediate used for synthesis of various biologically active compounds [4].

2. Results and discussion

Although trifluoromethylation of aromatics and olefinic halides [5] is readily achieved, few procedures are applicable for trifluoromethylation of carbonyl compounds. Compared with various trifluoromethylmetallic reagents used, for example, CF_3Cu, CF_3CO_2Na and $(CF_3)_2Hg$, TMS–CF_3 reacts quite well with a variety of aldehydes, ketones, etc. [6]. Many reports on the successful trifluoromethylation of carbonyl compound with TMS–CF_3 have been published [6,7]. So this compound was utilized as a trifluoromethylation reagent for Garner's aldehyde.



Scheme 1. (i) TMS–CF_3, TBAF, THF; (ii) TBAF, THF; (iii) PhOCSCl, *n*-BuLi, THF; (iv) Bu_3SnCl, AIBN, toluene; (v) I_2, MeOH; (vi) PDC, DMF.

Garner's aldehyde **2** reacted with TMS–CF_3 in the presence of catalytic TBAF for 24 h at room temperature, then 2 equiv. of TBAF was added in one pot and stirring was continued for another 24 h at the same temperature to give the key intermediate **3** (see Scheme 1). Compound **4** was prepared by the reaction of **3** with PhOCSCl-*n*-BuLi in THF at −78°C [8], and then radical deoxygenation of **4** (Bu_3SnH–AIBN in toluene) at refluxing temperature gave compound **5** [8].

Various reaction conditions have been used for selective cleavage of oxazolidine ring on similar compounds to the *N*-

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Boc aminoalcohol: 3 N HCl in MeOH at r.t. [9]; APTS in MeOH at r.t. [10]; Dowex 50 W × 8 in MeOH [8]. But these treatments were all proved to decompose of **5** into fully deprotected aminoalcohol or no reaction. Fortunately, deprotected product **6** was obtained using I_2 in MeOH at refluxing temperature which is a facile treatment for the cleavage of acetals and dithioacetals [11]. Finally, oxidation of **6** by using PDC in DMF, followed by flash chromatography, gave the target molecule **1**.

In conclusion, trifluoromethylated α-amino acid (**1**) was conveniently synthesized through trifluoromethylation of Garner's aldehyde, followed by deoxygenation, deprotection and oxidation.

3. Experimental

IR spectra were recorded pure as film for liquid and KBr plate for solid samples on a Shimadzu IR-440 Spectrometer. The ^{1}H NMR spectra were measured with $CDCl_3$ or $CO(CD_3)_2$ as the solvent and TMS as the internal standard. The ^{19}F NMR spectra were measured with the external CF_3COOH as the standard and with upfield shifts positive using a Varian EM-360L spectrometer at 56.4 MHZ. The MS were recorded by means of a HP5989A mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Garner's aldehyde was prepared from L-Serine [4].

*3.1. (2R)-2,2-Dimethyl-4-(hydroxytrifluoromethyl)-methyloxazolidine-3-carboxylic acid tert-butyl ester (**3**)*

A mixture of **1** (1.145 g, 5 mmol) and TMS–CF_3 (12 ml, 6 mmol) in 10 ml of THF cooled to 0°C in an ice-bath was treated with 10 mg of TBAF, then the reaction mixture was warmed to room temperature and stirred for 24 h. Subsequently, TBAF (3.155 g, 10 mmol) was added, and the reaction mixture was stirred for another 24 h at room temperature. After usual work up, **3** (1.076, 70%) was obtained as the key intermediate. ^{19}F NMR (56.4 MHz, $CDCl_3$) δ −1.7 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41–3.82 (m, 5H), 1.68–1.41 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.59, 126.51, 94.93, 80.94, 69.52, 63.41, 57.29, 28.16, 26.43, 26.19, MS: 300 (M^+ + 1, 0.62), 299 (M^+, 0.60), 284 (M^+ − 15, 4.00), 244 (12.08), 288 (22.81), 184 (44.29), 57 (100); HRMS calcd. for $C_{11}H_{19}F_3NO_4$: 284.1110 (M^+–CH_3) found 284.1079; $[\alpha]^{20}$ −23.07 (*c* = −1.38, $CHCl_3$).

*3.2. (2R)-2,2-Dimethyl-4(phenoxythionocarbonyloxy-trifluoromethyl)methyloxazolidine-3-carboxylic acid tert-butyl ester (**4**)*

To alcohol **3** (1.49 g, 5 mmol) in THF (15 ml) at −78°C was added *n*-BuLi (3.55 ml, 5.69 mmol, 1.6 M in hexane) and then phenyl thionochloroformate (1.04 ml, 7.52 mmol) was added to the resulting mixture. The reaction mixture was stirred at −78°C for 40 min and then at room temperature for 1 h before quenched with $NaHCO_3$ (aqueous, 2 ml), the ether extracts were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (0–2% EtOAc–petroleum ether) afforded **4** (1.67 g, 77%) as a yellow oil. ^{19}F NMR (56.4 MHz, $CO(CD_3)_2$) δ −3.7 (s); ^{1}H NMR (300 MHz, $CO(CD_3)_2$) δ 7.58–7.50 (m, 2H), 7.43–7.38 (m, 1H), 7.23–7.16 (m, 2H), 4.55–4.50 (m, 1H), 4.28–4.20 (m, 3H), 1.65–1.38 (m, 15H); ^{13}C NMR (75 MHz, $CO(CD_3)_2$) δ 154.483, 130.849, 130.551, 128.032, 122.369, 94.759, 81.585, 78.701, 63.300, 56.475, 28.480, 27.333; MS: 436 (M^+ + 1, 0.2), 380 (2.60), 336 (14.61), 320(52.31), 57 (100); HRMS calcd. for $C_{19}H_{24}F_3NO_5S$: 435.1328, found: 435.1335; $[\alpha]^{20}$ 5.25° (*c* = −1.38, $CHCl_3$).

*3.3. (2R)-2,2-Dimethyl-4-((trifluoromethyl)-methyl)oxazolidine-3-carboxylic acid tert-butyl ester (**5**)*

A solution of thiono carbonate **4** (1 g, 2.3 mmol), Bu_3SnH (0.88 ml, 3.29 mmol) in toluene (10 ml) was placed in a reaction flask under nitrogen, then was added AIBN (75.6 mg, 0.45 mmol). The reaction mixture was heated at refluxing temperature for 2 h. After evaporation of the volatiles in vacuo, flash chromatography (0–2% EtOAc–petroleum ether) yielded **5** as a colorless oil (501 mg, 75%). ^{19}F NMR (56.4 MHz, $CDCl_3$) δ −3.8 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05–3.88 (m, 3H), 2.54–2.20 (m, 2H), 1.66–1.37 (m, 15H); MS: 268 (M^+ − 15, 4.48), 212 (27.32), 168 (32.50), 57 (100); HRMS calcd. for $C_{11}H_{17}F_3NO_3$(M^+–CH_3) 268.1161 found: 268.1132; $[\alpha]^{20}$ −6.59° (*c* = −1.38, $CHCl_3$).

*3.4. (2R)-2-(1-Hydroxy-3-trifluoromethylpropyl)carbamic acid tert-butyl ester (**6**)*

A solution of the acetal **5** (300 mg, 1.06 mmol) in 1.0% iodine in methanol (w/v) (30 ml) was refluxed for 24 h. After evaporation of the solvent in vacuo, flash chromatography (10–25% EtOAc–petroleum ether) gave **6** as a white solid (257 mg, 54%). ^{19}F NMR (56.4 MHz, $CO(CD_3)_2$) δ −14.7(s); ^{1}H NMR (300 MHz, $CO(CD_3)_2$) δ 6.15–6.28 (br, 1H), 3.98–3.92 (br, 1H), 3.65–3.46 (m, 2H), 3.18–3.10 (m, 1H), 2.65–2.35 (m, 2H), 1.38 (m, 9H); ^{13}C NMR (75 MHz, $CO(CD_3)_2$) δ 155.170, 80.00, 79.541, 64.465, 48.446, 35.666, 28.845; MS: 245 (M^+ + 2, 0.62), 244 (M^+ + 1, 0.89), 212 (4.24), 189 (28.87), 188 (40.30), 170 (13.99), 57 (100); HRMS calcd. for $C_{10}H_{16}F_3NO_3$: 243.1083, found: 243.1124; $[\alpha]^{20}$ +7.73 (*c* = 0.64, $CHCl_3$).

*3.5. (2R)-N-Boc-2-amino-4,4,4-trifluorobutanoic acid (**1**)*

A solution of **6** (30 mg, 0.12 mmol) and PDC (226 mg, 0.6 mmol) in DMF (1 ml) was stirred at room temperature for 15 h. Then 1 N HCl (0.5 ml) in H_2O (0.5 ml) was added.

The crude reaction mixture was extracted with EtOAc (3×5 ml). The extracts were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (0–10% MeOH–EtOAc) yielded **1** as a colorless solid (15 mg, 47%). ^{19}F NMR (56.4 MHz, $CO(CD_3)_2$) $\delta -13.7$ (s); ^1H NMR (300 MHz, $CO(CD_3)_2$) δ 4.20 (m, 1H), 3.58 (s, 1H), 2.96–2.46 (m, 2H), 1.32–1.38 (m, 9H); ^{13}C NMR (75 MHz, $CO(CD_3)_2$) δ 207.590, 156.785, 79.875, 79.795, 52.207, 36.467, 28.932; MS: 237 (M^+–HF, 1.81), 220 (0.99), 219 (4.82), 202 (16.00), 57 (100); HRMS calcd. for $C_9H_{14}F_3NO_4$: 257.0876, found: 257.0850; $[\alpha]^{20}+7.62°$ ($c=0.44$, $CHCl_3$).

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