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1-Amino-3,3-difluorocyclobutanecarboxylic acid

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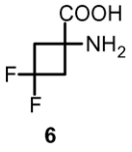
ABSTRACT

A new fluorinated analogue of 1-aminocyclobutane-1-carboxylate (ACBC) – 1-amino-3,3-difluorocyclobutanecarboxylic acid (**6**) – has been synthesized in six steps from acetone. The key step of the synthesis is a transformation of a ketone group into the CF_2-group using morpholino-sulphur trifluoride.

1. Introduction

1-Aminocyclobutane-1-carboxylic acid (ACBC) (Fig. 1) gained considered interest in medicinal chemistry in recent years. ACBC was shown to increase enzymatic stability of peptides, influence their biological properties [1,2], and promote certain peptide conformations [3,4]. Furthermore, ACBC moiety was found to be crucial for the activity of some aldose reductase inhibitors [5], as well as NK_1 antagonists [6]. ACBC-derivatives themselves are known to be highly active NMDA antagonists (**1**, [7]) and agonists (**2**, [8]). Moreover, due to efficient uptake by tumor cells and increased metabolic stability, boronated (**3**, [9]) and ^{18}F-labeled (**4**, **5**, [10–12]) analogues of ACBC are considered to be potential agents in boron neuron capture therapy (BNCT) and positron emission tomography (PET), respectively.

The substitution of hydrogen for fluorine in organic compounds is widely used to modify their physical, chemical, and biological characteristics [13,14]. In particular, application of this concept to amino acids is of significant practical interest, since fluorinated amino acids, upon replacing their natural analogues, have been used to improve pharmacological properties of peptides and peptidemimetics [15]. Surprisingly, despite a great potential of ACBC, there are only few fluorine-containing analogues of ACBC described in the literature [10–12,16]. Therefore, in this paper we wish to report the synthesis of a new fluorinated analogue of ACBC—the fluorinated amino acid **6**.



6

2. Results and discussion

The synthesis of **6** commenced from dibromide **7**, which was easily obtained from acetone by a one-step reaction (Scheme 1) [17]. Next, construction of the cyclobutane ring (**8**) was performed from **7** using the standard "malonate chemistry" approach [18–20]. Acidic cleavage of the ketal moiety in **8** gave ketone **9**. The key step of the synthesis – transformation of the ketone group in **9** into the CF_2-group to obtain **10** – smoothly proceeded at room temperature by using morpholino-sulphur trifluoride as a fluorinating agent. Thereafter, the obtained difluoride **10** was hydrolyzed under basic conditions to produce acid **11**. Finally, transformation of the carboxyl group into the amino group using the Curtius reaction, followed by cation-exchange chromatography afforded the target amino acid **6**.

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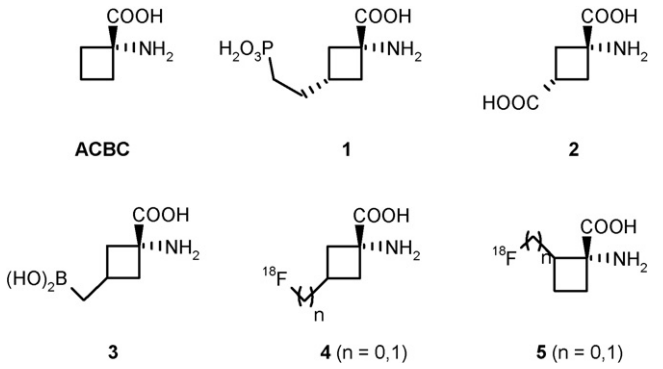
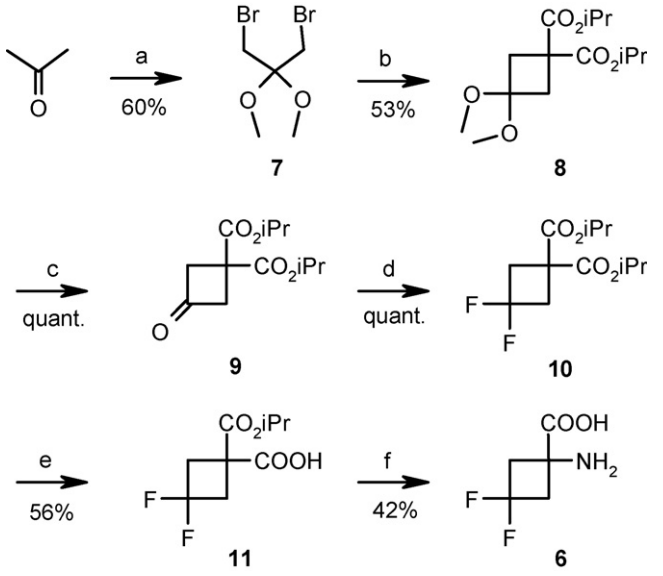


Fig. 1. Aminocyclobutane-1-carboxylic acid (ACBC) and its pharmacologically relevant derivatives **1**–**5**.



Scheme 1. Reagents and conditions: (a) 2.0 eq. Br_2, MeOH, 24 h; (b) 2.2 eq. $CH_2(CO_2iPr)_2$, 2.0 eq. NaH, DMF, 140 °C, 48 h; (c) HCl_{aq}, acetone, rt, 24 h; (d) 2.2 eq. $O(CH_2CH_2)_2NSF_3$, CH_2Cl_2, rt, 72 h; (e) (i) 1.0 eq. NaOH, water/MeOH, rt, 24 h; (ii) HCl_{aq}; (f) (i) 3.0 eq. $SOCl_2$, CH_2Cl_2, reflux, 3 h; (ii) 2.0 eq. NaN_3, water/acetone, 0 °C, 2 h; (iii) toluene, reflux, 2 h; (iv) 3N HCl, reflux, 6 h; (v) ion-exchange chromatography, "КУ-2".

3. Conclusions

We have developed simple and efficient strategy to a new fluorinated analogue of 1-aminocyclobutane-1-carboxylate (ACBC) – 1-amino-3,3-difluorocyclobutanecarboxylic acid (**6**). The synthesis commences from acetone and constitutes six steps. The key step of the synthesis is a transformation of the ketone group in **9** into the CF_2-group (**10**) using morpholino-sulphur trifluoride.

4. Experimental

4.1. General

Solvents were purified according to standard procedures. Compounds **7** and **8** were prepared as described previously [17,20]. All other materials were purchased from Fluka and Enamine. Melting points are uncorrected. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian Unity Plus 400 spectrometer (at 400.4, 100.7 and 376.7 MHz, respectively). Chemical shifts are reported in ppm downfield from TMS (^1H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. IR spectra were obtained on a Hewlett Packard UR 20 spectrometer. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument by chemical ionization (CI).

4.2. Preparation of diisopropyl 3-oxo-1,1-cyclobutanedicarboxylate (9)

The suspension of **8** (2.00 g, 6.9 mmol) in 6N HCl_{aq} (10 ml) was stirred for 24 h. The reaction mixture was extracted 3 times by CH_2Cl_2 (3 × 10 ml). Organic phase was separated, dried over Na_2SO_4, and evaporated at reduced pressure to produce ketone **9** (1.68 g, 6.9 mmol, 100%) as a colourless oil.

^1H NMR (400 MHz, $CDCl_3$), δ: 5.10 (m, J = 6.4 Hz, 2H, C*H*$(CH_3)_2$), 3.58 (s, 4H, CH_2), 1.26 (d, J = 6.4 Hz, 12H, CH(CH_3)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 200.95 (s, CH_2CO), 169.64 (s, *C*OO), 69.66 (s, *C*H$(CH_3)_2$), 54.98 (s, *C*H_2CO), 43.54 (s, *C*(COO*i*Pr)$_2$), 21.14 (s, CH(*C*H_3)$_2$).

MS (*m*/*z*): 243 (M+1).

4.3. Preparation of diisopropyl 3,3-difluoro-1,1-cyclobutanedicarboxylate (10)

$O(CH_2CH_2)_2NSF_3$ (1.40 g, 0.80 mmol, 2.2 eq.) was slowly added to a stirring solution of ketone **9** (900 mg, 3.7 mmol) in CH_2Cl_2 (10 ml) at 0 °C. The mixture was heated up to room temperature and stirred for 72 h. Thereafter, the reaction mixture was poured into a saturated solution of $NaHCO_{3aq}$. Organic phase was separated, and aqueous phase was washed 3 times with CH_2Cl_2 (3 × 10 ml). The combined organic phases were dried over Na_2SO_4, and gently evaporated at reduced pressure to produce **10** (970 mg, 3.7 mmol, 100%) as a yellowish oil.

^1H NMR (400 MHz, $CDCl_3$), δ: 5.10 (m, J = 6.4 Hz, 2H, C*H*$(CH_3)_2$), 3.07 (t, $^3J_{H\text{-}F}$ = 11.6 Hz, 4H, CH_2), 1.21 (d, J = 6.4 Hz, 12H, CH(CH_3)$_2$).

^{19}F NMR (377 MHz, $CDCl_3$), δ: −95.03 (quin, $^3J_{F\text{-}H}$ = 11.6 Hz, CF_2).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 169.35 (t, $^4J_{C\text{-}F}$ = 3.0 Hz, *C*OO), 117.60 (t, $^1J_{C\text{-}F}$ = 275.6 Hz, *C*F_2), 70.05 (s, *C*H$(CH_3)_2$), 42.81 (t, $^2J_{C\text{-}F}$ = 26.2 Hz, *C*H_2), 42.68 (t, $^3J_{C\text{-}F}$ = 11.1 Hz, *C*(COO*i*Pr)$_2$), 21.61 (s, CH(*C*H_3)$_2$).

IR (neat, ν cm^{-1}): 1731 (ν *C*=*O* in CO_2*i*Pr).

MS (*m*/*z*): 265 (M+1).

4.4. Preparation of 3,3-difluoro-1-(isopropoxycarbonyl)cyclobutanecarboxylic acid (11)

To a stirred solution of **10** (970 mg, 3.7 mmol) in MeOH (4 ml), a solution of NaOH (149 mg, 3.7 mmol, 1 eq.) in H_2O (5 ml) was added over 10 min at 0 °C. The reaction mixture was stirred at room temperature for 24 h and evaporated to remove the solvent. Water (20 ml) was added, and the mixture was washed 3 times with CH_2Cl_2 (3 × 10 ml). Organic phase was discarded, and the aqueous phase was acidified to pH 4 with concentrated HCl_{aq}. The suspension formed was extracted 3 times with EtOAc (3 × 10 ml), organic phase was separated, dried over Na_2SO_4, and evaporated at reduced pressure to produce **11** (457 mg, 2.1 mmol, 56%) as a yellowish oil, which crystallises upon standing. Mp = 61–62 °C.

^1H NMR (400 MHz, $CDCl_3$), δ: 9.40 (broad s, 1H, COO*H*), 5.05 (m, J = 6.4 Hz, 1H, C*H*$(CH_3)_2$), 3.10 (t, $^3J_{H\text{-}F}$ = 11.6 Hz, 4H, CH_2), 1.21 (d, J = 6.4 Hz, 6H, CH(CH_3)$_2$).

^{19}F NMR (377 MHz, $CDCl_3$), δ: −95.11 (AB system, d of quin, J = 199.8, 11.6 Hz, 1F, CF_2), −95.85 (AB system, d of quin, J = 199.8, 11.6 Hz, 1F, CF_2).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 175.50 (dd, $^4J_{C\text{-}F}$ = 4.0, 2.0 Hz, *C*OOH), 169.05 (dd, $^4J_{C\text{-}F}$ = 3.0, 2.0 Hz, *C*OOCH), 117.34 (t, $^1J_{C\text{-}F}$ = 275.9 Hz, *C*F_2), 70.79 (s, *C*H$(CH_3)_2$), 43.11 (t, $^2J_{C\text{-}F}$ = 26.2 Hz, *C*H_2), 42.68 (t, $^3J_{C\text{-}F}$ = 11.1 Hz, *C*COOH), 21.56 (s, CH(*C*H_3)$_2$).

IR (neat, ν cm^{-1}): 1732 (broad, ν *C*=*O*).

MS (*m*/*z*): 223 (M+1).

4.5. Preparation of 1-amino-3,3-difluorocyclobutanecarboxylic acid (6)

To a solution of monoacid **11** (200 mg, 0.9 mmol) in CH_2Cl_2 (5 ml), $SOCl_2$ (320 mg, 2.7 mmol, 3 eq.) was added. The reaction mixture was refluxed for 3 h and evaporated at reduced pressure. The residue was dissolved in acetone (5 ml) and cooled to 0 °C. To the obtained mixture a solution of NaN_3 (115 mg, 1.8 mmol, 2 eq.) in water (5 ml) was added and the reaction mixture was stirred at 0 °C for next 2 h. Thereafter, acetone was gently removed at reduced pressure and toluene (10 ml) was added. Water phase was discarded and organic phase was dried over Na_2SO_4 for 30 min. Next, toluene phase was refluxed for 2 h, evaporated, treated with 3N $HCl_{aq.}$ and the mixture formed was refluxed for 6 h. Evaporating of the solvent produced a white residue, which was purified by ion-exchange chromatography. White solid (57 mg, 0.38 mmol, 42%). Mp > 220 °C.

^{1}H NMR (400 MHz, D_2O), δ: 3.26 (m, 2H, C*H*H), 2.95 (m, 2H, CH*H*).

^{19}F NMR (377 MHz, $CDCl_3$), δ: −90.25 (d of quin, J = 196.0, 11.6 Hz, 1F, C*F*$_2$), −95.21 (d of quin, J = 196.0, 11.6 Hz, 1F, C*F*$_2$).

^{13}C NMR (100 MHz, D_2O), δ: 173.21 (dd, $^4J_{C\text{-}F}$ = 2.0, 1.0 Hz, *C*OOH), 115.0 (dd, $^1J_{C\text{-}F}$ = 273.9, 277.9 Hz, *C*F$_2$), 61.32 (s, *C*(NH$_2$)-COOH), 42.01 (t, $^2J_{C\text{-}F}$ = 25.2 Hz, *C*H$_2$).

MS (m/z): 152 (M+1).

Anal. Calcd. for $C_5H_7F_2NO_2$: C, 39.74%; H, 4.67%; N, 9.27%. Found: C, 39.53%; H, 4.32%; N, 9.45%.

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