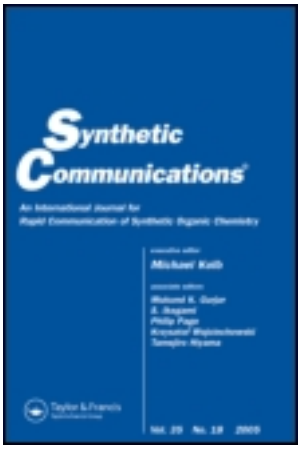

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A Practical Synthesis of 3,3-Difluorocyclobutane Carboxylic Acid

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A Practical Synthesis of 3,3-Difluorocyclobutane Carboxylic Acid

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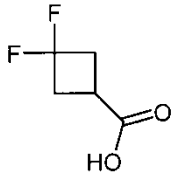
Abstract: We reported a straightforward, three step synthesis of 3,3-difluorocyclobutane carboxylic acid.

Keywords: 3,3-Difluorocyclobutane carboxylic acid, synthesis, lipophilicity

The synthesis of fluorinated compounds is of interest in the pharmaceutical industry because replacement of hydrogen by fluorine has the potential to modify potency, acidity or basicity, lipophilicity and metabolic stability with a minimal influence on steric size.[1]

We recently wished to prepare 3,3-difluorocyclobutane carboxylic acid (**1**), which we hoped might act as a bio-isostere of cyclohexane carboxylic acid (**2**) and 4,4-difluorocyclohexane carboxylic acid (**3**), with lower lipophilicity.



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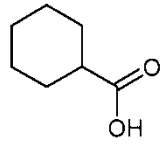

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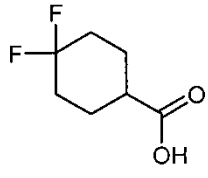
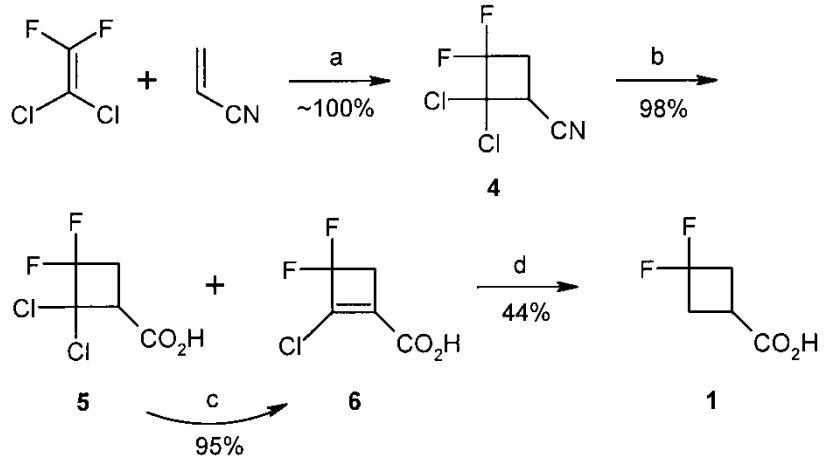


3

clogP =	0.09 ± 0.45	1.77 ± 0.19	0.86 ± 0.44	Ref. [2]

Received in the USA 4 November 2004
Address correspondence to M. Jonathan Fray, Discovery Chemistry Department, Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, UK. E-mail: jonathan.fray@pfizer.com



Scheme 1. Reagents and conditions: a) neat, autoclave, 160°C; b) HCl, H_2SO_4, 140°C; c) KOH, 20°C; d) H_2 (40 bar), Pt/C, CH_2Cl_2.

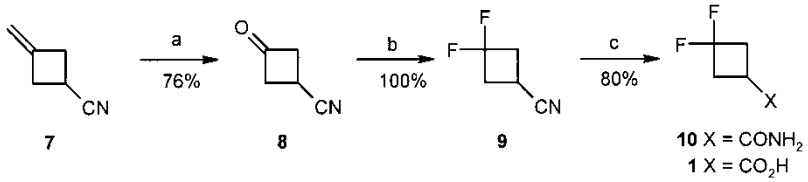
The preparation of **1** has been described by Dolbier[3] (Scheme 1). A 2 + 2 cyclo-addition reaction between 1,1-dichloro-2,2-difluoroethene and acrylonitrile afforded **4**, which was hydrolyzed under acidic conditions to give a mixture of **5** and **6**. Base treatment readily converted **5** into **6**. Hydrogenation of **6** over platinum on charcoal gave **1** in moderate yield.

We were reluctant to employ this route due to the toxicity of acrylonitrile[1] and the fact that it has been known to polymerize violently on heating.[4] In addition, 1,1-dichloro-2,2-difluoroethene is a low-boiling chlorofluorocarbon (CFC) whose use and availability is restricted due to environmental concerns. We therefore devised an alternative synthesis (Scheme 2) based on that reported for 3,3-difluoro-1-methylcyclobutane carboxylic acid.[5]

Commercially available 3-methylenecyclobutane carbonitrile **7**[6] was oxidized to the ketone **8**,[7] in good yield. Compound **8** was readily isolated as a colorless crystalline solid. Oxidative cleavage of the alkene in **7** using catalytic ruthenium trichloride proved superior to using catalytic osmium tetraoxide (2.5 mol%) and sodium metaperiodate (Et_2O/H_2O, 20°C, 18 h, 60% yield). Ketone **8** gave difluorocyclobutane carbonitrile **9**[2],[8] in almost quantitative yield on treatment with two equivalents of diethylaminosulfur trifluoride (DAST) in dichloromethane. We also briefly investigated the use of *bis*(2-methoxyethyl)aminosulfur trifluoride (BAST, "Deoxo-Fluor") as it has

[1]The material safety data sheet lists the following hazards: highly flammable, very toxic (EU definition), may cause cancer, causes burns, severe irritant.

[2]This paper reports the same transformation may be achieved using sulfur tetrafluoride, but the yield was not reported.



Scheme 2. Reagents and conditions: a) cat. $RuCl_3$, $NaIO_4$, $H_2O/MeCN/CH_2Cl_2$, 5–20°C; b) Et_2NSF_3, CH_2Cl_2, 0–20°C; c) NaOH, H_2O/MeOH, 20–60°C.

been reported to be more thermally stable than DAST.[9] Unfortunately, the reaction of **8** with BAST in tetrahydrofuran (THF) afforded a multicomponent mixture by thin layer chromatography (TLC). This was somewhat surprising and may be related to the fact that BAST was purchased as a 50% solution in THF and the hydrogen fluoride generated in the reaction may have caused polymerization of the solvent. The fluorination has not been attempted in dichloromethane solvent.

Nitrile **9** was then allowed to react with 2M aqueous sodium hydroxide in methanol at room temperature for 2 days followed by heating to 60°C for a further 4 hours. Acidic workup and extraction with dichloromethane gave **1** in 80% yield (from **8**) accompanied by a small amount (10%) of the intermediate 3,3-difluorocyclobutane carboxamide **10**.[3] When we attempted to accelerate the nitrile hydrolysis by heating the reaction mixture to reflux immediately, a multicomponent mixture resulted. It is possible that **9** undergoes a number of fragmentation reaction pathways if heated with base. Thus, prolonged exposure to hydroxide at room temperature is needed to ensure conversion to the carboxamide, which would appear to be hydrolyzed cleanly on heating.

CONCLUSION

We report a straightforward, three-step synthesis of 3,3-difluorocyclobutane carboxylic acid that is suitable for preparing multigram quantities.

EXPERIMENTAL

Melting points were determined using open glass capillary tubes and a Buchi B-545 melting point apparatus and are uncorrected. Spectroscopic data were recorded on a Perkin-Elmer 983 (IR), Finnigan Mat. Navigator [LRMS, either positive (ES^+) or negative (ES^-) electrospray mode], and Varian

[3]After 2 days at room temperature an approximately 70:30 mixture of **1** and **10** was formed.

Unity Inova-400 (^{1}H NMR 400 MHz) instruments and are consistent with the assigned structures. Combustion analyses were performed by Exeter Analytical (UK) Limited, Uxbridge, Middlesex. Reactions were performed under an atmosphere of dry nitrogen. Chromatography employed silica gel (Kieselgel 60, 230–400 mesh, from E. Merck, Darmstadt). Kieselgel 60 F_{254} plates from E. Merck were used for TLC, and compounds were visualized using 5% aqueous potassium permanganate solution. The DAST and BAST (50% solution in THF) were purchased from Sigma-Aldrich and Apollo Scientific, respectively.

3-Oxo-cyclobutanecarbonitrile, 8

Sodium meta periodate (4.1 eq., 284 g, 1.32 mol) was added portion-wise (over 30–45 minutes) to a cold (5°C) solution of 3-methylenecyclobutanecarbonitrile **7** (30 g, 370 mmol) and ruthenium trichloride monohydrate (2.2 mol%, 1.5 g, 7.23 mmol) in a mixture of dichloromethane:acetonitrile:water (645 mL: 645 mL: 945 mL). The reaction mixture was stirred using an overhead stirrer at room temperature for 18 hours. Upon consumption of all starting material [TLC: diethyl ether:pentane (1:1)], the organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic extracts were filtered through a pad of silica gel, and the pad was washed with dichloromethane. The filtrate was dried over magnesium sulfate and evaporated under reduced pressure to afford **8** as a colorless solid (23.4 g; 76%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 3.23 (1H, m, C***H***-CN), 3.57 (4H, m, C***H***$_2$CO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.2, 120.3, 50.9,17.2. IR (neat) υ_{max} 1715 cm^{-1}.

3,3-Difluorocyclobutanecarbonitrile, 9

Caution: Diethylaminosulfur trifluoride reacts exothermically with water to liberate hydrogen fluoride. It should not heated as it may decompose violently above 90°C. Diethylaminosulfur trifluoride (Aldrich, *neat*, 63.25 mL, 2 eq., 392 mmol) was added dropwise to a cold (0°C) solution of ketone **8** (23 g, 242 mmol) in dichloromethane (380 mL). The mixture was allowed to warm to room temperature and was stirred for 18 h. Upon consumption of all starting material (TLC: pentane:ether 2:1), the reaction mixture was poured slowly into ice-cold saturated aqueous sodium hydrogen carbonate (400 mL). The organic layer was separated and the aqueous solution extracted with dichloromethane (2 × 200 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was carefully removed under reduced pressure (rotary evaporator, 50 mmHg, water bath at 10°C) to afford **9** as a brown oil (28 g; quantitative). The crude product was taken on to the next step without further purification.

^{1}H NMR (400 MHz; $CDCl_3$) δ 2.98 (5H, m, ring protons). ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.4 (t, $^{1}J_{CF} = 271$ Hz, ***C***F_2), 115.2 (s, CN), 40.6 (t, 2C, $^{2}J_{CF} = 25$ Hz, $2 \times$ ***C***H_2), 11.9 (dd, $^{3}J_{CF} = 16$, 7 Hz, ***C***HCN). ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.0 (1F, d, $J = 190$ Hz), -98.0 (1F, d, $J = 190$ Hz). IR (neat) υ_{max} 2976 (C-H), 2247 (C≡N) cm^{-1}.

3,3-Difluorocyclobutanecarboxylic Acid, 1 and 3,3-Difluorocyclobutanecarboxamide, 10

To a solution of **9** (30 g, 256 mmol) in methanol (260 mL) sodium hydroxide pellets (12.5 g, 1.2 eq., 312 mmol) followed by water (120 mL) were added and the resulting mixture was stirred at room temperature for 72 h. The mixture was then warmed to 60°C and stirred for a further 3 hours. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was taken up in water (30 mL) and washed with ethyl acetate (2×30 mL). The combined ethyl acetate extracts were concentrated under reduced pressure to give the amide **10**, as an off-white solid (3.5 g, 10%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (5H, m, ring protons), 5.45 (2H, bs, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5 (s, C═O), 118.9 (dd, $^{1}J_{CF} = 268$, 268 Hz (rounded to nearest 1 Hz), ***C***F_2), 38.9 (t, $^{2}J_{CF} = 24$ Hz, 2C, $2 \times$ ***C***H_2), 27.65 (dd, $^{3}J_{CF} = 14.5$, 5 Hz, ***C***HCONH2). m/z (APCI$^+$) 136 (M + H$^+$, 100%), (APCI$^-$) 135 (M, 100%). IR (neat) $\upsilon_{max.}$ 3351, 3175 (NH), 1628 (C═O) cm^{-1}. The aqueous phase was then acidified to pH∼1 with 2M hydrochloric acid and extracted with dichloromethane (3×50 mL) and diethyl ether (2×50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent concentrated in vacuo. The brown residue was dissolved in a mixture of diethyl ether:pentane (2:1) and passed through a pad of silica gel (40–63 μ). The filtrate was concentrated under reduced pressure to afford an off-white solid. Recrystallization from diethyl ether/pentane afforded **1** (27.6 g, 80%), m.p. 48.6–49.5°C; [lit. m.p. 48–50°C].[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (4H, m, $2 \times$ C***H***$_2$), 3.05 (1H, m, C***H***-CO_2H), 11.4 (1H, bs, CO_2***H***). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1 (s, C═O), 118.6 (dd, $^{1}J_{CF} = 269$, and 270 Hz, ***C***F_2), 38.8 (t, $^{2}J_{CF} = 25$ Hz, $2 \times$ ***C***H_2), 26.7 (dd, $^{3}J_{CF} = 14$ and 8 Hz, ***C***HCO_2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.0 (1F, d, $J = 190$ Hz), -98 (1F, d, $J = 190$ Hz). m/z (ES$^-$) 135 (M-H$^+$, 80%), 271 (M_2-H$^+$, 100%). IR (neat) υ_{max}. 3350 (OH), 2968, 1704 (C═O) cm^{-1}. Found: C, 43.86; H, 4.43; $C_5H_6F_2O_2$ requires C, 44.13; H, 4.44%.

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