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Short communication

An efficient synthesis of 3,3-difluoro-pyrrolidine hydrochloride starting with 2-chloro-2,2-difluoroacetic acid

Lulin Wei [a,*], Teresa M. Makowski [a], Jennifer L. Rutherford [b]

[a] Chemical Research and Development, Pfizer Worldwide Research and Development, Eastern Point Road, PO Box 8013, Groton, CT 06340-8013, USA
[b] Lafayette College, Department of Chemistry, Hugel Science Center, Easton, PA 18042, USA

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ABSTRACT

A facile and fluorination-free synthesis of 3,3-difluoropyrrolidine hydrochloride (**3**), an important synthon in the synthesis of biologically active compounds, is reported. The seven-step synthesis starts from the commercially available 2-chloro-2,2-difluoroacetic acid (**1**) in a three-step telescoped process that produces crystalline *N*,*N*-diethyl-2,2-difluoro-3-hydroxy-4-nitrobutanamide (**2**). A convenient and high-yielding reductive nitromethylation of **2** followed by a catalytic hydrogenation/cyclization sequence and borane reduction affords **3** in good yield and purity.

1. Introduction

The introduction of a gem-difluoro moiety in a pharmaceutical agent can modify its biological activity, pharmacodynamism and metabolism and has gained popularity over the years [1–3]. Indeed, a *gem*-difluorocyclohexane was incorporated in maraviroc, the active ingredient of Selzentry™, a CCR5 inhibitor for the treatment of HIV [4]. The fluorination of ketones with (diethylamido)sulfur trifluoride (DAST) pioneered by Middleton [5] has been the leading method used for the synthesis of this type of fluorinated building blocks. Over the years, a number of alternatives to DAST have been reported to address safety concerns [6–8] and several new synthetic methods have attempted to address these issues [9,10].

The alternative to the preparation of fluorinated compound is to elaborate starting materials already containing the fluorine moiety. Due to the ozone depleting effect of many fluorocarbons, increasingly tougher regulations have been imposed on fluorine-substituted compounds around the world [11]. Traditionally used building blocks for **3**, such as geminally difluoro-substituted butenes, are at risk to disappear.

The 3,3-difluoropyrrolidine **3** is a structural motif which has been used in the synthesis of a large number of important biologically active compounds including several dipeptidyl peptidase IV inhibitors [12–16]. The original approach reported for the synthesis of **3** employed DAST-mediated fluorination of 3-pyrrolidione derived from (2*R*)-4-hydroxypyrrolidine-2-carboxylic acid in a multi-step synthesis that included hazardous and expensive reagents [17]. To address these issues, Xu developed an alternative process which did not rely on the fluorination of a pyrrolidone and featured a Claisen rearrangement to establish the difluoro quarternary center [18]. This approach also provided a route to **3** from commercially available starting material, difluorochloroacetic acid (**1**).

During the course of development of a Pfizer candidate [19], we were presented with the challenge to investigate an efficient/cost effective process for the synthesis of **3**, a key building block for this candidate. We also selected **1** as the starting point of our synthesis but sought an alternative synthetic sequence.

2. Results and discussion

As shown in Scheme 1, our retrosynthesis aimed at achieving the goals of employing the inexpensive and readily available starting material **1** and avoiding the use of expensive and unstable fluorinating reagents such as DAST. It was hoped that conversion of **1** to a suitable protected γ-aminocarboxylic acid derivative (**4**) would lead to the desired lactam (**5**) upon deprotection, release of the free amine and intramolecular cyclization. Reduction of the carbonyl of **5** would then provide the requisite fluorinated pyrolidine (**3**).

An ester or an amide was considered as a suitable carboxylate derivative. From a literature survey [20,21] we decided to explore ethyl 2,2-difluoro-3-hydroxy-4-nitrobutyrate and *N*,*N*-diethyl-2,2-difluoro-3-hydroxy-4-nitrobutanamide **2** as intermediates which would contain the carbon framework and the masked primary amine of our target. Upon preparation of both compounds,

* Corresponding author. Tel.: +1 860 441 8701; fax: +1 860 441 5540.
E-mail address: lulin.wei@pfizer.com (L. Wei).

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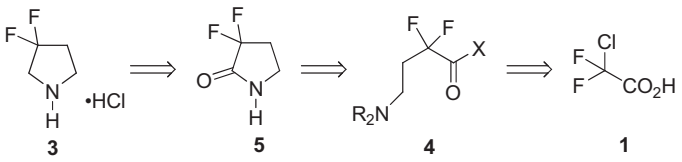
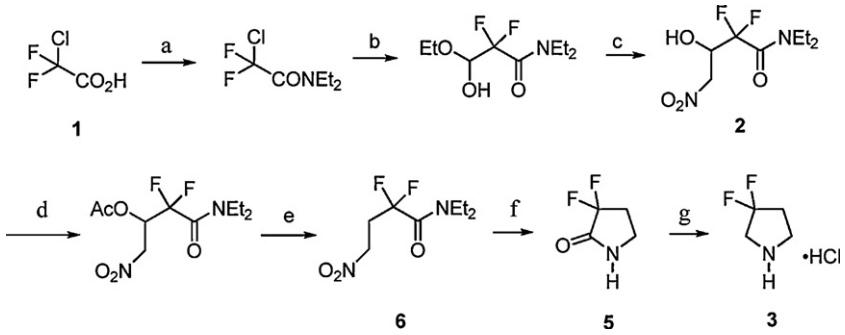


Scheme 1. Retrosynthesis of 3,3-difluoropyrrolidine (**3**).

amide **2** was selected for future work due to its crystallinity, ease of handling and facile purification.

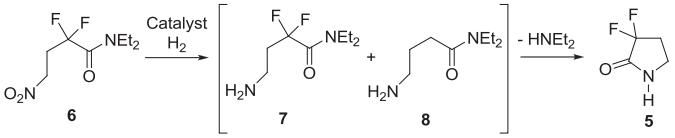
As shown in Scheme 2, compound **2** was readily prepared in a three-step process from chlorodifluoroacetic acid **1** using similar procedures as previously reported by Tsukamoto and Kitazume [20,21] and Mulliez et al. [22]. With **2** in hand, nitroalkane **6** was generated by reacting **2** with acetic anhydride with catalytic 4-dimethylaminopyridine. As expected, it was found that the acylation of **2** proceeded more rapidly with acetic anhydride when DMAP was used as a catalyst. The resulting acetate was telescoped to the next step and reacted with sodium borohydride to afford nitroamide **6** [23].

The conversion of **6** to lactam **5** required a more extensive study to identify conditions which provided high yielding and high quality material. Initial attempts at a transfer hydrogenation protocol produced only moderate yield (40%) [24]. Disappointed by the yield for this transformation, we engaged in a broad screen of catalysts known to be effective for the reduction of nitro groups. Aside from starting material (**6**) and product (**5**), two other compounds were observed; the uncyclized amide (**7**) and over-reduced alkane (**8**). As shown in Table 1, several variables



Scheme 2. Synthesis of 3,3-difluoropyrrolidine (**3**). (a) *N*,*N*-Diethylcarbamoyl chloride, Et_3N, room temp., 2 h; (b) ethyl toluene-*p*-sulfonate, Zn, DMF, 90 °C, 6 h followed by H_2SO_4, EtOH, 10 min; (c) $MeNO_2$, K_2CO_3, THF, room temp., 2 h; 55% for a–c; (d) Ac_2O/cat. DMAP; (e) 1 M $NaBH_4$ in EtOH, rt. 97% for d–e; (f) 5% Pt/C, JM 5R117, 70 psig, toluene; 90%; (g) BH_3·THF, 50 °C, 82%.

Table 1
Catalyst evaluation and reaction conditions for conversion of **6** to **5**.



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	Cat.	Composition	*T* °C	*P* psig	Sol.	% 6/5/7/8
1	A	5% Pd/C, 0.5% V/C	50	50	PhMe	93/7/0/0
2	B	1% Pt/C, 2% V/C	50	50	PhMe	92/8/0/0
3	C	5% Pt/C	50	50	PhMe	14/42/0/44
4	D	5% Pt(S)/C	50	50	PhMe	30/16/0/54
5	A	5% Pd/C, 0.5% V/C	70	70	PhMe	10/78/12/0
6	B	1% Pt/C, 2% V/C	70	70	PhMe	20/60/18/0
7	C	5% Pt/C	70	70	PhMe	12/88/0/0
8	E	5% Pt(S)/C	70	70	PhMe	22/78/0/0
9	F	5% Pt/C	70	70	PhMe	11/89/0/0
10	G	5% Pt/C	70	70	PhMe	14/86/0/0
11	C	5% Pt/C	70	70	PhMe	5/95/0/0
12	H	5% Pt/C	70	70	PhMe	23/77/0/0
13	D	5% Pt(S)/C	70	70	PhMe	5/95/0/0
14	E	5% Pt/AP	70	70	PhMe	4/96/0/0
15	C	5% Pt/C	60	70	MeOH	0/35/15/49
16	D	5% Pt(S)/C	60	70	MeOH	0/21/17/62
17	C	5% Pt/C	60	70	THF	10/63/24/3
18	D	5% Pt(S)/C	60	70	THF	9/59/32/0
19	C	5% Pt/C	60	70	DME	100/0/0/0
20	D	5% Pt(S)/C	60	70	DME	100/0/0/0
21	C	5% Pt/C	60	70	EtOAc	93/6/0/0
22	D	5% Pt(S)/C	60	70	EtOAc	90/8/0/0
23	C	5% Pt/C, 0.75 AcOH	70	70	PhMe	100/0/0/0
24	C	5% Pt/C, 0.5 AcOH	70	70	PhMe	82/18/0/0
25	C	5% Pt/C*	70	70	PhMe	1/99/0/0

All reductions unless noted were on the Biotage Endeavor™ for 24 h.
Catalyst source: A = Degussa CE105, B = Degussa CF105, C = JM 5R117, D = JM B106032-5, E = JM 5R94, F = JM 5R18, G = JM 5R103, H = JM 5R128 M.
* 5 g scale on Biotage Atlantis™.

were explored during our initial screen. While lower pressure did not appear effective (entries 1–4), the reaction seem to improve when conducted at 70 psig. Toluene was selected as the solvent of choice since the evaluation of alternative solvents did not lead to improvement (entries 15–22). Addition of acetic acid (entries 23–24) led to inhibition of the reaction. While several Pt/C sources proved to be suitable for this reaction in toluene at 70 °C and 70 psig, we narrowed our catalyst selection to the use of JM 5R117. While the screen afforded a 95:5 ratio of **5**:**6** (entry 11) it was further improved to 99:1 at a 5 g scale (entry 25). Better mixing of the gas, liquid, and solid phases in the larger reactor explains the difference between screening ratio of **5**:**6** and the isolated scaled ratio. The use of these conditions during the hydrogenation/cyclization produced the desired product **5** in a 90% isolated yield, which was then crystallized as a yellow solid from toluene.

The final part of the synthesis was accomplished by the reduction of lactam **5** with borane in THF at 50 °C. After the reduction, the reaction was quenched with dry MeOH followed by 4 M HCl in dioxane to hydrolyze the six-membered borazine derivative as well as to convert the volatile free base 3,3-difluoropyrrolidine to its HCl salt. The title compound **3** was isolated in good yield (82%) and excellent quality [25].

3. Conclusion

In conclusion, an efficient synthesis of 3,3-difluoro-pyrrolidine hydrochloride starting from the commercially available chlorodifluoroacetic acid (**1**) in about 40% overall yield was developed. The route involves 7 synthetic steps which upon telescoping led to a process containing only four isolations. An extensive catalyst screen identified preferred conditions for the reduction of the nitroalkyl moiety followed by subsequent cyclization to the 5-membered ring lactam (**5**) which was further reduced to the pyrrolidine (**3**) using borane-THF.

4. Experimental

4.1. General information

Melting points were determined on a capillary apparatus and were uncorrected. Solvents and reagents were reagent grade, obtained from commercial sources and used without further purification. Zinc powder purchased from Aldrich was freshly activated according to literature method [22]. All reactions were carried out in oven dried glassware under nitrogen. NMR spectra were run in $CDCl_3$ on a Bruker 400 MHz instrument and recorded at the following frequencies: proton (^{1}H, 400 MHz), carbon (^{13}C, 100 MHz). Chemical shifts (δ) are reported in ppm and coupling constant (J) in Hz. Compound **2** was prepared by formylation of α,α-difluorinated Reformatsky reagent and reaction with nitromethane, using known literature procedures [20–22]. Elemental analyses were performed by Intertek USA, Inc. using a Perkin-Elmer 2400 Elemental Analyzer.

4.2. Preparation of N,N-diethyl-2,2-difluoro-4-nitrobutanamide (6)

A solution of *N*,*N*-diethyl-2,2-difluoro-3-hydroxy-4-nitrobutanamide **2** (7.2 g, 30 mmol), DMAP (183 mg, 1.5 mmol), Ac_2O (3.33 g, 3.1 ml, 32.7 mmol), and ether (75 ml) was stirred at room temperature for 4 h and concentrated. A solution of $NaBH_4$ (2.25 g, 59.5 mmol) in EtOH (60 ml) was added dropwise to the above nitroacetate at 0 °C and the solution was stirred at room temperature overnight. The reaction was quenched with 1 N HCl (100 ml). Ethanol was evaporated and the aqueous layer was extracted with ethyl acetate (3× 100 ml). The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated to afford a crude mixture of **6** (6.5 g, 97%) which was used in the next step without further purification. The analytically pure sample was prepared by chromatography on silica gel (Merck silica gel 60, 40–63 μm) (heptanes/EtOAc, 5:1 as eluent) to give a light yellow oil ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3H, J = 7.0 Hz, NCH_2CH_3), 1.13 (t, 3H, J = 7.0 Hz, NCH_2CH_3), 2.80–2.92 (tt, 2H, J = 16.6 Hz, 7.03 Hz, CH_2CF_2), 3.26–3.30 (q, 2H, J = 7.0 Hz, 7.0 Hz, NCH_2CH_3), 3.41–3.45 (q, 2H, J = 7.0 Hz, 7.0 Hz, NCH_2CH_3), 4.55–4.58 (t, J = 7.0 Hz, 2H, O_2NCH_2); ^{13}C NMR ($CDCl_3$) δ 12.1 (CH_3), 14.0 (CH_3), 32.5 (t, J = 24.5 Hz, CH_2CF_2), 41.4 (NCH_2), 41.7 (NCH_2), 69.0 (O_2NCH_2), 118.0 (t, J = 257.8 Hz, CF_2), 161.3 (t, J = 28.3 Hz, CO). Elemental analysis: calcd for $C_8H_{14}F_2N_2O_3$: C, 42.86; H, 6.29; N, 12.49. Found: C, 42.90; H, 6.44; N. 12.32.

4.3. Preparation of 3,3-difluoropyrrolidin-2-one (5) using transfer hydrogenation

To a solution of crude **6** (5 g, 22 mmol) in MeOH (200 ml) was added 10% Pd on carbon (2.32 g, 2.18 mmol), ammonium formate (6.19 g, 98 mmol) under N_2 at room temperature. The mixture was heated at 45–50 °C overnight and cooled to room temperature. The catalyst was removed by filtration. The filtrate was concentrated and re-dissolved in THF (50 ml). The resulting mixture was heated at 50 °C overnight. The solution was concentrated and residue was purified by column chromatography (3/5 EtOAc/heptane followed by EtOAc) to afford 3,3-difluoropyrrolidin-2-one (**5**) (1.0 g, 40%) as light-yellow crystalline solid (40%). Mp 68–71 °C; ^{1}H NMR ($CDCl_3$) δ 2.49 (tt, 2H, J = 15.2, 6.4 Hz), 3.43 (tq, 2H, J = 6.4 Hz, 1.2 Hz), 8.18 (br, s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.4 (t, J = 23.0 Hz), 36.7 (t, J = 3.8 Hz), 117.8 (t, J = 249.4 Hz), 167.0 (t, J = 30.7 Hz); the data was in accordance with the reported data from an alternative synthesis [24].

4.4. Preparation of 3,3-difluoropyrrolidin-2-one (5)

To a solution of crude **6** (5 g, 22 mmol) in toluene (50 ml) was added 5% Pt/C (Johnson Matthey type 5R117). The reaction mixture was purged with nitrogen 4 times (pressurize to 50 psig and vent) and with hydrogen 4 times. The reaction was then heated to 70 °C, pressurized to 70 psig and hydrogenated for 16 h. The reaction was filtered through Celite to remove the catalyst, washed with toluene (10 ml), and concentrated to about 5 ml to precipitate **5** as a yellow solid (2.4 g, 90%).

4.5. Preparation of 3,3-difluoropyrrolidine HCl (3)

To a solution of 3,3-difluoropyrrolidin-2-one (**5**) (0.36 g, 30 mmol) in dry THF (4 ml) under N_2 was added borane in THF (10 ml of 1 M solution) dropwise. The reaction mixture was stirred at 50 °C for 4 h, cooled to 0 °C, quenched with dry MeOH (1.5 ml) followed by a 4 M solution of hydrogen chloride in 1,4-dioxane (5 ml, 20 mmol). The mixture was warmed to 50 °C for 1 h, concentrated and then treated with 1 ml of toluene to afford 3,3-difluoropyrrolidine hydrochloride (**3**) (0.35 g, 82%): ^{1}H NMR (CD_3OD) δ 3.72 (t, 2H, J = 11.9 Hz), 3.60 (t, 2H, J = 7.8 Hz), 2.60 (m, 2H). This NMR data was in accordance with the reported data from an alternative synthesis [18].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2011.08.009.

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