Synlett J. Giacoboni et al. Letter

Novel Approach toward 3,3-Difluoropiperidines from Easily Available Starting Materials and Synthesis of a New Phosphodiesterase Inhibitor

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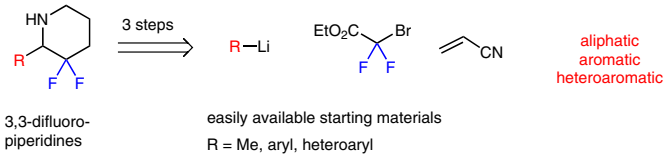

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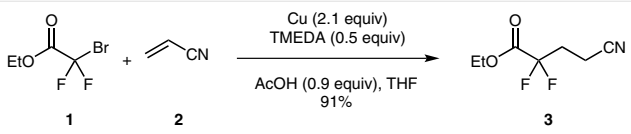
Abstract A novel methodology for the synthesis of 3,3-difluoropiperidines has been developed. The target compounds are prepared in three steps using a robust protocol and simple starting materials. The incorporation of the fluorine is achieved by using the cheap and easily available ethyl 2-bromo-2,2-difluoroacetate as building block. Using this methodology, a new potent in vitro phosphodiesterase 2A (PDE2A) inhibitor containing the functionalized fluorinated piperidine scaffold has been prepared.

Key words fluorine, piperidine, ethyl 2-bromo-2,2-difluoroacetate, reductive amination, phosphodiesterase

While fluorine-containing natural products are rare,[1] synthetic fluorinated compounds are widely used in a variety of fields due to the fact that molecules containing fluorinated groups often display unique properties that cannot be accomplished using other elements. Carbon–fluorine bonds have been incorporated in pharmaceuticals,[2–5] agrochemicals,[6,7] materials,[8,9] and tracers for positron emission tomography.[10,11] The introduction of fluorine into biologically active molecules can make them more bioavailable, improve metabolic stability, change the pK_a, and increase the strength of a compound's interaction with a target protein. At the same time, functionalized piperidines are common scaffolds in medicinal chemistry and they are present in many natural occurring and synthetic biologically active compounds.[5]

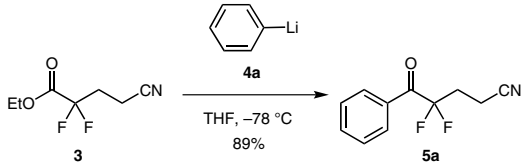
In this context, we here disclose a novel methodology for the synthesis of 3,3-difluoro-2-substitued-piperidines[12] that proceeds in good yields and that avoids the use of reactive fluorine sources.

Our synthetic strategy started from ethyl 4-cyano-2,2-difluorobutanoate (**3**), a versatile building block that can be prepared using the methodology reported by Lee et al.[13,14] starting from the commercially available ethyl 2-bromo-2,2-difluoroacetate (**1**) and acrylonitrile (**2**, Scheme 1). In our hands, the reaction proceeded well under mild conditions and in multigram scale.



Scheme 1 Multigram synthesis of building block **3**

This common intermediate **3** was easily functionalized and 4,4-difluoro-5-oxo-5-phenylpentanenitrile (**5a**) was obtained by addition of phenyl lithium **4a** (Scheme 2). Using 1.1 equivalents of the organolithium reagent in THF at –78 °C only minor amounts of diarylated products were observed resulting in a very satisfactory 89% yield. On the contrary, the reaction with the Grignard reagent phenyl magnesium bromide **4b** resulted in a lower conversion, and it was affected by the formation of other side products.

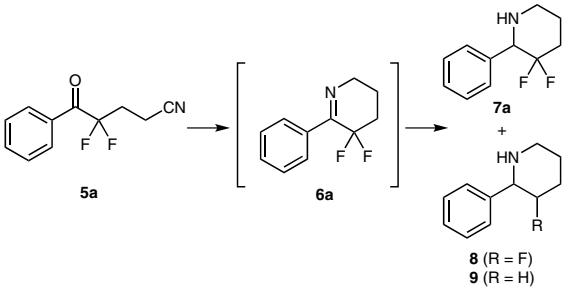


Scheme 2 Functionalization of intermediate **3** with organolithium reagent **4a**

The last step in the synthesis of fluorinated piperidines was a one-pot reduction of the nitrile group and subsequent reductive amination to form 3,3-difluoro-2-phenylpiperidine **7a** (Table 1). Initial attempts to reduce the nitrile in the H-Cube using Pd/C or PtO_2 did not yield any

product (Table 1, entries 1 and 2) while Raney nickel was quickly identified as a more promising catalytic system. Using methanol as solvent, at 50 °C and 50 bar of hydrogen, slow conversion of the nitrile into the amine **6a** and substantial formation of several defluorinated species were observed. After adding $NaBH_4$ to the crude reaction mixture, the desired product **7a** was finally isolated. However, the poor conversion and the concomitant formation of the undesired 3-fluoro-2-phenylpiperidine (**8**) and 2-phenylpiperidine (**9**) limited the yield to only 30% (Table 1, entry 3).[15] The yield of the hydrogenation from **5a** to intermediate **6a** could not be improved by extending the reaction time because the higher conversion was negatively compensated by a more extensive formation of the defluorinated side products. Using a mixture of acetic acid/methanol and lowering the flow to 0.2 mL/min to increase the residence time on the catalyst led to the formation of the difluorinated piperidine **7a** in good chemical yield (Table 1, entry 4). In order to accelerate the overall reaction and minimize the formation of the undesired defluorinated piperidines, acetic acid was tested as a solvent. In this reaction media, using a flow of 1 mL/min under 5 bar of hydrogen the product **7a** was obtained in 86% yield (Table 1, entry 5).

Table 1 Screening of Hydrogenation Conditions at the H-Cube for the One-Pot Reduction–Reductive Amination Reaction[a]



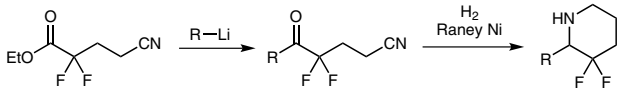
Entry	Catalyst	Solvent	*T* (°C)	*P* (bar)	Flow (mL/min)	Yield (%)[b]
1	Pd/C (10%)	MeOH	70	50	1	–
2	PtO_2	MeOH	21	10	1	–
3	Raney Ni	MeOH	50	50	1	30[c,d]
4	Raney Ni	MeOH–AcOH (1:1)	21	1	0.2	70[d]
5	Raney Ni	AcOH	50	5	1	86

[a] Reaction conditions: reaction performed using H-Cube continuous-flow hydrogenation, with sealed disposable cartridges, **5a** [0.01 M].
[b] Isolated yield after column chromatography.
[c] The reduction stops at intermediate **6a**. Yield determined after reduction with $NaBH_4$ (see Supporting Information).
[d] Formation of defluorinated piperidines **8** and **9** observed in the crude mixture.

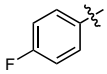
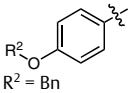
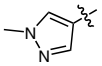
A drawback of using acetic acid is that the catalyst cartridge of the H-Cube deteriorates over time limiting the chance of upscaling the reaction.[16] Therefore, to further extend the applicability of this methodology we investigated whether the reduction could be performed also in batch mode. Using the Raney nickel catalyst in acetic acid under 5 bar of hydrogen in the autoclave, the desired product was isolated in 45% yield after one hour at room temperature. Although the yield is only moderate, it is a viable alternative to the use of the H-Cube.

Finally, we tested the scope of this two-step transformation and a diverse series of 3,3-difluoropiperidines could be prepared (Table 2). The various organolithium reagents were purchased as a solution from commercial suppliers or prepared in situ from the corresponding brominated aromatics and heteroaromatics.[17] The addition of (4-fluorophenyl)lithium proceeded very well (81% yield), and the intermediate **5b** was hydrogenated to produce the corresponding difluorinated piperidine **7b** in 68% yield (Table 2, entry 2). An electron-donating group such as 4-benzyloxy did not have a negative effect on the reaction, and the intermediate **5c** could be obtained in good yield under the same reaction conditions. During the hydrogenation, the benzyl protecting group was also cleaved and the 4-(3,3-difluoropiperidin-2-yl)phenol (**7c**) was isolated in 79% yield (Table 2, entry 3).[18] Notably, this approach works efficiently also for the preparation of heteroaryl-substituted piperidines.

Table 2 Scope of the Two-Step Preparation of 3,3-Difluoropiperidines from the Common Intermediate **3**[19,20]



3 **5a–g** **7a–g**

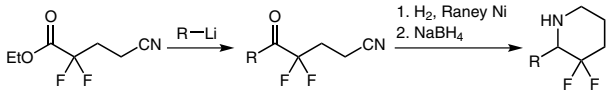
Entry	R	Product, yield (%)[a,c]	Product, yield (%)[b,c]
1		**5a**, 89	**7a**, 86
2		**5b**, 81	**7b**, 68
3		**5c** (R^2 = Bn), 72	**7c** (R^2 = H), 79
4		**5d**, 64[d]	**7d**, 89
5		**5e**, –[e]	**7e**, 40[f]

[a] General reaction conditions for the addition of the organolithium reagents: **3** (1 equiv, 0.3 M) in Et_2O, RLi (1.5 equiv) at –78 °C.
[b] Reaction performed using H-Cube continuous-flow hydrogenation, Raney Ni, **5a–e** [0.01 M] in AcOH, 1 mL/min, 5 bar, 50 °C.
[c] Isolated yield after column chromatography.
[d] Organolithium reagent prepared and added at –95 °C.
[e] Intermediate **5c** not purified due to the low boiling point.
[f] Overall yield for the transformation from **3** to **7e**. The crude piperidine was Boc-protected in situ and purified by flash chromatography; **7e** was isolated as HCl salt after deprotection.

Intermediate **5d** with a methylpyrazole functionality was efficiently ring-closed in high yield (Table 2, entry 4). The protocol is also applicable to the preparation of piperidines with alkyl side chains. The more volatile 4,4-difluoro-5-oxonitrile (**5e**) was not purified but after aqueous workup was directly reduced in the H-Cube (Table 2, entry 5).

A slightly modified procedure was applied in the presence of more sensitive heteroaromatic functionalities (Table 3). The addition of thiophen-2-yllithium to the ester **3** worked very well (87% yield). However, the final product **7f** could not be obtained using the standard conditions due to the reduction of the thiophene ring.[21] To minimize the undesired side reaction, the hydrogenation in the H-Cube was conducted at 20 °C (rather than the standard 50 °C). Under these milder conditions the nitrile group is reduced, but the reductive amination on the ketone does not occur. To complete the synthesis of the piperidine products, the reduction of the imine intermediate was obtained using $NaBH_4$ in methanol. With this updated protocol (no further optimisation was pursued), the final product **7f** could be obtained in 30% yield (Table 3, entry 1) and the racemic fluorinated analogue of the naturally occurring alkaloid anabasine **7g** was also isolated in 52% yield (Table 3, entry 2).

Table 3 Scope of the Three-Step Preparation of 3,3-Difluoropiperidines from the Common Intermediate **3**

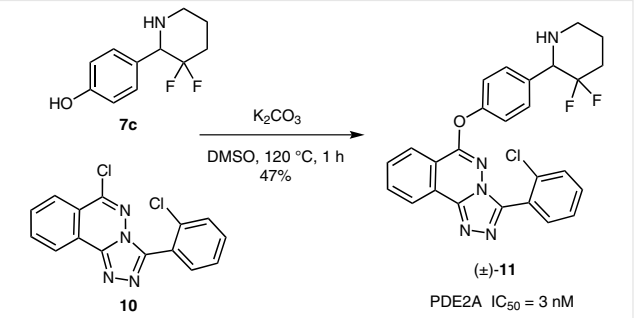


3 **5f–g** **7f–g**

Entry	R	Product, yield (%)[a,b]	Product, yield (%)[c,b]
1		**5f**, 87	**7f**, 30
2		**5g**, 71[d]	**7g**, 52

[a] General reaction conditions for the addition of the organolithium reagents: **3** (1 equiv, 0.3 M) in Et_2O, RLi (1.5 equiv) at –78 °C.
[b] Isolated yield after column chromatography.
[c] Reduction to the imine using H-Cube continuous-flow hydrogenation, Raney Ni, **5f–g** [0.01 M] in AcOH, 1 mL/min, 5 bar, 20 °C. After evaporation of the solvent, the crude intermediate was reduced with $NaBH_4$ (2 equiv) at 0 °C in MeOH.
[d] Organolithium reagent prepared and added at –95 °C.

As an example of the potential application of the 3,3 difluoropiperidines in drug discovery, the phenoxy-substituted product **7c** was easily incorporated in the structure of a novel nanomolar inhibitor of the phosphodiesterase PDE2A.[22,23] The new inhibitor **11** was obtained by nucleophilic aromatic substitution reaction of **7c** with 6-chloro-3-(2-chlorophenyl)-[1,2,4]triazolo[3,4-*a*]phthalazine (**10**, Scheme 3) and the IC_{50} was determined[20] to be fivefold more potent if compared with the nonfluorinated analogue.



Scheme 3 Incorporation of the piperidine **7c** into biologically active compounds; synthesis of potent in vitro PDE2A inhibitors

In conclusion, we developed a novel methodology for the preparation of functionalized 3,3-difluoropiperidines. Although this is a small study it demonstrates that the protocol is tolerant to a diverse range of substituents that have general application in drug discovery and the target molecules are prepared using easily available starting materials.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588313.

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(14) For examples of synthesis of fluorinated piperidines starting from 2-bromo-2,2-difluoroacetate, see: (a) Surmont, R.; Verniest, G.; Thuring, J. W.; Macdonald, G.; Deroose, F.; De Kimpe, N. *J. Org. Chem.* **2010**, *75*, 929. (b) Moens, M.; Verniest, G.; De Schrijver, M.; ten Holte, P.; Thuring, J. W.; Deroose, F.; De Kimpe, N. *Tetrahedron* **2012**, *68*, 9284.

(15) Formation of side products with mass corresponding to **8** and **9** was detected by LC–MS.

(16) Incompatibility of the catalyst cartridge with acetic acid as solvent is reported in the user manuals for H-Cube.

(17) For a detailed description of the preparation of the organolithium reagents, see Supporting Information.

(18) The hydrogenation of **5c** could also be conducted in batch mode using an autoclave. The benzyl protecting group was stable under these reaction conditions (see Supporting Information) and the fluorinated piperidine **7h** (R^2 = Bn) was isolated in 42% yield.

(19) **General Experimental Procedures for the Addition of the Organolithium Reagents to 4-Cyano-2,2-difluorobutanoate (3)**

To a solution of ethyl 4-cyano-2,2-difluorobutanoate (**3**, 1 equiv, 0.3 M) in Et_2O was added dropwise a solution of commercially available organolithium (1.1 equiv) at –78 °C. After 2 h the reaction was quenched with an aq sat. solution of NH_4Cl, EtOAc was added, and the phases were separated. The aqueous phase was further extracted twice with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, concentrated in vacuo, and purified using silica gel chromatography to provide the desired product.

4,4-Difluoro-5-oxo-5-phenylpentanenitrile (5a)

The title compound **5a** (1.51 g, 5.02 mmol, 89% yield) was obtained according to the general procedure starting from a solution of ethyl 4-cyano-2,2-difluorobutanoate (**3**) in Et_2O (5.56 mmol, 0.3 M) and a commercially available 1.8 M solution of **4a** in *n*-dibutyl ether (3.45 mL, 6.21 mmol) at –78 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.17–8.12 (2 H, m), 7.69–7.66 (1 H, m), 7.54–7.51 (2 H, m), 2.71–2.68 (2 H, m), 2.66–2.58 (2 H, m). ^{19}F NMR (471 MHz, $CDCl_3$): δ = –101.1 (t, *J* = 16.0 Hz). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 187.8 (C, t, *J* = 31.6 Hz), 135.0 (CH, s), 131.4 (C, t, *J* = 3.32 Hz), 130.4 (CH, t, *J*= 3.4 Hz), 128.9 (CH, s), 118.1 (C, s), 120.0–116.0 (CF_2, t, *J* = 255.8 Hz), 30.0–29.6 (CH_2, t, *J* = 23.5 Hz), 10.7–10.5 (CH_2, t, *J* = 6.71 Hz).

(20) **General Experimental Procedures for the Reduction–Reductive Amination Reaction**

A solution of **5** in acetic acid (0.01 M) was reduced using H-Cube Pro® (ThalesNano) continuous-flow hydrogenation system; CartCart Raney nickel THS01112; Temperature T = 50 °C and the flow rate of 1 mL/min. After full conversion of the starting material (reaction followed by LC–MS), the solvent was removed in vacuo, and the product was purified by flash column chromatography.

3,3-Difluoro-2-phenylpiperidine (7a)

The title compound **7a** (81 mg, 0.411 mmol, 86% yield) was obtained according to the general procedure starting from a solution of **5a** in AcOH (100.0 mg, 0.478 mmol, 0.01 M). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.46–7.43 (2 H, m), 7.38–7.32 (3 H, m), 3.89–3.84 (1 H, d, *J* = 23.2 Hz), 3.25–3.19 (1 H, m), 2.83–2.75 (1 H, m), 2.59 (1 H, br s), 2.35–2.25 (1 H, m), 1.95–1.80 (3 H, m). ^{19}F NMR (471 MHz, $CDCl_3$): δ = –99.5 (d, *J* = 240.7 Hz), –117.5 (m). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 135.9 (C, s), 128.8 (CH, s), 128.3 (CH, s), 128.1 (CH, s), 121.1–117.8 (CF_2, dd, *J* = 244.9, 248.0 Hz), 66.0–65.4 (CH, dd, *J* = 26.5, 22.0 Hz), 45.9 (CH_2, s), 33.8–33.4 (CH_2, dd, *J* = 25.9, 21.7 Hz), 24.0–23.9 (CH_2, d, *J* = 9.9 Hz). ESI-HRMS: *m/z* calcd for $C_{11}H_{13}F_2N$ [MH^+]: 198.1089; found: 198.1090.

(21) Formation of a product with mass corresponding to 2-butyl-3,3-difluoropiperidine was observed by LC–MS.

(22) For the determination of the PDE2A activity, see: Redrobe, J. P.; Jørgensen, M.; Christoffersen, C. T.; Montezinho, L. P.; Bastlund, J. F.; Carnerup, M.; Bundgaard, C.; Lerdrup, L.; Plath, N. *Psychopharmacology* **2014**, *231*, 3151.

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