Synthesis of aminomethylated 4-fluoropiperidines and 3-fluoropyrrolidines†

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Received 22nd February 2010, Accepted 6th April 2010
First published as an Advance Article on the web 21st April 2010
DOI: 10.1039/c003380d

A short and efficient synthesis of 4-aminomethyl-4-fluoropiperidines and 3-aminomethyl-3-fluoropyrrolidines is described. These fluorinated azaheterocycles are of specific interest as bifunctional building blocks for fluorinated pharmaceutical compounds. The key step of the synthetic pathway involves the regioselective bromofluorination of *N*-Boc-4-methylenepiperidine and 3-methylenepyrrolidine using $Et_3N.3HF$ and NBS.

Fluorinated azaheterocyclic compounds attract widespread attention as important components of pharmaceutical and agrochemical compounds. This is mainly due to the fact that the replacement of a hydrogen with fluorine often gives rise to drastic changes in biological activity due to the altered electronic distribution and changes in conformational properties.[1,2] The research dealing with the synthesis of site-specific fluorinated azaheterocyclic compounds has intensified considerably during the last decade and has resulted in numerous new synthetic approaches and new commercial applications in pharmaceutical chemistry and agrochemistry.[3–7] In particular, fluorinated pyrrolidines and piperidines, substituted with amino- or aminomethyl groups, have become increasingly popular as bifunctional building blocks towards bioactive compounds.

4-Fluorinated piperidines **1** (Fig. 1) are known as specific antagonists of T-type calcium channels and can be used for the treatment of neurological and psychiatric diseases.[8] The numerous papers concerning 4-aminomethyl-4-fluoropiperidines, such as compound **2**, as selective 5-HT1A agonist further emphasize the possibilities of these compounds in the development of new antidepressants[9] and analgesics.[10] In addition, 3-fluoro-3-aminomethylpyrrolidines have been used in the search for new bioactive compounds, such as anticancer agents **3**[11] and antibacterial compounds, such as **4**.[12]

Despite the biological relevance of aminomethylated 4-fluoropiperidines and 3-fluoropyrrolidines, few synthetic methodologies have been developed over the years. Only two methods have been reported to synthesize 4-aminomethyl-4-fluoropiperidines. In a first strategy, 4-piperidones are transformed into (1-oxa-6-azaspiro[2.5]oct-6-yl)phenylmethanones[13] and then treated with

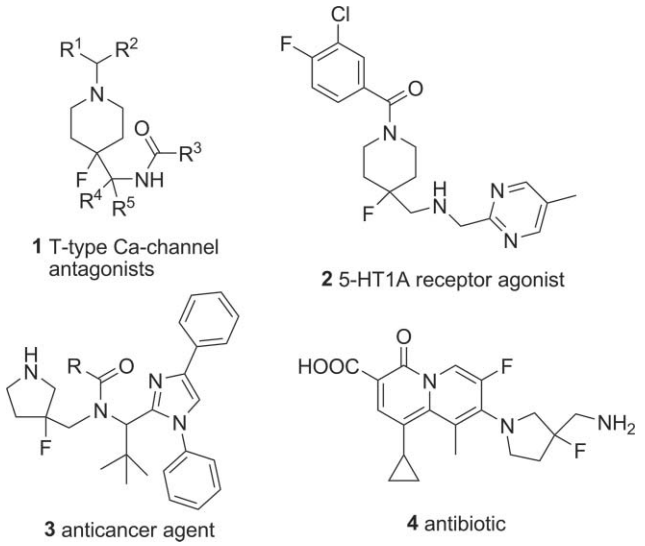

Fig. 1 Biologically active aminomethylated 4-fluoropiperidines and 3-fluoropyrrolidines.

an excess of HF.pyridine in order to effect a ring opening of the epoxide moiety. This sequence gives rise to 4-fluoro-4-hydroxymethylpiperidines, which can be used for the synthesis of the corresponding 4-aminomethyl derivatives *via* *O*-tosylation, followed by a Gabriel synthesis of the amine moiety.[14] A second method makes use of 4-fluoropiperidine-4-carboxylates, synthesized from piperidine-4-carboxylates *via* deprotonation by LDA and subsequent reaction with NFSI (*N*-fluorodibenzenesulfonimide).[15,16] Functional group transformation of the ester function finally leads to 4-fluoro-4-aminomethylpiperidines in 15% to 87% yield depending on the piperidine *N*-protecting group.[9,17] The main synthetic pathway towards 3-aminomethyl-3-fluoropyrrolidines, concerns the deoxofluorination of the cyanohydrins of *N*-protected 3-pyrrolidinones using DAST (diethylaminosulfur trifluoride) at −78 °C and subsequent reduction of the nitrile function towards the aminomethyl group.[18] As many reported methodologies either require difficult reaction conditions or make use of sensitive deoxofluorination reagents, there is a considerable interest in the development of generally applicable and efficient large scale syntheses of 4-aminomethyl-4-fluoropiperidines and 3-aminomethyl-3-fluoropyrrolidines. This paper describes the successful preparation of both classes of compounds *via* bromofluorination[19] of the double bonds of easily accessible 4-methylenepiperidines or 3-methylenepyrrolidines as a key step.

To establish a short and efficient synthesis of 4-aminomethyl-4-fluoropiperidines, commercially available 1-Boc-4-methylenepiperidine **5** was treated with *N*-bromosuccinimide

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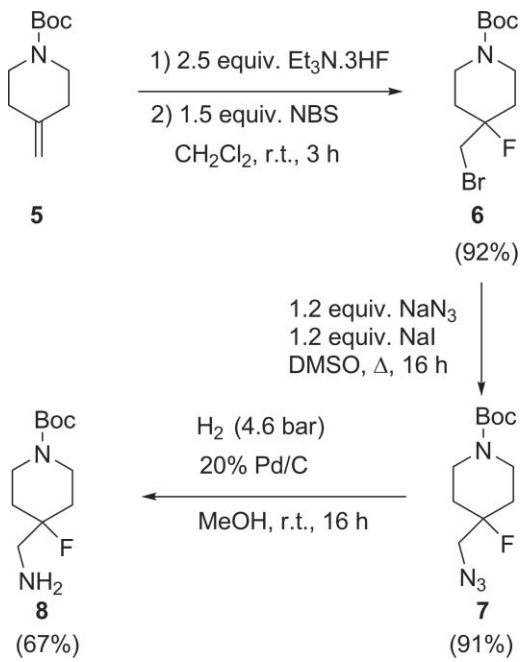
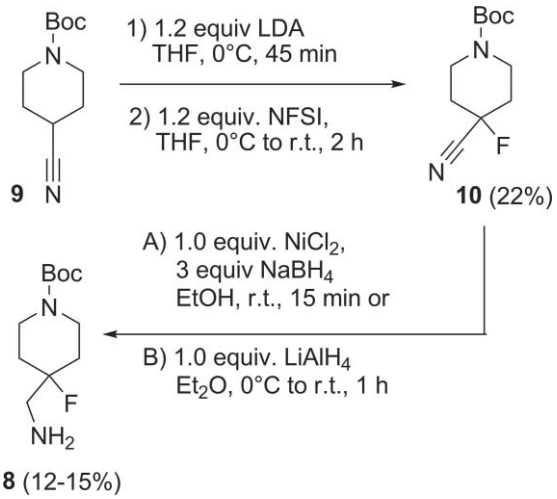
(NBS) and triethylamine trihydrofluoride in dry dichloromethane at room temperature during 3 h (Scheme 1). This bromofluorination reaction conveniently gave *tert*-butyl 4-bromomethyl-4-fluoropiperidine-1-carboxylate **6** in high yield, without the removal of the acid sensitive *N*-protecting group. It should be noted that the use of equimolar amounts of NBS and $Et_3N.3HF$ with respect to the starting material **5**, resulted in an incomplete conversion even after reaction for 15 h. Although the subsequent neopentylic displacement of bromine by ammonia in methanol (7 N) was not successful, even under pressure or under microwave conditions, an alternative route *via* substitution of the bromine atom by using sodium azide in the presence of sodium iodide in DMSO proceeded very smoothly and resulted in 4-azidomethyl-4-fluoropiperidine **7** in 91% yield. The obtained azide **7** was used without further purification in the Pd/C catalyzed hydrogenation reaction in methanol and gave rise to the desired 4-aminomethyl-1-Boc-4-fluoropiperidine **8** in 67% yield after purification *via* acid/base extraction. This three-step synthesis efficiently gives access to the desired 4-aminomethyl-4-fluoropiperidine **8** in 56% overall yield without the need for chromatographic purification of the intermediate bromomethyl- and azidomethylpiperidines **6** and **7**. The efficiency and ease of the reaction sequence clearly makes this an attractive route for the large scale preparation of **8**, which is of specific pharmaceutical interest. Next to the above described synthetic pathway to 4-aminomethyl-4-fluoropiperidine **8**, other routes towards aminomethylated 4-fluoropiperidines were also evaluated. At first, commercially available 1-Boc-4-cyanopiperidine **9** was deprotonated with LDA in THF at 0 °C and quenched with NFSI, yielding 1-Boc-4-cyano-4-fluoropiperidine **10** in a disappointing 22% yield (Scheme 2). In addition, also the subsequent reduction of the cyano function to the 4-aminomethyl group proceeded in low yield with either $LiAlH_4$ or $NaBH_4$ in the presence of $NiCl_2$. Obviously, this deprotonation/fluorination sequence is not suitable for the large scale preparation of piperidine **8**.

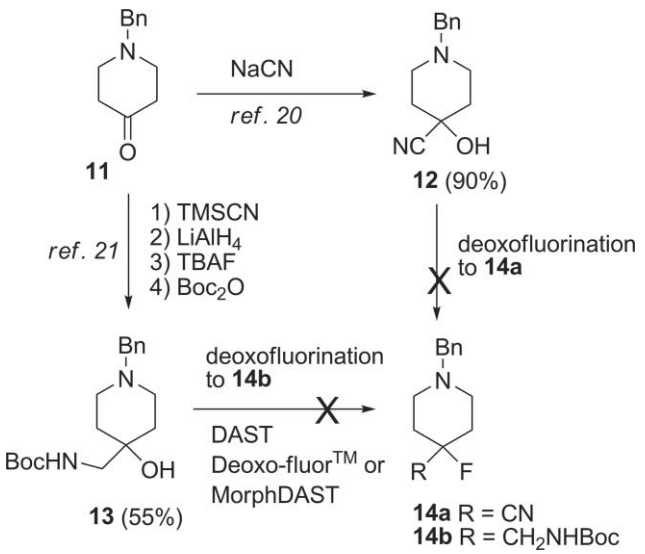


Scheme 1 Synthesis of 4-aminomethyl-4-fluoropiperidine **8**.



Scheme 2 Synthesis of 4-fluoropiperidine **8** *via* electrophilic fluorination.

To verify if a deoxofluorination strategy of 4-hydroxypiperidines could be used to synthesize 4-aminomethyl-4-fluoropiperidines, known compounds **12** and **13**,[20,21] which can be synthesized from piperidinone **11**, were subjected to reaction with DAST, morphDAST or di(2-methoxyethyl)amidosulfur trifluoride (Deoxo-fluor™) (Scheme 3). Unfortunately, all reaction conditions gave rise to complex reaction mixtures. These studies (Schemes 2 and 3) clearly demonstrate the value of the synthesis of piperidine **8** *via* bromofluorination of 4-methylenepiperidine **6** (Scheme 1).



Scheme 3 Attempted synthesis of fluoropiperidines *via* deoxofluorination of piperidinone **11**.

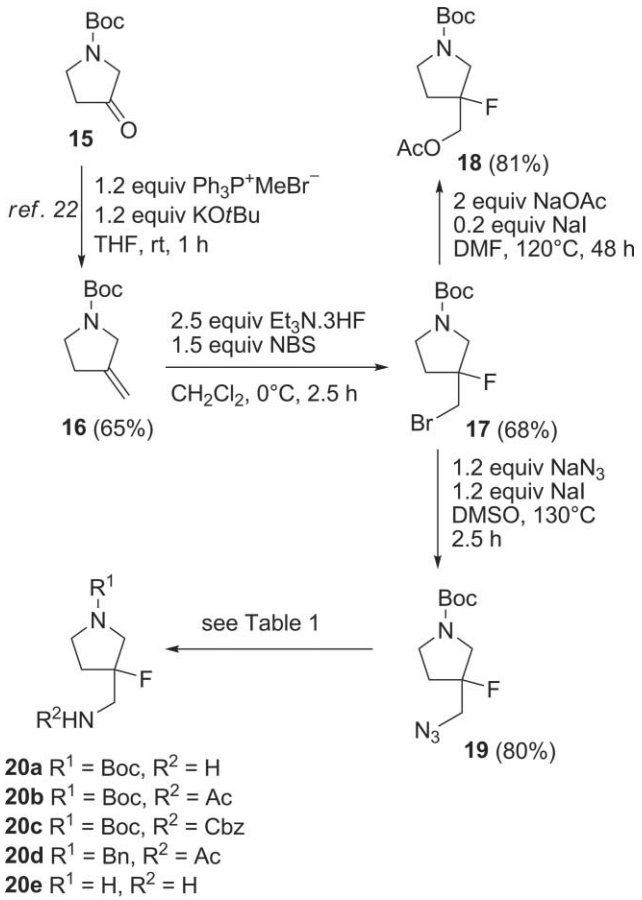
In addition to the synthesis of aminomethylated 4-fluoropiperidine **8**, the bromofluorination methodology was applied to synthesize various 3-aminomethyl-3-fluoropyrrolidines as important building blocks for bioactive compounds. For this purpose, 3-methylenepyrrolidine **16**, which can easily be obtained from 3-pyrrolidinone **15**,[22] was used as a starting material. The treatment of pyrrolidine **16** with triethylamine trihydrofluoride in the presence of NBS in dichloromethane at 0 °C for 2.5 h resulted in a regioselective bromofluorination

Table 1 Synthesis of various 3-aminomethyl-3-fluoropyrrolidines **20**

	R^1	R^2	Reaction conditions	Yield
1)	Boc	H	H_2 (4.9 bar), 10% Pd/C, MeOH, rt, 4.5 h	**20a** (90%)
2)	Boc	Ac	1) H_2 (4.9 bar), 10% Pd/C, MeOH, rt, 4.5 h; 2) excess Ac_2O, rt, 16 h	**20b** (82%)
3)	Boc	Cbz	1) H_2 (4.9 bar), 10% Pd/C, MeOH, rt, 4.5 h; 2) 1 equiv CbzCl, THF, rt, 4.5 h	**20c** (56%)
4)	Bn	Ac	1) H_2 (4.9 bar), 10% Pd/C, MeOH, rt, 4.5 h; 2) excess Ac_2O, rt, 16 h; 3) excess TFA, CH_2Cl_2, 0 °C, 7 h; 4) 1.2 equiv BnBr, 4 equiv Et_3N, CH_2Cl_2, rt, 5 h	**20d** (35%)
5)	H	H	1) H_2 (4.9 bar), 10% Pd/C, MeOH, rt, 4.5 h; 2) excess TFA, CH_2Cl_2, 0 °C, 7 h	**20e** (47%)[a]

[a] Compound **20e** was isolated as the double trifluoroacetic acid salt.

towards 3-bromomethyl-3-fluoropyrrolidine **17** in 68% after silica gel chromatography (Scheme 4). The nucleophilic substitution of the bromine atom was next evaluated using various nucleophiles. While the reaction of **17** with sodium methoxide resulted in complex mixtures due to dehydrofluorination, the reaction with the less basic sodium acetate yielded 3-acetoxymethyl-3-fluoropyrrolidine **18**, which can be regarded as a *N*- and *O*-protected 3-fluoro-3-hydroxymethylpyrrolidine, which is of interest in medicinal chemistry. For the synthesis of the corresponding 3-aminomethylpyrrolidines **20**, pyrrolidine **17** was treated with sodium azide in the presence of sodium iodide towards azidomethylpyrrolidine **19** and subsequently subjected to hydrogenation over Pd/C. This reaction sequence yielded the envisioned 3-aminomethyl-3-fluoropyrrolidine **20a** in 90% yield.



Scheme 4 Synthesis of 3-fluoropyrrolidines **20a–e**.

To enable the selective introduction of additional functionalities at both nitrogen atoms and to broaden the scope of reactions in which 3-aminomethyl-3-fluoropyrrolidine can be used as a building block, different *N*-protecting groups were introduced at both nitrogen atoms of pyrrolidines **20** (see Table 1). At first, the reaction of pyrrolidine **20a** with an excess of acetic anhydride or CbzCl resulted in the corresponding *N*,*N*-bisprotected pyrrolidines **20b** and **20c** (Table 1, entries 2 and 3). In addition, the reaction of *N*-Bocpyrrolidine **20b** with an excess of trifluoroacetic acid and subsequent standard *N*-benzylation gave rise to the corresponding *N*-benzylpyrrolidine **20d**. Fully *N*,*N*-deprotected 3-aminomethyl-3-fluoropyrrolidine **20e** was synthesized from **20a** *via* reaction with trifluoroacetic acid. The obtained pyrrolidine was precipitated from the reaction mixture as a double TFA salt, as evidenced by elementary analysis. It should be noted that in contrast to *N*,*N*-unprotected pyrrolidine **20e**, the ^{1}H NMR analysis of fluoropyrrolidines **20a–d** is complicated due to the hindered rotation of the carbamate or amide bonds in combination with H–F coupling causing extensive signal broadening.

Conclusions

In conclusion, a new synthesis of 4-aminomethyl-4-fluoropiperidine **8** and 3-aminomethyl-3-fluoropyrrolidines **20** *via* a bromofluorination reaction of the corresponding *exo*-methylene substituted piperidine or pyrrolidine was developed. Nucleophilic displacement of the bromine atom with sodium azide and subsequent azide reduction, smoothly resulted in the titled compounds in good overall yields. The efficiency and easy setup of the reaction sequence enables a large scale preparation of these building blocks, which are of considerable interest in pharmaceutical chemistry.

Acknowledgements

The authors are indebted to the Research Foundation – Flanders (FWO-Flanders), Ghent University (GOA, BOF) and Johnson & Johnson Pharmaceutical Research & Development, a Division of Janssen Pharmaceutica NV, for financial support.

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