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Practical Synthesis of Fluorinated Piperidine Analogues Based on the 2-Azaspiro[3.3]heptane Scaffold

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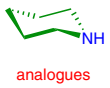

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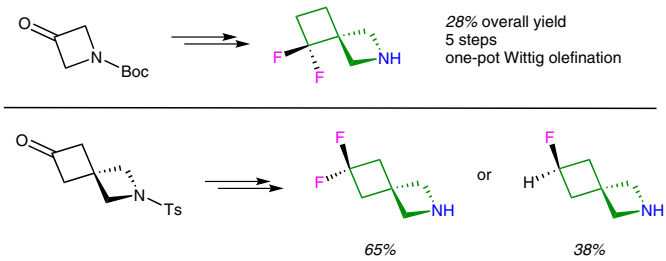

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Abstract The synthesis of a set of conformationally restricted fluorinated analogues of piperidine, based on a 2-azaspiro[3.3]heptane scaffold, is reported. Different pattern of fluorine substitution within the rigid skeleton make the analogues excellent candidates for use in drug design. The overall simplicity of the experimental procedures and the availability of inexpensive starting materials allow for multigram-scale syntheses of the described compounds.

Key words piperidine analogues, fluorinated building blocks, azaspiro[3.3]heptane, deoxofluorination, azetidine derivatives

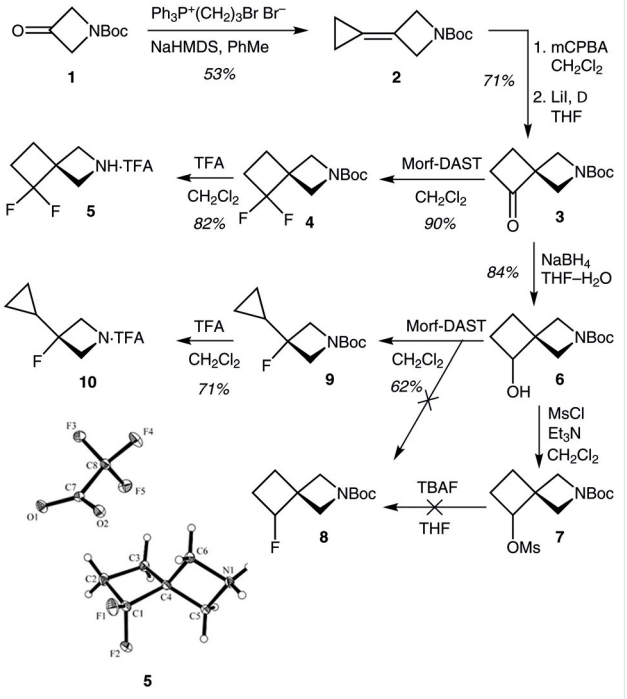
Among different trends in drug design, the introduction of fluorine-containing substituents proved to be one of the most useful,[1] and the use of nonaromatic, 3D-shaped building blocks is one of the most recent approaches.[2] Improvement in metabolic stability is the most prominent feature of fluorinated building blocks. Other beneficial properties associated with fluorination are increased solubility, permeability, potency, adjacent group pK_a modulation, and conformational control caused by a strong fluorine gauche effect.[3] Not surprisingly, fluorinated pharmaceuticals constitute a significant part of marketed drugs and agrochemicals. The use of rigid scaffolds in drug design also proved to be beneficial, and initially this led to a wide propagation of aromatic and heteroaromatic moieties among the drug candidates. Development of excellent methods for the synthesis and coupling of aromatic building blocks further popularize their use in medicinal chemistry. However, efforts to minimize toxicity, often associated with the presence of aromatic and heteroaromatic moieties, as well as the requirement for novelty and patentability have eventually led to an increase in the interest toward conformationally restricted, nonflattened, and nonaromatic building blocks.[4–6] It is reasonable to suggest that the availability of rigid, nonflattened and at the same time fluorinated building blocks would facilitate the drug discovery process, in particular, lead optimization.

Fluorinated piperidines[7,8] and their derivatives[9,10] have already attracted significant interest in the field of medicinal chemistry. Exchange of a fluorinated piperidine for the piperidine fragment has been extensively exploited to improve potency, bioavailability, and metabolic stability during hit-to-lead optimization.[11–16] Moreover, virtual absence of fluorine in living organisms allowed the use of fluorinated piperidine derivatives as a probe for metabolite tracing using ^{19}F NMR in cancer cells[17] as well as in vivo PET imaging.[18]

Azaspiro[3.3]heptane derivatives have been often considered as conformationally restricted analogues of piperidine with unique properties.[19] We have previously reported the synthesis and structural analysis of several spiro[3.3]heptane derivatives as aminocyclohexane analogues.[20,21] Herein, as a part of the strategy toward finding nonflattened, fluorinated building blocks we describe the synthesis of a set of 2-azaspiro[3.3]heptane-containing piperidine analogues.

Our general synthetic approach to the fluorinated 2-azaspiro[3.3]heptanes included preparation of corresponding ketones bearing a protected amino group as the starting reagents. Although an analogue of ketone **3** bearing a diphenylmethyl protecting group was previously used for the construction of the 5-oxo-2-azaspiro[3.3]heptane skeleton,[22] we decided to employ the *N*-Boc-protected derivative

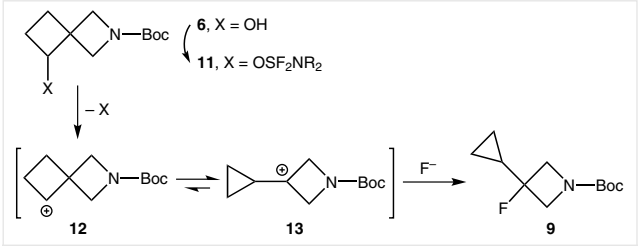
to avoid formation of possible byproducts during the removal of the diphenylmethyl moiety by hydrogenolysis. Other features of our synthesis of compound **3** are the use of cheap starting materials and the one-pot procedure for the Wittig olefination. We substituted commonly employed and rather expensive cyclopropylsulfonium tetrafluoroborate with the much cheaper (3-bromopropyl)triphenylphosphonium bromide that allowed for upscaling the protocol to a multigram scale.[23] The key transformation included a one-pot assembly of the cyclopropane ring by the intramolecular alkylation reaction, a formation of the corresponding ylide followed by the Wittig reaction. Subsequent epoxidation of the double bond in **2** and the rearrangement of the intermediate epoxide afforded **3** in 38% yield (Scheme 1).



Scheme 1 Synthesis of compounds **5** and **10** and X-ray structure of **5**. Thermal ellipsoids are shown with 30% probability

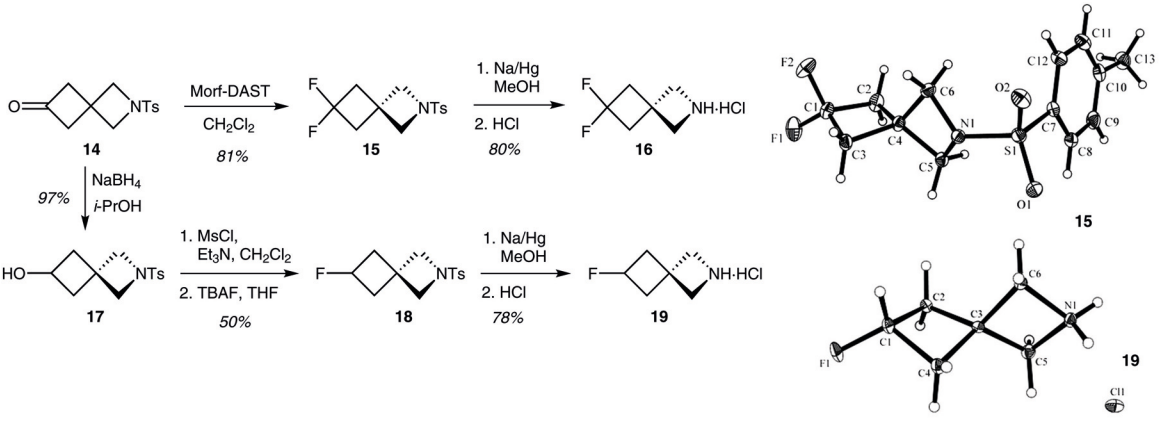
Treatment of spirocyclic ketone **3** with Morf-DAST led to a clean formation of difluoride **4**. Removal of the *N*-Boc protection with trifluoroacetic acid gave desired compound **5** in 28% overall yield starting from commercially available ketone **1**. The structure of trifluoroacetate **5** was confirmed by X-Ray analysis (Scheme 1). Initially, we considered compound **3** as a starting material for the synthesis of both difluoro- and monofluoro-substituted derivatives. Therefore, we synthesized *N*-Boc amino alcohol **6** by reduction of **3** with sodium borohydride. The alcohol was easily converted into mesylate **7**; however, nucleophilic substitution with the fluoride ion failed in our hands. Mesylate **7** proved to be quite resistant to the nucleophilic substitution, probably because of steric hindrance. Therefore, we switched to the deoxofluorination reaction of alcohol **6** using Morf-DAST. However, treatment of the alcohol with Morf-DAST led to the formation of rearrangement product **9** as the main product. No target compound **8** was observed in the crude mixture. Rearrangement product **9** was purified by column chromatography and characterized. The *N*-Boc protection was removed with trifluoroacetic acid yielding amine **10**.

The rearrangement of the alcohol **6** during the deoxofluorination reaction could be explained by dissociation of intermediate compound **11** with the formation of carbenium ion **12** (Scheme 2). Apparently, due to steric hindrance, the deoxofluorination reaction proceeded by an S_N1 mechanism rather than by S_N2. Secondary carbocation **12** could then undergo a reversible rearrangement to more stable tertiary carbenium ion **13**. Finally, addition of the fluoride ion gave 3-fluoro-3-substituted azetidine **9**.[24,25] Notably, no elimination product was detected. Previously, we observed a similar rearrangement of spiro[3.3]heptane-derived ketones and formation of the corresponding cyclopropanes in small amounts.[26]



Scheme 2 Possible rearrangement mechanism

Synthesis of amine **16** included deoxofluorination with MorfDAST of *N*-tosyl-protected amino ketone **14**,[27,28] followed by the tosyl group removal with sodium amalgam (Scheme 3). Our synthesis of **19** also started with protected amino ketone **14**; its reduction with sodium borohydride afforded amino alcohol derivative **17**. The fluorine substituent was then introduced by a nucleophilic substitution reaction via the corresponding mesylate. The moderate yield of this reaction could be rationalized taking into account that a significant amount of the corresponding alkene was formed as a result of the elimination reaction. Deprotection of the amino group in compound **18** finished the synthesis. The structures of compounds **15** and **19** were confirmed by X-ray analysis (Scheme 3).[29] The overall yields (calculated from ketone **14**) were 65% and 38% for the hydrochlorides **16** and **19**, respectively.



Scheme 3 Synthesis of amines **16** and **19** and their X-ray structures. Thermal ellipsoids are shown with 15% (**15**) and 30% (**19**) probability.

In conclusion, we reported a practical preparation of a set of fluorine-substituted amines based on the 2-azaspiro[3.3]heptane scaffold. The synthesized compounds could be considered as conformationally restricted fluorinated piperidine analogues. We also modified the procedure for the preparation of compound **3** using only easily available and cheap starting materials, thus enabling preparative scale synthesis of the reported amine. The synthesized compounds are expected to find applications in the field of medicinal chemistry and drug design.

Acknowledgment

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Supporting Information

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Primary Data

for this article are available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083 and can be cited using the following DOI: 10.4125/pd0077th.

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(23) ***tert*-Butyl 3-Cyclopropylideneazetidine-1-carboxylate (2)**
NaHMDS (1 M solution in THF, 312 mL, 312 mmol) was added to a suspension of (3-bromopropyl)triphenylphosphonium bromide (69.00 g, 148.70 mmol) in toluene (600 mL) under an Ar atmosphere at –30 °C. The orange solution was stirred for 2 h at room temperature, and then the solution of compound **1** (23.00 g, 134.35 mmol) in THF (100 mL) was slowly added dropwise to reaction mixture at –78 °C. The reaction mixture was stirred at –78 °C for 1 h, slowly warmed up to room temperature overnight, refluxed for 3 h, and poured into cold sat. aq NH_4Cl. The mixture was extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The resulting solid was washed with hexanes–EtOAc (7:1, 3 × 100 mL), and the combined organic extracts were evaporated. The residue was purified by column chromatography (hexanes–EtOAc = 7:1); yield 13.90 g (71.19 mmol, 53%); white solid; mp 90–93 °C. TLC: R_f = 0.37 (hexanes–EtOAc = 7:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.55–4.50 (m, 4 H), 1.44 (s, 9 H), 1.08–1.03 (m, 4 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.7, 116.9, 113.4, 91.4, 79.6, 28.5, 2.4. HRMS (EI): *m/z* calcd for $C_{11}H_{17}O_2N$ [M$^+$]: 195.1254; found: 195.1253.

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(29) The CCDC numbers 1451977–1451979 for compounds **5**, **15**, and **19** contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.