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Synthesis of 4-Substituted 3,3-Difluoropiperidines

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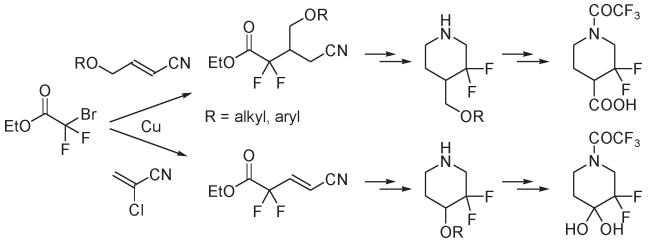

Synthetic strategies toward 4-substituted 3,3-difluoropiperidines were evaluated. 4-Alkoxymethyl- and 4-aryloxymethyl-3,3-difluoropiperidines were synthesized via 1,4-addition of ethyl bromodifluoroacetate to 3-substituted acrylonitriles in the presence of copper powder, followed by borane reduction of the cyano substituent, lactamization, and reduction of the lactam. This method was applied to establish the synthesis of N-protected 3,3-difluoroisonipecotic acid, a fluorinated γ-amino acid. 4-Benzyloxy-3,3-difluoropiperidine was prepared using an analogous methodology and was converted to N-protected 3,3-difluoro-4,4-dihydroxypiperidine, a compound with high potential as a building block in medicinal chemistry.

The unique properties of fluorine as a substituent in organic compounds have an undisputed effect on their bioactivity and have dramatically intensified the research in organofluorine chemistry. This is reflected by the numerous papers in this area as an answer to the increased need for new fluorinated building blocks for applications in agrochemistry and pharmaceutical chemistry.[1] Recently, we published convenient routes for the preparation of 3-aminomethyl-3-fluoropiperidines[2] and 3-alkoxy-4,4-difluoropiperidines,[3] and we introduced new entries toward valuable 2-substituted 3,3-difluoropiperidines via electrophilic α-fluorination of imines using *N*-fluorodibenzenesulfonimide (NFSI).[4] 4-Substituted 3,3-difluoropiperidines showed already their importance in medicinal chemistry; however, only limited synthetic pathways are available.[5] Focus was directed to a general synthetic route toward 4-substituted 3,3-difluoropiperidines with application to the synthesis of 3,3-difluoroisonipecotic acid, a new γ-amino acid and potential $GABA_A$ agonist.[6] Also 3,3-difluoro-4-piperidinone is a promising building block because 4-piperidones serve an important role as intermediates of bioactive piperidines.[7] In contrast to 3-fluoro-4-piperidinone,[8] only one synthetic route to 3,3-difluoro-4-piperidinone has been described recently via a Reformatsky reaction of ethyl bromodifluoroacetate, zinc, and ethyl 3-(benzotriazol-1-ylmethylbenzylamino)propioniate, followed by cyclization.[9] Deoxofluorination of 3-piperidinones is the most obvious way to synthesize 4-substituted 3,3-difluoropiperidines, although DAST ((diethylamino)sulfur trifluoride) is a reagent with limited stability and functional group tolerance and can induce rearrangements. Moreover, low yields were reported for the deoxofluorination of 4-substituted 3-piperidinones.[10] Highly substituted 3,3-difluoropiperidines have been synthesized for the preparation of anti-Alzheimer's agents and glycosidase inhibitors.[11,12] Earlier work from Beeler et al. resulted in a

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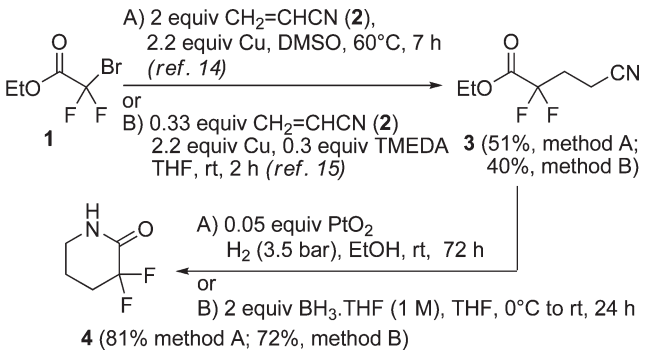
SCHEME 1. Synthesis of 3,3-Difluoro-2-piperidinone 4



synthesis of 4-hydroxy-4-phenyl-3,3-difluoropiperidine, a proneurotoxin, via a SmI_2-induced Reformatsky reaction of ethyl bromodifluoroacetate with 3-(*N*-methyl-*N*-benzylamino)-propiophenone, followed by cyclization to the 2-piperidinone and reduction of the lactam.[13] In the present report, ethyl bromodifluoroacetate was used as starting material to develop a general synthetic route to 4-substituted 3,3-difluoropiperidines, which is clearly lacking in the literature.

As a model study, the use of ethyl 4-cyano-2,2-difluorobutanoate **3** as a starting material for the synthesis of 3,3-difluoropiperidines was investigated. Ethyl 4-cyano-2,2-difluorobutanoate **3** was synthesized from ethyl bromodifluoroacetate **1** and acrylonitrile in the presence of copper in DMSO[14] or in THF in the presence of TMEDA (Scheme 1).[15] At first, various methods were evaluated to reduce selectively the nitrile function of compound **3**. Hydrogenation on Pd/C in ethanol did not result in any reduction of **3**, while the use of $NaBH_4$/$CoCl_2 \cdot 6H_2O$, $LiAlH_4$, or $BH_3 \cdot Me_2S$ gave complex mixtures. Upon platinum-catalyzed hydrogenation of nitrile **3** in ethanol for 3 days, spontaneous cyclization occurred to afford 3,3-difluoro-2-piperidinone **4** in 81% yield. Fortunately, a faster reduction was observed using 2 equiv of borane in THF at room temperature, resulting in piperidinone **4** in 72% yield after 24 h.

Having in hand an efficient method to access 3,3-difluoropiperidinone **4**, the above-described methodology was extended toward the synthesis of 4-alkoxymethyl-3,3-difluoro-2-piperidinones **7**, using 3-(alkoxymethyl)- and 3-(aryloxymethyl)acrylonitriles **5a**−**d**[16] as starting materials (Scheme 2). 3-Substituted acrylonitriles **5** were treated with ethyl bromodifluoroacetate **1** and copper in THF with TMEDA as an additive. In contrast to acrylonitrile **2**, the reaction of 3-alkyl-substituted acrylonitriles **5a**−**c** required reflux temperatures to complete the 1,4-addition reaction. In the case of the allyloxy derivative **5d**, the treatment with bromodifluoroacetate **1** and copper gave rise to complex mixtures. For the selective reduction of nitriles **6a**−**c**, the use of borane in THF was preferred over the PtO_2-catalyzed hydrogenation to avoid hydrogenolysis of the benzyloxy substituent of **6a**. After reduction of the nitrile of **6** at room temperature, spontaneous cyclization occurred, affording 3,3-difluoro-2-piperidinones **7** in 63−76% yields. The crystalline δ-lactams **7** were further reduced using 2 equiv of borane in THF at reflux temperature for 3 h, resulting in 4-alkyl-3,3-difluoropiperidines **8**. To cleave the obtained borane−amine complexes, compounds **8** were treated with Pd/C in methanol at room temperature before the final purification via flash chromatography or acid/base extraction.

Having in hand a good method for the synthesis of 4-benzyloxymethyl-3,3-difluoropiperidine **8a**, this compound was used to synthesize 3,3-difluoroisonipecotic acid. At first, *N*-H piperidine **8a** was protected at nitrogen with a trifluoroacetyl group resulting in piperidine **9**, which was subsequently O-debenzylated via Pd/C-catalyzed hydrogenolysis to give 3,3-difluoro-4-hydroxymethyl-1-(trifluoroacetyl)piperidine **10**. In contrast to various unsuccessful attempts to oxidize the hydroxymethyl group of **10** using ruthenium(IV) oxide, the use of CrO_3 afforded 3,3-difluoro-1-(trifluoroacetyl)-piperidine-4-carboxylic acid **11** in 55% yield.

In order to extend this methodology to 4-alkoxy-3,3-difluoropiperidines, which can serve as good precursors for the synthesis of the interesting 3,3-difluoro-4-piperidinone, ethyl bromodifluoroacetate was reacted with 2-chloroacrylonitrile **12** in the presence of copper in DMSO at 60 °C (Scheme 3). This reaction nicely gave rise to ethyl 4-cyano-2,2-difluoro-3-butenoate **13**, which occurred as a mixture of *E*- and *Z*-isomers (ratio 1:1). For spectroscopic purposes, these isomers were separated by column chromatography. The Michael acceptor ethyl 4-cyano-2,2-difluoro-3-butenoate **13** was considered as a good substrate for the synthesis of the target 3,3-difluoro-4-piperidinone. Because it is known that DBU efficiently catalyzes the 1,4-addition of alcohols to simple acrylonitriles under mild conditions,[17] it was decided to treat compound **13** with benzyl alcohol and a catalytic amount of DBU. The ideal catalytic load of DBU was found to be 0.2 equiv, affording 3-benzyloxy-4-cyano-2,2-difluorobutanoate **14** in 64% yield. Analogous to the synthesis of 4-alkoxymethyl-3,3-difluoropiperidines **8**, nitrile **14** was reduced using borane in THF, cyclized to 2-piperidinone **15**, and further reduced to 4-benzyloxy-3,3-difluoropiperidine **16** in good yields. Subsequently, the N-unsubstituted piperidine **16** was trifluoroacetylated toward difluoropiperidine **17** and O-debenzylated to give 3,3-difluoro-4-hydroxy-1-(trifluoroacetyl)piperidine **18**. Subsequently, alcohol **18** was oxidized using Dess−Martin periodinane to the corresponding 3,3-difluoro-4-piperidinone, which occurred as a hydrate **19**, in 56% yield. It was proven that this seven-step procedure is a convenient route for a multigram synthesis of 3,3-difluoro-4,4-dihydroxypiperidinone **19**. It should be noted that compound **19** cannot be synthesized via fluorination of 4-piperidinone, in contrast to the easily accessible 3-fluoro-4-piperidinone, which can be obtained via fluorination of the trimethylsilylenol ether of 4-piperidinone using

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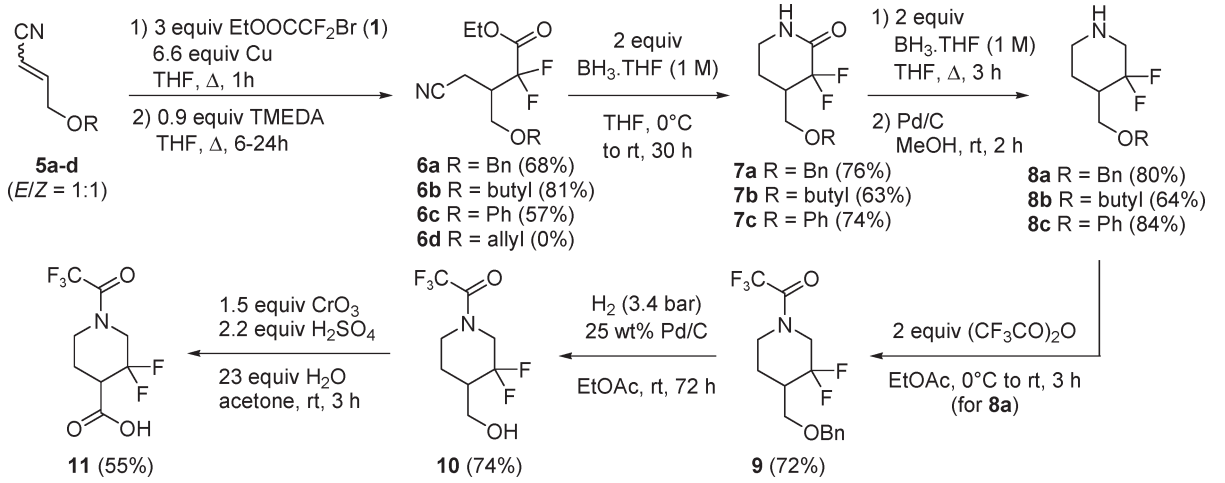
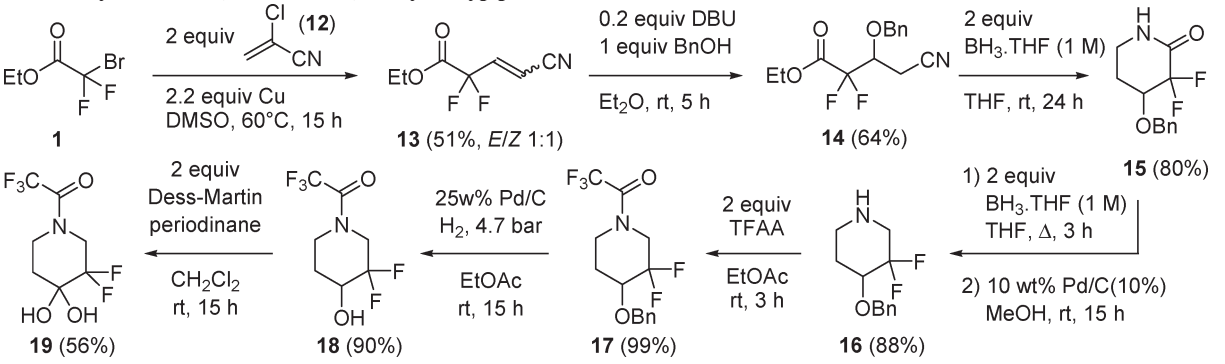
SCHEME 2. Synthesis of 4-Substituted 3,3-Difluoropiperidines 8 and Derivatization toward N-Protected 3,3-Difluoroisonipecotic Acid 11



SCHEME 3. Synthesis of 3,3-Difluoro-4,4-dihydroxypiperidine 19



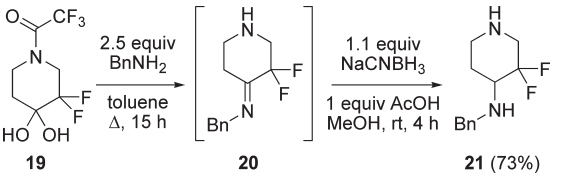
Selectfluor.[8] A second fluorination of 3-fluoro-4-piperidinone at the 3-position is problematic and results in mixtures of regioisomers.

To demonstrate the synthetic utility of difluoropiperidinone **19**, the synthesis of 4-amino-3,3-difluoropiperidine **21** was carried out. A one-step reductive amination of 3,3-difluoro-4,4-dihydroxypiperidinone **19** with benzylamine using $NaBH(OAc)_3$ resulted in a complex mixture containing starting material, 3-hydroxypiperidine **18**, and the corresponding N-deprotected derivatives (Scheme 4).

This is due to the lowered reactivity of the hydrate with benzylamine compared to the corresponding ketone and the presence of a labile *N*-trifluoroacetyl group. Therefore, the N-deprotected imine **20** was prepared through a Dean−Stark reaction in toluene, followed by reduction of the imine using $NaCNBH_3$ to obtain 4-benzylaminopiperidine **21** in good yield.

In conclusion, it can be stated that new entries toward new substituted fluorinated piperidines, a class of compounds with considerable potential as building blocks in medicinal chemistry, were developed. 3-Alkoxymethyl- and 3-aryloxymethyl-4-cyano-2,2-difluorobutanoates **6** were synthesized via reaction of ethyl bromodifluoroacetate with 3-substituted acrylonitriles as Michael acceptors in the presence of copper powder. The cyano substituent of these 1,4-addition adducts was successfully reduced to induce lactamization toward new 3,3-difluoro-2-piperidinones, which were further reduced to the corresponding 4-alkyl-3,3-difluoropiperidines in good yields.

SCHEME 4. Reductive Amination of Hydrate 19



This method was used to synthesize the new N-protected 3,3-difluoroisonipecotic acid **11**. In addition, 4-cyano-2,2-difluoro-3-butenoate was obtained via reaction of ethyl bromodifluoroacetate and 2-chloroacrylonitrile in the presence of copper. The 1,4-addition of benzyl alcohol to the obtained butenoate, followed by reduction, provided a new 4-benzyloxy-3,3-difluoro-2-piperidine which could be converted to 3,3-difluoro-4,4-dihydroxypiperidine **19**.

Experimental Section

Synthesis of 3,3-Difluoro-2-piperidinones 4, 7, and 15. Typical procedure for **4**: In a flask of 50 mL, 0.50 g of ethyl 4-cyano-2,2-difluorobutanoate **3** (2.82 mmol, 1 equiv) was dissolved in 20 mL of dry tetrahydrofuran. The solution was cooled to 0 °C, and 5.6 mL of $BH_3 \cdot THF$ (1 M in THF) (5.64 mmol, 2 equiv) was slowly added under nitrogen atmosphere. The reaction mixture was allowed to warm up to room temperature and stirred for 24 h. The reaction mixture was

quenched with 5 mL of methanol and poured in 20 mL of water and 20 mL of ethyl acetate. The separated aqueous phase was extracted twice with 20 mL of ethyl acetate, and the combined organic phases were dried over $MgSO_4$. After filtration, the solvent was evaporated in vacuo and the residue was crystallized in 9:1 Et_2O/MeOH, yielding 0.27 g of 3,3-difluoro-2-piperidinone **4** (2.03 mmol, 72% yield) as white crystals: mp = 105.1 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ 1.97−2.07 (2H, m, CH_2), 2.21−2.37 (2H, m, CH_2CF_2), 3.40 (2H, t, J = 5.4 Hz, NCH_2), 7.92 (1H, br s, NH); ^{19}F NMR ($CDCl_3$) δ −102.2 (2F, t, J = 14.5 Hz, CF_2); ^{13}C NMR ($CDCl_3$) δ 19.3 (t, J = 4.6 Hz), 31.7 (t, J = 22.5 Hz), 41.6, 112.5 (t, J = 244.0 Hz), 163.9 (t, J = 30.0 Hz); IR (ATR, cm^{-1}) ν = 3218 (NH), 3099, 1688 (C=O), 1340, 1195, 1146, 984; MS (ES+) m/z (%) 136 ($M + H^+$, 13), 153 ($M + NH_4^+$, 100). Anal. Calcd for $C_5H_7F_2NO$: C, 44.45; H, 5.22; N, 10.37. Found: C, 44.79; H, 5.19; N, 10.39.

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Supporting Information Available: General experimental methods, ^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.