Synthesis of (Fluoroalkyl)amines by Deoxyfluorination of Amino Alcohols

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Abstract: Deoxyfluorination of amino alcohols was achieved using $N,N$-diethyl-$\alpha,\alpha$-difluorobenzylamine (DFBA) to furnish $N$-benzoyl(fluoroalkyl)amines selectively.

Key words: amino alcohols, fluorination, deoxygenation, substitution, $N,N$-diethyl-$\alpha,\alpha$-difluorobenzylamine

Introduction of fluorine atoms into biologically active amines and amino acids is of great interest to medicinal chemists because the fluorine atom reduces the basicity of the amino group and modifies their metabolism and pharmacological properties. Furthermore, due to the development of $^{18}$F-labeled compounds for positron emission tomography (PET), the importance of the (fluoroalkyl)amine synthesis has increased remarkably. Fluoroamines can be prepared from amino alcohols via cyclic sulfamidates; however, it includes multi-step procedures and requires a long reaction time. Due to the short half-life of $^{18}$F, it is desirable to synthesize them as rapidly as possible, and a more direct method is required. Though the deoxyfluorination reaction of amino alcohols is the most suitable method for their synthesis, the application of deoxyfluorination reagents, such as diethylaminosulfur trifluoride (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor™), often results in undesired side reactions. Recently, we reported the deoxyfluorination reactions of alcohols, diols, aldehydes, and epoxides using $N,N$-diethyl-$\alpha,\alpha$-difluoro-(m-methylbenzyl)amine (DFMBA). We wish to report here that amino alcohols can be directly converted to $N$-benzoyl(fluoroalkyl)amines by $N,N$-diethyl-$\alpha,\alpha$-difluorobenzylamine (DFBA).

When 2-(phenylamino)ethanol (1a) was allowed to react with 2.4 equivalents of DFBA without solvent at 70 °C using conventional oil bath heating or microwave irradiation, the reaction was complete in 10 minutes and $N$-(2-fluoroethyl)-$N$-phenylbenzamide (2a) was obtained in 85% yield. A
The hydroxyl group in 1a was converted to a fluoride while an amino group was acylated by DFBA. The reaction must proceed through an oxazolinium intermediate 3 as in the case of diols. It was supported by the formation of oxazoline derivative 4 in the reaction of 2-aminoethanol with DFBA (Scheme 1).

Scheme 1

2-(Benzylamino)ethanol (1b) was less reactive than 1a and the corresponding (fluoroalkyl)amine (2b) was obtained in 70% yield by reaction with DFBA at 100 °C for ten minutes (Table 1). The fluorination of sec-hydroxy group of the amino alcohols 1c-e by DFBA also proceeded to give the corresponding (fluoroalkyl)amines 2c-e in good yields. Fluorination of a γ-amino alcohol is also possible and 3-(benzylamino)-1-porpanol (1f) could be converted to the corresponding (γ-fluoroalkyl)amide 2f in 71% yield. In the reaction with cis-2-(benzylamino)cyclohexanol (1g), N-benzyl-N-(trans-2-fluorocyclohexyl)benzamide (2g) was obtained in moderate yield and the formation of an olefinic by-product was observed. On the other hand, only a complex mixture was formed in the reaction of trans-2-(benzylamino)cyclohexanol with DFBA. When trans-2-(dibenzylamino)cyclohexanol (1h) was used, the fluorination took place with retention of the stereochemistry and N,N-dibenzyl(trans-2-fluorocyclohexyl)amine (2h) was obtained in high yield. In the case of N,N-disubstituted amino alcohols, the reaction must proceed through an aziridinium intermediate instead of the oxazolinium 3.
<table>
<thead>
<tr>
<th>Amino alcohol</th>
<th>Reaction conditions</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>H&lt;sub&gt;Bn&lt;/sub&gt;N&lt;sub&gt;H&lt;/sub&gt;OH</td>
<td>100 °C, 10 min</td>
<td>H&lt;sub&gt;Bn&lt;/sub&gt;N&lt;sub&gt;Bz&lt;/sub&gt;F&lt;sub&gt;2b&lt;/sub&gt;</td>
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<td>100 °C, 10 min</td>
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<td>100 °C, 10 min</td>
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<td>100 °C, 10 min</td>
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<td>100 °C, 10 min</td>
<td>H&lt;sub&gt;Bn&lt;/sub&gt;N&lt;sub&gt;Bz&lt;/sub&gt;F&lt;sub&gt;2f&lt;/sub&gt;</td>
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<td>100 °C, 10 min</td>
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<td>100 °C, 10 min</td>
<td>H&lt;sub&gt;Bn&lt;/sub&gt;N&lt;sub&gt;Bz&lt;/sub&gt;F&lt;sub&gt;2l&lt;/sub&gt;</td>
<td>86</td>
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<sup>a</sup> Unless otherwise stated, the reaction was carried out with DFBA (2.4 equiv) and 1 (1 equiv) without solvent.
<sup>b</sup> Isolated yield base on 1.
<sup>c</sup> Dioxane was used as the solvent.
Various optically active amino alcohols are easily accessible and can be converted into the corresponding optically active (fluoroalkyl)amines by DFBA. Thus, (S)-N-benzyl-N-(1-fluoromethyl-2-phenylethyl)benzamide (2k) and (S)-N-benzyl-N-(1-fluoromethyl-3-methylbutyl)benzamide (2l) could be prepared optically active from the corresponding optically active amino alcohols 1k and 1l in 78% and 86% yields, respectively. Enantiomerically pure (S)- and (R)-(2-fluoro-1-methylethyl)amines (5) were required for the synthesis of β-adrenoceptor ligands, and were prepared from the corresponding 2-(benzylamino)-1-propanol (1j) in a multi-step synthesis via cyclic sulfamidates in 21% and 26% overall yields, respectively. When (S)- or (R)-1j was treated with 2.4 equivalents of DFBA at 100 °C, the reaction was complete in 10 minutes and the corresponding (S)- or (R)-N-benzyl-N-(2-fluoro-1-methylethyl)benzamide (2j) was obtained in 84 and 86% yields, respectively. After removal of the protecting groups, the desired (S)- or (R)-(2-fluoro-1-methylethyl)amine (5) was obtained enantiomerically pure in 59% and 56% overall yields, respectively (Scheme 2).

References and notes.
(1) (a) Coutts, R. T.; Benderly, A.; Mak, A. L. C. J. Fluorine Chem. 1980, 16,


(5) The half-life of 18F is about 110 min.


(12) Due to the enolizable character of the amide function, the NMR spectra of the N-acylated products were sometimes complicated and the reduction of the amide function to the amine was necessary for the analysis. When DFBA was used for the reaction with N-benzylamino alcohols, N,N-dibenzylamine derivatives were formed after the reduction, and their NMR spectra are simpler than that of the product from DFMBA. Therefore, DFBA was used instead of DFMBA. DFBA showed reactivity comparable with DFMBA and can be prepared from N,N-diethylbenzamide as DFMBA.10


(14) To a reactor of a Teflon™ PFA tube with a diameter of 10 mm sealed at one end, 1a (137 mg, 1 mmol) and DFBA (478 mg, 2.4 mmol) were introduced. The open end of the reactor was connected to a reflux condenser. Then, the reactor part was submitted to microwave-irradiation (IDX microwave oven for organic synthesis IMCR-25003) for 10 min and during the irradiation, the temperature was kept at 70 °C. After cooling, the reaction mixture was poured into an aq NaHCO₃ solution. The product was extracted with Et₂O (3X) and the combined ethereal layers were dried over MgSO₄. Purification by column chromatography (silica gel/hexane- Et₂O) gave 2a (207 mg, 0.85 mmol) in 85 % yield.

N-(2-Fluoroethyl)-N-phenylbenzamide (2a): IR (neat): 1649, 1494, 1377 cm⁻¹. ¹H NMR: δ = 7.32-7.09 (m, 10H), 4.76 (dt, J = 47.6, 4.9 Hz, 2H), 4.20 (dt, J = 25.6, 4.9 Hz, 2H). ¹³C NMR: δ = 170.94, 144.08, 135.80, 129.94, 129.31 (2C), 128.90 (2C), 127.89 (2C), 127.83 (2C), 126.91, 81.52 (d, J = 168.7 Hz), 51.57 (d, J = 20.7 Hz). ¹⁹F NMR: δ = -222.60 - -222.98 (m, 1F). HRMS (EI): m/z cald for C₁₅H₁₄NOF: 243.1059; found: 243.1057.

(S)-1-Fluoro-2-aminopropane Hydrochloride (S)-(5)-HCl: White solid; mp 123-124°C (lit.12 127-127.5 °C); [α]²³_D +12.4 (c 1.01, MeOH) δ lit.¹⁴ [α]²³_D +12.7 (c 1.01, MeOH). (R)-MTPA amide of (S)-5 ¹⁹F NMR: δ = -69.54 (s, 3F), -232.36 (dt, J = 26.2, 47.0 Hz, 1F).

(R)-1-Fluoro-2-aminopropane Hydrochloride (R)-(5)-HCl: White solid; mp 123-124.5 °C (lit.¹⁴ 127-128 °C); [α]²²_D -13.7 (c 1.00, MeOH) δ lit.¹⁴ [α]²²_D -14.9 (c 1.10, MeOH). (R)-MTPA amide of (R)-5; ¹⁹F NMR: δ = -69.47 (s, 3F), -232.73 (dt, J = 26.2, 47.0 Hz, 1F).