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Lewis Acid-Promoted Reaction of β,β-Difluorinated *N,O*-Acetal with Silylated Nucleophiles

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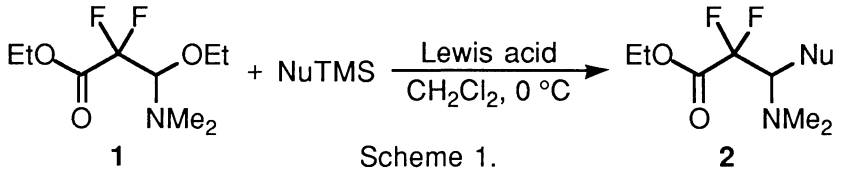
Lewis acid-promoted reaction of ethyl 3-ethoxy-2,2-difluoro-3-(dimethylamino)-propionate (**1**) with some silylated nucleophiles afforded β,β-difluoroamines in good yields. The formation of iminium ion intermediate from **1** and BF_3•OEt_2 was confirmed by ^{19}F and ^{13}C NMR spectroscopy.

β-Fluorinated amines and amino acids have attracted much attention as potent mechanism-based inhibitors of various PLP-dependent enzymes.[1] In addition, synthetic peptides containing fluorinated amino acids were successfully employed as substrates in enzymatic processes and probes of proteins.[2] Despite a large number of studies on those of fluoromethylated compounds, only a few reports have appeared on the biological investigation[3] or peptide synthesis[4] employing difluoromethylene-containing amines and amino acids in the literature, probably due to the difficulty of access to such amines.

Wade and co-workers reported the reaction of HF-pyridine with azirine to prepare β,β-difluoro-α-amino acids,[5] which were successfully introduced into peptide syntheses.[4] The Reformatsky reaction of iodo- and bromodifluoroacetates with imines reported by Taguchi and co-workers is an alternate route to β,β-difluorinated amines.[6] They have extended their work to the synthesis of difluoro derivative of aspartic acid by using 2,2-difluoroketene silyl acetal as a nucleophile. Silyl enol ether prepared from chlorodifluoroacetophenone was also an effective nucleophile, which reacted with protected 2-chloroglycinate to afford β,β-difluoro-γ-keto-α-amino acid after deprotection.[7] In contrast, there has not been a study on the reaction of difluoromethylene-containing imines with nucleophiles, mainly due to difficulty in obtaining such species.

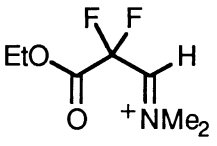
We have recently reported a facile preparation of difluorinated *N,O*-acetal **1** by Vilsmeier-type formylation of Reformatsky reagent derived from ethyl chlorodifluoroacetate.[8] This compound seems to be a promising building block for the synthesis of geminal difluorinated amines since *N,O*-acetals are known to form iminium ion upon treatment with Lewis acids and react with various nucleophiles to afford amino compounds.[9,10] In this paper, we wish to report the facile synthesis of β,β-difluoro amines by Lewis acid-promoted reaction of **1** with some silylated nucleophiles as shown in Scheme 1.



1 Scheme 1. **2**

Initial studies were carried out using trimethylsilyl cyanide as a nucleophile under various conditions. As shown in Table 1, both BF_3•OEt_2- and $TiCl_4$-mediated reactions proceeded promptly to afford **2a** (Nu = CN) in

good yields at 0 °C. Low yields of the product observed in the reaction at -78 °C are explained by the higher stability of tetrahedral acetal structure by the electron-withdrawning CF_2 group, which diminishes the formation of iminium ion **3**. In fact, when **1** was mixed with BF_3•OEt_2 at -78 °C and quenched with saturated aqueous sodium hydrogen carbonate solution at the same temperature, **1** was recovered in 71% yield. This result indicates that only a little amount of iminium ion **3** was generated at -78 °C. The same operation at 0 °C resulted in the formation of the mixture of ethyl hemiacetal **4a**[11] and *gem*-diol **4b**,[12] which were produced via hydrolysis of iminium ion intermediate **3**.



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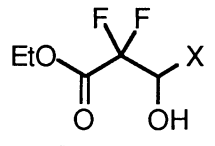


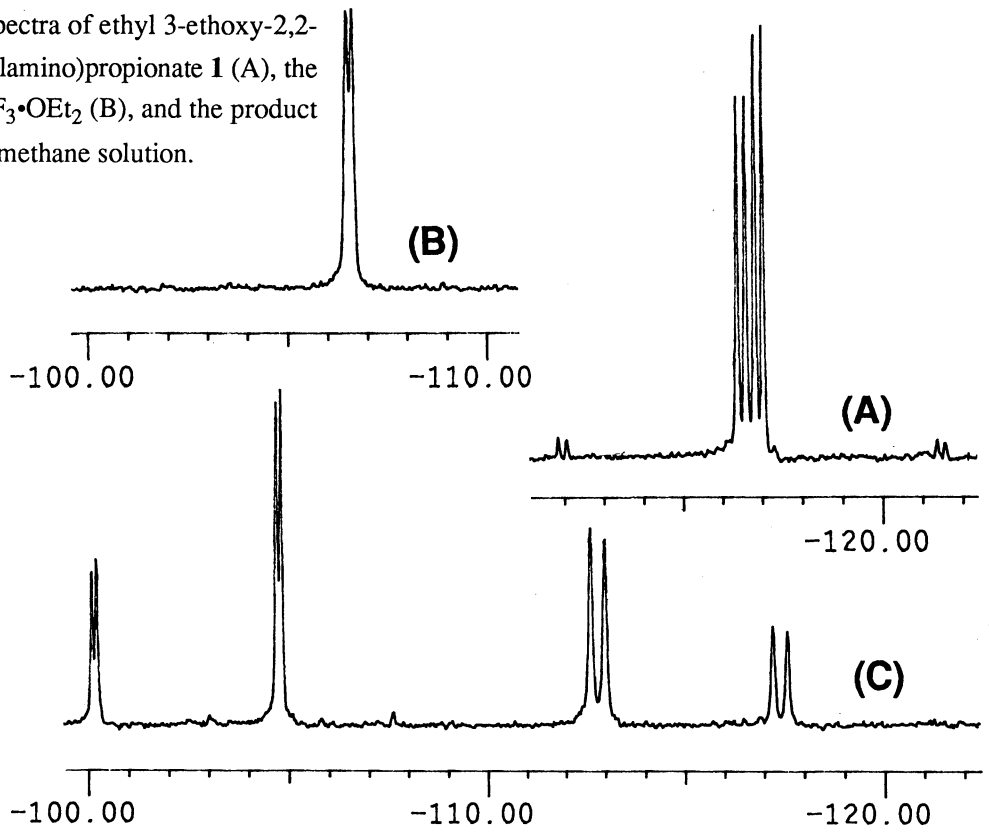
4a; X = OEt **4b**; X = OH

Table 1. Addition of trimethylsilyl cyanide to **1**

Entry	Lewis acid	Temp / °C	Time	Yield / %
1	BF_3•OEt_2	-78	1 h	15
2	BF_3•OEt_2	0	15 min	94
3	$TiCl_4$	-78	1 h	43
4	$TiCl_4$	0	15 min	87

To confirm the iminium ion formation, BF_3•OEt_2-promoted reaction of **1** with trimethylsilyl cyanide was monitored by using ^{19}F NMR spectroscopy. ^{19}F NMR spectrum of *N,O*-acetal **1** in dichloromethane exhibited AB doublet of doublets at -119.4 ppm and -114.5 ppm (Fig. 1A). When **1** was combined with BF_3•OEt_2, only one new doublet was observed at -106.5 ppm (Fig. 1B). This doublet is in agreement with the formation of iminium ion **3** which has no chiral center. Treatment of the mixture with trimethylsilyl cyanide gave **2a** quantitatively, which shows again AB doublet of doublets at -115.1 ppm and -102.5 ppm (Fig. 1C). Similar result was obtained in the case of $TiCl_4$, and iminium ion was observed at -104.9 ppm.

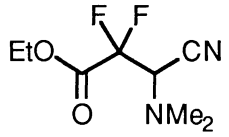
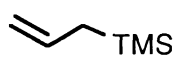
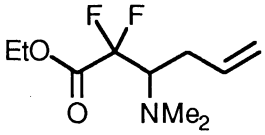
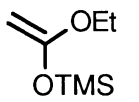
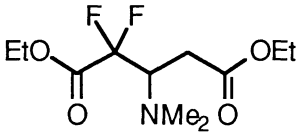
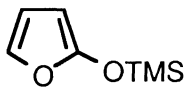
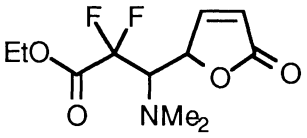
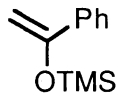
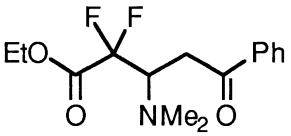
Fig. 1. ^{19}F NMR spectra of ethyl 3-ethoxy-2,2-difluoro-3-(dimethylamino)propionate **1** (A), the mixture of **1** and BF_3•OEt_2 (B), and the product **2a** (C) in a dichloromethane solution.



Additional evidence for the formation of iminium ion **3** was obtained by comparison of the ^{13}C NMR spectrum of *N,O*-acetal **1** and the mixture of **1** + BF_3•OEt_2. Acetal carbon of **1** exhibited triplet at 92.0 ppm ($J_{C,F}$ = 25.0 Hz), while that of **1** + BF_3•OEt_2 exhibits a chemical shift of 167.3 ppm ($J_{C,F}$ = 32.5 Hz), reflecting the change from sp^3 acetal to sp^2 imino carbon.

The results for the BF_3•OEt_2-promoted reaction of **1** with various nucleophiles are summarized in the Table 2. In all cases, the reaction proceeded smoothly to give the corresponding β,β-difluorinated amines **2** in good yields. Although allyl trimethylsilane was somewhat less reactive, by adding in large excess, the reaction was completed to give difluorinated homoallylamine in 82% yield.

Table 2. BF_3•OEt_2-Promoted reaction of **1** with silylated nucleophiles

Entry	Silylated nucleophile	Product **2**	Yield / % (diastereo ratio)[a]	^{19}F NMR[b] ($CDCl_3$) ppm
a	TMSCN		94	δ -116.1 (dd, *J* = 21.4, 261 Hz) δ -103.5 (dd, *J* = 6.1, 261 Hz)
b			82[c]	δ -121.6 (dd, *J* = 22.9, 256 Hz) δ -103.9 (dd, *J* = 7.6, 256 Hz)
c			93	δ -121.5 (dd, *J* = 23.7, 257 Hz) δ -104.9 (dd, *J* = 7.6, 257 Hz)
d			91[d] (66:34)	major: δ -112.7 (dd, *J* = 11.1, 265 Hz) δ -110.1 (dd, *J* = 17.6, 265 Hz) minor: δ -119.4 (dd, *J* = 23.7, 265 Hz) δ -99.9 (ddd, *J* = 4.6, 6.1, 265 Hz)
e			93	δ -120.7 (dd, *J* = 23.7, 256 Hz) δ -104.9 (dd, *J* = 7.6, 256 Hz)

a) Determined by ^{19}F NMR analysis of the crude mixture. b) C_6F_6 was used as an internal standard (δ_F = -162.9). c) Allyl trimethylsilane (4.0 equiv.) was added to a solution of **1** and BF_3•OEt_2. d) ^{19}F NMR yield of the crude product.[13]

In a typical experiment, to a solution of **1** (1.0 mmol) and trimethylsilyl cyanide (1.1 mmol) in dichloromethane (5 mL) was added dropwise neat BF_3•OEt_2 (1.1 mmol) at 0 °C, and the mixture was stirred at the same temperature for 15 min. After being diluted with dichloromethane (10 mL), the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution (15 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (15 mL x 2). The combined organic extracts were dried over $MgSO_4$ and evaporated. The residual oil was purified by bulb-to-bulb distillation at 150 °C (bath temperature) under 10 Torr to give **2a**[14] in 94 % yield.

In conclusion, we have developed a new method for the preparation of β,β-difluoro amines by the Lewis-acid promoted reaction of difluorinated *N,O*-acetal **1** with various silylated nucleophiles. This methodology should provide an alternate route to a variety of difluoromethylene-containing amino compounds difficult to obtain by other methods.

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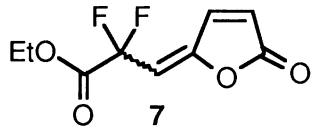
11) **4a**: ^{19}F NMR ($CDCl_3$) δ -125.1 (dd, J = 6.9, 266 Hz), -120.0 (dd, J = 6.1, 266 Hz).

12) **4b**: ^{19}F NMR ($CDCl_3$) δ -123.1 (d, J = 6.1 Hz).

13) The product was susceptible to deamination and afforded **7** after chromatographic purification.



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14) ^{1}H NMR ($CDCl_3$) δ 1.36 (t, J = 7.2 Hz, 3 H), 2.41 (s, 6 H), 4.24 (dd, J = 5.9, 21.5 Hz, 1 H), 4.36 (dq, J = 10.7, 7.2 Hz, 1 H), 4.40 (dq, J = 10.7, 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 43.2, 61.3 (dd, J = 21.5, 30.7 Hz), 63.7, 110.4, 112.8 (dd, J = 256, 266 Hz), 161.3 (dd, J = 28.4, 32.0 Hz); IR (neat) 3000, 1780 (cm^{-1}); MS (35 eV) *m/z* (rel intensity) 206 (M^+, trace), 180 (M^+-CN, trace), 161 (M^+-OEt, trace), 83 (M^+-CF_2CO_2Et, 100).

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