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First synthesis of 3,3-difluoroserine and cysteine derivatives via Mg(0)-promoted selective C–F bond cleavage of trifluoromethylimines

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Abstract

3,3-Difluoroserine and cysteine derivatives were synthesized via Mg(0)-promoted defluorination of trifluoromethylimines as a key step, followed by addition of alcohols and sulfenyl chloride, respectively.

Keywords: amino acids; defluorination; enamines; imines.

Among fluorinated amino acids, 3,3-difluoroamino acids are one of the most attractive synthetic targets, because some amino acids containing *gem*-difluoromethylene moiety have interesting biological activities[1] such as being an irreversible inhibitor of pyridoxal phosphate dependent enzymes.[2] In spite of the promising biological activities of 3,3-difluoroamino acids, only a few methods are available for the synthesis of these compounds.[3] The development of a systematic synthesis of the target amino acids is required.

2-*N*-Silylamino-3,3-difluoroacrylate would be nucleophilically or electrophilically alkoxylated, thioalkoxylated and alkylated at the difluoromethylene carbon atom and thus would be a useful intermediate for the synthesis of various kinds of 3,3-difluoroamino acids. Meanwhile, as for the creation of difluoromethylene moiety from a trifluoromethyl moiety, we have already established electroreductive methods for *N*-silylated difluoroenamines **2**, using trifluoromethyl imines **1** as starting materials.[4] Here, we describe the first synthesis of racemic 3,3-difluoroserine and 3,3-difluorocysteine derivatives **3** and **4** using a newly developed Mg(0)-promoted selective defluorination from trifluoromethyl imines **1** as a key step (Scheme 1). The Mg(0)-promoted defluorination provides many advantages for a practical preparation of difluoromethylene compounds, such as a less expensive process and the selective C–F bond cleavage from the trifluoromethyl group.[5]

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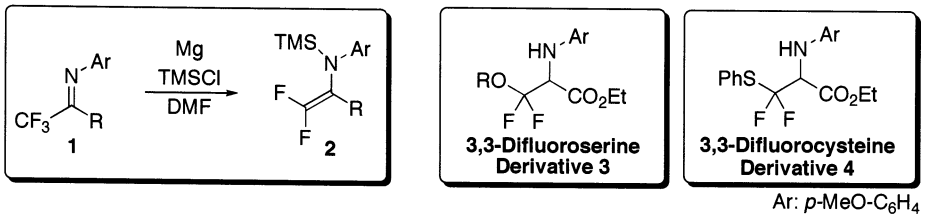
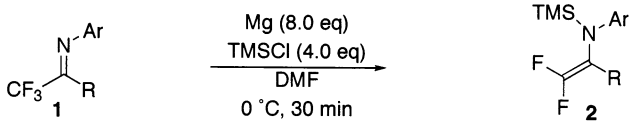
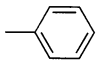
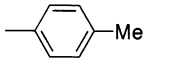
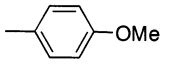
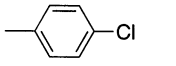
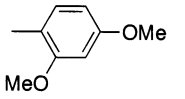


Scheme 1.

As shown in Table 1, the reaction of a variety of aromatic imines with either electron-withdrawing or electron-donating substituents on the aromatic ring (**1a–e**) and heteroaromatic imines (**1f**, **1g**) provided the desired enamines in excellent yields (entries 1–7). A ten gram-scale reaction proceeded in DMF at 0°C within 30 min using a commercially available magnesium[6a] and no special activation of the magnesium such as iodine and dibromoethane or ultrasound treatment was needed. Meanwhile, the less reducible aliphatic imine required the higher temperature (70°C, entry 8). Moreover, the simplest 3,3-difluoroenamine **2i** (R = H) could be prepared in a reasonable yield (entry 9) and would be employed as a key starting substrate for fluorinated polyvinylamines. It is noteworthy that reductive defluorination of ethyl 2-(*N*-*p*-anisyl)imino-3,3,3-trifluoropropanoate (**1j**) gave ethyl 2-amino-3,3-difluoroacrylate (**2j**) in 50% yield in the presence of NaI and Et_3N (entry 10).[6b]

Table 1
Mg(0)-promoted reductive defluorination of trifluoromethylimines **1**[a]

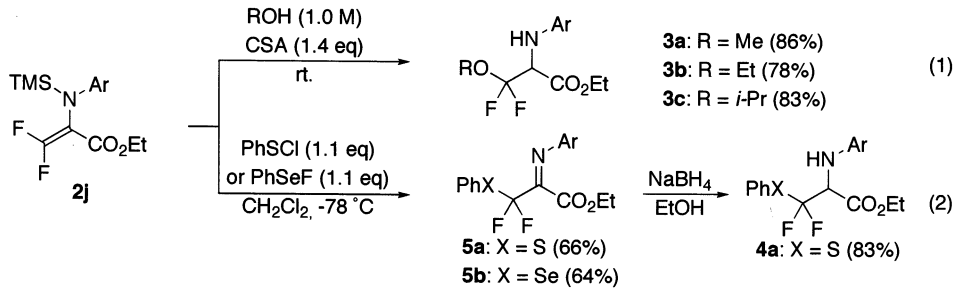


Entry	Imine **1**	R	% Yield of **2**[b]	Entry	Imine **1**	R	% Yield of **2**[b]
1	**1a**		82	6	**1f**		72
2	**1b**		88	7	**1g**		63
3	**1c**		quant.	8[d]	**1h**	—*n*-Hex	77[c]
4	**1d**		quant.	9	**1i**	—H	47
5	**1e**		quant.	10[e]	**1j**	—CO_2Et	50

[a] The reaction was carried out by the procedure shown in note 6. [b] Isolated yield. [c] NMR yield, which was calculated by ^{19}F NMR integration of product **2h** relative to 4,4'-difluorodiphenylmethane as an internal standard. [d] Conditions: 70 °C, 10 min. [e] 2.4 equiv of NaI and 4.2 equiv of Et_3N were used.

The fluorinated acrylate **2j** can be transformed into serine **3** and cysteine derivatives **4** as shown in Scheme 2. It is particularly noteworthy that **2j** reacted with both electrophiles and

nucleophiles smoothly without accompanying defluorination.[7,8] The difluoromethylene carbon of **2j** is highly reactive even with a weak nucleophile like alcohols, meanwhile it can accept an electrophile such as PhSCl and PhSeF at the β-carbon of the enamine **2j**. Thus, regioselective desilylative addition of various kinds of alcohols to **2j** proceeded smoothly under acidic conditions to give the corresponding 3,3-difluoroserine derivatives **3** in good yields (Eq. 1). **2j** was allowed to react with electrophiles such as benzenesulfenyl chloride or benzeneselenenyl fluoride,[9] affording 3-thio- and 3-seleno-3,3-difluoro-2-iminopropanoates **5**. Reduction of thioester **5a** with $NaBH_4$ provided 3,3-difluorocysteine derivative **4a** in a good yield (Eq. 2).



Scheme 2. Synthesis of 3,3-difluoroserine and cysteine derivatives

It has been clarified that the enaminoester **2j** can react with both electrophiles and nucleophiles under conditions where no defluorination occurs from the difluoromethylene group. This result suggests **2j** is a promising precursor for a variety of difluoroamino acid derivatives.

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5. Mg(0)-promoted transformation of trifluoromethylketones to difluoroenolsilyl ethers: Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. *Chem. Commun*. **1999**, 1323.
6. A typical reaction procedure is as follows; (a) TMSCl (18.2 mL, 143 mmol) and a solution of 2-(*N*-*p*-anisyl)imino-2-phenyl-1,1,1-trifluoroethane **1a** (10.0 g, 35.8 mmol) in freshly dried DMF (43 mL) were added to a suspension of magnesium (6.97 g, 287 mmol) in DMF (100 mL) at 0°C under an argon atmosphere. After stirring for 30 min at 0°C, TMSCl was removed under reduced pressure (22 mmHg) at rt and a 1/9 solution of Et_3N/hexane (100 mL) was added. Magnesium was separated by filtration through Celite® under reduced pressure and the filtrate was washed with H_2O (200 mL). The aqueous layer was extracted with hexane (100 mL×2) and the organic layer was washed with H_2O (50 mL) and then dried over $MgSO_4$. Evaporation of the solvent and bulb-to-bulb distillation (0.3 mmHg, 120°C) provided **2a** in 82% yield. (b) TMSCl (40.0 mmol) and a solution of ethyl 2-(*N*-*p*-anisyl)imino-3,3,3-trifluoropropanoate **1j** (10.0 mmol) in freshly dried DMF (10 mL) were added to a suspension of magnesium (80.0 mmol), Et_3N (42.0 mmol) and NaI (24.0 mmol) in DMF (30.0 mL) at 0°C under an argon atmosphere. After stirring for 30 min at 0°C, magnesium was separated by filtration through Celite® under reduced pressure and the filtrate was extracted with hexane (20 mL×3). Evaporation of solvent and bulb-to-bulb distillation (0.25 mmHg, 90°C) provided **2j** in 50% yield.
7. Defluorination is usually accompanied by the addition of nucleophiles to the difluorovinyl group. For example: (a) Huang, X.-H.; He, P.-Y.; Shi, G.-Q. *J. Org. Chem*. **2000**, *65*, 627. (b) Ichikawa, J.; Kobayashi, M.; Yokota, N.; Noda, Y.; Minami, T. *Tetrahedron* **1994**, *40*, 11637. (c) Shi, G.-Q.; Cao, Z.-Y.; Zang, X.-B. *J. Org. Chem*. **1995**, *60*, 6608.
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