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N-TMS-β,β-Difluoroenamines: Electrochemical Preparation and its Transformation

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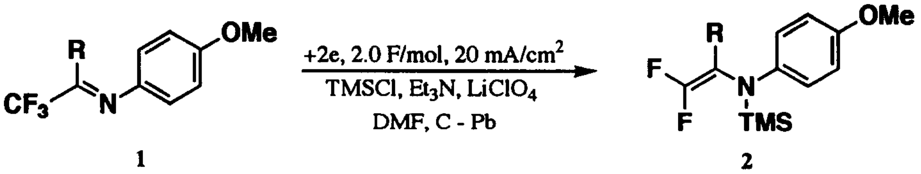
Abstract: The first preparation of *N*-trimethylsilylated β,β-difluoroenamines (**2**) from the trifluoromethyl imines (**1**) by electrochemical reduction and a preliminary study on alkylation of **2** for the synthesis of difluoromethylene compounds are described.

β,β-Difluoroamino acids are synthetic targets[1] which possess a potential biological activity and are relatively unexplored compounds. Constructions of the difluoromethylene moiety in the molecules are achieved by transformation of the carbonyl and thiocarbonyl groups by fluorinating reagents,[2] substitution of two methylene protons with fluorine atoms by N-F reagents,[3] utilization of difluoromethylene building blocks such as CF_2Br_2 and $BrCF_2CO_2R$,[4] and defluorination from trifluoromethyl compounds. The defluorination from a trifluoromethyl group is one of the promising methods for the purpose because of the easy availability of trifluoromethyl compounds and has been conducted by base-catalyzed dehydrofluorination of the trifluoroethyl group,[5] chemical[6] and electrochemical[7] reductive defluorination of trifluoromethyl aromatics, S_N2' addition to trifluoromethyl olefins,[8] and Brook-type rearrangement of trifluoroacetylsilanes.[9]

Benzyl β,β,β-trifluoro-α-iminopropanoate is a kind of trifluoromethylated heteroolefin which would undergo formally S_N2'-type nucleophilic addition to nitrogen leading to *N*-substituted difluoroenamines.[10] We herein describe an electrochemical approach to this problem in which an electron is a nucleophile, and which gives us the transformation of trifluoromethylimine (**1**) to *N*-trimethylsilylated α-amino-β,β-difluoropropenoic ester (**2a, 2b**), an useful intermediate to β,β-difluoroamino acids.

Electroreduction of trifluoromethylimines (**1**) in the presence of TMSCl resulted in defluorination of one of the three fluorine atoms in the CF_3 group, affording β,β-difluoroenamines, whose amino groups were trimethylsilylated (Scheme 1).

Scheme 1



A typical procedure is as follows: Ethyl 2-(*N*-*p*-anisyl)imino-3,3,3-trifluoropropanoate (**1a**) (1.0 mmol), TMSCl (3.0 mmol), triethylamine (3.2 mmol) and dry DMF (6.5 ml) were placed in the

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cathodic chamber of an H-type cell equipped with a lead plate (cathode) (1.5 x 1 cm^2). An H-type cell in which the cathodic and anodic chambers were separated by sintered glass and a carbon rod was set as an anode, was employed. A solution of $LiClO_4$ in dry DMF (7.5 ml) was placed in the anodic chamber. Constant current (30 mA) was passed at 0 ℃ under Ar. After 2 F/mol of electricity was passed, the catholyte was poured into ice water. Organic materials were extracted with ether and dried over $MgSO_4$. After removal of the solvent, ethyl 2-(*N*-*p*-anisyl-*N*-trimethylsilyl)amino-3,3-difluoro-2-propenoate (**2a**) (78%) was isolated by column chromatography of silica gel pretreated with triethylamine (hexane).

Reaction conditions were surveyed with **1a** and the results are summarized in Table 1. A combination of lead as a cathode and $LiClO_4$ as a supporting electrolyte was found to be favorable (Entries 2, 7-12). Current density of 20 mA/cm^2 or less was also suitable (Entries 2, 13-15). As for the temperature, the best result was obtained when the reaction was conducted at 0 ℃ (Entries 1-3). More than three mmol eq. of TMSCl to **1a** (1.0 mmol) was essential to obtain **2a** in a reasonable yield (Entries 2,4-6). Trapping of a fluoride anion which was formed from the imine (**1**) was essential to avoid desilylation of the product, *N*-silylated β,β-difluoroenamines (**2**).[11]

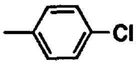
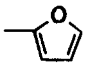
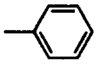
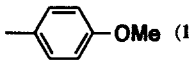
Table 1 Electroreducion of Ethyl 3,3,3-trifluoro-2-(*N*-*p*-anisyl)iminopropanoate (1a)

Entry	Temp. (℃)	TMSCl (mmol)	Cathode material	Supporting electrolyte	Current density (mA/cm^2)	Yield of **2a** (%)[a]
1	-12	3.0	Pb	$LiClO_4$	20	58
2	0	3.0	Pb	$LiClO_4$	20	86
3	rt	3.0	Pb	$LiClO_4$	20	52
4	0	1.0	Pb	$LiClO_4$	20	26
5	0	2.0	Pb	$LiClO_4$	20	46
6	0	5.0	Pb	$LiClO_4$	20	74
7	0	3.0	Pt	$LiClO_4$	20	65
8	0	3.0	Zn	$LiClO_4$	20	50
9	0	3.0	Ni	$LiClO_4$	20	55
10	0	3.0	Pb	Et_4NBr	20	62
11	0	3.0	Pb	Bu_4NBr	20	67
12	0	3.0	Pb	Et_4NClO_4	20	57
13	0	3.0	Pb	$LiClO_4$	6.7	82
14	0	3.0	Pb	$LiClO_4$	33	75
15	0	3.0	Pb	$LiClO_4$	67	58

a) Yields were determined by ^{19}F NMR.

As shown in Table 2, various *N*-silylated β,β-difluoroenamines (**2**) were electrochemically prepared from the corresponding imines (**1**) under similar reaction conditions. These reactions gave good results even if they were carried out at room temperature. All these electroreductive defluorinations proceeded effectively to complete at 2.0 F/mol. It was found that imines having either an alkyl group or an aryl group gave the corresponding *N*-silylated *β*,*β*-difluoroenamines (**2**) in moderate to good yields. Electroreduction of iminoesters (**1a**, **1b**) gave *β*,*β*-difluoroacrylates (**2a**, **2b**) in good yields (Entries 1, 2). These acrylates were expected to be useful precursors for various *β*,*β*-difluoro-*α*-amino acids. Electroreduction of imines having a phenyl group also gave the corresponding *N*-silylated *β*,*β*-difluoroenamines (**2**) in good yields (Entries 3-5). *β*,*β*-Difluoroenamine having a furyl group (**1f**) was so unstable toward moisture that it was desilylated gradually to give a *N*-protonated product (Entry 6). Because water in these reaction systems hydrolyzed TMSCl and the *N*-silylated *β*,*β*-difluoroenamine (**2**), careful removal of the water was required to get the products in good yields.

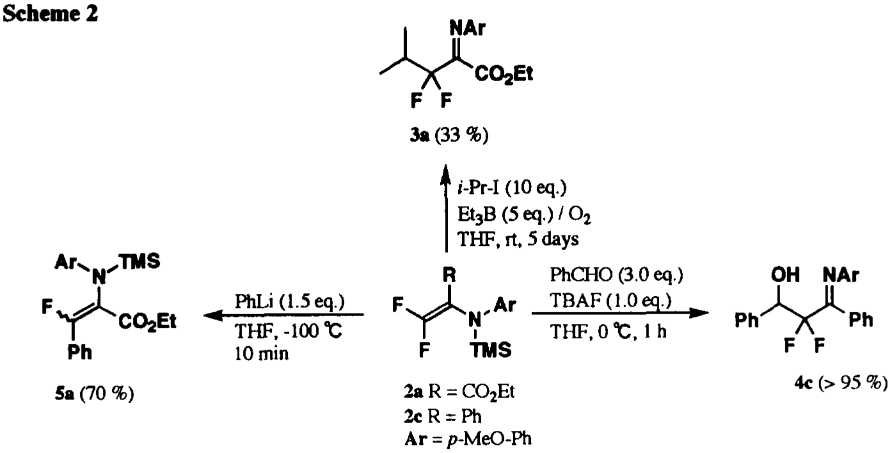
Table 2 Electroreductive Defluorination of Trifluoromethyl Imines (1)

Entry	—R	Yield of **2** (%)	Entry	—R	Yield of **2** (%)
1[c]	$—CO_2Et$ (**1a**)	78[a]	5	 (**1e**)	74[a]
2[c,d]	$—CO_2Bn$ (**1b**)	50[a]	6	 (**1f**)	57[a]
3	 (**1c**)	75[a]	7[e]	—Et (**1g**)	50[b]
4[d]	 (**1d**)	58[a]	8	—H (**1h**)	47[a]

a) Isolated yield b) Yield was determined by ^{19}F NMR analysis. c) 4.0 mmol of TMSCl and 4.2 mmol of Et_3N were used. d) CH_3CN as a solvent and Bu_4NBr as a supporting electrolyte were used. e) Reaction was conducted at rt.

As a preliminary study of alkylations of the flurorinated *β*-carbon atom of **2**, three types of reactions, radical addition of isopropyl radical, nucleophilic addition of phenyl lithium[12)], and the fluoride ion-promoted reaction were examined (Scheme 2). These reactions revealed that alkylations

Scheme 2



did occur on the CF_2 carbon. Thus, an isopropyl radical added to the β,β-difluoroacrylates (**2a** R=CO_2Et), affording ethyl 3,3-difluoro-2-(*N*-anisyl)imino-4-methylpentanoate (**3a**), a precursor of β,β-difluoro leucine.[13] Treatment of *N*-trimethylsilylated β,β-difluoroenamine (**2c** R=Ph) with a fluoride ion promoted the generation of 1,1-difluoro-2-(*N*-anisyl)imino-2-phenylethanide and its reaction with benzaldehyde leading to the formation of the adduct (**4**) in 72% (overall yield from **1c**).

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