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Preparation of 2,2-Difluoroenol Silyl Ethers by Electroreductive Defluorination of Trifluoromethyl Ketones

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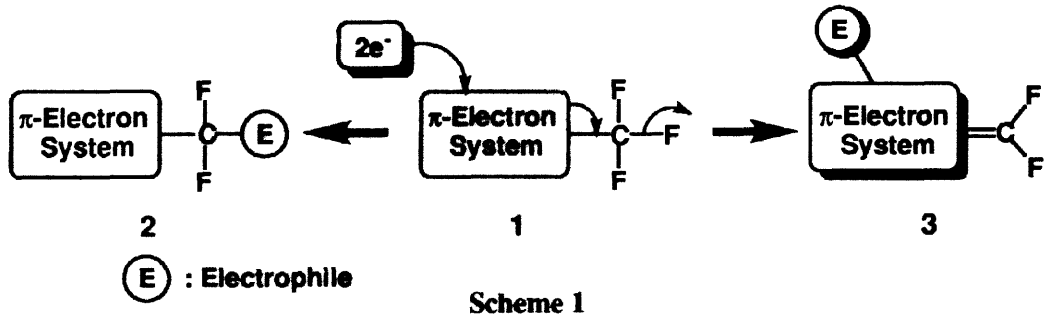
Abstract: 2,2-Difluoroenol silyl ethers (**5**) were prepared by electroreductive defluorination of trifluoromethyl ketones (**4**) in the presence of chlorotrialkylsilanes (TMSCl, TESCl, TBDMSCl).

Difluoromethylene compounds are current synthetic targets because of their unique biological activities.[1] Transformation of carbonyl,[2] thiocarbonyl[3] and thioacetal[4] groups to a difluoromethylene group with DAST and the related oxidative fluorinating reagents have been frequently used. Among these synthetic methods for difluoromethylene compounds, selective defluorination of trifluoromethyl compounds is promising due to the high availability of trifluoromethylated compounds. Dehalogenation from halodifluoromethyl groups[5] has been well established. However, there are very few successful cases of the selective demonofluorination from a trifluoromethyl group.[6]

The cleavage of a carbon-fluorine bond is not easy due to its large bond energy.[7] However, the bond breaking does easily occur when a CF_3 group is attached to the π-system as shown in Scheme **1**, where the accepted electron would push out a fluoride ion.[8] One of the problems in the conversion of **1** to **2**, however, is a further reduction of the initial product (**2**) and the contamination of monofluoro-compounds because of similar reduction potentials between **1** and **2**.[9] On the other hand, demonofluorination would exclusively predominate in the conversion of **1** to **3** due to the large difference in reduction potentials between **1** and **3**.[10] 2,2-Difluoroenol silyl ethers are synthons for the enolate of difluoroketones[5,11] and useful synthetic blocks for difluoro-compounds.



Scheme 1

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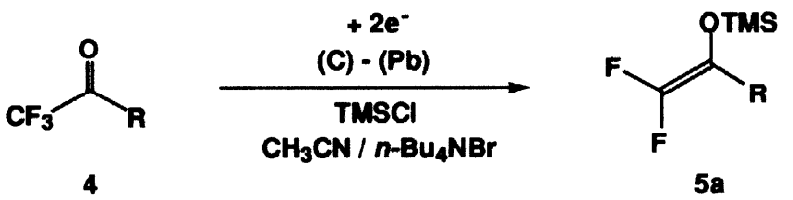
Here, we describe an electrochemical transformation of trifluoromethyl ketones to the 2,2-difluoroenol silyl ethers.



4 5a

Scheme 2

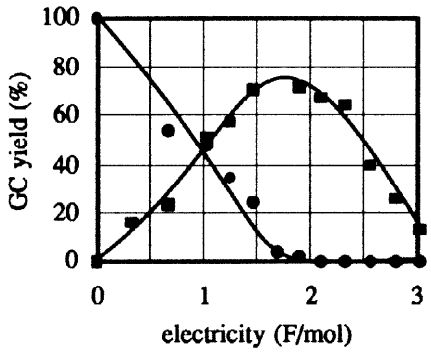
The electroreductive defluorination of trifluoromethyl ketones (**4**) (1 mmol) was carried out by using a Pb cathode (1 x 2 cm^2) and a carbon anode in anhydrous acetonitrile (7 + 7 ml) containing *n*-Bu_4NBr (4 mmol) and TMSCl (3 mmol) in an H-type divided cell. A constant current of 30 mA was passed at 0 ℃ under argon gas until **4** was consumed (2 F/mol). After the electrolysis, Et_3N (3 mmol) was added, and the yield of 2,2-difluoroenol silyl ether (**5a**) was determined by ^{19}F NMR because of the low stability of **5a** in silica gel column chromatographic purification.[12] Addition of Et_3N soon after electrolysis neutralized the reaction solution to avoid hydrolysis of **5a**. However, when Et_3N was added at the beginning of electrolysis, some ketones which have α-proton (substituents R were phenethyl, *n*-hexyl and so on) were transformed readily to 1-trifluoromethylenol silyl ethers under the electrolysis conditions which were electrochemically inactive for the purpose.

Table 1. Effects of Temperature, Current Density, and Amount of TMSCl[a)]

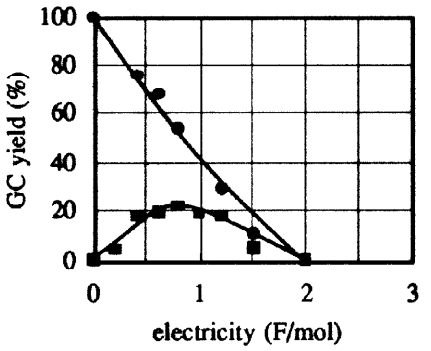
Entry	Temp. (°C)	Current density (mA/cm^2)	Equivalent of TMSCl (eq.)[b)]	Yield (%)[c)]
1	- 20	15	3	81
2	0	15	3	80
3	30	15	3	80
4	0	4	3	78
5	0	15	3	80
6	0	50	3	71
7	0	15	1	0
8	0	15	2	53
9	0	15	3	80
10	0	15	5	63

a) Substituent R was Ph, and Et_3N was added at the beginning of electrolysis.
b) Equimolar amount of TMSCl to **4** (R=Ph).
c) Yields were determined by ^{19}F NMR.

At first, effects of solvents and supporting electrolytes were examined. *n*-Bu_4NBr was a better supporting electrolyte than $LiClO_4$. Use of *n*-Bu_4NBr-CH_3CN system gave a better result (80 %) than those of $LiClO_4$-DMF (43 %) and $LiClO_4$-CH_3CN (39 %) system. The results obtained under several reaction conditions are summarized in Table 1. Temperature did not affect the yield of **5a** (entries 1-3) in the temperature range so far as examined. The lower current density at around 10 mA/cm^2 was found to be effective (entries 4-6). Cathode of Pb gave a good result so far as examined [Pb (80 %), carbon (77 %), and Pt (65 %)]. One of the critical



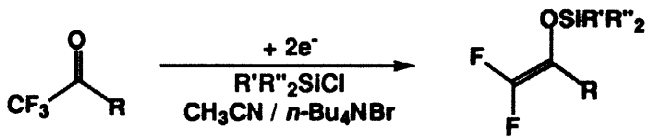
(a) Amount of TMSCl was 3 mol eq.



(b) Amount of TMSCl was 1 mol eq.

Figure 1. GC yields of 4 and 5a (R=Ph) vs electricity: ● and ■ indicate 4 and 5a, respectively.

Table 2. Preparation of Difluoroenol Silyl Ethers (5a-c)



5a: R'= R"= Me
5b: R'= R"= Et
5c: R'= t-Bu, R"= Me

Entry	Substituent R	Yield (%) 5a [a] (TMS)	5b [b] (TES)	5c [b] (TBDMS)
1	C_6H_4-OMe-*p*	(86)	70	85
2	Ph	(80)	84	84
3		(74)	64	- [c]
4	*n*-Hex	(71)	53	- [c]
5	*c*-Hex	(66)	55	- [c]
6	CH_2CO_2Et	(50)	42	- [c]
7		(55)	57	50

a) Yields were determined by ^{19}F NMR. (After the electrolysis, Et_3N was added.) b) Isolated yields. c) Not obtained.

factors for the yield of **5a** was the amount of TMSCl (entries 7-10). When three equivalents of TMSCl for **4** were used, the yield of **5a** was 80 % (entry 9). However, when only one equivalent of TMSCl for **4** was used(entry 7), **5a** was not obtained. To study the effect of the amount of TMSCl, the time-dependent distributions of **4** and **5a** were analyzed (Figure 1). According to Figure 1(a), the best yield of **5a** was obtained at about 2 F/mol in the presence of three equivalents of TMSCl. However, when one equivalent of TMSCl was used, the yield of **5a** reached the maximum on passing about 1 F/mol of electricity and then gradually decreased, and finally **5a** disappeared (Figure 1(b)). As the reaction proceeds, a fluoride ion is produced and it reacts with both TMSCl and product **5a**, thus losing **5a**. These experimental facts suggest that trapping of the fluoride ion produced *in situ* by TMSCl is essential.

This reaction can be applied to a variety of substituted trifluoromethyl ketones (**4**) (Table 2). Because of the instability TMS-enolates (**5a**), TES (**5b**) and TBDMS-enolates (**5c**) were prepared similarly and both of them were comparatively stable under silica gel column chromatography. Both aromatic and aliphatic trifluoromethyl ketones provided **5** in reasonable yields. Reactions of active methylene compounds (entry 6) and a heteroaromatic compound (entry 7) also gave the corresponding difluoroenol silyl ethers.

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9. For example, we have recently found that 1-substituted-2-trifluoromethylbenzimidazole (**6**) was easily defluorinated by electroreduction, but the product, 1-substituted-2-difluoromethylbenzimidazole (**7**) was also easily defluorinated because of its similar reduction potentials. So **6** and **7** were defluorinated competitively, producing 1-substituted-2-monofluoromethylbenzimidazole (**8**) as a by-product. When 4 F/mol electricity was passed, **6** (42 %, recovery of **6**), **7** (37 %) and **8** (5 %) were produced, respectively.
10. LUMO energies of **4**, **5a** (R=Ph) and difluoromethyl phenyl ketone (**9**) were -0.97 eV, -0.41 eV and -0.87 eV, respectively (calculated by PM3 geometry optimization of Mac Spartan Plus), suggesting different reducibility between **4** and **5a**, and similar one between **4** and **9**.
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12. The products, TMS-enolates (**5a**) were partially hydrolyzed to difluoromethyl phenyl ketone during the silica gel column chromatography. Pentane extract of the electrolysis product without further purification was subjected to alkylation with benzaldehyde in a $TiCl_4$-CH_2Cl_2 solution, which provided 2,2-difluoro-3-hydroxy-1,3-diphenyl-1-propanone [51% from **4** (R=Ph)]. The corresponding TES and TBDMS-enolates (**5b** and **5c**) were isolable by silica gel column chromatography.