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Non-defluorinative electrochemical silylation of ethyl trifluoroacetate: a practical synthesis of trifluoroacetyltrimethylsilane via its ethyltrimethylsilyl ketal

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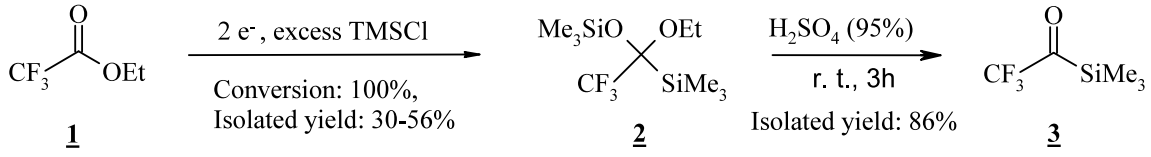
Abstract—An efficient method for the preparation of original trifluoroacetyltrimethylsilane, $CF_3COSiMe_3$ (**3**), in two steps from readily available ethyl trifluoroacetate is described. Electrochemical reduction of this ester using a sacrificial anode and performed on a semimolar scale afforded the unprecedented corresponding ketal, $CF_3C(SiMe_3)(OSiMe_3)OEt$ (**2**) in 30–56% isolated yield. Treated with concentrated sulphuric acid at room temperature, the latter directly led to pure acylsilane **3** in 86% yield.

Trifluoromethyl and difluoromethylene substituted molecules are of importance in organic synthesis because of their unique biological activity.[1] Consequently, the development of new strategies for the introduction of these groups into organic molecules has become a good challenge.[2] Among the methodologies used to make trifluoromethylated compounds,[3] trifluoroacetaldehyde remains one of the most useful building blocks. However, this compound being too volatile, reactive and commercially unavailable it almost never is used directly but is usually generated in situ from its hydrate, hemiacetal, ketal, hemiaminal or aminal-type precursors using protic or Lewis acid catalysis.[4] Here, we report the electrosynthesis, from the readily available and cheap ethyl trifluoroacetate (**1**), of trifluoroacetyltrimethylsilane ethyltrimethylsilyl ketal, $CF_3C(SiMe_3)(OSiMe_3)OEt$ (**2**), and its transformation into the original acylsilane $CF_3COSiMe_3$ (**3**) (Scheme 1). Both are new trifluoroacetaldehyde synthetic equivalents.

This new two-step-strategy generalises and makes more practical and less expensive the trifluoroacylsilane route to difluoroenoxysilanes[5] (Scheme 2a) which can be advantageously (or complementary) compared to the more classical method from acylsilanes and (trifluoromethyl)trimethylsilane[6] (Scheme 2b). Effectively, the trifluoroacylsilane route which involves the addition of an organometallic reagent to trifluoroacetyltriphenylsilane is up to now limited to the triphenylsilyl and phenyldimethylsilyl groups because it requires a silyllithium reagent for its preparation.[5,7]



Scheme 1.

Keywords: fluorine and compounds; electrochemistry; acylsilanes; ketals; silylation.

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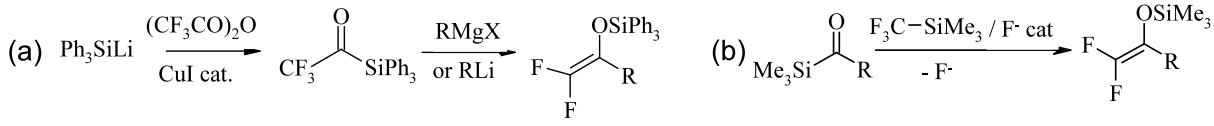


Scheme 2.

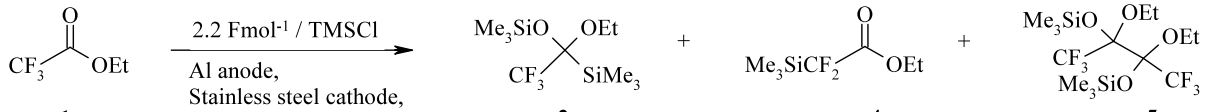
Difluoroenoxysilanes, when opposed to an electrophile, are now well known as excellent building blocks for the synthesis of *gem*-difluorinated compounds.[6] In addition, **3** could be a valuable starting material for the preparation of α-(trifluoromethyl)vinylsilane.[8]

While searching for anionic difluoromethylene group transfer agents, we have previously reported the molar scale electroreductive synthesis of (trimethylsilyldifluoromethyl)benzene from trifluoromethylbenzene[9] and of ethyl α-(trimethylsilyl)difluoroacetate, a Reformatsky reagent equivalent, from ethyl chlorodifluoroacetate (less expensive than bromodifluoroacetate).[10] This second silylated synthon is a more stable alternative to difluoroketene silylacetals for the transfer of the ethyl difluoroacetate group to electrophiles.[10,11] The electroreduction of ethyl trifluoroacetate is known to take place at relatively cathodic potentials: −2.36,[12a] −2.65,[12b] −2.58[12c] V versus SCE.

The electrochemical transformation of **1** to **2** was carried out using the versatile intensiostatic sacrificial anode technique with an undivided cell fitted with an aluminium anode and a cylindrical stainless steel cathode.[13] Electroreduction of **1** (21 mmol, 3 g) was first performed in THF (36 mL) and HMPA (6 mL) as the co-solvent containing *n*-Bu_4NBr (0.8 mmol) and excess chlorotrimethylsilane TMSCl (40 mL, 15 equiv.). A constant current of 100 mA (0.07 A dm^{-2}) was passed at room temperature under nitrogen gas until **1** was consumed (2.2 F mol^{-1}). Silylketal **2**, the new silylated first reduction product of **1**, was the major product (70%) along with α-silylester **4** (15%) resulting from monodefluorinative silylation of **1** and silyldiketal **5**, as a 50:50 diastereoisomeric mixture (Table 1, entry 2).

In order to improve the selectivity, conditions were varied (Table 1). In every case, conversion of **1** was quantitative and **2** was the major product. With HMPA as the co-solvent, varying the excess of chlorosilane at 25°C did not very much affect the GC yield of **2** (68–70%, entries 2 and 3) but a smaller amount of TMSCl favoured silyl ester **4** to the detriment of **5** (entry 3). Temperature was one of the critical factors for the yield of **2**. If increasing it to 50°C did not result in a noticeable change (entry 1), lowering it to −25°C is favourable to **2** (78%, entry 4). The best GC yield (89%) was obtained combining the lowest temperature with progressive addition of **1** by syringe pump at the electrolysis rate on a 0.25 mL initial amount (0.03 mol L^{-1}). Under these conditions, the formation of **5** was suppressed and the isolated yield of **2** was 56% (entry 5). As shown in Table 1, other co-solvents could be used in combination with THF: tris(2,5-dioxaheptyl)amine (THF/TDA-1: 6/1 vol.) gave a similar result at 25°C under batch conditions (65% of **2**, entry 6); *N*,*N*-

Table 1. Influence of co-solvent, amount of TMSCl, temperature and progressive addition of **1**



Entry[a]	THF (mL)/co-solvent (mL)	TMSCl (equiv.)	Temp. (°C)	**2** (%)	**4** (%)	**5** (%)
1	(36)/HMPA (6)	15	50	69[b]	15[b]	16[b]
2	(36)/HMPA (6)	15	25	70[b]	15[b]	15[b]
3	(36)/HMPA (6)	3	25	68[b]	27[b]	3[b]
4	(36)/HMPA (6)	15	−25	78[b]	3[b]	19[b]
5[c]	(48)/HMPA (8)	15	−25	89[b] (56)[d]	11[b]	0[b]
6	(36)/TDA-1 (6)	15	25	65[b]	16[b]	19[b]
7[c]	(30)/DMPU (15)[e]	15	10	74[b]	13[b]	0[b]
8[c]	(30)/DMPU (15)[e]	15	−20	81[f] (20)[d]	6[f]	0[f]
9[c]	(0)/DMPU (45)[g]	15	−10	76[f] (20)[d]	12[f]	4[f]
10[c]	(42)/DMPU (7)[e]	15	−25	75[f] (33)[d]	8[f]	1[f]

[a] Entries 1–4, 6 were performed on 21 mmol of **1** and 5, 7–10 on 42 mmol (6 g) of **1**.
[b] GC yields using nonane as the internal standard.
[c] Syringe pump addition of **1** at the reaction rate corresponding to 0.1 A constant current.
[d] Isolated.
[e] **3** (5%, entries 7 and 8; 8%, entry 10) and HCF_2COOEt (8%) were formed as by-products.
[f] ^{19}F NMR yields.
[g] **3** (8%) was a by-product.

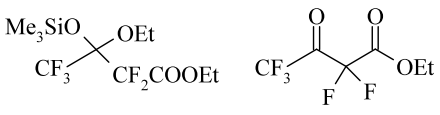
dimethylpropylene urea (THF/DMPU: 2/1 or 6/1 vol.) also gave a good selectivity for **2** (74–81% at +10, −10 and −25°C: entries 7, 8, 10) and lowering or suppression of **5** under progressive addition of **1**. With DMPU as the sole solvent, 76% of **2** were obtained at −10°C (entry 9). However, with DMPU as the co-solvent or solvent, **2** was more difficult to isolate likely due to its partial transformation into **3** (20–33% isolated yields).[14]

The reaction here observed in THF/co-solvent medium with an aluminium anode is totally different from these obtained in acetonitrile solution by Stepanov[12c] and Uneyama,[15] respectively. As a matter of fact, Stepanov, also using an aluminium anode, but a much higher concentration of **1** (75 mmol in 60 mL of ACN) and only 1.1 equiv. of TMSCl, essentially obtained the Claisen-type product **6** (Scheme 3). Uneyama, with a two-compartment cell (carbon anode, lead cathode), obtained at 0°C a small amount of **4** (<5%) together with 21% of the actual Claisen product **7**, but at higher temperature (50°C), **4** became the sole formed product (47% yield). These authors did not report any side reaction with acetonitrile. For our part we observed side reactions in this medium at 50°C due to its relative acidity.

As we can see, the mechanism of electroreduction of **1** is much more complex than the one of ethylchlorodifluoroacetate which only gives compound **4**.[10] This difference of behaviour could be searched in the radical-anion which is formed first. Effectively, as fluorine is a worse leaving group than chlorine, the radical-anion arising from trifluoroacetate is likely more stable than the one formed from chlorodifluoroacetate. A more complete study of this mechanism including the role of all experimental parameters will be reported in a forthcoming paper.

The best conditions without HMPA were applied to the synthesis of **2** at a larger scale in a THF/DMPU/TMSCl (400 mL/200 mL/400 mL) medium using a tubular flow cell[16] and progressive introduction of 75 mL of **1** by syringe pump under a current of 1 A. The reaction, carried out at 10°C and monitored by GC and ^{19}F NMR, led to 55 g of pure silyl ketal **2** ($bp_{20} = 70$°C, 74% selectivity, 30% isolated yield).[14]

Pure trifluoroacetyltrimethylsilane **3** was then readily obtained in 86% yield by mild protolysis of ketal **2** (Scheme 1).[17]



6 **7**

Scheme 3.

Acknowledgements

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14. *Isolation of **2** from THF/DMPU medium (tubular flow cell)*: After electrolysis, pentane was added (500 mL) and the salts were decanted. Pentane, THF and excess TMSCl were removed in vacuo (100 Torr). Pentane (400 mL) was added and the mixture was poured into 200 mL of ice-cold brine. The aqueous DMPU layer was extracted with pentane (3×100 mL) and the organic layer washed to neutrality by $NaHCO_3$ solution and water, then dried ($MgSO_4$). Distillation gave 55 g (30%) of **2**.
*Silyl ketal **2***: colourless liquid; bp 70°C/20 mmHg; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.18 (s, 9H, $CSiMe_3$), 0.19 (s, 9H, $OSiMe_3$), 1.21 (t, $J=7.0$ Hz, 3H), 3.68 (m, 2H); ^{19}F NMR ($CDCl_3$, 188 MHz, $PhCF_3$ as an internal standard −63.0 relative to $CFCl_3$) δ −75.5 (s, 3F); ^{13}C NMR ($CDCl_3$, 62.86 MHz) δ −2.5 (s, $CSiMe_3$), 1.6 (s, $OSiMe_3$), 15.5 (s, CH_3), 60.4 (s, CH_2), 98.6 (q, $^2J_{CF}=34.1$ Hz, C_q); 124.8 (q, $^1J_{CF}=289.3$ Hz, CF_3); ^{29}Si NMR ($CDCl_3$, 39.77 MHz) δ 5.0 (q, $^3J_{SiF}=3.1$ Hz, $CSiMe_3$), 14.8 (s, $OSiMe_3$); IR (neat) 2980.3, 2962.0, 1287.4, 1254.8, 1174.1, 1136.0, 1067.1 cm^{-1}; MS m/z 273 (M−15, 1), 259 (M−29, 15), 215 (M−73, 2), 165 (2), 151 (5), 117 (3), 103 (7), 77 (15), 73 (Me_3Si^+, 100), 55 (8), 45 (15), 43 (8). Anal. calcd for $C_{10}H_{23}F_3O_2Si_2$: C, 41.89; H, 8.14; F, 19.30. Found: C, 41.64; H, 8.04; F, 19.76.
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17. *Typical procedure for **3***: Pure **2** (3 g, 10.5 mmol) was added at room temperature to 1.5 mL (28 mmol, 2.8 equiv.) of concentrated sulphuric acid. After stirring at room temperature for 3 h, then heating at 40°C under 15–20 mbar reduced pressure, 1.54 g of pure product **3**, as a light-yellow liquid, were condensed into a cold trap (86% yield). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.3 (s, 9H); ^{19}F NMR ($CDCl_3$, 188 MHz, $PhCF_3$ as an internal standard −63.0 relative to $CFCl_3$) δ −80.3 (s, 3F); ^{13}C NMR ($CDCl_3$, 62.86 MHz) δ −3.3 (s, $SiMe_3$), 115.8 (q, $^1J_{CF}=296.5$ Hz, CF_3), 223.7 (q, $^2J_{CF}=35$ Hz, C=O); ^{29}Si NMR ($CDCl_3$, 39.77 MHz) δ −2.0 (s, $SiMe_3$); IR (neat) 1690 cm^{-1} (ν_{CO}); MS m/z 170 (M^+, 0.2), 155 (M−15, 0.04), 101 (M−CF_3, 62), 77 (Me_2SiF^+, 66), 73 (Me_3Si^+, 100), 69 (CF_3^+, 35), 58 (27), 45 (71), 43 (59).