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Defluorinative silylation toward a selective preparation of α-trimethylsilyl-α,α-difluoroacetates from trifluoroacetates

Kenji Uneyama* and Go Mizutani

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Okayama 700-8530, Japan. E-mail: uneyamak@cc.okayama-u.ac.jp

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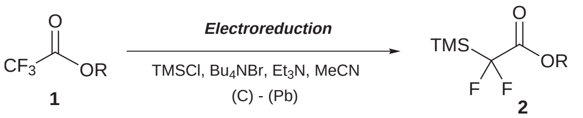
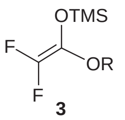
Electrochemical reduction of *n*-hexyl trifluoroacetate 1a in MeCN, involving Bu_4NBr, TMSCl, and Et_3N using an H-type divided cell equipped with carbon plate as an anode and lead plate as a cathode at 50 °C, provided *n*-hexyl α-trimethylsilyl-α,α-difluoroacetate 2a in 62% yield, which is a promising precursor of an alkoxycarbonyldifluoromethyl carbanion equivalent and can be alkylated at the α-carbon by fluoride ion catalysis.

Difluoromethylene compounds have become one of the most important synthetic targets because of their unique biological activity.[1] Among the various difluorinated building blocks, difluoroketene silyl acetals **3** have often been employed for syntheses of difluorinated β-amino-β-hydroxy esters and β-ethoxycarbonyldifluoromethyl-β-lactams under mild conditions.[2] However, they are unstable in the presence of moisture[3] and zinc salts, so that they must be employed mostly *in situ* soon after their generation by Reformatsky reaction of halodifluoroacetates, and are utilized for alkylation in Lewis acid catalyzed carbon–carbon bond formation at the difluoromethylene carbon. Here we describe a first selective preparation of α-trimethylsilyl-α,α-difluoroacetates **2**,[4,5] a stable and isolable alternative of **3**, by electrochemical reductive defluorination[6] of trifluoroacetates, which are more readily available than halodifluoroacetates, and its fluoride ion catalyzed selective alkylation at the α-carbon [eqn. (1)].[7]



(1)



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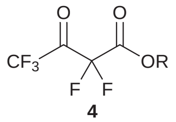

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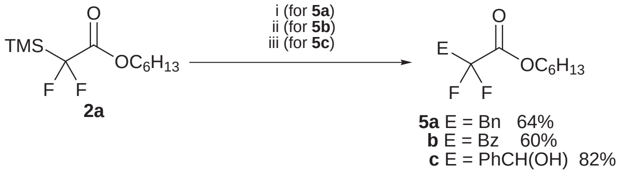
Electrochemical reduction of *n*-hexyl trifluoroacetate was conducted in MeCN involving Bu_4NBr, Et_3N and TMSCl using an H-type divided cell (with a sintered glass filter) equipped with carbon plate as an anode and lead plate as a cathode at 50 °C.† The product selectivity was found to be remarkably dependent on both reaction temperature and the concentration of TMSCl. At 50 °C the desired α-silylated acetate **2** was formed selectively in the presence of an excess of TMSCl (4 equiv.). On the other hand, a mixture of **2** and ketene silyl acetal **3** was formed at 0 °C in the presence of an excess of TMSCl (Table 1). Two-electron reduction followed by defluorination leads to the formation of the β,β-difluoro enolate which is trapped with TMSCl to give **3** as the kinetic product. *C*-Silylated product **2**[8,9] was the thermodynamic product since ketene silyl acetal **3** was found to be transformed to **2** under the electrolysis conditions at 50 °C. Meanwhile, formation of Claisen condensation product **4** was accompanied by **2** in the presence of only 1 equiv. of TMSCl. The selective formation of **2** was observed even in ethyl and *tert*-butyl esters [R = Et (47%), and Bu^t (58%)].

Table 1 Electrochemical preparation of **2**, **3** and **4**[a]

Entry	R	TMSCl/ equiv.[b]	T/°C	Yield(%)[c] **2**	**3**	**4**
1	n-C_6H_{13}	4	50	62 (68)	0	< 1
2	Bu^t	4	50	58 (68)	0	< 1
3	Et	4	50	47 (65)	0	< 1
4	n-C_6H_{13}	4	0	41	(18)	< 1
5	Et	1	0	< 5	0	(21)[d]

[a] *Reagents and conditions:* **1** (5 mmol), TMSCl (20 mmol), Et_3N (20 mmol), Bu_4NBr (12 mmol), in MeCN (70 ml), 80 mA cm^{-2}, 2 F mol^{-1}. [b] Relative to **1**, [c] Isolated yield (yield in parenthesis obtained by ^{19}F NMR). [d] **1** was recovered in 33%.

Fluoride ion catalyzed generation of the alkoxycarbonyldifluoromethyl carbanion and its alkylation were performed with benzyl bromide (64%), benzoyl chloride (60%) and benzaldehyde (82%), respectively (Scheme 1). This alkylation under basic conditions[9] is an alternative to Lewis acid catalyzed alkylation of ketene silyl acetals **3**.[2]



Scheme 1 *Reagents and conditions:* i, PhCHO (3.0 mmol), TBAF (1.0 mmol), THF, −78 °C, 1 h; ii, BnBr (1.0 mmol), KF (1.2 mmol), CuI (1.5 mmol), DMF, 80 °C, 5 h; iii, BzCl (3.0 mmol), KF (2.0 mmol), CuI (1.5 mmol), DMF, 80 °C, 10 h.

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Notes and references

† *Typical procedure* for **2a**: the electroreductive defluorination of *n*-hexyl trifluoroacetate **1a** (5 mmol) was carried out using a Pb cathode (2 × 5 cm^2) and a carbon anode in anhydrous MeCN (70 ml) containing Bu_4NBr (12 mmol), Et_3N (20 mmol) and TMSCl (20 mmol) in an H-type divided cell. A constant current of 80 mA was passed at 50 °C under an argon atmosphere until **1a** was consumed (2 F mol^{-1}). *Selected data* for **2a**: colorless oil, bp 80 °C (2 mmHg) (bath temperature) (62%); ν_{max}(neat)/cm^{-1} 1756 (C=O); δ_H($CDCl_3$, 200 MHz) 0.23 (s, 9 H), 0.89 (t, 3 H, J 6.6), 1.30–1.41 (m, 6 H), 1.62–1.72 (m, 2 H), 4.23 (t, 2 H, J 6.8); δ_F($CDCl_3$, 188 MHz, C_6F_6 as an internal standard) 38.7 (s, 2 F); δ_C($CDCl_3$, 50 MHz) 4.9, 13.9, 22.5, 25.4, 28.4, 31.3, 66.2, 121.0 (t, J_{CF} 269, CF_2), 166.3 (t, J_{CF} 26, C=O); *m/z* (GC/MS) 168 (M − C_6H_{12}), 152 (M − OC_6H_{12}), 73 (M − $CF_2CO_2C_6H_{13}$) (Found: C, 52.04; H, 8.99. Calc.: C, 52.35; H, 8.79%).

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