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Molar scale electrosynthesis of ethyl-2,2-difluoro-2-trimethylsilylacetate, a difluoromethylene building block precursor

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Abstract

Ethyl-2,2-difluoro-2-trimethylsilylacetate has been prepared by electrolysis of ethyl-2-chloro-2,2-difluoroacetate in one step, at a molar scale, in the presence of a large excess of chlorotrimethylsilane. The transfer of the ethyl-2,2-difluoroacetate moiety to various electrophiles has been achieved. © 2000 Elsevier Science Ltd. All rights reserved.

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The growing interest in difluoromethylated molecules due to their unique biological properties,[1a,b] have resulted in several efforts to provide viable electrosynthetic routes to their large scale preparation,[2] thus providing access to stable and stockable trimethylsilyldifluoromethylated synthons. We have recently reported the molar scale electroreductive synthesis of (trimethylsilyldifluoro)methylbenzene, an anionic difluorobenzylation agent, from trifluoromethylbenzene.[3] Our interest has since been focused on the electrochemical access to 2,2-difluoro-2-silylacetates prepared from trifluoro- or chlorodifluoroacetates in light of the synthetic potential in the synthesis of biologically-active compounds of difluoroketenesilylacetals[4] and 2,2-difluoro-2-trimethylsilylacetates ($TMSCF_2COOR$).[5] The synthesis of such compounds is generally difficult by conventional chemical routes, often requiring

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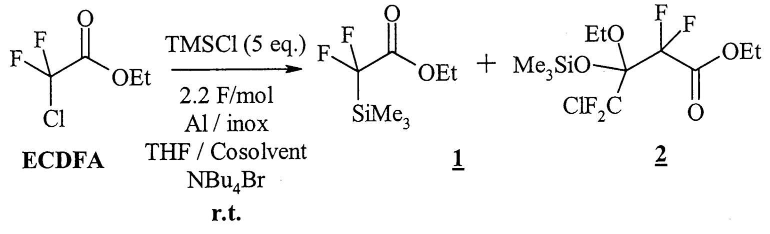
expensive bromodifluoroesters as starting materials. For example, the reported isolated yield of difluoroketenesilylacetals via a Reformatsky type reaction is very low (12%).[6] The selective reduction of ethylbromodifluoroacetate in NMP, leading to ethyl-2,2-difluorotrimethylsilyl-acetate, **1**, in 80% yield has been achieved by Yudin.[7] Nevertheless, no reaction has been reported from ethyltrifluoroacetate (ETFA) or ethylchlorodifluoroacetate (ECDFA) under these conditions. Burton and Easdon[8] have described the synthesis of **1**, by deprotonation/silylation of ethyldifluoroacetate, but the yield was not mentioned.

Encouraging studies on the silylation of ECDFA were in progress in our group[9] when Stepanov and co-workers[10] reported the electroreductive silylation of ethyltrifluoroacetate using the sacrificial anode electrochemical technique leading, in low yield (10–20%), to compound **1**; under their reactions conditions, the Claisen condensation product was mainly formed in 51% yield. A few months later, Uneyama et al.[5] found other electroreductive conditions providing at 0°C a mixture of **1** and its isomer, the difluoroketene silylacetal. Increasing the reaction temperature to 50°C allowed the sole ester **1** to be obtained in 47% isolated yield. However, the electrolytic conditions required a H-type divided cell, a low concentration of substrate and a high concentration of supporting electrolyte versus the substrate (4/1). Because of this, and the fact that the best yields were obtained with commercially unavailable esters (tertiobutyl and hexyltrifluoroacetate), their findings are not suitable for a large scale synthesis.

We report here the selective preparation of **1** from ECDFA, which is far cheaper than the corresponding bromo derivative. The first electroreduction of chlorodifluoroacetate was reported by Shono[11] who studied the addition of the resulting anion to aldehydes under electrolytic conditions that were similar to those used by Uneyama et al.[5] for the reduction of trifluoroacetates. In our particular case, we chose the sacrificial anode electrolysis technique[12] searching the best conditions for a molar scale synthesis. As shown in Scheme 1, the electrolysis performed in THF required the use of a cosolvent (HMPA, DMPU), a crucial large excess of trimethylchlorosilane (TMSCl) and a small amount of supporting electrolyte to insure the conduction at the very beginning of the reaction.

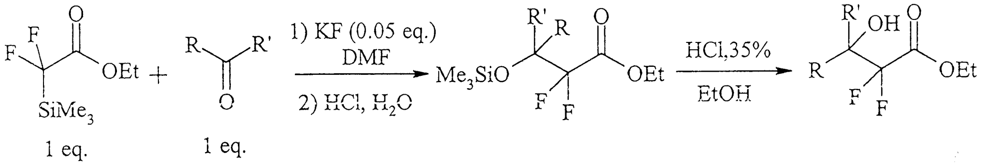


	Cosolvent :		
Conversion = 100%	HMPA	85%	15%
	DMPU	81%	10%

Scheme 1. Electrosynthesis of ethyl-2,2-difluoro-2-trimethylsilylacetate from ECDFA

At total conversion, the main product was found to be **1**, along with the product of the Claisen type reaction, **2**, without any trace of the corresponding difluoroketene silylacetal. In DMF as the sole solvent, the exclusive formation of **1** was achieved but the conversion was not complete (70%) due to a passivation of the electrodes. In order to progress towards a truly preparative electrolysis, we improved the conditions by increasing the concentration of the substrate while reducing the formation of side-product **2**. A typical electrolysis was carried out from 5 g (32.7 mmol) of ECDFA, 20 mL (158.2 mmol) of TMSCl, 16 mL of THF, 16 mL of DMPU and 250 mg (0.08 mmol) of tetrabutylammonium bromide as the supporting electrolyte. A previously described, an undivided cell[12] fitted with an aluminium rod as the anode and a concentric cylindrical stainless steel grid as the cathode was used, passing a 100 mA (0.07 A dm^{-2}) constant current (19 hours, 2.2 F mol^{-1}) at room temperature under a nitrogen atmosphere. At the end of the electrolysis, the selectivity, determined by GC, was found to be 93% in favour of **1**. The reaction mixture was then poured into 250 mL of iced water and extracted twice with 100 mL of diethyl ether. After drying the ethereal solution, 4.5 g of **1** was distilled (55°C/20 mmHg) with a 70% isolated yield. Spectroscopic data were identical to those reported in the literature.[5b] These conditions were applied to the synthesis of 140 g of **1** (65% isolated yield), using a tubular flow cell.[13]

The easy access to **1** in a large scale led us to study its nucleophilic reactivity towards various electrophiles under fluoride ion catalysis, according to Scheme 2 and Table 1.



Scheme 2. Anionic difluoroacetylation of diverse carbonyl compounds

KF/DMF was found to be a much better desilylating medium than TBAF/THF because of the faster hydrolysis of the F^-/**1** complex by the water in TBAF solution.[14] With acylchlorides, a stoichiometric amount of KF was required because the chloride ion that is liberated is unable to fulfil the desilylation reaction. Uneyama et al.[5] also reported the use of hexyldifluorotrimethylsilylacetate as a difluoromethyl building block but under rather different conditions: the silyl synthon was the hexyl ester, prepared from the commercially unavailable hexylchlorodifluluoroacetate, the electrophilic species was used in a threefold excess (which is not suitable when the electrophile is rare) and KF/CuI in a stoichiometric amount. Moreover, in our case, the resulting alcohols could be obtained, if wanted, in their trimethylsilylated protected forms. Additionally, the first example of the transfer of a CF_2COOEt moiety to an ester (ethyltrifluoroethylacetate) was achieved using a stoichiometric amount of KF.

Acknowledgements

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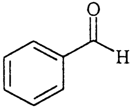
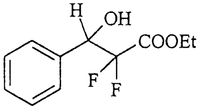
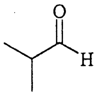
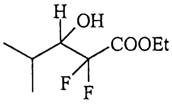
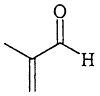
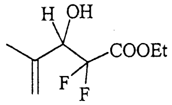
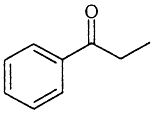
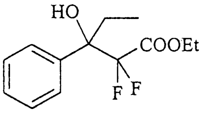
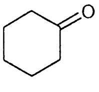
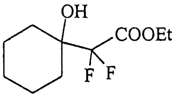
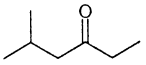
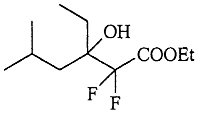
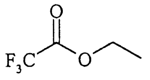
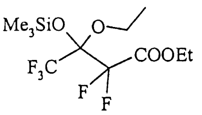
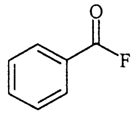
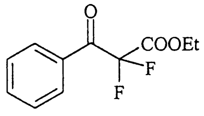
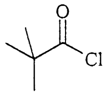
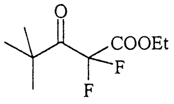
Table 1
2,2-Difluoro-2-trimethylsilylacetate as –CF_2-acetate building block

Electrophile	Product	Yield
		85%^{a}
		74%^{a}
		73%^{a}
		60%^{b}
		50%^{a}
		38%^{b}
		71%^{a}
		79%^{a}
		59%^{b,c}

[a] Isolated.
[b] Determined by ^{19}F NMR.
[c] KF stoichiometric.

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