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Electrochemical Synthesis of Fluorinated Ketones from Enol Acetates and Sodium Perfluoroalkyl Sulfinates

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ABSTRACT: The e and R_fSO_2Na in an The electrosynthesis perfluoroalkyl sulfina the resulting C radica	lectrochemical synthesis of flu undivided cell under constan proceeded via perfluoroalk te followed by addition to th al to a fluorinated ketone. The	uorinated ketones at current conditi cyl radical genera ne enol acetate an e method is applic	from enol acetates ons was developed. ation from sodium d transformation of able to a wide range	R _f SO₂Na		$R^1 \xrightarrow{\mathbf{O}}_{\mathbf{R}^2} R_f$

of enol acetates and results in the desired products in yields of 20 to 85%.

O rganofluorine compounds are attracting increasing attention, primarily because of their wide application in major areas of modern chemistry, such as the development of new functional materials and pharmaceuticals.^{1,2} Indeed, the number of fluorine-containing drugs and agrochemicals is impressive.³ Because of the importance of organofluorine compounds in medicinal chemistry and related fields,⁴ novel methods of introducing a perfluoroalkyl fragment into the specific position of organic molecules are highly desirable.

For a long time, two main approaches dominated this area: nucleophilic and electrophilic perfluoroalkylation.⁵ Nucleophilic perfluoroalkylation was achieved primarily using the silicon reagents, for example, the Ruppert–Prakash reagent (TMSCF₃).⁶ Two classes of reagents that are synthetic analogs of the R_f^+ cation have been developed for electrophilic perfluoroalkylation, perfluoroalkylchalcogen salts and iodonium salts,^{7,8} because the generation of the R_f^+ cation by a chemical reaction is extremely difficult.

In the past decade, radical fluoroalkylation processes have come to the forefront in the organofluorine chemistry.^{9–12} The main advantage of radical reactions is that they allow the introduction of fluorinated groups into a wider range of compounds for which the creation of corresponding carbanion or carbocationic centers is not available.^{13,14} Among the reagents for radical perfluoroalkylation, sulfinates, for example, Langlois reagent (CF₃SO₂Na), appear to be the most promising due to their stability, convenience of experimental manipulation, commercial availability, and ability to generate an R_f radical under the action of various oxidants.^{15–19}

We focus on the electrochemical radical perfluoroalkylation of enol acetates to produce fluorinated ketones using sodium perfluoroalkyl sulfinates. Enol acetates compare favorably to their analogs (silyl and alkyl enol ethers) due to their greater resistance to hydrolysis, which allows for electrolysis in wellconducting aqueous media. The few known examples of the electrochemical perfluoroalkylation of enol acetates are limited by low yields of products and the use of toxic, corrosive perfluorocarboxylic acids.^{20–22} Trifluoromethylation with stoichiometric amounts of chemical oxidants was performed using the Cu/TBHP system (Scheme 1a).^{23,24} The radical

Scheme 1. Fluoroalkylation of Enol Acetates and Their Electrochemical Sensitivity



approach to α -CF₃ ketones via the photoredox Ir-catalyzed trifluoromethylation of enol acetates using CF₃SO₂Cl was described (Scheme 1a).²⁵ Also α -CF₃ ketones can be prepared electrochemically from aryl alkynes and Langlois reagent.²⁶

The main idea of our work is to apply an electric current to the fluorinated ketone synthesis from enol acetates and R_fSO_2Na salts (Scheme 1b). An efficient electrochemical synthesis of fluorinated ketones from enol acetates and R_fSO_2Na was developed *via* R_f radical generation and its addition to enol acetates. The discovered process is unforeseen because enol acetates are electron-rich alkenes that can

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		CF ₃ SO ₂ Na ⁺ Ph 1a	$CCE \qquad Ph \qquad 2a$	CF3	
no.	A/C	electrolyte	current (mA)	N (F/mol)	yield 2a (%)
1	Pt/Pt	LiClO ₄	20	3	67
2	Pt/Pt	$NaBF_4$	20	3	68
3	Pt/Pt	<i>n</i> -Bu ₄ NClO ₄	20	3	68
4	Pt/Pt	$n-\mathrm{Bu}_4\mathrm{NBF}_4$	20	3	77
5	Pt/Pt	n-Bu ₄ NBF ₄	40	3	69
6	Pt/Pt	$n-\mathrm{Bu}_4\mathrm{NBF}_4$		0	n.r.
7	Pt/Pt		20	3	85
8	Pt/Pt		20	5	58
9	Pt/Pt		20	2.2	70
10	C/Pt		20	3	70
11	C/SS		20	3	73
12	GC/GC		20	3	72
13	Pt/GC		20	3	73
14	Pt/Cu		20	3	80
15 ^b	Pt/Pt		20	3	51
16 ^c	Pt/Pt		20	3	84
17^d	Pt/Pt		20	3	35
18 ^e	Pt/Pt		20	3	79
19 ^{<i>f</i>}	Pt/Pt		20	3	62
20 ^g	Pt/Pt		20	3	51

Table 1. α -CF₃ Ketone 2a Synthesis via Electrochemical Trifluoromethylation of Enol Acetate 1a^a

^{*a*}General procedure: undivided cell, plate cathode and anode (15 mm × 20 mm × 0.1 mm), constant current 20–40 mA (j = 6.7-13.3 mA/cm²), 1a (1.0 equiv, 1.0 mmol, 162.0 mg), CF₃SO₂Na (2.0 equiv, 2.0 mmol, 312.0 mg), electrolyte (0.5 equiv, 0.5 mmol), CH₃CN/H₂O (8 mL/2 mL), 20–25 °C, air atmosphere. Isolated yields. ^{*b*}1.0 equiv of CF₃SO₂Na. ^{*c*}3.0 equiv of CF₃SO₂Na. ^{*d*}DMSO/H₂O (8 mL/2 mL). ^{*e*}THF/H₂O (8 mL/2 mL). ^{*f*}CH₃CN (10 mL). ^{*s*}CH₃OH (10 mL). S, stainless steel; GC, glassy carbon.

undergo anodic oxidation to form α -acetoxy and α,β unsaturated carbonyl compounds (Scheme 1b).^{27–29}

In recent years, more and more attention has been paid to the use of electrochemistry in redox processes for the following reasons: the availability and the low cost of the electric current, the variety of electrochemical reaction mechanisms, and the decrease in waste.^{30–32} Electrolysis can be carried out in a divided or undivided cell under controlled potential (CPE) or constant current conditions (CCE).³³ Using an undivided cell is more practical, but at the same time, it is more difficult to implement because of the undesirable processes connected to the counter-electrode action.³⁴ The advantages of the constant current (CCE) conditions are the high current density, the small electrode surface, and the compact reaction vessels.

The study of the electrochemical perfluoroalkylation of enol acetates began by optimizing the electrosynthesis for the reaction between 1-phenylvinyl acetate 1a and CF₃SO₂Na, resulting in 3,3,3-trifluoro-1-phenylpropan-1-one 2a (Table 1). The use of silyl enol ether in this process did not lead to good results. (See the SI.) Silyl enol ethers were found^{35–37} to have oxidation potentials significantly lower than those of the enol acetates. The electron-accepting nature of the ester group in enol acetates is likely to be helpful in preventing the oxidation of the enol moiety.

Screening of the supporting electrolytes (entries 1-4) showed that the best yield of 2a (77%) was achieved with *n*-Bu₄NBF₄ (entry 4). A two-fold increase in the current density led to a slightly worse 2a yield (69%) (entry 5). Product 2a was not formed in the absence of an electric current (entry 6). Surprisingly, in the absence of a supporting electrolyte, the yield of 2a was 85% (entry 7). Thus all other experiments were conducted without a supporting electrolyte. Increasing (entry

8) or decreasing (entry 9) the electricity passed through the reaction mixture did not give better results. The reaction tolerated a wide range of electrode materials (entries 7 and 10-14). The **2a** yield was similar to that using 3 equiv of CF₃SO₂Na (entries 7 and 16) and dropped with the use 1 equiv of CF₃SO₂Na (entry 15). The use of DMSO/H₂O, THF/H₂O mixtures, CH₃CN, or CH₃OH as the solvent resulted in a lower yield of **2a** (entries 17-20). The conversion of enol acetate **1a** was >95% in most experiments.

Under the optimized reaction conditions (Table 1, entry 7), the scope of this electrochemical method for the α -CF₃ ketones 2 synthesis via the trifluoromethylation of enol acetates 1 was tested (Scheme 2).

The enol acetates from aryl ketones with methyl, methoxy, Cl, F, and Br groups reacted well to give corresponding products **2b–2f** in 63–79% yields. α -Alkyl-substituted α -CF₃ ketones **2g–2i** were synthesized in 67–81% yields. The naphthyl-containing enol acetate **1j** was converted into α -CF₃ ketone **2j** in a low 20% yield, probably due to the susceptibility of the naphthyl ring to oxidation.^{38,39} (The reaction was carried out in THF/H₂O (8:2) due to the insolubility of substrate **1j** in CH₃CN/H₂O (8:2).) To our delight, the reaction was compatible with aliphatic enol acetates **1k–1o** to give good (66–78%) yields of products **2k–2o**. It is worth noting that enol acetates from dicarbonyl compounds **1p** and **1q** did not react under our reaction conditions. The reaction with the oxidation-sensitive acetyl furan **1r** resulted in a mixture of inseparable products.

The established protocol was applied to the reaction of enol acetates 1 with C_4F_9 sulfinate (Scheme 3). The electrochemical perfluoroalkylation proceeded well to afford the corresponding C_4F_9 -containing ketones 3 in 32–58% yields. The moderate



Scheme 2. Scope of Synthesized α -CF₃ Ketones 2^{*a*}

"General procedure: undivided cell, platinum plate cathode and anode (15 mm \times 20 mm \times 0.1 mm), constant current 20 mA (j = 6.7 mA/cm²), 1 (1.0 equiv, 1.0 mmol), CF₃SO₂Na (2.0 equiv, 2.0 mmol, 312.0 mg), CH₃CN/H₂O (8:2, 10.0 mL), 3 F/mol, 20–25 °C, air atmosphere. ^bTHF/H₂O (8:2)

Scheme 3. Electrochemical Fluoroalkylation of Enol Acetates 1



yield of 3c can be explained by the electron-poor nature of the C=C bond due to protonation of the CH_3O group.

Finally, we focused on the reaction mechanism of the perfluoroalkylation. The electrolysis of enol acetate **1a** without

an R_f source resulted in a mixture of α -acetoxy and α -hydroxy products 4a and 5a (Scheme 4a), and thus it was



confirmed²⁷⁻²⁹ that enol acetates are sensitive toward anodic oxidation. The reaction with a TEMPO radical trap under the optimized conditions (Table 1, entry 7) afforded α -CF₃ ketone 2a in 34% yield with low 1a conversion, which may indicate the radical nature of the discovered process. The experiment in a divided electrochemical cell demonstrated the involvement of both the anodic and cathodic processes in efficient perfluoroalkylation (Schemes 4c and 5). A divided cell likely prevents the reactions (Scheme 5) of the intermediates generated on the anode and cathode. Also, the acidification of the anodic space in a divided cell leads to a significant yield of acetophenone formed as a result of the acid-catalvzed hydrolysis of the starting enol acetate 1a (Scheme 4c). Under an inert atmosphere, product 2a was obtained in low 42-47% yields (Scheme 4d), which emphasizes the participation of oxygen in the developed process. In both experiments (Scheme 4d), the insoluble residue was sedimented on the electrode surface, increasing the current resistance. The formation of the polymerization products on the anode surface probably decreases the conductivity.

Cyclic voltammetry (CV) was used to provide a study of the redox potentials of the substrates (Figure 1). The CV experiments showed the oxidation peak of CF_3SO_2Na at 1.2 V, which is in accordance with the CF_3SO_2 radical formation (Figure 1, curve b).^{40,41} The enol acetate 11 did not show considerable reactivity in anodic oxidation under the potential below 1.4 V (Figure 1, curve c). The mixture of CF_3SO_2Na with enol acetate 11 showed an irreversible anodic wave at 1.1 V, indicating that the mechanism involved a highly reactive species formed in the electron-transfer step (Figure 1, curve d). The current increase from 0.65 mA on curve b to 1.0 mA on curve d (Figure 1) may indicate the processes of the anodic oxidation to 11

Scheme 5. Proposed Mechanism of the Electrochemical Fluorinated Ketones 2 Synthesis





Figure 1. CV curves on a working glassy-carbon electrode (d = 3 mm) under a scan rate of 0.1 V/s for (a) background, (b) CF₃SO₂Na (0.05 M), (c) enol acetate 11 (0.025 M), and (d) CF₃SO₂Na (0.05 M) and enol acetate 11 (0.025 M) in 0.1 M *n*-Bu₄NBF₄ solution in CH₃CN/H₂O (8:2).

with radical C formation and the anodic oxidation of radical C into cation F (Scheme 5).

On the basis of CV studies, control experiments, and literature data,^{15,16} we propose the following pathway for the electrosynthesis of the fluorinated ketones **2**, presented in the example of α -CF₃ ketone synthesis (Scheme 5). The reaction begins with the anodic oxidation of the sulfinate anion to form the sulfonyl radical **A**,⁴² which further eliminates SO₂ to result in trifluoromethyl radical **B**.⁴³ Radical **B** is trapped with enol accetate **1**, resulting in the C-centered radical **C**.^{20–25} After that, there are a few possible pathways. The reaction of radical **C** with dissolved oxygen leads to acetoxy-hydroperoxide **D**.⁴⁴

The stability of peroxide **D** toward hydrolysis can be explained by stereoelectronic factors (especially the inverse α -effect⁴⁵ and the anomeric $n_0 \rightarrow \sigma^*_{C-0}$ interaction⁴⁶). Hydroperoxide **D** can be transformed into α -CF₃ ketone **2** by electrochemical reduction⁴⁷ or by the action of *in situ* formed sodium sulphite.⁴⁸ Also, the possibility of the direct anodic oxidation of radical **C** to cation $\mathbf{F}^{41,42}$ followed by the addition of water and the hydrolysis of acetal **E** cannot be excluded. In anhydrous CH₃CN, the elimination of acetyl cation from intermediate **F** also can provide **2**. The optimal amount of current passed through the reaction mixture is 3 F/mol, and the yield of **2a** is 85% (Table 1, entry 7). Thus the current yield of **2a** is in the range from 28 to 57% depending on the balance of reaction stages $\mathbf{C} \rightarrow \mathbf{F}$ and $\mathbf{C} \rightarrow \mathbf{D}$.

In summary, we have disclosed the electrochemical synthesis of fluorinated ketones from enol acetates and sodium perfluoroalkyl sulfinates in moderate to high yields. Langlois reagent serves as both the supporting electrolyte and the reagent. An electric current makes it possible to conduct the reaction without the application of unrecoverable chemical oxidants. The process was carried out under constant current conditions in an experimentally simple undivided electrochemical cell. With the help of CV and control experiments, a possible reaction pathway is suggested. Presumably, during the reaction, the perfluoroalkyl radical is generated followed by its capture by enol acetate and the subsequent transformation of the resulting C radical to the fluorinated ketone.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01643.

Experimental procedures, CV data, and characterization data of the starting and synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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