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Electrochemical fluoromethylation triggered lactonizations of alkenes under semi-aqueous conditions

Electrochemical difluoromethylation triggered lactonization of alkenes was realized under additional supporting electrolyte- and catalyst-free conditions. This method provides a direct route for the construction of unprecedented CF_2H -substituted lactones.

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Introduction

The introduction of fluorine atoms into organic molecules has attracted increasing interest because the incorporation of fluorine-containing groups can significantly modify the properties of bioactive molecules.1 In contrast to various methods for trifluoromethylation of organic substrates,2,3 direct difluoromethylation is still underdeveloped,4 even though the difluoromethyl group (CF₂H) is an intriguing structural motif in drug design.5 Among the existing methods for direct difluoromethylations, radical processes have played an important role in obtaining CF₂H-containing compounds.⁶ It is noteworthy that there are many recent reports of photoinduced difluoromethylations of heterocycles7 and alkenes.8 However, expensive Ir- or Ru-based photoredox catalysts and synthetically challenging CF₂H radical precursors are commonly required. Synthetic electrochemistry has the obvious advantage of generating radicals in a controllable way to minimize the possibilities of radical dimerizations, and can realize some transformations in ways that were previously difficult or inaccessible by traditional methods.9,10 In this context, Baran, Blackmond and co-workers disclosed an electrochemical difluoromethylation of heterocycles in a divided cell with zinc sulfinates as the difluoromethylating reagent and n-Bu₄NClO₄ as the supporting electrolyte (Scheme 1a).¹¹ Recently, a breakthrough in electrochemical difluoromethylation of alkynes with

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An electrochemical difluoromethylation triggered lactonization of alkenes was developed for the first time. This protocol employs readily prepared CF_2HSO_2Na as the difluoromethylating reagent, affording unprecedented CF_2H -containing lactones in moderate yields. Moreover, with CF_3SO_2Na as the trifluoromethylating reagent, a wide array of CF_3 -containing lactones were obtained under additional supporting electrolyte- and catalyst-free conditions.

 $CF_2HSO_2NHNHBoc$ was reported by Xu and co-workers with Et_4NBF_4 as the supporting electrolyte (Scheme 1b).¹² Given the importance of the CF_2H group in medicinal chemistry and the advantages of synthetic electrochemistry, the development of new electrochemical difluoromethylation reactions in a user-friendly single cell setup in the absence of an additional supporting electrolyte is attractive.

Lactones constitute useful building blocks in many pharmaceutically relevant molecules.¹³ In this regard, the construction of unprecedented CF₂H-containing lactones may be



readily prepared CF₂HSO₂Na or CF₃SO₂Na as the fluoromethylating reagents

Scheme 1 Electrochemical difluoromethylations.

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beneficial for medicinal chemistry.¹⁴ We have been interested in electrochemical lactonizations; however, only C-O bonds were constructed for these transformations.15,16 Considering the powerfulness of radical alkene difunctionalizations for the enhancement of molecular complexity in a single preparative operation,¹⁷ we speculated that it might be possible to construct CF₂H-containing lactones via an electrochemical difluoromethylation triggered lactonization of alkenes. The proposed synthetic pathway is shown in Scheme 1c. First, electrochemically generated fluoromethyl radical undergoes alkene addition to give a carbon radical intermediate. Further electrochemical oxidation gives a carbocationic intermediate, which undergoes subsequent nucleophilic cyclization to afford desired fluoromethylated lactones. While the proposed reaction pathway appears guite reasonable, its implementation proved to be challenging. First, the electrochemical oxidation of the carbon radical intermediate should occur quickly before H. abstraction. Second, the oxidation potentials of R_f radical precursors should be much lower than that of alkenes. Otherwise, the undesired single C-O bond formation would be the predominant process instead of desired alkene difunctionalization. In this report, we establish that electrochemical difunctionalization of alkenes can be achieved using semi-aqueous conditions to afford unprecedented CF2H-containing lactones with CF2-HSO₂Na¹⁸ as the CF₂H radical precursor under catalyst-free conditions. Moreover, this environmentally benign protocol could also be applicable for the access to CF₃-containing lactones in the absence of a metal catalyst, chemical oxidant, and additional supporting electrolyte.

Results and discussion

Initially, we commenced the electrochemical carboxydifluoromethylation reaction by using 1c and CF_2HSO_2Na (2) as



^{*a*} Reaction conditions: undivided cell, Pt plate ($1.5 \times 1.5 \text{ cm}^2$, $J = 6.7 \text{ mA} \text{ cm}^{-2}$), **1c** (0.5 mmol), **2** (1.25 mmol), CH₃CN/H₂O (7/1 mL, v/v), rt, 3 h, and 3.4 F. ^{*b*} Isolated yield.

the model substrates in an undivided cell equipped with platinum electrodes (Table 1). When HOAc was employed as the additive with a mixture of CH_3CN and H_2O as the solvent, the isolated yield of the corresponding CF_2H -containing lactone **3c** was obtained to be 67% (entry 1). Interestingly, adding supporting electrolytes into this reaction mixture led to a decrease in the yields (entries 2 and 3).¹⁹ Changing the Pt electrodes to graphite failed to maintain the reaction yield (entries 4 and 5). When the reaction was carried out in the absence of HOAc, only a trace amount of the desired product **3c** was detected (entry 6). This result suggested that the cathodic proton reduction may limit the overall reaction rate.²⁰ Replacing HOAc with HCl only led to a trace amount of the product **3c** (entry 7). Increasing or decreasing the current density failed to improve the yield (entries 8 and 9).

Having established the optimized reaction conditions, we then examined the substrate scope of electrochemical difluoromethylation triggered lactonization of alkenes. As shown in Table 2, the aromatic carboxylic acids were tolerated



^{*a*} Reaction conditions: undivided cell, Pt plate ($1.5 \times 1.5 \text{ cm}^2$, $J = 6.7 \text{ mA} \text{ cm}^{-2}$), **1** (0.5 mmol), **2** (1.25 mmol), additive HOAc (1.5 mmol), CH₃CN/H₂O (7/1 mL, v/v), 3 h, and 3.4 F. ^{*b*} Additive HOAc was replaced with TFA (1.5 mmol).

well to give the corresponding CF₂H-containing lactones in moderate yields (**3a-3o**). For the substituents on the Ar^2 ring, the *para*-substituents had little effect on the chemical yields (**3b-3i**). The *ortho*-substituted substrate **1j** showed decreased reactivity to give the corresponding product **3j** in 50% yield with TFA as the acidic additive instead of HOAc. When the fluoro group was placed at the *meta* position of the Ar^2 ring, the corresponding lactone **3k** was obtained in 79% yield. Replacing the phenyl group with the 1-naphthyl group decreased the yield of **3l** to 57%.

When Ar^2 was replaced with the methyl group, the corresponding lactone **30** was afforded in 46% yield. It is noteworthy that the challenging substrates of aliphatic carboxylic acids could also be tolerated to give the corresponding lactones **3p–3r** in 38–42% yields.

To make this synthetic methodology more appealing, the electrochemical trifluoromethylation triggered lactonization of alkenes was then examined. As shown in Table 3, moderate to excellent yields of CF₃-containing lactones were obtained regardless of the electronic nature of *para*-substitutions on the $Ar^2 ring (5a-5i)$. Changing the substitution on the $Ar^2 ring$ from the *para*-position to the *ortho*- or *meta*-position caused lower yields (5j–5l). The substrate containing a disubstituted Ar^2 group was also tolerated well affording the product 5m in 64% yield. The fused ring substituted substrates also underwent the



^{*a*} Reaction conditions: undivided cell, Pt plate ($1.5 \times 1.5 \text{ cm}^2$, $J = 6.7 \text{ mA} \text{ cm}^{-2}$), 1 (0.5 mmol), 4 (1.25 mmol, purity > 98%), additive HOAc (1.5 mmol), CH₃CN/H₂O (7/1 mL, v/v), 3 h, and 3.4 F. ^{*b*} Additive HOAc (1.5 mmol) was replaced with TFA (1.5 mmol).



Fig. 1 Cyclic voltammograms of substrates in 0.1 M LiClO₄/CH₃CN, using a Pt wire working electrode and glassy carbon and Ag/AgNO₃ (0.1 M in CH₃CN) as counter and reference electrodes at a 100 mV s⁻¹ scan rate: (a) background (0.1 M LiClO₄ in CH₃CN), (b) CF₃SO₂Na (5 mmol L⁻¹), (c) CF₂HSO₂Na (5 mmol L⁻¹), and (d) **1a** (5 mmol L⁻¹).

cyclizations smoothly to give the corresponding lactones 5n and 5p in 66% and 63% yields, respectively. Replacing the aromatic Ar^1 or Ar^2 group with aliphatic ones decreased the reaction efficiency, giving the corresponding lactones 5q and 5r in 53% and 69% yields, respectively. More importantly, the trisubstituted olefin was demonstrated to be a suitable substrate to give the lactone 5s in 42% yield.

In order to provide a rationale for the reaction pathway proposed in Scheme 1c, cyclic voltammetric (CV) experiments were carried out. As shown in Fig. 1, CF_2HSO_2Na and CF_3SO_2Na have the oxidation potentials of 0.72 V and 1.06 V, respectively. However, the oxidation potential of alkenes is 1.58 V. These results indicated that CF_2HSO_2Na and CF_3SO_2Na are much easier to be electrochemically oxidized to generate fluoromethyl radicals than the alkene moiety. The CV experiments which were carried out in $CH_3CN/HOAc$ or CH_3CN/H_2O also indicated that CF_2HSO_2Na and CF_3SO_2Na are much easier to be electrochemically oxidized than the alkene moiety (see the ESI† for details). The much lower oxidation potentials of CF_2H and CF_3 radical precursors than that of alkenes are the key to electrochemical carboxyfluoromethylation reactions.

Experimental

An undivided cell was equipped with a magnet stirrer and platinum plate ($1.5 \times 1.5 \text{ cm}^2$) electrodes. The substrate 2-(1-phenylvinyl)benzoic acid **1a** (112 mg, 0.5 mmol), CF₃SO₂Na **4** (195 mg, 1.25 mmol) and additive HOAc (86 µL, 1.5 mmol) were added to a mixed solvent of CH₃CN/H₂O (7/1 v/v). The resulting mixture was allowed to stir and electrolyze under constant current conditions ($J = 6.7 \text{ mA cm}^{-2}$) at room temperature for 3 hours. Then the volatile solvent was removed with a rotary evaporator and then water (10 mL) was added. The resulting mixture was extracted with ethyl acetate ($10 \times 3 \text{ mL}$). The combined organic layer was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography (ethyl acetate/petroleum ether = 1/15-1/10) on silica gel to afford the desired product **5a** in 93% yield.

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We have developed the first example of electrochemical difluoromethylation triggered lactonization of alkenes. Under additional supporting electrolyte- and catalyst-free conditions, a wide array of CF_2H -containing lactones were obtained in moderate yields. Moreover, this environmentally benign method is also applicable to access pharmaceutically important CF_3 -containing lactones in the absence of a metal catalyst, chemical oxidant, and additional supporting electrolyte.

Conflicts of interest

There are no conflicts to declare.

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