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Electrochemical trifluoromethylalkoxylation of endocyclic enamides in batch and flow

Elise Leclercq,^a Waël Barakat,^a Radhouan Maazaoui,^b Maël Penhoat,^a Isabelle Gillaizeau,^b and Laëtitia Chausset-Boissarie^{a,c*}

^a Lille Univ., CNRS, MSAP, USR 3290, 59000 Lille, France

^b Université d'Orléans, CNRS, UMR 7311, ICOA, 45067 Orléans, France

^c Normandy Univ. INSA Rouen Normandy, UNIROUEN, CNRS COBRA (UMR6014), 76000 Rouen, France
E-mail : laetitia.chausset@univ-rouen.fr

Abstract. A regioselective electrochemical oxytrifluoromethylation of endocyclic enamides is reported. The 1,2-difunctionalization proceeds under mild conditions and employs the inexpensive bench stable Langlois' reagent. This multicomponent strategy gives access to a wide range of α,β -substituted amines by means of various alcohols as nucleophiles in high yield and with good functional group tolerance. In addition, an electrochemically induced C-H trifluoromethylation of enamides has been developed. A continuous flow protocol using a commercial microflow electrochemical reactor was also developed with improved reaction performance and efficiency over traditional batch versions without any supporting electrolyte.

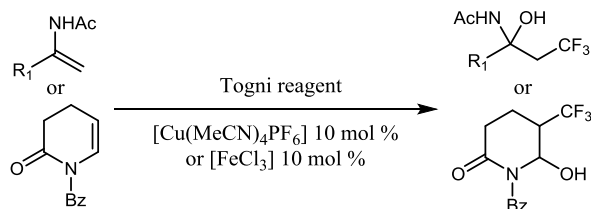
Keywords: enamides; electrochemical; 1,2-difunctionalization; trifluoromethylation; flow cell

Accessing trifluoromethylated compounds has long been a target in synthetic methodology. This prevalent structural motif has found multiple applications in pharmaceuticals, agrochemicals and materials science. Indeed, the introduction of a trifluoromethyl group prevents oxidative metabolism and hugely impacts the physical and pharmacokinetic properties such as lipophilicity and bioavailability, and more generally the overall biological activities of parent molecules.^[1] In this context, the development of efficient strategies for the direct introduction of a trifluoromethyl (CF_3) moiety has recently attracted considerable attention.^[2] Electron rich alkenes such as enamides have found widespread applications as they are a privileged motif in numerous bioactive natural products and pharmaceuticals and they are versatile building blocks for the synthesis of valuable complex amino derivatives.^[3] In particular, enamide 1,2-difunctionalization has been extensively recognized as an efficient atom economical procedure for the construction of α,β -substituted amines. Several synthetic strategies to access structural diversity have therefore been developed relying on two main approaches: radical mediated addition^[4] and transition-metal tandem catalysis.^[5] While these methods are useful, few trifluoroalkoxylation methodologies are reported. In 2012, Lho and co-workers developed a copper-catalysed system for the oxytrifluoromethylation of N-vinylacetamide derivatives using Togni's reagent as the

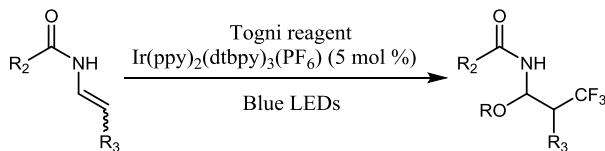
trifluoromethyl group.^[6] Following up, the group of Gillaizeau reported an iron-catalyzed version *via* an atom transfer radical mechanism, but with a unique example (Figure 1A).^[7] Another elegant example was demonstrated by the Magnier and Masson groups through an iridium catalyzed photocatalytic oxytrifluoromethylation of enecarbamates (Figure 1B).^[8] Despite these important contributions, these strategies have many challenges such as limited substrate scope, expensive metallic catalytic systems or CF_3 sources. Therefore, the development of an efficient, cost-effective and sustainable alternative to access β -trifluoromethyl amines is still highly desirable.

Recently, electrochemistry has been revived as an attractive sustainable and enabling method for redox processes as it employs clean electrical energy avoiding the use of stoichiometric amounts of oxidants that compromise the atom-economy.^[9] In this context, electrochemical oxytrifluoromethylation has attracted increasing attention for the 1,2-difunctionalization^[10] of alkenes notably *via* the use of the inexpensive bench stable Langlois reagent ($\text{CF}_3\text{SO}_2\text{Na}$) as radical CF_3 precursor.^[11] However to the best of our knowledge, the direct regioselective electrochemical oxytrifluoromethylation of enamides has remained an unexplored area. Based on our continuous interest in developing environmentally benign tools,^[12] we herein report a practical method for both the oxytrifluoromethylation and trifluoromethylation of N-protected dihydropyridinones as endocyclic enamides with Langlois reagent (Figure 1C). The metal free protocol is mild and displays a broad substrate scope. In addition, the use of continuous-flow electrochemical reactor improved the rate of the oxytrifluoromethylation and increased the yields in the absence of supporting electrolyte.

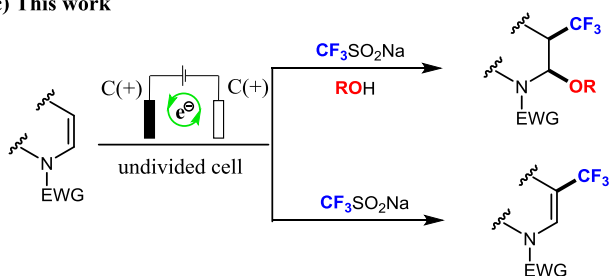
a) Metal catalyzed oxytrifluoromethylation of enamides



b) Photoredox-catalyzed oxytrifluoromethylation of enamides



c) This work



- Electricity as green oxidant
- Substrate generality
- Short reaction time in flow
- Mild reaction conditions

Figure 1. Approaches for the oxytrifluoromethylation of enamides.

At the outset, *N*-benzyl-3,4-dihydro-2(*1H*)-pyridinone (**1a**) was selected as the benchmark substrate to explore the direct oxytrifluoromethylation of cyclic enamides with Langlois reagent ($\text{CF}_3\text{SO}_2\text{Na}$) in an undivided electrochemical cell under constant current electrolysis (Table 1). The initial reaction was performed with glassy carbon (GC) plate electrodes in the presence of $n\text{Bu}_4\text{NBF}_4$ as the supporting electrolyte in a 9:1 acetonitrile/water mixture under galvanostatic conditions at $2.2 \text{ F}\cdot\text{mol}^{-1}$ (10 mA for 90 min) at room temperature, delivering the desired product **2aa** in 70% of yield (Entry 1). Performing the electrolysis with platinum plate (Pt) as anode led to a significant loss in the yield (Entry 2). Although the product yield of **2aa** was slightly lower with graphite plate as electrodes, unreacted starting material was recovered (20 %) due to incomplete conversion (Entry 3). Therefore, all subsequent experiments were conducted with graphite plate as electrodes. We then investigated the effects of different ratios of solvent mixtures and lower yields were obtained (Entries 4-5). Replacing $n\text{Bu}_4\text{NBF}_4$ with $n\text{Bu}_4\text{NClO}_4$ or LiClO_4 resulted in a lower yield, while better yields were obtained with $n\text{Et}_4\text{NBF}_4$ and $n\text{Et}_4\text{NOTs}$ (Entries 6-9). However, electrode consumption was observed with $n\text{Et}_4\text{NBF}_4$. Ultimately, on increasing the applied charge to $4 \text{ F}\cdot\text{mol}^{-1}$ at constant current (8 mA), an excellent yield for the desired product was achieved (Entries 10-11).

Interestingly, the reaction proceeded in the absence of any supporting electrolyte but with a lower yield (entry 12). Finally, control experiments demonstrated that the reaction did not proceed in the absence of electric current, confirming the electrochemical nature of the process (entry 13).

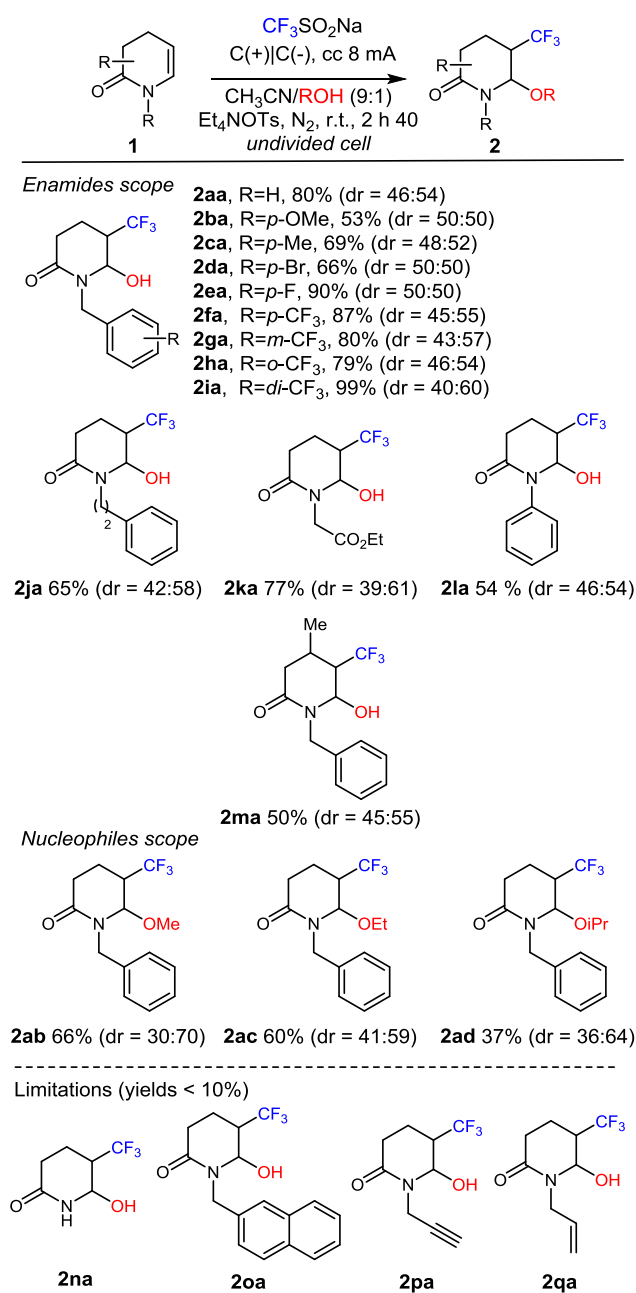
Table 1. Optimization of the reaction conditions.^[a]

Entry	Electrodes	Electrolyte	Q (F/mol)	Yield (%) ^[b]
1 ^[c]	GC(+) GC(-)	$n\text{Bu}_4\text{NBF}_4$	2.2	70
2 ^[d]	C(+) Pt(-)	$n\text{Bu}_4\text{NBF}_4$	2.2	42
3	C(+) C(-)	$n\text{Bu}_4\text{NBF}_4$	2.2	65
4 ^[e]	C(+) C(-)	$n\text{Bu}_4\text{NBF}_4$	2.2	53
5 ^[f]	C(+) C(-)	$n\text{Bu}_4\text{NBF}_4$	2.2	60
6	C(+) C(-)	$n\text{Bu}_4\text{NClO}_4$	2.2	50
7	C(+) C(-)	LiClO_4	2.2	38
8	C(+) C(-)	$n\text{Et}_4\text{NBF}_4$	2.2	73
9	C(+) C(-)	$n\text{Et}_4\text{NOTs}$	2.5	72
10	C(+) C(-)	$n\text{Et}_4\text{NOTs}$	3.5	75
11	C(+) C(-)	$n\text{Et}_4\text{NOTs}$	4	80
12	C(+) C(-)	none	4	70
13	C(+) C(-)	$n\text{Et}_4\text{NOTs}$	-	NR

^[a]Batch reaction conditions: **1a** (0.2 mmol, 1 equiv), $\text{CF}_3\text{SO}_2\text{Na}$ (0.6 mmol, 3 equiv), electrolyte [0.1 M] and a mixture of $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (9/1, 10 mL), IKA undivided cell, graphite plate electrodes ($8 \times 2 \times 40 \text{ mm}$), constant current at 8 mA, r.t. ^[b]Yield was determined by ^1H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. ^[c]Glassy carbon plate ($8 \times 2 \times 40 \text{ mm}$) as electrodes. ^[d]Pt plate cathode ($20 \times 60 \text{ mm}$). ^[e] $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (8/2, 10 mL). ^[f] $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (95/5, 10 mL).

With the optimized reaction conditions in hand, the scope of the electrochemical oxytrifluoromethylation of enamides was then evaluated in batch (Scheme 1). The reaction is compatible with various substituents on the para-position of the benzyl ring of 3,4-dihydro-2(*1H*)-pyridinones, affording the corresponding products **2da-fa** containing electron-withdrawing groups (trifluoromethyl and halides) with slightly higher yields than products **2ba-ca** containing electron-donating groups (methyl and methoxy). The variation of the steric hindrance was found to have little influence on the reaction efficacy smoothly to provide the desired products **2ga-ha** in high yields. Di-trifluoro *N*-benzyl dihydropyridinone was also a suitable substrate for this reaction, affording the desired product **2ia** in almost quantitative yield. Importantly, this protocol exhibits a broad tolerance to aliphatic substituents and a functionality such as ester (**2ka**) was tolerated,

providing opportunities for the late-stage functionalization of the molecule.

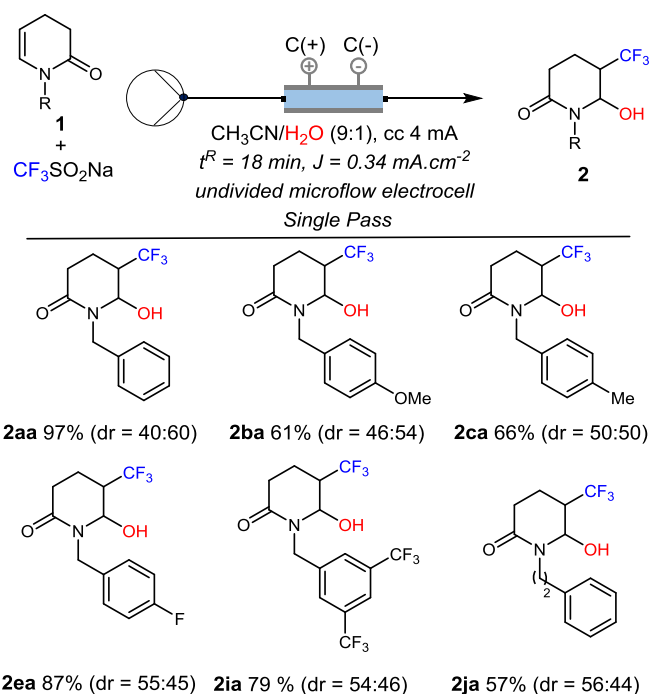


Scheme 1. Substrate scope for the oxytrifluoromethylation of enamide derivatives with different nucleophiles. Batch reaction conditions: **1** (0.2 mmol, 1 equiv), **2** (0.6 mmol, 3 equiv), *n*Et₄NOTs [0.1 M], CH₃CN/ROH (9/1, 10 mL), IKA undivided cell, graphite plate electrodes (8 × 2 × 40 mm), constant current = 8 mA, at room temperature for 2 h 40 ($J = 2.5 \text{ mA}\cdot\text{cm}^{-2}$, $4 \text{ F}\cdot\text{mol}^{-1}$), dr determined by ¹H analysis of crude mixtures.

Additionally, other enamides such as *N*-phenyl derivative **2la** provided a lower yield. The presence of a methyl substituent at the C4-position of the dihydropyridinone core did not adversely affect the reaction, yielding product **2ma** in 50% yield. Unfortunately, it was found that free endocyclic

enamides or enamides with naphthyl and terminal alkene or alkyne substituents (**2na-qa**) did not undergo productive reactions, as many undetermined by-products were observed. Reactions with other alcohols as nucleophiles were also tested and moderate to good yields were obtained (**2ab-ad**, 66-37%), the yield being directly correlated with the nucleophilic character of the alcohol.

The use of continuous-flow microreactors accelerates electrocatalytic reactions due to narrow diffusion distance between the electrodes, high electrode surface-to-volume ratio and enhanced mass transfer characteristics.^[13] Thus, in order to obtain higher conversions with shorter reaction times with a minimum amount of supporting electrolyte, we then evaluated this methodology under single-pass continuous flow conditions using a commercially available microflow electrocell (IKA Electrasyn Flow, 600 μL, 12 cm² surface area).^[14]



Scheme 2. Substrate scope for the oxytrifluoromethylation of enamide derivatives in flow. Reaction conditions: **1a** (0.2 mmol, 1 equiv), Langlois reagent (3 equiv), and CH₃CN/H₂O (9/1, 10 mL), IKA ElectraSyn Flow undivided cell (0.6 mL) with graphite plate electrodes (20 × 60 mm), PTFE gasket 0.50 mm, constant current = 4 mA ($J = 0.34 \text{ mA}\cdot\text{cm}^{-2}$, $3.8 \text{ F}\cdot\text{mol}^{-1}$) at room temperature for 18 min ($33.3 \mu\text{L}\cdot\text{min}^{-1}$), dr determined by ¹H analysis of crude mixtures.

Hence, based on batch experiments we reinvestigated the applied amount of charge (Table S1, Supporting Information) and the residence times (Table S1, SI). We were delighted to find that the reaction could be completed in flow in only 18 min in galvanostatic mode at 4 mA corresponding to a current density of

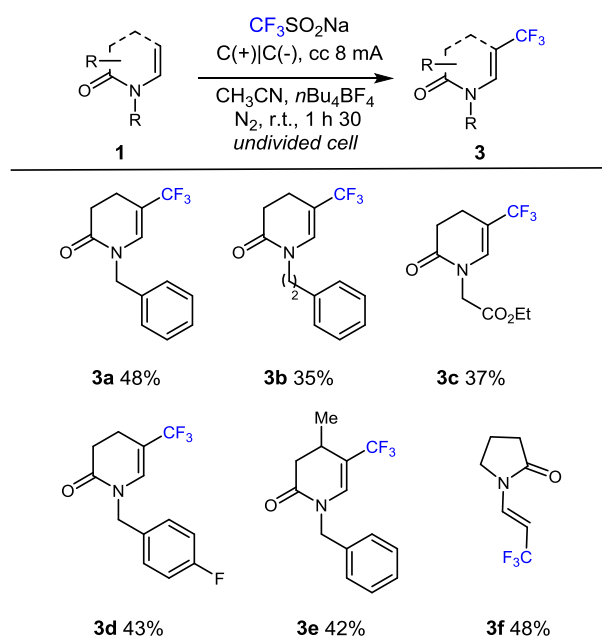
0.34 mA.cm⁻² and a total amount of charge of 3.8 F.mol⁻¹ at room temperature with excellent yield (Scheme 2). More importantly, the short interelectrode distance within the microflow cell which minimizes the ohmic drop, allowed to achieve excellent yields in the absence of any supporting electrolyte, making the process much greener. Interestingly, when the reaction was performed with the Vapourtec flow cell (625 μL, 12 cm² surface area) a lower reaction rate was obtained which could be due to a different cell geometry. Notably, higher yields with significantly shorter reaction times (18 min vs 4 h) were observed in most cases (97-55%). Finally, energy consumption of the reaction performed in flow is much lower compared to that of the batch process (5.47 kW.g⁻¹ in batch vs 2.75 kW.g⁻¹ in flow) making the transformation even more sustainable. The productivity of the optimized flow process is modest (0.99 mmol/day with 97% yield), hence to obtain better space-time yields flow cell with higher surface area in combination with a sizing up strategy are needed.^[15] In a similar vein, we turned our attention to the direct trifluoromethylation of enamides because to the best of our knowledge no electrochemical trifluoromethylation of endocyclic enamides has been reported.^[10c, 16] To our delight, the desired product **4a** was obtained in 48% yield under galvanostatic conditions (8 mA for 90 min, 2.2 F.mol⁻¹) at room temperature, in an undivided cell equipped with graphite plate electrodes and *n*Bu₄NBF₄ as the supporting electrolyte in dry acetonitrile (Table 2, entry 1).

Table 2. Optimization of the electrochemical trifluoromethylation of enamides.^[a]

Entry	Variation from the standard conditions	Yield (%) ^[b]
1	None	48
2 ^[c]	Pt as cathode	40
3 ^[d]	Ni as cathode	37
4	<i>n</i> Bu ₄ NPF ₆ as electrolyte	19
5	<i>n</i> Bu ₄ NClO ₄ as electrolyte	32
6	<i>I</i> = 10 mA	32
7	<i>I</i> = 4 mA	46
8	3.0 F.mol ⁻¹	33
9	No electric current	NR

^[a]Batch reaction conditions: **1a** (0.2 mmol, 1 equiv), **2** (0.6 mmol, 3 equiv), *n*Bu₄NBF₄ [0.1 M] in CH₃CN (10 mL), IKA undivided cell, graphite plate electrodes (8 × 2 × 40 mm), constant current at 8 mA, at room temperature for 1 h 30 (*J* = 2.5 mA.cm⁻², 2.2 F.mol⁻¹). ^[b]Yield was determined by ¹H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. ^[c]Pt plate cathode (20 × 60 mm). ^[d]Ni plate cathode (8 × 2 × 40 mm).

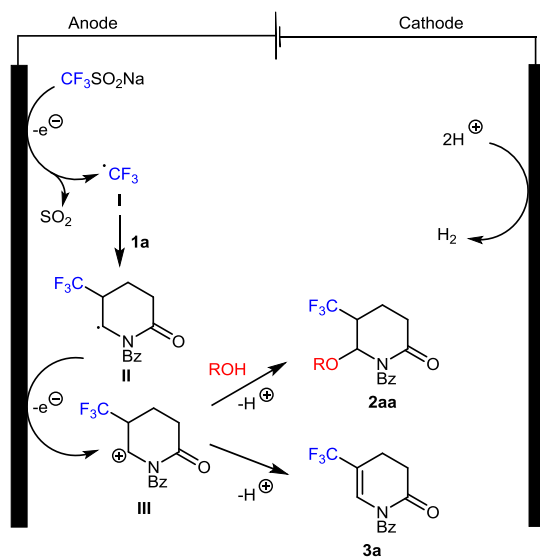
With a Pt or a Ni anode instead of a graphite anode, the efficiency of the reaction decreased (entry 2-3). The nature of the electrolyte significantly influenced the reaction efficiency. Replacing *n*Bu₄NPF₆ with *n*Bu₄NClO₄ led to lower yields (entries 4-5). Besides, higher or lower current density (e.g., 10 mA, 4 mA) was not conducive to this reaction (entries 6-7). Notably, the yield was also clearly diminished with an increase in charge to 3.0 F mol⁻¹ (entry 8). Electricity was essential for the reaction, and the reaction did not proceed at all without electrolysis (entry 9). With these optimized conditions in hand, the scope of enamides was explored (Scheme 3). The electrochemical trifluoromethylation showed total β-regioselectivity where only C3 trifluoromethylated products were found regardless of the substituents on the amine (**3e-f**). However, some by-products due to trifluoromethylation of the benzyl substituent were detected by NMR spectroscopy. Unfortunately, since the Langlois reagent is partially soluble in the reaction mixture translation of batch conditions to a continuous flow process was not possible.



Scheme 3. Substrate scope for the trifluoromethylation of enamide derivatives in batch. ^aReaction conditions: **1** (0.2 mmol, 1 equiv), Langlois reagent (0.6 mmol, 3 equiv), *n*Bu₄NBF₄ [0.1 M], CH₃CN (10 mL), IKA undivided cell, graphite plate electrodes (8 × 2 × 40 mm), constant current = 8 mA (*J* = 2.5 mA.cm⁻², 2.2 F.mol⁻¹) at room temperature for 1 h 30.

To obtain more insight into the reaction process, a series of control experiments was conducted. After the addition of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, 3.0 equiv) or butylated hydroxytoluene (BHT, 3.0 equiv) as radical scavenger, the oxytrifluoromethylation reaction was inhibited.

To gain further insight into the mechanism, cyclic voltammetry experiments were carried out. Cyclic voltammetry (CV) analysis of $\text{CF}_3\text{SO}_2\text{Na}$ in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (v/v 9:1) with LiClO_4 as electrolyte showed irreversible anodic oxidation waves at a potential lower than that of N-benzyl-3,4-dihydro-2(1*H*)-pyridinone (**1a**) (1.30 and 1.50 V vs Ag/AgCl, respectively), which indicates that $\text{CF}_3\text{SO}_2\text{Na}$ was oxidized preferentially at the anode (Figure S2, SI). Based on control experiments and literature precedents we suggest a plausible mechanism of these transformations as outlined in scheme 4.



Scheme 4. Proposed reaction mechanism.

The electrochemical transformation is initiated by a single electron transfer (SET) oxidation of $\text{CF}_3\text{SO}_2\text{Na}$ on the anode surface. The CF_3 radical, formed through the fast extrusion of SO_2 , could then add onto the double bond of N-benzyl-3,4-dihydro-2(1*H*)-pyridinone (**1a**) leading to the formation of the neutral radical **II**, which further undergoes a second oxidation event. Finally, the resulting cationic intermediate **III** could be trapped by the alcohol, affording the corresponding α -hydro- β -trifluoromethyl amide **3**. In the absence of alcohol, the release of proton afforded the desired product **3a**. Simultaneously with oxidative processes, hydrogen reduction occurs as a cathodic half-reaction.

In conclusion, we have developed an electrochemical oxytrifluoromethylation and trifluoromethylation of endocyclic enamides with Langlois reagent as a cheap and easy to handle source of the trifluoromethyl radical. Moreover, combining a flow process with the electrochemical process decreases the reaction time while maintaining good yields, eliminates the use of electrolyte and reduces the energy consumption of the reaction by nearly 50 %, demonstrating the sustainability of the presented methodology.

Experimental Section

General Procedure A for the electrochemical oxytrifluoromethylation of enamides **1** under batch conditions.

To a 10 mL undivided IKA ElectraSyn 2.0 vial, equipped with a stirrer bar and IKA graphite electrodes, were added enamides **1** (0.2 mmol, 1 eq), Langlois reagent (0.6 mmol, 3 eq) and then a mixture of $\text{MeCN}:\text{H}_2\text{O}$ (9:1, 10.0 mL). The electrolysis was conducted at constant current conditions at room temperature with 8 mA as current ($J = 2.5 \text{ mA}\cdot\text{cm}^{-2}$) during 4 h (4.0 $\text{F}\cdot\text{mol}^{-1}$) under N_2 . The mixture was washed with a saturated solution of NH_4Cl and extracted with EtOAc. The combined organics were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to afford the desired product **2**.

General Procedure B for the flow electrochemical oxytrifluoromethylation of enamides **1**.

A solution of enamides **1** (0.2 mmol, 1 eq), Langlois reagent (0.6 mmol, 3 eq) in a mixture of $\text{MeCN}:\text{H}_2\text{O}$ (9:1, 10.0 mL) was pumped through the ElectraSyn flow cell ($H = 500 \mu\text{m}$, $L = 60 \text{ cm}$, $l = 20 \text{ cm}$, $V = 0.6 \text{ mL}$) equipped with graphite electrodes and prefilled with the reaction mixture. The solution was pumped through the microflow cell at $0.033 \text{ mL}\cdot\text{min}^{-1}$ at a constant current of 4 mA at room temperature ($J = 0.34 \text{ mA}\cdot\text{cm}^{-2}$, 3.8 $\text{F}\cdot\text{mol}^{-1}$). The reaction mixture was collected in a round-bottom flask at the reactor output after 3 dead volumes of the reactor. The collected reaction mixture was then diluted in EtOAc, washed with NH_4Cl saturated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to afford the desired product **2**.

General Procedure C for the electrochemical trifluoromethylation of enamides **1** under batch conditions.

To a 10 mL undivided IKA ElectraSyn 2.0 vial, equipped with a stirrer bar and IKA Graphite electrodes, were added enamides **1** (0.2 mmol, 1 eq), Langlois reagent (0.6 mmol, 3 eq) and dry MeCN (10.0 mL). The electrolysis was conducted at constant current conditions at room temperature with 8 mA ($J = 2.5 \text{ mA}\cdot\text{cm}^{-2}$) as current during 90 min (2.2 $\text{F}\cdot\text{mol}^{-1}$) under N_2 . The mixture was washed with a saturated solution of NH_4Cl and extracted with EtOAc. The combined organics were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to afford the desired product **3**.

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