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An electrolyte free electrochemical C-H trifluoromethylation of 2-pyridones under batch and flow conditions

Elise Leclercq,^a Aurélien Moncomble,^b Céline Debavelaere,^{a, c} Mathieu Beaucamp,^a Maël Penhoat,^a and Laëtizia Chausset-Boissarie*^a

Herein, we report, a direct C3 trifluoromethylation of 2-pyridones including unprotected derivatives by an electrochemical approach using the readily available Langlois's reagent as the CF₃ source in the absence of electrolyte. The trifluoromethylation under transition metal- and oxidant-free conditions occurred site-selectively to give the desired products in moderate to good yields under ambient conditions. Interestingly, significant acceleration rate, improved yields and selectivity as well as reduce energy consumption were obtained under microfluidic conditions.

2-Pyridones are important structural motif widely found in many biologically active natural products¹ and pharmaceuticals² including lyconadin A (anticancer),^{1c} huperzine A (AChE inhibitor),³ HIV NNRT inhibitor,⁴ Pirfenidone (anti-idiopathic pulmonary fibrosis),⁵ and milrinone (anti heart failure)⁶ as show in figure 1.

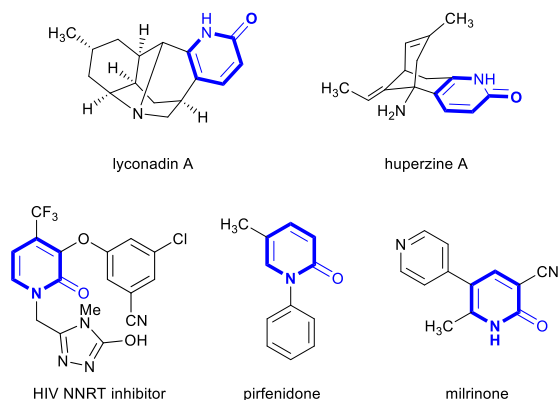


Figure 1 Representative biologically active compounds containing 2-pyridone scaffolds

The introduction of the trifluoromethyl (-CF₃) group can greatly alter the physico-chemical and electronic properties such as lipophilicity, metabolic stability and bioavailability of the parent bioactive molecules.⁷ Therefore, trifluoromethylation of pharmaceuticals and agrochemicals has emerged as one of the most attractive strategies to improve the success of discovery program.⁸ As a result, the development of direct C-H

trifluoromethylation methodologies of heterocycles has spurred tremendous efforts⁹ however, trifluoromethylation of electron-deficient pyridones which are known to be highly challenging and thus low yielding remains scarce (Figure 2). Initially reported direct radical trifluoromethylation protocols of pyridones suffered from the need of strongly oxidizing conditions (stoichiometric amount of XeF₂¹⁰ or Mn(OAc)₃¹¹), transition-metal catalysts in combination with an excess of base and oxidant¹² or expensive CF₃ source (Figure 2, A).¹³ Recently, visible light photoredox-catalyzed trifluoromethylation of pyridones have also been reported. Nevertheless, the use of unrecyclable noble heavy metal¹⁴ or scarce available organophotocatalysts,¹⁵ which generates environmentally hazardous waste greatly hamper their further application in the perspective of green and sustainable chemistry (Figure 2, B). As a consequence, the development of an efficient and environmentally friendly method for the selective introduction of CF₃ group into 2-pyridones is still in urgent demand. In the past few years, organic electrochemistry has re-emerged as a powerful sustainable tool for achieving C-H bond functionalization as it employs a clean and traceless energy source in place of dangerous and polluting oxidants that compromises the atom-economy.¹⁶ In this context, electrochemical C-H trifluoromethylation¹⁷ has attracted increasing attention for the construction of CF₃-containing heterocycles notably *via* the use of the bench stable, unexpensive and easily handle Langlois' reagent (CF₃SO₂Na) as radical CF₃ precursor.¹⁸ One major limitation of organic electrosynthesis however, is the need of an ionic medium of high conductivity to ensure the charge transport through the solution. In this regard, supporting electrolyte which is necessary for most organic electrosynthesis increases costs and waste production¹⁹ thus, electrolyte-free electrooxidation is important and remains underexplored.²⁰ This drawback can be circumvent using continuous microflow cells since a very small interelectrode distance increases heat and mass transfer as well as reaction efficiency and selectivity, enhances reaction rate and facilitates upscaling efforts.²¹ With extension of our continuous interest in developing efficient continuous flow protocols as environmentally benign tools,²² we herein firstly described an electrochemical method for the selective trifluoromethylation of 2-pyridones under electrolyte- and catalyst-free conditions at room temperature in batch and in flow. It is interesting to note that the reported procedure shows the better qualitative sustainability indicators and quantitative

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green metrics²³ among the reported procedures described above (Table S1, SI).

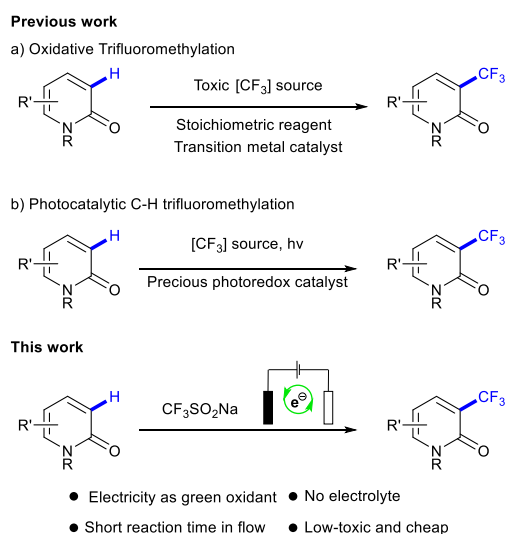
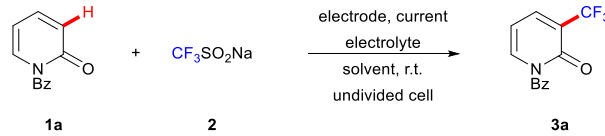


Figure 2 Strategies for the C-H trifluoromethylation of 2-pyridones.

We commenced our investigation with N-benzyl-2-pyridone (**1a**) and Langlois' reagent (**2**) as model substrates in an undivided cell to probe various reaction parameters under electrolytic conditions (Table 1). The initial reaction was performed with graphite plate electrodes and *n*Bu₄NBF₄ as the supporting electrolyte in acetonitrile (CH₃CN) under galvanostatic conditions at 10 mA for 2 h at room temperature, delivering the desired product **3a** in modest yield (Entry 1). Performing the electrolysis with glassy carbon plate electrodes led to an obvious loss in the yield (Entry 2). Although the product yield of **3a** could be slightly improved with platinum plate as anode (Entry 3), the use of graphite plate for the both electrodes would be more convenient and accessible for further investigation. Decreasing the current to 8 mA afforded the desired product in 31% of yield (Entry 4) while increasing the current to 15 mA led to a decrease in reaction yield (Entry 5). Additionally, the evaluation of the supporting electrolyte disclosed that LiClO₄ was superior and the desired product **3a** could be obtained in 34% (Entries 6-8). When the reaction was carried out in a mixture of acetonitrile and water (V/V 8:2) a better yield (43%, entry 9) was observed. Other ratio of solvent mixtures failed to improve the yields (Entries 10-11). A further increase of the reaction time to 3 h enhanced the yield of **3a** to 52% (Entry 12). To our delight, the desired product **3a** could be isolated in 41% yield (Entry 13) in the absence of an external supporting electrolyte; therefore, the addition of conducting salt considered as waste in the overall process could be

suppressed. Finally, when the reaction time was prolonged to 6 h, **3a** was obtained in 55% yield (Entry 14). It is noteworthy that there is no reaction in the absence of electric current confirming the electrochemical nature of the process (entry 15).

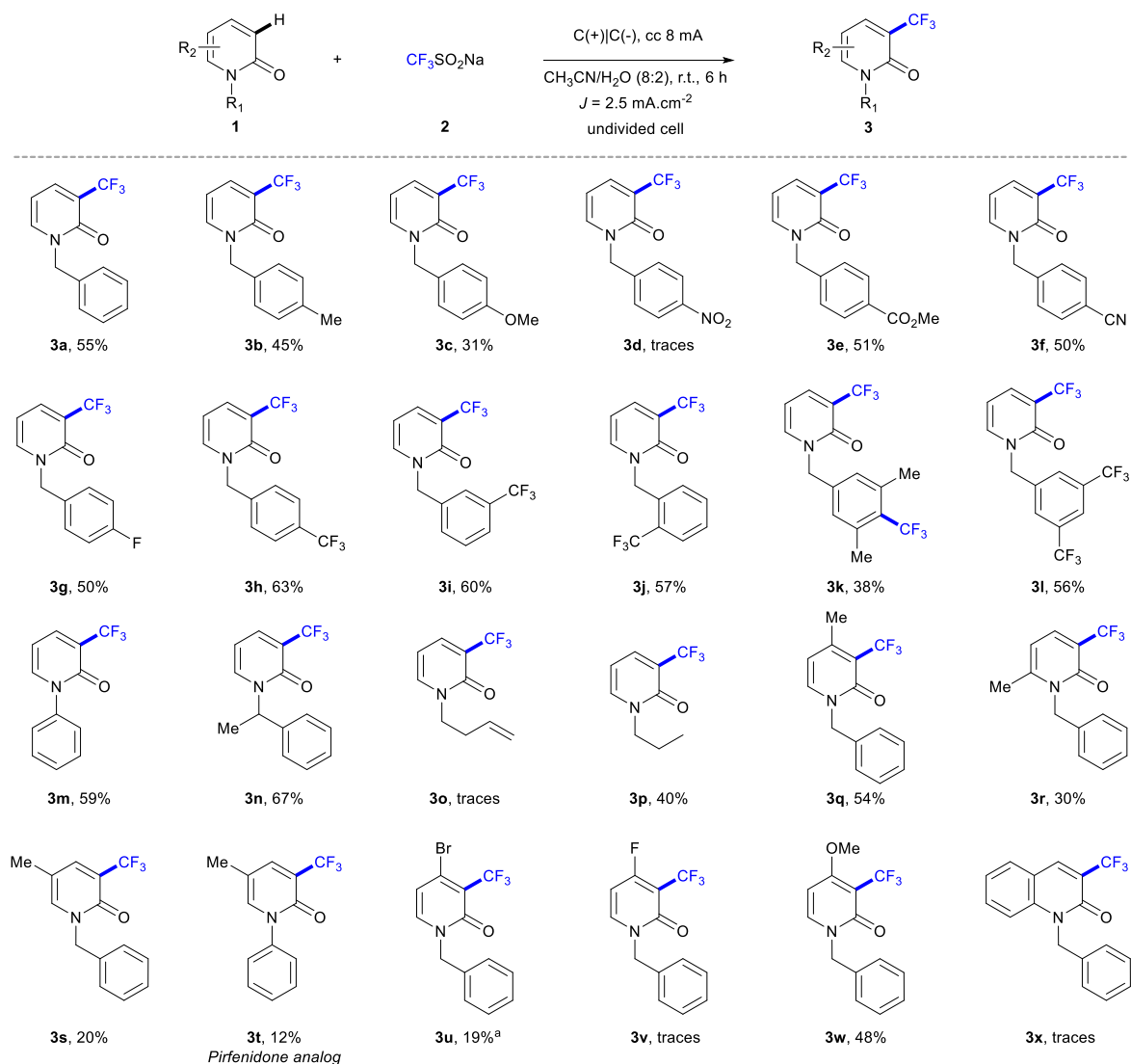
Table 1. Optimization studies for the electrochemical trifluoromethylation of N-benzyl-2-pyridone (**1a**)^a



Entry	Electrodes	Electrolyte	Solvent	Current (mA)	Yield (%) ^b
1	C(+) C(-)	<i>n</i> Bu ₄ NBF ₄	CH ₃ CN	10	24
2 ^c	GC(+) GC(-)	<i>n</i> Bu ₄ NBF ₄	CH ₃ CN	10	15
3 ^d	Pt(+) C(-)	<i>n</i> Bu ₄ NBF ₄	CH ₃ CN	10	30
4	C(+) C(-)	<i>n</i> Bu ₄ NBF ₄	CH ₃ CN	8	31
5 ^e	C(+) C(-)	<i>n</i> Bu ₄ NBF ₄	CH ₃ CN	15	20
6	C(+) C(-)	<i>n</i> Bu ₄ NClO ₄	CH ₃ CN	8	33
7	C(+) C(-)	<i>n</i> Bu ₄ NPF ₆	CH ₃ CN	8	30
8	C(+) C(-)	LiClO ₄	CH ₃ CN	8	34
9	C(+) C(-)	LiClO ₄	CH ₃ CN/H ₂ O (8:2)	8	43
10	C(+) C(-)	LiClO ₄	CH ₃ CN/H ₂ O (9:1)	8	40
11	C(+) C(-)	LiClO ₄	CH ₃ CN/H ₂ O (7:3)	8	34
12 ^f	C(+) C(-)	LiClO ₄	CH ₃ CN/H ₂ O (8:2)	8	52
13 ^f	C(+) C(-)	-	CH ₃ CN/H ₂ O (8:2)	8	41
14 ^g	C(+) C(-)	-	CH ₃ CN/H ₂ O (8:2)	8	55
15	C(+) C(-)	-	CH ₃ CN/H ₂ O (8:2)	-	N.R.

^aReaction condition in batch: **1a** (0.2 mmol, 1 equiv), **2** (0.6 mmol, 3 equiv), electrolyte and solvent (10 mL), IKA undivided cell, graphite plate electrodes (8 × 2 × 40 mm), constant current, r.t for 2 h. ^bYield was determined by ¹H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. ^cGlassy carbon plate (8 × 2 × 40 mm) as electrodes. ^dPt plate cathode (20 × 60 mm). ^e30 min. ^f3 h. ^g6 h.

With the optimized reaction conditions in hand, the scope of the electrochemical trifluoromethylation protocol, with respect to 2-pyridone derivatives **1** was explored (Scheme 1).



Scheme 1 Substrate Scope of trifluoromethylation of 2-pyridone derivatives. Reaction condition in batch: **1** (0.2 mmol, 1 equiv), **2** (0.6 mmol, 3 equiv), CH₃CN/H₂O (8/2, 10 mL), IKA undivided cell, graphite plate electrodes (8 × 2 × 40 mm), constant current = 8 mA, at room temperature for 6 h (8.9 F, Q = 172.8 C). ^aYield was determined by ¹H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

The reaction is compatible with various substituents on the para-position of the benzyl ring of 2-pyridones, furnishing the corresponding products **3e–j** containing electron-withdrawing groups (ester, cyano trifluoromethyl and halide) with slightly higher yields than products **3b–c** containing electron-donating groups (methyl and methoxy). However, the presence of an electron-withdrawing groups such as nitro gave only a trace amount of the desired product **3d**. The lower yield obtained with electrodonating groups can be attributed to the higher anodic current and lower oxidation potential of the corresponding pyridones (Fig S1, SI). Indeed, since the oxidation kinetics is more rapid the reaction is much less selective. Moreover, based on a pseudo-Hammet correlation (Fig S2, SI) the nature of the withdrawing substituent on the benzyl ring has no effect on the outcome of the trifluoromethylation of pyridones. Regarding the pyridone core the

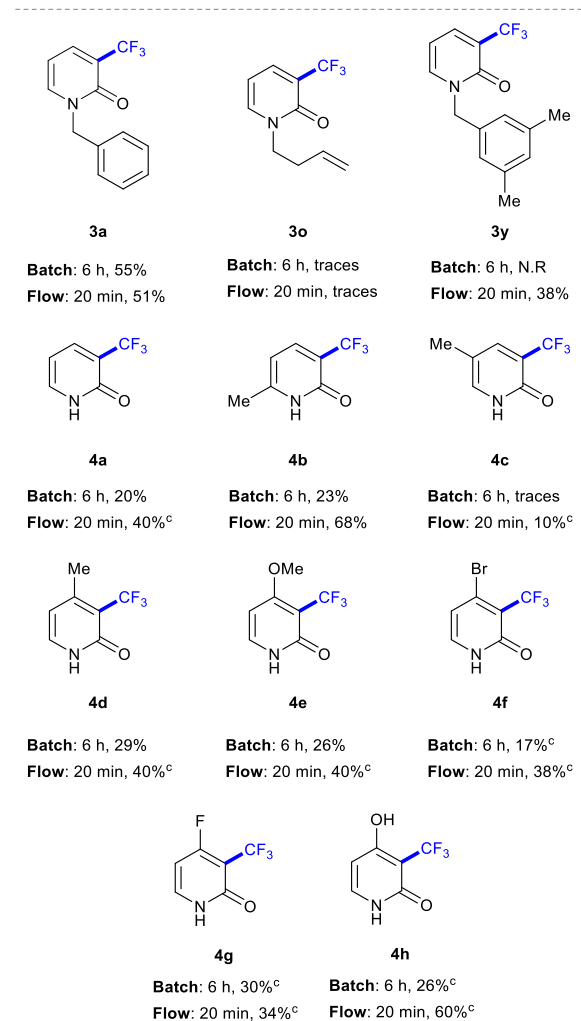
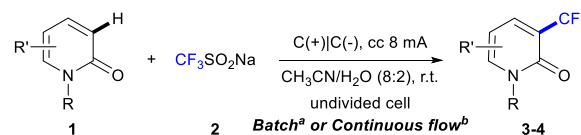
trifluoromethylation exclusively occurred at the C3 position regardless of the substituents on the benzyl ring. However, some by-products due to trifluoromethylation of the benzyl substituent could be detected by NMR spectroscopy. Moreover, when the benzyl group was functionalized with a methyl at both meta positions the bis-trifluoromethylated product **3k** was isolated as a single product with a 38% of yield. N-benzyl-2-pyridone with trifluoromethyl substituents at the meta and ortho position of the aromatic ring all provided the desired products, affording 60–57% yields (**3j–l**). Other pyridones such as N-phenyl-2-pyridone **3m** and N-phenylethyl-2-pyridone **3n** were efficiently substituted in 59% and 67% yields respectively while the N-propyl derivative **3p** was obtained in 40% yield. Unfortunately, no product was obtained when a sensitive terminal double bond is present on the pyridone, lots of

undetermined trifluoromethylated by-products being observed.

The presence of a methyl substituent at the 4-, 5-, or 6-position of the 2-pyridone core did not adversely affect the trifluoromethylation reaction and the respective products **3q-s** were obtained in moderate to good yields. Pirfenidone analogue was also regioselectively trifluoromethylated providing **3t** albeit in low yield. Unfortunately, 4-fluorinated N-benzyl pyridone was not good reaction partner as only traces of the corresponding pyridone **3v** were observed. Moreover, substantially lower yield was obtained with the 4-bromo analogue **3u** due to the direct debromination of the pyridone core at the electrode, the product **3a** being isolated as a by-product in 40% yield. An electron-donating methoxy group was well tolerated in the C4 position affording the corresponding product **3w** in 48% yield. It is worth mentioning that 1-benzyl-quinolone **3x** did not participate in the trifluoromethylation reaction.

With the successful results obtained in batch conditions, the reaction was evaluated under continuous flow conditions using the commercially available electrochemistry system from IKA (Electrasyn Flow) using a microflow electrocell (600 μL , 12 cm^2 surface area).²⁴ Hence, we started our preliminary flow experiments using the optimized solvent mixture and we evaluated different constant currents (Table S2, SI), different residence times (Table S2, SI), and different interelectrode distances (Tables S2, SI). We were delighted to find that product **3a** could be obtained in 51 % yield within a significant shorter reaction time than in batch (20 min vs 6 h) under galvanostatic conditions at 8 mA corresponding to 0.66 $\text{mA}\cdot\text{cm}^{-2}$ at room temperature thus, demonstrating the importance of the short interelectrode gap, high electrode surface-to-volume ratio and effective mixing provided by the microflow cell (Scheme 2). Moreover, unreacted starting material could be recovered after column chromatography (21 %) due to incomplete conversion which is not the case in batch. Unfortunately, longer reaction time causes the decomposition of the product **3a** by overoxidation under the electrochemical conditions. With sensitive functional group such as terminal double bond no product was observed under batch and flow conditions. Notably, under batch conditions only ditrifluoromethylated product **3k** was obtained starting from pyridine **1k** however, under the optimal flow conditions, product **3y** could be successfully obtained selectively with 38 % yield.

Next, to explore further the applications of our protocol, trifluoromethylation of unprotected 2-pyridones was carried out. Pleasingly, unprotected 2-pyridones were found to react with the Langlois reagent to yield NH-pyridone substrates **4a-g**, albeit with poor yields under batch conditions which could be due to oxidative degradation of the amine on the electrode surface. On the contrary, when the reaction was carried out in flow unprotected 2-pyridones **4a-g** were obtained with moderate to good yields showing again the benefit of microflow cell.



Scheme 2 ^aReaction condition in batch: **1** (0.2 mmol, 1 equiv), **2** (0.6 mmol, 3 equiv), $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (8/2, 10 mL), IKA undivided cell, graphite plate electrodes ($8 \times 2 \times 40$ mm), constant current = 8 mA ($J = 2.5 \text{ mA}\cdot\text{cm}^{-2}$) at room temperature for 6 h. ^bReaction conditions in continuous flow: **1a** (0.12 mmol, 1 equiv), **2** (0.36 mmol, 3 equiv), and $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (6 mL), IKA ElectraSyn undivided Flow cell (0.6 mL) with graphite plate electrodes (20×60 mm), PTFE gasket 0.50 mm, constant current = 8 mA ($J = 0.67 \text{ mA}\cdot\text{cm}^{-2}$), room temperature for 20 min ($30 \mu\text{L}\cdot\text{min}^{-1}$). ^cYield was determined by ^1H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

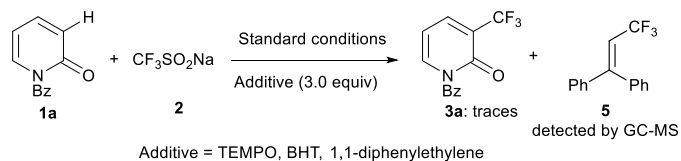
When the reaction was carried out in flow various unprotected 2-pyridone derivatives (**4a-g**) were obtained with moderate to good yields showing again the benefit of microflow cell. Sterically hindered pyridone with a methyl group at the C6 position of the pyridone moiety, was tolerated in the reaction, product **4b** being obtained in 68% yield. However, when 5-methylpyridone was used as coupling partner large amounts of by-products due to non-selective trifluoromethylation were obtained making impossible to obtain product **4c** in pure form. Furthermore, 4-methylpyridone underwent the reaction to provide the corresponding products **4d** in 40% yield as a single regioisomer. An electron-donating group, such as a methoxy group at the C4 position of the pyridone moiety, was also tolerated in the reaction, and the corresponding product **4e** was

obtained in 40% yield. 4-bromo-pyridone was successfully trifluoromethylated in synthetically useful yield (**4f**, 38% yield) with trace amount of debromation product in flow which enables further diversification. On the contrary when the reaction was carried out under batch condition the target compound was obtained with poor yield the debromation by-product being mostly isolated (24%). Thus, microflowcell helps to increase the reaction selectivity and prevents degradation of sensitive products. Similarly, 4-hydroxypyridone underwent C3-trifluoromethylation with a yield of 60% without reaching the full conversion in flow while the yield of compound **4g** with the 4-fluoro group was substantially lower at 34%.

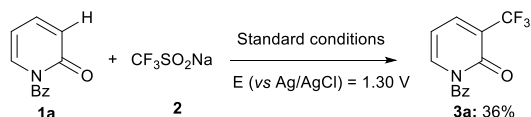
Finally, lower energy consumption is obtained (25.50 kW.g⁻¹ in batch vs 15.50 kW.g⁻¹ in flow) under continuous flow conditions making the transformation much more sustainable. The productivity of the optimized flow process is 0.120 g/day with 51% yield (0.240 g/day with 100% theoretical yield), hence to obtain a better space-time yields flow cell with higher surface area is needed.

To elucidate the mechanism insight, we carried out the electrochemical reactions in the presence of an excess of radical scavengers. The addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 3.0 equiv.) and 2,6-di-tert-butyl-4-methylphenol (BHT, 3.0 equiv.) completely suppressed the trifluoromethylation of 2-pyridone **1a** (Scheme 3, a).

a) Radical trapping



b) Constant voltage experiment



Scheme 3 Control experiments

Moreover, when 1,1-diphenylethylene (2 equiv.) was added in standard reaction, the trapping product due to the trifluoromethylation of 1,1-diphenylethylene **5** was detected by GC-MS implying that the reaction might involve a radical mechanism in accordance with previous reports.

To gain further insights about the mechanism, cyclic voltammetry experiments were carried out (Figure 3). Cyclic voltammetry (CV) analysis of CF₃SO₂Na (**2**) in CH₃CN/H₂O (v/v 8:2) with LiClO₄ as electrolyte showed irreversible anodic oxidation waves (Figure 3) at a potential lower than that of N-benzyl-2-pyridone **1a** (1.30 and 1.54 V vs Ag/AgCl, respectively). Based on these results, a control experiment was conducted with a constant anodic potential of 1.30 V vs. Ag/AgCl where pyridone **1a** could hardly be oxidized by direct anodic oxidation, and the desired product **3a** was isolated in 36% indicating that

2 is oxidized preferentially under the optimized conditions (Scheme 3, b).

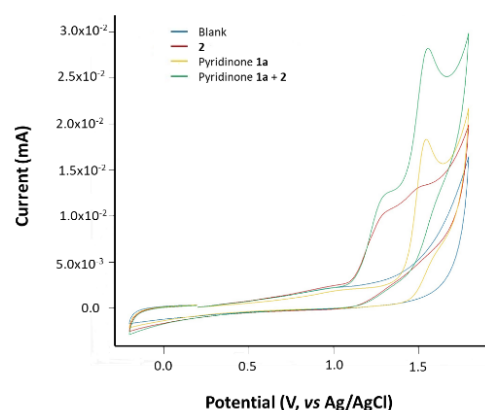


Figure 3 Cyclic voltammetry studies. Conditions: cyclic voltammogram of target molecule (1 mM) in a mixture of CH₃CN/H₂O (8:2) (20.0 mL containing 0.1 M LiClO₄) at room temperature using a glassy carbon working electrode, a platinum wire counter electrode, and a Ag/AgCl reference electrode at a scan rate of 20 mV.s⁻¹ with voltage ranging from -0.2 to 2.0 V. (blue line for blank, Red line for CF₃SO₂Na **2**, yellow line for pyridone **1a** and green line for **2** and **1a**).

To further verify the reaction mechanism and simplify the calculation process, the reaction pathway was examined by DFT with the PBE0 global hybrid functional²⁵ and the 6-311+G(d,p) basis set²⁶ (see figure S3, SI) using N-benzyl-2-pyridone (**1a**) and Langlois' reagent (**2**) as the starting materials. The free energy barriers in the rate determining addition step for C–CF₃ bond formation and the energy profiles of the reaction are demonstrated in Figure 4.

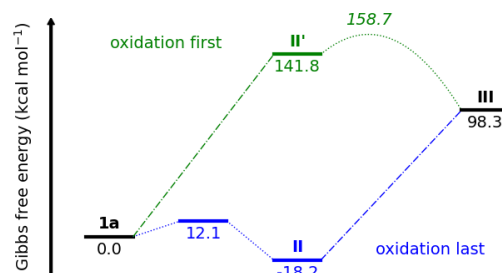
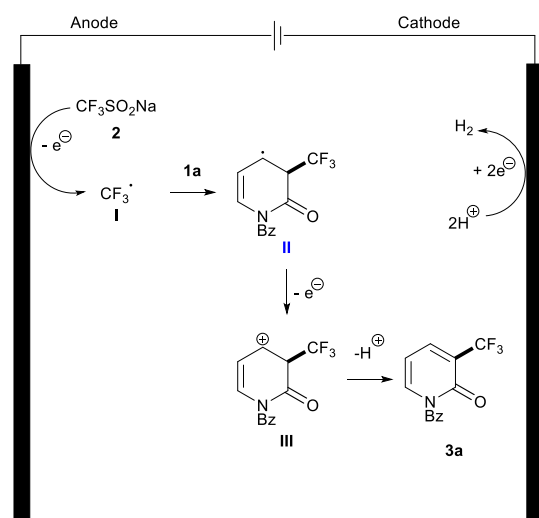


Figure 4. Relative Gibbs free energies for the first two steps for two plausible mechanisms leading to **III** from **1a** (and then to **3a** by proton release). The green (blue) values refer to the pathway 2 (1) where the oxidation step precedes (follows) the reaction with CF₃[•] (obtained from **2**). The dash-dotted lines represent electrochemical steps. For the estimation of the Gibbs free energy for the transition state between **II'** and **III** (italics), see computational details

To understand more clearly the regioselectivity of the addition, density analyses were carried out using several condensation schemes for charges and spin density localization. Two molecules were studied: **II'** (Figure S3, SI), and the radical cation of the product **3a** that could lead to a bis-trifluoromethylated product (See SI for the values per atom). The first conclusion, not so surprising, is that the Mulliken charges are not acceptable: they evolve in a way which is not chemically significant, whereas APT²⁷ and QT-AIM²⁸ charges evolve similarly in a more acceptable manner. Therefore, considering the spin densities from QT-AIM modelling; the spin is localized on the pyridone ring exclusively for both molecules. Therefore, the localization of the spin density is not the sole parameter influencing the addition of the CF₃ radical, as it reacts with the

pyridone ring in **II'** and in some case with the benzyl ring like in product **3k**.



Scheme 4 Proposed mechanism.

Based on the basis of the above results and literature reports, a plausible reaction mechanism for the electrochemical trifluoromethylation is illustrated in Scheme 4. $\text{CF}_3\text{SO}_2\text{Na}$ (**2**) loses one electron at the anode to access the CF_3 radical through the fast extrusion of SO_2 from the CF_3SO_2 radical. The regioselective addition of the CF_3 radical onto the double bond of 2-N-benzyl-2-pyridone (**1a**) provided radical intermediate **II**, which could be further oxidized to a cationic species **III** on the anode. Subsequently, the release of H^+ afforded the desired product **3a**. The cathodic reduction of protons to hydrogen gas, confirmed by detection at the outlet of the flow-cell using a Dräger X-am 5000 gaz detector, completes the overall electrochemical process.

Conclusions

To conclude, we have developed a direct trifluoromethylation of 2-pyridinones by using environmentally friendly electrochemical reaction conditions with Langlois reagent as a cheap and easy to handle source of the trifluoromethyl radical. Valuable trifluoromethylated pyridones were obtained regioselectively in modest to good yield under electrolyte- and oxidant free conditions demonstrating the sustainability of the presented methodology. Moreover, combining flow process with electrochemical process decreases the reaction time up to 18 times (6 h vs 20 min) while maintaining good yields, improves selectivity and reduces energy consumption of the reaction by nearly 30 % highlighting the potentials of this procedure especially for late stage functionalization.

Conflicts of interest

There are no conflicts to declare

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