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Electrochemical oxidative cyclization of *N*-allylamides for the synthesis of CF₃-containing benzoxazines and oxazolines†

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The introduction of trifluoromethyl (–CF₃) groups into compounds is a common synthetic strategy in organic chemistry. Commonly used methods for introducing trifluoromethyl groups are limited by harsh reaction conditions, low regioselectivity, or the need for excess reagents. In this study, a facile electrochemical oxidative and radical cascade cyclization of *N*-(2-vinylphenyl)amides for the synthesis of CF₃-containing benzoxazines and oxazolines was obtained. This sustainable protocol features inexpensive and durable electrodes, a wide range of substrates, diverse functional group compatibility under transition-metal-free, external-oxidant-free, and additive-free conditions, and can be applied in an open environment.

Introduction

Heterocyclic compounds are one of the most important skeletons in organic synthesis, pharmaceutical chemistry, materials science and bioscience. Heterocycles containing N and O atoms play a crucial role in pharmaceuticals and functional molecules.¹ Among these, benzoxazines and oxazolines are common privileged fragments frequently found in pharmaceutical molecules and biologically active compounds with remarkable biological activities,² such as anxiolytic,³ anti-HIV,⁴ progesterone receptor agonist,⁵ anti-tuberculosis,⁶ and anorectant activities⁷(Fig. 1).

Generally, the incorporation of fluorinated moieties into molecules can significantly change their physical, chemical, and biological properties. For example, the trifluoromethyl (–CF₃) moiety is widely present in a variety of drugs (celecoxib, fluoxetine, and trifloxystrobin *etc.*), which can improve the efficacy, solubility, lipophilicity, metabolic stability, and binding selectivity.⁸ Efavirenz containing trifluoromethyl benzoxazine shows potent anti-HIV activity.⁴ As a result, the potential values of these trifluoromethylated benzoxazines and oxazolines have attracted significant attention from chemists to develop efficient strategies for the construction of these intriguing molecule scaffolds.⁹ Xiao and co-workers reported

a visible-light-induced photocatalytic trifluoromethylation of *N*-allylamides for the synthesis of CF₃-containing benzoxazines and oxazolines under Umemoto's reagent and Ru(bpy)₃(PF₆)₂ (Scheme 1a).^{9m} Similarly, Kumar's group developed a copper-catalyzed approach for construction of trifluoromethylated benzoxazines by using Umemoto's reagent (Scheme 1b).¹⁰ These methods are effective and versatile, but are limited to transition-metal catalysts and Umemoto's reagent as CF₃ sources. In addition, Natarajan and colleagues disclosed a novel 9,10-phenanthrenedione visible-light photocatalysis protocol for the synthesis of trifluoromethylated benzoxazines by using *N*-(2-vinylphenyl)amides and trifluoromethylsulfinate under oxygen atmosphere (Scheme 1c).^{9a} Nevertheless, it still requires additional photocatalysts and oxidants. Therefore, it is highly desirable to develop alternatively efficient, sustainable, green, and environmentally friendly synthetic methods avoiding transition metal catalysts and chemical oxidants.

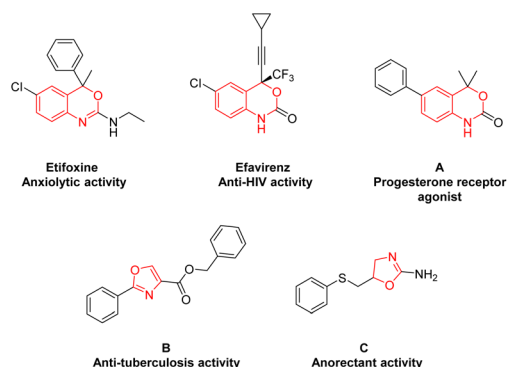


Fig. 1 Bioactive compounds containing benzoxazine or oxazoline motifs.

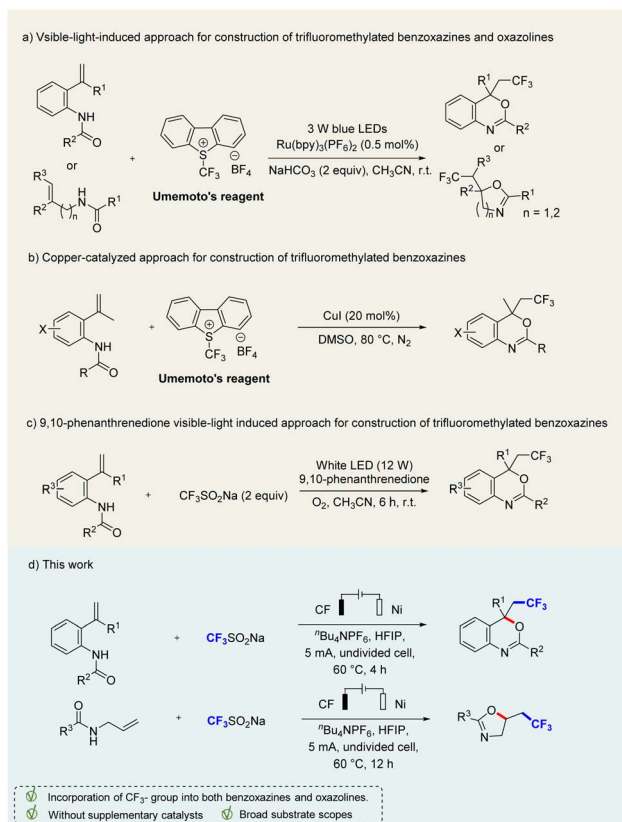
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Scheme 1 Strategies for the synthesis of trifluoromethylated benzoxazines.

Organic electrochemistry provides an effective and sustainable strategy for the synthesis of valuable chemicals, employing inexpensive and renewable electrons as redox reagents.¹¹ In our continuous efforts, our goal is to develop green, metal-free, and efficient methods to construct diversified heterocyclic scaffolds.¹² In our previous work, we reported a direct azidation of benzylic C(sp³)-H bonds through an electrochemical process.¹³ Herein, we'd like to report a new finding to construct trifluorinated benzoxazines and oxazolines through an effective electrochemical strategy, which may use cheap carbon fibre and nickel plates as electrodes in an undivided cell, without any external chemical oxidants, metal catalysts and additives (Scheme 1d). However, while we were preparing this manuscript, a similar work appeared, focusing on the construction of CF₂-substituted benzoxazines,¹⁴ in which the reaction system required trifluoroacetic acid as a catalyst, adding complexity to the reaction system. In contrast, our reaction system is simpler and environmentally benign without the need for a transition metal catalyst or external oxidant, and can proceed smoothly with diverse functional group compatibility.

Results and discussion

Based on the above conception, we have attempted to achieve the CF₃-containing benzoxazines by treatment of *N*-(2-(prop-1-en-2-yl)phenyl)benzamide (**1a**) with CF₃SO₂Na. The reaction

was carried out in an undivided cell equipped with a carbon fibre (CF) anode and a nickel plate (Ni) cathode under a constant current of 5 mA (Table 1). The desired product **2a** was obtained in 72% yield when ^tBu₄NPF₆ was used as the electrolyte in HFIP at 60 °C for 4 h (entry 1). We tried other electrolytes, such as Et₄NBF₄, ^tBu₄NOAc, ^tBu₄NBr, and ^tBu₄NI. Et₄NBF₄ resulted in a significant decrease (entry 2) in yield, only trace of the product was observed when using ^tBu₄NOAc and ^tBu₄NBr as electrolytes (entry 3), and the product was I-containing benzoxazine derivative when using ^tBu₄NI as the electrolyte (entry 4). Besides, the product **2a** also was observed in the absence of electrolyte (entry 5). When we replaced solvent with DMSO (entry 6), CH₃CN (entry 7), CH₃OH (entry 8), and DCE (entry 9), all of them resulted in a slight decrease in the yield. This could be attributed to the ability of HFIP to stabilize radical cation intermediates, thereby aiding in substrate oxidation while preventing the product of overoxidation.¹⁵ We further evaluated other electrode materials, including Pt plate (entry 10), Fe plate (entry 11) as anode, and Fe plate (entry 12), Al plate (entry 13) as cathode, none of them was more effective. We transformed the current to 2 mA (entry 14) or 10 mA current (entry 15), the reaction efficiency was noticeably dropped in 2 mA current. The product **2a** was decreased under 10 mA current, which

Table 1 Optimization of reaction conditions^a

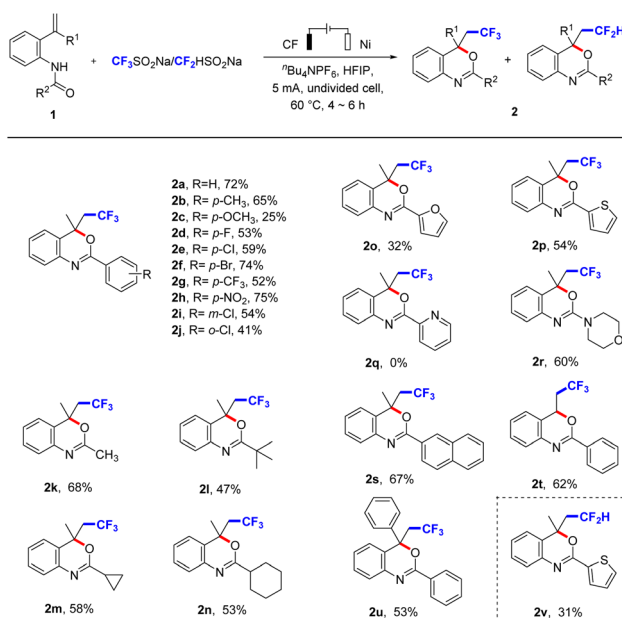
Entry	Variation from standard conditions	Yield ^b [%]
1	None	72
2	Et ₄ NBF ₄ as electrolyte	39
3	^t Bu ₄ NBr or ^t Bu ₄ NOAc as electrolyte	Trace
4	^t Bu ₄ NI as electrolyte	0
5	No electrolyte	13
6	DMSO as solvent	51
7	CH ₃ CN as solvent	38
8	CH ₃ OH as solvent	37
9	DCE as solvent	66
10	Pt plate as anode	25
11	Fe plate as anode	17
12	Fe plate as cathode	29
13	Al plate as cathode	56
14	2 mA	42
15	10 mA	60
16	r.t.	35
17	40 °C	64
18	80 °C	59
19	CF ₃ SO ₂ Na (1 equiv.)	63
20	No electricity	0

^a Reaction conditions: undivided cell, **1a** (0.25 mmol), CF₃SO₂Na (0.5 mmol), solvent (6 mL), ^tBu₄NPF₆ (0.5 mmol), 5 mA, 60 °C, 4 h (3.0 F mol⁻¹). ^b Isolated yield. Under air atmosphere. CF = Carbon fibre (1 × 1 × 0.01 cm), Pt = platinum (1 × 1 × 0.01 cm), Ni = nickel (1 × 1 × 0.01 cm). HFIP, 1,1,1,3,3,3-hexafluoro-2-propanol, DCE, 1,2-dichloroethane.

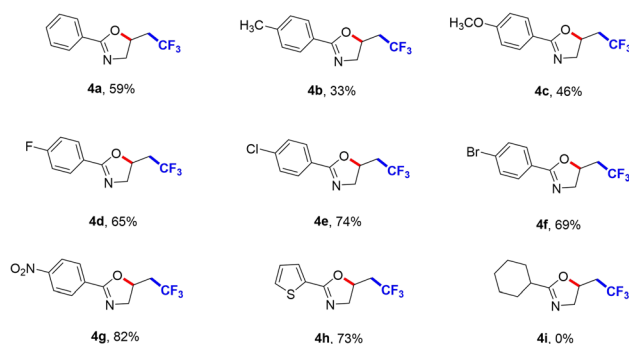


speculated that high current may cause peroxidation. The reaction temperature also was investigated, which led to lower yields (entries 16–18). When the equivalent of $\text{CF}_3\text{SO}_2\text{Na}$ was reduced to 1, it resulted in a slight decrease in the yield (entry 19). Furthermore, electricity (entry 20) was essential for the process of the reaction.

With the optimal conditions in hand, the substrate scope of CF_3 -containing benzoxazines was explored (Scheme 2). Firstly, we introduced electron-donating groups or electron-withdrawing groups into *N*-(2-(prop-1-en-2-yl)phenyl) benzamide (**1a**) and they reacted smoothly to obtain corresponding products **2** in moderate to good yields, such as methyl (**2b**), methoxy (**2c**), and halides (**2d**, **2e**, **2f**, **2i**, and **2j**), especially the strong electron-withdrawing groups trifluoromethyl (**2g**) and nitryl (**2h**) were all tolerant. Besides, we replaced the R^2 group by methyl (**2k**), tertiary butyl (**2l**), cyclopropyl (**2m**), cyclohexyl (**2n**), which reacted smoothly to afford the target product in good yields. Furyl (**2o**) or thienyl (**2p**) was transformed into the desired product in moderate yields, but pyridyl (**2q**) could not produce the target product. We speculated that the electron-withdrawing effect of pyridine made it difficult for **1q** to generate the corresponding intermediate **I** or **II**. We also introduced morpholinyl (**2r**) and naphthyl (**2s**) into R^2 group, the target products were obtained. Further explorations about the R^1 group were hydrogen (**2t**) and phenyl (**2u**), the corresponding target compounds were also generated and showed great compatibility. In this synthetic system, CF_2 -substituted benzoxazines were also successfully synthesized using $\text{CF}_2\text{-HSO}_2\text{Na}$ as the difluoromethylation reagent (31% yield for compound **2v**), which indicates that the reaction system has good applicability.



Scheme 2 Substrate scope of CF_3 -containing benzoxazines. ^aReaction conditions: undivided cell, **1** (0.25 mmol), $\text{CF}_3\text{SO}_2\text{Na}/\text{CF}_2\text{HSO}_2\text{Na}$ (0.5 mmol), $^t\text{Bu}_4\text{NPF}_6$ (0.5 mmol), HFIP (6 mL), under air atmosphere.



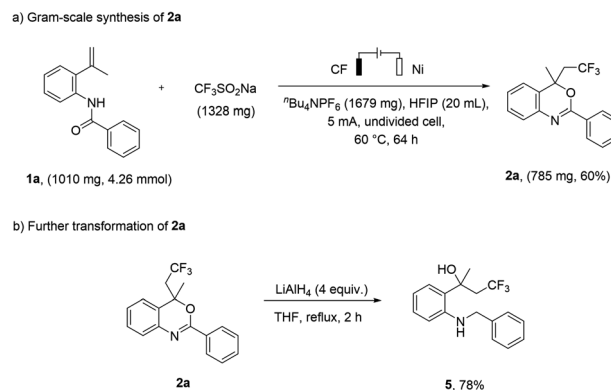
Scheme 3 Substrate scope of CF_3 -containing oxazolines. ^aReaction conditions: undivided cell, **3** (0.25 mmol), $\text{CF}_3\text{SO}_2\text{Na}$ (0.5 mmol), $^t\text{Bu}_4\text{NPF}_6$ (0.5 mmol), HFIP (6 mL), under air atmosphere.

We further explored the substrate scope of CF_3 -containing oxazolines, and the results were shown in Scheme 3. *N*-allylbenzamide **3a** was reacted with $\text{CF}_3\text{SO}_2\text{Na}$ to access the trifluoromethylation product 2-phenyl-5-(2,2,2-trifluoroethyl)-4,5-dihydrooxazole (**4a**) in 59% yield. *N*-allylbenzamides with various substituents such as methyl (**4b**), methoxy (**4c**), halides (**4d**, **4e** and **4f**) were all tolerant. The benzene rings with electron-deficient nitryl (**4g**) gave 82% yield. Meanwhile, when introducing furyl (**4h**) into the R^3 group, the corresponding target product also was obtained. But introducing cyclohexyl (**4i**) into R^3 group could not produce the target product, which indicated it had a very great influence on this transformation.

To further evaluate the practicality and potential applications of this method, we performed the reaction on a gram-scale preparation with **1a**, and the yield of product **2a** was 60% under a constant current of 5 mA for 64 h (Scheme 4a). In addition, the product **2a** can be further converted into 2-(2-(benzylamino)phenyl)-4,4,4-trifluorobutan-2-ol (**5**) at a yield of 78% (Scheme 4b).

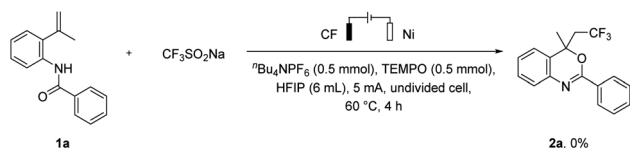
In order to investigate the possible mechanism of this transition, several control experiments were performed. No desired product was obtained when 2,2,6,6-Tetramethylpiperidoxyl (TEMPO) was added (Scheme 5).

A plausible mechanism for the formation of product has been proposed based on the related reports.¹⁶ As explained in Scheme 6, initially the HFIP undergoes cathodic reduction to

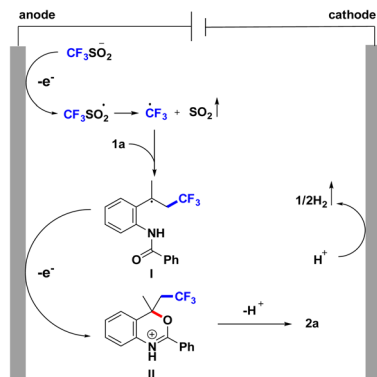


Scheme 4 Gram-scale synthesis and further transformation.

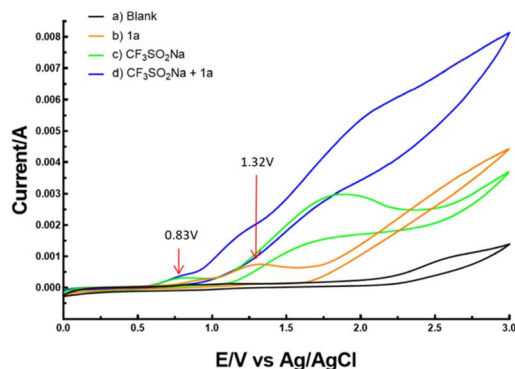




Scheme 5 Control experiments of the reaction.



Scheme 6 Proposal mechanism of the reaction.

Fig. 2 Cyclic voltammetric experiments of **1a** and $\text{CF}_3\text{SO}_2\text{Na}$.

generate hydrogen gas at the cathode. At the anode, $\text{CF}_3\text{SO}_2\text{Na}$ produces the CF_3SO_2 radical under anodic oxidation and further forms the CF_3 radical. Subsequently, CF_3 radicals are added to the double bonds of the olefins to generate the alkyl radical intermediate **I**. **I** undergoes a radical cyclization and anodic oxidation to furnish intermediate **II**. Afterwards, the intermediate **II** is finally converted into CF_3 -containing benzoxazine **2a** by deprotonation (Scheme 6).

To justify the proposed reaction pathway outlined in Scheme 6, we conducted cyclic voltammetric (CV) experiments. As shown in Fig. 2, the oxidation peak of $\text{CF}_3\text{SO}_2\text{Na}$ was 0.83 V, and **1a** had an oxidation peak of 1.32 V. These results indicated that $\text{CF}_3\text{SO}_2\text{Na}$ was oxidized preferentially at the anode (see the ESI† for details).

Conclusions

In summary, we have developed a mild and efficient electrochemical oxidative and radical cascade cyclization of olefinic

amides to afford trifluorinated benzoxazines and oxazolines using cheap and durable nickel plates as electrodes. This paper presents a simple, practical, green and environmentally benign protocol for the synthesis of fluorinated benzoxazines and oxazolines. In the absence of any transition metal catalysts, external oxidizers and additives, this protocol proceeds smoothly with diverse functional group compatibility.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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