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Catalyst-free, direct electrochemical trifluoromethylation/cyclization of *N*-arylacrylamides using TfNHNHBoc as a CF_3 source

Han Wang[a], Yongbin Xie[a], Yicheng Zhou[a], Nannan Cen[a], Wenbo Chen[a,b,*]

[a] Shanghai Key Laboratory of Materials Protection and Advanced Materials in Electric Power, Shanghai University of Electric Power, Shanghai 200090, China
[b] CAS Key Laboratory of Energy Regulation Materials, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

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ABSTRACT

A new electrochemical strategy for trifluoromethylation/cyclization using TfNHNHBoc as a CF_3 source was established. This approach was realized by the direct electrolysis of TfNHNHBoc under external oxidant-free and catalyst-free conditions, and afforded various trifluoromethylated oxindoles with good functional group compatibility and broad substrate scope. Preliminary mechanistic studies show that the reaction proceeds by a radical process.

Since trifluoromethyl group (CF_3) has unique chemical stability and metabolic stability, introducing trifluoromethyl group into organic compounds at the specific position has been used as an important strategy for the modification of medicine, pesticides and functional molecular materials [1]. In the past two decades, much effort has been made to develop various methodologies for the preparation of CF_3-containing compounds [2]. Among them, radical trifluoromethylation represents one of the most attractive strategies [3]. Trifluoromethylation reagents, such as $TMSCF_3$ [4], CF_3X (X = Br, I) [5], Langlois' reagent [6], Umemoto's reagents [7], Togni's reagents [8] are usually used as trifluoromethyl source. Traditional methods for generating CF_3 radical required transition metals catalyst, chemical oxidant, or reductant, nevertheless, the use of these reagents inevitably generates environmentally hazardous waste.

In recent years, electrochemical organic synthesis represented a green and powerful method, has attracted much attention due to the avoiding of additional oxidation and reduction reagents in the reaction [9]. So far, an increasing number of examples about electrochemical trifluoromethylation reactions have been reported, such as C–H trifluoromethylation [10], difunctionalization of olefins [11], tandem trifluoromethylation [12]. However, most of these reactions have been realized by using CF_3SO_2Na and $(CF_3SO_2)_2Zn$ as trifluoromethylation reagent, which was oxidized to generate CF_3 radical on the anode. Therefore, there is urgent need to study new reagents applied in electrochemical synthesis to accelerate the area.

Sulfonylhydrazides, which is easy to prepare, no bad smell, have been widely used in the reactions as arylation/alylating and thioetherification reagents [13]. In this regard, very recently, TfNHNHBoc has successfully been used as a trifluoromethylating for vicinal difunctionalization of terminal alkenes using TBHP or $K_2S_2O_8$ as the oxidant and trifluoromethylthiolation of indoles [14]. Inspired by the previous CF_3SO_2Na-based electrochemical trifluoromethylation, herein, we investigated the potential of TfNHNHBoc as CF_3 radical source under electrochemical conditions.

Trifluoromethylated indole compounds are the dominant heterocyclic scaffolds that are present in a variety of biologically active natural products and drugs [15]. Therefore, researchers are working to develop methods to provide various functionalized trifluoromethylated indole compounds [16]. In this context, the electrochemical trifluoromethylation/cyclization of *N*-arylacrylamide has significant advantages in the synthesis of fluoroalkylated indole compounds. Using CF_3SO_2Na (Scheme 1a), Zeng [17] developed an indirect electrochemical trifluoromethylation/cyclization of *N*-arylacrylamide using bromide as catalyst with a low loading. Subsequently, Mo [18] described Mn-mediated electrochemical trifluoromethylation/C(sp^2)–H functionalization cascade for the synthesis of nitrogen heterocyclic compounds. Meanwhile, Ackermann [19] also successfully established catalyst-free, direct electrochemical tri- and difluoroalkylation/cyclization to prepare functionalized oxindoles and quinolinones. In view of this, we re-

* Corresponding author.
E-mail address: wenbochen@shiep.edu.cn (W. Chen).

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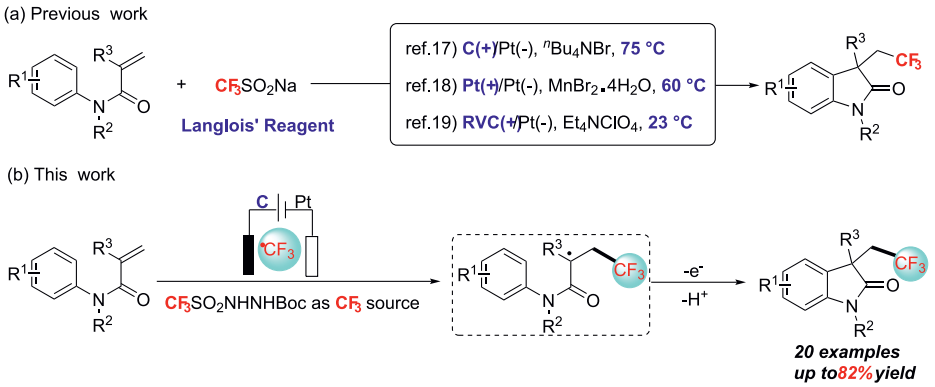


Scheme 1. Electrochemical trifluoromethylation/cyclization of *N*-arylacrylamide.

Table 1
Optimization of reaction conditions.[a]

Entry	Deviation from standard conditions	Yield (%)[b]
1	–	75
2	no H_2O	54
3	CH_3CN/H_2O (1:6) as solvent	14
4	CH_3CN/H_2O (8:1) as solvent	56
5	CH_3OH/H_2O (6:1) as solvent	32
6	reaction at r.t.	29
7	reaction at 40 °C	41
8	reaction at 100 °C	30
9	10 mA	50
10	20 mA	40
11	$^nBu_4NClO_4$ as the supporting electrolyte	52
12	Et_4NPF_6 as the supporting electrolyte	53
13	$^nBu_4NI$ as the supporting electrolyte	0
14	RVC (5 cm × 7 cm × 2 cm) as the anode	48
15	Pt plate (1 cm × 1 cm × 0.2 cm) as the anode	25
16	no electricity	0

[a] Reaction conditions: graphite rod (φ6 mm) anode, Pt plate (10 mm × 10 mm) cathode, constant current = 12 mA, **1** (0.9 mmol), **2a** (0.3 mmol), electrolyte (2 equiv.), base, solvent (0.06 mol/L), air, 4 h (6.0 F/mol based on **2a**).
[b] Isolated yield.

ported the direct electrochemical trifluoromethylation/cyclization using TfNHNHBoc as CF_3 source for the first time (Scheme 1b).

Initially, TfNHNHBoc (**1**) was prepared in one step by reacting commercially available Tf_2O and NH_2NHBoc [20]. To optimize the reaction conditions, *N*-arylacrylamide (**2a**) and TfNHNHBoc (**1**) were chosen as the model substrates. This reaction was carried out in an undivided cell equipped with a graphite rod anode and a platinum plate cathode. Under air, using Et_4NOTs (2 equiv.) as the supporting electrolyte and $MeCN/H_2O$ (6:1) as the solvent, the desired trifluoromethyl substituted oxindole product **3a** was isolated in 75% yield under constant current of 12 mA at 80 °C for 4 h (Table 1, entry 1). It was found that the mixed solvent of CH_3CN/H_2O (6:1) was better than the CH_3CN and others (Table 1, entries 2–5). The temperature was found to be crucial to this reaction. Lowering the temperature led to the decrease of the yield and the product was isolated in 29% yield when the reaction was carried out at room temperature. In contrast, increasing the temperature to 100 °C, the yield decreased to 30%, which might be ascribed to the decomposition of TfNHNHBoc at 100 °C (Table 1, entries 6–8, more details see Supporting information) [14b]. Furthermore, the reaction yields were decreased when the operating current was increased or decreased (Table 1, entries 9 and 10). The screening of the electrolyte showed that $^nBu_4NClO_4$ or Et_4NPF_6 was less efficient and $^nBu_4NI$ failed to offer the trifluoromethyl products (Table 1, entries 11–13). In addition, the replacement of graphite rod anode with reticulated vitreous carbon (RVC) or platinum plate led to lower yield (Table 1, entries 14 and 15). No product was observed in the absence of electricity (Table 1, entry 16).

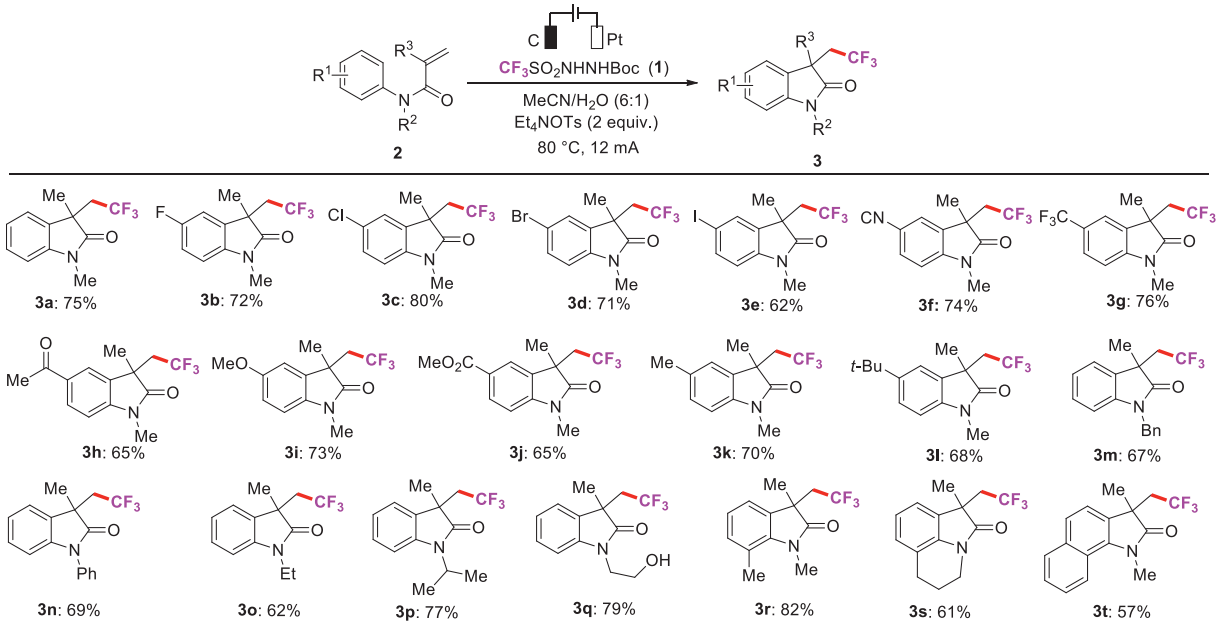
Under the above optimal reaction conditions, we investigated the scope of substrates (Scheme 2). In general, a variety of *N*-arylacrylamides derivatives were applicable and the corresponding trifluoromethylated oxindole products were obtained in moderate to good yields (**3a-3t**). Substrates with both electron-withdrawing (**3b-3h**, **3j**) and electron-donating (**3i**, **3k**, **3l**) groups at the aryl ring reacted to give the desired products in good yields. Notably, common functional groups were well tolerated under the electrochemical conditions, such as halogen (**3b-3e**), trifluoromethyl (**3g**), cyano (**3f**), ester (**3h**), alkyl (**3k**, **3l**) and hydroxyl groups (**3q**). The sterically hindered *N*-arylacrylamides with ortho-substituted group could also transform to the desired product in 82% yield (**3r**). Substrates bearing with various alkyl (**3m**, **3o**, **3p**, **3q**) and aryl group (**3n**) at nitrogen atom were also suitable for this reaction. Gratifying, tetrahydroquinoline derivative successfully reacted with reagent **1** to afford the tricycle oxlines product (**3s**) in 61% yield. In addition, the reaction of *N*-naphthylacrylamide with reagent **1** also gave the product in 57% yield (**3t**).

Considering the significant advantages of electro-oxidative trifluoromethylation without catalyst and oxidant, we had a strong interest in its reaction mechanism. For this purpose, we performed cyclic voltammetry (CV) experiments (Fig. 1 and Fig. S4 in Supporting information). An oxidation peak of **1** in MeCN was observed at 0.72 V (Fig. 1, curve b). At the same time, anodic oxidation of **2a**, followed by an irreversible reaction, occurred at a potential of *ca.* 2.03 V (*vs.* SCE) (Fig. 1, curve c). In addition, the oxidation potential of BHT was much higher than that of TfNHNHBoc **1**, *ca.* 1.45 V (*vs.* SCE) (Fig. 1, curve e), but lower than that of substrate **2a**. These results indicated that reagent **1** was likely to be first oxidized under electrolytic conditions.

To further explore the possible mechanism of the electrochemical trifluoromethylation/cyclization sequence, we carried out the control experiments. It was found that when 3.0 equiv. of radical scavengers such as BHT were added, the tandem sequences were fully suppressed. This experiment suggested that free radical intermediate was involved during the electrolysis (Scheme 3).

To evaluate the potential of this electrochemical protocol for the future application, a gram scale reaction of **2a** (7 mmol, 1.2 g) with **1** was performed at a constant current of 200 mA under air. To our delight, this reaction afforded the desired product **3a** with 55% yield in 5 h (Scheme 4).

Based on the above mechanism research and literature reports [21,14a], the possible mechanism of electrochemical trifluo-



Scheme 2. Catalyst-free electrochemical tandem trifluoromethyl-ation/cyclization using TfNHNHBoc as a CF_3 source. Reaction conditions: graphite rod (φ6 mm) anode, Pt plate (10 mm × 10 mm) cathode, **1** (0.9 mmol), **2** (0.3 mmol), electrolyte (2 equiv.), MeCN/H_2O = 6:1 (5 mL); the electrolysis was conducted at a constant current in an undivided cell; under air at 80 °C for 4 h. Isolated yields.

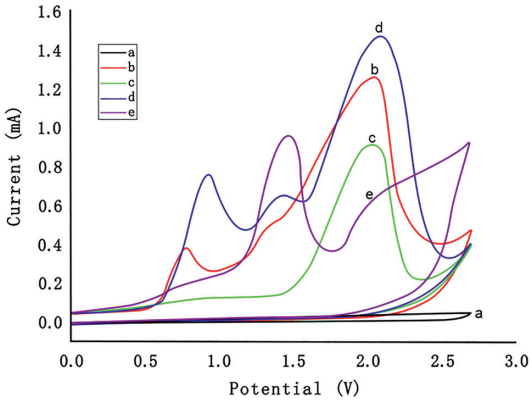
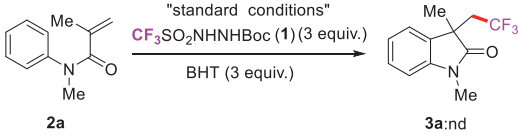
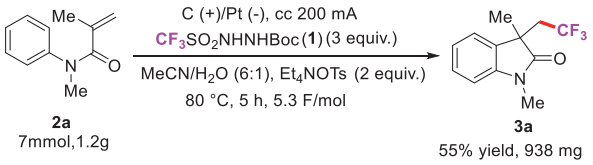


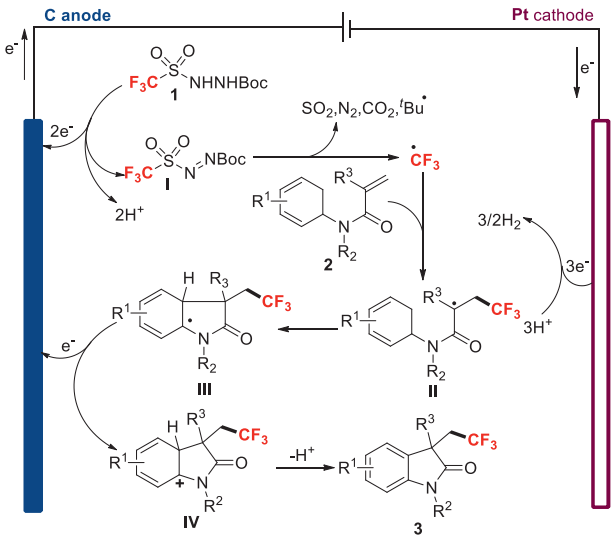
Fig. 1. Cyclic voltammetry studies. (a) Cyclic voltammograms of Et_4NOTs (0.1 mol/L) in acetonitrile (curve a). (b) TfNHNHBoc **1** (0.06 mol/L), Et_4NOTs (0.10 mol/L) in acetonitrile (curve b). (c) **2a** (0.06 mol/L), Et_4NOTs (0.10 mol/L) in acetonitrile (curve c). (d) TfNHNHBoc **1** (0.18 mol/L in CH_3CN), **2a** (0.06 mol/L), Et_4NOTs (0.10 mol/L) in acetonitrile (curve d). (e) BHT (0.06 mol/L), Et_4NOTs (0.10 mol/L) in acetonitrile (curve e). Scan rate: 100 mV/s.



Scheme 3. Radical trapping experiment.



Scheme 4. Gram-scale experiment.



Scheme 5. Proposed mechanism.

romethylation was proposed in Scheme 5. Reagent **1** was oxidized on the anode to generate diazene **I**, which decomposed to give trifluoromethyl radical ($^{\bullet}CF_3$) [22]. Next, the generated CF_3 radical regioselectively reacted with the alkene moiety of *N*-arylacrylamide **2** to give carbon center radical **II**, which was further converted to intermediate **III** through intramolecular radical cyclization. Finally, the oxidation of intermediate **III** and subsequent proton elimination afforded the trifluoromethylated oxindole **3**. Meanwhile, protons were reduced on the cathode to produce hydrogen.

In summary, we developed a new electrochemical strategy for trifluoromethylation/cyclization using TfNHNHBoc as a CF_3 source under oxidant-free and catalyst-free conditions. This method provided an efficient synthesis of various trifluoromethylated oxindoles with good functional group compatibility and broad substrate scope. Preliminary mechanistic studies indicate that the reaction proceeds by a radical process. Further application of TfNHNHBoc

as the CF_3 source in organic electrosynthesis is currently ongoing in our laboratory.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.06.008.

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