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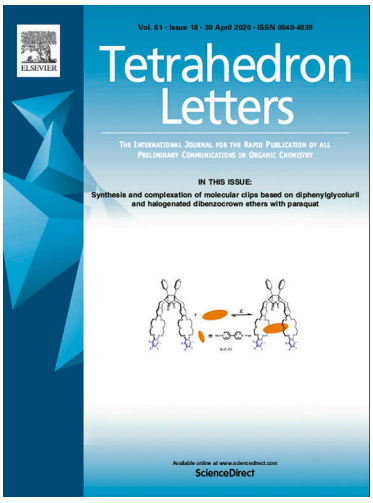

A metal-free picolinamide assisted electrochemical *ortho*-trifluoromethylation of arylamines

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PII: S0040-4039(20)31128-X
DOI: https://doi.org/10.1016/j.tetlet.2020.152623
Reference: TETL 152623

To appear in: *Tetrahedron Letters*

Received Date: 13 August 2020
Revised Date: 23 October 2020
Accepted Date: 29 October 2020

Please cite this article as: Wang, K., Hou, J., Wei, T., Zhang, C., Bai, R., Xie, Y., A metal-free picolinamide assisted electrochemical *ortho*-trifluoromethylation of arylamines, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152623

Tetrahedron Letters
journal homepage: www.elsevier.com

A metal-free picolinamide assisted electrochemical *ortho*-trifluoromethylation of arylamines

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
ortho-Trifluoromethylation
Arylamines
Electrochemical C-H functionalization
Metal- and oxidant-free

ABSTRACT

An eco-friendly and effective electrochemical process was developed for the *ortho*-trifluoromethylation of arylamines using CF_3SO_2Na as the trifluoromethyl source, affording the desired products in moderate to good yields with high regioselectivity under mild reaction conditions. Importantly, the requirement for both transition metals and oxidants as utilized in previous methods were avoided. A radical mechanism was proposed on the basis of various control experiments.

Introduction

Fluorine-containing organic compounds have attracted increasing attention in materials, [1] pharmaceutical [2] and agrochemical chemistry. [3] Especially, the incorporation of trifluoromethyl groups into organic compounds [4] has gained attention due to their special chemical characteristics and metabolic stabilities.

Traditional methods for trifluoromethylation have been implemented with aryl halides [5] or boronic acids, requiring dangerous fluoridation reagents and harsh reaction conditions. [6] Presently, with the development of transition-metal-catalyzed C-H activation, numerous direct functionalization reactions have been reported. [7] Among these reactions, direct trifluoromethylations [8] have gained significant attention, especially using arylamine derivatives. In 2010 and 2012, the *ortho*-trifluoromethylation of 2-phenylpyridines was developed by Yu and co-workers [7a] with $Pd(OAc)_2$ as the catalyst. Later, in 2013, and also with the participation of $Pd(OAc)_2$, Shi and co-workers reported the direct *ortho*-trifluoromethylation of acetamide [7b], and a similar reaction was demonstrated by Xi and co-workers with CuCl [7c]. However, the use of precious metals, large amounts of oxidants, and expensive trifluoromethylating reagents such as Umemoto's reagent [9], Togni's reagent [10] and $TMSCF_3$ [11] were required in these works.

In recent years, CF_3SO_2Na (a low-cost, hypotoxic and stable trifluoromethylated reagent) has proven to be effective in direct trifluoromethylation [12]. In 2017, Zhang and co-workers [12a] established a nickel(II)-catalyzed *ortho*-trifluoromethylation of arylamines. Next, in 2018, the photoinduced *ortho*-trifluoromethylation of arylamines was described by Xia and co-workers, employing ferrocene as the catalyst [12d]. In 2019, another visible-light mediated *ortho*-trifluoromethylation was reported by An, Li and co-workers [12f] (Fig. 1).

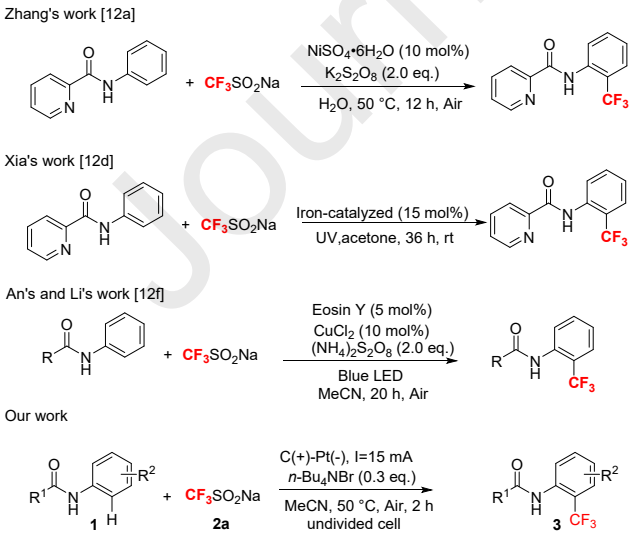


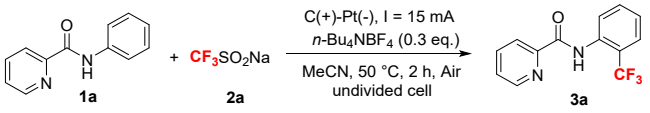
Figure 1. Representative examples of the direct *ortho*-trifluoromethylation of arylamines.

Recently, electrochemistry has received widespread attention as an effective method to realize radical reactions using electrons instead of traditional oxidants [13]. In 2018, Lei and co-workers [14d] developed a direct electrochemical oxytrifluoromethylation and aminotrifluoromethylation of alkenes. In the same year, Zeng and co-workers [14e] described an electrochemical trifluoromethylarylation of *N*-arylacrylamides catalyzed by bromide. Both of these reactions use CF_3SO_2Na as the trifluoromethyl source, which proves that the trifluoromethylation reaction can be realized under metal-free and oxidant-free conditions *via* electrochemistry. Inspired by these studies and in combination with our previous efforts in trifluoromethylation, [12e] we have developed a metal-free, electrochemical process for the *ortho*-trifluoromethylation of arylamine derivatives using CF_3SO_2Na as the trifluoromethylating reagent.

Results and Discussion

Initially, we commenced our investigation using the model reaction of *N*-phenylpicolinamide **1a** as the starting material and CF_3SO_2Na **2a** as the trifluoromethylated reagent. The electrochemical reaction was carried out in an undivided cell which was equipped with a C anode and a Pt cathode, and stirred at 50 °C under an air atmosphere for 2 h in the presence of *n*-Bu_4BF_4 using MeCN as the solvent. Gratifyingly, product **3a** was formed in 58% yield (Table 1, Entry 1). Encouraged by this result, we then screened several other anodes including reticulated vitreous carbon (RVC), Pt, Ni, and Cu; however, the yields decreased to 47%, 38%, 55%, and 17%, respectively (Table 1, Entries 2-5). At the same time, when the cathode was changed from Pt to C, no product was detected (Table 1, Entry 6). Solvents such as CH_3OH and 1,4-dioxane were inferior to MeCN (Table 1, Entries 7-8). Meanwhile increasing or decreasing the current density and replacement of the electrolyte did not improve the yield (Table 1, Entries 9-13). The transformation also did not take place without an electric current (Table 1, Entry 14).

Table 1.
Reaction optimization.[a,b]



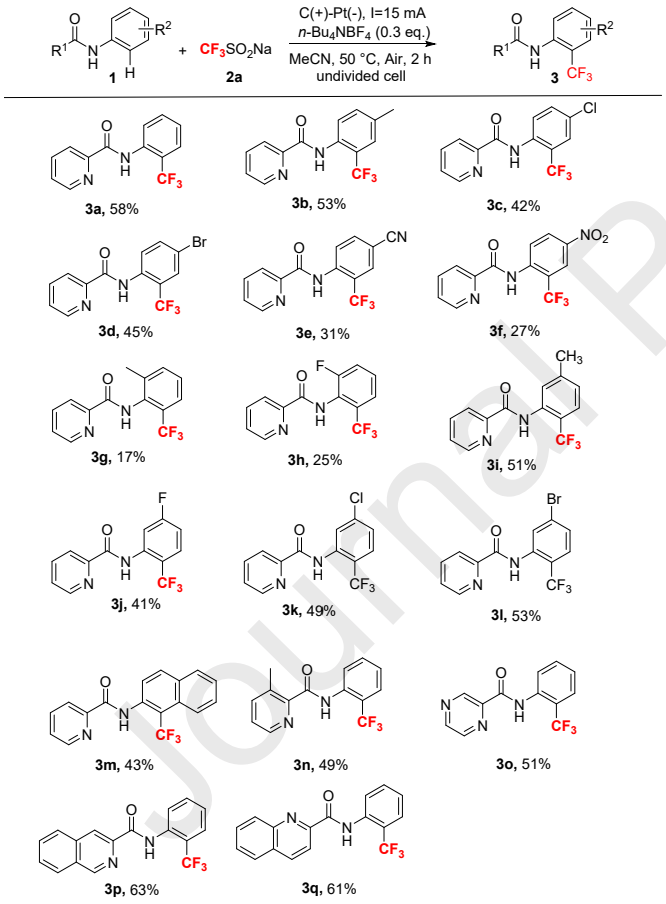
Entry	Variation from the standard conditions	Yield **3a** [%][b]
1	None	58
2	RVC anode instead of C anode	47
3	Pt anode instead of C anode	38
4	Ni anode instead of C anode	55
5	Cu anode instead of C anode	17
6	C cathode instead of Pt cathode	Trace
7	CH_3OH instead of CH_3CN	26
8	1,4-dioxane instead of CH_3CN	31
9	10 mA instead of 15 mA	50
10	20 mA instead of 15 mA	53
11	*n*-Bu_4NCl instead of *n*-Bu_4NBF_4	27
12	*n*-Bu_4NBr instead of *n*-Bu_4NBF_4	51
13	*n*-Bu_4NI instead of *n*-Bu_4NBF_4	46
14	No electricity	N.R.

[a] Reagents and conditions: C anode, Pt cathode, constant current = 15 mA, **1a** (0.3 mmol), **2a** (1.5 eq.), *n*-Bu_4NBF_4 (0.3 eq.), CH_3CN (3 mL), C anode (d = 6 mm), Pt plate cathode (5 mm × 5 mm × 0.3 mm), 50 °C, 2 h, air.
[b] Isolated yield.

[c] N.R. = No reaction.

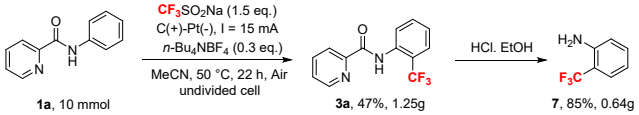
With the optimum electrolysis trifluoromethylation protocol in hand, we next examined the scope and limitations of the reaction using various arylamines. As shown in Table 2, electron-donating and electron-withdrawing arylamines were tolerated, and gave the desired products in 17-63% yield (Table 2, **3a-3l**), although electron-donating ones performed better. Specifically, taking *para*-substituted arylamines as an example (Table 2, **3b-3f**), the 4-CH_3 arylamine was isolated in 53% yield while the yield of 4-Cl, 4-Br, 4-CN, and 4-NO_2 arylamines were less than 45%. Furthermore, both *para*-substituted (Table 2, **3b-3f**) and *meta*-substituted arylamines (Table 2, **3i-3l**) gave higher yields than *ortho*-substituted arylamines (Table 2, **3g-3h**), which indicated that steric hindrance has a significant influence on this transformation. Finally, naphthyl derived picolinamides and other nitrogen heterocyclic amides also afforded the desired products in good yields (Table 2, **3m-3q**).

Table 2.
Substrate scope for the trifluoromethylation reaction.[a,b]



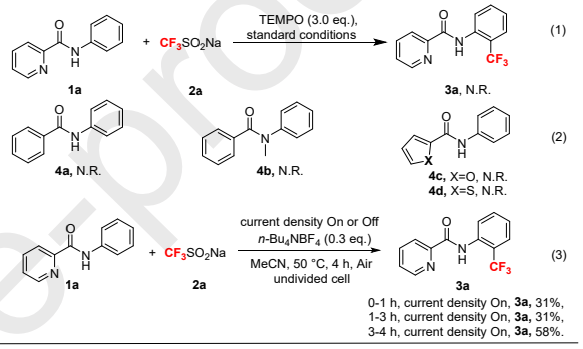
[a] Reagents and conditions: C anode, Pt cathode, constant current = 15 mA, **1a** (0.3 mmol), **2a** (1.5 eq.), *n*-Bu_4NBF_4 (0.3 eq.), CH_3CN (3 mL), C anode (d = 6 mm), Pt plate cathode (5 mm × 5 mm × 0.3 mm), 50 °C, 2 h, air.
[b] Isolated yield.

Considering that the initial substrates were readily obtained and the method was easy to operate, a gram scale reaction was performed (Scheme 1); the desired product **3a** was obtained in 47% yield and subsequently **7** was obtained in 85% using our previously described method. [12e]



Scheme 1. Gram scale reaction.

To gain further insight into the mechanism of this transformation, several control experiments were implemented (Scheme 3). Firstly, we conducted the trifluoromethylation reaction under the standard conditions with the addition of 3.0 equivalents of TEMPO. Unsurprisingly, none of the desired product was obtained, which revealed that a radical pathway could explain the process. Next, different amides were used instead of **1a**; however, none of the desired product was detected, which indicated that the pyridine ring was necessary for the reaction. Further research was carried out with an On/Off experiment, which showed that a continuous electric current was required (Scheme 2).



Scheme 2. Investigation of the mechanism.

We then carried out cyclic voltammetry (CV) experiments. It could be clearly observed that the oxidation potential ($E_{P/2}$) of CF_3SO_2Na was 1.43 V, which was oxidized to the trifluoromethyl radical. Meanwhile, the oxidation potential of **1a** was not detected. It was then found that the oxidation potential ($E_{P/2}$) changed to 1.56 V when CF_3SO_2Na was added, which presumably generated complex **C** (see Scheme 3).

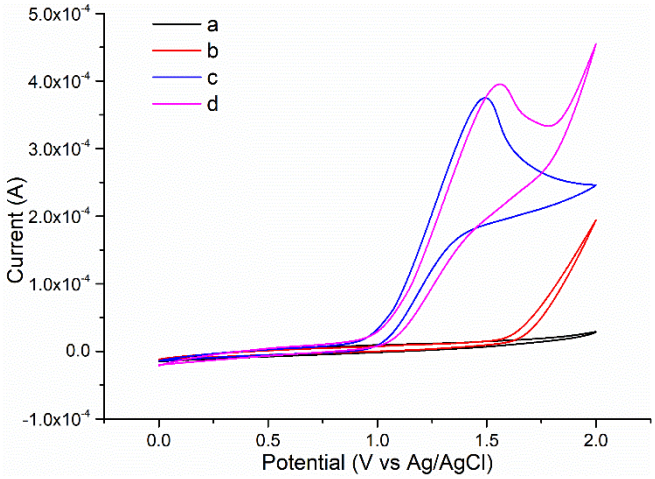
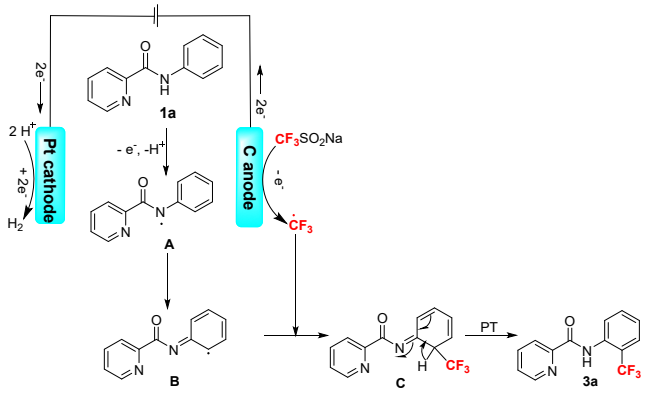


Figure 2. Cyclic voltammograms. a: blank; b: **1a** (10 mM, red); c: **2a** (15 mM, blue); d: **1a** (10 mM) + **2a** (15 mM, pink).

On the basis of above findings and previous reports [12a, 14i] we proposed the following plausible mechanism *via* a radical coupling pathway (Scheme 3).



Scheme 3. Plausible mechanism of trifluoromethylation

Initially, CF_3SO_2Na was transformed into the CF_3 radical through oxidation at the anode. Next, **1a** was oxidized into intermediate **A** through deprotonation at the anode. After which, **B** was formed *via* resonance from **A**. Then, species **C** was obtained by radical coupling between the CF_3 radical and **B**. Finally, the desired product **3a** was generated through a proton-transfer (PT) process.

Conclusion

In summary, we have developed an efficient and practical protocol for the electrochemical *ortho*-trifluoromethylation of anilines under transition metal-free and oxidant-free conditions. This electrochemical method tolerated a broad substrate scope and the expected products were obtained in moderate to good yields. Primary investigation demonstrated that a radical mechanism was involved.

Acknowledgements

This work was supported by the National Natural Science Foundation of China, NSFC (No. 21978273 and 21576239) and National Key R&D Program of China (No. 2018YFC0214100).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://

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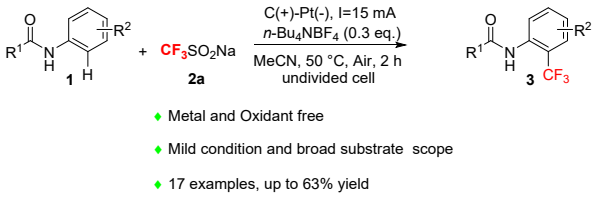
- An electrochemical method for the synthesis of *ortho*-trifluoromethylation of arylamines was developed.
- The addition of transition metals and oxidants was not required.
- The desired products were obtained in moderate to good yields.
- The study of the reaction mechanism revealed that a radical step was involved in this transformation.

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

A metal-free picolinamide assisted electrochemical *ortho*-trifluoromethylation of arylamines



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