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# Cathodic C–H Trifluoromethylation of Arenes and Heteroarenes Enabled by an in Situ-Generated Triflyltriethylammonium Complex

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**Supporting Information** 

**ABSTRACT:** While several trifluoromethylation reactions involving the electrochemical generation of CF<sub>3</sub> radicals via anodic oxidation have been reported, the alternative cathodic, reductive radical generation has remained elusive. Herein, the first cathodic trifluoromethylation of arenes and heteroarenes is reported. The method is based on the electrochemical reduction of an unstable triflyltriethylammonium complex generated in situ from inexpensive triflyl chloride and triethylamine, which produces CF<sub>3</sub> radicals that are trapped by the arenes on the cathode surface.



Recent years have witnessed a significant resurgence of electrochemical methods for the promotion of organic reactions,<sup>1</sup> not only as an inherently sustainable approach<sup>2</sup> but also as an elegant strategy for accessing high-energy intermediates under mild conditions.<sup>3</sup> Radical species, for example, can be generated from relatively unreactive reagents at room temperature,<sup>1,3</sup> providing access to challenging organic transformations difficult to achieve using conventional synthetic methods.<sup>4</sup> Radical trifluoromethylation reactions, pivotal transformations in modern organic and medicinal chemistry,<sup>5-7</sup> have also been explored by means of electrochemical methods. Trifluoromethyl radicals have been generated by anodic oxidation of sodium and zinc triflinate salts and utilized for the introduction of this moiety into unsaturated compounds.<sup>1</sup> Arene and heteroarene trifluoromethylations are arguably the most pursued perfluoroalkylation reactions.8 In fact, a majority of active pharmaceutical ingredients decorated with trifluoromethyl groups contain this moiety attached to an aromatic ring.<sup>9</sup> In addition to a range of methods for the trifluoromethylation of aromatic rings based on chemical oxidants or photoredox catalysis (Figure 1A),<sup>10,11</sup> electrochemical methods have also been reported.<sup>12,13</sup> These methods, as mentioned above, exclusively rely on the anodic oxidation of triflinate salts (Figure 1B). While the original report using the oxidation of KSO<sub>2</sub>CF<sub>3</sub> had a rather limited scope of aromatic hydrocarbons,<sup>12</sup> nitrogencontaining heteroarenes were successfully functionalized using  $Zn(SO_2CF_3)_2$  in a divided cell setup.<sup>13</sup>

During our recent work on anodic oxytrifluoromethylations involving oxidation of sodium triflinate,<sup>14</sup> we questioned whether the alternative cathodic generation of  $CF_3$  radicals, not reported so far, is possible and how such an unexplored strategy might broaden the scope of the electrochemical procedure for the functionalization of arenes and heteroarenes. In a reductive radical generation strategy (Figure 1C),

A Methods for the preparation of trifluoromethyl arenes



Figure 1. Strategies for arene trifluoromethylation.

trifluoromethylation of the aromatic ring occurs on the surface of the cathode. It was envisioned that such reductive radical generation, combined with an easily oxidized amine (to act as a reductant for the anodic oxidation and a base), might enable

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Figure 2. Development of a cathodic trifluoromethylation method for aromatic compounds via reduction of triflyl species.

electrochemical trifluoromethylation of oxidatively labile heteroarenes (e.g., thiophenes). Furthermore, development of a cathodic trifluoromethylation concept may unlock opportunities for other reductive perfluoroalkylation strategies of compounds that are difficult to perform using oxidation methods.

Trifluoromethanesulfonyl chloride (TfCl) was selected as trifluoromethyl source for this investigation. TfCl is an inexpensive, relatively easy to handle liquid.<sup>15</sup> In addition, its low negative reduction potential (-0.18 V vs Ag/AgCl)<sup>16</sup> makes it particularly attractive for an electrochemical reduction. We began our study with a series of experiments using mesitylene as a model substrate (Figure 2A) and an undivided cell setup (IKA ElectraSyn 2.0) using graphite as the anode and cathode material. Although we aimed for easily oxidized amine bases such as Et<sub>3</sub>N, several bases with different properties were also evaluated to gain some insight into the reaction mechanism. These bases included inorganic nonnucleophilic  $(K_2HPO_4)$  and organic bases of increasing nucleophilicity (2,6-lutidine, iPr<sub>2</sub>EtN, and Et<sub>3</sub>N). As expected, when  $K_2$ HPO<sub>4</sub> and 2,6-lutidine were used as the base (Figure 2A, entries 1 and 2, respectively), moderate conversion of the starting material was observed with poor selectivity. The lack of a suitable reductant in the reaction medium for the anodic oxidation resulted in high cell voltages (>4 V) and significant amounts of undesired aryl oxidation side products, including chlorination of the aromatic ring (3) and trapping of the aryl cation (resulting from oxidation of the starting material) with acetonitrile (4) (Figure 2B). The results improved with Hünig's base (entry 3). Remarkably, using Et<sub>3</sub>N as an additive, the side products were fully suppressed. After the application of 1 F/mol, 32% conversion of the starting material and 99% selectivity toward the desired trifloromethylated arene were observed (Figure 2A, entry 4). The cell voltage was also significantly lower than for the non-nucleophilic bases; 20 mA

 $(\sim 13 \text{ mA/cm}^2)$  resulted in a cell voltage of  $\sim 1.5 \text{ V}$ . No reaction was observed in the absence of electricity (entry 6). Interestingly, product formation was also observed when Zn or Mn was used as the stoichiometric reductant in the absence of electricity (entry 7). However, low conversions (10-12%) were obtained using 3 equiv of metal after 24 h (see the Supporting Information for experimental details).

When TfCl and Et<sub>3</sub>N were mixed in acetonitrile, with or without the substrate and supporting electrolyte, a rapid color change (from colorless to pale yellow) could be observed. As both reagents were used in equimolar amounts in the initial set of experiments, TfCl was most likely transformed into the corresponding triflyltriethylammonium chloride complex 5 (Figure 2C). <sup>19</sup>F NMR monitoring of the reaction mixture revealed that a complex mixture of triflyl-containing species was indeed formed upon mixing of the reagents. Signals corresponding to diethyl sulfonamide 6 and triflinate 7 were detected as the major side products. Formation of 6 takes place slowly via elimination of chloroethane, while triflinate 7 is produced when an excess of base is present. These observations, which could be confirmed by <sup>19</sup>F NMR monitoring of solutions containing variable amounts of TfCl and Et<sub>3</sub>N (see the Supporting Information), are in agreement with those reported by Netscher and Bohrer for mixtures of triflic anhydride and Et<sub>3</sub>N.<sup>17</sup> The presence of both species (6 and 7) in solution was undesirable because they do not release CF<sub>3</sub> radicals under the reaction conditions. This hypothesis was confirmed by preparing 6 and a mixture of sodium triflinate and Et<sub>3</sub>N and utilizing them as reagents for the cathodic trifluoromethylation under standard conditions in two separate control reactions. No conversion was observed (Figure 2C) (see the Supporting Information for details).

Identification of the triflyl species occurring in solution proved to be very valuable for understanding the reaction behavior and boosting further optimization. When an excess of

## Scheme 1. Reaction Scope and Limitations



<sup>d</sup>Yields were determined by <sup>19</sup>F NMR using fluorobenzene as the internal standard. Values in parentheses refer to isolated yields. <sup>b</sup>Method A: 0.3 mmol scale, 3 equiv of TfCl, 3 mL of acetonitrile. <sup>c</sup>Method B: 0.6 mmol scale, 3 mL of acetonitrile, 5 equiv of TfCl. <sup>d</sup>Obtained as a mixture of isomers (see the Supporting Information for details). <sup>e</sup>Bis-trifluoromethylation product also obtained.

Et<sub>3</sub>N over TfCl was used (Figure 2A, entry 8), low conversion and selectivity were achieved, as expected due to the faster generation of compound 7, which inhibits the reaction. Moreover, reactions in nonpolar solvents such as THF and acetone (entries 9 and 10, respectively) failed; when Et<sub>3</sub>N was added to the reaction mixture in these solvents, a white precipitate rapidly formed (most likely ionic complex 5). The lack of reagents in solution generated exceedingly high cell voltages (>5 V) and no conversion to the desired product. To minimize degradation of the active species 5 to 6 and 7, a rapid reaction was expected to be beneficial. Thus, the current was increased to 40 mA ( $\sim 26$  mA/cm<sup>2</sup>) [for sensitive substrates, the current was reduced to 20 or 10 mA (vide infra)]. A gradual increase in the amount of TfCl to 4 equiv and charge to 5 F/mol led to high conversion and selectivity (Figure 2A, entries 11 and 12, respectively). Ultimately, excellent results were achieved using a substrate concentration of 0.1 M (entry 13). As expected, at high conversions certain amounts ( $\sim$ 10%) of the bis-trifluoromethylated product were also detected for this relatively active substrate (GC-FID monitoring of a typical reaction mixture is shown in Figure S2).

With the optimal conditions in hand, a series of arenes and heteroarenes were functionalized using this cathodic trifluor-

omethylation strategy (Scheme 1A,B). An excess of current ranging from 2 to 8 F/mol was utilized depending on the substrate. The method tolerated several functional groups, including alkyl, halogen, ether, ester, nitrile, or ketone moieties. As expected, the reaction performed best for electron-rich substrates (e.g., 2a and 2b). Electron-withdrawing groups such as halogens (2m-o), esters (2q), or ketones (2r) decreased the efficiency of the reaction, and modest yields were achieved. The strongly deactivated nitrobenzene resulted in only traces of the target product (2s). Importantly, low conversions but no side reactions were observed for the low-yielding examples. Most likely, the poor radical trapping character of electronpoor aromatics led to dimerization of the CF<sub>3</sub> radicals to hexafluoroethane  $(F_3C-CF_3)$ , an effect probably enhanced by the fact that the radicals are formed on the electrode surface (probably leading to high local concentrations of  $CF_3$  radicals). Gratifyingly, thioanisole, containing an oxidatively labile sulfur atom, could also be successfully functionalized (2p). Yields reported in panels A and B of Scheme 1 were obtained under analogous conditions. Method A (0.3 mmol scale, 3 equiv of TfCl) was used for electron-rich substrates. In method B, utilized for electron-poor substrates, the scale was increased to 0.6 mmol and the excess of TfCl to 5 equiv.

Importantly, this method could also be utilized for the trifluoromethylation of heteroaromatics containing nitrogen, oxygen, and sulfur atoms (Scheme 1B). While nitrogencontaining heteroaromatics had been previously trifluoromethylated using an oxidative approach and a divided cell by Baran and Blackmond,<sup>13</sup> the latter two had not been reported so far using electrochemical approaches. N-Phenyl and Nmethyl pyrrole were successfully trifluoromethylated (2v and 2w, respectively). Trifluoromethylated heteroaromatics decorated with N and S atoms were also prepared in synthetically useful yields as well as thiophene (2y and 2z) and furane (2aband 2ae) derivatives. More complex heteroarenes such as caffeine (2af) or the drug pentoxifylline (2ag) were also successfully derivatized.

The proposed reaction mechanism involves a transformation that would mainly take place on the cathode surface (Figure 3A). One-electron reduction of triflylammonium complex **5** results in neutral radical **8**. Although satisfactory cyclic voltammetry measurements of compound **5** could not be obtained, DFT calculations showed that the reduction of the complex should be significantly favored compared to TfCl (Figure 3B), with a reduction potential that was ~0.5 V lower



B Radical trapping, control experiments and redox potential calculations



Figure 3. Proposed reaction mechanisms, control experiments, and reduction potentials of TfCl and compounds 5 and 6 calculated at the M06-2X/6-311G++(d,p) level and referenced to the experimental value of TfCl.

(less negative) (see the Supporting Information for calculation details). This indicates that even with the two species existing in equilibrium (particularly when TfCl is in excess over  $Et_3N$ ), 5 most likely is the species being reduced and the radical source. DFT calculations also confirmed that compound 6 has a very negative reduction potential and cannot be involved in the electrochemical process (Figure 3B), as demonstrated by the control experiments [Figure 2C (vide supra)]. Decomposition of 8 recovers the amine ( $Et_3N$ ), releasing SO<sub>2</sub> and the  $CF_3$  radical. Trapping of the latter by the aromatic ring generates the new radical 9, which then rearomatizes via hydrogen abstraction or a SET process followed by deprotonation. Such rearomatization after radical additions to aromatics in the absence of oxidants has often been reported in the literature.<sup>18</sup> The Et<sub>3</sub>N released during the reduction of **5** is oxidized on the anode. As oxidation of the amine is a twoelectron process, only 0.5 equiv of amine is required for the anodic oxidation. Several plausible products for the oxidation of triethylamine have been proposed. Most often, N,N-diethyl ethenamine has been suggested.<sup>19</sup> Anodic dealkylation of tertiary aliphatic amines has also been previously reported.<sup>20</sup> To assess the fate of triethylamine during the anodic oxidation in our procedure, electrolysis experiments were carried out in MeCN- $d_3$  as the solvent under the typical reaction conditions (see the Supporting Information for details). <sup>1</sup>H and <sup>13</sup>C NMR analysis of the crude reaction mixture ruled out the formation of an alkene and pointed to the generation of diethylamine via electrochemical dealkylation. This secondary amine is probably partially present in its hydrochloride form if the rearomatization of 9 releases a proton. The intermediacy of the trifluoromethylsulfonyl (CF<sub>3</sub>SO<sub>2</sub>) radical could be confirmed by its trapping with styrene (Figure 3B). Furthermore, the presence of TEMPO as an additive (1 equiv) inhibited the reaction, most likely by trapping most of the CF<sub>3</sub>SO<sub>2</sub> radical (no TEMPO-CF<sub>3</sub> was detected by GC analysis).

In summary, we have developed a method for the cathodic trifluoromethylation of arenes and heteroarenes based on the reduction of a trifluoromethyltriethylammonium complex (5), generated in situ from triflyl chloride and triethylamine. The method has shown a good functional group tolerance, and as the trifluoromethylation takes place at the cathode surface, oxidatively labile sulfur-containing aromatics could be successfully functionalized. Further extension of this concept to other perfluoroalkynation reactions is currently in progress.

# ASSOCIATED CONTENT

## **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b02948.

Experimental details, supplementary figures and tables, characterization data, and copies of NMR spectra (PDF)

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#### Notes

The authors declare no competing financial interest.

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