A general electrochemical strategy for the Sandmeyer reaction†

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Herein we report a general electrochemical strategy for the Sandmeyer reaction. Using electricity as the driving force, this protocol employs a simple and inexpensive halogen source, such as NBS, CBrCl3, CH2I2, CCl4, LiCl and NaBr for the halogenation of aryl diazonium salts. In addition, we found that these electrochemical reactions could be performed using anilines as the starting material in a one-pot fashion. Furthermore, the practicality of this process was demonstrated in the multigram scale synthesis of aryl halides using highly inexpensive graphite as the electrode. A series of detailed mechanism studies have been performed, including radical clock and radical scavenger study, cyclic voltammetry analysis and in situ electron paramagnetic resonance (EPR) analysis.

Introduction

The Sandmeyer reaction represents a fundamentally important method to convert an aryl amine to an aryl halide via the intermediacy of a diazonium salt.1 Discovered in 1884,2,3 this century-old transformation is still being extensively used in modern organic synthesis in both academic and industrial settings.4–8 To date, many synthetically useful variants of the Sandmeyer reaction have been reported, including a copper metal mediated process (Gattermann reaction),9 diazotization in organic phases (Doyle diazotization),10,11 a Cu(i)-catalyzed process12 and acetate-facilitated metal-free halogenation.13 Despite these valuable advances,9–15 the development of a new strategy for the Sandmeyer reaction is still of great importance.

The past decade has witnessed resurging interest in organic electrochemistry that dramatically improved organic chemists’ ability for green and sustainable synthesis.16–29 Our laboratory has been engaged in the development of organic electrochemistry to overcome unmet synthetic challenges.30,31 In this context, we have recently become interested in electrocatalytic transformations of diazonium salts (Scheme 1A). An efficient electrochemical method for the Sandmeyer reaction is hampered by several factors. First, diazonium salts can engage in undesired two-electron reduction,32,33 leading to the formation of an aryl anion that could be easily protonated to give a reduction product (Scheme 1B[a]). Second, known as the Gomberg–Bachmann reaction,34 the transient aryl radical intermediate can react with an arene or another aryl radical to give a biaryl side product (Scheme 1B[b]).35 Third, the well-documented reaction of diazonium salts with the electrode can alter its properties and reduce the efficiency of

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Results and discussion

The electrochemical bromination of aryl diazonium tetrafluoroborate 1a was selected as the model reaction with N-bromosuccinimide (NBS) as the halogen source. The results are depicted in Table 1 (entries 1–7). Acetonitrile and DMF were first evaluated due to the good solubility of substrates and electrolytes in these solvents. Under these conditions, the desired product ethyl 4-bromobenzoate (2a) was formed in low yields (entries 1 and 2). The major byproduct was found to be ethyl benzoate as indicated by GC-MS analysis of the crude reaction mixture, showing that protonation or hydrogen abstraction was the major undesired pathway. We then evaluated other solvents, and the use of a mixed solvent system consisting of MeOH and DMF (entries 3–6) provided a higher yield of 2a. Under the optimized reaction conditions using a 5 : 1 (v/v) mixture of MeOH/DMF as the solvent, Bu4NClO4 as the electrolyte and a constant current of 10 mA and a time of 3 h (3.7 F mol−1 electricity), the desired bromination product (2a) was formed in 83% yield. Finally, control experiments were conducted without current (entry 7), and a significantly lower yield of 2a was observed. This demonstrated that the desired product was predominantly obtained from the electrochemical process.

The iodination of 1a was next examined (entries 8–10). Compared with N-iodosuccinimide (NIS) (entry 8), CH3I was found to be a better iodinating agent in this electrochemical reaction. The desired product (3a) was obtained in 87% isolated yield under the optimized conditions (entry 9). Again, this iodination was unambiguously driven by electricity as revealed by the control experiment (entry 10).

Compared with bromination and iodination, the electrochemical chlorination of diazonium salts was more challenging. Due to the higher electronegativity of chlorine, NCS9 and TCCA20 behaved more like oxidants rather than chlorine donors. Inspired by Lin’s recent work on the electrocatalytic chlorination of alkenes,54,55 we used anodic oxidation to generate chlorine radicals from chlorine anions. A series of alkali chlorides, cathode materials and solvents were evaluated. Ultimately, LiCl was found to be the optimal chloride source with nickel as the cathode and acetonitrile as the solvent (entries 13–15).

With the optimal reaction conditions, we then surveyed the substrate scope (Table 2). For bromination using NBS, aryl diazonium salts with an electron-withdrawing group, including an ester (2a–2c), a nitro (2d–2g), a cyano (2h and 2i), a halogen (2j–2l), a trifluoromethyl (2m) and a sulfonyl group (2n), furnished the corresponding brominated products in good to excellent yields. For electron-neutral or electron-rich diazonium salts, the use of NBS led to polybromination as revealed by GC-MS analysis. In these cases, CBrCl3 proved to be a better brominating agent using DMF as the solvent (2o–2t).

Moreover, under analogous electrochemical conditions, the iodination of aryl diazonium salts bearing an electron-withdrawing group, such as an ester (3a–3c), a cyano (3h and 3i), a halogen (3j–3l), a trifluoromethyl (3m), a sulfonyl (3n) and an acetyl (3u, 3v), gave good yields (63–96%). Additionally, electron-neutral aryl diazonium salts were also suitable substrates for this procedure (3o–3q and 3s). Finally, a range of diazonium salts (4a, 4k, 4m, 4n and 4o) could be efficiently chlorinated using LiCl as the electrochemical chlorine reagent.

Table 1 Reaction development and optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>I (mA)</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>10</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>10</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>MeOH/DMF 10 : 1</td>
<td>10</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>MeOH/DMF 10 : 1</td>
<td>25</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>MeOH/DMF 10 : 1</td>
<td>50</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>MeOH/DMF 5 : 1</td>
<td>10</td>
<td>83 (73)</td>
</tr>
<tr>
<td>7</td>
<td>MeOH/DMF 5 : 1</td>
<td>0</td>
<td>20, 31*</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1a (0.3 mmol), halogenation reagent [X], electrolyte (0.25 mmol, 0.83 equiv.), solvent (3 mL), 20 °C, and 3 h. cc, constant current. Pt mesh electrodes (1 cm² each, 52 mesh) were used. a GC-FID yields using decane as an internal standard. Isolated yields in parentheses. *15 h. d MeCN (3 mL) as the solvent and nickel foam (1 cm²) as the cathode.
For instance, sulfone substituted product 4n was obtained in 64% isolated yield.

Anilines are broadly available starting materials for organic synthesis. Thus, it is highly desirable to perform an in situ diazotization/electrochemical reaction to directly employ anilines as the precursors for halogenation. As shown in Table 3, a diverse array of aryl amines were successfully transformed to the corresponding halogenated products in good to

Table 2  Scope of the diazonium salt electrochemical Sandmeyer reaction

<table>
<thead>
<tr>
<th>R</th>
<th>N₂BF₄⁻ + [X]</th>
<th>Bu₄NClO₄ (0.83 equiv), MeOH/DMF 5:1 (0.15 M)</th>
<th>20 °C, 10 mA, 3 h (-)Pr(+)Pt undivided cell, in air</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBS (2.0 equiv)</td>
<td>2a, 73% (83%)</td>
<td>2b, 42% (53%)</td>
<td>2c, 30% (52%)</td>
</tr>
<tr>
<td>Br</td>
<td>2h, 84%</td>
<td>2i, 84%</td>
<td>2j, 52% (64%)&lt;sup&gt;n&lt;/sup&gt; (NBS 3.0 equiv)</td>
</tr>
<tr>
<td>CBrCl₃ (3.0 equiv)</td>
<td>2o, (66%)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>2r, (55%)&lt;sup&gt;n&lt;/sup&gt;</td>
<td>2s, (75%)&lt;sup&gt;n&lt;/sup&gt;</td>
</tr>
<tr>
<td>CH₂Cl (3.0 equiv)</td>
<td>3a, 87%</td>
<td>3b, 87%</td>
<td>3c, 74%</td>
</tr>
<tr>
<td>I</td>
<td>3k (2l), 61% (89%)</td>
<td>3l, 56% (77%)</td>
<td>3m, 96%&lt;sup&gt;n&lt;/sup&gt;</td>
</tr>
<tr>
<td>MeO</td>
<td>3r, (37%)</td>
<td>3s, (78%)</td>
<td>3t, 48%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>LiCl (0.9 equiv)</td>
<td>4a, (36%)&lt;sup&gt;n&lt;/sup&gt;</td>
<td>4b (2j), (37%)&lt;sup&gt;n&lt;/sup&gt;</td>
<td>4c</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 1 (0.3 mmol), Bu₄NClO₄ (0.25 mmol, 0.83 equiv.), CH₃OH (2.5 mL) and DMF (0.5 mL), 20 °C, 3 h, and constant current 10 mA. Pt mesh electrodes (1 cm × 1 cm) were used. Isolated yields were given. GC-FID yields in parentheses were given due to either product volatility or difficulty in isolation with by-products (e.g. ArH).<sup>b</sup> CH₃OH/DMF 20 : 1 (total 3.0 mL).<sup>c</sup> 1 h.<sup>d</sup> ¹⁹F NMR yields determined using 4-(trifluoromethoxy) anisole as an internal standard.<sup>e</sup> DMF (3 mL).<sup>f</sup> 4.5 h.<sup>g</sup> 2 h.<sup>h</sup> MeCN (3 mL), LiClO₄ (0.5 mmol) as the electrolyte.<sup>i</sup> 20 mA, Ni foam cathode.
excellent yields (42–83%). This one-pot protocol tolerated a number of functional groups, such as a boronic ester (3aa), an amide (3ab–3ad) and an indole (3ae). In general, aryl amines with an electron-withdrawing group gave a relatively higher yield. For instance, bromination of 4-cyanoaniline under the one-pot protocol gave 83% GC yield (2h); iodination of N-(4-aminophenyl)acetamide gave 78% isolated yield (3ab). Moreover, it is noteworthy that the aniline derived from vitamin E was also iodinated in 59% isolated yield (3af).

To further demonstrate the utility of this electrochemical protocol, gram-scale experiments were next carried out. Since the electrochemical reduction of diazonium salts takes place at the cathode, we applied inexpensive graphite plate electrodes with a large size to lower the current density ($J = 2.78$ mA cm$^{-2}$). By using the setup shown in Scheme 2, 2h was prepared from 1h on a three-gram scale (15 mmol) in 76% yield. Similarly, 3h was prepared on a three-gram scale in 80% yield.

To probe this electrically generated aryl radical species, we carried out a range of mechanistic experiments. First, a radical clock experiment was performed by using diazonium salt 5 derived from 2-(allyloxy)aniline as the substrate (Scheme 3A). We obtained only the cyclized product 6 in 37% yield as determined by 1H NMR spectroscopy, and the acyclic product was not detected by GC-MS and 1H NMR analysis. Next, an excellent yields (42–83%). This one-pot protocol tolerated a number of functional groups, such as a boronic ester (3aa), an amide (3ab–3ad) and an indole (3ae). In general, aryl amines with an electron-withdrawing group gave a relatively higher yield. For instance, bromination of 4-cyanoaniline under the one-pot protocol gave 83% GC yield (2h); iodination of N-(4-aminophenyl)acetamide gave 78% isolated yield (3ab). Moreover, it is noteworthy that the aniline derived from vitamin E was also iodinated in 59% isolated yield (3af).
The electrochemical reaction of 1a with 2,2,6,6-tetramethyl-1-piperidinylxoy (TEMPO) was conducted, affording arylated product 7 in 62% isolated yield (Scheme 3B). This is well in accord with Studer’s report. In their paper, they have demonstrated that TEMPONa is capable of reducing diazonium salt to its aryl radical, thus facilitating the following transformation.

The mechanism of electrochemical reduction of diazonium salt has been studied by means of polarography. Here we further apply this technique in our reaction system. Thus, cyclic voltammetry (CV) measurements of 1a with a series of radical-reactive reagents were taken. The CV curve of 1a gave two waves, corresponded to the reduction of aryl diazonium to aryl radicals and further to aryl anions, respectively. This is in good agreement with a literature report. However the CV curves of 1a with reagents (TEMPO, NBS, CH2I2 and CCl4 in these cases, respectively) give only one reduction peak, indicating that the nascent aryl radical reacts with these reagents, and thus likely has no chance to be further reduced on the cathode (Fig. 1). These experimental results are consistent with the hypothesis shown in Scheme 1B(d).

Electron paramagnetic resonance (EPR) is a spectroscopic technique capable of detecting and identifying paramagnetic species, such as organic radicals, thus providing essential information on the nature of reactive intermediates in single electron transfer reactions. EPR spectroscopy has been
intermediates. Consequently, to the high reactivity and low concentration of these radical
the electrolyte. EPR signals were not observed, presumably due to
the high reactivity and low concentration of these radical
intermediates. Consequently, N-benzylidene-tert-butylamine N-
oxide (PBN) was introduced into the experiments as a spin-
trap.** Spin-traps react with short-lived radicals and convert
them to more stable, EPR detectable radical species. The choice
of PBN is based on Bard’s report,** where they found that PBN is
electroinactive between 1.5 and -2.4 V (vs. SCE). Thus, four
electrochemical reactions a-d were followed by in situ EPR
spectroscopy using PBN as the spin-trap (Fig. 2A). The EPR
spectrum was acquired in an interval of 30 s over the course of
100 min. These EPR signals were then compiled as a time
dependent 2D profile (for reaction b, see Fig. 2B; for reactions a,
c and d, see Fig. S5†). Fig. 2C shows the EPR signals of these
reactions at different reaction times, and Fig. 2D shows time
dependent double-integrated intensity of these in situ EPR
signals.

In these reactions, no major EPR signal is observed until
electricity is on. The isotropic g factor and hyperfine coupling
constants of these radical EPR signals were simulated using the
least-squares fitting method with EasySpin’s function garlic (for
details, see the ESI†). As expected, radicals in reactions a, b and
c are different and in d they resemble those in c (Fig. 2C). The
contrasting growth rates of intensity shown in Fig. 2D provided
valuable mechanistic information. By comparing reactions
a and b, a rapid growth observed in reaction b indicated that
diazonium salt 1a was rapidly reduced to an aryl radical upon
electrolysis. The resulting aryl radical was trapped by PBN to
afford an EPR active species. Based on a six-line EPR spectrum
(g = 2.0039, Δg = 13.02 G, and ΔH = 2.37 G)†† and HRMS data,
this radical could be likely attributed to compound 8. In reactions
c and d, the intensity grew slowly as compared with reaction b, indicating that the addition of NBS changes the
reaction pathway of electrically generated radicals. In reaction
d, the intensity rapidly decayed when the current was turned off,
also demonstrating an electricity driven radical generation
process. These in situ EPR electrochemical experiments and
previous cyclic voltammetry studies demonstrated that diazo-
nium salts can readily undergo single electron reduction
processes on the cathode, and the resulting aryl radical is a
highly reactive species that can be trapped by many radical
trapping reagents, such as NBS, CH3I2, PBN and TEMPO.
Meanwhile, the solvents (e.g. MeOH) can be oxidized on the
anode** to balance the overall transformation (Scheme 4).

Conclusion

In summary, we have developed a general electrochemical
protocol for the Sandmeyer halogenation process. A diverse
range of functional groups were compatible with this electro-
chemical reaction. Anilines can be directly employed as the
starting material, further expanding the utility of this method.
Moreover, this method is amenable to the large-scale synthesis
of aryl halides, and very inexpensive graphite can be employed
instead of platinum as the cathode material for this large-scale
preparation. Importantly, detailed mechanism studies,
including the application of rarely used in situ EPR measure-
ments, support a single electron reduction mechanism for the
halogenation of diazonium salts upon electrolysis. This elec-
trochemical process could be a complementary method for the
existing Sandmeyer halogenation reactions, and might inspire
other Sandmeyer type transformations (e.g. noble metal free
trifluoromethylation50–52) in the near future.

Conflicts of interest

There are no conflicts to declare.

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Notes and references