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Scalable electrochemical reduction of sulfoxides to sulfides†

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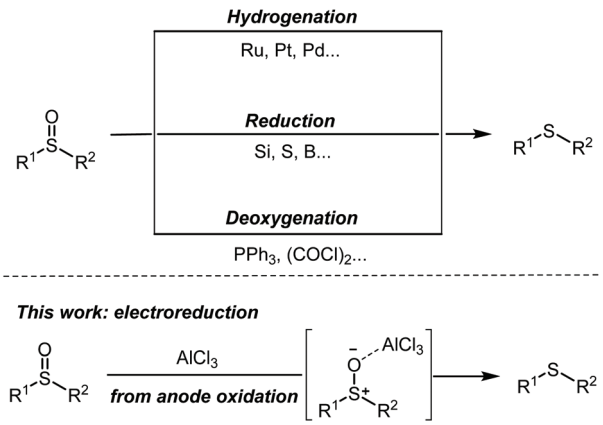
A scalable reduction of sulfoxides to sulfides in a sustainable way remains an unmet challenge. This report discloses an electrochemical reduction of sulfoxides on a large scale (>10 g) under mild reaction conditions. Sulfoxides are activated using a substoichiometric amount of the Lewis acid $AlCl_3$, which could be regenerated *via* a combination of inexpensive aluminum anode with chloride anion. This deoxygenation process features a broad substrate scope, including acid-labile substrates and drug molecules.

Organic sulfides are privileged structure motifs that are widely existing in natural products,[1] medicinal chemistry[2] and materials science.[3] Recently, many excellent methods have been explored for the synthesis of sulfides.[4] Among them, the reduction of sulfoxides is one of the most frequently used transformations.[5] Classical approaches for this kind of reaction can be categorized into three types as shown in Scheme 1: (1) catalytic hydrogenation,[6] usually relies on precious metals under harsh reaction conditions. (2) Reduction of hydride reagents, such as silane,[7] boron,[8] or sulfur reagents,[9] generates excess stoichiometric amounts of by-products. (3) Deoxygenation,[10] an alternative protocol using strong electrophiles (triphenylphosphorus and oxalyl chloride) to activate the sulfoxides results in poor functional group tolerance and undesired waste. Although the above procedures are efficient for the reduction of sulfoxides, most of them require a superstoichiometric amount of reductants or toxic reagents, which hampers practical generation of useful sulfides. Therefore, the development of a general, sustainable and scalable protocol to access sulfide derivatives is highly desirable.

Over the past decade, electrochemical synthesis has revitalized as an efficient, environmentally benign, and scalable approach for various useful transformations.[11] Employing traceless electrons as redox reagents, the use of traditional chemical oxidants or reductants can be avoided in electrochemical reactions. However, compared with the predominantly anodic oxidation,[12] the cathodic reduction is less investigated.[13] In 2019, Baran developed a scalable electrochemical Birch reduction using an inexpensive magnesium or aluminium plate as the sacrificial anode.[14] Recently, Lin and co-workers reported an electroreductive carbofunctionalization of alkenes at a Mg plate anode.[15] In addition, the Sevov group disclosed an efficient method for the electroreduction of triphenylphosphine oxide based on an Al plate anode.[16] Inspired by these works, we envisioned that the direct electrochemical reduction of sulfoxides to sulfides could be realized using an *in situ* generated Lewis acid to activate the S=O bond. Therefore, a substoichiometric amount of $AlCl_3$ could be enough by using a cheap aluminium plate as a sacrificial anode. In light of our continuous interest in electrochemical reactions,[17] we report herein an electrochemical reduction of sulfoxides to sulfides in an undivided cell under mild conditions (Scheme 1). In contrast to traditional synthetic methods, this protocol exhibits a broad substrate scope (including ester, amide, alcohol, and carbonyl group) and easy scalability (>10 g scale) and proceeds under reductant-free conditions.

We investigated the reaction using 1-bromo-4-(methylsulfinyl)benzene **1a** as a model substrate. After systematic



Scheme 1 Traditional methods and our strategy.

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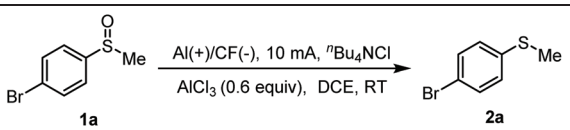
screening of the reaction conditions, the best yield of thioether **2a** was afforded in 94% by using an aluminum plate as the anode and a graphite felt electrode as the cathode in an undivided cell with a constant current of 10 mA at room temperature for 6 h (Table 1, entry 1). Changing the cathode to a graphite rod or nickel plate gave inferior results (entries 2 and 3). A similar yield was obtained by using a stoichiometric amount of $AlCl_3$ (entry 4). When the loading of $AlCl_3$ was reduced to 0.2 equivalent, the yield of **2a** was decreased to 84% (entry 5). Although 70% yield was obtained in the absence of $AlCl_3$ (entry 6), the voltage of the reaction mixture was quickly increased to 20 V and **2a** was not observed in the first two hours. This phenomenon indicated that the formation of $AlCl_3$–sulfoxide complex was crucial for the reaction (see the ESI† for details). The reaction using 1.0 equiv. $^nBu_4NCl$ provided **2a** in a diminished yield (entry 7). Replacing $^nBu_4NCl$ with $^nBu_4NBF_4$ produced product **2a** in 83% yield (entry 8). Using CH_3CN as the solvent decreased the yield of **2a** to 60% (entry 9). Reducing the current to 5 mA was less effective (entry 10). The reaction could also proceed under air with a slight decrease in yield (entry 11). The control experiment indicated that electricity was essential for the reaction (entry 12).

With the optimized reaction conditions in hand, we first examined sulfoxides with a single aryl group (Table 2). The reaction was well performed with substrates bearing electron-donating or electron-withdrawing groups at different positions on the phenyl ring (**2a–2e**). The acid-labile Boc-protected sulfoxide was also compatible, producing the desired product **2c** in moderate yield. 2-(Methylsulfinyl)naphthalene provided the corresponding sulfide **2f** in excellent yield. The reduction of bis(phenylsulfinyl)methane yielded bis(phenylthio)methane **2g** as the sole product. Sulfoxides containing an ester group or an amino acid derivative were tolerated, affording products **2h** and **2i** in moderate yields. Moreover, when a substrate containing both sulfoxide and sulfone groups was used, the sulfoxide was reduced selectively to provide sulfide **2j** with the sulfone group remaining intact. Substrates bearing cyclohexyl, cyclopropyl, and pyrrole groups were also compatible, generating sulfides **2k–2m** in good yields. The steric hindrance tertiary sulfoxide was tolerated in this transformation, producing **2n** in 46% yield. Notably, dialkyl sulfoxides were suitable for the electrochemical reduction, sulfides **2o** and **2p** were obtained in 64% and 88% yields, respectively.

The scope of diaryl sulfoxides was next investigated (Table 3). Symmetric diaryl sulfoxides bearing various functional groups (OMe, Cl, Br, and CF_3) on the phenyl ring were transformed into the desired products **3a–3e** in moderate to high yields. A substrate with an electron-donating group such as OMe gave excellent yield, whereas an electron-withdrawing CF_3-substrate led to lower yield. In addition, sulfoxides including two different aryl groups were also proved to be suitable substrates, producing sulfides **3f–3j** in excellent yields except for **3h** (30%) with a challenging free alcohol group. A variety of heterocycles such as pyrrole, pyridine, indole and thiophene were all tolerated, providing sulfides **3k–3o** in good yields.

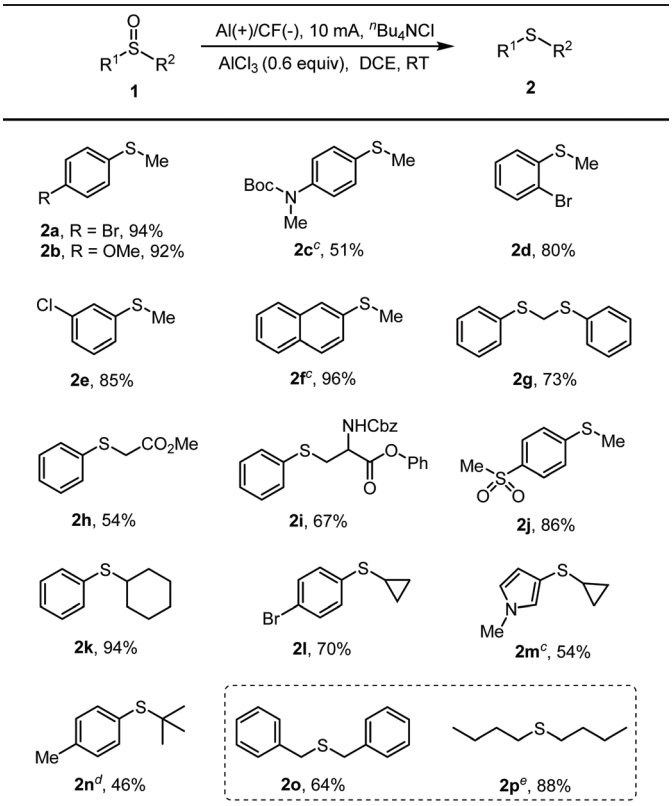
Table 1 Optimization of the reaction conditions[a]



Entry	Deviation from standard conditions	Yield[b] (%)
1	None	94
2	Graphite rod as the cathode instead of CF	81
3	Ni plate as the cathode instead of CF	21
4	1.0 equiv. $AlCl_3$	93
5	0.2 equiv. $AlCl_3$	84
6	No $AlCl_3$	70[c]
7	1.0 equiv. $^nBu_4NCl$	87
8	$^nBu_4NBF_4$ as the electrolyte	83
9	CH_3CN as the solvent	60
10	5 mA	40
11	Under air	88[c]
12	No current	n.d.

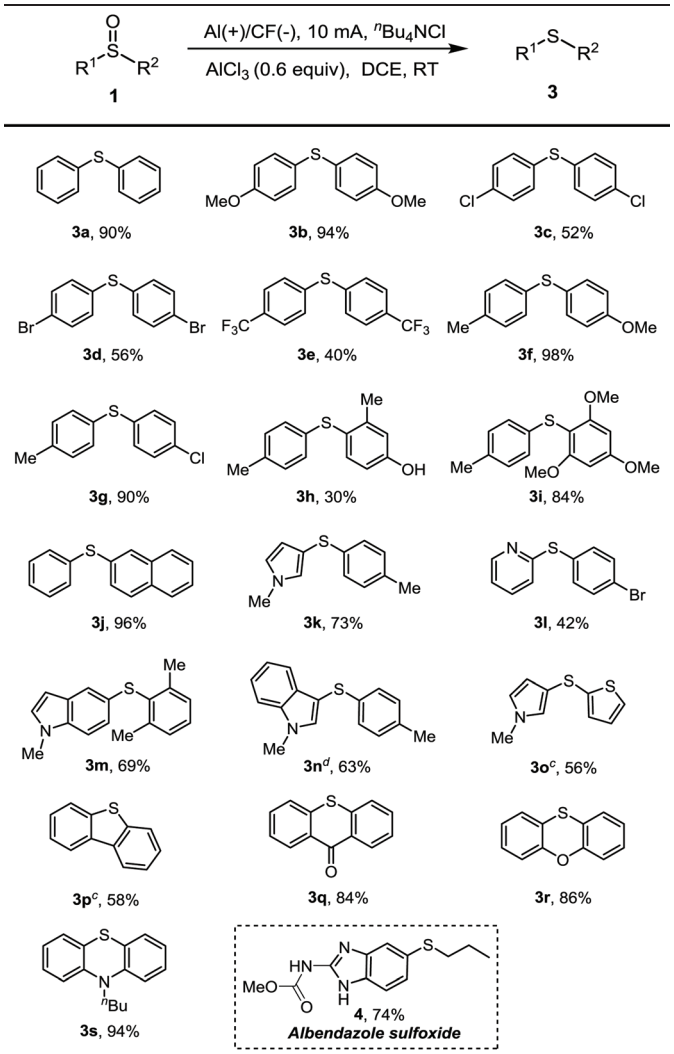
[a] Standard conditions: Al anode, CF cathode, constant current = 10 mA, **1a** (0.4 mmol), $AlCl_3$ (0.6 equiv.), $^nBu_4NCl$ (1.5 equiv.), DCE (5 mL), RT, N_2, 6 h (5.6 F mol^{-1}). [b] Isolated yields. [c] 8 h reaction time. n.d. not detected.

Table 2 Substrate scope of **2**[a,b]



[a] Standard conditions: Al anode, CF cathode, undivided cell, constant current = 10 mA, **1** (0.4 mmol), $AlCl_3$ (0.6 equiv.), $^nBu_4NCl$ (1.5 equiv.), DCE (5 mL), RT, N_2, 6 h (5.6 F mol^{-1}). [b] Isolated yields. [c] The reaction time was 4.5 h (4.2 F mol^{-1}). [d] Constant current = 14 mA, the reaction time was 3 h (3.9 F mol^{-1}). [e] The reaction time was 2 h (1.9 F mol^{-1}).

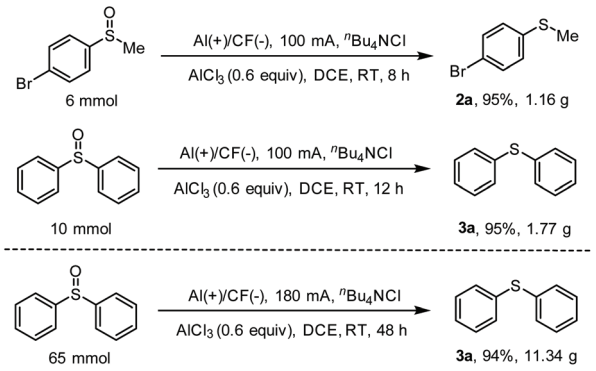
Table 3 Substrate scope of 3[a,b]



[a] Standard conditions: Al anode, CF cathode, undivided cell, constant current = 10 mA, **1** (0.4 mmol), $AlCl_3$ (0.6 equiv.), $^nBu_4NCl$ (1.5 equiv.), DCE (5 mL), RT, N_2, 6 h (5.6 F mol^{-1}). [b] Isolated yields. [c] The reaction time was 4.5 h (4.2 F mol^{-1}). [d] The reaction time was 2 h (1.9 F mol^{-1}).

Fused heterocyclic sulfoxides were also suitable for the reaction to produce the corresponding products **3p–3s**. The formation of sulfide **3q** was noteworthy as the carbonyl group was tolerated under the reductive conditions. Finally, we applied this new protocol for the synthesis of drug molecules. The anthelmintic drug albendazole **4** was successfully afforded in 74% yield from albendazole sulfoxide under the optimized conditions.

To further demonstrate the applicability of this protocol, sulfides **2a** and **3a** were afforded on a gram scale (1.16 and 1.77 g, respectively) with excellent yields (Scheme 2). The reaction of diphenyl sulfoxide could be further conducted on a 65 mmol scale to give **3a** (11.34 g) with a comparable yield. In contrast to the conventional methods, this electroreductive protocol will easily scale-up and is more environmentally



Scheme 2 Gram-scale reactions.

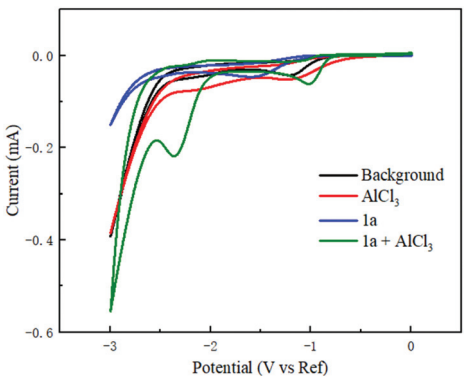
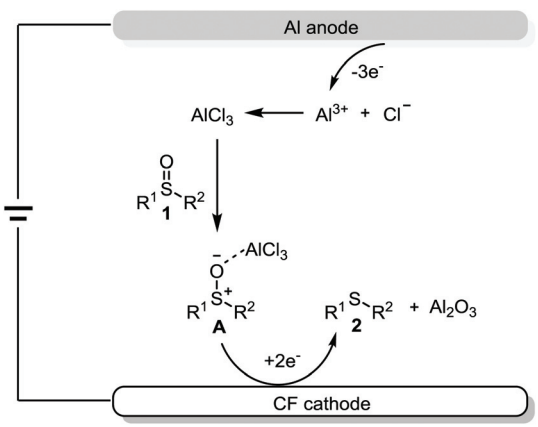


Fig. 1 Cyclic voltammetry of **1a** (25 mM) with and without $AlCl_3$ (15 mM) in DCE with 200 mM $^nBu_4NPF_6$ at a scan rate of 100 mV s^{-1}. Glassy carbon as the working electrode, Pt wire as the counter electrode, and Ag/AgCl as the reference electrode.

friendly. Moreover, this method exhibits potential for the practical access of valuable sulfides by using inexpensive aluminium and graphite felt electrodes.

Cyclic voltammetry (CV) experiments were conducted using glassy carbon as the working electrode with sulfoxide **1a** (Fig. 1). An obvious irreversible reductive peak was observed at −2.4 V in the presence of $AlCl_3$, indicating that the complex of



Scheme 3 Proposed reaction mechanism.

1a and $AlCl_3$ would be generated. The results of divided cell electrolysis and constant potential experiments could further support the formation of the $AlCl_3$–sulfoxide complex (see the ESI† for details). Based on the above experiments, the possible mechanism of the electrochemical process is proposed in Scheme 3. Initially, $AlCl_3$ could coordinate with sulfoxide **1** to generate the Lewis acid–base complex **A**, which is further reduced on the cathode by S–O bond cleavage to obtain the corresponding sulfide **2**. The Al^{3+} produced from the sacrificial Al anode could combine with the chloride anion to regenerate the $AlCl_3$.

Conclusions

In conclusion, we have developed a green and scalable electrochemical protocol for the reduction of sulfoxides to sulfides under mild conditions. The reaction proceeds well using a substoichiometric amount of the Lewis acid $AlCl_3$. The Lewis acid could be regenerated by a combination of chloride anions with Al^{3+} waste produced by the oxidation of the sacrificial Al anode. This method also features a broad substrate scope and is easily scaled-up. Further application of electrochemical reduction is currently under investigation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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