

High-efficiency Electrochemical Dehydrogenative Coupling Synthesis of S-N/S-S Bonds

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Research Article

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High-efficiency Electrochemical Dehydrogenative Coupling Synthesis of S-N/S-S Bonds

Tong Zhang·Ruke Wang·Linzheng Ma·Jing Liu·Jifu Sun·Bo Wang

Abstract: The catalytic dehydrogenative coupling of thiols with amines to produce desired sulfenamides and disulfides is an important catalytic reaction in industry. Presented herein is a protocol for the highly efficient electrochemical dehydrogenative coupling of thiols with amines/thiols to form S-N/S-S bonds, enabling the synthesis of S-N/S-S bonds under ambient conditions in the absence of oxidants, acids/bases or toxic (explosive) electrolytes, and the majority of the corresponding products are generated in yields of up to 99%. This protocol is believed to have great potential for industrial application.

Keywords Sulfenamide • Disulfide • Electrochemical dehydrogenative coupling • Mild conditions • Sustainable chemistry

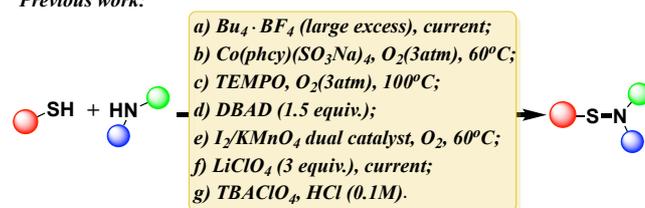
Introduction

S-N and S-S bonds are important building blocks for the construction of bioactive chemicals, agrochemicals, rubber accelerators and pharmaceuticals (Guin et al. 2020; Wu et al. 2021; Briggs et al. 2019; Zhang et al. 2020), and sulfenamides and disulfides, possessing S-N and S-S bonds, are recognized as important compounds that serve as crucial reagents in several organic transformations, such as oxidation, amination, and sulfuration (Liu et al. 2019). Despite the well-known applications of sulfenamides and disulfides, there are only limited examples of efficient clean and mild preparations. Typically, the currently used approaches for sulfenamides involve the reaction between amine nucleophiles and sulfonyl chlorides; nevertheless, sulfonyl chlorides are not widely available and are toxic, unstable reagents, whose preparation is cumbersome and requires a combination of oxidizing and chlorinating reagents, usually resulting in a large waste salt stream and possibly causing serious environmental concerns. In addition, disulfides are usually formed as byproducts during the preparation of sulfenamides, inevitably decreasing the yields of the desired product sulfenamides. Considering sustainability and to satisfy some principles of green chemistry, the direct coupling of thiols with amines for sulfenamides and disulfides is expected to be a better choice. Recent developments mainly include the use of pressurized oxygen as an ultragreen oxidant under the influence of 2,2,6,6-(tetramethylpiperidin-1-yl)oxyl (TEMPO) (Yang et al. 2017), the complex metal catalyst cobalt-phthalocyanine $\text{Co}(\text{phcy})(\text{SO}_3\text{Na})_4$ under heated conditions (Dou et al. 2017), Mitsunobu-type coupling using dibenzyl azodicarboxylate (DBAD) as the oxidant (Ryu et al. 2020), electrochemical dehydrogenative coupling pathways with excess $\text{Bu}_4\text{N}^+\text{BF}_4^-$ (Tang et al. 2019) or a combination of tetrabutylammonium perchlorate (TBAClO_4) and HCl (Laudadio et al. 2017) or toxic LiClO_4 (Yang et al. 2018) as the electrolyte to

additives (requiring neutralization before draining, leading to waste salt stream formation), strong oxidants, or explosive electrolytes might cause environmental concerns, and for those employing pressurized O_2 , (Liu et al. 2019) special pressurized vessels are required to prevent possible chemical production accidents (Shinkar et al. 2019).

Compared to conventional methods employing strong oxidant or pressured ultragreen oxidant O_2 in special pressured vessels, electrochemical dehydrogenative coupling pathways have proven to be more advantageous, as in most conditions, oxidizing/toxic reagents are not required (Wiebe et al. 2018; Anastas and Eghballi, 2010). However, there remain some issues with the currently used methods, such as the requirement of excess or toxic electrolytes, unsatisfactory low product yields (inefficient), and/or processing under acidic conditions.

Previous work:



This work:

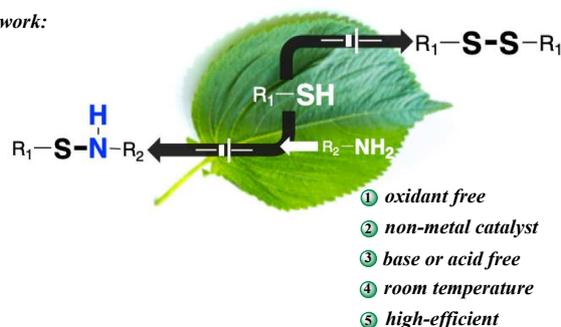


Figure 1. Selected examples of previous work on S-N bonds formation and schematic profile of electrochemical dehydrogenation coupling of thiols with amines.

The use of electrochemical activation not only permits the union of these stubborn coupling partners but also enables this transformation to be carried out under extremely mild conditions (room temperature, no hazardous reagents required, etc.) and to avoid the use of transition metal catalysis (Dou et al. 2017; Liu et al. 2019), and therefore, the electrochemical approach toward sulfenamides or disulfides described herein allows the development of more clean synthetic pathways, while addressing a fundamental and hitherto unanswered synthetic challenge of preparing sulfenamides and disulfides from thiol and amine feedstock inputs (Laudadio et al. 2019; Mulina et al. 2018; Wei et al. 2021; Cao et al. 2021); In particular, herein, the disulfides are

formed as main products, not only as byproducts as in conventional methods.

We envisioned a highly efficient electrochemical dehydrogenative coupling procedure to directly use thiols to couple with amines for clean and efficient synthesis of both sulfenamides and disulfides under ambient conditions in the absence of a combination of oxidizing and chlorinating reagents (Figure 1). Herein, disulfides were generated as the main products with excellent yields. In addition, neither acids nor bases were required during reaction processing and are believed to meet more principles of green chemistry. In this paper, we will detail how our plan was translated into experimental reality, leading to the development of a highly efficient electrochemical dehydrogenative coupling process for synthesizing an array of varying (various) sulfenamides and disulfides free of oxidizing reagents and metal catalysts.

Results and Discussion

Initial reactions were carried out to explore suitable reaction conditions at a 7 ml scale by employing 2-mercaptobenzothiazole **1a** and tert-butylamine **2a** as the model substrates to form the corresponding sulfenamide **3a**. The reaction parameters, for instance, the electrode, substrate ratios (**1a/2a**), loading of potassium iodide (KI), and solvents, were evaluated, and the results are summarized in Table 1.

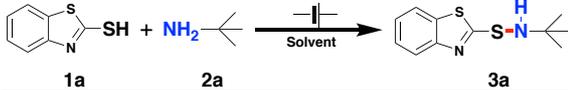
All reactions proceeded smoothly, and the results indicated that when the reaction was carried out in the solvent CH₃OH using a combination of a C anode and a Pt cathode, the proposed product **3a** was afforded in a yield of 99% (Entries 4 and 6, Table 1); a **1a/2a** ratio of either 1:3 or 1:5 provided product **3a** in a yield of 99% (Entries 4 and 6, Table 1), which was close to ideal, a higher ratio of 1:1 led to a reduced product yield (Entry 5, Table 1), and a lower ratio of 1:5 resulted in a reduced reaction time (Entry 6, Table 1). To satisfy more principles of green chemistry, a ratio of 1:3 was chosen for further evaluation (Entry 4, Table 1). We also tried to perform reactions in the ultragreen solvent H₂O, and almost no product formation was observed (Entry 15, Table 1). Additionally, we tried to perform the reaction using a higher current of 10 mA or a lower current of 5 mA (Entries 12 and 13, Table 1); however, decreased product yields resulted.

After determining the optimized conditions and to expand the substrate scopes, an array of varying thiols (**1**) and different amines (**2**) were then tested under the optimized conditions described in the footnote of Table 2, and the results are summarized in Table 2.

In addition to sulfenamides, disulfides play an important role in both the pharmaceutical and rubber accelerator industries. Coincidentally, it was found that when catalytic loading at 5% or less amine, rather than a stoichiometric or excess amount, was applied, an increase in the formation of disulfides and essentially no sulfenamides were observed. Therefore, the thiols listed in Table 3 were subjected to the conditions described in the footnote of Table 2 except the amines, and the results are summarized in Table 3. Similar to those reactions for the synthesis of sulfenamides, all reactions proceeded smoothly and afforded the corresponding product disulfides with yields of up to 99% (Entries 1-10, Table 3); essentially no side product formation was detected. Additionally, when substrates possessing a stable ring were used, a lower reactivity would be expected, leading to a reduced product

yield within the same reaction time. To achieve the same yield, a prolonged time was required (Entries 1, Table 3), which might be the reason why a twofold higher reaction time was needed in entry 1 in Table 3 compared to other reactions (Entries 2-10, Table 3)

Table 1. Conditions optimization^[a]



Entry	Anode/ Cathode	Solvent	Ratio (1a/2a)	Time (h)	Yield (3a , %) ^[e]
1	C/Pt	CH ₃ CN	1/3	3.0	95
2	C/Pt	CH ₃ CH ₂ OH	1/3	3.0	85
3	C/Pt	DMF	1/3	3.0	80
4	C/Pt	CH ₃ OH	1/3	3.0	99
5	C/Pt	CH ₃ OH	1/1	4.0	55
6	C/Pt	CH ₃ OH	1/5	1.5	99
7	C/C	CH ₃ OH	1/3	3.5	90
8	C/Cu	CH ₃ OH	1/3	4.0	95
9	C/Zn	CH ₃ OH	1/3	4.0	90
10	C/Ni	CH ₃ OH	1/3	4.0	93
11	Pt/Ni	CH ₃ OH	1/3	4.0	92
12 ^[f]	C/Pt	CH ₃ OH	1/3	5.0	86
13 ^[g]	C/Pt	CH ₃ OH	1/3	3.0	93
14 ^[d]	C/Pt	CH ₃ OH	1/3	3.0	trace
15	C/Pt	H ₂ O	1/3	3.0	trace

[a]Conditions: **1a**, 0.5 mmol; **2a**, 1.5 mmol; KI, 5 mol%; Solvent, 5 ml; Constant current, 8 mA; Carbon rod with diameter 5 mm and 15mm under solution. Pt, Cu, Ni and Zn plate (15 mm x 15 mm x 0.1 mm), all electrode materials were bought without any additional treatment, the distance between the electrodes (15 mm), undivided cell, r.t.; [b] Constant current, 5 mA; [c] Constant current, 10 mA; [d]KBr, 5% mol; [e]Yields were determined by HPLC analysis using a Shimadzu LC-20 instrument equipped with a C18 column (150 mm*2.5 μm)

To investigate the reaction mechanism, some control reactions using **1a** and **2a** as model substrates were performed, and the results are summarized in Scheme 1. When the reaction employed substrates **1a** and **2a** under the same conditions described in the footnote of Table 2, basically no formation of products, either **3a** or **4a**, was observed, which indicates that the reaction could not proceed in the absence of an electric current (Scheme 1a). Nevertheless, when the reaction was carried out at 8 mA without KI, only a trace amount of product was detected, indicating that KI played a vital role during dehydrogenative coupling synthesis. Interestingly, when excess I₂ was used in place of KI, even with no electric current, a good yield of **3a** was achieved, indicating that the role of I₂ in the dehydrogenative coupling of thiols with amines was the same as that of KI plus an electric current. With or without an electric current, it seemed that when disulfides came into contact with amines, the proposed

product sulfenamides could still form in acceptable yields (Scheme 1e), although in a much lower yield than that achieved in presence under electric current (99%, Scheme 1e, entry 1, Table 2); these findings explain why disulfides are generated as side products in conventional procedures.

Table 2. Substrate scope and reaction results^[a]

$R_1-SH + R_2-NH_2 \xrightarrow[CH_3OH, r.t.]{- } R_1-S-NH-R_2$					
1	2	3			
Entry	1	2	Time (h)	3	Yield (%) ^[b]
1			4		99
2			4		99
3			4		96
4			4		99
5			4		99
6			3		99
7			3		99
8			3		99
9			3		99
10			3		90
11			3		99
12			3		99
13			3		99
14			3		99
15			3		99
16			4		98
17			3		99
18			3		99

[a]All reactions were performed at a 7 ml scale, conditions: C (diameter 5 mm and 15 mm under solution) anode and Pt (15 mm x 15 mm x 0.1 mm) cathode, the distance between the electrodes (15 mm); thiols, 0.5 mmol; amines, 1.5 mmol; KI, 5 mol%; CH₃OH, 5 ml; Constant current, 8 mA, undivided cell; r.t.; [b]Yields were determined by HPLC analysis using a Shimadzu LC-20 instrument equipped with a C18 column (150 mm*2.5 μm).

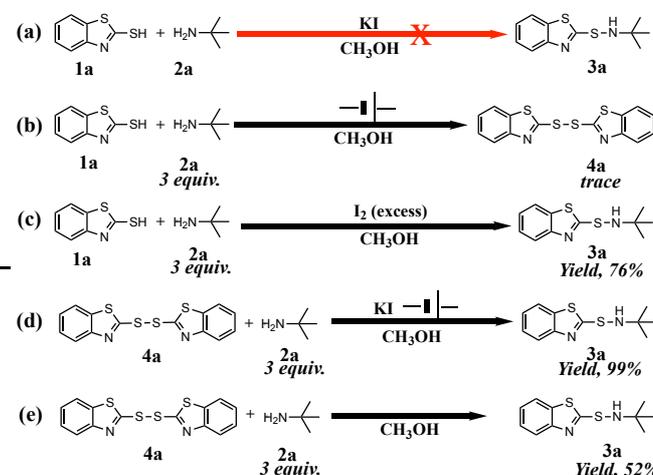
To further explore the electrochemical reaction process, some cyclic voltammetry experimental reactions were carried out using pure KI, 1a, 2a and a mixture of 1a and 2a, and the results are summarized in Figure 2. As shown in the cyclic voltammogram of

KI oxidized to I₂, an oxidation peak at -0.33 V was recorded. Next, 1a was tested in the presence of KI, and there was an obvious shift of the peak from -0.33 V to -0.4 V, which indicated that disulfides were formed. When 1a and 2a were mixed, a new peak appeared at -0.17 V, and the peak at -0.4 V disappeared simultaneously, indicating that disulfide, as a major byproduct, was suppressed and that sulfenamides became the major product, confirming the results from the control reactions. Notably, during the whole process, molecular hydrogen (H₂) was generated and could be observed.

Table 3. Dehydrogenative coupling of thiols for the synthesis of disulfides^[a]

$R-SH \xrightarrow[CH_3OH, r.t.]{- } R-S-S-R$				
1	4			
Entry	1	Time (h)	4	Yield (%) ^[b]
1		4		99
2		2		99
3		2		99
4		2		99
5		2		99
6		2		99
7		2		99
8		2		99
9		2		99
10		2		99

[a]All reactions were performed on a 7 ml scale. Conditions: C (diameter 5 mm and 15 mm under solution) anode and Pt (15 mm x 15 mm x 0.1 mm) cathode, the distance between the electrodes (15 mm); thiols, 0.5 mmol; KI, 5 mol%; CH₃OH, 5 ml; Constant current, 8 mA, undivided cell; r.t.; [b]Yields were determined by HPLC analysis using a Shimadzu LC-20 instrument equipped with a C18 column (150 mm*2.5 μm).



Scheme 1. Control reactions to explore possible reaction mechanism

Based on the experimental results and analysis of the cyclic voltammograms, a plausible reaction mechanism is proposed in

Figure 3. There are three distinct pathways to form disulfides 4 or sulfenamides 3 during the reaction: one leads to the generation of disulfides 4, which undergo later-stage ammonolysis in the presence of amines to finally form sulfenamides 3 and

simultaneously release H^+ (derived from 2). On the cathode, the released H^+ is reduced to form H_2 after obtaining an electron. The other pathway involves the direct formation of sulfenamides 3 via sulfonyl iodides by reaction with amine nucleophiles.

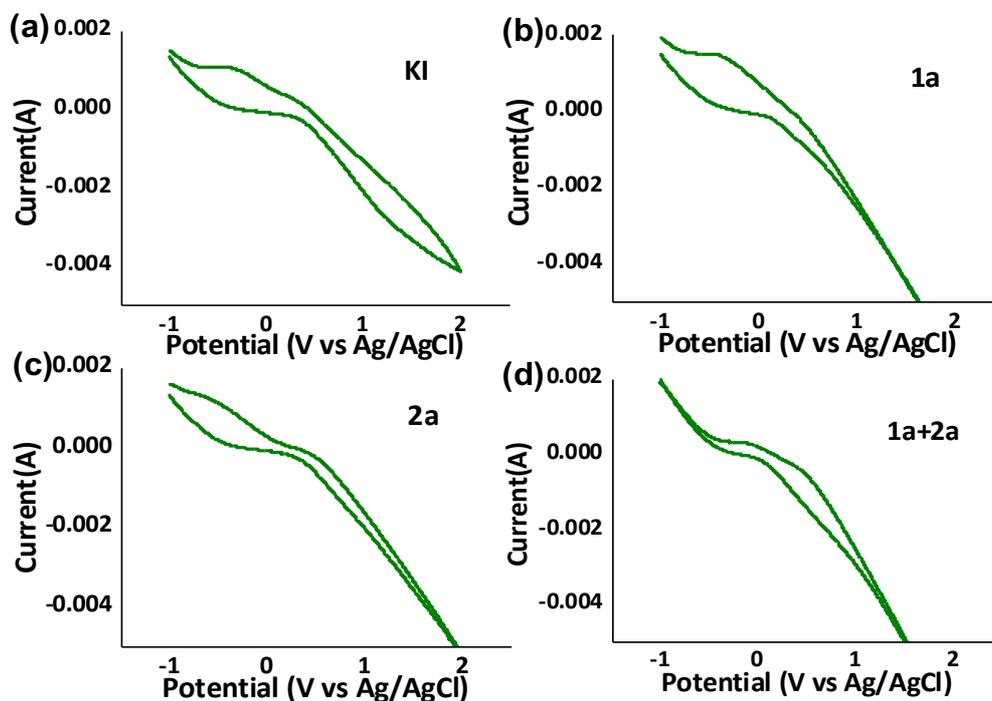


Figure 2. Cyclic voltammograms of 1a and 2a in CH_3OH with KI (5% mol) under an air atmosphere on a C anode, a Pt cathode and a Ag/AgCl reference electrode at a scan rate of $v = 0.1 \text{ V s}^{-1}$.

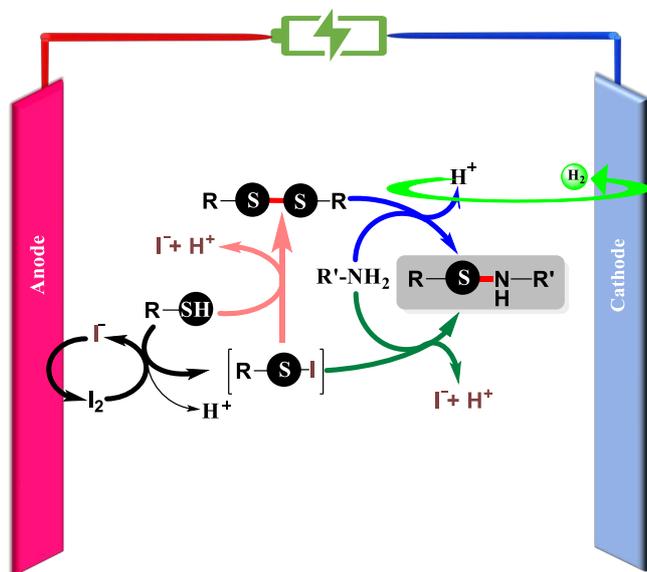


Figure 3. The proposed reaction mechanism.

Conclusion

In conclusion, we have developed an efficient electrochemical dehydrogenative coupling of thiols with amines for the construction of S-S and S-N bonds, which allows the

dehydrogenative coupling of a wide range of thiols and amines under ambient conditions without the addition of bases, acids or oxidizing reagents, and the majority of the corresponding disulfides and sulfenamides could be generated in yields of up to 99%, which is close to the ideal. Some control reactions and cyclic voltammetry experiments were performed to determine a possible reaction mechanism, indicating that there are three distinct reactions during the coupling processing and explaining why disulfides are generated as side products in typical methodologies. The products along with the developed procedures are expected to possess great potential for future sustainable and industrial applications.

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