Organic & Biomolecular Chemistry





View Article Online

Check for updates

Cite this: DOI: 10.1039/c8ob03211d

Received 27th December 2018, Accepted 9th January 2019 DOI: 10.1039/c8ob03211d

rsc.li/obc

Scalable electrochemical oxidant-and metal-free dehydrogenative coupling of S-H/N-H⁺

Shanyu Tang,^a Yan Liu,^b Longjia Li,^a Xuanhe Ren,^a Jiao Li,^a Guanyu Yang,^a Heng Li [®] *^a and Bingxin Yuan [®] *^a

A practical and scalable electrochemical oxidation of S–H and N–H was developed. This oxidant- and catalyst-free electrochemical process enables S–N bond formation with inexpensive nickel electrodes in an undivided cell. This procedure exhibits broad substrate scopes and good functional-group compatibility. A 50 g scale oxidative coupling augurs well for industrial applications.

Sulfenamides, a class of organosulfur compounds containing sulfur-nitrogen bonds, have drawn much interest in diverse fields due to their vital applications in organic synthesis, photoliable therapy, materials chemistry, and food science, pharmaceuticals particularly in and industrial manufacturing.¹⁻⁵ For instance, the sulfenamide derivatives of mercaptobenzothiazole (MBT), such as TBBS, CBS and NOBS, are widely applied rubber vulcanization accelerators with highest economical and technological importance (Fig. 1).^{6,7} Euparen-CM, Captan and Phaltanare are also commercially important sulfenamides (Fig. 1).8 Sulfenamide derivatives have been proved to show in vivo antitumor and antiviral activities (Fig. 1).^{8,9}

Despite classical methods described in the literature studies,¹⁰⁻¹⁸ the direct synthesis of sulfenamides *via* the oxidative coupling of thiols and amines shows an example of green transformation, since such substrates require no prefunctionalization. The copper-catalyzed aerobic cross-dehydrogenative coupling of arylthiols and primary amines was first reported by Taniguchi,¹⁹ and Jang *et al.* modified the reaction system to be able to deal with electron-deficient amides.²⁰ Recently, our group has reported a cobalt catalyzed aerobic dehydrogenative coupling of thiols and amines with water as the sole solvent.²¹ A hypervalent iodine promoted metal-free protocol was disclosed by Wacharasindhu and co-workers.²² Zeng *et al.* developed an iodine-catalyzed oxidative coupling of

sulfoximines and aniline with hydroperoxide as the oxidant.²³ TEMPO was also an efficient catalyst for the aerobic metal-free synthesis of sulfenamides.²⁴ However, these methods still suffer from some drawbacks, such as a limited substrate scope, toxic metal complexes, over-oxidation, and excess of oxidants. In this context, the development of novel synthetic tools to fulfill the criteria of green chemistry, atom economy, and great efficiency is highly desired.

The electrochemical oxidation process has emerged as a highly efficient and environmentally benign synthetic tool.^{25–36} Lei *et al.* reported electrochemical oxidant-free cross coupling reactions of S–H along with hydrogen evolution.^{37,38} Thiol could be oxidized at the anode to generate the sulfur radical. Inspired by these aspects and our continuous interest in green processes,^{21,24,39–41} a catalyst-free electrochemical oxidation of S–H and N–H was investigated as a scalable and sustainable strategy to produce sulfenamides.



Fig. 1 Representative significant sulfenamides.

^aDepartment of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou, Henan, China 450001. E-mail: hengli@zzu.edu.cn, bxyuan@zzu.edu.cn ^bSchool of Life Science, Zhengzhou University, Zhengzhou, Henan, China 450001 † Electronic supplementary information (ESI) available. See DOI: 10.1039/ c8ob03211d

2-Mercaptobenzothiazole 1a and t-butylamine 2a were chosen as model substrates to screen various reaction conditions for the envisioned electrochemical S-H/N-H coupling. The reaction was conducted at room temperature in a simple undivided test tube under a constant current (5 mA). We intended to avoid the usage of noble electrode materials at the start of this study. Nickel foam was purchased in a large piece and cut into a desired size to be used as an anode and a cathode (\$0.02 per electrode). The choice of electrolytes clearly has a substantial effect on the reaction outcome. The usage of Bu₄N·Br or Bu₄N·ClO₄ resulted in no product formation (Table 1, entries 1 and 2). LiClO₄ and Bu₄N·BF₄ led to the target compound in 40% and 82% yields (entries 3 and 4), respectively. After considerable experimentation, acetonitrile turned out to be the optimal solvent, while attempts to use other polar solvents such as DMF, EtOH, MeOH, and THF were much less effective (entries 4-8). Copper and iron foams were tested (entries 9 and 10), however, the electrode surface turned black during the reaction, indicating severe electrode corrosion. With the vitreous carbon electrode as the anode and nickel foam as the cathode, 30% yield was achieved (entry 11). By extending the reaction time to 6 h, the yield increased slightly (entry 12). However, at the end of the reaction, some black spots appeared on the surface of the nickel electrode. The electrochemical performance could be further improved by increasing the ratio of 2a against 1a to 10:1, while the electrode would retain the initial appearance unchanged (entries 13-15). Delightfully, the electrodes could be reused. Compared to nickel, the platinum electrode was almost equally effective

Table 1	Reaction	condition	screening ^a
---------	----------	-----------	------------------------

$\frac{1}{1a} = \frac{1}{2a}$		anode / cathode constant current = 5 mA seal tube N ₂ , solvent				
Entry	Electrolyte	(+)/(-)	Solvent	1a/2a	Time (h)	Yield ^b (%)
1	Bu₄N·Br	Ni/Ni	CH ₃ CN	1/5	5	n.p.
2	$Bu_4N \cdot ClO_4$	Ni/Ni	CH_3CN	1/5	5	n.p.
3	$LiClO_4$	Ni/Ni	CH_3CN	1/5	5	40
4	$Bu_4N \cdot BF_4$	Ni/Ni	CH_3CN	1/5	5	82
5	$Bu_4N \cdot BF_4$	Ni/Ni	DMF	1/5	5	20
6	$Bu_4N \cdot BF_4$	Ni/Ni	EtOH	1/5	5	15
7	$Bu_4N \cdot BF_4$	Ni/Ni	MeOH	1/5	5	30
8	$Bu_4N \cdot BF_4$	Ni/Ni	THF	1/5	5	15
9	$Bu_4N \cdot BF_4$	Cu/Cu	CH_3CN	1/5	0.5	20
10	$Bu_4N \cdot BF_4$	Fe/Fe	CH_3CN	1/5	5	Trace
11	$Bu_4N \cdot BF_4$	C/Ni	CH_3CN	1/5	5	30
12	$Bu_4N \cdot BF_4$	Ni/Ni	CH_3CN	1/5	6	86
13	$Bu_4N \cdot BF_4$	Ni/Ni	CH ₃ CN	1/7	6	94
14	$Bu_4N \cdot BF_4$	Ni/Ni	CH ₃ CN	1/10	6	95
15	$Bu_4N \cdot BF_4$	Ni/Ni	CH ₃ CN	1/12	6	97
16	Bu4N·BF4	Pt/Pt	CH ₃ CN	1/10	6	87
17^{c}	Bu₄N·BF₄	Ni/Ni	CH ₃ CN	1/10	6	93
18^d	Bu ₄ N·BF ₄	Ni/Ni	CH ₃ CN	1/10	6	n.p.

electrolyte (0.1 mol/L)

^{*a*} Unless otherwise noted, reaction conditions are as follows: Ni anode, Ni cathode, constant current = 5 mA, **1a** (0.30 mmol), $Bu_4N \cdot BF_4$ (0.5 mmol), MeCN (5 mL), room temperature, seal tube N₂, 6 h. ^{*b*} Isolated yield. ^{*c*} In air. ^{*d*} No current. (entry 16). A control experiment was performed under air, and a good reaction yield was still obtained (entry 17). Thus, the following reactions were conducted in a test tube without precautions to exclude air or moisture. The elimination of electric current led to no product under an air or a nitrogen atmosphere.

With the optimal reaction conditions in hand, the versatility of this electrochemical S-H/N-H coupling reaction was explored. Generally, aliphatic and benzyl amines were smoothly converted within the cross-coupling regime. Primary and secondary aliphatic amines gave the desired product in modest to excellent yields (3a-3j). The cross-coupling of linear primary amines with 1a occurred preferentially compared to cyclic systems, as illustrated by 3a-d. A similar trend was observed with secondary amines (3e-j). The reaction time was extended to 10 h for cyclohexayl scaffolds to achieve good yields (3g-j). We speculated that the steric effect might be responsible for the lower yield of 3g compared to that of 3f. Thus, diisopropylamine 2k and 2,2,6,6tetramethylpiperidine 2l were tested, and low yields of 3k and 31 confirmed the hypothesis. This electrochemical crosscoupling protocol exhibited compatibility with benzyl amines as well (3m-o). Unexpectedly, the cross-coupling of 2-pyridinethiol with tert-butylamine produced 3p instead of the monosulfurated product. Morpholine, as a representative of secondary amine scaffolds, was used and furnished the desired product 3q in modest yield. Other heteroaryl thiols, 4-mercaptopyridine, 2-mercaptopyrimidine, and 2-mercaptobenzoxazole (3r-t), were also suitable for this transformation. Unfortunately, no aryl amines furnished the desired sulfenamides (Table 2).

The robustness and feasibility of the scalable electrocatalysis were reflected by a large-scale synthesis of **3a**. The reaction was conducted in a glass tank open to air, using two Ni foam sheets as electrodes. **3a** was produced in 94% yield on a 50 g scale while the Ni sheets could be reused (Fig. S1, see the ESI†). The highlights of this large-scale test include operational simplicity, safe procedure, simple workup and ease of product isolation.

To understand dehydrogenative coupling's electrochemical mode of action, cyclic voltammetry experiments were carried out to study the anodic oxidation of the substrates (Fig. 2). An oxidation peak of **1a** in CH₃CN was observed at 1.22 V, while the oxidation peak of **2m** was observed at 1.55 V. The combination of **1a** and **2m** resulted in two oxidation peaks at 0.8 V and 1.23 V, respectively. Since the operating voltage was round 2 V, the oxidation of thiols and amines was feasible under the optimal reaction conditions.

To gain some insights into the reaction mechanism, we conducted several control experiments. One equivalent of 2, 2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), a typical free radical inhibitor, was added to the reaction of **1a** with **2a** under standard conditions. The product yield was lowered to 65%, suggesting that radical intermediates might be involved (Scheme 1, reaction a). In the absence of amine, thiol **1a** accomplished dehydrogenative homo-coupling to

Communication

Table 2 Substrate scope^a



^{*a*} Reaction conditions: **1** (0.3 mmol), **2** (3 mmol), Bu₄N·BF₄ (0.1 mol L⁻¹), Ni anode/Ni cathode, CH₃CN (5 ml), constant current = 5 mA, air, room temperature, 6 h. ^{*b*} t = 10 h.



Fig. 2 Cyclic voltammetry of **1a** and **2m** in CH₃CN with Bu₄N·BF₄ (0.1 M) under nitrogen at a platinum-wire electrode and a platinum counter electrode at a scan rate of v = 0.1 V s⁻¹.



Scheme 1 Mechanistic studies by experiments.

form disulfide 4a in fair yield. To be noticed, the control experiment (Scheme 1, reaction b) was conducted by using platinum electrodes. The electrolysis of thiols with no amines added caused severe Ni electrode corrosion, furnishing benzo [d]thiazole as the main product. The microscopic observation of Ni electrodes showed some yellow particles attached to the surface of the Ni foam (both the anode and the cathode), which presumably were sulfur particles formed owing to the

dethiolation. Actually, disulfide 4a was also observed during the reaction of 1a with 2a under the optimal reaction conditions at room temperature. When the temperature was increased to 30 °C, no disulfide 4a was detected during the reaction while the product was formed much more rapidly. In fact, the reaction could be completed in 2 h at 30 °C with 95% yield. However, a trace amount of benzo[*d*]thiazole was produced due to the dethiolation of substrate 1a. By adopting di-



sulfide 4a as a substrate, 3a was formed in quantitative yield (Scheme 1, Reaction c). In the absence of thiol, benzylamine 2m underwent electrochemical dehydrogenative coupling, furnishing N-benzyl-1-phenylmethanimine (N-BB) 5a in excellent yield (Scheme 1, Reaction d). Previous studies suggested that N-BB was formed with a nitrogen-centered radical intermediated participated.⁴²⁻⁴⁴ Thus, we proposed that a nitrogencentered radical generated from the amine should also be electrochemical coupling reaction. involved in the Furthermore, a radical scavenger 5,5-dimethyl-1-pyrrolinenoxide (DMPO) was added to the electrolysis of 1a and 2m under the standard conditions, respectively (Scheme 2). The corresponding adduct of radicals with DMPO was observed by HRMS analysis (Fig. S2 and S3, see the ESI[†]), demonstrating that the thiyl radical and the aminyl radical might be the key intermediates in the reaction.

Based on these pieces of experimental evidence and Lei's recent studies,^{37,38} a proposed mechanism is shown in Fig. 3. Initially, the single-electron-transfer oxidation of thiol and amine on the anode surface results in the generation of the thiyl radical and the amino radical, respectively. The coupling of the thiyl radical and the amino radical produced the desired sulfenamide. Meanwhile, the thiyl radical undergoes dimerization to form a disulfide. The disulfide gains an electron at the cathode to produce the corresponding radical anion. The cleavage of the radical anion reproduces the thiyl radical and a thiyl anion.



Fig. 3 Proposed reaction mechanism.

In summary, an electrochemical oxidant- and metal-free dehydrogenative S–H/N–H cross-coupling protocol is developed. The practical procedure enables the formation of sulfenamides in a simple fashion through the electrochemical process and utilizes inexpensive nickel foam as electrodes. Our method is further highlighted by its easy scalability, zero-precaution on setup, room temperature conditions, and reusability of nickel foam electrodes. Thus, the mild S–H/N–H coupling in the absence of catalysts and oxidants has the high potential to facilitate the synthesis of sulfenamide in industrial manufacturing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors would thank the National Natural Science Foundation of China (No. 21801229 and 21502174) for the funding support.

References

- 1 A. S. Karwa, A. R. Poreddy, B. Asmelash, T.-S. Lin, R. B. Dorshow and R. Rajagopalan, *ACS Med. Chem. Lett.*, 2011, 2, 828–833.
- 2 J. Pan and M. Xian, Chem. Commun., 2011, 47, 352-354.
- 3 T. Javorskis, G. Bagdžiūnas and E. Orentas, *Chem. Commun.*, 2016, **52**, 4325–4328.
- 4 J. Yoo, D. J. Kuruvilla, S. R. D'Mello, A. K. Salem and N. B. Bowden, *Macromolecules*, 2012, **45**, 2292–2300.
- 5 C. J. Nalbandian, Z. E. Brown, E. Alvarez and J. L. Gustafson, *Org. Lett.*, 2018, **20**, 3211–3214.
- 6 P. Charoeythornkhajhornchai, C. Samthong and A. Somwangthanaroj, J. Appl. Polym. Sci., 2017, 134, 44822.
- 7 G. Rong, Y. Chen, L. Wang, J. Li, J. Wang, M. J. Panzer and Y. Pang, *J. Appl. Polym. Sci.*, 2014, **131**, 39699.
- 8 F. Müller, P. Ackermann and P. Margot, Fungicides, Agricultural, 2. Individual Fungicides, in *Ullmann's Encyclopedia of Industrial Chemistry*, 2011, DOI: 10.1002/ 14356007.012_006.
- 9 G. R. Revankar, N. B. Hanna, K. Ramasamy, S. B. Larson, D. F. Smee, R. A. Finch, T. L. Avery and R. K. Robins, *J. Heterocycl. Chem.*, 1990, 27, 909–918.
- 10 N. Taniguchi, Synlett, 2007, 1917-1920.
- 11 K. Oka and S. Hara, Tetrahedron Lett., 1977, 18, 695-698.
- 12 H. Ikehira and S. Tanimoto, Synthesis, 1983, 716-717.
- 13 E. KÜHle, Synthesis, 1970, 561–580.
- 14 D. H. R. Barton, R. H. Hesse, A. C. O'Sullivan and M. M. Pechet, *J. Org. Chem.*, 1991, 56, 6702–6704.
- 15 N. Kharasch, S. J. Potempa and H. L. Wehrmeister, *Chem. Rev.*, 1946, **39**, 269–332.

- 16 M. D. Bentley, I. B. Douglass, J. A. Lacadie, D. C. Weaver, F. A. Davis and S. J. Eitelman, *J. Chem. Soc. D*, 1971, 1625– 1626.
- 17 F. A. Davis, A. J. Friedman, E. W. Kluger, E. B. Skibo, E. R. Fretz, A. P. Milicia, W. C. LeMasters, M. D. Bentley, J. A. Lacadie and I. B. Douglass, *J. Org. Chem.*, 1977, 42, 967–972.
- 18 T.-Z. Illyés, D. Molnár-Gábor and L. Szilágyi, *Carbohydr. Res.*, 2004, **339**, 1561–1564.
- 19 N. Taniguchi, Eur. J. Org. Chem., 2010, 2670-2673.
- 20 C. Lee, Y. N. Lim and H.-Y. Jang, *Eur. J. Org. Chem.*, 2015, 5934–5938.
- 21 Y. Dou, X. Huang, H. Wang, L. Yang, H. Li, B. Yuan and G. Yang, *Green Chem.*, 2017, **19**, 2491–2495.
- E. Rattanangkool, W. Krailat, T. Vilaivan, P. Phuwapraisirisan,
 M. Sukwattanasinitt and S. Wacharasindhu, *Eur. J. Org. Chem.*, 2014, 4795–4804.
- 23 L. Yang, J. Feng, M. Qiao and Q. Zeng, *Org. Chem. Front.*, 2018, 5, 24–28.
- 24 L. Yang, S. Li, Y. Dou, S. Zhen, H. Li, P. Zhang, B. Yuan and G. Yang, *Asian J. Org. Chem.*, 2017, **6**, 265–268.
- 25 M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, 117, 13230–13319.
- 26 A. Badalyan and S. S. Stahl, Nature, 2016, 535, 406.
- 27 E. J. Horn, B. R. Rosen, Y. Chen, J. Tang, K. Chen, M. D. Eastgate and P. S. Baran, *Nature*, 2016, 533, 77.
- 28 X. Gao, P. Wang, L. Zeng, S. Tang and A. Lei, *J. Am. Chem. Soc.*, 2018, **140**, 4195–4199.
- 29 M. D. Kärkäs, Chem. Soc. Rev., 2018, 47, 5786-5865.
- 30 S. Tang, Y. Liu and A. Lei, *Chem*, 2018, 4, 27–45.
- 31 N. Fu, G. S. Sauer, A. Saha, A. Loo and S. Lin, *Science*, 2017, 357, 575–579.

- 32 J. Wang, T. Qin, T.-G. Chen, L. Wimmer, J. T. Edwards, J. Cornella, B. Vokits, S. A. Shaw and P. S. Baran, *Angew. Chem.*, *Int. Ed.*, 2016, **55**, 9676–9679.
- 33 Y. Qiu, W.-J. Kong, J. Struwe, N. Sauermann, T. Rogge, A. Scheremetjew and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, 57, 5828–5832.
- 34 C. Tian, L. Massignan, T. H. Meyer and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, 57, 2383–2387.
- 35 J. B. Sperry and D. L. Wright, *Chem. Soc. Rev.*, 2006, 35, 605-621.
- 36 J.-I. Yoshida, K. Kataoka, R. Horcajada and A. Nagaki, *Chem. Rev.*, 2008, **108**, 2265–2299.
- 37 P. Wang, S. Tang, P. Huang and A. Lei, Angew. Chem., Int. Ed., 2017, 56, 3009–3013.
- 38 P. Huang, P. Wang, S. Tang, Z. Fu and A. Lei, *Angew. Chem.*, *Int. Ed.*, 2018, 57, 8115–8119.
- 39 X. Huang, Y. Chen, S. Zhen, L. Song, M. Gao, P. Zhang, H. Li, B. Yuan and G. Yang, *J. Org. Chem.*, 2018, 83, 7331– 7340.
- 40 Y. Zong, L. Yang, S. Tang, L. Li, W. Wang, B. Yuan and G. Yang, *Catalysts*, 2018, **8**, 48.
- 41 L. Zhang, X. Huang, S. Zhen, J. Zhao, H. Li,
 B. Yuan and G. Yang, *Org. Biomol. Chem.*, 2017, 15, 6306–6309.
- 42 P. Galletti, F. Funiciello, R. Soldati and D. Giacomini, *Adv. Synth. Catal.*, 2015, **357**, 1840–1848.
- 43 J. L. DiMeglio and B. M. Bartlett, *Chem. Mater.*, 2017, 29, 7579–7586.
- 44 A. T. Murray, M. J. H. Dowley, F. Pradaux-Caggiano,
 A. Baldansuren, A. J. Fielding, F. Tuna, C. H. Hendon,
 A. Walsh, G. C. Lloyd-Jones, M. P. John and D. R. Carbery,
 Angew. Chem., Int. Ed., 2015, 54, 8997–9000.