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Efficient electrosynthesis of sulfinic esters via oxidative cross-coupling between alcohols and thiophenols

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Abstract
A new protocol for S—O bond formation was developed by electrochemical oxidative cross-coupling between alcohols and thiophenols. With this strategy, a series of valuable sulfinic ester derivatives were synthesized up to 96% yield from basic starting materials. A preliminary mechanistic investigation reveals that this reaction involves oxygen reduction reaction (ORR).

KEYWORDS
electrosynthesis, mild conditions, sulfinic esters

Sulfinic esters are not only a basic scaffold of numerous pharmaceutically important molecules and synthetically fine chemicals, but also an important precursor in the synthesis of a series of useful biologically active molecules.[1] The traditional routes to sulfinic esters, such as the oxidation of diaryl disulfides in the presence of alcohols and the condensation of sulfinic acids with alcohols, usually suffer from prefunctionalization of the starting materials, harsh conditions, and excessive amount of oxidants or equivalent dehydrating agents.[2] In 2016, Pan reported a copper-catalyzed aerobic cross-coupling of sulfonylhydrazides with alcohols,[3] which was demonstrated as an efficient method to get access to sulfinic esters, but sulfonylhydrazides were employed instead of thiols to react with alcohols. Soon after, Jang and Zhang, respectively, realized the direct cross-coupling of thiols with alcohols by using copper or a cobalt nanocatalyst supported on N—SiO_2-doped activated carbon (Co/N—SiO_2—A), which significantly simplified the process.[4,5] However, the transition-metal catalysts are inevitable in these methods. Concerning environmental, step economy issues and the importance of sulfinic esters, the search for simple, efficient, and straightforward route to sulfinic esters is always highly attractive.

Over the past few decades, electrochemical anodic oxidation has been offering a mild and efficient strategy for the external oxidant-free dehydrogenative cross-coupling reactions, which has attracted considerable interest.[6] Recently, electrochemical oxidative C—H/S—H and S—H/S—H

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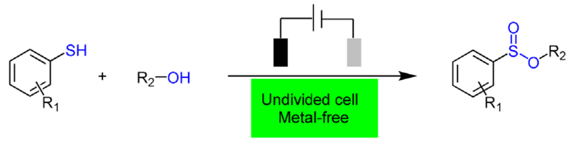
*Fengping Gong and Fangling Lu contributed equally to this study.

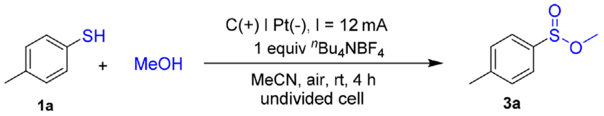


SCHEME 1 Electrosynthesis of sulfinic esters

cross-coupling reactions have been proven as a powerful tool for the synthesis of a series of C—S and unsymmetrical disulfide compounds.[7,8] In this regard, we conceived that green synthesis of sulfinic esters could be achieved via an electrochemical anodic oxidation intermolecular S—O bond formation. Here, we wish to report the first example to the synthesis of sulfinic esters via oxidative cross-coupling between thiophenols and alcohols by using electrosynthesis. At the atmosphere of air with stable thiophenols as the starting material, a series of sulfinic esters were obtained in moderate to high yields. This method provides a new and green pathway for the preparation of sulfinic esters (Scheme 1).

We decided to employ 4-methybenzenethiol **1a** as the test substrate for our study using ^{n}Bu$_4$NBF$_4$ as the electrolyte in a mixture of solvent MeCN/MeOH, which under 12 mA constant current for 4 hr in a simple undivided cell could furnish a product **3a** in 93% yield (Table 1, Entry 1).

TABLE 1 Impact of reaction parameters on the oxidative cross-coupling[a]



Entry	Variation from the standard conditions	Yield (%)[b]
1	None	93
2	DMF instead of CH_3CN	85
3	THF instead of CH_3CN	75
4	$CH_3CN/MeOH$ (10 ml, 9/1, v/v)	91
5	10 equiv. MeOH	72
6	8 mA instead of 12 mA	73
7	15 mA instead of 12 mA	92
8	^{n}BuNClO$_4$ instead of ^{n}BuNBF$_4$	88
9	^{n}BuNPF$_6$ instead of ^{n}BuNBF$_4$	86
10	C (+)-Fe (−) instead of C (+)-Pt (−)	65
11	C (+)-Ni (−) instead of C (+)-Pt (−)	70
12	Under O_2	90
13	Under N_2	n.d.
14	No electric current	n.d.

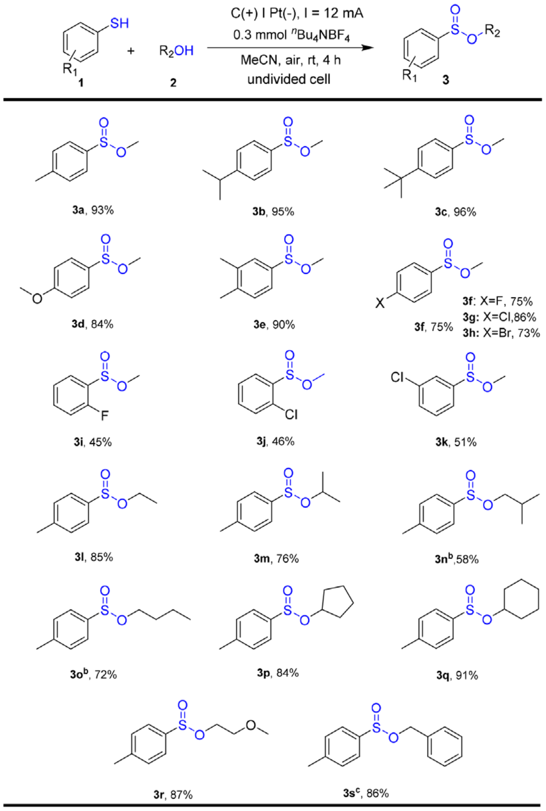
Abbreviation: n.d., not detected.

[a] Reaction conditions: **1a** (0.3 mmol), ^{n}Bu$_4$NBF$_4$ (0.3 mmol) in $CH_3CN/MeOH$ (10 ml, 8/2, v/v), graphite rod as the anode and platinum electrode as the cathode, undivided cell, $I = 12$ mA, rt, 4 hr.

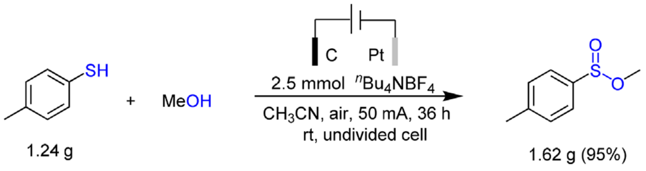
[b] Isolated yield.

Lower reaction reactivity was obtained by using THF or DMF as the cosolvent (Table 1, Entries 2 and 3), the use of cosolvent CH_3CN/CH_3OH with a ratio of 9:1 leads to the decrease in reaction yields. When we use 10 equiv. alcohols, we also get a good yield (Table 1, Entries 4 and 5). Both decreasing and increasing the constant current would lead to lower reaction yields (Table 1, Entries 6 and 7). Changing the electrodes or electrolytes led also to a lower efficiency (Table 1, Entries 8–11). Moreover, when the reaction was carried out in the presence of oxygen atmosphere instead of air, yield was decreased (Table 1, Entry 12). This reaction does not occur when the atmosphere is changed to nitrogen (Table 1, Entry 13). While the reaction was carried out without electricity under air atmosphere, no desired product was obtained in this transformation (Table 1, Entry 14).

With the optimized conditions in hand, various thiophenols were reacted with different alcohols to access to the corresponding products, in all cases, the reactions gave a moderate to high yields (Scheme 2). The scope of the coupling of para-substituted, meta-substituted, or ortho-substituted thiophenols, for example, Me-, Et-, isopropyl-, tert-butyl-, MeO-, Cl-, Br- and F-, was investigated (**3a–3h**).



SCHEME 2 Electrosynthesis of sulfinic esters via oxidative cross-coupling between thiophenols and alcohols. [a]Reaction conditions: **1** (0.3 mmol), ^{n}Bu$_4$NBF$_4$ (0.3 mmol) in CH_3CN/R_2OH (10 ml, 8/2, v/v), $I = 12$ mA, rt, 4 hr; [b] 10 equiv. of this alcohol used in the reaction; [c]Benzyl alcohol used 1 ml in the reaction

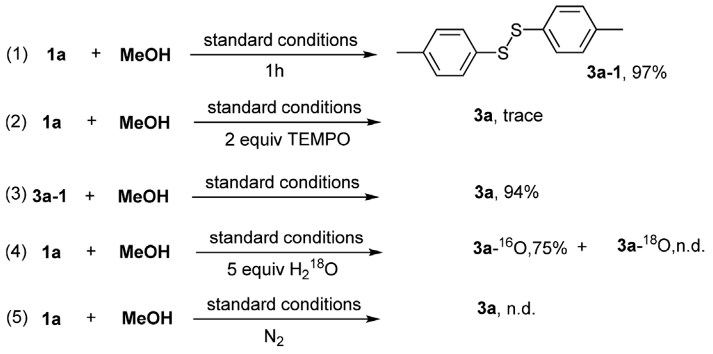


SCHEME 3 Reaction scale-up

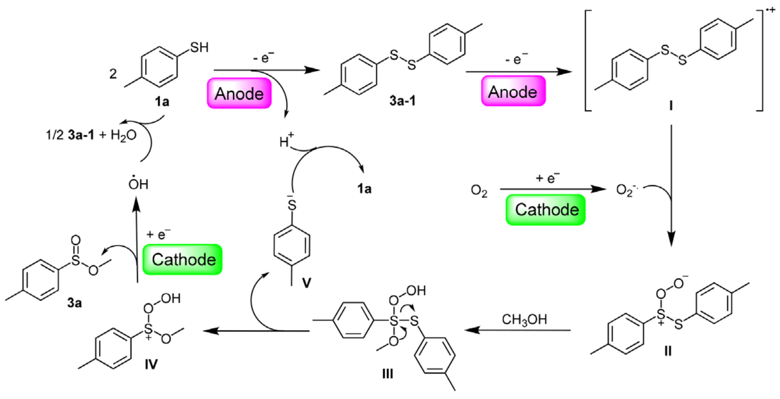
Otherwise, the influence of steric effects has been remarkable, the use of ortho-substituted, meta-substituted thiophenol leads to lower yields (**3i–3k**). To explore the utility of this approach, different alcohols were tested with **1a** as a coupling partners (Scheme 2). As depicted in Scheme 2, different oxidative cross-coupling could be performed obtaining good yields. The change of methanol to ethanol, isopropanol, isobutanol, n-butyl alcohol and cyclopentanol, cyclohexanol, and 2-methoxyethan-1-ol also led to the generation of desired sulfinic esters (**3l–3r**). Additionally, benzyl alcohol demonstrated to be a suitable coupling partner, giving product **3s** in 85% yield. It is noted that for isobutanol and n-butanol (**3n, 3o**), we used 10 equiv. alcohols and obtained 58 and 72% yields, respectively.

The scalability of this electrochemical oxidative cross-coupling was then evaluated by performing 10 mmol scale reaction, which was conducted using the inexpensive graphite rod as the anode in a beaker open to air. Under a constant current of 50 mA, the reaction of **2a** with alcohols afforded the desired products **3a** in excellent yield (Scheme 3). These results indicate a more economic access to the formation of sulfinic esters, and this approach was demonstrated to be applicable in chemical industry.

To investigate the possible radical mechanism of this transformation, a series of radical trap experiments were carried out (Scheme 4, Equation 1). The addition of 2 equiv. of (2,2,6,6-tetramethylpiperidin-1-yl)oxy in the reaction under the standard conditions shows that only trace product **3a** was observed. The reaction was carried out for 1 hr to control the experiment, the formation of the desired product **3a** was detected in trace obtaining disulfide **5a** in high yield 97%, (Scheme 4, Equation 2). To confirm the role of disulfide **3a-1**, and under the standard conditions, the reaction between disulfide **3a-1** and alcohol was conducted to obtain **3a** in excellent yield (94% after 4 hr of reaction; Scheme 4, Equation 3). Moreover, we conducted an $H_2{}^{18}O$-labeling experiment to investigate the source of sulfoxides oxygen. As shown in Scheme 3, the introduction of stoichiometric amount of $H_2{}^{18}O$ furnished the desired product **3a** in 75% yield. None of ^{18}O in the final products was detected (Scheme 4, Equation 4). In addition, when the reaction was conducted in the presence of N_2 atmosphere instead of air, no product was detected. These results clearly showed the source of sulfoxides oxygen comes from O_2 (Scheme 4, Equation 5). And then, we used cyclic voltammetry (CV) to measure the reduction potential of O_2 was −0.50 V (see Supporting Information for details). At the same time, we



SCHEME 4 The control experiments



SCHEME 5 Plausible mechanism

reviewed relevant literature[9] and it was very easy for O_2 to be reduced to $O_2^{-\cdot}$ at the cathode.

Based on the above results and the previous reports,[10] a plausible mechanism for this electorchemical oxidative cross-coupling is proposed in Scheme 5. First, the sulfur radical was formed by the oxidation and deprotonation of **1a.** The sulfur radical undergoes homocoupling to form a disulfide **3a-1** disulfide then undergoes a further one-electron oxidation to form a disulfide radical cation **I**. O_2 is reduced at the cathode to form $O_2^{-\cdot}$, which reacts with the intermediate **I** to produce intermediate **II**. After that, methanol addition to **II** produces intermediate **III**, which then releases sulfide anion **V** and intermediate **IV**. By getting a proton, **V** becames **1a**, while **IV** was reduced at the cathode to form the final product **3a.** At the same time, the hydroxide radical can get a hydrogen atom to become H_2O and **1a** can get the sulfur radical.

1 | CONCLUSIONS

In summary, we have demonstrated an efficient and new method for the synthesis of sulfinic esters via electorchemical intermolecular oxidative cross-coupling between alcohols and thiophenols. A wide variety of functional groups are compatible with this metal-free protocol, which can be carried out on a gram scale easily. A preliminary mechanistic study indicated that the reaction involves cathodic reduction of oxygen to produce superoxide ions

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REFERENCES

[1] a) M. E. Jung, T. I. Lazarova, *Tetrahedron Lett.* **1996**, *37*, 7. b) J. H. Kim, J. O. Lee, S. K. Lee, J. W. Moon, G. Y. You, S. J. Kim, S.-H. Park, J. M. Park, S. Y. Lim, P.-G. Suh, K.-O. Uhm, M. S. Song, H. S. Kim, *J. Biol. Chem.* **2011**, *286*, 7567. c) F. Yuste, A. Hernández Linares, V. M. Mastranzo, B. Ortiz, R. Sánchez-Obregón, A. Fraile, J. L. García Ruano, *J. Org. Chem.* **2011**, *76*, 4635. d) A. Tapia-Pineda, C. Perez-Arrieta, C. Silva-Cuevas, E. Paleo, J. A. Lujan-Montelongo, *J. Chem. Edu.* **2016**, *93*, 1470. e) N.-L. T. Nguyen, H.-T. Vo, F. Duus, T. X. T. Luu, *Molecules* **2017**, *22*, 1458. f) R. R. Tata, C. S. Hampton, M. Harmata, *Adv. Synth. Catal.* **2017**, *359*, 1232. g) X. Yang, Y. Bao, Z. Dai, Q. Zhou, F. Yang, *Green Chem.* **2018**, *20*, 3727.

[2] a) M. Xia, Z.-C. Chen, *Synthetic. Commun.* **1997**, *27*, 1321. b) I. Fernández, N. Khiar, A. Roca, A. Benabra, A. Alcudia, J. Espartero, F. Alcudia, *Tetrahedron Lett.* **1999**, *40*, 2029. c) J. W. Evans, M. B. Fierman, S. J. Miller, J. A. Ellman, *J. Am. Chem. Soc.* **2004**, *126*, 8134. d) A. R. Hajipour, A. R. Falahati, A. E. Ruoho, *Tetrahedron Lett.* **2006**, *47*, 2717. e) H.-J. Li, R. Wang, J. Gao, Y.-Y. Wang, D.-H. Luo, Y.-C. Wu, *Adv. Synth. Catal.* **2015**, *357*, 1393. f) J. Wei, Z. Sun, *Org. Lett.* **2015**, *17*, 5396. g) A. Tranquilino, S. R. C. P. Andrade, A. P. M. da Silva, P. H. Menezes, R. A. Oliveira, *Tetrahedron Lett.* **2017**, *58*, 1265.

[3] B. Du, Z. Li, P. Qian, J. Han, Y. Pan, *Chem. An Asian J.* **2016**, *11*, 478.

[4] P. K. Shyam, Y. K. Kim, C. Lee, H.-Y. Jang, *Adv. Synth. Catal.* **2016**, *358*, 56.

[5] C. Zhou, Z. Tan, H. Jiang, M. Zhang, *Green Chem.* **2018**, *20*, 1992.

[6] a) E. J. Horn, B. R. Rosen, P. S. Baran, *ACS Cent. Sci.* **2016**, *2*, 302. b) M. Schubert, P. Franzmann, A. Wünsche von Leupoldt, K. Koszinowski, K. Heinze, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2016**, *55*, 1156. c) M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230. d) C.-Y. Cai, H.-C. Xu, *Nat. Commun.* **2018**, *9*, 3551. e) Y. Jiang, K. Xu, C. Zeng, *Chem. Rev.* **2018**, *118*, 4485. f) T. H. Meyer, J. C. A. Oliveira, S. C. Sau, N. W. J. Ang, L. Ackermann, *ACS Catal.* **2018**, *8*, 9140. g) K. Mitsudo, Y. Kurimoto, K. Yoshioka, S. Suga, *Chem. Rev.* **2018**, *118*, 5985. h) B. M. Peterson, S. Lin, B. P. Fors, *J. Am. Chem. Soc* **2018**, *140*, 2076. i) G. S. Sauer, S. Lin, *ACS Catal.* **2018**, *8*, 5175. j) S. Tang, L. Zeng, A. Lei, *J. Am. Chem. Soc.* **2018**, *140*, 13128. k) S. R. Waldvogel, S. Lips, M. Selt, B. Riehl, C. J. Kampf, *Chem. Rev.* **2018**, *118*, 6706. l) Q.-L. Yang, X.-Y. Wang, J.-Y. Lu, L.-P. Zhang, P. Fang, T.-S. Mei, *J. Am. Chem. Soc.* **2018**, *140*, 11487. m) K. Liu, S. Tang, T. Wu, S. Wang, M. Zou, H. Cong, A. Lei, *Nat. Commun.* **2019**, *10*, 639. n) J. Wu, Y. Dou, R. Guillot, C. Kouklovsky, G. Vincent, *J. Am. Chem. Soc.* **2019**, *141*, 2832. o) Y. Yuan, J. Qiao, Y. Cao, J. Tang, M. Wang, G. Ke, Y. Lu, X. Liu, A. Lei, *Chem. Commun.* **2019**, *55*, 4230. p) Y. Yuan, A. Yao, Y. Zheng, M. Gao, Z. Zhou, J. Qiao, J. Hu, B. Ye, J. Zhao, H. Wen, A. Lei, *iScience* **2019**, *12*, 293.

[7] a) S. Shahrokhian, A. Hamzehloei, *Electrochem. Commun.* **2003**, *5*, 706. b) X.-Y. Qian, S.-Q. Li, J. Song, H.-C. Xu, *ACS Catal.* **2017**, *7*, 2730. c) P. Wang, S. Tang, A. Lei, *Green Chem.* **2017**, *19*, 2092. d) C. Huang, X.-Y. Qian, H.-C. Xu, *Angew. Chem. Int. Ed.* **2019**, *58*, 6650. e) Y. Yuan, Y. Cao, J. Qiao, Y. Lin, X. Jiang, Y. Weng, S. Tang, A. Lei, *Chin. J. Chem.* **2019**, *37*, 49.

[8] P. Huang, P. Wang, S. Tang, Z. Fu, A. Lei, *Angew. Chem. Int. Ed.* **2018**, *57*, 8115.

[9] a) X. Han, K. Wang, G. Zhang, W. Gao, J. Chen, *Adv. Synth. Catal.* **2019**, *361*, 2804. https://doi.org/10.1002/adsc.201900003. b) M. A. Casadei, *Eur. J. Org. Chem* **2001**, *2001*, 1689. c) C. Kaimakliotis, A. J. Fry, *Tetrahedron Lett.* **2003**, *44*, 5859. d) F. Barba, B. Batanero, I. Barba, *J. Electroanal. Chem.* **2017**, *793*, 66.

[10] a) S. Hemmati, M. M. Mojtahedi, M. S. Abaee, Z. Vafajoo, S. G. Saremi, M. Noroozi, A. Sedrpoushan, M. Ataee, *J Sulfur Chem* **2013**, *34*, 347. b) K. Lam, W. E. Geiger, *J. Org. Chem.* **2013**, *78*, 8020. c) A. K. Singh, H. Yi, G. Zhang, C. Bian, P. Pei, A. Lei, *Synlett* **2017**, *28*, 1558. d) C. Wen, Q. Chen, Y. Huang, X. Wang, X. Yan, J. Zeng, Y. Huo, K. Zhang, *RSC Adv.* **2017**, *7*, 45416. e) Y. Yuan, Y. Chen, S. Tang, Z. Huang, A. Lei, *Sci. Adv.* **2018**, *4*, eaat5312. f) V. Rathore, S. Kumar, *Green Chem.* **2019**,

21, 2670. g) J.-W. Xue, M. Zeng, S. Zhang, Z. Chen, G. Yin, *J. Org. Chem.* **2019**, *84*, 4179. h) X. Zhang, T. Cui, Y. Zhang, W. Gu, P. Liu, P. Sun, *Adv. Synth. Catal.* **2019**, *361*, 2014.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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