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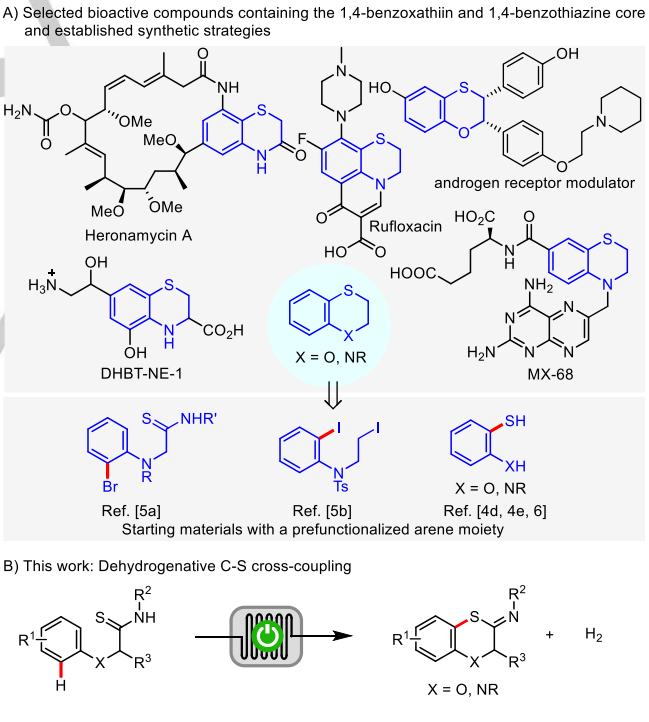
Continuous-Flow Electrosynthesis of Benzofused *S*-Heterocycles by Dehydrogenative C–S Cross-Coupling

Chong Huang,[+] Xiang-Yang Qian[+] and Hai-Chao Xu*

Abstract: Report herein is the synthesis of benzofused six-membered *S*-heterocycles through intramolecular dehydrogenative C–S coupling using a modular flow electrolysis cell. The continuous-flow electrosynthesis not only ensures efficient product formation, but also obviates the need for transition metal catalysts, oxidizing reagent and supporting electrolyte. Reaction scale up are conveniently achieved through extended electrolysis without changing the reaction conditions and equipment.

Dehydrogenative cross-coupling is among the most attractive strategies for the construction of carbon-carbon and carbon-heteroatom bonds because of the reduction in prefunctionalization step(s).[1] Despite extensive research in this field, efficient methods for the dehydrogenative C–S bond formation remain underdeveloped probably because S-based nucleophiles poison transition metal catalysts and are prone to several side reactions under oxidative conditions such as dimerization and overoxidation.[2] As a result, C(aryl)–S bonds are still commonly prepared through redox neutral cross-coupling reactions of aryl halides.[3] As examples, 1,4-benzothiazines and 1,4-benzoxathiins, which are structural motifs in many biologically active compounds (Scheme 1A, top),[4] are constructed using functionalized aryl halides[4c,5] or compounds with preinstalled C–S bond such as 2-aminothiophenol or 2-mercaptophenol derivatives (Scheme 1A, bottom).[4d,4e,6] The synthesis of these heterocycles from less functionalized materials through dehydrogenative C–S cross-coupling has yet to be reported.

Organic electrochemistry, which is a green and enabling synthetic technology, has been attracting increasing interests among the synthetic community.[7] The electricity powered dehydrogenative cross-coupling reactions proceed through H_2 evolution, obviating the need for oxidizing reagents and proton acceptors.[8] In this context, intermolecular dehydrogenative cross coupling of electron-rich arenes with thiophenols have been reported.[9] In addition, we and others have reported electrochemical intramolecular dehydrogenative C–S bond formation reactions for the synthesis of benzothiazoles.[10] These electrosynthetic methods require no transition metal catalysts and oxidizing reagents but do need supporting electrolyte such as tetraalkylammonium salts to increase the conductivity of the organic reaction mixture. Electrochemical synthesis using microflow cells provide several advantages over traditional batch reactors including large ratio of electrode surface to reactor volume, efficient mass transfer, reduction in use of supporting electrolyte and easy scale-up.[11,12] However, applications of this enabling technology in discovery of new reactions remained rare. In collaborative effort with the Wirth group, we have achieved the continuous-flow electrochemical synthesis of benzothiazoles under catalyst- and supporting electrolyte-free conditions.[13] Despite the extensive studies on the dehydrogenative C–S coupling for the synthesis of benzothiazoles, analogous reactions for the synthesis of benzofused six-membered heterocycles remain an unsolved challenge probably because thioamides, especially alkylthioamides, are prone to oxidative desulfurization.[14] Herein we report the synthesis of 1,4-benzoxathiins and 1,4-benzothiazines using a flow electrolysis cell via intramolecular dehydrogenative C–S cross-coupling (Scheme 1B). Key to the success is conducting the electrolysis under acidic conditions using a flow cell.



Scheme 1. Reaction design. Ts = toluenesulfonyl.

Thioamide **1** was chosen as a model substrate to search for optimal reaction conditions. The electrolysis was conducted using a flow electrolytic cell equipped with a Pt cathode and an anode made of carbon filled polyvinylidene fluoride (C/PVDF).[15]

Table 1. Optimization of reaction conditions.[a]

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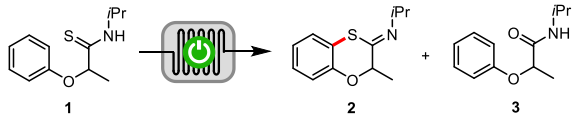
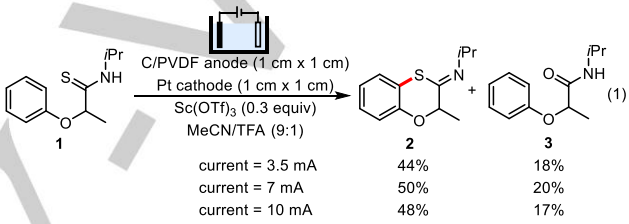
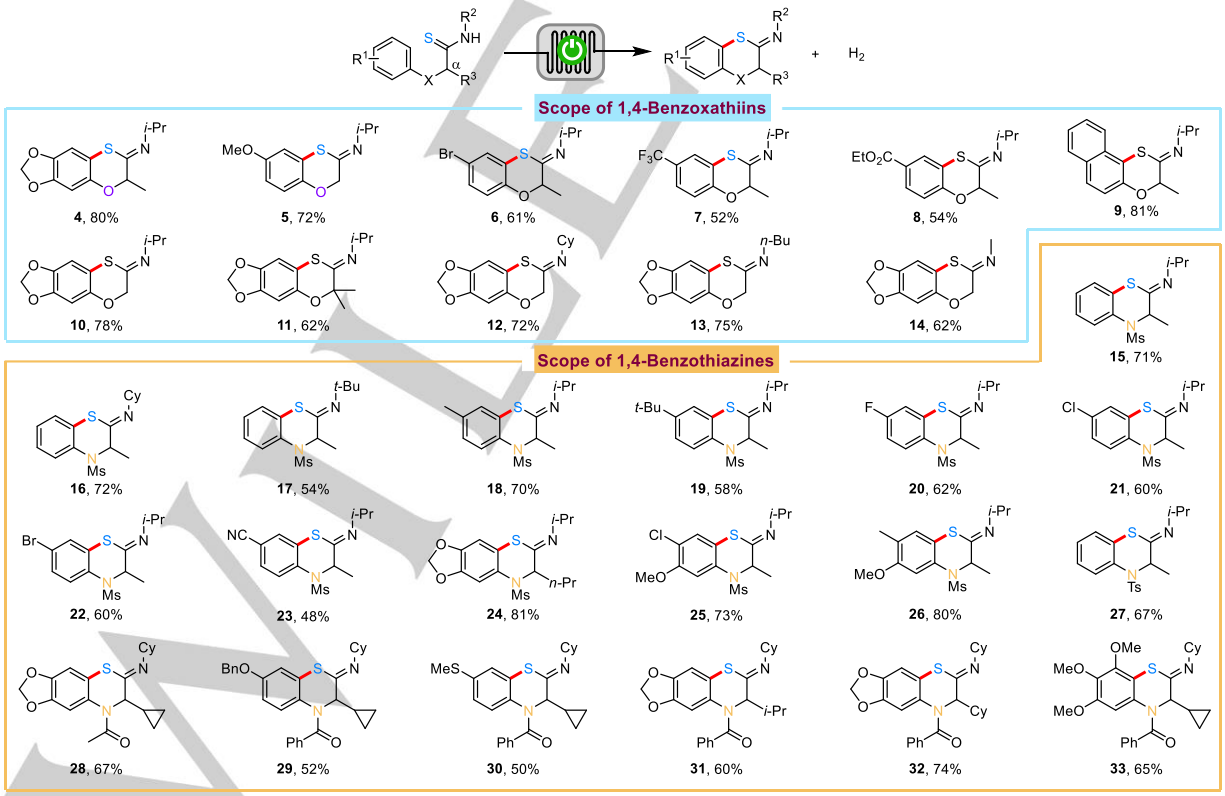


Entry	Deviation from standard conditions	Yield [%][b]	
		2	3
1	None	73[c]	0
2	No TFA	58 (20)	7
3	No $Sc(OTf)_3$	29 (10)	50
4	TfOH instead of $Sc(OTf)_3$	72	0
5	$Sm(OTf)_3$ instead of $Sc(OTf)_3$	70	<5
6	$Zn(OTf)_2$ instead of $Sc(OTf)_3$	43 (3)	33
7	$Y(OTf)_3$ instead of $Sc(OTf)_3$	55 (20)	5
8	graphite anode	71	<5
9	Ni cathode	67[c]	6
10	Stainless steel cathode	64[c]	0
11	Cu cathode	20 (12)	15

[a] Electrolysis conditions: C/PVDF anode, Pt cathode, electrode surface (10 cm^2), I = 35 mA, flow rate = 0.3 mL min^{-1}, RT, **1** (0.03 M, 0.3 mmol), $Sc(OTf)_3$ (0.3 equiv), MeCN/TFA (9:1), 33.3 min (2.4 F mol^{-1}). [b] Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. Recovered **1** is given in brackets. [c] Isolated yield. TFA = trifluoroacetic acid, Tf = trifluoromethanesulfonyl.

Extensive experimentation revealed that the desired 1,4-benzoxathiin **2** could be isolated in 73% yield when the continuous-flow electrolysis was conducted in a mixed solvent of MeCN/TFA (9:1) in the presence of $Sc(OTf)_3$ (0.3 equiv). The reaction consumed 2.4 F mol^{-1} of charge, slightly higher than the theoretical 2 F mol^{-1}. No desulfurized amide **3** was observed under the optimized conditions. TFA (entry 2) and $Sc(OTf)_3$ (entry 3) are important for optimal results as their absence led to reduced conversion and formation of **3**. $Sc(OTf)_3$ might be replaced with TfOH (entry 4) or $Sm(OTf)_3$ (entry 5) to obtained good yield of **2**, but not with $Zn(OTf)_2$ (entry 6) or $Y(OTf)_3$ (entry 7). The use of a graphite anode was also effective for promoting the formation of **2** (entry 8). Other cathode materials such as Ni (entry 9), stainless steel (entry 10) and Cu (entry 11) were inferior to Pt. In addition to the above parameters, appropriate flow rate, current density and interelectrode distance were also important for obtaining the optimal results (Table S1). In contrast to the reaction in flow, electrolysis of **1** in a batch reactor afforded a mixture of the **2** and **3** [Eq. (1)]. The addition of 1 equiv of Et_4NPF_6 resulted in a decrease in the yield of **2** and more desulfurization product **3**.





Scheme 2. Substrate scope. Reaction conditions: flow rate = 0.3 mL min^{-1}, RT, $Sc(OTf)_3$ (0.3 equiv), MeCN/TFA (9:1), substrate (0.3 mmol, 0.03 M). Ms = methanesulfonyl.

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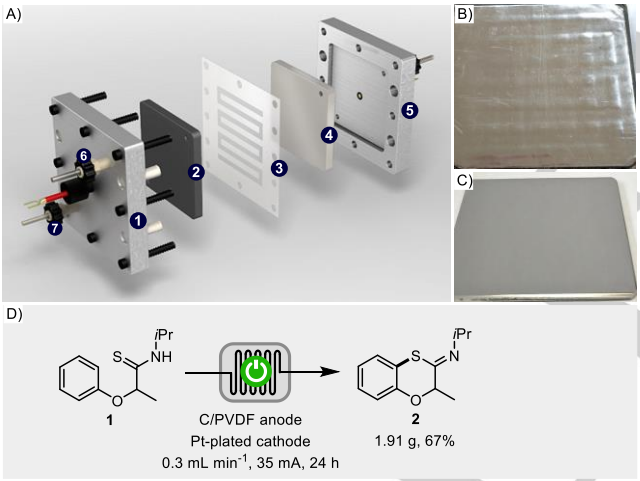
We next investigated the scope of the continuous-flow electrosynthesis of 1,4-benzoxathiins (Scheme 2). The reaction was shown to be compatible with phenyl rings bearing substituents of diverse electronic properties such as OCH_2O (**4**), OMe (**5**), Br (**6**), CF_3 (**7**), and CO_2Et (**8**), leading to the corresponding *S*,*O*-heterocycles in good yields. Replacing the phenyl ring with a 2-naphthyl ring did not affect the efficiency of the cyclization and afforded the naphtho-fused heterocycle **9** in 81% yield as the only regioisomer. On the other hand, the α-position of the thioamide could be unsubstituted (**10**) or disubstituted (**11**). The isopropyl group on the nitrogen atom of thioamide moiety could be replaced with other alkyl groups such as cyclohexyl (Cy, **12**), *n*-Bu (**13**), or Me (**14**).

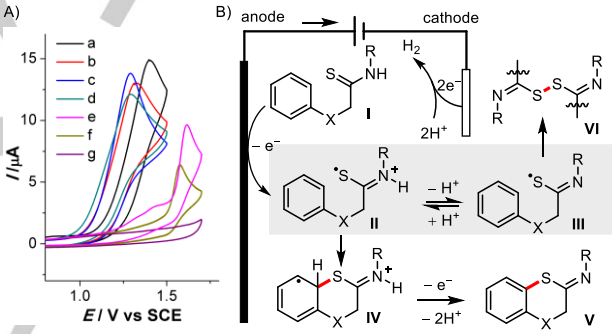
Further investigation revealed that the electrosynthesis could also be employed for the synthesis of 1,4-benzothiazines (Scheme 2). Importantly, the N-phenyl ring, the substituents on both nitrogen atoms, and the α-substituent of the thioamide all tolerated variation. Briefly, the substituent on the thioamide nitrogen atom tolerated *i*-Pr (**15**), Cy (**16**) and *t*-Bu (**17**). Substrates bearing electron rich and electron deficient phenyl rings were all reacted smoothly to afford the desirable *N*,*S*-heterocycles (**18**–**26**). Besides the methanesulfonyl (Ms) group, *p*-tulenesulfonyl (Ts; **27**) and acyl groups (**28**–**33**) were suitable substituents on the nitrogen linker.



Scheme 3. Design of the reactor and reaction scale up. A) Design of electrochemical flow cell. ① and ⑤: Electrode holder. ②: Anode. ③: Fluorinated ethylene propylene (FEP) foil. ④: Cathode. ⑥ and ⑦: Inlet and outlet. B) Pt foil electrode. C) Pt-plated electrode. D) Electrolysis of **1** using a cell equipped with a Pt-plated cathode.

The design of the flow electrolysis cell is shown in Scheme 3A (see Supporting Information for details), which is similar to that reported by Wirth and coworkers.[12a] Pt is an effective electrode material for electrosynthesis because of its high electrochemical stability and low overpotential for proton reduction. The device reported previously employed a Pt foil (0.1 mm thickness) as the cathode.[12a] In addition to its high cost, the Pt foil is prone to deformation during the experiment (Scheme 4B). In response to this problem, we decided to prepare a platinum-plated cathode using a cheap metal base. We found that a Pt-plated electrode could be manufactured using magnetron sputtering to deposit sequentially a thin layer of Ti (6 nm) and Pt (200 nm) on a stainless-steel plate (Scheme 4C). The Ti layer is important for stabilizing the Pt coating. The electrode with Pt deposited directly on a stainless-steel base pitted rapidly during the electrolysis. To test the effectiveness and stability of the Pt-plated electrode, a solution of **1** was pumped through the flow electrolysis cell equipped with the newly manufactured cathode for 24 h (Scheme 4D). The desired product **2** was obtained in 67% (1.91 g). The Pt coating remained largely intact as analyzed by scanning electron microscopy and energy dispersive X-ray spectroscopy (Figure S7).

Cyclic voltammetry experiments revealed that the oxidation potential of compound **1** was reduced in the presence of Lewis acid $Sc(OTf)_3$ or the protic acid TFA (Scheme 4A).[16] On the other hand, the oxidation potential of the cyclized product **2** became significantly more difficult in the presence of TFA and $Sc(OTf)_3$ or TfOH (Figure S8). These results demonstrated that TFA and $Sc(OTf)_3$ were helpful for promoting the oxidation of the thioamide substrate and in the meanwhile avoiding overoxidation of the heterocyclic product.



Scheme 4. A) Cyclic voltammograms of **1** and **2** (0.1 M Et_4NPF_6). a. **1** (3 mM), MeCN, $E_{p/2}$ = 1.26 V; b. **1** (3 mM), $Sc(OTf)_3$ (1 mM), MeCN, $E_{p/2}$ = 1.18 V; c. **1** (3 mM), MeCN/TFA (9:1), $E_{p/2}$ = 1.18 V; d. **1** (3 mM), $Sc(OTf)_3$ (1 mM), MeCN/TFA (9:1), $E_{p/2}$ = 1.15 V; e. **2** (3 mM), MeCN; f. **2** (3 mM), $Sc(OTf)_3$ (1 mM), MeCN; g. **2** (3 mM), $Sc(OTf)_3$ (1 mM), MeCN/TFA (9:1). B) Mechanistic proposal.

The mechanism for the electrosynthesis was proposed (Scheme 4B). One-electron anodic oxidation of thioamide substrate **I** leads to the formation of thioamidyl radical cation **II**,[17] which is in equilibrium with the neutral thioamidyl radical **III**. Radical cyclization followed by oxidative rearomatization afford the final product **V**. The cyclization via the protonated radical **II** is expected to be more efficient than the neutral species **III** because the S-radical in intermediates **II** is more electrophilic than that in **III** and thus more reactive toward the phenyl ring.[18] In the reaction mixture, TFA probably undergoes ligand exchange with $Sc(OTf)_3$ to generate stronger acid TfOH, which increases the concentration of the protonated form **II**. With a slow cyclization, the radical **III** can undergo dimerization and hydrolysis to give desulfurization product such as **3**.

In summary, 1,4-benzoxathiins and 1,4-benzothiazines are prepared efficiently through intramolecular dehydrogenative C–S coupling to construct the six-membered heterocyclic ring.

Oxidative desulfurization, a common side reaction for thioamides, is avoided by running the reactions under acidic conditions in a flow cell.

Acknowledgements

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Keywords: electrochemistry • continuous-flow • radical • heterocycles • C-H functionalization

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[16] The acid additives probably increase the polarity of the solution resulting in better solvation for the radical cation **II** and a lower oxidation potential. Also, the cyclization of **II** is facilitated under the acidic conditions, which might also lead to a decrease of the observed electrode potential.

[17] The oxidation potential ($E_{p/2}$, MeCN) of *N*-isopropyl-2-methylpropanethioamide (*i*-PrNHCS*i*-Pr) is 1.22 V vs SCE, which is close to that of **1** and suggests that the oxidation of **1** occurs at the thioamide moiety. For thioamides bearing an electron-rich phenyl ring, the reaction may start with the oxidation of the phenyl ring to an arene radical cation, which can react with the thioamide moiety to form the C-S bond.

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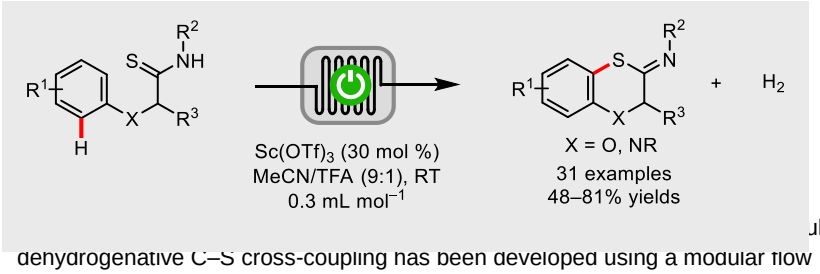

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ular dehydrogenative C–S cross-coupling has been developed using a modular flow electrolysis cell. The continuous-flow electrosynthesis not only ensures efficient product formation, but also obviates the need for transition metal catalysts, oxidizing reagent and supporting electrolyte.