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# Synthesis of 1,3-benzothiazines by intramolecular dehydrogenative C–S cross-coupling in a flow electrolysis cell

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Dehydrogenative cyclization of thioamides is an attractive approach for the synthesis of *S*-heterocycles. Reported herein is an electrochemical dehydrogenative cyclization reaction of *N*-benzyl thioamides in a flow electrolysis cell. The continuous-flow electrosynthesis has addressed the limitations associated with previously reported methods for the cyclization of alkylthioamides and provide a transition metal- and oxidizing reagent-free access to various functionalized 1,3-benzothiazines in good yields.

**C-H functionalization, electrochemistry, flow chemistry, heterocycles,**

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Dehydrogenative C–S cross-coupling is an attractive approach for the construction of S-containing organic molecules because of its step and atom economic features [1–6]. Ideally, these reactions should proceed through $H_2$ evolution and avoid the use of stoichiometric chemical oxidants [7]. Organic electrochemistry has been demonstrated to be an enabling tool to achieve dehydrogenative cross-coupling through $H_2$ evolution [8–17]. In this context, inter- and intramolecular dehydrogenative C–S cross-coupling has been reported using batch reactors [18–24]. We have been interested in the synthesis of heterocycles through electrochemical dehydrogenative cyclization and annulation reactions [25–31] and recently shown that dehydrogenative cyclization of thioamides proceeds more efficiently in a microflow electrochemical reactor than that in a batch reactor (Scheme 1(a)) [32]. We wonder if the continuous-flow electrosynthesis can be applied to the preparation of 1,3-benzothiazines through dehydrogenative cyclization of *N*-benzyl thioamides. Such cyclization reactions have been previously achieved chemically by employing hypervalent iodine as the chemical oxidant (Scheme 1(b)) [33] and electrochemically using a batch reactor (Scheme 1(c)) [34]. Under these established conditions, alkylthioamides remain to be difficult substrates probably because of competitive desulfurization, a common side reaction for the oxidation of thioamides. Herein, we report a continuous-flow electrosynthesis of 1,3-benzothiazines that is applicable to aryl- and alkyl-thioamides (Scheme 1(d)).

The dehydrogenative cyclization of thioamide **1** was chosen as a model reaction to search for optimal reaction conditions (Table 1). The electrolysis was conducted at r.t. using a flow cell equipped with a Pt cathode and a carbon filled with polyvinylidene fluoride (C/PVDF) anode [32]. After a screening of reaction parameters such as flow rate, solvent, additives and current, the optimal conditions were found to be passing a solution of **1** (0.03 M) and trifluoromethanesulfonic acid (TfOH, 0.06 M) in MeCN through the cell with a flow rate of 0.3 mL $min^{-1}$ and a constant current of 42 mA. No supporting salt was needed because the addition of TfOH increased the conductivity of

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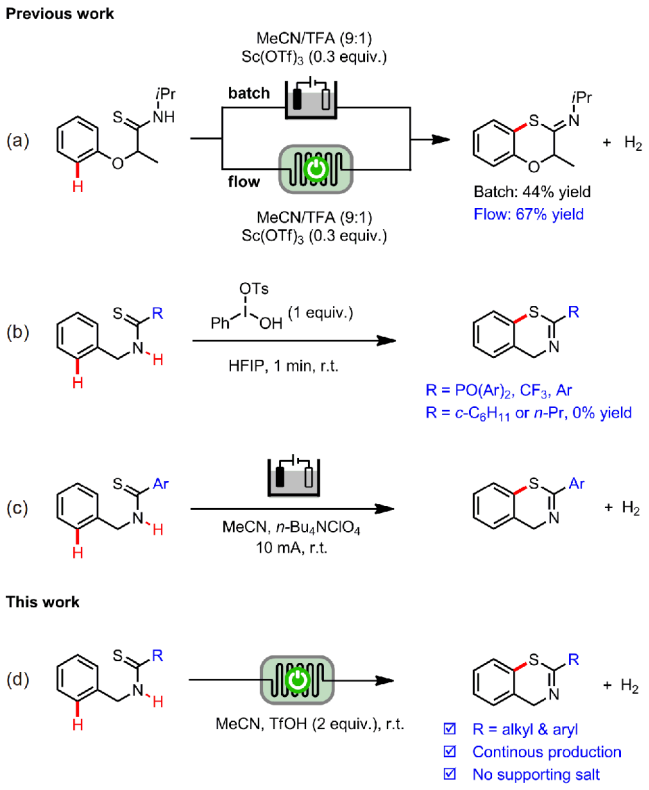
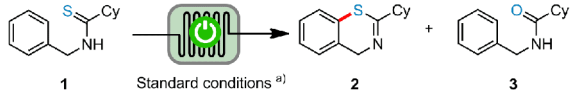



**Scheme 1** Dehydrogenative cyclization of thioamides (color online).

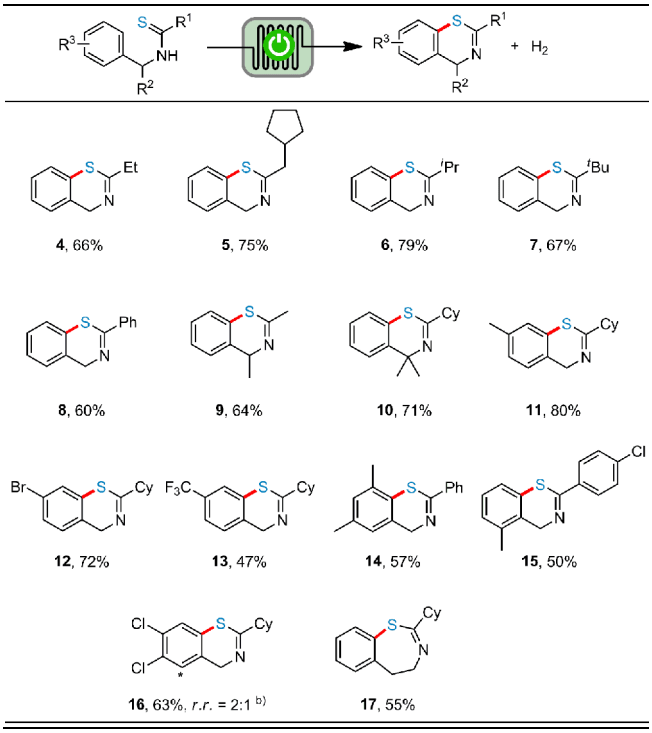
**Table 1** Optimization of reaction conditions [a]




| Entry | Deviation from standard conditions | Yield (%) [b] | |
|---|---|---|---|
| | | **2** | **3** |
| 1 | None | 83 [c] | Trace |
| 2 | No TfOH | 50(3) | 40 |
| 3 | 1.0 equiv. TfOH | 71 | 4 |
| 4 | TFA instead of TfOH | 26(10) | 55 |
| 5 | AcOH instead of TfOH | 25(31) | 23 |
| 6 | Ni cathode | 77 | 12 |
| 7 | Stainless steel cathode | 65 | 25 |
| 8 | Graphite anode | 74 | 14 |

a) Electrolysis conditions: C/PVDF anode, Pt cathode, electrode area= 10 $cm^2$, $I$=42 mA, flow rate=0.3 mL $min^{-1}$, r.t., **1** (0.03 M, 0.3 mmol), TfOH (2.0 equiv.), MeCN, 2.9 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. Cy, cyclohexyl.

**Table 2** Substrate scope [a]

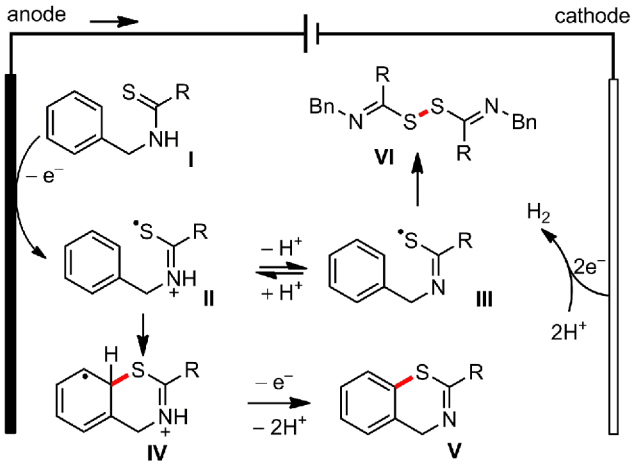



a) Reaction condition: flow rate=0.3 mL $min^{-1}$, r.t., TfOH (2.0 equiv.), MeCN, thioamide (0.3 mmol, 0.03 M); b) *r.r.*=regioisomeric ratio.

the reaction solution. Under these conditions, the reaction of **1** afforded the desired product **2** in 83% yield and only trace amount of desulfurized compound **3** (entry 1, Table 1). The presence of TfOH also prevented desulfurization. In the absence of TfOH, the yield of **2** was reduced to 50% with concomitant formation of amide **3** in 40% (entry 2). The reduction of TfOH to 1 equiv. (entry 3) or the use of other acidic additives such as trifluoroacetic acid (TFA) (entry 4) or AcOH (entry 5) all led to a decrease in the yield of **2**. Other cathode materials such as Ni (entry 6) and stainless steel (entry 7) and anode materials such as graphite (entry 8) were less efficient in promoting the formation of **2**.

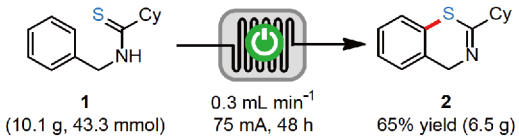
The scope of the dehydrogenative cyclization reaction was investigated by varying the substituents of the *N*-benzyl thioamide substrate (Table 2). The $R^1$ substituent tolerated primary (**4** and **5**), secondary (**6**) and tertiary (**7**) alkyl groups as well as a phenyl (**8**) group. Thioamides bearing at the benzylic position one (**9**) or two (**10**) methyl groups were also suitable substrates. The *N*-benzyl group tolerated substituents at various positions such as Me (**11**), Br (**12**) and $CF_3$ (**13**) at the para position, Me at the meta or ortho positions (**14**, **15**). Meta-, para-dichloro-substituted thioamide cyclized to give a mixture of regioisomers (**16**). The electrochemical dehydrogenative cyclization reaction was also applicable to seven-membered ring formation (**17**).

In continuous-flow electrosynthesis, reaction scale up can be achieved by passing more material through the very same reactor [35–38]. To increase the productivity, the substrate concentration and electric current was increased to 0.05 M and 75 mA, respectively. Under these conditions, the passing




**Scheme 2** A proposed mechanism (color online).

of 10.1 g of **1** through the flow electrolysis cell afforded 6.5 g of **2** (65% yield) in 48 h (Reaction (1)).




(1)

A possible mechanism was proposed based on the results of this work and our previous report (Scheme 2) [32]. The thioamide **I** is oxidized through single electron transfer (SET) at the anode to afford radical cation **II**, which undergoes cyclization and oxidative aromatization to afford the final heterocycle **V**. The intermediate **II** can lose a proton to give **III**, which is less reactive than **II** to undergo cyclization. The radical **III** can dimerize to give **VI** [39], which then undergo hydrolysis to furnish desulfurized material such as **3**. The added TfOH ensures a more favorable equilibrium to the side of **II** to reduce desulfurization.

In summary, we have developed a continuous-flow electrosynthesis of 1,3-benzothiazines through dehydrogenative cyclization of easily available thioamides. A variety of alkyl and arylthioamides undergo efficient intramolecular dehydrogenative C–S cross-coupling without the need for chemical oxidants and transition metal catalysts, providing clean access to *S*-heterocycles. The electrochemical protocol can be expanded to 7-membered ring formation.

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**Conflict of interest** The authors declare that they have no conflict of interest.

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