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Electrochemical Intramolecular Dehydrogenative C-S Bond Formation for the Synthesis of Benzothiazoles

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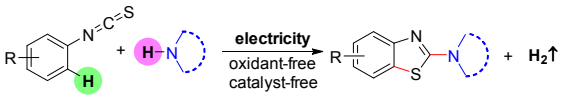
An external oxidant-free intramolecular dehydrogenative C-S cross-coupling has been developed under undivided electrolytic conditions. Various 2-aminobenzothiazoles could be synthesized with up to 99% yield from the direct combination of aryl isothiocyanates with amines. In the presence of base, this reaction protocol is also applicable for the synthesis of benzothiazoles from *N*-aryl thioamides.

Oxidative R^1–H/R^2–H cross-coupling has been recognized as one of the most atom economical and efficient ways to construct new chemical bonds.[1] Great progresses have been made in the construction of C-C,[2] C-N[3] and C-O[4] bonds. In comparison, selective oxidative C-S cross-coupling has received much less developments because of the facile over-oxidation of sulfur compounds under oxidative conditions.[5] For example, intramolecular dehydrogenative C-S cross-coupling of *N*-aryl thioureas or *N*-aryl thioamides has been developed as one of the most efficient and widely used approaches to access benzothiazoles.[6] However, these transformations require the use of external chemical oxidants to facilitate the dehydrogenation process, which generally face the problem of over-oxidation to afford ureas or amides. Thus, the developed methods usually suffer from limited substrate scope and low reaction efficiency. To deal with these problems, it is highly desirable to develop external oxidant-free dehydrogenative C-S bond formation protocols.[7]

Electrosynthesis is recognized as a versatile and environmentally friendly synthetic tool and has attracted continuous interests.[8] Electrochemical anodic oxidation represents an ideal choice for replacing external chemical oxidants in oxidative R^1–H/R^2–H cross-coupling reactions.[9] Since the operating voltage and current can be controlled in electrochemical reactions, it is possible to avoid the over-oxidation of sulfur compounds.[10] Herein, we would like to communicate our recent progress on an electrochemical dehydrogenative C-S cross-coupling under metal- and oxidant-free conditions (Scheme 1). This reaction protocol provides an atom-economical and sustainable way for the synthesis of benzothiazoles with up to 99% yield.



Scheme 1. Oxidant-free dehydrogenative C-S bond formation.

2-Aminobenzothiazoles and benzothiazoles are key structure motifs in many agrochemicals and pharmaceuticals.[11] The dehydrogenative C-S bond formation of *N*-phenyl thiourea **4a** generated in situ upon mixing phenyl isothiocyanate (**1a**) and morpholine (**2a**) was chosen as the model reaction for testing the reaction conditions in the synthesis of 2-aminobenzothiazoles. Cyclic voltammetry (CV) experiments of the substrates in acetonitrile were conducted. No obvious oxidation peak could be observed below 2.0 V for **1a** (see ESI, Fig. S1a) while an oxidation peak of **2a** could be observed at 1.24V (see ESI, Fig. S1b). Utilizing ^{n}Bu$_4$NBF$_4$ as the electrolyte and acetonitrile as the solvent, 2-aminobenzothiazole **3aa** could be obtained from the mixing of **1a** and **2a** in 22% yield under 7 mA constant current for 4 h in an undivided cell (Table 1, entry 1). The choice of co-solvent was important for achieving a high reaction efficiency. Alcohols such as methanol, isopropanol and hexafluoroisopropanol (HFIP) could not promote this transformation (Table 1, entries 2-4). However, an increased reaction yield could be obtained when water was used as the co-solvent (Table 1, entry 5). Attempt on decreasing and increasing the current density both led to decreased reaction yields (Table 1, entries 6 and 7). Delightfully, heating the reaction mixture could improve the reaction efficiency (Table 1, entries 8 and 9). An excellent yield of **3aa** could be obtained at 70 °C (Table 1, entry 9). As was expected, large amount of H_2 could be detected by GC under the optimized conditions. No desired product could be obtained without electricity either under nitrogen or

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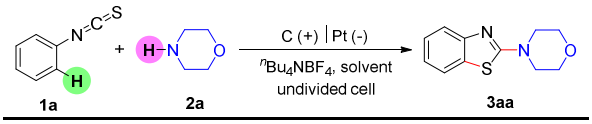
atmospheric conditions (Table 1, entries 10 and 11). The reactions didn't required deoxygenation. However, a slightly decreased reaction yield was obtained when the reaction was directly carried out under air atmosphere (Table 1, entry 12). It is possible to replace platinum plate cathode by cheaper electrodes (Table 1, entries 13-15).**Table 1.** Condition optimization[a]



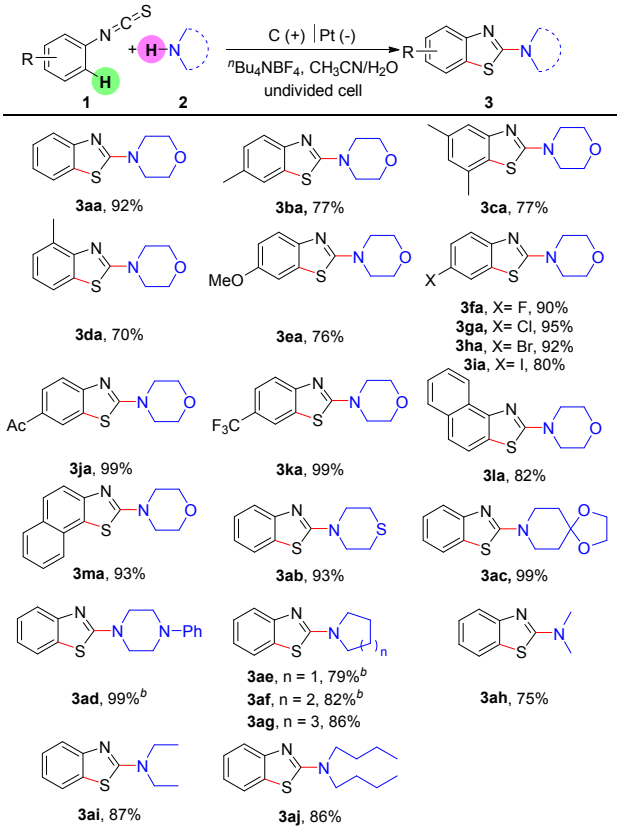
1a 2a 3aa

Entry	Solvents	Current density	Temperature	Yield[b]
1	CH_3CN	11.7 mA/cm^2	r.t.	22%
2	CH_3CN/MeOH[c]	11.7 mA/cm^2	r.t	22%
3	CH_3CN/^{i}PrOH[c]	11.7 mA/cm^2	r.t	15%
4	CH_3CN/HFIP[c]	11.7 mA/cm^2	r.t	10%
5[d]	CH_3CN/H_2O[c]	11.7 mA/cm^2	r.t	48%
6[e]	CH_3CN/H_2O[c]	8.3 mA/cm^2	r.t	18%
7	CH_3CN/H_2O[c]	15.0 mA/cm^2	r.t	13%
8	CH_3CN/H_2O[c]	11.7 mA/cm^2	50 °C	58%
9	CH_3CN/H_2O[c]	11.7 mA/cm^2	70 °C	95%
10	CH_3CN/H_2O[c]	0	70 °C	n.d.
11[f]	CH_3CN/H_2O[c]	0	70 °C	n.d.
12[f]	CH_3CN/H_2O[c]	11.7 mA/cm^2	70 °C	75%
13[g]	CH_3CN/H_2O[c]	11.7 mA/cm^2	70 °C	89%
14[h]	CH_3CN/H_2O[c]	11.7 mA/cm^2	70 °C	82%
15[i]	CH_3CN/H_2O[c]	11.7 mA/cm^2	70 °C	86%

[a] Standard conditions: graphite rod anode (ϕ 6 mm), platinum plate cathode (15 mm×15 mm×0.3 mm), constant current = 7 mA, **1a** (0.50 mmol), **2a** (1.0 mmol), ^{n}Bu$_4$NBF$_4$ (3.0 mmol), solvents (10.0 mL), undivided cell, N_2, 4 h (2.1 F). [b] Yields were determined by GC analysis with biphenyl as the internal standard, n.d. = not detected. [c] Co-solvent (1.0 mL) was used. [d] Constant current = 5 mA, 5.6 h (2.1 F). [e] Constant current = 9 mA, 3.1 h (2.1 F). [f] Under air atmosphere. [g] Graphite rod anode was used. [h] Graphite rod cathode was used. [i] Nickel plate cathode was used. [j] Stainless steel plate cathode was used.

Since the optimized condition has been obtained, efforts were then paid to the substrate scope of this transformation (Table 2). Firstly, different aryl isothiocyanates were applied as substrates to react with morpholine for the synthesis of 2-aminobenzothiazoles. Simple phenyl isothiocyanate could furnish the desired benzothiazole in an excellent yield (**3aa**). Phenyl isothiocyanates bearing electron donating substituents such as methyl group and methoxyl group gave slightly decreased reaction yields (**3ba-3ea**). Halide substituents including F, Cl, Br and I were well tolerated under electrochemical conditions, furnishing corresponding benzothiazoles in good to high yields (**3fa-3ia**). Strong electron-deficient phenyl isothiocyanates showed excellent reactivity in this transformation (**3ja** and **3ka**). Moreover, both 1-isothiocyanatonaphthalene and 2-isothiocyanatonaphthalene were able to furnish the desired products in good yields (**3la** and **3ma**). Then different secondary amines were applied as substrates in synthesizing benzothiazoles. Six-membered cyclic amines including thiomorpholine, 1,4-dioxa-8-azaspiro[4.5]decane and 1-phenylpiperazine were all showed excellent reactivity in the synthesis of 2-aminobenzothiazoles (**3ab-3ac**). Saturated cyclic amines without other heteroatom afforded the desired product in slightly decreased yields (**3ae-3ag**). Acyclic secondary amines were also suitable in this transformation, furnishing corresponding 2-aminobenzothiazoles in good to high yields (**3ah-3aj**). At this moment, primary amines could undergo addition to aryl isothiocyanates while no cyclization product could be obtained under the standard conditions.

Table 2. Synthesis of benzothiazoles from different aryl isothiocyanates and amines[a]



[a] Reaction conditions: graphite rod anode (ϕ 6 mm), platinum plate cathode (15 mm×15 mm×0.3 mm), constant current = 7 mA (j_{anode} ≈ 11.7 mA/cm^2), **1** (0.50 mmol), **2a** (1.0 mmol), ^{n}Bu$_4$NBF$_4$ (3.0 mmol), MeCN (9.0 mL), H_2O (1.0 mL), 70 °C, N_2, 4 h (2.1 F). Isolated yields were shown. [b] PhCOONa (1.0 mmol) was added.

The scalability of this electrochemical dehydrogenative C-S cross-coupling was then evaluated by performing a 5 mmol scale reaction. With almost the same ratio of F/mol of electricity, the reaction of **1a** and **2a** smoothly furnished the desired product in 82% yield (Scheme 2, **3aa**, 0.9 g). This result highlights the potential of this electrochemical hydrogen-evolution reaction in future applications.

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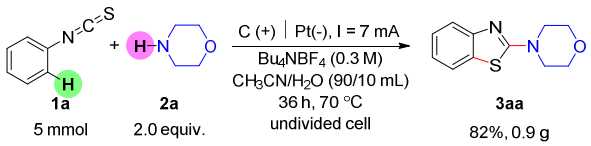
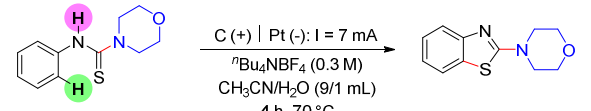


Scheme 2. Gram scale synthesis.

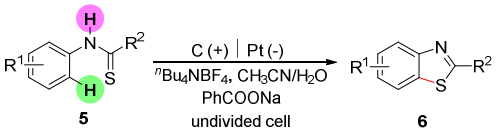
Since thiourea was observed to be generated during the reaction, the intramolecular dehydrogenative C-S cross-coupling of thiourea **4aa** was directly tested under electrolysis conditions (Scheme 3). A very low reaction yield could be obtained under the standard conditions. By adding sodium benzoate as a base into the reaction system, a high reaction yield of benzothiozole **3aa** could be obtained. To clarify the requirement of base, CV experiments of **4aa** were carried out. In the absence of base, an obvious oxidation peak of **4aa** was observed at 0.98 V (see ESI, Fig. S1c, $\mathbf{E_{pa}}$). When 1 equiv of sodium hydroxide was added, a new oxidation peak could be observed at 0.43V (see ESI, Fig. S1d, $\mathbf{E_{pb}}$). The reaction results in Scheme 3 and cyclic voltammogram in Figure S1 suggested that single electron transfer with sulfur anion intermediate generated *in situ* from the acid–base equilibrium would be much more favorable than the direct single electron transfer with *N*-phenylbenzothioamide **4aa**.

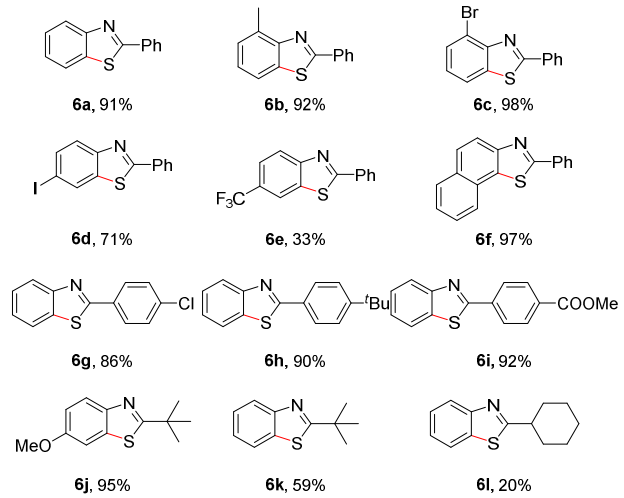


Additive	Yield
none	18%
2 equiv PhCOONa	82%

Scheme 3. Direct intramolecular dehydrogenative C-S cross-coupling of thiourea.

Table 3. Synthesis of benzothiazoles from different *N*-aryl thioamides[a]





[a] Reaction conditions: graphite rod anode (ϕ 6 mm), platinum plate cathode (15 mm×15 mm×0.3 mm), constant current = 7 mA (j_{anode} ≈ 11.7 mA/cm^2), **1** (0.50 mmol), **2a** (1.0 mmol), ^{n}Bu$_4$NBF$_4$ (3.0 mmol), MeCN (9.0 mL), H_2O (1.0 mL), 70 °C, N_2, 4 h (2.1 F). Isolated yields were shown. [b] PhCOONa (1.0 mmol) was added.

In the next step, the intramolecular dehydrogenative C-S cross-coupling of *N*-aryl thioamides was explored to further demonstrate the utility of this electrochemical method (Table 3). In the presence of 2 equiv of sodium benzoate, *N*-phenyl benzothioamide (**5a**) could furnish 2-phenyl benzothiazole (**6a**) in 91% yield. *N*-Phenyl benzothioamides bearing methyl group or bromide on the *ortho* position of the *N*-aryl moiety could both furnish the desired benzothiazoles in excellent yields (**6b** and **6c**). Notably, iodide could be well tolerated under the undivided electrolysis conditions (**6d**). Strong electron-donating substituents such as methoxyl group (**6j**) was beneficial for achieving a good reaction yield while strong electron-withdrawing groups such as trifluoromethyl group led to decreased reaction yields (**6e**). The reaction with *N*-naphthalene substituted benzothioamide could give an excellent yield in this transformation (**6f**). Moreover, chloride, methoxyl group and ester group at the 2-aryl moiety of *N*-phenyl benzothioamide were all tolerated under the electrolysis conditions (**6g-6i**). *N*-phenyl alkylthioamides were also tested under standard conditions (**6j-6l**). It is worthy of noting that α-hydrogen atoms had evident effects on the reaction efficiency. *N*-Phenyl *tert*-butylthioamide could afford corresponding benzothiazole in a moderate yield (**6k**) while only a low yield in the case of *N*-phenyl cyclohexylthioamide (**6l**).

Based on the experimental results and literature reports,[6c, 7] a plausible mechanism of the reaction between **1a** and **2a** is proposed in Scheme 4. In situ nucleophilic addition of amine **2a** to isothiocyanates **1a** generates thiourea **4a.** Following deprotonation by hydroxide generated from cathodic reduction of water can give a sulfur ion intermediate **I**. Single-electron-transfer (SET) oxidation of **I** by anode leads to the formation of a sulfur radical **II**. Alternatively, the sulfur radical **II** is also possible to be generated from the direct anodic oxidation of **4a**. The sulfur radical will then undergo quick intramolecular radical addition to generate **III**. Following anodic oxidation and deprotonation of **III** by base (excess amount of **1a** or PhCOONa) can furnish the final product **3aa**. At the same time, concomitant cathodic reduction of water can release hydrogen gas during the reaction.

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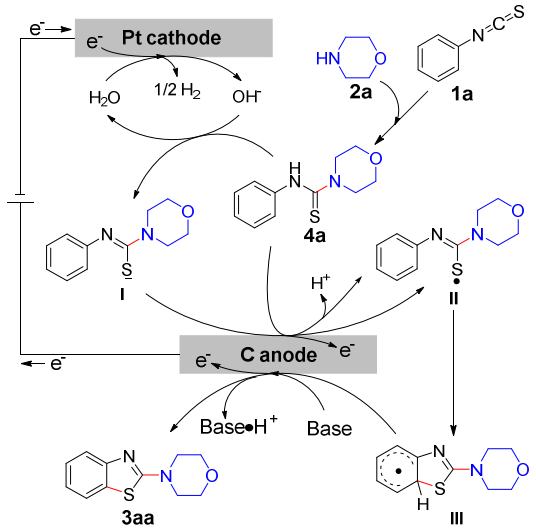

Scheme 4. Proposed mechanism.

Conclusions

In conclusion, an environmentally friendly electrochemical reaction protocol was developed to achieve intramolecular dehydrogenative C-S bond formation. Neither metal catalysts nor chemical oxidants were needed in this transformation. Under undivided electrolysis conditions, a series of 2-aminobenzothiazoles could be synthesized from the direct combination of aryl isothiocyanates with aliphatic amines. Importantly, this reaction could be conducted in gram scale, which is important for future application. By adding base into the reaction system, intramolecular dehydrogenative C-S bond formation of *N*-aryl thioamides could also be achieved to furnish benzothiazoles in good to high yields. This study provides a good example of electrochemical hydrogen-evolution cross-coupling, which will inspire people to replace external chemical oxidants by electrochemical anodic oxidation in more dehydrogenative cross-coupling reactions.

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