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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201901290

Link to VoR: http://dx.doi.org/10.1002/adsc.201901290

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DOI: 10.1002/adsc.201901290

Electrochemical Synthesis of 1,2,4-Thiadiazoles through Intermolecular Dehydrogenative S-N Coupling

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Received: ((will be filled in by the editorial staff))

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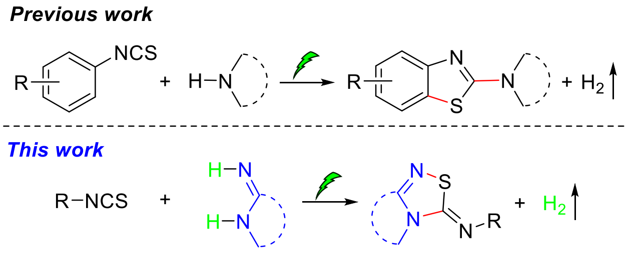
Abstract: An electrochemical intermolecular dehydrogenative coupling reaction of isothiocyanates with 2-aminopyridines/amidines was developed. Using *n*-Bu4NI as the catalyst and electrolyte, 1,2,4-thiadiazoles and pyrido-fused 1,2,4-thiadiazoles were readily accessed with good to excellent efficiency under the undivided electrolysis conditions. This electrochemical approach obviates the use of external oxidants and transition-metal catalysts.

Keywords: Electrosynthesis; Dehydrogenative coupling; S-N formation; 1,2,4-Thiadiazoles; Isothiocyanates

The cross dehydrogenative coupling (CDC) constitutes a fundamental strategy for chemical bond construction in organic synthesis.[1] Among these CDC processes, C-based coupling reactions have received the most extensive interest.[1a-g, 2] In contrast, coupling transformations between heteroatoms (e.g. P, S, N) have been addressed comparatively less.[1h, 3] The S-N moiety exists in a series of bioactive compounds, such as sulfonamides, thiadiazoles. The recent decade has witnessed great progress made on oxidative S-N bond formation.[3d, 4] However, the use of stoichiometric oxidants or transition metals is usually required. The main obstacle of dehydrogenative S-N coupling lies in the liability to over-oxidation of sulfur-containing components in the presence of external oxidants as hydrogen acceptors. Thus, it is much desirable to seek mild oxidative conditions to efficiently deliver S-N bond without concurrent over-oxidation side products.

Electrochemical synthesis has proven to be an emerging powerful and environmentally friendly tool in academic and industrial fields,[5] not only for the functional group transformations,[6] cross coupling reactions,[5b, 7] but also for the heterocycles construction.[8] The ease and simplicity to finely tune the reaction voltage and current renders it possible for sulfur compounds to be exclusively converted to desired oxidative products through mild oxidation.[9] Lei group has ever reported the electrochemical cross dehydrogenative coupling of aryl isothiocyanates with secondary aliphatic amines for synthesis of benzothiazoles via C-S bond formation (Scheme 1).[10] In continuation of our interests in heterocycles construction,[11] herein, we present an electrochemical dehydrogenative [3+2] annulation of isothiocyanates with 2-aminopyridines or amidines, without the involvement of external metal reagents and chemical oxidants, to furnish 1,2,4-thiadiazoles and heterocyclic fused analogues via the creation of S-N bond (Scheme 1).

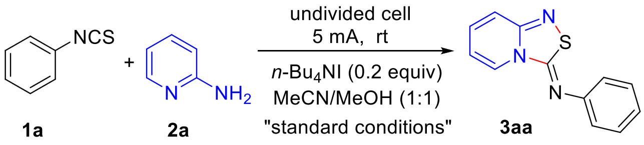
1,2,4-Thiadiazole scaffolds exist as prominent structural units in a considerable number of bioactive molecules including pharmaceuticals,[12] the assembly of which has attracted much attention.[9b, 13] Our efforts have been devoted to establishing the synthetic methodologies for heterocycle construction and modification. Thus we chose the annulation of phenyl isothiocyanate (**1a**) with 2-aminopyridine (**2a**) as the model reaction to seek optimum reaction conditions of electrochemical dehydrogenative S-N coupling for



Scheme 1 Electrochemical oxidative N-S/C bond formation from isothiocyanates.

access to 1,2,4-thiadiazole and its fused heterocycles. Electrolysis was performed in a three-necked flask charged with Pt plates as anode and cathode whilst stirring. Initially, the reaction was conducted in a mixture of MeCN and MeOH (1:1) at a constant current (5 mA) at room temperature using 0.25 equivalent of *n*-Bu_4NI. Delightedly, the desired product **3aa** was isolated in 86% yield (Table 1, entry 2). Other supporting electrolytes such as NH_4I, KI, NaI, *n*-Bu_4NBr and *n*-Bu_4NBF_4 were tested, and it was found that the iodide salts could trigger the electrochemical annulation in moderate to good yields, while the bromide or tetrafluoroborate salts are ineffective (Table 1, entries 3 vs 4). Notably, decreasing the loading amount of *n*-Bu_4NI to 0.2 equivalent gave the same yield (Table 1, entry 1), but the further shrinkage dramatically lowered the reaction yields (Table S1, entries 9-11). Thus, *n*-Bu_4NI (0.2 equivalent) as both supporting electrolyte and mediator was the best choice for this electrolysis. The current ranging from 2 to 6 mA delivered yields of 70-84% (Table 1, entry 5), but increasing the current to 10 mA or no electricity gave trace or no product (Table S1, entries 16, 18). The use of other solvent systems, such as MeCN, MeOH or their mixture with water (1:1) seriously diminished the reaction efficacy, and slightly adjusting the ratio of MeCN and MeOH exerted a limited impact (Table 1, entries 6-8). Furthermore, the electrodes were examined. Interestingly, graphite felt or Reticulated Vitreous Carbon (RVC) as anode afforded comparable yields, whereas the use of graphite rod as anode or Zn and Sn plates as cathode deteriorated the coupling efficiency (Table 1, entries 9-12). Slightly increasing the dose of substrate **1a** could help improve the product yield (Table 1, entries 1 & 13). Therefore, the optimized electrolysis conditions were established as follows: 0.2 equivalent of *n*-Bu_4NI in MeCN:MeOH (1:1) in a constant current (5 mA) under air at room temperature for 6 h.

Table 1 Optimization of the electrolysis conditions [a]

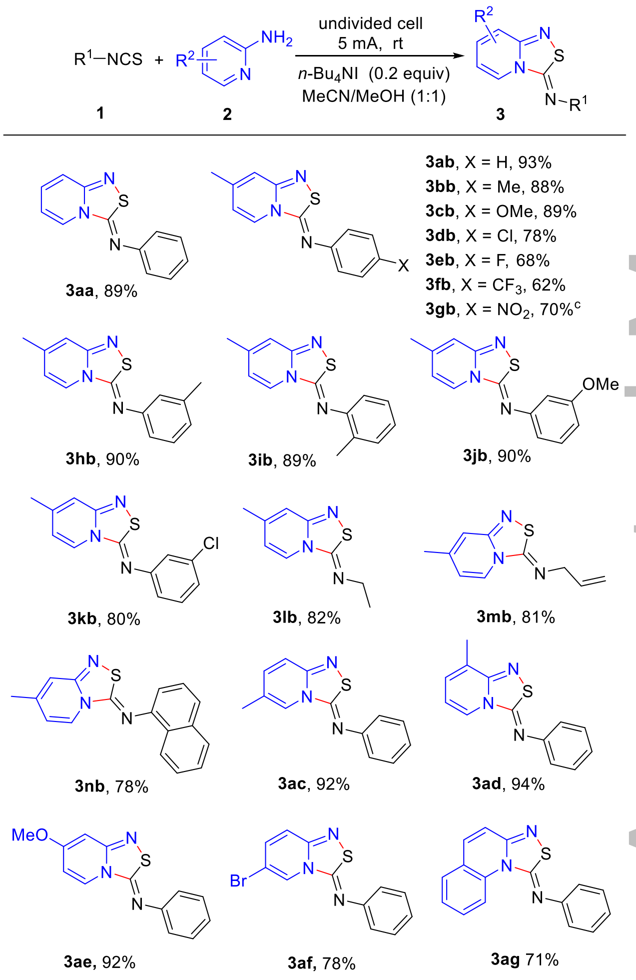


Entry	Deviation from standard conditions	Yield [%][b]
1[c]	none	89
2	with *n*-Bu_4NI (0.25 equiv)	86
3	entry 2 but with NH_4I, KI, or NaI	44, 74, 75
4	entry 2 but with *n*-Bu_4NBr, *n*-Bu_4NBF_4	trace, 0
5	with 2, 3, 4, or 6 mA	70 ~ 84
6	only with MeCN or MeOH	23, 37
7	with MeCN:H_2O (1:1) or MeOH:H_2O (1:1)	trace, 25
8	with MeCN:MeOH (2:1 or 1:2)	72, 79
9	using graphite felt as anode	81
10	using graphite rod as anode	15
11	using RVC as anode	88
12	using Zn or Sn plate as cathode	35, 25
13	using 1.5 equiv of substrate **1a**	89

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), *n*-Bu_4NI (0.2 equiv), MeCN: MeOH (1:1, 3 mL), Pt plates (1 cm × 1 cm) as anode and cathode, constant current = 5 mA (j_{anode} = 6.25 mA · cm^{-2}), undivided cell, under air atmosphere at room temperature for 6 h. [b] Yields are for isolated products. [c]**1a** (1.2 equiv).

Under the standard electrolysis conditions, the investigation of substrate scope was next conducted. All the isothiocyanates and aza-heterocycles containing a marked amidine moiety tested reacted smoothly to furnish their desired products in good to excellent yields (Table 2). Different substituents of aryl isothiocyanates (–Me, –OMe, –F, –Cl, –CF_3, and –NO_2) could be well tolerated in this electrolysis (**3ab-3gb**). As for substrates **1**, electron-donating groups (**3bb-3cb**) favored the reaction efficiency over

Table 2. Substrate scopes for the synthesis of fused thiadiazoles.[ab]

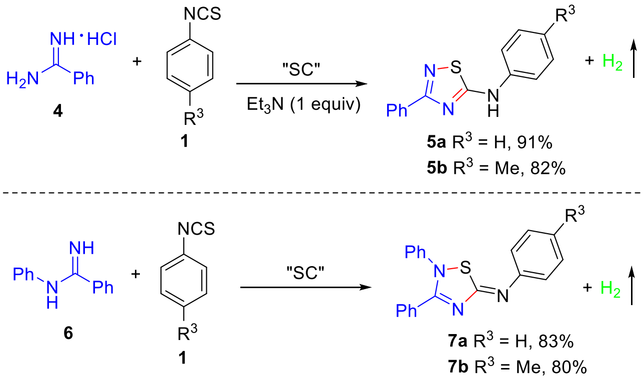


[a]Reaction conditions: Pt plate electrodes (1 cm × 1 cm), undivided cell, constant current = 5 mA (j_{anode} = 6.25 mA· cm^{-2}), **1** (0.24 mmol), **2** (0.2 mmol), *n*-Bu_4NI (20 mol%), solvent (3 mL), under air atmosphere at room temperature for 6 h (5.6 F/mol). [b] Isolated yield. [c] Reticulated Vitreous Carbon (RVC) as anode (100 PPI, 1 cm × 1 cm × 1.2 cm).

electron-withdrawing ones (**3db-3gb**). The use of *ortho*-, *meta*- or *para*-methylated phenyl isothiocyanates gave comparable yields of corresponding products (**3bb**, **3hb**, **3ib**), suggesting that the substituent steric properties of substrates **1** had no significant effects on the electrolysis. Besides, aliphatic isothiocyanates were found to be effective partners with yields of more than 80% (**3lb-3mb**). Noteworthy, this electrochemical transformation was compatible with an allyl group (**3mb**). Likewise, this electrochemical coupling reaction was applicable to various 2-aminopyridines, with groups like –Me, –OMe, and –Br. Notably, the reaction was greatly governed by electron properties of groups on the pyridine core (**3ac** vs **3af**), but not by steric effects (**3bb**, **3ac**, and **3ad**). Besides, 2-aminoquinoline was used instead to produce its desired thiadiazole in 71% yield (**3ag**).

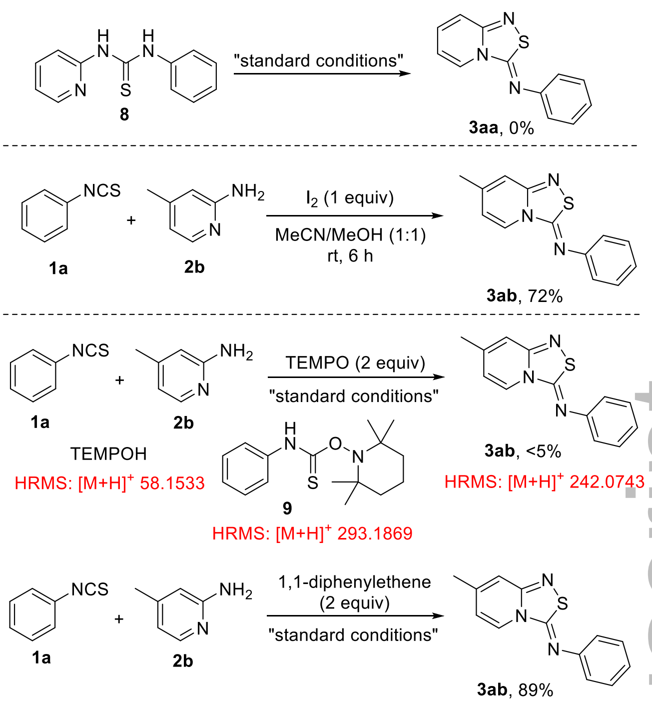
Next, we further examined unsubstituted benzimidine hydrochloride (**4**) and *N*-phenyl benzimidine (**6**) instead of 2-aminopyridines under the standard electrolysis conditions (Scheme 2). It turned out that both of them performed well with phenyl or 4-toly isothiocyanates to provide annulated products **5a**, **5b**, **7a** and **7b** with up to 91% yields. It should be pointed out that in the case of substrate **4**, one equivalent of additional base triethylamine was required to liberate free benzimidine.

To gain an insight into this electrolysis, we carried out the following controlled experiments (Scheme 3). When the thiourea **8**, readily available from the reaction of **1a** with **2a**, was subjected to the standard electrolysis conditions, no desired product **3aa** was detected. This excluded the possibility of undergoing a thiourea intermediate. The reaction of **1a** with **2b** under iodine (1 equiv) successfully delivered product **3ab** in 72%, suggesting iodine may be the real catalyst for this transformation. Further, TEMPO and 1,1-diphenylethene as radical trappers were added respectively in this electrochemical coupling. Interestingly, the use of TEMPO nearly stopped the reaction, while the addition of 1,1-diphenylethene hardly affected the electrolysis, giving **3ab** in 89% yield. The HRMS analysis of the crude reaction mixture involving TEMPO showed the presence of $[M+H]^+$ 58.1533 and 293.1869, which likely corresponds to the reduced TEMPO molecule generated in the cathode, and the nucleophilic adduct **9** of this TEMPO anion with **1a**, respectively. The competitive formation of **9** hindered the occurrence of the desired electrocatalytic coupling reaction. Thus, the radical process may not be involved in our electrochemical coupling reaction.



"SC" = standard conditions: *n*-Bu$_4$NI (0.2 equiv), MeCN/MeOH (1:1), Pt(+)|Pt(-), constant current = 5 mA, undivided cell, room temperature, 6 h

Scheme 2 Amidines as coupling partners with isothiocyanates for synthesis of 1,2,4-thiadiazoles



Scheme 3 Controlled experiments.

Considering that iodine could promote this dehyrogenative coupling without no electricity, we recorded the cyclic voltammetry (CV) curves, as shown in Figure 1, to identify the role of *n*-Bu$_4$NI. Within the scanning window (< 1.5 V), isothiocyanate **1a** displayed no recognizable oxidation peaks at the absence of the iodide salt (Figure S1, curve c), while 2-aminopyridine (**2a**) has marked oxidation signal at ca. 1.35 V (Figure S2, curve c). The curve b of *n*-Bu$_4$NI showed two oxidation peaks (the obvious at 0.72 V), corresponding to the oxidation of I^- to I_3^- and then to I_2 (Figure 1). The addition of *n*-Bu$_4$NI caused the decrease in the oxidation potential of **2a** by about 111 mV (Figure S2, curve d), thereby indicating *n*-Bu$_4$NI can promote the oxidation of **2a** likely through the interference of *in-situ* generated iodine. The CV behaviours of this iodide catalysed electrolysis are very similar to those of the cobalt catalysed electrosynthesis.[14]

On the base of the experimental results above, we proposed a tentative mechanism for this *n*-Bu$_4$NI-mediated electrochemical coupling reaction (Scheme 4). Initially, an iodide anion undergoes electro-oxidation in a platinum anode, generating an iodine molecule, I_2. Then 2-aminopyridine (**2a**) tautomerizes to generate an imine form **I**, and reacts with iodine to give *N*-iodopyridin-2-amine (**II**), which resembles the reaction of 2-methylquinolines with iodine.[15] The

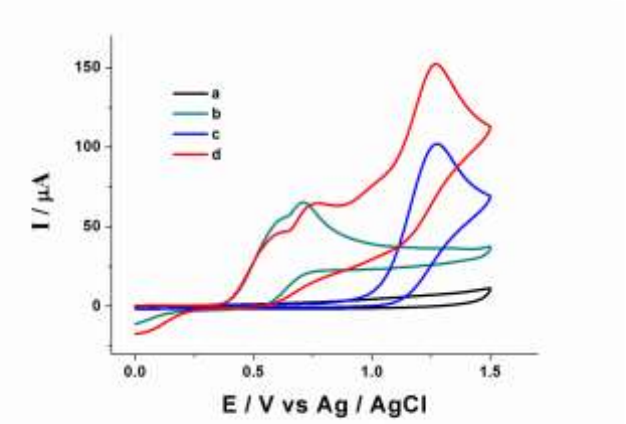
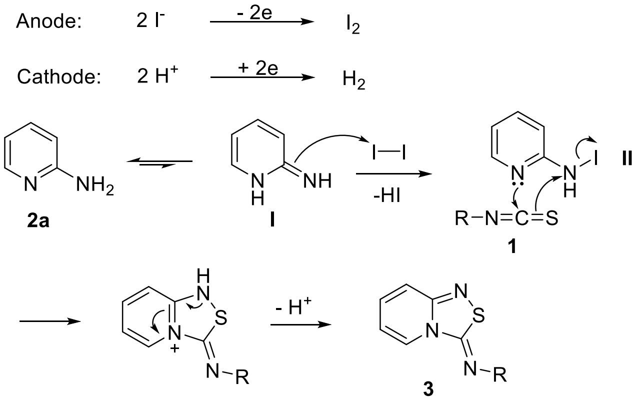


Figure 1. Cyclic voltammograms of reactants and their mixtures in 0.1 M *n*-Bu_4NPF_6/CH_3CN and CH_3OH (1:1, v/v) using a glassy carbon disk working electrode (diameter, 3 mm), Pt disk and Ag/AgCl (saturated KCl) as counter and reference electrode at 100 mV s^{-1} scan rate: (a) background, (b) *n*-Bu_4NI (3 mmol L^{-1}), (c) **1a** (8 mmol·L^{-1}) + **2a** (8 mmol·L^{-1}), (d) **1a** (8 mmol·L^{-1}) + **2a** (8 mmol·L^{-1}) + *n*-Bu_4NI (3 mmol·L^{-1}).



Scheme 4. Proposed mechanism.

active species **II** is subjected to a [3+2] annulation with an isothiocyanate **1** via deiodination and deprotonation to afford a 1,2,4-thiadiazole **3**.

In summary, we have demonstrated an electrochemical intermolecular dehydrogenative coupling reaction of isothiocyanates with 2-aminopyridines/amidines using *n*-Bu_4NI as the catalyst and electrolyte in an undivided cell. This electrochemical protocol enables ready access to 1,2,4-thiadiazoles and pyrido-fused 1,2,4-thiadiazoles under mild conditions, obviates the use of external oxidants and transition-metal catalysts. It offers an appealing and environmentally friendly strategy for the dehydrogenative S-N bond formation.

Experimental Section

Typical Procedure for the Electrosynthesis of the Cyclization Products.

The amidines or 2-amino azaheterocycles (0.2 mmol, 1.0 equiv), isothiocyanates (0.24 mmol, 1.2 equiv), *n*-Bu_4NI (0.04 mmol, 0.2 equiv) were placed in a 10 mL three-necked round-bottomed flask. The flask was equipped with platinum plate (1 cm × 1 cm) anode and a platinum plate (1 cm × 1 cm) cathode. MeOH (1.5 mL) and MeCN (1.5 mL) were added. The electrolysis was carried out at room temperature using a constant current of 5 mA until complete consumption of the substrate (monitored by TLC, about 6 h). The reaction mixture was concentrated and the residue was chromatographed through silica gel eluting with ethyl acetate/petroleum ether to give the products.

Acknowledgements

We would thank the Financial support from National Key R&D Program of China (No. 2017YFB0307200), Changsha Municipal Science and Technology Project (kq1801053), Young Teachers Development Project of CSUST (2019QJCZ039), Hunan Provincial Natural Science Foundation of China (2017JJ2275).

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COMMUNICATION

Electrochemical Synthesis of 1,2,4-Thiadiazoles through Intermolecular Dehydrogenative S-N Coupling

Adv. Synth. Catal. **2019**, *Volume*, Page – Page

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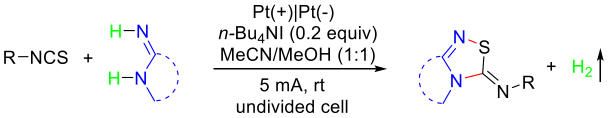

♥ *Electrochemical oxidation* ♥ *Metal-free*
♥ *External oxidant-free* ♥ *Mild reaction conditions*