Letter

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TEMPO-Catalyzed Electrochemical C–H Thiolation: Synthesis of Benzothiazoles and Thiazolopyridines from Thioamides

Xiang-Yang Qian,† Shu-Qi Li,† Jinshuai Song,*,‡ and Hai-Chao Xu*,†

† *i*ChEM, State Key Laboratory of Physical Chemistry of Solid Surfaces, and College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005 (P. R. China)

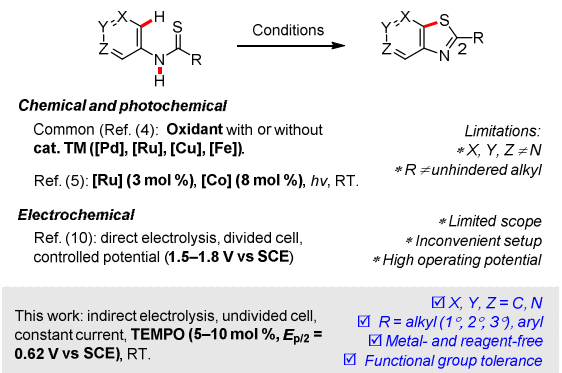
‡ Fujian Institute of Research on Structure of Matter, Chinese Academy of Sciences, Fuzhou 350002 (P. R. China)

ABSTRACT: Benzothiazoles and thiazolopyridines are widely prevalent in pharmaceuticals and organic materials. Herein, we report a metal- and reagent-free method for the uniform synthesis of benzothiazoles and thiazolopyridines through 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) catalyzed electrolytic C–H thiolation. This dehydrogenative coupling process provides access to a host of benzothiazoles and thiazolopyridines from *N*-(hetero)arylthioamides. Mechanistic studies suggested that the thioamide substrate was oxidized with the electrochemically generated $TEMPO^+$ through an inner-sphere electron transfer to afford a thioamidyl radical, which undergoes homolytic aromatic substitution to form the key C–S bond. KEYWORDS: *electrochemistry, radicals, benzothiazole, TEMPO, cyclization*

Cross-coupling of C–H and X–H (X = C or heteroatom) bonds is a powerful approach for the construction of carbon–carbon as well as carbon–heteroatom bonds because it offers several advantages including the use of simple and easily available starting materials and the elimination of substrate prefunctionalization.[1] Nonetheless, these methods frequently require the use of metal or organic stoichiometric oxidants, which create potential safety hazards for large-scale synthesis and frequently impose considerable amount of waste on the environment.[2] Hence, the development of more environment-friendly cross dehydrogenative-coupling reactions entails the reduction in use or complete elimination of oxidizing reagents.[3]

The oxidative cyclization of the easily available *N*-arylthioamides is an attractive method for the construction of the ubiquitous benzothiazole scaffold (Scheme 1).[4] Often, the reported reaction system comprises an oxidant of choice and optionally a transition metal catalyst.[4] The use of oxidants in these reactions cause, in addition to the above-mentioned problems, formation of undesirable side products such as amides as a result of desulfurization of the thioamides.[4a-c] To this end, Wu and Lei recently developed a novel Ru/Co-cocatalyzed photoredox process that obviates the need for oxidants by reducing the protons released to form H_2.[5] Despite these substantial advances, the construction of 2-alkyl substituted benzothiazoles and of the challenging thiazolopyridines remains difficult with the known C–H thiolation methods.[4–6] This is likely because alkylthioamides have strong propensity toward desulfurization,[4a,b,5] while the aza-arenes are electron-deficient and coordinating. In addition, the use of transition-metals in many of the reported methods entails additional procedures and cost to reduce the residual metals to ppm levels in order for the end products to qualify as pharmaceutical ingredients.[7]

Organic electrosynthesis, which accomplishes redox processes by employing electrons as "reagents", is accepted to be an environment-friendly and enabling synthetic tool.[8,9] The cyclization of *N*-arylthioamides through direct electrolysis was reported in 1979 but received little attention.[10] Although this process required the use of a divided cell and high potential (1.5–1.8 V vs SCE) and a full scope was not available, it did show promising results on the synthesis of benzothiazoles bearing 2-alkyl substituents. Indirect electrolysis, in which a redox catalyst is employed as the electron shuttle, is advantageous in its avoidance of electrode passivation and kinetic inhibition, as well as achievement of better (or different) selectivity and energy efficiency.[8b] We have recently developed electrochemical cross coupling reactions of N–H/C–H centers to synthesize *N*-heterocycles.[11a,b] Herein, we report a metal- and reagent-free method for the uniform synthesis of diversified benzothiazoles and thiazolopyridines via 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) catalyzed electrochemical C–H thiolation of *N*-(hetero)arylthioamides (Scheme 1).[12,13]

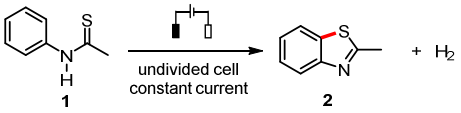


Scheme 1. Aromatic C–H Thiolation

We began our investigation with optimizing the reaction conditions for the cyclization of thioacetanilide (**1**), which failed under the chemical and photochemical conditions.[4a,b,5] Our previous work showed that TEMPO[11c] and ferrocene[11d]

were competent mediators for electrochemical activation of amidyl N–H bonds to generate nitrogen-centered radicals. After some screening with these redox catalysts, the optimal conditions were defined as running the electrolysis with 5 mol % of TEMPO as the redox-mediator and an electrolyte solution of nBu$_4$NBF$_4$ (0.2 equiv) in 1:1 MeCN/MeOH (Table 1). Under these conditions, the desired 2-methylbenzothiazole (**2**) was isolated in 68% yield without detection of acetanilide, a common type side product under oxidative conditions (entry 1).[4a-c] Running the electrolysis without TEMPO (entry 2) or the use of other redox mediators such as ferrocene (entry 3) or (4-BrPh)$_3$N (entry 4) all led to inferior results. The mixed solvent of MeOH and MeCN was important for reaction efficiency as the use of either MeOH (entry 5) or MeCN (entry 6) alone resulted in lower yield. Other anode materials such as platinum (entry 7) or graphite (entry 8) were found to be less efficient than RVC. The reaction could be conducted under atmospheric conditions, albeit with a slightly deceased yield (entry 9).

Table 1. Optimization of Reaction Conditions

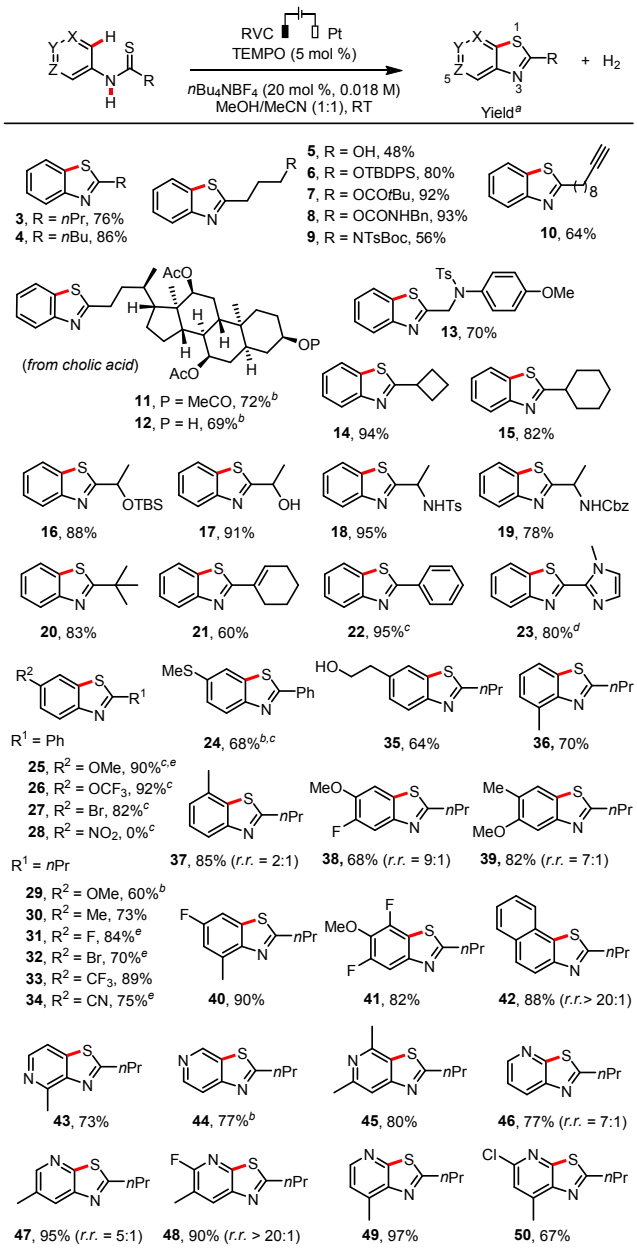


1 **2**

Entry	Electrolysis conditions[a]	Yield [%][b]
1	TEMPO (5 mol %), CH_3CN/MeOH (1:1), nBu$_4$NBF$_4$ (20 mol %), RT	68[c]
2	entry 1 but no TEMPO	46 (17)
3	entry 1 but Fc (5 mol %)	17 (56)
4	entry 1 but (4-BrPh)$_3$N (5 mol %)	6 (43)
5	entry 1 but MeOH as solvent	47 (17)
6	entry 1 but CH_3CN as solvent	30 (19)
7	entry 1 but Pt plate anode	13 (30)
8	entry 1 but graphite rod anode	34 (16)
9	entry 1 but under air	54 (2)

[a]Reticulated vitreous carbon (RVC) anode (100 PPI, 1 cm x 1 cm x 1.2 cm), Pt plate cathode (1 cm × 1 cm), undivided cell, constant current = 10 mA (j_{anode} ≅ 0.13 mA cm^{-2}), **1** (0.53 mmol), solvent (6 mL), argon, RT, 5.5 h (3.9 F). [b]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. Recovered **1** is given in brackets. [c]Isolated yield.

We next explored the substrate scope of the C–H thiolation reaction using a wide range of *N*-arylthioamides (Scheme 2). First, a series of primary (**3**–**13**) and secondary (**14**–**19**) alkyl thioamides underwent smooth cyclization. Many common functionalities such as free alcohol (**5**, **12**, **17**, **35**), silyl ether (**6**, **16**), ester (**7**, **11**), carbamate (**8**, **9** and **19**), alkyne (**10**), electron-rich arene (**13**), and sulfonamide (**18**) were tolerated. The retention of the hydroxyl group is particularly noteworthy because TEMPO is a well-known redox catalyst for the chemical and electrochemical oxidation of alcohols.[12a,b,f,14] The electrochemical reaction was also suitable for the synthesis of benzothiazoles bearing other 2-substituents such as *tert*-butyl (**20**), alkenyl (**21**), aryl (**22**, **24**–**27**) and heteroaryl (**23**) groups. The addition of small amount of water to the reaction mixture facilitated the formation of 2-arylbenzothiazoles (**22**, **25**–**27**).[15]

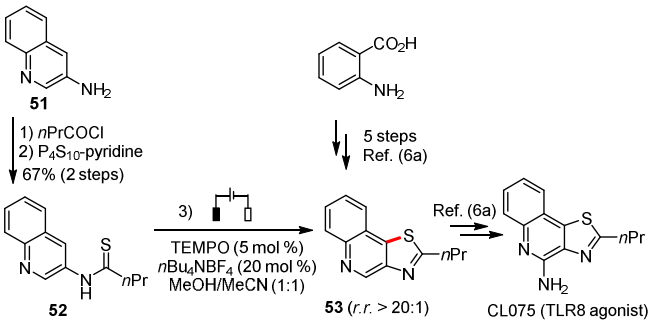


Scheme 2. Substrate Scope. Reaction conditions: Table 1, entry 1 (2.8–5.7 F). [a]Yield of isolated product. [b]Reaction run with TEMPO (10 mol %) and nBu$_4$NBF$_4$ (50 mol %). [c]0.2 mL of H_2O were added. [d]CF_3CH_2OH/MeCN (1:1) were used as solvent. [e]Reaction run with substrate (0.35 mmol), MeCN (5 mL), MeOH (5 mL), TEMPO (5 mol %), and nBu$_4$NBF$_4$ (50 mol %). TBDPS = *tert*-butyldiphenylsilyl, Ts = 4-toluenesulfonyl, Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl, Cbz = benzyloxycarbonyl.

The electronic and steric effects of the *N*-aryl group on the cyclization reaction was also probed. Electron-donating (SMe, OMe, Me) and -withdrawing (CN) substituents, halogens (F, Br) and fluorine-containing functionalities (OCF_3, CF_3) were all tolerated at the para position (Scheme 2, **24**–**27**, **29**–**34**). The highly electron-withdrawing nitro group, however, led to substrate decomposition and no benzothiazole formation (**28**). The selective oxidation of the thioamide group in the presence of a thioether further highlighted the mildness of the reaction

conditions.[16] Both ortho- (**36**) and meta-substituted (**37**) thioamides were viable substrates, although two regioisomers were obtained when the latter were used. In particular, the employment of thioamides bearing a multisubstituted *N*-aryl ring led to the production of highly functionalized benzothiazoles (**38**–**41**).[17] 2-Aminonapthalene-derived substrate reacted regioselectively to give naphtho[2,1-*d*]thiazole **42**.

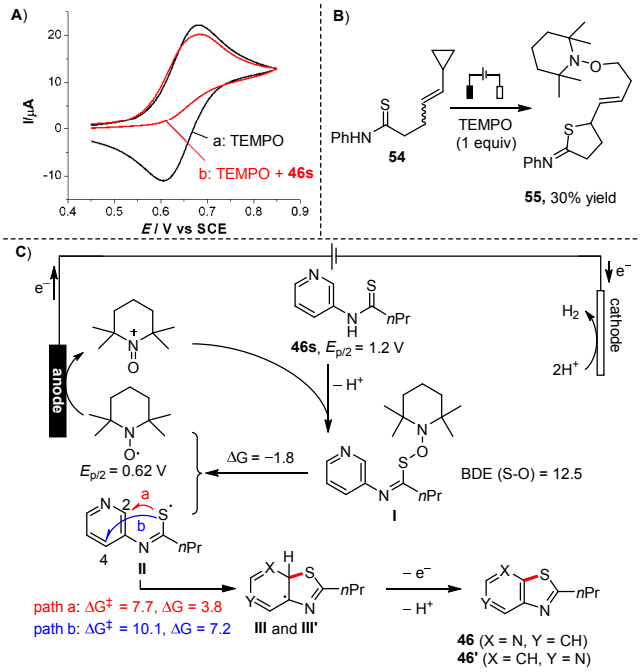
In addition to the production of benzothiazoles, the electrolytic C–H thiolation reaction could also be applied to the preparation of thiazolopyridines, which are synthetically more challenging.[6] Gratifyingly, thiazolopyridines (**43**–**50**) could be accessed without difficulty by employing aminopyridine-derived thioamides (Scheme 2). Notably, the 3-aminopyridine-based substrates reacted regioselectively at the α-position of the pyridyl ring to afford thiazolo[5,4,*b*]pyridines (**46**–**48**).



Scheme 3. Synthetic Application

To demonstrate its synthetic potential, the electrosynthetic method was incorporated as a key step for the synthesis of thiazolo[4,5-*c*]quinoline **53** (Scheme 3), which is an intermediate for the preparation of CL075, a toll-like receptor 8 (TRL8) agonist.[6a] A previously reported synthetic route to **53** required 5 steps from 2-aminobenzoic acid.[6a] In comparison, we accomplished the same synthesis in 3 steps from commercially available 3-quinolinamine (**51**) involving acylation, thiolation, and electrochemical cyclization. Unlike the 3-aminopyridine-derived substrates that cyclized at the α-position of the pyridyl ring, quinoline **52** reacted at the γ-position to furnish **53** in 92% yield.[18] Note that the electrolysis reaction could be scaled up by 20-fold to 2.3 g with even better current efficiency. The gram-scale reaction was conducted in a beaker-type cell with larger electrodes, allowing the use of higher current of 90 mA (see the Supporting Information, page S2).

To elucidate the mechanism of the electrochemical C–H thiolation reaction, the voltammograms of TEMPO (Scheme 4A) were recorded in the absence and presence of thioamide **46s** (Scheme 4C). The inclusion of thioamide **46s** ($E_{p/2}$ = 1.2 V vs SCE) resulted in the disappearance of the reduction wave in the voltammogram but without detection of a catalytic current. These data implied that the electrochemically generated $TEMPO^+$ reacted with **46s** but was not immediately reduced to TEMPO as a result. Next, thioamide **54** bearing a cyclopropyl group as the radical probe[19] was electrolyzed in the presence of 1 equiv of TEMPO (Scheme 4B). The ring-opening product **55** was obtained in 30% yield, suggesting that a thioamidyl radical was involved. Taken together, these mechanistic data indicated that the reaction of anode generated $TEMPO^+$ and the thioamide afforded an intermediate that could decompose into a thioamidyl radical and TEMPO.



Scheme 4. Mechanistic Investigation and Proposed Mechanism. A) cyclic voltammograms of TEMPO (0.003 M) in the absence (a) or presence (b) of thioamide **46s** (0.018 M). Conditions: glassy carbon working electrode, Pt wire counter electrode, SCE reference electrode, MeOH/MeCN (1:1), nBu$_4$NBF$_4$ (0.1 M), scan rate = 10 mV s^{-1}. B) radical clock experiment. C) Proposed mechanism. DFT-derived energetics (kcal mol^{-1}) were obtained at the level of B3LYP/6-31G*.

Based on the observations above, a possible mechanism for the C–H thiolation reaction was proposed. As illustrated in Scheme 4C, TEMPO first gets oxidized at the anode to give $TEMPO^+$, which then reacts with thioamide **46s** to give intermediate **I**[20] after a proton loss. The weak S–O bond (BDE = 12.5 kcal mol^{-1}) in **I** subsequently undergoes homolytic cleavage to furnish thioamidyl radical **II** and concomitantly regenerate TEMPO.[21] The oxidation through inner-sphere electron transfer allows *N*-arylthioamides with diverse electronic properties to participate efficiently in the electrochemical reaction. In addition, the formation of **I** reduces the concentration of thioamidyl radical and thus the chance of radical dimerization.[22] In the following step, radical cyclization of **II** at α-(path a) or γ-position (path b) of the pyridyl ring then produces the azacyclohexadienyl radicals **III** and **III′**, both of which can then rearomatize through electron and proton loss to give the corresponding thiazolopyrdines **46** and **46′**. Density functional theory (DFT)-based calculations suggested that formation of **III** was both kinetically and thermodynamically favored compared to that of **III′**, a possible explanation for the experimental observation that **46** was the predominant product. Similar computational investigation on the cyclization of **52**-derived radical showed that the opposite was true (see the Supporting Information, page S36).

In summary, we have developed a TEMPO-catalyzed electrochemical C–H thiolation reaction for the synthesis of benzothiazoles and thiazolopyridines. The use of TEMPO as a mild redox-mediator along with the metal- and reagent-free conditions allows a variety of *N*-(hetero)arylthioamides to participate in the reaction. Application of the electrochemical

C–H thiolation strategy in the synthesis of other *S*-heterocycles is underway in our laboratory.

AUTHOR INFORMATION

Corresponding Author

*haichao.xu@xmu.edu.cn
*jssong@fjirsm@ac.cn

Author Contributions

X.-Y.Q. and S.-Q.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information. The experimental procedure, characterization data, computational studies and copies of ^{1}H and ^{13}C NMR spectra. The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

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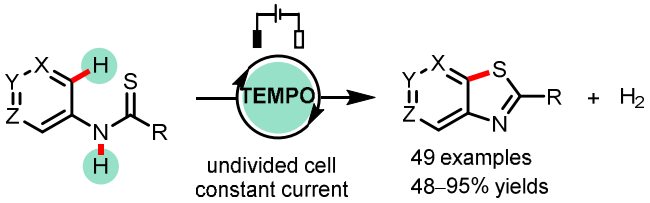

☑ R = alkyl (1°, 2°, 3°), aryl, alkenyl ☑ X, Y, Z = C, N