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Regioselective C−H Phosphorothiolation of (Hetero)arenes Enabled by the Synergy of Electrooxidation and Ultrasonic Irradiation

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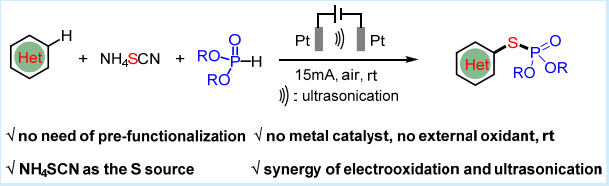
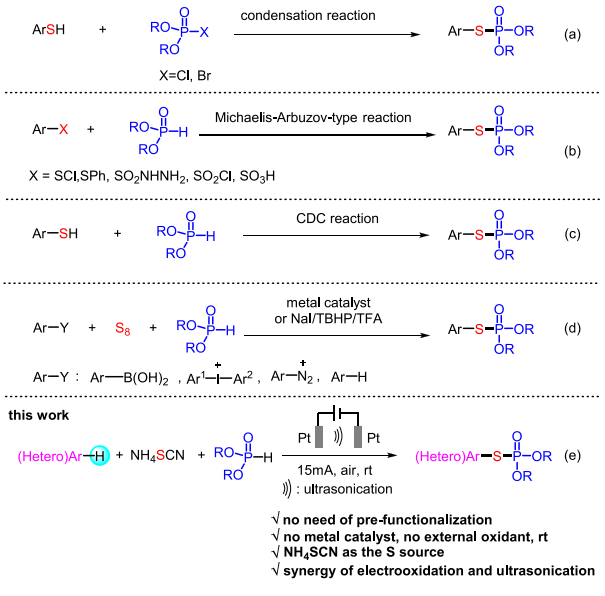
ABSTRACT: An electrochemically regioselective C−H phosphorothiolation of (hetero)arenes with thiocyanate as the S source under ultrasonic irradiation has been developed. The synergistic cooperation of electrooxidation and ultrasonication markedly accelerated the C−H phosphorothiolation reaction. This mechanistically different method is distinguished by its wide substrate scope and transition-metal-free and external-oxidant-free conditions, thus complementing the existing metal-catalyzed or peroxide-mediated protocols for the green synthesis of *S*-(hetero)aryl phosphorothioates.



Electrooxidation utilizes electrons as clean oxidants to afford reactive intermediates under mild conditions. Thus it has been recognized as a green synthetic tool for organic synthesis.[1] For the electrooxidation process, mass transport of reactants or mediators from a bulk electrolytic solution to an anode surface always plays a significant role in achieving high conversions and selectivities.[2] Recently, to address mass-transport limitations, the merger of electrooxidation and flow technology has provided new opportunities for green synthesis.[3] Ultrasonication is known to enhance mass transport based on a physical phenomenon called acoustic cavitation.[4] Consequently, a number of organic reactions can be carried out with improved efficiency under ultrasonic irradiation.[5] From a synthetic standpoint, the merger of electrooxidation and ultrasonication holds considerable potential to access previously challenging reactivity in a more efficient and environmentally friendly way; however, there have been limited successful examples to tap the full potential of the sustainability of electrooxidation and the acoustic cavitation of ultrasonication.[6]

S-(Hetero)aryl phosphorothioates constitute important structural motifs of natural products and biological molecules, which exhibit valuable antibacterial,[7] antitumor,[8] anticholinesterase,[9] and insecticidal activities.[10] Thus impressive efforts have been made to develop new synthetic methodologies for constructing *S*-(hetero)aryl phosphorothioates. Traditional methods for the preparation of *S*-aryl phosphorothioates have mainly relied on the condensation of arylthiols with prefunctionalized phosphorylation reagents, such as phosphorochloridates and phosphorobromidates (Scheme 1a),[11] or the Michaelis−Arbuzov-type reaction of sulfonyl halides, sulfenyl halides, disulfides, or other derivatives with phosphites (Scheme 1b).[12] However, the need for prefunctionalized substrates and the compatibility issues that result from the harsh conditions remain impediments of these methods. The cross-dehydrogenative coupling (CDC) of arylthiols with P(O)−H compounds provides an attractive alternative to obtain *S*-aryl phosphorothioates because prefunctionalization steps are avoided (Scheme 1c).[13] However, the limited availability of arylthiols restricts the structural diversity of the products. In addition, the smell of arylthiols is very strong and

Scheme 1. Strategies of *S*-(Hetero)aryl Phosphorothioates Syntheses



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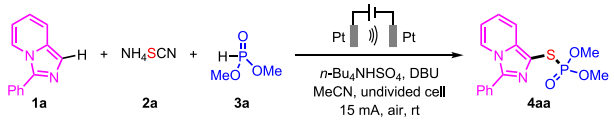
unpleasant. Therefore, the employment of suitable aryl precursors and odorless sulfur-containing reagents as the equivalent of aryl thiols is highly desirable. Recently, Tang and coworkers reported a series of Cu-catalyzed or I_2/TBHP-mediated phosphorothiolations of aryl precursors (arylboronic acids, diaryliodonium, or arenediazonium salts) with P(O)−H compounds and sulfur powder (Scheme 1d).[14] These powerful methods afforded diversely functionalized *S*-(hetero)aryl phosphorothioates in moderate to excellent yields. However, from the viewpoint of green synthesis, it would be much more attractive and yet challenging to synthesize *S*-(hetero)aryl phosphorothioates from readily available building blocks without the use of metal catalysts or external chemical oxidants. In a continuation of our research interest in electrosynthesis,[15] we herein report a green synthesis of *S*-(hetero)aryl phosphorothioates enabled by the synergy of electrooxidation and ultrasonic irradiation (Scheme 1e). This three-component oxidative cross-coupling strategy employs a combination of thiocyanate and dimethyl phosphite as the equivalent of thiophosphate, which has not yet been reported. The obviation of metal catalysts and chemical redox reagents makes this protocol attractive for the green synthesis of *S*-(hetero)aryl phosphorothioates.

Imidazo[1,5-*a*]pyridine, a N-containing fused heterocycle, has wide applications in the fields of pharmaceutical and material sciences.[16] As part of our ongoing research on the synthesis and functionalization of imidazo[1,5-*a*]pyridines,[17] we initiated our study by investigating the electrochemical coupling of 3-phenylimidazo[1,5-*a*]pyridine (**1a**) and NH_4SCN (**2a**) with dimethyl phosphite (**3a**) (Table 1).

Table 1. Selected Optimization of Reaction Conditions[a]



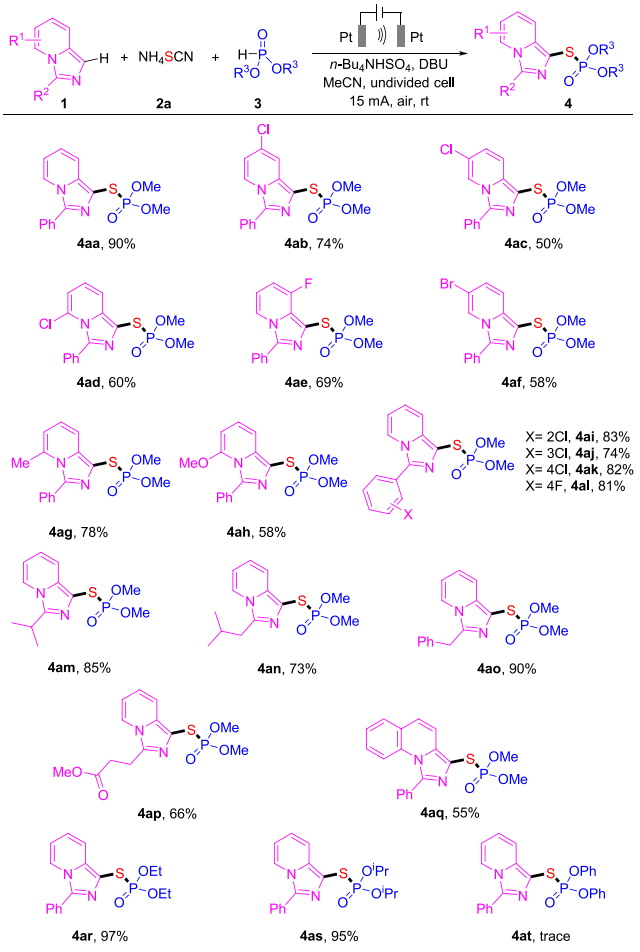
entry	deviation from standard conditions	yield (%)[b]
1	none	84
2	*n*-Bu_4NCl instead of *n*-Bu_4NHSO_4	trace
3	*n*-Bu_4NI instead of *n*-Bu_4NHSO_4	trace
4	DMSO as the solvent	74
5	DMF as the solvent	65
6	MeOH as the solvent	82
7	5 mL of CH_3CN was used	90
8	KSCN instead of NH_4SCN	trace
9	no DBU	trace
10	no electrolyte	trace
11	no electricity	ND
12	no ultrasonication	44

[a]Reaction conditions: platinum plate anode (1 × 1 cm^2), platinum plate cathode (1 × 1 cm^2), **1a** (0.3 mmol), **2a** (0.6 mmol), **3a** (0.9 mmol), *n*-Bu_4NHSO_4 (0.25 mmol), DBU (0.4 mmol), CH_3CN (7 mL), room temperature, 15 mA, undivided cell, ultrasonic irradiation (50 W, 40 kHz), 2−4 h. [b]Isolated yields. ND, not detected.

When the electrolysis was conducted at a constant current of 15 mA with *n*-Bu_4NHSO_4/CH_3CN as the electrolytic solution and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base in an undivided cell equipped with platinum electrodes under ultrasonic irradiation (50W, 40 kHz) at room temperature, the desired product **4aa** was obtained in 84% yield (entry 1). Changing the electrolyte to *n*-Bu_4NClO_4 or *n*-Bu_4NI resulted in the formation of the desired product in a trace amount (entries 2 and 3). When DMSO, DMF, or MeOH was employed as the solvent, the yield decreased to 74, 65, and 82%, respectively (entries 4−6). Increasing the substrate concentration improved the yield of **4aa** to 90% (entry 7). When KSCN was used instead of NH_4SCN, only a trace amount of product was observed (entry 8). In addition, control experiments showed that the base, electrolyte, and electricity were all crucial for the reaction (entries 9−11). Without ultrasonication, the yield of **4aa** decreased to 44% (entry 12), which demonstrated the synergy of electrooxidation and ultrasonic irradiation.

With the optimal reaction conditions in hand, we explored the substrate scope of this methodology. First, a variety of imidazo[1,5-*a*]pyridines were coupled to NH_4SCN (**2a**) and dimethyl phosphite (**3a**) under the optimized reaction conditions, and the results are shown in Scheme 2. The presence of electron-withdrawing substituents (−F, −Cl, and −Br) at the pyridine ring of imidazo[1,5-*a*]pyridines smoothly

Scheme 2. Electrochemical C−H Phosphorothiolation of Imidazo-Fused Heterocycles[a]



[a]Reaction conditions: platinum plate anode (1 × 1 cm^2), platinum plate cathode (1 × 1 cm^2), **1** (0.3 mmol), **2a** (0.6 mmol), **3** (0.9 mmol), *n*-Bu_4NHSO_4 (0.25 mmol), DBU (0.4 mmol), CH_3CN (5 mL), room temperature, constant current = 15 mA, undivided cell, ultrasonic irradiation (50 W, 40 kHz), room temperature, 2−4 h (the reaction time for each substrate is shown in the Supporting Information); isolated yields.

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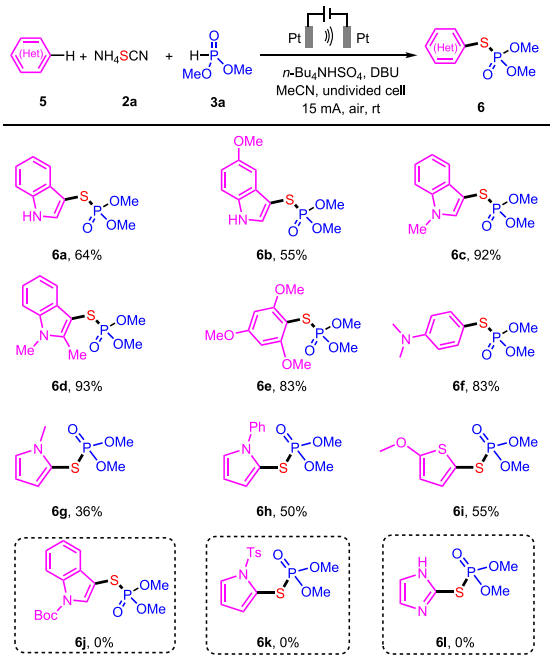
reacted with **2a** and **3a** to afford the desired products (**4ab**−**4af**) in moderate yields. Imidazo[1,5-*a*]pyridines bearing electron-donating groups (−Me and −OMe) also worked well to give **4ag** and **4ah** in 78 and 58% yields, respectively. Next, the effect of the substituent at the C-3 position of the imidazo[1,5-*a*]pyridines was examined. The imidazo[1,5-*a*]-pyridine moiety with halogen-substituted phenyl rings at the C-3 position gave the corresponding C-1 phosphorothiolated products (**4ai**−**4al**) in excellent yields. It is noteworthy to mention that no obvious steric hindrance was observed for this transformation (**4ai** and **4ak**). When R^2 was replaced by isopropyl or isobutyl, the reactions proceeded smoothly to produce **4am** and **4an** in good yields. The benzyl-substituted imidazo[1,5-*a*]pyridine was found to be very effective for phosphorothiolation (**4ao**). Interestingly, the presence of an ester group had no obvious influence on the reaction (**4ap**, 66%). In addition, imidazo[1,5-*a*]quinolines were amendable to the standard conditions, affording **4aq** in 55% yield. Furthermore, to extend the scope of this protocol, other phosphites were also examined under the standard conditions. It is gratifying that diethyl phosphite and diisopropyl phosphite also smoothly underwent C−H phosphorothiolation to provide the phosphorothiolated products (**4ar** and **4as**) in 97 and 95% yields, respectively. However, diphenyl phosphite failed to afford the target product, mainly due to its relatively weak nucleophilicity.

To illustrate the general applicability of the sonoelectrochemical methodology, we turned our attention to the scope of other (hetero)arenes (Scheme 3). Free (N−H) indoles underwent C−H phosphorothiolation, regioselectively affording C-3 phosphorothiolated products in moderate yields (**6a** and **6b**). By contrast, *N*-methylindoles gave the desired products in excellent yields (**6c** and **6d**). Gratifyingly, trimethoxybenzene and *N*,*N*-dimethylaniline were found to be suitable substrates for the reaction to give phosphorothiolated products (**6e** and **6f**) in good yield. *N*-Methyl pyrrole, 1-phenylpyrrole, and 2-methoxythiophene were also well tolerated in this reaction (**6g**−**6i**). However, substrates having higher oxidation potentials, such as *N*-Boc indole, *N*-Ts pyrrole, and imidazole, failed to give the corresponding products (**6j**−**6l**).

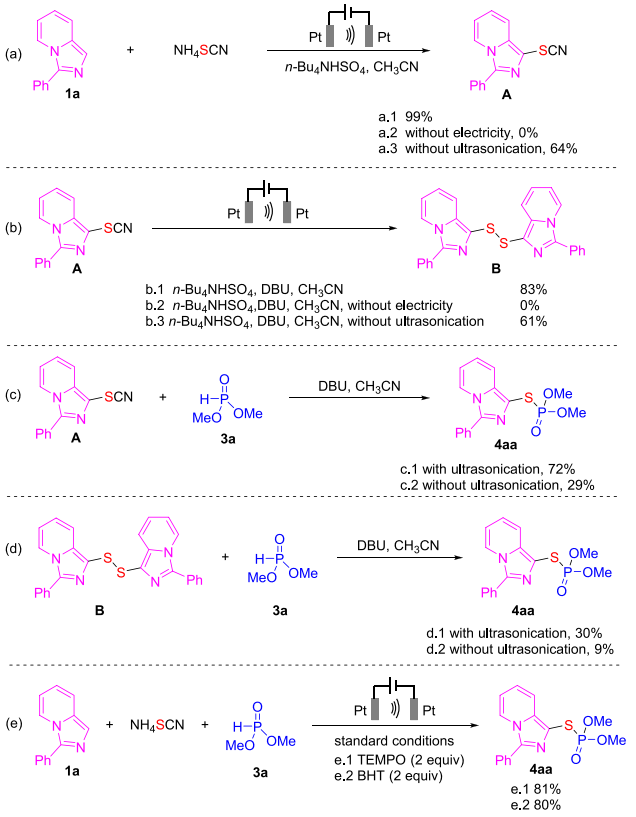
Scheme 3. Electrochemical C−H Phosphorothiolation of Other (Hetero)arenes[a]



[a]Standard reaction conditions are shown in Scheme 2; isolated yields.

To gain insight into the reaction mechanism, we carried out a series of control experiments. First, when **1a** and **2a** were electrolyzed in the absence of phosphite **3a** and DBU, thiocyanated intermediate **A** was isolated in 99% yield, whereas no conversion occurred without electricity (Scheme 4a). When the thiocyanated intermediate **A** was electrolyzed in the absence of phosphite **3a**, the disulfide intermediate **B** was separated in 83% yield, whereas intermediate **A** was recovered without electrolysis (Scheme 4b). As expected, intermediates **A** and **B** could react with phosphite **3a** in the presence of DBU without electrolysis to give the desired product **4aa** in 72 and 30% yields, respectively (Scheme 4c,d). These results showed that **A** and **B** were key intermediates of this three-component coupling reaction. When a radical scavenger such as 2,2,6,6-tetramethyl-1-piperidinyl-oxy (TEMPO) or 2,6-di*tert*-butyl-4-methylphenol (BHT) was added to the reaction mixture, the reaction was slightly inhibited to give **4aa** in 81 and 80% yields, respectively (Scheme 4e). These results implied that a radical species was not involved in the rate-determining steps. The effect of ultrasonic irradiation on different reaction steps was also investigated. The yields of **A**, **B**, and **4aa** significantly decreased in the absence of ultrasonic irradiation (Scheme 4a−d), which demonstrated that the previously mentioned reaction steps were all accelerated by ultrasonic irradiation.

Scheme 4. Control Experiments



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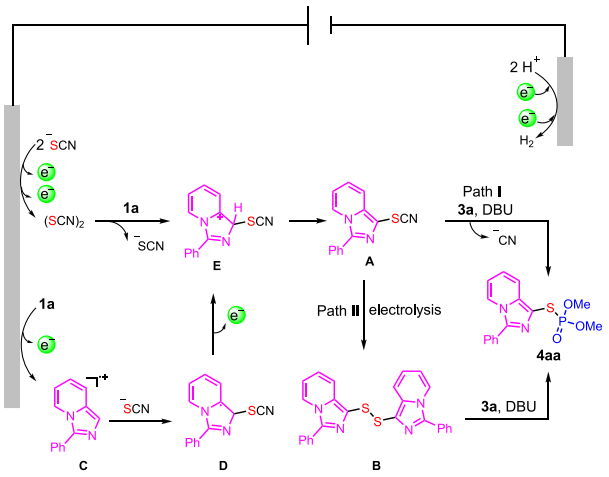
The reaction progress could be clearly monitored by TLC. (See Figure S2 in the Supporting Information for details.) When **1a** and **2a** were electrolyzed in the absence of phosphite **3a** and DBU, intermediates **A** and **B** appeared successively with time. When the substrate **1a** disappeared, phosphite **3a** and DBU were added to the reaction system. As the reaction progressed, intermediates **A** and **B** gradually disappeared, and the target products **4aa** accumulated.

Cyclic voltammetric (CV) experiments were then carried out to figure out which coupling component undergoes electrochemical oxidation first. (See Figures S3–S6 in the Supporting Information for details.) As shown in Figure S3 and S4, 3-phenylimidazo[1,5-*a*]pyridine (**1a**) and NH_4SCN (**2a**) have similar oxidation potentials, whereas phosphite **3a** remains intact within the tested potential window (Figure S5). In addition, the CV of NH_4SCN shows two oxidation processes between 0.7 and 1.7 V and a reduction process at 0.25 V, which correspond to the pseudohalide system of $\{SCN-(SCN)_3-(SCN)_2\}$ (Figure S4).[18]

On the basis of the control experiments and CV studies, a plausible mechanism was proposed, as shown in Scheme 5.

Scheme 5. Tentative Mechanistic Pathway



Initially, imidazo[1,5-*a*]pyridine (**1a**) undergoes electrooxidation to give radical cation **C**, which is attacked by ^{-}SCN to give radical **D**. Then, radical **D** has a further electrooxidation to afford carbocation **E**. Alternatively, ^{-}SCN could be oxidized at the anode and then undergo dimerization to produce the electrophilic intermediate $(SCN)_2$, which would then trapped by imidazo[1,5-*a*]pyridine (**1a**) to give carbocation **E**. Because substrates having higher oxidation potentials failed in this reaction (Scheme 3, **6j–6l**), the reaction sequence involving intermediate **C** should be the major reaction pathway. The resulting intermediate **E** subsequently undergoes deprotonation to produce the thiocyanated intermediate **A**, which is attacked by the nucleophilic phosphite **3a** to yield product **4aa** (path I). Meanwhile, intermediate **A** could also be transformed into disulfide **B**,[19] which would react with nucleophilic phosphite **3a** to produce product **4aa** (path II).

In summary, we have developed a green synthesis of *S*-(hetero)aryl phosphorothioates enabled by the synergy of electrooxidation and ultrasonic irradiation. The synergistic cooperation of electrooxidation and ultrasonication markedly accelerated the C–H phosphorothiolation reaction. This three-component oxidative cross-coupling strategy employs the combination of thiocyanate and phosphite as the equivalent of thiophosphate, which has not yet been reported. This mechanistically different method is distinguished by its wide substrate scope and transition-metal-free and external oxidant-free conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01161.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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