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Electrochemical Dehydrogenative Phosphorylation of Thiols

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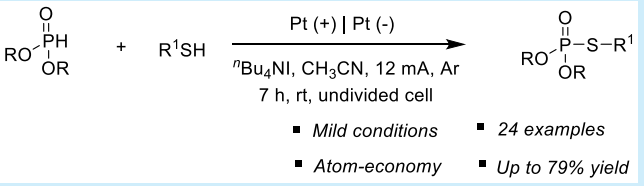
Supporting Information

ABSTRACT: We report herein a new approach for the synthesis of organothiophosphates from phosphonates and thiols through electrochemical reaction. The reactions were conducted without the addition of oxidant, transition-metal base, or base at room temperature. This system has a good substrate scope and functional group tolerance. Aryl and alkyl thiols worked well with phosphonates to afford the corresponding organothiophosphates in good yields.



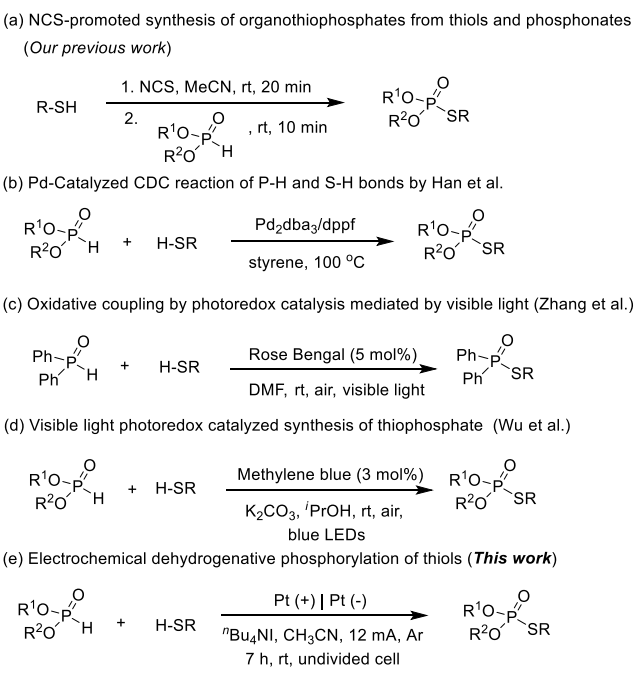
Organothiophosphates are ubiquitous structural motifs that have crucial biological and chemical properties and, furthermore, are employed in many fields such as pharmaceutical industry, organic synthesis, and pesticide chemistry.[1] Structure−activity relationship studies also revealed that many organothiophosphates display notable biological activities.[1j,k] Consequently, the development of novel strategies for synthesizing organothiophosphates is highly desirable. Conventionally, the synthesis of organothiophosphates has often been achieved through substitution reaction of $R_2P(O)X$ or RSX; this always results in limitations, for example, low functional group tolerance and tedious procedures.[2] Bearing in mind the importance of organothiophosphates as therapeutics and agrochemicals, considerable advancements have been achieved in their preparation.[3−7] In 2014, we have developed a method for preparing thiophosphates through *N*-chlorosuccinimide-promoted P(O)−S bond formations (Scheme 1a).[2l] Among the methods developed thus far for the formation of P(O)−S bonds, the oxidative cross-dehydrogenative coupling (CDC) reactions from the P(O)−H bond and S−H bond have become the most attractive path due to issues of atom economy and increasing the reaction efficiency.[3−6]

In 2016, Han et al. developed a palladium-catalyzed CDC reaction to prepare organothiophosphates from thiols and phosphonates at 100 °C (Scheme 1b).[4] Visible-light-mediated oxidative cross-coupling reaction of thiols with phosphonates is known for the synthesis of organothiophosphates (Scheme 1c,d).[5,6]

Over the past decade, organic electrosynthesis has been acknowledged as an environmentally benign and mild synthetic tool for various organic transformations.[7,8] Furthermore, various simple and elegant electrochemical CDC reactions for making carbon−carbon and carbon−heteroatom bonds have been extensively studied.[9−11] However, a P(O)−S bond formation by electrochemical CDC reaction is not well-established. Herein, we report the first electrochemical oxidative CDC of thiols with phosphonates in an undivided cell under remarkably mild reaction conditions (Scheme 1e).

To investigate the optimized electrochemical conditions for P(O)−S bond formation, we first selected di-*n*-butyl phosphite (**1a**) and 4-methoxythiophenol (**2a**) as substrates. Experiments

Scheme 1. Methods for P(O)−S Bond Formation



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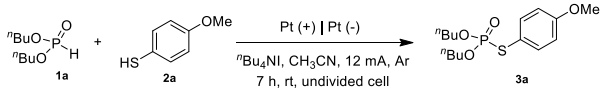
to optimize of the electrochemical CDC reaction indicated that the highest yield (72%) of thiophosphate **3a** was obtained by conducting electrolysis in an electrolyte solution of $^{n}Bu_4NI$ in CH_3CN by using a platinum anode and a platinum cathode with 12 mA at room temperature for 7 h (Table 1, entry 1).

Table 1. Screening of Electrochemical CDC Reaction of P(O)−S Bond Formation[a]



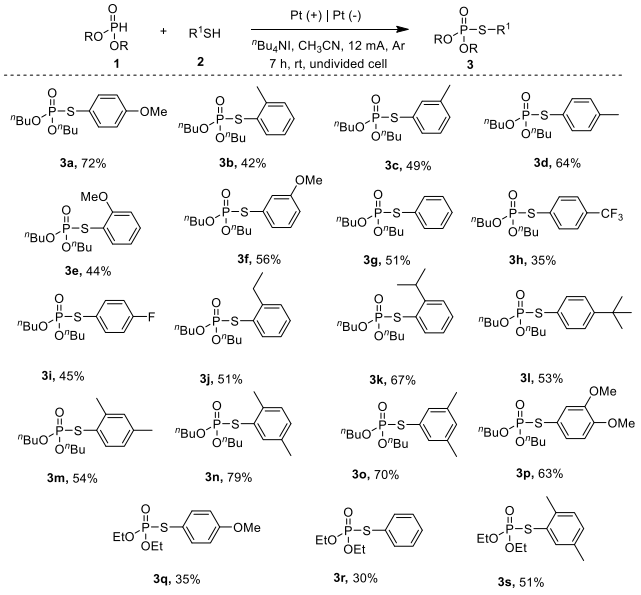
entry	variation from the standard conditions	yield (%)
1	none	72
2	NH_4I instead of $^{n}Bu_4NI$	ND
3	$LiClO_4$ instead of $^{n}Bu_4NI$	ND
4	$^{n}Bu_4NBF_4$ instead of $^{n}Bu_4NI$	25
5	$^{n}Bu_4NBr$ instead of $^{n}Bu_4NI$	41
6	without $^{n}Bu_4NI$	ND
7	CH_3OH instead of CH_3CN	54
8	DMF instead of CH_3CN	61
9	CH_2Cl_2 instead of CH_3CN	trace
10	9 mA instead of 12 mA	19
11	15 mA instead of 12 mA	23
12	under N_2	68
13	under air	63
14	6 h of reaction time	68
15	8 h of reaction time	72
16	1.8 equiv of thiol instead of 2.0 equiv	69
17	graphite rod as anode	61
18	diphenyl disulfide (1.0) instead of **2a**	72
19	with TEMPO (2 equiv)	52

[a]Standard conditions: platinum plate anode (0.5 mm × 0.5 mm × 10 cm), platinum plate cathode (0.5 mm × 0.5 mm × 10 cm), **1a** (1.0 mmol), **2a** (2.0 mmol), $^{n}Bu_4NI$ (1.0 mmol), solvent (4 mL), room temperature, argon atmosphere, 7 h. Isolated yields. ND = not detected.

No product was detected when $^{n}Bu_4NI$ was replaced with other electrolytes such as NH_4I and $LiClO_4$, whereas in the presence of $^{n}Bu_4NBF_4$ or $^{n}Bu_4NBr$ it was isolated in lower yields (Table 1, entries 2−5). No product was formed in the absence of $^{n}Bu_4NI$ during the reaction (Table 1, entry 6). The use of CH_3OH or DMF as solvent in place of acetonitrile produced inferior results compared with acetonitrile (Table 1, entries 7 and 8). When CH_2Cl_2 was used as the solvent, only a trace amount of **3a** was detected (Table 1, entry 9). Both a decrease and an increased in current provided lower product yields (Table 1, entries 10 and 11, respectively). Moreover, when the reaction was performed under a nitrogen atmosphere, a decrease in the product yield was observed, and under an air atmosphere, a lower yield was obtained (Table 1, entries 12 and 13, respectively). Decreasing or increasing the reaction times lowered the formation of product (Table 1, entries 14 and 15, respectively). A slightly lower yield was observed when thiol was loaded with decreased equivalents (Table 1, entry 16). The choice of electrode material proved critical; only 61% of the product was isolated when we used a graphite rod as the anode (Table 1, entry 17). When diphenyl disulfide was used, **3a** was obtained with 72% yield (Table 1, entry 18). The product was formed with 52% yield in the presence of 2 equiv of TEMPO (Table 1, entry 19). This result might rule out the radical mechanism.

With optimized reaction conditions in hand, we next investigated the scope of substrates in this electrochemical coupling reaction (Scheme 2). Thiophenols bearing electron-

Scheme 2. Scope of the Electrochemical CDC Reaction[a]



[a]Reaction conditions: platinum plate anode (0.5 mm × 0.5 mm × 10 cm), platinum plate cathode (0.5 mm × 0.5 mm × 10 cm), **1** (1.0 mmol), **2** (2.0 mmol), $^{n}Bu_4NI$ (1.0 mmol), acetonitrile (4 mL), room temperature, argon atmosphere, 7 h.

withdrawing and electron-donating groups at different positions on the phenyl ring proceeded to give the thiophosphates **3a−p** in good yields (35−79%). For example, when methyl and methoxy groups were present at the *ortho*-, *meta*-, and *para*-positions of the arylthiol, the corresponding thiophosphates (**3a−3f**) were obtained in moderate to good yields. Furthermore, thiophenol coupled well with di-*n*-butyl phosphite under the reaction conditions and produced thiophosphate (**3g**) in a moderate yield. The use of thiols containing electron-withdrawing groups for this electrochemical CDC reaction provided the products in lower yields (**3h** and **3i**). Bulky alkyl substituents on the aryl group of thiol did not considerably affect the yield of the product, obtaining it in moderate to good yields (**3j−3l**). In addition to these thiols, disubstituted arylthiols worked well with di-*n*-butyl phosphite under the reaction conditions, producing the corresponding thiophosphates (**3m−3p**) in good yields. In addition to the use of di-*n*-butyl phosphite, we also used diethyl phosphite (**1b**) to couple with aryl thiols, affording the corresponding thiophosphates in moderate yields (**3q−3s**).

After successful coupling of arylthiols with di-*n*-butyl phosphite (**1a**) and diethyl phosphite (**2a**) under electrochemical CDC conditions, we also used alkylthiols to couple with di-*n*-butyl phosphite and obtained the corresponding thiophosphates (**5a−5d**) in good yields. When we used diphenyl phosphite (**1c**) as a coupling partner to react with *n*-hexylmercaptan (**4c**), the corresponding product (**5e**) was obtained in lower yield (Scheme 3).

Successful development of the electrochemical dehydrogenative phosphorylation of thiols encouraged us to perform cyclic voltammogram (CV) experiments to know the redox behavior of the reactions (Figure 1). In curve b (in the absence of

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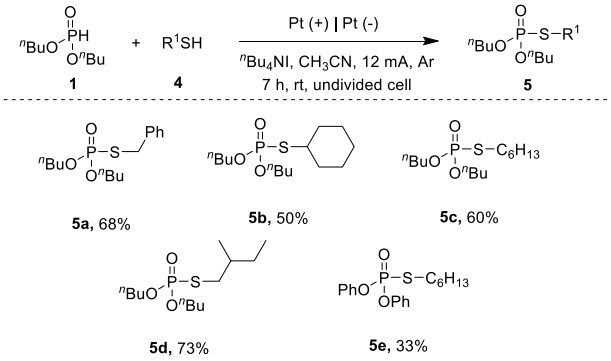
Scheme 3. Scope of the Alkylthiols in the Electrochemical CDC Reaction[a]



[a]Reaction conditions: platinum plate anode (0.5 mm × 0.5 mm × 10 cm), platinum plate cathode (0.5 mm × 0.5 mm × 10 cm), **1** (1.0 mmol), **4** (2.0 mmol), ^{n}Bu$_4$NI (1.0 mmol), acetonitrile (4 mL), room temperature, argon atmosphere, 7 h.

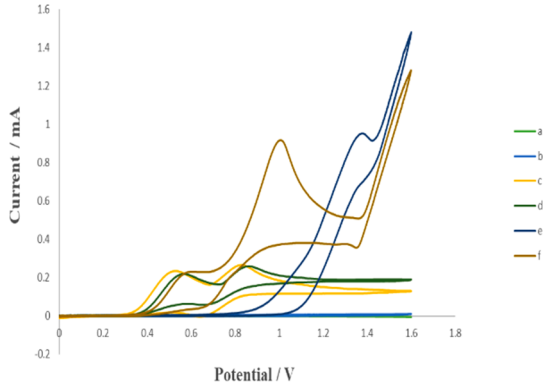
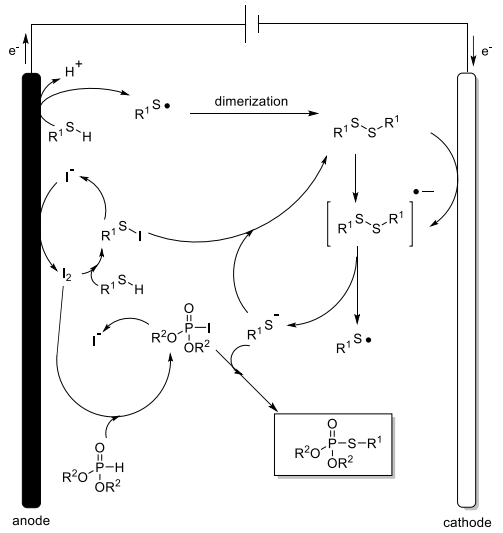


Figure 1. Cyclic voltammograms of reactants and the mixtures in 0.1 M $LiClO_4/CH_3CN$ using a glassy carbon-disk working electrode (diameter, 3 mm). Pt disk as counter; Ag/AgCl as reference electrode, at 100 mV/s scan rate: (a) background, (b) **1a** (10 mmol/L), (c) ^{n}Bu$_4$NI (2 mmol/L), (d) **1a** (10 mmol/L) + ^{n}Bu$_4$NI (2 mmol/L), (e) 1a (10 mmol/L) + **2a** (10 mmol/L), and (f) **1a** (10 mmol/L) + **2a** (10 mmol/L) + ^{n}Bu$_4$NI (2 mmol/L).

^{n}Bu$_4$NI), **1a** shows no oxidation peak (0.0−1.0 V versus Ag/AgCl) without ^{n}Bu$_4$NI. The CV of ^{n}Bu$_4$NI had two oxidation peaks at 0.53 and 0.83 V (curve c), which correspond to the oxidation of I^- to I_3^- and I_3^- to I_2, respectively. A similar curve was displayed when **1a** and ^{n}Bu$_4$NI were combined (curve d). Thus, **1a** cannot be oxidized to its corresponding radical. Interestingly, we found that the CV of the mixture of **1a** and **2a** presented an oxidation peak at 1.38 V, and we thought **2a** went through oxidation and formed disulfide without addition of electrolyte (curve e). The CV of the mixture of **1a**, **2a**, and ^{n}Bu$_4$NI demonstrated an apparent oxidation peak at 1.01 V (curve f), which illustrated there had been a chemical interaction between the three compounds.

On the basis of the above observations and literature reports,[11b] a proposed mechanism of electro-oxidative P−H/S−H cross coupling is depicted in Scheme 4. First, I_2 will be generated from ^{n}Bu$_4$NI in the reaction mixture, and I_2 can oxidize phosphonate and thiol to iodophosphate and sulfenyl iodide, respectively.[12] Disulfide is well-known to occur from thiol through an electrochemical approach.[11b] Cathodic reduction of the disulfide would generate the corresponding

Scheme 4. Proposed Mechanism for P−S Bond Formation



thiolate anion and thiyl radical, and thiolate anion would react with the iodophosphate to afford the product.

In summary, we have developed an efficient and green electrochemical dehydrogenative P−H/S−H cross coupling for synthesis of thiophosphates. This reaction protocol avoids the use of external chemical oxidants; H_2 is the only byproduct. Under undivided electrolytic conditions, a series of thiophosphates can be obtained in moderate to good yields. In this reaction case, electrochemical external oxidant-free dehydrogenative cross-coupling demonstrated a green approach compared to the traditional oxidative cross-coupling protocol, which may inspire people to use electrochemical methods in more oxidative cross-coupling reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02825.

Experimental procedures, spectroscopic data, copies of NMR and crystallographic data (PDF)

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Notes

The authors declare no competing financial interest.

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