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Electrochemical Dehydrogenative Coupling of Alcohols with Hydrogen Phosphoryl Compounds: A Green Protocol for P-O Bond Formation

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Abstract: This study reports the environment-friendly electrochemical transformation of structurally diverse phosphorus compounds and alcohol into phosphonates in the presence of ammonium iodide as electrolyte and redox catalyst in acetonitrile at ambient temperature. This method for P-O bond formation exhibits remarkable features, such as transition metal- and

oxidant-free conditions. A reliable mechanism is proposed after control and cyclic voltammetry experiments.

Keywords: Electroorganic chemistry; CDC reaction; P-O bond formation; NH₄I catalysis; Cyclic voltammetry

Introduction

In modern organic synthesis, production of chemical products in a green and sustainable manner is important.^[1] Oxidative R^1 –H/ R^2 –H dehydrogenation cross-coupling has been developed as a valuable method for constructing chemical bonds, because it uses readily available starting materials without substrate prefunctionalization, and it is one of the highest atom-economical methods in organic synthesis, with only one molecule of hydrogen gas byproduct.^[2] produced as However. the thermodynamics of oxidative R^1-H/R^2-H dehydrogenation cross-coupling with the elimination of one molecule of hydrogen gas is usually unfavorable.^[3] Thus, traditional oxidative R¹–H/R²– H dehydrogenation cross-coupling reactions usually require stoichiometric amounts of oxidants or precious metals as catalysts. The use of oxidants in reactions constantly leads to decreased atom economy and obtains oxidation side reactions (Scheme 1, Eq. 1).^[4] Thus, the development of a metal-free and oxidizing-agent-free oxidative R¹-H/R²–H dehydrogenation cross-coupling represents a major advancement toward achieving low cost and remarkable environmental sustainability in the preparation of new compounds.

Electroorganic chemistry is an ideal alternative method for synthesizing new compounds through R^1-H/R^2-H oxidative dehydrogenation crosscoupling and has attracted considerable interest in organic chemistry (Scheme Ea. $2).^{[3,5]}$ 1. Electroorganic synthesis utilizes electrons "reagents" to complete the redox process. In the previous decade, electrochemical anodic oxidation has emerged as a promising method to achieve R1-H/R²–H dehydrogenation cross-coupling.^[6] For example, Lei's group recently outlined the application of electrochemical oxidative R¹-H/R²-H dehydrogenation cross-coupling in C–O, C–C, N–N, C-N, and C-S bond formations.^[3] Xu's group realized the C-H/N-H electroorganic dehydrogenation cross-coupling reactions to construct various heterocyclic structures.^[7]



Scheme 1. Comparison of traditional coupling and electrocatalytic coupling

Organophosphorus compounds are an important class of compounds in organic chemistry, medicinal chemistry, and materials science.^[8] Development of new synthetic methods for this class of compounds has attracted an increasing amount of interest because of their various applications. The classical methods for the formation of phosphorus-oxygen phosphinate esters bond in include the Atherton–Todd reaction.^[9] Another approach is dehydrogenative/oxidative of coupling diaryl phosphites with alcohols, which can be achieved by using various stoichiometric amounts of oxidants or precious metals as catalysts.^[10] It's worth mentioning that Chen and Han reported a dehydrogenative coupling between H-phosphine oxides and alcohols with hydrogen release, in which cheap iron was used as a catalyst. In this study, we report an effective method for the synthesis of phosphinate esters through electrochemical construction of P-O bond with metal- and oxidant-free conditions based on our previous work in electrochemical oxidative R¹-H/R²–H dehydrogenation cross-coupling^[6c,6d]. After the submission of this manuscript, Han et al. reported a similar reaction also using electrochemical dehydrogenation coupling.^[11]

Table 1. Optimization of reaction conditions^a

0

$H \rightarrow H \rightarrow$				
1a 2a				3aa
Entry	Electrode	Electrolyte	Solvent	Yield ^b
1	RVC/Pt	NH4I	MeOH	70%
2	RVC/Pt	$\rm NH_4I$	DMSO	0%
3	RVC/Pt	$\rm NH_4I$	DCE	Trace
4	RVC/Pt	$\rm NH_4I$	toluene	20%
5	RVC/Pt	NH4I	CH ₃ CN	85%
6	RVC/RVC	$\rm NH_4I$	CH ₃ CN	0%
7	Pt/Pt	NH ₄ I	CH ₃ CN	32%
8	RVC/Pt	NaI	CH ₃ CN	49%
9	RVC/Pt	KI	CH ₃ CN	62%
10	RVC/Pt	<i>n</i> -Bu ₄ NI	CH ₃ CN	81%
11	RVC/Pt	NH ₄ Cl	CH ₃ CN	10%
12	RVC/Pt	$\mathrm{NH}_4\mathrm{Br}$	CH ₃ CN	57%
13 ^c	RVC/Pt	$\rm NH_4 I$	CH ₃ CN	82%
14 ^d	RVC/Pt	NH ₄ I	CH ₃ CN	0

^{a)} Reaction conditions: Reticulated vitreous carbon (RVC) anode (100 PPI, 1 cm \times 1 cm \times 1.2 cm), Pt plate cathode (1 cm \times 1 cm), undivided cell, constant current = 15 mA, **1a** (0.3 mmol, 1 equiv.), **2a** (0.9 mmol, 3 equiv.), NH₄I (15 mol%), solvent (5 mL), under air atmosphere at room temperature for 3.5 h. ^{b)} Isolated yield. ^{c)} NH₄I (20 mol%). ^{d)} Without electricity.

To optimize the reaction conditions, we initially selected 1a with 2a using 15 mol% NH₄I as catalyst and electrolyte containing the solvent of methanol with RVC as anode and platinum as cathode in an undivided cell at a constant current of 15 mA. We isolated the target product 3aa with a yield of 70% (Table 1, Entry 1). Replacement of methanol by other solvents, such as DMSO, DCE, and toluene caused no substantial improvement in the yield. No product was detected with DMSO. Acetonitrile was an excellent solvent for this reaction. The product was obtained with good yield of 85% (Table 1, Entries 2-5). No product was obtained in RVC, which is an anode and cathode at the same time (Table 1, Entry 6). 3aa was isolated in 32% yield in the experiment in which platinum was an anode and cathode (Table 1, Entry 7). **3aa** was obtained in $49\overline{9}$ and 62% yields, respectively, when NH₄I was substituted with NaI and KI (Table 1, Entries 8 and 9). The desired product was isolated in 81% yield when tetrabutyl NH₄I was used as electrolyte (Table 1, Entry 10). NH₄Cl and NH₄Br did not improve the yield of 3aa (Table 1, Entries 11 and 12). The product yield was unremarkably increased by increasing the amount of electrolyte to 20 mol% (Table 1, Entry 13). 3aa was not detected in the absence of electricity (Table 1, Entry 14).

Scheme 2. Phosphorylation of different alcohols^{*a*, *b*}



^{a)}Reaction conditions: RVC anode (100 PPI, 1 cm × 1 cm × 1.2 cm), Pt plate cathode (1 cm × 1 cm), undivided cell, constant current = 15 mA, **1a** (0.3 mmol), alcohols (0.9 mmol), NH₄I (15 mol%), and CH₃CN (5 mL), under air atmosphere at room temperature for 3.5 h. ^{b)}Isolated yield.

We investigated the phosphorylation of various alcohols under the optimized reaction conditions. Ethanol, isopropyl alcohol, and n-propanol were successfully phosphorylated by diphenylphosphinate 1a to afford products 3ab (83% yield), 3ac (82% yield), and **3ad** (80% yield), respectively (Scheme 2). 3-Phenylpropan-1-ol also underwent smooth reaction to provide product **3ae** in 80% yield. Similarly, propargyl alcohol reacted with 1a to provide the required product 3af in 75% yield. Cyclohexanol and substituted cyclohexanol successfully yielded products 3ag (79% yield) and 3ah (69% yield), respectively. Sterically hindered tricyclic and bicyclic alcohols furnished the desired products 3ai (71% yield) and **3aj** (66% yield), respectively. Ethylene glycol was monophophorylated by 1a to form the required product 3ak in 65% yield. The reaction failed to form the corresponding product 3al when compound 1a and phenol were used as the reaction substrates.

Scheme 3. Different phosphorus compounds reacting with $methanol^{a, b}$



^{a)}Reaction conditions: RVC anode (100 PPI, 1 cm \times 1 cm \times 1.2 cm), Pt plate cathode (1 cm \times 1 cm), undivided cell, constant current = 15 mA, **1a** (0.3 mmol), alcohols (0.9 mmol), NH₄I (15 mol%), and CH₃CN (5 mL), under air atmosphere at room temperature for 3.5 h. ^bIsolated yield.

We conducted various reactions to extend the substrate scope of phosphinates. Di-p-tolylphosphine oxide and bis(3,5-dimethylphenyl)phosphine oxide were esterified by methanol under the optimized reaction conditions to obtain products **3ba** (83% yield) and **3ca** (81% yield), respectively (Scheme 3). Similarly, bis(4-methoxy/fluorophenyl)phosphine oxide furnished products **3da** and **3ea** in 81% and 74% yield, respectively. Similarly, di(naphthalen-2-yl)phosphine oxide produced product **3fa** in 79% yield. The reaction with dibutylphosphine oxide was successful in forming the required product in 70%

yield. The generality of the reaction was demonstrated through the phosphorylation of diethyl phosphonate, methyl phenylphosphinate, and 6H-dibenzo[c,e][1,2]oxa-phosphinine 6-oxide, which yielded products in 79%, 48%, and 75% yields, respectively.







We performed the following reactions to clarify the reaction mechanism (Scheme 4). Only a trace amount of 3aa (23% yield) was observed when radical scavenger 2,2,6,6-tetramethylpiperidine Noxyl was added to the reaction. Meanwhile, 2aa was detected by high-resolution electrospray ionization mass spectrometry. Addition of other radical trapping reagents inhibited this reaction (Scheme 4, Eq. 1). The reaction of **1a** with **2a** was conducted b, using I₂ as the oxidant. A small amount of the desired product was observed (Scheme 4, Eq. 2). The reaction between diphenylphosphinyl chloride 6 and alcohol 2a was conducted under room temperature without electricity because of the instability of diphenylphosphinyl iodide. As expected, the desired product **3aa** was obtained with 45% yield (Scheme 4, Eq. 3). These experiments indicated that the reaction involved a partial radical pathway, and diphenyl phosphinyl iodide was a key intermediate for this reaction.



Figure 1. Cyclic voltammograms of reactants and their mixtures in 0.1 M LiClO₄/CH₃CN using a glassy carbondisk working electrode (diameter, 3 mm). Pt disk and

Ag/AgCl as counter and reference electrode, respectively, at 100 mV/s scan rate: (a) background, (b) **1a** (10 mmol/L), (c) **2a** (10 mmol/L), (d) **1a** (10 mmol/L) + NH₄I (2 mmol/L), (e) NH₄I (2 mmol/L), and (f) **1a** (10 mmol/L) + **2a** (10 mmol/L) + NH₄I (2 mmol/L).

We also conducted cyclic voltammograms (CV) experiments and cyclic voltagrams to determine the redox behavior of the reactants and their mixtures (Figure 1). As depicted in Figure 1, substrates 1a and 2a presented no evident oxidation peak in the range of 0.0-1.0 V versus Ag/AgCl (curves b and c) without NH4I. The CV of NH4I manifested two oxidation peaks at 0.45 V and 0.68 V (curve e), which correspond to the oxidation of I^- to I_3^- and $I_3^$ to I₂, respectively.^[12] A similar curve was displayed when **1a** and NH₄I were combined (curve d). Thus, **1a** cannot be oxidized to its corresponding radical. The CV of the mixture of 1a, 2a, and NH_4I demonstrated a remarkable increase in the catalytic current (curve f), which reflects the chemical interaction between the three compounds.



Scheme 5. Proposed mechanism

A possible mechanism is proposed based on the above results and DFT calculations (See supporting information for details), as shown in Scheme 5. At the anode surface, oxidation of iodide provides iodine radical or molecular iodine. The iodine radical can induce diphenylphosphine oxide to yield phosphorus radical 4 with the aid of alcohol, which is confirmed through CV experiments. Subsequently, radical coupling reaction occurs between 4 and iodine radical to afford intermediate 5 (Path A). Meanwhile, iodine cation can directly react with substrate 1 to produce intermediate 5 (Path B). The DFT calculated reaction free energy is exothermic for the two mechanisms, thereby indicating that the mechanisms two are thermodynamically approachable. The free energy barrier of P-H cleavage induced by I. species is much lower than the P-H cleavage process induced by I₂ species (14.4 kcal/mol vs. 37.4 kcal/mol). Therefore, the radical induced nucleophilic substitution mechanism is kinetically favorable. Then, nucleophilic а substitution reaction easily occurs between diphenylphosphinyl iodine 5 and alcohol 2 to provide the final product 3, At the cathode, alcohol 2 undergoes a reduction reaction to liberate alcohol anion and hydrogen, which completes the electrochemical cycle.

In conclusion, we developed a new metal- and oxidant-free electrochemical method for coupling of alcohols with phosphinates in high yields. The presented method exhibits a series of advantages, including excellent functional-group tolerance, high atom economy, and environment-friendly conditions. A reliable mechanism is proposed after control experiments and CV experiments.

Experimental Section

Diaryl(alkyl) phosphine oxides (0.3 mmol, 1.0 equiv) and NH₄I (15 mol%) were placed in 10 mL three-necked round-bottomed flask. The flask was equipped with RVC (100 PPI, 1 cm x 1 cm x 1.2 cm) anode and a platinum plate (1 cm x 1 cm) cathode. MeOH (5.0 mL) were added. Electrolysis was conducted at RT under a constant current of 15 mA until substrate consumption is completed (monitored by TLC, approximate 3.5 h). The reaction mixture was concentrated and the residue was chromatographed through silica gel eluting with ethyl acetate/petroleum ether to give the products.

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Electrochemical dehydrogenative coupling of alcohols with hydrogen phosphoryl compounds: A green protocol for P-O bond formation

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 $\begin{array}{c} O \\ R^{1} P \\ R^{2} + R^{3} - OH \\ R^{1}, R^{2} = Aryl, Alkyl \\ R^{3} = Alkyl \end{array} \xrightarrow{\begin{subarray}{c} 0 \\ RVC \\ RVC \\ Pt \\ evc \\ Pt \\ evc \\ Pt \\ evc \\ Pt \\ evc \\ R^{3} \\ R^{3}$

- Metal- and oxidant-free electrochemical method
- Mild, environmentally friendly conditions
- High atom economy
- 20 examples, 48-85% yields