Letter

Photoinduced Decarboxylative Phosphorothiolation of *N*-Hydroxyphthalimide Esters

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cheap, and commercially available. Scope studies show that this reaction

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has good compatibility of functional groups. Notably, both the synthesis of steric hindrance phosphorothioates and the later modification of some bioactive compounds are successfully achieved.

P hosphorothioates, which contain a phosphorus-sulfur single bond, have been regarded as important compounds in pharmaceuticals and agrochemicals.¹ For example, phosphorothiolate insecticides such as demeton-S and omethoate are widely used in agrochemicals.² As pharmaceuticals, phosphorothioates also serve as potential anticancer agents, antivirals, cardioprotective therapeutics, and the AChE inhibitor echothiopate (Scheme 1, top).³ Moreover, phosphor-



othioates can also service as synthetic intermediates to access complex molecules.⁴ Consequently, the development of efficient methods to access phosphorothioates is an important topic in phosphorus chemistry. Traditional methods are described as follows: (a) The Michaelis–Arbuzov-type reaction, which uses sulfornyl halides or disulfides as substrates, suffers from high temperature, sensitivity of sulfur reagents, and pollution of the environment⁵ as well as the nucleophilic substitution reaction of $(RO)_2P(O)Cl$ with thiols.⁶ However, $(RO)_2P(O)Cl$ is a toxic reagent and is sensitive to moisture. Recently, the transition-metal-catalyzed cross-coupling of

P(O)H compounds with different organic sulfides, which circumvents the use of stoichiometric activation reagents, has emerged as a powerful strategy to access phosphorothioates.⁷ So far, various organic sulfides including sulfonyl chlorides, disulfides, sulfenyl cyanides, and sulfonylhydrazides have been successfully introduced as coupling partners in the phosphorothiolation reactions.⁸ (b) Organic sulfides are sometimes foulsmelling and are not readily available. An ideal approach is the use of cheap and abundant inorganic sulfides as a surrogate. Tang reported a copper-catalyzed phosphorothiolation of aryl boronic acids using elemental sulfur as a sulfur source.^{9a} Later, the phosphorothiolation of $C(sp^3)$ -H and $C(sp^2)$ -H was also successfully achieved by Tang's group using the same strategy.^{9b,c} However, this approach was mainly restricted to S-aryl products. (c) Another synthesis strategy is to develop new phosphorothiolation reagents.¹⁰ So far, the successfully developed phosphorothiolation reagents include phosphorothioic acids, phosphorothiolate salts, O,O-dialkyl-S-(N-phthalimido) phosphorothioate, and dialkyl (2-cyanoethyl)phosphonate, which have enabled the phosphorothiolation of various substrates such as alkyl halides, arylboronic acids, and arenediazonium salts.^{10b} However, most of the phosphorothiolation reagents need to be preprepared. Despite these synthetic methods of important value to S-alkyl thiophosphates, the substrates are mainly limited to organic sulfides and alkyl halides. Thus it is highly desirable to develop readily available and low-toxicity reagents as substrates in alkyl phosphorothiolation reactions.

* readily available materials * tolerant to 3° alkyl * late-stage functionalization

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Aliphatic carboxylic acids are readily available, stable, and low-toxicity reagents. *N*-Hydroxyphthalimide (NHPI) esters, which can be easily synthesized from carboxylic acids, have recently been widely investigated as alkyl radical precursors, which then couple to radical acceptors or nucleophiles.^{11,12} Various nucleophiles such as alcohols, amines, and B₂Pin₂ have been successfully introduced in the decarboxylative reaction.¹³ With our ongoing interest in organic phosphor chemistry,¹⁴ we envisioned that P(O)SH might serves as a nucleophile in the decarboxylative coupling reaction, which could provide a method for accessing phosphorothioates. Herein we disclose a photoredox-catalyzed phosphorothiolation of NHPI esters via the decarboxylative reaction.

To validate our concept, cyclohexyl NHPI ester (1a) and $(EtO)_2P(O)SH$ (2a) were chosen as model substrates (Table 1). When using 2 mol % $Ir(ppy)_3$ as a photocatalyst and 2

Table 1. Optimization of Conditions^a

\sim	N-O O O O O O O O O O O O O O	photocatalyst Base Solvent, N ₂ , Blue LEDs		EtO P S
"				
	1a 2a			3a
entry	photocatalyst	base	solvent	yield (%) ^b
1	Ir(ppy) ₃	K ₂ CO ₃	CH ₃ CN	17
2	4CzIPN	K ₂ CO ₃	CH ₃ CN	10
3	Ir(ppy) ₂ (dtbbpy)PF ₆	K ₂ CO ₃	CH ₃ CN	25
4	Eosin Y	K ₂ CO ₃	CH ₃ CN	0
5	Rose Bengal	K ₂ CO ₃	CH ₃ CN	0
6	Ir(ppy) ₂ (dtbbpy)PF ₆	Et ₃ N	CH ₃ CN	trace
7	Ir(ppy) ₂ (dtbbpy)PF ₆	DBU	CH ₃ CN	trace
8	Ir(ppy) ₂ (dtbbpy)PF ₆	Et_2NH	CH ₃ CN	57
9	Ir(ppy) ₂ (dtbbpy)PF ₆	KHF ₂	CH ₃ CN	77
10	Ir(ppy) ₂ (dtbbpy)PF ₆	NaOH	CH ₃ CN	36
11	Ir(ppy) ₂ (dtbbpy)PF ₆	NaOAc	CH ₃ CN	44
12	Ir(ppy) ₂ (dtbbpy)PF ₆	K_3PO_4	CH ₃ CN	34
13	Ir(ppy) ₂ (dtbbpy)PF ₆	KHF ₂	DMF	trace
14	Ir(ppy) ₂ (dtbbpy)PF ₆	KHF ₂	DMSO	29
15	Ir(ppy) ₂ (dtbbpy)PF ₆	KHF ₂	toluene	17
16		KHF ₂	CH ₃ CN	NR
17	Ir(ppy) ₂ (dtbbpy)PF ₆		CH ₃ CN	NR
18 ^c	Ir(ppy) ₂ (dtbbpy)PF ₆	KHF ₂	CH ₃ CN	NR
-			,	

^aReaction conditions: **1a** (0.2 mmol), **2a** (2 equiv, 0.4 mmol) photocatalyst (1 mol %, 0.002 mmol), base (2 equiv, 0.4 mmol), solvent (2 mL) at room temperature, 5 W blue LEDs, 12 h in N_2 . ^bIsolated yield. ^cWithout light.

equiv of K_2CO_3 as base in CH₃CN under visible light, **3a** was formed in 17% yield (entry 1). A screening of photocatalysts, such as 4CzIPN, Eosin Y, and Rose Bengal, indicated that $Ir(ppy)_2(dtbbpy)PF_6$ was the best photocatalyst, yielding **3a** in 30% yield (entries 2–5). Subsequently, a variety of bases were tested, and the results showed that the yield was significantly affected. Most organic bases except Et₂NH resulted in only a trace amount of **3a** (entries 6–8). Among the inorganic bases investigated, KHF₂ provided the best result (entries 9–12). Several solvents such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and toluene were also screened; however, they were all less efficient than CH₃CN (entries 13–15). Finally, a series of controlled experiments suggested that visible light, the photocatalyst, and the base were all equally crucial for this reaction (entries 16–18). Having identified the optimal reaction conditions for this decarboxylative phosphorothiolation reaction, the scope of alkyl carboxylic acid was investigated (Scheme 2). First, various

Scheme 2. Substrate Scope for Primary and Secondary Acids^a



^{*a*}Reaction conditions: **1** (0.2 mmol), **2** (2 equiv, 0.4 mmol), [Ir(ppy)₂(dtbbpy)]PF₆ (1 mol %, 0.002 mmol), KHF₂ (2 equiv, 0.4 mmol), CH₃CN (2 mL) at room temperature, 5 W blue LEDs, 12 h in N₂. ^{*b*}**1**a (1 mmol), **2** (2 equiv, 2 mmol), [Ir(ppy)₂(dtbbpy)]PF₆ (1 mol %, 0.01 mmol), KHF₂ (2 equiv, 2 mmol), CH₃CN (5 mL) at room temperature, 5 W blue LEDs, 24 h in N₂.

carboxylic acids, for instance, primary, secondary, and tertiary acids, were all compatible in this decarboxylative reaction, and the yields were moderate to good. Primary carboxylic acids, including a benzylic substrate (1b-1f) with different substituents such as electron-neutral (1b-1d) and electronrich substituents (1e) at the para position of the aromatic rings, all smoothly furnished the desired organothiophosphates (3b-3e). For disubstituted aromatic rings (1f), the corresponding products 3f were procured in 67% yield. A wide range of functional groups were also evaluated. For example, heterocycles such as thiophene, alkanes, terminal alkynes, esters, heteroatoms, and adamantane with high steric hindrance all proved to be compatible under the standard reaction conditions (3g-3m). NHPI ester prepared from trans-3-hexenoic acid, which contains C=C bonds, could not afforded the desired product. Next, we studied secondary carboxylic acids. Cyclic acids, including three-membered, fourmembered, five-membered, and six-membered cyclic carboxylic acid, fluorinated alkyl carboxylic acid, and acyclic alkyl, were all converted to the corresponding S-aryl products in moderate yields (3n-3s). Interestingly, other alkoxy-substituted phosphorothioic acids such as dimethyl (2b), diisopropyl phosphorothioic acid (2c), and O-ethyl S-hydrogen phenylphosphorothioic acid (2d) were also suitable coupling partners for the decarboxylative reaction, which delivered 3u-3w in 52

to 71% yield. However, no desired product was observed with diphenylphosphinothioic S-acid as a substrate.

For tertiary carboxylic acids (Scheme 3), acyclic tertiary aliphatic acid esters were also suitable reaction substrates,

Scheme 3. Substrate Scope for Tertiary Acids and Complex Molecules



"Reaction conditions: 1 (0.2 mmol), 2 (2 equiv, 0.4 mmol), $[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol %, 0.002 mmol), KHF₂ (2 equiv, 0.4 mmol), CH₃CN (2 mL) at room temperature, 5 W blue LEDs, 12 h in N₂

generating 4a-4d in moderate to excellent yield. In particular, tertiary carboxylic acids in which the three carbon atoms were tied back into a ring structure, for example, bicyclo[2.2.2]-octane carboxylic acid, produced the corresponding products, respectively, with good efficiency (4d). The above results indicate that phosphorothioates with a large steric hindrance can also be readily synthesized by our method, which were difficult to synthesize via traditional nucleophilic substitution methods. Some bioactive compounds and drug molecules were evaluated to extend the substrates scope. For example, lauric acid, which is a long-chain carboxylic acid, was readily converted to the corresponding organothiophosphates 4e in 73% yield. Moreover, drug compounds, such as flurbiprofen and (S)-(+)-ibuprofen, were all smoothly incorporated into the final organothiophosphate derivatives (4f, 4g).

Several control experiments were carried out to indicate the mechanism of this decarboxylative phosphorothiolation reaction. As shown in Scheme 4, the reaction was completely suppressed in the presence of radical scavengers such as TEMPO or butylated hydroxytoluene (BHT) (Scheme 4, eq 1). When 1,1-Diphenylethylene was added, the reaction was also completely suppressed, and the radical trapping product 5

Scheme 4. Mechanistic Experiments



could be detected (Scheme 4, eq 2). The above results revealed a radical strategy in this photoredox reaction.

On the basis of control experiments and previous reports, a plausible catalytic cycle mechanism is proposed in Scheme 5.^{11–15} The visible-light-excited photocatalyst $Ir(III)^*$ under-

Scheme 5. Proposed Mechanism



goes single-electron transfer (SET) to NHPI ester 1 to form radical anion A, which then gives alkyl radical B by decarboxylation and a phthalimide anion. The coupling of alkyl radical B to sulfur anion C affords intermediate D. Finally, the Ir(IV) species is reduced by D to regenerate the Ir(III) catalyst to complete the catalytic cycle.

In conclusion, we have demonstrated a visible-light-induced photoredox-neutral decarboxylative phosphorothiolation reaction. In addition to primary, secondary, and tertiary carboxylic acids, structurally complicated natural products were all compatible with the reaction. This method provides a mild and straightforward entry to organothiophosphates from readily available alkyl carboxylic acids. The mild photocatalyst reaction not only broadens the substances scope but also provides a new synthesis strategy for accessing phosphorothioates. Considering the importance of phosphorothioates, a mechanism study and new radical phosphorothiolation reactions are currently under way in our laboratory.

ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02300.

General experimental procedures and spectroscopic data for the corresponding products (PDF)

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Notes

The authors declare no competing financial interest.

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