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Catalyst- and oxidant- free coupling of disulfides with H-phosphine oxide: construction of P-S bond leading to thiophosphinates

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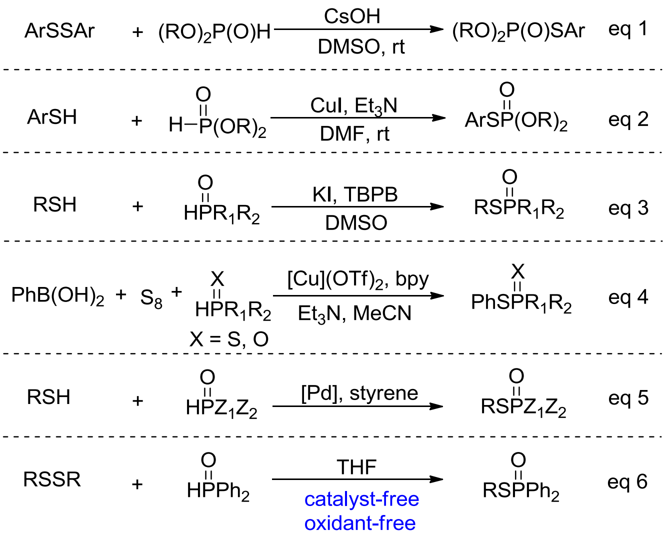
ABSTRACT

An efficient protocol for the synthesis of thiophosphinates is presented, involving direct coupling of P-S bond between disulfides and H-phosphine oxide in moderate to good yields with good functional group compatibility. This procedure shows some advantages: 1) catalyst- and oxidant- free; 2) high efficiency with operational simplicity.

Over the past decades, organophosphorus-sulfur compounds have attracted increasing attention because of their promising bioactivities,[1] as well as significant properties in crop protection.[2] Additionally, they served as important phosphoryl transfer reagents,[3] and key intermediates in synthetic organic chemistry.[4] Thus, numerous methodologies have been developed to construct such frameworks. For example, in 2013, Xu and coworkers reported a cesium hydroxide-catalyzed synthesis of *S*-arylphosphorothioates (Scheme 1, eq 1).[5] Afterwards, Yokomatsu developed the preparation of thiophosphates from benzenethiols catalyzed by copper (Scheme 1, eq 2).[6] Pan demonstrated an efficient method for the direct coupling of thiol/thiophenol with H-phosphine oxides or H-phosphinate esters, where no metallic catalyst was required (Scheme 1, eq 3).[7] Recently, Tang achieved a multicomponent reaction employing aryl boronic acids, elemental sulfur, and P(O)H compounds, leading to *S*-aryl phosphorothioates (Scheme 1, eq 4).[8] Very recently, a Pd-catalyzed dehydrogenative phosphorylation of thiols was developed by Han, which provided a general route to access valuable phosphorothioates including the *P*-chiral phosphorus compounds (Scheme 1, eq 5).[9]

However, most cases resulted in the formation of disulfides by-products by self-coupling of thiols, where large amount of thiols was required. In addition, the binding to metal of organic sulfur compounds may cause the deactivation of catalyst.[10] Herein, we wish to report the coupling of disulfides with H-phosphine oxide, where neither catalyst nor oxidant is required (Scheme 1, eq 6).



Scheme 1 Examples for the synthesis of thiophosphates

We commenced our study with the reaction of diphenylphosphine oxide **1** and diphenyl sulfide **2a** in the presence of AgOAc at 80 °C under N_2 for 4 h. To our delight, the desired product **3a** was isolated in 45% yield (Table 1, entry 1). The subsequent blank experiment without AgOAc afforded **3a** with a relatively high yield (77%, Table 1, entry 2), revealing silver was not required in this transformation at all. Afterwards, we screened a wide range of the solvents, such as benzene,

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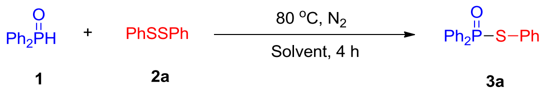
CH_3CN, *n*-hexane, diglyme, THF and 1,4-dioxane (Table 1, entries 3-8). Among them, THF was the best choice and the yield increased to 95% (Table 1, entry 7). Decreasing or increasing reaction temperature had no positive effect on the reaction efficiency (Table 1, entries 9-11). Further screening of reaction atmosphere (Table 1, entry 12) established the optimized condition as follows: diphenylphosphine oxide **1** (0.2 mmol) and diphenyl sulfide **2a** (0.2 mmol) in THF (2.0 mL) at 80 °C under N_2 for 4 h.

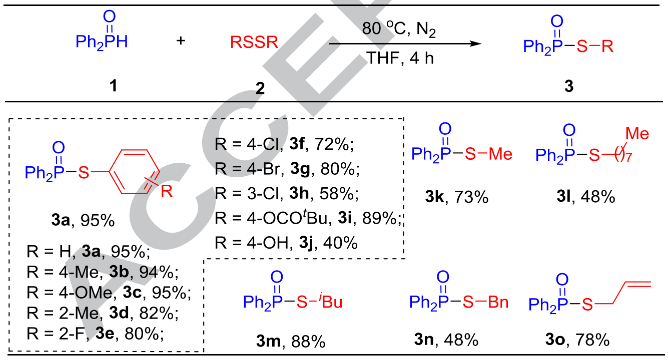
Table 1. The optimization of reaction conditions.[a]



entry	Catalyst	T/℃	Solvent	yield[b] (%)
1	AgOAc	80	DMSO	45[c]
2	--	80	DMSO	77
3	--	80	benzene	83
4	--	80	CH_3CN	93
5	--	80	*n*-hexane	91
6	--	80	diglyme	75
7	--	**80**	**THF**	**95**
8	--	80	1,4-dioxane	93
9	--	60	THF	72
10	--	70	THF	89
11	--	90	THF	93
12	--	80	THF	78[d],63[e]

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.2 mmol), solvent (2 mL), at 80 °C under N_2 for 4 h in a sealed tube. [b] Isolated yield. [c] Silver (0.02 mmol). [d] Under air. [e] Under O_2.

Fig 1 Thiolation of diphenylphosphine oxide with disulfides[a]

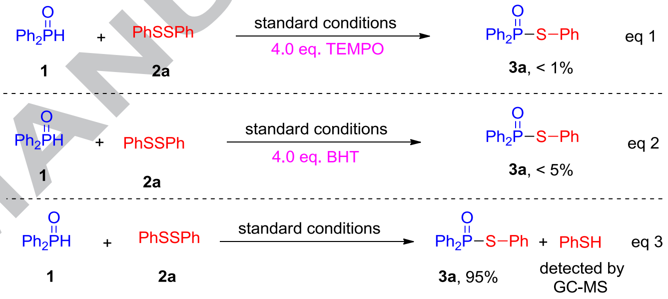


[a] Reaction conditions: diphenylphosphine oxide **1** (0.2 mmol) and diaryl sulfide **2** (0.2 mmol) in THF (2.0 mL) at 80 °C under N_2 for 4 h.

Now that the optimal reaction conditions had been identified, this approach was then applied to the coupling of diphenylphosphine oxide towards a series of disulfides (Shown in Fig 1). Generally, this procedure was not sensitive to the electronic effects as both electron-donating and electron-withdrawing groups substituted on the phenyl rings of diaryl disulfides could be all tolerated well, generating the corresponding products in moderate to good yields (Fig 1, **3b-3i**). Notably, the tolerance of fluoro, chloro and bromo provides potential handles for further functionalizations (Fig 1, **3e-3h**). To our delight, although the sensitive group OH was not compatible in many reports,[5,6,7,11] it did work under our process, which generated the corresponding product **3j** in 40% yields.

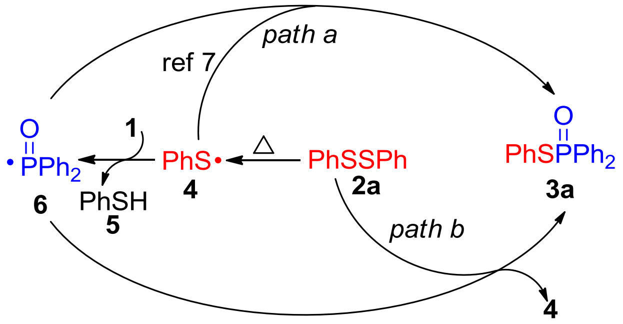
Meanwhile, dialkyl sulfides were examined to extend the application scope. Once again, dimethyl disulfide, dioctyl disulfide, diisobutyl disulfide and dibenzyl disulfide all worked smoothly, and delivered the corresponding products with yields ranging from 48-88% (**3k-3n**). Particularly, the product *S*-allyl diphenylphosphinothioate was generated in 48% yield (**3o**), which further extended the substrate scope. Unfortunately, when diethyl phosphite was used, no desired product was formed.

To investigate the mechanism of this transform, more experiments were carried out. Experiments in the presence of the radical-trapping reagents, such as 2,2,6,6-tetramethylpiperidinooxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT), were carried out under standard conditions (Scheme 2, eqs 1 & 2). The formation of product **3a** was suppressed. This phenomenon along with an important fact that thiophenol was detected by GC-MS in the standard procedure (Scheme 2, eq 3) indicated the transformation may proceed via a radical pathway.



Scheme 2. Preliminary Mechanism Study

Initially, thiophenyl radical **4** was generated from phenyl disulfide **2a** by homolytic cleavage. Subsequently, the radical **4** abstracted a hydrogen atom from diphenylphosphine oxide **1**, affording thiophenol **5** and radical **6**. Then the coupling of radicals **4** and **6** furnished the construction of thiophosphinate **3a** (*path a*). Alternatively, *path b* may be involved where the attack of **6** to **2a** to afford product **3a** and release of another radical **4** simultaneously.



Scheme 3 Proposed Mechanism

In conclusion, we have developed an efficient strategy for the synthesis of thiophosphinates via direct coupling of P-S bond between disulfides and H-phosphine oxide in moderate to good yields with good functional group compatibility. This procedure f shows some advantages: 1) catalyst- and oxidant-free; 2) high efficiency with operational simplicity.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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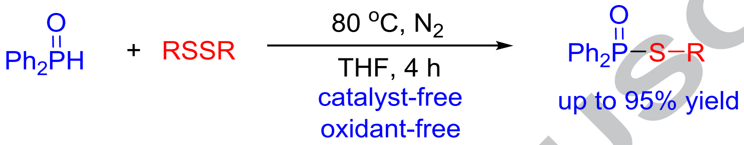

Highlights

1. Neither catalyst nor oxidant was required in this procedure.
2. This strategy features high efficiency with operational simplicity.
3. Silver was not required in this transformation at all.