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# Clean and green reactions of disulfides with DTSP generating thiophosphates under neat reaction condition

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Abstract: An efficient protocol for the synthesis of thiophosphates is described. Without using any metallic catalyst, base and solvent, the direct sulfur-phosphorus bond coupling reaction of disulfides and dialkyl trimethylsilyl phosphite (DTSP) was promoted under neat reaction condition in moderate to excellent yields with good functional group compatibility. The reaction condition is superior to other methods not only in predigesting process but also in shortening the reaction time apparently. Notably, these transformations are easy to conduct and can be readily applied to gram-scale preparation.

The S-P bond forming reaction is immensely valuable and has always been the unremitting pursuit in the field of medicine synthesis due to the widely application of thiophosphates in many therapeutic agents.<sup>[1]</sup> Apart from these applications, thiophosphates are also known as pesticides in agrochemistry (Scheme 1A).<sup>[2]</sup>

Consequently, thiophosphates are of enormous interests and numerous methodologies have been developed to construct the S-P(O) frameworks. Traditional methods for the preparation of thiophosphates are often based on nucleophilic substitution using RSX or R<sub>2</sub>P(O)X, which suffers drawbacks such as tedious procedures, low yields and lack of functionality tolerance.<sup>[3,5e]</sup> In 2013, Kaboudin and co-workers have found that copper(I) iodide catalyzed coupling of H-phosphine oxides/H-phosphonates with thiols proceeds effectively in the presence of triethylamine (Scheme 1B).<sup>[4]</sup> Afterwards, Nchlorosuccinimide or peroxide-mediated reactions have been successfully applied to activate thiols for S-P(O) bond formation, but these approaches are only suitable for highly active diphenylphosphine oxides (Scheme 1C).<sup>[5]</sup> Recently, Han and co-workers reported an efficient Pd-catalyzed dehydrogenative phosphorylation of the readily available P(O)H compounds with thiols to produce phosphorothioates in high yields while stoichiometric amounts of styrene and high reaction temperature were required for this coupling reaction (Scheme 1D).<sup>[6]</sup> In 2017, Jiao and co-workers presented the first example of direct oxidative cross-coupling of thiols with P(O)H compounds for the construction of S-P(O) bonds via Cs<sub>2</sub>CO<sub>3</sub> catalysis to produce phosphorothioate derivatives at 30°C under O2 atmosphere (Scheme 1E).<sup>[7]</sup> Furthermore, impressive results were obtained by using N-heterocyclic carbenes (NHCs) as organocatalyst to promote the challenging reactions in dry toluene (Scheme 1F).<sup>[8]</sup> As these strategies for S-P(O) bond formation require expensive

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transition metal catalysts, unstable carbene organocatalysts, oxidants, and/or longer reaction time, an alternative strategy to generate thiophosphates via a simple and environmentally benign protocol is still in great demand.

A) Thiophosphates in therapeutic molecules and thiophosphates



B) Cu(I)-catalyzed coupling of H-phossphonates with benzenethiols (2013)







D) Pd-catalyzed CDC reactions of P-S bond construction. (2016)

$$\begin{array}{cccc} R^{1}O & & \\ R^{2}O' & H & H-SR & \xrightarrow{Pd_{2}dba_{3}/P \text{ ligand}} & R^{1}O & \\ & \\ styrene, 100 \ ^{\circ}C, 20h & R^{2}O' & \\ \end{array}$$

E) Cs<sub>2</sub>CO<sub>3</sub>-catalyzed aerobic CDC reaction of P-H and S-H bonds. (2017)

F) N-heterocyclic carbenes (NHCs) as organocatalysts to promote phosphorylation reactions of disulfides. (2017)

$$\begin{array}{ccc} R^{10} & & \\ R^{20} & P & \\ \end{array} \begin{array}{c} & & \\ & & \\ \end{array} \begin{array}{c} & & \\ & & \\ & & \\ \end{array} \begin{array}{c} & & \\ & & \\ & & \\ \end{array} \begin{array}{c} & & \\ \end{array} \begin{array}{c} & & \\ & & \\ \end{array} \begin{array}{c} & & \\ \end{array} \end{array}{\begin{array}{c} & & \\ \end{array} \begin{array}{c} & & \\ \end{array} \end{array}{c} \end{array} \end{array}$$
{c} \end{array} \end{array}{c} \end{array} \end{array} \end{array} \\{c} \end{array} \end{array}{c} \end{array} \end{array} \\{c} \end{array} \end{array}{c} \end{array} \end{array}



$$R^{S}S^{R} + P^{O}OR^{1}$$
 neat  $R^{S}P^{O}OR^{1}$   
TMS-O' rt, 2-5min  $R^{10}OR^{1}OR^{10}OR^{10}$ 

 $\sqrt{}$  neat condition:metal-, oxidant-, halogen-, solvent-free  $\sqrt{}$  mild reaction conditions, broad scope, excellent yield quickly reaction, gram-scale preparation

Scheme 1. Application and strategies for the preparation of phosphinothioates.

In this context, we are interested in developing a convenient and "greener" protocol for S-P(O) bond formation. This new strategy, without using any catalyst, oxidants and even solvents in the reaction, has excellent yields. It is superior to other traditional approaches not only in its green and predigesting process but also in its much shortened reaction time.

As we all know, disulfides are important sulfur source in building P-S bonds, which have been proved to be more stable and have less odor in comparison with thiols. Under this background, we conducted a coupling reaction of 1,2-di-pchlorodisulfide 1a with diethyl trimethylsilyl phosphite 2a. To our delight, the initial investigations revealed that 1a and 2a reacted smoothly to afford the desired product 3a in MeCN at room temperature without using any oxidants or metals or bases under an air atmosphere for 20 min (Table 1, entries 1-3). A very high yield (92%) of thiophosphinate 3a was produced when 2.0 equiv of 2a was employed (Table 1, entry 4). The use of dichloromethane, acetone, ethyl acetate, N.Ndimethylformamide and diethyl ether as a solvent was similarly effective (87-90%, Table 1, entries 5-7, 10 and 14). The S-P(O) bond coupling reaction also proceeded in THF, DMSO and 1,4dioxane (Table 1, entries 9, 12-13). However, the reaction did not proceed well in toluene even the reaction time was prolonged (Table 1, entry 11).

Green chemistry is a set of principles and practices that aim to reduce the use of hazardous materials in chemical products and processes. The concept of neat reaction is now widely adopted to meet the scientific challenges of protecting environment while simultaneously achieving commercial viability. The trend in the field is oriented to explore alternative reaction conditions and reaction media to accomplish the desired chemical transformations with minimum waste generation, as well as to eliminate the use of conventional organic solvents.<sup>[9]</sup> Much to our delight, the targeted product 3a was obtained in 95% yield without any solvent under neat reaction conditions (Table 1, entry 15). The yield of 3a did not improve significantly when the reaction was run for 5 min (Table 1, entry 16). The result shows that the neat reaction condition is superior to other different solvents not only in predigesting process but also in shortening the reaction time apparently (Fig. 1). Herein, we demonstrate the first example of a neat reaction of disulfides with dialkyl trimethylsilyl phosphite to produce thiophosphinates. Without using any metals or bases or oxidants, thiophosphates can be obtained in excellent yields.

Table 1. Optimization of the reaction conditions.[a]

ci—	Ś-√_−ci ⁺	EtO P-OEt - TMS-O	Solvent	EtO OEt
1a	1	2a		3a
Entry	1a:2a (equiv.)	Solvent	Time (min)	Yield (%) <sup>b</sup>
1	1:1.0	MeCN	60	80
2	1:1.2	MeCN	30	85
3	1:1.5	MeCN	20	89
4	1:2.0	MeCN	20	92
5	1:2.0	DCM	20	90
6	1:2.0	acetone	20	87
7	1:2.0	EA	20	90

8	1:2.0	MeOH	60	trace
9	1:1.0	THE	40	80
10	1:1.2	DMF	30	90
11	1:1.5	toluene	60	NR
12	1:2.0	DMSO	40	81
13	1:2.0	dioxane	60	66
14	1:2.0	Diethyl ether	20	87
15	1:2.0	1	2	95
16	1:2.0	1	5	96

[a] Reaction conditions: 0.5 mmol 1,2-di-p-chlorodisulfide (**1a**), 1.0 mmol diethyl trimethylsilyl phosphite (**2a**), [b]  ${}^{31}$ P NMR yield using triphenylphosphine as an internal standard. NR = no reaction.



Figure 1. Variation of isolated yield of thiophosphates with change in neat condition and different solvents. Conditions: 0.5 mmol 1,2-di-p-chlorodisulfide (1a), 1.0 mmol diethyl trimethylsilyl phosphite (2a).

After optimizing the reaction conditions with disulfides (1a) and commercially available diethyl trimethylsilyl phosphite (2a) as model system. We also explored several other substituted silylphosphites in this reaction. These reagents were either commercially available or readily synthesized in one step by the silylation of the corresponding phosphonates with TMSCI (trimethylsilyl chloride) in the presence of  $Et_3N$ .<sup>[10, 12]</sup> Efficient product formation was also observed by applying dimethoxyl (trimethyl)silyl phosphite (Table 2, entry 1) and chloromethylsubstitutde silvl phosphite (Table 2, entry 2), furnishing the corresponding thiophosphate 3x in an excellent yield. Substituents on the phosphite nucleophiles did not lead to an obvious difference in reactivity. Other alkyl like triethyltriisopropyl, and chloromethyl-substituted phosphites (2d-2g) also survived, facilitating further functionalization of the products (3a). Strikingly, a benzene ring derivative was also phosphorylated in 95% yield under the optimized reaction con ditions (2h). Isopropyl-substituted phosphite 2i was also proved to be a good substrate (Table 2, entry 8). Interestingly, silylphosphites bearing two nonidentical alkoxy and phenyl sub-

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Table 2. Phosphite scope of the coupling reaction.<sup>[a]</sup>

Scheme 2. Scope of the coupling reactions.[a]





[a] Reaction conditions: 0.5 mmol 1,2-di-p-chlorodisulfide (1a), 1.0 mmol silylphosphites (2), [b] Yields of isolated products are given.

stituents were also investigated (Table 2, entries 9). Notably, dialkyl(trimethyl)silyl phosphite furnished the desired product in good yields (Table 2, entries 10).

With the optimized reaction conditions in hand, the scope of the reaction was studied, various disulfides (1) were first tested with diethyl trimethylsilyl phosphite (2a) as the reaction partner to produce the corresponding thiophosphates (3) in good to excellent yields (Scheme 2). Electronic effects on the aryl thiols did lead to a less obvious difference in reactivity, diaryl disulfides with methyl, methoxyl and *tert*-butyl substituent at the *para*, *meta*- and *ortho*- position of the aromatic ring all furnished the

desired thiophosphates in good yields (see 3c, 3d, 3g, 3r and 3w), but the substrates with electron-withdrawing groups like cyano coupled less readily with diethyl trimethylsilyl phosphite, generating the coupling products in reduced yield (3k). Halogens like chloro-, fluoro- and bromo- groups were well tolerated (see 3a, 3e-f and 3u). To our delight, sensitive groups, such as free amine and hydroxyl, were well persevered under oxidative conditions and gave good yields (see 3I and 3m). Besides, functionalities including amide, ester, ketone, olefin and sulfonyl groups also gave excellent yields (see 3i-3j, 3n, 3p, 3s and 3t). However, naphthalene-2-disulfide and benzyl disulfide were proved to have lower yields (see 3h and 3v). Meanwhile, the ortho- substituted substituent (3t) revealed less reactivity when compared with their para- analogs (3j). Strikingly, a benzyloxygroup derivative was also phosphorylated in 90% yield under the optimized reaction conditions (3q). In addition, the disulfide scope of the coupling reactions was not limited to the phenyl disulfides with same substituents (Scheme 2A), instead, the heteroaryl disulfides (see 3ac, 3ad and 3ae) and different substituents (see 3af and 3ag) could also be coupled with diethyl trimethylsilyl phosphite to afford the corresponding thiophosphates in moderate to excellent yields (Scheme 2B).



Scheme 4. Gram-scale reaction.

Subsequently, to illustrate the practical synthetic utility of our methodology, a scale-up reaction was conducted to demonstrate the utility of ultrasound promoted P-S bonds coupling reaction. As shown in Scheme 4, under the standard conditions, 2.80 g (10.0 mmol) of **1a** could be converted to **3a** in 90% yield.



Based on the experimental results and previously reported works,<sup>[13]</sup> the proposed mechanism of the synthesis of thiophosphates derivatives was outlined in Scheme 5. Initially, the dialkyl trimethylsilyl phosphite (2) was coordinated to the disulfide (1) to generate S-P intermediate 2'. Subsequently, 2' was attacked by the nucleophile formed by disulfide to provide the corresponding thiophosphate 3.

In summary, we have established a very green and simple methodology for coupling reactions between disulfides and diethyl trimethylsilyl phosphite under neat reaction condition. Different substituted silylphosphites and disulfides have been utilized in this study, providing a clean and effective access to functionalized thiophosphates. Without using any oxidants, metals or bases, thiophosphates, which are widely present in agrochemicals and therapeutic molecules, can be obtained in good to excellent yields under mild conditions and much shorter reaction time. The transformation is easy to conduct and can be scaled-up with good functional group tolerability. This strategy would therefore of great interest in medicinal chemistry and organic chemistry. Further investigation of this method will focus on the detailed mechanism and applications in organic synthesis.

#### **Experimental Section**

General information

Unless otherwise indicated, all reactions were performed under air atmosphere in glass tube equipped with a magnetic stir bar. Solvents were purified and dried according to standard methods prior to use. All the reactions were monitored by thin-layer chromatography (TLC) and visualization was accomplished with UV light. The products were purified by flash column chromatography on silica gel (100-200 meshes). All new compounds were characterized by NMR spectroscopy, high resolution mass spectroscopy (HRMS), and melting point (if solids). Proton and carbon nuclear magnetic resonance spectra (<sup>1</sup>H NMR and <sup>13</sup>C NMR) were recorded on a Varian INOVA-400/54, Agilent DD2-600/54 in CDCl3 with TMS as the internal standard (1H NMR: TMS at 0.00ppm, CHCl3 at 7.260 ppm; <sup>13</sup>C NMR: CDCI<sub>3</sub> at 77.16 ppm) and 31P NMR spectra were obtained by using the same NMR spectrometers and data were relative to H<sub>3</sub>PO<sub>4</sub> (85% solution in D<sub>2</sub>O, 0 ppm). Coupling constants are given in Hz. Chemical shifts ( $\delta$ ) were reported as parts per million (ppm) downfield from tetramethylsilane and the following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q =quartet, m = multiplet, br = broad and all combinations thereof can be explained by their integral parts. HRMS spectra were recorded on a Waters Q-TOF Premier. Melting points (m.p.) were recorded on an INESA SGW X-4 melting point apparatus. Commercial reagents from Adamas Reagent Co., Ltd., Best Reagent, Astatech Chemical Technology Co., Ltd. and etc were used without further purification. Highresolution mass spectra were recorded using the EI method with a double focusing magnetic mass analyzer. Unless otherwise noted, the yields of products reported were all isolated yields.

General procedure for the coupling of disulfides with silyl phosphites

An oven-dried sealed tube equipped with a magnetic stir bar was charged with 1,2-bis(4-chlorophenyl)disulfane (0.5 mmol, 1.0 equiv.) and diethyl (trimethylsilyl) phosphite (1.0mmol, 2.0 equiv.) under an air atmosphere. The resulting mixture was vigorously stirred at room temperature for 2 min. After this time, the crude product was further purified by column chromatography on silica gel to afford desired product.

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#### **Conflicts of interest**

There are no conflicts to declare.

**Keywords:** S-P bond coupling • neat reaction • thiophosphates • disulfides • dialkyl trimethylsilyl phosphite

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# COMMUNICATION



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Clean and green reactions of disulfides with DTSP generating thiophosphates under neat reaction condition

An efficient protocol for the synthesis of thiophosphates is described. Without using any metallic catalyst, base and solvent, the direct sulfur-phosphorus bond coupling reaction of disulfides and dialkyl trimethylsilyl phosphite (DTSP) was promoted under neat reaction condition in moderate to excellent yields with good functional group compatibility. The reaction condition is superior to other methods not only in predigesting process but also in shortening the reaction time apparently. Notably, these transformations are easy to conduct and can be readily applied to gram-scale preparation.