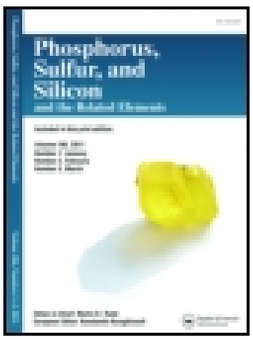

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Trichloroisocyanuric acid-promoted thiolation of phosphites by thiols

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ABSTRACT

A simple and convenient method for the synthesis of thiophosphates by coupling of phosphites with thiols under mild conditions has been developed. The reactions were promoted by trichloroisocyanuric acid (TCCA) and were carried out at room temperature in a one-pot two-step procedure within 20 min. A variety of substrates was tolerated in this method. Notably, both aryl and alkyl thiols could afford the corresponding thiophosphates in good yields.

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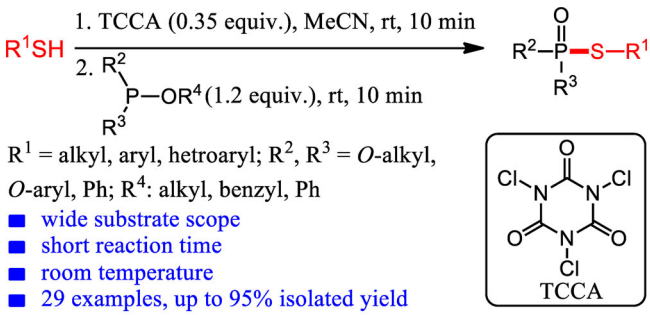
Trichloroisocyanuric acid; S – P bond formation; phosphites; thiols

GRAPHICAL ABSTRACT



Introduction

Thiophosphates are important intermediates in the areas of organic synthesis, agricultural and medicinal chemistry because of their unique chemical and biological properties.[1–12] Accordingly, the development of efficient, convenient and environmentally friendly methods to synthesize thiophosphates has gained much attention.

Traditional synthesis work of this class of compounds proceeded via the reaction between thiols and phosphorochloridates or phosphorobromidates. However phosphorochloridates and phosphorobromidates were usually prepared from H-phosphonates and halogen which were toxic and difficult to control.[13–15] In recent years, the cross-dehydrogenative coupling (CDC) between H-phosphonates and thiols to synthesize thiophosphates was gradually developed.[16–26] The CDC reaction was also applied to the synthesis of thiophosphinates from H-phosphine oxides/silyl phosphites and thiols/disulfides.[18,22–24,26–33] In 2013, Kaboudin's group reported a CuI-catalyzed coupling of thiols with H-phosphonates in the presence of triethylamine (Scheme 1(a)). In their research, only benzenethiols were tested.[16] In 2014, a simple N-chlorosuccinimide-promoted synthesis of thiophosphates through the coupling of thiols and H-phosphonates was reported by Lee *et al.* Both aryl and alkyl thiols could react with a broad spectrum of H-phosphonates successfully (Scheme 1(b)).[17] A Pd-catalyzed CDC of thiols and P(O)-H compounds, including H-phosphonates, H-phosphinates and H-phosphine oxides, was developed by Han *et al* in 2016 (Scheme 1(c)).[18] In addition, an efficient Cs_2CO_3-catalyzed oxidative coupling of thiols with H-phosphonates was proposed by Jiao's group (Scheme 1(d)).[22] H-phosphonates could also couple with disulfides to form thiophosphates with N-heterocyclic carbenes (NHCs) as an organocatalyst.[34]

Comparing with H-phosphonates, phosphites are relatively inexpensive and readily available.[35–40] In Michaelis-Arbuzov and modified Michaelis-Arbuzov reactions, phosphites were usually used as the raw materials to react with halides to prepare phosphonates.[41–50] Watanabe's group reported thiophosphates could be prepared by the treatment of phosphites with thiols in the presence of tellurium(IV) chloride in a redox-type reaction (Scheme 1(e)).[51] It was reported that thiophosphates could also be produced via the elimination of an alcohol between phosphites and thiols (Scheme 1(f)).[52] Unfortunately, this method was not

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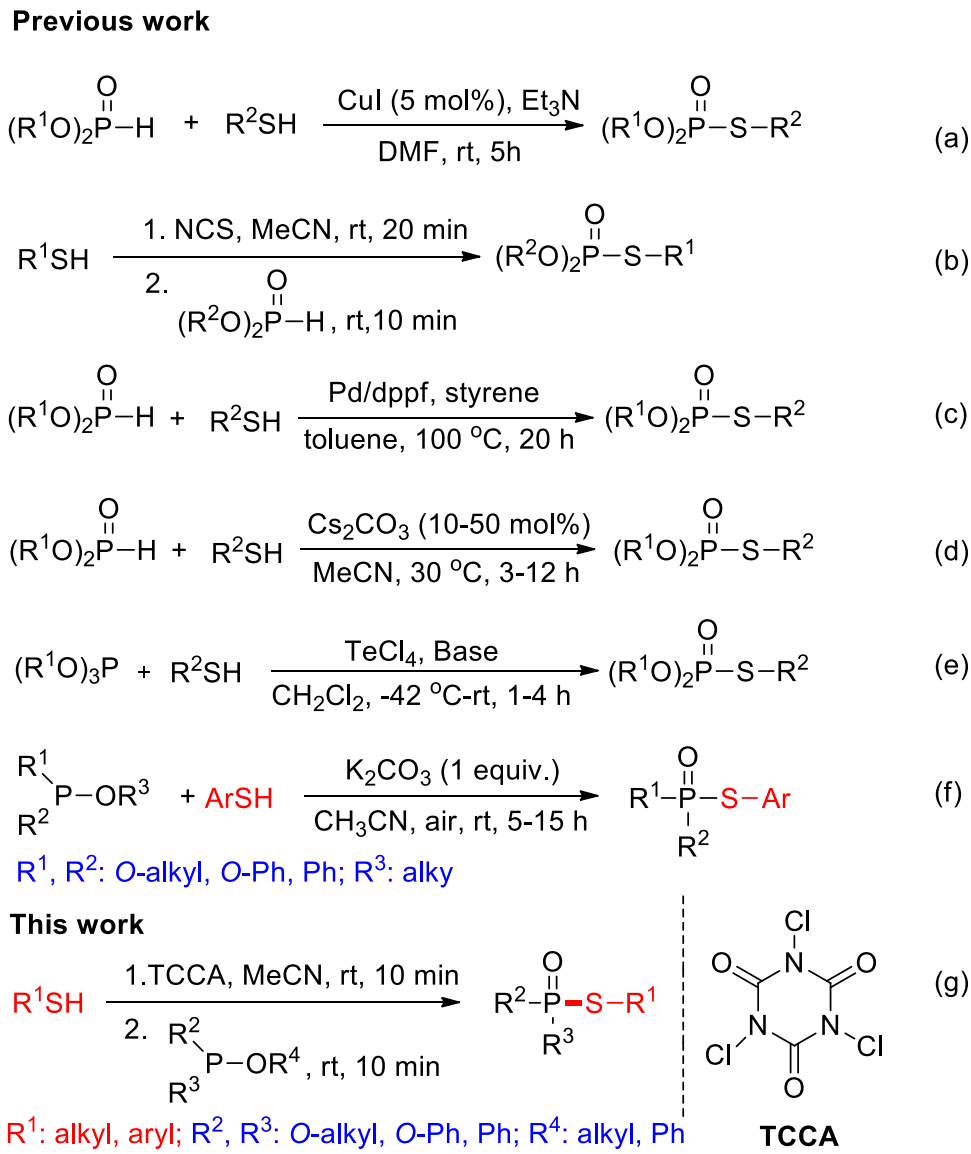


Scheme 1. Preparation of thiophosphates.

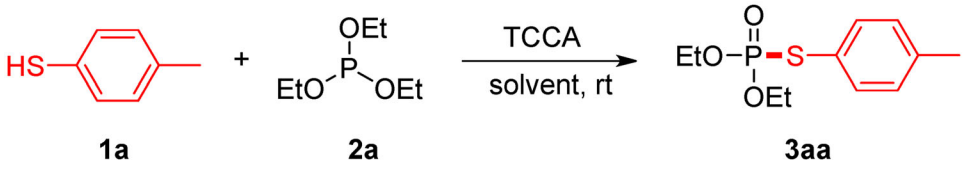
applicable to aliphatic thiols. There were two examples of using *N*-chlorosuccinimide as the promoter in the reaction of trimethyl phosphite and thiols to synthesize corresponding thiophosphates.[53,54] Perbromomethane was utilized in the reaction of phosphites and thiols for the synthesis of some bioactive compounds.[55–57] In addition, other reagents such as $SOCl_2$[58] and $BrCCl_3$[59] could also be used for the synthesis of thiophosphates from phosphites and thiols.

Inspired by the aforementioned works, and in continuation of our work on mercaptan chemistry,[60–64] we attempted to develop a new strategy for the synthesis of thiophosphates from phosphites and thiols. Herein, we report a simple method to achieve thiophosphates by coupling of phosphites with thiols using trichloroisocyanuric acid (TCCA) as the promoter.[65–71] This approach is very convenient and efficient. The reactions are carried out at the ambient temperature and can be completed in a short time. Most importantly, a wide range of substrates both aromatic and aliphatic thiols can be tolerated in this method and afford the corresponding thiophosphates in good yields.

Results and discussion

Initially, the coupling of *p*-toluenethiol (**1a**) with triethyl phosphite (**2a**) was chosen as a model reaction to identify and optimize the reaction conditions. Firstly, the reaction of **1a** (1 mmol) with **2a** was carried out in 2 mL of MeCN at room temperature. Without TCCA, no reaction occurred (Table 1, entry 1). Then the reaction was performed in the presence of TCCA (0.4 equiv.). When **1a**, **2a** and TCCA were added to the reaction system together, the conversion of **1a** was 92% and the selectivity to the product *O*,*O*-diethyl *S*-p-tolyl phosphorothioate (**3aa**) was 80% after 10 min (Table 1, entry 2). Then the reaction was performed in a one-pot two-step procedure. The first-step reaction of **1a** and TCCA was carried out for 10 min. After **2a** was added,

Table 1. Optimization of reaction conditions.[a]



1a **2a** **3aa**

Entry	**2a** (equiv.)	TCCA (equiv.)	Solvent	Conv.[c,d] (%)	Select.[d] (%)
1	2	0	MeCN	N.R.	N.R.
2[b]	2	0.4	MeCN	92	80
3	2	0.4	MeCN	100	>99
4	2	0.4	CH_2Cl_2	100	72
5	2	0.4	THF	100	88
6	2	0.4	DMF	100	98
7	2	0.4	Toluene	99	58
8	2	0.4	DMSO	59	82
9	2	0.4	1,4-dioxane	100	68
10	2	0.4	MeOH	82	17
11	1.5	0.4	MeCN	100	>99
12	1.2	0.4	MeCN	100	98
13	1	0.4	MeCN	100	94
14	1.2	0.35	MeCN	100	98
15	1.2	0.33	MeCN	100	94

[a]Reaction conditions: **1a** (1.0 mmol), TCCA, solvent (2 mL), rt, 10 min; then **2a**, rt, another 10 min.
[b]**1a** (1.0 mmol), **2a** (2.0 mmol), TCCA (0.4 equiv.), MeCN (2 mL), rt, 10 min.
[c]Conversion of **1a**.
[d]Determined by GC with area normalization method.

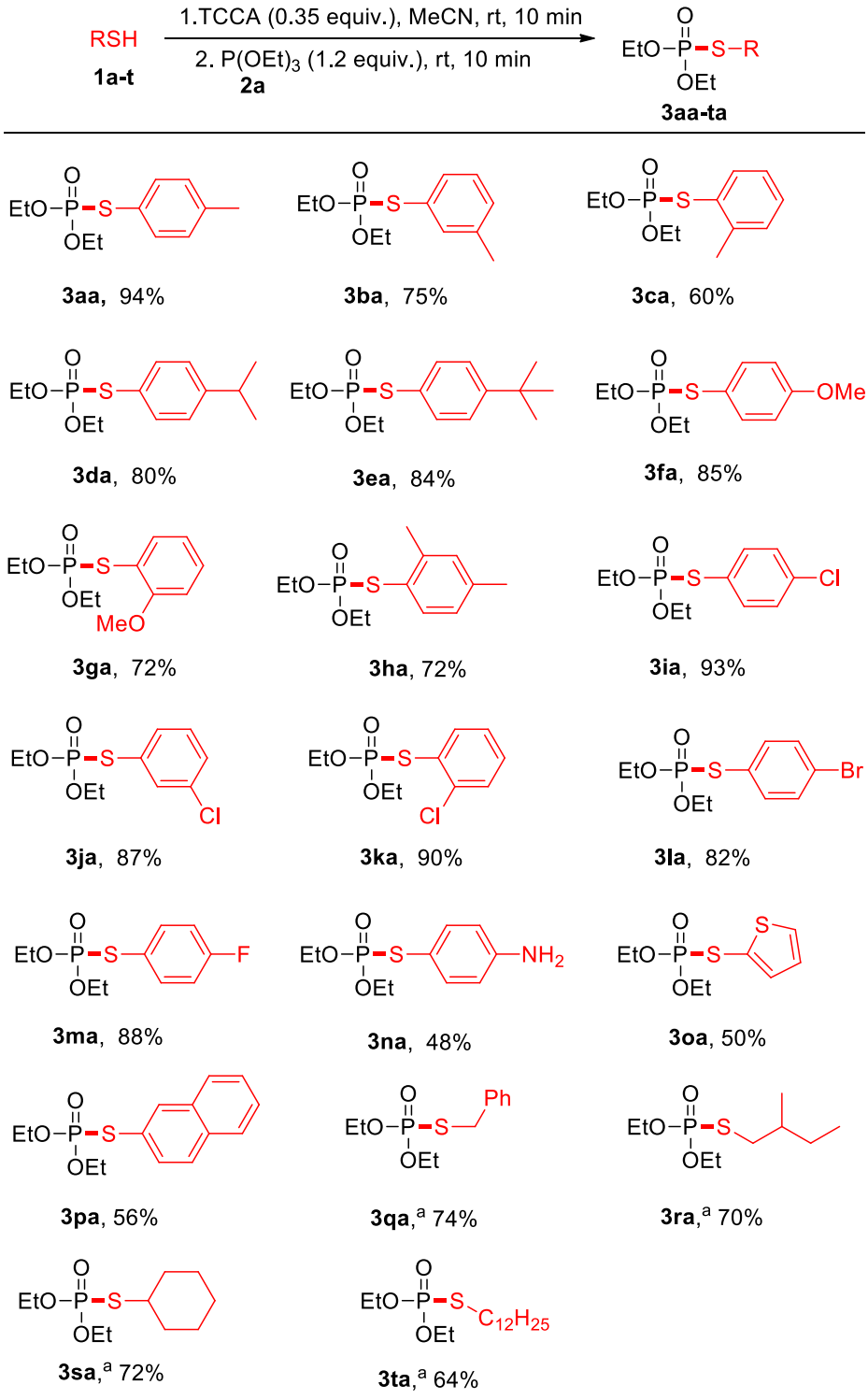
the reaction continued for another 10 min. It was found **1a** could be completely converted into **3aa** (Table 1, entry 3). Then we examined a variety of solvents under the same conditions (Table 1, entries 4 – 10), the results indicated that MeCN was the best choice. Although an excellent result could be obtained in DMF (Table 1, entry 6), MeCN was better as a solvent than DMF according to the solvent selection guides due to the reprotoxicity issue of DMF.[72]

Later on, the loading of **2a** was also attempted to be reduced. When the loading of **2a** was reduced to 1.2 equiv., **1a** could be fully converted, and the selectivity to **3aa** was as high as 98% (Table 1, entry 12), whereas further reducing the loading of **2a** to 1 equiv., decreased the selectivity of **3aa** to 94% (Table 1, entry 13). In addition, the influence of the loading of TCCA was also tested. The complete conversion of **1a** and 98% selectivity to **3aa** could be achieved when the loading of TCCA was reduced from 0.4 equiv. to 0.35 equiv. in the presence of 1.2 equiv. of **2a** (Table 1, entry 14). However, decreasing the loading of TCCA to less than 0.35 equiv. would lead to a lower selectivity to **3aa** (Table 1, entry 15). Thus we concluded that the optimal reaction conditions for the coupling of **1a** with **2a** was a one-pot two-step procedure with 1 equiv. of **1a**, 0.35 equiv. of TCCA and 1.2 equiv. of **2a** in MeCN at ambient temperature (Table 1, entry 14).

With the optimized reaction conditions in hand, we then examined the scope of the substrates in this reaction. Firstly, we investigated the coupling of triethyl phosphite (**2a**) with a variety of thiols **1a**–**t**, the results are illustrated in Scheme 2. The results showed that most of the aryl thiols underwent smooth transformations to afford the corresponding *O*,*O*-diethyl *S*-aryl phosphorothioates in good to excellent yields (**3aa**–**pa**). This protocol could tolerate a variety of benzenethiols bearing electron-donating and electron-withdrawing groups. The reactions of benzenethiols with electron-donating groups such as *p*-methyl, *p*-^{i}propyl, *p*-^{t}butyl, and *p*-methoxy proceeded smoothly to give the corresponding products **3aa**, **3 da**–**fa** in 80 – 94% isolated yields. *m*-Methylbenzenethiol was selectively converted into *O*,*O*-diethyl *S*-*m*-tolyl phosphorothioate (**3ba**) in 75% isolated yield. It was found that the yields of the products would be decreased with electron-donating groups in the ortho position of benzenethiols. *o*-Methylbenzenethiol and *o*-methoxybenzenethiol could afford their corresponding phosphorothioates **3ca** and **3ga** in 60% and 72% isolated yields, respectively. The multisubstituted phosphorothioates product **3 ha** could also be produced in 72% yield from 2,4-dimethylbenzenethiol (**1 h**) and **2a**. Benzenethiols bearing electron-withdrawing groups such as *p*-chloro, *p*-bromo, and *p*-fluoro could also give the expected products (**3ia**, **3la** and **3ma**) in excellent yields. *o*-Chloro and *m*-chlorobenzenethiols could be smoothly converted into their corresponding phosphorothioates (**3ja** and **3ka**) efficiently.

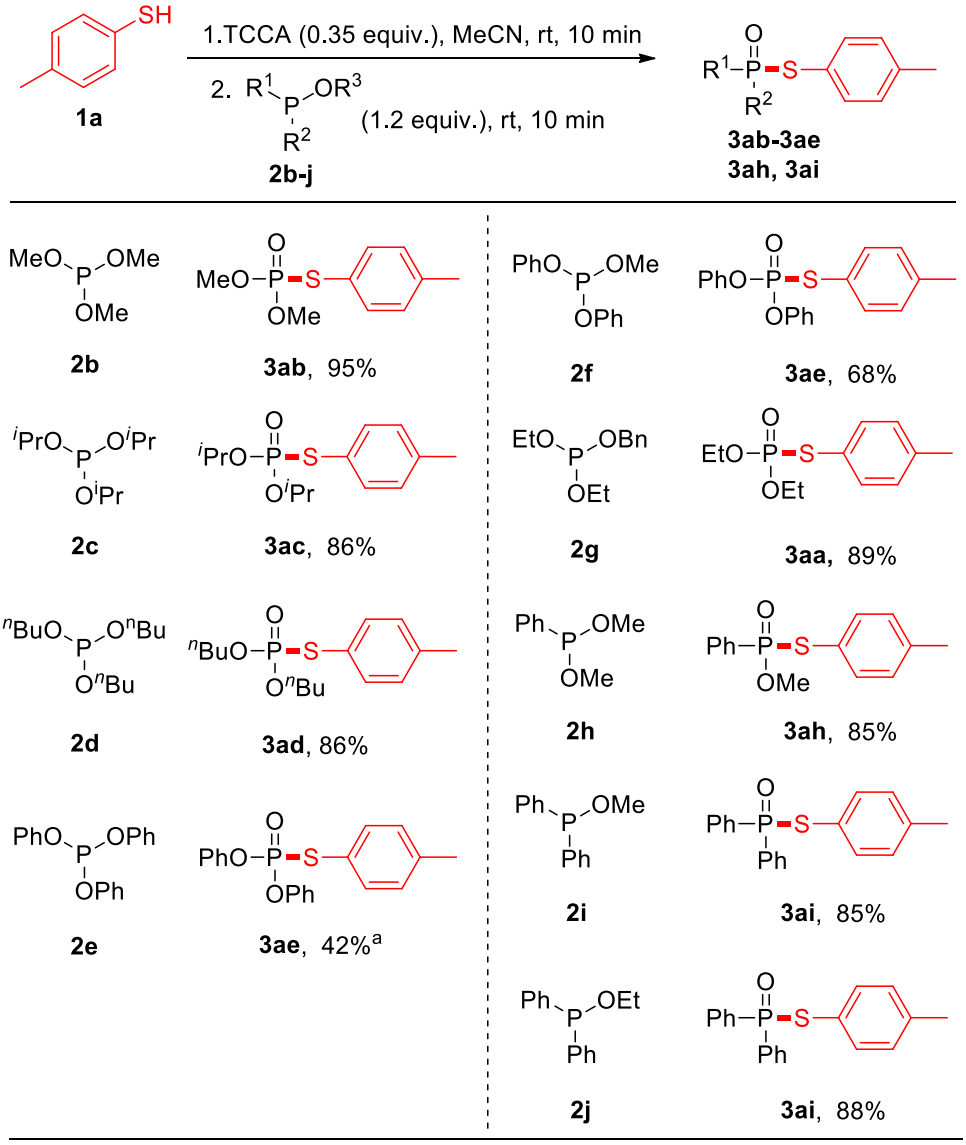
However, when *p*-aminobenzenethiol (**1n**) was used as the substrate, only 48% isolated yield of **3na** was achieved. When the heteroaromatic benzenethiol, thiophene-2-thiol (**1o**) was subjected to the reaction, the isolated yield of **3oa** was 50%. A representative polycyclic substrate could be tolerated this reaction giving the product **3pa** in 56% isolated yield. Notably, aliphatic thiols could successfully react with **2a** to give the corresponding thiophosphates **3qa**–**ta** in good isolated yields, though the loadings of **2a** and TCCA should be increased to 2 equiv. and 0.5 equiv., respectively.

Next we explored the generality of the coupling of phosphites and their derivatives with *p*-toluenethiol (**1a**) under the optimized conditions, and the results are showed in

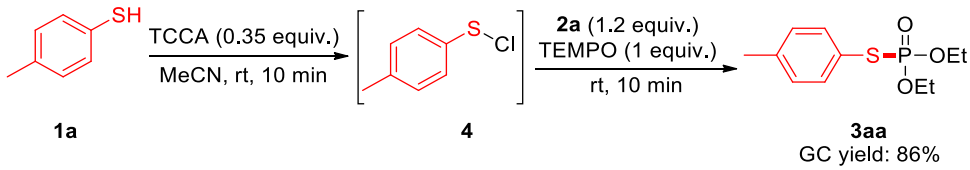


Scheme 2. Scope of thiols. Reaction conditions: **1** (1.0 mmol), TCCA (0.35 equiv.), MeCN (2 mL), rt, 10 min; then **2a** (1.2 mmol), rt, another 10 min (isolated yields are given). [a] TCCA (0.5 equiv.), **2a** (2.0 mmol).

Scheme 3. Both trimethyl phosphite (**2b**), triisopropyl phosphite (**2c**) and tributyl phosphite (**2d**) could give the desired product **3ab**, **3ac** and **3ad** in excellent isolated yields. Triphenyl phosphite (**2e**), which could not react with **1a** in the previous work,[52] could also afford the desired product **3ae** with this protocol. However, the product **3ae** and the by-product triphenyl phosphate could not be completely separated by column chromatography. Other phosphites **2f** and **2g** could also react efficiently with **1a**. Diphenyl methyl phosphite (**2f**) would afford **3ae** in 68% isolated yield, which was the same as the product from **1a** and **2e**. When benzyl diethyl phosphite (**2g**) was employed as the phosphorous nucleophile, the corresponding coupling product **3aa** was given in 89% isolated yield. Aside from phosphites, dimethyl phenylphosphonite (**2h**) could also be coupled with **1a** to produce *O*-methyl *S*-*p*-tolyl phenylphosphonothioate (**3ah**) in 85% isolated yield. Much to our delight, some other phosphorous nucleophiles, such as



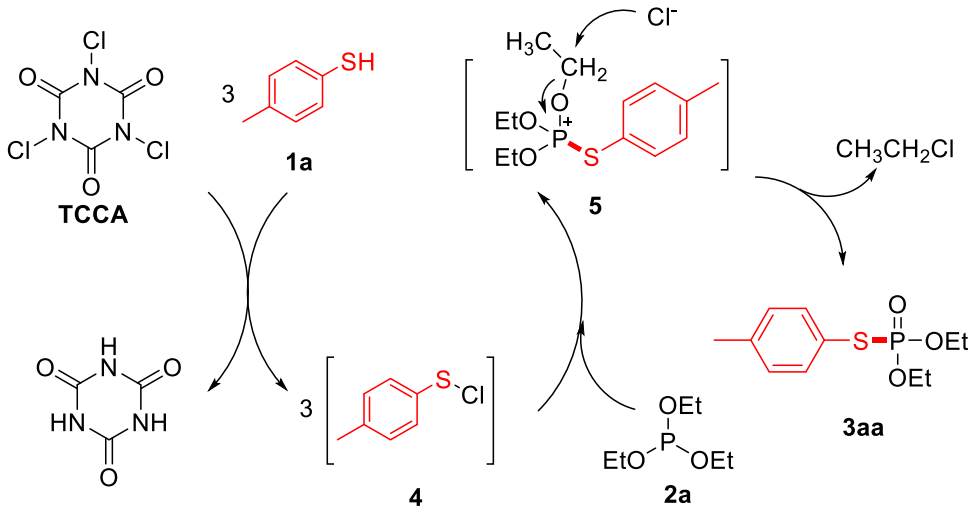
Scheme 3. Scope of P(III) compounds. Reaction conditions: **1** (1.0 mmol), TCCA (0.35 equiv.), MeCN (2 mL), rt, 10 min; then **2** (1.2 mmol), rt, another 10 min (isolated yields are given). [a]Determined by ^{1}H NMR.



Scheme 4. Reaction in the presence of radical scavenger.

methoxydiphenylphosphine (**2i**) and ethoxydiphenylphosphine (**2j**) also worked well in this method. In addition, diethyl phosphonate was also used as the phosphorous nucleophile, however the GC yield of **3aa** was only 77%.

According to the previous report of the coupling of thiols with phosphites,[52] thiols were initially oxidized into disulfides, then disulfides reacted with phosphites to afford the desired thiophosphates. However, in our method for coupling of *p*-toluenethiol (**1a**) with triethyl phosphite (**2a**) no 1,2-di-*p*-tolyldisulfane was observed at the first step by thin layer chromatography (TLC) analyses. TLC showed **1a** was consumed and a new compound was formed. Meanwhile isocyanuric acid which was confirmed by NMR, could be filtered and obtained almost quantitatively at the first step. Therefore, we speculated that a chlorinated intermediate 4-methylbenzenesulfenyl chloride (**4**) was generated in the first step.[17,73] Then a radical trapping experiment was carried out in the reaction of **4** and **2a** to gather more information on the mechanism. The result showed that even in the presence of 1 equiv. of TEMPO **3aa** could be produced in 86% GC yield (Scheme 4). This experiment strongly ruled out a radical mechanism.



Scheme 5. Proposed reaction mechanism.

On the basis of precedent reports and our observations,[17,44,73] a plausible reaction mechanism is presented in Scheme 5. *p*-Toluenethiol (**1a**) reacts with TCCA to afford the intermediate **4** along with the generation of isocyanuric acid. Isocyanuric acid can be easily recovered from the reaction mixture by filtration after the coupling reaction is completed, and can act as the material for preparing TCCA. Then the lone pair of electrons of triethyl phosphite (**2a**) attacks the sulfur atom of the intermediate **4** to form the intermediate **5**. The nucleophilic attack of chloride ion on the ethyl carbon of **5** with concomitant C-O bond cleavage generates the product **3aa** and the co-product chloroethane, which is confirmed by GC-MS.

Conclusions

In conclusion, we have developed a convenient synthetic method of thiophosphates through the coupling of thiols with phosphites. The reactions were promoted by TCCA and were carried out at room temperature. A wide substrate scope was exhibited, both aryl and alkyl thiols could react with phosphites to give the corresponding products successfully. On the other hand, phosphonite and phosphine were also tolerated in this reaction. Notably, the starting materials were commercial available and the reaction can be finished in 20 min. This method provides an efficient way to afford thiophosphates which are useful in the areas of organic synthesis, agricultural and medicinal chemistry.

Experimental

All reactions were carried out at room temperature and all reagents were purchased from commercial suppliers and used without further purification. Column chromatography was carried out with silica gel (200-300 mesh). GC analyses were conducted on an Agilent GC6890N system with a flame ionization detector (FID) and a SH-Rtx-1701 capillary column. GC-MS was performed on Thermo Trace ISQ instrument with TG 5MS capillary column. High-resolution mass spectra were recorded in the EI mode on Waters GCT Premier TOF MS. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained on a Bruker Avance III spectrometer. ^{31}P NMR (162 MHz) and ^{19}F NMR (376 MHz) spectra were obtained on a Bruker BioSpin AG spectrometer. Melting points (uncorrected) were determined on a BUCHI M-565 apparatus.

Typical procedure for the preparation of phosphites

A mixture of thiol **1** (1 mmol) and TCCA (0.35 mmol) in MeCN (2 mL) was stirred for 10 min at room temperature under air atmosphere. Then phosphite **2** (1.2 mmol) was added to the above reaction mixture, and the reaction solution was stirred for another 10 min. The resulting solution was directly filtered through a pad of silica gel. After removal of the volatiles under vacuum, the crude product was purified by column chromatography on silica gel with petroleum ether/ethyl acetate to give the corresponding product. The characterization data and NMR spectra (^{1}H, ^{13}C, ^{31}P and ^{19}F) for the products **3** were contained in the Supplemental Materials (Figures S1 – S79).

Funding

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