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K_2CO_3-promoted aerobic oxidative cross-coupling of trialkyl phosphites with thiophenols†

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Convenient, practical and economical phosphorylation of thiols has been achieved *via* halogen- and metal-free K_2CO_3-promoted aerobic oxidative cross-coupling of trialkyl phosphites, dimethyl phenylphosphonite, or methyl diphenylphosphinite with thiophenols using air as the oxidant at room temperature. This transformation provides a straightforward route to the construction of phosphorus–sulfur bonds with wide functional group compatibility, which affords phosphorothioates in up to 94% yield.

In recent years, the development of new methods to construct phosphorus–sulfur bonds has been of particular interest due to the wide applications of organophosphorus–sulfur compounds in biological chemistry, organic synthesis, and agrochemistry.[1] A variety of useful synthetic methods have been well documented. The traditional preparation of this class of compounds mainly relies on the use of toxic and moisture sensitive reagents or pre-functionalized substrates (*e.g.*, $R_2P(O)X$, RSX and RSSR).[2] On the other hand, the cross-dehydrogenative coupling (CDC) between P(O)H compounds and commercially available thiols is gradually developed (Fig. 1, eqn (1)).[3–7] In 2013, Kaboudin reported a copper-catalyzed coupling of H-phosphonates with thiols in the presence of Et_3N.[3] In 2015, Pan reported a TBPB-promoted oxidative coupling of secondary phosphine oxides or H-phosphonates with thiols.[4] In 2016, Li and Zhang reported a visible-light-mediated oxidative coupling of P(O)H compounds with thiols in the presence of a photocatalyst.[5] Interestingly, Chen and Han recently reported an oxidant-free Pd-catalyzed dehydrogenative phosphorylation of thiols.[6] Most recently, Song and Jiao reported a Cs_2CO_3-catalyzed aerobic oxidative CDC reaction of phosphonates with thiols.[7] The possible mechanism showed that disulfides are reaction intermediates generated *via* the oxidative coupling of thiols in the presence of Cs_2CO_3 and O_2.[7] Undoubtedly, this strategy represents more straightforward, efficient, and atom-economic to construct phosphorus–sulfur bonds. However, the CDC reactions suffered from limitations with regard to high cost and less availability of P(O)H compounds. Thus, the development of a convenient, practical and economical protocol for the synthesis of phosphorothioates is still a significant issue.

With our recent studies on the construction of carbon–sulfur, phosphorus–aryl, phosphorus–fluorine, and phosphorus–oxygen bonds,[8] we have been interested in studying the construction of phosphorus–sulfur bonds based on an economical approach. In comparison with P(O)H compounds, trialkyl phosphites are relatively inexpensive and readily available as phosphorus nucleophiles, which have also been widely used for the synthesis of various organophosphorus compounds.[9] In consideration of searching phosphorus nucleophiles instead of P(O)H compounds, we envision that the interaction between trialkyl phosphites and thiols might produce phosphorothioates *via* the elimination of an alcohol. Herein, we report an alternative approach to the synthesis of phosphorothioates based on K_2CO_3-promoted aerobic oxidative cross-coupling of trialkyl phosphites with thiophenols using air as the oxidant at room temperature.

According to the reaction conditions of the CDC reactions between dialkyl phosphites and thiols developed by Song and Jiao,[7] our hypothesis was tested by using a model reaction of triethyl phosphite **1a** with *p*-toluenethiol **2a** in solvents under

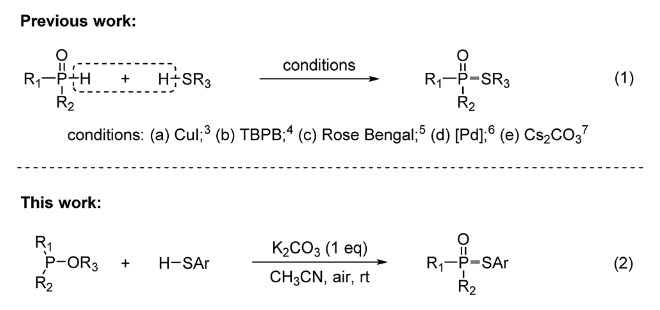

Fig. 1 Current developments in the synthesis of phosphorothioates from phosphites and thiols.

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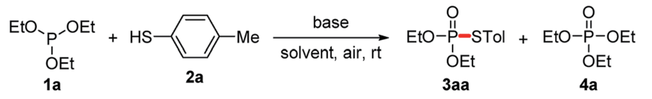
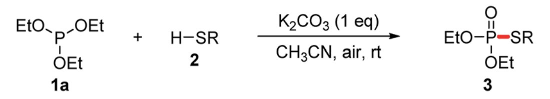
Table 1 Optimization of reaction conditions[a,b]

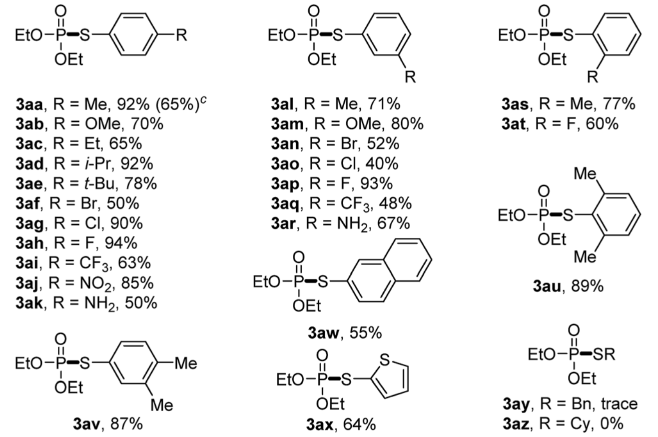


Entry	Base (equiv.)	Solvent	T (°C)	Yield **3aa** (%)	Yield **4a** (%)
1		CH_3CN	40	Trace	Trace
2	Cs_2CO_3 (1)	CH_3CN	40	68	24
3[c]	Cs_2CO_3 (1)	CH_3CN	40	Trace	Trace
4	Cs_2CO_3 (1)	THF	40	18	3
5	Cs_2CO_3 (1)	Dioxane	40	28	4
6	Cs_2CO_3 (1)	DMSO	40	Trace	Trace
7	K_2CO_3 (1)	CH_3CN	40	98	1
8	Na_2CO_3 (1)	CH_3CN	40	71	16
9	K_3PO_4 (1)	CH_3CN	40	55	14
10	Et_3N (1)	CH_3CN	40	82	8
11	K_2CO_3 (1)	CH_3CN	rt	97	1
12	K_2CO_3 (0.5)	CH_3CN	rt	87	8
13	K_2CO_3 (0.1)	CH_3CN	rt	81	12

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.46 mmol), base, solvent (1 mL), open air, 5 h. [b] Yield based on **1a** was determined by ^{31}P NMR analysis of crude products using an internal standard. [c] The reaction was carried out under N_2.

Table 2 Scope of thiols[a,b]





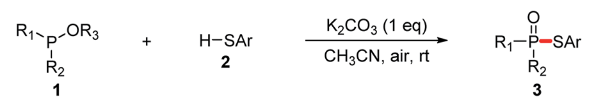
[a] Reaction conditions: **1a** (0.40 mmol), **2** (0.92 mmol), and K_2CO_3 (0.40 mmol) in CH_3CN (2 mL) stirring at room temperature under air for 5–12 h. [b] Isolated yield based on **1a**. [c] The reaction was performed in a 4 mmol scale.

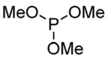
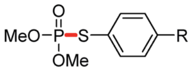
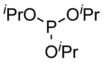
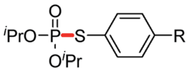
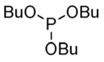
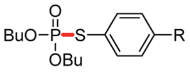
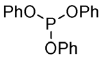
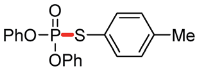
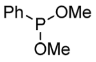
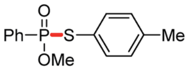
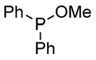
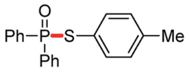
air atmosphere at 40 °C, and the results were shown in Table 1. Initially, the reaction of **1a** with **2a** in CH_3CN under air in the absence of bases gave only trace amounts of the desired coupling product **3aa** (entry 1). When Cs_2CO_3 (1 equiv.) was added, the reaction proceeded smoothly to afford **3aa** in 68% yield, while the oxidation product **4a** was also obtained in 24% yield (entry 2). When the reaction was carried out under N_2, only trace amounts of **3aa** were detected (entry 3). This result demonstrates that this reaction involved an aerobic oxidative cross-coupling. Switching the solvent from CH_3CN to THF, dioxane, or DMSO decreased the yield of **3aa** (entries 4–6). We then turned to screen other bases (entries 7–10). To our delight, the use of cheaper base K_2CO_3 gave **3aa** in excellent yield (98%, entry 7), while the yield of the side product **4a** was significantly decreased. We then carried out the reaction at room temperature, the yield of **3aa** was only slightly decreased (97%, entry 11). The catalytic efficiency of K_2CO_3 was then tested. When 0.5 or 0.1 equiv. of K_2CO_3 was introduced, **3aa** was still obtained in 87% or 81% yield (entries 12 and 13). It is noteworthy that disulfide **5a**, which was generated *via* an aerobic oxidative homocoupling of thiol **2a**,[10] was observed in all cases (in the presence of bases and air). Finally, we concluded that the optimized combination for the cross-coupling reaction of trialkyl phosphites with thiols was to use 1 equiv. of K_2CO_3 as the base, CH_3CN as the solvent, and the reaction was set at room temperature under air atmosphere (entry 11).

We then set out to explore the generality of the cross-coupling of trialkyl phosphites with thiols. We first applied the optimized conditions to the coupling of triethyl phosphite **1a** with a variety of thiols **2**, and the results are illustrated in Table 2. The results showed that thiophenol substrates bearing different groups such as alkyl groups, OMe, NH_2, Br, Cl, F, CF_3, and NO_2 at *para*, *ortho* or *meta* or at both positions of aromatic rings, as well as 2-naphthalenethiol and thiophene-2-thiol, were all well tolerated. The corresponding products **3aa–3ax** were isolated in moderate to high yields, indicating that the electronic and steric effects were not evident in this reaction. However, the phosphorylation of aliphatic thiols such as benzylthiol and cyclohexylthiol failed to give the desired **3ay** or **3az**. The scale-up of the reaction of **1a** with **2a** was also attempted. When we increased the scale of the reaction from 0.4 to 4 mmol, **3aa** was also isolated in good yield (65%).

We then turned to explore the generality of the cross-coupling of trialkyl phosphites and their derivatives with *p*-toluenethiol **2a** and/or *p*-chlorobenzenethiol **2g** under the optimized conditions, and the results were shown in Table 3. Trimethyl phosphite **1b** afforded the desired **3ba** and **3bg** in low yields probably due to its relatively weak nucleophilicity, while triisopropyl phosphite **1c** and tributyl phosphite **1d** smoothly gave the desired **3ca**, **3cg**, **3da**, and **3dg** in high yields. However, triphenyl phosphite **1e** failed to give the coupling product **3ea**. In addition, the cross-coupling of P(III) compounds bearing one or two methoxy substituents were also attempted. Pleasingly, the protocol was found to work well when dimethyl phenylphosphonite **1f** or methyl diphenylphosphinite **1g** was employed as the phosphorus nucleophile. The corresponding coupling products **3fa** and **3ga** were isolated in 45% and 55% yields, respectively. Notably, the side products **4** and disulfides **5** were detected in most cases of Tables 2 and 3.

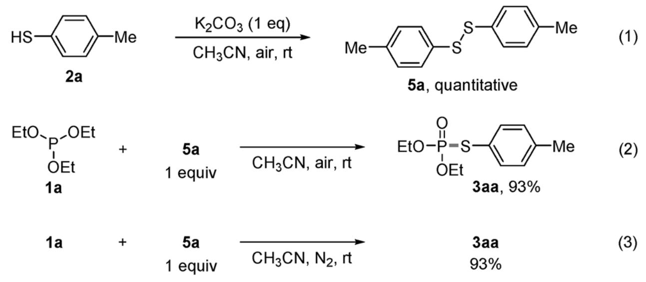
Table 3 Scope of P(III) compounds[a,b]



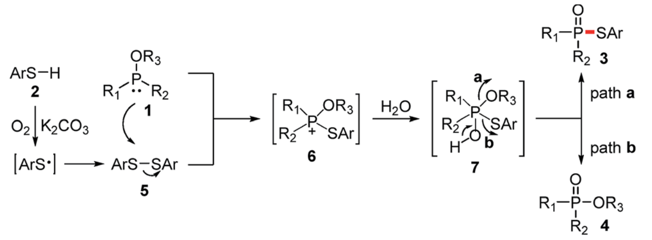
1	3
 **1b**	 **3ba**, R = Me, 40% **3bg**, R = Cl, 15%
 **1c**	 **3ca**, R = Me, 91% **3cg**, R = Cl, 88%
 **1d**	 **3da**, R = Me, 88% **3dg**, R = Cl, 80%
 **1e**	 **3ea**, 0%
 **1f**	 **3fa**, 45%
 **1g**	 **3ga**, 55%

[a] Reaction conditions: **1** (0.40 mmol), **2** (0.92 mmol), and K_2CO_3 (0.40 mmol) in CH_3CN (2 mL) stirring at room temperature under air for 5–12 h. [b] Isolated yield based on **1**.

The above experimental results (Table 1, entries 1 and 3) showed that both bases and air are indispensable for the cross-coupling reaction. To gain more insight into the mechanism of this reaction, a couple of control experiments were then conducted (Scheme 1). In consideration of the generation of disulfides in all cases, the reaction of thiol **2a** with K_2CO_3 under air was carried out, leading to the formation of disulfide **5a** in quantitative yield (eqn (1)), which suggests that K_2CO_3 might increase the oxidation rate of thiols with dioxygen.[11,12] In addition, the reaction of **1a** with disulfide **5a** under air or N_2 in the absence of K_2CO_3 also gave **3aa** in high yield (eqn (2) and (3)). The above results suggest that disulfide might be an intermediate in the cross-coupling reaction.



Scheme 1 Mechanistic studies.



Scheme 2 Proposed mechanism.

According to the literatures and our observations, together with the generation of side products **4**, a plausible reaction mechanism is outlined in Scheme 2. Initially, thiyl radical is generated from a single electron oxidation of thiol **2** in the presence of dioxygen, followed by the loss of the proton with the assistance of K_2CO_3. Thiyl radical could undergo homocoupling to produce disulfide **5**.[7,11–13] Then the nucleophilic attack of P(III) compound **1** on disulfide **5** affords phosphonium cation **6**, which reacts with water to form the unstable intermediate **7**. Subsequent alcohol elimination of **7** gives the desired phosphorothioate **3** (path a), whereas the thiophenol elimination affords the oxidation product **4** (path b).

Conclusions

In conclusion, we have developed the K_2CO_3-promoted aerobic oxidative cross-coupling of trialkyl phosphites, dimethyl phenylphosphonite, or methyl diphenylphosphinite with thiophenols, which provides a convenient, practical and economical protocol for the synthesis of phosphorothioates with wide functional group compatibility. We envision that the reaction mode outlined here will have potential applications in organic synthesis. Further studies on the transformations of thiols with electrophiles are ongoing and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

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