RSC Advances

ROYAL SOCIETY
OF CHEMISTRY

PAPER

View Article Online
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Cite this: *RSC Adv.*, 2022, **12**, 32350

Received 9th October 2022
Accepted 2nd November 2022

DOI: 10.1039/d2ra06351d

rsc.li/rsc-advances

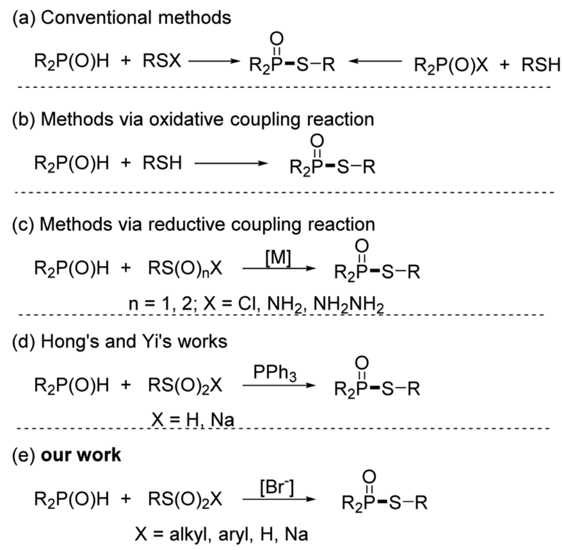
Bromide ion promoted practical synthesis of phosphinothioates of sulfinic acid derivatives and H-phosphine oxides†

Haoyuan Li,‡ Wenjie Yan,‡ Peipei Ren, Huimin Hu, Runbo Sun, Meixia Liu, Zhengjiang Fu, Shengmei Guo * and Hu Cai *

A feasible method for the synthesis of phosphinothioates from sulfinic acid derivatives and phosphine oxides is described. This reaction can be carried out in an open flask at room temperature and in an aqueous medium. The scope of the sulfinic acid derivatives is extensive, with a wide range of sulfinate esters, sulfinic acids, and sodium sulfinates compatible with these conditions, with good to excellent yields of phosphinothioates. In addition, a gram-scale synthesis with this reaction is achieved. A mechanism of this procedure was proposed.

The S–P(O) structural unit is often found in pharmacologically active chemicals, organophosphorus insecticides, and natural products, and also serves as a building block in the preparation of a variety of compounds.[1] Given its vast applications, numerous efforts have been made to develop efficient methods to approach the S–P(O) structurally contained compounds.[2] Conventional methods for the construction of such compounds are involved in nucleophilic substitution of $R_2P(O)X$ or R–SX with nucleophiles.[3] However, the toxicity and instability of $R_2P(O)X$ and R–SX limit their applications. As a result, green and efficient strategies for the synthesis of S–P(O) bonds attracted considerable attention. In recent years, catalysed oxidative coupling reactions utilizing inexpensive and readily available RS–H (RS–SR) and P(O)–H have emerged as appealing and potent techniques for the synthesis of these compounds.[4] Working with thiol and sulfide reagents, however, may be a highly unpleasant experience, especially for large-scale synthesis and industrial processes.[5] Alternatively, the reductive coupling reaction of RS(VI) or RS(IV) with P(O)–H has appeared as a new strategy for accessing these molecules. Among them, coupling reactions of RSO_2Cl, RSO_2NH_2, and $RSO_2NH_2NH_2$ with P(O)–H were well investigated.[6] In these reactions, transition metals as catalysts are required. To overcome upon drawback, Hong and Yi separately devised elegant metal-free reductive coupling reactions using sulfinic acids or sodium sulfinates to construct S–P(O) bonds,[7] while external reducer (PPh_3) or H_2SO_4 were necessary. Despite significant progress, more practical synthetic methods for the formation of phosphinothioates are desirable. Based on our ongoing works on C–P and S–P bond formation,[8] herein, we disclose a bromide ion accelerated reductive-coupling for the producing phosphinothioates from sulfinic acid derivatives and phosphine oxides.[9] This method is suited for practical synthesis since it is free of metal reagents and external reducers, and allows to be carried out under an open flask and in an aqueous medium Scheme 1.

Initially, we chose methyl benzenesulfinate (**1a**, 0.2 mmol) and diphenylphosphine oxide (**2a**, 0.5 mmol) as model reactants to optimize the reaction conditions (Table 1). A tiny quantity of desired product was identified after 1 hour at room



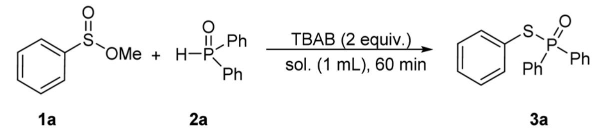
Scheme 1 Methods for the formation of phosphinothioates.

Department of Chemistry, Nanchang University, No. 999, Xuefu Rd, Nanchang, 330031, P. R. China. E-mail: smguo@ncu.edu.cn; Caihu@ncu.edu.cn

† Electronic supplementary information (ESI) available. CCDC 2184647 and 2184646. For ESI and crystallographic data in CIF or other electronic format see DOI: **https://doi.org/10.1039/d2ra06351d**

‡ These authors contributed equally.

Table 1 Optimization of the conditions[a]



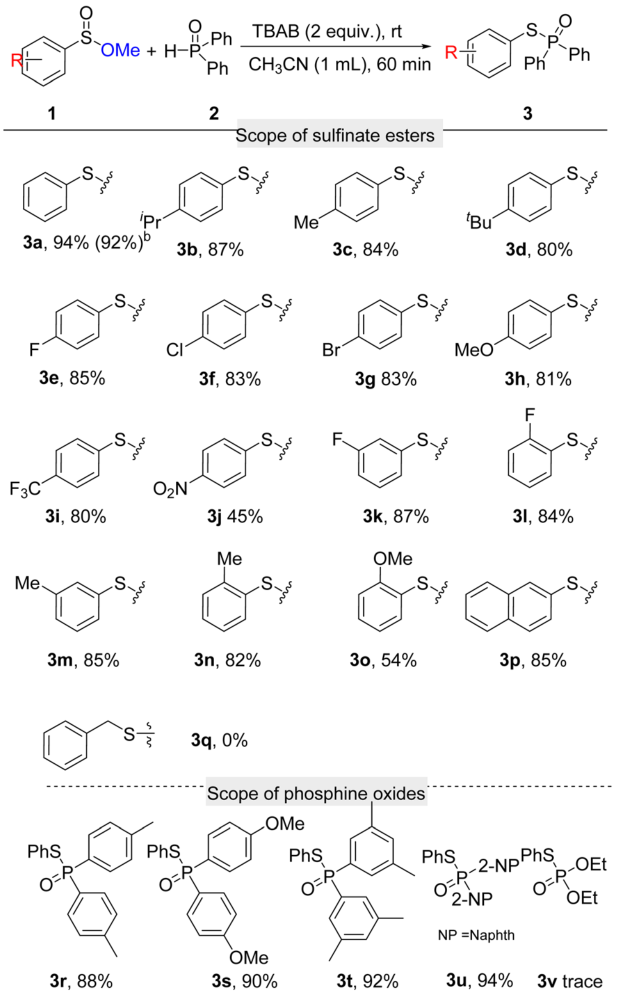
Entry	Promoter	Solvent	1a : 2a	Yield[b] (%)
1	None	None	1 : 2.5	Trace
2	TBAB	None	1 : 2.5	30
3[c]	TBAB	None	1 : 2.5	32
4	TBAB	CH_3CN	1 : 2.5	94
5	TEAB	CH_3CN	1 : 2.5	62
6	HTAB	CH_3CN	1 : 2.5	68
7	TBAF	CH_3CN	1 : 2.5	Trace
8	TBAI	CH_3CN	1 : 2.5	60
9	TBAC	CH_3CN	1 : 2.5	45
10	LiBr	CH_3CN	1 : 2.5	78
11	KBr	CH_3CN	1 : 2.5	73
12	KI	CH_3CN	1 : 2.5	32
13	K_2CO_3	CH_3CN	1 : 2.5	28
14	TBAB	THF	1 : 2.5	36
15	TBAB	Dioxane	1 : 2.5	31
16	TBAB	CH_3OH	1 : 2.5	20
17[c]	TBAB	H_2O	1 : 2.5	85
18	TBAB	CH_3CN	1 : 1	48
19	TBAB	CH_3CN	1 : 2	79
20	TBAB	CH_3CN	1 : 3	92
21[d]	TBAB	CH_3CN	1 : 2.5	92
22[e]	TBAB	CH_3CN	1 : 2.5	92

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), TBAB (0.4 mmol), CH_3CN (1 mL) in an open flask at rt for 1 h. [b] Isolated yields. [c] 4 h. [d] Under N_2. [e] 30 min.

temperature without using any solvent (Table 1, entry 1). Then, TBAB (tetrabutylammonium bromide) was added to the reaction to increase the possibility of reactants exposure, and the product **3a** was afforded in 30% yield (Table 1, entry 2). Inspired by this, we prolonged the reaction time to 4 h, but the yield of product had no significant increase (Table 1, entry 3). Interestingly, the product of **3a** was isolated in 94% yield when CH_3CN (1 mL) was employed as a solvent (Table 1, entry 4). In the upon solvent, TEAB (tetraethylammonium bromide) and HTAB (hexadecyl trimethyl ammonium bromide) were tested, and found that they could promote the reaction with the yields of 62% and 68%, respectively (Table 1, entries 5 and 6). Other quaternary ammonium salts with different anions like TBAF (tetrabutylammonium fluoride), TBAI (tetrabutylammonium iodide), or TBAC (tetrabutylammonium chloride) showed inefficient in this transformation (Table 1, entries 7–9). Considering the bromide anion has a positive effect on this coupling reaction, LiBr and KBr were independently applied to the reaction, and the **3a** was obtained in 78% and 72% yields (Table 1, entries 10 and 11), whereas KI and K_2CO_3 delivered the desired product in 32% and 28% yields (Table 1, entries 13 and 14). Other solvents such as THF, dioxane, and CH_3OH were studied, but lower yields were obtained in each case (Table 1, entries 14–16). It should be noted that the coupling product was isolated in 85% yield when H_2O was utilized as a solvent after increasing the reaction duration to 4 h (Table 1, entry 17). Next, the ratio of reactants was examined. We found that decreasing the amount of phosphine oxide would reduce the yield; while increasing the ratio of **1a** and **2a** to 1 : 3, the product has no improvement (Table 1, entries 18–20). Besides, 92% yield of product was obtained when the reaction was carried out under N_2 (Table 1, entry 21). In addition, the reaction could deliver the desired product in 92% yield in 30 minutes (Table 1, entry 22).

Ethyl, *n*-butyl, benzyl, and phenethyl benzenesulfinate (**1b–1f**) afforded the desired products (**3a**) above 80% yields but inefficient than OMe group. Besides, large steric hindrance group esters such as isopropyl, *t*-butyl, and cyclohexyl showed poor reactivity, which was probably due to the prohibition of the attack from phosphine oxide (please see ESI†).

Having identified the optimal reaction conditions, the scope of sulfinate esters in this transformation was studied (Scheme 2). Firstly, we investigated the effect of the groups on the aryl ring on the reaction. Alkyl groups at the 4-position of aryl such as isopropyl, methyl, and *tert*-butyl reacted smoothly



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.5 mmol), TBAB (0.40 mmol), CH_3CN (1 mL) in an open flask at rt for 1 h; Isolated yields. [b] 1.14 g, 4 h.

Scheme 2 Scope of sulfinate esters and phosphine oxides.[a]

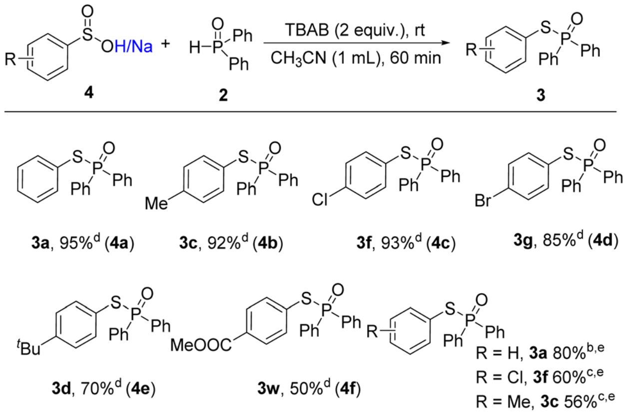
with diphenylphosphine oxide (**2a**) to afford **3b**, **3c**, and **3d** in good yields. Halogens at the 4-position of the benzene ring have little effect on the reaction, which gave the desired products above 80% yields (**3e**, **3f**, **3g**). When –OMe and $-CF_3$ groups were donated on the phenyl ring, the desired products **3h** and **3i** were afforded in 81% and 80% yields, respectively. Substrate with a strong electron-withdrawing group such as $-NO_2$ at the 4-position of aryl showed weaker activity under the standard conditions, which gave the corresponding product in 45% yield (**3j**). Group on the other positions of aryl rings were also studied. 3-F, 2-F, 3-Me, 2-Me, and 3-OMe substituted sulfinate esters were successfully carried out to contribute the desired products in 87%, 84%, 85%, 82%, and 54% yields respectively (**3k**, **3l**, **3m**, **3n**, **3o**). Naphthalenesulfinate ester was also compatible with the reaction, leading to **3p** in 85% yield. Unfortunately, benzyl sulfinate ester was unsuitable for the conversion (**3q**). In addition, gram-scale synthesis of **3a** was achieved with more reaction time (4 h), and excellent yield can be maintained.

Next, the compatibility of phosphine oxides was evaluated. Di-*p*-tolylphosphine oxide and bis(4-methoxyphenyl)phosphine oxide afforded the expected products in 88% and 90% yields (**3r**, **3s**). Bis(3,5-dimethylphenyl)phosphine oxide delivered the coupling product **3t** in 92% yield. Di(naphthalen-2-yl) phosphine oxide also displayed high reaction activity, which provided **3u** in 94% yield. Despondently, diethyl phosphonate did not anticipate this reaction.

The compatibility of sulfinic acids and their salts were also tested under the standard conditions (Scheme 3). Benzenesulfinic acid delivered the reductive coupling product **3a** in 95% yield. 4-Methylbenzenesulfinic acid **4b**, 4-chlorobenzenesulfinic acid **4c** and 4-bromobenzenesulfinic acid **4d** also showed excellent reactive activities, leading to the desired products in 92%, 93% and 85% yields, respectively. Besides, **4e** and **4f** delivered the desired coupling products in moderate yields (**3d**, **3w**). Although a longer reaction time was required (12 h), benzene sulfinic acid sodium could undergo the reductive coupling procedure, which gave the corresponding product **3a** in 80% yield. When sodium 4-chlorobenzenesulfinate and sodium 4-methyl benzenesulfinate were subjected to the transformation, moderate yields of coupling products were obtained after prolonging the reaction time to 24 h (**3f**, **3c**), which might be owing to the salts' solubility.

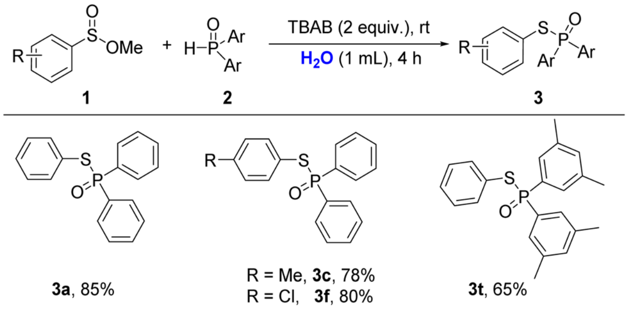
Green synthesis is one of the main themes in modern organic chemistry. Water is considered a green solvent in reaction. Interestingly, this reaction may also be carried out in aqueous medium (Scheme 4). When **1a** and **2a** were subjected to water instead of CH_3CN and were stirring for 4 h, the coupling product **3a** was obtained in 85% yield. Methyl 4-methylbenzenesulfinate and 4-chlorobenzenesulfinate were compatible with these reaction conditions, which delivered the desired products in 78% and 80% yields (**3c**, **3f**), respectively. The other phosphine oxide like di-*p*-tolylphosphine oxide was also tested in water, which gave the product **3t** in 65% yield.

To investigate the mechanism of this transformation, several control experiments were conducted (Scheme 5). When BHT (butylated hydroxytoluene) and 1,1-diphenylethylene (DPE)



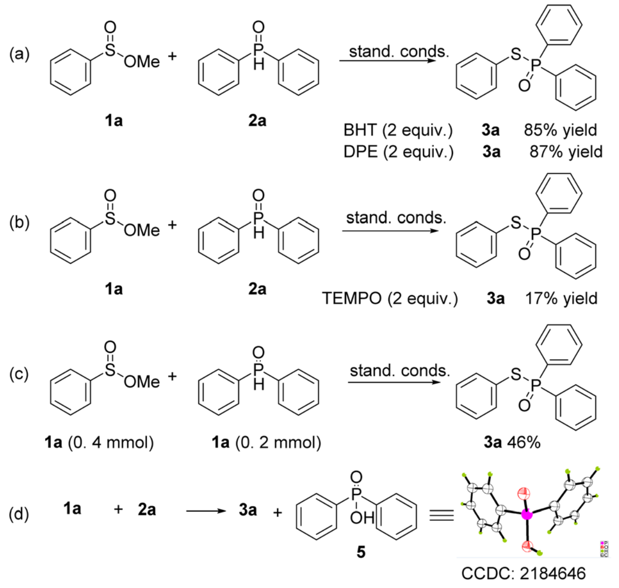
[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.5 mmol), TBAB (0.5 mmol) in CH_3CN (1 mL) under an open flask at rt for 1 h; Isolated yields; [b] 12 h; [c] 24 h.[d] From sulfinic acids; [e] Fromf sulfinic acids salts.

Scheme 3 Scope of sulfinic acids and their salts.[a]

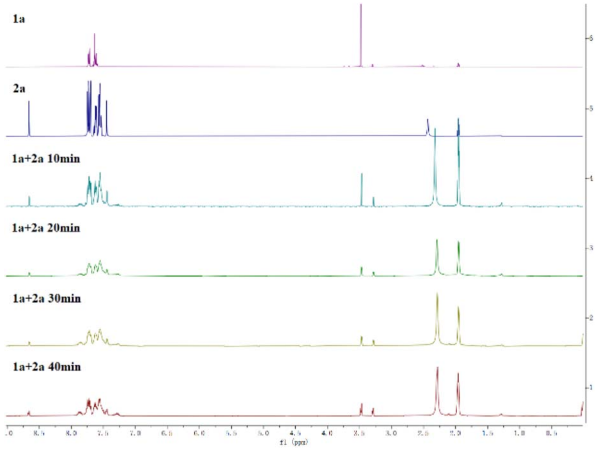


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.5 mmol), TBAB (0.5 mmol) in H_2O (1 mL) under open flask at rt for 4 h; Isolated yields.

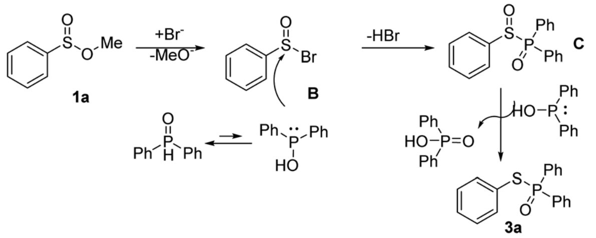
Scheme 4 Water as a solvent.[a]



Scheme 5 Control experiments (a–c) and investigation of byproduct (d).



Scheme 6 ^{1}H NMR experiments (CD_3CN).



Scheme 7 Proposed mechanism of the reaction.

were added to the model reaction under the standard conditions, the yields of **3a** were obtained in 85% and 87% yields, which suggested that the reaction does not undergo a radical route (Scheme 5a and b). However, when TEMPO was employed in the reaction, a 17% yield of the coupling product was obtained. This is because TEMPO is an oxidant, which will disrupt the reductive reaction conditions. When the ratio of **1a** and **2a** was lowered to 2 : 1, the corresponding product was obtained in 46% yield, this indicated that one molecule of **2a** is served as a reducer (Scheme 5c). Moreover, lots of diphenylphosphinic acid was precipitated as a colorless solid from the reaction solution, and the crystal diffraction of this compound was obtained (Scheme 5d). The ^{1}H NMR track experiments showed that the shift of 3.45–3.50 (–OMe group of **1a**) appeared several peaks, suggested that **1a** was affected in the conditions (Scheme 6, and please ESI†).

According to literature and the results of our experiments,[6,7,9] a plausible mechanism of this transformation is proposed (Scheme 7). Firstly, bromide anion acts on the sulfinate esters **1a** to produce **B**. Then the P(V) in phosphine oxide maintains equilibrium with P(III) phosphorus anion to attacks **B** to obtain the intermediate **C** and release a molecular of HBr. After that, **C** is reduced by **2a** to give the desired product **3a** and **D**.

Conclusions

In conclusion, we have developed an efficient and practical method for the synthesis of phosphinothioates from sulfinate esters (sulfinic acids) and phosphine oxides. TBAB play an accelerator role this reaction in the absence of a metal catalyst an external reducer. The reaction may also be carried out in an open flask and aqueous conditions, and rapidly converted into phosphinothioate at room temperature, which can significantly reduce pollution and expense. A range of sulfinate esters and phosphine oxides may be compatible with the transformation. Furthermore, gram-scaled synthesis was achieved with excellent yield. Mechanism studies revealed that the reaction might go through a nucleophilic substitution and a reduction procedure.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the financial support from the National Natural Science Foundation of China (21861024, 21861026, 21761021).

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