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Phosphorothiolation of Aryl Boronic Acids Using P(O)H Compounds and Elemental Sulfur

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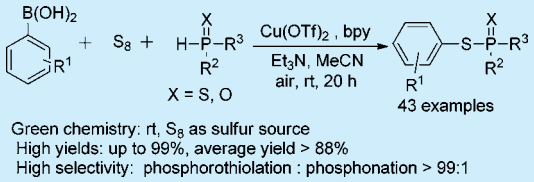
Supporting Information

ABSTRACT: The first multicomponent reaction (MCR) involving aryl boronic acids, elemental sulfur, and P(O)H compounds is presented. It proceeds with excellent yields and provides an attractive approach for the construction of valuable *S*-aryl phosphorothioates and *S*-aryl phosphorodithioates using a one-step strategy. Moreover, this method can be easily adapted to large-scale preparation.



Phosphorothioates and phosphorodithioates are particularly attractive due to their biological properties.[1] *S*-Benzyl *O*,*O*-diethyl phosphorothioate was developed as a fungicide for rice blast, and several organophosphorus compounds having a sulfur heteroatom are now put into practical use to control this disease.[2] Phosphorodithioate-modified siRNA is a prime candidate for introducing critical new features to further improve siRNA efficacy both in vitro and in vivo.[3] In particular, the S−P(O) substituted moiety serves as an important structural element in DNAzymes and pharmaceuticals.[4] Additionally, *S*-aryl phosphorothioates are key synthetic intermediates for a variety of complex molecules.[5]

The construction of organophosphorus compounds having a sulfur heteroatom at the bridging position of a phosphate group as in a C−S−P(O) functionality has received significant attention. Generally, S-aryl phosphorothioates are prepared either by the nucleophilic reaction of trialkyl phosphites with sulfenyl chlorides,[6] or by the condensation reaction between phosphorylation reagents and thiols (Scheme 1).[7] The reaction of potassium *O*,*O*-diethyl phosphorothioate with *δ*-aryl metal complexes has also been reported.[8] Although these methods efficiently lead to the desired S-aryl phosphorothioates, they generally require moisture-sensitive starting materials. In 2009, our group reported the direct coupling of readily available P(O)H compounds with diaryl disulfides in the presence of catalytic amounts of copper iodide.[9a] *S*-Aryl phosphorothioates can also be obtained by the reactions of dialkyl phosphites with diaryldisulfdes in the presence of a catalytic amount of cesium hydroxide.[9c] Different thiophenol substances were investigated for their reactivity with P(O)H compounds.[10] In 2014, Wu, Cui, and Kumaraswamy developed the sulfenylation of *H*-phosphonates with arylsulfonyl derivatives.[11] These breakthroughs for the preparation of *S*-aryl phosphorothioates are highly efficient and compatible with a variety of functional groups.

With regard to sulfur sources, disulfides, thiols, sulfonyl chlorides, or sulfonyl hydrazines were well developed to construct C−S−P bonds. In comparison with those aforementioned sulfur species, sulfur powder (S_8) is cheap and more abundant in nature.[12] Utilization of common and readily available chemicals as the components and involvement of selective formation of the C(aryl)−S−P bond should make this multicomponent reaction (MCR) much more attractive both fundamentally and synthetically. Herein we report a novel and efficient one-step synthesis of *S*-aryl phosphorothioates via multicomponent coupling of aryl boronic acids, elemental sulfur (S_8), and P(O)H compounds (Scheme 1).

As an initial attempt, reacting phenylboronic acid (0.36 mmol) with diethyl *H*-phosphonate (0.36 mmol) and elemental sulfur (0.30 mmol, 9.6 mg) in the presence of $Cu(OAc)_2$ as catalyst, bpy (0.12 mmol) as ligand, and K_2CO_3 as base under air in CH_3CN at 80 °C was investigated. The reaction provided the product **1** in 19% yield, albeit along with a 5% yield of P-arylation product (Table 1, entry 1; also see the Supporting

Scheme 1. C(aryl)−S−P Bond-Forming Reactions

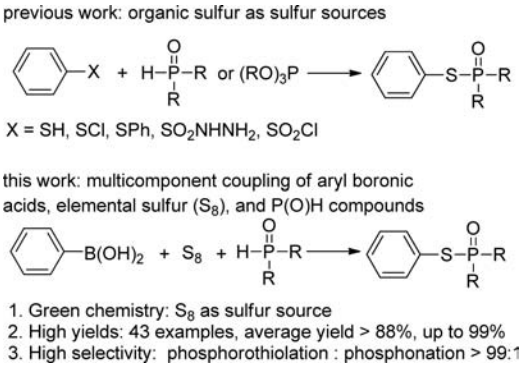


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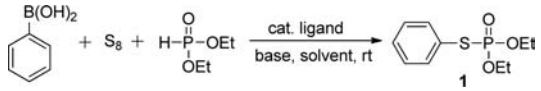
Table 1. Optimization of Reaction Conditions[a–e]



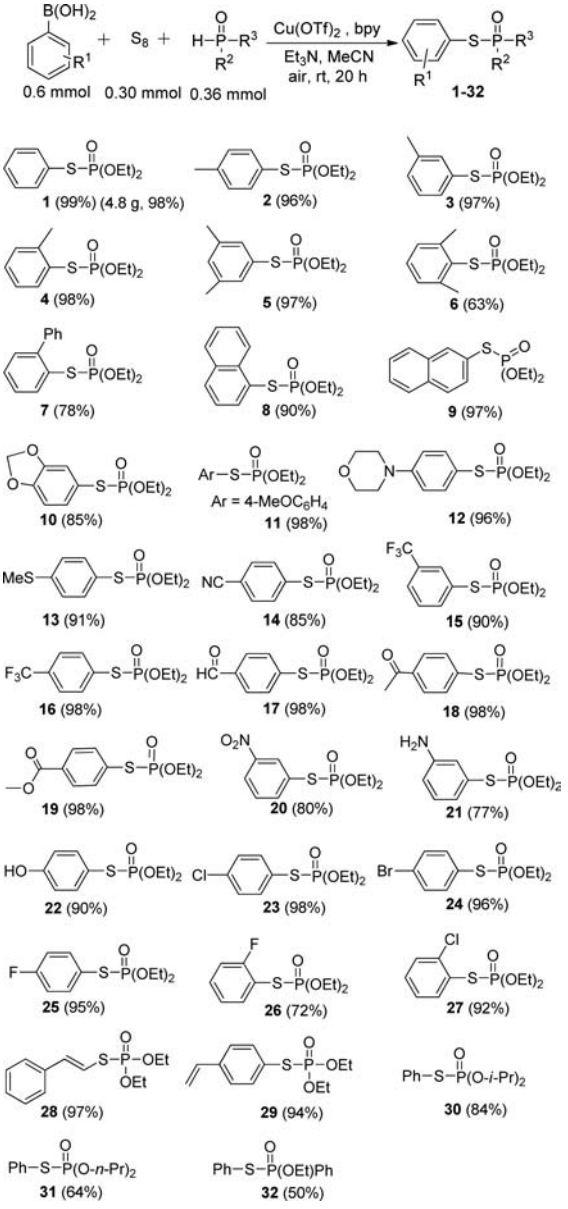
entry	cat.	ligand	solvent	base	yield (%)[b]
1	$Cu(OAc)_2$	bpy	CH_3CN	K_2CO_3	19,[c] 50
2	$Cu(OTf)_2$	bpy	CH_3CN	K_2CO_3	63 (60)
3	–	bpy	CH_3CN	K_2CO_3	0
4	$Cu(OTf)_2$	1,10-phen	CH_3CN	K_2CO_3	4
5	$Cu(OTf)_2$	TMEDA	CH_3CN	K_2CO_3	37
6	$Cu(OTf)_2$	bpy	EtOH	K_2CO_3	50
7	$Cu(OTf)_2$	bpy	DCM	K_2CO_3	7
8	$Cu(OTf)_2$	bpy	dioxane	K_2CO_3	23
9	$Cu(OTf)_2$	bpy	CH_3CN	*t*-BuOK	50
10	$Cu(OTf)_2$	bpy	CH_3CN	Cs_2CO_3	69
11	$Cu(OTf)_2$	bpy	CH_3CN	$(i\text{-Pr})_2EtN$	90
12	$Cu(OTf)_2$	bpy	CH_3CN	pyridine	0
13	$Cu(OTf)_2$	bpy	CH_3CN	Et_3N	91, 94[d]
14[e]	$Cu(OTf)_2$	bpy	CH_3CN	–	0
15[e]	$Cu(OTf)_2$	bpy	CH_3CN	Et_3N	(99)

[a]Reaction conditions: phenylboronic acid (0.36 mmol), diethyl *H*-phosphonate (0.36 mmol), elemental sulfur (0.30 mmol, 9.6 mg), catalyst (0.06 mmol), ligand (0.12 mmol), base (0.6 mmol), and solvent (2.0 mL) in an open flask at room temperature for 20 h. [b]Yield determined by ^{31}P NMR. Values in parentheses indicate yield based on S_8 after purification. [c]At 80 °C. [d]S_8 (1.8 mmol, 5 equiv) was used. [e]Phenylboronic acid (0.60 mmol) was used.

Information (SI)). Experimentally, the yield of product **1** was increased to 50% and P-arylation could be completely suppressed when the temperature was decreased from 80 °C to room temperature. Subsequently, various copper salts were screened under similar conditions, of which $Cu(OTf)_2$ showed the highest activity, whereas other tested salts, CuI, CuO, $CuSO_4$, and $CuCl_2$, were less effective (see SI). For this process, examination of various ligands indicated that 2,2′-bipyridine (bpy) was optimal (60% yield, Table 1, entry 2). Conducting the reaction in EtOH, DCM, and 1,4-dioxane gave the product in low yield (entries 5–8), while the reaction conducted in MeCN gave a high yield (entries 9–11). The effect of the bases was also investigated; Et_3N and $(i\text{-Pr})_2EtN$ were found to be the most suitable bases (entries 8–13). Pyridine, a weak organic base, was ineffective (entry 12). No *S*-phenyl phosphorothioate was obtained without any bases (entry 14). Triethylamine, an organic base, plays important roles in this transformation: (1) H-phosphonates (V) readily tautomerize to the corresponding phosphite (III) under the basic conditions, and phosphite (III) performs a good soft nucleophile; (2) Et_3N can neutralize the intermediate, S-hydrogen phosphorothioate; (3) among the bases such as K_2CO_3, Cs_2CO_3, and Et_3N, Et_3N has good solubility in acetonitrile and gives the best yield. A further increase in the molar equivalents of elemental sulfur led to no significant increase in the yield (entry 13; also see SI). Other inorganic sulfides such as $Na_2S_2O_3$, $K_2S_2O_8$, K_2S instead of elemental sulfur were investigated (SI). K_2S was also effective, giving the product **1** in 92% yield. No reaction occurred when $K_2S_2O_8$ was used. $Na_2S_2O_3$ gave a 90% yield of P-arylation product (see SI). To our delight, the yield of **1** was further improved to 99% by increasing the amount of phenylboronic acid to 2.0 equiv (entry 15).

With the optimized conditions in hand, the generality of the method was explored under the optimized conditions (Table 1, entry 15), and the results are summarized in Scheme 2. The

Scheme 2. Scope of Phosphorothiolation of Aryl Boronic Acids



methyl substituted aryl boronic acids, such as *para*- methyl, *meta*-methyl, *ortho*-methyl, and 3,5-dimethyl groups on the aryl ring, reacted with diethyl *H*-phosphonate efficiently and gave the desired products **2**–**5** in almost quantitative yields. Gratifyingly, sterically hindered substrates such as 2,6-dimethyl-, 2-phenyl-, *α*-naphthalenyl-, or *β*-naphthalenyl-phenylboronic acid were also good substrates (**6**–**9**). A series of electron-rich and -deficient aryl boronic acids can be transformed into their corresponding *S*-aryl phosphorothioates **10**–**29** in good yields. The mild reaction conditions employed allowed for the phosphorothiolation of aryl boronic acids with a broad range of functional groups including acetal, ether, amino, methylmercapto, cyano, formyl, keto, ester, and nitro (**10**–**20**). Phenylboronic acid bearing more oxidizable functionalities,

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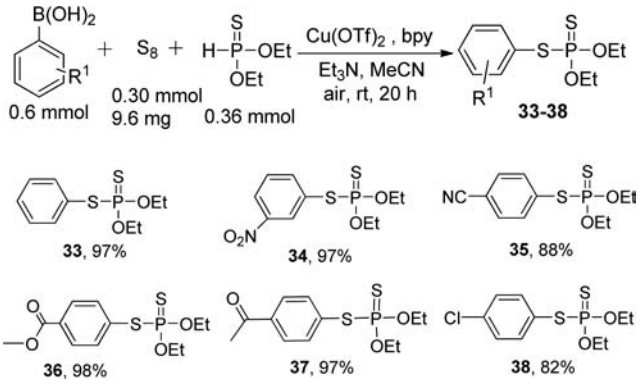
such as thioether, amino, and hydroxyl, could be tolerated; corresponding products were obtained in satisfied yields (**13**, **21**, **22**). Halogen atoms such as bromo, chloro, and fluoro on the aromatic ring were unaffected under the present reaction conditions to afford the corresponding products **23**−**27** in good yields, which could allow for further synthetic transformations. Aryl boronic acids having a reactive double bond could also be used in the reaction to give the desired *S*-aryl phosphorothioates selectively without damaging the double bond (**28**, **29**). Similarly, the Cu-catalyzed phosphorothiolation also took place with a hydrogen phosphinate (**32**). Aliphatic boronic acids did not work well under these conditions. In order to demonstrate the practical application of this method, a gram scale preparation of *O*,*O*-diethyl *S*-phenyl phosphorothioate (**1**, 4.8 g) was obtained in 98% yield (Scheme 2).

Importantly, the substrates are not limited to the above-mentioned P(O)H compounds, and diethyl *H*-phosphonothioate [P(S)H] was also tested for this reaction to produce the corresponding *S*-aryl phosphorodithioates (Scheme 3, **33**−**38**)

Scheme 3. Synthesis of S-Arylphosphorodithioates

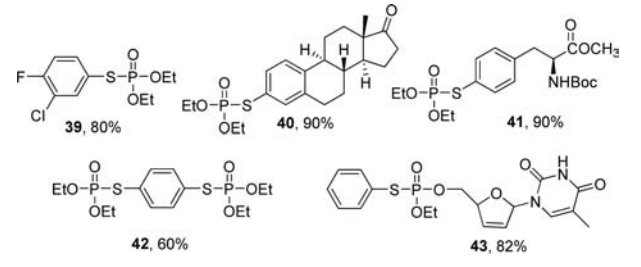


directly in high yields. The conversion rate of diethyl *H*-phosphonothioate [P(S)H] could reach up to 80% at room temperature within 10 h. After 20 h, the product **33** was obtained in 97% isolated yield.

It was particularly noteworthy that when the highly functionalized aryl boronic acids, estrone, phenylalanine, and nucleotide analogues that show unique biological activities were used as the substrates, corresponding products were obtained in satisfactory yields, clearly demonstrating the great potential of this new methodology to allow access to highly functionalized targets (Scheme 4, **39**−**43**).

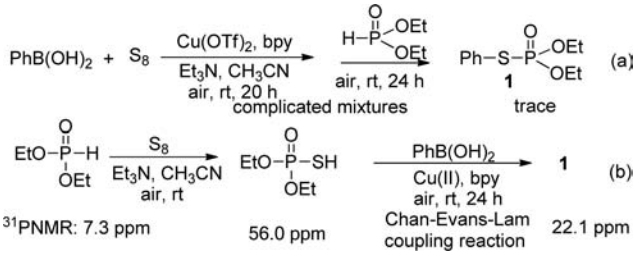
To further identify the role of elemental sulfur in this transformation, the following experiments were performed. First, the reaction of phenylboronic acid with elemental sulfur

Scheme 4. Formation of Various Highly Functionalized Targets



for 20 h led to a complicated mixture, and a trace amount of the product **1** was obtained after addition of diethyl *H*-phosphonate (Scheme 5a). This result suggests that the reaction could not

Scheme 5. Mechanistic Experiments



proceed via benzenethiol and diaryl disulfide intermediates.[13] To determine whether *S*-hydrogen phosphorothioate is the active phosphorothiolating reagent, a mixture of diethyl *H*-phosphonate and sulfur powder (S_8) was treated with phenylboronic acid, and the reaction was monitored by ^{31}P NMR spectroscopy (Scheme 5b). The starting diethyl *H*-phosphonate in CH_3CN showed signal in the ^{31}P NMR spectrum at δ = 7.3 ppm. When sulfur powder (S_8) and Et_3N were added to the solution, the peak of diethyl *H*-phosphonate decreased quickly while a new peak at 56.0 ppm corresponding to intermediate *S*-hydrogen phosphorothioate emerged in 30 min.[9b,14] No *S*-hydrogen phosphorothioate was obtained within 5 h in the absence of Et_3N. Addition of phenylboronic acid, $Cu(OTf)_2$, and bpy resulted in a peak (at 22.1 ppm) that rapidly increased, meanwhile the peaks at 56.0 ppm gradually decreased, indicating formation of the desired C(aryl)−S−P bond. The reaction was almost complete after 24 h according to the ^{31}P NMR spectra. On the basis of these preliminary results, a tentative mechanistic pathway is proposed (Scheme 5b). *H*-Phosphonate was first converted to *S*-hydrogen phosphorothioate in the presence of elemental sulfur.[15] *S*-Hydrogen phosphorothioate then reacted with phenylboronic acid in the presence of $Cu(OTf)_2$ as a catalyst to give the phosphorothioated product **1** via the well-known Chan−Evans−Lam coupling reaction.[16]

In conclusion, we have successfully developed a facile catalytic method for the preparation of *S*-aryl phosphorothioates via phosphorothiolation of aryl boronic acids with P(O)H compounds and sulfur powder. This method provides rapid access to a broad spectrum of *S*-aryl phosphorothioates in high yields. Moreover, this method can be easily adapted to large-scale preparations. In addition, the use of an inexpensive Cu(II) catalyst, using readily available sulfur powder (S_8) and P(O)H compounds, means that this facile protocol will be attractive for academia and industry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00118.

Spectral data for all compounds and copies of ^{1}H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

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