JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis of *S*-Aryl Phosphorothioates by Copper-Catalyzed Phosphorothiolation of Diaryliodonium and Arenediazonium Salts

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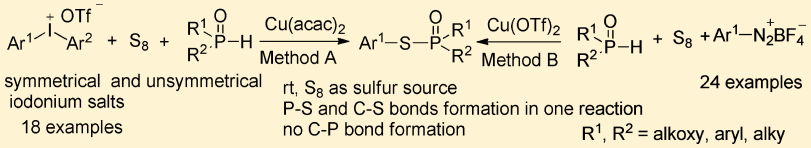
Supporting Information



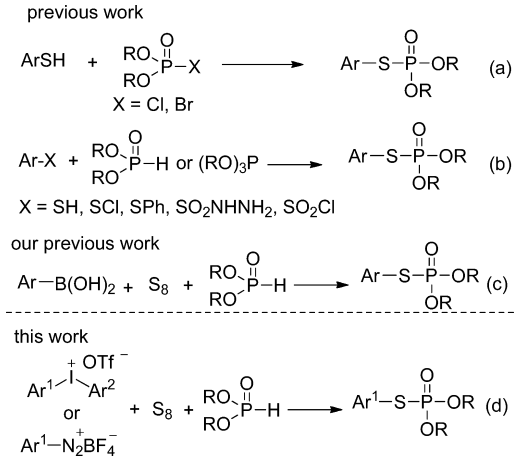
ABSTRACT: Green methods for the synthesis of *S*-aryl phosphorothioates have been developed based on copper-catalyzed multicomponent reactions involving diaryliodonium/arenediazonium salts, elemental sulfur, and $R_2P(O)H$ compounds. Most target products are obtained with these two methods in good to high yields at room temperature. These transformations allow the direct formation P−S and C−S bonds in one reaction.

INTRODUCTION

Compounds incorporating the phosphorus−sulfur bond are versatile reagents in both organic and inorganic synthesis. The best known example, Lawesson's reagent $[(4\text{-}MeOC_6H_4)P = S(\mu\text{-}S)]_2$, is widely used in organic chemistry, for example, for the conversion of C═O to C═S groups.[1] Phosphate esters have broad applications in the fields of pharmaceuticals and agrochemicals owing to its unique properties. Among the phosphate esters, phosphorothioates have received considerable attention for more than 60 years because of their biological properties, for example, as pesticides, insecticides, enzyme modifiers, and potential HIV-1 and ACHE inhibitors.[2] Additionally, *S*-aryl phosphorothioates are also key synthetic intermediates for a variety of complex molecules.[3]

In contrast to the P═S functionality, the synthesis of analogues bearing a sulfur atom at the bridging position of a phosphate group as in a C−S−P(O) functionality is usually a more complicated task. Traditional synthesis work of *S*-aryl phosphorothioates often proceeds via the reaction between arylthiols and phosphorylation reagents (phosphorochloridates and phosphorobromidates); however, chlorine and bromine are both toxic and difficult to control. In addition, the preparation of phosphorochloridates and phosphorobromidates is required (Scheme 1a).[4] As we know, thiols emit a pungent odor during and after use. Various substituted aryl sulfides (disulfides, sulfuryl chloride, and sulfonylhydrazides) instead of thiophenol were well developed to construct C−S−P(O) bonds (Scheme 1b).[5] In 2009, our group reported the direct coupling of readily available $R_2P(O)H$ compounds with diaryl disulfides in the presence of catalytic amounts of copper iodide.[5b] Recently, we successfully developed a facile catalytic method for the preparation of *S*-aryl phosphorothioates via phosphorothiolation of aryl boronic acids with $R_2P(O)H$ compounds and sulfur powder (Scheme 1c).[6] Hence, there is still great need for the development of a convenient protocol to produce various phosphorothioate derivatives.

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



Diaryliodonium salts, as important and valuable electrophilic arylation reagents, have recently received considerable attention due to their high reactivity and nontoxicity.[7] The regioselective preparation of arylphosphonates using unsymmetrical diaryliodonium salts was discovered by our group in 2013.[8] Moreover, owing to the efforts of Beringer, Olofsson, and others, symmetrical and unsymmetrical diaryliodonium triflates can now be easily synthesized from both electron-deficient and electron-rich arenes and aryl iodides with *m*CPBA and triflic

Received: April 23, 2016
Published: May 31, 2016

DOI: 10.1021/acs.joc.6b00925
J. Org. Chem. 2016, 81, 5588−5594

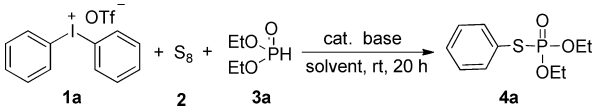
acid in one pot.[9] Furthermore, diaryliodonium salts are stable and can be stored for one year or more at room temperature.

On the other hand, in comparison with those aforementioned sulfur species, sulfur powder (S_8) is cheap and more abundant in nature.[10] Utilization of common and readily available chemicals as the components and involvement of selective formation of C(aryl)−S−P bond should make this reaction much more attractive. Herein, we report a novel and efficient one-step synthesis of *S*-aryl phosphorothioates via multicomponent coupling of diaryliodonium salts, elemental sulfur (S_8), and $R_2P(O)H$ compounds (Scheme 1d).

RESULTS AND DISCUSSION

As an initial attempt, reacting diphenyliodonium triflate (**1a**, 0.30 mmol) with elemental sulfur (**2**, 0.45 mmol, 14.4 mg) and diethyl *H*-phosphonate (**3a**, 0.30 mmol) in the presence of $Cu(OAc)_2$ as catalyst and Et_3N as base under air in CH_3CN at room temperature was investigated. Pleasingly, the reaction provided the product **4a** in 92% yield (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	base	solvent	yield (%)
1	$Cu(OAc)_2$	Et_3N	CH_3CN	92
2	$Cu(OTf)_2$	Et_3N	CH_3CN	75
3	**$Cu(acac)_2$**	**Et_3N**	**CH_3CN**	**100**[a,b] **(95)**[a,c]
4	CuCl	Et_3N	CH_3CN	70
5	CuI	Et_3N	CH_3CN	44
6	Cu_2O	Et_3N	CH_3CN	66
7		Et_3N	CH_3CN	0
8	$Cu(acac)_2$	K_2CO_3	CH_3CN	86
9	$Cu(acac)_2$	Cs_2CO_3	CH_3CN	85
10	$Cu(acac)_2$	NaOAc	CH_3CN	38
11	$Cu(acac)_2$	K_3PO_4	CH_3CN	70
12	$Cu(acac)_2$	Et_3N	THF	89
13	$Cu(acac)_2$	Et_3N	DMF	80
14	$Cu(acac)_2$	Et_3N	toluene	95,[a] 35[d]

[a]Reaction conditions: diphenyliodonium triflate (0.30 mmol), diethyl H-phosphonate (0.30 mmol), elemental sulfur (0.45 mmol, 14.4 mg), catalyst (0.03 mmol), base (0.45 mmol), solvent (1.5 mL) in a 10-mL tube at room temperature for 20 h in air. Yield determined by ^{31}P NMR. Values in parentheses indicate yield after purification. [b]1.0 equiv of TEMPO was added. [c]2,2′-Bipyridine (0.06 mmol) was added as ligand; reaction time 5 h. [d]Under a nitrogen atmosphere.

Without sulfur powder, P-arylation product could be obtained in 70% yield within 10 min.[8] Once sulfur powder was added, P-arylation could be completely suppressed. Subsequently, various Cu(II) and Cu(I) salts were further investigated, and the results showed that Cu(II) salts were more effective to give the desired product (entries 1−6). $Cu(acac)_2$ showed the highest activity and gave **4a** in almost quantitative yield within 20 h (entry 3a). When 2,2′-bipyridine was added as ligand, the reaction could be completed in 5 h (entry 3b). No desired product was afforded without copper salt (entry 7). Other inorganic bases, such as K_2CO_3, Cs_2CO_3, NaOAc, and K_3PO_4, could also execute this reaction but with lower efficiency (entries 8−11). In addition to CH_3CN, other tested solvents, such as THF, DMF, and toluene, all gave good yields. Other inorganic sulfides such as $Na_2S_2O_3$, $K_2S_2O_8$, and K_2S instead of elemental sulfur were investigated. K_2S was also effective, giving the product **4a** in 50% yield. The same yield was obtained when 1.0 equiv of TEMPO was added in the reaction under the optimal conditions (entry 3c). Reactions performed under a nitrogen atmosphere led to a 35% yield (entry 14d). These results suggest that the mechanism is like the well-known Chan−Evans−Lam coupling reaction.[6]

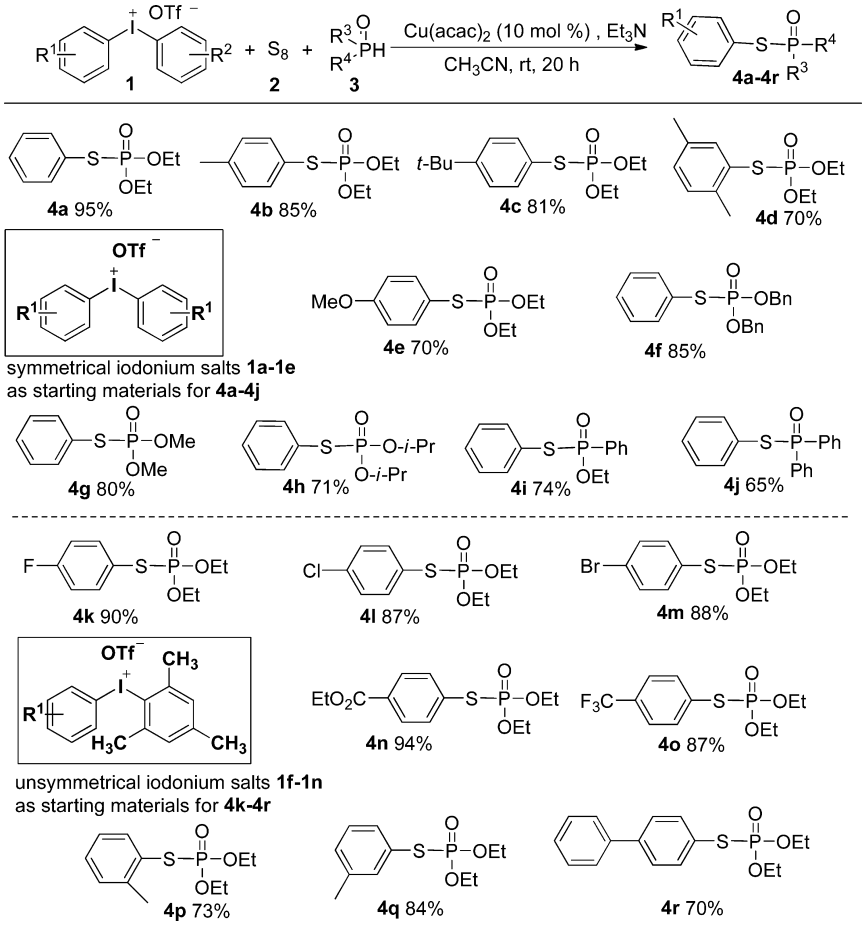
With the optimized conditions in hand, the generality of the method was explored under the optimized conditions (Table 1, entry 3a), and the results are summarized in Scheme 2. First, symmetrical iodonium salts with electron-donating groups such as methyl, *tert*-butyl, and methoxy all afforded the desired products (**4b−e**) in good yields. Gratefully, steric bulk posed no problem in this reaction, as exemplified by 2,5-dimethyl product **4d**. In regard to the *H*-phosphonates, in addition to diethyl *H*-phosphonate, dibenzyl, dimethyl, and diisopropyl all could be used as the substrates, generating the corresponding *S*-aryl phosphorothioates in 71−85% yields (**4f−h**). When ethyl phenylphosphinate was used, **4i** was obtained in 74% yield. Diphenylphosphine oxide was used in the phosphorothiolation of iodonium salt and led to the formation of product **4j** in 65% yield, indicating that the reactivities of these P(O)−H compounds are almost independent of the alkoxy and alkyl moieties. Symmetrical iodonium salts with electron-withdrawing groups were less effective, giving the corresponding products **4k−o** in 10−40% yields. Raising the temperature to 60 °C slightly increased the yield.

We then designed unsymmetrical diaryliodonium salts with one mesityl group and one electron-deficient aryl group. 4-Fluoro-, 4-chloro-, and 4-bromophenyliodonium triflates were examined for reactivity with diethyl *H*-phosphonate and sulfur powder under the same reaction conditions to give the expected products **4k−m** in excellent yields. Unsymmetrical iodonium salts with electron-withdrawing groups such as 4-acyl and 3-trifluoromethyl afforded **4n** and **4o** with satisfactory results. Substituted phenyl rings with electron-donating *o*-methyl, *p*-methyl, and *p*-phenyl groups of the salts reacted with diethyl *H*-phosphonate and sulfur powder to result in the corresponding *S*-aryl phosphorothioates **4p−r** in 70−84% yields. Unsymmetrical iodonium salts with pyridine group did not work with this method.

Encouraged by the findings described above, we continued to explore the synthesis of *S*-aryl phosphorothioates from diazonium salts. As we know, diazonium compounds are standard reagents used in the synthesis of organic compounds, especially aryl derivatives.[11] Arenediazonium cations are very versatile and useful synthons and show several reactions in which the N_2 group is replaced by another group or ion.[12] Furthermore, arenediazonium tetrafluoroborate salts are prepared via treatment of cheap aromatic amines with sodium nitrite in the presence of tetrafluoroboric acid. The pure arenediazonium tetrafluoroborate salts are stable at room temperature and can be stored below 8 °C for several months. To our delight, when diazonium tetrafluoroborates were employed as the aryl source, the reaction took place under slightly modified conditions. The optimal reaction conditions are as follows: (1) $Cu(OTf)_2$ (0.06 mmol), $R_2P(O)H$ (0.30 mmol), elemental sulfur (0.45 mmol), Et_3N (0.45 mmol), in CH_3CN (1.0 mL) for 20 min; (2) adding arenediazonium salt (0.36 mmol, in CH_3CN 0.5 mL) into the above reaction mixture and stirring at room temperature for 12 h. No **4a** was obtained when 1.0 equiv of TEMPO is added. The yield of **4a**

DOI: 10.1021/acs.joc.6b00925
J. Org. Chem. 2016, 81, 5588−5594

Scheme 2. Scope of Phosphorothiolation of Iodonium Salts



was decreased to 10% when the reaction was performed in the open air. Although the detailed mechanism remains ambiguous at present, we reasoned that directly generating *S*-hydrogen phosphorothioate by reaction of $R_2P(O)H$ and elemental sulfur would react with arenediazonium salt leading to the formation of *S*-aryl phosphorothioates via a radical pathway in the presence of copper catalyst.[6,13]

We next examined the reactions of various substituted arenediazonium tetrafluoroborates **5** with sulfur powder and $R_2P(O)H$ compounds to probe the scope of the reaction (Scheme 3). It was found that a wide range of arenediazonium tetrafluoroborates proceeded efficiently. With a methyl substitutent on benzene, such as *p*-, *m*-, and *o*-methyl groups (**5b**−**d**), these compounds reacted efficiently to give the desired products in good yields. Halogen atoms such as fluorine, chlorine, bromine, and iodine (**5e**−**k**) have little influence under the optimized reaction conditions to afford the corresponding products in moderate to good yields. The *ortho*-substituted diazonium salts gave much lower yields because of their steric effects (**5c**,**h**−**j**).

Diazonium salts with electron-donating (methoxy) or electron-withdrawing (CN, CH_3CO, CF_3, NO_2, COOEt, and $CONH_2$) groups all produced the desired products in good yields, suggesting that the substituted groups did not have a significant influence on the reaction (**5l**−**r**). In regard to the H-phosphonates, in addition to **3a**, dibenzyl (**3b**), dimethyl (**3c**), and diisopropyl (**3d**) all could be used as the substrates, generating the corresponding *S*-aryl phosphorothioates (**4f**−**h**) in 70−81% yields. When ethyl phenylphosphinate (**3e**) was used, **4i** was obtained in good yield. Diphenylphosphine oxide was also examined. Unfortunately, only a 22% yield of the desired P−S−C bond-forming product was obtained.

In order to demonstrate the practical application of these methods, phosphorothiolation of diaryliodonium (5 mmol) and arenediazonium (6 mmol) salts was conducted and afforded **4a** in good yields (Scheme 4).

■ CONCLUSION

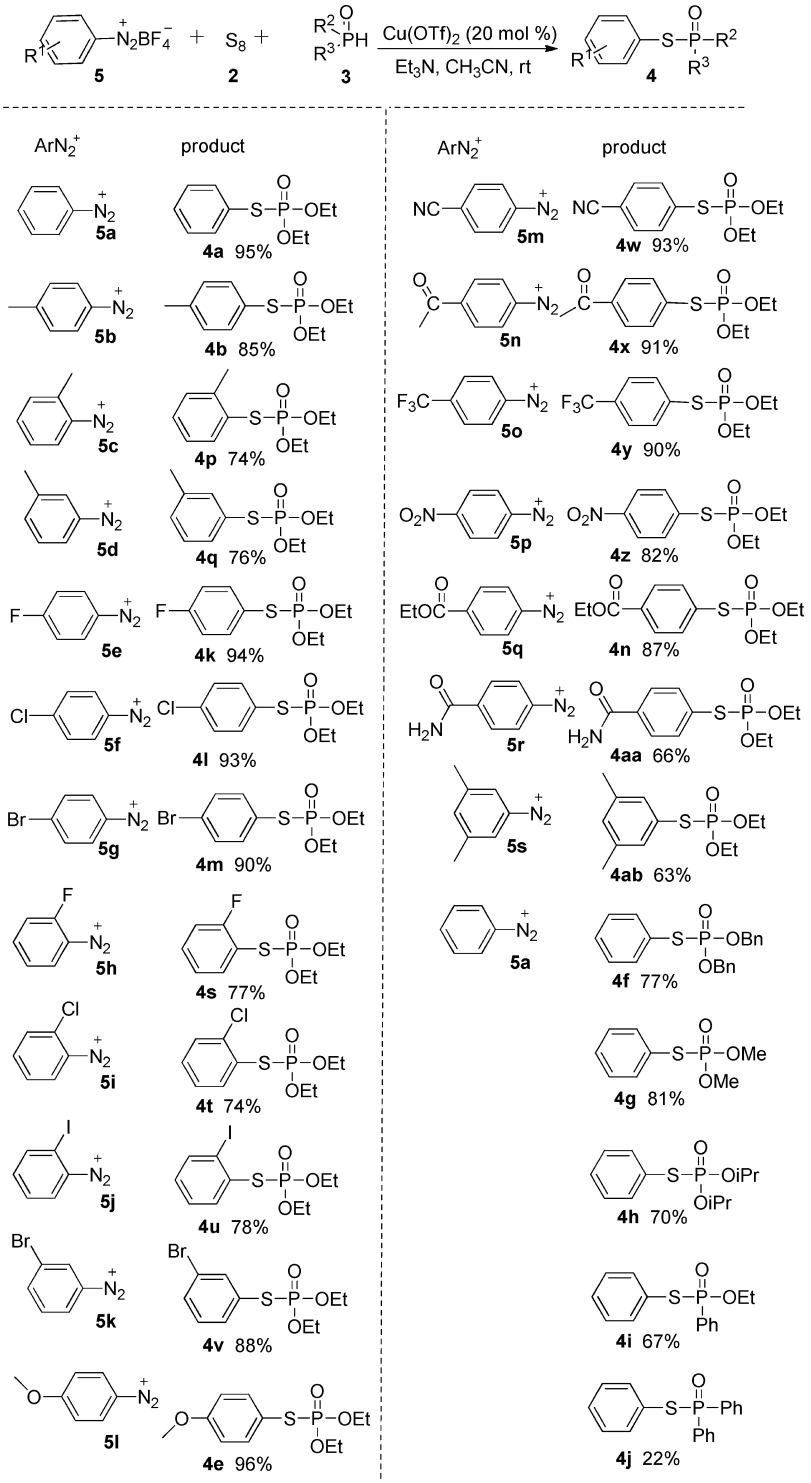
In conclusion, we have developed two novel copper-catalyzed phosphorus−sulfur−carbon(aryl) bond-forming reactions which proceed in good yield via phosphorothiolation of diaryliodonium or diazonium salts with $R_2P(O)H$ compounds and sulfur powder. The reactions described provide novel accesses to *S*-aryl phosphorothioates and cover a broad scope of substrates. Importantly, this transformation would provide a new pathway for the formation of P−S and C−S bonds in one reaction. Moreover, the diaryliodonium salts and diazonium salts can be readily prepared from the corresponding cheap arene compounds. In addition, the use of an inexpensive Cu(II) catalyst without any ligands, using readily available sulfur powder (S_8) and $R_2P(O)H$ compounds, means that this facile protocol will have wide application for the construction of biologically active *S*-aryl phosphorothioates.

■ EXPERIMENTAL SECTION

General Methods. All reagents were purchased and used without further purification. The solvent was freshly distilled. All new

DOI: 10.1021/acs.joc.6b00925
J. Org. Chem. 2016, 81, 5588−5594

Scheme 3. Scope of Phosphorothiolation of Diazonium Salts



compounds were further characterized by HRMS (FT-ICR-MS) and electrospray ionization source in positive-ion mode.

1. General Procedure for the Phosphorothiolation of Diaryliodonium Salts (Method A). A 10 mL tube was charged with $Cu(acac)_2$ (0.03 mmol, 7.8 mg), $R_2P(O)H$ (0.30 mmol), elemental sulfur (0.45 mmol, 14.4 mg), diaryliodonium triflate (0.30 mmol), Et_3N (0.45 mmol, 45.5 mg), and CH_3CN (1.5 mL), and the reaction mixture was stirred at room temperature open to air for 20 h. After completion, the crude reaction mixture was purified by flash chromatography using petroleum−AcOEt (3:1, v/v) as the eluent to give *S*-aryl phosphorothioates.

The preparations of symmetrical and unsymmetrical iodonium salts are shown in ref 9.

2. General Procedure for the Phosphorothiolation of Arenediazonium Salts (Method B). An oven-dried Schlenk tube with a magnetic stir bar containing $Cu(OTf)_2$ (0.06 mmol, 21.7 mg), $R_2P(O)H$ (0.30 mmol), and elemental sulfur (0.45 mmol, 14.4 mg) was evacuated and purged with nitrogen three times. Et_3N (0.45 mmol, 45.5 mg) and CH_3CN (1.0 mL) were added to the system at room temperature, and the reaction mixture was stirred at room temperature for 20 min. Then, arenediazonium salt (0.36 mmol) in CH_3CN (0.5 mL) was added to the system at room temperature. The resulting

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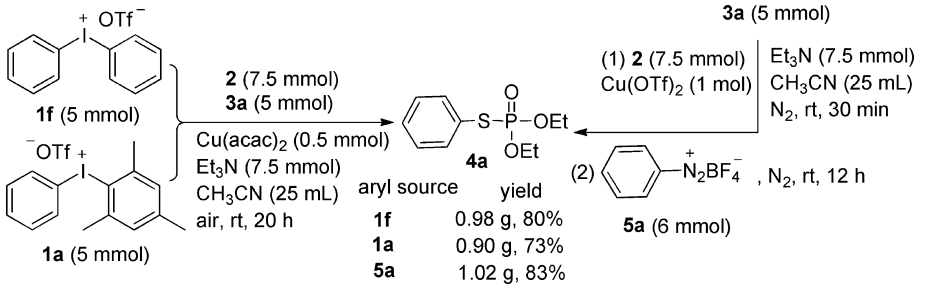
Scheme 4. Scale-up Preparation of 4a



mixture was stirred at room temperature for 12 h. After completion, the crude reaction mixture was purified by flash chromatography using petroleum−AcOEt (3:1, v/v) as the eluent to give *S*-aryl phosphorothioates.

The preparations of arenediazonium salts are shown in ref 11f.

*O,O-Diethyl S-Phenyl Phosphorothioate (**4a**) (CAS Registry No. 1889-58-3).*[6] Yield: 69.8 mg, 95% (method A); 70.1 mg, 95% (method B). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) (method B): δ 7.58−7.55 (m, 2 H), 7.35−7.31 (m, 3 H), 4.26−4.11 (m, 4 H), 1.32−1.28 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 134.6 (d, J = 5.2 Hz), 129.4 (d, J = 2.0 Hz), 129.0 (d, J = 2.6 Hz), 126.6 (d, J = 7.2 Hz), 64.1 (d, J = 6.3 Hz), 16.0 (d, J = 7.1 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 22.8. MS-ESI: m/z 268.8, $[M + Na]^+$.

*O,O-Diethyl S-p-Tolyl Phosphorothioate (**4b**) (CAS Registry No. 4143-38-8).*[6] Yield: 66.0 mg, 85% (method A); 66.3 mg, 85% (method B). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) (method B): δ 7.45−7.43 (m, 2 H), 7.15 (d, J = 8.1 Hz, 2 H), 4.26−4.11 (m, 4 H), 2.34 (d, J = 1.8 Hz, 3 H), 1.32−1.29 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 139.3 (d, J = 3.0 Hz), 134.6 (d, J = 5.0 Hz), 130.1 (d, J = 2.3 Hz), 122.8 (d, J = 7.3 Hz), 64.0 (d, J = 6.1 Hz), 21.2, 16.0 (d, J = 7.3 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 23.3. MS-ESI: m/z 282.8, $[M + Na]^+$.

*S-(4-(tert-Butyl)phenyl) O,O-Diethyl Phosphorothioate (**4c**).* Yield: 73.4 mg, 81% (method A). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.48−7.46 (m, 2 H), 7.35 (d, J = 8.3 Hz, 2 H), 4.26−4.13 (m, 4 H), 1.32−1.30 (m, 15 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 152.5 (d, J = 3.1 Hz), 134.5 (d, J = 4.9 Hz), 126.6 (d, J = 2.3 Hz), 122.9 (d, J = 7.2 Hz), 64.1 (d, J = 6.1 Hz), 34.8, 31.3, 21.1, 16.1 (d, J = 7.3 Hz). $^{31}P\{^1H\}$NMR (162 MHz, $CDCl_3$, ppm): δ 23.4. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{14}H_{23}NaO_3PS^+$ 325.0998, found 325.0988).

*S-(2,5-Dimethylphenyl) O,O-Diethyl Phosphorothioate (**4d**) (CAS Registry No. 1628447-77-7).*[5i] Yield: 57.6 mg, 70% (method A). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.41 (s, 1 H), 7.12 (d, J = 7.9 Hz, 1 H), 7.06 (d, J = 7.9 Hz, 1 H), 4.22−4.09 (m, 4 H), 2.47 (s, 3H), 2.30 (s, 3 H), 1.31−1.28 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 139.2 (d, J = 5.6 Hz), 136.9 (d, J = 3.9 Hz), 136.4 (d, J = 2.6 Hz), 130.7 (d, J = 2.6 Hz), 130.4 (d, J = 3.3 Hz), 125.3 (d, J = 7.3 Hz), 64.2 (d, J = 6.7 Hz), 21.0, 20.9, 16.1 (d, J = 7.2 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 23.4. MS-ESI: m/z 296.9, $[M + Na]^+$.

*O,O-Diethyl S-(4-Methoxyphenyl) Phosphorothioate (**4e**) (CAS Registry No. 56806-76-9).*[5j] Yield: 58.0 mg, 70% (method A); 79.5 mg, 96% (method B). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) (method B): δ 7.48−7.46 (m, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 4.25−4.10 (m, 4 H), 3.80 (s, 3 H), 1.33−1.29 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 160.5 (d, J = 2.9 Hz), 136.3 (d, J = 4.7 Hz), 116.6 (d, J = 7.5 Hz), 115.0 (d, J = 2.6 Hz), 64.0 (d, J = 6.3 Hz), 55.4, 16.0 (d, J = 7.1 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 23.5. MS-ESI: m/z 298.9, $[M + Na]^+$.

*O,O-Dibenzyl S-Phenyl Phosphorothioate (**4f**) (CAS Registry No. 1608108-22-0).*[5c] Yield: 94.3 mg, 85% (method A); 85.5 mg, 77% (method B). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) (method B): δ 7.48−7.46 (m, 2 H), 7.30−7.23 (m, 13 H), 5.14−5.05 (m, 4 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 135.3 (d, J = 7.6 Hz), 134.8 (d, J = 5.3 Hz), 129.4 (d, J = 2.2 Hz), 129.1 (d, J = 2.8 Hz), 128.6, 128.5, 128.0, 125.9 (d, J = 7.3 Hz), 69.4 (d, J = 6.4 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 23.9. MS-ESI: m/z 370.9, $[M + H]^+$.

*O,O-Dimethyl S-Phenyl Phosphorothioate (**4g**) (CAS Registry No. 4237-00-7).*[5j] Yield: 52.3 mg, 80% (method A); 53.0 mg, 81% (method B). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) (method B): δ 7.56−7.54 (m, 2 H), 7.38−7.32 (m, 3 H), 3.82 (s, 3 H), 3.79 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 134.7 (d, J = 5.4 Hz), 129.6 (d, J = 1.9 Hz), 129.3 (d, J = 3.2 Hz), 126.1 (d, J = 7.4 Hz), 54.3 (d, J = 6.4 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 26.2. MS-ESI: m/z 240.8, $[M + Na]^+$.

*O,O-Diisopropyl S-Phenyl Phosphorothioate (**4h**) (CAS Registry No. 15267-38-6).*[6] Yield: 58.4 mg, 71% (method A); 57.4 mg, 70% (method B). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) (method B): δ 7.61−7.58 (m, 2 H), 7.35−7.32 (m, 3 H), 4.80−4.72 (m, 2 H), 1.32 (d, J = 6.2 Hz, 6 H), 1.25 (d, J = 6.2 Hz, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 134.3 (d, J = 5.3 Hz), 129.2 (d, J = 1.8 Hz), 128.7 (d, J = 2.4 Hz), 127.4 (d, J = 7.0 Hz), 73.4 (d, J = 6.8 Hz), 23.9 (d, J = 4.2 Hz), 23.6 (d, J = 5.7 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 20.4. MS-ESI: m/z 297.0, $[M + Na]^+$.

*O-Ethyl S-Phenyl Phenylphosphonothioate (**4i**) (CAS Registry No. 1629085-78-4).*[6] Yield: 61.7 mg, 74% (method A); 55.9 mg, 67%, (method B). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) (method B): δ 7.67−7.62 (m, 2 H), 7.50−7.46 (m, 1 H), 7.38−7.33 (m, 2 H), 7.30−7.26 (m, 3 H), 7.19 (t, J = 7.7 Hz, 2 H), 4.42−4.22 (m, 2 H), 1.41−1.38 (m, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 135.5 (d, J = 4.2 Hz), 132.5 (d, J = 3.1 Hz), 131.5 (d, J = 10.6 Hz), 131.6 (d, J = 151.3 Hz), 129.2 (d, J = 2.1 Hz), 129.0 (d, J = 2.7 Hz), 128.3 (d, J = 15.0 Hz), 126.7 (d, J = 5.6 Hz), 62.5 (d, J = 6.9 Hz), 16.4 (d, J = 6.8 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 41.7. MS-ESI: m/z 278.8, $[M + H]^+$.

*S-Phenyl Diphenylphosphinothioate (**4j**) (CAS Registry No. 5510-78-1).*[5g] Yield: 60.4 mg, 65% (method A); 20.5 mg, 22% (method B). White solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) (method B): δ 7.87−7.82 (m, 4 H), 7.56−7.38 (m, 8 H), 7.26−7.17 (m, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 135.5 (d, J = 4.0 Hz), 132.7 (d, J = 106.8 Hz), 132.4 (d, J = 2.9 Hz), 131.7 (d, J = 10.2 Hz), 129.2 (d, J = 1.2 Hz), 129.0 (d, J = 1.8 Hz), 128.6 (d, J = 13.2 Hz), 126.3 (d, J = 5.3 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 41.4. MS-ESI: m/z 333.1, $[M + Na]^+$.

*O,O-Diethyl S-(4-Fluorophenyl)phosphorothioate (**4k**) (CAS Registry No. 333-42-6).*[6] Yield: 71.2 mg, 90% (method A); 74.4 mg, 94% (method B). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) (method B): δ 7.54−7.50 (m, 2 H), 7.03 (t, J = 8.5 Hz, 2 H), 4.23−4.10 (m, 4 H), 1.30−1.27 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 163.4 (dd, J = 250.0 Hz, J = 2.7 HZ), 136.8 (dd, J = 8.4 Hz, J = 4.9 Hz), 121.8 (dd, J = 7.3 Hz, J = 3.0 Hz), 116.7 (dd, J = 22.1 Hz, J = 1.9 Hz), 64.3 (d, J = 6.3 Hz), 16.1 (d, J = 7.1 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 22.6. $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$, ppm): δ −111.6 (d, J = 4.9 Hz). MS-ESI: m/z 286.8, $[M + Na]^+$.

*S-(4-Chlorophenyl) O,O-Diethyl Phosphorothioate (**4l**) (CAS Registry No. 4524-70-3).*[6] Yield: 73.1 mg, 87% (method A); 78.1 mg, 93% (method B). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) (method B): δ 7.52−7.49 (m, 2 H), 7.32 (d, J = 8.4 Hz, 2 H), 4.27−4.11 (m, 4 H), 1.34−1.30 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 135.8 (d, J = 5.2 Hz), 135.5 (d, J = 3.5 Hz), 129.6 (d, J = 2.2 Hz), 125.2 (d, J = 7.3 Hz), 64.3 (d, J = 6.3 Hz), 16.0 (d, J = 7.1

DOI: 10.1021/acs.joc.6b00925
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Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 22.1. MS-ESI: m/z 302.9, $[M + Na]^+$.

*S-(4-Bromophenyl) O,O-Diethyl Phosphorothioate (**4m**) (CAS Registry No. 15224-36-9).*[6] Yield: 85.8 mg, 88% (method A); 87.5 mg, 90% (method B). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm) (method B): δ 7.49−7.42 (m, 4 H), 4.27−4.11 (m, 4 H), 1.33−1.30 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 136.0 (d, J = 5.3 Hz), 132.5 (d, J = 2.0 Hz), 125.8 (d, J = 7.3 Hz), 123.6 (d, J = 3.6 Hz), 64.3 (d, J = 6.4 Hz), 16.0 (d, J = 7.0 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 21.9. MS-ESI: m/z 346.9, $[M + Na]^+$.

*Ethyl 4-((Diethoxyphosphoryl)thio)benzoate (**4n**).* Yield: 89.6 mg, 94% (method A); 83.0 mg, 87% (method B). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm) (method B): δ 8.01 (d, J = 8.2 Hz, 2 H), 7.66−7.64 (m, 2 H), 4.41−4.36 (m, 2 H), 4.29−4.13 (m, 4 H), 1.39 (t, J = 7.1 Hz, 3 H), 1.34−1.30 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 165.8, 133.7 (d, J = 5.7 Hz), 132.8 (d, J = 7.0 Hz), 130.8 (d, J = 3.0 Hz), 130.2 (d, J = 1.6 Hz), 64.4 (d, J = 6.4 Hz), 61.3, 16.0 (d, J = 7.2 Hz), 14.3. $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 21.4. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{13}H_{19}NaO_5PS^+$ 341.0583, found 341.0575).

*O,O-Diethyl S-(3-(Trifluoromethyl)phenyl) Phosphorothioate (**4o**) (CAS Registry No. 38726-06-6).*[6] Yield: 82.0 mg, 87% (method A). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.81(s, 1 H), 7.47 (d, J = 7.9 Hz, 1 H), 7.76 (d, J = 7.8 Hz, 1 H), 7.60 (t, J = 7.8 Hz, 1 H), 4.25−4.13 (m, 4 H), 1.31−1.28 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 137.9 (d, J = 5.2 Hz), 131.8 (dd, J = 32.8 Hz, J = 1.8 Hz), 131.4−131.2 (m), 129.88 (d, J = 2.7 Hz), 128.4 (d, J = 7.1 Hz), 125.8 (q, J = 3.28 Hz), 123.6 (d, J = 272.5 Hz), 64.5 (d, J = 6.4 Hz), 16.0 (d, J = 7.2 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 21.6. ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ −62.9. MS-ESI: m/z 337.0, $[M + Na]^+$.

*O,O-Diethyl S-o-Tolyl Phosphorothioate (**4p**) (CAS Registry No. 94583-02-5).*[6] Yield: 56.9 mg, 73% (method A); 57.7 mg, 74% (method B). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm) (method B): δ 7.60 (d, J = 8.2 Hz, 1 H), 7.26−7.24 (m, 2 H), 7.20−7.15 (m, 1 H), 4.23−4.08 (m, 4 H), 2.52 (d, J = 1.0 Hz, 3 H), 1.31−1.27 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 142.2 (d, J = 5.4 Hz), 136.2 (d, J = 4.0 Hz), 130.9 (d, J = 2.6 Hz), 129.5 (d, J = 2.9 Hz), 126.8 (d, J = 2.5 Hz), 125.8 (d, J = 7.4 Hz), 64.2 (d, J = 6.7 Hz), 21.4, 16.1 (d, J = 7.1 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 23.0. MS-ESI: m/z 283.0, $[M + Na]^+$.

*O,O-Diethyl S-m-Tolyl Phosphorothioate (**4q**) (CAS Registry No. 108481-79-4).*[6] Yield: 65.5 mg, 84% (method A); 59.3 mg, 76% (method B). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm) (method B): δ 7.37 (d, J = 10.3 Hz, 2 H), 7.22 (d, J = 7.6 Hz, 1 H), 7.16 (d, J = 7.6 Hz, 1 H), 4.28−4.11 (m, 4 H), 2.34 (s, 3 H), 1.33−1.29 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 139.3 (d, J = 2.2 Hz), 135.2 (d, J = 5.2 Hz), 131.6 (d, J = 5.2 Hz), 129.9 (d, J = 2.8 Hz), 129.2 (d, J = 2.1 Hz), 126.2 (d, J = 7.2 Hz), 64.1 (d, J = 6.1 Hz), 21.3, 16.0 (d, J = 7.2 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 23.1. MS-ESI: m/z 282.9, $[M + Na]^+$.

*S-[1,1′-Biphenyl]-4-yl O,O-Diethyl Phosphorothioate (**4r**).* Yield: 67.6 mg, 70% (method A). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.64−7.62 (m, 2 H), 7.57 (d, J = 7.8 Hz, 4 H), 7.44 (t, J = 7.6 Hz, 2 H), 7.38−7.35 (m, 1 H), 4.29−4.16 (m, 4 H), 1.35−1.32 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 142.1 (d, J = 3.0 Hz), 140.0, 135.0 (d, J = 5.3 Hz), 129.0, 128.1 (d, J = 2.0 Hz), 127.9, 127.2, 125.4 (d, J = 7.3 Hz), 64.2 (d, J = 6.1 Hz), 16.2 (d, J = 7.2 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 22.8. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{19}NaO_3PS^+$ 345.0685, found 345.0669).

*O,O-Diethyl S-(2-Fluorophenyl) Phosphorothioate (**4s**) (CAS Registry No. 1883501-47-0).*[6] Yield: 61.0 mg, 77% (method B). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm) (method A): δ 7.64−7.60 (m, 1 H), 7.41−7.35 (m, 1 H), 7.17−7.11 (m, 2 H), 4.30−4.16 (m, 4 H), 1.34−1.31 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 162.7 (dd, J = 248.8 Hz, J = 5.6 Hz), 137.6 (d, J = 4.3 Hz), 131.7 (dd, J = 8.0 Hz, J = 2.76), 124.9−125.0 (m), 116.4 (dd, J = 22.9 Hz, J = 2.3 Hz), 113.9 (dd, J = 18.5 Hz, J = 7.5 Hz), 64.3 (d, J = 6.0 Hz), 16.0 (d, J = 7.0 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 21.3 (d, J = 2.8 Hz). ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ −106.2 (d, J = 4.0 Hz). MS-ESI: m/z 286.8, $[M + Na]^+$.

*S-(2-Chlorophenyl) O,O-Diethyl Phosphorothioate (**4t**) (CAS Registry No. 15224-41-6).*[6] Yield: 62.2 mg, 74% (method B). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.76 (d, J = 7.5 Hz, 1 H), 7.46 (d, J = 7.6 Hz, 1 H), 7.32−7.24 (m, 2 H), 4.30−4.16 (m, 4 H), 1.34−1.30 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 137.9 (d, J = 6.9 Hz), 136.8 (d, J = 4.0 Hz), 130.3 (d, J = 6.7 Hz), 127.5, 126.4 (d, J = 6.8 Hz), 64.4 (d, J = 6.3 Hz), 16.0 (d, J = 7.3 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 21.2. MS-ESI: m/z 302.9, $[M + Na]^+$.

*O,O-Diethyl S-(2-Iodophenyl) Phosphorothioate (**4u**).* Yield: 87.0 mg, 78% (method B). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.90 (d, J = 8.0 Hz, 1 H), 7.83−7.80 (m, 1 H), 7.37−7.33 (m, 1 H), 7.02 (t, J = 7.7 Hz, 1 H), 4.31−4.16 (m, 4 H), 1.34−1.30 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 140.2 (d, J = 2.1 Hz), 135.3 (d, J = 4.0 Hz), 132.9 (d, J = 6.7 Hz), 130.2, 129.1 (d, J = 2.0 Hz), 105.6 (d, J = 8.1 Hz), 64.5 (d, J = 6.4 Hz), 16.1 (d, J = 7.2 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 21.6. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{10}H_{15}IO_3PS^+$ 372.9519, found 372.9515).

*S-(2-Bromophenyl) O,O-Diethyl phosphorothioate (**4v**) (CAS Registry No. 1807788-31-3).*[5j] Yield: 85.5 mg, 88% (method B). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.71−7.69 (m, 1 H), 7.51−7.46 (m, 2 H), 7.21 (t, J = 7.9 Hz, 1 H), 4.26−4.11 (m, 4 H), 1.33−1.29 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 137.0 (d, J = 5.3 Hz), 133.0 (d, J = 5.3 Hz), 132.1 (d, J = 2.7 Hz), 130.6 (d, J = 2.1 Hz), 128.8 (d, J = 7.0 Hz), 122.7 (d, J = 2.7 Hz), 64.3 (d, J = 6.4 Hz), 16.0 (d, J = 7.1 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 21.77. MS-ESI: m/z 346.9, $[M + Na]^+$.

*S-(4-Cyanophenyl) O,O-Diethyl Phosphorothioate (**4w**) (CAS Registry No. 179637-16-2).*[6] Yield: 75.5 mg, 93% (method B). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.69−7.67 (m, 2 H), 7.61 (d, J = 8.2 Hz, 2 H), 4.25−4.14 (m, 4 H), 1.32−1.30 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 134.2 (d, J = 6.0 Hz), 134.0 (d, J = 6.7 Hz), 132.7, 118.0, 112.5 (d, J = 2.3 Hz), 64.7 (d, J = 6.5 Hz), 16.0 (d, J = 6.9 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 20.3. MS-ESI: m/z 294.0, $[M + Na]^+$.

*S-(4-Acetylphenyl) O,O-Diethyl Phosphorothioate (**4x**) (CAS Registry No. 1883501-44-7).*[6] Yield: 78.6 mg, 91% (method B). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.88 (d, J = 8.3 Hz, 2 H), 7.65−7.63 (m, 2 H), 4.25−4.11 (m, 4 H), 2.56 (s, 3 H), 1.30−1.27 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 197.2 (s), 137.0, 133.9 (d, J = 5.8 Hz), 133.2 (d, J = 6.9 Hz), 129.0 (d, J = 1.2 Hz), 64.4 (d, J = 6.4 Hz), 26.7, 16.0 (d, J = 7.0 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 21.2. MS-ESI: m/z 310.8, $[M + Na]^+$.

*O,O-Diethyl S-(4-(Trifluoromethyl)phenyl) Phosphorothioate (**4y**) (CAS Registry No. 1883501-42-5).*[6] Yield: 84.8 mg, 90% (method B). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.70 (d, J = 7.8 Hz, 2 H), 7.60 (d, J = 8.4 Hz, 2 H), 4.28−4.13 (m, 4 H), 1.34−1.30 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 134.3 (d, J = 5.6 Hz), 132.0 (d, J = 6.6 Hz), 131.0 (m, J = 17.7.0 Hz), 126.2, 123.8 (d, J = 272.1 Hz), 64.5 (d, J = 6.4 Hz), 16.0 (d, J = 7.1 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 21.3. $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$, ppm): δ −62.9. MS-ESI: m/z 336.9, $[M + Na]^+$.

*O,O-Diethyl S-(4-Nitrophenyl) Phosphorothioate (**4z**).* Yield: 71.6 mg, 82% (method B). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 8.20 (d, J = 8.6 Hz, 2 H), 7.78−7.75 (m, 2 H), 4.32−4.15 (m, 4 H), 1.36−1.33 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 147.9, 136.3 (d, J = 6.5 Hz), 134.2 (d, J = 6.0 Hz), 124.2, 64.8 (d, J = 6.4 Hz), 16.1 (d, J = 7.0 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 19.8. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{10}H_{14}NaNO_5PS^+$ 314.0223, found 314.0218.

*S-(4-Carbamoylphenyl) O,O-Diethyl Phosphorothioate (**4aa**).* Yield: 57.2 mg, 66% (method B). Yellow solid. Mp: 144.5−146.8 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.78 (d, J = 8.0 Hz, 2 H), 7.64 (t, J = 4.1 Hz, 2 H), 6.33 (s, 1 H), 5.89 (s, 1 H), 4.26−4.13 (m, 4 H), 1.33−1.30 (m, 6 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 168.6, 134.3 (d, J = 5.4 Hz), 133.9 (d, J = 2.6 Hz), 131.6 (d, J = 6.6 Hz), 128.3, 64.6 (d, J = 6.4 Hz), 16.1 (d, J = 7.0 Hz); $^{31}P\{^1H\}$ NMR

DOI: 10.1021/acs.joc.6b00925
J. Org. Chem. 2016, 81, 5588−5594

(162 MHz, $CDCl_3$, ppm): δ 21.7. HRMS-ESI: m/z $[M + Na]^+$ calcd for $C_{11}H_{16}NaNO_4PS^+$ 312.0430, found 312.0415.

*S-(3,5-Dimethylphenyl) O,O-Diethyl Phosphorothioate (**4ab**) (CAS Registry No. 1883501-37-8).*[6] Yield: 51.8 mg, 63% (method B). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.17 (s, 2 H), 6.97 (s, 1 H), 4.24−4.12 (m, 4 H), 2.29 (s, 6 H), 1.32−1.29 (m, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 139.1 (d, J = 2.0 Hz), 132.3 (d, J = 5.2 Hz), 131.0 (d, J = 2.8 Hz), 125.8 (d, J = 7.1 Hz), 64.1 (d, J = 6.2 Hz), 21.3, 16.1 (d, J = 7.3 Hz). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$, ppm): δ 23.4. MS-ESI: m/z 296.8, $[M + Na]^+$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00925.

^1H and ^{13}C NMR spectra of compounds **4a−z** and **4aa,ab** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the Chinese National Natural Science Foundation (21232005, 21375113), the National Basic Research Program of China (2012CB821600), and the Fundamental Research Funds for the Central Universities (20720160030).

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DOI: 10.1021/acs.joc.6b00925
J. Org. Chem. 2016, 81, 5588−5594