Copper(I) Iodide Catalyzed Synthesis of Thiophosphates by Coupling of *H*-Phosphonates with Benzenethiols

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Abstract: A simple, efficient, and new method has been developed for the preparation of thiophosphates from benzenethiols. The method involves copper(I) iodide catalyzed coupling of thiols with *H*-phosphonates in the presence of triethylamine. The reaction proceeds effectively to afford the corresponding thiophosphates in moderate to good yields via an aerobic dehydrogenative coupling of *H*-phosphonates with benzenethiols. This method is easy, rapid, and good-yielding for the synthesis of thiophosphates from benzenethiols.

Key words: thiophosphates, copper iodide, thiols, *H*-phosphonates, coupling

Phosphate esters are valuable intermediates in organic synthesis.[1] Among the phosphate esters, thiophosphate derivatives are of interest as effective pesticides.[2] A number of dialkyl aryl thiophosphates have been studied as nerve gases, insecticides, and enzyme modifiers.[3] *S*-Aryl phosphorothioates can be also used to construct an intramolecular pyrophosphate linkage[4] and for the thiophosphorylation of terminal alkynes.[5] In recent years a number of thiophosphates have been introduced as potential HIV-1 and ACHE inhibitors.[6] The synthesis of thiophosphates is an important objective in organic synthesis, since they have found use in the preparation of biologically active molecules, and are also versatile intermediate in organic synthesis. Despite the wide range of industrial and synthetic applications, the synthesis of thiophosphates has received little attention. Synthetic routes to thiophosphates, not generally applicable, involve the reactions of dialkyl phosphonates with sulfenyl chlorides,[7] sulfenyl cyanides,[8] thiosulfonates,[9] disulfides,[10] and sulfur,[11] and condensation of phosphorochloridates with thiols.[12] However, most of the methodologies for the synthesis of *S*-aryl phosphorothioates have involved special reagents sensitive to air or moisture, thus they must be performed under special reaction conditions and this limits their application. The traditional method for the preparation of *S*-aryl phosphorothioates is through the nucleophilic substitution reaction of dialkyl phosphorochloridates $(RO)_2P(O)Cl$ with alkali metal salts such as sodium arenethiolates ArSNa, which suffer from drawbacks such as low yields, tedious procedures, and lack of functionality tolerance.[13] To the best of our knowledge, there is no general and efficient method for the synthesis of thiophosphates.

Copper is an important metal, available in the earth's crust. From an industrial viewpoint, simple and inexpensive copper catalysts play an important role in numerous organic reactions. As part of our efforts to use copper catalysts in organic transformations and to develop novel methods for the synthesis of organophosphorus compounds,[14] herein we report a new method for the synthesis of phosphorothioates via an aerobic dehydrogenative coupling of *H*-phosphonates with benzenethiols. We have found that copper(I) iodide catalyzed coupling of thiols with *H*-phosphonates proceeds effectively in the presence of triethylamine.

Initially, the *H*-phosphonate coupling of diethyl phosphonate (**2a**) with *p*-toluenethiol (**1a**) was chosen as the model reaction and the experimental data for screening conditions are listed in Table 1. A mixture of diethyl phosphonate (**2a**; 1 equiv), *p*-toluenethiol (**1a**; 1.2 equiv), and triethylamine (2.5 equiv) as base was stirred in the presence of copper(I) chloride (5 mol%) as the catalyst in *N*,*N*-dimethylformamide (1 mL) at room temperature for five hours under air to give **3a** in 63% yield (entry 1). Even if copper(I) bromide salt was used instead of copper(I) chloride, the yield was not significantly improved (entry 2). Addition of ligands such as 1,10-phenanthroline or *N*,*N*,*N*′,*N*′-tetramethylethylenediamine was found to enhance the copper(I) chloride catalyzed coupling reaction (entries 3 and 4). When the reaction was carried out in the presence of copper(I) iodide for five hours at room temperature with 1,10-phenanthroline or *N*,*N*,*N*′,*N*′-tetramethylethylenediamine as a ligand, the reaction yield was increased to 93 and 94%, respectively (entries 5 and 6).

In the presence of the ligands, the dehydrogenative homocoupling product of *H*-phosphonates was also detected by ^{31}P NMR.[15] The ligand-free coupling reaction of **1a** with diethyl phosphonate (**2a**) when using copper(I) iodide gave **3a** in 96% yield (entry 7). Screening of various copper(II) salts showed that use of copper(II) chloride and copper(II) sulfate resulted in lower yields compared with that of copper(I) iodide (entries 8 and 9). Solvent screening indicated that *N*,*N*-dimethylformamide was still the best solvent for this reaction (entries 10–12). It should be noted that the reaction failed to give thiophosphate **3a** under an atmosphere of argon instead of air or without copper catalyst under air at room temperature.

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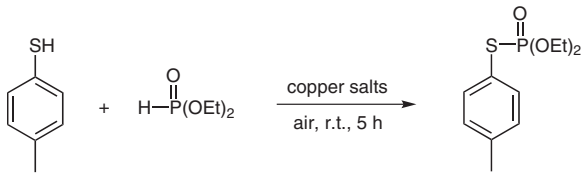
Table 1 Coupling of Diethyl Phosphonate (**2a**) with *p*-Toluenethiol (**1a**) under Different Reaction Conditions[a]



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

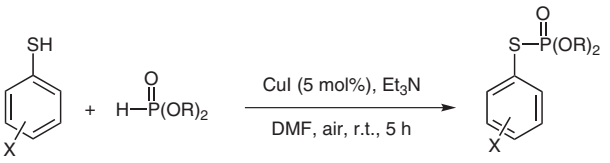
Entry	Copper salt	Solvent	Ligand	Yield (%)[b]
1	CuCl	DMF	–	63
2	CuBr	DMF	–	65
3	CuCl	DMF	1,10-phenanthroline[c,d]	76
4	CuCl	DMF	TMEDA[c,d]	76
5	CuI	DMF	1,10-phenanthroline[c,d]	93
6	CuI	DMF	TMEDA[c,d]	94
7	CuI	DMF	–	96 (91)[e]
8	$CuCl_2$	DMF	–	73
9	$CuSO_4$	DMF	–	70
10	$CuSO_4$	EtOH	–	63
11	CuI	EtOH	–	77
12	CuI	CH_2Cl_2	–	55

[a] Reaction conditions: **2a** (1 mmol), **1a** (1.2 equiv), Et_3N (2.5 equiv), copper salt (5 mol%), solvent (1 mL), air, r.t., 5 h.
[b] Yields are based on **2a** and determined by ^{31}P NMR by comparison to an internal standard.
[c] Ligand (10 mol%) was used.
[d] In the presence of the ligand, the homocoupling product of the *H*-phosphonate was also detected by ^{31}P NMR as a byproduct.
[e] Isolated yield.

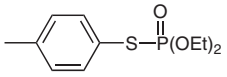
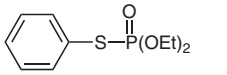
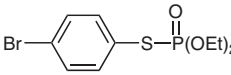
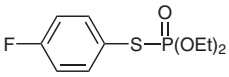
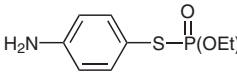
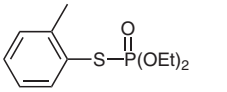
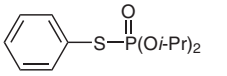
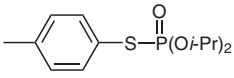
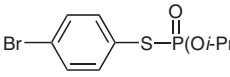
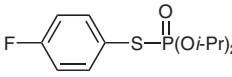
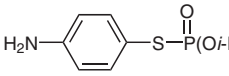
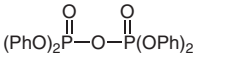
With the optimal conditions established above, we then examined the general applicability of the aerobic dehydrogenative coupling of *H*-phosphonates with benzenethiols, and the results are summarized in Table 2. Diethyl phosphonate offered excellent yields and diisopropyl phosphonate was also employed with high efficiency under the same reaction conditions (Table 2). The unstable diphenyl phosphonate afforded a mixture of unknown products. The reaction of 4-fluorobenzenethiol with diphenyl phosphonate and copper(I) iodide (5 mol%) as the catalyst in *N*,*N*-dimethylformamide (1 mL) at room temperature for five hours under air gave only pyrophosphate **4** in 80% isolated yield (Scheme 1 and entry 13).

Subsequently, our investigations were focused on the use of various benzenethiols. As illustrated in Table 2, the use of substituted benzenethiols bearing electron-withdrawing and -donating groups had no influence on the yields of the products. Benzenethiols bearing a coordinating group such as the amino group could also be used to obtain the

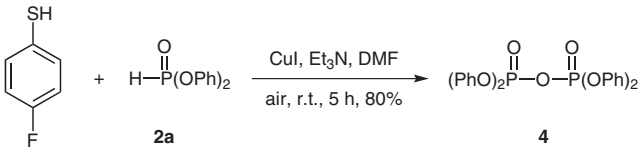
Table 2 Coupling of *H*-Phosphonates with Benzenethiols



1 **2** **3**

Entry	X	R	Product	3[a]	Yield (%)[b]
1	4-Me	Et		**3a**	91
2	H	Et		**3b**	88
3	4-Br	Et		**3c**	92
4	4-F	Et		**3d**	87
5	4-NH_2	Et		**3e**	92
6	2-Me	Et		**3f**	83
7	H	*i*-Pr		**3g**	90
8	4-Me	*i*-Pr		**3h**	93
9	4-Br	*i*-Pr		**3i**	92
10	4-F	*i*-Pr		**3j**	85
11	4-NH_2	*i*-Pr		**3k**	91
12	4-Me	Ph	–	–	–
13	4-F	Ph		**4**	80

[a] Conversions were monitored by TLC.
[b] Yields refer to those of isolated, pure products.



2a **4**

Scheme 1 Reaction of *p*-fluorobenzenethiol with diphenyl phosphonate

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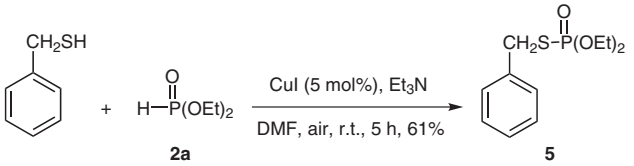
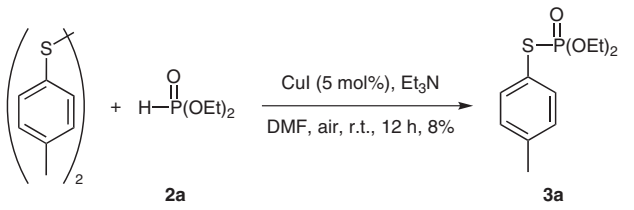
desired coupling product in excellent yield (entries 5 and 11).

It was also possible to carry out this reaction for phenylmethylthiol. The reaction gave the corresponding thiophosphate adduct in a moderate yield (61%), which was possibly due to the lower acidity of phenylmethylthiol compared to that of benzenethiol (Scheme 2).



Scheme 2 Reaction of phenylmethylthiol with diethyl phosphonate

Finally the coupling reaction of disulfides with diethyl phosphonate was studied. The reaction of bis-*p*-tolyl disulfide with diethyl phosphonate in the presence of five mol% of copper(I) iodide and triethylamine in *N*,*N*-dimethylformamide at room temperature for 12 hours gave only 8% of the corresponding thiophosphate **3a** (Scheme 3). The same reaction proceeded smoothly at 40 °C for 24 hours, giving **3a** in 50% yield. Gao et al. reported that diethylamine as a base has a crucial role in the copper-catalyzed coupling reaction of diphenyl disulfide with diisopropyl phosphonate in dimethyl sulfoxide.[10d]



Scheme 3 Reaction of bis-*p*-tolyl disulfide with diethyl phosphonate

We reported here a copper-catalyzed synthesis of thiophosphates by coupling of benzenethiols with dialkyl phosphonates in *N*,*N*-dimethylformamide at room temperature in air. Copper(I) iodide, which is easily available, was found to be an effective catalyst for this transformation. Simple workup, mild reaction conditions, good to excellent yields, and clean reactions make this method an attractive and useful contribution to present methodologies.

All chemicals were commercial products and distilled or recrystallized before use. NMR spectra were obtained on a 400 MHz Bruker Avance instrument. Column chromatography was carried out over silica gel 100 (Merck No. 10184). Merck silica-gel 60 F254 plates (No. 5744) were used for preparative TLC. Mass spectra were measured on a LCMASS micromass LCT and Micromass Autospec instrument. Melting points are uncorrected.

Phosphorothioates 3; General Procedure

The dialkyl phosphonate **2** (1 mmol) was added to a stirred mixture of CuI (0.05 mmol, 5 mol%) and Et_3N (2.5 mmol) in DMF (1 mL). The thiol **1** (1.2 mmol) was added to the reaction mixture and the mixture was stirred for 5 h at r.t. The resulting soln was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The organic layer was washed with brine (50 mL) and dried (Na_2SO_4). The pure product was obtained after column chromatography (silica gel, *n*-hexane–EtOAc, 9:1 to 6:4). All products gave satisfactory spectral data in accord with the assigned structures and literature reports.

***O*,*O*′-Diethyl *S*-4-Tolyl Phosphorothioate (3a)**[10d]

Yield: 237 mg (91%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (dd, *J* = 6.4, 2.4 Hz, 2 H), 7.30–7.31 (m, 3 H), 4.08–4.20 (m, 4 H), 1.25 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.3 (d, *J* = 3 Hz), 134.6 (d, *J* = 5 Hz), 130.2 (d, *J* = 3 Hz), 122.8 (d, *J* = 7 Hz), 64.0 (d, *J* = 6 Hz), 21.2, 16.0 (d, *J* = 8 Hz).

^{31}P NMR (400 MHz, $CDCl_3$): δ = 23.4.

***O*,*O*′-Diethyl *S*-Phenyl Phosphorothioate (3b)**[10d]

Yield: 216 mg (88%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (dd, *J* = 6.4, 2.4 Hz, 2 H), 7.30–7.31 (m, 3 H), 4.08–4.20 (m, 4 H), 1.25 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.5 (d, *J* = 6 Hz), 129.3 (d, *J* = 3 Hz), 129.0 (d, *J* = 3 Hz), 126.5 (d, *J* = 7 Hz), 64.0 (d, *J* = 6 Hz), 15.9 (d, *J* = 7 Hz).

^{31}P NMR (400 MHz, $CDCl_3$): δ = 22.8.

***O*,*O*′-Diethyl *S*-4-Bromophenyl Phosphorothioate (3c)**[16]

Yield: 298 mg (92%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.49 (m, 4 H), 4.13–4.25 (m, 4 H), 1.30 (t, *J* = 7.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9 (d, *J* = 5 Hz), 132.3 (d, *J* = 2 Hz), 125.7 (d, *J* = 7 Hz), 123.6 (d, *J* = 6 Hz), 64.2 (d, *J* = 7 Hz), 16.0 (d, *J* = 7 Hz).

^{31}P NMR (400 MHz, $CDCl_3$): δ = 22.0.

***O*,*O*′-Diethyl *S*-4-Fluorophenyl Phosphorothioate (3d)**[16]

Yield: 230 mg (87%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (m, 2 H), 7.06 (t, *J* = 7.6, 2 H), 4.13–4.25 (m, 4 H), 1.32 (t, *J* = 7.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3 (dd, *J* = 248, 3 Hz), 136.7 (dd, *J* = 10, 5 Hz), 121.6 (d, *J* = 4 Hz), 116.5 (dd, *J* = 22, 2 Hz), 64.1 (d, *J* = 7 Hz), 16.0 (d, *J* = 7 Hz).

^{31}P NMR (400 MHz, $CDCl_3$): δ = 22.7 (d, *J* = 4 Hz).

***O*,*O*′-Diethyl *S*-4-Aminophenyl Phosphorothioate (3e)**

Yield: 240 mg (92%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 8, 2 Hz, 2 H), 6.64 (d, *J* = 8 Hz, 2 H), 4.13–4.24 (m, 4 H), 4.13–4.13 (br, 2 H), 1.32 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 137.3 (d, *J* = 4 H), 115.9 (d, *J* = 2 Hz), 113.2 (d, *J* = 7 Hz), 63.9 (d, *J* = 6 Hz), 16.0 (d, *J* = 7 Hz).

^{31}P NMR (400 MHz, $CDCl_3$): δ = 24.1.

HRMS: *m*/*z* [MH^+] calcd for $C_{10}H_{17}NO_3SP$: 262.0667; found: 262.0663.

***O*,*O*′-Diethyl *S*-2-Tolyl Phosphorothioate (3f)**[17]

Yield: 234 mg (83%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8 Hz, 2 H), 6.86 (d, *J* = 8 Hz, 2 H), 6.77 (m, 2 H), 3.80–3.69 (m, 4 H), 2.12 (s, 3 H), 0.88 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.8 (d, *J* = 3 Hz), 135.8 (d, *J* = 4 Hz), 130.5 (d, *J* = 2 Hz), 129.1 (d, *J* = 3 Hz), 126.3 (d, *J* = 3 Hz), 125.2 (d, *J* = 7 Hz), 63.7 (d, *J* = 7 Hz), 20.9, 15.6 (d, *J* = 7 Hz).

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^{31}P NMR (400 MHz, $CDCl_3$): δ = 22.1.

***O*,*O′*-Diisopropyl *S*-Phenyl Phosphorothioate (3g)**[10d]
Yield: 247 mg (90%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (m, 2 H), 7.31 (m, 3 H), 4.71–4.77 (m, 2 H), 1.30 (d, *J* = 2 Hz, 6 H), 1.23 (d, *J* = 1.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.2 (d, *J* = 6 Hz), 129.2 (d, *J* = 3 Hz), 128.6 (d, *J* = 3 Hz), 127.3 (d, *J* = 3 Hz), 73.3 (d, *J* = 7 Hz), 23.8 (d, *J* = 4 Hz), 23.5 (d, *J* = 6 Hz).

^{31}P NMR (400 MHz, $CDCl_3$): δ = 20.43.

***O*,*O′*-Diisopropyl *S*-4-Tolyl Phosphorothioate (3h)**[10d]
Yield: 268 mg (93%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (dd, *J* = 8, 1.6 Hz, 2 H), 7.16 (d, *J* = 8 Hz, 2 H), 4.75–4.80 (m, 4 H), 2.35 (s, 3 H), 1.35 (d, *J* = 6 Hz, 6 H), 1.28 (d, *J* = 6.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9 (d, *J* = 3 Hz), 134.3 (d, *J* = 5 Hz), 130.0 (d, *J* = 2 Hz), 123.5 (d, *J* = 7 Hz), 73.2 (d, *J* = 7 Hz), 23.8 (d, 5 Hz), 23.5 (d, *J* = 5 Hz), 21.1.

^{31}P NMR (400 MHz, $CDCl_3$): δ = 20.9.

***O*,*O′*-Diisopropyl *S*-4-Bromophenyl Phosphorothioate (3i)**
Yield: 324 mg (92%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (s, 4 H), 4.74–4.80 (m, 2 H), 1.35 (d, *J* = 6.4 Hz, 6 H), 1.29 (d, *J* = 6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6 (d, *J* = 8 Hz), 132.3 (d, 2 Hz), 126.6 (d, *J* = 7 Hz), 123.2 (d, *J* = 3 Hz), 73.7 (d, *J* = 7 Hz), 23.8 (d, *J* = 6 Hz), 23.5 (d, *J* = 5 Hz).

^{31}P NMR (400 MHz, $CDCl_3$): δ = 19.5.

HRMS: *m*/*z* [MH^+] calcd for $C_{12}H_{19}O_3SBrP$: 352.9976; found: 352.9974.

***O*,*O′*-Diisopropyl *S*-4-Fluorophenyl Phosphorothioate (3j)**
Yield: 248 mg (85%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (m, 2 H), 7.05 (t, *J* = 7.6 Hz, 2 H), 4.74–4.79 (m, 2 H), 1.33 (d, *J* = 6.4 Hz, 6 H), 1.28 (d, *J* = 6.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ =163.2 (dd, *J* = 248, 3 Hz), 136.4 (dd, *J* = 8, 5 Hz), 121.6 (dd, *J* = 8, 4 Hz), 116.4 (dd, *J* = 22, 2 Hz), 73.5 (d, *J* = 6 Hz), 23.8 (d, *J* = 4 Hz), 23.5 (d, *J* = 6 Hz).

^{31}P NMR (400 MHz, $CDCl_3$): δ = 20.3 (d, *J* = 4 Hz).

HRMS: *m*/*z* [MH^+] calcd for $C_{12}H_{19}O_3FSP$: 293.0777; found: 293.0768.

***O*,*O′*-Diisopropyl *S*-4-Aminophenyl Phosphorothioate (3k)**
Yield: 263 mg (91%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 8, 2 Hz, 2 H), 6.64 (d, *J* = 8 Hz, 2 H), 4.73–4.78 (m, 2 H), 4.69 (br, 2 H), 1.34 (d, *J* = 6 Hz, 6 H), 1.29 (d, *J* = 6.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4 (d, *J* = 2 Hz), 136.2 (d, *J* = 5 Hz), 115.6 (d, *J* = 2 Hz), 113.6, 73.0 (d, *J* = 7 Hz), 23.9 (d, *J* = 4 Hz), 23.6 (d, *J* = 6 Hz).

^{31}P NMR (400 MHz, $CDCl_3$): δ = 21.8.

HRMS: *m*/*z* [MH^+] calcd for $C_{12}H_{21}NO_3SP$: 290.0980; found: 290.0979.

Tetraphenyl Pyrophosphate (4)[18]
Yield: 131 mg (80%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (t, *J* = 8 Hz, 2 H), 7.22–7.29 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.4 (d, *J* = 7 Hz), 129.9, 125.6, 120.1 (d, *J* = 5 Hz).

^{31}P NMR (400 MHz, $CDCl_3$): δ = –17.6 (reported: δ = –25.5 in the reaction mixture).

***O*,*O′*-Diethyl *S*-Benzyl Phosphorothioate (5)**[19]
Yield: 158 mg (61%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.39 (m, 5 H), 4.11–4.15 (m, 2 H), 4.04–4.07 (m, 4 H), 1.31 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5 (d, *J* = 5 Hz), 128.9, 128.6, 127.6, 63.5 (d, *J* = 6 Hz), 34.9 (d, 4.0 Hz), 15.9 (d, *J* = 7.0 Hz).

^{31}P NMR (400 MHz, $CDCl_3$): δ = 26.7.

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