Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2024, **22**, 7492

Received 2nd July 2024,
Accepted 22nd August 2024

DOI: 10.1039/d4ob01099j

rsc.li/obc

Synthesis of unsymmetrical phosphorus disulfides†

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A sulfur-mediated umpolung strategy employing *N*-thiosuccinimides and $(EtO)_2P(O)SH$ has been developed to synthesize unsymmetrical organophosphorus disulfides (P(O)–S–S motif). A pronucleophile $(EtO)_2P(O)SH$, Brønsted acid and phosphorothioate nucleophile, converts *N*-thiosuccinimides into unsymmetrical phosphorus disulfides. This protocol achieves catalyst- and additive-free reaction conditions, uses a renewable solvent (EtOH), and avoids harsh reagents.

Introduction

Organophosphorus and organosulfur chemistry have attracted significant research interest due to their widespread applications.[1] Especially, organophosphorus disulfides (P(O)–S–S) have received substantial attention in a plethora of fields since they are promising antioxidants and prodrugs as well as pesticides.[2] For example, they serve as a key chemical motif of molecular umbrella–nucleoside conjugates (Fig. 1, **A**).[2a] The conjugates are amphiphilic molecules interconverting their status in response to environmental changes in cells. This amphiphilic feature of conjugates improves the lipid bilayer transport; thus, they have potential therapeutic applications such as drug delivery. In addition, bisphosphorothioates have shown antioxidant activities (Fig. 1, **B**).[2b] They act as metal-ion chelators (Fe, Cu) and radical scavengers. The oligonucleotide phosphorothioates demonstrated improved cellular uptake *via* a pseudo-disulfide exchange, which has generated a few FDA-approved drugs (Fig. 1, **C**).[3] Furthermore, phosphorus disulfide derivatives have been used for potent pesticides (Fig. 1, **D**, **E**).[2c] These examples highlight several important applications of organophosphorus disulfides.

The synthesis of unsymmetrical disulfides poses challenges due to the undesired homodimers.[4] To access unsymmetrical disulfides, there are three major approaches: an oxidative dehydrogenative coupling reaction, a masked strategy of a coupling reaction, and an umpolung strategy. The oxidative dehydrogenative coupling reaction employs two sterically distinct thiols to utilize the reactivity differences rendered by sterics and kinetics of oxidation.[5] A masked strategy of coupling reactions, such as a copper-catalyzed Suzuki and Hiyama-type cross-coupling reaction, affords unsymmetrical disulfides.[6,7] This approach demonstrated the late-stage functionalization of biomolecules under borane catalysis.[8] Other catalysts such as rhodium, palladium, and *N*-fluorobenzenesulfonimide catalysts also have been used.[9] In addition, the umpolung strategy has been employed to reduce the homodimer by-products. For example, thiol nucleophiles react with preactivated sulfur electrophiles: sulfenamides, thiosulfonate, mercaptobenzotriazole, mercaptobenzothiazole, phosphorothioate bromide, 2-pyridyl disulfide, thiosuccinimide, and Bunte salts.[10] By overcoming the homodimer by-product challenges, significant progress on unsymmetrical disulfide synthesis has been made with a rational design of substrates and reactivity differences.

Despite the recent advance in synthesizing unsymmetrical disulfides, the synthetic approach to directly access the phosphorus disulfides is underdeveloped. Recently, the Cao group has reported a mechanochemical disulfur transfer between trisulfide dioxides and secondary phosphine oxides using ball milling to form P(O)–S–S bonds.[11] The substrate scope to access the P(O)–S–S bond motif, however, is limited to alkyl

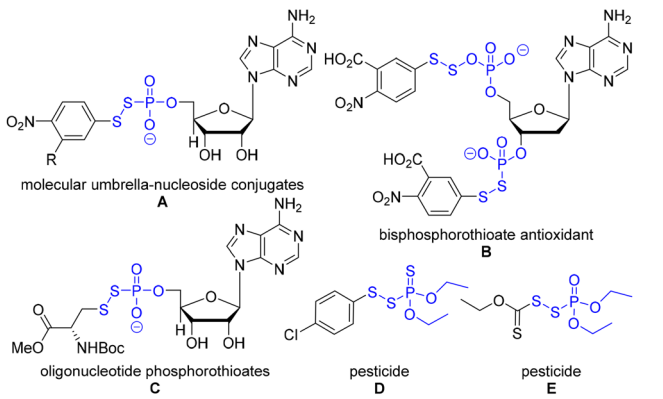

Fig. 1 Representative examples of phosphorus disulfide.

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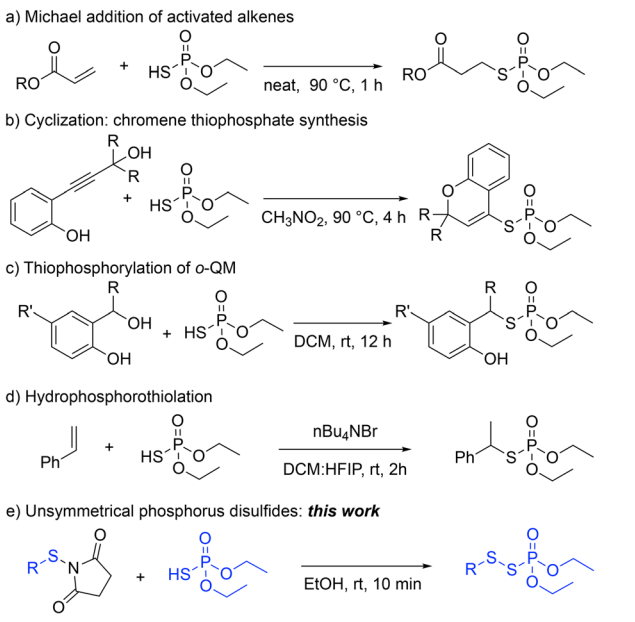
†Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4ob01099j

dithioperoxoate; when aryl dithioperoxoates were used, an alternative thiophosphate product (P(O)–S) was generated *via* different reaction pathway. To the best of our knowledge, a synthetic method to access aryl phosphorus disulfides (P(O)–S–S–Ar unit) – a major functionality of the current applications (Scheme 1) – remains elusive.

Harnessing inherent chemical properties and reactivities creates new chemical space and contributes to green synthesis.[12] These advantages have been achieved by multifunctional reagents and catalysts.[13] Multifunctional reagents can eliminate the need for additives and allow for increased chemoselectivity.[13] In this regard, phosphorothioic acid, $(EtO)_2P(O)SH$, has served as a multifunctional reagent – Brønsted acid and phosphorothioate nucleophile – in different transformations (Scheme 1). For example, $(EtO)_2P(O)SH$ has been used in a Michael reaction of activated alkenes to synthesize functionalized thiophosphates (Scheme 1, a).[14] The Xiao group also reported the utility of $(EtO)_2P(O)SH$ by coupling with a propargylic alcohol partner to construct *S*-(2*H*-chromen-4-yl) phosphorothioates and polycyclic thiophosphates *via* a cascade reaction as well as the synthesis of allenyl thiophosphates under elevated temperatures (Scheme 1, b).[15] We also demonstrated a bifunctional role of $(EtO)_2P(O)SH$ in the thiophosphorylation reaction of *in situ* formed *ortho*-quinone methide (*o*-QM) to synthesize functionalized thiophosphates (Scheme 1, c).[16] In addition, the Hajra group used hydrophosphorothiolation of alkenes to form benzyl phosphorothioates employing hexafluoroisopropanol (HFIP) to enhance the acidity of $(EtO)_2P(O)SH$ (Scheme 1, d).[17] Furthermore, The Wu group used $(EtO)_2P(O)SH$ and a Ga $(OTf)_3$ catalyst under photochemical conditions.[18,19] Nevertheless, the synthesis of unsymmetrical organophosphorus disulfides (P(O)–S–S) using $(EtO)_2P(O)SH$ hasn't been reported (Scheme 1, e).



Scheme 1 $(EtO)_2P(O)SH$ as a pronucleophile.

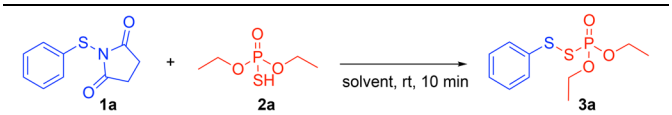
Since both thiophosphates and disulfides possess useful properties, small molecules containing P(O)–S–S bonds would be of great interest to chemists in academia and industry.[2] Based on our previous work on searching for the bifunctionality of $(EtO)_2P(O)SH$,[16] serving as both Brønsted acid and phosphorothioate nucleophile, we hypothesized that this reagent would react with *N*-thiosuccinimides to form P(O)–S–S bond motif (Scheme 1, e).

Results and discussion

To test our hypothesis, we used *N*-thiosuccinimide **1a** and phosphorothioic acid ($(EtO)_2P(O)SH$) **2a** as model substrates in ethanol (Table 1). The reaction gave the desired product **3a** in a 95% yield (Table 1, entry 1). Other solvents also provided the product **3a** in high yields (Table 1, entries 2–7). However, ethanol was selected since it is environmentally friendly and readily available through biomass fermentation.[20] Importantly, the reaction conditions address many of the 12 principles of green chemistry as defined by the American Chemical Society.[21] For example, the reaction is an atom-economical approach since no additives or excess reagents are required. In addition, the reaction is energy neutral as no heating or cooling is necessary. Furthermore, the use of safer solvents and renewable feedstocks is achieved by ethanol. Lastly, the procedure runs without transition metal catalysts typically used for disulfide synthesis.

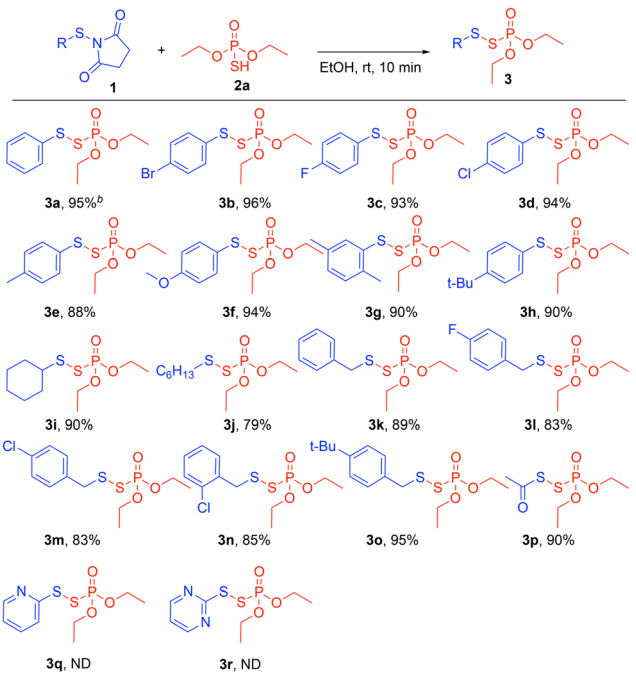
With the optimized reaction conditions in hand, the scope of *N*-thiosuccinimide electrophiles was evaluated to study the steric and electronic effects on the reaction outcome (Scheme 2). First, halogenated aryl *N*-thiosuccinimides **1b–1d** generated the target products **3b–3d** in high yields (93–96%). Aryl *N*-thiosuccinimides bearing electron-donating groups **1e**, **1f** (4-Me, 4-MeO) yielded the corresponding products **3e**, **3f** in 88% and 94%, respectively. Next, aryl *N*-thiosuccinimides **1g** and **1h** containing sterically demanding groups (2,5-dimethyl,

Table 1 Optimization of reaction conditions[a]



Entry	**1a** : **2a**	Solvent	**3a** yield[b] (%)
1	1.0 : 1.0	EtOH	95
2	1.0 : 1.0	DCM	94
3	1.0 : 1.0	Acetone	74
4	1.0 : 1.0	ACN	92
5	1.0 : 1.0	THF	92
6	1.0 : 1.0	Ether	94
7	1.0 : 1.0	Toluene	75

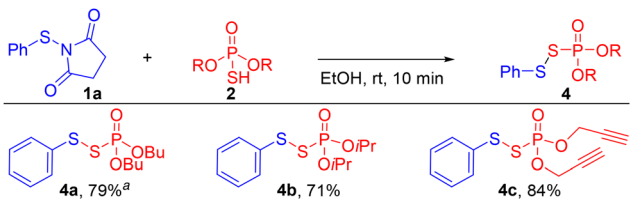
[a] Reaction conditions: **1a** (0.1 mmol) and **2a** (0.1 mmol) in solvent (0.5 mL) for 10 min. [b] Isolated yield.



Scheme 2 Substrate scope of *N*-thiosuccinimide. Reaction conditions: **1** (0.1 mmol) and **2a** (0.1 mmol) in EtOH (0.5 mL) for 10 min. [a] The reported yields are isolated yields. ND: not determined.

4-tertbutyl) afforded the desired products **3g**, **3h** in 90% yields. Alkyl *N*-thiosuccinimides **1i**, **1j** (cyclohexyl, *n*-hexyl) were also well tolerated, providing the target products **3i**, **3j** in 90% and 79% yields, respectively. Additionally, benzylic *N*-thiosuccinimide **1k** furnished the product **3k** in an 89% yield; no competing substitution reactions at the benzylic carbon on the product occurred. Benzylic *N*-thiosuccinimides containing halogens and electron donating groups **1l–1o** (4-fluoro, 4-chloro, 2-chloro, and 4-tertbutyl) also generated the target products **3l–3o** in high yields (83–95%). Furthermore, acyl *N*-thiosuccinimide **1p** was tolerated and furnished the product **3p** in a high yield of 90%. Heteroaryl *N*-thiosuccinimides **1q**, **1r**, however, provided the corresponding products **3q**, **3r** as inseparable mixtures from succinimide byproduct. Overall, the reaction provided the desired products **3a–3p** in high yields and the steric, electronic factors of the *N*-thiosuccinimides were well tolerated.

Next, the scope of the phosphorothioic acid nucleophile was examined (Scheme 3). Thioacids with different alkoxy substituents **2b**, **2c**, and **2d** (butyl, isopropyl, and propargyl) were treated with *N*-thiosuccinimide **1a** and they were well tolerated to give the target products **4a**, **4b**, and **4c** in 79%, 71%, and 84% yields, respectively. However, when diphenylthiophosphinic acid was tested, no desired product was formed even at elevated temperatures, presumably due to a weaker acidity than **2a** ($pK_a = -5.14$).[22]



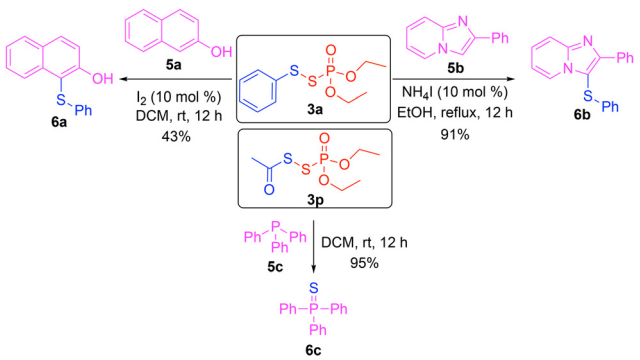
Scheme 3 Substrate scope of phosphorothioic acids. Reaction conditions: **1a** (0.1 mmol) and **2** (0.1 mmol) in EtOH (0.5 mL) for 10 min. [a] The reported yields are isolated yields.

Having studied an array of substrates, the synthetic utility of this transformation was evaluated (Scheme 4). When beta naphthol **5a** was treated with phosphorus disulfide **3a**, it was successfully thiolated to give thionaphthol **6a**. Imidazopyridine **5b** was also effectively thiolated with **3a** to give **6b** under the catalytic conditions. The imidazopyridine structural motif has shown antibacterial properties.[23] In addition, the phosphorus disulfide **3p** was used for sulfurization of triphenylphosphine **5c** to triphenylphosphine sulfide **6c**. These results demonstrated that phosphorus disulfides **3** can serve as electrophilic sulfur sources to functionalize arenols, heteroarenes, and phosphines.

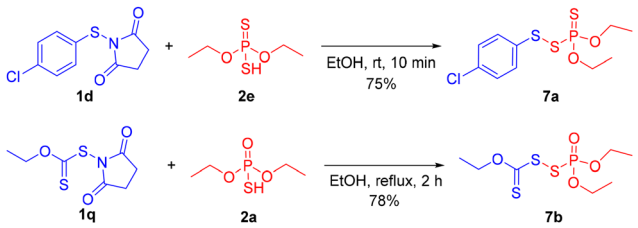
To further demonstrate the utility of this methodology, we carried out the synthesis of known pesticides **7a**, **7b** (Scheme 5).[2c] Pesticide **7a** was synthesized by treating *N*-thiosuccinimide **1d** and phosphorodithioic acid **2e** under the standard reaction conditions. Pesticide **7b** was also readily prepared from *N*-thiosuccinimide **1q** and phosphorothioic acid **2a** under elevated thermal conditions. These results provide a direct application of this methodology toward various pesticide syntheses.

To gain insight into the reaction mechanism, control experiments were performed (Scheme 6). The reaction between *N*-thiosuccinimide **1a** and diphenyl phosphoric acid **2f** ($pK_a = -3.95$)[24] did not yield the target product **4d**. This outcome reveals that a stronger acid and more nucleophilic thiolate are necessary for a successful reaction. Next, the role of the proton was tested by using the potassium phosphorothioate **2g**. This phosphorothioate, however, generated the desired product **3a** in a poor yield (29%) compared to **2a** (Scheme 2). This result suggests that a proton donor (Brønsted acid) is necessary to increase the electrophilicity and the reactivity of **1a**.

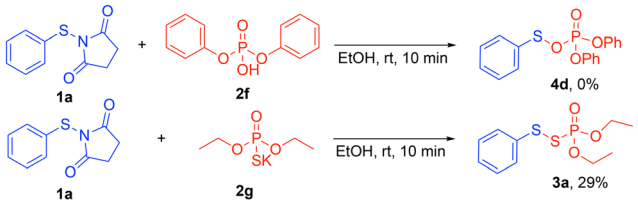
Based on our previous work and the control experiments,[16] a plausible mechanism is proposed in Scheme 7. Concomitantly, the oxygen atom on **1a** is protonated by



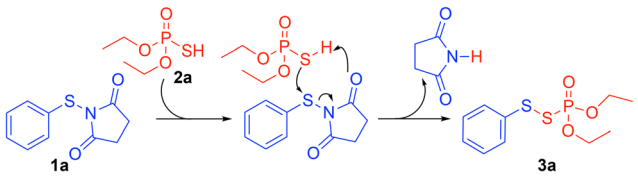
Scheme 4 Synthetic utility.



Scheme 5 Pesticide synthesis.



Scheme 6 Control experiments.



Scheme 7 Proposed mechanism.

$(EtO)_2P(O)SH$ **2a** and the resulting thiophosphate attacks the protonated **1a** to give succinimide and the target product **3a**.

Conclusion

In summary, we have developed a new mild method to synthesize unsymmetrical organophosphorus disulfides (P(O)–S–S) from $(EtO)_2P(O)SH$. This method addresses the persistent homodimerization issues in unsymmetrical disulfide synthesis. In addition, a wide range of substrate scopes of both *N*-thiosuccinimide sulfur electrophiles and phosphorothioic acids were well tolerated. Furthermore, the synthetic utility of unsymmetrical organophosphorus disulfides demonstrated an efficient thiolation of arenol, heteroarene, and phosphine as well as the synthesis of several pesticides. Finally, the control experiments support a plausible mechanism. Further studies to understand these novel phosphorus disulfide compounds are under investigation, and they will be reported in due course.

Experimental section

General information

All reactions were carried out under air atmosphere in oven-dried glassware with magnetic stirring bar. Dry solvents (THF, toluene, ACN, diethyl ether, and DCM) were obtained by solvent purification system under argon. All commercially available reagents were used as received without further purification. The tubes used for the reaction were showed in Fig. S1.† Purification of reaction products was carried out by flash column chromatography using silica gel 60 (230–400 mesh). Analytical thin layer chromatography was performed on 0.25 mm aluminum-backed silica gel 60-F plates. Visualization was accompanied with UV light and $KMnO_4$ solution. Concentration under reduced pressure refers to the removal of volatiles using a rotary evaporator attached to a dry diaphragm pump (10–15 mm Hg) followed by pumping to a constant weight with an oil pump (<300 mTorr). Infrared (IR) spectra were recorded on an IR spectrometer with KBr wafers or a film on KBr plate. High-resolution mass spectra (HRMS) were recorded on LCMS-IT-TOF mass spectrometer using ESI (electrospray ionization) or APCI (Atmospheric Pressure Chemical Ionization). ^1H NMR spectra were recorded in $CDCl_3$ on 400 MHz NMR spectrometer. The ^1H chemical shifts are referenced to residual solvent signals at δ 7.26 ($CHCl_3$) or δ 0.00 (TMS). ^1H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicities are indicated as follows: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), tt (triplet of triplets). ^{13}C NMR spectra were proton decoupled and recorded in $CDCl_3$ on 100.5 MHz NMR spectrometer. The ^{13}C chemical shifts are referenced to solvent signals at δ 77.16 ($CDCl_3$). ^{31}P NMR spectra were proton decoupled and recorded in $CDCl_3$ on 162 MHz NMR spectrometer. ^{31}P chemical shifts are reported relative to 85% H_3PO_4 (0.00 ppm) as an external standard.

General procedure: synthesis of phosphrous disulfide 3 and 4

To a solution of thiophosphoric acid **2** (0.10 mmol) in ethanol (0.5 mL) was added *N*-thiosuccinimide **1** (0.10 mmol) at room temperature. The reaction mixture was stirred for 10 minutes. After stirring for 10 minutes at room temperature, the reaction mixture was concentrated under reduced pressure and subjected to column chromatography on silica gel to give the corresponding phosphorus disulfide product **3** or **4**.

Synthetic utility: synthesis of 6a–6c

To a solution of **3a** (0.1 mmol) in DCM (0.5 mL) was added beta naphthol **5a** (0.1 mmol), followed by iodine (0.01 mmol). The reaction was stirred at room temperature for 12 hours. After stirring for 12 hours, the reaction mixture was concentrated under reduced pressure, and directly purified by column chromatography (hexane : EtOAc = 8 : 2) to give **6a** (10.8 mg, 43%).

To a solution of **3a** (0.1 mmol) in EtOH (0.5 mL) was added imidazopyridine **5b** (0.2 mmol), followed by an ammonium iodide (0.01 mmol). The reaction was refluxed for 12 hours. After stirring for 12 hours, the reaction mixture was concentrated under reduced pressure, and directly purified by column chromatography (hexane : EtOAc = 7 : 3) to give **6b** (27.4 mg, 91%).

To a solution of **3p** (0.1 mmol) in DCM (0.5 mL) was added triphenylphosphine (0.1 mmol). The reaction was stirred at room temperature for 12 h. After stirring for 12 hours, the reaction mixture was concentrated under reduced pressure, and directly purified by column chromatography (hexane : EtOAc = 95 : 5) to give **6c** (16.7 mg, 95%).

Pesticide synthesis of 7a and 7b

To a solution of dithiophosphoric acid **2e** (0.2 mmol) in EtOH (1.0 mL) was added thiosuccinimide **1d** (0.2 mmol). The reaction was stirred for 10 minutes. After stirring for 10 minutes, the reaction mixture was concentrated under reduced pressure, and directly purified by column chromatography (hexane : DCM = 8 : 2) to give **7a** (49.3 mg, 75%).

To a solution of thiophosphoric acid **2a** (0.1 mmol) in EtOH (0.5 mL) was added thiosuccinimide **1q** (0.1 mmol). The reaction was refluxed for 2 hours. After stirring for 2 hours, the reaction mixture was concentrated under reduced pressure, and directly purified by column chromatography (hexane : EtOAc = 7 : 3) to give **7b** (22.6 mg, 78%).

Compound characterization

Phenyl diethoxyphosphinyl disulfide (3a).[25] 26.4 mg, 95%; as an oil; **IR** 2981, 1577, 1477, 1438, 1390, 1255, 1162, 1024, 744, 688ν (thin film, cm^{-1}); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.63 (m, 2H), 7.38–7.30 (m, 3H), 4.20–4.10 (m, 2H), 4.02–3.92 (m, 2H), 1.26–1.22 (m, 6H); ^{13}C NMR δ 135.41 (d, J = 1.4 Hz), 130.82 (d, J = 1.5 Hz), 129.0, 128.5, 64.3 (d, J = 6.0 Hz), 15.8 (d, J = 7.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.15.

4-Bromophenyl diethoxyphosphinyl disulfide (3b). 34.3 mg, 96%; as an oil; **IR** ν (thin film, cm^{-1}) 2981, 1471, 1386, 1255, 1161, 1010, 812, 750; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53–7.51 (m, 2H), 7.48–7.47 (m, 2H), 4.21–4.14 (m, 2H), 4.06–3.99 (m, 2H), 1.29–1.25 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 134.6, 132.2, 132.1, 122.8, 64.5 (d, J = 6.0 Hz), 15.9 (d, J = 6.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.80; HRMS (ESI): m/z calcd for $C_{10}H_{15}O_3PS_2Br$ ($[M + H]^+$): 356.9366; found: 356.9378.

4-Fluorophenyl diethoxyphosphinyl disulfide (3c). 26.8 mg, 93%; as an oil; **IR** ν (thin film, cm^{-1}) 2983, 1587, 1489, 1255, 1157, 1014, 833; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.66 (m, 2H), 7.07–7.02 (m, 2H), 4.20–4.12 (m, 2H), 4.03–3.96 (m, 2H), 1.30–1.26 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 163.2 (d, J = 248.6 Hz), 134.2 (d, J = 8.2 Hz), 130.6 (d, J = 3.7 Hz), 116.3 (d, J = 22.3 Hz), 64.4 (d, J = 6.0 Hz), 15.9 (d, J = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.29; HRMS (ESI): m/z calcd for $C_{10}H_{15}O_3PS_2F$ ($[M + H]^+$): 297.0184; found: 297.0184.

4-Chlorophenyl diethoxyphosphinyl disulfide (3d).[25] 29.2 mg, 82%; as an oil; **IR** ν (thin film, cm^{-1}) 2981, 1570, 1473, 1388, 1255, 1012, 815, 744; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 4.20–4.14 (m, 2H), 4.05–3.99 (m, 2H), 1.27 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 134.8, 133.9, 132.2, 129.2, 64.5 (d, J = 6.0 Hz), 15.9 (d, J = 7.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.86.

4-Methylphenyl diethoxyphosphinyl disulfide (3e).[25] 23.5 mg, 88%; as an oil; **IR** ν (thin film, cm^{-1}); 2981, 1720, 1489, 1392, 1255, 1014, 808, 750; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 4.18–4.12 (m, 2H), 4.00–3.93 (m, 2H), 2.35 (s, 3H), 1.25 (t, J = 7.6 Hz, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 139.2, 133.7, 131.2 (d, J = 1.5 Hz), 129.8, 64.2 (d, J = 6.0 Hz), 21.1, 15.9 (d, J = 7.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.58; HRMS (ESI): m/z calcd for $C_{11}H_{18}O_3PS_2$ ($[M + H]^+$): 293.0435; found: 293.0442.

4-Methoxyphenyl diethoxyphosphinyl disulfide (3f). 29.1 mg, 94%; as an oil; **IR** ν (thin film, cm^{-1}) 2981, 1589, 1492, 1390, 1253, 1014, 829, 752; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.62 (m, 2H), 6.88–6.85 (m, 2H), 4.18–4.12 (m, 2H), 4.00–3.93 (m, 2H), 3.81 (s, 3H), 1.30–1.26 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 160.8, 135.1, 125.7, 114.6, 64.1 (d, J = 5.2 Hz), 55.4, 15.9 (d, J = 7.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.13; HRMS (ESI): m/z calcd for $C_{11}H_{18}O_4PS_2$ ($[M + H]^+$): 309.0379; found 309.0379.

2,5-Dimethylphenyl diethoxyphosphinyl disulfide (3g). 27.5 mg, 90%; as an oil; **IR** ν (thin film, cm^{-1}) 2980, 1600, 1390, 1255, 1016, 812; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 1H), 7.04 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 4.17–4.07 (m, 2H), 3.95–3.85 (m, 2H), 2.49 (s, 3H), 2.31 (s, 3H), 1.26–1.22 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 140.7 (d, J = 1.5 Hz), 139.9, 134.1, 131.3, 130.3, 127.3, 64.0 (d, J = 5.2 Hz), 21.1, 20.5, 15.8 (d, J = 7.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.05; HRMS (ESI): m/z calcd for $C_{12}H_{20}O_3PS_2$ ($[M + H]^+$): 307.0585; found 307.0591.

4-*tert*-Butylphenyl diethoxyphosphinyl disulfide (3h). 27.6 mg, 90% as an oil; **IR** ν (thin film, cm^{-1}) 2962, 1772, 1591, 1487, 1392, 1257, 1163, 1016, 827, 752; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.58 (m, 2H), 7.37–7.35 (m, 2H), 4.17–4.13 (m, 2H), 3.98–3.91 (m, 2H), 1.30 (s, 9H), 1.25–1.20 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 152.3, 131.8, 131.5, 126.1, 64.2 (d, J = 5.6 Hz), 34.6, 31.1, 15.8 (d, J = 7.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.51; HRMS (ESI): m/z calcd for $C_{14}H_{24}O_3PS_2$ ($[M + H]^+$): 335.0904; found 335.0904.

Cyclohexyl diethoxyphosphinyl disulfide (3i). 25.6 mg, 90% as an oil; **IR** ν (thin film, cm^{-1}) 2929, 1444, 1390, 1255, 1016, 974, 790, 750; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29–4.16 (m, 4H), 3.037–3.034 (m, 1H), 2.12–2.09 (m, 2H), 1.81–1.78 (m, 2H), 1.64–1.62 (m, 1H), 1.43–1.23 (m, 11H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 64.3 (d, J = 6.0 Hz), 49.0, 32.2, 25.8, 25.5, 16.1 (d, J = 7.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.78; HRMS (ESI): m/z calcd for $C_{10}H_{22}O_3PS_2$ ($[M + H]^+$): 285.0748; found 285.0763.

Hexyl diethoxyphosphinyl disulfide (3j). 22.6 mg, 79%; as an oil; **IR** ν (thin film, cm^{-1}) 2927, 1454, 1255, 1016, 974, 750; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29–4.17 (m, 4H), 2.88 (t, J = 7.2 Hz, 2H), 1.73–1.66 (m, 2H), 1.44–1.34 (m, 8H), 1.30–1.28 (m, 4H), 0.89 (t, J = 6.0 Hz, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 64.4 (d, J = 5.9 Hz), 38.7, 31.2, 28.5, 28.0, 22.4, 16.1 (d, J = 7.4 Hz), 13.9; ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.88; HRMS (ESI): m/z calcd for $C_{10}H_{24}O_3PS_2$ ($[M + H]^+$): 287.0904; found 287.0896.

Benzyl diethoxyphosphinyl disulfide (3k). 26.0 mg, 89%; as an oil; **IR** ν (thin film, cm^{-1}) 2981, 1494, 1390, 1257, 1016, 972, 765; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 4.31–4.18 (m, 4H), 4.14 (d, J = 2.0 Hz, 2H), 1.40 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 135.8, 129.4, 128.6, 127.8, 64.6 (d, J = 6.7 Hz), 43.1 (d, J = 5.6 Hz), 16.2 (d, J = 6.7 Hz); ^{31}P NMR

(162 MHz, $CDCl_3$): δ 24.64; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{18}O_3PS_2$ ($[M + H]^+$): 293.0434; found 293.0429.

4-Fluorobenzyl diethoxyphosphinyl disulfide (3l). 24.0 mg, 83%; as an oil; **IR** ν (thin film, cm^{-1}) 2981, 1598, 1508, 1255, 1222, 1014, 974, 839, 754; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 2H), 7.01 (t, J = 8.8 Hz, 2H), 4.29–4.18 (m, 4H), 4.15 (s, 2H), 1.42–1.36 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 162.3 (d, J = 162.3 Hz), 131.7 (d, J = 3.0 Hz), 131.2 (d, J = 8.2 Hz), 115.5 (d, J = 21.5 Hz), 64.7 (d, J = 6.7 Hz), 42.2, 16.2 (d, J = 6.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.47; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{17}FO_3PS_2$ ($[M + H]^+$): 311.0340; found 311.0336.

4-Chlorobenzyl diethoxyphosphinyl disulfide (3m). 26.9 mg, 83%; as an oil; **IR** ν (thin film, cm^{-1}) 2981, 1489, 1255, 1161, 1093, 1016, 808, 740; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.26 (m, 4H), 4.30–4.18 (M, 4H), 4.10 (d, J = 2.0 Hz, 2H), 1.41–1.38 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 134.4, 133.7, 130.8, 128.7, 64.7 (d, J = 6.7 Hz), 42.2, 16.2 (d, J = 6.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.33; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{17}ClO_3PS_2$ ($[M + H]^+$): 327.0045; found 327.0054.

2-Chlorobenzyl diethoxyphosphinyl disulfide (3n). 27.6 mg, 85%; as an oil; **IR** ν (thin film, cm^{-1}) 2981, 1473, 1444, 1390, 1255, 1161, 1014, 759; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.38 (m, 2H), 7.27–7.23 (m, 2H), 4.32–4.20 (m, 6H), 1.44–1.37 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 134.2, 133.8, 131.7, 129.8, 129.2, 126.7, 64.7 (d, J = 6.7 Hz), 40.6 (d, J = 1.5 Hz) 16.2 (d, J = 6.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.42; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{17}ClO_3PS_2$ ($[M + H]^+$): 327.0045; found 327.0053.

4-*tert*-Butylbenzyl diethoxyphosphinyl disulfide (3o). 34.4 mg, 95%; as an oil; **IR** ν (thin film, cm^{-1}) 2962, 1514, 1390, 1255, 1161, 1014, 974, 837, 790, 754; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 4.28–4.12 (m, 4H), 4.12 (d, J = 1.6 Hz, 2H), 1.42–1.38 (m, 6H), 1.30 (s, 9H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 150.9, 132.7, 129.1, 125.6, 64.5 (d, J = 6.7 Hz), 42.9, 34.5, 32.1, 16.2 (d, J = 6.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.71; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{26}O_3PS_2$ ($[M + H]^+$): 349.1061; found 349.1053.

Acetyl diethoxyphosphinyl disulfide (3p). 21.6 mg, 90%; as an oil; **IR** ν (thin film, cm^{-1}) 2906, 1714, 1390, 1294, 1180, 1016, 790, 639; ^1H NMR (400 MHz, $CDCl_3$) δ 4.30–4.22 (m, 4H), 2.48 (s, 3H), 1.39–1.35 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 191.0, 64.7 (d, J = 5.9 Hz), 28.8, 15.9 (d, J = 7.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.18; HRMS (ESI): *m*/*z* calcd for $C_6H_{14}O_4PS_2$ ($[M + H]^+$): 245.0071; found 245.0083.

Phenyl dibutoxyphosphinyl disulfide (4a). 26.4 mg, 79%; as an oil; **IR** ν (thin film, cm^{-1}) 2906, 1714, 1390, 1294, 1180, 1016, 790, 639; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.63 (m, 2H), 7.36–7.29 (m, 3H), 4.12–4.04 (m, 2H), 3.94–3.86 (m, 2H), 1.59–1.52 (M, 4H), 1.37–1.28 (m, 4H), 0.94–0.86 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 135.5 (d, J = 1.5 Hz), 130.6, 129.0, 128.3, 68.1 (d, J = 7.4 Hz), 32.0 (d, J = 7.4 Hz), 18.5, 13.5; ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.28; HRMS (ESI): *m*/*z* calcd for $C_{14}H_{24}O_3PS_2$ ($[M + H]^+$): 335.0904; found 335.0916.

Phenyl diisopropoxyphosphinyl disulfide (4b). 21.6 mg, 71%; as an oil; **IR** ν (thin film, cm^{-1}) 2980, 1465, 1384, 1255, 1101, 1008, 744, 688; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.63 (m, 2H), 7.35–7.26 (m, 3H), 4.76–4.71 (m, 2H), 1.36–1.31 (m, 6H), 1.22–1.20 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 135.6, 130.3, 129.0, 128.1, 73.9 (d, J = 6.7 Hz), 23.8 (d, J = 3.8 Hz), 23.4 (d, J = 6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 20.78; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{20}O_3PS_2$ ($[M + H]^+$): 307.0591; found 307.0603.

Phenyl di(prop-2-yn-1-yl)oxy phosphinyl disulfide (4c). 25.0 mg, 80%; as an oil; **IR** ν (thin film, cm^{-1}) 3294, 2938, 2131, 1577, 1476, 1370, 1258, 801, 744; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.67 (m, 2H), 7.38–7.34 (m, 3H), 4.75–4.67 (m, 2H), 4.62–4.55 (m, 2H), 2.95–2.57 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 134.7 (d, J = 1.5 Hz), 131.6 (d, J = 1.5 Hz), 130.4, 129.3, 129.0, 128.2, 55.6 (d, J = 4.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.2; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{12}O_3PS_2$ ($[M + H]^+$): 298.9966; found 298.9966.

1-(Phenylthio)naphthalen-2-ol (6a).[26] 10.8 mg; 43%; as a white solid; mp: 65–67 °C (lit. 66–67 °C); **IR** ν (thin film, cm^{-1}) 3400, 3019, 2921, 1620, 1476, 1255, 936, 864, 818, 738, 689; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.51–7.47 (m, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 9.2 Hz, 1H), 7.18–7.14 (m, 3H), 7.11–7.08 (m, 1H), 7.03–7.01 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 156.9, 135.4, 135.3, 132.8, 129.4, 129.2, 128.5, 127.9, 126.3, 125.8, 124.6, 123.8, 116.8, 108.0.

2-Phenyl-3-(phenylthio)imidazo[1,2-*a*]pyridine (6b).[27] 27.4 mg, 91%; as a yellow solid; mp: 95–97 °C (lit. 96–97 °C); **IR** ν (thin film, cm^{-1}) 3068, 2930, 1631, 1496, 1361, 1232, 1100, 1034, 968, 775, 692; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 6.8 Hz, 1H), 8.22–8.20 (m, 2H), 7.73 (d, J = 9.2 Hz, 1H), 7.43 (t, J = 7.2 Hz, 2H), 7.38–7.30 (m, 2H), 7.22–7.17 (m, 2H), 7.13 (t, J = 7.2 Hz, 1H), 7.0 (d, J = 8.0 Hz, 2H), 6.86–6.83 (m, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 151.4, 147.1, 135.2, 133.3, 129.4, 128.6, 128.4, 128.3, 126.6, 126.0, 125.5, 124.5, 117.6, 113.0, 106.2.

Triphenyl phosphine sulfide (6c).[28] 16.7 mg, 95%; as a solid; mp: 160–163 °C (lit. 161–163 °C); **IR** ν (thin film, cm^{-1}) 3056, 2361, 1585, 1419, 1433, 1307, 1103, 996, 752, 692; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75–7.69 (m, 6H), 7.52–7.48 (m, 3H), 7.46–7.41 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 132.9 (d, J = 84.9 Hz), 132.3 (d, J = 11.2 Hz), 131.5 (d, J = 2.9 Hz), 128.5 (d, J = 12.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 43.8.

4-Chlorophenyl diethoxythiophosphinyl disulfide (7a). 49.3 mg, 75%; as an oil; **IR** ν (thin film, cm^{-1}) 3076, 2935, 1571, 1442, 1387, 1263, 1160, 818, 744; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 4.21–4.14 (m, 2H), 3.93–3.86 (m, 2H), 1.26–1.22 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 134.6, 134.3 (d, J = 2.3 Hz), 131.9 (d, J = 1.5 Hz), 129.2, 64.5 (d, J = 5.2 Hz), 15.6 (d, J = 8.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 86.2; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{15}ClO_2PS_3$ ($[M + H]^+$): 328.9660; found 328.9660.

Ethoxy carbonothioic diethoxyphosphinyl disulfide (7b). 22.6 mg, 78%; as an oil; **IR** ν (thin film, cm^{-1}) 2984, 2935, 1735, 1442, 1393, 1261, 1025, 789; ^1H NMR (400 MHz, $CDCl_3$) δ 4.76–4.69 (m, 2H), 4.32–4.18 (m, 4H), 1.52–1.48 (m, 3H), 1.42–1.36 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 207.9 (d, J = 1.5 Hz), 71.7 (d, J = 9.7 Hz), 64.8 (d, J = 6.0 Hz), 16.1 (d, J = 6.7

Hz), 13.6; ^{31}P NMR (162 MHz, $CDCl_3$): δ 20.5; HRMS (ESI): m/z calcd for $C_7H_{15}O_4PS_3Na$ ($[M + Na]^+$): 312.9768; found 312.9767.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Knowledge Fund which is administered by the Nevada Governor's Office of Economic Development (GOED). The Troesh Center Grant and the University of Nevada Las Vegas are acknowledged for their support of this work. Shishir Bhowmik is acknowledged for his support on preparation of some substrates.

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