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A robust methodology for the synthesis of phosphorothioates, phosphinothioates and phosphonothioates.

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Abstract. A robust methodology for the synthesis of phosphorothioates, phosphinothioates and phosphonothioates, including those bearing low molecular weight *S*-alkyl side-chains, is presented. Application of the "caesium effect" in conjunction with the disulfide 3,3'-dithiobis(propionitrile), which acts as a shelf-stable sulfur source, avoids recourse to malodorous alkanethiols and toxic P–Cl precursors. A diverse range of sulfur-containing organophosphorus targets, including phosphorus-based heterocycles, may be prepared in consistently high yields. This chemistry also provides ready access to the corresponding DBU salts which are potential substrates for Pd-catalysed coupling reactions.

Keywords: Phosphorus; sulfur; caesium effect; phosphorothioates; phosphinothioates; phosphonothioates.

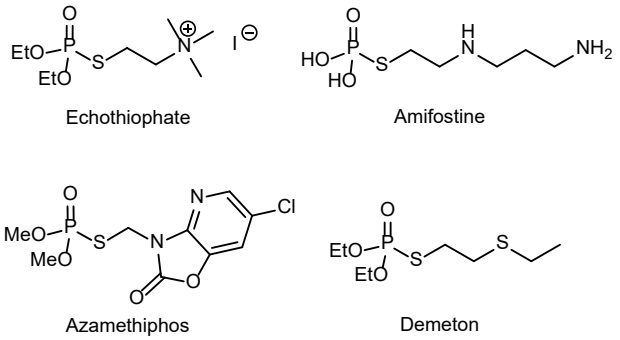
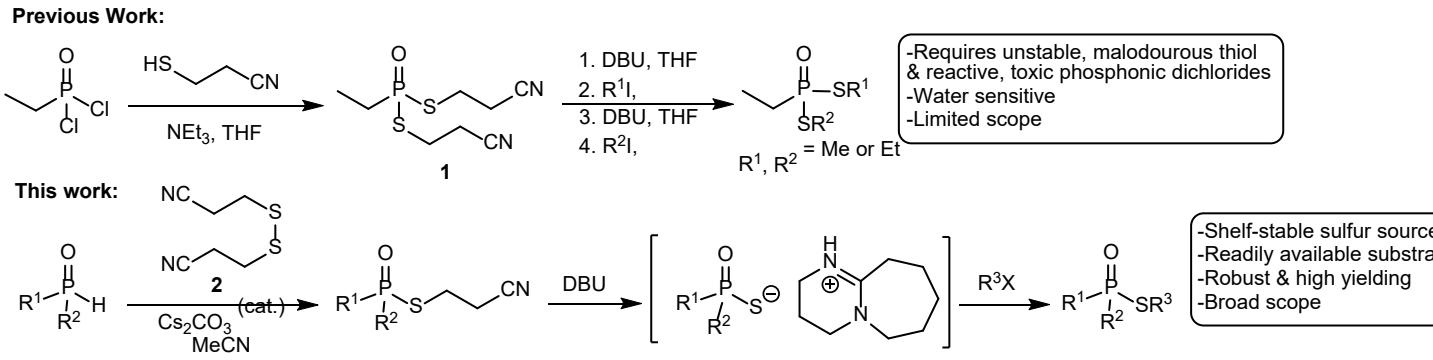


Figure 1. Commercially important sulfur-containing organophosphorus compounds.

Phosphorothioates, phosphonothioates and phosphinothioates are all examples of P(V) organophosphorus compounds which contain a phosphorus-sulfur single bond.[1] These classes of compound are particularly important in agrochemicals, where a significant number of pesticides incorporate phosphorus-sulfur bonds.[2] In particular, the insecticides Azamethiophos and Demeton, alongside related analogues, have enjoyed widespread application in crop protection (Figure 1).[3] Molecules containing the P–S(alkyl) bond include potential anti-cancer agents,[4] antivirals,[5] cardioprotective therapeutics[6] and acetylcholine esterase inhibitors.[7] The therapeutic potential of sulfur-containing organophosphorus compounds has already been realised in the broad-spectrum radioprotector[8] and anti-cancer[9] drug, Amifostine, as well as the anti-glaucoma drug, Echothiophate.[10] These compounds also have broad application in synthetic chemistry, particularly in heterocyclic synthesis and in C–C and C–F bond-forming reactions.[11]

The preparation of these compounds using P–S bond forming chemistry has been the subject of extensive study in recent years. Metal-catalysed coupling reactions employing copper,[12] rhodium,[13] palladium,[14] iron[15] and iridium[16] catalysts have been developed. Unfortunately, these routes are largely restricted to *S*-aryl products and are often low yielding or incompatible with *S*-alkyl targets. Methods for the preparation of *S*-alkyl products with low molecular weight sidechains (e.g. *S*-methyl or *S*-ethyl) are conspicuously absent in the literature, despite the pervasiveness of these motifs in organophosphorus chemistry. *S*-Alkyl organophosphorus compounds prepared *via* non-metal-catalysed methods typically employ the corresponding thiocyanate,[17] disulfide,[18] thiol[19] or sulfonyl chloride[20] as starting materials which, for complex substrates, may not be readily available. These methods may also suffer from limited substrate scope with respect to the organophosphorus precursor. If the desired P–S bond is already in place in the starting material, alkylation at sulfur represents an



Scheme 1. Previous and current work.

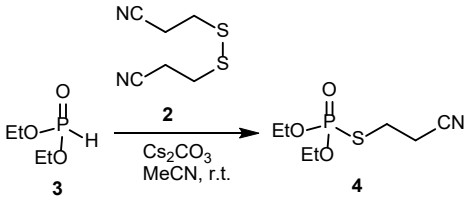
attractive alternative to these other methods.[21] Recent work by Gooßen and co-workers has demonstrated that the alkylation of shelf stable tetraalkylammonium phosphorothioate salts, generated from the corresponding silyl phosphite and elemental sulfur, afforded high yields of the corresponding phosphorothioates.[22] It is unclear, however, whether this approach could be adapted to other classes of *S*-alkyl organophosphorus compounds. A general method with broad substrate scope which provides ready access to *S*-alkyl phosphonothioates, phosphorothioates and phosphinothioates would be highly desirable.

In the course of our work in the synthesis of potentially bioactive phosphonodithioates, we communicated that phosphonodithioate **1**, undergoes rapid E1cB deprotection when treated with DBU (Scheme 1).[23] Exploiting this reaction allowed us to prepare either symmetrically or unsymmetrically substituted phosphonodithioates bearing low molecular weight alkyl side-chains. Harnessing the *S*-(2-cyanoethyl) group as a synthon in a similar fashion would constitute a versatile route to a range of *S*-alkyl derivatives of other organophosphorus compounds. We initially investigated a general method for the incorporation of the *S*-(2-cyanoethyl) moiety into a range of organophosphorus substrates.

The synthesis of **1** was previously achieved through nucleophilic substitution of commercially available ethyl phosphonic dichloride with 3-mercaptopropionitrile in the presence of base in anhydrous solvent (Scheme 1).[23] We were keen to avoid utilising a similar route in this study as these reactive P–Cl reagents are toxic and prone to hydrolysis, often leading to depressed yields as well as handling difficulties. Likewise, while 3-mercaptopropionitrile had served as an adequate sulfur transfer reagent, we had hoped to avoid its use given its high propensity toward oxidation and its malodorous nature which required special precautions.

We postulated that 3,3'-dithiobis(propionitrile) (**2**), a shelf-stable, crystalline compound, might constitute a superior sulfur transfer reagent (Scheme 1). In support of this approach, Song *et al.* recently reported the oxidative phosphorylation of a range of thiols employing caesium carbonate as a base, presumably proceeding *via* their corresponding disulfides, to afford phosphorothioates in good to excellent yields.[24] Extending this methodology to encompass disulfide **2** was an interesting synthetic challenge, owing to the base-lability of the 2-cyanoethyl groups. However, this chemistry would completely obviate the use of malodourous 3-mercaptopropionitrile and thus warranted further investigation. If successful, this approach would also provide access to other organophosphorus compounds, including phosphinothioates and phosphonothioates. Accordingly, an initial solvent screen confirmed acetonitrile as the optimum reaction medium (Table 1, entry 5). As predicted, using stochiometric quantities of Cs_2CO_3 led to base-induced deterioration of the product resulting in low yields (entries 1-5). Reducing the loading of Cs_2CO_3 to just 20 mol% resulted in a 83% yield of phosphorothioate **4** (entry 7). Further reductions saw a deleterious effect on yields (entries 8, 9).

Table 1. Optimisation of caesium-mediated sulfur transfer using base-labile **2**.[a)]



Entry	Solvent	Cs_2CO_3 (eq.)	Yield
1	THF	1	19%
2	DMSO	1	27%
3	DMF	1	23%
4	MeOH	1	14%
5	MeCN	1	31%
6	MeCN	0.50	70%
7	MeCN	0.20	83%
8	MeCN	0.10	69%
9	MeCN	0.05	40%

[a)] Screening conducted with 1.00 mmol **2** & 1.00 mmol **3**.

Importantly, this methodology could also be extended to other phosphonates, phosphinates and phosphine oxides allowing us to synthesise novel phosphorothioate **5**, phosphinothioate **6** and phosphonothioate **7** in high yields on a multi-millimolar scale, thus demonstrating the generality of

this approach across the three main sulfur-containing organophosphorus groups (Figure 2).

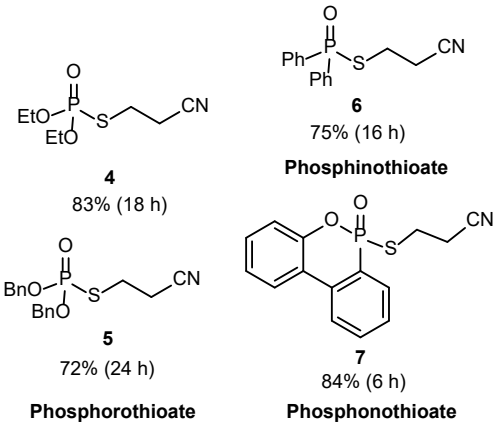
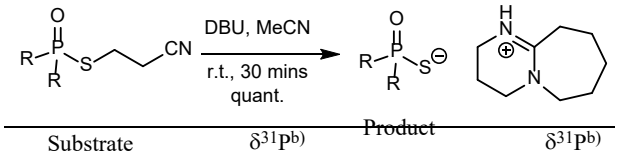
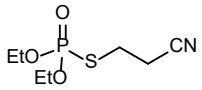
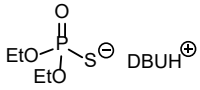
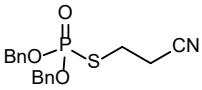
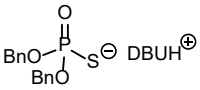
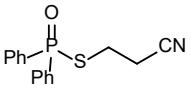
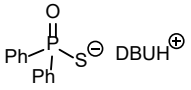
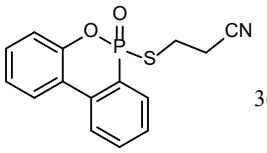
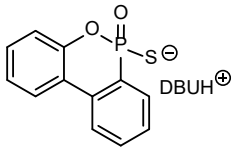


Figure 2. Application of optimised conditions to selected phosphorothioates, phosphinothioates and phosphonothioates targets.

We next explored the DBU-mediated cleavage of the cyanoethyl groups from **4-7**. Although this reaction had previously proven uncomplicated with phosphonodithioate **1**, it was not clear whether the corresponding reaction with more complex substrates would be similarly straightforward. Pleasingly, treatment of **4-7** with an equimolar amount of DBU in MeCN furnished the corresponding DBU salts **8-11** quantitatively, all as pale oils (Table 2). The reactions were monitored by ^{31}P NMR and were found to be complete after 30 minutes in all cases. Notably, a distinctive increase in the value of the ^{31}P NMR chemical shift was observed for each product. This clear difference in chemical shift facilitates the determination of reaction progress by ^{31}P NMR and is useful for reaction monitoring.

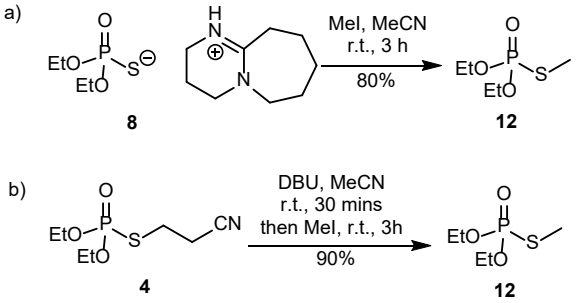
Table 2. Deprotection reaction monitoring *via* ^{31}P NMR.[a)]



Substrate	δ^{31}P[b)]	Product	δ^{31}P[b)]
 **4**	25.2	 **8**	55.8
 **5**	26.3	 **9**	57.2
 **6**	44.0	 **10**	54.6
 **7**	36.7	 **11**	58.4

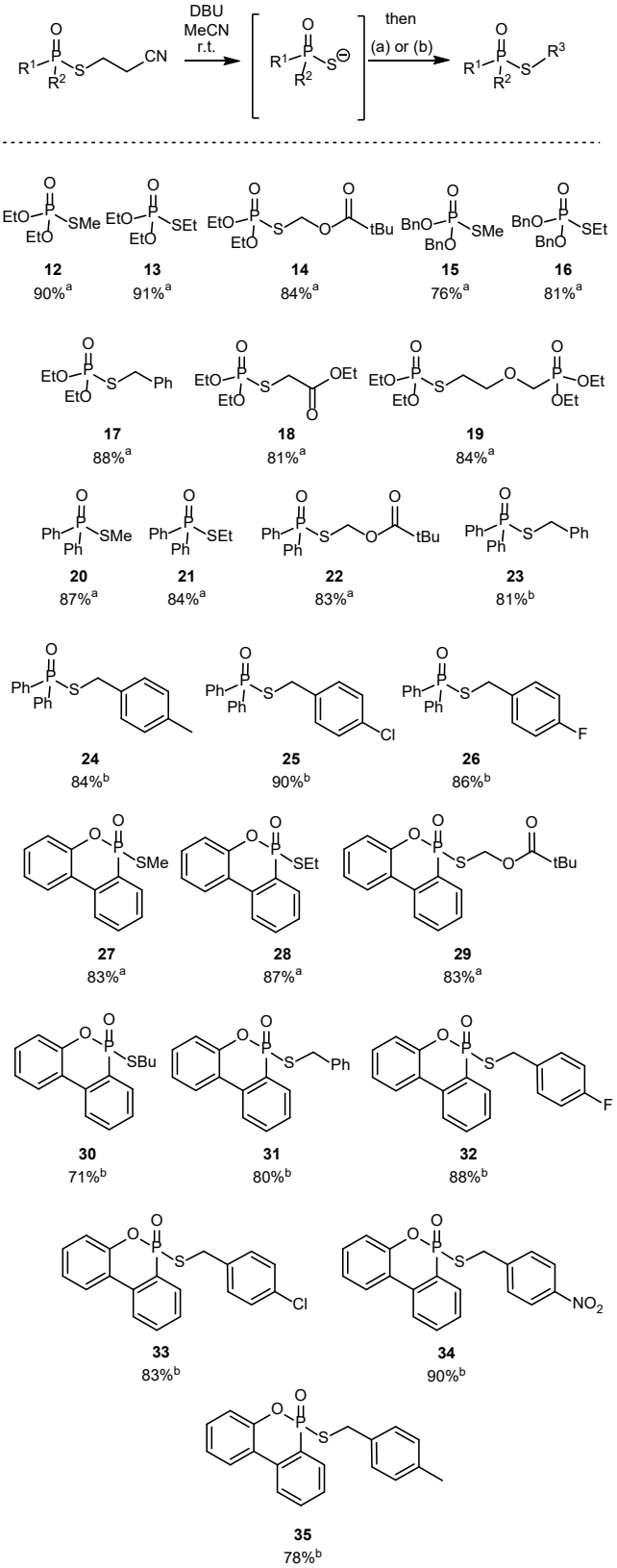
[a)] Reactions conducted using 0.3 mmol **4-7** in 3 mL MeCN. [b)] ^{31}P NMR chemical shift data were recorded at 175 MHz in $CDCl_3$ at 20 °C using 85% aqueous phosphoric acid as an external standard and are reported in ppm.

Interestingly, DBU salts **8-11** were soluble in a variety of organic solvents such as dichloromethane, chloroform, toluene and tetrahydrofuran, in addition to water. Similar soluble quaternary ammonium salts of phosphorothioates have recently been employed by Schoenebeck and co-workers in *S*-arylation reactions under Pd(I)-catalysed conditions.[14b] Since deprotection of our *S*-(2-cyanoethyl)-functionalised compounds affords soluble salts, it may be possible to extend the scope of this Pd(I)-catalysed *S*-arylation reaction to previously unexplored phosphinothioate and phosphonothioate substrates. The salts exist in the liquid state at room temperature and are therefore ionic liquids – a class of materials with widespread application in organic chemistry.[25] As subsequent alkylation of **8** with methyl iodide to afford phosphorothioate **12** also proved successful (Scheme 2a), we wondered whether a telescoped approach was feasible. Gratifyingly, phosphorothioate **12** was prepared from **4** in a one pot process in improved yield compared to the two-step process (Scheme 2b).



Scheme 2. Step-wise *vs.* telescoped preparation of phosphorothioate **12**.

This telescoped approach was applied to the synthesis of a variety of phosphorothioates **12**-**19**, phosphinothioates **20**-**26**, and phosphonothioates **27**-**35** resulting in consistently excellent yields (Scheme 3). Previously reported routes have suffered from much higher variability in yields.[21b] Of the twenty-four products produced in this manner, sixteen constitute novel compounds. Both alkyl bromides and iodides were found to be suitable alkylating agents, although alkyl bromides required heating to reflux in order to achieve complete consumption of the salt intermediate.



Scheme 3. Investigation of substrate scope of telescoped process. [a] R^3I (1.0 mmol), r.t., 3 h; [b] R^3Br (1.00 mmol), reflux, 3 h.

The alkylation reactions were highly regiospecific, as only trace amounts of the corresponding *O*-alkylated products were detectable in ^{31}P NMR spectra of the crude reaction mixtures. With iodomethyl pivalate as

the alkylating agent, the resulting pivaloxymethyl esters **14**, **22** and **29** were also obtained in excellent yields. It is difficult to envisage an alternative synthesis of these *S*-(pivaloxymethyl) products through standard P–S bond formation as the corresponding thiol, a hemithioacetal ester, is unlikely to be stable. This result is also noteworthy as the pivaloxymethyl group is an important prodrug moiety in medicinal chemistry and to the best of our knowledge, this represents the first method for the synthesis of *S*-(pivaloxymethyl) organophosphorus compounds.[26] The alkyl iodide used in the preparation of **19** was recently exploited as an advanced intermediate in the synthesis of several antiviral analogues and demonstrates that more complex, drug-like, alkylating agents are compatible with our methodology.[27]

In summary, a robust methodology for the synthesis of various *S*-alkyl organophosphorus compounds has been presented. We have demonstrated the application of disulfide **2** as a shelf-stable sulfur transfer reagent for the preparation of *S*-(2-cyanoethyl)phosphorothioates, phosphonothioates and phosphinothioates in high yields. Furthermore, quantitative removal of the *S*-(2-cyanoethyl) group with DBU may be monitored by ^{31}P NMR to afford soluble salts which are valuable compounds in their own right. A telescoped deprotection-realkylation process was successfully applied to the synthesis of several novel derivatives in consistently high yields. As a single precursor molecule can be readily diversified to give multiple target compounds, including drug-like and *S*-(pivaloxy) derivatives, our methodology may prove useful for the future preparation of libraries of *S*-alkyl organophosphorus compounds.

Experimental Section

*Disulfide **2***: To a stirred solution of *S*-(2-cyanoethyl) isothiouronium chloride[28] (56.0 mmol, 1.00 eq.) in deionised water (60 ml) at 0 °C was added dichloromethane (45 ml) followed by sodium perborate tetrahydrate (32.0 mmol, 0.57 eq.). To the cooled stirring suspension, 3M NaOH (30 mL, 1.60 eq.) was added dropwise at a rate of 1 mL/ minute. The reaction was then allowed to warm gradually to room temperature and stirred rapidly for five hours. The methylene chloride layer was separated and the aqueous layer was extracted with methylene chloride (3 x 25 mL portions). The combined organic phases were washed with brine (1 x 25 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford disulfide **2** (3.56 g, 78%, 20.0 mmol) as a colourless crystalline solid.[29]

Sulfur transfer: To a stirred solution of disulfide **2** (10.00 mmol, 1.00 eq.) in acetonitrile (50 mL) was added the organophosphorus substrate (10.00 mmol, 1.00 eq.) and caesium carbonate (2.00 mmol, 0.20 eq.). The resulting suspension was stirred at room temperature for the time indicated in Figure 3 after which time the starting material was no longer evident by ^{31}P NMR. The reaction mixture was filtered and concentrated *in vacuo* and the resulting residue was purified by column chromatography on silica gel.

Telescoped alkylation: To a stirred solution of **4**-**7** (0.50 mmol, 1.00 eq.) in MeCN (5 mL) was added DBU (0.50 mmol, 1.00 eq.). The resulting solution was stirred for 30 minutes after which time the required alkyl iodide or alkyl bromide (1.00 mmol, 2.00 eq.) was added. After three hours at room temperature (alkyl iodides) or reflux (alkyl bromides), the solvent was removed *in vacuo* and the resulting residue was purified by column chromatography on silica gel.

Acknowledgements

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