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S-(1,3-Dioxoisoindolin-2-yl)*O*,*O*–diethyl phosphorothioate (SDDP): A practical electrophilic reagent for the phosphorothiolation of electron-rich compounds

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ABSTRACT

An efficient synthesis of the electrophilic reagent, *S*-(1,3-dioxoisoindolin-2-yl)*O*,*O*–diethyl phosphorothioate (SDDP) is described. Moreover, the synthetic applications of SDDP wherein the transfer of the $SP(O)(OEt)_2$ moiety occurs were investigated. In this manner, SDDP underwent facile $SP(O)(OEt)_2$ transfer with electron-rich substrates such as ketones, indoles, and thiols to form α-phosphorothiolated ketones, 3-phosphorothiolated indoles and *S*-phosphorothiolated thioethers, respectively.

Thiophosphates are an important class of organothiophosphorus compounds widely applicable as pharmaceuticals, agrochemicals, and intermediates in materials and organic synthesis (Scheme 1) [1–13]. Traditionally, thiophosphates are prepared by the nucleophilic substitution reactions of thiohalide, RS-Y with $R^1R^2P(O)$-H compounds or phosphorus halide, $R^1R^2P(O)$-X with thiol, RS-H (Schemes 2a and b) [14–19]. However, in recent years, there have been significant improvement in the development of alternative methods of synthesis of thiophosphates. For instance, the direct cross-coupling of RS-H with $R^1R^2P(O)$-H compounds have been developed under oxidative conditions (Scheme 2c) [20–32]. Furthermore, the use of S_8 as the sulfur source in multicomponent reactions to access thiophosphates have been described (Scheme 2d) [33–42]. Another example involves the palladium-catalyzed synthesis of chiral *S*-aryl phosphorothioates *via* the coupling of chiral phosphorothioate salts with aryl iodides [43]. Recently, Tang and Zhao's group reported the C–H phosphorothiolation, and phosphorotrithioates, phosphor-amidodithioates and tetrathiophosphates preparation with white phosphorus [44–48]. Although a number of approaches for the synthesis of thiophosphates *via* S-P(O) bond formation have been established, the development of a robust and general method for the direct introduction of a S-P(O) moiety onto organic molecules is highly desirable. Herein, we report the preparation of diverse thiophosphates *via* the novel reaction of *S*-(1,3-dioxoisoindolin-2-yl)*O*,*O*–diethyl phosphorothioate (SDDP) with ketones, indoles and thiols (Scheme 2e).

The SDDP reagent was synthesized from inexpensive and readily accessible raw materials as illustrated by the synthetic route in Scheme 3 (see Supporting information for more details). The first step involves the high yielding conversion of phthalimide **1** into the *N*-chloro derivative **1a**, with trichloroisocyanuric acid (TCCA) in water at room temperature [49]. Meanwhile, sodium diethylphosphite was obtained quantitatively in two steps, initially *via* the reaction of diethylphosphite **1′** with sodium in anhydrous ether at 40 °C, and then engaging *in situ*, the resulting mixture with a solution of S_8 in benzene [50]. Finally, the reaction of the preformed intermediates *i.e.*, **1a** and **1′a** in toluene at room temperature for 30 min furnished SDDP (**1b**) in 96% yield (*i.e.*, 82% yield over three steps). Moreover, the scale-up reaction using 50 mmol each of phthalimide (**1**) and diethyl phosphite (**1′**) was successfully carried out to produce 14.2 g of SDDP. Notably, the solid SDDP is stable to air, light and moisture, and can be stored for more than two months without any decomposition.

With the synthesized SDDP in hand, we turned our attention towards investigating its synthetic applications. Initially, we examined its reaction with aryl ketones, selecting acetophenone (**2a**) as model substrate. No product was detected in the reaction of **2a** with SDDP (Table 1, entry 1), so we try to add promotor to initiate the reaction. After screening some promotors, we found that trimethylsilyl chloride (TMSCl) could effectively promote the reaction to take place (Table 1, entry 7). Furthermore, we carried out a careful screening of the solvent, amount loading of **1b**, temperature and time (Table 1, entries 8–18, see Tables S1–S3 in Support-

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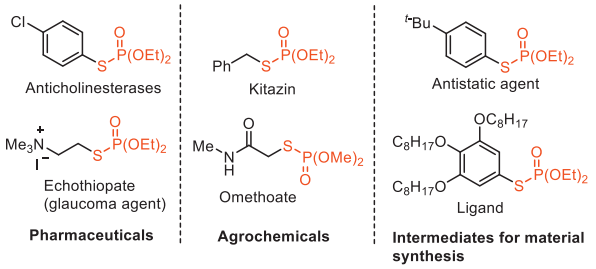
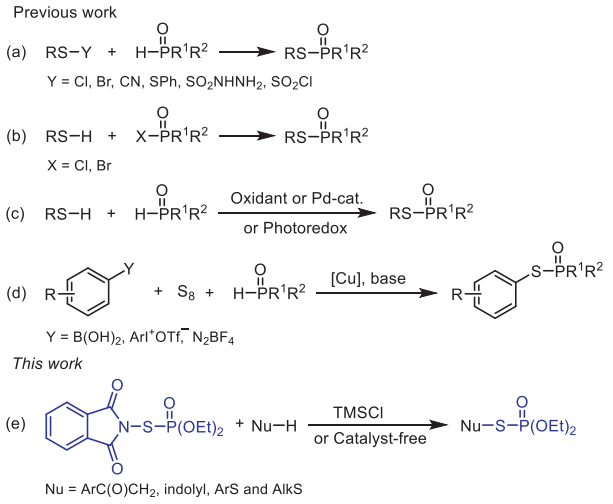
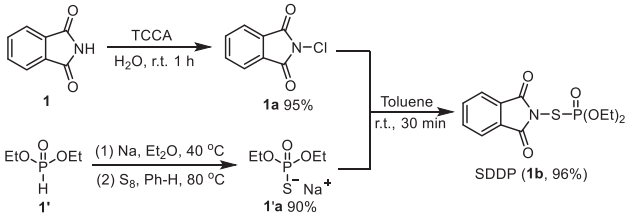


Scheme 1. Some examples of thiophosphate applications.



Scheme 2. Strategies for synthesis of thiophosphates.



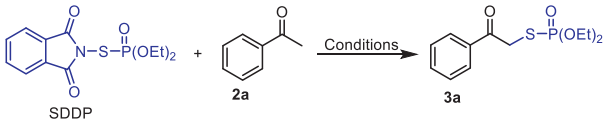
Scheme 3. Strategy for synthesis of SDDP (**1b**).

ing information for more details), we identified the optimal conditions to be the reaction of acetophenone (**2a**, 0.2 mmol) with SDDP (0.3 mmol) in the presence of TMSCl (0.4 mmol) in acetonitrile at 90 °C for 12 h under argon atmosphere (97%, entry 11).

With the optimal conditions in hand, the scope of the aryl ketones was examined (Scheme 4). In general, we found that all tested aryl ketones showed remarkable reactivity with SDDP. For instance, acetophenones substituted by methyl, halo groups, as well as naphthyl, benzyloxy, thienyl ketones all underwent facile transformation into the corresponding products in good to excellent yields (**3a**-**c** and **3g**-**n**) except substrates bearing methoxy or hydroxyl groups (**3d**–**f**). Similarly, the reaction of propiophenone took place smoothly to furnish the expected α-phosphorothiolated product **3o** in 81% yield. In addition, aliphatic ketones such as cyclohexanone and 2-butanone were used as substrates for the reaction, the two cases all gave the desired products **3p** (63% yield) and **3q** (28% yield), respectively.

To further expand the synthetic utility of SDDP, we tested its reactivity towards the electron-rich indoles (Scheme 5). We were pleased to discover that 2.0 equiv. of TMSCl could prompt the phosphorothiolation of indole derivatives with SDDP in DMF at

Table 1
Optimization of the reaction conditions.[a]

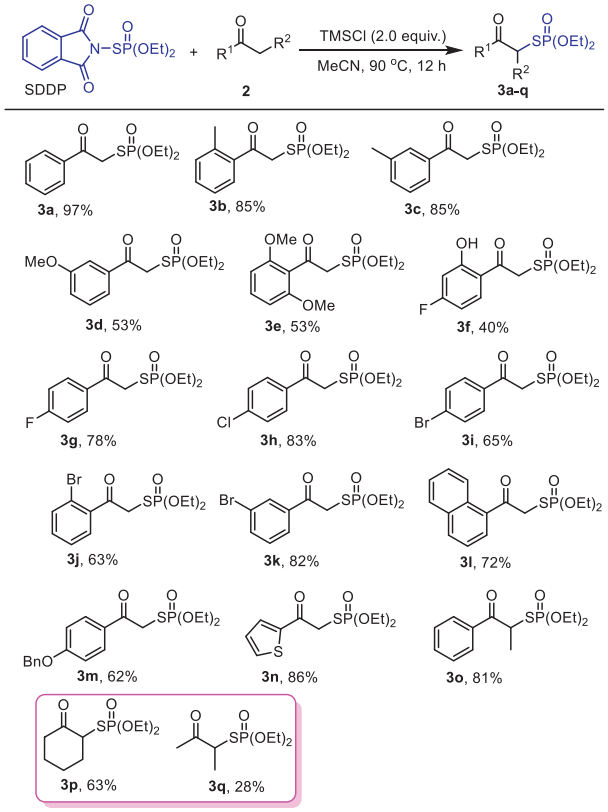


Entry	Promotor (equiv.)	SDDP (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	–	1.2	DCE	90	12	N.D.[c]
2	NaCl (2)	1.2	DCE	90	12	N.D.[c]
3	TfOH (2)	1.2	DCE	90	12	N.D.[c]
4	$CuCl_2$ (2)	1.2	DCE	90	12	41
5	$CuBr_2$ (2)	1.2	DCE	90	12	33
6	TMSBr (2)	1.2	DCE	90	12	42
7	TMSCl (2)	1.2	DCE	90	12	85
8	TMSCl (2)	1.2	Toluene	90	12	59
9	TMSCl (2)	1.2	DMF	90	12	81
10	TMSCl (2)	1.2	MeCN	90	12	90
11	TMSCl (2)	1.5	MeCN	90	12	97
12	TMSCl (2)	2.0	MeCN	90	12	96
13	TMSCl (2)	1.5	MeCN	25	12	N.D.[c]
14	TMSCl (2)	1.5	MeCN	50	12	29
15	TMSCl (2)	1.5	MeCN	80	12	77
16	TMSCl (2)	1.5	MeCN	90	8	86
17	TMSCl (2)	1.5	MeCN	90	6	59
18	TMSCl (2)	1.5	MeCN	90	4	44

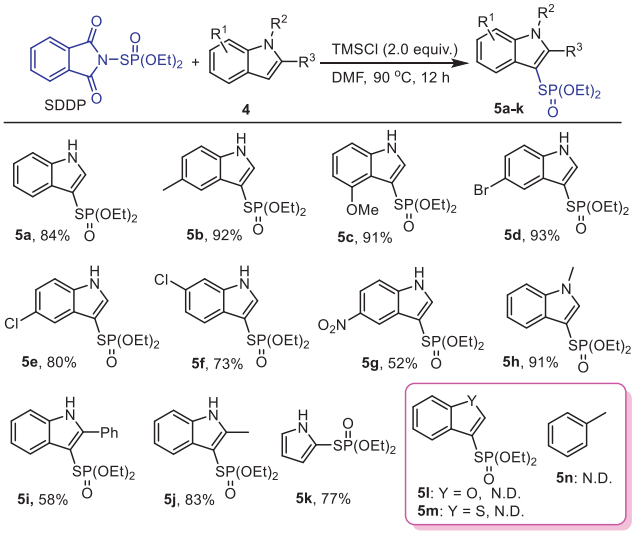
[a] Reaction conditions: **2a** (0.2 mmol), SDDP, promotor, in solvent (2 mL) at varied temperature for 4–12 h under argon atmosphere.
[b] Isolated yield.
[c] N.D. means not detected.

90 °C after 12 h. As observed with the aryl ketones, the indole derivatives including those containing electron-donating (methyl & methoxy) or weak electron-withdrawing (halo)substituent groups on the phenyl ring all underwent smooth conversion into the corresponding 3-phosphorothiolated products in good to excellent yields (**5a**–**f**) except 5-nitroindole gave the desired product **5g** in moderate yield (52%), this was presumably due to the strong electron-withdrawing effect of nitro group. Moreover, the *N*-protected substrate, 1-methyl-1*H*-indole reacted favorably to give high yield of the desired product **5h** (91%). Meanwhile, 2-phenyl- and 2-methylindoles afforded the corresponding products **5i** and **5j** in 58% and 83% yields, respectively. The diminished yield of **5i** was presumably due to the steric hindrance caused by the 2-phenyl group. Notably, pyrrole underwent efficient conversion to furnish the desired phosphorothiolation product **5k** in 77% yield. However, no expected products **5l**-**n** were detected in the reactions using benzofuran, benzothiophen and toluene as substrates.

Furthermore, the reactivity of SDDP was investigated with respect to thiols, and we found that a variety of *S*-phosphorothiolated thioethers can be furnished under inert conditions in DCM at 60 °C (Scheme 6). Notably, the reaction does not require the addition of a promotor or catalyst. A wide range of aryl thiols bearing methyl, methoxy and halo groups were successfully transformed into the desired products in satisfactory yields (**7a–j**). Pleasingly, aliphatic thiols were also amenable to the



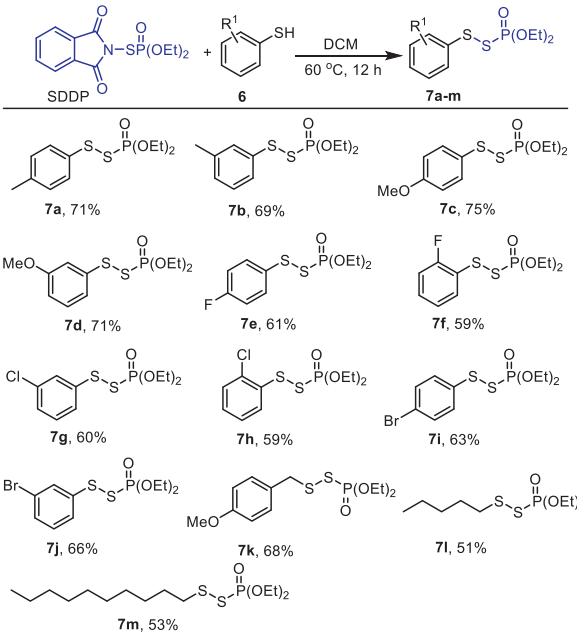
Scheme 4. Scope of ketones. Reaction conditions: **2** (0.2 mmol), SDDP (0.3 mmol), TMSCl (0.4 mmol) in MeCN (2 mL) at 90 °C for 12 h under argon atmosphere. Isolated yield.



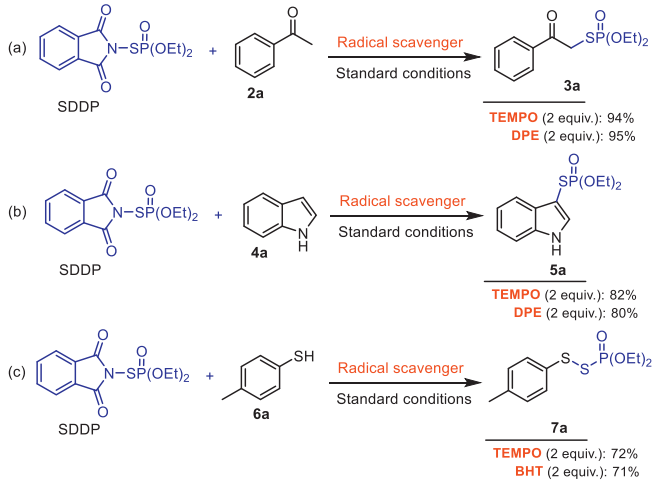
Scheme 5. Scope of indols. Reaction conditions: **4** (0.2 mmol), SDDP (0.3 mmol), TMSCl (0.4 mmol) in DMF (2 mL) at 90 °C for 12 h under argon atmosphere. Isolated yield.

reaction with SDDP. (4-Methoxyphenyl)methanethiol, pentanethiol and decanethiol produced the corresponding *S*-phosphorothiolated thioethers **7k–m** in the yields range of 51%–68%.

In order to elucidate the mechanism of these reactions, some control experiments were carried out. Initially, we observed that the addition of radical scavengers such as TEMPO (2,2,6,6-tetramethyl-1-piperidin-1-yl)oxyl, DPE (1,1-diphenylethylene) or BHT (2,6-di-*tert*-butyl-4-methylphenol) to the reaction mixture under standard conditions did not inhibit the formation of any of products **3a**, **5a**, or **7a** (Schemes 7a–c). These results effectively rule out the participation of radical intermediates in the reactions of SDDP with these compounds, *i.e.*, ketones, indoles and thiols.



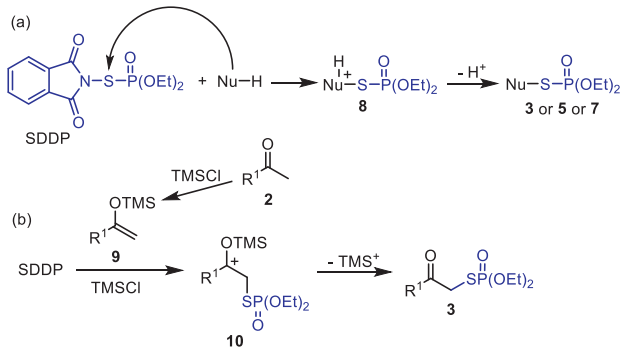
Scheme 6. Scope of thiols. Reaction conditions: **6** (0.2 mmol), SDDP (0.3 mmol) in DCM (2 mL) at 60 °C for 12 h under argon atmosphere. Isolated yield.



Scheme 7. Control experiments.

Based on these observations, we proposed a mechanism for the reaction of SDDP with the electron-rich substrates (Scheme 8). In general, the reaction of SDDP reagent proceeds *via* the initial nucleophilic attack on the *S*-atom by electron-rich substrates to furnish a cationic intermediate, **8**. Thereafter, deprotonation takes place to yield the target products **3**/**5**/**7** (Scheme 8a). With ketones, the terminal end of the double bond in the silyl enol ether **9** (generated *in situ* from the reaction of ketones and TMSCl) attacks the *S*-atom of SDDP to form the cationic intermediate **10**. This is followed by the formation of product **3**, alongside the departure of trimethylsilyl cation (TMS^+) as a leaving group (Scheme 8b).

In summary, we have developed an efficient protocol for the synthesis of the electrophilic reagent SDDP. Furthermore, we studied its reaction (*i.e.*, $SP(O)(OEt)_2$ transfer) with a range of electron-rich substrates including ketones, indoles and thiols to furnish α-



Scheme 8. Proposed mechanism.

phosphorothiolated ketones, 3-phosphorothiolated indoles and *S*-phosphorothiolated thioethers, respectively. Preliminary mechanistic studies implicate a nucleophilic substitution pathway wherein the electron-rich substrate attacks the electron-deficient *S*-atom in SDDP to form a cationic intermediate, followed by detrimethylsilylation or deprotonation to afford the observed products.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.109076.

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