# Phosphorothioate Synthesis Based on the Redox Reaction of Phosphite with Tellurium(IV) Chloride

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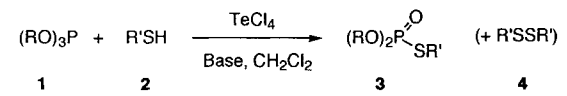
Phosphoric thiol esters are conveniently prepared by the treatment of phosphorous triesters with thiols in the presence of tellurium(IV) chloride in a redox-type reaction.

Phosphoric thiol esters (phosphorothioates) have been prepared as pesticides and thio-analogues of biologically active phosphoric mono- and diesters.[1] Their synthesis has been accomplished by a variety of methods, e.g. (a) the reaction of phosphoric diester monochloridate with a thiol; and (b) the reaction of a phosphite with sulfenic acid derivatives such as disulfide, sulfenyl chloride, thiocyanate and sulfenamide.[2] We recently reported a novel synthetic preparation of phosphoric triesters by the redox reaction of a phosphorous triester (**1**, trialkyl phosphite) with an alcohol in the presence of $TeCl_4$ and *tert*-amine.[3] This methodology prompted us to try the use of a thiol in place of the alcohol in the above reaction, expecting formation of *S*- and *O,O*-trisubstituted phosphorothioate **3**. We here report that the reaction provides an efficient phosphorylation method for a thiol.




| 1-3 | R | R' |
|---|---|---|
| a | Me | $CH_3(CH_2)_{11}$ |
| b | *n*-Bu | $CH_3(CH_2)_{11}$ |
| c | $PhCH_2$ | $CH_3(CH_2)_{11}$ |
| d | Me | $PhCH_2$ |
| e | Me | $CH_3(CH_2)_{17}$ |
| f | $PhCH_2$ | $CH_3(CH_2)_{17}$ |
| g | Me | $CH_3CHCO_2Et$ |
| h | Me | *p*-ClPh |
| i | Me | Ph |

**Scheme**

Following the procedure for the phosphoric triester synthesis, trimethyl phosphite (**1**, R = Me, 1.2 equiv) was treated with dodecane thiol (**2**, R' = $C_{12}H_{25}$) in the presence of $TeCl_4$ (0.8 equiv) and 2,6-lutidine (1.4 equiv) in $CH_2Cl_2$ at room temperature for 1 h to afford the corresponding phosphorothioate **3a** in 96% yield. In a similar manner, various phosphorothioates were prepared using alkane thiols in high yields (Table). With arene thiols, the use of tertiary amines such as lutidine and triethylamine gave lower yields of the products than that of alkane thiols due to the side reaction forming disulfides **4**. Dissociation of thiols promotes the oxidation. Therefore, to prevent their ionization, $Ca_2CO_3$, insoluble in the organic solvent, was employed as an acid captor.

**Table.** Compounds **3** Prepared[a]

| Product | Base | Time (h) | Yield (%) | $^1$H NMR ($CDCl_3$/TMS) $\delta$, *J* (Hz) | $^{31}$P NMR ($CDCl_3/H_3PO_4$) $\delta$, *J* (Hz) |
|---|---|---|---|---|---|
| **3a** | lutidine | 1 | 96 | 0.85–1.82 (br, 23H), 2.85 (dt, 2H, *J* = 7.8, 14, $CH_2S$), 3.80 (d, 6H, *J* = 12, | 32.54 |
| **3a** | $CaCO_3$ | 1 | 94 | OMe) | |
| **3b** | lutidine | 1 | 93 | 0.93 (t, *J* = 5.1, 3H, $CCH_3$), 0.95 (t, 3H, *J* = 6.3, $CCH_3$), 1.28 (br, 18H, $CH_2 \times 9$), 1.30 (m, 4H, $CH_2 \times 2$), 1.7 (complex, 6H, $CH_2 \times 3$), 2.8 (dt, 2H, *J* = 7.5, 14.7, $OCH_2$), 4.1 (dt, 4H, *J* = 7.2, 14.7, $OCH_2$) | 29.18 |
| **3c** | lutidine | 1 | 91 | 0.85–1.70 (br, 23H), 2.80 (dt, 2H, *J* = 7.8, 14.0, $CH_2S$), 5.1 (d, 4H, *J* = 8.0, $PhCH_2$), 7.4 (s, 10H, arom H) | 30.11 |
| **3d** | lutidine | 3 | 94 | 3.7 (d, 6H, *J* = 12.4, $OCH_3$), 4.1 (d, 2H, *J* = 14.6, $PhCH_2$), 7.4 (s, 5H, arom H) | 30.96 |
| **3e** | lutidine | 1.5 | 91 | 0.87 (br, 3H, $CH_3$), 1.26 (br, 30H, $CH_2 \times 15$), 1.67 (m, 2H, $\beta$-$CH_2$), 2.83 (dt, 2H, *J* = 14.0, 7.01, $CH_2S$), 3.80 (d, 6H, *J* = 12.8, $OCH_3$) | 32.50 |
| **3f** | lutidine | 1.5 | 83 | 0.92 (t, 3H, *J* = 6.4, $CH_3$), 1.26 (br, 30H, $CH_2 \times 15$), 1.63 (m, 2H, $\beta$-$CH_2$), 2.80 (dt, 2H, *J* = 7.32, 14.3, $CH_2S$), 5.15 (d, 2H, *J* = 8.55, $PhCH_2$), 5.16 (d, 2H, *J* = 8.24, $PhCH_2$), 7.40 (complex, 10H, arom H) | 30.20 |
| **3g** | lutidine | 1.5 | 97 | 1.30 (t, 3H, *J* = 7.02, $CH_2CH_3$), 1.61 (dd, 3H, *J* = 7.32, $CHCH_3$), 3.81 (d, 3H, *J* = 12.52, $OCH_3$), 3.83 (d, 3H, *J* = 12.82, $OCH_3$), 3.92 (dq, 1H, *J* = 7.32, 13.42, CHS), 4.22 (q, 2H, *J* = 7.02, $CH_2$) | 29.10 |
| **3h** | $CaCO_3$ | 1 | 90 | 3.81 (d, 6H, *J* = 12.5, $CH_3$), 7.32 (d, 2H, *J* = 8.55, arom H), 7.48 (dd, 2H, *J* = 1.83, 8.55, arom H) | 26.10 |
| **3i** | $CaCO_3$ | 4 | 95 | 3.90 (d, 6H, *J* = 12.6, $CH_3$), 7.30–7.80 (complex, 5H, arom H) | 26.86 |

[a] Satisfactory microanalyses obtained for **3a**–**3h**: C ± 0.40 (except **3g** ± 0.43), H ± 0.2. For **3i**, satisfactory MS was obtained.

This change of the base dramatically improved the yield of the *S*-aryl esters. Calcium carbonate performed equally well in the case of an alkane thiol (94% for **3a**).

Since various phosphorous mixed triesters **1** derived even from three different alcohols are readily available, a variety of phosphorothioates **3** may be prepared by the present redox phosphorylation procedure. The reaction has further advantages: the thiol itself is used for the reaction without converting to sulfenate derivatives, the yield is excellent and the procedure so simple. Thus, the present procedure provides a convenient alternative for the synthetic method of phosphorothioates.

**Phosphorothioates 3a–i; General Procedure:**
A solution of a thiol [dodecane thiol, R′ = $Me(CH_2)_{11}$: 1 mL, 4.17 mmol], trialkyl phosphite (trimethyl phosphite, R = Me: 591 μL, 5.01 mmol) and *tert*-amine (lutidine: 681 μL, 5.84 mmol) or calcium carbonate (1.4 mol equiv based on the thiol) in $CH_2Cl_2$ (20 mL) was cooled to −42 °C in an MeCN–solid $CO_2$ bath and $TeCl_4$ (0.8 equiv) was added. The mixture was stirred at the same temperature for 5–10 min and then, after removal of the bath, stirring was continued at r. t. for the specified period of time (Table). Precipitate(s) were filtered off and the filtrate was washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the phosphorothioates (1.24 g, 96% yield for **3a**) were isolated by column chromatography on silica gel.

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