A General Synthesis of *S*-(β-Oxoalkyl) *O,O*-Dialkyl Thio- and Dithiophosphates

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A novel, general synthesis of *S*-(β-oxoalkyl) and *S*-(β-oxocycloalkyl) *O,O*-dialkyl thio- and dithiophosphates based on the reaction of silyl enol ethers with *O,O*-dialkyl chlorothio- and *O,O*-dialkyl bromodithiophosphonates is described.

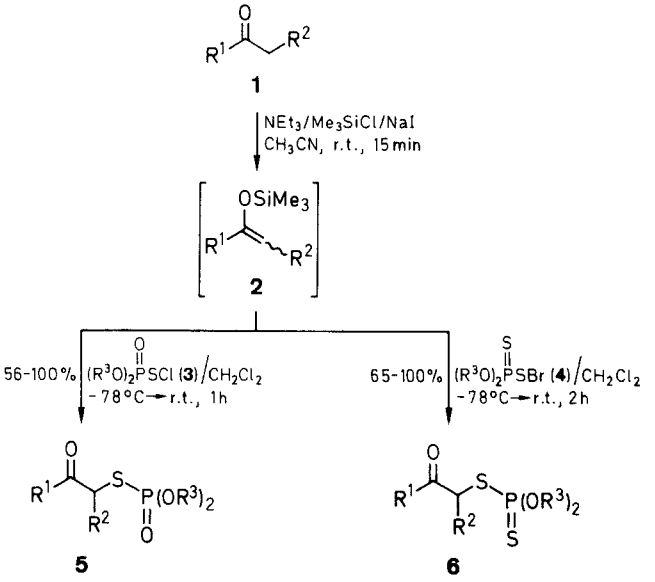
S-(β-Oxoalkyl) *O,O*-dialkyl thiophosphates **5** and *S*-(β-oxoalkyl) *O,O*-dialkyl dithiophosphates **6** are an important class of organophosphorus compounds. They are known to possess biological properties.[1] We are interested in these compounds as convenient intermediates in the regio- and stereoselective conversion of aldehydes and ketones into olefins and functionalized olefins.[2] Thiophosphates **5** and dithiophosphates **6** are generally synthesized by the reaction of the α-halocarbonyl compounds with the salts of thiophosphoric and thiophosphoric *S*-acids.[3] However, the scope of this method is limited and in several cases the yields are moderate.

We now describe a novel, efficient synthesis of acyclic and hitherto unknown cyclic compounds **5** and **6** of a broad range of structural types.

The reaction scheme involves generation of silyl enol ether **2** from the appropriate aldehydes or ketones **1** followed by thiophosphorylation with chlorothio- or bromodithiophosphonate, **3** or **4**.

The starting materials are readily available and there are several ways in which silyl enol ethers **2** may be prepared.[4] The chlorothio- **3**[5] and bromodithiophosphonates **4**[6,7] are both readily accessible and are among the best reagents for introduction of the thiophosphoryl function into organic compounds.[6,8]

Thus, the treatment of **2** with equimolar amounts of **3** or **4** in dichloromethane solution at −78 °C and stirring at room temperature for 1–2 h affords *S*-(β-oxoalkyl) *O,O*-dialkyl thiophosphates **5** and *S*-(β-oxoalkyl) *O,O*-dialkyl dithiophosphates **6** in good yields (56–100 %). Silyl enol ethers **2** with bulky substituents (R^1 and R^2) must be used in slight excess. Analytically pure samples **5** and **6** are obtained after purification by column chromatography on silica gel.



1–6	R^1	R^2	R^3
a	Me	H	Et
b	Me	H	Bu
c	Et	Me	Et
d	Et	Me	Bu
e	*i*-Pr	H	Et
f	*i*-Bu	*i*-Pr	Et
g	Ph	Me	Et
h	Ph	Ph	Et
i	4-FC_6H_4	Me	Et
j	2,5-$(Me)_2C_6H_3$	Me	Et
k	$-(CH_2)_3-$		Et
l	$-(CH_2)_4-$		Et
m	$-(CH_2)_4CH(Me)-$		Et
n	$-(CH_2)_2CH(t\text{-Bu})CH_2-$		Et
o	$-(CH_2)_2CH(t\text{-Bu})CH_2-$		Bu
p	H	Me	Et
r	H	$n\text{-}C_8H_{17}$	Et
s	H	Bu	Et

The reaction of **2** with **3** or **4** is regioselective. In fact, the regioselectivity of thiophosphorylation in such a procedure is assured by the use of silyl enol ethers (which can be generated with the desired regiochemistry, isolated and purified before the reaction). Finally, it is noteworthy that the reaction is also stereoselective in the case of a rigid cyclic structure. For example silyl enol ether **2n** (R^1,R^2 = $-(CH_2)CH(t\text{-Bu})CH_2-$) reacts with diethyl chlorothiophosphonate **3** to give **5n** as a mixture of diastereoisomers in the ratio 77:23. The isomers can be separated by column chromatography on silica gel yielding predominantly the pure *trans*-diastereoisomer. Isomerically pure *cis*-diastereoisomer is difficult to obtain. The diastereoisomeric ratio was determined by ^{31}P-NMR spectroscopic analysis of the crude mixture. The configuration of the dominating diastereoisomer **5n** was established to be *trans* on the basis of $^3J_{H^3aH^2e} = 4.8$ Hz and $^3J_{H^3eH^2e} = 3.0$ Hz. These values of the vicinal coupling constants of the ring protons H^3 and H^2 are a good indication of an equatorial position for proton H^2 and an axial position for thiophosphoryl $(RO)_2P(O)S$ substituent. (The values of the vicinal coupling constants between axial protons are large: 12.0–18.0 Hz).[9]

The results presented in the Table illustrate the synthetic scope of our method. Spectroscopic data of **5** and **6** were in full agreement with the anticipated structures.

In summary, our approach to compounds **5** and **6** is very useful in terms of easy availability of starting reagents, simple procedure, efficiency and very wide application. Furthermore, compounds **5** and **6** prepared in this way (except of **5a** and **6a**) are hitherto unknown.

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Table. *S*-(β-Oxoalkyl) *O*,*O*-Dialkyl Thiophosphates **5** and *S*-(β-Oxoalkyl)*O*,*O*-Dialkyl Dithiophosphates **6** Prepared

Product	Yield[a,b] (%)	Molecular[c] Formula	IR (film/KBr) ν(cm^{-1})[d] C=O, P=O	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)	^{31}P-NMR[e] δ, J(Hz)
5a	100	[f]	1712, 1250	1.16 (td, 6H, $J = 7\,\Delta\nu < 1$, $OCH_2C\underline{H}_3$), 2.09 (s, 3H, CH_3CO), 3.54 (d, 2H, $^3J_{PH} = 14.8$, CH_2SP), 3.98 (m, 4H, $OC\underline{H}_2CH_3$)	25.28[g]
5b	81	$C_{11}H_{23}O_4PS$ (282.3)	1712, 1260	0.76 (t, 6H, $J = 7.3$, $O(CH_2)_3C\underline{H}_3$), 1.24 (sext, 4H, $J = 7.3$, $O(CH_2)_2C\underline{H}_2CH_3$), 1.50 (quin, 4H, $J = 7$, $OCH_2C\underline{H}_2CH_2CH_3$), 2.11 (s, 3H, CH_3CO), 3.56 (d, 2H, $^3J_{PH} = 14.64$, CH_2SP), 3.95 (m, 4H, $OC\underline{H}_2(CH_2)_2CH_3$)	25.38[g]
5d	82	$C_{13}H_{27}O_4PS$ (310.4)	1715, 1250	0.67 (t, 6H, $J = 7.3$, $O(CH_2)_3C\underline{H}_3$), 0.80 (t, 3H, $J = 7.3$, $C\underline{H}_3CH_2CO$), 1.15 (sext, 4H, $J = 7.3$, $O(CH_2)_2C\underline{H}_2CH_3$), 1.23 (d, 3H, $J = 7.2$, $C\underline{H}_3CHS$), 1.41 (quin, 4H, $J = 7.3$, $OCH_2C\underline{H}_2CH_2CH_3$), 2.41 (ABq, 2H, $J_{AB} = 24$, $J = 7.3$, $CH_3C\underline{H}_2CO$), 3.81 (m_c, 4H + 1H, $OC\underline{H}_2(CH_2)_2CH_3$ and $CH_3C\underline{H}S$)	24.68[g]
5e	82	$C_9H_{19}O_4PS$ (254.28)	1709, 1240–1260	1.15 (d, 6H, $J = 7$, $(C\underline{H}_3)_2CH$), 1.37 (t, 6H, $J = 7$, $C\underline{H}_3CH_2O$), 2.79 (sept, 1H, $(CH_3)_2C\underline{H}$), 3.83 (d, 2H, $^3J_{PH} = 13.7$, CH_2SP), 4.19 (m, 4H, $OC\underline{H}_2CH_3$)	25.62 (71%)[h]
				1.37 (t, 6H, $J = 7$, $C\underline{H}_3CH_2O$), 1.62 (s, 6H, $(CH_3)_2C$), 2.38 (s, 3H, CH_3CO), 4.2 (m, 4H, $CH_3C\underline{H}_2O$)	21.79 (29%)[h]
5f	94	$C_{14}H_{28}O_4PS$ (323.4)	1700, 1240	0.94 and 1.04 (d, 6H, $J = 6.7$ $(C\underline{H}_3)_2CH$), 1.35 (t, 6H, $J = 7$, $C\underline{H}_3CH_2O$), 2.19 (sept., 2H, $J = 6.7$, $(CH_3)_2C\underline{H}$), 2.53 (ABd, 2H, $J_{AB} = 17.2$, $J = 6.7$, $(CH_3)_2CHC\underline{H}_2CO$), 3.77 (dd, 1H, $^3J_{PH} = 14.9$, $J = 6.7$, $PSC\underline{H}$), 4.16 (m, 4H, $OC\underline{H}_2CH_3$)	25.42[g]
5h	98	$C_{18}H_{21}O_4PS$ (364.4)	1684, 1268	1.1 and 1.33 (td, 3H, $J = 7$, $J = 1$, $C\underline{H}_3CH_2O$), 4.08 (m, 4H, $OC\underline{H}_2CH_3$), 6.25 (d, 1H, $^3J_{PH} = 10.4$, $C\underline{H}SP$), 7.03–8.15 (m, $10H_{arom}$)[i]	25.42
5i	95	$C_{13}H_{18}FO_4PS$ (320.6)	1700, 1250	1.33 (q ≈ 2t, 6H, $J = \Delta\nu = 7$, CH_3CH_2O), 1.68 (d, 3H, $J = 7$, $C\underline{H}_3CHSP$), 4.13 (dq, 4H, $^3J_{PH} = 15$, $J = 7$, $CH_3C\underline{H}_2O$), 5.03 (dq, 1H, $^3J_{PH} = 15$, $J = 7$, $CH_3C\underline{H}SP$), 7.0–7.35 and 8.0–8.35 (m, $^3H_{arom}$)[i]	25.34
5k	80	$C_9H_{17}O_4PS$ (252.3)	1750, 1265	1.31 (td, 6H, $J = 7.2$, $J = 2.7$, $C\underline{H}_3CH_2O$), 1.75–2.60 (m, 6H, ring protons), 3.57 (dddd, 1H, $^3J_{PH} = 17.5$, $J = 10.5$, $J = 8.5$, $J < 1$, $\underline{H}CSP$), 4.14 (m, 4H, $OC\underline{H}_2CH_3$)	25.12
5l	97	$C_{10}H_{19}O_4PS$ (266.3)	1700, 1230	1.37 (m, 6H, $C\underline{H}_3CH_2O$), 1.5–3.70 (m, 9H, ring protons), 4.15 (m, 4H, $CH_3C\underline{H}_2O$)	27.21
5m	95	$C_{11}H_{21}O_4PS$ (280.3)	1705, 1250	1.22 (td, 6H, $J = 7\,\Delta\nu = 3$, $C\underline{H}_3CH_2O$), 1.51[k] (s, 3H, $C\underline{H}_3CSP$), [1.58 (m, 2H), 1.77 (m, 1H), 1.94 (m, 2H), 2.2 (m, 2H), 2.98 (m, 1H)-ring protons], 4.04 (m, 4H, $CH_3C\underline{H}_2O$)	21.75[g] (81%)[j]
					23.37[g] (19%)[j]
5n	84	$C_{14}H_{27}O_4PS$ (322.4)	1705, 1260	0.93 (S, 9H, $C(CH_3)_3$), 1.37 (t, 6H, $J = 7$, $C\underline{H}_3CH_2O$), [1.45 (m, 2H), 1.68 (m, 2H), 2.13 (m, 1H), 2.45 (tdd, 1H, $J = 13$, $J = 6$, $J = 1$), 2.59 (ddd, 1H, $J = 13.8$, $J = 4.8$, $J = 3$)-ring protons], 4.20 (m, 4H, $OC\underline{H}_2CH_3$)	26.49 ($^3J_{PSCH} = 14$) (77%) *trans*
					24.43 (23%) *cis*
5o	56	$C_{18}H_{35}O_4PS$ (378.5)	1705, 1260	0.91 (m_c, 15H, $C\underline{H}_3(CH_2)_3O$ and $C(CH_3)_3$), on signals 1.40 (sext, 4H, $J = 7$, $CH_3C\underline{H}_2(CH_2)_2O$), 1.66 (quin, 4H, $J = 7$, $CH_3CH_2C\underline{H}_2CH_2O$), – ring protons are superimposed [2.15 (m, 1H), 2.45 (tdd, 1H, $J = 13$, $J = 6$, $J = 1$), 2.6 (ddd, 1H, $J = 13.8$, $J = 4.5$, $J = 3$)-ring protons], 4.0 (m, 4H, $OC\underline{H}_2(CH_2)_2CH_3$)	26.39 (78%) *trans*
					24.58 (22%) *cis*
5p	84	$C_7H_{15}O_4PS$ (226.25)	1735, 1230	1.25 (td, 6H, $J = 7$, $J = 1$, $C\underline{H}_3CH_2O$), 1.44 (dd, 3H, $J = 7$, $J = 1.5$, $C\underline{H}_3CHSP$), 3.83 (dqd, 1H, $^3J_{PH} = 15.8$, $J = 7$, $J = 1.5$, $PSC\underline{H}$), 4.16 (m, 4H, $OC\underline{H}_2CH_3$), 9.52 (d, 1H, $J = 1.5$, CHO)	24.62
5r	100	$C_{14}H_{29}O_4PS$ (324.4)	1730, 1230		23.57

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Table. (continued)

Product	Yield[a,b] (%)	Molecular[c] Formula	IR (film/KBr) ν(cm^{-1})[d] C=O, P=O	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)	^{31}P-NMR[e] δ, J(Hz)
5s	95	$C_{10}H_{21}O_4PS$ (268.31)	1730, 1260	0.78–2.55 (m_c, ≈9H, $(CH_2)_3CH_3$) superimposed with 1.38 (t, ≈6H, J = 7.5, OCH_2CH_3), 3.78 (dtd, 1H, $^3J_{PH}$ = 15, J = 7.5, J = 2, CHSP), 4.20 (dq, 4H, $^3J_{PH}$ = 7.5, J = 7, OCH_2CH_3), 9.50 (d, 1H, J = 2, CHO)[i]	25.10 (d quin, $^3J_{PSCH}$ = 14.5 $^3J_{POCH}$ = 8)
6a	100	[f]	1710, –	1.25 (t, 6H, J = 7, OCH_2CH_3), 2.19 (s, 3H, CH_3CO), 3.63 (d, 2H, $^3J_{PH}$ = 16.5, CH_2SP), 4.06 (m, 4H, OCH_2CH_3)	92.3
6c	85	$C_9H_{19}O_3PS_2$ (270.3)	1710, –	1.09 (t, 3H, J = 7, CH_3CH_2CO), 1.37 and 1.371 (td, 3H, J = 7, J = 1, CH_3CH_2O), 1.50 (d, 3H, J = 7, CH_3CHSP), 2.68 (ABq, 2H, J_{AB} = 18, J = 7, $CH_3CH_2C(O)$), 4.02 (dq, 1H, $^3J_{PH}$ = 16.2, J = 7, CH_3CHSP), 4.19 (m, 4H, OCH_2CH_3)	92.26
6g	70	$C_{13}H_{19}O_3PS_2$ (318.4)	1700, –	1.28 (td, 6H, J = 7, J = 1, CH_3CH_2O), 1.65 (d, 3H, J = 7, CH_3CHSP), 4.13 (m, 4H, CH_3CH_2O), 5.0 (dq, 1H, $^3J_{PH}$ = 16.2, J = 7, CHSP), 7.3–8.15 (m, $5H_{arom}$)	93.9 (d quin, $^3J_{PSCH}$ = 16 $^3J_{POCH}$ = 9)
6j	65	$C_{15}H_{23}O_3PS_2$ (346.4)	1700, –	1.28 (t, 6H, J = 7, CH_3CH_2O), 1.60 (d, 3H, J = 7, CH_3CHSP), 2.13 (m, 6H, CH_3ArCH_3), 4.13 (m, 4H, CH_3CH_2O), 4.85 (dq, 1H, $^3J_{PH}$ = 16.7, J = 7, CH_3CHSP), 7.0–7.72 (m, $3H_{arom}$)[i]	94.15 (72%)[l]
				1.37 (t, 6H, J = 7, CH_3CH_2O), 1.87 (d, 3H, J = 7, CH_3CHSP), 2.13 (m, 6H, CH_3ArCH_3), 4.13 (m, 4H, CH_3CH_2O), 5.07 (dq, 1H, $^3J_{PH}$ = 16.7, J = 7, CH_3CHSP), 7.0–7.72 (m, $3H_{arom}$)[i]	93.56 (d quin, $^3J_{PSCH}$ = 16 $^3J_{POCH}$ = 9.2) (28%)[l]
6p	68	$C_7H_{15}O_3PS_2$ (242.3)	1730, –	1.36 (tdd, 6H, J = 7 $\Delta\nu$ = 2.7, J = 1, CH_3CH_2O), 1.46 (dd, 3H, J = 7, J = 1, CH_3CHCHO), 3.89 (dqd, 1H, $^3J_{PH}$ = 16.6, J = 7, J = 1.5, $PSCH$), 4.20 (m, 4H, OCH_2CH_3), 9.55 (d, 1H, J = 1.5, CHO)	92.04 (d quin, $^3J_{PSCH}$ = 17 $^3J_{POCH}$ = 9.7)
6s	65	$C_{16}H_{21}O_3PS_2$ (284.37)	1730, –	0.75–2.55 (m_c, ≈9H, $(CH_2)_3CH_3$), superimposed with 1.38 (td, ≈6H, J = 7.5 $\Delta\nu$ = 3, OCH_2CH_3), 3.9–4.55 (m_c, 4H + 1H, OCH_2CH_3 and CHSP), 9.50 (d, 1H, J = 2, CHO)[i]	92.06 (d quin, $^3J_{PSCH}$ = 17 $^3J_{POCH}$ = 8)

[a] Yield of pure isolated product based on **3** or **4**.
[b] All compounds isolated as oils except **5h**; mp 84–85 °C (benzene, uncorrected).
[c] Satisfactory microanalyses obtained: C ±0.35, H ±0.35, P ±0.35, except **5n** C (+0.47).
[d] Recorded on Specord 71IR Spectrophotometer.
[e] Obtained on a Bruker instrument at 300. 13 MHz for ^{1}H and at 121.49 MHz for ^{31}P.
[f] These compounds are reported in Ref. 10.
[g] Recorded on a JEOL FX 60, without solvent.
[h] Regioisomers obtained from a mixture of regioisomers **2** containing 71% of **2e**.
[i] Recorded on Tesla BS 587 A spectrometer at 80.018 MHz in $CDCl_3$.
[j] Rotamers
[k] δ = 1.675 (C_6D_6).
[l] Regioisomers obtained from mixture of regioisomers **2** containing 81% of **2m**.

Silyl enol ethers **2a–s**,[4a] dialkyl chlorothiophosphonates[5] **3** and dialkyl bromodithiophosphonates[6] **4** were prepared according to the published procedures.

***S*-(β-Oxoalkyl) *O,O*-Dialkyl Thiophosphates 5 and *S*-(β-Oxoalkyl) *O,O*-Dialkyl Dithiophosphates 6; General Procedure:**

A solution of dialkyl chlorothio- **3** or dialkyl bromodithiophosphonates **4** (0.1 mol) in CH_2Cl_2 (50 mL) is added dropwise to a stirred solution of freshly prepared silyl enol ether **2** (0.1 mol) in CH_2Cl_2 (200 mL) at −78 °C. Stirring is continued at r.t. for additional 1–2 h. Then the solvent and trimethylsilyl halide are removed under reduce pressure to give crude **5** or **6**, which are purified by column chromatography [silica gel 70–230 mesh; benzene/EtOAc 1:1, as eluent]. Yields of analytically pure compounds and properties are listed in the Table.

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(1) Fest, C.; Schmidt, K.J. *The Chemistry of Organophosphorus Pesticides*, Springer-Verlag, Berlin, Heidelberg, New York, **1973**, p. 130–135.
Kado, M.; Maeda, T.; Yoshinoga, E. *Japanese Patent* 7327468; *C.A.* **1974**, *80*, 12924.
(2) Skowrońska, A.; Dybowski, P. *Phosphorus, Silicon, Sulfur and Relat. Elem.*, in press.
(3) *Houben-Weyl, Vol. E2*, Georg Thieme Verlag, Stuttgart, **1982**, p. 584, 715.
(4) (a) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075.
(b) Brownbridge, P. *Synthesis* **1983**, *1*, and references cited.
(c) Takai, K.; Kataoka, Y.; Okazoe, T.; Utimoto, K. *Tetrahedron Lett.*, **1988**, *29*, 1065.
(5) Skowrońska, A.; Dembiński, R.; Gwara, J., Michalski, J. *Phosphorus Sulfur* **1988**, *39*, 119, and references therein.
(6) Łopusiński, A.; Potrzebowski, M. *Phosphorus Sulfur* **1987**, *32*, 5564.
Łopusiński, A.; Łuczak, L.; Michalski, J. *Phosphorus Sulfur* **1988**, *40*, 233.

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(7) Michalski, J.; Potrzebowski, M.; Łopusiński, A. *Angew. Chem. Int. Ed. Engl.* **1982**, *94*, 135.
(8) Michalski, J. *Bull. Soc. Chim. Fr.* **1963**, *11*, and references therein.
Skowrońska, A.; Krawczyk, E.; Burski, J. *Phosphorus Sulfur* **1983**, *18*, 233.
Skowrońska, A.; Dembiński, R.; Kamiński, R.; Michalski, J. *Tetrahedron Lett.* **1987**, *28*, 4209, and references therein.
(9) Garbisch, B.W. Jr. *J. Am. Chem. Soc.* **1964**, *86*, 1780.
Zervos, M., Wartski, L., Goasdoue, N.; Platzer, N. J. *Org. Chem.* **1986**, *51*, 1293.
Carreno, M.C.; Dominguez, E.; Garcia-Ruano, J.L.; Rubio, L. *J. Org. Chem.* **1987**, *52*, 3619.
(10) Cremlin, R.J.W. *J. Chem. Soc.* **1964**, 2475.
Mastriukova, T.A.; Butorina, L.C.; Kushnir, W.N.; Kabachnik, M.I. *Zh. Obshch. Khim.* **1977**, *47*, 981.

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