A Useful Horner Reagent for the Synthesis of Some α-Methyl-α,β-Unsaturated *S*-Propyl Thioesters

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S-Alkyl 2-(dialkoxyphosphoryl)alkanethioates **3** can readily be prepared by the reaction of 2-(dialkoxyphosphoryl)alkanoyl chlorides **1** with thiols **2** in the presence of triethylamine. Only *S*-propyl 2-(dialkoxyphosphoryl)propanethioate (**3b**) gave synthetically useful Horner reactions: it was converted into the α-potassiopropanethioate anion by treatment with potassium carbonate in a small amount of water at room temperature. The Horner reaction between this anion and aldehydes **4** gave various α,β-unsaturated thioesters **5** with an α-substituted methyl group. Application of this method to the *cis/trans* ethyl 2-formyl-3,3-dimethyl-1-cyclopropylcarboxylate esters **4f** led to the 2-(propylthiocarbonyl)-2-propenyl pyrethroid derivatives **5f**.

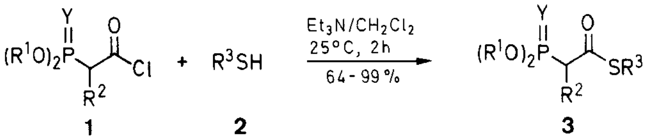
Coenzyme A thioester derivatives are well-known important intermediates in biochemical processes and acyl transfer reactions. In recent years thioesters have attracted a great deal of attention as latent active esters for synthetic laboratory purposes, especially in the synthesis of α,β-unsaturated carboxylic acids or esters under mild and specific conditions and in the synthesis of macrocyclic α,β-unsaturated lactones.[1]

Hence, the preparation of the α,β-unsaturated thioester precursors of α,β-unsaturated carboxylic acids or esters seems very attractive. Unsaturated thioesters also have interesting insecticidal properties.[2]

There are only a few reports of the preparation of α,β-unsaturated thioesters by a general base induced condensation procedure, the difficulty with thioester condensation reactions being the high propensity of this group to undergo nucleophilic attack resulting in thioester destruction. However, of the possible methods for the synthesis of α,β-unsaturated thioesters, the Wittig[3] and the Peterson[4] reactions, which are two of the most convenient for two-carbon chain extension, have been described.

In continuation of our investigations on the different applications of the 2-(dialkoxyphosphoryl)alkanoic acids in synthesis,[5] we report here the preparation of the corresponding thioester derivatives and their Horner reaction with carbonyl compounds.

The *S*-alkyl 2-(dialkoxyphosphoryl)alkanethioates **3a–k** were obtained by the reaction of acid chlorides **1a–k**[6] with thiols **2a–k** in the presence of triethylamine in dichloromethane at room temperature. The reaction was monitored by IR spectroscopy. The carbonyl absorption band of the acid chlorides **1a–k** ($\nu = 1790\,\mathrm{cm}^{-1}$)



1–3	Y	R¹	R²	R³
a	O	Et	H	Pr
b	O	Et	Me	Pr
c	O	Et	*n*-C_5H_{11}	Pr
d	O	Et	Ph	Pr
e	O	Et	SPh	Pr
f	O	Et	Cl	Pr
g	O	*i*-Pr	F	Pr
h	O	Et	Me	CH_2CH_2OH
i	O	Et	Me	4-MeC_6H_4
j	O	Et	Me	4-$NH_2C_6H_4$
k	S	Me	Me	Pr

Scheme A

Table 1. *S*-Alkyl 2-(Dialkoxyphosphoryl)alkanethioates or *S*-Propyl 2-(Dimethoxythiophosphoryl)propanethioates **3** Prepared

Product[a]	Yield[b] (%)	Molecular Formula[c]	^{1}H-NMR (CCl_4/TMS) δ, J(Hz)
3a	98[d]	$C_9H_{19}O_4PS$ (254.3)	0.8–1.5 (m, 11H), 2.4–2.95 (m, 4H), 3.9–4.4 (dq, 4H, $J = 7$)
3b	98 (70)	$C_{10}H_{21}O_4PS$ (268.3)	1 (t, 3H, $J = 6$), 1.2–1.8 (m, 11H), 2.85 (t, 2H, $J = 6$), 2.8–3.15 (m, 1H), 3.9–4.4 (m, 4H)
3c	98 (74)	$C_{14}H_{29}O_4PS$ (324.4)	1 (t, 3H, $J = 6$), 1.2–1.7 (m, 19H), 2.8–3 (m, 1H), 2.85 (t, 2H, $J = 6$), 3.9–4.3 (m, 4H)
3d	95 (85)	$C_{15}H_{23}O_4PS$ (330.4)	0.9–1.7 (m, 11H), 2.6–3.2 (m, 1H), 2.8 (t, 2H, $J = 7$), 3.7–4.15 (m, 4H), 7.2–7.7 (m, 5H)
3e	98[d]	$C_{15}H_{23}O_4PS_2$ (362.4)	0.9–1.7 (m, 11H), 2.6–3.1 (m, 1H), 2.8 (t, 2H, $J = 7$), 3.8–4.6 (m, 4H), 7.2–7.7 (m, 5H)
3f	95 (32)	$C_9H_{18}ClO_4PS$ (288.7)	1.1 (t, 3H, $J = 7$), 1.25–1.55 (m, 8H), 2.9 (t, 2H, $J = 9$), 3.2–3.6 (m, 1H), 3.9–4.45 (m, 4H)
3g	92[d]	$C_{11}H_{22}FO_4PS$ (300.3)	1.05 (t, 3H, $J = 7$), 1.4 (d, 12H, $J = 7$), 1.5–1.9 (m, 2H), 2.5–3.1 (m, 2H), 4.5–5.5 (m, 3H)
3h	84 (48)	$C_9H_{19}O_5PS$ (270.3)	1–1.8 (m, 9H), 2.7–3.2 (m, 1H), 2.8 (t, 2H, $J = 7$), 3.4 (s, 1H), 3.6–4.4 (m, 6H)
3i	90–99 (36)	$C_{14}H_{21}O_4PS$ (316.3)	1.1–1.7 (m, 9H), 2.3 (s, 3H), 3–3.5 (m, 1H), 3.8–4.4 (m, 4H), 6.9–7.5 (m, 4H)
3j	64[d]	$C_{13}H_{20}NO_4PS$ (317.3)	1.15–2 (m, 9H), 3.4–3.8 (m, 1H), 3.95–4.25 (m, 4H), 4.25 (s, 2H), 6.5–7.5 (m, 4H)
3k	78[d]	$C_8H_{17}O_3PS_2$ (256.3)	1–1.8 (m, 8H), 2.7 (t, 2H, $J = 7$), 2.8–3.4 (m, 1H), 3.8 (d, 6H, $J = 14$)

[a] All the products were obtained as oils exhibiting $\nu_{C=O}$ at 1680 cm^{-1} in IR (film).

[b] Yield of crude product. Yields in parenthesis denote to pure products isolated by column chromatography.

[c] The C, H analyses were in satisfactory agreement with the calculated values: C ±0.35, H ±0.24.

[d] Partial decomposition was observed.

Table 2. *S*-Propyl 2-Methyl-2-alkenethioates **5** Prepared

Product[a]	Reaction Time (h)	Yield[b] (%)	*Z*/*E*[c]	Molecular Formula[d]	^{1}H-NMR (CCl_4/TMS) δ, J(Hz)
5a	48	62	8:93	$C_{13}H_{24}OS$ (228.4)	*Z*: 0.9 (t, 3H, $J = 8$), (t, 3H, $J = 8$), 1.3 (m, 8H), 1.6 (m, 2H), 1.85 (s, 3H), 2.2 (m, 2H), 2.9 (t, 2H, $J = 7$), 5.7 (t, 1H, $J = 8$) *E*: 0.9 (t, 3H, $J = 8$), 1 (t, 3H, $J = 8$), 1.3 (m, 8H), 1.6 (m, 2H), 2.0 (s, 3H), 2.2 (m, 2H), 2.9 (t, 2H, $J = 7$), 6.75 (t, 1H, $J = 8$)
5b	48	50	40:60	$C_{10}H_{18}OS$ (186.3)	*Z*: 1 (m, 10H), 1.6 (m, 2H), 1.95 (d, 3H, $J = 2$), 2.86 (q, 2H, $J = 7.5$), 5.4 (dq, 1H, $J = 10, 1.5$) *E*: 1 (m, 10H), 1.6 (m, 2H), 1.9 (d, 3H, $J = 2$), 2.86 (q, 2H, $J = 7.5$), 6.5 (dq, 1H, $J = 10, 1.5$)
5c	48	64	6:94	$C_{13}H_{16}OS$ (220.3)	*Z*: 1.05 (t, 3H, $J = 7.5$), 1.65 (m, 2H), 2.1 (d, 3H, $J = 1.5$), 2.8 (t, 2H, $J = 7.5$), 7.15–7.4 (m, 4H), 6.5 (d, 1H, $J = 1.5$) *E*: 1.05 (t, 3H, $J = 7.5$), 1.65 (m, 2H), 2.1 (d, 3H, $J = 1.5$), 2.95 (t, 2H, $J = 7.5$), 7.15–7.4 (m, 4H), 7.6 (d, 1H, $J = 1.5$)
5d	22	70	10:90	$C_{14}H_{18}O_2S$ (250.5)	*Z*: 0.95 (t, 3H, $J = 8$), 1.6 (m, 2H), 2.1 (s, 3H), 2.9 (t, 2H, $J = 8$), 3.8 (s, 3H), 6.45 (s, 1H), 6.8 (d, 2H, $J = 9$), 7.2 (d, 2H, $J = 9$) *E*: 1.0 (t, 3H, $J = 8$), 1.65 (m, 2H), 2.15 (s, 3H), 3.0 (t, 2H, $J = 8$), 3.85 (s, 3H), 6.95 (d, 2H, $J = 9$), 7.45 (d, 2H, $J = 9$), 7.65 (s, 1H)
5e	48	46	9:91	$C_{13}H_{15}ClOS$ (254.8)	*Z*: 1 (t, 3H, $J = 8$), 1.6 (m, 2H), 2.1 (d, 3H, $J = 1.5$), 2.8 (t, 2H, $J = 8$), 6.4 (s, 1H), 7.1–7.3 (m, 5H) *E*: 1 (t, 3H, $J = 8$), 1.65 (m, 2H), 2.15 (d, 3H, $J = 1.5$), 2.95 (t, 2H, $J = 8$), 7.15–7.35 (m, 5H), 7.5 (s, 1H)
5f	72	70	5:23[e]	$C_{15}H_{24}O_3S$ (284.4)	*cis-Z*: 1.0 (t, 3H, $J = 7.5$), 1.2–1.4 (m, 11H), 1.74 (d, 1H, $J = 5.5$), 1.95 (s, 3H), 2.2 (dd, 1H, $J = 8, 5.5$), 2.9 (t, 2H, $J = 7.5$), 4.02–4.22 (m, 2H), 6.14 (d, 1H, $J = 9.5$) *cis-E*: 1.0 (t, 3H, $J = 7.5$), 1.2–1.4 (m, 11H), 1.74 (d, 1H, $J = 5.5$), 1.97 (s, 3H), 2.2 (dd, 1H, $J = 8, 5.5$), 2.9 (t, 2H, $J = 7.5$), 4.02–4.22 (m, 2H), 7.17 (d, 1H, $J = 9.5$)
			5:67[f]		*trans-Z*: 1.0 (t, 3H, $J = 7.5$), 1.2–1.4 (m, 11H), 1.74 (d, 1H, $J = 5.5$), 1.93 (s, 3H), 2.2 (dd, 1H, $J = 8, 5.5$), 2.9 (t, 2H, $J = 7.5$), 4.02–4.22 (m, 2H), 5.4 (d, 1H, $J = 9.5$) *trans-E*: 1.0 (t, 3H, $J = 7.5$), 1.2–1.4 (m, 11H), 1.74 (d, 1H, $J = 5.5$), 1.97 (s, 3H), 2.2 (dd, 1H, $J = 8, 5.5$), 2.9 (t, 2H, $J = 7.5$), 4.02–4.22 (m, 2H), 6.47 (d, 1H, $J = 9.5$)

[a] All the products are oils and showed the following characteristic IR data.
IR (film): $\nu_{C=O} = 1660\,cm^{-1}$, $\nu_{C=C} = 1620\,cm^{-1}$.

[b] Yield of pure products isolated by column chromatography.

[c] Determined by ^{1}H-NMR analyses of the crude products.

[d] Microanalyses showed following deviations: C ±0.49, H ±0.8, S ±0.59, Cl ±0.22.

[e] Ratio of *cis-Z*/*E*.

[f] Ratio of *trans-Z*/*E*.

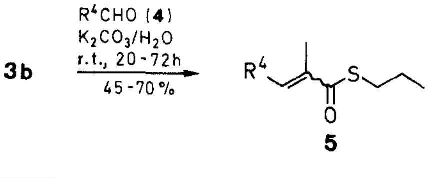
progressively disappeared in favor of the carbonyl absorption band of the thioesters **3a–k** (ν = 1680 cm^{-1}). The reaction was complete after two hours (Scheme **A**).

In this way the thioates **3a–k** were obtained in good yield (64–99%), sufficiently pure for subsequent use without purification.

As expected, the thioesters **3a–k** were unstable and partially or completely degraded during purification, especially during distillation. However, flash chromatography on alumina enabled analytically pure products to be obtained for the most stable compounds (Table 1).

The reaction between the enolates derived from the thioates **3a–k** and carbonyl compounds has been studied with various bases. By performing the condensation with a carbonyl compound by the usual method, under anhydrous conditions (lithium diisopropylamide or sodium hydride in tetrahydrofuran), only poor yields of products **5** could be obtained. Similar observations have been made by others regarding the closely related reactions between carbonyl compounds and the enolates derived from *O*-alkyl (dimethoxyphosphinyl)thio or dithioacetates.[7] Only the reagent **3b** gave fair yields of **5** with *p*-methoxy- (53% yield) or *p*-chlorobenzaldehyde (50% yield) when sodium hydride in tetrahydrofuran was used as base.

In a two-phase system containing aqueous potassium carbonate as base,[8] the reaction between **3b** (R^2 = Me, R^3 = Pr) and aldehydes gave better yields (Scheme **B**) (Table 2).



4, 5	a	b	c	d	e
R^4	*n*-C_6H_{13}	*i*-Pr	Ph	4-$MeOC_6H_4$	2-ClC_6H_4

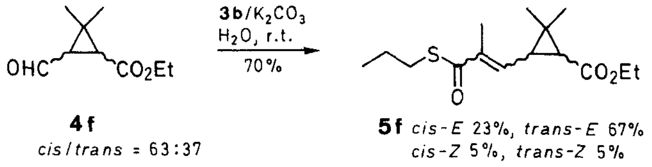
Scheme **B**

It should be noted that the same trend for the *trans* selectivity is exhibited by **3b** as compared to the analogous Wittig reagent (ethylthiocarbonylmethylene)triphenylphosphorane.[3]

In all other studied cases, the reaction did not succeed with aldehydes or ketones, even by increasing the duration of the reaction at room temperature. Attempts to carry out the reaction at increased temperature (40 °C) also failed; the sole observed result being the saponification of the thioester function.

To demonstrate the synthetic utility of the method, it was used for the synthesis of ethyl 3,3-dimethyl-2-[2-(propylthiocarbonyl)-1-propenyl]-1-cyclopropanecarboxylates **5f** with the aim of obtaining compounds, which combine the insecticidal properties of the α,β-unsaturated thioester function with the well-known properties of the pyrethroid group.

Reaction under the above conditions between **3b** and the ethyl esters of a mixture of ethyl esters *cis*- and *trans*-caronaldehyde (ethyl 2-formyl-3,3-dimethyl-1-cyclopropanecarboxylate; *cis*/*trans* = 63 : 37) gave a mixture of the four expected stereoisomers **5f** in good yields (70%) (Scheme **C**) (Table 2).



Scheme **C**

In conclusion it has been shown that 2-(dialkoxyphosphoryl)alkanethioate derivatives could be easily prepared from 2-(dialkoxyphosphoryl)alkanoyl chloride. Of all these compounds, *only the thioester* **3b** presents a synthetic utility in the Horner reaction with aldehydes and gave access to the α,β-unsaturated *S*-propyl thioesters with a trisubstituted double bond. Thus, this reagent fortunately complements the known Wittig reagents, which led to the same type of α,β-unsaturated thioesters with a bi- or trisubstituted double bond.[3] It should prove useful in organic synthesis, particularly in the synthesis of new pyrethroid derivatives.

All reagents were of commercial quality from freshly opened containers. Alkanethiols were purchased from Aldrich Chemical Co. Analytical TLC plates and silica gel (70–230 mesh) were purchased from E. Merck, Darmstadt. IR spectra were obtained using a Perkin-Elmer 580 B spectrophotometer. ^{1}H-NMR spectra were obtained using Bruker 80 MHz and Bruker AM 400 MHz instruments.

S-Alkyl 2-(Dialkoxyposphoryl)alkanethioates 3a–g, i–j and *S*-Propyl-2-(Dimethoxythiophosphoryl)propanethioate (3k); General Procedure:

A solution of Et_3N (0.15 g, 1.5 mmol) and alkanethiol **2** (1.5 mmol) in CH_2Cl_2 (20 mL) is added dropwise at 25 °C to a solution of 2-(dialkoxyphosphoryl)alkanoyl chloride **1** (1.5 mmol) or to a solution of 2-(dimethoxythiophosphoryl)propanoyl chloride (**1k**; 1.5 mmol) in CH_2Cl_2 (10 mL).[6] The mixture is stirred at rt and the reaction is monitored by IR spectroscopy. After 2 h the reaction is completed (the C=O absorption band of **1** at ν = 1790 cm^{-1} has completely disappeared in favor of the C=O absorption band of **3** at ν = 1680 cm^{-1}). The solvent is immediately evaporated. The product is taken up in benzene (15 mL), the triethylammonium chloride is filtered and the filtrate is evaporated under reduced pressure to leave the crude product as an oil, which is purified by chromatography on alumina (hexane/Et_2O) (Table 1).

S-Propyl 2-Methyl-2-alkenethioates 5; General Procedure:

To a stirred solution of *S*-propyl 2-(diethoxyphosphoryl)-propanethioate (**3b**; 1.1 g, 4 mmol) and the aldehyde **4** (4 mmol) under N_2 atmosphere is added a solution of K_2CO_3 (1 g, 7 mmol) in water (1 mL). The mixture is stirred for 22 to 72 h at r.t. and the progress of the reaction is followed by IR spectroscopy. Then water (10 mL) is added and the aqueous layer is extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts are dried ($MgSO_4$), and evaporated. The residue is purified by chromatography on silica gel using hexane/Et_2O as eluent (Table 2).

Received: 28 March 1990; revised: 31 July 1990

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