Synthesis of Alkyl 2-Alkenimidothioates from Alkyl 2-(Diethoxyphosphinyl)-alkanimidothioates and Aldehydes via Wittig-Horner Olefination

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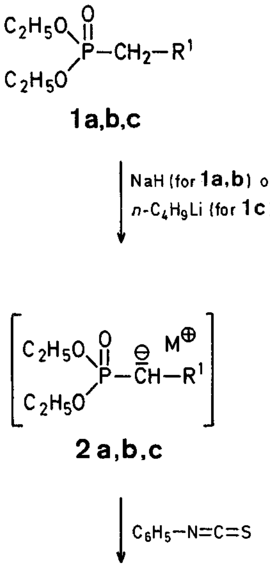
Imidothioic esters (thioimidates) are synthetically useful as amide equivalents the carbonyl group of which is activated for nucleophilic attack[1]. α,β-Unsaturated representatives (alkyl 2-alkenimidothioates) merit additional interest as they may act as 1-azadiene components in Diels-Alder reactions[2] and have potential as Michael acceptors[3]. Synthesis of the title compounds has so far been accomplished via Wittig reaction[4,5] or an aldol-type condensation[6]. We envisaged the versatile Wittig-Horner olefination[7] to provide ready access to a variety of alkyl 2-alkenimidothioates (**9**).

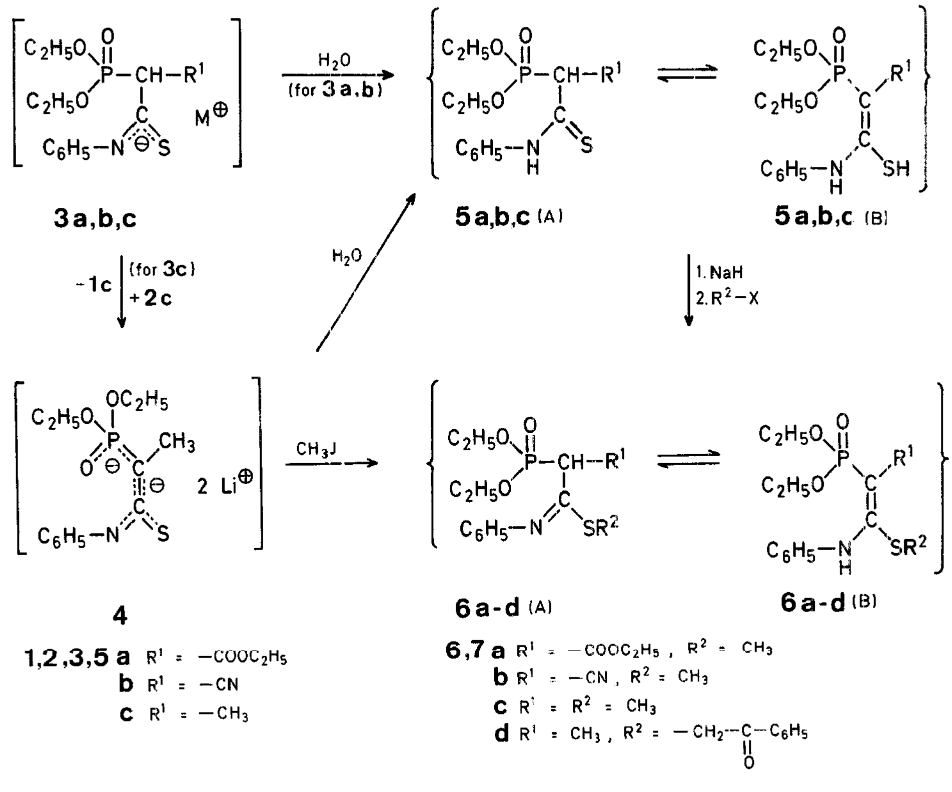


Alkyl 2-(diethoxyphosphinyl)-alkanimidothioates **6** (A) or the tautomeric ketene *S*,*N*-acetals **6** (B) should be precursors of the alkyl 2-alkenimidothioates **9** in an olefination reaction. The synthesis of **6a, b** from **1a, b** has been reported[8]. The method can be extended to examples with a less electron-withdrawing group R as demonstrated by the synthesis of **6c**. However, only half of **2c** can be converted into **3c** as the remaining hydrogen is highly acidic and a proton transfer from **3c** to unreacted **2c** interferes. *S*-Monomethylation of dianion **4** to give **6c** can be carried out *in situ*. More readily purified alkylation products **6** are obtained, when thioamides **5** are treated with methyl iodide or ω-bromoacetophenone.

Whereas the constitution **6** (B) has been established for **6a, b**[8], the spectroscopic evidence suggests structure **6** (A) for **6c, d**. Characteristic features of the ^{1}H-N.M.R. spectra of **6c,d** (A) are the occurrence of the signals of P—C—C<u>H</u> as doublets of a doublet due to ^3J coupling with the α-hydrogen and with phosphorus, while the signal of P—C<u>H</u> is observed as a doubled quartet and triplet, respectively. Moreover, the absence of an SH absorption in the I.R. spectra points toward tautomer **6** (A).

Anions **7a, b, c** are conveniently generated using sodium hydride in tetrahydrofuran. With added benzaldehyde (**8a**), anions **7a, b** fail to react, probably due to reduction of the nucleophilicity by the electron-withdrawing groups R^1. However, anion **7c** reacts smoothly with benzaldehyde at room temperature to give thioimidate **9a** in 80% yield. The versatility of the approach is demonstrated by the successful olefination even of electron-rich aromatic aldehydes such as **8c**, of a heteroaromatic aldehyde (**8g**), of a 2-alkenal (**8h**), and of alkanals (**8i, j, k**). However, anion **7c** did not react with ketones.

Starting from aldehydes **8a–h, j**, the methyl 2-alkenimidothioates **9a–h, j** are obtained as pure diastereoisomers. For products **9a–h**, the ^{1}H-N.M.R. signal of the vinylic proton seems to be in the range of the aromatic hydrogens. For **9j**, the corresponding resonance is observed at $\delta = 5.92$ ppm. This low-field position suggests the (*E*)-configuration by



1,2,3,5 **a** R^1 = $-COOC_2H_5$
b R^1 = $-CN$
c R^1 = $-CH_3$

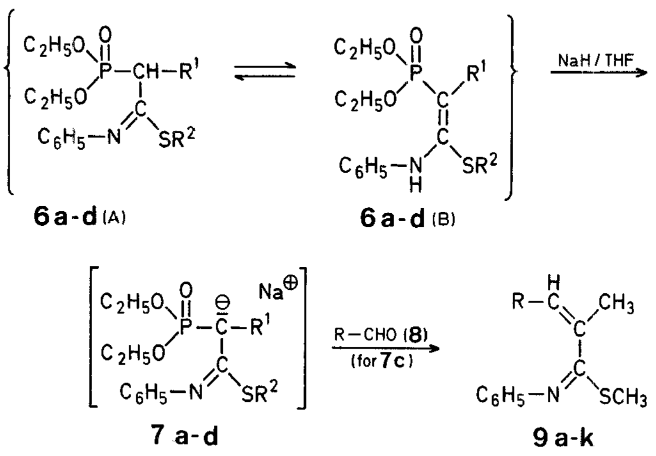
6,7 **a** R^1 = $-COOC_2H_5$, R^2 = CH_3
b R^1 = $-CN$, R^2 = CH_3
c R^1 = R^2 = CH_3
d R^1 = CH_3, R^2 = $-CH_2-CO-C_6H_5$

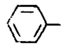
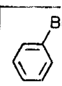
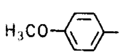
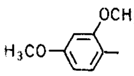
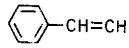
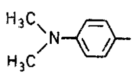
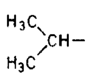
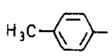
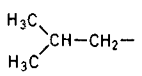
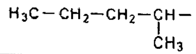
Table. Methyl *N*-Phenyl-2-alkenimidothioates (**9**) prepared

9	Yield [%]	m.p. [°C]	Molecular Formula[a]	I.R. (KBr or film) ν [cm^{-1}]		^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$) δ [ppm]		
				C=C	C=N	=CCH$_3$ (broad s)	SCH$_3$ (s)	other important signals
a	80	oil[b]	$C_{17}H_{17}NS$ (267.4)	1620	1580	1.80	2.42	
b	72	oil	$C_{18}H_{19}NOS$ (297.4)	1600	1580	1.80	2.40	3.75 (s, 3H)
c	61	82	$C_{19}H_{21}NO_2S$ (327.4)	1590	1570	1.73	2.40	3.77 (s, 6H)
d	75	85-87°	$C_{19}H_{22}N_2S$ (310.5)	1605	1575	1.80	2.37	2.92 (s, 6H)
e	76	oil	$C_{18}H_{19}NS$ (281.4)	1620	1585	1.80	2.40	2.33 (s, 3H)
f	75	oil	$C_{17}H_{16}BrNS$ (346.3)	?	1585	1.65	2.41	
g	86	oil	$C_{15}H_{15}NOS$ (257.4)	1620	1580	1.87	2.31	
h	88	oil	$C_{19}H_{19}NS$ (293.4)	1600	1580	1.73	2.33	
i	51	oil	$C_{14}H_{19}NS$ (233.4)	1620	1590	1.51	2.33	5.16 (d, J = 10 Hz, 0.15 H); 5.68 (d, J = 9 Hz, 0.85 H)
j	45	oil	$C_{15}H_{21}NS$ (247.4)	1620	1600	1.51	2.30	5.92 (t, J = 7 Hz, 1H)
k	74	oil	$C_{16}H_{23}NS$ (261.4)	1620	1590	1.50	2.30	4.96 (d + q, J = 10.6 + 1.2 Hz, 0.09H); 5.56 (d + q, J = 9 + ~1 Hz, 0.91 H)

[a] The microanalytical results were in satisfactory agreement with the calculated values: C ±0.37 except for **9h** (−1.0); H ±0.12, N ±0.31, S ±0.26, Br −0.03, for **9h**, high resolution M.S. gave $\Delta m = 0.00133$ (M$^+$).

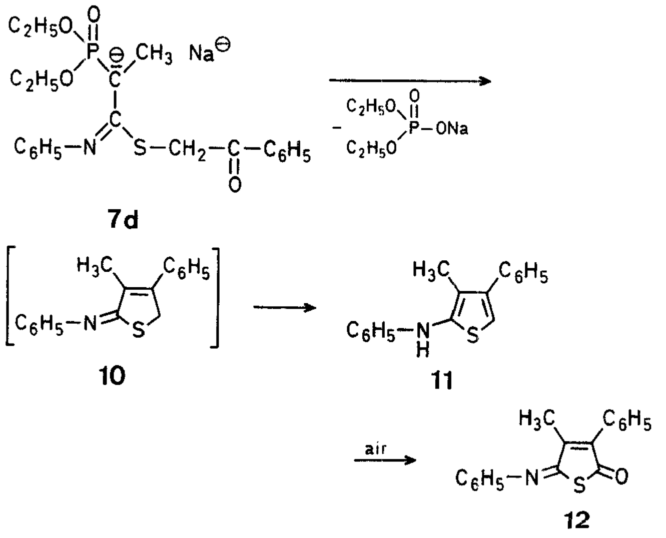
[b] Yield by Wittig olefination: 53%[4].



8, 9	R	**8, 9**	
a		**f**	
b		**g**	
c		**h**	
d		**i**	 $(H_3C)_2CH-$
e		**j**	 $(H_3C)_2CH-CH_2-$
		k	 $H_3C-CH_2-CH_2-CH(CH_3)-$

comparison with data for similar unsaturated carboxylic acid derivatives[9,10]. Olefination of **8h,i**, leads to mixtures of (*E*/*Z*)-isomers in which the (*E*)-isomer predominates.

The structure of phosphonate **6d** is suitable for intramolecular cycloolefination. Upon addition of sodium hydride, cyclization of the resultant sodio derivative **7d** takes place to give, apparently, the iminodihydrothiophene **10** as the primary product which undergoes aromatization to thiophene **11** via 1,5 hydrogen shift. Product **11** is sensitive to oxidation; on contact with air (for example, during attempted chromatographic purification or on evaporation of its solution) it is oxidized to 2-oxo-5-phenylimino-2,5-dihydrothiophene (**12**).



The diethyl phosphonates **6a**, **b** were prepared according to Ref.[8].

Diethyl 1-Methylthio-1-phenyliminopropane-2-phosphonate (6c) from 1c:
A 1.6 molar solution of butyllithium in hexane (7.5 ml, 12 mmol) is added to a stirred solution of diethyl ethanephosphonate[11] (**1c**; 2.0 g, 12 mmol) in dry tetrahydrofuran (25 ml) at −78 °C. Then, a solution of phenyl isothiocyanate (0.81 g, 6 mmol) in dry tetrahydrofuran (5 ml) is added dropwise over a 20 min period at −78 °C. The mixture is allowed to warm to 20 °C and stirred overnight. Then, methyl iodide (0.38 ml, 6 mmol) is added with stirring. After 6 h at 20 °C, the mixture is diluted with water (30 ml) and extracted with ether (3 × 50 ml) to remove excess **1c**. The aqueous phase is then extracted with dichloromethane (3 × 50 ml). The combined dichloromethane extracts are dried with sodium sulfate and evaporated to dryness in vacuo. Flash chromatography[12] (silica gel, eluent petroleum ether/ethyl acetate, 1/9) affords pure **6c** as an oil; yield: 0.945 g (50 %, based on phenyl isothiocyanate).

$C_{14}H_{22}NPO_3S$ calc. C 53.32 H 7.03 P 9.82 N 4.44
(315.4) found 53.13 7.07 10.09 4.24

I.R. (film): $\nu = 1605$; 1595 (C=N), 1250 (P=O); 1040, 1020, 940 (POC); 960, 760 cm^{-1}.

^1H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.29$ (t, $J_{HH} = 7.5$ Hz, 6H); 1.45 (d + d, $J_{HH} = 7.2$ Hz, $J_{HP} = 19$ Hz, 3H); 2.41 (s, 3H); 3.49 (d + q, $J_{HP} = 22$ Hz, $J_{HH} = 7.2$ Hz, 1H); 4.15 (m, 4H); 6.7–7.5 ppm (m, 5H).

Diethyl 1-Methylthio- (6c) and Diethyl 1-Phenacylthio-1-phenyliminopropane-2-phosphonate (6d) from 5c and 5d, respectively:
2-Diethoxyphosphinyl-*N*-phenylpropanethioamide[10] (**5c**: 903 mg, 3 mmol) is added in small portions to a stirred suspension of oil-free sodium hydride (72 mg, 3 mmol) in dry tetrahydrofuran (10 ml) at −20 °C under nitrogen. After the hydrogen evolution has subsided, methyl iodide (426 mg, or ω-bromoacetophenone (598 mg, 3 mmol) is added slowly. The mixture is stirred overnight, poured onto ice (50 g), and the product extracted with dichloromethane (3 × 20 ml). The combined organic phases are dried with sodium sulfate and evaporated to dryness to give pure **6c** (yield: 930 mg, 98 %) or **6d** (yield: 1140 mg, 91 %) as oils which may be further purified by preparative T. L. C. using ethyl acetate/petroleum ether (9/1) and plates of silica gel. Product **6d** is isolated as a viscous, rather unstable oil which can be characterized spectrometrically.

I.R. (film) of **6d**: $\nu = 1685$ (C=O); 1590 (C=N); 1200 (P=O); 1045, 1020, 960 (POC); 940 cm^{-1}.

^1H-N.M.R. ($CDCl_3/TMS_{int}$) of **6d**: $\delta = 1.30$ (t, $J_{HH} = 7.5$ Hz, 6H); 1.49 (d + d, $J_{HH} = 7$ Hz, $J_{HP} = 18$ Hz, 3H); 4.15 (m, 4H); 4.53 (m, 2H); 6.6–7.6 (m, 8H); 7.9–8.2 ppm (m, 2H).

Methyl *N*-Phenyl-2-alkenimidothioates (9); General Procedure: To a suspension of oil-free sodium hydride (72 mg, 3 mmol) in dry tetrahydrofuran (12 ml) at 20 °C is added diethyl 1-methylthio-1-phenyliminopropane-2-phosphonate (**6c**; 946 mg, 3 mmol), followed immediately by aldehyde **8** (3 mmol). After stirring at 20 °C for 18 h, the mixture is poured into water (50 ml), and the flask is washed with water (10 ml) and with ether (10 ml). The combined aqueous phases are extracted with ether (3 × 30 ml). The combined organic phases are washed with sodium hydrogen sulfite (3 × 30 ml of a 20 % solution). After drying with sodium sulfate, the mixture is evaporated to dryness in vacuo, and the residue purified by flash chromatography[12] (silica gel; eluent: petroleum ether/ethyl acetate 6/1). In the synthesis of **9d, f, g, i**, additional purification by preparative T.L.C. is required (silica gel plates; eluent: petroleum ether/ethyl acetate 6/1).

3-Methyl-4-phenyl-2-phenylaminothiophene (11) and 4-Methyl-2-oxo-3-phenyl-5-phenylimino-2,5-dihydrothiophene (12):
A solution of compound **6d** (838 mg, 2 mmol) in dry tetrahydrofuran (5 ml) is added to a stirred suspension of oil-free sodium hydride (48 mg, 2 mmol) in tetrahydrofuran (10 ml). Hydrogen is evolved and the mixture turns dark brown. After 2 h, the starting-material can no longer be detected by T. L. C. The mixture is poured into water (50 ml), and the product extracted with ether (3 × 30 ml). The combined ether extracts are washed with saturated sodium chloride solution (50 ml) and dried with sodium sulfate. The solvent is evaporated in vacuo using a bath temperature below 20 °C. The residue is the crude product **11** which can be characterized spectrometrically; yield of crude **11**: 500 mg (95 %).

I.R. (film): $\nu = 3480$ (NH); 1490, 1300, 1200, 750, 690 cm^{-1}.

^1H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 2.05$ (s, 3H); 5.43 (br. s, 1H); 6.6–7.5 (m, 6H); 7.38 ppm (s, 5H).

On standing at room temperature, attempted chromatographic purification, or evaporation of solutions at 45 °C, compound **11** decomposes to give **12** as a brown powder. Product **12** can be purified with considerable loss of material by preparative T. L. C. (silica gel plates; eluent ethyl acetate/petroleum ether = 1/1) to give yellow crystals; yield: 65 mg (12 %); m.p. 155–156 °C.

$C_{17}H_{13}NOS$ calc. C 73.09 H 4.69 N 5.01 S 11.47
(279.4) found 73.00 4.72 5.01 11.75

I.R. (KBr): $\nu = 1695$ (C=O); 1640, 1610; 1585 (C=N); 1380, 1115, 800, 760, 710, 690 cm^{-1}.

^1H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 2.36$ (s, 3H); 6.9–7.5 (m, 5H); 7.30 ppm (s, 5H).

^{13}C-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 192.2$ (C=O); 161.8 (C=N); 154.0, 150.7, 144.6, 130.3–128.9, 126.1, 120.2, 13.7 ppm.

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