Synthesis and Wittig-Horner Reactions of 1-(Functionally)Substituted 2,2-Dimethylpropanephosphonic Esters (1-*t*-Butyl-substituted Phosphonic Esters)

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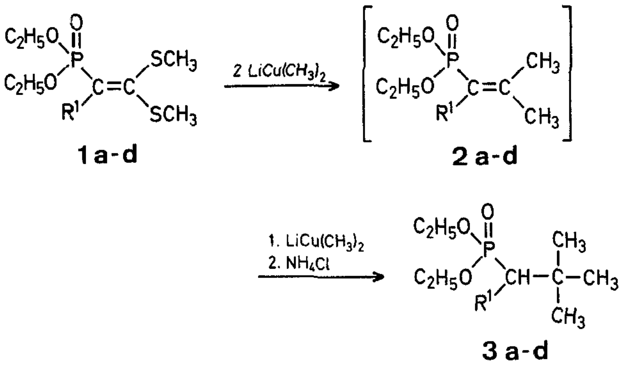
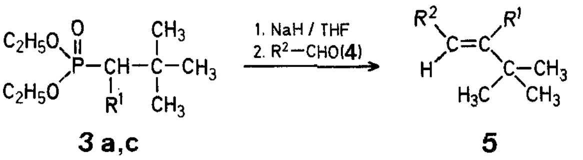
1-Alkoxy-2,2-dimethylpropanephosphonic esters have been described[1] but the conventional methods of organophosphorus chemistry fail in the synthesis of other 2,2-dimethylpropanephosphonic esters functionally substituted at the 1-position (**3**)[2]. We envisioned the introduction of the *t*-butyl group into suitably functionalized phosphonic esters as a promising approach to the title compounds (**3**) and in this context studied the reaction of dialkoxyphosphinylketene *S*,*S*-acetals with lithium dimethylcuprate[3]. In fact, the readily accessible diethyl 2,2-bis[methylthio]ethenephosphonates[4] (**1**) were found to react smoothly with lithium dimethylcuprate to give, after work-up, the desired 1-substituted diethyl 2,2-dimethylpropanephosphonates (**3**) in moderate to good yields. The 1-substituted diethyl 2-methyl-1-propenephosphonates **2** which are assumed to be intermediates in the reaction could not be detected, thus indicating that the Michael-type addition of the third molecule of dimethyl cuprate is a fast reaction.



a $R^1 = -CN$
b $R^1 = -COOCH_3$
c $R^1 = -COOC_2H_5$
d $R^1 = -\underset{\overset{\|}{O}}{C}-C_6H_5$

In spite of the bulky *t*-butyl group, phosphonates **3** can be used in Wittig-Horner olefinations[5] to a limited extent. Thus, the anions of **3a–d** can be conveniently generated with sodium hydride in tetrahydrofuran but, on addition of an aldehyde (**4**), only **3a** and **3c** give a satisfactory olefination reaction, phosphonate **3c** being more reactive than **3a**. In our attempts to achieve olefination of benzaldehyde with the anion of **3b**, the cation was changed from sodium to potassium or magnesium (use of potassium *t*-butoxide or ethylmagnesium iodide) without significant effect. Similarly, addition of sodium hydride/15-crown-5 did not improve the olefination step in the reaction with 4-methoxybenzaldehyde.



The yields of 2-*t*-butyl-3-arylpropenoic esters (**5a, b, c**) and 2-*t*-butyl-2-alkenenitriles (**5d–g**) obtained from phosphonic acid derivatives **3a**, **c** and aldehydes depend on the nature of the aldehyde. Thus, with 4-methoxybenzaldehyde lower yields of **5** are obtained than with benzaldehyde due to electronic deactivation whereas with 4-nitrobenzaldehyde side reactions involving the nitro group interfere. The low yield of nitrile **5g** obtained from the reaction of diethyl phosphonate **3a** with 2-methylpropanal probably marks the steric limit of the Wittig-Horner olefination investigated here.

Although (*E*/*Z*)-isomers are conceivable, products **5** are isolated as pure diastereoisomers. Comparison of the chemical shift of the vinyl proton signal with that found for the (*E*/*Z*)-isomers of similar olefins[6] leads to assignment of the (*Z*)-configuration to **5a–g**. This configuration is sterically favored due to the voluminous *t*-butyl group.

Ketene *S*,*S*-acetals **1a**, **b**, **c** were prepared according to the literature procedure[4].

Diethyl 1-Benzoyl-2,2-bis[methylthio]-ethenephosphonate (1d):

A solution of diethyl 2-oxo-2-phenylethanephosphonate[7] (1.29 g, 5.0 mmol) in ether (20 ml) is slowly added to a stirred suspension of oil-free sodium hydride (0.24 g, 10 mmol) in ether (20 ml) at 20 °C under nitrogen. After 1 h, carbon disulfide (0.32 ml, 5.3 mmol) in ether (2 ml) is added. Stirring is continued for 1 h. Then, methyl iodide (0.62 ml, 10 mmol) in ether (5 ml) is added rapidly which leads to additional hydrogen evolution. Finally, a solid separates from the mixture. After 12 h, the mixture is poured onto ice (50 g), and the product is extracted with chloroform (3 × 50 ml). The extracts are dried with sodium sulfate and evaporated to dryness. The residue is recrystallized from ethyl acetate/petroleum ether to give pure **1d**; yield: 1.22 g (68%); m.p. 67 °C.

$C_{15}H_{21}O_4PS_2$	calc.	C 49.99	H 5.87	P 8.59
(360.4)	found	49.79	5.95	8.83

I.R. (KBr): ν = 1660 (C=O); 1240 (P=O); 1020, 960 (POC) cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): δ = 1.18 (t, J_{HH} = 7 Hz, 6 H); 2.22 (d, J_{PH} = 0.9 Hz, 3 H); 2.47 (s, 3 H); 3.8–4.3 (m, 4 H); 7.2–8.2 ppm (m, 5 H).

1-(Functionally)Substituted Diethyl 2,2-Dimethylpropanephosphonates (3); General Procedure:

A solution of methyllithium (30 mmol) in ether (25 ml) is added to dry copper(I) iodide (3.0 g, 15 mmol) under nitrogen at 0 °C. To the resultant solution (~0.25 molar) of lithium dimethylcuprate, a solution of the ketene *S,S*-acetal **1** (10 mmol) in ether (15 ml) is added with stirring and ice cooling. The mixture which immediately turns black is stirred overnight. It is then hydrolyzed by the addition of saturated aqueous ammonium chloride (150 ml), and extracted with ether (3 x 100 ml). The combined organic phases are dried with sodium sulfate and evaporated to dryness in vacuo. Products **3** are isolated by distillation except for **3d** which is preferentially purified by chromatography on silica gel (eluent: ethyl acetate/petroleum ether, 9/1).

2-*t*-Butyl-2-alkenoic Acid Derivatives 5 by Wittig-Horner Olefination of Aldehydes 4; General Procedure:

The diethyl phosphonate **3** (3.0 mmol) is added to a stirred suspension of oil-free sodium hydride (0.79 g, 3.3 mmol) in dry tetrahydrofuran (15 ml). Stirring is continued for 30 min at room temperature (for **3a**) or 35 °C (for **3c**). Then, a solution of the aldehyde **4** (3.3 mmol) in tetrahydrofuran (1 ml) is added and stirring is continued overnight. Separation of a sirupy deposit is completed by refluxing the mixture for 6 h. The mixture is then poured onto ice (50 g), the aqueous phase is extracted with chloroform (3 x 50 ml), and the combined extracts are dried with sodium sulfate. The oily residue is purified by preparative T.L.C. (eluent ethyl acetate/petroleum ether 1/4 or 1/9).

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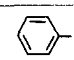
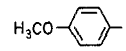
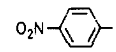
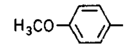
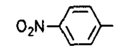
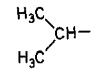
Table 1. 1-(Functionally)Substituted Diethyl 2,2-Dimethylpropanephosphonates (3) prepared

3	Yield [%]	b.p. [°C/torr]	Molecular formula[a]	I.R. (film) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$) δ [ppm]	
					C(C$\underline{H}_3$)$_3$	P—C$\underline{H}$
a	69	98°/0.1	$C_{10}H_{20}NO_3P$ (233.3)	2240, 1260, 1040, 1020, 960	1.31 (s)	2.92 (d, J = 24 Hz)
b	80	93–95°/0.1	$C_{11}H_{23}O_5P$ (266.3)	1730, 1250, 1040, 1020, 960	1.21 (s)	2.94 (d, J = 22 Hz)
c	75	93°/0.05	$C_{12}H_{25}O_5P$ (280.3)	1730, 1250, 1060–1020, 960	1.20 (s)	2.90 (d, J = 22 Hz)
d	40	140–145°/ 0.005[b]	$C_{16}H_{25}O_4P$ (312.4)	1680, 1240, 1060, 1020, 960	1.26 (s)	4.14 (d, J = 22 Hz)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.24; H, ±0.36; N, ±0.18, for **3a, b, c**; for **3d**, high resolution M.S. gave Δm = 0.00385 (M$^+$).

[b] The compound partially decomposes on distillation.

Table 2. 2-*t*-Butyl-2-alkenoic Esters (**5a, b, c**) and 2-*t*-Butyl-2-alkenenitriles (**5d–g**) prepared

4	R^1	R^2	Yield [%]	m.p. [°C] or b.p. [°C]/ torr	Molecular formula[a]	I.R. (film or KBr) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$) δ [ppm]	
							C(C$\underline{H}_3$)$_3$	=C$\underline{H}$
a	$-COOC_2H_5$		60	oil	$C_{15}H_{20}O_2$ (232.3)	1720, 1460, 1020	1.24 (s)	6.53 (s)
b	$-COOC_2H_5$		11	oil	$C_{16}H_{22}O_3$ (262.4)	1720, 1460, 1040, 1020	1.26 (s)	6.50 (s)
c	$-COOC_2H_5$		20	oil	$C_{15}H_{19}NO_4$ (277.3)	1720, 1480–1460, 1040	1.29 (s)	6.59 (s)
d	$-CN$		75	oil	$C_{13}H_{15}N$ (185.3)	2200, 1480–1440	1.27 (s)	6.93 (s)
e	$-CN$		62	oil	$C_{14}H_{17}NO$ (215.3)	2200, 1460	1.31 (s)	6.85 (s)
f	$-CN$		15	72°	$C_{13}H_{14}N_2O_2$ (230.3)	2200	1.36 (s)	7.07 (s)
g	$-CN$		10	30°/0.5	$C_{10}H_{17}N$ (151.2)	2200, 1470, 1460	1.23 (s)	5.97 (d, J = 9.5 Hz)

[a] The microanalyses or high-resolution M.S. data were in satisfactory agreement with the calculated values: C, ±0.32; H, ±0.19; N, ±0.20; Δm = +0.00823.

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