Synthesis of δ-Ketonic and δ-Thioacetalated Phosphonium Salts and Their Use in Wittig Reactions for Carbonyl n + 4 Homologation

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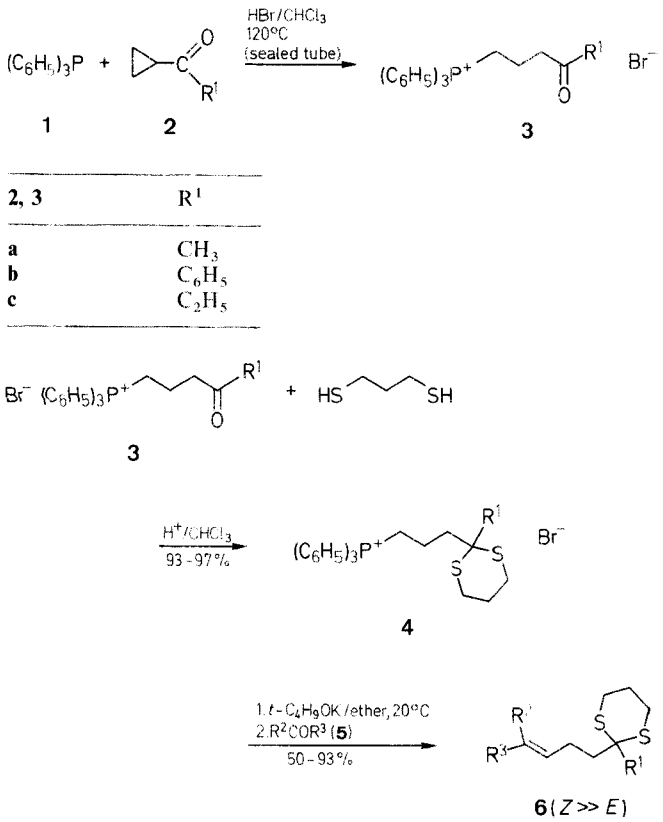
The δ-thioacetalated phosphonium salts **4** are obtained by addition of triphenylphosphine on cyclopropylketones **2** followed by carbonyl thioacetalization. The corresponding ylides are converted into 2-(3'-alkenyl)-1,3-dithianes **6** with predominant *Z*-stereochemistry in good yields.

The transformation of carbonyl compounds into n + 1 to n + 4 higher homologs has been the subject of numerous studies.[1] In this field the use of phosphonium ylides has been scarcely documented, but we have developed previously Wittig reagents which allow the synthesis of the corresponding n + 2[2] and n + 3[3] higher homologs. In order to obtain the n + 4 homologation of carbonyl compounds, we have now prepared phosphonium salts **4** in which the ketonic group is protected by thioacetalization in order to prevent intra or intermolecular Wittig reactions,[4] or basic catalyzed degradations.[5,6]

The previously described methods for the preparation of salts **3** involve the reaction of triphenylphosphine with δ-halogenoketones or aldehydes.[7,8] By analogy with the addition on α,β-unsaturated carbonyl compounds,[6,9,10] we have used the addi-



tion of triphenylphosphine on cyclopropylketones, resulting in the opening of the ring, to obtain the δ-ketonic phosphonium salts **3** (Table 1)

The Wittig reaction of the corresponding thioacetalized ylides **4** (Table 1) with aliphatic or aromatic aldehydes and ketones **5** gave good yields of 2-(3′-alkenyl)-1,3-dithianes **6** (Table 2). The ^{1}H-, ^{13}C-NMR and HPLC or GC analyses show the predominant *Z*-stereoselectivity, as normally expected for unstabilized ylides (Table 3).

The melting points were determined with a Mettler FP 51 apparatus. ^{1}H-NMR spectra were recorded on Varian A 60 and EM 360 (60 MHz) spectrometers. ^{31}P- and ^{13}C-NMR were recorded on a Brucker WP 80 DS. IR und UV spectra were respectively recorded on a Perkin Elmer 377 and Beckman DKI spectrophotometers. The quantitative isomer determination of 2-(3′-alkenyl) 1,3-dithianes **6** was performed with a HPLC Watter M 6000 A (refractometer detector R 401) and GPC Intersmat IGC 120 GEL with flame ionisation detector column (1.5 mm × 3 m) with the stationary phase 5% methylsilicone SE 30 on 80/100 chromosorb PLA. The ketones **2** which are not commercial have been prepared by reaction of Grignard reagent with cyclopropylcarbonitrile.[14]

δ-Ketoalkylphosphonium Salts 3; General Procedure:
A heterogeneous mixture of triphenylphosphine **1** (2.88 g, 11 mmol), chloroform (40 ml), cyclopropyl ketone **2** (20 mmol) and 48% hydrobromic acid (2.4 ml, 20 mmol) is placed in a glass tube, which is sealed and introduced into a steel tube. After heating at 120°C for 24 h, the sealed tube is cooled to 0°C, and opened. The chloroform layer is separated, washed with water (4 × 20 ml) and dried with sodium sulfate. The organic phase is concentrated to 20 ml and the residue is added to ether (500 ml) with stirring. The precipitate is filtered, dried over phosphorus pentoxide *in vacuo* (33 mbar) and recrystallized from chloroform/ethyl acetate (Table 1).

Thioacetalization of δ-Ketoalkylphosphonium Salts 3; General Procedure:
To a solution of salt **3** (10 mmol) in chloroform (40 ml) is added 1,3-propanedithiol (1.3 ml, 12 mmol). The flask is fitted with a water separator and the mixture is refluxed for 4 h and cooled. The chloroform layer is separated, washed with water (4 × 20 ml), dried with sodium sulfate, concentrated to 20 ml and added dropwise under stirring to ether (500 ml). The precipitate is filtered, dried over phosphorus pentoxide at 33 mbar and recrystallized from chloroform/ethyl acetate.

Table 1. Phosphonium Salts **3** and **4** Prepared

Product	Yield[a] (%)	m.p. (°C)	Molecular Formula[b]	IR (KBr) ν(cm^{-1})	^{31}P-NMR ($CDCl_3$/H_3PO_4) δ(ppm)	^{1}H-NMR ($CDCl_3$/TMS) δ(ppm)
3a	98	200	$C_{23}H_{24}BrOP$ (427.3)	1700 (C=O), 1112, 997 (C–P)	24.5	1.65–2.20 (m, 2H, $^3J_{HP}$ = 6 Hz, PCH_2CH_2); 2.20 (s, 3H, CH_3); 3.16 (t, 2H, J = 5 Hz, CH_2CO); 3.60–4.20 (m, 2H, $^2J_{HP}$ = 12.6 Hz, PCH_2); 7.75–8.50 (m, 15H$_{arom}$)
3b	95	195	$C_{28}H_{26}BrOP$ (498.4)	1678 (C=O), 1112, 998 (C–P)	24.5	1.83–2.43 (m, 2H, PCH_2CH_2); 3.68 (t, 2H, J = 6 Hz, CH_2CO); 3.70–4.30 (m, 2H, PCH_2); 7.40–7.63 (m, 3H$_{arom}$); 7.63–8.20 (m, 17H$_{arom}$)
3c	92	139	$C_{24}H_{26}IOP$ (488.4)	1708 (C=O), 1112, 998 (C–P)	24.0	1.60 (t, 3H, J = 7 Hz, CH_3CH_2); 1.50–2.20 (m, 2H, PCH_2CH_2); 2.57 (q, 2H, J = 7 Hz, CH_3CH_2); 3.16 (t, 2H, J = 6 Hz, $CH_2COC_2H_5$); 3.53–4.16 (m, 2H, $^2J_{HP}$ = 12.6 Hz, PCH_2); 7.60–8.29 (m, 15H$_{arom}$)
4a	97	188.9	$C_{26}H_{30}BrPS_2$ (517.5)	1420, 912 (C–S), 1112, 998 (C–P)	24.6	1.40 (s, 3H, CH_3); 1.60–2.25 (m, 4H, 2 × β-SCH_2); 2.25–2.88 (m, 4H, 2 × α-SCH_2); 2.90–5.50 (m, 2H, PCH_2CH_2); 3.98 (t d, 2H, $^3J_{HH}$ = 8 Hz, $^2J_{HP}$ = 13 Hz, PCH_2); 7.65–8.15 (m, 15H$_{arom}$)
4b	93	241.5	$C_{31}H_{32}BrPS_2$ (588.6)	1418, 910 (C–S), 1112, 980 (C–P)	24.1	1.30–2.10 (m, 4H, 2 × β-SCH_2); 2.35–3.20 (m, 6H, 4H, 2 × α-SCH_2, PCH_2CH_2); 3.35–4.00 (m, 2H, PCH_2); 7.20–7.43 (m, 3H$_{arom}$); 7.50–8.10 (m, 17H$_{arom}$)
4c	94	160.5	$C_{27}H_{32}IPS_2$ (577.9)	1425, 910 (C–S), 1112, 998 (C–P)	24.1	0.98 (t, 3H, J = 7 Hz, CH_3CH_2); 1.10–2.20 (m, 6H, 3 × β-SCH_2); 2.20–3.50 (m, 6H, 4H, 2 × α-SCH_2, PCH_2CH_2); 3.50–4.30 (m, 2H, PCH_2); 7.60–8.28 (m, 15H$_{arom}$)

[a] Yield after recrystallization.
[b] The microanalyses are in good agreement with the calculated values: C ±0.40, H ±0.12, P +0.25, Br/I +0.28.

Table 2. 2-(3′-Alkenyl)-1,3-dithianes **6a–r** Prepared

Product	R^1	R^2	R^3	Yield[a] (%)	n_D^{20}	b.p. (°C)/mbar[b]	Molecular Formula[c]	UV (CH_3CN) λ_{max} (nm, log ε)	^{1}H-NMR (CCl_4/TMS) δ (ppm)[d]
6a	CH_3	H′[e]	H″[e]	66	1.548	130/0.4	$C_9H_{16}S_2$ (188.3)	–	5.02 (ddt, 1H, H′, $^4J_{H'H}$ = 1 Hz); $^2J_{H'H''}$ = 2.1 Hz, $^3J_{H'H}$ = 17 Hz); 5.10 (ddt, 1H, H″, $^4J_{H''H}$ = 1 Hz, $^2J_{H''H'}$ = 2.1 Hz, $^3J_{H''H}$ = 9.50 Hz); 5.80 (ddt, 1H, =CH, $^3J_{HH'}$ = 9.5 Hz, $^3J_{HH'}$ = 17 Hz)
6b	CH_3	C_2H_5	H″	68	1.528	176/0.7	$C_{11}H_{20}S_2$ (216.4)	–	1.00 (t, 3H, J = 7.5 Hz, CH_3CH_2); 5.00–5.66 (m, 2H, H″C=CH)
6c	CH_3	C_6H_5	H″	93	1.604	oil	$C_{15}H_{20}S_2$ (264.4)	245 (3.89)	2.20–2.55 (m, 2H, =CHCH_2); 5.50 (dt, 1H, =CH, $^3J_{HH}$ = 7 Hz, $^3J_{HH'}$ = 12 Hz); 6.40 (dt, 1H, H″, $^3J_{H''H}$ = 1.5 Hz, $^3J_{H''H}$ = 12 Hz); 7.10–7.40 (m, 5H_{arom})
6d	C_6H_5	H	H″	64	1.596	170/0.7	$C_{14}H_{18}S_2$ (250.4)	–	4.70–5.15 (m, 2H, H_2C=CH); 5.30–6.10 (m, 1H, H_2C=CH); 7.10–7.65 (m, 3H_{arom}); 7.80–8.15 (m, 2H_{arom})
6e	C_6H_5	C_2H_5	H″	63	1.584	190/0.4	$C_{16}H_{22}S_2$ (278.5)	–	0.86 (t, 3H, J = 6.5 Hz, CH_3CH_2); 5.00–5.40 (m, 2H, CH =CH); 7.00–7.55 (m, 3H_{arom}); 7.70–8.05 (m, 2H_{arom})
6f	C_6H_5	C_6H_5	H″	90	1.632	oil	$C_{20}H_{22}S_2$ (326.5)	245 (4.56)	5.41 (dt, 1H, =CH, $^3J_{HH}$ = 6 Hz, $^3J_{HH'}$ = 12 Hz); 6.33 (d, 1H″, $^3J_{H''H}$ = 12 Hz); 6.80–7.50 (m, 8H_{arom}); 7.65–8.05 (m, 2H_{arom})
6g	CH_3	CH_3	CH_3	78	1.541	142/0.4	$C_{11}H_{20}S_2$ (216.4)	–	1.64 (s, 3H, CH_3, *trans* to =CH); 1.68 (d, 3H, CH_3, *cis* to =CH); $^4J_{HH}$ = 1.5 Hz); 5.12 (tq, 1H, =CH, $^4J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 6.5)
6h	CH_3	C_6H_5	CH_3	85	1.587	oil	$C_{16}H_{22}S_2$ (278.5)	242 (3.96)	4.49 (tq, 0.9H, =CH, $^4J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 6.5 Hz, *Z*-isomer); 5.82 (tq, 0.1H, =CH, $^4J_{HH}$ = 1 Hz, $^3J_{HH}$ = 6.5 Hz, *E*-isomer); 7.00–7.50 (m, 5H_{arom})
6i	CH_3	C_6H_5	C_6H_5	89	1.619	oil	$C_{21}H_{24}S_2$ (340.5)	252 (4.29)	6.11 (t, 1H, =CH, $^3J_{HH}$ = 7 Hz); 7.10–7.50 (10H_{arom})
6j	C_6H_5	CH_3	CH_3	76	1.584	oil	$C_{16}H_{22}S_2$ (278.5)	–	1.46–1.56 (2s, 6H, $2CH_3$); 4.95 (m, 1H, =CH); 7.05–7.56 (m, 3H_{arom}); 7.70–8.10 (m, 2H_{arom})
6k	C_6H_5	C_6H_5	CH_3	74	1.614	oil	$C_{21}H_{24}S_2$ (340.5)	255 (4.00)	1.93 (s, 2.6H, CH_3); 1.98 (s, 0.4H, CH_3); 5.28 (tq, 0.9H, =CH, $^4J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 4.75 Hz, *Z*-isomer); 5.93 (m, 0.1H, =CH, *E*-isomer); 6.80–7.50 (m, 8H_{arom}); 7.60–8.10 (m, 2H_{arom})
6l	C_6H_5	C_6H_5	C_6H_5	72	1.629	oil	$C_{26}H_{26}S_2$ (214.4)	237 (4.54)	5.90 (t, 1H, =CH, $^3J_{HH}$ = 7 Hz); 6.90–7.50 (m, 13H_{arom}); 7.70–8.00 (m, 2H_{arom})
6m	CH_3	CH_2=CH	H″	65	1.570	180/0.9	$C_{11}H_{18}S_2$ (214.4)	227 (4.44)	1.58 (s, 3H, CH_3); 4.90–7.00 (m, 5H_{olefin})
6n	CH_3	CH_3CH=CH–	H″	50	1.568	185/0.9	$C_{12}H_{20}S_2$ (228.4)	232 (5.48)	1.58 (s, 3H, CH_3); 5.00–6.60 (m, 4H_{olefin})
6o	CH_3	C_6H_5CH=CH–	H″	84	1.642	oil	$C_{17}H_{22}S_2$ (290.5)	228 (4.15)	1.60 (s, 3H, CH_3); 5.30–7.00 (m, 4H_{olefin})
6p	C_6H_5	CH_2=CH–	H″	74	1.600	oil	$C_{16}H_{20}S_2$ (276.4)	230 (4.28)	4.80–6.80 (m, 4H_{olefin}); 7.10–8.15 (m, 5H_{arom})
6q	C_6H_5	CH_3CH=CH	H″	72	1.601	oil	$C_{17}H_{22}S_2$ (290.5)	232 (4.50)	4.80–6.36 (m, 4H_{olefin}); 7.00–8.10 (m, 5H_{arom})
6r	C_6H_5	C_6H_5CH=CH–	H″	72	1.620	oil	$C_{22}H_{24}S_2$ (352.5)	229 (4.00) 236 (3.85)	5.06–7.00 (m, 4H_{olefin}); 7.00–8.20 (m, 10H_{arom})

[a] Yields obtained after purification by column chromatography.

[b] Temperature of Kugelrohr distillation apparatus.

[c] Microanalyses are in good agreement with the calculated values: C ±0.43, H ±0.17.

[d] ^{1}H-NMR spectra of compounds **6** and **4** (Table 1) show two characteristic broad peaks for the dithiane ring: one (4H, 2.40–3.0 ppm) can be attributed to the protons α-to the sulfur and the other one (2H, 1.70–2.45 ppm) to the protons in the β-position.

[e] H′ and H″ represent hydrogen as R^2 or R^3 substituent, respectively.

Table 3. Stereochemistry of 2-(3'-Alkenyl)-1,3-dithianes **6**[a]

Product	Isomer[b]	^{13}C-NMR ($CDCl_3$/TMS) δ(ppm)[c]		Z/E-Ratio[d] (%)
		=CH–$\underline{C}H_2$	R^2 or R^3	
6b	*Z*	22.72 (23.20)	20.57 (20.98) ($\underline{C}H_2$)	95
	E	–[e] (28.68)	25.59 (26.06) ($\underline{C}H_2$)	5
6c	*Z*	24.22 (22.85)		95
	E	28.47 (28.66)		5
6e	*Z*	22.02 (22.38)	20.39 (20.87) ($\underline{C}H_2$)	95
	E	27.10 (27.89)	25.55 (25.95) ($\underline{C}H_2$)	5
6f	*Z*	23.45 (22.03)		95
	E	28.28 (27.87)		5
6h	*Z*	24.59 (25.53)	25.64 (24.69) ($\underline{C}H_3$)	95
	E	24.41 (19.72)	15.88 (19.45) ($\underline{C}H_3$)	5
6k	*Z*	23.90 (24.74)	25.50 (24.51) ($\underline{C}H_3$)	95
	E	23.68 (18.90)	–[e] (19.29) ($\underline{C}H_3$)	5

[a] For R^1, R^2 and R^3, see Table 2.
[b] Identification of *Z*- and *E*-isomers are carried out on the basis of the chemical shift of the allylic carbons[13]; for compounds **6h** and **6k**, the identification is also corroborated by ^{1}H-NMR, using an empirical formula[14] to calculate the vinylic proton chemical shift: from these calculations, the *E*-isomer may be attributed to the most deshielded peak and the *Z*-isomer to the least deshielded one.
[c] Calculated values are given in parenthesis.
[d] The *Z*/*E*-ratio [(±) 3%] are determinated by HPLC and GC analysis.
[e] Undetected.

1,3-Dithianes 6; General Procedure:
To a solution of potassium *tert*-butoxide (1.12 g, 10 mmol) in dry ether (120 ml) is added phosphonium salt **4** (11 mmol) under nitrogen atmosphere. After stirring for 15 min the carbonyl compound **5** (10 mmol) is added. The mixture is stirred for 4 h, and hydrolysed with a 1 normal solution of hydrobromic acid (5 ml), the etheral layer is washed with water (3 × 15 ml), dried with sodium sulfate and the solvent is removed in vacuum. The residual oil is purified by column chromatography on silica gel (20 g silica gel for 1 g oil) using gradient of hexane/dichloromethane as eluent.

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