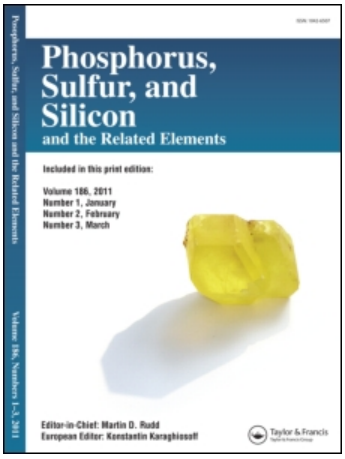

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REACTION OF LITHIUM DERIVATIVE OF DIETHYL PHENYLMETHANE-PHOSPHONATE WITH KETONES

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REACTION OF LITHIUM DERIVATIVE OF DIETHYL PHENYLMETHANE-PHOSPHONATE WITH KETONES

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The reaction of the lithium derivative of diethyl ester of phenylmethanephosphonic acid (**1**-Li) with alkanones, cycloalkanones, alkylaryl and diarylketones **2a–h** is studied at −70°C in THF. The corresponding adducts—diethyl esters of 1-phenyl-2,2-dialkyl(phenyl)-2-hydroxyethanephosphonic acids **3a–h** are isolated, their yields being usually higher at short reaction time. The olefination of **3**-Li as well as of **3** (both by thermolysis or in acidic media) proceeds in low degree, while in the case of **3**-Na the yields of alkenes **4** are good. The relative configurations of **3b**, **3f** and **3g** are determined by IR and NMR-spectra, as well as by their stereospecific olefination. "Threo"-stereoselectivity of the addition stage of the reaction of **1**-Li with **2b**, **2f** and **2g** is observed, the "threo"/"erythro" ratio remaining independent on the reaction time.

Key words: Benzylphosphonate carbanion; reaction with ketones; threo/erythro ratio; 2-hydroxyethanephosphonates.

INTRODUCTION

It is known that the carbonylolefination with phosphonate carbanions (Horner-Wadsworth-Emmons reaction) can be stopped at the addition stage only in some rare cases[1] in contrast to Horner's reaction, i.e. carbonylolefination with phosphineoxide carbanions.[2–4] The isolated β-hydroxyphosphonate adducts of alkylphosphonic esters with carbonyl compounds as well as their alkaline metal salts do not undergo this reaction.[5] In the cases when a strong electron-acceptor group (CN, COOR, COR) is present α- to carbanion, the sodium and lithium salts of the intermediate adducts decompose spontaneously to alkenes even at −100°C.[6] The tetramethyldiamides of arylmethanephosphonic acids occupy an intermediate position since the aryl group is a weak electron acceptor. Their lithium derivatives afford with carbonyl compounds (after hydrolysis) β-hydroxyphosphonamide adducts in high yields and erythro-diastereoisomeric purity.[7–9] The olefination of the erythro-isomers thus obtained by thermolysis or in acidic medium represents a convenient method for synthesis of (Z)-alkenes.[7–10] In the present work we report our results on the addition reaction of the phenylmethanephosphonic ester to ketones via intermediate lithium derivative as well as further olefination of the obtained adducts.

RESULTS AND DISCUSSION

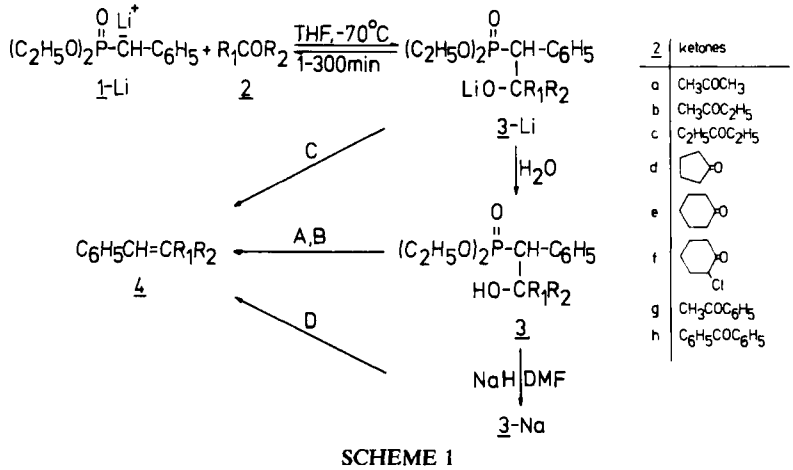
We have studied the interaction of the lithium derivative of the diethyl ester of phenylmethanephosphonic acid **1**-Li and some alkanones, arylalkanones and cycloalkanones **2**. The metallation of the ester was carried out by BuLi in THF at −70°C and then the reaction of **1**-Li thus obtained with ketones **2a–h** was carried out at the same temperature in the interval 1–300 minutes. After hydrolysis the diethyl esters of 1-phenyl-2,2-dialkyl(phenyl)-2-hydroxy-ethanphosphonic acids **3** were obtained (Scheme 1, Table I).

It was established, by ^{1}H-NMR studies, that the crude reaction products **3b** and **3g** represent diastereomeric mixtures, the RR,SS ("threo")-isomer being the prevailing one (see Table I). The reaction with 2-chlorocyclohexanone **2f** led to "threo"-**3f** only. The relative configurations of the diastereoisomers were determined both by direct spectral studies and by stereospecific olefination of the free adducts[11] or their sodium salts.[12] Preliminary IR-spectral studies in a diluted (10^{-3} mole) tetrachloromethane solution of the adducts **3e** and "threo"-**3g** showed the almost exclusive presence of conformers with intramolecular hydrogen bond (Figure 1), (ν_{OH} 3445 and 3400 cm^{-1}, respectively).

In the case of **3e** the conformer without intramolecular hydrogen bond PO···HO at 3570 cm^{-1} is in an amount of only 7%, and less than 1% is observed with threo-**3g**.

The relative configuration of the diastereoisomeric adducts **3g** was confirmed by ^{13}C-NMR spectroscopy as well. On the basis of the Karplus-like relationship between J and the dihedral angle[13] it was established that the isomer with higher $^3J_{CH}$ is related to the RR,SS ("threo")-serie, i.e. $^3J_{CH}^{threo} > {}^3J_{CH}^{erythro}$ ($^3J_{CH}^{threo}$ = 13.1 Hz; $^3J_{CH}^{erythro} < 2.0$ Hz).

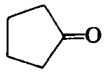
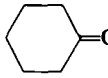
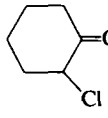
In the ^{1}H-NMR-spectra it was observed, that $\Delta\delta_{CH_3}^{threo} < \Delta\delta_{CH_3}^{erythro}$ ($2CH_3$ in OCH_2CH_3 are non-equivalent), as well as that $\delta_{OH}^{threo} > \delta_{OH}^{erythro}$, which is in accordance with previous investigations on β-hydroxyphosphonoamides[14] (Table III). Further, we have examined the olefination of the free adducts **3** (methods A and B) as well as their alkaline metal salts **3**-Li and **3**-Na (methods C and D) (Table II).



SCHEME 1

TABLE I

Yields and constants of the compounds **3** obtained from **1**-Li and **2**

No.	Ketone	Reaction time, min	Yields %*(†) of **3**	"Erythro"/ "threo" **3**	M.p.‡ °C
3a	CH_3COCH_3	15	(80)	—	31–33
		180	60	—	
3b	$CH_3COC_2H_5$	1	(88)	35:65†	oil
		15	(82)	39:61	
		180	(80)	33:67	
3c	$C_2H_5COC_2H_5$	15	66(63)	—	85–86
		300	40(50)	—	
3d		15	52	—	38–40
		90	40	—	
3e		15	81(83)	—	92–94
		180	60	—	
3f		15	67(80)	0:100	85:87
		300	68	0:100	
3g	$CH_3COC_6H_5$	1	(5)	20:80	
		5	27(33)	26:74	
		15	58(56)	20:80	
		180	41(40)	23:77	104–106
3h	$C_6H_5COC_6H_5$	15	(5)	—	
		300	28	—	174–175

The elemental analyses for **3** are in good agreement with the theoretical values. IR(nujol): 1030–1040 and 1050–1060 cm^{-1}(ν_{P-O-C}); 1210–1230 cm^{-1}($\nu_{P=O}$); 3350–3450 cm^{-1}(ν_{OH} bonded)

* Yield of product washed with hexane.

† And (**) determined by NMR. For erythro/threo ratio the signals ^1H(250 MHz) were used as follows: **3b** (δ): 4.30 and 4.33; **3g**: 5.04 and 5.60. For the determination of the yields of **3** the integral intensity of the signals for CH_2 (for **1**) and CH (for **3**) protons are used.

‡ M.p. of recrystallised compounds **3**.

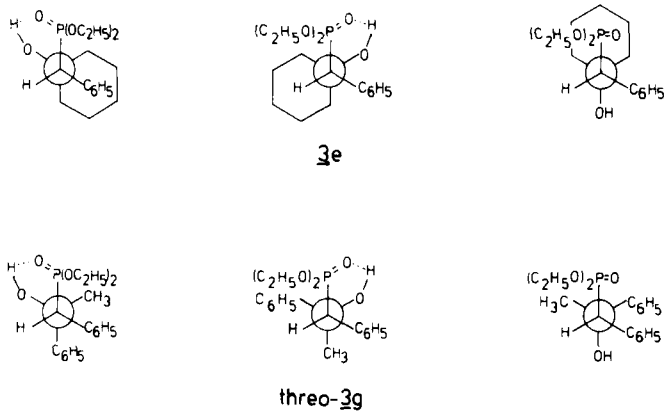


FIGURE 1 Possible conformations of **3e** and RR,SS ("threo")-**3g**.

TABLE II

Yields and Z/E ratio of the olefins **4**

No.	Olefin	Yield % (Z/E ratio) A	B	C	D	Ref.
4e	$C_6H_5CH=$ 	26	26	8*	50	16
4f	$C_6H_5CH=$ 				40 (0:100)†	17
4g	$C_6H_5CH=C(CH_3)C_6H_5$	14 (0:100)†	19 (0:100)†	5 (60:40)	40 (20:80)‡	18
4h	$C_6H_5CH=C(C_6H_5)_2$			40	50	19

A—Olefination of **3** by thermolysis[11]
B—Olefination of **3** in acidic media[10]
C—Olefination of **3**-Li by direct reaction (see experimental)
D—Olefination of **3**-Na by[12]

* After reflux 30 min. of the reaction mixture the yield of **4e** is 12%.
† Obtained from pure "threo"-**3f** and "threo"-**3g**, resp.
‡ Obtained from "erythro"/"threo" **3g** 23:77.

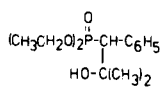
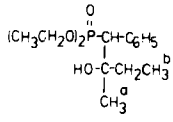
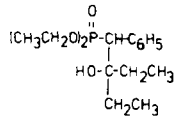
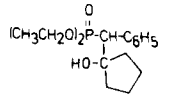
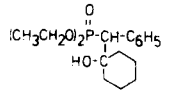
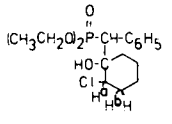
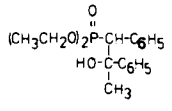
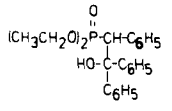
As it should be expected, the elimination occurs to the greatest extent in the sodium salts of the adducts while with the lithium salts the yield of alkenes was insignificant even when heating was applied. Only **3h**-Li (obtained from **1**-Li and benzophenone **2h**) represents an exception since olefination is favoured by the steric effect in the intermediate; the yield of the alkene is considerably higher than that of the adduct (compare Tables I and II). The thermal olefination of adducts **3** according to Corey[11] and olefination in an acidic medium proceed to one and the same low extent (Table II), while under the same conditions olefins are obtained from the respective β-hydroxyphosphonamide adducts in high yields.[9,10] This can be explained by the low electron density and basicity of the oxygen atom of the PO-group in the esters as compared with amides. It is shown that the first stage in these two types of elimination is characterized by an electron transfer from the hydroxyl group[11] (attack of a proton from the acid[10]) to the oxygen atom of the PO-group.

The stereospecific olefination of RR,SS-**3f** to (E)-**4f** as well as of RR,SS-**3g** to (E)-**4g** can be considered as a chemical proof of their relative configurations.

As seen in Table I, the yields of adducts **3** are the highest at a short reaction time (1–15 minutes). Taking into account the low degree of olefination of **3**-Li at low (and even at high) temperature (Table II), the decrease in the yield of **3** at longer reaction times could not be explained by its partial transformation into an alkene. Actually, in the reaction mixtures after hydrolysis mainly the starting **1** and **2** can be detected together with traces of the respective olefins. A possible explanation of the decrease in the yield of **3** at longer reaction times could be the autocatalytic decomposition of **3**-Li to the starting **1** and **2**. When the reaction of **1**-Li with **2b** and **2g** was carried out for various reaction times, a diastereoisomeric

TABLE III

^{1}H-NMR spectral data of the adducts **3** in DCl_3

3a		δ 0.99 (t, $^3J_{HH}$ = 7 Hz) and 1.32 (t, $^3J_{HH}$ = 7 Hz, 6H, OCH_2CH_3), 1.21 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 3.17 (d, $^2J_{PH}$ = 23 Hz, 1H, CH), 3.6–4.2 (m, 4H, OCH_2), 4.35 (s, 1H, OH), 7.29–7.42 (m, 5H, C_6H_5)
RS,SR "Erythro"- **3b**		δ 0.82 (t, $^3J_{HH}$ = 7 Hz) and 0.92 (t, $^3J_{HH}$ = 7 Hz, 6H, OCH_2CH_3), 1.30 (q, $^3J_{HH}$ = 7 Hz, 2H, CH_2), 1.34 (t, $^3J_{HH}$ = 7 Hz, 3H, CH_3^b), 1.41 (s, 3H, CH_3^a) 3.20 (d, $^2J_{PH}$ = 24 Hz, 1H, CH), 3.37–4.22 (m, 4H, OCH_2), 4.30 (s, 1H, OH), 7.3–7.5 (m, 5H, C_6H_5).
RR,SS "Threo"- **3b**		δ 0.95 (t, $^3J_{HH}$ = 7 Hz) and 0.98 (t, $^3J_{HH}$ = 7 Hz, 6H, OCH_2CH_3), 1.12 (s, 3H, CH_3^a), 1.32 (t, $^3J_{HH}$ = 7 Hz, 3H, CH_3^b), 1.67 (q, $^3J_{HH}$ = 7 Hz, 2H, CH_2), 3.24 (d, $^2J_{PH}$ = 23 Hz, 1H, CH), 3.52–4.22 (m, 4H, OCH_2), 4.33 (s, 1H, OH), 7.3–7.5 (m, 5H, C_6H_5).
3c		δ 0.74 (t, $^3J_{HH}$ = 7.5 Hz) and 0.94 (t, $^3J_{HH}$ = 7.5 Hz, 6H, CH_3), 0.86 (t, $^3J_{HH}$ = 7 Hz, 6H, OCH_2CH_3), 1.1–1.3 (m) and 1.7–2.0 (m, 4H, CH_2), 3.24 (d, $^2J_{PH}$ = 24 Hz, 1H, CH), 3.2–3.4 (m) and 3.7–3.8 (m) and 4.0–4.2 (m, 4H, OCH_2), 4.25 (s, 1H, OH), 7.2–7.6 (m, 5H, C_6H_5).
3d		δ 0.92 (t, $^3J_{HH}$ = 7 Hz) and 1.35 (t, $^3J_{HH}$ = 7 Hz, 6H, OCH_2CH_3), 1.3–2.1 (m, 8H, CH_2), 3.15 (d, $^2J_{PH}$ = 23 Hz, 1H, CH), 3.39–3.54 (m) and 4.01–4.26 (m, 4H, OCH_2), 4.17 (s, 1H, OH), 7.23–7.49 (m, 5H, C_6H_5).
3e		δ 0.91 (t, $^3J_{HH}$ = 7 Hz) and 1.32 (t, $^3J_{HH}$ = 7 Hz 6H, OCH_2CH_3), 1.2–1.9 (m, 10H, CH_2), 3.23 (d, $^2J_{PH}$ = 23 Hz, 1H, CH), 3.4–4.2 (m, 4H, OCH_2), 4.16 (s, 1H, OH), 7.25–7.96 (m, 5H, C_6H_5).
3f		δ 1.14 (t, $^3J_{HH}$ = 7 Hz) and 1.27 (t, $^3J_{HH}$ = 7 Hz, 6H, OCH_2CH_3O, 1.0–2.2(m, 8H, CH_2), 2.49 (d, $^3J_{H^a H^b}$ = 10 Hz, 1H, H^a), 3.48 (s, 1H, CH), 3.8–4.2 (m, 4H, OCH_2), 4.09 (s, 1H, OH), 7.32–7.55 (m, 5H, C_6H_5).
3g		δ 0.80 (t, $^3J_{HH}$ = 7.5 Hz) and 0.83 (t, $^3J_{HH}$ = 7.5 Hz, 6H, OCH_2CH_3), 1.25 (s, 3H, CH_3), 3.2–3.8 (m, 4H, OCH_2), 3.60(d, $^2J_{PH}$ = 23 Hz 1H, CH), 5.60(s, 1H, OH), 7.20–7.50 (m, 10H, C_6H_5).
3h		δ 0.82(t, $^3J_{HH}$ = 7 Hz) and 0.87 (t, $^3J_{HH}$ = 7 Hz, 6H, OCH_2CH_3), 3.1–3.4 (m) and 3.6–3.7 (m, 4H, OCH_2), 4.38 (d, $^2J_{PH}$ = 24 Hz, 1H, CH), 6.25(s, 1H, OH), 6.9–7.8(m, 15H, C_6H_5).

mixture with almost the same composition, the "threo"-isomer being the prevailing one, (Table I), was formed. In the case of adducts **3b** it can be assumed that the equilibrium

$$\text{"erythro"-3-Li} \rightleftharpoons \text{1-Li} + 2 \rightleftharpoons \text{"threo"-3-Li}$$

is established in 1 minute and the ratio 35:65 is the equilibrium one, while in the case of **3g** the "threo"-adduct is probably the favoured one, both kinetically and thermodynamically. A similar coincidence of the kinetically and thermodynamically controlled stereochemical result is observed by other authors as well.[15]

EXPERIMENTAL

The reaction of the diethyl ester of phenylmethanephosphonic acid **1** with ketones **2** was carried out under dry argon in anhydrous THF. The ketones were distilled before use. The NMR spectra of the adducts **3** and olefins **4** were recorded on a Brucker WM-250 spectrometer with TMS as internal standard and $CDCl_3$ as solvent. The olefins were determined using ^{1}H-NMR and UV spectroscopy. They were purified by column filtration on Al_2O_3 with hexane. The adducts **3b** and **3d** were purified by chromatography on silicagel-60 size 0.063—0.200 nm using hexane-ethylacetate as eluent. The qualitative tlc investigations were carried out on silicagel 60 F_{254} (aluminium sheets "Merck") using ethylacetate-hexane 1:1 as mobile phase (for adducts) or hexane (for olefins).

Synthesis of diethyl esters of 1-phenyl-2,2-dialkyl (phenyl)-2-hydroxyethanephosphonic acids **3**. General procedure. To a solution of **1** (10 mmol) in 20 ml anhydrous THF, cooled to −70°C, butyllithium (10 mmol, 1.5 M in hexane), diluted with 6 ml THF, added under argon. The mixture is stirred 15 min, the ketone **2** (10 mmol) in 4 ml THF is added and stirring continued for another 1–300 min at −70°C. The mixture is hydroyzed with 10 ml water, then extracted with CH_2Cl_2 (3 × 20 ml), the extract washed with water and dried with magnesium sulfate. After evaporation of the solvents the crude products **3** were studied by ^{1}H-NMR and tlc. The crude products **3** were purified by washing and recrystallization from hexane* before determination of their physical constants and elemental analysis.

Conversion of the hydroxyphosphonate adducts **3** *or their alkaline salts into olefins* **4**. Method A[11]: Thermal olefination of **3** by reflux 5 hrs in toluene. Method B[10]: The mixture of 0.5 mmole **3**, 5 ml anhydrous ethanol and 0.1 ml 25% hydrochloric acid is refluxed 1 hr with stirring, the solvent is evaporated in vacuum and 3 ml 10% Na_2CO_3 is added. The residue is extracted with ether (3 × 10 ml), the organic layer is washed with water (2 × 2 ml) and dried over $MgSO_4$. After evaporation of the solvent the product is purified by column chromatography on alumina using hexane as eluent.
Method C: The reaction mixture is obtained from **1**-Li and **2** using the general procedure. After keeping it 15 min. at −70°C it is allowed to warm to room temperature and kept one day at this temperature under argon. The mixture is hydrolyzed with water (10 ml), extracted with CH_2Cl_2 (20 ml) as well as with ether (2 × 20 ml) and then treated as in method B.
Method D:[12] The mixture of equimolar quantity **3** and NaH in DMF is stirred 3 hrs at room temperature under argon. After hydrolysis with water, extraction with hexane and ether, the reaction mixture is treated as in method B.

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* Pure "threo"-**3g** was obtained by recrystallization from hexane-ether 4:1.

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