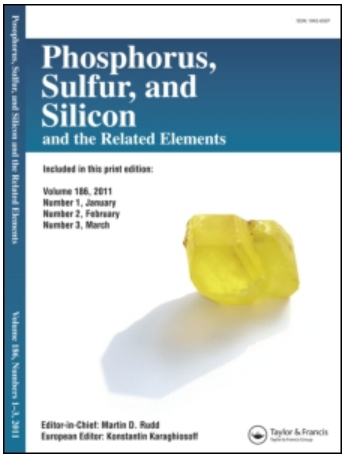


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# OLEFIN SYNTHESIS USING LITHIUM DERIVATIVES OF *N,N,N′,N′*-TETRAMETHYLDIAMIDES OF ARYLMETHANEPHOSPHONIC ACIDS

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# OLEFIN SYNTHESIS USING LITHIUM DERIVATIVES OF *N,N,N′,N′*-TETRAMETHYLDIAMIDES OF ARYLMETHANEPHOSPHONIC ACIDS

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The reaction of lithium derivatives of *N,N,N′,N′*-tetramethyldiamides of arylmethanephosphonic acids (**1**-Li) with aldehydes **2** is studied. It is found that under certain reaction conditions (THF, 5 hrs at −70°C and then allowing to warm to room temperature) the aldol stage of the reaction is highly stereoselective, only erythro adducts (2-hydroxyphosphonamides) **3**, **4** being formed in 47–75% yields. By heating of **3** and **4** in neutral medium the corresponding (Z)-olefins **5**, **6** are obtained (yields 64–74%). It is established that an acid catalyzed olefination of 2-hydroxyphosphonamides is also possible, but the reaction is not stereospecific.



## INTRODUCTION

The olefin synthesis by means of carbonyl compounds and phosphonium ylides (Wittig reaction) as well as by phosphonate carbanions (Horner–Emmons reaction) is known to be in most cases more or less stereoselective as regard to (E)-isomer. The (Z)/(E) ratio increases when the substituents attached to the carbonyl carbon atom are branched[1] as well as when the aldol stage of the reaction is irreversible (kinetically controlled with respect to the erythro adducts).[2–4] In the latter case, low temperature usually is indispensable for stereoselective (Z)-olefin synthesis.[2–4] The intermediate adducts (betains or 2-hydroxyphosphonamides) can also be isolated[2,5] and then they or their anions converted into olefins. In these cases (Z)-olefin synthesis requires the ylides to be free of salt,[2] or separation of a diastereomeric mixture of intermediate 2-hydroxyphosphonamides becomes necessary.[5]

## RESULTS

We now report a simple synthesis of (Z)-stilbenes and some (Z)-styrenes using lithium derivatives[6] of *N,N,N′,N′*-tetramethyldiamides of arylmethanephosphonic acids[7] (**1**-Li) and aldehydes **2**.

The starting phosphonamides **1a, b** were metalated by BuLi in THF at −70°C.[6] When the reaction of **1**-Li and **2** is carried out for 5 hrs at the same temperature (−70°C) in THF (method A) both diastereomers—erythro and threo adducts—are formed and isolated as corresponding mixtures of *N,N,N′,N′*-tetramethyldiamides

TABLE I

Yields and configurations of *N,N,N',N'*-tetramethyldiamides of 1-aryl-2-aryl(alkyl)-2-hydroxyethanephosphonic acids **3, 4**, $ArCH_a(RCH_b{-}OH){-}P(O)[N(CH_3)_2]_2$, obtained from **1** and **2** by methods A and B

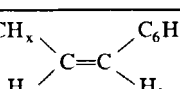
| no | Ar | R | Method* | Yield % 3, 4 | Config. 3, 4 | M.p. °C |
|---|---|---|---|---|---|---|
| **3a** | $C_6H_5$ | $C_6H_5$ | A | 80 | er + thr | |
| **3a** | $C_6H_5$ | $C_6H_5$ | B | 72 | er | 158–159 |
| **3b** | $C_6H_5$ | $C_6H_4OCH_3$-(4) | A | 58 | er + thr | |
| **3b** | $C_6H_5$ | $C_6H_4OCH_3$-(4) | B | 47 | er | 137–138 |
| **3c** | $C_6H_5$ | $C_6H_4$—Cl-(4) | A | 87 | er + thr | |
| **3c** | $C_6H_5$ | $C_6H_4$—Cl-(4) | B | 75 | er | 138–140 |
| **3d** | $C_6H_5$ | $(CH_3)_2CH$ | A | 55 | er + thr | |
| **3d** | $C_6H_5$ | $(CH_3)_2CH$ | B | 54 | er | 116–117 |
| **4a** | $C_6H_4$—Cl-(4) | $C_6H_5$ | A | 68 | er + thr | |
| **4a** | $C_6H_4$—Cl-(4) | $C_6H_5$ | B | 67 | er | 165–167 |
| **4b** | $C_6H_4$—Cl-(4) | $C_6H_4$—$OCH_3$-(4) | A | 58 | er + thr | |
| **4b** | $C_6H_4$—Cl-(4) | $C_6H_4$—$OCH_3$-(4) | B | 47 | er | 150–152 |
| **4c** | $C_6H_4$—Cl-(4) | $C_6H_4$—Cl-(4) | A | 89 | er + thr | |
| **4c** | $C_6H_4$—Cl-(4) | $C_6H_4$—Cl-(4) | B | 68 | er | 173–175 |
| **4d** | $C_6H_4$—Cl-(4) | $(CH_3)_2CH$ | B | 56 | er | 122–123 |

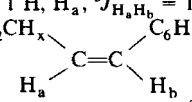
**Method A*: 5 hrs in THF at −70°C; *Method B*: 5 hrs at −70°C and then allowing to warm for 0.5 hr to 20°C. The elemental analyses of **3, 4** (erythro or mixture of erythro + threo) were in good agreement with the calculated values. **3, 4** IR (nujol): 980–990 $cm^{-1}$ ($\nu_{P-N}$), 1150–1200 $cm^{-1}$ ($\nu_{P=O}$), 3300–3400 $cm^{-1}$ ($\nu_{OH}$ associated). Erythro-**3a** $^1H$ NMR ($CDCl_3$): $\delta$ 2.20 (d, $J$ = 8 Hz) and 2.78 (d, $J$ = 8 Hz; $NCH_3$, 12 H); 3.29 (dd, 1 H, $H_a$, $^3J_{H_aH_b}$ = 2 Hz, $^2J_{H_aP}$ = 15.2 Hz); 5.38 (dd, 1 H, $H_b$, $^3J_{H_aH_b}$ = 2 Hz, $^3J_{H_bP}$ = 6.0 Hz); 5.80 (s, 1 H, OH); 6.75–7.20 (m, 10 H, 2 Ph).

TABLE II

Yields and (Z)/(E) ratios of olefins **5, 6** (RCH = CHAr), obtained by thermal decomposition of erythro-**3,4**

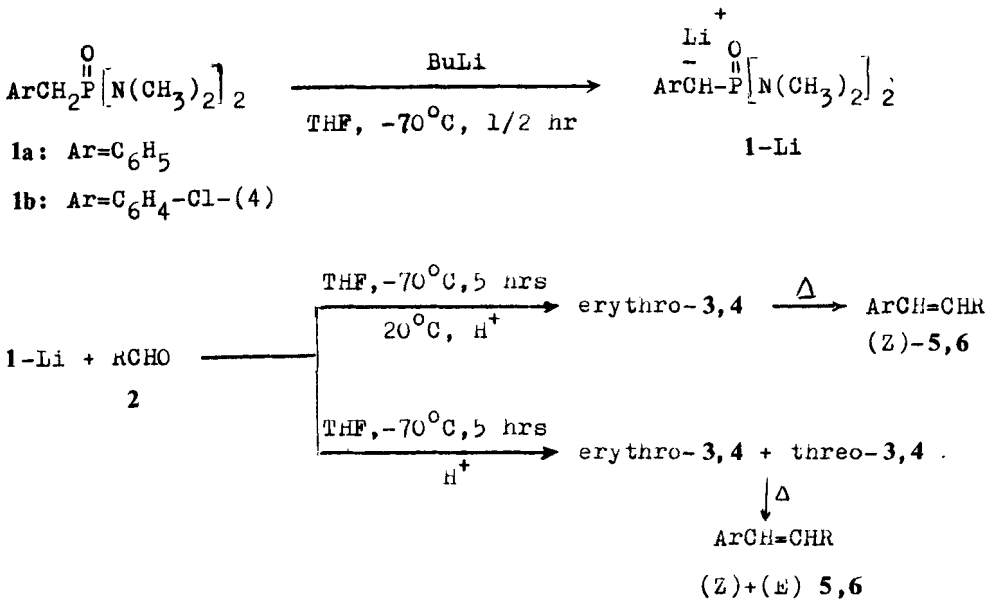
| no | Ar | R | Yield % | (Z)/(E) |
|---|---|---|---|---|
| **5a** | $C_6H_5$ | $C_6H_5$ | 74 | 100/0 |
| **5b** | $C_6H_5$ | $C_6H_4$—$OCH_3$-(4) | 74 | 95/5 |
| **5d** | $C_6H_5$ | $(CH_3)_2CH$ | 65 | 98/2 |
| **6a** | $C_6H_4$—Cl-(4) | $C_6H_5$ | 73 | 97/3 |
| **6c** | $C_6H_4$—Cl-(4) | $C_6H_4$—Cl-(4) | 64 | 100/0 |
| **6d** | $C_6H_4$—Cl-(4) | $(CH_3)_2CH$ | 70 | 97/3 |

**5d**  : $^1H$ NMR ($CDCl_3$): $\delta$ 1.0 (d, 6 H, $2CH_3$, $J$ = 8 Hz); 2.9 (m, 1 H, $H_x$); 5.4 (dd, 1 H, $H_a$, $^3J_{H_aH_b}$ = 11 Hz, $^3J_{H_aH_x}$ = 9 Hz); 6.2 (d, 1 H, $H_b$, $^3J_{H_bH_a}$ = 11 Hz).

**6d**  : $^1H$ NMR ($CDCl_3$): $\delta$ 0.98 (d, 6 H, $2CH_3$, $J$ = 7 Hz); 2.8 (m, 1 H, $H_x$); 5.36 (dd, 1 H, $H_a$, $^3J_{H_aH_x}$ = 9 Hz); 6.1 (d, 1 H, $H_b$, $^3J_{H_bH_a}$ = 11 Hz).

**5a, 5b** and **6a** identified on the basis of the UV and $^1H$ NMR data according ref. 8; **6c** identified by glc according ref. 9. (Z)/(E) ratio determined by glc, 8% PEGA Chromosorb P/NAW.

of 1-aryl-2-aryl(alkyl)-2-hydroxyethanephosphonic acids **3**, **4**. However, if the reaction is carried out for 5 hrs at $-70°C$, and then the reaction mixture is allowed to warm for 0.5 hr to room temperature only erythro 2-hydroxyphosphonamides (erythro-3,4) are isolated in 47–75% yields in all cases (see Table I). By heating erythro-**3**,**4** in toluene (see Corey *et al.*)[5] for 3–5 hrs, the corresponding (Z)-olefins **5**, **6** are obtained in 64–74% yield and in high purity (95–100%) (see Table II and Scheme 1):




| 2 | R |
|---|---|
| a | $C_6H_5$ |
| b | $C_6H_4$-$OCH_3$-(4) |
| c | $C_6H_4$-Cl-(4) |
| d | $(CH_3)_2CH$ |

**3,5**: Ar = $C_6H_5$

**4,6**: Ar = $C_6H_4$-Cl-(4)

SCHEME 1

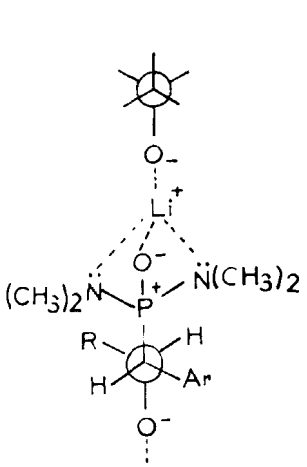
## DISCUSSION

Our results show that the intermediate erythro adducts **3**-Li and **4**-Li are thermodynamically controlled products, in contrast to many other cases of the Wittig–Horner

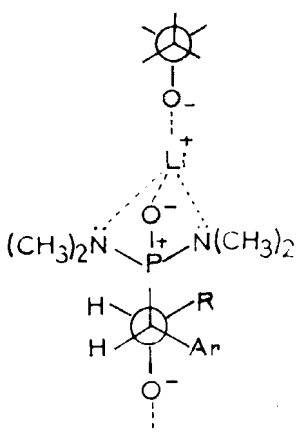
reaction[2] where erythro isomers are kinetically controlled products. This unexpected fact was confirmed by treating the pure erythro **3a** with BuLi in the conditions of nonstereoselective synthesis (5 hrs, −70°C, THF). It was found that the reaction mixture contained only erythro-**3a**, i.e. under these conditions the reaction is irreversible and no isomerisation erythro → threo takes place. An increase in the reaction temperature from −70°C to +20°C seems to make the reaction reversible and helps the isomerisation threo → erythro. In fact when a mixture of erythro-**3a** and threo-**3a** was treated with BuLi in THF for 1 hr at −70°C and then for ½ hr at 20°C, no threo-**3a** but only erythro-**3a** and the starting materials **1** and **2** were found in the crude reaction mixture, i.e. a complete conversion threo → erythro took place.

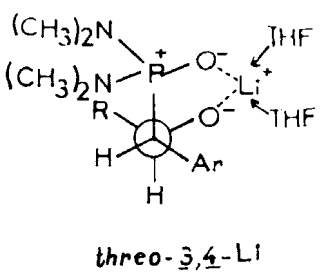
$$\text{threo-3a} \xrightarrow[1\text{ hr}\ -70°C,\ 20°C]{\text{BuLi}} \text{threo-3a-Li} \longrightarrow \text{1a-Li} + \text{2a} \longrightarrow \text{erythro-3a}$$

The following explanation of the above results could be possible. The metal derivatives of the threo forms of similar 2-hydroxy- and 2-arylaminophosphonates exist usually as inner chelates including the PO group, while for erythro isomers the conformation with anti dentate groups (PO and $O^-$ or $\overline{N}Ar$) are sterically favourable. The presence of two dimethylamido groups at the P-atom seems to lead to the formation of a very stable complex of four-coordinated $Li^+$ due to a chain-polymer association, i.e. without coordination of solvent molecules (see Figure 1).




erythro 3,4-Li




threo-3,4-Li

FIGURE 1

TABLE III

Coupling constants and conformations of intermediate 2-hydroxyphosphonamides **3** and **4** [in Hz]

| Configuration | $^3J_{H_aH_b}$ | $^2J_{H_aP}$ | $^3J_{H_bP}$ |
|---|---|---|---|
| erythro-**3,4** | 2 | 15–16 | 5–7 |
| threo-**3,4** | 8–9 | 11–12 | 10–11 |

Recently it was shown[10] that at low temperature, the equilibrium between contact and solvent separated ion pairs of alkaline salts of some arylmethanephosphonate carbanions is controlled by the solvation effect, while at elevated temperatures the coordinating effect of the PO group is predominant. In our case this corresponds to the conversion of the solvated threo adduct into erythro adduct with four coordinated lithium ions as ligands, i.e. without participation of the solvent molecules (Figure 1).

The configuration and favourable conformations of the isolated 2-hydroxyphosphonamides **3**, **4** were determined by NMR[11] (Table III) and IR spectral data. IR spectra in diluted ($10^{-3}$ m/l) $CCl_4$ solution show the absence of conformations $E_3$ and $T_3$ without an intramolecular hydrogen bond (P=O... H—O—) ($\nu_{OH}$ 3375 $cm^{-1}$). According to the IR and NMR spectral data the order of preference for the conformers in erythro and threo isomers (see Figure 2) is: $E_1 > E_2 \gg E_3$; $T_1 > T_2 \gg T_3$.

Our results lead to the conclusion that a simple way for the synthesis of some (Z)-olefins (stilbenes and substituted styrenes) of high purity is found by achieving very high stereoselectivity in the aldol step of the reaction in respect to erythro

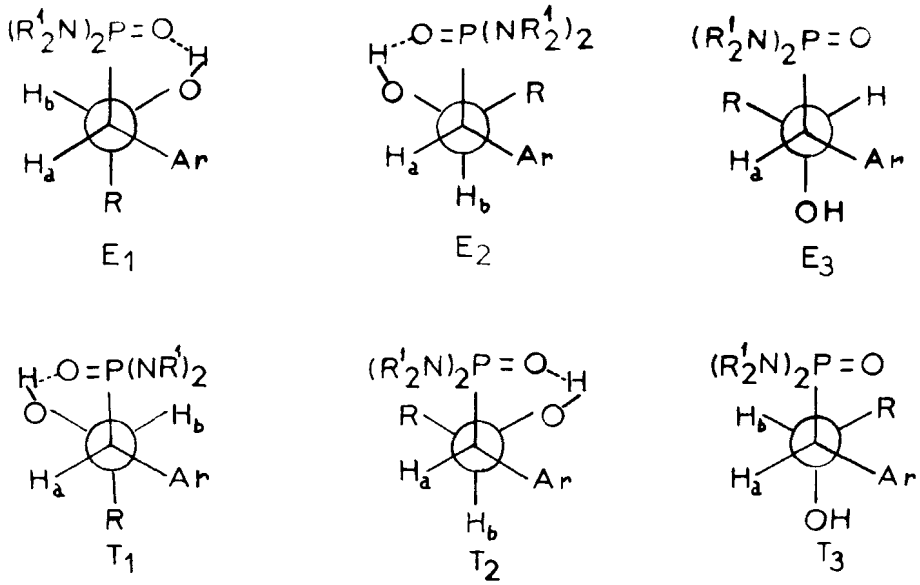



FIGURE 2 Possible conformations of erythro phosphonamides **3,4**(E) and threo phosphonamides **3,4**(T).

2-hydroxyphosphonamides (2-hydroxyadducts). In this way some experimental difficulties of the other methods, based on organophosphorus olefinating agents, are avoided.

When erythro 2-hydroxyphosphonates **3**, **4** are heated with HCl (25% soln) a nonstereospecific olefination takes place, mixtures of (Z) and (E) olefins being formed. This is the first observed case of olefination in acidic media of 2-hydroxyphosphonamides. Hitherto an olefination in acidic media of adducts, obtained from *d*-metalated esters of arylmethanephosphonic acids and *N*-benzoylketimines was described.[12] Two different mechanisms are possible (see Scheme 2), the first (a) involving a nonstereospecific olefin formation. According to the second route (b), however, the formation of (E), (Z)-mixtures could be a result of acid catalyzed Z → E isomerisation[13] under the reaction conditions. Experiments to clarify the mechanism of the observed acid catalyzed olefination are now in progress.

## EXPERIMENTAL



The reaction of **1** with BuLi and RCHO was carried out under dry argon. THF, used as a water free solvent was treated with $LiAlH_4$ and after distillation was boiled with Na in the presence of benzophenone. *n*-Buthyllithium (Fluka) was dissolved in hexane (1.6 m). All aldehydes were distilled before use. The olefinic products were examined by UV and NMR spectroscopy[11] in order to verify their structures. The (Z)/(E) ratio was determined by glc (8% PEGA Chromosorb P/NAW), using an internal standard obtained as described in ref. 14. In some cases olefins were purified by column chromatography on $Al_2O_3$ with hexane. The qualitative TLC investigations were carried out on silica gel 60 $F_{254}$ (aluminium sheets "Merck"), using ethylacetate–heptane 2 : 1 as a mobile phase (for adducts) or hexane (for olefins).

The $^1H$ NMR spectra were measured on a JEOL-J NM-100 spectrometer at 100 MHz at normal probe temperature in $CDCl_3$. The chemical shifts are relative to internal TMS or HMDSO.

Preparation of *N*,*N*,*N*′,*N*′-tetramethyldiamides of 1-aryl-2-aryl(alkyl)-2-hydroxyethanephosphonic acids **3**, **4**.

*Method A.* To a solution of **1** (5 mmole) in 10 ml anhydrous THF, cooled to −70°C, buthyllithium (5 mmole, 1.6 m in hexane) diluted with 5 ml THF was added under argon. After stirring for $\frac{1}{2}$–1 hr aldehyde **2** (5 mmole) in 5 ml THF was added and the stirring continued for 5 hrs at −70°C. The mixture was hydrolyzed with 5 ml water, then extracted with $CH_2Cl_2$ (3 × 20 ml), the extracts were washed with water and dried over magnesium sulfate. After evaporation of the solvent both NMR and TLC analysis show that the crude products contain mixtures of erythro and threo isomers of hydroxyphosphonamide adducts **3**, **4**.

*Method B.* The reaction of **1**, BuLi and **2** is carried out as described in method A. After stirring the reaction mixture for 5 hrs at −70°C it is allowed to warm to room temperature for $\frac{1}{2}$ hr, then is hydrolyzed and treated as in method A. According to NMR and TLC analysis the crude products **3**, **4** contain only the corresponding erythro isomers.

The crude **3**, **4** were purified by washing with ether/hexane (1 : 2) and recrystallized from ether (or ether/pentane). The washed crude **3**, **4** can be used in the reactions of olefination.

*Conversion of 2-hydroxyphosphonamides* **3**, **4** *into olefins* **5**, **6**

*1. Thermal decomposition of the adducts* **3**, **4**

*General procedure.* A stirred mixture of 1 mmol **3**, **4**, 0,700 g silicagel and 8 ml toluene is heated at reflux for 3 hrs. After cooling the reaction mixture is filtered and the silicagel washed with ether (30 ml) the combined filtrates washed with water (2 × 5 ml) and dried over $MgSO_4$. The solvents are evaporated in vacuum and the residue purified by column chromatography on alumina (20 g) using hexane as eluent.

*2. Olefination of the* **3**, **4** *in acid media.* The mixture of 1 mmol **3a** in 0,5 ml 25% HCl is heated at 110°C for 1 hr. After cooling the reaction mixture is made alkaline by 10% $Na_2CO_3$ to pH = 9, 15 ml ether added and the alkaline layer extracted with ether (2 × 10 ml) and dried over $MgSO_4$. After evaporation of

the solvent the residue is purified by column chromatography using hexane as eluent. Yield 0.138 g (77%) stilbene, (Z)/(E) = 35/65.

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