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Tandem Michael Addition Alkylation of Vinylphosphonates

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Abstract: Benzylation of α-phosphonoenolate **2a** is highly selective in favour of the like products **3**. Hydrogenation as well as reactions with simple alkyl halogenides are less selective. The stereochemical outcome of these reactions is discussed. © 1997 Elsevier Science Ltd.

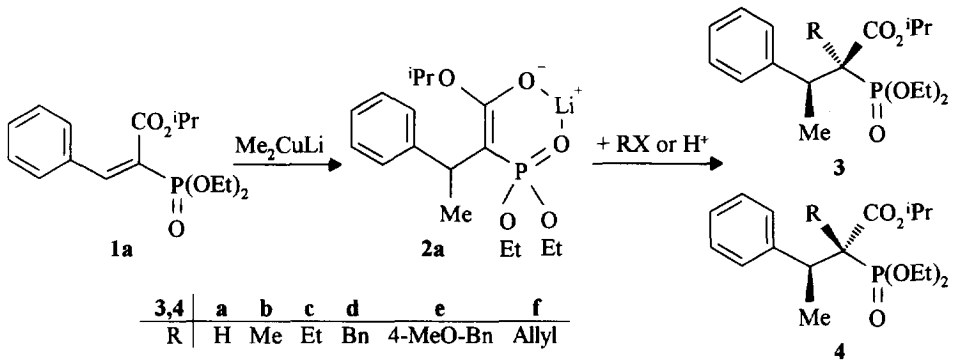
Phosphonic acid analogues of naturally occurring phosphates or of carboxylic acids continue to attract considerable interest as potential regulators, mediators or inhibitors of metabolic processes.[1] Their preparation requires access to all synthetic methods known in organic chemistry. Conjugate addition of carbanions to α,β-unsaturated carbonyl compounds followed by a reaction with electrophiles is one of these strategies.[2] Recently also enantioselective variants of the Michael addition to vinyl phosphonates have been reported. But the protonation of the new enolates formed did not influence the stereochemical outcome of these reactions.[3]

In general, less is known about the diastereoselectivity of reactions of α-phosphorus substituted enolates with electrophiles. The focus on Horner-Wadsworth-Emmons reaction is perhaps the reason for this omission.[4] This thesis is supported by the fact that the alkylation of phosphonate carbanions is also a neglected area of organophosphorus chemistry.[5,6] To the best of our knowledge, there is only one report on monoalkylation of acyclic β-oxophosphonates.[7]

In this paper we present the first study of a tandem Michael addition alkylation reaction of vinylphosphonates. α-Phosphonocinnamate **1**[8] was chosen as the Michael acceptor. Addition of methyllithium gave the appropriate adduct but also a lot of side products. The change to Me_2CuLi allowed the selective formation of the desired carbanion **2** carrying a representative diastereogenic center (Ph-CH-Me)[9] (see scheme 1).

The stereochemical outcome of the hydrogenation of α-carbon was independent of the proton source. Even sterically demanding Broenstedt acids like 2,6-di-*tert*-butylphenol gave no improvement in the diastereomeric ratio (see table , entries 1-3).

Alkylation was complete only when Lewis bases like HMPA or TMU (tetramethyl urea) were added (entries 5-10). In further reactions we preferred TMU as the less toxic compound. Reaction with ethyl iodide was not quantitative even in the presence of TMU. Higher alkyl iodides gave no alkylation products. Similar observations have been reported.[7] The like/unlike-ratio is not influenced by Lewis bases, showing that the geometry of the transition state of alkylation reactions is not affected by simple complexing reagents. The diastereoselectivity of hydrogenation, methylation and ethylation is very poor.



Scheme 1

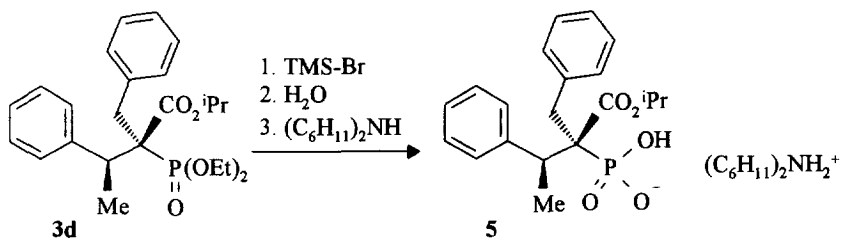
Table 1. Hydrogenation and alkylation of enolate **2a**

entry	RX (or acid), Lewis base	3/4	yield(%)	ratio l:u (3:4)[a]
1	(NH_4Cl)	**a**	95	1.9:1
2	(PivOH)	**a**	96	1.9:1
3	(2,6-di-^{t}Bu-Ph-OH)	**a**	95	1.8:1
4	MeI	**b**	78[b)]	1.2:1
5	MeI, HMPA	**b**	80	1.3:1
6	MeI; TMU	**b**	87	1.7:1
7	EtI, TMU	**c**	75[b)]	1.4:1
8	BnBr, TMU	**d**	75	8:1
9	p-MeO-BnBr, TMU	**e**	95	7:1
10	Allyl-Br, TMU	**f**	81	3.6:1

[a)] determined by integration of ^{31}P NMR signals [b)] contains impurities of **3a** and **4a**

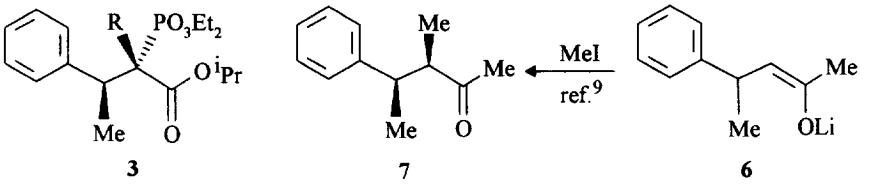
An improvement was observed if activated halogen compounds were used (entries 8-10) which yielded the like-products **3** as the major compounds. X-ray analysis of a crystalline derivative of **3d**, the dicyclohexylammonium salt **5d**, (see scheme 2) has confirmed this result. Treatment of **3d** with trimethylsilyl bromide[10] followed by hydrolysis and addition of dicyclohexylamine gave this product (see scheme 2).

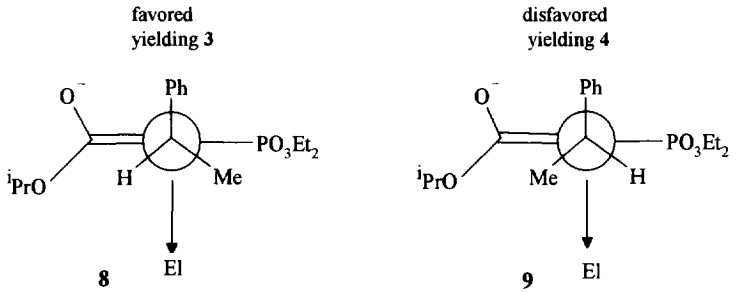
Alkylation of enolate **2** led to products with a quaternary, asymmetric carbon atom. Surprisingly, the stereogenic center used by us (Ph-CH-Me) shows the same stereocontrol also in enolates carrying hydrogen at C-2, e.g. **6**.[9] Regarding the methyl groups, both the products **3** and **7** have syn-configuration (see scheme 3).



Scheme 2

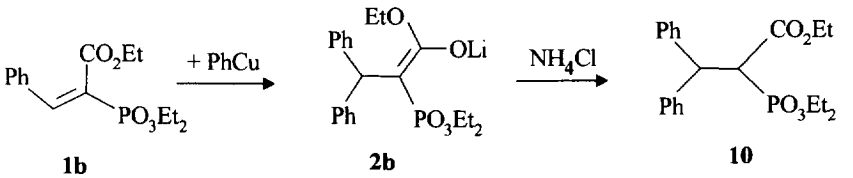
This result confirms the general rule of stereocontrol of electrophilic attack[9] - a transition state like **9** is less favoured due to allylic strain interactions. Even the enolate **2a**, with a large substituent at C-2 (PO_3Et_2), mainly follows the pathway by way of **8**.





Scheme 3

In a similar reaction the vinylphosphonate **1b** was treated with PhCu (see scheme 4). The enolate formed is not very reactive. Alkylation or olefination with benzaldehyde[11] failed. Quenching of **2b** gave the phosphonopropionate **10** as a crystalline compound.



Scheme 4

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Ether and dioxane were distilled from sodium before use. All reactions involving organometallic reagents were conducted under an argon atmosphere. NMR spectra (^1H, ^{13}C, ^{31}P) were recorded on a Bruker WP 200 SY . Chemical shifts are expressed in ppm to high frequency of tetramethylsilane (internal, ^1H, ^{13}C) and 85% H_3PO_4 (external, ^{31}P), respectively. Mass spectra were determined with a FISONS Instruments VG Auto Spec.

All compounds gave the appropriate M^+-peak. X-ray analysis was performed on a Turbo CAD4 (ENRAF-NONIUS, software: SHELX-S86, SHELX-S93).

Isopropyl α-diethylphosphonocinnamate (**1a**) was prepared as an E/Z mixture from isopropyl diethylphosphonoacetate and benzaldehyde in the presence of $(^iPrO)_3TiCl$.[8]

Ethyl α-diethylphosphonocinnamate (**1b**) was prepared as an E/Z mixture from ethyl diethylphosphonoacetate and benzaldehyde in the presence of $TiCl_4$.[12]

Generation of Enolate 2a: A 1.6 M solution of methyllithium in ether was added dropwise at -25 °C to a stirred mixture of CuI (190 mg, 1 mmol) and 1.7 mL of ether until a clear solution was obtained. After further stirring at -15 °C for 10 min and cooling to -78 °C a solution of phosphonocinnamate **1a** (322.5 mg, 0.99 mmol) in 1.3 ml of ether was added within 10 min. Stirring was continued for 1 h at -78 °C giving the enolate **2a**.

Enolate 2b: see compound **10**

(2R,3R*)- and (2R*,3S*)-Isopropyl 2-(diethoxyphosphoryl)-3-phenyl-butyrate* (**3a/4a,** *entry 1*): The solution of **2a** (see above) was quenched with saturated aqueous NH_4Cl solution and ether (10 ml each), allowed to warm to room temperature and filtered over silica. The organic layer was washed with pH7-buffer and brine and dried over Na_2SO_4. The solvent was removed at reduced pressure. The products **3a** and **4a** were isolated as a mixture by flash chromatography[13] (Merck KG-60, ethyl acetate/heptane 4:1).
3a/4a, *entries 2 and 3*: Pivaloylic acid (306 mg, 3 mmol, entry 2) and 2,6-di-*tert.*-butyl phenol (618 mg, 3 mmol, entry 3), respectively, were added to the enolate solution. The mixture was stirred for 10 min at -78 °C, quenched with pH7-buffer and treated as described above, colourless oil, ^1H NMR (δ, $CDCl_3$) 7.3-6.9 (m, 5H), 5.05 (sept, J= 6 Hz) and 4.65 (sept, J= 6 Hz, 1H), 4.2-4.0 (m) and 3.9-3.7 (m, 4H), 3.7-3.25 (m, 1H), 3.17 (d, J= 19 Hz) and 3.11 (d, J= 19 Hz, 1H), 1.3-0.7 (m, 15H), ^{13}C NMR (δ, $CDCl_3$)[14]: 168.3, 167.8, 144.1 (d, J= 4 Hz), 143.6, 68.9, 68.3, 53.6 (d, J= 130 Hz), 53.5 (d, J= 135 Hz), 39.8 (d, J= 4 Hz), 39.1(d, J= 4 Hz), ^{31}P NMR (δ, CH_3CN): 21.85 (major), 21.01(minor).

General Procedure of 3b-f and 4b-f: 1.5 ml of Lewis base (see table) were added to the solution of **2a** (see above). Stirring was continued (1 min at -78°C, 5 min at 0 °C). The mixture was again cooled to -78 °C and 4 mmol of the appropriate alkyl halogenide were added. The reaction mixture was stirred for 3 h at 0 °C and then allowed to warm to room temperature. Quenching and work up according to entry 1 gave the products **3b-f** and **4b-f** as a mixture of isomers.

(2R,3R*)- and (2R*,3S*)-Isopropyl 2-(diethoxyphosphoryl)-2-methyl-3-phenyl-butyrate* (**3b/4b**): isolated as a mixture by flash chromatography (Merck KG-60, ethyl acetate/heptane 4:1), ^1H NMR (δ, $CDCl_3$) 7.4-7.0 (m, 5H), 5.05 (sept, J= 6 Hz) and 4.85 (sept, J= 6 Hz, 1H), 4.2-4.05 (m) and 3.95-3.7 (m, 4H), 3.7-3.5 (m, 1H), 1.7-0.9 (m, 18H), ^{13}C NMR (δ, $CDCl_3$)[14]: 170.0, 141.7 (d, J= 6 Hz), 141.3, 69.1, 68.8, 53.9 (d, J= 136 Hz), 53.8 (d, J= 130 Hz), 42.3, 13.5, 12.2, ^{31}P NMR (δ, CH_3CN): 26.25 (minor), 25.1 (major).

(2R,3R*)- and (2R*,3S*)-Isopropyl 2-(diethoxyphosphoryl)-2-ethyl-3-phenyl-butyrate* (**3c/4c**): isolated as a mixture by flash chromatography (Merck KG-60, ethyl acetate/heptane 4:1), ^1H NMR (δ, $CDCl_3$) 7.4-7.1 (m, 5H), 5.1 (sept, J= 6 Hz) and 4.75 (sept, J= 6 Hz, 1H), 4.3-3.95 (m, 8H), 3.95-3.6 (m, 1H), 2.0-1.4 (m, 1H),m 1.4-0.8 (m, 18H), ^{13}C NMR (δ, $CDCl_3$)[14]: 171.0, 170.3, 141.9 (d, J= 4 Hz), 141.6 (d, J= 4 Hz), 68.9, 68.6, 58.6 (d, J= 135 Hz, minor), 58.0 (d, J= 130 Hz, major), 44.9 (d, J= 2.7 Hz, minor), 43.5 (d, J= 2.6 Hz, major), 17.9, 17.7, 10.62 (d, J= 2.5 Hz), 10.58 (d, J= 2.5 Hz), ^{31}P NMR (δ, CH_3CN): 25.54 (minor), 25.09 (major).

(2R,3R*)-Isopropyl 2-(diethoxyphosphoryl)-2-benzyl-3-phenyl-butyrate* **(3d, major)**: **3d** was isolated together with the (2R*,3S*)-isomer **4d** by flash chromatography (Merck KG-60, ethyl acetate/heptane 3:1) but separation of chromatographic zones was good enough to isolate pure **3d**, ^{1}H NMR (δ, $CDCl_3$) 7.4-7.0 (m, 10H), 5.08 (sept, J= 6.2 Hz, 1H), 4.0-3.5 (m, 5H), 3.13 (dd, J_{PH}= 31.8 Hz, J_{HH}= 13.8 Hz, 1H), 2.79 (dd, J_{PH}= 5.1 Hz, J_{HH}= 13.8 Hz, 1H), 1.44 (d, J= 7.3 Hz, 3H), 1.23 (d, J= 6.2 Hz, 6H), 1.05 (t, J= 7 Hz, 3H), 0.89 (t, J= 7 Hz, 3H), ^{13}C NMR (δ, $CDCl_3$)[14]: 170.5, 141.9 (d, J= 6.6 Hz), 137.9 (d, J= 3 Hz), 69.4, 58.8 (d, J= 143 Hz), 44.4, 38.1, 18.4 (d, J= 5.6 Hz), ^{31}P NMR (δ, CH_3CN): 23.80 ppm.

(2R,3S*)-Isopropyl 2-(diethoxyphosphoryl)-2-benzyl-3-phenyl-butyrate* **(4d, minor)**: ^{31}P-NMR (δ, CH_3CN): 23.37 ppm.

(2R,3R*)-Isopropyl 2-(diethoxyphosphoryl)-2-(4-methoxybenzyl)-3-phenyl-butyrate* **(3e, major)**: was isolated together with the (2R*,3S*)-isomer **4e** by flash chromatography (Merck KG-60, ethyl acetate/heptane 3:1), ^{1}H NMR (δ, $CDCl_3$) 7.3-7.0 (m, 7H), 6.61 (d, J= 6Hz, 2H), 5.04 (sept, J= 6.3 Hz), 4.0-3.5 (m, 5H), 3.77 (s, 3H), 3.07 (dd, J_{PH}= 31.8 Hz, J_{HH}= 13.9 Hz, 1H), 2.74 (dd, J_{PH}= 5.2 Hz, J_{HH}= 13.9 Hz, 1H), 1.40 (d, J= 7.2 Hz, 3H), 1.21 (d, J= 6.3 Hz, 6H), 1.04 (t, J= 7 Hz, 3H), 0.91 (t, J= 7 Hz, 3H), ^{13}C NMR (δ, $CDCl_3$)[14]: 170.5, 158.1, 141.9 (d, J= 6.1 Hz), 112.5, 69.4, 58.9 (d, J= 142 Hz), 55.1, 44.4 (d, J= 1.5 Hz), 37.0 (d, J= 2.5 Hz), 18.4 (d, J= 6 Hz), ^{31}P NMR (δ, CH_3CN): 24.05 ppm.

(2R,3S*)-Isopropyl 2-(diethoxyphosphoryl)-2-(4-methoxybenzyl)-3-phenyl-butyrate* **(4e, minor)**: ^{31}P NMR (δ, CH_3CN): 23.61 ppm.

(2R,3R*)- and (2R*,3S*)-Isopropyl 2-(diethoxyphosphoryl)-2-allyl-3-phenyl-butyrate* **(3f/4f)**: isolated as a mixture by flash chromatography (Merck KG-60, ethyl acetate/heptane 4:1), ^{1}H NMR (δ, $CDCl_3$) 7.3-7.0 (m, 5H), 6.1-5.9 (m, 1H), 5.2-4.7 (m, 3H), 4.2-3.6 (m, 5H), 2,7-2.3 (m, 2H), 1.5-0.8 (m, 15H), ^{13}C NMR (δ, $CDCl_3$)[14]: 169.9 and 169.8, 141.3 (d, J= 4.5 Hz, major) and 141.1 (d, J= 3.5 Hz, minor), 135.1 (d, J= 4.5 Hz, major) and 135.0 (d, J= 2.8 Hz, minor), 117.1 (minor) and 116.7 (major), 69.0 (major) and 68.7 (minor), 57.8 (d, J= 139 Hz, minor) and 57.3 (d, J= 139 Hz, major), 44.2 (d, J= 2.8 Hz, minor) and 43.1 (d, J= 2.7 Hz, major), 34.3 (d, J= 2.8 Hz, major) and 32.4 (d, J= 2.1 Hz, minor), 17.8 (d, J= 10 Hz), ^{31}P NMR (δ, CH_3CN): 24.99 (minor), 24.44 (major).

(1R,2R*)-Dicyclohexylammonium 1-(isopropoxycarbonyl)-1-benzyl-2-phenyl-propanephosphonate* **(5)**: Pure major isomer **3d** (432 mg, 1 mmol), 5 mL of dioxane and Me_3SiBr (0,396 mL, 3 mmol) were heated to 60 °C for 8 h.[10] The solvent was removed at reduced pressure and 3 mL of water were added. After 1 h at room temperature, the water was removed at reduced pressure, too. The residue was dissolved in 3 mL of methanol and treated with a solution of dicyclohexylamine (0.242 mL, 1.2 mmol) in 2 mL methanol. Addition of 2 mL of water and slow evaporation of methanol allowed the isolation of **5** in crystalline form.

Ethyl 2-(diethoxyphosphoryl)-3,3-diphenyl-propionate **(10):** A 1.8 M solution of phenyl lithium in ether was added dropwise at 0 °C to a stirred mixture of CuBr (143 mg, 1 mmol) and 2.5 mL of ether until a clear brownish solution was obtained. After further stirring at 0 °C for 5 min a solution of phosphonocinnamate **1b** (250 mg, 0.8 mmol) in 1 ml of ether was added within 10 min. Stirring was continued for 30 min at 0 °C yielding the enolate **2b**. The enolate solution was quenched with saturated aqueous NH_4Cl solution and ether (10 ml each), allowed to warm to room temperature and filtered over silica. The organic phase was washed with pH7-buffer and brine and dried over Na_2SO_4. The solvent was removed at reduced pressure. Product **10** was obtained by crystallisation from hexane, colourless needles, yield: 190 mg (61 %), mp 87 °C, ^{1}H NMR (δ, $CDCl_3$) 7.5-7.0 (m, 10H), 4.64 (dd, J_1 =J_2= 12 Hz, 1H), 4.0-3.5 (m, 6H), 3.6-2.79 (m, 1H), 1.07 (t, J= 7 Hz, 3H), 1.00 (7, J= 7 Hz, 3H), 0.90 (t, J= 7 Hz, 3H), ^{13}C NMR (δ, $CDCl_3$): 168.0, 142.1 (d, J= 18 Hz), 141.3, 128.5, 128.4, 127.5, 126.9, 126.8, 62.4, 62.32, 61.2, 51.6 (d, J= 131 Hz), 50.6, 16.2, 16.1, 13.7, ^{31}P NMR (δ, CH_3CN): 21.76.

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11. Enolate **2a** reacts with benzaldehyde giving the appropriate olefin as an E/Z-mixture. The same products are obtained from a **3a/4a** mixture, NaH and PhCHO. These reactions were not investigated further.
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14. $PO\underline{C}H_2CH_3$ and $POCH_2\underline{C}H_3$ gave groups of signals in the area of 62.8-61.4 ppm, and 17.0-15.9 ppm (covers in most cases C-4), respectively, which are not compiled. This large number of signals is caused by P-C-coupling, chemical nonequivalence of groups and the presence of more than one isomer. Also the shifts of $OCH(\underline{C}H_3)_2$ (area: 21.7-20.9 ppm) and of aromatic carbon (area: 130-126 ppm) - except those of the ipso atoms - are not given.

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