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Synthesis of Some Phosphonocarbonyl Compounds via Horner–Emmons Reaction of Methylenbisphosphonate

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Summary. The γ-carbonyl substituted vinylphosphonates **6–9** were synthesized from the α-dicarbonyl compounds **2–5** and the methylenbisphosphonate **1** by a Horner–Emmons reaction in different yields.

Keywords. Horner–Emmons reaction; Vinylphosphonates; Methylenbisphosphonates; α-Dicarbonyl-compounds.

Synthese von Phosphonocarbonylverbindungen durch Horner–Emmons-Reaktion von Methylenbisphosphonsäuretetraethylester

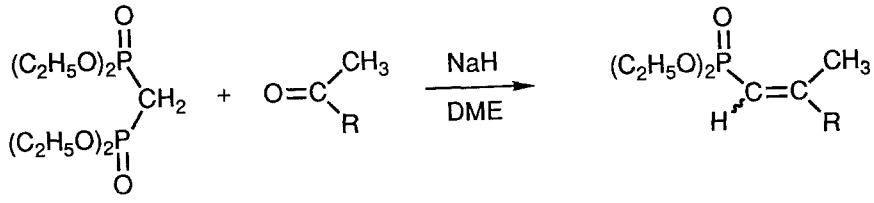
Zusammenfassung. Es wurden die γ-carbonylsubstituierten Vinylphosphonate **6–9** mittels Horner–Emmons-Reaktion aus den α-Dicarbonylverbindungen **2–5** und Methylenbisphosphonat **1** in verschiedenen Ausbeuten hergestellt.

Introduction

Phosphonates and phosphinates recently have found interests because of their high potential in biological systems [1–4] as enzyme inhibitors. In the course of our studies of phosphorous analogues of natural compounds, especially vitamins like the 25-Oxa-25-phosphavitamin D_3 [4], we encountered the problem of preparing vinylphosphonates carrying a carbonyl-group in γ-position. Although there were many methods reported to synthesize vinylphosphonates [5], Horner–Emmons [6–9] reactions of **1** with dicarbonyl compounds like **2–5** has not been described in the literature yet.

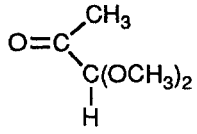
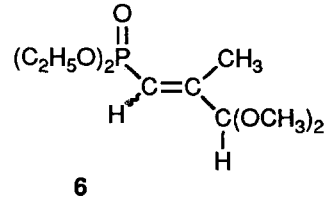
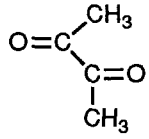
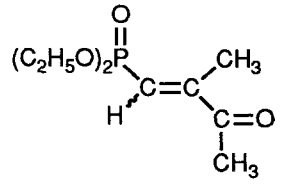
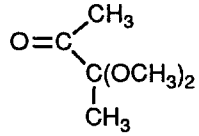
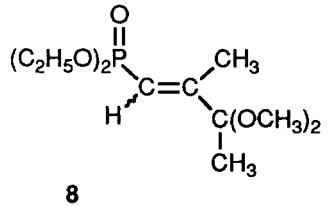
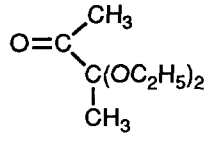
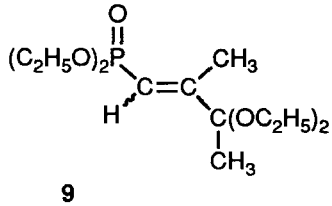
Results and Discussion

The γ-carbonyl substituted vinylphosphonates **6–9** were synthesized from the carbonyl compounds **2–5** and the methylenbisphosphonate **1** by a Horner–Emmons reaction. The compounds **4** and **5** were obtained by the methods described in Ref. [10–11].



1 2-5 6-9

Table 1. Horner–Emmons reactions

Dicarbonyl	Vinylphosphonate
	
2	6
	
3	7
	
4	8
	
5	9

The reaction proceeds satisfactorily in 1,2-dimethoxyethan (*DME*) under argon using NaH as a base. After the reaction took place the reaction mixture was hydrolized by sat. aqueous KH_2PO_4, followed by extraction with Et_2O. All compounds could be only obtained after short-path destillation of the combined organic layers. Only compound **6** could be obtained as a mixture of *E*- and *Z*-isomer (4:1) in form of a colourless oil (in elementary analysis purity) in a good yield (80%). **7–9** were obtained in form of viscous yellow oils, which partially decomposed during destillation. Only **7** was obtained in moderate yield (21%) and gave satisfactory spectroscopical data, but elementary analysis failed. **8–9** could be identified by high resolution mass spectroscopy (HRMS). Appropriate ^1H-$\{^1H\}$-NOE experiments allowed the distinction between (*E*)-**6a** and (*Z*)-**6b**; saturation of the signal of the vinylic proton of (*E*)-**6a** resulted in a significant NOE for the acetalic proton. Our results are in an excellent accordance with previous findings [12] that the $^3J(C, P)$ coupling constants of *β*-substituted *trans*-vinylphosphonates are higher than in their *cis* configurated analogues. This observation resulted in a rapid method of determination of the geometric structure of the new vinylphosphonates. The $^3J(C, P)$ coupling constants of **7** showed that only the (*E*)-isomer could be isolated.

Experimental Part

IR spectra were recorded on a Perkin Elmer 325 spectrometer. Mass spectra were obtained with a Varian MAT 311A spectrometer. Elemental analysis were performed at the Department of Chemistry at the University of Heidelberg. NMR spectra: Bruker WM-250 in $CDCl_3$ with *TMS* as internal standard. All solvents were purified in the usual way.

General Procedure for the Preparation of the γ-Carbonyl Substituted Vinylphosphonates **6–9**

To a suspension of NaH in 25 ml *DME* was added a solution of **1** in 20 ml *DME* at −10 °C. The reaction mixture was heated to 20 °C for 2 h and stirring was continued. After cooling to −10 °C, the solution of **2–5** in 10 ml *DME* was added. The yellow solution was also allowed to heat up to 20 °C for 18 h. After hydrolysis with 15 ml sat. aqueous KH_2PO_4 the aqueous phase was extracted five times with 20 ml Et_2O and the combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo.

3,3-Dimethoxy-2-methylprop-1-enylphosphonicacid Diethylester (**6**)

6 was prepared by the general procedure from 0.6 g (20 mmol) 80% suspension of sodium hydride, 4.4 g (15 mmol) **1** and 2.7 g (20 mmol) **2**. Yield 3.0 g = 80%. Purification by short-path destillation. B.p. 70 °C (bath), 0.1 mbar. ^1H-NMR (250, 13 MHz, *δ*, $CDCl_3$): (*E*)-Form **6a**: 1.33 (t, $^3J(H, H) = 7$ Hz, 6H, $P(OCH_2CH_3)_2$), 2.10 (dd, $^4J(P, H) = 3.5$ Hz, $^4J(1\text{-}H, 4\text{-}H) = 1.4$ Hz, 3H, CH_3), 3.30 (s, 6H, $CH(OCH_3)_2$), 4.10–4.20 (m, 4H, $P(OCH_2CH_3)_2$), 4.62 (br., 1H, $CH(OCH_3)_2$), 5.87 (m, $^2J(P, H) = 18.2$ Hz, 1H, C=CH). (*Z*)-Form **6b**: 1.33 (t, $^3J(H, H) = 7$ Hz, 6H, $P(OCH_2CH_3)_2$), 1.95 (t(dd), $^4J(P, H) = 1,5$ Hz, $^4J(H, H) = 1.5$ Hz, 3H, CH_3), 3.45 (s, 6H, $CH(OCH_3)_2$), 4.10–4.20 (m, 4H, $P(OCH_2CH_3)_2$), 5.55 (dq, $^2J(P, H) = 15.7$ Hz, $^4J(H, H) = 1.5$ Hz, 1H, C=CH), 5.62 (br., $^4J(P, H) \approx 1$ Hz, 1H, $CH(OCH_3)_2$). IR (film, NaCl): 1650 (C=C), 1450, 1390, 1250 (P=O), 1170, 1110, 1060, 1040 (P-O-Alkyl) cm^{-1}. MS (70 eV 83 °C): *m/e* (%) = 251 (31) [M^+-H], 237 (5) 221 (8), 177 (6), 161 (5), 149 (10), 133 (12), 115 (6), 75 (100). Analysis for $C_{10}H_{21}O_5P$ (252.25): calcd. C 47.62, H 8.39, P 12.28; found C 47.90, H 8.57, P 12.37.

2-Methyl-3-oxobut-1-enylphosphonicacid Diethylester (**7**)

7 was prepared following the general procedure from 0.25 g (8.3 mmol) 80% NaH-suspension, 1.9 g (6.6 mmol) **1** and 1.6 g (18.6 mmol) **3**. Yield 0.3 g = 21%. Purification by short-path destillation. B.p. 90–105 °C (bath), 0.07 mbar. ^{1}H-NMR (250,13 MHz, δ, $CDCl_3$): δ = 1.38 (t, ^3J(H, H) = 6 Hz, 6H, $P(OCH_2CH_3)_2$), 2.20 (dd, ^4J(P, H) = 3.8 Hz, ^4J(H, H) = 1.2 Hz, 3H, C=C–CH_3), 2.40 (s, 3H, $COCH_3$), 4.10–4.30 (m, 4H, $P(OCH_2CH_3)_2$), 6.45 (dd, ^2J(P, H) = 16.1 Hz, ^4J(H, H) = 1.2 Hz, 1H, C=CH). MS (70 eV 79 °C): *m/e* (%) = 220 (32) [M^+], 205 (1), 192 (4), 177 (48), 149 (48), 121 (100), 81 (19), 65 (14), 43 (68). Analysis for $C_9H_{17}O_4P$ (220.20): HRMS calcd. 220.0864; found 220.0865.

3,3-Dimethoxy-2-methylbut-1-enylphosphonicaciddiethyl Ester (**8**)

8 was prepared from 0.25 g (8.3 mmol) 80% NaH-suspension, 1.8 g (6.2 mmol) **1** and 1.0 g (7.6 mmol) **4**. Purification by short-path destillation. B.p. 80–105 °C (bath), 0.04 mbar. Analysis for $C_{11}H_{23}O_4P$ (266.28): HRMS calcd. 266.1283; found 266.1283.

3,3-Diethoxy-2-methylbut-1-enylphosphonicaciddiethyl Ester (**9**)

9 was prepared from 0.5 g (17 mmol) 80% NaH-suspension, 4.0 g (14 mmol) **1** and 2.4 g (15 mmol) **5**. Purification by short-path destillation. B.p. 110–120 °C (bath), 0.04 mbar. Analysis for $C_{13}H_{27}O_4P$ (294.33): HRMS calcd. 294.1596; found 294.1597.

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