

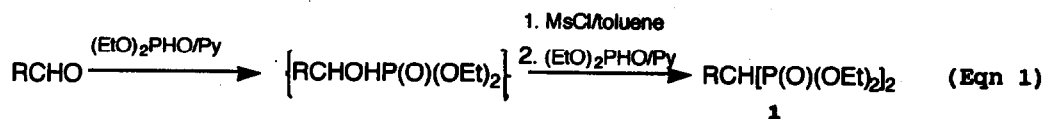
Studies on Organophosphorus Compounds 68. A New and Facile Synthetic Approach to Alkylidenebisphosphonates.

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Abstract: Condensation of aldehydes with diethyl phosphite followed by sulfonylation of the α -hydroxy group formed with methanesulfonyl chloride and subsequent substitution by another molecule of diethylphosphite provides corresponding alkylidenebisphosphonates in one-pot procedure with good yield.

Methylenebisphosphonic acid and its derivatives are of considerable interest in medicinal applications.¹ Being an important derivatives of methylenebisphosphonate, alkylidenebisphosphonates **1** were usually prepared by monoalkylation of **1a**.² This method, however, suffers from the contamination of dialkylated by-product and is inaccessible to **1g-1j**. Other methods including phosphorylation of carbanions derived from alkylphosphonates³ or Michael additions of ethenylidenebisphosphonate⁴⁻⁵ require rigid experimental conditions and sometimes provide lower yield. Herein we wish to report a convenient method for the synthesis of **1** directly from aldehydes.



As shown in equation 1, base catalyzed condensation of aldehyde with diethyl phosphite gives corresponding 1-hydroxyalkylphosphonate.⁶ Upon the addition of MsCl, the hydroxy function turns to a good leaving group and therefore can be easily substituted by a phosphite anion. As a result, product **1** is synthesized by one-pot procedure in high yield. The present method can be considered as a general procedure for the preparation of compounds **1** as indicated by its wide scope of application. (Table 1)

As a typical procedure, the mixture of benzaldehyde (1.0 mL, 10 mmol), pyridine (1.8 mL, 22 mmol), and diethyl phosphite (2.6 mL, 20 mmol) was

Table 1. Compounds 1 synthesized.

Entry	R	Time(h)	Yield(%) ^{a,b}
a	H	1	75
b	Me	2	80
c	Et	2	85
d	n-Pr	2	85
e	i-Pr	3	82
f	n-Pen	3	73
g	Ph	4	93
h	p-F-Ph	4	90
i	p-Cl-Ph	4	92
j	p-MeO-Ph	4	87
k	PhCH ₂	4	81

a. Isolated yield based on the corresponding aldehyde.

b. Satisfactory spectra analyses and elemental analyses were obtained.

heated at 70°C for 2 h. Toluene(100 mL) was added to the resulting mixture and the solution was cooled to 0°C. MsCl(0.78 mL, 10 mmol) was added dropwise to the solution. After the addition, the solution was allowed to warm up to r.t. and stirred for 30 min and then refluxed for 4 h. The solution was filtered and the filtrate, by vacuum distillation, gave pure 1g as a colorless liquid. Yield: 3.39 g(93%). B.p. 160°C/0.2mmHg. IR(film) ν 3025, 1605, 1251, 1025, 971. EIMS: m/z 365 (M⁺+H). ¹H NMR (CDCl₃) δ 1.32(12H, t, J=7, CH₃), 4.08 (1H, t, J=22, CHP₂), 4.12 (8H, q, J=7, CH₂), 7.35 (5H, m, C₆H₅). Anal. Calcd for C₁₅H₂₆O₆P₂: C, 49.46; H, 7.20. Found: C, 49.55; H, 7.13.

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