Tetrahedron Letters, Vol. 34, No. 10, pp. 1585-1588, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

PHOSPHONATE *VS.* PHOSPHINATE ELIMINATION DURING OLEFINATION OF ALDEHYDES

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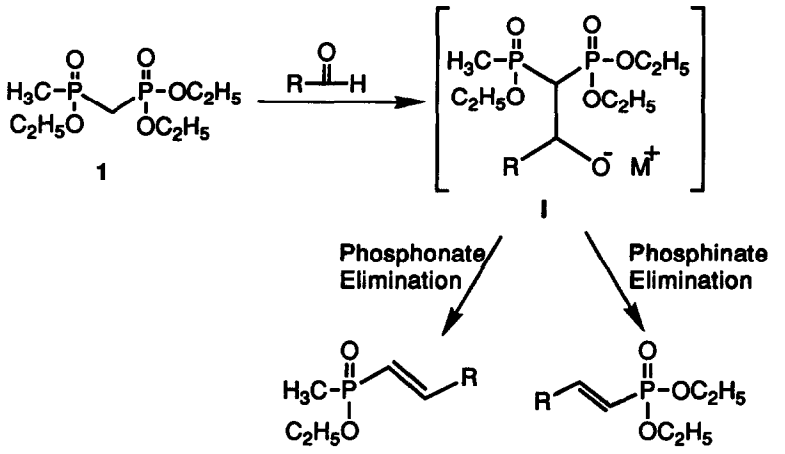
Abstract: Olefination of aldehydes with O,O,O-triethyl methylmethylenephosphonophosphinate in the presence of magnesium bromide etherate and triethylamine leads to a selective elimination of the phosphonate group over the phosphinate to yield alkenyl(methyl)phosphinates in a convenient manner.

Isoprenoids containing the phosphinylformate group are known Squalene Synthetase inhibitors.[1] In a program on the synthesis of Squalene Synthetase inhibitors we were interested in a general synthetic route to alkenyl(methyl)phosphinates because a methyl group directly attached to phosphorous atom in this class of compounds could serve as a possible prodrug in vivo for a carboxylic acid moiety leading to a phosphinylformate group. We reasoned that alkenyl(methyl)phosphinates could be prepared by a reaction of an aldehyde with a carbanion stabilized by two phosphorous groups, phosphonate and phosphinate, followed by a selective elimination of the phosphonate group from the resulting intermediate. Reactions of carbanions stabilized by two phosphorous groups with aldehydes have been a topic of interest over the years.[2-4] In this paper we describe a convenient synthesis of alkenyl(methyl)phosphinates (**2-7**) by a reaction of O,O,O-triethyl methylmethylenephosphonophosphinate (**1**)[5] with aldehydes via a selective elimination of the phosphonate group over the phosphinate in the intermediate **I** (Scheme 1).

Olefination of isobutyraldehyde with **1** was used as a representative example to study phosphonate *vs.* phosphinate elimination. Reaction of **1** with isobutyraldehyde in the presence of sodium hydride, potassium t-butoxide or n-butyl lithium in dry tetrahydrofuran at room temperature gave a mixture of phosphinate (**2**) and phosphonate (**8**) in 1:1.55, 1:1.58 and 1:1.2 ratio respectively (Table 1). In contrast, when the reaction was

carried out in the presence of magnesium bromide etherate and triethylamine[6] the ratio of **2** and **8** was 9.6:1 (Table 2, entry 1). The desired phosphinate (**2**) was isolated as the major product in 58% yield. To study the general synthetic utility, several aldehydes were olefinated with **1** under these conditions. The results are listed in Table 2. Inspection of Table 2 reveals that aldehydes in general yielded the desired phosphinates (**2-7**) in good yields and with high selectivity over phosphonates (**8-13**). In all cases the product was the E-isomer. A possible explanation for this selectivity involves the better ability of the phosphonate group to chelate with magnesium in the intermediate **I** (Scheme 1) thereby making it a better leaving group for elimination over the phosphinate group.



R = Isobutyl	2	8
R = Phenyl	3	9
R = Cyclohexyl	4	10
R = 2-Phenethyl	5	11
R = n-Hexyl	6	12
R = Farnesyl	7	13

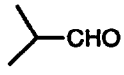
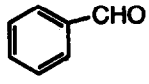
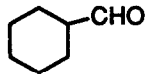
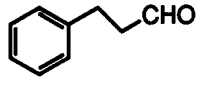
(Scheme 1)

Thus, magnesium bromide etherate with triethylamine as a base leads to a selective phosphonate elimination during olefination of aldehydes with **1**. This provided a general and a convenient synthesis of alkenyl(methyl)phosphinates.

Table 1: Reaction of 1 with Isobutyraldehyde

Entry	Conditions	Isolated Yields (%) 2	8
1	NaH, THF, Room Temp.	31	48
2	Potassium t-butoxide, THF, Room Temp.	31	49
3	n-BuLi, THF, Room Temp.	45	54

Table 2: Reaction of 1 with aldehydes in the presence of magnesium bromide etherate and triethylamine

Entry	Aldehyde	Products[a]	Isolated Yields (%)
1		2	58
		8	6
2		3	83
		9	7
3		4	74
		10	b
4		5	63
		11	5
5		6	59
		12	6
6		7	66
		13	3

a) All the compounds gave satisfactory spectral and analytical data.
b) Not detected.

General Experimental Procedure: To a stirred suspension of magnesium bromide etherate (1.2 mmol) in dry tetrahydrofuran (3 mL) was added **1** (1 mmol) dropwise at room temperature under an argon atmosphere. The mixture turned into a clear solution. After stirring for 5 min triethylamine (1.12 mmol) was added and the mixture stirred for an additional 10 min. This was followed by the addition of an appropriate aldehyde (1.18 mmol) and the mixture was allowed to stir at room temperature for 16 hr. The mixture was quenched with 3N hydrochloric acid and extracted with methylene chloride. The combined organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude mixture was purified by flash chromatography over silica gel to yield pure phosphonates (**8-13**) followed by desired phosphinates (**2-7**).

Acknowledgements: We thank Drs. J. Tomesch, J. Wareing and F. Kathawala for their support and NMR, IR, MS and Elemental Analysis laboratories for spectral and analyses data.

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(Received in USA 8 December 1992; accepted 29 December 1992)