Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 22 Aug 2006.

To cite this article: Isabelle Truel, Abdourahman Mohamed-Hachi, Elie About-Jaudet & Noël Collignon (1997) A Convenient (E)-Stereoselective Synthesis of Alkenylphosphonates, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:2, 297-302

To link to this article: http://dx.doi.org/10.1080/00397919708005031

SYNTHETIC COMMUNICATIONS, 27(2), 297-302 (1997)

A CONVENIENT (E)-STEREOSELECTIVE SYNTHESIS OF ALKENYLPHOSPHONATES

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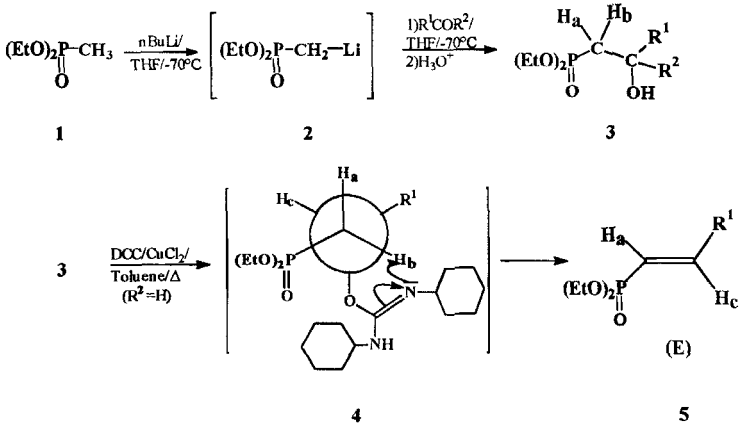
Abstract : Diethyl (E)-alkenylphosphonates have been prepared stereoselectively by dehydration of the corresponding β-hydroxyphosphonates using DCC/$CuCl_2$ in refluxing toluene. Starting β-hydroxyphosphonates were obtained in high yield from diethyl methylphosphonate.

Alkenylphosphonates have been widely used as building blocks in organic chemistry[1] but few convenient synthetic routes to such compounds are known[2,3]. As part of our program directed towards synthesis of phosphonic Diels-Alder reagents, we recently reported an efficient synthesis of phosphonic dienes[4] and O-silylated or O-acetylated dienoxyphosphonates[5]. Moreover the recent work of Lee and al.[3] prompted us to present here a general two-step synthesis of (E)-alkenylphosphonates **5** from the readily available diethyl methylphosphonate **1**[6]. The key-step of this method lies in the dehydration of the known



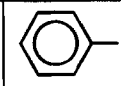
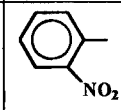
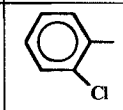
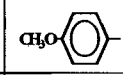
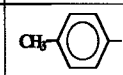
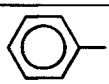
Scheme 1

intermediate β-hydroxyalkylphosphonates[7] **3**, achieved under non acidic or non basic conditions, by the DCC/$CuCl_2$ system in refluxing toluene (Scheme 1).

In the first step lithiated carbanion **2** (^{31}P NMR : δ_{THF} = 56.2 ppm) was generated, from phosphonate **1** (^{31}P NMR : δ_{THF} = 29.3 ppm) by deprotonation with 1.05 equivalents of BuLi in THF at -70°C, and reacted smoothly with aromatic and aliphatiques aldehydes and ketones at -70°C, leading, after acidic hydrolysis and usual workup, to the alcohol **3** as the sole product and in quasi quantitative crude yield. (Table)

Subsequent dehydration of alcohols **3**, using dicyclohexylcarbiimide (DCC)[8] catalyzed by anhydrous $CuCl_2$ in refluxing toluene for 6 hours, led stereoselectively to alkenylphosphonates **5** with (E)-configuration (Table). This (E)-stereoselectivity can be explained by the thermal syn-elimination (Chugaev-type reaction) of the more stable carbamidate conformer **4** (R^1 more bulky than R^2), giving **5** and the stable N,N'-dicyclohexylurea as by-product. In the case of alcohol **3g** the reaction was not regioselective (Scheme 2) and led to a mixture of **5i** and **6** in a 35/65 ratio as determinated on the crude product by ^{31}P NMR spectroscopy. Other dehydrating agents were tried (tosic acid, Amberlist, MsCl/Et_3N) in order to improve the yield in **5i** left the alcohol **3i** unchanged.

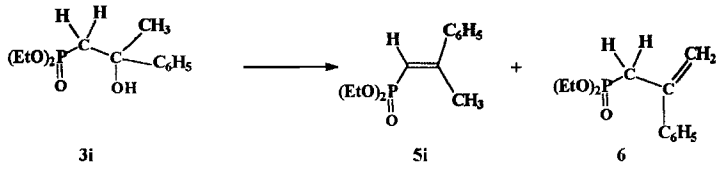
TABLE : **Compounds 3 and 5**

			Compounds 3		**Compounds 5**		
Entry	**R^1**	**R^2**	**Yield (%)[a]**	**^{31}P NMR[b,c] (δ_{ppm})**	**Yield[a] (%)**	**^{31}P NMR[b] (δ_{ppm})**	**$^3J_{Hc-P}$[c] (Hz)**
a		**H**	95	27.1	85	17.7	18.2
b		**H**	96	26.6	70	14.7	21.2
c		**H**	94	27.2	70	16.2	21.6
d		**H**	95	27.2	85	18.2	22.5
e		**H**	94	27.4	90	18.1	22.5
f	**i-Pr**	**H**	92	29.7	65	17.6	22.4
g	**n-Pentyl**	**H**	93	28.6	70	16.9	22.8
h	**i-Butyl**	**H**	92	28.5	64	16.4	22.5
i		**CH_3**	93	27.1	10	16.3	-

a) After flash chromatography. Purity controlled by GC and ^{31}P NMR

b) In $CDCl_3$

c) All the compounds were fully characterized by ^1H NMR spectroscopy.[2,9]



3i 5i 6

Scheme 2

All the compounds 5 were purified by column chromatography and fully characterized by NMR spectroscopy.[2,9] The (E)-configuration was assigned by the $^3J_{H-P}$ coupling constant measurement in ^1H NMR spectra[2,9] or by comparison of their chemical schifts (δ) in the ^{31}P NMR spectra[8] (Table).

In summary, we report here a new highly stereoselective and general synthesis of (E)-alkenylphosphonates 5 using cheap commercially reagents and the readily available diethyl methylphosphonate. This valuable method allows the preparation in two steps of useful vinylphosphonates, substituted at the 2-position by aromatic as well as aliphatic residues.

Experimental.

Gas chromatography (GC) was performed on a Girdel 300 chromatograph equipped with a 2m OV17 column. Elemental microanalyses were carried out on a Carlo Erba 1106 analyser. The NMR spectra were recorded in $CDCl_3$, on a Brucker AC-200 spectrometer; the chemical shifts (δ) are expressed in ppm relative to tetramethylsilane for ^1H nucleus and to H_3PO_4 for ^{31}P nucleus, the coupling constants (J) are given in Hz and conventional abbreviations are used. Solvents were dried and distilled just before use. All metallation reactions were carried out under dry inert gas.

Preparation of 1-Diethoxyphosphonyl-2-hydroxy-2-(4-methoxyphenyl)ethane 3d. ***Typical procedure*** : To a stirred 1 6 M solution of *n*-BuLi (0.055 mol) in hexane, an equal volume of THF (~65 mL) is added and the mixture was cooled at -78°C, then a solution of

methanephosphonate **1**[6] (7.5 g, 0.05mol) in THF (25 mL) was added dropwise. After 10 min, a solution of p-anisaldehyde (7.3 g, 0.055 mol) in THF (25 mL) was added dropwise at -78°C under stirring; then the mixture was allowed to warm slowly to room temperature and 4M hydrochloric acid was added until pH 3. The aqueous solution was extracted with CH_2Cl_2 (3x50mL). The combined organic layers were dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the crude product, which was purified by column chromatography over SiO_2 (eluent : hexane/ether = 1/1), leading to the pure oily product **3d** (13.3 g, yield 95%).

^{1}HNMR:1.2&1.23(2t,^{3}J=7Hz,6H,$CH_2C\underline{H}_3$),2.1(m,H_a&H_b),3.7(s,$OC\underline{H}_3$),4.0(m,4H,$C\underline{H}_2O$), 4.2(s,O<u>H</u>),5.0(ddd,C<u>H</u>O,$^3J_{HHb}$=9.4Hz,$^3J_{HaH}$=3.9Hz,$^2J_{HP}$=9.4Hz),6.8&7.25(2d,$^3J_{HH}$=8.3 Hz, $4H_{arom}$)

Preparation of (E)-1-Diethoxyphosphonyl-2-phenylethylene 5a. *Typical procedure* : To a stirred solution of **3a** (2.6 g, 0.01 mol) in anhydrous toluene (25 mL) was added a solution of DCC (2.1 g, 0.01 mol) in toluene (10 mL). After addition of $CuCl_2$ (~20mg) the mixture was refluxed for 6 hours. Dicyclohexylurea was separated by filtration from the cooled mixture and the toluene was evaporated under reduced pressure to give the crude product, which was purified by column chromatography over SiO_2 (eluent : hexane/ether = 1/1), leading to the pure oily product **5a**. (2.05 g, yield 85%).

^{1}HNMR:1.3(t,^{3}J=7.4Hz,6H,$CH_2C\underline{H}_3$),4.1(qui,4H,$C\underline{H}_2O$),4.9(t,$^3J_{HH}$=$^2J_{PH}$=17.6Hz,P-C<u>H</u>=),6.1-6.25(m,6H,$C_6\underline{H}_5$-C<u>H</u>=)

Preparation of (E)-1-Diethoxyphosphonyl 2-phenylprop-1-ene 5i and **1-Diethoxyphosphonyl-2-phenylprop-2-ene 6** : To a stirred solution of **3g** (2.4 g, 0.02 mol) in anhydrous toluene (25 mL) was added a solution of DCC (4.2 g, 0.02 mol) in toluene (20 mL). After addition of $CuCl_2$ (~20mg) the mixture was refluxed for 6 hours. Dicyclohexylurea was separated by filtration from the cooled mixture and the toluene was evaporated under reduced pressure to give the crude product, which was purified by column chromatography over SiO_2 (eluent : hexane/ether) leading to the pure oily **5i** (0.22 g, yield 10 %) and **6** (0.66 g, yield 30%).

5g :^{31}P NMR : δ =.16.3 ppm. ^{1}H NMR : 1.3 (t,$^3J_{HH}$=$^3J_{HP}$=7 Hz, 6H, $C\underline{H}_3CH_2O$), 2.5 (d, $^4J_{HP}$=1.7 Hz, 3H, $C\underline{H}_3$-C=), 4.1 (qui,$^3J_{HH}$=$^3J_{HP}$=7 Hz, 4H, $CH_3C\underline{H}_2O$), 5.9 (d,$^2J_{HP}$=16.3

Hz, $\underline{H}C=$), 7.5 (m, $5H_{arom}$)

6 : ^{31}P NMR : δ =. 24.7 ppm. ^{1}H NMR : 1.15 (t, $^{3}J_{HH}=^{3}J_{HP}$=7.3 Hz, 6H, $C\underline{H}_3CH_2O$), 3.0 (d, $^{2}J_{HP}$=22.1 Hz, 2H, $C\underline{H}_2$-P), 4.0 (m, 4H, $CH_3C\underline{H}_2O$), 5.3 & 5.5 (2d, $^{3}J_{HH}$=5.3 Hz, $C\underline{H}_2=$), 7.3 (m, $5H_{arom}$)

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(Received in The Netherlands 16 July 1996)