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Preliminary Communication

A convenient stereoselective synthesis of disubstituted alk-1-enyl phosphonates

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Abstract

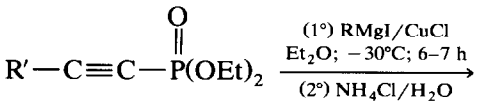
A stereoselective synthesis of disubstituted diethyl alk-1-enylphosphonates has been developed via *syn* addition of RMgX/CuCl to alk-1-inylphosphonates.

Key words: Phosphonate; Stereoselective synthesis; Cuprate addition; Phosphorus

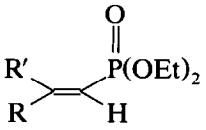
Vinyl phosphonates are useful intermediates in the synthesis of biologically active compounds; for example, in the preparation of phosphomycin *via* stereospecific epoxidation of an unsaturated phosphonate [1]. Furthermore they may undergo useful transformations as reagents for organic synthesis [2].

Few methods are known for the preparation of vinyl phosphonates; they are not easily obtained using the classical Arbuzov–Michaelis reaction [3], and so their efficient synthesis is of interest. Alk-1-enyl phosphonates are generally prepared by the Wittig reaction of acylphosphonates with methylene bisphosphonate [2,4], dehydration of β-hydroxyethyl phosphonate [2], oxidative elimination of organosulfenyl and organoselenyl moieties from α-sulfenyl and α-selenylalkyl phosphonates [2], via catalytic subsitution on alk-1-enylbromide [2,5], and finally by β-elimination of nitrous acid from α-nitroalkyl phosphonate [6].

Here we report a new and easy synthesis of disubstituted vinyl phosphonates starting from readily available alk-1-ynyl phosphonates, **1** [7] and an excess of alkyl- or aryl-magnesium iodide with cuprous salt at −30°C in ether. This affords the corresponding vinyl phosphonates **2** in good yields (Table 1).



(1)



2
(75%–85%)

R = Oct^n, Ph or 4-Tol, R′ = Pr^n or Ph

This addition is a typically regioselective and *syn*-addition process like the addition of organo-copper species to disubstituted alkynes [8]. The *syn*-stereoselective addition of organo-copper to α,β-alkynyl phosphonate **1** has been established unambiguously by ^{1}H and ^{13}C NMR spectroscopy for compounds **2a–c**; the ^3J coupling constants between ^{13}C and ^{31}P is typical of a *trans* value, between 21 and 24 Hz [9] (Table 2).

The addition of lithium organocuprate to diethyl

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TABLE 1. Synthesis of diethyl alk-1-enyl phosphonates, **2**

Compound	R	R′	Reaction time (h)	Yield [a] (%)	IR cm^{-1}		δ ^{31}P ($CDCl_3$, ppm)
					$\nu_{C=C}$	$\nu_{P=O}$	
2a	Oct^n	Ph	6	77	1615	1240	17.1
2b	Oct^n	Pr^n	7	85	1620	1250	19.2
2c	Ph	Pr^n	6	88	1610	1250	18.5
2d	4-Tol	Ph	7	75	1590	1250	17.6

[a] Isolated pure compounds.

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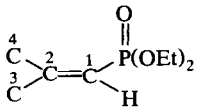
TABLE 2. ^{1}H and ^{13}C NMR spectra of diethyl alk-1-enyl phosphonates, **2**



Compound	R	R'	^{1}H ($CDCl_3$/TMS) (ppm, Hz)	^{13}C ($CDCl_3$) (ppm, Hz)
2a	Oct^n	Ph	5.65 (d, 1H, $^{2}J_{P-H}$ = 17.8, C=C*H*P-); 2.45 (t, 2H, $^{2}J_{H-H}$ = 6.74, CH_2-C=C)	162.9 (C_2, $^{2}J_{P-C}$ = 3.9) 139.8 (C_4, $^{3}J_{P-C}$ = 7.8, *cis*) 113.4 (C_1, $^{1}J_{P-C}$ = 191.3) 41.2 (C_3, $^{3}J_{P-C}$ = 21.1, *trans*)
2b	Oct^n	Pr^n	5.28 (d, 1H, $^{2}J_{P-H}$ = 18.7, C=C*H*-P); 2.4 (dt, 2H, $^{4}J_{P-H}$ = 2.2, $^{3}J_{H-H}$ = 5.7 (*cis*) $C_2H_5CH_2$-C=C-); 2.1 (t, 2H, $^{3}J_{H-H}$ = 7, C_3H_7-C=C-) CH_2	167.1 (C_2, $^{2}J_{P-C}$ = 6.8) 110.8 (C_1, $^{1}J_{P-C}$ = 189) 37.8 (C_3, $^{3}J_{P-C}$ = 22.5, *trans*) 35.3 (C_4, $^{3}J_{P-C}$ = 7.0, *cis*)
2c	Ph	Pr^n	5.73 (d, 1H, $^{2}J_{P-H}$ = 17.2, C=C*H*-P); 2.95 (dt, 2H, $^{4}J_{P-H}$ = 2.4, $^{3}J_{H-H}$ = 7.8 CH_2-C=C)	163.7 (C_2, $^{2}J_{P-C}$ = 8.7) 140.6 (C_3, $^{3}J_{P-C}$ = 23.7, *trans*) 113.8 (C_1, $^{1}J_{P-C}$ = 189) 34.2 (C_4, $^{3}J_{P-C}$ = 6.5, *cis*)
2d	4-Tol	Ph	6.1 (d, 1H, $^{2}J_{P-H}$ = 15.6, C=C*H*-P)	159.8 (C_2, $^{2}J_{P-C}$ = 6.1) 138.7 (C_4, $^{3}J_{P-C}$ = 7.5, *cis*) 138.4 (C_3, $^{3}J_{P-C}$ = 22.3, *trans*) 113.4 (C_1, $^{1}J_{P-C}$ = 194)

alk-1-enyl phosphonates takes place in a similar way, but our first result suggest poorer selectivities and yields (they are under further investigations).

In a typical experiment, one equivalent of CuCl is introduced into a solution of five equivalents of Grignard reagent in anhydrous ether (with less than five equivalents, the reaction is slower and produces more by-products). The temperature is then lowered to −30°C and one equivalent of alk-1-ynyl phosphonate is slowly added and the mixture is stirred at −30°C for 6 to 7 h. After hydrolysis by an aqueous solution of NH_4Cl the aqueous phase is extracted with ether and the organic phases are dried with Na_2SO_4 before concentration. The resulting crude oil is purified by column chromatography on silica gel, with ether as eluent.

In summary, the protocol represents a short regio- and stereoselective way to new disubstituted vinyl phosphonates in high yields.

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