Conjugate Addition of Alkyl- and Vinyl-copper Complexes to α,β-Unsaturated Phosphonic Esters. Stereospecific Syntheses of γ,δ-Unsaturated Phosphonates

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Alkylcopper complexes add to diethyl ethenylphosphonate to afford phosphonic esters with the alkyl chain increased by two carbon atoms; analogously vinylcopper complexes afford γ,δ-unsaturated phosphonic esters with retention of configuration in the double bond.

Phosphonic acid analogues of naturally occurring phosphates or carboxylic acids have attracted interest as potential inhibitors or regulators of metabolic processes.[1—4]. Their syntheses usually involve reactions by which the alkyl group of an alkyl halide is directly linked to the phosphorus atom (*e.g.* the Arbuzov and related reactions,[5] path a of Scheme 1) or to a methanephosphonic moiety[4] (path b of Scheme 1). In the former case, phosphonates with the same number of carbon atoms as the starting alkyl halide are formed, whilst the latter procedure affords compounds with one more carbon atom.

$CH_2{=}C(H)PO(OEt)_2$ **(2)** $R'C{\equiv}CH$ **(4)**

We report herein that the alkylcopper complexes $RCuMgX_2$ (**1**) (Scheme 2) undergo conjugate addition to diethyl ethenylphosphonate (**2**) whereby an alkyl halide can be converted into the phosphonic ester (**3**) with two more carbon atoms in the alkyl chain (path c, Scheme 1). Furthermore, the vinylcopper complexes (**5**) add to the same reagent (**2**) to give γ,δ-unsaturated phosphonic esters (**6**) in which the configuration of the double bond is retained.

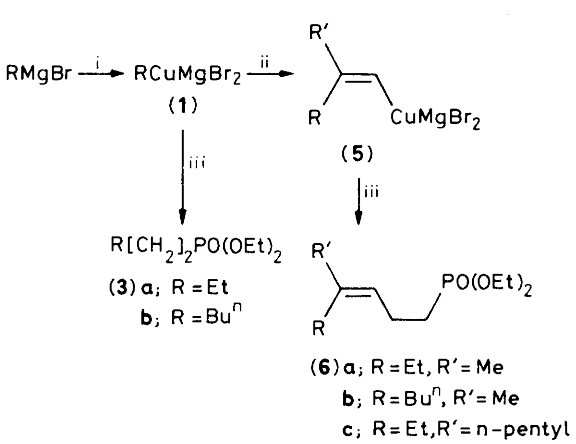
The alkylcopper complexes (**1**) were obtained (Scheme 2) by adding the corresponding Grignard reagents with stirring to a solution of $CuBr{\cdot}Me_2S$ (1 equiv.) in $Et_2O{-}Me_2S$ (3:2) at −45 °C under dry nitrogen. The conjugate addition occurred when (after 1 h) diethyl ethenylphosphonate[6] (**2**) (1 equiv.) was added and the temperature raised to 20 °C over 3 h.

$$\begin{tikzcd} \mathrm{RPO(OR')_2} & \mathrm{RBr} \arrow[l, "a"'] \arrow[r, "b"] \arrow[d, "c"] & \mathrm{RCH_2PO(OR')_2} \\ & \mathrm{R[CH_2]_2\,PO(OR')_2} & \end{tikzcd}$$

Scheme 1

The vinylcopper complexes (**5**) were formed by adding at −45 °C the alkyne (**4**) to a stirred solution of (**1**) prepared as above [propyne was bubbled through the solution for 30 min; hept-1-yne (1 equiv.) was added over a 2 min period].[7] The temperature was then raised to −25 °C and hexamethylphosphoric triamide (HMPT) (3 equiv.) and $P(OEt)_3$ (2 equiv.) were added to stabilize the complexes[8] (in the absence of these reagents the yields were drastically lowered, see entry 3 of Table 1). After 2 h (**2**) (1 equiv.) was added and the temperature raised to 20 °C over a 3 h period. Usual work-up of the reaction mixture afforded for each reaction a single product (by v.p.c., SE 30-10%, 150 °C) which was purified by flash chromatography. The yields of compounds (**3a,b**) and (**6a—c**) are given in Table 1.

The configuration of the double bond in (**5**) was retained in the γ,δ-unsaturated phosphonates, as evidenced by the n.m.r.



Scheme 2. i, $CuBr{\cdot}Me_2S$ (1 equiv.), −45 °C; ii, $R'C{\equiv}CH$ (**4**), −45 to −25 °C; iii, $CH_2{=}C(H)PO(OEt)_2$ (**2**).

Table 1

Entry	R	R′	Product[a]	Yield (%)[b]
1	Et	—	(**3a**)[c]	70
2	Bu^n	—	(**3b**)[c]	80
3	Et	Me	(**6a**)	25
4[d]	Et	Me	(**6a**)	90
5[d]	Bu^n	Me	(**6b**)	70
6[d]	Et	n-pentyl	(**6c**)	70

[a] All products gave satisfactory ^1H and ^{13}C n.m.r., and mass spectra, and elemental analysis. [b] Isolated yield. [c] Ref. 9. [d] HMPT (3 equiv.) and $P(OEt)_3$ (2 equiv.) were added to the vinylcopper complexes before the addition of (**2**).

spectra of (**6a**) and (**6b**); in the ^1H n.m.r. spectra the protons of the vinylic methyl group resonate at δ 1.68, a typical value for *Z* isoprenoid structures;[10] while in the ^{13}C n.m.r. the chemical shifts of the vinylic methyl groups (δ 22.8 and 22.7 p.p.m. respectively), and C-5 (δ 24.7 and 30.2 p.p.m. respectively) are in agreement with a *Z* configuration of the double bond.[11]

To our knowledge this is the first example of conjugate addition of organocopper complexes to α,β-unsaturated phosphonates. The mild conditions used and the good yields of this reaction may make it a useful synthetic method.

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