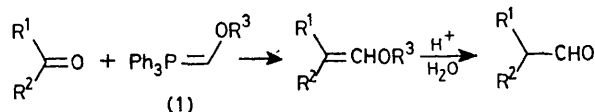


Stereo- and Regio-specific Vinyl Ether Synthesis by the Horner-Wittig Reaction

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Summary α -Methoxyalkyl diphenylphosphine oxides react with aldehydes and ketones to give adducts which decompose with base to give single geometrical isomers of vinyl ethers.

CONVERSION of aldehydes or ketones into the homologous aldehyde (Scheme 1) has been accomplished *via* vinyl ethers with various alkyloxy- and aryloxy-methyl phosphonium ylides (**1**).¹⁻⁵

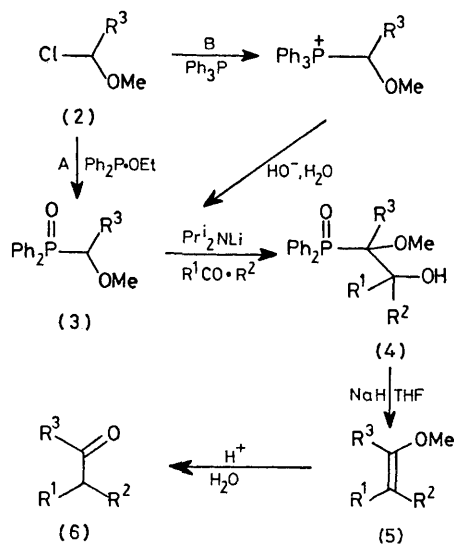


SCHEME 1

The ylides (**1**) are unstable,² poor yields of vinyl ethers are often obtained,^{1,2,4} particularly with enolisable aldehydes or ketones, and it is difficult to separate the vinyl ethers from triphenylphosphine oxide. In attempts to convert an acyl indole into the homologous aldehyde,⁶ we found that Horner-Wittig reactions with the phosphine oxide (**3**, R³ = H) largely solved these problems and we have developed a general route to vinyl ethers based on these compounds.

The phosphine oxide (**3**, R³ = H) is available by routes A (89%) or B⁷ (our yield 90%) (Scheme 2). Its anion [Prⁱ₂NLi, tetrahydrofuran (THF), room temperature] adds to aldehydes and ketones, even enolisable ones, to give good yields of adducts, *e.g.* the propionaldehyde adduct (**4**; R¹ = R³ = H, R² = Et) (70%), and the cyclohexanone

adduct (**4**; R¹R² = [CH₂]₆, R³ = H) (87%). Aldehydes give a mixture of diastereoisomers which can usually be separated by chromatography. Thus anisaldehyde gave 85% of a 6:5 mixture of (*RS,SR*:*RS,RS*-**4**; R¹ = R³ = H, R² = *p*-MeOC₆H₄) separated into the crystalline diastereoisomers by preparative t.l.c. (silica, eluted with EtOAc).



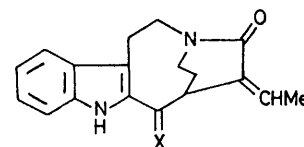
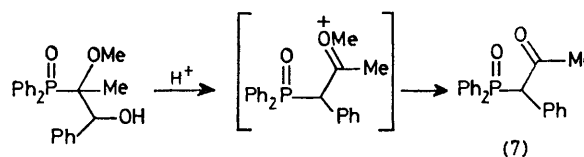
SCHEME 2

Completion of the Horner–Wittig reaction (NaH, THF, room temperature) gives the vinyl ethers. The cyclohexanone adduct gives the vinyl ether (**5**; $R^1R^2 = [CH_2]_5$, $R^3 = H$) in 57% yield. Each diastereoisomer of the anisaldehyde adduct gave a single geometrical isomer:⁸ (**5**; $R^1 = p\text{-MeOC}_6\text{H}_4$, $R^2 = R^3 = H$) in 88% and (**5**; $R^1 = R^3 = H$, $R^2 = p\text{-MeOC}_6\text{H}_4$) in 70% yield. Conversion of any of the vinyl ethers into the corresponding aldehydes (**6**, $R^3 = H$) is rapid and quantitative.^{1,2}

The method is superior to that using the ylides (**1**) in scope, yield, use of stable crystalline reagents (**3**), and ease of separation of products, but its special advantage is the formation of pure geometrical isomers of the vinyl ethers. *E* and *Z* isomers of vinyl ethers give anions of different types,⁹ each being of some promise in organic synthesis.^{9,10} It is superior as an aldehyde synthesis to the method using sulphenylated phosphine oxides¹¹ in that the vinyl ethers are much more easily hydrolysed than the vinyl sulphides.

The homologous reagent (**3**, $R^3 = \text{Me}$), available by route B (60%, some elimination of Ph_3P occurs during the hydrolysis) from the chloroether (**2**, $R^3 = \text{Me}$),¹² also reacts with aldehydes to give adducts, *e.g.* the acetaldehyde adduct (**4**; $R^1 = H$, $R^2 = R^3 = \text{Me}$) in 57% yield and the anisaldehyde adduct (**4**; $R^1 = H$, $R^2 = p\text{-MeOC}_6\text{H}_4$, $R^3 = \text{Me}$) in 75% yield, again separated into diastereoisomers each giving a single isomer of the vinyl ether (**5**; $R^3 = \text{Me}$; $R^1, R^2 = H$, $p\text{-MeOC}_6\text{H}_4$). One of these adducts (**4**; $R^1 = \text{Ph}$, $R^2 = H$, $R^3 = \text{Me}$) rearranged with Ph_2PO migration¹³

in acid to give the ketone (**7**). The scope and applications of these reactions to organic synthesis are being explored.



(8), X = O

(9), X = CHOMe

Schlosser refers briefly in a recent communication¹⁴ to the formation of the vinyl ether (**5**; $R^1R^2 = [CH_2]_5$, $R^3 = H$) in one step from the phosphine oxide (**3**, $R^3 = H$) and cyclohexanone in 35% yield. In general we find the two step process better (49.5% for this example), but we were able to convert the acyl indole (**8**) into the vinyl ether (**9**) in one step in 69% yield.

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