A Convenient One-pot Synthesis of Polyenic Enol Ethers

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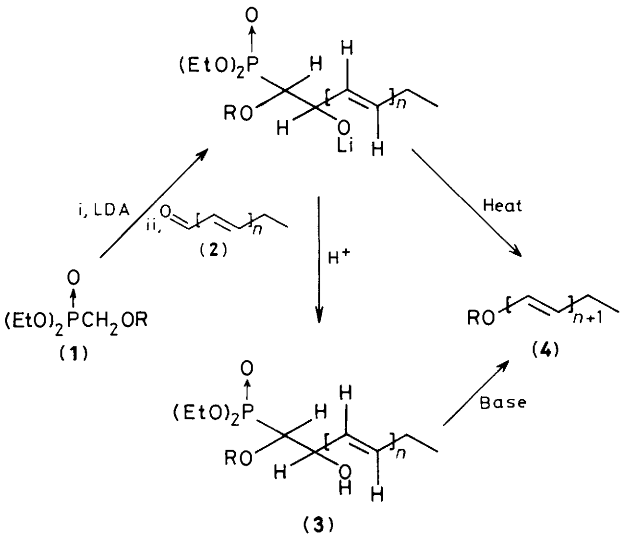
Diethyl alkoxymethylphosphonates react with unsaturated aldehydes to give polyenic enol ethers with a good stereoselectivity.

Polyene synthesis by Wittig-type reactions has been well documented.[1] The high stereoselectivity and experimental simplicity of the phosphonate olefin synthesis[2] have made it a popular method for the introduction of unsaturation concurrently with chain lengthening, particularly in the field of natural products and their analogues.[1–3]

This synthetic tool seemed particularly useful for the synthesis of the polyenic enol ethers required for our studies on the synthesis of a mutagen and its analogues. Several phosphonate reagents have been developed for the preparation of enol ethers from carbonyl compounds,[4–6] but unfortunately their use has presented some problems.[7,8] A diphenylphosphine oxide reagent has recently been reported to give satisfactory yields of methyl enol ethers.[9,10]

The present paper describes a convenient and highly stereoselective method for the synthesis of the polyenic enol ethers (3) by the reaction of the polyenal (2) with a carbanion of the diethyl alkoxymethylphosphonate (1). Several methods are available for the extension of double bond conjugation in systems containing an aldehyde function.[4] Two of these were selected as being the most appropriate for the present work.[11]



The diethyl alkoxymethylphosphonates (**1**) (R = Me, Et, $PhCH_2$, $MeOCH_2CH_2OCH_2$) were readily prepared by the Michaelis-Arbuzov reaction of the chloromethyl ethers with triethylphosphite in 85—95% yields. Their anions [lithium di-isopropylamine (LDA) (1.5 equiv.), tetrahydrofuran–hexane, −80 to −100 °C, argon] when added to the polyenals (**2**), gave good yields of the isolated adducts (**3**) (80—90%).†

The adducts (**3**), when treated with $KOBu^t$ or KH (2 equiv., 50 °C, 15 min), gave the polyenic enol ethers (**4**) (15—25% yield of distilled product).† In a one-pot procedure, the lithiated adduct of (**1**) was condensed with (**2**) and the reaction mixture was heated to reflux and left for $\geqslant$ 4 h at this temperature. A yield of distilled product of *ca.* 45—50% was obtained† [b.p. °C/mmHg, R = $PhCH_2$, $n = 0$ 98/0.05, $n = 1$ 118/0.05, $n = 2$ 162/0.05; R = Et, $n = 2$ 76/0.05; R = Me, $n = 2$ 98/0.5; R = $MeOCH_2CH_2OCH_2$, $n = 2$ (40% yield of crude oil)].

This synthesis of the unsaturated polyenic enol ethers is highly stereoselective: the newly-formed double bond has predominantly the *E* configuration ($n = 0$ E:Z 80:20; $n = 1,2$ E:Z 100:0; determined by ^1H n.m.r. spectroscopy). The structures of the vinyl ethers were evident from their ^1H n.m.r. spectra; the vinyl protons next to oxygen resonate at low field, and the *Z* (7 Hz) and *E* (13 Hz) ^3J coupling constants were unambiguous.[9,12]

It is of note that, in preliminary experiments using diphenylbenzyloxyphosphine oxide, prepared according to the method of Warren *et al.*,[9] the ratio of the geometrical isomers of (**4**) was 50:50 for $n = 0$. Preliminary results, obtained with Li–Zn exchange in a one-pot procedure, seem promising but the reaction is less stereoselective.

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† Reaction conditions were not optimized. Satisfactory i.r. spectra were obtained for all products. For (**3**, $n = 0$), ^1H n.m.r. (100 MHz, $CDCl_3$–Me_4Si, assignment by spin decoupling and [P] irradiation), δ 0.92 (2 × t, 3H, Me), 1.32 (t, 6H, OCH_2CH_3), 1.60 (m, 2H, CH_2), 3.05 (br. s, OH, exch. D_2O), 3.75 (m, 2H, CH–O and CH–P), 4.18 (m, 4H, OCH_2CH_3), 4.72 (m, 2H, CH_2Ph), 7.35 (s, 5H, Ph); corresponding spectra for (**3**, $n = 1, 2$) are similar. For *E*-(**4**, $n = 0$), ^1H n.m.r. [conditions as for (**3**)], δ 1.05 (t, 3H, Me), 2.85 (m, 2H, CH_2), 4.70 (s, 2H, CH_2Ph), 4.90 and 6.31 (both dt, 1H each, ^3J 12.5 Hz, vinyl H), 7.35 (s, 5H, Ph); spectra for [**4**, $n = 0$ (*Z*), 1, 2] are analogous.

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