The Mechanism of the Horner–Emmons Modification of the Wittig Reaction

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Summary The decomposition of *erythro*- and *threo*-β-hydroxyphosphonates in basic medium shows that they partly revert to benzaldehyde and the anion (1) to an extent which is solvent-dependent, and partly interconvert directly; the ratios of *cis*- to *trans*-cinnamonitrile formed from the two β-hydroxyphosphonates are very similar.

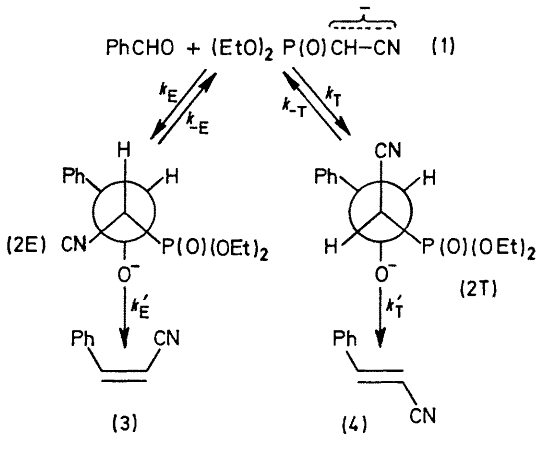
THE formation of cinnamonitriles from benzaldehyde and cyanomethyldiethylphosphonate anion (1) under Horner–Emmons conditions is thought to occur *via* the mechanism indicated in the Scheme.[1,2]

The reversibility of the first step has been evidenced by an indirect experiment in protic medium.[3] The stereochemistry of the reaction should depend upon the degree of reversibility of the formation of the intermediate oxy-anions (2 E) and (2 T) if they do not interconvert directly, and of the rates of their decomposition into cinnamonitriles *cis*-(3) and *trans*-(4).

We have prepared *erythro* (5 E) and *threo* (5 T) diethyl 1-cyano-2-hydroxy-2-phenylethylphosphonates in order to study their behaviour under Horner–Emmons reaction conditions.

Compounds (5 E) and (5 T) were obtained by the reaction of benzaldehyde with the reagent formed from cyanomethyldiethylphosphonate and Pr^{i}MgCl in tetrahydrofuran at $-70°$. They are separated by fractional crystallization from diethyl ether and a mixture of diethyl ether (70) and pentane (30). Compound (5 E) has m.p. 108°; (5 T) m.p. 66°.

The n.m.r. spectra, elemental analysis, and i.r. spectra are in agreement with the structures.



PhCHOH·CHCN·P(O)(OEt)$_2$ (5E and T)

SCHEME

0·001 Mole (5 T) or (5 E), 0·002 mole of p-ClC$_6$H$_4$CHO, 35 mg NaH (55—60% pure, in mineral oil) and 5 ml solvent were stirred for 15 min. The molar ratios of p-chlorocinnamonitriles to cinnamonitriles were determined by g.l.c.: in tetrahydrofuran they are 80/20 from (5 E), 75/25 from (5 T); in hexamethylphosphoramide they are 62/38 from (5 E), 57/43 from (5 T). A competitive direct reaction from (1), C_6H_5CHO, and p-ClC_6H_4CHO shows that the relative reactivities of the two aldehydes are the same in tetrahydrofuran and hexamethylphosphoramide. Therefore, the first step of the Horner–Emmons reaction is reversible in aprotic media also, but to a different extent according to the solvent.

We examined then the *cis*-(3)/*trans*-(4) ratios of cinnamonitriles obtained in tetrahydrofuran[†] either *via* direct reaction[4] or from (5 E) and (5 T), with and without the competing aldehyde which should trap any of compound (1) formed *via* a retroaldolization process. If (2 E) and (2 T) are only epimerized *via* retroaldolization, we should obtain higher percentages of (3) from (5 E) and of (4) from (5 T) than in the direct reaction. In the presence of p-ClC_6H_4CHO, which is more reactive than benzaldehyde, we should obtain a mixture very rich in (3) from (5 E) and in (4) from (5 T). The stereochemical results (Table) are reproducible.

TABLE: *Ratio of* (3) *to* (4)

Direct reaction	From (5 E)		From (5 T)	
	without p-ClC_6H_4CHO	with p-ClC_6H_4CHO	without p-ClC_6H_4CHO	with p-ClC_6H_4CHO
14/86	17/83	15/85	12/88	10/90

In fact, the (3)/(4) ratios are nearly the same in whatever way the reaction is carried out, *i.e.*, the two oxy-anions (2) should partly interconvert directly, a finding which is different from that observed for the Wittig reaction with stabilized ylides.[1][‡] So, in tetrahydrofuran, the stereochemistry of the Horner–Emmons reaction depends mainly upon the relative rates of olefin formation from the oxy-anions (2 E) and (2 T).

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[†] This experiment can only be performed in tetrahydrofuran. In hexamethylphosphoramide (3) and (4) are epimerized in basic medium.

[‡] As the referee pointed out, our results suggest also pseudorotation or rapid bond-making–bond-breaking of a 5-co-ordinate intermediate as well as direct interconversion of the two oxy-anions, but we actually cannot assess which is the process involved.

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