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Abstract

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THE INFLUENCE OF EXTERNAL FACTORS ON THE MECHANISM AND STERIC DIRECTION OF THE WITTIG REACTION

The stereochemistry of the Wittig reaction has so far still been scarcely studied. The nonstereospecificity of this reaction has been noted repeatedly, and trans isomers have usually predominated in the mixture of final products (see ([1])). Recently we found that the steric direction of the reaction can be changed by carrying it out in specific solvents ([2]). Since elucidation of the conditions for selective preparation of cis isomers by means of the Wittig reaction would be of substantial importance for the synthesis of many natural substances, we undertook a systematic study of the influence of various external factors on the steric direction of this reaction. As the first object of study we chose the reaction of benzylidenetriphenylphosphorane (I) with propionic aldehyde:

$$[C_6H_5CH_2PPh_3]^+Cl^- \xrightarrow[\text{ation}]{\text{base}} C_6H_5C^{\ominus}H{-}P^{\oplus}Ph_3 \xrightarrow{OCHC_2H_5} C_6H_5CH{=}CHC_2H_5{+}Ph_3PO$$

(*I*)

It turned out that in benzene this reaction proceeds nonselectively, although it leads predominantly to the formation of trans-β-ethylstyrene. When the reaction is carried out in ether, tetrahydrofuran, or alcohol, the relative amount of the cis isomer increases somewhat; in dimethylformamide its direction changes toward predominance of the cis form (see Table 1).

Table 1

Influence of solvents and additives on the ratio of cis- and trans-β-ethylstyrenes formed in the Wittig reaction*

Solvent	Additives	Base	Ratio of cis- and trans-β-ethylstyrenes
Benzene	–	C_4H_9Li	26 : 74
Benzene	Aniline **	C_4H_9Li	40 : 60

Solvent	Additives	Base	Ratio of cis- and trans-β-ethylstyrenes
Benzene	Butylamine **	C_4H_9Li	36 : 64
Benzene	Piperidine **	C_4H_9Li	33 : 67
Benzene	LiBr ***	C_4H_9Li	91 : 9
Benzene	LiJ ***	C_4H_9Li	93 : 7
Ether	–	C_2H_5ONa	31 : 69
Tetrahydrofuran	–	C_2H_5ONa	33 : 67
Alcohol	–	C_2H_5ONa	47 : 53
Dimethylformamide	–	C_2H_5ONa	65 : 35
Dimethylformamide	LiJ ***	C_2H_5ONa	96 : 4

* The reaction of ylide (I) with propionic aldehyde was carried out with a 50% excess of ylide at 20° (20 h) with subsequent heating at 80° (3 h) in a nitrogen atmosphere. The ratio of cis and trans isomers was determined by gas-liquid chromatography of a hexane solution of the mixture of β-ethylstyrenes on diatomaceous brick impregnated with silicone elastomer (column size 200$×$5 mm, temperature 130°, nitrogen flow rate 50 ml/min). The total error of this method lies within 3–4 relative percent.

** 4 mol per mole of phosphor ylide.

*** Suspensions of LiBr or LiJ (1 mol per mole of phosphor ylide) were prepared by neutralizing a benzene solution of butyllithium with dry hydrogen bromide or hydrogen iodide. When a suspension of LiI prepared by dissolving LiI in benzene was used, the effect was considerably weaker (ratio of cis- and trans-β-ethylstyrenes 35 : 65).

An increase in the relative amount of the cis form can also be achieved when the reaction is carried out in benzene in the presence of amines. Additions of lithium bromide or iodide exert the greatest influence on the direction of the reaction. In the presence of these salts the reaction even in benzene

becomes selective, whereas in dimethylformamide it leads practically only to cis-β-ethylstyrene.

The data obtained by us, summarized in Table 1, make it possible to put forward a number of fundamental considerations concerning the factors that determine the mechanism and stereochemical course of the Wittig reaction. It seems probable that the reaction in benzene and other nonpolar solvents initially has the character of a dipole interaction. As they approach one another, the two dipoles (ylide and aldehyde) orient themselves so that, with maximum attraction of the dipoles, repulsion between the substituents R and R′ is minimal, which ultimately leads to formation of the trans-olefin. The same result will be obtained if the reaction begins with attack by ylidic phosphorus on the oxygen of the carbonyl group (Scheme 1).

Scheme 1: reaction scheme showing dipolar orientation of ylide and aldehyde leading to Ph3PO + trans-olefin

Figure 1: Scheme 1: reaction scheme showing dipolar orientation of ylide and aldehyde leading to Ph3PO + trans-olefin

Scheme 2: reaction scheme involving Lewis base B (or B—), intermediates II-IV, leading to Ph3P=O and cis-olefin

Figure 2: Scheme 2: reaction scheme involving Lewis base B (or B—), intermediates II-IV, leading to Ph3P=O and cis-olefin

Scheme 1

In the presence of amines, the polarity of the C—P bond decreases as a result of interaction of the unshared electron pair of the nitrogen atom with phosphorus, which tends to complete its electron octet to a decet. An analogous (but still stronger) interaction occurs when bromide or iodide ions (but not chloride) are present in the reaction mixture. Under these conditions phosphorus becomes less electrophilic and at the same time sterically less accessible, as a result of which the reaction can no longer proceed according to Scheme 1, but begins with nucleophilic attack on the carbon of the carbonyl group (Scheme 2, where B is a Lewis base); moreover, the mutual orientation of the reactants in the prereaction complex (II) is determined no longer by attraction of the dipoles, but by steric interaction between the substituents R and R$'$. It is easy to see that in this case an orientation of the reactants is possible in the prereaction complex (II) that leads to the erythro configuration of the intermediate complex (III); conversion of the latter into the intermediate four-membered compound (IV) is associated with rotation about the C—C bond, which ultimately leads to formation of the cis-olefin.

Scheme 2

The course of the reaction according to Scheme 2 rather than Scheme 1 could also be a consequence of interaction of cations with the negative end of the carbonyl dipole. However, the fact that in the presence of LiCl mainly the trans-isomer is formed shows that interaction of the Li$^+$ ion with the carbonyl dipole does not play an essential role, and that the stereochemical course of the reaction depends chiefly on the interaction of the added substances with the ylide. The presence of such interaction is indicated by significant changes in the IR spectrum of ylide (I) upon addition of LiI to its benzene solution (see Fig. 1). It is also confirmed by complete or partial decolorization of the dark-red benzene solution of this ylide in the presence of amines, LiBr, or LiI, the colorless compounds obtained being

do not lose the ability to react with aldehydes with formation of olefins. In the case of LiBr and LiI, decolorization of the ylide occurs already upon addition of an equimolecular amount of the halide salts, which indicates the formation of a

Fig. 1. IR spectrum of ylide (I) in benzene: 1 —in the absence of LiI; 2 —in the presence of 1 mole of LiI per 1 mole of ylide (see footnote *** to Table 1)

Figure 3: Fig. 1. IR spectrum of ylide (I) in benzene: 1 —in the absence of LiI; 2 —in the presence of 1 mole of LiI per 1 mole of ylide (see footnote *** to Table 1)

coordination compound. The formation of the latter involves Br^- and I^- ions, but not Li^+ and Cl^- ions, since addition of LiCl does not cause decolorization of the ylide. For decolorization of a benzene solution of the ylide under the influence of amines, a considerable excess of the latter is required (10 moles per 1 mole of ylide and more). At the same time, as the amount of amines increases, the relative yield of the cis isomer also increases (see Table 2). Such a dependence indicates that, in the case of amines, the equilibrium between the coordination complex (III) and its components is shifted toward the latter, or else that the products of interaction of the ylide with amines have the character of solvates.

Fig. 1. IR spectrum of ylide (I) in benzene: **1** —in the absence of LiI; **2** —in the presence of 1 mole of LiI per 1 mole of ylide (see footnote *** to Table 1)

The influence of substances of the same type on increasing the relative yield of the cis isomer becomes stronger with increasing nucleophilicity, increasing in the series Cl, Br, I or ethyl *p*-aminobenzoate, aniline, phenylhydrazine, N,N-dimethyl-*p*-phenylenediamine (see Table 3). At the same time, the influence of amines on the relative yield of the cis isomer depends very strongly on steric factors and decreases sharply in the series butylamine—diethylamine—triethylamine. As for dimethylformamide, its strong influence despite its slight basicity may be explained by the fact that in this case the ylidic phosphorus interacts not with nitrogen, but with the strongly polarized oxygen atom. The influence of oxygen-containing compounds on increasing the relative yield of the cis isomer is also dependent on their nucleophilicity and increases in the series ether —tetrahydrofuran—alcohol (ethoxide ion)—dimethylformamide (see Table 1).

Table 2

Ratio of cis- and trans-β-ethylstyrenes when carrying out the Wittig reaction in benzene in the presence of various amounts of aniline*

Number of moles of aniline per 1 mole of ylide	1	4	6	10
Ratio of cis- and trans-β-ethylstyrenes	28 : 72	40 : 60	45 : 55	51 : 49

* See footnote * to Table 1.

It is significant that amines, while promoting the formation of the cis isomer, at the same time slow the overall rate of the reaction (see Table 4). This phenomenon is explained by the fact that interaction of the ylide with amines makes the phosphorus atom sterically less accessible and at the same time increases its electron density, which hinders formation of the four-membered compound (IV). Recently, a similar decrease in reactivity was noted by Wittig (^{3}) when comparing betaines obtained from triaryl- and tripiperidylphosphoranes. Our data show that an increase in the stability of betaine (III) can be achieved not only by replacing stationary substituents at phosphorus with more nucleophilic ones (for example, a phenyl group by a methoxyphenyl or piperidyl group (^{3})), but also by introducing into the reaction mixture extraneous substances that are Lewis bases.

A similar influence of external factors on the ratio of cis and trans olefins was also observed by us in other cases, in particular, in the case of ···

···as the reaction of phosphor ylide (I) with benzaldehyde proceeds. Thus, to obtain the maximum relative yield of cis-olefins, it is recommended to carry out the Wittig reaction in the presence of Br^- or J^- ions in a polar solvent, preferably in dimethylformamide.

Table 3

Effect of amines of different basicity on the steric direction of the Wittig reaction in benzene*

Amine**	K_B (in water)	Ratio of cis- and trans-β-ethylstyrenes
N,N-dimethyl-*n*-phenylenediamine	$3.9 \cdot 10^{-8}$ (K_{B2} $8 \cdot 10^{-12}$) (4)	62 : 38
Phenylhydrazine	$1.6 \cdot 10^{-5}$ (5)	54 : 46
Aniline	$3.8 \cdot 10^{-10}$ (5)	51 : 49

Amine**	K_B (in water)	Ratio of cis- and trans-β-ethylstyrenes
Ethyl ester of *n*-aminobenzoic acid	$6 \cdot 10^{-12}$ (6)	44 : 56
Butylamine	$4.1 \cdot 10^{-4}$ (5)	43 : 57
Diethylamine	$9.6 \cdot 10^{-4}$ (5)	32 : 68
Triethylamine	$5.65 \cdot 10^{-4}$ (5)	24 : 76
Piperidine	$1.6 \cdot 10^{-3}$ (5)	36 : 64

* See footnote* to Table 1. ** 10 moles per 1 mole of ylide.

However, the steric direction of the reaction depends not only on external factors, but also on the structure of the ylide. Thus, the course of the reaction

$$C_6H_5CHO + Ph_3P^{\oplus}—C^{\ominus}HCO_2Et \rightarrow$$
$$\rightarrow C_6H_5CH = CHCO_2Et + Ph_3PO$$

is practically independent of the solvent and of the presence of Br^- ions, and in all cases leads predominantly to the trans-cinnamic ester.

The regularities set forth above were used by us for the stereospecific synthesis of natural higher unsaturated fatty acids with the cis-configuration of the double bond (7). In particular, by this method the total synthesis of cis-eicos-11-enoic and cetoleic acids was carried out for the first time.

Table 4

Yield of β-ethylstyrenes (total) and triphenylphosphine oxide under various conditions for carrying out the reaction of ylide (I) with propionaldehyde

Solvent	Additive	Reaction conditions	Yield, % $(C_6H_5)_3PO$	Yield, % β-ethylstyrene**
Benzene	–	20°, 20 h	88	68
Benzene	Aniline*	20°, 20 h	12	–
Benzene	Aniline*	20°, 20 h, then 80°, 3 h	31	23
Benzene	Aniline*	20°, 20 h, then 80°, 8 h	67	52
Dimethylformamide	LiJ***	20°, 20 h	38	31
Dimethylformamide	–	20°, 20 h	64	58

Solvent	Additive	Reaction conditions	Yield, % $(C_6H_5)_3PO$	Yield, % β-ethylstyrene**
Piperidine	–	20°, 20 h, then 80°, 8 h	26	18

* 4 moles per 1 mole of phosphor ylide. ** Yield determined by gas-liquid chromatography (see footnote* to Table 1). *** See footnote*** to Table 1.

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Note: Figure translations are in progress. See original paper for figures.