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OLEFIN SYNTHESIS WITH P(O)-ACTIVATED REAGENTS

A.V.Dombrovskii and V.A.Dombrovskii

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I. INTRODUCTION

When arylphosphoranes of the type $(Ar)_3P=CR'R''$ are allowed to act upon carbonyl compounds in the well-known Wittig reaction[1-4], various olefins with double bonds in specified positions may be obtained. This reaction has found wide application in practical organic synthesis. However, it has important limitations. Aldehydes with strongly electron-donor substituents near the reaction centre do not enter into this reaction[5]; phosphoranes containing electron-acceptor groups, for example CN, $COOC_2H_5$, etc., do not as a rule react with ketones under the usual conditions[6,7]. Attempts have been made to overcome these difficulties, for example by heating the components for many hours at 100–170° in sealed tubes[8], by carrying out the reaction in high-boiling solvents, etc.[9,10] However, severe reaction conditions of this kind have an unfavourable effect on the yields of unsaturated compounds and in many cases are altogether inadmissible. It has recently been observed[11,12] that benzoic acid catalyses the reaction of ethoxycarbonylethylenetriphenylphosphorane with ketones, but the region of applicability of this catalytic effect has not yet been determined.

However, perhaps the most important disadvantage of the Wittig reaction consists in the difficulty of isolating in the majority of cases the unsaturated product. In this connection development and modification of the Wittig reaction is of considerable interest.

In 1958 Horner and coworkers[13-20] discovered the P(O)-activated olefin synthesis in which olefins and their derivatives with various functional groups are obtained by the reaction of aldehydes and ketones with organophosphorus compounds containing the $P(O)-CH_2$ group. Phosphonate salts, phosphonate esters, and phosphine oxides have been suggested as P(O)-activated reagents for olefin synthesis. The formation of unsaturated compounds by P(O)-activated synthesis can be represented by the reaction

$$R'-CO-R''+R_2P(O)-CH_2-R'''\rightarrow R'R''C=CHR'''+R_2P(O)OH.$$

The use of P(O)-activated reagents for olefin synthesis has a number of advantages over the Wittig reaction. Such reagents are more reactive with respect to carbonyl compounds, in particular ketones, since they are more nucleophilic than phosphoranes. In a special study Horner and coworkers[21] compared olefin synthesis using P(O)-activated reagents with olefin synthesis using phosphoranes in the Wittig reaction, and showed that, in the presence of the competing reactions of $(C_6H_5)_3P=CH-C_6H_5$ and $(C_6H_5)_2P(O)-CH_2-C_6H_5$ with carbonyl compounds in proportions of 1:1:1, the olefin $C_6H_5-CH=CRR'$ forms preferentially from benzyldiphenylphosphine oxide. The isolation of olefins in P(O)-activated synthesis is much simpler, since the unsaturated compounds produced can be readily separated from the highly water-soluble alkali metal salts of alkylphosphoric acids, while in the Wittig reactions special procedures must be used to separate the olefin from triphenylphosphine oxide. Finally, compared with the Wittig reagents (phosphoranes), the reagents for P(O)-activated olefin synthesis are more readily accessible, since they can be obtained relatively simply by the well-known reactions of Arbuzov, Michaelis–Becker, and others.

Like the Wittig reactions, P(O)-activated olefin synthesis makes it possible to increase the length of the carbon chain and introduce C=C bonds in specified positions. The yields of the unsaturated compounds are usually much higher than in the Wittig reaction.

The present article reviews the publications concerned with P(O)-activated olefin synthesis.

II. REAGENTS FOR P(O)-ACTIVATED OLEFIN SYNTHESIS

The methods for the preparation of organophosphorus compounds containing the $P(O)-CH_2$ group, which is essential for P(O)-activated olefin synthesis, have been thoroughly developed and the chemical properties of these compounds have been investigated fairly completely. There exist many reviews and monographs on this problem (see, for example, Refs. 22–33).

The reagents usually employed for P(O)-activated olefin synthesis are esters (most often ethyl) of phosphonic acids $(RO)_2P(O)-CH_2-R'$ (R' may be an aliphatic or an aromatic radical or any functional group) and esters of β-oxophosphonic acids $(RO)_2P(O)-CH_2-CO-R'$ (R' is an alkyl or aryl residue). In many cases alkyldiphenylphosphine oxides, and in particular benzyldiphenylphosphine oxide, proved to be satisfactory reagents for this synthesis[34]. Phosphonoacetic ester, first obtained by Arbuzov and Dunin[35] in 1914, is very often used in P(O)-activated olefin synthesis; the method of synthesis of this ester was improved in subsequent work[36-40]. To introduce two ethylene bonds, reagents for P(O)-activated diolefin synthesis, containing two P(O) groups, are used. The substances which have become important for these purposes are the tetraethyl esters of bisphosphonic acids, $(C_2H_5O)_2P(O)-(CH_2)_n-P(O)(OC_2H_5)_2$ (n = 1–8) and $(C_2H_5O)_2P(O)-CH_2-X-CH_2-P(O)(OC_2H_5)_2$ (X is one or several vinylene groups or benzene rings), and also the very readily available so-called "dioxide" $(C_6H_5)_2P(O)-CH_2-P(O)(C_6H_5)_2$.[41,42]

The most important method for synthesising phosphonic esters is the Arbuzov reaction[43-46], discovered in 1905, which is known as the "Arbuzov rearrangement":

$$(RO)_3P+R'—Hal \rightarrow (RO)_2P(O)—R'+R—Hal \quad (Hal=Cl, Br, I).$$

The possibilities of the Arbuzov reaction have been by no means exhausted. New papers continue to appear in which organophosphorus compounds suitable for P(O)-activated olefin synthesis are described[47,48]. It should be noted that the limitations which may arise when the Arbuzov reaction is applied to α-halogeno-carbonyl compounds in connection with the so-called Perkow reaction or rearrangement[49-59] (see Lichtentahler's review[60]) are unimportant in the preparation of valuable reagents for P(O)-activated olefin synthesis in which the methylene group is between the P(O) and carbonyl groups. In 1965 Arbuzov and coworkers[61] established that the reactions of diphenylphosphinous acid with chloroacetone yield mixtures containing predominantly β-oxophosphonic esters together with unsaturated phosphate esters. On the other hand with ω-bromoacetophenone, the Arbuzov reaction takes place almost exclusively with good yields of diphenylphenylacylphosphine oxide which is a valuable reagent for P(O)-activated olefin synthesis. According to the communication of Imaev and coworkers[62], dialkylphosphonoacetophenones having the general formula $(RO)_2P(O)-CH_2-CO-C_6H_5$ (R = CH_3 and $n-C_3H_7-C_8H_{17}$) can be obtained, in high yield, by the Arbuzov reaction from ω-bromoacetophenone and a number of phosphite tri-esters (except the ethyl ester). Since the reaction of α-halogeno-aldehydes with trialkyl phosphites gives virtually no normal products of the Arbuzov reaction[60], Razumov and Moskva[63] used the acetal of bromoacetaldehyde to prepare phosphonoacetaldehyde in 70% yield:

$$CH_2Br—CH(OC_2H_5)_2+(C_2H_5O)_3P \rightarrow C_2H_5Br+$$

$$+(C_2H_5O)_2P(O)—CH_2—CH(OC_2H_5)_2 \xrightarrow[HCl]{H_2O} 2C_2H_5OH+(C_2H_5O)_2P(O)—CH_2—CHO.$$

The Michaelis–Becker reaction[64] is of practical importance for the synthesis of reagents for P(O)-activated olefin synthesis; it is based on the reaction of alkali metal salts of phosphite di-esters with organic compounds containing reactive halogen atoms:

$$(RO)_2P(O)Na+R'—Hal \rightarrow (RO)_2P(O)—R'+NaHal \quad (Hal=Cl, Br, I).$$

The applicability of the Michaelis–Becker method is somewhat reduced as a result of a number of side-reactions. In particular the reaction with α-halogeno-carbonyl compounds is as a rule anomalous, since esters of epoxyphosphonic acid are formed preferentially[65,66]. The method developed by Normant and coworkers[67] for the preparation of phosphonates containing a carbonyl group, by the reaction of sodium diethyl phosphite with ethers derived from the enols of α-halogeno-carbonyl compounds, is of interest in this connection. The ethers are readily obtained by the pyrolysis of α-halogeno-diacetals. The resulting normal products of the Michaelis–Becker reaction are converted after hydrolysis into β-diethylphosphonocarbonyl compounds:

$$R—CH_2—C(OR')_2—CH_2—X \rightarrow R'—OH+R—CH=C(OR')—CH_2—X \rightarrow$$
$$\xrightarrow[NaX]{+(C_2H_5O)_2P(O)Na} R—CH=C(OR')—CH_2—P(O)(OC_2H_5)_2 \rightarrow$$
$$\xrightarrow[-R'—OH]{+H_2O} (C_2H_5O)_2P(O)—CH_2—CO—CH_2—R.$$

A number of β-oxophosphonic esters have been prepared by this method[68].

The third fundamentally important method for the preparation of organophosphorus compounds of various complexity containing $P(O)-CH_2$ groups consists in the addition of dialkylphosphorous acids and acid esters of alkyl- and aryl-phosphonous acids to ethylenic hydrocarbons and their various derivatives. This method has been proposed and largely developed by Pudovik and coworkers; data concerning the preparation of many compounds suitable for P(O)-activated olefin synthesis are presented in Pudovik's review[26]. Subsequently a number of papers were published with data on the synthesis of organophosphorus compounds of this kind using unsaturated compounds[69-75].

The hydrogen atoms in the methylene group of organophosphorous compounds containing the $P(O)-CH_2$ unit are reactive. This reactivity is due to the effect of the adjacent P(O) group involving the semipolar phosphorus–oxygen bond[76-79], with the negative charge located on the oxygen atom, i.e. $\rangle P=O \leftrightarrow P^+-O^-$. Since 1929 Arbuzov showed[80,81] that the hydrogen atoms of the methylene group in phosphonoacetic and alkylphosphonic esters, etc. are similar to those in acetoacetic ester, being readily replaced by alkali metals. In some cases the hydrogen atoms of the methylene group are so reactive that on reacting with a Grignard reagent they cause the evolution of the hydrocarbon and form an organophosphorus–magnesium compound[82]; the reaction with phenyl-lithium is similar[13] and in the Chugaev–Tserevitinov [Zerevitinov] reaction the evolution of active hydrogen reaches quantitative yields[15]. The mobility of the hydrogen atoms of the methylene group is also revealed in Claisen condensation with carboxylic acid esters[15,83,84], in condensation of the crotonic acid type with aldehydes[42,85,86], and in addition reactions to double carbon–carbon bonds in electrophilic unsaturated compounds[26].

III. MECHANISM OF P(O)-ACTIVATED OLEFIN SYNTHESIS

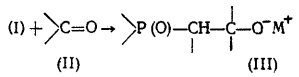
In practice the P(O)-activated olefin synthesis is carried out under mild conditions, often with slight and brief heating of the initial reactants in a suitable solvent (dimethylformamide, 1,2-dimethoxyethylene, cyclohexane, benzene, toluene). It has been found that in ether and anisole the olefin yields are low, while in chlorobenzene the reaction virtually does not occur at all[20]. Usually the condensing reagent and then the carbonyl component are added to a solution of a P(O)-activated reagent for olefin synthesis. At the end of the reaction the mixture is treated with water which dissolves the phosphonate salts, the olefins being isolated from the organic layer.

In a special investigation devoted to the study of the mechanism of the P(O)-activated olefin synthesis, Horner and coworkers[20] concluded that the reaction involves three stages, from each of which it is possible to isolate and characterise the intermediate products in some cases. In the first stage the reactive hydrogen atom of the methylene group of the P(O)-activated reagent is replaced by a metal to give a *C*-metallated compound (I):

$$\rangle P(O)—\underset{|}{CH_2}+M^+ \rightarrow \rangle P(O)—\underset{|}{\overset{-}{C}H}M^+ + {}^1/_2H_2 \quad (M=Li, Na, K).$$
$$\text{(I)}$$

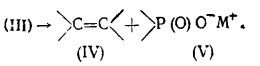
When alkali metal hydrides, amides, or alkoxides and metal alkyls or metal aryls are used as metallating agents, hydrogen, ammonia, alcohols, or hydrocarbons are evolved respectively. In the second stage compound (I), which behaves as a usual organometallic compound, reacts with the

carbonyl compound (II) to form a β-hydroxy-derivative (III) of the P(O)-compound:



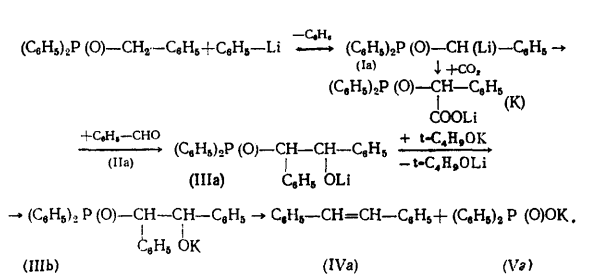
Cases of this type of condensation in which compounds of type (III) were isolated, have been described [87-93].

In the third stage compound (III) decomposes into an olefin (IV) and a phosphorus-containing acid anion (V):

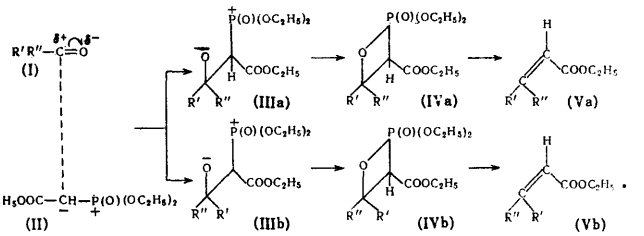


The third stage is due to the characteristic high affinity of phosphorus for organic oxygen (carbonyl oxygen) [94,95]. On the basis of the available data concerning the mechanism of the Wittig reaction between alkylidenephosphoranes and carbonyl compounds [2,3], the similarity of this reaction to P(O)-activated olefin synthesis, and the similarity of the electronic structures of P(O)-activated reagents for such synthesis, Wadsworth and Emmons [96] proposed a mechanism for P(O)-activated olefin synthesis similar to that described above.

The stages of the P(O)-activated olefin synthesis described above are to some extent hypothetical, since in most cases the intermediate compounds (I) and (III) cannot be isolated or identified. The stability of the metallated compound (I) and the hydroxy-derivative (II) of the P(O)-compound has been found to depend significantly on the nature of the alkali metal. When lithium metallating agents are used, compound (I) can be identified and compound (III) can be isolated [15,19]. Using the synthesis of stilbene as an example, Horner and coworkers [15] showed that stilbene forms in the reaction between benzyldiphenylphosphine oxide and benzaldehyde in the presence of lithium-, sodium-, and potassium-containing condensing agents. When sodium or potassium derivatives are used, the intermediates (I) and (III) cannot be detected. However, in the presence of phenyl-lithium the *C*-lithium compound (Ia) formed in the first stage was identified by its reaction with carbonic acid which yields a carboxylic acid (K). In the second stage of the reaction [after the addition of benzaldehyde to a solution of compound (Ia)] the β-hydroxy derivative (IIIa) of the P(O)-compound was isolated; on heating in toluene with potassium t-butoxide, it was converted into stilbene (IVa) and a salt of diphenylphosphinic acid (Va). It is assumed that the lithium compound (IIIa) is initially converted into an unstable potassium derivative (IIIb) which then decomposes into substances (IVa) and (Va). This can be represented as follows:



Yanovskaya and Kucherov [9] studied the stereochemistry of P(O)-activated olefin synthesis and established, on the basis of numerous experimental data, that the reaction of, for example, aldehydes with diethyl ethoxycarbonylmethylphosphonate is stereospecific and yields only the *trans*-isomers. Later these workers showed that sterically hindered ketones virtually do not enter into this reaction. Sterically unhindered ketones form with P(O)-activated reagents for olefin synthesis mixtures of *cis*- and *trans*-isomers. The absence of stereospecificity is the principal difference between the behaviour of aldehydes and ketones in this reaction. This can be explained in terms of the latest data on the mechanism of the Wittig reaction [97-100] and Yanovskaya and Kucherov's interpretation [9] of the stereospecificity of the formation of unsaturated compounds from phosphoranes and aldehydes and ketones. In P(O)-activated olefin synthesis, the formation of geometrical isomers can be represented by the scheme given below. As in the Wittig reaction, the nucleophilic attack by the carbon atom of the P(O)-activated reagent (II) for olefin synthesis on the carbon atom of the carbonyl compound (I) can result in the formation of *cis*- and *trans*-betaines (IIIa) and (IIIb) which lead to *cis*- and *trans*-olefins (Va) and (Vb) via the cyclic transition states (IVa) and (IVb):



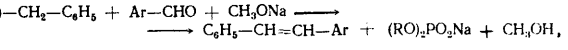
In conformity with Cramm's rule [101], with aldehydes (R′ = H) the formation of the betaine (IIIb) occurs preferentially, which results in *trans*-olefins. With ketones having unbranched R′ and R″ radicals, the formation of (IIIa) and (IIIb) is equally likely, which implies an equal probability of the formation of the *cis*- and *trans*-isomers.

IV. SYNTHESIS OF OLEFINS

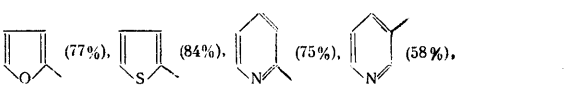
The main application of the method of P(O)-activated olefin synthesis has been to prepare olefins of various complexities with aromatic substituents and some of their heterocyclic analogues and also unsaturated acids and their derivatives.

1. Mono-Olefins and Their Hydrocarbon Derivatives

Stilbene and its analogues are obtained on condensation of carbonyl compounds with various condensing agents and P(O)-activated reagents for olefin synthesis. Stilbene, 2-stilbazole, 2-styrylfuran, and 2-styrylthiophen are obtained most simply on slight and brief heating of benzaldehyde or the corresponding heterocyclic aldehyde with diethyl benzylphosphonate in dimethylformamide in the presence of sodium methoxide [102]:



where Ar = C_6H_5 (yield 85%),



(here and below R = C_2H_5).

3-Stilbazole was obtained in the same way [15,20]. Stilbene can be synthesised in high yields also by the condensation of benzaldehyde with benzyldiphenylphosphine oxide [15,18], and if instead of benzaldehyde acetophenone is used, the product is α-methylstilbene [15]. By selecting suitable reactants with various substituents in the benzene rings, it is possible to obtain stilbenes with substituents in specified positions, for example [20]:

$$(RO)(C_6H_5)P(O)-CH_2-C_6H_4OCH_3\text{-}p + p\text{-}ClC_6H_4-CHO \longrightarrow (RO)(C_6H_5)P(O)OH + p\text{-}CH_3OC_6H_4-CH=CH-C_6H_4Cl\text{-}p.$$

Horne and coworkers [16,18] described two interesting methods for the preparation of stilbenes and their analogues by P(O)-activated olefin synthesis. In the first method triphenylphosphine oxide is heated in succession with sodium hydride and an aromatic aldehyde. This results in the formation of an olefin, benzene, and sodium diphenylphosphinate:

$$2(C_6H_5)_3P=O + 2NaH + 2Ar-CHO \longrightarrow Ar-CH=CH-Ar + 2(C_6H_5)_2PO_2Na + C_6H_6,$$

where Ar = C_6H_5, p-ClC_6H_4, α-$C_{10}H_7$, 9-$C_{14}H_{11}$ (from anthracene-9-aldehyde). If benzophenone is used instead of aldehydes, the product is tetraphenylethylene [17].

It was established that the olefin forms in stages. Initially when triphenylphosphine oxide is fused with sodium hydride (at about 200°), the products are benzene and sodium diphenylphosphine oxide (I), which then reacts with the added aldehyde, yielding the alkoxide of (α-hydroxybenzyl)diphenylphosphine oxide (II). The latter reacts with compound (I) and gives sodium diphenylphosphinate and a C-metallated derivative of benzyldiphenylphosphine oxide (III). Finally, compound (III) reacts with a second molecule of the aldehyde to form the olefin and a second molecule of sodium diphenylphosphinate. The reactions can be expressed as follows:

$$(C_6H_5)_3P=O + NaH \longrightarrow C_6H_6 + (C_6H_5)_2P(O)Na, \quad (I)$$
$$(I) + Ar-CHO \rightleftarrows (C_6H_5)_2P(O)CH(ONa)-Ar, \quad (II)$$
$$(I) + (II) \longrightarrow (C_6H_5)_2P(O)ONa + (C_6H_5)_2P(O)CH(Na)-Ar, \quad (III)$$
$$(III) + Ar-CHO \longrightarrow (C_6H_5)_2P(O)ONa + Ar-CH=CH-Ar.$$

In the second method stilbenes are obtained on auto-oxidation of derivatives of phosphine oxides or phosphonic esters. For example, benzyldiphenylphosphine oxide in benzene solution is mixed or shaken with potassium t-butoxide in an atmosphere of oxygen, the reaction mixture is then treated with water, and stilbene is isolated from the benzene layer. In general, stilbene synthesis can be represented thus:

$$2(C_6H_5)_2P(O)-CH_2-Ar + t\text{-}C_4H_9OK \xrightarrow{O_2} Ar-CH=CH-Ar + 2(C_6H_5)_2P(O)OK + t\text{-}C_4H_9OH,$$

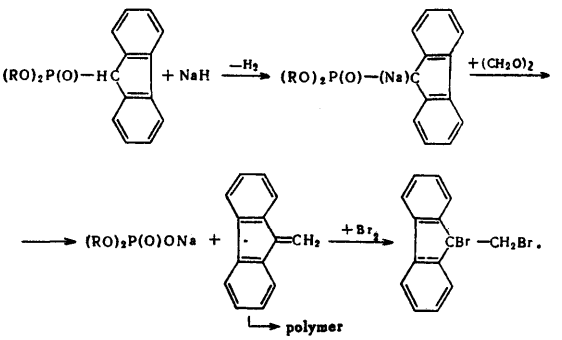
where Ar = C_6H_5, 3,4-$Cl_2C_6H_3$, and α-$C_{10}H_7$ (yield about 90%).

The study of this reaction showed [18] that the first stage involves the formation of a C-metallated phosphine oxide which is readily oxidised by molecular oxygen to a hydroxy-derivative, like the usual organometallic compounds. It is assumed that the oxidation goes via a stage in which a peroxy-compound is formed. As already mentioned, O-metallated oxides of α-hydroxyphosphines can break down reversibly into a phosphinic acid salt and a carbonyl compound [17], which immediately reacts with the C-metallated derivative of phosphine oxide to give the final reaction product — the olefin and the phosphinic acid salt. The various stages of the process can be represented in the following way:

$$(C_6H_5)_2P(O)-CH_2-Ar + t\text{-}C_4H_9OK \longrightarrow t\text{-}C_4H_9OH + (C_6H_5)P(O)CH(K)-Ar \xrightarrow{+O_2} (C_6H_5)_2P(O)-CH(O-OK)-Ar \xrightarrow{+(C_6H_5)_2P(O)CH(K)-Ar} \longrightarrow 2(C_6H_5)_2P(O)-CH(OK)-Ar \rightleftarrows 2(C_6H_5)_2P(O)K + 2Ar-CHO,$$
$$(C_6H_5)_2P(O)-CH(K)-Ar + Ar-CHO \longrightarrow Ar-CH=CH-Ar + (C_6H_5)_2P(O)OK.$$

It has been found that, when lithium-containing metallating agents are used, it is possible to isolate O-lithium hydroxy-derivatives, which are stable unlike the O-sodium or O-potassium derivatives, since they have a lower affinity for carbonyl oxygen.

Apart from stilbenes, mono-olefins such as 1,1-diphenylethylene [13], 1-methyl-2,2-diphenylethylene [13,15], 2,2-diphenyl-1-n-propylethylene, 1-ethyl-1-methyl-2-phenylethylene [15], benzylidenecyclohexane [15,20], and triphenylethylene [13,15,18,20,96] have been obtained by the P(O)-activated synthesis. An interesting case of the P(O)-activated synthesis of mono-olefins is the reaction of diethyl fluorenylphosphonate with paraformaldehyde in the presence of sodium hydride [96]:



Since the resulting 9-methylenefluorene rapidly polymerises (particularly in the absence of solvent), the olefin formed is converted into the dibromo-derivative without being isolated first.

2. Diene and Polyene Hydrocarbons

P(O)-activated olefin synthesis has been successfully used to prepare unsaturated compounds containing two and more multiple carbon–carbon bonds. On combining together in the condensation process P(O)-activated reagents for mono- and di-olefin synthesis with mono- or di-carbonyl compounds, olefins with various degrees of unsaturation are obtained. Thus the reaction of diethyl benzylphosphonate with cinnamaldehyde yields 1,4-diphenylbuta-1,3-diene [20,96] and the reaction of benzyldiphenylphosphine with benzil gives 1,2,3,4-tetraphenylbuta-1,3-diene: [15]

$$(RO)_2P(O)-CH_2-C_6H_5 + C_6H_5-CH=CH-CHO \xrightarrow{t\text{-}C_4H_9OK} \longrightarrow (RO)_2P(O)OK + C_6H_5-CH=CH-CH=CH-C_6H_5\ (80\%),$$
$$2(C_6H_5)_2P(O)-CH_2-C_6H_5 + C_6H_5-CO-CO-C_6H_5 \xrightarrow[(\text{or } NaH)]{t\text{-}C_4H_9OK} \longrightarrow 2(C_6H_5)_2P(O)OK + C_6H_5-CH=C(C_6H_5)-C(C_6H_5)=CH-C_6H_5\ (50\%).$$

Phenyl-substituted polyenes with a conjugated system of double bonds are formed when bis-P(O)-activated reagents for olefin synthesis and aliphatic-atomatic aldehydes or

ketones are used in the reaction. For example, 1,10-diphenyldeca-1,3,5,7,9-pentaene and 1,1,6,6-tetraphenylhexatriene are formed in the following process [20]:

$$(RO)_2P(O)-CH_2-CH=CH-CH_2-P(O)(OR)_2 + C_6H_5-CH=CH-CHO \longrightarrow$$
$$\xrightarrow{t\text{-}C_4H_9OK} C_6H_5-\overset{(A)}{(CH=CH)_3}-C_6H_5 + 2(RO)_2P(O)OK,$$
$$(A) + (C_6H_5)_2C=O \longrightarrow (C_6H_5)_2C=CH-CH=CH-CH=C(C_6H_5)_2 + 2(RO)_2P(O)OH.$$

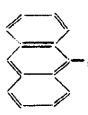
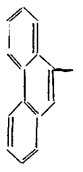
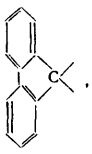
Aliphatic-aromatic dienes with methylene bridges which interrupt the conjugation chain are obtained when the oxides of n-alkylene-$\alpha\omega$-bisdiphenylphosphines are condensed with carbonyl compounds. For example [20]:

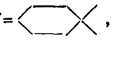
$$(C_6H_5)_2P(O)-(CH_2)_n-P(O)(C_6H_5)_2 + 2(C_6H_5)_2C=O \xrightarrow{t\text{-}C_4H_9OK}$$
$$\longrightarrow 2(C_6H_5)_2P(O)OK + (C_6H_5)_2C=CH-(CH_2)_{n-2}-CH=C(C_6H_5)_2 \quad (n=2, 4, 6).$$

The P(O)-activated synthesis has proved particularly valuable for the preparation of olefins such as distyryls [20], which are difficult to prepare otherwise and which have found application recently as light-protective media, as stabilisers for polymers and polyolefins, and as optical bleaching agents for high-molecular compounds. Thus the condensation of tetraethyl (*p*-phenylenedimethylene)-bisphosphonate (TEPP) with various aldehydes and ketones in dimethylformamide in the presence of sodium methoxide [103] or potassium t-butoxide [20] gives distyryls of various complexity in yields of 65–90%:

$$(RO)_2P(O)-CH_2-C_6H_4-CH_2-P(O)(OR)_2 + 2R'R''C=O \rightarrow$$
$$\rightarrow 2(RO)_2P(O)OH + R'R''C=HC-C_6H_4-CH=CR'R'',$$

where R′ = H and R″ = C_6H_5, R′ = H and R″ = *p*-$O_2NC_6H_4$, R′ = H and R″ = *p*-$(CH_3)_2NC_6H_4$, R′ = H and R″ = *p*-C_6H_5-C_6H_4,

R′ = H and R″ = , R′ = H and R″ = , R′ = R″ = ,

R′ = H and R″ = α-$C_{10}H_7$, R′ = H and R″ = , R′ = R″ = , and R′ = R″ = C_6H_5.

1,4-Distyryl is also obtained on condensing TEPP with terephthalic aldehyde, and the reaction of the same bis-P(O)-activated reagent for olefin synthesis with cinnamaldehyde gives an 84% yield of 1,4-di-(4-phenylbutadienyl)-benzene [20,96]. The same olefin is also the product of the condensation of cinnamaldehyde and (*p*-phenylenedimethylene)bis(diphenylphosphine oxide) [20]:

$$(RO)_2P(O)-CH_2-C_6H_4-CH_2-P(O)(OR)_2 + 2C_6H_5-CH=CH-CHO \rightarrow$$
$$\rightarrow 2(RO)_2P(O)OH + C_6H_5-(CH=CH)_2-C_6H_4-(CH=CH)_2-C_6H_5.$$

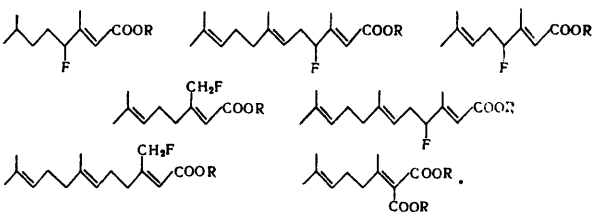
3. Synthesis of Aliphatic and Aliphatic-Aromatic Unsaturated Acids

P(O)-Activated olefin synthesis is a good method for preparing derivatives of unsaturated aliphatic and aliphatic-aromatic acids. This method has been used to synthesise quite a large number of esters and nitriles of $\alpha\beta$-unsaturated acids. The readily available (diethyl phosphono)acetic ester is usually employed as the P(O)-activated reagent for this type of olefin synthesis. The reaction is carried out in a suitable solvent (dimethylformamide, toluene, and others) in the presence of condensing agents (alkali metal alkoxides, metallic sodium, etc.). The reaction can be represented in the following general form:

$$(RO)_2P(O)-CH_2-COOR + R'R''C=O \rightarrow R'R''C=CH-COOR + (RO)_2P(O)OH.$$

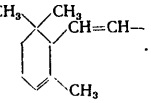
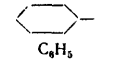
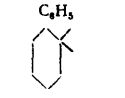
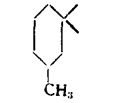
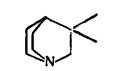
The Table gives the yields of the esters prepared in this way.

The P(O)-activated olefin synthesis with participation of phosphonoacetic ester and $\alpha\beta$-unsaturated ketones containing atoms or groups of atoms with pronounced electron-acceptor properties takes place particularly smoothly. Ketones of this kind have yielded a number of ethyl esters of γ-fluoro-substituted and other $\alpha\beta$-unsaturated acids [11]. For example:



Wadsworth and Emmons [96] proposed a simple method for the preparation of esters of α-substituted $\alpha\beta$-unsaturated acids in which a number of consecutive reactions are carried out in a single apparatus without isolating the intermediates. Phosphonoacetic ester in solution in 1,2-dimethoxyethylene

TABLE. Ethyl esters of $\alpha\beta$-unsaturated acids (R′R″C=CH-COOR) obtained from aldehydes and ketones by P(O)-activated olefin synthesis.

From aldehyde			From ketones			
R′ (R″=H)	yield, %	refs.	R′	R″	yield, %	refs.
CH_3	39	9	CH_3	CH_3	61	96,104
CCl_3	50	96	CH_3	CH_2Cl	58	105
			CH_3	CH_2Br	20	105
n-C_3H_7	67	104,106	CH_3	C_2H_5	58	9
$(CH_3)_2CH$	74	9,96	CH_3	$C(CH_3)_3$	15	9
$CH_2=CH$	14	9	CH_3	n-C_7H_{15}	43	9
			CH_3	n-C_9H_{21}	64	107
$CH_3-CH=CH-$	56	9,104	CH_3	$(C_2H_5O)_2CH-CH-$	31	108
$CH_3-(CH=CH)_2-$	53	9	CH_3	$(CH_3)_2C=CH-CH_2-CH_2-$ $-CH=C(CH_3)-CH_2-$	54	9,108
$CH_3-(CH=CH)_3-$	75	9	CH_3		44	9
$(CH_3O)_2CH-$	63	9	CH_3		35	109
C_6H_5	84	96,104, 106	CH_3	C_6H_5	32	96,106
p-$O_2NC_6H_4-$	62	106	CH_3	*p*-$C_2H_5-C_6H_4-$	51	106
p-$(CH_3)_2C_6H_4$	81	106	C_2H_5	C_2H_5	64	96,107
$C_6H_5COO-CH=CH-$	72	9	C_6H_5	C_6H_5	87	104,107
$C_6H_5COO-(CH=CH)_2-$	51	9			70	106,107
$C_6H_5COO-(CH=CH)_3-$	60	9			70	107
	71	106			100	110

is successively metallated with sodium hydride, the resulting alkyl derivative is metallated again and finally condensed with the carbonyl compound. The preparation of the ester of α-n-butylacrylic acid (yield 60%), for example, can be described thus:

$$(RO)_2P(O)-CH_2-COOR + NaH \xrightarrow{-H_2} (RO)_2P(O)-CH(Na)-COOR \rightarrow$$

$$\xrightarrow[-NaBr]{+R'-Br} (RO)_2P(O)-CHR'-COOR \xrightarrow[-H_2]{+NaH} (RO)_2P(O)-CR'(Na)-COOR \longrightarrow$$

$$\xrightarrow{+CH_2=O} (RO)_2P(O)ONa + CH_2=C(R')-COOR \quad (R' = n\text{-}C_4H_9).$$

If after the first metallation stage bromine is introduced into the reaction mixture instead of an alkyl halide, the final reaction product is the ester of an α-bromo-αβ-unsaturated acid. For example, α-bromo-β-isopropylacrylic acid is obtained in this way (yield 65%):

$$(RO)_2P(O)-CH(Na)-COOR + Br_2 \rightarrow NaBr + (RO)_2P(O)-CH(Br)-COOR \longrightarrow$$

$$\xrightarrow{+NaH,\ (CH_3)_2CH-CHO} (CH_3)_2C=C(Br)-COOR + (RO)_2P(O)ONa.$$

If instead of bromine, iodine is used and the resulting iodophosphonate is further metallated and then condensed with a carbonyl compound, acetylene derivatives are obtained. For example, ethyl phenylpropiolate can be synthesised in this way (yield about 60%):

$$(RO_2)P(O)CHI-COOR + 2NaH + C_6H_5-CHO \rightarrow$$

$$\rightarrow C_6H_5-C\equiv C-COOR + H_2 + NaI + (RO)_2P(O)ONa.$$

The carbonyl groups of ketens can take part in P(O)-activated olefin synthesis as well as those of aldehydes and ketones. Under the conditions described above, (diethyl phosphono)acetic ester reacts with ethyl(phenyl)keten to give 1-ethoxycarbonyl-3-ethyl-3-phenylallene [96]:

$$(RO)_2P(O)-CH_2-COOR + NaH + C_6H_5(C_2H_5)C=C=O \rightarrow$$

$$\rightarrow H_2 + (RO)_2PO_2Na + C_6H_5(C_2H_5)C=C=CH-COOR.$$

Under these conditions ethyl levulinate reacts via its ketone group with (diethyl phosphono)acetic ester, forming 1,2-diethoxycarbonyl-2-methylbut-1-ene in good yield:

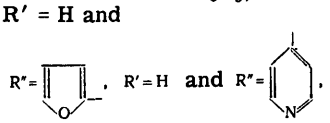
$$(RO)_2P(O)-CH_2-COOR + CH_3-CO-CH_2-CH_2-COOR + NaH \rightarrow$$

$$\rightarrow H_2 + CH_3-CH=C(COOR)-CH_2-CH_2-COOR + (RO)_2P(O)ONa.$$

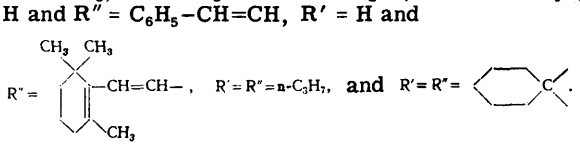
P(O)-Activated olefin synthesis has also proved valuable for the preparation of αβ-unsaturated acid nitriles which have recently become important in organic synthesis as intermediates in the synthesis of dyes, pharmaceutical preparations, and others. The nitriles are synthesised by condensing carbonyl compounds with the readily available diethyl ester of cyanomethylphosphonic acid. The following nitriles of αβ-unsaturated acids have been obtained in this way [96,103-105]:

$$(RO)_2P(O)-CH_2-CN + R'R''C=O \rightarrow R'R''C=CH-CN + (RO)_2P(O)OH,$$

where R′ = R″ = H, R′ = H and R″ = CH_3, R′ = H and R″ = $CH_2=C(CH_3)$, R′ = H and R″ = C_6H_5, R′ = H and R″ = 2,6-$Cl_2C_6H_3$, R′ = H and



R′ = R″ = CH_3, R′ = CH_3 and R″ = CH_2Cl, R′ = R″ = C_6H_5, R′ = H and R″ = C_6H_5–CH=CH, R′ = H and



It has been found that the yields of the nitriles are quite satisfactory (60–80%) and the reaction takes place under mild conditions (at 20–50°) in various solvents (alcohols, toluene, xylene, dioxan, dimethylformamide) in the presence of different condensing agents (alkali metal hydroxides and alkoxides, the amides of alkali and alkaline-earth metals, and organic bases).

4. Isoprenoids and Compounds Related to Natural Substances

P(O)-Activated olefin synthesis can be used to prepare αβ-unsaturated carbonyl compounds. Thus the condensation of the ethyl acetal of (diethyl phosphono)acetaldehyde with benzaldehyde gives the diacetal of cinnamaldehyde which is smoothly hydrolysed to cinnamaldehyde itself [104]:

$$(RO)_2P(O)-CH_2-CH(OC_2H_5)_2 + C_6H_5-CHO + NaH \rightarrow$$

$$\rightarrow H_2 + (RO)_2P(O)ONa + C_6H_5-CH=CH-CH(OC_2H_5)_2 \xrightarrow[H^+]{H_2O} C_6H_5-CH=CH-CHO + 2C_2H_5OH.$$

The acetal $(RO)_2CH-CH_2-C(CH_3)=CH-COOR$ was obtained similarly [108] from phosphonoacetic ester and the diethyl acetal of acetoacetaldehyde.

Pommer [112] showed that P(O)-activated olefin synthesis gives better results in the preparation of carotenoids and related compounds than the Wittig olefin synthesis. Thus the synthesis of the dimethyl ester of crocetin (VI) takes place via a series of consecutive reactions, two of which are P(O)-activated condensations involving olefin synthesis. For this purpose, the tetraethyl ester of but-2-ene-1,4-diphosphonic acid (I) (yield 90%) is first prepared from 1,4-dichlorobut-2-ene and triethyl phosphite by the Arbuzov reaction and then condensed with two moles of methylglyoxal acetal (II). The resulting bisacetal of the C_{10} aldehyde (III) is hydrolysed to the C_{10} aldehyde (IV) itself. The latter is then condensed with the diethyl ester of 3-methoxycarbonylbut-2-enylphosphonic acid (V)† [the ester (V) is obtained by the Arbuzov reaction from the methyl ester of γ-bromotiglic acid and triethyl phosphite] to give the ester of crocetin (VI); the general mechanism of the synthesis can be represented by the following reactions:

$$(RO)_2P(O)-CH_2-CH=CH-CH_2P(O)(OR)_2 + 2(RO)_2CH-\underset{\displaystyle CH_3}{\underset{|}{C}}=O \rightarrow$$

(I) (II)

$$\xrightarrow{2CH_3ONa} 2(RO)_2P(O)ONa + (RO)_2CH-C(CH_3)=CH-CH=CH-CH=C(CH_3)-CH(OR)_2 \longrightarrow$$

(III)

$$\xrightarrow[HCl]{H_2O} 4C_2H_5OH + O=CH-C(CH_3)=CH-CH=CH-CH=C(CH_3)-CH=O \quad (IV).$$

$$(IV) + 2H_3COOC-C(CH_3)=CH-CH_2-P(O)(OR)_2 \xrightarrow{+2CH_3ONa}$$

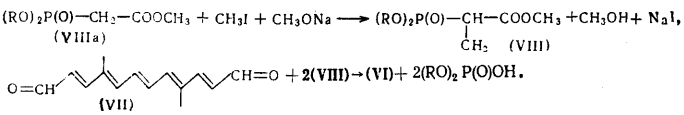
(V)

$$\longrightarrow 2(RO)_2P(O)ONa + H_3COOC\text{–}(CH=CH)_4\text{–}C(CH_3)=CH\text{–}COOCH_3 \quad (VI).$$

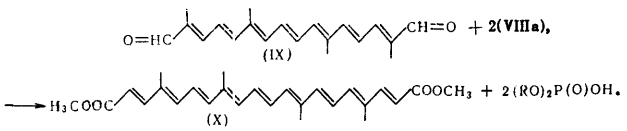
The same derivative of crocetin (VI) is obtained on condensing the C_{14} dialdehyde (VII) with the diethyl ester of α-methoxycarbonylethylphosphonic acid (VIII) which in turn is obtained by methylating the ester (VIIIa). Thus this method of the

† The C_{10} diol $CH_2OH-C(CH_3)=CH-CH=CH-CH=C(CH_3)-CH_2OH$ was obtained similarly from compound (I) and hydroxyacetone [112].

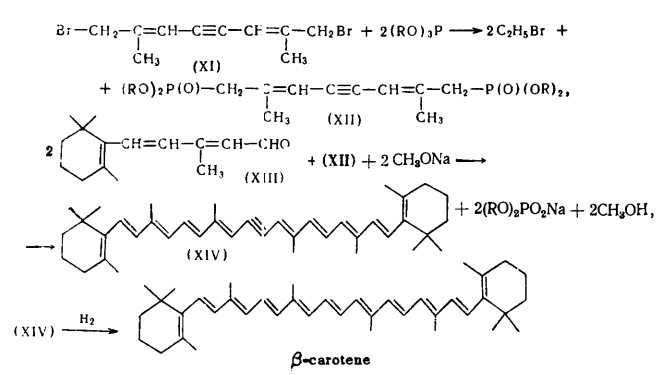
preparation of the diester (VI) can be described as follows:



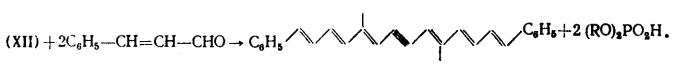
Similarly the condensation of the C_{20} dialdehyde (IX) with the ester (VIIIa) gave methylbixin (X):



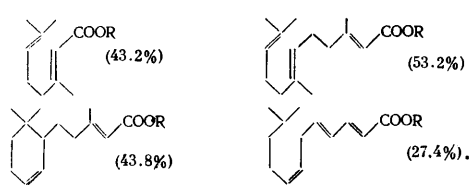
β-Carotene, the most important and most widely distributed plant pigment, was also prepared by P(O)-activated olefin synthesis. Pommer showed[112] that this method of synthesising β-carotene is superior, as regards the small number of stages and the availability of the starting materials, to all earlier procedures, including that involving the Wittig reaction[3]. The diethyl ester of 2,7-dimethylocta-2,6--dien-4-yne-1,8-diphosphonic acid (XII), prepared by the Arbuzov reaction from 1,8-dibromo-2,7-dimethylocta-2,6--dien-4-yne (XI) and triethyl phosphite, is condensed with two moles of β-ionylideneacetaldehyde (XIII) in the presence of sodium methoxide. The resulting 15,15′-dehydro--β-carotene (XIV) is smoothly converted into β-carotene after partial hydrogenation:



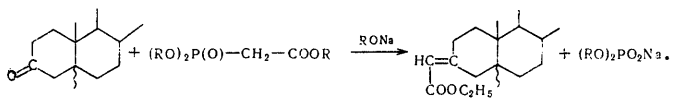
The ester (XII) reacts with cinnamaldehyde[113] by the usual mechanism of P(O)-activated olefin synthesis to yield the isoprenoid olefin 5,10-dimethyl-1,14-diphenyltetradeca-1,3,5,9,11,13-hexaen-7-yne:



By condensing phosphonoacetic ester with methylheptenone, geranylacetone, α-ionone, and α-dihydroionone in dimethylformamide in the presence of sodium methoxide, Kovalev et al.[108] obtained a number of esters of isoprenoid acids (yields are given in brackets):



The use of P(O)-activated olefin synthesis in the steroid series appears to be promising. The work of Bose and coworkers shows that 3-oxosteroids react via the carbonyl group with phosphonoacetic ester to form ethoxycarbonylmethylene derivatives[114]:



The data compiled in the present review on the methods of preparation, properties, and applications of P(O)-activated reagents for olefin synthesis show that this new method permits relatively simple preparation of unsaturated compounds with a specified structure; the compounds may belong to different classes and may be of various complexity. It is noteworthy that the possibilities of P(O)-activated olefin synthesis have been by no means exhausted as regards application to syntheses involving many organic compounds with carbonyl groups. There is no doubt that further studies in this field will yield new results of value for organic synthesis.

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Faculty of Chemistry,
Chernovtsy State University

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SYNTHETIC OPTICALLY ACTIVE POLYMERS

I. N. Topchieva

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I. INTRODUCTION

Recently a new field of study has arisen in the chemistry of monomers, associated with the synthesis of optically active polymeric substances. Their synthesis and the study of their properties are of great theoretical and practical interest. From the theoretical standpoint, asymmetric synthesis of polymers constitutes a higher type of control of stereoregularity, compared with the synthesis of the usual regular crystalline polymers. It represents a further advance in the control of the synthesis of macromolecular materials. The synthesis of optically active polymers has introduced into polymer chemistry a new parameter — the specific rotation of polymers which is due to the presence of uncompensated asymmetry and constitutes the overall stereochemical result of the reaction. The studies of the changes in the optical rotation of the polymer as a function of polymerisation conditions makes it possible to establish the relation between the specific rotation, structural regularity, and the molecular weight of the polymer. Investigation of the optical activity of the degradation products of optically active polymers can reveal the steric relations which obtain between the monomer, the catalytic system, and the polymer.

On the other hand, successful synthesis of optically active polymers in the presence of small amounts of an asymmetric cocatalyst constitutes a first approximation to the modelling of processes in nature, where protein molecules are formed in the presence of small amounts of highly specific enzymes as a result of a series of complex consecutive reactions.

Since optically active polymers and oligomers have highly specific structures, they may prove important as components of very selective catalysts in polymerisation and polycondensation processes and they may also be used in the asymmetric synthesis of small molecules, as model systems in the study of biocatalysis, and as adsorbents for the separation of racemic mixtures.

Optically active polymers prepared from optically active monomers exhibit improved mechanical properties and thermal stability compared with polymers synthesised from the analogous racemic monomers, which is of undoubted practical interest. In recent years optically active polymers have been increasingly attracting the attention of investigators. This interest was stimulated, on the one hand, by the study of the structural features of proteins and nucleic acids in solutions and, on the other hand, by the advances in stereospecific polymerisation. Up to 1956 there were only seven papers on optically active polymers, while in 1961 alone about thirty publications appeared, including a number of reviews[1-4].

There exist three fundamental approaches to the study of optically active polymers. One of them is associated with the determination of the laws governing the asymmetric synthesis of macromolecular substances, the second deals with the study of the properties of optically active polymers, and finally, the third is concerned with the application of optically active labels in experiments designed to solve a wide range of problems in polymerisation chemistry: elucidation of the nature of active centres in catalytic systems, the conformation of macromolecules in solution, the microtactic properties of chains, the polymerisation kinetics, etc.

The author has attempted to elucidate mainly the first and the last of these problems. She wished to demonstrate the wide variety of possible uses of the optically active label; by virtue of its simplicity and availability, the procedure based on such labelling will undoubtedly form part of the arsenal of the methods available in polymer chemistry.