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SYNTHESIS
of
CARBON-PHOSPHORUS
BONDS

Robert Engel

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Synthesis of Carbon-Phosphorus Bonds

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PREFACE

Interest in the synthesis of organophosphorus compounds was at one time relatively limited, being of concern chiefly to those involved in the preparation of materials of certain commercial interest (e.g., insecticides, flame retardants, and detergents). With this situation existing, it has been relatively rare to find university courses being taught on the topic of synthesis of these materials.

However, recent developments have made an understanding of organophosphorus compounds and their syntheses of significantly more general value. Not only have there been found applications for organophosphorus compounds in a wide range of commercial applications, but also these materials have become of great utility for the facilitation of other organic transformations. Yet, the university-trained organic chemist is provided with little guidance to the performance of organophosphorus chemical conversions or to the organophosphorus literature. It is in an attempt to provide direction to the organic chemist lacking specific training in organophosphorus chemistry that this book is presented.

A major portion of the effort of preparing this manuscript was performed while I was on sabbatical leave from Queens College at the Rohm and Haas Company in Spring House, Pa. I wish to thank Queens College for the time and the Rohm and Haas Company for their hospitality, both of which were important for this work. In addition, I would dedicate this work to my children, Cheryl and Erik.

Robert Engel, 1987

THE AUTHOR

Robert Engel, Ph.D., is Professor of Chemistry and Biochemistry at Queens College of the City University of New York. Dr. Engel received his B.S. from Carnegie Institute of Technology in 1963 and his Ph.D. from The Pennsylvania State University in 1966.

From 1966 to 1968 Dr. Engel served in the U.S. Army at the U.S. Army Edgewood Arsenal Chemical Research Laboratories. Upon completion of his tour of duty, Dr. Engel took up his position on the faculty at Queens College. For two years he served as Chairman of the Chemistry Department.

Dr. Engel has worked in several areas of chemistry. These have included the investigation of reaction mechanisms and the spectroscopic study of complexes of paramagnetic transition metal ions. The major portion of his work has been concerned with studies of organophosphorus compounds, their synthesis, reaction mechanisms associated with them, and their use as specific metabolic regulators. His current research interests continue in all of these latter areas.

Dr. Engel is a member of the American Chemical Society, the New York Academy of Sciences, the Royal Society of Chemistry, and Sigma Xi. He has published over 70 articles and has given presentations at 20 scientific meetings.

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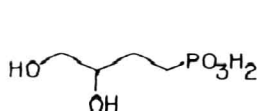
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Chapter 1

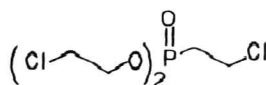
INTRODUCTION

In recent years there has been a broadly expanding interest in the synthesis of organo-phosphorus compounds, i.e., those bearing a carbon atom bound directly to a phosphorus atom. This interest has resulted from the recognition of the value of such materials for a variety of industrial, biological, and chemical synthetic uses. Several categories of such compounds should be noted as being of particular significance for modern organic chemistry. These include: (1) quinquivalent [P(V)] phosphorus oxyacids and their derivatives as end products for a variety of applications;



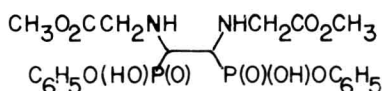
3,4-Dihydroxybutyl-1-phosphonic Acid

[Metabolic Probe]



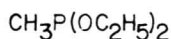
bis(2-Chloroethyl) Chloroethylphosphonate

[Flame Retardant]

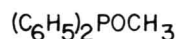
Diphenyl 1,2-Di(methoxycarbonylmethylamino)-
ethylene-1,2-diphosphonate

[Herbicide]

(2) trivalent neutral [P(III)] species, often used as intermediates in the synthesis of other organophosphorus compounds with direct applications;

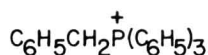


Diethyl Methylphosphonite



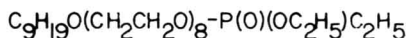
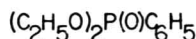
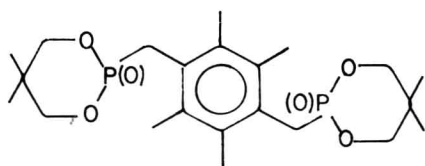
Methyl Diphenylphosphinite

and (3) tetravalent cationic [P(IV)] species of utility for general synthetic organic applications.



Triphenylbenzylphosphonium Bromide

Examples of the utility of compounds in the first category are numerous. Esters of phosphonic acids (phosphonates) or phosphinic acids (phosphinates) find significant application in a wide range of areas. These materials have been demonstrated to have industrial use as flame-retardants, either by admixture with polymeric materials¹ or by copolymerization with other monomers,^{2,3} inhibitors of oxidation in lubricants,⁴ and as surfactants.⁵



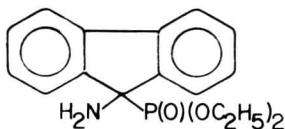
These applications, among many others of commercial significance, have been reviewed recently.⁶

Applications of this category of P(V) organophosphorus materials for biological regulation have received considerable attention in recent years. Many compounds of this category have been synthesized for use in the regulation of plant growth. Included here are series of compounds related to glyphosphate⁷ and diphenyl ethers,⁸ as well as morphactins.⁹



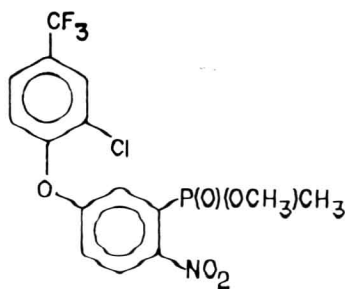
N-(Phosphonomethyl)glycine

[Glyphosate]



Diethyl

9-Aminofluorene-9-phosphonate

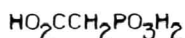


Methyl

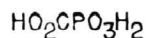
2-Nitro-5-(2'-chloro-4'-

trifluoromethylphenoxy)phenylmethylphosphinate

Significant effort has also been devoted to the synthesis of P(V) organophosphorus compounds, particularly phosphonates, for medicinal applications. Major programs of laboratory synthesis of the antibiotic phosphonmycin (fosfomycin)¹⁰ and structurally related molecules,¹¹ as well as potential antiviral materials in the phosphonoacetate and phosphonoformate series^{12,13} have been undertaken.



Phosphonoacetic Acid

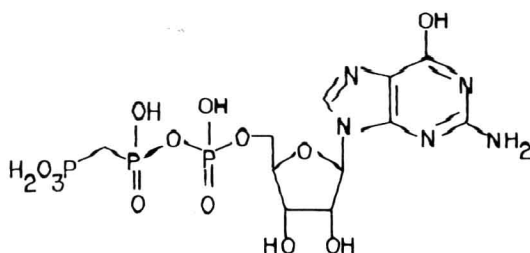


Phosphonoformic Acid

Studies of the use of such materials in both of these areas have been reviewed recently^{14,15} and will not be discussed further here.

A further biological application of organophosphorus compounds of the P(V) category has been for the mechanistic probing of metabolic processes. Compounds which are structural analogues of natural phosphate esters, contain a C-C-P linkage in place of the natural C-O-P linkage, might be anticipated to be stable to natural hydrolytic enzymes and could be used to provide information regarding biological mechanisms.

Beginning with the methylene analogue of GTP, of use in the determination of the individual steps of protein biosynthesis,¹⁰ data regarding details of a variety of metabolic processes have been obtained.^{17,18}

Guanosine 5'-(α,β -methylene)

Triphosphate

It should be noted that the syntheses necessary to allow these biological investigations to be performed are often quite complex. Usually the introduction of the carbon-phosphorus linkage needs to be made into species rich in reactive chemical functionalities. The available reactions for forming the desired carbon-phosphorus bond(s) must be of sufficient variety to allow its introduction in the presence of a wide range of such functionalities.

Compounds in the second category [P(III) species] generally have associated with them their own significant reactivity and are of greatest interest as precursors of the other two categories of compounds. Exceptions to this generalization are found with oxyacids of interest as analogues of carboxylic acid species in biological systems.

Finally, there should be noted the utility of organophosphorus compounds of the third category [P(IV) species] for the facile performance of chemical transformations, without which long and arduous synthetic routes would often be required. The Wittig reaction opened for organic chemists a one-step method for the substitution of a carbonyl oxygen by a multiply-bonded carbon function. The general utility of the Wittig approach was broadened through the Horner and the Wadsworth-Emmons modifications, which use stabilized phosphonate species, derived from compounds of the P(V) category.¹⁹⁻²²

Quite recently, investigations of carbon-phosphorus bond formation reactions have been spurred by the potential application of these materials as *umpolung* reagents. Compounds bearing the phosphoryl linkage accompanied by a suitable functionality on an adjacent carbon atom conveniently provide a reactivity equivalent to a carbonyl function of polarity inverted from the normal situation.²³ This application of organophosphorus chemistry to general organic synthetic procedures has relied greatly on the use of silylated derivatives of P(V) phosphorus oxyacids, reagents themselves of relatively recent vintage.

The purpose of this volume is not to address the application of organophosphorus compounds to the attack of a variety of problems, but rather to survey the recent advances in the procedures for their preparation. While particular emphasis is given to that work reported since 1970, earlier efforts of fundamental significance will be noted. This volume is intended to serve as a manual for the general synthetic organic chemist in the design and performance of organophosphorus syntheses. Attention will be given to compounds in categories 1 and 2 as noted previously. Attention will *not* be given to the synthesis of phosphonium species of category 3 nor to their applications.

Carbon-phosphorus bond formation in the present discussion is viewed with regard to both the type of reaction used to produce the linkage and the nature of the bond to be generated. In all, carbon-phosphorus bond formation is viewed here in five parts. First, displacement reactions at aliphatic carbon by a phosphorus ester [P(III) species] is considered. In each instance a (formally) trivalent phosphorus atom is converted to a quinquivalent [P(V)] species in the process. A comparison of the feasibility of the several approaches available will be made with regard to the target organophosphorus product. Particular attention is given to the recently developed use of silylated phosphorus reagents.

Second, reactions are reviewed in which treatment of an organometallic reagent with a phosphorus halide is involved. Several oxidation and coordination states of phosphorus are considered, including mixed ester-halides. The alkylation of phosphorus halides mediated by Lewis acids are also reviewed, along with several other methods.

Polar addition reactions at unsaturated carbon are considered in two categories. The first of these involves addition at carbonyl-type carbon sites, and the second is concerned with conjugate addition processes at olefinic sites. Again, particular attention is given to silylated phosphorus reagents for these reactions.

Finally, attention is given to the variety of methods available for the direct generation of carbon-phosphorus bonds at vinylic and aromatic sites. Secondary approaches to such materials, starting with aliphatic carbon-phosphorus linkages, are not reviewed.

In each instance examples of experimental procedures are included as well as a tabulation of syntheses performed using the approaches. These tabulations are not encyclopedic, but rather give representative examples of the use of the various procedures.

It is in order here to provide a brief survey of organophosphorus nomenclature. This is done in an outline-tabular form organized with regard to the oxygen coordination about the phosphorus atom in the free-acid state. The naming system provided will be used throughout this review and is the standard notation for the classes of materials in the English-language literature. It should be noted that where an "R" group is indicated and described as an "alkyl" function, aromatic or vinylic functions may also exist and be named in an analogous manner.

$P(OH)_2R$	$OP(OH)_2R$	$P(OH)_3$	$OP(OH)_3$
<i>Phosphonous Acid</i>	<i>Phosphonic Acid</i>	<i>Phosphorous Acid</i>	<i>Phosphoric Acid</i>
$P(OH)(OR')R$	$OP(OH)(OR')R$	$P(OH)_2OR'$	$OP(OH)_2OR'$
<i>Monoalkyl Phosphonite</i>	<i>Monoalkyl Phosphonate</i>	<i>Monoalkyl Phosphite</i>	<i>Monoalkyl Phosphate</i>
$P(OR')_2R$	$OP(OR')_2R$	$P(OH)(OR')_2$	$OP(OH)(OR')_2$
<i>Dialkyl Phosphonite</i>	<i>Dialkyl Phosphonate</i>	<i>Dialkyl Phosphite</i>	<i>Dialkyl Phosphate</i>
		$P(OR')_3$	$OP(OR')_3$
		<i>Trialkyl Phosphite</i>	<i>Trialkyl Phosphate</i>
PR_3	OPR_3	$P(OH)R_2$	$OP(OH)R_2$
<i>Phosphine</i>	<i>Phosphine Oxide</i>	<i>Phosphinous Acid</i>	<i>Phosphinic Acid</i>
		$P(OR')R_2$	$OP(OR')R_2$
		<i>Alkyl Phosphinite</i>	<i>Alkyl Phosphinate</i>

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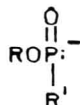
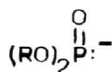
Chapter 2

NUCLEOPHILIC DISPLACEMENT AT CARBON BY PHOSPHORUS

I. INTRODUCTION

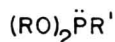
Displacement of a suitable leaving group from carbon by a nucleophilic trivalent phosphorus species is the most commonly used method for the formation of carbon-phosphorus bonds. In addition to those reactions which lead to phosphoryl-type compounds, such as the Michaelis-Becker and Michaelis-Arbuzov reactions, phosphonium ion and phosphine generation are usually performed in this manner. The present review is concerned only with a background summary and recent advances for the formation of phosphoryl-type compounds. Several recent reviews of phosphonium ion formation are available.¹⁻⁵

The discussion here will be divided into two major parts. The first of these will be concerned with the nucleophilic reactions of the anionic forms of tricoordinated phosphorus species, such as phosphite diesters, phosphonite monoesters, and phosphinites.



Such reactions, generally known as Michaelis-Becker reactions, will be reviewed with a particular emphasis on recent advances toward increasing their efficiency in the generation of phosphoryl-type products and their practical application to syntheses.

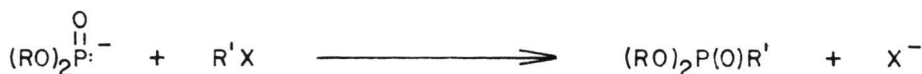
The second part of this discussion will center on the nucleophilic displacement reactions (Michaelis-Arbuzov reactions) of neutral trivalent phosphorus species. Although some variants will be noted, the compounds of interest will be fully esterified forms of phosphorous, substituted phosphonous, and substituted phosphinous acids.



Particular attention will be given to recent advances in the use of silyl esters of phosphorus acids and the variety of leaving groups from carbon.

II. MICHAELIS-BECKER REACTIONS AND MECHANISM

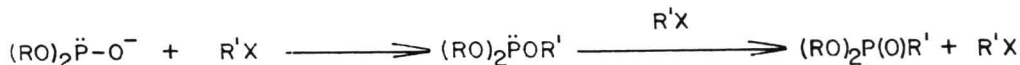
The displacement of halide ion from saturated carbon by a dialkyl phosphite anion has been known for quite some time.⁶



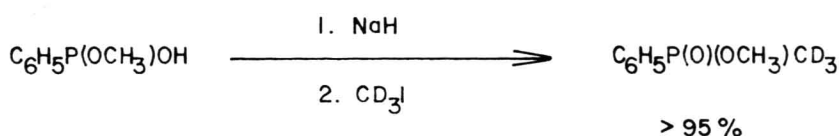
Much of the important early work has been summarized in a review by Crofts⁷ and in further reviews of the Michaelis-Arbuzov reaction.⁸

Several mechanisms have been postulated to account for the overall conversion. In spite of the complex kinetics and product variation with structure that has been noted,⁹ it would appear that initial attack is by phosphorus rather than oxygen on carbon. A possibility

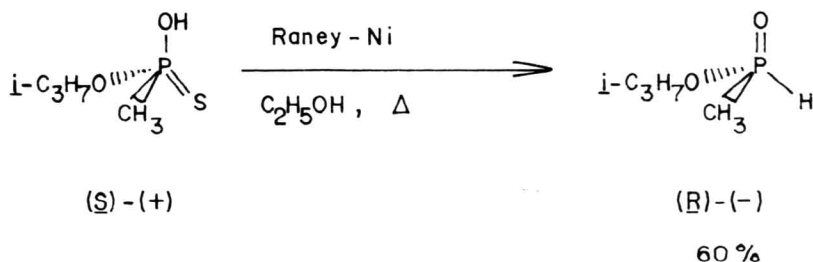
considered at one time involved displacement of halide by oxygen, followed by Michaelis-Arbuzov reaction of the fully esterified species.



This route is eliminated as a possibility for simple alkylations upon consideration of the Michaelis-Becker reaction of methyl phenylphosphonite with d_3 -methyl iodide.¹⁰ A nearly quantitative yield of methyl d_3 -methylphenylphosphinate is isolated, indicating that direct attack by phosphorus on carbon occurs, presumably in a classically $\text{S}_{\text{N}}2$ manner with regard to the carbon center. Displacement by oxygen has been reported in one instance in reaction involving an imidoyl chloride.¹¹



However, there remains uncertainty regarding the coordination about phosphorus in this reaction. An understanding of the process with regard to the phosphorus center has been facilitated by the preparation in recent years of phosphonite monoesters with a chiral phosphorus center. The first preparation of such species¹² proceeded via the Raney-nickel desulfurization of a chiral *O*-monoester of a phosphonothioic acid, obtained in optically active form by a standard resolution technique.¹³

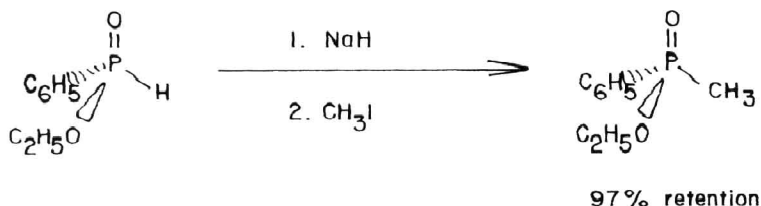


Within 3 months of the initial report, two other approaches were described which allowed isolation of chiral phosphonite monoesters. One involved the fractional crystallization of diastereoisomeric forms of menthyl phenylphosphonite, prepared from an achiral phosphorus reagent (phenylphosphonous dichloride) and a chiral alcohol, (–)-menthol.¹⁴ The other utilized the selective inclusion of the levorotatory enantiomer of isopropyl methylphosphonite in cyclohepta-amylose,¹⁵ a reagent previously explored as a resolving agent.^{15,16}

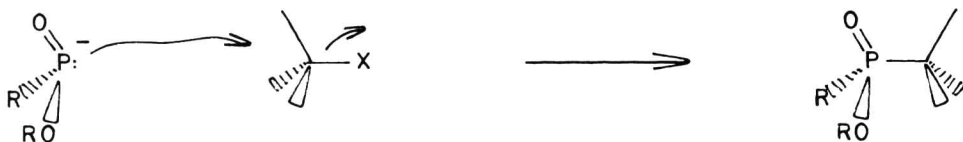
In solution, the “phosphoryl” form is dominant in the equilibrium with the “hydroxyl” form. The stereochemical integrity of the phosphorus center is maintained in this equilibration, and appears to be stable to acid-catalyzed racemization.¹²



Upon generation of the anion using sodium hydride, followed by addition of an alkyl halide, alkylation of the phosphorus occurs with net retention of configuration at the chiral center.^{10,18}

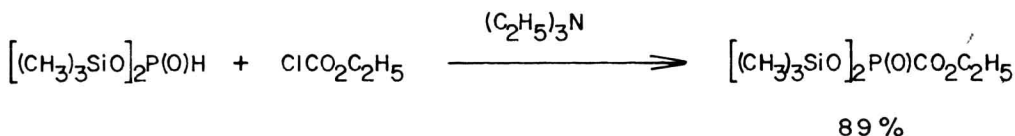


From this result one may conclude that the anion maintains significant stereochemical integrity in solution, and that the halide displacement occurs with direct generation of a tetracoordinated phosphorus species¹⁰

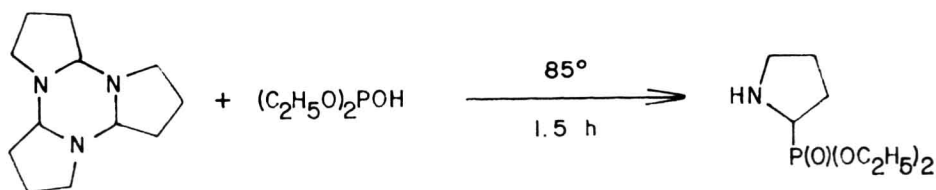


Early efforts would indicate that standard procedure in the performance of the Michaelis-Becker reaction involves formation of the sodium salt of the monobasic trivalent phosphorus acid (phosphite diester, phosphonite monoester, or secondary phosphine oxide). In much of the current work this is certainly reinforced, although the use of sodium metal has been replaced by sodium hydride. However, other approaches to the anionic species have been developed which are quite useful.

Tertiary amines have been found to be quite suitable as bases for the Michaelis-Becker reaction. This is particularly the situation with highly reactive substrates. Triethylamine has been used successfully with dialkyl phosphites in their reaction with imidoyl chlorides,¹¹ carboxylic acid chlorides,¹⁹ and chloroformates.^{20,21}

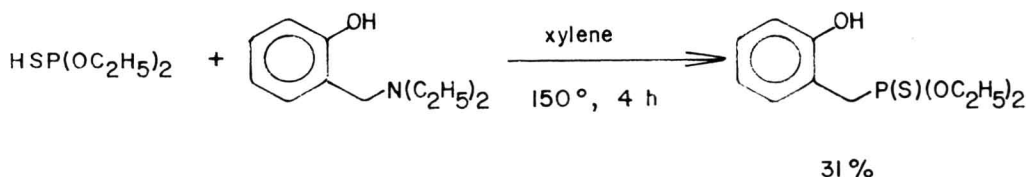


Tertiary amines have also been used to serve the dual purpose of base and leaving group. With diethyl phosphite, symmetrical cyclic 1,1-diaminomethane derivatives have been used for the preparation of 1-aminoalkylphosphonates.^{22,23} Reaction presumably occurs by displacement of a protonated nitrogen from the central carbon.



The α -alkoxyalkylureas represent an interesting related class of compounds for reaction with dialkyl phosphites.²⁴ Simply warming the substituted urea and the dialkyl phosphite results in reaction, the urea serving both as base and substrate.

A similar reaction is found between the more acidic *O,O*-diethyl thiophosphite and tertiary *o*-hydroxybenzylic amines.²⁵ Displacement of dialkylamine from the benzylic carbon leads to formation of substituted benzylthiophosphonates, albeit in only fair yield. Use of this particular reaction for synthetic purposes is plagued by side reactions involving the sulfur and the phenolic site.



Of course, the use of amines to generate the anionic forms of dialkyl phosphites has been used for quite some time in the Todd reaction for the preparation of phosphorochloridates.²⁶⁻²⁸ Sodium salts may also be used, but the tertiary amines provide a clean and experimentally convenient alternative. The use of amines rather than sodium or sodium hydride with dialkyl phosphites to generate the anions is one approach to help overcome an important difficulty often found in performing Michaelis-Becker reactions. That difficulty is the relatively low solubility of the salts in a variety of compatible solvents. Another recent approach to overcoming this difficulty has been the use of phase transfer catalysts. Biphasic solvent systems with quaternary ammonium salts added have been used to good result in several instances.²⁹⁻³¹ Potassium carbonate with catalytic amounts of 18-crown-6 has also been used in a solid-liquid two phase system for the alkylation of dialkyl phosphites.³²

Preformed heavy-metal salts of dialkyl phosphites have been used in several syntheses of phosphonate derivatives of carbohydrates. Facilitated by silver³³ and mercury³⁴⁻³⁶ salts, dialkyl phosphites undergo addition to acylium ions derived from 2-*O*-acetylglucosyl-bromides to generate dioxolanephosphonates.

