THE SYNTHESIS OF NEW PHENYLHYDROXYIODONIUM PHOSPHATES FROM (DIACETOXYIODOBENZENE) AND DIALKYL PHOSPHATES AND THEIR USE IN THE α–PHOSPHORYLATION OF KETONES TO MONO-KETOL PHOSPHATES

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Ousainou A. Keita
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THE SYNTHESIS OF NEW PHENYLHYDROXYIODONIUM PHOSPHATES FROM (DIACETOXYIODOBENZENE) AND DIALKYL PHOSPHATES AND THEIR USE IN THE α–PHOSPHORYLATION OF KETONES TO MONO-KETOL PHOSPHATES

Thesis

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ABSTRACT

The synthesis of new phenylhydroxyiodonium phosphates from (diacetoxyiodo) benzene and dialkyl phosphates, and their use in the α–phosphorylation of ketones was investigated. Reaction of diphenyl phosphate, $(PhO)_2P(O)OH$, with (diacetoxyiodo) benzene, $PhI(OAc)_2$, in the presence of water gave [hydroxy((bis(phenyl)phosphoryl)-oxy)iodo] benzene, $(PhI(OH)OPO(OPh)_2$, HPIB) as a white solid in excellent yield. Similarly prepared are $PhI(OH)OPO(OCH_3)_2$, $PhI(OH)OPO(OCH_2CH_3)_2$, $PhI(OH)$-$OPO(OCH_2CH_2Cl)_2$, $PhI(OH)OPO(OCH_2CCl_3)_2$, and $PhI(OH)OPO(OCH_2CF_3)_2$ from the corresponding monobasic acid phosphates $(RO)_2P(O)OH$ (R= CH_3, CH_3CH_2, CH_2ClCH_2, CCl_3CH_2, and CF_3CH_2) in 77-93 % yield .

These ketones (acetophenone, 4-methoxyacetophenone, p-nitroacetophenone, acetone, and pinacolone) were directly phosphorylated at the α–carbon with the iodine (III) reagent, HPIB, or its alkyl derivatives to give the corresponding α-phosphoryloxy derivatives in 41-89 % yield.

DEDICATION

I would like to dedicate this thesis to my wife (Fatimah), children (Mariam and Hassan) parents, and family members for their love, encouragement, patience and understanding.

ACKNOWLEDGEMENT

I would like to thank Dr. Kim C. Calvo for his guidance, important suggestions, support, patience and understanding, Dr. Gerald F. Koser and the Department of Chemistry at The University of Akron for providing teaching assistantship. I would like to also thank all my friends for their support and encouragement.

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BACKGROUND

1.1. Introduction.

There are three major and significant classes of organic esters: carboxylic acid esters, phosphoric acid esters, and sulfonic acid esters.[1] Phosphate esters play a key role in mechanistic and bioorganic chemistry, [9] and they are biologically important molecules. [9, 10] They are found in virtually every metabolic pathway, and are present in proteins, carbohydrates and lipids.[11]

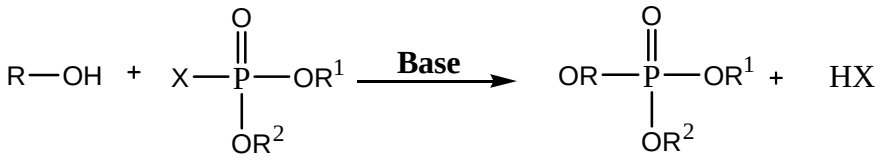
There are various chemical methods for the synthesis of novel and naturally occurring phosphate esters. [2-7] Like carboxylate esters, phosphate esters are normally prepared by reaction of an appropriate phosphorus halide with the respective alcohol, or an enolate if a vinyl phosphate ester is desired.[8] Phosphate esters can also be prepared by the condensation of an alcohol with hydrogen phosphate. The research presented in this thesis concerns the chemistry of tris-ketol phosphates. These are phosphotriesters containing ketol ligands, which are notable for their rapid hydrolysis in dilute alkaline solution, and are therefore, by virtue of this enhanced reactivity, different from other phosphotriesters. [12-15] The ease of the regioselective removal of the ketoxide ligand from the tris-ketol phosphate under relatively mild conditions, [7,16] makes it quite possible that

it will become widely used for the temporary masking of the phosphate moiety. Already, in Koser's group, the phosphorylation of nucleosides with bis-ketol phosphates has been achieved. [17-19]

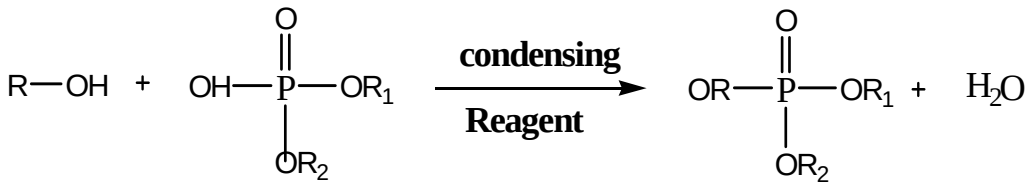
1.2. Synthesis of Phosphate Esters.

The classical synthesis of phosphate esters involves two main methods. In one method, a phosphorus compound with a leaving group attached is reacted with a hydroxyl-containing molecule to replace the P-X bond with a P-OR bond (eq.1). X is the leaving group in these reactions, and is usually a halogen (for example from phosphorus halide), but can also be other groups, such as amines, sulphonates or even phosphates. In the other method, a hydrogen phosphate is condensed with an alcohol with the help of a condensing reagent to form the P-OR bond (eq. 2). Carbodiimides can be used as the condensing agents.

Eq. 1.

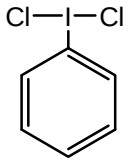


Eq.2.

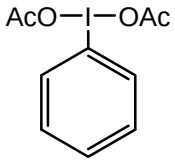


Functionalization of Carbon with Hypervalent Iodine Reagents.

Recently, hypervalent iodine reagents have attracted much interest and have been extensively used in organic syntheses because of their unique reactivity, ready availability and easy handling. [20-25,] These are compounds in which the iodine atom is bound to 2-5 ligands and is in the +3 or +5 oxidation state. The first hypervalent iodine compound (dichloroiodo) benzene, ($PhICl_2$, **1**) was prepared by the German chemist Willgerodt 110 years ago in 1886. [25]. This was rapidly followed by the preparation of (diacetoxyiodo) benzene, ($PhI(OAc)_2$, **2**), $Ar_2I^+HSO_4^-$, **3** the first iodonium salt, and many others. [20] They were found to be versatile and mild reagents for various oxidation and oxygenation reactions.



1



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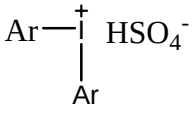


3

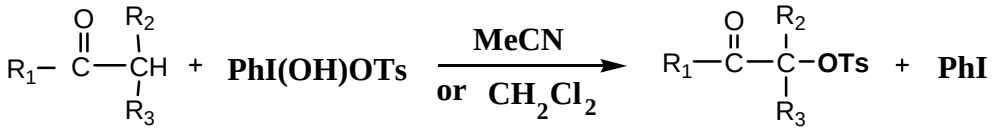
They can substitute for various toxic and heavy metal containing reagents, which have traditionally been used in oxidations. These reagents have been used mainly for C-C bond formation [26] and for the oxidation of alcohols, phenols and sulfides. Besides the oxidation of alcohol with the Dess-Martin periodinane [27-29] to the corresponding carbonyl compounds, hypervalent iodine reagents are also used as electrophilic reagents for lactonisation of carboxylic acids, α-oxytosylation of ketones or dioxytosylations of alkenes. [30,33,36]

Hypervalent iodine compounds, besides the versatility and diversity in their chemical behaviour, exhibit biocidal properties against a wide spectrum of microorganisms, such as bacteria, fungi, and yeast. [63] Moreover, they are environmentally safe. They are usually prepared by ligand exchange reactions from other iodine (III) reagents [20] and with a few exceptions they are stable towards heat, oxygen and humidity.

Koser and his coworkers are known for their work in the chemistry of hypervalent iodine compounds and the iodine (III) tosylate reagent, [Hydroxy(tosyloxy)iodo] benzene {PhI(OH)OTs, HTIB}, [30-31] is a well known one that is marketed by Aldrich Chemical Company as “Koser’s reagent”. Neiland and Karele were first to report its synthesis from (diacetoxyiodo) benzene and p-toluenesulfonic acid in 1970. [31] Koser and coworkers later reported the synthesis of HTIB from silver tosylate and iodosobenzene dichloride. [30] HTIB is a very useful reagent for the α– functionalization of carbonyl compounds. A number of ketones, β–diketones and β–ketoesters are converted to the corresponding α–tosyloxy-ketones in a one step reaction with HTIB in organic solvents such as acetonitrile or methylene chloride (eq. 3). [32] HTIB and its ring-substituted derivatives

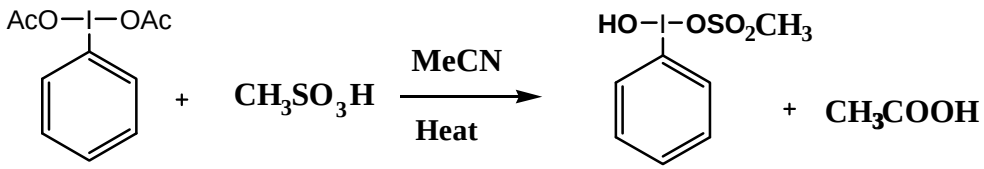
have been used to prepare α–hydroxyketones from ketones in water under reflux in this and Koser's laboratories. A possible mechanism for this reaction involves attack of the iodine reagent on the enolic form of the ketone to give an α–phenyliodonioketone intermediate. Nucleophilic displacement of iodobenzene by water would give the α–hydroxyketone.[33]

Eq .3.



Another hypervalent iodine reagent that has been useful in the funtionalization of α–carbons is [hydroxy(mesyloxy)iodo) benzene, (HMIB, **4**). In 1986, Zefirov and his coworkers reported the synthesis of HMIB and its reaction with acetone to give α– (mesyloxy) acetone. [38] Precedent to this publication, HMIB had been prepared in Koser's group from (diacetoxyiodo) benzene and methanesulfonic acid in acetonitrile as a nearly colorless crystalline solid in excellent yield (eq.4).

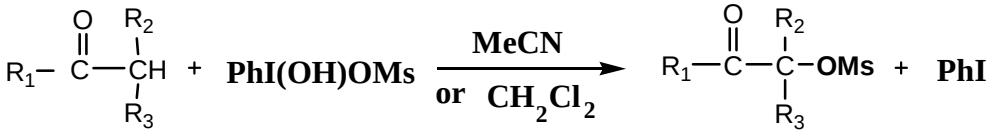
Eq. 4.



4

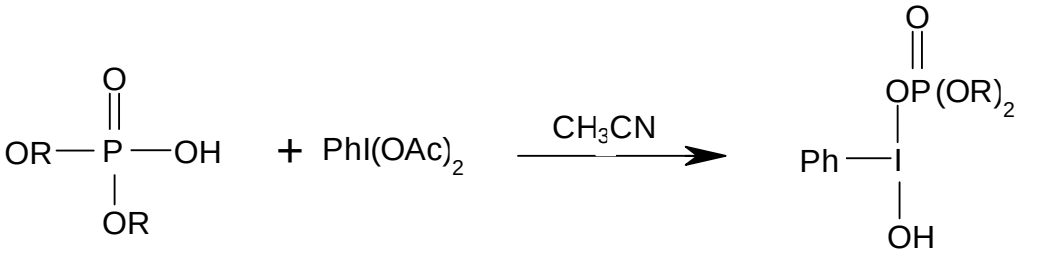
This iodine (III) mesylate has been used for the mesyloxylation of a variety of ketones and β–dicarbonyl compounds at the α–carbon (eq.5). [39, 40] Thus, a solution of HMIB and 2-petanone in acetonitrile was heated at reflux, and concentrated to an oil. The oil was taken in methylene chloride and treated with water followed by chromatography on silica gel to give 2-(mesyloxy)-3-pentanone in 87 % yield.

Eq.5.



It is the usefulness of HTIB and HMIB in the functionalization of carbonyl compounds that prompted an investigation on the synthesis of analogous iodine (III) phosphate reagents in Koser's group. In 1988, Koser and his coworkers reported the syntheses and the direct α-phosphorylation of ketones and β–dicarbonyl compounds with the iodine (III) phosphate reagent, [hydroxy((bis(phenyl)phosphoryl)oxy)iodo] benzene, ($PhI(OH)OPO(OPh)_2$, HPIB, **5**) and its benzyl analog, **6**. [40] HPIB is efficiently prepared from (diacetoxyiodo) benzene and diphenyl phosphate in the presence of water (eq.6). In one typical preparation, a solution of diphenyl phosphate (61 mmol) and water (120 mmol) in acetonitrile was added to a mixture of (diacetoxyiodo) benzene (60 mmol) in acetonitrile. The mixture was stirred for 4 hrs at room temperature and refrigerated. HPIB was separated out as a white crystalline solid and was isolated in 90% yield.

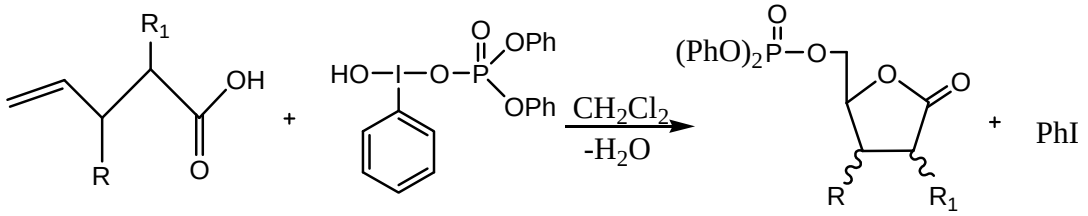
Eq.6.



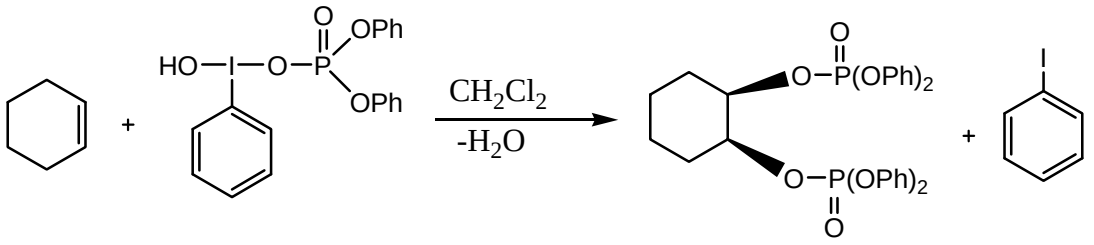
5, R = Ph; 6, R = Bz

In Koser's laboratory, HPIB has been used for the preparation of phosphoryloxy-lactones from alkenoic acids. For example, 4-pentenoic acid and its 2-methyl analog gave 5-[bis(phenyl)phosphoryl)oxy]-4-pentanolactones, in yields of 55% and 64% respectively (eq.7).[18] Like HTIB and HMIB, HPIB have also been used in the conversion of cyclohexene and some terminal alkenes to vicinal diphosphoryloxyalkanes in yields ranging from 22% - 46% yield (eq.8). [18] For example, the reaction of cyclohexene with HPIB gives the cis-diphosphate in 46% yield (eq.8).

Eq.7.

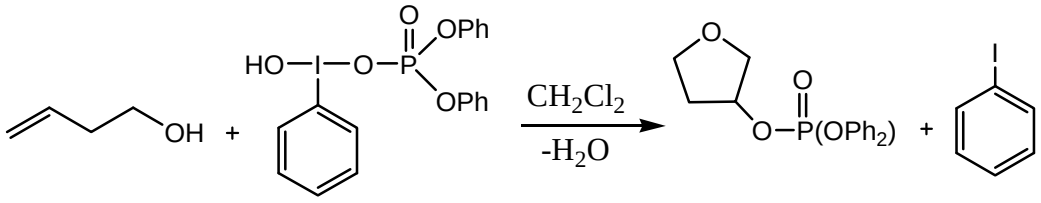


Eq.8.



Phosphate esters with a cyclic ether structure are produced, when HPIB was reacted with unsaturated alcohols in methylene chloride. [18] Thus, 3-buten-1-ol was treated with HPIB in methylene chloride, 3-((bis(phenyl)phosphoryl)oxy) tetrahydrofuran was obtained in 20% yield (eq.9). Styrenes also react with HPIB to give vicinal and/or geminal diphosphates. [18]

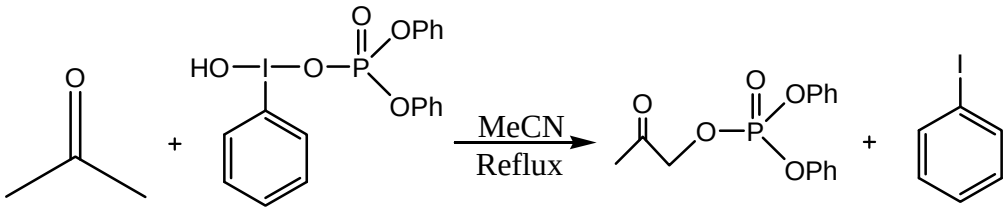
Eq.9.



HPIB is a very useful compound in the phosphorylation of ketones at the α–carbon. Thus, a mixture of HPIB and acetone in acetonitrile was heated under reflux and the reaction mixture concentrated. The residual oil was taken in dichloromethane, washed

(H_2O and 5% $NaHCO_3$) and warmed under vacuum to remove volatile impurities where-upon α–((bis(phenyl)phosphoryl)oxy) acetone was obtained in 82% yield (eq.10).

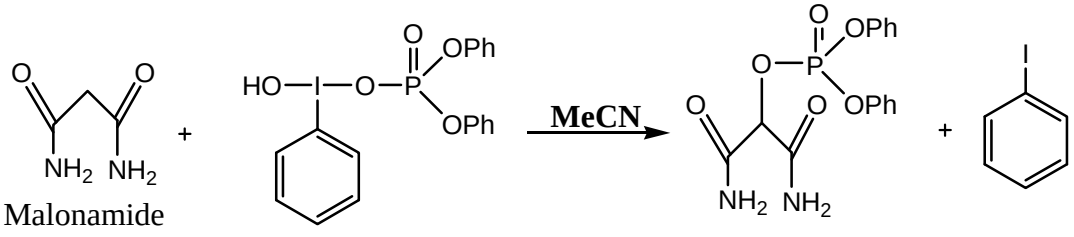
Eq.10.



The reaction of HPIB with ketones to give mono-ketol phosphates is an important reaction in that it makes the efficient and direct synthesis of ketol phosphates from ketones possible. Thus, the conversions of acetophenone, cyclopropyl methyl ketone, cyclohexanone, dibenzoylmethane, and 2, 4-pentanedione with HPIB to the corres-ponding ketol phosphates were also achieved.[39, 40]

The functionalization of carbonyl compounds with HTIB, and HPIB relies on the ability of the substrate to enolize, meaning that any compound that readily enolizes should react with HPIB or its alkyl analogs. Thus, α–((bis(phenyl)phosphoryl)oxy) malonamide was obtained in 49% when malonamide was treated with HPIB (eq.11). [40]

Eq.11.



The reactions of HPIB with ketones were mainly conducted in acetonitrile at reflux, because HPIB is not soluble in acetonitrile at room temperature. But these conditions are too severe for the conversion of cyclohexanone to its ketol phosphate, and the reaction of cyclohexanone with HPIB was instead conducted in methylene chloride at room temperature.[39] The reactions of HPIB were conveniently monitored by thin layer chromatography (silica gel), and the HPIB spot remains near the origins and develops a characteristic pink color in the presence of iodine vapor.

The use of trimethylsilyl enol ethers instead of ketones as the substrates for HPIB give a higher yield. For example, when 1-phenyl-1-(trimethylsilyloxy) ethylene was treated with HPIB, α-((bis(phenyl)phosphoryl)oxy)acetophenone was isolated in 87 % yield (eq.12), substantially higher than that from the direct reaction of acetophenone with HPIB (59 %). Similar treatment of 1-(trimethylsilyloxy) cyclopentene and 1-(trimethyl-silyloxy) cyclohexene with HPIB gave the corresponding ketol phosphates in 68 % and 59.5 % yields.

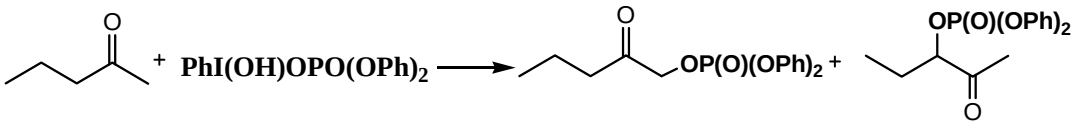
The ketol phosphates of acetophenone and cyclohexanone were identified by spectral comparison with authentic materials while the ketol phosphate of cyclopentanone was characterized by spectral analysis (^{1}H, ^{13}C, ^{31}P) and elemental analysis. [39]

The regiochemistry of the phosphoryloxylation of ketones vs. silyl enol ethers with HPIB was studied with 2-pentanone as the reference substrate. [39] While the direct reaction of 2-pentanone with HPIB gave a 1:1.5 mixture of the 3-phosphoryloxy and 1-(phosphoryloxy) pentanones, **11** and **12** (eq.13). The (2-trimethylsilyloxy)-1-pentene (prepared from 2-pentanone, LDA and trimethylsilyl chloride) gave 1-(phosphoryloxy)-2-pentanone as the exclusive product in 84 % yield.

Eq.12.

The ketol phosphate was identified by comparison of its ^{1}H NMR (300 MHz, $CDCl_3$) with that of authentic material (prepared by the reaction of HPIB with 1-pentyne). [39]

Eq.13.

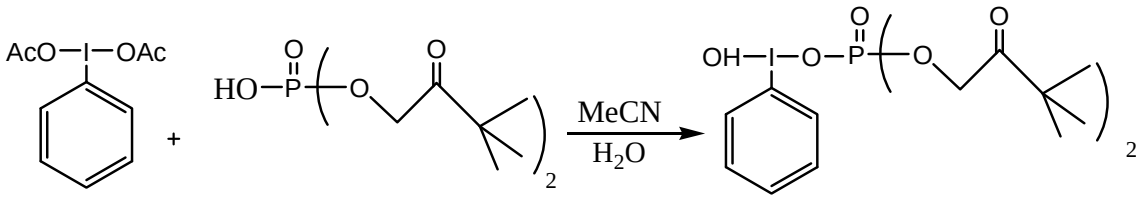


11 **12**

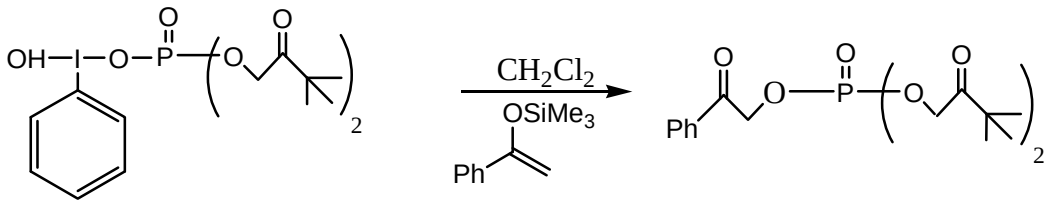
Synthesis of Phenylhydroxyiodonium Dialkyl Phosphates.

Phosphates with a free hydroxyl group (i.e. mono- and dibasic phosphates) react with (diacetoxyiodo) benzene to give iodine (III) phosphates. It was mentioned how HPIB, **5** was prepared by the treatment of (diacetoxyiodo) benzene with diphenyl phosphate and water in acetonitrile (eq.6). [39, 40] The [hydroxy((bis(2,2-dimethylpropanoyl-methyl) phosphoryl)oxy)iodo] benzene was also prepared by Summers by reacting bis(2,2-dimethylpropanoylmethyl) hydrogen phosphate, H_2O, and (diacetoxyiodo) benzene in acetonitrile (eq.14), [55] which she used with silyl enol ether of acetophenone for the synthesis of a mixed tris-ketol phosphates (eq.15). [55]

Eq. 14.

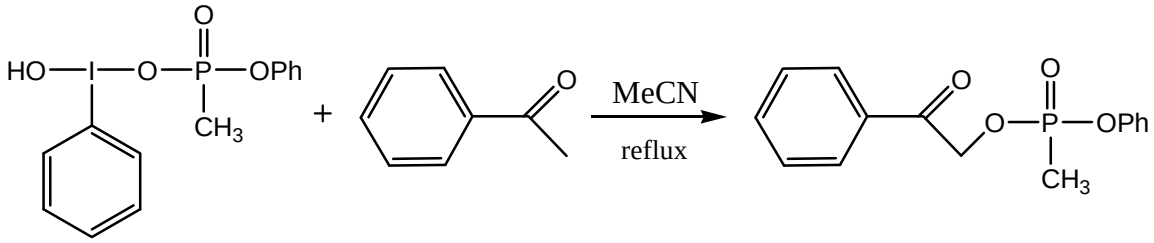


Eq. 15.



Moriarty and coworkers reported the preparation of three analogs of HPIB from iodosobenzene and the appropriate phosphonic or phosphinic acid in acetonitrile in 1997 (eq.16). [26] The reaction of these iodine (III) phosphate reagents with selected ketones and phenylacetylene gave monoketol phosphonates and phosphinates. For example, α-(((-phenyloxy)(methyl)phosphonyl)oxy) acetophenone was obtained in 44 % yield, when acetophenone was treated with [hydroxy(((phenyloxy)methyl)phosphonyl)oxy)iodo] benzene in acetonitrile (eq.16).

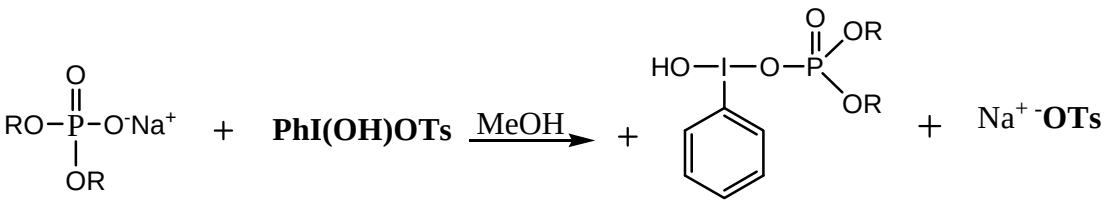
Eq. 16.



Stang and coworkers reported the synthesis of phenylhydroxyiodonium diethyl and dimethyl phosphates from [hydroxy(tosyloxy)iodo] benzene, HTIB, and the sodium salts of diethyl or dimethyl phosphate in methanol (eq.17). [57] For example, a solution of HTIB and sodium diethyl phosphate in methanol was stirred for 12 hrs at room temperature under argon. The methanol was evaporated off, and methylene chloride was added to precipitate sodium tosylate, which was filtered off, and the filtrate concentrated. Phenyl-hydroxyiodonium diethyl phosphate was obtained as a pale yellow viscous oil in almost quantitative yield. We have applied this method to prepare some of the phenylhydroxy-iodonium dialkyl phosphates in this work, which are used to make the mono-ketol dialkyl phosphates.

Stang and coworkers used the phenylhydroxyiodonium diethyl and dimethyl phosphates via the interaction with terminal alkynes in the preparation of alkynyl dialkyl phosphates. [57] It has been recently reported that alkynyl phosphates are potent inhibitors of serine enzymes. [58]

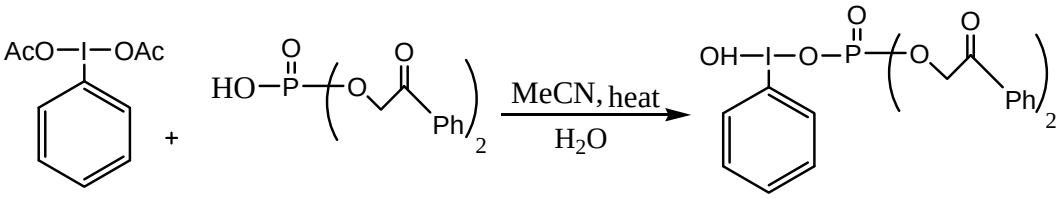
Eq.17.



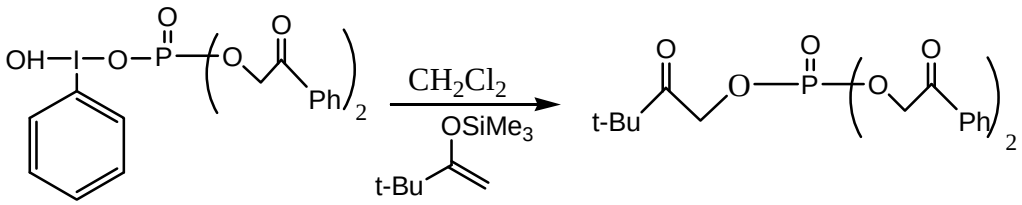
9a; R = Me, **9b;** R = Et. 1**0a**; R = Me, **10b;** R = Et

In 1998, Moore reported in his Ph.D dissertation the synthesis of [hydroxy(bis((-phenacyl)phosphoryl)oxy)iodo]benzene from (diacetoxyiodo) benzene and bis(phenacyl) hydrogen phosphate in the presence of water in acetonitrile in 92% yield (eq.18). [56] This iodine (III) phosphate also gives the mixed tris-ketol phosphate. For example, when a mixture of [hydroxy((bis(phenacyl)phosphoryl)oxy)iodo]benzene in CH_2Cl_2 and a stirred solution of 1-(t-butyl)-1-trimethylsilyloxyethylene in CH_2Cl_2 were added together and stirred for 1 hr at rt, [bis(phenacyl)pivaloylmethyl]phosphate was obtained as a viscous colorless oil in 20% yield (eq.19). [56] In this work, we prepared mono-ketol dialkyl phosphate of pinacolone in higher yield, by the interaction of HPIB or its alkyl analogs with pinacolone.

Eq.18.



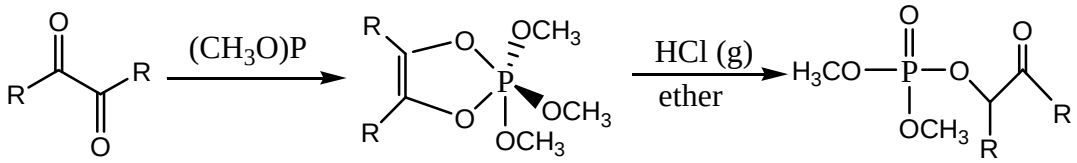
Eq.19.



Synthesis of Mono-Ketol Phosphates.

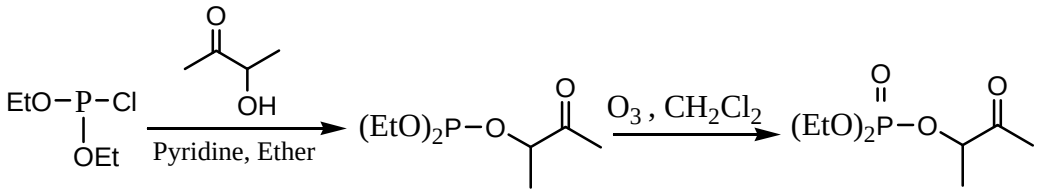
The synthesis of mono-ketol phosphates from the 2,2,2-trialkyloxy-1, 3, 2-dioxa-phospholenes, readily prepared from α–dicarbonyl compounds and trialkyl or triaryl phosphites was reported by Ramirez and his coworkers in 1960. [62] These compounds react with a variety of electrophiles to give ketol phosphates. For example, the treatment of biacetyl with trimethyl phosphite in benzene at room temperature give 2,2,2-tri-methoxy-4, 5-dimethyl-2, 2-dihydro-1, 3,3-dioxaphospholene, which reacts with anhydrous hydrogen chloride in ether to give α–ketol mono-phosphates (eq.20).

Eq.20.



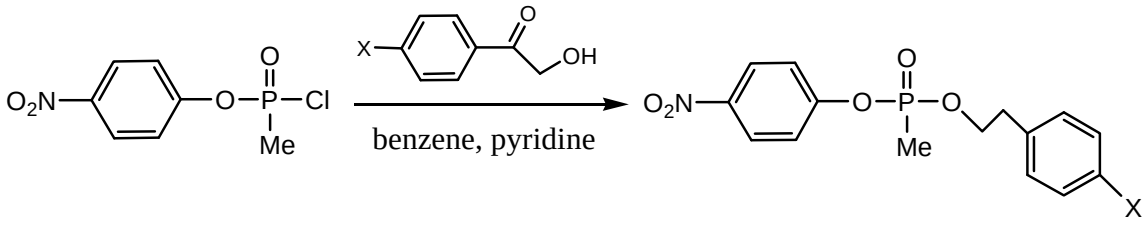
In 1991, Kluger and Taylor reported the synthesis of mono-ketol phosphates from dialkyl phosphochloridites and α–hydroxy ketones in the presence of a base. In this reaction a P-Cl bond is replaced by a P-OR bond resulting from a base catalyzed nucleophilic attack of a hydroxyl-containing compound. For example, the treatment of diethyl phosphochloridite with 10% molar excess of 3-hydroxy-2-butanone (acetoin) and pyridine in dry ether gave methylacetoin diethyl phosphite, which was oxidized with ozone to give methylacetoin diethyl phosphate in 93% yield (eq.21).

Eq. 21.



In 1993, Kovach and coworkers reported the synthesis of mono-ketol phosphonates, in which a series of p-nitrophenyl methyl 4-substituted phenyl phosphonate esters were prepared for use in hydrolysis experiments. [67] For example, the reaction of *p*-nitrophenyl methyl phosphonochloridate and α-hydroxyacetophenones in benzene/pyridine (eq.22).

Eq.22.



HTIB and its benzyl and alkyl analogues have been used for the preparation of a number of mono-ketol phosphates from ketones and β–dicarbonyl compounds. [39] Thus, in this work the treatment of acetone, acetophenone, p-methoxyacetophenone, p-nitro-acetophenone and pinacolone with HPIB or its alkyl analogs all gave the corresponding mono-ketol phosphate esters. For example, a mixture of HPIB and acetone in acetonitrile was stirred at reflux for 30 mins and the mixture concentrated. The residual oil was taken

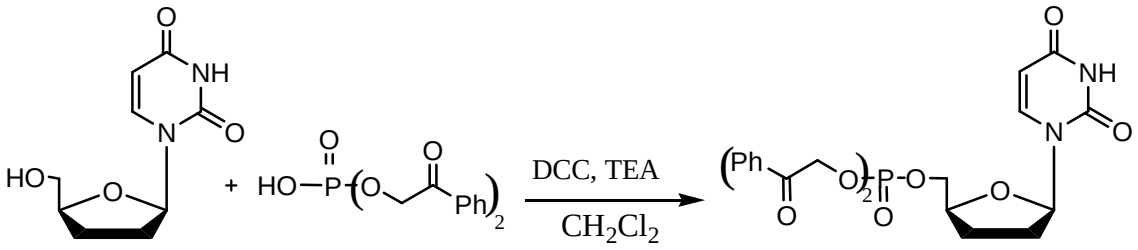
in methyllene chloride and washed with 5% $NaHCO_3$ and water, dried ($MgSO_4$), filtered and the filtrate concentrated to an oil. Removal of the volatile impurities gave α-((bis-(phenyl)phosphoryl)oxy) acetone in excellent yield. The alkyl analogues of HPIB that were prepared also directly phosphorylated ketones in a similar reaction to the corresponding ketol phosphate esters in 41-89% yield.

The ketol phosphate esters were also prepared at room temperature, but the yields are much smaller than when the reaction mixture is heated to reflux. This is partly because HPIB and its alkyl analogues are not too soluble in acetonitrile at room temperature, but dissolve to form a yellow solution at near the boiling point. At room temperature a good amount of the starting materials remain unreacted. The phosphorylation reaction occurred in methylene chloride at room temperature as well.

Phosphorylation of Nucleosides with Bis-ketol Phosphates

Already, in Koser's group, the phosphorylation of nucleosides with bis-ketol phosphates has been achieved. [17-19, 45] For example, when a solution of dicyclohexyl carbodiimide (DCC) in methylene chloride was added to a stirred solution of bis-(phenacyl)hydrogen phosphate in methylene chloride at room temperature, followed by the addition of the nucleoside (ddU) and then triethylamine, 5'-bis (phenacyloxy) phosphoryl]oxy- 2',3'-dideoxyuridine was isolated in 64 % yield (eq.23). [45] The ddU of bis- (pivaloylmethyl) and bis(heptanoylmethyl) were also prepared in 64 and 32 % yield respectively.

Eq.23.



ddU

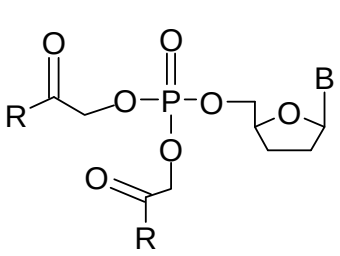
CHAPTER II

RESULTS AND DISCUSSION

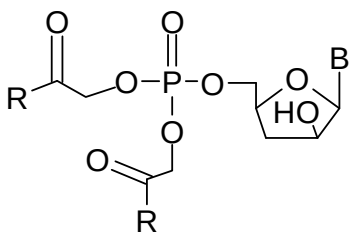
Introduction

The research described herein proposed to devise simple, standard methods for the preparation of mono-ketol dialkyl phosphate triesters and to study the alkaline hydrolysis of the initial ligand. Hence we wish to report a general, simple procedure for the preparation, via a tricoordinate iodonium species, as well as the spectral characterization of a variety of mono-ketol dialkyl phosphates.

Scheme 1. Bis-Ketol Nucleoside Analog Monophosphates and Bis-Nucleoside Analog Ketol Monophosphates.



1



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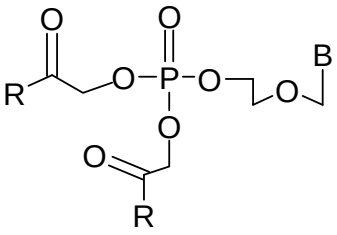

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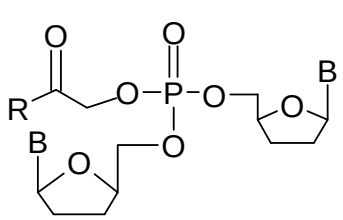
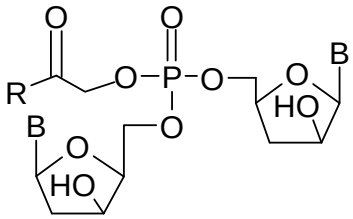
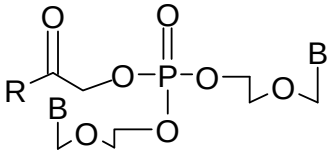


4



5



6

The original intent of this research work was to synthesize the bis-ketol nucleoside analog monophosphates **1**-**3** and bis-nucleoside analog ketol monophosphates **4**-**6** (scheme 1). These include bis-ketol monophosphate derivatives of antiviviral 2`, 3`-dideoxy (dd), 2`, 3`-didehydro-2`, 3`-dideoxy (d4) (including 3`-substituted dd nucleoside such as AZT), acyclic nucleosides, the bis-ketol monophosphate derivatives of the antineoplastic nucleosides and bis-ketol derivatives of acyclic nucleoside analog phosphonates (scheme 2).[52] A number of synthetic methods for 2`, 3`-dideoxynucleoside from the corresponding ribonucleosides have been reported. [51]

It is the triphosphate form of the drug that is active against HIV. [68] Therefore, all the nucleoside analogs are only prodrugs of the bioactive form. The nucleoside analogs are used therapeutically because they provide a form that is neutral and readily permeable to the cells in the absence of specific membrane transport system.

However, the nucleoside form is more susceptible to metabolism to an inactive form than the nucleotide form. For example, ddU is not phosphorylated in vivo by cellular kinases, but the triphosphate of ddU is a potent inhibitor of HIV-1 reverse transcriptase. These problems can be overcome with a nucleotide prodrug that could be metabolized to a nucleoside monophosphate. But on the other hand, nucleotide analogs have low cellular

permeability and low bioactivity, because of the double negative charges on the phosphates. We hope that this problem can be overcome by masking the negative charges with the ketol group. It is believed that these compounds will hydrolyze at biologically significant rates under physiological conditions to yield the nucleoside analog mono-phosphates. The phosphotriesters of ddT and d4T have already been synthesized and tested for the inhibition of HIV-1 reverse transcriptase by Koser's group and were found to be more active than AZT, although they are more cytotoxic. [17-19]

Synthesis of Phenylhydroxyiodonium Dialkyl Phosphates.

In this work, various new phenylhydroxyiodonium dialkyl phosphates were prepared by the (diacetoxyiodo) benzene methodology developed in Koser's group.[39,40] All new phenylhydroxyiodonium dialkyl phosphates were characterized by spectral means (NMR) as summarized in Table I and the experimental section. Thus, when a solution of diphenyl phosphate in acetonitrile and water was added to a stirred mixture of (diacetoxyiodo) benzene in acetonitrile, a white crystalline solid was obtained and identified as [hydroxy((bis(phenyl)phosphoryl)oxy)iodo] benzene in 92 % yield. Similarly prepared are the phenylhydroxyiodonium phosphates of dimethyl, diethyl, 2-chloroethyl, trichloroethyl, and trifluoroethyl. They were isolated, purify and charac-terized by spectral means (Table I). However, attempts to crystallize these compounds failed and some were isolated as solid/oil mixtures. These iodine (III) phosphate reagents were each successfully reacted with acetophenone, acetone, p-methoxyacetophenone, p-nitroacetophenone and pinacolone to give the mono-ketol phosphates in good yield.

Table I**.** Summary of yield and spectral properties of Phenylhydroxyiodonium Dialkyl Phosphates.

Compound	Yield (%)	NMR Spectra		
		^{1}H NMR ($CDCl_3$, δ)	^{13}C NMR ($CDCl_3$, δ)	^{31}P NMR ($CDCl_3$, δ)
[hydroxy((bis(phenyl) (phos phoryl)oxy) iodo]Benzene	84	6.97-7.16(m, 6H), 7.17-7.37(m, 6H), 7.35-7.43 (t, 1H), 7.75-7.95 (d, 2H)	120.5(d, J = 5.2 Hz), 124.2 (s), 129.6 (S), 131.73 (d, J = 6.5 Hz), 135.05 (S), 152 (d, J = 7.3 Hz)	-12.7(s)
[hydroxy((bis(methyl) (phos phoryl)oxy) iodo]Benzene	87	3.39 (d, J = 11.3 Hz, 6H, CH_3), 7.21-7.47 (m, ArH), 7.84-7.95 (m, ArH), 11.33 (br s, OH);	49.2 (d, J = 7.0 Hz, OCH_3), 124.0 1(s), 130.80 (s), 131.17 (s), 133.01 (s).	?
[hydroxy((bis(ethyl) (phos phoryl)oxy) iodo]Benzene	85	1.19 (t, J = 7.32 Hz, 6H, CH_3), 3.87 (q, J = 7.32 Hz, 4H, CH_2), 7.23-7.49 (m, ArH), 7.85-7.97 (m, ArH), 11.33 (br s, OH);	16.05 (d, J = 7.3 Hz, CH_3), 62.01 (d, J = 6.3 Hz, OCH_2), 125.05 (s) 130.47 (s), 131.07 (s), 132.71 (s),	?
[hydroxy((bis(2,2,2-trichloroethyl)(phos - phoryl)oxy) iodo] Benzene	77	4.36 (m, 2H, OCH_2), 7.23-7.49 (m, ArH), 7.85-7.97 (m, ArH), 11.5 (br s, 1H, POH);	83.71 (d, J = 4.6 Hz, OCH_2), 94.47 (d, J = 11.7 Hz, $CHCl_3$), 127.83 (s), 129.75 (s), 133.53 (s), 135.37 (s)	?
[hydroxy((bis(2,2,2-trifluoroethyl)(phos - phoryl)oxy) iodo] Benzene	93	4.17-4.28 (m, J = 8.10 Hz, 2H, OCH_2), 7.23-7.49 (m, ArH), 7.85-7.97 (m, ArH), 11.5 (br s, 1H, POH);	62.56-64.17 (dq, J = 4.6 Hz), 120.68-124.35 (dd, J = 10.6 Hz), 127.66 (s), 128.54(s), 130.45 (s), 137.69 (s)	-2.86 (s)
[hydroxy((bis(2-chloroethyl)(phos - phoryl)oxy) iodo] Benzene	79	3.78 (t, J = 6.5 HZ, 2H, $CLCH_2$), 4.31(q, 2H, CH_2),), 7.23-7.49 (m, ArH), 7.85-7.97 (m, ArH), 10.13 (s, 1H, POH);	42.73 (d, J = 8.2 Hz, $ClCH_2$), 67. 69 (d, J = 5.6 Hz, OCH_2), 127.71 (s), 129. 19 (s), 131.27 (s), 135.33 (s)	?

Preparation of Dialkyl Phosphates.

The monobasic acid phosphates have been known for quite a long time now, and they have been used in many synthetic applications as precursors of phosphate esters. They are mainly prepared by the aqueous hydrolysis of the corresponding bis(alkyl) phosphorochloridates or bis(alkyl) phosphorobromidates, [59,69,71] but they are also prepared directly from the corresponding alcohols [60] or acidification of the dialkyl phosphate salts.[54]

In this work dialkyl phosphates were mainly obtained from the aqueous hydrolysis of the dialky phosphorochloridates, $(RO)_2P(O)Cl$ or the trialkyl phosphates. [59] Thus, when dimethyl phosphorochloridate in acetonitrile and water was stirred at room temperature for 24 hrs and the reaction mixture concentrated and distilled, the reaction gave dimethyl phosphate as a clear liquid.

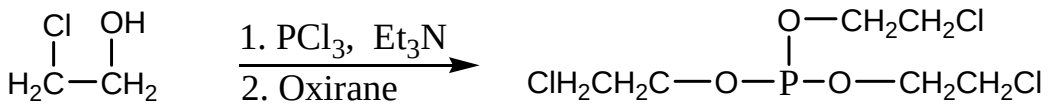
In 1956 McIvor and coworkers reported the synthesis of dialkyl phosphates directly from the alcohols.[60] Thus, to a solution of the appropriate alcohol cooled to 5 ^{o}C in dry benzene was added dropwise PCl_3 in dry benzene, the reaction temperature was maintained at below 10 ^{o}C. Distillation of the reaction mixture at room temperature gave the phosphates.

Synthesis of Tris-alkyl Phosphites.

The synthesis of tris-alkyl phosphites from alcohols is an effective way of the preparation of these compounds. One of the best methods of preparing tris(2-haloalkyl) phosphites is by reacting a phosphorus trihalide with an alkylene oxide in the presence of a tertiary amine hydrohalide catalyst and dichloromethane as the solvent. These tris(2-haloalkyl) phosphites are useful intermediates in the preparation of flame retardant

phosphate esters. [61] Tris(2-chloroethyl) phosphite is an intermediate for the synthesis of 2-chloroethylphosphonic acid and its derivatives, which are important substances for obtaining some plant growth regulators. The two main methods reported for the synthesis of tris(2-chloroethyl) phosphite are through ethoxylation of phosphorus trichloride and the esterification of phosphorus trichloride with 2-chloroethanol (eq.24).

Eq.24.



99 %

In this work, the tris(alkyl)phosphites were prepared by the reaction of the respective alcohols with PCl_3. In most cases the tris(alkyl)phosphites were used in the next reaction step without purification (distillation).

Dialkyl Chlorophosphates.

Dialkyl chlorophosphates have been prepared in a variety of ways, some of which include the reaction of trialkyl phosphate with phosphorus oxychloride. Also, several dialkyl phosphites have been converted to dialkyl chlorophosphates by treatment with sulfuryl chloride.

In this thesis, the dialkyl phosphorochloridates were prepared from the chlorination of the tris(alkyl) phosphites $(RO)_3P$, which proceeded smoothly in dichloromethane.[69,70] Thus, bubbling chlorine gas into a solution of the phosphite (0.20mol) in dry methylene chloride (50 ml) until the yellow color persisted, removal of the solvent and distillation of

the residue gave the bis(alkyl)phosphorochloridates $(RO)_2P(O)Cl$ in excellent yield. The bis(alkyl)phosphorochloridates were isolated, purify and characterized by spectral means (NMR) as summarized in Table II below.

Table II**.** Summary of yield and spectral properties of the Dialkyl Chlorophosphates.

Compound	Yield (%)	NMR Spectra		
		^{1}H NMR ($CDCl_3$, δ)	^{13}C NMR ($CDCl_3$, δ)	^{31}P NMR ($CDCl_3$, δ)
bis(2,2,2-trifluoro ethyl) phosphoro-chloridate	89	4.30-4.58 (m, J = 8.10 Hz, 4H, OCH_2)	65.16 (dq, J = 4.9 Hz, OCH_2), 127.44 (dd, J = 4.9 Hz, CF_3)	6.83 (s)
bis(2-chloroethyl) phosphorochloridate	93	3.77 (t, J = 6.5 Hz, 4H, $ClCH_2$), 4.36-4.51 (m, 4H, OCH_2)	42.2 (d, J = 5.7 Hz, $ClCH_2$), 62.7 (d, J = 5.4 Hz, OCH_2)	?
bis(2,2,2-trichloro ethyl) phosphoro-chloridate	82	4.75 (m, 4H, OCH_2)	78.3 (d, J = 4.6 Hz, OCH_2), 95.8 (d, J = 12 Hz, CCl_3)	3.80 (s)

Some of the dialkyl chlorophosphate were found to be very sensitive to heat, so that modifications of the standard procedure had to be employed in the synthesis of some of them. Despite all precautions, considerable decomposition occurred during distillation, and there was left in each case a viscous polymer-like residue, which was not analyzed.

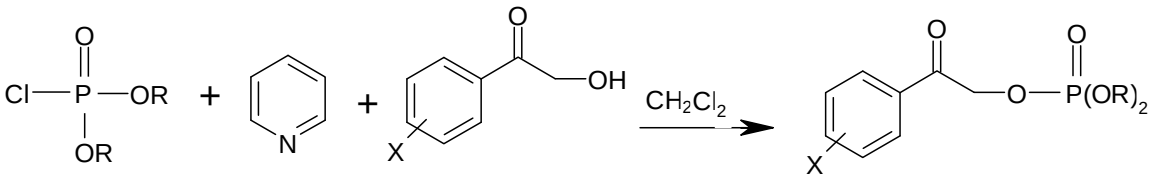
Synthesis of Mono-Ketol Phosphate.

The preparation of phosphate esters continues to be an important objective for chemists involved in the synthesis of biologically active molecules. [3, 6, 53] In this work, we present the synthesis of mono-ketol dialkyl phosphates via a tricoordinate iodonium

species, which was developed in Koser's laboratories. Using this method, the phosphorylation of ketones was accomplished in moderate yield under mild conditions.

Several attempts were made to prepare mono-ketol dialkyl phosphates by the interaction of dialkyl phosphorochloridates with α–hydroxyketones in the presence of a tertiary base (i.e. pyridine, 2,6-lutidine or diisopropylethylamine) in methylene chloride at 0 ^{o}C and at room temperature (eq.25). For example, to a solution of dimethyl phosphorochloridate in methylene chloride cooled at 0 ^{o}C was added dropwise a solution of α-hydroxyacetophenone and base (pyridine, or 2,6-lutidine or diisopropylethylamine) in CH_2Cl_2 at 0 ^{o}C. After the addition was completed, the reaction mixture was allowed to stir at room temperature for 24 hrs and the solvent was removed on a rotary evaporator to give a slurry. ^{1}H NMR analysis of this slurry showed no presence of the ketol phosphate.

Eq.25.



Synthesis of MonoKetol Dialkyl Phosphate Triesters.

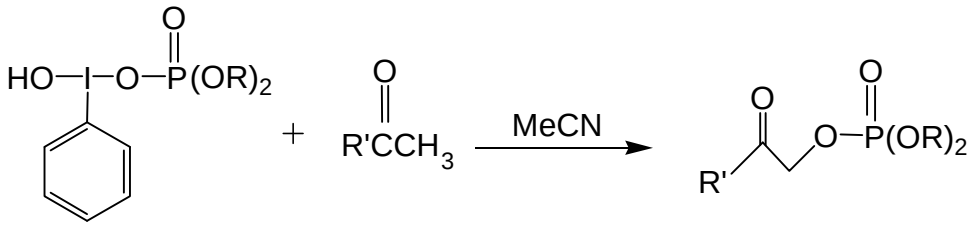
The ability of HPIB to effect the α-phosphorylation of ketones (Table III) suggested that the phenylhydroxyiodonium dialkyl phosphates should react in the same manner, because of their structural proximity. This is actually the case with these phenylhydroxy-

Table III**.** Summary of yield and spectral properties of the Mono-Ketol Diphenyl Phosphate esters.

Compound	Yield (%)	NMR Spectra		
		^{1}H NMR ($CDCl_3$, δ)	^{13}C NMR ($CDCl_3$, δ)	^{31}P NMR ($CDCl_3$, δ)
α– ((bis(phenyl) (phosphoryl)oxy) acetophenone	62	5.48 (d, 10.1 Hz 2H, CH_2), 7.16-7.43(m, 10H), 7.47-7.68 (m, 3H), 7.95 (d, 2H)	69.81 (d, J = 5.7 Hz, CH_2), 120.7 (d, J = 4.9 Hz), 125.39 (s), 127.65 (s), 128.76 (s), 133.93 (s), 150.31 (d, J = 7.5 Hz), 191.07 (d, J =5. 7 Hz, C=O)	-12.4 (s)
α– ((bis(phenyl) (phosphoryl)oxy) acetone	89	2.18 (s, 3H, CH_3), 4.71 (d, J = 9.4 Hz, 2H, CH_2), 7.19-7.39 (m, ArH)	26.16 (s, CH_3), 71.86 (d, J = 6.3 Hz, CH_3), 120.26 (d, J = 4.9 Hz), 125.83 (s), 130.05 (s), 150.47 (d, J = 7.4 Hz), 201.85 (d, J = 6.6 Hz, C=O)	-11.54 (s)
α– ((bis(phenyl) (phosphoryl)oxy) p-methoxyacetophenone	65	3.87 (s, 3H, OCH_3), 5.41 (d, J = 5.9 Hz, 2H, CH_2), 6.92 (d, J = 8.5 Hz, 2H, CH_2), 7.17 -7.39 (m, 10 H, ArH), 7.87 (d, J = 8.5 Hz, CH_2)	55.77 (s, OCH_3), 69.92 (d, J = 5.7 Hz, CH_2), 114.34 (s, 2H), 120.45 (d, J = 4.9 Hz), 125.71 (s), 130.01 (s), 130.41 (s), 158.51 (d, J = 7.5 Hz), 208.03 (d, J = 5.7 Hz, C=O)	-12.4 (t)
α– ((bis(phenyl) (phosphoryl)oxy) p-nitroacetophenone	73	5.37 (d, J = 10.2 Hz, 2H, CH_2), 7.27-7.40 (m, 10H, ArH), 8.03-8.16 (dd, J = 8.5 Hz, 2H), 8.29-8.35 (t, J = 8.5Hz, 2H)	70.21 (d, J = 5.4 Hz, 2H, CH_2), 120.37 (d, J = 4.9 Hz), 124.1 (s), 124.3 (s), 129.42 (s), 130.10 (s), 141.7 (s), 149.3 (s), 151.6 (s), 196.3 (d, J = 5.7 Hz, C=O)	-11.08 (s)
α– ((bis(phenyl) (phosphoryl)oxy) pina-colone	79	1.16 (s, 9H, $(CH_3)_3$), 5.01 (d, J = 10.2 Hz, 2H, CH_2), 7.08-7.37 (m, 10H, ArH)	26.29 (s, $(CH_3)_3$), 40.97, (s, $C(CH_3)_3$), 68.56 (d, J = 5.7 Hz, CH_2), 120.37 (d, J = 4.9 Hz), 125.39 (s), 130.41 (s), 150.55 (d, J = 7.5 Hz), 206.85 (d, J = 5.7 Hz, C=O)	-10.94 (s)

iodonium dialkyl phosphates. For example, when a reagent grade acetone was added to a solution of [hydroxy((bis(methyl)phosphoryl)oxy)iodo]benzene in acetonitrile stirred and heated under reflux for 20 mins, the mixture concentrated and the residue taken in methylene chloride, washed with water and $NaHCO_3$, dried ($MgSO_4$) and concentrated to an oil. After the residual oil was warmed under vacuum, a pale yellow oil was obtained, which was identified by spectral analysis (^1H, ^{13}C, and ^{31}P NMR) as α-((bis(methyl)-(phosphoryl)oxy) acetone (eq.26). Similar treatment of acetophenone, 4-methoxyaceto-phenone, p-nitroacetophenone and pinacolone gave the corresponding mono-ketol dialkyl phosphates. The treatment of the other phenylhydroxyiodonium dialkyl phosphates with these ketones gave similar results. The yield and spectral properties (NMR) of these novel compounds are summarized in Table IV.

Eq.26.



The ketol phosphates are easy to identify by NMR analysis; the α–hydrogens (-CH_2-OPO(O) $(OR)_2$) are deshielded, and both the α–hydrogens and α–carbon are coupled with phosphorus. For example, the ^1H and ^{13}C spectra of α–((bis(phenyl)phosphoryl)-oxy) acetone exhibit doublets at δ 4.71 (J_{HP} = 9.4 Hz) and at δ 71.86 (J_{CP} = 6.3 Hz).

Table IV. Summary of yield and spectral properties of the Mono-Ketol Dialkyl Phosphate esters.

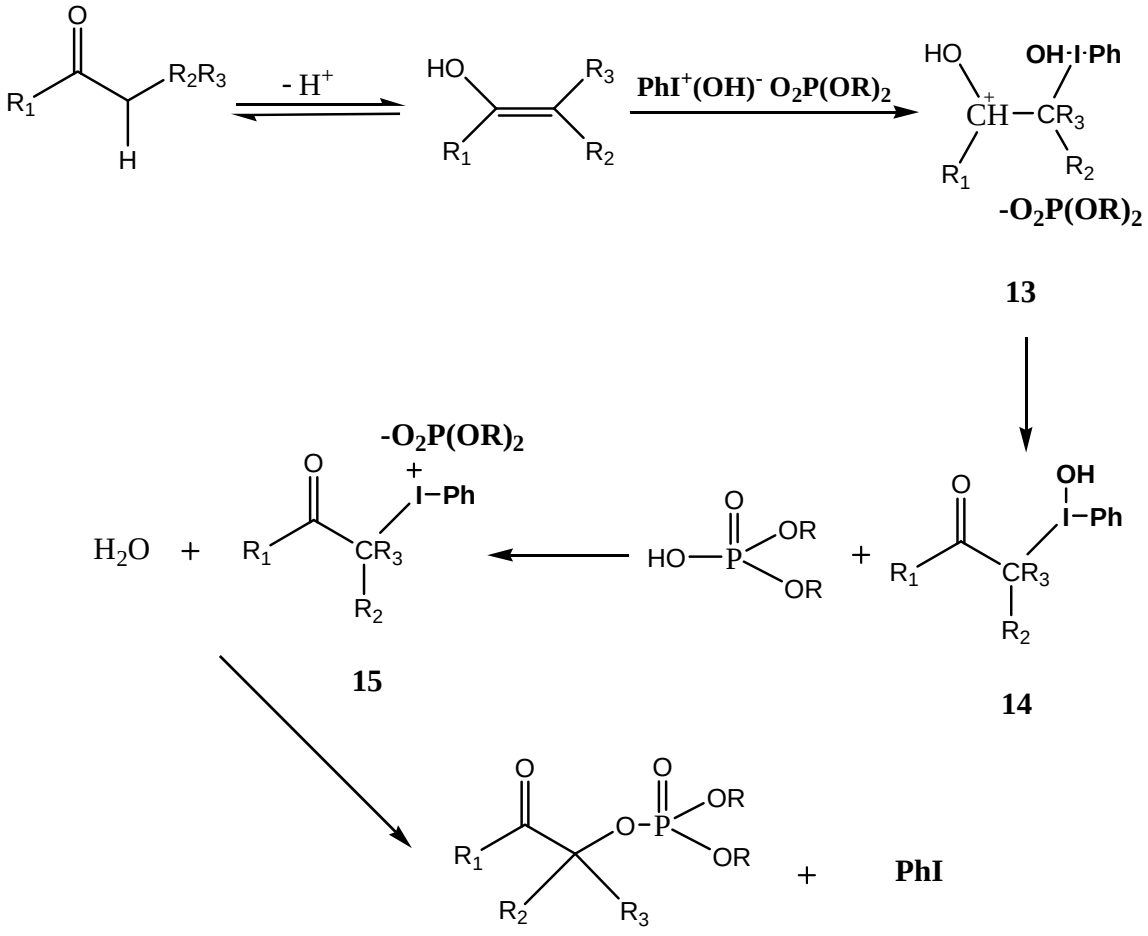
Compound	Yield (%)	NMR Spectra		
		^{1}H NMR ($CDCl_3$, δ)	^{13}C NMR ($CDCl_3$, δ)	^{31}P NMR ($CDCl_3$, δ)
α– ((bis(methyl) (phosphoryl)oxy) acetophenone	70	3.87 (d, J = 11.3 Hz, 6H, CH_3), 5.34 (d, 10.5 Hz, 2H, CH_2), 7.47-7.52 (t, J = 7.5 Hz, 2H), 7.59-7.65 (t, J = 7.5 Hz, 1H), 7.90 (d, J = 8.2 Hz, 2H)	54.98 (d, J = 6.0 Hz, OCH_3), 69.14 (d, J = 5.4 Hz, CH_2), 127.91 (s), 129.13 (s), 134.25 (s), 136.80 (s), 192.28 (d, J = 4.6 Hz, C=O)	1.90 (s)
α– ((bis(methyl) (phosphoryl)oxy) acetone	86	2.20 (s, 3H, CH_3), 3.83 (d, J = 11.1 Hz, 6H, OCH_3), 4.58 (d, J = 9.8 Hz, 2H, CH_2)	26.07 (s, CH_3), 54.95 (d, J = 6.0 Hz), 71.04 (d, J = 6.0 Hz, CH_2), 202.25 (d, J = 5.4 Hz, C=O)	1.59 (s)
α– ((bis(methyl) (phosphoryl)oxy) p-methoxyacetophenone	65	2.69 (s, OCH_3), 3.88 (d, J = 11.3 Hz, 6H, CH_3), 5.31 (d, J = 10.5 Hz, 2H, CH_2), 8.11 (d, J = 8.5 Hz, 2H, CH_2), 8.32 (d, J = 8.5 Hz, 2H, CH_2)	27.21 (s, OCH_3), 55.17 (d, J = 5.1 Hz, H_3), 69.29 (d, J = 5.7 Hz, CH_2), 124.08 (s), 129.57 (s), 131.36 (s), 151.80 (d, J = 7.3 Hz), 196.54 (d, J = 5.7 Hz, C=O)	1.98 (s)
α– ((bis(2,2,2-trichloro ethyl) phosphoryl)oxy) p-nitroacetophenone	55	4.73-4.85 (m, J = 6.4 Hz, 4H, OCH_2), 5.51 (d, J = 12.7 Hz, 2H, CH_2), 8.10 (d, J = 8.7 Hz, 2H), 8.30 (d, J = 8.7 Hz, 2H)	69.81 (d, J = 5.7 Hz, CH_2), 77.64 (d, J = 4.3 Hz, OCH_2), 94.79 (d, J = 11.7 Hz, CCl_3), 120.7 (d, J = 4.9 Hz), 129.67 (s), 133.93 (s), 150.3 (d, J = 7.5 Hz), 191.07 (d, J = 5.7 Hz, C=O)	?
α– ((bis(2,2,2-trichloro ethyl) phosphoryl)oxy) acetophenone	50	4.73-4.87 (m, 4H, OCH_2), 5.48 (d, J = 13.0 Hz, 2H, CH_2), 7.51 (t, J = 7.8 Hz, 2H), 7.65 (t, J = 7.3 Hz, 1H), 7.89 (d, J = 7.3 Hz, 2H)	70.23 (d, J = 5.7 Hz, CH_2), 77.64 (d, J = 4.3 Hz, OCH_2), 94.79 (d, J = 11.7 Hz, CCl_3), 127.91 (s), 129.26 (s), 133.61 (s), 134.59 (s), 191.70 (d, J = 5.7 Hz, C=O)	-3.51 (s)
α– ((bis(2,2,2-trichloro ethyl) phosphoryl)oxy) acetone	60	2.20 (s, 3H, CH_3), 4.73-4.87 (m, J = 10.1 Hz, 4H, OCH_2), 5.48 (d, J = 12.9 Hz, 2H, CH_2);	26.06 (s, CH_3), 71.17(d, J = 5.7 Hz, CH_2), 77.23 (d, J = 4.6 Hz), 94.79 (d, J = 11.7 Hz), 203.07 (d, J = 5.7 Hz, C=O)	-4.68 (s)

Table IV. Summary of yield and spectral properties of the Mono-Ketol Dialkyl Phosphate esters [Continued].

Compound	Yield (%)	NMR Spectra		
		^{1}H NMR ($CDCl_3$, δ)	^{13}C NMR ($CDCl_3$, δ)	^{31}P NMR ($CDCl_3$, δ)
α– ((bis(2,2,2-trifluoro ethyl)phosphoryl)oxy) acetophenone	41	4.29-4.40 (m, J = 8.10 Hz, 4H, OCH_2), 5.45 (d, J = 12.9 Hz, 2H, CH_2), 7.49-7.68 (m, 3H), 7.90 (d, J = 8.8Hz, 2H)	63.68 - 65.21 (dq, J = 4.3 Hz), 70.19 (d, J = 5.7 Hz, CH_2), 120.71- 124.39 (dd, J = 10.6 Hz), 128.76 (s), 129.29 (s), 133.93 (s), 150.3 (d, J = 7.5 Hz), 191.64 (d, J = 5.7 Hz, C=O)	-1.49 (s)
α– ((bis(2,2,2-trifluoro ethyl) phosphoryl)oxy) acetone	72	2.20 (s, 3H, CH_3), 4.41-4.58 (m, J = 8.10 Hz, 4H, OCH_2), 4.71 (d, J = 12.5 Hz, 2H, CH_2)	25.73 (s), 63.67-65.18 (dq, J = 4.3 Hz), 71.82 (d, J = 5.7 Hz, CH_2), 120.71- 124.39 (dd, J = 10.6 Hz), 200.64 (d, J = 5.7 Hz, C=O)	-2.96 (s)
α– ((bis(2,2,2-trifluoro ethyl) phosphoryl)oxy) pinacolone	53	1.20 (s, 9H, $(CH_3)_3$), 4.38-4.60 (m, J = 8.10 Hz, 4H, OCH_2), 4.95 (d, J = 13.6 Hz, 2H, CH_2)	63.67- 65.18 (dq, J = 4.3 Hz), 69.81 (d, J = 5.7 Hz, CH_2), 120.71- 124.39 (dd, J = 10.6 Hz), 191.07 (d, J = 5.7 Hz, C=O)	-2.19 (s)
α– ((bis(2-chloroethyl) phosphoryl)oxy) acetophenone	45	4.73-4.85 (m, J = 6.4 Hz, 4H), 5.51 (d, J = 12.7 Hz, 2H, CH_2), 7.48-7.54 (t, J = 7.5 Hz), 7.61-7.66 (t, J = 7.5 Hz), 7.97 (d, J = 8.8Hz)	42.65 (d, J = 8.2 Hz), 67.63 (d, J = 5.2 Hz), 69.96 (d, J = 5.7 Hz, CH_2), 127.65 (s), 128.76 (s), 129.67 (s), 133.93 (s), 191.07 (d, J = 5.7 Hz)	?
α– ((bis(2-chloroethyl phosphoryl)oxy) acetone	62	3.75 (t, J = 10.1 Hz, 2H, CH_2Cl), 4.27-4.38 (m, 2H, OCH_2), 4.73 (d, J = 10.5 Hz, 2H, CH_2)	42.65 (d, J = 8.2 Hz, $ClCH_2$), 67.63 (d, J = 5.2 Hz, OCH_2), 69.81 (d, J = 5.7 Hz, CH_2), 191.07 (d, J = 5.7 Hz, C=O)	?
α– ((bis(2-chloroethyl phosphoryl)oxy) p-methoxyacetophenone	60	3.86 (t, J = 10.1 Hz, 2H), 4.73-4.4.87 (m, J = 10.1 Hz, 2H), 5.48 (d, J = 12.9 Hz, 2H, CH_2), 7.49-7.68 (m, 2H), 7.90 (d, J = 8.8Hz)	42.65 (d, J = 8.2 Hz), 55.93 (s), 67.63 (d, J = 5.6 Hz), 69.81 (d, J = 5.7 Hz), 114.27 (s), 129.67 (s), 130.73 (s), 164.62 (s), 195.48 (d, J = 5.7 Hz, C=O),	?

The proposed mechanism for the α−phosphorylation of ketones by phenyl Hydroxyliodonium dialkyl phosphates (scheme 2) is similar to the one proposed for the α−phosphorylation of ketones by HPIB, [29] which in turn is similar to the mechanism proposed for the α−tosyloxylation of ketones by HTIB. [32] This reaction can be described mechanistically by an electrophilic attack of the phenylhydroxyiodium ion at the double

Scheme 2. Proposed Mechanism for the α−Phosphorylation of Ketones by Phenyl Hydroxyliodonium Dialkyl Phosphates.



bond of the enol form of the ketone to form an α–phenyliodonium phosphate species **13**, and proton abstraction from **13** will give the phenyliodonioketone **14**. Nucleophilic displacement of iodobenzene from the α–carbon of **15** would give the α–phosphoryloxyketone.

Monoketol phosphates have been used as intermediates in the preparation of unsymmetrical phosphodiesters.[12,71,72] This approach has been applied to oligonucleotide synthesis.

The mono-ketol dialkyl phosphates in this work were primarily prepared to be used to study the rate of their initial ketol hydrolysis. This is because we hope to be able to use these ketol groups to mask the nucleotide prodrugs, which is the original intent of this research work. It is believed that these compounds will hydrolyze at biologically significant rates under physiological conditions to yield the nucleoside analog monophosphates.

CHAPTER III

EXPERIMENTAL

Materials and Methods.

Solvents were distilled under nitrogen and stored over molecular sieves. Methylene chloride was distilled from calcium hydride. Acetonitrile was used as received. The ketones (acetophenone, p-methoxyacetophenone, p-nitroacetophenone and pinacolone) were purchased from Aldrich and were used as received. Acetone was dried with anhydrous $CaSO_4$ and then distilled. The alcohols (2-chloroethanol 99+%, 2,2,2-trichloroethanol 99%, and 2,2,2-trifluoroethanol 99+%) used for the preparation of the tris(alkyl)phosphites were purchased from Acros (New Jersey, USA), and were used as received. Methylene chloride, acetonitrile (reagent grade) and acetone (reagent grade) were all purchased from Fisher chemicals (Fairlawn, NJ). Diphenyl chlorophosphate was bought from Aldrich (Milwaukee, WI). (Diacetoxyiodo) benzene was prepared by direct treatment of iodobenzene with 32% peracetic acid according to literature procedure.[74]

The sodium salts of dimethyl and diethyl phosphates were prepared by literature procedure. [54]

The ^{1}H, ^{31}P, and ^{13}C NMR spectra reported in this dissertation were recorded on a Varian model Gemini-300 NMR spectrometer at resonance frequencies of 300 MHz

(^{1}H), 75 MHz (^{13}C) and 121 MHz (^{31}P). ^{1}H chemical shifts are referenced to residual protonated solvent in $CDCl_3$ (δ 7.27) or d_6-DMSO (δ 2.50) depending on the NMR solvent that was employed. ^{13}C chemical shifts are given relative to $CDCl_3$ (δ 77.23) or d_6-DMSO (δ 39.5). ^{31}P spectra are proton decoupled and referenced to external 85 % H_3PO_4 (sealed capillary, δ 0.00) in the appropriate solvent. Negative values were assigned to signals that were upfield of the reference.

The reactions were generally conducted under dried nitrogen gas in distilled solvents, in oven-dried glassware. Reaction mixtures were stirred with a magnetic bar. Solvent removal from reaction mixtures was accomplished with a rotary evaporator under aspirator vacuum. Isolated compounds were dried by using an oil vacuum pump at reduced pressure. The melting points reported here were obtained on a Thomas-Hoover Unimelt apparatus (uncorrected).

Synthesis of Tris(Alkyl) Phosphites.

Tris(2,2,2-trifluoroethyl) phosphite

To 2,2,2-trifluoroethanol, CF_3CH_2OH (15.0 g, 0.15 mol) in a 50 ml flask equipped with a stirrer, reflux condenser and a funnel was cooled (0-5 ^{o}C) in ice-bath. Phosphorus trichloride, PCl_3 (6.87 g, 4.36 ml, 0.05 mol), was added dropwise while stirring. Hydrogen chloride (HCl) was vigorously evolved during the addition. After the addition was completed the resulting mixture was allowed to warm to room temperature and slowly heated to 80-90 ^{o}C and stirred for 4 hrs. The reaction mixture was then fractionally distilled through a vigreux column to give a water-white liquid, identified by

^{1}H NMR analysis as tris(2,2,2-trifluoroethyl) phosphite; boiling point 129-131 ^{o}C (743 mm) [lit. bp 130-131 ^{o}C] ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16-4.27 (m, J = 8.10 Hz, 6H, OCH_2); ^{13}C NMR ($CDCl_3$) 61.22 (dq, J = 4.3 Hz, OCH_2), 124.96 (dd, J = 4.3 Hz, CF_3); ^{31}P NMR ($CDCl_3$) 140.40 (s)

Tris(2,2,2-Trichloroethyl) Phosphite

To 2,2,2-trichloroethanol, CCl_3CH_2OH (22.4 g, 0.15 mol) in a 50 ml flask equipped with a reflux condenser and a dropper cooled (0-5 ^{o}C) in ice-bath, was added dropwise PCl_3 (6.87 g, 4.36 ml, 0.05 mol) while stirring. Hydrogen chloride (HCl) was vigorously evolved at the beginning of the addition and after the addition was completed the resulting mixture was allowed to warm to room temperature and slowly raised up to 80-90 ^{o}C and stirred for 4 hrs. The reaction mixture was then fractionally distilled through a vigreux column to give a clear liquid, boiling point 125-126 ^{o}C. It was identified by ^{1}H NMR analysis as tris(2,2,2-trichloroethyl) phosphite. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (d, J = 6.6 Hz, 6H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 75.89 (d, J = 5.7 Hz, OCH_2), 96.50 (d, J = 5.4 Hz, CCl_3); ^{31}P NMR ($CDCl_3$) δ138.12 (s)

Tris(2-Chloroethyl) Phosphite

To 2-chloroethanol, CH_2ClCH_2OH (11.78 g, 0.15 mol) in a 50 ml flask equipped with a stirrer, reflux condenser and a dropper cooled (0-5 ^{o}C) in ice-bath was added dropwise phosphorus trichloride, PCl_3 (6.87 g, 4.36 ml, 0.05 mol) while stirring. Hydrogen chloride (HCl) was vigorously evolved during the addition. After the addition was

completed the temperature was allowed to warm to room temperature and slowly raised up to 80-90 ^{o}C and stirred for 4 hrs. The reaction mixture was then fractionally distilled through a vigreux column to give a water-white liquid, identified by ^{1}H NMR analysis as tris(2-chloroethyl) phosphite; boiling point 112-115 ^{o}C (2 mm) [literature 119 ^{o}C (0.15 Torr). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.5 (t, J = 6.5 Hz, 6H, $ClCH_2$), 4.08 (q, J = 5.6 Hz, 6H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 43.99 (d, J = 5.7 Hz, $ClCH_2$), 63.00 (d, J = 5.4 Hz, OCH_2)

Tris(ethyl) Phosphite

To ethanol, CH_3CH_2OH (6.91 g, 0.15 mol) in a 50 ml flask equipped with a stirrer, reflux condenser and a dropper cooled (0-5 ^{o}C) in ice-bath was added dropwise phosphorus trichloride, PCl_3 (6.87 g, 4.36 ml, 0.05 mol) while stirring. Hydrogen chloride (HCl) was vigorously evolved during the addition. After the addition was completed the temperature was allowed to warm to room temperature and slowly raised up to 80-90 ^{o}C and stirred for 4 hrs. The reaction mixture was then fractionally distilled through a vigreux column to give a water-white liquid, identified by ^{1}H NMR analysis as tris(ethyl) phosphite; boiling point 61-65 ^{o}C (25 mm). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, J = 7.02 Hz, 9H, CH_3), 3.62 (q, J = 7.02 Hz, 6H, OCH_2). ^{13}C NMR ($CDCl_3$) δ 16.91 (d, J = 5.7 Hz, CH_3), 57.73 (d, J = 5.4 Hz, OCH_2)

Synthesis of Bis(Alkyl) Phosphorochloridate

Bis((2,2,2-Trifluoroethyl) Phosphorochloridate

To a solution of tris(2,2,2-trifluoroethyl) phosphite (6.56 g, 20 mmol) in dry methylene chloride stirred and cooled (-76 ^{o}C, dry-ice/acetone), was bubbled chlorine gas until the yellow color persisted. After the addition, the reaction mixture was allowed to warm to 25 ^{o}C and stirred for 2 hrs. Removal of the solvent and distillation of the residue gave a water-white liquid, identified by ^{1}H NMR analysis as bis(2,2,2- trifluoroethyl) phosphorochloridate, yield 5.00 g, (89 %), boiling point 62 ^{o}C (10 mm): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30-4.58 (m, J = 8.10 Hz, 4H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 65.16 (dq, J = 4.9 Hz, OCH_2), 127.44 (dd, J = 4.9 Hz, CF_3); ^{31}P NMR ($CDCl_3$) δ 6.83 (s)

Bis(2-Chloroethyl) Phosphorochloridate

To a solution of tris(2-Chloroethyl) phosphite (5.39 g, 20 mmol) in dry methylene chloride stirred and cooled (-76 ^{o}C, dry-ice/acetone), was bubbled chlorine gas (gas cylinder) until the yellow color persisted. After the addition, the reaction mixture was allowed to warm to 25 ^{o}C and stirred for 2 hrs. Removal of the solvent and distillation of the residue gave a white liquid, yield 4.49g (93 %); identified by ^{1}H NMR analysis as bis(2-chloroethyl) phosphorochloridate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (t, J = 6.5 Hz, 4H, $ClCH_2$), 4.36-4.51 (m, 4H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 42.2 (d, J = 5.7 Hz, $ClCH_2$), 62.7 (d, J = 5.4 Hz, OCH_2)

Bis(2,2,2-Trichloroethyl) Phosphorochloridate

To a solution of tris(2,2,2-trichloroethyl) phosphite (9.52 g, 20 mmol) in dry methylene chloride stirred and (-76 ^{o}C, dry-ice/acetone), was bubbled chlorine gas until the yellow color persisted. After which the reaction mixture was allowed to warm to 25 ^{o}C and stirred for 2 hrs. Some white solid was precipitated, which was filtered off and the filtrate was concentrated to a syrupy white slurry and freeze-dried to a solid, identified by ^{1}H NMR analysis as bis(2,2,2-trichloroethyl) phosphorochloridate; yield 6.22 (82 %), melting point 46- 48 ^{o}C [Literature 51-53 ^{o}C] . ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (m, 4H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 78.3 (d, J = 4.6 Hz, OCH_2), 95.8 (d, J = 12 Hz, CCl_3); ^{31}P NMR ($CDCl_3$) δ 3.80 (s)

Synthesis of Diphenyl Phosphate and Dialkyl Phosphates.

Diphenyl Phosphate

A mixture of diphenyl phosphorochloridate (9.40 g, 35 mmol) and water (0.76 g, 42 mmol) in acetonitrile (40 mL) was allowed to stir for 12 hrs at room temperature. The precipitate that formed was filtered off and the filtrate concentrated to a slurry, which was freeze dried to give a white solid, identified by ^{1}H NMR analysis as diphenyl phosphate; yield 5.93 g, (68 %), melting point 63-65 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95-7.14 (m, 6H), 7.14-7.34 (m, 6H), 11.19 (br s, 1H, POH), ^{13}C NMR ($CDCl_3$) 120.40 (d, J = 5.2 Hz), 125.31 (s), 129.84 (s), 151.8 (d, J = 7.3 Hz); ^{31}P NMR ($CDCl_3$) -10.72 (s)

Bis(2,2,2-Trichloroethyl) Phosphate

A mixture of bis(2,2,2-trichloroethyl) phosphorochloridate (10.0 g, 26.4 mmol) and water (0.52 g, 29mmol) in acetonitrile (30 mL) was allowed to stirred for 24 hrs at room temperature. The precipitate was filtered off and the filtrate concentrated to a slurry, which was freeze dried to give a white solid; by ^{1}H NMR analysis as bis(2,2,2-trichloroethyl) phosphate; yield 7.75g (81 %), melting point 83-86 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (d, J = 6.6 Hz, 4H, OCH_2), 9.74 (s, 1H, POH); ^{13}C NMR ($CDCl_3$) δ 76.9 (d, J = 4.6 Hz, OCH_2), 96.6 (d, J = 12 Hz, CCl_3); ^{13}P NMR ($CDCl_3$) -2.49 (s)

In another experiment, water (0.80 g, 44.5 mmol) was added to bis(2,2,2-trichloroethyl) phosphochloridate (15.17 g, 40 mmol) that had been melted and maintained at 80-85 ^{o}C and stirred for 30 min. The resulting mixture was thoroughly evacuated leaving a crystalline mass. Recrystallization from hexane gave a white solid, identified by ^{1}H NMR analysis as bis(2,2,2-trichloroethyl) phosphate; yield 12.58 g (87 %); melting point 83-86 ^{o}C: ^{1}H NMR ($CDCl_3$) 4.61 (d, 4H, J = 6.5 Hz, OCH_2), 9.74 (s, 1H, POH); ^{13}C NMR ($CDCl_3$) δ 76.9 (d, J = 4.3 Hz, OCH_2), 96.6 (d, J = 12 Hz, CCl_3); ^{13}P NMR ($CDCl_3$) -2.49 (s)

Bis((2,2,2-Trifluoroethyl) Phosphate

A mixture of bis(2,2,2-trifluoroethyl) phosphorochloridate (10.0 g, 35.6 mmol) and water (0.71 g, 39.2 mmol) in acetonitrile (50 mL) was allowed to stir for 24 hrs at room temperature. The precipitate that formed was filtered off and the filtrate concentrated to a white liquid which was freeze dried, no solid was formed, identified by ^{1}H NMR analysis

as bis((2,2,2-trifluoroethyl) phosphate; yield 7.74 g (83 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (m, J = 8.10 Hz, 4H, OCH_2), 11.16 (s, 1H, POH); ^{13}C NMR ($CDCl_3$) 63.01- 64.52 (dq, J = 4.6 Hz, OCH_2), 117.65-128.21 (d, J = 4.6 Hz, CF_3); ^{31}P NMR ($CDCl_3$) -3.75 (s)

Dimethyl Phosphate

A mixture of dimethyl chlorophosphate (3.61 g, 25 mmol) and water (0.63 g, 35 mmol) in acetonitrile (35 mL) was allowed to stir for 12 hrs at room temperature. The precipitate that formed was filtered off and the filtrate concentrated to a white liquid which was freeze dried, no solid was formed, identified by ^{1}H NMR analysis as dimethyl phosphate; yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (d, J = 11.3 Hz, 6H), 6.22 (br s, 1H, POH), ^{13}C NMR (CDCl3) 56.5 (d, J = 5.1 Hz); ^{31}P NMR (CDCl3) -3.98 (s)

Bis(2-Chloroethyl) Phosphate

A mixture of bis(2-chloroethyl) phosphorochloridate (8.45 g, 35 mmol) and water (0.70 g, 39 mmol) in acetonitrile (40 mL) was allowed to stirred for 24 hrs at room temperature. The precipitate that formed was filtered off and the filtrate concentrated to a white liquid which was freeze dried, no solid was formed, identified by ^{1}H NMR analysis as bis(2-chloroethyl) phosphate; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (t, J = 6.5 Hz, 4H, $ClCH_2$), 4.31-4.47 (m, 4H, OCH_2), 11.68 (br s, 1H, POH); ^{13}C NMR (CDCl3) 42.65 (d, J = 8.3 Hz), 67.63 (d, J = 5.2 Hz), ^{31}P NMR (CDCl3) -11.23 (s)

Synthesis of [Hydroxy((Bis(phenyl)Phosphoryl)oxy)iodo] Benzene (HPIB).

A solution of diphenyl phosphate (3.82 g, 15.3 mmol) in acetonitrile (25 mL) was added to a mixture of (diacetoxyiodo) benzene (4.83 g, 15 mmol) in acetonitrile (25 mL) and water (0.54 g, 30 mmol). The reaction mixture was stirred at room temperature to give a greenish-yellow solution. After about 10 min a white solid started to precipitate out, and the stirring was allowed to continue for 4 hrs at room temperature and the mixture was refrigerated overnight. HPIB was filtered off as a white solid, which was recrystallized in acetonitrile, identified by ^{1}H NMR analysis as HPIB; yield 6.04g, (84 %), melting point 101-103 ^{o}C [lit.102-105 ^{o}C]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97-7.16 (m, 6H), 7.17-7.37 (m, 6H), 7.35-7.43 (t, 1H) 7.75-7.95 (d, 2H); ^{13}C NMR ($CDCl_3$) 120.5 (d, J = 5.2 Hz), 124.2 (s) 129.6 (s), 131.73 (d, J = 6.5 Hz), 135.05(s), 152 (d, J = 7.2 Hz) ^{31}P NMR ($CDCl_3$) -12.7 (s)

Synthesis of [hydroxy((bis(alkyloxy)phosphoryl)oxy)iodo] benzene

[Hydroxy((Bis(methyl)Phosphoryl)oxy)iodo] Benzene (HMIB)

A solution of dimethyl phosphate (1.93 g, 15.3 mmol) in acetonitrile (25 mL) was added to a mixture of (diacetoxyiodo) benzene (4.83 g, 15 mmol) in acetonitrile (25 mL) and water 0.54 g (30 mmol).The reaction mixture was stirred at room temperature to give a greenish-yellow solution. The resulting reaction mixture was allowed to stir for 4 hrs at room temperature, after which it was refrigerated overnight. Only a tiny amount of crystalline solid was separated out. The acetonitrile was evaporated off and the residual oil was dried under vacuum to give a pale yellow viscous oil, identified by ^{1}H NMR analysis as [hydroxy((bis(methyl)phosphoryl)oxy)iodo] benzene; Yield 4.60 g (87 %).

Attempts to crystallize the oil failed. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (d, J = 11.3 Hz, 6H, CH_3), 7.21-7.47 (m, ArH), 7.84-7.95 (m, ArH), 11.33 (br, s, OH); ^{13}C NMR ($CDCl_3$) δ 49.2 (d, J = 7.00 Hz, CH_3), 124.0 (s) 130.8 (s), 131.17 (s), 133 (s)

In another experiment, a solution of HTIB (3.9 g, 10 mmol) and sodium dimethyl phosphate (1.48 g, 10 mmol) in methanol (35 ml) was stirred for 12 hrs at room temperature under nitrogen. The resulting reaction mixture was evaporated off, and the residue taken in methylene chloride to precipitate sodium tosylate, which was filtered off. The methylene chloride was evaporated off and the residual oil was dried under vacuum to give a pale yellow viscous oil, identified by ^{1}H NMR analysis as [hydroxy((bis-(methyl)phosphoryl)oxy)iodo] benzene; Yield 3.22 g (93 %). Attempts to recrystallize the oil failed; the viscous oil was used as is: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (d, J = 11.3 Hz, 6H, CH_3), 7.21-7.47 (m, ArH), 7.84-7.95 (m, ArH), 11.33 (br s, OH); ^{13}C NMR ($CDCl_3$) δ 49.2 (d, J = 7.00 Hz, CH_3), 124.01 (s) 130.80 (s), 131.17 (s), 133.01 (s)

[Hydroxy((Bis(ethyl)Phosphoryl)oxy)iodo] Benzene

A solution of diethyl phosphate (2.36 g, 15.3 mmol) in acetonitrile (25 mL) was added to a mixture of (diacetoxyiodo) benzene (4.83 g, 15 mmol) in acetonitrile (25 mL) and 0.54 g (30 mmol) of water was added to this mixture and stirred at room temperature to give a greenish-yellow solution. The resulting mixture was allowed to stir for 4 hrs at room temperature, after which it was refrigerated overnight. Only a tiny amount of crystalline solid was separated out. The acetonitrile was evaporated off and the residual

oil was dried under vacuum to give a pale yellow viscous oil, yield 4.87 g (85 %) identified by ^{1}H NMR analysis as [hydroxy((bis(ethyl)phosphoryl)oxy)iodo] benzene. Attempts to crystallize the oil failed. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, J = 7.3 Hz, 6H, CH_3), 3.87 (q, J = 7.3 Hz, 4H, OCH_2), 7.23-7.49 (m, ArH), 7.85-7.97 (m, ArH), 11.33 (br s, OH); ^{13}C NMR ($CDCl_3$) δ 16.05 (d, J = 7.3 Hz, CH_3), 62.01 (d, J = 6.3 Hz, OCH_2), 125.05 (s) 130.47 (s), 131.07 (s), 132.71 (s)

In another experiment, a solution of HTIB (3.9 g, 10 mmol) and sodium diethyl phosphate (1.76 g, 10 mmol) in methanol (35 ml) was stirred for 12 hrs at room temperature under nitrogen. The resulting reaction mixture was evaporated off, and the residue taken in methylene chloride to precipitate sodium tosylate, which was filtered off. The methylene chloride was evaporated off and the residual oil was dried under vacuum to give a pale yellow viscous oil, identified by ^{1}H NMR analysis as [Hydroxy((bis(ethyl)-phosphoryl)oxy)iodo] benzene.

[Hydroxy((Bis(2,2,2-trichloroethyl)Phosphoryl)oxy)iodo] Benzene

A solution of bis(2,2,2-trichloroethyl) phosphate (7.75 g, 21.5 mmol) in acetonitrile (35 mL) was added to a mixture of (diacetoxyiodo) benzene (7.03 g, 21.8 mmol) in acetonitrile (35 mL) and water 0.77 g (43 mmol). The resulting mixture was allowed to stir for 4 hrs at room temperature, after which it was refrigerated overnight. The acetonitrile was evaporated off and the residual oil was dried under vacuum to give a pale yellowish white solid, wash with acetonitrile and dried in a desiccator under vacuum to give 9.89 g of the product. Recrystallization from acetonitrile give a yield of 9.62 g, (77

%), melting point 115-116 ^{o}C, identified by ^{1}H NMR analysis as [hydroxy((bis(2,2,2-trichloroethyl)phosphoryl)oxy)iodo]benzene. ^{1}H NMR ($CDCl_3$) 4.36 (m, 2H), 7.23-7.49 (m, ArH), 7.85-7.97 (m, ArH) 11.33 (br, s, OH)

[Hydroxy((Bis(2,2,2-Triflouroethyl)Phosphoryl)oxy)iodo] Benzene

A solution of bis(2,2,2-triflouroethyl) phosphate (5..63 g, 21.5 mmol) in acetonitrile (35 mL) was added to a mixture of (diacetoxyiodo) benzene (7.03 g, 21.8 mmol) in acetonitrile (35 mL) and water (0.77 g, 43 mmol). The resulting mixture was allowed to stir for 4 hrs at room temperature, after which it was refrigerated overnight. Only a tiny, amount of crystalline solid was separated out, which was filtered off. The filtrate was concentrated and the residual oil was dried under vacuum to give a pale yellow viscous oil. Identified by ^{1}H NMR analysis as [hydroxy((bis(2,2,2-triflouroethyl)phosphoryl)-oxy)iodo] benzene, yield 9.63 g, (93 %). Attempts to crystallize the oil failed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17-4.28 (m, J = 8.10 Hz, 4H, OCH_2), 7.23-7.49 (m, ArH), 7.85-7.97 (m, ArH) 11.5 (br s, 1H, POH); ^{13}C NMR ($CDCl_3$) δ 62.56 – 64.17 (dq, J = 4.6 Hz), 120.68 -124.35 (dd, J = 10.6 Hz), 127.66 (s), 128.54 (s), 130.45 (s), 137.69 (s); ^{31}P NMR ($CDCl_3$) -2.86 (s)

[Hydroxy((Bis(2-chloroethyl)Phosphoryl)oxy)iodo] Benzene

A solution of bis(2-chloroethyl) phosphate (3.42 g, 15.3 mmol) in acetonitrile (25 mL) was added to a mixture of (diacetoxyiodo) benzene (4.83 g, 15 mmol) in acetonitrile (25 mL) and water 0.54 g (30 mmol). The resulting mixture was allowed to stir for 4 hrs at room temperature, after which it was refrigerated overnight. Only a tiny, amount of

crystalline solid was separated out, which was filtered off. The filtrate was concentrated and the residual oil was dried under vacuum to give a pale yellow viscous oil, yield 5.37g (79 %): Identified by ^{1}H NMR analysis as [hydroxy((bis(2-chloroethyl)phosphoryl)oxy) iodo]benzene. Attempts to crystallize the oil failed; it was used as is. ^{1}H NMR ($CDCl_3$) δ 3.78 (t, J = 6.5 Hz, 4H, CH_2Cl), 4.31 (q, J = 5.6 Hz, 4H, OCH_2), 7.23-7.49 (m, ArH), 7.85-7.97 (m, ArH) 11.33 (br, s, OH)

Synthesis of Mono-Ketol Dialkyl Phosphate esters.

α-((Bis(phenyl)Phosphoryl)oxy) Acetophenone

To a mixture of HPIB (2.37 g, 5.04 mmol) in acetonitrile (40 mL) stirred at reflux to give a yellow solution, was added a solution of acetophenone (1.25 g, 10.4 mmol) in acetonitrile (5 mL) and the mixture was stirred at reflux for 4 hrs. The solvent was removed on a rotary evaporator to give a brown oil, which was taken in methylene chloride (70 mL) and washed with 5% $NaHCO_3$ (2 x 3 0 mL) and then with water (2 x 30 mL), dried ($MgSO_4$). Filtration and removal of the solvent gave an orange oil, which was warmed (45 ^{o}C) under vacuum to remove the impurities (iodobenzene and acetophenone) Identified by ^{1}H NMR analysis as the title compound; yield 1.15 g, (62 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (d, J = 10.1 Hz, 2H, CH_2), 7.16-7.43 (m, 10H), 7.47-7.68 (m, 3H) 7.9 (d, J = 2H), ^{13}C NMR ($CDCl_3$) δ 69.81 (d, J = 5.7 Hz, CH_2), 120.7 (d, J = 4.9 Hz), 125.39 (s), 127.65 (s) 128.76 (s), 129.67 (s), 133.93 (s), 150.3 (d, J = 7.5 Hz), 191.07 (d, J = 5.7 Hz,); ^{31}P NMR ($CDCl_3$) δ -12.4 (s)

α-((Bis(phenyl)Phosphoryl)oxy) p-Methoxyacetophenone

To a mixture of HPIB (2.37 g, 5.04 mmol) in acetonitrile (40 mL) stirred at reflux to give a yellow solution, was added p-methoxyacetophenone (1.56 g, 10.4 mmol) in acetonitrile (5 mL) and the mixture was stirred at reflux for 4 hrs. The solvent was removed on a rotary evaporator to give an oil, which was taken in methylene chloride (70 mL) and washed with 5 % NaHCO3 (2 x 30 mL) and then with water (2 x 30 mL), dried ($MgSO_4$). Filtration and concentration of the filtrate gave a brown solid, which was triturated in warmed hexane to remove the impurities (iodobenzene and p-methoxy-acetophenone). A light brown cottony-solid was obtained and identified by ^{1}H NMR analysis as the title compound; yield 1.32g (65 %), melting point 91-93 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H, OCH_3), 5.41 (d, J = 9.9 Hz, 2H, CH_2), 6.92 (d, J = 8.5 Hz, 2H), 7.17-7.39 (m, 10H), 7.87 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.77 (s, OCH_3), 69.92 (d, J = 5.7 Hz, CH_2), 114.34 (s, 2H), 120.45 (d, J = 4.9 Hz), 125.71 (s), 130.01 (s), 130.41 (s), 158.5 (d, J = 7.5 Hz), 208.03 (d, J = 5.7 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ −12.4 (t)

α-((Bis(phenyl)Phosphoryl)oxy) Acetone

To a mixture of HPIB (2.37 g, 5.04 mmol) in acetonitrile (40 mL) stirred at reflux to give a yellow solution, was added dry reagent grade acetone (10 mL , 135 mmol) and the mixture was stirred at reflux for 25 mins to give a colorless solution. The solvent was removed on a rotary evaporator to give a yellow oil, which was taken in methylene chloride (70 mL) and washed with 5 % $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30

mL), dried ($MgSO_4$). Filtration and concentration of the filtrate gave a light yellow oil, which was warmed under vacuum the impurities (iodobenzene and acetone). The isolated yellow oil was dried, identified by ^1H NMR analysis as the title compound, yield 1.37 g (89 %): ^1H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H, CH_3), 4.71 (d, J = 9.4 Hz, 2H, CH_2), 7.19-7.39 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ 26.16 (s, CH_3), 71.86 (d, J = 6.3 Hz, CH_2), 120.26 (d, J = 4.9 Hz) 125.83 (s), 130.05 (s), 150.47 (d, J = 7.4Hz), 201.85 (d, J = 6.6 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ -11.54 (s)

α-((Bis(phenyl)Phosphoryl)oxy) p-Nitroacetophenone

To a mixture of HPIB (2.37 g, 5.04 mmol) in acetonitrile (40 mL) stirred at reflux to give a yellow solution, was added p-nitroacetophenone (1.29 g, 7.81 mmol) in acetonitrile (5 mL) and the mixture was stirred at reflux for 4 hrs. The solvent was removed on a rotary evaporator to give a yellow oil, which was taken in methylene chloride (70 mL) and washed with 5 % $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL), dried ($MgSO_4$). Filtration and concentration of the filtrate gave a brown solid (crude 1.69 g, mp 65-68 ^oC), which was triturated in warmed hexane to remove the impurities (iodobenzene and p-nitroacetophenone). The isolated brown solid was dried and identified by ^1H NMR analysis as the title compound, yield 1.52 g (73 %), melting point 67-69 ^oC: ^1H NMR (300 MHz, $CDCl_3$) δ 5.37 (d, J = 10.2 Hz, 2H, CH_2), 7.27-7.40 (m, 10H, ArH), 8.03-8.16 (dd, J = 8.5 Hz, 2H), 8.29-8.35 (t, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 70.21 (d, J = 5.4 Hz, CH_2), 120.37 (d, J = 4.9 Hz), 124.1 (s), 124.3 (s), 129.52 (s), 130.10 (s), 141.7 (s), 149.3 (s), 151.6 (s), 196.3(d, C=O); ^{31}P NMR ($CDCl_3$) δ -11.08 (s)

α-((Bis(phenyl)Phosphoryl)oxy) Pinacolone

To a mixture of HPIB (2.08 g, 4.42 mmol) in acetonitrile (35 mL) stirred at reflux to give a yellow solution, was added a solution of pinacolone (3,3-dimethyl-2-butanone, tert-butyl methyl ketone) (0.85 g, 8.50 mmol) in acetonitrile (5 mL) and the mixture was stirred at reflux for 4 hrs. The solvent was removed on a rotary evaporator to give a yellow oil, which was taken in methylene chloride (70 mL) and washed with 5 % $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL), dried ($MgSO_4$). Filtration and concentration of the filtrate gave 2.01 g (crude) of yellow oil, which was warmed (45 ^oC) under vacuum to remove the impurities (iodobenzene and pinacolone). The yellow oil that was isolated was identified by ^1H NMR analysis as the title compound, yield 1.21 g, (79 %). ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 9H, $(CH_3)_3$), 5.01 (d, J = 10.07 Hz, 2H, CH_2), 7.08-7.37 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ 26.29 (s, $(CH_3)_3$), 40.97 (s, $C(CH_3)_3$), 68.56 (d, J = 5.7 Hz, CH_2), 120.37 (d, J = 4.9 Hz), 125.39 (s), 130.41 (s), 150.55 (d, J = 7.5 Hz), 206.85 (d, J = 5.7 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ -10.94 (s)

α-((Bis(methyl)Phosphoryl)oxy) Acetophenone

To a mixture of [hydroxy((bis(methyl)phosphoryl)oxy)iodo] benzene (2.37 g, 6.85 mmol) in acetonitrile (40 mL) stirred at reflux to give a yellow solution, was added acetophenone (1.25 g , 10.4 mmol) in acetonitrile (5 mL) and the mixture was stirred at reflux for 4 hrs. The solvent was removed on a rotary evaporator to give a brown oil, which was taken in methylene chloride (70 mL) and washed with 5 % $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL), dried ($MgSO_4$). Filtration and concentration of the

filtrate gave a brown oil, which was warmed (45 ^{o}C) under vacuum to remove the impurities (iodobenzene and acetophenone). The brown oil that was isolated was identified by ^{1}H NMR analysis as the title compound, yield 1.17 g (70 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (d, J = 11.3 Hz, 6H, CH_3), 5.34 (d, J = 10.5 Hz, 2H, CH_2), 7.47-7.52 (t, J = 7.5 Hz, 2H), 7.59-7.65 (t, J = 7.5 Hz, 1H), 7.90 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 54.98 (d, J = 6.0 Hz, OCH_3), 69.14 (d, J = 5.4 Hz, CH_2), 127.91 (s), 129.13 (s), 134.25 (s), 136.8 (s), 192.28 (d, J = 4.6 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ1.90 (s)

α-((Bis(methyl)Phosphoryl)oxy) Acetone

To a mixture of [hydroxy((bis(methyl)phosphoryl)oxy)iodo] benzene (2.37 g, 6.85 mmol) in acetonitrile (40 mL) stirred at reflux to give a yellow solution, was added (10 mL) of dry reagent grade acetone and the mixture was stirred at reflux for 25 mins. The solvent was removed on a rotary evaporator to give a brown oil, which was taken in methylene chloride (70 mL) and washed with 5 % $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL), dried ($MgSO_4$). Filtration and concentration of the filtrate gave a light brown oil, which was warmed (45 ^{o}C) under vacuum to remove the impurities (iodobenzene and acetone). The brown oil that was isolated was identified by ^{1}H NMR analysis as the title compound, yield 1.07g, (86 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3), 3.83 (d, J = 11.1 Hz, 6H, CH_3), 4.58 (d, J = 9.8 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 26.07 (s, CH_3), 54.95 (d, J = 6.0 Hz, OCH_3), 71.04 (d, J = 6.0 Hz, CH_2), 202.25 (d, J = 5.4 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ 1.59 (s)

α-((Bis(methyl)Phosphoryl)oxy) p-Methoxyacetophenone

To a mixture of [hydroxy((bis(methyl)phosphoryl)oxy)iodo] benzene (2.37 g, 6.85 mmol) in acetonitrile (40 mL) stirred at reflux to give a yellow solution, was added p-methoxyacetophenone (1.56 g , 10.4 mmol) in acetonitrile (5 mL) and the mixture was stirred at reflux for 4 hrs. The solvent was removed on a rotary evaporator to give an oil, which was taken in methylene chloride (70 mL) and washed with 5% $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL), dried ($MgSO_4$). Filtration and concentration of the filtrate gave a brown oil which was warmed (45 ^oC) under vacuum to remove the impurities (iodobenzene and p-methoxyacetophenone). The resulting oil was identified by ^1H NMR analysis as the title compound, yield 1.26 g (67 %). ^1H NMR (300 MHz, $CDCl_3$) δ 2.69 (s, 3H, OCH_3), 3.88 (d, J = 11.3 Hz, 6H, CH_3), 5.31 (d, J = 10.5, 2H, CH_2), 8.11 (d, J = 8.5 Hz, 2H), 8.32 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 27.21 (s, OCH_3), 55.17 (d, J = 5.1 Hz, OCH_3), 69.29 (d, J =5.7 Hz, CH_2), 124.08 (s), 129.57 (s), 131.36 (s), 151.80 (d, J = 7.3 Hz), 196.54 (d, J = 5.7 Hz, C=O; ^{31}P NMR ($CDCl_3$) δ 1.98 (s)

α-((Bis(2,2,2-trichloroethyl)Phosphoryl)oxy) Acetophenone

To a mixture of [hydroxy((bis(trichloroethyl)phosphoryl)oxy)iodo] benzene (2.93 g, 5.04 mmol) in acetonitrile (40 mL) stirred at reflux to give a yellow solution, was added a solution of acetophenone (1.25 g , 10.4 mmol) in acetonitrile (5 mL) and the mixture was stirred at reflux for 4 hrs. The solvent was removed on a rotary evaporator to give a brown oil, which was taken in methylene chloride (70 mL) and washed with 5 %

$NaHCO_3$ (2 x 3,0 mL) and then with water (2 x 30 mL), dried ($MgSO_4$). Filtration and concentration of the filtrate gave a light brown oil, which was warmed (45 ^oC) under vacuum. The resulting brown solid was triturated in hexane filtered off and dried. It was identified by ^1H NMR analysis as the title compound, yield 1.21 g (50 %). ^1H NMR (300 MHz, $CDCl_3$) δ 4.73-4.87 (m, 4H, OCH_2), 5.48 (d, J = 13.0 Hz, 2H, CH_2), 7.51 (t, J = 7.8 Hz, 2H), 7.65 (t, J = 7.3 Hz, 1H), 7.89 (d, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 70.23 (d, J = 5.7 Hz, CH_2), 77.64 (d, J = 4.3 Hz, OCH_2), 94.79 (d, J = 11.7 Hz, CCl_3), 127.91 (s), 129.26 (s), 133.61 (s), 134.59 (s), 191.70 (d, J = 5.7 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ -3.51 (s)

α-((Bis(2,2,2-trichloroethyl)Phosphoryl)oxy) p-Methoxyacetophenone

To a mixture of [hydroxy((bis(trichloroethyloxy)phosphoryl)oxy)iodo] benzene (2.93 g, 5.04 mmol) in acetonitrile (40 mL) stirred at reflux to give a yellow solution, was added a solution of p-methoxyacetophenone (1.25 g , 8.32 mmol) in acetonitrile (5 mL) and the mixture was stirred at reflux for 4 hrs. The solvent was removed on a rotary evaporator to give a brown oil, which was taken in methylene chloride (70 mL) and washed with 5 % $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL), dried ($MgSO_4$). Filtration and concentration of the filtrate gave a brown oil, which was warmed (45 ^oC) under vacuum and refrigerated overnight to give a brown solid. The resulting solid was trituration in hexane, filtered off and dried. It was identified by ^1H NMR analysis as the title compound, yield 1.33 g, (52 %), melting point 61-63 ^oC: ^1H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H, OCH_3), 4.75-4.87 (m, J = 10.1 Hz, 4H, OCH_2), 5.43 (d, J = 12.9

Hz, 2H, CH_2), 6.97 (d, J = 9.0 Hz, 2H), 7.87 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.79 (s, OCH_3), 69.96 (d, J = 5.7 Hz, CH_2), 77.64 (d, J = 4.3 Hz, OCH_2), 94.91 (d, J = 11.7 Hz, CCl_3), 114.47 (s), 126.58 (s), 30.27 (s), 164.63 (s), 190.07 (d, J = 5.7 Hz, C=O), ^{13}P NMR ($CDCl_3$) -3.46 (s)

α-((Bis(2,2,2-trichloroethyl)Phosphoryl)oxy) Acetone

To a mixture of [hydroxy((bis(trichloroethyl)phosphoryl)oxy)iodo] benzene (2.93 g, 5.04 mmol) in acetonitrile (40 mL) stirred at reflux to give a yellow solution, was added dry reagent grade acetone (10 mL, 135 mmol) and the mixture was stirred at reflux for 30 mins. The solvent was removed on a rotary evaporator to give a brown oil, which was taken in methylene chloride (70 mL) and washed with 5 % $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL) and dried ($MgSO_4$). Filtration and concentration of the filtrate gave a yellow oil, which was identified by ^1H NMR analysis as the title compound, yield 1.26 g (60 %): ^1H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3), 4.73-4.87 (m, J = 10.1 Hz, 4H, OCH_2), 5.48 (d, J = 12.9 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$) 26.06 (s, CH_3), 71.17(d, J = 5.7 Hz, CH_2), 77.23 (d, J = 4.6 Hz, OCH_2), 94.79 (d, J = 11.7 Hz, CCl_3), 203.07 (d, J = 5.7 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ -4.68 (s)

α-((Bis(2,2,2-trichloroethyl)Phosphoryl)oxy) p-Nitroacetophenone

To a mixture of [hydroxy((bis(2,2,2-trichloroethyl)phosphoryl)oxy)iodo]benzene (2.93 g, 5.04 mmol) in acetonitrile (40 mL) stirred at reflux to give a light yellow solution, was added a solution of p-nitroacetophenone (1.45 g , 8.80 mmol) in acetonitrile

(5 mL) and the mixture was stirred at room temperature for 12 hrs. The solvent was removed on a rotary evaporator to give a brown oil, which was taken in methylene chloride (70 mL) and washed with 5 % $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL) and dried ($MgSO_4$). Filtration concentration of the filtrate gave a brown solid, which was triturated in hexane filtered off and dried, identified by ^1H NMR analysis as the title compound, yield 1.45 g (55 %), melting point 53-55 ^oC: ^1H NMR (300 MHz, $CDCl_3$) δ 4.73-4.85 (m, J = 6.4 Hz, 4H, OCH_2), 5.51 (d, J = 12.7 Hz, 2H, CH_2), 8.10 (d, J = 8.7 Hz, 2H), 8.3 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 69.81 (d, J = 5.7 Hz, CH_2), 77.64 (d, J = 4.3 Hz, OCH_2), 94.79 (d, J = 11.7 Hz, CCl_3), 120.7 (d, J = 4.9 Hz), 129.67 (s), 133.93 (s), 150.3 (d, J = 7.5 Hz), 191.07 (d, J = 5.7 Hz, C=O)

α-((Bis(2,2,2-trifluoroethyl)Phosphoryl)oxy) Acetophenone

To a mixture of [hydroxy((bis(trifluoroethyl)phosphoryl)oxy)iodo] benzene (2.43 g, 5.04 mmol) in acetonitrile (40 mL) stirred at room temperature to give a light yellow solution, was added a solution of acetophenone (1.25 g , 10.4 mmol) in acetonitrile (5 mL) and the mixture was stirred at room temperature for 12 hrs. The solvent was removed on a rotary evaporator to give a brown oil, which was taken in ethylene chloride (70 mL) and washed with 5% $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL) and dried ($MgSO_4$). Filtration and concentration of the filtrate gave a brown oil, which was warmed (45 ^oC) under vacuum, identified by ^1H NMR analysis as the title compound, yield 0.79 g (41 %): ^1H NMR (300 MHz, $CDCl_3$) δ 4.29-4.40 (m, J = 8.10 Hz, 4H, OCH_2), 5.45 (d, J = 12.9 Hz, 2H, CH_2), 7.49-7.68 (m, 3H), 7.90 (d, J = 8.8Hz,

2H); ^{13}C NMR ($CDCl_3$) δ 63.68 - 65.21 (dq, J = 4.3 Hz), 70.19 (d, J = 5.7 Hz, CH_2), 120.71- 124.39 (dd, J = 10.6 Hz), 128.76 (s), 129.29 (s), 133.93 (s), 150.3 (d, J = 7.5 Hz), 191.64 (d, J = 5.7 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ -1.49 (s)

α-((Bis(2,2,2-trifluoroethyl)Phosphoryl)oxy) Acetone

To a mixture of [hydroxy((bis(trifluoroethyl)phosphoryl)oxy)iodo] benzene (1.77 g, 3.67 mmol) in acetonitrile (30 mL) stirred at room temperature to give a light yellow solution, was added dry reagent grade acetone (7.00 mL, 94.50 mmol) and the mixture was stirred at room temperature for 12 hrs. The solvent was removed on a rotary evaporator to give a brown oil, which was taken in methylene chloride (70 mL) and washed with 5% $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL) and dried ($MgSO_4$). Filtration and concentration of the filtrate gave a light yellow oil, which was warmed (45 ^oC) under vacuum, and identified by ^1H NMR analysis as the title compound, yield 0.84 g (72 %). ^1H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3), 4.41-4.58 (m, J = 8.10 Hz, 4H, OCH_2), 4.71 (d, J = 12.5 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 25.73 (s, CH_3), 63.67- 65.18 (dq, J = 4.3 Hz), 71.82 (d, J = 5.7 Hz, CH_2), 200.64 (d, J = 5.7 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ -2.96 (s)

α-((Bis(2,2,2-trifluoroethyl)Phosphoryl)oxy) Pinacolone

To a mixture of [hydroxy((bis(trifluoroethyl)phosphoryl)oxy)iodo]benzene (2.43 g, 5.04 mmol) in acetonitrile (40 mL) stirred at room temperature to give a light yellow solution, was added a solution of pinacolone (3,3-dimethyl-2-butanone, tert-butyl methyl

ketone) (1.00 g, 10.00 mmol) in acetonitrile (5 mL) and the mixture was stirred at room temperature for 12 hrs. The solvent was removed on a rotary evaporator to give a brown oil, which was taken in methylene chloride (70 mL) and washed with 5% $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL) and dried ($MgSO_4$). Filtration and concentration of the filtrate gave a yellow oil, which was warmed (45 ^oC) under vacuum and identified by ^1H NMR analysis as the title compound, yield 0.96 g (53%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H, $(CH_3)_3$), 4.38-4.60 (m, J = 8.10 Hz, 4H, OCH_2), 4.95 (d, J = 13.6 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 63.67- 65.18 (dq, J = 4.3 Hz), 69.81 (d, J = 5.7 Hz, CH_2), 120.71- 124.39 (dd, J = 10.6 Hz), 206.87 (d, J = 5.7 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ -2.19 (s)

α-((Bis(2-Chloroethyl)Phosphoryl)oxy) Acetophenone

To a mixture of [hydroxy((bis(2-chloroethyl)phosphoryl)oxy)iodo] benzene (2.23 g, 5.04 mmol) in acetonitrile (40 mL) stirred at reflux to give a yellow solution, was added a solution acetophenone (1.25 g , 10.4 mmol) in acetonitrile (5 mL) and the mixture was stirred at reflux for 4 hrs. The solvent was removed on a rotary evaporator to give a brown oil, which was taken in methylene chloride (70 mL) and washed with 5% $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL) and dried ($MgSO_4$). Filtration and concentra- tion of the filtrate gave a light brown oil, which was warmed (45 ^oC) under vacuum and identified by ^1H NMR analysis as the title compound, yield 0.77 g (45 %): ^1H NMR (300 MHz, $CDCl_3$) δ 3.74-3.83 (m, 4H, $ClCH_2$), 4.33-4.47 (m, 4H, OCH_2), 5.41 (d, J = 12.9 Hz, 2H, CH_2), 7.48-7.54 (t, J = 7.5 Hz, 2H), 7.61-7.66 (t, J = 7.5 Hz,

1H), 7.97 (d, J = 8.8Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 42.65 (d, J = 8.2 Hz, $ClCH_2$), 67.63 (d, J = 5.2 Hz, OCH_2), 69.96 (d, J = 5.7 Hz, CH_2), 127.65 (s), 128.76 (s), 129.67 (s), 133.93 (s), 191.07 (d, J = 5.7 Hz, C=O)

α-((Bis(2-Chloroethyl)Phosphoryl)oxy) p-Methoxyacetophenone

To a mixture of [hydroxy((bis(2-chloroethyl)phosphoryl)oxy)iodo] benzene (2.23 g, 5.04 mmol) in acetonitrile (40 mL) stirred at reflux to give a yellow solution, was added a solution p-methoxyacetophenone (1.56 g , 10.4 mmol) in acetonitrile (5 mL) and the mixture was stirred at reflux for 4 hrs. The solvent was removed on a rotary evaporator to give a brown oil, which was taken in methylene chloride (70 mL) and washed with 5% $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL) and dried ($MgSO_4$). Filtration and concentration of the filtrate gave a oil, which was warmed (45 ^oC) under vacuum to give a brown solid. The solid was triturated in hexane and identified by ^{1}H NMR analysis as the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (t, J = 10.1 Hz, 2H, CH_2Cl), 4.73-4.4.87 (m, J = 10.1 Hz, 2H, OCH_2), 5.48 (d, J = 12.9 Hz, 2H, CH_2), 7.49-7.68 (m, 2H), 7.90 (d, J = 8.8Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 42.65 (d, J = 8.2 Hz, $ClCH_2$), 55.93 (s, OCH_3), 67.63 (d, J = 5.6 Hz, OCH_2), 69.81 (d, J = 5.7 Hz, CH_2), 114.27 (s), 129.67 (s), 130.73 (s), 164.62(s), 195.48 (d, J = 5.7 Hz, C=O);

α-((Bis(2-Chloroethyl)Phosphoryl)oxy) Acetone

To a mixture of [hydroxy((bis(2-chloroethyl)phosphoryl)oxy)iodo] benzene (2.23 g, 5.04 mmol) in acetonitrile (40 mL) stirred at reflux to give a yellow solution, was added dry reagent grade acetone (10 mL , 135 mmol) and the mixture was stirred at reflux for

30 mins. The solvent was removed on a rotary evaporator to give a brown oil, which was taken in methylene chloride (70 mL) and washed with 5% $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL) and dried ($MgSO_4$). Filtration and removal of the solvent gave a light yellow oil, which was warmed under vacuum to give 1.15 g (62 %) of the title compound .^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (t, J = 10.1 Hz, 2H, CH_2Cl), 4.27-4.38 (m, 2H, OCH_2), 4.73 (d, J = 10.5 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 42.65 (d, J = 8.2 Hz, $ClCH_2$), 67.63 (d, J = 5.2 Hz, OCH_2), 69.81 (d, J = 5.7 Hz, CH_2), 191.07 (d, J = 5.7 Hz, C=O)

α-((Bis(Ethyl)Phosphoryl)oxy) Acetophenone

To a mixture of [hydroxy((bis(ethyl)phosphoryl)oxy)iodo] benzene (1.89 g, 5.04 mmol) in acetonitrile (40 mL) stirred at reflux to give a yellow solution, was added a solution acetophenone (1.25 g ,10.4 mmol) in acetonitrile (5 mL) and the mixture was stirred at reflux for 4 hrs. The solvent was removed on a rotary evaporator to give a brown oil, which was taken in methylene chloride (70 mL) and washed with 5 % $NaHCO_3$ (2 x 30 mL) and then with water (2 x 30 mL) and dried ($MgSO_4$). Filtration and removal of the solvent gave a light yellow solid, which was recrystallized in hexane gave 1.15 g (62%) of the title compound . ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, J = 6.1 Hz, 6H, CH_3), 4.23 (m, 4H, OCH_2), 5.29 (d, J = 9.9 Hz, 2H, CH_2), 7.48 (t, 2H), 7.61 (t, 1H), 7.87 (d, J = 8.8Hz, 2H): ^{13}C NMR ($CDCl_3$) δ 43.32 (d, CH_3), 65.72 (d, OCH_2), 70.21 (d, J = 5.4 Hz, CH_2), 129.32 (s), 129.52 (s), 130.11 (s), 136.33 (s), 196.50 (d, J = 5.7 Hz, C=O); ^{13}P NMR ($CDCl_3$) δ -11.03 (s)

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