INTERMOLECULAR ADDITION OF ALDEHYDES TO KETONES VIA ACYL PHOSPHONATES

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INTERMOLECULAR ADDITION OF ALDEHYDES TO KETONES VIA ACYL PHOSPHONATES

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

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ABSTRACT

INTERMOLECULAR ADDITION OF ALDEHYDES TO KETONES VIA ACYL PHOSPHONATES

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This thesis presents a new developed method for first intermolecular aldehyde/ketone cross benzoin coupling. Protected α-keto tertiary alcohols are synthesized starting from easily available acyl phosphonates and ketones via Brook rearrangement in the presence of catalytic amount of cyanide ion. The scopes and the limitations of the methods for the synthesis of tertiary alcohols with α-keto group are discovered.

Keywords: Intermolecular Aldehyde/ketone Coupling, Cross Benzoin Reaction, Unsymmetric Benzoin Reaction, Brook Rearrangement, Umpolung, α-Keto Tertiary Alcohols

ÖZ

AÇİL FOSFONATLAR YOLUYLA ALDEHİTLERİN KETONLARA İNTERMOLEKÜLER KATILIMI

Esiringü, İlker

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Ayhan S. Demir

Mart 2008, 75 sayfa

Bu çalışma moleküller arası aldehitlerin ketonlara çarpraz katılmaları için ilk methodu sunmaktadır. α-Keto tersiyer alkoller, Brook düzenlenmesi ile acilfosfonatlar ve ketonların katalitik miktarda siyanürün varlığında tepkimesinden elde edilmiştir. α-Keto grubu içeren tersiyer alkollerin sentezi için önerilen bu methodun olanakları ve kısıtlamaları ile ilgili çalışmalar yapılmıştır.

Anahtar kelimeler: Moleküller Arası Aldehit/Keton Katılması, Çapraz Benzoin Reaksiyonu, Simetrik Olmayan Benzoin Reaksiyonu, Brook Düzenlenmesi, Umpolung, α-Keto Tersiyer Alkol

To My Family,

ACKNOWLEDGEMENTS

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TABLE OF CONTENTS

LIST OF TABLES

TABLES

LIST OF FIGURES

FIGURES

CHAPTER 1

INTRODUCTION

The subject of synthetic organic chemistry has undergone a vigorous and rich evolution for the over a century. Nonetheless, it continues to advance in power and scope and to develop in new directions at a remarkable pace. There exists infinite number of carbon containing molecules differing in number and types of constituent atoms, in size, in topology, in three dimensional arrangements and construction of these molecules necessitates hard-work for the synthetic organic chemists. Even efficient synthesis require multistep reaction pathway; each meets different requirements. To solve complexity of synthetic problems, a chemist really needs to a rich of synthetic methodology pool to solve different problems with different requirement. As a consequence, new approaches for the construction of either complex synthetic targets or small synthetic building blocks and developments in bond forming or functional group interconversion reaction have been introduced by synthetic organic chemists. The developments related with catalytic methods carbon-carbon bond may be the most important because of operational simplicity, atom economy and steriocontrol over the newly created functionalities. So it is normal to see that many researches are reported for the aim of to develop new methods that are either providing improved solutions to known methods or introducing new synthetic routes.

From early stage of organic chemistry until modern times, organic chemists have given much attention to structure of molecules may exist as natural or synthesized in laboratory and their transformations. In complex or natural product synthesis more systematic approach is needed even if we think complexity of the problem. That depends on the perception of structural feature in reaction products and manipulation of structure in reverse synthetic sense. This method is known as now retrosythetic

analysis. In order to carry out transformations based on polar reactions, it is necessary to identify proper molecular fragments or **synthons** by retrosynthetic analysis. Synthon, which was coined by E. J. Corey, is a structural unit within a molecule which is related to a possible synthetic operation. Since this work is mainly related with cross benzoin reaction, umpolung d^1 synthons and intermolecular aldehyde/ketone cross benzoin coupling will be emphasized where possible.

1.1 Synthons in the synthesis of carbon chains

"Synthons" are defined as units which can be joined to (organic) molecules by known or conceivable synthetic operations. A synthon may be as simple as a methyl anion or as complex as a steroid anion. Since most synthetic reactions, which produced carbon-carbon bonds, are polar, synthon usually contains a nucleophilic electron donor centre (d) or an electrophilic electron acceptor centre (a). When negatively polarized carbon atom (electron donor, d) of one reagent is combined with a positively polarized carbon atom (electron acceptor, a) of another reagent, a new covalent carbon-carbon bond is formed. According to this point of view a simple organic molecule, ethane, can be yielded from the combination of methyl donor synthon "CH_3^-" from the reagent of CH_3Li and methyl acceptor synthon "CH_3^+" from the reagent of CH_3I (Figure1).

$$\underset{(d)}{CH_3Li} + \underset{(a)}{CH_3I} \longrightarrow CH_3 - CH_3 + LiI$$

(a new carbon-carbon bond)

Figure 1.1. Formation of ethane

Synthons are numbered according to the relative positions of a functional group (FG) and the reactive carbon atom.

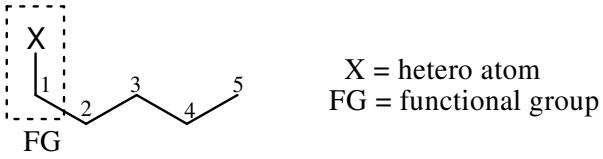


Figure 1.2. Numbering of synthons

If the carbon atom C-1 of the functional group itself is reacting, one has a d^1- or a^1-synthon. If the carbon atom C-2 next to the functional group (the α-carbon atom) is the reaction centre, we call it a d^2- or a^2- synthon. If the β-carbon atom C-3 is the reactive one, we assign d^3 or a^3 to the corresponding synthon, etc. Alkyl synthons without functional groups are called alkylating synthons. The electronegative hetero atom of the functional group may also form covalent bonds with acceptor synthons. In such cases we speak of d^0- synthons. Some examples of synthons are given in Figure 3.

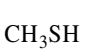
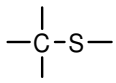
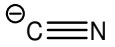
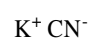
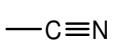
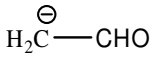
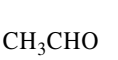
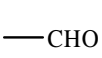
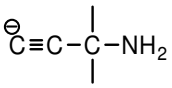
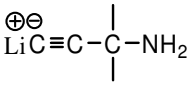
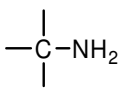
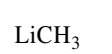
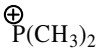
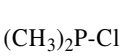
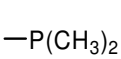
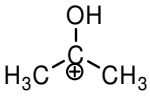
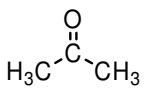
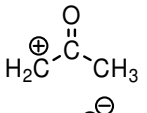
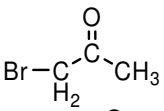
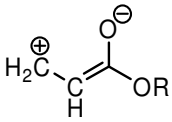
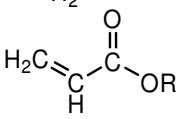
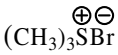
Synthon type	Example	Reagent	Functional group
d^0			
d^1			
d^2			
d^3			
alkyl d			
a^0			
a^1			
a^2			
a^3			
alkyl a			

Figure 1.3. Some examples of synthons

Except from d^0*-synthons,* the combination of two reagents corresponding to one *d-synthon* and one *a-synthon* under appropriate conditions yields an additional carbon-carbon bond. The following obvious rules apply to the arrangement of functionality in the target molecule.

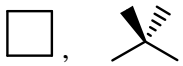
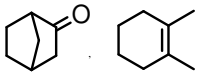
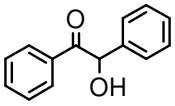
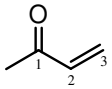
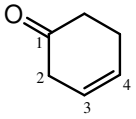
Reacting synthons	Target molecule	Examples
alkyl a + alkyl d	non-functional	
alkyl a+ d^1, alkyl d + a^1	monofunctional	
a^1 + d^1	1,2-difunctional	
a^1 + d^2, a^2 + d^1	1,3-difunctional	
a^1 +d^3, a^2 + d^2, a^3 + d^1	1,4-difunctional	
and so on.		

Figure 1.4. Combination of d-synthons and a-synthons

Reagents with carbonyl type groupings exhibit *a^1or a^3* properties if the carbonyl compound has α,β-unsaturated system. In the presence of acidic or basic catalyst they may react as enol type electron donors such as *d^2* or *d^4* reagents. This reactivity pattern is considered as "normal reactivity" and this type reactivity allows, for example, 1,3- and 1,5-difunctional systems via aldol type Micheal addition reactions. If hetero atoms are introduced or exchanged, the normal reactivity of carbon atoms may be inverted, or a given reactivity may shift from one carbon atom to another. It is also possible to change reactivity by adding carbon fragments to functional groups. All these processes leading to changes of the synthon type have been called "umpolung" which means dipole inversion. In rare cases the polarity of hetero atoms may also be inverted, for instance, R-$S^{(d)}$-H → R-$S^{(a)}$-$S^{(a)}$-H. In retro-synthetic analysis it is often useful to consider an umpolung of a given reagent, especially if the target molecule contains 1,2- or 1,4- difunctional systems. The schemes given

below summarize some typical umpolung reactions and some specific synthons with their equivalent reagents.

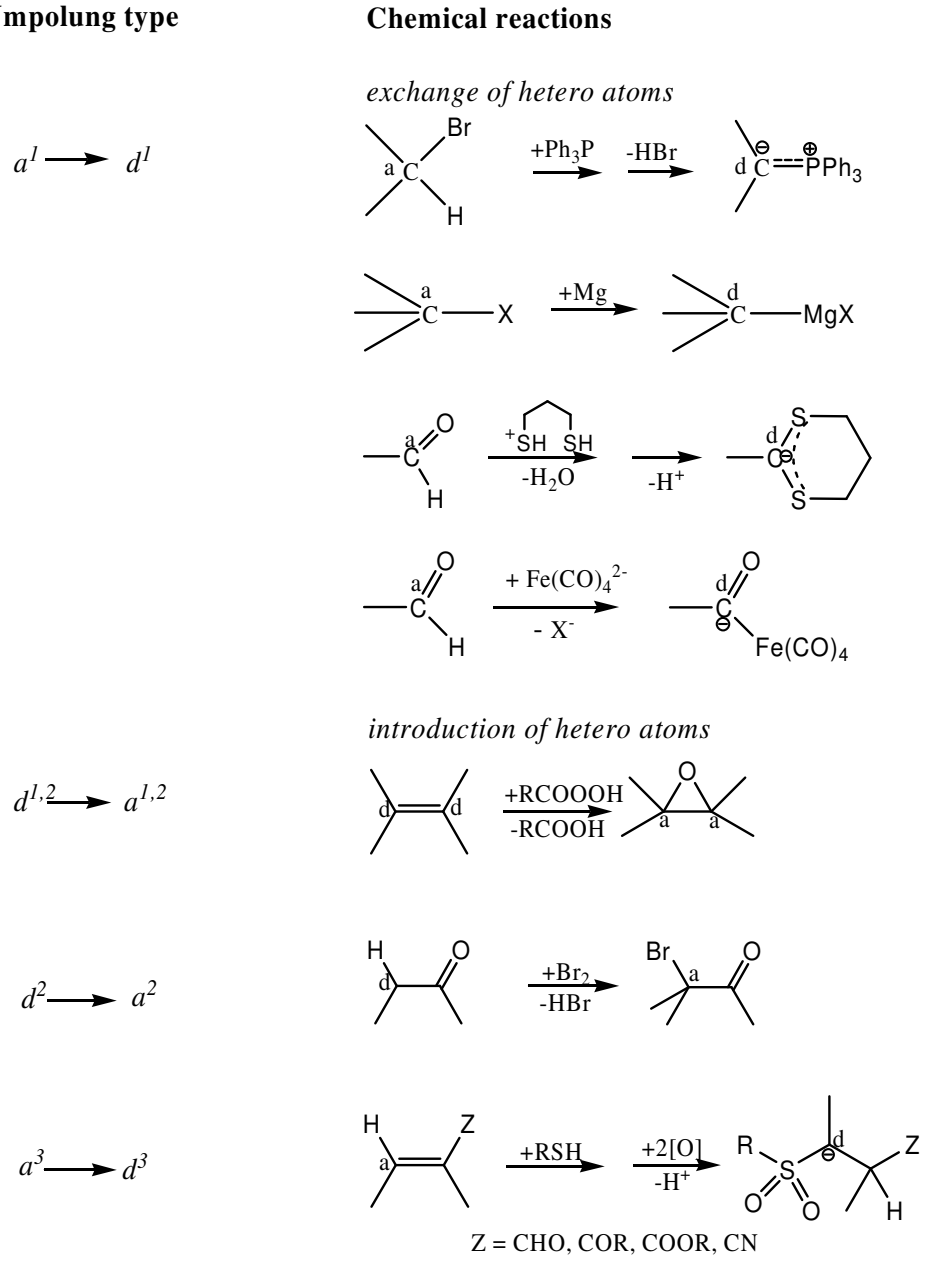


Figure 1.5. Some typical umpolung reactions and some specific synthons

Fortunately methods of reactivity Umpolung is not restricted with exchange of hetero atoms or introduction of hetero atoms. The organic chemistry also achieves the inversion of polarity by addition of carbon fragments [1].

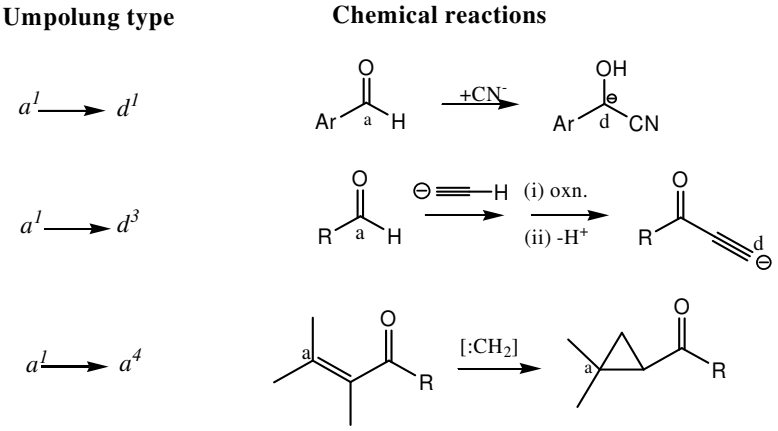


Figure 1.6. Inversion of polarity by addition of carbon fragments

Inverting the inherent chemical reactivity of functional groups would give rise to chemists an alternative approach for the synthesis of target organic molecules. The importance of this approach would be more obvious if we examine the charge affinity pattern of benzoin and derivatives of this molecule. Benzoin molecules consist of α-hydroxy ketone functionality and this functional group will be created by reverse polar coupling of corresponding carbonyl moieties. As depicted in Figure 7, this process needs conversion of charge affinity pattern of one of the carbonyl compounds.

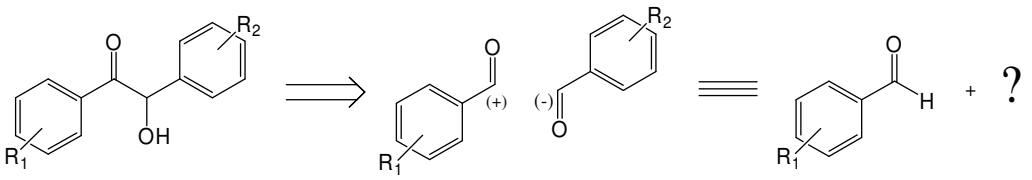


Figure 1.7. Retrosynthesis of benzoin

Nucleophilic carbonyl moieties (as in figure 7) are generally named as "acyl anion equivalents". These d^1 synthons have important role in synthetic organic chemistry so the chemists have found methods to convert the natural charge pattern of carbonyl compound into nucleophilic d^1 center. The next part of this introductory part will introduce developments in acyl anion chemistry and benzoin synthesis reactions that are the most important example of acyl anion chemistry.

1.2 Benzoin condensation reactions

1.2.1 Cyanide ion catalyzed benzoin condensation

The cyanide-ion catalyzed benzoin reaction is an expeditious route to α-hydroxy ketones. The reaction proceeds via a catalytically-generated hydroxyl nitrile anion that functions as an acyl anion equivalent [2]. Benzoin reaction was first discovered by Liebig and Wöhler more than a centry ago [3]. Then Lapworth establish the mechanism of the reaction [4]**.** According to mechanism of benzoin reaction, cyanide ion plays an important role during the reaction. The cyanide ion is a very specific catalyst and serves three different purposes in the course of the reaction. First of all, it acts as a nucleophile to form the corresponding cyanohydrin. Second, it facilitates

the proton abstraction in the umpolung by its inductive effect. The last but not least, it behaves as a leaving group to form benzoin dimerization product and re-enter the catalytical cycle. During the reaction, once the acyl anion of the corresponding aldehyde is formed **3**, it reacts with another molecule of aldehyde and release the cyanide ion to form benzoin dimer product **6**.

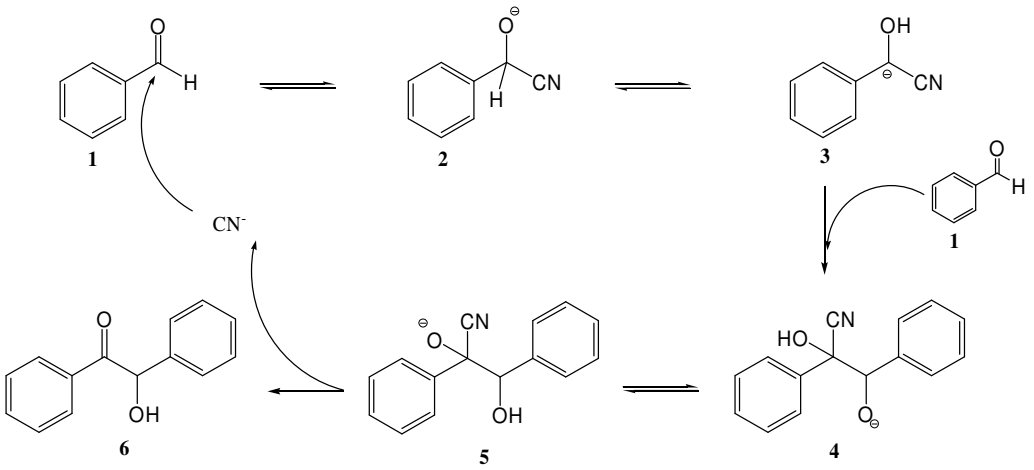


Figure 1.8. Mechanism of benzoin reaction

Although benzoin condensation reaction is one of the easiest synthetic routes for the synthesis of α-hydroxy ketones, this synthetic methodology has some drawbacks. For one thing, aldehydes with strong electron-donating or electron-withdrawing groups do not produce the corresponding benzoin product with a meaningful yield. Secondly, as it is shown, the mechanism of the benzoin reaction, the synthetic route contains reversible steps that cause incomplete dimerization reaction between two aldehyde molecules. Finally, the aim of synthesis of unsymmetrical benzoin will end up with four different benzoin products. In a mixture of two different aldehydes in

the presence of cyanide ion, there will be two different acyl anions to react with two different acceptor aldehydes. This means that a meaningful unsymmetrical benzoin synthesis under classical condition is impossible. Even though it is hard to predict the product distribution, it is safe to say that the synthesis design for an unsymmetrical benzoin product will end up with four different isomers of the desired product. To illustrate the above discussion, we can examine the cross benzoin reaction of the mixture of benzaldehyde and p- fluorobenzaldehyde in the presence of cyanide ion as a catalyst (Figure 9).

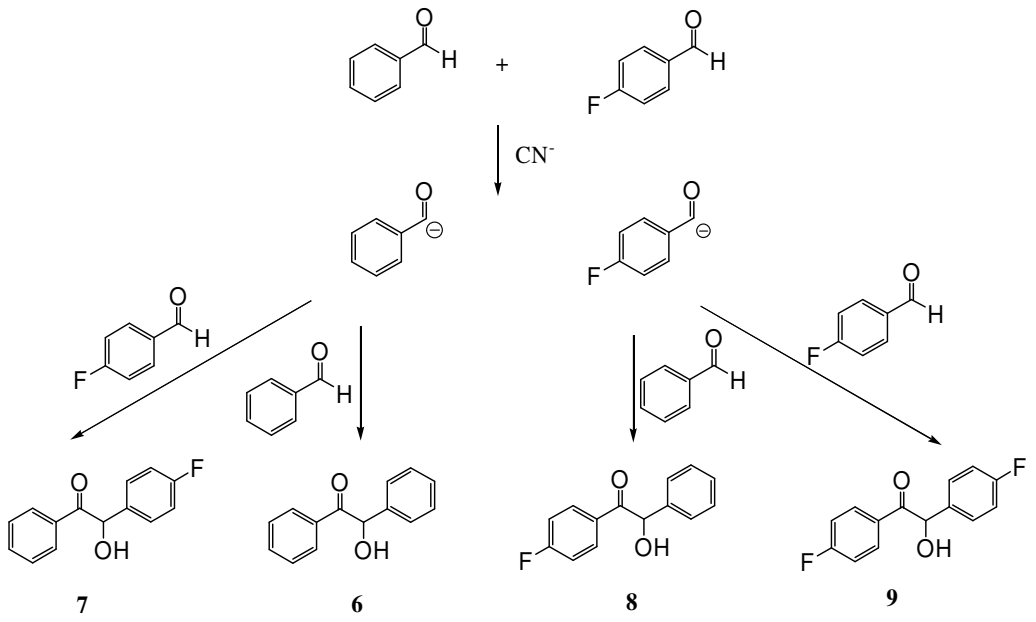
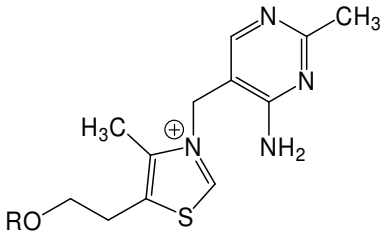


Figure 1.9. Cross benzoin reaction of the mixture of benzaldehyde and p- florobenzaldehyde

Although classical benzoin condensation reaction is a useful reaction, it has drawbacks especially in the synthesis of unsymmetrical benzoin products. On the other hand, there are still synthetic routes in organic chemistry. To overcome this handicap, the chemist should produce kinetically controlled acyl anion equivalents to react with acceptor carbonyl compounds to synthesize a variety of unsymmetrical benzoin derivatives. Developments in the generation of acyl anion equivalents will be discussed also in the following chapters of this thesis.

1.2.2 Thiamine catalyzed benzoin condensation

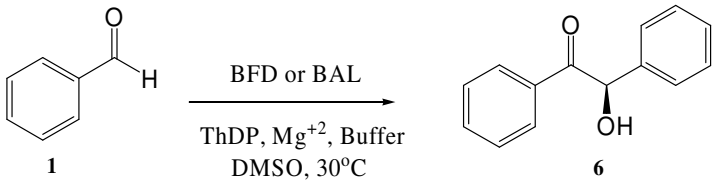
Wöhler and Liebig accidentally discovered the benzoin condensation in 1832 [3]. Their research was focused on cyanohydrins, the products obtained from addition of cyanide ion to aldehydes. For over a hundred years, the cyanide ion was the only observed chemical species as a catalyst in benzoin reactions. In 1958, Breslow discovered that in basic solutions, thiazolium salts are also effective catalysts for the benzoin condensation. Actually, millions of years ago, benzoin reaction was originally developed by nature in nucleophilic acylation reactions catalyzed by lyases in the presence of coenzyme thiamine **10a**. In biochemical terminology, thiamine functions as a coenzyme, a biological molecule that assists in enzymatic reactions. In most cases, coenzymes are directly involved in the biochemical reaction that the enzyme catalyzes since they usually bind the substrate for the reaction. Without the coenzyme, no reaction will take place. Thiamine **10a**, in the form of its pyrophosphate **10b**, is the coenzyme for a number of important biochemical reactions, including the nonoxidative decarboxylations of α-keto acids, the oxidative decarboylations of α-keto acids, and the formation of α-hydroxy ketones [5].



10a, R= H
10b, R=P(O)(OH)OP(O)(OH)$_2$

Figure 1.10. Thiamine and thiaminepyrophosphate

Most biochemical processes are no more than organic chemical reactions carried out under special conditions. Like most reactions in organic chemistry, many biochemical reactions can now be explained using familiar reaction mechanism. To enhance reactivity, and to be stereoselective, enzymes are used to bind substrate in a manner that allows only a single reaction, with stereoselectivity to occur. In addition, enzymatic reactions can be carried out in mild conditions and at moderate pH values. Because of these reasons, it is necessary to point out that there are enzymes providing benzoin products from corresponding aldehydes or pyruvates [6].



1 **6**

BFD = Benzoylformate decarboxylase
BAL = Benzaldehyde lyase
ThDP = Thiamin diphosphate

Figure 1.11. Enzymatic benzoin reactions

Breslow proposed a mechanism for thiamine catalyzed benzoin condensation based on Lapworth's benzoin condensation mechanism in the presence of cyanide ion [5]. Breslow introduced thiazolium unit **11** as a nucleophilic carbene. In basic medium thiazolium unit loses acidic proton attached to C2 carbon to form carbene **12**, which will behave as a new catalyst for acyloin reaction like cyanide ion. This nucleophilic carbene **12** couples with an aldehyde to form enamine **14**. This activated intermediate is actually an acyl anion equivalent of the corresponding aldehyde and reacts with another aldehyde molecule to provide benzoin **6** product and release the carbene to catalytical cycle.

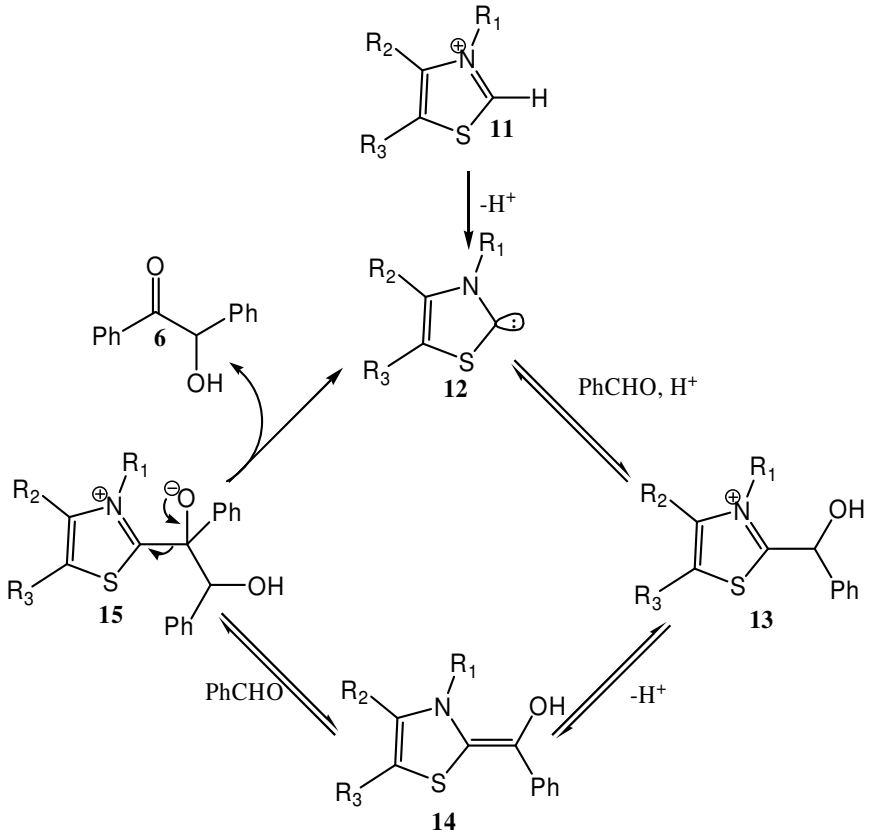


Figure 1.12. Breslow mechanism for thiamine catalyzed benzoin condensation

1.3 Chemistry of reactivity umpolung

1.3.1 Stoichimetric umpolung acylanion precursors; benzoin condensation

Most reactions of organic synthesis are polar and can be described as the reaction of a nucleophile (donor d) with an electrophile (acceptor a). The umpolung of the "natural" reactivity of a functional group opens up an avenue to a new set of reactions. Umpolung strategy converts aldehydes' electrophilic carbonyl functionality into nucleophilic carbanion centers. The resulting d^1 nucleophiles can react with aldehydes (benzoin condensation) or with electron poor polarized olefins (Stetter reaction) [7].

Synthetic chemists have succeeded to generate important organic target with stoichiometic Umpolung approach. One of the most important examples was introduced by Stork G. et al. for the total synthesis of prostaglandin $F_{2\alpha}$ **20,** which is a member of a group of lipid compounds that are derived enzymatically from fatty acids and have important functions in the animal body [8]. They described the successful construction of prostaglandin $F_{2\alpha}$ from D-Glucose (Figure 13). The synthetic plan involves reduction of synthesized molecule **16** with DIBAL-H then addition of HCN to the reduced molecule. The synthetic route continues with the Umpolung strategy and the synthetic approach will end up with the desired target molecule **20**.

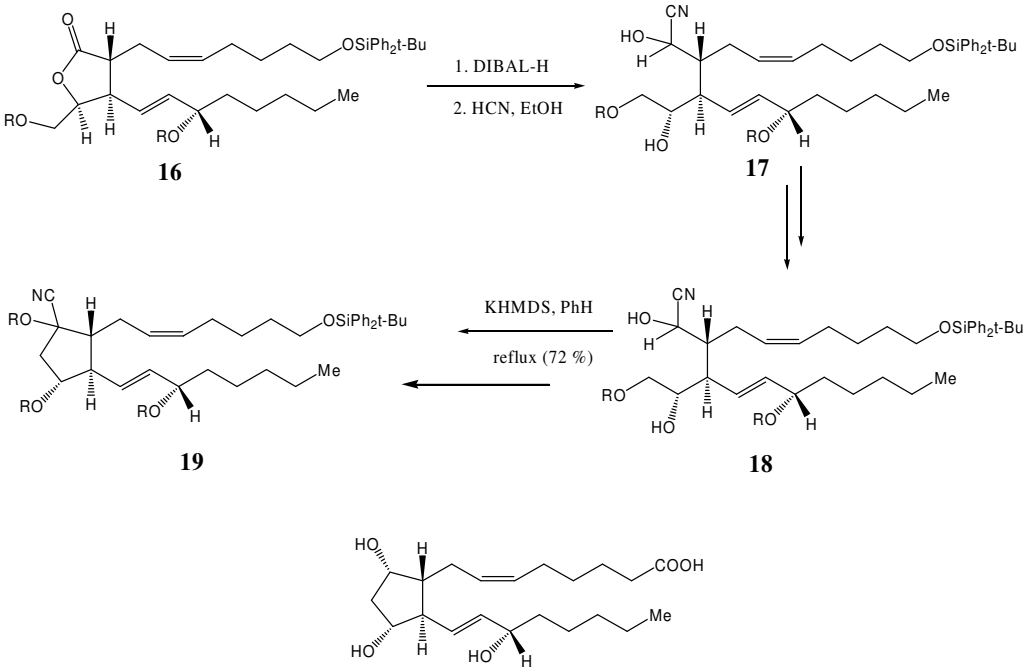
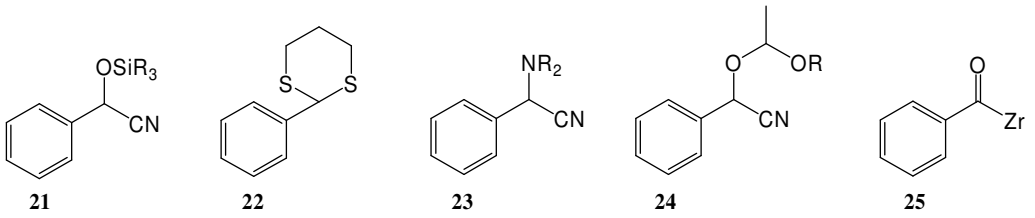


Figure 1.13. Total synthesis of prostaglandin $F_{2\alpha}$

For the design of functionally inverted d^1 reactive center, chemists have introduced many precursors some of which are shown in Figure 14 [9]. These acyl anion precursors have some functioanal groups which stabilize the carbanion like in the case of activated aldehydes intermediates of benzoin condensation. Among the introduced precursors O-silyl- cyanohydrins **21** and dithianes **22** are the most applicable and popular umpolung intermediates developed so far.



21 **22** **23** **24** **25**

Figure 1.14. Popular umpolung intermediates

Hunig introduced O-trimethylsilyl cyanohydrins as a carbanion intermediate for the synthesis of stoichimetric benzoin condensation [9b, c]. Protection of oxygen atom with trimethylsilyl group stabilize the intermediate; otherwise negatively charged oxygen atom will eliminate the cyanide unit to form the corresponding aldehyde molecule. O-trimethylsilyl cyanohydrins are generally used acyl anion precursor in the synthesis of cross benzoin adduct as shown in scheme 9. According to reaction mechanism, O-trimethylsilyl cyanohydrins can be synthesized from the reaction of the corresponding aldehyde and stoichimetric amount TMSCN in the presence of the Lewis acid catalyst. When strong base (LDA) abstracts the acidic proton from O-trimethylsilyl cyanohydrins, the acyl anion equivalent **27** will be generated. Then, the acyl anion reacts with the electrophile **28** to form the intermediate **29**. Hydrolysis of the intermediate will eventually yield the cross benzoin product **31** from two proposed mechanism.

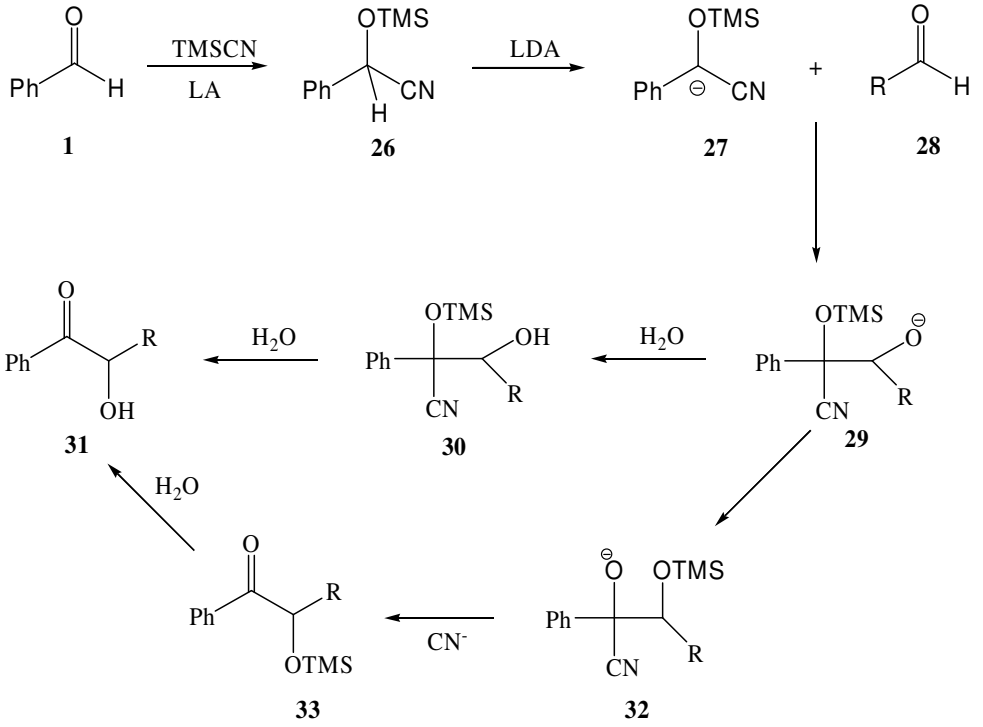


Figure 1.15. O-trimethylsilyl cyanohydrins as a carbnion intermediate for the synthesis of stoichimetric benzoin condensation

Dithiane **22** introduced by Corey-Seebach**,** is another acyl anion precursor used for cross benzoin condensation [9a]. Umpolung benzoin reaction performed by dithiane is a very similar approach with Hunig's O-trimethylsilyl cyanohydrin cross benzoin synthesis. In Corey-Seebach approach, aldehyde **1** is converted to the corresponding dithiane molecule **34** that is deprotonated with again a strong base (BuLi) to produce acyl anion equivalent **35**. The generated carbanion reacts with the electrophile **28** to produce protected α-hydroxy ketone intermediate **36**. The hydrolysis of the intermediate **36** will end up with the cross benzoin product **31**.

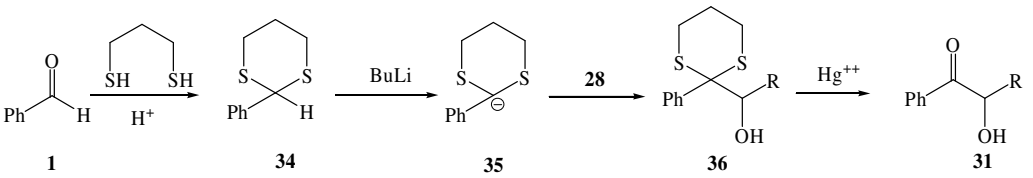


Figure 1.16. Dithiane, acyl anion precursor used for cross benzoin condensation

Although Hunig's O-trimethylsilyl cyanohydrin and Corey-Seebach's dithiane approaches are successful in the synthesis of cross benzoin reactions, the methods suffer from some drawbacks. First of all, atom economy of the methods is low since the methods contain many protection and deprotection steps. Moreover, generation of acyl anion requires strong bases like LDA and BuLi that necessitates controlled temperature. The last but not least, as depicted the mechanisms, synthetic routes contain many steps that cause low overall yield. Considering these limitations, chemist should do better in dealing with generating the acyl anion equivalents.

1.3.2 Cataytic methods for umpolung; benzoin condensation

In comparison to catalytic reactions involving enolates, research addressing analogous catalytic chemistry of acyl anion equivalents has received considerably less attention [10]. This may be due in part to the attendant challenges in the latter class of reactions. Whereas the activation steps of a direct catalytic Michael or aldol reaction may, in the simplest analysis, be broken down into acid-base chemistry, the conversion of an aldehyde into a nucleophilic d^1 center is a less straightforward problem in reaction design [11]. Organic chemists typically find recourse in the conversion of aldehydes into umpolung reagents such as dithianes and protected cyanohydrin derivatives, which may be converted into the derived carbanionic species with a strong base. Such approaches have proven extremely useful in a large

number of contexts, but lack the step economy and aesthetic appeal of their enolate counterparts as we discussed earlier. Increasingly, efforts are being directed at circumventing these shortcomings by accessing and augmenting classic reaction manifolds for effecting carbonyl-polarity reversal: the benzoin and Stetter reactions. Reaction of aldehydes with other aldehydes mediated by cyanide or heterazolium carbenes comprise the most direct methods of acyl anion equivalence based on Brook Rearrangment and have been developed accordingly [12].

The intramolecular 1,2- anionic migration of a silyl group from a carbon atom to an oxygen atom was originally recognized and studied by A.G. Brook in the late 1950s and early 1960s [13]. The migratory aptitude of silyl groups in this context has since been observed to be more general, comprising a family of [1,n]-carbon to oxygen silyl migration commonly referred to as Brook rearrangments (Figure 1.17.). The reverse process, intramolecular migration of a silyl group from oxygen to carbon, was first reported by Speier in 1952 [14] and was later more carefully studied by West et al [15]. As with the carbon to oxygen migrations, further reports established the board scope of oxygen to carbon migrations, which are now typically called retro-Brook rearrangements. The reversibility of the Brook/retro-brook reaction manifold has been demonstrated under variety of circumstances. In addition, many studies have provided evidence suggesting that these reactions proceed via the intermediacy of a pentacoordinate silyl species [16].

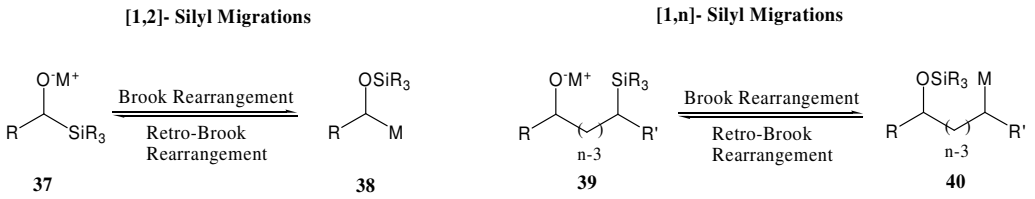


Figure 1.17. Intramolecular anionic migrations of a silyl group from a carbon atom to an oxygen atom

1.3.2.1 Acylsilanes as acyl anion precursors

Acylsilanes are valuable compounds in organic synthesis primarily due to their ability to access the Brook rearrangement manifold upon the addition of a strong nucleophile. Since the formation of an acyl anion equivalent via the reaction of an aldehyde with cyanide ion or thiazolium carbene is the key step in the benzoin condensation, Johnson and coworkers speculated that regiocontrolled direct cross benzoin condensation reactions may be achieved if alternative methods of acyl anion formation could place the reaction under kinetic control. Then, they introduced in situ generation of (silyloxy)nitrile anions from acylsilanes by cyanide-promoted [1,2]-Brook rearrangement as a potent of acyl anion equivalents [17]. The application of this particular silicon migration has been reported by several groups. Degl'Innocenti demonstrated that enones are acylated by acylsilanes under the influence of cyanide catalysis [18], while Reich reported that cyanide triggers an addition/rearrangement/elimination sequence with an α-thiophenyl acylsilane [19]. Takeda's group has shown that (silyloxy)nitrile anions generated by the Brook Rearrangement in the reaction of (β-(trimethylsilyl)-acryloylsilane can undergo methylation at the γ-position. Most recently, cyanide-catalyzed cyanation/1,2-Brook/acylation of acylsilanes have been disclosed [20]. Johnson anticipated that

with cyanide as the catalyst, unsymmetrical α-silyloxy ketone products could be prepared by trapping (silyloxy)nitrile anions with aldehydes (Figure 18).

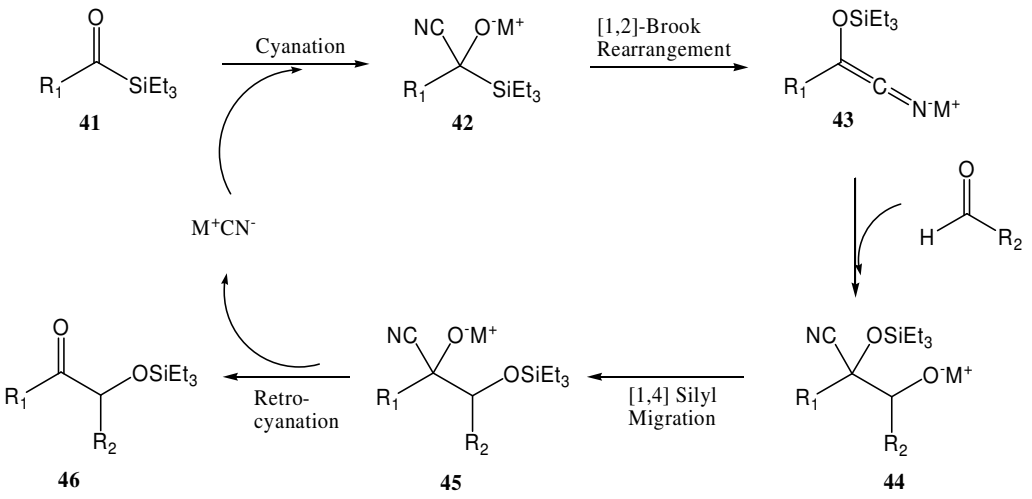
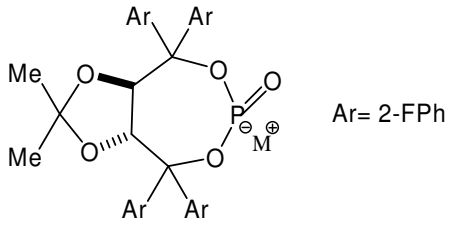


Figure 1.18. Synthesis unsymmetrical α-silyloxy ketone products

KCN in combination with the phase transfer catalyst, 18-crown-6, is an effective reagent for cyanation of electrophilic substrates and an effective catalyst for initiation of the Brook rearrangement. With 10 mol % 18-crown-6 and 30 % equivalent of KCN, silyl-protected benzoin adduct can be obtained in 90 % yield in an operationally convenient reaction time. The method introduced a variety of cross benzoin products resulted from the reaction of different acylsilanes and aldehydes. Reactions between aryl acylsilanes and aryl or heteroaromatic aldehydes give good to exellent yields of α-silyloxy ketone products at ambient temperature. Electron-poor and electron-rich substrates display little difference in reactivity. Significant steric demand is tolerated without a decrease in yield or an increase in reaction time. The more challenging aryl-alkyl and alkyl-aryl benzoin adducts are obtained in

moderate to good yields. Either regioisomeric benzoin adduct can be prepared simply though judicious selection of the acylsilane and the aldehyde. By way of comparision, thiazolium carbene-catalyzed benzoin reaction between benzaldehyde and isobutyraldehyde provides a 2:1 mixture of regioisomeric cross acyloin [21], while the analogous cross silyl benzoin reaction gives only one isomer.

The use of acylsilanes in benzoin synthesis was also expanded to enantioselective variant of this reaction. Important precedent for this hypotesis was provided by Takeda, who demonstrated that lithium diethyl phosphite reacts stoichiometrically with acylsilane to give carbanion after Brook rearrangement [22]. Further, Zimmer had shown that the addition of (silyloxy)phosphanate anion to aldehydes can afford silyl benzoin products [23]. Later, Johnson has shown that the use of chiral metallophosphite **47** provides moderate to high enantioselectivity (81-91 % ee).



47

Figure 1.19. Chiral metallophosphite

It is obvious that cyanide promoted Brook rearrangement of acylsilanes is a good method for not only the catalytic cross benzoin reaction but also enantioselective benzoin condensation. Even though it is well-established method utilizing catalyzed

reactions of acyl anion equivalents, the major limitation of the reaction is the availability of the starting acysilanes. There are various methods for the synthesis of acylsilanes some of which is shown in Figure 20 [24]. The conversion of α,α-dibromobenzyl-silane **49** to acylsilanes on silica gel, and the hydroboration of silylalkynes **50** are the approaches introduced by chemists. The trapping of deprotonated dithianes with chlorosilanes has been employed for years, but this strategy always requires the unmasking of the α-silyl dithiane **51**, which is not always compatible with the substrate. Although the addition of anionic silyl nucleophiles to acid chlorides **52** is typically the most direct method for the synthesis of acylsilanes, this method requires higher amount of silyllithium reagent and suffers from stoichiometric copper(I) cyanide required for the reaction to proceed in high yield.

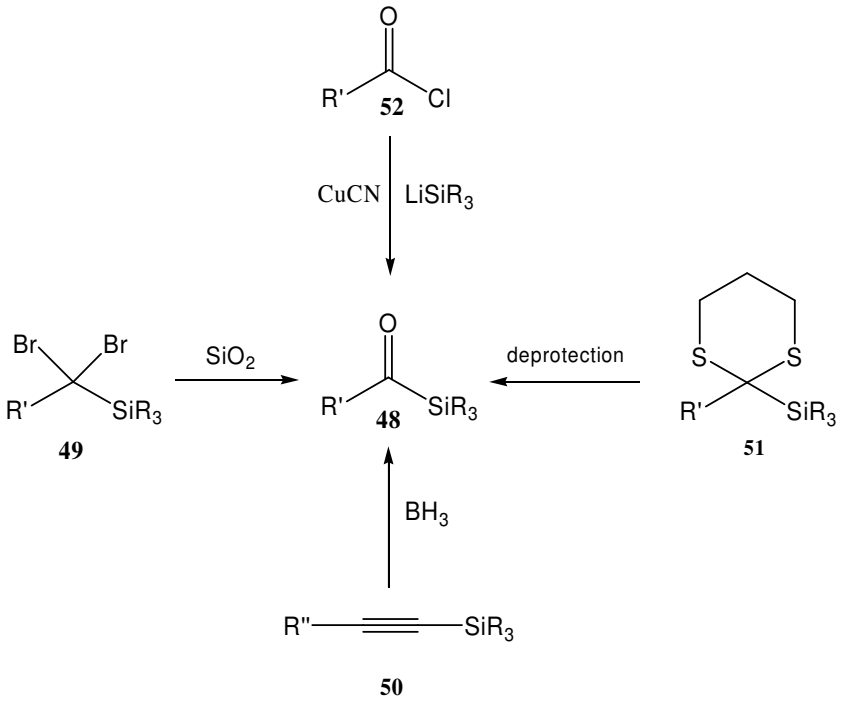
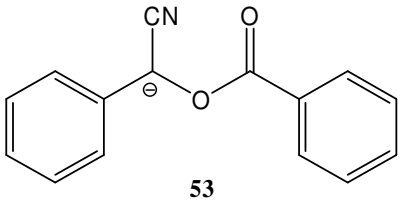


Figure 1.20. Methods for the synthesis of acylsilanes

1.3.2.2 Cleavage of benzil as acyl anion precursors

In 1923, Dakin and Harington showed that the cyanide ion catalyses the cleavage of benzil to benzaldehyde and the ester of benzoic acid [25]. Later, the mechanism and kinetics of the reaction were investigated by Kwart and Beavsky, demonstrating the intermediacy of **53** [26]. Trisler and Frye showed that **53,** in aprotic solvent DMSO where it is highly nucleophilic, reacts with another molecule of benzil present in the reaction solution to form trans-α,α'-stilbendiol di benzoate [27]. This work showed that **53** is a potent nucleophile and can react with an electrophile in the medium. Later, Kuebrich and Schowen used benzil and cyanide in DMF to generate the intermediate **53** and examined its reaction with benzaldehyde and furfural [28]. Although **53** could be generated efficiently under aprotic conditions, utilizing it to unsymmetrical benzoins has only been exemplified with furfural and not well developed and understood whether it is useful for unsymmetrical benzoin synthesis. Finally, Demir A. S. focused on understanding the nature of **53** and its derivatives together with its possible utilization for the synthesis of unsymmetrical benzoins [29].



53

Figure 1.21. Intermediate resulted from benzil and cyanide

In their research, Demir and his coworker, they treated a solution of benzil **54** and a potentially competent electrophile, 2-trifluoromethylbenzaldehyde **59**, in DMF with KCN for the synthesis of unsymmetrical benzoins. Product of benzoyl protected form of cross benzoin **58** was obtained as expected, in agreement with the mechanisms proposed by Kuebrich et al., as shown in Figure 22.

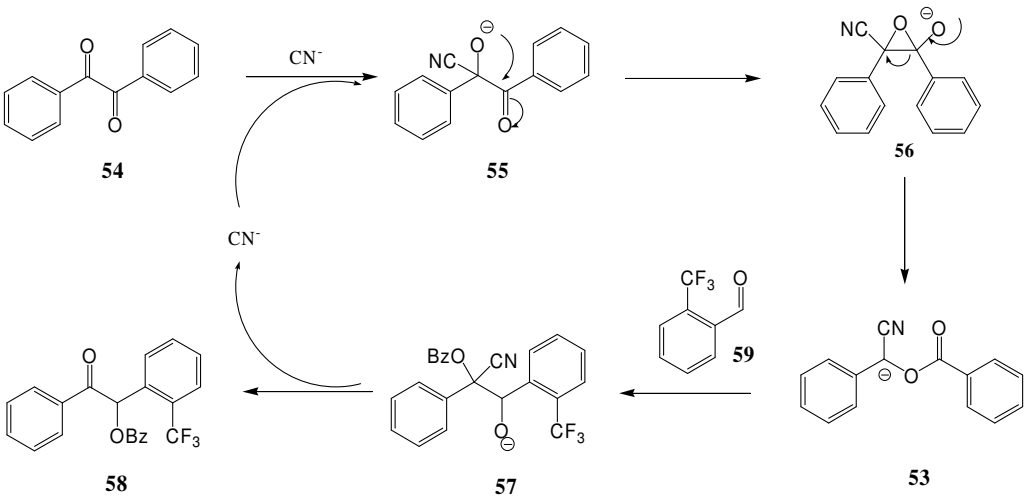


Figure 1.22. Synthesis of unsymmetrical benzoins from benzil

Cleavage of benzil as acyl anion precursors is one of the successful methods for the catalytical synthesis of cross benzoin reaction introduced up to now. On the other hand, it is seem to that this synthetic procedure has some drawbacks. First of all, electron-rich aldehydes have a propensity to yield isomeric products. Then, the procedure necessitates the benzil form of corresponding donor aldehyde. Finally, hydrolysis of the obtained protected benzoin products is not atom economical.

1.3.2.3 Acyl Phosphonates as acyl anion precursors

Acyl phosphonates are potent acyl anion procersors that generate acyl anion equivalents under the promotion of cyanide anion via phosphonate-phosphate rearrangement [30]. Phosphorus, like silicon, has the ability to migrate from carbon to oxygen and oxygen to carbon. In fact deprotonation of α-hydroxyphosphonates and base-catalyzed addition of dialkyl phosphites to acylphosphanates induce such phosphonate-phosphate rearrangements, which have a close analogy to the 1,2-Brook rearrangement of acylsilanes [31]. Demir et al envisioned that the typical nucleophilic catalysis of benzoin and Stetter reactions might promote acyl phosphonates to generate an appropriate concentration of the corresponding acyl anion equivalents that are sufficiently nucleophilic in order to participate in the reactions with electrophiles. It is important to note that Kurihara has reported stoichiometric strong base deprotonation of α-cyanophosphates generating cyano-phosphate anions **61** that react with a variety of electrophiles including aldehydes to provide **65**. As a result, Demir's research group reported their preliminary results in the realization of this idea utilizing acyl phosphonates **59** as the acyl anion precursors and aldehydes as electrophiles in the presence of a cyanide catalyst to provide cross-benzoin product **65** (Figure 23).

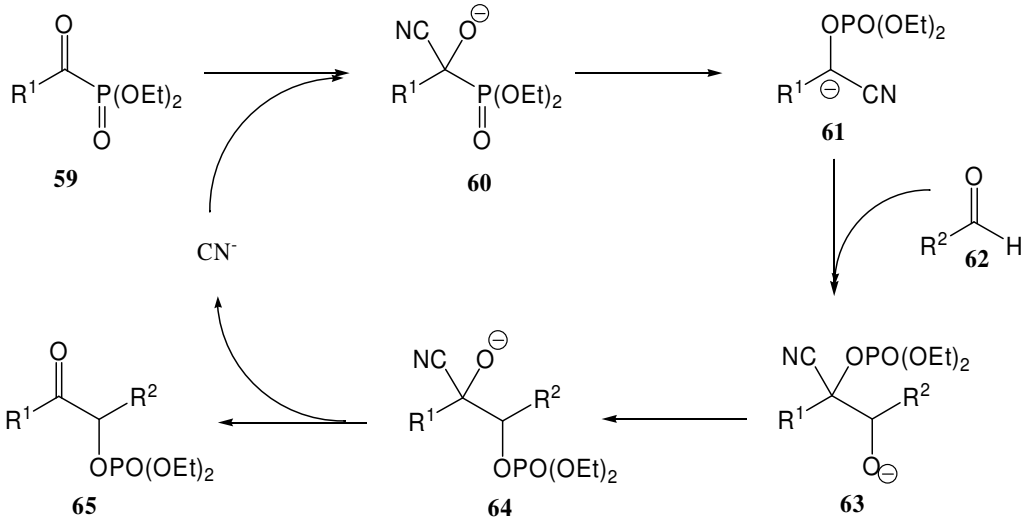


Figure 1.23. Synthesis of unsymmetrical benzoins *via* acylphosphonates

Demir initially investigated the reaction of benzoylphosphonate with p-anisaldehyde catalyzed by 10% KCN in the precence of phase transfer catalyst (Bu_4NBr or 18-crown-6) in various solvents and observed very slow or no conversion in many solvents at ambient temperature. Although heating provided varying degrees of conversions in different solvents, reaction in DMF provided a smooth and fast formation into the desired product in 93% yield at ambient temperature without using a phase transfer catalyst. The method introduced various aromatic-aromatic, aromatic-aliphatic, and aliphatic-aromatic cross benzoin products in good to excellent yields. It seemed that the introduced method had no drawbacks for the synthesis of cross unsymmetrical benzoins. Moreover, the preparation of acylphosphanates is simpler than the synthesis of acylsilanes. Acylphosphanates are readily available on a multigram scale from acyl chlorides and trialkyl phosphites via Arbuzov reaction without need to use any special condition or apparatus [32]. On the other hand, this method failed in the synthesis of aliphatic-aliphatic cross unsymmetrical benzoin synthesis but according to my best knowledge, a meaningful

chemical synhesis for aliphatic-aliphatic cross unsymmetrical benzoin has not been introduced yet.

1.4 Intramolecular aldehyde-ketone coupling

Considering the difficulties with the cross benzoin condensation that requires the regioselective coupling of two different aldehydes, it is not suprising that there is no catalytic method for the intermolecular coupling of an aldehyde with a ketone. Decarboxylative benzoin-type additions to ketones with pyruvate donors had previously been documented to proceed with a variety of thiamin diphosphate dependent enzymes [33]. The termodynamics of an aldehyde/ketone coupling in the absence CO_2 extrusion were uncertain until recent work by Suzuki and co-workers demonstrated that more traditional conditions (alcohol solvent, thiazolium carbene catalysis) could be used to effect intramolecular cross-benzoin reactions between an aldehyde and a ketone (Figure 24) [34].

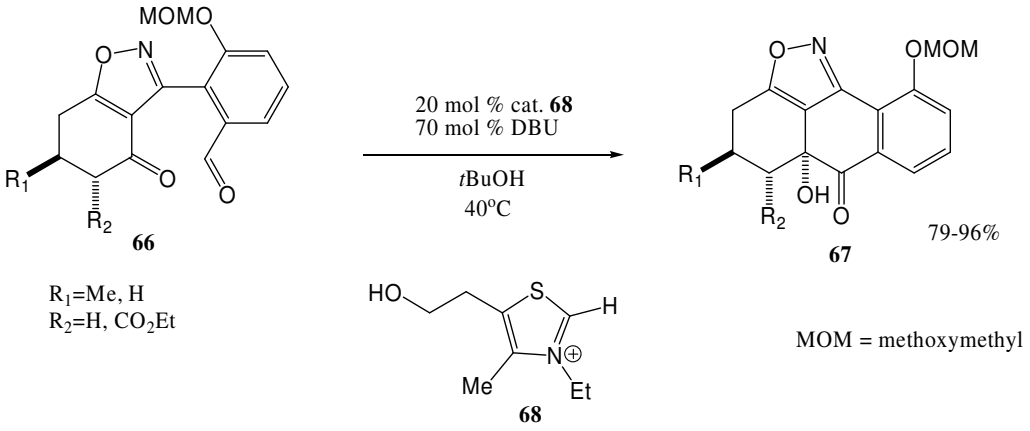
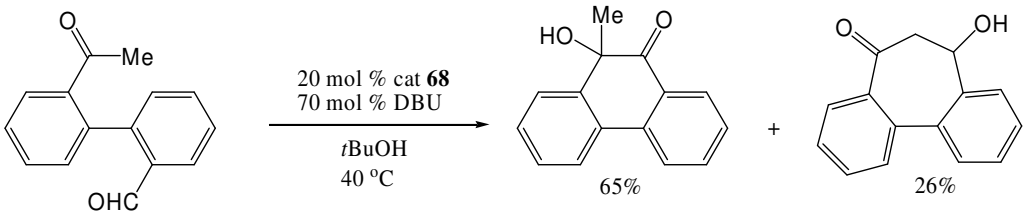


Figure 1.24. Intramolecular cross-benzoin reactions between an aldehyde and a ketone

Notably, the reactions require no preactivation of either functional group. The products are significantly value-added: the reaction results in an annulation and a stereocontrolled introduction of a tertiary alcohol. The thiazolium carbene variant is significantly higher-yielding than its cyanide-catalyzed counterpart. Intermolecular aldehyde dimerization was notably suppressed. The absence of homo-benzoin product is likely due to a simple rate difference ($k_{intra} > k_{inter}$), but it is also conceivable that the dimeric benzoin is formed reversibly and that the intramolecular benzoin adduct acts as a thermodynamic sink. Unfortunately, significant amounts of the thiazolium salt precursor and base (DBU) are required; however, when higher concentrations are employed, the reactions are in some cases feasible at 5 mol% catalyst loading.

An interesting chemoselective benzoin condensation occurs in preference to intramolecular aldol addition: the six-membered ring α-hydroxycyclohexanone benzoin **70** is favored over the β-hydroxycycloheptanone aldol **71** as depicted in Figure 25 [35]. These results also beg the question: can the highly desirable intermolecular aldehyde/ketone cross-benzoin coupling be achieved under any circumstances?



69 **70** **71**

Figure 1.25. Chemoselective benzoin condensation occurs in preference to intramolecular aldol addition

Enantioselective catalysis of intramolecular Stetter reactions was originally achieved by Enders et al. [10], and recent efforts by Rovis and co-workers established the benchmark for enantiocontrol in this family of reactions [36]. Thiazolium carbene catalyst derived from scalemic aminoindanol provided the annulated products with excellent enantioselectivity and chemical yield (Figure 26). An electron-donating group on the aromatic ring of the thiazolium carbene provided the optimum combination of chemical yield and enantioselectivity. The catalyzed annulation reactions are notably tolerant of a range of linkers, although the benzofuranone product is extremely suspectible to racemization. To date, the challenging intermolecular enantioselective Stetter reaction has met with limited success. Competitive formations of a stable conjugate adduct between the Micheal acceptor and the carbene may be a culprit [37].

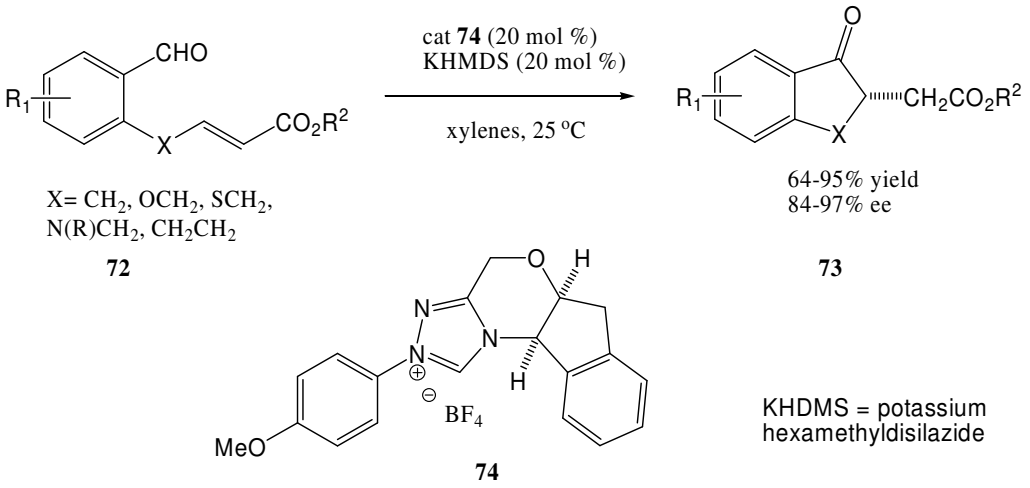
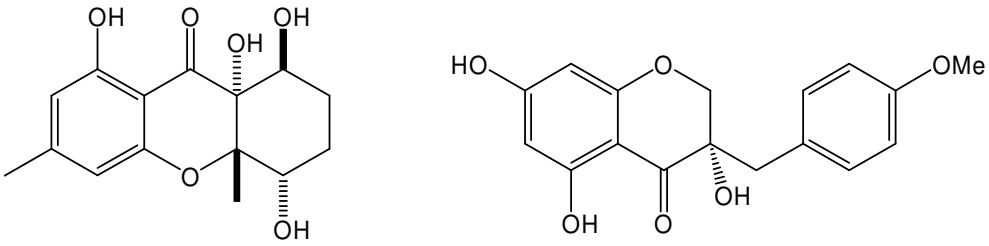


Figure 1.26. Intermolecular enantioselective Stetter reaction

It is important to conclude that synthetic methods for intramolecular aldeyde/ketone coupling is very important role in synthetic organic chemistry because this method

enable the chemist to synthesis some biologically active compounds with α-keto tertiary alcohols like diversonol **75** and eucomol **76**. It is also very important that the chemists have not introduced a synthetic method for the intermolecular cross benzoin reaction between aldehyde and ketone.



75 **76**

Figure 1.27. Diversonol and eucomol

1.5 Aim of the work

Many research reports were published about new developments in cross benzoin synthesis. The scientists introduce more active catalysts, new methods for the generation of umpoled d^1 nucleophiles and new methods for the generation of acyl anion precursors. On the other hand, there is no success in the area of intermolecular coupling of generated umpoled d^1 nucleophiles with ketones. Thus we aimed to develop a method for the synthesis α-keto tertiary alcohols by cross benzoin coupling of acyl anion equivalents generated from acyl phosphonates with ketones. This could be the first method for the intermolecular aldehyde-ketone coupling.

CHAPTER 2

RESULTS AND DISCUSSION

This study proposes to introduce the first intermolecular aldehyde/ketone cross-benzoin coupling. Acyl anion intermediates generated via phosphonate-phosphate rearrangement of acyl phosphonate in the presence of catalytic amount of cyanide are used as umpoled d^1 anion in this study. We investigated the scope and limitation of this approach for the synthesis of α-keto tertiary alcohols, a highly important functional group present in structure of many biologically active compounds [38].

2.1 Synthesis of acyl phosphonates

It is known that phosphorous has the ability to migrate both from carbon to oxygen and oxygen to carbon. Because of this ability phosphorous has been used as a typical nucleophile to participate in cross-benzoin reaction. However, this synthetic route has not been used in the intermolecular cross-benzoin coupling of aldeydes with ketones. We thought that the generated acyl anion equivalent via phosphonate-phosphate rearrangement of acyl phosphonate will be appropriate to couple with ketone to produce tertiary alcohols with α-carbonyl functionality.

Perkow reaction is probably the most famous example of migrating ability of phosphorous. In this reaction, it is proposed that a trivalent-phosphorous ends up with a pentavalent-phosphorous resulted by migration of phosphorous from carbon to oxygen as depicted in Figure 2.1.

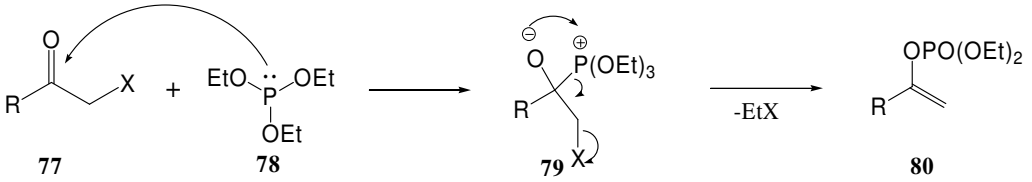


Figure 2.1. Mechanism of Perkow reaction

Arbuzov reaction, which is known to compete with Perkow reaction, is generally more dominant reaction related with ability of phosphorous. This reaction again yields a different pentavalent-phosphorous product (Figure 2.2.).

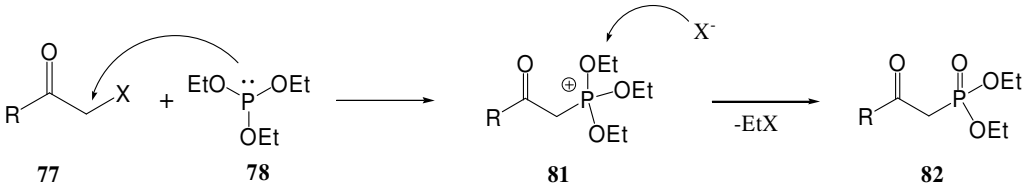


Figure 2.2. Mechanism of Arbuzov reaction

A variety of cyanohydrins of O-diethylphosphates treated with base **83** have been introduced as potential acyl anion equivalent by Kurihara et al [39]. Based on this idea, we can propose a strategy to generate an acyl anion precursor by adding cyanide ion to the acyl phosphonates (Figure 2.3.). The generation of acyl anion involves 1,2-rearrangement of phosphorous from carbon to oxygen. This arrangement has close analogy to the corresponding 1,2-Brook rearrangement. The first example of cyanide ion promoted rearrangement of acylphosphanate **84** in the presence of alkali cyanide solution was introduced in 1957. It is very obvious that

cyanide provides considerable stabilization to the carbanion **86** that provides cyanohydrin O-diethylphosphates upon protonation as figured out in the report [41]. Even though no yields were given, this is a very helpful report showing the potential of cyanide ion promoted rearrangement of acyl phosphonates.

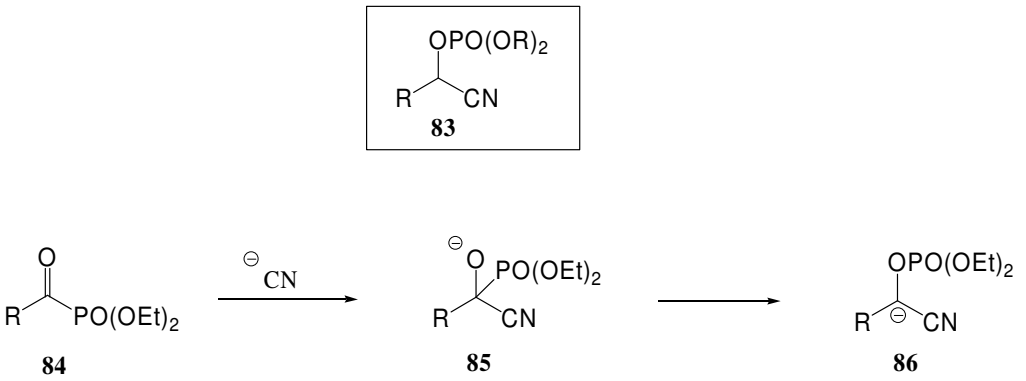


Figure 2.3. Cyanohydrin O-diethylphosphates as potential acyl anion equivalent

The synthesis of acyl phosphonates is not arduous work. The most direct synthesis to get these compounds is the well-known Arbuzov reaction between acylchlorides **87** and trialkylphosphites **88** [32]. Reaction proceeds via formation of unstable intermediate **89** that eventually leads to acyl phosphonates **90**. It is generally carried out by mixing neat reactants at or below room temperature. Synthetic work ends up with acyl phosphonate as a main product in high to excellent yield. The only side product of the reaction is gaseous alkyl chloride; it leaves the medium during synthesis (Figure 2.4.).

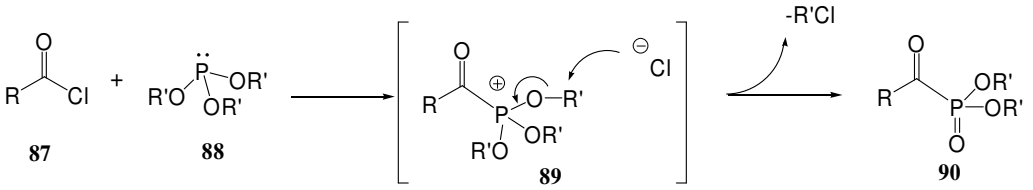


Figure 2.4. Synthesis of acyl phosphonates

A variety of acyl phosphonates **90a-m** were synthesized from corresponding acyl chlorides and used for the synthesis of intermolecular aldehyde/ketone cross benzoin coupling. In this study, various acyl phosphonate compounds were synthesized via Arbuzov reaction described in literature [32]. All synthesized acyl phosphonate derivatives were purified by vacuum distillation. We observed that Arbuzov reaction generally provides quite pure products from the NMR data. Arbuzov synthetic route ends up with good to excellent yield for the synthesis of acyl phosphonates (87-98 %). When the area under the ethyl group signals of phosphonates at about 1.3 and 4.2 ppm are compatible with those of other hydrogen atoms in ^{1}H NMR, one can conclude that the desired acyl phosphonate is formed. Moreover formation of acyl phosphanates can be supported by ^{13}C and ^{31}P NMR. It is also observed that freshly distilled acyl phosphonate derivatives are more reactive in aldehyde/ketone cross benzoin coupling. The reaction performed with acyl phosphonate prepared beforehand will not yield the desired product.

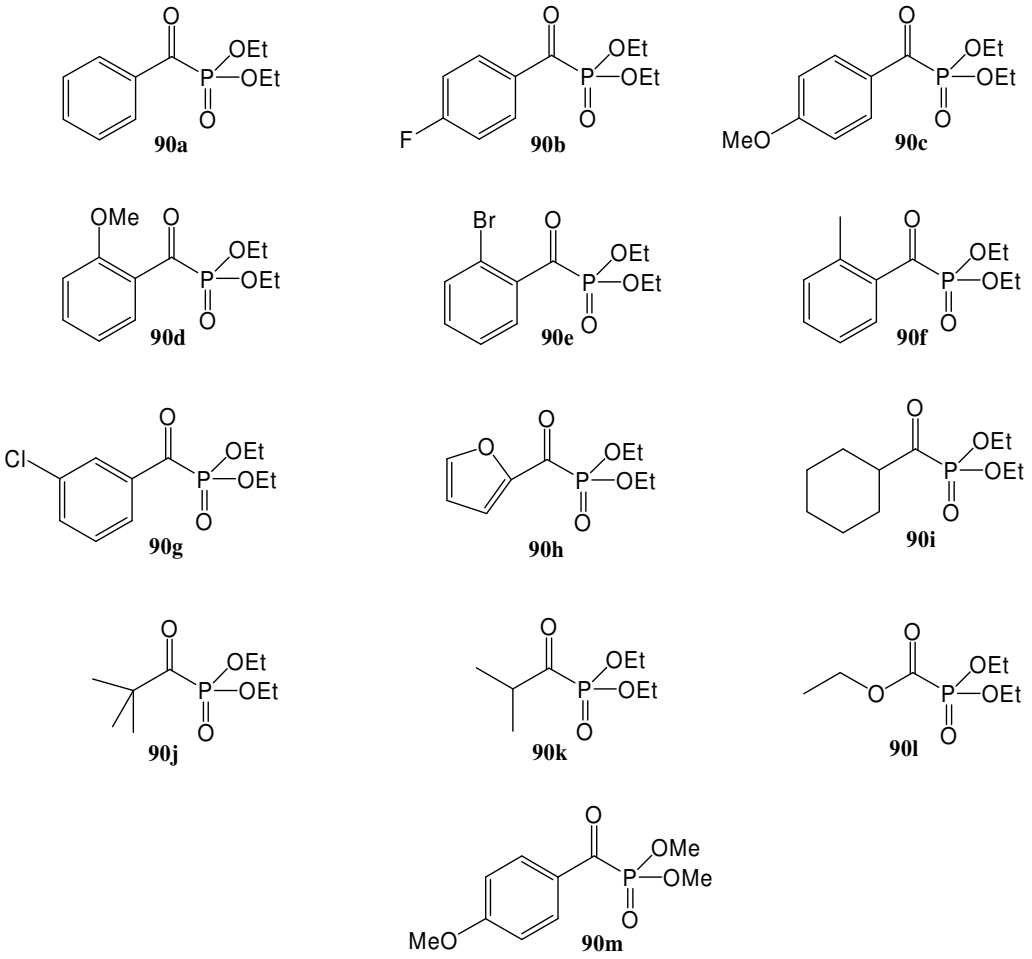


Figure 2.5. Acyl phosphonates synthesized and used in this study

2.2 Intermolecular aldehyde/ketone cross benzoin coupling via acyl phosphonates

As explained in the earlier chapters of this thesis, a synthetic method related with intermolecular aldehyde/ketone cross benzoin coupling has not been introduced yet. Thus, we proposed the idea of using acylphosphonates in cross coupling of aldehyde with ketone in the presence of catalytic amount of cyanide ion. Mechanism of

proposed catalytic cycle has common steps with cross benzoin reactions mediated with acylsilanes, benzils and acyl phosphonates. Generated acyl anion promoted by rearrangement of acyl phosphonates **59** in the presence of cyanide ion reacts with ketone **91** to afford intermediate **63.** The intermediate undergoes a 1,4-phosphate migration producing protected α-keto tertiary alcohols **65**.

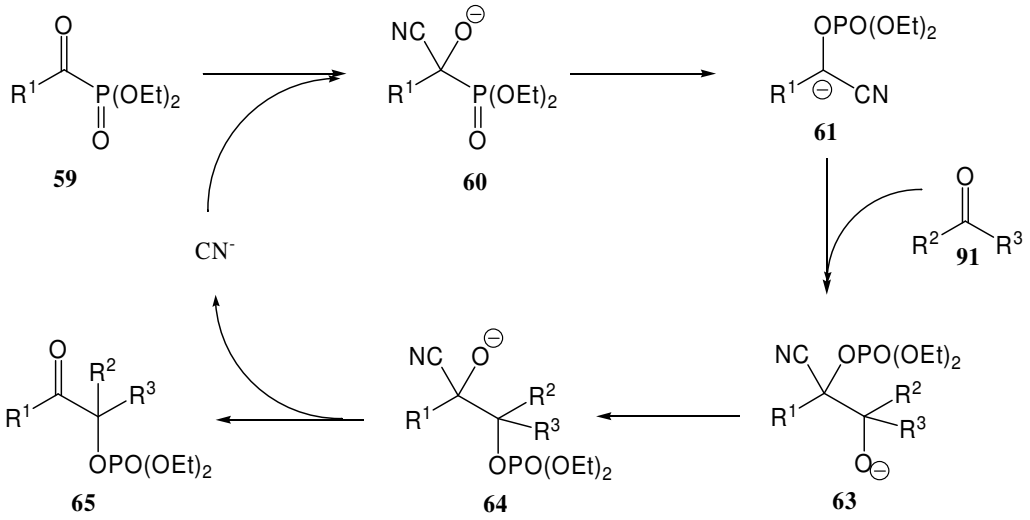


Figure 2.6. Mechanism of cross coupling of aldehyde with ketone *via* acyl phosphonates

To investigate the feasibility of the method, we chose benzoylphosphonate **90a** and 2,2,2-trifluoroacetophenone as model substrates. Thus, the mixture of 0.5 M solution of benzoylphosphonate **90a** and 2,2,2-trifluoroacetophenone treated with % 20 KCN in various dry solvents (dichloromethane, hexane, toluene, THF, DMF) at room temperature. We monitored the reactions with TLC and we observed that the reaction proceed smoothly to form protected α-keto tertiary alcohols in less than half an hour (Figure 2.7).

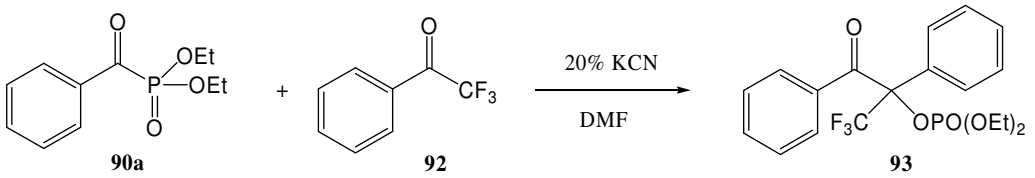


Figure 2.7. Synthesis of protected α-keto tertiary alcohols *via* acyl phosphonates

The reaction performed with other solvents (hexane, toluene, THF, dichloromethane) ended up with protonation of acylanion of corresponding acyl phosphonate (Figure 2.8.). The presence of doubled at about 6 ppm in NMR spectrum is due to the protonation products. Protonation of acyl anion of acyl phosphonate is the main problem for the reaction because formation of the protected cyanohydrin is not only a side product for the reaction but also responsible for locking the reaction. When acylanion accepts proton from the medium, there will be no cyanide catalyst in the medium that means that the reaction will not proceed anymore. To overcome this problem, reactions are repeated with addition of 100 mg of molecular sieve. When we add molecular sieve to the medium, protonated products of corresponding acylanion is not formed. Still, the expected aldehyde/ketone cross benzoin products do not form.

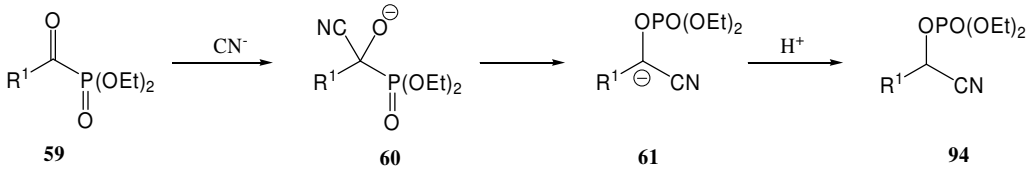
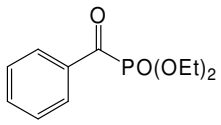
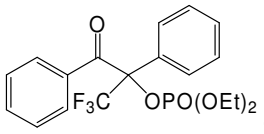
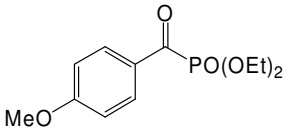
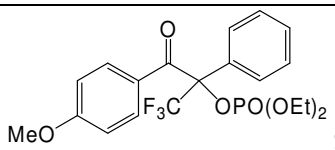
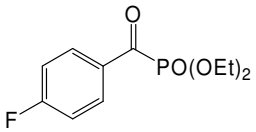
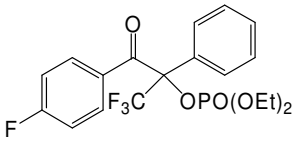
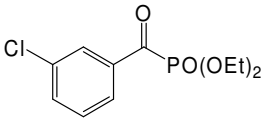
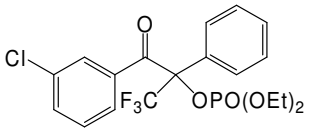
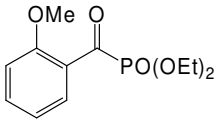
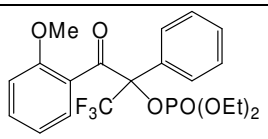
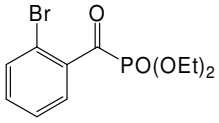
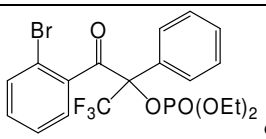
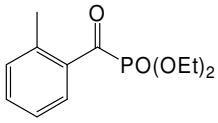
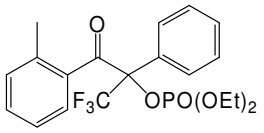
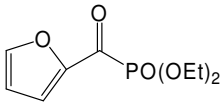
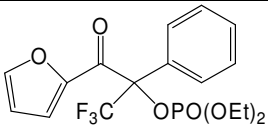


Figure 2.8. Protonation of acylanion of corresponding acyl phosphonate

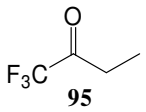
The results of reactions of various aromatic acyl phosphonates with 2,2,2-trifluoroacetophenone in DMF are shown in the Table 2.1. The synthetic route ends up with quite a high yield for the m- or p-substituted aromatic acyl phosphonates. Reactions with o-substituted acyl phosphonate resulted with proton abstraction product. To monitor the reaction conditions, the reaction of o-substituted acyl phosphonate are repeated with benzaldehyde, which is more electrophilic than ketones. The reaction of o- substituted acylphosphanates with aldehydes occurs in a few minutes to produce cross benzoin products. In addition to that, the protonated side products are not observed in the coupling reaction of acylphosphanates and aldehydes. This fact points to a conclusion that 2,2,2-trifluoroacetophenone is not electropositive enough to react with sterically hindered o- substituted acyl phosphonate. As a result, o-substituted acylanions prefer taking a proton than attacking less electropositive ketone. A similar observation is pointed out by Reis in his PhD thesis [40]. He pointed out that when a solution of benzoylphosphonate is treated with the mixture of 4-fluoro-benzaldehyde and 4-methoxy-benzaldehyde, only the product resulting from the reaction of benzoylphosphonate and 4-fluoro-benzaldehyde was observed. This showed us that the acylanion generated from the corresponding acyl phosphonate reacts preferentially with more reactive aldehydes. Since the cross benzoin reaction depends on the electropositive nature of the acceptor molecule, the synthetic route is not successful in the coupling of sterically hindered o-substituted acyl phosphonate and less electropositive ketones. To optimize the reaction condition for the reaction of o-substituted acyl phosphonates with 2,2,2-trifluoroacetophenone, we used CuCN as a cyanide ion source. The aim of using CuCN is to activate the carbonyl compound by using Lewis acid methodology. We think that increase the electropositive nature of the carbonyl group and Cu^{+} ion will produce the desired product. Unfortunately, this strategy was also resulted with proton abstraction of generated acyl anion. To diminish the proton abstraction reaction, we performed the reaction at – 30 ^{o}C. At this temperature, the reaction in different solvents again resulted with proton abstraction product. As a result, we could not succeed to optimize the reaction conditions for the coupling of o-substituted acyl phosphonate and ketones.

The results of aromatic acyl phosphonate with 2,2,2-trifluoroacetophenone show that; when reaction is carried out with assumingly more reactive 4-fluoro-benzoylphosphanate **90b**, we observed interestingly longer reaction time and poorer yield than reaction of 4-methoxy-benzoylphosphanate **90c**. The reason for this might be that flourine present in p- position decrease the nucleophilic character of generated acylanion because of its electron withdrawing ability. Increasing the catalyst load is resulted with slightly higher reaction rate. The synthetic route can be also used for the coupling of acylphosphanate with hetero aromatic ring like **90h** and 2,2,2-trifluoroacetophenone.

Table 2.1. Reaction of aromatic acyl phosphonates with 2,2,2-trifluoroacetophenone

Entry	Acylphosphanate	Procut	Yield (%)
1	 **90a**	 **93a**	87
2	 **90c**	 **93b**	92
3	 **90b**	 **93c**	79
4	 **90g**	 **93d**	87
5	 **90d**	 **93e**	No reaction
6	 **90e**	 **93f**	No reaction
7	 **90f**	 **93g**	No reaction
8	 **90h**	 **93h**	83

Coupling of aldehydes having α-proton and ketones in benzoin reactions is always problematic. This is obvious from a few reactions utilizing aliphatic aldehydes in acyl anion chemistry. The difficulties of reaction with aliphatic acceptors are also valid in our research. In our initial investigation we chose benzoylphosphonate **90a** and 1,1,1-trifluorobutan-2-one **95** as a model substrates for aryl-alkyl aldehyde/ketone cross benzoin coupling.



95

Figure 2.9. 1,1,1-trifluorobutan-2-one

To perform coupling reaction, 0.5 M solution of benzoylphosphonate and 2 equivalent amounts of **95** was treated with various solvents (hexane, diethylether, dichloromethane, THF, and DMF) at room temperature. The reactions were either resulted with protonation of acyl anion or not occurred at all. The addition of phase transfer catalyst like 18-crown-6 and Bu_4NBr in the above solvents did not provide the optimum condition for the coupling reaction. In our previous research topic, we introduced an optimized method for the cross benzoin reaction of aroylphosphonates and aliphatic aldehydes [30]. During our investigations toward understanding the nature and reactivity of aroylphosphonates and corresponding acyl anion equivalents, we observed that O-silyl cyanohydrin **91** decomposes with CsF in the presence of aliphatic aldehyde **99** to afford the benzoin adduct in an instantaneous reaction (Figure 2.10.).

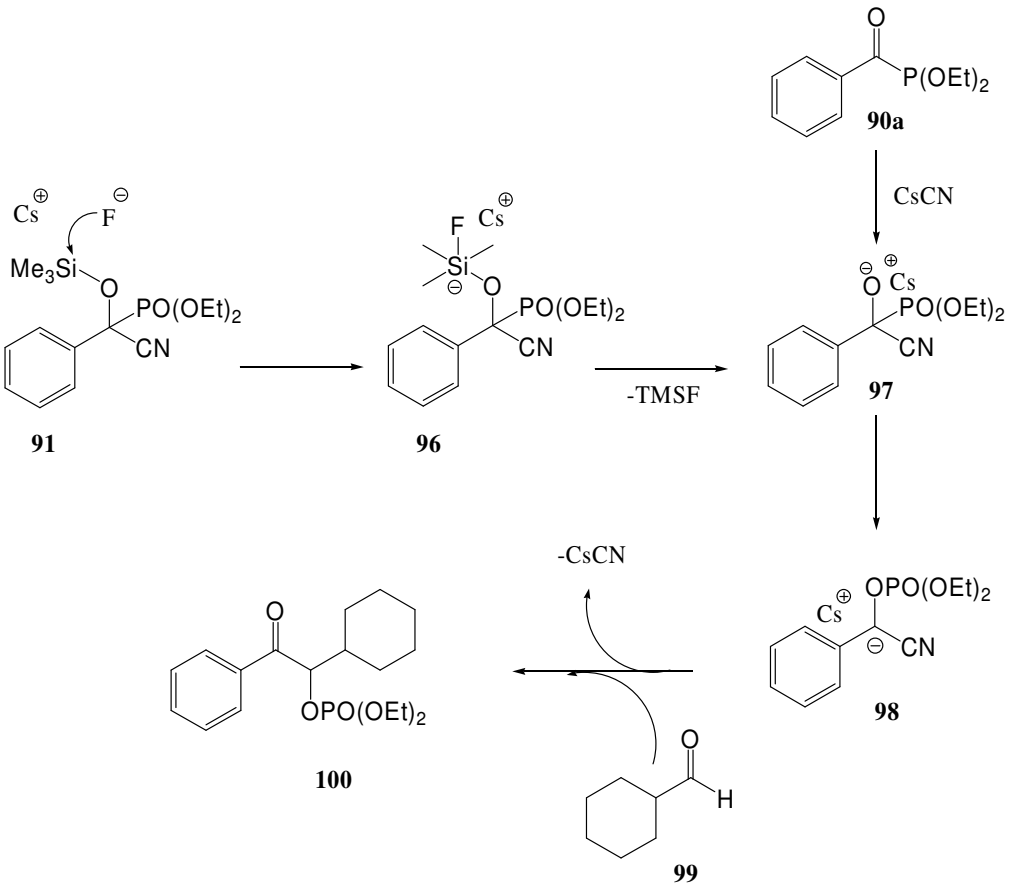


Figure 2.10. Decomposition of O-Silyl cyanohydrin with CsF

One easily suggests that the synthetic procedure (using of TMSCN+CsF) can also be applicable for the aryl-aliphatic aldehyde/ketone cross benzoin coupling. On the other hand, this synthetic method also failed for the intermolecular coupling of **90a** and **95**. The last but least, when 0.5 M solution of **90a** in DMF treated with **95** in the presence of Cu(OTf), the desired product **101** is observed in crude NMR spectrum, but yield for the reaction was very low (yield = 7 %) (Figure 2.11.).

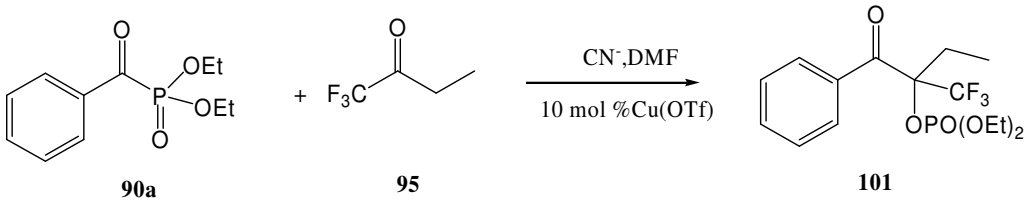


Figure 2.11. Reaction aryl-aliphatic aldehyde/ketone cross benzoin coupling

The use of alkyl donor in benzoin type catalytic acyl anion reaction is also troublesome. Our early attempts using aliphatic phosphonate **90i** resulted in very low yields or irreproducible results in both KCN/DMF and CsF+TMSCN/DMF systems. The most frequent problem was the presence of side products observed under various reaction conditions. The first side product of the reaction is protonation of the acyl anion equivalent that blocks the proceeding of the cross benzoin coupling as we discussed in previous chapters. The second side product resulted from the reaction of acyl phosphonates and diethyl phosphites **104** that is formed in alkaline KCN solution [42]. It is also important to note that when the generated acyl anion abstracts proton from the medium, reaction medium will be more alkaline and formation of side product **106** is easy in the alkaline medium (Figure 2.12.).

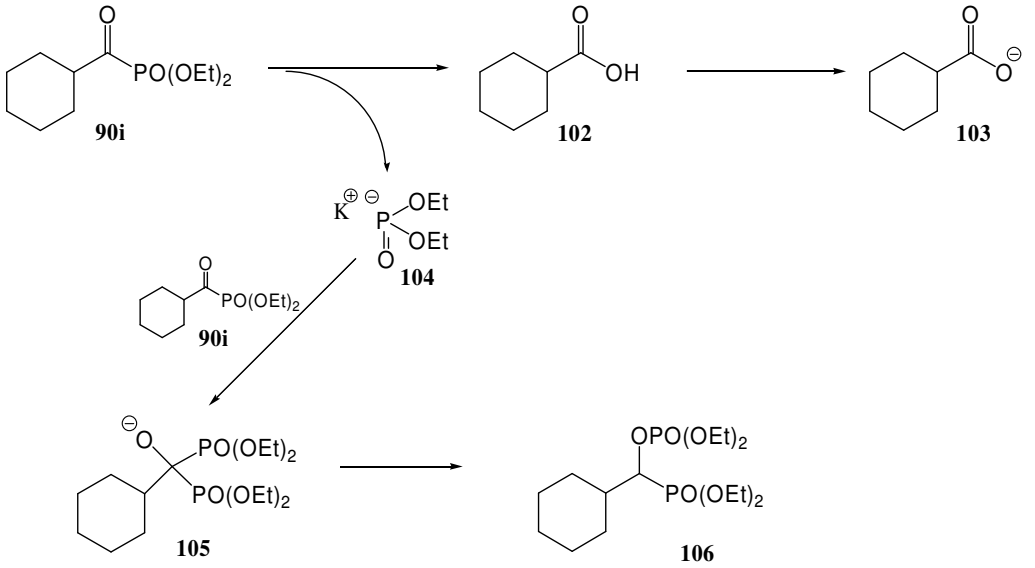
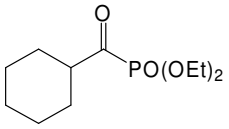
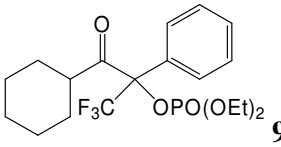
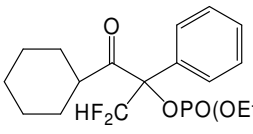
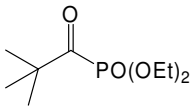
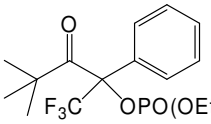
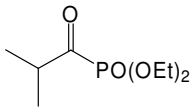
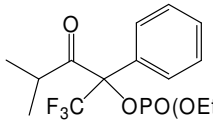
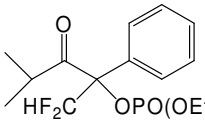


Figure 2.12. The reaction of acyl phosphonates and diethyl phosphites

Fortunately, we can accomplish aliphatic acyl phosphonates with 2,2,2-trifluoroacetophenone in tolune in the presence of 18-Crown-6 at 80 ^{o}C. The results for the aliphatic-aromatic aldehyde/ketone intermolecular cross benzoin reaction are depicted in Table 2.2.

Table 2.2. Reaction of aliphatic acyl phosphonates with 2,2,2-trifluoroacetophenone

Entry	Acylphosphanate	Procut	Total Yield (%)
1		 **93i** +  **112a**	66 (can not be purified)
2		 **93j**	78
3		 **93k** +  **112b**	62 (can not be purified)

As stated in Table 2, products **93i** and **93k** can not be purified by various separation techniques. From the NMR spectrum, another side product has occurred besides the desired product. We determined the side product as protected α-keto tertiary alcohols with $–CF_2H$ from NMR spectrum and LC-MASS spectrum. Detailed information related with the intermediate **109** has been introduced recently by Demir and Eymur

[43]. The proposed mechanism for the formation of the side product in alkaline KCN solution is depicted in Figure 2.13.

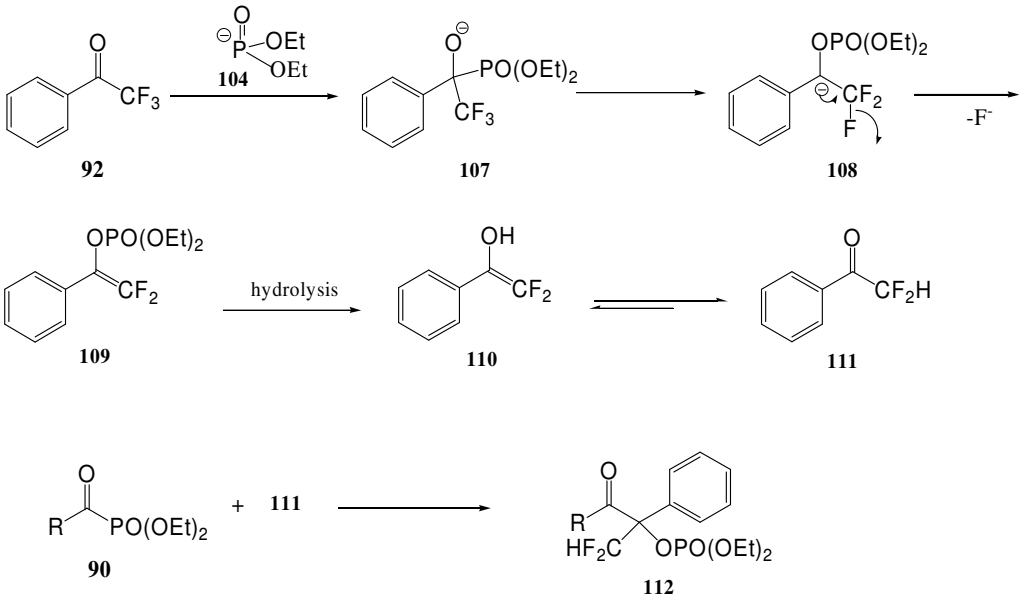
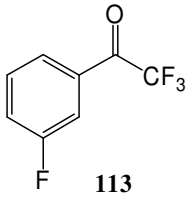
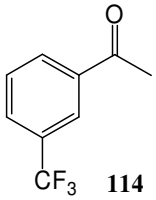


Figure 2.13. Formation of 2,2- Difluoroacetophenone

Early attempts for the intermolecular aldehyde/ketone intermolecular aldehyde/ketone coupling with acetophenone that is not as reactive as 2,2,2-trifluoroacetophenone was not very successful. On the other hand the synthetic approach resulted with high yield in aromatic-aromatic intermolecular coupling when the acceptor carbonyl compound was 2,2,2-trifluoroacetophenone. The results simply state that the reaction is dependent on the electropositive nature of the ketone. To prove this idea we used activated ketones like 3'-fluoro-2,2,2-trifluoroacetophenone **113** and m-trifluoromethylacetophenone **114** as acceptor ketone.



113

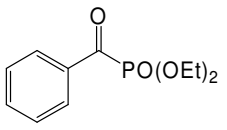
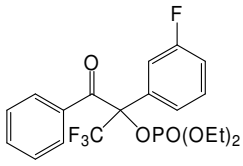
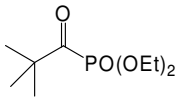
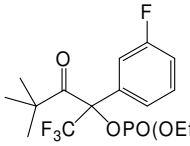
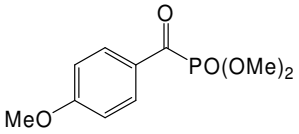
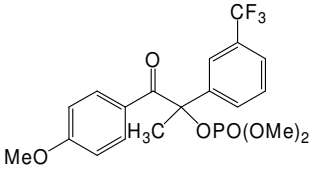


114

Figure 2.14. 3'-fluoro-2,2,2-trifluoroacetophenone and m-trifluoromethylacetophenone

The reaction with **113** in DMF took place faster and higher yield was observed with respect to reactions with 2,2,2-trifluoroacetophenone. Moreover, reaction with the activated derivatives of acetophenone **114** in THF produced good results as shown in Table 2.3.

Table 2.3. Reaction of aromatic acyl phosphonates with active acetophenone derivatives

Entry	Acyl phosphonate	Product	Yield (%)
1		 **93m**	95
2		 **93n**	82
3		 **93o**	78

The products of the reaction of intermolecular aldehyde/ketone cross benzoin introduced until now are resulted from the coupling of corresponding acyl phosphonates and $–CF_3$ activated ketones. We used some methods for different starting materials and substrates. Unfortunately, all these methods were unsuccessful in intermolecular cross benzoin coupling of acyl phosphonates with simple ketones like acetophenone or cyclohexanone. On the other hand, above discussion shed light onto this limitation of the synthetic method. Now, we know that if we activate the acceptor carbonyl compound, we will get better result for both yield for the reaction and time required for the completeness of the synthesis. The reaction of acetophenone with an additional electron withdrawing groups on the benzene ring resulted with product **93o** in good yield. These results bring the idea that if we activate simple ketones with additives, will we synthesize the desired compounds. We chose cyclohexanone as our acceptor substrate. Our initial attempt to activate cyclohexanone was using Lewis acid like $LiClO_4$ and metal triflates. Lewis acid activation in different solvents (hexane, THF, dichloromethane, toluene, DMF) resulted with protonation of generated acyl anion equivalent and no product was observed from NMR spectrum. Later, we decided to use thiourea derivatives **115** and **116** to activate cyclohexanone in dry toluene, dichloromethane and THF [44]. As a result, we could isolate corresponding product in the presence of 18-crown-6 as a catalyst at ambient temperature (Figure 2.15.). The isolated yield for the reaction was 44 %.

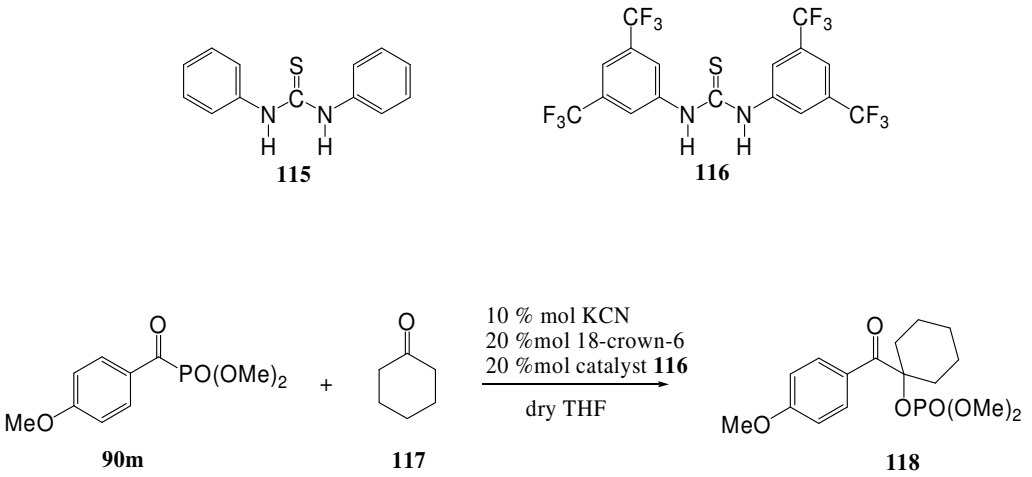
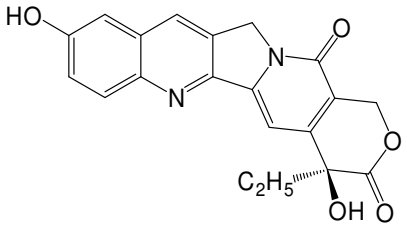


Figure 2.15. Reaction of acyl phosphonates with cyclohexanone

The last but least, we were also dealing with intermolecular cross benzoin coupling of acyl phosphonate **90l** with 2,2,2-trifluoroacetophenone. On the other hand, all reaction condition introduced in this study did not give a proper synthetic procedure. Indeed, it is worthy to discover proper synthetic condition for this coupling because the synthesis will be resulted in a functionality present in many biologically active compounds such as camptothecin **119**. Camptothecin, which is a qunoline-based alkaloid, is the only known naturally-occuring DNA topoisomarase I inhibitor. Because of the importance of the desired product, coupling of **90l** with 2,2,2-trifluoroacetophenone is under investigation.



119

Figure 2.16. Camptothecin

CHAPTER III

EXPERIMENTAL

NMR spectra were recorded on a Bruker DPX 400 Spectrometer. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^1H: δ = 7.26) and $CDCl_3$ (^{13}C: δ = 77.0) as an internal standard. Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, coupling constant(s) in Hz. Purification of products was carried out by automatic flash column chromatography and colomn chromatography which was conducted on silica gel 60 (mesh size 40-63 um). Visualization was accomplished with UV light and anisaldehyde or 2,4-dinitrophenylhydrazine followed by heating. Acyl phosphonates were prepared according to well established procedures and purified by vacuum distillation [32]. All acyl phosphonates were stored in flasks under nitrogen and they were stable at least for months. KCN was dried under vacuum at 100 °C. 18-crown-6 was recrystallized from acetonitrile and dried under vacuum at ambient temperature.

3.1. Intermolecular aldehyde/ketone cross benzoin coupling

3.1.1 General procedure for aromatic-aromatic acyl phosphonate/ketone coupling

To a solution of 1 mmol acyl phosphonate in 2 mL dry DMF was added 1.1 mmol ketone (2,2,2-trifluoroacetophenone) and 10 % mol KCN. Reaction was monitored by TLC. After competition of the reaction, mixture was diluted by 10 mL of ether and water. Organic phase was separated and aqueous phase extracted with 10 mL ether three times. Combined organic phase extracted with brine solution, separated and dried over $MgSO_4$. Organic phase was concentrated under reduced pressure. Crude product was purified by flash column chromatography on silica gel with eluents ether or mixture of ether:petroleum ether.

Diethy 3,3,3-triflluro-1-oxo-1,2-diphenylpropan-2-yl phosphate (93a): white crystals, mp: 94.9-95.3 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.07 (3H, dt, J=1.0, 7.1 Hz), 1.20 (3H, dt, J=1.0, 7.1 Hz), 3.61-3.78 (2H, m), 3.93-4.09 (2H, m), 7.15-7.21 (2H, m), 7.32- 7.37 (4H,m), 7.45-7.55 (2H,m), 7.60-7.63 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.7 (d, J=3.7 Hz), 15.8 (d, J=3.8 Hz), 64.2 (d, J=6.1 Hz), 64.7 (d, J=6.1 Hz), 86.3 (d, J=28 Hz), 125 (q, J=287 Hz), 126.4, 128.0, 128.9, 130.0, 130.3, 132.1(d, J=10.4 Hz), 133.0, 134.0, 189.6; ^{31}P NMR ($CDCl_3$) δ -6.38

Diethyl 3,3,3-trifluro-1-(4-methoxyphenyl)-1-oxo-2-phenylpropan-2-yl phosphate (93b): white crystals; ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, t, J=6.9 Hz), 1.21 (3H, t, J=7.1 Hz), 3.71 (3H,s), 3.76-3.86 (2H, m), 3.99-4.05 (2H, m), 6.67 (2H, d, J=8.9 Hz), 7.33- 7.35 (3H,m), 7.48-7.50 (2H,m), 7.62 (2H, d, J=8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.7, 14.8, 14.9, 54.1, 63.0 (d, J=6.1 Hz), 63.5 (d, J=6.0 Hz), 112.1, 119.7, 125.4, 125.5, 127.6, 128.7, 131.5, 131.6, 131.7, 162.0, 186.5; ^{31}P NMR ($CDCl_3$) δ -6.33

Diethyl 3,3,3-trifluoro-1-(4-fluorophenyl)-1-oxo-2-phenylpropan-2yl phosphate (93c): white crystals; ^{1}H NMR ($CDCl_3$) δ 1.13 (3H, t, J=7.1 Hz), 1.22 (3H, t, J=7.1 Hz), 3.69-3.85 (2H,m), 3.95-4.10 (2H, m), 6.87 (2H, t, J=8.6 Hz), 7.36-7.37 (3H, m), 7.45- 7.52 (2H,m), 7.63- 7.67 (2H,m); ^{13}C NMR ($CDCl_3$) δ 15.8 (t, J=6.1 Hz), 64.1 (d, J=6.0 Hz), 64.6 (d, J=5.9 Hz), 115.1 (d, J=25.3 Hz), 126.4, 128.9, 130.0, 130.3, 132.1 (d, J=6.1 Hz),132.9, 133.0, 165.3 (d, J=255 Hz), 187.5; ^{31}P NMR ($CDCl_3$) δ -6.32

1-(3-chlorophenyl)-3,3,3-trifluoro-1-oxo-2-phenylpropan-2yl diethyl phosphate (93d): white crystals; ^{1}H NMR ($CDCl_3$) δ 1.13 (3H, t, J=7.1 Hz), 1.24 (3H, t, J=7.1 Hz), 3.68-3.82 (2H, m), 3.98-4.25 (2H, m), 7.15 (1H, t, J=7.8 Hz), 7.31 (1H, d, J=7.8 Hz), 7.37-7.39 (3H,m), 7.47-7.50 (3H, m), 7.54 (1H, s); ^{13}C NMR ($CDCl_3$) δ 15.8 (d, J=4.3 Hz), 15.9 (d, J=4.4 Hz), 64.2 (d, J=5.8 Hz), 64.7 (d, J=5.9 Hz), 86.3, 120.6, 126.3, 128.4, 129.0, 129.3, 130.1, 130.2, 131.8, 131.9, 132.7, 134.1, 135.5, 187.0; ^{31}P NMR ($CDCl_3$) δ -5.66

Diethyl 3,3,3-trifluoro-1-(furan-2-yl)-1-oxo-2-phenylpropan-2yl phosphate (93h): brown crystals; ^{1}H NMR ($CDCl_3$) δ 1.19-1.25 (6H, m), 3.92-4.08 (4H, m), 6.31-6.32 (1H, m), 6.84 (1H, d, J=3.6 Hz), 7.33-7.34 (3H, m), 7.39 (1H,m), 7.47-7.49 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.8 (d, J=7.4 Hz), 14.9 (d, J=7.4 Hz), 63.2 (d, J=5.1 Hz), 63.7 (d, J=6.0 Hz), 110.9, 119.5, 125.5, 127.5 128.8, 131.0, 145.4, 148.3, 176.6; ^{31}P NMR ($CDCl_3$) δ -6.86

Diethy 3,3,3-triflluro-2-(3-fluorophenyl)-1-oxo-1-phenylpropan-2-yl phosphate (93m): white crystals, mp; ^{1}H NMR ($CDCl_3$) δ 1.10 (3H, t, J=6.9 Hz), 1.21 (3H, t, J=6.9 Hz), 3.62-3.78 (2H, m), 3.92-4.09 (2H, m), 7.06-7.10 (1H, m), 7.19- 7.24 (3H,m), 7.30-7.39 (3H,m), 7.62 (2H, d, J=7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 15.7, 15.8, 15.9, 64.2 (d, J=5.9 Hz), 64.7 (d, J=5.8 Hz), 113.8, 114.0, 117.1, 117.3, 122.4, 128.1, 130.2, 130.5, 133.0, 133.8, 164.1 (d, J=253 Hz), 188.8; ^{31}P NMR ($CDCl_3$) δ -6.38

3.1.2 General procedure for aliphatic-aromatic acyl phosphonate/ketone coupling

20 % mol KCN and 20 % mol 18-crown-6 were placed in a round bottom flask and 5 mL dried toluene was added via syringe. 1 mmol aliphatic acylphoshonate and 2mmol 2,2,2-trifluoroacetophenone was added onto the reaction mixture under inert atmosphere. Reaction mixture was heated to 80 ^{o}C and reaction monitored by TLC or NMR (40-50 min). After completion reaction mixture was diluted with 15 mL ether and worked up as aromatic-aromatic reactions. Column chromatography provided partially cross benzoin products.

1-cyclohexyl- 3,3,3-triflluro-1-oxo-2-diphenylpropan-2-yl diethyl phosphate (93i): yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.06-1.96 (16H, m), 2.85-2.94 (1H, m), 4.04-4.27 (4H, m), 7.40-7.46 (5H, m)

Diethyl 1,1,1-trifluoro-4,4-dimethyl-3-oxo-2-phenylpentan-2-yl phosphate (93j): yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.16 (9H, s), 1.32-1.38 (6H, m), 4.06-4.29 (4H, m),

7.36-7.54 (3H, m), 7.61-7.63 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.9, 16.0, 16.1, 28.9, 45.9, 64.7(d, J=6.2 Hz), 64.9 (d, J=6.0 Hz), 126.7, 127.2, 128.4, 129.3 130.0, 131.0 (d, J=9.1 Hz), 205.1; ^{31}P NMR ($CDCl_3$) δ -6.94

Diethyl 1,1,1-trifluoro-4-methyl-3-oxo-2-phenylpentan-2-yl phosphate (93k): yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.82 (3H, d, J=6.9 Hz), 1.13 (3H, d, J=6.7 Hz), 1.28-1.38 (6H, m), 3.07-3.20 (1H, m), 3.97-4.24 (4H, m), 7.39-7.46 (5H, m)

Diethyl 1,1,1-trifluoro-2-(3-fluorophenyl)-4,4-dimethyl-3-oxopentan-2-yl phosphate (93n): yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.10 (9H, s), 1.26-1.32 (6H, m), 4.12-4.19 (4H, m), 7.06-7.10 (1H, m), 7.19-7.25 (2H, m), 7.29-7.36 (1H, m) ; ^{13}C NMR ($CDCl_3$) δ 14.8, 14.9, 15.0, 27.9, 45.0, 63.8 (d, J=6.0 Hz), 64.0 (d, J=6.0 Hz), 113.7 (d, J=24.5 Hz), 116.1 (d, J=21.3 Hz), 119.6, 122.1, 128.9 (d, J=7.9 Hz),132.5, 162.8 (d, J=254 Hz), 203.6; ^{31}P NMR ($CDCl_3$) δ -7.60

3.1.3 Procedure for coupling of aromatic acyl phosphonates with m-trifluoromethylacetophenone

Reactions were carried out as for aromatic-aromatic acyl phosphonate/ketone coupling. The only difference is that dry THF used as solvent instead of dry DMF. This procedure is only valid for the coupling of dimethyl (4-methoxyphenyl) oxom ethyl phosphonate and m-trifluoromethylacetophenone.

2-(3-(trifluoromethyl)phenyl)-1-(4-methoxypheny)-1-oxopropan-2-yl dimethyl phos-phate (93o): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.94 (3H, s), 3.42 (3H, d, J=11.4 Hz), 3.61 (3H, d, J=11.4 Hz), 3.71 (3H, s), 6.70 (2H, d, J=9,0 Hz), 7.41 (1H, t, J=7.8 Hz), 7.51 (2H, t, J=8.3 Hz), 7.67-7.69 (3H, m); ^{13}C NMR ($CDCl_3$) δ 27.9, 54.1(d, J=5.4 Hz), 54.2 (d, J=6.0 Hz), 55.2, 88.2 (d, J=4.6 Hz), 113.3, 120.8, 124.9, 126.9, 127.5, 129.4, 131.4, 132.7, 142.9, 143.0, 163.0, 194.0; ^{31}P NMR ($CDCl_3$) δ -2.50

3.1.4 Procedure for coupling of aromatic acyl phosphonates with cyclohexanone

20 % mol KCN, 20 % mol 18-crown-6 and 25 % mol catalyst **116** were placed in a round bottom flask and 2 mL freshly dried THF was added via syringe. 1 mmol aromatic acyl phosphonate and 2 mmol cyclohexanone was added onto the reaction mixture under inert atmosphere at ambient temperature. After completion reaction (1 hour)mixture was diluted with 15 mL ether and worked up as aromatic-aromatic reactions. This procedure is only valid for the coupling of dimethyl (4-methoxyphenyl) oxom ethyl phosphonate and cyclohexanone.

(118): white crystals; ^{1}H NMR ($CDCl_3$) δ 1.24-1.33 (2H, m), 1.55-1.60 (3H, m), 1.67-1.77 (2H, m), 1.95-2.01 (2H, m), 2.17-2.25 (2H, m), 3.54 (6H, d, J=11.3 Hz), 3.79 (3H, s), 6.84 (2H, d, J=9.0 Hz), 8.07 (2H, d, J=8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.6, 23.9, 33.5, 33.6, 53.3 (d, J=5.5 Hz), 54.4, 88.0 (d, J=6.9 Hz),112,4, 126.4, 131.3, 162,0, 196.1; ^{31}P NMR ($CDCl_3$) δ -1.67

CHAPTER 4

CONCLUSION

This study mainly based on intermolecular aldehyde/ketone cross benzoin reactions. There are some methods for the intramolecular aldehyde/ketone coupling with thiazolium carbene catalyst in literature. On the other hand, a synthetic method for the intermolecular aldehyde/ ketone cross coupling has not been introduced yet. Here in, we introduce first intermolecular aldehyde/ketone coupling by using acyl phosphonate as acyl anion precursors. Acyl phosphonates were found so effective as acyl anion equivalents by means of yields, purity of product and reaction times in cross benzoin reactions. These reagents are superior to other acyl anion precursors in terms of easy availability. Scope and limitations of the introduced synthetic method was examined and variety of cross benzoin products of aldehyde/ketone coupling was synthesized. On the other hand, it is obvious that the method is new and open to improvements. Limitations of the method can be eliminated with further investigations.

As a conclusion, we developed a new method for aldehyde/ketone cross benzoin coupling. The method makes easier to synthesize α-keto tertiary alcohols, a functional group present in many biologically active compounds.

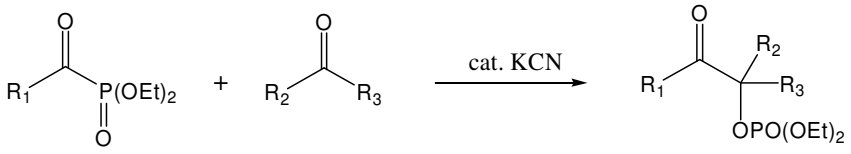


Figure 4.1. Intermolecular aldehyde/ketone coupling reaction

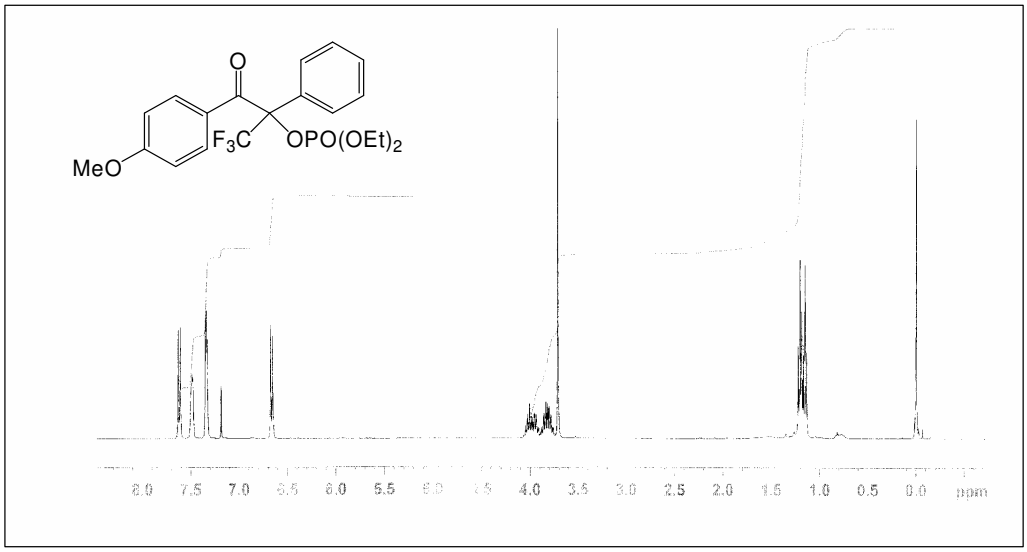


Figure 4.2. ^{1}H spectrum of **93b**

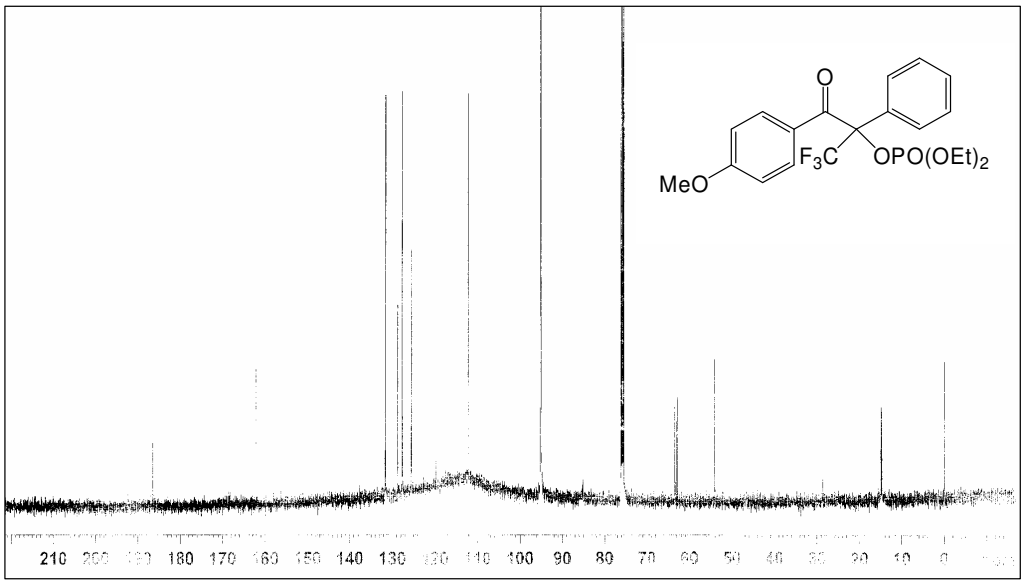


Figure 4.3. ^{13}C spectrum of **93b**

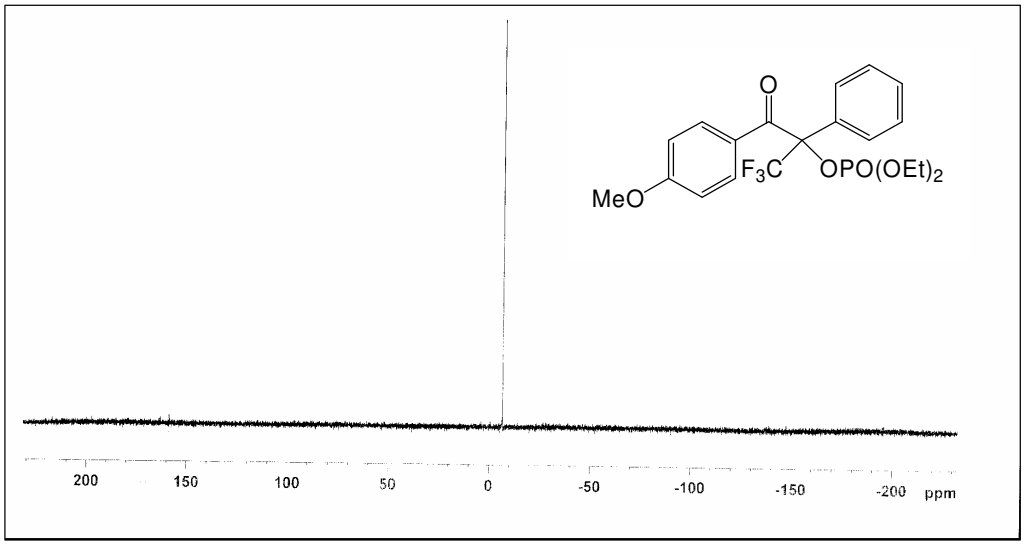


Figure 4.4. ^{31}P spectrum of **93b**

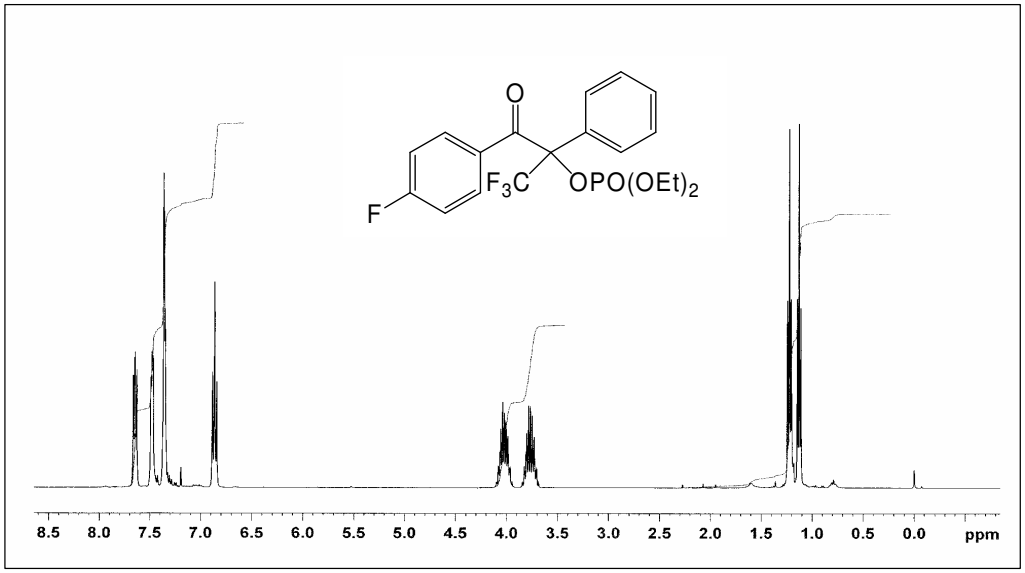


Figure 4.5. ^{1}H spectrum of **93c**

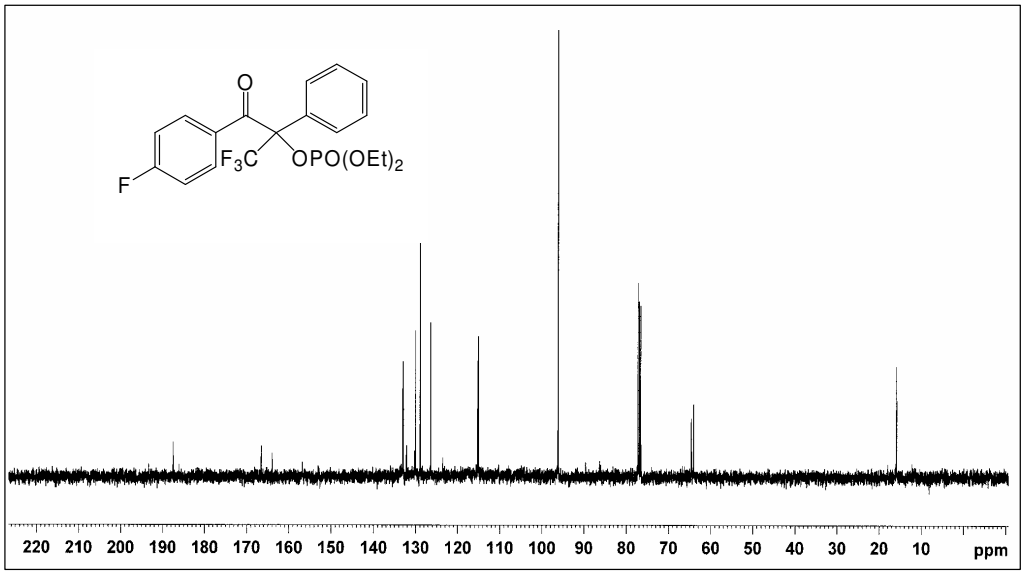


Figure 4.6. ^{13}C spectrum of **93c**

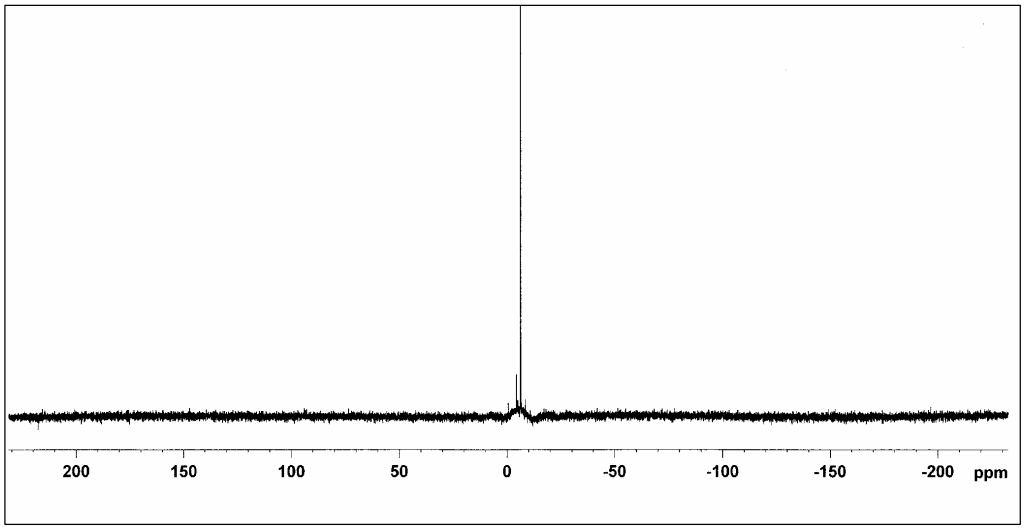


Figure 4.7. ^{31}P spectrum of **93c**

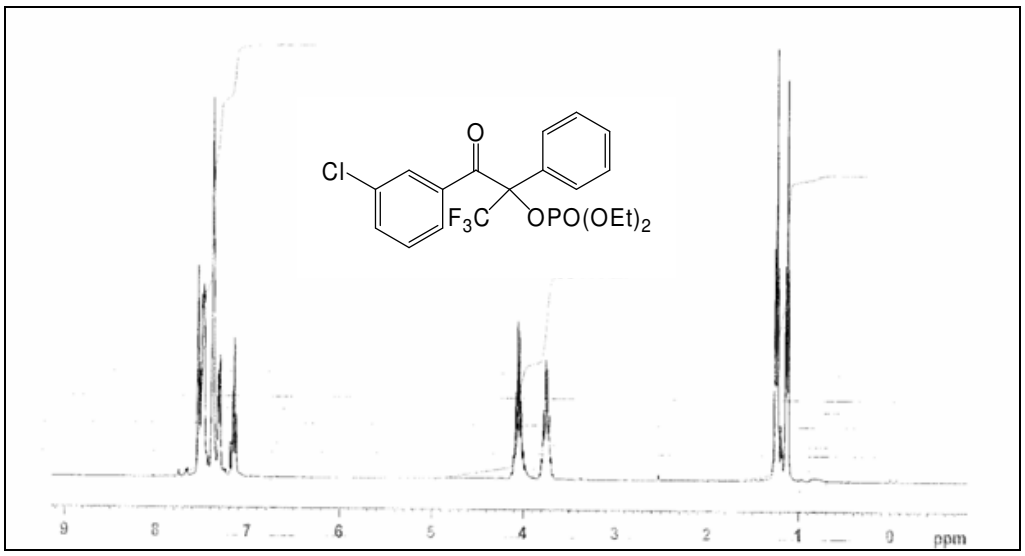


Figure 4.8. ^{1}H spectrum of **93d**

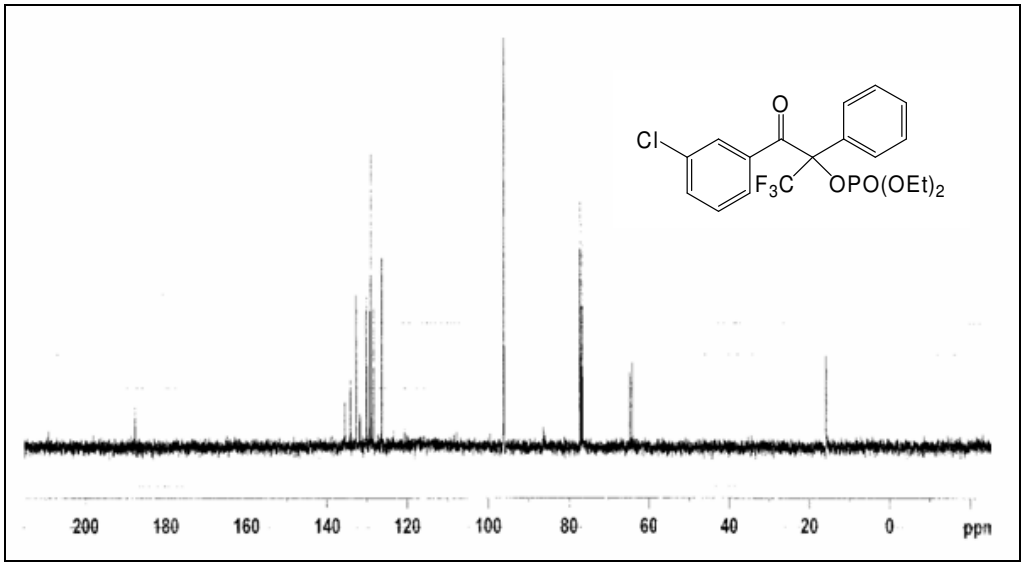


Figure 4.9. ^{13}C spectrum of **93d**

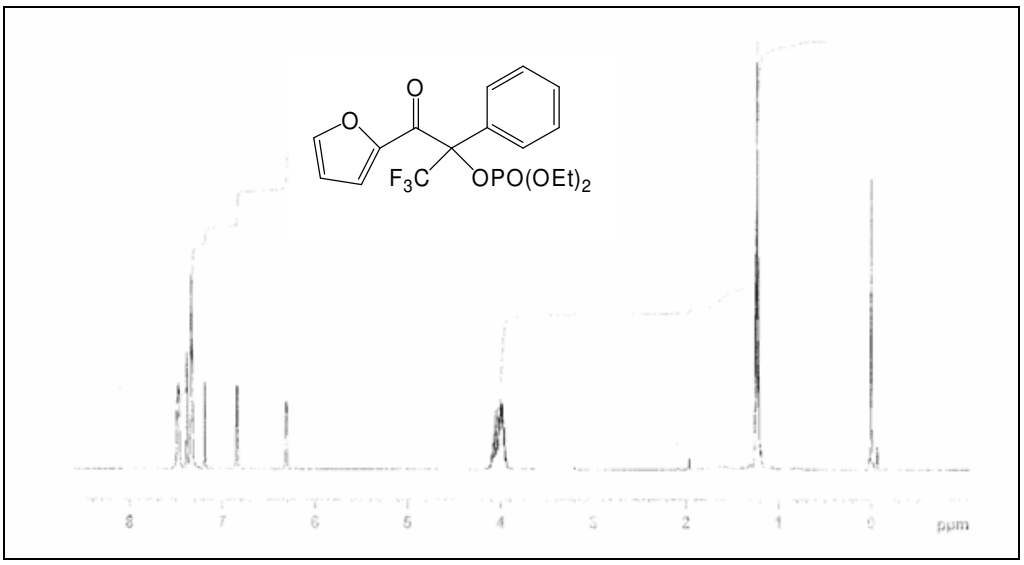


Figure 4.10. ^{1}H spectrum of **93h**

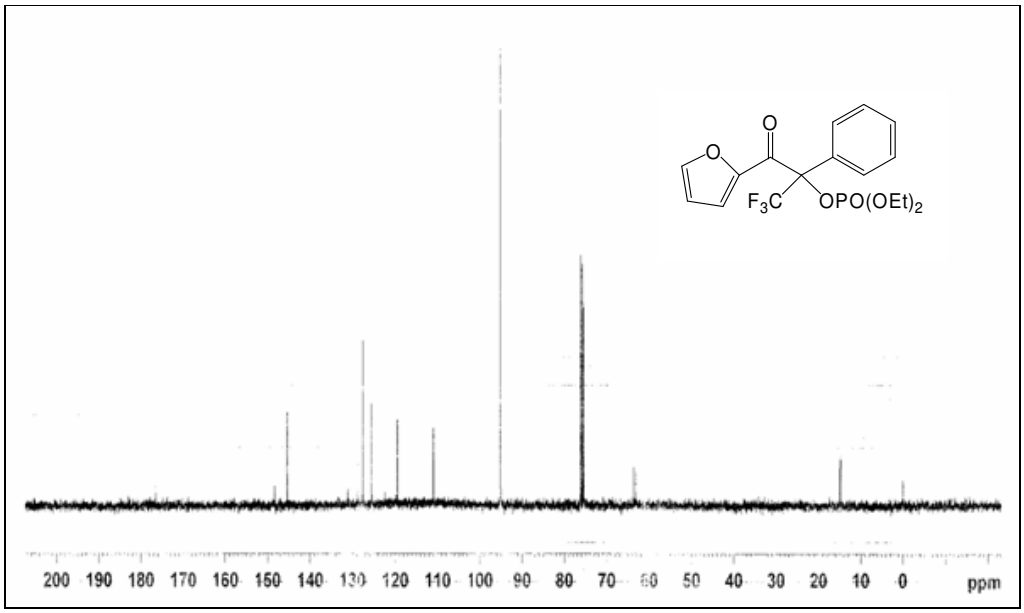


Figure 4.11. ^{13}C spectrum of **93h**

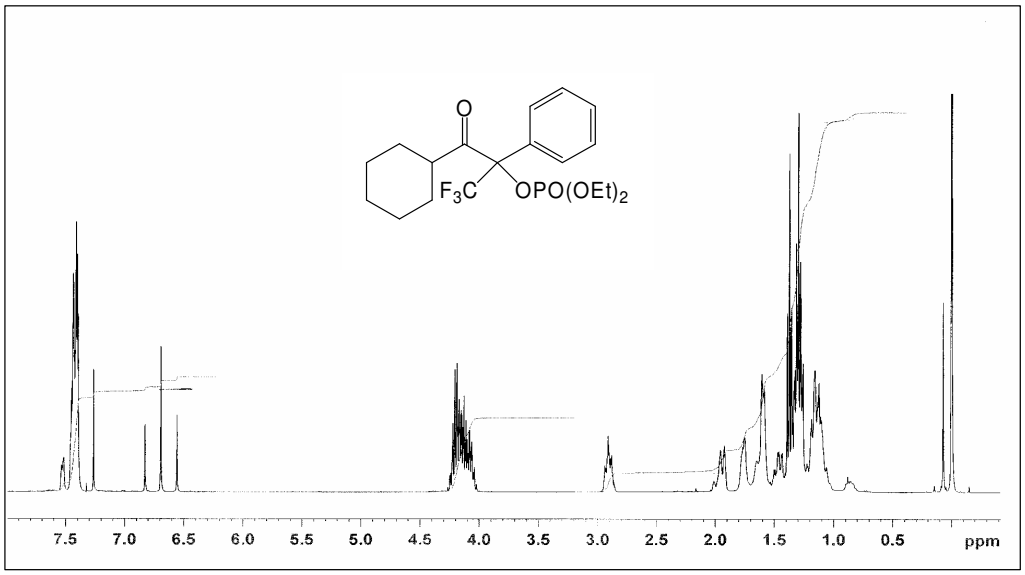


Figure 4.12. ^{1}H spectrum of **93i**

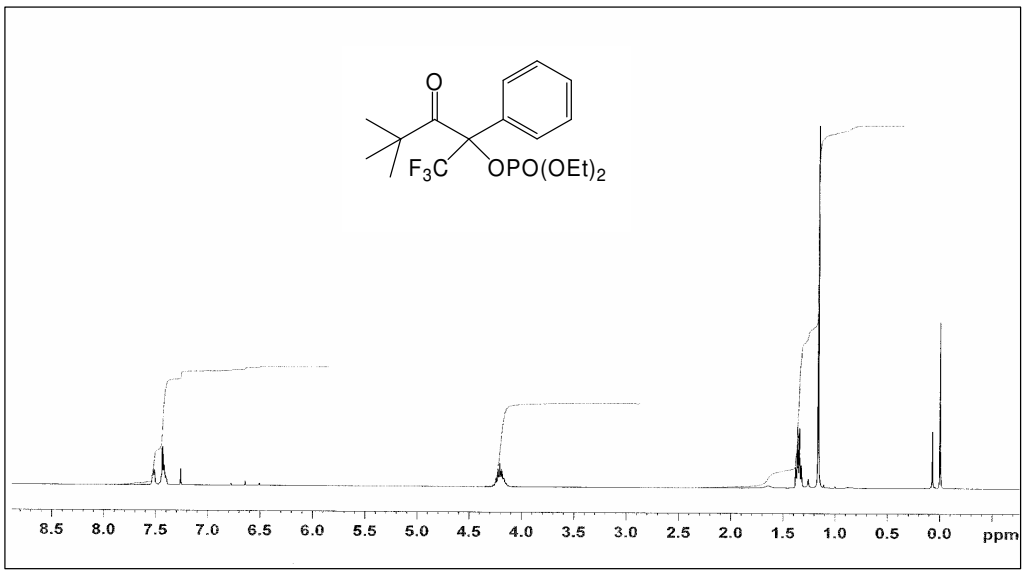


Figure 4.13. ^{1}H spectrum of **93j**

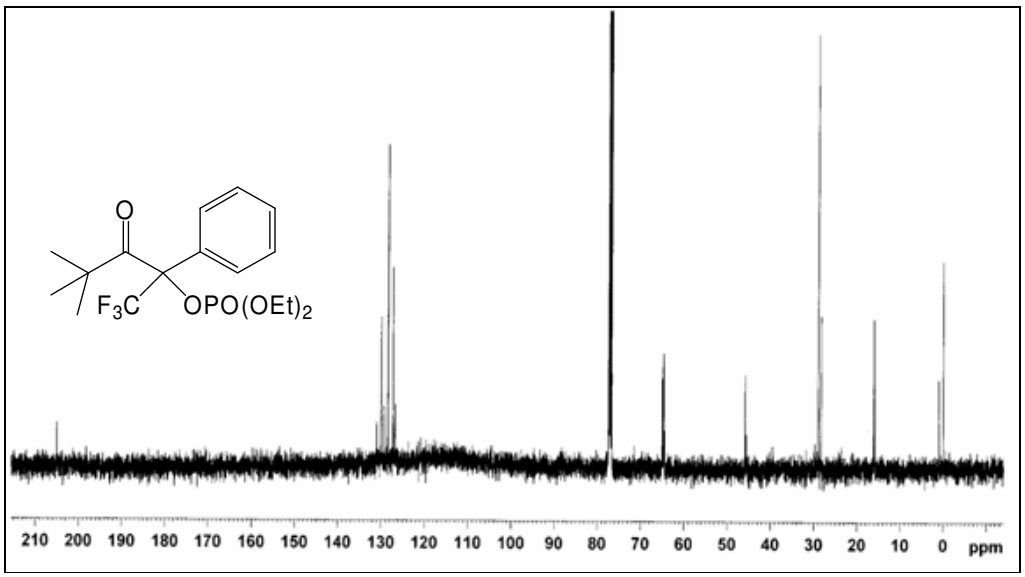


Figure 4.14. ^{13}C spectrum of **93j**

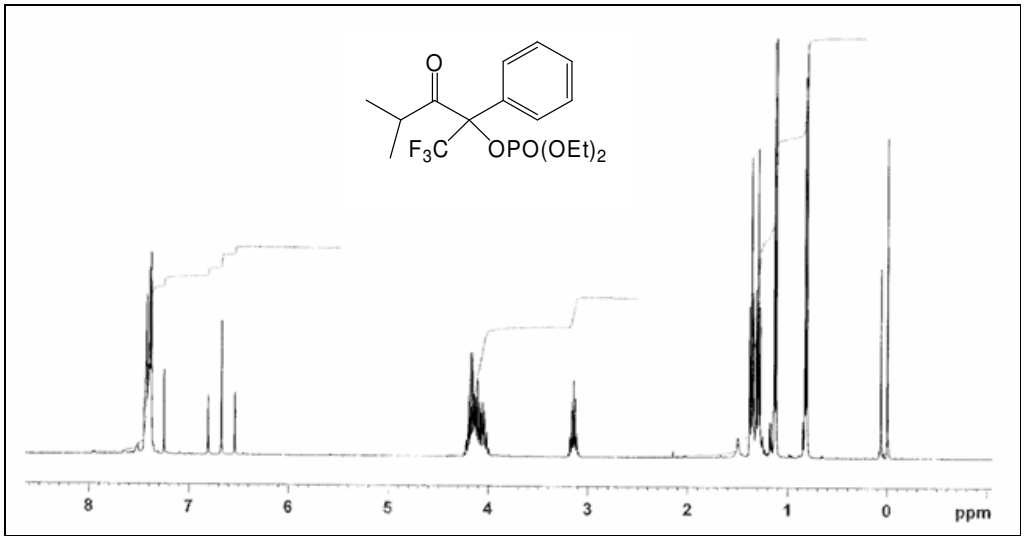


Figure 4.15. ^{1}H spectrum of **93k**

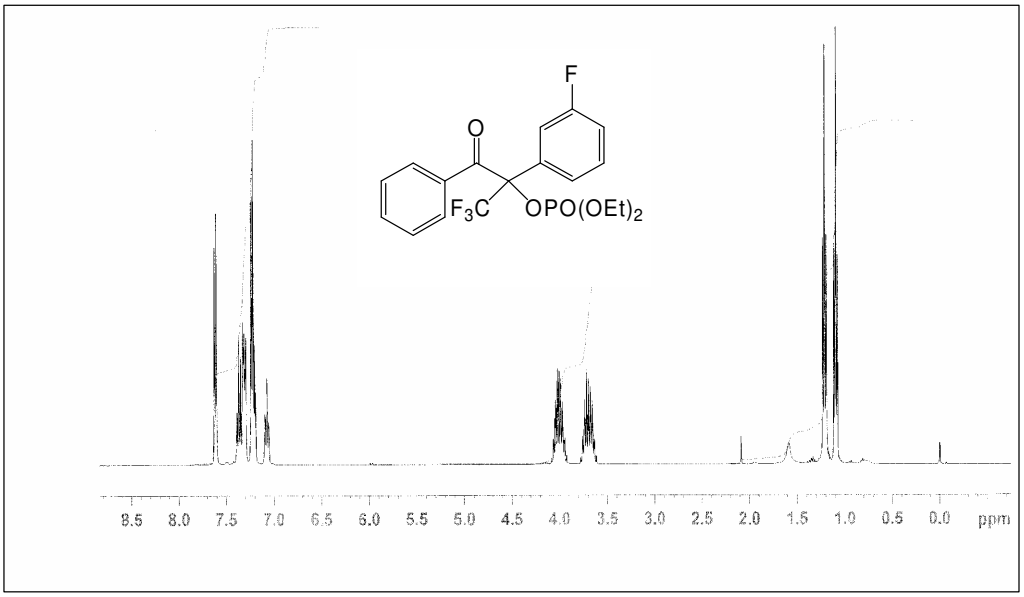


Figure 4.16. ^{1}H spectrum of 93m

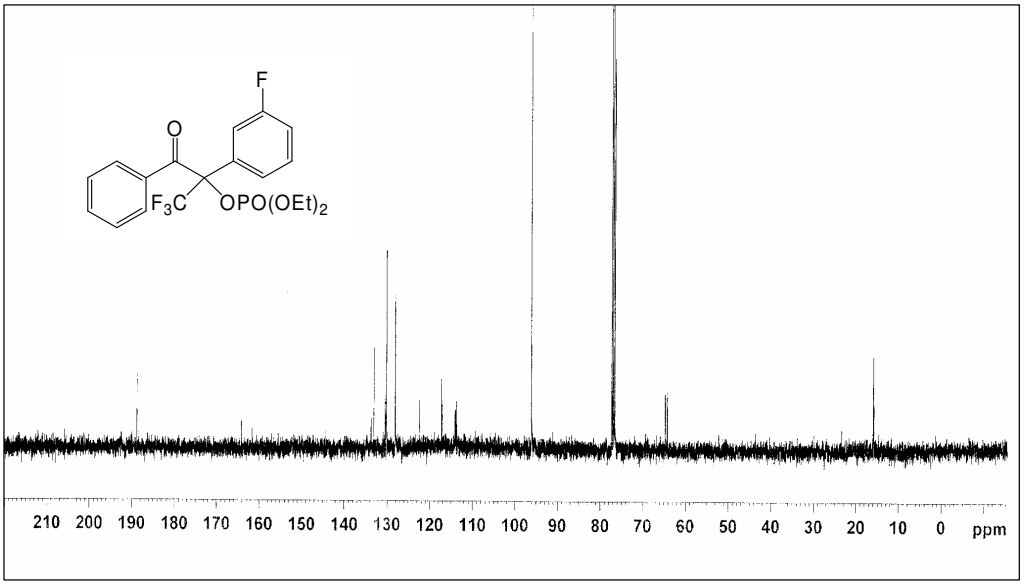


Figure 4.17. ^{13}C spectrum of **93m**

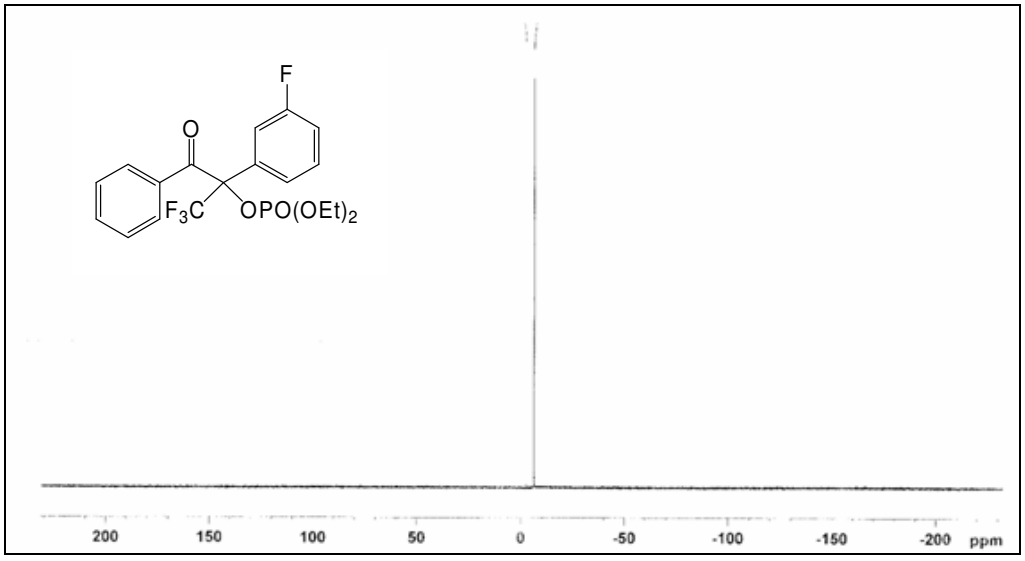


Figure 4.18. ^{31}P spectrum of **93m**

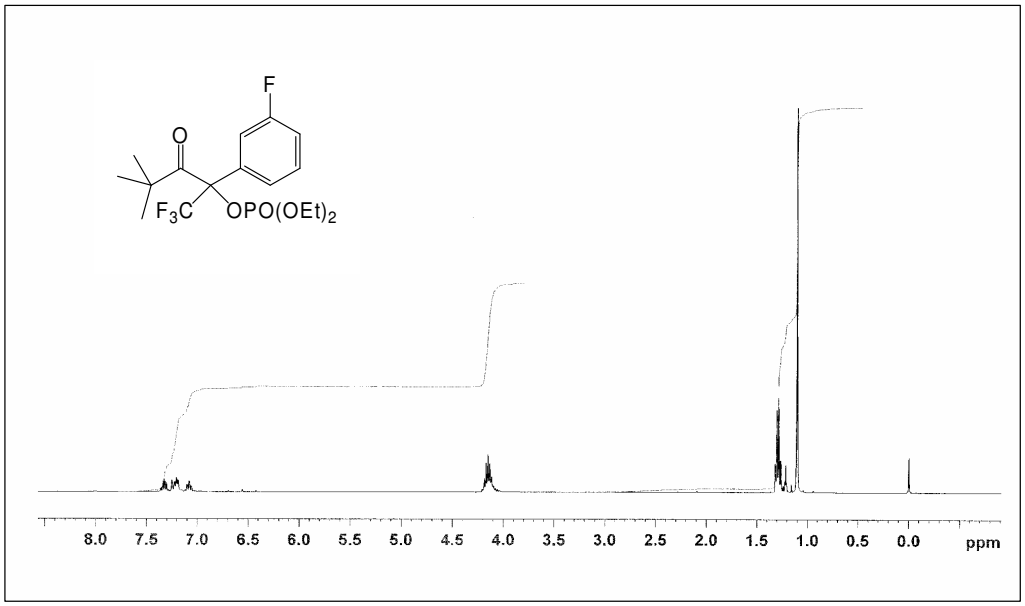


Figure 4.19. ^{1}H spectrum of **93n**

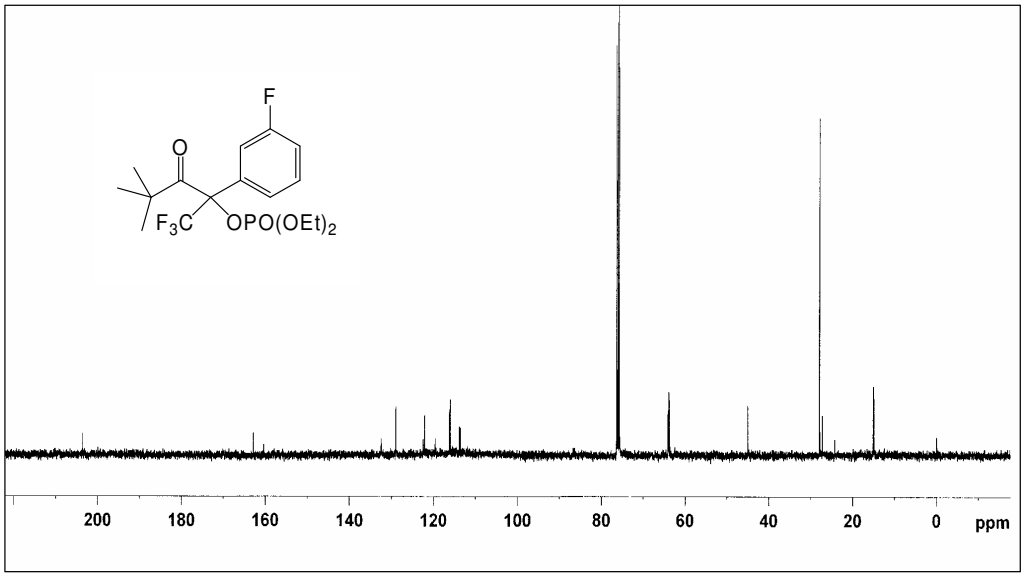


Figure 4.20. ^{13}C spectrum of **93n**

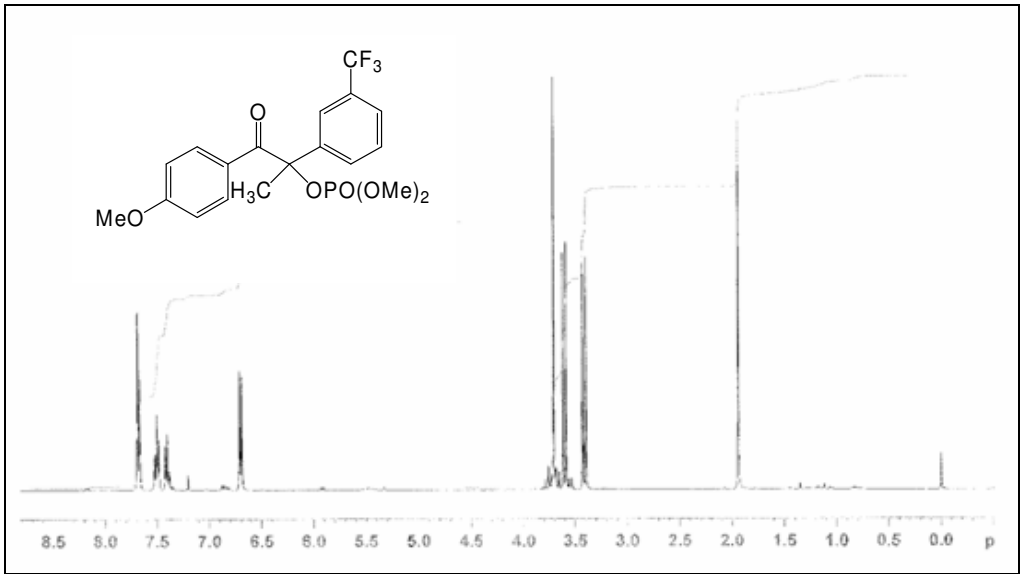


Figure 4.21. ^{1}H spectrum of **93o**

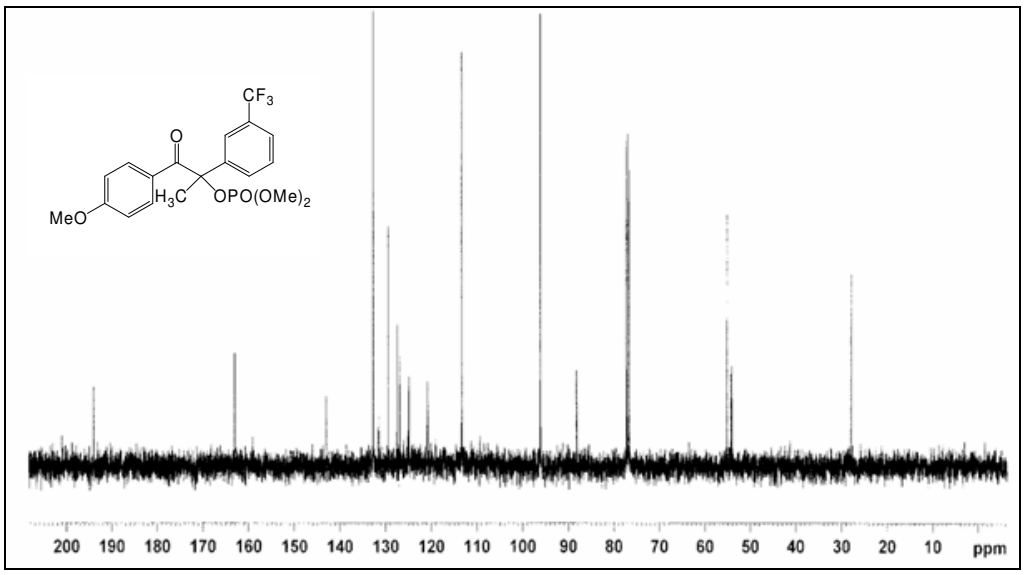


Figure 4.22. ^{13}C spectrum of **93o**

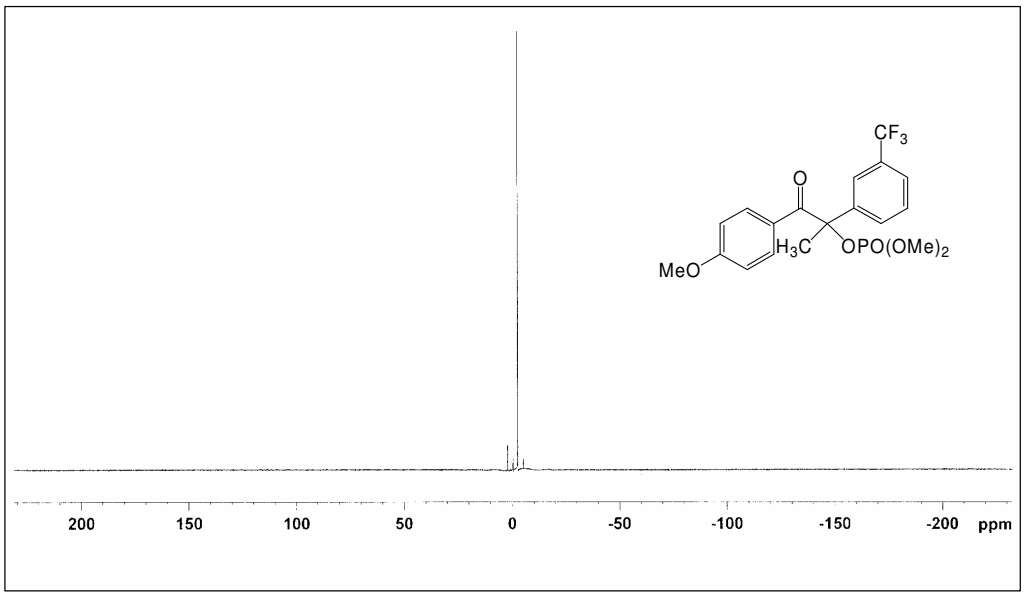


Figure 4.23. ^{31}P spectrum of **93o**

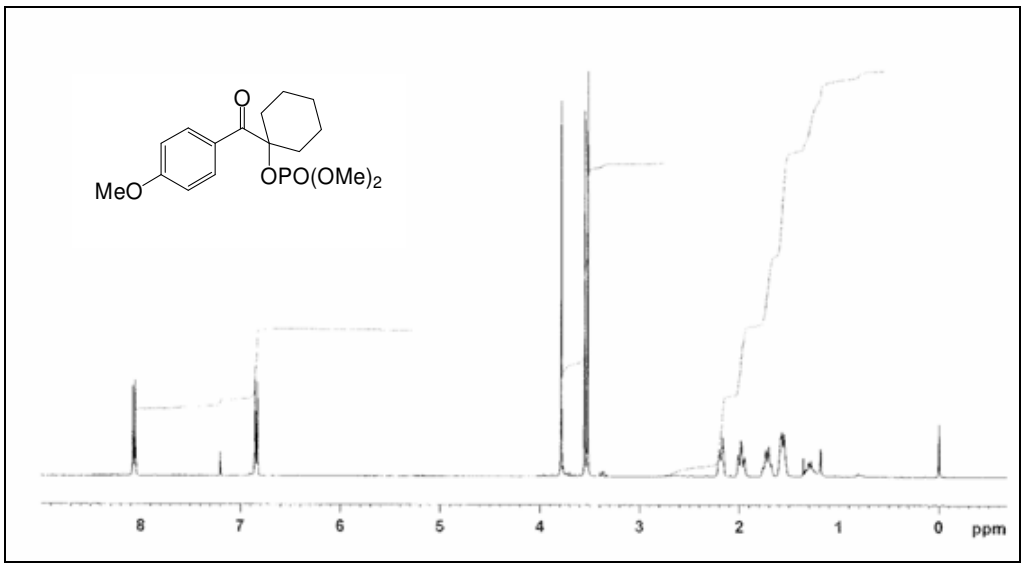


Figure 4.24. ^{1}H spectrum of **108**

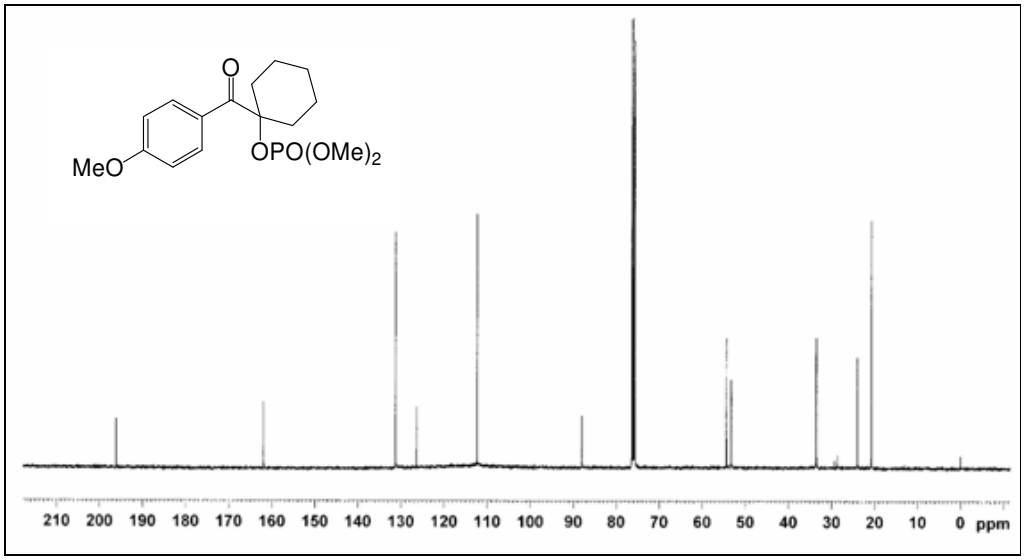


Figure 4.25. ^{13}C spectrum of **108**

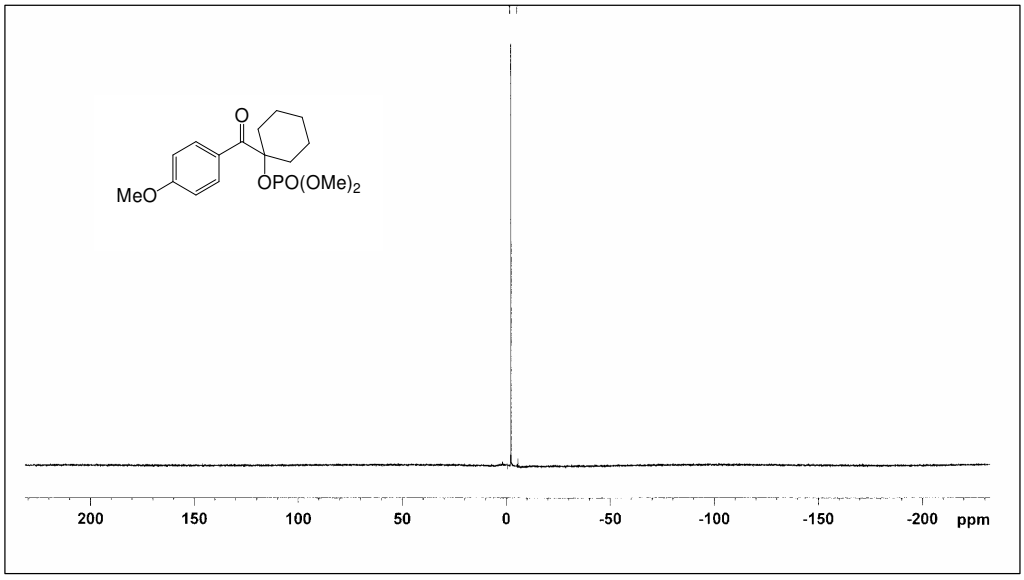


Figure 4.26. ^{31}P spectrum of **108**

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