STUDIES ON THE REACTION OF ACYL PHOSPHONATES WITH ALDEHYDES IN THE PRESENCE OF PROLINE

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STUDIES ON THE REACTION OF ACYL PHOSPHONATES WITH ALDEHYDES IN THE PRESENCE OF PROLINE

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ABSTRACT

STUDIES ON THE REACTION OF ACYL PHOSPHONATES WITH ALDEHYDES IN THE PRESENCE OF PROLINE

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Acyl phosphonates are interesting precursors for the synthesis of biologically active compounds. In the first part, the acyl phosphonates are synthesized starting from the corresponding acyl chloride. The acyl chlorides are converted into acyl phosphonates by using trialkylphosphites.

The reaction of acyl phosphonates with aldehydes in the presence of proline furnished not the suggested aldol products via proline catalyzed aldol reaction but bicyclic products via one pot tricomponent 1,3-dipolar cycloaddition reaction. The formation of the bicyclic compound was suggested as followed; The formation of iminium salt of proline with aldehyde followed by decarboxylation furnished azomethine. The 1,3-dipolar cycloaddition of the formed azomethine with carbonyl

group of acyl phosphonate afforded substituted hexahydro pyrrolo oxazole structures.

1,3-Dipolar cycloaddition forms the basis of the most preparatively useful procedures for the synthesis of five-membered heterocycles. One example is the 1,3-dipolar cycloaddition of azomethine ylides (from imines) and alkenes, which allows the stereoselective synthesis of pyrrolidines or proline derivatives.

Keywords: Organocatalysis, 1,3-dipolar cycloaddition reaction, Azomethine ylide, acyl phosphonate.

ÖZ

PROLİN VARLIĞINDA AÇİL FOSFONATLARIN ALDEHİTLERLE REAKSİYONLARI ÜZERİNE ÇALIŞMALAR

Yalçınkaya, Hatice
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Tez Yöneticisi: Prof. Dr. Ayhan S. Demir

Şubat 2009, 58 sayfa

Açil fosfonatlar biyolojik aktivite gösteren bileşiklerin sentezlerinde önemli başlangıç ürünleridirler. Çalışmanın ilk bölümünde, açil fosfonatlar açil klorürden başlanarak trialkil fosfit kullanılarak sentezlenmiştir.

Yapılan reaksiyonlarda pirolin varlığında aldehit ve açil fosfonatların reaksiyonu yapılmış ve beklenen aldol ürünü yerine tek basamakta bisiklik 1,3-dipolar 3 bileşenli siklokatılma ürünü elde edilmiştir. Bu bisiklik ürünün oluşması şu şekilde önerilmektedir; Aldehitle prolinin iminyum ürünü oluşturmasının ardından dekarboksilasyonla azometin yapısı elde edilmektedir. Oluşan azometinin açil fosfonatın karbonil grubuyla 1,3-dipolar siklo katılmasıyla hekzahidro pirolo oksazol yapısı oluşmaktadır.

1,3-dipolar siklokatılım reaksiyonları 5'li halkalı heterosiklik yapıların sentezinde en yararlı yöntemlerden biridir. Azometin ylür (iminlerden) ve alkenler 1,3-dipolar siklokatılım reaksiyonlarına bir örnektirler. Ayrıca bunlar pirolidinlerin ve prolin türevlerinin stereoselektif sentezini mümkün kılar.

Anahtar kelimeler: Organokatalizör, 1,3-dipolar siklokatılım reaksiyonları, Azomethin ylür, Açil fosfonat.

To My Parents and Lovely Brother İhsan,

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INTRODUCTION

1.1 Organocatalysts in Asymmetric Reactions

Catalytic enantioselective synthesis of organic compounds is a subject of deep research efforts. In the past decades, there has been a tremendous progress in the development of such strategies [1].

Until recently the catalysts used for enantioselective reactions in organic chemistry were mainly divided into two main categories, chiral transition metal complexes and enzymes. At the beginning of this decade, a new approach has been established in which small organic molecules, named as organocatalysts, can be highly selective and efficient catalysts [1, 2].

Organocatalysis is the acceleration of chemical reactions with a catalytic amount of an organic compound and no transition metals are required for this catalysis [1, 3]. Organocatalysts have a lot of advantages. First of all, they are usually strong. Because, they are not affected from moisture and oxygen, and moreover, necessary reaction conditions such as inert atmosphere, low temperatures, absolute solvents, etc. are, in many cases, not required. Furthermore, they are cheap, readily accessible and non-toxic. Finally, organocatalysis is a very effective method for preparation of compounds which do not tolerate metal contamination such as pharmaceutical products [1].

As a result, organocatalysis has gained high importance and become a main focus of research in asymmetric synthesis [2].

Most but not all organocatalysts can be abundantly categorized as either Lewis base, Lewis acid, Brønsted base, or Brønsted acid catalysts. The basic catalytic cycle is shown (Figure 1.1).

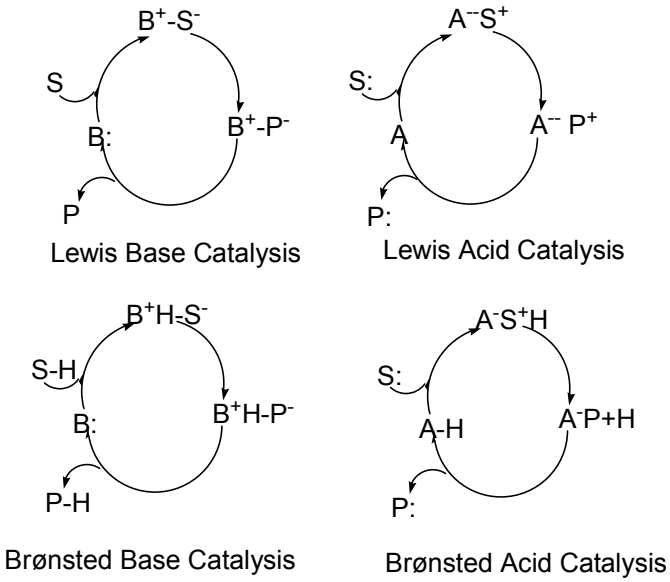

Figure 1.1 Organocatalytic cycles

According to this cycles, Lewis base catalysts (B) start the catalytic cycle with nucleophilic addition to the substrate (S). The resulting intermediate undergoes a transformation and releases product (P) and completes the catalytic cycle. Lewis acid catalysts (A) activate nucleophilic substares (S) in a similar way. Brønsted base and Brønsted acid catalysts start the cycles with the protonation or deprotonation of the substrate that activates it for further transformations [2].

1.1.1 Lewis base catalysis

Lewis bases convert the substrates into activated nucleophiles or electrophiles and well-known reactive intermediates are iminium ions and enamines (Figure 1.2) [2].

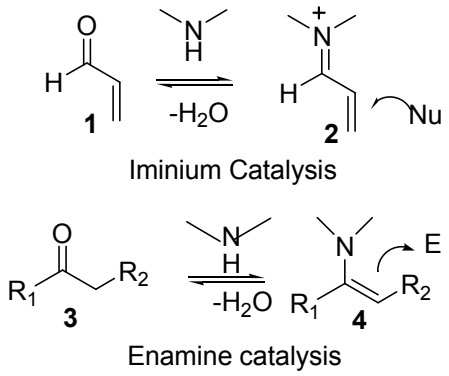

Figure 1.2 Examples of Lewis base organocatalysis

The active reagent in iminium catalysis is an iminium ion. It which is formed from a carbonyl compound and primary or secondary amines, has high reactivitiy against nucleophiles. The increased reactivity of iminium ions can be explained on the basis of decrease in the energy of LUMO orbital of conjugated double bonds upon formation of the iminium ion. This higher reactivity of iminium ion makes it possible the catalysis of various transformations such as cycloadditions and Michael additions.

In 2000, Macmillan and co-workers reported the one important example of enantioselective iminium catalysis. They introduced imidazolidinones **6** as effective iminium activation catalysis. This type of catalysis has been shown to be successful in various cycloadditions, Michael and Friedel-Craft type nucleophilic additions to α, β- unsaturated aldehydes and ketones (Figure 1.3) [3].

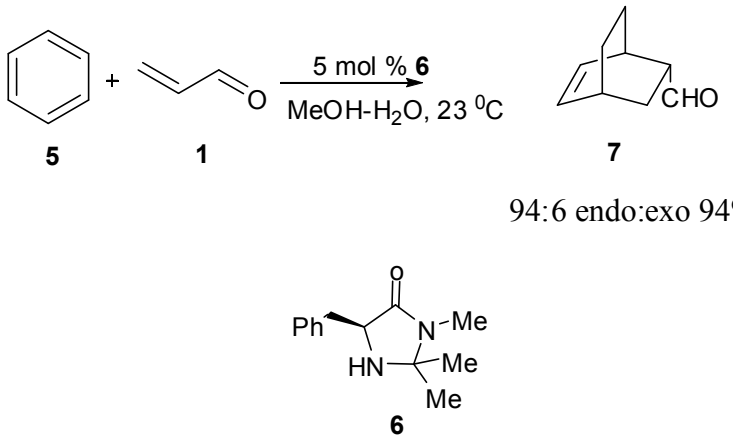

Figure 1.3 Diels-Alder reaction of α, β- unsaturated aldehydes

Enamine catalyts is observed followed by the deprotonation of an imine or iminium ion resulting in a strong nucleophilic character that can react with various electrophiles. Enamine catalysts are widely used in aldol and Mannich type reactions, Michael additions, α-heteroatom functionalizations of enolizable aldehyde and ketones. In 1970's Hajos, Parrish and Eder, Sauer and Wiechert discovered the first example of asymmetric enamine catalysis in an intramolecular aldol reaction catalyzed by proline [4]. Almost three decades later, List, Barbas and Lerner discovered intermolecular aldol reaction by using proline between aromatic aldehydes and acetone (Figure 1.4) [5, 6].

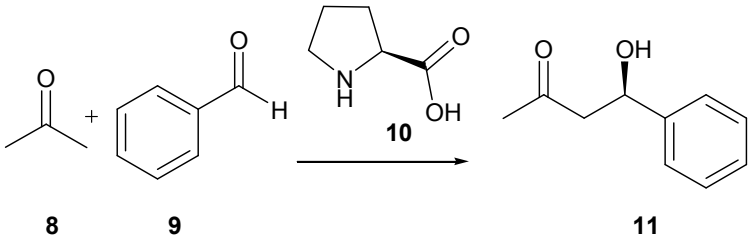

Figure 1.4 Proline catalyzed aldol reaction

1.1.2. Lewis acid catalysis

An important class of organic catalysts are phase transfer catalysts, that can be considered as Lewis acids

Phase transfer catalysis is very successful approach because it is not only operates in mild reactions conditions and basic experimental methods but also it is inexpensive [7]. Phase transfer reactions were firstly developed with the use of catalysts derived from cinchona alkaloids. The pioneering example of phase transfer catalyst was accomplished by using N-benzyl cinchonine salt for asymmetric α-methylation of indanone [8]. Same type of cinchonine and cinchonidine based catalysts were widely used for α-alkylation of glycine derivatives to form stereoselective α-amino acids. Moreover, Corey and co-workers introduced new cinchonidium salts that brought a new approach to chiral phase transfer catalysts and they synthesized highly enantiomerically rich products via α-alkylation of glycine derivatives **(**Figure 1.5) [9].

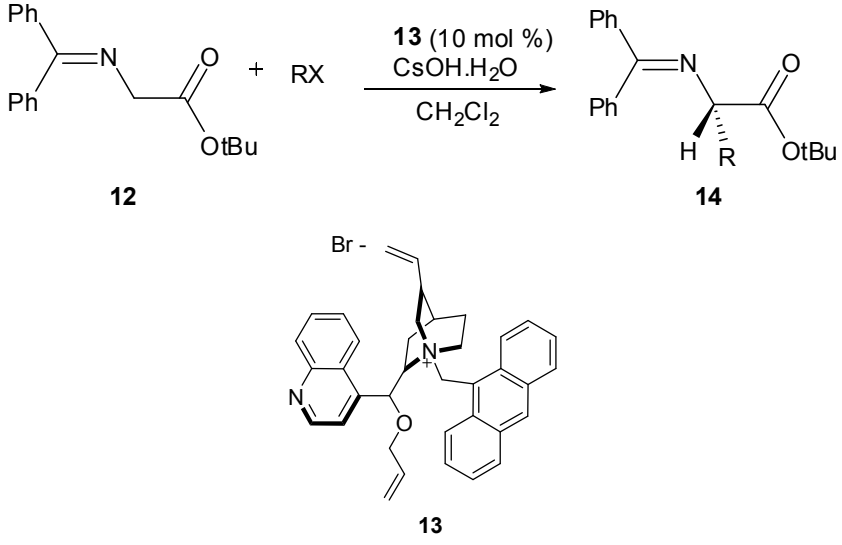

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Figure 1.5 Enantioselective catalytic Phase Transfer Alkylation

1.1.3. Brønsted base catalysis

Well-known reactions of Brønsted base in asymmetric synthesis is hydrocyanation such as cyanohydrin synthesis and Strecker reaction.

Corey and Grogan have shown the asymmetric synthesis of α-amino nitriles and α-amino acids by using bicyclic guanidine in Strecker reaction (Figure 1.6).

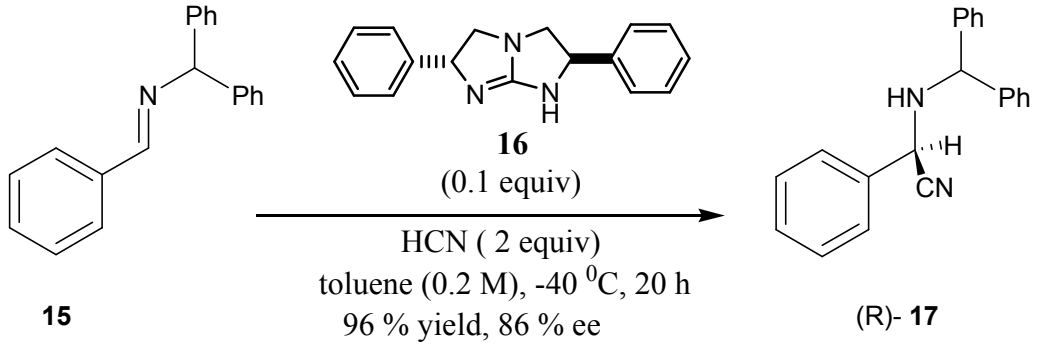


Figure 1.6 Strecker reaction of α-amino nitriles

In this reaction, HCN interact with catalyst to generate a cyanide ion which can then serve as a hydrogen bond donor to the carbonyl compound or imine which is activated with hydrogen bonding [10].

1.1.4 Brønsted acid catalysis

Recently, catalysis through hydrogen bonding **20** has been introduced as a powerful methodology for asymmetric catalysis. Similarly to enzymatic catalysis where H-bonding to a transition state occurs, this type of catalysis may be described as general acid catalysis.

The research was reported an enantioselective chiral proton source (containing a polar ionic hydrogen bond) as a catalyst for the aza-Henry reaction. For example, the reaction of nitroethane and the *p*-nitrobenzylimine **18** in the presence of **20** yielded the corresponding aza-Henry adduct in 90% ee (Figure 1.7) [11].

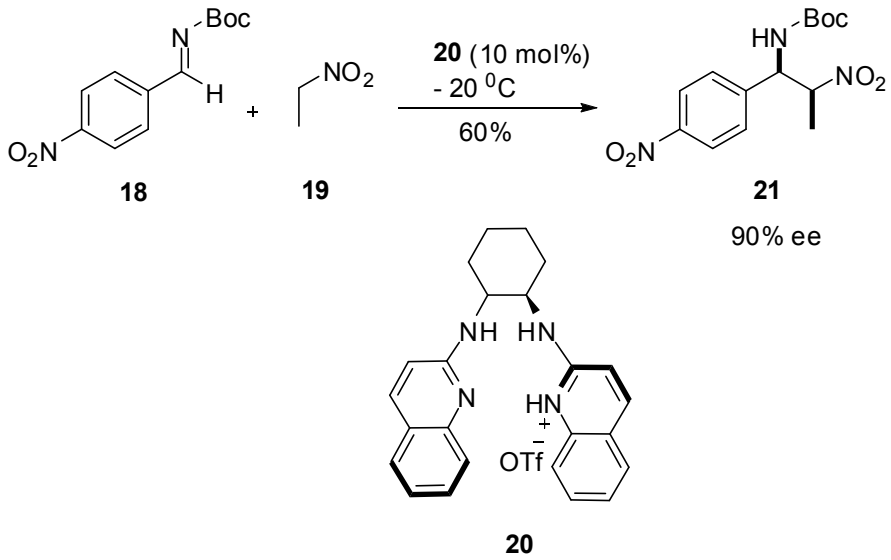


Figure 1.7 Example of N-H- based Brønsted acid catalyst

The enantioselective asymmetric Morita–Baylis–Hillman reaction is catalyzed by a chiral BINOL-derived Brønsted acid **24** (Figure 1.8) [12]. Here the Brønsted acid promotes the conjugate addition step of the reaction, and then remains hydrogen-bonded to the resulting enolate in the enantioselectivity-determining aldehyde addition step.

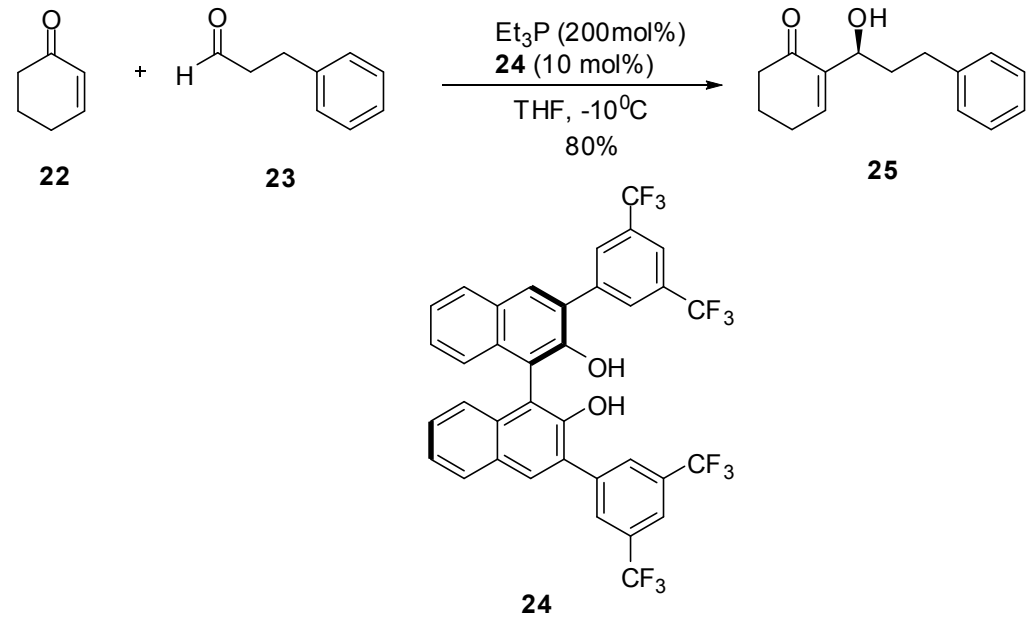


Figure 1.8 Enantioselective asymmetric Morita–Baylis–Hillman reaction

Akiyama *et al*. have made the very exciting discovery that even relatively strong acids can be efficient asymmetric catalysts. Recently, it has been reported Mannich reactions using chiral Brønsted acid catalyst (Figure 1.9) [13].

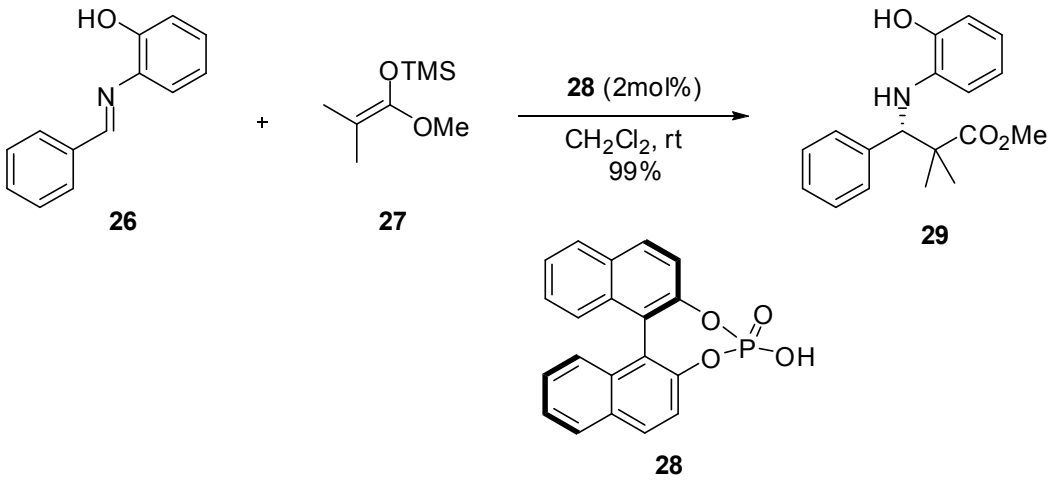


Figure 1.9 Example of Mannich reaction

1.2 Amino Acids as Organocatalysts

The initial reports on the Hajos–Parrish–Eder–Sauer–Wiechert reaction were disclosed in the early 1970s (Figure 1.4) [14], the use of small molecules to catalyze organic reactions remained largely unexplored for several decades. The year 2000 saw a renaissance of organocatalysis, and thereafter proline emerged as one of the most prominent catalysts in a wide range of asymmetric reactions [15]. It has been regarded as the simplest enzyme [16]. To date, a large number of proline analogues were prepared and were used more or less successfully in a huge number of organocatalytic reactions. Nature is an absolute master of performing asymmetric synthesis, and enzymes are highly efficient biocatalysts in living systems. While the catalytic efficiencies of enzymes are astonishing, the interaction forces that enzymes utilize to engage substrates at their active sites are quite trivial, such as hydrogen bonding, Van der Waals forces, and electrostatic, hydrophobic and dipole–dipole interactions. Small molecule catalysts also make use of the above interactions in catalysis. Developing small organic catalysts into enzyme mimics represents a very interesting and intriguing, yet extremely formidable task. Similar to aldol reactions catalyzed by proline, natural class I aldolases catalyze aldol reactions in water *via* the enamine mechanism, in which the enamine is formed at the lysine residue in the enzyme active site [17].

1.2.1 Primary amino acids as organocatalysts in intramolecular aldol reactions

Although not well appreciated by the scientific community, primary amino acids were investigated as potential catalysts for intramolecular Hajos–Parrish–Eder–Sauer–Wiechert reactions some time ago, as described in a number of early reports [14]. Eder, Sauer and Wiechert showed that phenylalanine was a quite good catalyst, only slightly inferior to proline [14a]. In the initial report by Hajos and Parrish [14b], phenylalanine was tested as an alternative catalyst in intramolecular aldol reactions, albeit the chemical and optical yields of the desired product were rather poor. Subsequently, Buchschacher *et al.* [18] reported that primary β-amino acids, such as β-homophenylalanine [15], as well as amino acids, were effective catalysts in intramolecular asymmetric aldol condensations. Danishefsky and co-workers [19] found that employing a slight excess of phenylalanine, in combination with $HClO_4$,

yielded the intramolecular condensation product with high optical purity, whereas proline only led to disappointing results for the same reaction. Tsuji[20a], Hagiwara[20b] and Corey[20c] later employed phenylalanine with either $HClO_4$ or camphorsulfonic acid to effect key intramolecular aldol reactions in steroid synthesis. In addition, there were a number of reports on applications of amino acid-catalyzed Hajos–Parrish–Eder–Sauer–Wiechert reactions in total syntheses [21]. Recently, Davies and Smith reported [22] that the β-amino acid (1*R*,2*S*)-cis pentacin promoted the Hajos–Parrish–Eder–Sauer–Wiechert reaction with a level of enantioselectivity comparable to that observed with the proline-catalyzed reaction. This represents the best enantioselectivity obtained for this particular reaction using an amino acid catalyst containing a primary amino functionality (Figure 1.10) demonstrated the power and potential of primary amino group-mediated organic catalysis, thus paving the way for the further exploration of such catalysts in a broader scope of organic transformations.

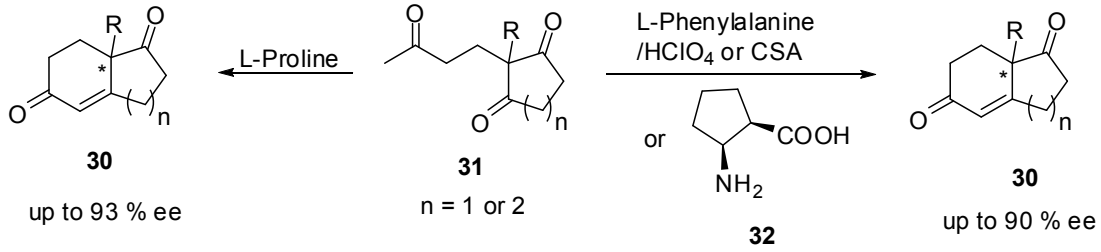


Figure 1.10 L-Proline and primary amino acid-promoted Hajos–Parrish–Eder–Sauer–Wiechert reactions.

1.2.2. Primary *versus* secondary amino acids in intermolecular condensations: mechanistic considerations

Aminocatalysis *via* the enamine mechanism has become one of the most important activation methods in asymmetric organocatalysis. The key of such activation is the transformation of the carbonyl group into an enamine intermediate, which would increase the HOMO of the nucleophiles. In this context, proline and its structural

analogues have been demonstrated to be powerful catalysts for a large variety of reactions, including aldol reactions, Mannich reactions, Michael reactions and α-functionalizations of carbonyl compounds, among others. However, primary amino acid-promoted enamine catalysis is rather limited. In fact, in the initial report by List and Barbas on proline-catalyzed direct intermolecular asymmetric aldol reactions [15a,b], it was shown that primary amino acids, such as valine and phenylalanine, were poor catalysts for aldol reactions under the reaction conditions investigated. The catalytic cycles of enamine catalysis by proline and primary amino acids are compared in Figure 1.11. It has long been thought that a secondary enamine is better stabilized by hyperconjugation, whereas a primary amine gives the predominant imine form. For primary amino acids to serve as efficient catalysts in enamine catalysis, effective tautomerization of their imine form (**a**', Figure 1.11) to the enamine form (**b**', Figure 1.11) is absolutely essential. In a recent report [23], Wong and co-workers found that water molecules participated in a proton relay *via* a hydrogen-bonding network to effect the conversion of an imine formed between a lysine residue and acetaldehyde to the enamine form. Amedjkouh [24] subsequently demonstrated that the presence of water was crucial for the primary amino acid-mediated aldol reactions to take place. Tanaka and Barbas also showed that organic solvent (*e.g.* DMSO) with a small amount of water as the additive facilitated enamine based reactions involving primary amines [25]. Taken together, these results suggest that it is certainly feasible to employ primary amino acids as potential catalysts in reactions involving enamine intermediates, provided that the corresponding enamines can be generated effectively. In addition, the presence of an extra N–H in the enamine (**b**', Figure 1.11) intermediate derived from the primary amino group may facilitate the control of the enamine structure, and direct the reaction to occur with specific reactivity and selectivity, which may not be attainable *via* proline catalysis. Moreover, the ready availability of natural amino acids offers great flexibility in structural variation for the design of chiral organocatalysts. All these factors combined make primary amino acids interesting and promising catalysts in organocatalysis.

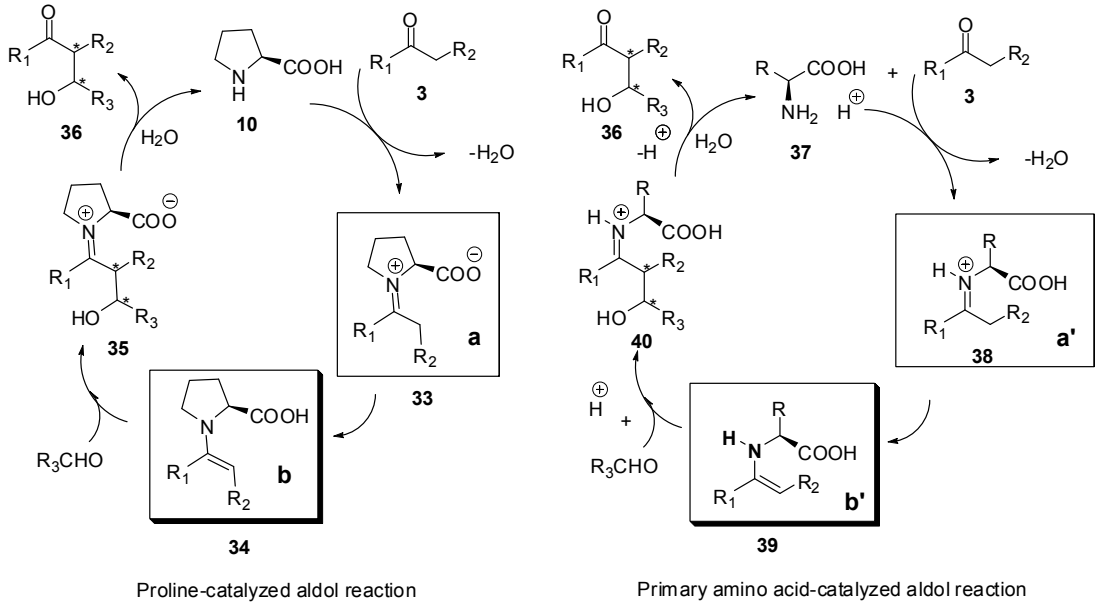


Figure 1.11 L-Proline and primary amino acid-promoted intermolecular aldol reactions *via* the enamine mechanism.

1.2.3. Mannich reaction

Proline has also been used as a catalyst for the direct Mannich reaction [26 and 27]. Preformed enolates and imines are not required. It is thus possible to mix together a substoichiometric quantity of proline (35 mol%), a ketone (acetone or hydroxyacetone), an aldehyde, and a primary amine (*p*-anisidine), and isolate the desired *para*-methoxyphenyl-protected amine in good to excellent enantioselectivity (70–96%) and modest to excellent yield (35–90%, Figure 1.12). This is particularly interesting considering both catalyst and primary amines are able to form Schiff bases with both ketone and aldehyde, opening various avenues for undesired reactivity. DMSO and $CHCl_3$ are used as co-solvents in some cases.

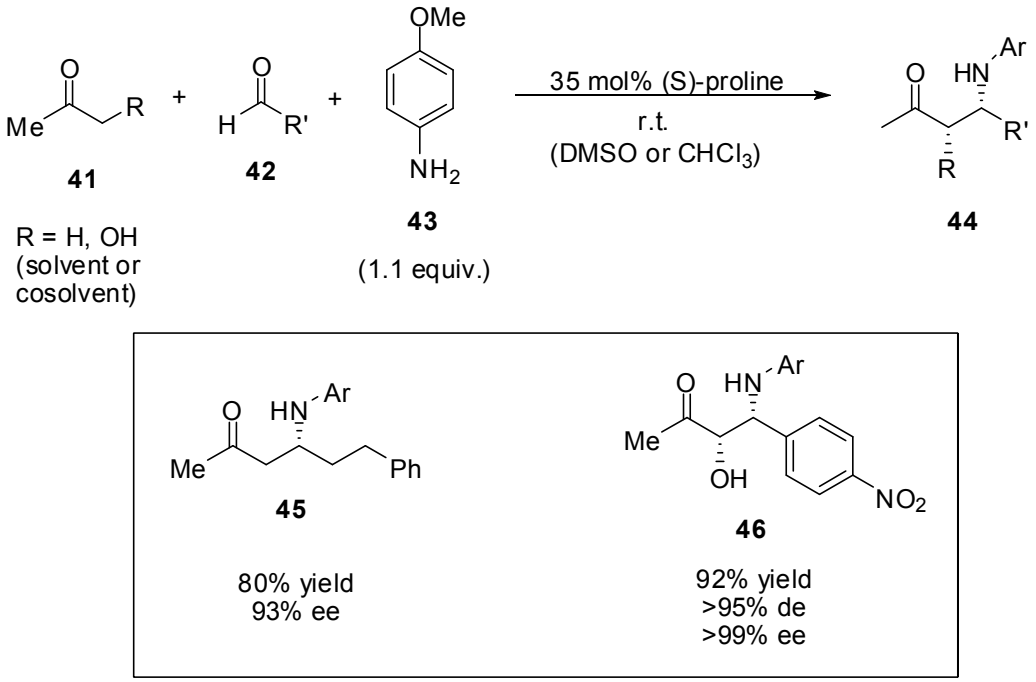


Figure 1.12 Three component catalytic asymmetric Mannich reaction.

This reaction exhibits opposite enantiofacial selectivity to the proline-catalyzed aldol reaction (attack on *si*-enantioface as compared to *re*-enantioface). A number of models have been proposed, culminating in the view presented in Figure 1.13. List proposes that the reaction of (*E*)-imine (which will be present in higher concentrations than the (*Z*)-imine) with the (*E*)-enamine could proceed as shown in Figure 1.13 (a). Comparison of this transition state to the proposed transition state for the aldol reaction (Figure 1.13 (b)) provides an explanation for the opposite enantiofacial selectivity of the two reactions: in the Mannich reaction steric interactions between the aromatic and pyrrolidine ring dominate while in the aldol reaction steric interactions between the aldehyde and enamine substituents may be the most important.

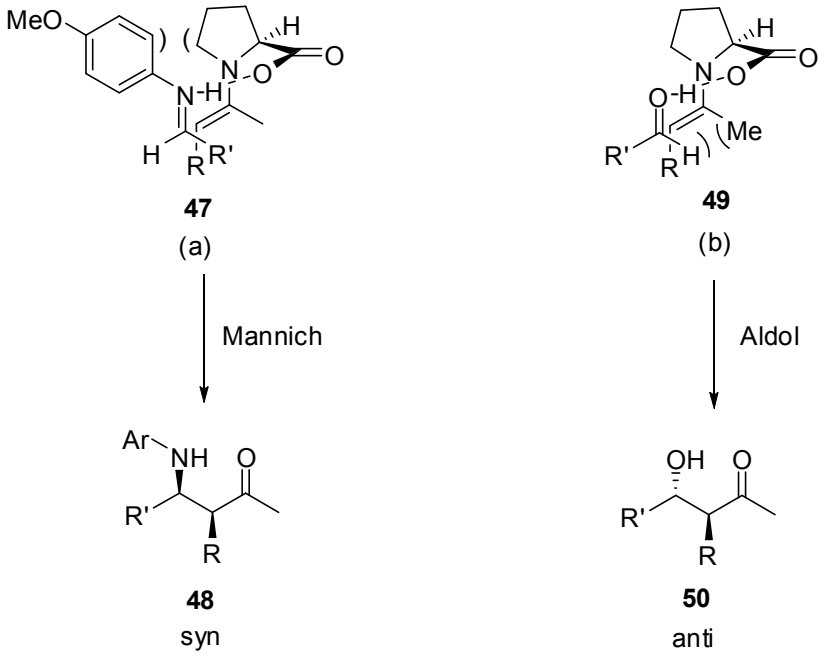


Figure 1.13 Proposed transition states for the proline-catalyzed asymmetric Mannich and aldol reactions.

1.2.4. Michael addition

The rubidium salt of (*S*)-proline has been used as a catalyst for the enantioselective addition of malonate to enones by Yamaguchi and co-workers (Figure 1.14) [28]. Michael addition products are formed with moderate to good enantioselectivities and yields. Both the carboxylate and secondary amine were found to be essential for catalysis. Various countercations, including alkali metals and tetraalkylammoniums were examined, with the rubidium salt proving the most enantioselective [29]. Rigorous exclusion of water slows the reaction rate, suggesting that the reaction may proceed through an intermediate iminium ion. The reaction exhibits an absence of a non-linear effect. This salt has also been used as a catalyst for the addition of nitroalkanes to enones [30], with modest to good enantioselectivities and yields (ee's ranging from 41–84%, yields 47–91%, Figure 1.14). Use of prochiral nitroalkanes yields products with low diastereoselectivities.

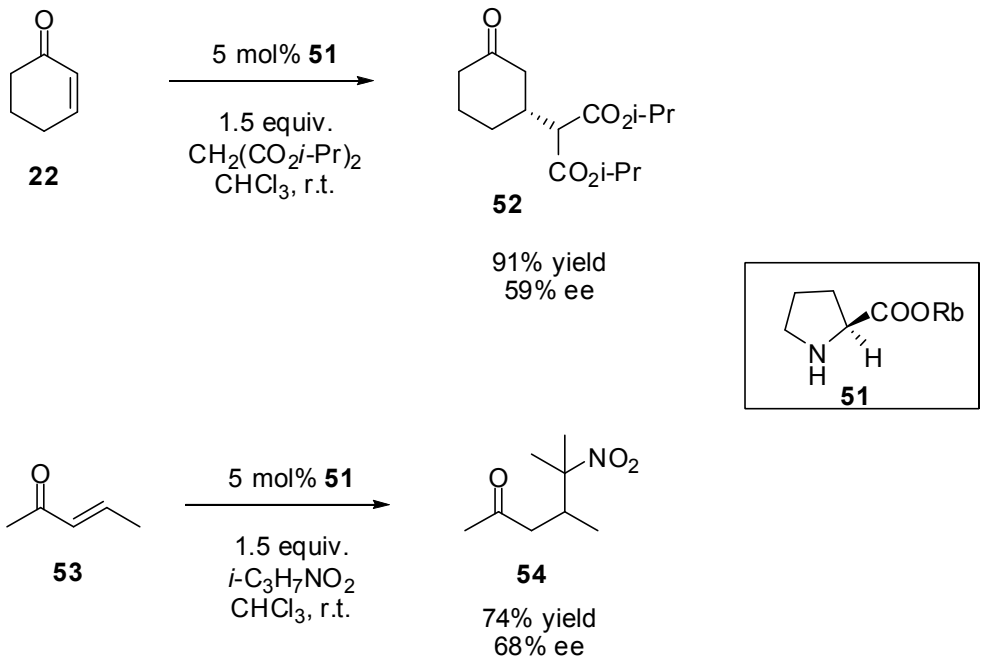


Figure 1.14 Rb-Prolinate catalyzed conjugate additions.

Hanessian and Pham have examined a related system, using a catalytic quantity of L-proline and a stoichiometric amount of *trans*-2,5-dimethylpiperazine as an additive [31]. Enantioselectivities in the conjugate additions of nitroalkanes to cyclic enones are improved compared to Rb-prolinate systems, with ee's ranging from 62–93% (Figure 1.15). Diastereoselectivities in reactions with primary nitroalkanes remain low. This reaction exhibits a pronounced nonlinear effect suggesting the involvement of a multicomponent catalyst. Furthermore, alcoholic solvents decrease enantioselectivities. Rigorous exclusion of water inhibits the reaction, lending credence to a hydrolytic step in the catalytic cycle.

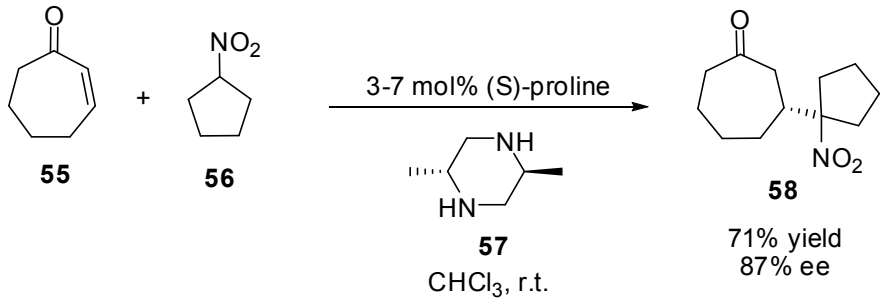


Figure 1.15 Proline catalyzed conjugate additions of nitroalkanes.

A small molecule **60** derived from (*S*)-proline has been shown to catalyze the Michael addition of ketones to alkylidene malonates [32 and 33]. Addition of acetone to aryl substituted diethylmalonates proved to be the best system with enantioselectivities ranging from 31 to 70% and yields ranging from 17 to 70% (Figure 1.16).

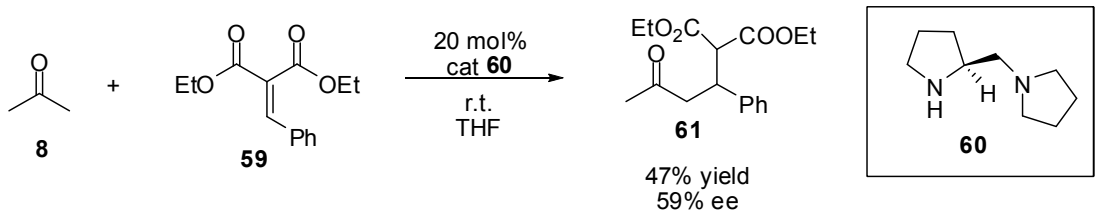


Figure 1.16 Bisamine catalyzed Michael addition.

1.3. 1,3-Dipolar Cycloadditions

1,3-Dipolar cycloadditions have been recognized as extremely important transformations in organic chemistry, as evidenced by the large number and wide scope of targets than can be prepared by this chemistry. Over the years, this reaction has developed into a generally useful method for the construction of five-membered heterocycles, whose importance is enhanced by the wide selection of 1,3-dipoles and dipolarophiles and the regio- and stereoselectivity during the cycloaddition. The method is also useful for the further transformations of the cycloadducts into a

variety of functional molecules. Numerous natural and unnatural products have been prepared by synthetic routes that have a 1,3-dipolar cycloaddition as a crucial step [34].

The 1,3-dipolar cycloaddition, also known as the Huisgen cycloaddition [35], is a classic reaction in organic chemistry consisting of the reaction of a dipolarophile with a 1,3-dipolar compound that allows the production of various five-membered heterocycles. This reaction represents one of the most productive fields of modern synthetic organic chemistry. Most of dipolarophiles are alkenes, alkynes and molecules possessing related heteroatom functional groups (such as carbonyls and nitriles). The 1,3-dipoles can be basically divided into two different types: the allyl anion type such as nitrones, azomethine ylides, nitro compounds, bearing a nitrogen atom in the middle of the dipole, carbonyl ylides, or carbonyl imines, bearing an oxygen atom in the middle of the dipole and the linear propargyl/allenyl anion type such as nitrile oxides, nitrilimines, nitrile ylides, diazoalkanes, or azides. Two p-electrons of the dipolarophile and four electrons of the dipolar compound participate in a concerted, pericyclic shift. The addition is stereoconservative (suprafacial), and the reaction is therefore a [2S+4S] cycloaddition (Figure 1.17).

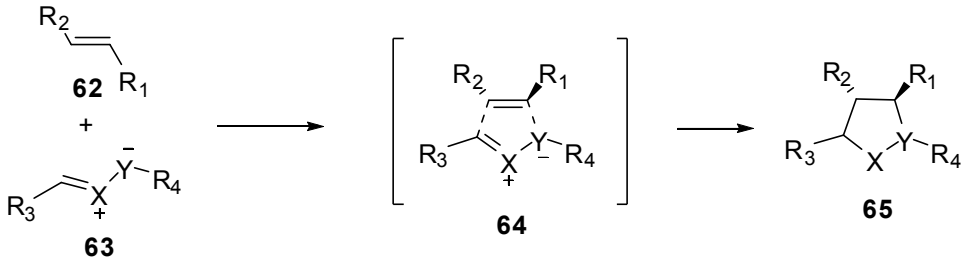


Figure 1.17 General concerted 1,3-dipolar cycloaddition.

However, the dipole might be stabilised by the adjacent central heteroatom X (nitrogen, oxygen, or sulfur) through resonance, and a non-concerted reaction pathway might also occur. Consequently, in some cases, the original stereochemistry of the alkene is not necessarily conserved, as depicted in (Figure 1.18) [36].

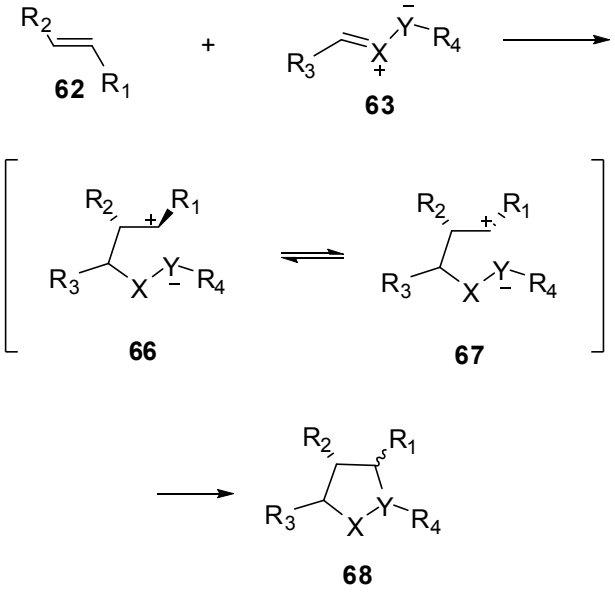


Figure 1.18 Non-concerted 1,3-dipolar cycloaddition.

1.3.1. Azomethine imines and azomethine ylides

In recent years, azomethine ylides have become one of the most investigated classes of 1,3-dipoles and, based on their cycloaddition chemistry, various methods for the synthesis of pyrrolidine derivatives have been developed. Azomethine ylides are planar 1,3-dipoles composed of one nitrogen and two terminal sp2 carbon atoms. Their cycloadditions to olefinic dipolarophiles provide a direct and general method for the synthesis of pyrrolidine derivatives. Although there are examples of stable, isolable azomethine ylides, they are normally generated in situ and trapped by almost any multiple C–C or C–X (X=heteroatom) bond. A number of methods have been developed for their generation, including the ring opening of aziridines, the desilylation of various silylamino derivatives, the decarboxylation condensation of amino acids, the 1,2-prototropy/metallo-azomethine ylides of amino acid-derived imines and the deprotonation of iminium salts. Advances in this area, over the last few decades, have made cycloaddition reactions of azomethine ylides a powerful synthetic tool, extensively used in the synthesis of natural products as well as other biologically interesting compounds [37].

Recently, Dogan and Garner *et. al.* have made a novel zinc(II) catalyst for the [3+2] cycloaddition between three glycine methyl ester aldimine derived azomethine ylides and a representative set of dipolarophile types (acrylate, fumarate, maleate, and maleimide). This procedure utilizes a novel ferrocenyl-substituted aziridino alcohol as the chiral ligand. The ease of ligand preparation is a particularly attractive feature of this new catalyst system. Under optimized reaction conditions, substituted pyrrolidine products are formed in generally high yields and with ee's ranging from 68 to 95% (Figure 1.19) [38].

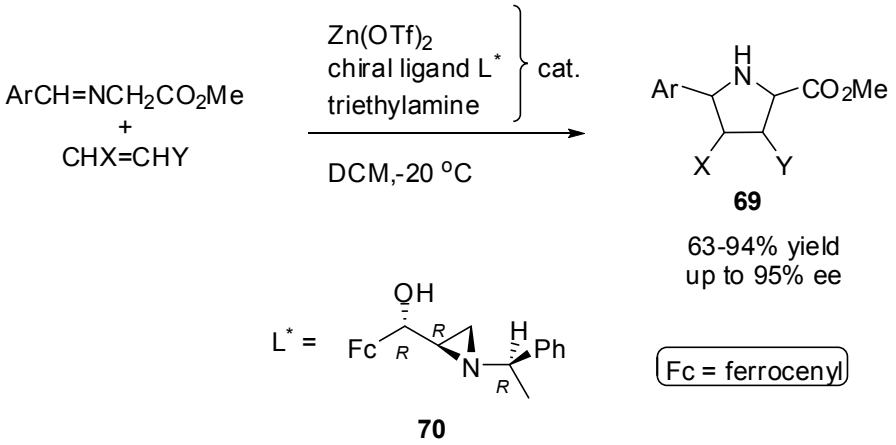


Figure 1.19 New zinc(II)-based catalyst for asymmetric azomethine ylide cycloaddition reaction

Azomethine ylides are precursors to pyrrolidines, dihydropyrroles, and pyrroles [39]. They have been generated by thermolysis or photolysis of aziridines, fluorine-mediated desilylation protocols, and by the deprotonation of the imines derived from α-amino acids [40]. Azomethine imines act as precursors to pyrazolidines and have been prepared by the reaction of 1,2-disubstituted hydrazines with carbonyl compounds (Figure 1.20) [41].

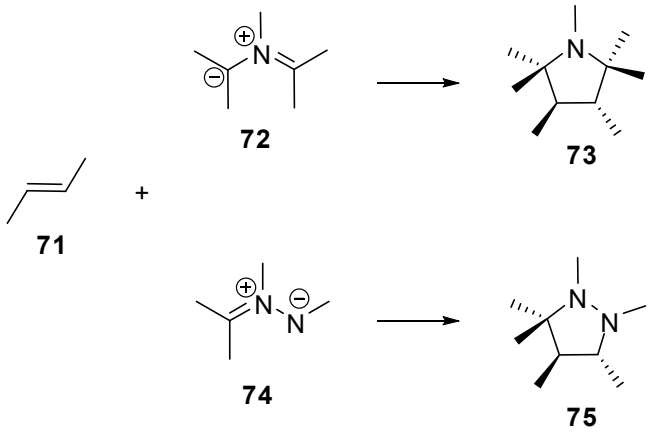


Figure 1.20 The reaction of 1,2-disubstituted hydrazines with carbonyl compounds

An intramolecular azomethine imine–alkene cycloaddition has been employed for the synthesis of a differentially protected trifunctional spiro-diamino acid scaffold, which finds use in combinatorial synthesis. The sequence of events involves an intramolecular Michael addition of hydrazone **76** to afford the azomethine imine **77**, which then reacts with the terminal olefin in an intramolecular dipolar cycloaddition to afford the tricyclic pyrazoline **78**. Reductive cleavage of the N–N bond and further routine synthetic manipulations afforded spiro-diamino acid **79** in 30% overall yield from **76**. The ketone precursor of **76** can be directly transformed into **78** in one-pot by treating with tert-butyl carbazate, albeit in lower yield (Figure 1.20) [42].

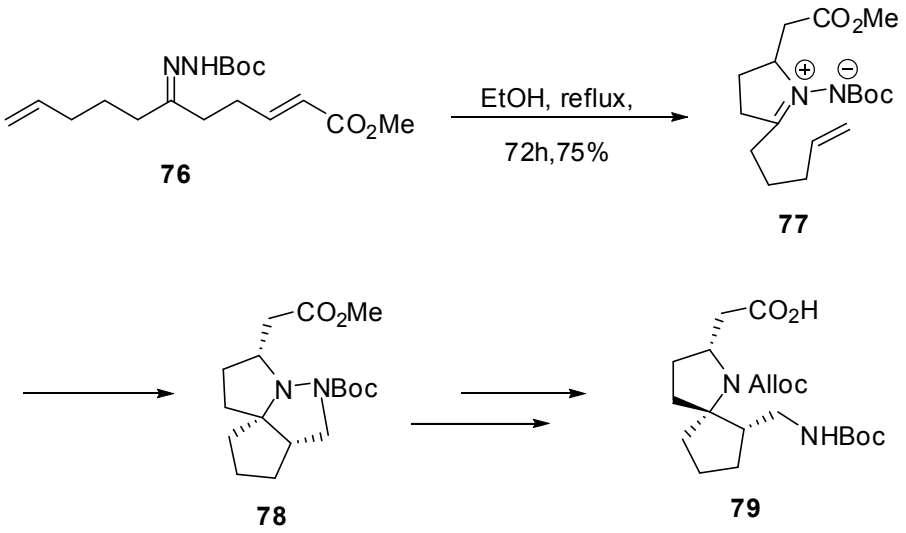


Figure 1.21 Synthesis of spiro diamino acid

1-[3-(Dimethylamino)propyl]-5-methyl-3-phenyl-1H-indazole (FS-32) **82** is a reserpine antagonist and it also potentiates amphetamine-induced self-stimulation and L-dopa-induced increase in motor activity. The fused pyrazole core of FS-32 has been prepared by the intramolecular dipolar cycloaddition reaction of a 3-alkyl sydnone **80**, which serves as a masked azomethine imine moiety with an alkene ether. Substrate **80** on boiling in xylene underwent the intramolecular dipolar cycloaddition reaction, followed by a rapid aromatization with the ejection of CO_2, finally resulting in the formation of the fused pyrazole **81**. The cyclohexane ring was oxidized under air using Pt/C, $HClO_4$, and acetic acid to complete the synthesis of the pyrazole-ring system (Figure 1.22) [43].

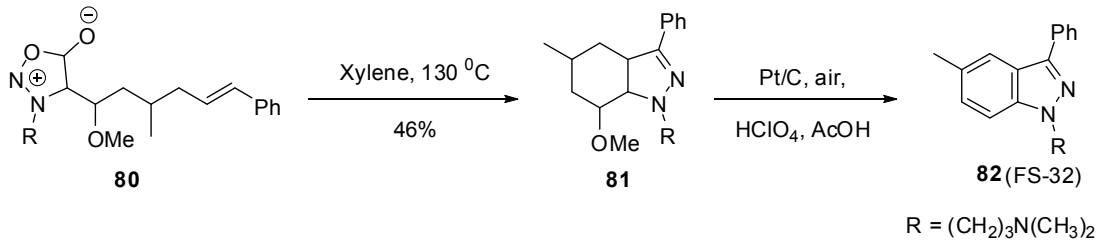


Figure 1.22 Synthesis of pyrazole ring system

Overman reported the synthesis of triazacyclopenta[*cd*]pentalenes **85** by the intramolecular dipolar cycloaddition reaction of azomethine imines. The dipole was generated by the condensation of dihydropyrrole α-ketoester **83** with thiosemicarbazide. The construction of the target ring system is a crucial step in the synthesis of complex guanidine alkaloids such as palauamine and styloguanidine. It is noteworthy that the intramolecular dipolar cycloaddition reaction exhibits a good degree of functional-group tolerance (Figure 1.23) [44].

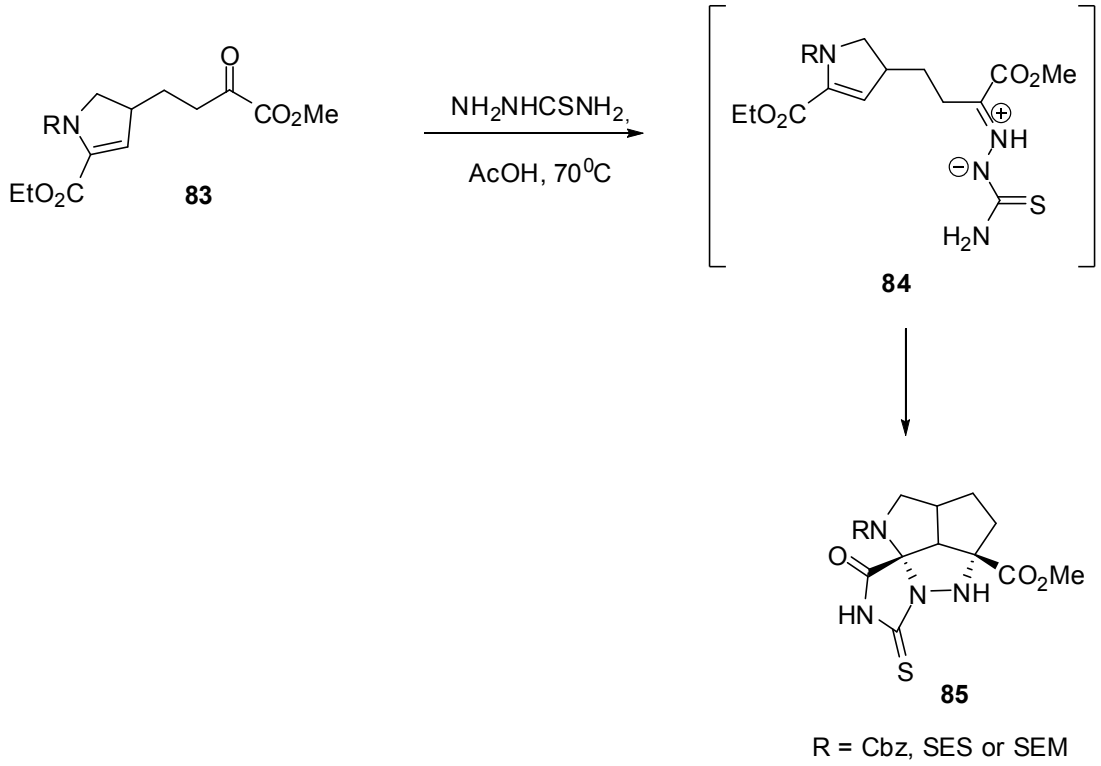


Figure 1.23 Synthesis of guanidine alkaloids

Alloc : allyloxycarbonyl

Cbz : benzyloxycarbonyl

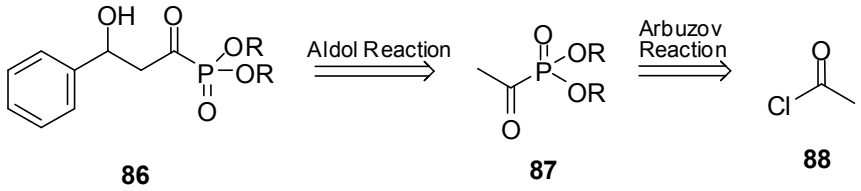
SEM : 2-(trimethylsilyl)ethoxycarbonyl

SES : 2-(trimethylsilyl)ethylsulfonyl

Tf : trifluoromethylsulfonyl

1.4 Aim of the work

Asymmetric organic reactions can be accelerated by a catalytic amount of a chiral organic molecule. Most of the reactions are carried out with aldehydes and ketones as donor substrates. Acyl phosphonates are interesting precursors for the synthesis of biologically active compounds and they can be used as acyl anion equivalence substrate.



86 **87** **88**

Figure 1.24 Retrosynthetic pathway of α-keto-γ-hydroxy-phosphonates

The aim of the work is to synthesize acyl phosphonates starting from trialkyl phosphite and acyl chloride derivatives, then organocatalytic addition of acyl phosphonates to aldehydes to obtain new optical active phosphono aldols (Figure 1.24).

Many organocatalytic methods such as imine-enamine activation, using Lewis acid, Lewis base, Bronsted acid, Bronsted base and H-Bonding catalyst will be applied to obtain products in high chemical an optical yields.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Reaction of acyl phosphonates with aldehydes in the presence of proline

2.1.1 Synthesis of acyl phosphonates

Phosphonate esters have found a wide range of applications in the areas of industrial, aggricultural, an medicinal chemistry owing to their physical properties as well as their utility as synthetic intermediates. Phosphonates are interesting complements to phosphates in terms of biological activity. Within this class of compounds there exist an important subdivision, the α-ketophosphonates or acyl phosphonates. Acyl phosphonates (α-ketophosphonates) are very useful compounds. They were used as precursors to biologically active α-aminophosphonic acids and α-hydroxyphosphonic acids. The reactivity of acyl phosphonates is particularly interesting. Inspection of the literature reveals a reactivity pattern that can be defined as hybrid of wide range of carbonyl compounds of varying oxidation states. Their reactivity is enhanced by the electron- withdrawing phosphonate moiety making them as excellent electrophiles and they are generally compared to ketones in this respect [45]. Some of their properties sometimes directly compared with trihaloketones [46]. Their reactions with Grignard reagents provide the corresponding ketones upon hydrolysis that can classify them as reminiscent of secondary amides [45]. On the other side they are very good acylating reagents and can easily be hydrolysed under the proper reaction conditions or reacts with secondary amines to afford secondary amides that put them into the same row with

activated carboxylic acids [47]. In this study acyl phosphonates were used as a nucleophile and aldol type product with acyl phosphonates aimed to be synthesized. Acyl phosphonates are easily accessible compounds. The Michael Arbuzov reaction is a general method for the preparation of acyl phosphonates from acylchlorides **90** and trialkylphosphites **89** [48]. Reaction is initiated with the attack of the nucleophilic phosphite with the electrophilic acyl halide to give unstable phosphonium intermediate **91**. The displaced halide anion reacts via another S_N2 reaction with the phosphonium intermediate to give the desired acylphosphonate **92**. (Figure 2.1). It is generally carried out by mixing neat reactants at or below room temperature. In cases one of the reactants is solid, it can be carried out in organic solvents. Gaseous alkyl chloride is the only side product.

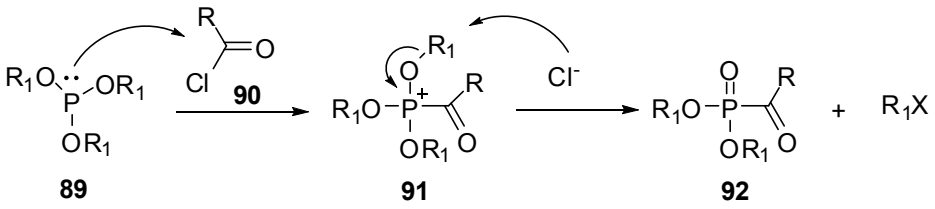


Figure 2. 1 Synthesis of acyl phosphonates

As a result, acyl phosphonates used in that study were synthesized via classical Arbuzov route according to literature procedures and purification was done by vacuum distillation. Their synthesis does not require any other special conditions or apparatus. Since they are sensitive to moisture, they should be stored under argon filled flasks to prevent decomposition or hydrolysis. Figure 2.2 is shown the acyl phosphonates synthesized in this study. All of the acyl phosphonates have α-methyl group for aldol reactions.

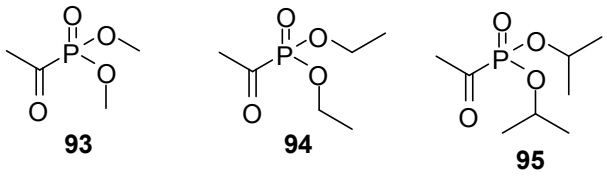


Figure 2.2 Acyl phosphonates synthesized in this study

2.1.2 Reaction of acyl phosphonates with aldehydes in the presence of proline

In this study, we examined organocatalytic aldol reactions with acyl phosphonates and non enolizable aldehydes. This type of aldol reactions are not described in the literature.

As an initial reaction, acyl phosphonate **93** was reacted with benzaldeyde **9** in the presence of %20 of L-proline in DMSO and monitored by TLC. After 5 hours new spot on TLC was observed and this spot was isolated. The NMR spectrum of the crude product looked like that the reaction proceeded the desired aldol product with some impurities but the yield of the reaction was very low. (Figure 2.3)

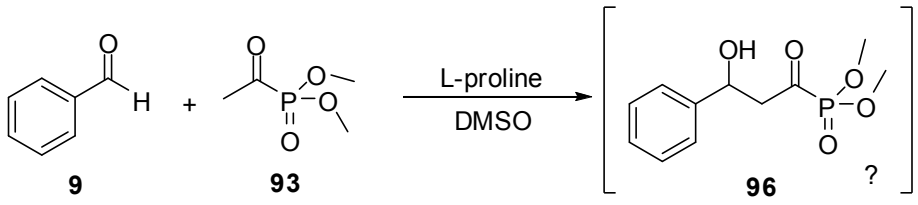


Figure 2.3 Addition of acyl phosphonate to benzaldehyde

The next reaction was carried out with p-nitrobenzaldehyde. Similar result was obtained as in case of benzaldehyde. Then, the reactions were carried out by using different solvents at various temperatures. (Figure 2.4). DMSO, dichloromethane, THF, chloroform, DMF, dimethoxyethane and water were used as solvent but none of them worked as well as DMSO. Therefore the reactions performed in DMSO at different temperatures. At low temperature no product formation was observed (80% DMSO, 20% THF). At high temperatures acyl phosphonates were decomposed. In

literature, L-proline in bmim [BF_4] (1-Butyl-3-methylimidazolium Tetrafluoroborate) ionic liquid has been successfully used as an efficient and reusable catalyst for the direct asymmetric aldol reaction of acetone with different heteroaromatic aldehydes to afford higher selectivity of the aldol products with good enantioselectivity. The reaction was carried out at room temperature in bmim [BF_4] ionic liquid. However in our reactions we didn't get any success. The maximum yield was 15 % in DMSO at room temperature. Again the crude NMR spectrum looked like the desired product with little impurities.

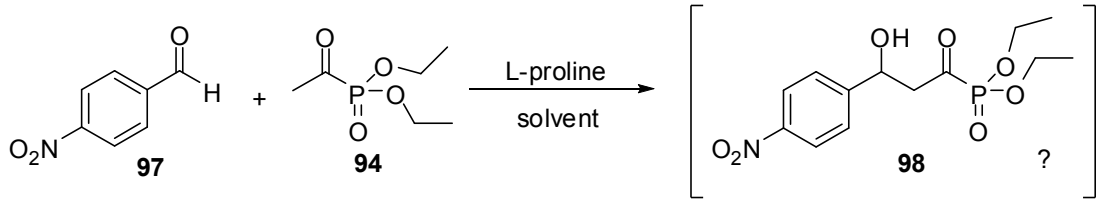


Figure 2.4 Addition of acyl phosphonate to p-nitrobenzaldehyde

Table 2.1 The reaction of p-nitrobenzaldehyde with acyl phosphonate under different reaction conditions

Entry	T (^oC)	Solvent	Proline (%)	Yield (%)
1	0	DMSO+ THF	20	-
2	25	DMSO	20	13
3	60	DMSO	20	-
4	25	CH_2Cl_2	20	7
5	25	THF	20	9
6	25	$CHCl_3$	20	5
7	25	DMF	20	-
8	25	Dimethoxy ethane	20	-
9	25	H_2O	20	-

(L)-Proline, known as the simplest enzyme, is a cornerstone in the field of organocatalysis due to the fact that it has been used as a catalyst in a wide range of asymmetric reactions with excellent results in many cases, its high efficiency being clearly demonstrated in the enantioselective direct aldol reaction. The reaction scope was studied using a variety of catalyst and additives (Table 2).

Table 2.2 The reaction of acyl phosphonate with p-nitro benzaldehyde in the presence of catalysts

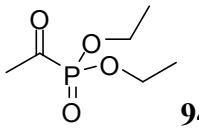
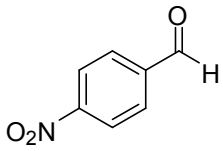
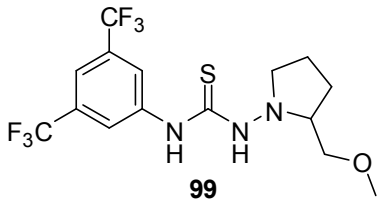
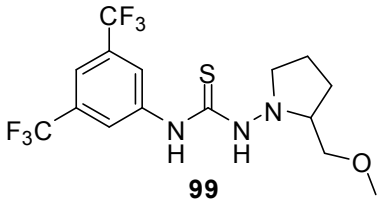
Acyl Phosphonate	Aldehyde	Catalyst
 **94**	 **97**	L-proline (20%) Triethylamine (10%)
94	**97**	,  **99** (10%) L-proline (20%)
94	**97**	 **99** (10%)

Table 2.2 continued

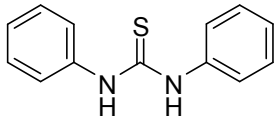
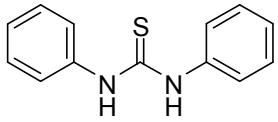
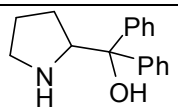
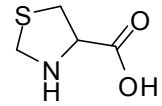
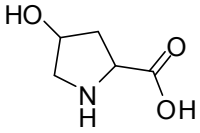
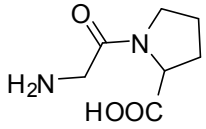
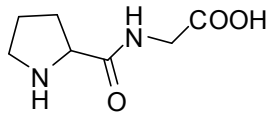
Acyl Phosphonate	Aldehyde	Catalyst
94	**97**	 **100** (20%) L-proline (20%)
94	**97**	 **100** (60%) L-proline (20%)
94	**97**	 **101** (10%)
94	**97**	 **102** (20%)
94	**97**	 **103** (20%)
94	**97**	 Gly-Pro **104** (20%)

Table 2.2 continued

Acyl Phosphonate	Aldehyde	Catalyst
94	**97**	 Pro-Gly **105** (20%)

L-proline was used with thiourea. It's functionality was responsible for catalytic activity and that the carbonyl group of aldehyde interacts with the catalyst via a dual H-bond interaction to the urea protons (Figure 2.5).

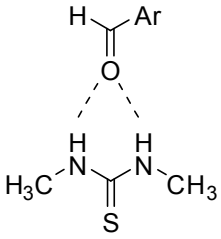


Figure 2.5 Dual H-bond interaction of thiourea with aldehyde

L-proline was also used with triethyl amine to increase the basicity of reaction medium to facilitate the formation of enamine. However any of these catalysts didn't work as well as L-proline.

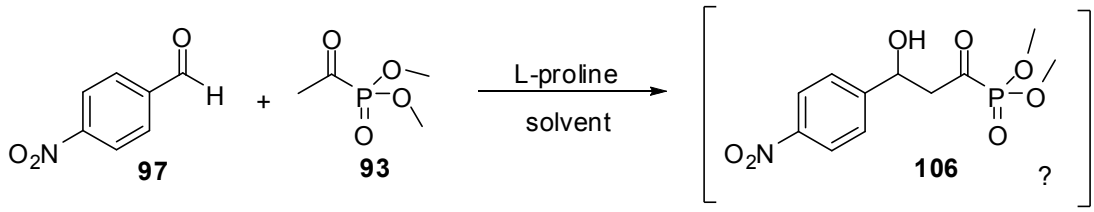


Figure 2.6 Addition of dimethyl alkyl phosphonate to p-nitrobenzaldehyde

The reaction was repeated with acyl phosphonate **93** and p-nitrobenzaldehyde (Figure 2.6). The obtained crude product was purified several times. According to TLC it was pure. Closely inspection of the NMR and MS data resulted that the structure of **107a** or **107b** could be the products.

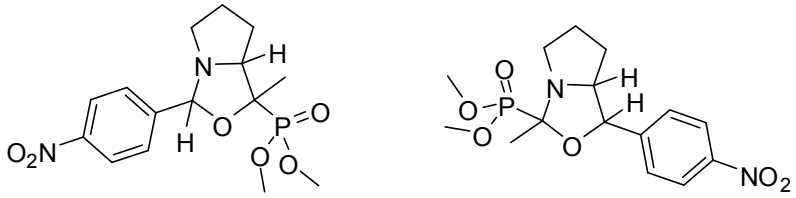


Figure 2.7 Cyclization products

The suggested mechanism for the formation of **107a** and **107b** outlined in Figure 2.8 and 2.9.

The suggested mechanism for **107a**. The reaction of p-nitrobenzaldehyde with proline gives iminium salt which then gives decarboxylation to form azomethine like structure. The 1,3-dipolar cycloaddition of this azomethine with carbonyl group of acyl phosphonate furnished the product **107a**. (Figure 2.8)

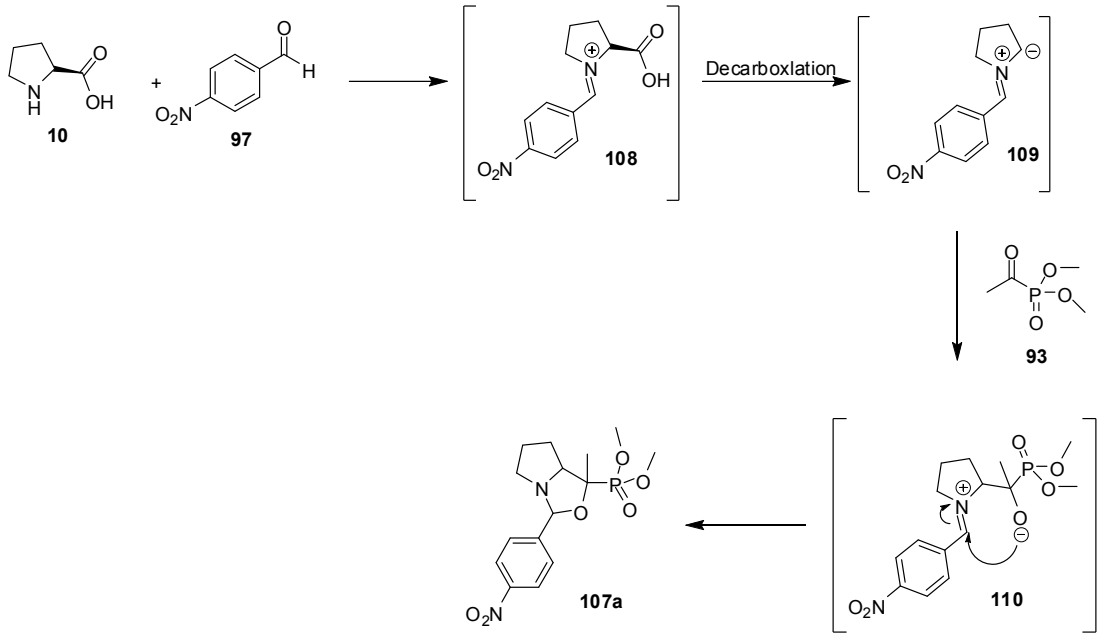


Figure 2.8 Reaction mechanism route A

It is also possible that first iminium ion is formed with acyl phosphonate then decarboylation furnished azomethine which gives 1,3-dipolar cycloaddition reaction to form the product **107b** (Figure 2.9)

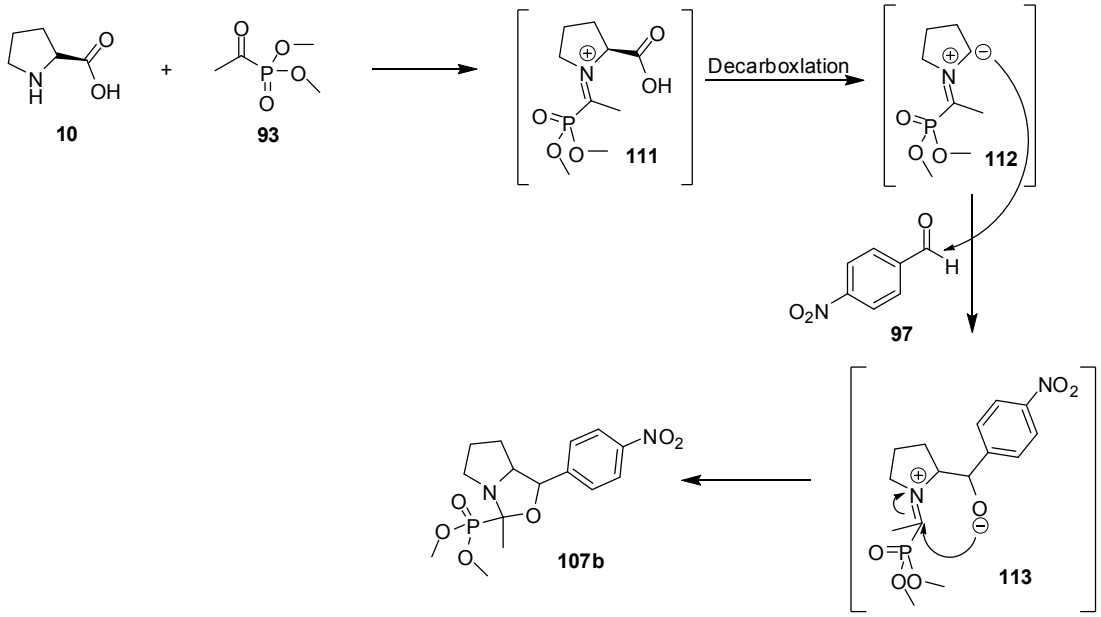


Figure 2.9 Reaction mechanism route B

Closly inspection of the both product by ^{1}H-NMR, ^{13}C-NMR and COSY experiment the structure is rather **107a** than **107b**. According to ^{1}H-NMR all peaks are in aggreement with the structure **107a**. In ^{1}H-NMR and COSY experiment the proton **d** has any interaction with proline ring protons **b b'**. No interaction of proton **a** with proton **c** is observed. Proton **d** has long range coupling with aromatic protons (Figure 2.13 COSY). As it is seen from the ^{1}H-NMR in Figure 2.11 proton **a** gives a doublet of doublet signal at 5.12 ppm and proton **d** gives a doublet signal at 5.26 ppm. ^{13}C-NMR demostrates two CH and one quaternary C signals besides aromatic carbon peaks from C_x, C_y, C_z. Two CH carbons give doublet at 97.2 ppm and 82.6 ppm because of C-P coupling. One quaternary carbon gives a singlet at 67.5 ppm (Figure 2.12). Moreover, LS-MS analysis gives correct M^+ peak for structure **107a**; M^+ (357), M^+ - 110 (247) and M^+ - 151 (206) (Figure 2.14).

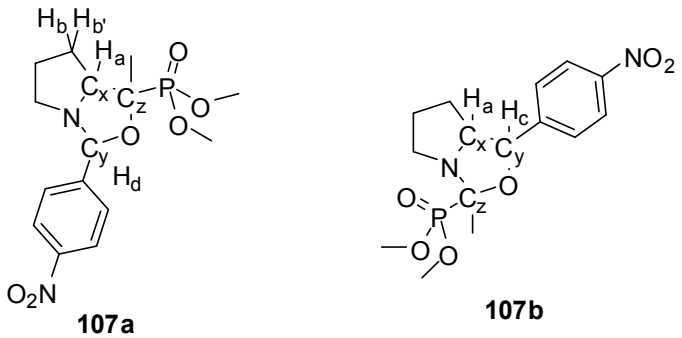


Figure 2.10 Possible cyclization products

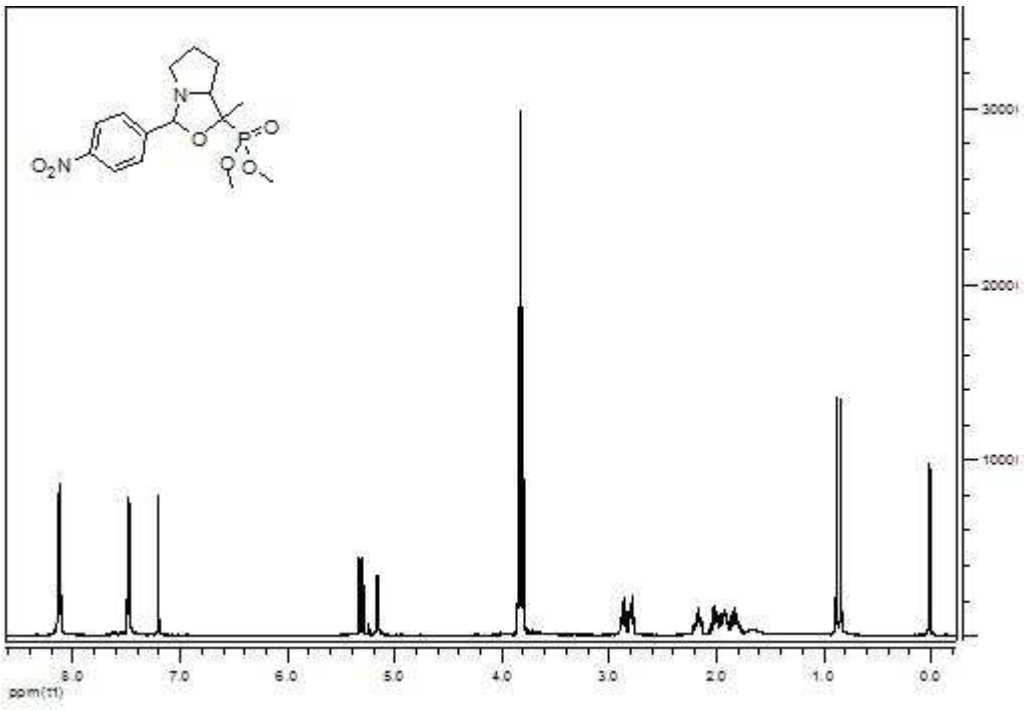


Figure 2.11 [1]H-NMR of dimethyl 1-methyl-3-(4-nitrophenyl) hexahydropyrrolo[1,2-c] oxazol-1-ylphosphonate

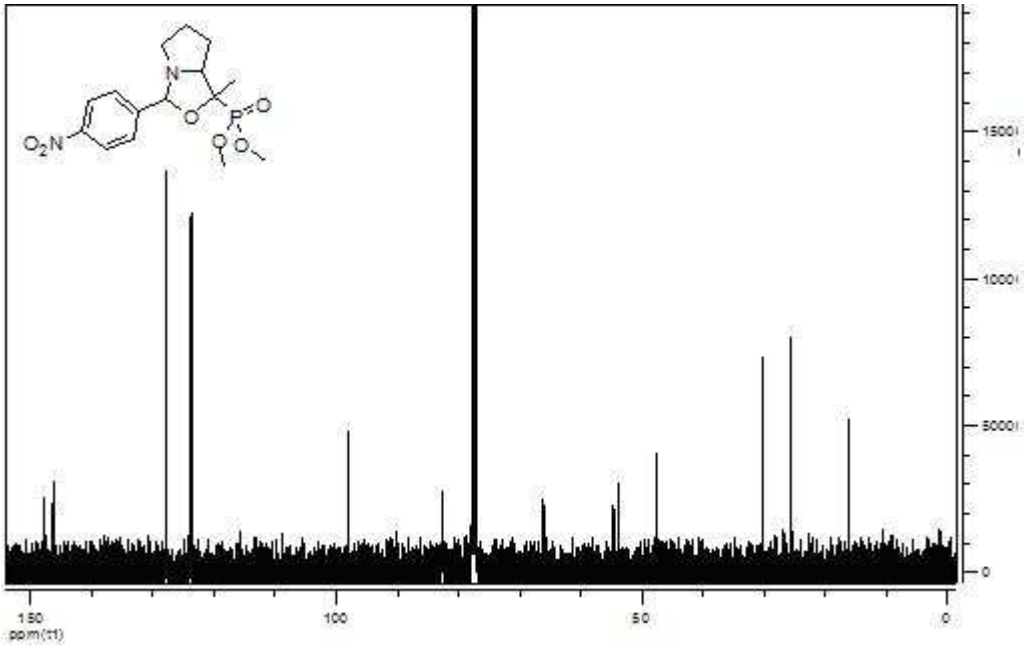


Figure 2.12 ^{13}C-NMR of dimethyl 1-methyl-3-(4-nitrophenyl) hexahydropyrrolo[1,2-c] oxazol-1-ylphosphonate

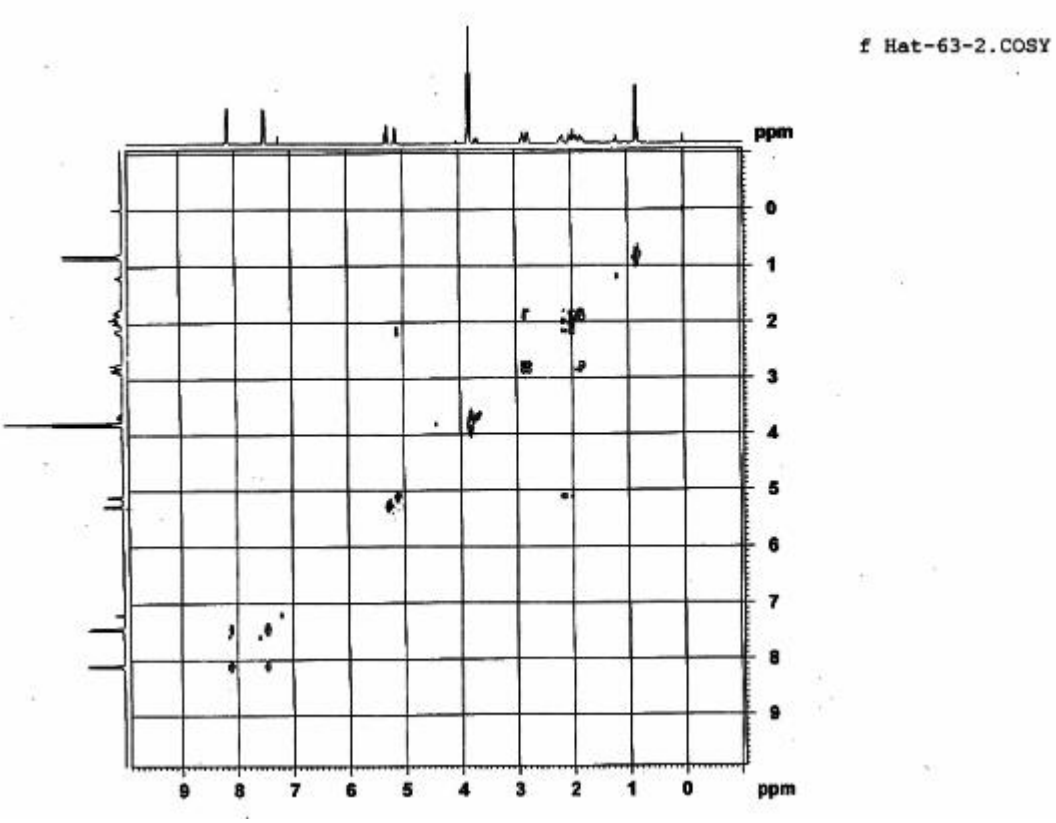


Figure 2.13 COSY of dimethyl 1-methyl-3-(4-nitrophenyl)hexahydropyrrolo [1,2-c]oxazol-1-ylphosphonate

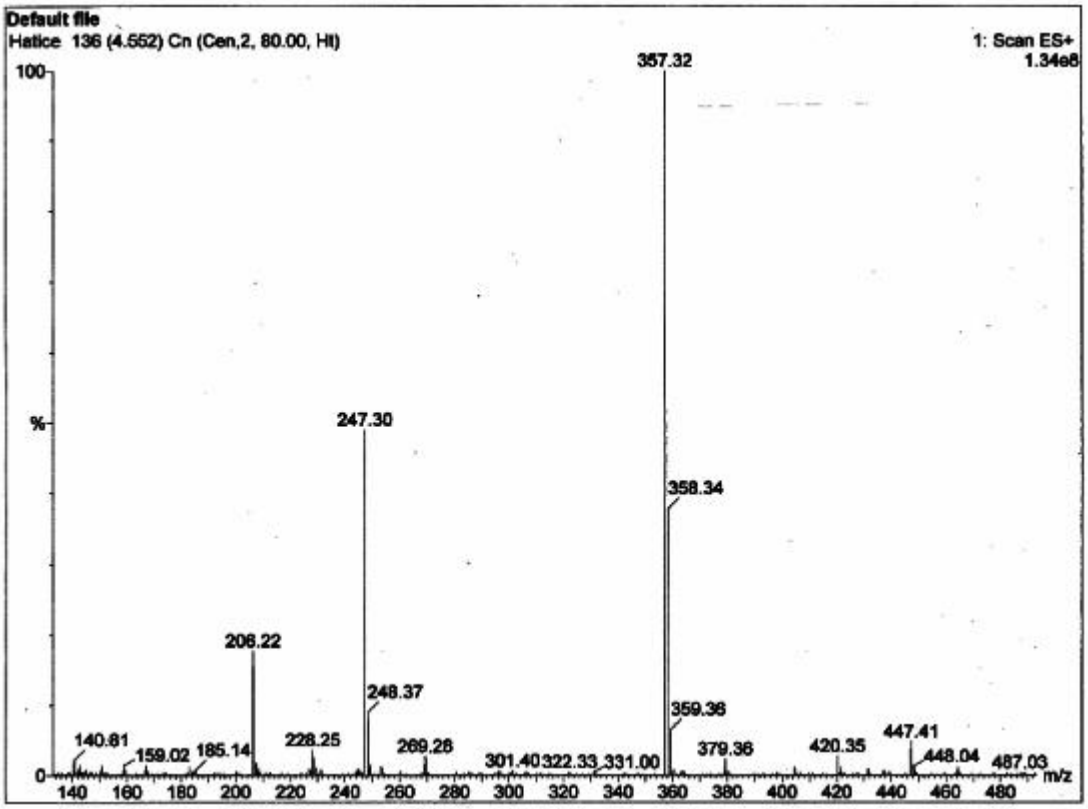


Figure 2.14 LC-MS of dimethyl 1-methyl-3-(4-nitrophenyl)hexahydropyrrolo[1,2-c] oxazol-1-ylphosphonate

After the structure of compound is determined, we tried to increase the yield. First we used 1 equivalent of L-proline and changed the addition order of reactant to get maximum yield. Also we changed the addition order and stochiometric amounts of reactants.

The optimum condition was obtained by using 1 equivalent of benzaldehyde **9**, 2 equivalent of acyl phosphonate **93** and 2 equivalent of L-proline (Figure 2.15). Acyl phosphonate and proline was added to benzaldehyde dropwise separately. Under this conditions dimethyl 1-methyl-3-phenylhexahydropyrrolo[1,2-c]oxazol-1-yl phosphonate **114** was obtained up to 65 % yield after purification by column chromatography (Table 3). The change of alkoxy groups of the acyl phosphonate effected slightly the yield of the reaction (Table 3, **107a**, **115**, **116**).

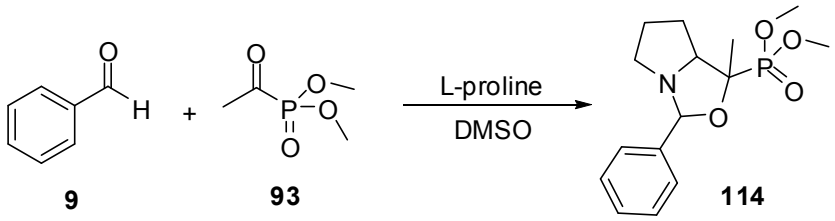
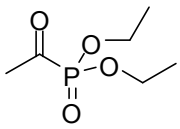
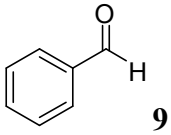
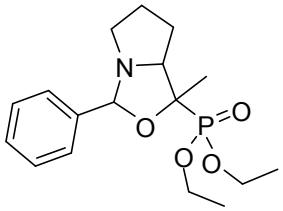
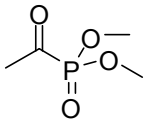
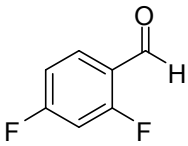
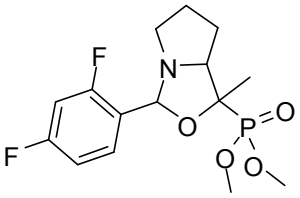


Figure 2.15 Cyclization reaction between banzaldehyde, acyl phosphonate and L-proline

Table 2.3 The reaction of acyl phosphonates with aryl aldehyde in the presence of proline

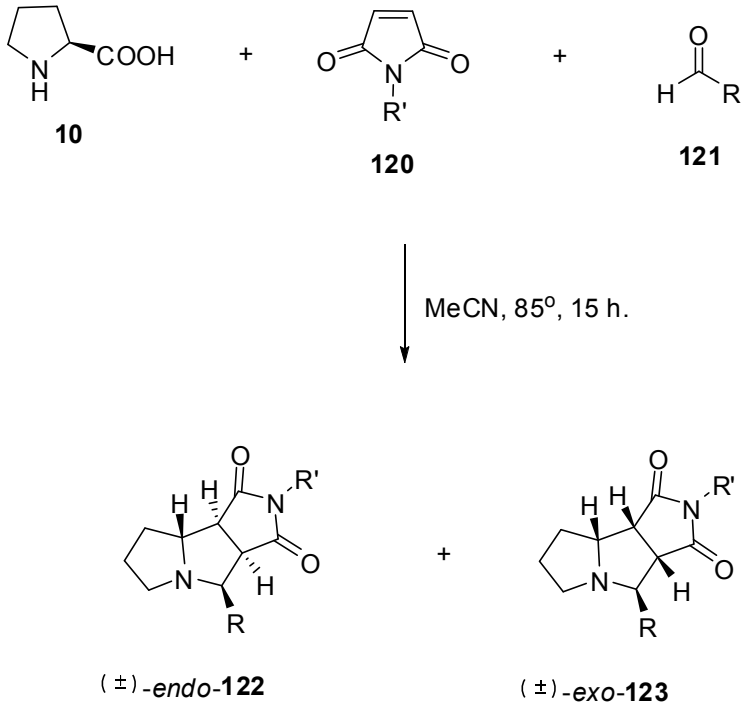
Acyl Phosphonate	Aldehyde	Product	Yield (%)
93	**97**	**107a**	60
94	**97**	**115**	65
95	**97**	**116**	54
93	**9**	**114**	45

Table 2.3 continued

Acyl Phosphonate	Aldehyde	Product	Yield (%)
 **94**	 **9**	 **117**	51
 **93**	 **118**	 **119**	40

As shown in Table 3 only benzaldehyde, 4-nitrobenzaldehyde and 2,4-difluorobenzaldehyde gave the products. On the other hand 4-fluorobenzaldehyde, 4-(trifluoromethyl)benzaldehyde, 2,3,4,5,6-pentafluorobenzaldehyde, 4-methoxy benzaldehyde, 3,5-dimethoxybenzaldehyde, 2-bromobenzaldehyde didn't give the pruducts. This unusual result have to be study with more examples under various conditions for making general comment about the effect of the substituents on the course of the reaction.

The reaction which proceeds through 1,3 dipolar cycloaddition with decarboxylation of proline is also obtained by Siegrist *et. al.* (Figure 2.16) [49].



R' = Benzyl or Piperonyl (1,3-benzodioxol-5-yl)methyl)
R = Naphthalen-2-yl or Phenyl or Pentafluorophenyl

Figure 2.16 1,3-Dipolar Cycloaddition between L-Proline and Azomethine Ylides Obtained from Maleimides and Aromatic Aldehydes

In conclusion, we aimed to carry out enantioselective aldol reaction starting with acyl phosphonate but without success. Instate of aldol reaction we obtained tricyclic ring system via 1,3-dipolar cycloaddition reaction. We developed a new cyclization reaction starting with readily available acyl phosphonates, derivatives of benzaldehydes and L-proline under mild conditions in good yields (40-65%). Additional work about the reaction is under investigation.

CHAPTER 3

EXPERIMENTAL

3.1 Materials and Methods

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ solutions at 300 MHz or 400 MHz and 75 MHz or 100MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. All reactions were analyzed by TLC on silica gel 60 F_{254}. TLC was carried out on aluminum sheets precoated with silica gel 60F254 (Merck), and the spots were visualized with UV light (l = 254 nm).Column chromatography was performed on silica gel 60 (70-230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

3.2 General Procedures

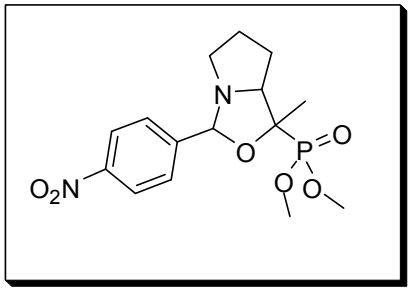
3.2.1 Preparation of acyl phosphonates

Acyl phosphosphonates **93-95** were synthesized according to literature procedures. Briefly 1 equiv. of neat triethylphosphite was added drop wise onto the neat acylchloride in a water bath under a positive inert atmosphere. After completion of the addition, resulting mixture was stirred at room temperature for 60 min. The products were purified by vacuum distillation.

3.2.2 General procedure for preparation of cyclization product

3.2.1 Synthesis of dimethyl 1-methyl-3-(4-nitrophenyl)hexahydropyrrolo[1,2-c] oxazol-1-ylphosphonate (107a)

1 mmole (152 mg) of p-nitro benzaldehyde was dissolved in DMSO (1 ml). Then, 2 mmole (304 mg) of dimethyl alkyl phosphonate, which was dissolved in DMSO (1 ml), and seperately 1 mmole (115 mg) of L-proline was added slowly to the stirred solution of p-nitro benzaldehyde at room temperature under an argon atmosphere. The reaction mixture was stirred for 2 days. The reaction is monitored by TLC. The reaction was diluted with ethyl acetate and brine solution was added. The aquous phase was extracted wirh ethyl acetate three times. Collected organic phase was dried over MgSO4 and evaporated under reduced 45 pressure. The crude mixture was purifed on silica gel with EtOAc as eluent. The yield was 60 %.

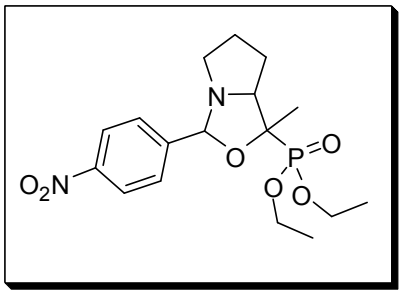


213.6 mg, yellow solid, ^{1}H NMR ($CDCl_3$) δ 0.85 (d, *J*=17.3 Hz, 3H), 1.76-1.85 (m, 1H); 1.86-2.04 (m, 2H); 2.11-2.20 (m, 1H); 2.74-2.79 (m, 1H); 2.82-2.89 (m, 1H); 3.76-3.84 (m, 6H); 5.12 (dd, J_1=1.0 Hz, J_2=5.2 Hz, 1 H); 5.26 (d, *J*= 13.6 Hz, 1 H); 7.78 (dd, J_1=8.6 Hz, J_2=261.3 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 25.1, 29.7, 47.3 (d, J_{C-P}=10.8 Hz), 53.2(d, J_{C-P}=7.6 Hz), 54.1(d, J_{C-P}=8.1 Hz), 67.5, 82.6(d, J_{C-P}=1.3 Hz), 97.2(d, J_{C-P}=6.2 Hz), 123.1, 127.3, 146.3(d, J_{C-P}=5.0 Hz), 147.7.

3.2.2 Synthesis of diethyl 1-methyl-3-(4-nitrophenyl)hexahydropyrrolo[1,2-c] oxazol-1-ylphosphonate (115)

1 mmole (152 mg) of p-nitro benzaldehyde was dissolved in DMSO (1 ml). Then, 2 mmole (360 mg) of diethyl alkyl phosphonate, which was dissolved in DMSO (1 ml), and seperately 1 mmole (115 mg) of L-proline was added slowly to the stirred

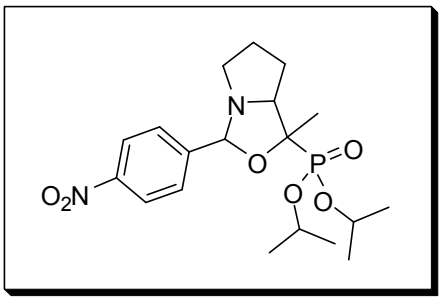
solution of p-nitro benzaldehyde at room temperature under an argon atmosphere. The reaction mixture was stirred for 4 hours. The reaction is monitored by TLC. The reaction was diluted with ethyl acetate and brine solution was added. The aquous phase was extracted wirh ethyl acetate three times. Collected organic phase was dried over $MgSO_4$ and evaporated under reduced 45 pressure. The crude mixture was purifed on silica gel with EtOAc as eluent. The yield was 65 %.



249.6 mg, yellow solid, ^{1}H NMR ($CDCl_3$) δ 0.83 (d, *J*=17.0 Hz, 3H); 1.28-1.36 (m, 6H); 1.76-1.84 (m, 1H); 1.87-2.03 (m, 2H); 2.11-2.20 (m, 1H); 2.72-2.78 (m, 1H); 2.81-2.90 (m, 1H); 4.04-4.21 (m, 4H); 5.13 (dd, J_1=1.5 Hz, J_2=5.5 Hz, 1 H); 5.29 (d, *J*= 13.7 Hz, 1 H); 7.79 (dd, J_1=8.8 Hz, J_2=251.4 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 15.6, 16.1, 24.8, 29.4, 47.3 (d, J_{C-P}=11.0 Hz), 63.1 (d, J_{C-P}=7.6 Hz), 64.4 (d, J_{C-P}=7.5 Hz), 68.1, 82.1 (d, J_{C-P}=10.0 Hz), 97.4, 123.4, 127.2, 146.1,147.6.

3.2.3 Synthesis of diisopropyl 1-methyl-3-(4-nitrophenyl)hexahydropyrrolo [1,2-c]oxazol-1-ylphosphonate (116)

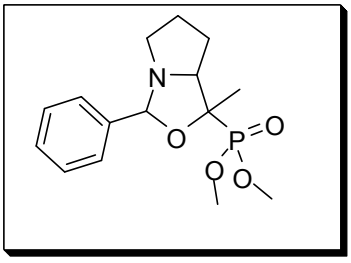
1 mmole (152 mg) of p-nitro benzaldehyde was dissolved in DMSO (1 ml). Then, 2 mmole (416 mg) of diisopropyl alkyl phosphonate, which was dissolved in DMSO (1 ml), and seperately 1 mmole (115 mg) of L-proline was added slowly to the stirred solution of p-nitro benzaldehyde at room temperature under an argon atmosphere. The reaction mixture was stirred for 2 days. The reaction is monitored by TLC. The reaction was diluted with ethyl acetate and brine solution was added. The aquous phase was extracted wirh ethyl acetate three times. Collected organic phase was dried over $MgSO_4$ and evaporated under reduced 45 pressure. The crude mixture was purifed on silica gel with EtOAc as eluent. The yield was 54 %.



222.5 mg, orange oil, ^{1}H NMR ($CDCl_3$) δ 0.82 (d, *J*=16.8 Hz, 3H); 1.24-1.37 (m, 12H); 1.72-1.83 (m, 1H); 1.87-2.03 (m, 2H); 2.11-2.21 (m, 1H); 2.72-2.77 (m, 1H); 2.82-2.88 (m, 1H); 4.70-4.86 (m, 2H); 5.25 (dd, J_1=1.6 Hz, J_2=6.4 Hz, 1 H); 5.31 (d, *J*=14.0 Hz, 1 H); 7.81 (dd, J_1=8.8 Hz, J_2=249.7 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 23.7(d, J_{C-P}=0.1 Hz, 2C), 24.1(d, J_{C-P}=0.1 Hz, 2C), 25.1, 29.8, 47.6 (d, J_{C-P}=11.7 Hz), 65.3, 70.9 (d, J_{C-P}=18.1 Hz), 72.2 (d, J_{C-P}=7.5 Hz), 82.1 (d, J_{C-P}=11.9 Hz), 97.7(d, J_{C-P}=5.2 Hz), 123.3, 127.4, 145.3,147.5.

3.2.4 Synthesis of dimethyl 1-methyl-3-phenylhexahydropyrrolo[1,2-c]oxazol-1-ylphosphonate (114)

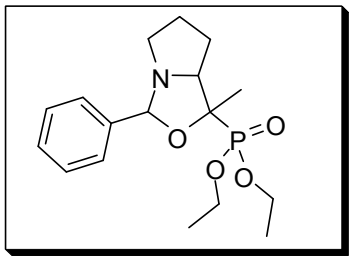
1 mmole (106 mg) of benzaldehyde was dissolved in DMSO (1 ml). Then, 2 mmole (304 mg) of dimethyl alkyl phosphonate, which was dissolved in DMSO (1 ml), and seperately 1 mmole (115 mg) of L-proline was added slowly to the stirred solution of benzaldehyde at room temperature under an argon atmosphere. The reaction mixture was stirred for 1 day. The reaction is monitored by TLC. The reaction was diluted with ethyl acetate and brine solution was added. The aquous phase was extracted wirh ethyl acetate three times. Collected organic phase was dried over $MgSO_4$ and evaporated under reduced 45 pressure. The crude mixture was purifed on silica gel with EtOAc as eluent. The yield was 45 %.



140 mg, light yellow solid, ^{1}H NMR ($CDCl_3$) δ 0.85 (d, *J*=15.5 Hz, 3H); 1.74-1.83 (m, 1H); 1.85-2.01 (m, 2H); 2.08-2.17 (m, 1H); 2.72-2.78 (m, 1H); 2.87-2.94 (m, 1H); 3.75-3.83 (m, 6H); 5.1 (dd, J_1=1.7 Hz, J_2=5.5 Hz, 1 H); 5.22 (d, *J*=13.6 Hz, 1 H); 7.13-7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7, 24.2, 28.7, 46.0 (d, J_{C-P}=11.1 Hz), 52.3(d, J_{C-P}=16.9 Hz), 53.2(d, J_{C-P}=7.3 Hz), 66.3, 82.1 (d, J_{C-P}=10.7 Hz), 95.9 (d, J_{C-P}=6.5 Hz), 125.6, 126.5, 127.0, 137.2.

3.2.5 Synthesis of diethyl 1-methyl-3-phenylhexahydropyrrolo[1,2-c]oxazol-1-ylphosphonate (117)

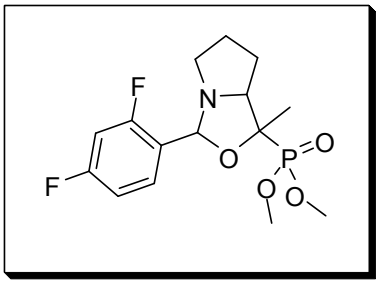
1 mmole (106 mg) of benzaldehyde was dissolved in DMSO (1 ml). Then, 2 mmole (360 mg) of diethyl alkyl phosphonate, which was dissolved in DMSO (1 ml), and seperately 1 mmole (115 mg) of L-proline was added slowly to the stirred solution of benzaldehyde at room temperature under an argon atmosphere. The reaction mixture was stirred for 5 hours. The reaction is monitored by TLC. The reaction was diluted with ethyl acetate and brine solution was added. The aquous phase was extracted wirh ethyl acetate three times. Collected organic phase was dried over $MgSO_4$ and evaporated under reduced 45 pressure. The crude mixture was purifed on silica gel with EtOAc as eluent. The yield was 51 %.



172,9 mg, orange solid, ^{1}H NMR ($CDCl_3$) δ 0.84 (d, *J*=17.3 Hz, 3H), 1.28-1.34 (m, 6H); 1.73-1.82 (m, 1H); 1.85-2.01 (m, 2H); 2.08-2.16 (m, 1H); 2.71-2.76 (m, 1H); 2.88-2.94 (m, 1H); 4.08-4.21 (m, 4H); 5.1 (dd, J_1=1.6 Hz, J_2=5.5 Hz, 1 H); 5.22 (d, *J*= 13.6 Hz, 1 H); 7.11-7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 15.8, 16.6, 25.2, 29.9, 47.1 (d, J_{C-P}=11.9 Hz), 62.1 (d, J_{C-P}=7.6 Hz), 62.9 (d, J_{C-P}=7.5 Hz), 65.8, 83.1 (d, J_{C-P}=10.0 Hz), 97.2, 126.6, 127.4, 127.9, 139.6; ^{31}P NMR: ($CDCl_3$) δ 25.852.

3.2.6 Synthesis of dimethyl 3-(2,4-difluorophenyl)-1-methylhexahydropyrrolo [1,2-c]oxazol-1-ylphosphonate (119)

1 mmole (142 mg) of 2,4-diflouro benzaldehyde was dissolved in DMSO (1 ml). Then, 2 mmole (304 mg) of dimethyl alkyl phosphonate, which was dissolved in DMSO (1 ml), and seperately 1 mmole (115 mg) of L-proline was added slowly to the stirred solution of 2,4-diflouro benzaldehyde at room temperature under an argon atmosphere. The reaction mixture was stirred for 1 day. The reaction is monitored by TLC. The reaction was diluted with ethyl acetate and brine solution was added. The aquous phase was extracted wirh ethyl acetate three times. Collected organic phase was dried over $MgSO_4$ and evaporated under reduced 45 pressure. The crude mixture was purifed on silica gel with EtOAc as eluent. The yield was 40 %.

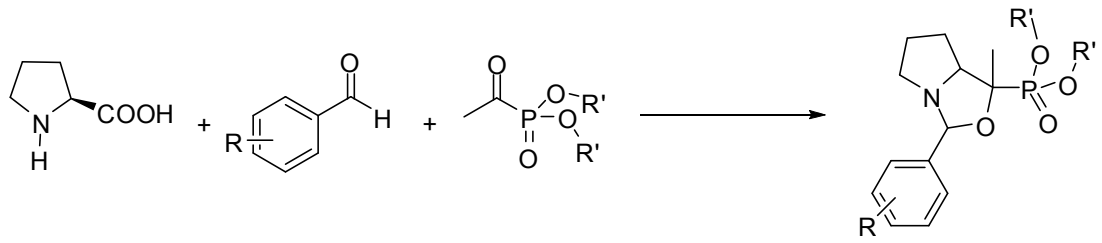


138,8 mg, colorless oil, ^{1}H NMR ($CDCl_3$) δ 0.88 (d, *J*=15.8 Hz, 3H); 1.76-1.85 (m, 1H); 1.88-2.02 (m, 2H); 2.09-2.21 (m, 1H); 2.75-2.83 (m, 1H); 2.86-2.93 (m, 1H); 3.73-3.84 (m, 6H); 5.26 (d, *J*=5.1 Hz, 1 H); 5.46 (d, *J*= 13.8 Hz, 1 H); 6.68-6.83 (m, 2H); 7.32-7.38 (m, 1H).

CHAPTER 4

CONCLUSION

In this work, we describe for the first time a one pot three component reaction, starting from readily available acyl phosphonates, derivatives of benzaldehyde and L-proline under mild conditions in moderate yields. This method works only with three aromatic aldehydes. In this stage we cannot make any comment about the effect of the substituents on the aromatic ring. In the first step, formation of iminium ion between L-proline and aldehyde is followed by decarboxylation to form dipolar intermediate. The cycloaddition of the dipolar intermediate with acyl phosphonate furnished bicyclic product as shown in Figure 4.1. The stereochemistry of the reaction and reactions with other aldehydes are under investigation.



Figıre 4.1 General rection scheme of 1,3 dipolar cycloaddition

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APPENDIX A

NMR DATA

NMR spectra were recorded on a Bruker DPX 400.

Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^1H: δ=7.27), $CDCl_3$ (^{13}C: δ=77.0) and CCl4 (^{13}C: δ=96.4) as internal standards.

^1H and ^{13}C NMR spectra of products are given below.

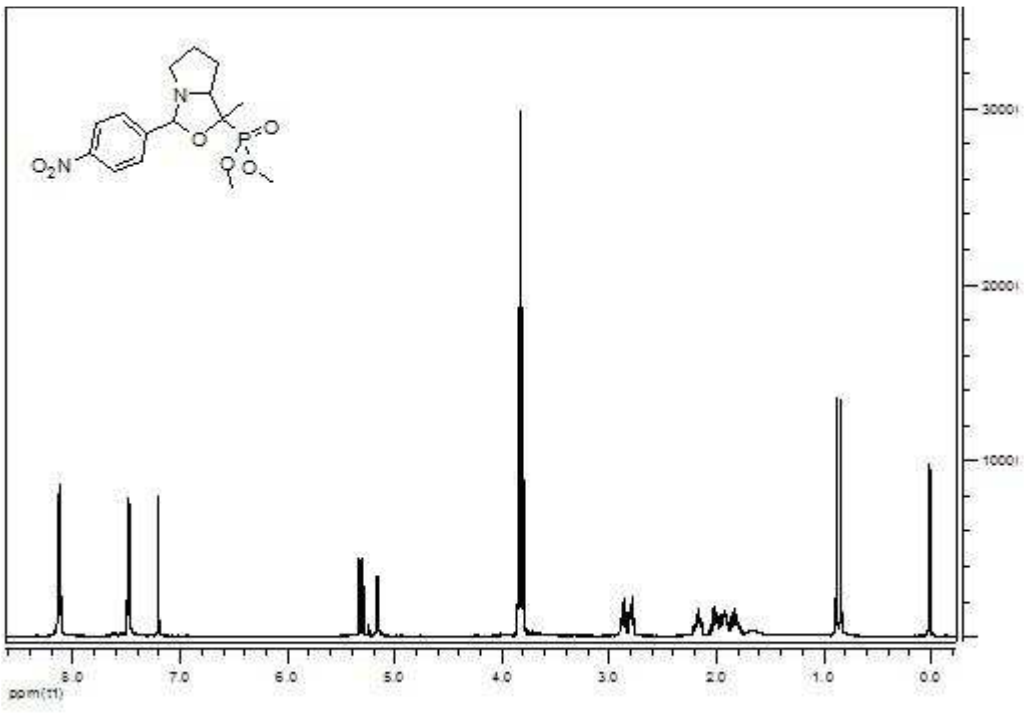

Figure A. 1 dimethyl 1-methyl-3-(4-nitrophenyl) hexahydro pyrrolo[1,2-c]oxazol-1-ylphosphonate **107a**

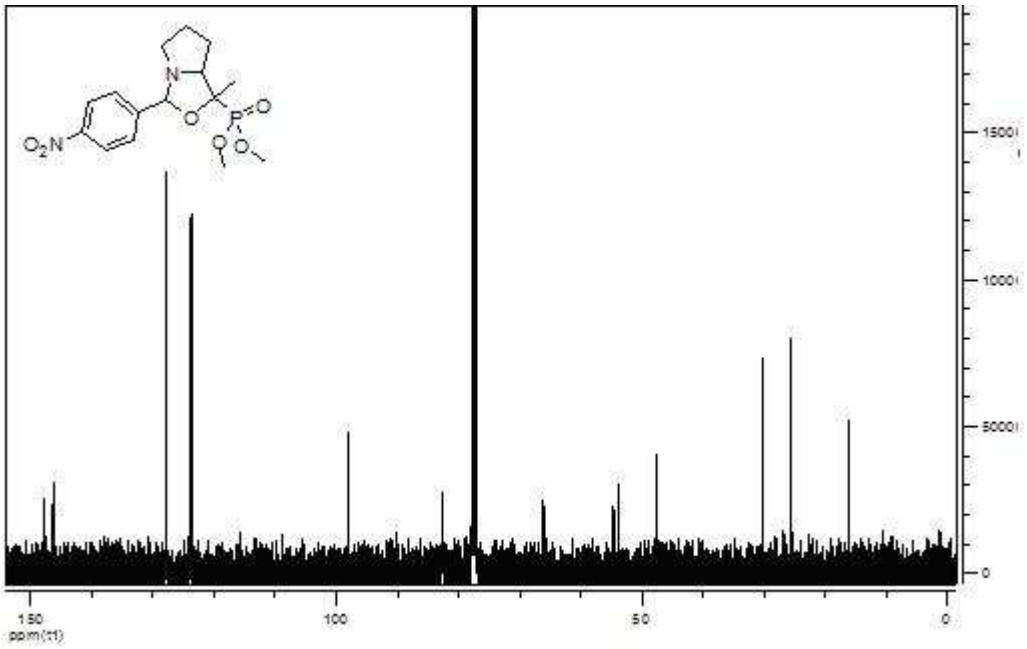

Figure A. 2 dimethyl 1-methyl-3-(4-nitrophenyl) hexahydro pyrrolo[1,2-c]oxazol-1-ylphosphonate **107a**

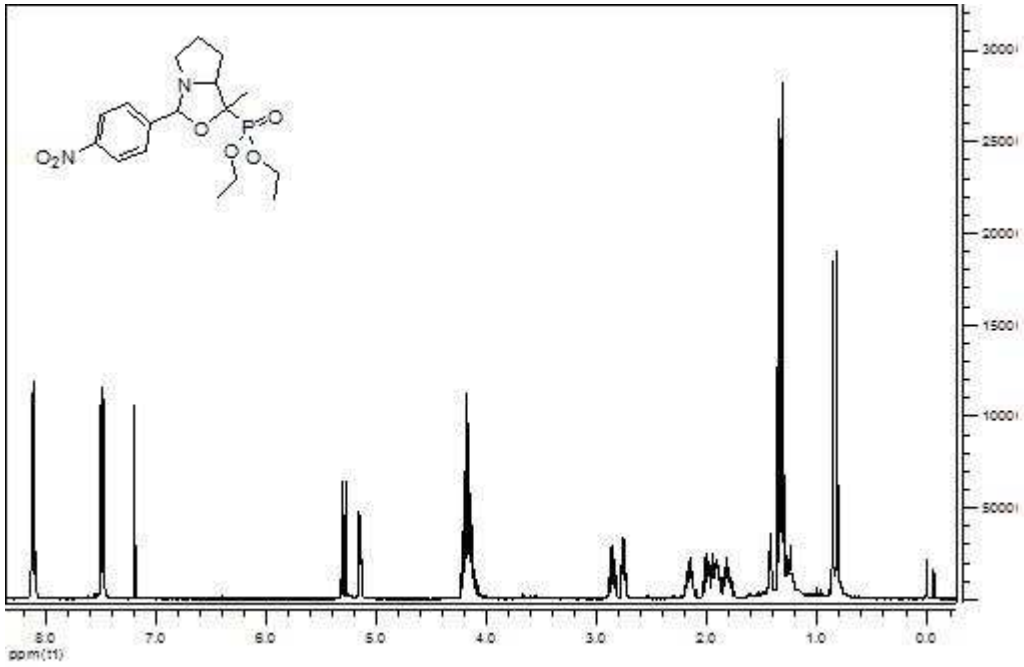

Figure A. 3 diethyl 1-methyl-3-(4-nitrophenyl) hexahydropyrrolo[1,2-c]oxazol-1-ylphosphonate **115**

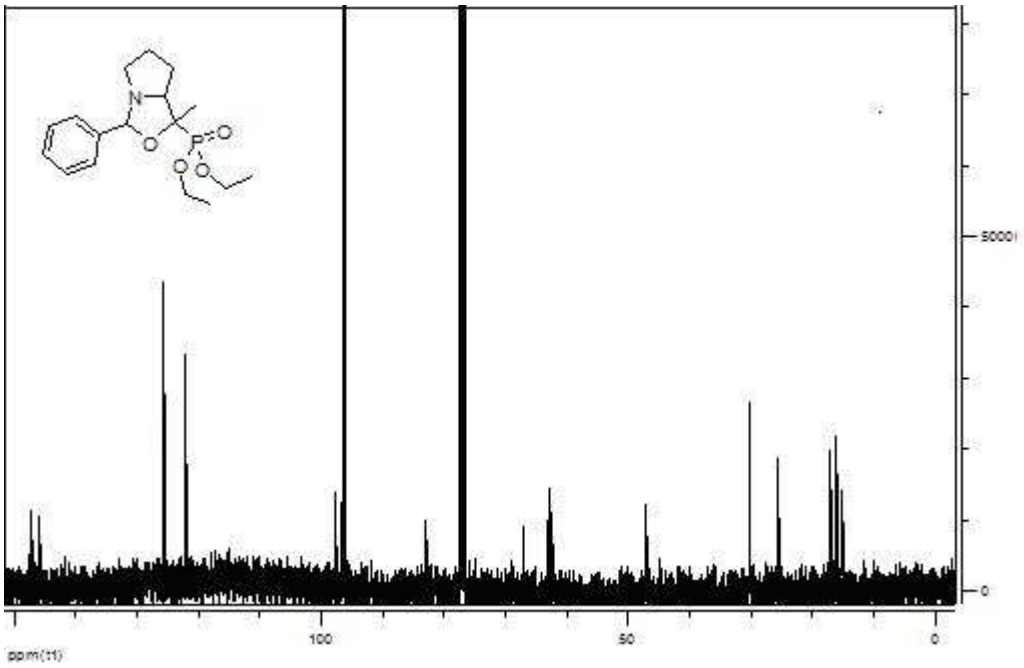

Figure A. 4 diethyl 1-methyl-3-(4-nitrophenyl) hexahydro pyrrolo[1,2-c]oxazol-1-ylphosphonate **115**

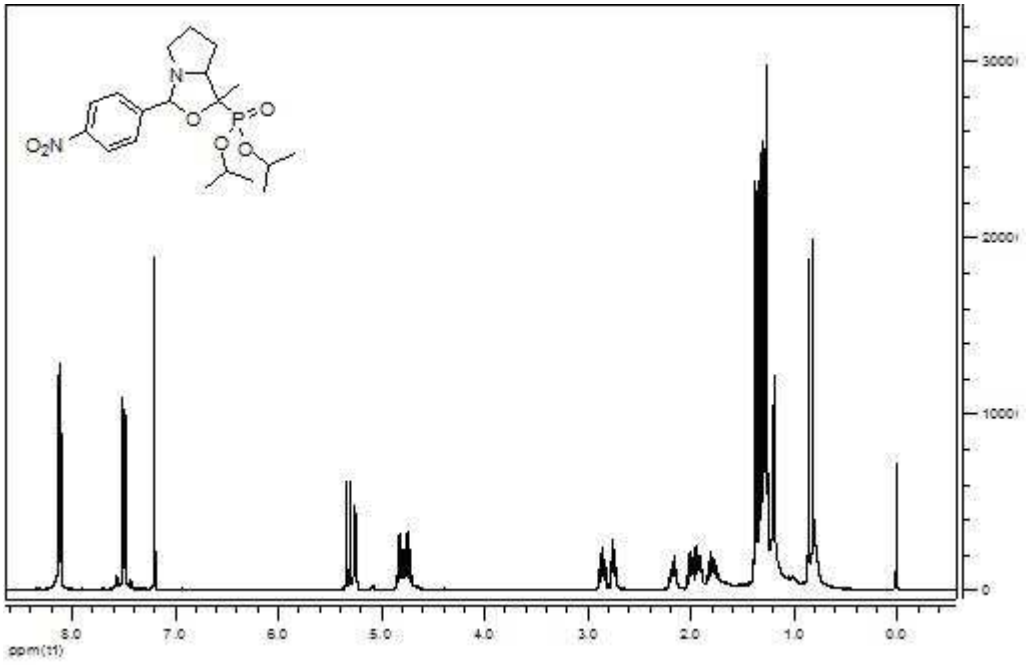

Figure A. 5 diisopropyl 1-methyl-3-(4-nitrophenyl) hexa hydro pyrrolo [1,2-c] oxazol-1-ylphosphonate **116**

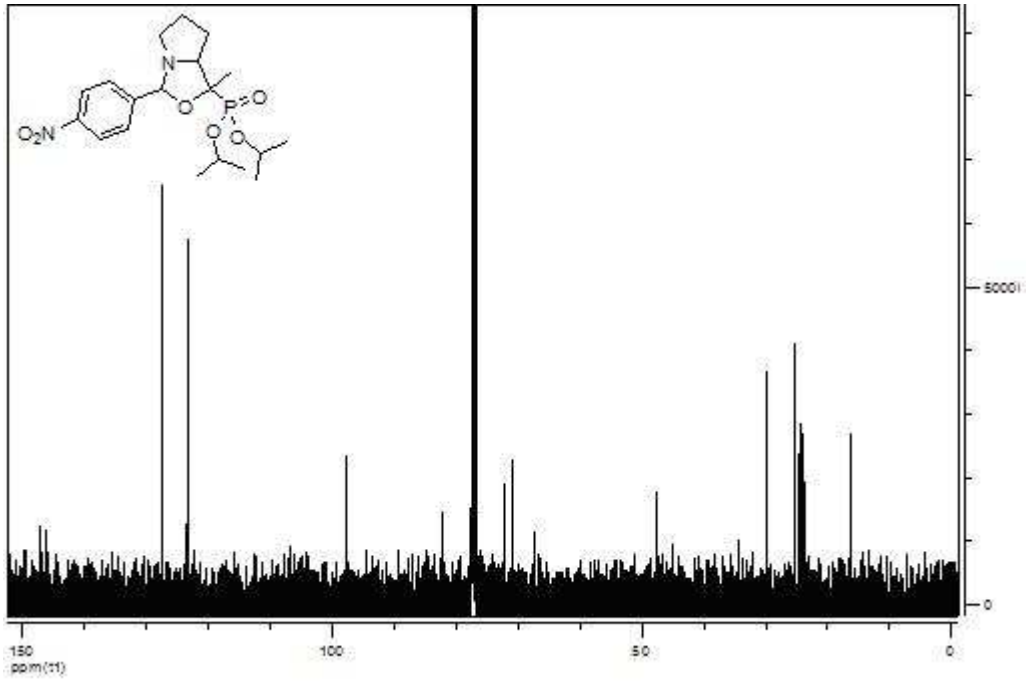

Figure A. 6 diisopropyl 1-methyl-3-(4-nitrophenyl) hexa hydro pyrrolo [1,2-c] oxazol-1-ylphosphonate **116**

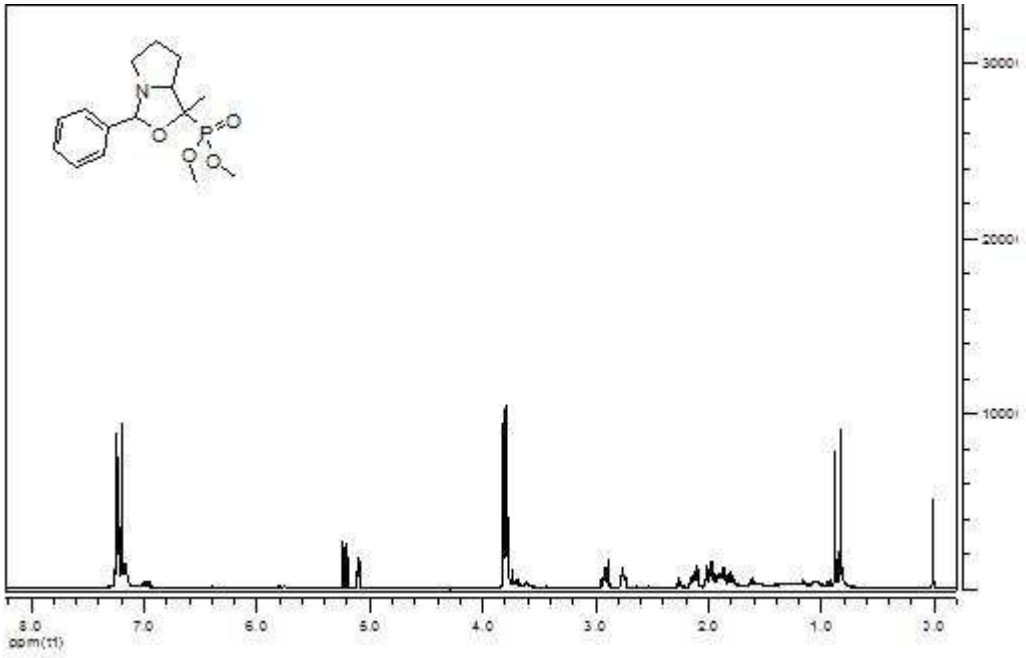

Figure A. 7 dimethyl 1-methyl-3-phenylhexahydropyrrolo[1,2-c] oxazol-1-yl phosphonate **114**

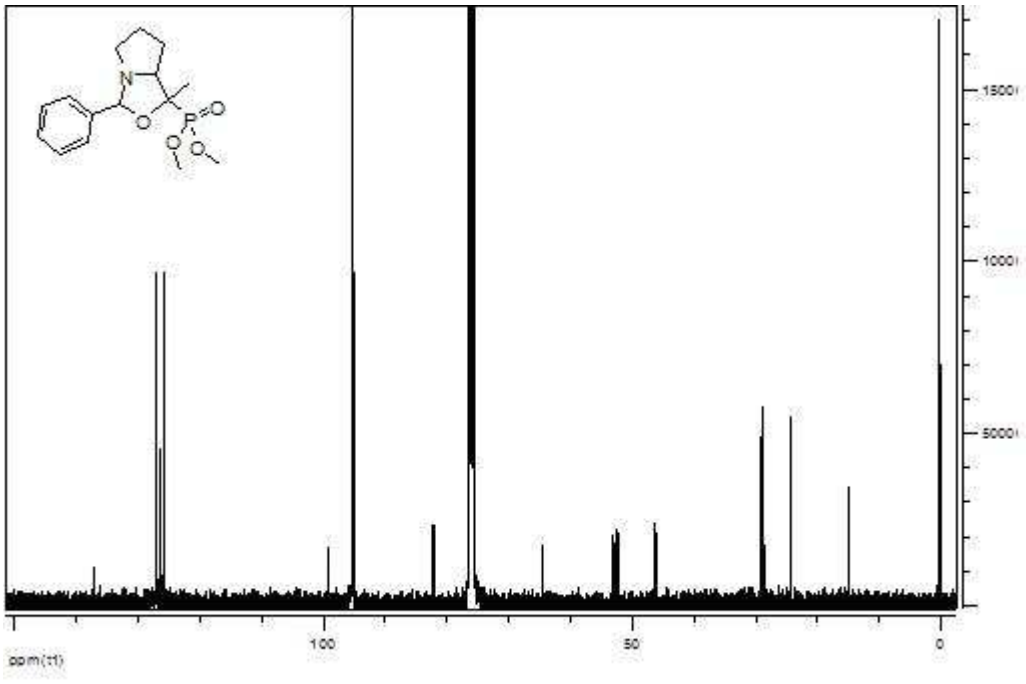

Figure A. 8 dimethyl 1-methyl-3-phenylhexahydropyrrolo[1,2-c] oxazol-1-yl phosphonate **114**

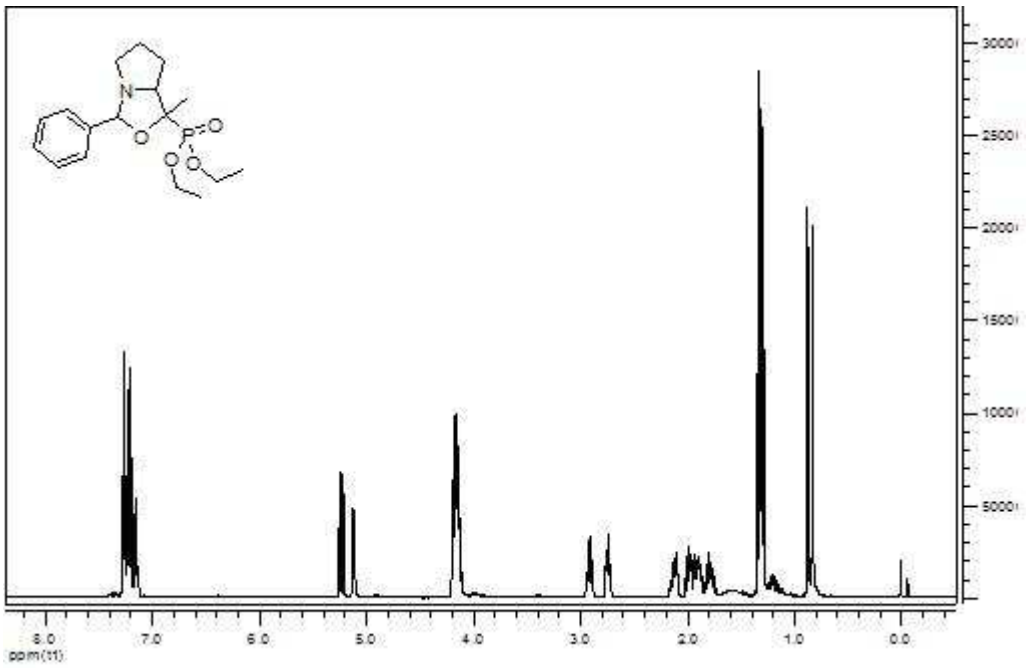

Figure A. 9 diethyl 1-methyl-3-phenylhexahydropyrrolo[1,2-c] oxazol-1-yl phosphonate **117**

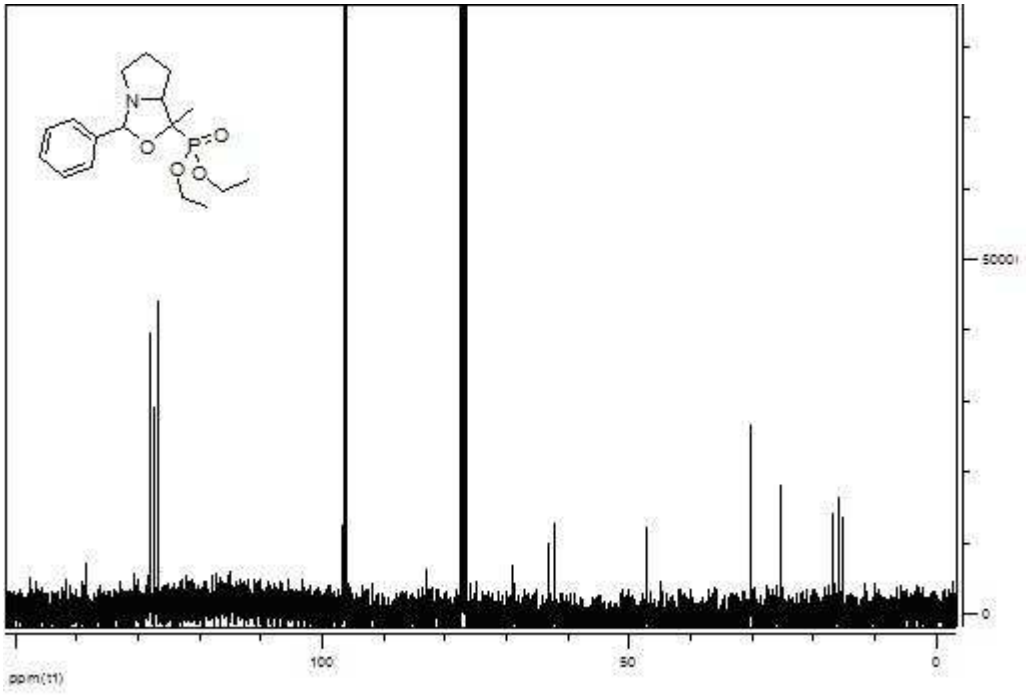

Figure A. 10 diethyl 1-methyl-3-phenylhexahydropyrrolo[1,2-c] oxazol-1-yl phosphonate **117**

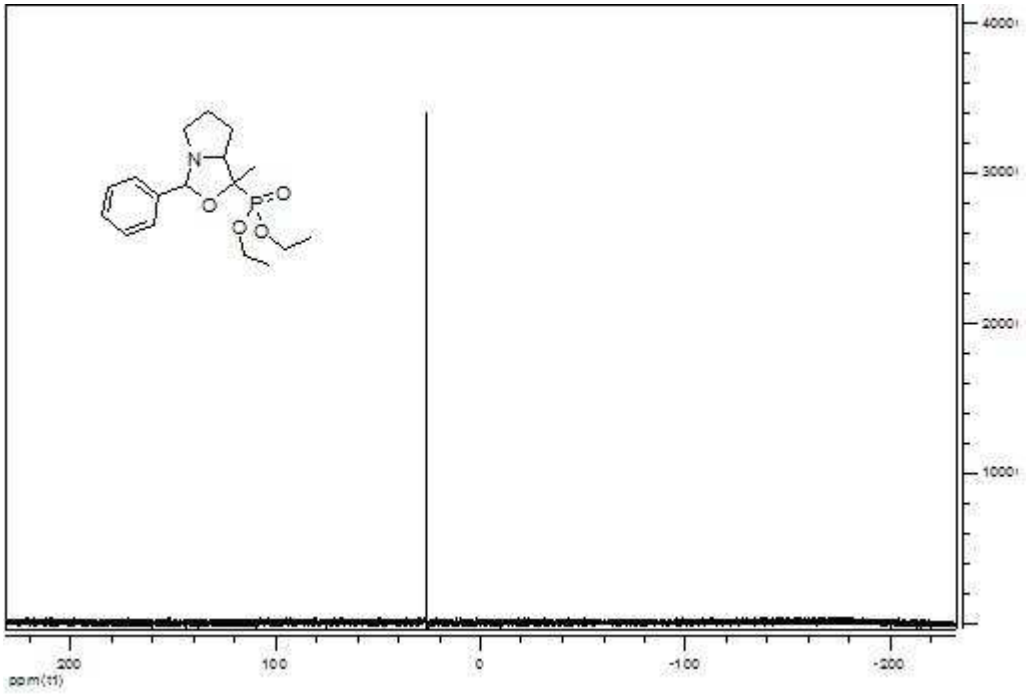

Figure A. 11 diethyl 1-methyl-3-phenylhexahydropyrrolo[1,2-c] oxazol-1-yl phosphonate **117**

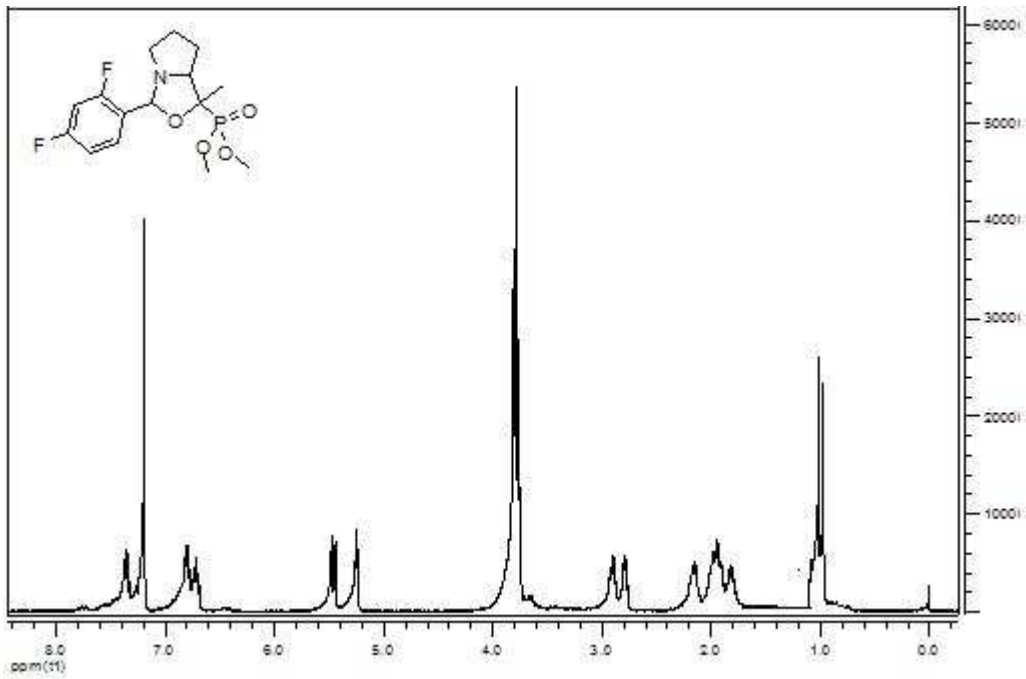

Figure A. 12 dimethyl 3-(2,4-difluorophenyl)-1-methylhexahydro pyrrolo [1,2-c] oxazol-1-ylphosphonate **119**