A NEW METHOD FOR SYNTHESIS OF AZIRIDINE 2-PHOSPHONATES AND THEIR BIOLOGICAL ACTIVITIES

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A NEW METHOD FOR SYNTHESIS OF AZIRIDINE 2-PHOSPHONATES AND THEIR BIOLOGICAL ACTIVITIES

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ABSTRACT

SYNTHESIS OF AZIRIDINE 2-PHOSPHONATES AND THEIR BIOLOGICAL ACTIVITIES

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A systematic study was carried out for the synthesis of aziridine 2-phosphonates by using two methods. First method is the classical Gabriel-Cromwell reaction and the second one is the modified version of Gabriel-Cromwell reaction which was developed in this thesis. In the first method, vinyl phosphonate was used as the starting material, then it was brominated to get 1,2-dibromoethyl phosphonate. HBr elimination from this compound, then reaction with different primary amines gave desired aziridinyl phosphonates in good yields. In the second method, easily available acetyl phosphonate was used as the starting material which was reacted with DBU and tosyl chloride to get α-tosylated vinyl phosphonate. Reaction of this compound with the same amines gave aziridinyl phosphonates in good yields, as well. Biological activities of all newly synthesized compounds were studied against different bacteria.

Key words: Aziridinyl phosphonates, Gabriel-Cromwell reaction, biological activity.

ÖZ

AZİRİDİNE 2-FOSFONATLARIN SENTEZİ VE BİYOLOJİK AKTİVİTELERİ

Babiz, Hakan
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Aziridin 2-fosfonatların sentezi için iki ayrı yöntem kullanılarak sistematik bir çalışma yapılmıştır. Birinci yöntem klasik Gabriel-Cromwell tepkimesi ve ikinci yöntem bu tez kapsamında geliştirilmiş olan modifiye Gabriel-Cromwell tepkimesidir. Birinci yöntemde başlangıç maddesi olarak vinil fosfonat kullanılmış ve bu maddenin bromlanmasıyla 1,2-dibromoetil fosfonat elde edilmiştir. Bu bileşikten HBr ayrılması sonra farklı birinci derece aminlerle tepkimesiyle beklenen aziridinil fosfonatlar iyi verimlerle elde edilmiştir. İkinci yöntemde ise bulunması daha kolay asetil fosfonat başlangıç maddesi olarak kullanılmıştır. Bu bileşiğin DBU ve tosil klorür ile tepkimesinden α-tosillenmiş vinil fosfonat elde edilmiştir. Bu bileşiğin aynı aminlerle tepkimesinden de beklenen aziridinil fosfonatlar yine iyi verimlerle elde edilmiştir. Sentezlenen tüm yeni bileşiklerin biyolojik aktiviteleri farklı bakteriler üzerinde çalışılmıştır.

Anahtar kelimeler: aziridinil fosfonatlar, Gabriel-Cromwell reaksiyonu, biyolojik aktivite.

To my dear parents...

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LIST OF ABBREVIATIONS

Boc	*t*-Butyloxycarbonyl
°C	Degrees Celcius
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
d	Doublet (spectral)
g	Gram(s)
Hz	Hertz
IR	Infrared
J	Coupling constant
m	Multiplet (spectral)
mL	Milliliter(s)
min	Minutes
mmol	Millimole(s)
NMR	Nuclear magnetic resonance
Ph	Phenyl
ppm	Parts per million (in NMR)
PTSA	Toluene-4-sulfonamide
q	Quartet (spectral)
rt	Room temperature
s	Singlet (spectral)
t	Triplet (spectral)
TLC	Thin layer chromatography
TsCl	*p*-Toluenesulfonyl chloride

CHAPTER 1

INTRODUCTION

The chemistry of three-membered ring heterocycles, especially epoxides and aziridines, has attracted the attention of synthetic chemists for more than a century. This is primarily due to the essentially high reactivity of these small-ring heterocycles, which makes them versatile species in organic synthesis [1]. The main target of this study was to synthesize functionalized nitrogen-containing three-membered rings. Aziridines **1** are saturated three-membered ring compounds containing two carbons and one nitrogen atom (Figure 1). Aziridine has also been called as azacyclopropane and ethylenimine.

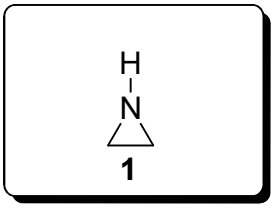


Figure 1. Structure of simple aziridine.

The aziridine moieties are commonly used in synthesis for chemical bond expansions and functional group transformations. The synthetic applications of aziridines usually take advantage of their ring-strain by reaction with nucleophiles to afford functional ring opened products, or opening the rings to produce reactive intermediates such as dipoles or radicals to yield cycloaddition products. In these cases, the aziridine functionalities serve as synthetic building blocks to be further

transformed into more valuable products. Activation of aziridine ring is usually necessary for ring opening reactions. As well, they exhibit better stability towards oxidation. So that, aziridine functionalities show unusual chemoselectivities, regioselectivities or stereoselectivities in various transformations [2].

1.1 Properties of aziridines

Three-membered ring structure of aziridines has two important impacts on their properties. It causes a substantial increase of ring-strain energy (26.8 kcal/mol) [3]. The strain is contributed by the distortion of bond angle from an ideal tetrahedral angle, (Baeyer Strain), eclipsing strain of non-bonded substituent groups on the ring (Pitzer Strain), and the transannular van der Waals interactions of groups attached to the non-adjacent ring atoms (Prelog Strain) (Figure 2) [4].

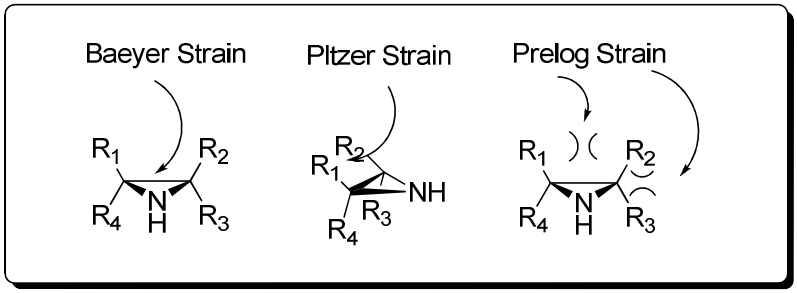


Figure 2. Types of strain in aziridine structures.

1.1.1 Structure of aziridines

Similar to other strained rings, the most remarkable feature of aziridine structures is that the bond angles deviate away from the regular tetrahedral angle of 109° in order to fit their 60° triangular structures. X-ray crystallography indicates that the average bond length of C-C bond in aziridines is 1.480 Å and C-N bond is 1.472 Å. The value for C-C bond is between the standard values of Csp^2-Csp^2 (1.33

Å) and Csp^3-Csp^3 (1.54 Å); whereas, the value for C-N is close to the standard values of Csp^3-Nsp^3 (1.469 Å) [5].

1.1.2 Acidity of aziridines

The basicity of aziridine nitrogen can be correlated to the pK_{aH} of the molecule, in which the pK_{aH} is defined as the pK_a value of corresponding conjugate acid [6]. The comparison between simple aziridine **1** and other amine species are illustrated in Figure **3.**

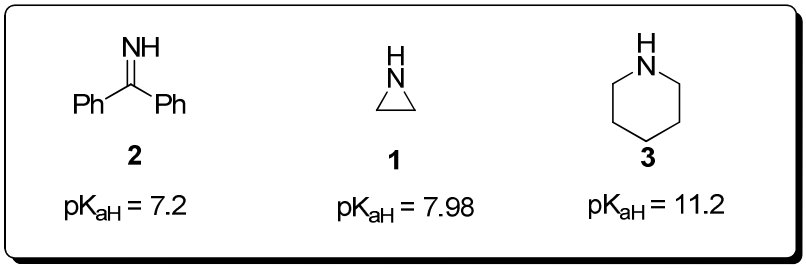


Figure 3. Comparisons of the pK_{aH} values.

The basicity of aziridine nitrogen lone pair is significantly lower than that of piperidine **3**. The pK_{aH} value of aziridine is closer to the corresponding sp^2 hybridized imine **2**. This can be explained by the higher *s*-character component in its hybridization.

1.1.3 Spectroscopic Properties of aziridines

The existence of ring strain in aziridine has been further confirmed by infra-red spectroscopy, this is reflected in the increase in the C-H vibrational frequency from 1465 cm^{-1} to 1475 cm^{-1} and a decrease in the N-H vibrational frequency to

1441 cm^{-1} which is lower than that observed for secondary amines (1460 cm^{-1}). The calculated dipole moment value for aziridine is 2.09-2.40 D [7].

Aziridines have conformationally flexible nitrogen atom. Therefore, NMR spectroscopy has found wide application in the study of structure and stereochemistry of aziridines. The use of vicinal proton-proton coupling constants of 2-6 Hz for *trans* protons and of 5-9 Hz for *cis* protons has enabled the stereochemistry at C-2 and C-3 to be determined in several substituted aziridine molecules.

1.2 Synthetic Methods for Aziridines

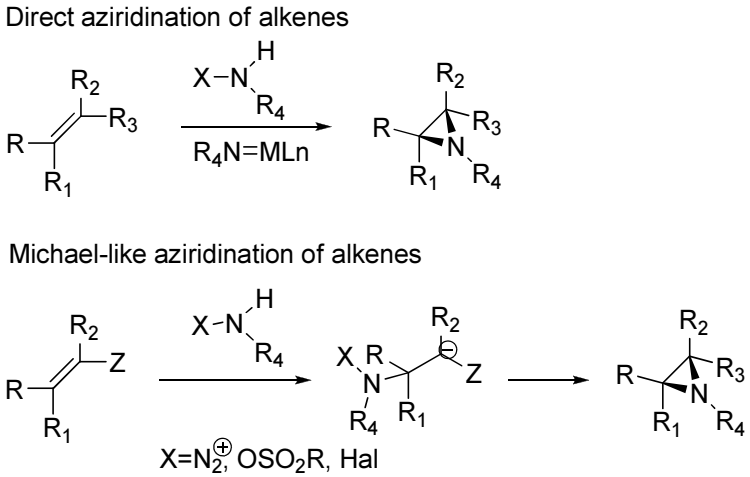
Aziridine derivatives have been prepared by a number of important methods.

1.2.1 Addition to Alkenes

Nitrogen atom transfer to alkenes is a mostly appealing approach for the synthesis of aziridines due to the availability of olefinic starting materials and the nature of such a route. There are two common methods for the addition of nitrene and nitrenoid to alkenes, including a one or a two-step mechanism [8].

1.2.1.1 Addition of Nitrenes and Nitrenoids to Alkenes

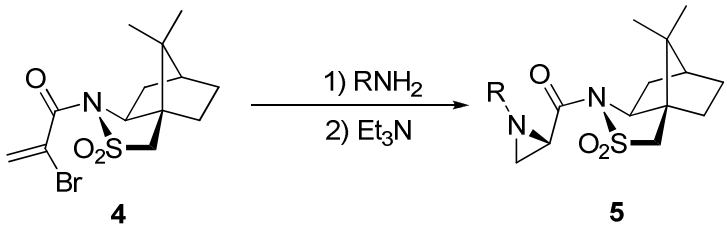
There are two common ways in this subcategory, involving one or two step mechanisms. Nitrenes and metalonitrenes can be added to alkenes directly used for the aziridination. However nonmetallic nitrenoids usually react through an addition-elimination process (Scheme 1) [9].



Scheme 1. Aziridination via nitrene addition to alkenes.

1.2.1.2 Aziridines by Addition-Elimination Processes

Gabriel-Cromwell aziridine synthesis involves nucleophilic addition of a formal nitrene equivalent to a 2-haloacrylate or similar reagent [10]. Hence, there is a Michael addition, followed by protonation and ring-closure.



Scheme 2. Azirdination via addition-elimination processes.

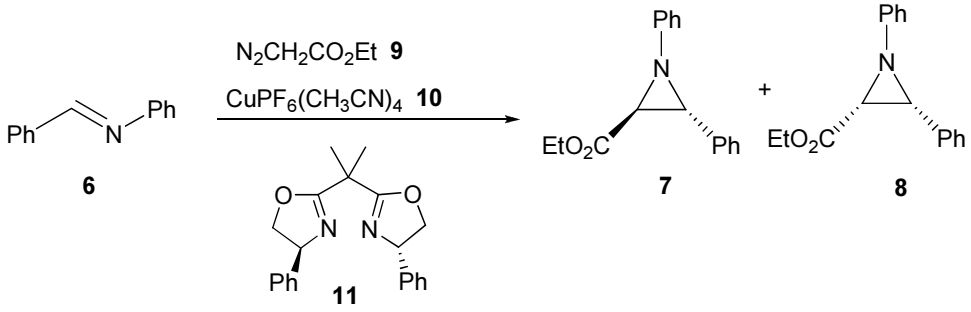
Asymmetric alternatives of Gabriel-Cromwell aziridine synthesis have been reported. *N*-(2-Bromo)acryloyl camphor sultam **4**, for instance, reacts with amines to provide *N*-substituted (aziridinyl)acylsultams **5** (Scheme 2) [11,12].

1.2.2 Addition to Imines

Since alkenes are quite important precursors to aziridines, especially about stereoselective reactions, significantly advances have been made in this arena through the addition reactions to imine which can be subdivided into three categories concerning the reactions of imines with carbenes, α-haloenolates and ylides [9].

1.2.2.1 Carbene Methodology

Reactions between carbenes or carbenoids and imines are a useful method for aziridine synthesis. Other than carbenes and carbenoids, ylides have similarly been used for aziridinations of imines; in all classes of this reaction type the mechanism commonly consist of a stepwise addition-elimination process, instead of a synchronous bond-forming event.



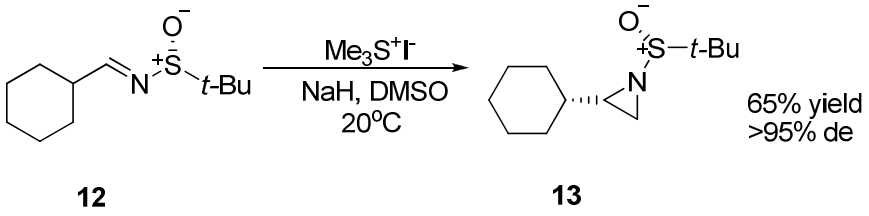
Scheme 3. Aziridination via carbene.

Organic chemists have newly paying attention to this area of research, but there has been an impressive activity in the synthesis of aziridine with carbene methodology. Simple (i. e., unstabilized) carbenes suffer from the problems of

nitrenes. For that reason, most reported procedures use carbenoids as carbene source. The majority of recent reports have focused upon reactions between α-diazoesters and imines in the presence of a range of catalysts [9]. In one of the earliest reports of enantioselective carbene-imine reactions, for instance, Jacobsen and Finney reported that ethyl diazoacetate **9** reacts with *N*-arylaldimines **6** in the presence of copper(I) hexafluorophosphate **10** with ordinary stereoselectivity to give *N*-arylaziridine carboxylates **7, 8** (Scheme 3) [13].

1.2.2.2 Aza-Darzens and Analogous Reactions

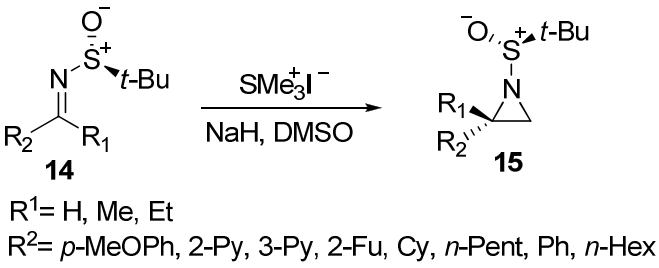
The reaction of sulfur (and analogous iodine ylide [14]) with imines to form aziridines is a Darzens-like reaction. Such ylides react to give β-sulfonium or β-iodonium amide anions, which are not isolated, but are instead allowed to react by ring-closure to give aziridines directly. Thus, Corey-Chakovsky sulfonium ylide have been used in asymmetric aziridination reactions of chiral sulfinyl imines **12**. Stockman et al. deduced the initial findings of Garcia-Ruano [15,16] and Davis [17] and found that a range of aryl, aliphatic, and vinyl aziridines could be prepared in good yield and with high stereoselectivity (Scheme 4) [18].



12 **13**

Scheme 4. Aziridination via aza-Darzen reaction.

1.2.2.3 Ylide-mediated aziridination

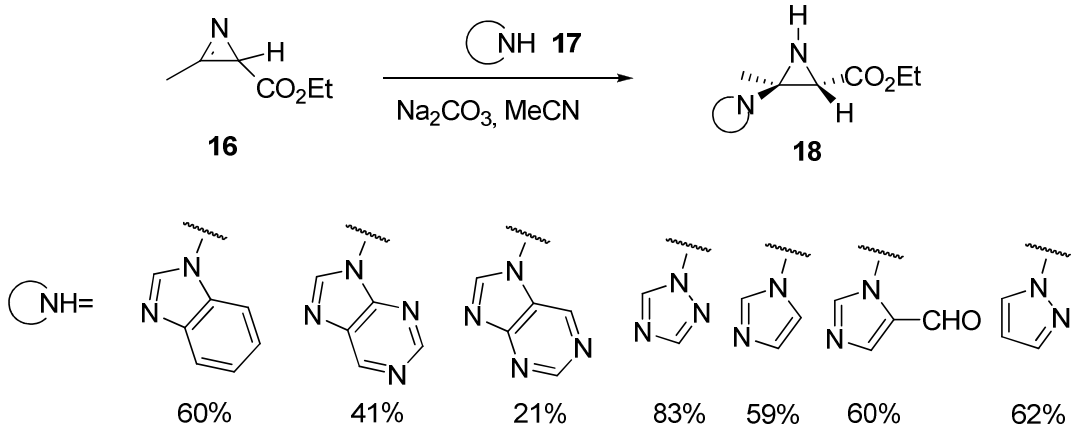


Scheme 5. Ylide-mediated aziridination.

In addition to carbenes, carbenoids and α-haloenolates, ylides have also been commonly used for asymmetric aziridine synthesis starting from imines. The reaction among an imine and an ylide results a betaine, following by ring-closing to form aziridine by the elimination of the heteroatom containing leaving group originating from the ylide. Stockman et al. have developed asymmetric reactions of dimethylsulfonium methylide derived from trimethylsulfonium iodide with a wide range of aromatic, heterocyclic and aliphatic *t*-butylsulfinylaldimines **14**, providing the corresponding chiral aziridines **15** in good yields and diastereoselectivities [18,19] as shown in (Scheme 5).

1.2.3 Addition to Azirines

Azirines are three membered heterocyclic unsaturated (i.e. they contain a double bond) compounds containing a nitrogen atom and related to the saturated analogue aziridine. Substituted azirines are versatile compounds [20], and have been used for the synthesis of substituted aziridine derivatives. Reactivity of these compounds is caused by ring strain of three-ring system, the electron rich C=N bond and the nitrogen lone pair. Asymmetric nucleophilic addition to azirines is a



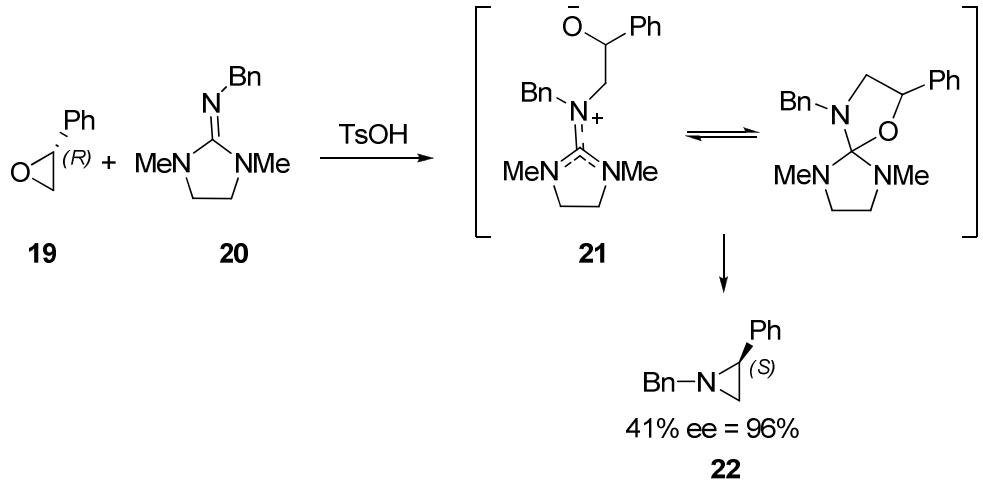
Scheme 6. Aziridine formation from azirines.

potentially striking entry to enantio enriched aziridine synthesis. Alves et al. have developed nucleophilic additions of nitrogen heterocycles **17** to a chiral 2*H*-azirine-2-carboxylic ester **16**, giving access to optically active aziridine esters **18** showed in (Scheme 6) [21].

1.2.4 Aziridines through Cyclization

1.2.4.1 From Epoxides

In 2004, Ishikawa et al. demonstrated that it was possible to directly convert chiral epoxides into chiral aziridines by using guanidines **20** as a nitrene source [22]. The reaction of guanidine **20** with the epoxide **19** was supposed to afford a betaine species **21**, depicted in (Scheme 7), which produced the corresponding aziridine **22** via a spiro intermediate. This process proceeded via inversion of configuration at the asymmetric carbon on (*R*)-styrene oxide with high chirality control (96% ee).

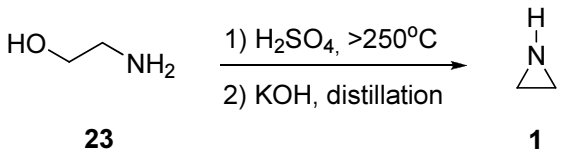


19 20 21 22

Scheme 7. Aziridination starting from epoxide.

1.2.4.2 From 1,2-Aminoalcohols and 1,2-Aminohalides

In 1888, Gabriel reported that aziridines could be prepared in a two-step process, by chlorination of ethanolamines with thionyl chloride, followed by alkali-induced cyclization [23,24]. Wenker reported that heating of ethanolamine **23** with 96% sulfuric acid at high temperature formed β-aminoethyl sulphuric acid; it was distilled from aqueous base to get aziridine itself [25] (Scheme 8).

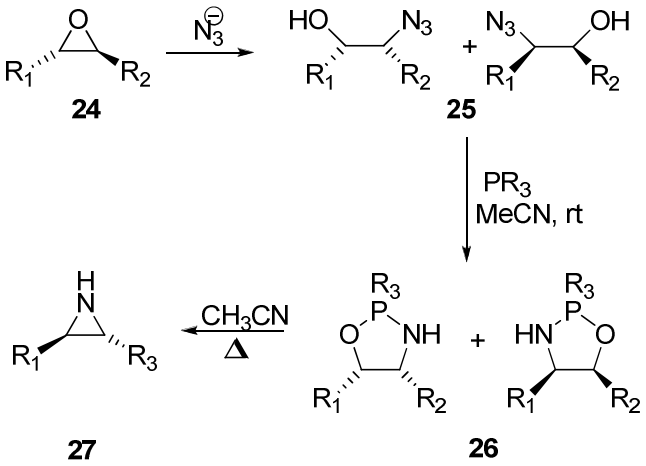


23 **1**

Scheme 8. Aziridination starting from 1,2-Aminoalcohols.

1.2.4.3 From 1,2-Azidoalcohols

Since the development of new asymmetric epoxide syntheses, there has been a ready supply of enantiomerically pure epoxides. There have been abundant reports of multistep preparation of aziridines from these precursors. Particularly, phosphine

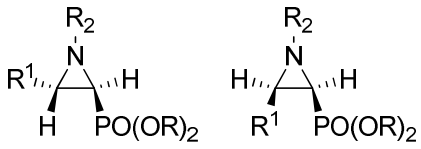


Scheme 9. Aziridination starting from 1,2-Azidoalcohols.

mediated ring closures of azidoalcohols, obtained from chiral epoxides **24** by ring opening reactions through the usage of nucleophilic azide sources, have been widely examined. Treatment of hydroxyazides **25** with trialkylphosphine or triarylphosphine produce oxazaphospholidines **26**, which are rapidly formed. However oxazaphospholidines **26** slowly formed *N*-unsubstituted aziridines **27** by heating in acetonitrile (Scheme 9).

1.3 Aziridine 2-phosphonates

The importance of synthetic amino acids in the modification of peptides to improve bioactivity and stability and their utility in peptide therapeutics makes the asymmetric synthesis of α- and β-amino phosphonic acids a significant objective. α-amino phosphonic acids are considered to be surrogates for amino acids and as such exhibit a broad range of biological activities [26-28]. For example, they have found usage as enzyme inhibitors [29-31], and references therein [32,33], haptens for catalytic antibodies [34], antibacterial agents [35,36], anti-HIV agents[37-39] and biotrytcides [40].

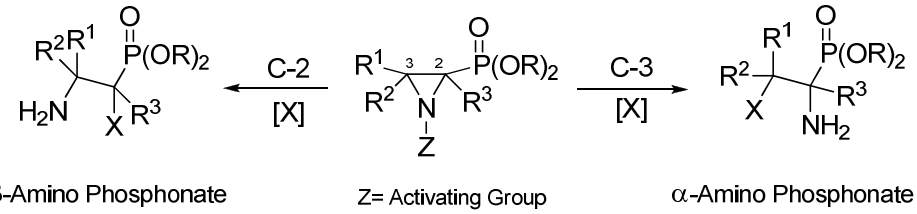


28 **29**

Scheme 10. *trans*- and *cis*-aziridine-2-phosphonates.

Moreover, aziridines have been widely used as versatile chiral building blocks for the synthesis of a variety of biologically and pharmaceutically important molecules. More recently, methods for the syntheses of analogous chiral nonracemic *trans*-aziridine-2-phosphonates **28** and *cis*-aziridine-2-phosphonates **29** have been developed, and their uses as chiral building blocks have also emerged (Scheme 10) [41].

Chiral aziridines have found widespread use in organic synthesis [42-44]. The strained three-membered ring readily opens with excellent stereo- and regiocontrol to afford a wide variety of more stable ring-opened or ring-expanded chiral amines.



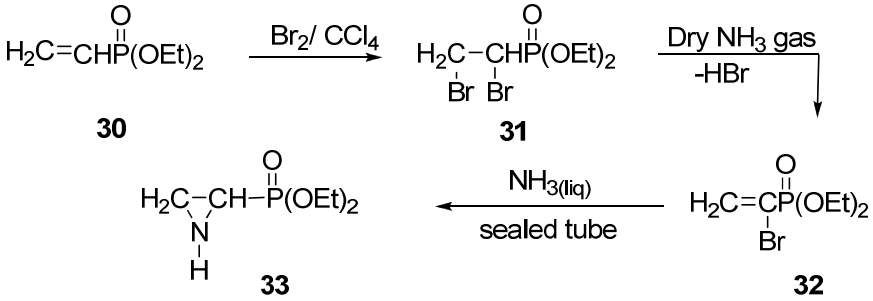
Scheme 11. Ring opening of aziridine 2-phosphonate with C-2 and C-3 attack.

Consequently, aziridine 2-phosphonates are expected to be important sources of diversely substituted amino phosphonates. Activation of the aziridine nitrogen by an electron-withdrawing group, by protonation, or by Lewis acids promotes either C-2 attack to give β-amino phosphonates or C-3 attack to give α-amino phosphonates (Scheme 11). The stereo- and regioselectivity is determined by the ring substituents and the reaction conditions, with the majority of nucleophiles expected to react at C-3.

1.3.1 Synthesis of Aziridine 2-Phosphonates

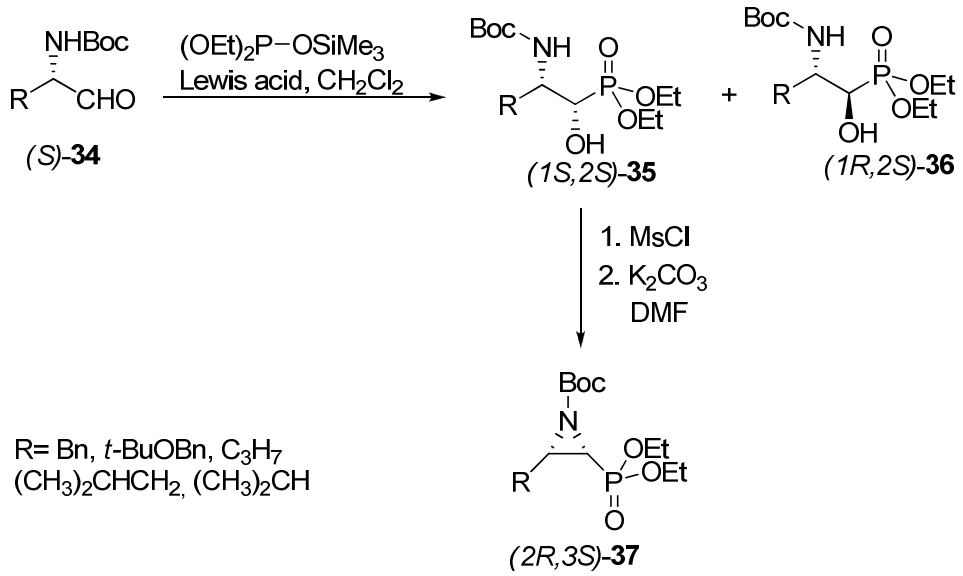
1.3.1.1 Ring Closure by Nucleophilic Substitution

The simplest way to make the aziridine-2-phosphonates is by intramolecular nucleophilic substitution of a hydroxy or a halogen function by an amino group. α,β-unsaturated phosphonates can serve as a template to introduce the necessary functionalities to perform this intramolecular nucleophilic substitution. Fast bromination of diethyl vinylphosphonate **30** using bromine in CCl_4, gave the crude dibromo compound **31**. Followed by reaction with aqueous ammonia and hydrolysis gave the product **32**. Reaction of vinyl bromide **32** with liquid ammonia in a sealed tube at room temperature gave the aziridine **33** (Scheme 12) [45].



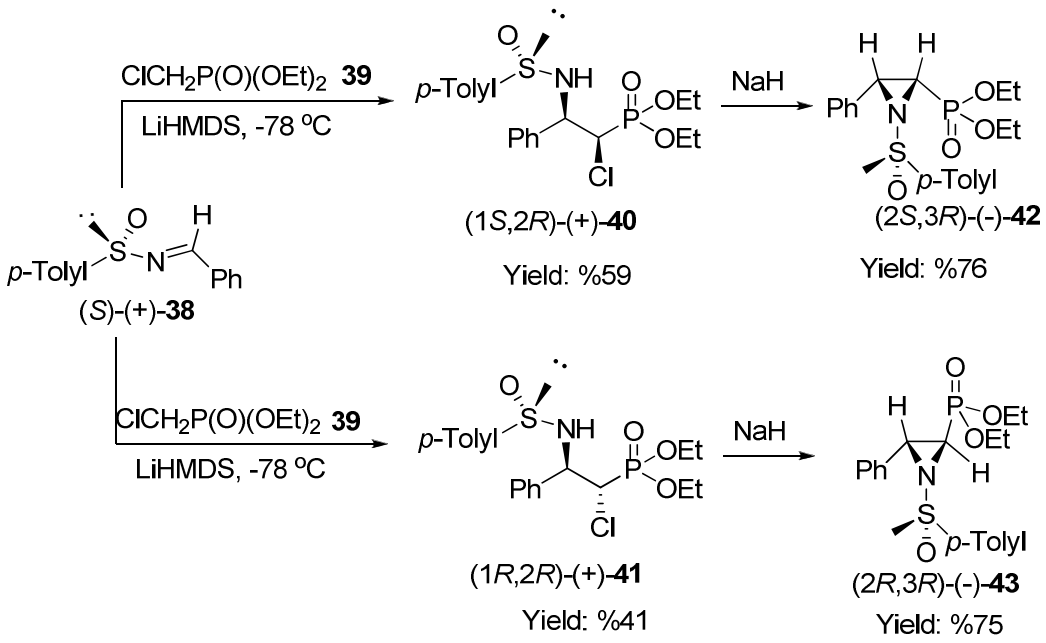
Scheme 12. Aziridination with ring closing by nuclephilic substitution.

Larcheveque and co-workers reported that the nucleophilic addition of phosphites to α-aminoaldehydes **34** gave α-hydroxy amino phosphonates **35** and **36** (Scheme 13) [46]. The best diastereoselectivity was 82:18 (*syn:anti*) with a yield of 75%. The mixture of diastereomers was mesylated and after separation, **35** was cyclized to give exclusively the aziridine 2-phosphonates **37**.



Scheme 13. Synthesis of *N*-Boc Aziridine 2-phosphonate.

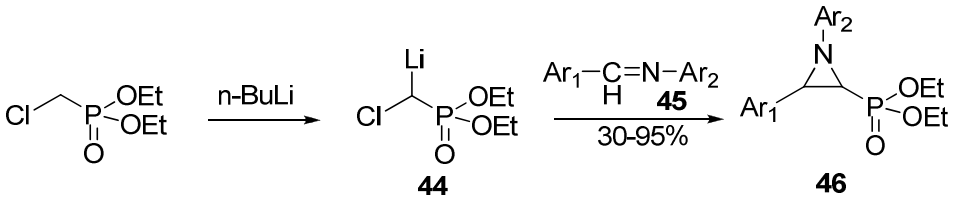
Davis and McCoull developed a new approach for the asymmetric synthesis of aziridine 2-phosphonates via enantiopure sulfinimines (Scheme 14) [47]. A Darzens-type reaction was utilized to obtain the three-membered aziridine ring. The phosphonate group was introduced by treating diethyl 1-chloromethylphosphonate **39** with LiHMDS followed by the addition of (*S*)-(+)-*N*-(benzylidene)-*p*-



Scheme 14. Synthesis of aziridine 2-phosphonates via enantiopure sulfinimines.

toluenesulfinamide **38.** The diastereomers **40** and **41** could be separated by column chromatography in 58% and 40% yield, respectively. Ring closure was performed using NaH, resulting in diastereomers **42** and **43** in 76% and 75% yield, respectively.

A racemic pathway consisted of the stereoselective synthesis of 3-aryl aziridine-2-phosphonates **46** via the reaction of diethyl 1-lithio-l-chloromethylphosphonate **44** and aromatic imines **45** (Scheme 15) [48]. The major, *cis*-aziridine, was separated by column chromatography, to give the racemic 3-aryl aziridine 2-phosphonates **46.**

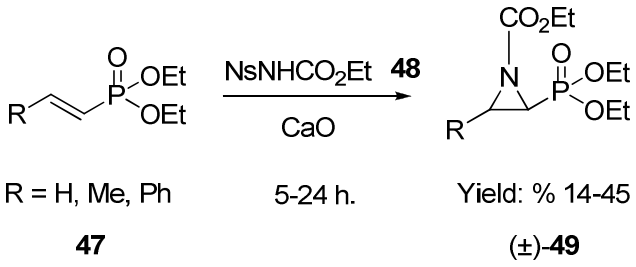


Ar^1= Ph, *m*-ClPh, *p*-ClPh, *m*-NO_2Ph, *p*-NO_2Ph, *o*-CH_3Ph, *p*-CH_3OPh
Ar^2= Ph, *p*-BrPh

Scheme 15. Synthesis of 3-aryl aziridine 2-phosphonates (**46**).

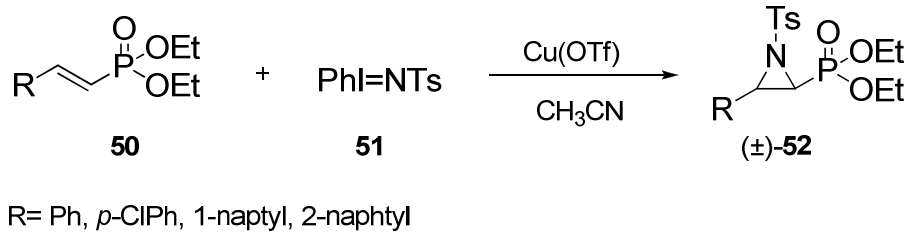
1.3.1.2 Aziridination using Nitrenes

Aziridination of vinylphosphonates with nitrene reagents is also a commonly used strategy for the synthesis of aziridine 2-phosphonates. As a nitrene precusor, ethyl *N*-{[4-nitrobenzene)sulphonyl]oxy}carbamate ($NsONHCO_2Et$) **48** was used to form the aziridine (Scheme 16) [49]. The aziridination reactions were carried out with generation of the (ethoxycarbonyl)nitrene by α-elimination of **48** with CaO. Aziridination of the α,β-unsaturated phosphonic esters **47** gave the expected aziridine phosphonate **49** with yield of 14-45%. There was no reaction when the R in **47** was a phenyl group.



Scheme 16. Aziridination via nitrene source ($NsONHCO_2Et$) (**48**).

The same type of aziridination via a nitrene precursor was used by Kim and Rhie (Scheme 17) [50]. In their case [*N*-(*p*-toluenesulfonyl)imino]phenyliodonane (PhI=NTs) **51** and a copper catalyst were used to form *N*-tosyl substituted aziridine 2-phosphonate **52** starting from vinylphosphonates **50**. Aziridination of the α,β-unsaturated phosphonic esters gave the expected aziridine 2-phosphonate with yield of 82-95% (Table 1).



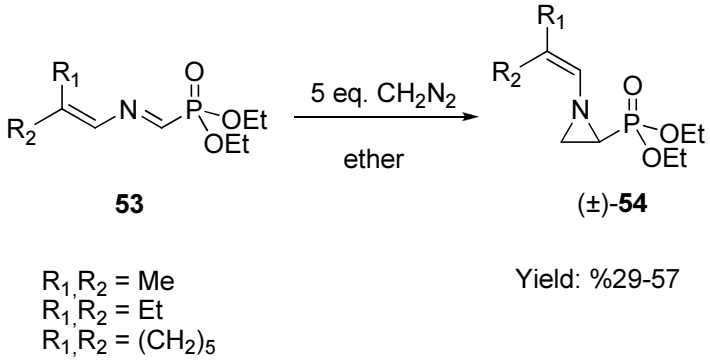
Scheme 17. Aziridination via nitrene source (PhI=NTs) (**51**).

Table 1. Aziridination via nitrene source (PhI=NTs) (**51**).

R	**% Yield**
Ph	82
p-ClC_6H_4	95
1-Naphthyl	87
2-Naphthyl	85

1.3.1.3 Aziridination using Carbenoids

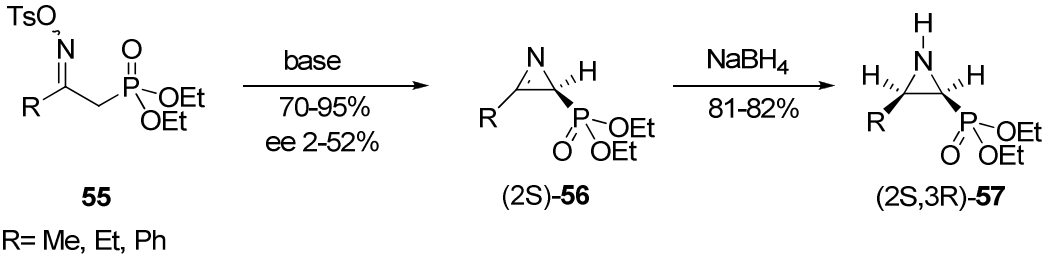
Reaction of the azadienes **53** with an excess of diazomethane led to the generation of 1-vinyl aziridine 2-phosphonates **(±)-54** in low yields (Scheme 18) [51]. As carbenes are known to react with different kinds of olefins, no formation of the corresponding cyclopropane was detected in this case.



Scheme 18. Aziridination using Carbenoids.

1.3.1.4 Reduction of 2*H* Azirine-2-Phosphonates

Palacious et al. reported the synthesis of the 2*H*-azirine 2-phosphonates **56** from tosyl oximes **55** by a Neber reaction (Scheme 19) [51,52]. This process was also extended to the asymmetric synthesis of azirines **56** when stochiometric amounts of chiral bases (quinidine, sparteine, quinine, hydroquinidine) were used. However, the enantiomeric excess varied from 2% to 52%. The reduction of these azirines with $NaBH_4$ led to the corresponding aziridine 2-phosphonates **57**.



Scheme 19. Reduction of 2*H* Azirine-2-Phosphonates (**57**).

1.4 Aim of the work

One of the reason of why aziridines have attracted great interest to chemists for many years is that their easy transformation into diverse compounds. Their presence as structural subunits in natural compounds might be given as another reason. Therefore, they have found applications as antitumor active compounds, precursors for chiral ligands and chiral building blocks for the construction of various chiral nitrogen compounds, such as chiral amines, amino acids, β-aminosulfonic acids, amino alcohols, alkaloids, β-lactam antibiotics, etc [53].

Although aziridine phosphonates are very important compounds, there are limited numbers of studies reporting the synthesis of these compounds. Moreover, none of these studies are systematic aziridine synthesis, some of them report the synthesis of very specific ones and the others are limited with a few examples or forms aziridines in low yields at longer reaction times. Therefore it is necessary to develop a method for the synthesis of aziridine phosphonates having general applicability. There is also no study reporting the biological activities of these compounds. Therefore we also aimed to investigate the biological activities of the synthesized aziridine phosphonates.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of aziridines

In this study, we synthesized *N*-subtituted aziridine 2-phosphonates by using two different methods. Firstly, we developed a new method for the synthesis of aziridine 2-phosphonates by using a modification of Gabriel-Cromwell reaction. Secondly; Gabriel-Cromwell reaction was used in order to synthesize aziridine 2-phosphonates starting from vinyl phosphonate.

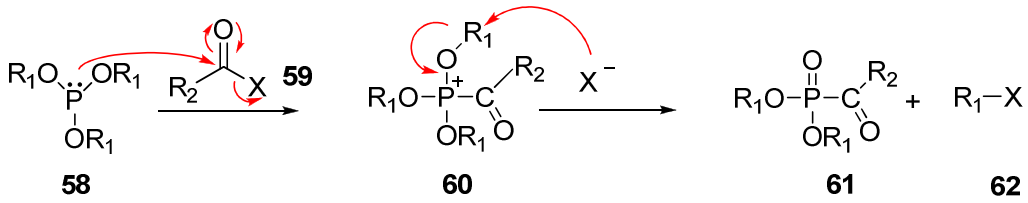
2.1.1 Synthesis of aziridines starting from α-tosylated vinyl phosphonate

With the aim of synthesizing our target molecules, it was necessary to synthesize α-tosylated vinyl phosphonate first.

2.1.1.1 Synthesis of α-tosylated vinyl phosphonate

In order to prepare α-tosylated vinyl phosphonate, acetyl phosphonate was used as the starting material which can be synthesized from triethoxyphosphine and acetyl chloride by Michaelis-Arbuzov reaction.

2.1.1.1.1 **Mechanism of Michaelis-Arbuzov reaction**

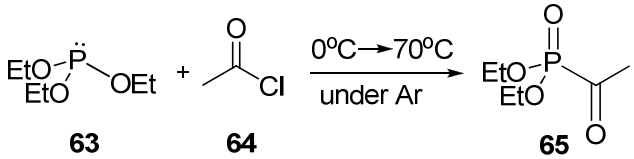


Scheme 20. Mechanism of Michaelis-Arbuzov reaction.

The Michaelis-Arbuzov reaction is initiated with the addition-elimination reaction of the nucleophilic phosphite **58** with the electrophilic acyl halide **59** to give a phosphonium intermediate **60**. The displaced halide anion reacts via S_N2 reaction with the phosphonium intermediate to give the desired phosphonate **61** and alkyl halide **62** (Scheme 20).

According to Michaelis–Arbuzov reaction, we treated triethylphosphite **63** with acethyl chloride **64** under argon gas and 0°C, we obtained acetyl phosphonate **65** in high purity and high yield after purification (Scheme 21). ^{1}H and ^{13}C NMR results confirmed the structure of acetyl phosphonate **65**. NMR spectra are shown in Figure A.1 and Figure A.2 of Appendix A.

Furthermore, we also tried to synthesize acetyl phosphonates starting from trimethylphosphite, but synthesis of aziridines from this compound was not

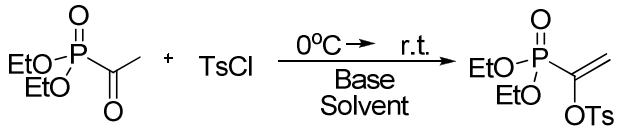


Scheme 21. Synthesis of acetylphosphonate **65**.

successful. In addition, we also tried the synthesis of acryloyl phosphonate starting from acryloyl chloride, but the product formation did not take place.

2.1.1.1.2 Synthesis of α-tosylated vinyl phosphonate

For the synthesis of α-tosylated vinyl phosphonate **66**, we treated acetyl phosphonate **65** with *p*-toluenesulfonyl chloride in the presence of a base. In order to increase yields we did some optimization studies (Table 2). We changed the solvent, base, concentration, and equivalents. First of all, NEt_3 was tried as the base but the



65 **66**

Scheme 22. Synthesis of α-tosylatedvinyl phosphonate **66**.

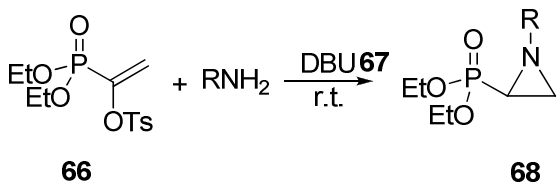
product formation could not be increased more than 38% yield. So, DBU was used as the second base which gave the product in better yield (87%). After determining the proper base, different solvents (DCM, THF, DMF, CH_3CN) were used. Among the solvents employed, acetonitrile gave the highest yield. Finally, equivalents of the base and TsCl were changed. Better results were obtained when 1.5 equivalents of both substrates were used. After these studies, the optimum conditions were determined to be: DBU (1.5 equiv.), TsCl (1.5 equiv.), concentration (0.2M), and CH_3CN as the solvent.

Table 2. Synthesis of α-tosylated vinyl phosphonate (**66**).

Entry	DBU (Equiv.)	Et_3N (Equiv.)	Solvent	TsCl (Equiv.)	Molarity [M]	Time (hours)	Yield (%)
1	---	1.5	DCM	1.5	0.43	72	18.0
2	---	2.4	DCM	1.2	0.83	72	38.0
3	1.0	---	THF	1.5	0.5	2.5	57,7
4	1.0	---	DMF	1.5	0.3	2.5	37.9
5	1.0	---	THF	1.5	0.2	16	56.4
6	1.50	---	THF	1.1	0.2	3.0	69.2
7	1.50	---	CH_3CN	1.1	0.2	3.0	74.9
8	1.50	---	CH_3CN	1.5	0.2	3.0	87.0

2.1.1.1.3 Synthesis of aziridine 2-phosphonate derivatives

For the synthesis of aziridine 2-phosphonates, α-tosylated vinyl phosphonate **66** in acetonitrile was mixed with DBU. Then, reaction mixture was treated with primary amines to obtain *N*-subtituted aziridines (Scheme 23). In order to obtain best result, some optimization studies were performed. Highest yields were obtained when DBU was used as the base and CH_3CN as the solvent. The reactions were also performed under solvent free conditions. Benzylamine, isopropylamine and

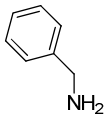
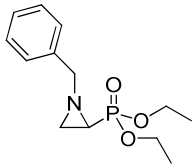
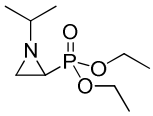
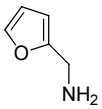
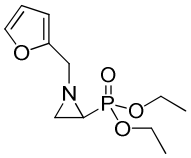
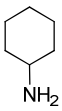
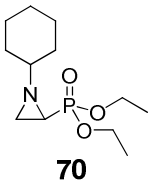
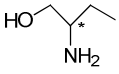
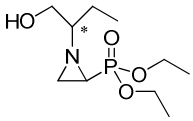
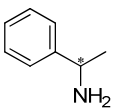
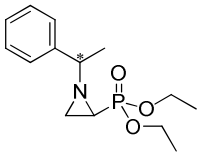


66 **68**

Scheme 23. Synthesis of aziridine 2-phosphonates **68**.

cyclohexylamine formed the aziridines in highest yields without a solvent. Absolute stereochemistry of aziridines synthesized from (*R*)-2-amino-1-butanol (**71** and **72**) and (*R*)-1-phenylethylamine (**73** and **74**) were not assigned. The results of aziridine synthesis were summarized in Table 3.

Table 3. Synthesis of aziridines from α-tosylated vinyl phosphonate (**66**).

Amine	Amine (Equiv.)	DBU (Equiv.)	Molarity (Solvent)	Time (h)	Product	Yield (%)
	1.4	1.0	No solvent	24 h.	 **67**	87.5
	1.4	1.0	No solvent	24 h.	 **68**	88.4
	2.0	1.0	1.0 (CH_3CN)	48 h.	 **69**	92.0
	1.4	1.0	No solvent	24 h.	 **70**	85.2
	2.0	1.0	1.0 ($CHCl_3$)	72 h.	 **71**,**72**	71.1
	2.0	1.0	1.0 (CH_3CN)	72 h.	 **73**,**74**	82.0

In the proposed mechanism, first step is the 1,4-addition (conjugate addition) of primary amine, followed by the protonation of α-position. Ring closure by S_N2 displacement of tosylate results in the formation of protonated aziridine. Finally, proton transfer to the base gives neutral aziridine 2-phosphonates.

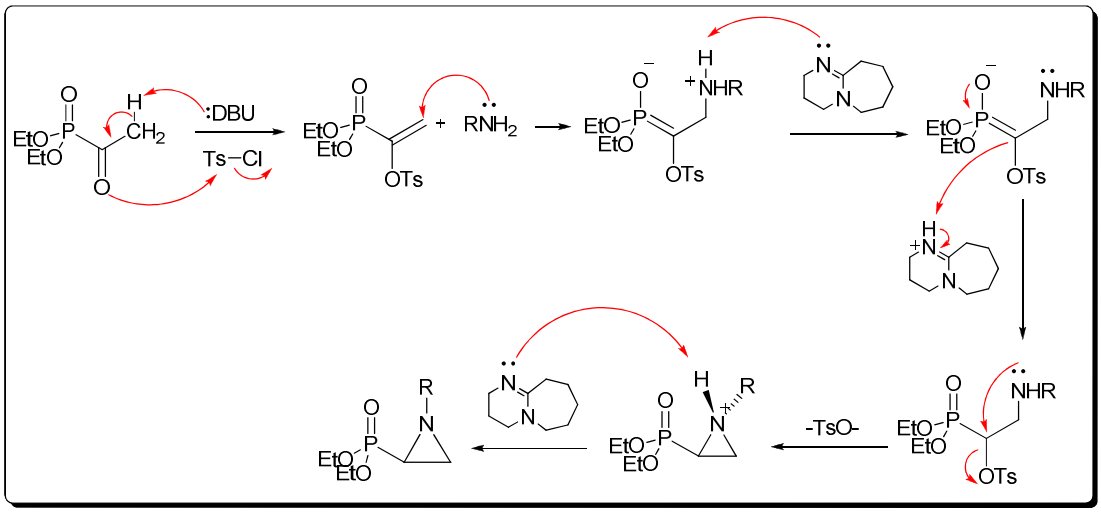


Figure 4. Proposed mechanism for aziridination.

This mechanism is very similar to the mechanism of the Gabriel-Cromwell reaction which has only two differences. First, in Gabriel-Cromwell reaction starting material is vinyl phosphonate while in our method starting material is acetyl phosphonate. Second, Gabriel-Cromwell reaction uses bromide as the leaving group while in our method tosylate is the leaving group.

All the aziridines were characterized by ^{1}H, ^{13}C NMR, and HRMS. For example on the ^{1}H NMR spectrum (Figure A.6 in Appendix A) of diethyl 1-benzylaziridin-2-ylphosphonate (**67**), phenyl protons gives signals between 7.07 and 7.40 ppm as multiplet. CH_2 protons of ethoxy group resonate between 3.71-4.14 ppm as multiplets. There is an AB system for the benzylic protons at 3.24 and 3.55 with

the coupling constant of J = 13.0 Hz. At 2.12 ppm, CH proton of aziridine ring gives doublet of doublet with the coupling constants of J= 3.5 and 9.2 Hz due to the coupling with phosphorus. CH_2 protons of aziridine ring give signals between 1.39-1.77 ppm as multiplets. The signals of CH_3 of ethoxide are at 1.13 and 1.20 ppm as triplets.

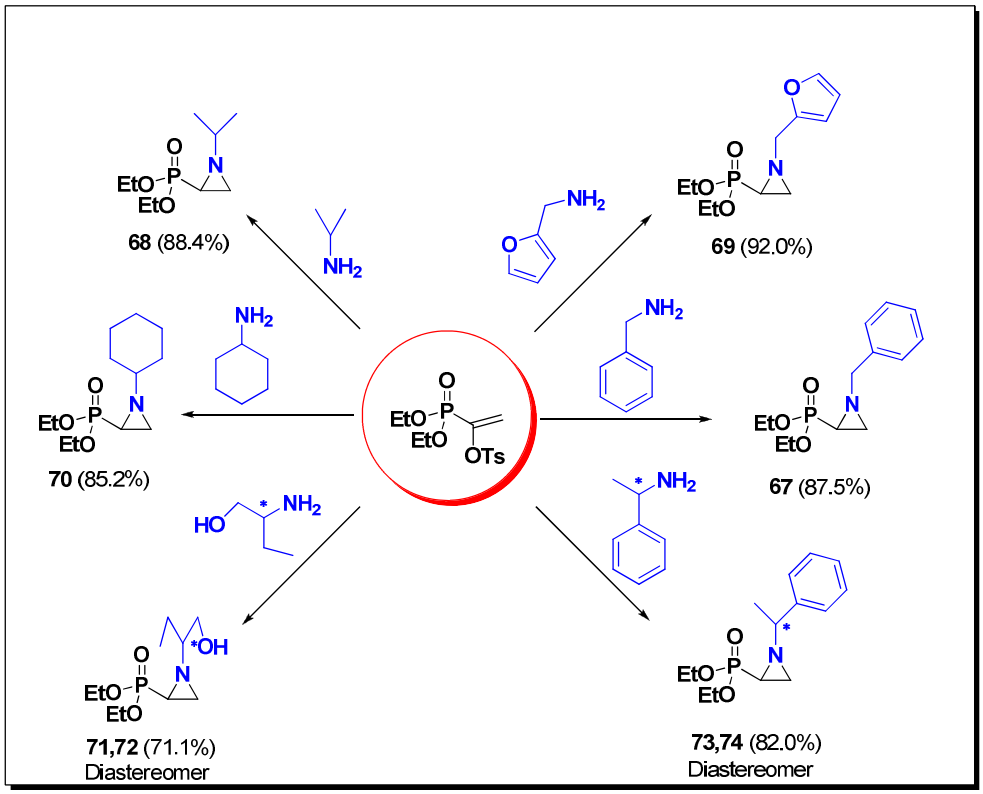


Figure 5. Synthesized aziridine 2-phosphonates.

On the ^{13}C NMR spectrum (Figure A.7 in Appendix A) of diethyl 1-benzylaziridin-2-ylphosphonate (**67**), phenyl carbons resonate at 127.34, 128.28, 128.38, 137.78 ppm. Benzylic carbon resonates at 65.27 ppm as doublet (J= 7.3 Hz). CH_2 carbons of ethoxy groups give doublets at 61.96 and 62.29 ppm (J= 6.1 and 6.2 Hz). These couplings are due to the phosphorus group. CH_2 carbon of aziridine ring gives signal at 31.92 ppm with the coupling constant of J= 216.9 Hz due to the

phosphorus. Finally, CH_3 carbons of ethoxy groups give signals at 16.33 and 16.39 ppm as singlets. On the ^{31}P NMR, a signal was observed at 22.48 ppm as singlet. HRMS results also support the aziridine structure.

For the characterization of diethyl (1-(1-hydroxybutan-2-yl)aziridin-2-yl)phosphonate (**71**), a COSY spectrum was taken (Figure 6). CH proton of aziridine ring at 2.01 ppm (appeared as a doublet) have the cross-peaks with one of the CH_2 proton of aziridine ring (appeared as a ddd at 1.72 ppm *J*= 2.6, 6.6 and 20.5 Hz). The other cross-peaks of the same proton was observed with the other CH_2 proton (resonated at 1.57 ppm as a triplet, *J*= 7.1 Hz).

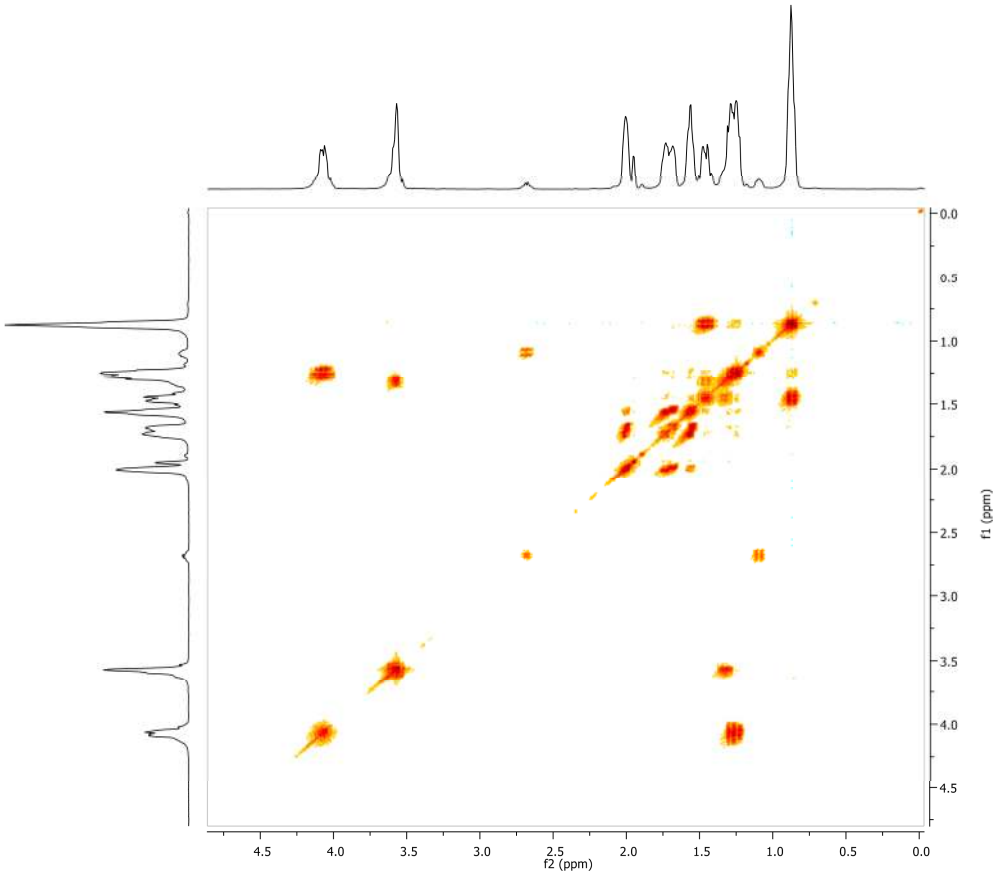
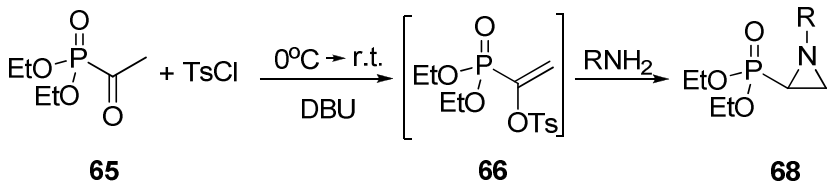


Figure 6. COSY Spectrum of aziridine **71**.

We have also tried to form aziridines starting from aromatic amines, liquid ammonia, hydrazines, and *p*-toluene sulfonamide (PTSA). Unfortunately, none of them formed the desired aziridine. Starting materials were collected. The reason for this result could be the lower nucleophilicity of these amine sources.

2.1.2 One-pot synthesis of aziridine 2-phosphonate

In order to synthesize aziridines by a one-pot reaction without isolating α-tosylated vinyl phosphonate **66** (Scheme 24), acetyl phosphonate **65** was stirred with TsCl and DBU, following that amine was added. In order to increase the yield some optimization studies were carried out as summarized in Table 4. As can be seen from this table, changing the equivalent of TsCl or using the different solvent the yields of aziridines could not be increase to more than 62%.



65 **66** **68**

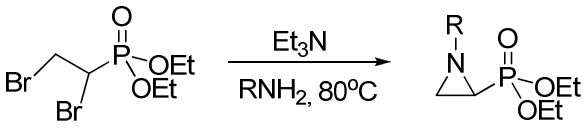
Scheme 24. Synthesis of aziridine 2-phosphonate with single step.

Table 4. One-pot synthesis of aziridine 2-phosphonate.

Entry	Amine (Equiv.)	TsCl (Equiv.)	DBU (Equiv.)	Molarity	Time (h)	Yield (%)
1	BenzylAmine	1.1 TsCl	1.1	1.0(DCM)	67	39.0
2	BenzylAmine	1.1 TsCl	2.0	1.0(DCM)	67	62.0
3	BenzylAmine	1.1 TsCl	2.0	0.5(DCM)	73	40.0
4	BenzylAmine	1.1MsCl	2.0	0.5(DCM)	73	13.0
5	BenzylAmine	1.1 TsCl	2.0	1.0($CHCl_3$)	70	49.2
6	BenzylAmine	1.5 TsCl	2.0	1.0(THF)	25	49.5

2.1.3 Synthesis of aziridines starting from 1,2-dibromoethyl phosphonate via Gabriel-Cromwell reaction

For the synthesis of aziridine 2-phosphonates **68**, Gabriel-Cromwell reaction was used. 1,2 dibromoethyl phosphonate **76** in acetonitrile was mixed with triethyl amine for β-elimination of HBr. Then reaction with different primary amines gave desired aziridinyl phosphonates in good yields (Scheme 25).



76 **68**

Scheme 25. Synthesis of aziridine-2-phosphonates **68**.

The proposed mechanism of Gabriel-Cromwell reaction takes place in 5 steps starting from α,β-unsaturated carbonyl compound (Figure 7). First step is the bromination of unsaturated group. Second step is β-elimination of HBr by

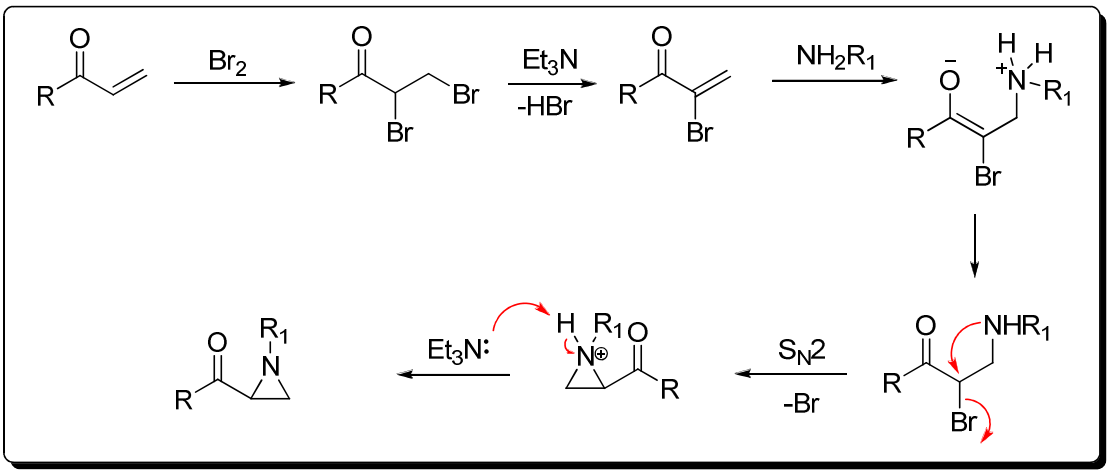
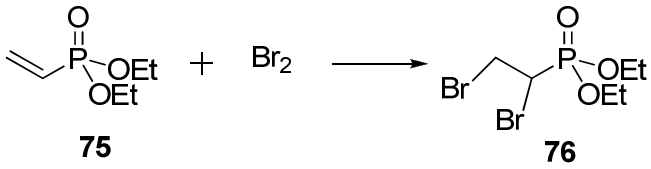


Figure 7. Mechanism of Gabriel-Cromwell reaction.

triethylamine. Third step is 1,4-addition of primary amine followed by α-protonation. Fourth step is ring closure by S_N2 displacement of bromide. Fifth step is the deprotonation of aziridine nitrogen to form aziridine-2-carboxylate.

2.1.3.1 Synthesis of starting material 1,2-dibromoethyl phosphonate

With the aim of synthesizing 1,2-dibromoethyl phosphonate **76**, commercially available diethyl vinylphosphonate **75** was dissolved in CH_2Cl_2 and the reaction mixture was cooled to 0°C. Bromine was added to this solution (Scheme 26). After the reaction was judged to be completed by TLC, the crude product was purified by flash chromatography using silica gel.

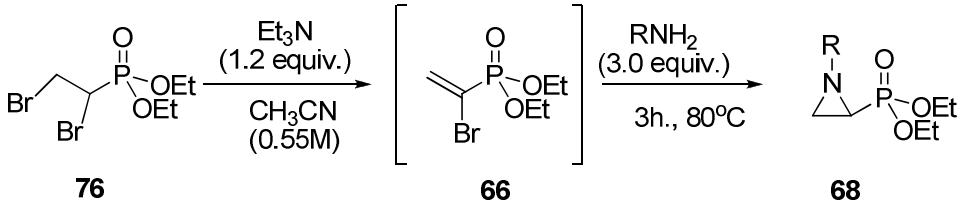


75 **76**

Scheme 26. Synthesis of 1,2-dibromoethylphosphonate **76**.

2.1.3.2 Synthesis of aziridine derivatives

1,2-Dibromoethylphosphonate **76** was treated with NEt_3 to form α-bromovinyl phosphonate. Without isolating this compound, primary amine was added to the same reaction flask to yield desired aziridine **68** (Scheme 27). The results of aziridine synthesis were summarized in Table 5.



Scheme 27. Synthesis of aziridine derivatives **68**.

Table 5. Synthesis of aziridine 2-phosphonates starting from diethyl 1,2-dibromoethylphosphonate (**76**).

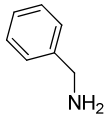
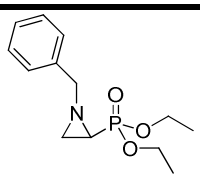
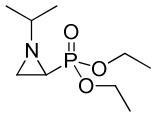
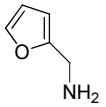
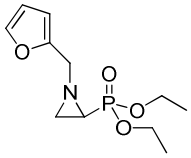
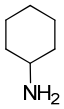
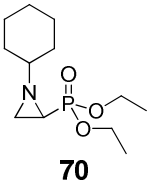
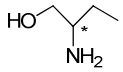
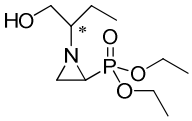
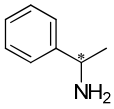
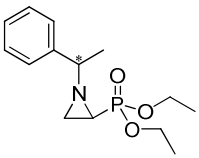
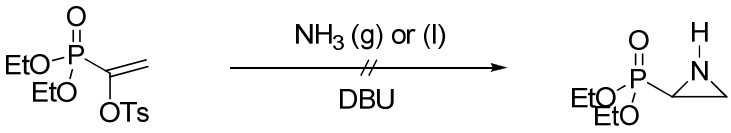
Amine	Product	Yield (%)
	 **67**	**85.4**
	 **68**	**79.3**
	 **69**	**73.4**
	 **70**	**95.9**

Table 5. Continued

Amine	Product	Yield (%)
	 **71**,**72**	**90.9**
	 **73**,**74**	**71.4**

2.1.4 Synthesis of *N*-H aziridine 2-phosphonate by benzyl cleavage

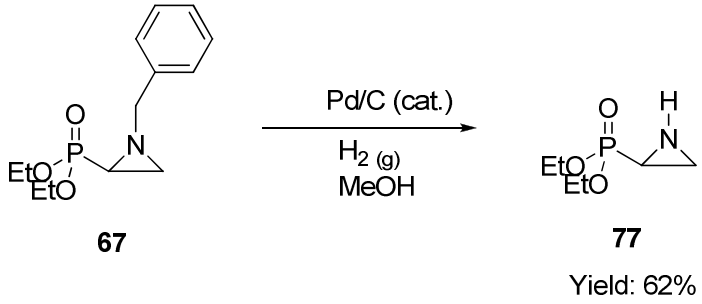
In order to synthesis of *N*-H aziridine 2-phosphonate **77**, first we tried our method. Treatment of α-tosylated vinyl phosphonate **66** with liquid ammonia in the presence of DBU didn't form the expected product, starting material was recovered (Scheme 28).



66 **77**

Scheme 28. Synthetic approach of *N*-H aziridine 2-phosphonate **77**.

Therefore we used initially synthesized *N*-benzyl substituted aziridine. Cleavage of benzyl group from aziridine nitrogen by Pd/C-catalyzed hydrogenolysis gave desired *N*-H aziridine.



67 **77**

Yield: 62%

Scheme 29. Synthesis of *N*-H aziridine-2-phosphonate **77** with Pd/C catalyst.

2.1.5 Comparision of two methods

The results of our method and classical Gabriel-Cromwell reaction are summarized in Table 5. The main difference between the two methods is the starting material. Our method starts with easily available acetyl phosphonate. The other method starts with vinyl phosphonate which is difficult to synthesize and expensive. In terms of yields, our method forms the products in better yields for isopropyl amine, furfuryl amine, and methylbenzyl amine. The other method forms the product in better yields for cyclohexyl amine and 2-amino-1-butanol. When we look at the reaction times our method requires 24-48 h. but the other method requires only 3h.

Table 6. Comparison of aziridine synthesis methods.

	Aziridines from α-tosyl vinyl phosphonates					Aziridines from 1,2-dibromoethylphosphonate				
Amine	**Amine (equiv.)**	**DBU (equiv.)**	**Molarity (Solvent)**	**Time (h.)**	**Yield (%)**	**Amine (equiv.)**	**NEt_3 (equiv.)**	**Molarity (Solvent)**	**Time (h.)**	**Yield (%)**
Benzyl Amine	1.4	1.0	No solvent	24	***87.5***	3.0	1.2	0.55 (CH_3CN)	3.0	***85.4***
Isopropyl Amine	1.4	1.0	No solvent	24	***88.4***	3.0	1.2	0.55 (CH_3CN)	3.0	***79.3***
Furfuryl Amine	2.0	1.0	1.0 (CH_3CN)	48	***92.0***	3.0	1.2	0.55 (CH_3CN)	3.0	***73.4***
Cyclohexyl Amine	1.4	1.0	No solvent	24	***88.9***	3.0	1.2	0.55 (CH_3CN)	3.0	***95.9***
2-Amino-1-Butanol	2.0	1.0	1.0 (CH_3CN)	72	***70.2***	3.0	1.2	0.55 (CH_3CN)	3.0	***90.9***
MethylBenzyl Amine	2.0	1.0	1.0 (CH_3CN)	72	***82.0***	3.0	1.2	0.55 (CH_3CN)	3.0	***71.4***

2.1.6 The antibacterial activities of the compounds

After synthesizing the aziridines, biological activities were tested against different bacteria. The antibacterial activities of aziridine 2-phosphonates **67**, **68**, **69**, **70**, **71**, **72**, **73**, **74**, **77** were tested by performing disc diffusion assays [54]. *Bacillus subtilis, Escherichia coli DH5α, isolate Fs48 (Gordonia spp), Fs30 (Brevundimonas spp), Fs24 (Kocuria spp)* were grown in nutrient broth (Merck, Germany) 24 hours at 28 ºC. Fs48, 30 and 24 were isolated from freshwater fish surface mucus and identified at genus level with 16s ribosomal DNA sequencing. The 100 μL volumes from liquid cultures were spreaded onto nutrient agar in plates (Merck, Germany).

A 100 µL volume from each aziridine 2-phosphonate was dissolved in 400 µl 25% DMSO (DMSO final concentration was 20%). 50 µL volumes from DMSO dissolved aziridine 2-phosphonate were incorporated in sterile disc filters. The discs contained aziridine 2-phosphonates and only 25% DMSO (control) were introduced into the middle of the bacteria inoculated agar surfaces in petri plates. The cultures were incubated 24 hours at 28 ºC. Each aziridine 2-phosphonate type was tested in triplicates for each of the five bacteria. The diameters of growth inhibition zones were measured and expressed in mm ± standard deviation in Table 7.

Table 7. Antibacterial activities of aziridines tested against 5 bacteria.

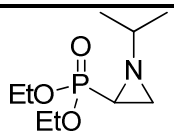
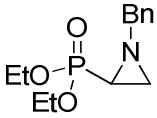
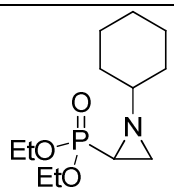
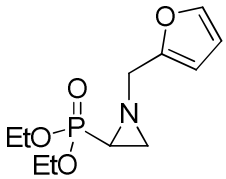
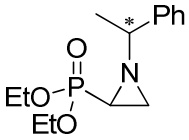
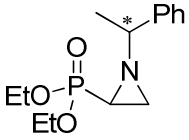
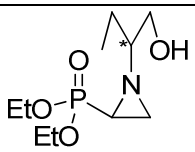
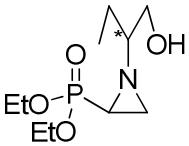
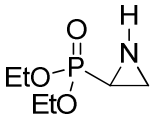
AZIRIDINES	Inhibition zone diameters (mm)				
	Bacillus subtilis	Escherichia coli	Fs48 Gordonia spp	Fs30 Brevundimonas spp	Fs24 Kocuria spp
 **68**	19.33 ±1.15	9.00 ±0.00	15.66 ±3.78	16.00 ±3.60	19.00 ±2.64
 **67**	10.00 ±0.00	8.00 ±0.00	13.00 ±0.00	13.66 ±1.15	18.00 ±1.73
 **70**	9.66 ±0.57	10.00 ±0.00	23.33 ±2.88	14.33 ±0.57	18.33 ±2.88
 **69**	10.33 ±0.57	13.33 ±0.88	14.66 ±0.57	15.00 ±0.00	14.66 ±0.57

Table 7. Continued

AZIRIDINES	Inhibition zone diameters (mm)				
	Bacillus subtilis	Escherichia coli	Fs48 Gordonia spp	Fs30 Brevundimonas spp	Fs24 Kocuria spp
 **73**	11.66 ±1.15	12.00 ±0.00	16.33 ±1.51	13.33 ±0.57	19.00 ±1.00
 **74**	10.00 ±0.00	13.00 ±1.00	13.33 ±1.15	13.66 ±1.15	12.00 ±2.00
 **71**	11.00 ±2.00	10.66 ±1.15	11.00 ±1.41	20.00 ±0.00	25.00 ±0.00
 **72**	17.00 ±0.00	20.00 ±0.00	15.33 ±4.61	13.00 ±3.46	18.66 ±1.51
 **77**	11.33 ±2.30	11.33 ±2.30	11.66 ±2.88	12.33 ±2.51	12.33 ±2.51

As can be seen from Table 7, *N*-isopropyl substituted aziridine **68** showed high activity against *Bacillus subtilis* and *Fs24 Kocuria spp*. *N*-benzyl substituted aziridines **67** and *N*-cyclohexyl substituted aziridines **70** showed high activity against *Fs24 Kocuria spp*. *N*-furfuryl substituted aziridines **69** showed similar activities against all five bacteria. In the case of *N*-(1-phenylethyl) substituted aziridine diastereomers **73** and **74**, diastereomer **73** showed high activity against *Fs24 Kocuria spp*., other diastereomer **74** showed similar activities against all five bacteria. When

we look at the other diastereomeric aziridines **71** and **72**, diastereomer **71** showed the highest activity against *Fs30 Brevundimonas spp* and Fs24 Kocuria spp., the other diastereomer **72** showed the highest activitiy against *Escherichia coli* and *Fs24 Kocuria spp.* Finally; *N*-H substituted aziridine **77** showed similar activities against all five bacteria.

CHAPTER 3

CONCLUSION

As a result, we developed a new method for the synthesis of aziridine 2-phosphonates and synthesized seven different *N*-substituted aziridine derivatives. Two of these aziridines are chiral. The method developed in this study starts with easily available acetyl phosphonate. Conversion of this compound to α-tosylated vinyl phopsphonate was easily achieved by treatment with DBU and tosyl chloride. Reaction of this compound with primary amines gave desired aziridines in 70-92% yield.

We have also used classical Gabriel-Cromwell reaction for the synthesis of same aziridines that were obtained in 71-96% yield. Initially this method was used only for the synthesis of *N*-H aziridinyl phosphonate. When two methods are compared, our method starts from the easily available compound, starting material (vinyl phosphonate) of Gabriel-Cromwell reaction on the other hand is difficult to synthesize and highly expensive. In terms of yields, both methods gave similar results. The main advantage of Gabriel-Cromwell reaction is the time, reactions are finished in 3 h.

The antibacterial activities of synthesized aziridines were tested for the first time in this study by performing disc diffusion assays in collaboration with Biology Department. These studies showed that aziridine derivatives have different activities against different bacteria. The substituent on the nitrogen has a strong effect on the activity. The stereochemistry is also important, diasteromers **71**, **72** and **73**, **74**

showed different activity against bacteria. Especially for the diastereomers **73** and **74**, there is a significant difference in terms of antibacterial activity.

CHAPTER 4

EXPERIMENTAL

4.1 Instrumentation

Following instruments and materials were used for the purification and characterization of products during the study.

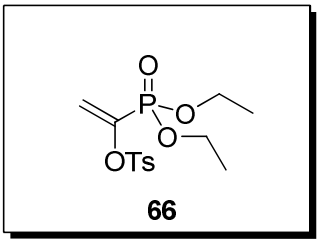
^{1}H, ^{13}C and ^{31}P NMR spectra were obtained in $CDCl_3$-CCl_4 (1:1) solvent system, recorded in a Brucker Spectrospin Avance DPX-400 Ultra shield instrument at 400 MHz, 100 MHz and 162 MHz respectively. The ^{1}H NMR data reported as chemical shifts (δ, ppm) relative to tetramethylsilane (δ 0.00), peak multiplicity (abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad) and coupling constants in Hertz integrated number of protons. In ^{13}C NMR, the chemical shifts were reported relative to $CDCl_3$ triplet centered at 77.0 ppm. IR spectra are reported in reciprocal centimeters (cm^{-1}). High resolution mass data were obtained using electron impact (EI) ionization.

Optical rotations were measured in a 1 dm cell using a Rudolph Research Analytical Autopol III, automatic polarimeter at specified temperatures.

Flash chromatography was performed using E. Merck silica gel 60 (particle size: 0.040-0.063 mm, 230-400 mesh ASTM). Reactions were monitored by TLC using 250 µm Silica Gel 60 F_{254} plates and visualized by UV-light at 254 nm. Phosphomolybdic acid in ethanol and ninhydrin was used for TLC dye. The relative portions of solvents are in volume:volume ratio used in column chromatography as eluent.

4.2 Synthesis and Characterization of Compounds

4.2.1 Synthesis and Characterization of 1-(diethoxyphosphoryl) vinyl 4-methylbenzenesulfonate (**66**)

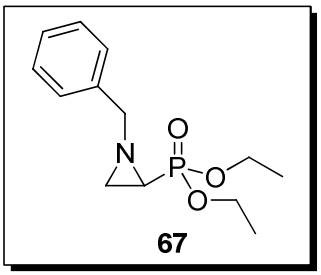


66

To a dry two-necked round bottom flask with a magnetic stir bar under N_2 atmospher, diethyl acetylphosphonate (100 µL, 0.616 mmol) and 4-methylbenzene-1-sulfonyl chloride (176 mg, 0.924 mmol, 1.5 equiv.) in CH_3CN (2.7 ml) was added. The reaction flask was cooled to 0^oC in an ice-water bath. Then, 1,8-diazabicyclo[5.4.0]undec-7-ene (141 µL, 0.924 mmol, 1.5 equiv.) was slowly added. The resulting mixture was stirred at room temperature for 3 hours. At the end of this time, extraction was done with water and CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash column chromatography on silica gel (EtOAc, R_f = 0.69) to yield 1-(diethoxyphosphoryl) vinyl 4-methylbenzenesulfonate (**66**) (179 mg, 0.535 mmol, 87 % yield) as a light yellow solid. ^{1}H NMR δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 5.89 (ddd, *J* = 12.8, 11.8, 2.6 Hz, 2H), 4.10–3.84 (m, 4H), 2.41 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR δ 147.21 (Ar), 144.95 (Ar), 133.43 (CH_2CP), 129.64 (Ar), 128.44 (Ar), 118.98 (d, J_{P-C} = 23.16 Hz), 62.86 (CH_2CH_3), 62.81 (CH_2CH_3), 21.64 (CH_3Ar), 16.18 (CH_3CH_2), 16.12 (CH_3CH_2).^{31}P NMR δ 5.238. HRMS-EI (m/z): calcd for $C_{13}H_{19}O_6PSNa$ ($M+Na^+$): 357.0538; found: 357.0527.

4.2.2 Synthesis of aziridin-2-ylphosphonate by modified Gabriel-Cromwell reaction

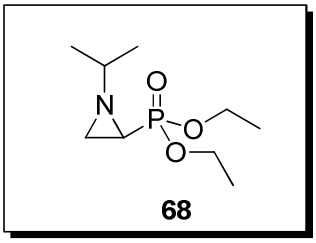
4.2.2.1 Synthesis and Characterization of diethyl 1-benzylaziridin-2-ylphosphonate (**67**)



67

A mixture of 1-(diethoxyphosphoryl)vinyl 4-methylbenzenesulfonate (**66**, 278 mg, 0.83 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (127 µL, 0.83 mmol, 1.0 equiv.) was stirred at room temperature. Then benzylamine (127 µL, 1.16 mmol, 1.4 equiv.) was added and the resulting mixture was stirred at room temperature for 24 hours. The crude product was purified by silica gel chromatography (EtOAc, R_f = 0.1) to yield diethyl 1-benzylaziridin-2-ylphosphonate (195 mg, 0,723 mmol, 87 % yield) as a colorless oil. ^{1}H NMR δ 7.40–7.07 (m, 5H), 4.14–3.71 (m, 4H), 3.55 (d, *J* = 13.0 Hz, 1H), 3.24 (d, *J* = 13.0 Hz, 1H), 2.12 (dd, *J* = 9.2, 3.5 Hz, 1H), 1.77–1.39 (m, 2H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR δ 137.78 (CH), 128.38 (CH), 128.28 (CH), 127.34 (CH), 65.27 (d, *J* = 7.3 Hz, CH_2Ph), 62.29 (d, J = 6.2 Hz, CH_2CH_3), 61.96 (d, *J* = 6.1 Hz, CH_2CH_3), 31.92 (d, *J* = 5.3 Hz, CH_2N), 31.71 (d, J_{P-C} = 216.9 Hz, PCH), 16.39 (CH_3), 16.33 (CH_3). ^{31}P NMR δ 22.48 . IR (neat, cm^{-1}) 3062, 2981, 2930, 2906, 1454, 1019, 766. HRMS-EI (m/z): calcd for $C_{13}H_{21}NO_3P$ ($M+H^+$): 270.1259; found: 270.1254.

4.2.2.2 Synthesis and Characterization of diethyl 1-isopropylaziridin-2-ylphosphonate (**68**)

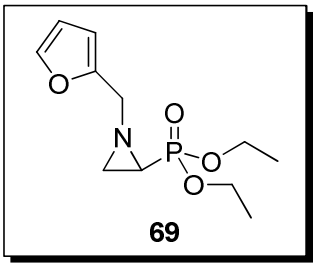


68

A mixture of 1-(diethoxyphosphoryl)vinyl 4-methylbenzenesulfonate (**66**, 282 mg, 0.843 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (128.7 µL, 0.843 mmol, 1.0 equiv.) was stirred at room temperature. Then isopropylamine (100.6 µL, 1.181

mmol, 1.4 equiv.) was added and the resulting mixture was stirred at room temperature for 24 hours. The crude product was purified by silica gel chromatography (EtOAc, R_f = 0.14) to yield diethyl 1-isopropylaziridin-2-ylphosphonate (165 mg, 0.746 mmol, 88.4 % yield) as a colorless oil. ^{1}H NMR δ 4.17–3.94 (m, 4H), 2.00 (ddd, *J* = 8.9, 3.5, 1.0 Hz, 1H), 1.45 (td, *J* = 7.1, 1.1 Hz, 1H), 1.41–1.32 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 6H), 1.10 (d, *J* = 8.9 Hz, 3H), 1.08 (d, *J* = 8.9 Hz, 3H). ^{13}C NMR δ 62.36 (d, *J* = 7.1 Hz, $CH(CH_3)_2$), 62.18 (d, *J* = 6.4 Hz, CH_2CH_3), 61.67 (d, *J* = 6.3 Hz, CH_2CH_3), 31.36 (d, J_{P-C} = 219.3 Hz, PCH), 31.07 (d, *J* = 5.2 Hz, CH_2N), 21.87 (C), 16.36 (CH_3), 16.30 (CH_3), 16.23 (CH_3). ^{31}P NMR δ 23.11. IR(neat, cm^{-1}) 3345, 2970, 2931, 2874, 1370, 1234, 1024, 970. HRMS-EI (m/z): calcd for $C_9H_{21}NO_3P$ ($M+H^+$): 222.1259; found: 222.1251.

4.2.2.3 Synthesis and Characterization of diethyl 1-(furan-2-ylmethyl)aziridin-2-ylphosphonate (**69**)

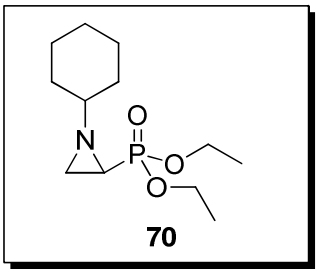


69

A mixture of 1-(diethoxyphosphoryl)vinyl 4-methylbenzenesulfonate (**66**, 887 mg, 2.65 mmol) in CH_3CN (0.9 ml) and 1,8-diazabicyclo[5.4.0]undec-7-ene (397 µL, 2.65 mmol, 1.0 equiv.) was stirred at room temperature. Then furfurylamine (469 µL, 5.30 mmol, 2.0 equiv.) was added and the resulting mixture was stirred at room temperature for 24 hours. The crude product was purified by silica gel chromatography (EtOAc, R_f = 0.24) to yield diethyl 1-(furan-2-ylmethyl)aziridin-2-ylphosphonate (642 mg, 2.47 mmol, 93 % yield) as a colorless oil. ^{1}H NMR δ 7.29 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.25 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.21 (d, *J* = 3.2 Hz, 1H), 4.07–3.92 (m, 4H), 3.62 (d, *J* = 13.9 Hz, 1H), 3.29 (d, *J* = 13.9 Hz, 1H), 2.09 (ddd, *J* = 9.2, 3.2, 1.2 Hz, 1H), 1.70–1.56 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR δ 151.22 (OCCH), 142.09 (OCHCH), 110.25 (CHCO), 108.35 (CHCHO), 62.33 (d, *J* = 6.2 Hz, CH_2CH_3), 62.01 (d, *J* = 6.1 Hz, CH_2CH_3), 56.27 (d, *J* = 7.5 Hz, CH_2CCH), 31.23 (d, *J* = 5.4 Hz, CH_2CHP), 31.03 (d, J_{P-C}= 216.7 Hz), 16.43 (CH_3), 16.37 (CH_3). ^{31}P NMR

δ 22.40. IR(neat, cm^{-1}) 3113, 2983, 2931, 2908, 1505, 1243, 1017, 796. HRMS-EI (m/z): calcd for $C_{11}H_{19}NO_4P$ ($M+H^+$): 260.1052; found: 260.1058.

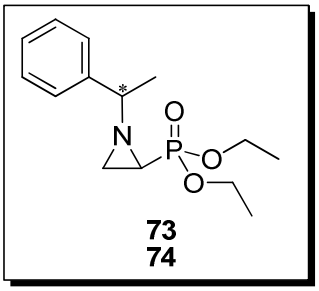
4.2.2.4 Synthesis and Characterization of diethyl 1-cyclohexylaziridin-2-ylphosphonate (**70**)



70

A mixture of 1-(diethoxyphosphoryl)vinyl 4-methylbenzenesulfonate (**66**, 302 g, 0.903 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (135 µL, 0.903 mmol, 1.0 equiv.) was stirred at room temperature. Then cyclohexylamine (145 µL, 1.265 mmol, 1.4 equiv.) was added and the resulting mixture was stirred at room temperature for 24 hours. The crude product was purified by silica gel chromatography (EtOAc, R_f = 0.29) to yield diethyl 1-cyclohexylaziridin-2-ylphosphonate (209.8 mg, 0.803 mmol, 88.9 % yield) as a colorless oil.^{1}H NMR δ 4.15–3.99 (m, 4H), 2.04–1.95 (m, 1H), 1.73 (m, 4H), 1.58–1.31 (m, 5H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.21–0.97 (m, 4H). ^{13}C NMR δ 70.08 (d, *J* = 6.7 Hz, CHNCHP), 62.29 (d, *J* = 6.3 Hz, CH_2CH_3), 61.82 (d, *J*= 6.3 Hz, CH_2CH_3), 32.41 (CH_2CHCH_2), 30.78 (d, J_{P-C} = 219.2 Hz, PCH), 30.59 (d, *J* = 5.2 Hz, CH_2NCH), 25.93 (CH_2CH_2CH), 24.46 ($CH_2CH_2CH_2CH$), 16.45 (d, *J*= 6.1 Hz, CH_3CH_2), 16.36 (d, *J*= 6.2 Hz, CH_3CH_2). ^{31}P NMR δ 23.36. IR(neat, cm^{-1}) 2980, 2927, 2854, 1449, 1245, 1022, 961. HRMS-EI (m/z): calcd for $C_{12}H_{25}NO_3P$ ($M+H^+$): 262.1572; found: 262.1569.

4.2.2.5 Synthesis and Characterization of diethyl 1-(1-phenylethyl) aziridin-2-ylphosphonate (**73, 74**)



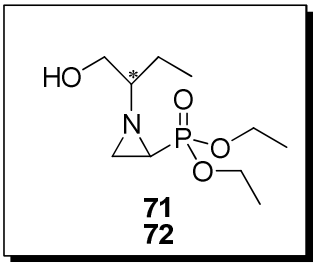
73
74

A mixture of 1-(diethoxyphosphoryl)vinyl 4-methylbenzenesulfonate (**66**, 541 mg, 1.62 mmol) in CH_3CN (0.94 ml) and 1,8-diazabicyclo[5.4.0]undec-7-ene (247 µL, 1.62 mmol, 1.0 equiv.) was stirred at room temperature. Then 1-phenylethanamine (417 µL, 3.24 mmol 2.0 equiv.) was added and the resulting mixture was stirred at room temperature for 24 hours. The crude product was purified by silica gel chromatography (EtOAc, R_f = 0.38) to yield diethyl 1-(1-phenylethyl)aziridin-2-ylphosphonate (**73**) (224.7 mg, 0.796 mmol, 49.2 % yield) as a colorless oil. $[\alpha]_D^{21}$ = +44 (*c*, 0.1, CH_2Cl_2); ^{1}H NMR δ 7.34–7.08 (m, 5H), 4.21–4.01 (m, 4H), 2.35 (q, *J* = 6.5 Hz, 1H), 1.97 (dd, *J* = 8.9, 3.3 Hz, 1H), 1.55 (ddd, *J* = 19.3, 6.8, 3.6 Hz, 1H), 1.45 (t, *J* = 7.0 Hz, 1H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR δ 143.79 (Ph), 128.28 (Ph), 127.14 (Ph), 126.58 (Ph), 70.97 (d, *J* = 7.1 Hz, CHPh), 62.41 (d, *J* = 6.5 Hz, CH_2OP), 62.19 (d, *J* = 6.3 Hz, CH_2OP), 32.59 (d, $J_{P\text{-}C}$ = 218.6 Hz, CHP), 31.53 (d, *J* = 5.2 Hz, CH_2N), 23.54 (CH_3CH), 16.52 (d, $J_{P\text{-}C}$ = 5.7 Hz, CH_3CH_2), 16.46 (d, $J_{P\text{-}C}$ = 5.8 Hz, CH_3CH_2).^{31}P NMR δ 22.76. IR(neat, cm^{-1}) 3060, 2978, 2929, 2906, 1245, 1021, 961. HRMS-EI (m/z): calcd for $C_{14}H_{21}NO_3PNa$ ($M+Na^+$): 306.1235; found: 306.1237.

Diethyl 1-(1-phenylethyl)aziridin-2-ylphosphonate (**74**) was purified (EtOAc, R_f = 0.14) to yield (149.3 mg, 0,529 mmol, 32.6 % yield) as a colorless oil. $[\alpha]_D^{21}$ = +26 (*c*, 0.1, CH_2Cl_2); ^{1}H NMR δ 7.40–7.10 (m, 5H), 3.96–3.54 (m, 4H), 2.32 (q, *J* = 6.5 Hz, 1H), 2.19 (dd, *J* = 9.1, 3.6 Hz, 1H), 1.60 (t, *J* = 7.0 Hz, 1H), 1.52 – 1.42 (m, 1H), 1.40 (d, *J* = 6.6 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR δ 143.21 (Ph), 128.23 (Ph), 127.34 (Ph), 127.13 (Ph), 71.42 (d, *J* = 6.9 Hz, CH_3CH), 62.14 (d, *J* = 6.2 Hz, CH_2CH_3), 61.48 (d, *J* = 6.0 Hz, CH_2CH_3), 31.97 (d, *J* = 5.2 Hz, CH_2N), 31.28 (d, $J_{P\text{-}C}$ = 216.4 Hz, CHP), 22.93 (CH_3CH), 16.30 (CH_3CH_2),

16.23 (CH_3CH_2). ^{31}P NMR δ 21.49. IR(neat, cm^{-1}) 3060, 2978, 2929, 2906, 1246, 1022, 954. HRMS-EI (m/z): calcd for $C_{14}H_{21}NO_3PNa$ ($M+Na^+$): 306.1235; found: 306.1225.

4.2.2.6 Synthesis and Characterization of diethyl (1-(1-hydroxybutan-2-yl)aziridin-2-yl)phosphonate (**71,72**)



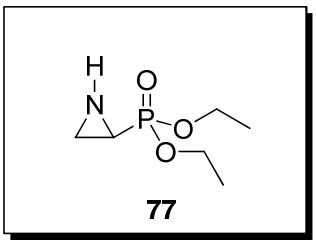
71
72

A mixture of 1-(diethoxyphosphoryl)vinyl 4-methylbenzenesulfonate (**66**, 918 mg, 2.74 mmol) in CH_3Cl_3 (0.9 ml) and 1,8-diazabicyclo[5.4.0]undec-7-ene (419 µL, 2.74 mmol, 1.0 equiv.) was stirred at room temperature. Then 2-aminobutan-1-ol (527 µL, 5.48 mmol 2.0 equiv.) was added and the resulting mixture was stirred at room temperature for 24 hours. The crude product was purified by silica gel chromatography (EtOAc/MeOH=10:1, R_f =0.32) to yield diethyl 1-(1-phenylethyl)aziridin-2-ylphosphonate (**71**) (210 mg, 0.839 mmol, 30.6 % yield) as a colorless oil. $[\alpha]_D^{21}$ = -63 (*c*, 0.1, CH_2Cl_2); ^1H NMR δ 4.20–4.01 (m, 4H), 3.68–3.53 (m, 2H), 3.33 (s, 1H), 2.01 (dd, *J* = 8.9, 3.6 Hz, 1H), 1.72 (ddd, *J* = 20.5, 6.6, 3.6 Hz, 1H), 1.57 (t, *J* = 7.1 Hz, 1H), 1.50–1.42 (m, 2H), 1.37–1.32 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR δ 72.52 (d, *J* = 6.8 Hz, $CHCH_2OH$), 65.52 (CH_2OH), 63.01 (d, *J* = 6.0 Hz, CH_2CH_3), 62.08 (d, *J* = 6.6 Hz, CH_2CH_3), 31.11 (d, J_{P-C} = 218.3 Hz), 29.53 (d, *J* = 5.9 Hz, CH_2N), 24.65 (CH_2CHN), 16.35 (d, *J* = 2.8 Hz, CH_3CH_2O), 16.30 (d, *J* = 2.2 Hz, CH_3CH_2O), 10.47 (CH_3CH_2CH). ^{31}P NMR δ 23.84. IR(neat, cm^{-1}) 3403, 2977, 2933, 2877, 1233, 1019, 965, 795. HRMS-EI (m/z): calcd for $C_{10}H_{23}NO_4P$ ($M+H^+$): 252.1364; found: 252.1359.

Diethyl 1-(1-phenylethyl)aziridin-2-ylphosphonate (**72**) was purified (EtOAc/MeOH=10:1, R_f =0.25) to yield (281 mg, 1.123 mmol, 41.0 % yield) as a colorless oil. $[\alpha]_D^{21}$ = +38 (*c*, 0.1, CH_2Cl_2); ^1H NMR δ 4.15–4.00 (m, 4H), 3.68–3.55

(m, 2H), 2.37 (s, 1H), 2.09 (dd, *J* = 9.1, 3.6 Hz, 1H), 1.67 (t, *J* = 7.1 Hz, 1H), 1.64–1.57 (m, 1H), 1.55–1.43 (m, 2H), 1.37–1.31 (m, 1H), 1.31–1.28 (m, 3H), 1.28–1.24 (m, 3H), 0.89 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR δ 73.08 (d, *J* = 6.7 Hz, $CHCH_2OH$), 63.85 (CH_2OH), 62.52 (d, *J* = 6.4 Hz, CH_2O), 62.00 (d, *J* = 6.3 Hz, CH_2O), 31.34 (CH_2N), 29.73 (d, J_{P-C} = 219.5 Hz), 23.93 (CH_2CHN), 16.45 (d, J_{P-C} = 5.9 Hz, CH3CH2), 16.39 (d, J_{P-C} = 6.1 Hz, CH_3CH_2), 10.26 (CH_3CH_2CH). ^{31}P NMR δ 22.86. IR(neat, cm^{-1}) 3394, 2979, 2931, 2878, 1233, 1019, 964, 795. HRMS-EI (m/z): calcd for $C_{10}H_{23}NO_4P$ ($M+H^+$): 252.1364; found: 252.1354.

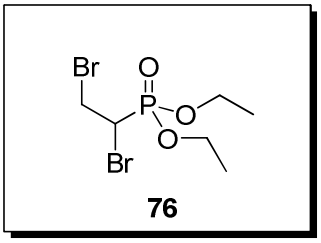
4.2.3 Synthesis and Characterization of diethyl aziridin-2-ylphosphonate with cleavage of diethyl 1-benzylaziridin-2-ylphosphonate (**77**)



77

Diethyl 1-benzylaziridin-2-ylphosphonate (**67**, 50 mg, 0.186 mmol,1 equiv.) and Palladium on Charcoal, (50mg 10% wt.Pd) was dissolved in CH_3OH (0.63ml, 0.3M) under N_2 atmospher. Then H_2 gas inserted to reaction medium. When the reaction was complete according to TLC control, the mixture was filtered through celite and the solvent was removed in vacuum. The crude product purified by silica gel chromatography (EtOAc/MeOH = 4:1) to yield diethyl aziridin-2-ylphosphonate (23 mg, 0.128 mmol, 62.0 % yield) as a colerless oil. ^{1}H NMR δ 4.11–3.91 (m, 4H), 1.89 (d, *J* = 11.1 Hz, 1H), 1.79–1.61 (m, 2H), 1.30–1.15 (m, 6H). ^{13}C NMR δ 62.03 (t, *J* = 5.5 Hz), 22.54 (d, *J* = 2.4 Hz), 21.97 (d, J_{P-C} = 195.6 Hz), 16.38 (CH_3), 16.32 (CH_3). ^{31}P NMR δ 27.15. IR(neat, cm^{-1}) 3450, 3256, 2983, 2909, 1235, 1018, 958. HRMS-EI (m/z): calcd for $C_6H_{15}NO_3P$ ($M+H^+$): 180.0783; found: 180.0789.

4.2.4 Synthesis and Characterization of diethyl 1,2-dibromoethylphosphonate (**76**)

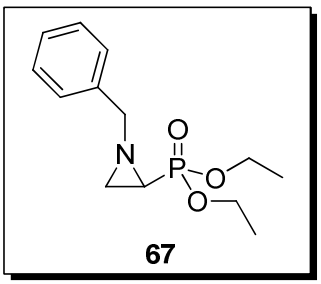


76

Diethyl vinylphosphonate (**75**, 0.2 mL, 1.243 mmol) was added into a pre-dried two necked flask and was dissolved in CH_2Cl_2 (13 mL) and the reaction mixture cooled to 0°C. Br_2 (0.83.1 mL, 1.665 mmol, 1.3 equiv. in 2.4 mL CH_2Cl_2) was added to this solution. After 30 minutes the reaction was judged to be complete by TLC. Then the crude product was purified by silica gel chromatography (EtOAc) to yield of diethyl 1,2-dibromoethylphosphonate (382.8 mg, 1.181 mmol, 95.0% yield) as a light yellow oil. ^{1}H NMR δ 4.26–4.12 (m, 4H), 4.03–3.88 (m, 2H), 3.61–3.48 (m, 1H), 1.33 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR δ 64.01 (d, *J* = 7.0 Hz, CH_2CH_3), 63.70 (d, *J* = 6.9 Hz, CH_2CH_3), 41.88 (d, $J_{P\text{-}C}$ = 150.8 Hz), 31.72 (CH_2Br), 16.37 (CH_3CH_2), 16.32 (CH_3CH_2). ^{31}P NMR δ 15.27.

4.2.5 Synthesis of aziridin-2-ylphosphonate by using Gabriel-Cromwell reaction

4.2.5.1 Synthesis and Characterization of diethyl 1-benzylaziridin-2-ylphosphonate (**67**)

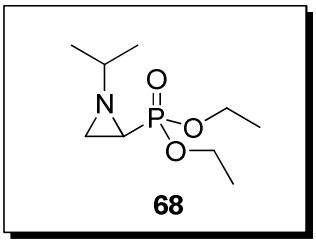


67

Diethyl 1,2-dibromoethylphosphonate (**76**, 329 mg, 1.015 mmol) was weighed into a pre-dried two necked flask and was dissolved in CH_3CN (1.85 mL). NEt_3 (169 µL, 1.219 mmol, 1.2 equiv.) was added at room temperature. After addition of base, white solids observed. Then benzylamine (332.8 µL, 3.047 mmol, 3.0 equiv.) was added and the resulting

mixture was refluxed at 80-85°C for 3 hours. At the end of this time, the reaction mixture was treated with 0.1 N HCl (10 mL) and CH_2Cl_2 (10mL) was added. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography on silica gel (EtOAc, R_f = 0.1) to yield diethyl 1-benzylaziridin-2-ylphosphonate (233.6 mg, 0.867 mmol, 85.4 % yield) as a colorless oil. ^1H and ^{13}C NMR spectra are the same as the one reported for the same compound on page 42.

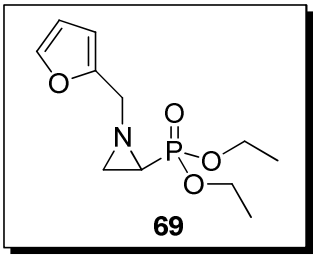
4.2.5.2 Synthesis and characterization of diethyl 1-isopropylaziridin-2-ylphosphonate (**68**)



68

Diethyl 1,2-dibromoethylphosphonate (**76**, 222 mg, 0.685 mmol) was weighed into a pre-dried two necked flask and was dissolved in CH_3CN (1.25 mL). NEt_3 (114 µL, 1.038 mmol, 1.2 equiv.) was added at room temperature. After addition of base, white solids observed. Then isopropylamine (175.1 µL, 2.055 mmol, 3.0 equiv.) was added and the resulting mixture was refluxed at 80-85°C for 3 hours. At the end of this time, the reaction mixture was treated with 0.1 N HCl (10 mL) and CH_2Cl_2 (10mL) was added. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography on silica gel (EtOAc, R_f = 0.14) to yield diethyl 1-isopropylaziridin-2-ylphosphonate (120.2 mg, 0.543 mmol, 79.3 % yield) as a colorless oil. ^1H and ^{13}C NMR spectra are the same as the one reported for the same compound on page 42.

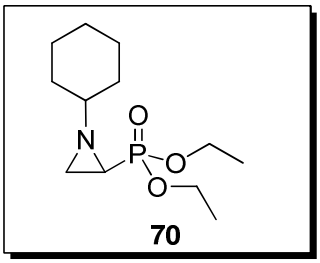
4.2.5.3 Synthesis and Characterization of diethyl 1-(furan-2-ylmethyl)aziridin-2-ylphosphonate (**69**)



69

Diethyl 1,2-dibromoethylphosphonate (**76**, 310 mg, 0.957 mmol) was weighed into a pre-dried two necked flask and was dissolved in CH_3CN (1.73 mL). NEt_3 (159.2 µL, 1.148 mmol, 1.2 equiv.) was added at room temperature. After addition of base, white solids observed. Then furfurylamine (271 µL, 2.871 mmol, 3.0 equiv.) was added and the resulting mixture was refluxed at 80-85°C for 3 hours. At the end of this time, the reaction mixture was treated with 0.1 N HCl (10 mL) and CH_2Cl_2 (10mL) was added. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography on silica gel (EtOAc, R_f = 0.24) to yield diethyl 1-(furan-2-ylmethyl)aziridin-2-ylphosphonate (182 mg, 0.702 mmol, 73.4 % yield) as a colorless oil. ^1H and ^{13}C NMR data are the same as the one reported for the same compound on page 43

4.2.5.4 Synthesis and Characterization of diethyl 1-cyclohexylaziridin-2-ylphosphonate (**70**)

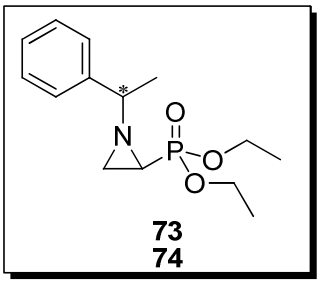


70

Diethyl 1,2-dibromoethylphosphonate (**76**, 332 mg, 1.025 mmol) was weighed into a pre-dried two necked flask and was dissolved in CH_3CN (1.86 mL). NEt_3 (170.5 µL, 1.23 mmol, 1.2 equiv.) was added at room temperature. After addition of base, white solids observed. Then cyclohexylamine (352.5 µL, 3.075 mmol, 3.0 equiv.) was added and the resulting mixture was refluxed at 80-85°C for 3 hours. At the end of this time, the

reaction mixture was treated with 0.1 N HCl (10 mL) and CH_2Cl_2 (10mL) was added. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography on silica gel (EtOAc, R_f = 0.29) to yield diethyl 1-cyclohexylaziridin-2-ylphosphonate (256.9 mg, 0.983 mmol, 95.9 % yield) as a colorless oil. ^1H and ^{13}C NMR data are the same as the one reported for the same compound on page 44.

4.2.5.5 Synthesis and Characterization of diethyl 1-(1-phenylethyl)aziridin-2-ylphosphonate (**73,74**)

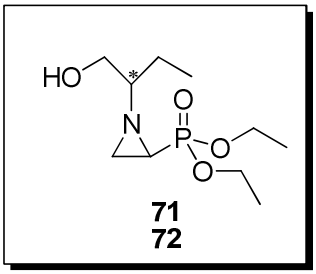


73
74

Diethyl 1,2-dibromoethylphosphonate (**76**, 323.3 mg, 0.998 mmol) was weighed into a pre-dried two necked flask and was dissolved in CH_3CN (1.87 mL). NEt_3 (166 µL, 1.197 mmol, 1.2 equiv.) was added at room temperature. After addition of base, white solids observed. Then 1-phenylethanamine (381.9 µL, 2.99 mmol, 3.0 equiv.) was added and the resulting mixture was refluxed at 80-85°C for 3 hours. At the end of this time, the reaction mixture was treated with 0.1 N HCl (10 mL) and CH_2Cl_2 (10mL) was added. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography on silica gel (EtOAc, R_f = 0.38) to yield diethyl 1-(1-phenylethyl)aziridin-2-ylphosphonate (**73**) (103.6 mg, 0.367 mmol, 36.8% yield) as a colorless oil. ^1H and ^{13}C NMR data are the same as the one reported for the same compound on page 45.

Diethyl 1-(1-phenylethyl)aziridin-2-ylphosphonate (**74**) was purified (EtOAc, R*f* = 0.14) to yield (99.2 mg, 0.351 mmol, 35.2% yield) as a colorless oil. ^1H, ^{13}C, ^{31}P NMR, IR(neat, cm^{-1}) and HRMS-EI results were given at page 45.

4.2.5.6 Synthesis and Characterization of diethyl (1-(1-hydroxybutan-2-yl)aziridin-2-yl)phosphonate (**71,72**)



71
72

Diethyl 1,2-dibromoethylphosphonate (**76**, 333.8 mg, 1.030 mmol) was weighed into a pre-dried two necked flask and was dissolved in CH_3CN (1.87 mL). NEt_3 (171.4 µL, 1.236 mmol, 1.2 equiv.) was added at room temperature. After addition of base, white solids observed. Then 2-aminobutan-1-ol (297 µL, 3.091 mmol, 3.0 equiv.) was added and the resulting mixture was refluxed at 80-85°C for 3 hours. At the end of this time, the reaction mixture concentrated under reduced pressure, and purified by flash column chromatography on silica gel (EtOAc/MeOH=10:1, R_f =0.32) to yield diethyl (1-(1-hydroxybutan-2-yl)aziridin-2-yl)phosphonate (**71**) (131.1 mg, 0.521 mmol, 50.6 % yield) as a colorless oil. ^1H and ^{13}C NMR data are the same as the one reported for the same compound on page 46.

Diethyl (1-(1-hydroxybutan-2-yl)aziridin-2-yl)phosphonate (**72**) was purified by flash column chromatography on silica gel (EtOAc/MeOH=10:1, R*f* =0.25) to yield (104.3 mg, 0.415 mmol, 40.3 % yield) as a colorless oil. ^1H and ^{13}C NMR data are the same as the one reported for the same compound on page 46.

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APPENDIX A

NMR SPECTRUMS

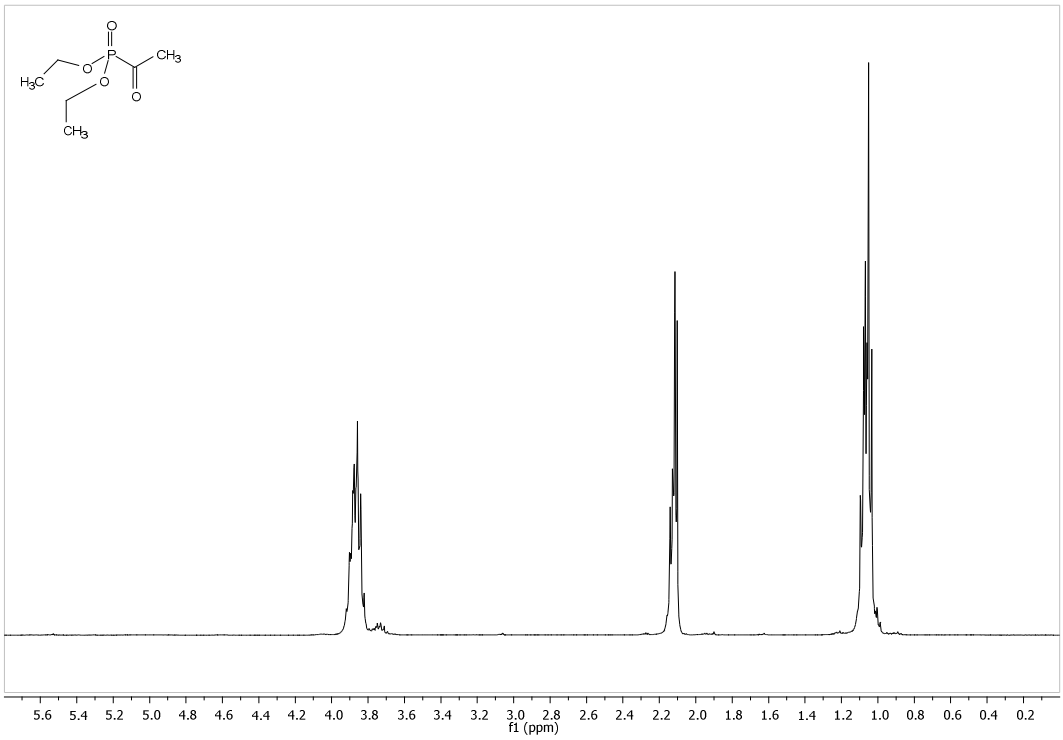

Figure A. 1. ^{1}H NMR spectrum of compound **65.**

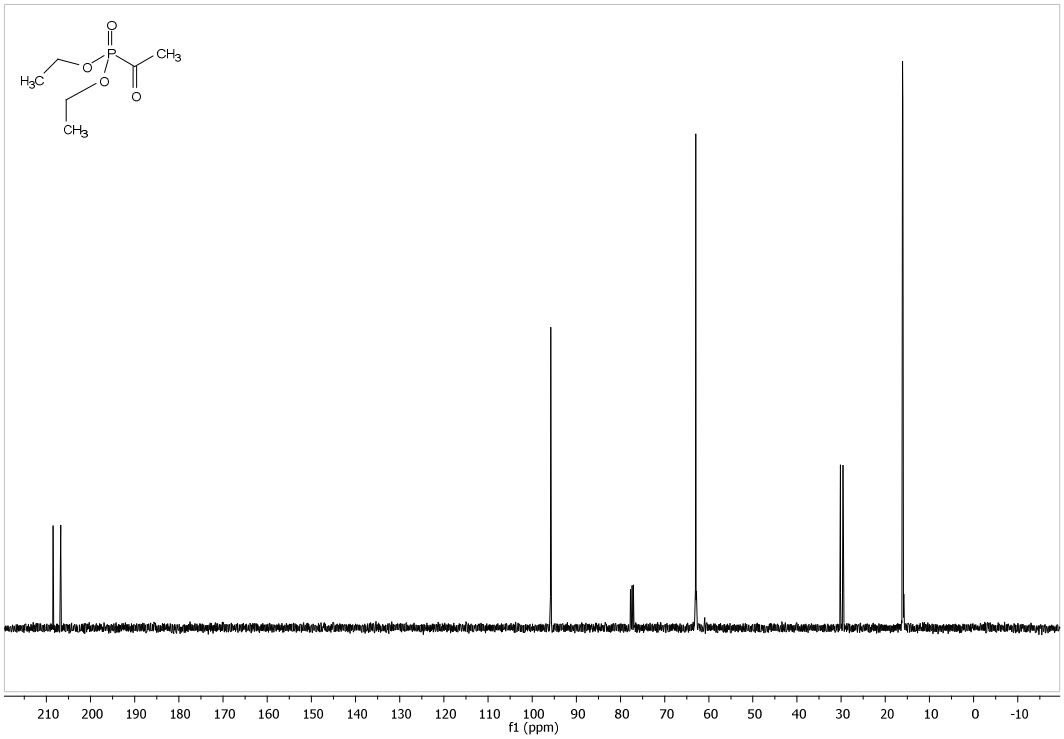

Figure A. 2. ^{13}C NMR spectrum of compound **65.**

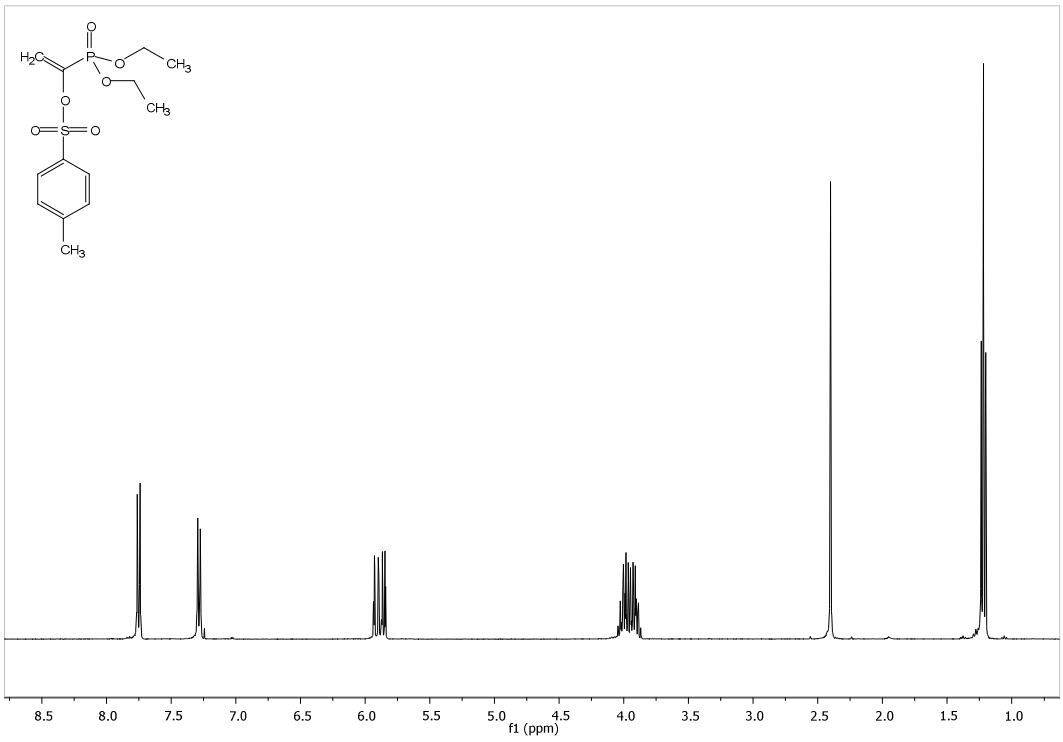

Figure A. 3. ^{1}H NMR spectrum of compound **66.**

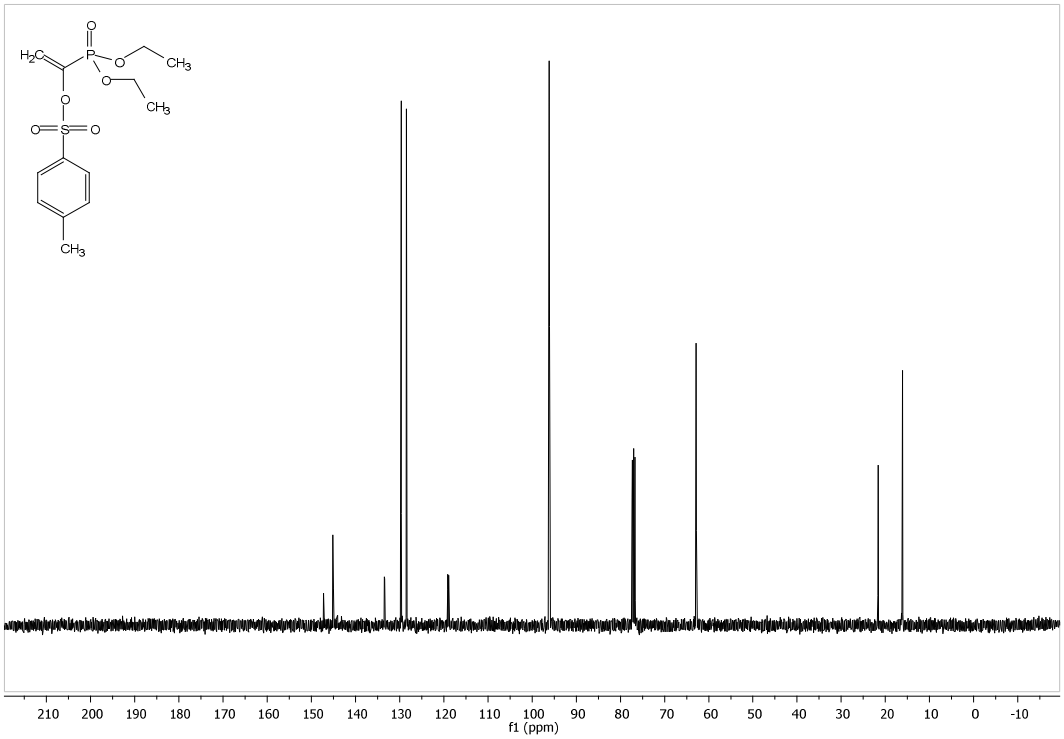

Figure A. 4. ^{13}C NMR spectrum of compound **66.**

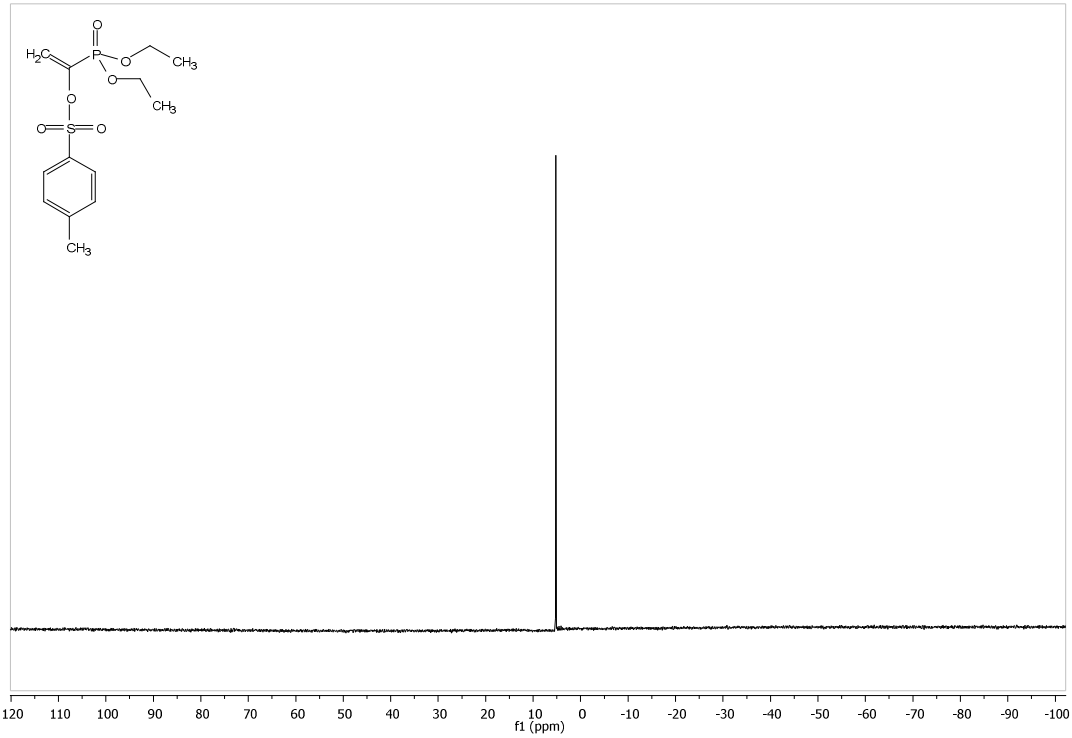

Figure A. 5. ^{31}P NMR spectrum of compound **66.**

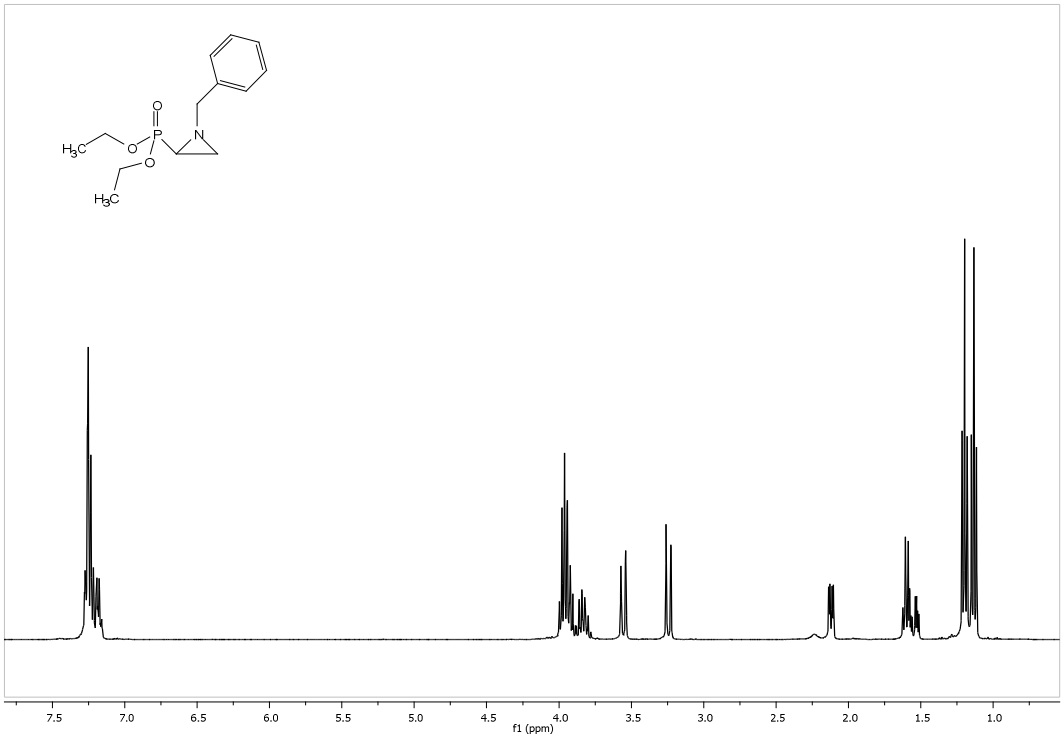

Figure A. 6. ^{1}H NMR spectrum of compound **67.**

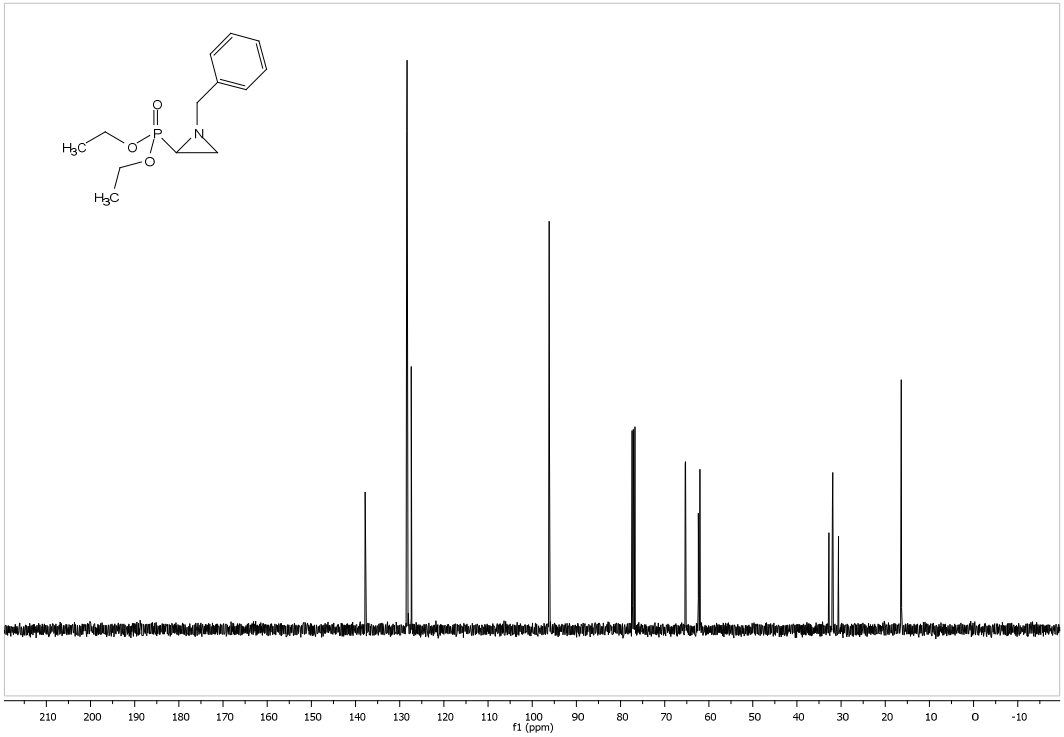

Figure A. 7. ^{13}C NMR spectrum of compound **67.**

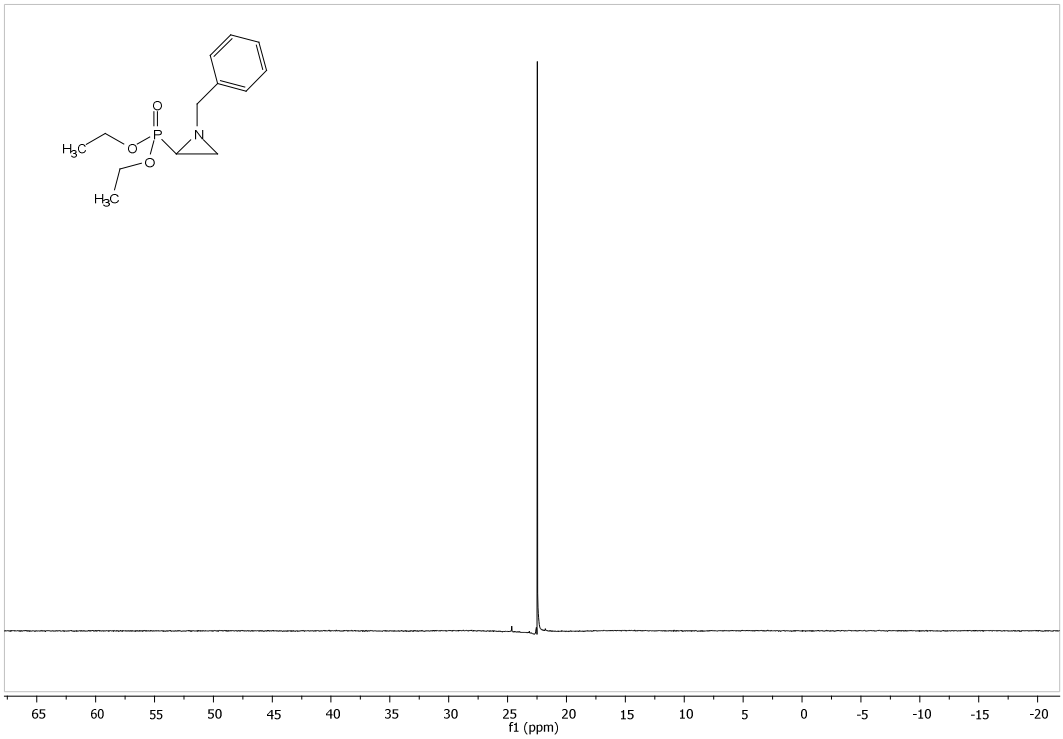

Figure A. 8. ^{31}P NMR spectrum of compound **67.**

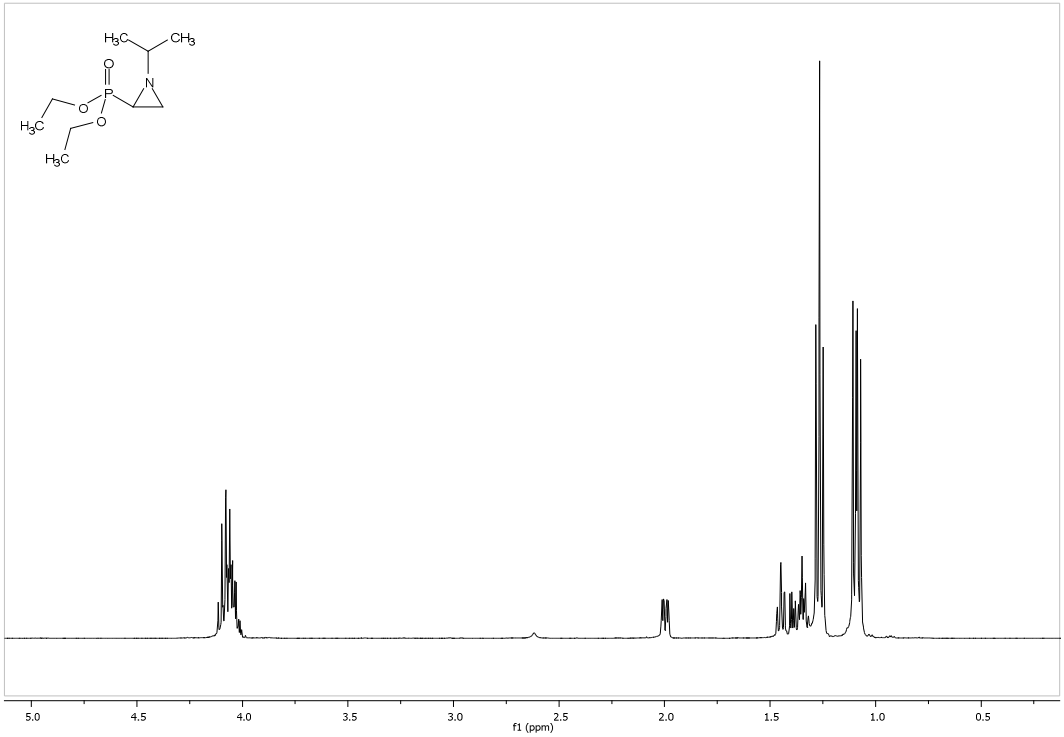

Figure A. 9. ^{1}H NMR spectrum of compound **68.**

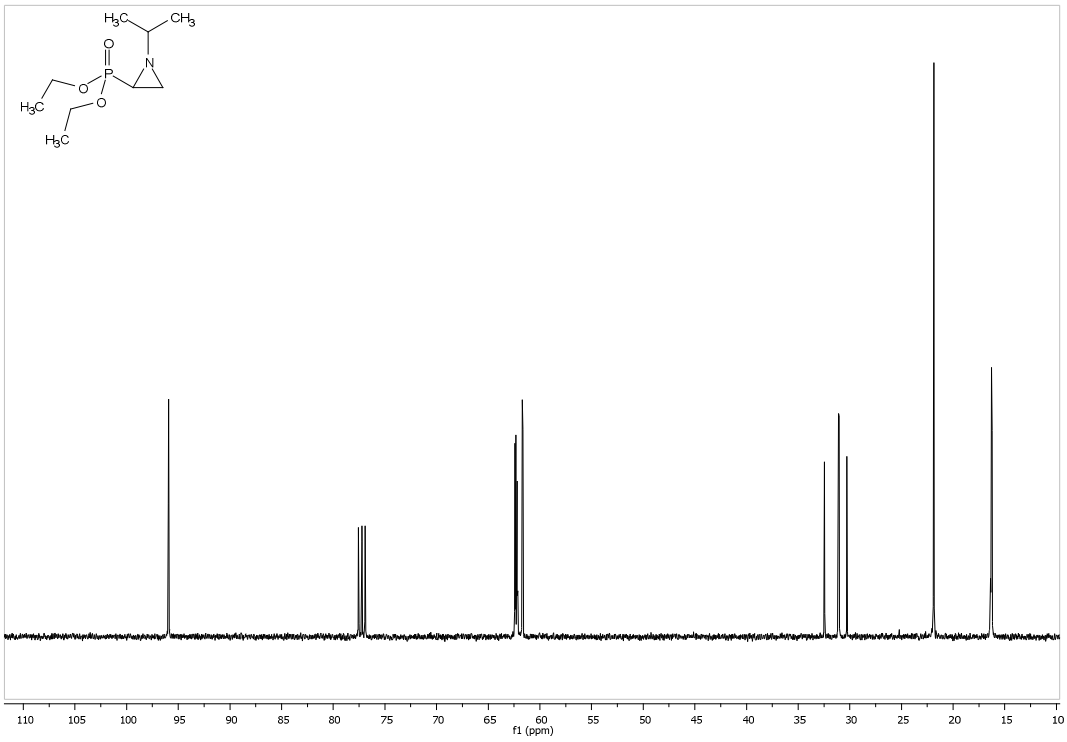

Figure A. 10. ^{13}C NMR spectrum of compound **68.**

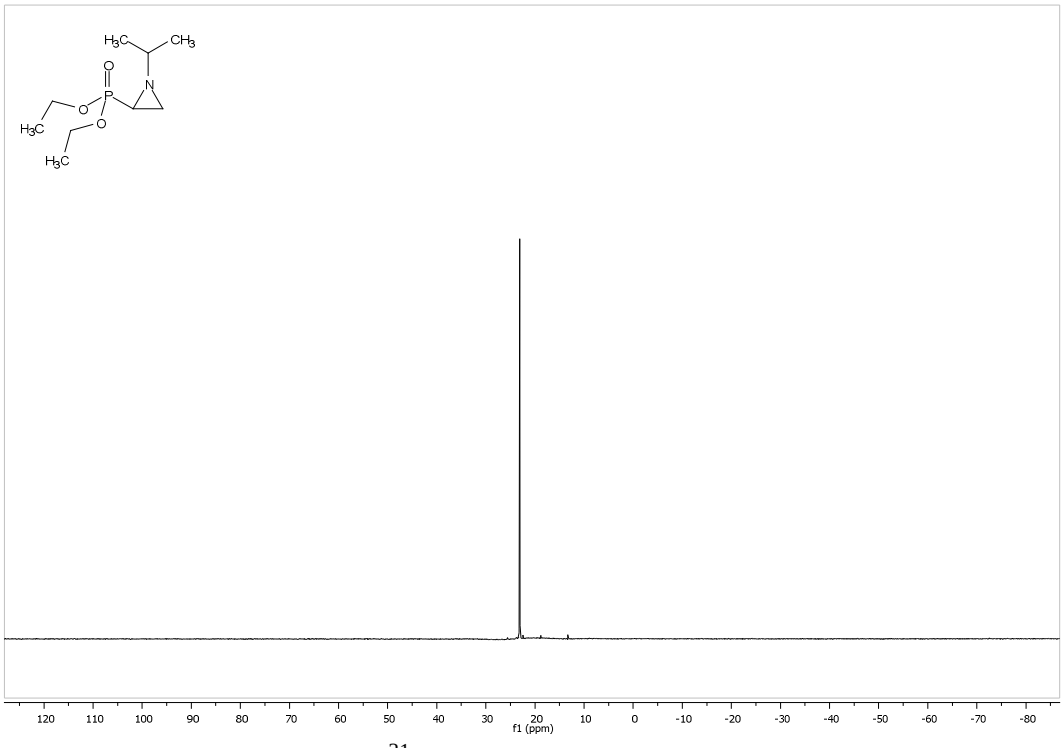

Figure A. 11. ^{31}P NMR spectrum of compound **68.**

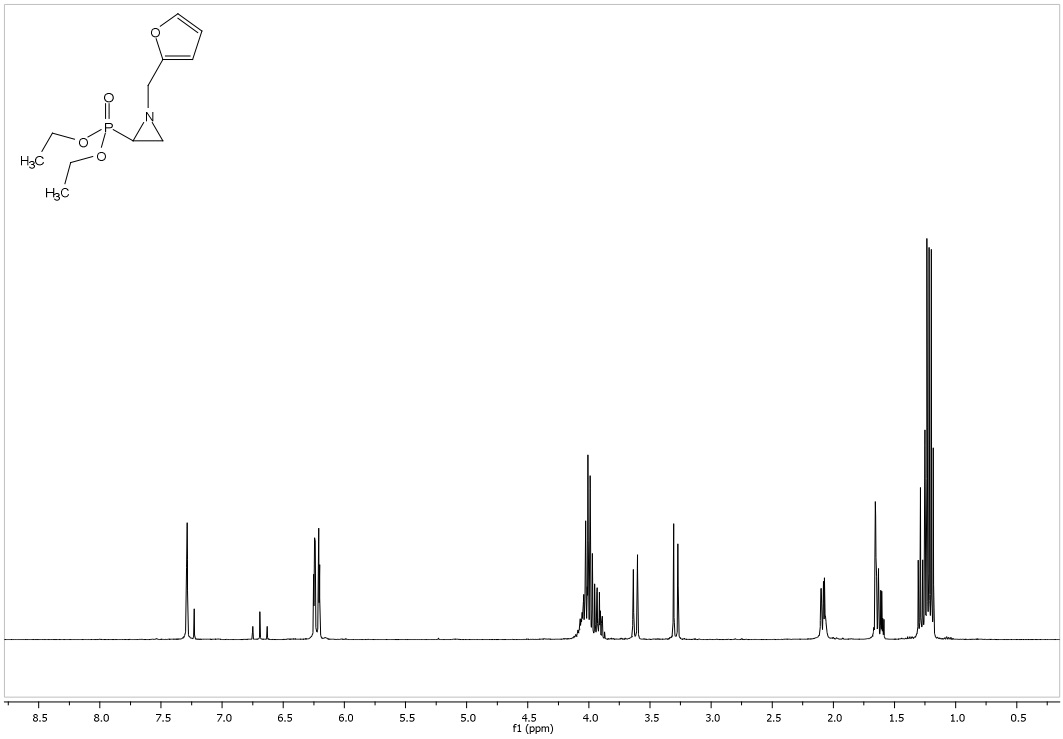

Figure A. 12. ^{1}H NMR spectrum of compound **69.**

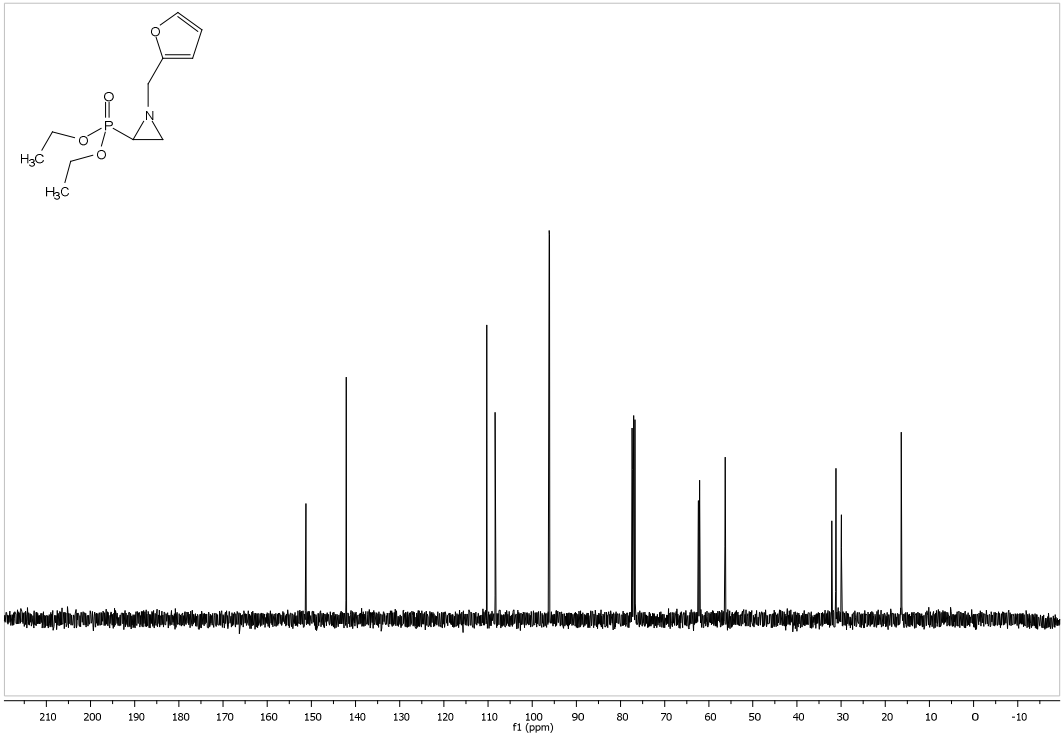

Figure A. 13. ^{13}C NMR spectrum of compound **69.**

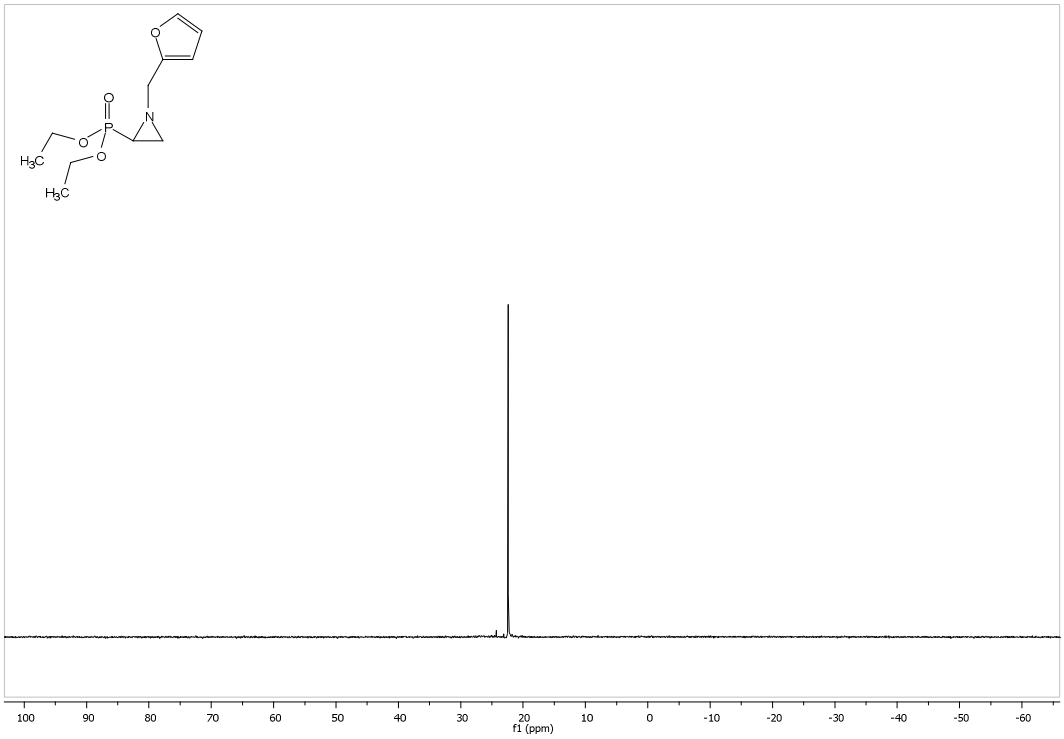

Figure A. 14. ^{31}P NMR spectrum of compound **69.**

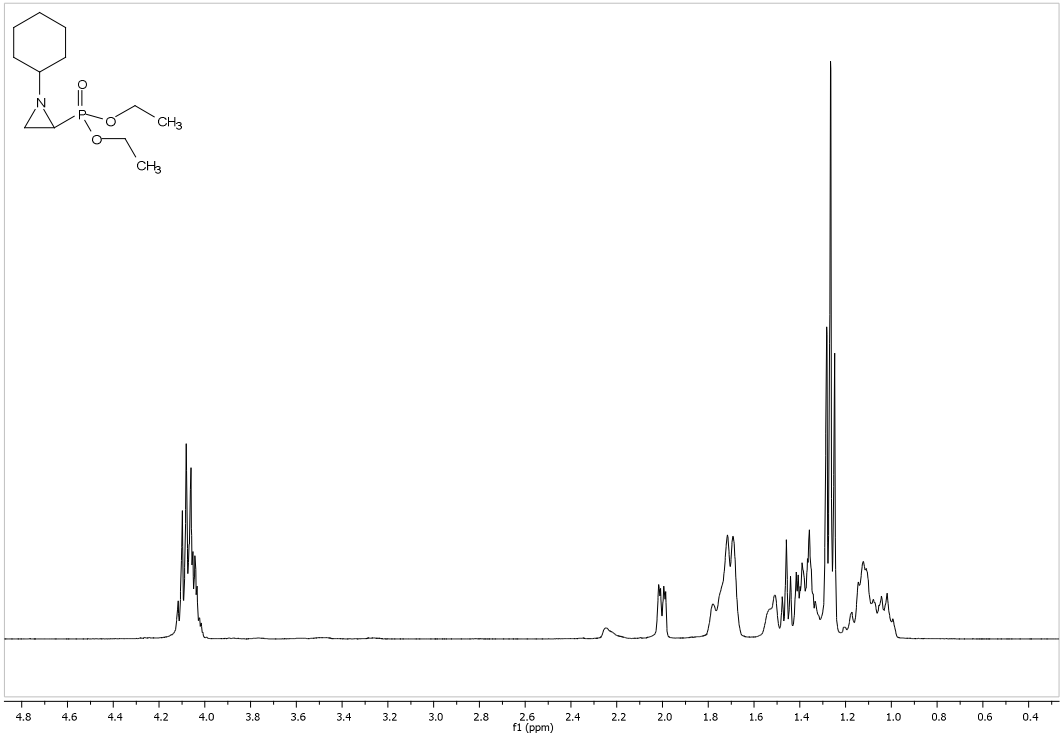

Figure A. 15. ^{1}H NMR spectrum of compound **70.**

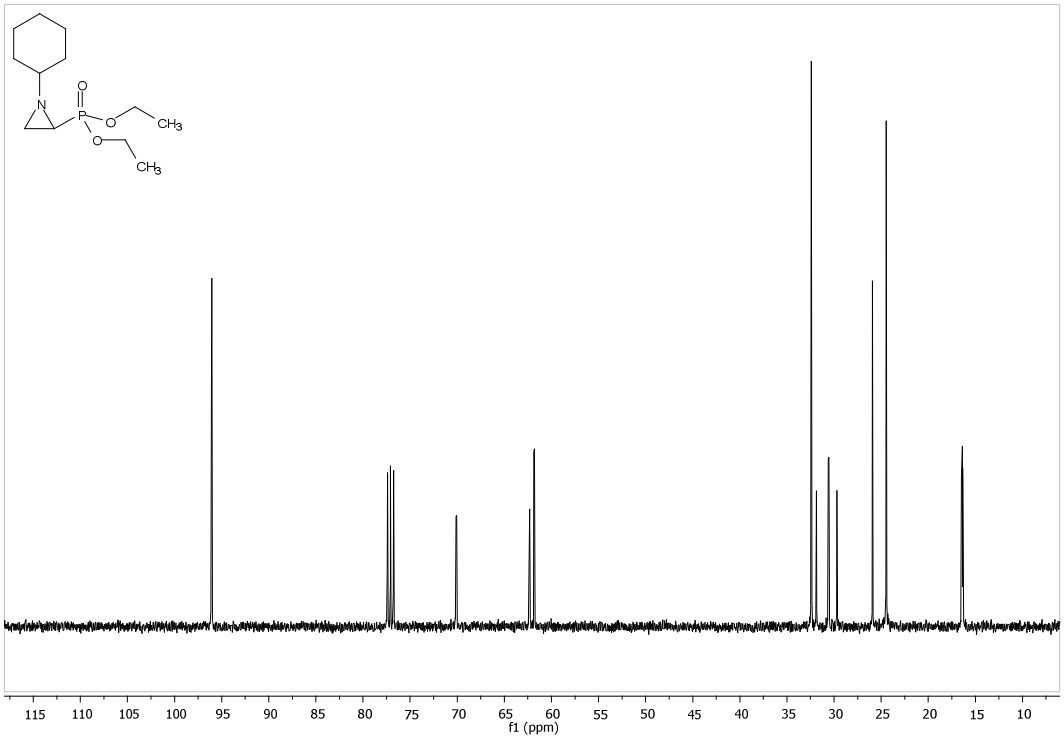

Figure A. 16. ^{13}C NMR spectrum of compound **70.**

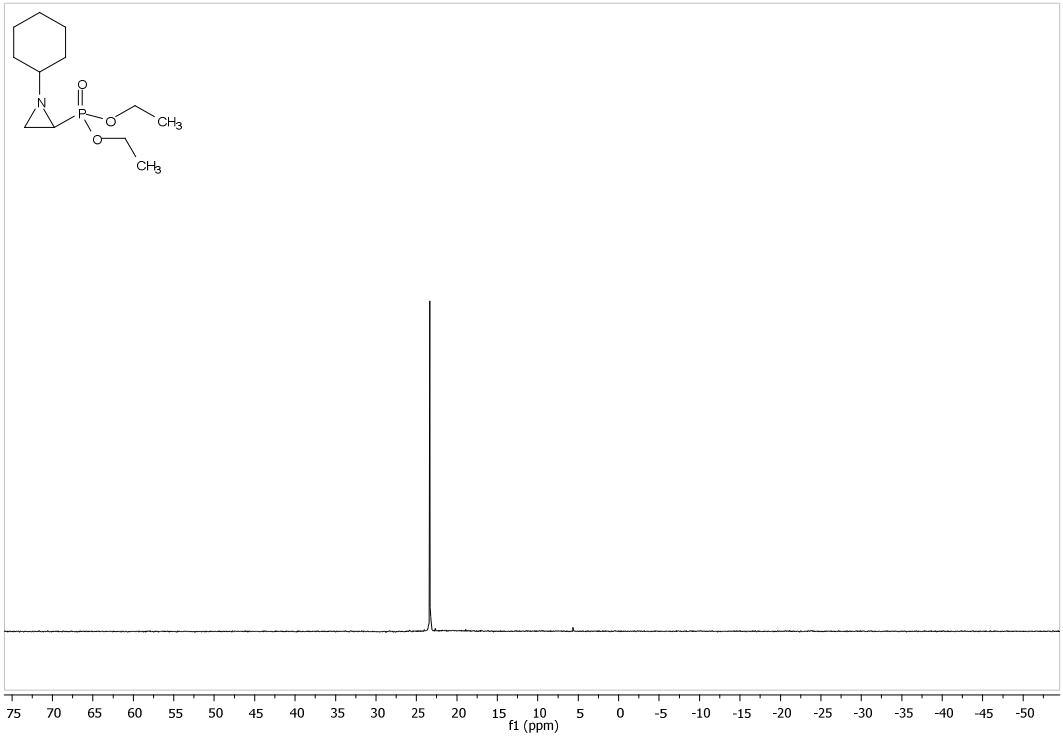

Figure A. 17. ^{31}P NMR spectrum of compound **70.**

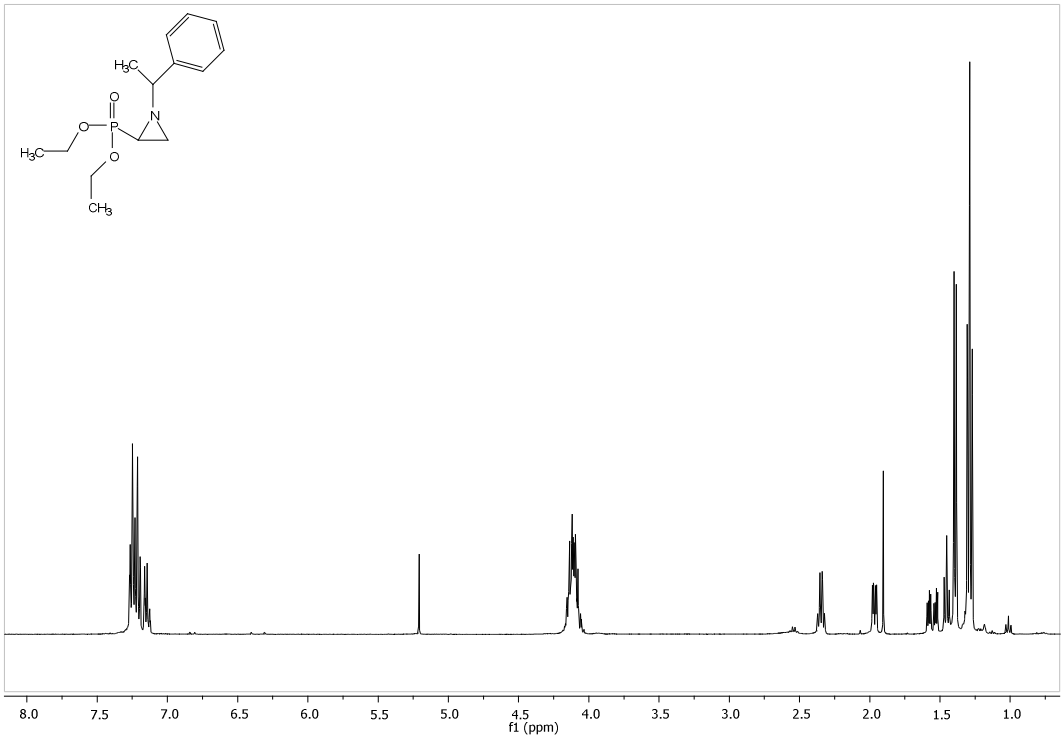

Figure A. 18. ^{1}H NMR spectrum of compound **73.**

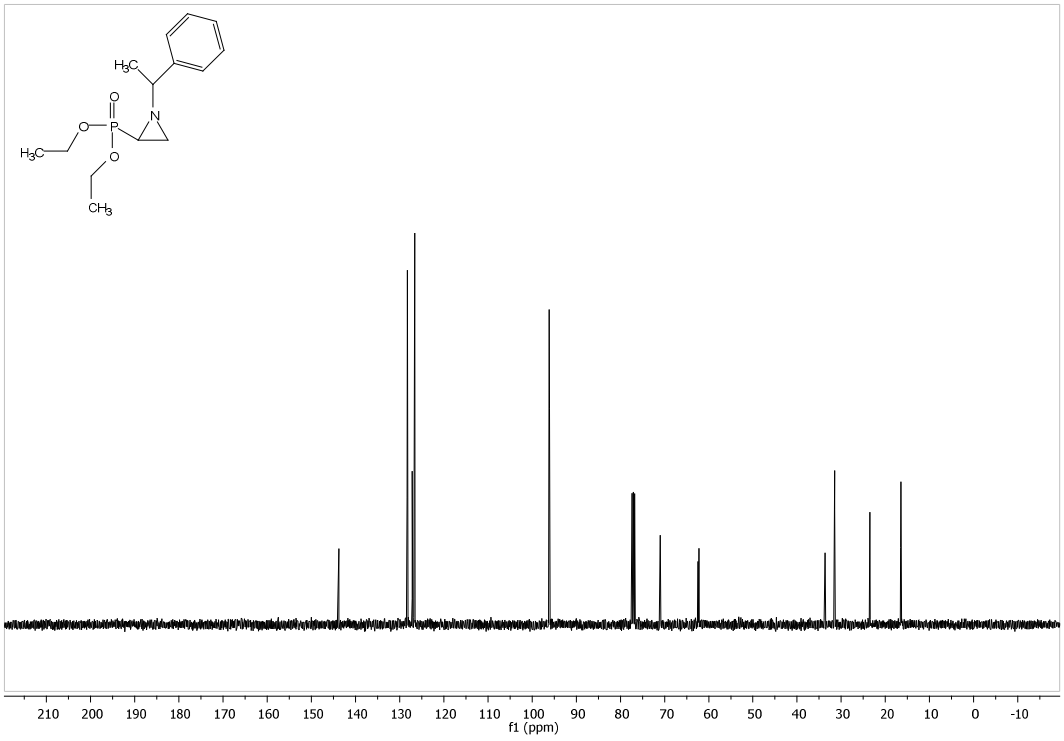

Figure A. 19. ^{13}C NMR spectrum of compound **73.**

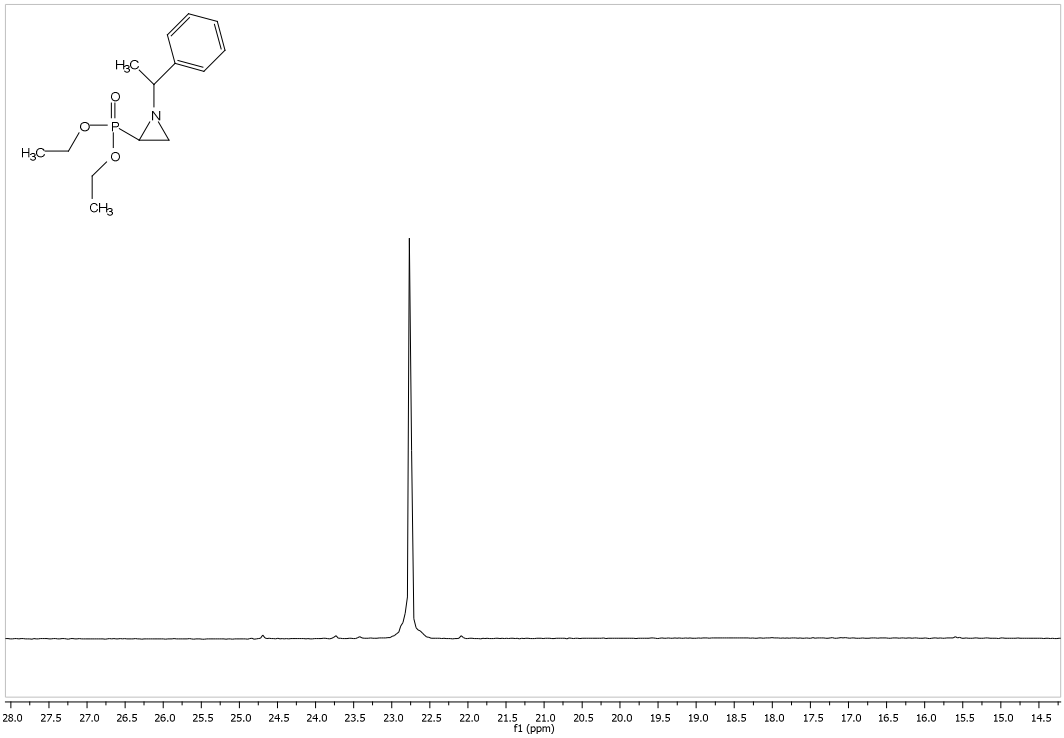

Figure A. 20. ^{31}P NMR spectrum of compound **73.**

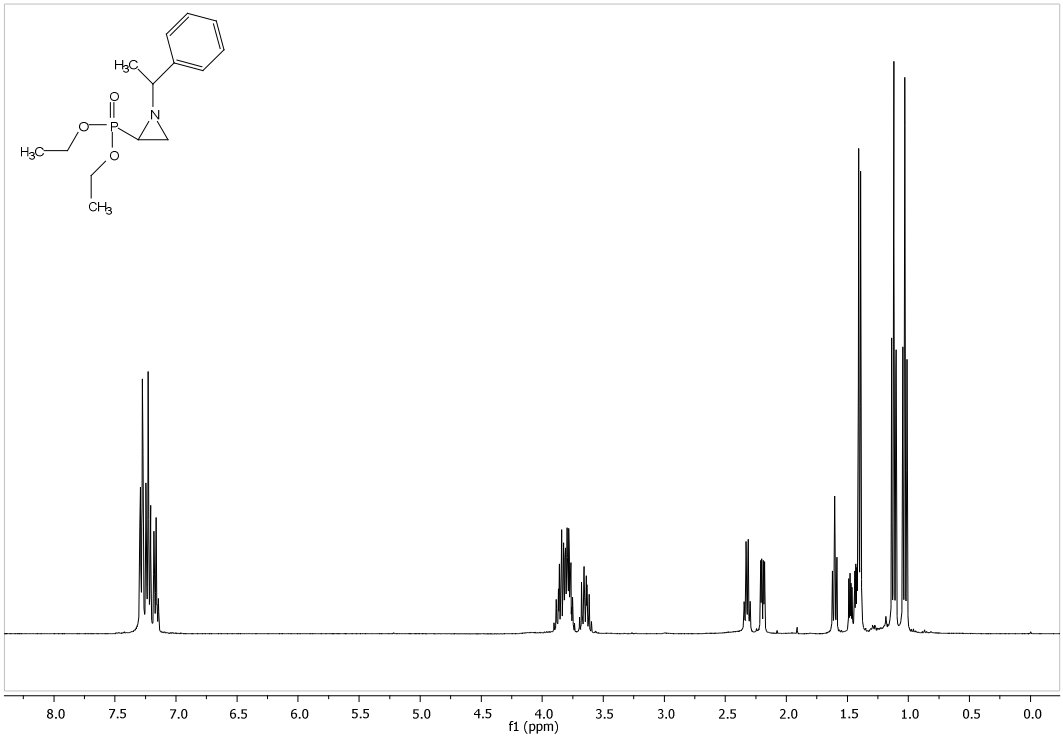

Figure A. 21. ^{1}H NMR spectrum of compound **74.**

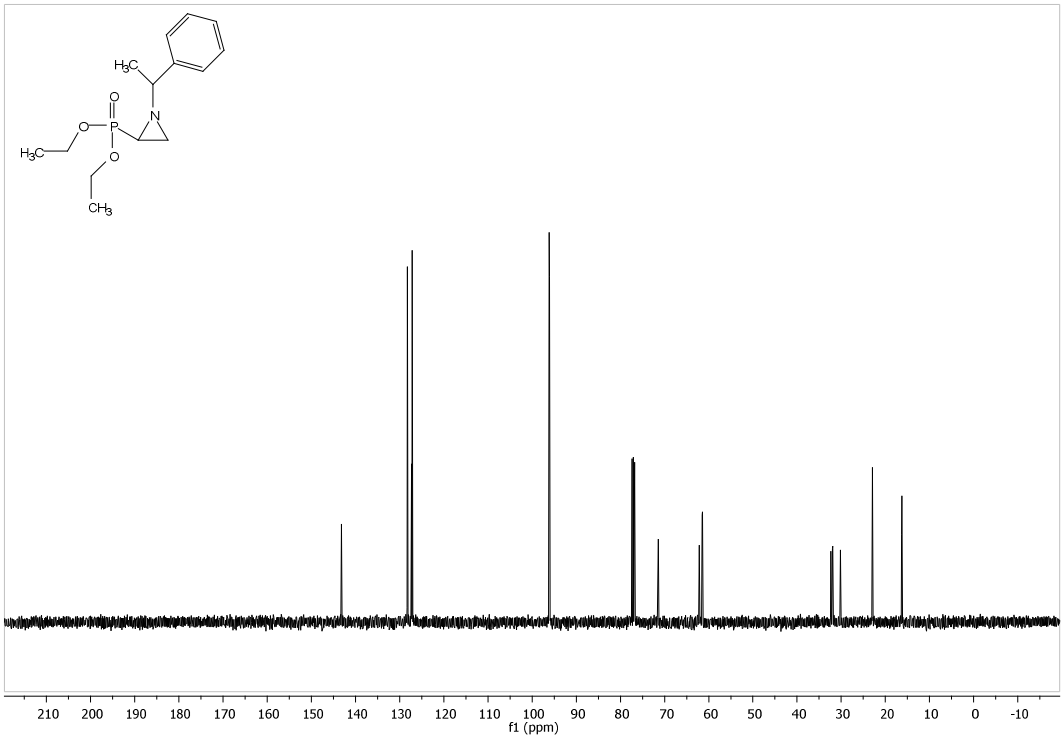

Figure A. 22. ^{13}C NMR spectrum of compound **74.**

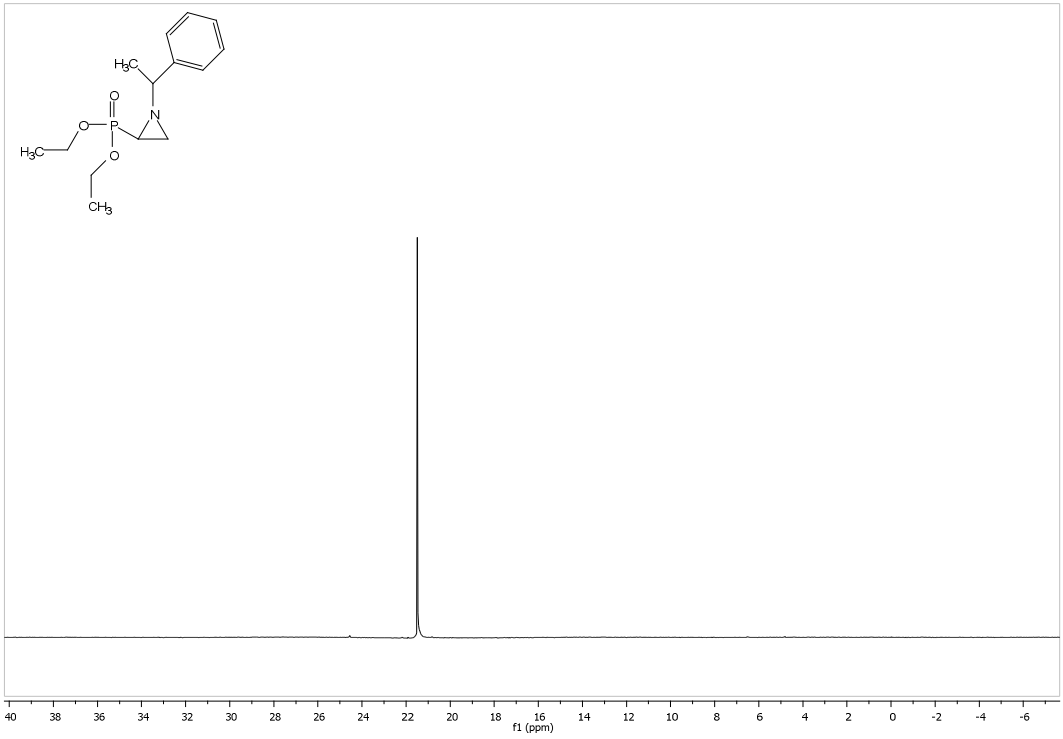

Figure A. 23. ^{31}P NMR spectrum of compound **74.**

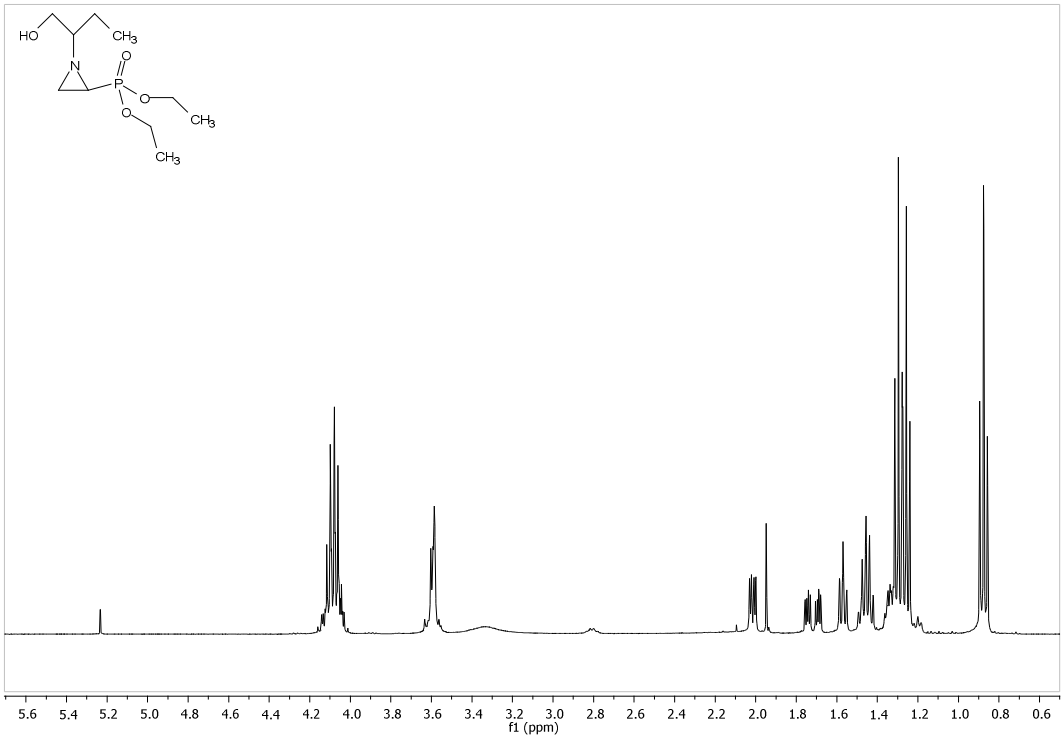

Figure A. 24. ^{1}H NMR spectrum of compound **71.**

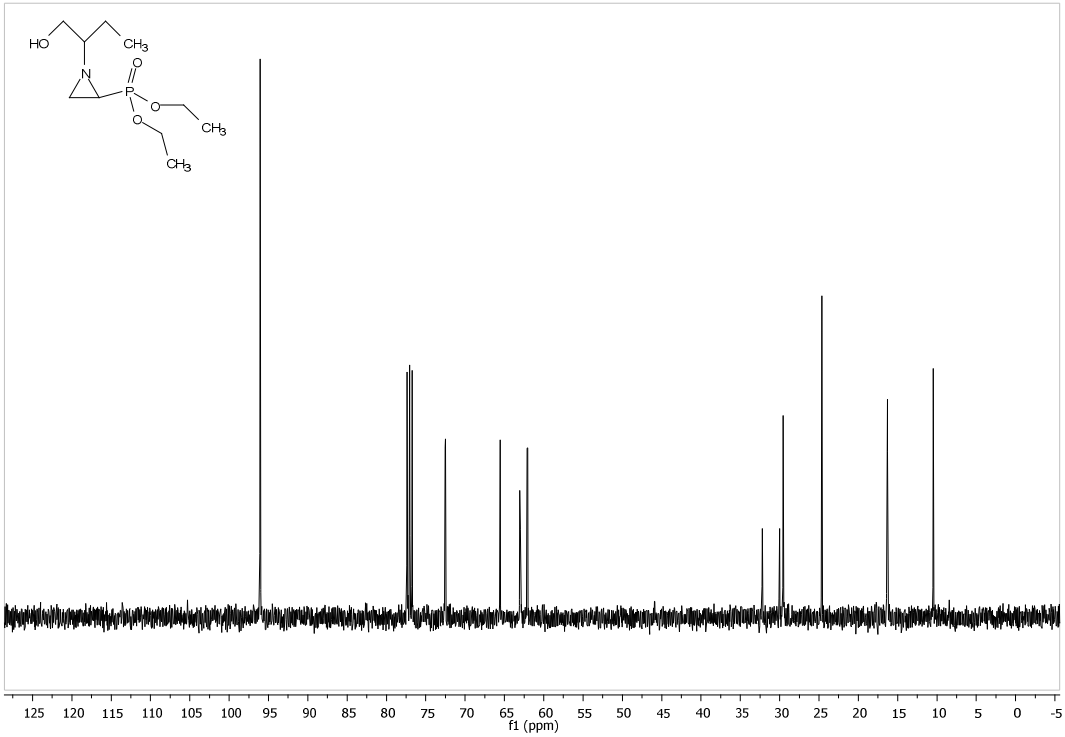

Figure A. 25. ^{13}C NMR spectrum of compound **71.**

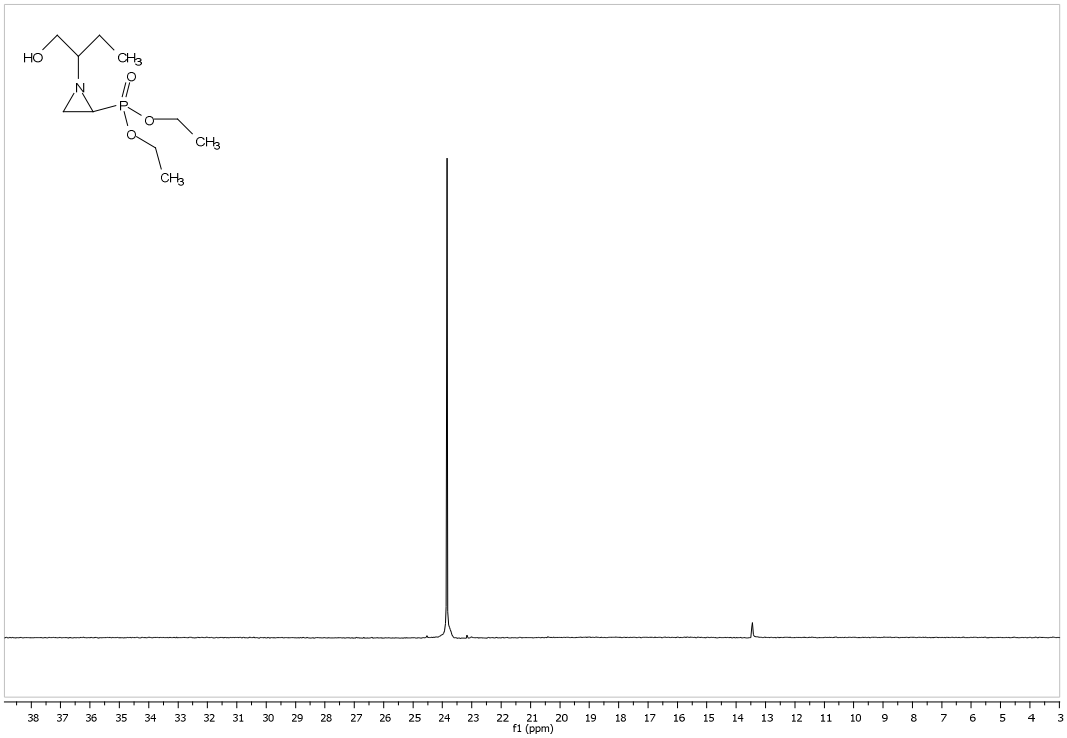

Figure A. 26. ^{31}P NMR spectrum of compound **71.**

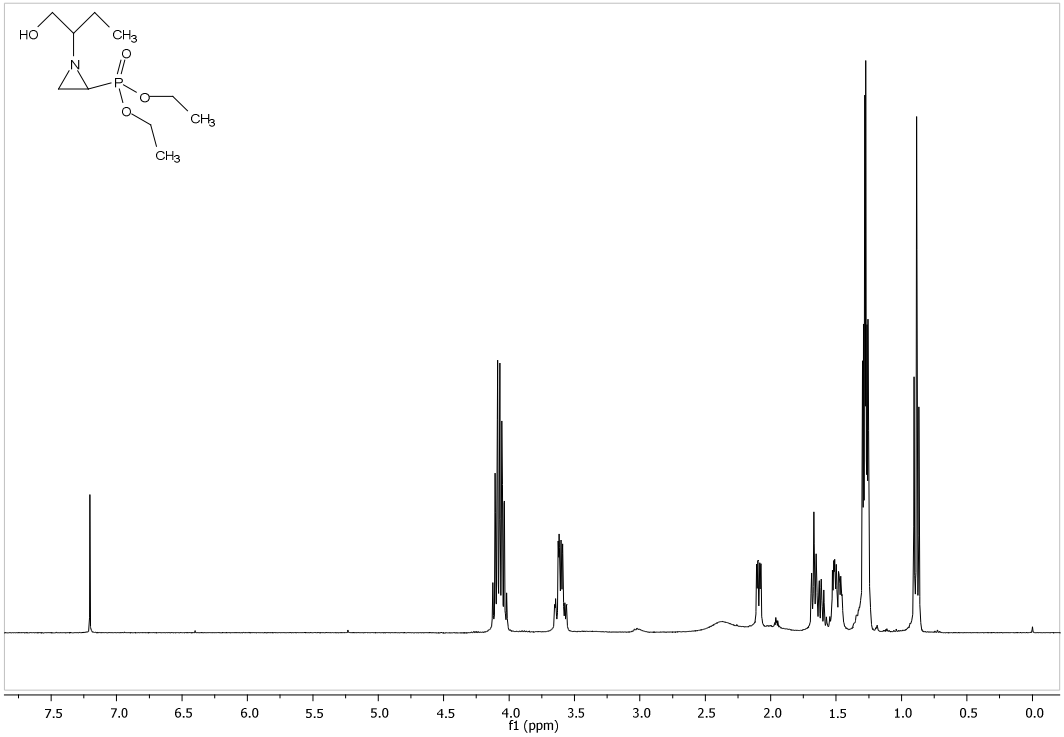

Figure A. 27. ^{1}H NMR spectrum of compound **72.**

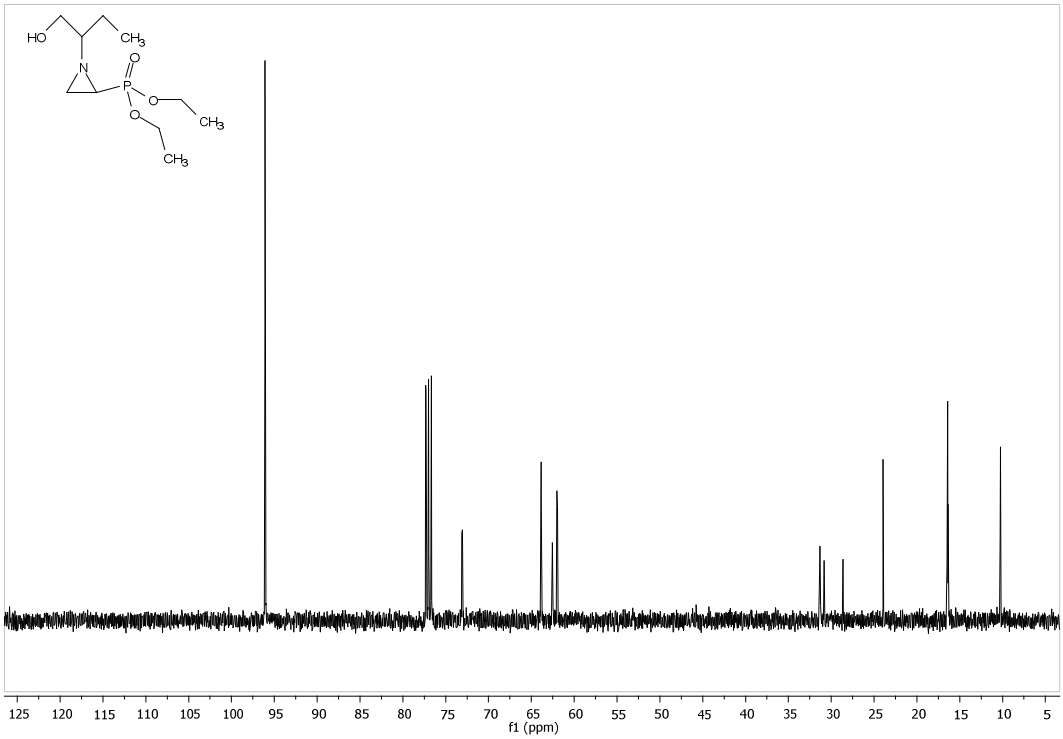

Figure A. 28. ^{13}C NMR spectrum of compound **72.**

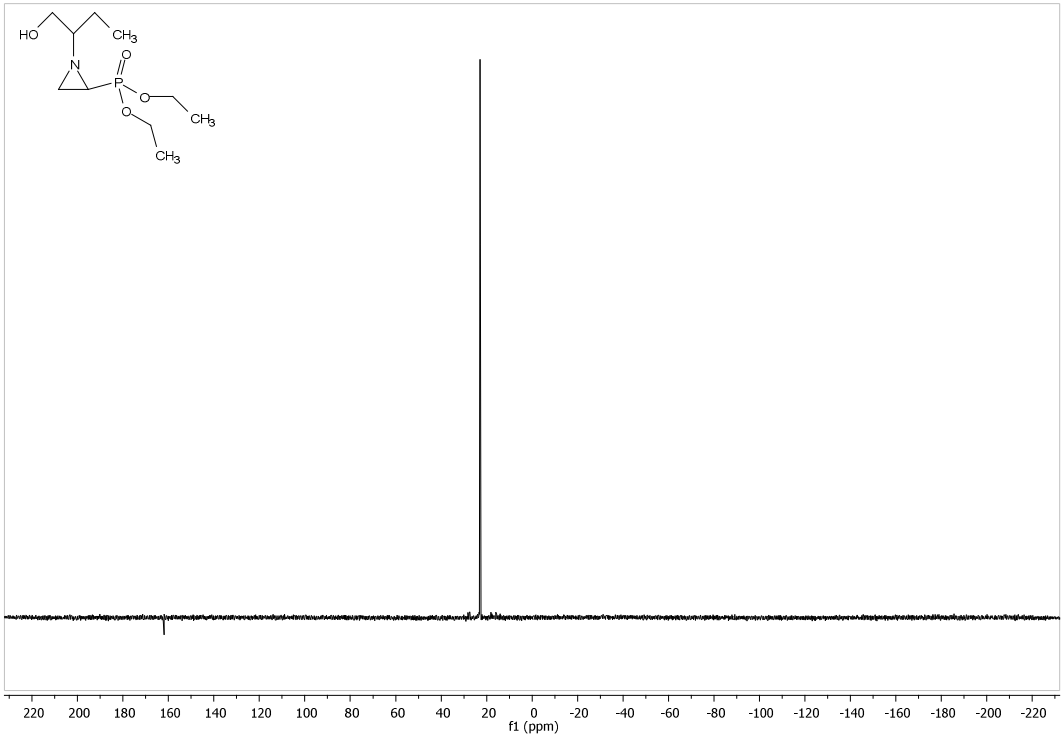

Figure A. 29. ^{31}P NMR spectrum of compound **72.**

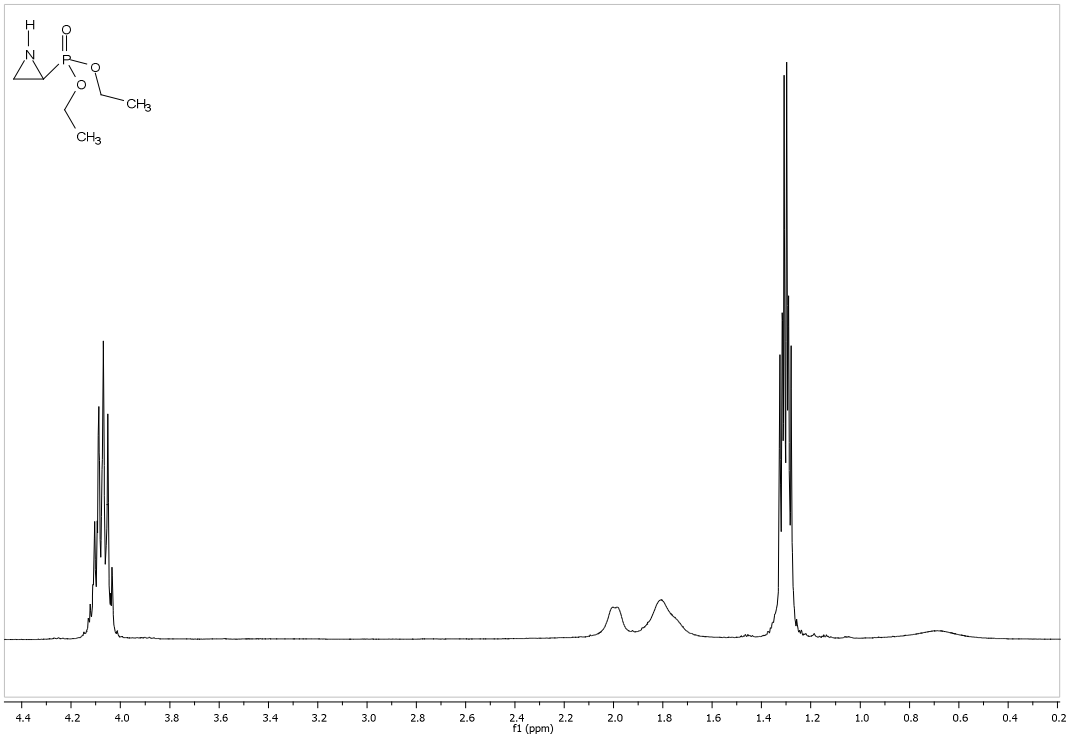

Figure A. 30. ^{1}H NMR spectrum of compound **77.**

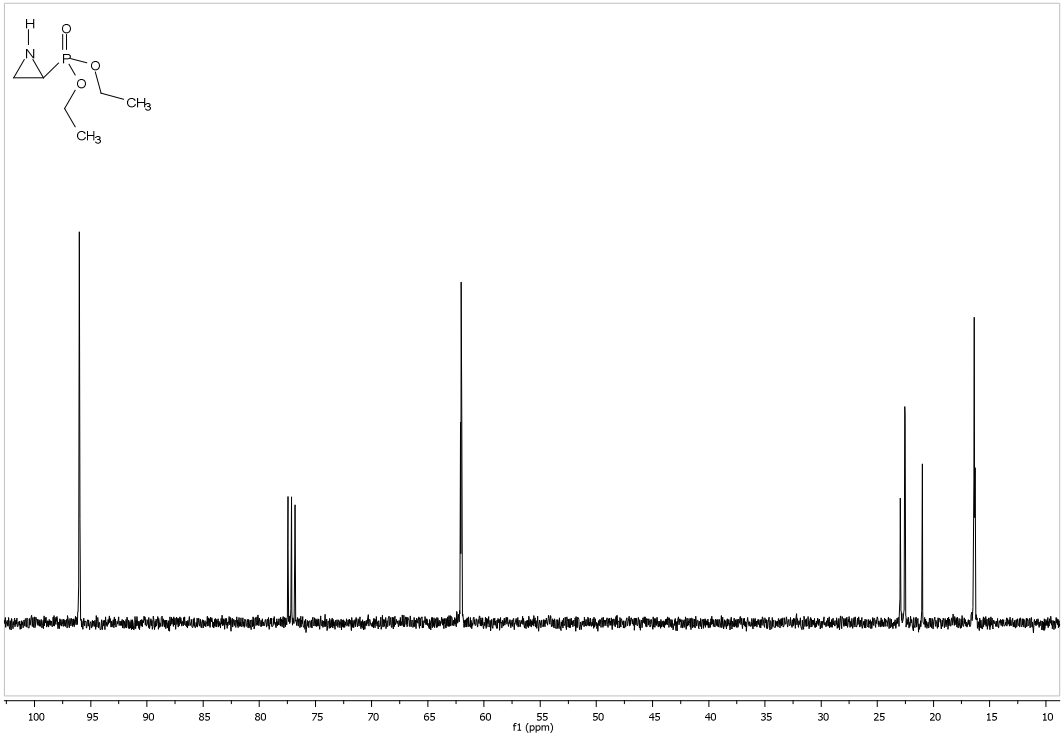

Figure A. 31. ^{13}C NMR spectrum of compound **77.**

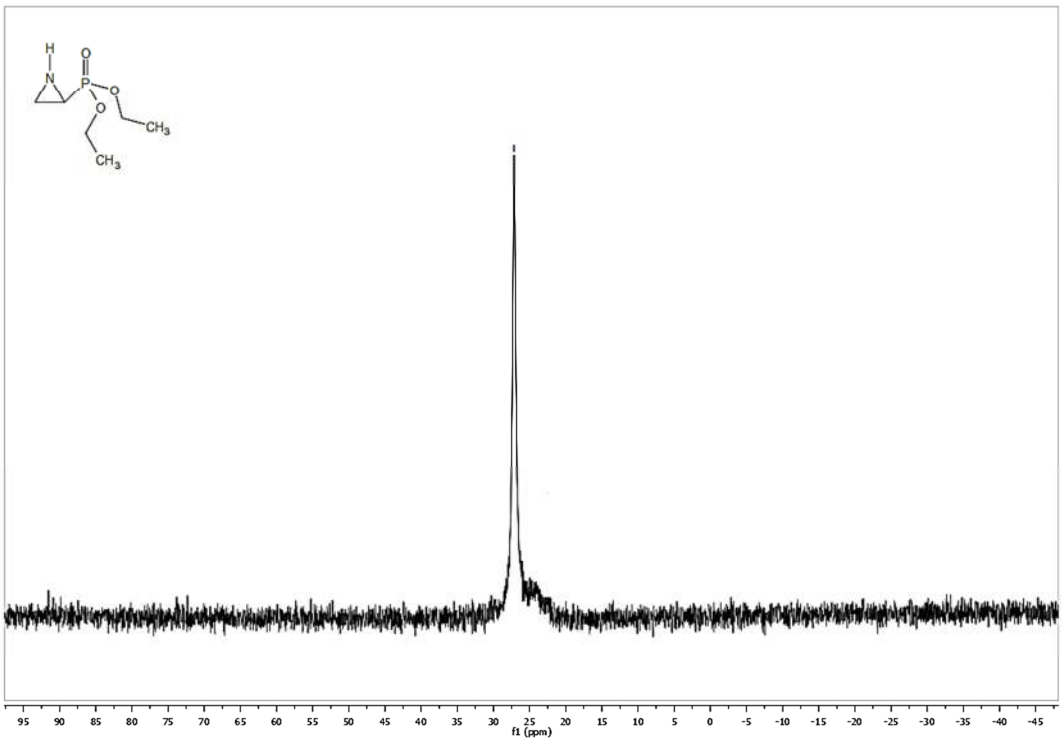

Figure A. 32. ^{31}P NMR spectrum of compound **77.**

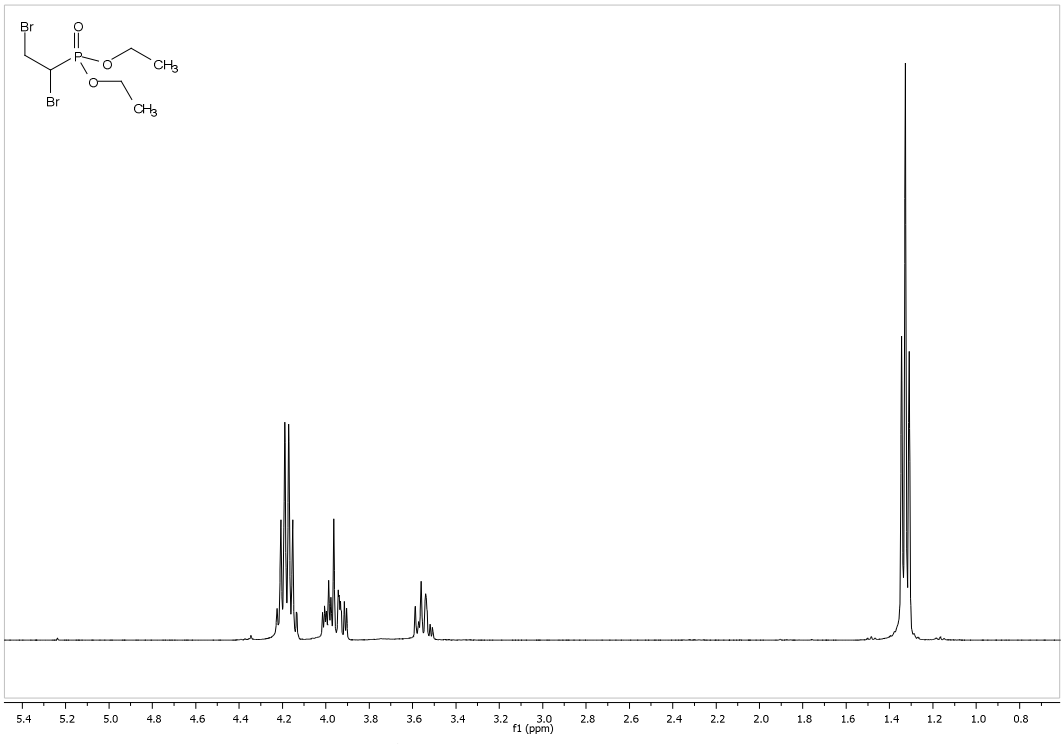

Figure A. 33. ^{1}H NMR spectrum of compound **76.**

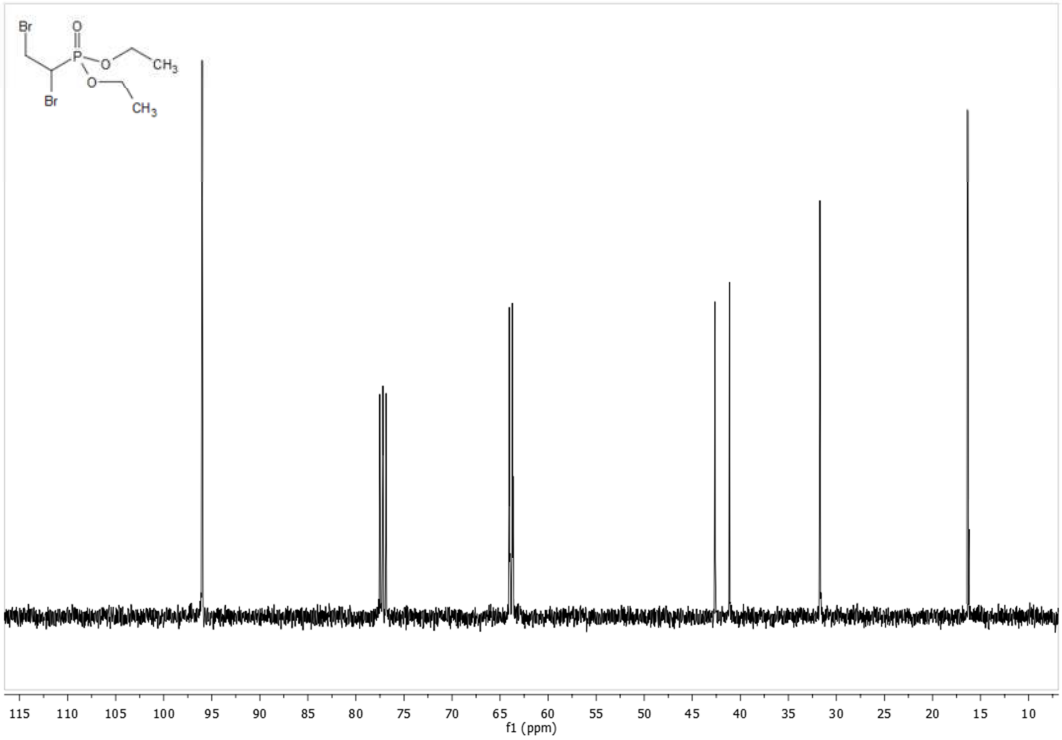

Figure A. 34. ^{13}C NMR spectrum of compound **76.**

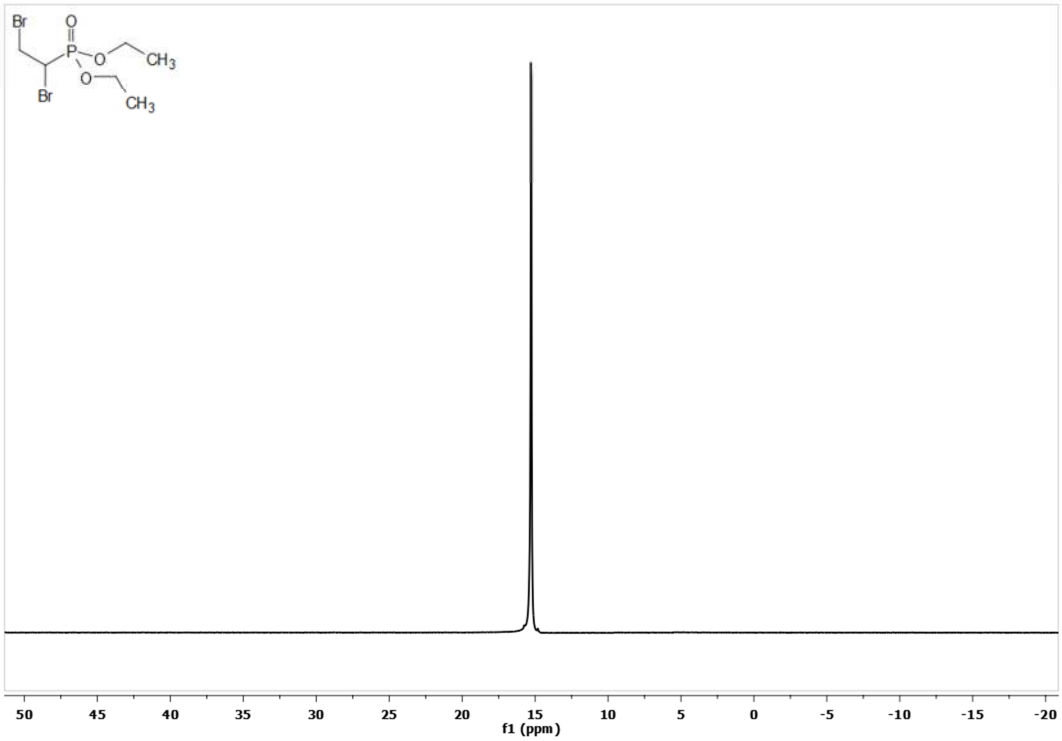

Figure A. 35. ^{31}P NMR spectrum of compound **76.**