STUDIES IN SYNTHESIS AND TRANSFORMATIONS OF SUBSTITUTED AZETIDIN-2-ONES

VIDYESH V. GOVANDE

DIVISION OF ORGANIC CHEMISTRY (SYNTHESIS)

NATIONAL CHEMICAL LABORATORY

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VIDYESH GOVANDE

DIVISION OF ORGANIC CHEMISTRY (SYNTHESIS)

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Studies in Synthesis and Transformations of Substituted Azetidin-2-ones"** submitted by Mr. Vidyesh Vinayak Govande was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

Date:

National Chemical Laboratory (Dr. A. R. A. S. Deshmukh)

Pune 411 008 Research Guide

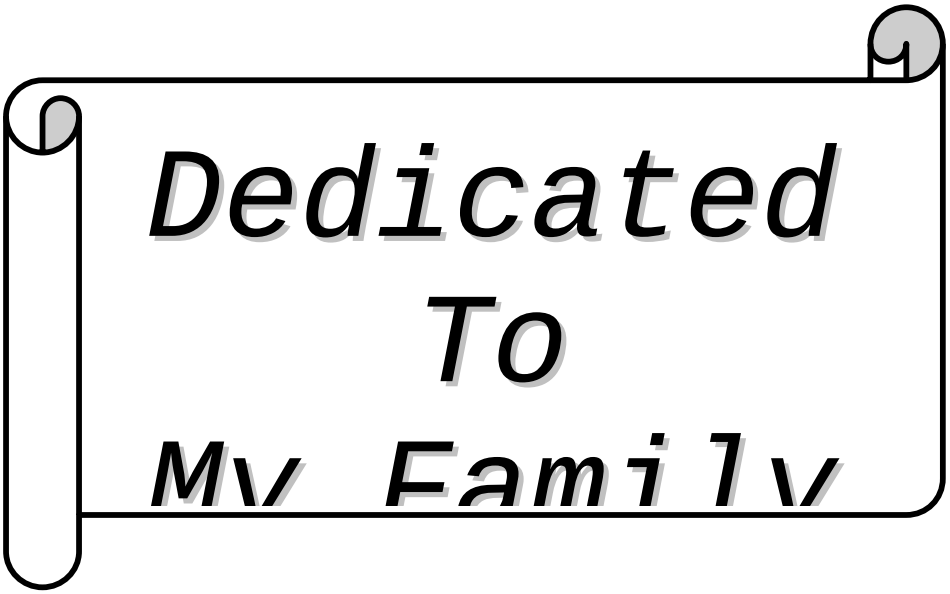
DECLARATION

I hereby declare that the work incorporated in the thesis entitled **"Studies in Synthesis and Transformations of Substituted Azetidin-2-ones"** submitted for the degree of Doctor of Philosophy to the University of Pune, has been carried out by me at the National Chemical Laboratory, Pune under the supervision of Dr. A. R. A. S. Deshmukh. The work is original and has not been submitted in part or full by me for any other degree or diploma to this or any other university.

Date:

National Chemical Laboratory (Vidyesh V. Govande)

Pune 411 008 Research Student



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Science is fun doing and pleasure giving. Above all we get paid reasonably well for doing what we like most. We have absolute freedom to do what we like and enjoy. It was that freedom Dr. Deshmukh rendered us during the whole course of work. With zealous pride I take this pleasant opportunity to express my deep sense of gratitude to him for his expert and inspiring guidance. His attributes like huge capacity to work, exemplary patience, optimistic attitude, logical planning, and strict execution served as milestones through the entire tenure of the work.

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Vidyesh V. Govande

GENERAL REMARKS

1. All melting points (recorded on a Thermonik Campbell and Yanco Micro melting point apparatus) are uncorrected and are recorded on the Celsius scale.

2. IR spectra were recorded as nujol mull or in chloroform, or neat on a Perkin-Elmer Infrared Spectrometer Model 599-B, Model 1600 FTIR and Shimadzu FTIR, using sodium chloride optics. IR bands are expressed in frequency (cm^{-1}).

3. Proton NMR spectra were recorded using tetramethylsilane as internal reference on Bruker AC-200, MSL-300 and DRX-500 spectrometer. Chemical shifts were recorded in parts per million (δ, ppm). Abbreviations, *viz.*, s = singlet, d = doublet, t = triplet, dd = doublet of doublet, q = quartet, bs = broad singlet and m = multiplet have been used to describe the spectral data. $CDCl_3$ was used as the solvent unless otherwise mentioned.

4. ^{13}C NMR spectra were recorded on Bruker AC-200, MSL-300 and Bruker DRX-500 instrument operating at 50.3 MHz, 75 MHz and 125.8 MHz respectively.

5. Elemental analyses (C, H, N, S) were obtained on a Carlo-Erba, 1100 automatic analyzer.

6. Optical rotations were measured on a JASCO-181 digital Polarimeter, JASCO P-1020 Polarimeter and ADP-220 Polarimeter using sodium D line (5893 A°). Concentration is expressed in g/ 100 ml.

7. EI Mass spectra were recorded on a Finnigan Mat-1020 Spectrometer with a direct inlet system or electron spray ionization method (EI).

8. Petroleum ether refers to the fraction boiling between 60-80 °C.

9. The progress of the reaction was monitored by analytical thin layer chromatography plates precoated with silica gel 60 F_{254} (Merck) and glass

chromatography plates precoated with silica gel 60 F_{254} (Merck) and glass plates coated with silica gel F_{254}.

10. Silica Gel used for column chromatography was 60-120 mesh, 100-200 mesh or 230-400 mesh size.

11. ^{1}H NMR and ^{13}C NMR spectra of the representative compounds are attached at the end of the corresponding chapter. For all the samples containing methylene and quaternary carbons, DEPT spectrum was scanned after scanning ^{13}C NMR spectra and then the assignment of the peaks in ^{13}C NMR was done.

12. Solvents for column chromatography were distilled at their respective constant boiling points.

13. All the dry reactions were performed under an inert atmosphere of argon, using freshly distilled, degassed solvents.

14. Dichloromethane was dried over anhydrous P_2O_5 and stored over 4Å molecular sieves. THF was freshly distilled over sodium benzophenone ketyl. Triethyl amine was dried over potassium hydroxide.

15. Chromium (II) chloride ($CrCl_2$) was used as obtained from Aldrich and Strem chemicals.

16. All other solvents were dried following the procedures given in the book 'Purification of Laboratory Chemicals' by Armarego and Perrin (third edition).

17. Compounds have been named based on nomenclature provided by CS-ChemDraw software.

ABBREVIATIONS

Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile [$(CH_3)_2C(CN)N=NC(CH_3)_2CN$]
Ar	Aryl
Bn	Benzyl
Boc	*t*-Butoxy carbonyl
Bu	Butyl
Bu_3SnH	Tributyltin hydride
CAN	Ceric ammonium nitrate
CSI	*N*-chlorosulfonyl isocynate
DAM	Bis-(4-methoxyphenyl)-methyl
DBU	1,8-diazabicyclo [5.4.0] undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarization transfer
DIBAL-H	Disiobutylaluminium hydride
DIPEA	*N*,*N*'-Diisopropylethyl amine
DMAP	*N*,*N*'-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPA	Diphenyl phosphoryl azide

EDC	Dichloroethane or ethylene dichloride
Equiv.	Equivalent(s)
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
EWG	Electron withdrawing group
g	Gram(s)
h	Hour(s)
HOMO	Highest occupied molecular orbital
Hz	Hertz
IR	Infrared
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyl disilazide
LUMO	Lowest unoccupied molecular orbital
MAP	*p*-Methoxy acetophenone
Me	Methyl
MEM	(2-Methoxyethoxy) methyl
Mes or Ms	Methanesulfonyl
min	Minute(s)
mL	Milli litre(s)
mmol	Milli mole(s)
MOM	Methoxy methyl
MP or Mp	Melting point

MS	Mass spectrum
NMR	Nuclear magnetic resonance
Nu	Nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot Programme
Pet ether	Petroleum ether
Pf	9-Phenylfluoren-9-yl
Ph	Phenyl
PhthN	Phthalimido
PMP	*p*-Methoxyphenyl
PNA	Peptide nucleic acid
PNB	*p*-Nitro benzyl
Pr	*n*-Propyl
PTC	Phase transfer catalyst
PTSA or TSOH	*p*-Toluenesulfonic acid
Py	Pyridine
RCM	Ring closing metathesis
rt or RT	Room temperature
SAR	Structure activity relationship
TBDMS	*t*-Butyldimethylsilyl
TEA or Et_3N	Triethyl amine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Thz	2-Thiozolyl

TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMSOTf	Trimethyl silyl trifluoromethane sulfonate
TMST	2-(Trimethyl silyl)-thiazole
TP	Triphosgene
TPP or PPh_3	Triphenylphosphine
Ts	*p*-Toluenesulfonyl

Name of the candidate: **Vidyesh V. Govande**

Name of the research guide: **Dr. A. R. A. S. Deshmukh**

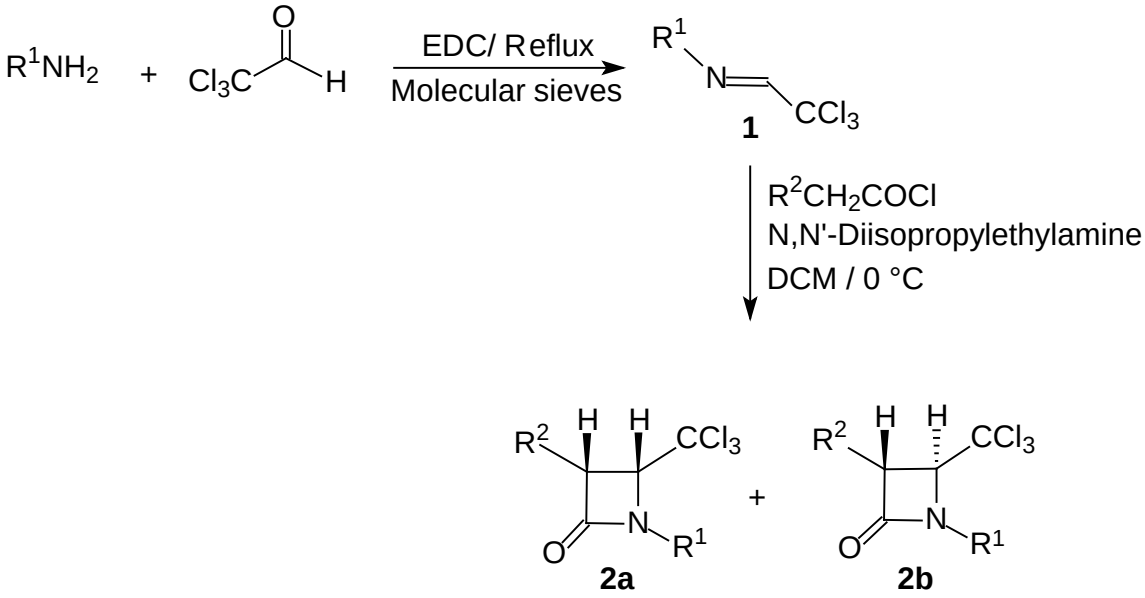
Abstract of the thesis entitled: **Studies in Synthesis and Transformations of Substituted Azetidin-2-ones**

Chapter I

Section A: Synthesis of 4-trichloromethyl-azetidin-2-ones from chloral-derived imines using Staudinger cycloaddition reaction

Staudinger cycloaddition reaction is widely used for the synthesis of variety of β-lactams. This reaction involves the cycloaddition of imines and *in situ* generated ketenes from acid chlorides in the presence of tertiary amines. Although, several β-lactams are prepared by this method, there is only one report for the synthesis of 4-trichloromethyl-β-lactams. We were interested in the preparation of 4-trichloromethyl-β-lactams as trichloromethyl group can serve as a masked carboxylic acid equivalent, other groups can substitute it and it can be transformed to chlorovinyl group. Also the electron withdrawing property of the chlorinated methyl group at this position will increase the chemical reactivity of the β-lactam ring, which is correlated with its biological activity.

Scheme 1



R^1 = -Phenyl, -Benzyl, -PMP, -Cyclohexyl

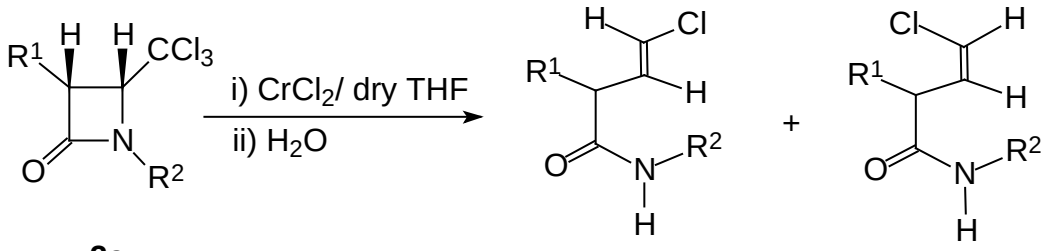
R^2 = PhO-, AcO-, MeO-, BnO-, PhthN-

Anhydrous chloral was treated with different aliphatic and aromatic amines in ethylene dichloride at lower temperature and the resultant mixture was then refluxed with removal of water by using molecular sieves, to give chloral-imines **1** in excellent yields. Cycloaddition of imines **1** with ketenes derived from various acid chlorides in the presence of tertiary amine, such as *N*,*N*'-diisopropylethylamine, gave the required 4-trichloromethyl-β-lactams **2a** and **b** as a mixture of *cis* and *trans* isomers in good yields with high stereoselectivity (Scheme 1). In the cases of *N*-alkyl substrates *cis*-β-lactams were obtained exclusively. However, in the case of *N*-aryl substrates, small amount of *trans* isomers were also formed along with the major *cis* isomers. This was confirmed by the coupling constant of β-lactam ring protons from the proton NMR spectra. Several β-lactams were prepared by applying these reaction conditions.

Section B: Studies on $CrCl_2$ mediated transformations of 4-trichloromethyl-azetidin-2- ones

Azetidin-2-ones having unsaturation directly on the ring system are known for increased antibacterial and β-lactamase inhibitor activity. We were interested in the preparation of β-lactams having exocyclic unsaturation at C-4 position. It is also well documented that trichloromethyl group can be easily transformed to chlorovinyl group by using $CrCl_2$ *via* reductive elimination. Having developed a very good method for the synthesis of 4-trichloromethyl azetidin-2-ones, we were interested in studying the reaction of $CrCl_2$ on our substrates.

Scheme 2



2a R^1 = PhO-, AcO-, MeO-; R^2 = -Benzyl, -PMP **3** **4**

Thus 4-trichloromethyl-β-lactams **2a** were subjected to reaction with $CrCl_2$ in dry THF. Surprisingly, we did not get the desired β-lactams with chlorovinyl group at C-4 position. Instead, we got N(1)-C(4) ring cleaved chlorovinyl compounds **3**, **4** (Scheme 2). This is, may be due to the ring strain and the ring nitrogen co-ordination with $CrCl_2$. The

generality of this reaction was proved by applying these reaction conditions to several other trichloromethyl-azetidin-2-ones. The mode of reductive elimination was governed by the steric bulk of the group at C-3 position in the β-lactam ring.

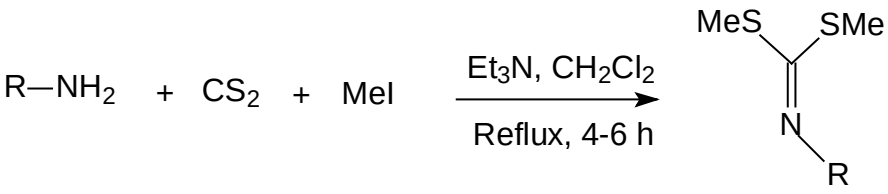
Chapter II

Section A: Synthesis of 4,4-bismethylsulfanyl-azetidin-2-ones from carbonimidodithioic acid dimethyl esters using Staudinger cycloaddition reaction

This section of the chapter deals with the synthesis of 4,4-bismethylsulfanyl-azetidin-2-ones by using Staudinger cycloaddition reaction. The development of approaches for the synthesis of monocyclic β-lactams with various substitution patterns is an area of active research after the discovery of biologically important monocyclic β-lactams such as nocardicins and monobactams. Similarly strained 4-oxo-β-lactams have been shown to possess anti-inflammatory and sedative properties, some of them also possess hypnotic inducing property. In view of these, we were interested in the synthesis of 4-oxo and protected-4-oxo analogs, which can serve as useful intermediates for variety of β-lactam antibiotics. We have employed a new acid activator, triphosgene, in the Staudinger cycloaddition reaction.

The starting carbonimidodithioic acid dimethyl esters **5**, which served as imine components in the Staudinger reaction, were prepared in very good yields by the reaction of aliphatic and aromatic amines with carbon disulphide in the presence of Et_3N, followed by methylation with methyl iodide (Scheme 3).

Scheme 3

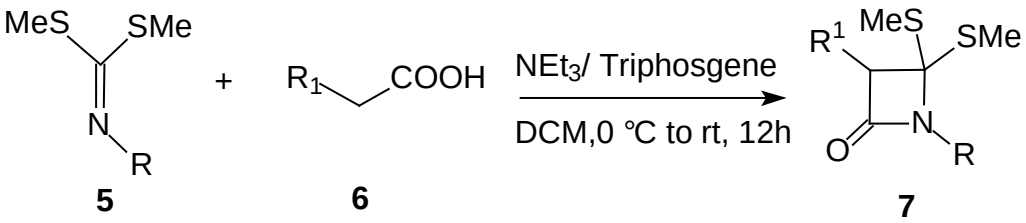


5

R = -Phenyl, -Benzyl, -PMP, -Propyl, -Cyclohexyl, -Furfuryl, -Allyl

The cycloaddition reaction of these dithioesters **5** with various acids **6** using triphosgene as an activator gave moderate to good yields of 4,4-bismethylsulfanyl-azetidin-2-ones **7** (Scheme 4).

Scheme 4

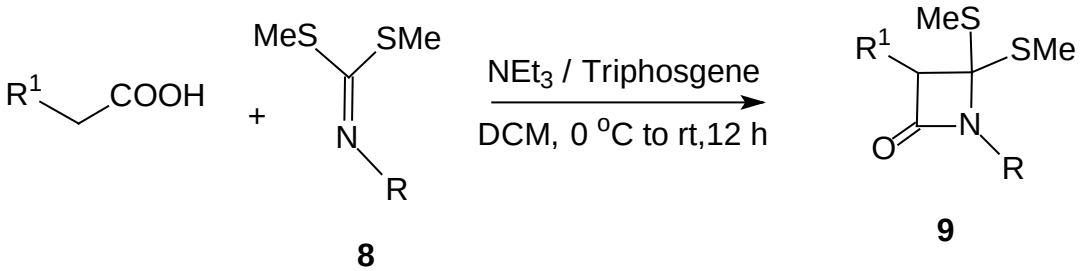


5 **6** **7**

R = -Ph, -CH_2Ph, -PMP, -Furfuryl, -Cyclohexyl, -Propyl, -Allyl
R^1 = PhO-, MeO-, BnO-, AcO-, PhthN-

The same strategy was employed for the preparation of β-lactams **9** from amino acid esters. Amino acids were first converted to their ester hydrochlorides by treatment with thionyl chloride in dry methyl or ethyl alcohol. The hydrochlorides formed were used as such for further preparation of the dithioesters **8**. Then following the same procedure as above, variously substituted β-lactams **9** were synthesized (Scheme 5) in good yields.

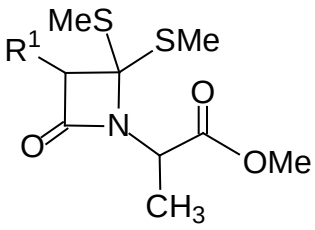
Scheme 5



8 **9**

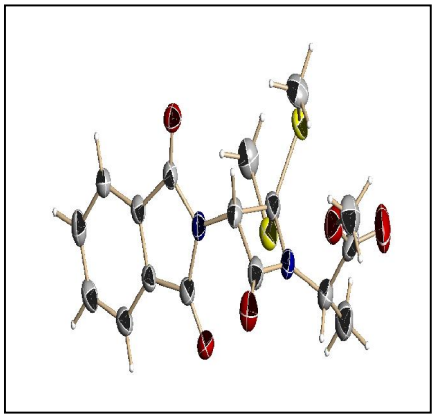
R^1 = PhO-, BnO-, MeO-, AcO-, PhthN-
R = -CH_2COOMe, -CH_2COOEt, -CH(CH_3)COOMe

A mixture of diastereomers (70:30) was obtained in case of reaction of chiral imine, alanine methyl ester derived carbonimididithioic acid dimethyl ester with ketenes derived from phenoxy, acetoxy and phthalimidoacetyl chloride. In case of ketenes derived from potassium azido acetate and benzyloxyacetyl chloride, the diastereomeric mixture (50:50) of β-lactams was obtained. The stereochemistry of one of the major diastereomers **9b'**, obtained from phthalimidoacetyl chloride and alanine methyl ester derived imine was determined by single crystal X- ray analysis.



9

9a, R^1 = PhO-
9b, R^1 = PhthN-
9c, R^1 = AcO-
9d, R^1 = N_3-
9e, R^1 = BnO-

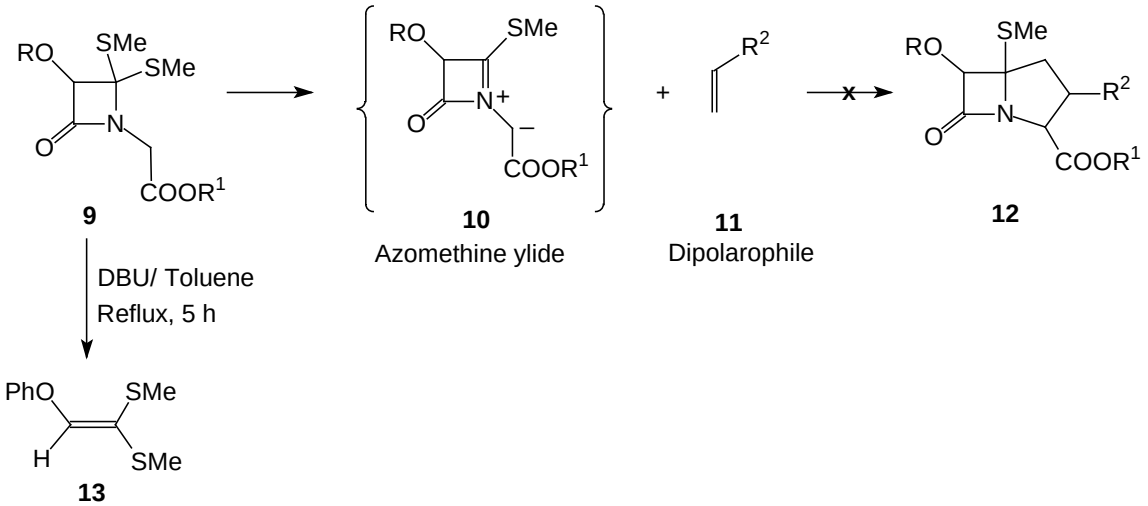


X-ray structure of **9b** (major diastereomer)

Section B: Transformations of 4,4-bismethylsulfanyl-azetidin-2-ones under acidic and basic conditions

We were interested in exploring the possibility of the above 4-oxo protected β-lactams **9** to generate azomethine ylides which can be trapped by dipolar cycloaddition reaction with dipolarophiles. This will generate variety of bicyclic β-lactam framework with interesting biological activities (Scheme 6). In view of this we treated azetidin-2-one **9** with dipolarophiles in the presence of acids, bases and Lewis acids. A mixture of azetidin-2-one (**9**, R = Ph, R^1 = Me, Scheme 6), maleic anhydride and catalytic amount of DBU in toluene was refluxed for 5 hours. However, we did not get the desired dipolar cycloaddition product and the product obtained was found to be a ring cleavage product **13** (Scheme 6).

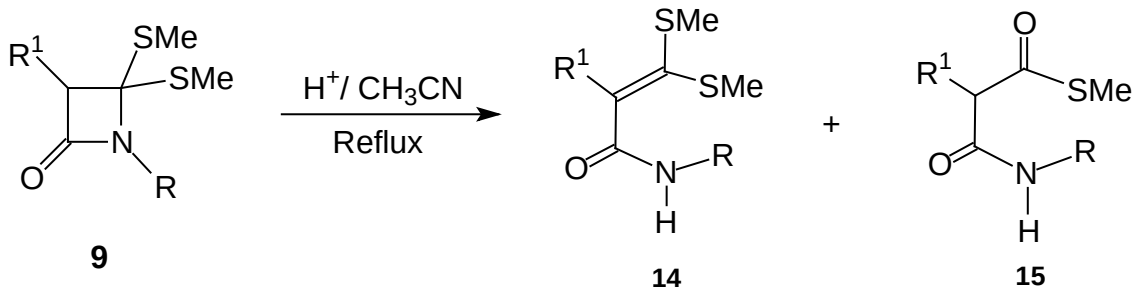
Scheme 6



This product may be formed by the thermal cleavage of the strained azetidinone ring. The thermal decomposition was found to be a common process in basic medium even in the absence of dipolarophile, as similar type of products were obtained when other β-lactam derivatives were heated in toluene and DBU.

Other reaction conditions such as PTSA/acetonitrile reflux, TMS-triflate/DCM reflux, I_2/DCM reflux, $Hg(OAc)_2$/DCM room temperature were tried for the dipolar cycloaddition reaction of **9** (R = Ph, R^1 = Me, Scheme 6) with maleic anhydride. In all the cases no cycloaddition product was observed. However, various ring cleavage products were isolated from the reaction. Therefore, we planned to study the mode of azetidinone ring cleavage under different reaction conditions and the catalysts.

Scheme 7



9 **14** **15**

When β-lactam **9** (R = -CH_2COOMe, R^1 = PhO, Scheme 7) was refluxed in acetonitrile in the presence of an acid catalyst PTSA, a mixture of ring cleavage product **14c** and **15c** were obtained. The ring cleavage product **15** may be arising from the hydrolysis of preformed **14**. Similar type of cleavage was observed when **9** was refluxed with iodine in DCM. Several other β-lactams were studied for the selective ring cleavage using PTSA in refluxing acetonitrile and iodine in refluxing DCM and the results obtained are summarized in the Table 1.

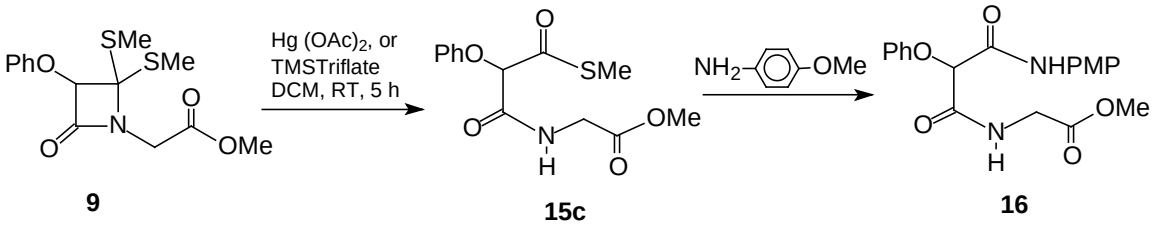
Table 1: Azetidinone ring cleavage products **14a-g** and **15a-g** under acidic conditions

Compound	**R^1**	**R**	**Compound**	**R^1**	**R**
14a	PhO	PMP	**15a**	PhO	Ph
14b	PhO	Cyclohexyl	**15b**	PhO	Cyclohexyl
14c	PhO	CH_2COOMe	**15c**	PhO	CH_2COOMe
14d	PhO	Allyl	**15d**	PhO	CH_2COOEt
14e	BnO	Ph	**15e**	AcO	CH_2COOMe
14f	AcO	Allyl	**15f**	MeO	CH_2COOMe
14g	MeO	$CH(CH_3)COOMe$	**15g**	BnO	Ph

The reaction of azetidin-2-one **9** (R = -CH_2COOMe, R^1 = PhO, Scheme 7) was carried out by using Lewis acid such as mercuric acetate or TMS-triflate in DCM at room temperature. The only product obtained was **15c**, which is a 1,4-ring cleavage followed by

hydrolysis product. This was confirmed by reacting **15c** with *p*-anisidine, which gave the diamide **16** in very good yield (Scheme 8).

Scheme 8



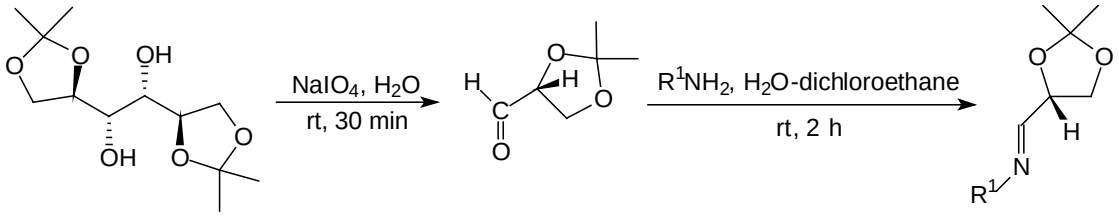
9 **15c** **16**

Chapter-III

Section A: 4-Formylazetidin-2-ones as useful building blocks for the synthesis of optically pure 4-aminopiperidin-2-ones

Piperidin-2-ones serve as very important synthetic intermediates for several piperidine alkaloids and azasugars, also it forms a part structure of biologically important molecules like Streptothricine, cisapride etc. We have used 4-formylazetidin-2-ones as synthon for the synthesis of 4-aminopiperidin-2-ones. The 4-formylazetidin-2-ones are readily prepared in enantiomerically pure form by using asymmetric Staudinger reaction of chiral imines and ketenes. The chiral imines **17** were derived from glyceraldehyde acetonide by reaction with amines (Scheme 9).

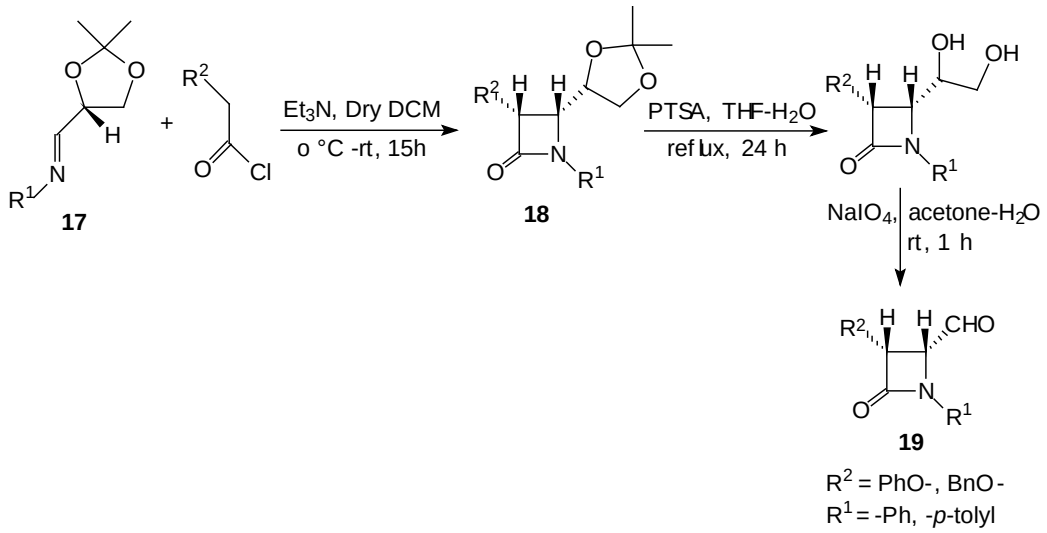
Scheme 9



17

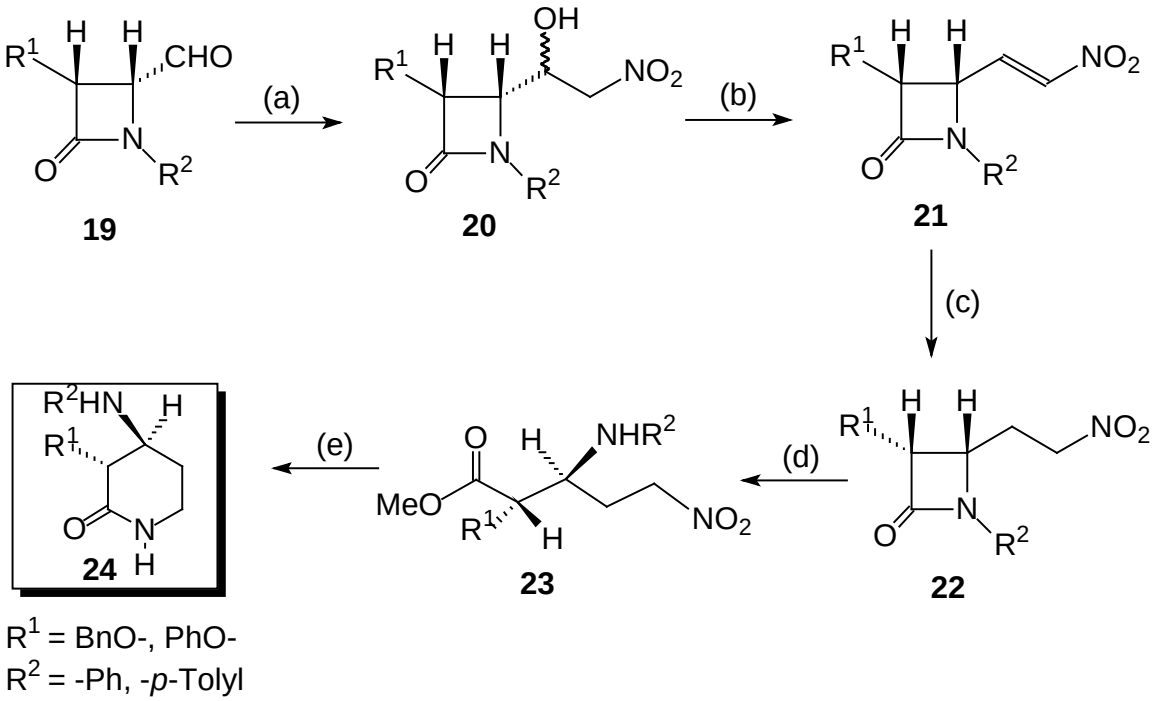
These chiral imines were then reacted with phenoxy and benzyloxy acid chlorides in the presence of triethyl amine at 0 ^{o}C to furnish β-lactams **18**. The deprotection of acetonide by refluxing with PTSA in THF/water followed by oxidative cleavage of the diol by sodium periodate furnished optically pure 4-formylazetidin-2-ones **19** in moderate to good yields (Scheme 10).

Scheme 10



The β-lactams **19** on treatment with nitromethane in the presence of catalytic triethylamine underwent nitro aldol reaction to yield nitroaldols **20**, which were converted to acetates followed by elimination using sodium bicarbonate to get the nitroalkenes **21.** The double bond was reduced using tributyltin hydride to get the nitroalkanes **22**, which was on treatment with methanolic HCl gave β-amino esters **23**. Reductive cyclization of the nitro group of the ester by transfer hydrogenation using 10% Pd-C and ammonium formate gave optically pure 4-aminopiperidin-2-ones **24** (Scheme 11).

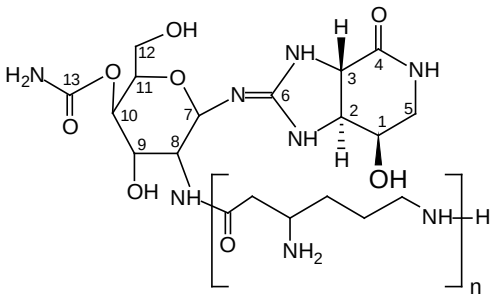
Scheme 11



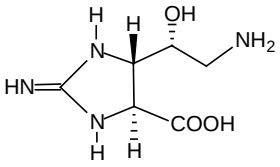
***Reagents and Conditions*:** [a] CH_3NO_2, Et_3N, rt [b] (i) Ac_2O, Conc. H_2SO_4 (ii) $NaHCO_3$-Benzene, Reflux [c] Bu_3SnH, DCM-MeOH, rt [d] 20% methanolic HCl [e] $HCOONH_4$, 10% Pd-C, Dry MeOH.

Section B: Studies towards the synthesis of Streptolidine, an amino acid component of Streptothricine F

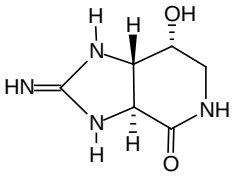
Streptothricine F is a complex of broad-spectrum antibiotic, which shows the potent activity against wide range of bacteria as well as some pathogenic fungi, was first isolated in 1942 by Waksman and its structure was deduced by van Tamelen in 1961. However, the precise location of the carbamate group was in doubt until recently, when it was established by a total synthesis. Each member of the Streptothricine family contains a central carbamoylated D-glucosamine unit bearing a lactam form of novel heterocyclic amino acid component Streptolidine.



Streptothricin



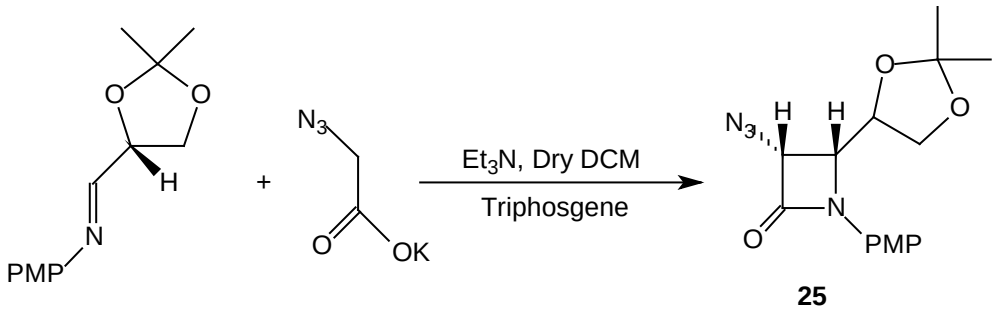
Streptolidine



Streptolidine lactam

We planned the synthesis for precursor of Streptolidine lactam using appropriately substituted 3-azido-β-lactam **25**. This could be easily obtained by ketene-imine cycloaddition reaction of imine derived from glyceraldehyde acetonide and *p*-anisidine with potassium azido acetate (Scheme 12).

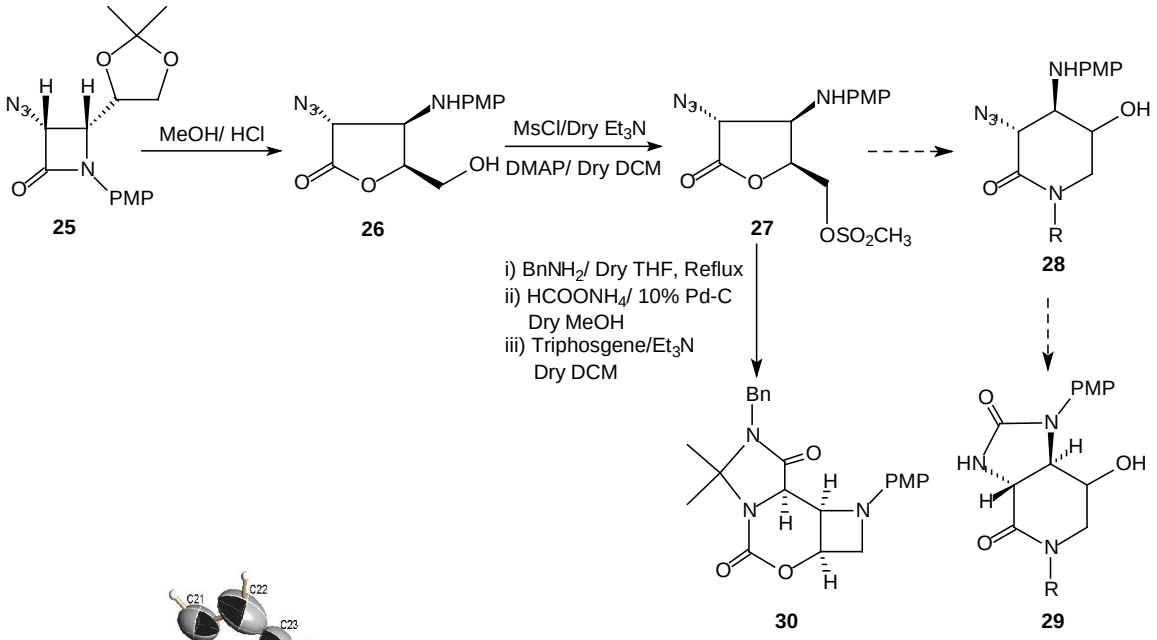
Scheme 12

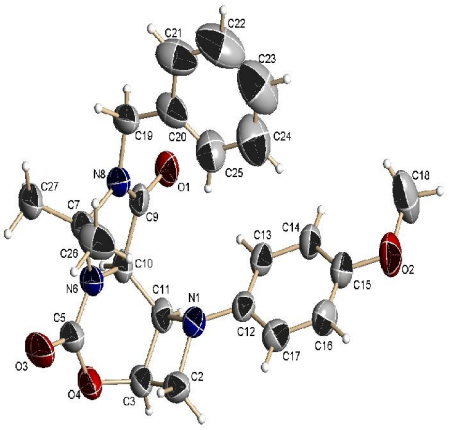


25

The 3-azido-β-lactam **25** was subjected to methanolysis using methanolic HCl, to get rearranged γ-lactone **26** in good yield. The free primary hydroxyl group was protected as the mesylate **27**. The reaction of benzylamine with lactone **27** in refluxing THF should give the required precursor, **28** *via* opening of the lactone ring followed by intramolecular cyclization with concomitant displacement of the mesylate group (Scheme 13). This on reduction and treatment with triphosgene should give the required lactam **29**. However, the reaction of benzylamine with the lactone **27**, followed by reduction of azido group, the treatment of crude product with triphosgene and purification and crystallization of the product from acetone-petroleum ether mixture gave a white crystalline product. A single crystal X-ray analysis showed that the product was a novel tricyclic compound **30** instead of the desired product.

Scheme 13





CONTENTS

Chapter 2

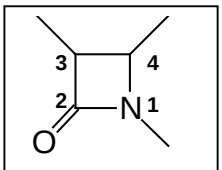
Chapter 3

1.1 : Introduction

Antibiotics form an important group of life saving drugs and occupy a prominent position in the drug industry. The discovery of penicillin in 1921 by Alexander Fleming[1] was the beginning of a new era in man's fight against disease and death. This discovery proved to be a milestone in the history of medicinal and heterocyclic chemistry. The structure of penicillin was debated until 1940. Sir Robert Robinson proposed thiazolidine-oxazolone structure while Prof. R. B. Woodward strongly supported structure based on a 4-membered amide framework. Finally, in 1949 Dorothy Hodgkins[2] and Barbara Low completed a three dimensional X-ray crystallographic analysis of benzyl penicillin. With this discovery it was established for the first time the presence of a 4-membered amide in the form of β-lactam, which was responsible for the effective biological activity of antibiotics.

The β-lactam antibiotics are the maximum selling pharmaceuticals by volume in the world for the clinical applications, which account for 50% of the world's total antibiotic market. There are more than 40 β-lactam antibiotics in clinical use today. These compounds retain the β-lactam ring but have been developed to include various side chains resulting in varied pharmacological properties.

Azetidin-2-one, a four membered cyclic amide ring (β-lactam) forms a part structure of many of these antibiotics and occupies a unique place in the heterocyclic chemistry.



Azetidin-2-one

The antibiotic activity of azetidin-2-ones, their effectiveness as inhibitors of cholesterol absorption and many other enzymes and their applications as synthons for various biologically important compounds make them appealing targets for medicinal as well as synthetic chemists. They have high antibacterial activity and low toxicity.

Staudinger reported the first synthesis of β-lactam ring way back in 1907.[3] Until 1970, penicillin and cephalosporins[4] were the only examples of naturally occurring β-lactam antibiotics. The discovery of 7-α-methoxycephalosporins[5] from "*Streptomyces*" in

1971 stimulated the search for novel antibiotics. The β-lactam antibiotics can be classified into several groups based on their structures (Figure 1).

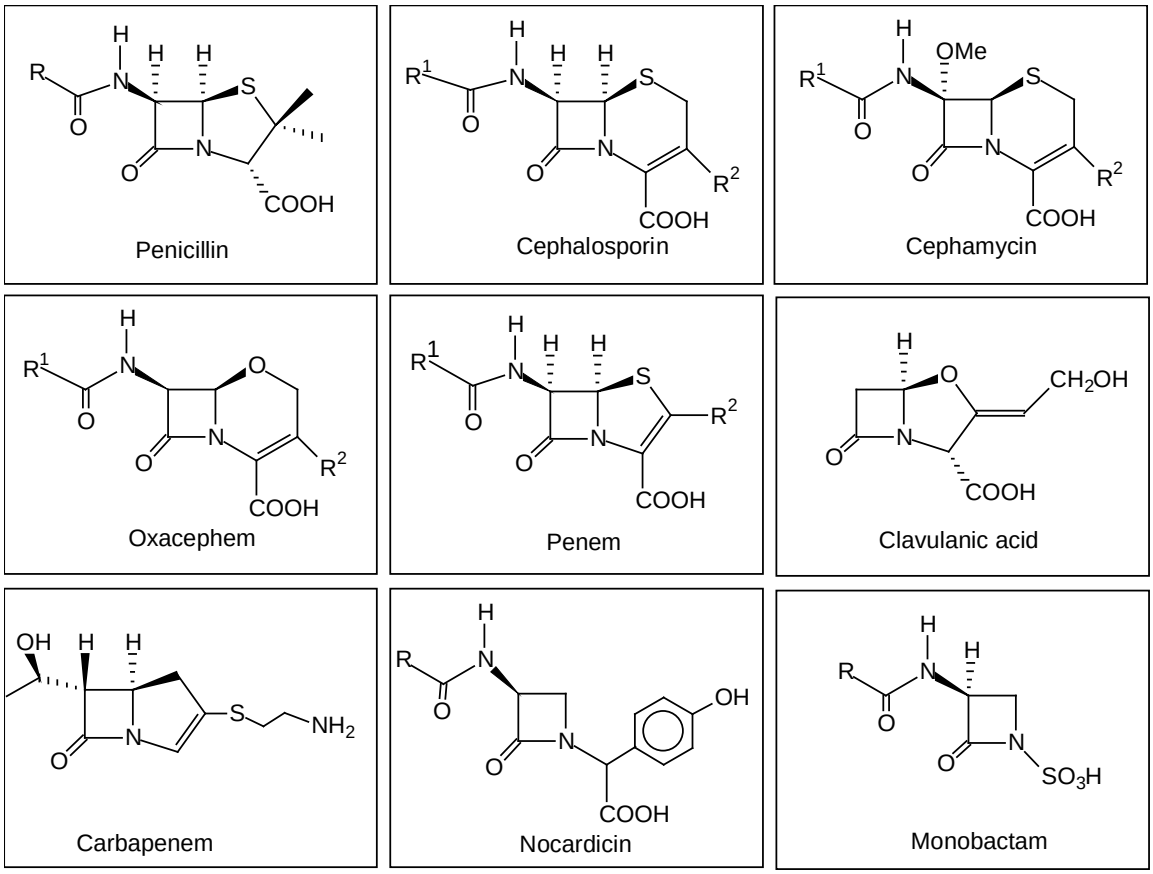


Figure 1 Classification of β-lactam antibiotics based on structure

Carbacephems,[6] which are carbon analogues of cephalosporins are also being used as antibiotics. They have superior stability over cephalosporin. Loracarbef (lorabid) is the first carbacephem approved for clinical use (Figure 2).

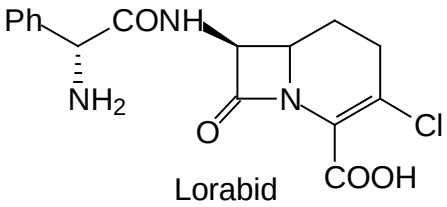
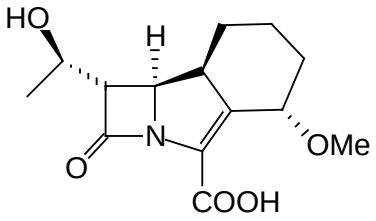


Figure 2

Tricyclic β-lactam antibiotics called trinems[7] (Figure 3) belong to a new class of tricyclic carbapenems. GV 104326, a highly potent, broad-spectrum antibacterial agent, effective against gram-positive, gram-negative and anaerobic pathogenic bacteria, is an example of tribactam antibiotic.



GV 104326 (tribactam)

Figure 3

In 1995, a new class of compounds was reported in which the antibiotic property of β-lactams and the antiviral property of nucleosides were incorporated together to afford dual properties of the drug.[8] Kehagia et al.[9] reported a new class of β-lactams in which a steroidal and β-lactam units were coupled together *via* Ugi reaction in a one step process (Figure 4).

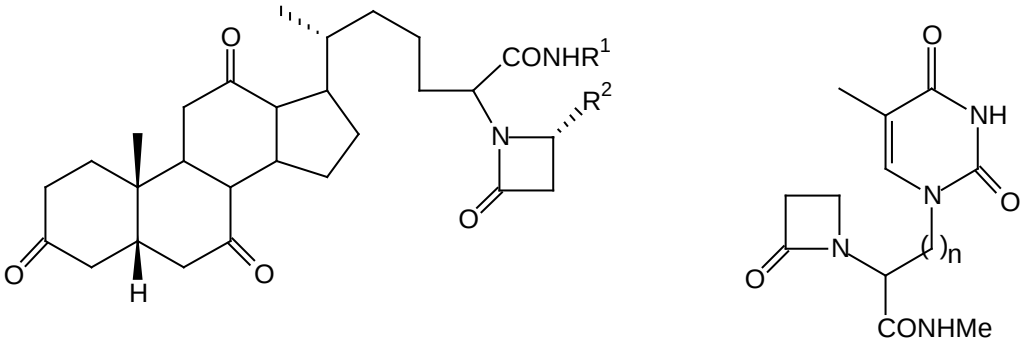


Figure 4

Apart from their antibacterial activities, β-lactams also show other biological activities that include cholesterol absorption inhibition[10] and human leukocyte elastase (HLE).[11]

All these biologically active β-lactams, except the monobactams, have a common feature i.e. a fused bicyclic lactam ring with nitrogen at the ring junction. Because of the rigid conformation and the ring strain the lactam functionality is no more planer and there is no delocalization of nitrogen lone pair of electrons to the carbonyl group, which enhances the reactivity of these compounds towards nucleophilic attack, an essential criteria for the antibiotic activity of these compounds.

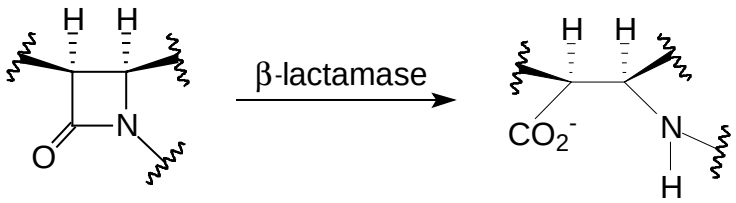
Mode of action

The biological activity of β-lactam antibiotics is mainly due to the presence of the azetidin-2-one ring (β-lactam ring). The SAR[12] studies have shown that the main requirement for the antibiotic is that it should be able to penetrate the outer spheres of the bacterial cell wall and then bind in active form to the targets, which are the inner membrane enzymes that are responsible for the biosynthesis of the cell wall, thereby inactivating one or more enzymes involved in the cell wall synthesis. Penicillin binds to the target proteins, so-called 'penicillin-binding proteins' (PCBs), which are group of transpeptidases within the bacterial cell membrane that mediates the cell wall biosynthesis. The binding of penicillin to the PCBs causes termination of the peptide chain linking and inhibits the formation of normal peptidoglycan structure. This leads to the weakening of cell wall and lysis.[13]

β-Lactamases and β-lactamase inhibitors

The β-lactamases[14] are group of bacterial enzymes that catalyze the hydrolysis of β-lactam antibiotics (Scheme 1.01). Since the hydrolyzed β-lactam has no antibiotic activity, the β-lactamases represents a source of bacterial resistance against β-lactam antibiotic.

Scheme 1.01



β-Lactamases are the enzymes that bacteria produce to defend themselves against β-lactam antibiotics, which limits the effectiveness of the drug and contributes to the savages of infectious diseases.

This phenomenon of bacterial resistance led to a serious research in this field and paved the way for development of novel β-lactams called β-lactamase inhibitors.[15] They are essentially structural variants of the classical β-lactams with modified skeleton. They may not have antibiotic activity of their own, but they are used in combination with the β-lactam antibiotic. Specifically they associate themselves with the β-lactamases, thereby protecting the antibiotic against the hydrolytic action of β-lactamase. Thus the antibiotic activity of the β-lactam is safeguarded and it can penetrate through the bacterial cell wall.

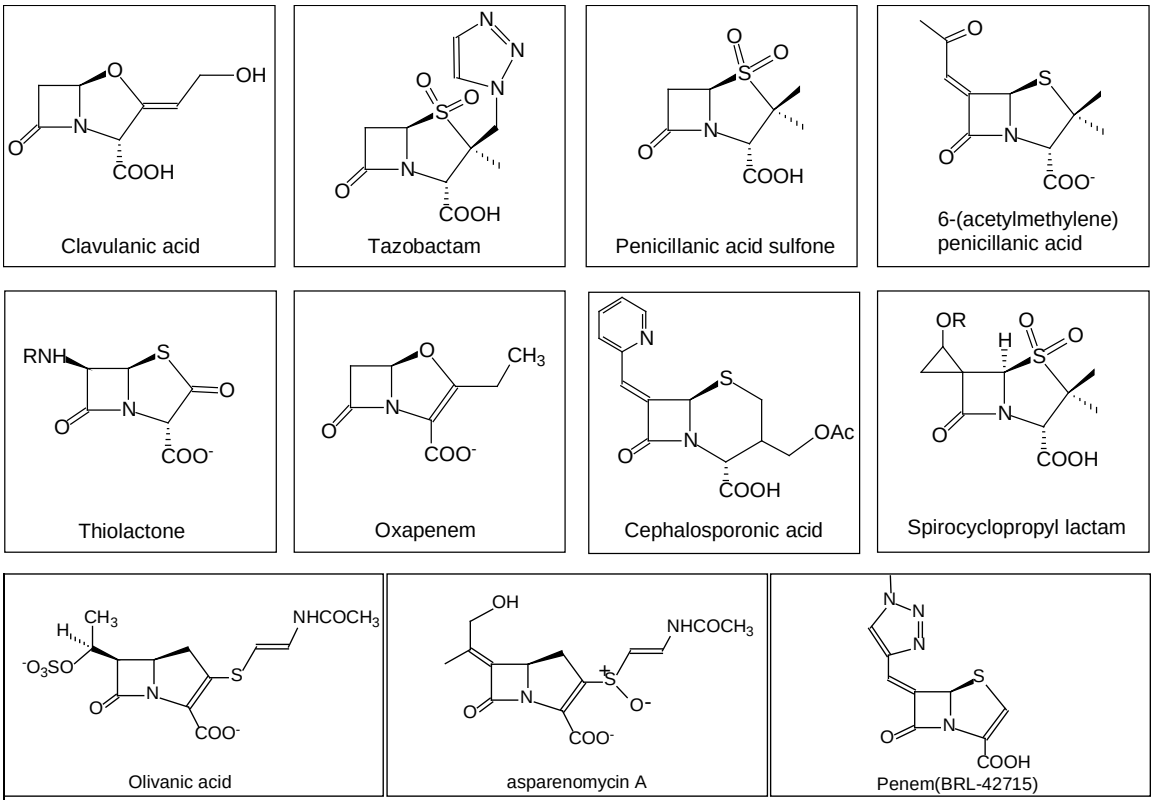
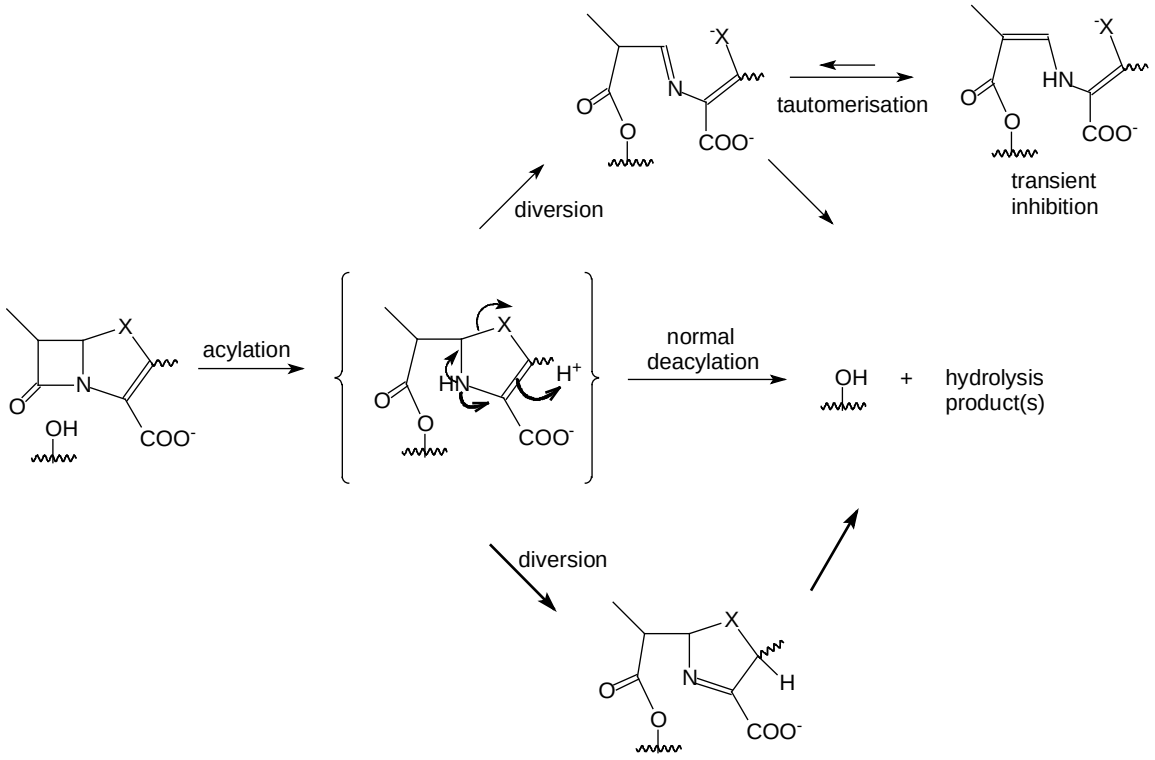


Figure 5 Different β-lactamase inhibitors

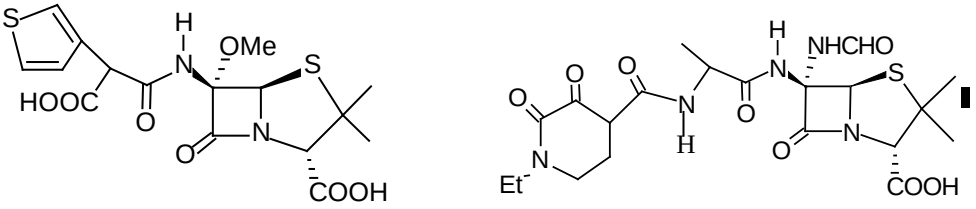
Most effective and specific β-lactamase inhibitors to date are the β-lactams themselves i.e. the substrate analogues (Figure 5). The inactivating agent may be antibiotic itself or it could be a separate molecule administered in synergy with the antibiotic. Most of the recently developed inhibitors are mechanism based i.e. they are the substrates which contain additional functionality, which acts during the turnover so as to divert normal enzyme substrate intermediate into less labile form. The combination of β-lactam antibiotic and inhibitor has proved to be the most effective antibiotic strategies e.g. clavulanic acid with amoxicillin is distributed as Augmentin while Penicillanic acid sulfone with ampicillin as Sulfamicillin.

The β-lactamases produced by the bacteria inactivates the β-lactam antibiotics but are themselves the targets for the inhibitory action of β-lactamase inhibitors. The first step in the process is the nucleophilic substitution at carbonyl carbon followed by formation of acyl-enzyme intermediate, which in turn is hydrolyzed to give the product with the regeneration of β-lactamase (Scheme 1.02).

Scheme 1.02 Generalized scheme for the inhibition of β-lactamases



Temocillin and Formidacillin[15a] are some of the examples of β-lactamase inhibitors, which are the result of extensive SAR studies of penicillin (Figure 6).



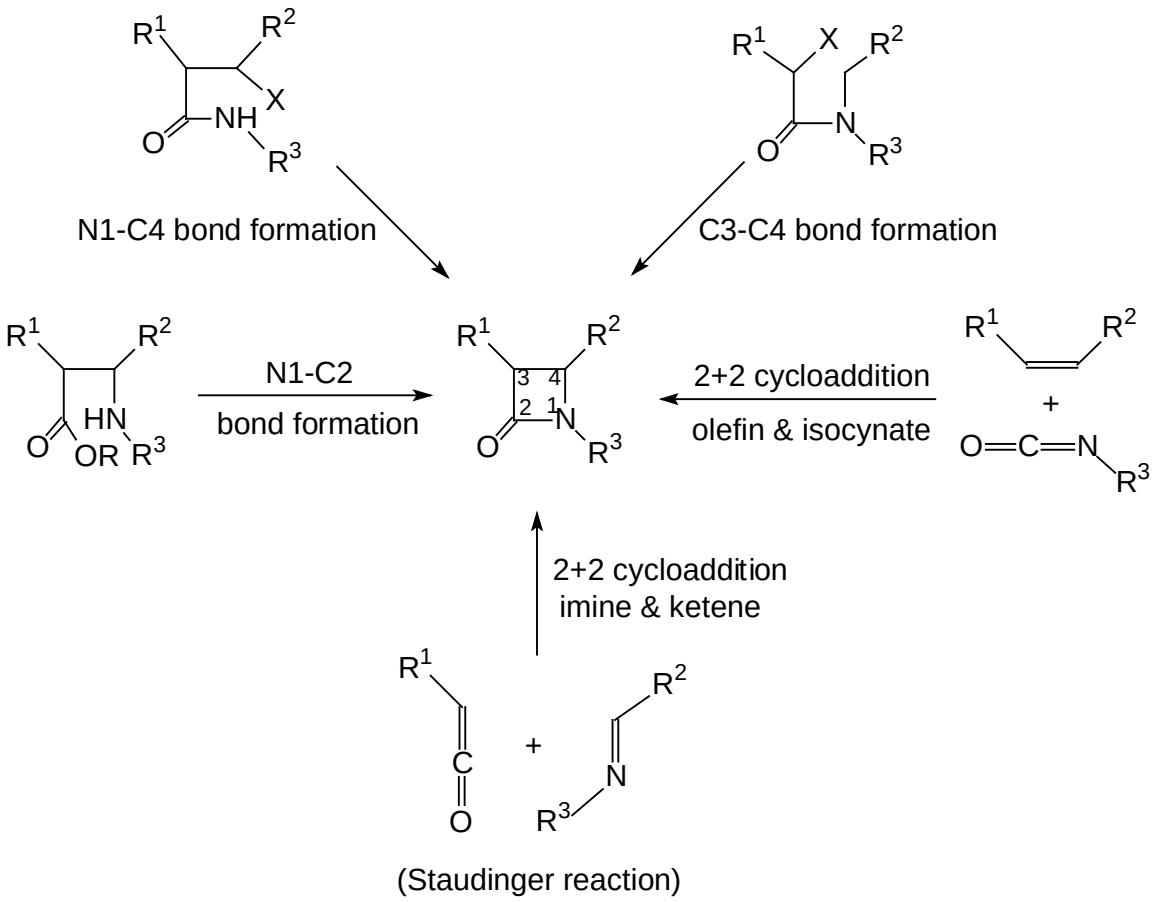
Temocillin Formidacillin

Figure 6 Different mechanism and structure based lactamase inhibitors

General methods for constructing azetidin-2-one (β-lactam) ring:

Over the past few decades, several methodologies[16] have been developed for the construction of the β-lactam ring. The following scheme shows the different ways of constructing the β-lactam ring. A few important methods are discussed here.

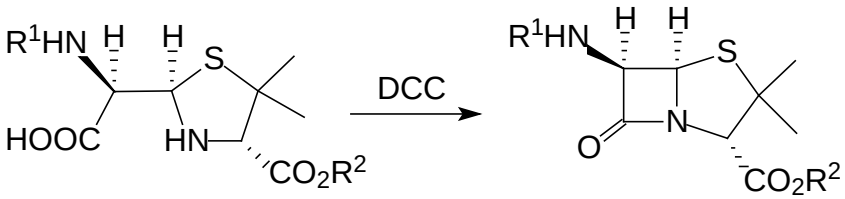
Scheme 1.03 General methods for construction of azetidin-2-one (β-lactam)



Formation of N(1)-C(2) bond:

Staudinger, Klever and Kober[17] first reported this approach in 1910. Sheehan and Henery-Logan have used this method for their landmark synthesis of penicillin[18] by cyclization of β-amino acid using dicyclohexylcarbodiimide (DCC) as a condensing reagent (Scheme 1.04).

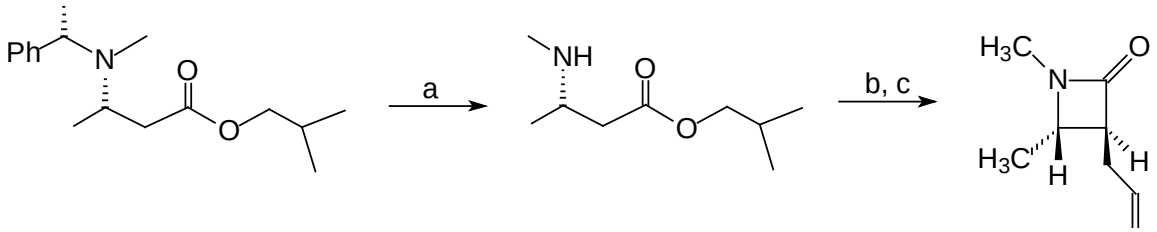
Scheme 1.04



Mc Whorter and coworkers[19] recently reported the N(1)-C(2) bond formation for azetidinone ring construction in a reaction sequence for the preparation of *N*-Methyl-*N*-{(1*S*)-1-[(3*R*)-pyrrolidine-3-yl]ethyl}amine, a key intermediate in preparation of

premafloxacin (Scheme 1.05). Premafloxacin is an antibiotic used against pathogens of veterinary importance.

Scheme 1.05

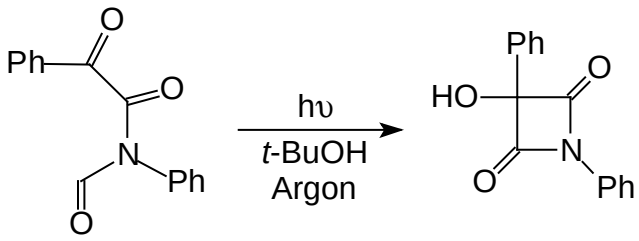


***Reagents and conditions*:** (a) $Pd(OH)_2$, H_2, EtOH; (b) LDA (2.2 equiv.), THF, -40 ^oC; (c) allyl bromide (1.9 equiv.).

Formation of C(2)-C(3) bond:

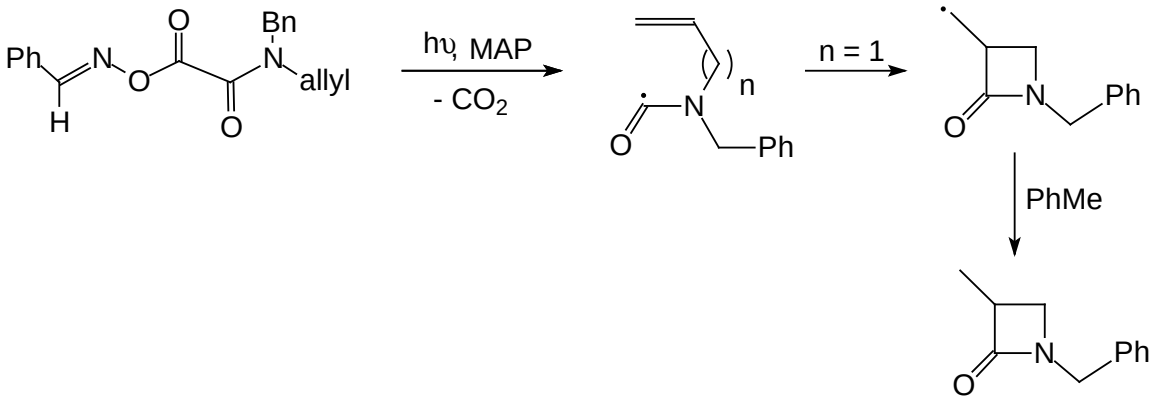
Compared to the amide (N1-C2) bond formation, azetidinone formation at the C(2)-C(3) position is complicated by the difficulty in forming a C-C bond versus an amide bond. Hence this method is least used. A photochemical approach leading to formation of 4-keto-β-lactams has been developed[20] (Scheme 1.06).

Scheme 1.06



Recently Walton and coworkers[21] have reported the photo irradiation of oxime oxalate amides to generate amino acyl radical that furnishes β-lactams by C(2)-C(3) bond formation (Scheme 1.07).

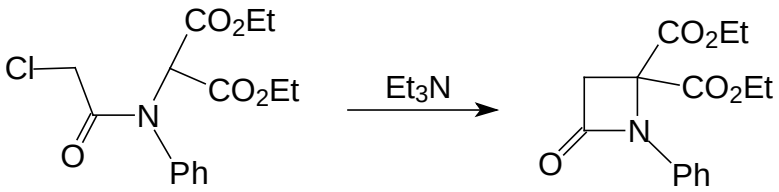
Scheme 1.07



Formation of C(3)-C(4) bond:

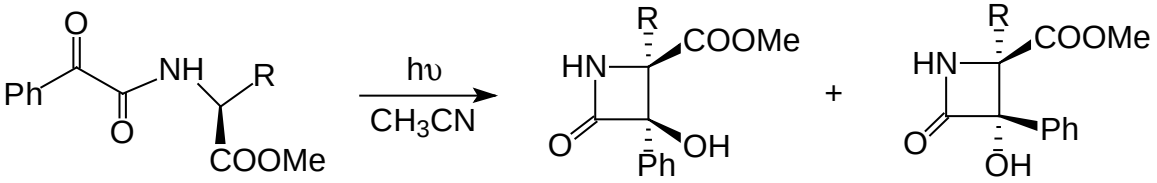
This involves formation of a nucleophilic center at C-3 and an electrophilic center at C-4 or *vice versa*. Sheehan and Bose[22] have reported the first example of such an intramolecular nucleophilic displacement reaction wherein haloacylamino malonate is cyclized in an intramolecular fashion in the presence of a base (Scheme 1.08).

Scheme 1.08



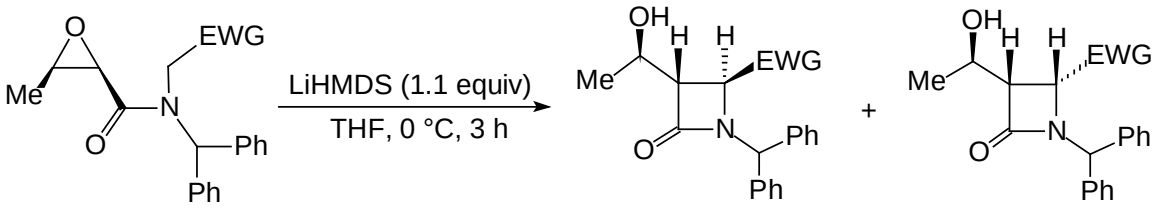
Recently, a photocyclization of phenylglyoxyamides of α-amino acid methyl esters to 3-hydroxy β-lactams has been reported, [23] which involves the formation of C(3)-C(4) bond (Scheme 1.09).

Scheme 1.09



Brynaert has reported[24] intramolecular C(3)-C(4) bond formation with simultaneous epoxide ring opening in the synthesis of β-lactam ring (Scheme 1.10).

Scheme 1.10

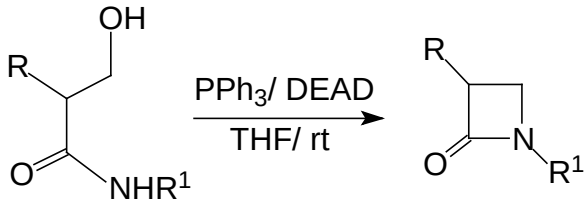


EWG : -COBu^t; -COPh; -COBu^t; -CN

Formation of N(1)-C(4) bond:

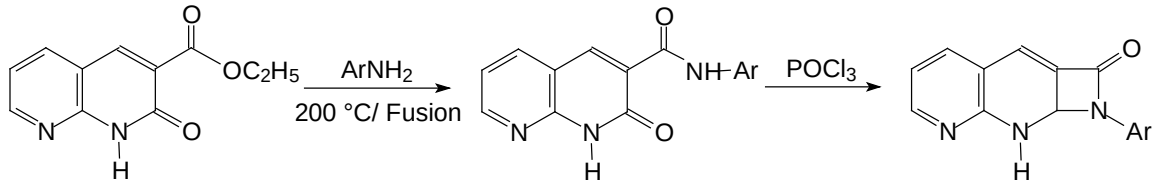
This is the route selected by nature for the biosynthesis of azetidinone containing antibiotics.[25] The essential strategy involved in the synthesis of β-lactams through N(1)-C(4) bond is the intramolecular displacement of a leaving group attached to C-4 with appropriately activated nitrogen. Miller and coworkers[26] have made significant contribution to this methodology. The key feature of the Miller's hydroxamate approach is the intramolecular cyclization of chiral β-hydroxy amides under Mitsunobu reaction conditions (Scheme 1.11).[27]

Scheme 1.11



In synthesis of azetidinones with benzo(b)thiophene nucleus as potent antitubercular and antimicrobial agents, Mogilaiah[28] reported the use of N(1)-C(4) bond formation in *N*-aryl-1,8-naphthyridin-2-one-3-carboxamides (scheme 1.12).

Scheme 1.12

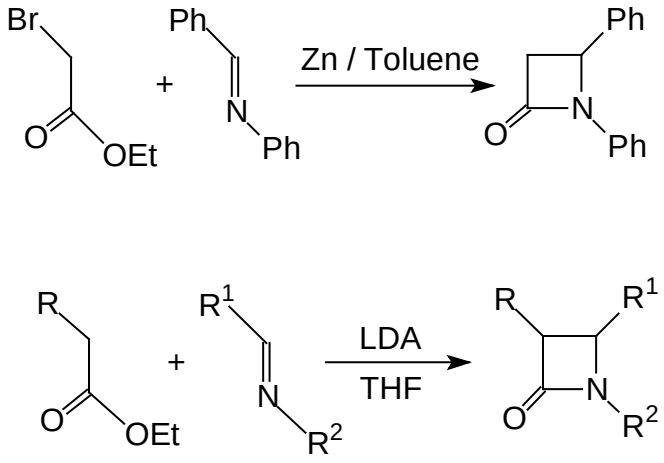


Enolate-Imine condensation:

Gilman and Speeter first reported this reaction.[29] The authors constructed the β-lactam ring by condensation of Zn enolate (Reformatsky reagent) with imines. Later on, other

metal enolates have also been used in the enolate imine condensation reaction to achieve good selectivities and yields in β-lactam formation (Scheme 1.13).[30]

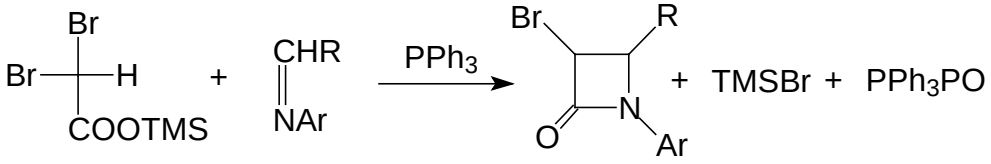
Scheme 1.13



Manhas's α-Bromo-β-Lactam approach:

Manhas et al.[31] have developed this approach, which involves condensation of halo ester with imines in the presence of triphenyl phosphine (Scheme 1.14).

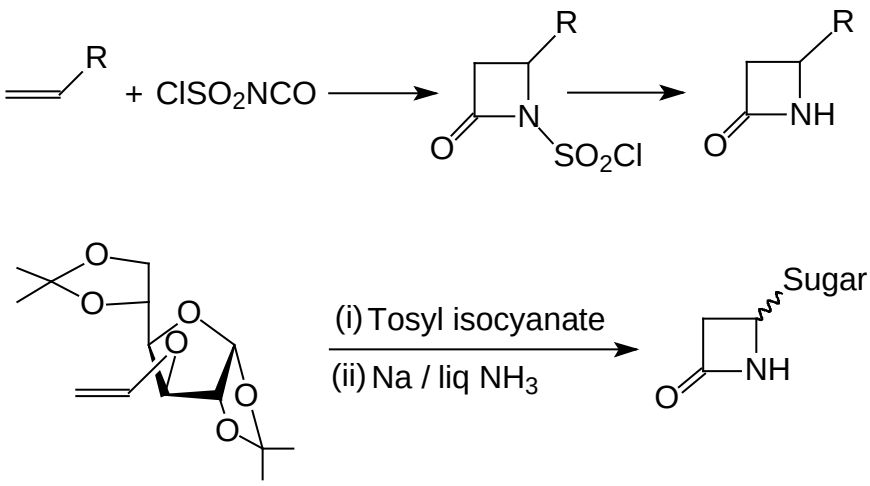
Scheme 1.14



Isocyanate addition to alkenes:

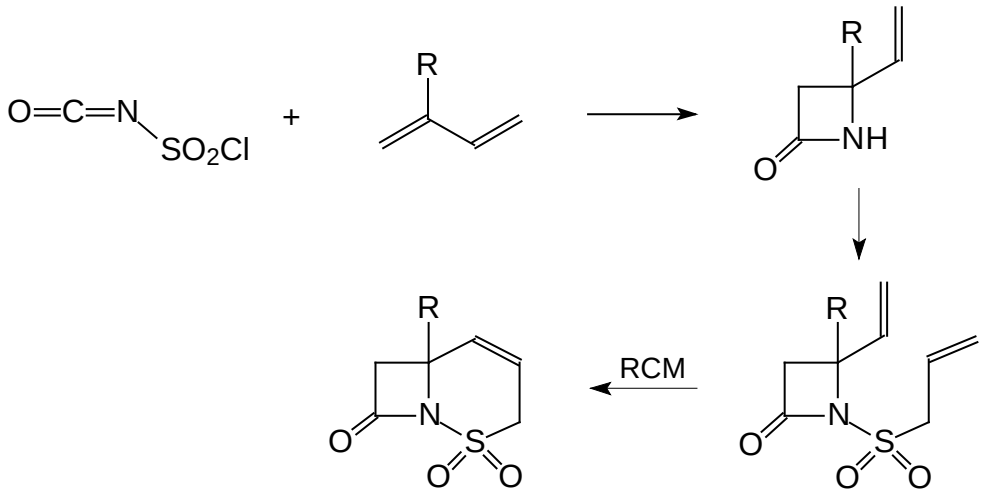
Graf[32] reported the cycloaddition of *N*-chlorosulfonyl isocynate (CSI) with alkenes to get 1-chlorosulfonyl azetidin-2-ones. Subsequent removal of the chlorosulfonyl group furnishes the NH β-lactam. The cycloaddition is promoted by activated alkenes like vinyl acetates. Chmielewski and coworkers have used the cycloaddition reaction between tosyl isocynate and sugar derived vinyl acetates to obtain good diastereoselectivities in β-lactam formation (Scheme 1.15).[33]

Scheme 1.15



Peter Metz[34] has recently employed the same approach of chlorosulfonyl isocynate-olefin cycloaddition for the preparation of β-lactam sulfonamide hybrids (Scheme 1.16).

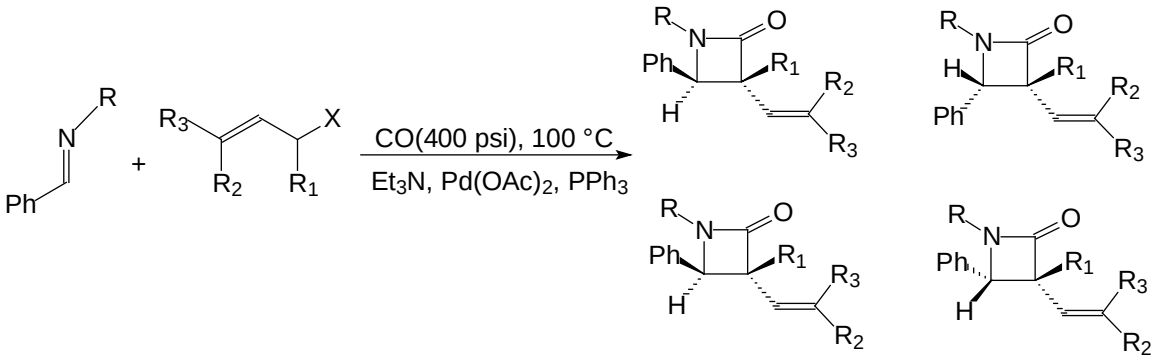
Scheme 1.16



Miscellaneous methods for construction of azetidin-2-one ring:

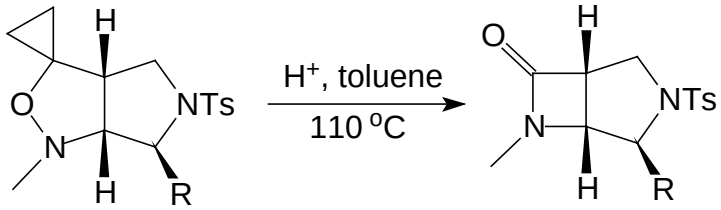
Troisi et al.[35] have used Palladium catalyzed [2+2] carbonylative cycloaddition reaction for the stereoselective synthesis of alkenyl-β-lactams (Scheme 1.17).

Scheme 1.17



Recently, Cordero et al.[36] have reported that spirocyclopropane isoxazolidines undergo ring contraction to yield β-lactams on heating in the presence of protic acid (Scheme 1.18).

Scheme 1.18

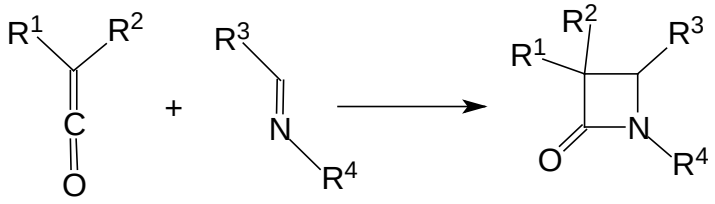


R = Me, *iso*-propyl

Staudinger Reaction:

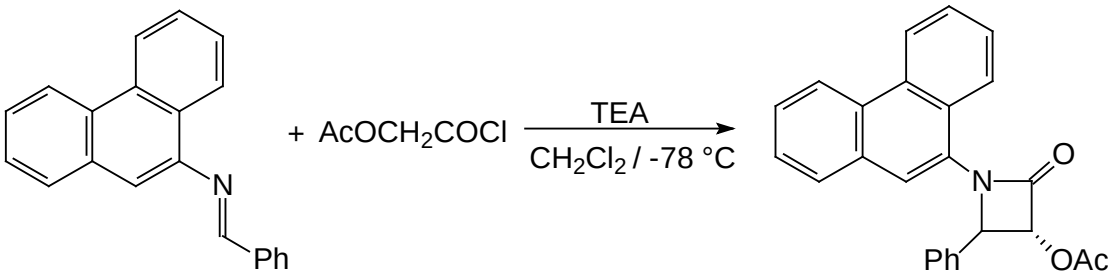
Staudinger achieved the first chemical synthesis of β-lactam ring in 1907 by [2+2] cycloaddition of ketenes with imines. This reaction is referred to as Staudinger reaction or ketene-imine cycloaddition reaction[37] (Scheme 1.19). Later it was modified, wherein acid chlorides or activated carboxylic acids were used in the presence of a base as ketene precursor.

Scheme 1.19



Banik and his group[38] recently demonstrated the mechanistic correlation between the β-lactams derived from polyaromatic imines with their anticancer activity (Scheme 1.20).

Scheme 1.20



The ketenes required for cycloaddition can also be prepared from corresponding carboxylic acids by using an acid activator. In one of such reactions β-lactams were synthesized by using Lawesson's reagent as an activator.[39a] The synthesis and chemistry of azetidinones has been extensively reviewed recently by Singh.[39b]

Asymmetric Synthesis of β-lactams:

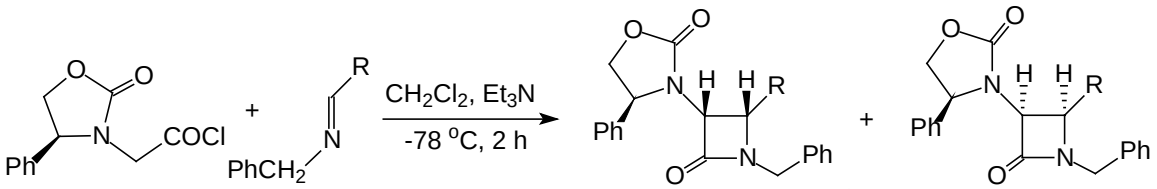
Asymmetric synthesis of β-lactams is an important area of research, as biological activity of β-lactam antibiotics is closely related to the stereochemistry. Among the various methods available for the asymmetric synthesis of β-lactams, the asymmetric Staudinger reaction[37,40] (ketene-imine cyclization) is the most widely used. This is mainly because of the simplicity in reaction procedures and versatility. Asymmetry can be induced in a ketene-imine cycloaddition reaction by using a chiral ketene or chiral imine or both (referred as double stereo differentiation).

Asymmetric Staudinger reaction using chiral ketene precursors*:*

Various levels of diastereoselectivities in β-lactam formation using chiral auxiliary in the ketene component have been reported in literature. Following is a brief review of asymmetric Staudinger reaction using chiral ketenes.

Evans and Sjogren[41] developed a (*S*)-phenylglycine derived oxazolidinone as a chiral auxiliary attached to ketene component in the asymmetric Staudinger reaction and obtained very high diastereoselectivity (>95%) in the *cis* β-lactam formation. No trace of the *trans* isomer was detected (Scheme1.21).

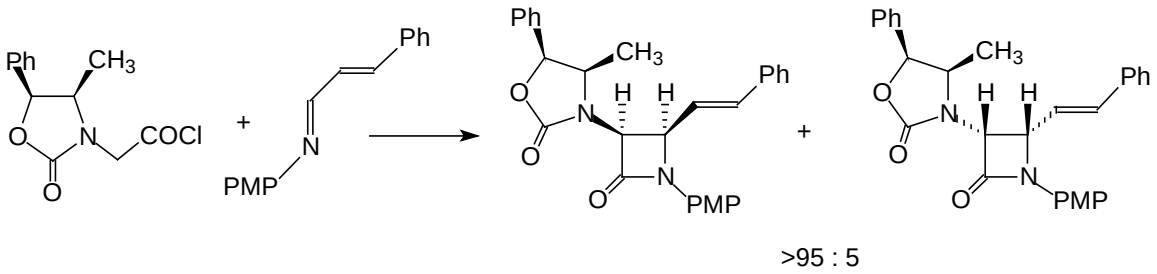
Scheme 1.21



Boger and Myers[42] used the enantiomeric oxazolidinone to synthesize the other diastereomer of the β-lactam with very good diastereoselectivity.

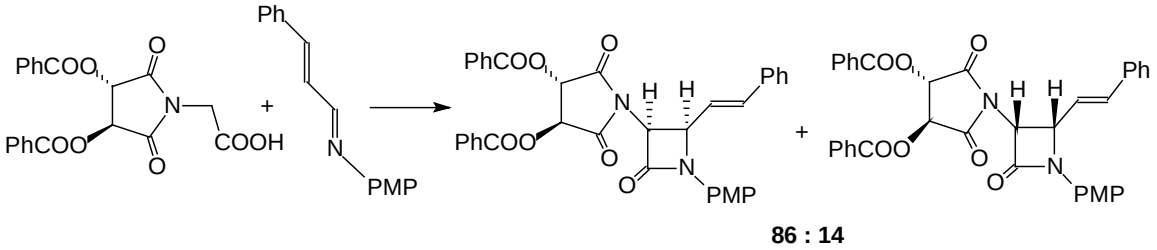
Cooper et al.[43] have used a norephedrine derived oxazolidinone as the chiral auxiliary in the ketene component and achieved very high diastereoselectivity (>95%) in the *cis* β-lactam formation *via* asymmetric Staudinger reaction (Scheme 1.22).

Scheme 1.22



Cooper et al.[43] have also reported the use of a tartarimidoacetic acid derived from *S*, *S*-tartaric acid as a chiral ketene precursor in the asymmetric Staudinger reaction. However, there was only moderate diastereoselectivity in the β-lactam formation (de up to 72%) as the chiral center is farther away from the amide nitrogen (Scheme 1.23).

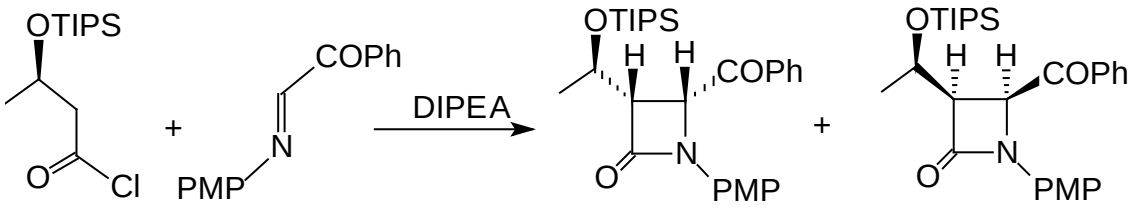
Scheme 1.23



An acid chloride derived from *O*-protected 3-hydroxybutyric acid was used in the asymmetric Staudinger reaction to yield diastereomeric mixture of β-lactams. The ratio

depends on the solvent used. Increase in the diastereoselectivity was observed with the increase in bulkiness of the *O*-protecting group (Scheme 1.24).[44]

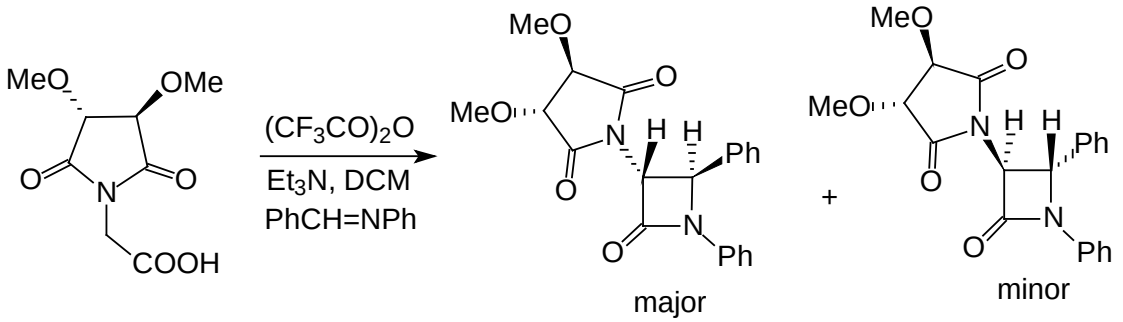
Scheme 1.24



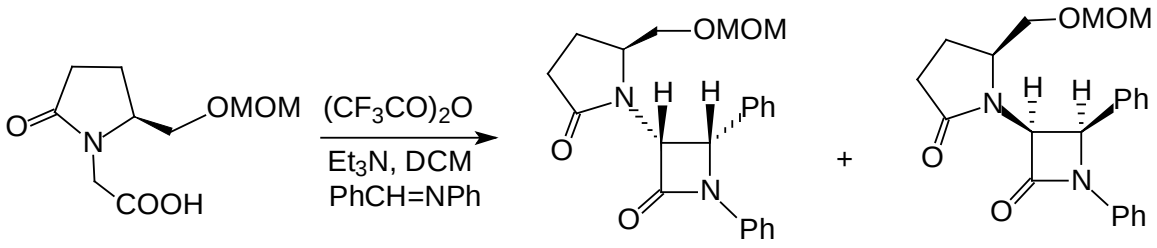
1:4 in DCM
1:7 in DMP

Ikota et al.[45] have used mixed anhydride of acetic acid derived form (*L*)-(+)-Tartaric acid, (*S*)-Glutamic acid, and (*S*)-Serine as the chiral ketene precursor in the asymmetric Staudinger reaction with imines derived from benzylideneaniline and obtained very good diastereoselectivity in β-lactam formation (Scheme 1.25). The removal of the chiral auxiliary gave the 3-amino β-lactam derivatives.

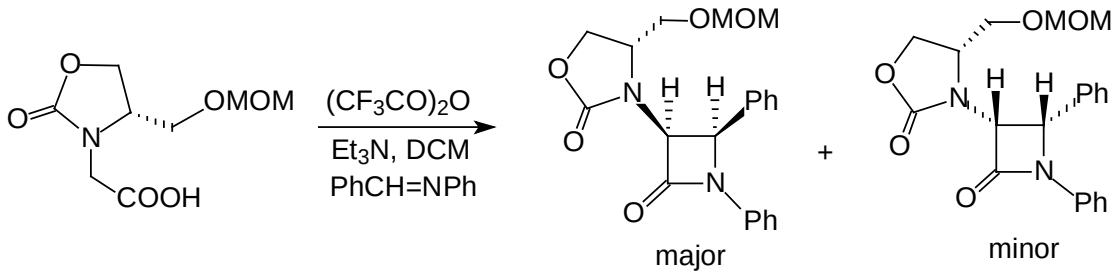
SCHEME 1.25



68% de



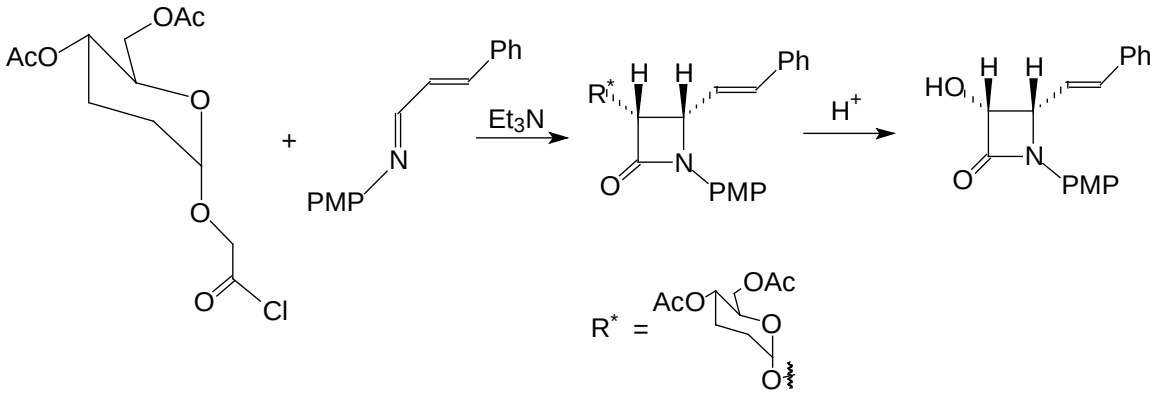
94 - 96% de



92 - 94% de

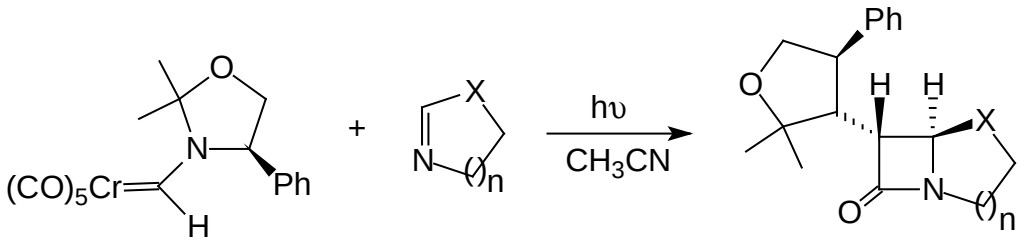
Borer and Balogh[46] have used a chiral ketene derived from carbohydrate (tri-*O*-acetyl-D-glucal) in the asymmetric Staudinger reaction to get *cis* β-lactams with good diastereoselectivity. Removal of the chiral auxiliary by hydrolysis using 4:1:1 THF/ H_2O/ AcOH gave the *cis* β-lactams with 70% enantiomeric excess (Scheme 1.26). An excellent review by Chemielewski, on the use of carbohydrates in β-lactam synthesis has appeared in 1994.[47]

Scheme 1.26



Hegedus et al.[48] have prepared *trans* β-lactams in excellent yields (75-95%) and diastereoselectivity (>95%) by the photolysis of optically active chromium carbene complexes with cyclic imines (Scheme 1.27).

Scheme 1.27

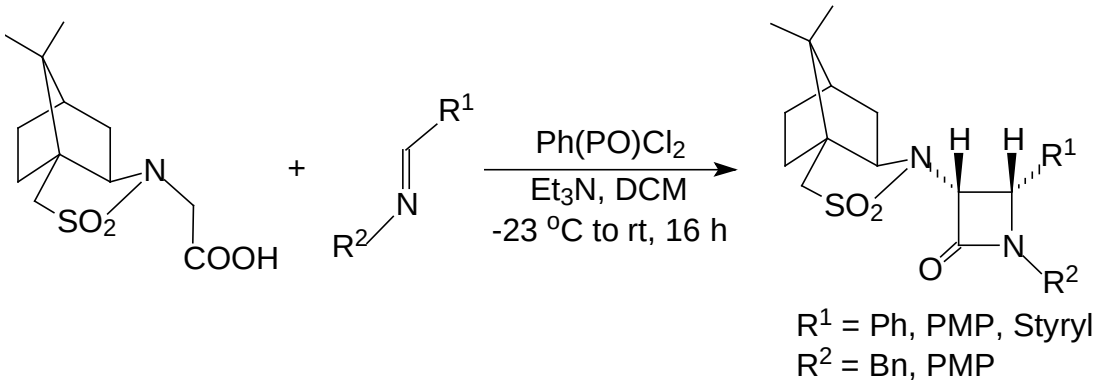


n = 2, 3

X = CH_2, O

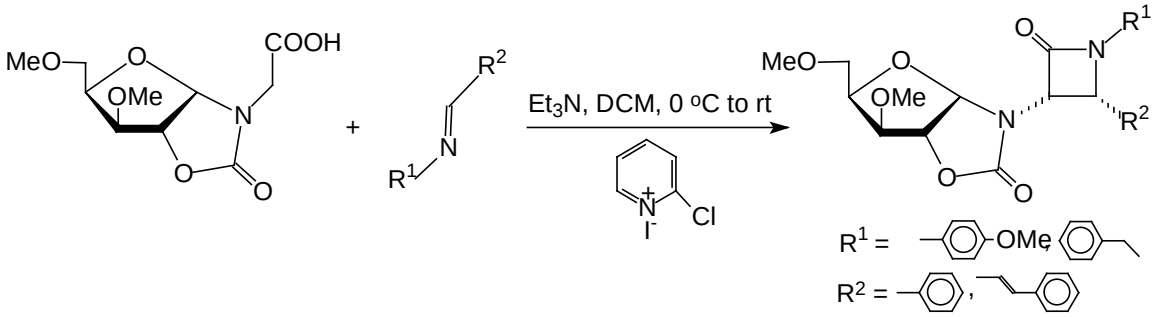
Chiral acid derived from Oppolzer's sultam has been used as chiral ketene precursor in the asymmetric Staudinger reaction to get diastereospecifically a single *cis* β-lactam[49] in good yields (Scheme 1.28).

Scheme 1.28



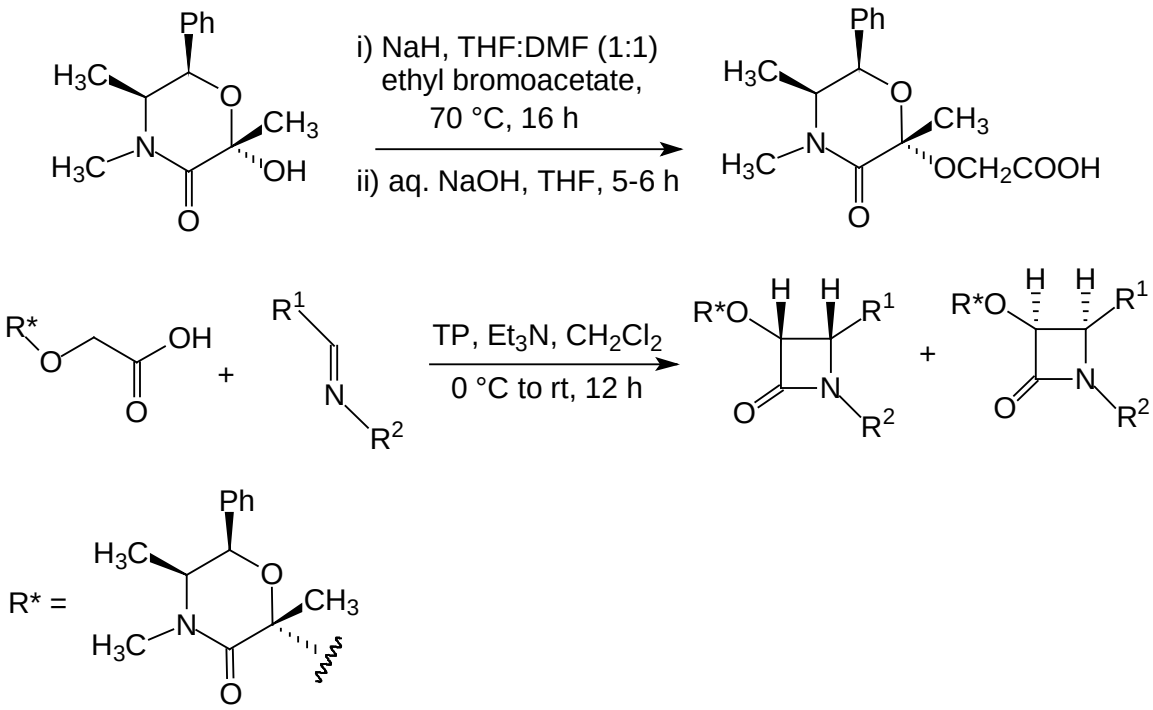
Recently Saul et al.[50] have achieved excellent diastereoselectivity (>99%) in β-lactam formation using a chiral oxazolidinone auxiliary based on D-Xylose as a ketene precursor in the asymmetric Staudinger reaction (Scheme 1.29).

Scheme 1.29



Shinkre et al.[51] have used (-)-ephedrine derived chiral acid for diastereoselective synthesis of various β-lactams (Scheme 1.30). They have demonstrated an efficient use of (-)-ephedrine derived chiral auxiliary, which can be removed at a later stage by using acid hydrolysis and recycled. This significantly improves the practical scope of large-scale preparation of enantiopure 3-hydroxy-*cis*-β-lactams, one of which is a key intermediate for the taxol side-chain.

Scheme 1.30



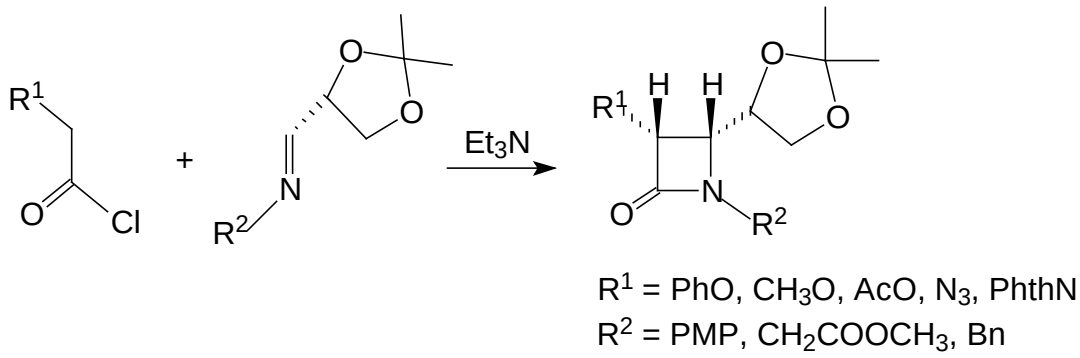
Asymmetric Staudinger reaction using chiral imines:

Asymmetric induction *via* chiral imines can be achieved by using either chiral aldehydes or chiral amines. The use of chiral aldehydes and chiral amines will be briefly discussed below.

Chiral Aldehydes:

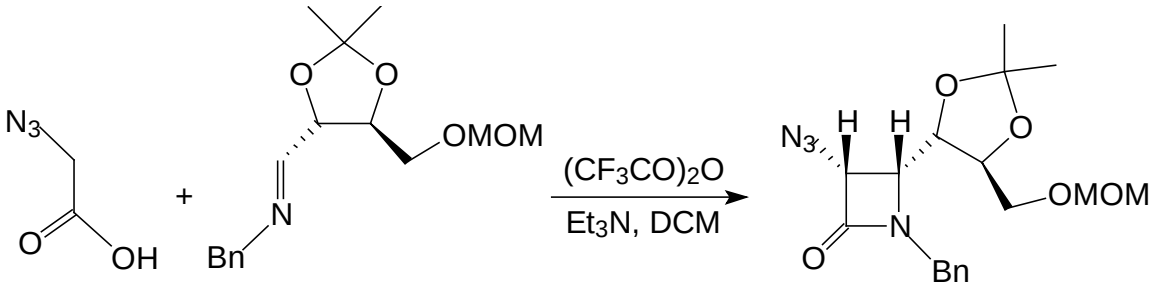
Imines derived from D- and L-glyceraldehyde acetonide[52] gave complete *cis* diastereoselectivity in β-lactam formation *via* asymmetric Staudinger reaction (Scheme 1.31). Bose and co-workers, in series of papers,[53] have reported similar observation.

Scheme 1.31



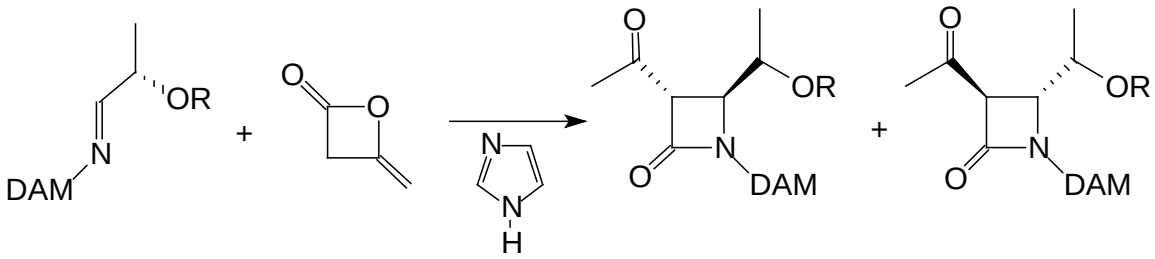
Ikota has reported the use of an imine derived from 2,3-*O*-isopropylidene-L-threitol in the asymmetric Staudinger reaction and achieved very good diastereoselectivity (Scheme 1.32).[54]

Scheme 1.32



Ito et al.[55] have used the diketenes along with the imine derived from commercially available (*S*)-ethyl lactate as the chiral aldehyde component in the asymmetric Staudinger reaction. The diastereoselectivities were solvent dependent, with acetonitrile giving the best results (90% de) (Scheme 1.33).

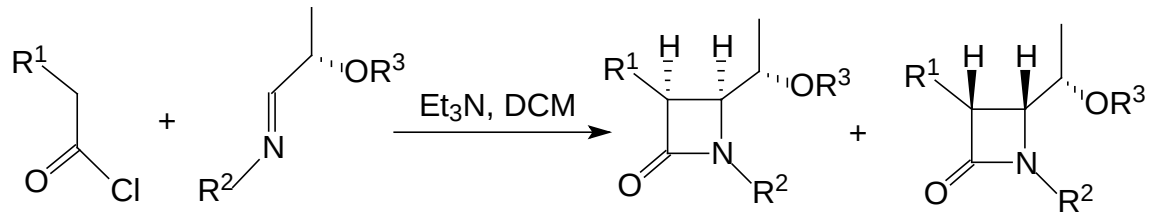
Scheme 1.33



R = Bn, TBDMS

Palomo et al.[56] and Brown[57] have also used the chiral aldehyde derived from (*S*)-ethyl lactate in the ketene-imine cycloaddition reaction and achieved excellent diastereoselectivity by careful optimization of the protecting groups (Scheme 1.34).

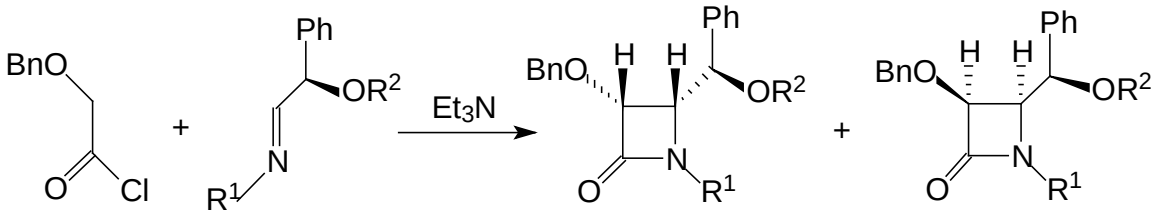
Scheme 1.34



R^1 = PhO, AcO, CH_3O, BnO.
R^2 = PMP, Bn
R^3 = TBDMS

Terashima and co-workers[58] have reported the ketene-imine cycloaddition reaction with imines derived from optically active mandelate. The diastereoselectivity was dictated by the bulkiness of the protecting group (Scheme 1.35).

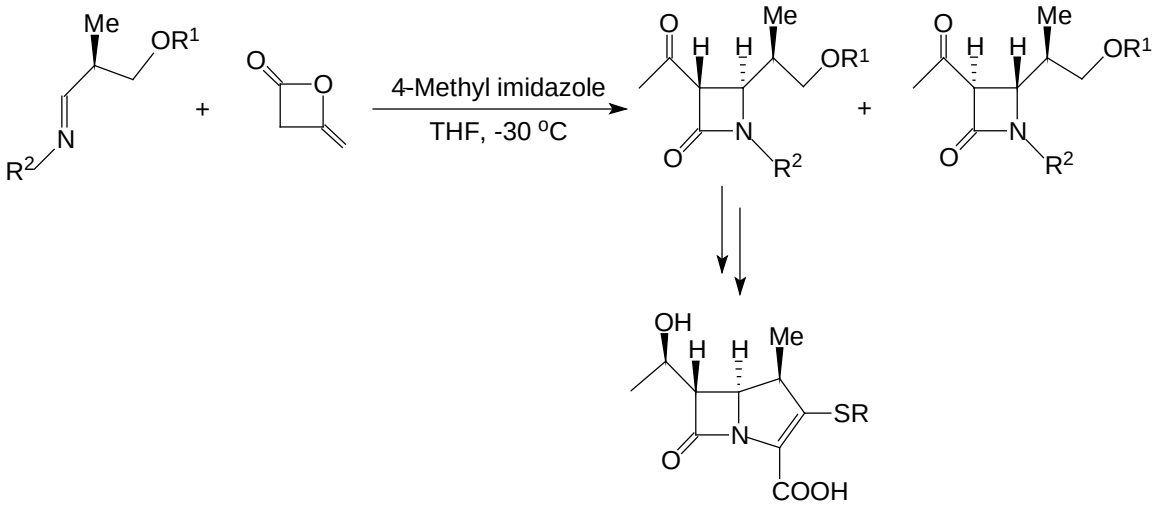
Scheme 1.35



R^1 = DAM, Bn
R^2 = TBDMS, *t*-Bu

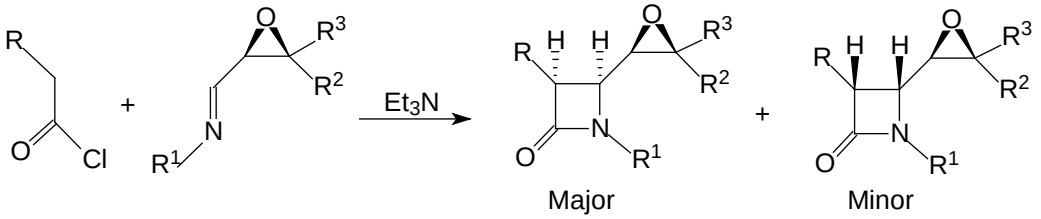
Imines derived from (*S*)-Methyl-3-hydroxy-2-methyl propionate were used in the asymmetric Staudinger reaction to synthesize important precursor of 1-β-methyl carbapenem[59] (Scheme 1.36). A careful optimization of the reaction condition and protecting groups gave 15:1 ratio in favor of the desired diastereomer.

Scheme 1.36



Imines derived from chiral α,β-epoxyaldehydes[60] have also been employed in Staudinger reaction to achieve very high diastereoselectivity. The epoxy aldehydes were synthesized from (*S*)-Malic acid,[61] (+)-Tartaric acid[62] or Sodium erythorbate[60] (Scheme 1.37).

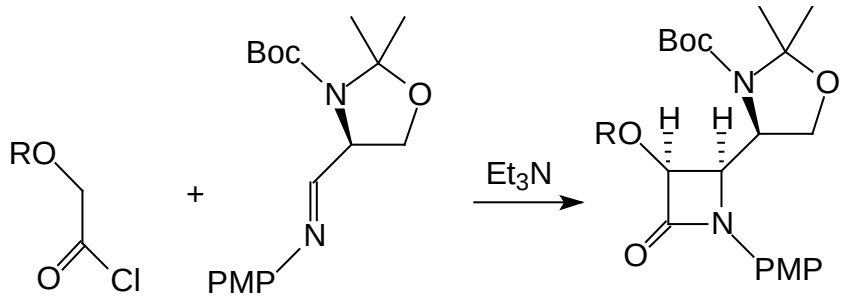
Scheme 1.37



R = PhthN, R^1 = PMP, Bn, R^2 = CH_3, H, R^3 = CH_3, Ph

Palomo et al.[63] have used the imines derived from *N*,*O*-diprotected L-Serinal in the asymmetric Staudinger reaction and diastereospecifically obtained a single *cis* β-lactam (Scheme 1.38).

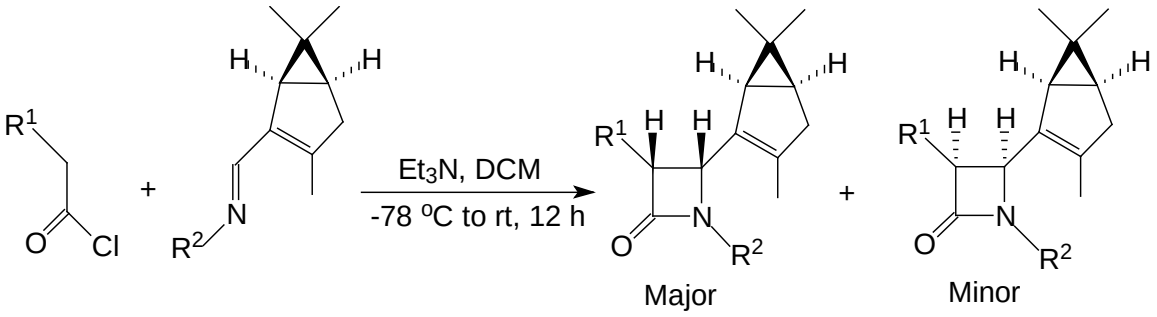
Scheme 1.38



R = CH_3CO, CH_3, Bn

Jayaraman et al.[64] have utilized the imine prepared from chiral aldehyde derived from (+) 3-carene in the ketene-imine cycloaddition reaction. Good diastereoselectivity in the β-lactam formation was achieved, in spite of the chiral directing group being far away from the aldehyde carbon (Scheme 1.39).

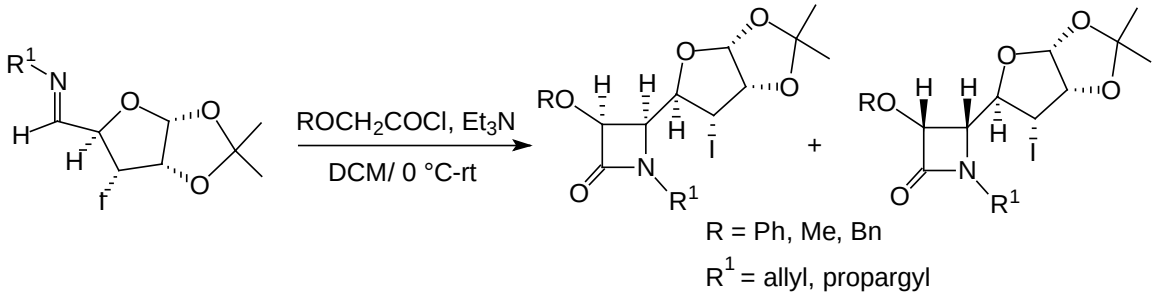
Scheme 1.39



R^1 = PhthN, PhO, R^2 = PMP, Bn

Recently Jayanthi et al.[65] from our group have utilized the imine obtained from glucose derived chiral template for the synthesis of azetidin-2-ones. They obtained a 50:50 mixture of diastereomers during the cycloaddition reaction (Scheme 1.40).

Scheme 1.40

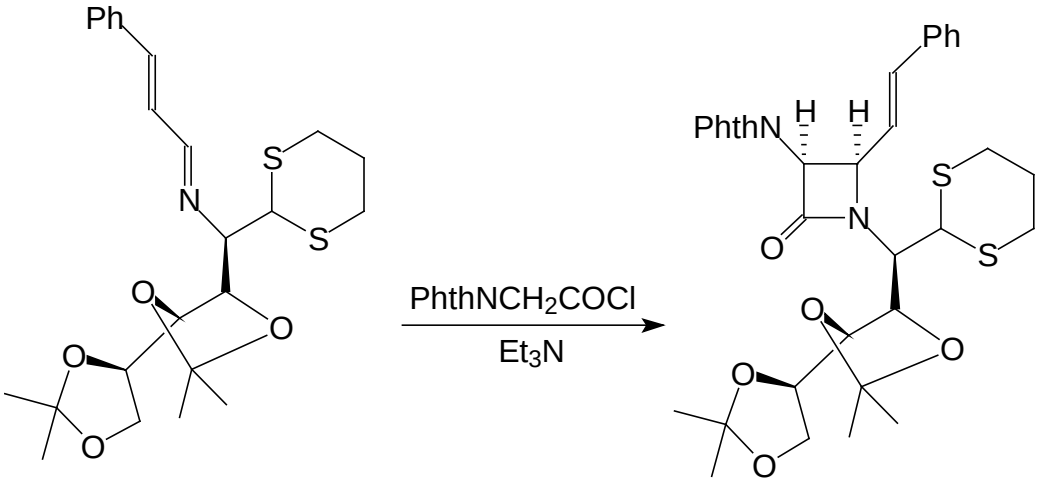


Chiral Amines:

Asymmetric Staudinger reaction using imines derived from achiral aldehydes and chiral amines often result in poor diastereoselectivity in β-lactam formation. This is because the stereo directing group in the chiral amine is far away from the newly formed chiral center. However there are few reports on efficient use of chiral amines in the asymmetric Staudinger reaction, which will be discussed here.

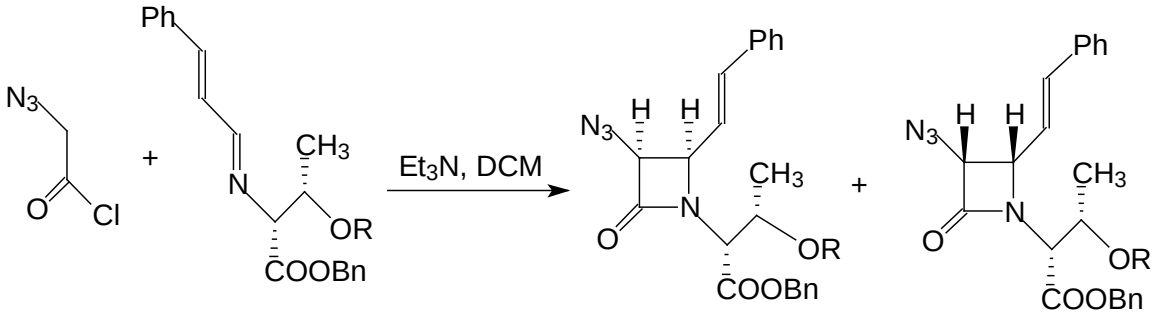
Asymmetric Staudinger reaction using imines derived from D-Glucosamine[66] and cinnamaldehyde have resulted in diastereospecific formation of single *cis* β-lactam (Scheme 1.41).

Scheme 1.41



D-Threonine has also been used as chiral auxiliary in the Staudinger reaction. In this case the diastereoselectivity was dependent on the bulkiness of the substituents (Scheme 1.42).[67]

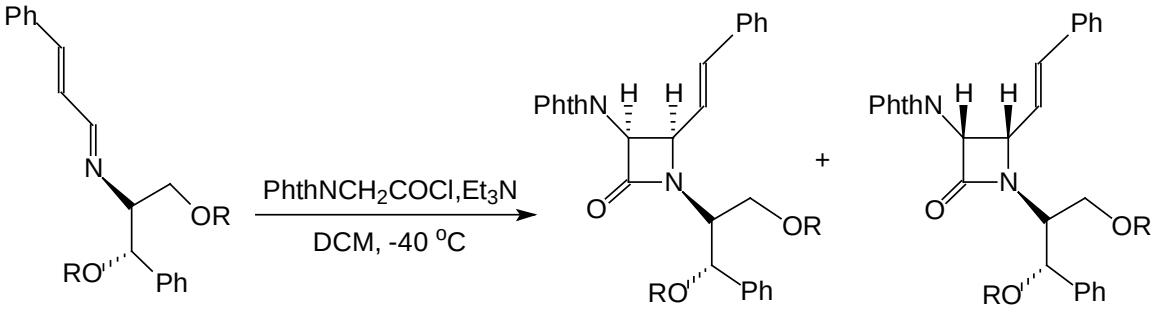
Scheme 1.42



R = TBDMS (ratio 90:10)
R = H (ratio 1:1)
R = $SiPh_3$ (ratio 95:5)

Gunda[68] has used a chiral imine derived from (1*S*, 2*S*)-2-amino-1-phenyl-1,3-propanediol in the ketene-imine cycloaddition reaction and here too, the hydroxy protecting group dictated the diastereoselectivity (Scheme 1.43).

Scheme 1.43

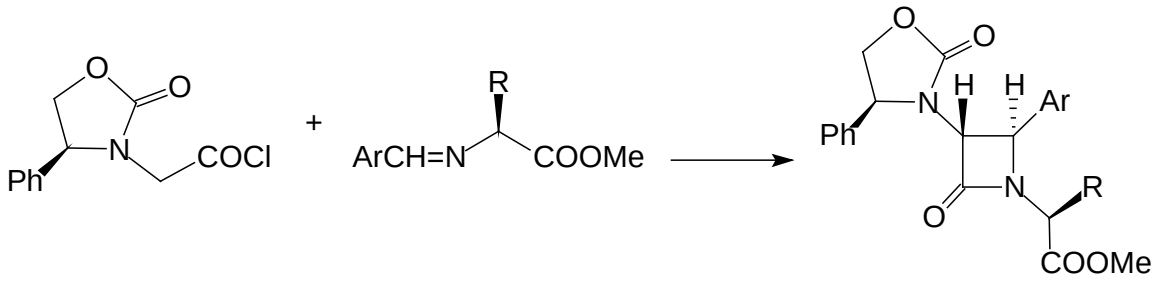


R = TBDMS (ratio 90:10)

Double Stereodifferentiation:

The concept of double asymmetric induction has been applied to Staudinger reaction with variable success. High levels of asymmetric induction have been achieved in Staudinger reaction between the Evans-Sjogrens ketene and imines derived from (*R*) and (*S*)-α-amino acid esters[69] (Scheme 1.44).

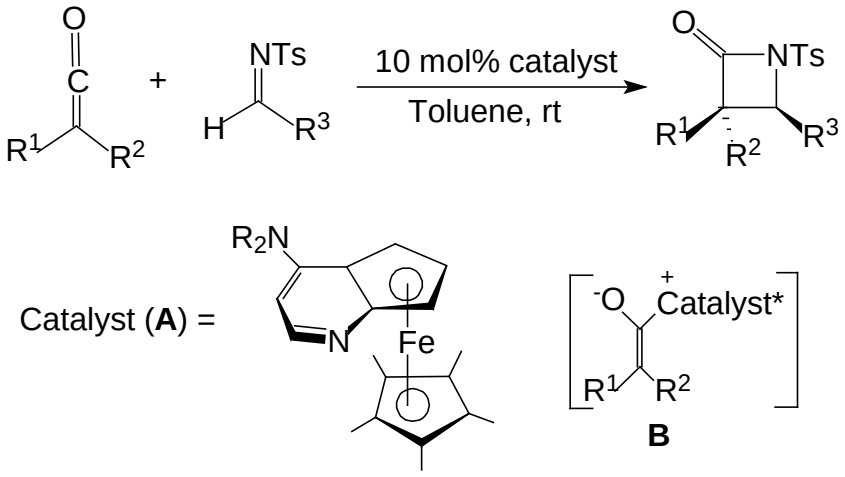
Scheme 1.44



Catalytic Asymmetric Staudinger reaction:

Recently Hodous and Fu[70] have reported a highly enantioselective synthesis of β-lactams catalyzed by a planar chiral nucleophile (**A**). This chiral catalyst (**A**) was found to be very effective in promoting the [2+2] cycloaddition reaction of symmetrical and unsymmetrical ketenes with variety of imines (Scheme 1.45). The reaction was proposed to proceed through the intermediate (**B**), similar to what Lectka[71] has observed.

Scheme 1.45



Mechanism of Staudinger reaction:

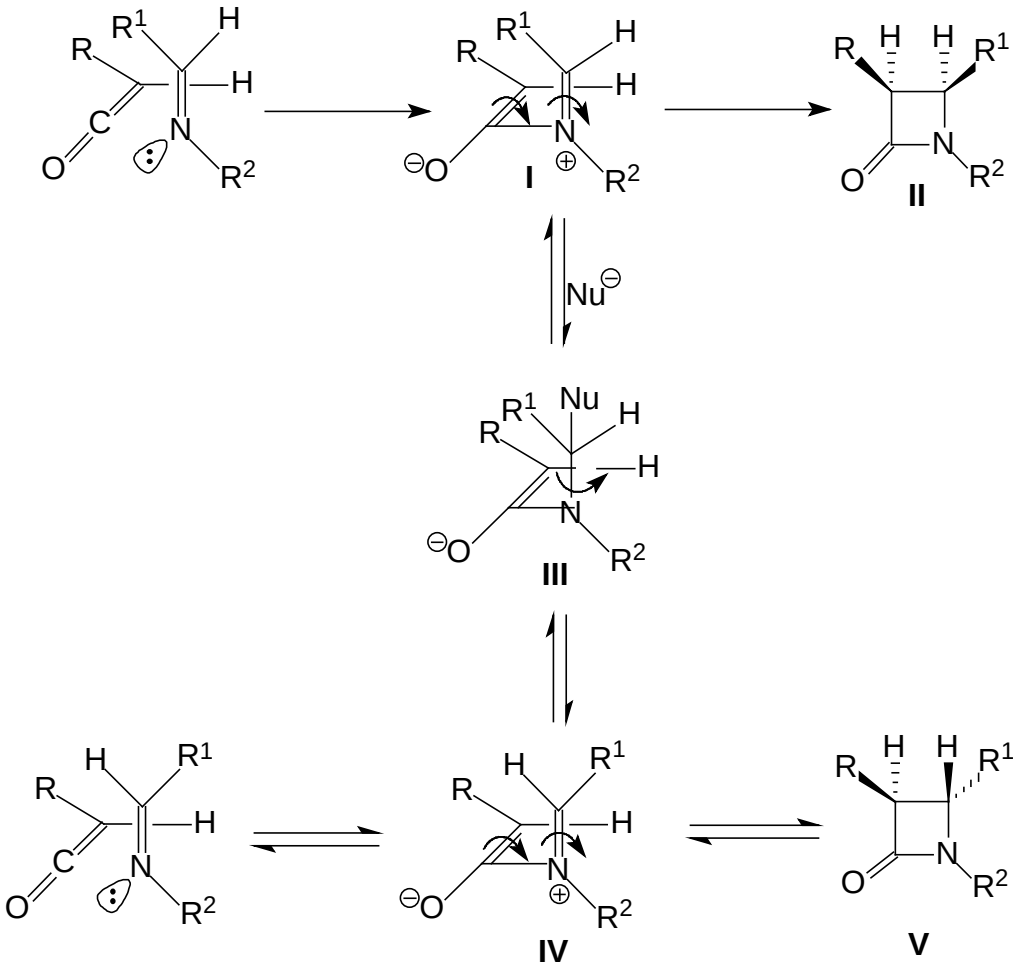
Although the ketene-imine cycloaddition reaction (Staudinger reaction) has been known for several decades, the mechanism and stereo chemical outcome of this reaction is still obscure. Efforts in this aspect have resulted in several papers by various groups.[72] Based on these results; a two-step zwitterionic mechanism has been preferred over a concerted [2+2] cycloaddition reaction. Lynch et al.[73] have established the formation of intermediate ketene. They found that the treatment of (*R*)-3-hydroxybutyric acid chloride with diisopropylamine in a FT-IR cell displayed a strong band at 2120, which they assigned to a ketene. The involvement of zwitterionic intermediate has also been proven by various spectroscopic methods and trapping experiments.[74] The possibility of acylation of imine with acid chloride under the reaction condition has been ruled out as the acid chloride when it reacts with imine in the absence of base leads to the formation of amide instead of β-lactam.

It has been postulated that the LUMO of the ketene carbonyl is attacked by the HOMO of the imine in an orthogonal approach, in a plane perpendicular to the substituents of the ketene, resulting in the formation of the zwitterionic intermediate **I** (Scheme 1.46).[75] This hypothesis was supported by semi-empirical molecular orbital calculations (MNDO) of a transition intermediate between ketene and *N*-methyl-2-methylimine.[43] It is further believed that the attack of the imine occurs from the less hindered side of the ketene, resulting in the zwitterionic intermediate **I**. Rotation of the imine into the plane of the ketene followed by a conrotatory ring closure produces the thermodynamically less stable *cis* β-lactam **II** in which the two hydrogen's (or small substituents) are *cis* to each other. The well-known preference for the formation of *trans* β-lactams with cyclic imines can be explained similarly. An orthogonal approach between the ketene and imine will produce the

zwitterionic intermediate **IV**, which on conrotatory ring closure will give *trans* β-lactam (Scheme 1.46).

This mechanism also successfully explains the formation of *cis-trans* mixture in the Staudinger reaction. A nucleophile can add to the zwitterionic intermediate **I** or **IV** to form an intermediate **III**. The loss of nucleophile from intermediate **III** after C-N bond rotation can result in formation of **IV** and subsequent *trans* β-lactam **V**. The intermediate **III** can also revert back to **I** and form *cis* β-lactam **II**. Thus the ratio of *cis* and *trans* isomers depends upon the formation and stability of intermediate **I** and **IV** (Scheme 1.46). It was also observed that the initially formed *cis* product could undergo base catalyzed isomerisation to produce more stable *trans* product.[76]

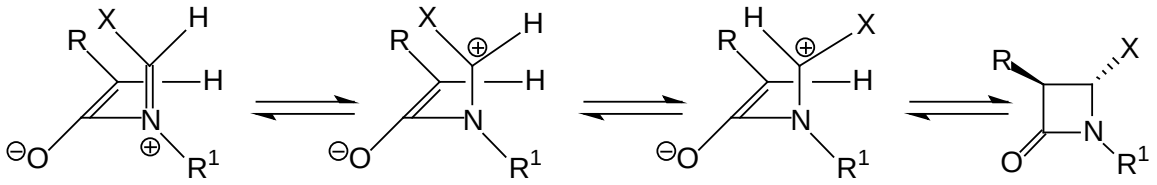
Scheme 1.46



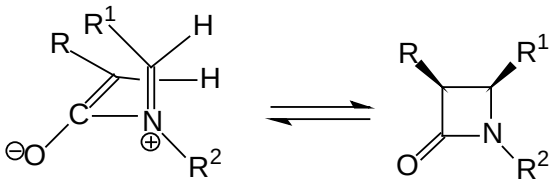
The formation of *trans* isomer by using imidates, thioimidates and sometimes C-aryl imines and potentially C-alkyl imines can be explained by the ability of these groups to stabilize the positive charge of the zwitterionic intermediate by the inductive or mesomeric effect. This allows the isomerisation of *trans* iminium ion to the sterically less crowded *cis*

iminium ion, which on ring closure will generate, *trans* β-lactam (Scheme 1.47). On the contrary, imine-possessing electron withdrawing substituents on the imine carbon, like α-carbonyl group or halo methyl group, prevents the C-N bond rotation of the zwitterionic intermediate and produces *cis* isomer. A detailed account of semi-empirical calculation reported by Cossio et al.[72c] also supports the ketene-imine cycloaddition mechanism.

Scheme 1.47



X = OR, SR, aryl, alkyl



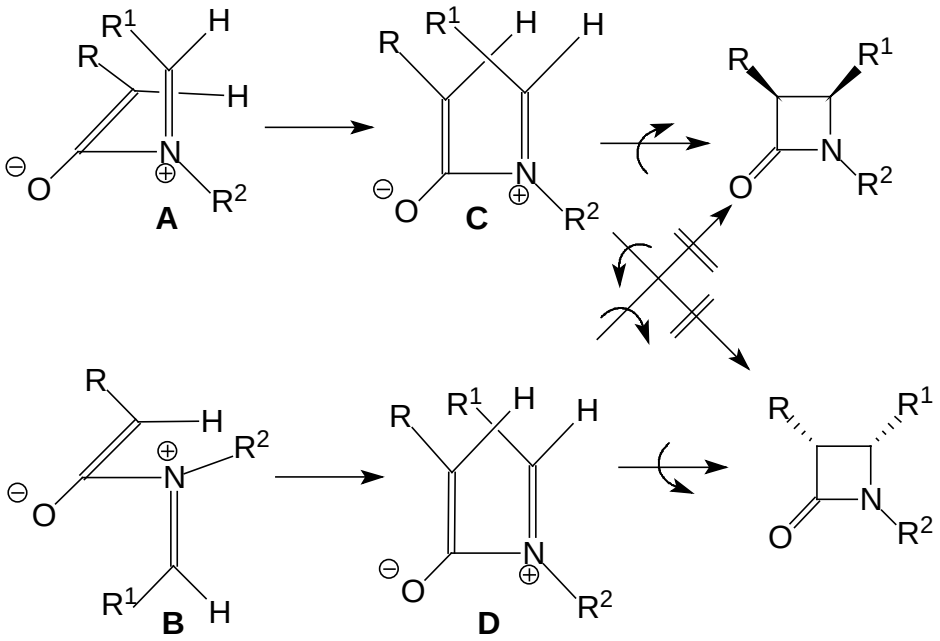
R^1 = COPh, $COOCH_3$, CH_2Cl, CH_2F

Asymmetric Induction:

Asymmetry can be induced in ketene-imine cycloaddition by controlling the orientation of the imine with respect to the plane of the ketene. The ketene can be approached by the imine either from the top face or from bottom face to produce two possible zwitterionic intermediates **A** and **B** respectively (Scheme 1.48). Before conrotatory ring closure can take place, the intermediates **A** and **B** have to undergo 90° rotation around the C-N bond to produce two more intermediates **C** and **D** respectively. The conrotatory ring closure of these intermediates **C** and **D** will produce enantiomeric *cis* β-lactams. These intermediates **C** and **D** can also be formed from **A** and **B** by rotating through 270° around the C-N bond. According to the principle of least motion, the transformation of **A** to **C** and **B** to **D** is favored, as this requires only 90° rotation.

It has been pointed out by Hegedus et al.[72a] that the conrotatory ring closure of the intermediate **C** can occur only in clockwise direction as the counterclockwise ring closure would necessitate that the hydrogen of the ketene and R^1 of the imine to pass through each other. This is of importance for chiral induction, because a counterclockwise rotation would generate the enantiomeric β-lactam. The opposite is true for intermediate **D**, which can undergo only counterclockwise conrotatory ring closure.

Scheme 1.48

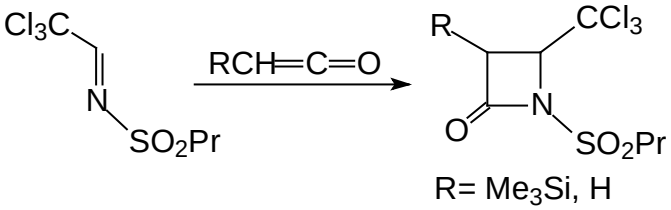


1.2 : Background for the present work

Apart from the part structure of widely used antibiotics such as penicillin, cephalosporins, monobactams etc. azetidin-2-ones (β-lactams) are important building blocks in stereoselective synthesis of biologically important compounds. Some of the synthetic β-lactams display protease inhibitor, cholesterol absorption inhibitor and antiviral activities. As a consequence, the interest of organic chemists for the synthesis of new β-lactam derivatives has been maintained. Out of the numerous methods available for the construction of β-lactam ring, the [2+2] cyclocondensation of ketenes to the imines, known as the Staudinger reaction is the most widely used. In particular this method has provided useful and economic entries to β-lactams, mainly due to the ready availability of both Schiff's bases and ketenes.

We were interested in the preparation of 4-trichloromethyl-β-lactams as trichloromethyl group can serve as a masked carboxylic acid equivalent, other groups can replace it and also it can be transformed to chlorovinyl group. Literature search revealed that there wasn't much work done on the synthesis of such β-lactams bearing trichloromethyl group at C-4 position. This may be due to the fact that chloral forms highly stable aminols[77] when reacted with amines and in some cases oligomerizes[78] in the presence of amines. There is only one report on the preparation of 4-trichloromethyl-β-lactams from *N*-(propanesulfonyl) chloralimine and trimethylsilylketene by Novikova et al.[79] They have synthesized these 4-trichloromethyl-azetidin-2-ones by employing cycloaddition reaction of highly reactive silyl ketene and reactive imine derived from chloral and propanesulphonamide (Scheme 1.49).

Scheme 1.49

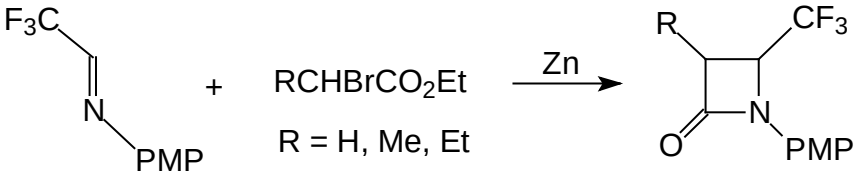


Apart from only one report on 4-trichloromethyl-azetidin-2-ones, there are some reports for the synthesis of 4-trifluoromethyl-azetidin-2-ones. The interest in the synthesis

of trifluoromethyl-azetidin-2-ones[80a] stems from the fact that 4α-methyl-1-sulfoazetidin-2-one derivatives are biologically potent and the electron withdrawing property of the fluorinated methyl group increases the chemical reactivity of the β-lactam ring that is correlated with its biological activity.[80b]

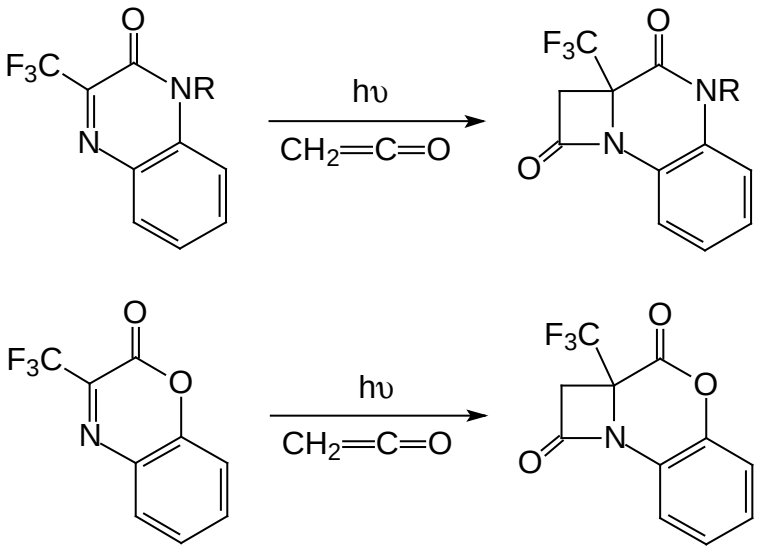
In one of the reports Kato et al.[81] have reported the synthesis of trifluoromethyl-azetidin-2-ones by the use of Reformatsky reaction (Scheme 1.50).

Scheme 1.50



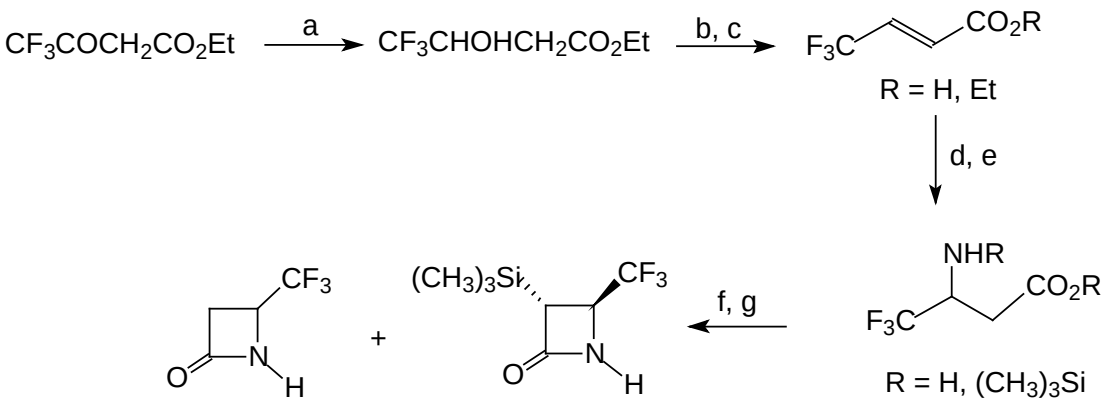
In 1986 Katagiri and co-workers[80a] reported the synthesis of 4-trifluoromethyl-azetidin-2-ones by [2+2] photocycloaddition of 3-trifluoromethyl-quinoxalin-2-one or 1, 4-benzoxazin-2-one and ketene (Scheme 1.51).

Scheme 1.51



Alternatively the 4-trifluoromethyl-azetidin-2-ones have been synthesized from a β-amino acid, effecting N(1)-C(2) bond formation by treatment of the bis (trimethylsilyl) derivative with a Grignard reagent[82] as shown in the scheme 1.52.

Scheme 1.52



Reagents and conditions : (a) 5% Pd/C, H_2, 125 °C, 1500 psi; (b) DEAD, Ph_3P, Et_2O; (c) 1N NaOH, THF; (d) NH_3, 100 °C; (e) $(CH_3)SiCl$, Et_3N, PhH; (f) MeMgBr, Et_2O; (g) CH_3OH, 50 °C

4-trifluoromethyl- and difluoromethyl-β-lactams have been employed as useful building blocks for the synthesis of fluorinated amino acids, dipeptides and fluoro-taxoids by Ojima[83] and also for the synthesis of nonracemic methyl *syn*-(3-Fluoroalkyl)isoserinates. These can be further employed as peptidomimetics units.[84]

The introduction of a methyl substituent at C-4 in the monobactam has provided compounds like aztreonam, which display potent activity against a broad spectrum of Gram-negative organisms as well as good β-lactamase activity. We envisioned that the hydrogen atoms of the methyl group at C-4 position, when replaced with chlorine atoms, which are electronegative, would cause the β-lactam to be even more susceptible to nucleophilic attack. Thus, we hoped that replacing the methyl group by trichloromethyl would have good effect on the antibacterial activity. Also a trihalomethyl group at the C-4 position of the β-lactam ring will increase the susceptibility of the lactam ring towards nucleophilic attack, which may improve the antibacterial activity of these compounds.[80b, 85]

1.3 : Present work

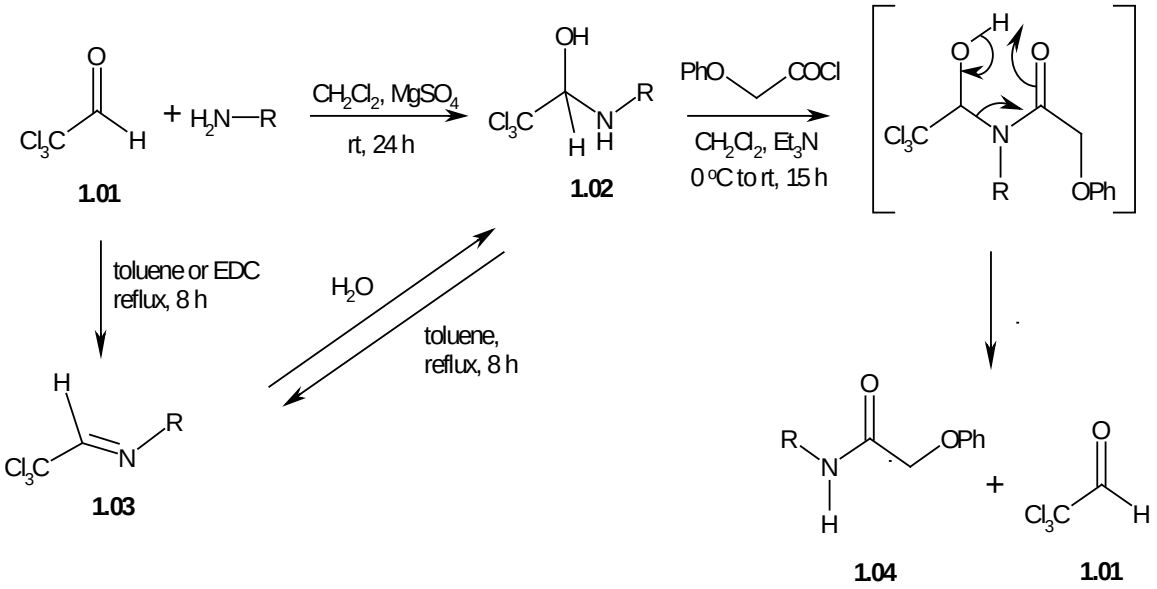
Thus keeping in mind the importance of trihalogenated methyl group at C-4 position of the β-lactam and only one report on the synthesis of 4-trichloromethyl-β-lactams led us to develop a general methodology for the synthesis of 4-trichloromethyl-β-lactams. This part of the chapter deals with the synthesis of various chloral imines derived from chloral and

various aliphatic as well as aromatic amines and their application in the synthesis 4-trichloromethyl-β-lactams.

1.4 : Results and Discussion

A solution of anhydrous chloral in dichloroethane was treated with aniline at 0-5 °C in the presence of dehydrating agent such as anhydrous $MgSO_4$ or 4Å molecular sieves and stirred at room temperature for 24 h. The desiccating agent was removed and the solution was treated with phenoxyacetyl chloride in the presence of triethylamine.

Scheme 1.53

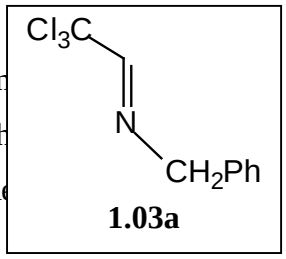


The product formed was not the desired 4-trichloromethyl-azetidin-2-one but was found to be *N*-phenyl phenoxyacetamide **1.04**. This might be forming by the reaction of the aminol **1.02** with acid chloride followed by molecular rearrangement with the expulsion of chloral as shown in Scheme 1.53. However, we could get the desired chloralimine **1.03** required for the ketene-imine cycloaddition reaction by refluxing the aminol **1.02** in toluene or in dichloroethane with the removal of water formed in the reaction using molecular sieves. Moreover, chloral imines **1.03** were also prepared directly from amine and chloral by refluxing in toluene or dichloroethane with removal of water using molecular sieves.

Benzyl amine was reacted with chloral **1.01** in ethylene dichloride (EDC) and the resultant turbid solution was refluxed with continuous removal of water over molecular sieves. The reaction mixture was passed through a short bed of silica gel to get benzyl-

(2,2,2-trichloroethylidene)-amine **1.03a** as a pale yellow oil. The structure of imine **1.03a** was confirmed from its spectral data.

The IR spectrum of imine **1.03a**, showed a band at 1666 cm^{-1} corresponding to imine double bond.



1.03a

The ^{1}H NMR spectrum of **1.03a** showed two singlets, on at 4.87 ppm for benzyl protons and another at 7.81 ppm for th imine proton, while the aromatic protons appeared as a multiple between 7.30-7.40 ppm.

The ^{13}C spectrum of **1.03a** showed a peak at 61.38 ppm corresponding to methylene carbon attached to the benzene ring. The trichloromethyl carbon appeared at 94.02 ppm. The olefinic carbon was seen at 157.17 ppm. The aromatic quaternary carbon appeared at 136.66 ppm, while the remaining aromatic carbons appeared at 127.39, 127.80, 128.50 ppm.

Several other chloral imines were also prepared starting from aniline, *p*-anisidine, and cyclohexyl amine by following the same above procedure in very good yields and were characterized completely by spectral and analytical data (Table 1). Most of these imines were found to be moisture sensitive and give back the aminols.

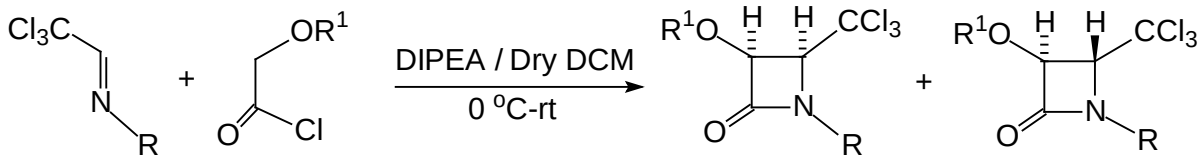
Table 1: Synthesis of imines **1.03a-d** from chloral and various amines

Entry No.	Imine	R	Yield[b] (%)	MP (˚C)
1	**1.03a**	-CH_2Ph	82	oil
2	**1.03b**	-Cyclohexyl	80	oil
3	**1.03c**	-PMP[a]	82	57
4	**1.03d**	-Ph	78	oil

[a] PMP = *p*-methoxyphenyl, [b] Isolated yield

The cycloaddition reaction of these imines **1.03a-d** with ketenes derived from different acid chlorides (phenoxyacetyl chloride, acetoxyacetyl chloride, benzyloxyacetyl chloride, methoxyacetyl chloride and phthalimidoacetyl chloride) in the presence of excess *N*, *N*-diisopropylethylamine (0 °C to rt, 15 h) provided a mixture of *cis* and *trans* β-lactams (**1.05a-k, 1.06a-k**) in fairly good yields (Scheme 1.54).

Scheme 1.54



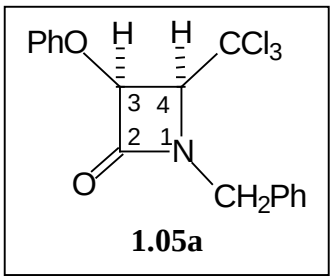
1.03a-d **1.04** **1.05a-k** **1.06a-k**

The ^{1}H NMR spectral analysis of the crude reaction mixture revealed that in all cases *cis* isomer was obtained as a major product (J = 4-5 Hz for *cis* isomer and J = 1-2 Hz for *trans* isomer). In the case of imines derived from aliphatic amines and chloral, exclusive *cis*-β-lactam formation was observed in the ketene-imine cycloaddition. However, imines derived from aromatic amines and chloral gave a mixture of *cis* and *trans* β-lactam with selectivity for the *cis* isomers (Table 2, **1.05d, j, k** and **1.06d, j, k**).

The cycloaddition reaction of chloral imine **1.03a** with ketene derived from phenoxyacetyl chloride in the presence of tertiary base like *N*, *N*-diisopropylethylamine gave *cis*-1-benzyl-3-phenoxy-4-trichloromethyl-azetidin-2-one **1.05a** in 65% yield as a white crystalline solid after crystallization of the crude reaction mixture from methyl alcohol. The structure of **1.05a** was established by spectral and analytical data.

The IR spectrum of β-lactam **1.05a** showed a strong band at 1774 cm^{-1} corresponding to the β-lactam carbonyl.

The ^{1}H NMR spectrum of **1.05a** showed two doublets at 4.35 & 5.10 ppm corresponding to the benzyl protons with coupling constant of 15.1 Hz. The C-3 and C-4 β-lactam protons appeared as two doublets at 5.35 & 4.55 ppm with J = 4.9 Hz indicating *cis* relationship between the ring protons. The aromatic protons appeared as two multiplets, one between 7.00-7.20 ppm for three protons and other at 7.30-7.50 ppm for the remaining protons.



1.05a

The ^{13}C spectrum of **1.05a** showed a peak at 44.74 ppm, which was attributed to the methylene carbon and confirmed by ^{13}C DEPT experiment. The C-3 and C-4 β-lactam carbons appeared at 81.31 ppm and 69.48 ppm respectively. The trichloromethyl carbon was seen at 97.08 ppm.

The aromatic quaternary carbons appeared at 157.55 ppm and 134.28 ppm, while the remaining aromatic carbons appeared at 116.05, 122.63, 128.07, 128.32, 128.84 and 129.35

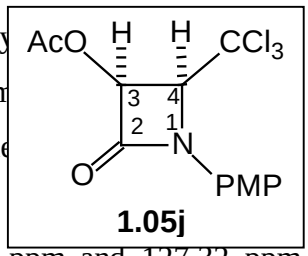
ppm. The β-lactam carbonyl carbon appeared at 166.37 ppm. This compound also gave satisfactory elemental analysis and the mass spectrum showed a molecular ion peak at m/z 371 (M+1).

The reaction of the imine **1.03c** derived from *p*-anisidine and chloral with acetoxyacetyl chloride in the presence of *N*, *N*-diisopropylethylamine afforded a mixture of *cis* and *trans* isomers **1.05j** & **1.06j** in the ratio of 72:28 as determined by the ^{1}H NMR of the crude reaction mixture. There was no appreciable increase in the ratio of *trans* isomer formation, even after doing the reaction at room temperature or at reflux temperature.

The ^{1}H NMR of the crude reaction mixture showed two sets of doublets at 5.18 and 6.32 ppm for C-4 and C-3 protons with coupling constant of 4.8 Hz indicating the *cis* stereochemistry for the β-lactam ring protons. The other set of doublet was observed at 4.97 and 5.82 ppm for C-4 and C-3 protons with J = 2.00 Hz indicating the *trans* stereochemistry for the β-lactam ring protons. The white crystalline solid obtained by crystallization of the above mixture from methanol was found to be the pure *cis* isomer **1.05j**, which showed characteristic bands at 1780 and 1762 cm^{-1} in the IR spectrum corresponding to the lactam and acetoxy carbonyl groups respectively.

The ^{1}H NMR spectrum of **1.05j** showed two singlets at 2.19 and 3.81 ppm, which were attributed to the acetoxy methyl and the methoxy methyl protons. The C-3 and C-4 β-lactam protons appeared as doublets at 6.32 and 5.18 ppm with J = 4.8 Hz, characteristic of *cis* coupling between the respective protons. The aromatic protons were seen as two doublets at 6.91 and 7.40 ppm integrating for two protons each with J = 9.0 Hz.

The ^{13}C spectrum of **1.05j** showed peaks at 20.65 and 55.46 ppm for the acetoxy methyl carbon and the methoxy carbon respectively. The C-3 and C-4 carbons of the β-lactam ring appeared at 72.88 and 70.05 ppm respectively. The trichloromethyl carbon appeared at 96.89 ppm.



1.05j

The aromatic quaternary carbons appeared at 158.09 ppm and 127.32 ppm that disappeared in the ^{13}C DEPT experiment, while the remaining aromatic carbons were seen at 114.27 and 123.24 ppm. The amide carbonyl and acetoxy carbonyl were observed at 163.27 and 169.08 ppm respectively. This compound also gave satisfactory elemental analysis and the mass spectrum showed peak at m/z 353 (M+1).

Several other 4-trichloromethyl-β-lactams (Table 2) were prepared from imines derived from aniline, allyl amine, cyclohexyl amine, benzyl amine and *p*-anisidine and

ketenes derived from acetoxyacetyl chloride, benzyloxyacetyl chloride, methoxyacetyl chloride, phenoxyacetyl chloride and phthalimidoacetyl chloride. In all the cases *cis* β-lactams were formed selectively. All these 4-trichloromethyl-β-lactams were also characterized by spectral and analytical data. These compounds gave satisfactory elemental analysis, and were further confirmed with their mass spectra.

Table 2: Synthesis of 4-trichloromethyl-β-lactams **1.05a-k** and **1.06a-k** from chloral imines **1.03a-d**

β-Lactams 1.05 & 1.06		R	R^1	Ratio 1.05:1.06	YIELD[B] (%)	MP (°C)
1.05a	**1.06a**	-CH_2Ph	Ph	100:00	68	127
1.05b	**1.06b**	-Cyclohexyl	Ph	100:00	67	175
1.05c	**1.06c**	-Allyl	Ph	100:00	62	99
1.05d	**1.06d**	-PMP[a]	Ph	96:4	61	214[c]
1.05e	**1.06e**	-CH_2Ph	$PhCH_2$	100:00	61	63-64
1.05f	**1.06f**	-CH_2Ph	Me	100:00	65	oil
1.05g	**1.06g**	-CH_2Ph	PhthN[a]	100:00	52	221
1.05h	**1.06h**	-CH_2Ph	Ac	100:00	63	103-104
1.05i	**1.06i**	-Cyclohexyl	Ac	100:00	65	172-173
1.05j	**1.06j**	-PMP	Ac	72:28	62	204[c]
1.05k	**1.06k**	Ph	Ac	55:45	45	180-182[c]

[a] PMP = *p*-methoxyphenyl , PhthN = phthalimido

[b] Isolated yield (based on imine consumed), [c] Mp of *cis* isomer

Some of these 4-trichloromethyl-β-lactams were tested for their larvicidal activity against *Aedes aegypti* and *Culex quinquefasciatus* species, but were found to be inactive against any of these species. They were also tested for the antifeedant activity on

spodoptera litura and *Helicoverpa armigera* but unfortunately in this case also they proved to be inactive.

1.5 : Conclusion

A general method has been developed for the synthesis of 4-trichloromethyl-azetidin-2-ones from chloral imines and ketenes using Staudinger cycloaddition reaction. The generality of this method was established by the synthesis of several 4-trichloromethyl substituted β-lactams. The reaction was found to be stereoselective and *cis* β-lactams were formed in major amount, which could be obtained in pure form by crystallization from methanol. The *cis* β-lactams were formed exclusively when the imines used for cycloaddition were derived from chloral and aliphatic amines. However, imines derived from aromatic amines and chloral gave a mixture of *cis* and *trans* isomers during cycloaddition with ketenes with selectivity for the *cis* isomers.

1.6 : Experimental

1. 6. 1: General procedure for the synthesis of Imines derived from chloral

A solution of amine (1.0 mmol), in anhydrous EDC (5 mL), was added slowly to a solution of chloral (1.0 mmol) in EDC (10 mL) at 0 ^{o}C. After the addition, the reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. The reaction mixture was then refluxed for 5-6 h by continuous removal of water formed during the course of reaction over molecular sieves. After the reaction is over (TLC), the reaction mixture was cooled and the solvent was evaporated to get the crude product. This was then purified by column chromatography on small silica gel bed and eluted with petroleum ether to furnish the pure imines **1.03a-d**.

1. 6. 1a: Preparation of benzyl-(2,2,2-trichloro-ethylidene)-amine 1.03a

Following the above-optimized procedure, treatment of benzyl amine (0.11 g, 1.0 mmol) with chloral (0.15 g, 1.0 mmol) in dry EDC followed by refluxing the resulting solution with continuous removal of water over molecular sieves gave the imine **1.03a** as a pale yellow oil (0.20 g, 82%).

MP : pale yellow oil

IR ($CHCl_3$) : 1666, 1496, 1454 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 4.87 (s, 2H), 7.30-7.40 (m, 5H), 7.81 (s, 1H).
(200 MHz)

^{13}C NMR ($CDCl_3$) : δ 61.38, 94.02, 127.39, 127.80, 128.50, 136.66, 157.17.
(50.3 MHz)

1. 6. 1b: Preparation of cyclohexyl-(2,2,2-trichloro-ethylidene)-amine 1.03b

Following the above-optimized procedure, treatment of cyclohexyl amine (0.10 g, 1.0 mmol) with chloral (0.15 g, 1.0 mmol) in dry EDC followed by refluxing the resulting solution with continuous removal of water over molecular sieves gave the imine **1.03b** as a pale yellow oil (0.18 g, 80%).

MP : pale yellow oil

IR ($CHCl_3$) : 1664, 1450 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 1.20-1.90 (m, 10H), 3.25-3.40 (m, 1H), 7.75 (s, 1H).

(200 MHz)

^{13}C NMR ($CDCl_3$) : δ 24.25, 25.24, 33.29, 66.78, 94.31, 154.52.
(50.3 MHz)

1. 6. 1c: Preparation of (4-methoxyphenyl)-(2,2,2-trichloro-ethylidene)-amine 1.03c

Following the above optimized procedure, treatment of *p*-anisidine (0.12 g, 1.0 mmol) with chloral (0.15 g, 1.0 mmol) in dry EDC followed by refluxing the resulting solution with continuous removal of water over molecular sieves gave the imine **1.03c** as a reddish white crystalline solid (0.20 g, 82%).

MP : 57 ^{o}C.

IR ($CHCl_3$) : 1647, 1502 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 3.80 (s, 3H), 6.90 (d, *J* = 9.0 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H), 7.91 (s, 1H).
(200 MHz)

^{13}C NMR ($CDCl_3$) : δ 55.45, 94.49, 114.57, 123.15, 139.63, 152.72, 159.86.
(75.5 MHz)

1. 6. 1d: Preparation of phenyl-(2,2,2-trichloro-ethylidene)-amine 1.03d

Following the optimized procedure, treatment of aniline (0.10 g, 1.0 mmol) with chloral (0.15 g, 1.0 mmol) in dry EDC followed by refluxing the resulting solution with continuous removal of water over molecular sieves gave the imine **1.03d** as a pale yellow oil (0.18 g, 78%).

MP : pale yellow oil

IR ($CHCl_3$) : 1647, 1485 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 6.75-6.90 (m, 2H), 7.20-7.45 (m, 3H), 7.96 (s, 1H).
(200 MHz)

^{13}C NMR ($CDCl_3$) : δ 94.06, 113.97, 121.14, 127.83, 129.32, 129.43, 147.09, 154.99.
(50.3 MHz)

1. 6. 2: General procedure for the synthesis of azetidin-2-ones 1.05a-k & 1.06a-k

A solution of acid chloride (1.5 mmol) in anhydrous CH_2Cl_2 (10 mL), was added slowly to a well-stirred mixture of imine (1.0 mmol) and *N*,*N*-diisopropylethylamine (4.5 mmol) at 0 ^oC. After the addition, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was then washed with water (20 mL), saturated sodium bicarbonate solution (2 x 15 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated to get the crude product, which was then purified by either column chromatography or crystallization from methanol to give pure β-lactam. A similar general procedure, as above was employed for the synthesis of β-lactams **1.05a-k & 1.06a-k** starting from the acid chloride **1.04** and imines **1.03a-d**.

1. 6. 2a: Preparation of 1-benzyl-3-phenoxy-4-trichloromethyl-azetidin-2-one 1.05a

Following the optimized procedure, treatment of phenoxyacetyl chloride (0.20 mL, 1.5 mmol) with imine **1.03a** (0.23 g, 1.0 mmol) derived from chloral and benzyl amine in the presence of *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol) gave the β-lactam **1.05a** as a white solid (0.25 g, 68%).

MP	**:**	127 ^oC
IR ($CHCl_3$)	**:**	1774 cm^{-1}.
^1H NMR ($CDCl_3$) (200 MHz)	**:**	δ 4.35 (d, *J* = 15.1 Hz, 1H), 4.55 (d, *J* = 4.9 Hz, 1H), 5.10 (d, *J* = 15.1 Hz, 1H), 5.35 (d, *J* = 4.9 Hz, 1H), 7.00-7.20 (m, 3H), 7.30-7.50 (m, 7H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	**:**	δ 44.74, 69.48, 81.31, 97.08, 116.05, 122.63, 128.07, 128.32, 128.84, 129.35, 134.28, 157.55, 166.37.
MS (m/z)	**:**	371 (M+1).
Analysis ($C_{17}H_{14}NO_2Cl_3$)	**:**	Calculated: C, 55.08; H, 3.80; N, 3.77; Cl, 28.69 Observed: C, 55.22; H, 3.76; N, 3.80; Cl, 28.60.

1. 6. 2b: Preparation of 1-cyclohexyl-3-phenoxy-4-trichloromethyl-azetidin-2-one 1.05b

Following the optimized procedure, treatment of phenoxyacetyl chloride (0.20 mL, 1.5 mmol) with imine **1.03b** (0.23 g, 1.0 mmol) derived from chloral and cyclohexyl amine in the presence of *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol) gave the β-lactam **1.05b** as a white solid (0.24 g, 67%).

MP	:	175 ^{o}C
IR ($CHCl_3$)	:	1774 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 1.10-1.40 (m, 3H), 1.60-2.20 (m, 7H), 3.45-3.65 (m, 1H), 4.70 (d, *J* = 4.9 Hz, 1H), 5.35 (d, *J* = 4.9 Hz, 1H), 6.95-7.15 (m, 3H), 7.25-7.40 (m, 2H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 25.07, 25.21, 25.50, 30.50, 30.72, 55.17, 70.68, 80.64, 97.88, 116.18, 122.62, 129.45, 157.79, 166.03.
MS (m/z)	:	363 (M+1).
Analysis ($C_{16}H_{18}NO_2Cl_3$)	:	Calculated: C, 52.98; H, 5.00; N, 3.86; Cl, 29.32 Observed: C, 52.72; H, 5.09; N, 3.86; Cl, 29.30.

1. 6. 2c: Preparation of 1-allyl-3-phenoxy-4-trichloromethyl-azetidin-2-one 1.05c

Following the optimized procedure, treatment of phenoxyacetyl chloride (0.20 mL, 1.5 mmol) with allyl-(2,2,2-trichloroethylidene)-amine (0.18 g, 1.0 mmol) derived from chloral and allyl amine in the presence of *N*,*N*-diisopropylethylamine (0.78 ml, 4.5 mmol) gave the β-lactam **1.05c** as a white solid (0.20 g, 62%).

MP	:	99 ^{o}C
IR ($CHCl_3$)	:	1760 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 3.80 (dd, *J* = 15.6 & 7.4 Hz, 1H), 4.30 (dd, *J* = 15.6 & 5.0 Hz, 1H), 4.65 (d, *J* = 4.6 Hz, 1H), 5.20-5.25 (m, 2H), 5.30 (d, *J* = 4.6 Hz, 1H), 5.70-5.80 (m, 1H), 6.95-7.00 (m, 3H), 7.20-7.25 (m, 2H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 43.60, 70.07, 81.29, 97.18, 116.13, 120.01, 122.73, 129.47, 130.21, 157.65, 166.26.
MS (m/z)	:	321 (M+1), 339 (M+18).
Analysis ($C_{13}H_{12}NO_2Cl_3$)	:	Calculated: C, 48.70; H, 3.77; N, 4.39; Cl, 33.17 Observed: C, 48.56; H, 3.64; N, 4.63; Cl, 32.94.

1. 6. 2d: Preparation of 1-(4-methoxyphenyl)-3-phenoxy-4-trichloromethyl-azetidin-2-one 1.05d

Following the optimized procedure, treatment of phenoxyacetyl chloride (0.20 mL, 1.5 mmol) with imine **1.03c** (0.25 g, 1.0 mmol) derived from chloral and *p*-anisidine in the

presence of *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol) gave a mixture of *cis* and *trans* β-lactams **1.05d** & **1.06d** in the ratio of 96:4 as a white solid (0.23 g, 61%). The major *cis* isomer **1.05d** was separated by crystallization from methyl alcohol.

MP : 214 ^{o}C (Mp of *cis* isomer).

IR (Nujol) : 1762 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.80 (s, 3H), 5.25 (d, *J* = 4.9 Hz, 1H), 5.55 (d, *J* = 4.9 Hz, 1H), 6.95 (d, *J* = 9.3 Hz, 2H), 7.05-7.20 (m, 2H), 7.30-7.40 (m, 3H), 7.45 (d, *J* = 9.3 Hz, 2H).
Visible peaks for the *trans* isomer **1.06d**
5.08 (d, *J* = 1.5 Hz, 1H), 5.35 (d, *J* = 1.5 Hz, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 55.48, 73.34, 85.00, 97.08, 114.39, 116.95, 123.30, 124.67, 127.36, 129.71, 157.30, 158.58, 162.85.

MS (m/z) : 351 (M-Cl).

Analysis ($C_{17}H_{14}NO_3Cl_3$) : Calculated: C, 52.80; H, 3.64; N, 3.62; Cl, 27.50
Observed: C, 52.59; H, 3.40; N, 3.47; Cl, 27.23.

1. 6. 2e: Preparation of 1-benzyl-3-benzyloxy-4-trichloromethyl-azetidin-2-one 1.05e

Following the optimized procedure, treatment of bezyloxyacetyl chloride (0.23 mL, 1.5 mmol) with imine **1.03a** (0.23 g, 1.0 mmol) derived from chloral and benzyl amine in the presence of *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol) gave the β-lactam **1.05e** as a white solid (0.23 g, 61%).

MP : 63-65 ^{o}C

IR ($CHCl_3$) : 1776 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 4.30 (d, *J* = 14.9 Hz, 1H), 4.40 (d, *J* = 4.4 Hz, 1H), 4.80 (d, *J* = 4.4 Hz, 1H), 4.83 (d, *J* = 7.4 Hz, 2H), 5.00 (d, *J* = 14.9 Hz, 1H), 7.30-7.50 (m, 10H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 44.54, 69.83, 73.99, 82.73, 97.69, 127.39, 127.91, 128.06, 128.39, 128.87, 134.56, 136.47, 167.64.

MS (m/z) : 348 (M-Cl).

Analysis ($C_{18}H_{16}NO_2Cl_3$) : Calculated: C, 56.19; H, 4.19; N, 3.64; Cl, 27.64
Observed: C, 56.12; H, 4.17; N, 3.84; S, 27.52.

1. 6. 2f: Preparation of 1-benzyl-3-methoxy-4-trichloromethyl-azetidin-2-one 1.05f

Following the optimized procedure, treatment of methoxyacetyl chloride (0.13 mL, 1.5 mmol) with imine **1.03a** (0.23 g, 1.0 mmol) derived from chloral and benzyl amine in the presence of *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol) gave the β-lactam **1.05f** as a pale yellow oil (0.20 g, 65%).

MP : oil

IR ($CHCl_3$) : 1774 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.60 (s, 3H), 4.25 (d, *J* = 15.1 Hz, 1H), 4.35 (d, *J* = 4.8 Hz, 1H), 4.60 (d, *J* = 4.8 Hz, 1H), 5.00 (d, *J* = 15.1 Hz, 1H), 7.20-7.30 (m, 2H), 7.30-7.45 (m, 3H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 44.37, 60.65, 69.84, 85.35, 97.60, 127.88, 128.14, 128.69, 134.43, 167.47.

MS (m/z) : 308 (M^+).

Analysis ($C_{12}H_{12}NO_2Cl_3$) : Calculated: C, 46.70; H, 3.91; N, 4.54; Cl, 34.46
Observed: C, 46.59; H, 3.94; N, 4.70; Cl, 34.22.

1. 6. 2g: Preparation of 1-benzyl-3-phthalimido-4-trichloromethyl-azetidin-2-one 1.05g

Following the optimized procedure, treatment of phthalimidoacetyl chloride (0.33 g, 1.5 mmol) with imine **1.03a** (0.23 g, 1.0 mmol) derived from chloral and benzyl amine in the presence of *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol) gave the β-lactam **1.05g** as a white solid (0.21 g, 52%).

MP : 221 °C

IR ($CHCl_3$) : 1774, 1726 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 4.35 (d, *J* = 15.1 Hz, 1H), 4.55 (d, *J* = 4.9 Hz, 1H), 5.15 (d, *J* = 15.1 Hz, 1H), 5.40 (d, *J* = 4.9 Hz, 1H), 7.30-7.50 (m, 5H), 7.75-7.95 (m, 4H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 50.81, 64.39, 78.65, 96.89, 127.77, 128.82, 129.05, 129.35, 129.51, 134.13, 160.98, 169.20.

MS (m/z) : 424 (M^+).

Analysis : Calculated: C, 53.86; H, 3.09; N, 6.61; Cl, 25.96
($C_{19}H_{13}N_2O_3Cl_3$) Observed: C, 53.66; H, 3.14; N, 6.52; Cl, 25.73.

1. 6. 2h: Preparation of 3-acetoxy-1-benzyl-4-trichloromethyl-azetidin-2-one 1.05h

Following the optimized procedure, treatment of acetoxyacetyl chloride (0.16 mL, 1.5 mmol) with imine **1.03a** (0.23 g, 1.0 mmol) derived from chloral and benzyl amine in the presence of *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol) gave the β-lactam **1.05h** as a white solid (0.21 g, 63%).

MP : 103-104 ^oC
IR ($CHCl_3$) : 1784, 1760 cm^{-1}.
^1H NMR ($CDCl_3$) (200 MHz) : δ 2.15 (s, 3H), 4.30 (d, *J* = 15.2 Hz, 1H), 4.45 (d, *J* = 4.8 Hz, 1H), 5.05 (d, *J* = 15.2 Hz, 1H), 6.10 (d, *J* = 4.8 Hz, 1H), 7.25-7.30 (m, 2H), 7.35-7.40 (m, 3H).
^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 20.36, 44.98, 68.88, 73.25, 96.81, 128.20, 128.87, 134.01, 165.18, 168.67.
MS (m/z) : 337 (M+1).
Analysis : Calculated: C, 46.38; H, 3.59; N, 4.16; Cl, 31.59
($C_{13}H_{12}NO_3Cl_3$) Observed: C, 46.54; H, 3.89; N, 4.11; Cl, 31.52.

1. 6. 2i: Preparation of 3-acetoxy-1-cyclohexyl-4-trichloromethyl-azetidin-2-one 1.05i

Following the optimized procedure, treatment of acetoxyacetyl chloride (0.16 mL, 1.5 mmol) with imine **1.03b** (0.23 g, 1.0 mmol) derived from chloral and cyclohexyl amine in the presence of *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol) gave the β-lactam **1.05i** as a white solid (0.21g, 65%).

MP : 172-173 ^oC
IR ($CHCl_3$) : 1770 cm^{-1}.
^1H NMR ($CDCl_3$) (200 MHz) : δ 1.20-1.30 (m, 3H), 1.60-2.00 (m, 7H), 2.13 (s, 3H), 3.40-3.60 (m, 1H), 4.60 (d, *J* = 4.7 Hz, 1H), 6.06 (d, *J* = 4.7 Hz, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 20.61, 24.99, 25.10, 25.43, 30.43, 30.69, 55.28, 69.91, 72.55, 97.55, 164.74, 169.04.

MS (m/z) : 329 (M+1).

Analysis : Calculated: C, 43.85; H, 4.90; N, 4.26; Cl, 32.36

($C_{13}H_{16}NO_3Cl_3$) Observed: C, 43.66; H, 4.77; N, 4.41; Cl, 32.11.

1. 6. 2j: Preparation of 1-(4-methoxyphenyl)-3-acetoxy-4-trichloromethyl-azetidin-2-one 1.05j

Following the optimized procedure, treatment of acetoxyacetyl chloride (0.16 mL, 1.5 mmol) with imine **1.03c** (0.25 g, 1.0 mmol) derived from chloral and *p*-anisidine in the presence of *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol) gave a mixture of *cis* and *trans* β-lactams **1.05j &1.06j** in the ratio of 72:28 as a white solid (0.22 g, 62%). The major *cis* isomer was separated by crystallization from methyl alcohol.

MP : 204 ^{o}C (Mp of *cis* isomer).

IR ($CHCl_3$) : 1780, 1762 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.19 (s, 3H), 3.81 (s, 3H), 5.18 (d, *J* = 4.8 Hz, 1H), 6.32 (d, *J* = 4.8 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 9.0 Hz, 2H).

Visible peaks for *trans* isomer **1.06j**

2.22 (s, 3H), 4.97 (d, *J* = 2.0 Hz, 1H), 5.82 (d, *J* = 2.0 Hz, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 20.65, 55.46, 70.05, 72.88, 96.89, 114.27, 123.24, 127.32, 158.09, 163.27, 169.08.

MS (m/z) : 353 (M+1).

Analysis : Calculated: C, 44.28; H, 3.43; N, 3.97; Cl, 30.16

($C_{13}H_{12}NO_4Cl_3$) Observed: C, 44.46; H, 3.24; N, 3.82; Cl, 30.33.

1. 6. 2k: Preparation of 1-phenyl-3-acetoxy-4-trichloromethyl-azetidin-2-one 1.05k

Following the optimized procedure, treatment of acetoxyacetyl chloride (0.16 mL, 1.5 mmol) with imine **1.03d** (0.22 g, 1.0 mmol) derived from chloral and aniline in the presence of *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol) gave a mixture of *cis* and *trans* β-lactams **1.05k &1.06k** in the ratio of 55:45 as a white solid (0.14 g, 45%). The major *cis* isomer was separated by crystallization from methyl alcohol.

MP	**:**	180-182 ^{o}C (Mp of *cis* isomer).
IR ($CHCl_3$)	**:**	1784, 1762 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ 2.22 (s, 3H), 5.28 (d, *J* = 5.1 Hz, 1H), 6.33 (d, *J* = 5.1 Hz, 1H), 7.25-7.50 (m, 5H). Visible peaks for *trans* isomer **1.06k** 2.20 (s, 3H), 5.07 (d, *J* = 1.9 Hz, 1H), 5.87 (d, *J* = 1.9 Hz, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	**:**	δ 20.65, 69.54, 72.77, 96.96, 120.89, 126.51, 129.09, 137.25, 163.31, 169.04.
MS (m/z)	**:**	323 (M+1).
Analysis ($C_{12}H_{10}NO_3Cl_3$)	**:**	Calculated: C, 44.86; H, 3.14; N, 4.36; Cl, 32.68 Observed: C, 44.66; H, 3.29; N, 4.52; Cl, 32.43.

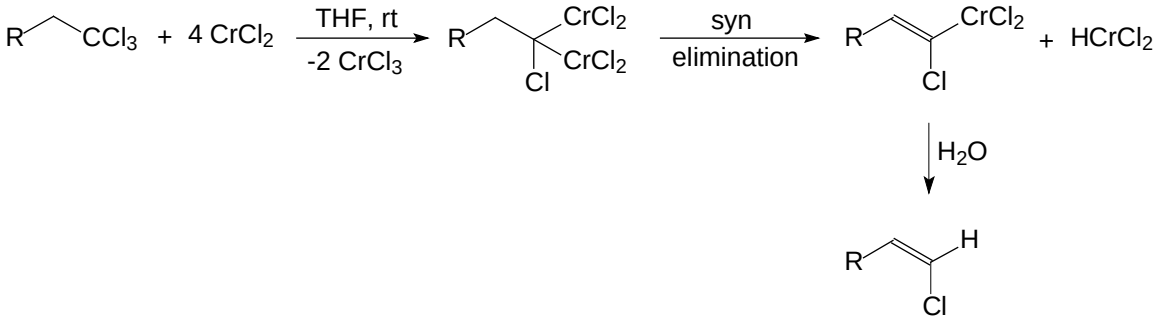
1.7 : Background for the present work

Azetidin-2-ones bearing unsaturation directly on the ring system are known to increase the antibacterial[86] and β-lactamase inhibitor activity. Merchand-Brynaert and coworkers[87] have reviewed these class of compounds. Some of the β-lactam antibiotics with exo methylene double bonds have been reported as inhibitors of Human Leukocyte Elastase.[88] Therefore the synthetic approaches towards the azetidin-2-ones having exocyclic double bond is an active area of research.

The 4-alkylidene-β-lactams were synthesized from the corresponding 4-thioxo-2-azetidinones[89] and 4-acetoxy azetidinones[90,91] using diazo compounds. The acetoxy group at C-4 position of the β-lactam ring can be obtained from the trichloromethyl group. The trichloromethyl group being a masked carboxylic acid equivalent and can be converted into the acetate group employing lead tetra acetate.[92]

It is well documented that the trichloromethyl group is known to give chloro olefins by reaction with chromium (II) chloride *via* reductive elimination (Scheme1.55).[93] This methodology is used for the preparation of the (*Z*)-1-chloro-1-alkenes, some of which are useful synthetic intermediates[94] and used in the synthesis of medicinally important pharmaceuticals.[95]

Scheme 1.55



lactams, we envisioned that double bond could be obtained at the C-4 position of these β-lactams using the trichloromethyl substituent in one pot. This would directly give the 4-alkylidene-β-lactams with various other substitutions at C-2, C-3 and N-1 positions.

1.8 : Present work

We were interested in the preparation of β-lactams having exocyclic unsaturation at C-4 position. Having developed a very good method for the synthesis of 4-trichloromethyl-azetidin-2-ones, we were interested in studying the reaction of $CrCl_2$ on our substrates so that unsaturation could be obtained at C-4 position. This section of the chapter deals with the reaction of chromium (II) chloride with variously substituted 4-trichloromethyl-azetidin-2-ones.

1.9 : Results and Discussion

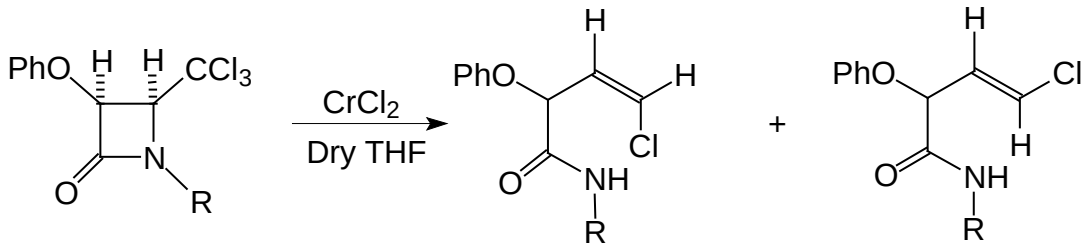
1. 9. 1 Preparation of *E*- and *Z*-chlorovinyl compounds

A solution of *cis*-1-(4-methoxyphenyl)-3-phenoxy-4-trichloromethyl-β-lactam **1.05d** in dry THF was slowly added to a suspension of anhydrous $CrCl_2$ in dry THF and the reaction mixture was stirred overnight (10-12 h). The reaction mixture was then quenched with water and extracted with ethyl acetate. The drying and evaporation of the solvent furnished the chlorovinyl compounds **1.06a** and **1.07a** (Scheme 1.56) *via* N(1)-C(4) bond cleavage of the β-lactam ring. The formation of *E* and *Z* isomers was confirmed on the basis of their spectral data.

For the *E*-isomer the coupling constant of around 10-16 Hz was observed for the vinylic protons while for the *Z*-isomer it was found to be around 3-7 Hz. We also observed that the alkoxy group present at the C-3 position of the β-lactam ring governs the formation of these isomeric products. The ring strain and the co-ordination of the ring nitrogen with $CrCl_2$ may be the factors responsible for the β-lactam ring cleavage.

Both the *E* (47%) and *Z* (33%) isomers in the above reaction were separated by column chromatography (silica Gel 60-120 mesh) and characterized by the spectral and analytical data.

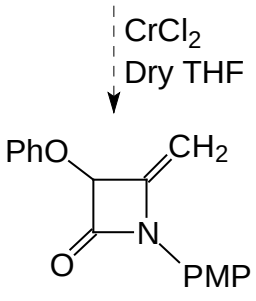
Scheme 1.56



R = PMP, **1.05d**
R = Bn, **1.05a**

R = PMP, **1.06a**
R = Bn, **1.06b**

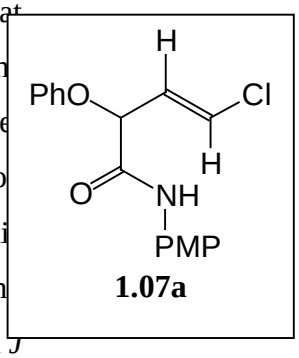
R = PMP, **1.07a**
R = Bn, **1.07b**



1.08

The *E*-chlorovinyl compound **1.07a** showed bands at 3406, 1685, 1527 and 1512 cm^{-1} in the IR spectrum corresponding to the amino, amide and the olefinic functional groups respectively.

The ^{1}H NMR spectrum of **1.07a** showed a sharp singlet at 3.72 ppm, corresponding to the methoxy protons. The methine proton on carbon attached to carbonyl carbon appeared as a double at 5.07 ppm with J = 5.5 Hz. The terminal olefinic methine proto was seen as a doublet at 6.42 ppm with J = 13.5 Hz, characteristi of *trans* olefinic coupling constant (J = 10-16 Hz). The remainin methine proton appeared as a doublet of doublet at 6.14 ppm with J = 5.5 & 13.5 Hz.



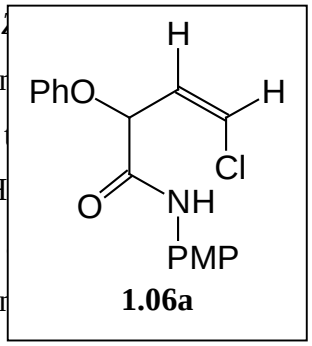
1.07a

The four aromatic protons of the PMP group were observed as two separate doublets at 6.78 and 7.35 ppm with J = 8.7 Hz. The remaining protons of the phenyl ring were observed at 6.90 as a doublet with J = 8.2 Hz and two multiplets between 6.95-7.00 ppm and 7.25-7.30 ppm. The broad singlet at 8.06 ppm was assigned to the proton on nitrogen atom.

The ^{13}C NMR of **1.07a** showed a peak at 55.46 ppm corresponding to the methoxy carbon. The carbon attached to carbonyl group was seen at 78.03 ppm. The vinylic and aromatic carbons appeared at 114.24, 115.85, 121.71, 121.77, 121.84, 123.13, 128.02, 129.82 along with the *ipso* carbons attached to nitrogen and oxygen at 130.00 and 156.76 ppm. The amide carbonyl carbon appeared at 166.14 ppm.

This compound **1.07a** showed a molecular ion peak at m/z 318 (M+1) and also gave satisfactory elemental analysis.

A similar pattern of the peaks was observed for the chlorovinyl compound **1.06a** also, with difference in the couplin constants of the protons. The methine proton on carbon attached carbonyl carbon appeared as a doublet at 5.62 ppm with J = 8.6 H The terminal olefinic methine proton was observed as a doublet 6.40 ppm with J = 7.4 Hz, characteristic of *cis* olefinic couplin constant (J = 3-7 Hz).



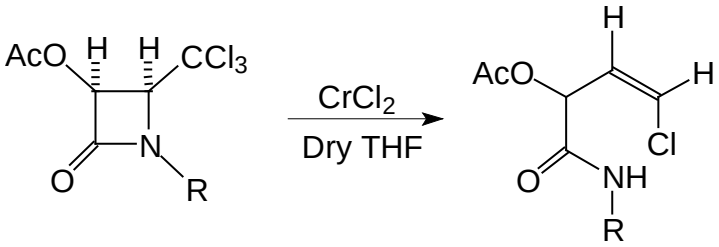
1.06a

The remaining methine proton appeared as a doublet of doublet at 5.85 ppm with J = 8.6 & 7.4 Hz. The pattern of aromatic protons was same as observed in case of the *E*-isomer **1.07a** with the NH proton at 8.20 ppm as a broad singlet.

Similar type of formation of *E* (48%) and *Z* (32%) chlorovinylic compounds **1.07b & 1.06b** was observed when *cis*-1-benzyl-3-phenoxy-azetidin-2-one **1.05a** was subjected to the reaction with chromium (II) chloride (Scheme 1.56).

In the case of reaction of *cis*-3-acetoxy-1-(4-methoxyphenyl)-4-trichloromethyl azetidin-2-one **1.05j** and *cis*-3-acetoxy-1-benzyl-4-trichloromethyl azetidin-2-one **1.05h** with chromium (II) chloride, the exclusive formation of the *Z*-chlorovinyl compounds **1.10** and **1.09** was observed (Scheme 1.57). The structure of both the compounds **1.10** and **1.09** was confirmed from their spectral data.

Scheme 1.57



R = -CH_2Ph **1.05h**
R = -PMP **1.05j**

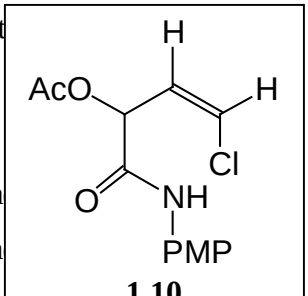
R = -CH_2Ph **1.09**
R = -PMP **1.10**

The IR spectrum of **1.10** showed bands at 3433, 3298, 1730, 1672, 1533 $cm^{-1,}$ corresponding to the secondary amide NH, acetoxy group, amide carbonyl and the olefinic group respectively.

A sharp singlet at 2.21 ppm in the ^{1}H NMR spectrum of compound **1.10** was assigned to the acetoxy methyl protons. The methoxy protons attached to the aromatic ring were observed at 3.79 ppm as a singlet. A doublet at 6.08 ppm (J = 2.4 Hz) and another doublet at 6.13 ppm (J = 4.3 Hz) were attributed to the methine proton on carbon attached to carbonyl group and the terminal methine proton respectively. The remaining methine proton was seen as a doublet of doublet at 6.45 ppm with coupling constants of 2.4 Hz (vicinal coupling) and 4.3 Hz (characteristic of *cis* olefinic coupling).

The aromatic protons appeared as two separate doublet with J = 9.0 Hz at 6.86 and 7.42 ppm. The NH proton showed broad singlet at 7.69 ppm.

The ^{13}C spectrum of **1.10** showed peaks at 20.72 an 55.42 ppm corresponding to the acetoxy methyl carbon an methoxy carbon respectively.



1.10

The carbon attached to carbonyl carbon was observed at 69.94 ppm.

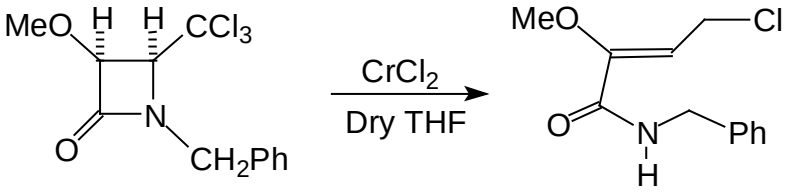
The olefinic and the aromatic carbons appeared at 114.13, 121.81, 124.53 and 125.56 ppm along with the *ipso* carbons attached to nitrogen and oxygen at 129.89 and 156.76 ppm. The amide and the acetoxy carbonyl carbons appeared at 164.74 and 169.74 ppm respectively.

The compound **1.10** gave satisfactory elemental analysis and showed a molecular ion peak m/z 284 (M+1) and at 306 (M+Na).

A similar pattern of peaks was observed for the vinylic protons in ^{1}H NMR of the compound **1.09** with molecular ion peak m/z 268 (M+1).

When *cis*-3-methoxy-1-benzyl-4-trichloromethyl azetidin-2-one **1.05f** was treated with $CrCl_2$, the isomerised product **1.11** was isolated in 72% yield (Scheme 1.58).

Scheme 1.58

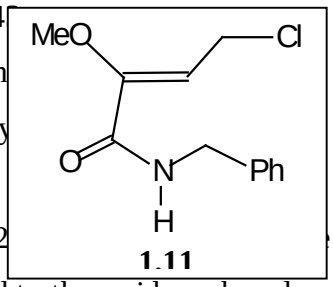


1.05f **1.11**

The spectral analysis gave the structural evidence for the compound **1.11**. The IR spectrum showed bands at 3461 and 1697 cm^{-1} which were attributed to the secondary amide NH and the amide carbonyl groups respectively.

The ^{1}H NMR spectrum of compound **1.11** showed a sharp singlet at 3.62 ppm, corresponding to the methylene protons attached to chlorine. The benzylic protons appeared at 4.50 ppm as a singlet while the methoxy protons were seen at 4.06 ppm as a singlet. The aromatic and vinylic protons appeared as a multiplet in the region of 7.10-7.25 ppm.

The carbon attached to chlorine was observed at 46.4 ppm in ^{13}C spectrum of **1.11**. The benzylic carbon and th methoxy carbon appeared at 50.12 and 58.59 ppm respectively The olefinic carbons observed at 115.16 and 144.11 ppm.



1.11

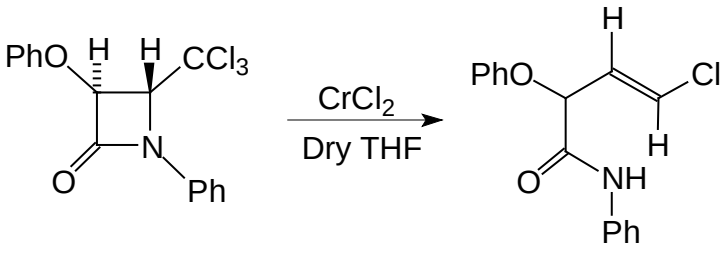
The aromatic carbons appeared at 127.89, 128.13, 12 *ipso* carbon at 136.27 ppm. The peak at 164.85 ppm was attributed to the amide carbonyl carbon. This compound **1.11** gave a molecular ion peak at m/z 240 (M+1) in its mass spectrum.

The ketene derived from phenoxyacetyl chloride on reaction with the imine derived from aniline and chloral furnished the *trans* β-lactam **1.12.** We were also interested in the

reaction of *trans* β-lactam with chromium (II) chloride, to study the effect of the stereochemistry of the lactam ring protons on the product formation.

This β-lactam **1.12** was subjected to reaction with excess $CrCl_2$, the exclusive formation of *trans* product was observed as seen from the ^1H NMR of the crude reaction mixture (Scheme 1.59). It was further confirmed from the spectral analysis of the purified product obtained by column chromatography.

Scheme 1.59

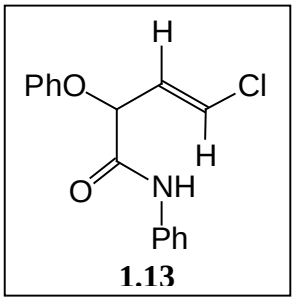


1.12 **1.13**

The IR spectrum of **1.13** showed peaks at 3404 and 1691 cm^{-1}, which were attributed to the -NH and amide carbonyl groups respectively.

The ^1H NMR spectrum of **1.13** showed a doublet of doublet at 5.18 ppm with J = 5.5 & 1.6 Hz, assigned to the methine proton on carbon attached to carbonyl group. This proton was showing the coupling constant of 5.5 Hz corresponding to the vicinal coupling while the coupling constant of 1.6 Hz corresponds to the allylic coupling. The terminal vinylic proton appeared at 6.53 ppm as a doublet of doublet with J = 13.5 Hz (for *trans* coupling with the vicinal proton) & 1.6 Hz (for the allylic coupling). The remaining methine proton was observed again as a doublet of doublet at 6.24 ppm with coupling constants of 13.5 & 5.5 Hz.

The aromatic protons were observed as a multiplet within the range of 7.00-7.60 ppm, while the amide proton appeared as a broad singlet at 8.27 ppm.



1.13

The ^{13}C spectrum of **1.13** showed peaks at 78.01 ppm, which was attributed to the methine carbon attached to carbonyl carbon.

The aromatic and the vinylic carbons appeared at 115.84, 119.99, 123.07, 123.23, 125.02, 127.86, 129.08, 130.00 along with the aromatic *ipso* carbons at 136.65 and 156.25 ppm. The amide carbonyl was observed at 166.33 ppm.

The compound **1.13** gave a molecular ion peak at m/z 288 (M+1) in its mass spectrum.

All the above results obtained, when a panel of various substituted 4-trichloromethyl-azetidin-2-ones were subjected to reaction with $CrCl_2$ are summarized in Table 3 to illustrate the generality of the product formation.

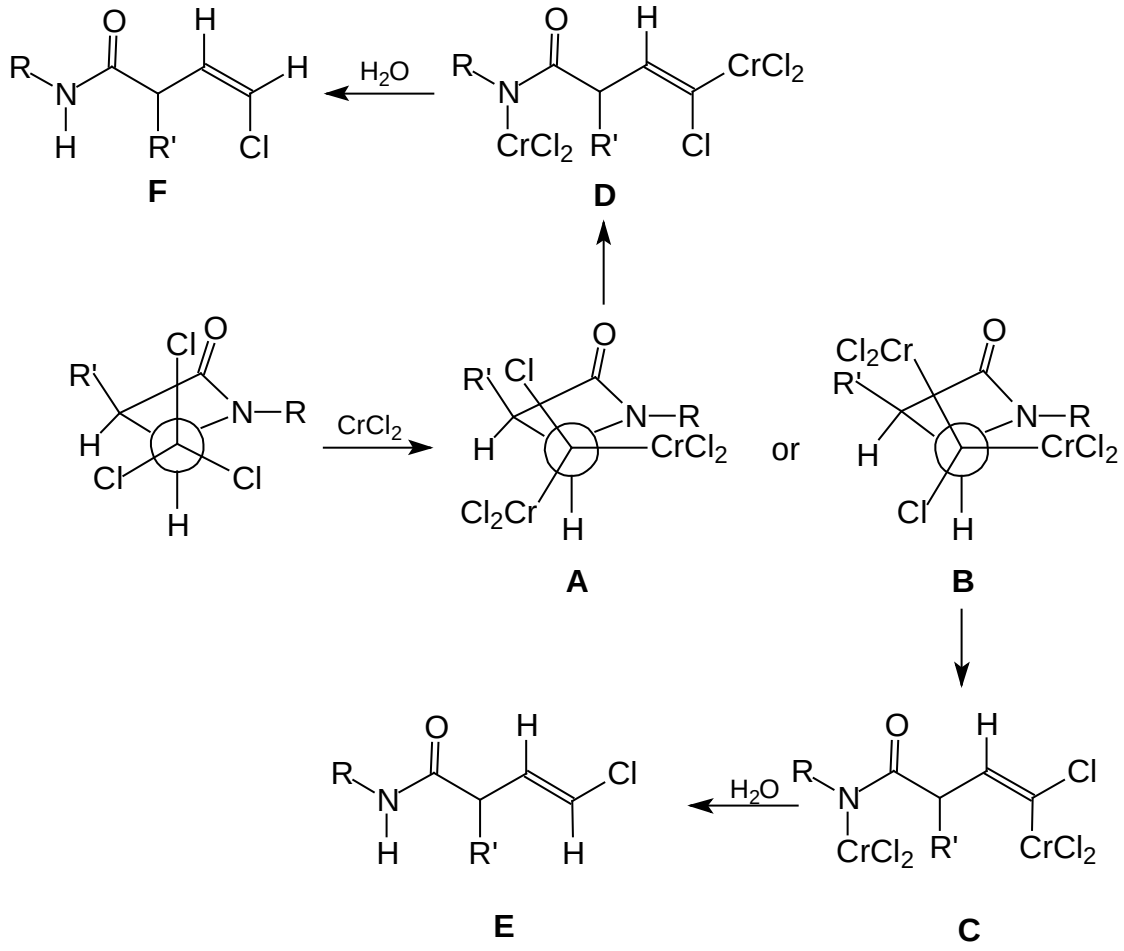
Table 3: Formation of *E* and *Z* chlorovinyl compounds from azetidin-2-ones

Sr. No	Azetidin-2-one	*E*-chloroolefin yield (%)	*Z*-chloroolefin Yield (%)	Isomerised product Yield (%)
1.	**1.05a**	47	33	-
2.	**1.05d**	48	32	-
3.	**1.05h**	-	82	
4.	**1.05j**		85	
5.	**1.05f**	-	-	72
6.	**1.12**	62	-	-

1. 10 : Proposed Mechanism

The formation of the ring opened chlorovinyl amide derivatives with either *Z* or *E* geometry could be rationalized based on the following mechanism (Scheme 1.60).

Scheme 1.60



Initially dichromium carbenoid complex **A** or **B** is formed by oxidative addition of Cr (II) into C-Cl bond of *cis*-trichlormethyl-β-lactam *via* single electron transfer process. This is followed by β-lactam ring cleavage and migration of $CrCl_2$ from carbon to ring nitrogen to give complex **C** or **D**. These two complexes on reaction with water give the respective vinyl amides **E** and **F**. As a consequence of high steric presentation of two $CrCl_2$ and a *cis* substituent at C-3 in dichromium carbenoid complex, there are two conformations possible. The groups at C-3 position of the β-lactam ring, which favor the conformation **A,** those β-lactams results in the formation of *Z* isomer only. In the case of other substituents formation of *E* and *Z* isomers is observed with *E* isomer in major amount. Conformation **A** is preferred over **B** when there is a bulky group at C-3 position of the β-lactam ring.

Phenoxy group at C-3 position and benzyl or PMP group on nitrogen of the β-lactam ring on reaction with $CrCl_2$ gave a mixture of two isomeric vinyl amides **1.06** and **1.07a-b** with the *E* isomers **1.07a-b** in major amount. Acetoxy group at C-3 position and benzyl or PMP group on nitrogen of the β-lactam ring must be favoring the conformer **A**, hence the

reaction with $CrCl_2$ furnishes the *Z* isomers **1.09** and **1.10** exclusively. Methoxy group at C-3 position of the β-lactam ring gives the isomerised product **1.11**.

1. 11 : Conclusion

Selectivity in the formation of *E*- and *Z*- chloro olefins was observed in case of the reaction of *cis*-4-trichloromethyl-β-lactams with $CrCl_2$ (Table 3). This selectivity depends upon the stereochemistry of the β-lactam ring as well as the group attached at C-3 position. *cis* β-Lactam with substituent, such as phenoxy at C-3, furnished mixture of *E* and *Z* isomers with *E* isomer as a major product. The β-lactam with acetoxy group gave the formation of *Z* isomer exclusively. The mode of reductive elimination was also governed by the steric bulk of the group at C-3 position in the β-lactam ring. However, *E*- isomer was formed selectively in the ring cleavage of the *trans* β-lactam, with phenoxy group at C-3 position and phenyl group on nitrogen.

1. 12 : Experimental

1. 12. 1: General procedure for the synthesis of *E*- and *Z*-chloro olefins

To a suspension of anhydrous $CrCl_2$ (0.12 g, 10 mmol) in dry THF (5 mL), was added a solution of 4-trichloromethyl-azetidin-2-one (1.0 mmol) in dry THF (3 mL) under argon at room temperature. The reaction mixture was stirred for 10-12 h and then quenched with water and extracted with ethyl acetate. The combined organic extract was dried over sodium sulphate and the solvent was evaporated under reduced pressure. The residue was then purified by column chromatography (silica gel 60-120 mesh).

1. 12. 1a: Preparation of *E*- & *Z*-4-chloro-2-phenoxy-but-3-enoic acid-(4-methoxyphenyl) amide 1.07a & 1.06a

Following the optimized general procedure, treatment of *cis*-1-(4-methoxyphenyl)-3-phenoxy-4-trichloromethyl-azetidin-2-one **1.05d** (0.38 g, 1.0 mmol) with anhydrous chromium (II) chloride in dry THF and usual work up gave a mixture of *E*- and *Z*-4-chloro-2-phenoxy-but-3-enoic acid-(4-methoxyphenyl) amide. The purification of the mixture by column chromatography gave **1.07a** and **1.06a** as white solids.

Data for *E*-4-chloro-2-phenoxy-but-3-enoic acid-(4-methoxyphenyl) amide 1.07a

MP	:	132 °C
IR ($CHCl_3$)	:	3406, 1685, 1527, 1512 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 3.72 (s, 3H), 5.07 (d, *J* = 5.5 Hz, 1H), 6.14 (dd, *J* = 5.5 & 13.5 Hz, 1H), 6.42 (d, *J* = 13.5 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 2H), 6.90-7.00 (m, 1H), 7.25-7.30 (m, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 8.06 (bs, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 55.46, 78.03, 114.24, 115.85, 121.71, 121.77, 121.84, 123.13, 128.02, 129.82, 130.00, 156.76, 166.14.
MS (m/z)	:	318 (M+1), 335 (M+18).
Analysis ($C_{17}H_{16}NO_3Cl$)	:	Calculated: C, 64.25; H, 5.07; N, 4.40; Cl, 11.15 Observed: C, 64.49; H, 5.29; N, 4.47; Cl, 11.38.

Data for *Z*-4-chloro-2-phenoxy-but-3-enoic acid-(4-methoxyphenyl) amide 1.06a

MP	:	105-107 °C
IR ($CHCl_3$)	:	3407, 1689, 1527, 1512 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ 3.71 (s, 3H), 5.62 (d, *J* = 8.6 Hz, 1H), 5.85 (dd, *J* = 8.6 & 7.4 Hz, 1H), 6.40 (d, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 6.8 Hz, 2H), 6.93 (d, *J* = 7.4 Hz, 2H), 6.95-7.00 (m, 1H), 7.20-7.30 (m, 2H), 7.40 (d, *J* = 6.8 Hz, 2H), 8.20 (bs, 1H).
MS (m/z)	**:**	318 (M+1), 335 (M+18).
Analysis ($C_{17}H_{16}NO_3Cl$)	**:**	Calculated: C, 64.25; H, 5.07; N, 4.40; Cl, 11.15 Observed: C, 64.28; H, 5.23; N, 4.16; Cl, 11.29.

1. 12. 1b: Preparation of *E*- & *Z*-4-chloro-2-phenoxy-but-3-enoic acid benzyl amide 1.07b & 1.06b

Following the optimized general procedure, treatment of *cis*-1-benzyl-3-phenoxy-4-trichloromethyl-azetidin-2-one **1.05a** (0.37 g, 1.0 mmol) with anhydrous chromium (II) chloride in dry THF and usual work up gave a mixture of *E*- and *Z*-4-chloro-2-phenoxy-but-3-enoic acid benzyl amide. The purification of the mixture by column chromatography gave **1.07b** and **1.06b** as white solids.

Data for *E*-4-chloro-2-phenoxy-but-3-enoic acid benzyl amide 1.07b

MP	**:**	92 °C
IR ($CHCl_3$)	**:**	3427, 1677, 1525, 1492 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ 4.50 (d, *J* = 5.5 Hz, 2H), 5.15 (d, *J* = 5.5 Hz, 1H), 6.20 (dd, *J* = 5.5 & 13.5 Hz, 1H), 6.48 (d, *J* = 13.5 Hz, 1H), 6.85 (bs, 1H), 6.92 (d, *J* = 8.4 Hz, 2H), 7.05-7.10 (m, 1H), 7.25 (d, *J* = 7.1 Hz, 2H), 7.30-7.40 (m, 5H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	**:**	δ 43.27, 77.72, 115.72, 122.77, 122.90, 127.57, 127.66, 128.18, 128.76, 129.89, 137.49, 156.44, 168.33.
MS (m/z)	**:**	302 (M+1), 319 (M+18).
Analysis ($C_{17}H_{16}NO_2Cl$)	**:**	Calculated: C, 67.66; H, 5.34; N, 4.64; Cl, 11.74 Observed: C, 67.48; H, 5.19; N, 4.61; Cl, 11.48.

Data for *Z*-4-chloro-2-phenoxy-but-3-enoic acid benzyl amide 1.06b

MP	:	81 °C
IR ($CHCl_3$)	:	3429, 1681 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 4.53 (d, *J* = 5.9 Hz, 2H), 5.70 (d, *J* = 8.6 Hz, 1H), 5.90 (dd, *J* = 8.6 & 7.5 Hz, 1H), 6.50 (d, *J* = 7.5 Hz, 1H), 6.90-7.10 (m, 5H), 7.20-7.35 (m, 6H).
MS (m/z)	:	302 (M+1), 319 (M+18).
Analysis ($C_{17}H_{16}NO_2Cl$)	:	Calculated: C, 67.66; H, 5.34; N, 4.64; Cl, 11.74 Observed: C, 67.42; H, 5.19; N, 4.46; Cl, 11.56.

1. 12. 1c: Preparation of *Z*-acetic acid-1-benzyl carbamoyl-3-chloro-allyl ester 1.09

Following the optimized general procedure, treatment of *cis*-1-benzyl-3-acetoxy-4-trichloromethyl-azetidin-2-one **1.05h** (0.34 g, 1.0 mmol) with anhydrous chromium (II) chloride in dry THF and usual work up gave *Z*-acetic acid-1-benzyl carbamoyl-3-chloro-allyl ester **1.09** as a colorless oil.

MP	:	oil
IR ($CHCl_3$)	:	3433, 1743, 1685, 1525 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 2.15 (s, 3H), 4.46 (d, *J* = 5.8 Hz, 2H), 5.95-6.05 (m, 2H), 6.35-6.45 (m, 2H), 7.25-7.40 (m, 5H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 20.57, 43.45, 69.66, 124.30, 125.69, 127.51, 128.68, 137.52, 167.01, 169.51.
MS (m/z)	:	268 (M+1), 285 (M+18).
Analysis ($C_{13}H_{14}NO_3Cl$)	:	Calculated: C, 58.32; H, 5.27; N, 5.23; Cl, 13.24 Observed: C, 58.48; H, 5.48; N, 5.45; Cl, 13.52.

1. 12. 1d: Preparation of *Z*-acetic acid-3-chloro-1-(4-methoxyphenyl carbamoyl)-allyl ester 1.10

Following the optimized general procedure, treatment of *cis*-3-acetoxy-1-(4-methoxyphenyl)-4-trichloromethyl-azetidin-2-one **1.05j** (0.35 g, 1.0 mmol) with anhydrous chromium (II) chloride in dry THF and usual work up gave a *Z*-acetic acid-3-chloro-1-(4-methoxy phenyl carbamoyl)-allyl ester **1.10** as a white solid.

MP	:	130-132 °C
IR ($CHCl_3$)	:	3433, 3298, 1730, 1672, 1533 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 2.21 (s, 3H), 3.79 (s, 3H), 6.08 (d, *J* = 2.4 Hz, 1H), 6.13 (d, *J* = 4.3 Hz, 1H), 6.45 (dd, *J* = 2.4 & 4.3 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 9.0 Hz, 2H), 7.69 (bs, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 20.72, 55.42, 69.94, 114.13, 121.81, 124.53, 125.56, 129.89, 156.76, 164.74, 169.74.
MS (m/z)	:	284 (M+1), 306 (M+Na).
Analysis ($C_{13}H_{14}NO_4Cl$)	:	Calculated: C, 55.03; H, 4.97; N, 4.94; Cl, 12.49 Observed: C, 54.94 H, 5.11; N, 4.65; Cl, 12.22.

1. 12. 1e: *Preparation of 4-chloro-2-methoxy-but-2-enoic acid benzyl amide 1.11*

Following the optimized general procedure, treatment of *cis*-3-methoxy-1-benzyl-4-trichloromethyl-azetidin-2-one **1.05f** (0.31 g, 1.0 mmol) with anhydrous chromium (II) chloride in dry THF and usual work up gave 4-chloro-2-methoxy-but-2-enoic acid benzyl amide **1.11** as a white solid.

MP	:	74-75 °C
IR ($CHCl_3$)	:	3461, 1697, 1666, 1454, 1215 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 3.62 (s, 2H), 4.06 (s, 3H), 4.50 (s, 2H), 7.10-7.25 (m, 6H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 46.43, 50.12, 58.59, 115.16, 127.89, 128.13, 128.86, 136.27, 144.11, 164.85.
MS (m/z)	:	240 (M+1).
Analysis ($C_{12}H_{14}NO_2Cl$)	:	Calculated: C, 60.13; H, 5.88; N, 5.84; Cl, 14.78 Observed: C, 60.40 H, 5.62; N, 5.65; Cl, 14.39.

1. 12. 1f: Preparation of *E*-4-chloro-2-phenoxy-but-3-enoic acid-(phenyl) amide 1.13

Following the optimized general procedure, treatment of *trans*-1-phenyl-3-phenoxy-4-trichloromethyl-azetidin-2-one **1.12** (0.35 g, 1.0 mmol) with anhydrous chromium (II)

chloride in dry THF and usual work up gave the *E*-4-chloro-2-phenoxy-but-3-enoic acid-phenyl amide **1.13** as a white solid.

MP	:	122-123 °C
IR ($CHCl_3$)	:	3404, 1691, 1600, 1529, 1492, 1217 cm^{-1}.
^1H NMR ($CDCl_3$) (200 MHz)	:	δ 5.18 (dd, *J* = 5.5 & 1.6 Hz, 1H), 6.24 (dd, *J* = 13.5 & 5.5 Hz, 1H), 6.53 (dd, *J* = 13.5 & 1.6 Hz, 1H), 7.00-7.20 (m, 4H), 7.20-7.40 (m, 4H), 7.55-7.60 (m, 2H), 8.27 (bs, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 78.01, 115.84, 119.99, 123.07, 123.23, 125.02, 127.86, 129.08, 130.00, 136.65, 156.25, 166.33.
MS (m/z)	:	288 (M+1).
Analysis ($C_{16}H_{14}NO_2Cl$)	:	Calculated: C, 66.88; H, 4.91; N, 4.87; Cl, 12.18 Observed: C, 66.60; H, 4.72; N, 4.65; Cl, 12.39.

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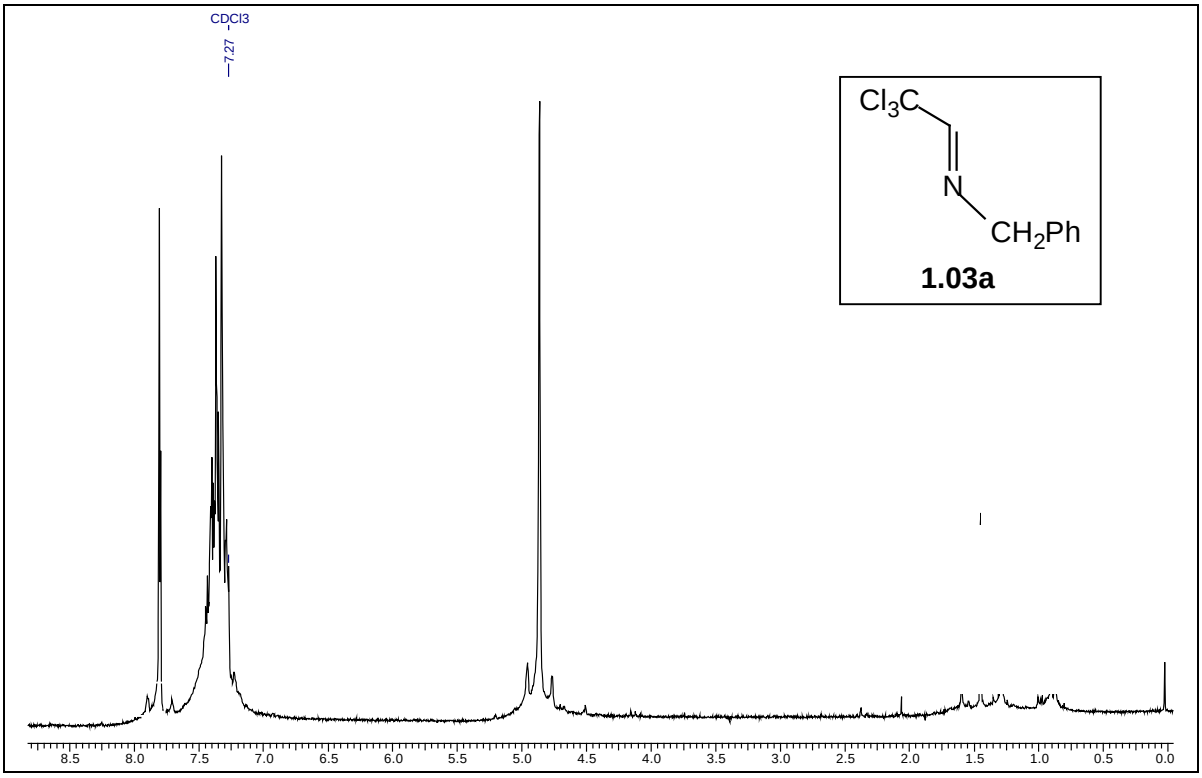
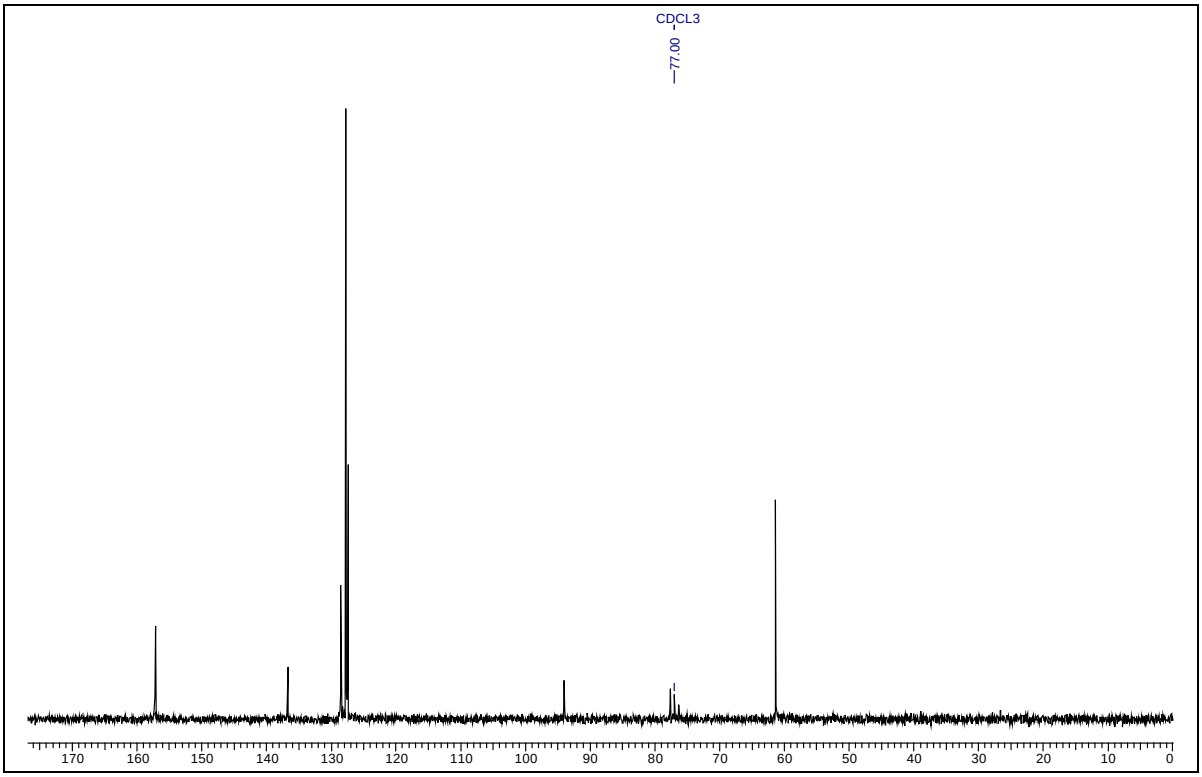
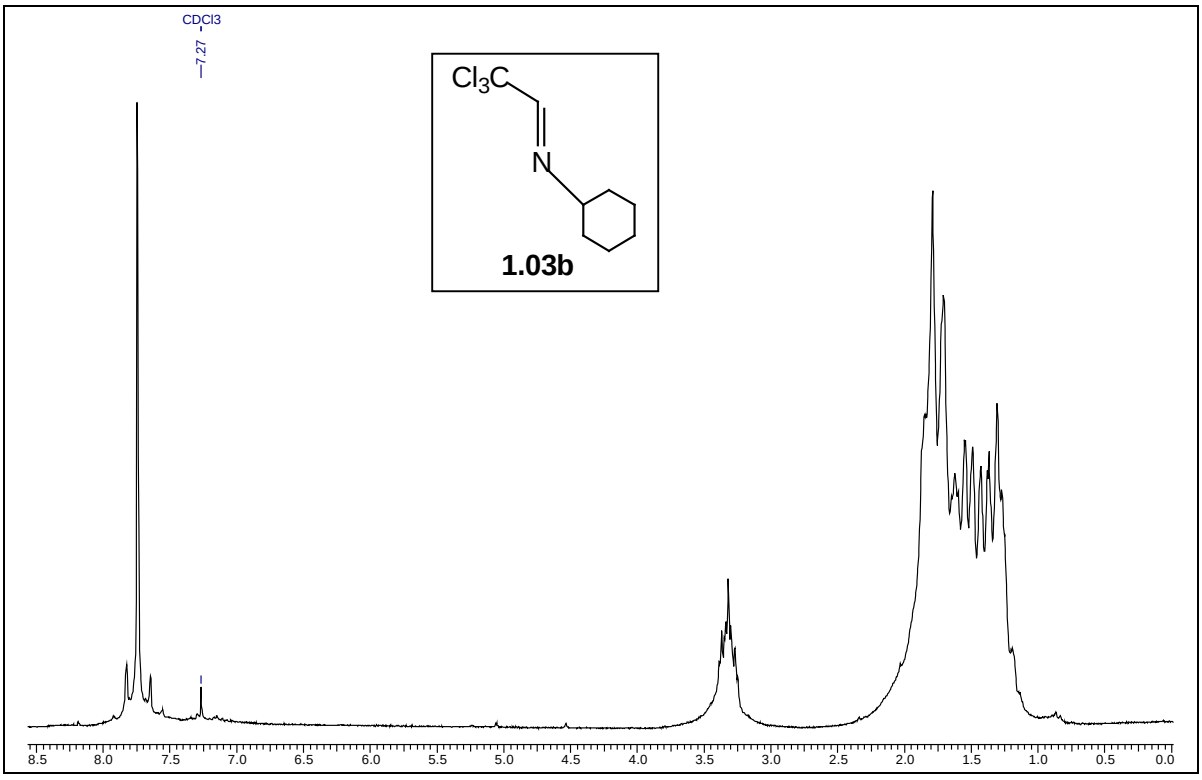
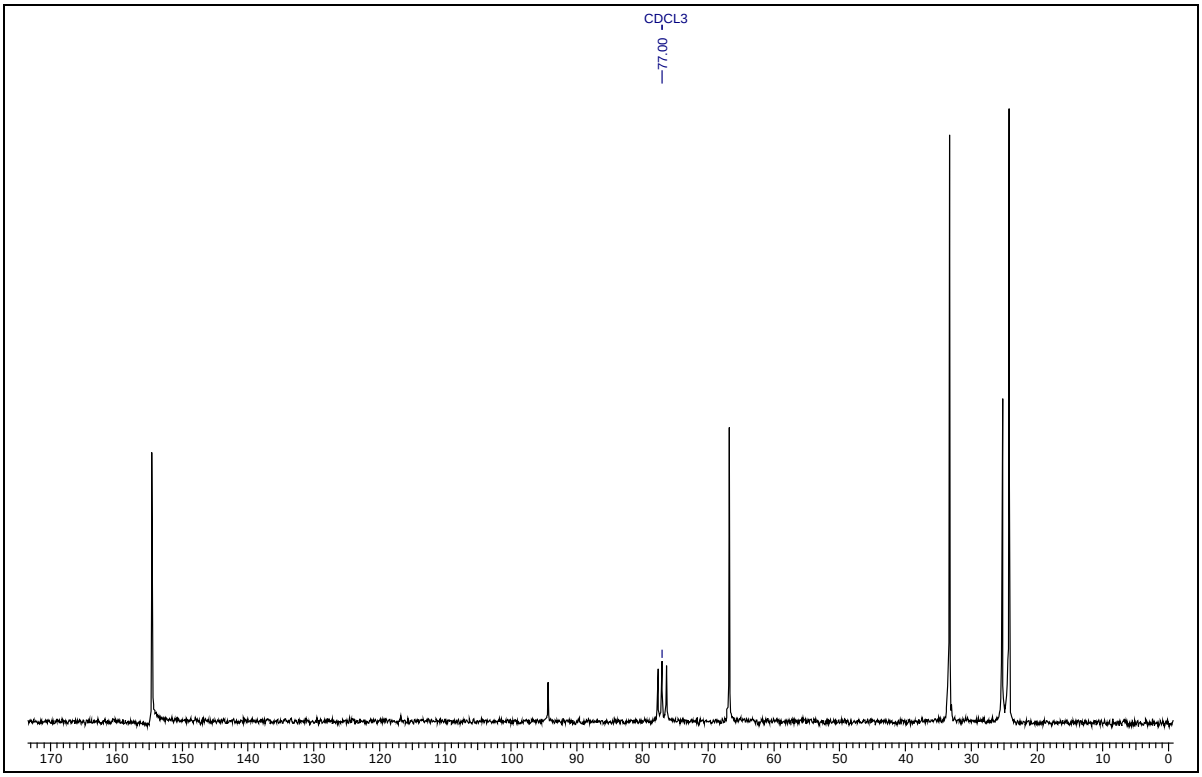
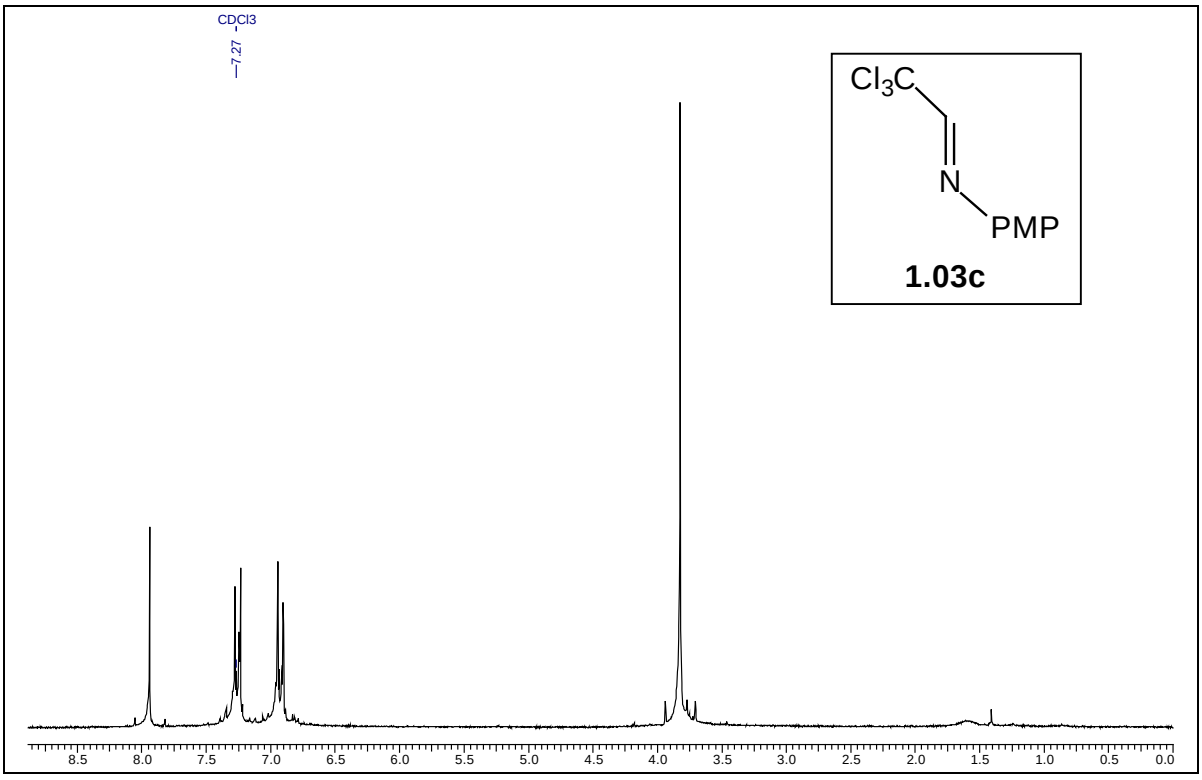
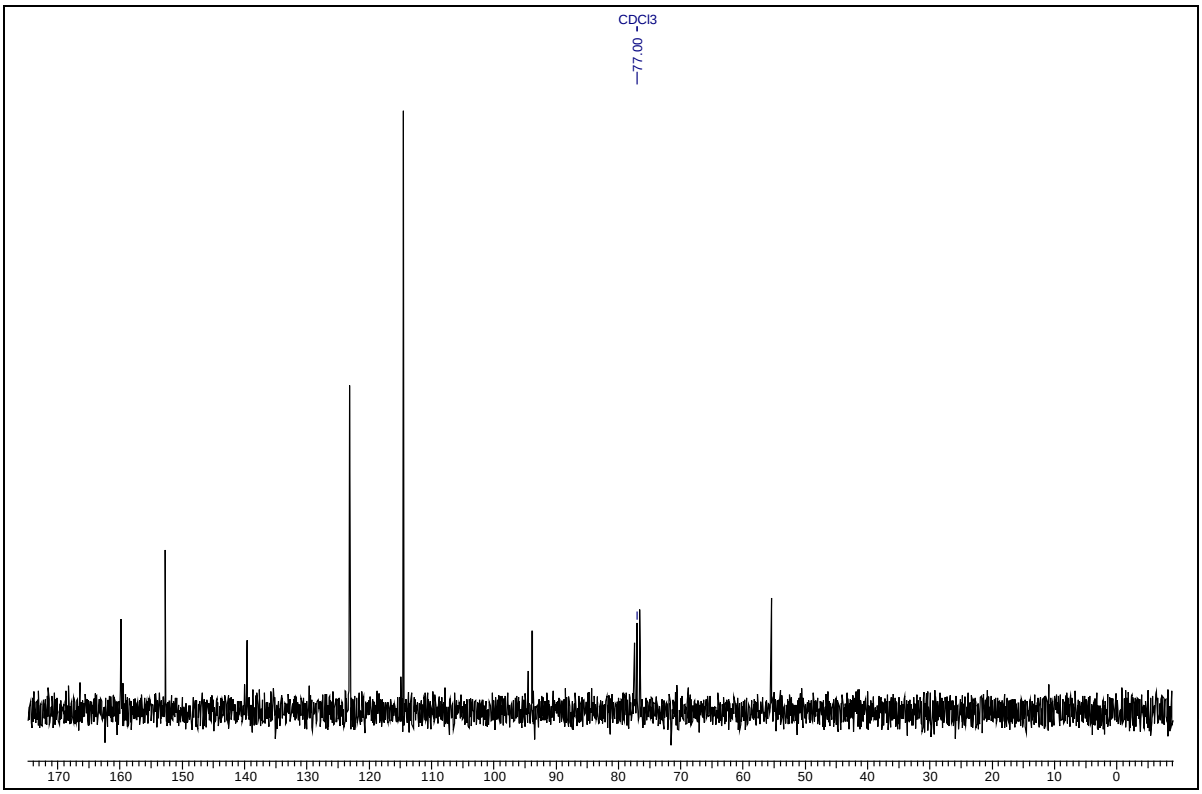


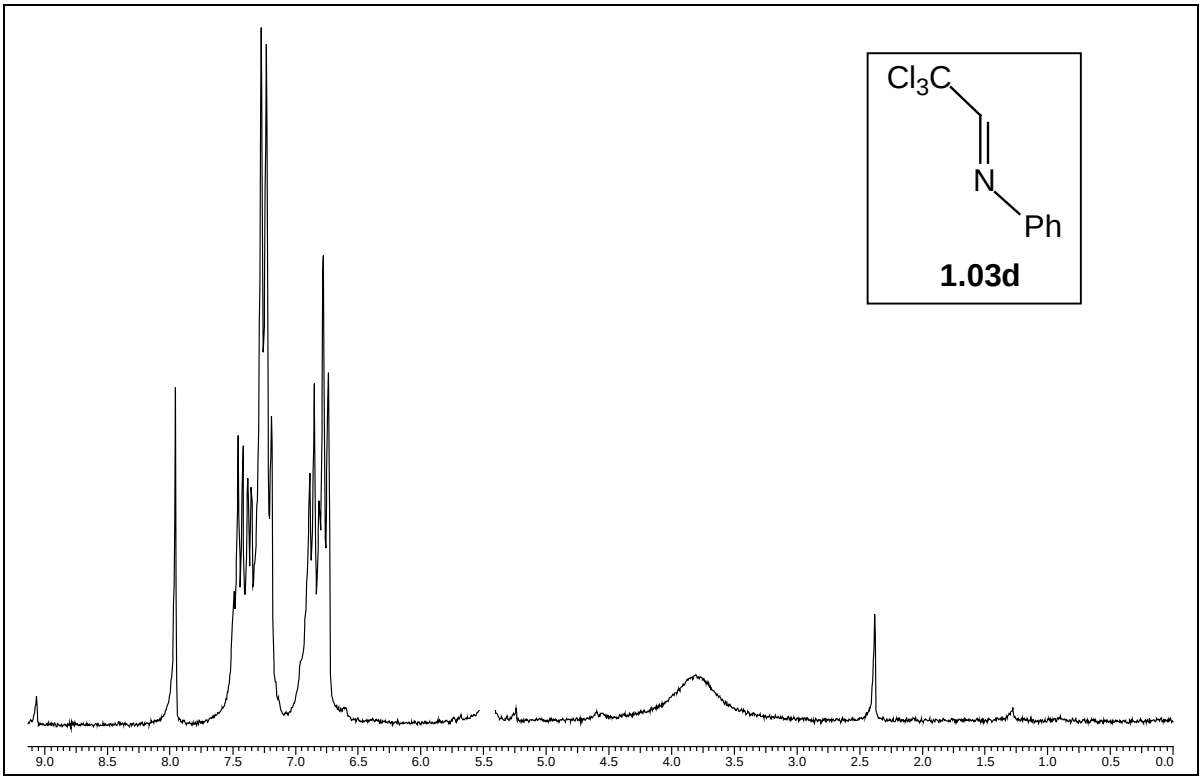


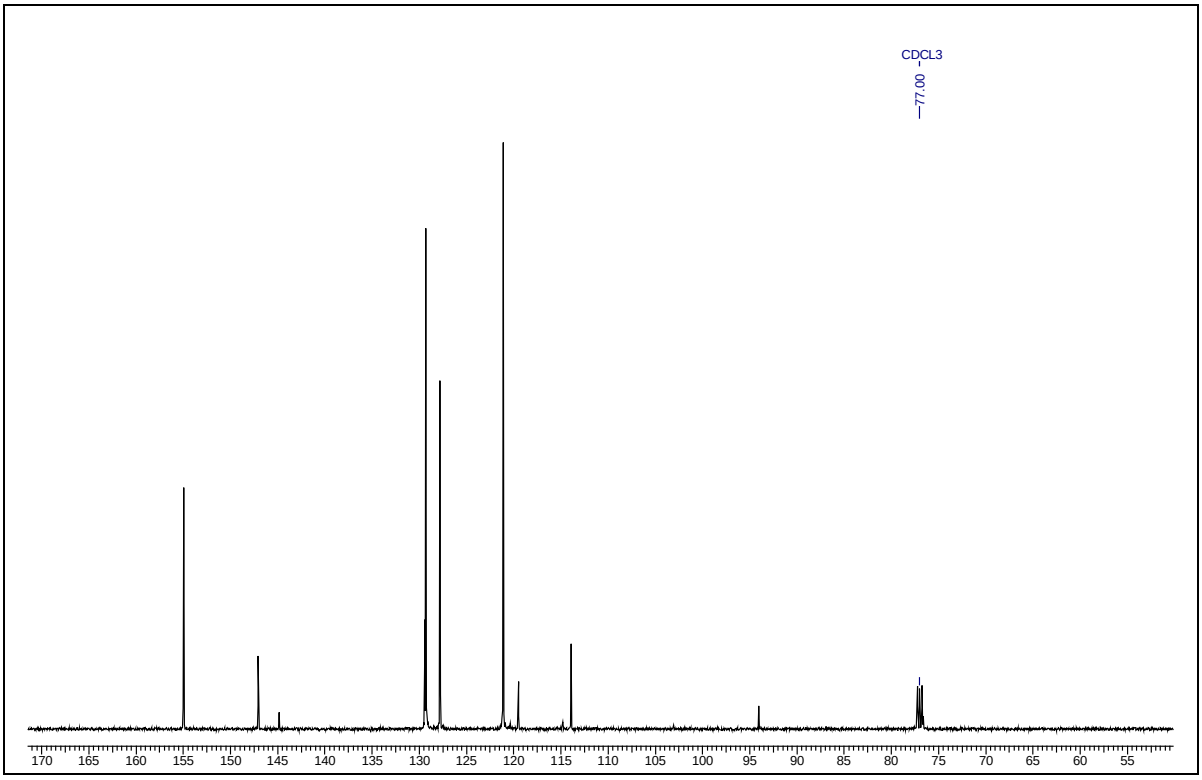


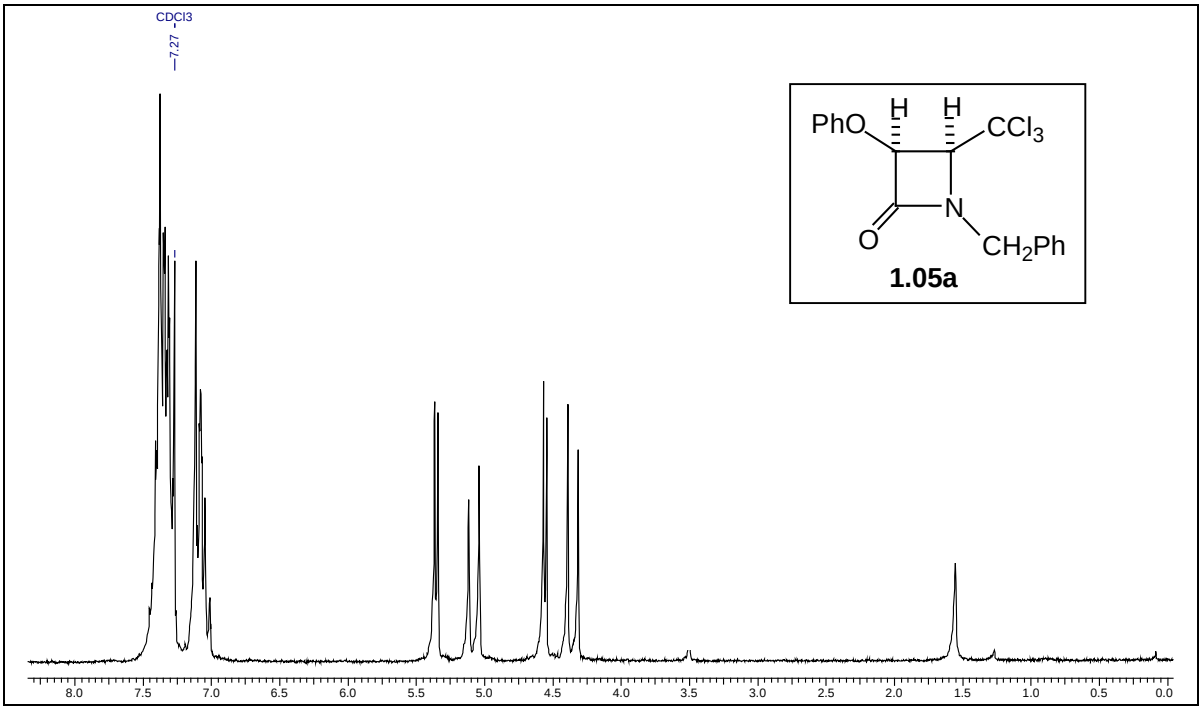


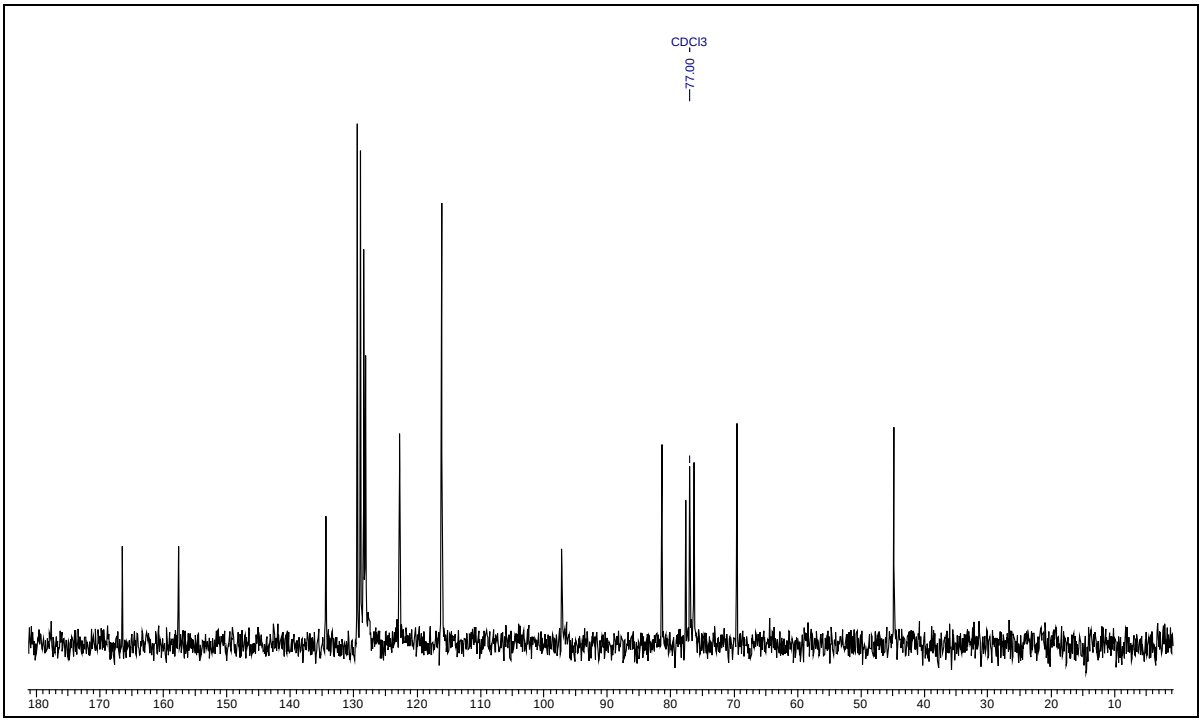


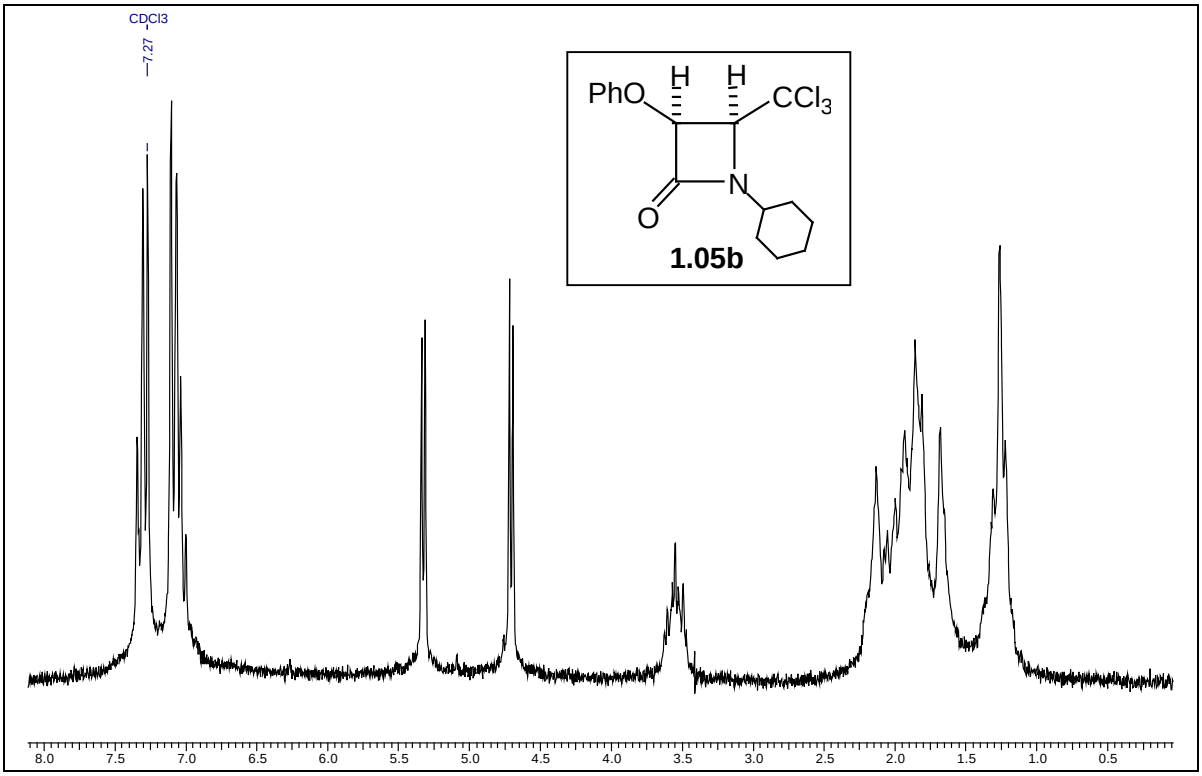


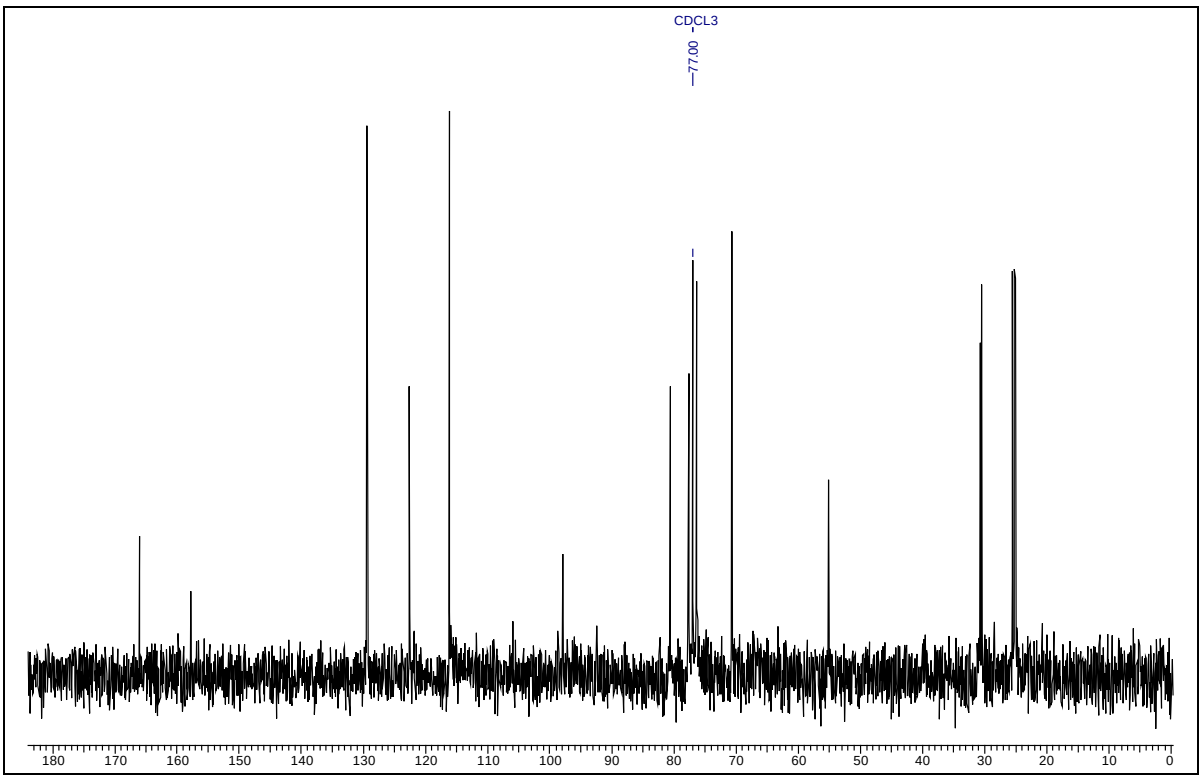


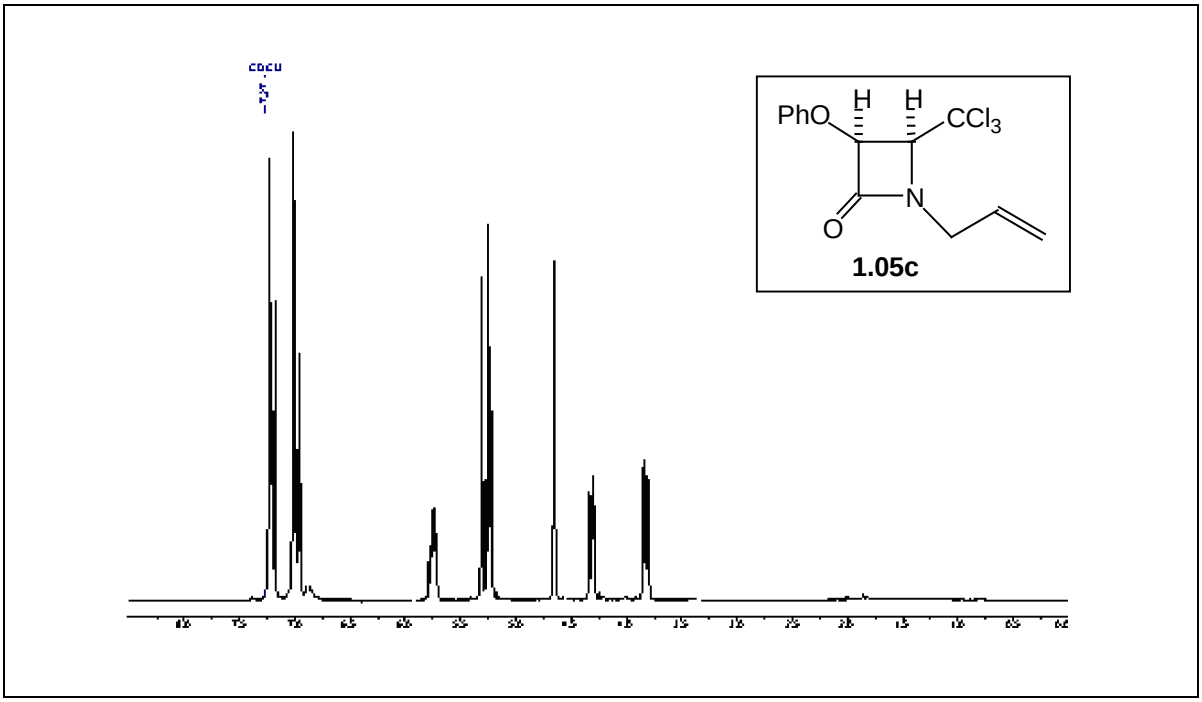


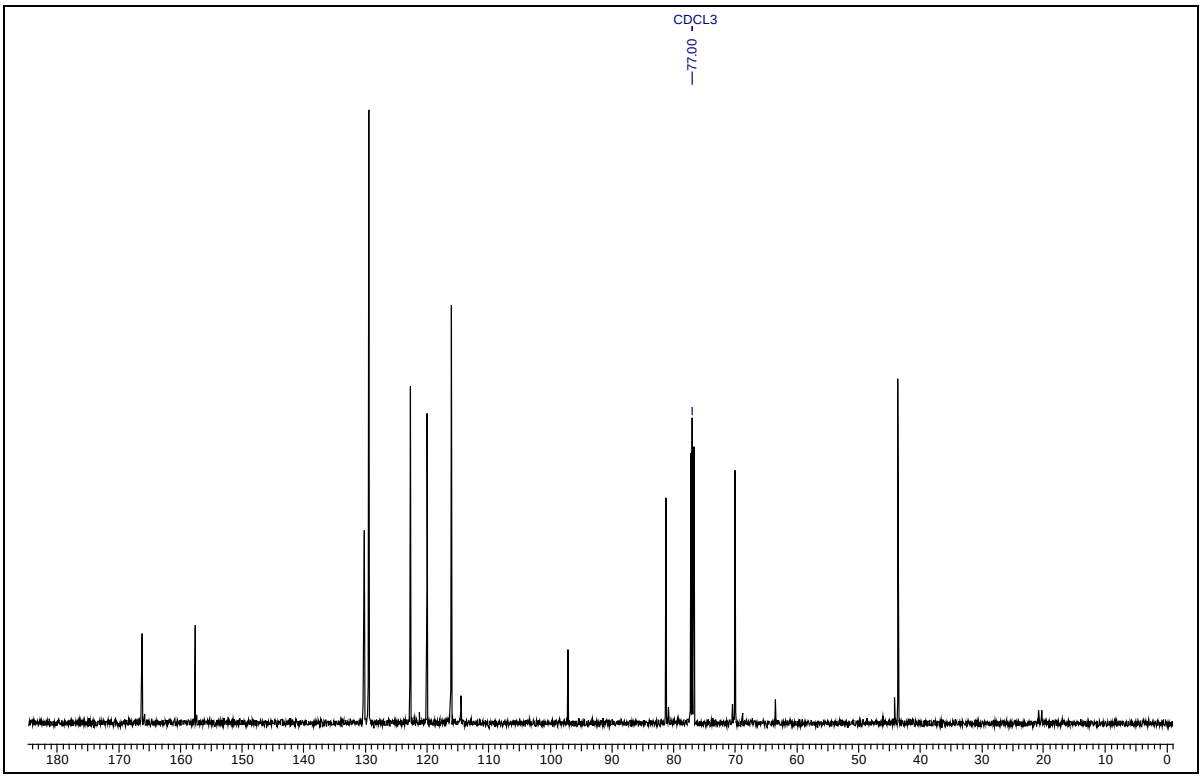


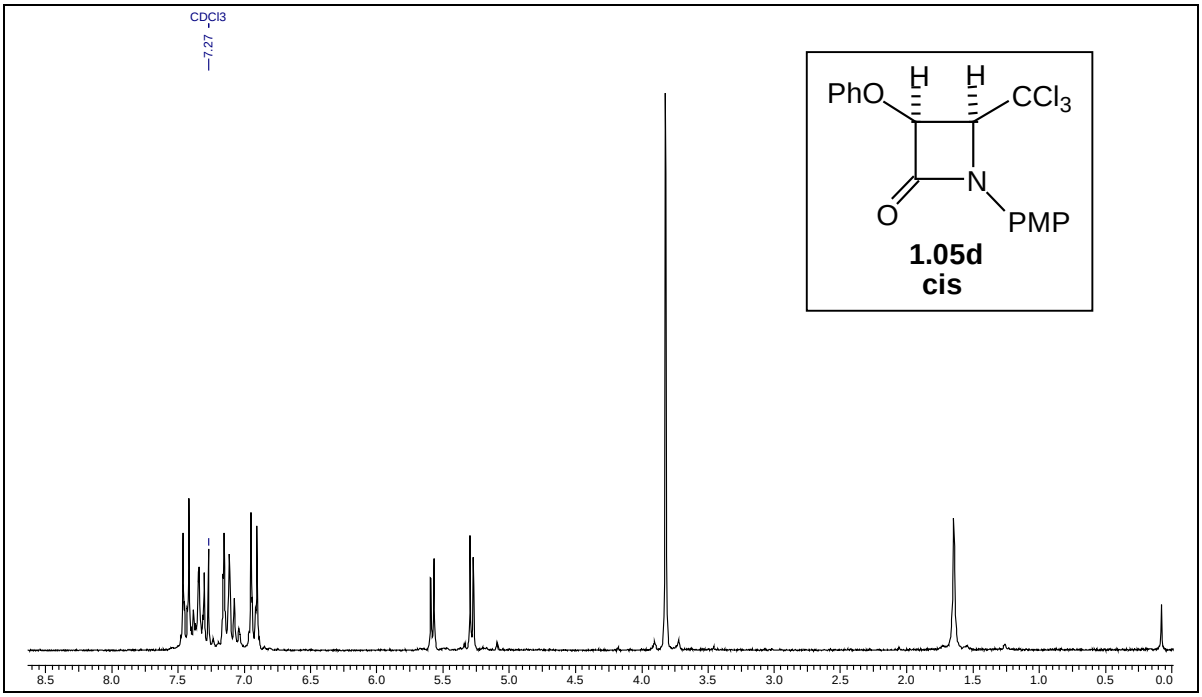


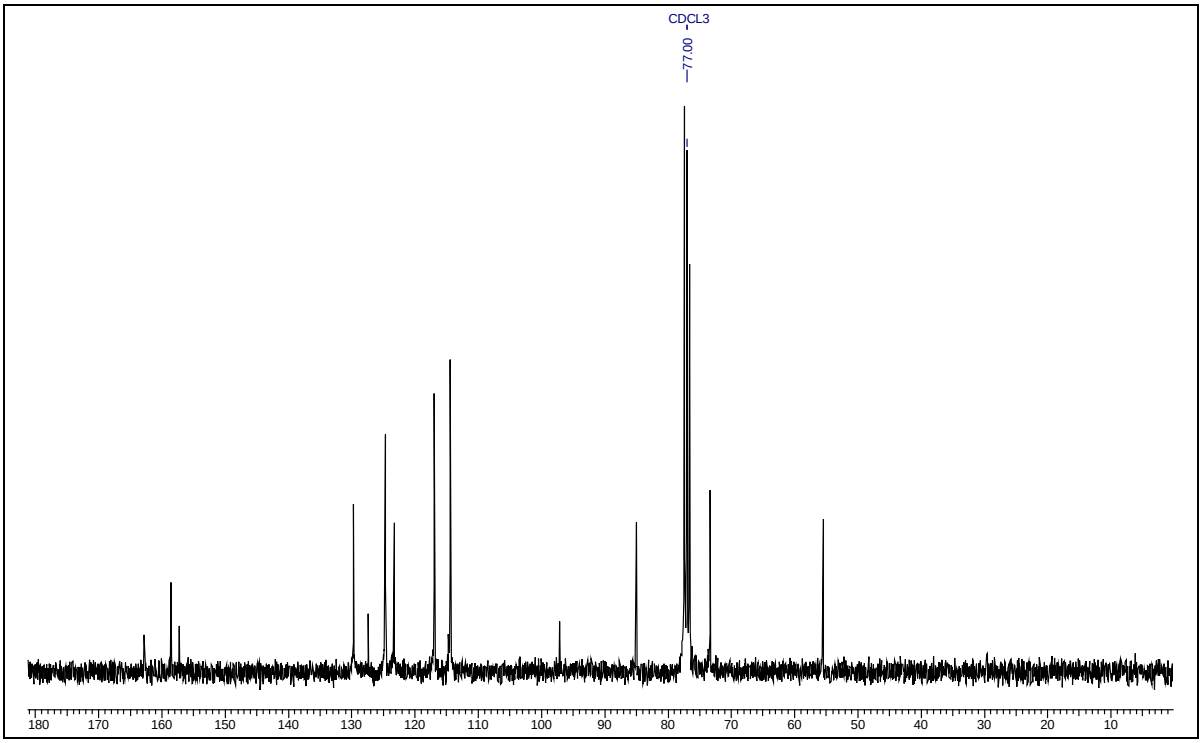


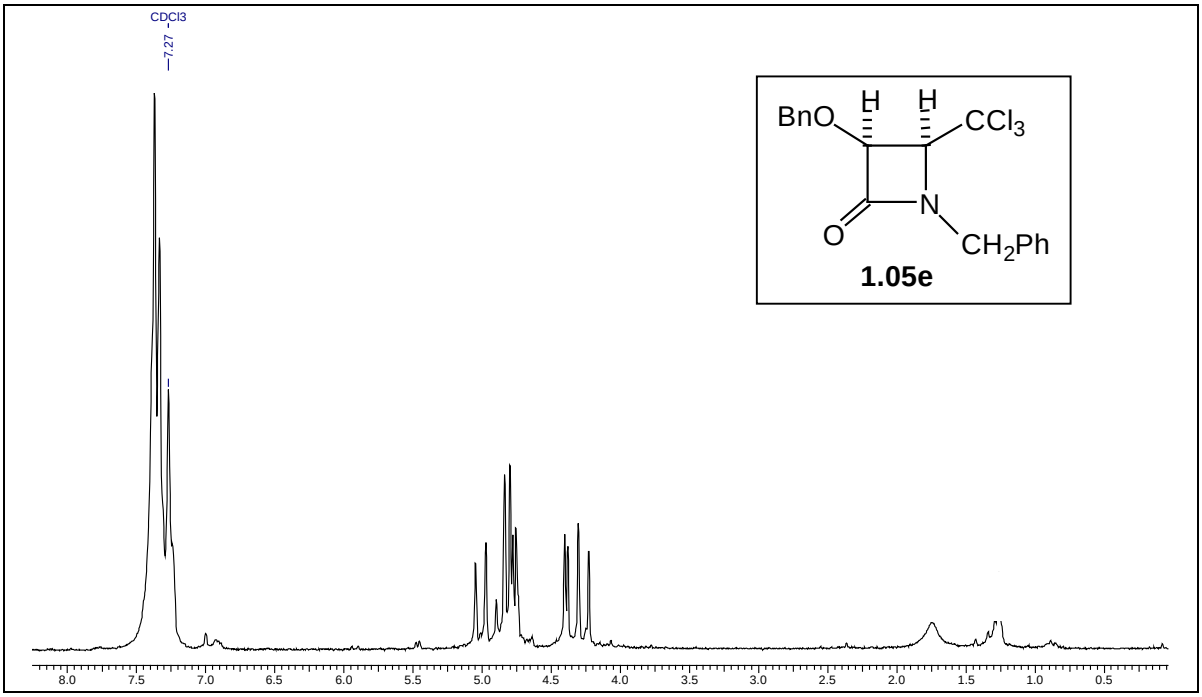


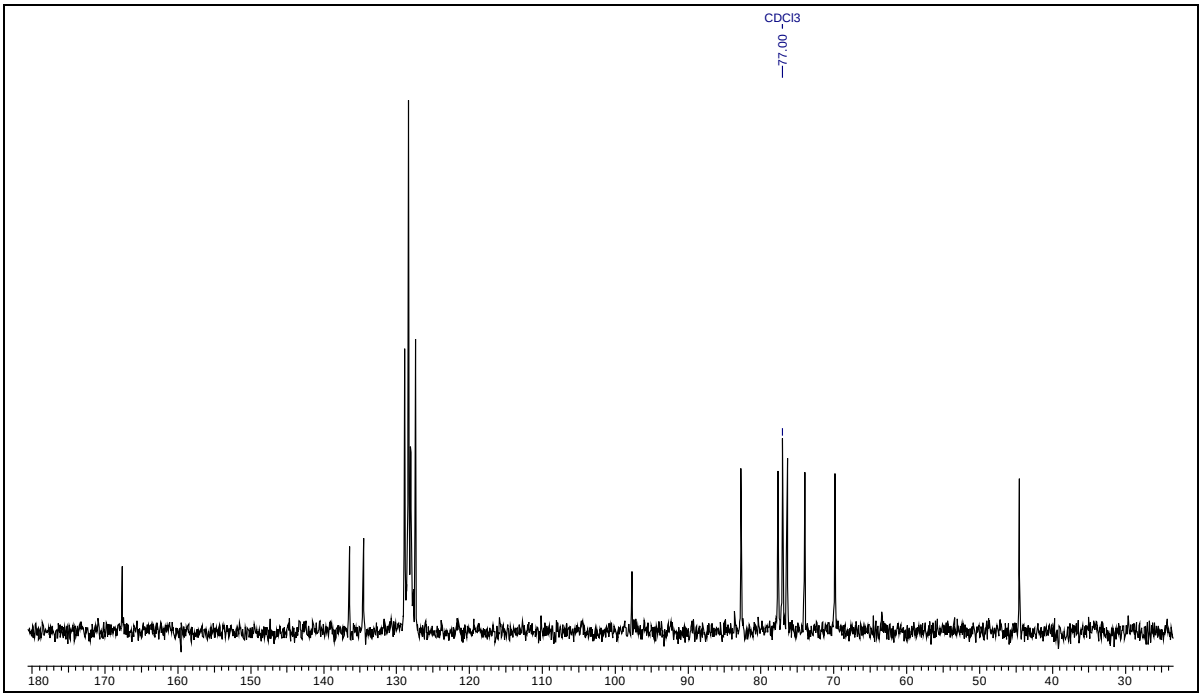


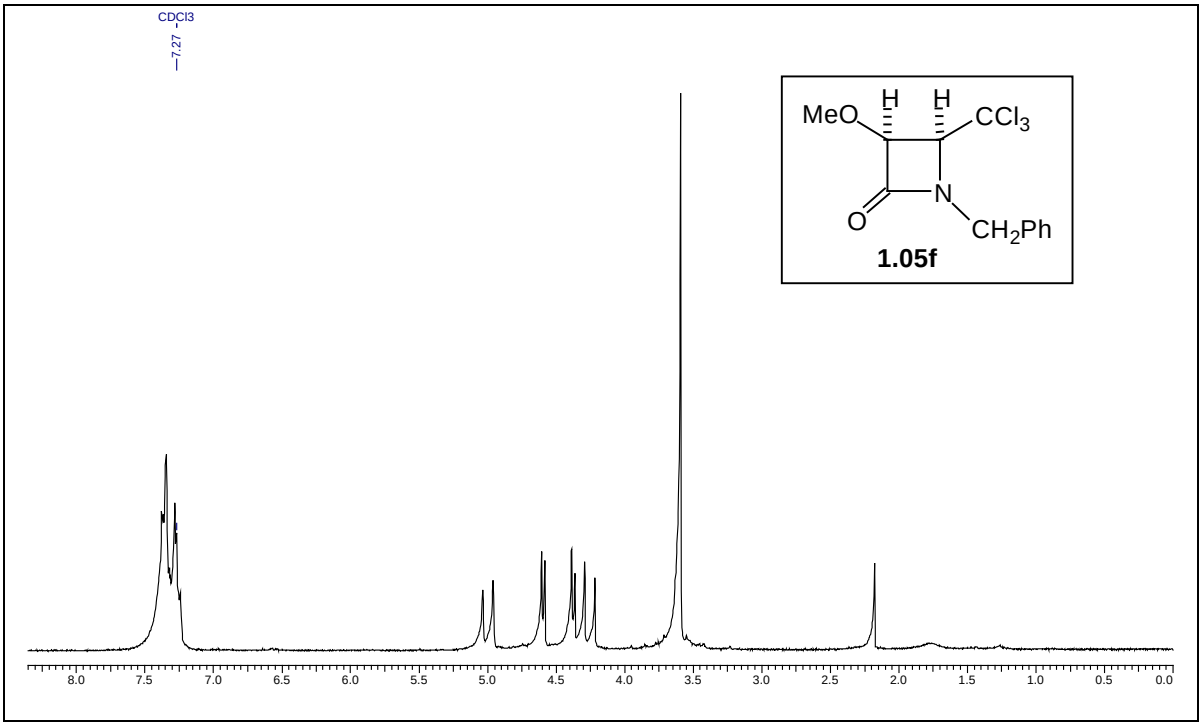


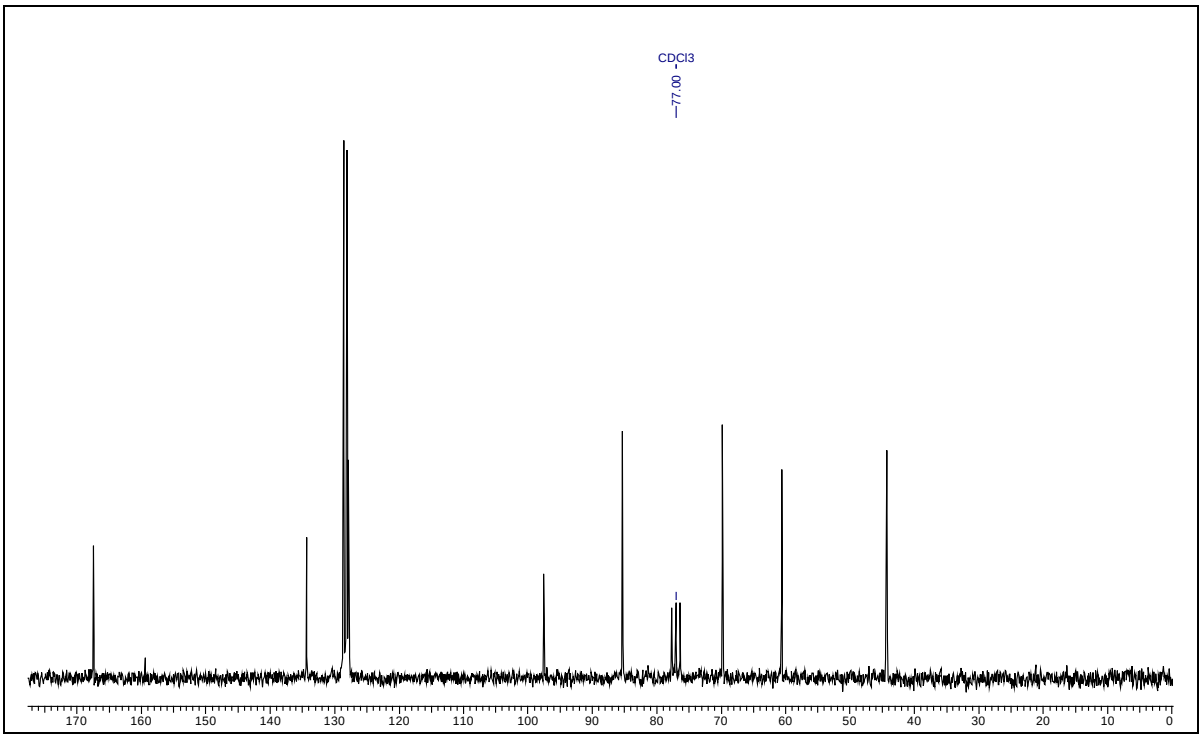


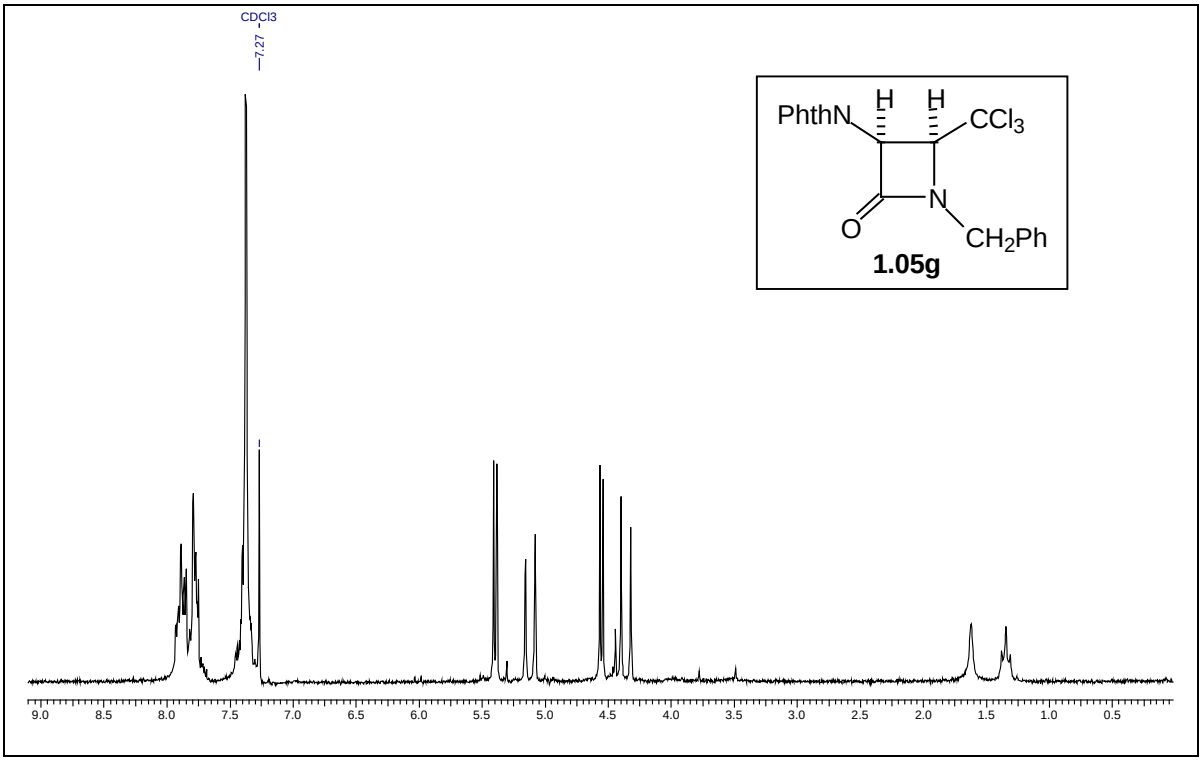


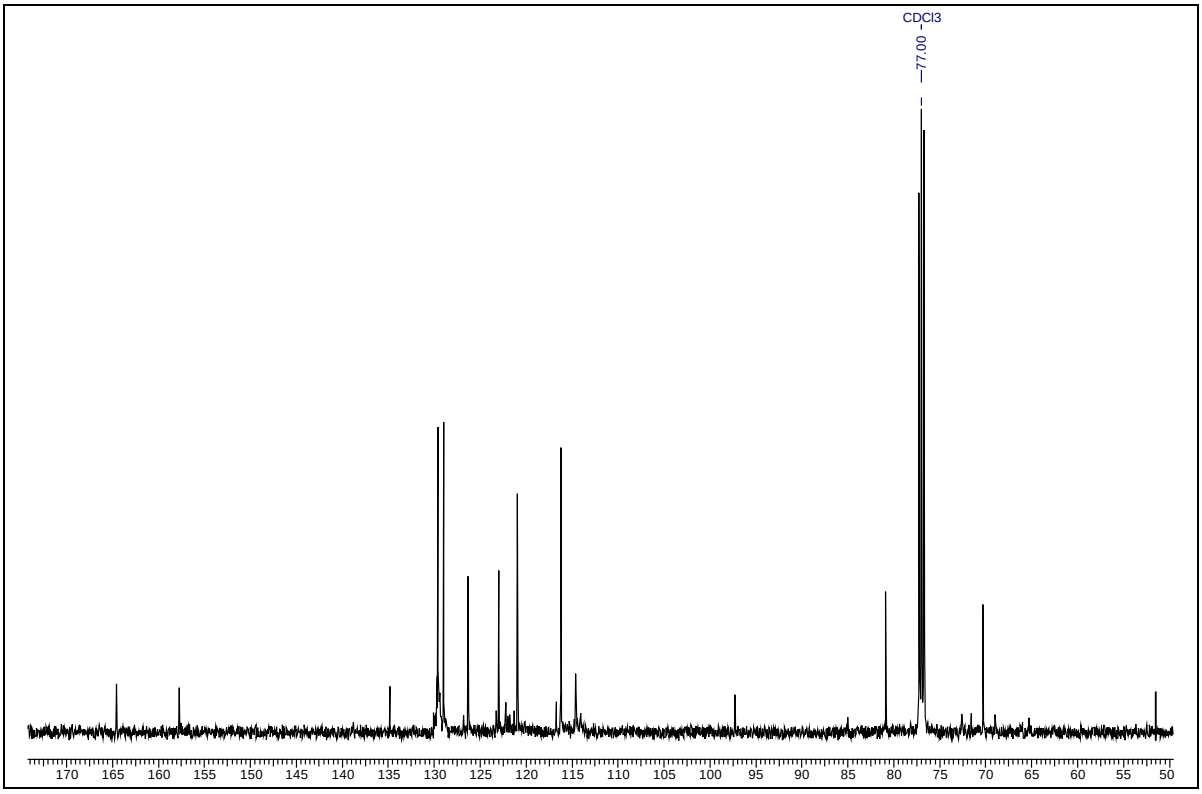


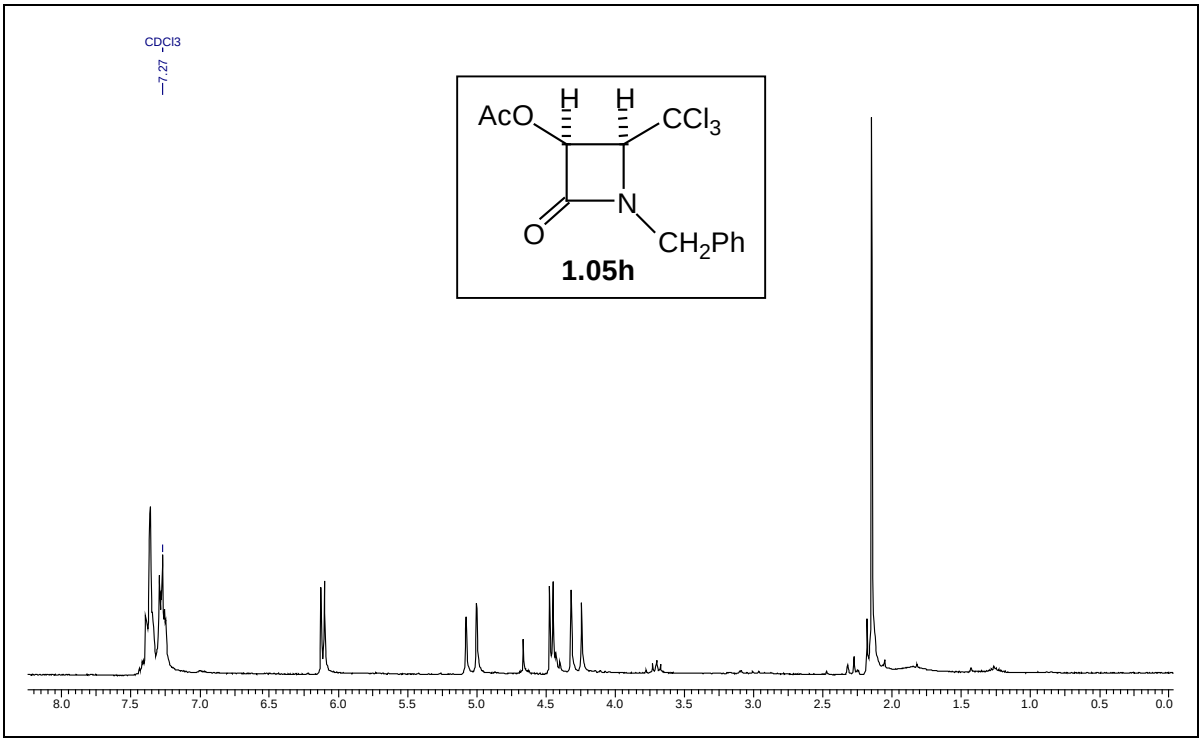


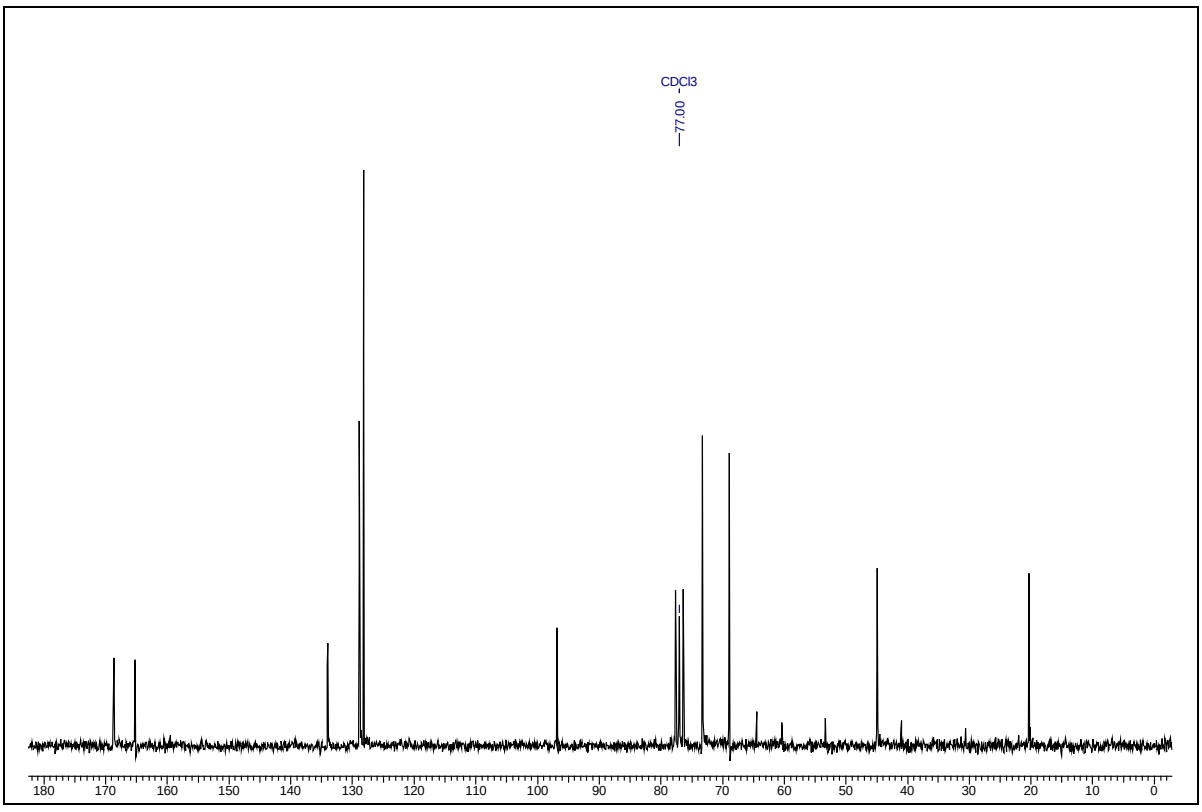


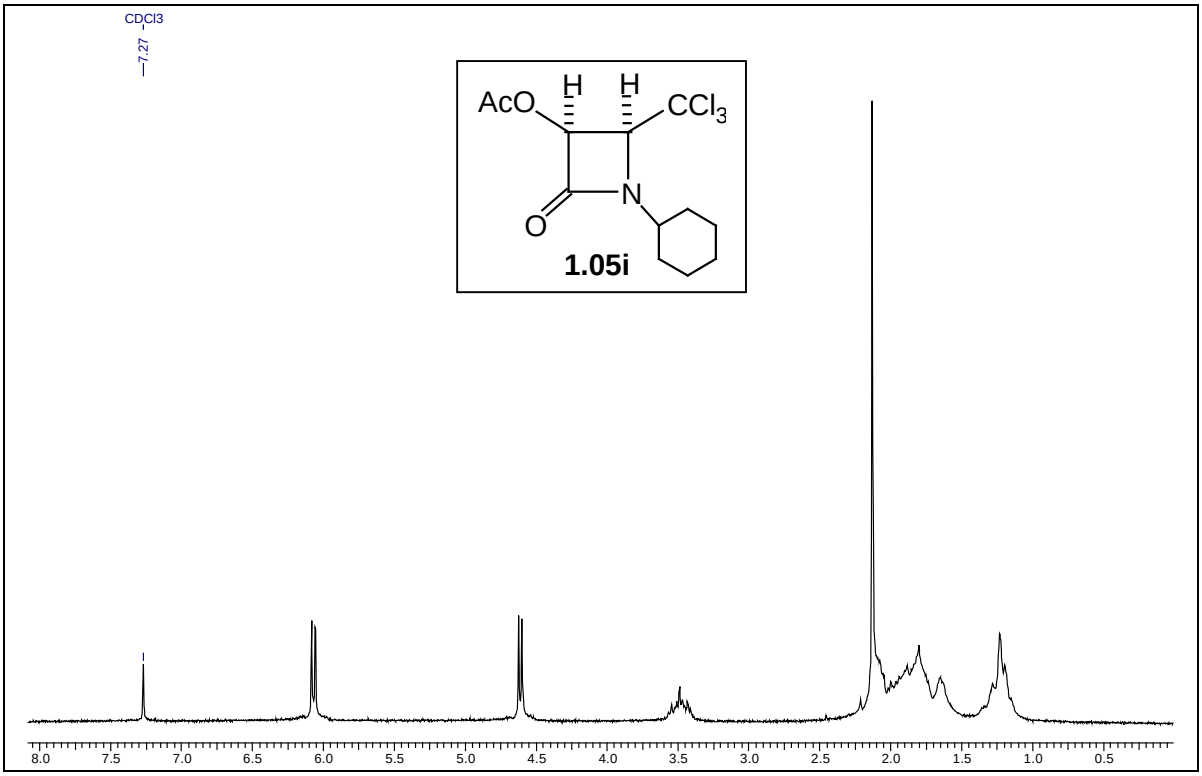


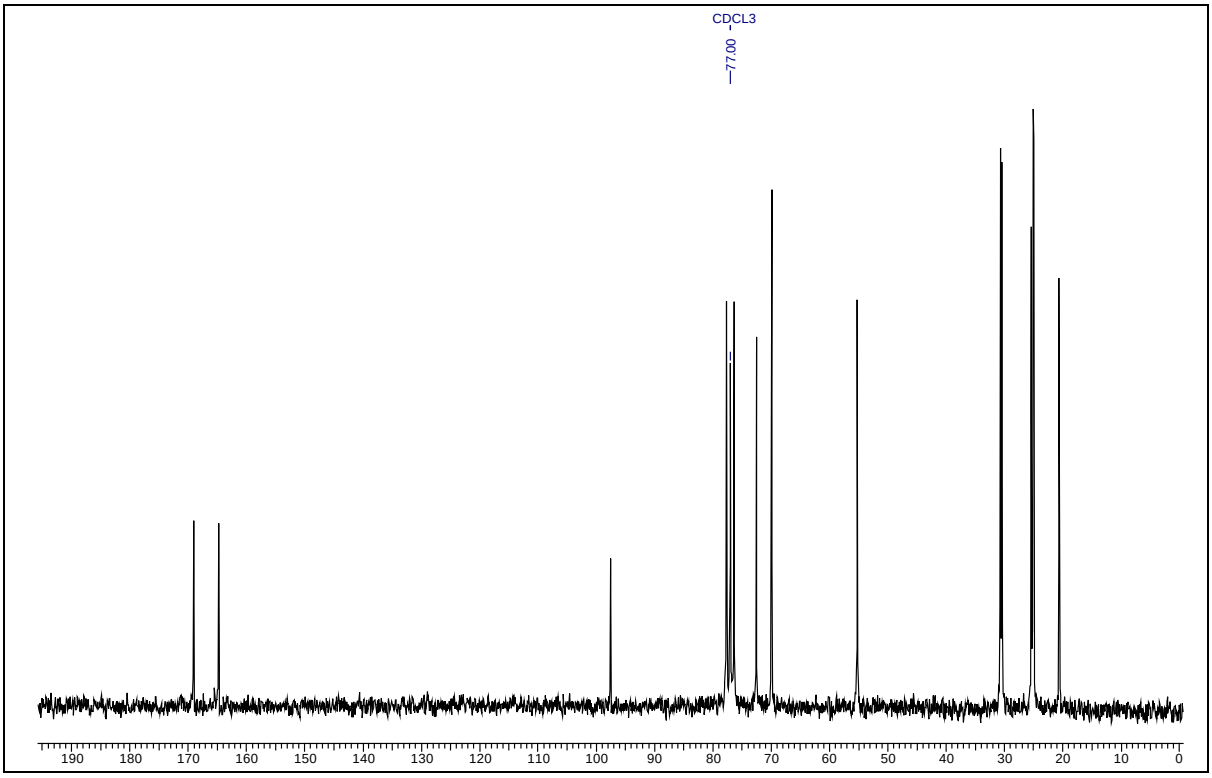


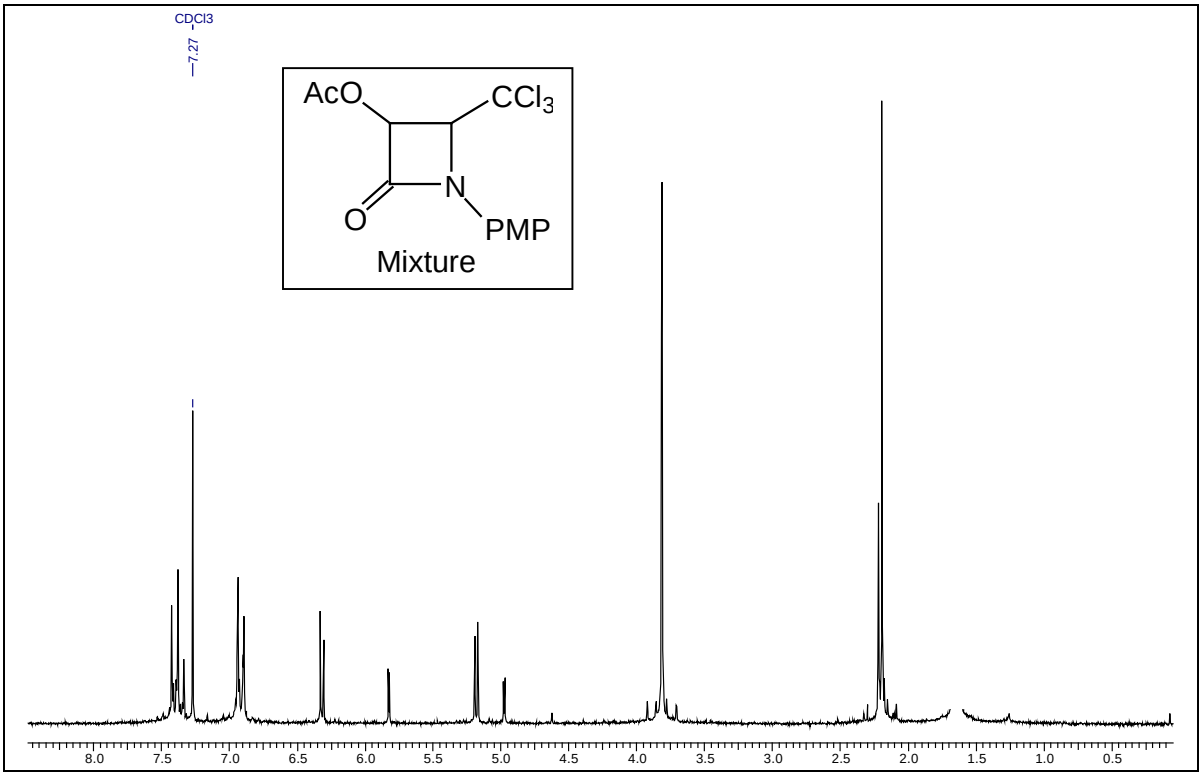


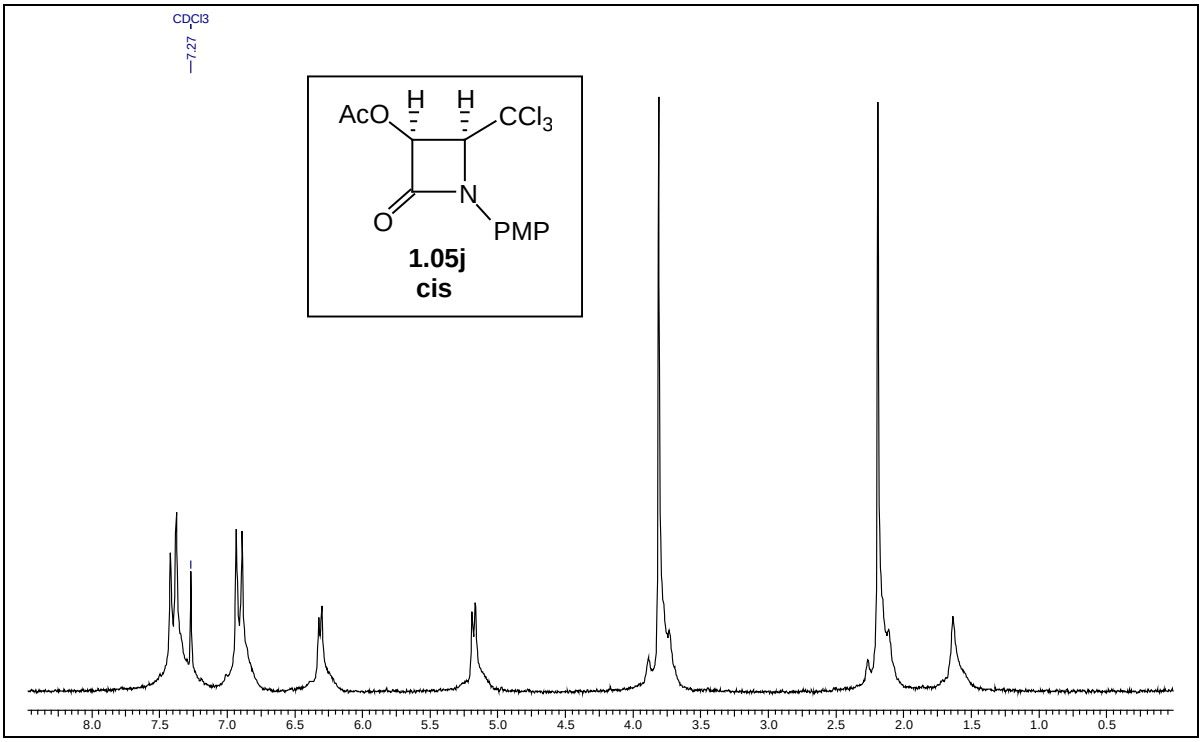


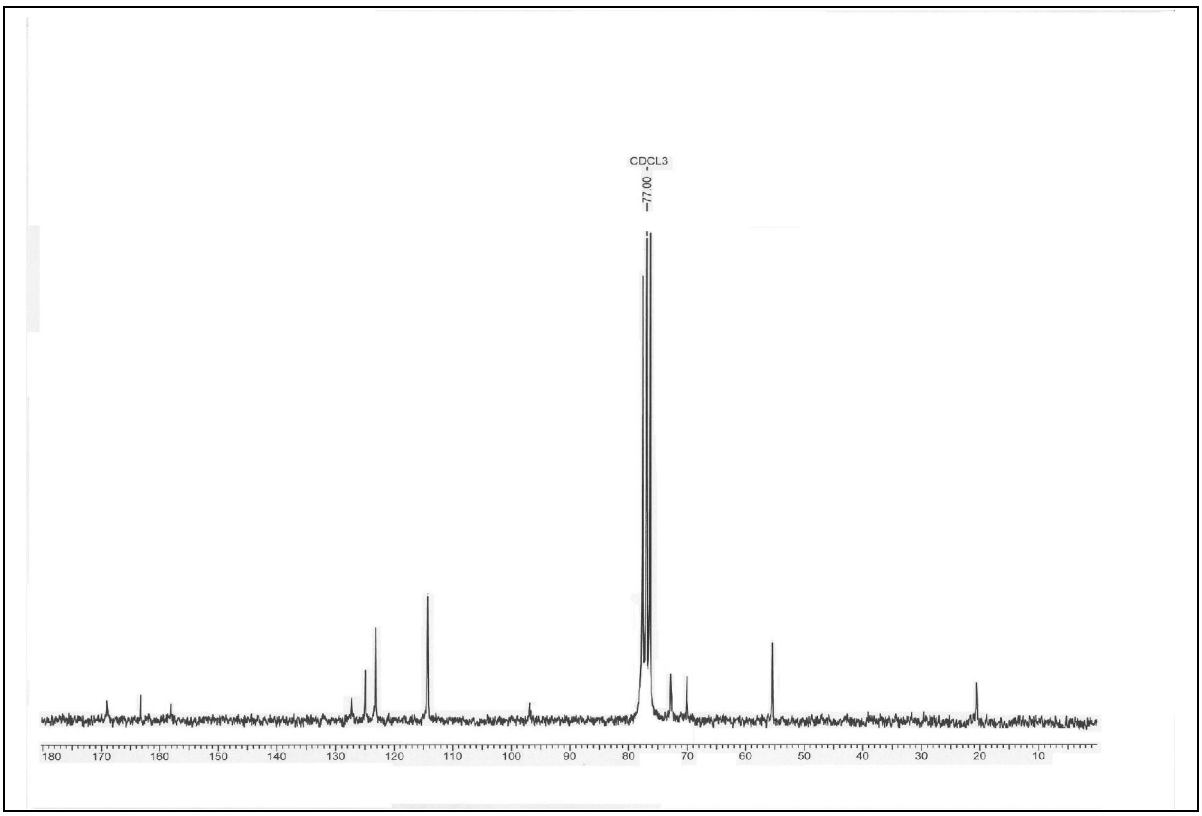


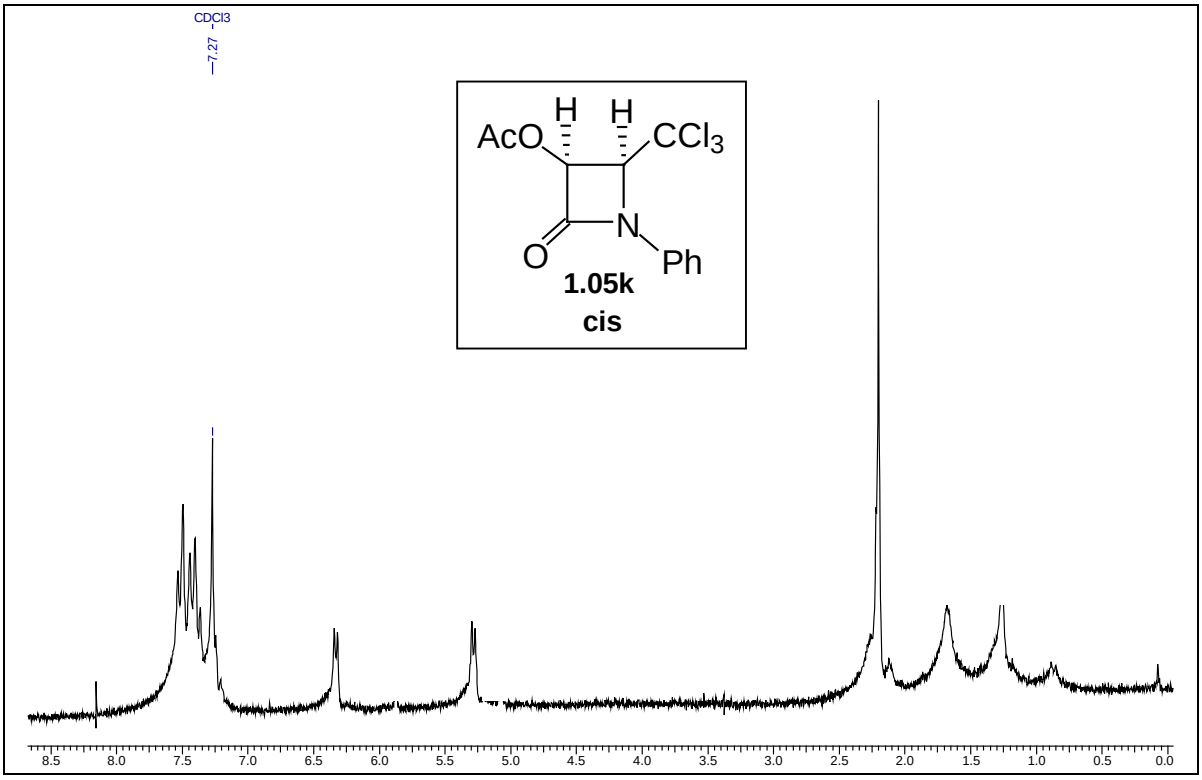


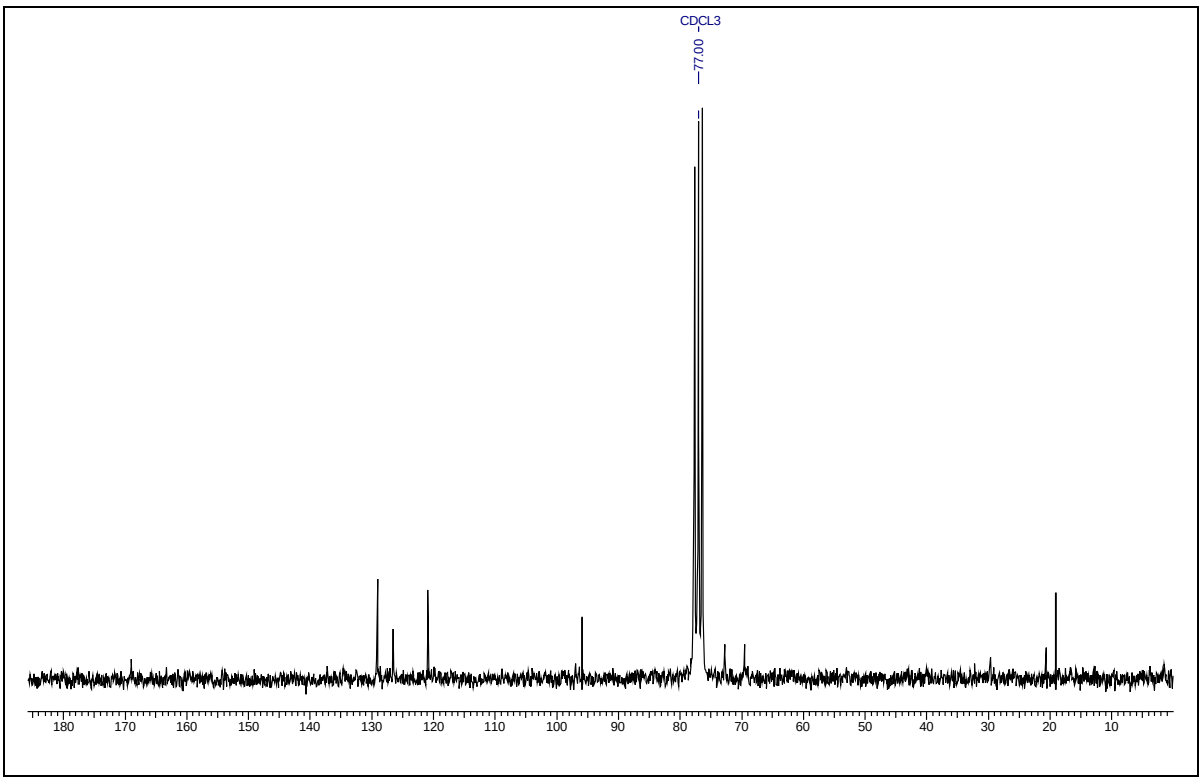


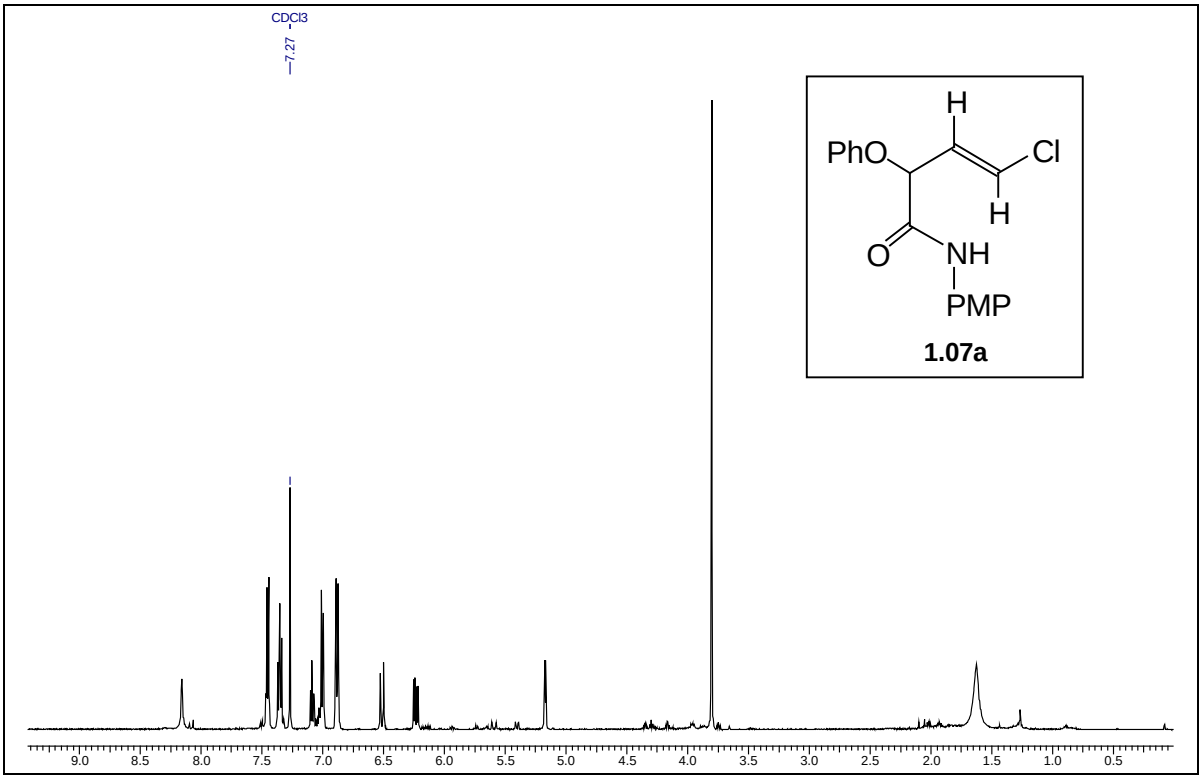


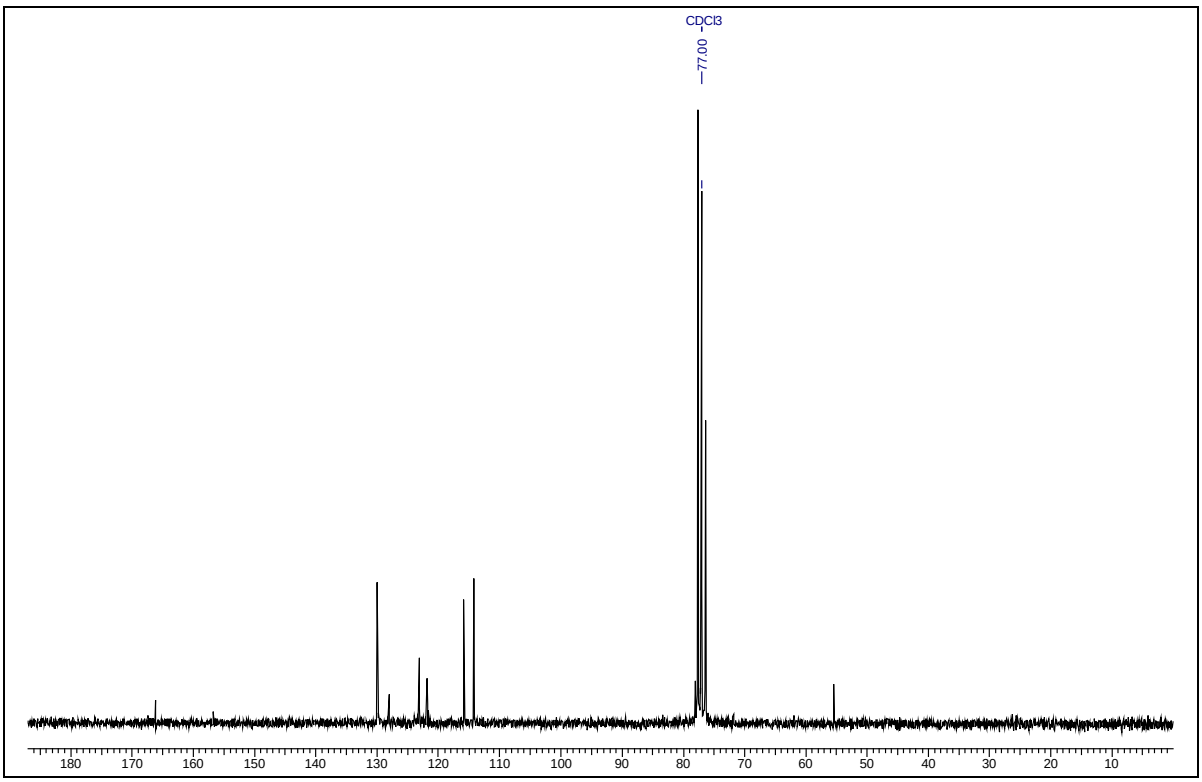


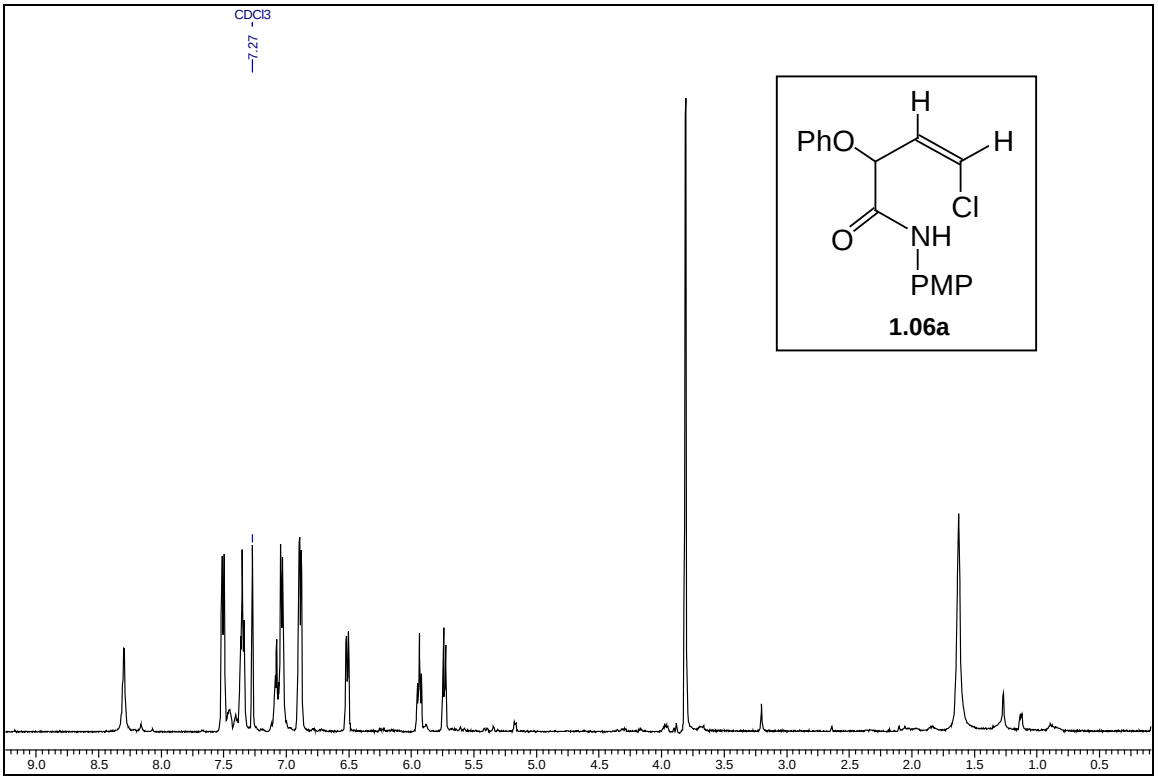


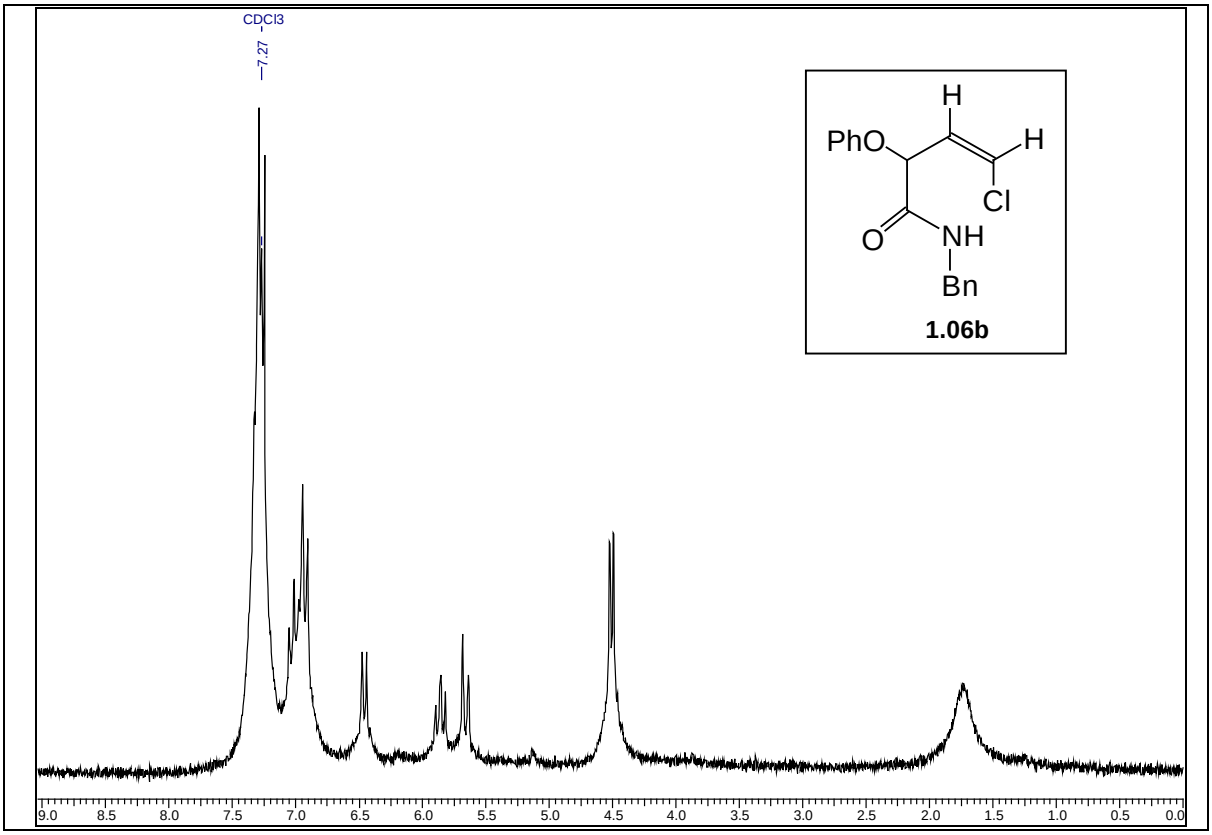


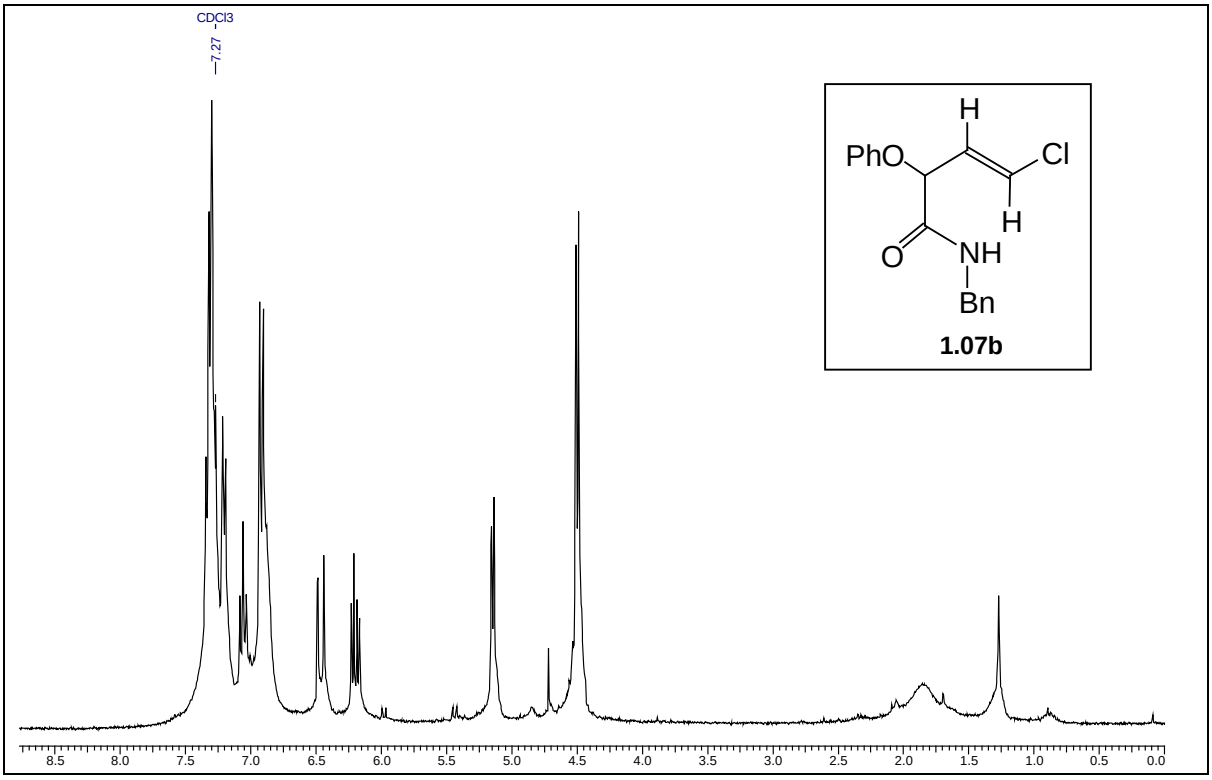


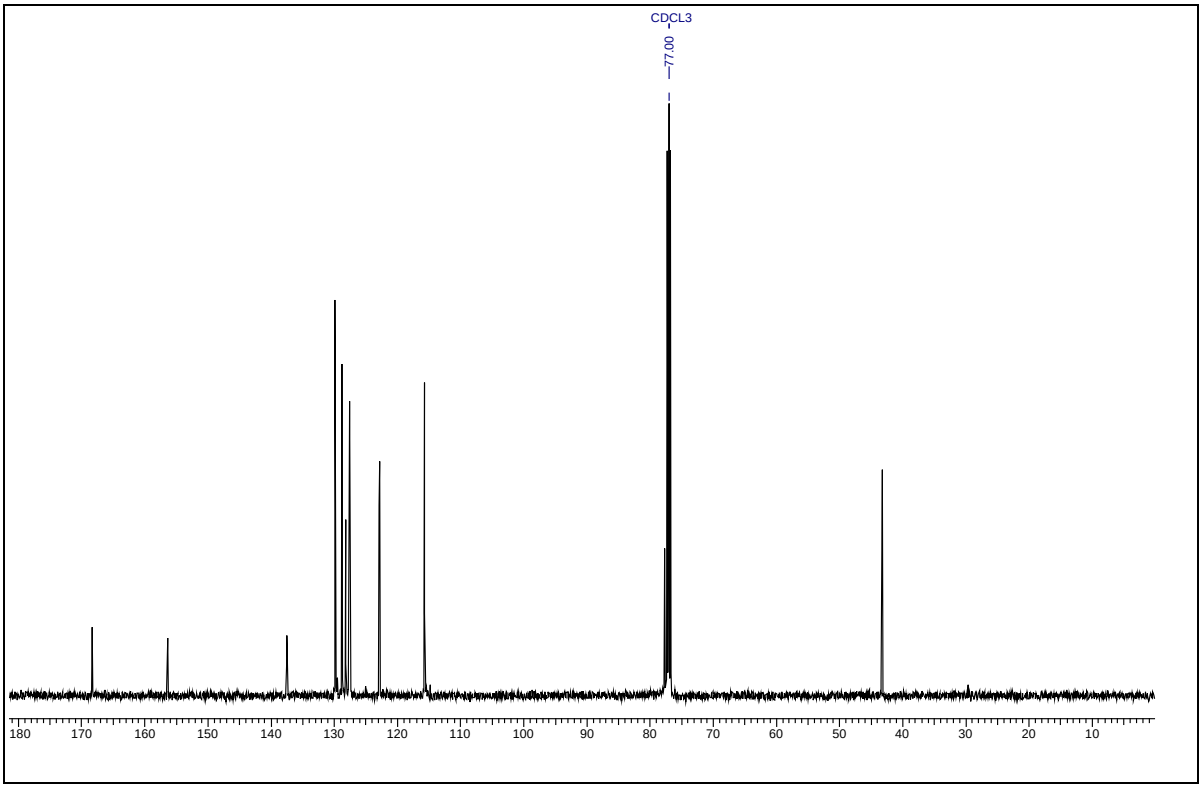


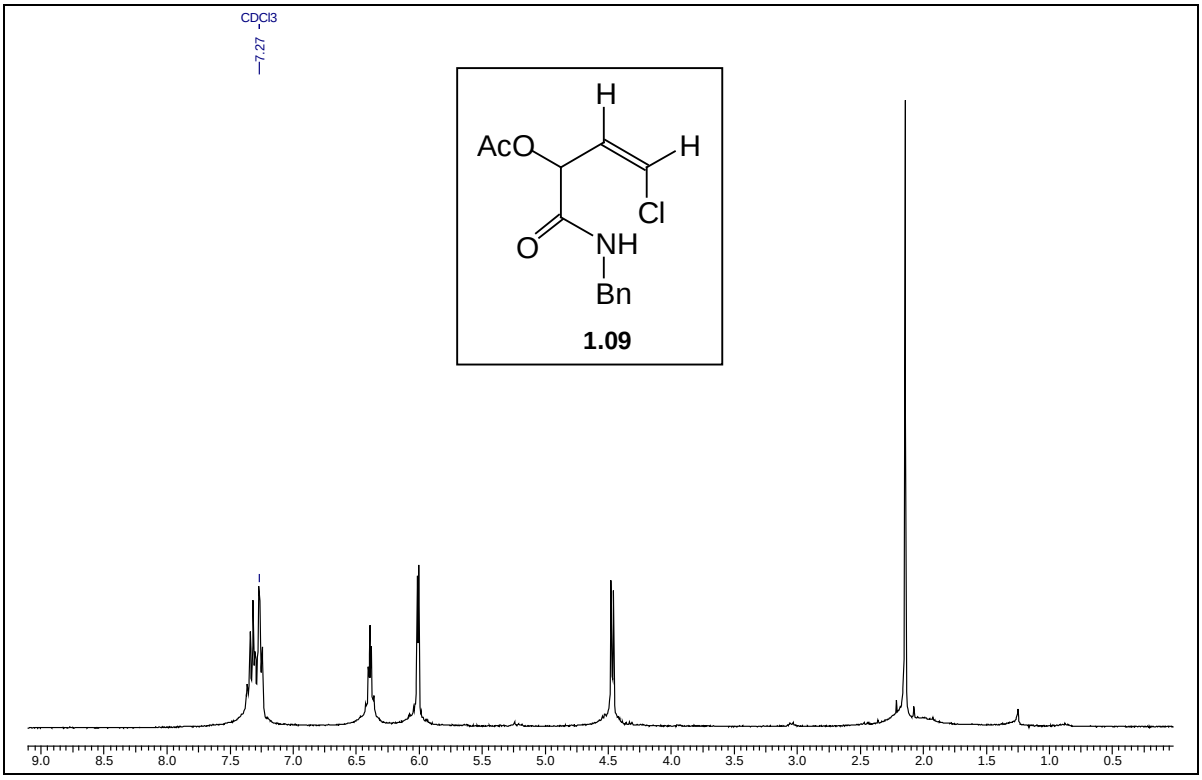


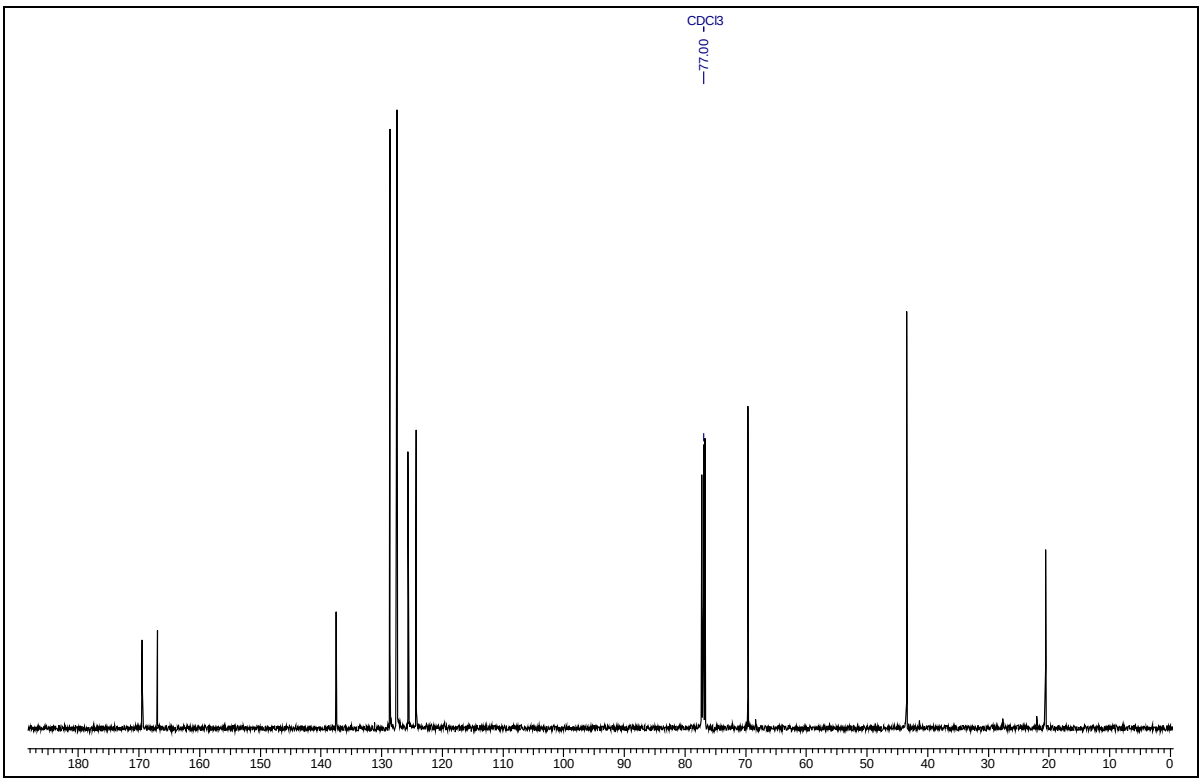


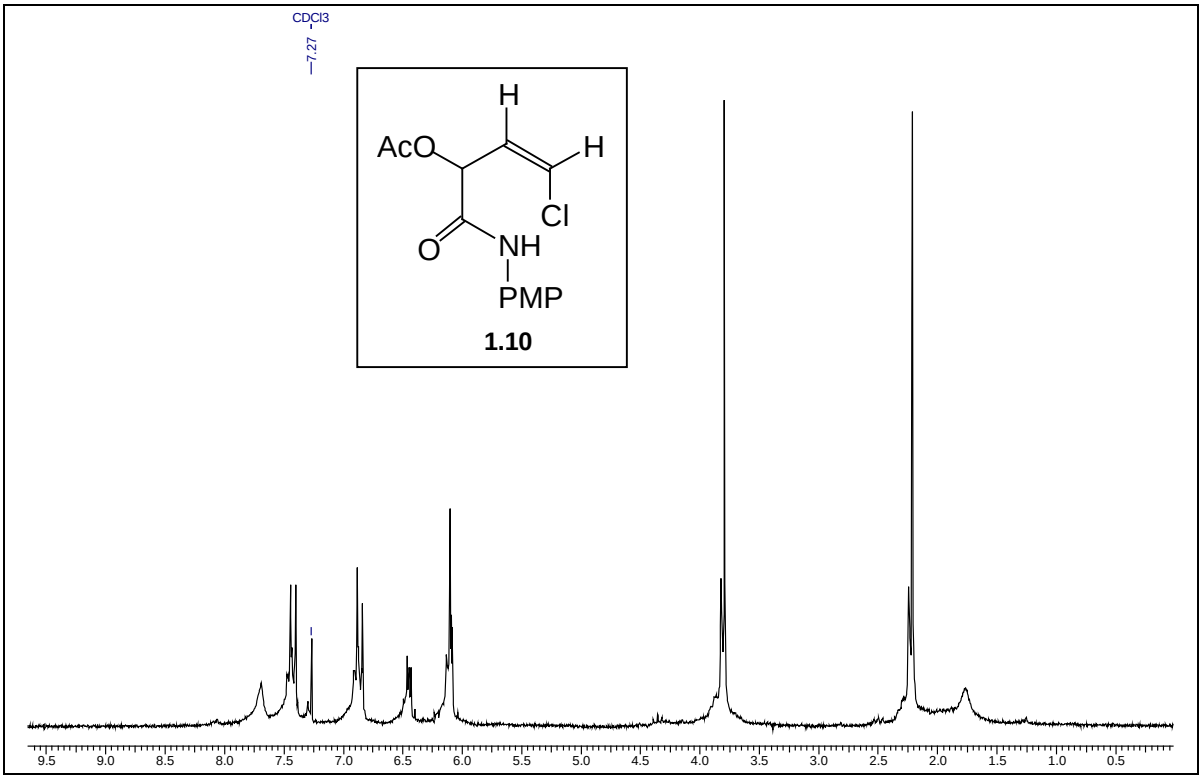


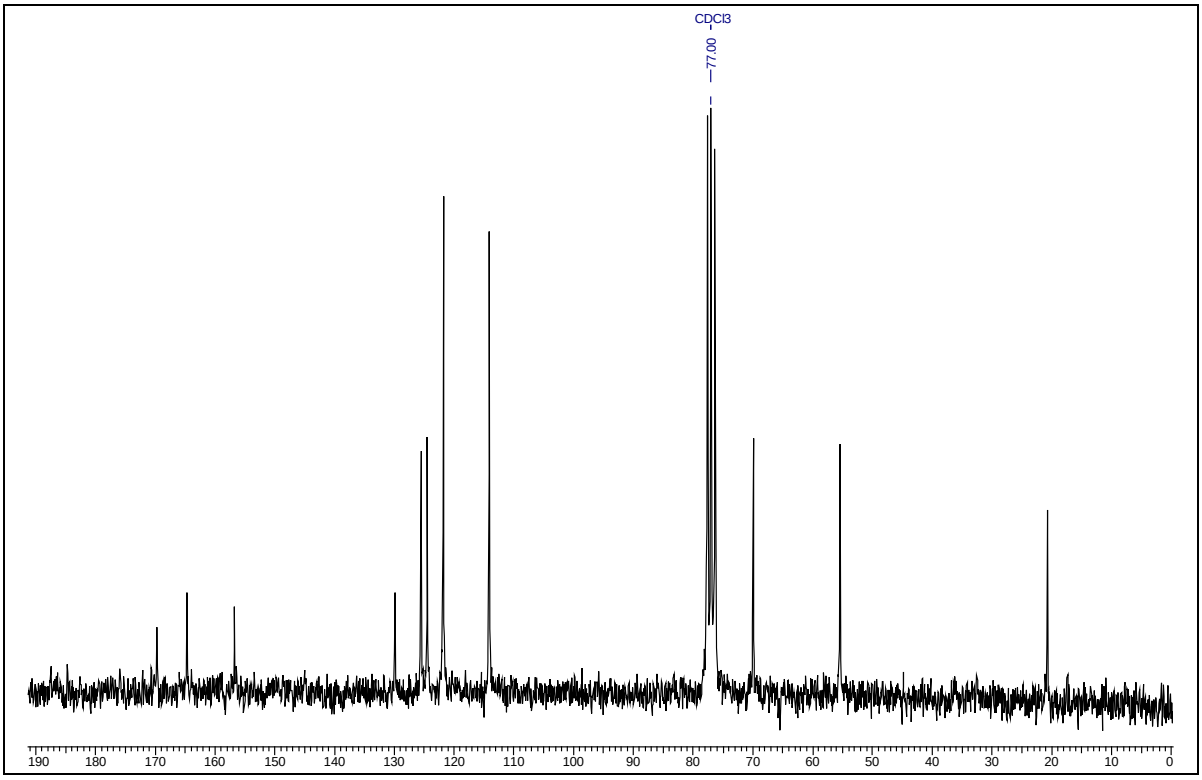


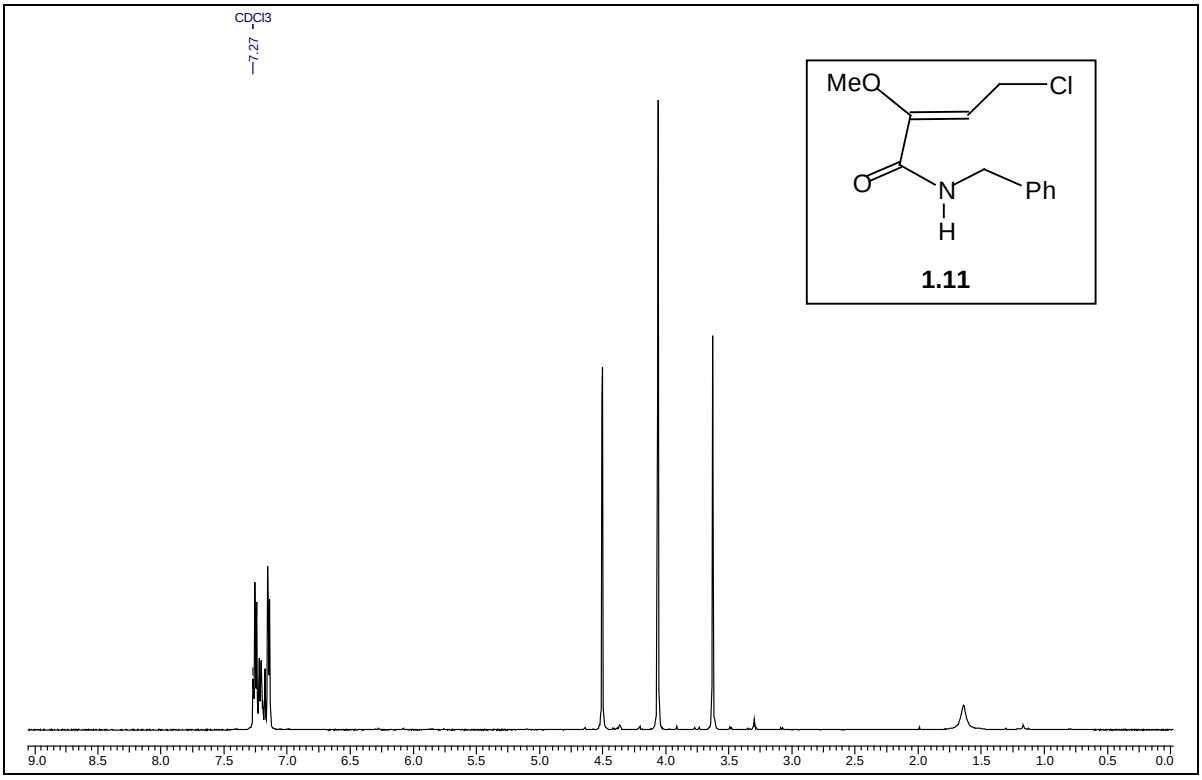


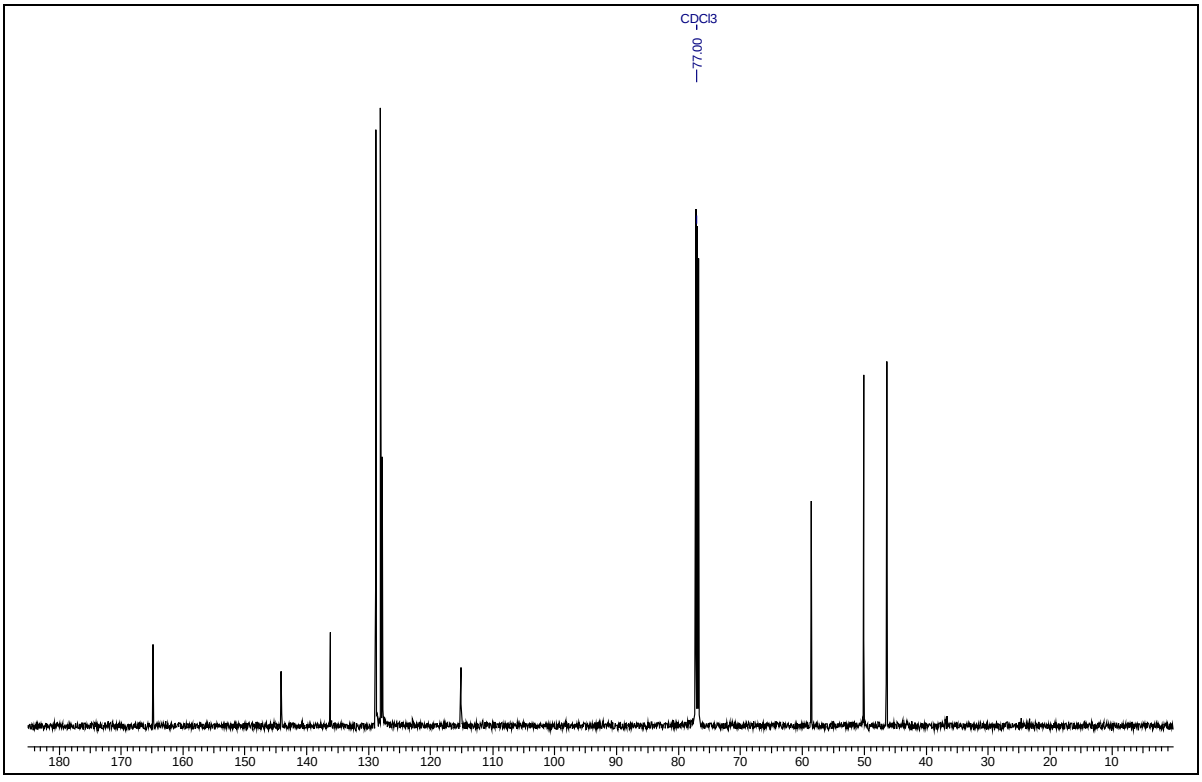


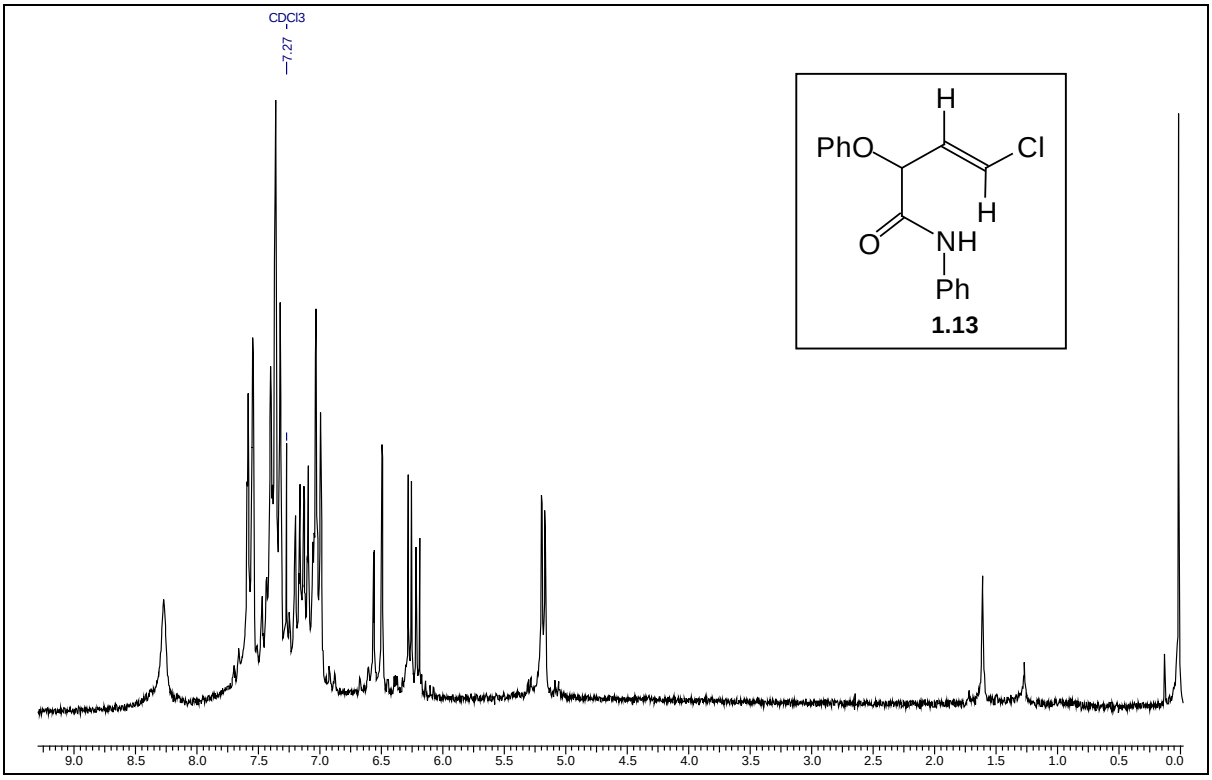


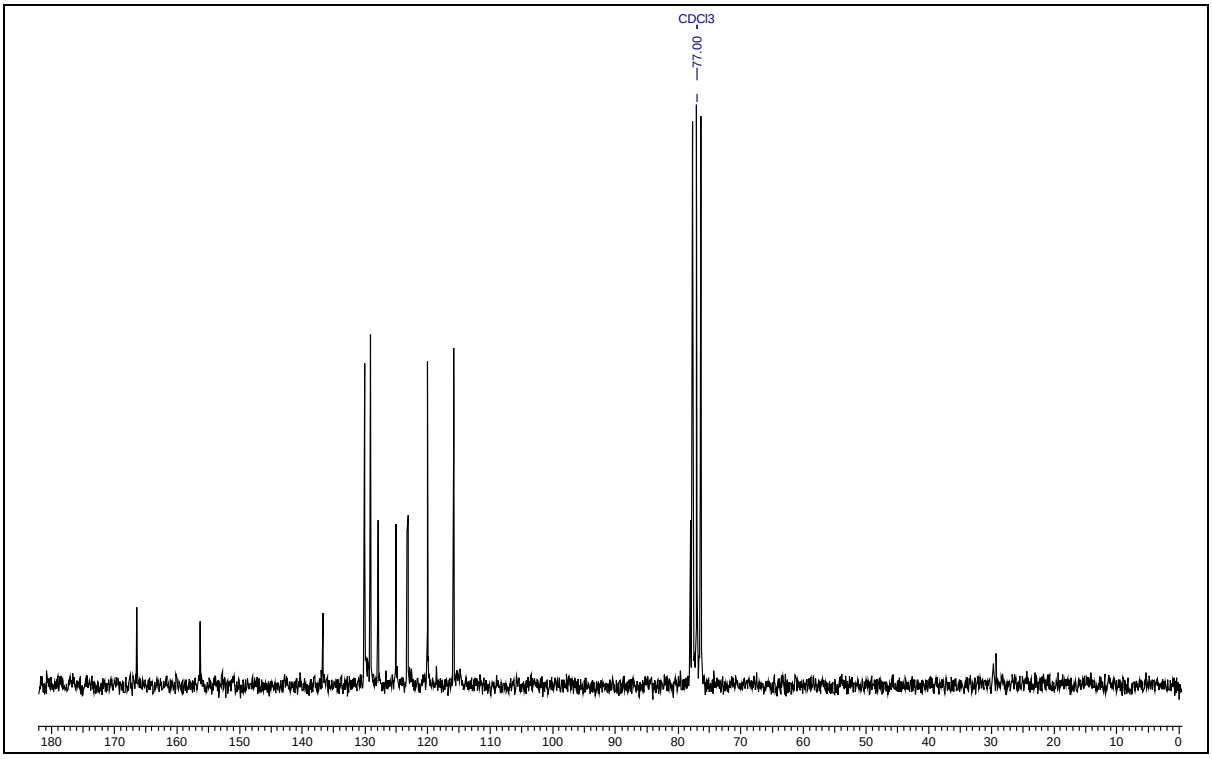


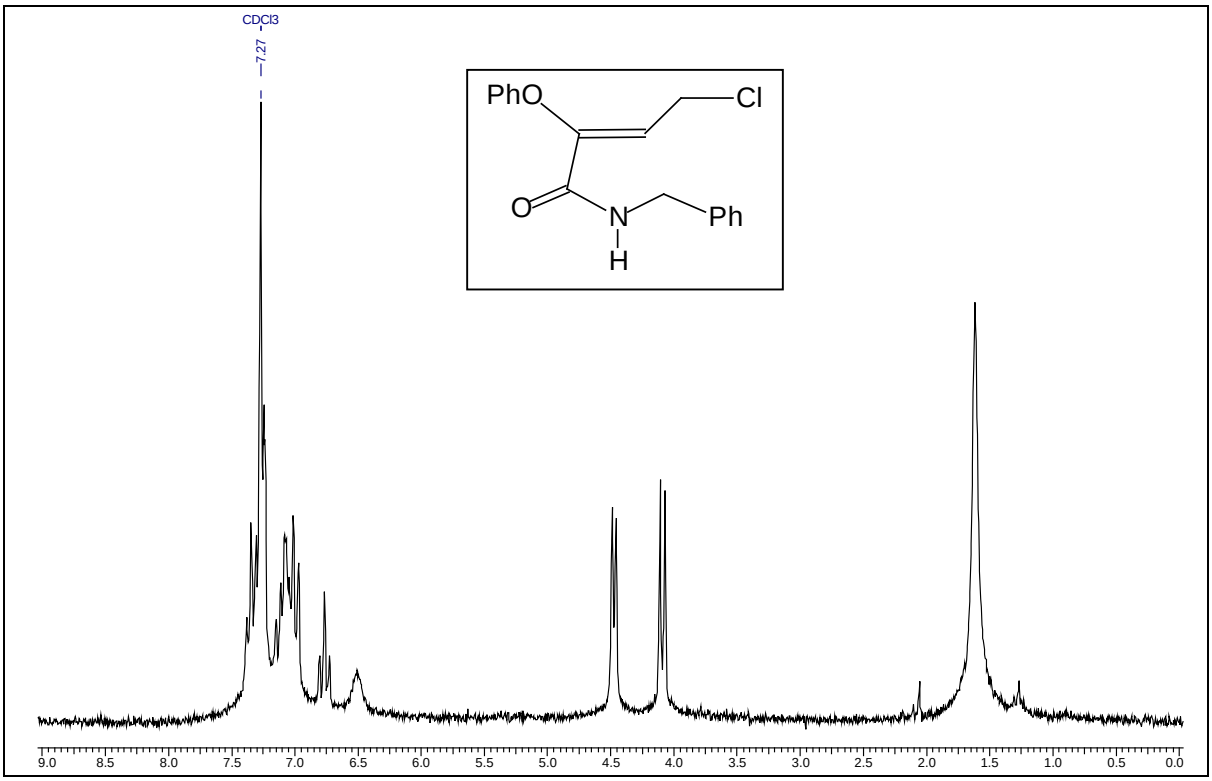






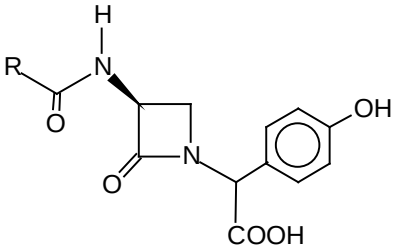




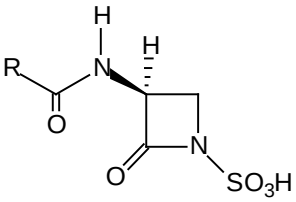


2.1 : Background for the present work

Many monocyclic β-lactams are known to have interesting biological activities such as antibacterial, anti-inflammatory and antifungal. The high potency of non-classical β-lactam antibiotics such as Nocardicins[1] and Monobactams[2] against Gram-negative organisms has highlighted the importance of developing methods for preparation of monocyclic β-lactams (Figure 1). A recently developed β-lactam antibiotic fosfomycin[3] has high antibacterial activity against urinary track infection caused by E-coli. Other azetidinones[4,5] were also found to exhibit a wide range of biological activities e.g. fungicidal, bactericidal. Many penems, carbapenems, monobactams and trinems can be prepared from suitably substituted monocyclic azetidin-2-ones. The synthetic approach towards the preparation of these compounds involves the construction of azetidinone ring followed by appropriate functionalizations at N-1, C-3 and C-4 positions.



Nocardicin



Monobactam

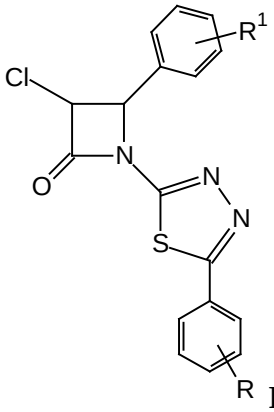


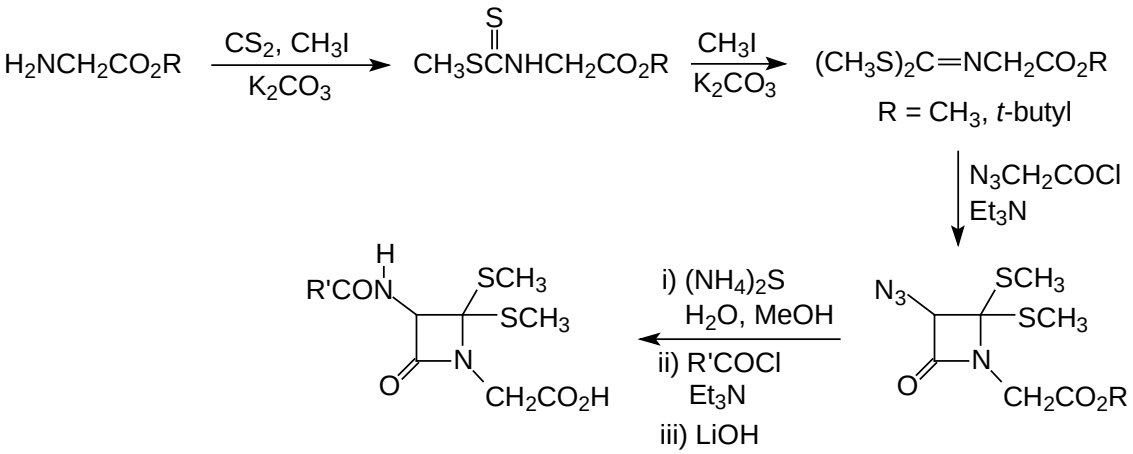
Figure 1

The most widely used Staudinger reaction gives easy access to a variety of β-lactams having O, S, P, Si and halogens directly attached at C-4 position. One of such class is the azetidinone having dithioalkyl groups at C-4 position. The dithioalkyl group is a masked carbonyl group and can be converted into azetidin-2,4-diones, which are highly strained molecules. These are known to show anti-inflammatory and sedative properties,[6] also they are active as hypnotic inducing drugs. Bachi and co-workers[7] have reported that this category of compounds along with their 4-thioxo analogs can serve as useful intermediates for a variety of β-lactam antibiotics.[8] Additional oxo group placed at C-4 of azetidin-2-one ring is suitable for functionalizations leading to interesting compounds. The

dithioalkyl group can be removed to get 4-unsubstituted β-lactams, which are otherwise difficult to prepare by well known acid chloride-imine cycloaddition.

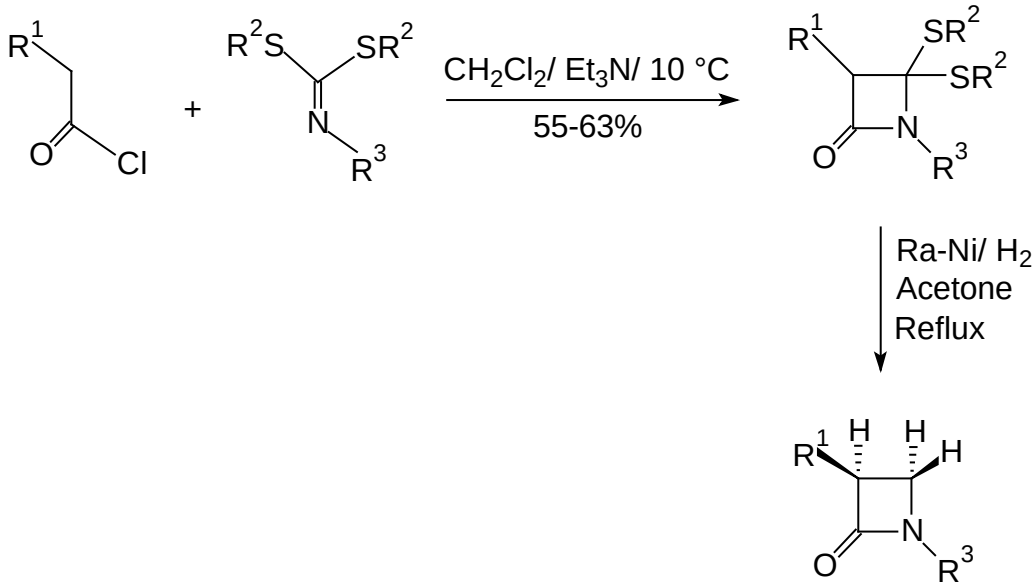
Edward et al.[9] reported the synthesis of β-lactams bearing thioalkyl substituents at C-4 position *via* cycloaddition of iminodithiocarbonate esters, prepared from methyl or *tert*-butyl ester of glycine with azidoketenes. The azido group at C-3 position was then reduced and the acylamido side chain was introduced. This was followed by the hydrolysis of the ester group on nitrogen to get the required functionalities having resemblance with penicillin structure (Scheme 2.01).

Scheme 2.01



Sharma and coworkers[10] have reported the preparation of 4,4-dithioalkyl-2-azetidinones employing the usual [2+2] cycloaddition reaction (Scheme 2.02).

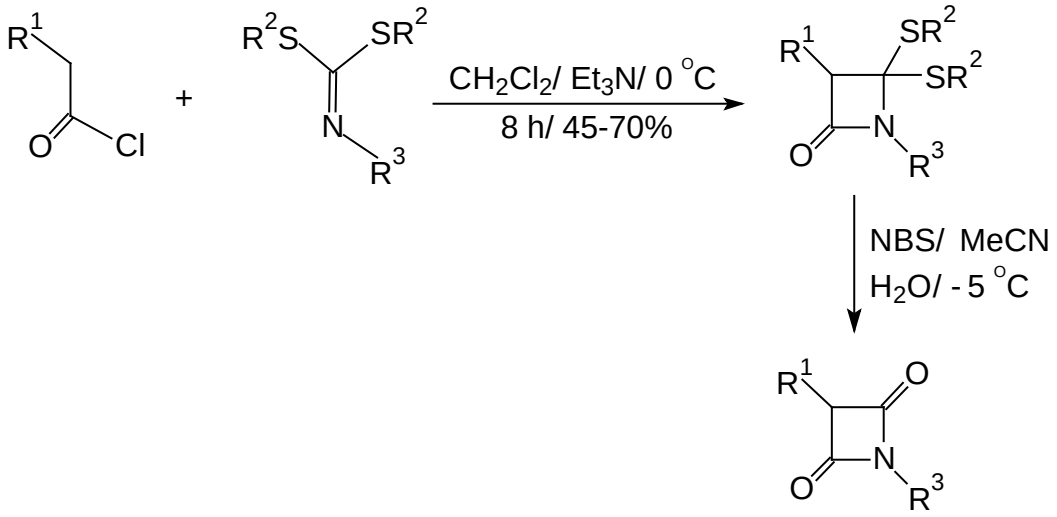
Scheme 2.02



These were then converted to 4-unsubstituted azetidin-2-ones by desulfurization of 4,4-dithioalkyl groups using activated Raney-Nickel and acetone in 40-45% yields (Scheme 2.02).

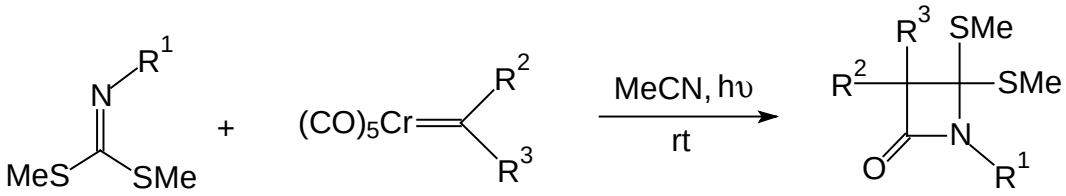
Bari et al.[11] have also reported the synthesis of 4,4-*bis*(alkylthio)-azetidin-2-ones *via* annelation of thioimidates with ketenes derived from different acid chlorides (Scheme 2.03).

Scheme 2.03



Alcaide[12] also reported the preparation of such class of compounds bearing thioalkyl substituents at C-4 position of β-lactams. These compounds were prepared by photo-induced cycloaddition of iminodithiocarbonates with chromium carbene (Fischer) complexes (Scheme 2.04).

Scheme 2.04

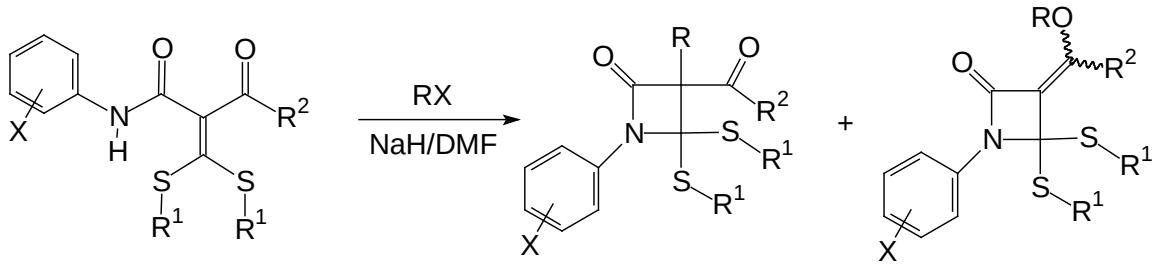


R^1 = Ph, PMP, Bn, Allyl
R^2 = Me, Ph, H
R^3 = OMe, OPr^i

Recently Ashok kumar et al.[13] reported the synthesis of *N*-substituted-3-chloro-4-dithiocarbamato-azetidin-2-ones and these compounds were tested for their antimicrobial activity against *B.* subtilis. The activity shown by these compounds follows the pattern *B.* subtilis> *E.* coli. > *S.* aureus. > *R.* rhodochrous > *P.* diminuta.

Azetidin-2-ones with 4,4-dithioalkyl substituents were also prepared by Pak and coworkers[14] starting from acylketene dithioacetal α-anilide, alkyl halide (MEMCl, MOMCl or MeI) and sodium hydride in DMF (Scheme 2.05).

Scheme 2.05



The Staudinger reaction has found wide acceptance among the various methods available for the synthesis of β-lactams, due to its simplicity, versatility and predictability of the stereochemical outcome. Usually the ketenes employed for the cycloaddition in Staudinger reaction are prepared thermally,[15] photochemically,[16] or from

acid chlorides in the presence of a tertiary base. The preparation of some of the acid chlorides requires use of sodium, other fuming chemicals. Some of them are not commercially available, in such cases carboxyl group activating reagents (the acid activators) are generally employed. Various reagents[17] like ethylchloroformate,[18] trifluoroacetic anhydride,[19] p-toluene sulphonyl chloride[20] and several phosphorous derived reagents[21] have been employed as acid activators in ketene imine cycloaddition reaction.

Other reagents include cyanuric chloride,[22] 2-chloro-N-methylpyridinium iodide[23] etc. Our group has also reported the combination of trichloroacetonitrile-triphenylphosphine[24] and hexachloroacetone-triethylphosphite[25] as efficient acid activators for the Staudinger reaction.

2.2 : Present work

As a part of ongoing programme in our group on the use of triphosgene as a reagent for various organic transformations, we were interested in using triphosgene

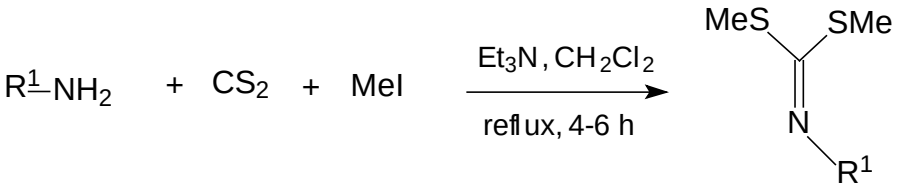
as an acid activator for generation of β-lactams. This white crystalline solid compound has some definite advantages over its gaseous congener, phosgene and has proved to be more safe. Since it has been already used in the preparation of acid chlorides and anhydrides from carboxylic acids,[26] we envisioned that it could function as an acid activator under mild reaction conditions for the synthesis of β-lactams. We have successfully employed this reagent for *in situ* conversion of acid to acid chloride and used for the synthesis of various substituted 4,4-dithioalkyl-azetidin-2-ones *via* Staudinger cycloaddition reaction.

2.3 : Results and Discussion

The imines required for the cycloaddition were prepared by a modified procedure[27] from amines, CS_2 and methyl iodide in the presence of triethyl amine. In a reaction sequence triethylamine was added slowly to a mixture of aliphatic or aromatic amine and carbon disulfide in dichloromethane. After stirring for 30 min, methyl iodide was added to the reaction mixture and the resulting solution was refluxed for 2-3 h. Initially *S*-methyl thiocarbamate derivative was formed which was then refluxed with second mole of methyl

iodide and triethyl amine to get the carbonimidodithioic acid dimethyl ester. In some cases the carbonimidodithioic acid dimethyl esters were obtained by reacting the *S*-methyl thiocarbamate derivatives with K_2CO_3 and alkyl halide in acetone. These compounds were found to be stable and purified by column chromatography. Several carbonimidodithioic acid dimethyl esters were prepared (Scheme 2.06) from aliphatic and aromatic amines in good yields and are summarized in Table **1**.

Scheme 2.06



2.01 **2.02a-f**

R^1 = -Phenyl, -Benzyl, -PMP, -Propyl, -Furfuryl, -Allyl

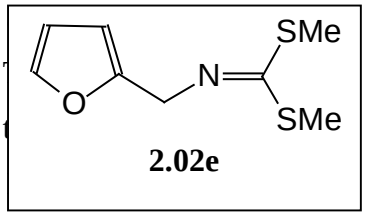
Table 1: Synthesis of carbonimidodithioic acid dimethyl esters **2.02a-f**

Entry No.	Compd.	R^1	Yield (%)
1	**2.02a**	-Ph	74
2	**2.02b**	$-CH_2Ph$	79
3	**2.02c**	4-MeOPh	72
4	**2.02d**	$-CH_2CH_2CH_3$	72
5	**2.02e**	Furfuryl	74
6	**2.02f**	Allyl	72

Furfuryl amine on treatment with CS_2 followed by methyl iodide in the presence of triethylamine gave the *S*-methyl thiocarbamate derivative, which was then alkylated with second mole of methyl iodide to get *N*-furfuryl carbonimidodithioic acid dimethyl ester **2.02e** as a pale yellow oil after passing through a short silica gel bed using petroleum ether as an eluent. The structure of this imine **2.02e** was confirmed by spectral data.

The IR spectrum of imine **2.02e** showed a strong band at 1571 cm^{-1} corresponding to C=N.

The ^1H NMR spectrum showed two singlets at 2.44 2.60 ppm corresponding to the two *S*-methyl protons. methylene carbon was seen at 4.62 ppm as a singlet. The furan ring protons appeared as separate doublets with J = 3 at 6.27 and 7.37 ppm.



2.02e

The remaining furan ring proton was observed as a multiplet between 6.30-6.40 ppm.

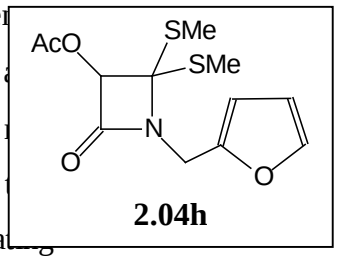
The ^{13}C spectrum of **2.02e** showed two peaks at 14.44 and 14.59 ppm corresponding to *S*-methyl carbons. The methylene carbon appeared at 49.65 ppm. The furan ring carbons were observed at 106.30, 110.05, 141.44, 153.35 ppm, while the imine carbon appeared at 161.59 ppm.

The cycloaddition of *N*-furfuryl carbonimidodithioic acid dimethyl ester **2.02e** with acetoxyacetic acid in the presence of triphosgene and Et_3N as a base furnished 3-acetoxy-4,4-*bis*-methylsulfanyl-1-furfuryl-azetidin-2-one **2.04h**. The structure of which was confirmed by spectral and analytical data.

The IR spectrum of β-lactam **2.04h**, showed bands at 1778 and 1764 cm^{-1} corresponding to the β-lactam and acetoxy carbonyls respectively.

The ^1H NMR spectrum of **2.04h** showed two singlets at 2.17 and 2.19 ppm corresponding to the two *S*-methyl protons. The acetoxy methyl appeared as a singlet at 2.03 ppm.

The methylene protons attached to nitrogen were seen at 4.44 ppm as a singlet and the C-3 proton of β-lactam ring was observed as a singlet at 5.90 ppm. The protons of the furan ring appeared at 6.35-6.40 ppm as a multiplet integrating for two protons and another multiplet between 7.35-7.45 ppm integrating for one proton.



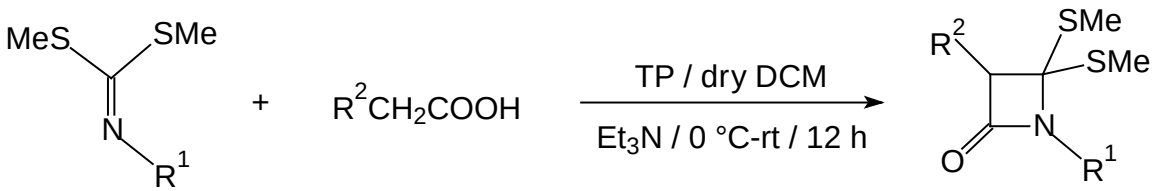
2.04h

The ^{13}C spectrum of the above β-lactam **2.04h** showed two peaks at 13.26 and 13.34 ppm corresponding to methyl carbons attached to sulphur. The acetoxy methyl was seen at 20.25 ppm. The methylene carbon appeared at 36.02 ppm. The C-3 and C-4 carbons were observed at 82.26 and 80.42 ppm respectively. Three carbons of the furan ring appeared at 109.46, 110.56 and 142.54 ppm. The quaternary carbon was seen at 147.65 ppm. The peaks at 162.13 and 168.60 ppm were assigned to the β-lactam carbonyl and the acetoxy carbonyl carbon respectively.

The β-lactam **2.04h** gave satisfactory elemental analysis and showed a molecular ion peak at m/z 301 (M^+) and 286 (M-15) in the mass spectrum.

In order to explore the generality of the acid activating reagent triphosgene, several other substituted β-lactams **2.04a-j** were prepared from various carbonimidodithioic acid dimethyl esters **2.02a-f** (Scheme 2.07), which are summarized in Table **2**. The C-3 proton of the β-lactam ring in all the cases was observed as a singlet between 5.00-6.00 ppm. All other compounds were also characterized by spectral and analytical data. In all these cases triphosgene was found to be better than other acid activators in terms of yields as well as the simplicity of work up procedures.

Scheme 2.07



2.02 **2.03** **2.04**

R^1 = -Ph, -CH_2Ph, -PMP, -Furfuryl, *n*-Propyl, -Allyl
R^2 = PhO-, BnO-, AcO-, PhthN-
TP = triphosgene

Table 2: Synthesis of azetidin-2-ones **2.04a-j** from acids **2.03** and imines **2.02a-f** and Chemical Shift (δ) of C3-*H*

Entry No.	Compound	R^2	R^1	Chemical Shift (δ) C3-*H*	Yield (%)	Mp (°C)
1	**2.04a**	PhO	Ph	5.49	68	110-111
2	**2.04b**	PhO	Bn	5.33	65	79-80
3	**2.04c**	PhO	PMP	5.46	66	147-149
4	**2.04d**	PhO	Propyl	5.28	66	thick oil
5	**2.04e**	PhO	Allyl	5.29	67	oil
6	**2.04f**	PhO	furfuryl	5.31	58	84-85
7	**2.04g**	AcO	Propyl	5.79	67	oil
8	**2.04h**	AcO	Furfuryl	5.90	62	oil
9	**2.04i**	BnO	Ph	4.95	60	68-69
10	**2.04j**	PhthN	Propyl	5.43	58	98-100

PMP = *p*-methoxy phenyl,

Bn = benzyl,

PhthN = phthalimido

Similarly amino acid ester derived carbonimidodithioic acid dialkyl esters were used for the synthesis of β-lactams. The amino acid was first converted into its methyl or ethyl

ester using thionyl chloride and dry methyl or ethyl alcohol. The hydrochloride salt formed during the reaction was used as such for further preparation of the carbonimidodithioates (Scheme 2.08). The same procedure was followed which was used for the preparation of imines from aliphatic and aromatic amines.

Scheme 2.08

2.05 **2.06**

R^2= Me, allyl
R^1= -CH_2COOMe, -CH_2COOEt, -$CH(CH_3)COOMe$

Table 3: Synthesis of carbonimidodithioic acid dimethyl esters **2.06a-c**

Entry No.	Compd.	R^1	Yield (%)
1	**2.06a**	CH_2CO_2Me	70
2	**2.06b**	CH_2CO_2Et	76
3	**2.06c**	$CH(Me)CO_2Me$	74

Thus treatment of ethyl glycinate hydrochloride with CS_2 followed by methyl iodide in the presence of triethylamine furnished *N*-[*bis*(methylthio)methylene] glycine ethyl ester **2.06b** as a pale yellow oil. It was purified by passing through a short silica bed using 5% acetone-petroleum ether as an eluent and the structure was confirmed by spectral data.

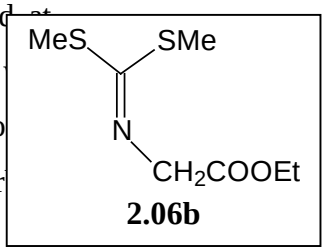
The IR spectrum of this imine **2.06b** showed a band at 1579 cm^{-1} corresponding to imine double bond and a band at 1753 cm^{-1} corresponding to the ester carbonyl.

The ^1H NMR spectrum of imine **2.06b** showed a triplet at 1.28 ppm with J = 7.3 Hz corresponding to the methyl protons of the ethyl group. Two singlets at 2.44 & 2.56 ppm were assigned to the *S*-methyl protons. A singlet at 4.22 was attributed to the methylene

protons attached to nitrogen. The methylene protons from the ester group appeared as a quartet at 4.20 ppm with J = 7.3 Hz.

The ^{13}C spectrum of **2.06b** showed a peak at 13.52 ppm corresponding to methyl carbon of ethyl group.

The two methyl carbons attached to sulphur appeared at 13.85 and 14.14 ppm. The methylene carbon of ester group was observed at 60.05 ppm while methylene attached to nitro appeared at 53.51 ppm. The imine carbon and the carbonyl car appeared at 162.24 and 169.23 ppm respectively.



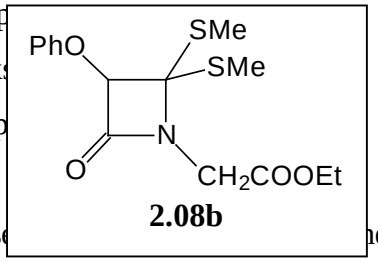
2.06b

The cycloaddition of *N*-[*bis*(methylthio)methylene] glycine ethyl ester **2.06b** with phenoxyacetic acid in the presence of triphosgene as an acid activator and Et_3N as a tertiary base furnished (2,2-*bis*-methylsulfanyl-4-oxo-3-phenoxy-1-yl) acetic acid ethyl ester **2.08b** as a white crystalline solid. The structure of **2.08b** was confirmed by spectral and analytical data.

The IR spectrum of β-lactam **2.08b** showed bands at 1749 and 1780 cm^{-1} corresponding to the ester carbonyl and β-lactam carbonyl respectively.

The ^{1}H NMR spectrum of **2.08b** showed a triplet at 1.32 ppm with J = 7.3 Hz corresponding to methyl protons from ester group. Two singlets at 2.20 and 2.33 ppm were attributed to two *S*-methyl protons. The methylene protons attached to nitrogen were observed as two doublets at 4.00 and 4.10 ppm with coupling constant of 17.6 Hz (geminal coupling, AB system) and the other two methylene protons were seen as a quartet at 4.25 ppm with J = 7.3 Hz. A sharp singlet at 5.41 ppm was attributed to C-3 proton of β-lactam ring. The aromatic protons appeared as a multiplet between 7.05- 7.40 ppm.

The ^{13}C spectrum of **2.08b** showed a peak at 12.76 p for methyl carbon in the ester group. Two very close peak 13.86 ppm were assigned to methyl carbons attached to sulp atoms.



2.08b

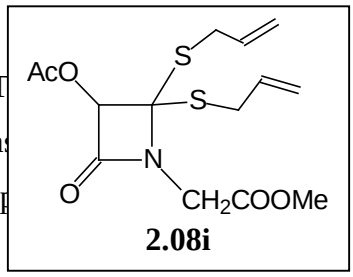
The methylene carbon attached to nitrogen was obs ner methylene carbon attached to oxygen was observed at 61.76 ppm. The C-3 and C-4 carbons were seen at 87.34 and 80.28 ppm. The aromatic quaternary carbon appeared at 156.78 ppm while the other aromatic ring carbons at 115.61, 122.63 and 129.46 ppm. The peaks at 162.95 and 166.81 ppm were attributed to the β-lactam and the ester carbonyls.

The compound **2.08b** showed a molecular ion peak at m/z 341 (M^+) in mass spectrum and also gave satisfactory elemental analysis.

Following the same general procedure for the preparation of imines, when methyl glycinate hydrochloride was allowed to react with carbon disulphide and allyl bromide as the alkylating agent in the presence of triethylamine furnished the imine *N*-[*bis*(allylthio)methylene] glycine methyl ester. The cycloaddition of this imine with acetoxyacetic acid in the presence of triphosgene as an acid activator and Et_3N gave 3-acetoxy-4,4-*bis*-allylsulphanyl-azetidin-2-one **2.08i** as a pale yellow oil and its structure was confirmed by spectral analysis.

The IR spectrum of β-lactam **2.08i** showed bands at 1757 and 1784 cm^{-1} corresponding to the ester carbonyl and β-lactam carbonyl respectively.

The ^1H NMR spectrum of **2.08i** showed a singlet 2.23 ppm corresponding to the acetoxy methyl protons. T four methylene protons attached to sulphur were observed a multiplet between 3.35-3.50 ppm. A sharp singlet at 3.79 pp was attributed to the methoxy protons.



2.08i

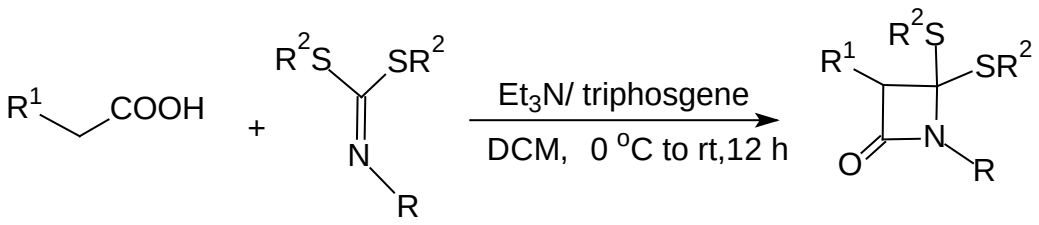
The methylene protons attached to nitrogen appeared as two separate doublets at 3.90 and 4.04 ppm with J = 17.6 Hz. The terminal methylene protons of the allyl group appeared as a multiplet within the range of 5.10-5.35 ppm. Both the methine protons appeared as a multiplet between 5.70-5.90 ppm. A singlet at 6.06 ppm was assigned to the C-3 proton of β-lactam ring.

The ^{13}C spectrum of **2.08i** showed a peak at 20.36 ppm for methyl carbon of acetyl group. The *S*-methylene carbons were observed at 33.92 and 34.18 ppm. The methylene carbon attached to nitrogen appeared at 40.79 ppm. The methoxy carbon was seen at 52.59 ppm. The C-3 and C-4 carbons were observed at 82.04 and 81.23 ppm respectively. The terminal methylene carbons of allyl groups appeared at 118.61 and 118.94 ppm. Two very close peaks at 132.36 and 132.50 ppm were attributed to methine carbons of the allyl groups. The β-lactam carbonyl was observed at 162.39 ppm while the two-ester carbonyls appeared at 167.71 and 168.56 ppm. The compound **2.08i** showed a molecular ion peak at m/z 345 (M^+) in mass spectrum and also gave satisfactory elemental analysis.

Following the same general procedure, several other substituted β-lactams were prepared from the imines derived from glycine methyl and ethyl ester to explore the

generality of the acid activating reagent triphosgene (Scheme 2.09). The results are summarized in Table 4.

Scheme 2.09



2.07 **2.06** **2.08**

R = - CH_2COOMe, -CH_2COOEt
R^1 = PhO-, BnO-, MeO-, AcO-, PhthN-
R^2 = Me, allyl

Table 4: Synthesis of azetidin-2-ones **2.08a-j** from acids **2.07** and imines **2.06a-c**

Entry No.	Compd.	R^1	R	R^2	Yield (%)	Mp (°C)
1	**2.08a**	PhO	CH_2CO_2Me	Me	64	93-94
2	**2.08b**	PhO	CH_2CO_2Et	Me	62	99-100
3	**2.08c**	MeO	CH_2CO_2Me	Me	62	oil
4	**2.08d**	MeO	CH_2CO_2Et	Me	60	oil
5	**2.08e**	PhthN	CH_2CO_2Me	Me	56	127-129
6	**2.08f**	PhthN	CH_2CO_2Et	Me	55	112
7	**2.08g**	AcO	CH_2CO_2Me	Me	67	oil
8	**2.08h**	AcO	CH_2CO_2Et	Me	65	oil
9	**2.08i**	AcO	CH_2CO_2Me	allyl	65	oil
10	**2.08j**	BnO	CH_2CO_2Me	Me	64	oil

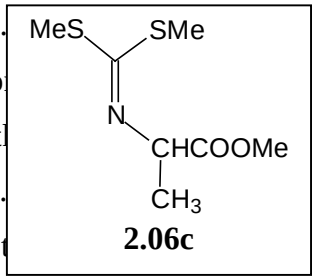
The antibiotic activity of β-lactams depends on the relative configuration of the substituents as well as the absolute configuration of certain chiral centers for instance; the penicillin with 6*R* configuration is active against bacteria while the 6-*epi*-penicillin is devoid of activity. The diastereoselectivity in β-lactam ring formation varies with the nature of the substituents in Schiff's bases.

We were interested in the synthesis of β-lactams by ketene-imine cycloaddition using chiral imine derived from alanine methyl ester and study the diastereoselectivity in the β-lactam ring formation.

Imine *N*-[*bis*(methylthio)methylene] alanine methyl ester **2.06c** was prepared from alanine methyl ester hydrochloride, CS_2 and methyl iodide in the presence of triethylamine. The imine thus obtained was purified by column chromatography and analyzed by spectral analysis.

The IR spectrum of imine **2.06c** showed bands at 1573 and 1745 cm^{-1} corresponding to imine double bond and the ester carbonyl group respectively.

The ^1H NMR spectrum of **2.06c** showed a doublet at 1. ppm with J = 6.8 Hz corresponding to the alanine methyl proto Two singlets at 2.40 and 2.55 ppm were assigned to the *S*-met protons. The methoxy protons were observed as a singlet at 3. ppm. The quartet at 4.50 ppm with J = 6.8 Hz was attributed to methine proton.

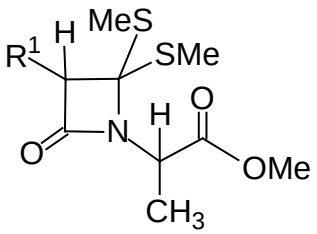


2.06c

The ^{13}C spectrum of **2.06c** showed a peak at 14.14 ppm corresponding to methyl carbon from alanine part. Two peaks at 14.36 and 18.04 ppm were assigned to *S*-methyl carbons. The peaks at 51.38 and 59.50 ppm were attributed to methine and methoxy carbons. The imine carbon appeared at 160.70 ppm while the ester carbonyl carbon appeared at 172.35 ppm.

The imine **2.06c** was allowed to react with ketenes derived from different acid chlorides like phenoxy, benzyloxy, acetoxy and phthalimidoacetyl chloride. Similarly imine **2.06c** was also reacted with ketene from potassium azidoacetate in the presence of triphosgene as acid activator. In both the cases the cycloaddition reaction furnished a mixture of diastereomers and it was observed that the diastereomeric ratio was governed by the acid group present at C-3 position in the β-lactam ring. The ratio was found to be 70:30,

when the acid groups were phenoxy, acetoxy or phthalimido while in the case of benzyloxy and azido the ratio of the diastereomers was found to be 50:50.



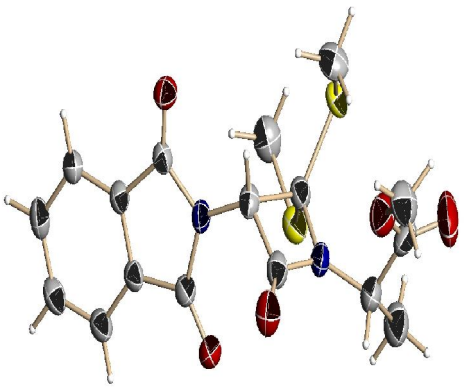
2.09a, R^1 = PhO-
2.09b, R^1 = AcO-
2.09c, R^1 = N_3-
2.09d, R^1 = BnO-
2.09e, R^1 = PhthN-

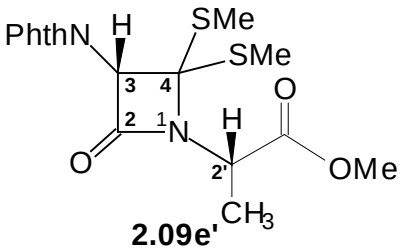
2.09

Table 5: Synthesis of azetidin-2-ones **2.09a-e** from imines **2.06c**

Entry. No.	Compound	R^1	Diastereomeric ratio	Yield (%)
1.	**2.09a**	Phenoxy	70:30	61
2.	**2.09b**	Acetoxy	70:30	62
3.	**2.09c**	Azido	50:50	62
4.	**2.09d**	Benzyloxy	50:50	60
5.	**2.09e**	Phthalimido	70:30	61

One of the major diastereomers **2.09e'** was separated by careful crystallization of the mixture of 3-phthalimido-4,4-*bis*-methylsulphanyl-azetidin-2-one **2.09e** from methanol and the absolute stereochemistry of it was confirmed by single crystal X-ray analysis and found to be *3S*, *2'S*.





2.09e'

ORTEP diagram of major isomer of **2.09e'**

Crystal data and structure refinement for 2.09e'

Empirical formula	$C_{17}H_{18}N_2O_5S_2$
Formula weight	394.45
Temperature	293 (2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, Pī
Unit cell dimensions	a = 7.937 (4) Å b = 8.001 (4) Å β = 92.806 (8) c = 17.261 (8) Å
Volume	934.5 (8) $Å^3$
Z, Calculated density	2, 1.402 mg/m^3
Crystal size	0.22 x 0.34 x 0.26 mm
Theta range for data collection	1.22 to 25.00 deg.
Reflections collected / unique	8758 / 3277 [R (int) = 0.0203]
Completeness to theta = 25.00	99.2%
Refinement method	Full-matrix least-squares on F^2
Final R indices [I>2sigma(I)]	R1 = 0.1004, wR2 = 0.3139
R indices (all data)	R1 = 0.1041, wR2 = 0.3197

The spectral and analytical data resolved the structure of the mixture as well as the major diastereomer separated by crystallization.

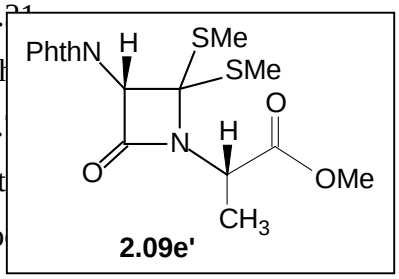
The IR spectrum of the mixture of diastereomers **2.09e** showed bands at 1789, 1778 and 1728 cm^{-1} corresponding to β-lactam, ester and phthalimido carbonyls respectively.

The ^1H NMR spectrum of the mixture showed two sets of doublets at 1.75 and 1.80 ppm with *J* = 7.3 Hz for the methyl protons in the alanine part in major and minor isomer respectively. Two sets of singlets at 2.09, 2.30 ppm and 2.12, 2.34 ppm were attributed to *S*-methyl protons in both the isomers. The methoxy protons of ester group appeared as two different singlets at 3.83 and 3.87 ppm in the major and the minor isomer. Two sets of

quartets at 4.10 and 4.30 ppm (J = 7.3 Hz) were assigned for the methine protons in the alanine part. Two singlets at 5.50 and 5.54 ppm correspond to the C-3 methine proton of the β-lactam ring in the two isomers. The aromatic protons were also observed as different sets of multiplets between 7.75-7.95 ppm.

The major diastereomer was separated by crystallization from methanol. The ^{1}H NMR of **2.09e'** showed a doublet at 1.75 ppm with J = 7.3 Hz for the methyl protons in alanine part. Two *S*-methyl protons appeared as two singlets at 2.09 and 2.30 ppm integrating for three protons each. The methoxy protons were seen as a sharp singlet at 3.83 ppm. A quartet at 4.30 ppm with J = 7.3 Hz was observed for the methine proton of the alanine part. A sharp singlet at 5.50 ppm was attributed to C-3 proton of the β-lactam ring. Two sets of multiplets for aromatic protons appeared in the range of 7.75-7.95 ppm.

The ^{13}C spectrum of **2.09e'** showed a peak at 17.21 ppm for methyl carbon of the alanine part. The meth carbons attached to sulphur were seen at 18.19 and 18. ppm. The methine carbon attached to nitrogen from t alanine group came at 48.66 ppm. The methoxy carb was observed at 52.37 ppm.



2.09e'

The C-3 and C-4 carbons appeared at 81.61 and 65.83 ppm respectively. The four aromatic carbons appeared at 123.76, 131.84, 134.84 and 161.25 ppm. The three-carbonyl carbons were observed at 166.36, 166.58 and 173.01 ppm.

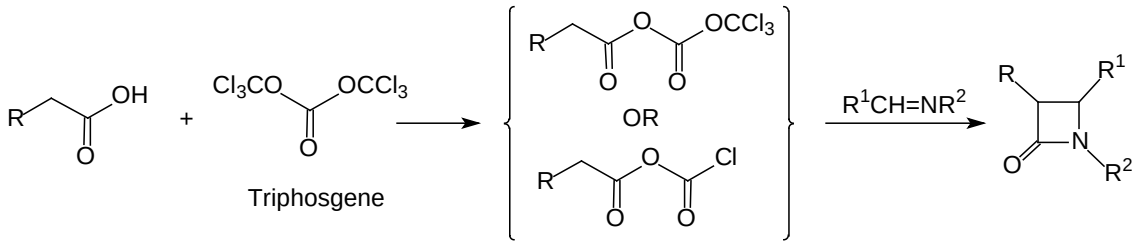
The white crystalline compound **2.09e'** showed a molecular ion peak at m/z 394 (M^{+}) in mass spectrum and also gave satisfactory elemental analysis.

Similarly the other β-lactams prepared from alanine methyl ester derived imines were also characterized with spectral analysis.

2.4 : Mechanism

We envisaged that the reaction proceeds *via* initial formation of a mixed anhydride from the acid and triphosgene (acid activator). This activates the acid part and then in the presence of tertiary base it forms a ketene that subsequently undergoes cycloaddition with the imine to yield the azetidin-2-one (Scheme 2.10).

Scheme 2.10



2.5 : Conclusion

In conclusion we have successfully synthesized the imine components i.e. carbonimidodithioic acid dialkyl esters from various aliphatic, aromatic amines and amino acid esters in around 70-80% yield. These imines were further employed for the synthesis of 4,4-*bis*-methylsulfanyl-azetidin-2-ones using triphosgene as an acid activator *via* Staudinger cycloaddition reaction. The β-lactams were obtained in overall 55-70% yield. To explore the synthetic utility, generality and the versatility of the reagent several-substituted β-lactams having dithioalkyl substituents at C-4 position were synthesized.

Chiral amino acid alanine was used for the preparation of imine **2.06c**, which was then used to study the diastereoselectivity in the β-lactam ring formation. It was observed that the diastereoselectivity depends on the nature of the alkoxy group present at C-3 position of the β-lactam ring. One of the major diastereomer **2.09e'** was separated by careful crystallization of the mixture of diastereomers **2.09** from methanol and the absolute stereochemistry was determined based on the single crystal X-ray analysis and was found to be 3*S*, 2'*S*.

2. 6 : Experimental

2. 6. 1 : General procedure for the synthesis of carbonimidodithioic acid dimethyl esters (2.02a-f) from aliphatic and aromatic amines

To a solution of aliphatic or aromatic amine (10 mmol) and carbon disulfide (10 mmol) in dichloromethane (50 mL), triethylamine (10 mmol) was added slowly at 20 ^{o}C and the reaction mixture was stirred for 30 min. Methyl iodide (12 mmol) was then added drop wise and the resulting mixture was refluxed for 2-3 h. The reaction mixture was then cooled to room temperature and triethylamine (12 mmol), methyl iodide (12 mmol) were successively added drop wise. The reaction mixture was further refluxed for 2-3 h. After complete conversion of dithiocarbamate to carbonimidodithioate (TLC), the reaction mixture was washed with water (2 x 20 mL), brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was then purified by column chromatography to get the desired product **2.02a-f** in overall 70-79% yield.

2. 6. 1a: Preparation of *N*-phenyl carbonimidodithioic acid dimethyl ester 2.02a

Following the optimized procedure, treatment of aniline (0.93 g, 10 mmol) with CS_2 (0.60 mL, 10 mmol) in the presence of triethylamine (1.40 mL, 10 mmol) and methyl iodide (0.75 mL, 12 mmol) as alkylating agent, gave the imine **2.02a** as a pale yellow oil (1.45 g, 74%).

MP : oil

IR ($CHCl_3$) : 1587 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.34 (s, 3H), 2.45 (s, 3H), 7.00-7.30 (m, 5H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 14.44, 119.90, 123.35, 128.46, 149.50, 162.02.

MS (m/z) : 197 (M^+).

Analysis ($C_9H_{11}NS_2$) : Calculated: C, 54.81; H, 5.62; N, 7.10; S, 32.45
Observed: C, 54.67; H, 5.44; N, 7.12; S, 32.23.

2. 6. 1b: Preparation of *N*-benzyl carbonimidodithioic acid dimethyl ester 2.02b

Following the optimized procedure, treatment of benzyl amine (1.07 g, 10 mmol) with CS_2 (0.60 mL, 10 mmol) in the presence of triethylamine (1.40 mL, 10 mmol) and methyl iodide (0.75 mL, 12 mmol) as alkylating agent, gave the imine **2.02b** as a yellow oil (1.66 g, 79%).

MP : oil

IR ($CHCl_3$) : 1590 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 2.40 (s, 3H), 2.55 (s, 3H), 4.60 (s, 2H), 7.00-7.30 (m, 5H). (200 MHz)

^{13}C NMR ($CDCl_3$) : δ 14.52, 56.06, 126.45, 127.33, 128.14, 140.09, 158.76. (50.3 MHz)

MS (m/z) : 211 (M^+).

Analysis : Calculated: C, 56.85; H, 6.20; N, 6.63; S, 30.29

($C_{10}H_{13}NS_2$) Observed: C, 56.64; H, 6.08; N, 6.74; S, 30.56.

2. 6. 1c: Preparation of *N*-(4-methoxyphenyl) carbonimidodithioic acid dimethyl ester 2.02c

Following the optimized procedure, treatment of *p*-anisidine (1.23 g, 10 mmol) with CS_2 (0.60 mL, 10 mmol) in the presence of triethylamine (1.40 mL, 10 mmol) and methyl iodide (0.75 mL, 12 mmol) as alkylating agent, gave the imine **2.02c** as a pale yellow oil (1.63 g, 72%).

MP : oil

IR ($CHCl_3$) : 1585 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 2.43 (s, 3H), 2.49 (s, 3H), 3.78 (s, 3H), 6.75-7.00 (m, 4H). (200 MHz)

^{13}C NMR ($CDCl_3$) : δ 14.62, 55.02, 113.87, 121.22, 142.72, 155.99, 161.73. (50.3 MHz)

MS (m/z) : 227 (M^+).

Analysis : Calculated: C, 52.85; H, 5.77; N, 6.16; S, 28.16

($C_{10}H_{13}NOS_2$) Observed: C, 52.68; H, 5.54; N, 6.32; S, 28.05.

2. 6. 1d: Preparation of *N*-propyl carbonimidodithioic acid dimethyl ester 2.02d

Following the optimized procedure, treatment of propyl amine (0.59 g, 10 mmol) with CS_2 (0.60 mL, 10 mmol) in the presence of triethylamine (1.40 mL, 10 mmol) and methyl iodide (0.75 mL, 12 mmol) as alkylating agent, gave the imine **2.02d** as a pale yellow oil (1.17 g, 72%).

MP : oil

IR ($CHCl_3$) : 1590 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.00 (t, *J* = 7.2 Hz, 3H), 1.65 (m, 2H), 2.35 (s, 3H), 2.55 (s, 3H), 3.40 (t, *J* = 7.2 Hz, 2H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 11.53, 13.96, 14.07, 23.70, 54.25, 156.14.

MS (m/z) : 163 (M^+).

Analysis : Calculated: C, 44.15; H, 8.03; N, 8.58; S, 39.22

($C_6H_{13}NS_2$) Observed: C, 43.98; H, 7.97; N, 8.69; S, 39.08.

2. 6. 1e: Preparation of *N*-furfuryl carbonimidodithioic acid dimethyl ester 2.02e

Following the optimized procedure, treatment of furfuryl amine (0.97 g, 10 mmol) with CS_2 (0.60 mL, 10 mmol) in the presence of triethylamine (1.40 mL, 10 mmol) and methyl iodide (0.75 mL, 12 mmol) as alkylating agent, gave the imine **2.02e** as a pale yellow oil (1.48 g, 74%).

MP : oil

IR ($CHCl_3$) : 1571 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.44 (s, 3H), 2.60 (s, 3H), 4.62 (s, 2H), 6.27 (d, *J* = 3.0 Hz, 1H), 6.30-6.40 (m, 1H), 7.37 (d, *J* = 3.0 Hz, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 14.44, 14.59, 49.65, 106.30, 110.05, 141.44, 153.35, 161.59.

MS (m/z) : 201 (M^+).

Analysis : Calculated: C, 47.75; H, 5.51; N, 6.96; S, 31.80
($C_8H_{11}NOS_2$) Observed: C, 47.54; H, 5.44; N, 7.12; S, 32.03.

2. 6. 1f: Preparation of *N*-allyl carbonimidodithioic acid dimethyl ester 2.02f

Following the optimized procedure, treatment of allyl amine (0.57 g, 10 mmol) with CS_2 (0.60 mL, 10 mmol) in the presence of triethylamine (1.40 mL, 10 mmol) and methyl iodide (0.75 mL, 12 mmol) as alkylating agent, gave the imine **2.02f** as a pale yellow oil (1.15 g, 72%).

MP : oil
IR ($CHCl_3$) : 1576 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.42 (s, 3H), 2.56 (s, 3H), 4.08 (d, *J* = 5.2 Hz, 2H), 5.10-5.35 (m, 2H), 5.95-6.10 (m, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 13.31, 15.17, 54.48, 114.60, 134.32, 158.46.
MS (m/z) : 161 (M^+).
Analysis ($C_6H_{11}NS_2$) : Calculated: C, 44.71; H, 6.88; N, 8.69; S, 39.09
Observed: C, 44.54; H, 6.64; N, 8.82; S, 39.23.

2. 6. 2: General procedure for the synthesis of azetidin-2-ones 2.04a-j

A solution of triphosgene (0.15 g, 0.5 mmol) in anhydrous CH_2Cl_2 (10 mL), was added slowly to a mixture of acid (1.0 mmol), imines **2.02a-f** (1.0 mmol) and triethylamine (0.42 mL, 3.0 mmol) at 0 ^oC. After the addition, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was then washed with water (20 ml), saturated sodium bicarbonate solution (2 x 15 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated to get the crude product, which was then purified by column chromatography to give pure β-lactams. By following the above general procedure various β-lactams **2.04a-j** were prepared from acid **2.03** and imines **2.02a-f**.

2. 6. 2a: Preparation of 4,4-*bis*-methylsufanyl-3-phenoxy-1-phenylazetidin-2-one 2.04a

Following the optimized procedure, treatment of phenoxyacetic acid (0.15 g, 1.0 mmol) with *N*-phenyl carbonimidodithioic acid dimethyl ester **2.02a** (0.19 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.04a** as a white solid (0.22 g, 68%).

MP : 110-111 ^{o}C

IR ($CHCl_3$) : 1766 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.22 (s, 3H), 2.23 (s, 3H), 5.49 (s, 1H), 7.05-7.50 (m, 8H), 8.00 (d, *J* = 8.3 Hz, 2H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 12.77, 14.20, 79.44, 88.23, 115.99, 118.40, 122.78, 125.71, 129.18, 129.58, 135.73, 157.10, 161.03.

MS (m/z) : 331 (M^{+}).

Analysis ($C_{17}H_{17}NO_2S_2$) : Calculated: C, 61.61; H, 5.17; N, 4.23; S, 19.31
Observed: C, 61.82; H, 5.40; N, 4.29; S, 19.10.

2. 6. 2b: Preparation of 1-benzyl-4,4-*bis*-methylsulfanyl-3-phenoxyazetidin-2-one 2.04b

Following the optimized procedure, treatment of phenoxyacetic acid (0.15 g, 1.0 mmol) with *N*-benzyl carbonimidodithioic acid dimethyl ester **2.02b** (0.21 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.04b** as a white solid (0.22 g, 65%).

MP : 79-80 ^{o}C (Lit.[11] m.p. 79-80 ^{o}C).

IR (Nujol) : 1770 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.00 (s, 6H), 4.50 (AB syst, *J* = 15.2 Hz, 2H), 5.33 (s, 1H), 7.05-7.60 (m, 10H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 12.70, 13.67, 43.55, 80.69, 88.48, 115.91, 122.63, 127.85, 128.49, 128.85, 129.46, 135.23, 157.08, 163.19.

MS (m/z) : 330 (M-15).

Analysis ($C_{18}H_{19}NO_2S_2$) : Calculated: C, 62.59; H, 5.54; N, 4.05; S, 18.53
Observed: C, 62.43; H, 5.60; N, 4.12; S, 18.36.

2. 6. 2c: Preparation of 1-(4-methoxyphenyl)-4,4-*bis*-methylsulfanyl-3-phenoxyazetidin-2-one 2.04c

Following the optimized procedure, treatment of phenoxyacetic acid (0.15 g, 1.0 mmol) with *N*-(4-methoxyphenyl) carbonimidodithioic acid dimethyl ester **2.02c** (0.23 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.04c** as a white solid (0.24 g, 66%).

MP : 147-149 ^{o}C (Lit.[11] m.p. 148-149 ^{o}C).

IR ($CHCl_3$) : 1760 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.20 (s, 3H), 2.22 (s, 3H), 3.83 (s, 3H), 5.46 (s, 1H), 6.95 (d, *J* = 9.0 Hz, 2H), 7.10-7.40 (m, 5H), 7.95 (d, *J* = 9.0 Hz, 2H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 12.75, 14.18, 55.35, 79.61, 88.21, 114.38, 115.96, 120.23, 122.73, 128.83, 129.56, 157.13, 157.39, 160.59.

MS (m/z) : 361 (M^+).

Analysis ($C_{18}H_{19}NO_3S_2$) : Calculated: C, 59.82; H, 5.30; N, 3.87; S, 17.70
Observed: C, 59.59; H, 5.56; N, 3.83; S, 17.53.

2. 6. 2d: Preparation of 1-propyl-4,4-*bis*-methylsulfanyl-3-phenoxyazetidin-2-one 2.04d

Following the optimized procedure, treatment of phenoxyacetic acid (0.15 g, 1.0 mmol) with *N*-propyl carbonimidodithioic acid dimethyl ester **2.02d** (0.16 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.04d** as a thick brown oil (0.19 g, 66%).

MP : oil

IR ($CHCl_3$) : 1770 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.03 (t, *J* = 7.3 Hz, 3H), 1.80-1.90 (m, 2H), 2.20 (s, 3H), 2.26 (s, 3H), 3.26 (t, *J* = 7.4 Hz, 2H), 5.28 (s, 1H), 7.10-7.40 (m, 5H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 11.61, 12.56, 13.56, 21.20, 41.60, 79.68, 87.70, 115.52, 122.32, 129.23, 156.73, 163.01.

MS (m/z) : 297 (M^+).

Analysis : Calculated: C, 56.55; H, 6.44; N, 4.71; S, 21.52
($C_{14}H_{19}NO_2S_2$) Observed: C, 56.79; H, 6.56; N, 4.83; S, 21.23.

2. 6. 2e: Preparation of 1-allyl-4,4-*bis*-methylsulfanyl-3-phenoxyazetidin-2-one 2.04e

Following the optimized procedure, treatment of phenoxyacetic acid (0.15 g, 1.0 mmol) with *N*-allyl carbonimidodithioic acid dimethyl ester **2.02f** (0.16 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.04e** as a pale yellow oil (0.20 g, 67%)

MP : oil
IR ($CHCl_3$) : 1770 cm^{-1}.
^{1}H NMR ($CDCl_3$) (300 MHz) : δ 2.19 (s, 3H), 2.25 (s, 3H), 3.85-4.00 (m, 2H), 5.25-5.45 (m, 2H), 5.29 (s, 1H), 5.95-6.10 (m, 1H), 7.05-7.40 (m, 5H).
^{13}C NMR ($CDCl_3$) (75.5 MHz) : δ 12.85, 13.64, 42.21, 80.02, 88.38**,** 115.70, 118.84, 122.44, 129.28, 130.81, 156.87, 162.61.
MS (m/z) : 295 (M^+).
Analysis : Calculated: C, 56.93; H, 5.80; N, 4.74; S, 21.67
($C_{14}H_{17}NO_2S_2$) Observed: C, 56.96; H, 5.55; N, 4.68; S, 21.51.

2. 6. 2f: Preparation of 1-furfuryl-4,4-*bis*-methylsulfanyl-3-phenoxyazetidin-2-one 2.04f

Following the optimized procedure, treatment of phenoxyacetic acid (0.15 g, 1.0 mmol) with *N*-furfuryl carbonimidodithioic acid dimethyl ester **2.02e** (0.20 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.04f** as a light brown solid (0.19 g, 58%).

MP : 84-85 ^oC
IR (Nujol) : 1774 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.08 (s, 3H), 2.14 (s, 3H), 4.50 (d, J = 2.4 Hz, 2H), 5.31 (s, 1H), 6.35-6.45 (m, 2H), 7.00-7.40 (m, 5H), 7.43 (d, J = 1.9 Hz, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 12.49, 17.01, 35.61, 80.01, 87.88, 106.81, 109.38, 114.75, 122.58, 129.34, 141.69, 147.76, 155.88, 161.25.

MS (m/z) : 335 (M^+).

Analysis : Calculated: C, 57.29; H, 5.10; N, 4.17; S, 19.11

($C_{16}H_{17}NO_3S_2$) Observed: C, 57.37; H, 5.37; N, 4.17; S, 19.21.

2. 6. 2g: Preparation of 1-propyl-4,4-*bis*-methylsulfanyl-3-acetoxyazetidin-2-one 2.04g

Following the optimized procedure, treatment of acetoxyacetic acid (0.12 g, 1.0 mmol) acid with *N*-propyl carbonimidodithioic acid dimethyl ester **2.02d** (0.16 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.04g** as a colorless oil (0.17 g, 67%).

MP : oil

IR ($CHCl_3$) : 1764 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 0.91 (t, *J* = 7.4 Hz, 3H), 1.60-1.80 (m, 2H), 2.08 (s, 3H), 2.13 (s, 3H), 2.18 (s, 3H), 3.05-3.25 (m, 2H), 5.79 (s, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 11.46, 13.30, 13.37, 20.14, 21.35, 41.86, 80.12, 82.15, 162.39, 168.49.

MS (m/z) : 263 (M^+).

Analysis : Calculated: C, 45.61; H, 6.51; N, 5.32; S, 24.30

($C_{10}H_{17}NO_3S_2$) Observed: C, 45.72; H, 6.30; N, 5.51; S, 24.54.

2. 6. 2h: Preparation of 1-furfuryl-4,4-*bis*-methylsulfanyl-3-acetoxyazetidin-2-one 2.04h

Following the optimized procedure, treatment of acetoxyacetic acid (0.12 g, 1.0 mmol) acid with *N*-furfuryl carbonimidodithioic acid dimethyl ester **2.02e** (0.20 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.04h** as a pale yellow oil (0.19 g, 62%).

MP : oil

IR (Nujol) : 1778, 1764 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 2.03 (s, 3H), 2.17 (s, 3H), 2.19 (s, 3H), 4.44 (s, 2H), 5.90 (s, 1H), 6.35-6.40 (m, 2H), 7.35-7.45 (m, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 13.26, 13.34, 20.25, 36.02, 80.42, 82.26, 109.46, 110.56, 142.54, 147.65, 162.13, 168.60.

MS (m/z) : 301 (M^+).

Analysis : Calculated: C, 47.83; H, 5.02; N, 4.65; S, 21.24

($C_{12}H_{15}NO_4S_2$) Observed: C, 47.62; H, 5.30; N, 4.51; S, 21.54.

2. 6. 2i: Preparation of 4,4-*bis*-methylsufanyl-3-bezyloxy-1-phenylazetidin-2-one 2.04i

Following the optimized procedure, treatment of benzyloxyacetic acid (0.16 g, 1.0 mmol) with *N*-phenyl carbonimidodithioic acid dimethyl ester **2.02a** (0.20 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.04i** as a white crystalline solid (0.21 g, 60%).

MP : 68-69 ^oC

IR (Nujol) : 1760 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 2.15 (s, 3H), 2.23 (s, 3H), 4.80 (d, *J* = 11.3 Hz, 1H), 4.95 (s, 1H), 5.05 (d, *J* = 11.3 Hz, 1H), 7.15-7.25 (m, 1H), 7.40-7.50 (m, 7H), 7.94 (d, *J* = 7.3 Hz, 2H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 12.89, 13.85, 73.32, 79.13, 88.87, 118.24, 125.15, 127.95, 128.24, 128.83, 135.67, 136.03, 162.17.

MS (m/z) : 345 (M^+), 286 (M-15).

Analysis : Calculated: C, 62.59; H, 5.55; N, 4.05; S, 18.53

($C_{18}H_{19}NO_2S_2$) Observed: C, 62.62; H, 5.60; N, 4.05; S, 18.74.

2. 6. 2j: Preparation of 3-phthalimido-4,4-*bis*-methylsulfanyl-1-propyl-azetidin-2-one 2.04j

Following the optimized procedure, treatment of phthalimidoacetic acid (0.20 g, 1.0 mmol) with *N*-propyl carbonimidodithioic acid dimethyl ester **2.02d** (0.16 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.04j** as a white crystalline solid (0.20 g, 58%).

MP : 98-100 ^oC

IR (Nujol) : 1774, 1728 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 1.06 (t, *J* = 7.4 Hz, 3H), 1.70-1.85 (m, 2H), 2.11 (s, 3H), 2.23 (s, 3H), 3.15-3.40 (m, 2H), 5.43 (s, 1H), 7.70-7.90 (m, 4H).

^{13}C NMR ($CDCl_3$) : δ 11.43, 13.30, 13.57, 21.62, 42.68, 65.84, 81.20, 123.58,

(50.3 MHz) 131.19, 134.35, 160.97, 166.30.

MS (m/z) : 335 (M-15).

Analysis : Calculated: C, 54.84; H, 5.18; N, 8.00; S, 18.26

($C_{16}H_{18}N_2O_3S_2$) Observed: C, 54.96; H, 5.05; N, 8.08; S, 18.01.

2. 6. 3 : General procedure for the synthesis of carbonimidodithioic acid dimethyl esters 2.06a-c from amino acid ester hydrochlorides

To a solution of amino acid ester hydrochloride (10 mmol) and carbon disulfide (10 mmol) in dichloromethane (50 mL), triethylamine (10 mmol) was added slowly at 20 ^oC and the reaction mixture was stirred for 30 minutes. Alkyl halide (12 mmol) was then added drop wise and the resulting mixture was refluxed for 2-3 h. The reaction mixture was then cooled to room temperature and triethylamine (12 mmol), alkyl halide (12 mmol) were added drop wise successively. The reaction mixture was then refluxed for 2-3 h. After complete conversion of dithiocarbamate to carbonimidodithioate (TLC), the reaction mixture was washed with water (2 x 20 mL), brine (20 mL), dried (anhydrous Na_2SO_4) and concentrated *in vacuo* to get the crude product, which was then purified by column chromatography to get the desired product **2.06a-c** as a pale yellow oil in 70-79% yield.

2. 6. 3a: Preparation of *N*-[*bis*(methylthio)methylene] glycine methyl ester 2.06a

Following the optimized procedure, treatment of glycine methyl ester hydrochloride (1.25 g, 10 mmol) with CS_2 (0.60 mL, 10 mmol) in the presence of triethylamine (1.40 mL, 10 mmol) and then CH_3I (0.75 mL, 12 mmol), gave the imine **2.06a** as a pale yellow oil (1.35 g, 70%).

IR (Neat) : 1751, 1579 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 2.43 (s, 3H), 2.56 (s, 3H), 3.75 (s, 3H), 4.24 (s, 2H).
(200 MHz)

^{13}C NMR ($CDCl_3$) : δ 14.18, 14.51, 51.42, 53.73, 162.79, 170.07.
(50.3 MHz)

MS (m/z) : 193 (M^+).

Analysis : Calculated: C, 37.30; H, 5.74; N, 7.25; S, 33.12

($C_6H_{11}NO_2S_2$) Observed: C, 37.58; H, 5.63; N, 7.51; S, 33.39.

2. 6. 3b: Preparation of *N*-[*bis*(methylthio)methylene]glycine ethyl ester 2.06b

Following the optimized procedure, treatment of glycine ethyl ester hydrochloride (1.39 g, 10 mmol) with CS_2 (0.60 mL, 10 mmol) in the presence of triethylamine (1.40 mL, 10 mmol) and then CH_3I (0.75 mL, 12 mmol), gave the imine **2.06b** as a pale yellow oil (1.57 g, 76%).

IR (Neat) : 1753, 1579 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.28 (t, *J* = 7.3 Hz, 3H), 2.44 (s, 3H), 2.56 (s, 3H), 4.20 (q, *J* = 7.3 Hz, 2H), 4.22 (s, 2H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 13.52, 13.85, 14.14, 53.51, 60.05, 162.24, 169.23.

MS (m/z) : 207 (M^+).

Analysis ($C_7H_{13}NO_2S_2$) : Calculated: C, 40.57; H, 6.32; N, 6.76; S, 30.88
Observed: C, 40.36; H, 6.25; N, 6.87; S, 30.76.

2. 6. 3c: Preparation of *N*-[*bis*(methylthio)methylene] alanine methyl ester 2.06c

Following the optimized procedure, treatment of alanine methyl ester hydrochloride (1.39 g, 10 mmol) with CS_2 (0.60 mL, 10 mmol) in the presence of triethylamine (1.40 mL, 10 mmol) and then CH_3I (0.75 mL, 12 mmol), gave the imine **2.06c** as a pale yellow oil (1.53 g, 74%).

IR (Neat) : 1745, 1573 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.40 (d, *J* = 6.8 Hz, 3H), 2.40 (s, 3H), 2.55 (s, 3H), 3.72 (s, 3H), 4.50 (q, *J* = 6.8 Hz, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 14.14, 14.36, 18.04, 51.38, 59.50, 160.70, 172.35.

MS (m/z) : 207 (M^+).

Analysis ($C_7H_{13}NO_2S_2$) : Calculated: C, 40.57; H, 6.32; N, 6.76; S, 30.88
Observed: C, 40.31; H, 6.59; N, 6.78; S, 30.81.

2. 6. 4: General procedure for the synthesis of azetidin-2-ones 2.08a-j

A solution of triphosgene (0.15 g, 0.5 mmol) in anhydrous CH_2Cl_2 (10 mL), was added slowly to a mixture of acid (1.0 mmol), imines **2.06a-b** (1.0 mmol) derived from amino acid ester hydrochloride and triethylamine (0.42 mL, 3.0 mmol) at 0 ^oC. After the addition, the reaction mixture was allowed to warm up to room temperature and stirred for 12 h. The reaction mixture was then washed with water (20 mL), saturated sodium bicarbonate solution (2 x 15 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated to get crude product, which was purified by column chromatography to give pure β-lactams. By following the above general procedure various β-lactams **2.08a-j** were prepared from acid **2.07** and imines **2.06a-b**.

2. 6. 4a: Preparation of (2,2-*bis*-methylsulfanyl-4-oxo-3-phenoxy-1-yl)-acetic acid methyl ester 2.08a

Following the optimized procedure, treatment of phenoxyacetic acid (0.15 g, 1.0 mmol) with glycine methyl ester carbonimidodithioic acid dimethyl ester **2.06a** (0.19 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.08a** as a white crystalline solid (0.21 g, 64%).

MP	**:**	93-94 ^oC
IR ($CHCl_3$)	**:**	1782, 1755 cm^{-1}.
^1H NMR ($CDCl_3$) (200 MHz)	**:**	δ 2.21 (s, 3H), 2.33 (s, 3H), 3.81 (s, 3H), 3.96 (d, *J* = 17.6 Hz, 1H), 4.16 (d, *J* = 17.6 Hz, 1H), 5.41 (s, 1H), 7.05-7.40 (m, 5H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	**:**	δ 12.72, 13.79, 40.25, 61.68, 80.25, 87.34, 115.61, 122.59, 129.43, 156.78, 162.95, 166.74.
MS (m/z)	**:**	327 (M^+).
Analysis ($C_{14}H_{17}NO_4S_2$)	**:**	Calculated: C, 51.36; H, 5.23; N, 4.28; S, 19.55 Observed: C, 51.20; H, 5.34; N, 4.36; S, 19.36.

2. 6. 4b: Preparation of (2,2-*bis*-methylsulfanyl-4-oxo-3-phenoxy-1-yl)-acetic acid ethyl ester 2.08b

Following the optimized procedure, treatment of phenoxyacetic acid (0.15 g, 1.0 mmol) with glycine ethyl ester carbonimidodithioic acid dimethyl ester **2.06b** (0.21 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5

mmol) as an acid activator, gave the β-lactam **2.08b** as a white crystalline solid (0.21 g, 62%).

MP	:	99-100 ^{o}C (Lit.[11] m.p. 100-101 ^{o}C).
IR ($CHCl_3$)	:	1780, 1749 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 1.32 (t, *J* = 7.3 Hz, 3H), 2.20 (s, 3H), 2.33 (s, 3H), 4.00 (d, *J* = 17.6 Hz, 1H), 4.10 (d, *J* = 17.6 Hz, 1H), 4.25 (q, *J* = 7.3 Hz, 2H), 5.41 (s, 1H), 7.05-7.40 (m, 5H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 12.76, 13.86, 40.29, 61.76, 80.28, 87.34, 115.61, 122.63, 129.46, 156.78, 162.95, 166.81.
MS (m/z)	:	341 (M^{+}).
Analysis ($C_{15}H_{19}NO_4S_2$)	:	Calculated: C, 52.77; H, 5.61; N, 4.10; S, 18.75 Observed: C, 52.53; H, 5.74; N, 4.16; S, 18.62.

2. 6. 4c: Preparation of (2,2-*bis*-methylsulfanyl-4-oxo-3-methoxy-1-yl)-acetic acid methyl ester 2.08c

Following the optimized procedure, treatment of methoxyacetic acid (0.09 g, 1.0 mmol) with glycine methyl ester carbonimidodithioic acid dimethyl ester 2.06a **(0.19 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam** 2.08c **as a pale yellow oil (0.16 g, 62%).**

MP	:	oil
IR ($CHCl_3$)	:	1778, 1755 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200MHz) : δ 2.18 (s, 3H), 2.24 (s, 3H), 3.63 (s, 3H), 3.76 (s, 3H), 4.00 (d, *J* = 17.6 Hz, 1H), 4.05 (d, *J* = 17.6 Hz, 1H), 4.67 (s, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 13.38, 16.10, 40.66, 51.91, 58.48, 79.99, 91.53, 162.47, 169.82.

MS (m/z) : 265 (M^+).

Analysis ($C_9H_{15}NO_4S_2$) : Calculated: C, 40.74; H, 5.70; N, 5.28; S, 24.12
Observed: C, 40.60; H, 5.55; N, 5.38; S, 24.38.

2. 6. 4d: Preparation of (2,2-*bis*-methylsulfanyl-4-oxo-3-methoxy-1-yl)-acetic acid ethyl ester 2.08d

Following the optimized procedure, treatment of methoxyacetic acid (0.09 g, 1.0 mmol) with glycine ethyl ester carbonimidodithioic acid dimethyl ester **2.06b** (0.21 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.08d** as a colorless oil (0.17 g, 60%).

MP : oil

IR ($CHCl_3$) : 1782, 1747 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.28 (t, *J* = 7.3 Hz, 3H), 2.18 (s, 3H), 2.25 (s, 3H), 3.64 (s, 3H), 3.85 (d, *J* = 17.5 Hz, 1H), 4.05 (d, *J* = 17.5 Hz, 1H), 4.20 (q, *J* = 7.3 Hz, 2H), 4.67 (s, 1H).

^{13}C NMR ($CDCl_3$) (75.4 MHz) : δ 13.40, 16.17, 18.04, 40.74, 51.94, 58.57, 80.08, 91.77, 162.45, 169.81.

MS (m/z) : 279 (M^+).

Analysis ($C_{10}H_{17}NO_4S_2$) : Calculated: C, 43.00; H, 6.14; N, 5.02; S, 22.91
Observed: C, 42.86; H, 6.32; N, 5.20; S, 23.11.

2. 6. 4e: Preparation of (2,2-*bis*-methylsulfanyl-4-oxo-3-phthalimido-1-yl)-acetic acid methyl ester 2.08e

Following the optimized procedure, treatment of phthalimidoacetic acid (0.21 g, 1.0 mmol) with glycine methyl ester carbonimidodithioic acid dimethyl ester **2.06a** (0.19 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.08e** as a white solid (0.21 g, 56%).

MP	:	127-129 ^{o}C
IR ($CHCl_3$)	:	1787, 1776, 1728 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 2.10 (s, 3H), 2.33 (s, 3H), 3.83 (s, 3H), 4.02 (d, *J* = 17.6 Hz, 1H), 4.16 (d, *J* = 17.6 Hz, 1H), 5.56 (s, 1H), 7.75-7.95 (m, 4H).
^{13}C NMR ($CDCl_3$) (75.4 MHz)	:	δ 13.58, 13.70, 41.35, 52.25, 65.37, 81.58, 123.69, 131.42, 134.35, 160.44, 165.96, 167.15.
MS (m/z)	:	380 (M^+).
Analysis ($C_{16}H_{16}N_2O_5S_2$)	:	Calculated: C, 50.52; H, 4.24; N, 7.37; S, 16.82 Observed: C, 50.44; H, 4.41; N, 7.60; S, 16.63.

2. 6. 4f: Preparation of (2,2-*bis*-methylsulfanyl-4-oxo-3-phthalimido-1-yl)-acetic acid ethyl ester 2.08f

Following the optimized procedure, treatment of phthalimidoacetic acid (0.21 g, 1.0 mmol) with glycine ethyl ester carbonimidodithioic acid dimethyl ester **2.06b** (0.21 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.08f** as a white solid (0.22 g, 55%).

MP	:	112 ^{o}C
IR ($CHCl_3$)	:	1787, 1778, 1728 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 1.32 (t, *J* = 7.3 Hz, 3H), 2.09 (s, 3H), 2.30 (s, 3H), 4.04 (d, *J* = 17.5 Hz, 1H), 4.14 (d, *J* = 17.5 Hz, 1H), 4.26 (q, *J* = 7.3 Hz, 2H), 5.57 (s, 1H), 7.70-7.95 (m, 4H).
^{13}C NMR ($CDCl_3$) (75.4 MHz)	:	δ 12.68, 13.82, 14.00, 40.51, 61.68, 65.21, 81.50, 123.69, 132.00, 134.50, 160.86, 166.81, 167.80.
MS (m/z)	:	394 (M^+).
Analysis ($C_{17}H_{18}N_2O_5S_2$)	:	Calculated: C, 51.76; H, 4.60; N, 7.10; S, 16.22 Observed: C, 51.54; H, 4.81; N, 6.92; S, 16.13.

2. 6. 4g: Preparation of (2,2-*bis*-methylsulfanyl-4-oxo-3-acetoxy-1-yl)-acetic acid methyl ester 2.08g

Following the optimized procedure, treatment of acetoxyacetic acid (0.12 g, 1.0 mmol) with glycine methyl ester carbonimidodithioic acid dimethyl ester **2.06a** (0.19 g, 1.0

mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.08g** as a colorless oil (0.19 g, 67%).

MP	:	oil
IR ($CHCl_3$)	:	1782, 1755 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 2.15 (s, 3H), 2.21 (s, 3H), 2.29 (s, 3H), 3.78 (s, 3H), 3.90 (d, *J* = 17.6 Hz, 1H), 4.08 (d, *J* = 17.6 Hz, 1H), 5.99 (s, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 13.30, 13.67, 20.25, 40.32, 52.56, 80.60, 81.37, 162.46, 167.17, 168.64.
MS (m/z)	:	278 (M-15).
Analysis ($C_{10}H_{15}NO_5S_2$)	:	Calculated: C, 40.95; H, 5.16; N, 4.78; S, 21.82 Observed: C, 40.74; H, 4.91; N, 4.80; S, 21.63.

2. 6. 4h: Preparation of (2,2-*bis*-methylsulfanyl-4-oxo-3-acetoxy-1-yl)-acetic acid ethyl ester 2.08h

Following the optimized procedure, treatment of acetoxyacetic acid (0.12 g, 1.0 mmol) with glycine ethyl ester carbonimidodithioic dimethyl ester **2.06b** (0.21 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.08h** as a pale yellow oil (0.20 g, 65%).

MP	:	oil
IR ($CHCl_3$)	:	1789, 1755 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 1.30 (t, *J* = 7.3 Hz, 3H), 2.16 (s, 3H), 2.22 (s, 3H), 2.30 (s, 3H), 3.88 (d, *J* = 17.5 Hz, 1H), 4.08 (d, *J* = 17.5 Hz, 1H), 4.26 (q, *J* = 7.3 Hz, 2H), 5.99 (s, 1H).
^{13}C NMR ($CDCl_3$) (75.4 MHz)	:	δ 13.18, 13.49, 13.76, 20.05, 40.56, 61.62, 80.57, 81.49, 162.24, 166.54, 168.41.
MS (m/z)	:	292 (M-15).
Analysis ($C_{11}H_{17}NO_5S_2$)	:	Calculated: C, 42.99; H, 5.58; N, 4.56; S, 20.82 Observed: C, 42.74; H, 5.29; N, 4.80; S, 20.65.

2. 6. 4i: Preparation of (2,2-*bis*-allylsulfanyl-4-oxo-3-acetoxy-1-yl)-acetic acid methyl ester 2.08i

methyl ester 2.08i

Following the optimized procedure, treatment of acetoxyacetic acid (0.12 g, 1.0 mmol) with glycine methyl ester carbonimidodithioic acid diallyl ester (0.24 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.08i** as a yellow oil (0.22 g, 65%).

MP	:	oil
IR ($CHCl_3$)	:	1784, 1757 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 2.23 (s, 3H), 3.35-3.50 (m, 4H), 3.79 (s, 3H), 3.90 (d, *J* = 17.6 Hz, 1H), 4.04 (d, *J* = 17.6 Hz, 1H), 5.10-5.35 (m, 4H), 5.70-5.90 (m, 2H), 6.06 (s, 1H).
^{13}C NMR ($CDCl_3$) (75.4 MHz)	:	δ 20.36, 33.92, 34.18, 40.79, 52.59, 81.23, 82.04, 118.61, 118.94, 132.36, 132.50, 162.39, 167.17, 168.56.
MS (m/z)	:	345 (M^+).
Analysis ($C_{14}H_{19}NO_5S_2$)	:	Calculated: C, 48.67; H, 5.34; N, 4.05; S, 18.56 Observed: C, 48.43; H, 5.56; N, 4.18; S, 18.33.

2. 6. 4j: Preparation of (2,2-*bis*-methylsulfanyl-4-oxo-3-benzyloxy-1-yl)-acetic acid methyl ester 2.08j

Following the optimized procedure, treatment of benzyloxyacetic acid (0.16 g, 1.0 mmol) with glycine methyl ester carbonimidodithioic acid dimethyl ester **2.06a** (0.19 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator, gave the β-lactam **2.08j** as a thick brown oil (0.22 g, 64%).

MP	:	oil
IR ($CHCl_3$)	:	1775, 1747 cm^{-1}.
^{1}H NMR ($CDCl_3$) (300.1 MHz)	:	δ 2.17 (s, 3H), 2.21 (s, 3H), 3.77 (s, 3H), 3.88 (d, *J* = 17.2 Hz, 1H), 4.08 (d, *J* = 17.2 Hz, 1H), 4.76 (d, *J* = 11.7 Hz, 1H), 4.94 (d, *J* = 11.7 Hz, 1H), 4.86 (s, 1H), 7.35-7.50 (m, 5H).
^{13}C NMR ($CDCl_3$) (75.4 MHz)	:	δ 13.08, 13.67, 39.84, 52.34, 73.14, 80.09, 88.25, 128.06, 128.28, 135.92, 164.34, 167.39.
MS (m/z)	:	341(M^+).
Analysis ($C_{15}H_{19}NO_4S_2$)	:	Calculated: C, 52.77; H, 5.61; N, 4.10; S, 18.74 Observed: C, 52.54; H, 5.81; N, 4.28; S, 18.53.

2. 6. 5a: Preparation of (2,2-*bis*-methylsulfanyl-4-oxo-3-phenoxy-1-yl)-α-methyl acetic acid methyl ester 2.09a

To a solution of alanine methyl ester carbonimidodithioic acid dimethyl ester 2.06c **(0.21 g, 1.0 mmol) and triethylamine (0.42 mL, 3.0 mmol) in dry DCM (10 mL), was added drop wise a solution of phenoxyacetyl chloride (0.17 g, 1.0 mmol) in dry DCM (5 mL). The reaction mixture after work up provided the diastereomeric mixture of** β**-lactams** 2.09a **in the ratio of 70:30 as a light brown oil (0.20 g, 61%).**

MP	:	oil
IR ($CHCl_3$)	:	1776, 1747 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ Mix. of` diastereomers 1.75 & 1.80 (2 d, *J* = 7.4 Hz & 7.8 Hz, 3H), 2.22, 2.31, 2.27 & 2.30 (4 s, 6H), 3.81 (s, 3H), 4.10 & 4.20 (2 q, *J* = 7.4 Hz & 7.8 Hz, 2H), 5.32 & 5.36 (2 s, 1H), 7.05-7.40 (m, 5H).
MS (m/z)	:	341 (M^+).

2. 6. 5b: Preparation of (2,2-*bis*-methylsulfanyl-4-oxo-3-acetoxy-1-yl)-α-methyl acetic acid methyl ester 2.09b

To a solution of alanine methyl ester carbonimidodithioic acid dimethyl ester 2.06c **(0.21 g, 1.0**

mmol) and triethylamine (0.42 mL, 3.0 mmol) in dry DCM (10 mL), was added drop wise a solution of acetoxyacetyl chloride (0.14 g, 1.0 mmol) in dry DCM (5 mL). The reaction mixture after work up provided the diastereomeric mixture of β-lactams 2.09b **in the ratio of 70:30 as a pale yellow oil (0.19 g, 62%).**

MP	**:**	oil
IR ($CHCl_3$)	**:**	1784, 1755 cm^{-1}.
^1H NMR ($CDCl_3$) (200 MHz)	**:**	δ Mix. of` diastereomers 1.68 & 1.72 (2 d, *J* = 7.8 Hz, 3H), 2.18, 2.21, 2.23 & 2.28 (4 s, 6H), 3.78 (s, 3H), 4.10 & 4.18 (2 q, *J* = 7.8 Hz, 2H), 5.92 & 5.94 (2 s, 1H).
MS (m/z)	**:**	307 (M^+).

2. 6. 5c: Preparation of (2,2-*bis*-methylsulfanyl-4-oxo-3-azido-1-yl)-α-methyl acetic acid methyl ester 2.09c

Following the optimized procedure, treatment of azidoacetic acid potassium salt (0.14 g, 1.0 mmol) with alanine methyl ester carbonimidodithioic acid dimethyl ester 2.06c **(0.21 g, 1.0 mmol) in the presence of triethylamine (0.42 mL, 3.0 mmol) and triphosgene (0.15 g, 0.5 mmol) as an acid activator in dry DCM (15 mL),**

gave the diastereomeric mixture of β-lactams 2.09c **in the ratio of 50:50 as a pale yellow oil (0.18 g, 62%).**

MP	:	oil
IR ($CHCl_3$)	:	2113, 1776, 1743 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ Mix. of` diastereomers 1.66 & 1.70 (2 d, *J* = 7.3 Hz, 3H), 2.23 & 2.28 (2 s, 6H), 3.78 (s, 6H), 3.95-4.15 (2 q, *J* = 7.3 Hz, 1H), 4.67 & 4.75 (2 s, 1H).
MS (m/z)	:	259 (M-31).

2. 6. 5d: Preparation of (2,2-*Bis*-methylsulfanyl-4-oxo-3-benzyloxy-1-yl)-α-methyl acetic acid methyl ester 2.09d

To a solution of alanine methyl ester carbonimidodithioic acid dimethyl ester 2.06c **(0.21 g, 1.0 mmol) and triethylamine (0.42 mL, 3.0 mmol) in dry DCM (10 mL), was added drop wise a solution of benzyloxyacetyl chloride (0.14 g, 1.0 mmol) in dry DCM (5 mL). The reaction mixture after work up provided the diastereomeric mixture of β-lactams** 2.09d **in the ratio of 50:50 as a pale yellow oil (0.21 g, 60%).**

MP	:	oil
IR ($CHCl_3$)	:	1776, 1745 cm^{-1}.
^{1}H NMR ($CDCl_3$)	:	δ Mix. of` diastereomers 1.68 & 1.74 (2 d, *J* = 7.3 Hz, 3H),

(200 MHz) 2.15, 2.19, 2.25 & 2.30 (4 s, 3H), 3.77 & 3.78 (2 s, 3H), 4.05 & 4.15 (2 q, *J* = 7.3 Hz, 1H), 4.75-4.95 (2 merged doublets, 2H), 4.78 & 4.80 (2 s, 1H).

MS (m/z) : 355 (M^+).

2. 6. 5e: Preparation of (2,2-*Bis*-methylsulfanyl-4-oxo-3-phthalimido-1-yl)-α-methyl acetic acid methyl ester 2.09e

To a solution of alanine methyl ester carbonimidodithioic acid dimethyl ester 2.06c **(0.21 g, 1.0 mmol) and triethylamine (0.42 mL, 3.0 mmol) in dry DCM (10 mL), was added drop wise a solution of phthalimidoacetyl chloride (0.22 g, 1.0 mmol) in dry DCM (5 mL). The reaction mixture after work up provided the diastereomeric mixture of β-lactams** 2.09e **in the ratio of 70:30 as a pale yellow oil (0.24 g, 61%).**

MP : oil

IR ($CHCl_3$) : 1789, 1778, 1728 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ Mix. of diastereomers 1.75 & 1.80 (2 d, *J* = 7.3 Hz, 3H), 2.09, 2.12, 2.30 & 2.34 (4 s, 3H), 3.83 & 3.87 (2 s, 3H), 4.10 & 4.30 (2 q, *J* = 7.3 Hz, 1H), 5.50 & 5.54 (2 s, 1H), 7.75-7.95 (m, 5H).
(200 MHz)

MS (m/z) : 394 (M^+).

The major diastereomer **2.09e'** from the mixture of β-lactams **2.09e** was separated by careful crystallization from methyl alcohol. This white crystalline solid showed the following data.

MP	:	111 ^{o}C
IR ($CHCl_3$)	:	1789, 1778, 1728 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 1.75 (d, *J* = 7.3 Hz, 3H), 2.09 (s, 3H), 2.30 (s, 3H), 3.85 (s, 3H), 4.25 (q, *J* = 7.3 Hz, 1H), 5.50 (s, 1H), 7.75-7.95 (m, 5H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 17.31, 18.19, 18.70, 48.66, 52.37, 65.83, 81.61, 123.76, 131.84, 134.84, 161.25, 166.36, 166.58, 173.01.
MS (m/z)	:	394 (M^{+}).
Analysis ($C_{17}H_{18}N_2O_5S_2$)	:	Calculated: C, 51.76; H, 4.60; N, 7.10; S, 16.22 Observed: C, 51.69; H, 4.85; N, 7.11; S, 16.43.

2.7 : Background for the present work

The β-lactam ring construction is an active area of research so also the β-lactam ring cleavage. Azetidin-2-ones are susceptible to ring cleavage reaction due to the ring strain associated with the ring. Several research groups[28] have exploited this property by employing β-lactams as synthon for the synthesis of a variety of compounds. In many of these reports, β-lactams are used for generating valuable synthons *via* ring cleavage or ring expansion.

Opening of β-lactam can occur through cleavage of any of the single bonds of the four membered ring (Figure 2).

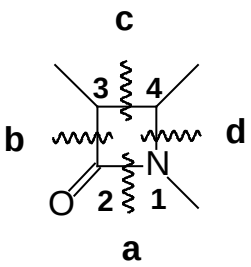


Figure 2 Various modes of ring opening of β-lactam nucleus

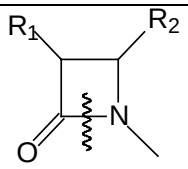
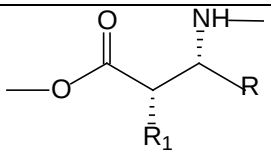
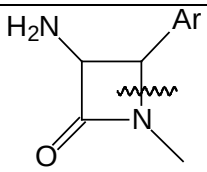
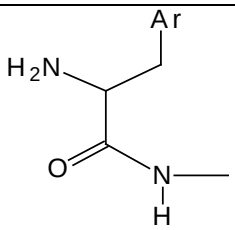
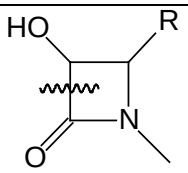
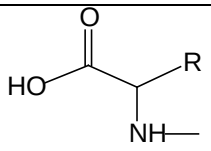
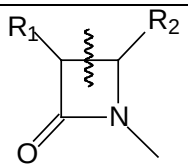
The cleavage of the amide bond, N(1)-C(2) (a in Figure 2) is the most common one and has been extensively employed for the preparation of macrocyclic alkaloids,[29] cyclic polyamines,[30] taxoids,[31] sphingolipids[32] and β-amino acids.[33] The N(1)-C(2) bond cleavage is responsible for the antibiotic activity of β-lactams[34] as well as for the inhibition of Human Leukocyte elastase.[35]

C(2)-C(3)[36](b in Figure 2) and C(3)-C(4)[37] (c in Figure 2) bond cleavages are also known and are generally applied in the ring expansion of β-lactams to give heterocycles such as *N*-carboxyanhydrides,[36a-e] pyrazines and oxazines.[37c-d]

Ojima et al.[38] have employed the N(1)-C(4) (d in Figure 2) bond cleavage of 4-aryl-azetidine-2-ones for the synthesis of novel amino acids and peptidomimetics.

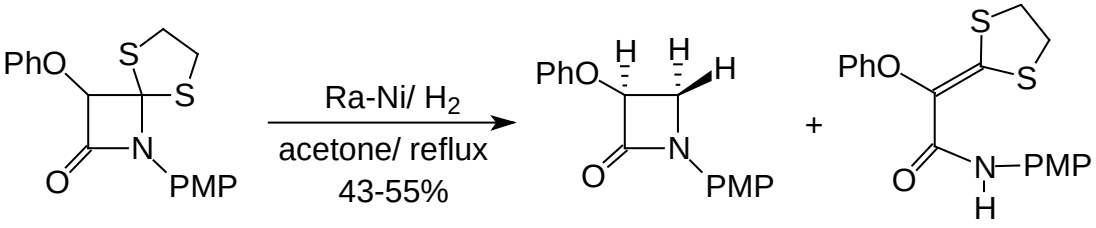
Heteroatom substitution at C-4 renders β-lactams susceptible to 1,4-ring cleavage. The ring cleavage occurs under acidic,[39] basic[40] and neutral conditions[41] depending upon the nature of the substituents at C-1 and C-3 positions.

Table 6: Modes of ring opening of β-lactams

Entry No.	Scheme	Product	Reference
1	 N(1)-C(2) bond cleavage	 β-amino acids	**34**
2	 N(1)-C(4) bond cleavage	 α-amino acids	**33d-e**
3	 C(2)-C(3) bond cleavage	 α-amino acid derivatives and peptide synthesis.	**35**
4	 C(3)-C(4) bond cleavage	Pyrazines and Oxazines	**36**

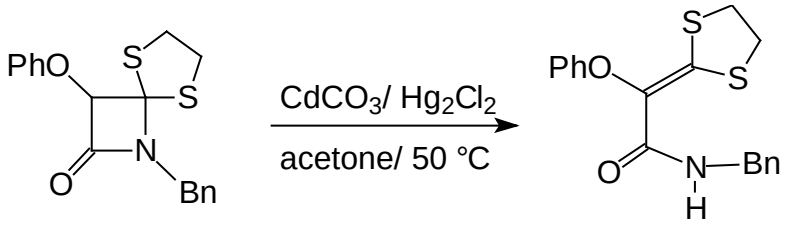
Sharma and coworkers[10] have reported the formation of minor quantities of open chain amide during desulphurization of 4,4-dithioalkyl-2-azetidinone with Raney-Ni (Scheme 2.11).

Scheme 2.11



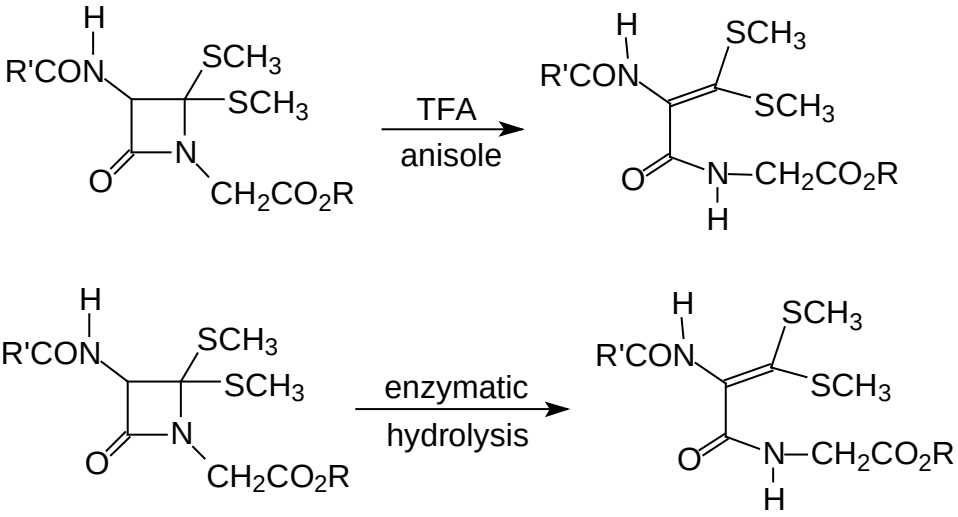
4,4-dithioprotected-1-benzyl-β-lactam underwent 1,4-ring cleavage during the reaction with cadmium carbonate in the presence of mercurous chloride (Scheme 2.12).

Scheme 2.12



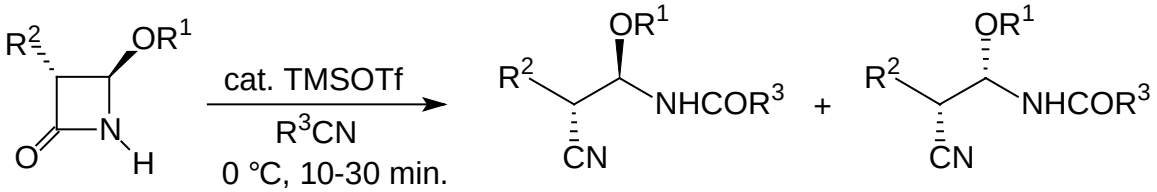
Edward et al.[9] also reported the formation of ring-opened products during hydrolysis of the ester side chain on nitrogen atom of the β-lactam. Enzymatic hydrolysis of the ester also gives similar N(1)-C(4) ring cleavage acrylamide derivative.

Scheme 2.13



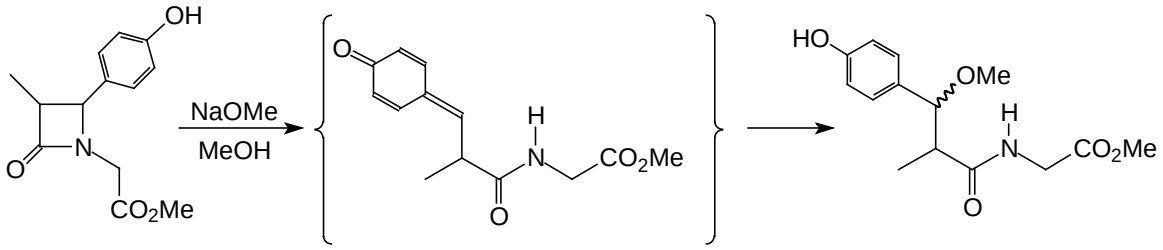
Kita et al.[36f] have developed a new method for the synthesis of chiral β-amido cyanides by means of the regioselective cleavage of 4-acetoxy as well as 4-sulfinyl azetidin-2-ones in the presence of catalytic TMSOTf and RCN (Scheme 2.14).

Scheme 2.14



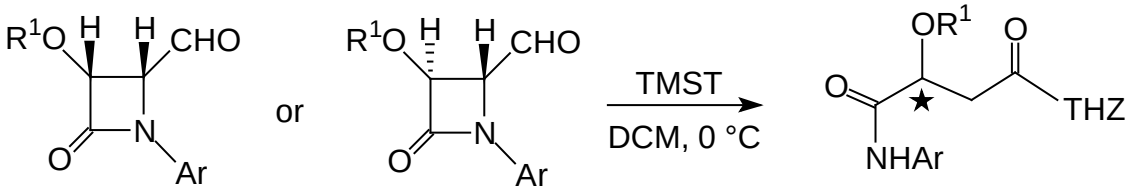
McMurray et al.[42] have reported a unique cleavage of the N(1)-C(4) bond of monocyclic β-lactams that leads to α,β-disubstituted-4-hydroxyhydrocinnamides (Scheme 2.15).

Scheme 2.15



Recently novel N(1)-C(4) β-lactam bond cleavage of 4-formyl-β̃-lactams has been shown by Alcaide et al.[43] to generate enantiopure α-alkoxy-γ-keto acid derivatives.

Scheme 2.16

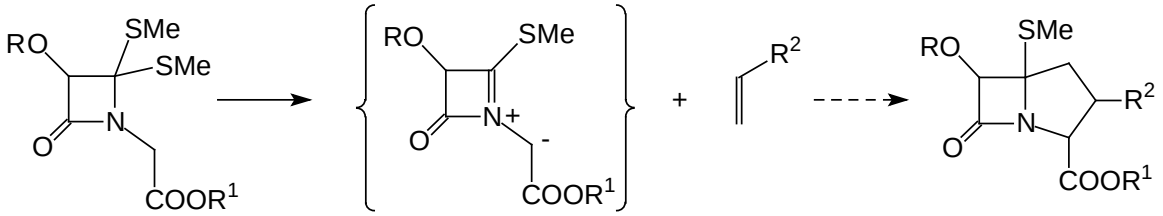


TMST = 2-(trimethylsilyl)thiazole
THZ = 2-thiazolyl

2.8 : Present work

Since we were already having the 4,4-dithioalkyl substituted β-lactams in hand, we planned to explore their use as potential azomethine ylide intermediates for ring cyclization with appropriate dipolarophile which will furnish the corresponding bicyclic framework as shown in the strategy depicted in the Scheme 2.17.

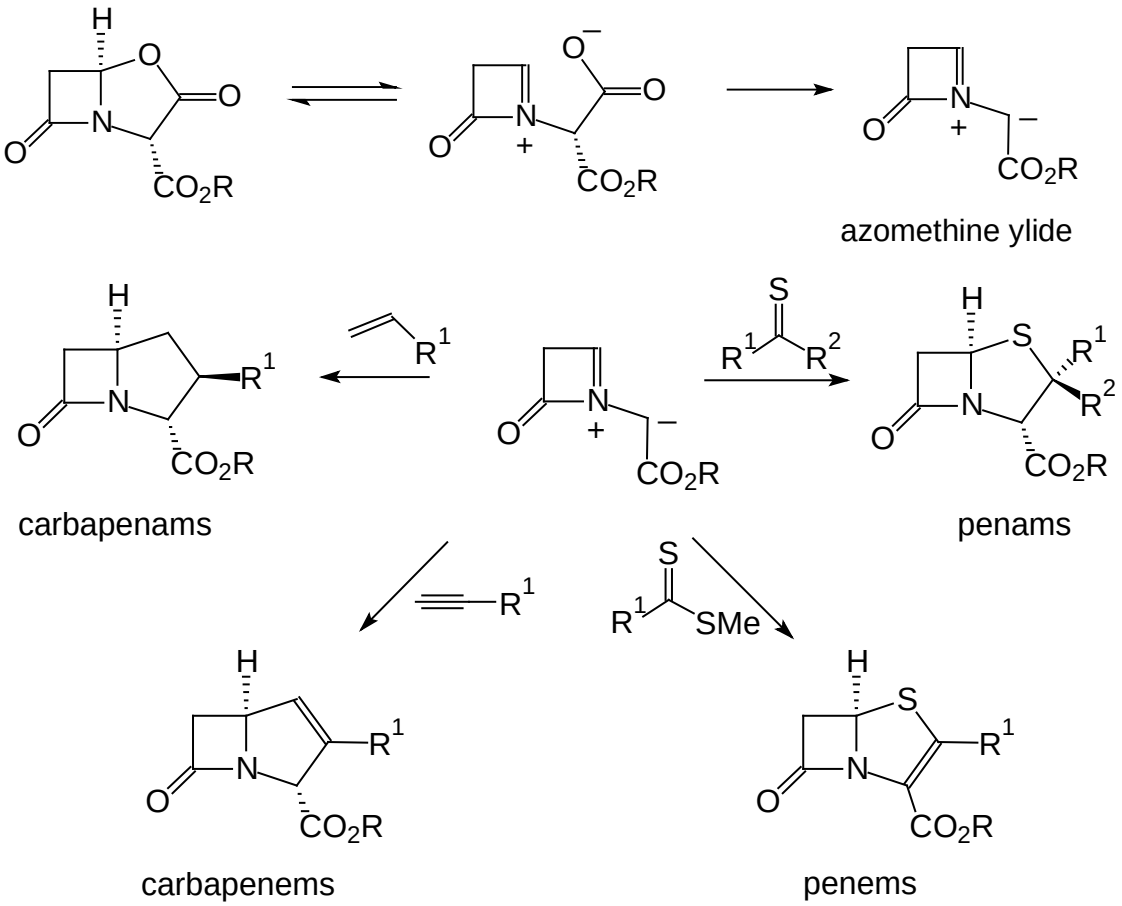
Scheme 2.17



azomethine ylide dipolarophile

It is well documented in the literature that the bicyclic framework present in carbapenams, carbapenems, penams and penems[44] can be synthesized from substituted β-lactams based on 1,3-dipolar cycloaddition using azomethine ylide strategy. Gallagher and co-workers[45] have used 1,3-dipolar cycloaddition reaction with the azomethine ylides generated from the azetidinone skeleton for the synthesis of the antibacterial units.

Scheme 2.18

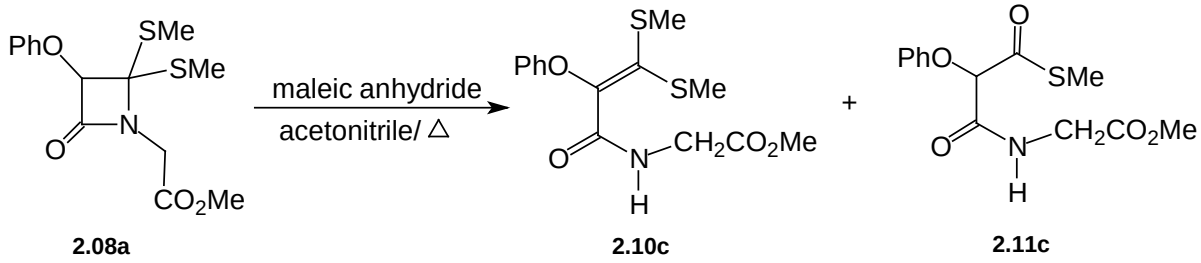


This section of the chapter deals with our efforts in employing the 4,4-dithioalkyl-azetidin-2-ones for generating the azomethine ylides.

2.9 : Results and discussion

The reaction of (2,2-*bis*-methylsulfanyl-4-oxo-3-phenoxy-1-yl) acetic acid methyl ester **2.08a** (Section A) with maleic anhydride as a dipolarophile in acetonitrile under reflux conditions gave two products as shown from TLC, which were separated by column chromatography and characterized fully with the spectral analysis (Scheme 2.19). The first less polar *N*-methyl glycine-3,3-*bis*(methylthio)-2-phenoxy acrylamide **2.10c** was obtained as a white crystalline solid. Based on the spectral and analytical data the structure of this compound was established.

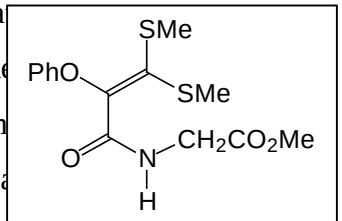
Scheme 2.19



2.08a **2.10c** **2.11c**

The IR spectrum of acrylamide **2.10c** showed bands at 3427, 1747 and 1658 cm^{-1} corresponding to the amino group, ester and the amide carbonyl respectively.

The ^{1}H NMR spectrum of **2.10c** showed two singlets a 2.26 and 2.47 ppm corresponding to the *S*-methyl protons. The methoxy protons were observed as a sharp singlet at 3.70 ppm. The methylene protons attached to nitrogen appeared as a doublet at 4.04 ppm with J = 5.1 Hz.



2.10c

A broad singlet at 6.84 ppm was attributed to NH proton, while the aromatic protons appeared as two sets of multiplets between 6.95-7.10 and 7.25-7.35 ppm.

The C-3 proton of the β-lactam ring was seen as a singlet at 5.41 ppm, which was not observed in the NMR spectra of the acrylamide derivative **2.10c**. This further proved the ring-opened structure.

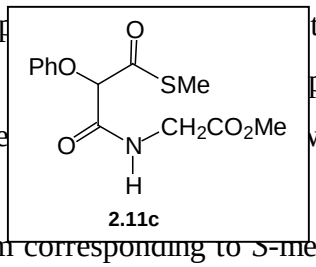
The ^{13}C spectrum of **2.10c** showed peaks at 17.06 and 18.25 ppm, which were attributed to methyl carbons attached to sulphur. The methylene carbon attached to nitrogen was observed at 41.05 ppm. The methoxy carbon was seen at 52.07 ppm. The aromatic carbons appeared at 115.00, 122.75 and 129.65 ppm along with the *ipso* carbon attached to oxygen at 156.20 ppm. The olefinic carbons were seen at 140.05 and 140.72 ppm. The peaks at 161.72 and 169.78 ppm were due to amide and ester carbonyl respectively. The compound showed a molecular ion peak m/z at 327 (M^{+}) in mass spectrum and also gave satisfactory elemental analysis.

The second more polar product obtained was also characterized fully by spectral data and its structure was found to the thioate derivative **2.11c**. The formation of this thioate derivative could be rationalized assuming the hydrolysis of the preformed acrylamide derivative **2.10c.**

The IR spectrum of thioate derivative **2.11c** showed bands at 3419 and 1749 indicating the presence of amino and ester group respectively. The absorption band at 1706 cm^{-1} was due to the thioate group.

The ^{1}H NMR spectrum of **2.11c** showed only one singlet at 2.35 corresponding to the *S*-methyl protons.

The methoxy protons appeared as a singlet at 3.75 pp tons attached to nitrogen appeared as a multiplet between 4.10-4.20 ppm was due to the methine proton while the aromatic protons appe veen 6.90-7.40 ppm.



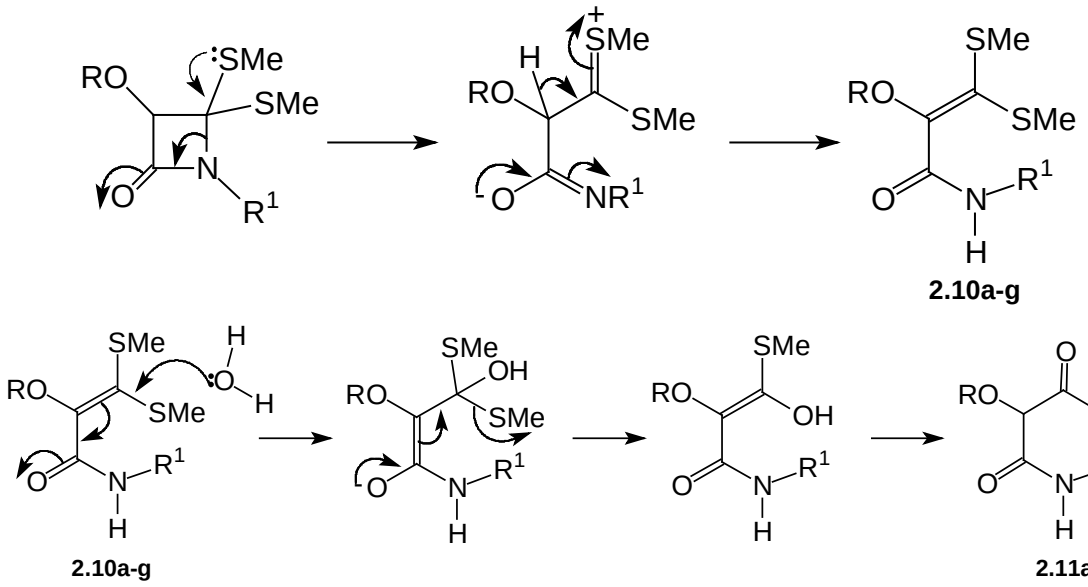
2.11c

The ^{13}C spectrum of **2.11c** showed a peak at 11.17 ppm corresponding to *S*-methyl carbon. The peaks at 40.94 ppm and 52.15 ppm were due to methylene and methoxy carbons respectively. The methine carbon appeared at 83.32 ppm. The aromatic carbons appeared at 115.52, 123.02, and 129.67 ppm along with the *ipso* carbon attached to oxygen at 156.21 ppm, which disappeared in the ^{13}C DEPT. The amide, ester and the thioate carbonyls were seen at 164.19, 169.37 and 194.70 ppm respectively.

The compound showed a peak at m/z 298 (M+1) in mass spectrum and gave satisfactory elemental analysis.

The formation of these N(1)-C(4) ring cleavage products is envisioned on the basis of the following mechanism (Scheme 2.20) that proceeds through the anchimeric assistance of the lone pair on the sulphur atom. This is followed by the N(1)-C(4) bond cleavage of the β-lactam ring so as to be free from the ring strain. Also it gives an extra stability due to extended conjugation in the product.

Scheme 2.20



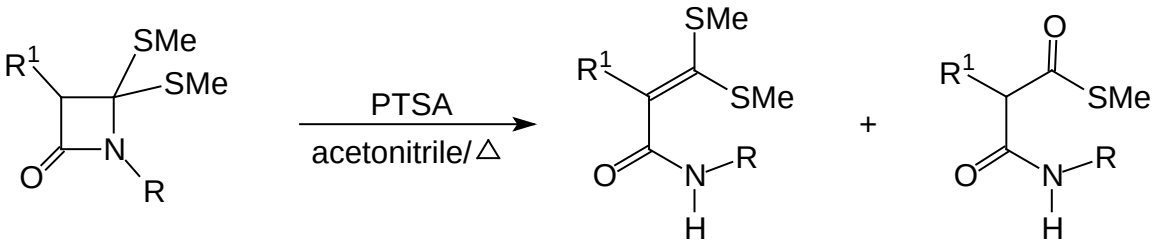
2.10a-g **2.11a-g**

Instead of undergoing the ring cyclization with the dipolarophile, the β-lactams were cleaved in N(1)-C(4) manner to produce the acrylamide derivatives **2.10a-g**, which were further hydrolyzed to produce the thioates **2.11a-g**.

We wanted to prove that the formation of acrylamide could be possible only in acidic medium and in the absence of the dipolarophile. Hence we treated the β-lactam **2.08a** with PTSA in refluxing toluene in the absence of the dipolarophile. The same acrylamide **2.10c** and thioate derivative **2.11c** were obtained as the products.

To study the generality of this ring opening, various substituted β-lactams were subjected to reaction with PTSA in acetonitrile under reflux conditions. The products obtained were characterized by spectral and analytical data and the results are summarized in the Table 7.

Scheme 2.21



2.04 or 2.08 **2.10a-g** **2.11a-g**

Table 7: Azetidinone ring cleavage products **2.10a-g** and **2.11a-g** under acidic conditions

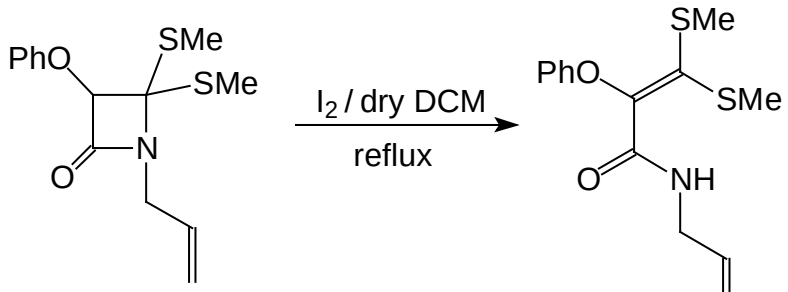
Compound	**R^1**	**R**	**Compound**	**R^1**	R
2.10a	PhO	cyclohexyl	**2.11a**	PhO	cyclohexyl
2.10b	BnO	Ph	**2.11b**	BnO	Ph
2.10c	PhO	CH_2COOMe	**2.11c**	PhO	CH_2COOMe
2.10d	PhO	PMP	**2.11d**	PhO	Ph
2.10e	PhO	allyl	**2.11e**	PhO	CH_2COOEt
2.10f	AcO	allyl	**2.11f**	AcO	CH_2COOMe
2.10g	MeO	$CH(CH_3)COOMe$	**2.11g**	MeO	CH_2COOMe

In some cases the hydrolysis of the preformed acrylamide derivative was observed producing the thioate derivatives **2.10a-c & 2.11a-c** and we were able to isolate both the products. While in some cases only the acrylamide derivatives **2.10d-g** or the thioate derivatives **2.11d-g** were isolated.

The β-lactam ring cleavage was due to the anchimeric assistance of the lone pair on sulphur atom. Hence it was planned to block the sulphur lone pair which was attempted with either iodine or mercury salt like mercuric acetate.

The acrylamide **2.10d** was obtained as the sole product during the reaction of 1-allyl-3-phenoxy-4,4-*bis*-methylsulfanyl-azetidin-2-one **2.04e** with iodine in DCM under reflux conditions (Scheme 2.22). This ring cleavage may be attributed to the inherent acidity of iodine.

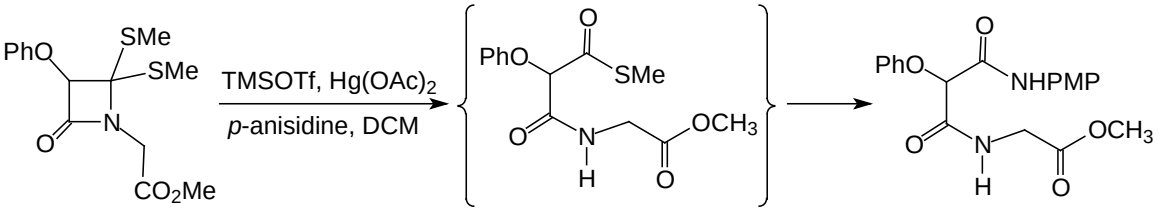
Scheme 2.22



2.04e **2.10d**

The reaction of (2,2-*bis*-methylsulfanyl-4-oxo-3-phenoxy-1-yl) acetic acid methyl ester **2.08a** with TMSOTf in the presence of mercuric acetate in dichloromethane afforded the thioate derivative **2.11c**. Whereas the same reaction in the presence of *p*-anisidine furnished the substituted diamide **2.12** (Scheme 2.23). The formation of this diamide **2.12** involves the displacement of the *S*-methyl group form the corresponding initially formed thioate derivative **2.11c** by the amino group.

Scheme 2.23



2.08a **2.11c** **2.12**

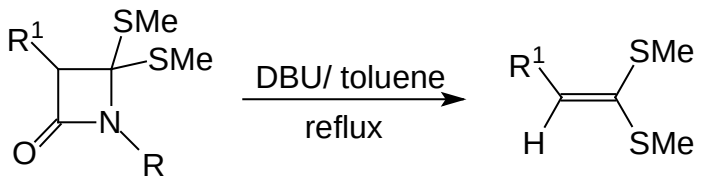
The IR spectrum of this diamide **2.12** showed bands at 3402, 3280, 1749, 1681 and 1668 cm^{-1} corresponding to the amino group, the ester and the amide carbonyls respectively.

Further the ^{1}H NMR spectrum also supported the diamide structure. The spectrum showed two singlets at 3.75 and 3.79 ppm assigned to the methoxy protons of the PMP and ester group. The methylene protons appeared as a doublet at 4.10 ppm with J = 4.9 Hz. The

methine proton appeared as a singlet at 5.26 ppm, while the NH protons appeared as two broad singlets at 7.60 and 8.77 ppm. The aromatic protons of PMP group were observed as two sets of doublets at 6.85 and 7.48 ppm with J = 9.0 Hz. The remaining aromatic protons appeared as two multiplets between 7.00-7.10 and 7.30-7.35 ppm integrating for three and two protons respectively.

Since the cycloaddition under neutral and acidic conditions was unsuccessful we planned to do the reaction under basic medium using mild base such as DBU. Thus the reaction of two **2.04i** and **2.08a** of the 4,4-dithiomethyl-β-lactams was carried out with DBU in toluene under reflux conditions. The reaction was carried out first with the dipolarophiles like maleic anhydride or *N*-phenyl maleimide. In this case the ring scission products **2.13a-b** were obtained (Scheme 2.24). The formation of same products was observed during the reaction of **2.04i** and **2.08a** with DBU in the absence of dipolarophile also.

Scheme 2.24



2.04i; R^1 = BnO, R = Ph
2.08a; R^1 = PhO, R = $-CH_2CO_2Me$

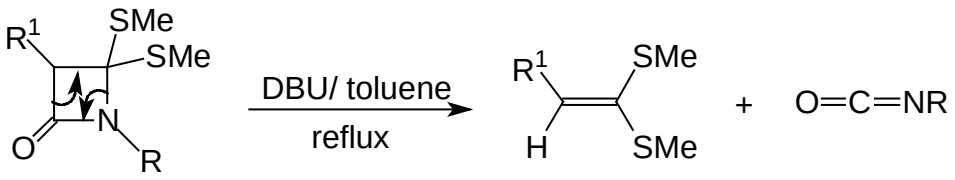
2.13a; R^1 = BnO
2.13b; R^1 = PhO

The IR spectrum of **2.13a** showed bands at 1687 and 1598 cm^{-1}. The ^1H NMR of **2.13a** showed two singlets at 2.18 and 2.29 ppm corresponding to the *S*-methyl protons. A sharp singlet at 4.95 ppm was assigned to the methylene protons. The vinylic methine proton appeared at 6.86 ppm as a singlet and the aromatic protons were observed as a multiplet between 7.35-7.55 ppm.

Similarly the compound **2.13b** showed bands at 1581 and 1488 cm^{-1}. The *S*-methyl protons in ^1H NMR appeared at 2.30 and 2.38 ppm. The vinylic methine proton was seen as a singlet at 7.15 ppm and the aromatic protons appeared as two separate multiplets between 7.00-7.10 ppm and 7.25-7.40 ppm for three and two protons respectively.

The formation of products of the type **2.13** may be due to the retro thermal cleavage of the strained azetidinone ring (Scheme 2.25). But all our attempts to isolate the isocynate part proved to be unsuccessful.

Scheme 2.25



2.13a-b

2. 10 : Conclusion

Though the generation of azomethine ylides from the 4,4-dithiomethyl-azetidin-2-ones was unsuccessful, we were able to study the mode of β-lactam ring cleavage under acidic and basic conditions. Under acidic conditions the N(1)-C(4) bond cleavage was observed in all the β-lactams giving the acrylamide derivatives **2.10a-g** and the thioate derivatives **2.11a-g**. The thioate derivatives must be arising from the hydrolysis of the preformed acrylamide under the reaction conditions. The reaction of 4,4-dithiomethyl-azetidin-2-ones with sulphur activating compounds like mercuric acetate or iodine also furnished the thioate derivative **2.11c**, which was trapped by an amine to afford the diamide derivative **2.12**. Under basic conditions (DBU) the retro ring cleavage was observed giving *S,S-bis*(alkylketene) dithioacetals **2.13a-b**.

2. 11 : Experimental

2. 11. 1: General procedure for the synthesis of acrylamides 2.10a-g and thioate derivatives 2.11a-g.

To a solution of azetidin-2-one (1.0 mmol) in acetonitrile (10 mL) was added PTSA (0.17 g, 1.0 mmol). The resulting solution was then refluxed for 1-3 h. After the reaction was over (TLC), acetonitrile was removed under reduced pressure and the products were obtained by purification of the crude reaction mixture by column chromatography.

2. 11. 1a: Preparation of *N*-cyclohexyl-3,3-*bis*(methylthio)-2-phenoxy acrylamide 2.10a

Following the optimized procedure, treatment of 1-cyclohexyl-4,4-*bis*-methylsulfanyl-3-phenoxy-azetidin-2-one (0.34 g, 1.0 mmol) with PTSA (0.17 g, 1.0 mmol) in acetonitrile (10 mL), gave the acrylamide **2.10a** as a white solid (0.18 g, 53%) along with the thioate derivative **2.11a** as a white solid (0.08 g, 25%).

MP	:	128-130 ^{o}C
IR ($CHCl_3$)	:	3429, 3303, 1650 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 0.95-1.10 (m, 2H), 1.20-1.35 (m, 2H), 1.45-1.60 (m, 3H), 1.65-1.85 (m, 3H), 2.35 (s, 3H), 2.45 (s, 3H), 3.65-3.90 (m, 1H), 6.01 (d, *J* = 7.9 Hz, 1H), 6.90-7.15 (m, 3H), 7.30-7.40 (d, *J* = 7.8 Hz, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 16.97, 18.30, 24.44, 25.43, 32.63, 47.96, 115.30, 122.87, 129.71, 136.81, 156.40, 159.67, 160.77.
MS (m/z)	:	337 (M^{+}).
Analysis ($C_{17}H_{23}NO_2S_2$)	:	Calculated: C, 60.51; H, 6.87; N, 4.15; S, 18.97 Observed: C, 60.72; H, 6.98; N, 4.21; S, 19.23.

Data for *S*-methyl-3-(cyclohexylamino)-3-oxo-2-phenoxy propanethioate 2.11a

MP	:	120-121 ^{o}C
IR ($CHCl_3$)	:	3417, 3303, 1703, 1687 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 1.15-1.35 (m, 6H), 1.70-1.75 (m, 2H), 1.90-2.05 (m, 2H), 2.35 (s, 3H), 3.70-3.90 (m, 1H), 5.15 (s, 1H), 6.55 (d, *J* = 7.3 Hz, 1H), 6.95-7.10 (m, 3H), 7.30-7.40 (m, 2H).
^{13}C NMR ($CDCl_3$) (75.4 MHz)	:	δ 11.20, 24.47, 25.28, 32.52, 48.37, 83.73, 115.56, 123.02, 129.71, 156.32, 163.02, 194.67.
MS (m/z)	:	308 (M+1).
Analysis ($C_{16}H_{21}NO_3S$)	:	Calculated: C, 62.51; H, 6.89; N, 4.56; S, 10.41 Observed: C, 62.57; H, 7.16; N, 4.56; S, 10.27.

2. 11. 1b: Preparation of *N*-phenyl-3,3-*bis*(methylthio)-2-benzyloxy acrylamide 2.10b

Following the optimized procedure, treatment of azetidin-2-one **2.04i** (0.34 g, 1.0 mmol) with PTSA (0.17 g, 1.0 mmol) in acetonitrile (10 mL), gave the acrylamide **2.10b** as a white solid (0.19 g, 56%) along with the thioate derivative **2.11b** as a white solid (0.07 g, 23%).

MP	**:**	104 ^{o}C
IR ($CHCl_3$)	**:**	3444, 3427, 1660 cm^{-1}.
^{1}H NMR ($CDCl_3$) (300 MHz)	**:**	δ 2.41 (s, 3H), 2.43 (s, 3H), 4.95 (s, 2H), 7.10-7.15 (m, 1H), 7.30-7.35 (m, 2H), 7.35-7.45 (m, 3H), 7.45-7.55 (m, 4H), 8.17 (bs, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	**:**	δ 12.75, 13.74, 73.21, 118.13, 125.08, 127.84, 128.13, 128.50, 128.76, 132.52, 135.92, 162.09.
MS (m/z)	**:**	346 (M+1).
Analysis ($C_{18}H_{19}NO_2S_2$)	**:**	Calculated: C, 62.59; H, 5.55; N, 4.06; S, 18.53 Observed: C, 62.67; H, 5.88; N, 3.95; S, 18.77.

Data for *S*-methyl-3-anilino-2-benzyloxy-3-oxo-propanethioate 2.11b

MP	**:**	83-84 ^{o}C
IR ($CHCl_3$)	**:**	3390, 1706, 1683 cm^{-1}.
^{1}H NMR ($CDCl_3$) (300 MHz)	**:**	δ 2.38 (s, 3H), 4.60 (d, J = 11.7 Hz, 1H), 4.70 (s, 1H), 4.90 (d, J = 11.7 Hz, 1H), 7.10-7.60 (m, 10H), 8.40 (bs, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	**:**	δ 11.06, 73.32, 84.39, 119.57, 124.49, 128.13, 128.46, 128.74, 135.37, 136.58, 162.46, 195.73.
MS (m/z)	**:**	316 (M+1).
Analysis ($C_{17}H_{17}NO_3S$)	**:**	Calculated: C, 64.74; H, 5.43; N, 4.44; S, 10.14 Observed: C, 64.64; H, 5.67; N, 4.39; S, 10.25.

2. 11. 1c: Preparation of methyl {[3,3-*bis*(methylthio)-2-phenoxyacryloyl] amino} acetate 2.10c

Following the optimized procedure, treatment of azetidin-2-one **2.08a** (0.33 g, 1.0 mmol) with PTSA (0.17 g, 1.0 mmol) in acetonitrile (10 mL), gave the acrylamide **2.10c** as a white solid (0.18 g, 56%) along with the thioate derivative **2.11c** as a white solid (0.07 g, 24%).

MP	**:**	79-80 ^{o}C
IR ($CHCl_3$)	**:**	3427, 1747, 1658 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ 2.26 (s, 3H), 2.47 (s, 3H), 3.70 (s, 3H), 4.04 (d, *J* = 5.1 Hz, 2H), 6.84 (bs, 1H), 6.95-7.10 (m, 3H), 7.25-7.35 (m, 2H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	**:**	δ 17.06, 18.25, 41.05, 52.07, 115.00, 122.75, 129.65, 140.05, 140.72, 156.20, 161.72, 169.78.
MS (m/z)	**:**	327 (M^{+}).
Analysis ($C_{14}H_{17}NO_4S_2$)	**:**	Calculated: C, 51.36; H, 5.24; N, 4.28; S, 19.55 Observed: C, 51.46; H, 5.43; N, 4.19; S, 19.28.

Data for methyl {[3-(methylthio)-3-oxo-2-phenoxypropanoyl] amino} acetate 2.11c

MP	**:**	107-108 ^{o}C
IR ($CHCl_3$)	**:**	3419, 1749, 1706 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ 2.35 (s, 3H), 3.75 (s, 3H), 4.10-4.20 (merged dd, 2H), 5.25 (s, 1H), 6.90-7.40 (m, 5H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	**:**	δ 11.17, 40.94, 52.15, 83.32, 115.52, 123.02, 129.67, 156.21, 164.19, 169.37, 194.70.
MS (m/z)	**:**	298 (M+1).
Analysis ($C_{13}H_{15}NO_5S$)	**:**	Calculated: C, 52.51; H, 5.09; N, 4.71; S, 10.76 Observed: C, 52.34; H, 5.32; N, 4.47; S, 10.75.

2. 11. 1d: Preparation of *N*-(4-methoxyphenyl)-3,3-*bis*(methylthio)-2-phenoxy acrylamide 2.10d

Following the optimized procedure, treatment of azetidin-2-one **2.04c** (0.36 g, 1.0 mmol) with PTSA (0.17 g, 1.0 mmol) in acetonitrile (10 mL), gave the acrylamide **2.10d** as a white solid (0.27 g, 76%).

MP	**:**	133-135 ^{o}C
IR ($CHCl_3$)	**:**	3420, 1637 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ 2.48 (s, 3H), 2.60 (s, 3H), 3.86 (s, 3H), 6.90 (d, *J* = 8.7 Hz, 2H), 7.10-7.20 (m, 3H), 7.35-7.50 (m, 4H), 8.07 (bs, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	**:**	δ 17.34, 18.26, 55.31, 113.98, 114.93, 121.51, 122.98, 129.86, 130.37, 140.44, 140.92, 156.14, 156.43, 159.45.
MS (m/z)	**:**	361 (M^{+}).
Analysis ($C_{18}H_{19}NO_3S_2$)	**:**	Calculated: C, 59.82; H, 5.30; N, 3.87; S, 17.71 Observed: C, 59.54; H, 5.53; N, 3.95; S, 17.48.

2. 11. 1e: Preparation of *N*-allyl-3,3-*bis*(methylthio)-2-phenoxy acrylamide 2.10e

Following the optimized procedure, treatment of azetidin-2-one **2.04e** (0.29 g, 1.0 mmol) with PTSA (0.17 g, 1.0 mmol) in acetonitrile (10 mL) or with iodine in refluxing DCM gave the acryl amide **2.10e** as a pale yellow oil (0.21 g, 72%).

MP	**:**	oil
IR ($CHCl_3$)	**:**	3430, 1637 cm^{-1}.
^{1}H NMR ($CDCl_3$) (300 MHz)	**:**	δ 2.23 (s, 3H), 2.41 (s, 3H), 4.00-4.15 (m, 2H), 5.15-5.35 (m, 2H), 5.85-6.00 (m, 1H), 6.95-7.05 (m, 3H), 7.30-7.35 (m, 2H), 9.26 (bs, 1H).
^{13}C NMR ($CDCl_3$) (125.7 MHz)	**:**	δ 10.57, 16.71, 47.04, 114.30, 116.26, 121.86, 126.30, 129.29, 134.42, 155.80, 158.17, 187.11.
MS (m/z)	**:**	296 (M+1).
Analysis ($C_{14}H_{17}NO_2S_2$)	**:**	Calculated: C, 56.93; H, 5.80; N, 4.74; S, 21.67 Observed: C, 56.70; H, 5.96; N, 4.94; S, 21.52.

2. 11. 1f: Preparation of *N*-allyl-3,3-*bis*(methylthio)-2-acetoxy acrylamide 2.10f

Following the optimized procedure, treatment of 1-allyl-4,4-*bis*-methylsulfanyl-3-acetoxy-azetidin-2-one (0.26 g, 1.0 mmol) with PTSA (0.17 g, 1.0 mmol) in acetonitrile (10 mL) or with iodine in refluxing DCM gave the acryl amide **2.10f** as a colorless oil (0.20 g, 76%).

MP	:	oil
IR ($CHCl_3$)	:	3434, 1737, 1637 cm^{-1}.
^1H NMR ($CDCl_3$) (300 MHz)	:	δ 2.26 (s, 6H), 2.34 (s, 3H), 4.00-4.15 (m, 2H), 5.10-5.30 (m, 2H), 5.80-5.95 (m, 1H), 9.05 (bs, 1H).
^{13}C NMR ($CDCl_3$) (125.7 MHz)	:	δ 10.65, 17.08, 20.48, 47.21, 116.39, 123.71, 134.25, 154.17, 170.04, 185.46.
MS (m/z)	:	262 (M+1).
Analysis ($C_{10}H_{15}NO_3S_2$)	:	Calculated: C, 45.97; H, 5.79; N, 5.36; S, 24.49 Observed: C, 45.74; H, 5.85; N, 5.45; S, 24.49.

2. 11. 1g: Preparation of methyl-2-{[2-methoxy-3,3-*bis*(methylthio)acryloyl] amino} propionate 2.10g

Following the optimized procedure, treatment of 4,4-bismethylsulfanyl-3-methoxy-1-(α-methyl methyl acetate)-azetidin-2-one (0.28 g, 1.0 mmol) with PTSA (0.17 g, 1.0 mmol) in acetonitrile (10 mL), gave the acryl amide **2.10g** as a colorless oil (0.21 g, 76%).

MP	:	oil
IR ($CHCl_3$)	:	3406, 1743, 1681, 1508, 1488 cm^{-1}.
^1H NMR ($CDCl_3$) (200 MHz)	:	δ 1.43 (d, *J* = 7.3 Hz, 3H), 2.29 (s, 3H), 2.33 (s, 3H), 3.67 (s, 3H), 3.72 (s, 3H), 4.60-4.85 (m, 1H), 6.90 (d, *J* = 6.8 Hz, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 16.31, 18.08, 47.81, 52.26, 58.62, 58.99, 161.81, 164.37, 172.94.
MS (m/z)	:	280 (M+1).
Analysis ($C_{10}H_{17}NO_4S_2$)	:	Calculated: C, 42.99; H, 6.13; N, 5.01; S, 22.95 Observed: C, 42.74; H, 6.15; N, 5.27; S, 22.54.

2. 11. 1h: Preparation of *S*-methyl-3-anilino-3-oxo-2-phenoxy propanethioate 2.11d

Following the optimized procedure, treatment of azetidin-2-one 2.04a (0.33 g, 1.0 mmol) with PTSA (0.17 g,

1.0 mmol) in acetonitrile (10 mL) gave the thioate derivative 2.11d as a white solid (0.24 g, 80%).

MP : 100 ^{o}C

IR ($CHCl_3$) : 3404, 1710, 1687 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.37 (s, 3H), 5.29 (s, 1H), 7.00-7.20 (m, 4H), 7.35-7.40 (m, 4H), 7.60 (d, *J* = 8.3 Hz, 2H), 8.40 (bs, 1H).

^{13}C NMR ($CDCl_3$) (75.4 MHz) : δ 11.24, 83.58, 115.52, 119.93, 123.09, 124.82, 128.79, 129.71, 136.55, 156.03, 161.80, 194.81.

MS (m/z) : 286 (M-15).

Analysis ($C_{16}H_{15}NO_3S$) : Calculated: C, 63.77; H, 5.02; N, 4.65; S, 10.62
Observed: C, 63.55; H, 4.87; N, 4.55; S, 10.72.

2. 11. 1i: Preparation of ethyl{[3-(methylthio)-3-oxo-2-phenoxypropanoyl] amino} acetate 2.11e

Following the optimized procedure, treatment of azetidin-2-one **2.08b** (0.34 g, 1.0 mmol) with PTSA (0.17 g, 1.0 mmol) in acetonitrile (10 mL) gave the thioate derivative **2.11e** as a white crystalline solid (0.24 g, 77%).

MP : 87-88 ^{o}C

IR ($CHCl_3$) : 3417, 1743, 1704 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.25 (t, *J* = 7.3 Hz, 3H), 2.35 (s, 3H), 4.05-4.10 (merged dd, 2H), 4.30 (q, *J* = 7.3 Hz, 2H), 5.25 (s, 1H), 6.90-7.15 (m, 3H), 7.25-7.40 (m, 3H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 11.13, 13.85, 41.12, 61.34, 83.40, 115.56, 122.98, 129.64, 156.29, 164.15, 168.86, 194.66.

MS (m/z) : 311 (M^{+}).

Analysis ($C_{14}H_{17}NO_5S$) : Calculated: C, 54.00; H, 5.51; N, 4.50; S, 10.28
Observed: C, 53.89; H, 5.38; N, 4.21; S, 10.22.

2. 11. 1j: Preparation of methyl{[2-(acetoxy)-3-(methylthio)-3-oxopropanoyl] amino} acetate 2.11f

Following the optimized procedure, treatment of azetidin-2-one **2.08g** (0.29 g, 1.0 mmol) with PTSA (0.17 g, 1.0 mmol) in acetonitrile (10 mL) gave the thioate derivative **2.11f** as a white solid (0.19 g, 74%).

MP	**:**	71 ^{o}C
IR ($CHCl_3$)	**:**	3367, 1753, 1703, 1693 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ 2.26 (s, 3H), 2.32 (s, 3H), 3.74 (s, 3H), 4.05 (merged dd, 2H), 5.70 (s, 1H), 7.14 (bs, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	**:**	δ 10.84, 19.80, 40.68, 51.82, 77.25, 162.24, 168.05, 168.97, 193.82.
MS (m/z)	**:**	204 (M-59).
Analysis ($C_9H_{13}NO_6S$)	**:**	Calculated: C, 41.06; H, 4.98; N, 5.32; S, 12.15 Observed: C, 41.21; H, 5.19; N, 5.38; S, 12.42.

2. 11. 1k: Preparation of methyl{[2-methoxy)-3-(methylthio)-3-oxopropanoyl] amino} acetate 2.11g

Following the optimized procedure, treatment of azetidin-2-one **2.08c** (0.26 g, 1.0 mmol) with PTSA (0.17 g, 1.0 mmol) in acetonitrile (10 mL) gave the thioate derivative **2.11g** as a colorless oil (0.17 g, 74%).

MP	:	oil
IR ($CHCl_3$)	:	3407, 1745, 1703, 1697 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 2.32 (s, 3H), 3.57 (s, 3H), 3.76 (s, 3H), 4.15 (merged dd, 2H), 4.38 (s, 1H), 7.20 (bs, 1H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 11.13, 40.90, 52.37, 59.28, 86.85, 165.73, 171.61, 196.10.
MS (m/z)	:	236 (M+1).
Analysis ($C_8H_{13}NO_5S$)	:	Calculated: C, 40.84; H, 5.57; N, 5.95; S, 13.60 Observed: C, 40.71; H, 5.29; N, 5.84; S, 13.42.

2. 11. 2: General procedure for the synthesis of *S,S-bis*(alkylketene) dithioacetals 2.13a-b

To a solution of azetidin-2-one (1.0 mmol) in toluene (10 mL) was added DBU (0.15 mL, 1.0 mmol). The resulting solution was then refluxed for 5-6 h. After the reaction was over (TLC), toluene was removed under reduced pressure and the product was obtained by purification of the crude reaction mixture by column chromatography.

2. 11. 2a: Preparation of ({[2,2-bis(methylthio)vinyl] oxy} methyl) benzene 2.13a

Treatment of azetidin-2-one 2.04i (0.34 g, 1.0 mmol) with DBU (0.15 mL, 1.0 mmol) in refluxing toluene (10 mL)

gave the ring opened product 2.13a as a pale yellow oil (0.12 g, 53%).

MP : oil

IR ($CHCl_3$) : 1598 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.18 (s, 3H), 2.29 (s, 3H), 4.95 (s, 2H), 6.86 (s, 1H), 7.35-7.55 (m, 5H).

^{13}C NMR ($CDCl_3$) (75.4 MHz) : δ 15.86, 17.98, 74.42, 127.37, 127.95, 128.09, 128.47, 136.43, 150.68.

2. 11. 2b: Preparation of {[2,2-bis(methylthio)vinyl] oxy} benzene 2.13b

Treatment of azetidin-2-one **2.08a** (0.33 g, 1.0 mmol) with DBU (0.15 mL, 1.0 mmol) in refluxing toluene (10 mL) gave the ring opened product **2.13b** as a pale yellow oil (0.11 g, 52%).

MP : oil

IR ($CHCl_3$) : 1581 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.30 (s, 3H), 2.38 (s, 3H), 7.00-7.15 (m, 3H), 7.15 (s, 1H), 7.25-7.40 (m, 2H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 15.69, 17.67, 116.48, 122.69, 129.42, 144.97, 155.85.

2. 11. 3: Procedure for the synthesis of diamide derivative 2.12

To a solution of azetidin-2-one 2.08a (0.33 g, 1.0 mmol), p-anisidine (0.12 g, 1.0 mmol) and mercuric acetate (0.33 g, 1.05 mmol) in dry DCM (10 mL)

was added TMSOTf (0.2 mL, 1.05 mmol) dropwise at room temperature. The resulting solution was then stirred for 10 h. After the reaction was over (TLC), the reaction mixture was diluted with DCM and washed with saturated sodium bicarbonate. The organic extract was dried (Na_2SO_4) and concentrated under reduced pressure and the product was obtained by purification of the crude reaction mixture by column chromatography.

MP : 143 ^oC

IR ($CHCl_3$) : 3402, 3280, 1749, 1699, 1681, 1668 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ 3.75 (s, 3H), 3.79 (s, 3H), 4.10 (d, *J* = 4.9 Hz, 2H), 5.26 (s, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 7.00-7.10 (m, 3H), 7.30-7.35 (m, 2H), 7.48 (d, *J* = 9.0 Hz, 2H) 7.60 (bs, 1H), 8.77 (bs, 1H).
MS (m/z)	:	372 (M^+).
Analysis ($C_{19}H_{20}N_2O_6$)	:	Calculated: C, 61.27; H, 5.42; N, 7.53 Observed: C, 61.37; H, 5.29; N, 7.64.

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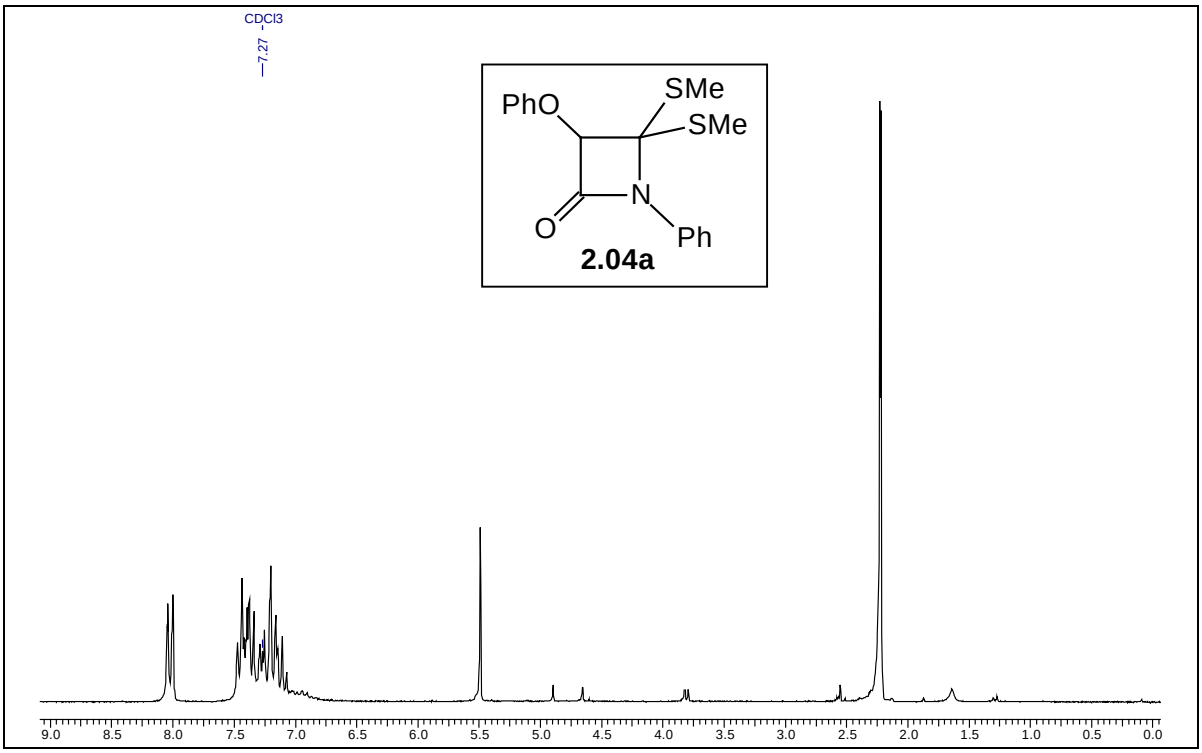
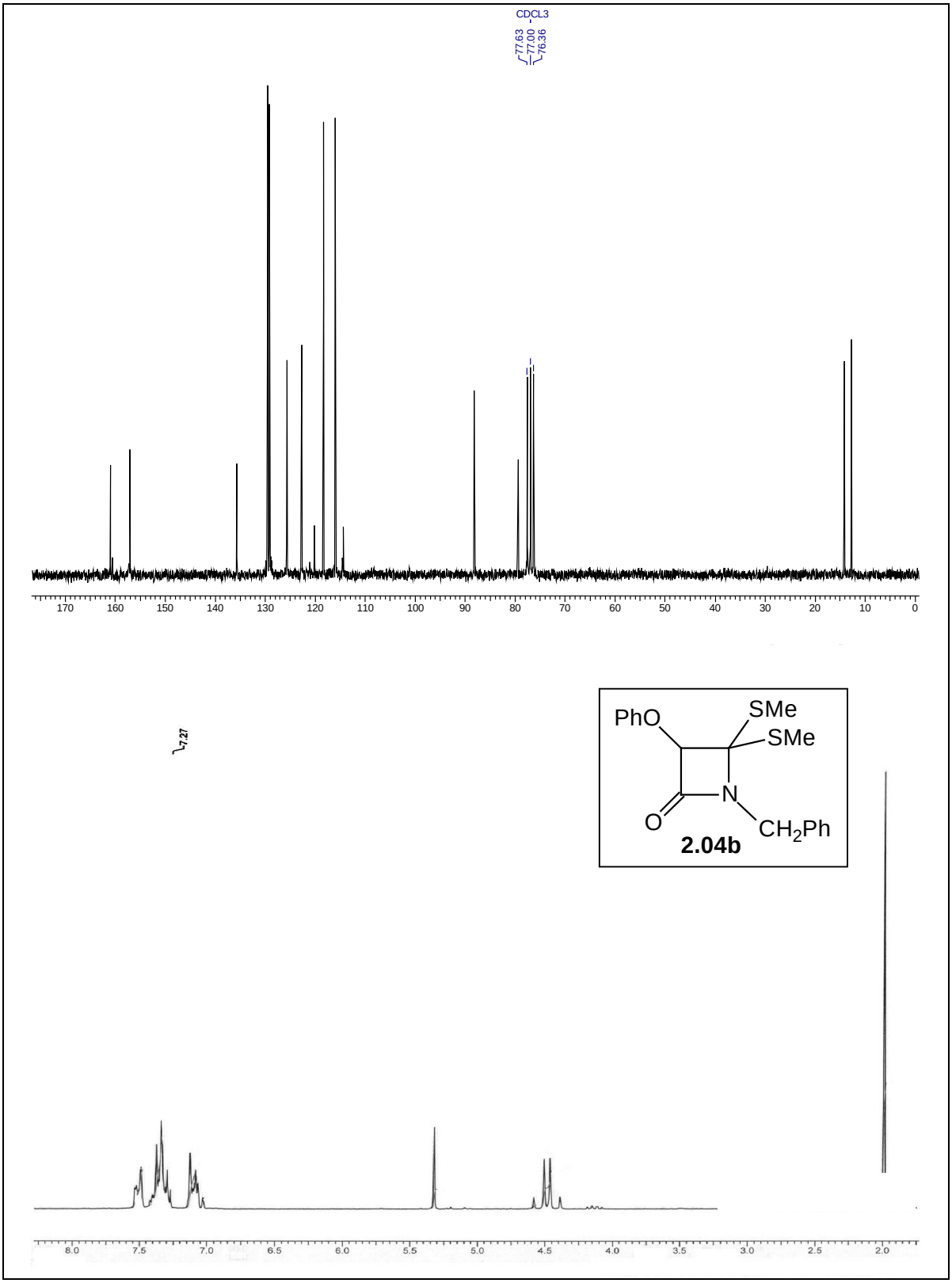
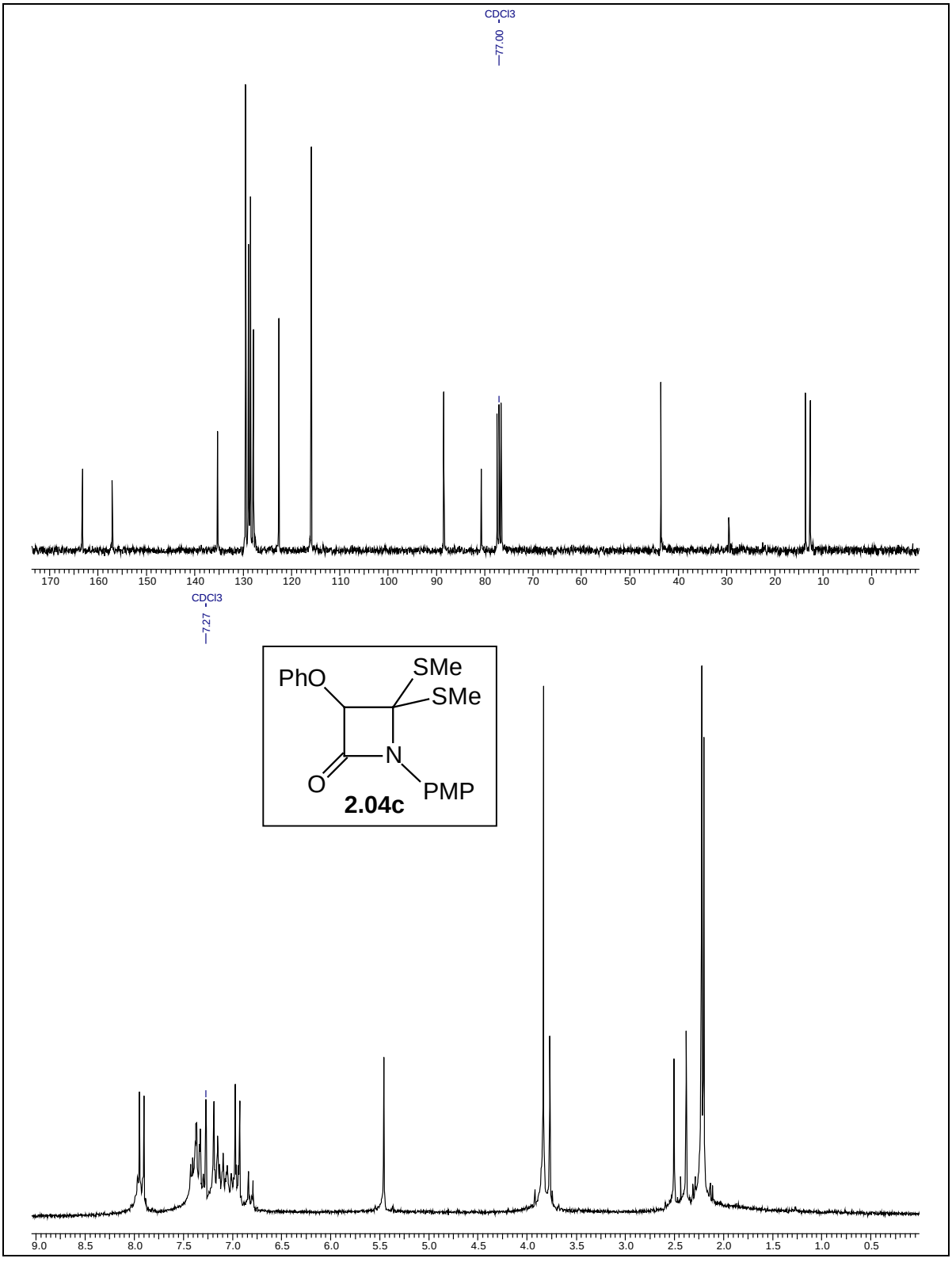
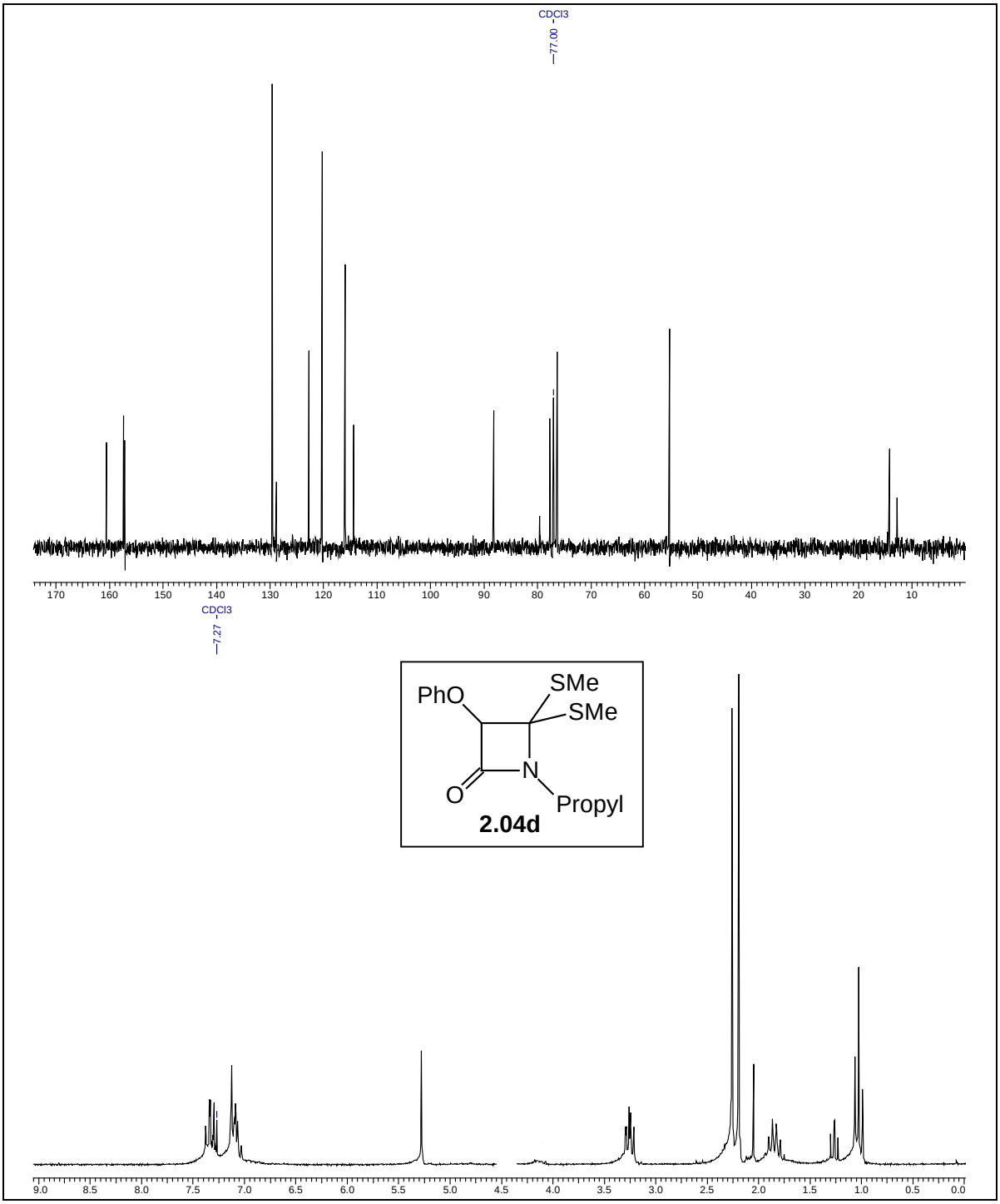
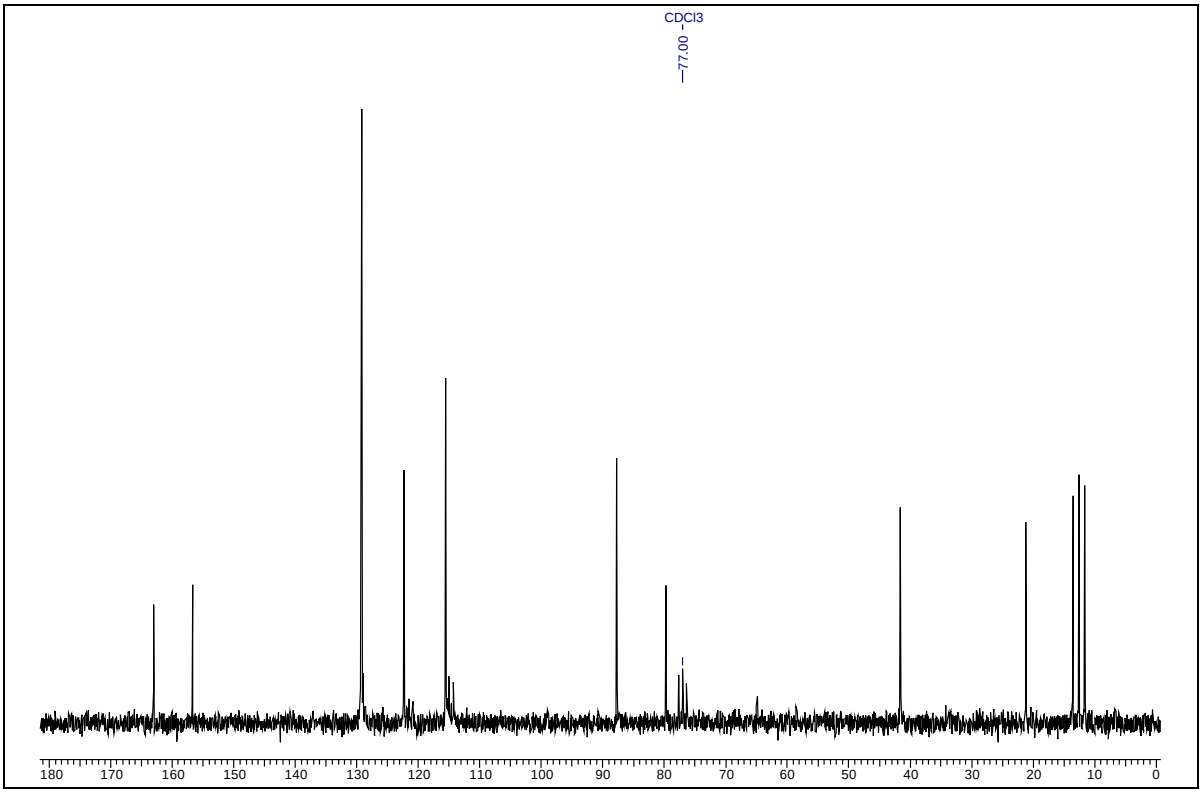
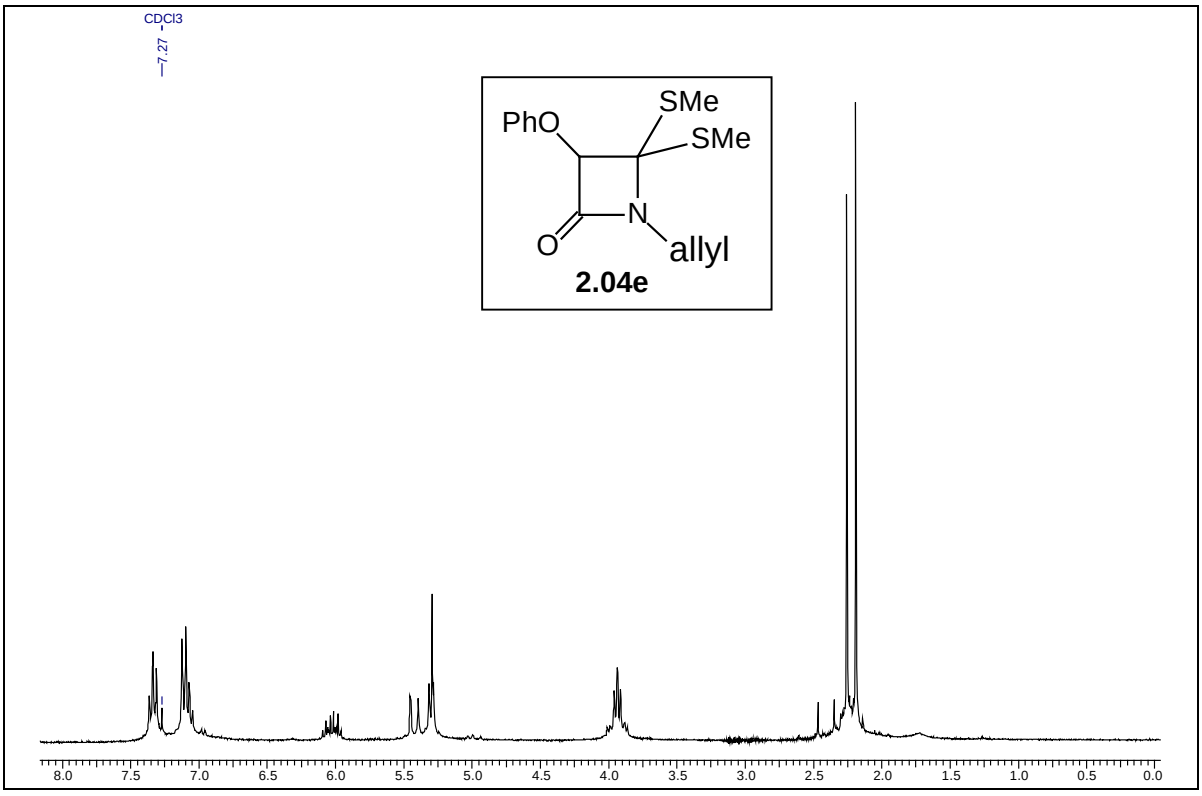


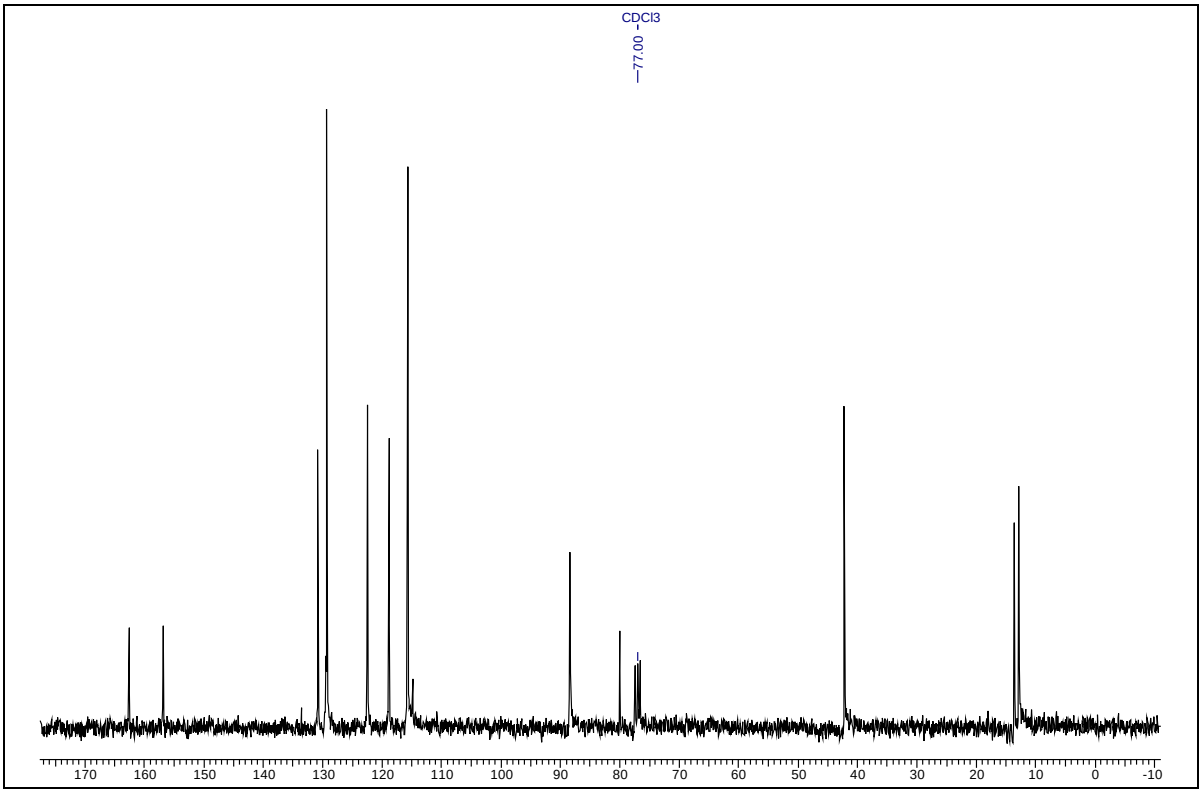


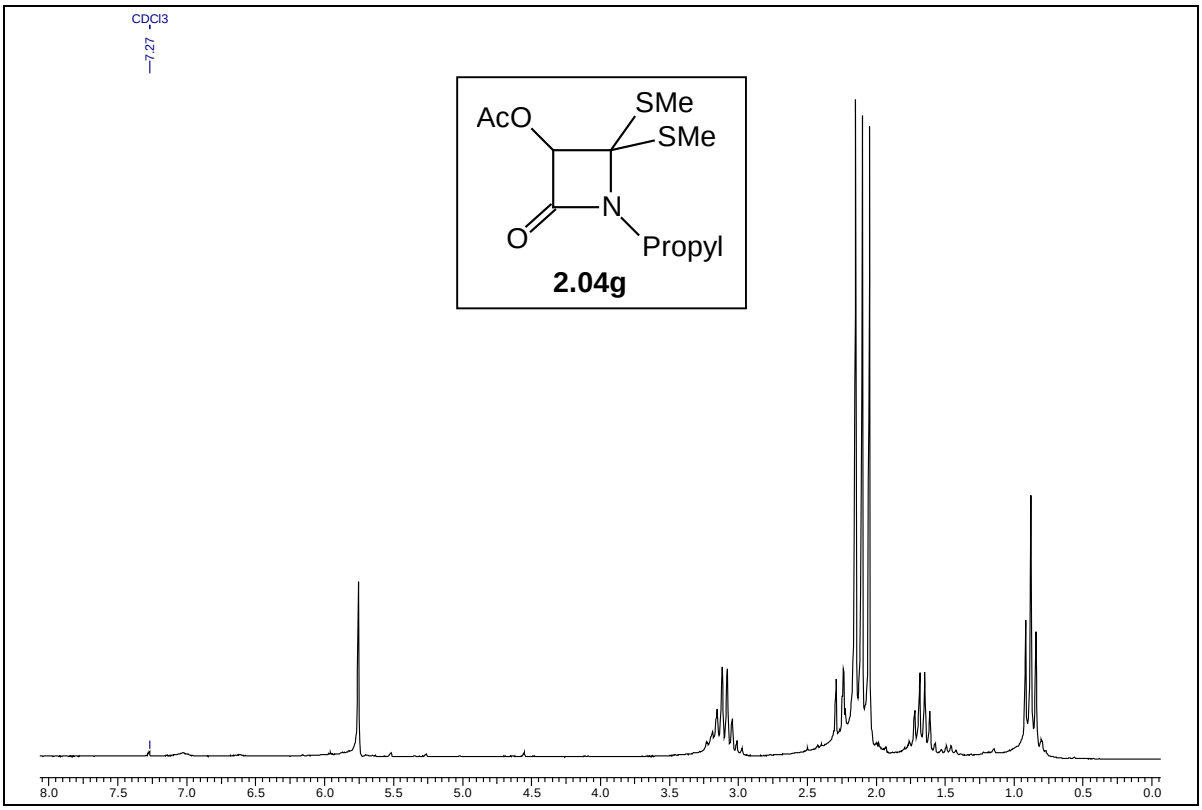


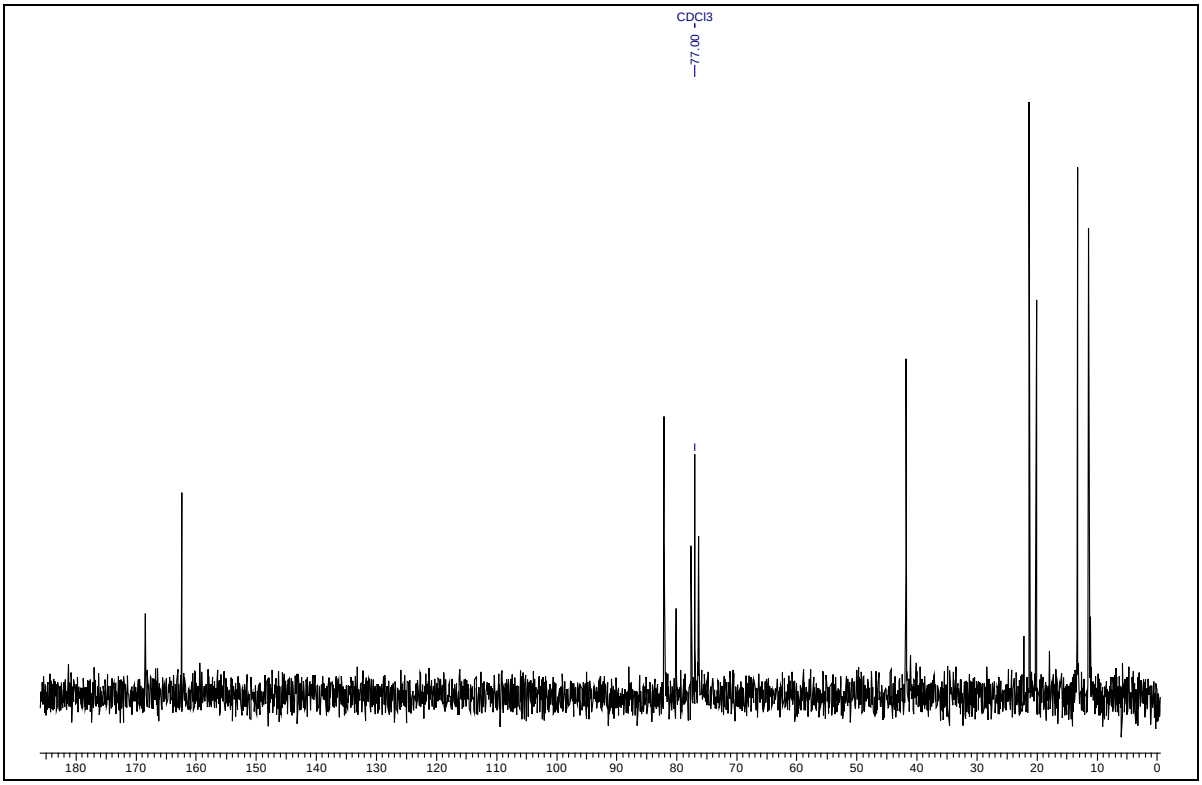


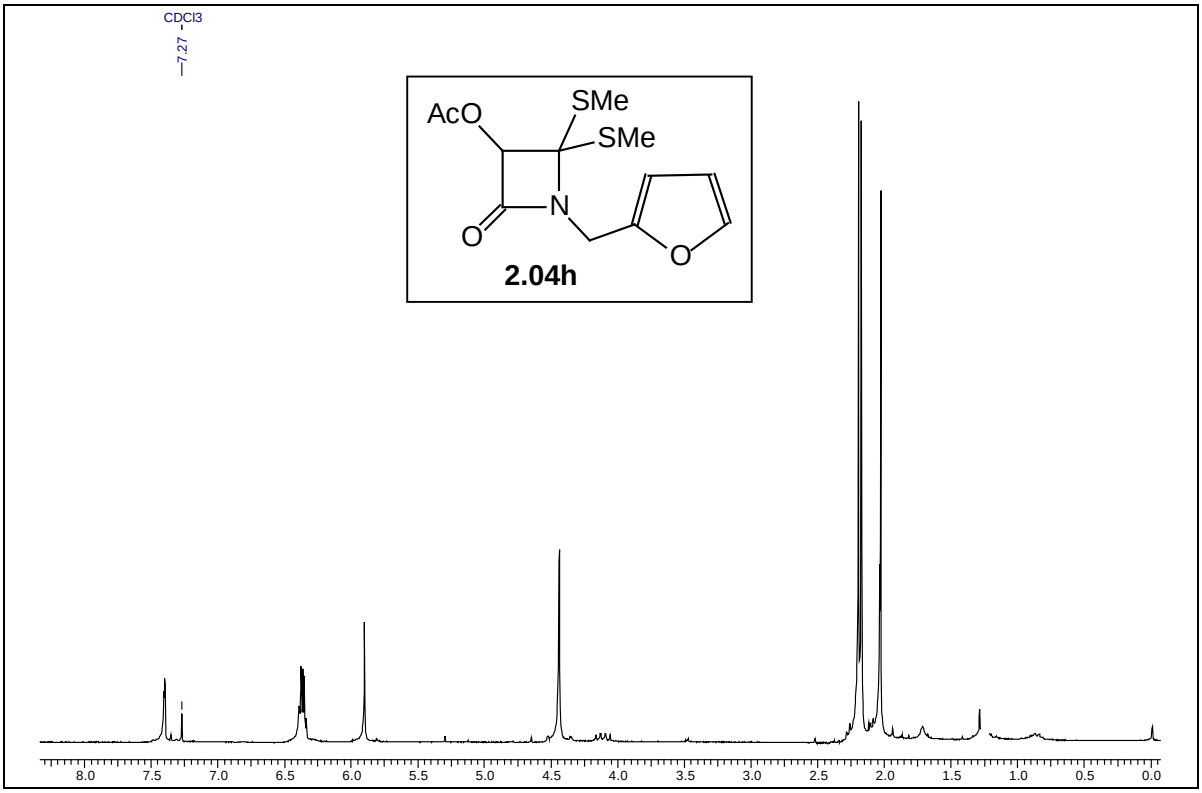


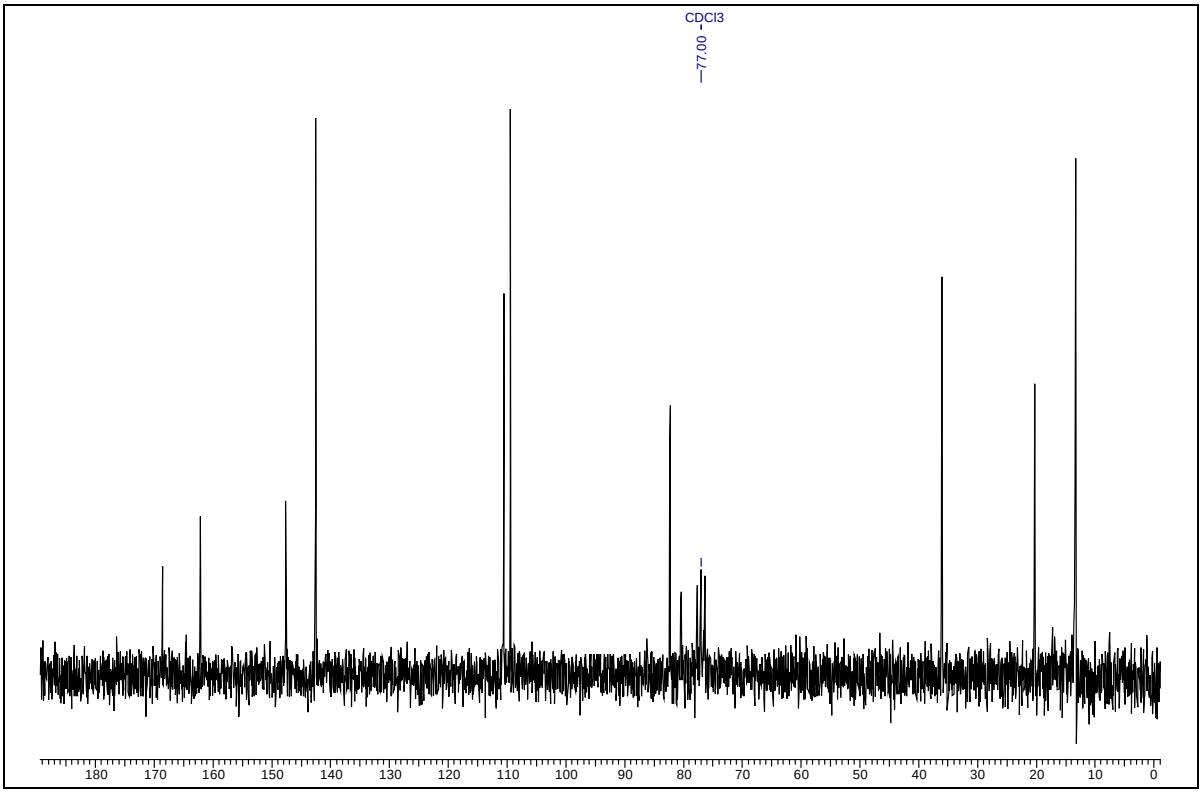


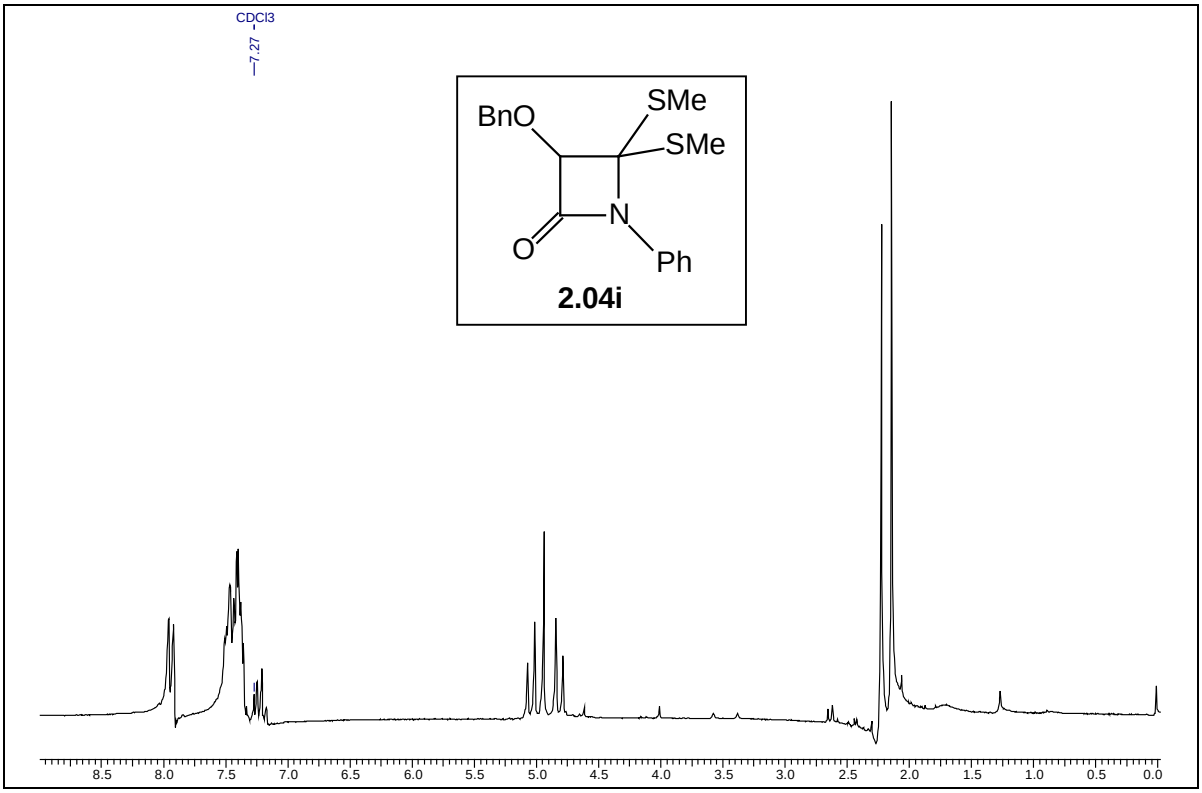


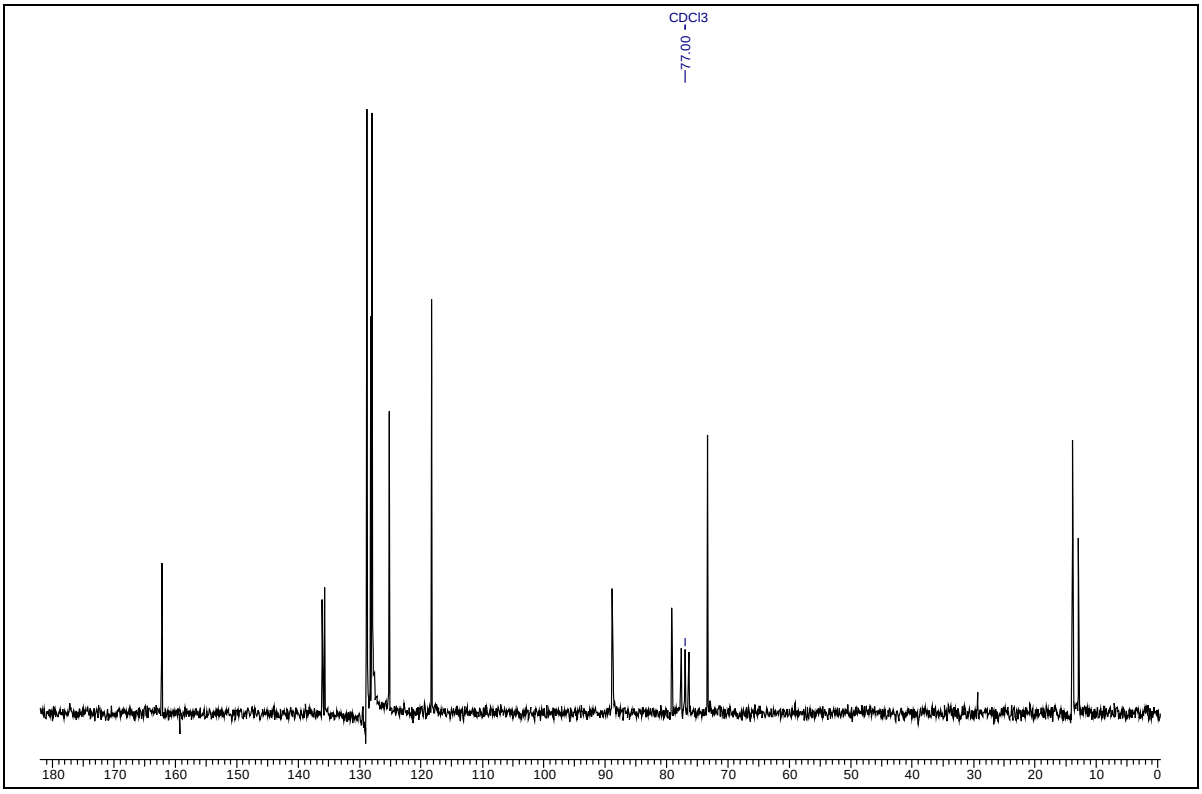


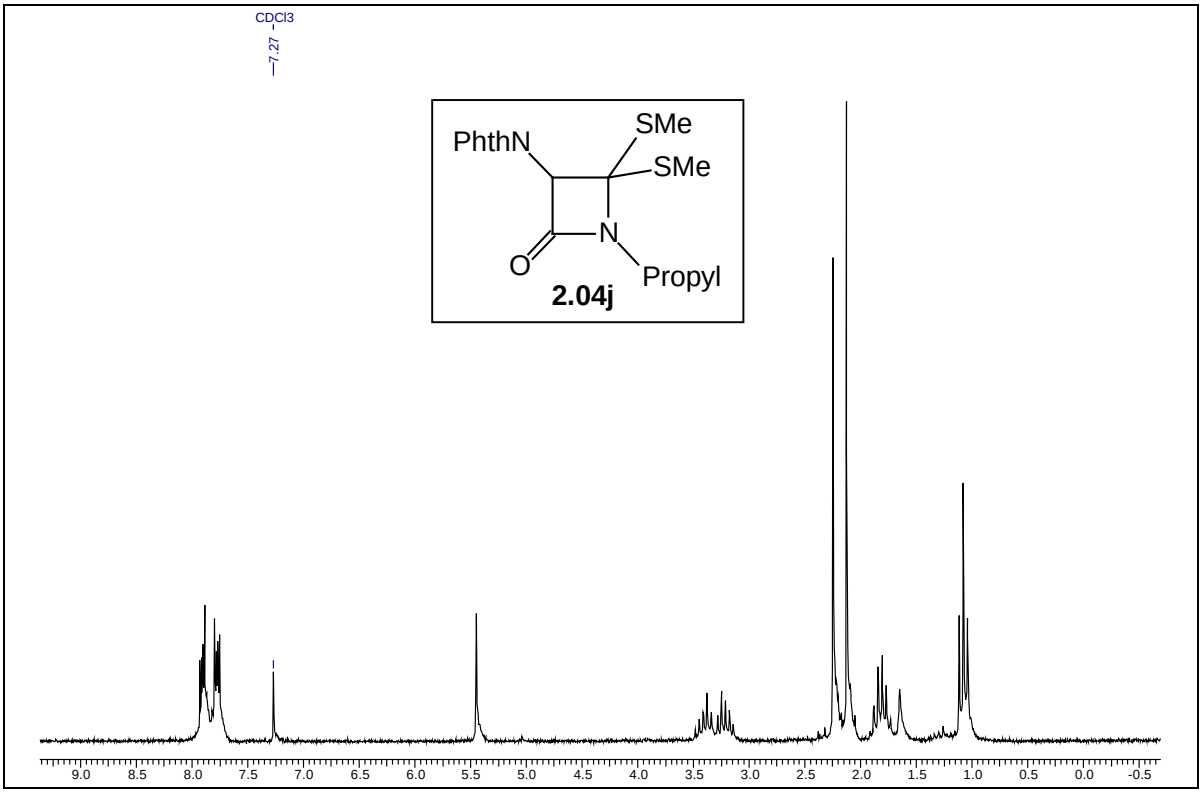


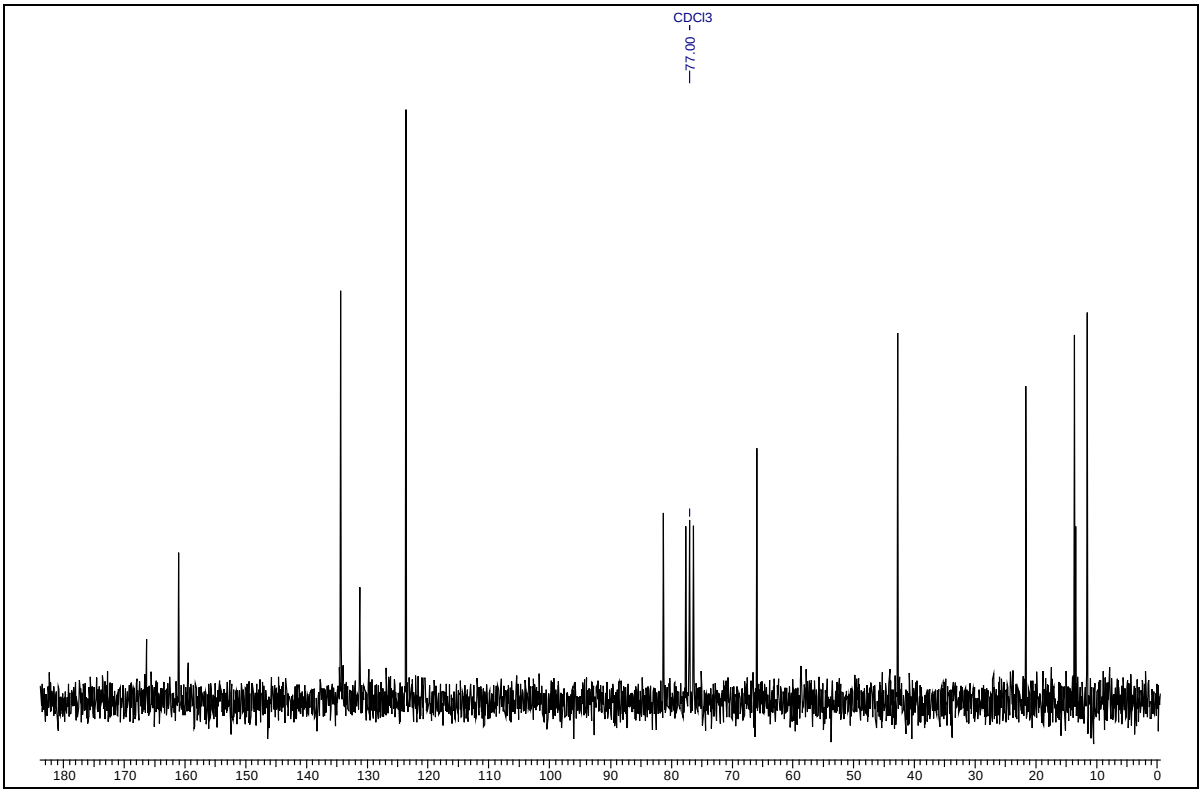


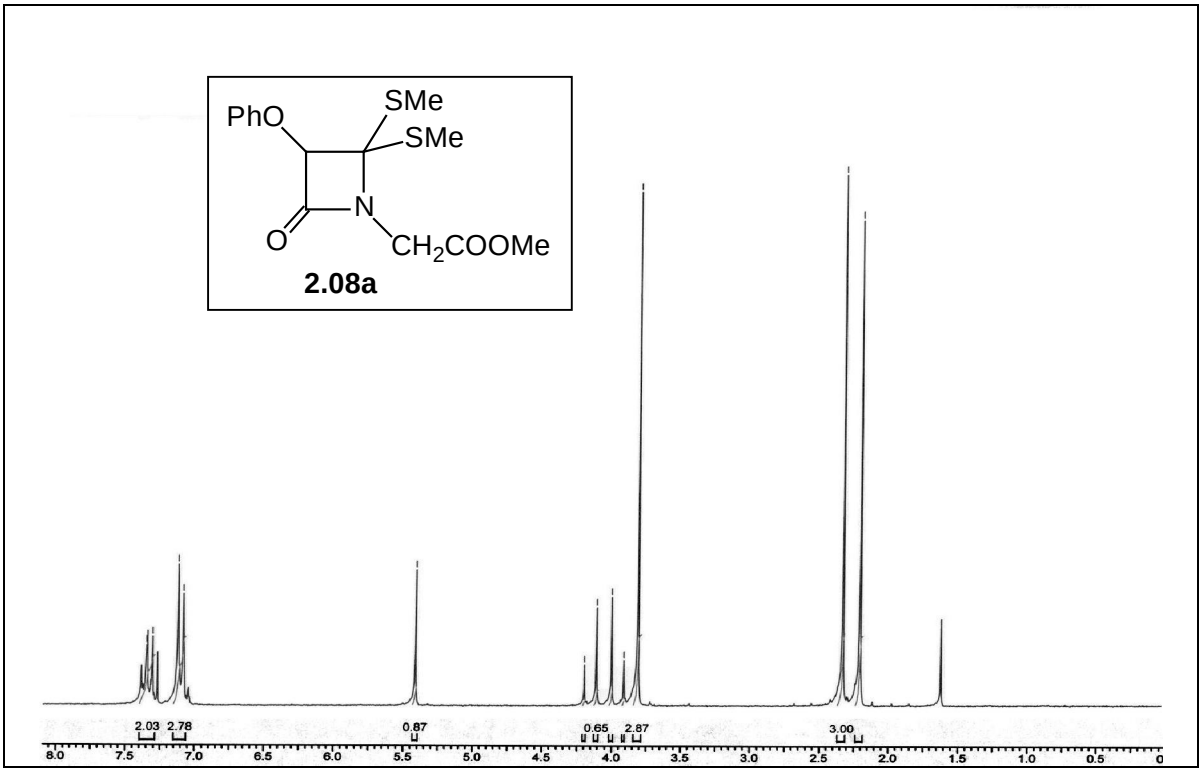


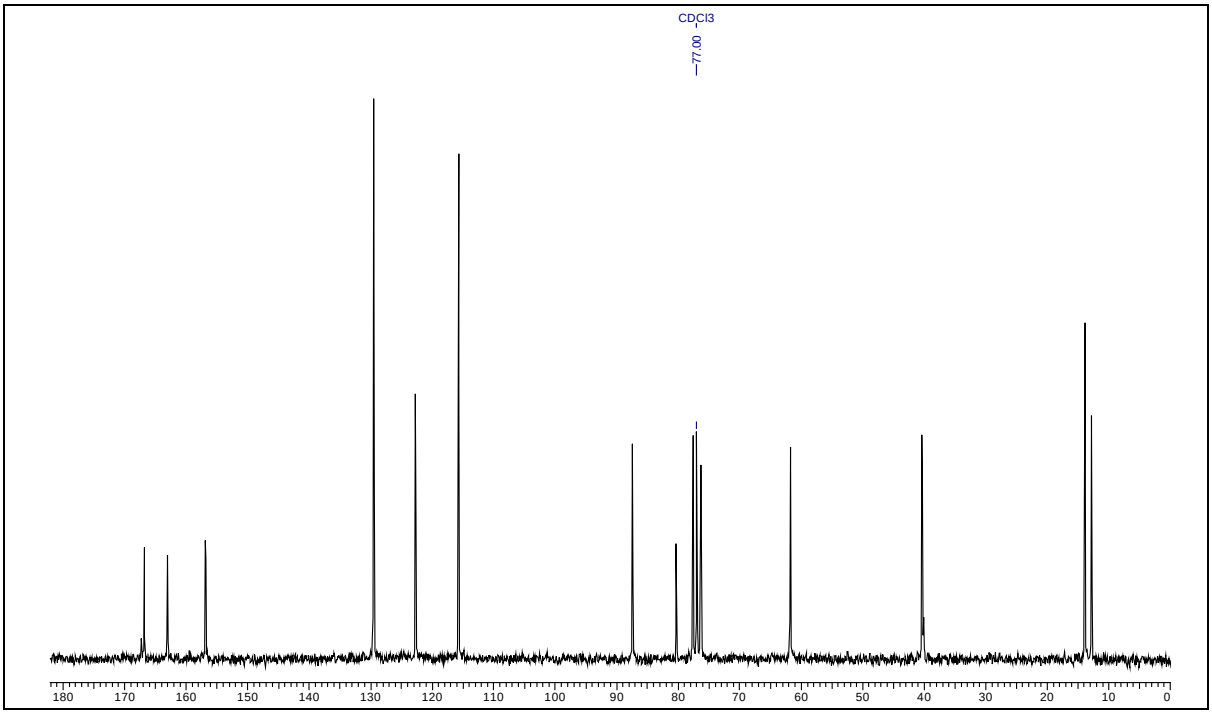


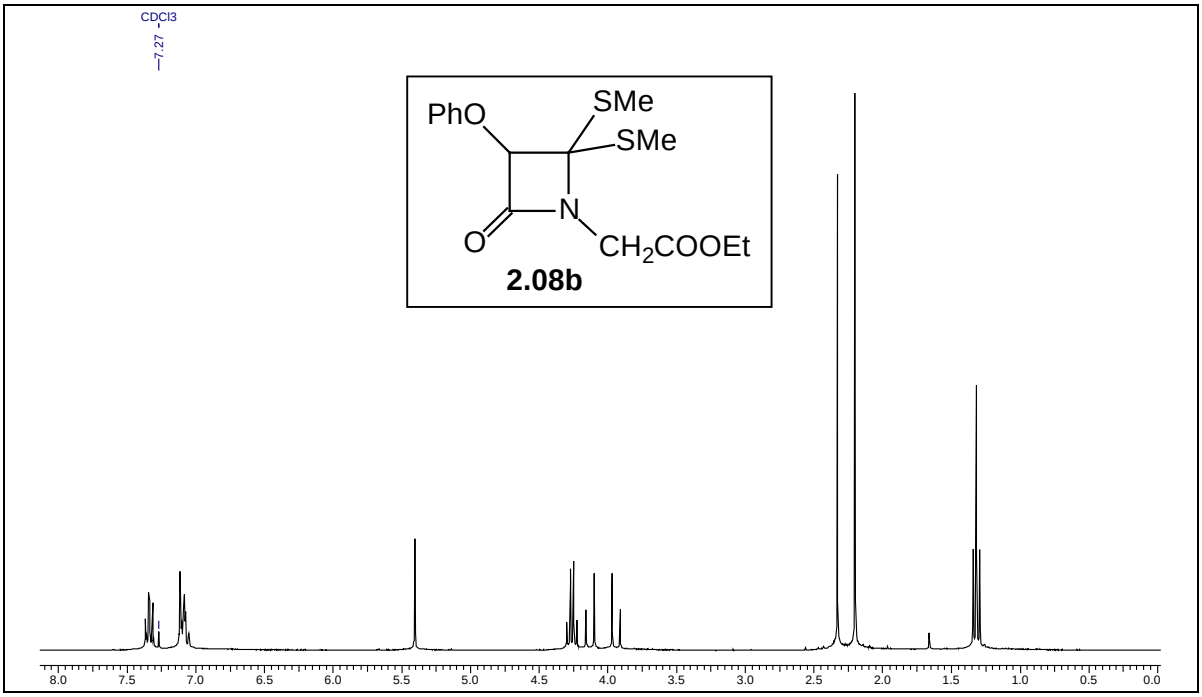


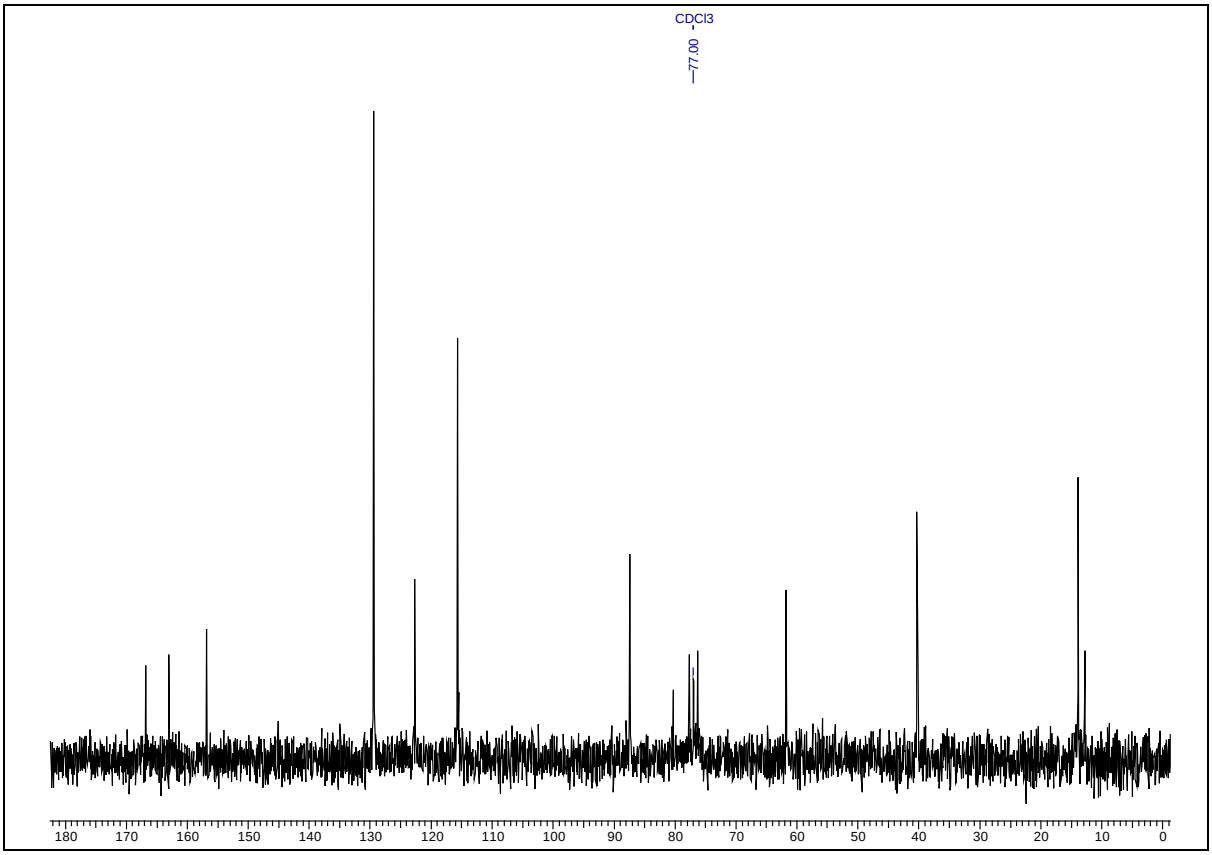


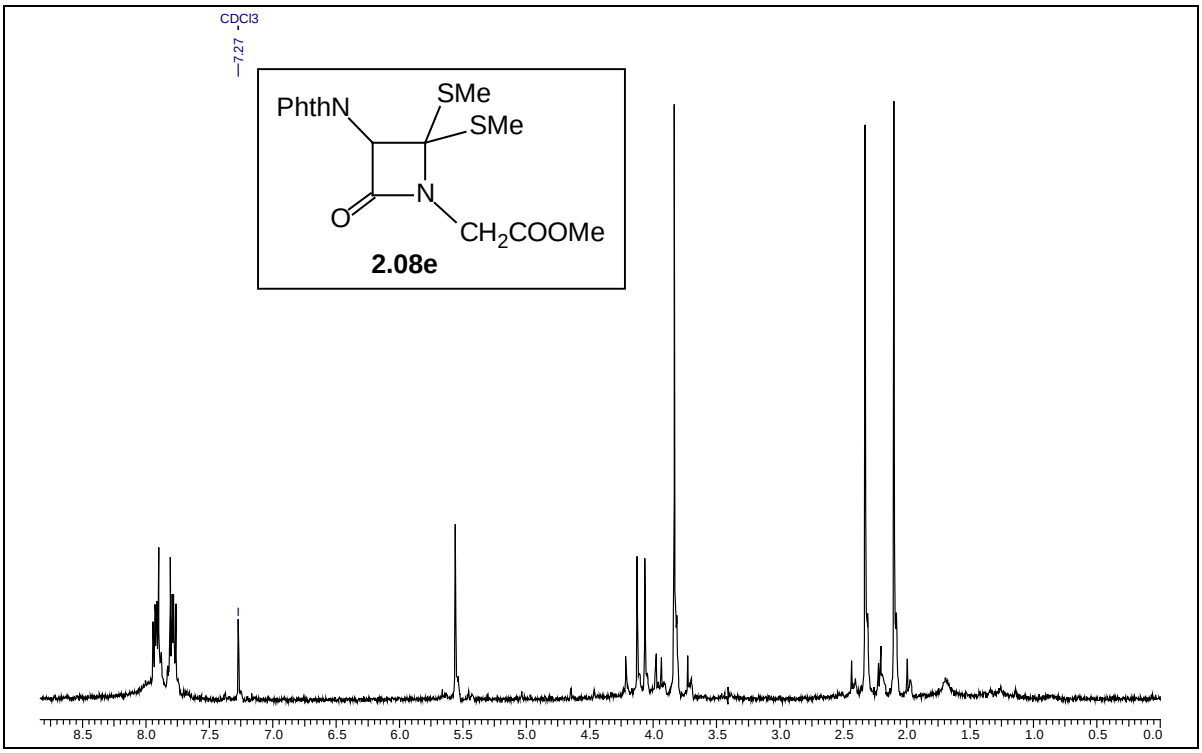


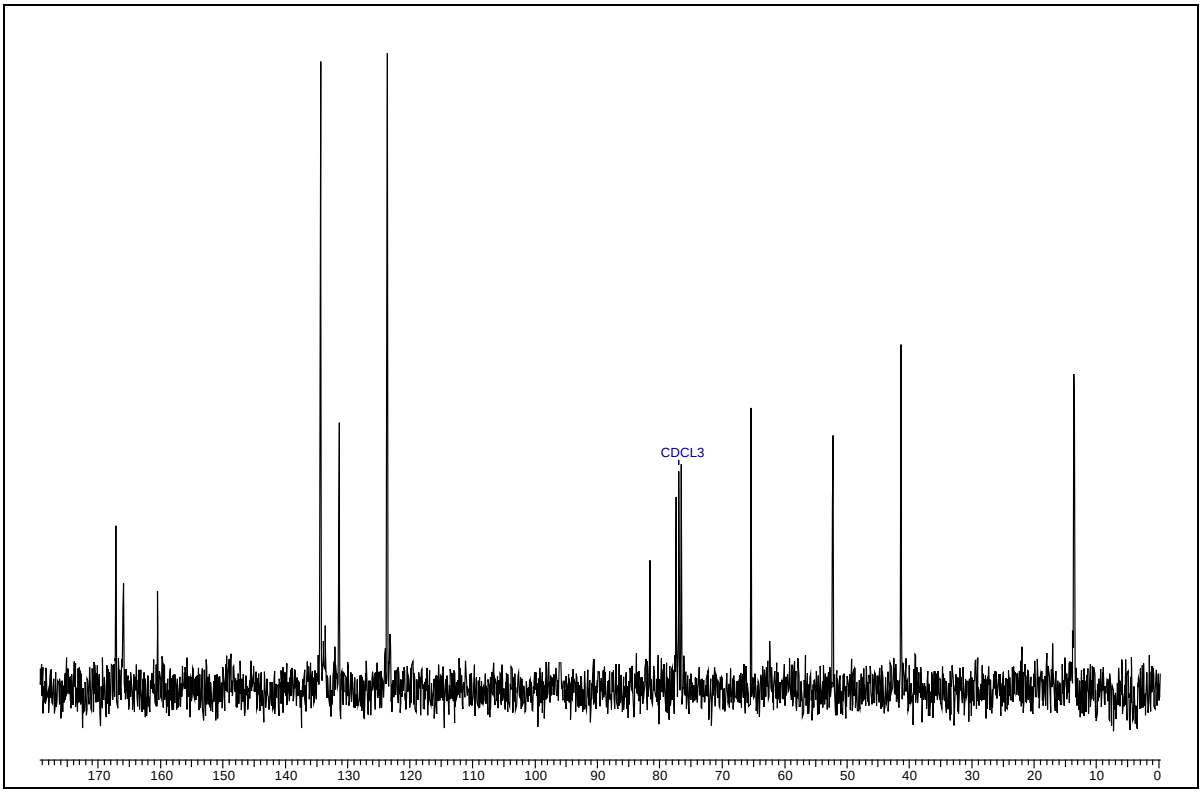


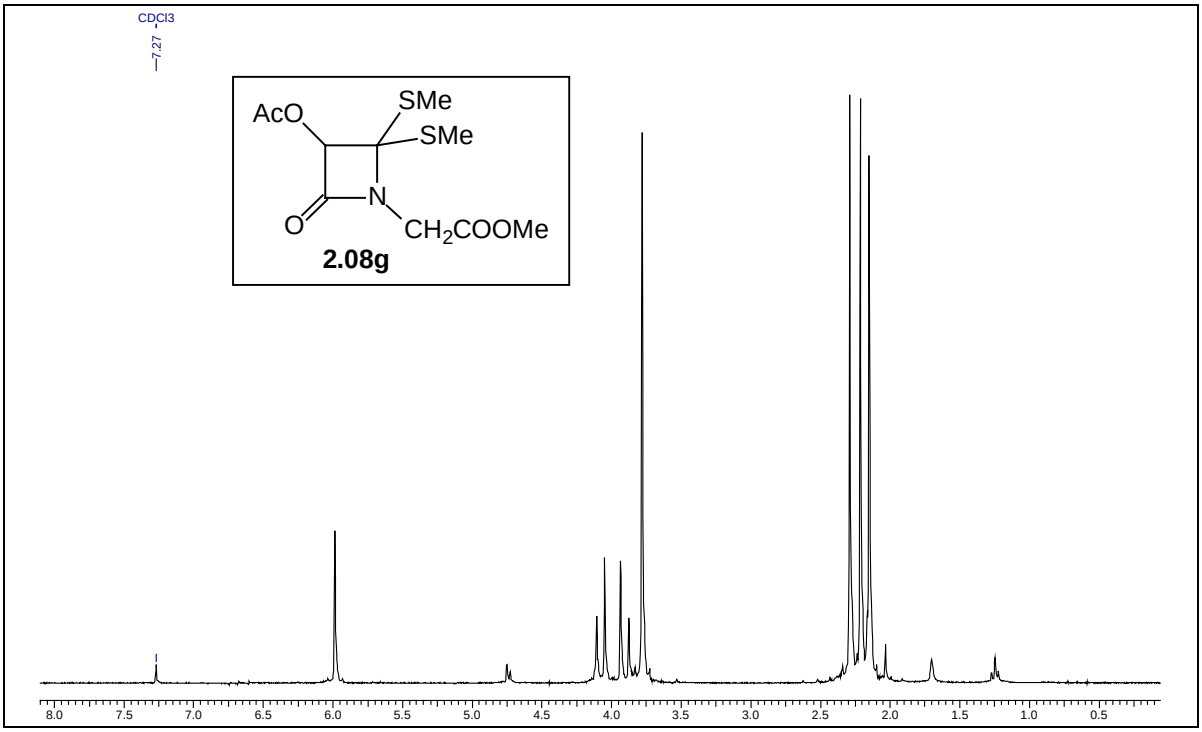


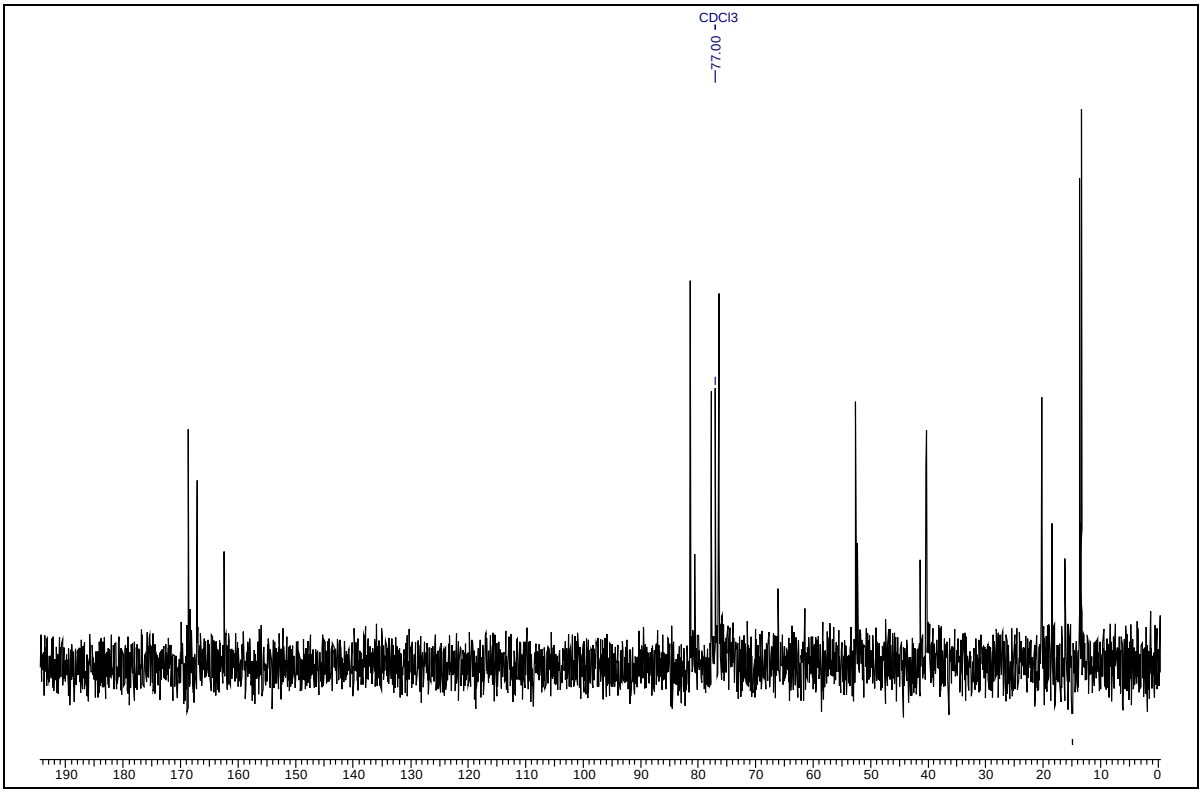


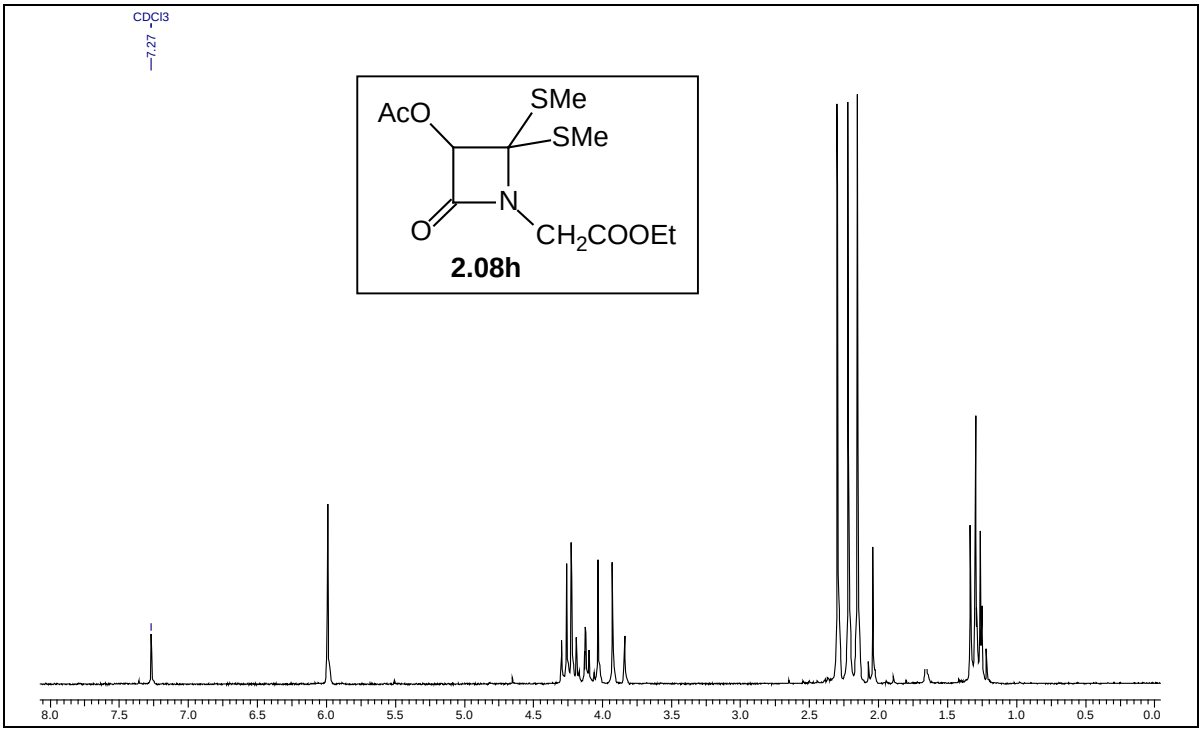


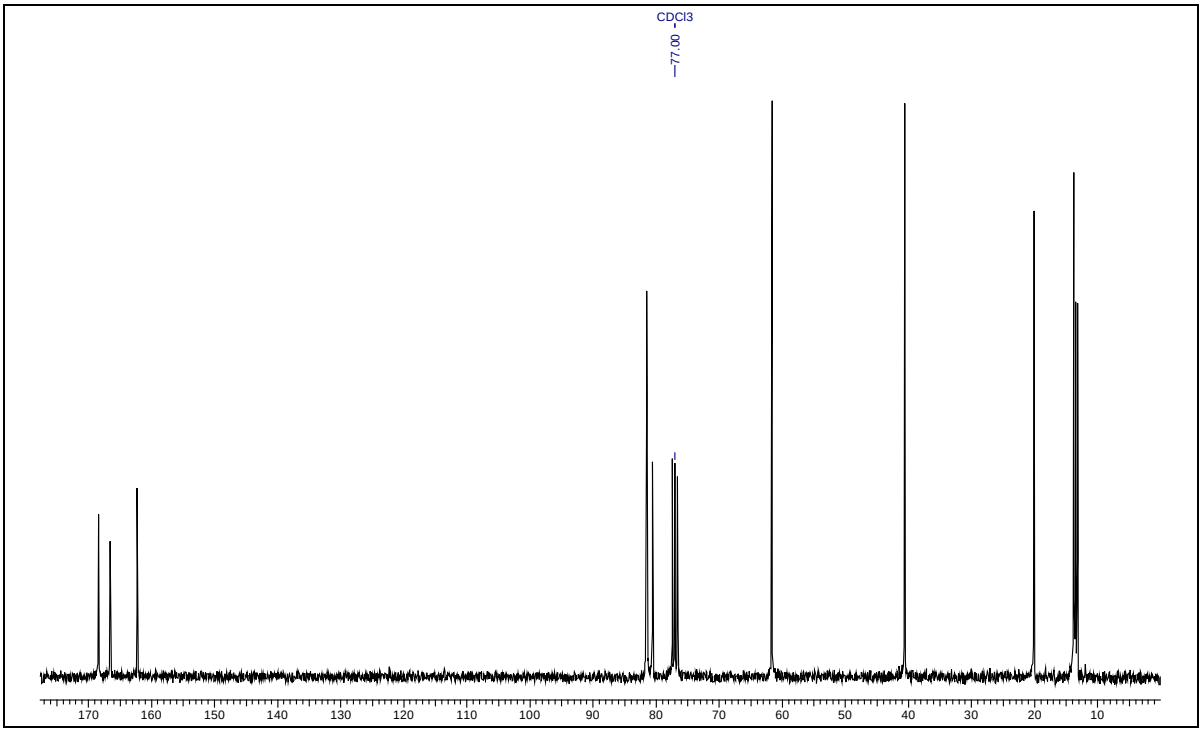


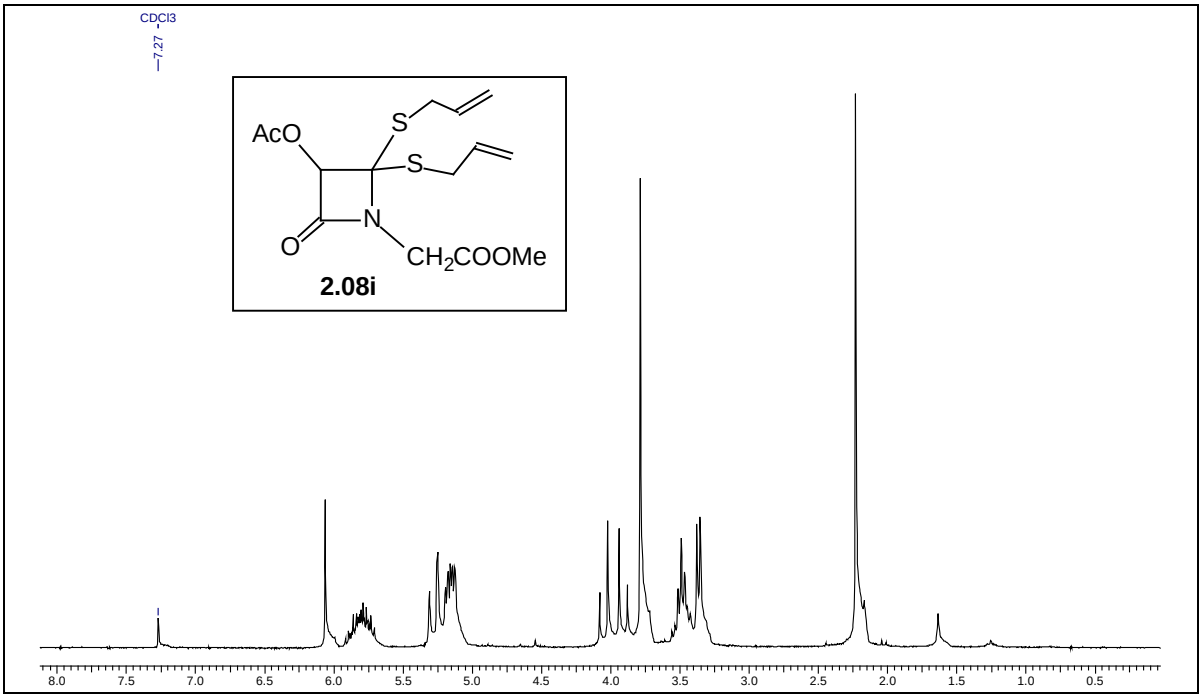


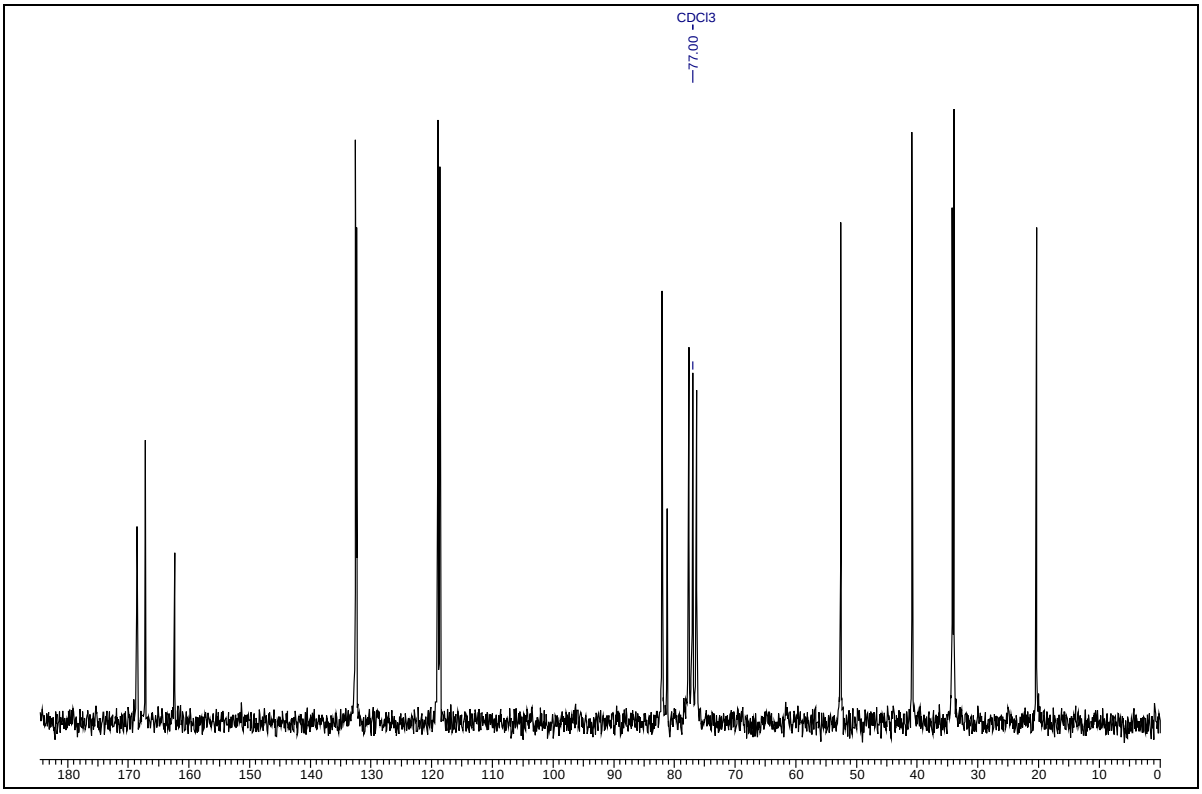


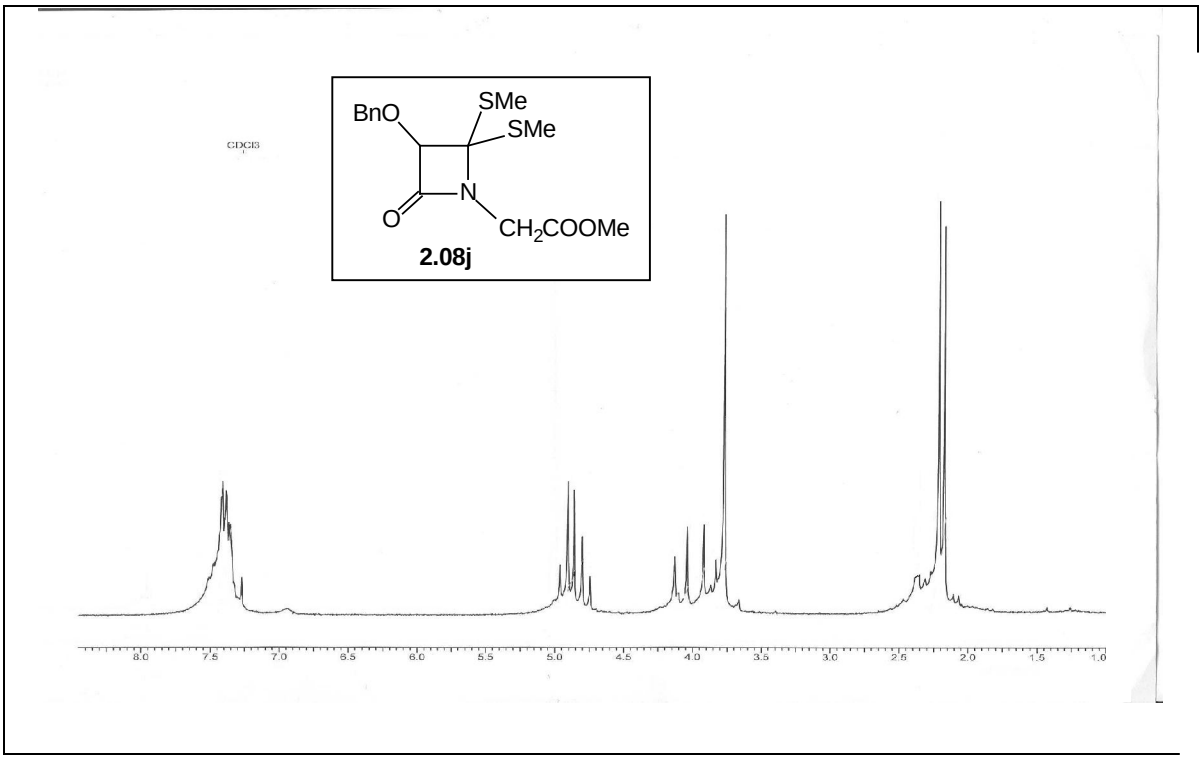


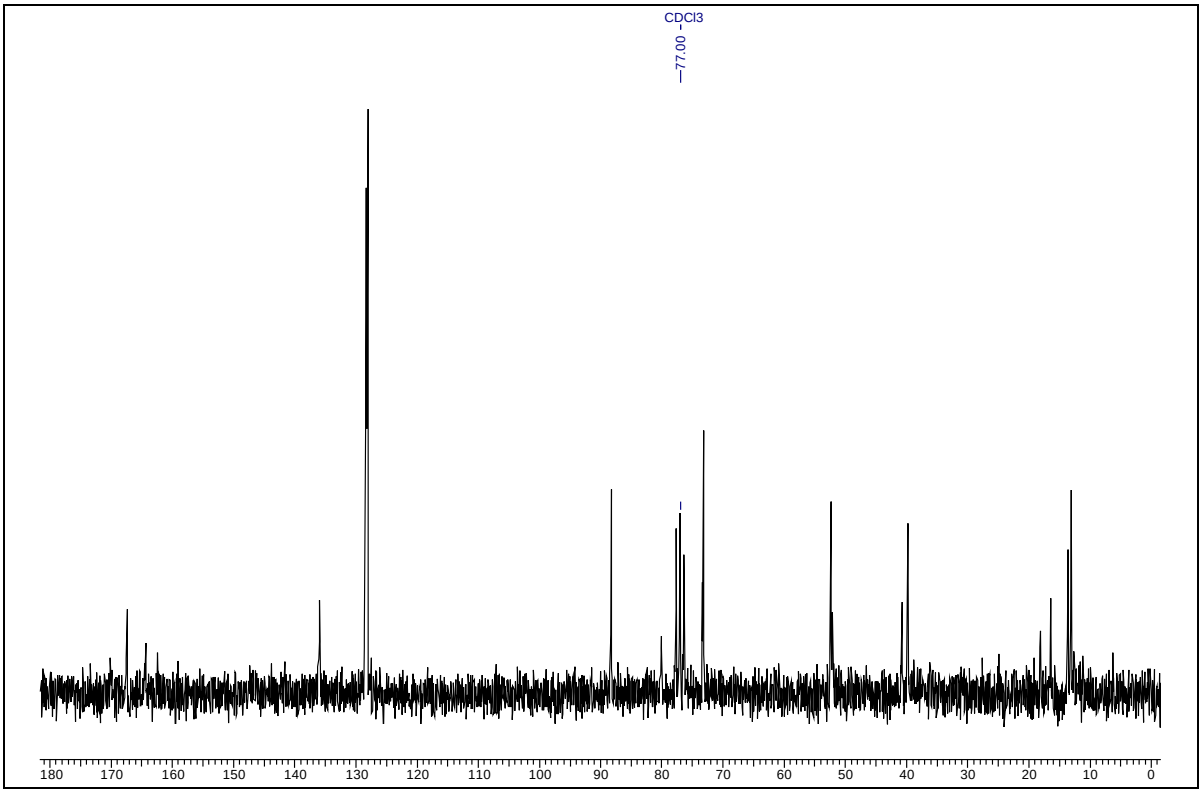


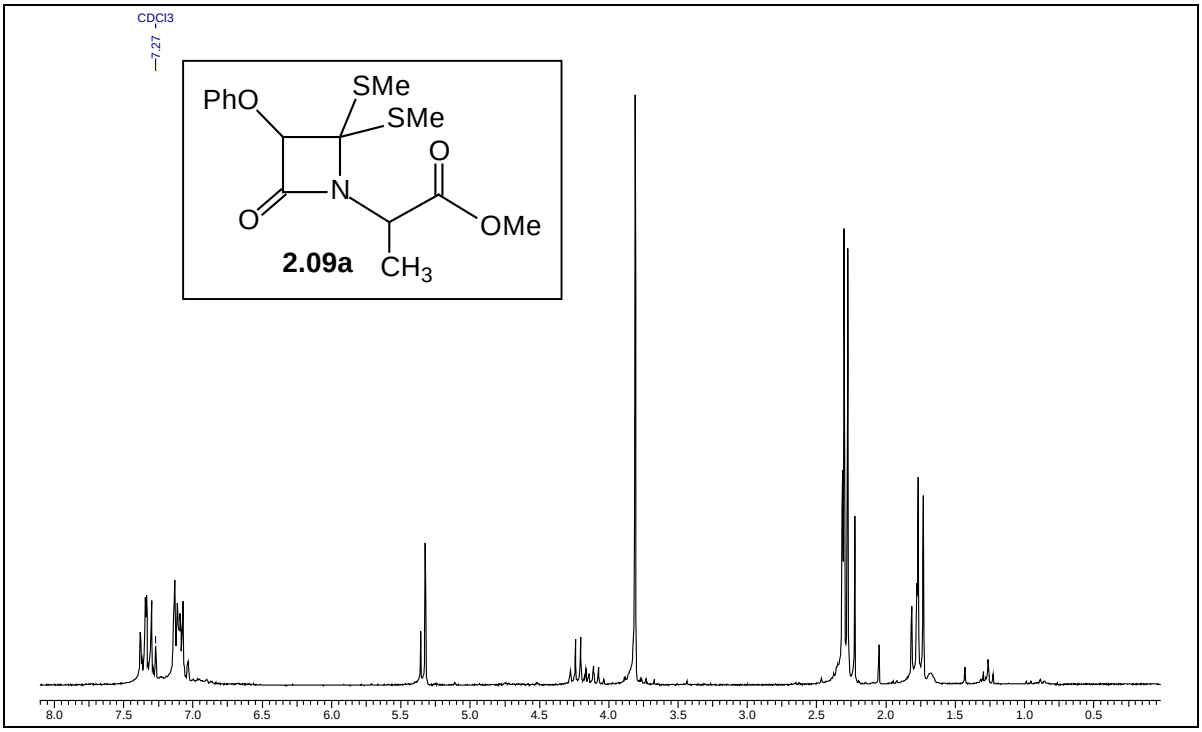


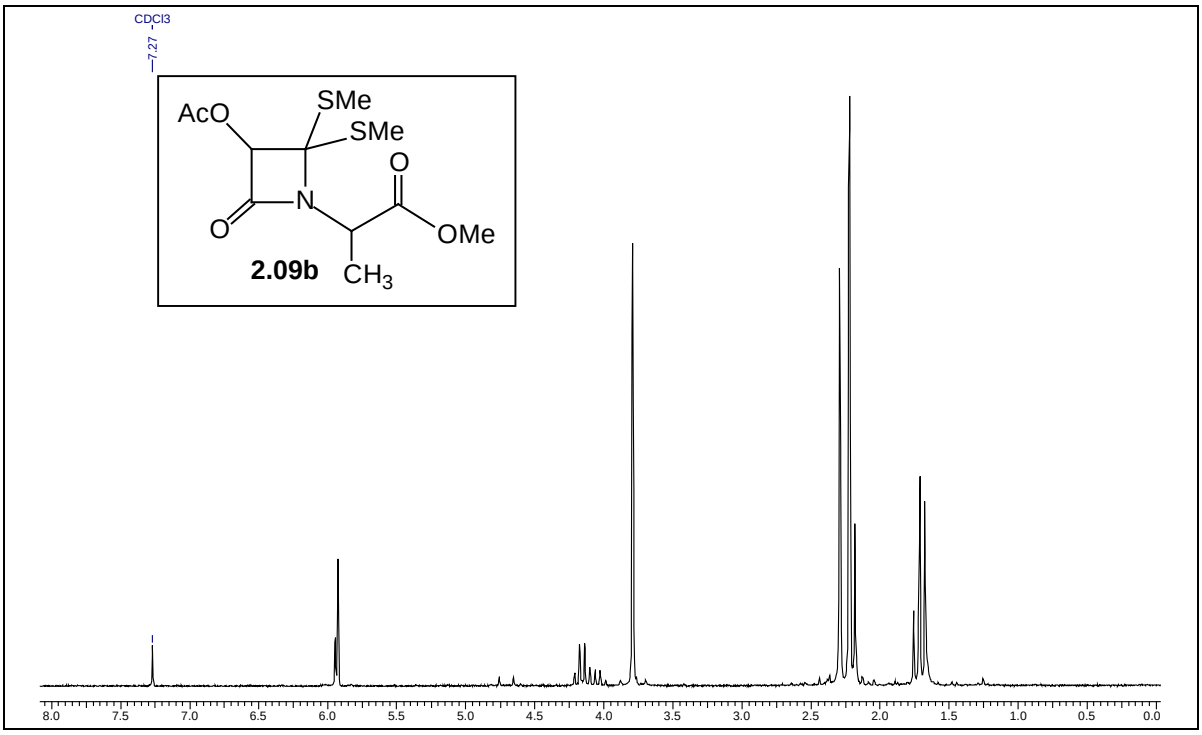


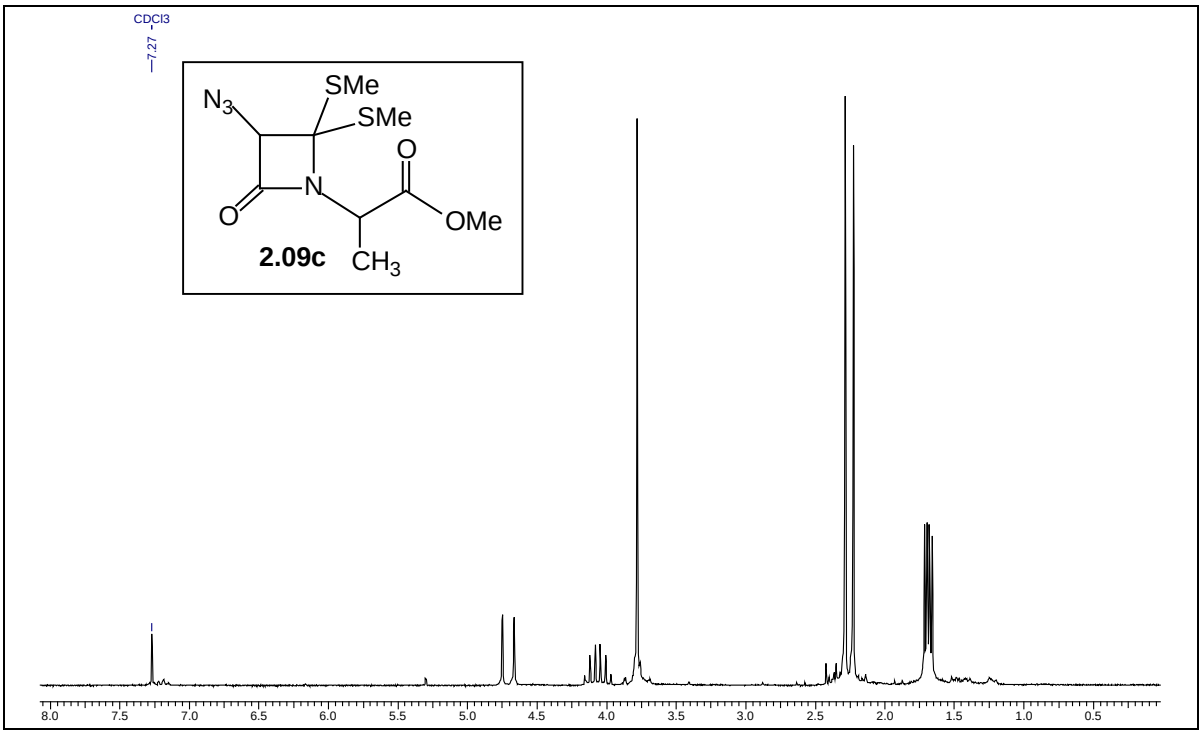


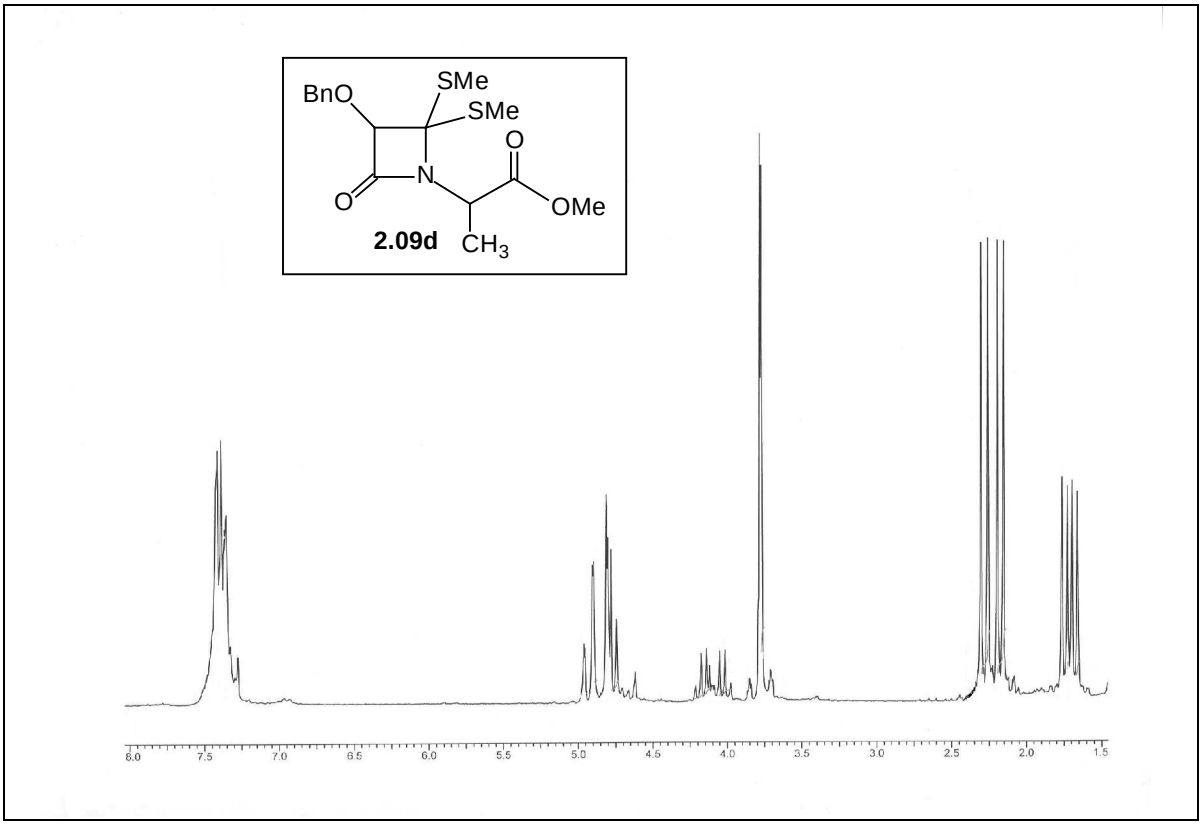


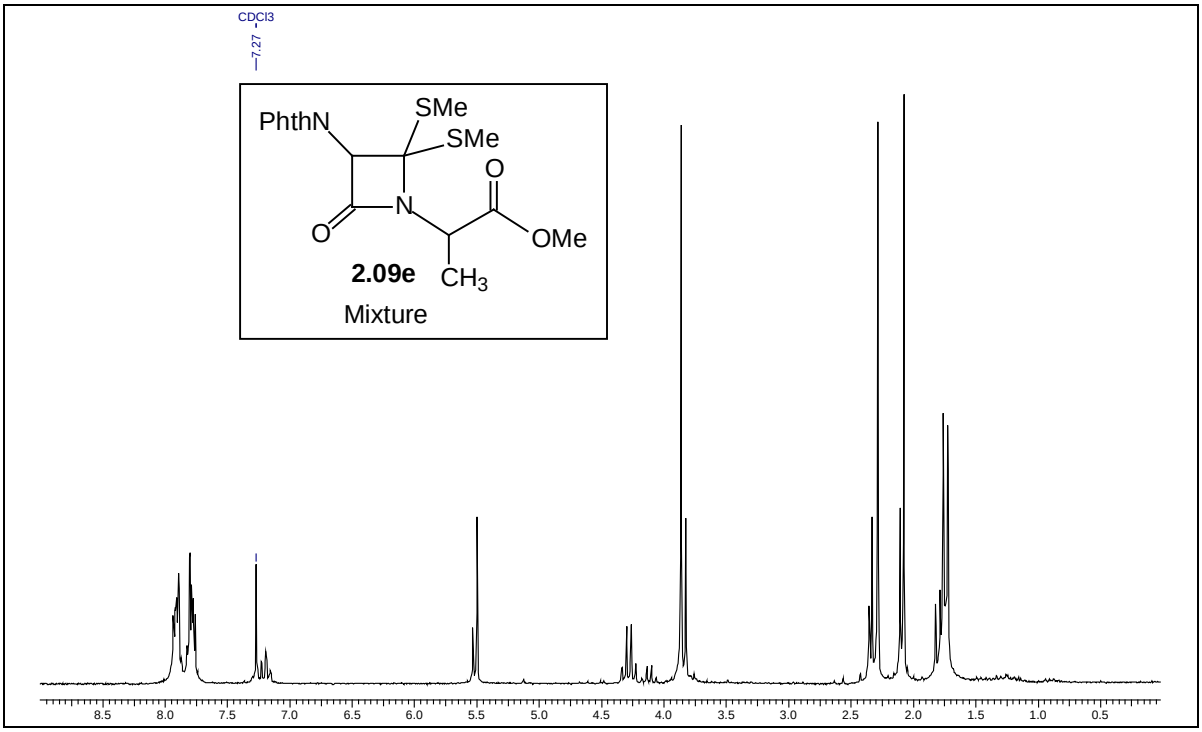


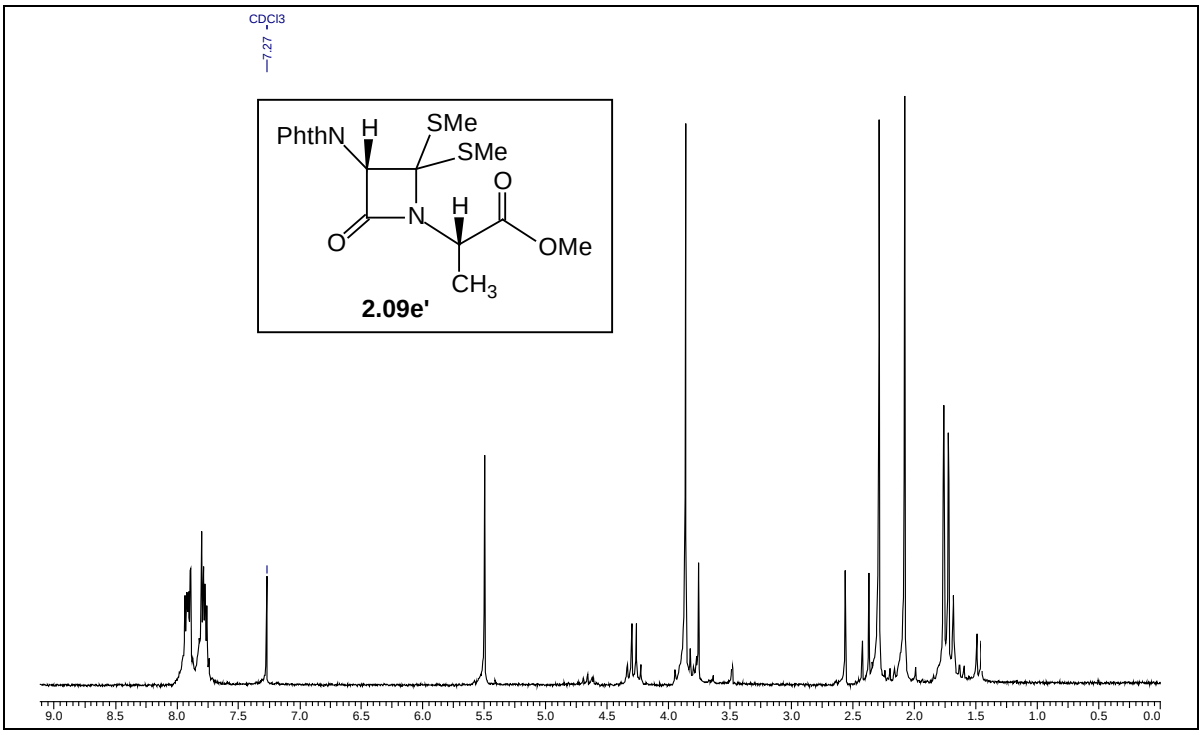


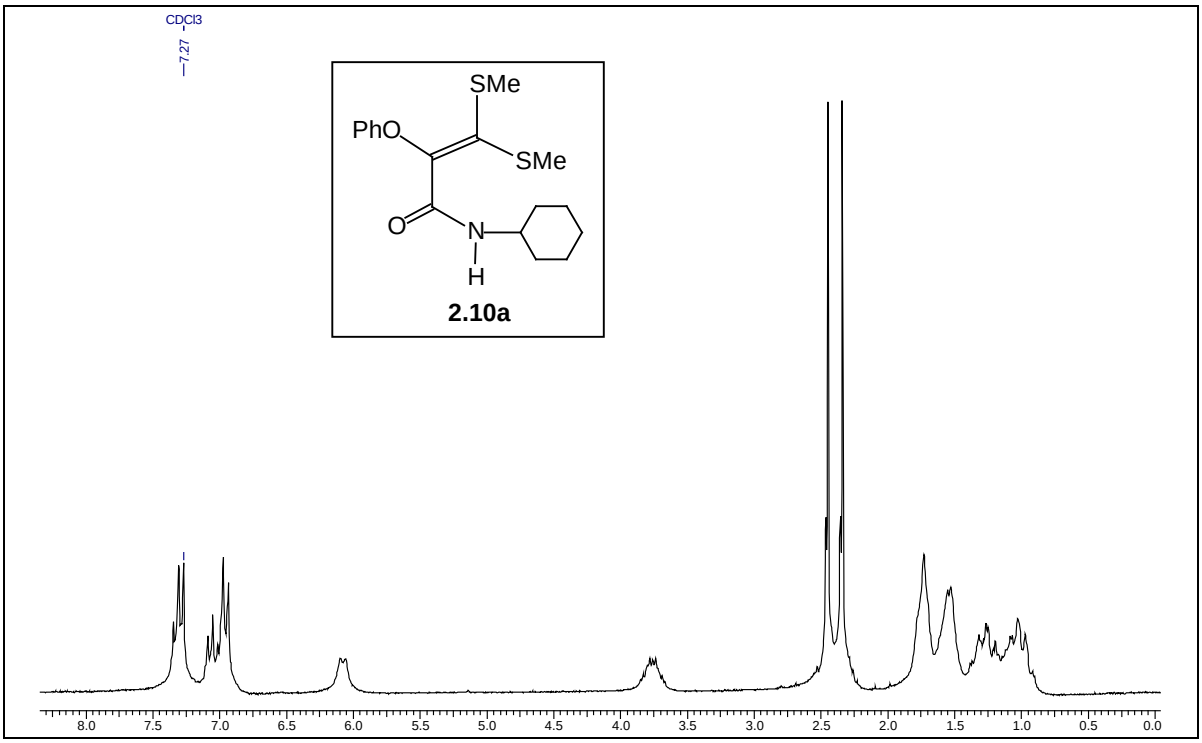


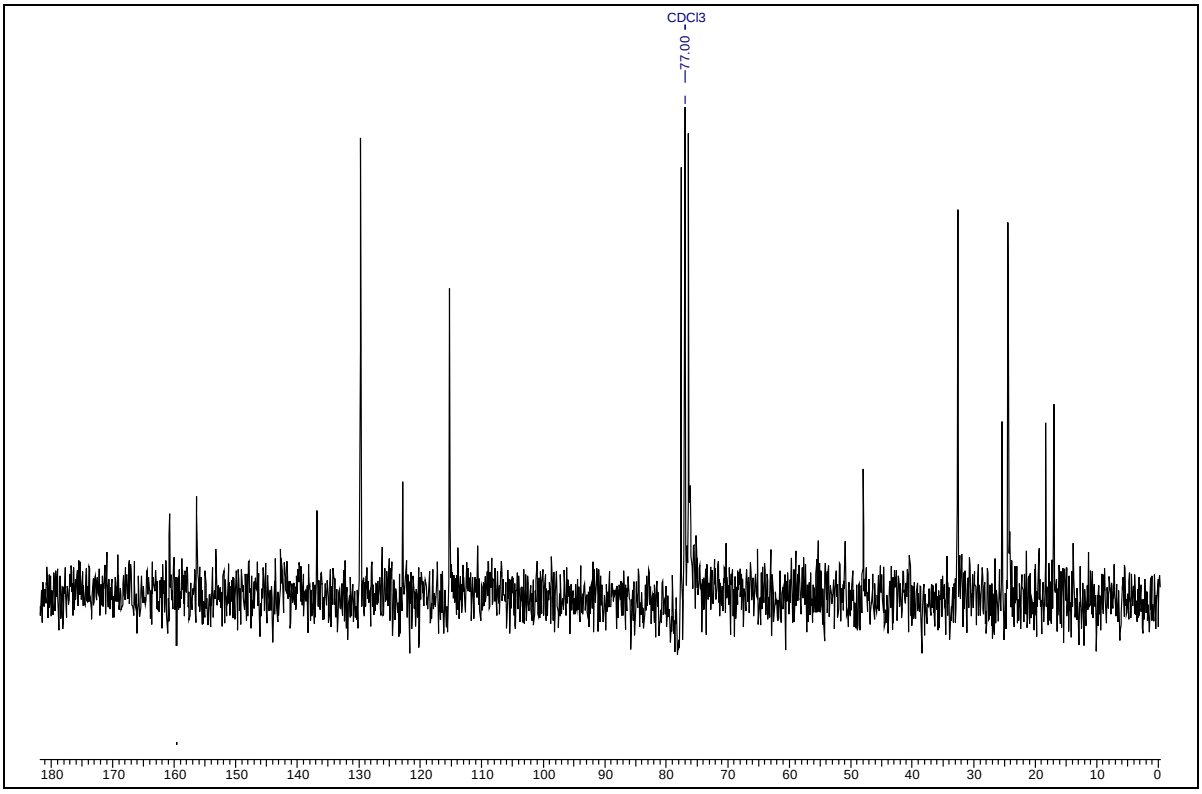


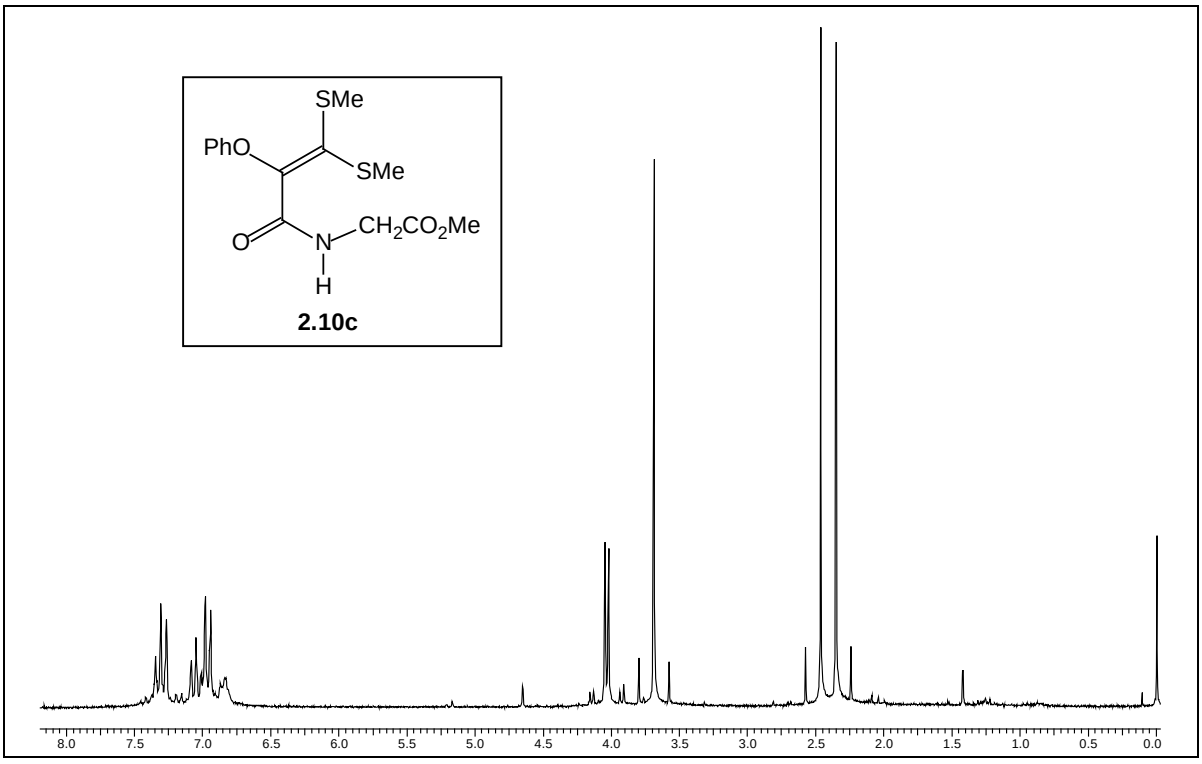


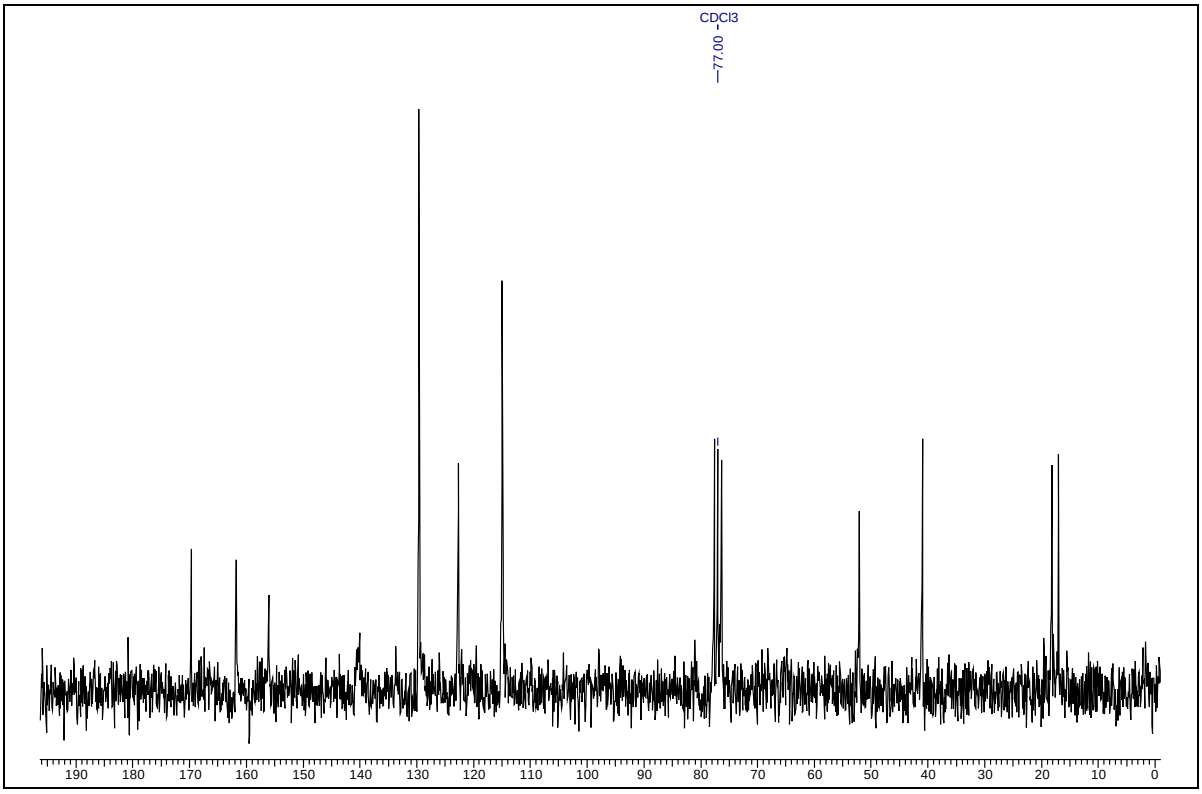


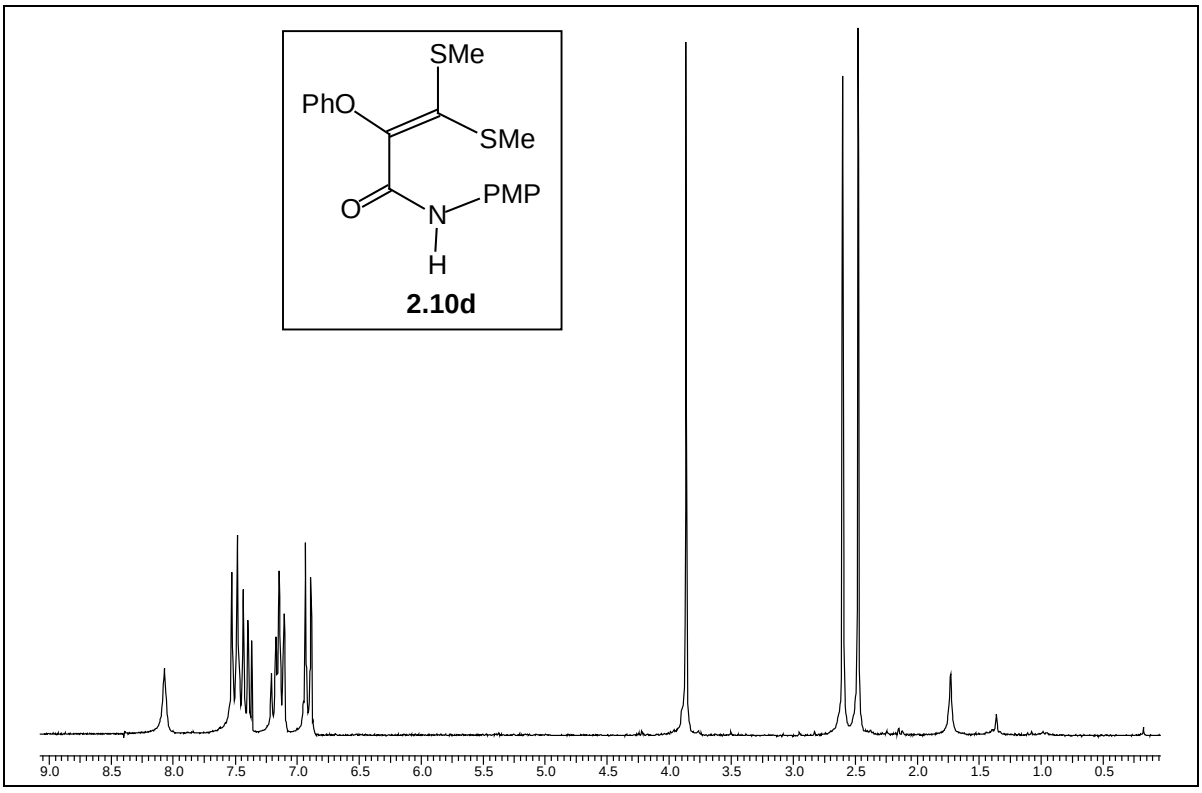


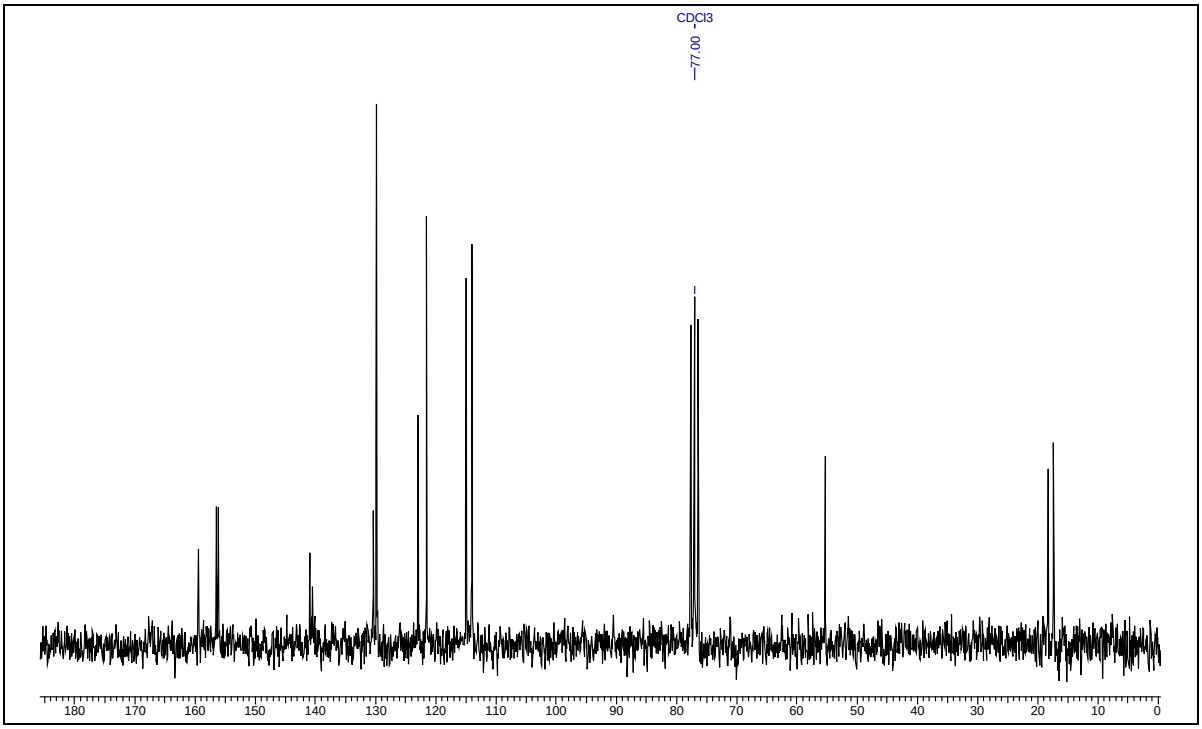


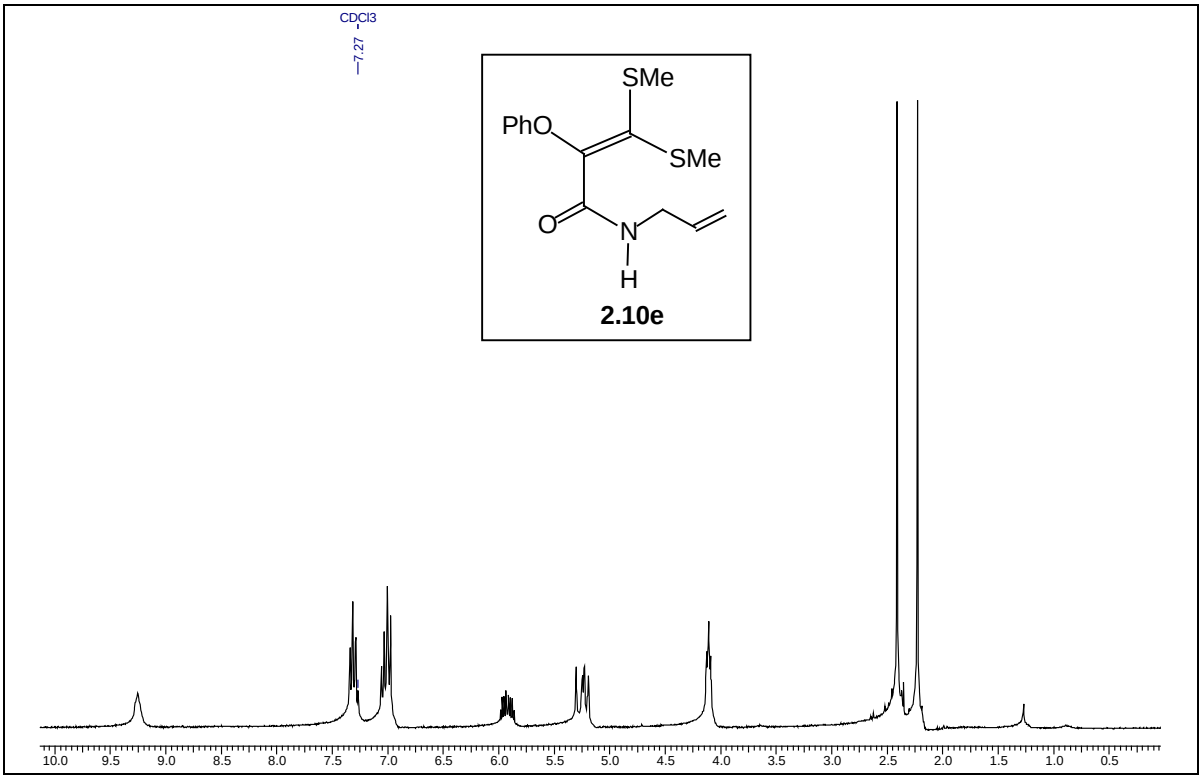


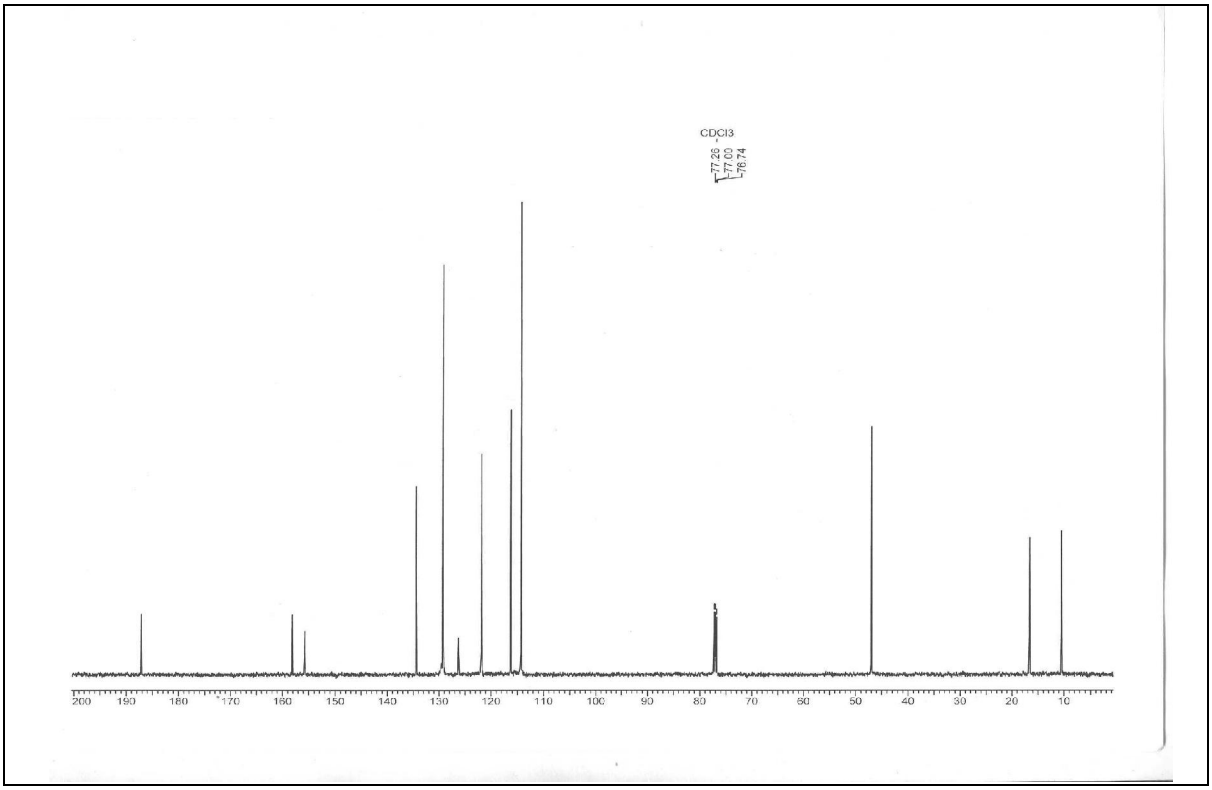


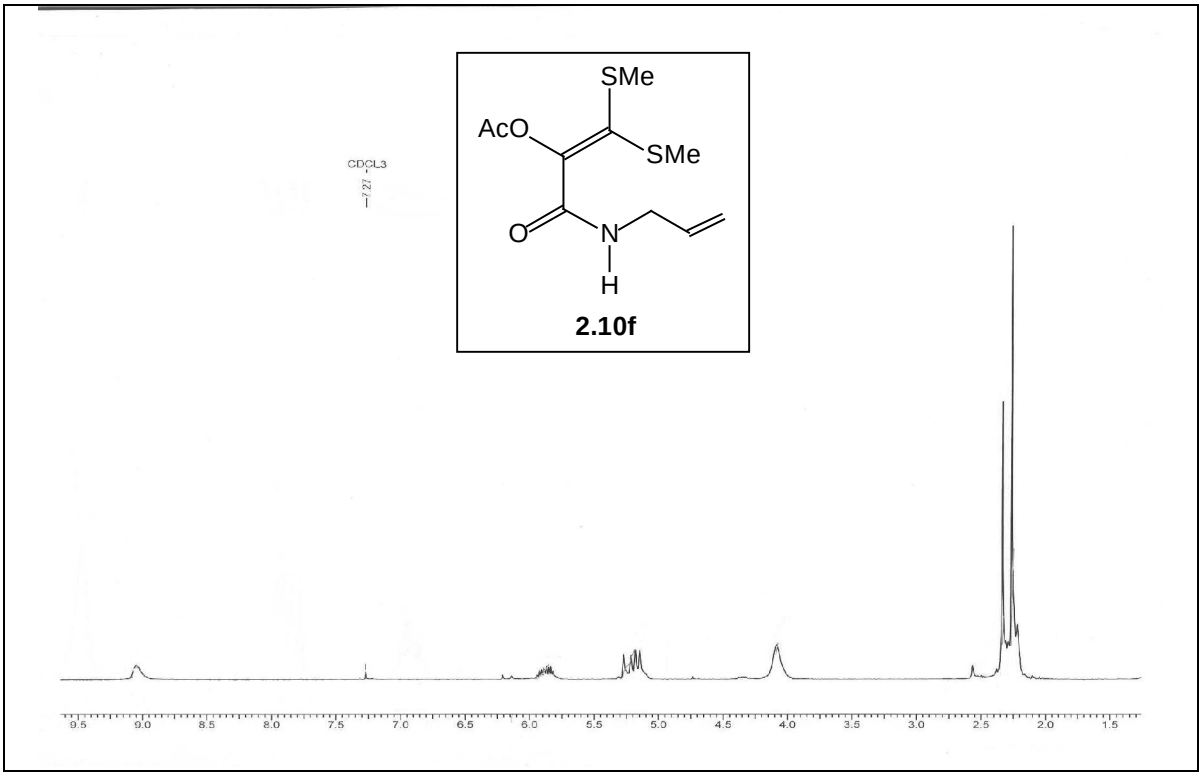


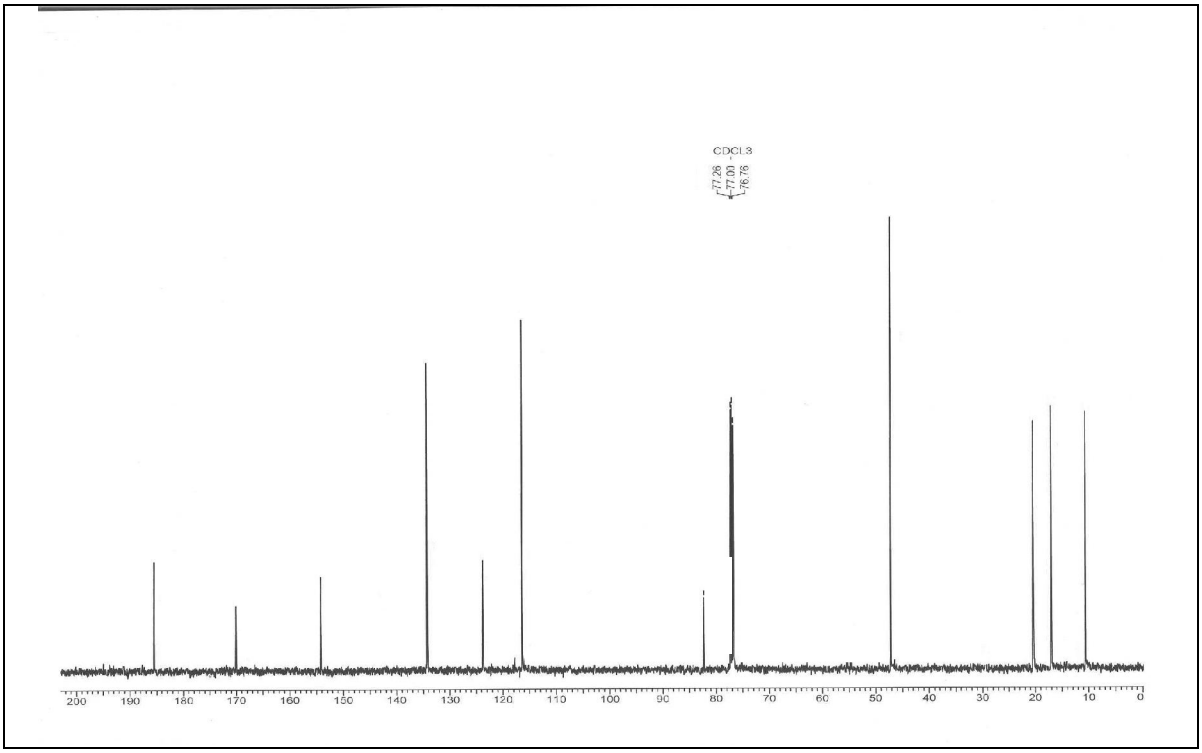


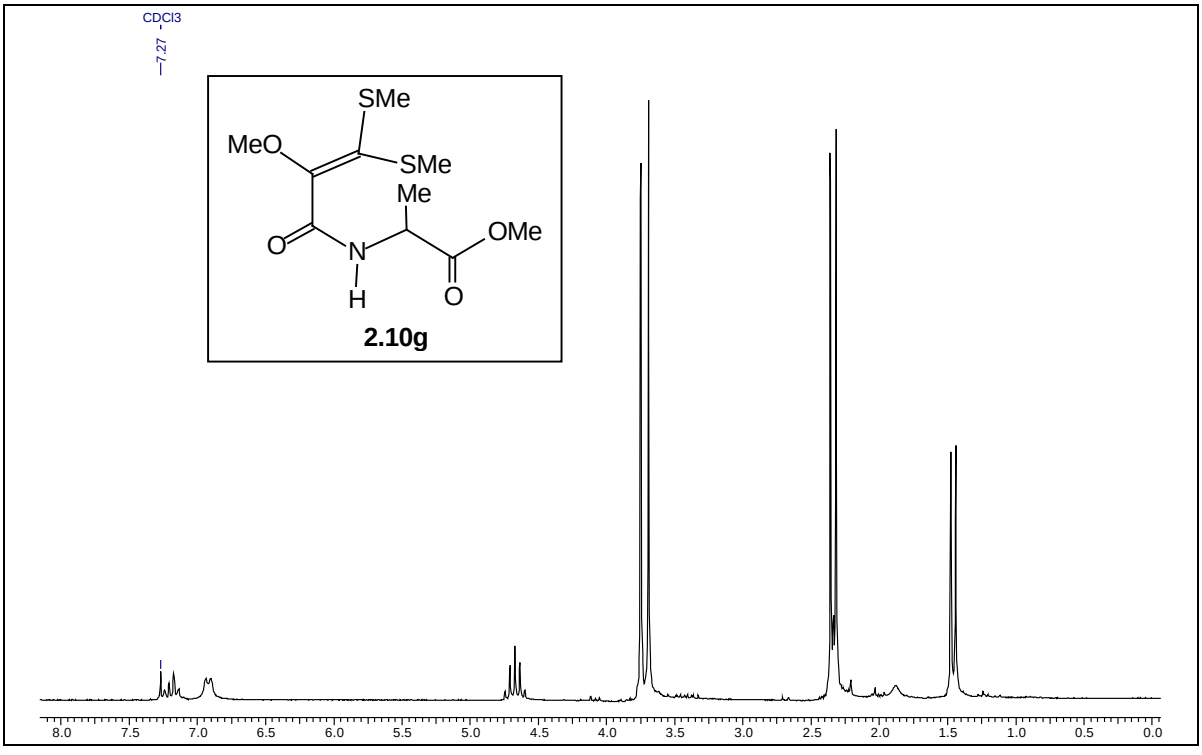


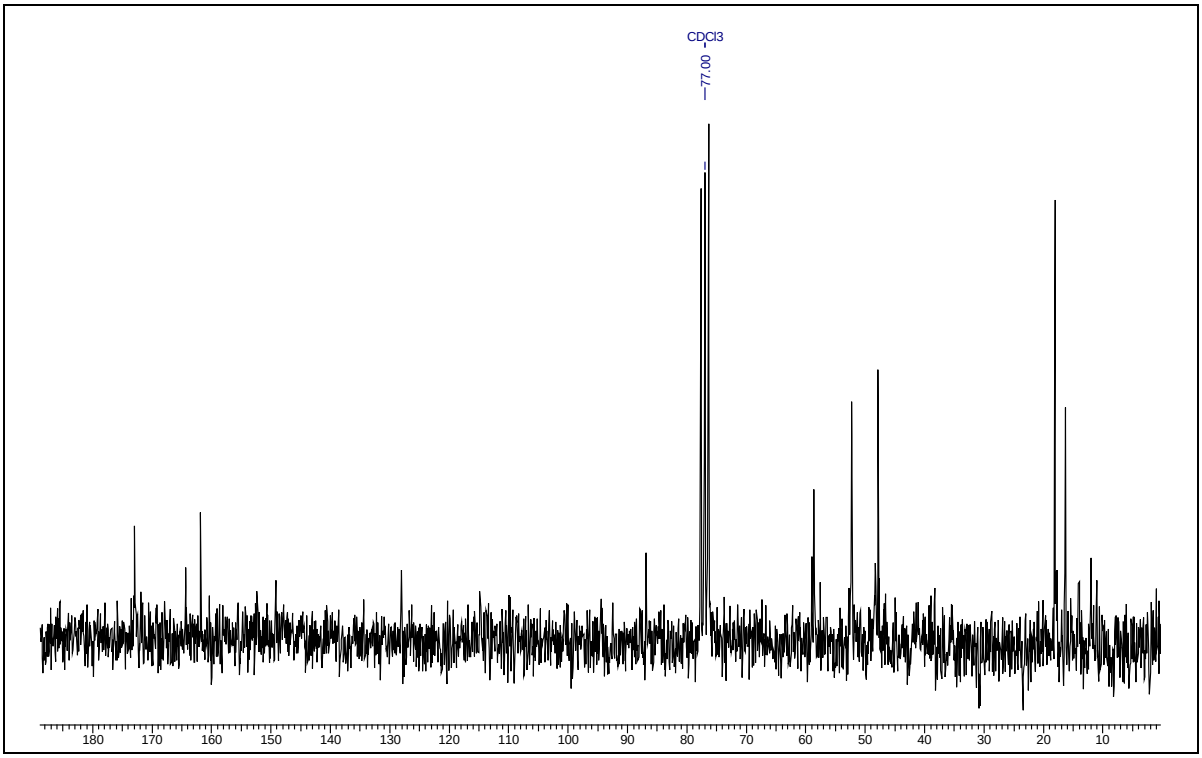


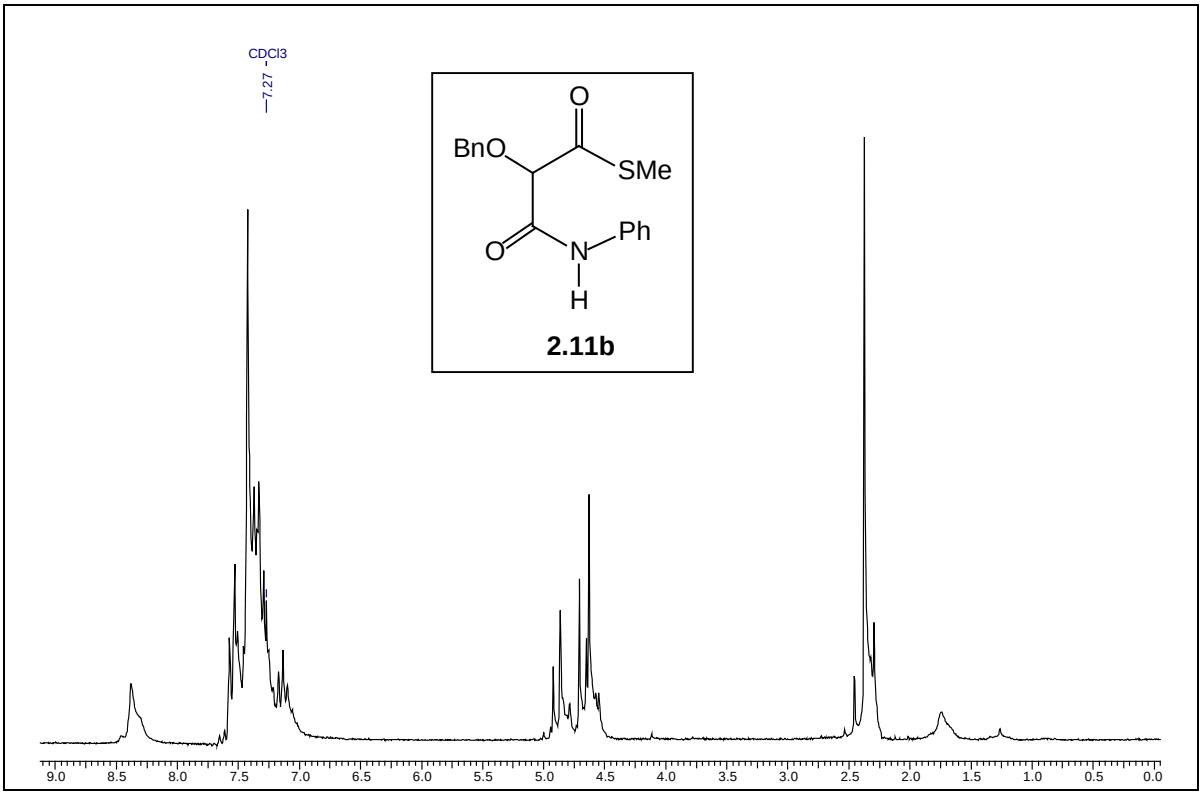


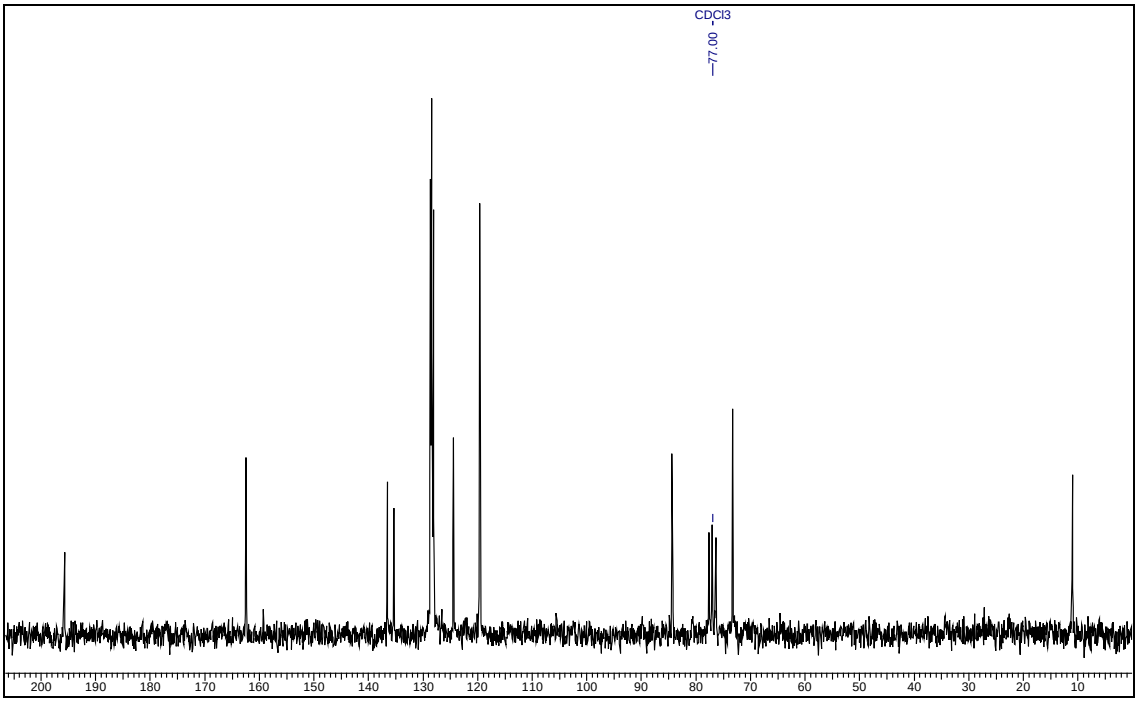


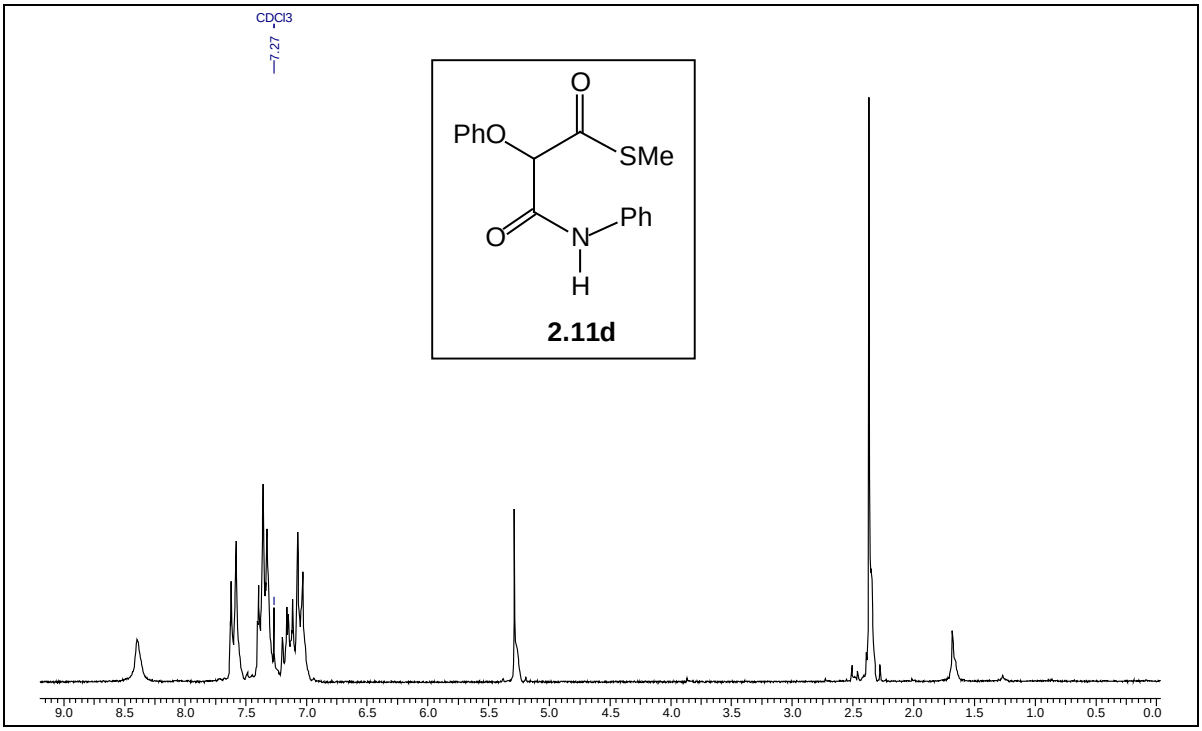


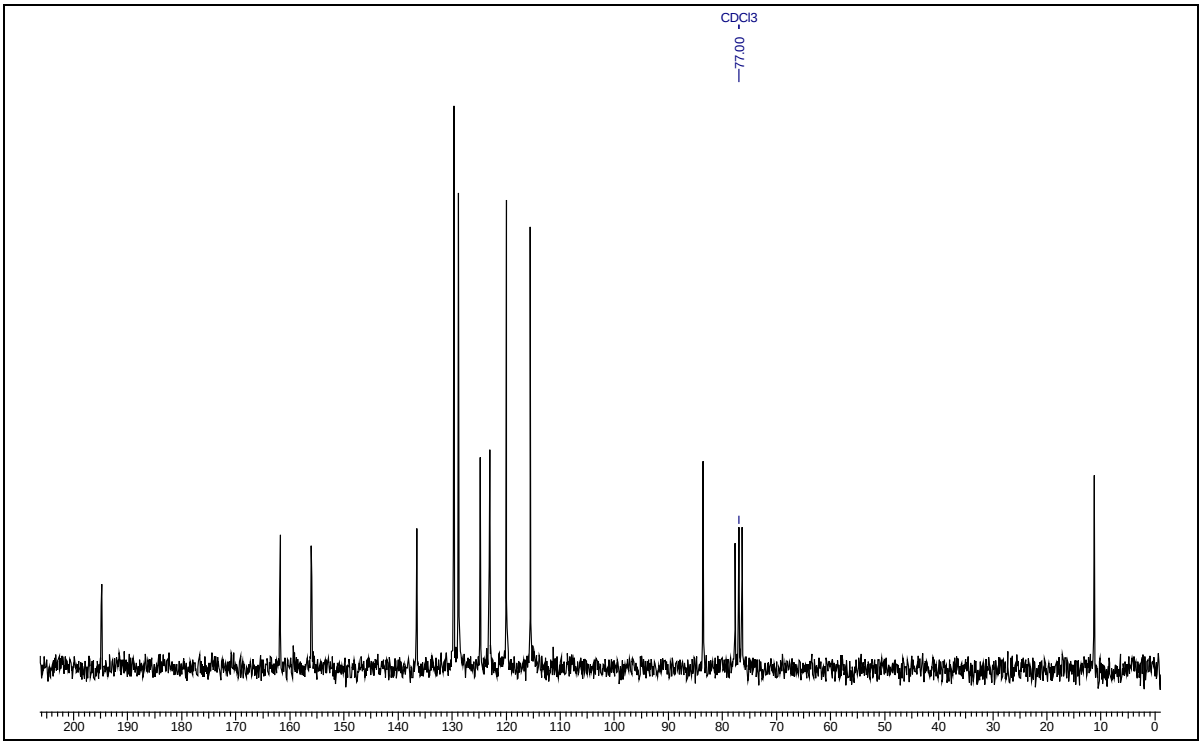


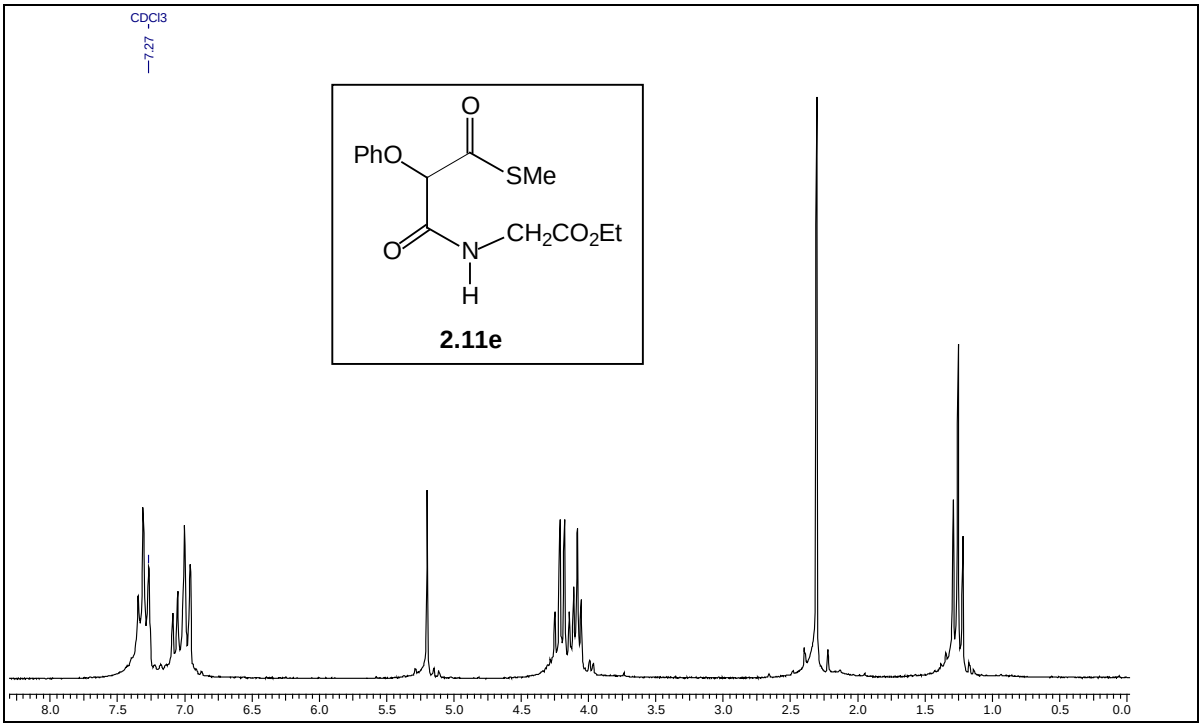


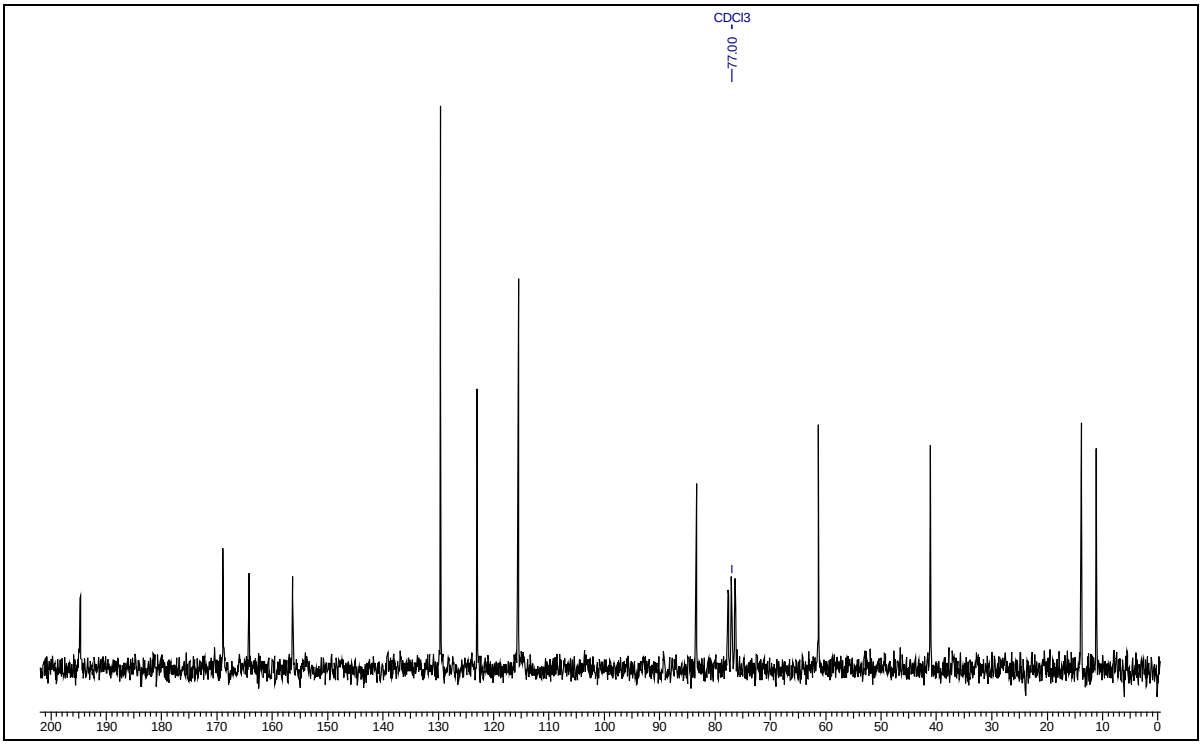


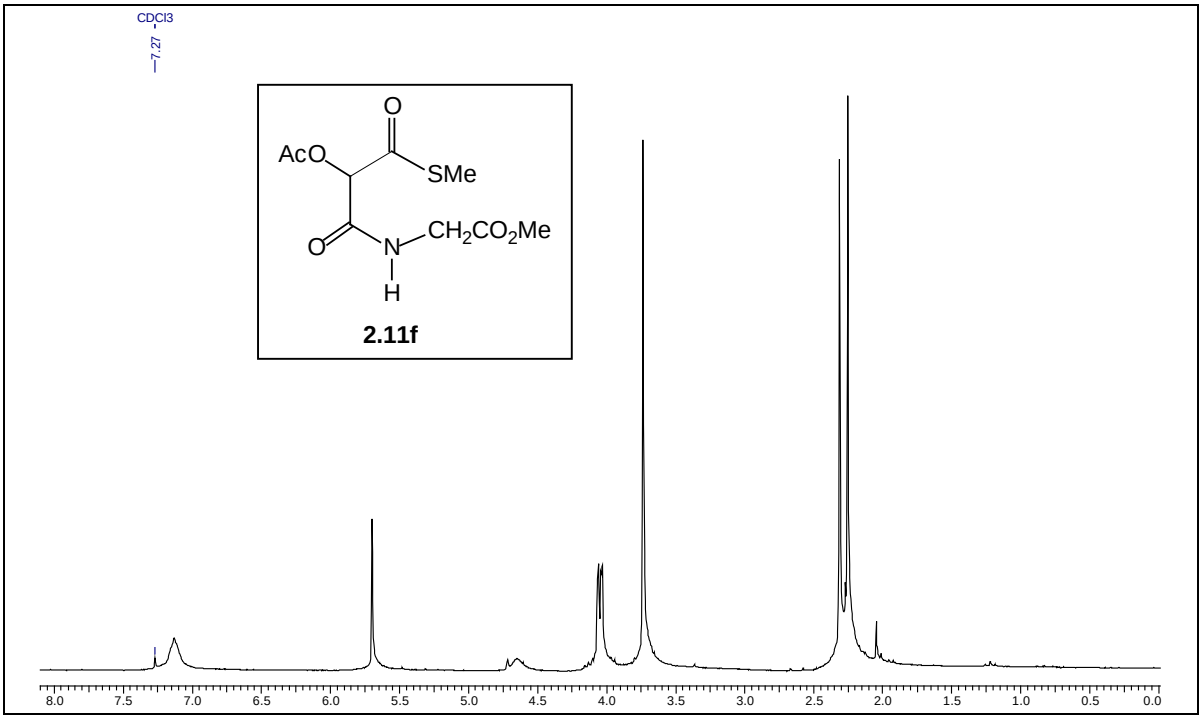


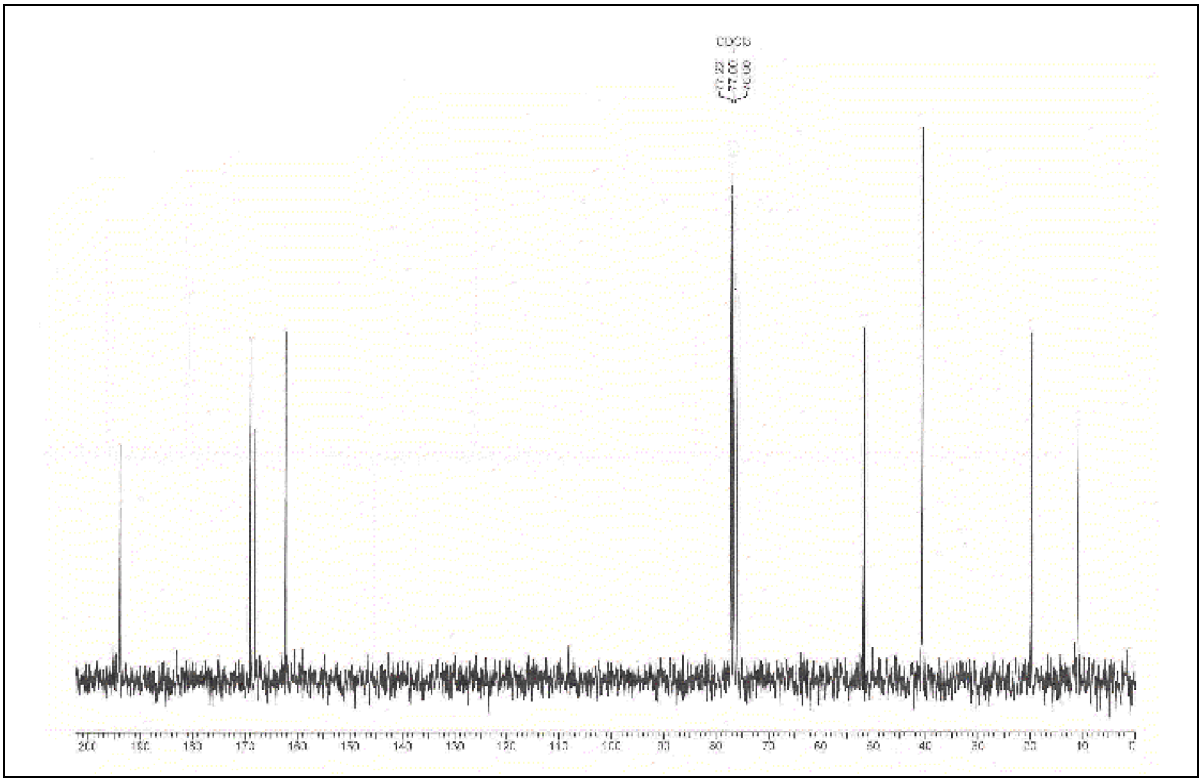


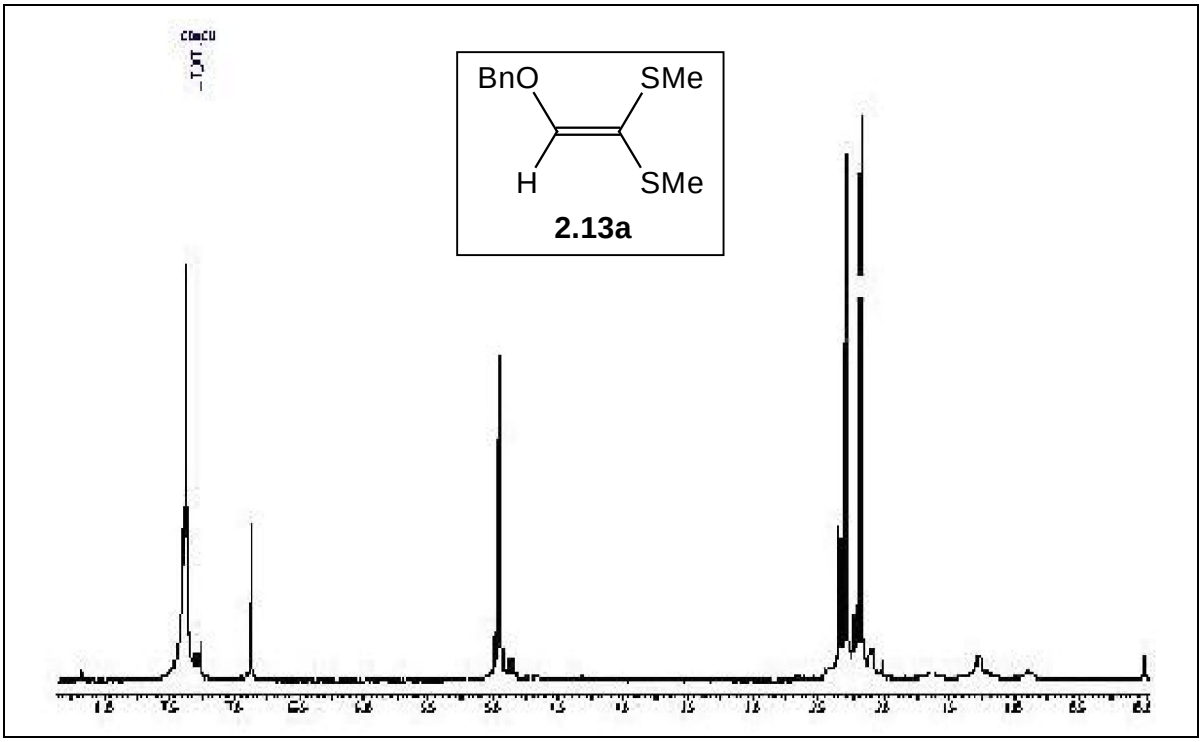


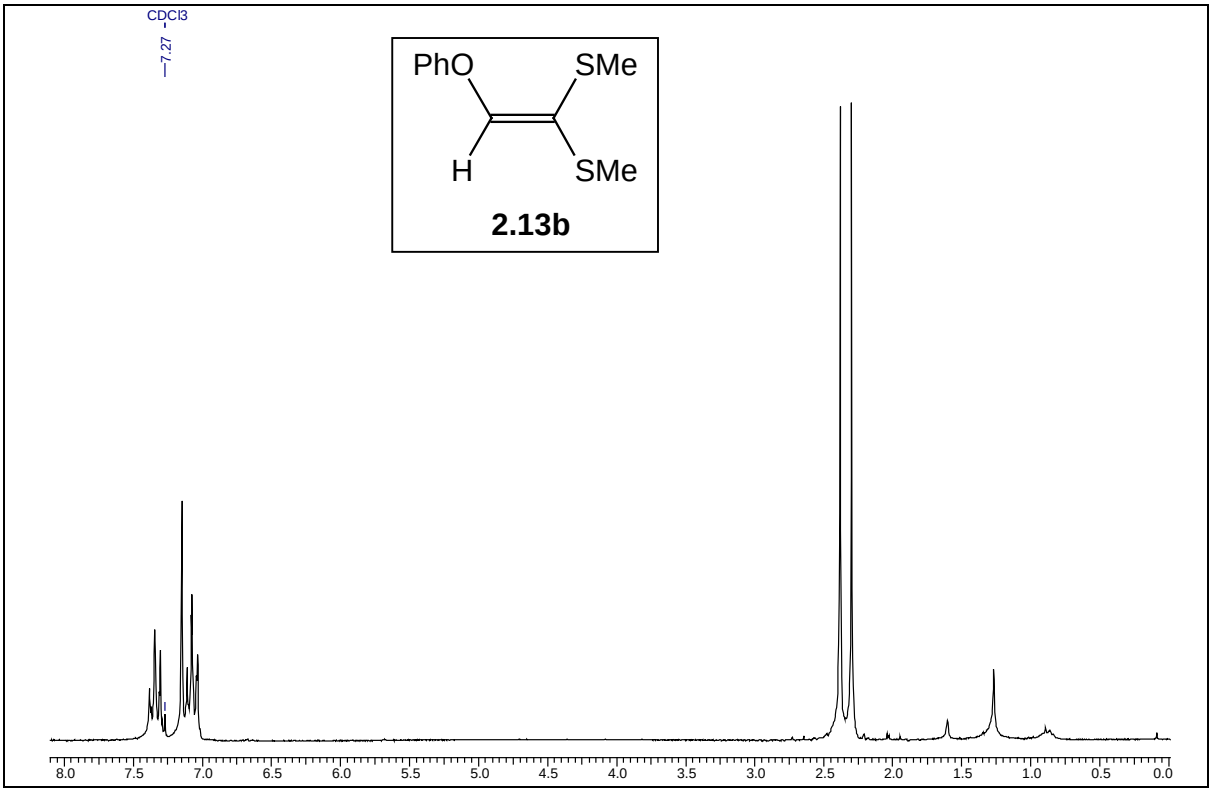


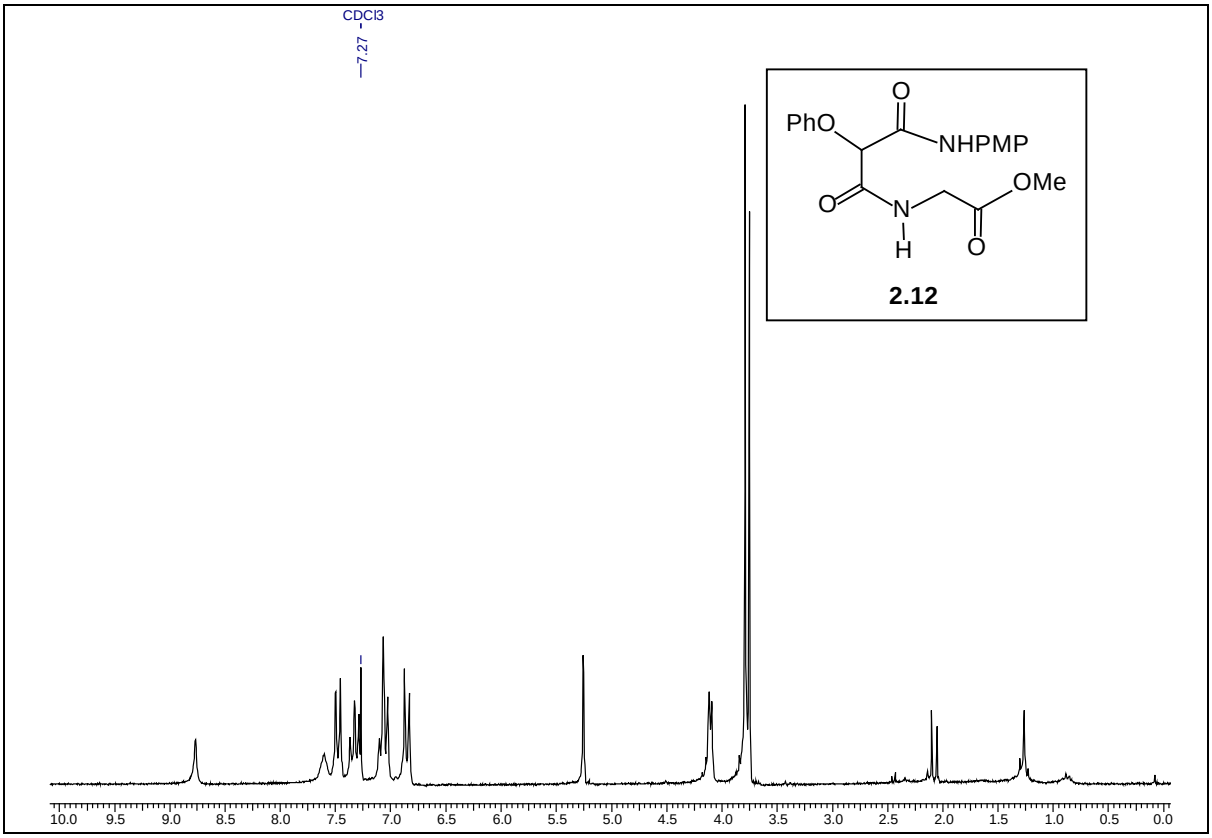


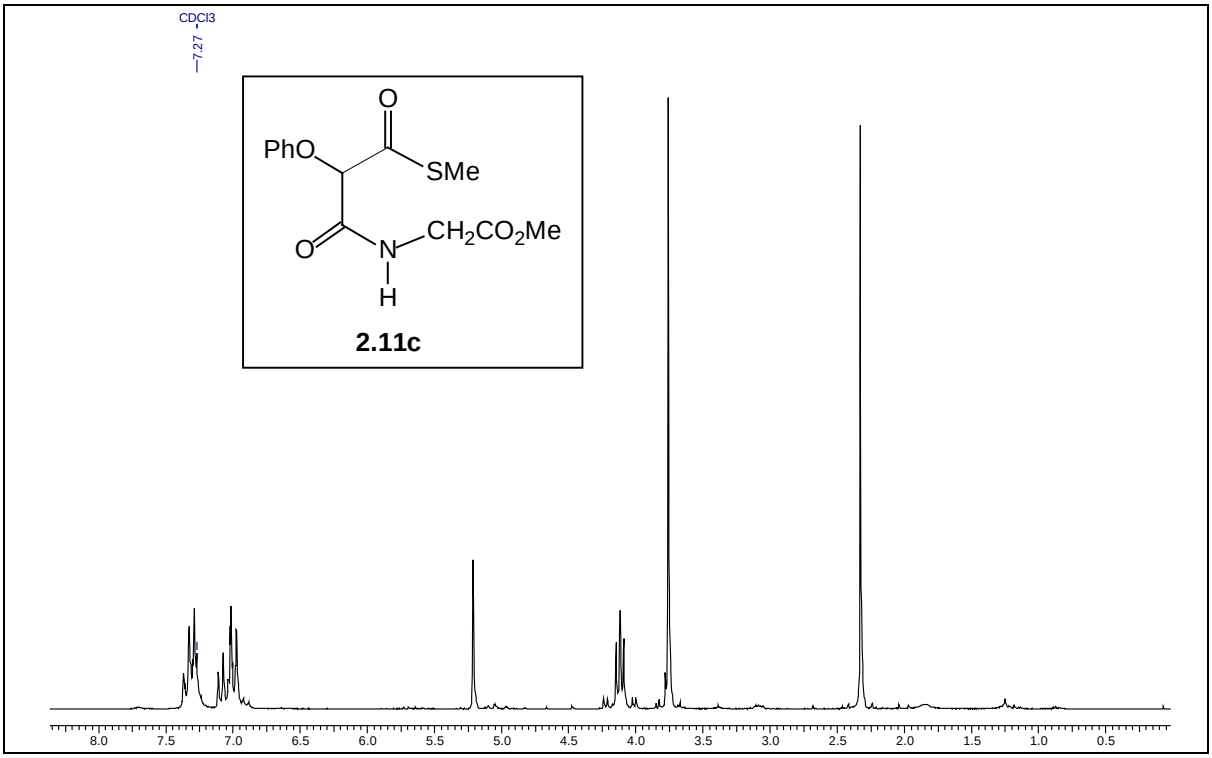


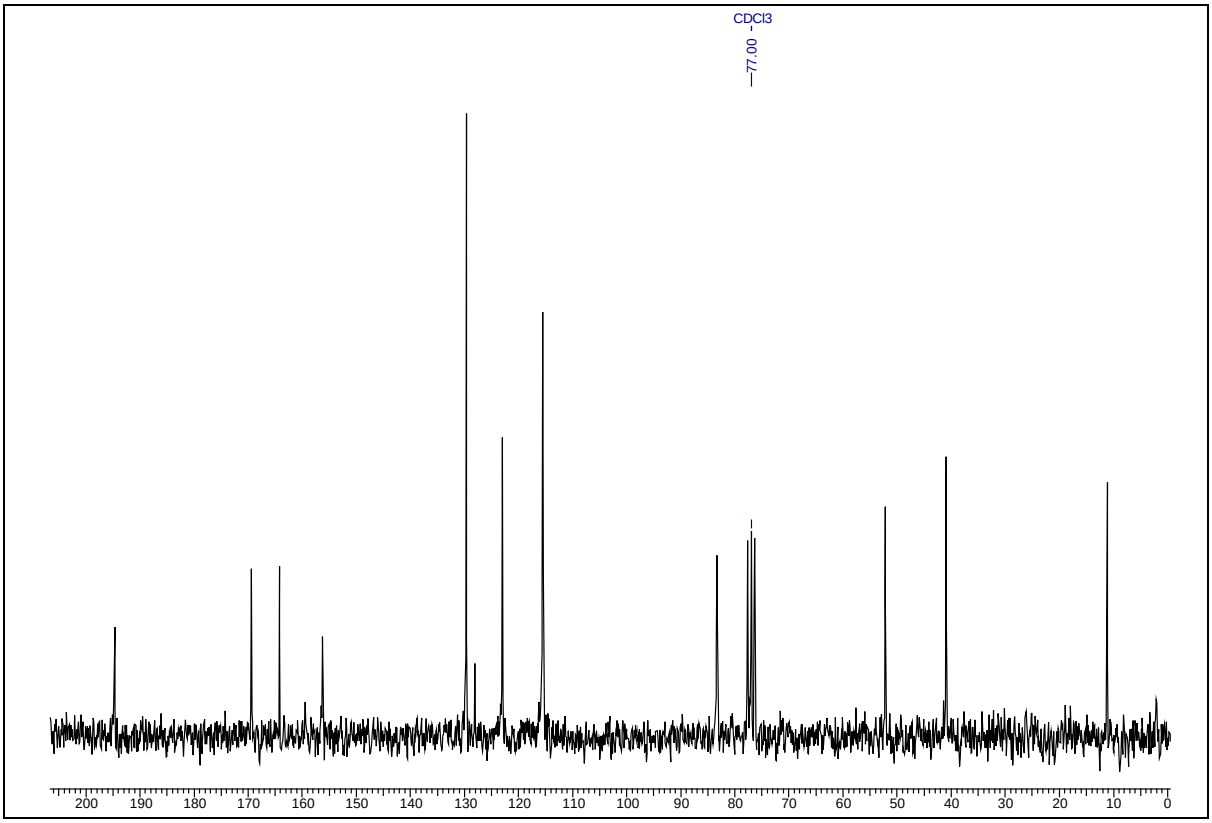


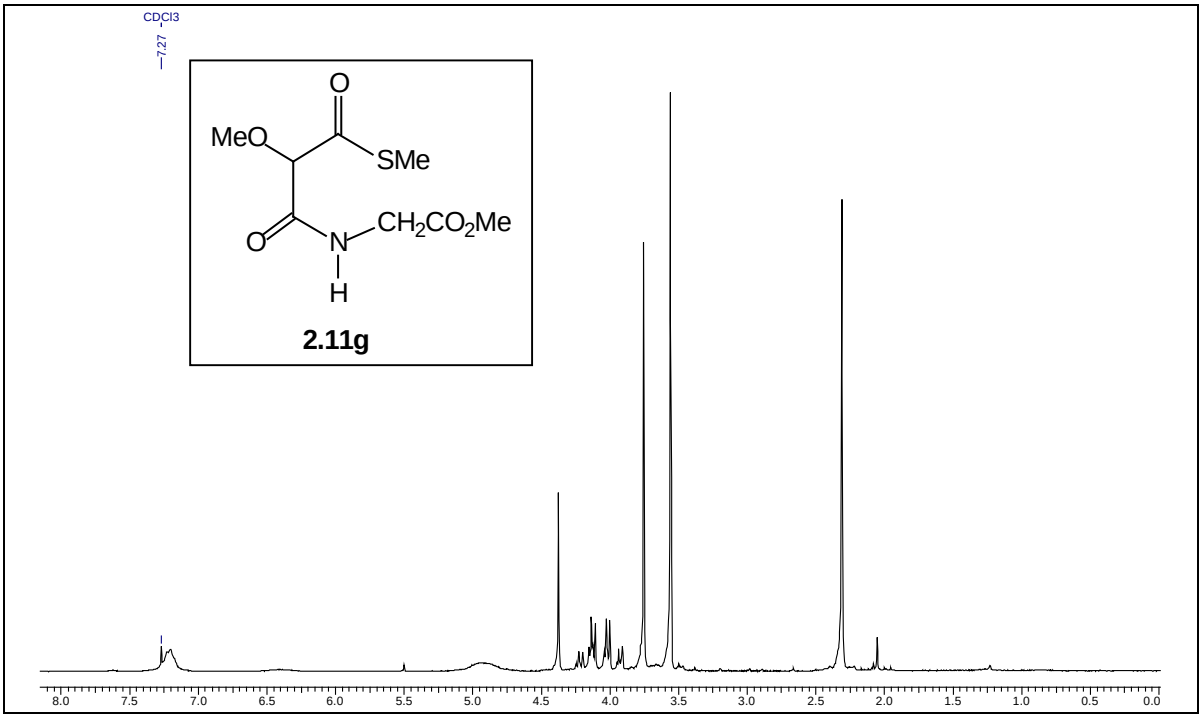


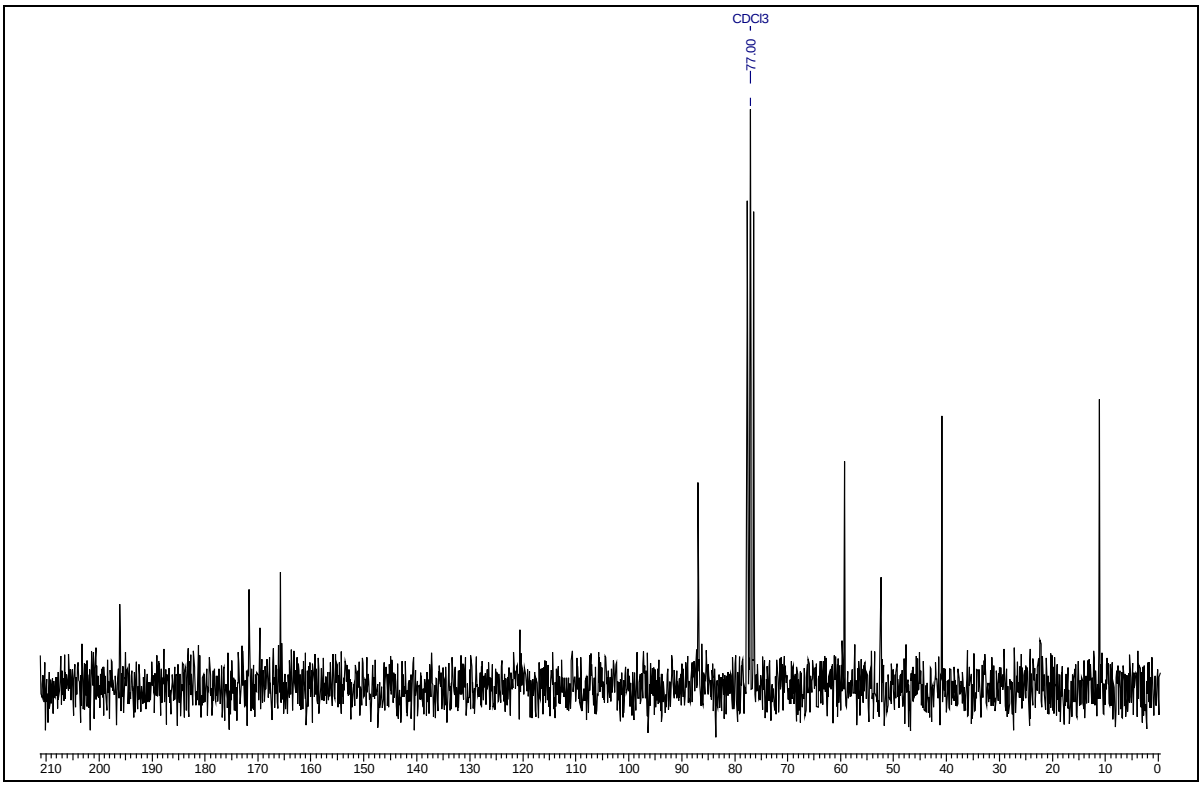






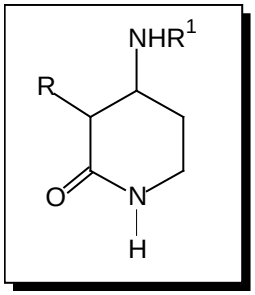






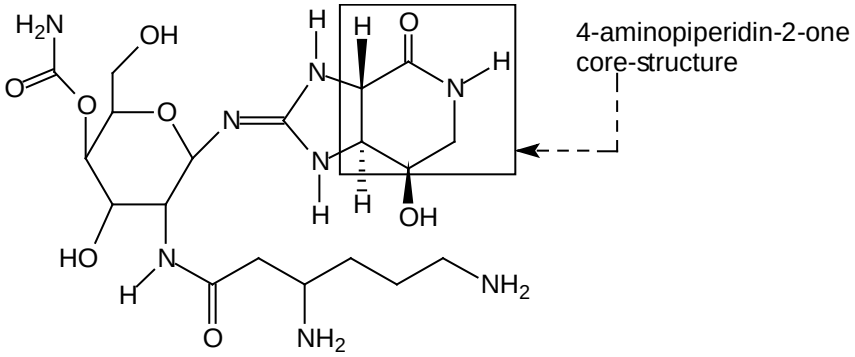
3.1 : Background for the present work

4-Aminopiperidin-2-ones are versatile building blocks for variety of heterocyclic compounds. They are also used as conformationally locked β-amino acid equivalents and peptide surrogates in peptidomimetics. They have been used extensively in the design and development of enzyme inhibitors and neuroreceptor ligands.[1] They are also utilized as a monomer for more rigid peptide nucleic acids (PNA) and pseudopeptide mimic of natural nucleic acids.[2]

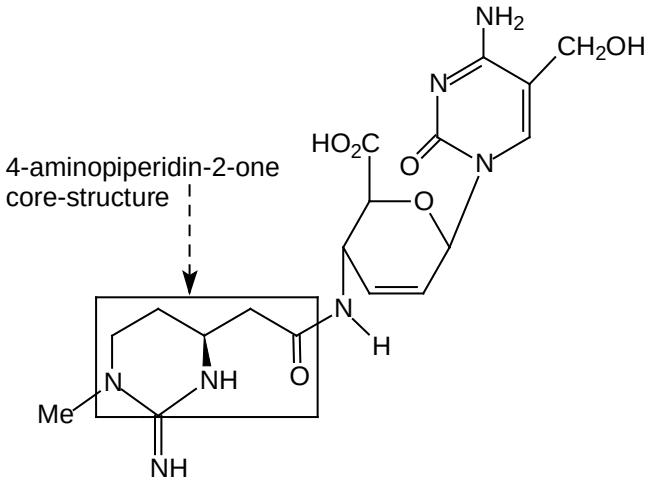


4-aminopiperidin-2-one

Apart from their potential use in peptidomimetics, 4-aminopiperidin-2-one motif also forms a part structure of important molecules like Streptothricine F, a potent antibiotic,[3] 5′-hydroxymethyl cytomycin, new nucleoside antibiotic from Streptomyces sp. HKI-0052[4] and Blastidic acid.[5]

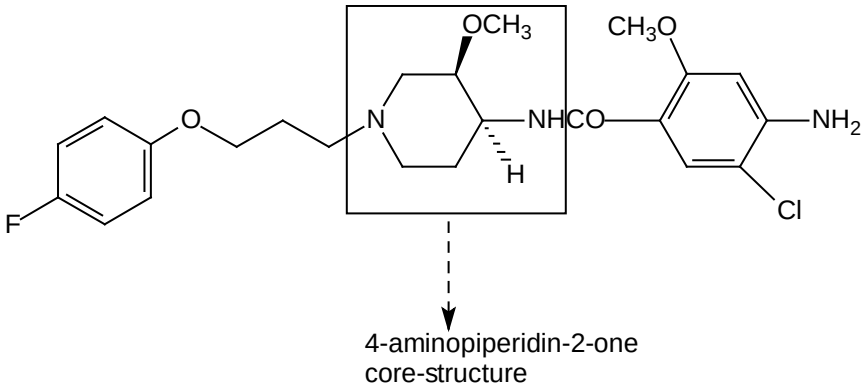


Streptothricine F



5′-Hydroxymethyl cytomycin

Cisapride,[6] an important drug used for gastro-esophageal reflux disease has a 4-aminopiperidine as a core structure, which can be obtained by reduction of 4-aminopiperidin-2-one.



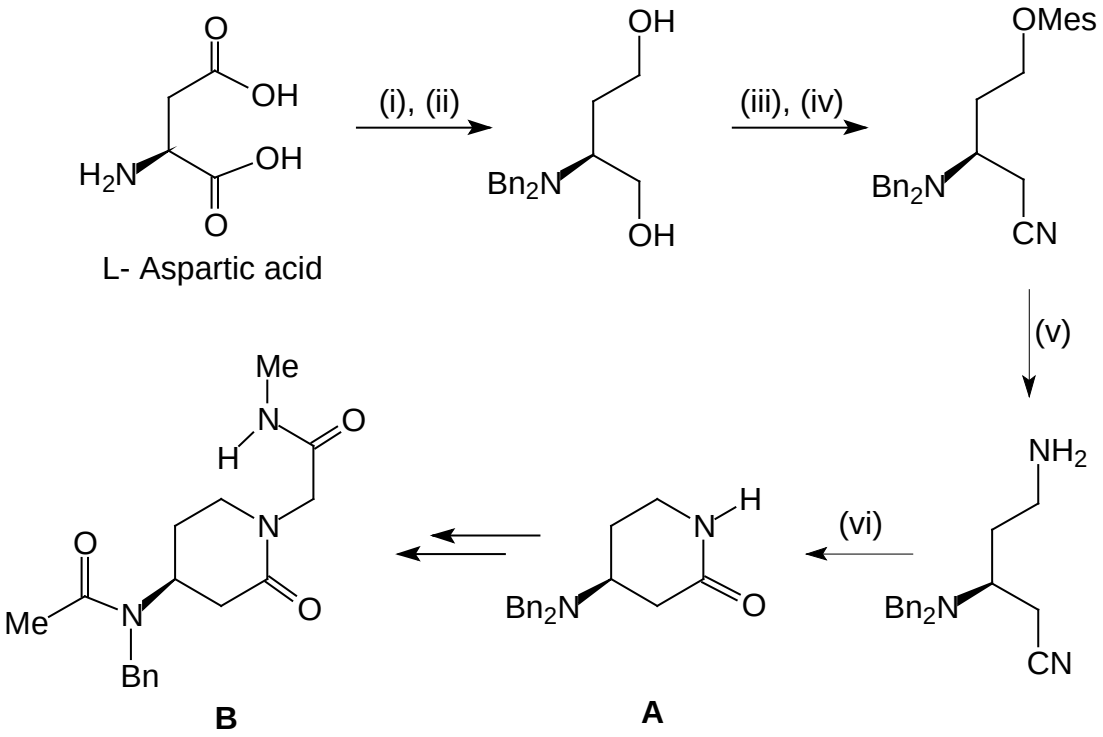
(3′*R*, 4′*S*)-Cisapride

Although, 4-aminopiperidin-2-ones are very important intermediates for number of biologically important compounds, there are very few synthetic methods available for their synthesis.

Gmeiner et al.[7] have developed a stereoselective synthesis of 4-aminopiperidin-2-one derivatives (A) starting from L-aspartic acid and have also studied their conformational characteristics as bioactive β-turn mimetics (Scheme 3.01). Conformational analysis of the 4-aminopiperidin-2-one derivative (B) in dilute solution by IR and NMR spectroscopy at room temperature clearly indicated that it predominantly adopts a reverse turn structure stabilized by CO-NH hydrogen bond in an 11 membered ring. Reverse turn templates

assume importance because of the presence of β- or γ-turn conformations[1c,1d,8] in many small peptides having regulatory roles in organisms.

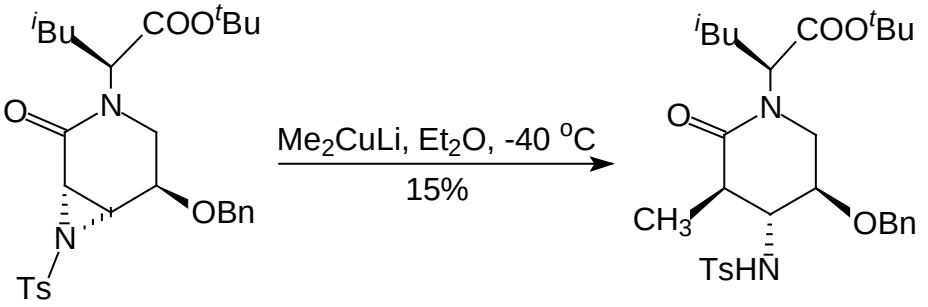
Scheme 3.01



***Reagents and conditions*:** (i) excess $C_6H_5CH_2Br$, H_2O and K_2CO_3. (ii) LAH reduction. (iii) MsCl (2.5 Equiv.), Et_3N, -25 ^oC, 25 min. (iv) LiCN (1.2 equiv.), THF / DMF, rt, 3 h. (v) NH_3 / MeOH, - 30 ^oC to rt, 4 d. (vi) HCl (MeOH:H_2O, 99:1), 60 ^oC, 12 h.

Diez et al.[9] have synthesized 4-aminopiperidin-2-one **C**, a conformationally restricted β-alanine derivative, by opening of aziridine ring of 3,4-aziridinolactams by dimethyl lithium cuprate (Scheme 3.02).

Scheme 3.02



Ts-{β-Ala-Leu}-O^{t}Bu

C

3.2 : Present work

The azetidin-2-one skeleton has attracted significant interest among the synthetic and medicinal chemists over the years mainly because it is the core structure of natural and synthetic β-lactam antibiotics. However, recently the use of azetidin-2-ones as synthetic intermediate has found considerable interest in organic syntheses. As large number of methods available for the synthesis of azetidin-2-ones, the applications of azetidin-2-ones as efficient chiral synthons for other classes of molecules has been a active area of research.[10] In fact the development of a methodology based on the azetidin-2-one nucleus has reached such a level of importance as to merit its own name, "the β-lactam synthon method" by Ojima.[11]

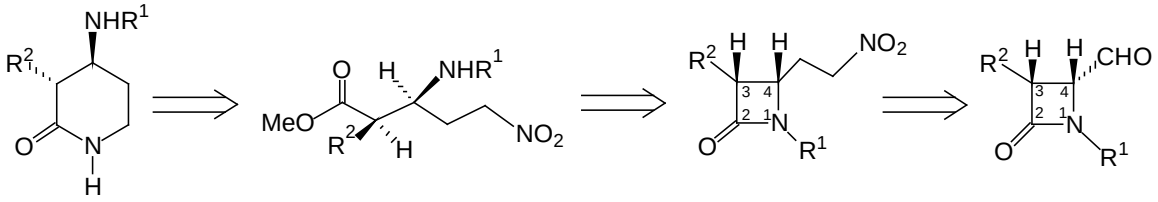
4-Formylazetidin-2-ones are important building blocks in the synthesis of biologically active compounds like α- and β-amino acids, polyhydroxy amino acids, polycyclic β-lactams, alkaloids and complex natural products.[12] They exhibit a valuable dual reactivity of protected α-amino aldehydes as well as masked β-amino acids. The transformation of 4-formylazetidin-2-ones into functionalized open chain products is usually carried out by doing many functional group transformations, which involves initial preparation of appropriately substituted β-lactam followed by the selective ring opening. The selective bond cleavage and rearrangement gives either fused nitrogen heterocyclic system or a carbocyclic structure.

This section describes our efforts towards the synthesis of optically pure 4-aminopiperidin-2-ones starting from appropriately substituted 4-formylazetidin-2-ones by functional group transformations followed by regioselective β-lactam ring cleavage.

3.3 : Results and Discussions

We envisaged the introduction of an amino ethyl side chain on C-4 of optically pure 4-formylazetidin-2-one followed by intramolecular nucleophilic ring opening by the amino group would give us the required 4-aminopiperidin-2-one in enantiomerically pure form (Scheme 3.03).

Scheme 3.03



Synthesis of optically pure 4-aminopiperidin-2-ones

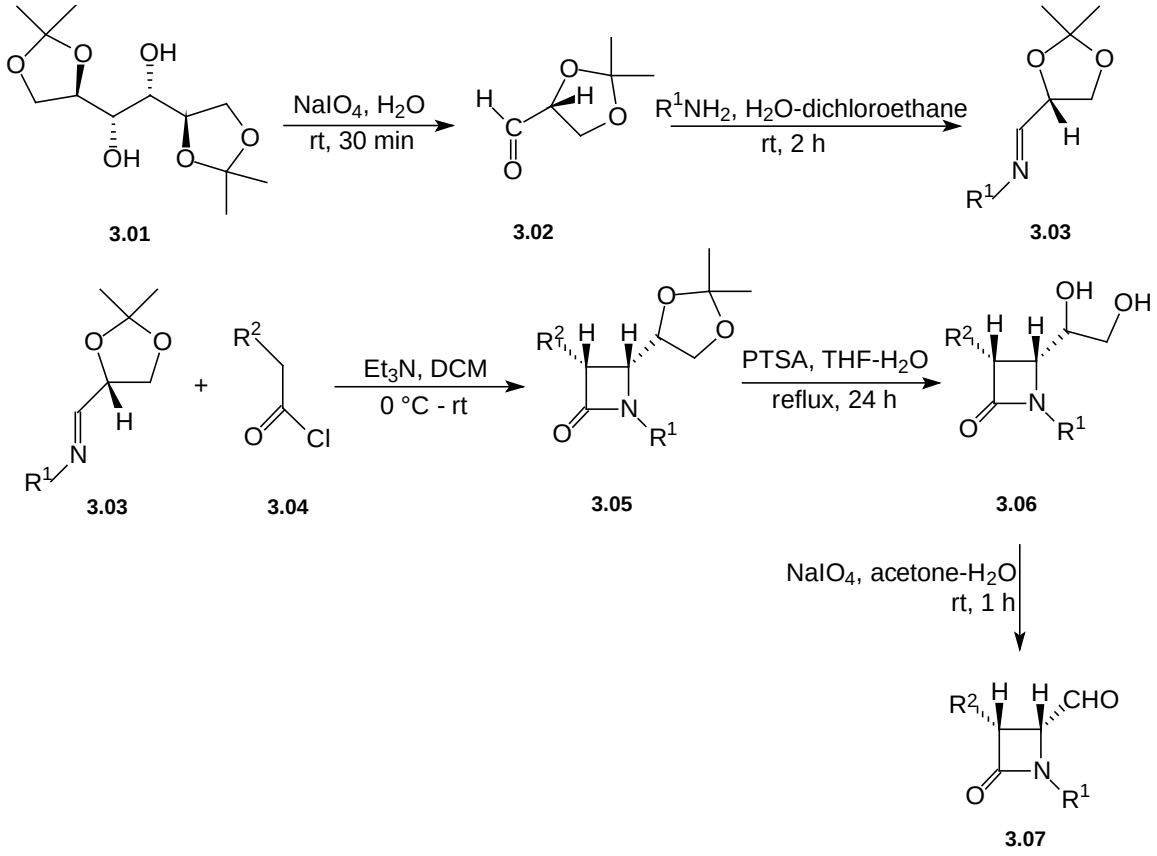
We were interested in the synthesis of enantiopure 4-aminopiperidin-2-ones, starting from optically pure 4-formylazetidin-2-ones. The retro synthesis is as shown in Scheme 3.03. The optically pure 4-formylazetidin-2-ones could be easily synthesized from the enantiopure β-lactams which in turn can be synthesized by cycloaddition reaction of imine derived from D-glyceraldehyde acetonide and ketene.[13]

The commercially available D-mannitol was protected as its diacetonide using anhydrous zinc chloride in dry acetone. The vicinal diol of this diacetonide **3.01** was cleaved by sodium metaperiodate to get optically pure D-glyceraldehyde acetonide **3.02**. The Schiff's base **3.03a** was prepared by stirring a mixture of aqueous solution of D-glyceraldehyde acetonide **3.02** with a solution of *p*-toludine in dichloroethane for 2 h. The imine thus formed was then reacted with ketene generated *in situ* from phenoxyacetyl chloride and triethylamine to afford the β-lactam **3.05a**. The acetonide group of the β-lactam **3.05a** was cleaved by PTSA[14] to get the diol **3.06a**, which was then oxidized by $NaIO_4$ to get the required enantiopure 4-formylazetidin-2-one **3.07a** (Scheme 3.04).[15] Several other optically pure 4-formyl-β-lactams **3.07b-d** were prepared by using the above synthetic protocol and well characterized by spectral data.

The IR spectrum of **3.07a** showed bands at 1766 and 1735 cm^{-1} corresponding to the β-lactam and aldehydic carbonyl respectively.

The ^1H NMR spectrum of **3.07a** showed a singlet at 2.34 ppm corresponding to methyl protons attached to aromatic ring. The C-3 and C-4 β-lactam protons appeared as doublet at 5.55 ppm (J = 5.1 Hz) and doublet of doublet at 4.76 ppm with J = 5.1 Hz and 3.5 Hz respectively. The coupling constant of 5.1 Hz indicated the *cis* stereochemistry of the C-3 and C-4 β-lactam protons. The aromatic protons appeared as a multiplet between 7.05-7.40 ppm. The aldehydic proton appeared as a doublet at 9.78 ppm (J = 3.5 Hz).

Scheme 3.04



3.07a R^1 = *p*-tolyl, R^2 = PhO

3.07b R^1 = *p*-tolyl, R^2 = BnO

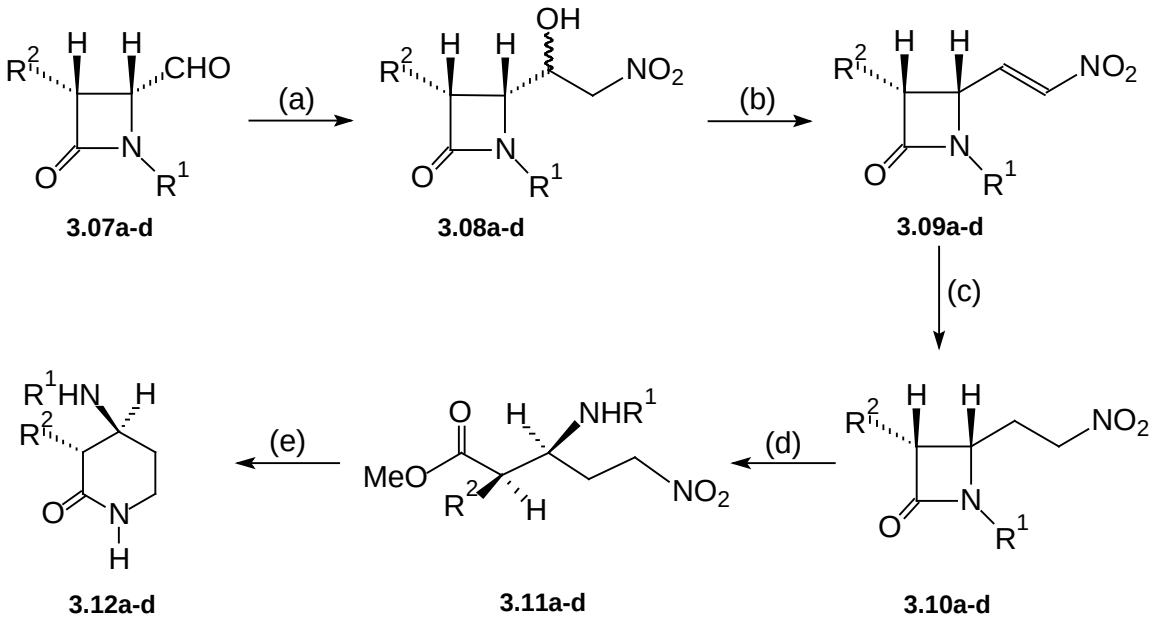
3.07c R^1 = Ph, R^2 = PhO

3.07d R^1 = Ph, R^2 = BnO

The 4-formylazetidin-2-one **3.07a** was then subjected to nitroaldol reaction using nitromethane and Et_3N at room temperature. After completion of the reaction (TLC), the excess nitromethane was removed under reduced pressure to furnish a diastereomeric mixture (80:20) of nitroalcohol **3.08a**. The hydroxy group of the nitroaldol product **3.08a**

was acylated with acetic anhydride in the presence of catalytic Conc. sulphuric acid at 0 ^{o}C to get the diastereomeric nitroacetate, which on refluxing in benzene with solid sodium bicarbonate furnished nitroalkene **3.09a**.

Scheme 3.05

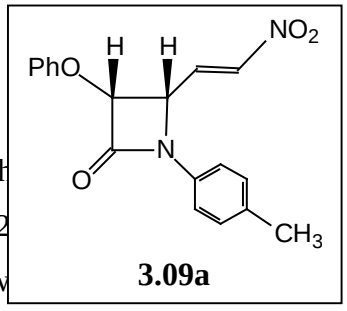


Reagents and conditions: (a) CH_3NO_2, Et_3N, rt, 4 h. (b) (i) Ac_2O, Conc. H_2SO_4, 0 ^{o}C, 1 h, (ii) $NaHCO_3$, benzene, reflux, 5 h. (c) Bu_3SnH, DCM:MeOH (10:1), rt, 24 h (d) methanolic HCl (20%), rt, 12-24 h (e) 10% Pd/C, $HCOONH_4$, MeOH, rt or heat, 3-10 h.

IR spectrum of **3.09a** showed a sharp band at 1764 cm^{-1} corresponding to the β-lactam carbonyl. The bands at 1533 cm^{-1} and 1357 cm^{-1} correspond to the nitro group.

The ^{1}H NMR spectrum of **3.09a** showed a singlet for methyl protons at 2.35 ppm. The spectrum showed a doublet of doublets at 5.10 ppm with coupling constant values of 5.1 and 10.6 Hz for the C-4 proton. The C-3 proton of β-lactam ring appeared as a doublet at 5.60 ppm with J = 5.1 Hz. The aromatic and the olefinic protons appeared as a multiplet between 6.90-7.50 ppm.

The ^{13}C spectrum of **3.09a** showed a peak at 20.75 ppm corresponding to the methyl carbon. The C-3 and C-4 β-lactam carbons appeared at 81.61 ppm and 55.27 ppm respectively. Th aromatic quaternary carbons appeared at 156.72, 142.92, 135.2 ppm, while the remaining aromatic carbons along with the tw



3.09a

olefinic carbons appeared at 115.49, 116.95, 122.96 129.74, 129.91, 133.80 and 134.62 ppm.

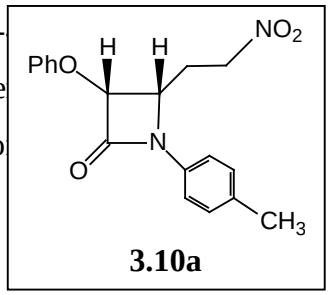
The peak at 161.39 ppm was assigned to the β-lactam carbonyl carbon. This compound **3.09a** also gave satisfactory elemental analysis and the mass spectrum showed peak at m/z 325 (M+1).

The reduction of the olefinic double bond was carried out with the help of tributyltin hydride[16] in anhydrous dichloromethane-methanol (10:1). Tributyltin hydride was added at room temperature and the mixture was stirred for 24 h. After the completion of the reaction the solvent was removed to get the crude product, which was subsequently purified by column chromatography to afford pure nitroalkane 3.10a as a white solid. The

structure of 3.10a was established by spectral and analytical data.

The IR spectrum of nitroalkane **3.10a** showed a band at 1758 cm^{-1} corresponding to the β-lactam carbonyl. The bands at 1556 cm^{-1} and 1382 cm^{-1} were due to the nitro group.

The ^{1}H NMR spectrum of **3.10a** showed a singlet at 2.35 ppm for methyl protons. The methylene protons attached to C- of β-lactam ring appeared as two separate multiplets betwee 2.50-2.70 ppm and 2.80-3.00 ppm. Other methylene protons o carbon attached to nitro group and the C-4 proton appeared as multiplet between 4.50-4.70 ppm.



3.10a

The doublet at 5.42 ppm with J = 5.4 Hz was assigned to C-3 proton of β-lactam ring. The aromatic protons appeared as a multiplet between 7.05-7.40 ppm.

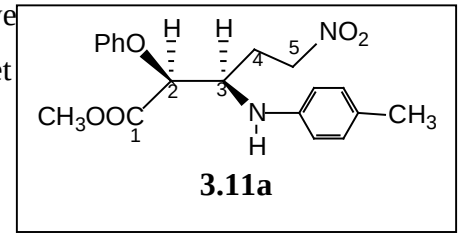
The ^{13}C spectrum of **3.10a** showed a peak at 20.81 ppm for the methyl carbon. The methylene carbon attached to nitro group was observed at 71.48 ppm, while the other methylene was observed at 25.03 ppm. The C-3 and C-4 β-lactam carbons appeared at 79.72 ppm and 54.17 ppm respectively. The aromatic quaternary carbons were seen at 157.11, 134.71 and 133.89 ppm, while the remaining aromatic carbons appeared at 115.70, 117.16, 122.78, 129.74 and 129.89 ppm. The peak at 162.49 ppm corresponds to the β-lactam carbonyl carbon. This compound **3.10a** also gave satisfactory elemental analysis and the mass spectrum showed a peak at m/z 327 (M+1).

The β-lactam ring of the nitroalkane **3.10a** was cleaved by stirring with methanolic HCl (20%) at room temperature for 24 h to get the β-amino-nitroester **3.11a**. The structure of nitroester **3.11a** was also confirmed from spectral and analytical data.

The IR spectrum of **3.11a** showed bands at 3392 cm^{-1}, 1757 cm^{-1}, 1554 cm^{-1} and 1379 cm^{-1} corresponding to amino, carbonyl and nitro groups respectively.

The ^{1}H NMR spectrum of **3.11a** showed a singlet at 2.26 due to the methyl group attached to aromatic ring. A multiplet between 2.35-2.50 ppm was due to the C-4 methylene protons. The methoxy protons of the ester group appeared as a sharp singlet at 3.52 ppm.

The C-3 proton appeared as a multiplet betwe 4.20-4.40 ppm. The C-2 proton was seen as a doublet



3.11a

4.78 ppm (J = 2.3 Hz). The C-5 methylene protons attached to nitrogen and the NH proton appeared as a multiplet between 4.50-4.65 ppm.

The four aromatic protons were observed as two sets of doublets at 6.60 ppm and 6.90 ppm with J = 8.6 Hz respectively. Two multiplets between 7.00-7.10 ppm and 7.25-7.35 ppm integrating for three and two protons were observed for the remaining aromatic protons.

The peaks at 20.25 and 53.47 ppm in the ^{13}C NMR spectrum of nitroester **3.11a** were assigned to the methyl carbon and the methoxy carbon respectively. The C-4 and C-5 methylene carbons were seen at 29.99 and 72.22 ppm respectively. The C-2 and C-3 methine carbons appeared at 77.15 and 52.15 ppm respectively. The aromatic quaternary carbons attached to oxygen, nitrogen and carbon appeared at 157.17, 143.94 and 127.98 ppm respectively, while the remaining aromatic carbons were observed at 114.16, 114.97, 122.14, 129.56 and 129.78 ppm and the peak at 169.67 ppm corresponds to the carbonyl carbon. The ester **3.11a** gave satisfactory elemental analysis and the mass spectrum showed a molecular ion peak at m/z 358 (M^+).

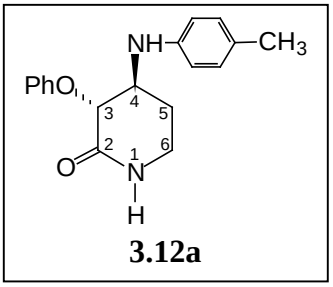
The reductive cyclization of the nitroester **3.11a** to the 3-phenoxy-4-aminopiperidin-2-one **3.12a** was successfully achieved by transfer hydrogenation[17] using ammonium formate and Pd/C (10%) in methanol as solvent. To a solution of the ester **3.11a** in dry methanol, Pd/C (10%) and ammonium formate was added and the reaction mixture was refluxed under argon for 3 h. After completion of the reaction (TLC) the catalyst was filtered through celite. The solvent was removed under reduced pressure and the residue was taken in dichloromethane, washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent gave the crude product, which was then purified by column chromatography to afford pure 4-aminopiperidin-2-one **3.12a** the structure of which was confirmed by its spectral and analytical data.

The IR spectrum of **3.12a** showed bands at 3346 and 1658 cm^{-1} corresponding to the amino and amide functional groups respectively.

The ^{1}H NMR spectrum of **3.12a** showed two separate multiplets between 1.95-2.10 ppm and 2.40-2.60 ppm corresponding to C-5 methylene protons. A singlet at 2.25 ppm was due to the methyl group. Another multiplet at 3.60-3.80 ppm was attributed to C-6 methylene protons. The C-4 proton of the lactam ring appeared as a multiplet between 3.90-4.05 ppm and the C-3 proton appeared as a doublet at 4.76 ppm with J = 5.5 Hz. The aromatic protons were observed as doublets at 6.56, 6.96 and 7.32 ppm with J = 8.2, 7.8 and

7.8 Hz respectively. The remaining aromatic protons appeared as a multiplet between 7.05-7.15 ppm.

The ^{13}C NMR spectrum of the **3.12a** showed a peak at 20.32 ppm for the methyl carbon attached to the aromatic ring. The C-5 and C-6 methylene carbons appeared at 23.88 and 46.16 ppm respectively. The C-3 and C-4 methine carbons were observed at 77.52 and 51.38 ppm correspondingly.



3.12a

The aromatic quaternary carbons attached to oxygen, nitrogen and carbon appeared at 158.23, 143.57 and 127.98 ppm respectively, while the remaining aromatic carbons appeared at 114.13, 116.51, 122.25, 129.53 and 129.82 ppm. The piperidin-2-one carbonyl carbon was observed at 162.54 ppm. This piperidin-2-one **3.12a** showed a peak at m/z 297 (M+1) and gave satisfactory elemental analysis.

Following the similar procedures mentioned above, all other nitroalkenes **3.09b-d,** nitroalkanes **3.10b-d** β-amino nitroesters **3.11b-d** and the corresponding piperidin-2-ones **3.12b-d** were also prepared in fairly good yields and characterized completely by spectral analysis. All of them gave satisfactory elemental analysis. All the data for these compounds is summarized in the following Table (Table 1).

Table 1: Synthesis of nitroalkenes **3.09 a-d**, nitroalkanes **3.10 a-d**, β-amino nitroesters **3.11 a-d** and 4-aminopiperidin-2-ones **3.12 a-d**

Compound No.	R^1	R^2	MP (°C)	$[\alpha]_D^{28}$	Yield[a] (%)
3.09a	*p*-tolyl	PhO	145-146	+103.8 (*c* 1.04, $CHCl_3$)	72
3.09b	*p*-tolyl	BnO	138-140	+124 (*c* 1.04, $CHCl_3$)	73
3.09c	Ph	PhO	152	+115 (*c* 0.6, $CHCl_3$)	73
3.09d	Ph	BnO	147	+121.4 (*c* 0.55, $CHCl_3$)	75
3.10a	*p*-tolyl	PhO	75-76	+222.7 (*c* 1.01, $CHCl_3$)	78
3.10b	*p*-tolyl	BnO	96-98	+122.5 (*c* 0.8, $CHCl_3$)	81
3.10c	Ph	PhO	125	+242.5 (*c* 0.4, $CHCl_3$)	75
3.10d	Ph	BnO	114-115	+169.7 (*c* 0.7, $CHCl_3$)	79
3.11a	*p*-tolyl	PhO	117	-72 (*c* 1.0, $CHCl_3$)	84
3.11b	*p*-tolyl	BnO	oil	-4.76 (*c* 1.26, $CHCl_3$)	85
3.11c	Ph	PhO	114-116	-77 (*c* 0.4, $CHCl_3$)	82
3.11d	Ph	BnO	oil	-9.1 (*c* 0.55, $CHCl_3$)	85
3.12a	*p*-tolyl	PhO	oil	+58.7 (*c* 0.7, $CHCl_3$)	68
3.12b	*p*-tolyl	BnO	oil	+68.57 (*c* 0.7, $CHCl_3$)	68
3.12c	Ph	PhO	oil	+35.5 (*c* 2.25, $CHCl_3$)	65
3.12d	Ph	BnO	oil	+57.7 (*c* 0.23, $CHCl_3$)	66

3.4 : Conclusion

We have successfully employed 4-formylazetidin-2-ones as efficient building blocks for the synthesis of optically pure 4-aminopiperidin-2-ones *via* methanolysis of the β-lactam ring and reductive cyclization of nitroethyl side chain at C-4 position. Enantiopure 4-

aminopiperidin-2-ones **3.12a-d** were synthesized in good overall yields from the corresponding optically pure 4-formylazetidin-2-ones **3.07a-d**.

3. 5 : Experimental

3. 5. 1: General procedure for the preparation of azetidin-2-ones 3.05a-d

***Preparation of Schiff base* 3.03**

$NaIO_4$ (2.14 g, 10 mmol) was dissolved in H_2O (20 mL) and cooled to 0 ^oC. To the above cooled solution, 1,2,5,6-Di-*O*-isopropylidine-D-mannitol **3.01** (2.62 g, 10 mmol) was added in portions with stirring. After completion of addition, the reaction mixture was stirred at room temperature for 30 min and was filtered to provide an aqueous solution of D-glyceraldehyde acetonide **3.02**. To the cooled (0-5 ^oC) filtrate, was added a solution of amine (20 mmol) in 1,2-dichloroethane (20 mL). The reaction mixture was stirred at room temperature for 2 h after which the organic layer was separated. The aqueous layer was saturated with sodium chloride and extracted with dichloroethane (2 x 20 mL). The combined organic layer containing the Schiff base **3.03** was dried over anhydrous sodium sulphate, evaporation of the organic solvent provided the Schiff's base that was used as such for the next reaction.

***Preparation of azetidin-2-ones* 3.05a-d *from Schiff base* 3.03**

To the dichloromethane solution of Schiff base **3.03** and triethyl amine (6.7 mL, 48 mmol) was added drop wise a solution of the corresponding acid chloride **3.04** (24 mmol) at 0 ^oC. The reaction mixture was then allowed to warm to room temperature and stirred for additional 12-15 h. The reaction mixture was then diluted with dichloromethane (30 mL) and the organic layer was washed with water (3 x 15 mL), saturated sodium bicarbonate solution (3 x 15 mL), saturated brine solution (15 mL) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to get the crude product, which was purified by column chromatography to get pure azetidin-2-ones **3.05a-d**.

3. 5. 1a: Preparation of (3*R*, 4*S*)-1-*p*-tolyl-3-phenoxy-4-[(*R*)-2,2-di-methyl-1,3-dioxolan-4-yl] azetidin-2-one 3.05a

Following the general procedure, imine **3.03a** prepared from D-glyceraldehyde acetonide **3.02** and *p*-toludine (2.14 g, 20 mmol) was treated with triethylamine (6.7 mL, 48

mmol) and phenoxyacetyl chloride (3.3 mL, 24 mmol) at 0 °C to get azetidin-2-one **3.05a** as a white solid (4.51 g, 64%).

MP : 146 °C

$[\alpha]^{28}_{D}$: + 240 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) : 1753 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.38 (s, 3H), 1.57 (s, 3H), 2.35 (s, 3H), 3.75-3.88 (m, 1H), 4.35-4.45 (m, 2H), 4.55-4.60 (m, 1H), 5.35 (d, *J* = 5.5 Hz, 1H), 7.08-7.20 (m, 5H), 7.30-7.40 (m, 2H), 7.67 (d, *J* = 7.1 Hz, 2H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 20.83, 24.77, 26.53, 61.41, 67.00, 77.00, 79.21, 109.82, 115.74, 118.10, 122.62, 129.20, 129.60, 134.23, 135.00, 157.28, 163.53.

MS (m/z) : 353 (M^+).

Analysis ($C_{21}H_{23}NO_4$) : Calculated: C, 71.35; H, 6.56; N, 3.96
Observed: C, 71.20; H, 6.51; N, 3.79.

3. 5. 1b: Preparation of (3*R*, 4*S*)-1-*p*-tolyl-3-benzyloxy-4-[(*R*)-2,2-di-methyl-1,3-dioxolan-4-yl] azetidin-2-one 3.05b

Following the general procedure, imine **3.03a** prepared from D-glyceraldehyde acetonide **3.02** and *p*-toludine (2.14 g, 20 mmol) was treated with triethylamine (6.7 mL, 48 mmol) and benzyloxyacetyl chloride (3.8 mL, 24 mmol) at 0 °C to get azetidin-2-one **3.05b** as a white crystalline solid (4.77 g, 65%).

MP : 111-113 °C (Lit.[13] 110 °C).

$[\alpha]^{28}_{D}$: + 140.7 (*c* 1.4, $CHCl_3$).

IR ($CHCl_3$) : 1751 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.33 (s, 3H), 1.54 (s, 3H), 2.33 (s, 3H), 3.75 (dd, *J* = 6.5 & 8.8 Hz, 1H), 4.20-4.35 (m, 2H), 4.40-4.45 (m, 1H), 4.71 (d, *J* = 5.1 Hz, 1H), 4.75 (d, *J* = 11.5 Hz, 1H), 5.00 (d, *J* = 11.5 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.30-7.40 (m, 5H), 7.62 (d, *J* = 8.5 Hz, 2H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 20.69, 24.78, 26.52, 61.53, 66.93, 73.06, 76.91, 79.62, 109.56, 118.02, 127.78,128.00, 128.39, 129.07, 133.86, 135.20, 136.64,

165.08.

MS (m/z) : 367 (M^+).

Analysis : Calculated: C, 71.90; H, 6.86; N, 3.81

($C_{22}H_{25}NO_4$) Observed: C, 71.64; H, 7.04; N, 3.59.

3. 5. 1c: Preparation of (3*R*, 4*S*)-1-phenyl-3-phenoxy-4-[(*R*)-2,2-di-methyl-1,3-dioxolan-4-yl] azetidin-2-one 3.05c

Following the general procedure, imine **3.03b** prepared from D-glyceraldehyde acetonide **3.02** and aniline (1.86 g, 20 mmol) was treated with triethylamine (6.7 mL, 48 mmol) and phenoxyacetyl chloride (3.3 mL, 24 mmol) at 0 ^oC to get azetidin-2-one **3.05c** as a white solid (4.20 g, 65%).

MP : 122 ^oC

$[\alpha]^{28}_D$: + 259 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) : 1758 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 1.38 (s, 3H), 1.57 (s, 3H), 3.77-3.88 (m, 1H), 4.35-4.50 (m, 2H), 4.55-4.70 (m, 1H), 5.35 (d, *J* = 5.5 Hz, 1H), 7.08-7.20 (m, 4H), 7.33-7.40 (m, 4H), 7.77 (d, *J* = 7.4 Hz, 2H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 24.77, 26.57, 61.49, 67.00, 76.97, 79.17, 109.90, 115.74, 118.17, 122.69, 124.67, 128.76, 129.67, 137.47, 157.24, 163.86.

MS (m/z) : 340 (M+1).

Analysis : Calculated: C, 70.76; H, 6.24; N, 4.13

($C_{20}H_{21}NO_4$) Observed: C, 70.66; H, 6.49; N, 4.29.

3. 5. 1d: Preparation of (3*R*, 4*S*)-1-phenyl-3-benzyloxy-4-[(*R*)-2,2-di-methyl-1,3-dioxolan-4-yl] azetidin-2-one 3.05d

Following the general procedure, imine **3.03b** prepared from D-glyceraldehyde acetonide **3.02** and aniline (1.86 g, 20 mmol) was treated with triethylamine (6.7 mL, 48 mmol) and benzyloxyacetyl chloride (3.8 mL, 24 mmol) at 0 ^oC to get azetidin-2-one **3.05d** as a white solid (4.37 g, 62%).

MP : 119 ^oC (Lit.[13] 118 ^oC).

$[\alpha]^{28}_D$: + 140 (*c* 0.6, $CHCl_3$).

IR ($CHCl_3$) : 1751 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz)	:	1.31 (s, 3H), 1.52 (s, 3H), 3.70-3.80 (m, 1H), 4.15-4.30 (m, 2H), 4.40-4.50 (m, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.75 (d, *J* = 5.5 Hz, 1H), 5.00 (d, *J* = 11.7 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 1H) 7.24-7.40 (m, 7H), 7.70 (d, *J* = 8.8 Hz, 2H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	24.73, 26.53, 61.45, 66.89, 73.07, 76.93, 79.46, 109.60, 117.95, 124.31, 127.80, 128.06, 128.42, 128.61, 136.51, 137.58, 165.37.
MS (m/z)	:	353 (M^+).
Analysis ($C_{21}H_{23}NO_4$)	:	Calculated: C, 71.35; H, 6.56; N, 3.96 Observed: C, 71.46; H, 6.43; N, 4.17.

3. 5. 2: General procedure for preparation of 4-formylazetidin-2-ones 3.07a-d

A mixture of azetidin-2-one **3.05a-d** (10 mmol) and *p*-toluenesulphonic acid monohydrate (0.57 g, 3.0 mmol) in THF (40 mL) and water (15 mL) was refluxed for 24 h. After completion of reaction (TLC), the reaction mixture was neutralized with $NaHCO_3$ and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (25 mL) and the organic layer was washed with saturated brine solution (10 mL) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford the diol **3.06a-d**, which was dissolved in acetone (50 mL) and water (25 mL) and cooled to 0 ^{o}C. To the cooled solution of diol, $NaIO_4$ (2.56 g, 12 mmol) was added in portions. After completion of addition the reaction mixture was stirred at room temperature for 1 h. After completion of reaction (TLC), the solid was filtered off and washed with acetone. The solvent from the filtrate was removed and the residue was taken in dichloromethane (30 mL) and the organic layer was washed with water (2 x 10 mL), saturated sodium bicarbonate solution (2 x 10 mL), saturated brine solution (15 mL) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford the 4-formylazetidin-2-ones **3.07a-d**.

3. 5. 2a: Preparation of (3*R*, 4*R*)-1-*p*-tolyl-3-phenoxy-4-formylazetidin-2-one 3.07a

Following the general procedure, treatment of azetidin-2-one **3.05a** (3.53 g, 10 mmol) with PTSA monohydrate (0.57 g, 3.0 mmol) followed by oxidation of the diol **3.06a**

using $NaIO_4$ (2.56 g, 12 mmol) gave the 4-formylazetidin-2-one **3.07a** as a white solid (2.44 g, 87%).

MP : 152-153 ^oC

$[\alpha]^{28}_D$: + 184 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) : 1766, 1735 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 2.34 (s, 3H), 4.76 (dd, *J* = 5.1 Hz & 3.5 Hz, 1H), 5.55 (d, *J* = 5.1 Hz, 1H), 7.05-7.40 (m, 9H), 9.78 (d, *J* = 3.5 Hz, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 20.91, 62.92, 81.41, 115.60, 116.70, 123.09, 129.75, 129.93, 134.38, 135.22, 156.76, 161.62, 197.38.

MS (m/z) : 282 (M+1).

3. 5. 2b: Preparation of (3*R*, 4*R*)-1-*p*-tolyl-3-benzyloxy-4-formylazetidin-2-one 3.07b

Following the general procedure, treatment of azetidin-2-one **3.05b** (3.67 g, 10 mmol) with PTSA monohydrate (0.57 g, 3.0 mmol) followed by oxidation of the diol **3.06b** using $NaIO_4$ (2.56 g, 12 mmol) gave the 4-formylazetidin-2-one **3.07b** as a white solid (2.50 g, 85%).

MP : 158 ^oC

$[\alpha]^{28}_D$: + 186 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) : 1758, 1735 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 2.32 (s, 3H), 4.50 (dd, *J* = 5.5 Hz & 3.5 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 11.5 Hz, 1H), 5.02 (d, *J* = 5.5 Hz, 1H), 7.10-7.50 (m, 9H), 9.70 (d, *J* = 3.5 Hz, 1H).

^{13}CNMR ($CDCl_3$) (50.3 MHz) : δ 20.87, 63.17, 73.58, 82.65, 116.71, 128.24, 128.46, 128.64, 129.92, 134.68, 135.02, 135.90, 163.28, 198.65.

MS (m/z) : 296 (M+1).

3. 5. 2c: Preparation of (3*R*, 4*R*)-1-phenyl-3-phenoxy-4-formylazetidin-2-one 3.07c

Following the general procedure, treatment of azetidin-2-one **3.05c** (3.39 g, 10 mmol) with PTSA monohydrate (0.57 g, 3.0 mmol) followed by oxidation of the diol **3.06c**

using $NaIO_4$ (2.56 g, 12 mmol) gave the 4-formylazetidin-2-one **3.07c** as a white solid (2.26 g, 85%).

MP : 115 °C

$[\alpha]^{28}_D$: + 182.7 (*c* 0.52, $CHCl_3$).

IR ($CHCl_3$) : 1770, 1735 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 4.76 (dd, *J* = 5.5 Hz & 3.5 Hz, 1H), 5.54 (d, *J* = 5.5 Hz, 1H), 7.00-7.45 (m, 10H), 9.77 (d, *J* = 3.5 Hz, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 62.81, 81.26, 115.49, 116.70, 123.02, 125.30, 129.38, 129.67, 139.69, 156.69, 161.73, 197.01.

MS (m/z) : 267 (M^+).

3. 5. 2d: Preparation of (3*R*, 4*R*)-1-phenyl-3-benzyloxy-4-formylazetidin-2-one 3.07d

Following the general procedure, treatment of azetidin-2-one **3.05d** (3.53 g, 10 mmol) with PTSA monohydrate (0.57 g, 3.0 mmol) followed by oxidation of the diol **3.06d** using $NaIO_4$ (2.56 g, 12 mmol) gave the 4-formylazetidin-2-one **3.07d** as a white solid (2.47 g, 88%).

MP : 144-145 °C

$[\alpha]^{28}_D$: + 149.4 (*c* 0.85, $CHCl_3$).

IR ($CHCl_3$) : 1753, 1728 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 4.40 (dd, *J* = 5.5 Hz & 3.7 Hz, 1H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.70 (d, *J* = 11.9 Hz, 1H), 4.90 (d, *J* = 5.5 Hz, 1H), 7.00-7.10 (m, 1H), 7.20-7.35 (m, 9H), 9.60 (d, *J* = 3.7 Hz, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 62.97, 73.45, 82.43, 116.55, 125.04, 128.15, 128.38, 128.51, 129.30, 135.65, 136.85, 163.30, 198.40.

MS (m/z) : 282 (M+1).

3. 5. 3: General procedure for the preparation of nitroalkenes 3.09a-d

To a solution of 4-formylazetidin-2-one **3.07a-d** (6.0 mmol) in nitromethane (20 mL), was added triethylamine (0.1 mL, 1.0 mmol) at room temperature and the reaction mixture was stirred for 4-5 h. The excess nitromethane was removed under reduced pressure

to afford a viscous oil of diastereomeric mixture of nitroalcohols **3.08a-d**. This mixture was dissolved in acetic anhydride (20 mL) and cooled to 0 ^{o}C. A drop of Conc. H_2SO_4 was added to the reaction mixture and stirred at 0 ^{o}C for 1 h. After completion of reaction (TLC), 2 mL water was added at 0 ^{o}C and stirred for 30 minutes. It was extracted with ethyl acetate (2 x 15 mL) and the organic layer was washed with saturated $NaHCO_3$ (3 x 10 mL), brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford diastereomeric mixture of nitroacetates, which was refluxed with benzene (20 mL) in the presence of solid $NaHCO_3$ (4.0 g, 48 mmol) for 5 h. After completion of reaction (TLC), solid was removed by filtration and the solvent from the filtrate was removed under reduced pressure to afford the crude nitroalkene, which was further purified by column chromatography to get pure nitroalkenes **3.09a-d**.

3. 5. 3a: Preparation of (3*R*, 4*S*)-1-*p*-tolyl-4-(2-nitrovinyl)-3-phenoxy-azetidin-2-one 3.09a

Following the general procedure, treatment of 4-formylazetidin-2-one **3.07a** (1.68 g, 6.0 mmol) with nitromethane and triethylamine, followed by acylation and elimination gave the nitroalkene **3.09a** (1.39 g, 72%).

MP : 145-146 ^{o}C

$[\alpha]^{28}_{D}$: + 103.8 (*c* 1.04, $CHCl_3$).

IR ($CHCl_3$) : 1764, 1533, 1357 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.35 (s, 3H), 5.10 (dd, *J* = 5.1 Hz & 10.6 Hz, 1H), 5.60 (d, *J* = 5.1 Hz, 1H), 6.90-7.50 (m, 11H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 20.75, 55.27, 81.61, 115.49, 116.95, 122.96, 129.74, 129.91, 133.80, 134.62, 135.20, 142.92, 156.72, 161.39.

MS (m/z) : 325 (M+1).

Analysis ($C_{18}H_{16}N_2O_4$) : Calculated: C, 66.64; H, 4.97; N, 8.64
Observed: C, 66.48; H, 4.96; N, 8.65.

3. 5. 3b: Preparation of (3*R*, 4*S*)-1-*p*-tolyl-4-(2-nitrovinyl)-3-benzyloxy-azetidin-2-one 3.09b

Following the general procedure, treatment of 4-formylazetidin-2-one **3.07b** (1.77 g, 6.0 mmol) with nitromethane and triethylamine, followed by acylation and elimination gave the nitroalkene **3.09b** (1.48 g, 73%).

MP	:	138-140 ^{o}C
$[\alpha]^{28}_{D}$	:	+ 124 (*c* 1.04, $CHCl_3$).
IR ($CHCl_3$)	:	1755, 1552, 1515, 1388 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 2.31 (s, 3H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.70-4.75 (m, 1H), 4.86 (d, *J* = 11.7 Hz, 1H), 5.03 (d, *J* = 4.7 Hz, 1H), 7.00-7.35 (m, 11H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 20.69, 55.58, 74.07, 83.47, 116.86, 128.39, 128.45, 128.58, 129.80, 133.95, 134.80, 135.44, 135.90, 142.28, 162.76.
MS (m/z)	:	339 (M+1).
Analysis ($C_{19}H_{18}N_2O_4$)	:	Calculated: C, 67.43; H, 5.36; N, 8.28 Observed: C, 67.48; H, 4.96; N, 8.32.

3. 5. 3c: Preparation of (3*R*, 4*S*)-1-phenyl-4-(2-nitrovinyl)-3-phenoxy-azetidin-2-one 3.09c

Following the general procedure, treatment of 4-formylazetidin-2-one **3.07c** (1.60 g, 6.0 mmol) with nitromethane and triethylamine, followed by acylation and elimination gave the nitroalkene **3.09c** (1.35 g, 73%).

MP	:	152 ^{o}C
$[\alpha]^{28}_{D}$	:	+ 115 (*c* 0.6, $CHCl_3$).
IR ($CHCl_3$)	:	1751, 1529, 1353 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 5.08-5.15 (m, 1H), 5.59 (d, *J* = 5.1 Hz, 1H), 7.00-7.40 (m, 12H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 55.24, 81.45, 115.38, 116.92, 123.02, 125.37, 129.49, 129.78, 134.53, 136.14, 142.94, 156.54, 161.62.
MS (m/z)	:	310 (M^{+}).
Analysis ($C_{17}H_{14}N_2O_4$)	:	Calculated: C, 65.78; H, 4.55; N, 9.03 Observed: C, 65.66; H, 4.69; N, 8.99.

3. 5. 3d: Preparation of (3*R*, 4*S*)-1-phenyl-4-(2-nitrovinyl)-3-benzyloxy-azetidin-2-one 3.09d

Following the general procedure, treatment of 4-formylazetidin-2-one **3.07d** (1.68 g, 6.0 mmol) with nitromethane and triethylamine, followed by acylation and elimination gave the nitroalkene **3.09d** (1.44 g, 75%).

MP : 147 ^{o}C

$[\alpha]^{28}_{D}$: + 121.45 (*c* 0.55, $CHCl_3$).

IR ($CHCl_3$) : 1756, 1533, 1498, 1355 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 4.55 (d, *J* = 12.2 Hz, 1H), 4.65 (dd, *J* = 5.5 Hz & 13.4 Hz, 1H), 4.75 (d, *J* = 12.2 Hz, 1H), 4.95 (d, *J* = 5.5 Hz, 1H), 6.90 (d, *J* = 13.4 Hz, 1H), 6.95-7.00 (m, 1H), 7.05-7.10 (m, 1H), 7.15-7.35 (m, 9H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 55.62, 74.18, 83.44, 116.91, 125.09, 128.48, 128.52, 128.68, 129.40, 135.35, 135.87, 136.43, 142.33, 163.04.

MS (m/z) : 325 (M+1), 342 (M+18).

Analysis ($C_{18}H_{16}N_2O_4$) : Calculated: C, 66.64; H, 4.97; N, 8.64
Observed: C, 66.48; H, 5.06; N, 8.60.

3. 5. 4: General procedure for the preparation of nitroalkanes 3.10a-d

To a solution of nitroalkenes **3.09a-d** (3.5 mmol) in anhydrous dichloromethane (15 mL) and methanol (1.5 mL), tributyltin hydride (1.1 mL, 4.2 mmol) was added at room temperature and stirred for 24 h. After completion of reaction (TLC), the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography to get the pure nitroalkanes **3.10a-d**.

3. 5. 4a: Preparation of (3*R*, 4*S*)-1-*p*-tolyl-4-(2-nitroethyl)-3-phenoxy-azetidin-2-one 3.10a

Following the general procedure, nitroalkene **3.09a** (1.13 g, 3.5 mmol) was stirred with tributyltin hydride (1.1 mL, 4.2 mmol) at room temperature for 24 h to get the nitroalkane **3.10a** as a white solid (0.88 g, 78%).

MP : 75-76 ^{o}C

$[\alpha]^{28}_{D}$: + 222.7 (*c* 1.01, $CHCl_3$).

IR ($CHCl_3$) : 1758, 1556, 1382 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 2.35 (s, 3H), 2.50-2.70 (m, 1H), 2.80-3.00 (m, 1H), 4.50-4.70 (m, 3H), 5.42 (d, *J* = 5.4 Hz, 1H), 7.05-7.25 (m, 5H), 7.30-7.40 (m, 4H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 20.81, 25.03, 54.17, 71.48, 79.72, 115.70, 117.16, 122.78, 129.74, 129.89, 133.89, 134.71, 157.11, 162.49.
MS (m/z)	:	327 (M+1).
Analysis ($C_{18}H_{18}N_2O_4$)	:	Calculated: C, 66.23; H, 5.56; N, 8.58 Observed: C, 66.29; H, 5.55; N, 8.42.

3. 5. 4b: Preparation of (3*R*, 4*S*)-1-*p*-tolyl-4-(2-nitroethyl)-3-benzyloxy-azetidin-2-one 3.10b

Following the general procedure, nitroalkene **3.09b** (1.18 g, 3.5 mmol) was stirred with tributyltin hydride (1.1 mL, 4.2 mmol) at room temperature for 24 h to get the nitroalkane **3.10b** as a white solid (0.96 g, 81%).

MP	:	96-98 ^oC
$[\alpha]^{28}_D$	:	+ 122.5 (*c* 0.8, $CHCl_3$).
IR ($CHCl_3$)	:	1743, 1552, 1382 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 2.33 (s, 3H), 2.40-2.50 (m, 1H), 2.60-2.80 (m, 1H), 4.25-4.35 (m, 1H), 4.50-4.60 (m, 2H), 4.76 (d, *J* = 11.5 Hz, 1H), 4.82 (d, *J* = 5.1 Hz, 1H), 5.00 (d, *J* = 11.5 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.40-7.50 (m, 5H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 20.83, 24.89, 53.80, 71.49, 73.25, 80.28, 116.96, 127.98, 128.25, 128.57, 129.86, 133.99, 134.45, 136.56, 164.21.
MS (m/z)	:	341 (M+1).
Analysis ($C_{19}H_{20}N_2O_4$)	:	Calculated: C, 67.03; H, 5.92; N, 8.23 Observed: C, 67.29; H, 5.64; N, 8.42.

3. 5. 4c: Preparation of (3*R*, 4*S*)-1-phenyl-4-(2-nitroethyl)-3-phenoxy-azetidin-2-one 3.10c

Following the general procedure, nitroalkene **3.09c** (1.08 g, 3.5 mmol) was stirred with tributyltin hydride (1.1 mL, 4.2 mmol) at room temperature for 24 h to get the nitroalkane **3.10c** as a white solid (0.81 g, 75%).

MP	:	125 ^{o}C
$[\alpha]^{28}_{D}$	:	+ 242.5 (*c* 0.4, $CHCl_3$).
IR ($CHCl_3$)	:	1760, 1556, 1379 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 2.55-2.70 (m, 1H), 2.80-2.95 (m, 1H), 4.55-4.65 (m, 3H), 5.45 (d, *J* = 5.5 Hz, 1H), 7.10-7.25 (m, 5H), 7.35-7.50 (m, 5H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 24.88, 54.06, 71.41, 79.57, 115.60, 117.10, 122.84, 125.01, 129.49, 129.78, 136.25. 156.99, 162.72.
MS (m/z)	:	312 (M^{+}), 313 (M+1)

Analysis : Calculated: C, 65.36; H, 5.16; N, 8.97

($C_{17}H_{16}N_2O_4$) Observed: C, 65.29; H, 5.12; N, 8.85.

3. 5. 4d: Preparation of (3*R*, 4*S*)-1-phenyl-4-(2-nitroethyl)-3-benzyloxy-azetidin-2-one 3.10d

Following the general procedure, nitroalkene **3.09d** (1.13 g, 3.5 mmol) was treated with tributyltin hydride (1.1 mL, 4.2 mmol) at room temperature for 24 h to get the nitroalkane **3.10d** as a white crystalline solid (0.90 g, 79%).

MP : 114-115 ^oC

$[\alpha]^{28}_D$: + 169.7 (*c* 0.7, $CHCl_3$).

IR ($CHCl_3$) : 1751, 1554, 1379 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 2.30-2.40 (m, 1H), 2.60-2.70 (m, 1H), 4.25-4.30 (m, 1H), 4.40-4.45 (m, 2H), 4.70 (d, *J* = 11.4 Hz, 1H), 4.75 (d, *J* = 5.5 Hz, 1H), 5.90 (d, *J* = 11.4 Hz, 1H), 7.05-7.10 (m, 1H), 7.25-7.30 (m, 9H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 24.90, 53.93, 71.45, 73.28, 80.36, 117.01, 124.64, 127.94, 128.21, 128.52, 129.34, 136.51, 164.41.

MS (m/z) : 327 (M+1).

Analysis : Calculated: C, 66.23; H, 5.56; N, 8.58

($C_{18}H_{18}N_2O_4$) Observed: C, 66.54; H, 5.23; N, 8.70.

3. 5. 5: General procedure for the preparation of nitroesters 3.11a-d

A solution of nitroalkanes **3.10a-d** (3.0 mmol) in methanolic HCl (20%, 10 mL) was stirred at room temperature for 12-24 h. After completion of the reaction (TLC), solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (20 mL), washed with saturated sodium bicarbonate solution (10 mL), brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to get the crude nitroester, which was then purified by column chromatography to afford the pure nitroesters **3.11a-d**.

3. 5. 5a: Preparation of methyl (2*R*, 3*S*)-3-[(4-*p*-tolyl)amino]-5-nitro-2-phenoxypentanoate 3.11a

Following the general procedure, nitroalkane **3.10a** (0.98 g, 3.0 mmol) was stirred in methanolic HCl (20%) for 24 h (TLC) to get the nitroester **3.11a** as a white solid (0.90 g, 84%).

MP : 117 ^{o}C

$[\alpha]^{28}_{D}$: - 72 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) : 3392, 1757, 1554, 1379 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.26 (s, 3H), 2.35-2.50 (m, 2H), 3.52 (s, 3H), 4.20-4.40 (m, 1H), 4.50-4.65 (m, 2H), 4.78 (d, *J* = 2.3 Hz, 1H), 6.60 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 7.00-7.10 (m, 3H), 7.25-7.35 (m, 2H).

^{13}C NMR ($CDCl_3$) (75.5 MHz) : δ 20.25, 29.99, 52.15, 53.47, 72.22, 77.15, 114.16, 114.97, 122.14, 127.98, 129.56, 129.78, 143.94, 157.17, 169.67.

MS (m/z) : 358 (M^{+}).

Analysis ($C_{19}H_{22}N_2O_5$) : Calculated: C, 63.66; H, 6.19; N, 7.82
Observed: C, 63.77; H, 5.96; N, 7.93.

3. 5. 5b: Preparation of methyl (2*R*, 3*S*)-3-[(4-*p*-tolyl)amino]-5-nitro-2-benzyloxypentanoate 3.11b

Following the general procedure, nitroalkane **3.10b** (1.02 g, 3.0 mmol) was stirred in methanolic HCl (20%) for 24 h (TLC) to get the nitroester **3.11b** as a pale yellow oil (0.94 g, 85%).

MP : oil

$[\alpha]^{28}_{D}$: - 4.76 (*c* 1.26, $CHCl_3$).

IR ($CHCl_3$) : 3421, 1745, 1552, 1379 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.19 (s, 3H), 2.20-2.30 (m, 2H), 3.55 (s, 3H), 4.00-4.05 (m, 2H), 4.35-4.50 (m, 2H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.90 (d, *J* = 11.6 Hz, 1H), 6.52 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 7.35-7.45 (m, 5H).

^{13}C NMR ($CDCl_3$) : δ 20.21, 29.84, 51.80, 53.48, 72.27, 72.68, 77.70, 113.98,

(75.5 MHz) 127.58, 128.21, 128.31, 128.47, 129.66, 136.68, 144.11, 170.78.

MS (m/z) : 372 (M^+).

Analysis : Calculated: C, 64.48; H, 6.50; N, 7.52

($C_{20}H_{24}N_2O_5$) Observed: C, 64.77; H, 6.68; N, 7.79.

3. 5. 5c: Preparation of methyl (2*R*, 3*S*)-3-[(4-phenyl)amino]-5-nitro-2-phenoxypentanoate 3.11c

Following the general procedure, nitroalkane **3.10c** (0.94 g, 3.0 mmol) was stirred in methanolic HCl (20%) for 24 h (TLC) to get the nitroester **3.11c** as a pale yellow solid (0.84 g, 82%).

MP : 114-116 ^oC

$[\alpha]^{28}_D$: - 77 (*c* 0.4, $CHCl_3$).

IR ($CHCl_3$) : 3396, 1757, 1554, 1379 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 2.30-2.55 (m, 2H), 3.50 (s, 3H), 4.25-4.40 (m, 1H), 4.55-4.65 (m, 2H), 4.77 (d, *J* = 2.8 Hz, 1H), 6.65-6.90 (m, 5H), 7.00-7.10 (m, 2H), 7.15-7.35 (m, 3H).
(200 MHz)

^{13}C NMR ($CDCl_3$) : δ 30.09, 52.13, 53.35, 72.24, 77.27, 114.17, 115.15, 118.93, 122.29, 129.34, 129.62, 146.31, 157.30, 169.63.
(75.5 MHz)

MS (m/z) : 344 (M^+).

Analysis : Calculated: C, 62.76; H, 5.85; N, 8.13

($C_{18}H_{20}N_2O_5$) Observed: C, 62.77; H, 5.98; N, 7.89.

3. 5. 5d: Preparation of methyl (2*R*, 3*S*)-3-[(4-phenyl)amino]-5-nitro-2-benzyloxypentanoate 3.11d

Following the general procedure, nitroalkane **3.10d** (0.98 g, 3.0 mmol) was stirred in methanolic HCl (20%) for 12 h (TLC) to get the nitroester **3.11d** as a pale yellow oil (0.91 g, 85%).

MP : oil

$[\alpha]^{28}_D$: - 9.1 (*c* 0.55, $CHCl_3$).

IR (Neat) : 3384, 1741, 1550, 1379 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 2.20-2.35 (m, 2H), 3.54 (s, 3H), 4.05-4.10 (m, 2H), 4.30-4.50 (m, 2H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.90 (d, *J* = 11.7 Hz, 1H), 6.59 (d, *J* = 7.6 Hz, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.35-7.40 (m, 5H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 29.97, 51.79, 53.32, 72.30, 72.82, 77.89, 113.90, 118.48, 128.27, 128.36, 128.52, 129.22, 136.76, 146.58, 170.10.
MS (m/z)	:	358 (M^+).
Analysis ($C_{19}H_{22}N_2O_5$)	:	Calculated: C, 63.66; H, 6.19; N, 7.82 Observed: C, 63.76; H, 6.34; N, 7.68.

3. 5. 6: General procedure for preparation of 4-aminopiperidin-2-ones 3.12a-d

To a solution of nitroesters **3.11a-d** (1.6 mmol) in anhydrous methanol (10 mL), 10% Pd/C (0.10 g) was added followed by ammonium formate (0.50 g, 8.0 mmol) and the reaction mixture was stirred at room temperature under argon for 2-10 h or if required refluxed until the starting material disappears. After completion of reaction (TLC), the reaction mixture was filtered through celite bed and the bed was washed with methanol. The solvent from the filtrate was removed under reduced pressure and the residue was dissolved in dichloromethane (20 mL), washed with water (5 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. Removal of solvent gave crude product, which was purified by column chromatography to afford pure 4-aminopiperidin-2-ones **3.12a-d**.

3. 5. 6a: Preparation of (3*R*, 4*S*)-4-[(4-*p*-tolyl)amino]-3-phenoxy-piperidin-2-one 3.12a

Following the general procedure, nitroester **3.11a** (0.57 g, 1.6 mmol) was treated with 10% Pd/C (0.10 g) and ammonium formate (0.50 g, 8.0 mmol) and was refluxed for 3 h to get the 4-aminopiperidin-2-one **3.12a** as a thick pale yellow oil (0.32 g, 68%).

MP	:	Thick oil
$[\alpha]^{28}_D$	:	+ 58.7 (*c* 0.7, $CHCl_3$).
IR ($CHCl_3$)	:	3346, 1658 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 1.95-2.10 (m, 1H), 2.25 (s, 3H), 2.40-2.60 (m, 1H), 3.60-3.80 (m, 2H), 3.90-4.05 (m, 1H), 4.76 (d, *J* = 5.5 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 7.8 Hz, 2H), 7.05-7.15 (m, 3H), 7.32 (d, *J* = 7.8 Hz, 2H)

^{13}C NMR ($CDCl_3$) : δ 20.32, 23.88, 46.16, 51.38, 77.52, 114.13, 116.51, 122.25, 127.98, 129.53, 129.82, 143.57, 158.23, 162.54.
(50.3 MHz)

MS (m/z) : 297 (M+1).

Analysis : Calculated: C, 72.93; H, 6.80; N, 9.45
($C_{18}H_{20}N_2O_2$) Observed: C, 72.68; H, 6.64; N, 9.57.

3. 5. 6b: Preparation of (3*R*, 4*S*)-4-[(4-*p*-tolyl)amino]-3-benzyloxy-piperidin-2-one 3.12b

Following the general procedure, nitroester **3.11b** (0.59 g, 1.6 mmol) was treated with 10% Pd/C (0.10 g) and ammonium formate (0.50 g, 8.0 mmol) and was refluxed for 3 h to get the 4-aminopiperidin-2-one **3.12b** as a thick brown oil (0.34 g, 68%).

MP : Thick oil

$[\alpha]^{28}_D$: + 68.6 (*c* 0.7, $CHCl_3$).

IR ($CHCl_3$) : 3396, 1639 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 1.80-2.00 (m, 1H), 2.25 (s, 3H), 2.35-2.55 (m, 1H), 3.65-3.75 (m, 3H), 4.00 (d, *J* = 5.7 Hz, 1H), 4.75 (d, *J* = 11.6 Hz, 1H), 4.95 (d, *J* = 11.6 Hz, 1H), 6.45 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 7.30-7.40 (m, 5H).
(200 MHz)

^{13}C NMR ($CDCl_3$) : δ 20.23, 24.20, 46.18, 51.82, 73.28, 77.24, 113.90, 127.60, 127.88, 128.27, 129.74, 137.52, 143.84, 163.89.
(50.3 MHz)

MS (m/z) : 311 (M+1).

Analysis : Calculated: C, 73.51; H, 7.15; N, 9.03
($C_{19}H_{22}N_2O_2$) Observed: C, 73.63; H, 7.36; N, 9.24.

3. 5. 6c: Preparation of (3*R*, 4*S*)-4-[(4-phenyl)amino]-3-phenoxy-piperidin-2-one 3.12c

Following the general procedure, nitroester **3.11c** (0.55 g, 1.6 mmol) was treated with 10% Pd/C (0.10 g) and ammonium formate (0.50 g, 8.0 mmol) and was refluxed for 3 h to get the 4-aminopiperidin-2-one **3.12c** as a thick brown oil (0.29 g, 65%).

MP : Thick oil

$[\alpha]^{28}_D$: + 35.5 (*c* 2.25, $CHCl_3$).

IR ($CHCl_3$) : 3400, 1676 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 1.75-1.95 (m, 1H), 2.30-2.40 (m, 1H), 3.30-3.40 (m, 2H), 3.95-4.05 (m, 1H), 4.60 (d, *J* = 7.1 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 2H), 6.77 (t, *J* = 7.4 Hz, 1H), 7.00-7.30 (m, 7H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 25.72, 38.33, 52.52, 77.77, 114.35, 116.44, 118.98, 121.95, 126.51, 129.31, 145.63, 158.71, 169.63.
MS (m/z)	:	283 (M+1).
Analysis ($C_{17}H_{18}N_2O_2$)	:	Calculated: C, 72.30; H, 6.43; N, 9.92 Observed: C, 72.16; H, 6.28; N, 9.76.

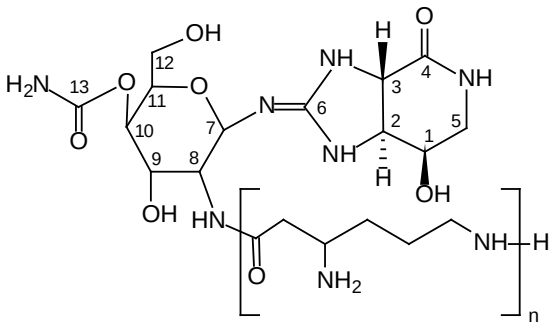
3. 5. 6d: Preparation of (3*R*, 4*S*)-4-[(4-phenyl)amino]-3-benzyloxy-piperidin-2-one 3.12d

Following the general procedure, nitroester **3.11d** (0.57 g, 1.6 mmol) was treated with 10% Pd/C (0.10 g) and ammonium formate (0.50 g, 8.0 mmol) at room temperature for 6 h to get the 4-aminopiperidin-2-one **3.12d** as light brown oil (0.31 g, 66%).

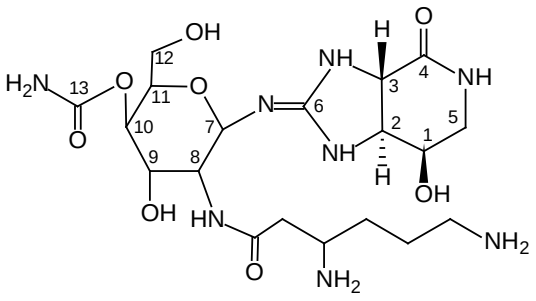
MP	:	oil.
$[\alpha]^{28}_{D}$	:	+ 57.7 (*c* 0.23, $CHCl_3$).
IR ($CHCl_3$)	:	3398, 1674 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 1.75-1.90 (m, 1H), 2.30-2.40 (m, 1H), 3.35-3.40 (m, 2H), 3.70-3.80 (m, 1H), 3.92 (d, *J* = 7.1 Hz, 1H), 4.75 (d, *J* = 11.5 Hz, 1H), 5.05 (d, *J* = 11.5 Hz, 1H), 6.50 (bs, 1H), 6.65 (d, *J* = 8.3 Hz, 2H), 6.80 (t, *J* = 6.9 Hz, 1H), 7.15 –7.40 (m, 7H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 25.61, 38.45, 53.04, 73.57, 76.63, 114.59, 119.39, 128.02, 128.48, 128.59, 129.38, 137.63, 142.58, 171.40.
MS (m/z)	:	297 (M+1).
Analysis ($C_{18}H_{20}N_2O_2$)	:	Calculated: C, 72.93; H, 6.80; N, 9.45 Observed: C, 72.73; H, 6.74; N, 9.27.

3.6 : Background for the present work

Streptothricine belongs to a class of strongly basic and water-soluble antibiotics; isolated from microbial sources.[18] It shows potent activity against wide range of bacteria as well as some pathogenic fungi. It is also known to show insecticidal activity, fish toxicity and plant growth inhibitory activity.[19] This was first isolated in 1942 by Waksman[20] but none of these class of compounds were used clinically due to their inherent toxicity. Each member of the Streptothricine family is composed of 2-amino-2-deoxy-D-glucose (D-gulosamine), L-β-lysine and lactam form of novel heterocyclic amino acid component 'Streptolidine'. The only variable component is the number of the β-lysine units.



Streptothricine



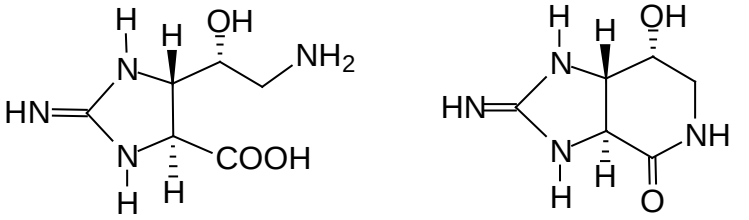
Streptothricine-F (n = 1)

Figure 1

Van Tamelen[21] deduced the total structure of Streptothricine-F in 1961 however; the precise location of the carbamate group was in doubt. Shiba and co-workers[22] assigned its structure from the total synthesis and on the basis of the proposal by Van Tamelen (Figure 1). Glucopyranoside was used as a synthon, which was converted into β-glycosyl skeleton followed by coupling with the streptolidine part in THF at room temperature. They have also studied the structure activity relationship and the toxicity.

Streptolidine is an amino acid component present in Streptothricine, which was first isolated from the acid hydrolysis of Streptothricin and Streptolin.[23] It consists of 2-amino-2-

imidazoline ring with three asymmetric centers. In 1961 Carter et al.[21] deduced the chemical structure of this amino acid by means of degradation studies and its absolute configuration was established by X-ray crystallography (Figure 2).[21]

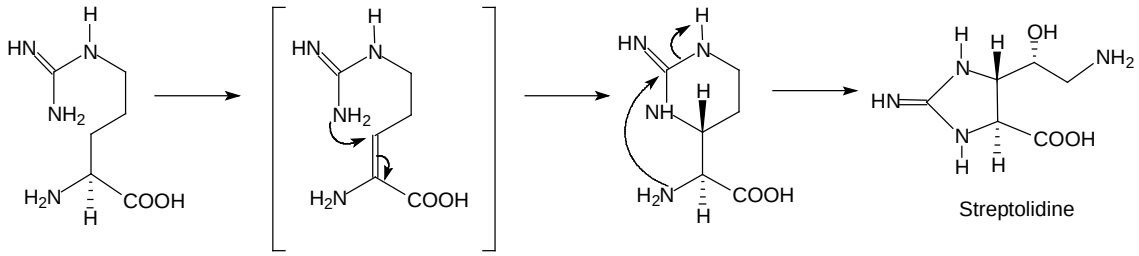


Streptolidine Streptolidine lactam

Figure 2

In 1972 Bycroft et al.[24] proposed a chemically rational biogenesis of Streptolidine starting from arginine via a dehydroamino acid followed by the rearrangement of a 6-membered cyclic guanidine as shown in Scheme 3.06.

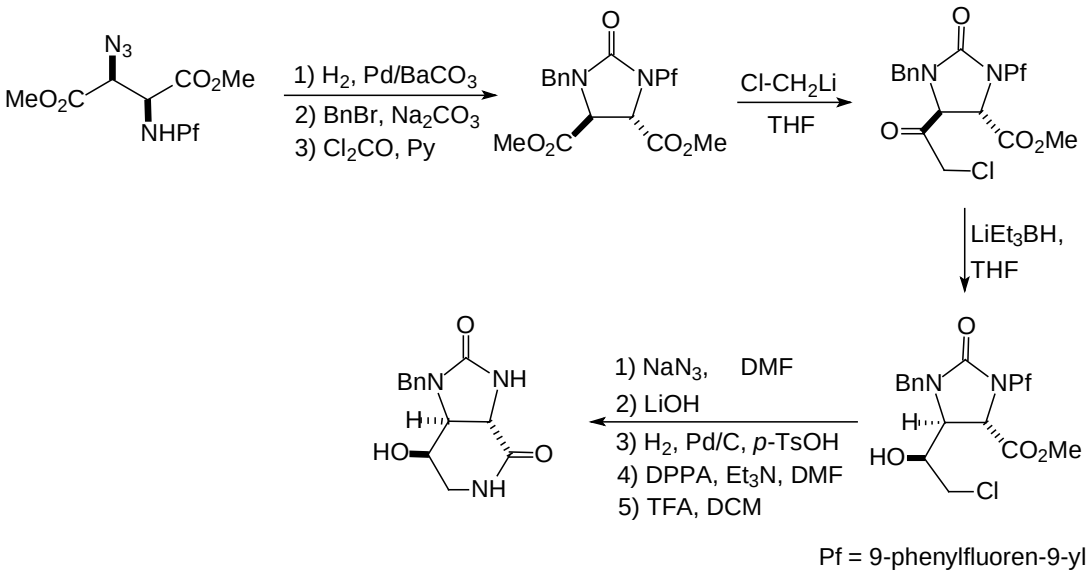
Scheme 3.06



Based on the above biogenesis the biosynthesis of Streptolidine moiety i.e. 2,5-diamino-3-*O*-benzyloxymethyl-3-t-butoxycarbonylamino-2,3,5-trideoxy-D-arabinono-1,5-lactam (Figure 2) was reported by Gould and his group.[25] L-Arginine was used as a precursor for the preparation of streptolidyl moiety. The synthesis was further supported with the labeling studies.

The second synthesis towards the Streptolidine lactam was reported by Sardina et al.[26] from azido aspartic acid derivative. Mild hydrogenation of *N*-Pf-3-azido aspartate followed by *N*-monobenylation and cyclization of the resulting diamine with phosgene provided the cyclic urea (Scheme 3.07). The chemoselective chain elongation of one of the ester groups was effected with chloromethyl lithium to give the ketone. The carbonyl group of ketone on reduction with trimethyl lithium borohydride gave the corresponding alcohol.

Scheme 3.07

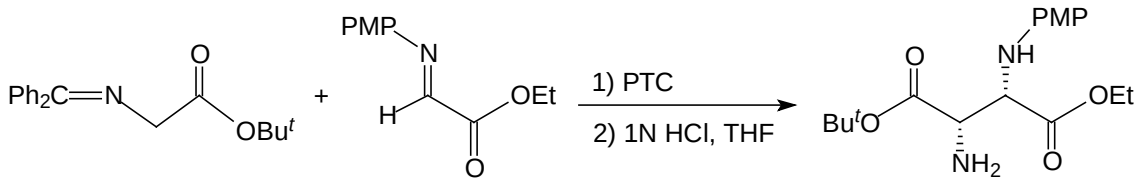


Pf = 9-phenylfluoren-9-yl

Chloride group displacement by azide followed by ester hydrolysis, azide reduction and cyclization of the resulting amino acid with diphenylphosphoryl azide (DPPA) furnished the precursor for the Streptolidine lactam.

Recently Maruoka et al.[27] have used the phase-transfer-catalyzed direct Mannich reaction of glycinate Schiff base with α-imino esters. The reaction furnishes protected 3-aminoaspartate (Scheme 3.08).

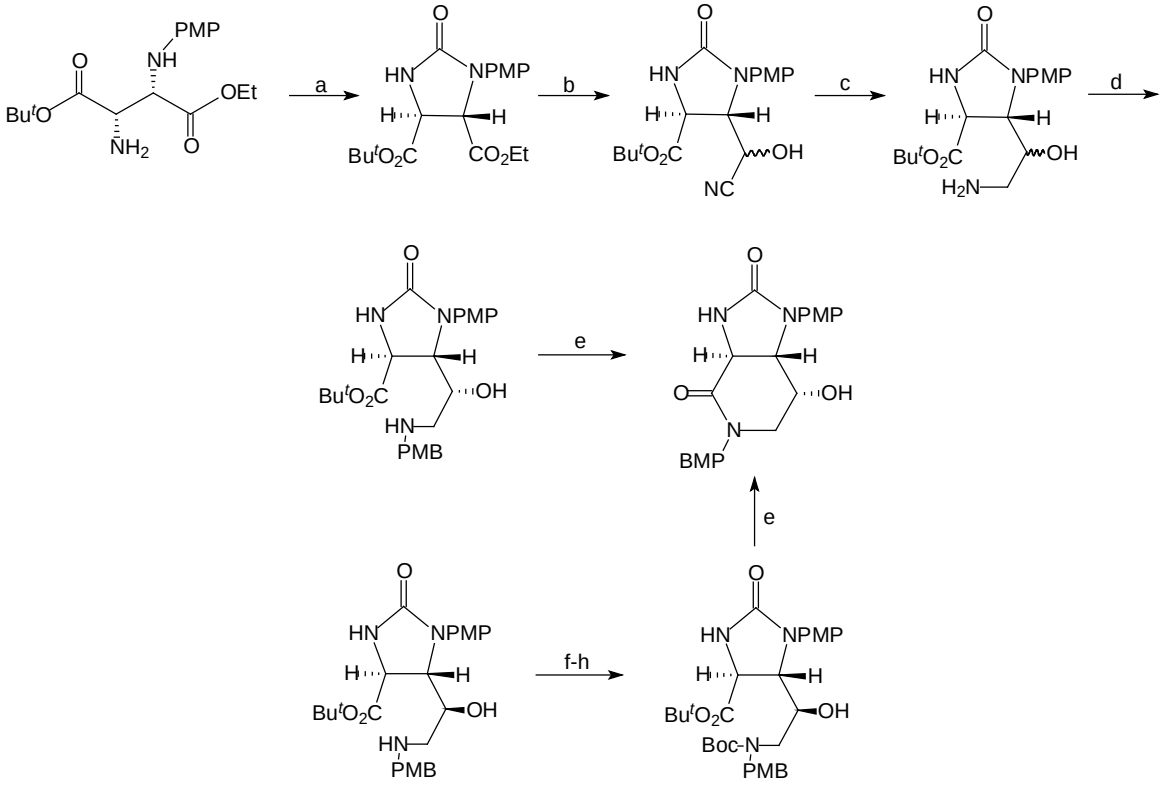
Scheme 3.08



This differentially protected 3-aminoaspartate derivative was then employed for concise stereoselective

construction of Streptolidine lactam precursor as depicted in the Scheme 3.09. It was initially transformed into a cyclic urea, subsequent selective reduction-cyanation of ethyl ester furnished the cynohydrin. Hydrogenation and protection of the primary amine formed, followed by ring closure via hydrolysis of the ester furnished the precursor for the Streptolidine lactam.

Scheme 3.09



Reagents and conditions: (a) triphosgene, Et_3N, CH_2Cl_2, rt, 69%, 99% (*trans* after a single crystallization); (b) DIABLH, ether-CH_2Cl_2, -78 °C, then Me_3SiCN, -78-0 °C, 80% (dr = 1:1.5); (c) H_2, PtO_2, AcOH, rt, 90%; (d) anisaldehyde, Na_2SO_4, CH_2Cl_2, rt, then $NaBH_4$, EtOH, 0 °C, 71%; (e) HCO_2H, 60 °C, then DPPA, Et_3N, DMF, 65%; (f) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C-rt, 98%; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 97%; (h) $ZnBH_4$, ether, 0 °C, 53%.

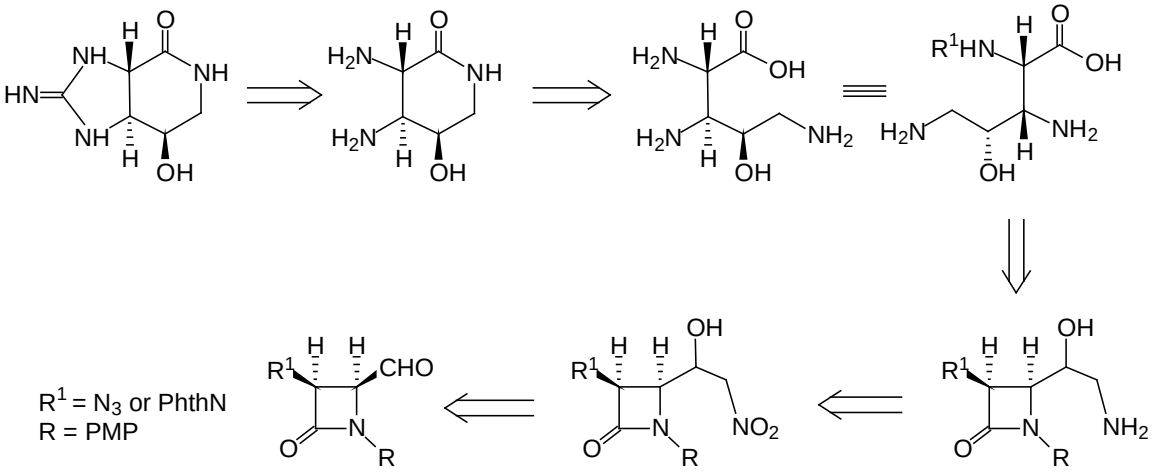
3.7 : Present work

This section of the chapter describes our efforts towards the synthesis of Streptolidine lactam, an amino acid part of antibiotic Streptothricine-F using azetidin-2-one as a synthon. The starting azetidin-2-one with either azido or the phthalimido group at C-3 position could be preferred as it can be further converted at a later stage into an amino functional group, which is an essential part of the Streptolidine lactam.

3.8 : Results and Discussions

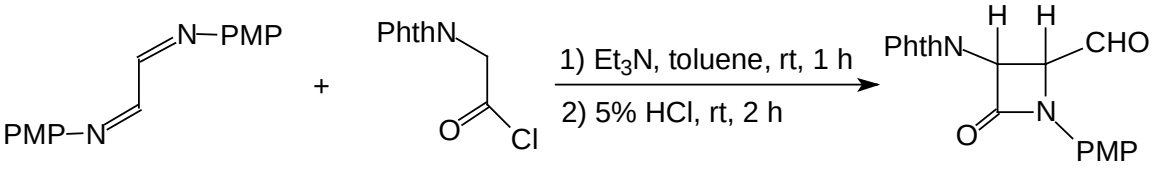
Our strategy to synthesize 3,4-diamino-5-hydroxy-piperidin-2-one using the synthetic protocol is depicted in the following retro synthetic scheme (Scheme 3.10). The substituted 4-aminopiperidin-2-one can be further transformed into the Streptolidine lactam by rational functional group transformations.

Scheme 3.10



Initially we chose racemic 3-phthalimido-4-formyl-azetidin-2-one **3.15** as a synthon for the synthesis of 3,4-diamino-piperidin-2-one, so that the phthalimido group can be converted to amino group[28] at later stages of the synthesis. The β-lactam **3.15** was synthesized from phthalimidoacetyl chloride **3.14** and bisimine **3.13** following a reported procedure (Scheme 3.11).[29]

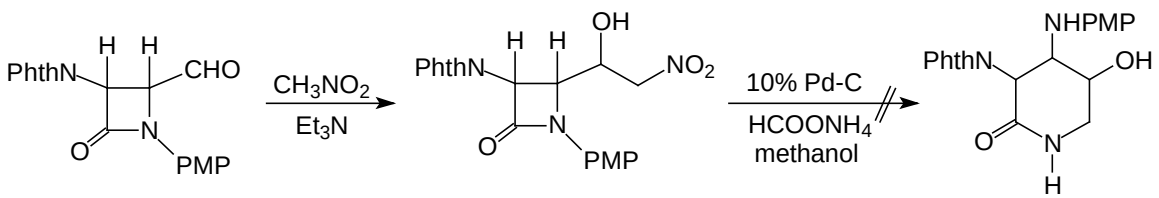
Scheme 3.11



3.13 **3.14** **3.15**

The *cis*-4-formyl-β-lactam **3.15** was then subjected to nitroaldol reaction by treating it with nitromethane in the presence of triethyl amine (Scheme 3.12).

Scheme 3.12



3.15 **3.16** **3.17**

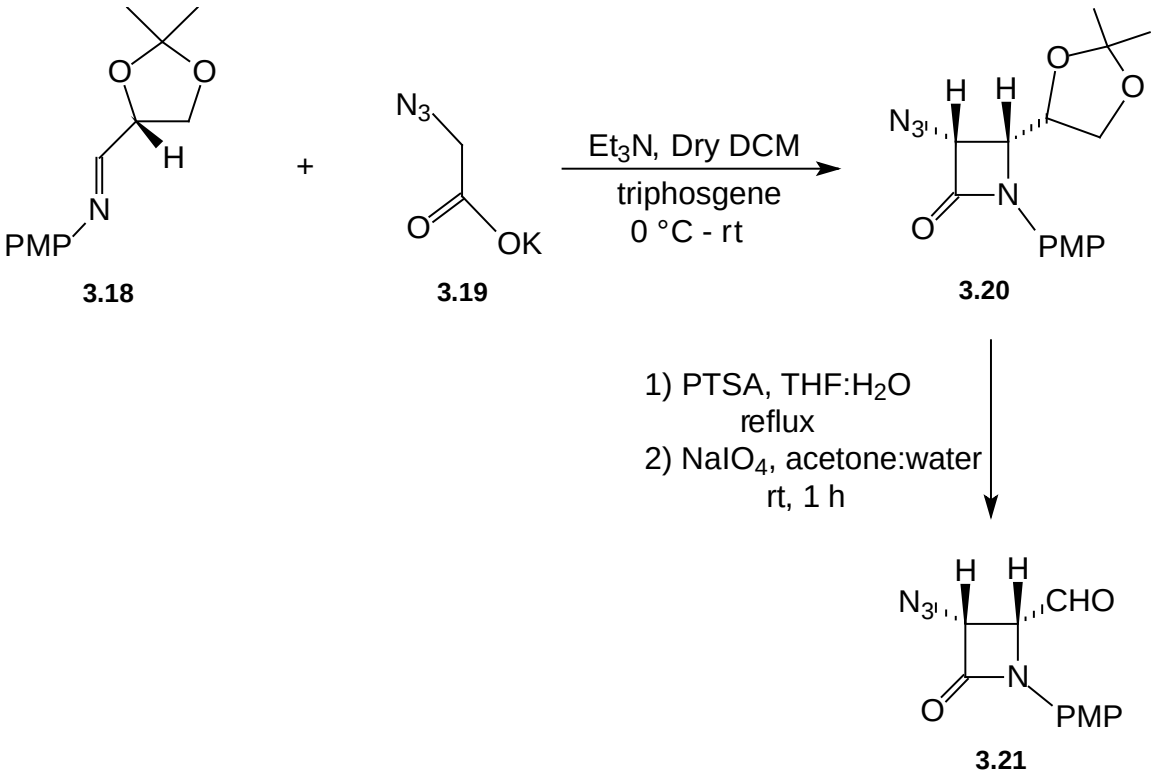
The nitroaldol product **3.16** showed a broad band between 3200-3500 cm^{-1} corresponding to the hydroxy, bands at 1749 and 1720 corresponding to the β-lactam and phthalimido carbonyl groups and bands at 1560 and 1384 cm^{-1} for the nitro group.

The ^{1}H NMR spectrum of **3.16** showed a singlet at 3.75 ppm corresponding to the methoxy protons. The C-3 proton of the β-lactam ring appeared as a doublet at 5.55 ppm with J = 5.4 Hz. The remaining three protons along with the C-3 proton of the β-lactam ring were seen as a multiplet between 4.40-4.75 ppm. The aromatic protons of PMP group appeared as two separate doublets at 6.85 and 7.60 ppm with J = 8.8 Hz. A multiplet between 7.70-7.95 ppm was due to the remaining four aromatic protons.

One pot reduction and cyclization of the nitroaldol product **3.16** was carried out by transfer hydrogenation using ammonium formate and 10% Pd-C in methanol under reflux conditions (Scheme 3.12). However, there was solubility problem of the formed product and the reaction also gave complex mixture of products, which were difficult to purify either by chromatography or by crystallization.

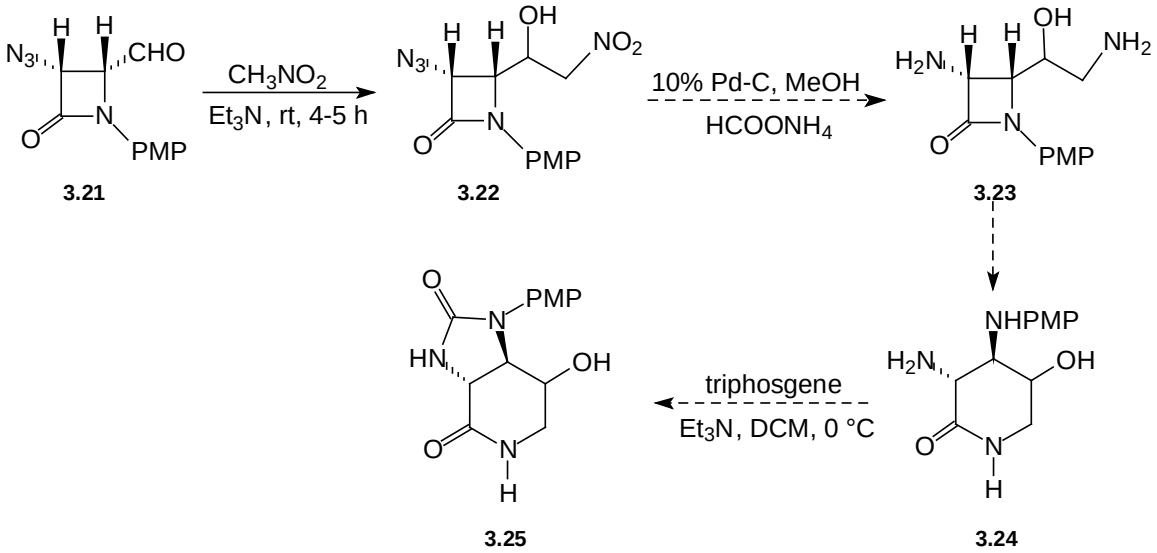
Therefore, we planned an alternative synthetic route towards the synthesis of Streptolidine lactam from enantiopure azetidin-2-one **3.20** as described in the Schemes 3.13 and 3.14.

Scheme 3.13



3-Azido-4-formyl-β-lactam **3.21** was easily obtained from 3-azido-β-lactam **3.20**. The required enantiopure 3-azido-β-lactam **3.20** was prepared from potassium azido acetate **3.19** and chiral imine **3.18** derived from D-glyceraldehyde acetonide and *p*-anisidine using triphosgene as an acid activator (Scheme 3.13). The starting potassium azido acetate was easily obtained by reaction of ethyl bromoacetate and sodium azide followed by hydrolysis of the ethyl azido acetate.

Scheme 3.14



The acetonide group of 3.20 was hydrolyzed (PTSA, THF-H_2O) to the diol, which was then oxidatively cleaved using sodium periodate to get the 3-azido-4-formyl-azetidin-2-one 3.21 (Scheme 3.13).

The structure of this 3-azido-4-formyl-β-lactam 3.21 was established based on its spectral data. The 4-formyl-azetidinone 3.21 was then reacted with nitromethane in the presence of catalytic triethyl amine at room temperature to furnish the diastereomeric mixture (70:30) of nitroalcohols 3.22 (Scheme 3.14). Major isomer of the nitroalcohol 3.22 was characterized by IR and ^{1}H NMR.

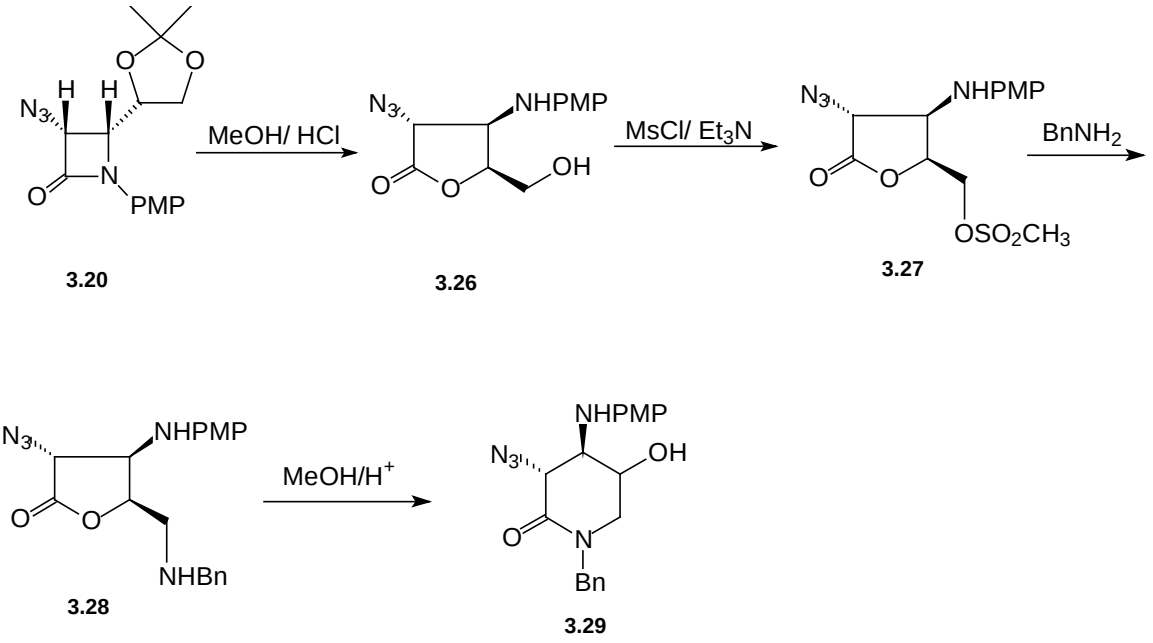
The major isomer of nitroaldol **3.22** showed a broad band between 3200-3500 cm^{-1} corresponding to the hydroxy group, bands at 2119 and 1745 were due to the azido and β-lactam carbonyl and bands at 1556 and 1382 cm^{-1} were for the nitro group.

The ^{1}H NMR spectrum showed a singlet at 3.80 ppm corresponding to the methoxy protons. The C-3 proton of the β-lactam ring appeared as a doublet at 5.00 ppm with J = 5.5 Hz. The C-4 proton and the methylene protons of the C-4 side chain appeared as a multiplet between 4.50-4.65 ppm. A multiplet between 4.80-4.85 ppm was due to the methine proton of the C-4 side chain. The aromatic protons of PMP group appeared as two separate doublets at 6.90 and 7.40 ppm with J = 9.0 Hz.

We were interested in simultaneous reduction of nitro and azido group using transfer hydrogenation using Pd-C (10%) and ammonium formate or catalytic hydrogenation using Pd-C (10%). Transfer hydrogenation of nitroaldol in refluxing methanol gave a complex mixture of products instead of the desired 3,4-diamino-5-hydroxy-piperidin-2-one **3.24**. The catalytic hydrogenation also was not fruitful and gave complex mixture of undesired inseparable mixture of products.

To overcome the difficulties encountered in the above routes, we planned another synthetic strategy based on azetidinone ring expansion. It is reported in the literature that the azetidin-2-one with acetonide group at C-4 rearranges to γ-lactone under acidic conditions.[30] Based on this we planned our synthesis of precursor for the Streptolidine lactam as depicted in Scheme 3.15.

Scheme 3.15



3.20 **3.26** **3.27** **3.28** **3.29**

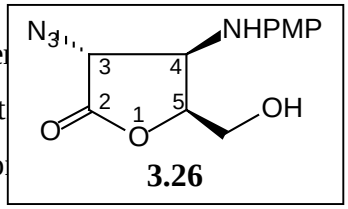
We envisaged the displacement of mesylate group of **3.27** by benzyl amine followed by acid catalyzed lactone ring opening of **3.28** and one pot cyclization would give us the desired amino piperidinone **3.29**.

The β-lactam **3.20** on treatment of with methanolic HCl (20%) for about 24-30 h (Scheme 3.15) gave rearranged γ-lactone **3.26** in good yield. The formation of this γ-lactone **3.26** must be arising from the hydrolysis of acetonide group and lactam ring followed by intramolecular cyclization of the preformed β-amino ester involving the secondary hydroxyl group. The structure of this γ-lactone **3.26** was confirmed from the IR spectrum that showed

bands at 2115 and 1782 cm^{-1} corresponding to azido and the lactone carbonyl. The hydroxy and secondary amino groups were observed at 3382 and 3400 cm^{-1}.

The ^{1}H NMR spectrum of **3.26** showed a singlet at 3.76 ppm corresponding to the methoxy protons. The C-3 proton attached to azido group was seen as a doublet at 4.75 ppm with J = 9.0 Hz.

The other protons including -OH, -NH protons wer observed as a multiplet between 3.80-4.35 ppm. The aromat protons appeared as two doublets at 6.72 ppm and 6.82 pp with J = 9.0 Hz.



3.26

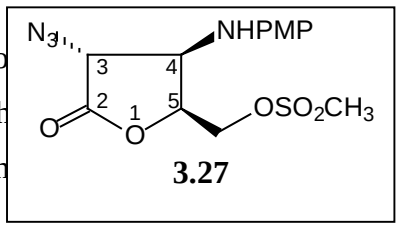
The ^{13}C spectrum of this hydroxy lactone **3.26** showed a peak at 55.64 ppm corresponding to the methoxy carbon. The peak at 60.34 ppm was due to the methylene carbon. The C-3, C-4 and C-5 lactone carbons appeared at 79.62, 58.60 and 62.66 ppm respectively. The aromatic quaternary carbons appeared at 153.27 ppm and 139.93 ppm, while the remaining aromatic carbons appeared at 115.21 ppm. The lactone carbonyl appeared at 172.43 ppm. The mass spectrum of this compound showed a molecular ion peak at m/z 296 (M+18).

The free primary hydroxy group of the lactone **3.26** was then protected as its mesylate by treatment with mesityl chloride in dry dichloromethane in the presence of triethyl amine with catalytic DMAP at 0 ^{o}C. This afforded the mesylated lactone **3.27** in 78% yield.

The mesylated lactone **3.27** showed the bands at 3362, 2117, and 1789 cm^{-1} in the IR spectrum that correspond to secondary amino, azido and the lactone carbonyl functional groups respectively.

The ^{1}H NMR spectrum of **3.27** showed two singlets at 3.10 and 3.76 ppm corresponding to the methyl and methoxy group protons. The C-3 proton appeared as a doublet at 4.95 ppm with J = 7.5 Hz.

The remaining five protons including –NH proto were seen as a multiplet in the range of 4.30-4.60 ppm. Th aromatic protons appeared as two doublets at 6.68 ppm an 6.82 ppm with J = 8.8 Hz.



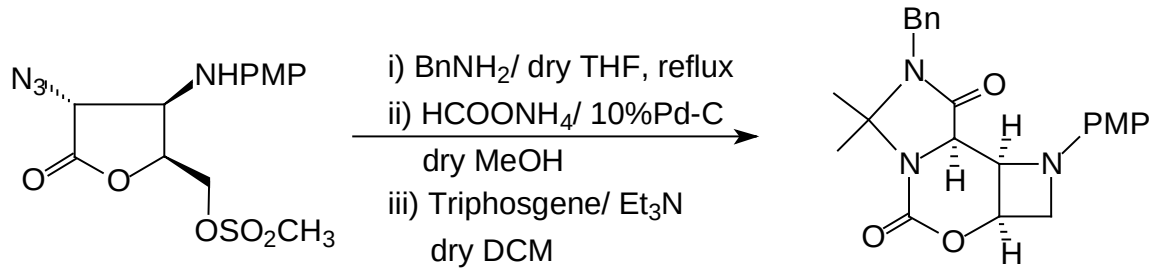
3.27

The ^{13}C spectrum of **3.27** showed a peak at 37.20 ppm which was attributed to the methyl carbon from mesityl group. The methylene carbon appeared at 66.84 ppm while the methoxy carbon appeared at 55.66 ppm.

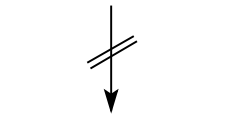
The C-3, C-4 and C-5 lactone carbons appeared at 76.72, 57.56 and 61.04 ppm respectively. The aromatic quaternary carbons were seen at 153.30 ppm and 139.17 ppm, while the remaining aromatic carbons appeared at 115.18 and 114.72 ppm and the peak at 170.66 ppm was due to the lactone carbonyl carbon. This compound also gave satisfactory elemental analysis and the mass spectrum showed a peak at m/z 357 (M+1).

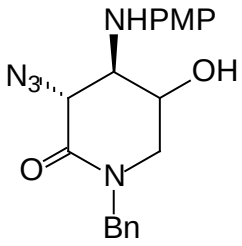
The mesylated lactone **3.27** was treated with benzyl amine in THF under reflux conditions followed by the reduction of the azido group by transfer hydrogenation using ammonium formate and Pd-C (10%). The intermediate was trapped with triphosgene and subsequent purification by column chromatography and recrystallization from acetone-petroleum ether afforded tricyclic compound **3.30** instead of the desired piperidinone **3.29** (Scheme 3.16). The compound **3.30** has the azetidine ring fused with six membered cyclic carbamate and the acetonide functionality.

Scheme 3.16



3.27 **3.30**





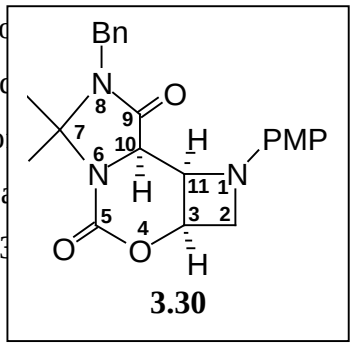
3.29

The tricyclic compound **3.30** was characterized fully with spectral data and its structure was confirmed based on its single crystal X-ray analysis.

The IR spectrum of the tricyclic compound **3.30** showed bands at 1714 and 1703 cm^{-1} corresponding to the carbamate and cyclic amide carbonyls.

The ^{1}H NMR spectrum of **3.30** showed two singlets at 1.54 and 1.59 ppm which were attributed to the gem dimethyl protons. A sharp singlet at 3.78 ppm was due to the methoxy protons. The methylene protons of the azetidine ring appeared as a multiplet between 4.05-4.10 ppm. The benzylic protons were observed as two separate doublets at 4.16 and 4.86 ppm with J = 15.9 Hz.

The methine proton on carbon (C10-*H*) attached to carbonyl on one side and nitrogen on the other side appeared as a doublet at 4.30 ppm with J = 2.0 Hz. The C-11 proton of the azetidine ring was observed between 5.05-5.10 ppm as a doublet of doublet with J = 2.0 and 7.6 Hz. The remaining C-3 proton was observed as a multiplet between 5.10-5.20 ppm.



3.30

The aromatic protons of the PMP group were observed as two separate doublets at 6.70 and 6.88 ppm with J = 9.0 Hz, while the remaining five aromatic protons appeared as a multiplet between 6.95-7.20 ppm.

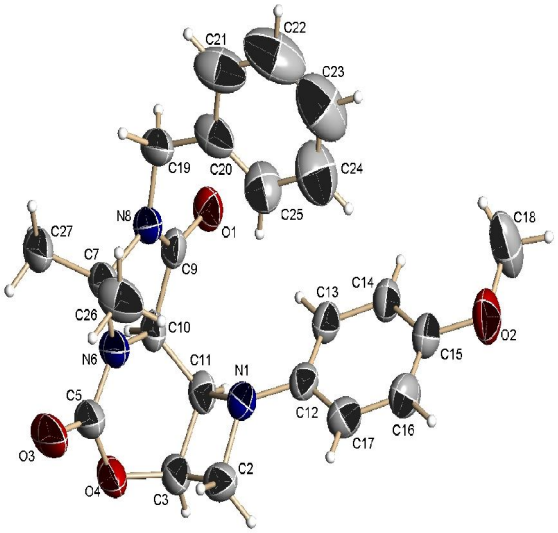
The ^{13}C NMR spectrum of the tricyclic compound **3.30** showed two peaks at 24.46 and 25.24 ppm for the methyl carbons of the acetonide moiety. The benzylic and the other methylene carbon of the azetidine ring appeared at 43.01 and 60.58 ppm respectively. A peak at 55.88 ppm was due to methoxy carbon. The C-11, C-3 and C-10 carbons were seen at 70.57, 66.70 and 58.78 ppm respectively. The quaternary carbon C-6 resonated at 80.14 ppm that disappeared in the ^{13}C DEPT experiment. The aromatic carbons were observed at 113.86, 114.85, 127.14, 127.40, 128.45, 136.47, 142.89 and 149.94 ppm along with the carbonyl carbons at 153.35 and 166.18 ppm.

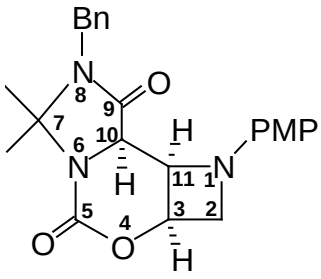
This tricyclic azetidine **3.30** showed a molecular ion peak at m/z 408 (M+1) and gave satisfactory elemental analysis. The structure of this cyclic carbamate was further confirmed from its single crystal X-ray analysis.

X-ray structure determination of 3.30

The structure of the tricyclic compound **3.30** was ascertained from the single crystal X-ray analysis. X-ray quality crystals of **3.30** were obtained by careful crystallization from acetone-petroleum ether. The data was collected on *Bruker SMART APEX* CCD

diffractometer using Mo K_α radiation. Based on the crystal structure, the stereochemistry was assigned as 3*R*, 10*R* and 11R.





3.30

ORTEP diagram of 3.30

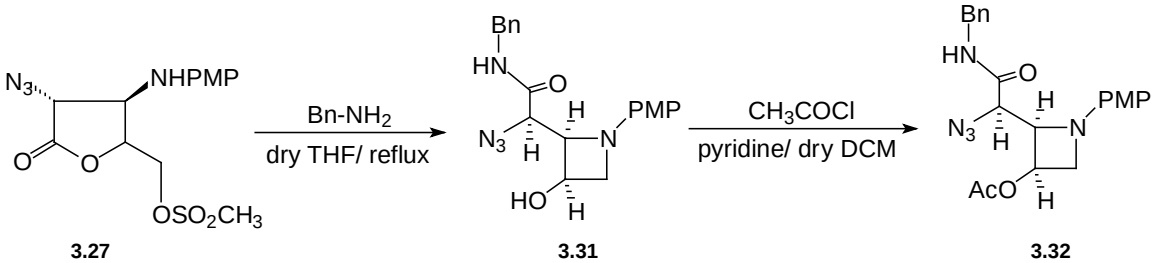
Crystal data and structure refinement for 3.30

Empirical formula	$C_{23}H_{25}N_3O_4$
Formula weight	407.46
Temperature	293 (2) K
Wavelength	0.71073 Å

Crystal system, space group	Monoclinic, $P2_1$
Unit cell dimensions	a = 9.9613 (4) Å b = 11.952 (1) Å β = 113.620 (1) c = 10.1982 (9) Å
Volume	1112.44 (17) $Å^3$
Z, Calculated density	2, 1.216 Mg/m^3
Crystal size	0.47 x 0.27 x 0.22 mm
Theta range for data collection	2.23 to 25.00 deg.
Reflections collected / unique	5647 / 3492 [R (int) = 0.0237]
Completeness to theta = 25.00	99.8%
Refinement method	Full-matrix least-squares on F^2
Final R indices [I>2sigma(I)]	R1 = 0.0428, wR2 = 0.1095
R indices (all data)	R1 = 0.0544, wR2 = 0.1173

The intermediates involved during the formation of this novel tricyclic compound **3.30** were isolated as in the following reaction sequences (Scheme 3.17 and 3.18). The opening of the lactone ring with benzyl amine followed by intramolecular cyclization of the secondary amino group with the expulsion of mesylate group furnished the azetidine derivative **3.31**.

Scheme 3.17

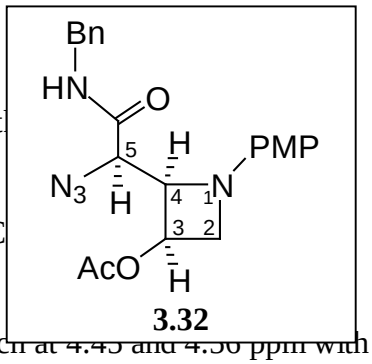


3.27 **3.31** **3.32**

The azetidine derivative **3.31** was viscous oil hence its structure could not be confirmed based on its spectral analysis only. The free secondary hydroxy of this azetidine **3.31** was protected as its acetate to give the acetyl azetidine **3.32**. This was then crystallized from acetone-petroleum ether as white needles. The spectral as well as single crystal X-ray

analysis gave the structural evidence of this intermediate to be the azetidine ring derivative **3.31**.

The IR spectrum of azetidine **3.32** showed sharp bands at 2119, 1745 and 1676 cm^{-1} corresponding to the azido, acetate ester and the amide functional groups, while the amino NH was observed at 3411 cm^{-1}.



3.32

The ^{1}H NMR spectrum of **3.32** showed two singlets at 2.19 and 3.78 ppm corresponding to the methyl protons of the acetyl group and methoxy protons.

A doublet at 4.10 ppm with J = 4.7 Hz was due to the C methylene protons of the azetidine ring.

The benzylic protons were observed as two doublets each at 4.45 and 4.56 ppm with J = 5.8 Hz. The methine proton (C5-*H*) on carbon attached to azido and carbonyl group appeared as a doublet at 4.56 ppm with J = 3.8 Hz. The C-4 methine proton was observed as a doublet of doublet at 4.87 ppm with J = 3.8 and 7.5 Hz.

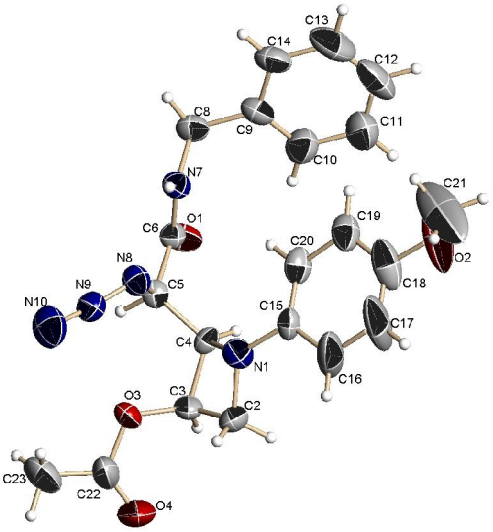
The C-3 proton of the azetidine ring appeared as a multiplet between 5.50-6.65 ppm. The aromatic protons of the PMP group were observed as two separate doublets at 6.56 and 6.80 ppm with J = 8.8 Hz, while the remaining aromatic protons appeared as a multiplet between 7.25-7.35 ppm. A broad singlet at 7.12 ppm was due to the amide NH proton.

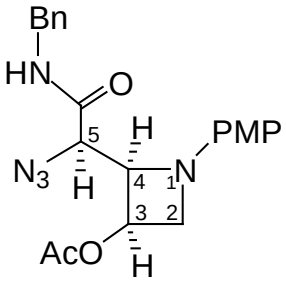
The ^{13}C NMR spectrum of this azetidine derivative **3.32** showed a peak at 20.85 ppm for the methyl carbon of the acetyl group. The benzylic carbon and the C-2 carbon were observed at 43.66 and 59.96 ppm. The peak at 55.56 ppm was due to the methoxy carbon. The peaks at 63.05, 64.92 and 67.90 ppm were attributed to C-5, C-4 and C-3 carbons. The aromatic quaternary carbons attached to nitrogen, carbon and oxygen appeared at 137.23, 143.17 and 152.95 ppm respectively. The remaining aromatic carbons appeared at 113.50, 114.54, 127.57, 127.84 and 128.64 ppm. The two carbonyls were observed at 167.85 and 169.85. This azetidine derivative **3.32** showed a molecular ion peak at m/z 410 (M+1) and gave satisfactory elemental analysis.

The decoupling of protons at 4.87 and 5.55 ppm further supported the structure. When the proton at 4.87 ppm was decoupled the multiplet between 5.50-5.60 ppm for the C-3 protons changed to a triplet with J = 7.0 Hz. When the C-3 proton was decoupled the C-2 methylene protons appeared as a sharp singlet at 4.09 ppm while the C-4 proton changed to doublet at 4.84 with J = 3.0 Hz. The single crystal X-ray analysis further confirmed the structure and the configuration for the azetidine ring was found to be 3*R*, 4*R* and 5R.

X-ray structure determination of 3.32

The structure of the azetidine derivative **3.32** was ascertained from the single crystal X-ray analysis. X-ray quality crystals of **3.32** were obtained by careful crystallization from acetone-petroleum ether. The data was collected on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation. Based on the crystal structure, the stereochemistry was assigned as 3*R*, 4*R* and 5R.





3.32

ORTEP diagram for 3.32

Crystal data and structure refinement for 3.32

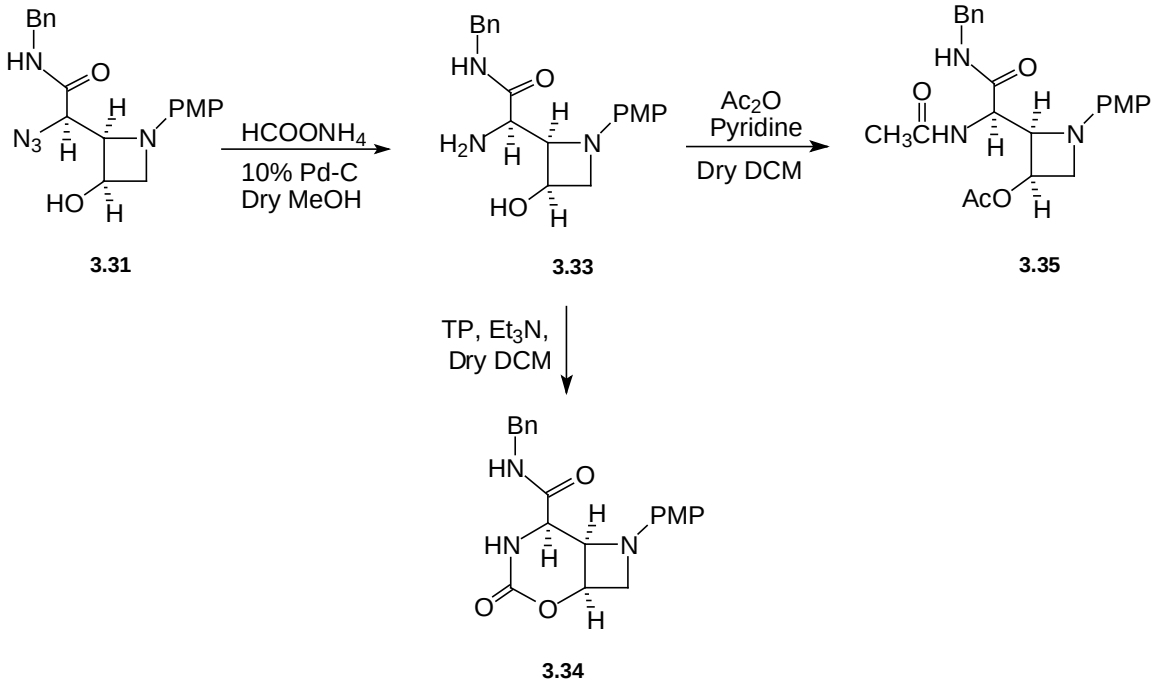
Empirical formula	$C_{21}H_{23}N_5O_4$
Formula weight	409.44
Temperature	293 (2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, C_2
Unit cell dimensions	a = 39.352 (8) Å b = 5.0998 (11) Å β = 102.136 (4)

	c = 10.613 (2) Å
Volume	2082.2 (8) $Å^3$
Z, Calculated density	4, 1.306 mg/m^3
Crystal size	0.32 x 0.14 x 0.04 mm
Theta range for data collection	2.12 to 24.99 deg
Reflections collected / unique	5158 / 3324 [R (int) = 0.0929]
Completeness to theta = 24.99	99.7%
Max. and min. transmission	0.9817 and 0.9618
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	0.978
Final R indices [I>2sigma(I)]	R1 = 0.0869, wR2 = 0.1672
R indices (all data)	R1 = 0.2193, wR2 = 0.2137

The azido group of **3.31** was reduced by transfer hydrogenation to furnish the amino azetidine **3.33,** which was highly polar hence it was isolated as its diacetate derivative **3.35**. The amino azetidine **3.33** was reacted with excess acetic anhydride in the presence of pyridine to afford **3.35** as white floppy solid (Scheme 3.18). Its structure was confirmed based on its spectral analysis.

The IR spectrum of azetidine **3.35** showed sharp bands at 3417, 3400, and 1739 cm^{-1} corresponding to the amino and the ester functionality, while the peaks at 1658 and 1639 cm^{-1} were due to the amide carbonyls.

Scheme 3.18

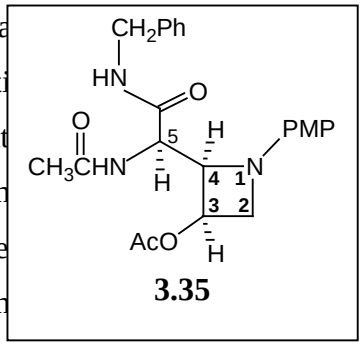


3.31 **3.33** **3.35**

3.34

The ^{1}H NMR spectrum of **3.35** showed two singlets at 2.00 and 2.10 ppm corresponding to the methyl protons of the amide and the acetyl group. A sharp singlet at 3.76 ppm was assigned to the methoxy protons. The methylene protons of the azetidine ring (C2-*H*) were observed as a multiplet between 3.85-4.00 ppm. The benzylic protons appeared as a multiplet between 4.40-4.60 ppm. The methine proton (C5-*H*) on carbon attached to amino and carbonyl group and the methine proton of the azetidine ring on carbon attached to oxygen atom (C3-*H*) also appeared as a multiplet between 4.70-4.80 ppm.

The remaining methine proton of the ring (C4-*H*) wa seen as a multiplet between 5.35-5.45 ppm. The four aromati protons of the PMP group were observed as two separat doublets at 6.71 and 6.85 ppm with J = 9.0 Hz, while th remaining aromatic protons appeared as a multiplet betwee 7.25-7.35 ppm. A broad singlet at 7.57 ppm was due to th NH proton.



3.35

The ^{13}C NMR spectrum of this azetidine **3.35** showed two peaks at 20.47 and 23.19 ppm for the methyl carbons of the amide and the acetyl group. The benzylic carbon and the C-2 methylene carbon appeared at 43.75 and 58.62 ppm respectively. The methoxy carbon attached to aromatic ring was observed at 55.59 ppm.

The methine carbon C-5 attached to NH and the carbonyl group appeared at 50.81 ppm, while the C-4 and C-3 carbons of the azetidine ring appeared at 65.39 and 66.91 ppm. The three aromatic quaternary carbons of the two aromatic rings were seen at 137.91, 143.43 and 153.75 ppm, while the remaining aromatic carbons were observed at 114.49, 114.80, 127.45, 127.73 and 128.60 ppm.

The three carbonyl carbons appeared at 169.31, 170.51 and 170.64 ppm. This azetidine **3.35** showed a molecular ion peak at m/z 426 (M+1) and gave satisfactory elemental analysis.

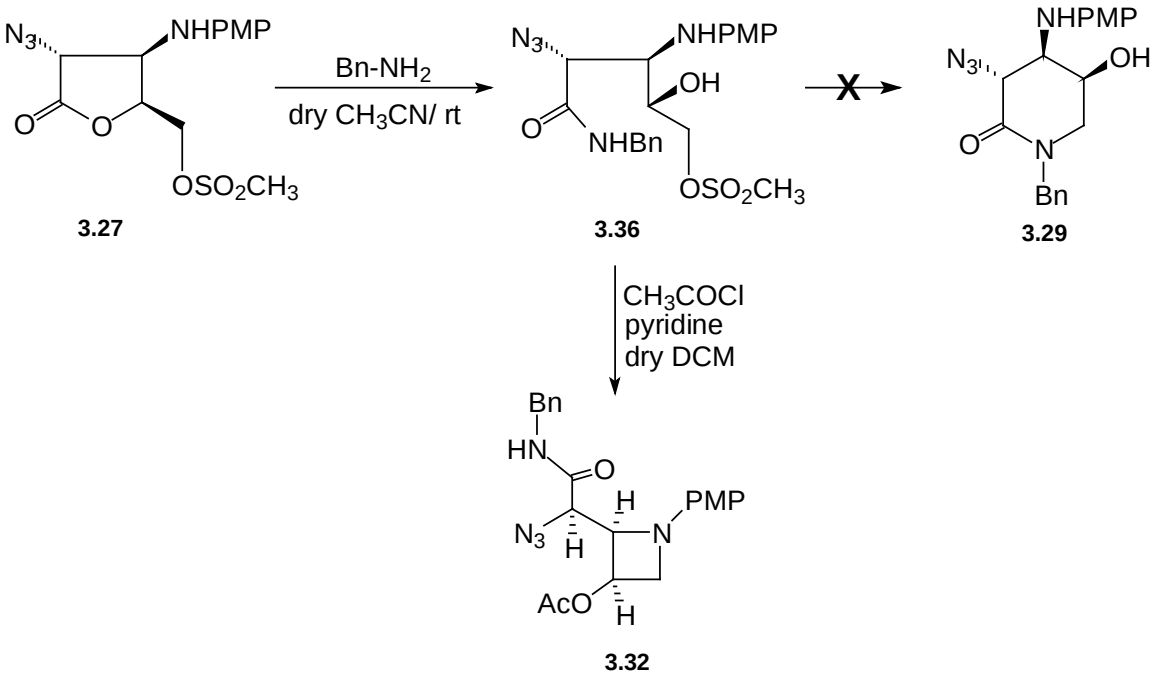
The azetidine **3.33** without isolation on treatment with triphosgene and triethyl amine in dry dichloromethane should furnish the bicyclic carbamate **3.34** and the tricyclic compound may be arising during the purification and crystallization of the carbamate derivative **3.34** using acetone-petroleum ether.

We thought the reflux temperature of the reaction of mesylated lactone **3.27** with benzyl amine might be the cause for the formation of the azetidine ring. Hence it was planned to do the reaction at room temperature.

Thus the reaction of mesylated lactone **3.27** with benzyl amine at room temperature for 4 h, gave the ring opened product **3.36** in 82% yield (scheme 3.20).

The IR spectrum of **3.36** showed bands at 3407, 2117 and 1670 cm^{-1} corresponding to the NH, azido and amide groups. The absence of the lactone carbonyl in IR further supported the opened amide structure.

Scheme 3.20



3.27 **3.36** **3.29** **3.32**

The ^{1}H NMR spectrum of **3.36** showed a singlet at 2.97 ppm due to methyl protons of the mesylate group. Another singlet at 3.78 ppm was due to the methoxy protons. The methine proton on carbon attached to azido group appeared at 3.94 ppm as a doublet with *J* = 4.5 Hz. The remaining six protons appeared as a multiplet in the region of 4.05-4.50 ppm. The aromatic protons were observed as two sets of multiplets between 6.75-6.95 and 7.20-7.40 ppm.

In order to prepare the desired lactam ring **3.29** in one pot, we planned to protect both the hydroxy and amino group with two equivalents of acetyl chloride. Opening of the epoxide ring formed *in situ* with the amino group in the presence of the base will provide the lactam ring. But unfortunately we obtained a white solid whose spectral data exactly matched with that of the azetidine **3.32** (Scheme 3.20).

3.9 : Conclusion

Our attempts to isolate the precursor lactam obtained from racemic 3-phthalimido **3.15** as well as optically pure 3-azido-4-formyl-azetidin-2-one **3.21** were unsuccessful. Optically pure azetidinone **3.20** rearranged to γ-lactone **3.26** when reacted with methanolic HCl. But all our attempts to get the six membered lactam ring from the mesylated γ-lactone **3.27** were unsuccessful. Instead, a novel tricyclic compound **3.30** was obtained, the structure of which was confirmed from the spectral and X-ray crystal data.

Reaction of benzyl amine with mesylated lactone **3.27** afforded azetidine derivative **3.31**, which was characterized as its acetyl derivative **3.22**. Subsequent reduction of the azido group of azetidine **3.31** afforded the amino alcohol **3.33** that was isolated as its diacetate derivative **3.35**. The reaction of amino alcohol **3.33** with triphosgene should give the bicyclic carbamate derivative **3.34** and the tricyclic compound **3.30** may be arising during the purification and crystallization of the carbamate derivative **3.34** using acetone-petroleum ether.

The reaction of mesylated lactone **3.27** with benzyl amine at room temperature gave only the ring-opened product **3.36**. The reaction of **3.36** with excess acetyl chloride in the presence of the base afforded the acetyl protected azetidine compound **3.32** instead of the desired lactam **3.29**.

3. 10 : Experimental

3. 10. 1: Preparation of *N*,*N*′-bis(*p*-anisyl) ethylenediimine 3.03a

Glyoxal (40% aqueous solution, 10 mL, 69 mmol) was added dropwise to a hot solution of *p*-anisidine (16.99 g, 138 mmol) in methanol (80 mL). A yellow solid precipitated and isopropyl alcohol was added and methanol distilled until solution occurred. Cooling to room temperature gave the bisimine, **3.13** as yellow needles (11 g, 60%), MP 156-158 ^{o}C (Lit[11] 153-154 ^{o}C).

3. 10. 2: Preparation of 1-(4-methoxyphenyl)-3-phthalimido-4-formylazetidin-2-one 3.15

To a stirred suspension of bisimine **3.13** (2.68 g, 10 mmol) and triethylamine (1.67 mL, 12 mmol) in anhydrous toluene, was added an anhydrous toluene solution of phthalimidoacetyl chloride **3.14** (2.45 g, 11 mmol) dropwise at room temperature under argon. The resulting mixture was stirred at room temperature for 1 h. After completion of reaction (TLC), 5% aqueous HCl (25 mL) was added and the heterogeneous mixture was stirred at room temperature for 2 h. The organic layer was then diluted with toluene, washed with 5% aqueous HCl, water, brine and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford the crude product, which was purified by crystallization from methanol to give the 4-formylazetidin-2-one **3.15** as a white solid (2.45 g, 70%).

MP : 246 ^{o}C (Lit[12] 246-248 ^{o}C)

IR ($CHCl_3$) : 1758, 1712 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.75 (s, 3H), 4.75 (dd, *J* = 5.5 & 2.5 Hz, 1H), 5.80 (d, *J* = 5.5 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 9.0 Hz, 2H), 7.70-7.95 (m, 4H), 9.90 (d, *J* = 2.5 Hz).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 55.61, 62.88, 77.62, 114.97, 118.21, 124.01, 130.63, 131.59, 134.78, 157.28, 160.48, 166.76, 197.27.

MS (m/z) : 351 (M+1).

3. 10. 3: Preparation of 1-(4-methoxyphenyl)-4-(1-hydroxy-2-nitroethyl)-3-phthalimido-azetidin-2-one 3.16

To a solution of 4-formylazetidin-2-one **3.15** (2.10 g, 6.0 mmol), in nitromethane (20 mL), was added triethylamine (0.1 mL, 1.0 mmol) at room temperature and the reaction mixture was stirred for 4-5 h. The excess nitromethane was removed under reduced pressure to afford nitro alcohol **3.16**, as a thick oil (2.01 g, 85%).

IR ($CHCl_3$) : 3500-3200, 1749, 1720, 1560, 1384 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.75 (s, 3H), 4.40-4.75 (m, 4H), 5.55 (d, *J* = 5.4 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.70-7.95 (m, 4H).

MS (m/z) : 412 (M+1).

3. 10. 4: Preparation of (3*R*, 4S) 3-azido-1-(4-methoxyphenyl)-4-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl] azetidin-2-one 3.20

Following the general procedure for the preparation of imines as described in **Section A**, imine **3.18** was prepared from D-glyceraldehyde acetonide and *p*-anisidine (2.46 g, 20 mmol) and was then treated with triethylamine (6.7 mL, 48 mmol) and potassium azido acetate in the presence of triphosgene as an acid activator in dry DCM. The purification of the crude reaction mixture by column chromatography furnished azetidin-2-one **3.20** as a white crystalline solid (3.30 g, 52%).

MP : 121 °C (Lit[14] 119-120 °C).

IR ($CHCl_3$) : 2109, 1749 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.35 (s, 3H), 1.53 (s, 3H), 3.80 (s, 3H), 4.20-4.25 (m, 2H), 4.30-4.40 (m, 2H), 4.84 (d, *J* = 5.4 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 24.80, 26.57, 55.35, 61.64, 67.04, 79.28, 109.86, 113.90, 115.78, 119.57, 129.64, 156.54, 163.27.

MS (m/z) : 318 (M^+).

Analysis ($C_{15}H_{18}N_4O_4$) : Calculated: C, 56.58; H, 5.70; N, 17.61
Observed: C, 56.42; H, 5.68; N, 17.32.

3. 10. 5: Preparation of 3-azido-4-formyl-azetidin-2-one 3.21

A mixture of azetidin-2-one **3.20** (3.18 g, 10 mmol) and *p*-toluenesulphonic acid monohydrate (0.57 g, 3.0 mmol) in THF (40 mL) and water (15 mL) was refluxed for 24 h. After completion of reaction (TLC) the reaction mixture was neutralized with sodium bicarbonate and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (25 mL) and the organic layer was washed with saturated brine solution (10 mL) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford the diol, which was dissolved in acetone (50 mL) and water (25 mL) and cooled to 0 ^{o}C. To the cooled diol solution, $NaIO_4$ (2.60 g, 12 mmol) was added in portions. After completion of addition, the reaction mixture was stirred at room temperature for 1 h. After completion of reaction (TLC), the solid was filtered off and washed with acetone. The solvent was removed and the residue was taken in dichloromethane (30 mL) and the organic layer was washed with water (2 x 10 mL), saturated sodium bicarbonate solution (2 x 10 mL), saturated brine solution (15 mL) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford the 3-azido-4-formylazetidin-2-ones **3.21**.

MP : 128-130 ^{o}C

IR ($CHCl_3$) : 2109, 1751, 1712 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.79 (s, 3H), 4.60 (dd, *J* = 5.5 & 3.0 Hz, 1H), 5.15 (d, *J* = 5.5 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 9.76 (d, *J* = 3.0 Hz, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 55.48, 61.40, 66.29, 114.72, 118.23, 130.01, 157.30, 159.89, 197.25.

MS (m/z) : 247 (M+1).

3. 10. 6: Preparation of 1-(4-methoxyphenyl)-4-(1-hydroxy-2-nitroethyl)-3-azido-azetidin-2-one 3.22

To a solution of 4-formylazetidin-2-one **3.21** (1.47 g, 6.0 mmol), in nitromethane (20 mL), was added triethylamine (0.1 mL, 1.0 mmol) at room temperature and the reaction mixture was stirred for 4-5 h. The excess nitromethane was removed under reduced pressure to afford a diastereomeric mixture of nitro alcohol **3.22** as a thick oil (1.52 g, 83%). The major isomer showed the following data.

IR ($CHCl_3$) : 3500-3200, 2109, 1745, 1556, 1382 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 3.80 (s, 3H), 4.50-4.60 (m, 3H), 4.80-4.85 (m, 1H), 5.00 (d, *J* = 5.5 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 9.0 Hz, 2H).

MS (m/z) : 308 (M+1).

3. 10. 7: Preparation of 3-azido-5-hydroxymethyl-4-(4-methoxyphenylamino)-dihydro-furan-2-one 3.26

Methanolic HCl (20%, 10 mL) was added to azetidin-2-one **3.20** (0.32 g, 1.0 mmol) and the resultant solution was stirred overnight. After the reaction was over (TLC) methanol was evaporated under reduced pressure and the residue was diluted with DCM and neutralized with saturated sodium bicarbonate solution. The organic layer was separated and aqueous layer was extracted with dichloromethane. The combined organic extract was dried over anhydrous sodium sulphate and evaporation of the solvent furnished the crude lactone, which on further purification by column chromatography (Silica gel 60-120 mesh, 25% acetone-petroleum ether) gave pure lactone **3.26** as a thick brown oil (0.18 g, 65%).

MP : Thick oil

$[\alpha]^{28}_D$: + 67.74 (*c* 0.62, $CHCl_3$).

IR ($CHCl_3$) : 3400, 3382, 2115, 1782 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 3.76 (s, 3H), 3.80-4.35 (m, 6H), 4.75 (d, *J* = 9.0 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H).

^{13}C NMR ($CDCl_3$) (75.4 MHz) : δ 55.64, 58.60, 60.34, 62.66, 79.62, 115.21, 139.93, 153.27, 172.43.

MS (m/z) : 296 (M+18).

Analysis ($C_{12}H_{14}N_4O_4$) : Calculated: C, 51.78; H, 5.07; N, 20.14

Observed: C, 51.65; H, 5.18; N, 20.32.

3. 10. 8: Preparation of 3-azido-5-mesyloxymethyl-4-(4-methoxyphenylamino)-

dihydro-furan-2-one 3.27

To a solution of lactone 3.26 (0.28 g, 1.0 mmol), dry triethylamine (0.20 mL, 1.5 mmol) and catalytic DMAP in dry DCM (10 mL), was added slowly methane sulphonyl chloride (0.1 mL, 1.3 mmol) at 0 °C. The reaction mixture was then stirred overnight at room temperature. After the reaction was over (TLC), the reaction mixture was washed with saturated sodium bicarbonate solution and saturated brine. The organic layer was separated and dried over anhydrous sodium

sulphate. Evaporation of the solvent furnished the crude mesylated lactone, which on further purification by column chromatography (Silica gel 60-120 mesh, 25% acetone-petroleum ether) gave pure mesylated lactone 3.27 as a thick brown oil. (0.28 g, 78%)

MP	:	Thick oil
$[\alpha]^{28}_{D}$	:	+ 81.18 (*c* 1.01, $CHCl_3$).
IR ($CHCl_3$)	:	3362, 2117, 1789 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 3.10 (s, 3H), 3.76 (s, 3H), 4.30-4.60 (m, 4H), 4.95 (d, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H).
^{13}C NMR ($CDCl_3$) (75.4 MHz)	:	δ 37.20, 55.66, 57.56, 61.04, 66.84, 76.72, 114.72, 115.18, 139.17, 153.30, 170.66.
MS (m/z)	:	357 (M+1).
Analysis ($C_{13}H_{16}N_4O_6S$)	:	Calculated: C, 43.81; H, 4.53; N, 15.73; S, 8.98 Observed: C, 43.65; H, 4.38; N, 15.52; S, 8.76.

3. 10. 9: Preparation of 1-(4-methoxyphenyl)-2-(2-azido-*N*-benzyl acetamido)-3-

hydroxy azetidine 3.31

To a solution of mesylated lactone **3.27** (0.36 g, 1.0 mmol) in dry THF (10 mL), was added benzyl amine (0.11 mL, 1.02 mmol) and the reaction mixture was refluxed for 4-5 h. After the reaction was over (TLC), THF was evaporated to get the crude product, which on purification by flash column chromatography (20% acetone-petroleum ether) afforded the azetidine ring derivative **3.31** as a thick oil. (0.22 g, 61%)

MP	:	Thick oil
$[\alpha]^{28}_{D}$	:	- 163.15 (*c* 1.33, $CHCl_3$).
IR ($CHCl_3$)	:	3406, 3325, 2117, 1656, 1510 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 3.76 (s, 3H), 3.85-3.95 (m, 2H), 4.05-4.15 (m, 1H), 4.45-4.50 (m, 1H), 4.65-4.75 (m, 2H), 6.70 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 7.10-7.20 (m 2H), 7.25-7.40 (m, 3H).
^{13}CNMR ($CDCl_3$) (75.5 MHz)	:	δ 43.35, 55.44, 60.14, 62.66, 63.48, 70.40, 113.11, 114.37, 127.55, 128.31, 128.64, 136.96, 144.71, 152.52, 168.70.
MS (m/z)	:	368 (M+1).
Analysis ($C_{19}H_{21}N_5O_3$)	:	Calculated: C, 62.09; H, 5.76; N, 19.07

Observed: C, 62.35; H, 5.78; N, 19.32.

3. 10. 10: Preparation of 1-(4-methoxyphenyl)-2-(2-azido-*N*-benzyl acetamido)-3-acetoxy azetidine 3.32

A mixture of azetidine derivative **3.31** (0.36 g, 1.0 mmol), acetic anhydride (0.11 mL, 1.2 mmol) and pyridine (0.12 mL, 1.5 mmol) in dry DCM (10 mL) was stirred overnight. After the reaction was over (TLC), it was diluted with dichloromethane and was washed with copper sulphate solution to remove excess pyridine. The organic layer on separation, drying and evaporation of the solvent gave the crude product which was purified by flash column chromatography (20% acetone-petroleum ether) to get the acylated azetidine derivative **3.32** as a white crystalline solid (0.35 g, 85%).

MP	:	138-139 °C
$[\alpha]^{28}_{D}$	:	- 133.82 (*c* 0.68, $CHCl_3$).
IR ($CHCl_3$)	:	3411, 2119, 1745, 1676 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 2.19 (s, 3H), 3.78 (s, 3H), 4.10 (d, *J* = 4.7 Hz, 2H), 4.45 (d, *J* = 5.8 Hz, 1H), 4.52 (d, *J* = 5.8 Hz, 1H), 4.56 (d, *J* = 3.8 Hz, 1H), 4.87 (dd, *J* = 3.8 & 7.5 Hz 1H), 5.50-5.65 (m, 1H), 6.56 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 7.12 (bs, 1H), 7.25-7.35 (m, 5H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 20.85, 43.66, 55.56, 59.96, 63.05, 64.92, 67.90, 113.50, 114.54, 127.57, 127.84, 128.64, 137.23, 143.17, 152.95, 167.85, 169.85.
MS (m/z)	:	410 (M+1).
Analysis ($C_{21}H_{23}N_5O_4$)	:	Calculated: C, 61.58; H, 5.66; N, 17.11

Observed: C, 61.57; H, 5.78; N, 17.33.

3. 10. 11: Preparation of 1-(4-methoxyphenyl)-2-acetylamino-benzylcarbamoyl-methyl-3-acetoxy-azetidine 3.35

To a solution of azetidine derivative **3.31** (0.36 g, 1.0 mmol) in anhydrous methanol (10 mL), 10% Pd/C (0.10 g) was added followed by ammonium formate (0.31 g, 5.0 mmol), and the reaction mixture was refluxed for 1 h under argon. After completion of the reaction (TLC), the reaction mixture was filtered through celite bed and the bed was washed repeatedly with methanol. The solvent from the filtrate was removed under reduced pressure and the residue was dissolved in DCM (20 mL), washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent furnished the reduced product to which acetic anhydride (0.2 mL, 2.2 mmol), excess pyridine and catalytic DMAP were added and the resultant solution was stirred overnight. After the reaction was over (TLC), DCM was added to it and the organic layer was washed with copper sulphate solution, water and brine.

Evaporation of the solvent and purification of the crude reaction mixture by column chromatography (Silica gel 60-120 mesh, 20% acetone-petroleum ether) furnished the diacetate derivative **3.35** as a white floppy solid.

MP : 221-223 °C

$[\alpha]^{28}_{D}$: - 65.33 (*c* 0.75, $CHCl_3$).

IR ($CHCl_3$) : 3417, 3400, 1739, 1658, 1639, 1215 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.00 (s, 3H), 2.10 (s, 3H), 3.76 (s, 3H), 3.85-4.00 (m, 2H), 4.40-4.60 (m, 2H), 4.70-4.80 (m, 2H), 5.35-5.45 (m, 1H), 6.71 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 7.25-7.35 (m, 5H), 7.57 (bs, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 20.47, 23.19, 43.75, 50.81, 55.59, 58.62, 65.39, 66.91, 114.49, 114.80, 127.45, 127.73, 128.60, 137.91, 143.43, 153.75, 169.31, 170.51, 170.64.

MS (m/z) : 426 (M+1).

Analysis ($C_{23}H_{27}N_3O_5$) : Calculated: C, 64.91; H, 6.40; N, 9.88

Observed: C, 64.77; H, 6.28; N, 9.63.

3. 10. 12: Preparation of tricyclic compound 3.30

To a solution of azetidine derivative **3.31** (0.36 g, 1.0 mmol) in anhydrous methanol (10 mL), 10% Pd/C (0.10 g) was added followed by ammonium formate (0.31 g, 5.0 mmol), and the reaction mixture was refluxed for 1 h under argon. After completion of the reaction (TLC), the reaction mixture was filtered through celite bed and the bed was washed repeatedly with methanol. The solvent from the filtrate was removed under reduced pressure and the residue was dissolved in DCM (20 mL), washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent furnished the reduced product to which triethyl amine (0.3 mL, 2.2 mmol), dry DCM (10 mL) was added followed by the dropwise addition of solution of triphosgene (0.32 g, 1.1 mmol) in dry DCM (5 mL). The resultant mixture was stirred at room temperature overnight. After the reaction was over (TLC), the reaction mixture was diluted with DCM and washed with saturated sodium bicarbonate and brine

solution. The organic layer was separated dried over anhydrous sodium sulphate and concentrated to give crude product, which on purification by flash column chromatography using 15% acetone-petroleum ether and crystallization of the product from acetone-petroleum ether furnished tricyclic compound **3.30**.

MP	:	200-202 °C
$[\alpha]^{28}_{D}$	:	- 194.59 (*c* 0.18, $CHCl_3$)
IR ($CHCl_3$)	:	1714, 1703 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 1.54 (s, 3H), 1.59 (s, 3H), 3.78 (s, 3H), 4.05-4.10 (m, 2H), 4.16 (d, *J* = 15.9 Hz, 1H), 4.30 (d, *J* = 2.0, 1H), 4.86 (d, *J* = 15.9 Hz, 1H), 5.05-5.10 (dd, *J* = 7.6 & 2.0 Hz, 1H), 5.10-5.20 (m, 1H), 6.70 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.95-7.20 (m, 5H).
^{13}C NMR ($CDCl_3$) (50.3 MHz)	:	δ 24.46, 25.24, 43.01, 55.88, 58.78, 60.58, 66.70, 70.57, 80.14, 113.86, 114.85, 127.14, 127.40, 128.45, 136.47, 142.89, 149.94, 153.35, 166.18.
MS (m/z)	:	408 (M+1).
Analysis ($C_{23}H_{25}N_3O_4$)	:	Calculated: C, 67.78; H, 6.18; N, 10.32

Observed: C, 67.59; H, 6.39; N, 10.58.

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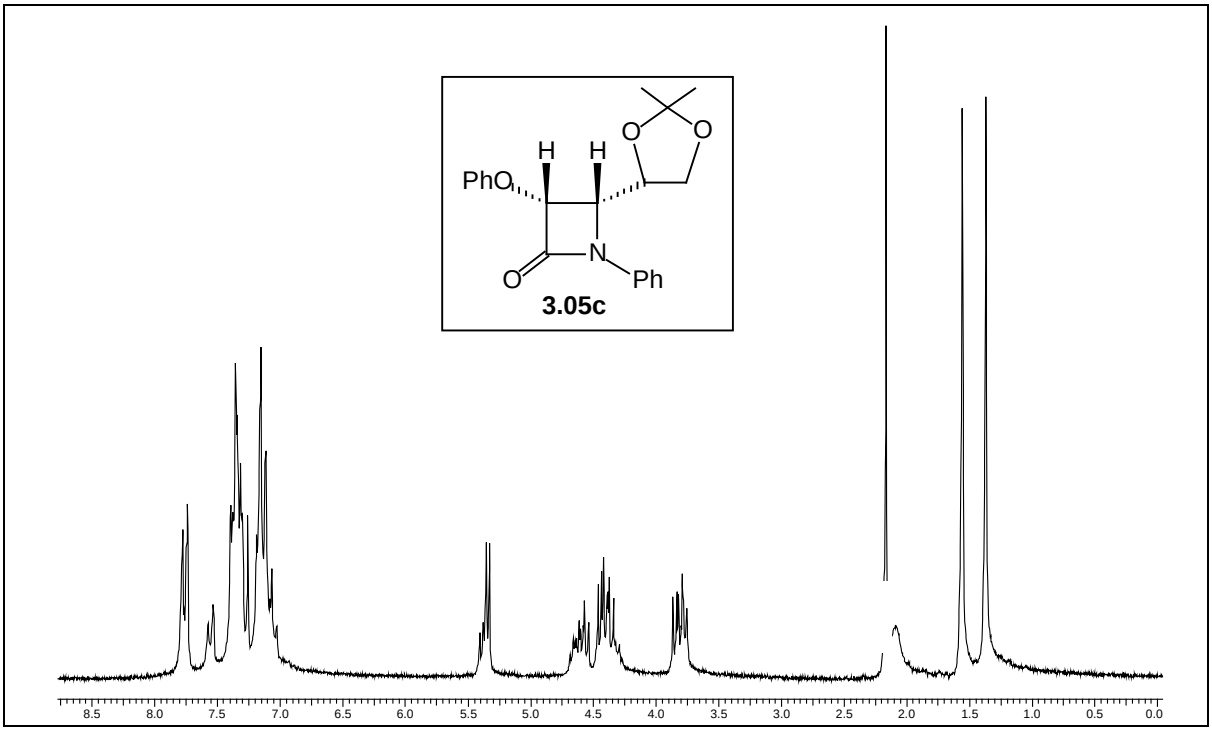

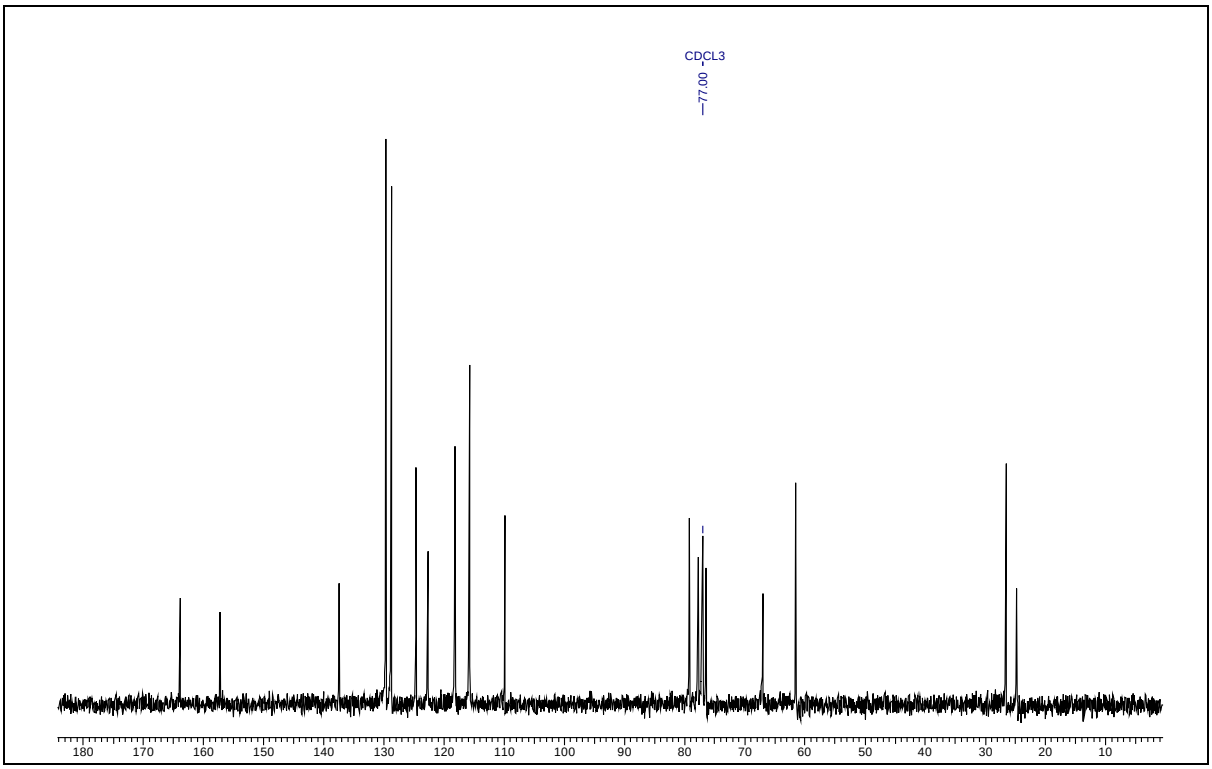

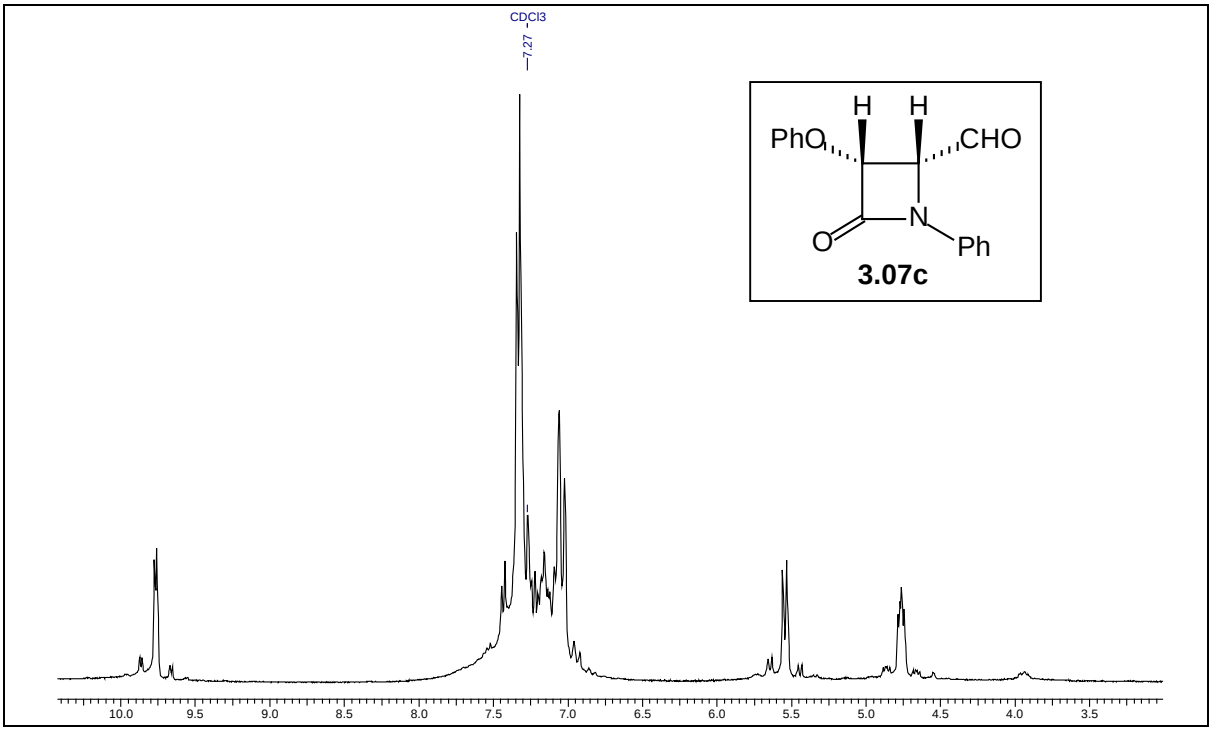

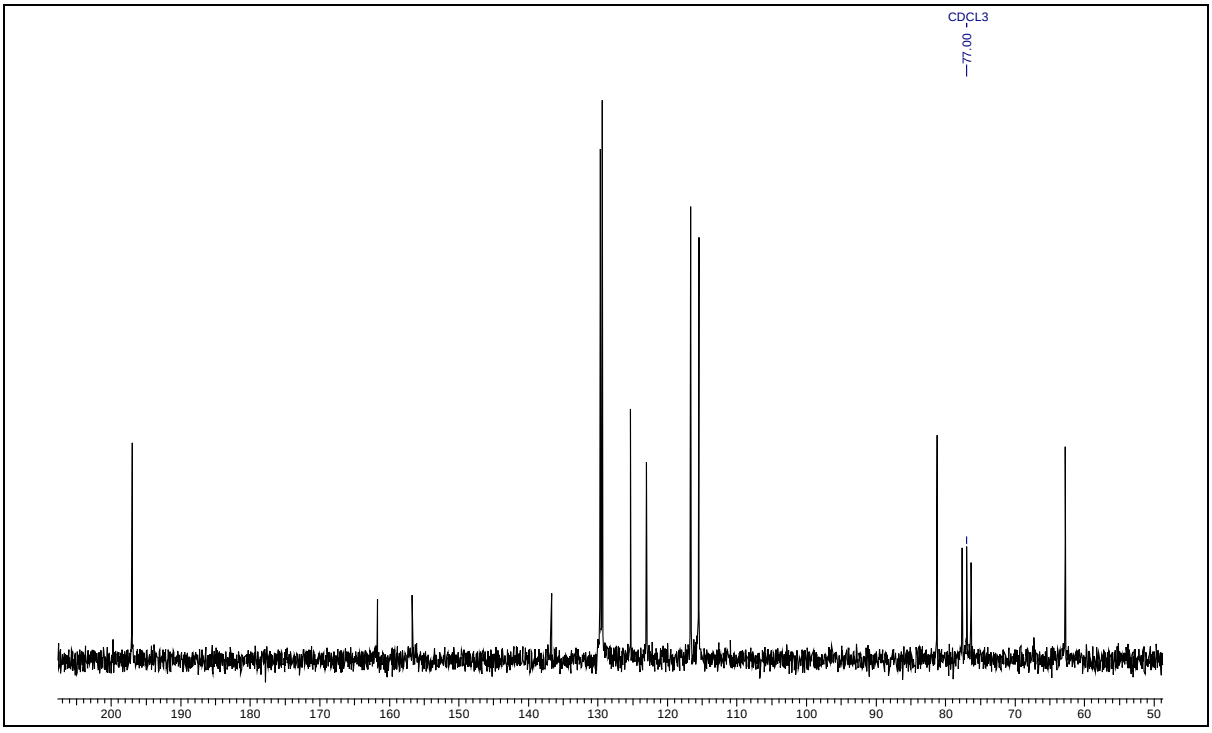

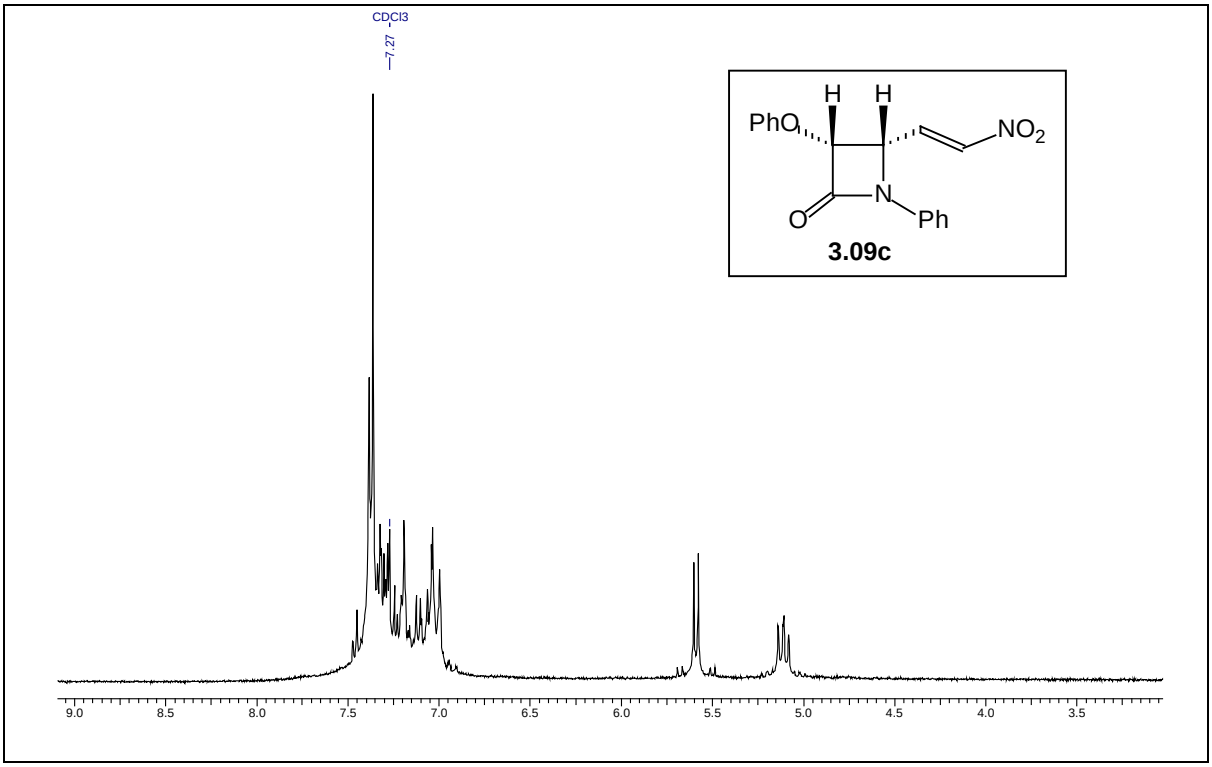

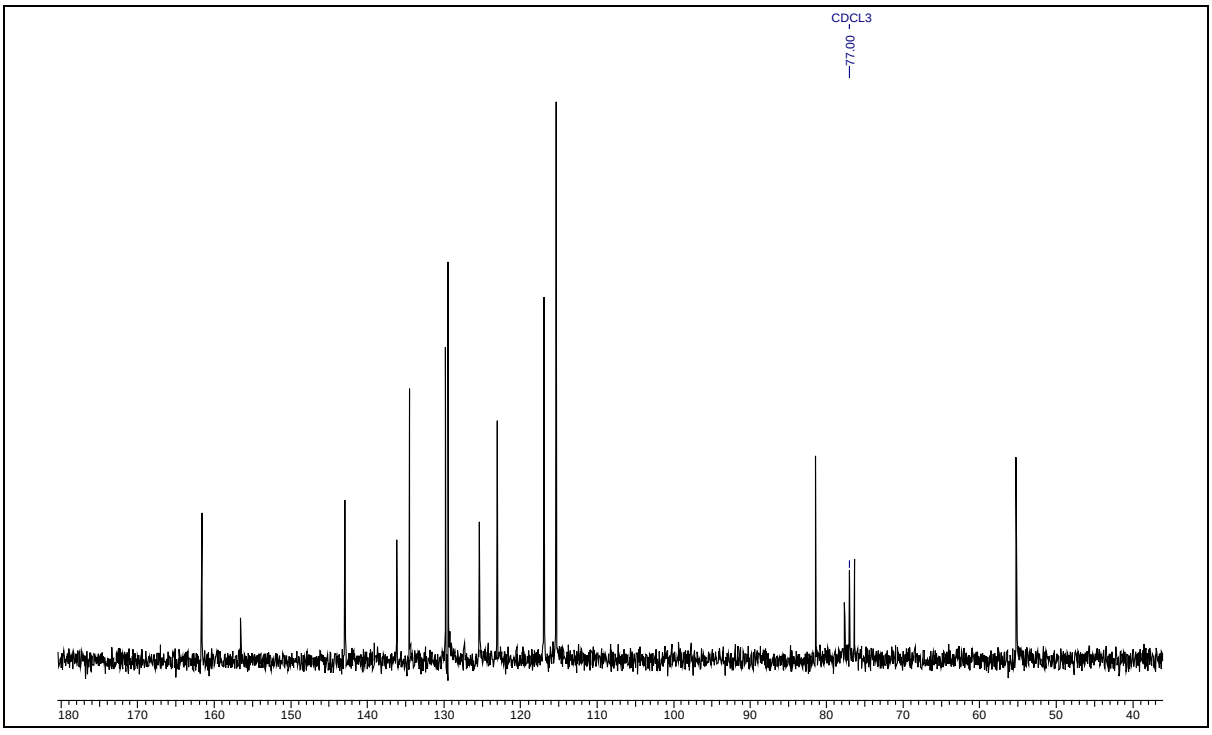

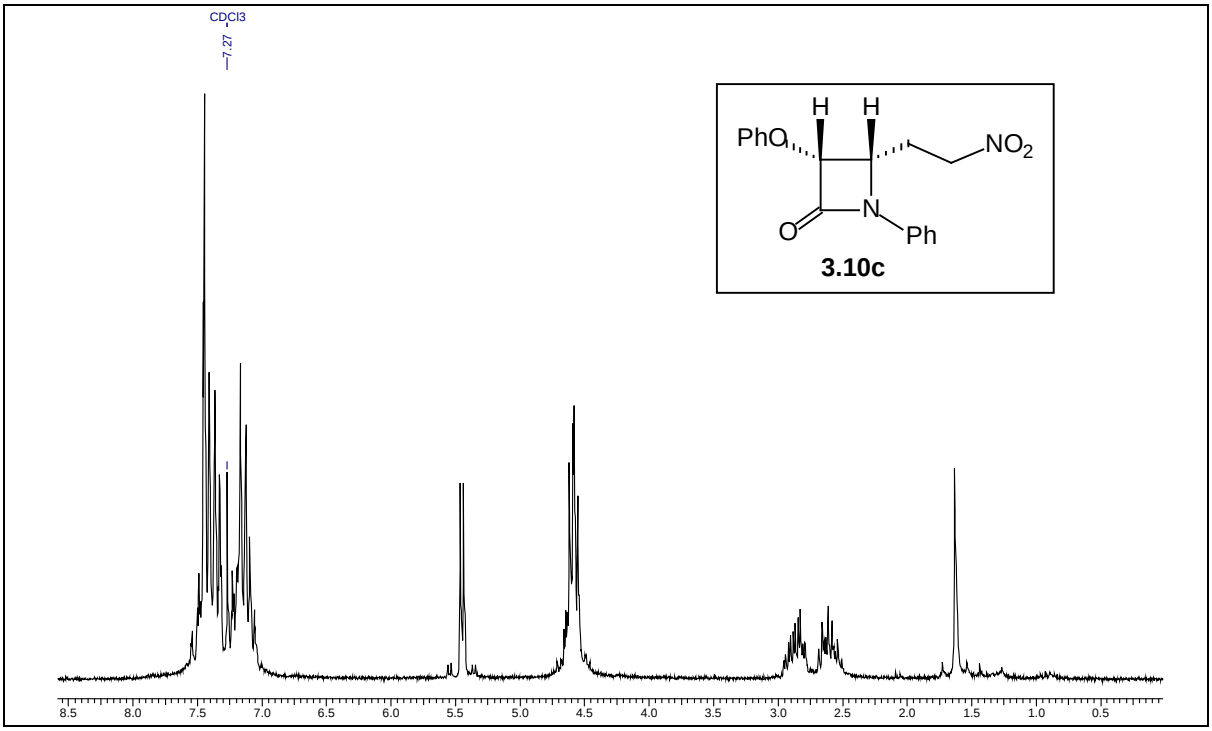

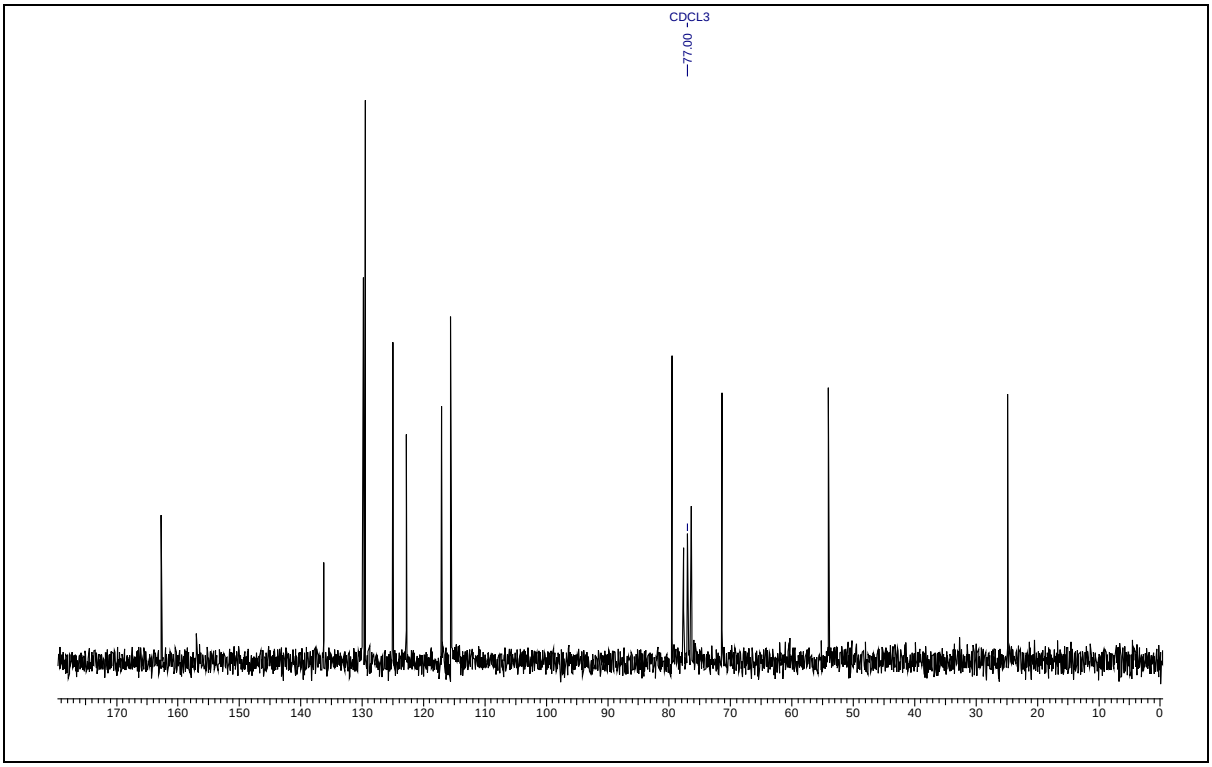

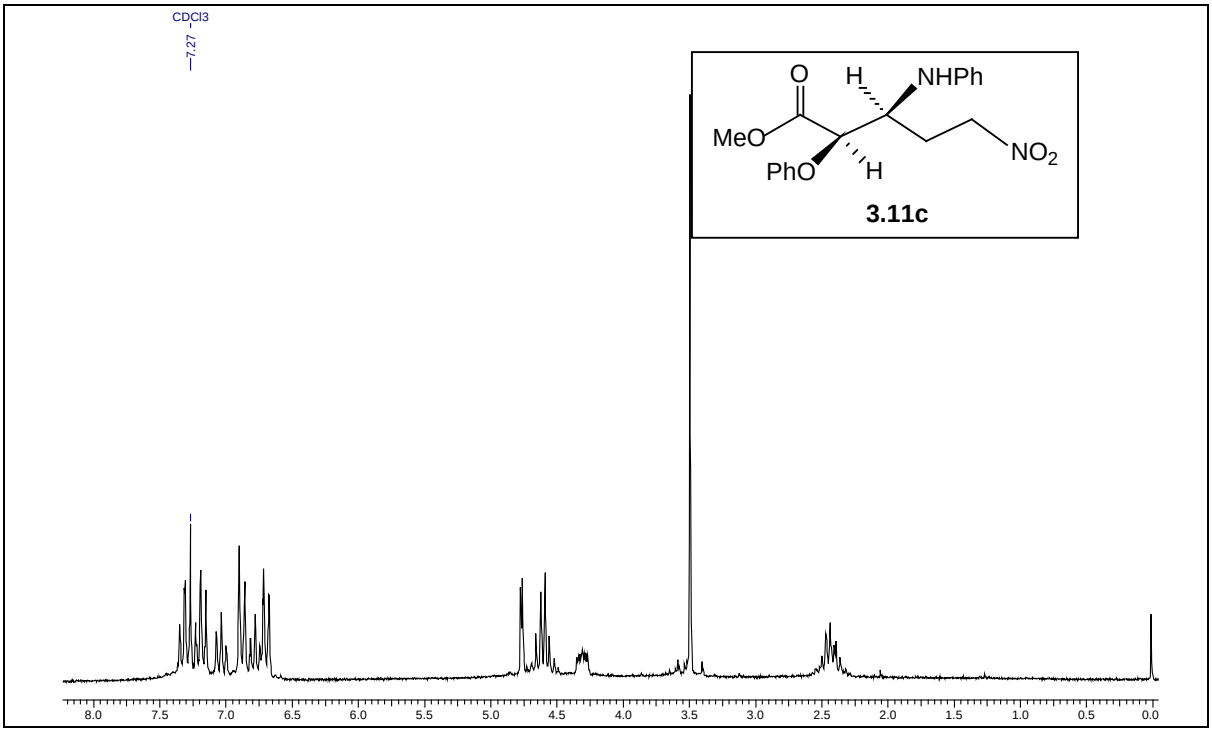

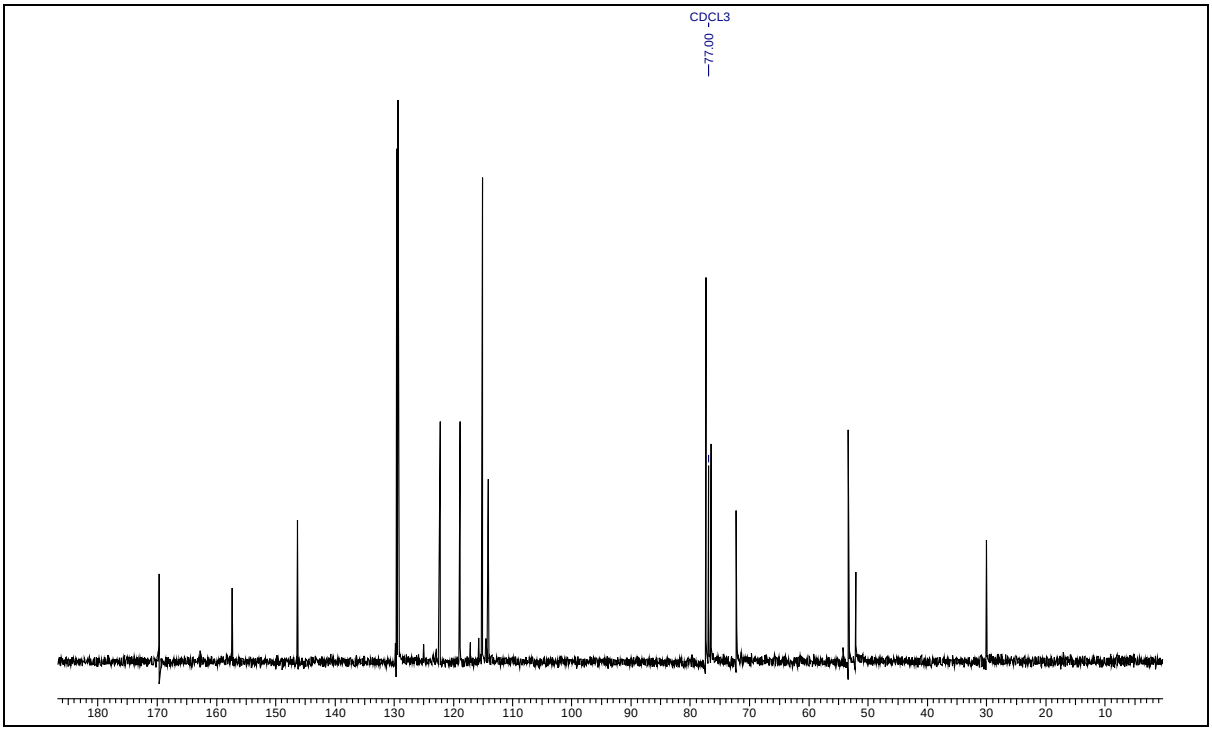

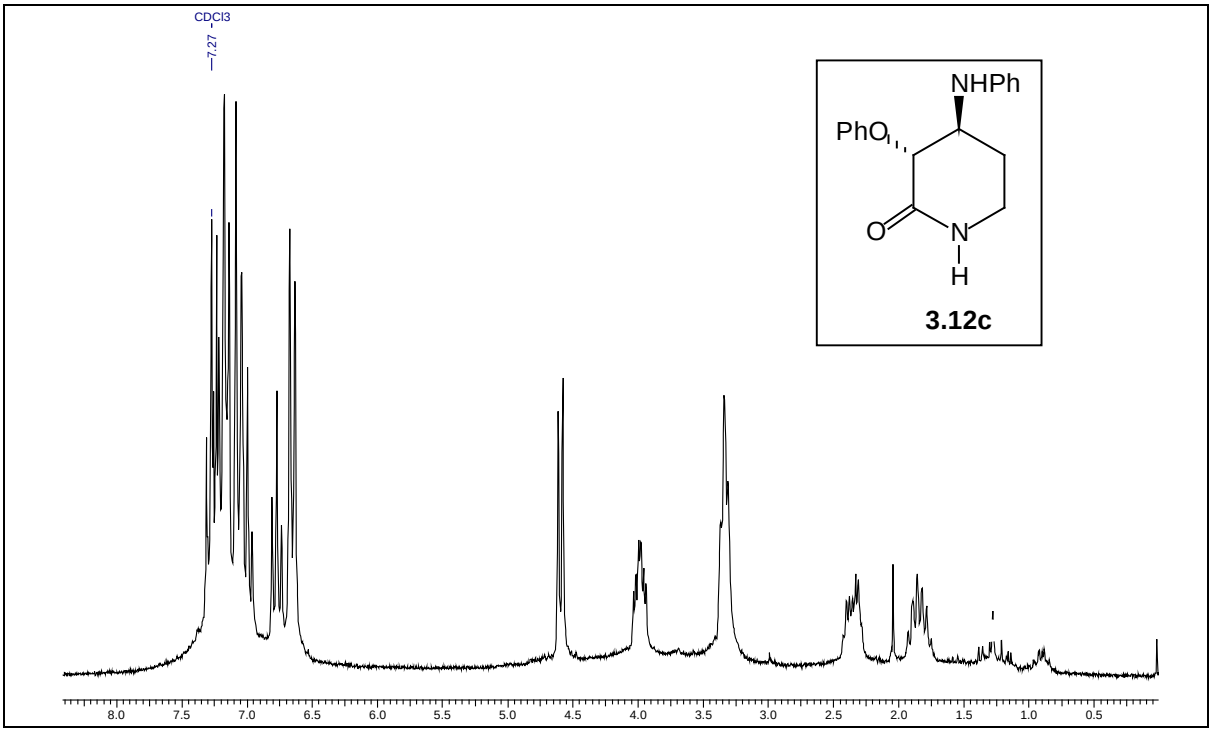

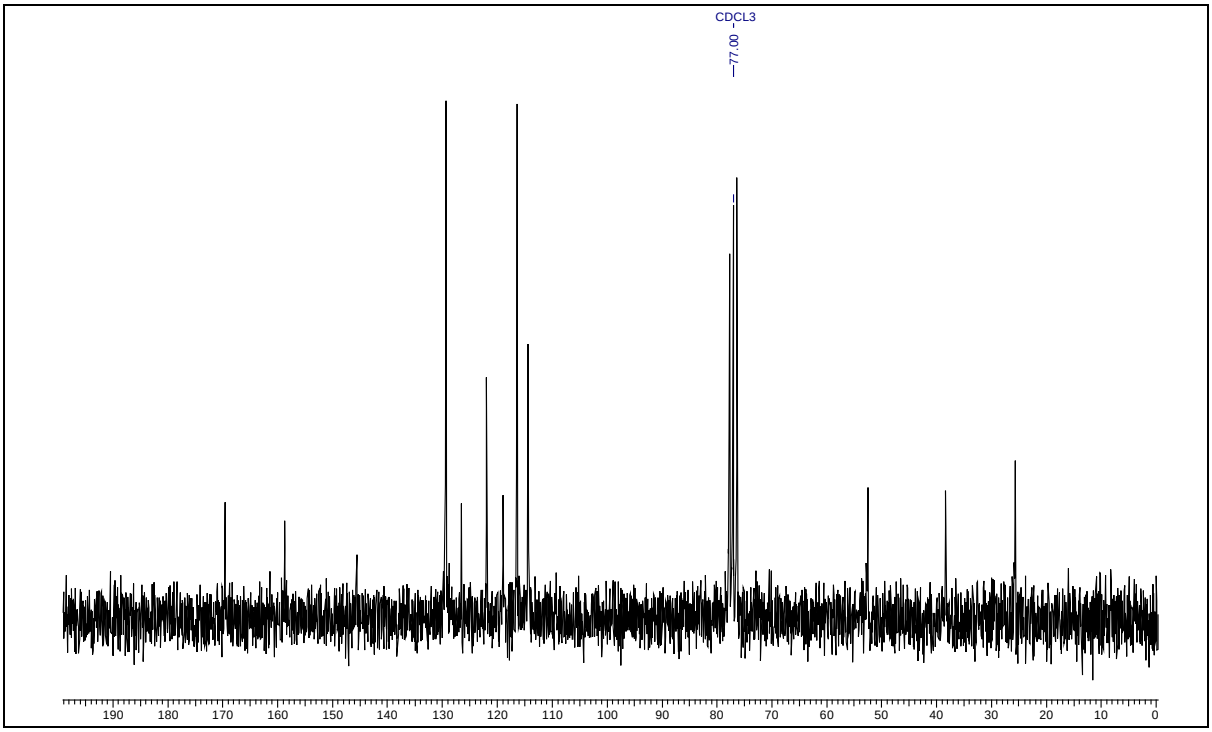

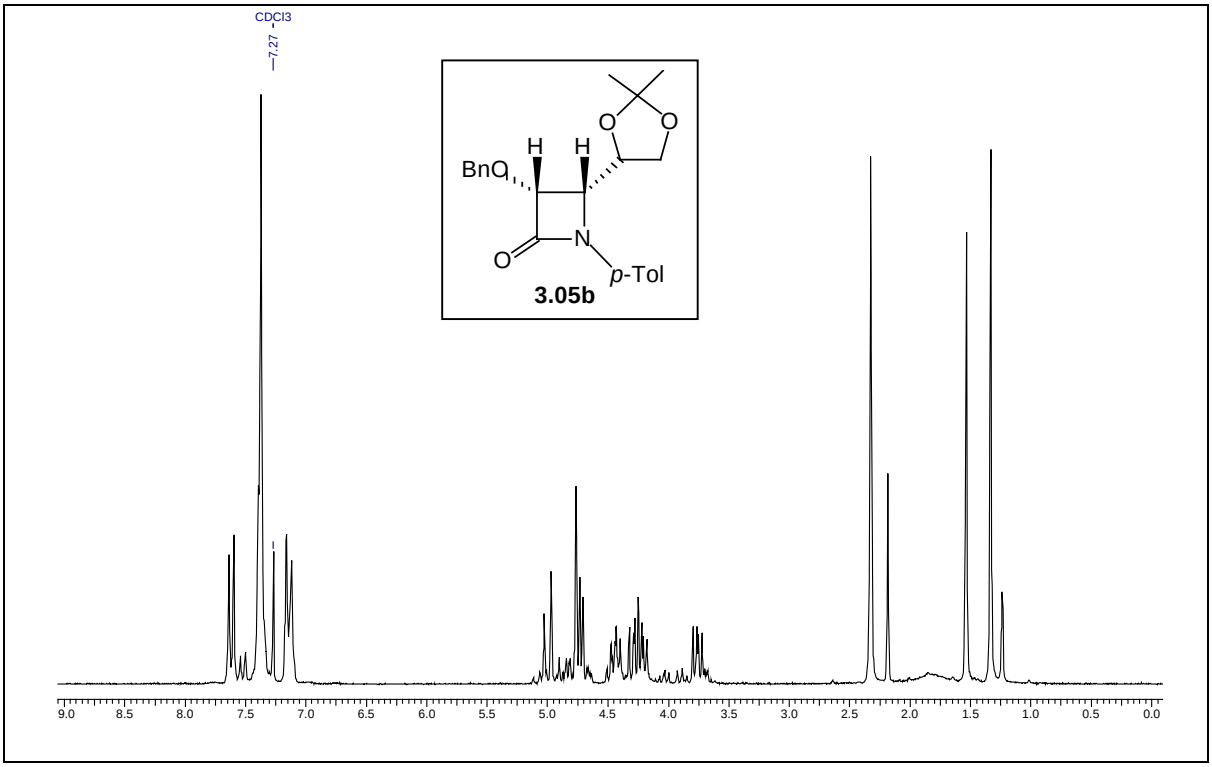

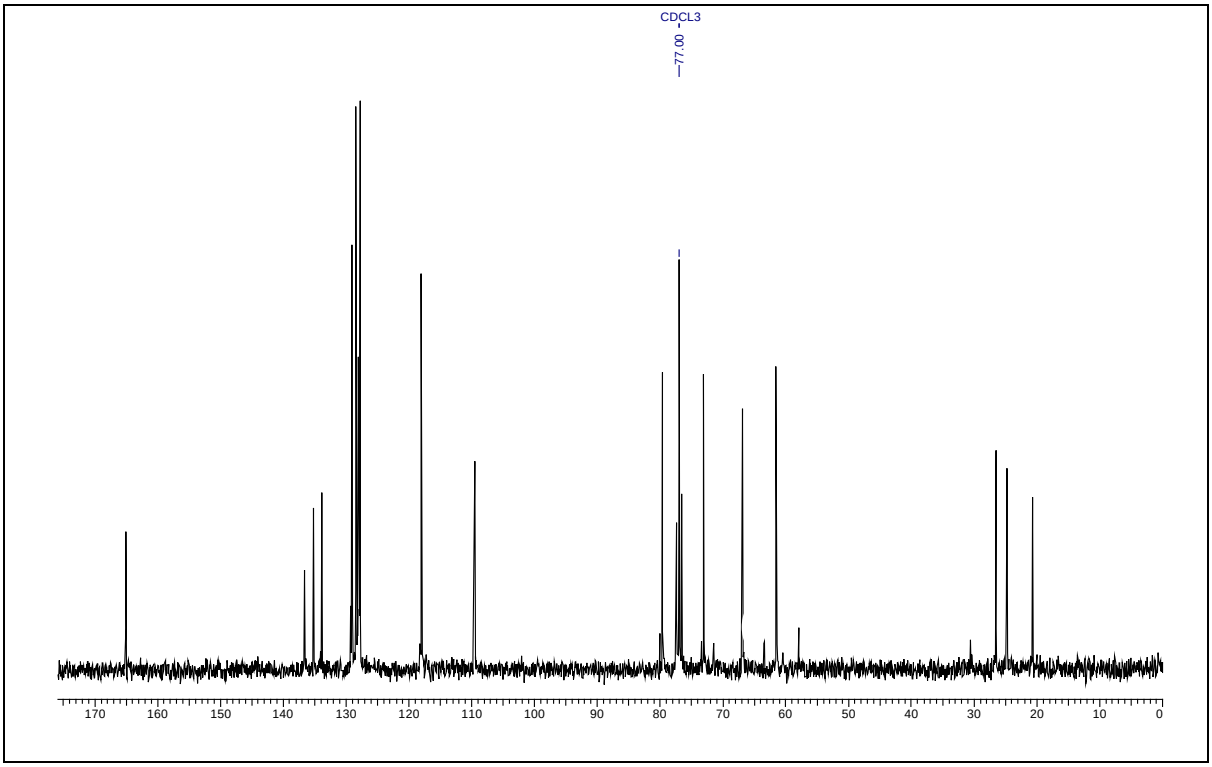

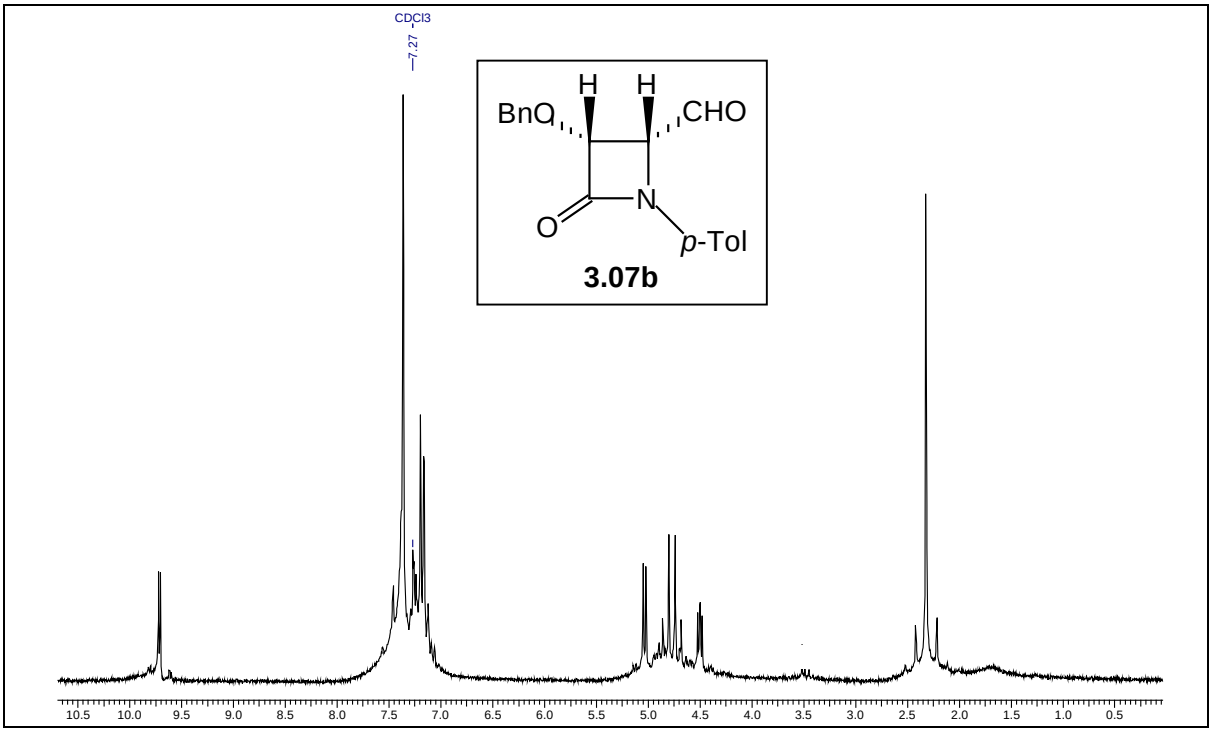

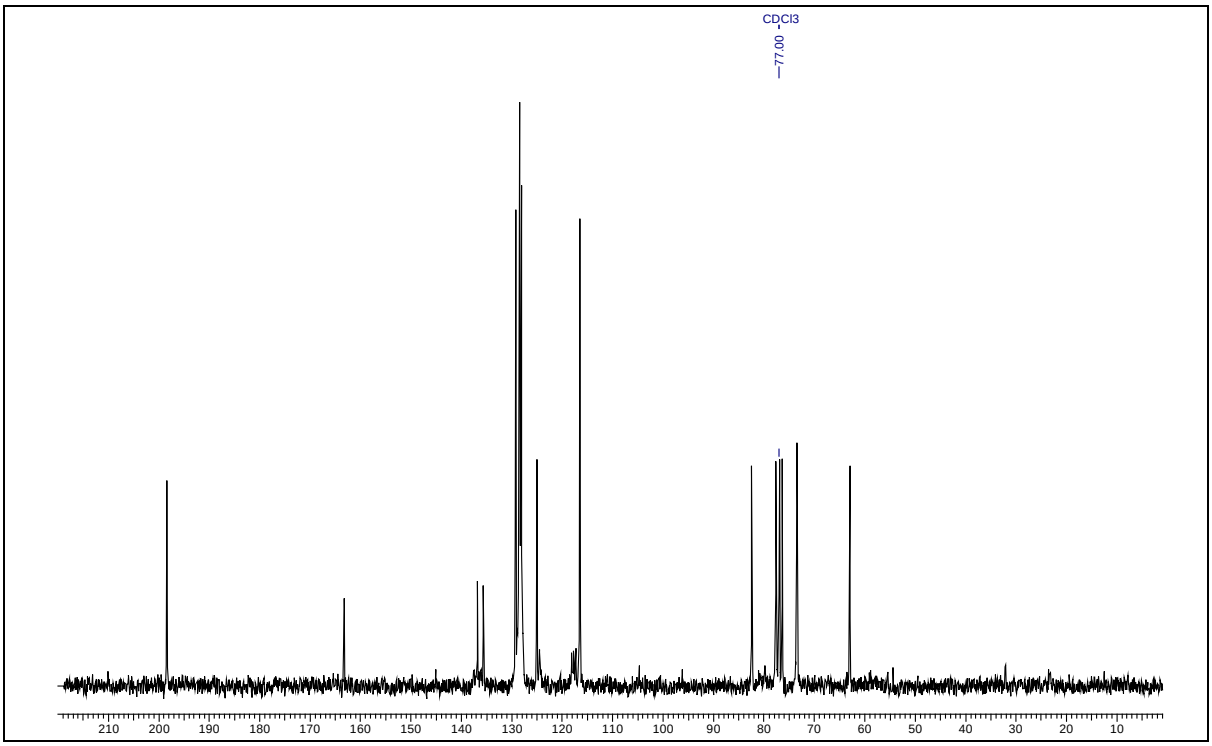

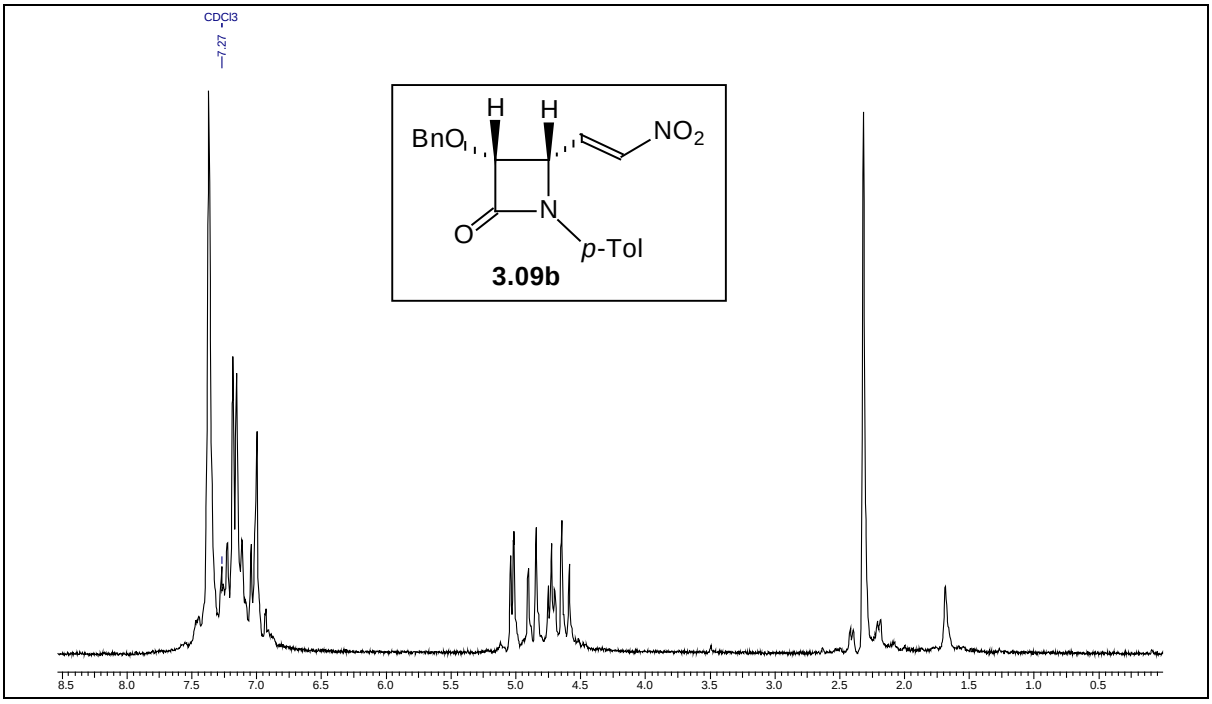

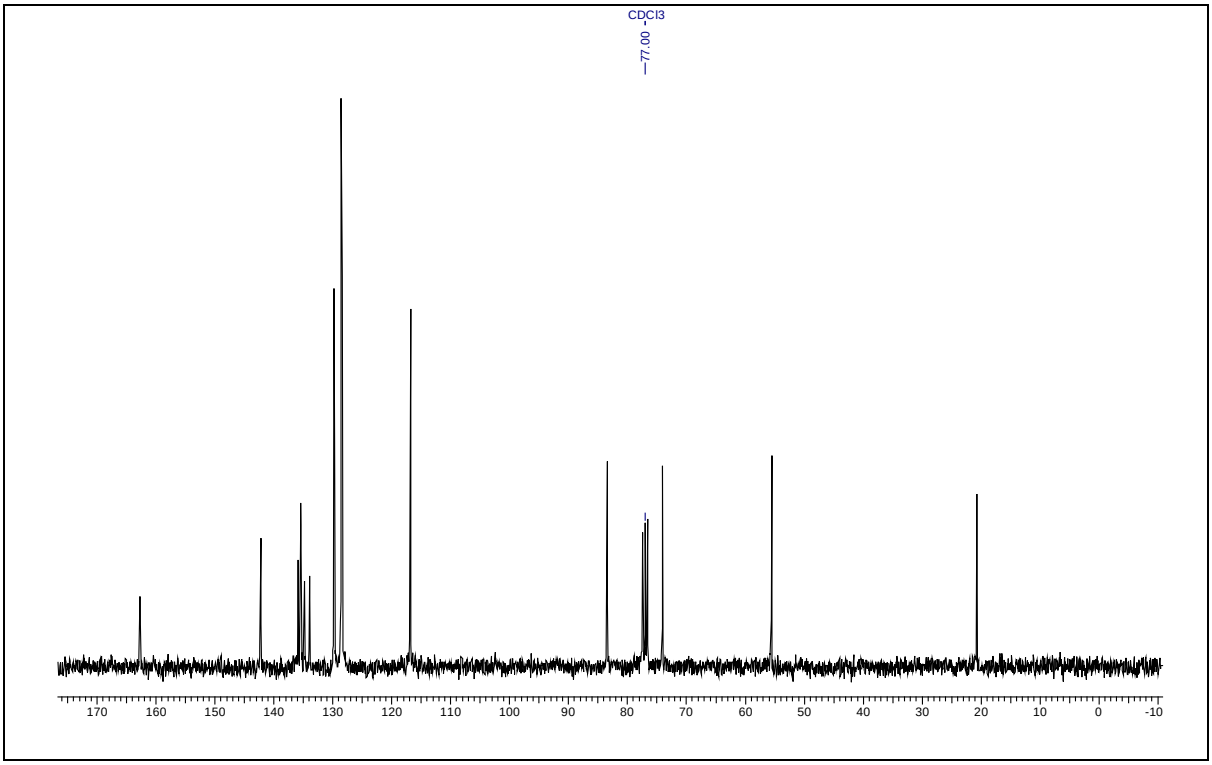

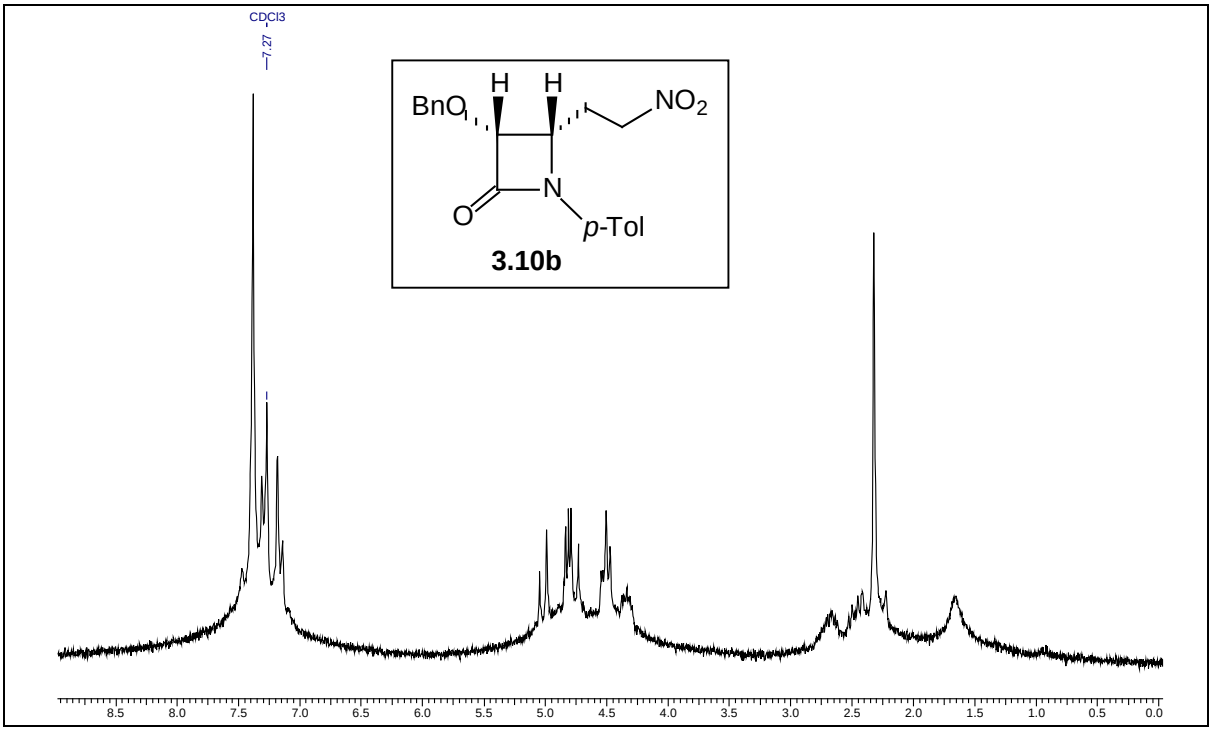

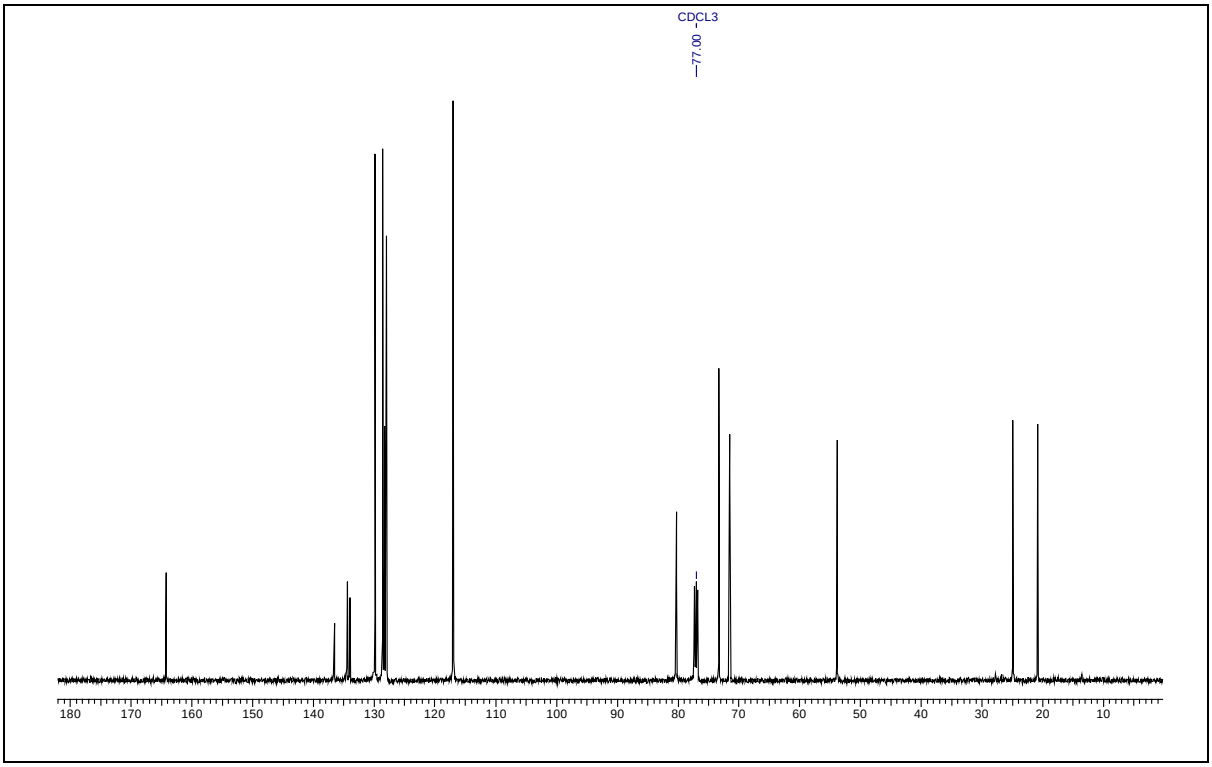

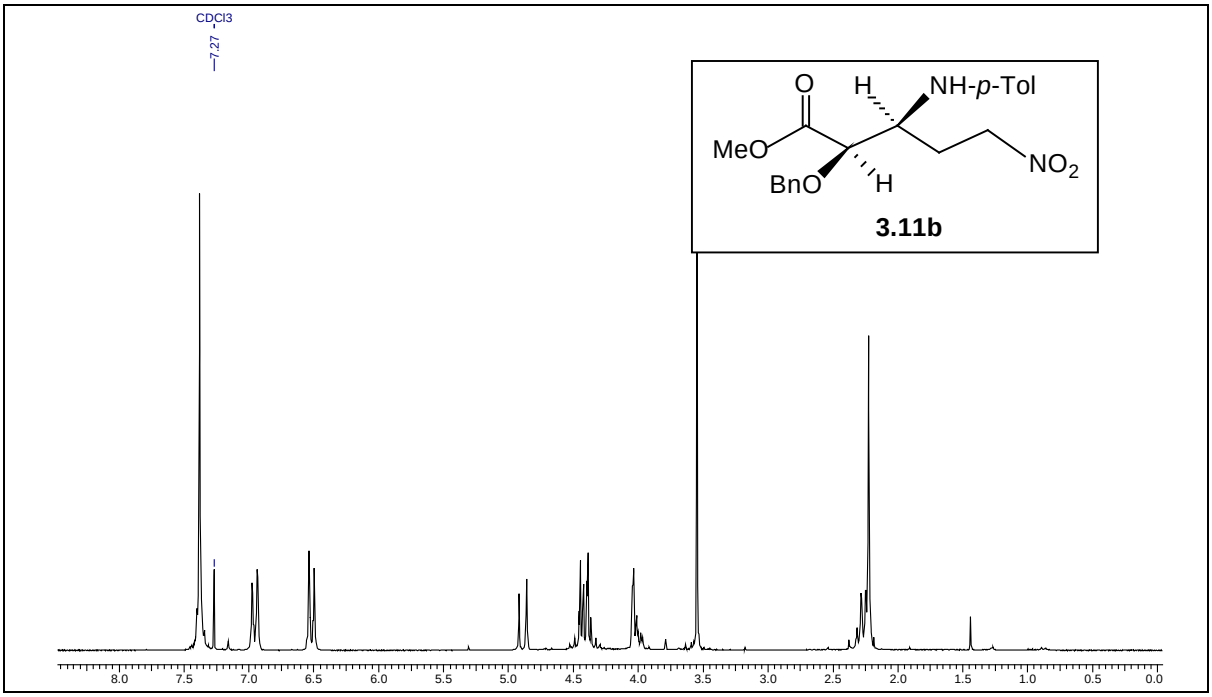

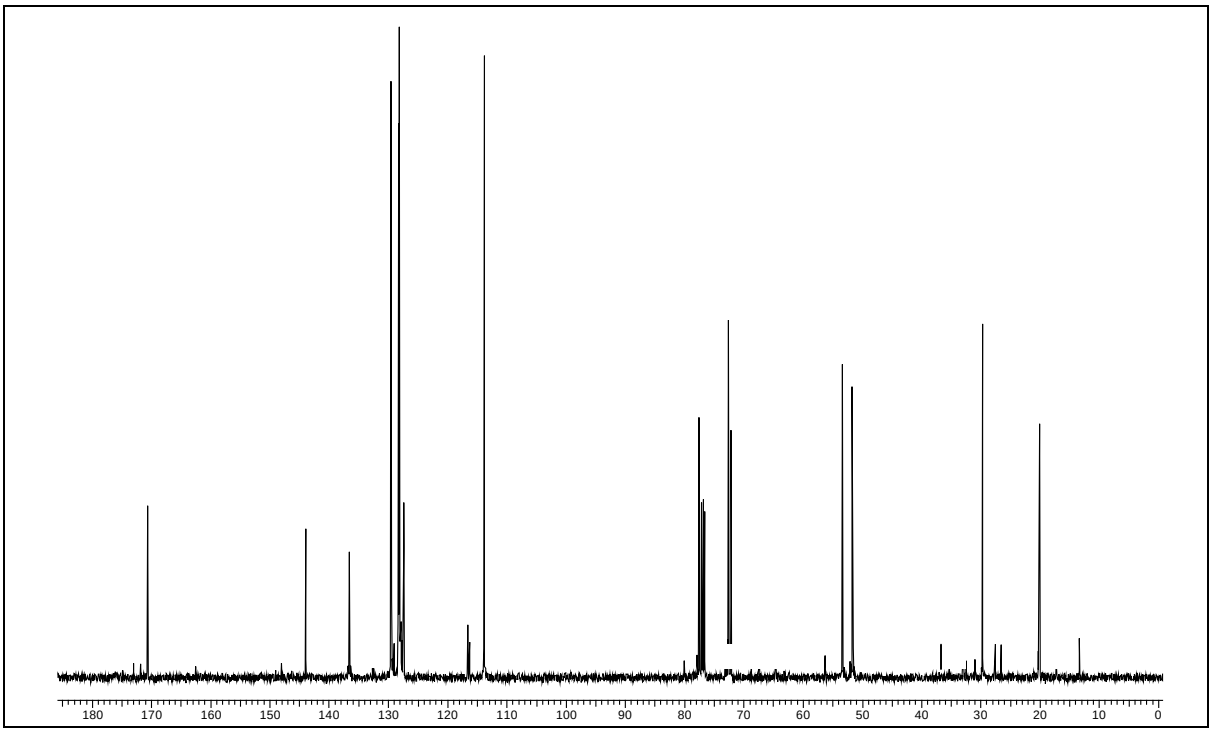

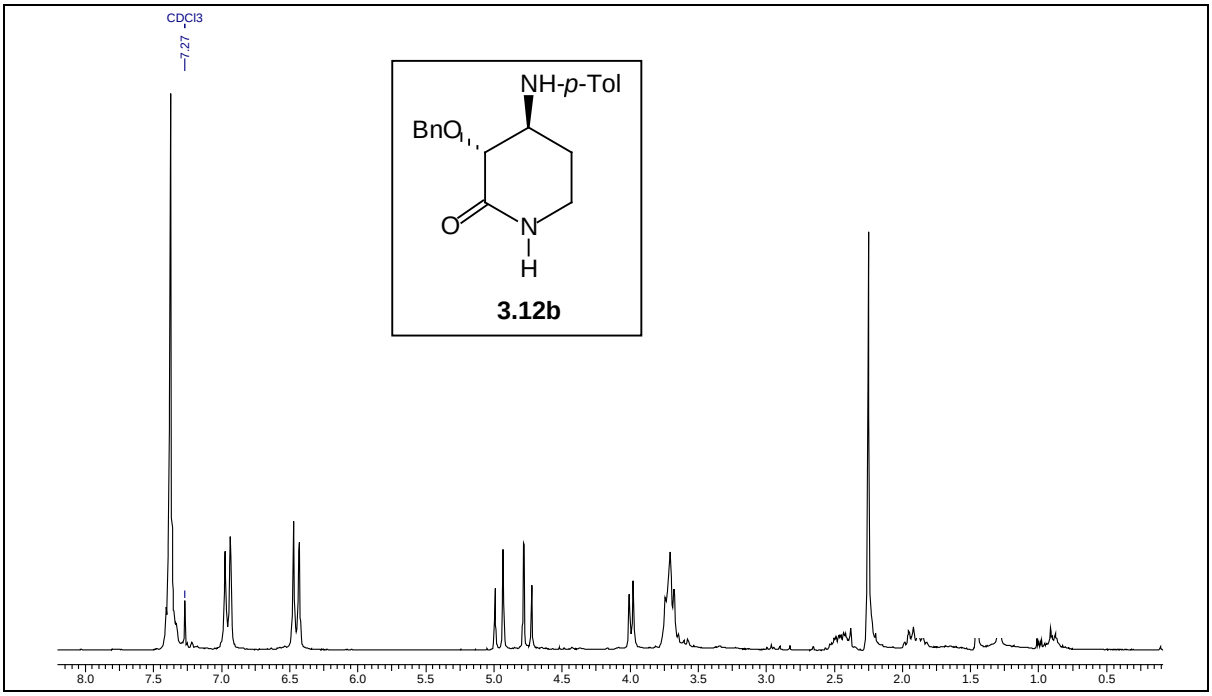

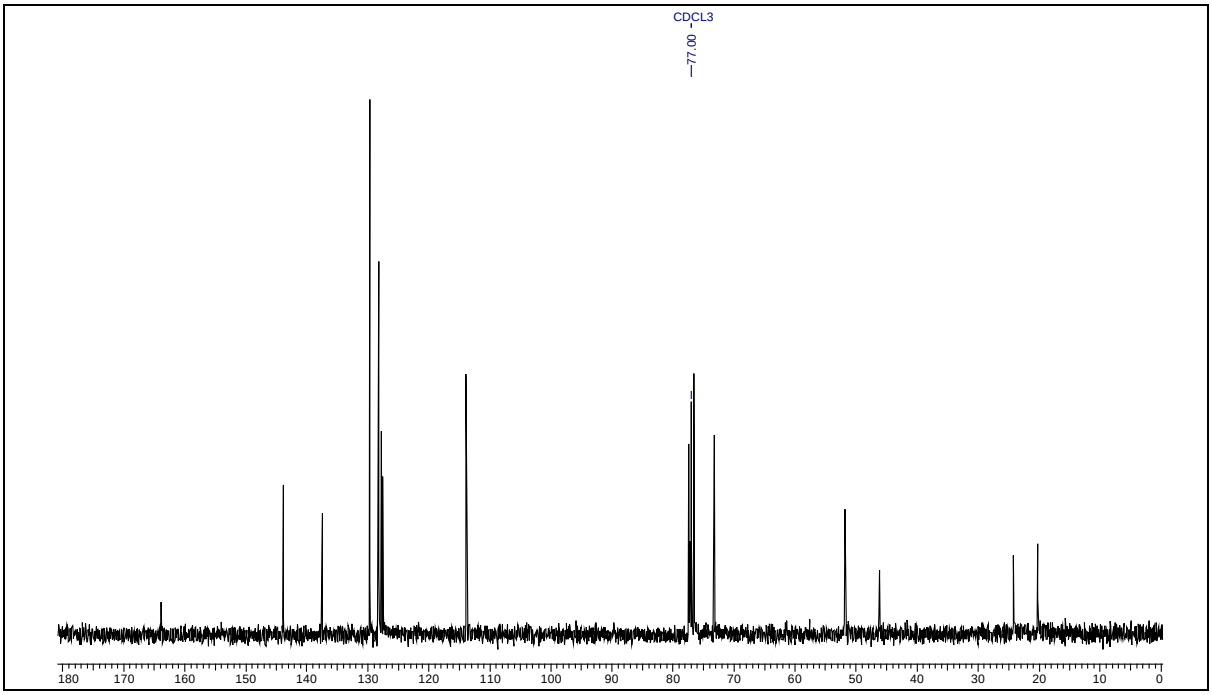

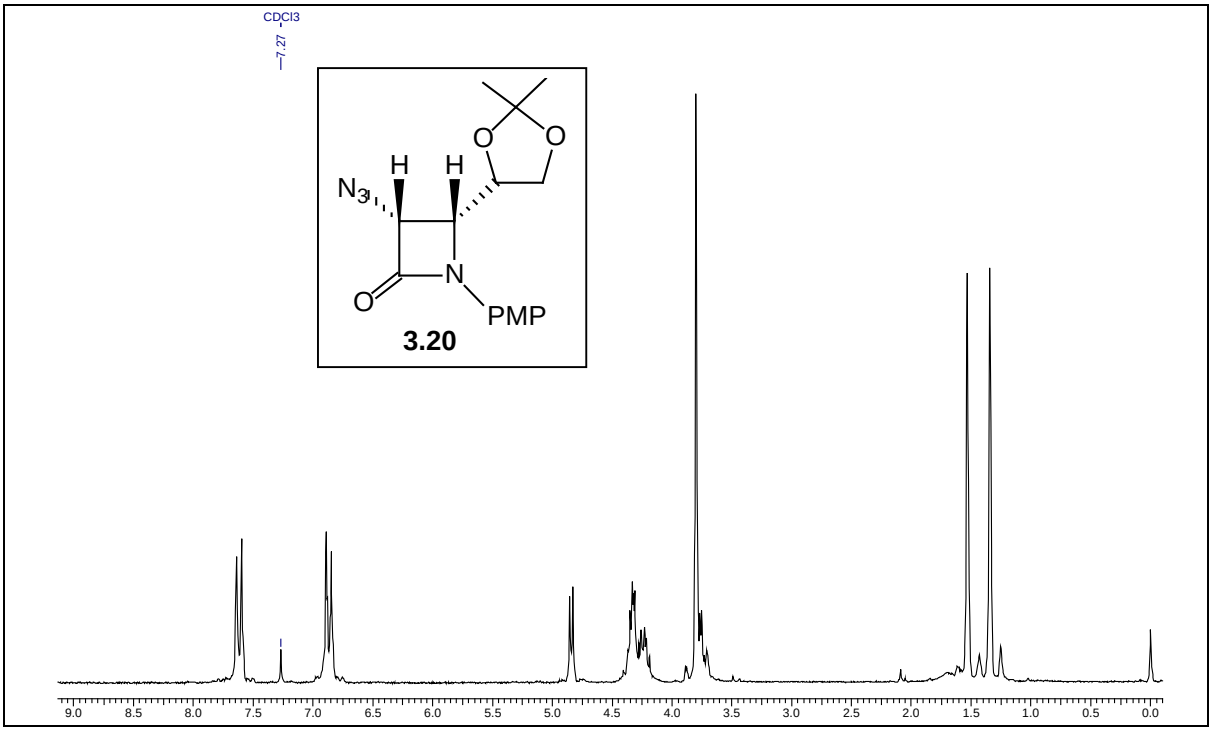

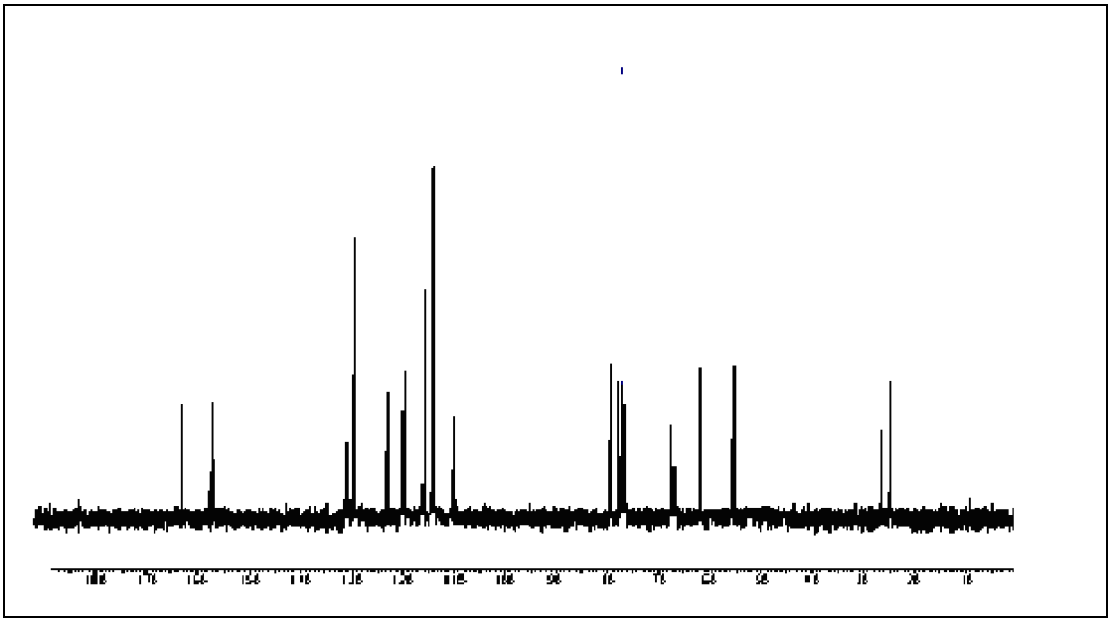

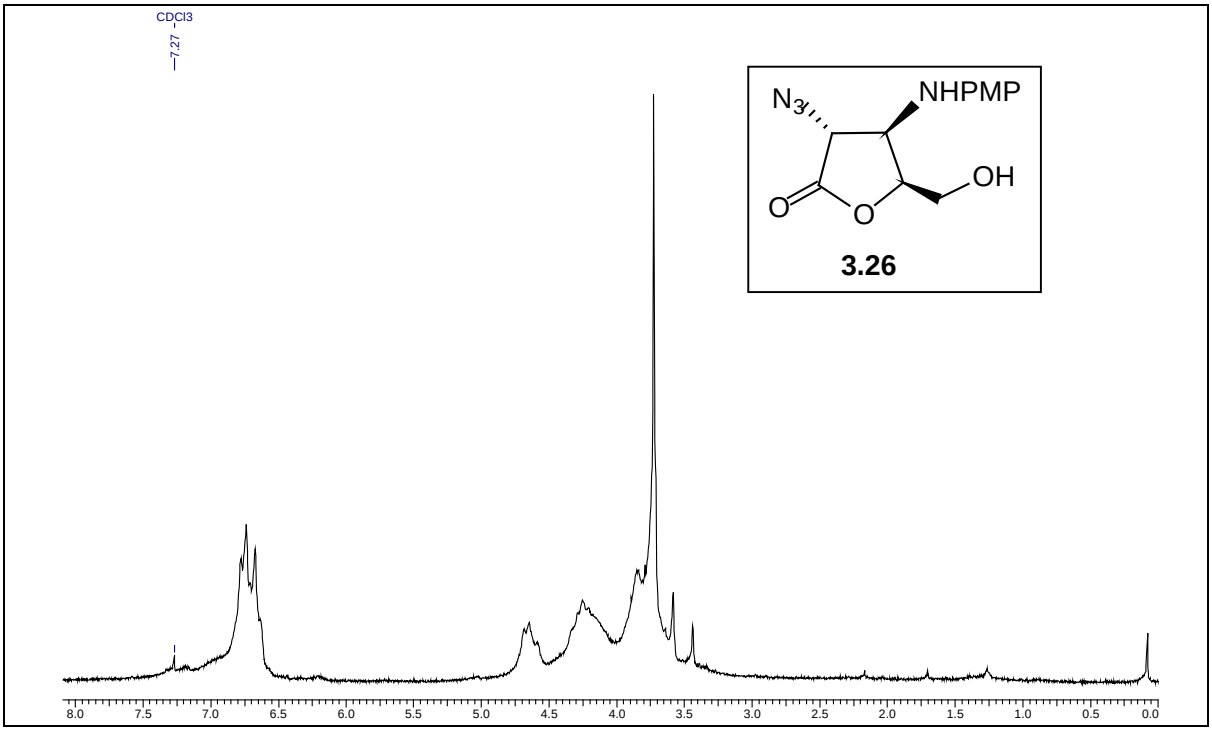

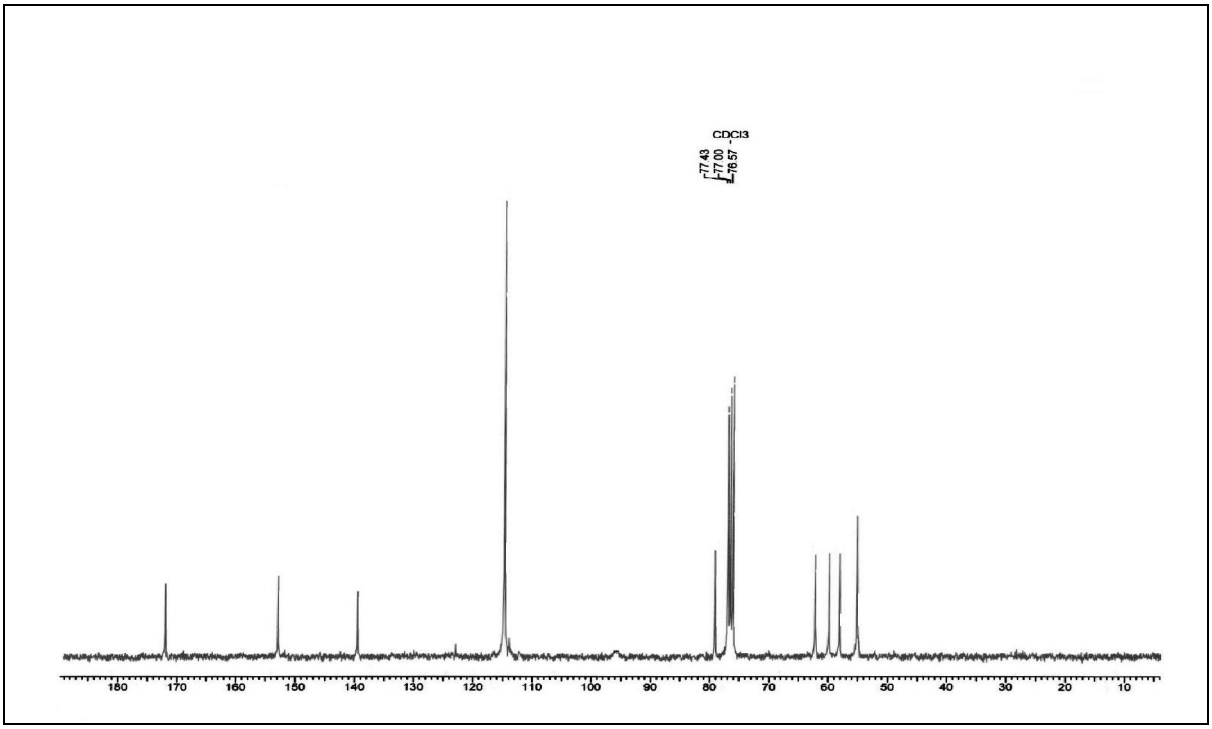

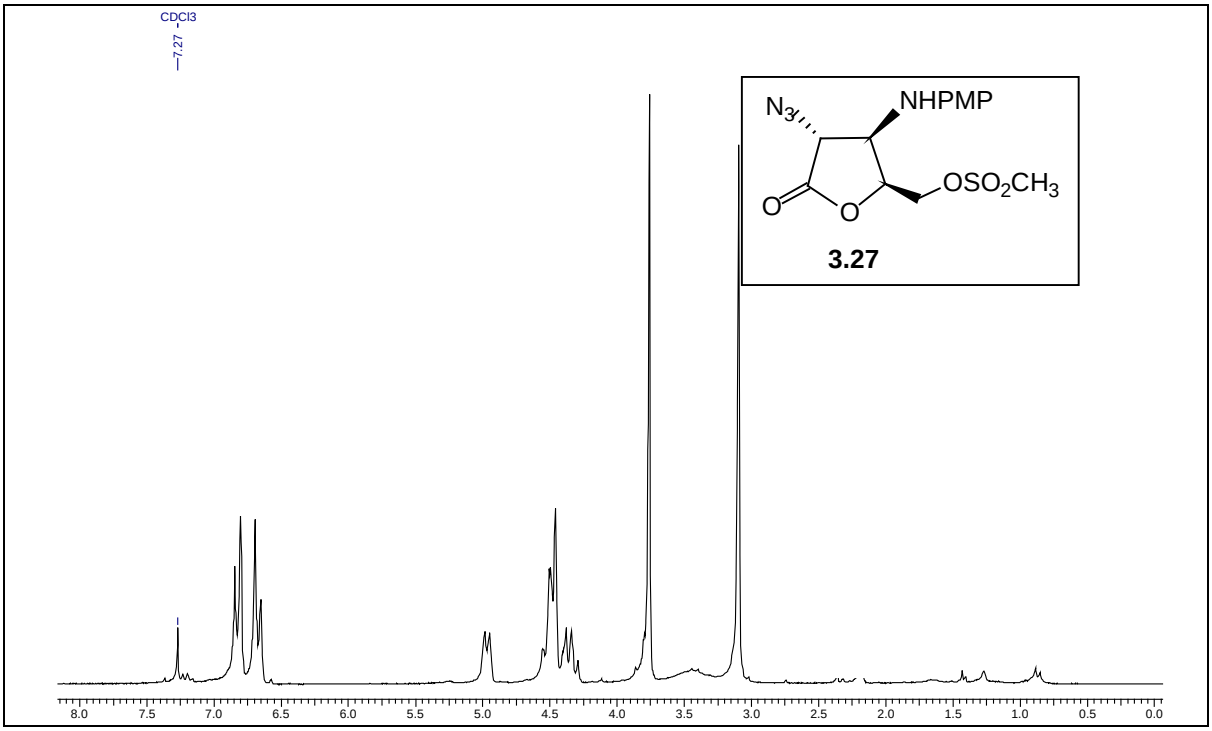

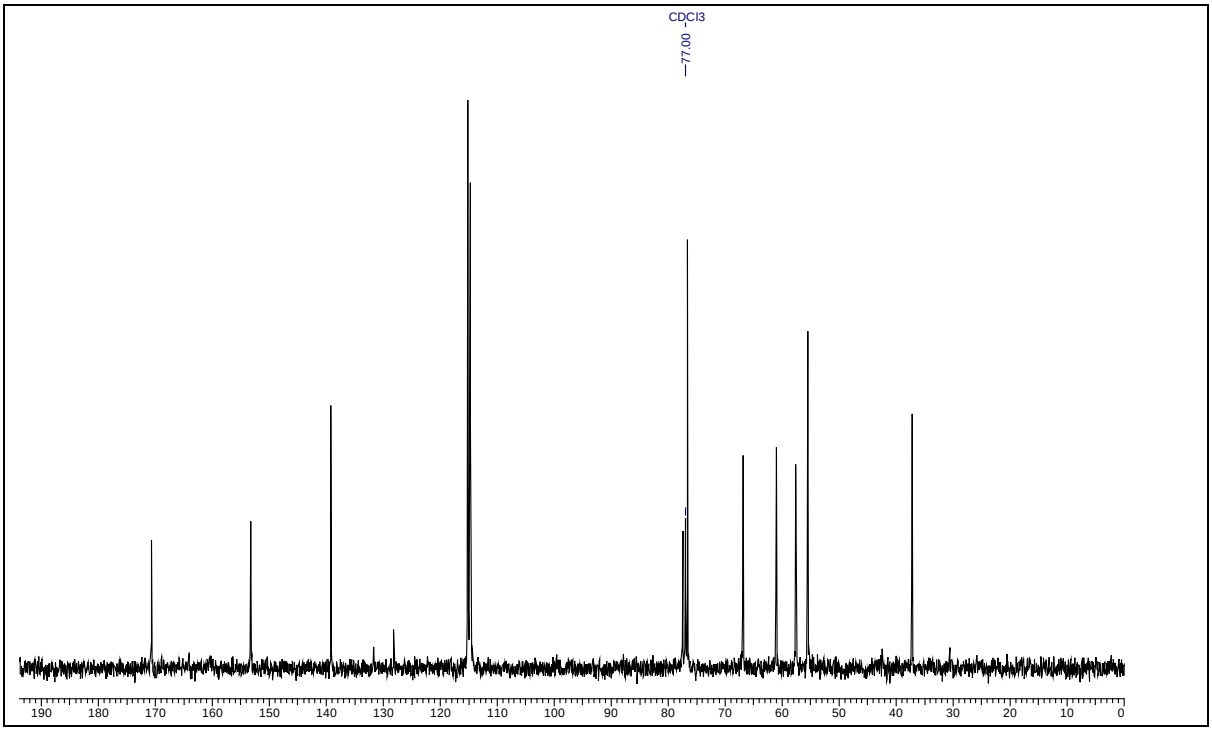

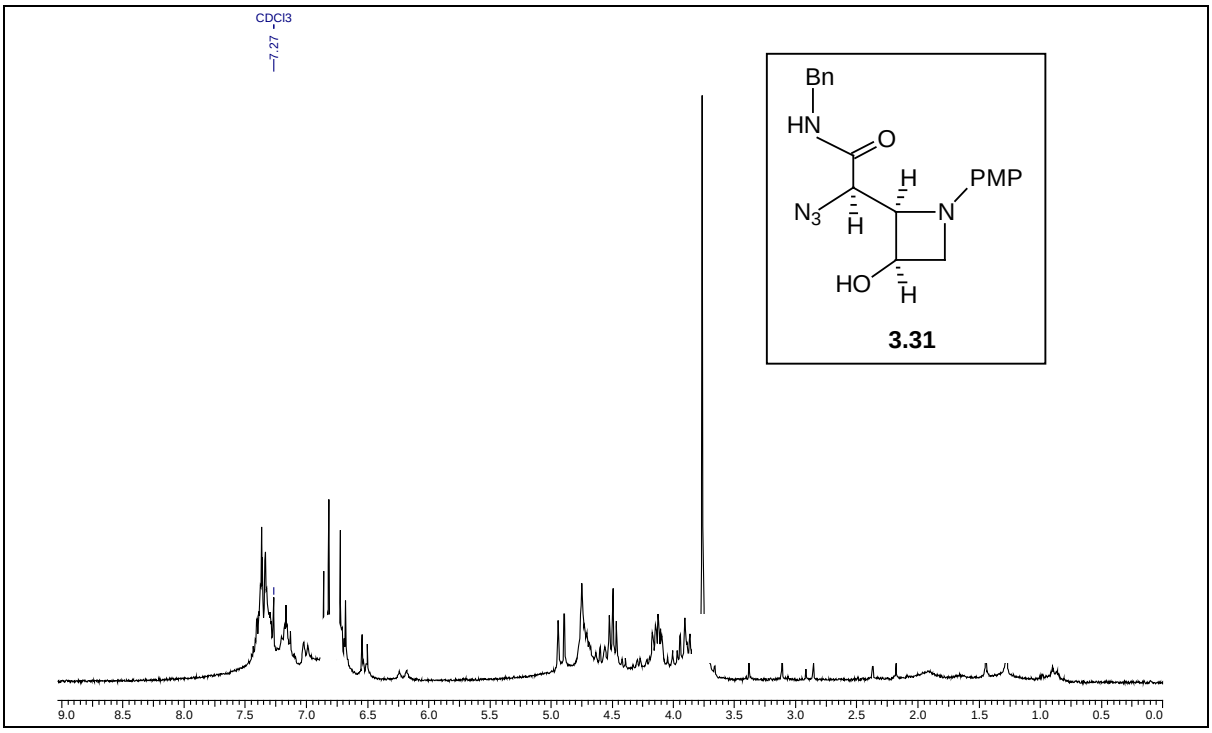

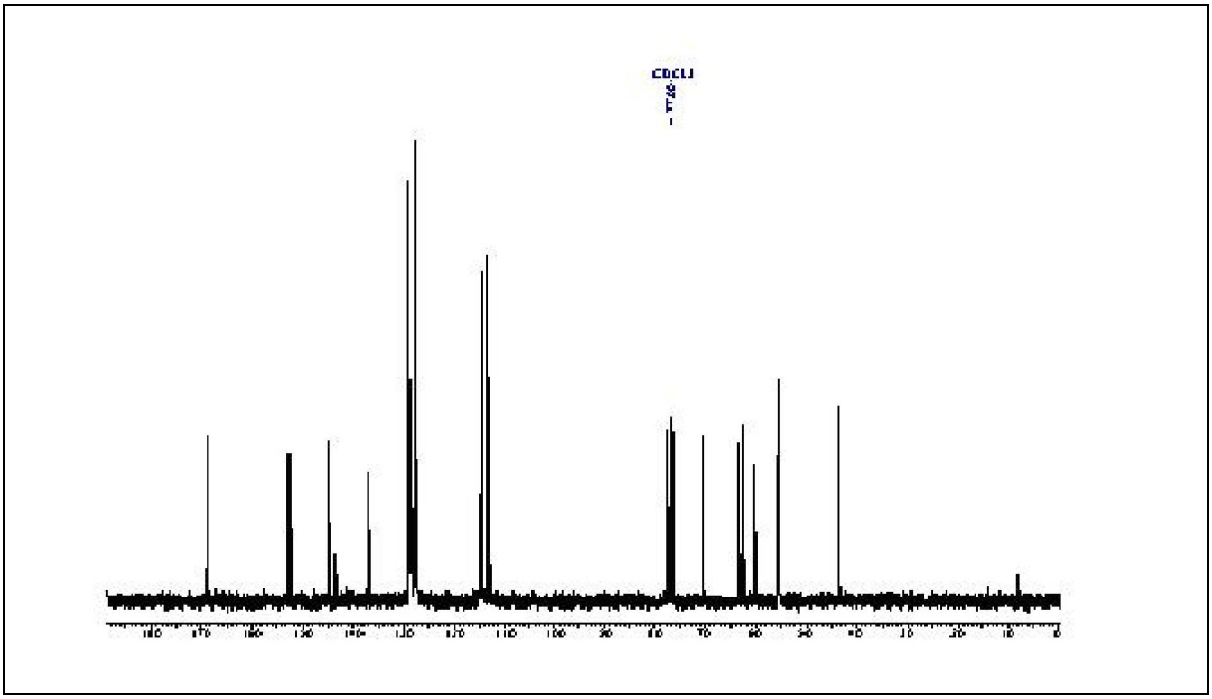

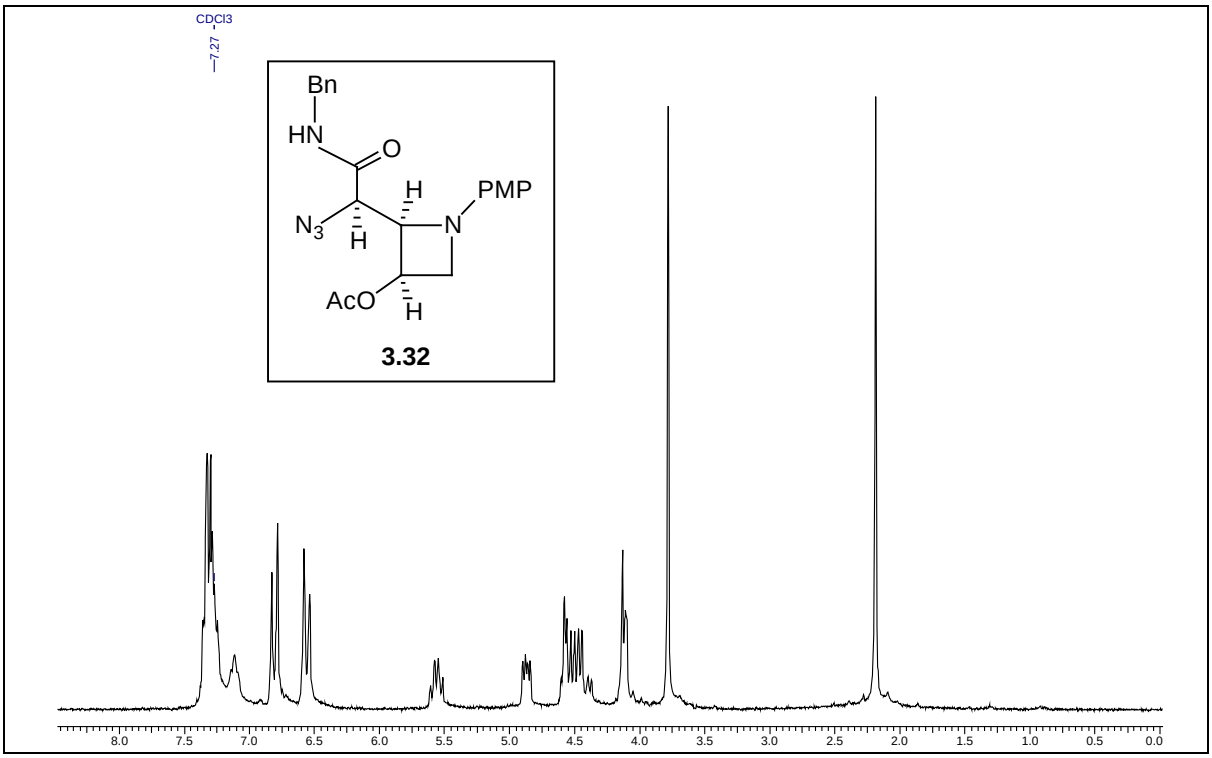

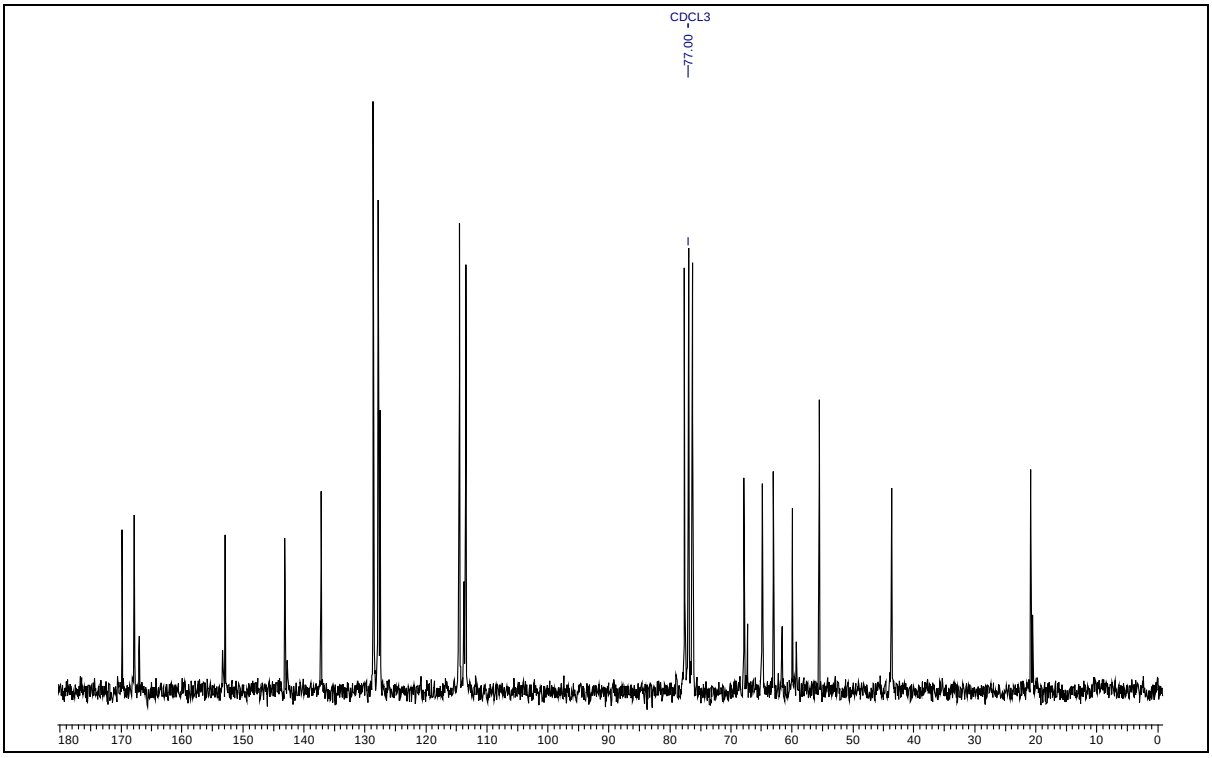

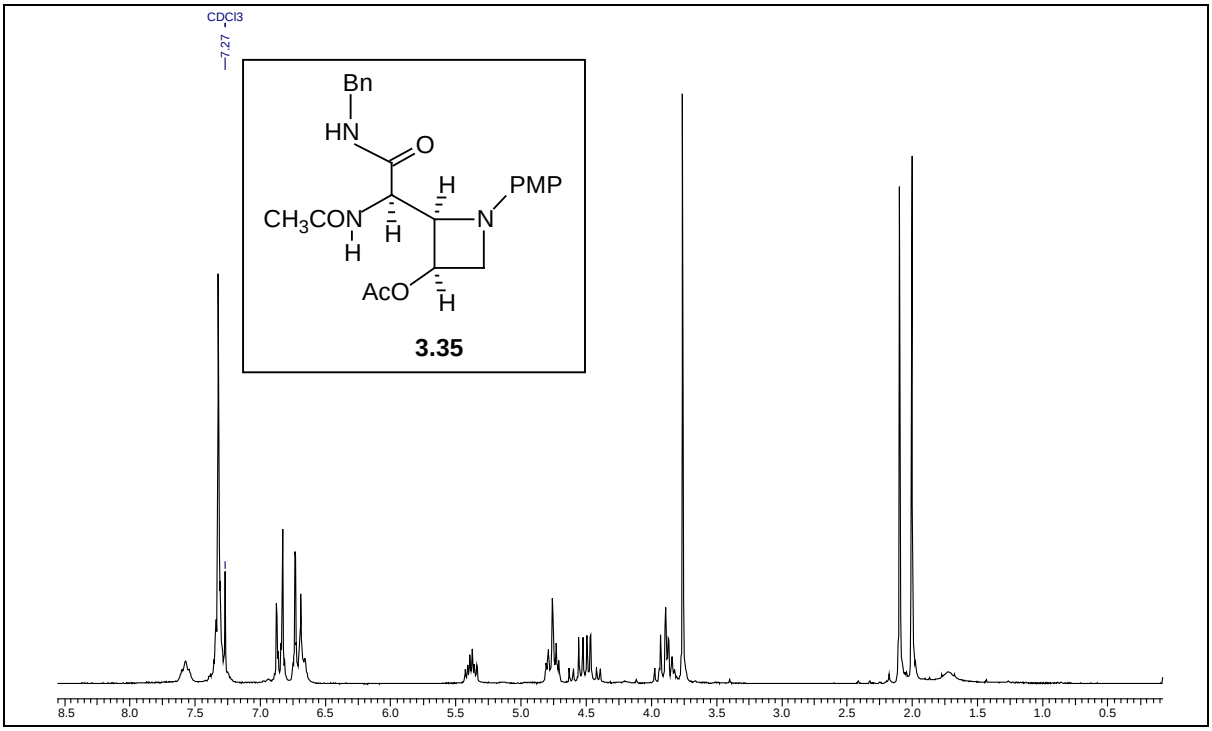

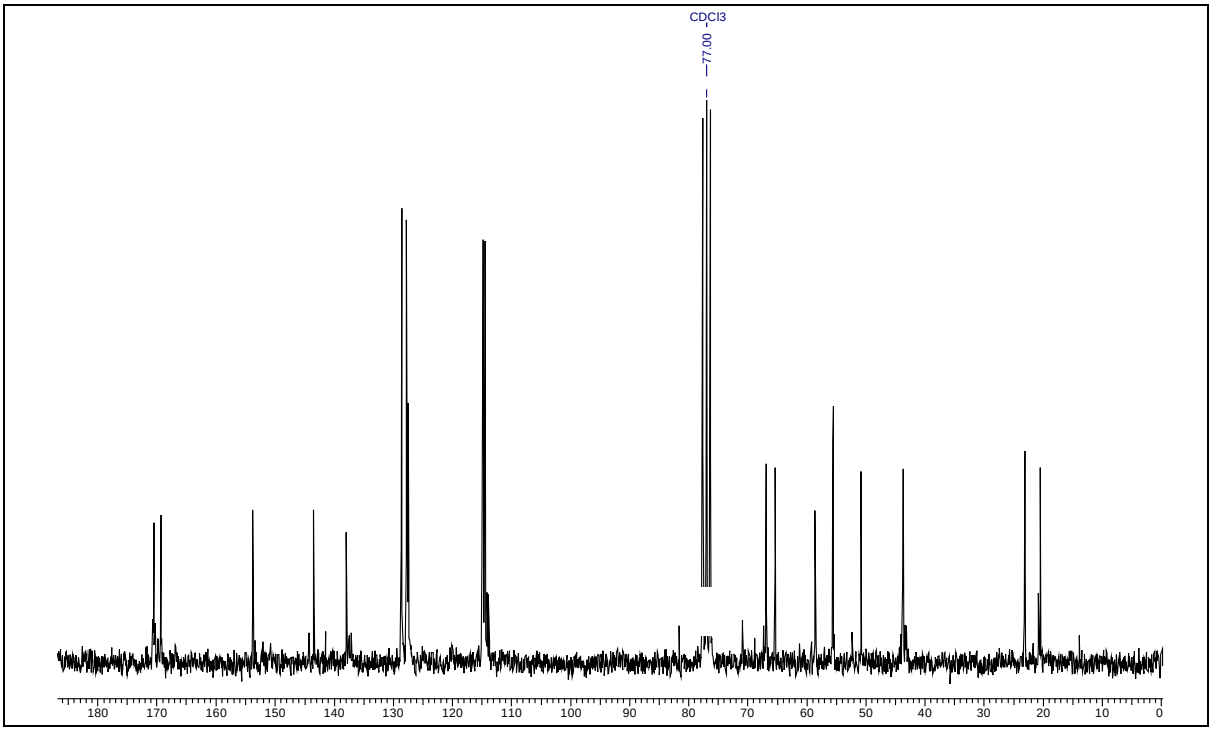

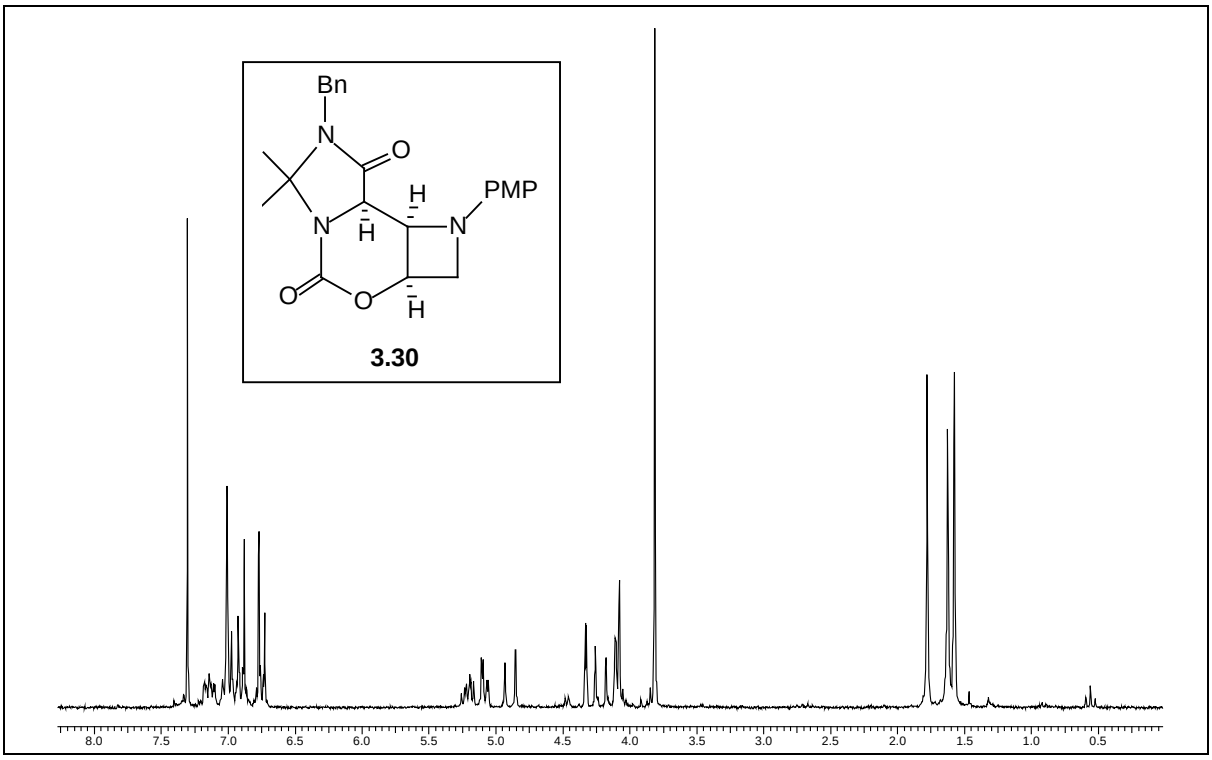

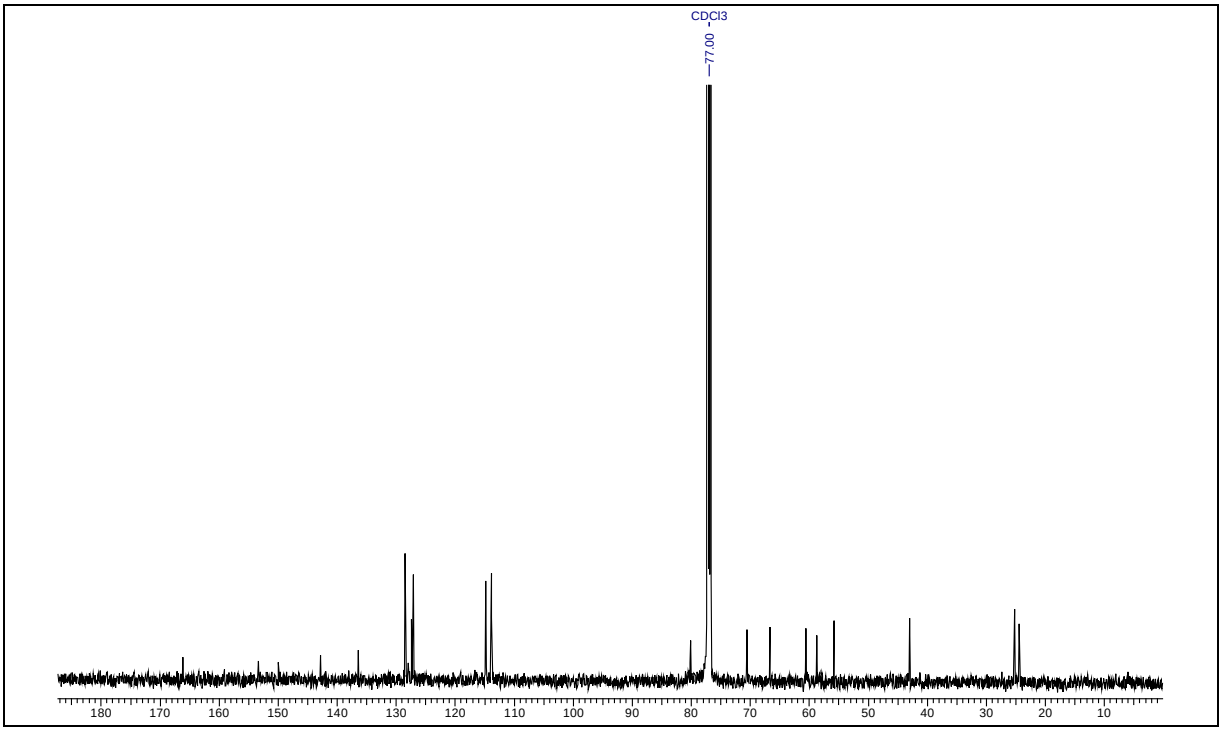

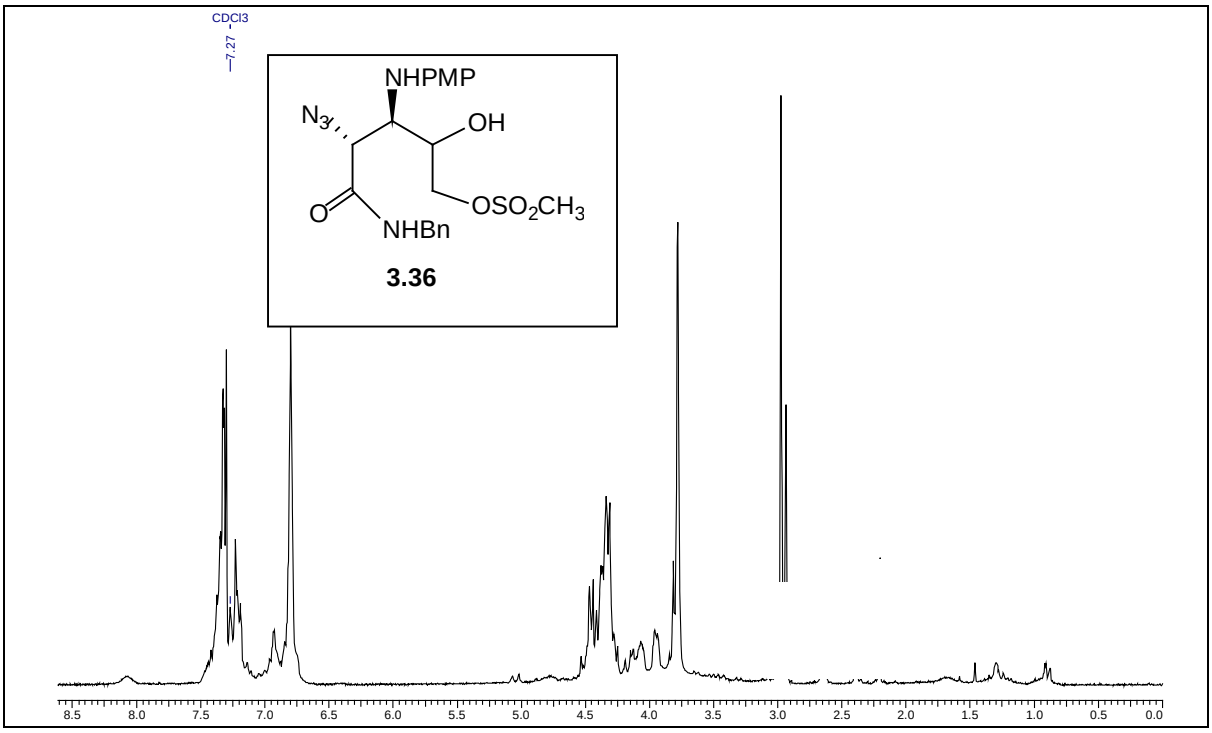

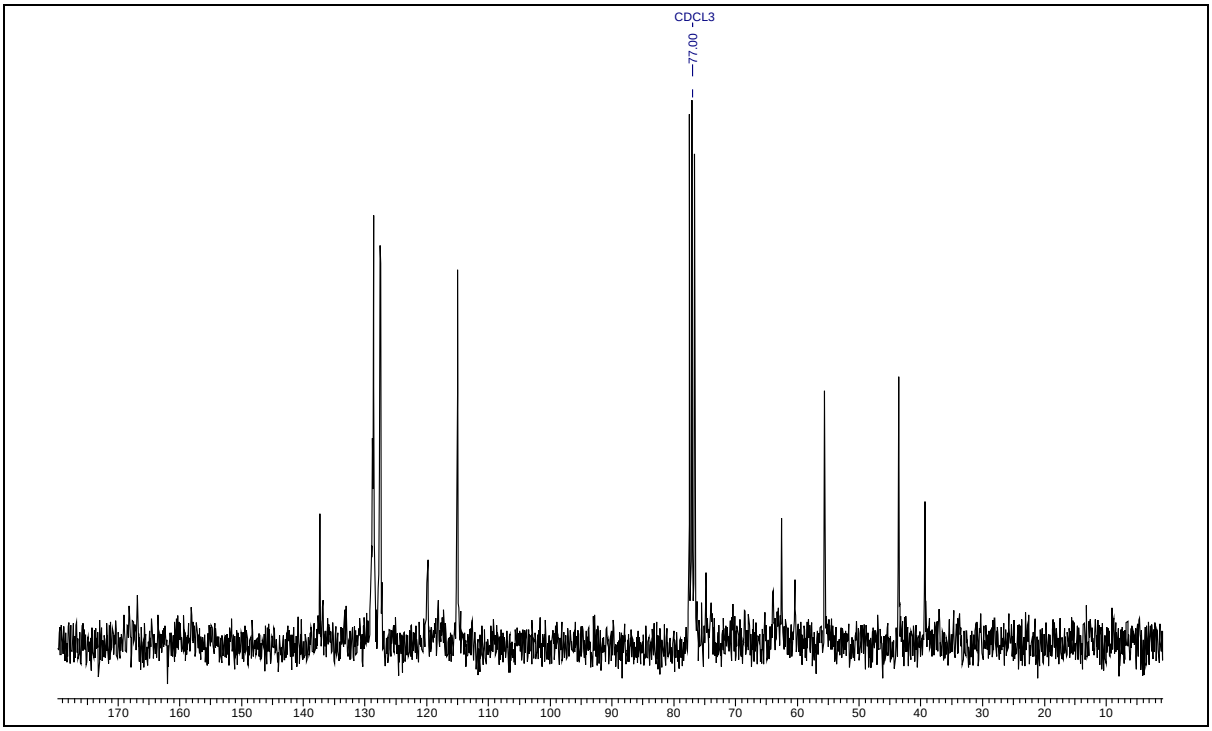

List of publications

1. Azetidin-2-ones, Synthon for Biologically Important Compounds
   A. R. A. S. Deshmukh, B. M. Bhawal, D. Krishnaswamy, **Vidyesh V. Govande**, Bidhan A. Shinkre and A. Jayanthi *Curr*. *Med*. *Chem*. **2004**, *11*, 1889.
2. Facile stereoselective Synthesis of 1,3-disubstituted-4-trichloromethyl azetidin-2-ones
   V. V. Govande, A. R. A. S. Deshmukh. *Tetrahedron Lett*. **2004**, *45*, 6563.
3. 4-formylazetidin-2-ones, Synthon for the Facile Synthesis of Enantiopure 4-Aminopiperidin-2-ones
   Devanathan Krishnaswamy, **Vidyesh V. Govande**, Abdul Rakeeb A. S. Deshmukh. *Synthesis* **2003**, *12*, 1903.
4. Triphosgene: a versatile reagent for the synthesis of azetidin-2-ones
   D. Krishnaswamy, **V. V. Govande**, V. K. Gumaste, B. M. Bhawal and A. R. A. S. Deshmukh. *Tetrahedron* **2002**, *58*, 2215.
5. Synthesis of azetidin-2-one via in situ generated acid chlorides using hexachloroacetone-triethylphosphite
   M. Arun, **V. V. Govande**, A. R. A. S. Deshmukh, B. M. Bhawal. *Indian J*. *Chem*. **2002**, *41B*, 856.
6. Synthesis of Azetidin-2-ones from Imines and Acids Using Trichloroacetonitrile triphenylphosphine Reagent.
   Vidyesh V. Govande, M. Arun, A. R. A. S. Deshmukh, B. M. Bhawal. *Synth. Commun*. **2000**, *30*, 4177.

Erratum