Application of Oxyma Based Reagents in Relevant Organic Transformations

A Dissertation Submitted to the
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Doctor of Philosophy in Chemistry

Submitted by

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Dedicated

to

My Family

Indian Institute of Technology Guwahati

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STATEMENT

I do hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India, under the supervision of Prof. Bhubaneswar Mandal.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

24th September, 2021

Tapasi Kalita

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Indian Institute of Technology Guwahati

Certificate

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CERTIFICATE

This is to certify that **Ms. Tapasi Kalita** has been working under my supervision since Dec 2014 as a regular registered Ph. D. student. I am forwarding her thesis entitled "**Application of Oxyma Based Reagents in Relevant Organic Transformations**" for being submitted for the Ph. D. (Science) degree from this institute. I certify that she has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in her thesis and this work has not been submitted elsewhere for a degree.

24th September, 2021

Prof. Bhubaneswar Mandal

Thesis Supervisor

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Synopsis

The contents of the thesis entitled, "Application of Oxyma based reagents in relevant organic transformations" have been divided into five chapters based on the results of the experimental work performed during the complete course of the doctoral studies. The abstracts of the chapters are described below.

Chapter 1: Introduction

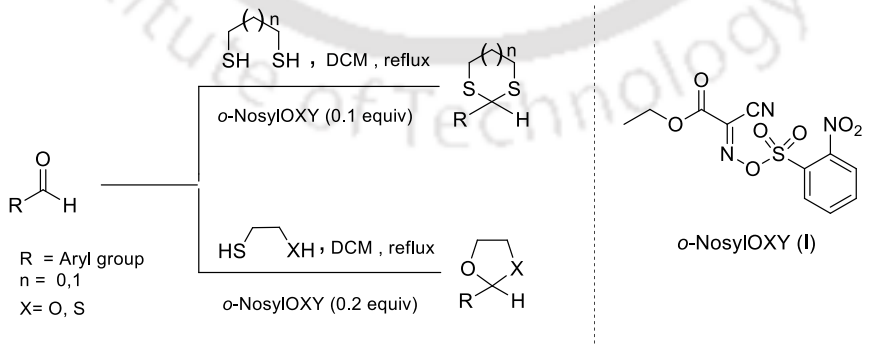
Coupling reagents are mainly used for amide bond formation. Different type of coupling reagents such as carbodiimide, phosphonium, and aminium/uranium salts have been developed already. Most of them involve benzotriazole and azabenzotriazole ring structure as an important fragment, which is converted to an excellent leaving group. After dominating for almost two decades, benzotriazole has been replaced by a new class of reagent, i.e., ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma)-based reagents. Due to its mild and racemization-suppression nature, it has become an excellent alternative to benzotriazole-based chemistry. These coupling reagents are used for various organic transformations, including amide and peptide synthesis. Therefore, further exploration of these coupling reagents is necessary.

Amides and peptides are the backbones of proteins and are responsible for various actions in our bodies. The formation of the peptide bond is one of the most important topics in chemistry as it is present in many biologically active molecules and natural products. Due to its numerous applications, it is challenging for the researcher to find newer amide and peptide synthesis approaches. Although many advancements have been made for amide and peptide synthesis, including coupling reagents, few disadvantages

like epimerization, chemical waste generation, multi-step synthesis of the reagent are still associated with it. Therefore, simple methods with the least drawbacks are welcomed.

Chapter 2: Ethyl-2-cyano-2-(2-nitrophenylsulfonyloximino)acetate (*o*-NosylOXY) mediated acetalization and thioacetalization of aldehydes

Acetals and thioacetals play a major role in carbonyl group protection in multi-step organic synthesis. There are many protocols published for acetalization and thioacelalization. Although it is a well-established topic, most of these methodologies have certain drawbacks, including the release of by-product water, involvement of metals, lower substrate scope, and use of a stoichiometric amount of the catalyst. To overcome all these drawbacks, we developed a simple methodology for acetalization and thioacetalization of aldehydes using Ethyl 2-Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*ortho*-NosylOXY), a coupling reagent that was reported by our group recently. First to a mixture of aldehyde, dithiol/diol, and *o*-NosylOXY, distilled DCM was added. Then the reaction mixture was stirred for 3 hours under reflux conditions.

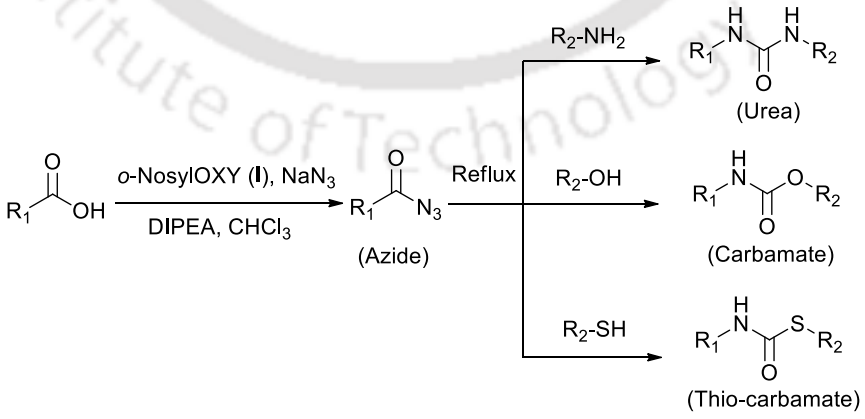


Scheme 1. *o*-NosylOXY mediated acetalization and thioacetalization

We prepared 1,3-dithiolanes and 1,3-dithaines from aldehydes containing different electron-withdrawing and donating substituents with dithiols. Trans-cinnamaldehyde and decanal gave their corresponding 1,3-dithiolane with good yield. In acetal synthesis, this protocol is applicable for aldehydes containing nitro, methoxy, and hydroxyl group as substituents. We also checked the utility of the reaction for gram-scale synthesis.

Chapter 3: *o*- NosylOXY mediated racemization free synthesis of ureas, carbamates, and thiocarbamates via Curtius rearrangement

Urea and carbamate derivatives are present in many pharmacologically active compounds and have a wide range of pesticides, dyes, and polymer chemistry applications. Many methods have already been published to synthesize ureas, but drawbacks, including the difficulties of removing the by-products, involvement of costly and harsh reagent, racemization, are still associated with it. In this chapter, we report one-pot conversion of carboxylic acids to ureas, di-peptidyl ureas, carbamates, and thiocarbamates via Curtius rearrangement using *o*-NosylOXY.

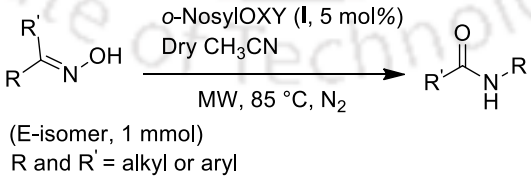


Scheme 2. Synthesis of ureas, carbamates, and thiocarbamates using the *o*-NosylOXY

Initially, the carboxylic acid is treated with *o*-NosylOXY and DIPEA for preactivation of the acid, which upon addition of sodium azide at 0 ℃, forms carboxylic acid azide. Under reflux condition, it rearranges to isocyanate, which is *in situ* trapped by amine, alcohol, and thiol to give corresponding urea, carbamate, and thiocarbamate, respectively. The process is racemization-free and compatible with a diverse range of carboxylic acids. Di-peptidyl ureas were successfully obtained from amino acids with N-protecting groups such as Boc, Fmoc, Cbz, and tert-butyl protected OH group. A detailed NMR-based mechanism study was also done to understand the reaction pathway.

Chapter 4: Mechanistic investigation of Beckmann rearrangement using *o*-NosylOXY

Beckmann rearrangement is a well-known reaction of organic chemistry. Synthesis of amide from ketoxime via Beckmann rearrangement using *o*-NosylOXY was already established by one group member (Scheme 3). Various amides containing different substituents such as methoxy, bromo, chloro, hydro, etc., and few lactams were successfully synthesized by this procedure. A plausible mechanism was also stated, and NMR based study was done in $CDCl_3$ solvent.



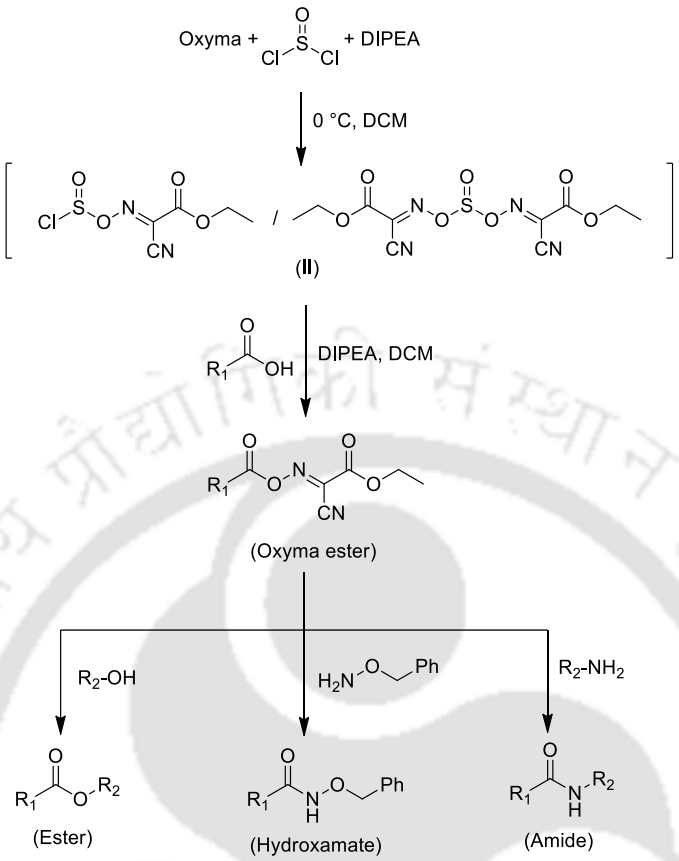
Scheme 3. Synthesis of amide from ketoxime using *o*-NosylOXY

In this chapter, we expanded the above-mentioned work. Using the same reaction condition (Scheme 3), here, we extended the substrate scope of this protocol to ketoxime containing the strongly electron-withdrawing group cyano, cyclic ring cyclopropyl, and

aliphatic ketoximes, and good yield was obtained for these too. We focused on the mechanistic pathway of the reaction and performed the time-dependent NMR study in CD_3CN solvent. Acetophenone oxime and *o*-NosylOXY in CD_3CN were refluxed, and spectra were recorded. It was observed that the reaction rate is faster in CD_3CN than $CDCl_3$.

Chapter 5: A One-Pot Methodology for Converting a Carboxylic Acid into Amide, Peptide, Ester, and Hydroxamate Using Oxyma and Thionyl Chloride

In the previous chapters, we demonstrated the involvement of *o*-NosylOXY in some necessary organic transformations. In this chapter, we presented a thionyl chloride-based protocol to convert carboxylic acids into amides, peptides, ester, and hydroxamates using Oxyma as an additive. NMR studies suggest that the reaction may proceed via two new intermediates, Oxyma-sulfinyl chloride and sulfinyl diOxyma (**II**, Scheme 4), which are successfully used as a precursor for these syntheses via Oxyma esters. Acid followed by amine to **II** leads to the formation of amide at room temperature. Reaction worked well with carboxylic acid-containing different substituents like nitro, iodo, methoxy, etc., and amino acids with common N-protection such as Fmoc, Boc, and Cbz. Methyl esters of amino acids, aliphatic and aromatic amines were used as nucleophiles. HPLC study indicates that adding Oxyma to thionyl chloride decreases the final amide's racemization. The process is recyclable as the only by-product Oxyma can be recovered and reused to repeat the process.



Scheme 4. Synthesis of amide, hydroxamate, and ester using Oxyma and thionyl chloride

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Chapter 3: *ortho*-NosylOXY Mediated Racemization Free Synthesis of Ureas, Carbamates, and Thiocarbamates via Curtius Rearrangement

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Chapter 5: A One-Pot Methodology for Converting a Carboxylic Acid into Amide, Peptide, Ester, and Hydroxamate Using Oxyma and Thionyl Chloride

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Tapasi Kalita

List of abbreviations

AOP	(7-azabenzotriazol-1-yl)oxytris(dimethylamino)phosphonium hexafluorophosphate
ACN	Acetonitrile
BDDC	Bis[[4-(2,2-dimethyl-1,3-dioxolyl)]-methyl]-carbodiimide
BEC	*N*-*tert*-butyl-*N*′-ethylcarbodiimide
Boc	*tert*-Butyloxycarbonyl
Boc-Oxyma	Ethyl 2-(*tert*-butoxycarbonyloxyimino)-2-cyanoacetate
BOP	Benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate
Cbz	Benzyloxycarbonyl
CDI	*N*,*N*-Carbonyldiimidazole
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
CIC	*N*-cyclohexyl, *N*′-isopropyl carbodiimide
COMU	1-[(1-(cyano-2-ethoxy-2-oxoethylideneamino-oxy)-dimethylamino-morpholinomethylene)]methanaminium hexafluorophosphate
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCM	Dichloromethane
DIC	*N*,*N*′-diisopropylcarbodiimide
DIPEA	Diisopropylethyl amine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EDC	1-[3-(dimethyamino)propyl]-3-ethylcarbodiimide hydrochloride
ESI-MS	Electrospray Ionisation Mass Spectrometry

EtOAc	Ethyl Acetate
Fmoc	9-fluorenylmethyloxcarbonyl
FT-IR	Fourier Transformation Infrared Spectroscopy
Gly	Glycine
HATU	*N*-[(Dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl-methylene)-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
HBTU	*N*-[(1*H*-Benzotriazol-1-yl)(dimethylamino)-methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
HMPA	Hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HOAt	1-hydroxy-7-azabenzotriazole
HPLC	High Pressure Liquid Chromatography
HRMS	High-resolution Mass Spectrometry
InF_3	Indium(III)fluoride
KPF_6	Potassium hexafluorophosphate
MeOH	Methanol
NMR	Nuclear Magnetic Resonance
Oxyma	Ethyl 2-cyano-2-(hydroxyimino)acetate
o-NosylOXY	Ethyl 2-cyano-2-(2-nitrophenylsulfonyloxyimino)acetate
PIC	*N*-phenyl, *N*-isopropylcarbodimide
p-NosylOXY	Ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate
PS-HOBt	Polymer supported 1-hydroxy benzotriazole
PyBOP	Benzotriazole-1-yloxytri(pyrrolidino)phosphonium hexafluorophosphate
PyBroP	Bromotri(pyrrolidino)phosphonium

	hexafluorophosphate
PyOxm	*O*-[(cyano(ethoxycarbonyl)methyliden)-amino]-yloxytri(pyrrolidino) phosphonium hexafluorophosphate
Phe	Phenylalanine
T3P	Propylphosphonic anhydride
tBu	*tert*-Butyl
TCBOXY	*(E)*-Ethyl-2-cyano-2-((2,4,6-trichlorobenzoyl)oxy)imino)acetate
TCT	Cyanuric Chloride
THF	Tetrahydrofuran
TLC	Thin layer chromatography

Abbreviations for intensities of ^{1}H-NMR signals

s	singlet
d	doublet
dd	doublet of doublet
t	triplet
q	quartet
m	multiplet
brs	broad signal
Hz	Hertz
MHz	Mega-hertz

Chapter 1: Introduction

1.1. Introduction

The thesis describes the application of a novel coupling reagent, *o*-NosylOXY, to synthesize acetals, thioacetals, ureas, dipeptidyl ureas, carbamates, and thiocarbamates. A newer methodology for synthesizing amides, dipeptides, esters, and hydroxamates using Oxyma and thionyl chloride is also reported. In this chapter, a brief discussion about the coupling reagent is done. In addition, the importance of the above-cited molecules, their existing methodologies, and the limitation associated are also described here in detail.

1.2. Coupling Reagents

The combination of two amino acid residues to form a peptide bond is known as a coupling reaction. Amide or peptide bond formation are some of the most basic and essential reactions in organic chemistry and are present in many pharmaceutically active compounds and natural products. For amide bond formation, activation of the carboxylic acid is usually done by coupling reagents, and many have been developed in recent years. This era started with the development of the carbodiimide approach using dicyclohexylcarbodiimide (DCC).[1] Due to some practical drawbacks associated with DCC, it was replaced by some other carbodiimide coupling reagents such as DIC,[2] EDC,[2,] and CIC.[3] These are suitable for Fmoc based solid-phase synthesis due to their better solubility in DCM. Other variations of this kind of coupling reagents are BEC,[4] BDDC[5],

and PIC[6], suitable for Boc-amino acids, and the by-product generated can be easily removed.

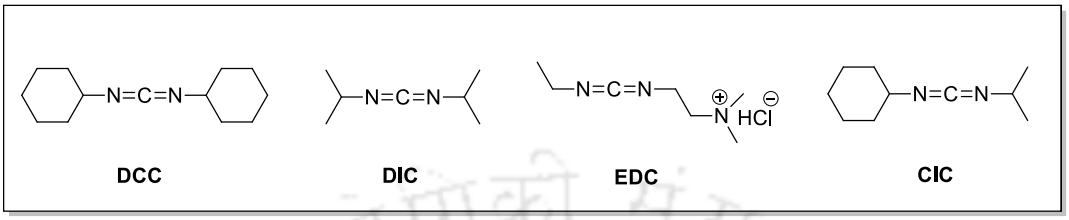


Figure 1.2.1. Carbodiimide-based coupling reagent

Benzotriazole and azabenzotriazole-based additives were used with the coupling reagents to improve their efficiency. HOBt,[7] 6-NO_2-HOBt,[6] HOAt,[8] 6-Cl-HOBt[9], and 6-HOAt[10] are a few of them. As compared to others, HOAt gives wonderful results in terms of yield and racemization suppression in both solution and solid-phase peptide synthesis.

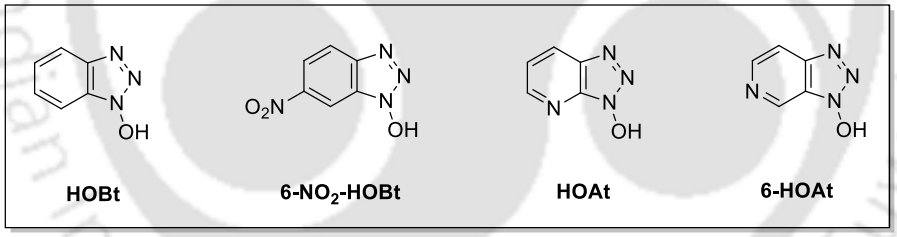


Figure 1.2.2. Benzotriazole and azabenzotriazole based additives

Further, these additives were used with a different types of coupling reagents such as phosphonium salts, ammonium salts, and organosulfur reagents, etc. Kenner and coworkers first introduced acylphosphonium salts as coupling reagents. Some coupling reagents of these types are BOP,[11] PyBOP,[12] PyBrOP,[13] AOP[14], and PyAOP[14], etc. HBTU,[15] HATU[16], and HCTU[17], etc., are few reagents that belong to the ammonium salt type. PS-HOBt[18] is one example of a benzotriazole-based polymer-supported coupling reagent. Although having widespread utilization of benzotriazole moiety, it is restricted

due to its explosive nature. After two decades, El-Faham and Albericio introduced a new additive, Ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma), a suitable replacement for benzotriazole.

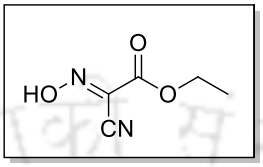


Figure 1.2.3. Ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma)

Oxyma is mild in nature and has tremendous racemization suppression ability. For that reason, many Oxyma-based coupling reagents have been developed in recent times. Some of the recently introduced reagents are PyOxm (Phosphonium salt)[19] and COMU (Uronium salt).[20] COMU is compatible with microwave irradiation and shows results similar to the manual synthesis in a shorter time. Four Oxyma-based reagents such as *ortho*-NosylOXY,[21] *para*-NosylOXY,[22] Boc-Oxyma[23], and TCBOXY[24] have been introduced from our group recently. These coupling reagents were successfully used to synthesize amide, peptide, ester, hydroxamic acid, ureas, carbamate, thiocarbamate, nitrile, alcohol, benzoxazole, and benzothiazole. The unique features associated with them are ease of synthesis, racemization suppression, and recyclability. Oxyma is generated as a by-product, which can be easily recovered and reused to synthesize the reagent again. Therefore, further exploration of these coupling reagents is necessary.

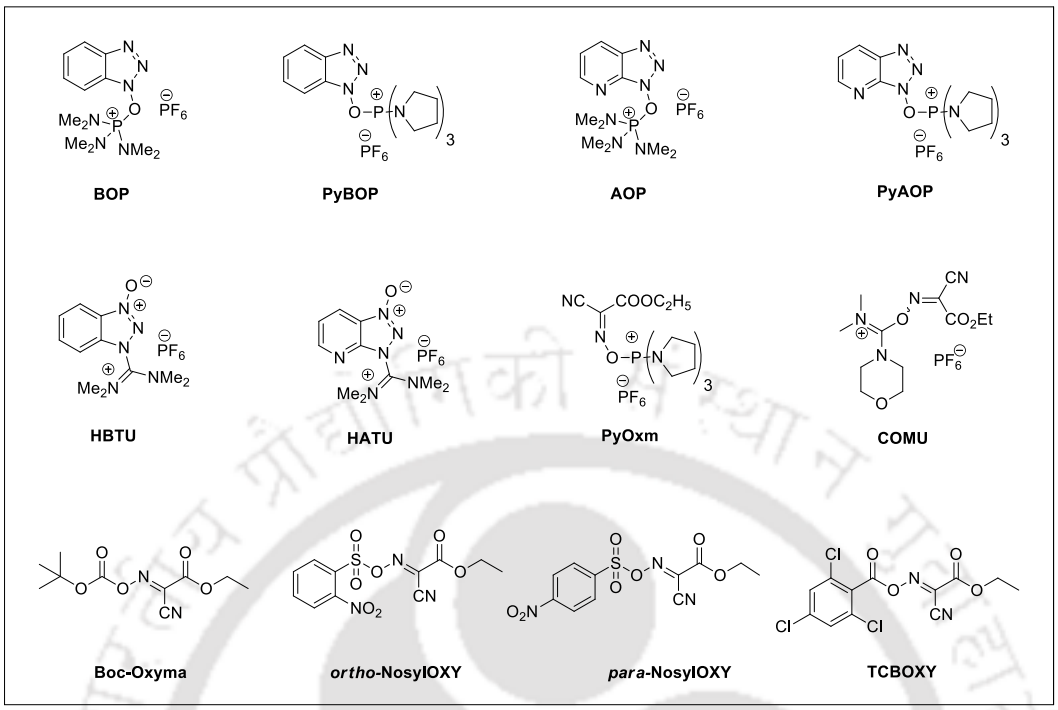


Figure 1.2.4. Some important coupling reagents

1.3. Importance of acetals, thioacetals, urea, carbamates, thiocarbamates, amide, peptides, esters, and hydroxamates

1.3.1. Importance of acetals and thioacetals

An acetal is a functional group with the connectivity $R_2C(OR')_2$, where R groups can be the organic moiety or hydrogen (at least one R group should be hydrogen). Still, R' groups must be the organic fragments. Thioacetals are the sulfur analog of acetals, and they are more stable than the corresponding oxygen compounds. Acetals and thioacetals are used as protecting groups of carbonyl compounds. They are resistant to various non-acidic reagents, oxidizing, and reducing agents and therefore have a wide range of applications in drug designing, pharmaceuticals, and manufacturing industries. Carbonyl group protection is necessary for multi-step organic synthesis, especially for natural

products. It is not easy to carry out the multi-step organic syntheses without the use of any protective groups. Hence, the development in the field of protection and deprotection chemistry is still getting important. In the biochemical context, an important example of acetal formation is the glycosidic bonds. It is the linkage of the two individual sugar monomers to form polysaccharides.

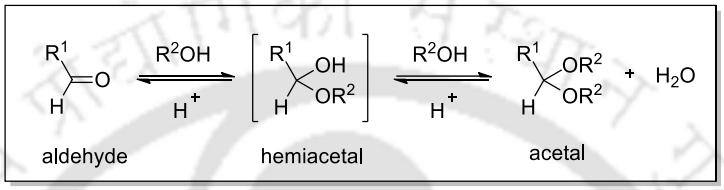


Figure 1.3.1.1. Conversion of aldehydes to acetals

Aldehydes can be stored as acetals. Acetaldehyde, while treating with traces of the acid, it forms a cyclic acetal named paraldehyde without any use of the alcohol. Acetaldehyde can be distilled from paraldehyde upon heating in the presence of acid. Similarly, formaldehyde can be stored as its acetal polymer, paraformaldehyde.

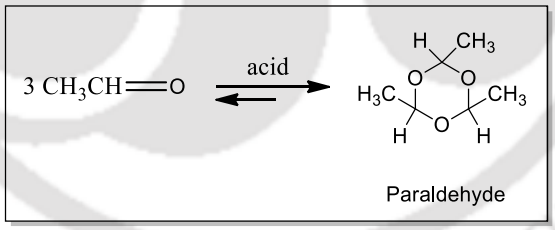


Figure 1.3.1.2. Storage of acetaldehyde as paraldehyde

1.3.2. Importance of ureas

Urea and its derivatives constitute a common framework of biologically active compounds with therapeutic and pharmacological properties, such as antiviral, anti-inflammatory, and anti-tumor effects. Many urea-based drugs have been marketized to date to treat different diseases, and therefore the development of this kind of molecule is

getting importance by researchers. Sorafenib[25] is diaryl urea used for the treatment of hepatocellular carcinoma, produced by Bayer and Onyx. Lenvatinib was approved for the treatment of thyroid cancers in 2015. It is applied as an immunosuppressive drug for the treatment of hepatocellular carcinoma.[26] Regorafenib is a fluorinated analog of the Sorafenib, was approved in 2012 for the treatment of metastatic colorectal cancer. It was again expanded to treat hepatocellular carcinoma.[27] A novel urea derivative, boceprevir, is useful against the hepatitis C virus.[28] Dopamine agonists such as lisuride and cabergoline were approved to treat Parkinson's disease.[29] In 2015, a drug called cariprazine was used for the treatment of the bipolar disorder.[30]

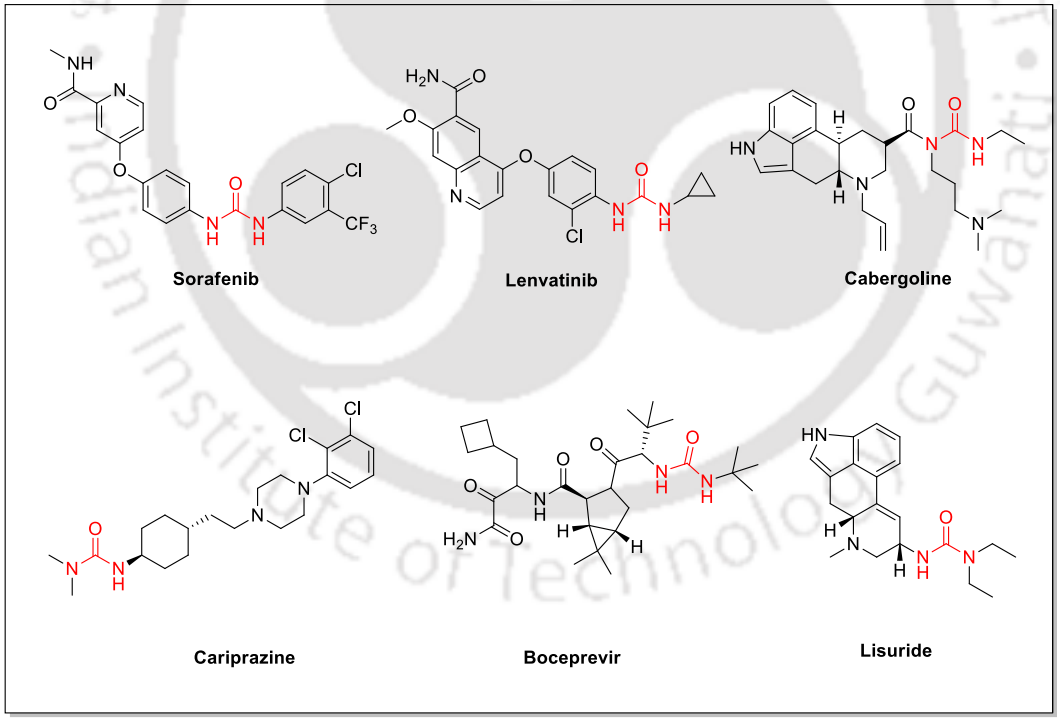


Figure 1.3.2.1. Some biologically active compounds containing urea moieties

1.3.3. Importance of carbamates and thiocarbamates

Carbamate-bearing molecules are the key elements of many approved therapeutic agents. Due to their chemical stability, carbamates are widely used as peptide bond surrogates. They have the ability to permeate cell membranes and interact with the target receptors or enzymes. Carbamate derivatives are widely represented as pesticides, herbicides, and fungicides and play a major role in the chemical and paint industries. In addition, organic carbamates serve as protecting groups for amines and amides. Rivastigmine, a carbamate derivative, is used to treat Alzheimer's disease and dementia due to Parkinson's disease.[31-32] Roxifiban, a methyl ester carbamate, is used as an antagonist of the IIb/IIIa receptor.[33] Albendazole[34] and Mebendazole[35] are broad-spectrum anthelmintic carbamate drug. Flupirtine is an ethyl carbamate drug used as a nonopioid analgesic[36] and Mitomycin C, a complex carbamate derivative used as an anti-tumor antibiotic.[37]

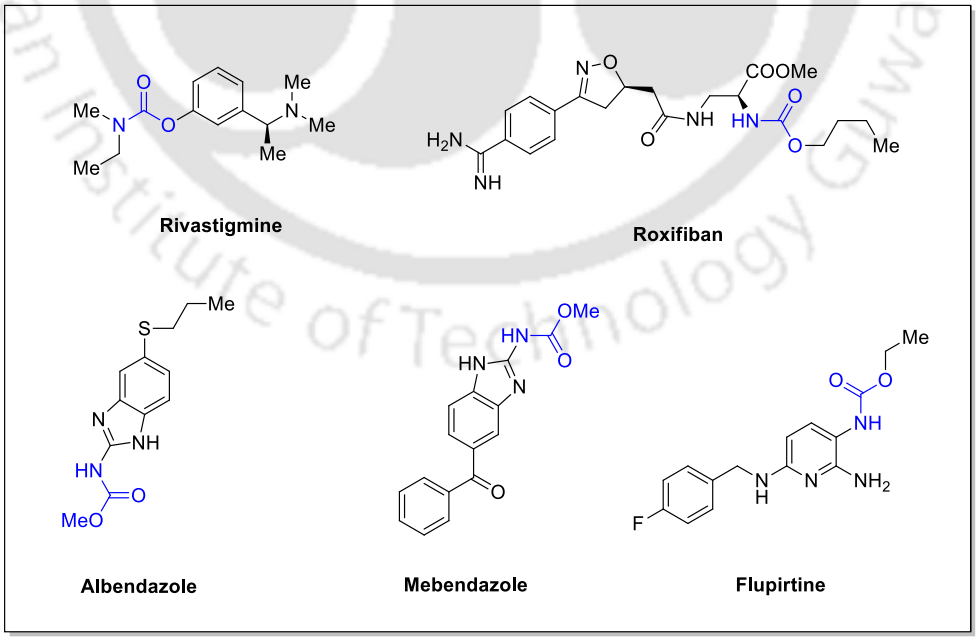


Figure 1.3.3.1. Some biologically active compounds containing carbamate moiety

Like carbamates, thiocarbamate also contains many pharmacological activities such as fungicides, bactericides, anesthetics, and antiviral agents. A few examples of the potent herbicides containing thiocarbamate fragments are Molinate,[38] Orbencarb,[39] and Thiobencarb[40], etc.

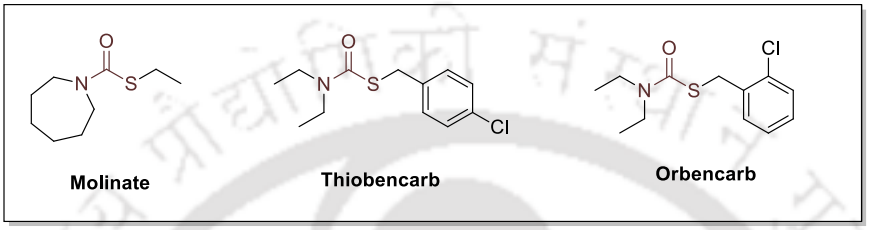


Figure 1.3.3.2. Some herbicides containing thiocarbamate moiety

1.3.4. Importance of amides and peptides

The amide bond is one of the most native chemical bonds and is present in many biomolecules such as peptides, protein, DNA, and RNA. It is highly stable towards various acidic and basic conditions, high temperature, etc. Due to the ability to form resonating structures, it adopts a particular three-dimensional conformation, which in turn is responsible for various biological actions. For example, Lidocaine[41] is used as an antiarrhythmia agent, which prevents pain. Lisinopril[42] is used for the treatment of high pressure, and heart failure is an angiotensin-converting enzyme inhibitor. Atorvastatin[43] is a drug, which blocks the production of cholesterol. Imatinib[44], a tyrosine kinase inhibitor, is used for the treatment of acute lymphoblastic leukemia and chronic myeloid leukemia. Peptide drugs such as Cyclosporin A (CyA)[45] are used as an immunosuppressive agent and clinically used in the treatment of autoimmune disorders. The peptide KLVFF[46] can bind full-length Aβ-peptide and arrest its assembly into amyloid fibrils.

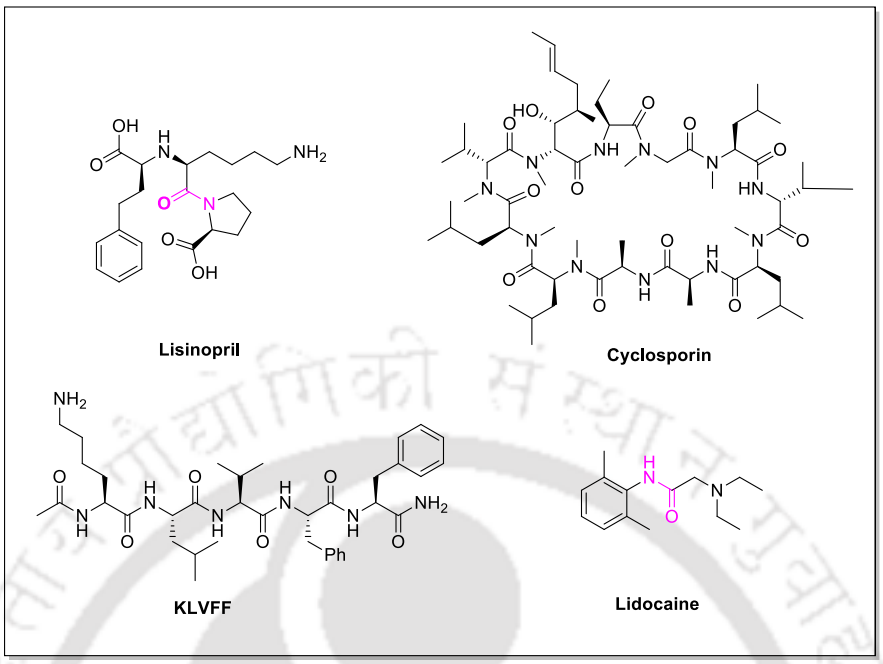


Figure 1.3.4.1. Biologically active amides and peptides

1.3.5. Importance of esters and hydroxamates

Esters and hydroxamate bonds are present in many medicinally important compounds. Aspirin[47] is an important drug used to treat various medical conditions such as fever, pain, rheumatoid arthritis, and Kawasaki disease. Beclometasone dipropionate[48] is a medicine used for asthma, allergic rhinitis, and nasal polyps. Procaine[49] is a local anesthetic, which is used during surgery. Due to the pleasant taste and smell, esters are utilized in food industries as flavors. They are also used in the manufacturing of soaps, and this process is known as the saponification process. Actinonin[50] is a potent peptide deformylase inhibitor and shows anti-tumor activity. Hydroxamates have application as histone deacetylase inhibitors for the treatment of cancer.

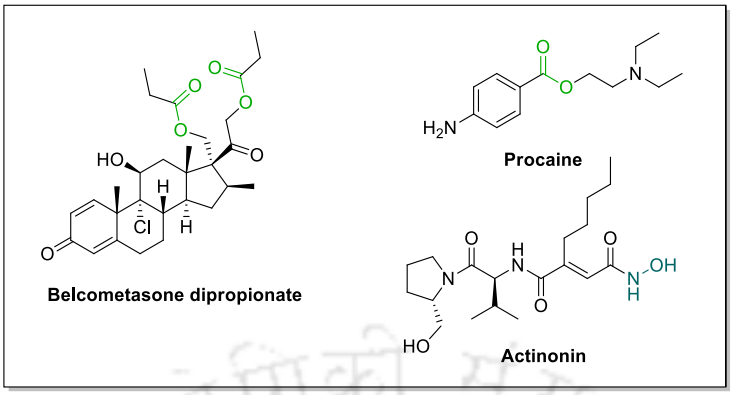


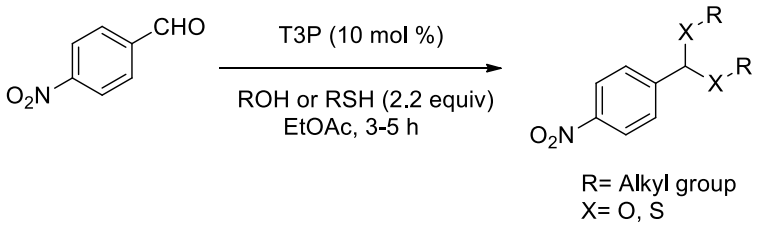
Figure 1.3.5.1. Biologically active esters and hydroxamates

1.4. Existing methods for the synthesis of acetals, thioacetals, ureas, carbamates, amide, peptide, ester, and hydroxamate

1.4.1. Existing methods for acetal and thioacetal synthesis

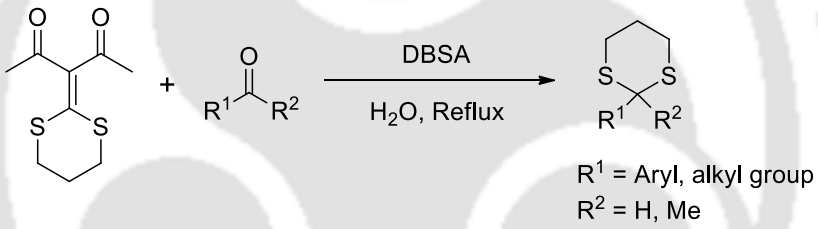
The fundamental method for the synthesis of acetals is the reaction between an aldehyde and alcohol in the presence of an acidic catalyst,[51-52] heteropoly acids,[53] Solid acidic catalyst[54-56,] and lewis acid-based ionic liquid[57-58] have been studied for the transformation of carbonyl compounds into acetals/ketals. Also, various metal complexes have been used as a catalyst for this process.[59-60] As an alternative to the metal-based processes, non-metallic catalysts such as complexes of carbon tetrabromide and sodium triphenylphosphine-m-sulfonate,[61] and N-bromobutanimide[62] are reported, which is compatible with the acid-sensitive groups.

Augustine and his group reported a well-known peptide coupling reagent T3P mediated chemoselective acetalization/thioacetalization of aldehydes in the presence of ketone at room temperature with a catalytic amount of the reagent (*Scheme 1.4.1.1*).[63]



Scheme 1.4.1.1. T3P mediated acetalization and thioacetalization

Dong's group replaced 1,3 propanedithiol with a novel, nonthiolic equivalent, 3-(1,3-dithian-2-ylidene)pentane-2,4-dione for thioacetalization purpose. This procedure is chemoselective and catalyzed by *p*-dodecylbenzenesulfonic acid in water under reflux conditions (*Scheme 1.4.1.2*).[64]

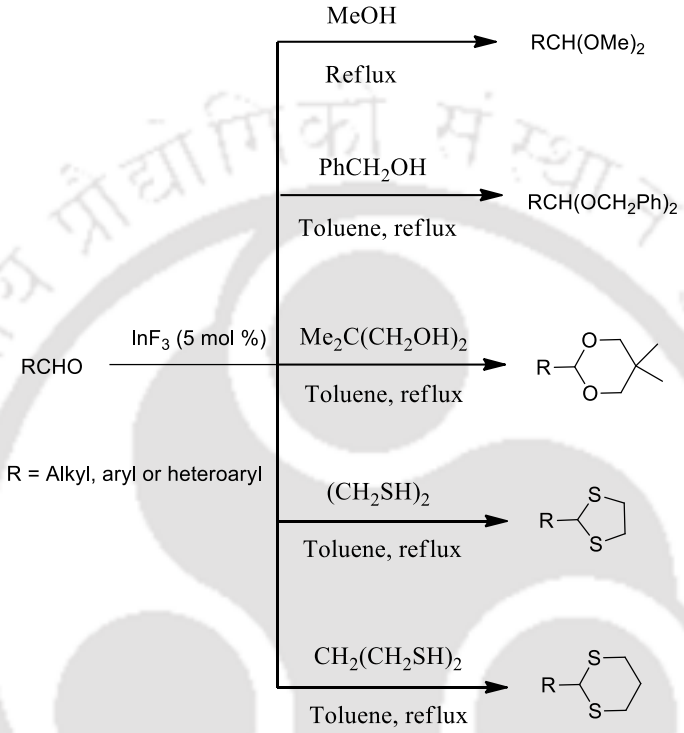


Scheme 1.4.1.2. DBSA catalyzed thioacetalization of aldehyde and ketone

Lei's group designed a protocol for acetalization of aldehydes by photochemical reaction under visible light irradiation. Here, a catalytic amount of Eosin Y is used as a photocatalyst. This methodology is applicable to both acid-sensitive and sterically hindered aldehydes and chemoselective to aldehydes (*Scheme 1.4.1.3*).[65]

Scheme 1.4.1.3. Visible-light-induced acetalization of aldehydes

Sridhar and his group developed an efficient methodology for acetalization and thioacetalization of different types of aliphatic, aromatic, and heteroaromatic aldehydes using InF_3 as a reusable catalyst (*Scheme 1.4.1.4*).[66]



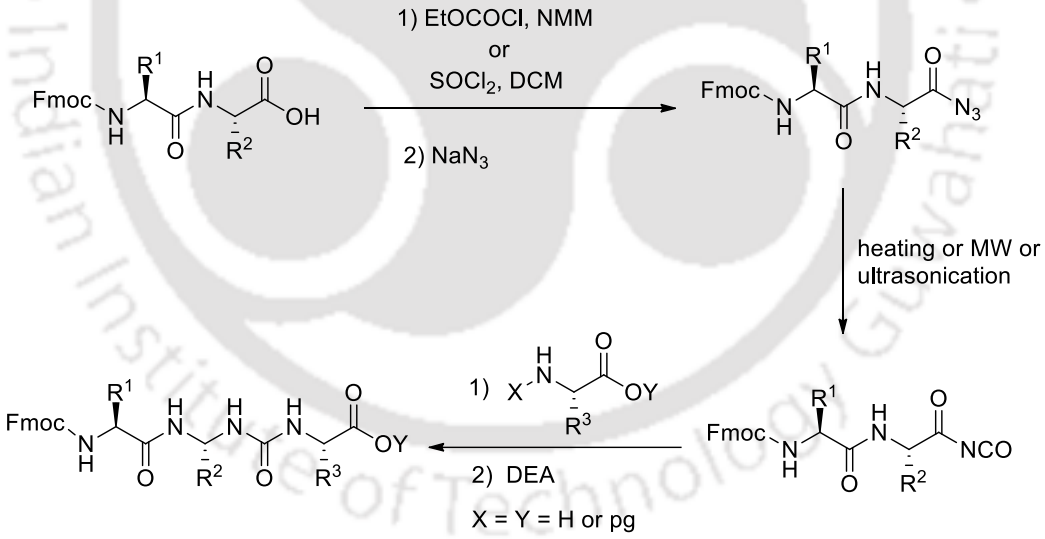
Scheme 1.4.1.4. Acetalization and thioacetalization of aldehyde using InF_3 as a catalyst

Some other methodologies are also well developed during recent times. For example; Xie's group used the trace of conventional acid, but without removing water from the system,[67] Yang's group developed a solvent-free reaction of a polyhydric alcohol with carbonyl compounds catalyzed by cobaloxime,[68] Patel's group reported the formation of acetals in the presence of trialkylorthoformate and a catalytic amount of tetrabutylammonium tribromide,[69] and Habib and his group described chemoselective thioacetalization catalyzed by iodine.[70]

1.4.2. Existing methods for urea and carbamate synthesis

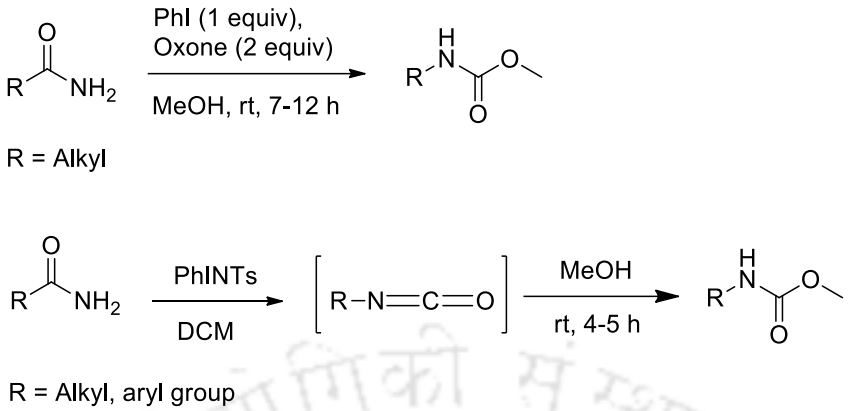
The industrial synthesis of urea and carbamate generally depends on the reaction of phosgene (or phosgene equivalents) with amines.[71] In some methodologies, Boc is used as protecting group for amines to synthesize ureas.[72] Over the last years, many protocols, including rearrangement reactions such as Curtius, Hofmann, and Lossen, have been developed to synthesize urea, carbamate, and thiocarbamate.

Sureshbabu and his coworkers designed a protocol for the solution-phase synthesis of oligo-α-peptidyl ureas from Fmoc-peptide-isocyanates via Curtius rearrangement. The isocyanates have been prepared from Fmoc-azides upon heating, microwave irradiation, and ultrasonic condition (*Scheme 1.4.2.1*).[73]



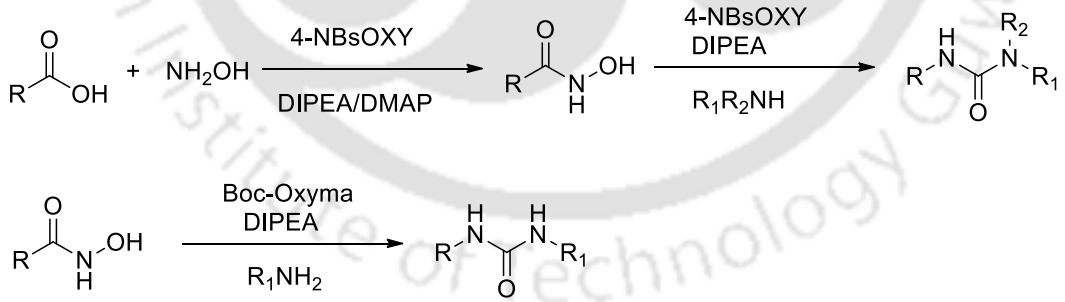
Scheme 1.4.2.1. Synthesis of oligo-α-peptidyl ureas

Zhdankin's group developed a protocol for the synthesis of methyl carbamates from alkyl carboxamides using hypervalent iodine species via Hofmann rearrangement. Further, they modified the method to prepare carbamate from both alkyl and aryl carboxamides using highly selective (tosylimino)-phenyl-λ^3-iodane, PhINTs, as a reagent (*Scheme 1.4.2.2*).[74]



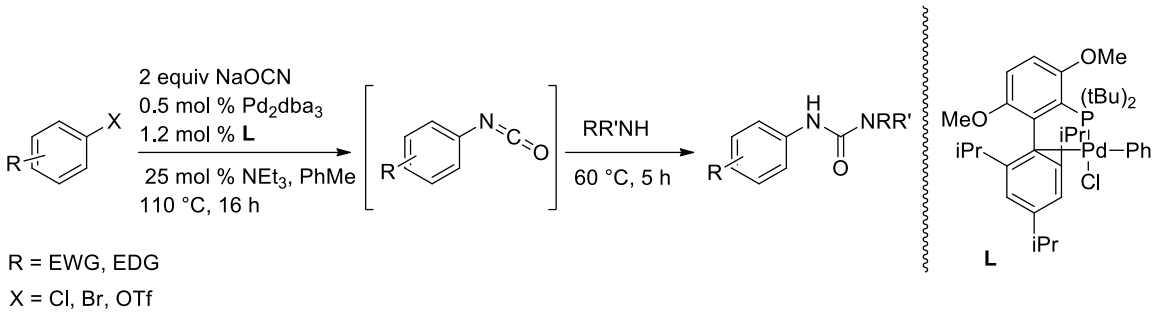
Scheme 1.4.2.2. Synthesis of methyl carbamate via Hofmann rearrangement

Our group reported the coupling reagent mediated urea and carbamate synthesis via Lossen rearrangement. Two novel coupling reagents such as 4-NBsOXY and Boc-Oxyma, have been used to transform hydroxamic acid to urea successfully. The starting material hydroxamic acids were prepared from carboxylic acids using the same reagents. The protocol is applicable to aliphatic, aromatic, and long-chain amino acids with good yield (*Scheme 1.4.2.3*).[22, 75]



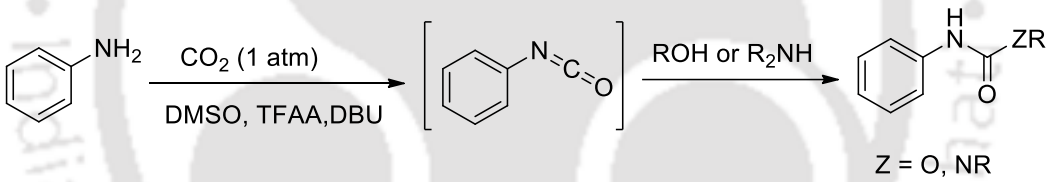
Scheme 1.4.2.3. Synthesis of ureas via Lossen rearrangement

Buchwald's group designed a cross-coupling reaction of aryl chlorides and triflates with sodium cyanate using palladium as a catalyst to synthesize isocyanates, which further addition of amine finally produces unsymmetrical *N,N′*-di- and *N,N,N′*-trisubstituted ureas (*Scheme 1.4.2.4*).[76]



Scheme 1.4.2.4. Synthesis of ureas using palladium

Rousseaux's group developed a metal-free method for the synthesis of unsymmetrical ureas and carbamates from CO_2 and amines. The intermediate isocyanate is detected by IR and finally trapped by amines or alcohols to produce urea and carbamate, respectively (*Scheme 1.4.2.5*).[77]

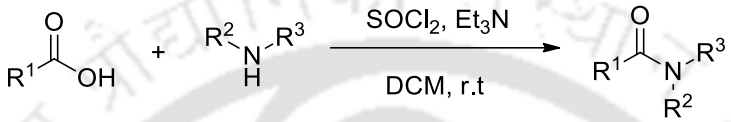


Scheme 1.4.2.5. Synthesis of ureas from CO_2 and amine

1.4.3. Existing methods for amide, peptide, ester, and hydroxamates synthesis

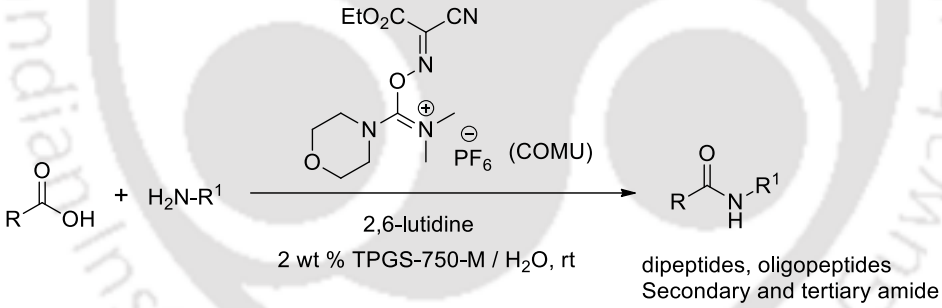
Amide or ester bond formation is one of the most important reactions in organic chemistry. It is the condensation between the carboxylic acid and an amine or alcohol, respectively. For that, activation of the carboxylic group is necessary and is usually done by coupling reagents, such as carbonic anhydrides, acid chlorides, active esters.[78] Small peptides are usually prepared by solution phase, but for longer peptides, solid-phase synthesis was introduced by R. B. Merrifield in 1963.[79] Many methodologies using coupling reagent, metals have been developed to date.

Katritzky's group synthesized N-acylbenzotriazoles[80] from carboxylic acids using $SOCl_2$ and benzotriazole, which can be used as a precursor for amide synthesis. Leggio and his group members developed a one-pot synthesis of secondary and tertiary amides from carboxylic acids using $SOCl_2$. The process shows retention of stereochemical integrity of chiral substrates (*Scheme 1.4.3.1*).[81]



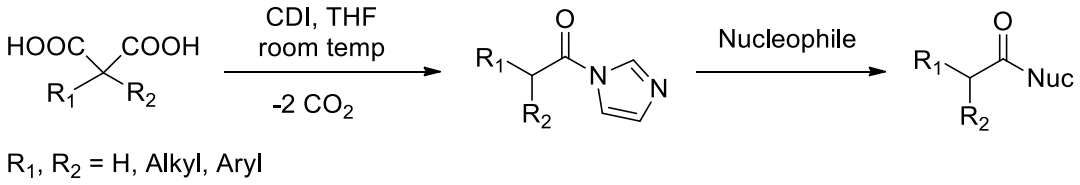
Scheme 1.4.3.1. Synthesis of amides using $SOCl_2$

Lipshutz's group reported amide and peptide bond formation in water at room temperature by an Oxyma-based coupling reagent named COMU (*Scheme 1.4.3.2*).[82]



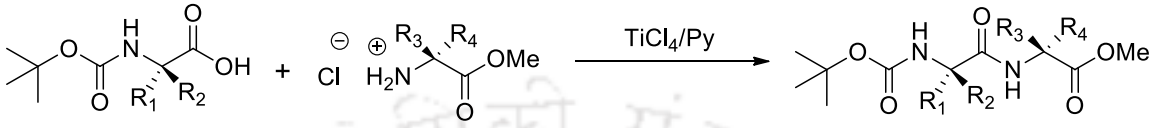
Scheme 1.4.3.2. Synthesis of amides using COMU

Rafka's group described mild decarboxylative activation of malonic acid derivatives by CDI coupling reagent (*Scheme 1.4.3.3*).[83]



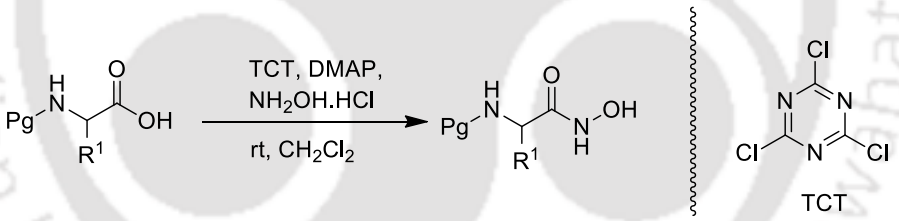
Scheme 1.4.3.3. Synthesis of amides using CDI

Leggio and his coworkers designed a titanium tetrachloride-based methodology for dipeptide synthesis. A series of dipeptides were prepared from N-protected amino acid and methyl ester of amino acid in pyridine (*Scheme 1.4.3.4*).[84]



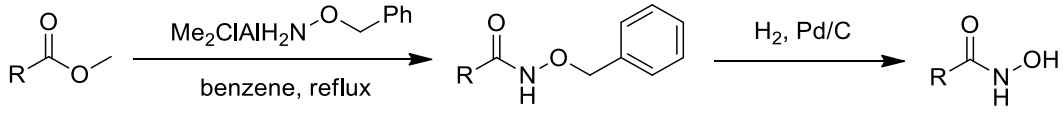
Scheme 1.4.3.4. Synthesis of *N*-Boc protected dipeptide using $TiCl_4$

Hydroxamic acids are generally synthesized from carboxylic acid and hydroxylamine hydrochloride using many catalysts and reagents. Giacomelli's group developed a cyanuric chloride (TCT) mediated methodology to synthesize hydroxamic acid from *N*-protected amino acid (*Scheme 1.4.3.5*).[85]



Scheme 1.4.3.5. TCT mediated hydroxamate synthesis

Chau and his coworkers prepared hydroxamic acid from amino acid ester and (*O*-Benzylhydroxylamine) methyl aluminum chloride in benzene under reflux condition (*Scheme 1.4.3.6*).[86]



Scheme 1.4.3.6. Hydroxamate synthesis from amino acid ester

1.5. Drawbacks of existing methods

The literature report says that acetals/dithianes are usually synthesized by the reaction between aldehyde and alcohol/thiol in the presence of different acidic catalysts. However, these catalysts are not environment friendly, harsh, and not suitable for the compounds containing acid-sensitive groups such as Boc, alkenes, and tertiary butyl. Another drawback is the release of the by-product water, which must be removed by suitable physical and chemical methods; otherwise, the reaction may be shifted to the reverse direction. Furthermore, these methodologies involved some other limitations such as the use of metal complexes, high temperature, a stoichiometric amount of the reagent, lower substrate scope, etc. There are many methodologies that have been developed in the literature to synthesize urea and carbamates to date. One of the most traditional approach is the Hofmann rearrangement, utilizes strong hypervalent iodine reagents and are therefore not suitable for large scale synthesis. Curtius rearrangement-based urea synthesis also involves the use of acid chlorides, which are difficult to handle and generate toxic by-products. Other methods involve using phosgene and its equivalents, which are associated with potential health risks due to their toxicity. In recent years, many coupling reagents have also been introduced to develop ureas. However, major disadvantages associated with these coupling reagents are the formation of undesired by-products, high cost, chemical waste generation, and racemization. Amide and peptide bond formation is the most basic reaction of organic chemistry. In literature, there are many coupling methods available, for example, carboxylic halides, anhydrides, and coupling reagent-based. In the case of the carboxylic chloride and anhydride method, due to their reactivity, many side reactions are possible, which is difficult to control.The additives used with the reagents are explosive in nature and increases the degree of

racemization. Synthesis of the reagents also involves harsh reaction conditions. For example, while synthesizing BOP, carbon tetrachloride is used as a solvent, which is carcinogenic in nature. In addition, it involves the use of KPF_6 (which causes severe skin damage) and HOBt (explosive in nature). Again, the synthesis of COMU, an Oxyma based reagent, also uses phosgene. Generation of chemical waste is also a practical problem associated with the coupling reagents. For example, hexamethylphosphoramide (HMPA) and HOBt are released as by-products when BOP and HBTU are used, respectively. Most of the coupling reagents are non-recyclable and hence are not environment-friendly.

1.6. Objectives of thesis

Based on the above observations, the aim of the thesis is to design various applications of the novel coupling reagent, Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY), to perform important organic transformations. To achieve that, we have proposed the following objectives.

1 Synthesis of acetals and thioacetals from aldehydes using *o*-NosylOXY.

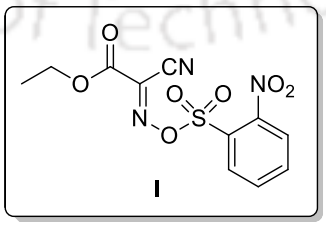
2 Synthesis of ureas, carbamates, and thiocarbamates via Curtius rearrangement using *o*-NosylOXY

3 Mechanistic investigation of Beckmann rearrangement using *o*-NosylOXY.

4 Synthesis of amides, dipeptides, esters, and hydroxamates using Oxyma and thionyl chloride.

Chapter 2: *o*- NosylOXY Mediated Acetalization and Thioacetalization of Aldehydes

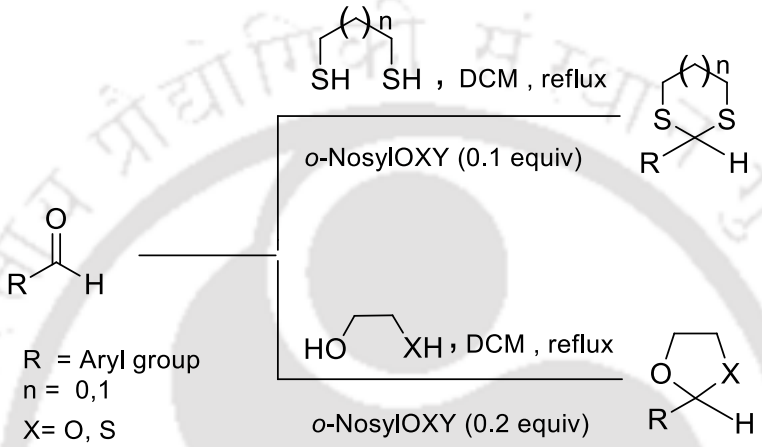
Acetals and thioacetals play a vital role in carbonyl group protection in multi-step organic synthesis. These are stable towards non-acidic reagents and have plenty of applications in drug designing and pharmaceutical industries. There are many protocols published for acetalization and thioacetalization (Chapter 1, section 1.4.1). Although it is a well-investigated topic, most of these methodologies have certain drawbacks, including the use of harsh catalysts unsuitable for acid-sensitive groups, the release of by-product water, involvement of metals, corrosive acids, etc. Again, some methods show poor selectivity, lower substrate scope, and use a stoichiometric amount of the catalyst. Recently, our group has developed an efficient and versatile coupling reagent, Ethyl-2-cyano-2-(2-nitrophenylsulfonyloximino)acetate (*o*-NosylOXY, **I**). This reagent is successfully utilized to synthesize esters, hydroxamates, peptides (solid and solution phase)[21], and other organic transformations.[87] Racemization suppression and recyclability are added benefits of this reagent.



I

Figure 2.1. Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY, **I**)

This chapter demonstrates a gentle and effective approach for acetalization and thioacetalization of aldehydes using **I** as a catalyst. Aldehyde is successfully converted into cyclic acetal, 1,3-dithiolanes, and 1,3-dithianes with different diols and dithiols (*Scheme 2.1*).



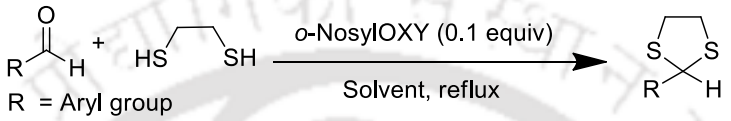
Scheme 2.1. *o*-NosylOXY mediated acetalization and thioacetalization

2.1. Optimization and substrate scope for the synthesis of acetals and thioacetals using *o*-NosylOXY (I)

We optimized the thioacetalization reaction using 4-nitrobenzaldehyde as model substrate (*Table 2.1.1*). For that, we refluxed 4-nitrobenzaldehyde (1 equiv), 1,2-ethanedithiol (1.5 equiv), and **I** (1 equiv) in distilled DCM for almost 3 hours. After doing work up with 5% sodium bicarbonate solution, the reaction mixture was purified by column chromatography. The desired product was obtained in a 91% yield. Further, we studied the catalytic nature of the reagent (*Table 2.1.1, entry 1-4*), and it was found that 0.1 equiv of the reagent was sufficient for maximum conversion of aldehydes into thioacetal. On the other hand, only a trace amount of the product was obtained without **I** (5%). The

reaction was tried in different solvents like DCM, EtOAc, CH_3CN, THF, $CHCl_3$, and toluene (*Table 2.1.1*), and DCM was turned out to be the most suitable solvent among those.

Table 2.1.1. Optimization of reaction[a]



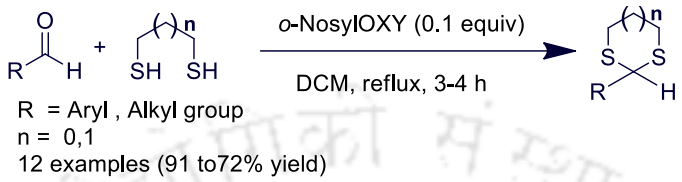
Entry	Solvent	*o*-NosylOXY(equiv)	Time(hour)	Yield(%)[b]
1	DCM	1	3	91
2	DCM	0.5	3	91
3	DCM	0.2	3	91
4	**DCM**	**0.1**	**3**	**91**
5	ACN[c]	0.1	11	42
6	THF[c]	0.1	8	57
7	EtOAc[c]	0.1	11	52
8	$CHCl_3$[c]	0.1	4	85
9	Toluene[c]	0.1	7	62

[a] Performed with 4-nitrobenzaldehyde (1 equiv), 1,2-ethanedithiol (1.5 equiv) under reflux condition. [b] refer to the isolated yield after column chromatography. [c] Reflux at 70 °C.

Using this optimized reaction condition, we prepared 1,3-dithiolanes and 1,3-dithianes from aldehydes containing different electron-withdrawing and donating substituents with dithiols (*Table 2.1.2*). Trans-cinnamaldehyde showed satisfactory yields with both 1,2-ethane dithiol and 1,3-propane dithiol (*Table 2.1.2, entries 7 and 10*). One example of aliphatic aldehyde (decanal) was also examined, and it gave its corresponding 1,3-

dithiolane with a 72% yield (*Table 2.1.2, entry 8*). However, chlorobenzaldehyde did not provide the desired product even with a longer reaction time.

Table 2.1.2. The substrate scope of 1,3-dithiolanes and 1,3-dithianes using **I**[a]



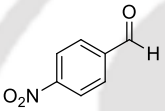
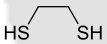
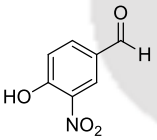
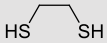
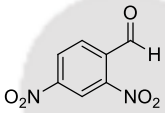
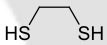
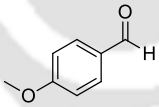
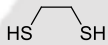
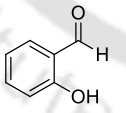
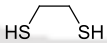
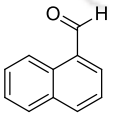
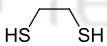
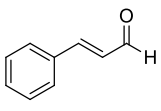
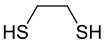
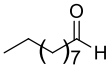
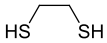
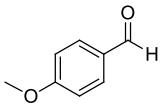
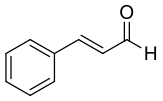
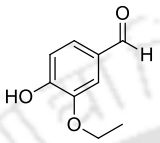
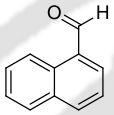
Entry	Aldehyde	Dithiol	Product id	Yield (%)[b]
1			3a	91
2			3b	87
3			3c	89
4			3d	82
5			3e	87
6			3f	81
7			3g	89
8			3h	72

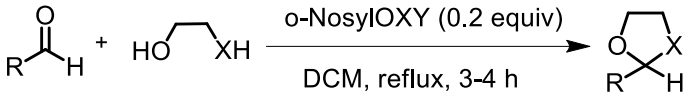
Table 2.1.2 continued…

9			3i	87
10			3j	75
11			3k	84
12			3l	74

[a] Performed with aldehyde (1 equiv), dithiol (1.5 equiv) under reflux condition . [b] refer to the isolated yield after column chromatography.

After successfully synthesizing thioacetals, we applied the same reaction condition to synthesize 1,2-dioxolanes, 1,3-dioxanes, and dimethoxy acetal using saturated and unsaturated diols, mercaptanol, and methanol (*Table 2.1.3*). Diols were used in 1.5 equiv except for methanol, which was needed in excess to get the maximum yield. In addition to methanol, we used some other alcohols such as isopropanol and ethanol but could not get the desired product. This protocol is applicable for aldehydes containing nitro, methoxy, and hydroxyl group as substituents. Three different acetals were obtained from trans-cinnamaldehyde in good yields (*Table 2.1.3, entry 13-15*). In acetal synthesis, a 0.2 equiv of **I** was required for the highest conversion under reflux of 3-4 hours.

Table 2.1.3. The substrate scope of acetals using **I**[a]



R = Aryl group
X = O. S
15 examples (90 to 71% yield)

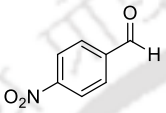
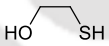
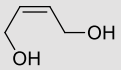
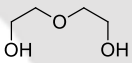
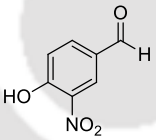
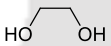
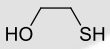
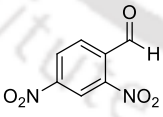
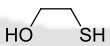
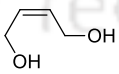
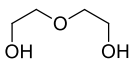
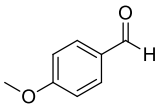
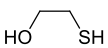
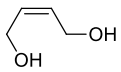
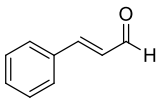
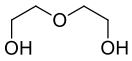
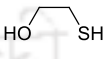
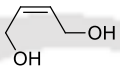
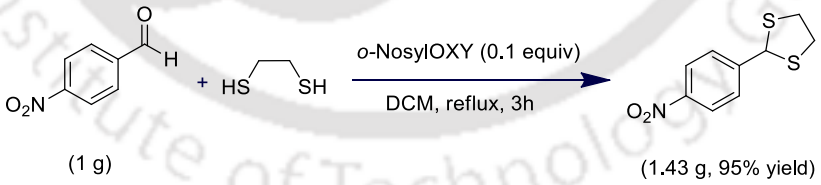
Entry	Aldehyde	Alcohol	Product id	Yield (%)[b]
1			5a	90
2			5b	71
3			5c	86
4			5d	87
5			5e	82
6			5f	84
7			5g	81
8			5h	82
9			5i	87
10			5j	79
11			5k	77

Table 2.1.3 continued…

12			5l	80
13			5m	74
14			5n	76
15			5o	77

[a] Performed with aldehyde (1 equiv), diol (1.5 equiv) under reflux condition . [b] refer to the isolated yield after column chromatography.

We also checked the utility of the reaction for gram-scale synthesis. For that, we performed the reaction between 4-nitrobenzaldehyde and 1,2-ethanedithiol on a large scale. We took 1g of the aldehyde this time and other reagents accordingly, maintaining the same reaction condition. As a result, a relatively good yield of 95%, 1.43 g of the product was obtained compared to the milligram scale (*Table 2.1.2, entry 1*) when repeated on a gram scale.



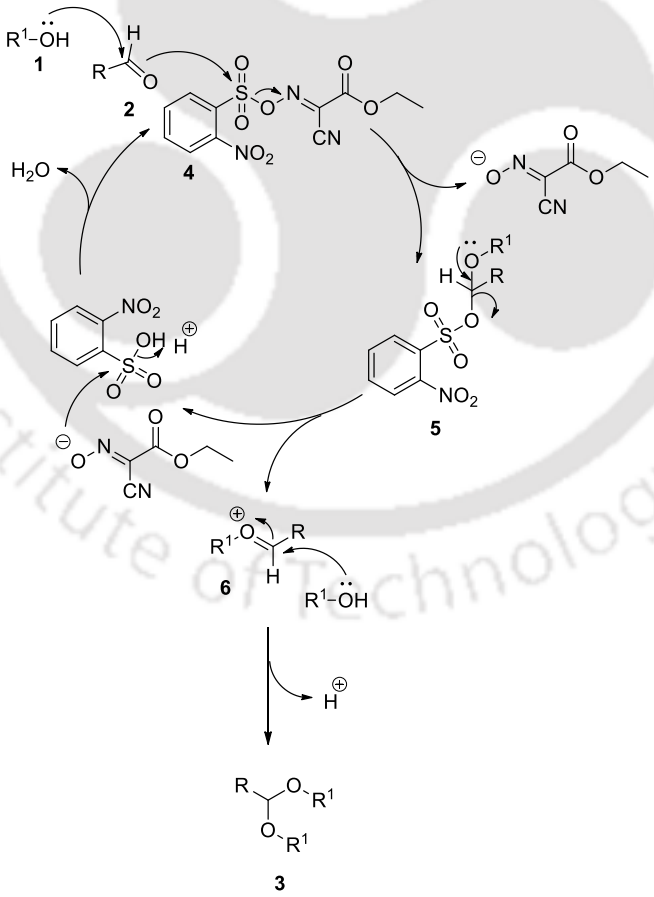
Scheme 2.1.1. Gram scale synthesis of 3a (*Table 2.1.2, entry 1*)

Few methodologies with good yields were introduced recently. One similar protocol for acetals synthesis using T3P as a coupling reagent was established where 88-98% yield was reported.[63] Efficient and chemoselective acetalization have been obtained using InF_3

as a reusable catalyst with almost 80-92% yield.[66] Our current protocol also carries important features such as high yield and wide substrate scope.

2.2. Plausible mechanism

Based on the existing literature,[63] the plausible mechanism for acetal synthesis with *o*-NosylOXY can be explained (*Scheme 2.2.1*). The reaction of alcohol (*1*), aldehyde (*2*), and *o*-NosylOXY (*4*) generate oxocarbenium ion (*6*) via intermediate (*5*), which upon attack of another molecule of alcohol gives the desired acetal (*3*). Oxyma anion and 2-nitrobenzenesulfonic acid are released as by-products that further generate *o*-NosylOXY.



Scheme 2.2.1. Synthesis of acetals using *o*-NosylOXY

2.3. Conclusion

We have introduced here an application of *o*-NosylOXY for the successful transformation of aldehydes into acetals and thioacetals. The present methodology was associated with necessary features such as good yields, lesser by-products, broad substrate scope, easy isolation of the products, and a catalytic amount of the reagent. All these make this work is an alternative to the existing ones.

2.4. Experimental Section

2.4.1. General consideration

All chemicals were purchased from commercial sources and used without any purification. Solvents DCM and MeOH were distilled via the standard procedure. Reactions were observed using thin-layer chromatography. Chromatograms were run in the glass plate coated with silica gel G and silica gel GF254 using EtOAc/Hexane as the solvent. Column chromatography was used as a purification technique (Silica gel 60-120 mesh, EtOAc/Hexane as eluent). Solvents are removed under reduced pressure using the Buchi rotary evaporator. ^{1}H and ^{13}C spectra were recorded on 600 and 400 MHz using $CDCl_3$ as solvent and tetramethylsilane as an internal standard. FT-IR spectra and melting points were recorded on Perkin Elmer FT-IR Spectrometer and Buchi melting point apparatus, respectively.

2.4.2. General procedure for the synthesis of 1,3-dithiolanes and 1,3-dithianes

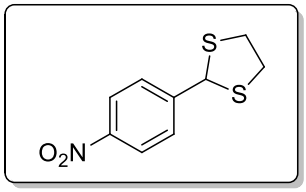
To a mixture of aldehyde (1 mmol), dithiol (1.5 mmol), and *o*-NosylOXY (0.1 mmol), distilled DCM (5 ml) was added, and the reaction mixture was stirred for 3 hours under reflux conditions. After completion of the reaction, checked by TLC, it was allowed to cool and washed with 5% $NaHCO_3$ solution and brine. The organic phase was dried over $CaCl_2$, and the product was purified by column chromatography.

2.4.3. General procedure for the synthesis of acetals

To a mixture of aldehyde (1 mmol), diol (1.5 mmol), and *o*-NosylOXY (0.2 mmol), distilled DCM (5 ml) was added, and the reaction mixture was refluxed for 3-4 hours. The reaction was monitored by TLC, and after completion, it was allowed to cool and washed with 5% $NaHCO_3$ solution and brine. The organic phase was dried over $CaCl_2$, and the product was purified by column chromatography. In the case of dimethoxy acetal formation, methanol was taken in a slightly excess amount.

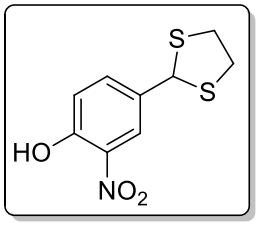
2.5. Characterization data

2-(4-Nitrophenyl)-1,3-Dithiolane (entry 1, Table 2.1.2)



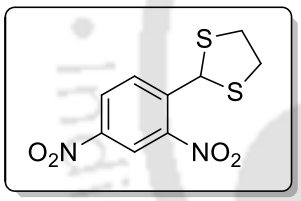
Yield: 206 mg (91%); white solid; R_f = 0.70 (EtOAc:Hexane, 1.0:9.0);mp: 58-60 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11-8.09 (d, *J* = 8.4 Hz, 2H), 7.62-7.60 (d, *J* = 8.4 Hz, 2H), 5.59 (s, 1H), 3.49-3.42 (m, 2H), 3.38-3.32(m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 147.4, 128.9, 123.8, 54.9, 40.6; FT-IR (KBr): 2924, 1514, 1346, 865, 725, 692, 493, 428.

4-(1,3-Dithiolan-2-yl)-2-Nitrophenol (entry 2, Table 2.1.2)



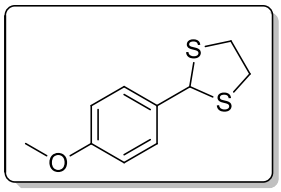
Yield: 211 mg (87%); yellow solid; R_f = 0.50 (EtOAc:Hexane, 4.0:6.0);mp: 94-96 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ 10.52 (broad, OH), 8.14 (s, 1H), 7.73-7.71 (d, *J* = 8.4 Hz, 1H), 7.06-7.04 (d, *J* = 8.8 Hz, 1H), 5.53 (s, 1H), 3.47-3.41 (m, 2H), 3.35-3.29 (m, 2H), 3.31-3.18 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 137.4, 133.3, 132.7, 123.8, 120.2, 54.6, 40.3; FT-IR (KBr): 3226, 2949, 2862, 1628, 1533, 1422, 1224, 1163, 901, 753, 655, 539.

2-(2,4-Dinitrophenyl)-1,3-Dithiolane (entry 3, Table 2.1.2)



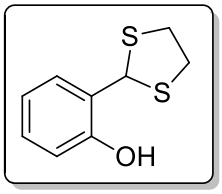
Yield: 241 mg (89%); orange semi solid; R_f = 0.50 (EtOAc:Hexane, 2.5:7.5);^{1}H NMR (600 MHz, $CDCl_3$): δ 8.74-8.74 (d, *J* = 2.4 Hz, 1H), 8.43-8.41 (d, *J* = 10.8 Hz, 1H), 8.32-8.31 (d, *J*= 9 Hz, 1H), 6.21(s,1H), 3.46-3.43 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 148.2, 147.0, 144.5, 132.28, 127.4, 120.4, 50.2, 40.3; FT-IR (KBr): 3513, 3398, 1673, 1523, 1344, 1243, 880, 819, 727, 634, 492.

2-(4-Methoxyphenyl)-1,3-Dithiolane (entry 4, Table 2.1.2)



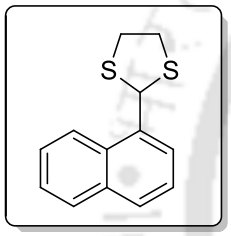
Yield: 173 mg (82%); white semi solid; R_f = 0.50 (EtOAc:Hexane,1.5:8.5);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.44 (d, *J* = 8.8 Hz, 2H), 6.85-6.83 (d, *J* = 8.8 Hz, 2H), 5.64 (s, 1H), 3.79 (s, 3H), 3.52-3.46 (m, 2H), 3.37-3.31(m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 131.9, 129.3, 114.0, 56.2, 55.4, 40.3; FT-IR (KBr): 2924, 2835, 1607, 1508, 1249, 1170, 1031, 834, 754, 557.

2-(1,3-Dithiolan-2-yl)phenol (entry 5, Table 2.1.2)



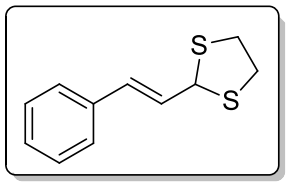
Yield: 172 mg (87%); red oil; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.35 (d, *J* = 8 Hz, 1H), 7.21-7.18 (t, *J* = 7.6 Hz, 1H), 6.88-6.85 (m, 2H), 5.85 (s, 1H), 3.51-3.45 (m, 2H), 3.36-3.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 129.9, 122.3, 120.4, 117.2, 53.8, 39.8; FT-IR (KBr): 3333, 2922, 1559, 1455, 1227, 1087, 861, 752, 687.

2-(Naphthalen-1-yl)-1,3-Dithiolane (entry 6, Table 2.1.2)



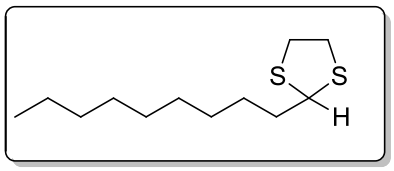
Yield: 187 mg (81%); yellow oil; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0);^{1}H NMR (600 MHz, $CDCl_3$): δ 8.26-8.25 (d, *J* = 8.4 Hz, 1H), 8.11-8.10 (d, *J* = 7.2 Hz, 1H), 7.93-7.91 (d, *J* = 7.8 Hz, 1H), 7.84-7.83 (d, *J* = 8.4 Hz, 1H), 7.63-7.61 (t, *J* = 6.6 Hz, 1H), 7.57-7.51 (m, 2H), 6.50 (s, 1H), 3.51-3.46 (m, 2H), 3.44-3.39 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 135.6, 133.8, 131.1, 128.8, 128.5, 126.3, 125.8, 125.3, 124.8, 123.3, 52.8, 39.6; FT--IR (KBr): 3049, 2920, 1507, 1393, 1218, 906, 801, 776, 731, 628, 544.

(E)-2-Styryl-1,3-Dithiolane (entry 7, Table 2.1.2)



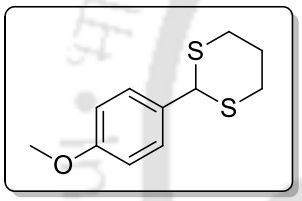
Yield: 185 mg (89%); white solid; R_f = 0.50 (EtOAc:Hexane, 2.5:7.5);mp: 58-59 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.38 (d, *J* = 7.2 Hz, 2H), 7.34-7.30 (t, *J* = 7.2 Hz, 2H), 7.27-7.23 (t, *J* = 14.4 Hz, 2H), 6.54-6.50 (d, *J* = 15.6 Hz, 1H), 6.27-6.21 (dd, J = 9.2 Hz,1H), 5.26-5.24 (d, *J* = 9.2 Hz, 1H), 3.39-3.33 (m, 2H), 3.31-3.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 130.1, 129.1, 128.6, 127.9, 126.6, 54.5, 39.6; FT-IR (KBr): 2922, 1447, 1164, 966, 849, 886, 759, 504, 481.

2-nonyl-1,3-dithiolane (entry 8, Table 2.1.2)



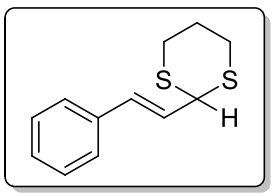
Yield: 167 mg (72%); colourless oil; R_f = 0.50 (EtOAc:Hexane, 0.5:9.5);^{1}H NMR (400 MHz, $CDCl_3$): δ 4.46-4.43-7.35 (t, *J* = 8 Hz, 1H), 3.25-3.13 (m, 4H), 1.82-1.76 (m, 2H), 1.43-1.37 (m, 2H), 1.25-1.24 (m, 12H), 0.87-0.84 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.0, 39.5, 38.4, 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 22.8, 14.2; FT-IR (KBr): 2921, 2852, 1464, 1259, 1015, 797, 756, 721, 683, 667.

2-(4-Methoxyphenyl)-1,3-Dithiane (entry 9, Table 2.1.2)



Yield: 197 mg (87%); white solid; R_f = 0.50 (EtOAc:Hexane,2.0:8.0);mp: 114-115 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.38 (d, *J* = 8.4 Hz, 2H), 6.86-6.84 (d, *J* = 8.8 Hz, 2H), 5.13 (s, 1H), 3.77 (s, 3H), 3.06-2.99 (m, 2H), 2.89-2.84 (m, 2H), 2.16-2.09 (m, 1H), 1.94-1.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 131.3, 128.9, 114.1, 55.3, 50.7, 32.2, 25.1; FT-IR (KBr): 2929, 2890, 1610, 1511, 1256 1175, 1024, 844, 816, 769, 758, 674, 520.

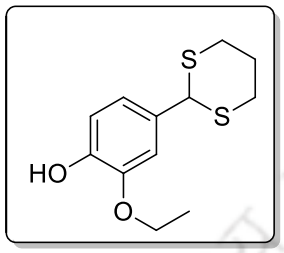
(E)-2-Styryl-1,3-Dithiane (entry 10, Table 2.1.2)



Yield: 166 mg (75%); white semi solid; R_f = 0.50 (EtOAc:Hexane, 2.5:7.5);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.38 (d, *J* = 7.2 Hz, 2H), 7.34-7.30 (t, *J* = 7.2 Hz, 2H), 7.27-7.24 (m, 1H), 6.78-6.74 (d, *J* = 15.6 Hz, 1H), 6.30-6.24 (dd, *J* = 7.6 Hz,1H), 4.83-4.81 (d, *J* = 8 Hz, 1H), 2.98-2.86 (m, 4H), 2.17-2.16 (m, 1H), 1.95-1.85 (m, 1H); ^{13}C NMR (100

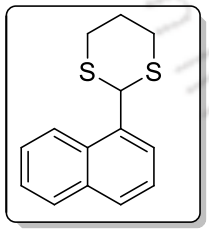
MHz, $CDCl_3$): δ 136.2, 133.5, 128.7, 128.2, 126.8, 126.1, 47.8, 30.3, 25.3; FT-IR (KBr): 3025, 2895, 1575, 1421, 1274, 1168, 959, 865, 763, 691, 505.

4-(1,3-Dithian-2-yl)-2-Ethoxyphenol (entry 11, Table 2.1.2)



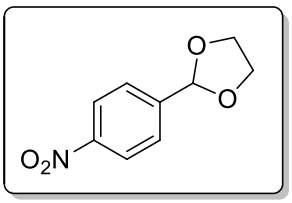
Yield: 215 mg (84%); white solid; R_f = 0.50 (EtOAc:Hexane,2.0:8.0);mp: 101-102 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98-6.98 (d, *J* = 2 Hz, 1H), 6.94-6.92 (dd, *J* = 2 Hz, 1H), 6.86-6.84 (d, *J* = 8 Hz, 1H), 5.74 (broad, OH), 5.09 (s, 1H), 4.14-4.09 (m, 2H), 3.07-3.00 (m, 2H), 2.90-2.85 (m, 2H), 2.17-2.10 (m, 1H), 1.95-1.84 (m, 1H), 1.43-1.40 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 145.9, 131.1, 120.8, 114.4, 111.19, 64.6, 51.4, 32.3, 25.2, 14.9; FT-IR (KBr): 3541, 3373, 2932, 2899, 1510, 1434, 1237, 1038, 974, 803, 764, 594.

2-(Naphthalen-1-yl)-1,3-Dithiane (entry 12, Table 2.1.2)



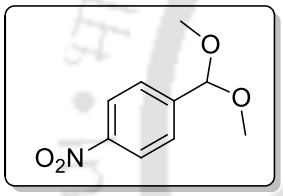
Yield: 182 mg (74%); white solid; R_f = 0.50 (EtOAc:Hexane, 1.5:8.5);mp: 133-134 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27-8.24 (d, *J* = 8.8 Hz, 1H), 7.82-7.80 (d, *J* = 8 Hz, 1H), 7.76-7.73 (t, *J* = 8 Hz, 2H), 7.54-7.49 (t, *J* = 8.4 Hz, 1H), 7.46-7.39 (m, 2H), 5.88 (s, 1H), 3.21-3.14 (t, *J* = 14.8, 2H), 2.93-2.91 (t, *J* = 3.6 Hz, 1H), 2.24-2.17 (m, 1H), 2.02-1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.0, 133.9, 130.2, 129.1, 129.0, 126.4, 126.2, 125.9, 125.6, 123.3, 32.8, 29.7, 25.5; FT-IR (KBr): 2921, 2850, 1512, 1274, 1191, 907, 803, 777, 612, 546,407.

2-(4-Nitrophenyl)-1,3-Dioxolane (entry 1, Table 2.1.3)



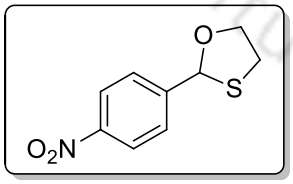
Yield: 157 mg (90%); yellow solid; R_f = 0.60 (EtOAc:Hexane, 1.5:8.5);mp: 85-87 °C;^{1}H NMR (600 MHz, $CDCl_3$): δ 8.22-8.20 (d, *J* = 8.4 Hz, 2H), 7.64-7.62 (d, *J* = 9 Hz, 2H), 5.87 (s, 1H), 4.11-4.04(m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 148.4, 145.0, 127.5, 123.7, 102.3, 65.6; FT-IR (KBr): 2964, 2894, 1607, 1518, 1345, 1259, 1075, 1014, 979, 834, 796, 749, 697.

1-(Dimethoxymethyl)-4-Nitrobenzene (entry 2, Table 2.1.3)



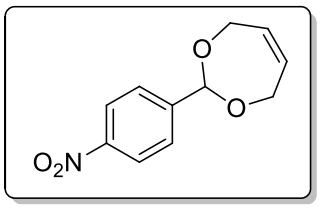
Yield: 140 mg (71%); white oil; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0);^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19-8.17 (d, *J* = 8.8 Hz, 2H), 7.60-7.58 (d, *J* = 11.2 Hz, 2H), 5.43 (s, 1H), 3.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 145.2, 128.0, 123.6, 101.7, 52.9; FT-IR (KBr): 2962, 1512, 1338, 1259, 1116, 1039, 864, 797, 661.

2-(4-Nitrophenyl)-1,3-Oxathiolane (entry 3, Table 2.1.3)



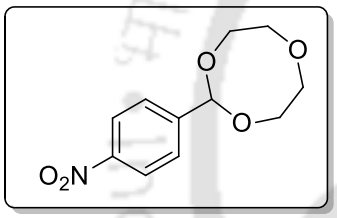
Yield: 181 mg (86%); orange solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0);mp: 72-74 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18-8.16 (d, *J* = 8.8 Hz, 2H), 7.57-7.55 (d, *J* = 8.8 Hz, 2H), 6.09 (s, 1H), 4.54-4.50(m, 1H), 4.02-3.96 (m, 1H), 3.26-3.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 147.1, 127.2, 123.8, 85.4, 72.5, 34.2; FT-IR (KBr): 2859, 1602, 1519, 1343, 1227, 1064, 979, 856, 712, 441.

2-(4-Nitrophenyl)-4,7-Dihydro-1,3-Dioxepine (entry 4, Table 2.1.3)



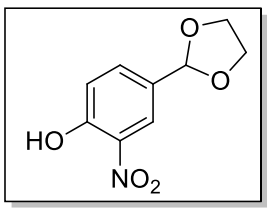
Yield: 192 mg (87%); brown solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0);mp: 102-103 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21-8.19 (d, *J* = 8.8 Hz, 2H), 7.70-7.68 (d, *J* = 8.8 Hz, 2H), 5.86 (s, 1H), 5.76 (s, 2H), 4.38-4.27(m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 145.9, 129.8, 127.7, 123.5, 101.1, 65.0; FT-IR (KBr): 2884, 1602, 1513, 1338, 1261, 1201, 1103, 1029, 851, 748, 644, 407.

2-(4-Nitrophenyl)-1,3,6-Trioxocane (entry 5, Table 2.1.3)



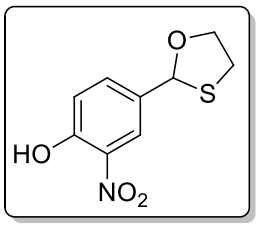
Yield: 195 mg (82%); yellow solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0);mp: 85-87 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21-8.19 (d, *J* = 8.8 Hz, 2H), 7.65-7.63(d, *J* = 8.4 Hz, 2H), 5.70(s, 1H), 4.06-3.95(m, 4H), 3.88-3.77(m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 146.7, 127.5, 123.6, 103.8, 72.9, 70.2; FT-IR (KBr): 3376, 2927, 2854, 1703, 1343, 1194, 1054, 849, 812, 737, 677, 536.

4-(1,3-Dioxolan-2-yl)-2-Nitrophenol (entry 6, Table 2.1.3)



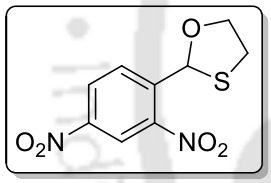
Yield: 177 mg (84%); yellow solid; R_f = 0.50 (EtOAc:Hexane, 4.0:6.0);mp: 102-104 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ 10.63 (broad, OH), 8.23-8.22 (d, *J* = 2 Hz, 1H), 7.71-7.67 (dd, *J* = 2 Hz, 1H), 7.18-7.16 (d, *J*= 8.8 Hz, 1H), 5.76 (s, 1H), 4.14-4.02 (m, 4H);^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 135.9, 133.4, 130.9, 123.6, 120.3, 102.3, 65.6; FT-R (KBr): 3269, 2959, 2899, 1635, 1540, 1244, 1085, 944, 887, 762, 664, 580.

2-Nitro-4-(1,3-Oxathiolan-2-yl)phenol (entry 7, Table 2.1.3)



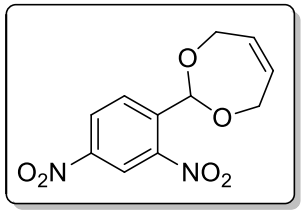
Yield: 183 mg (81%); yellow solid; R_f = 0.50 (EtOAc:Hexane, 4.0:6.0);mp: 87-89 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ 10.61 (broad, OH), 8.18-8.18 (d, *J* = 2.4 Hz, 1H), 7.69-7.67 (dd, *J* = 2.4 Hz, 1H), 7.15-7.13 (d, *J*= 8.8 Hz, 1H), 5.96 (s, 1H), 4.54-4.49 (m, 1H), 3.97-3.91 (m, 1H), 3.31-3.18 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 136.3, 133.2, 132.2, 123.4, 120.4, 85.6, 72.2, 34.3; FT-IR (KBr): 3266, 2962, 2874, 1622, 1512, 1338, 1263, 1023, 950, 763, 693, 569.

2-(2,4-Dinitrophenyl)-1,3-Oxathiolane (entry 8, Table 2.1.3)



Yield: 209 mg (82%); orange semi solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0);^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89-8.88 (d,*J*= 2.4 Hz, 1H), 8.48-8.45(dd, *J*= 2 Hz, 1H), 8.10-8.08 (d, *J*= 8.4 Hz, 1H), 6.61(s, 1H), 4.66-4.62 (m, 1H), 4.12-4.06 (m, 1H), 3.21-3.16 (m, 1H), 3.13-3.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 146.6, 144.6, 129.0, 128.1, 120.5, 81.4, 73.3, 33.4; FT-IR (KBr): 2877, 1605, 1534, 1345, 1210, 1059, 905, 836, 727, 663, 572.

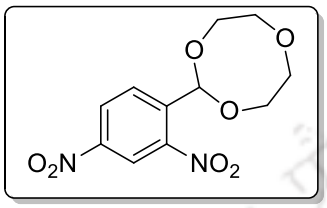
2-(2,4-Dinitrophenyl)-4,7-Dihydro-1,3-Dioxepine (entry 9, Table 2.1.3)



Yield: 231 mg (87%); orange semi solid; R_f = 0.60 (EtOAc:Hexane, 2.5:7.5);^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62-8.62 (d,*J* = 2 Hz,1H), 8.43-8.40 (dd, *J* = 2 Hz, 1H), 8.09-8.07 (d, *J* = 8.8 Hz, 1H), 6.27 (s, 1H), 5.75(s, 2H), 4.44-4.33(m, 4H);

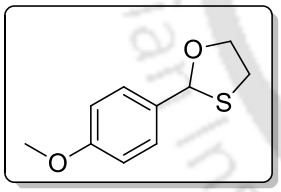
^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 147.9, 139.5, 129.7, 129.0, 126.6, 119.8, 98.6, 67.3; FT-IR (KBr): 2849, 1607, 1530, 1343, 1109, 1086, 882, 741, 651.

2-(2,4-Dinitrophenyl)-1,3,6-Trioxocane (entry 10, Table 2.1.3)



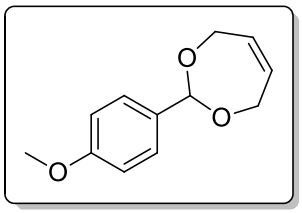
Yield: 224 mg (79%); orange semi solid; R_f = 0.60 (EtOAc:Hexane, 3.0:7.0);^{1}H NMR (600 MHz, $CDCl_3$): δ 8.62-8.62 (d, *J* = 2.4 Hz, 1H), 8.41-8.39 (dd, *J* = 1.8 Hz, 1H), 8.07-8.06 (d, *J* = 8.4 Hz, 1H), 6.14(s, 1H), 4.04-4.02 (d, *J*= 11.4 Hz, 4H), 3.95-3.90 (m, 2H), 3.75-3.71 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 148.7, 147.8, 140.9, 129.5, 126.7, 119.7, 102.4, 74.1, 73.5;FT-IR (KBr): 2919, 1607, 1530, 1344, 1299, 1134, 1066, 974, 833, 738, 715, 521.

2-(4-Methoxyphenyl)-1,3-Oxathiolane (entry 11, Table 2.1.3)



Yield: 150 mg (77%); white solid; 2H), 6.90-6.88 (d, *J* = 8.4 Hz, 2H), 6.01 (s, 1H), 4.52-4.48 (m, 1H), 3.93-3.86(m, 1H), 3.79 (s, 3H), 3.30-3.23 (m, 1H), 3.19-3.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 131.0, 128.2, 113.8, 87.0, 71.7, 55.3, 34.1; FT-IR (KBr): 3326, 2835, 2919, 1605, 1508, 1253, 1171, 1160, 1070, 818, 761, 607.

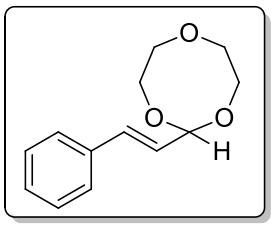
2-(4-Methoxyphenyl)-4,7-Dihydro-1,3-Dioxepine (entry 12, Table 2.1.3)



Yield: 164 mg (80%); white semi solid; R_f = 0.50 (EtOAc:Hexane, 2.5:7.5);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.44 (d, *J* = 8.4 Hz, 2H), 6.91-6.89 (d, *J* = 8.8 Hz, 2H), 5.82 (s, 1H), 5.76 (s, 2H), 4.40-4.436 (m, 2H), 4.26-4.23 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (100

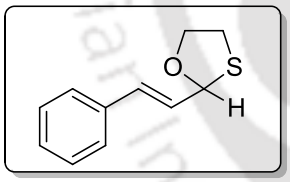
MHz, $CDCl_3$): δ 159.7, 131.3, 130.1, 127.8, 113.5, 102.1, 64.4, 55.3; FT-IR (KBr): 3406, 2837, 1650, 1596, 1510, 1256, 1158, 1022, 831, 731, 597.

(E)-2-styryl-1,3,6-trioxocane (entry 13, Table 2.1.3)



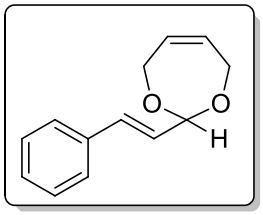
Yield: 163 mg (74%); white semi solid; R_f = 0.50 (EtOAc:Hexane, 1.5:8.5);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.39 (d, *J* = 6.8 Hz, 2H), 7.33-7.30 (t, *J* = 7.2 Hz, 2H), 7.27-7.25 (t, *J* = 4 Hz, 1H), 6.76-6.72 (d, *J* = 16 Hz, 1H), 6.21-6.16 (dd, *J* = 4 Hz,1H), 5.28-5.27 (d, *J* = 5.2 Hz, 1H), 4.05-4.0 (m, 2H), 3.96-3.91 (m, 2H), 3.82-3.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3, 132.3, 128.7, 128.2, 127.0, 126.9, 104.2, 72.9, 69.3; FT-IR (KBr): 2917, 2852, 1676, 1345, 1259, 1135, 969, 871, 750, 583.

(E)-2-styryl-1,3-oxathiolane (entry 14, Table 2.1.3)



Yield: 146 mg (76%); white semi solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.39 (d, *J* = 7.6 Hz, 2H), 7.34-7.30 (t, *J* = 7.2 Hz, 2H), 7.28-7.24 (t, *J* = 8 Hz, 1H), 6.68-6.64 (d, *J* = 16 Hz, 1H), 6.31-6.25 (dd, *J* = 7.6 Hz,1H), 5.71-5.69 (d, *J* = 7.6 Hz, 1H), 4.42-4.38 (m, 1H), 3.93-3.87 (m, 1H), 3.20-3.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 132.3, 128.7, 128.3, 127.3, 126.9, 86.4, 71.8, 33.8; FT-IR (KBr): 2932, 2869, 1449, 1205, 1129, 1056, 961, 751, 690, 536.

(E)-2-styryl-4,7-dihydro-1,3-dioxepine (entry 15, Table 2.1.3)



Yield: 156 mg (77%); white semi solid; R_f = 0.50 (EtOAc:Hexane, 1.5:8.5);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.39 (d, *J* = 7.2 Hz,

2H), 7.32-7.29 (t, *J* = 6.8 Hz, 2H), 7.26-7.22 (t, *J* = 7.2 Hz, 1H), 6.81-6.77 (d, *J* = 16.4 Hz, 1H), 6.25-6.20 (dd, *J* = 4 Hz,1H), 5.73 (s, 2H), 5.45-5.44 (d, *J* = 4 Hz, 1H), 4.46-4.42 (d, *J* = 15.6 Hz, 2H), 4.24-4.20 (d, *J* = 15.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.2, 133.0, 128.6, 128.1, 126.8, 125.7,101.7, 64.5; FT-IR (KBr): 3029, 2852, 1657, 1445, 1200, 1135, 1022, 986, 749, 693, 639, 578.

2.6. ^{1}H NMR and ^{13}C NMR spectra of selected compounds

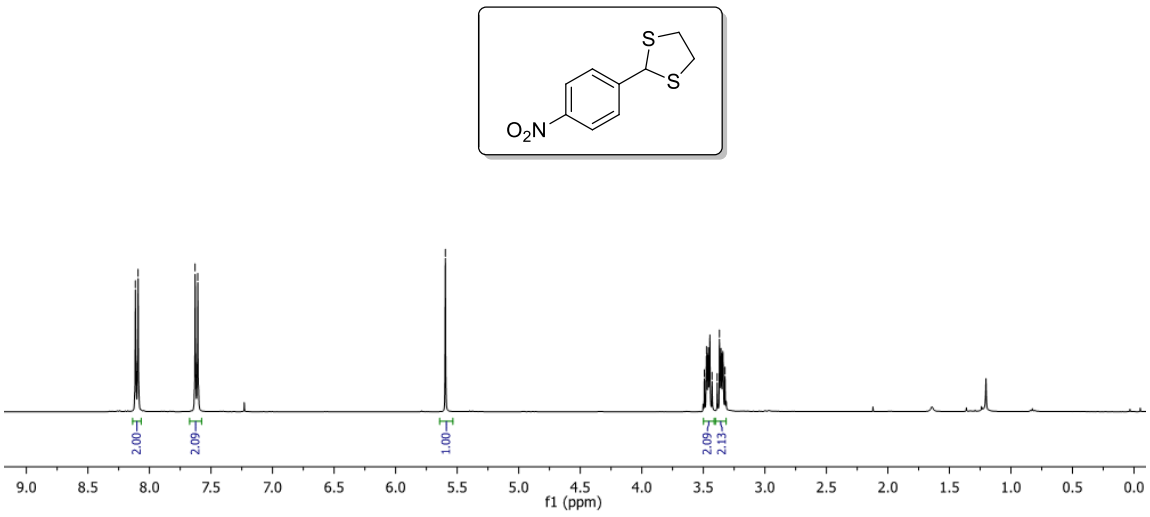


Figure 2.6.1.1. ^{1}H-NMR spectrum of 2-(4-Nitrophenyl)-1,3-Dithiolane (entry 1, Table 2.1.2)

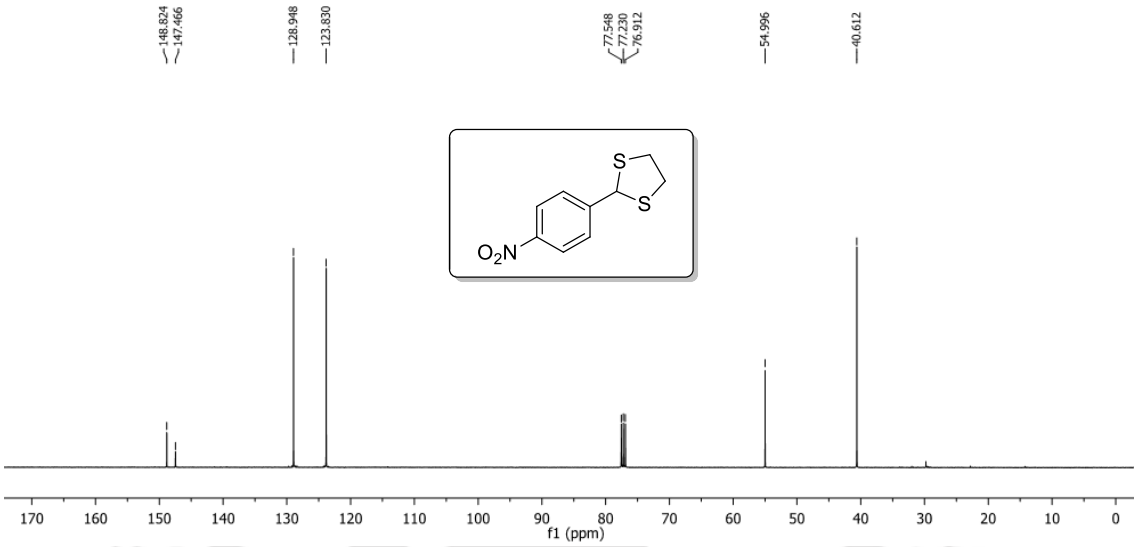


Figure 2.6.1.2. ^{13}C-NMR spectrum of 2-(4-Nitrophenyl)-1,3-Dithiolane (entry 1, Table 2.1.2)

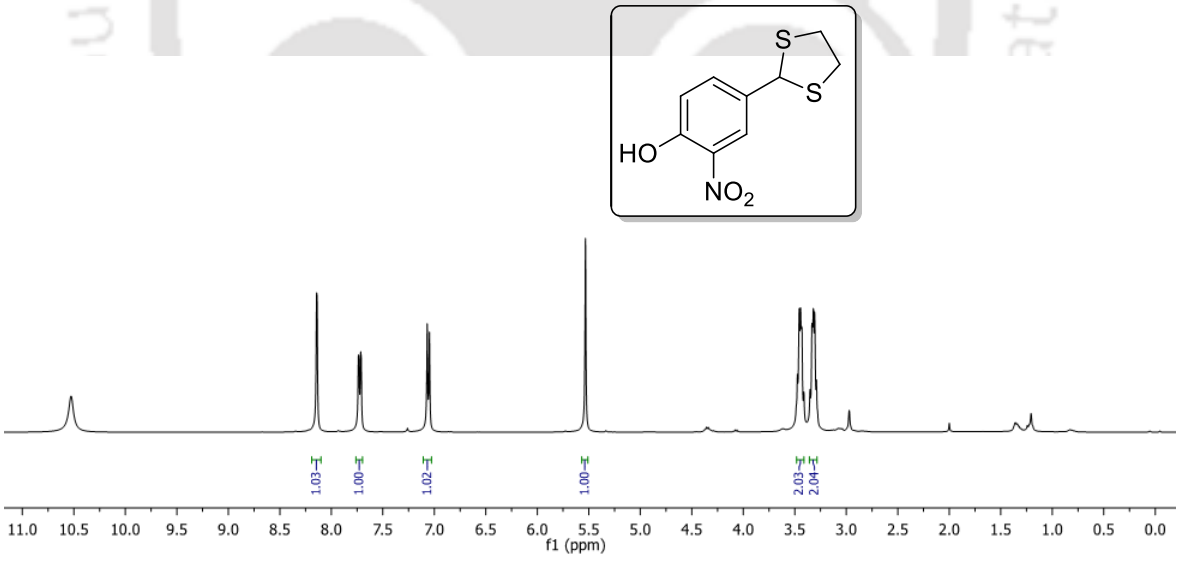


Figure 2.6.1.3. ^{1}H-NMR spectrum of 4-(1,3-Dithiolan-2-yl)-2-Nitrophenol (entry 2, Table 2.1.2)

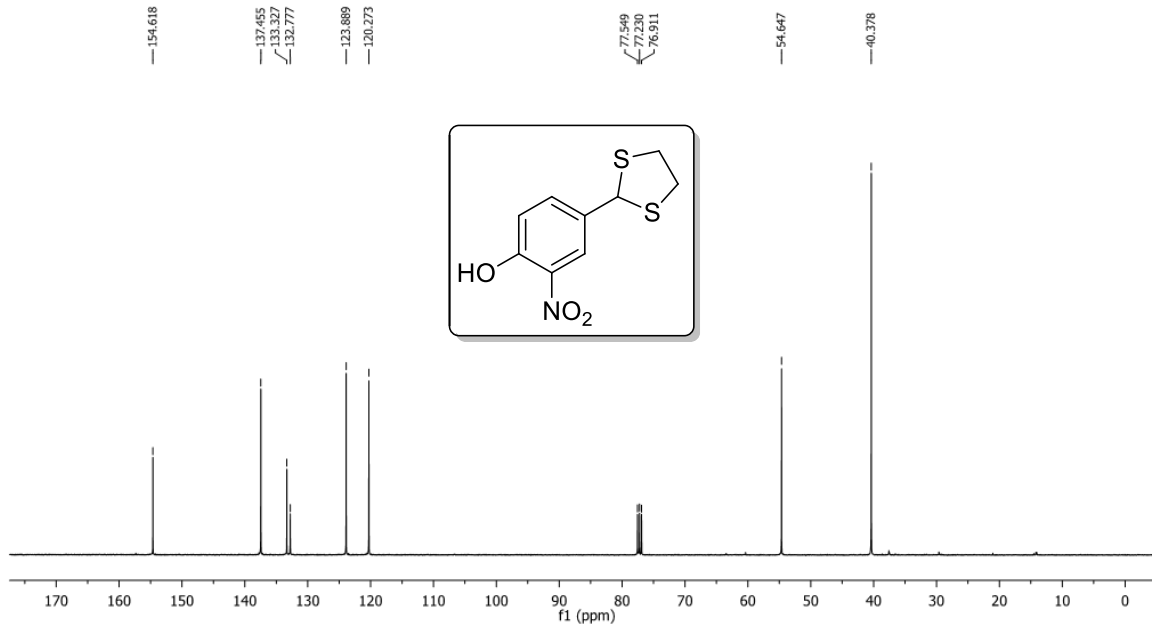


Figure 2.6.1.4. ^{13}C-NMR spectrum of 4-(1,3-Dithiolan-2-yl)-2-Nitrophenol (entry 2, Table 2.1.2)

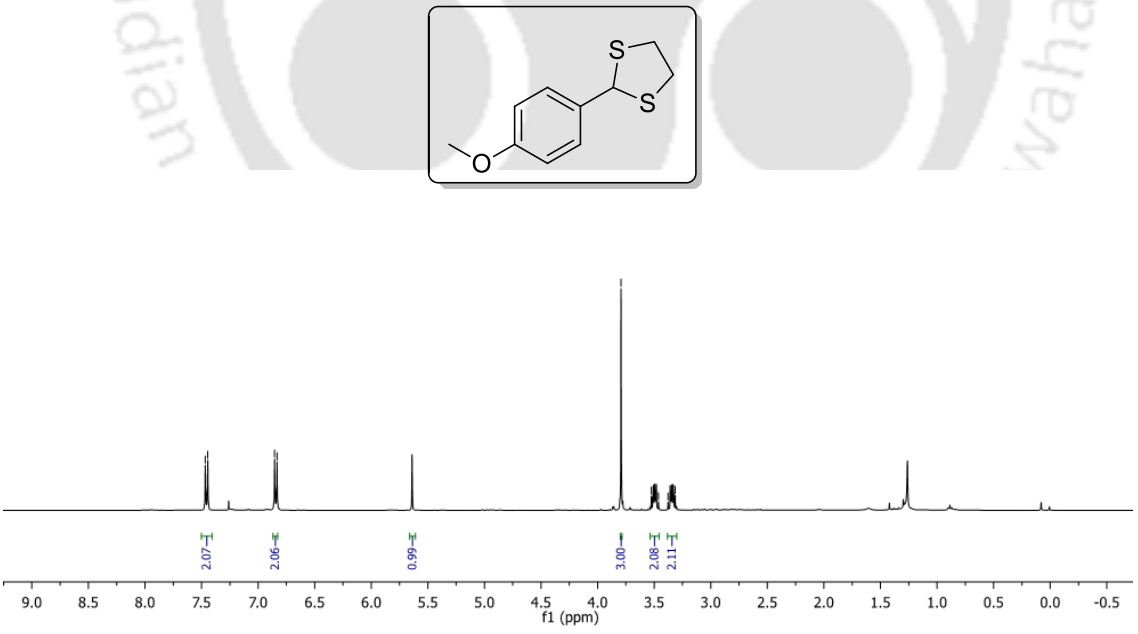


Figure 2.6.1.5. ^{1}H-NMR spectrum of 2-(4-Methoxyphenyl)-1,3-Dithiolane (entry 4, Table 2.1.2)

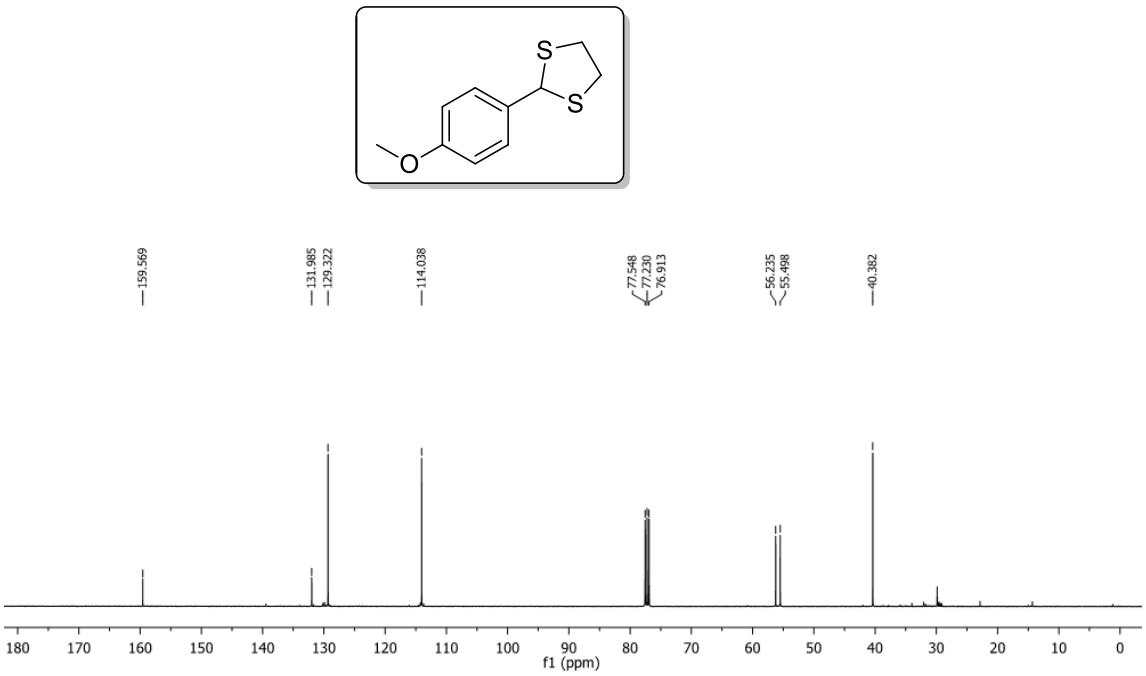


Figure 2.6.1.6. ^{13}C-NMR spectrum of 2-(4-Methoxyphenyl)-1,3-Dithiolane (entry 4, Table 2.1.2)

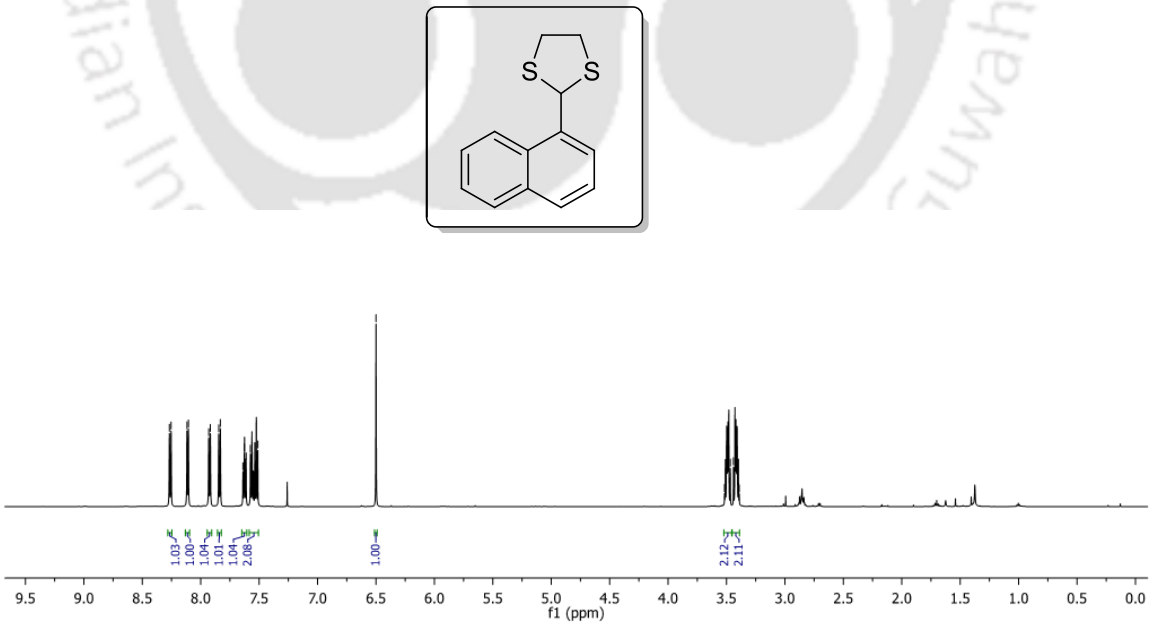


Figure 2.6.1.7. ^{1}H-NMR spectrum of 2-(Naphthalen-1-yl)-1,3-Dithiolane (entry 6, Table 2.1.2)

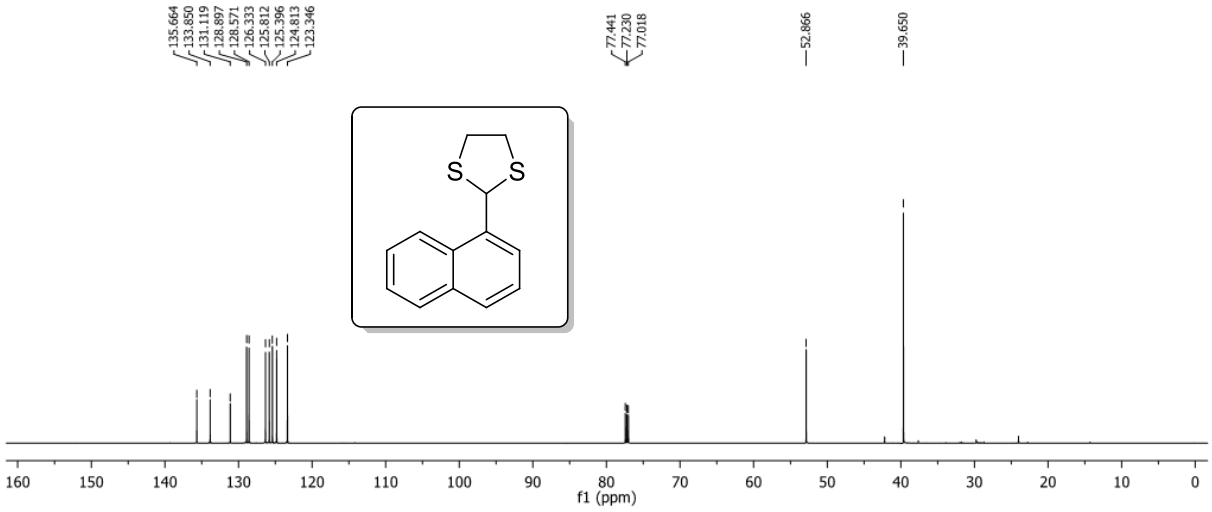


Figure 2.6.1.8. ^{13}C-NMR spectrum of 2-(Naphthalen-1-yl)-1,3-Dithiolane (entry 6, Table 2.1.2)

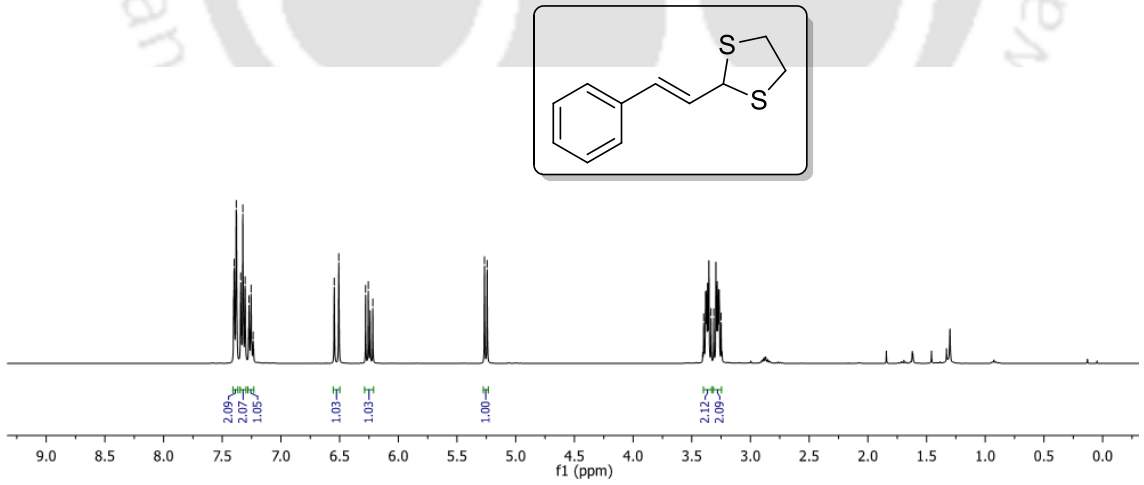


Figure 2.6.1.9. ^{1}H-NMR spectrum of (E)-2-Styryl-1,3-Dithiolane (entry 7, Table 2.1.2)

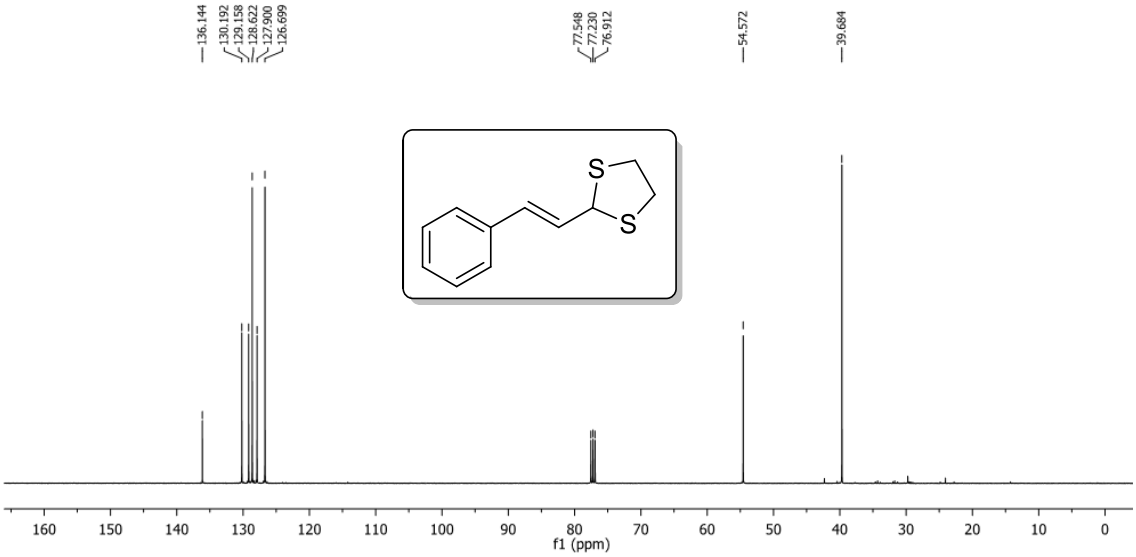


Figure 2.6.1.10 ^{13}C-NMR spectrum of (E)-2-Styryl-1,3-Dithiolane (entry 7, Table 2.1.2)

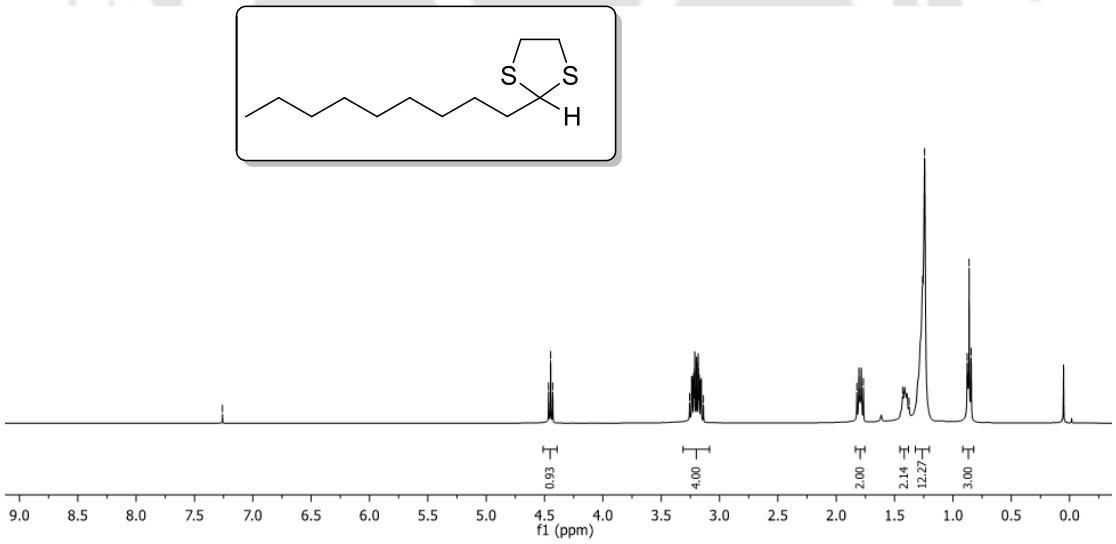


Figure 2.6.1.11. ^{1}H-NMR spectrum of 2-nonyl-1,3-dithiolane (entry 8, Table 2.1.2)

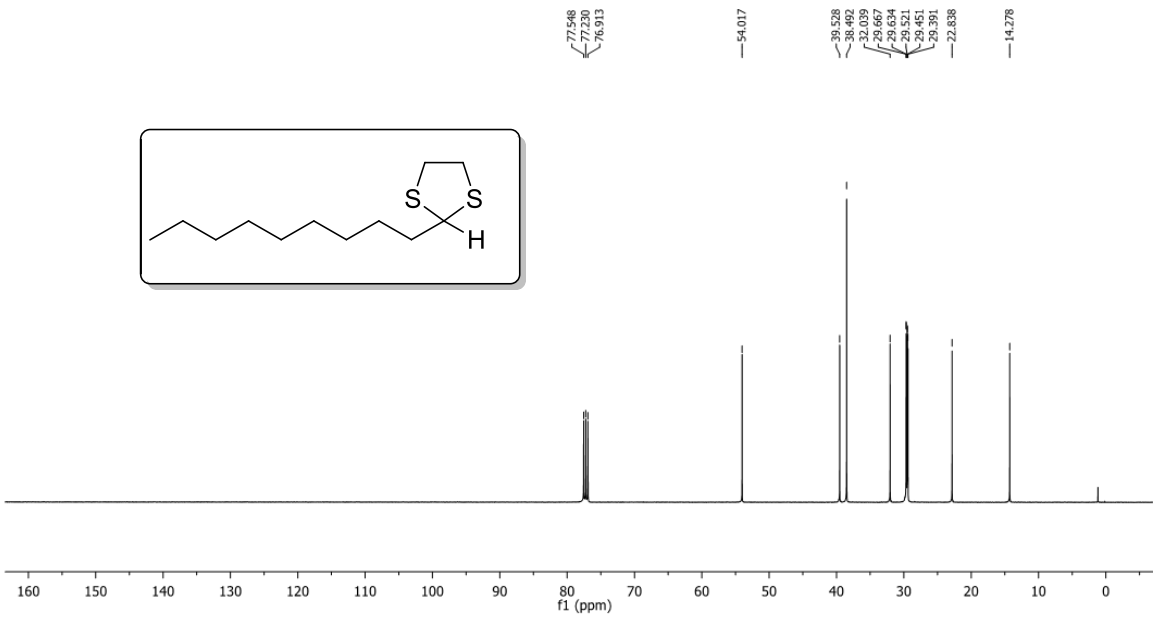


Figure 2.6.1.12. ^{13}C-NMR spectrum of 2-nonyl-1,3-dithiolane (entry 8, Table 2.1.2)

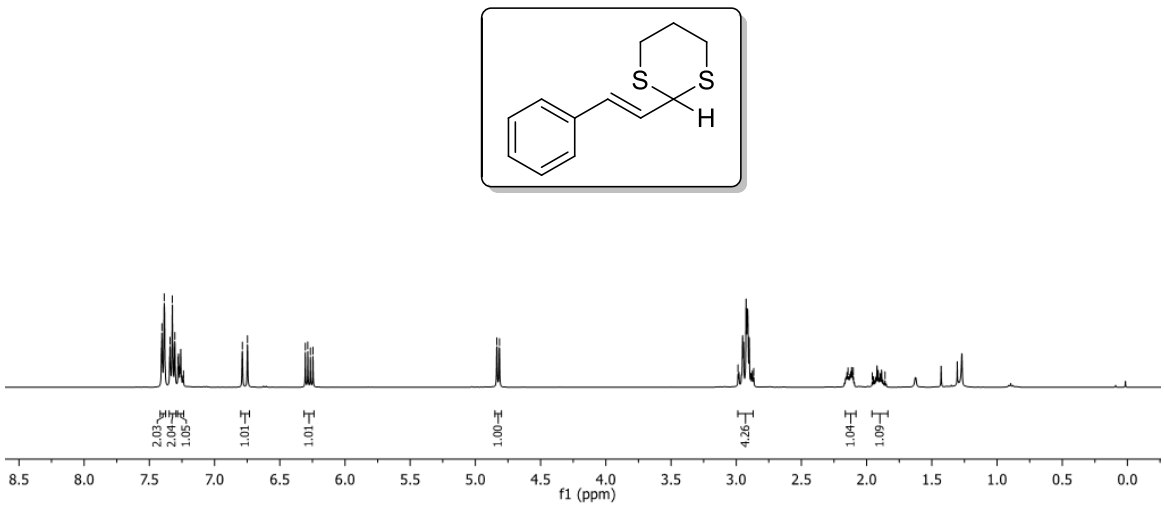


Figure 2.6.1.13. ^{1}H-NMR spectrum of (E)-2-Styryl-1,3-Dithiane (entry 10, Table 2.1.2)

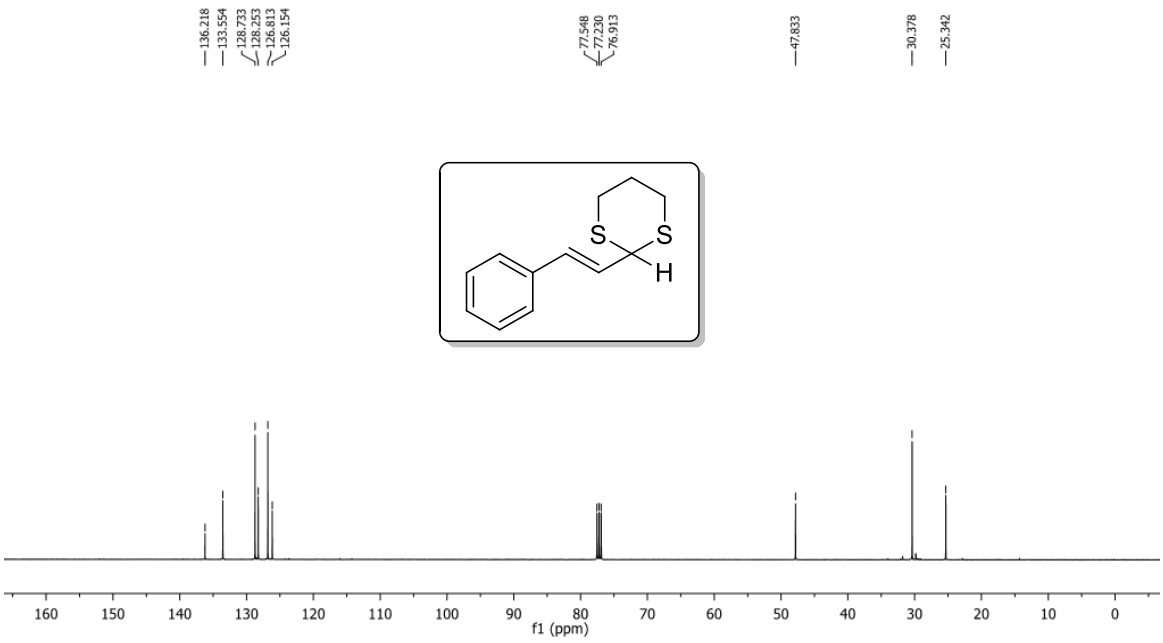


Figure 2.6.1.14. ^{13}C-NMR spectrum of (E)-2-Styryl-1,3-Dithiane (entry 10, Table 2.1.2)

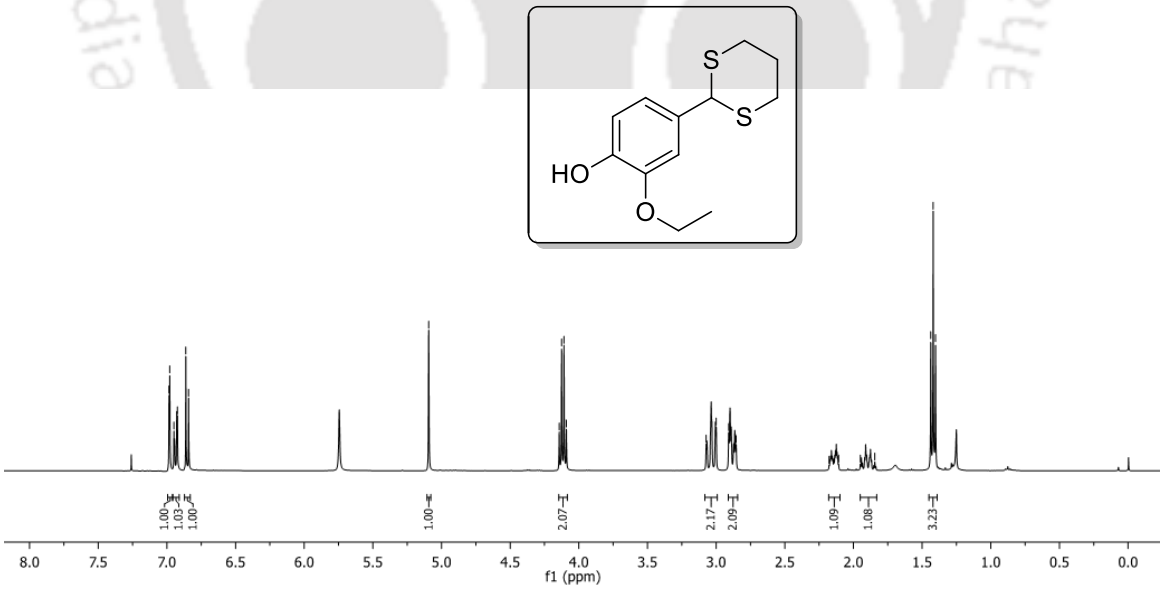


Figure 2.6.1.15. ^{1}H-NMR spectrum of 4-(1,3-Dithian-2-yl)-2-Ethoxyphenol (entry 11, Table 2.1.2)

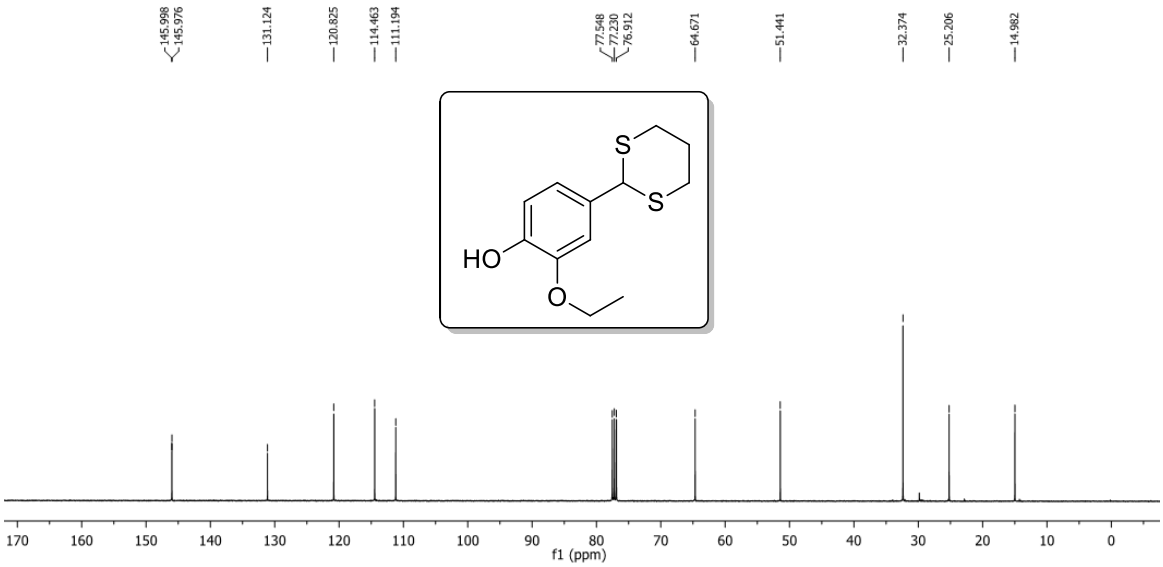


Figure 2.6.1.16. ^{13}C-NMR spectrum of 4-(1,3-Dithian-2-yl)-2-Ethoxyphenol (entry 11, Table 2.1.2)

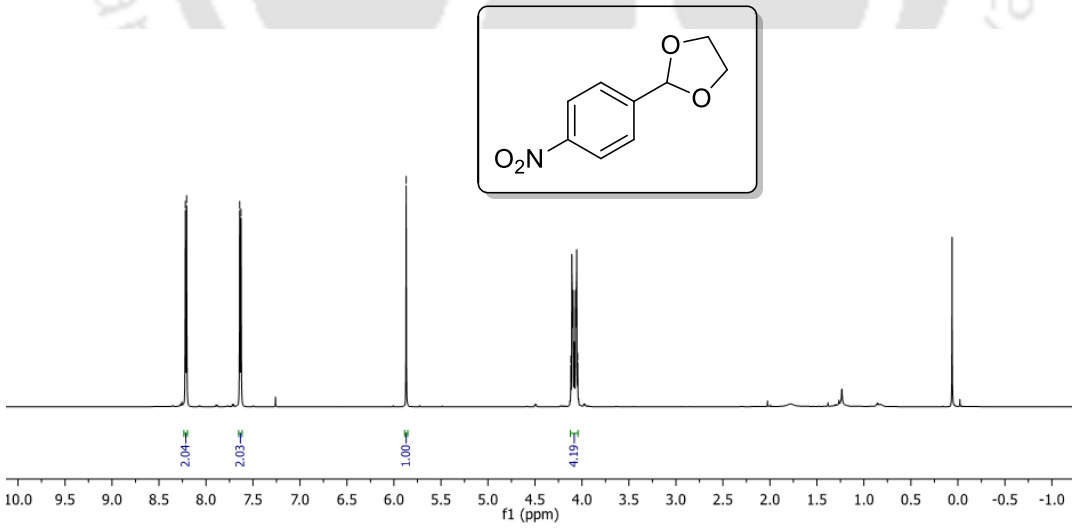


Figure 2.6.1.17. ^{1}H-NMR spectrum of 2-(4-Nitrophenyl)-1,3-Dioxolane(entry 1, Table 2.1.3)

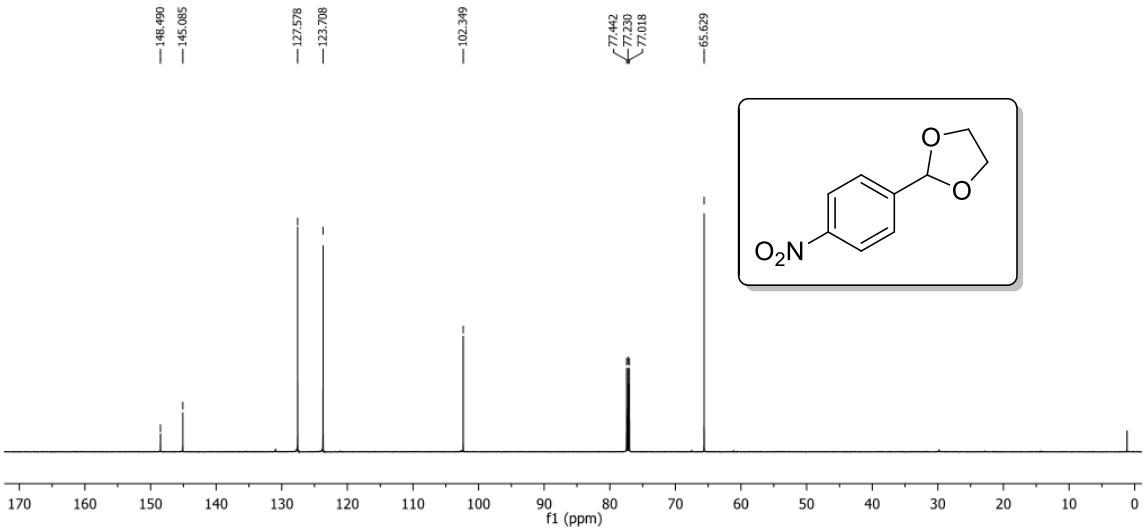


Figure 2.6.1.18. ^{13}C-NMR spectrum of 2-(4-Nitrophenyl)-1,3-Dioxolane(entry 1, Table 2.1.3)

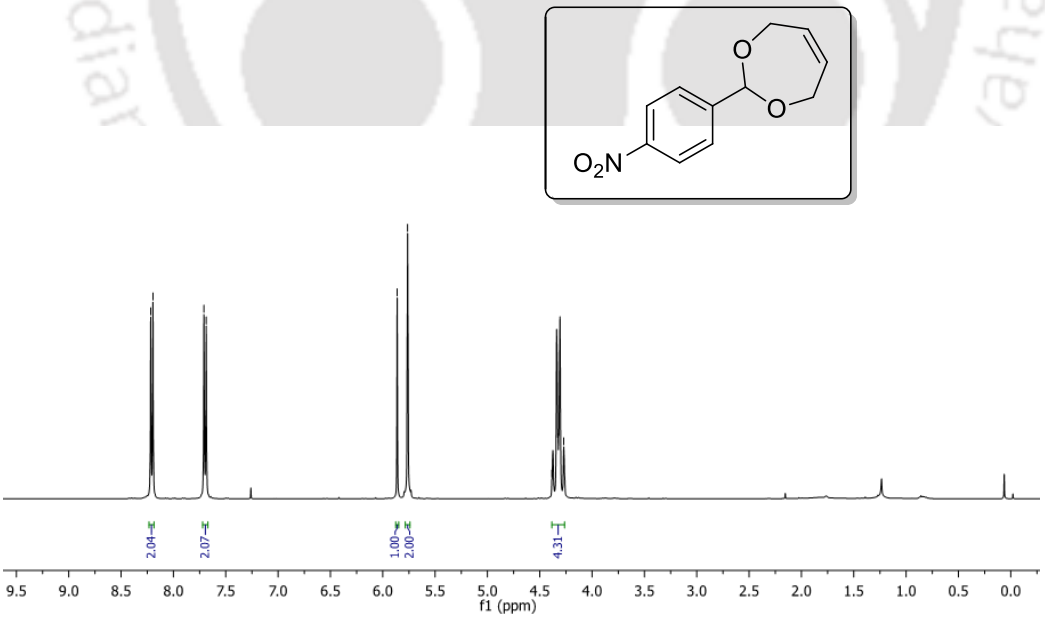


Figure 2.6.1.19. ^{1}H-NMR spectrum of 2-(4-Nitrophenyl)-4,7-Dihydro-1,3-Dioxepine (entry 4, Table 2.1.3)

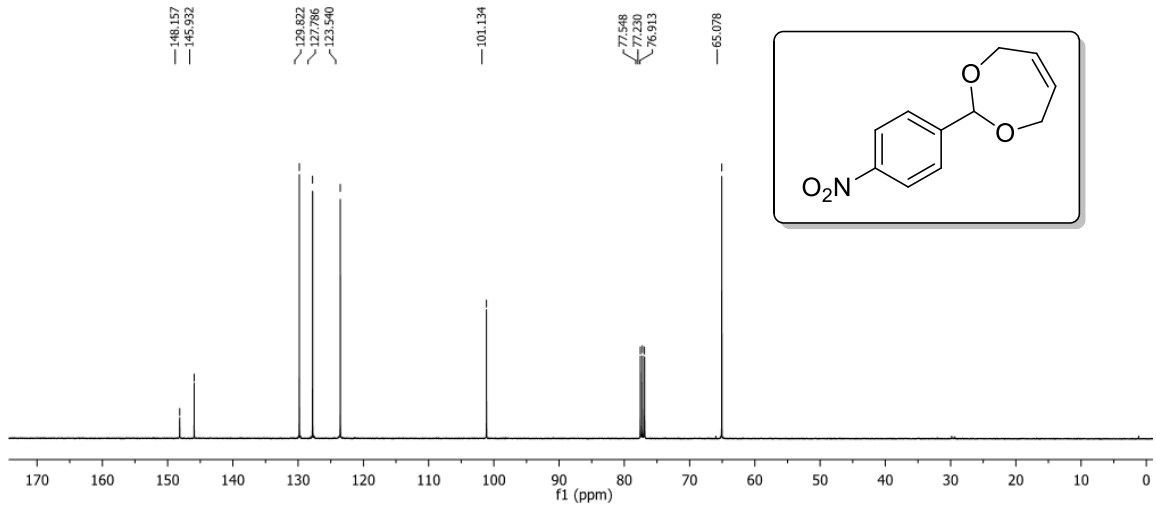


Figure 2.6.1.20. ^{13}C-NMR spectrum of 2-(4-Nitrophenyl)-4,7-Dihydro-1,3-Dioxepine (entry 4, Table 2.1.3)

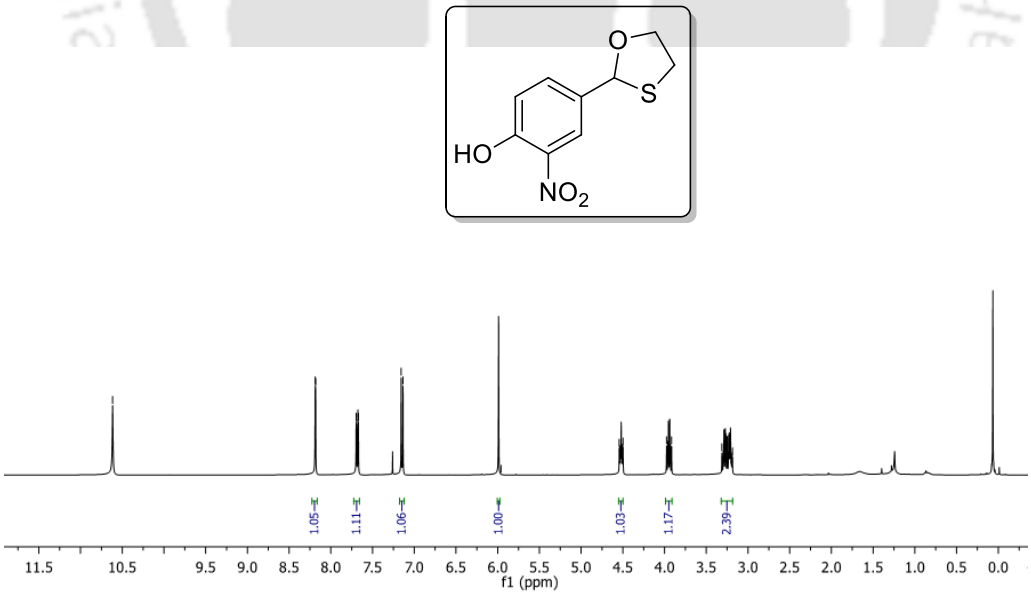


Figure 2.6.1.21. ^{1}H-NMR spectrum of 2-Nitro-4-(1,3-Oxathiolan-2-yl)phenol (entry 7, Table 2.1.3)

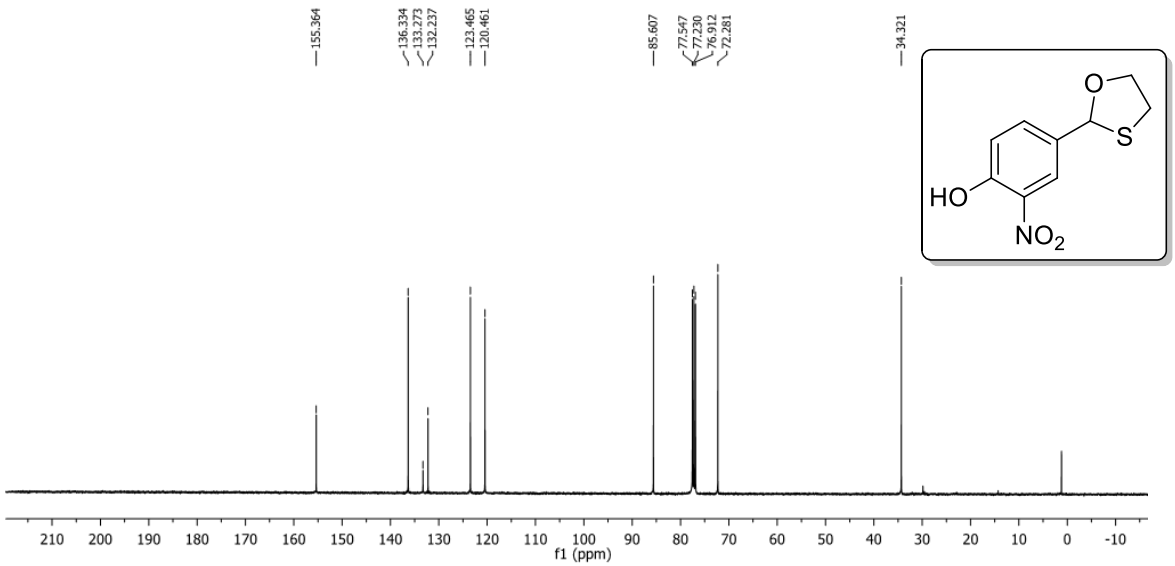


Figure 2.6.1.22. ^{13}C-NMR spectrum of 2-Nitro-4-(1,3-Oxathiolan-2-yl)phenol (entry 7, Table 2.1.3)

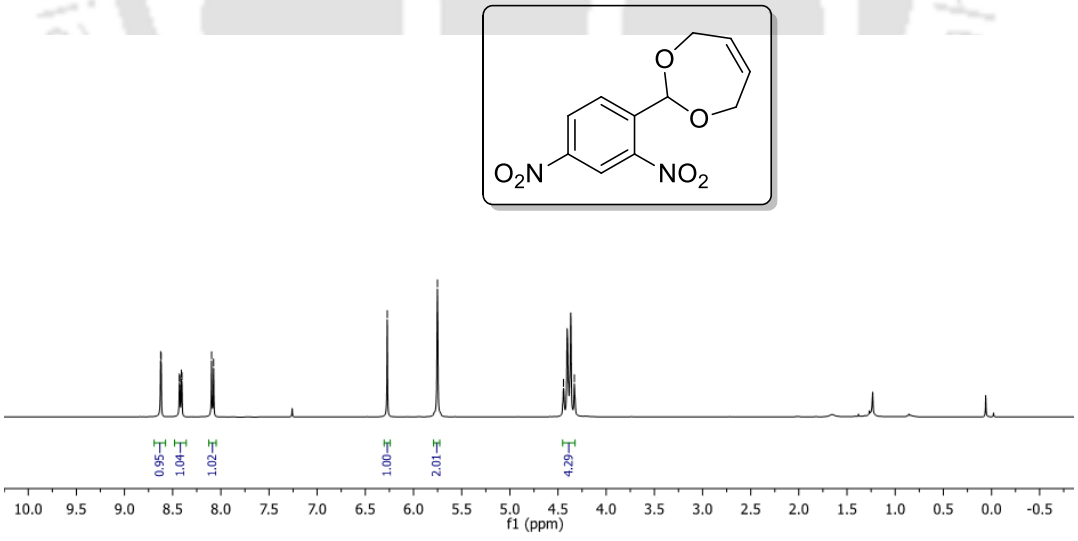


Figure 2.6.1.23. ^{1}H-NMR spectrum of 2-(2,4-Dinitrophenyl)-4,7-Dihydro-1,3-Dioxepine (entry 9, Table 2.1.3)

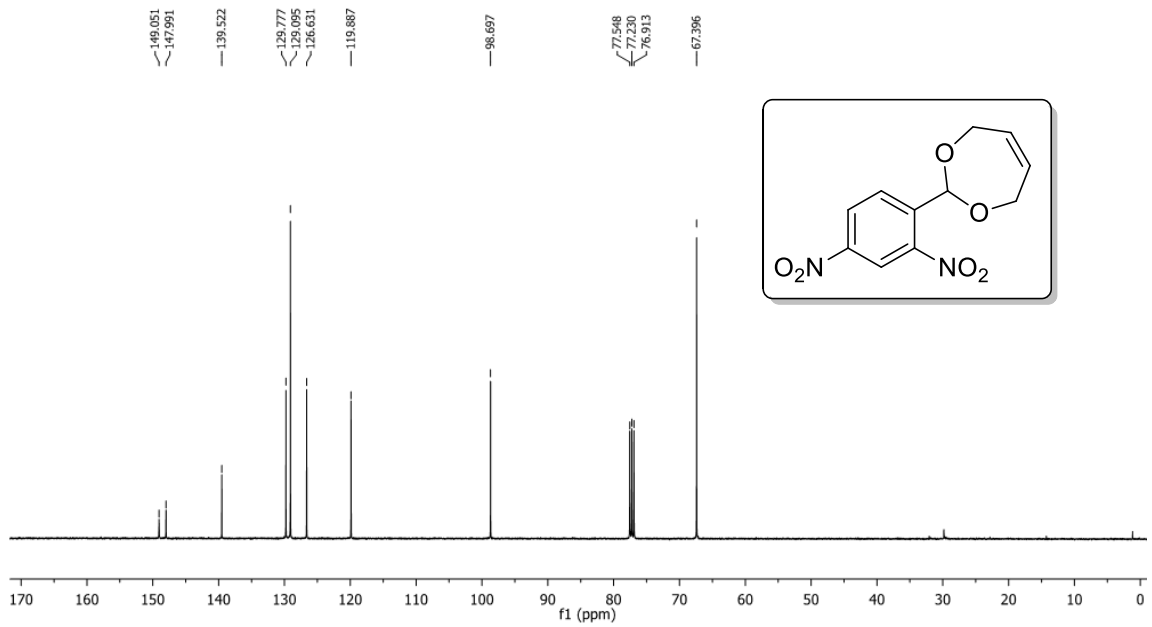


Figure 2.6.1.24. ^{13}C-NMR spectrum of 2-(2,4-Dinitrophenyl)-4,7-Dihydro-1,3-Dioxepine (entry 9, Table 2.1.3)

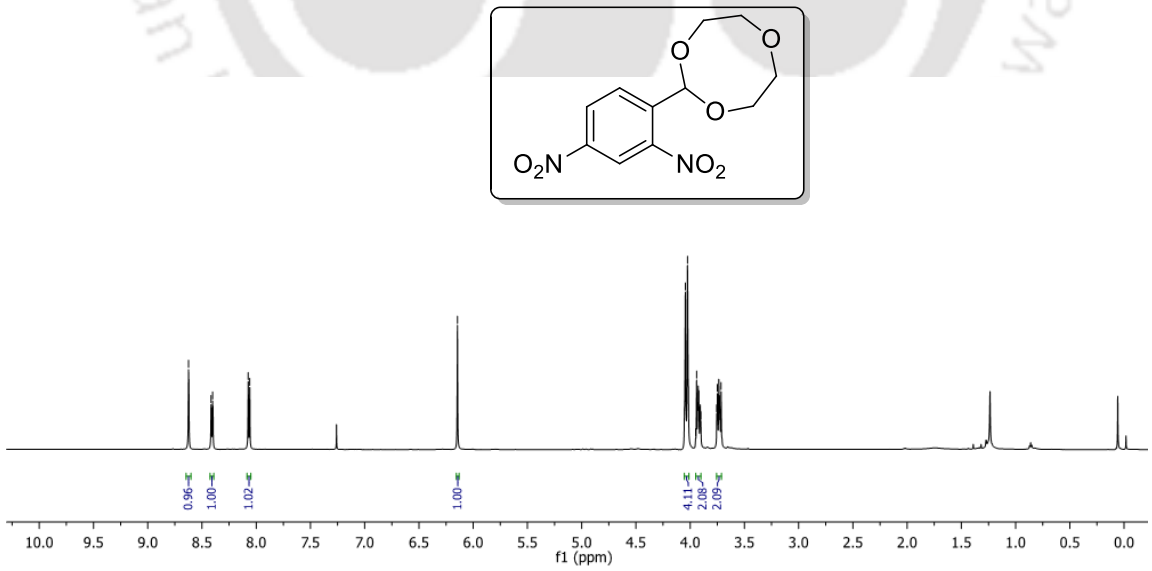


Figure 2.6.1.25. ^{1}H-NMR spectrum of 2-(2,4-Dinitrophenyl)-1,3,6-Trioxocane (entry 10, Table 2.1.3)

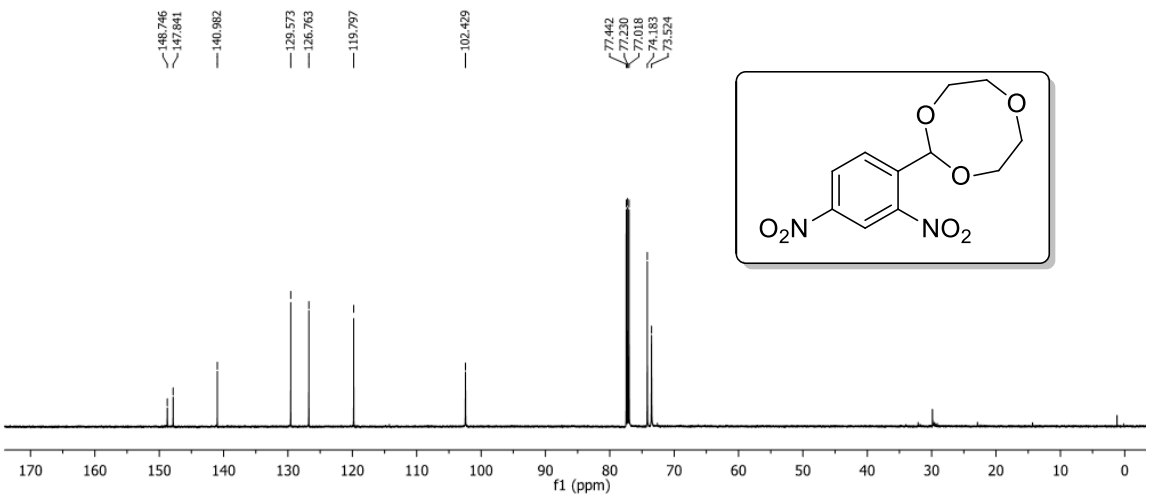


Figure 2.6.1.26. ^{13}C-NMR spectrum of 2-(2,4-Dinitrophenyl)-1,3,6-Trioxocane (entry 10, Table 2.1.3)

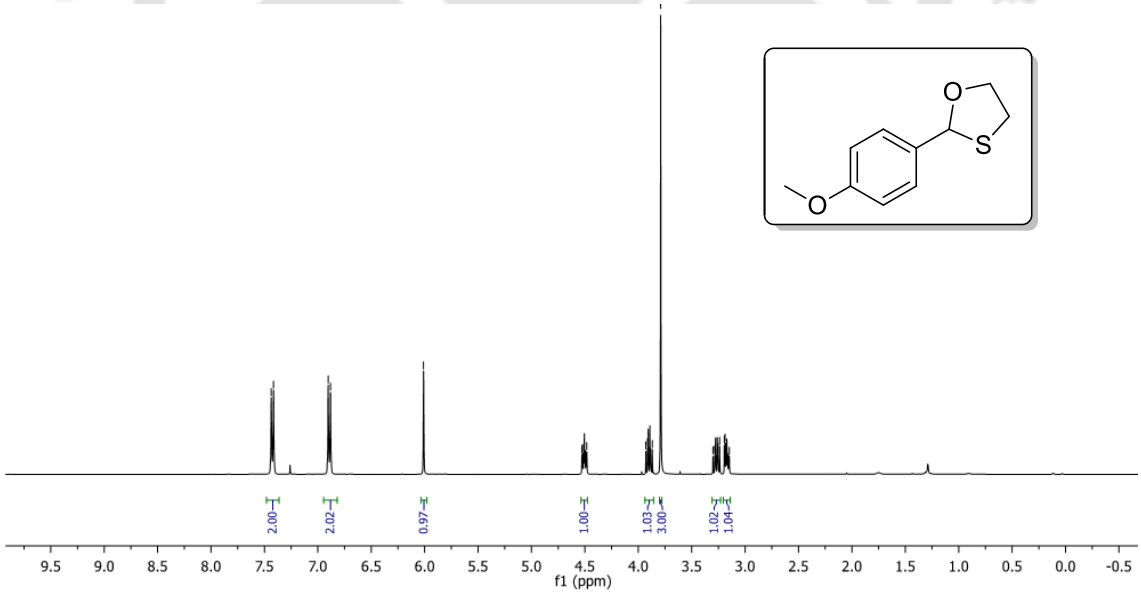


Figure 2.6.1.27. ^{1}H-NMR spectrum of 2-(4-Methoxyphenyl)-1,3-Oxathiolane (entry 11, Table 2.1.3)

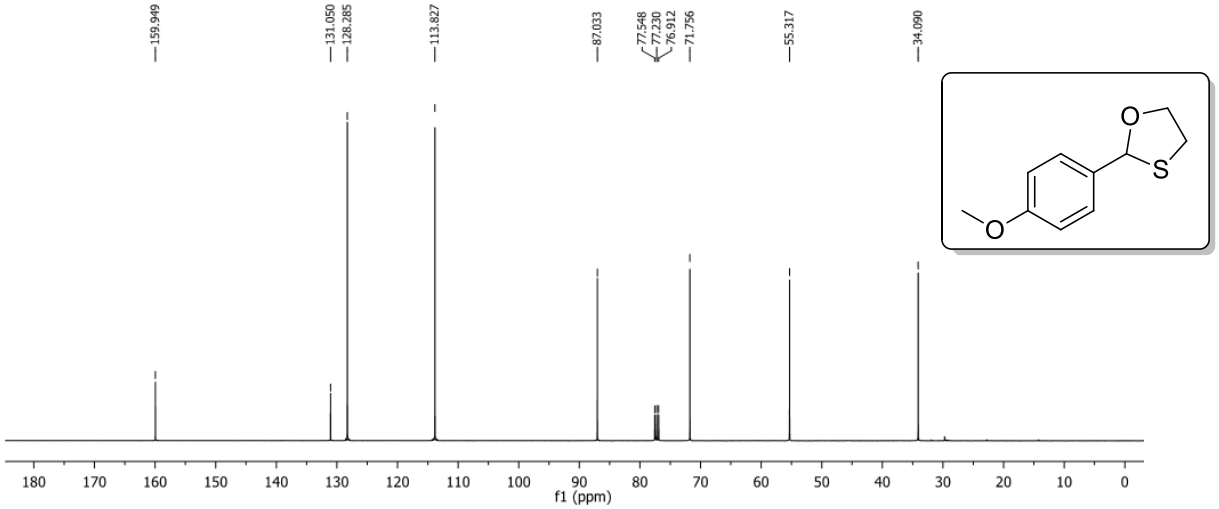


Figure 2.6.1.28. ^{13}C-NMR spectrum of 2-(4-Methoxyphenyl)-1,3-Oxathiolane (entry 11, Table 2.1.3)

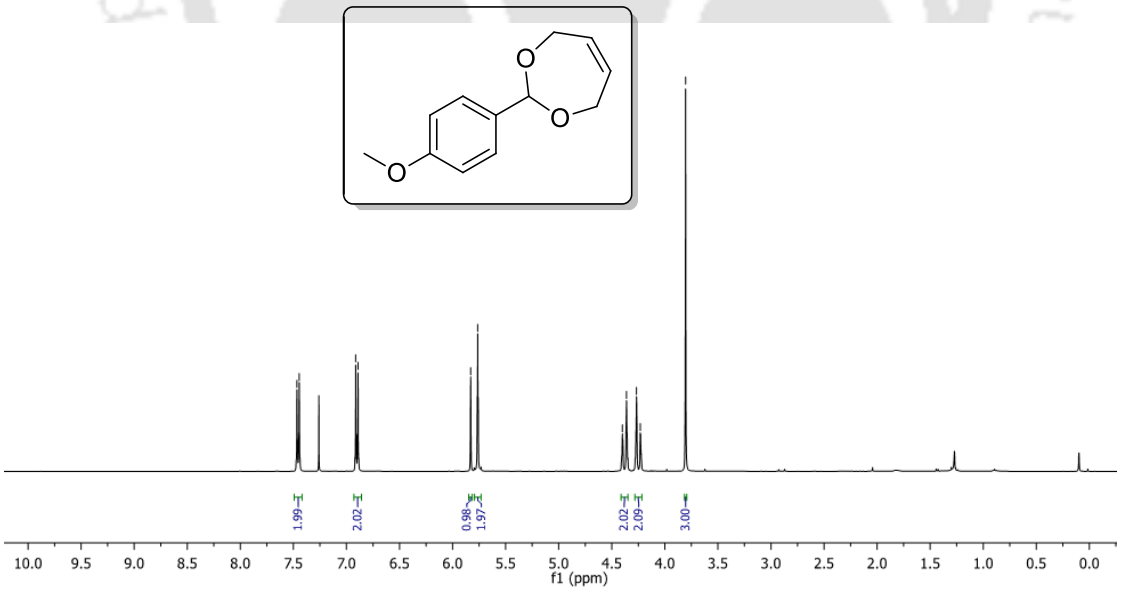


Figure 2.6.1.29. ^{1}H-NMR spectrum of 2-(4-Methoxyphenyl)-4,7-dihydro-1,3-Dioxepine (entry 12, Table 2.1.3)

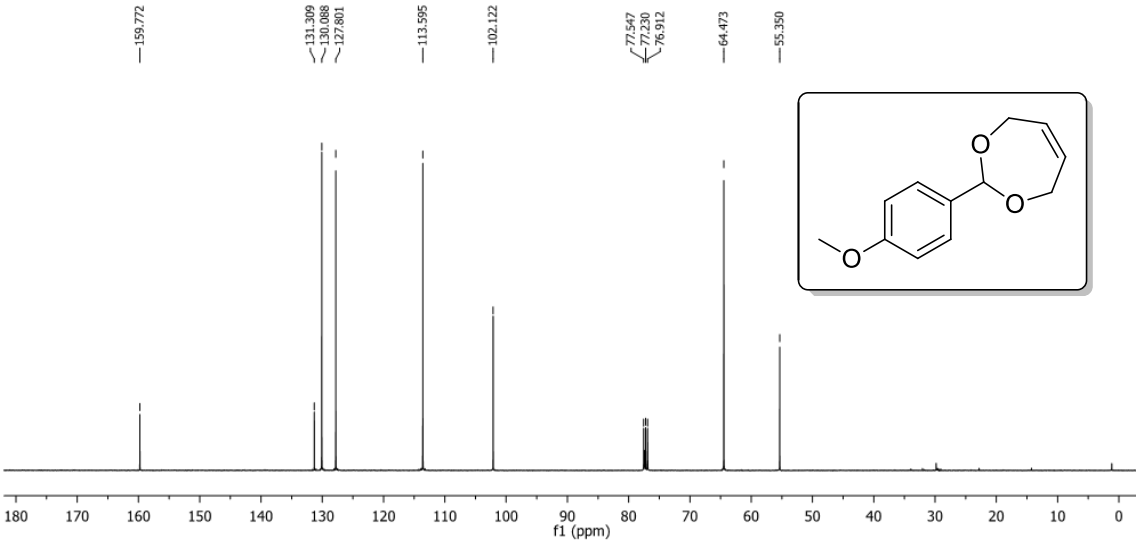


Figure 2.6.1.30. ^{13}C-NMR spectrum of 2-(4-Methoxyphenyl)-4,7-dihydro-1,3-Dioxepine (entry 12, Table 2.1.3)

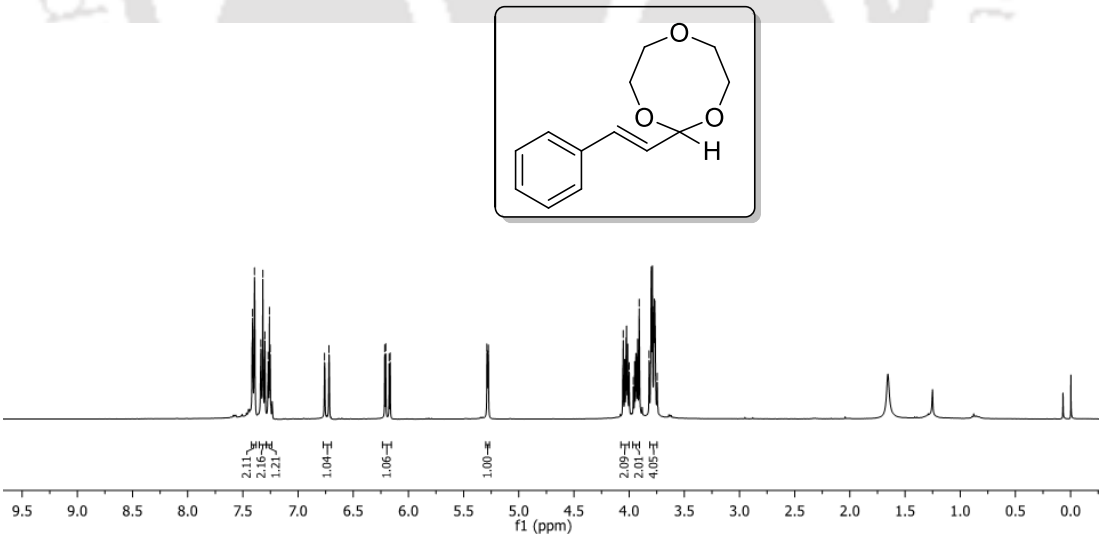


Figure 2.6.1.31. ^{1}H-NMR spectrum of (E)-2-styryl-1,3,6-trioxocane (entry 13, Table 2.1.3)

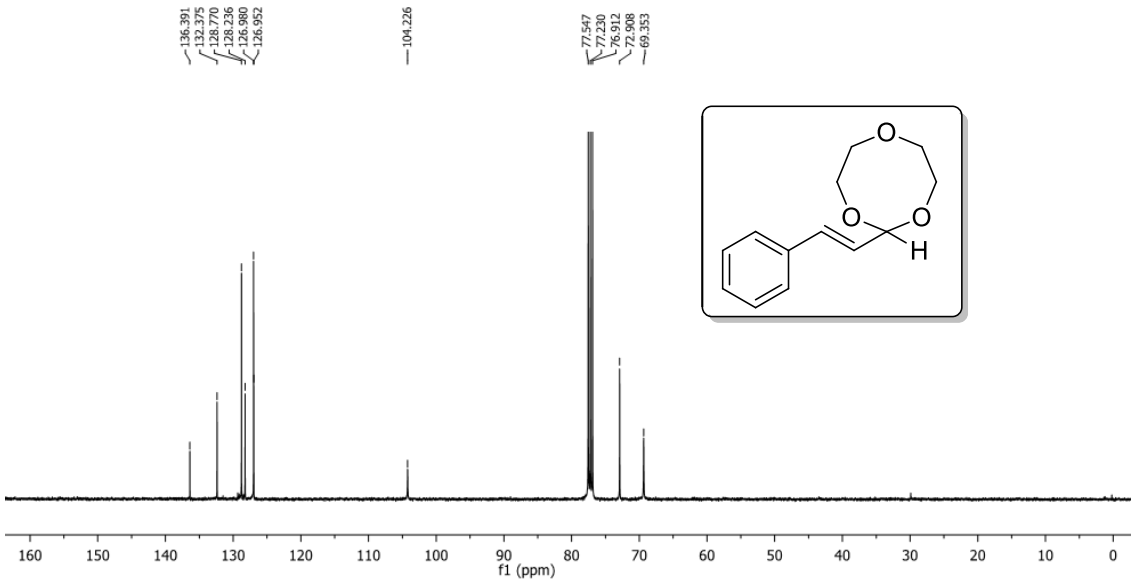
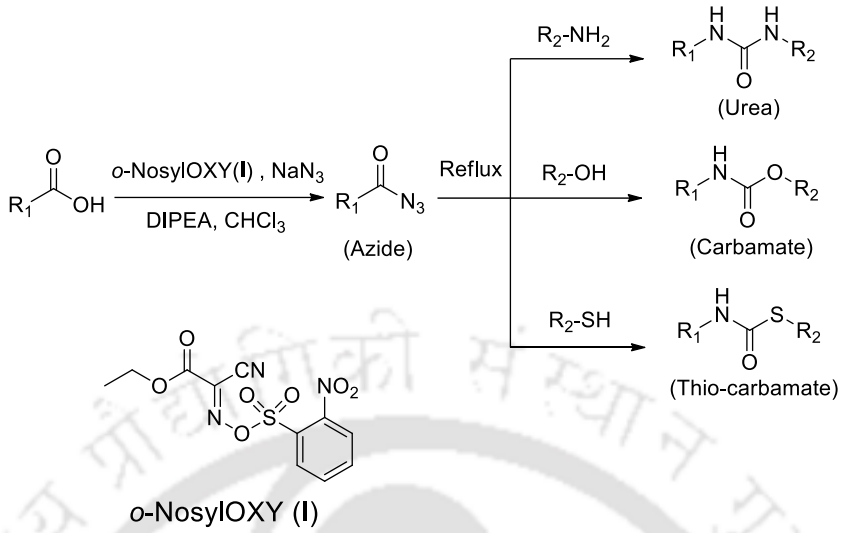


Figure 2.6.1.32. ^{13}C-NMR spectrum of (E)-2-styryl-1,3,6-trioxocane (entry 13, Table 2.1.3)

Chapter 3: *o*-NosylOXY Mediated Racemization Free Synthesis of Ureas, Carbamates, and Thiocarbamates via Curtius Rearrangement

In the previous chapter, we described the application of ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxy imino)acetate (*o*-NosylOXY, **I**) for the synthesis of acetals and thioacetals from aldehydes. In continuation to that, this chapter demonstrates another application of *o*-NosylOXY to synthesize ureas, carbamates, and thiocarbamates via Curtius rearrangement. Urea and carbamate derivatives are present in many biologically active compounds, dyes, pesticides, and antioxidants in gasoline.[88] Many methods have already been published to synthesize ureas (Chapter 1, section 1.4.2), but drawbacks are still associated. Involvement of costly and harsh reagents, the difficulties of removing the by-products, and racemization are a few of them. Here, we report the synthesis of ureas, carbamates, di-peptidyl ureas, and thiocarbamates from carboxylic acids via Curtius rearrangement using *o*-NosylOXY (*Scheme 3.1*). The process is racemization-free, and a detailed NMR study is also performed to determine the reaction pathway. This protocol is compatible with aromatic carboxylic acids, including N-protected amino acids. Various amines such as methyl esters of amino acids, aromatic amines, tertiary butylamine, and alcohols are used as a nucleophile to give the products. Broad substrate scope, minimal waste generation, racemization suppression, recyclability of the reagent make this methodology a useful one.



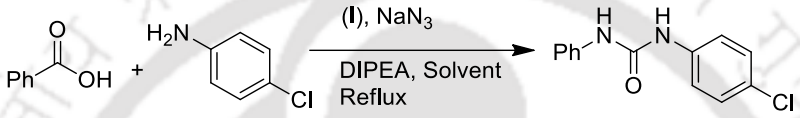
Scheme 3.1. Synthesis of urea, carbamate, and thiocarbamate using *o*-NosylOXY via Curtius rearrangement

3.1. Reaction optimization and substrate scope of synthesis of ureas and carbamates using *o*-NosylOXY (I)

In this current study, carboxylic acid was first pre-activated with *o*-NosylOXY, which converted to acid azide after the addition of sodium azide. Then, under the heating condition, acid azide rearranged to isocyanate, which was *in situ* trapped by the nucleophile such as amine, alcohol, and thiol to give urea, carbamate, and thiocarbamate, respectively. For optimization of the reaction conditions, benzoic acid (1 equiv) was used as model acid, 4-chloroaniline (1.2 equiv) as amine, and DIPEA (2.2 equiv) as the base. We tried the reaction in different solvents like $CHCl_3$, ACN, EtOAc, MeOH, and THF applying reflux conditions. In EtOAc and MeOH, low yields were obtained compared to the other solvents, even at a longer reaction time. We also examined the effect of adding different equivalents of *o*-NosylOXY (*Table 3.1.1, entry 7-9*). It was analyzed that the yield of the reaction is directly proportional to the amount of the reagent, and no reaction

happened in the absence of the reagent (*Table 3.1.1, entry 9*). Chloroform was the best solvent giving 82% yield (*Table 3.1.1, entry 5*) under 5 hours of reflux with one equiv. of **I**. Like ureas, we also obtained carbamates and thiocarbamates in good yield with this same optimized reaction condition.

Table 3.1.1. Optimization of the reaction conditions[a]



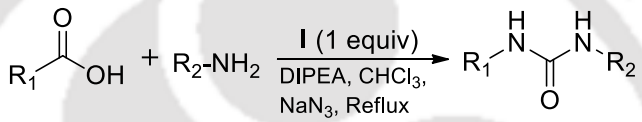
Entry	Solvent	(*o*-NosylOXY)(equiv.)	Time (hour)[b]	Yield(%)[c]
1	THF	1	7	78
2	EtOAc	1	12	52
3	ACN	1	10	69
4	MeOH	1	12	62
5	**$CHCl_3$**	**1**	**5**	**82**
6	$CHCl_3$	1	12	82
7	$CHCl_3$	0.5	12	40
8	$CHCl_3$	0.2	12	15
9	$CHCl_3$	0	24	0

[a] Reaction Condition: benzoic acid (0.5 mmol), DIPEA (1.1 mmol), NaN_3 (0.75 mmol), 4-chloroaniline (0.6 mmol), solvent (5 ml); temperature: first 30 min at 0 °C, then reflux for 30 min, then added amine and continued the reflux till reaction completed. [b] Reflux time after the addition of amine. [c] Isolated yield.

Using this optimized reaction condition, we prepared various substrates of ureas and di-peptidyl ureas. We used aromatic carboxylic acids containing methoxy, iodo, bromo, and methyl as substituents for urea synthesis (*Table 3.1.2*). It worked well with aromatic and aliphatic amines such as cyclohexylamine, benzylamine, aniline, chloroaniline, and tert-butylamine. A few examples of di-peptidyl ureas were obtained from amino acids with N-

protecting groups such as Boc, Fmoc, Cbz, and tert-butyl protected OH group (*Table 3.1.2, entry 9-12*). Sterically hindered amino acids like phenyl glycine, phenylalanine, and serine gave a satisfactory yield of 69-74%. In this case, methyl esters of phenyl glycine, glycine, phenylalanine were used as the nucleophile. Previously, for this kind of rearrangement, toluene was considered a suitable solvent. But in this methodology, the use of chloroform eliminates the difficulties of removing such high boiling solvent.

Table 3.1.2. Synthesis of ureas using *o*-NosylOXY[a]



R_1 = Aryl group, N-protected aminoacids
R_2 = Aryl, alkyl or methyl esters of amino acid
12 examples (69 to 82% yield)

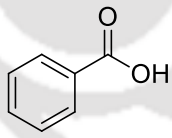
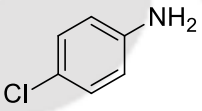
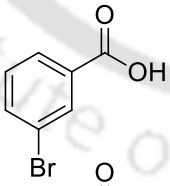
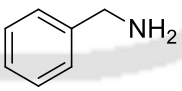
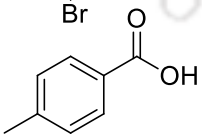
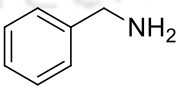
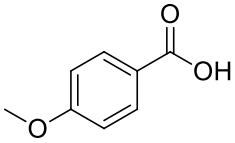
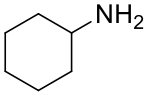
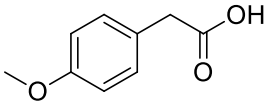
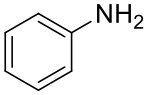
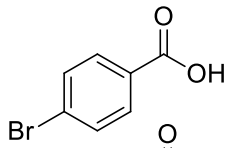
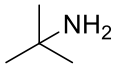
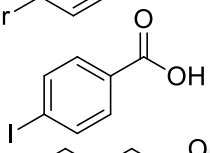
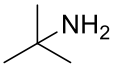
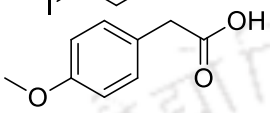
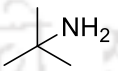
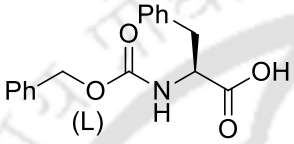
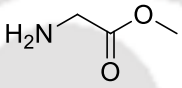
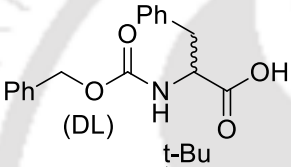
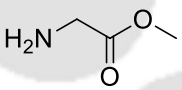
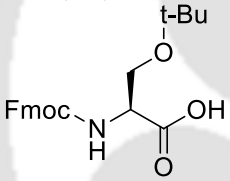
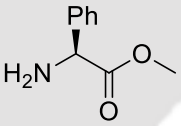
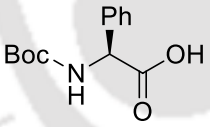
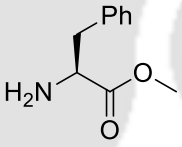
Entry	R_1COOH	R_2NH_2	Product id	Yield (%)[b]
1			3a	82
2			3b	78
3			3c	80
4			3d	76
5			3e	81

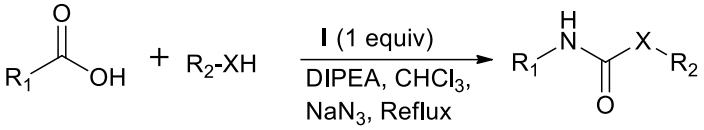
Table 3.1.2 continued…

6			3f	80
7			3g	77
8			3h	81
9			3i	74
10			3j	73
11			3k	69
12			3l	71

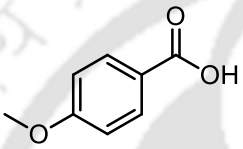
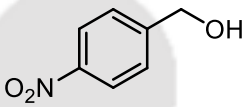
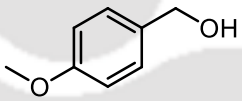
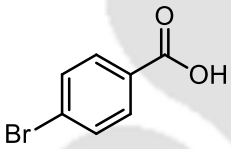
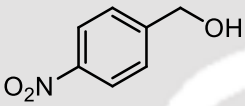
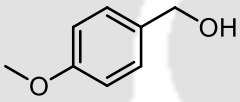
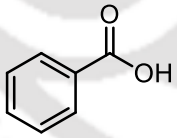
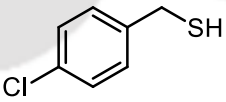
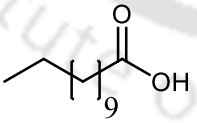
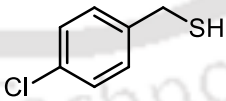
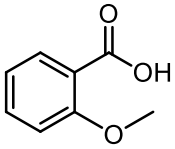
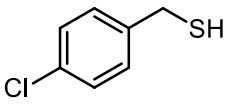
[a] Reaction Condition: acid (0.5 mmol), o-NosylOXY (0.5 mmol), DIPEA (1.1 mmol), NaN_3 (0.75 mmol, dissolved in 0.5 ml of DMSO), amine (0.6 mmol), chloroform (5 ml); temperature: first 30 min at 0 ℃, then reflux for 30 min and then continued the reflux for about 5 h after the addition of amine, total reaction time 6-7 h . [b] Isolated yield.

After successfully synthesizing ureas and di-peptidyl ureas, we extended the methodology to synthesize carbamates and thiocarbamates (*Table 3.1.3*). A total of seven examples were reported with 70-82% yield. It was observed that thiocarbamates were giving a slightly better result as compared to carbamates.

Table 3.1.3. Synthesis of carbamates and thiocarbamates using *o*-NosylOXY[a]



R_1, R_2 = Aryl, Alkyl group
X = O, S; 7 examples (70 to 82% yield)

Entry	R_1COOH	R_2XH (X= O,S)	Product id	Yield (%)[b]
1			6a	72
2			6b	76
3			6c	70
4			6d	75
5			6e	80
6			6f	82
7			6g	79

[a] Reaction Condition: acid (0.5 mmol), o-NosylOXY (0.5 mmol), DIPEA (1.1 mmol), NaN_3 (0.75 mmol, dissolved in 0.5 ml of DMSO), alcohol / thiol (0.6 mmol), chloroform (5 ml); temperature: first 30 min at 0 °C, then reflux for 30 min and then continued the reflux for about 5 h after the addition of alcohol/thiol, total reaction time 6-7 h . [b] Isolated yield.

A few recent methodologies with good yield are mentioned below. An efficient method for *N,N′*-di- and *N,N,N′*-trisubstituted ureas synthesis via Pd-catalyzed cross-coupling of aryl chlorides and triflates with sodium cyanate was reported with almost 67-88% yield.[76] N^{α}-Fmoc-peptide isocyanates were synthesized by the Curtius Rearrangement of N^{α}-Fmoc-peptide acid azides under the thermal condition with 71-94% yield.[73] These isocyanates were coupled with bis-TMS/tris-TMS amino acids, and N^{α}-Fmoc-peptidyl urea acids were obtained with almost 88-89% yield.

3.2. Racemization study

To investigate the stereochemical aspects, we synthesized Cbz-DL-Phe-Gly-OMe and Cbz-L-Phe-Gly-OMe using *o*-NosylOXY and the same reaction conditions. We compared the HPLC spectra of both the isomers (*Figure 3.2.1*). In the HPLC chromatogram, two distinct peaks were obtained for the DL analog corresponds to two enantiomers. However, a single peak was observed for the L isomer while run through a chiral column in the same isocratic solvent system (*Figure 3.7.2.1-3.7.2.2*). From that, we can conclude that no detectable racemization happened during the rearrangement.

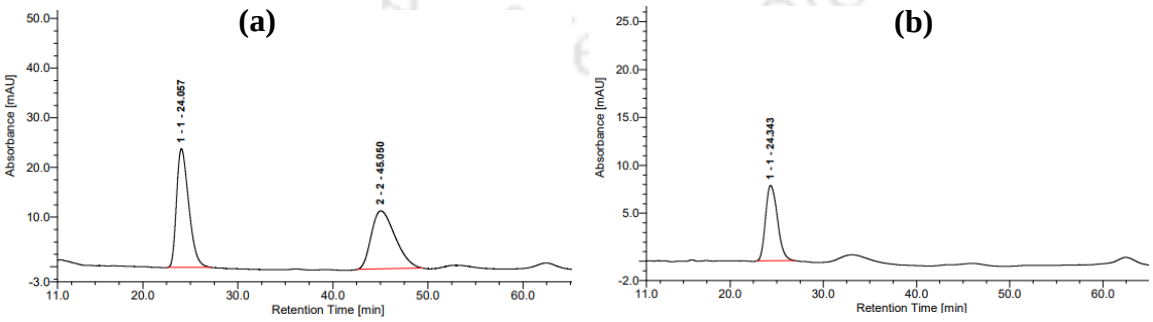
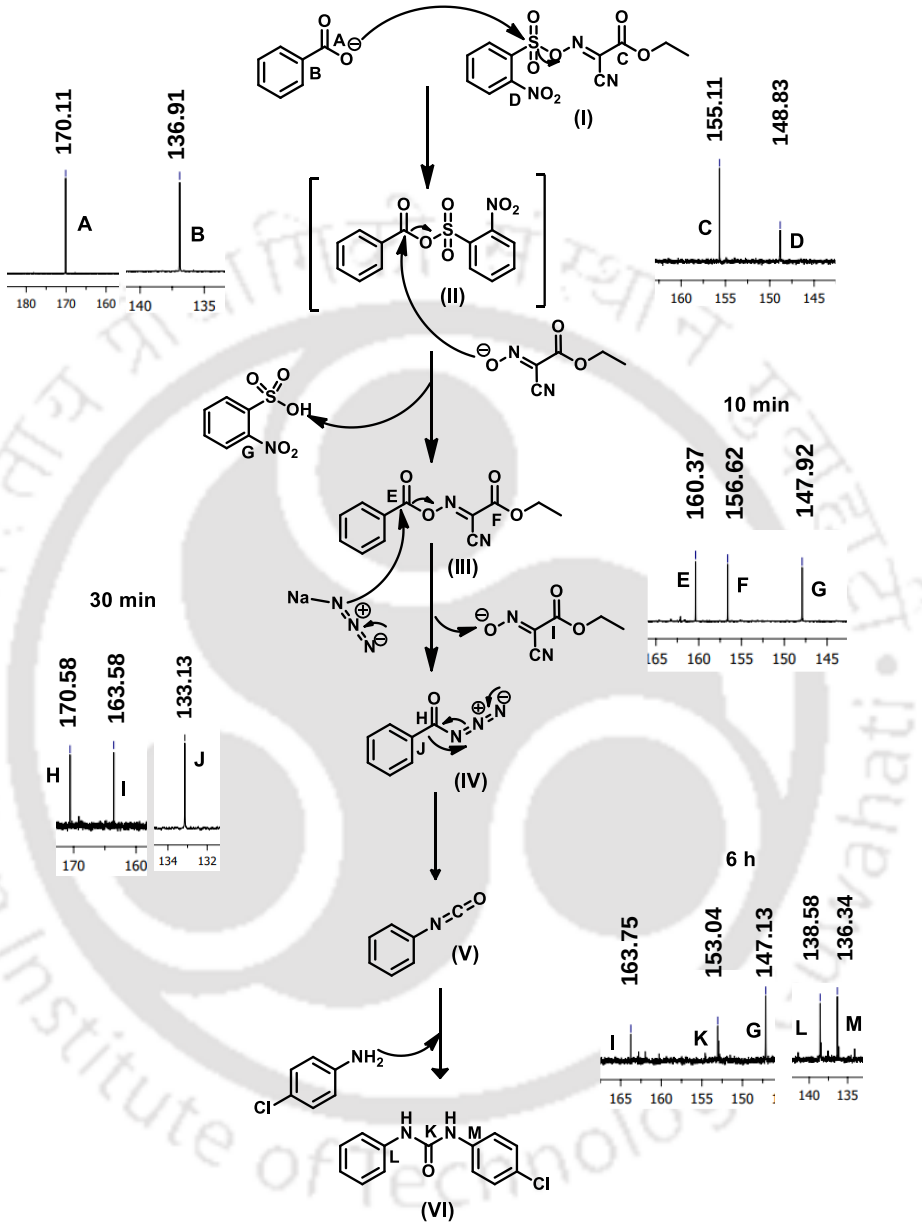


Figure 3.2.1. HPLC profile of products (a) DL & (b) L form of Cbz-Phe-Gly-Ome urea

3.3. Mechanism study



Scheme 3.3.1. A plausible mechanism for urea synthesis by *o*-NosylOXY (**I**)

A plausible reaction mechanism to synthesize urea from a carboxylic acid using *o*-NosylOXY is shown in scheme 3.3.1. The carboxylic acid is deprotonated using base DIPEA, which attacks the electrophilic center of **I,** forming an Oxyma ester of carboxylic

acid (**III**) via unstable intermediate (**II**). In this step, 2-nitrobenzenesulfonic acid is released as a by-product. Then, sodium azide reacts with **III** and is converted to carboxylic acid azide (**IV**) by releasing Oxyma. Finally, **IV** rearranges to unstable isocyanate (**V**) under the refluxing condition, trapped by an amine, producing the desired urea (**VI**).

We performed a time-dependent NMR study (*Figure 3.7.3.1-3.7.3.8*) with benzoic acid (1 equiv), **I** (1 equiv), DIPEA (2.2 equiv), sodium azide (1.5 equiv), 4-chloroaniline (1.2 equiv) in $CDCl_3$ to support the proposed mechanism. We observed noticeable changes in ^{13}C NMR Spectra while recorded at specific time intervals. Peak **A** at 170.11 ppm and peak **B** at 136.91 ppm corresponds to the carbonyl carbon of acid anion and the carbon attached to it, respectively (*Figure 3.7.3.1*). Similarly, peaks at 155.11 and 148.83 ppm (**C** and **D**) correspond to the carbonyl carbon and the NO_2 group attached carbon of **I** (*Figure 3.7.3.2*). The formation of the Oxyma ester of benzoic acid (**III**) was evident by the appearance of the new peaks at 160.37, 156.62 ppm (**E** and **F**) when spectra were recorded after 10 min of the reaction (*Figure 3.7.3.5*). Again, the peak at 147.92 ppm (**G**) corresponds to the NO_2 group attached carbon of the by-product 2-nirobenzenesulfonic acid (*Figure 3.7.3.5*). After 30 min of addition of sodium azide to the reaction mixture, shifting of the peak **E** and **F** occurred to 170.58 and 163.58 ppm (**H** and **I**), which indicates to the azide group (CON_3) of **IV** and the carbonyl group of the Oxyma anion, respectively (*Figure 3.7.3.6*). We also noticed the peak at 133.13 ppm (**J**) represents the carbon attached to the CON_3 group (*Figure 3.7.3.6*). The reaction was refluxed for 30 min, and then 4-chloroaniline was added to it. Finally, one new peak at 153.04 ppm (**K**) confirmed the formation of urea (**VI**) when spectra were recorded after 6 hours (*Figure 3.7.3.8*). The rearrangement probably went via isocyanate (**V**), but we could not get any

trace of it due to its transient nature. The by-products Oxyma and 2-nitrobenzenesulfonic acid remained (**I** and **G**) till the end of the reaction.

We synthesized benzoyl azide (**IV**) and well-characterized it via ^{1}H and ^{13}C NMR spectroscopy (*Figure 3.7.4.1-3.7.4.2*). The sharp peak at 2133 cm^{-1} in IR spectra confirms the presence of the azide group (*Figure 3.3.1*).

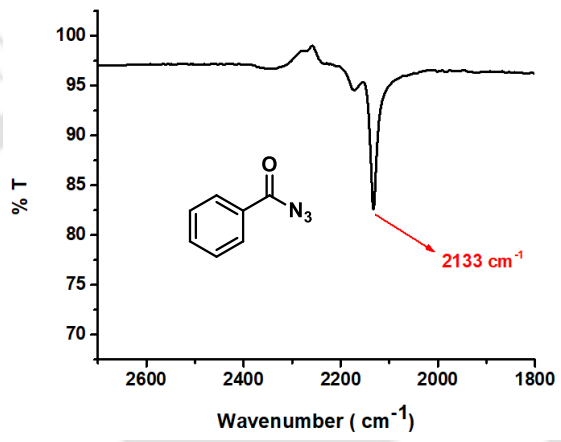


Figure 3.3.1. FT-IR spectra of benzoyl azide (**IV**)

3.4. Conclusions

In conclusion, we have reported a highly efficient method for the Curtius rearrangements of carboxylic acids into ureas, carbamates, and thiocarbamates in one pot using *o*-NosylOXY (**I**) under ambient conditions. A plausible mechanism is suggested, and the time-dependent NMR study supports it. Again, it is worthy of mentioning that the process is racemization free which is checked using HPLC. The by-products formed during the reaction can be recovered and reused to synthesize the *o*-NosylOXY again. Therefore, this methodology is a cost-effective and environmentally friendly alternative to the other existing ones.

3.5. Experimental Section

3.5.1. General consideration

All chemicals were purchased from commercial sources and used without any purification. Chloroform was distilled via the standard procedure. Reactions were observed using thin-layer chromatography. Chromatograms were run in the glass plate coated with silica gel G and silica gel GF254 using EtOAc/Hexane as the solvent. Column chromatography was used as a purification technique (Silica gel, 60-120 mesh, EtOAc/Hexane as eluent). Solvents are removed under reduced pressure using the Buchi rotary evaporator. ^{1}H NMR (600 and 400 MHz) and ^{13}C NMR (150 and 100 MHz) were recorded using $CDCl_3$, CD_3OD, DMSO-d_6 as solvents and tetramethylsilane as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (*J*) are given in Hz. Abbreviations to denote the multiplicity of the signals are s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). High-resolution mass spectra were recorded on a Q-TOF ESI-MS instrument. HPLC analysis was carried out with a chiral column (5 µm, 2.1×150 mm) and C18 (4 µm, 4.6×100 mm) reverse-phase column coupled to a UV detector. HPLC grade solvents were used for HPLC analysis. FT-IR spectra and melting points were recorded on Perkin Elmer FT-IR Spectrometer and Buchi melting point apparatus, respectively.

3.5.2. General procedure for the synthesis of ureas, carbamates, and thiocarbamates

o-NosylOXY (reagent **I**, 0.5 mmol, 1 equiv) was added to a stirred solution of carboxylic acid / N-protected amino acid (0.5 mmol, 1 equiv) and DIPEA (1.1 mmol, 2.2 equiv) in distilled chloroform (5 ml) at room temperature. The reaction mixture was stirred for

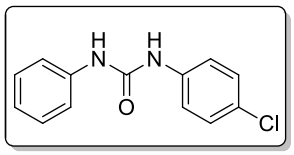
about 10 min, followed by the addition of sodium azide (0.75 mmol, 1.5 equiv) dissolved in 0.5 ml of DMSO at 0 ℃. The reaction was allowed to continue for another 20 min (in case of amino acid 45 min), maintaining 0 ℃ till complete conversion into azides checked by TLC. Then the reaction mixture was refluxed for about 30 min followed by the addition of amine/methyl ester of amino acid/alcohol/thiol (0.6 mmol, 1.2 equiv) and continued for about 5 hours. After completion of the reaction, the solvent was evaporated using a rotary evaporator, and 20 ml of ethyl acetate was added to the reaction mixture, washed with 5% citric acid (2 × 5 ml), 5% $NaHCO_3$ (2 × 5 ml), saturated NaCl (2 × 5 ml) solution and dried over anhydrous Na_2SO_4. The organic phase was evaporated, and the residue was purified on silica gel column chromatography using hexane and ethyl acetate.

3.5.3. Procedure for the synthesis of benzoyl azide (IV, Scheme 3.3.1)

o-NosylOXY (reagent **I**, 0.5 mmol, 1 equiv) was added to a stirred solution of benzoic acid (0.5 mmol, 1 equiv) and DIPEA (0.5 mmol, 1 equiv) in distilled chloroform (5 ml) at room temperature. The reaction mixture was stirred for about 10 min, followed by the addition of sodium azide (0.75 mmol, 1.5 equiv) dissolved in 0.5 ml of DMSO at 0 ℃ and allowed to continue for another 20 min. The solvent was evaporated using a rotary evaporator, and 20 ml of ethyl acetate was added to the reaction mixture, washed with 5% citric acid (2 × 5 ml), 5% $NaHCO_3$ (2 × 5 ml), saturated NaCl (2 × 5 ml) solution and dried over anhydrous Na_2SO_4. The organic phase was evaporated, and the residue was purified on silica gel column chromatography using hexane and ethyl acetate.

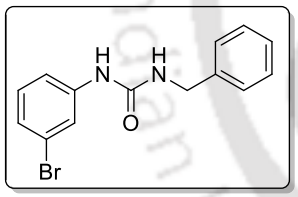
3.6. Characterization data

1-(4-chlorophenyl)-3-phenylurea (entry 1, Table 3.1.2)



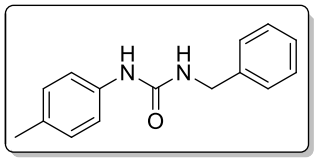
Yield: 100 mg (82%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 239-241 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.87 (s, 1H), 8.76 (s, 1H), 7.55-7.53 (d, *J* = 9 Hz, 2H), 7.51-7.50 (d, *J* = 7.8 Hz, 2H), 7.39-7.37 (d, *J* = 9 Hz, 2H), 7.35-7.32 (t, *J* = 8.4 Hz, 2H), 7.04-7.02 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 152.8, 139.9, 139.1, 129.2, 129.1, 125.7, 122.4, 120.1, 118.7; FT-IR (KBr): 3440, 2922, 2852, 1636, 1594, 1563 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{13}H_{11}ClN_2O$ 247.0638, found 247.0638.

1-benzyl-3-(3-bromophenyl)urea (entry 2, Table 3.1.2)



Yield: 118 mg (78%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 163-165 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.78 (s, 1H), 7.82 (s, 1H), 7.33-7.28 (m, 4H), 7.24-7.22 (t, *J* = 6.6 Hz, 2H), 7.18-7.15 (t, *J* = 7.8 Hz, 1H), 7.06-7.05 (d, *J* = 7.8 Hz, 1H), 6.72-6.70 (t, *J* = 5.4 Hz, 1H), 4.28 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 155.0, 142.2, 140.2, 130.6, 128.3, 127.1, 126.8, 123.6, 121.7, 119.9, 116.5, 42.7; FT-IR (KBr): 3320, 2926, 2871, 1629, 1552, 1232 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{14}H_{13}BrN_2O$ 305.0290, found 305.0297.

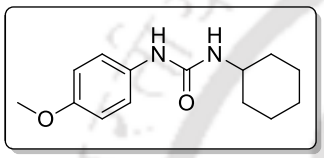
1-benzyl-3-(p-tolyl)urea (entry 3, Table 3.1.2)



Yield: 96 mg (80%); white solid; R_f = 0.50 (EtOAc:Hexane, 2.5:7.5); mp: 176-178 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ

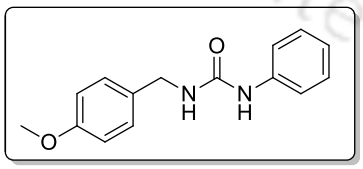
8.44 (br s, 1H), 7.34-7.32 (t, *J* = 7.8 Hz, 2H), 7.30-7.28 (t, *J* = 7.2 Hz, 4H), 7.25-7.23 (t, *J* = 7.2 Hz, 1H), 7.03-7.02 (d, *J* = 7.8 Hz, 2H), 6.56 (br s, 1H), 4.28 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 155.3, 140.4, 137.9, 129.8, 129.1, 128.3, 127.1, 126.7, 117.8, 42.7, 20.3; FT-IR (KBr): 3309, 2920, 2877, 1626, 1449, 810 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$, calculated for $C_{15}H_{16}N_2O$ 241.1341, found 241.1345.

1-cyclohexyl-3-(4-methoxyphenyl)urea (entry 4, Table 3.1.2)



Yield: 94 mg (76%); white solid; R_f = 0.50 (EtOAc:Hexane, 2.5:7.5); mp: 180-182 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.07 (br s, 1H), 7.26-7.25 (d, *J* = 9 Hz, 2H), 6.80-6.79 (d, *J* = 9 Hz, 2H), 5.92 (br s, 1H), 2.51-2.50 (m, 1H), 1.80-1.77 (m, 2H), 1.66-1.64 (m, 2H), 1.54-1.52 (m, 1H), 1.32-1.26 (m, 2H), 1.17-1.11 (m, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 154.7, 153.8, 133.7, 119.2, 113.9, 55.1, 47.6, 33.1, 25.3, 24.4; FT-IR (KBr): 3306, 2931, 2849, 1629, 1566, 1245 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{14}H_{20}N_2O_2$ 249.1603, found 249.1604.

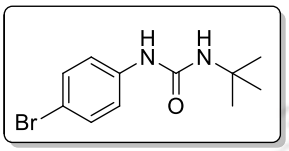
1-(4-methoxybenzyl)-3-phenylurea (entry 5, Table 3.1.2)



Yield: 103 mg (81%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 130-132 °C; ^{1}H NMR (600 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 7.27-7.25 (m, 4H), 7.21-7.19 (d, *J* = 12.6 Hz, 2H), 7.07-7.03 (m, 1H), 6.84-6.82 (d, *J* = 12.6 Hz, 2H), 6.72 (br s, 1H), 5.27 (br s, 1H), 4.32 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 159.0, 156.2, 138.9, 131.3, 129.2, 128.9,

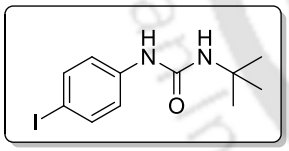
123.4, 120.4, 114.1, 55,4, 43.6; FT-IR (KBr): 3320, 2915, 2852, 1631, 1552, 1240 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{15}H_{16}N_2O_2$ 257.1290, found 257.1295.

1-(4-bromophenyl)-3-(tert-butyl)urea (entry 6, Table 3.1.2)



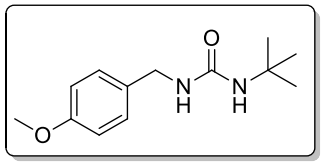
Yield: 108 mg (80%); light yellow solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 199-201 °C; ^{1}H NMR (600 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 7.80 (br s, 1H), 7.30-7.24 (m, 2H), 7.15-7.14 (d, *J* = 8.4 Hz, 2H), 5.63 (br s, 1H), 1.28 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 155.5, 138.8, 131.6, 120.3, 114.2, 50.2, 29.1; FT-IR (KBr): 3323, 2966, 2928, 1648, 1487, 1210 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{11}H_{15}BrN_2O$ 271.0446, found 271.0449.

1-(tert-butyl)-3-(4-iodophenyl)urea (entry 7, Table 3.1.2)



Yield: 122 mg (77%); white solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 178-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.74 (d, *J* = 8 Hz, 1H), 7.65-7.63 (d, *J* = 7.6 Hz, 1H), 7.21-7.15 (m, 1H), 6.70-6.62 (m, 1H), 5.56 (br s, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 154.8, 139.9, 139.1, 129.0, 124.9, 122.8, 91.1, 50.8, 29.3; FT-IR (KBr): 3301, 2961, 2923, 1650, 1509, 1210 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{11}H_{15}IN_2O$ 319.0307, found 319.0309.

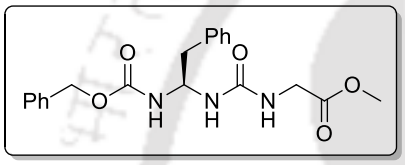
1-(tert-butyl)-3-(4-methoxybenzyl)urea (entry 8, Table 3.1.2)



Yield: 95 mg (81%); yellow solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 96-98 °C; ^{1}H NMR (400

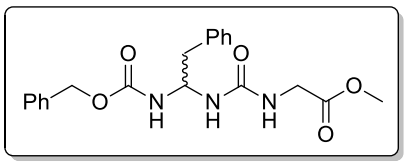
MHz, $CDCl_3$): δ 7.13-7.11 (d, *J* = 8.4 Hz, 2H), 6.79-6.77 (d, *J* = 8.4 Hz, 2H), 5.16 (br s, 1H), 4.85 (br s, 1H), 4.13 (s, 2H), 3.74 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 158.8, 158.0, 131.9, 128.7, 114.0, 55.4, 50.3, 43.6, 29.6; FT-IR (KBr): 3358, 2964, 2917, 1629, 1509, 1245 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{13}H_{20}N_2O_2$ 237.1603, found 237.1605.

(S)-methyl 5-benzyl-3,7-dioxo-1-phenyl-2-oxa-4,6,8-triazadecan-10-oate (entry 9, Table 3.1.2)



Yield: 142 mg (74%); white solid; R_f = 0.50 (EtOAc:Hexane, 7.0:3.0); mp: 160-162 °C; ^1H NMR (600 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 7.37-7.18 (m, 10H), 6.04 (br s, 1H), 5.23 (br s, 1H), 5.05 (s, 2H), 3.92 (s, 2H), 3.71 (s, 3H), 3.18-3.08 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 171.7, 157.9, 156.4, 136.8, 136.2, 129.3, 128.5, 128.4, 128.1, 127.7, 126.7, 66.6, 60.4, 52.1, 41.6, 40.2; FT-IR (KBr): 3483, 3290, 2950, 2858, 1691, 1533, 1237 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{20}H_{23}N_3O_5$ 386.1716, found 386.1732.

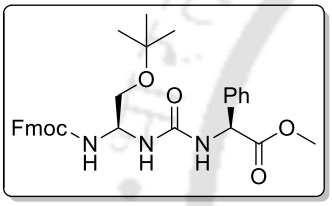
Methyl 5-benzyl-3,7-dioxo-1-phenyl-2-oxa-4,6,8-triazadecan-10-oate (entry 10, Table 3.1.2)



Yield: 140 mg (73%); white solid; R_f = 0.50 (EtOAc:Hexane, 7.0:3.0); mp: 160-162 °C; ^1H NMR (600 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 7.33-7.12 (m, 10H), 6.38 (br s, 1H), 6.21 (br s, 1H), 5.17 (br s, 1H), 5.02 (s,

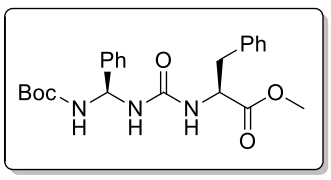
2H), 3.89 (s, 2H), 3.70 (s, 3H), 3.15-3.03 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 171.7, 157.8, 156.4, 136.8, 136.3, 129.4, 128.6, 128.5, 128.1, 127.8, 126.8, 66.7, 60.6, 52.2, 41.7, 40.2; FT-IR (KBr): 3391, 3295, 2917, 2849, 1697, 1648, 1226 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{20}H_{23}N_3O_5$ 386.1716, found 386.1727.

(5S,9S)-methyl 5-(tert-butoxymethyl)-1-(9H-fluoren-9-yl)-3,7-dioxo-9-phenyl-2-oxa-4,6,8-triazadecan-10-oate (entry 11, Table 3.1.2)



Yield: 188 mg (69%); light yellow solid; R_f = 0.50 (EtOAc:Hexane, 5.0:5.0); mp: 161-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$,): δ 7.69-7.67 (d, *J* = 7.6 Hz, 2H), 7.45-7.41 (t, *J* = 8 Hz, 2H), 7.33-7.10 (m, 9H), 6.81 (br s, 1H), 5.79 (br s, 1H), 5.53 (br, s, 1H), 5.43-5.41 (d, *J* = 7.2 Hz, 1H), 5.34-5.30 (t, *J* = 8.8 Hz, 1H), 4.24-4.12 (m, 2H), 4.05-3.96 (m, 1H), 3.60 (s, 3H), 3.53-3.42 (m, 2H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 172.3, 156.6, 156.4, 143.9, 141.4, 137.1, 128.8, 128.4, 127.9, 127.5, 127.2, 125.2, 120.1, 74.1, 67.4, 63.9, 58.9, 57.5, 52.7, 47.1, 27.5; FT-IR (KBr): 3317, 3067, 2977, 2923, 1694, 1642, 1243 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{31}H_{35}N_3O_6$ 546.2604 found 546.2716.

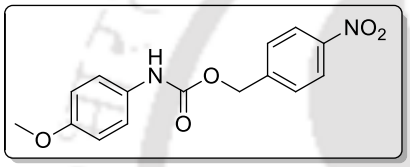
(2S,6S)-methyl 2-benzyl-10,10-dimethyl-4,8-dioxo-6-phenyl-9-oxa-3,5,7-triazaundecan-1-oate (entry 12, Table 3.1.2)



Yield: 151 mg (71%); white solid; R_f = 0.50 (EtOAc:Hexane, 5.0:5.0); mp: 170-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$,): δ 7.33-7.32 (d, *J* = 4.4 Hz, 4H), 7.27-7.20

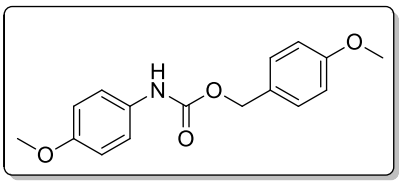
(m, 4H), 7.12-7.10 (d, *J* = 6.8 Hz, 2H), 6.15-6.11 (t, *J* = 8 Hz, 1H), 5.97 (br s, 1H), 5.84 (br, s, 1H), 5.72 (br s, 1H),4.76-4.71 (m, 1H), 3.63 (s, 3H), 3.12-3.07 (m, 1H), 3.03-2.98 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 173.2, 156.7, 155.6, 139.7, 136.5, 129.5, 128.8, 128.6, 128.1, 127.0, 125.9, 80.6, 61.3, 54.4, 52.3, 38.6, 28.5; FT-IR (KBr): 3323, 3029, 2953, 2975, 1680, 1645, 1514 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calculated for $C_{23}H_{29}N_3O_5$ 450.2005 found 450.2030.

4-nitrobenzyl (4-methoxyphenyl)carbamate (entry 1, Table 3.1.3)



Yield: 108 mg (72%); light yellow solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$,): δ 8.18-8.16 (d, *J* = 8 Hz, 2H), 7.50-7.48 (d, *J* = 8 Hz, 2H), 7.24-7.22 (d, *J* = 9.6 Hz, 2H), 6.82-6.80 (d, *J* = 8.4 Hz, 2H), 6.70 (br s, 1H), 5.23 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 156.3, 153.3, 147.8, 143.8, 130.5, 128.4, 123.9, 121.0, 114.5, 66.5, 55.7; FT-IR (KBr): 3271, 3078, 2964, 2852, 1683, 1512, 1229 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{15}H_{14}N_2O_5$ 303.0981, found 303.0988.

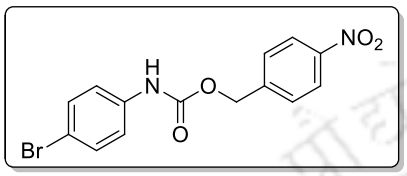
4-methoxybenzyl (4-methoxyphenyl)carbamate (entry 2, Table 3.1.3)



Yield: 109 mg (76%); light yellow solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 84-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$,): δ 7.34-7.32 (d, *J* = 8.8 Hz, 2H), 7.28-7.26 (d, *J* = 8 Hz, 2H), 6.90-6.88 (d, *J* = 8.4 Hz, 2H), 6.84-6.82 (d, *J* = 8.8 Hz, 2H), 6.63 (br s, 1H), 5.11 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 159.8, 156.1, 154.0, 131.0, 130.3, 128.4, 120.9, 114.4, 114.1, 66.9, 55.6, 55.4; FT-IR (KBr):

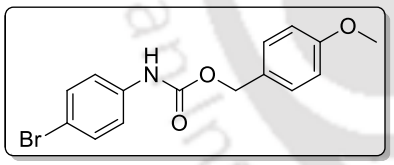
3325, 2915, 2839, 1697, 1514, 1226 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calculated for $C_{16}H_{17}NO_4$ 310.1055, found 310.1069.

4-nitrobenzyl (4-bromophenyl)carbamate (entry 3, Table 3.1.3)



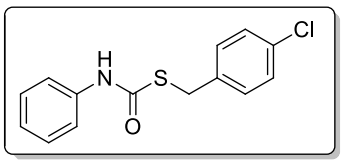
Yield: 123 mg (70%); yellow solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 163-165 °C; ^{1}H NMR (600 MHz, DMSO-d_6,): δ 10.08 (br s, 1H), 8.27-8.25 (d, *J* = 9 Hz, 2H), 7.69-7.68 (d, *J* = 8.4 Hz, 2H), 7.48-7.43 (m, 4H), 5.30 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.0, 147.1, 144.4, 138.3, 131.6, 128.5, 123.6, 120.1, 114.2, 64.6; FT-IR (KBr): 3355, 3081, 2966, 2852, 1721, 1487, 1346 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{14}H_{11}BrN_2O_4$ 352.9960, found 352.2970.

4-methoxybenzyl (4-bromophenyl)carbamate (entry 4, Table 3.1.3)



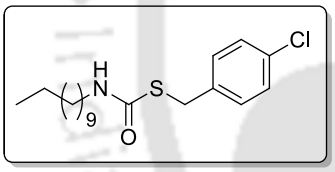
Yield: 125 mg (75%); light yellow solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 107-109 °C; ^{1}H NMR (400 MHz, $CDCl_3$,): δ 7.40-7.38 (d, *J* = 8.8 Hz, 2H), 7.34-7.32 (d, *J* = 6.8 Hz, 2H), 7.27-7.26 (d, *J* = 6.8 Hz, 2H), 6.91-6.89 (d, *J* = 8.8 Hz, 2H), 6.66 (br s, 1H), 5.12 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 160.0, 153.4, 137.1, 132.2, 130.4, 128.1, 120.4, 116.1, 114.2, 67.2, 56.5 ; FT-IR (KBr): 3331, 2915, 2849, 1699, 1520, 1221 cm^{-1}; HRMS (ESI): m/z $[M]^+$ calculated for $C_{15}H_{14}BrNO_3$ 335.0157, found 335.2310.

S-4-chlorobenzyl phenylcarbamothioate (entry 5, Table 3.1.3)



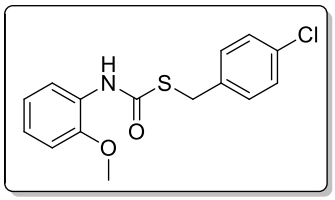
Yield: 110 mg (80%); light yellow solid; R_f = 0.50 (EtOAc:Hexane, 1.5:8.5); mp: 116-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$,): δ 7.42-7.40 (d, *J* = 7.6 Hz, 2H), 7.33 (br s, 1H), 7.32-7.26 (m, 6H), 7.15-7.11 (t, *J* = 7.2 Hz, 1H), 4.18 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 165.2, 137.6, 136.8, 133.2, 130.4, 129.3, 128.9, 124.8, 120.1, 33.9; FT-IR (KBr): 3336, 3252, 2964, 2849, 1648, 1484, 1259 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{14}H_{12}ClNOS$ 278.0406, found 278.0406.

S-4-chlorobenzyl undecylcarbamothioate (entry 6, Table 3.1.3)



Yield: 145 mg (82%); white solid; R_f = 0.50 (EtOAc:Hexane, 1.5:8.5); mp: 83-85 °C; ^{1}H NMR (600 MHz, $CDCl_3$,): δ 7.32-7.29 (m, 4H), 5.58 (br s, 1H), 4.15 (s, 2H), 3.34-3.32 (m, 2H), 1.62-1.50 (m, 2H), 1.35-1.25 (m, 16H), 0.95-0.93 (t, *J* = 6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$,): δ 166.3, 137.3, 133.0, 130.2, 128.7, 41.7, 41.6, 33.5, 32.0, 29.74, 29.72, 29.6, 29.4, 29.3, 26.9, 22.8, 14.2; FT-IR (KBr): 3276, 2923, 2849, 1631, 1523, 1215 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{19}H_{30}ClNOS$ 356.1815, found 356.1877.

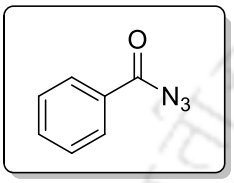
S-4-chlorobenzyl (2-methoxyphenyl)carbamothioate (entry 7, Table 3.1.3)



Yield: 121 mg (79%); yellow semi-solid; R_f = 0.50 (EtOAc:Hexane, 1.5:8.5); ^{1}H NMR (600 MHz, $CDCl_3$,): δ 8.17-8.16 (d, *J* = 7.8 Hz, 1H), 7.69 (s, 1H), 7.32-7.30 (d, *J* = 8.4 Hz, 2H), 7.28-7.26 (d, *J* = 8.4 Hz, 2H), 7.06-7.03 (t, *J* = 9 Hz, 1H), 6.97-6.94 (t, *J* =

7.8 Hz, 1H), 6.87-6.85 (d, *J* = 7.8 Hz, 1H), 4.18 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$,): δ 164.4, 147.6, 136,9, 133.1, 130.3, 128.8, 127.5, 124.0, 121.2, 119.7, 110.2, 56.7, 33.8; FT-IR (KBr): 3385, 3314, 2964, 2836, 1680, 1514, 1251 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calculated for $C_{15}H_{14}ClNO_2S$ 330.0331, found 330.0341.

benzoyl azide (IV, Scheme 3.3.1)



Yield: 65 mg (89%); yellow semi-solid; R_f = 0.50 (EtOAc:Hexane, 1.5:8.5); ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 7.90-7.88 (d, *J* = 8.4 Hz, 2H), 7.52-7.48 (t, *J* = 7.6 Hz, 1H), 7.36-7.32 (t, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 172.8, 134.4, 130.4, 129.3, 128.6; FT-IR (KBr): 2926, 2855, 2133, 1697, 1240 cm^{-1}.

3.7. Selected Spectra

3.7.1. ^{1}H NMR and ^{13}C NMR spectra of selected compounds

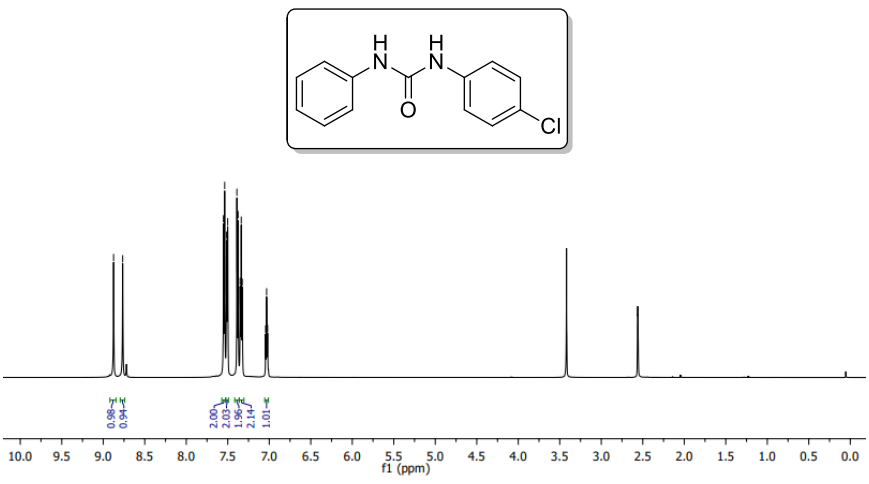


Figure 3.7.1.1. ^{1}H-NMR spectrum of 1-(4-chlorophenyl)-3-phenylurea (entry 1, Table 3.1.2)

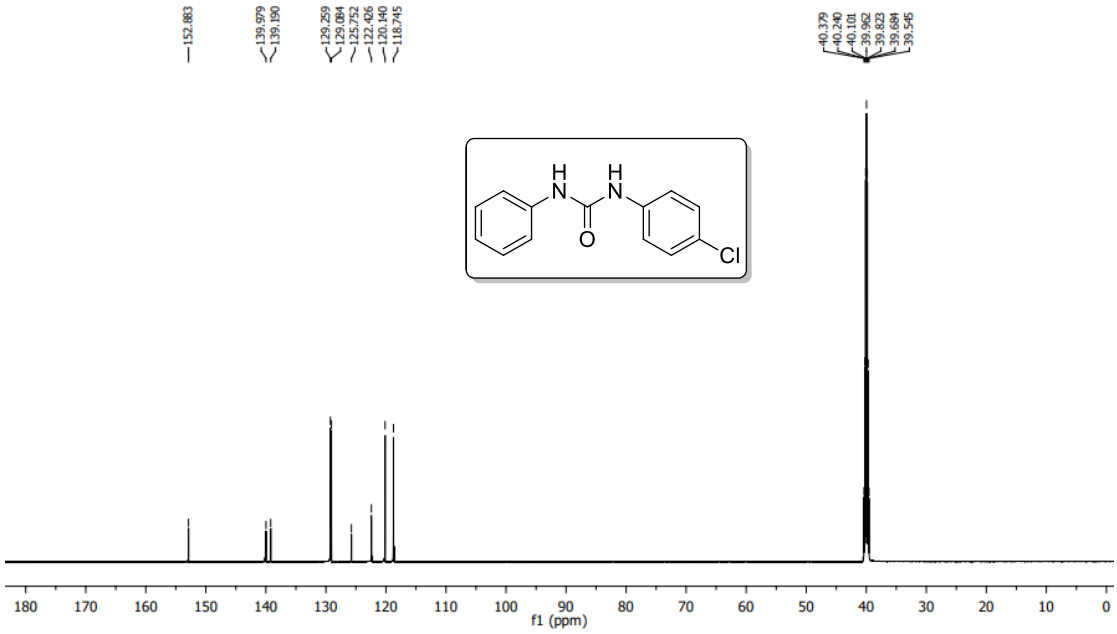


Figure 3.7.1.2. ^{13}C-NMR spectrum of 1-(4-chlorophenyl)-3-phenylurea (entry 1, Table 3.1.2)

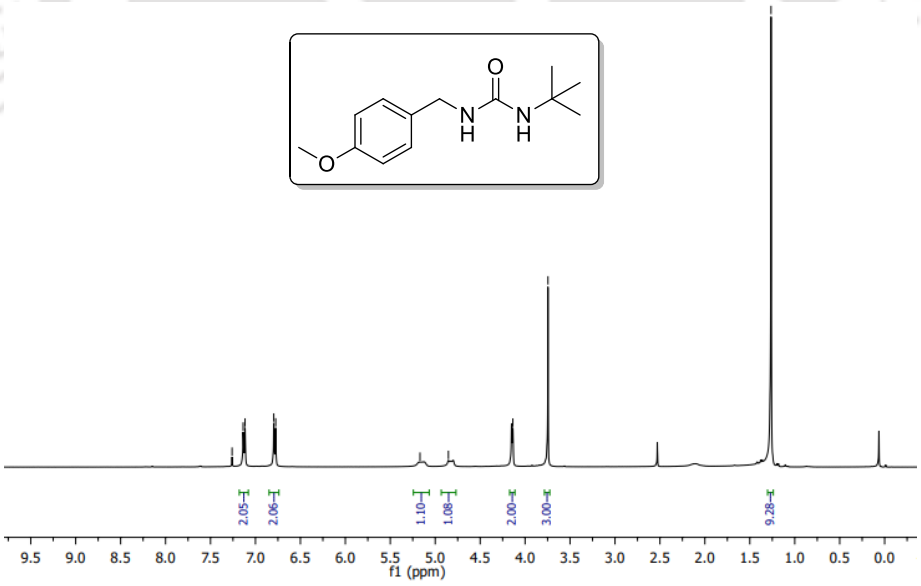


Figure 3.7.1.3. ^{1}H-NMR spectrum of 1-(tert-butyl)-3-(4-methoxybenzyl)urea (entry 8, Table 3.1.2)

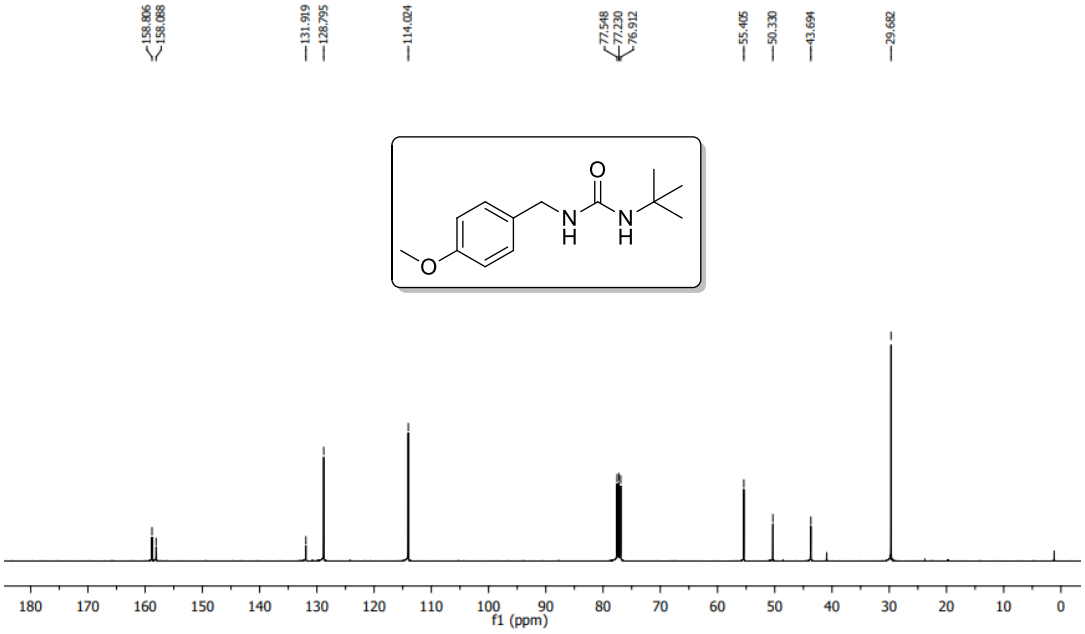


Figure 3.7.1.4. ^{13}C-NMR spectrum of 1-(tert-butyl)-3-(4-methoxybenzyl)urea (entry 8, Table 3.1.2)

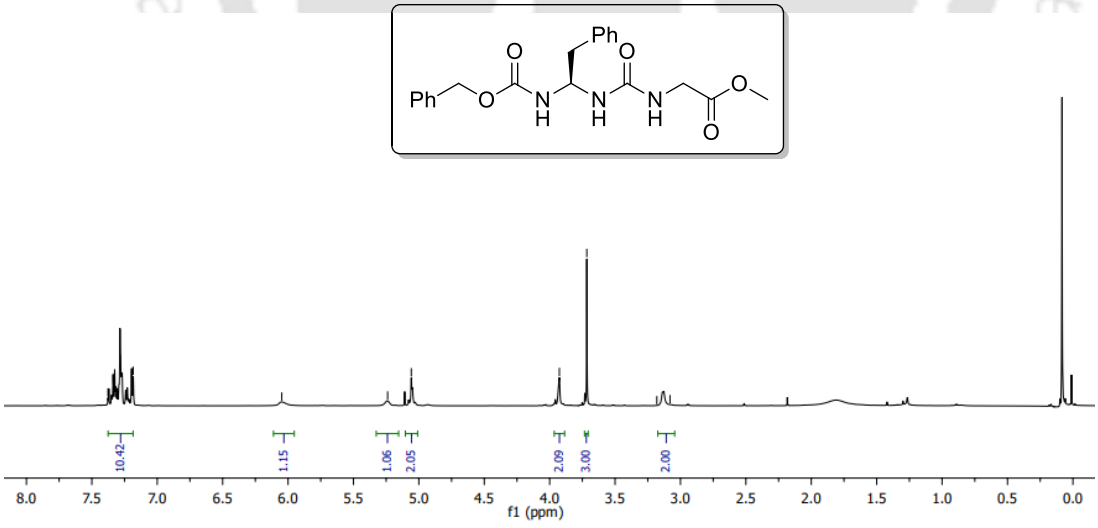


Figure 3.7.1.5. ^{1}H-NMR spectrum of (S)-methyl 5-benzyl-3,7-dioxo-1-phenyl-2-oxa-4,6,8-triazadecan-10-oate (entry 9, Table 3.1.2)

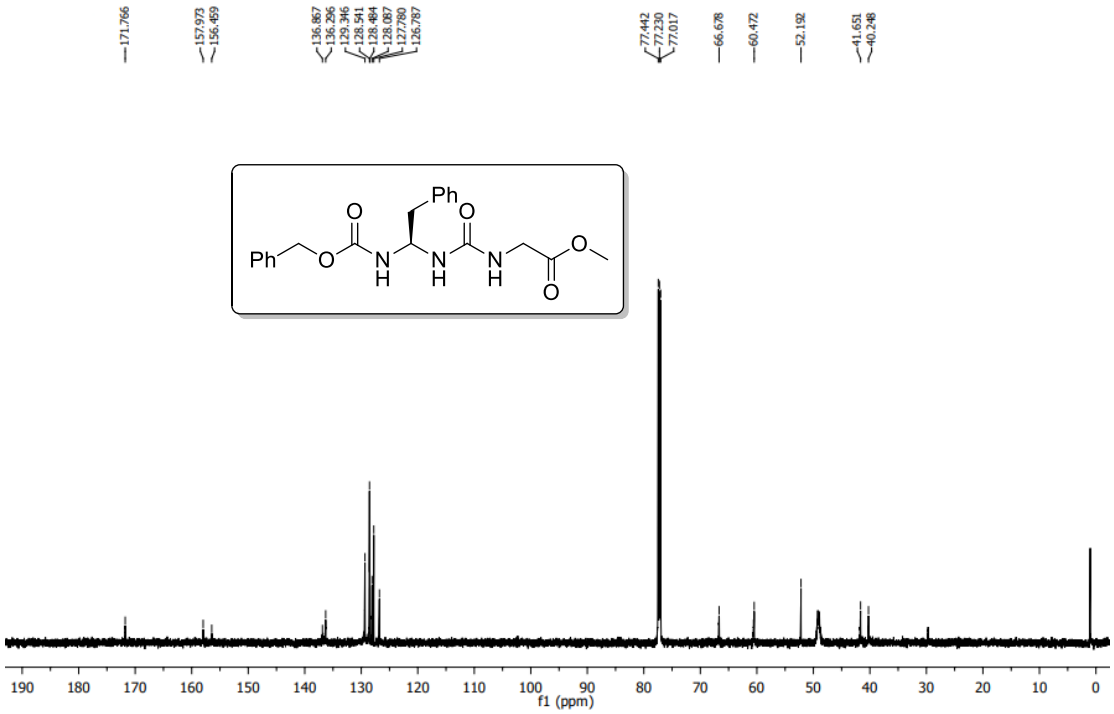


Figure 3.7.1.6. ^{13}C-NMR spectrum of (S)-methyl 5-benzyl-3,7-dioxo-1-phenyl-2-oxa-4,6,8-triazadecan-10-oate (entry 9, Table 3.1.2)

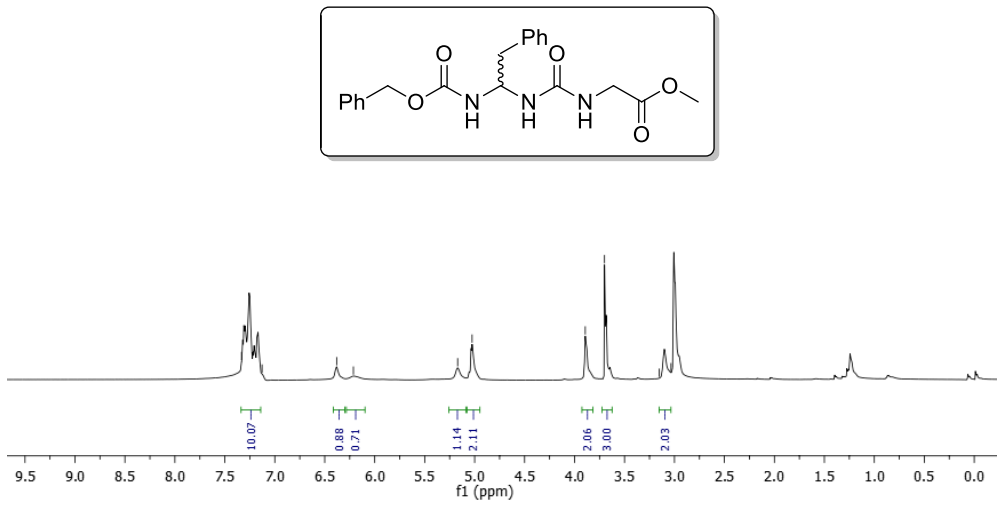


Figure 3.7.1.7. ^{1}H-NMR spectrum of Methyl 5-benzyl-3,7-dioxo-1-phenyl-2-oxa-4,6,8-triazadecan-10-oate (entry 10, Table 3.1.2)

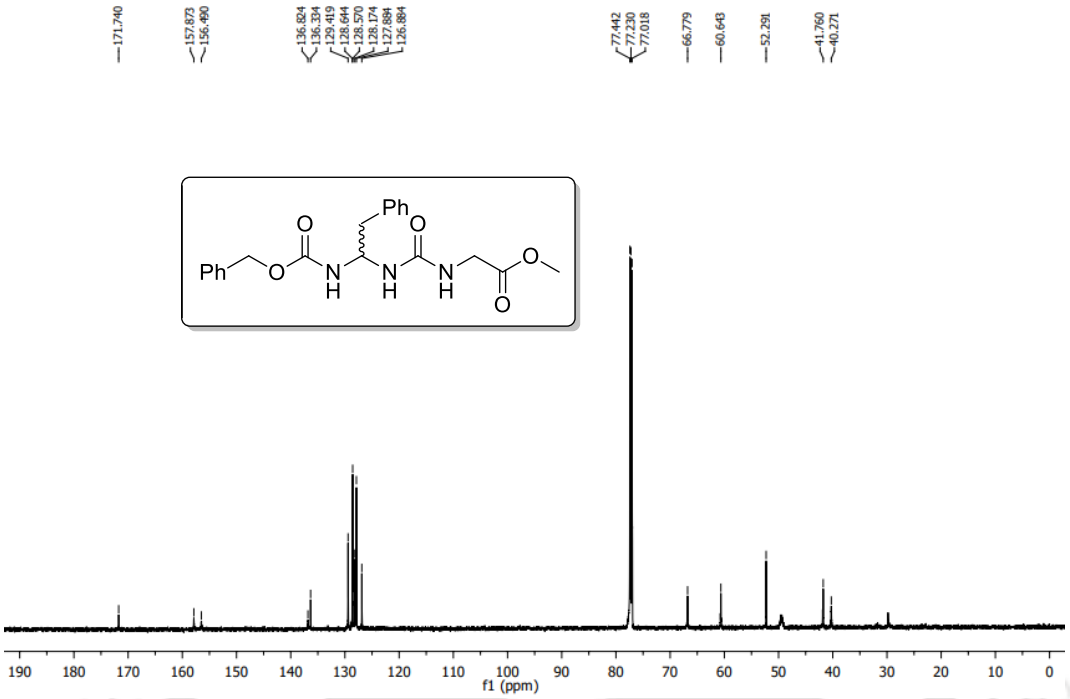


Figure 3.7.1.8. ^{13}C-NMR spectrum of Methyl 5-benzyl-3,7-dioxo-1-phenyl-2-oxa-4,6,8-triazadecan-10-oate (entry 10, Table 3.1.2)

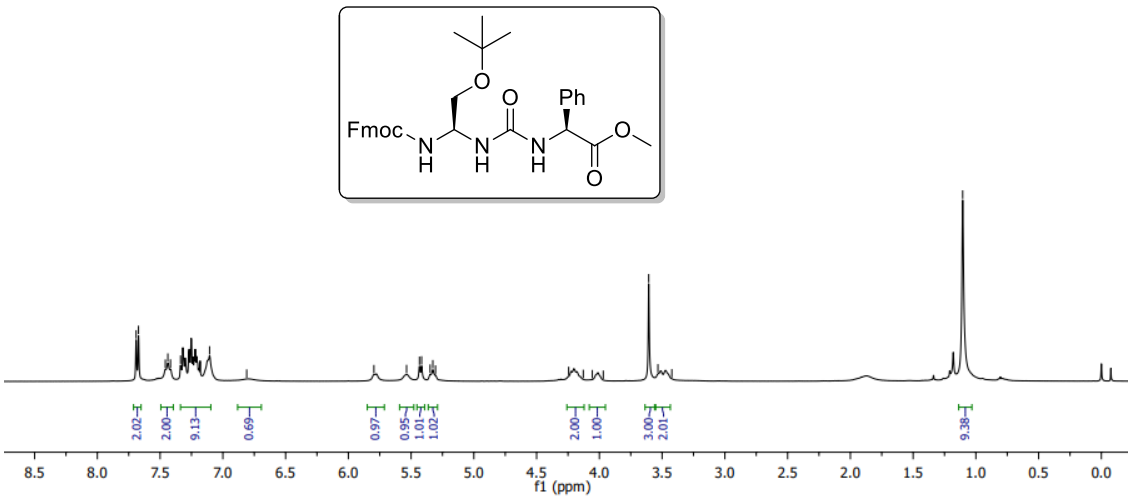


Figure 3.7.1.9. ^{1}H-NMR spectrum of (5S,9S)-methyl 5-(tert-butoxymethyl)-1-(9H-fluoren-9-yl)-3,7-dioxo-9-phenyl-2-oxa-4,6,8-triazadecan-10-oate (entry 11, Table 3.1.2)

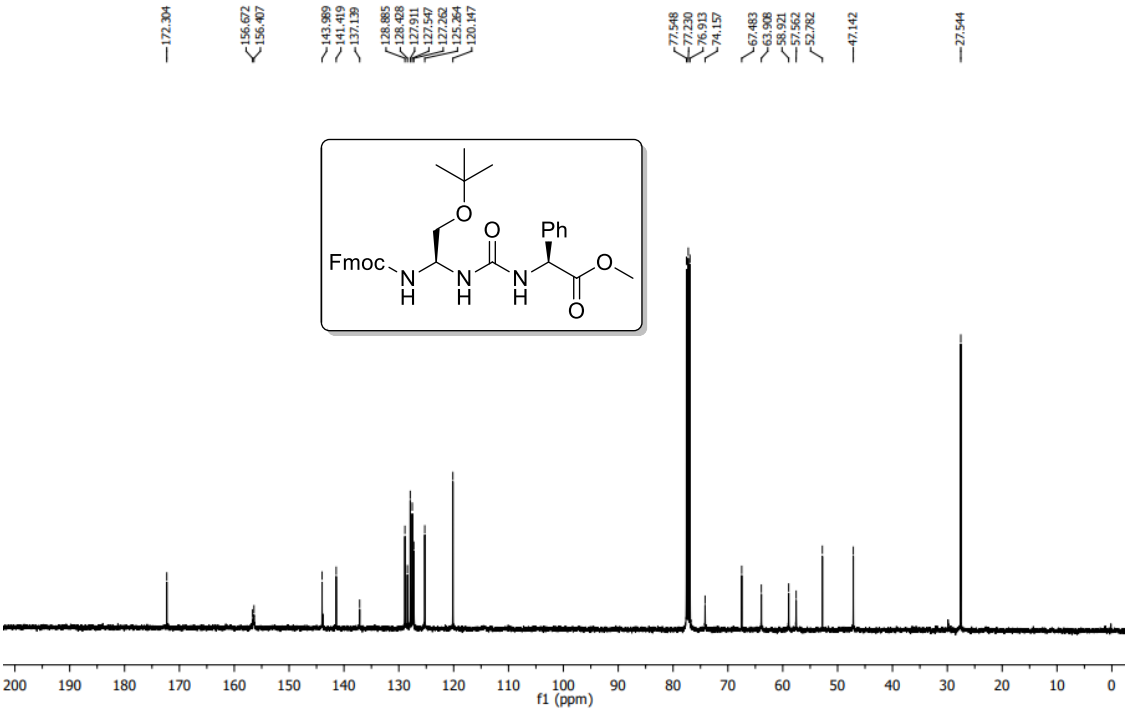


Figure 3.7.1.10. ^{13}C-NMR spectrum of (5S,9S)-methyl 5-(tert-butoxymethyl)-1-(9H-fluoren-9-yl)-3,7-dioxo-9-phenyl-2-oxa-4,6,8-triazadecan-10-oate (entry 11, Table 3.1.2)

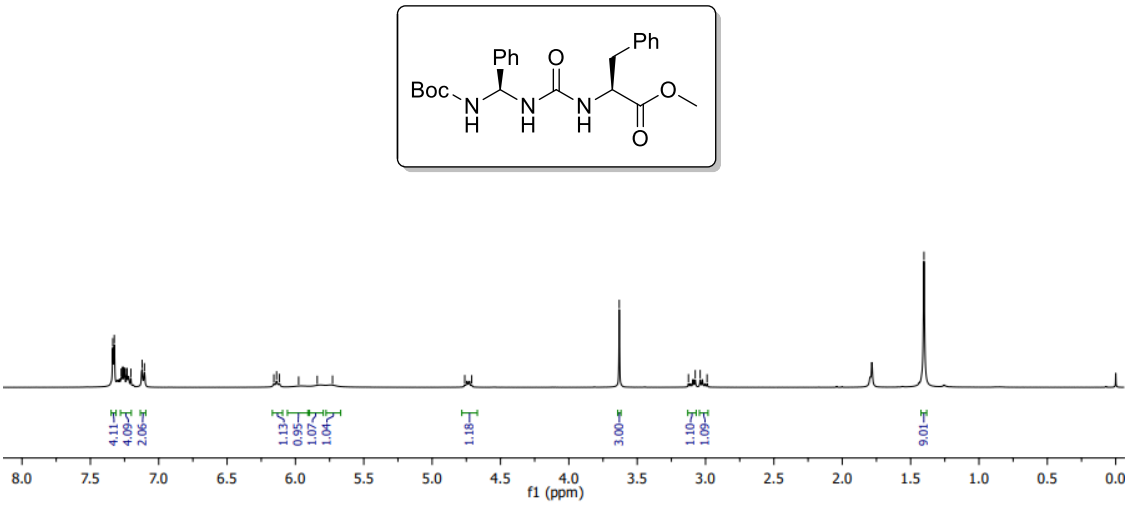


Figure 3.7.1.11. ^{1}H-NMR spectrum of (2S,6S)-methyl 2-benzyl-10,10-dimethyl-4,8-dioxo-6-phenyl-9-oxa-3,5,7-triazaundecan-1-oate (entry 12, Table 3.1.2)

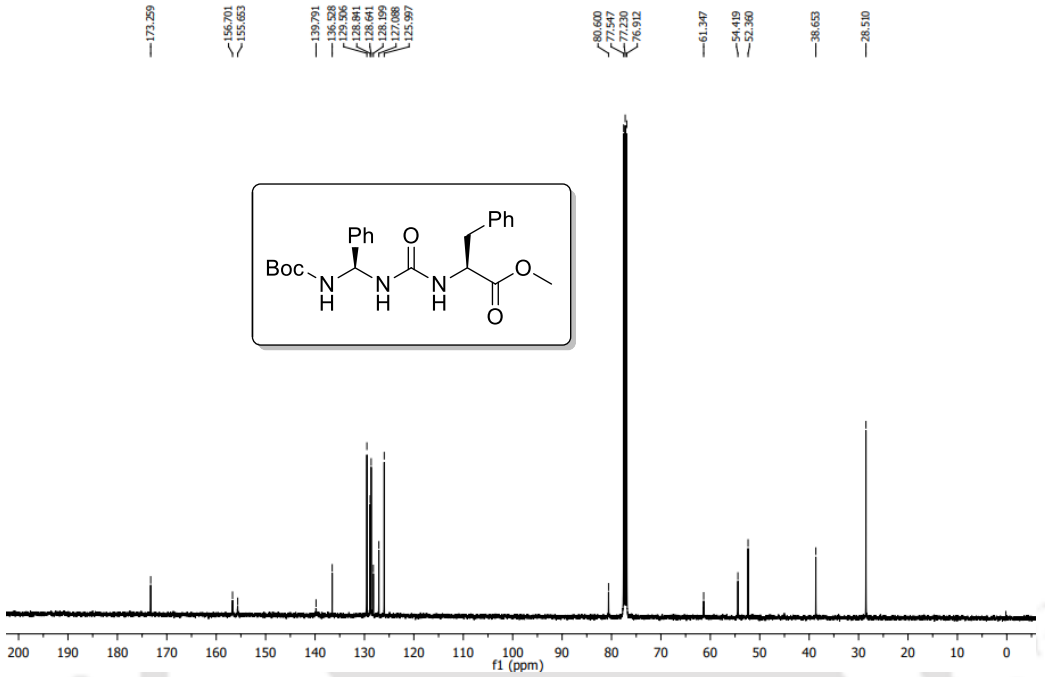


Figure 3.7.1.12. ^{13}C-NMR spectrum of (2S,6S)-methyl 2-benzyl-10,10-dimethyl-4,8-dioxo-6-phenyl-9-oxa-3,5,7-triazaundecan-1-oate (entry 12, Table 3.1.2)

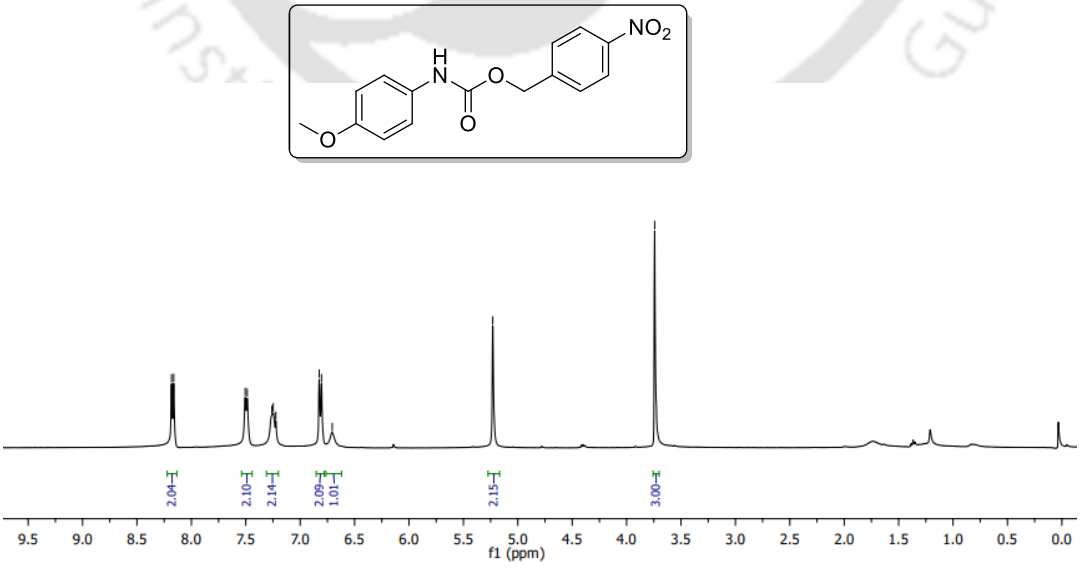


Figure 3.7.1.13. ^{1}H-NMR of 4-nitrobenzyl (4-methoxyphenyl)carbamate (entry 1, Table 3.1.3)

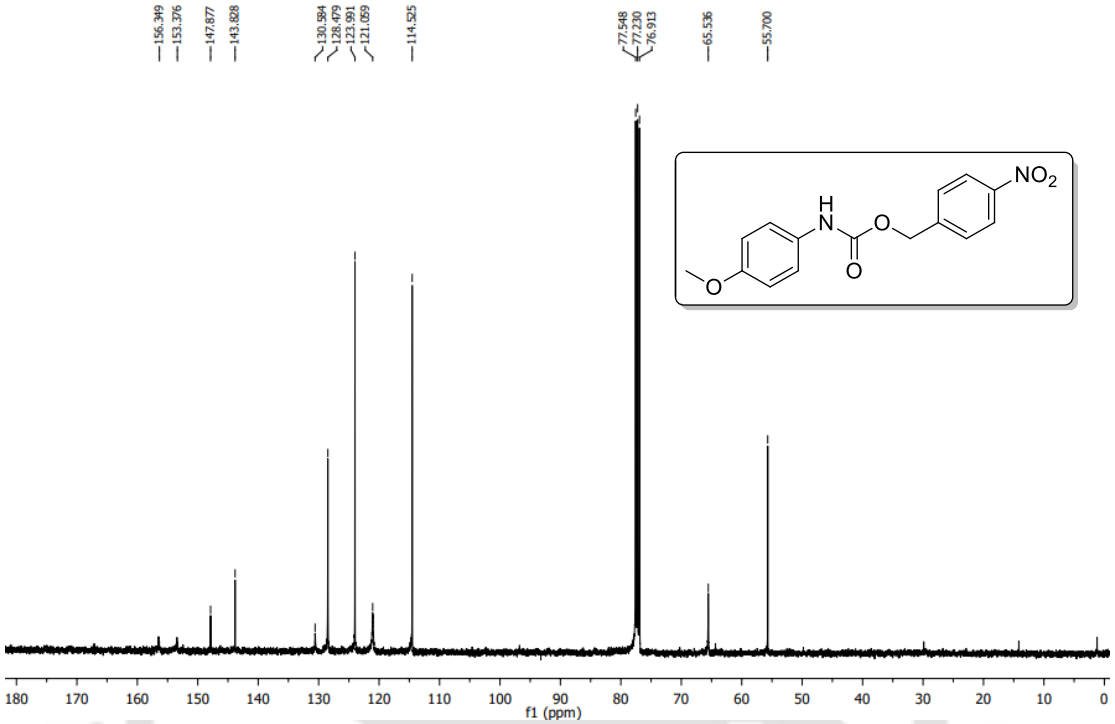


Figure 3.7.1.14. ^{13}C-NMR spectrum of 4-nitrobenzyl (4-methoxyphenyl)carbamate (entry 1, Table 3.1.3)

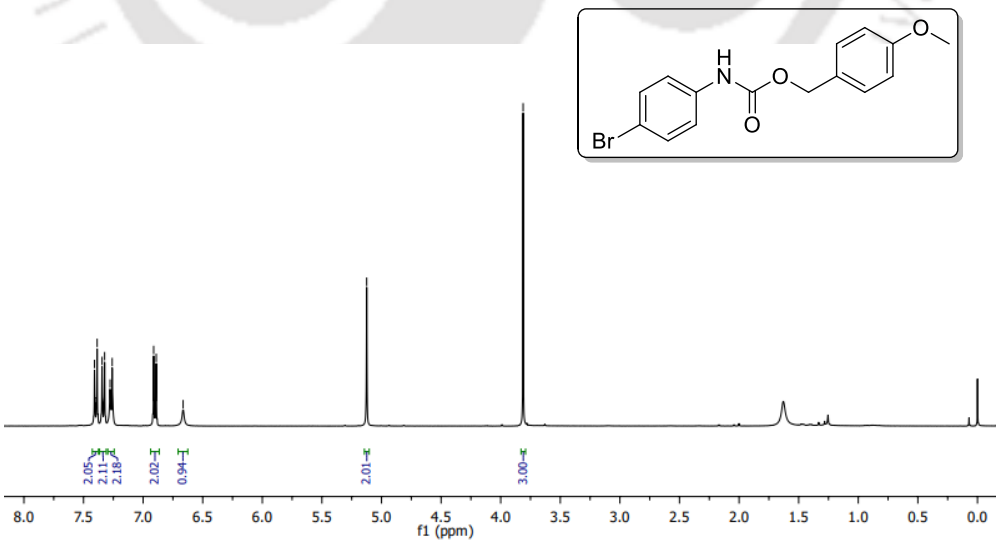


Figure 3.7.1.15. ^{1}H-NMR of 4-methoxybenzyl (4-bromophenyl)carbamate (entry 4, Table 3.1.3)

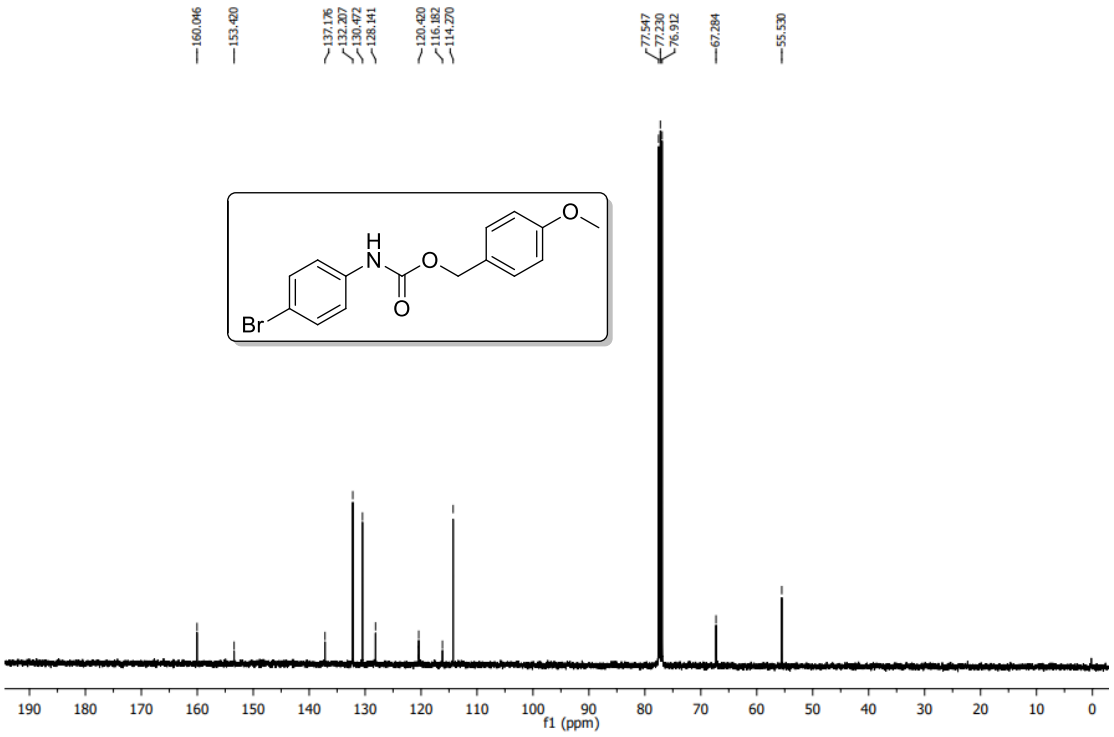


Figure 3.7.1.16. ^{13}C-NMR spectrum of 4-methoxybenzyl (4-bromophenyl)carbamate (entry 4, Table 3.1.3)

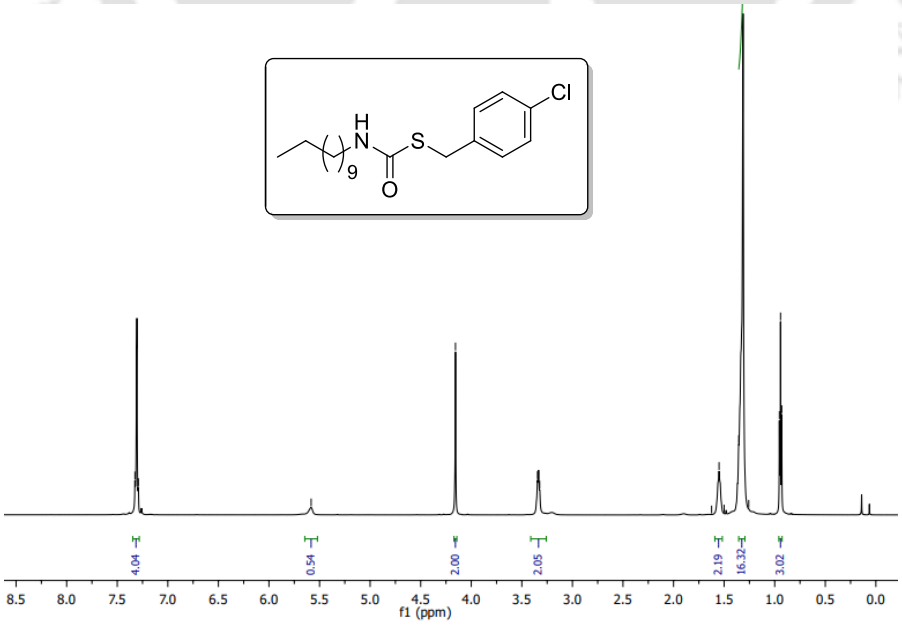


Figure 3.7.1.17. ^{1}H-NMR spectrum of S-4-chlorobenzyl undecylcarbamothioate (entry 6, Table 3.1.3)

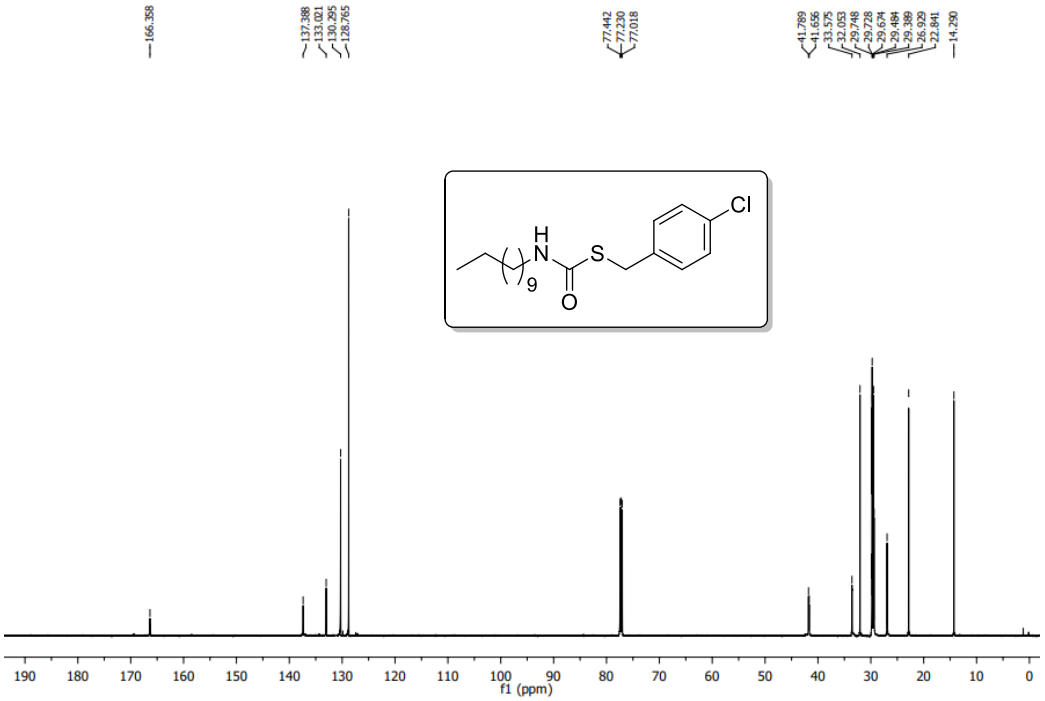
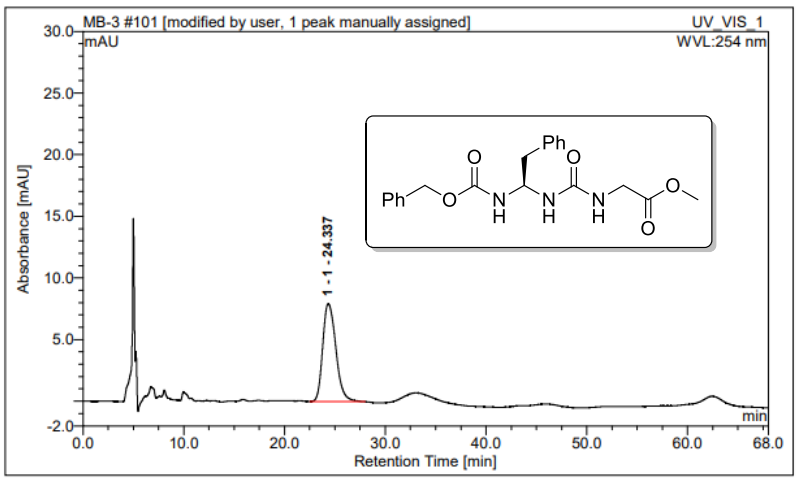


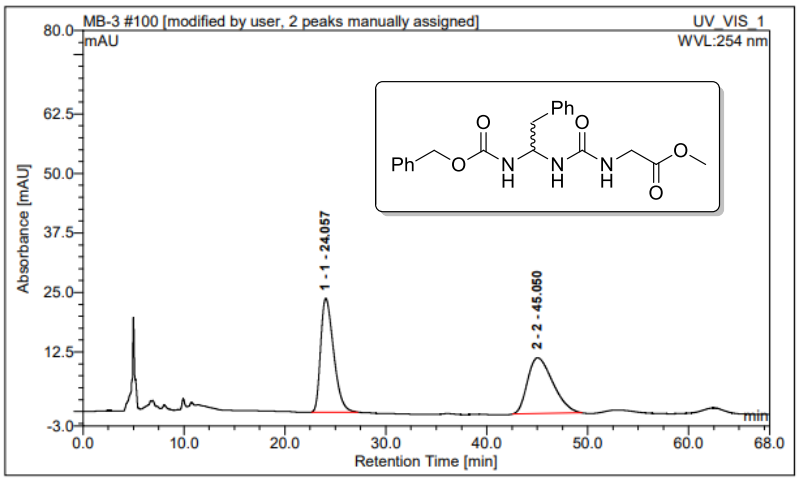
Figure 3.7.1.18. ^{13}C-NMR spectrum of S-4-chlorobenzyl undecylcarbamothioate (entry 6, Table 3.1.3)

3.7.2. HPLC data for racemization test



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	24.34	12.00236	100	7.95218	n.a.

Figure 3.7.2.1. HPLC spectrum of (S)-methyl 5-benzyl-3,7-dioxo-1-phenyl-2-oxa-4,6,8-triazadecan-10-oate (entry 9, Table 3.1.2); run in chiral column (5 µm, 2.1×150 mm) (Isocratic, isopropanol-hexane solvent system)



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	24.06	35.57248	51.06423737	23.92333	n.a.
2	2	45.05	34.090	48.93576263	11.704	n.a.

Figure 3.7.2.2. HPLC spectrum of Methyl 5-benzyl-3,7-dioxo-1-phenyl-2-oxa-4,6,8-triazadecan-10-oate (entry 10, Table 3.1.2); run in chiral column (5 µm, 2.1×150 mm) (Isocratic, isopropanol-hexane solvent system)

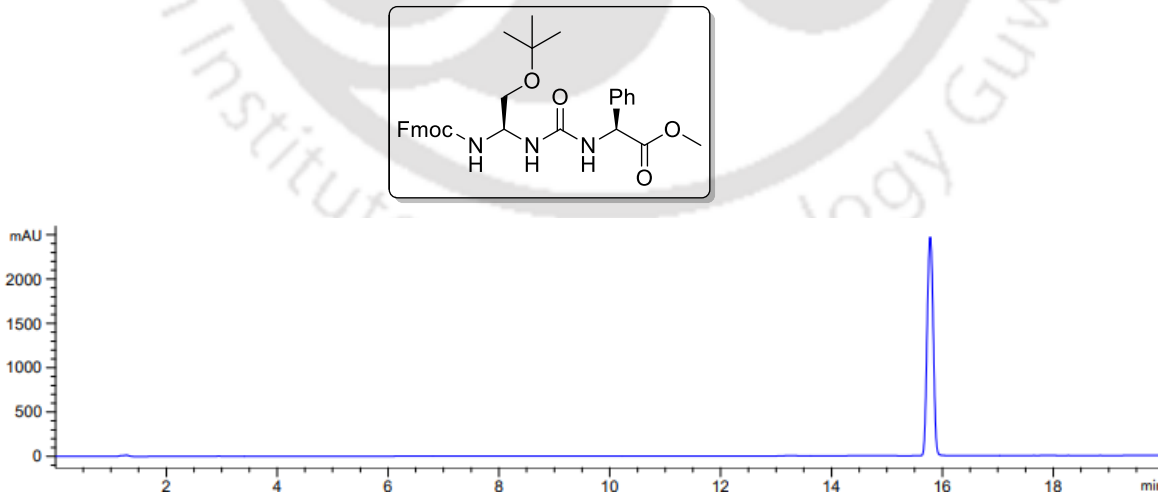


Figure 3.7.2.3. HPLC spectrum of (5S,9S)-methyl 5-(tert-butoxymethyl)-1-(9H-fluoren-9-yl)-3,7-dioxo-9-phenyl-2-oxa-4,6,8-triazadecan-10-oate (entry 11, Table 3.1.2); run in C18 reverse-phase column (4 µm, 4.6×100 mm) (gradient, acetonitrile-water solvent system

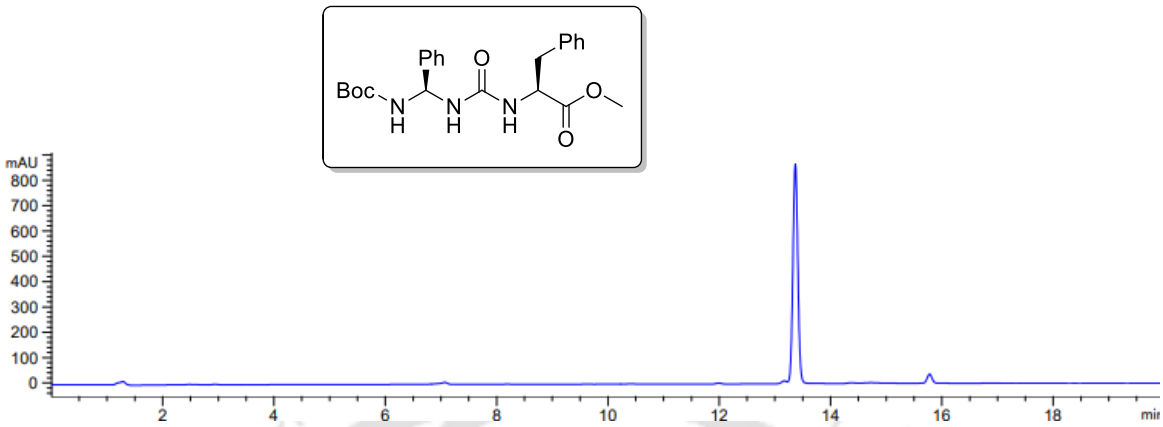


Figure 3.7.2.4. HPLC spectrum of (2S,6S)-methyl 2-benzyl-10,10-dimethyl-4,8-dioxo-6-phenyl-9-oxa-3,5,7-triazaundecan-1-oate (entry 12, Table 3.1.2); run in C18 reverse-phase column (4 µm, 4.6×100 mm) (gradient, acetonitrile-water solvent system

3.7.3. Mechanism study

^{13}C NMR Spectra

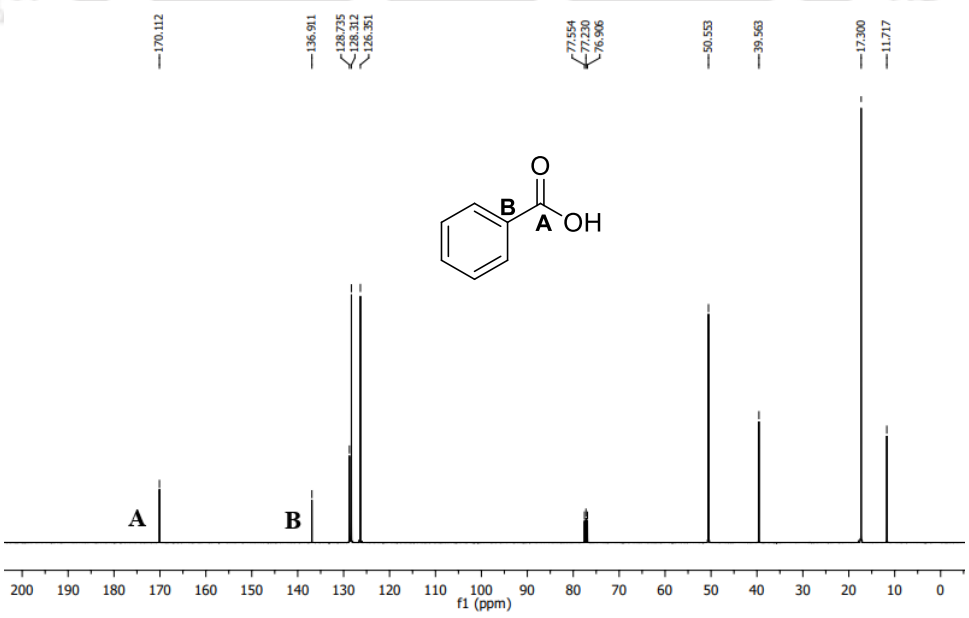


Figure 3.7.3.1. ^{13}C-NMR spectrum of benzoic acid in the presence of base DIPEA

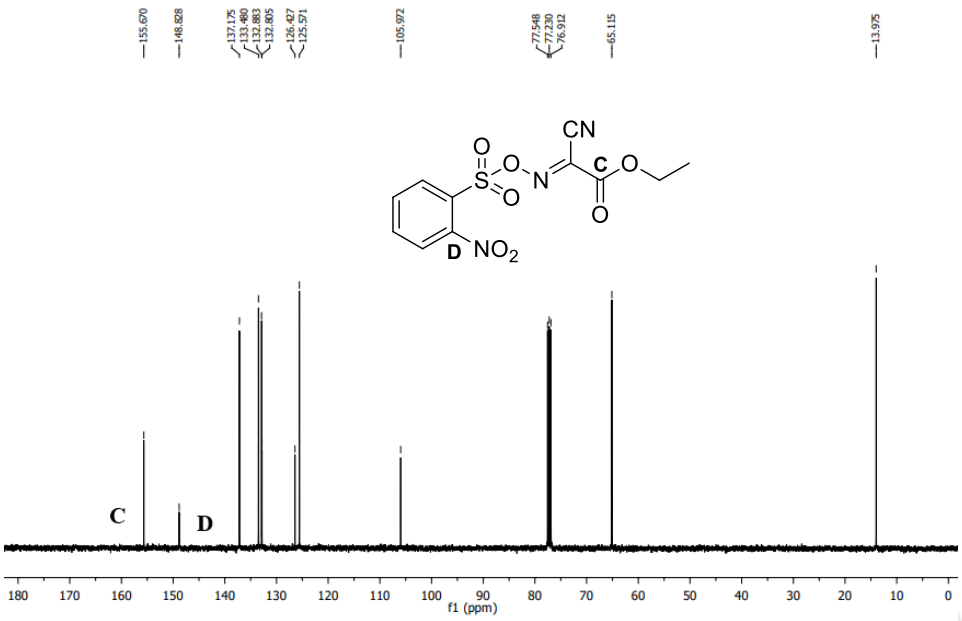


Figure 3.7.3.2. ^{13}C-NMR spectrum of *o*-NosylOXY (**I**)

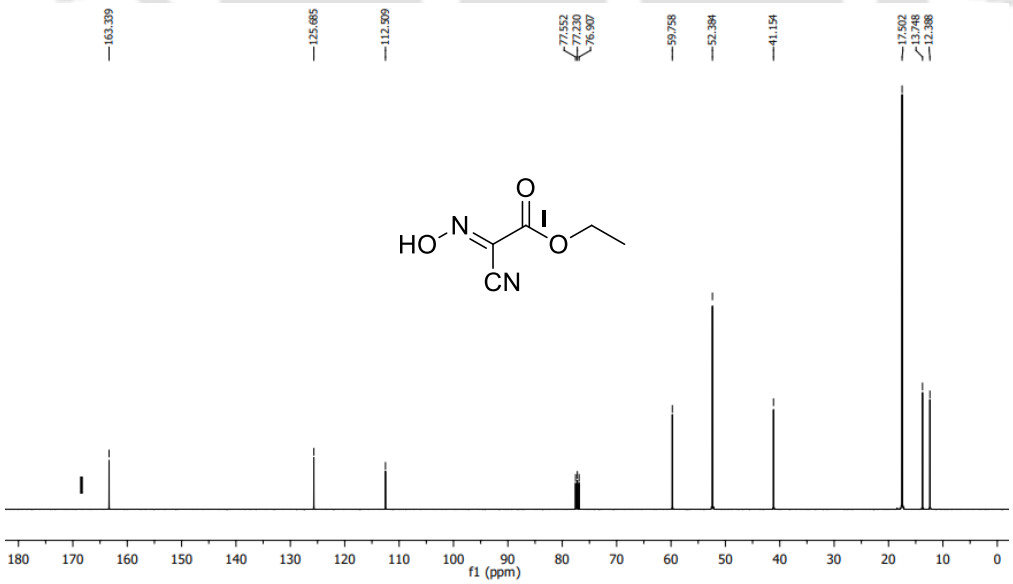


Figure 3.7.3.3. ^{13}C-NMR spectrum of Oxyma in presence of base DIPEA

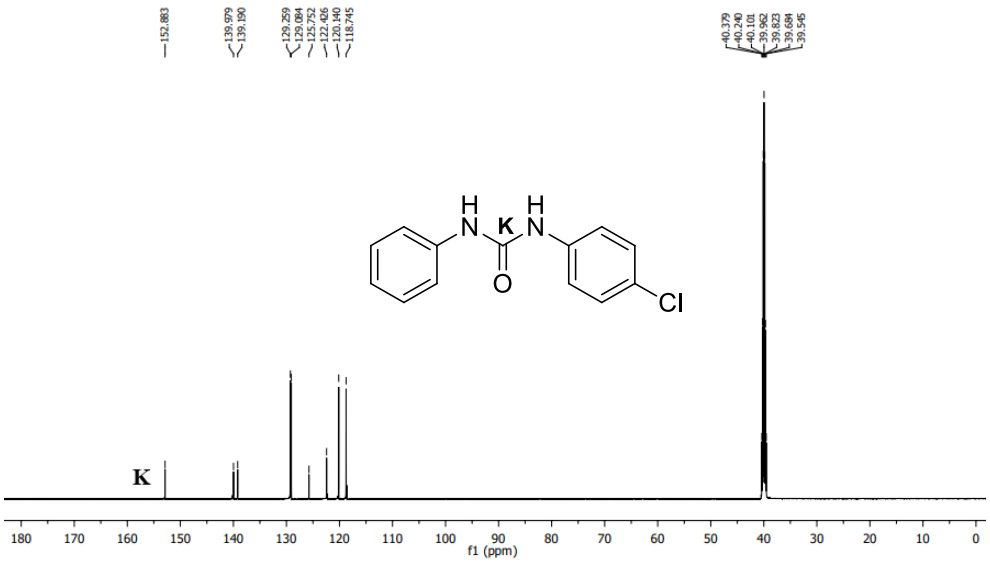


Figure 3.7.3.4. ^{13}C-NMR spectrum of product **3a** (1-(4-chlorophenyl)-3-phenylurea)

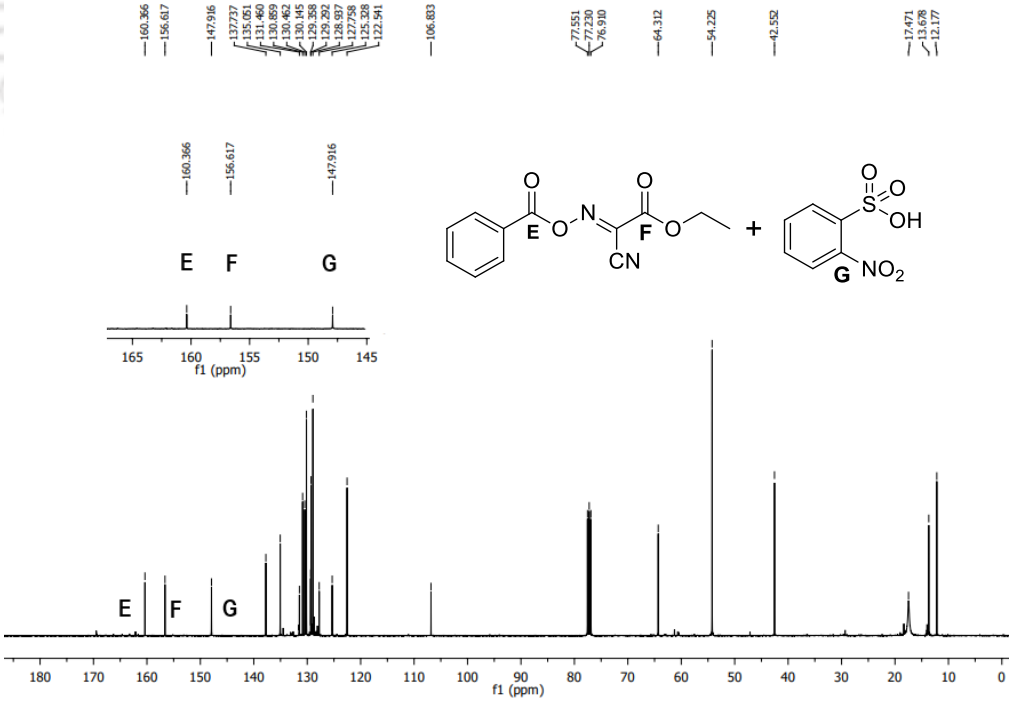


Figure 3.7.3.5. ^{13}C-NMR spectrum of reaction after 10 min

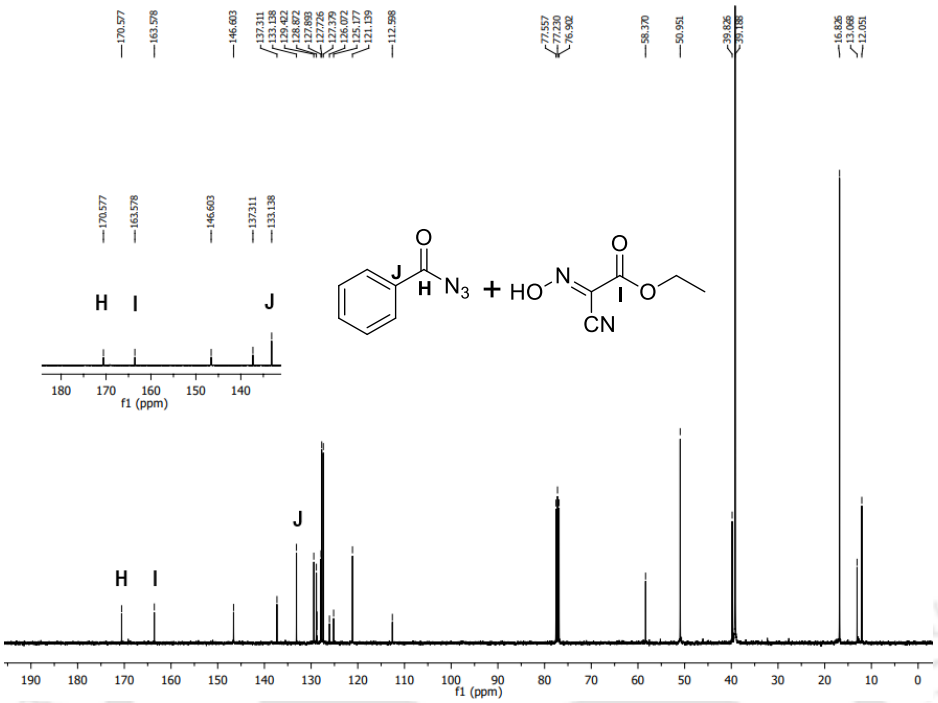


Figure 3.7.3.6. ^{13}C-NMR spectrum of reaction after 30 min

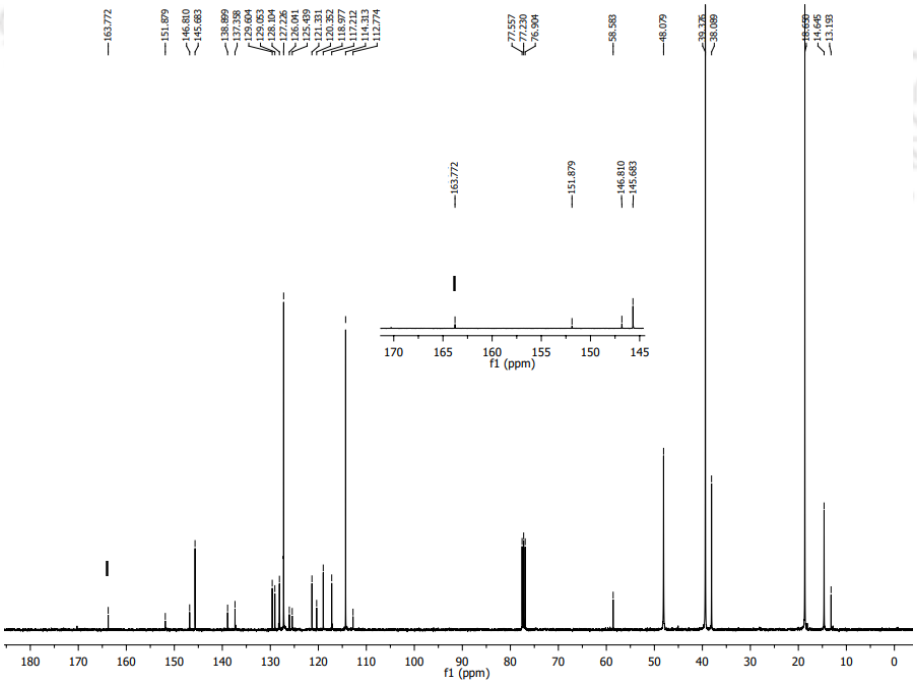


Figure 3.7.3.7. ^{13}C-NMR spectrum of reaction after 50 min

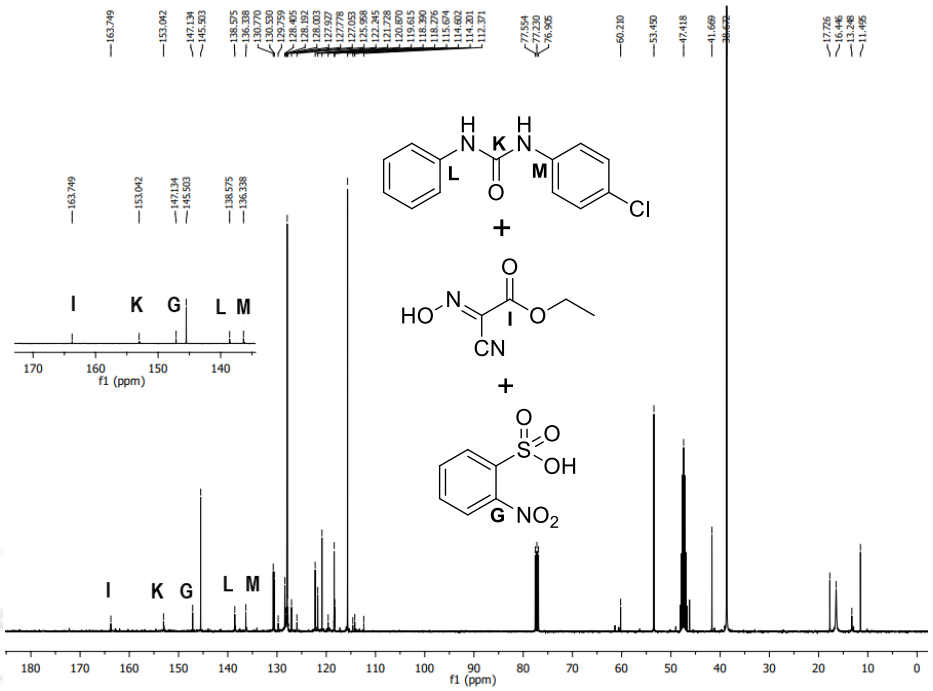
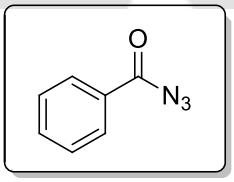


Figure 3.7.3.8. ^{13}C-NMR spectrum of reaction after 6 h

3.7.4. ^{1}H and ^{13}C-NMR spectrum of benzoyl azide (IV, Scheme 3.3.1)



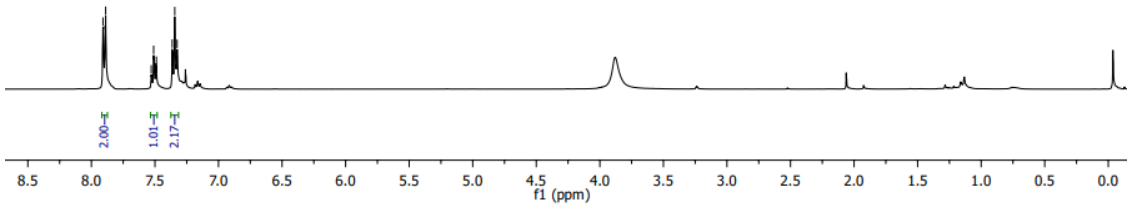


Figure 3.7.4.1. ^{1}H-NMR spectrum of benzoyl azide

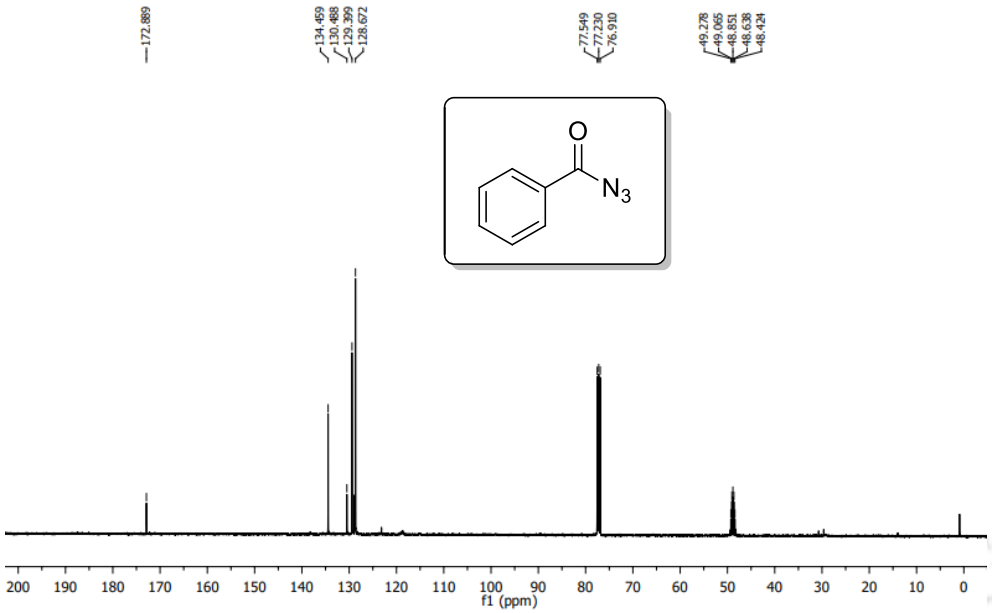
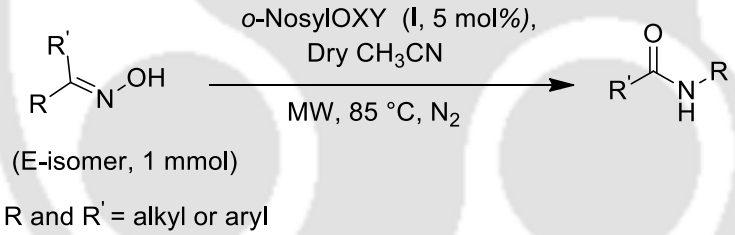


Figure 3.7.4.2. ^{13}C-NMR spectrum of benzoyl azide

Chapter 4: Mechanistic investigation of Beckmann rearrangement using *o*-NosylOXY

One of our senior group members already established the conversion of ketoxime to amide via Beckmann rearrangement using *o*-NosylOXY (*Scheme 4.1*).[89] The reaction mixture of ketoxime and *o*-NosylOXY in dry acetonitrile was refluxed for 10-20 min under microwave conditions to get the product. This procedure was used to synthesize various amides containing different substituents such as chloro, bromo, hydro, methoxy, etc., and few lactams. A plausible mechanism was also stated, and NMR based study was done in $CDCl_3$ solvent.[89]



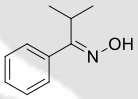
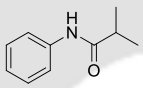
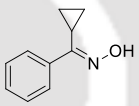
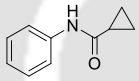
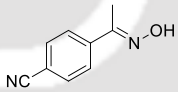
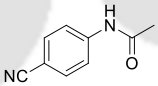
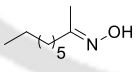
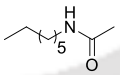
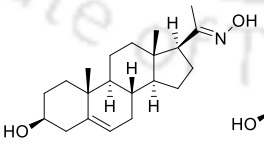
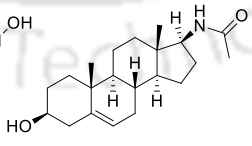
Scheme 4.1. Synthesis of amide from ketoxime using *o*-NosylOXY

In this chapter, we describe some extended work to the above-mentioned methodology developed in our lab. Using the same reaction condition (*Scheme 4.1*), we extended the substrate scope of this protocol (*Table 4.1.1*), and a very good yield was obtained for these too. All the products are well- characterized by ^{1}H, ^{13}C, and mass spectrometry. Also, we focused on the mechanistic pathway of the reaction and performed the time-dependent NMR study in CD_3CN solvent (*Scheme 4.2.1*).

4.1. Substrates scope for the synthesis of an amide using *o*-NosylOXY

Considering this protocol's utility, we synthesized substrates containing the strongly electron-withdrawing group cyano and cyclic ring cyclopropyl. They were subjected to Beckmann rearrangement using this procedure, and excellent yields were obtained. One alkyl amide was also synthesized from nonanone oxime with an 81% yield (*Table 4.1.1, entry 4*). Pregnenolone oxime rearranged smoothly to its corresponding steroidal amide with 80% yield within a short time of 20 min (*Table 4.1.1, entry 5*).

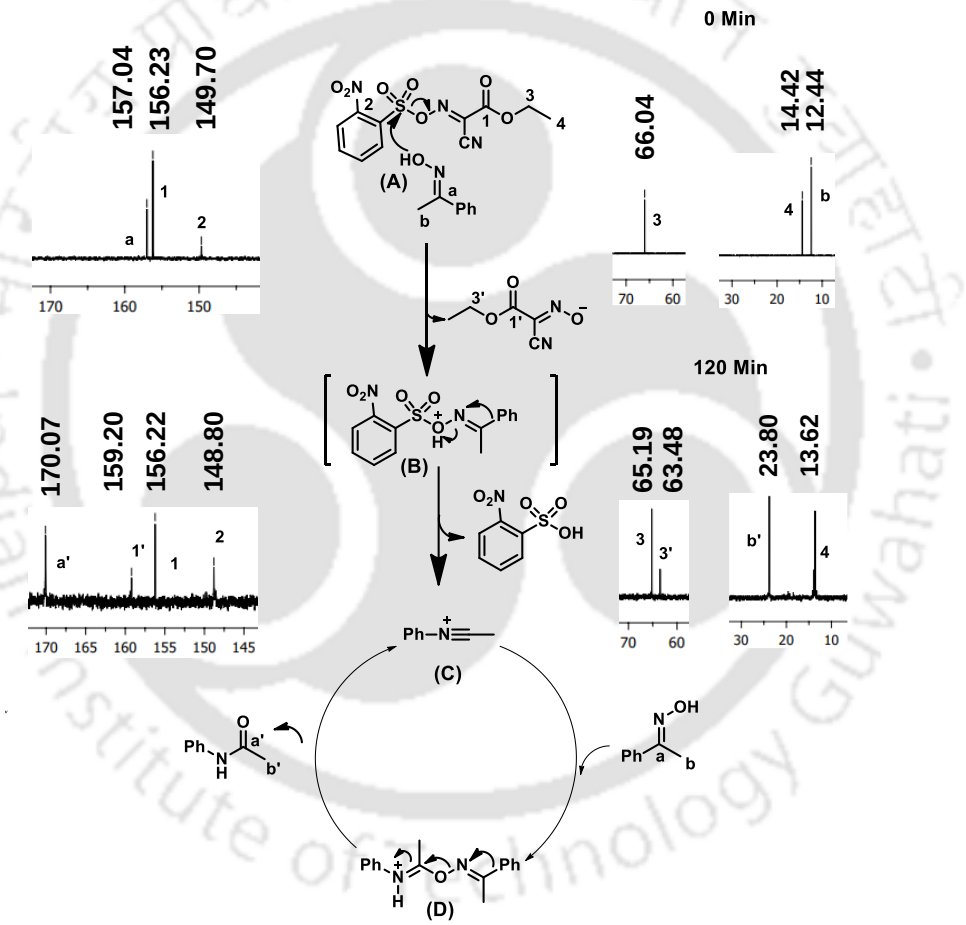
Table 4.1.1. Synthesis of amides using **I**[a]

Entry	Oxime	Amide	Yield [%][b]
1			92
2			90
3			71
4			81
5			80

*[a] Performed with oxime (1 equiv) and reagent **I** (5 mol%) MW (100 Watt) at 85 °C under nitrogen. [b] Yields refer to the isolated yield after column chromatography.*

4.2. Mechanism study

A plausible mechanism for synthesizing *N*-phenylacetamide from acetophenone oxime via Beckmann Rearrangement with *o*-NosylOXY is shown in scheme 4.2.1. We recorded time-dependent ^{1}H and ^{13}C NMR, with 1 equiv of acetophenone oxime and 0.5 equiv of *o*-NosylOXY in CD_3CN as solvent under reflux condition (*Figure 4.6.2.1-4.6.2.10*).

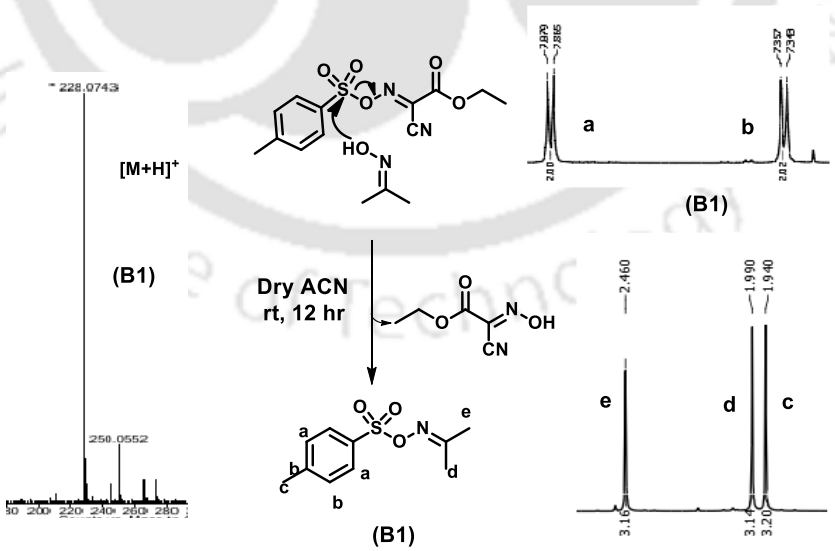


Scheme 4.2.1. A plausible mechanism of Beckmann rearrangement using *o*-NosylOXY, ^{13}C NMR spectra of reaction at 0 min and 120 min

We took NMR spectra at different time intervals of 10, 20, 30, 40, 60, 90, and 120 min. It was observed that, In ^{13}C NMR, the product peak a' and b' started appearing, and the

starting material peak a and b started disappearing within 20 min of the reaction (*Figure 4.6.2.11-4.6.2.12*). The reaction was about to complete after 120 min, i.e., no starting material peak a and b remain left after that. The new peaks 1' and 3' represents the free Oxyma. It was seen that the rate of the reaction is fast enough in CD_3CN solvent even in the absence of microwave heating. It is faster in CD_3CN than $CDCl_3$, which was also noted during solvent optimization.[89]

From this mechanism study, we could not characterize intermediate B due to its transient nature. Therefore, we carried out some other experiments to find out the actual pathway of the reaction. We performed the reaction between two similar substrate acetoxime and the reagent TosylOXY in dry acetonitrile for about 12 hours (*Scheme 4.2.2*) at room temperature. After column purification, we could characterize the intermediate B1 by ^1H NMR and HRMS (*Figure 4.6.1.16-4.6.1.17*). Therefore, we concluded from this evidence that our reaction indeed passed via intermediate **B,** but previously we could not characterize it just because of its reactive nature.



Scheme 4.2.2. Synthesis of intermediate **B1:** ^1H NMR spectra and ESI-MS spectra of intermediate **B1** after 12 hours of reaction and column purification, $[M+H]^+$ calculated. 228.0694, found 228.0743

4.3. Conclusion

In conclusion, we have synthesized several amides from ketoximes under milder conditions using *o*-NosylOXY as a catalyst via Beckmann rearrangement. A time-dependent NMR study is also done to understand the pathway of the reaction using CD_3CN as solvent.

4.4. Experimental Section

4.4.1. General consideration

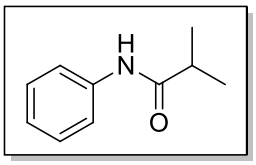
As described in chapter 2, section 2.4.1

4.4.2. General procedure for mechanism study by NMR

In a cleaned and dry NMR tube, acetophenone oxime (1 equiv) and *o*-NosylOXY (0.5 equiv) were dissolved in 0.80 mL CD_3CN. Then ^{1}H and ^{13}C were recorded immediately. This time point was considered as 0 min. The reaction mixture was then transferred to a 5 mL round bottom flask and refluxed in the respective solvent. After 10 min, it was again transferred to an NMR tube, and spectra are recorded. The reaction mixture was interchanged between the NMR tube and the round bottom flask alternatively, and ^{1}H and ^{13}C were recorded at different time intervals of 10, 20, 30, 40, 60, 90, and 120 min. These are the total reaction time of refluxing the mixture.

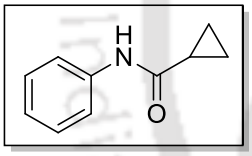
4.5. Characterization data

_N_-Phenylisobutyramide[90] (entry 1, Table 4.1.1)



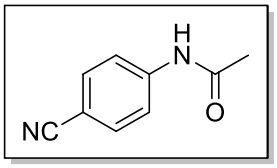
Yield: 150 mg (92%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 103-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (br, 1H), 7.56-7.54 (d, *J* = 7.2 Hz, 2H), 7.28-7.25 (t, *J* = 7.8 Hz, 2H), 7.10-7.06 (t, *J* = 7.2 Hz, 1H), 2.59-2.52 (m, 1H), 1.22-1.89 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 138.4, 128.9, 124.2, 120.3, 36.5, 19.7; IR (KBr): 3284, 3299, 2969, 1659, 1440, 1305, 1248, 754, 692, 514 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{10}H_{14}NO$ 164.1070, found 164.1074.

_N_-Phenylcyclopropanecarboxamide[90] (entry 2, Table 4.1.1)



Yield: 145 mg (90%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 110-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (br, 1H), 7.51-7.49 (d, *J* = 8.0 Hz, 2H), 7.25-7.22 (t, *J* = 7.6 Hz, 2H), 7.06-7.02 (t, *J* = 7.2 Hz, 1H), 1.58-1.53 (m, 1H), 1.03-0.99 (m, 2H), 0.77-0.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 138.4, 128.9, 124.1, 120.2, 15.6, 7.9; IR (KBr): 3284, 3251, 2917, 1652, 1595, 1433, 1248, 951, 694, 502 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{10}H_{11}NO$ 162.0914, found 162.0919.

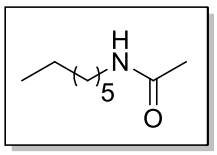
_N_-(4-Cyanophenyl)acetamide[91] (entry 3, Table 4.1.1)



Yield: 114 mg (71%); white solid; R_f = 0.50 (EtOAc:Hexane, 6.0:4.0); mp: 203-205 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.65 (d, *J* = 8.4 Hz, 2H), 7.57-7.55 (d, *J* = 8.4 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 142.6, 133.4, 119.6, 119.2, 106.7, 24.5; IR

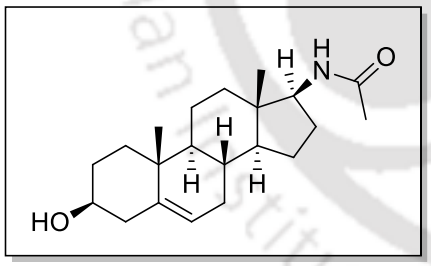
(KBr): 3304, 2924, 2855, 1732, 1669, 1215, 749, 669, 544 cm^{-1}; LRMS (ESI): m/z $[M+H]^+$ calculated for $C_9H_9N_2O$ 161.0710, found 161.0610.

***N*-Heptylacetamide[92] (entry 4, Table 4.1.1)**Yield: 127 mg (81%); colourless oil; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); ^1H NMR (400 MHz, $CDCl_3$): δ 6.09 (br, 1H), 3.18-3.13



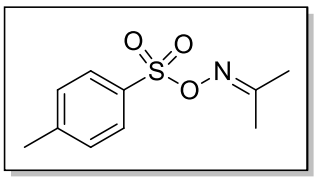
(q, *J* = 6.4 Hz, 2H), 1.92 (s, 3H), 1.45-1.43 (m, 2H), 1.24-1.22 (m, 8H), 0.84-0.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 39.8, 31.8, 29.7, 29.1, 27.0, 23.3, 22.7, 14.2; IR (KBr): 3286, 2924, 2854.9, 1647, 1552, 1240, 1043, 756, 602 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calculated for $C_9H_{19}NNaO$ 180.1359, found 180.1364.

***N*-((3S,8R,9S,10R,13S,14S,17S)-3-hydroxy-10,13-di-methyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradeca-hydro-1*H*-cyclopenta[a]phenanthren-17-yl) acetamide[93] (entry 5, Table 4.1.1)**



Yield: 265 mg (80%), white solid; R_f = 0.30 (MeOH:DCM, 2.0:8.0); mp: 231-233 °C. ^1H NMR ($CDCl_3$ and 1 drop CD_3OD, 400 MHz): δ 5.31-5.30 (m, 1H), 5.26 (d, *J* = 8.4 Hz, 1H), 3.85-3.79 (m, 1H), 3.50-3.42 (m, 1H), 2.27-2.02 (m, 3H), 1.99-1.97 (m, 1H), 1.94 (s, 3H), 1.81-1.78 (m, 2H), 1.67-1.59 (m, 2H), 1.55-1.15 (m, 10H), 1.10-1.04 (m, 2H), 0.96 (s, 3H) 0.94-0.90 (m, 1H), 0.66 (s, 3H); ^{13}C NMR ($CDCl_3$ and 1 drop CD_3OD, 100 MHz): δ 171.2, 140.9, 121.1, 71.2, 58.9, 52.8, 50.1, 42.9, 41.8, 37.2, 36.8, 36.5, 32.0, 31.5, 31.1, 27.9, 23.6, 22.8 20.6, 19.3, 11.8; IR(KBr): 3348, 2932, 1630, 1550, 1260, 1058, 799, 554 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{21}H_{34}NO_2$ 332.2584, found 332.2590.

Propan-2-one *O*-tosyl oxime (B1, Scheme 4.2.2)



Yield: 60 mg (70%); yellow solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 83-85°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87-7.86 (d, *J* = 8.4 Hz, 2H), 7.35-7.34 (d, *J* = 8.4 Hz, 2H), 2.46 (s, 3H), 1.99 (s, 3H), 1.94 (s, 3H); ESI-MS: m/z $[M+H]^+$calculated for $C_{10}H_{14}NO_3S$ 228.0694, found 228.0743.

4.6. Selected spectra

4.6.1. ^{1}H NMR, ^{13}C NMR, and ESI-MS spectra of compounds

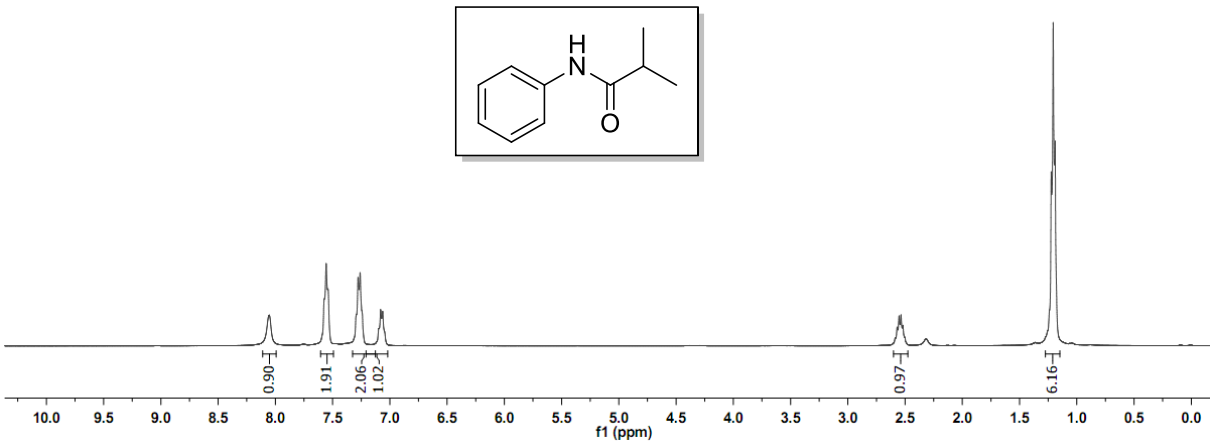


Figure 4.6.1.1. ^{1}H-NMR spectrum of *N*-phenylisobutyramide (entry 1, Table 4.1.1)

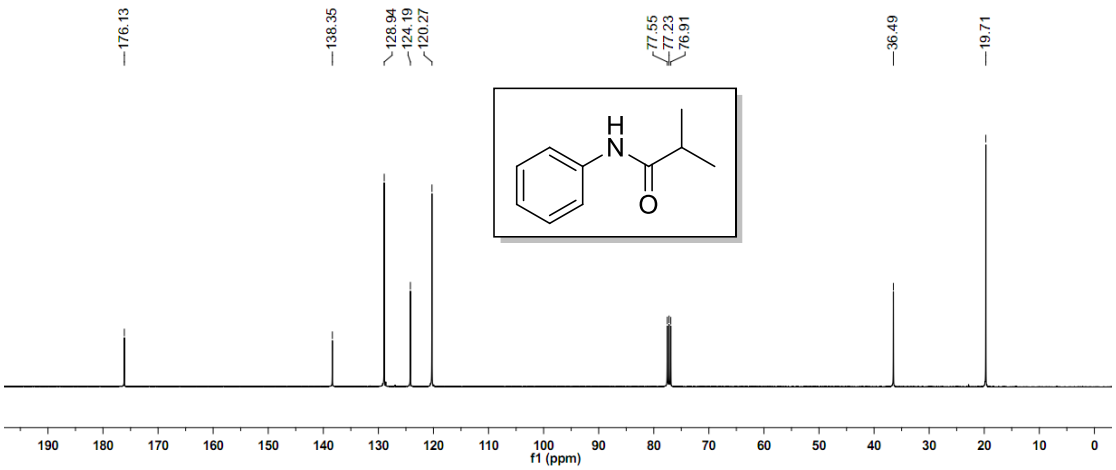


Figure 4.6.1.2. ^{13}C-NMR spectrum of *N*-phenylisobutyramide (entry 1, Table 4.1.1)

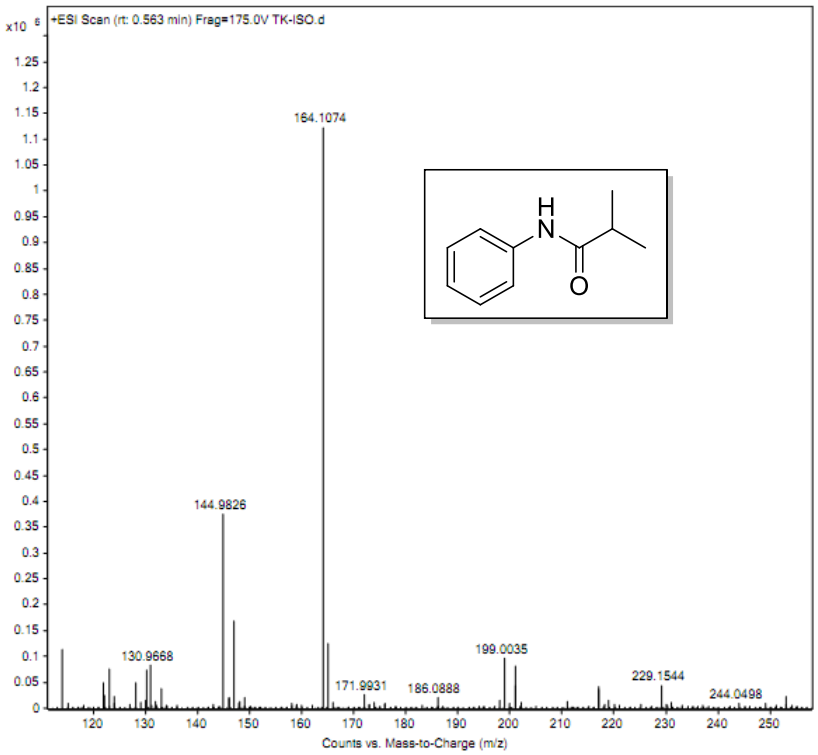


Figure 4.6.1.3. HRMS spectrum of *N*-phenylisobutyramide (entry 1, Table 4.1.1, HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{10}H_{14}NO$ 164.1070, found 164.1074)

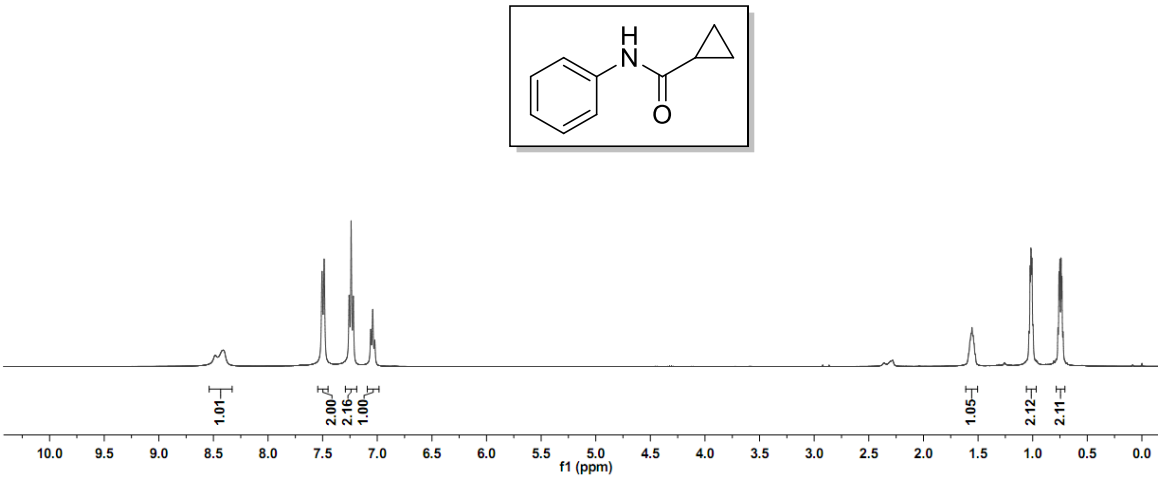


Figure 4.6.1.4. ^{1}H-NMR spectrum of *N*-phenylcyclopropanecarboxamide (entry 2, Table 4.1.1)

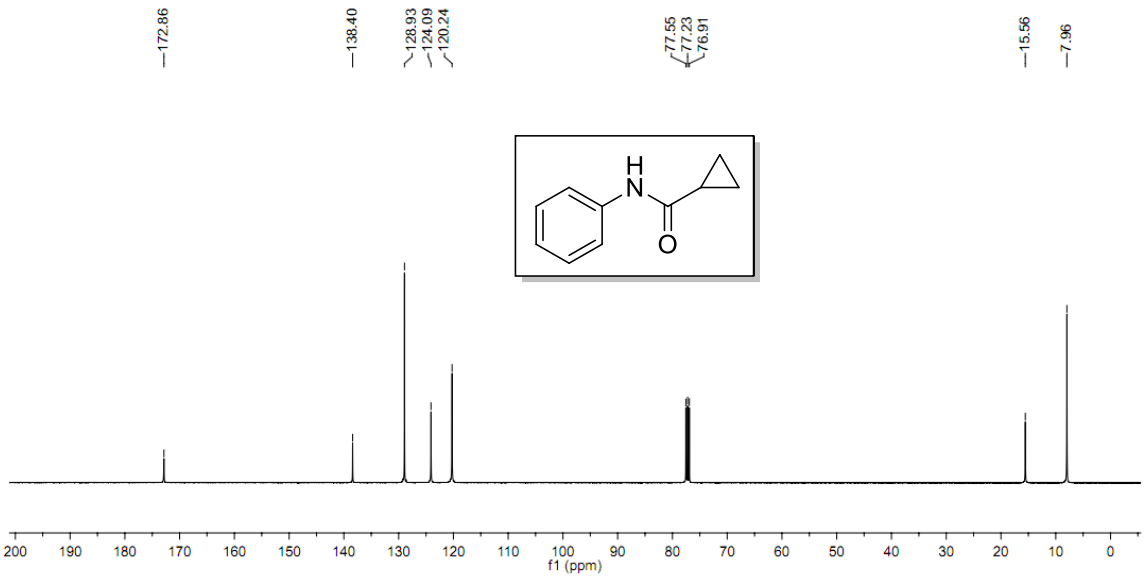


Figure 4.6.1.5. ^{13}C-NMR spectrum of *N*-phenylcyclopropanecarboxamide (entry 2, Table 4.1.1)

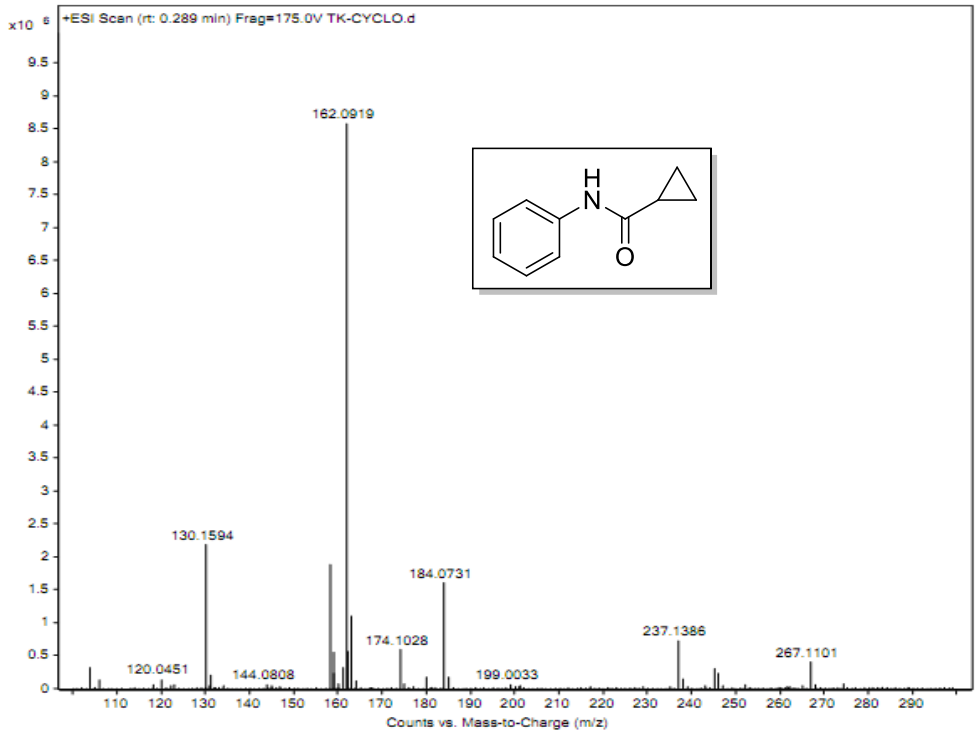


Figure 4.6.1.6. HRMS spectrum of *N*-phenylcyclopropanecarboxamide (entry 2, Table 4.1.1, HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{10}H_{11}NO$ 162.0914, found 162.0919)

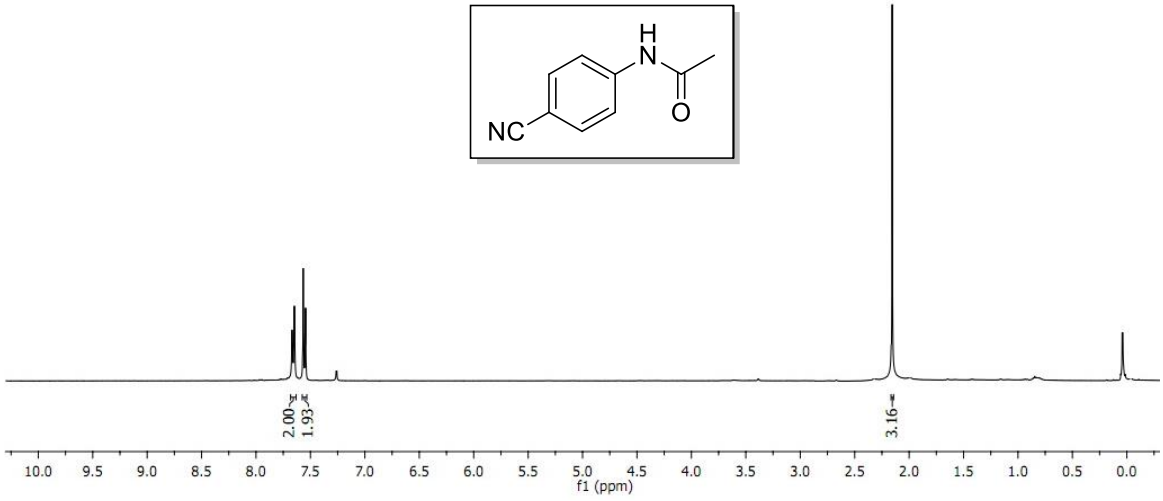


Figure 4.6.1.7. ^{1}H-NMR spectrum of *N*-(4-cyanophenyl)acetamide (entry 3, Table 4.1.1)

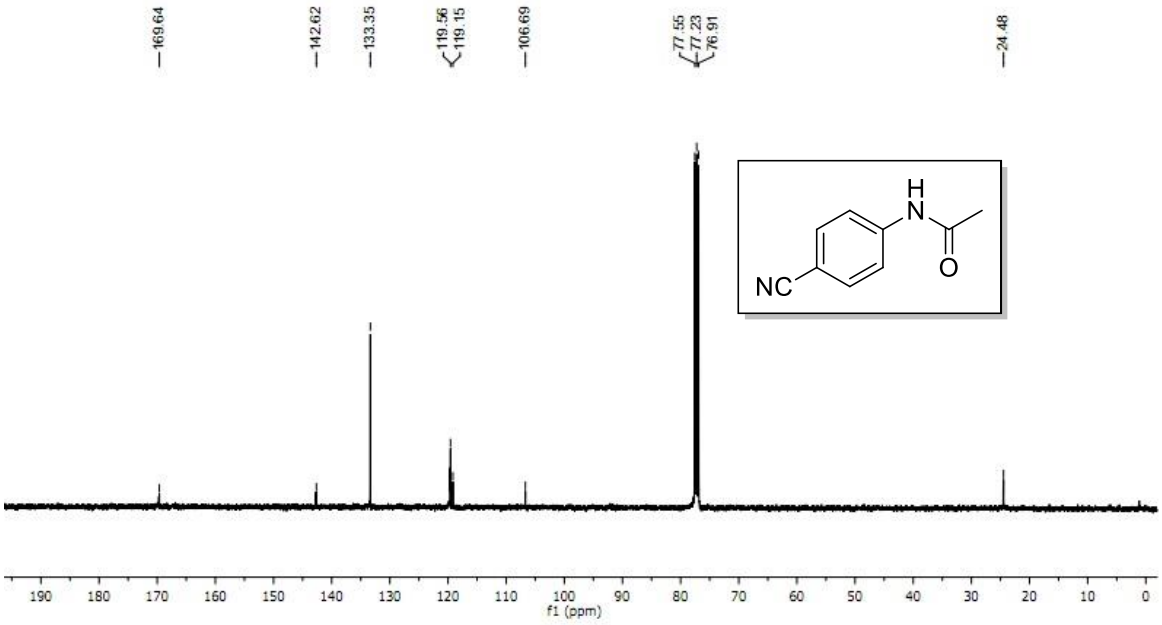


Figure 4.6.1.8. ^{13}C-NMR spectrum of *N*-(4-cyanophenyl)acetamide (entry 3, Table 4.1.1)

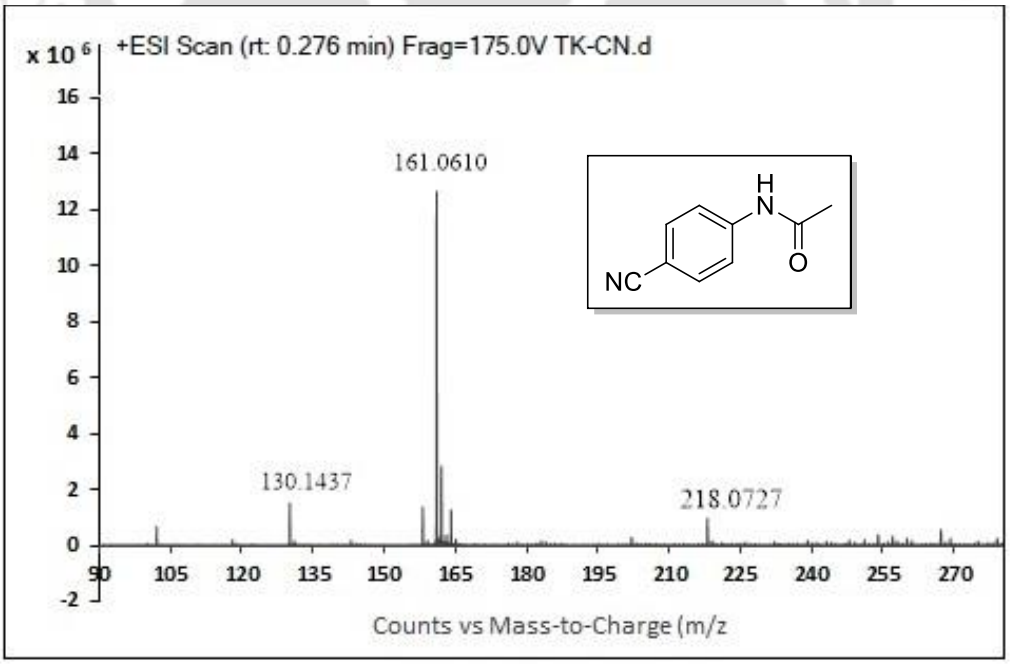


Figure 4.6.1.9. LRMS spectrum of *N*-(4-cyanophenyl)acetamide (entry 3, Table 4.1.1, HRMS (ESI): m/z $[M+H]^+$ calculated for $C_9H_9N_2O$ 161.0710, found 161.0610)

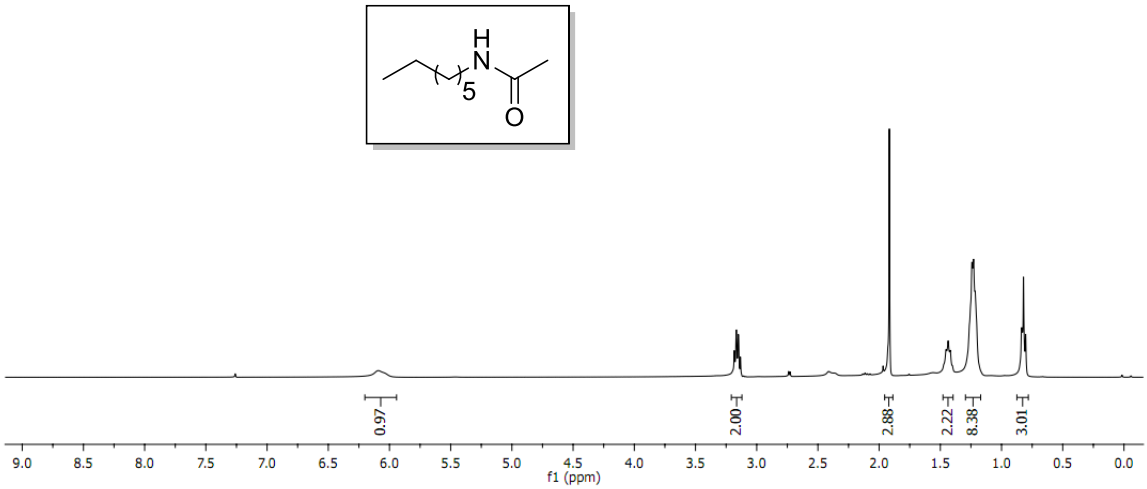


Figure 4.6.1.10. ^{1}H-NMR spectrum of *N*-heptylacetamide (entry 4, Table 4.1.1)

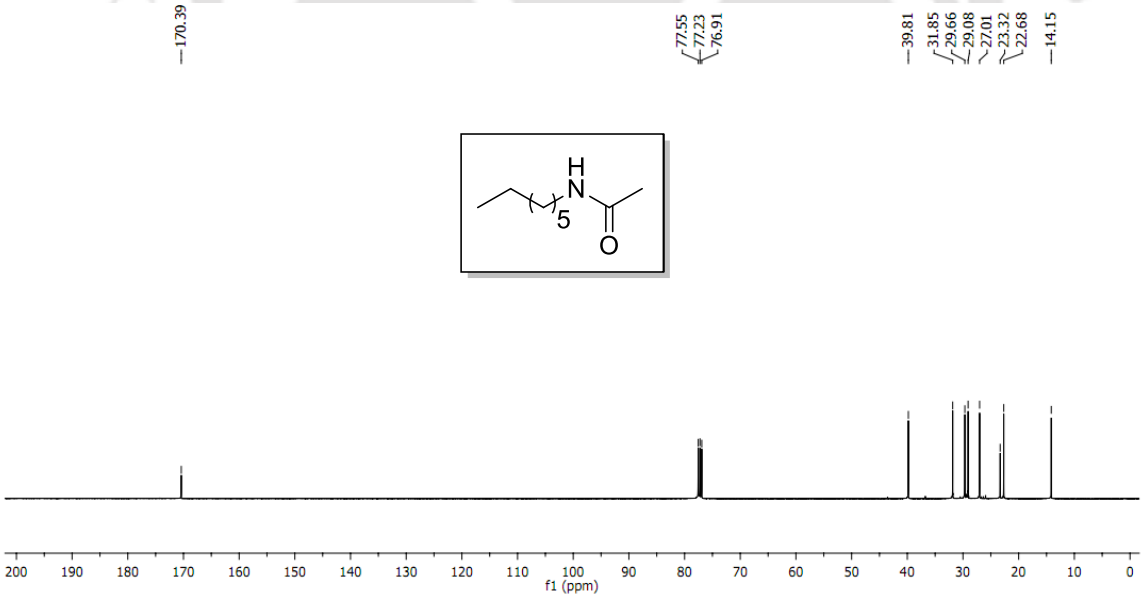


Figure 4.6.1.11. ^{13}C-NMR spectrum of *N*-heptylacetamide (entry 4, Table 4.1.1)

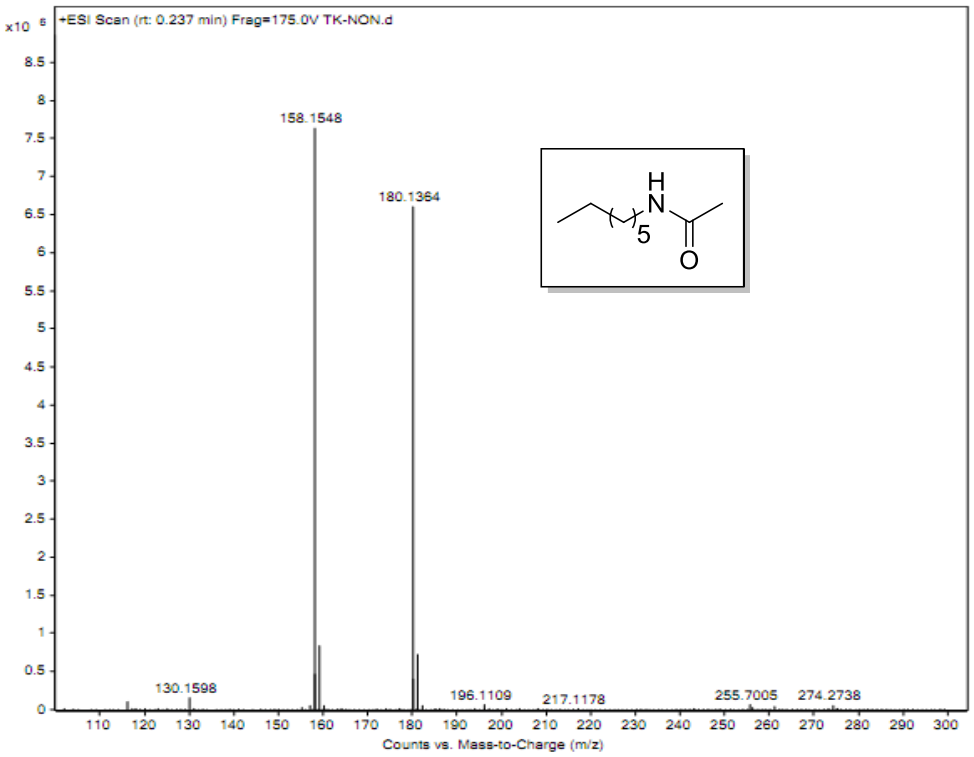


Figure 4.6.1.12. HRMS spectrum of *N*-heptylacetamide (entry 4, Table 4.1.1, HRMS (ESI): m/z $[M+Na]^+$ calculated for $C_9H_{19}NO$ 180.1359, found 180.1364)

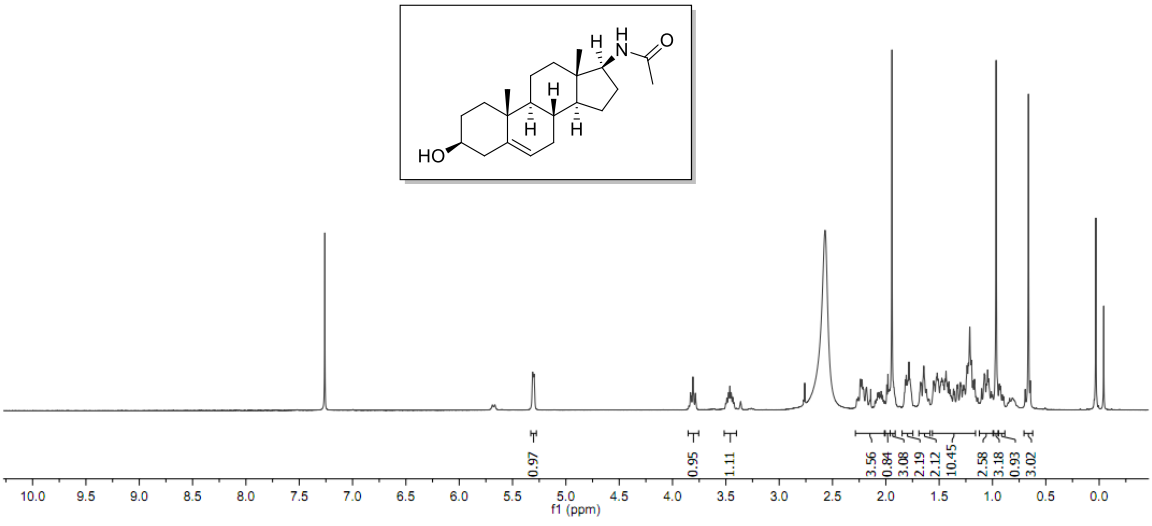


Figure 4.6.1.13. ^{1}H-NMR spectrum of *N*-((3S,8R,9S,10R,13S,14S,17S)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10, 11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)acetamide (entry 5, Table 4.1.1)

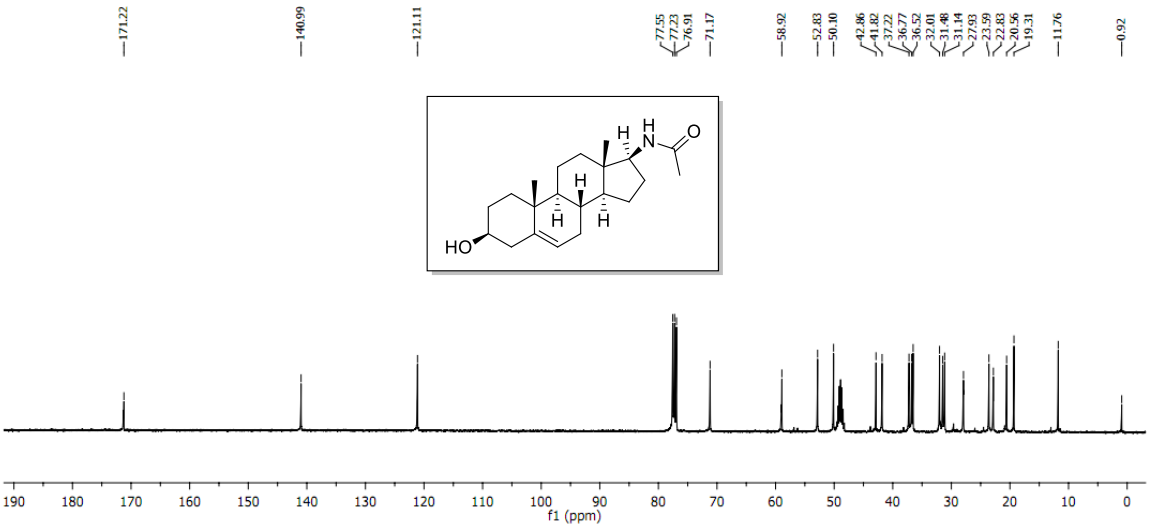


Figure 4.6.1.14. ^{13}C-NMR spectrum of *N*-((3S,8R,9S,10R,13S,14S,17S)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10, 11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)acetamide (entry 5, Table 4.1.1)

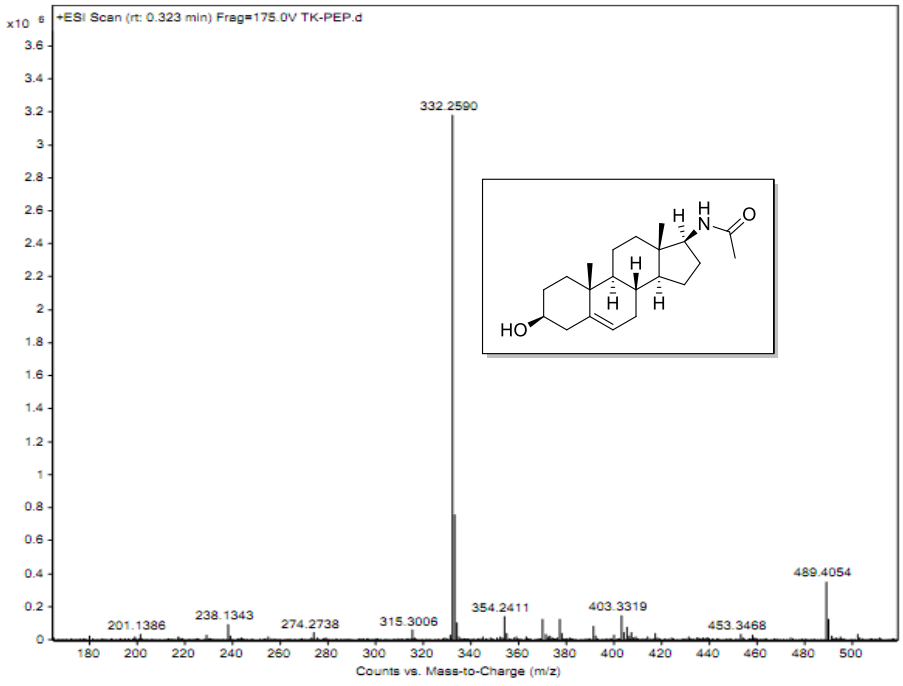


Figure 4.6.1.15. HRMS spectrum of *N*-((3S,8R,9S,10R,13S,14S,17S)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12, 13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)acetamide (entry 5, Table 4.1.1, HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{21}H_{34}NO_2$ 332.2584, found 332.2590)

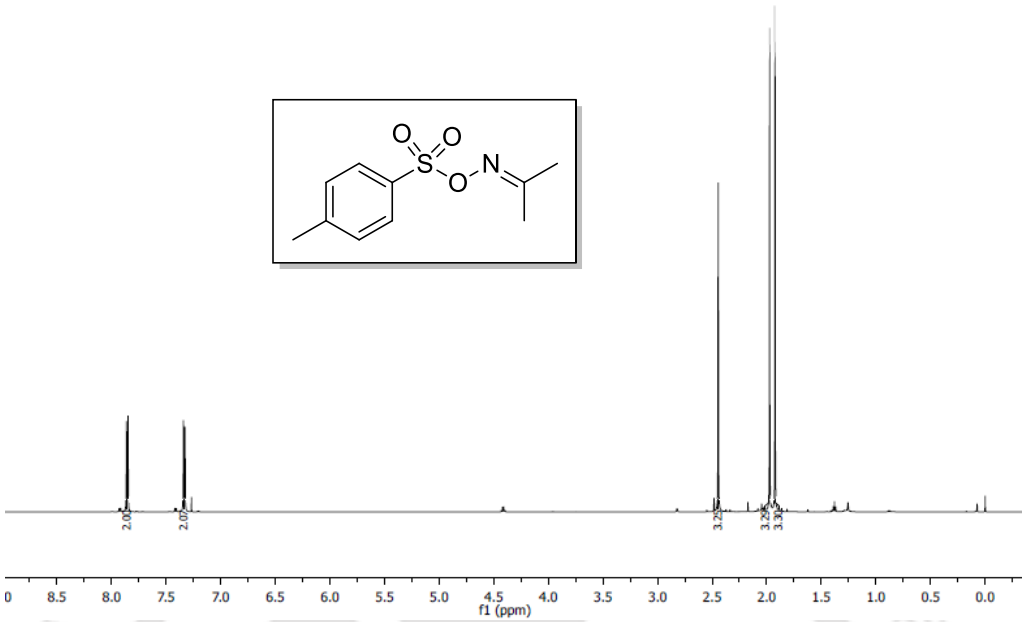


Figure 4.6.1.16. ^{1}H-NMR spectrum of Propan-2-one *O*-tosyl oxime (B1, Scheme 4.2.2)

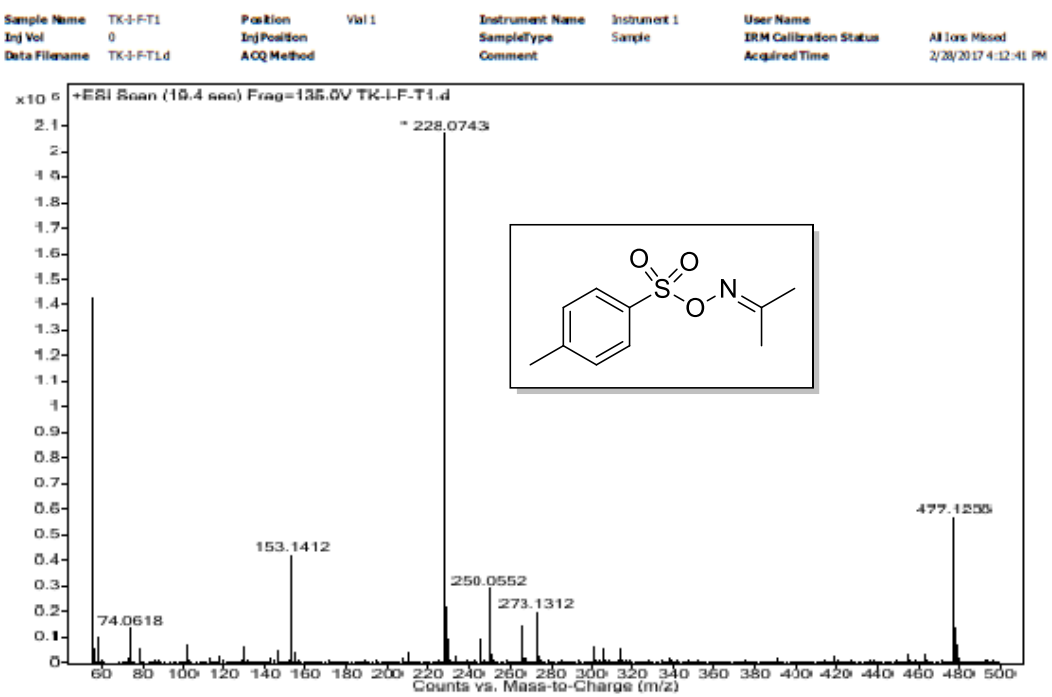


Figure 4.6.1.17. LRMS spectrum of Propan-2-one *O*-tosyl oxime (B1, Scheme 4.2.2, HRMS (ESI): m/z $[M+H]^{+}$ calculated 228.0689, found 228.0743)

4.6.2. Spectra of mechanism study (in Acetonitrile-d_3)

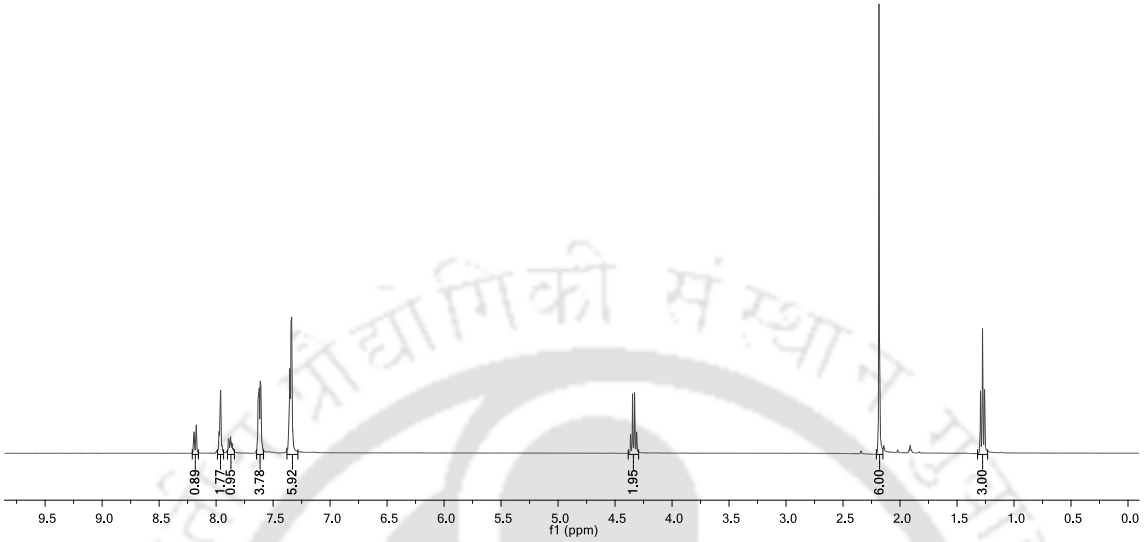


Figure 4.6.2.1. ^{1}H-NMR spectrum of the reaction mixture at 0 minute

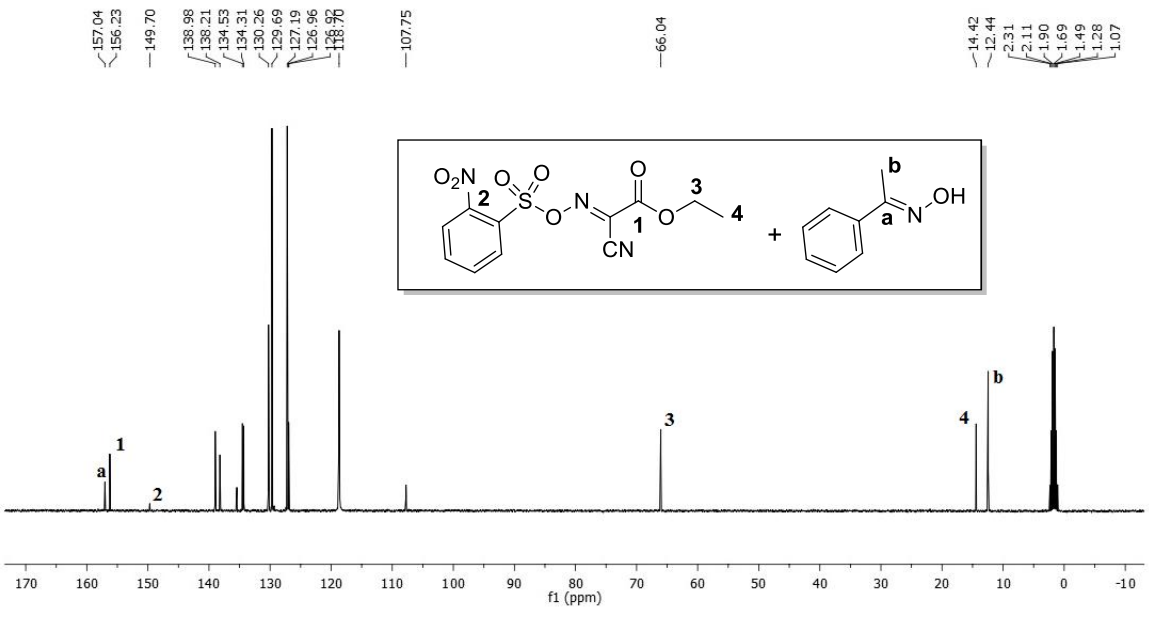


Figure 4.6.2.2. ^{13}C-NMR spectrum of the reaction mixture at 0 minute

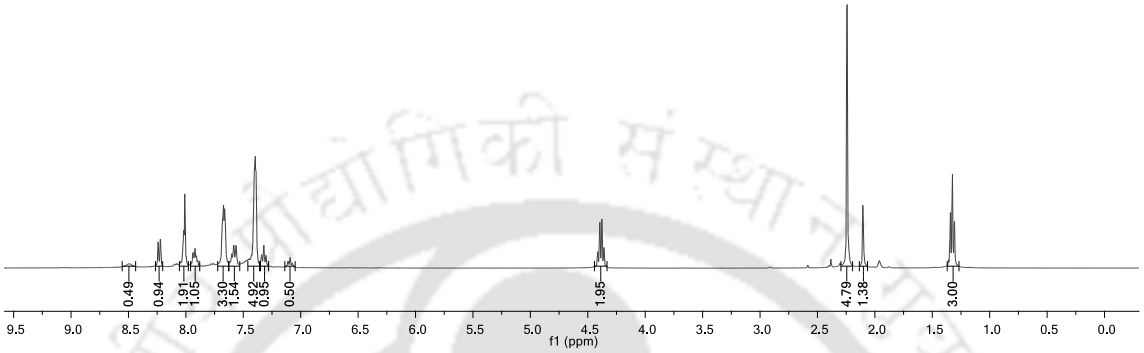


Figure 4.6.2.3. ^{1}H-NMR spectrum of the reaction mixture at 20 minutes

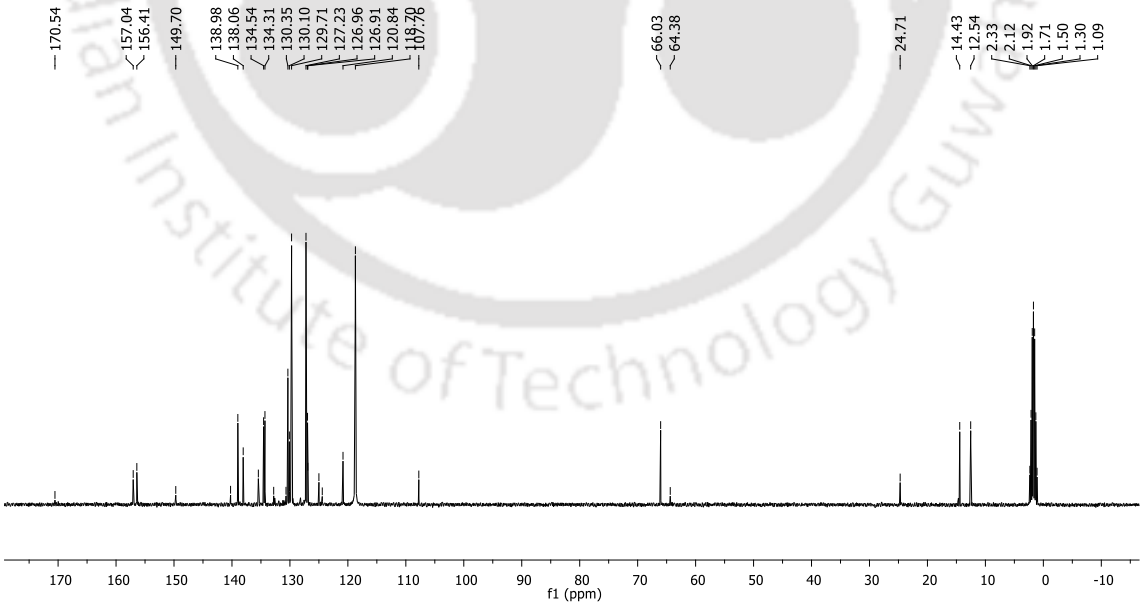


Figure 4.6.2.4. ^{13}C-NMR spectrum of the reaction mixture at 20 minutes

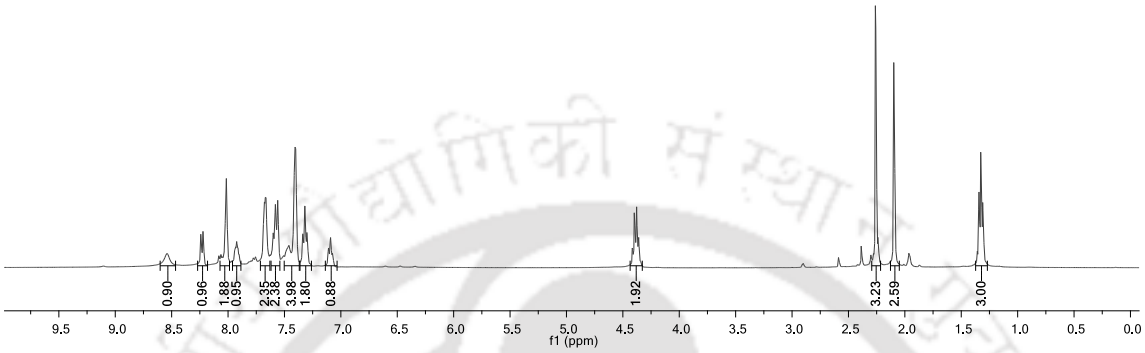


Figure 4.6.2.5. ^{1}H-NMR spectrum of the reaction mixture at 60 minutes

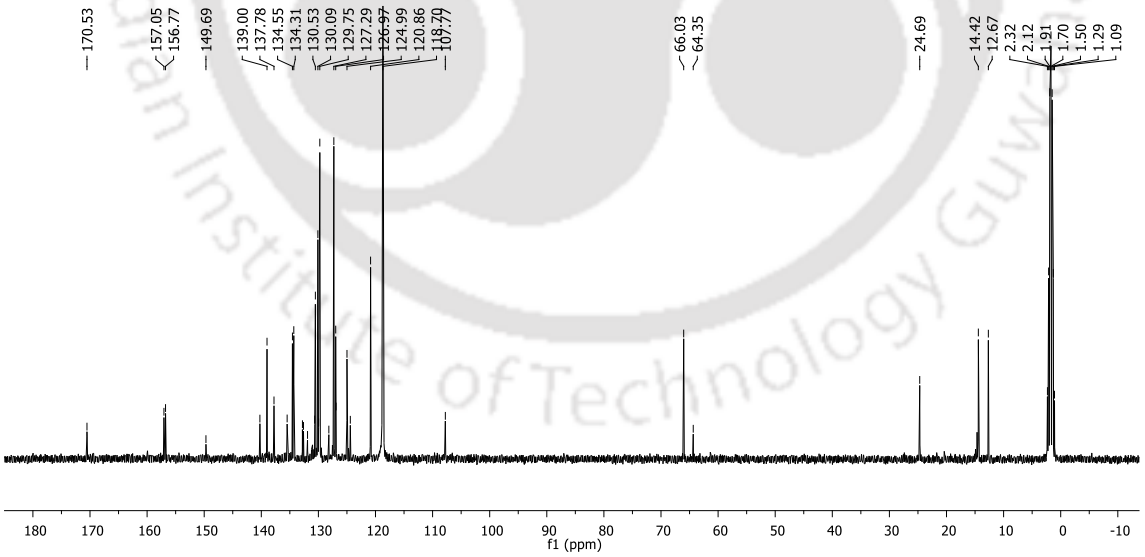


Figure 4.6.2.6. ^{13}C-NMR spectrum of the reaction mixture at 60 minutes

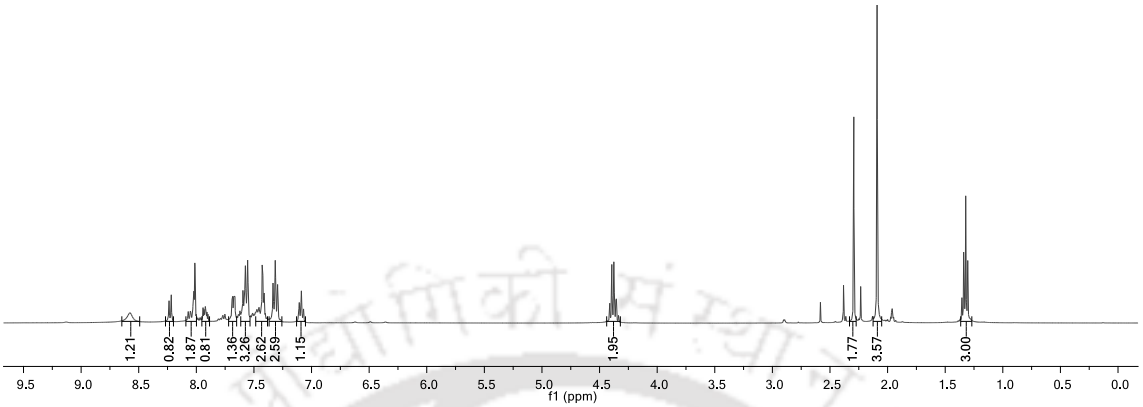


Figure 4.6.2.7. ^{1}H-NMR spectrum of the reaction mixture at 90 minutes

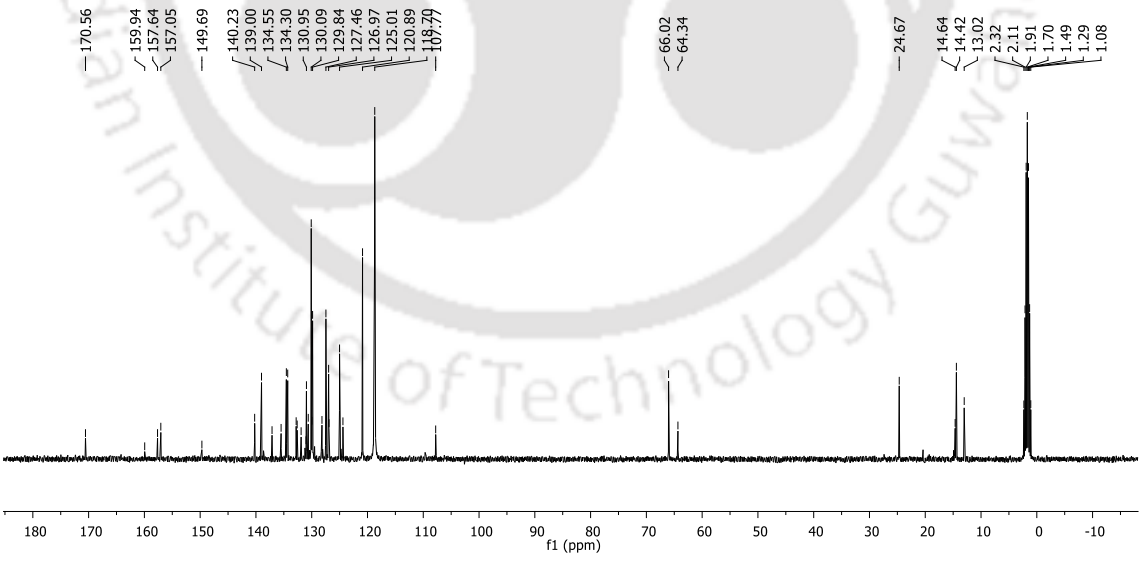


Figure 4.6.2.8. ^{13}C-NMR spectrum of the reaction mixture at 90 minutes

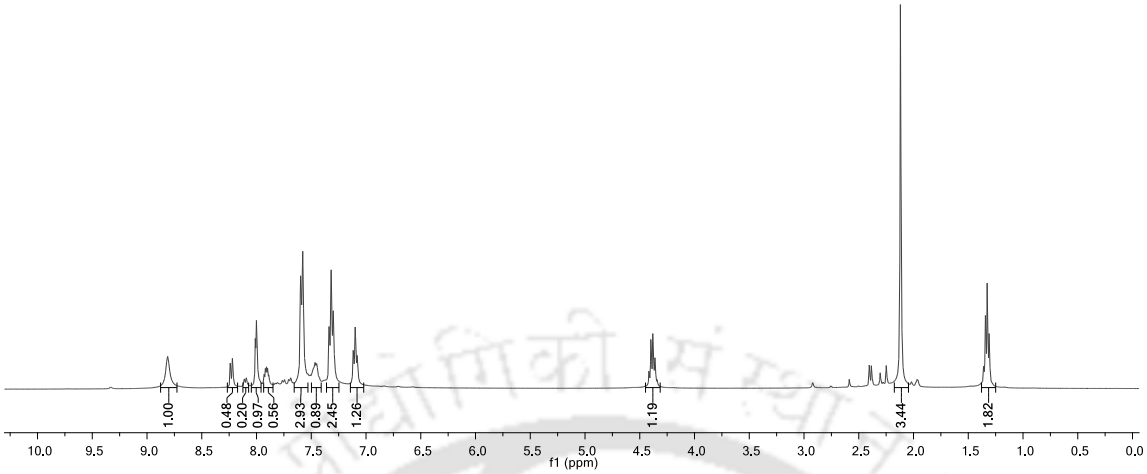


Figure 4.6.2.9. ^{1}H-NMR spectrum of the reaction mixture at 120 minutes

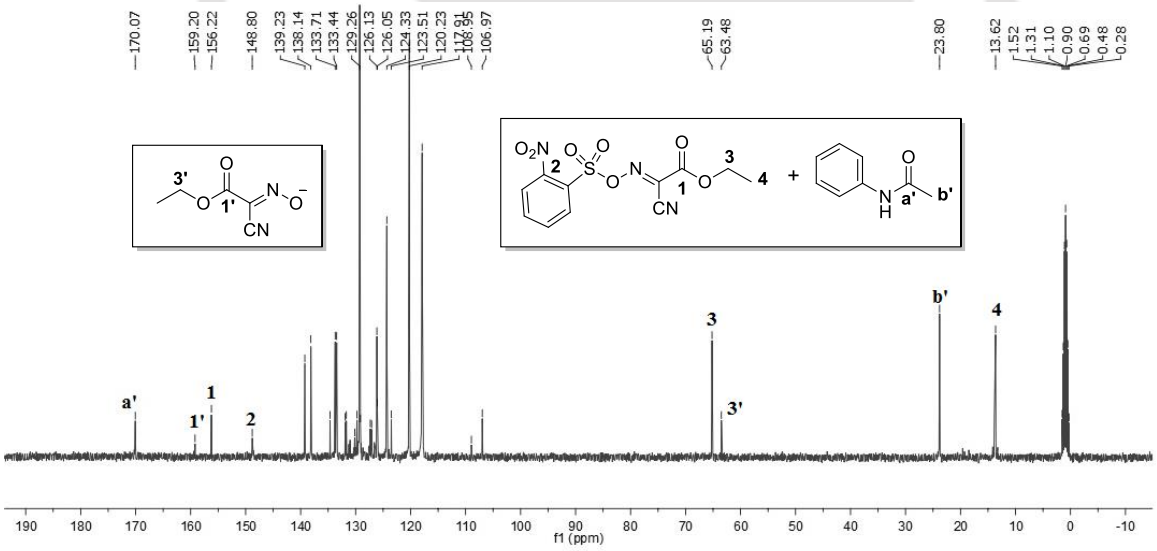


Figure 4.6.2.10. ^{13}C-NMR spectrum of the reaction mixture at 120 minutes

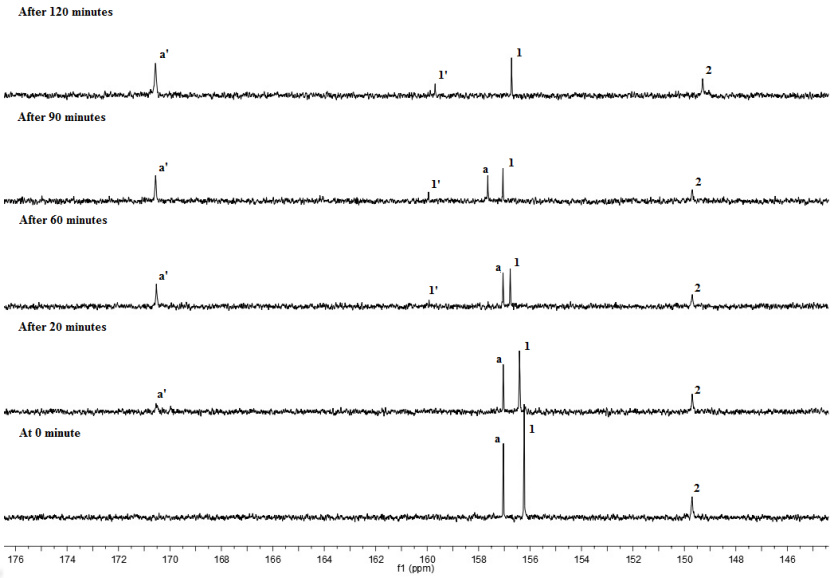


Figure 4.6.2.11. Time-dependent ^{13}C NMR of carbonyl region (After 20 minutes, the disappearance of the peak a and appearance of the peak a' represents the formation of the product amide. The peak 1' correspond to the byproduct Oxyma, and peak 1 and 2 represent the unreacted reagent *o*-NosylOXY)

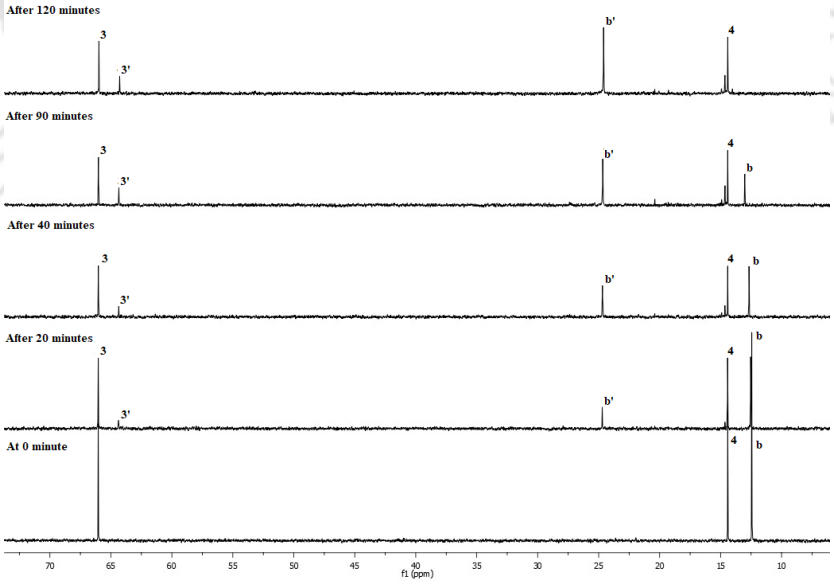


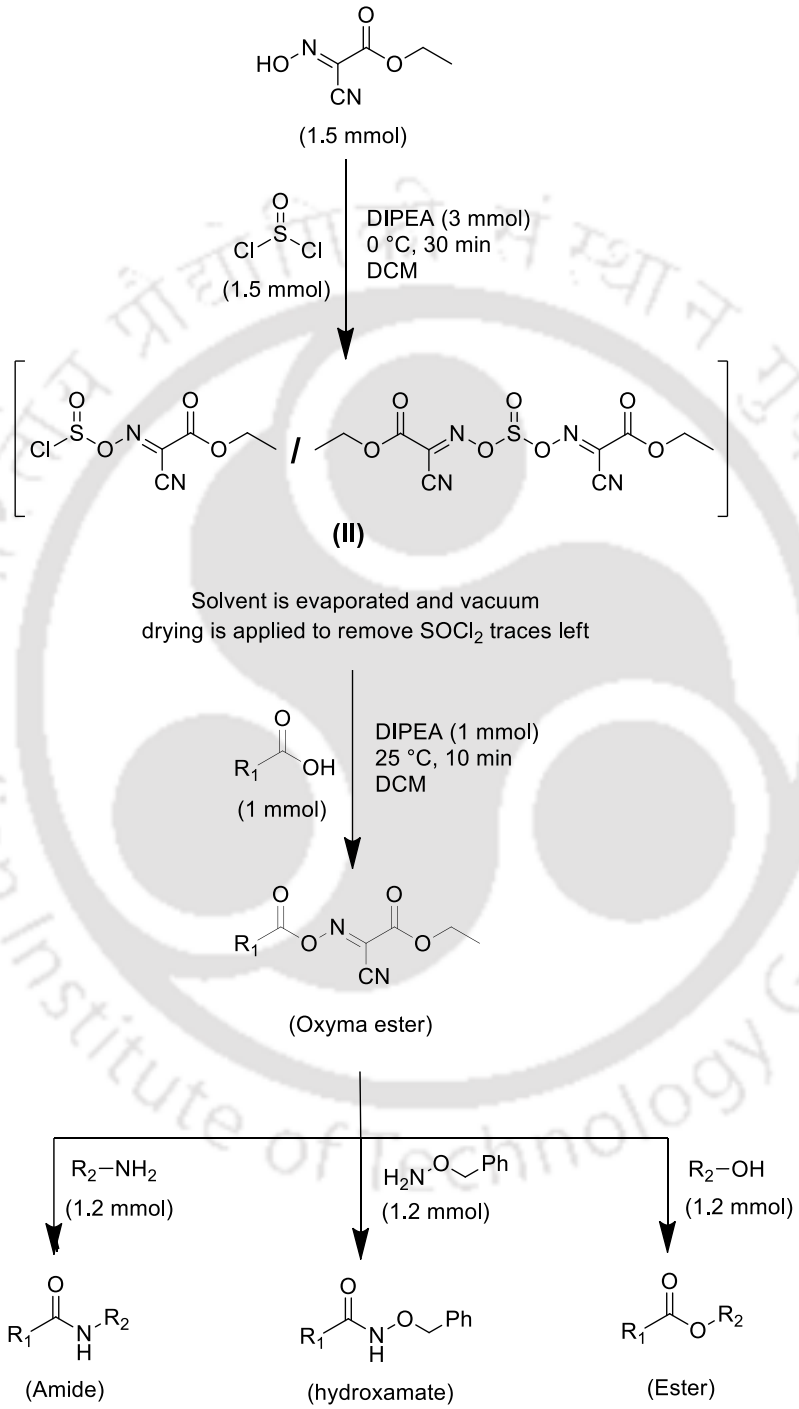
Figure 4.6.2.12. Time-dependent ^{13}C NMR of the aliphatic region (after 20 minutes, the appearance of peak b' and 3' represent the methyl carbon of the product and byproduct Oxyma, respectively. The peak 3 and 4 correspond to the unreacted reagent)

Chapter 5: A One-Pot Methodology for Converting a Carboxylic Acid into Amide, Peptide, Ester, and Hydroxamate Using Oxyma and Thionyl Chloride

In the previous chapters, we demonstrated the involvement of *o*-NosylOXY in some necessary organic transformations. This chapter presents a one-pot, two-step methodology for amide synthesis using Oxyma and thionyl chloride. Amide and peptides are responsible for various actions in our body and having a wide range of applications in drug discovery.[94-95] Numerous coupling reagents involving benzotriazole or azabenzotriazole moiety have been introduced to form amide or peptide bonds (Chapter 1, section 1.4.3). Due to the mild and racemization-suppressing nature of ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma)[19-20] it has become an excellent alternative to benzotriazole-based chemistry. But a few disadvantages like chemical waste generation, multi-step synthesis of the reagents, harmful by-products, and poor atom economy are still associated with it.

Here, we demonstrate a thionyl chloride-based protocol to convert carboxylic acids into amides, dipeptides, esters, and hydroxamates using Oxyma as an additive. NMR studies suggest that the reaction may proceed via two new intermediates, Oxyma-sulfinyl chloride and sulfinyl diOxyma (**II**, *Scheme 5.1*), which are successfully used as a precursor for these syntheses via Oxyma esters. Acid followed by amine to **II** leads to the formation of amide at room temperature. HPLC analysis shows that adding Oxyma to thionyl chloride lowers the final amide's racemization (*Figure 5.2.1*). The by-product

Oxyma can be easily recovered and recycled. Minimal racemization and least waste generation imply the importance of adding Oxyma.



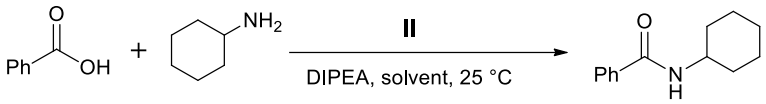
Scheme 5.1. Synthesis of amide, hydroxamate, and ester using Oxyma and thionyl chloride

5.1. Optimization of the reaction condition and substrate scope of synthesis of amide, dipeptide, ester, and hydroxamate using Oxyma and thionyl chloride via II

In this current protocol, thionyl chloride (1.5 mmol) was added to the mixture of Oxyma (1.5 mmol) and DIPEA (3 mmol) in distilled DCM. The solvent was evaporated after 30 min. The reaction mixture was washed thoroughly with DCM 2-3 times, followed by vacuum drying to remove traces of thionyl chloride if left any. Finally, carboxylic acid and the nucleophiles were added to get the desired amide, hydroxamate, and ester. In the second step, solvent optimization was needed. For this purpose, we took benzoic acid (1equiv) as model substrate and cyclohexylamine (1.2 equiv) as amine nucleophile using DIPEA (1 equiv) as a base (*Table 5.1.1*). Various solvents, including EtOAc, ACN, THF, DCM, DMF, $CHCl_3$, and DMSO, were screened at 25 ℃. DCM was the most suitable solvent with an 86% yield (*Table 5.1.1, entry 5*) in 1.5 h. Notably, extending the reaction time up to 7 h did not improve the yield of the reaction (*Table 5.1.1, entry 4*). Again, we observed the changes by decreasing the reaction time from 1.5 h to 1 h and 0.5 h, but a low yield was obtained compared to the earlier one (*Table 5.1.1, entries 6 and 7*). THF and DMSO gave poor yield even after continuing the reaction for a longer time. This optimized procedure was also applied to esters and hydroxamates synthesis.

We also analyzed the impact of increasing the amount of Oxyma, keeping the amount of thionyl chloride the same as before. We used Oxyma (3 mmol) and thionyl chloride (1.5 mmol) in DCM solvent, but increasing Oxyma did not improve the yield. Therefore we preferred to use the equivalent amount of Oxyma and thionyl chloride.

Table 5.1.1. Optimization of the reaction conditions[a]

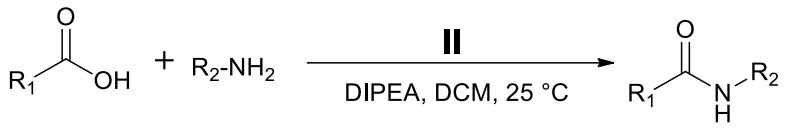


Entry	Solvent	Time (h)[b]	Yield (%)[c]
1	ACN	11	61
2	EtOAc	8	65
3	THF	11	42
4	DCM	7	86
5	**DCM**	**1.5**	**86**
6	DCM	1	70
7	DCM	0.5	40
8	DMF	7	75
9	$CHCl_3$	3	71
10	DMSO	11	25

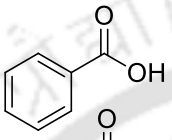
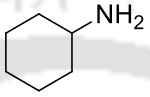
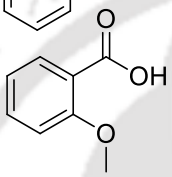
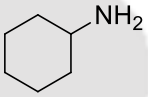
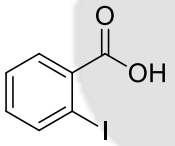
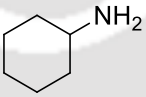
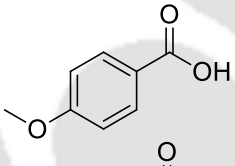
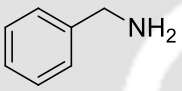
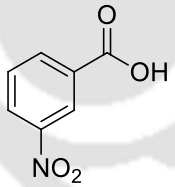
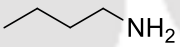
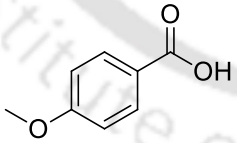
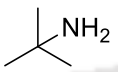
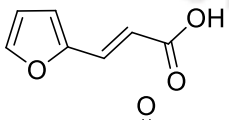
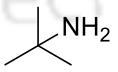
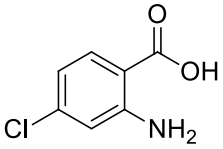
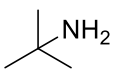
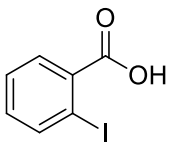
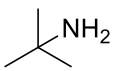
[a] Reaction Condition: ***II*** *[Oxyma (1.5 mmol), DIPEA (3 mmol), thionyl chloride (1.5 mmol)]; benzoic acid (1 mmol), DIPEA (1 mmol), cyclohexylamine (1.2 mmol), solvent (5 ml) at 25 ℃. [b] time after the addition of amine. [c] isolated yield.*

Using the optimized reaction conditions, we efficiently converted various carboxylic acids containing different substituents such as methoxy, iodo, and nitro to amides (*Table 5.1.2*). Aliphatic and aromatic amines such as cyclohexylamine, benzylamine, n-butylamine, and aniline, were used as nucleophiles. 3-(2-Furyl)acrylic acid, an α,β-unsaturated acid, was successfully transformed to its corresponding amide with 78% yield when tert-butylamine was used (*Table 5.1.2, entry 7*). Four anilides could be prepared from benzoic acid, phenylacetic acid, anthralinic acid, and Fmoc-phenylalanine in good yield (*Table 5.1.2, entry 10-13*).

Table 5.1.2. Substrate scope for the synthesis of amides and dipeptides[a]



R_1 = Aryl or N-protected amino acid, R_2 = Aryl, alkyl or methyl esters of amino acid
19 examples (72 to 86% yield)

Entry	R_1COOH	R_2NH_2	Product id	Yield (%)[b]
1			3a	86
2			3b	84
3			3c	80
4			3d	84
5			3e	82
6			3f	81
7			3g	78
8			3h	73
9			3i	81

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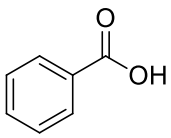
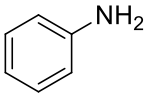
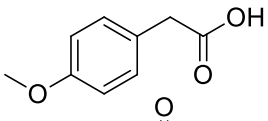
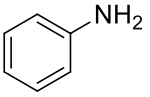
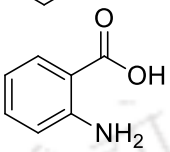
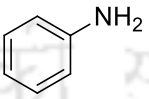
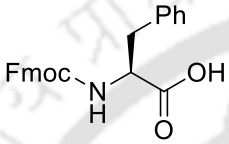
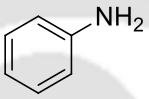
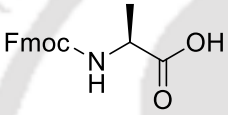
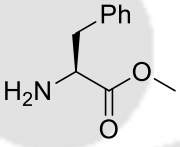
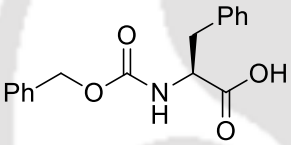
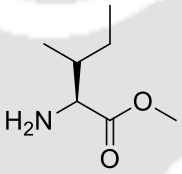
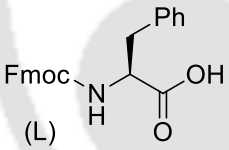
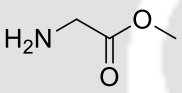
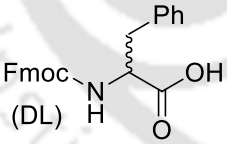
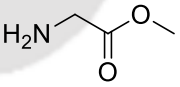
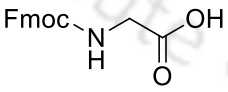
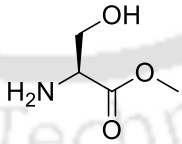
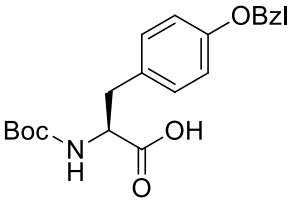
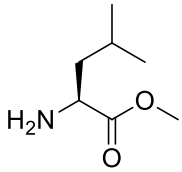
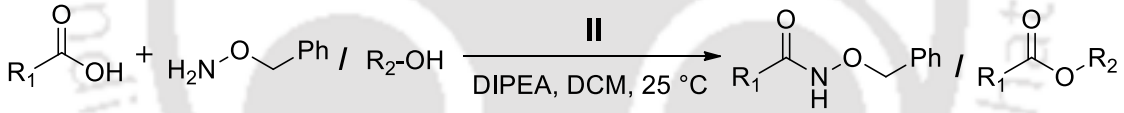
10			3j	78
11			3k	77
12			3l	72
13			3m	78
14			3n	79
15			3o	79
16			3p	82
17			3q	81
18			3r	77
19			3s	72

[a] Reaction Condition: ***II*** *[Oxyma (1.5 mmol), DIPEA (3 mmol), thionyl chloride (1.5 mmol)], acid (1 mmol), DIPEA (1 mmol), amine (1.2 mmol), DCM (5 ml) at 25 ℃ for 1.5-2 h. [b] Isolated yield.*

While synthesizing 3h (*Table 5.1.2, entry 8*) and 3l (*Table 5.1.2, entry 12*), the self-condensation products could not be characterized and isolated, probably due to less nucleophilicity of aniline. The reaction worked well with common N-protections, such as Fmoc, Boc, and Cbz with a satisfactory yield of 72-82% (*Table 5.1.2, entry 14-19*). Methyl esters of phenylalanine, glycine, isoleucine, serine, and leucine were successfully used as amine nucleophiles. The protocol was extended to hydroxamate and ester synthesis (*Table 5.1.3, entry 1-9*). For this, *o*-benzylhydroxylamine, methanol, and 4-nitrobenzyl alcohol were used as nucleophiles. All the products were characterized by ^{1}H, ^{13}C NMR, and ESI-MS except 6g (*Table 5.1.3, entry 7*), not ionized in mass spectrometry.

Table 5.1.3. Substrate scope for the synthesis of hydroxamates and esters[a]



R_1 = Aryl or fmoc-amino acid, R_2 = Aryl, alkyl group
9 examples (67 to 85% yield)

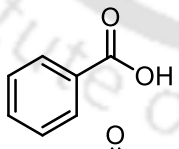
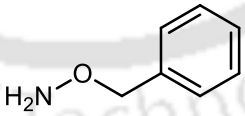
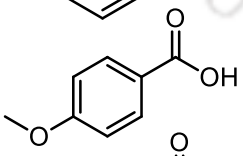
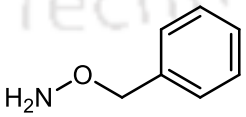
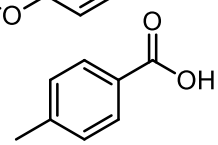
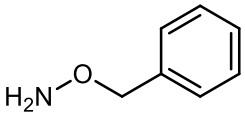
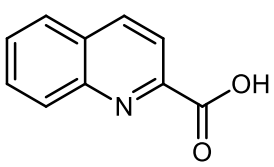
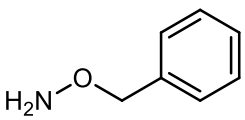
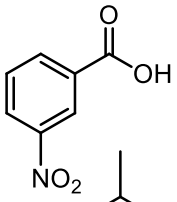
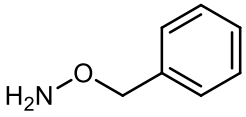
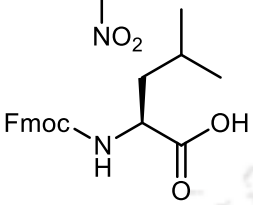
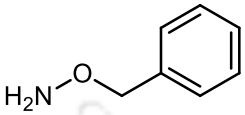
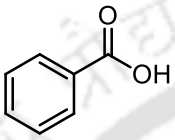
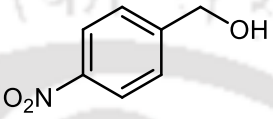
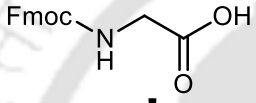
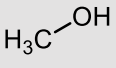
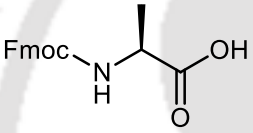
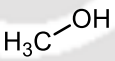
Entry	R_1COOH	R_2XH (X= NH_2, O)	Product id	Yield (%)[b]
1			6a	85
2			6b	84
3			6c	81
4			6d	79

Table 5.1.3 continued....

5			6e	81
6			6f	80
7			6g	67
8			6h	71
9			6i	70

[a] Reaction Condition: ***II*** *[Oxyma (1.5 mmol), DIPEA (3 mmol), thionyl chloride (1.5 mmol)], acid (1 mmol), DIPEA (1 mmol), O-benzylhydroxylamine/alcohol (1.2 mmol), DCM (5 ml) at 25 ℃ for 1.5-2 h. [b] Isolated yield.*

Protocols using important coupling reagents and metal for amide synthesis are mentioned below. Formation of amide and peptide bonds in an aqueous micellar medium using COMU as a coupling reagent was reported with almost 82-99% yield.[82] Mild decarboxylative activations of malonic acid derivatives using CDI results in amide with 83-100% except for few substrates.[83] A series of the dipeptide was achieved through $TiCl_4$ assisted condensation reaction with a 60-87% yield.[84]

5.2. Racemization study

We synthesized Fmoc-DL-Phe-Gly-Ome (*Table 5.1.2, entry 17*) and Fmoc-L-Phe-Gly-Ome (*Table 5.1.2, entry 16*) using the current protocol. Again we prepared the L analog

with thionyl chloride in the absence of Oxyma. To investigate the stereochemical aspects, we compared the HPLC spectra of these three (*Figure 5.2.1*). All were passed through the chiral column in the same isocratic solvent system. In the HPLC chromatogram, two distinct peaks corresponding to the two enantiomers for DL analog were obtained (*Figure 5.8.2.1*). The L isomer synthesized from thionyl chloride without Oxyma showed a 2.29 percent minor isomer (*Figure 5.8.2.2*). Interestingly, it decreases to 0.14 percent while using the present protocol (*Figure 5.8.2.3*). Moreover, we could not find any evidence of diastereomer formation while characterizing the dipeptides (*Table 5.1.2, entries 14, 15, and 19*). From these results, it can be concluded that the addition of Oxyma to thionyl chloride significantly decreases the extent of racemization.

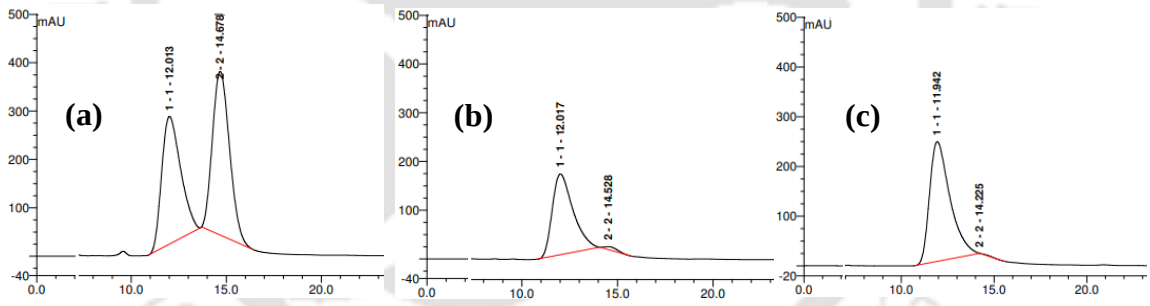
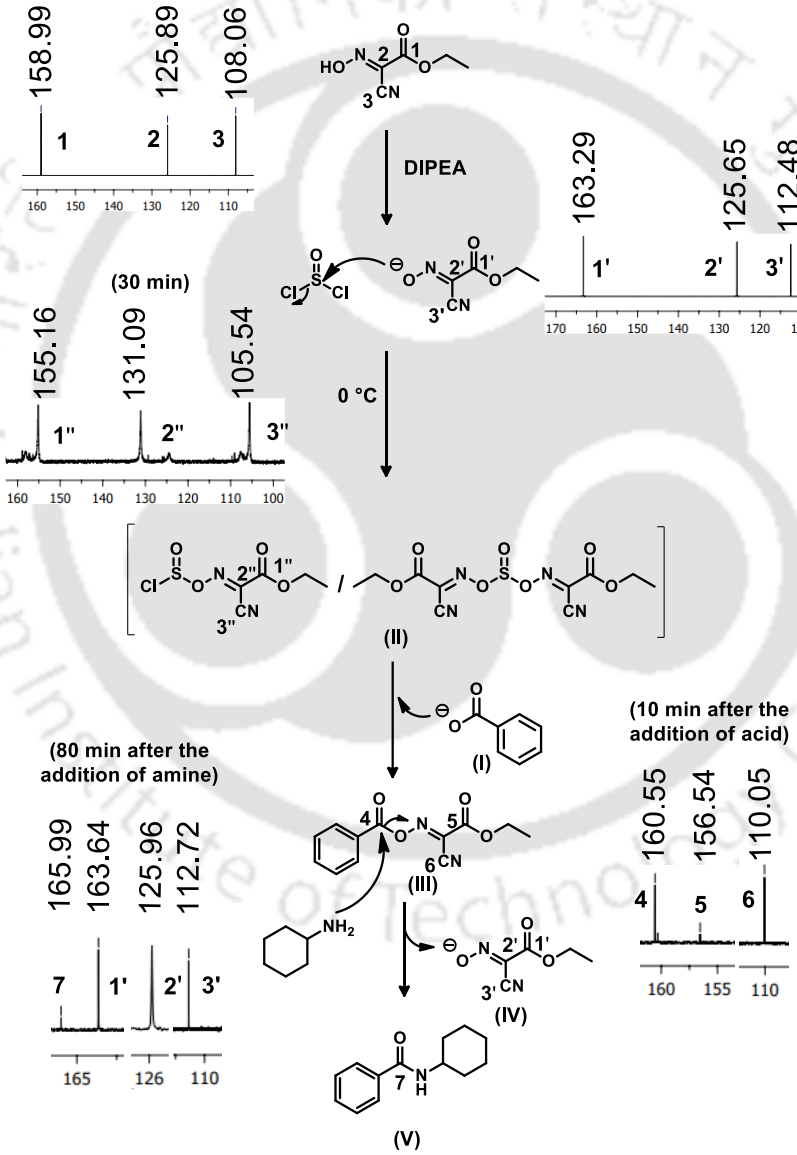


Figure 5.2.1. HPLC profile of (a) DL analog of Fmoc-Phe-Gly-OMe using the current protocol, (b) L analog synthesized using thionyl chloride devoid of Oxyma, (c) L analog synthesized using the current protocol, chiral column (5 µm, 2.1×150 mm, Isocratic isopropanol-hexane solvent system)

5.3. Mechanism study

We propose a plausible mechanism for amide synthesis by Oxyma and thionyl chloride (*Scheme 5.3.1*). In the first step, thionyl chloride was added to Oxyma in the presence of

DIPEA, resulting in a yellow-colored reaction mixture (**II**) probably containing Oxyma sulfinyl chloride and sulfinyl diOxyma. In the next step, the carboxylic acid (**I**) was added to **II**, forming Oxyma ester of carboxylic acid (Intermediate **III**). Finally, amine reacted to **III** producing the desired amide (**V**) and by-product Oxyma (**IV**).



Scheme 5.3.1. A plausible mechanism for the synthesis of an amide using **II** starting from Oxyma and $SOCl_2$ via Oxyma ester

To demonstrate the proposed mechanism, we performed an NMR-based study in $CDCl_3$ solvent as per scheme 5.1 (*Figure 5.8.3.1-5.8.3.5*). We took Oxyma (1.5 equiv), DIPEA (3 equiv), thionyl chloride (1.5 equiv) for the first step, and benzoic acid (1 equiv), DIPEA (1 equiv), cyclohexylamine (1.2 equiv) for the second step. Noticeable changes were seen in ^{13}C NMR. The peaks at 158.99, 125.89, and 108.06 ppm in ^{13}C NMR of pure Oxyma assigned to the carbons denoted as **1**, **2**, and **3** (*Figure 5.8.3.1*) shifted to 163.29, 125.65, and 112.48 ppm (**1**', **2**' and **3**') in the presence of DIPEA (*Figure 5.8.3.2*) which after addition of $SOCl_2$ further changed to 155.16, 131.09, and 105.54 ppm (**1**'', **2**'' and **3**'') of **II** (*Figure 5.8.3.3*). The shifting of the peaks indicated the introduction of Oxyma moiety in thionyl chloride to generate Oxyma sulfinyl chloride. Spectra were recorded 10 min after the addition of benzoate anion to **II**. Three new peaks appeared at 160.55, 156.54, and 110.05 ppm (**4**, **5**, and **6**), corresponding to two carbonyl centers and the cyano group of **III**, respectively (*Figure 5.8.3.4*). Then, cyclohexylamine was added, and one new peak appeared at 165.99 ppm (**7**), confirming amide formation (*Figure 5.8.3.5*). The simultaneous appearance of peaks **1**', **2**', and **3**' at 163.64, 125.96, and 112.72 ppm referred to the release of by-product Oxyma.

While carefully examining the ^{13}C NMR spectra of the reaction mixture **II** containing Oxyma sulfinyl chloride, we revealed the presence of some sister peaks (*green, Figure 5.3.1*). To understand further, we performed a control reaction between 2 equiv of Oxyma and 1 equiv of thionyl chloride in $CDCl_3$ using the same reaction conditions (*Figure 5.8.4.2*). In the presence of a higher amount of Oxyma, the relative intensity of those sister peaks **1**''', **2**''' and **3**''' in the magenta curve (*Figure 5.3.1*) were increased. These sister peaks may arise if Oxyma substitute both of the chlorines of $SOCl_2$, generating

sulfinyl diOxyma. However, all the efforts to isolate and purify Oxyma sulfinyl chloride and sulfinyl diOxyma went in vain. Therefore, in situ generations of these reagents and immediate utilization is recommended.

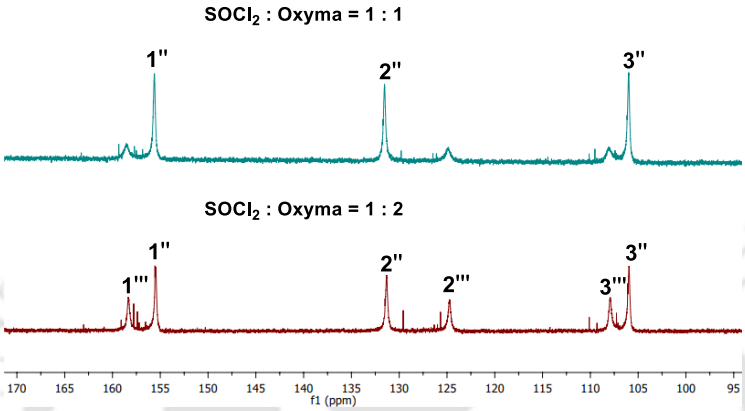
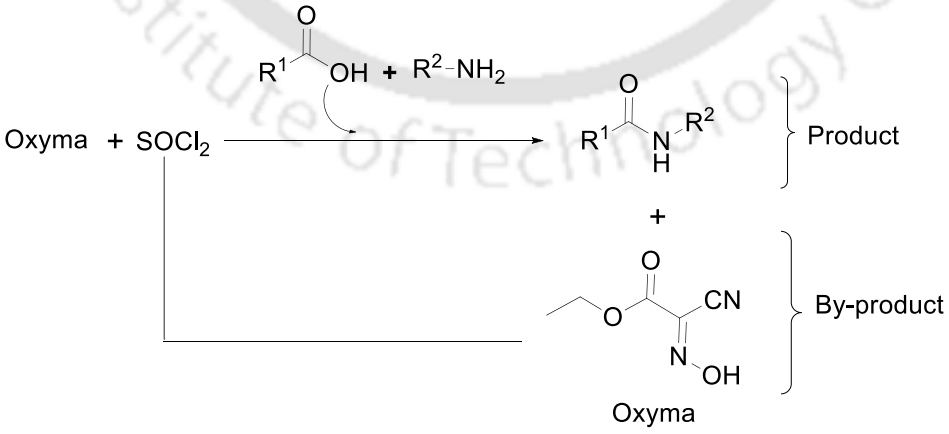


Figure 5.3.1. ^{13}C NMR comparison spectra using different equivalents of Oxyma.

5.4. Recyclability

In this protocol, the only by-product obtained is Oxyma. After completion of the reaction, the organic layer was washed with 5% citric acid (3×5 ml) and then purified via column chromatography. The Oxyma recovered in this way could be reused (*Scheme 5.4.1*).



Scheme 5.4.1. Recyclability of this protocol

5.5. Conclusion

In conclusion, we have reported a one-pot, Oxyma-based methodology to synthesize amides, dipeptides, esters, and hydroxamates in good yields. The process is recyclable and applicable to a diverse range of substrates. The addition of Oxyma decreases the extent of racemization in this process which is understood by HPLC analysis. A detailed NMR-based mechanistic investigation indicates that reactions proceed via the formation of Oxyma sulfinyl chloride and sulfinyl diOxyma. Unlike other methods, it avoids the complex synthesis of coupling reagents, catalysts, and chemical waste generation. All these features make this methodology a useful one.

5.6. Experimental Section

5.6.1. General consideration

As described in chapter 3, section 3.5.1

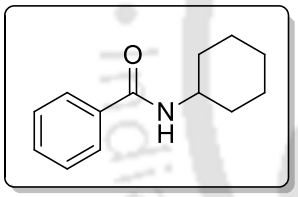
5.6.2. General procedure for the synthesis of amides, peptides, hydroxamates, and esters

To a solution of Oxyma (1.5 mmol, 1.5 equiv) and DIPEA (3 mmol, 3 equiv) in distilled DCM (5ml), thionyl chloride (1.5 mmol, 1.5 equiv) was added at 0 °C, and the stirring was continued for 30 min. After that, the solvent was evaporated using a rotary evaporator, and the reaction mixture was washed with DCM 2-3 times, followed by vacuum drying to remove the traces of thionyl chloride, if left any. Carboxylic acid / N-protected amino acid (1 mmol, 1 equiv), DIPEA (1 mmol, 1 equiv), and 5ml DCM were added to this mixture. It is noteworthy that slightly basic condition should be maintained

for acid-sensitive compounds, which was checked by pH paper. 10 min later, amine/methyl ester of second amino acid/alcohol/*O*-benzylhydroxylamine (1.2 mmol, 1.2 equiv) was added. The reaction was continued for more than 1.5-2 h 25 °C. After completion, the organic layer was washed with 5% citric acid (3 × 5 ml), 5% $NaHCO_3$ (3 × 5 ml) solution, and dried over $CaCl_2$. Finally, the solvent was evaporated, and the residue was purified by silica gel column chromatography.

5.7. Characterization data

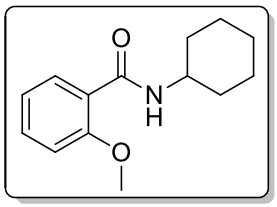
N-cyclohexylbenzamide (entry 1, Table 5.1.2)



Yield: 174 mg (86%); colourless solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 147-149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75-7.73 (d, *J* = 7.6 Hz, 2H), 7.47-7.44 (t, *J* = 7.2 Hz, 1H), 7.41-7.37 (t, *J* = 7.6 Hz, 2H), 6.09 (br s, 1H), 4.00-3.91 (m, 1H), 2.02-1.99 (m, 2H), 1.76-1.71 (m, 2H), 1.66-1.61 (m, 1H), 1.45-1.35 (m, 2H), 1.27-1.14 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 135.3, 131.3, 128.6, 127.0, 48.8, 30.3, 25.7, 25.1; FT-IR (KBr): 3236, 2949, 2928, 1623, 1550, 1331, 1076, 694 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{13}H_{17}NO$ 204.1388, found 204.1379.

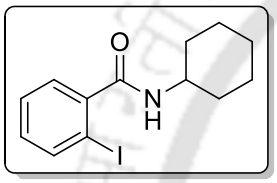
N-cyclohexyl-2-methoxybenzamide (entry 2, Table 5.1.2)

Yield: 195 mg (84%); white solid; R_f = 0.50 (EtOAc:Hexane, 2.5:7.5); mp: 68-70 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18-8.17 (d, *J* = 9.6 Hz, 1H), 7.79 (br s, 1H), 7.41-7.38 (t, *J* = 6 Hz, 1H), 7.06-7.03 (t, *J* = 7.2 Hz, 1H), 6.94-6.93 (t, *J* = 8.4 Hz, 1H), 4.03-3.98 (m,



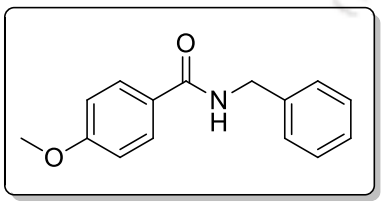
1H), 3.93 (s, 3H), 1.98-1.97 (m, 2H), 1.70-1.68 (m, 2H), 1.61-1.59 (m, 1H), 1.45-1.40 (m, 2H), 1.31-1.24 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.3, 157.5, 132.5, 132.3, 122.3, 121.4, 111.5, 56.1, 48.1, 33.1, 25.9, 24.8; FT-IR (KBr): 3335, 2928, 2852, 1631, 1530, 1241, 759 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{14}H_{19}NO_2$ 234.1494, found 234.1501.

N-cyclohexyl-2-iodobenzamide (entry 3, Table 5.1.2)



Yield: 263 mg (80%); white solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 149-151 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80-7.79 (d, *J* = 7.8 Hz, 1H), 7.36-7.31 (m, 2H), 7.08-7.00 (m, 1H), 5.77 (br s, 1H), 4.01-3.88 (m, 1H), 2.04-2.02 (m, 2H), 1.73-1.71 (m, 2H), 1.62-1.60 (m, 1H), 1.42-1.32 (m, 2H), 1.26-1.16 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.6, 142.7, 139.8, 130.9, 128.3, 128.2, 92.6, 49.0, 33.0, 25.6, 24.9; FT-IR (KBr): 3290, 2928, 2852, 1634, 1533, 1014, 680 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{13}H_{16}INO$ 330.0355, found 330.0358.

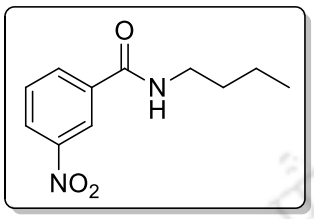
N-benzyl-4-methoxybenzamide (entry 4, Table 5.1.2))



Yield: 202 mg (84%); yellow solid; R_f = 0.50 (EtOAc:Hexane, 2.5:7.5); mp: 127-129 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76-7.74 (d, *J* = 13.2 Hz, 2H), 7.35-7.34 (m, 4H), 7.32-7.27 (m, 1H), 6.92-6.90 (d, *J* = 13.2 Hz, 2H), 6.36 (br s, 1H), 4.63 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.0, 162.3, 138.5, 128.96, 128.94, 128.0, 127.7, 126.7, 113.9, 55.6, 44.2; FT-IR (KBr): 3309, 2931, 2832, 1659,

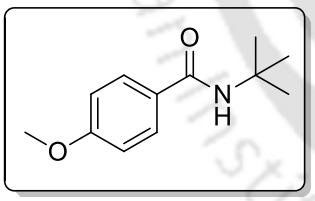
1598, 1239, 756 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{15}H_{15}NO_2$ 242.1181, found 242.1173

N-butyl-3-nitrobenzamide (entry 5, Table 5.1.2)



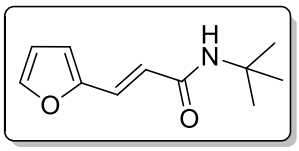
Yield: 182 mg (82%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 68-70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58-8.56 (m, 1H), 8.29-8.27 (d, *J* = 8 Hz, 1H), 8.14-8.12 (d, *J* = 8 Hz, 1H), 7.60-7.56 (t, *J* = 8 Hz, 1H), 6.89 (br s, 1H), 3.47-3.42 (m, 2H), 1.63-1.56 (m, 2H), 1.42-1.33 (m, 2H), 0.93-0.89 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 148.2, 136.6, 133.4, 129.8, 125.9, 121.9, 40.3, 31.6, 20.2, 13.8; FT-IR (KBr): 3304, 2942, 2877, 1631, 1225, 902, 683 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{11}H_{14}N_2O_3$ 223.1083, found 223.1063.

N-(tert-butyl)-4-methoxybenzamide (entry 6, Table 5.1.2)



Yield: 167 mg (81%); yellow solid; R_f = 0.50 (EtOAc:Hexane, 1.5:8.5); mp: 113-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.66 (d, *J* = 8.8 Hz, 2H), 6.90-6.88 (d, *J* = 8.8 Hz, 2H), 5.87 (br s, 1H), 3.83 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 162.0, 128.6, 128.4, 113.8, 55.5, 51.6, 29.1; FT-IR (KBr): 3326, 2970, 2919, 1626, 1031, 837 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{12}H_{17}NO_2$ 208.1338, found 208.1326.

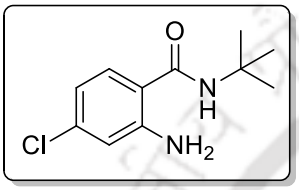
(E)-N-(tert-butyl)-3-(furan-2-yl)acrylamide (entry 7, Table 5.1.2)



Yield: 150 mg (78%); grey solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 151-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-

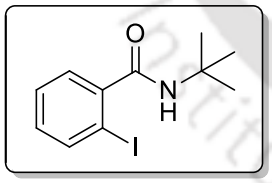
7.26 (m, 2H), 6.50-6.45 (m, 1H), 6.38-6.37 (m, 1H), 6.28-6.24 (m, 1H), 5.69 (br s, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 151.7, 143.8, 127.2, 120.2, 113.1, 112.1, 51.5, 29.0; FT-IR (KBr): 3326, 2970, 2919, 1626, 1031, 837 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{11}H_{15}NO_2$ 194.1181, found 194.1145.

2-amino-N-(tert-butyl)-4-chlorobenzamide (entry 8, Table 5.1.2)



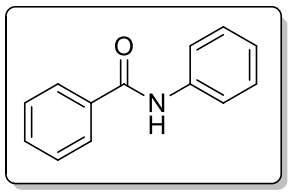
Yield: 171 mg (76%); grey solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 108-110 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.17-7.15 (d, *J* = 8.4 Hz, 1H), 6.64 (s, 1H), 6.58-6.57 (d, *J* = 10.2 Hz, 1H), 5.78 (br s, 1H), 5.53 (br s, 1H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.5, 149.6, 137.7, 128.5, 116.75, 116.7, 116.2, 51.8, 29.1; FT-IR (KBr): 3469, 3318, 2964, 2925, 1626, 1255, 770 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{11}H_{15}ClN_2O$ 227.0951, found 227.0951.

N-(tert-butyl)-2-iodobenzamide (entry 9, Table 5.1.2)



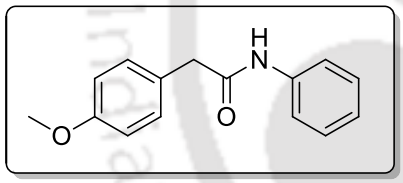
Yield: 245 mg (81%); yellow solid; R_f = 0.50 (EtOAc:Hexane, 1.5:8.5); mp: 123-125 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83-7.82 (d, *J* = 7.8 Hz, 1H), 7.38-7.34 (m, 2H), 7.08-7.05 (t, *J* = 7.8 Hz, 1H), 5.54 (br s, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 143.5, 139.9, 130.9, 128.36, 128.35, 92.5, 52.4, 28.9; FT-IR (KBr): 3239, 2970, 1637, 1328, 1014, 747 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{11}H_{14}INO$ 304.0198, found 304.0125.

N-phenylbenzamide (entry 10, Table 5.1.2)



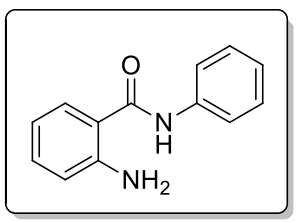
Yield: 153 mg (78%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 163-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 8.52 (br s, 1H), 7.84-7.82 (d, *J* = 7.6 Hz, 2H), 7.62-7.60 (d, *J* = 8 Hz, 2H), 7.51-7.47 (t, *J* = 7.2 Hz, 1H), 7.43-7.40 (t, *J* = 7.6 Hz, 2H), 7.33-7.29 (t, *J* = 7.6 Hz, 2H), 7.12-7.08 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 166.6, 138.1, 135.0, 131.8, 129.0, 128.7, 127.2, 124.6, 120.65; FT-IR (KBr): 3343, 2959, 2874, 1657, 1435, 747 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{13}H_{11}NO$ 198.0919, found 198.0915.

2-(4-methoxyphenyl)-N-phenylacetamide (entry 11, Table 5.1.2)



Yield: 185 mg (77%); yellow solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 113-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.40 (d, *J* = 8 Hz, 2H), 7.27-7.21 (m, 4H), 7.08-7.04 (t, *J* = 7.6 Hz, 1H), 6.91-6.89 (d, *J* = 8.4 Hz, 2H), 3.80 (s, 3H), 3.64 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 159.2, 137.8, 130.8, 129.0, 126.5, 124.5, 120.0, 114.7, 55.4, 44.0; FT-IR (KBr): 3309, 2931, 2832, 1662, 1239, 691 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{15}H_{15}NO_2$ 242.1181, found 242.1173.

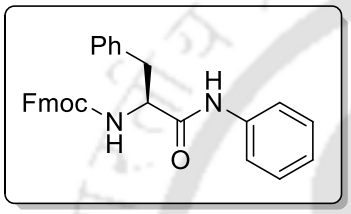
2-amino-N-phenylbenzamide (entry 12, Table 5.1.2)



Yield: 159 mg (75%); pale yellow solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 126-128 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (br s, 1H), 7.56-7.55 (d, *J* = 7.5 Hz, 2H), 7.47-7.45 (d, *J* = 9.5 Hz, 1H), 7.37-7.34 (t, *J* = 7.5 Hz, 2H), 7.26-7.23

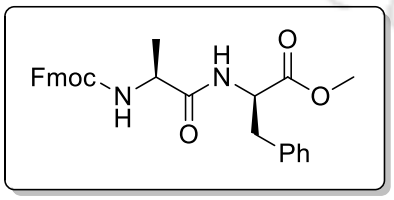
(t, *J* = 7 Hz, 1H), 7.15-7.12 (t, *J* = 7 Hz, 1H), 6.72-6.70 (d, *J* = 8 Hz, 2H), 5.48 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$,): δ 167.7, 149.2, 138.1, 132.9, 129.3, 127.3, 124.7, 120.7, 117.8, 117.0, 116.5; FT-IR (KBr): 3419, 3290, 2919, 2852, 1620, 1435, 1250, 742 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{13}H_{12}N_2O$ 213.1028, found 213.1026.

S)-(9H-fluoren-9-yl)methyl (1-oxo-3-phenyl-1-(phenylamino)propan-2-yl)carbamate (entry 13, Table 5.1.2)



Yield: 360 mg (78%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 223-225 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.04 (br s, 1H), 7.87-7.06 (m, 18H), 4.49-4.39 (m, 1H), 4.20-4.11 (m, 3H), 3.07-2.90 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6,): δ 170.9, 156.3, 144.2, 141.1, 139.2, 138.2, 129.7, 129.1, 128.5, 128.0, 127.5, 126.8, 125.7, 123.9, 120.5, 119.9, 66.1, 57.3, 47.0, 38.0; FT-IR (KBr): 3416, 3293, 2122, 1643, 1438, 1008, 820 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{30}H_{26}N_2O_3$ 463.2022, found 463.2295.

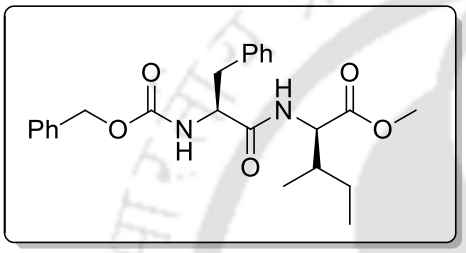
(R)-methyl 2-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-3-phenylpropanoate (entry 14, Table 5.1.2)



Yield: 372 mg (79%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 159-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78-7.76 (d, *J* = 7.2 Hz, 2H), 7.60-7.58 (d, *J* = 7.2 Hz, 2H), 7.42-7.38 (t, *J* = 7.6 Hz, 2H), 7.33-7.29 (t, *J* = 7.2 Hz, 2H), 7.24-7.16 (m, 3H), 7.08-7.06 (d, *J* = 6.8 Hz, 2H), 6.49 (br s, 1H), 5.35 (br s, 1H), 4.88-4.83 (m, 1H), 4.42-4.31 (m, 2H), 4.29-4.18 (m, 2H), 3.71 (s, 3H), 3.18-3.04 (m, 2H),

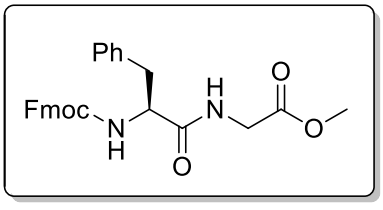
1.36-1.34 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 171.8, 156.0, 143.9, 141.5, 135.8, 129.4, 128.7, 127.9, 127.3, 127.2, 125.2, 120.2, 67.3, 53.4, 52.5, 50.5, 47.3, 38.0, 18.7; FT-IR (KBr): 3293, 2959, 2852, 1648, 1533, 1258, 733 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{28}H_{28}N_2O_5$ 473.2076, found 473.2070.

(2R,3S)-methyl 2-((S)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropanamido)-3-methylpentanoate (entry 15, Table 5.1.2)



Yield: 336 mg (79%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 104-106 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36-7.18 (m, 10H), 6.36 (br s, 1H), 5.41 (br s, 1H), 5.08 (s, 2H), 4.50-4.46 (m, 2H), 3.68 (s, 3H), 3.12-3.02 (m, 2H), 1.86-1.73 (m, 2H), 1.36-1.29 (m, 1H), 0.87-0.85 (t, *J* = 7.2 Hz, 3H), 0.80-0.79 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.8, 170.7, 156.1, 136.4, 136.2, 129.5, 128.8, 128.7, 128.3, 128.2, 127.2, 67.2, 56.7, 56.3, 52.2, 38.5, 37.9, 25.2, 15.4, 11.7; FT-IR (KBr): 3276, 2964, 2877, 1659, 1267, 1194, 700 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{24}H_{30}N_2O_5$ 427.2233, found 427.2239.

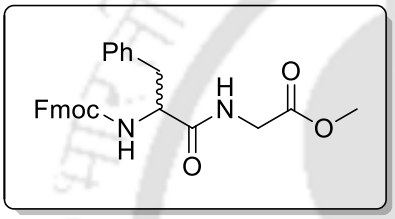
(S)-methyl 2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)acetate (entry 16, Table 5.1.2)



Yield: 375 mg (82%); white solid; R_f = 0.50 (EtOAc:Hexane, 5.0:5.0); mp: 175-177 °C; ^{1}H NMR (600 MHz, $CDCl_3$,): δ 7.76-7.75 (d, *J* = 7.2 Hz, 2H), 7.53-7.50 (t, *J* = 11.4 Hz, 2H), 7.41-7.38 (t, *J* = 7.8 Hz, 2H), 7.31-7.20 (m, 7H), 6.35 (br

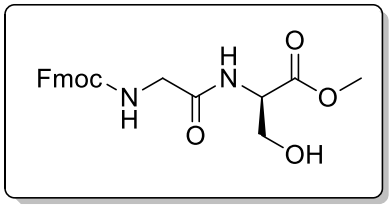
s, 1H), 5.36 (br, s, 1H), 4.48-4.33 (m, 3H), 4.19-4.16 (t, *J* = 7.2 Hz, 1H), 4.04-3.90 (m, 2H), 3.72 (s, 3H), 3.17-3.03 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$,): δ 171.2, 169.9, 156.2, 143.8, 141.5, 136.4, 129.4, 128.9, 127.9, 127.3, 127.2, 125.2, 120.2, 67.2, 56.2, 52.6, 47.3, 41.3, 38.5; FT-IR (KBr): 3298, 3032, 2952, 2851, 1690, 1257, 740 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{27}H_{26}N_2O_5$ 459.1920 found 459.1894

Methyl 2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)acetate (entry 17, Table 5.1.2)



Yield: 370 mg (81%); white solid; R_f = 0.50 (EtOAc:Hexane, 5.0:5.0); mp: 175-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$,): δ 7.76-7.74 (d, *J* = 7.2 Hz, 2H), 7.53-7.50 (t, *J* = 7.2 Hz, 2H), 7.41-7.37 (t, *J* = 7.6 Hz, 2H), 7.31-7.19 (m, 7H), 6.35 (br s, 1H), 5.36 (br, s, 1H), 4.56-4.28 (m, 3H), 4.19-4.15 (t, *J* = 6.8 Hz, 1H), 4.04-3.88 (m, 2H), 3.71 (s, 3H), 3.16-3.00 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$,): δ 171.2, 169.9, 143.9, 141.5, 136.4, 129.5, 128.9, 127.9, 127.35, 127.30, 125.2, 120.2, 67.3, 56.3, 52.5, 47.3, 41.4, 38.6; FT-IR (KBr): 3315, 3267, 3065, 2945, 2925, 2894, 2880, 1685, 1264, 1039, 731 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{27}H_{26}N_2O_5$ 459.1920 found 459.1840.

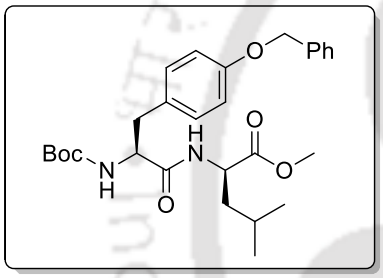
(R)-methyl 2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)acetamido)-3-hydroxypropanoate (entry 18, Table 5.1.2)



Yield: 322 mg (81%); white solid; R_f = 0.50 (EtOAc:Hexane, 7.0:3.0); mp: 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$,): δ 7.75-7.73 (d, *J* = 7.6 Hz, 2H),

7.57-7.56 (d, *J* = 7.2 Hz, 2H), 7.39-7.36 (t, *J* = 7.6 Hz, 2H), 7.30-7.26 (t, *J* = 7.6 Hz, 2H), 7.19 (br s, 1H), 5.81 (br, s, 1H), 4.67-4.63 (m, 1H), 4.39-4.37 (d, *J* = 6.8 Hz, 2H), 4.21-4.17 (t, *J* = 7.2 Hz, 1H), 3.97-3.88 (m, 4H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 171.0, 169.6, 157.1, 143.9, 141.5, 127.9, 127.3, 125.2, 120.2, 67.6, 62.9, 54.9, 52.9, 47.2, 44.6; FT-IR (KBr): 3419, 3371, 3321, 2947, 1651, 1530, 1286, 756 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{21}H_{22}N_2O_6$ 399.1556, found 399.1533.

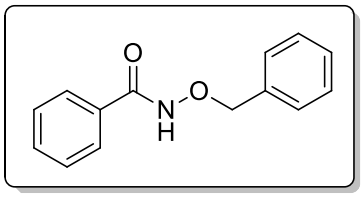
(R)-methyl 2-((S)-3-(4-(benzyloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanamido)-4-methylpentanoate (entry 19, Table 5.1.2)



Yield: 398 mg (80%); grey solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 114-116 °C; ^{1}H NMR (600 MHz, $CDCl_3$,): δ 7.42-7.41 (d, *J* = 7.2 Hz, 2H), 7.39-7.36 (t, *J* = 7.2 Hz, 2H), 7.33-7.30 (t, *J* = 7.2 Hz, 1H), 7.13-7.11 (d, *J* = 7.8 Hz, 2H), 6.90-6.89 (d, *J* = 8.4 Hz, 2H), 6.29 (br s, 1H), 5.03 (s, 2H), 4.60-4.52 (m, 1H), 4.34-4.25 (m, 1H), 3.68 (s, 3H), 3.04-2.97 (m, 2H), 1.79-1.66 (m, 2H), 1.49-1.45 (m, 1H), 1.41 (s, 9H), 0.90-0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 173.0, 171.2, 158.0, 155.6, 137.1, 130.6, 129.0, 128.7, 128.1, 127.6, 115.1, 80.4, 70.2, 55.9, 52.4, 50.9, 41.8, 37.3, 28.4, 24.8, 22.9, 22.0; FT-IR (KBr): 3329, 2917, 2852, 1657, 1239, 1014, 739 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{28}H_{38}N_2O_6$ 499.2808, found 499.2805.

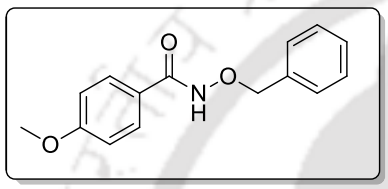
N-(benzyloxy)benzamide (entry 1, Table 5.1.3)

Yield: 192 mg (85%); pale yellow solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 104-106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (br s, 1H), 7.68-7.66 (d, *J* = 7.2 Hz, 2H),



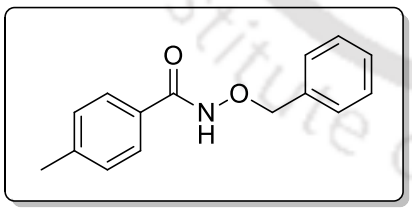
7.50-7.46 (t, *J* = 7.6 Hz, 1H), 7.42-7.34 (m, 7H), 4.99 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 135.4, 132.1, 132.0, 129.4, 128.9, 128.8, 128.7, 127.2, 78.5; FT-IR (KBr): 3236, 2919, 2849, 1645, 1505, 1003, 694 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{14}H_{13}NO_2$ 228.1025, found 228.1096.

N-(benzyloxy)-4-methoxybenzamide (entry 2, Table 5.1.3)



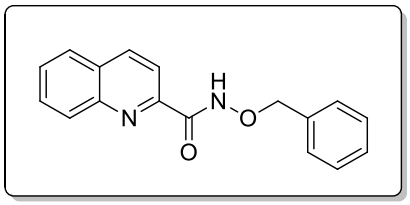
Yield: 215 mg (84%); pale yellow solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 106-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (br s, 1H), 7.66-7.64 (d, *J* = 8.8 Hz, 2H), 7.41-7.38 (m, 2H), 7.34-7.30 (m, 3H), 6.84-6.82 (d, *J* = 8.8 Hz, 2H), 4.97 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 162.7, 135.5, 129.4, 129.1, 128.8, 128.7, 124.2, 114.0, 78.4, 55.5; FT-IR (KBr): 3217, 2936, 2835, 1645, 1457, 840 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{15}H_{15}NO_3$ 258.1130, found 258.1141.

N-(benzyloxy)-4-methylbenzamide (entry 3, Table 5.1.3)



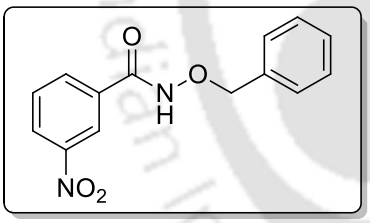
Yield: 195 mg (81%); grey solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 129-131 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.64 (br s, 1H), 7.56-7.55 (d, *J* = 7.8 Hz, 2H), 7.44-7.43 (d, *J* = 6 Hz, 2H), 7.40-7.35 (m, 3H), 7.20-7.19 (d, *J* = 6 Hz, 2H), 5.01 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.7, 142.8, 135.5, 129.5, 129.5, 129.2, 128.9, 128.8, 127.2, 78.5, 21.7; FT-IR (KBr): 3211, 2939, 2835, 1643, 1023, 739 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{15}H_{15}NO_2$ 242.1181, found 242.1144.

N-(benzyloxy)quinoline-2-carboxamide (entry 4, Table 5.1.3)



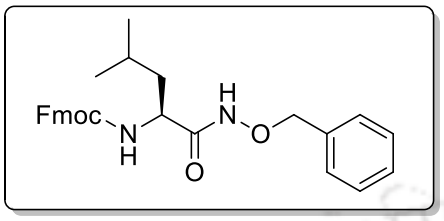
Yield: 219 mg (79%); grey solid; R_f = 0.50 (EtOAc:Hexane, 4.0:6.0); mp: 155-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.38 (br s, 1H), 8.33-8.31 (d, *J* = 8.4 Hz, 1H), 8.27-8.25 (d, *J* = 8.4 Hz, 1H), 8.02-8.00 (d, *J* = 8.8 Hz, 1H), 7.88-7.86 (d, *J* = 8 Hz, 1H), 7.77-7.72 (t, *J* = 8 Hz, 1H), 7.64-7.60 (t, *J* = 8 Hz, 1H), 7.52-7.50 (d, *J* = 9.6 Hz, 2H), 7.43-7.38 (m, 3H), 5.12 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 149.1, 146.6, 137.8, 135.4, 130.4, 129.9, 129.7, 129.5, 129.0, 128.8, 128.4, 128.0, 118.9, 78.9; FT-IR (KBr): 3206, 2959, 2849, 1654, 1255, 1017, 697 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{17}H_{14}N_2O_2$ 279.1134, found 279.1090.

N-(benzyloxy)-3-nitrobenzamide (entry 5, Table 5.1.3)



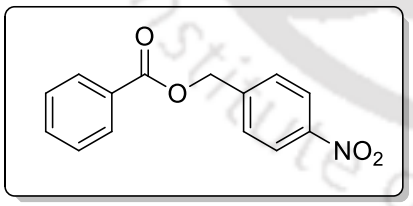
Yield: 220 mg (81%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 137-139 °C; ^{1}H NMR (600 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 11.04 (br s, 1H), 8.49 (s, 1H), 8.25-8.21 (m, 1H), 8.04-7.97 (m, 1H), 7.58-7.52 (m, 1H), 7.46-7.38 (m, 2H), 7.30-7.26 (m, 3H), 4.95 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 163.9, 148.0, 135.1, 133.6, 133.5, 129.8, 129.4, 128.8, 128.6, 126.3, 122.3, 78.41; FT-IR (KBr): 3248, 2961, 1917, 1651, 1524, 697 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{14}H_{12}N_2O_4$ 273.0875, found 273.0881.

(S)-(9H-fluoren-9-yl)methyl (1-((benzyloxy)amino)-4-methyl-1-oxopentan-2-yl)carbamate (entry 6, Table 5.1.3)



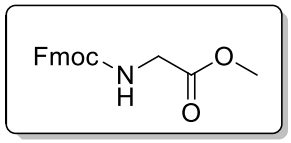
Yield: 366 mg (80%); grey solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 164-166 °C; ^{1}H NMR (600 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 10.68 (br s, 1H), 7.81-7.77 (m, 2H), 7.63-7.60 (m, 2H), 7.45-7.35 (m, 9H), 6.30 (br s, 1H), 4.91 (s, 2H), 4.44-4.32 (m, 2H), 4.24-4.21 (m, 1H), 4.01-3.96 (m, 1H), 1.56-1.53 (m, 2H), 1.41-1.27 (m, 1H), 0.92-0.86 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 169.9, 156.5, 143.7, 141.3, 135.1, 129.3, 128.7, 128.4, 127.7, 127.1, 125.0, 119.9, 78.0, 67.0, 50.7, 47.1, 41.1, 24.5, 22.4, 22.0; FT-IR (KBr): 3307, 3220, 2956, 2869, 2249, 1662, 1528, 1166, 728 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{28}H_{30}N_2O_4$ 459.2284 found 459.2326.

4-nitrobenzyl benzoate (entry 7, Table 5.1.3)



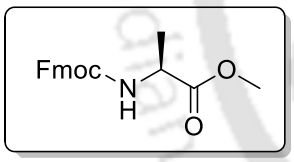
Yield: 172 mg (67%); colourless solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 87-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26-8.24 (d, *J* = 8.8 Hz, 2H), 8.10-8.08 (d, *J* = 7.2 Hz, 2H), 7.62-7.58 (t, *J* = 8.4 Hz, 3H), 7.49-7.45 (t, *J* = 8 Hz, 2H), 5.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 147.9, 143.5, 133.6, 129.9, 129.6, 128.7, 128.5, 124.0, 65.3; FT-IR (KBr): 3424, 3085, 2925, 2855, 1718, 1337, 1112, 708.

Methyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)acetate (entry 8, Table 5.1.3)



Yield: 220 mg (71%); grey solid; R_f = 0.50 (EtOAc:Hexane, 2.5:7.5); mp: 86-88 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77-7.76 (d, *J* = 7.8 Hz, 2H), 7.61-7.60 (d, *J* = 7.2 Hz, 2H), 7.41-7.39 (t, *J* = 7.2 Hz, 2H), 7.33-7.30 (t, *J* = 7.2 Hz, 2H), 5.37 (br s, 1H), 4.42-4.41 (d, *J* = 7.2 Hz, 2H), 4.25-4.22 (t, *J* = 7.2 Hz, 1H), 4.00 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.6, 156.4, 143.9, 141.4, 127.8, 127.2, 125.2, 120.1, 67.35, 52.5, 47.2, 42.8; FT-IR (KBr): 3312, 2953, 2855, 1685, 1528, 1208, 739 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calculated for $C_{18}H_{17}NO_4$ 334.1055, found 334.1026.

(S)-methyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanoate (entry 9, Table 5.1.3)



Yield: 227 mg (70%); grey solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 99-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$,): δ 7.77-7.75 (d, *J* = 7.6 Hz, 2H), 7.61-7.58 (m, 2H), 7.41-7.38 (t, *J* = 7.2 Hz, 2H), 7.33-7.29 (t, *J* = 7.2 Hz, 2H), 5.36 (br s, 1H), 4.43-4.35 (m, 3H), 4.24-4.20 (t, *J* = 6.8 Hz, 1H), 3.76 (s, 3H), 1.44-1.42 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 173.7, 155.8, 144.0, 141.5, 127.9, 127.2, 125.2, 120.1, 67.2, 52.6, 49.8, 47.3, 18.8; FT-IR (KBr): 3329, 2928, 2855, 1688, 1530, 1034, 736 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calculated for $C_{19}H_{19}NO_4$ 348.1212 found 348.1306.

5.8. Selected spectra

5.8.1. ^{1}H-NMR and ^{13}C-NMR spectra of compounds

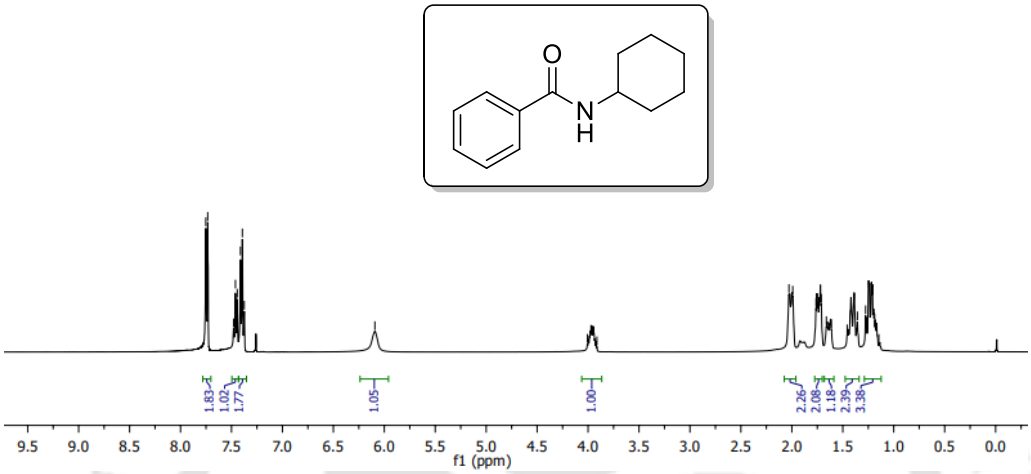


Figure 5.8.1.1. ^{1}H-NMR spectrum of N-cyclohexylbenzamide (entry 1, Table 5.1.2)

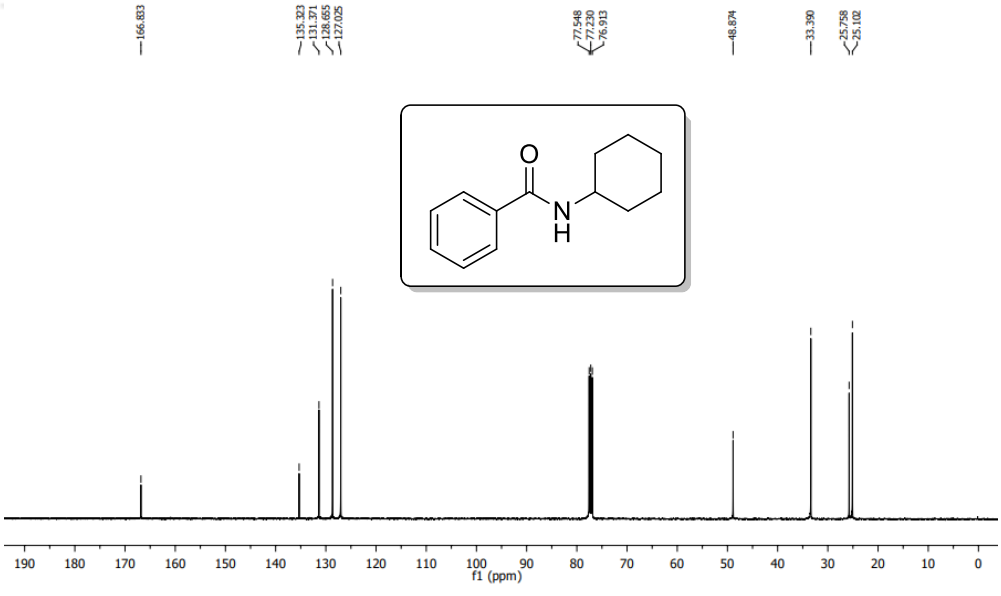


Figure 5.8.1.2. ^{13}C-NMR spectrum of N-cyclohexylbenzamide (entry 1, Table 5.1.2)

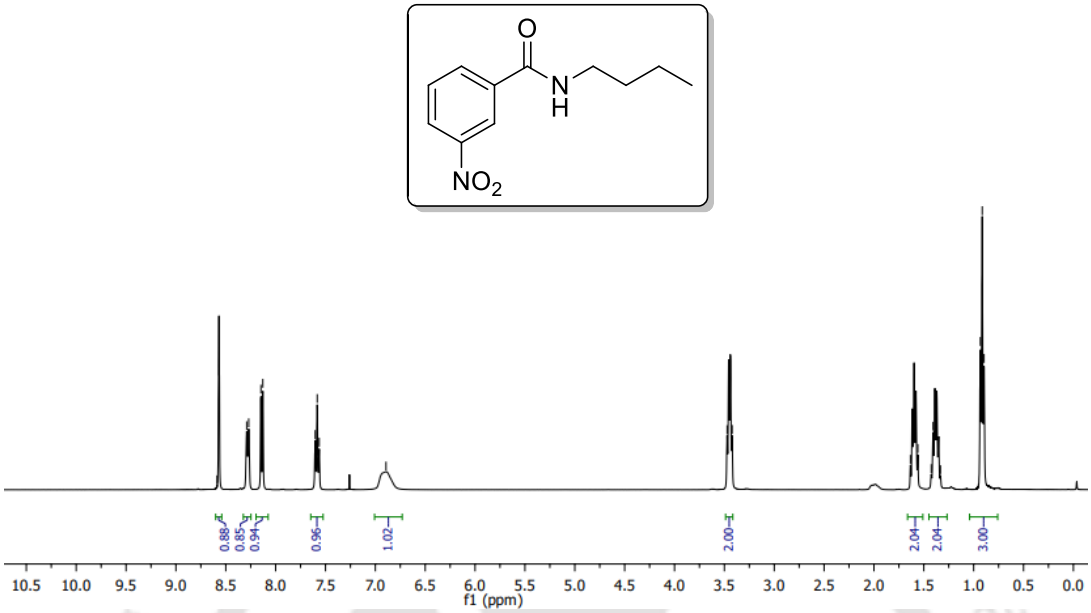


Figure 5.8.1.3. ^{1}H-NMR spectrum of N-butyl-3-nitrobenzamide (entry 5, Table 5.1.2)

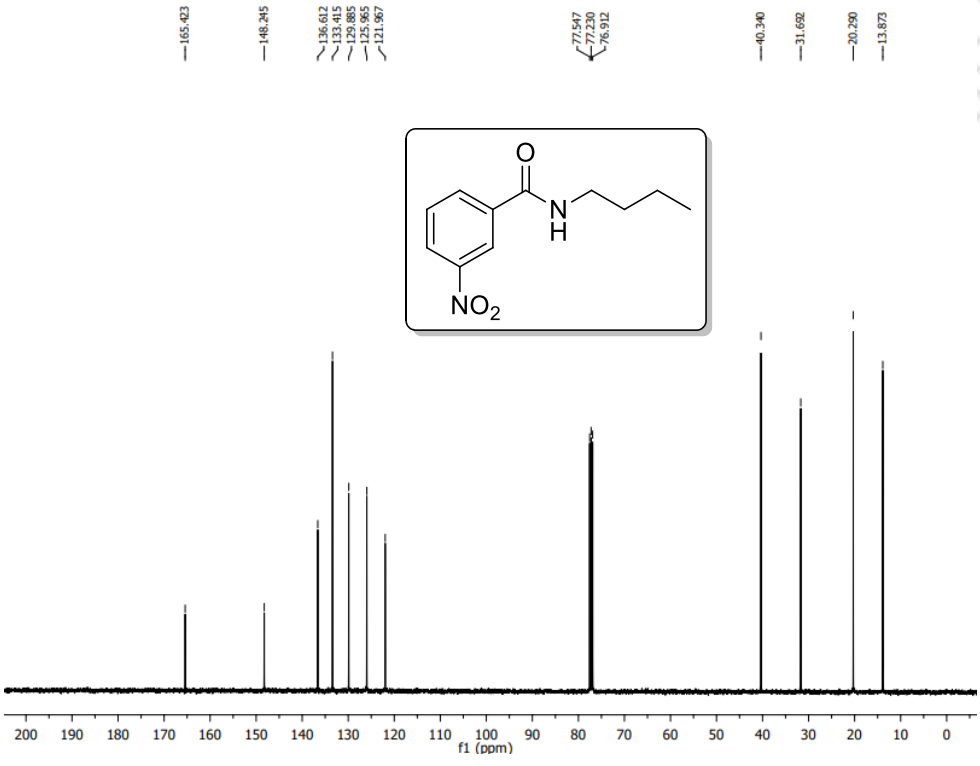


Figure 5.8.1.4. ^{13}C-NMR spectrum of N-butyl-3-nitrobenzamide (entry 5, Table 5.1.2)

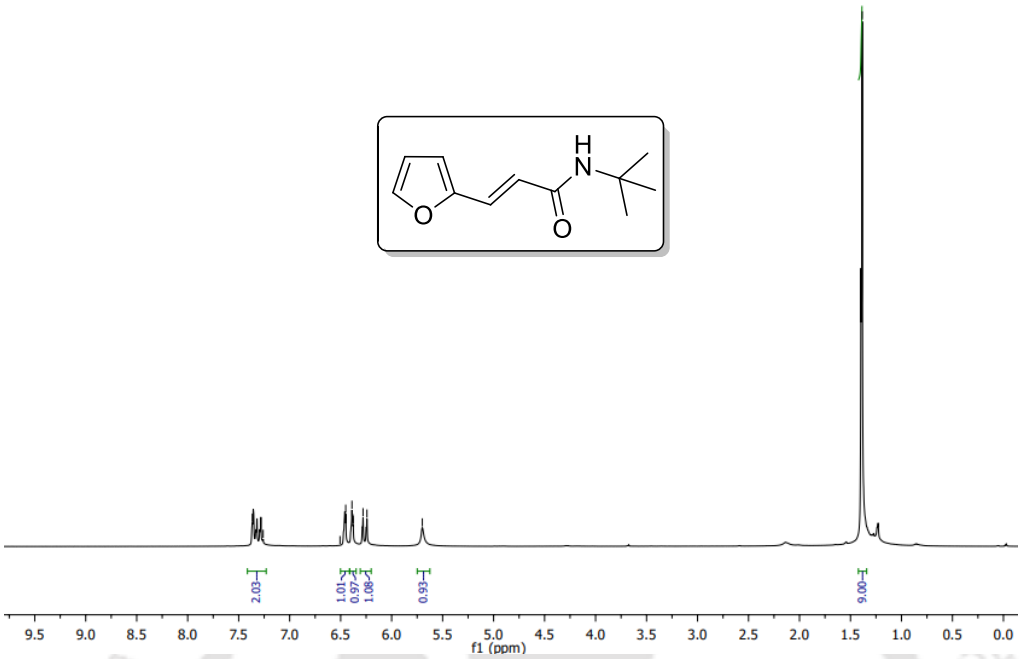


Figure 5.8.1.5. ^{1}H-NMR spectrum of (E)-N-(tert-butyl)-3-(furan-2-yl)acrylamide (entry 7, Table 5.1.2)

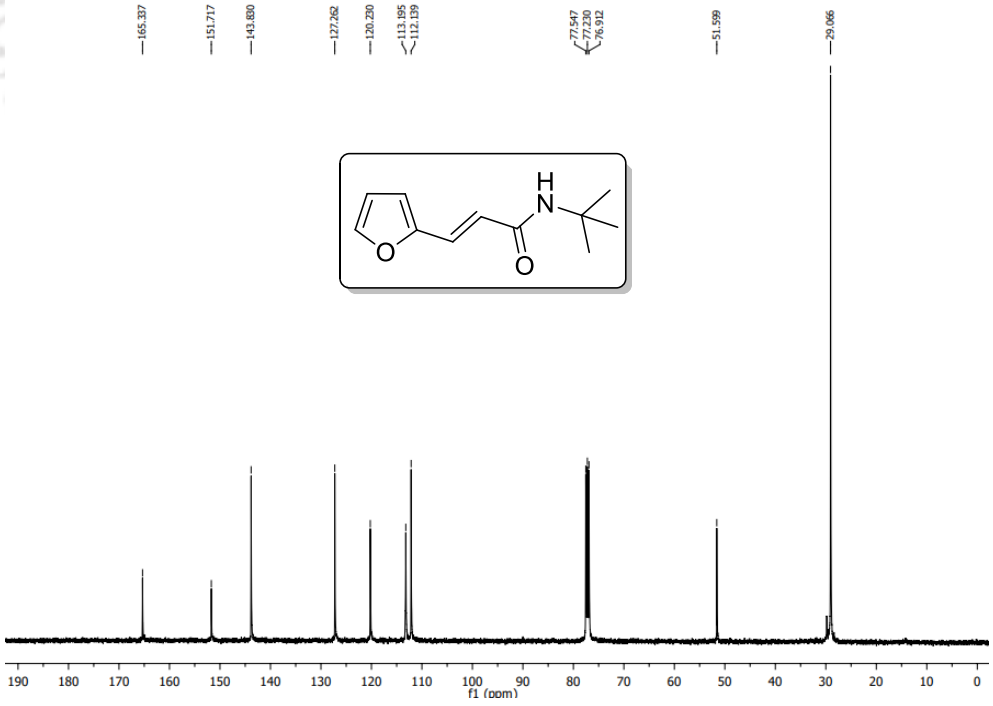


Figure 5.8.1.6. ^{13}C-NMR spectrum of (E)-N-(tert-butyl)-3-(furan-2-yl)acrylamide (entry 7, Table 5.1.2)

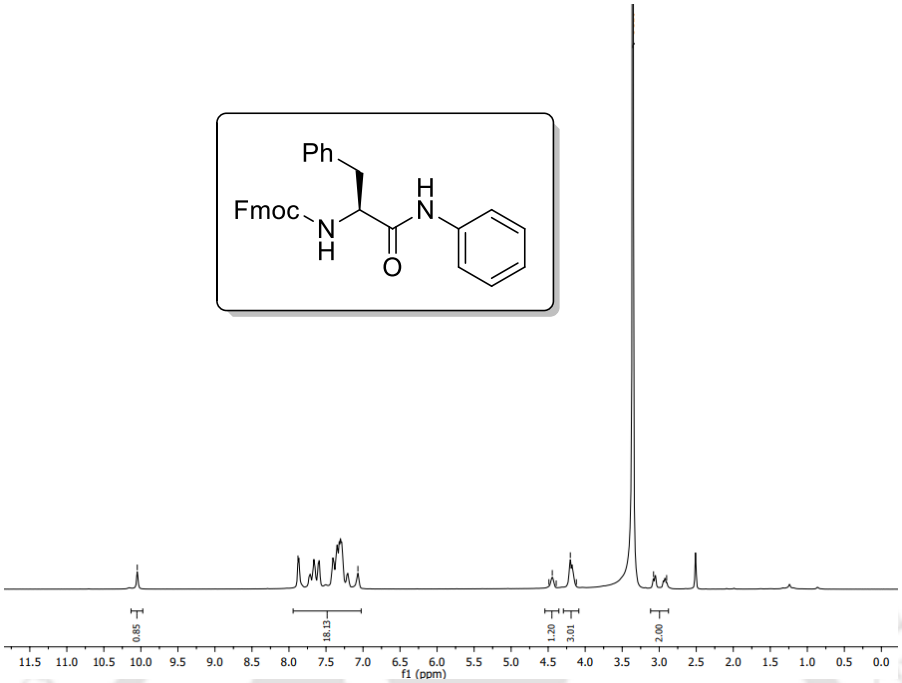


Figure 5.8.1.7. ^{1}H-NMR spectrum of (S)-(9H-fluoren-9-yl)methyl (1-oxo-3-phenyl-1-(phenylamino)propan-2-yl)carbamate (entry 13, Table 5.1.2)

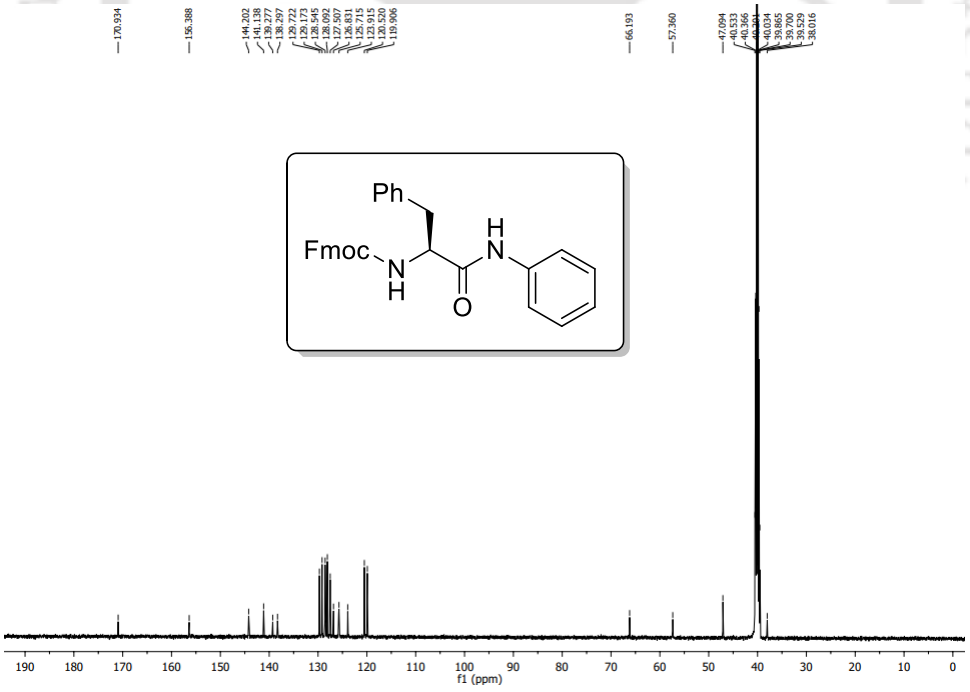


Figure 5.8.1.8. ^{13}C-NMR spectrum of (S)-(9H-fluoren-9-yl)methyl (1-oxo-3-phenyl-1-(phenylamino)propan-2-yl)carbamate (entry 13, Table 5.1.2)

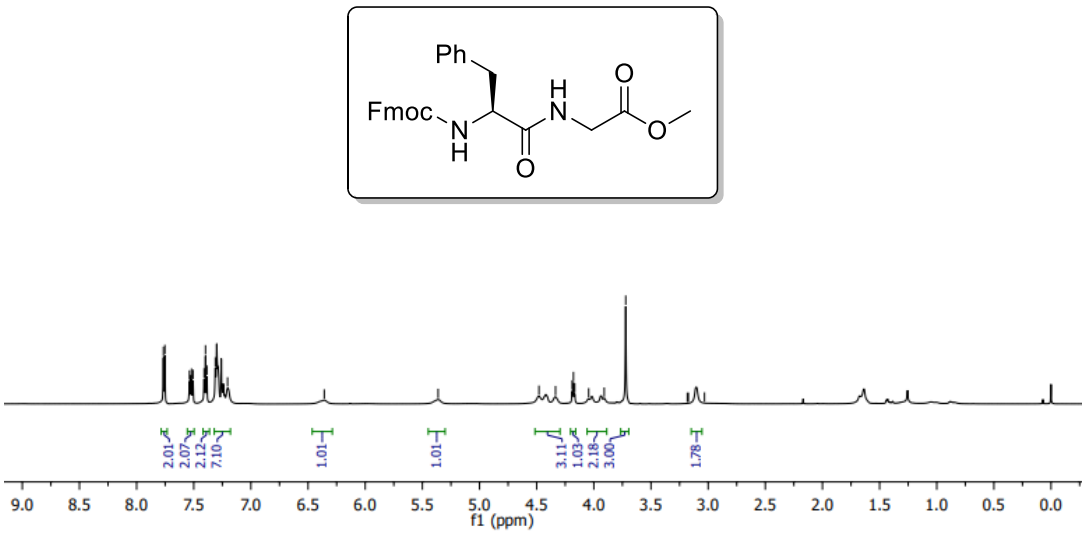


Figure 5.8.1.9. ^{1}H-NMR spectrum of (S)-methyl 2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)acetate (entry 16, Table 5.1.2)

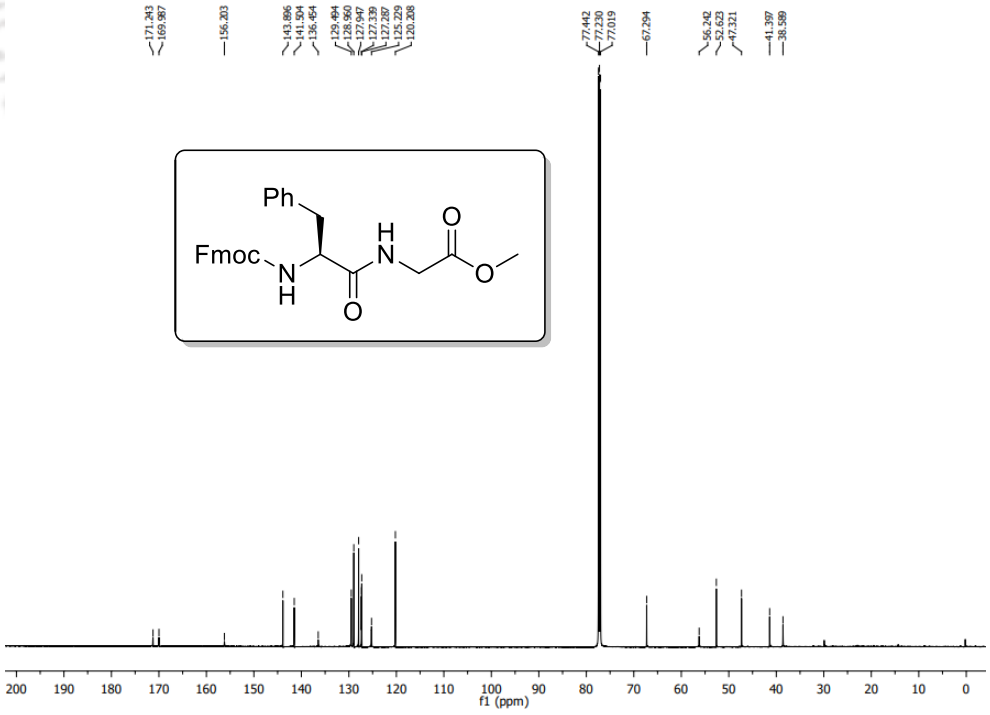


Figure 5.8.1.10. ^{13}C-NMR spectrum of (S)-methyl 2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)acetate (entry 16, Table 5.1.2)

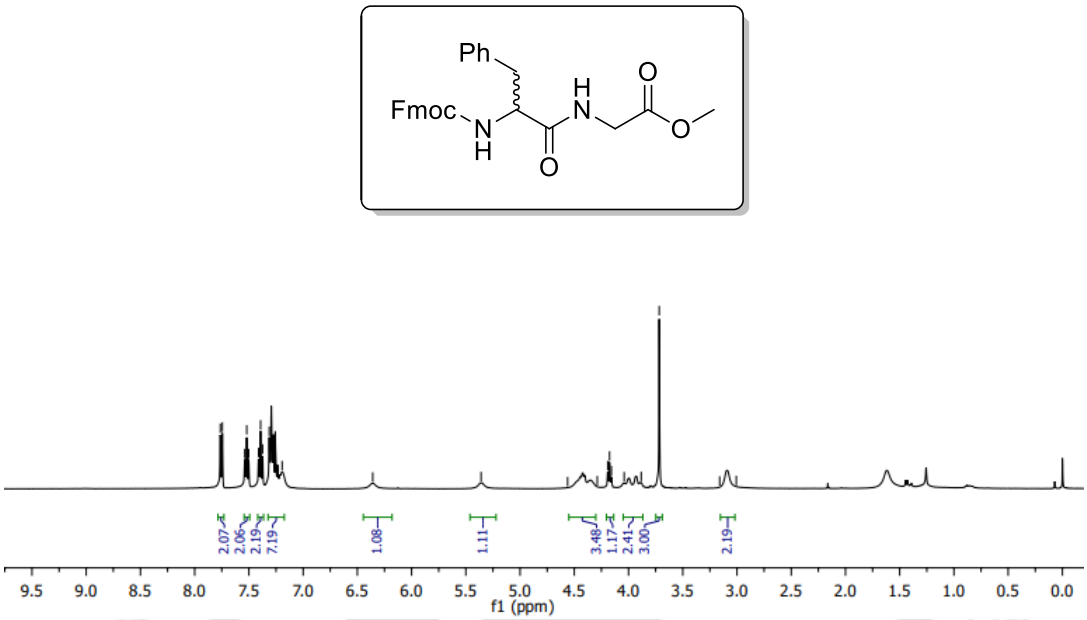


Figure 5.8.1.11. ^{1}H-NMR spectrum of Methyl 2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)acetate (entry 17, Table 5.1.2)

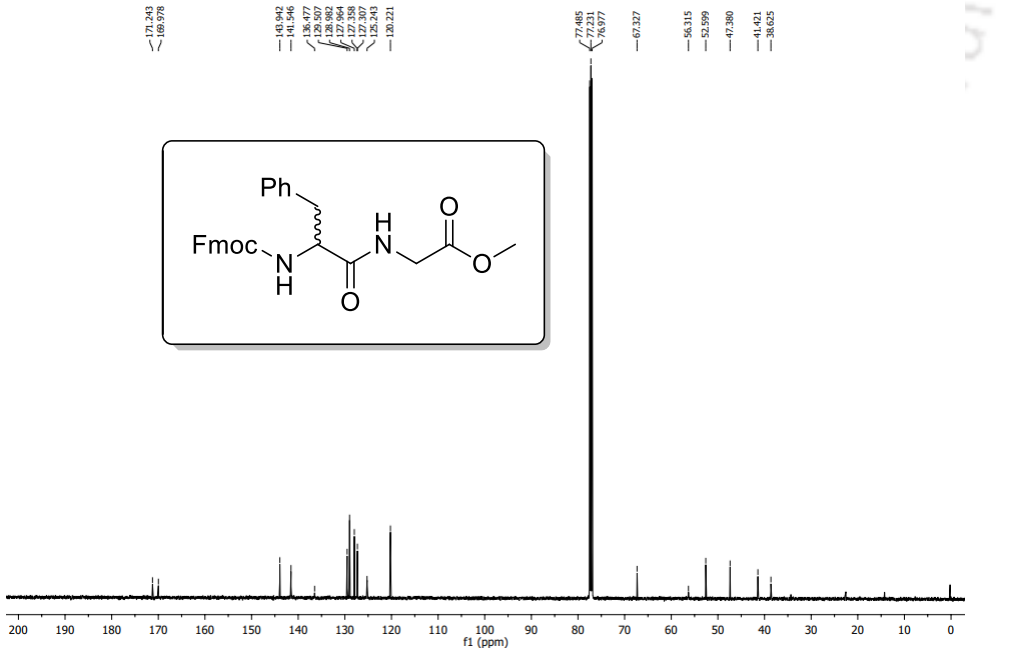


Figure 5.8.1.12. ^{13}C-NMR spectrum of Methyl 2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)acetate (entry 17, Table 5.1.2)

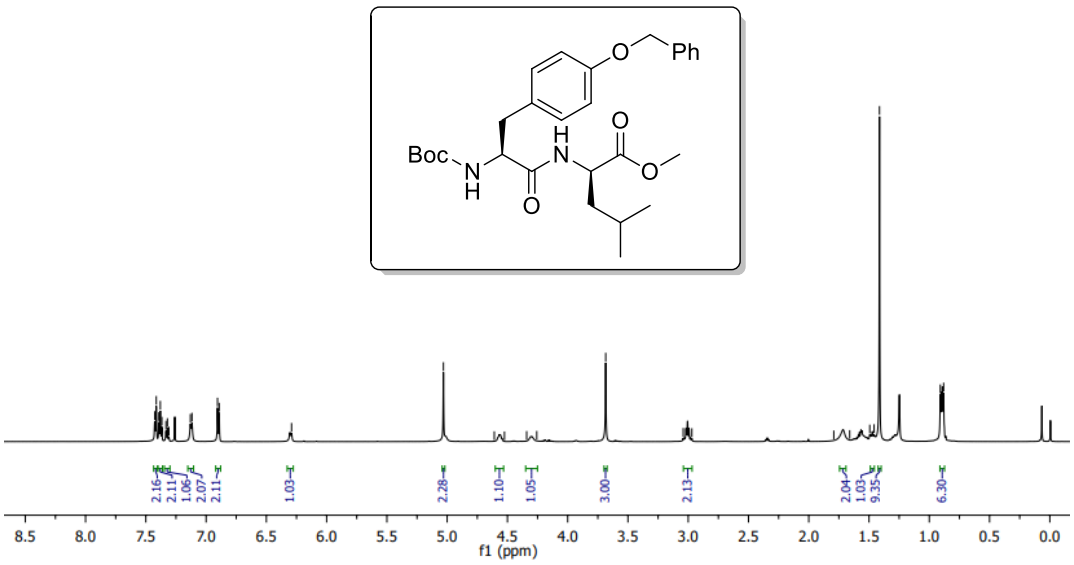


Figure 5.8.1.13. [1]H-NMR spectrum of (R)-methyl 2-((S)-3-(4-(benzyloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanamido)-4-methylpentanoate (entry 19, Table 5.1.2)

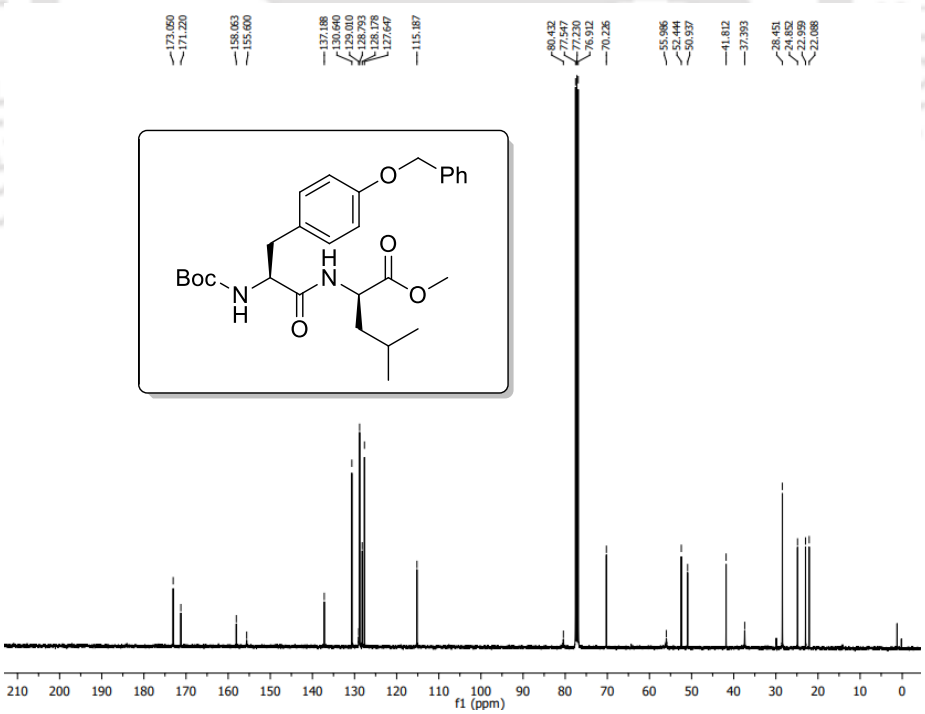


Figure 5.8.1.14. [13]C-NMR spectrum of (R)-methyl 2-((S)-3-(4-(benzyloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanamido)-4-methylpentanoate (entry 19, Table 5.1.2)

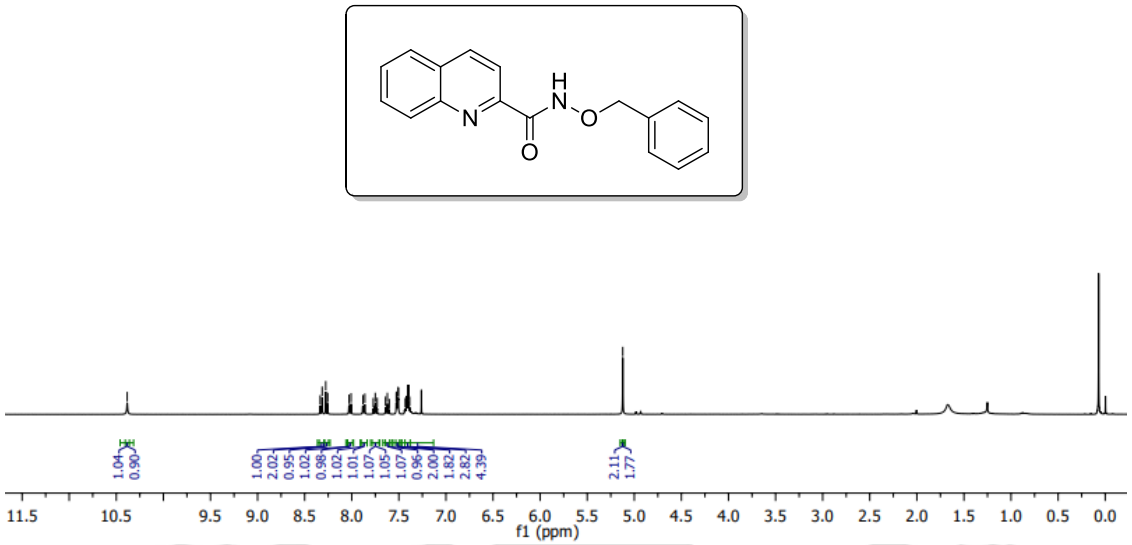


Figure 5.8.1.15. ^{1}H-NMR spectrum N-(benzyloxy)quinoline-2-carboxamide (entry 4, Table 5.1.3)

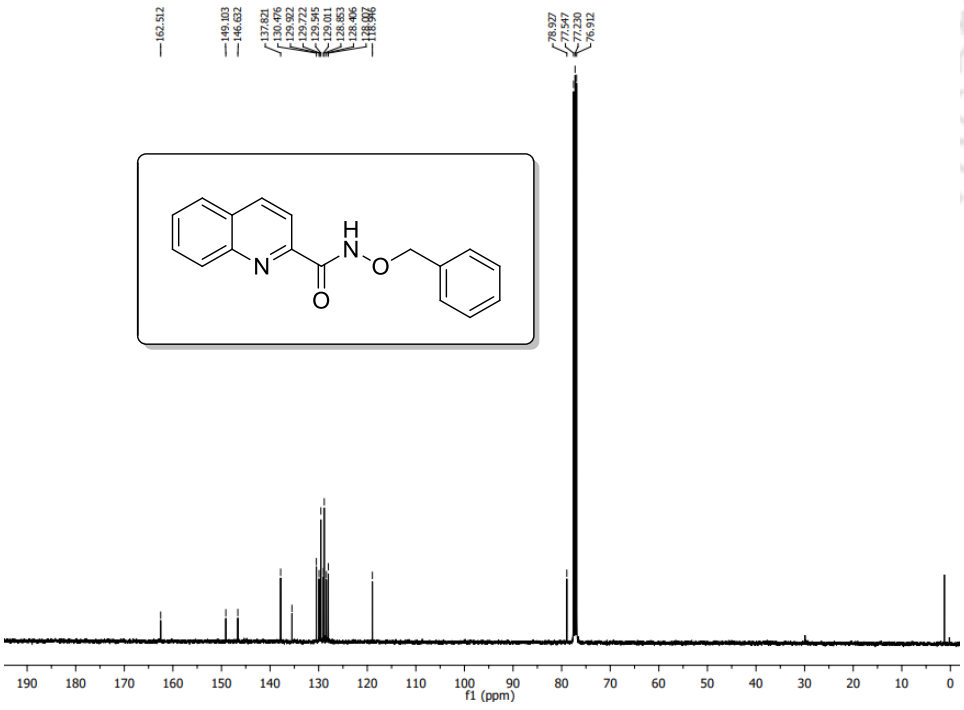


Figure 5.8.1.16. ^{13}C-NMR spectrum of N-(benzyloxy)quinoline-2-carboxamide (entry 4, Table 5.1.3)

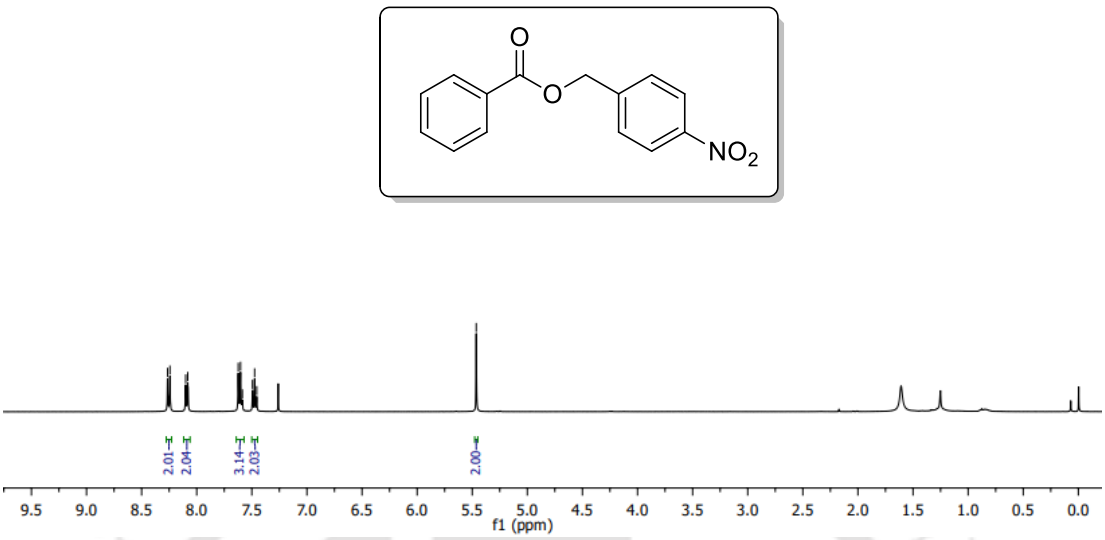


Figure 5.8.1.17. ^{1}H-NMR spectrum 4-nitrobenzyl benzoate (entry 7, Table 5.1.3)

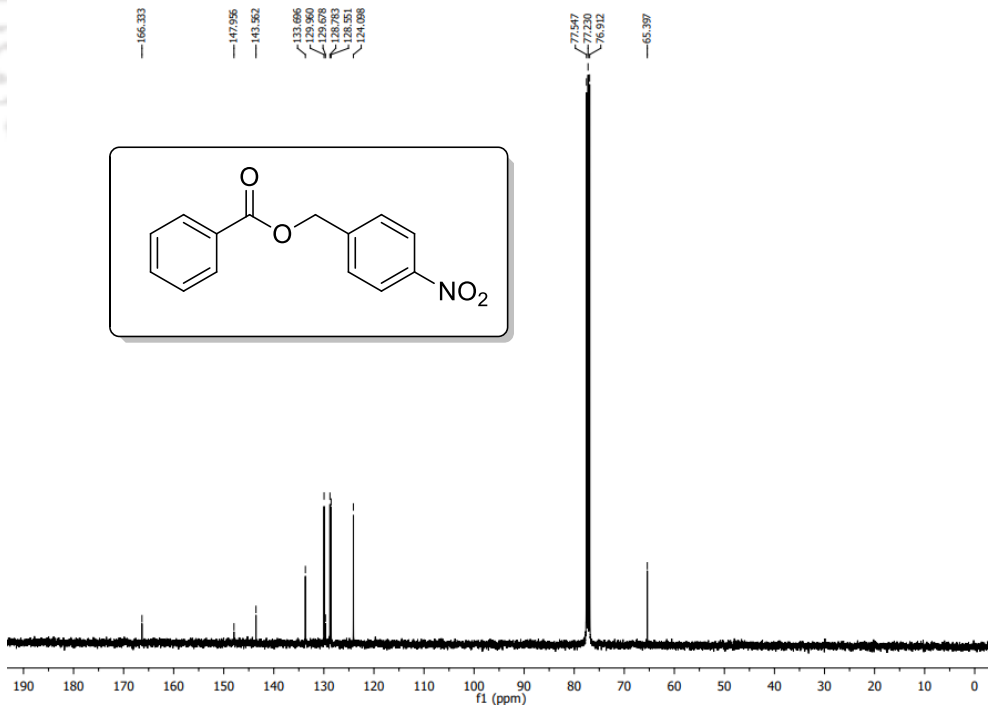
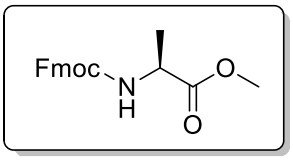


Figure 5.8.1.18. ^{13}C-NMR spectrum of 4-nitrobenzyl benzoate (entry 7, Table 5.1.3)



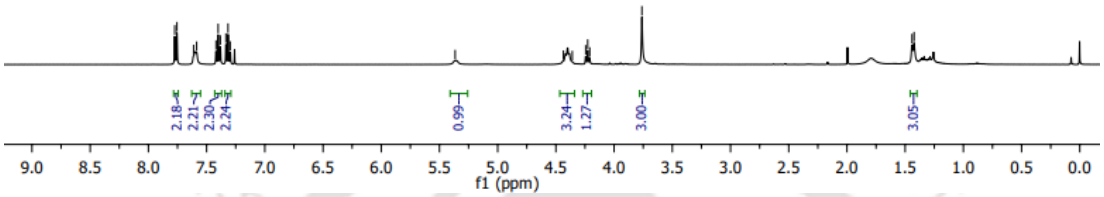


Figure 5.8.1.19. ^{1}H-NMR spectrum (S)-methyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanoate (entry 9, Table 5.1.3)

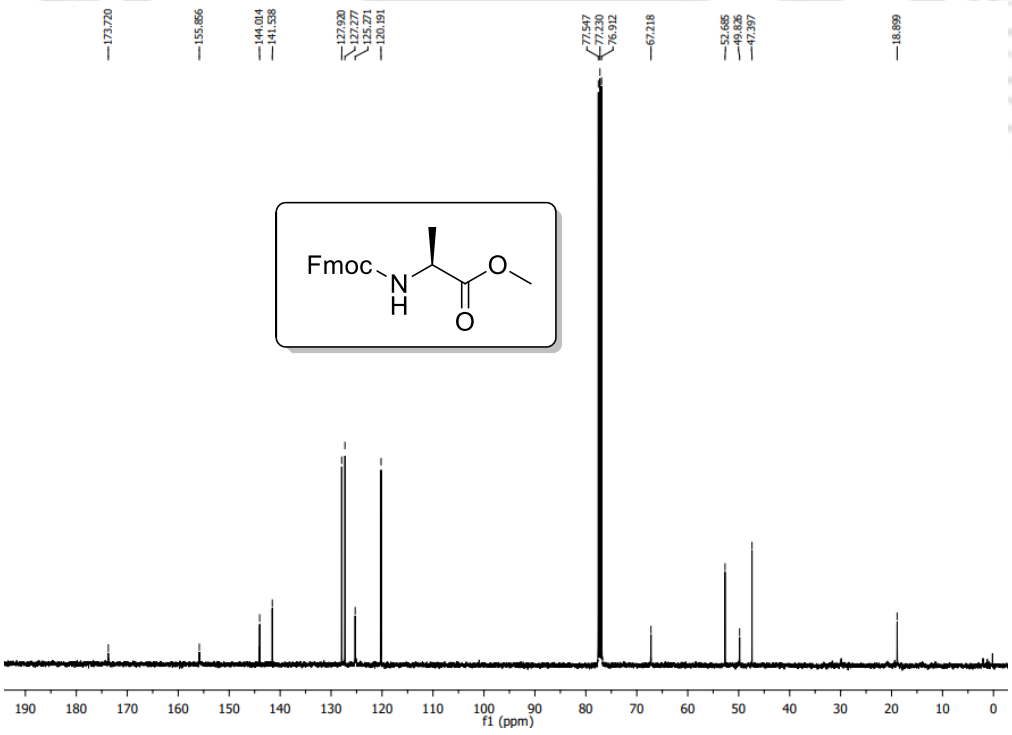
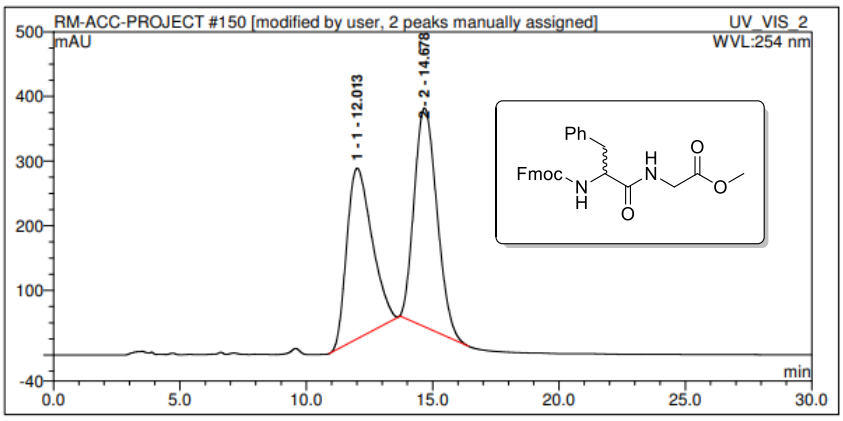


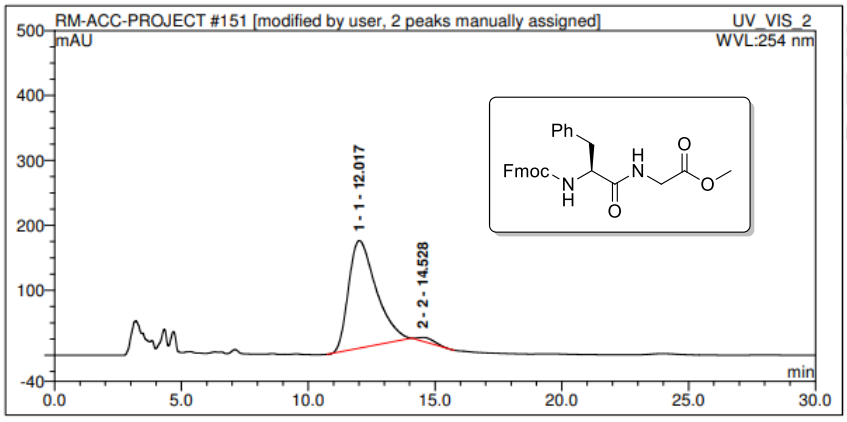
Figure 5.8.1.20. ^{13}C -NMR spectrum (S)-methyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanoate (entry 9, Table 5.1.3)

5.8.2. HPLC data for racemization test



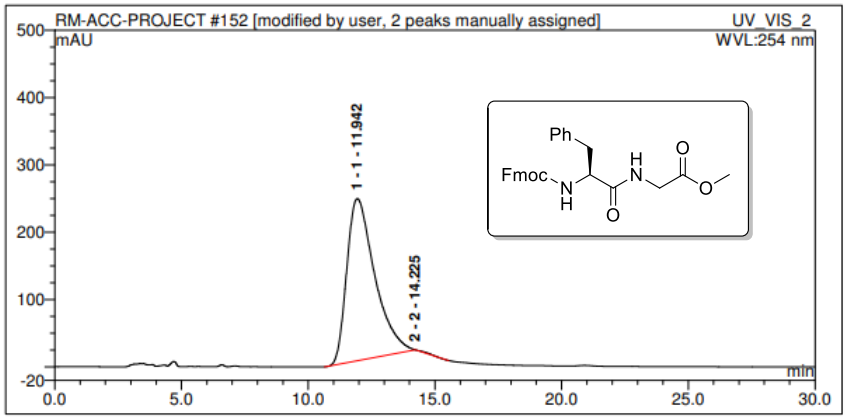
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	12.01	304.232	46.25391537	263.9528	n.a.
2	2	14.68	353.511	53.74608463	338.554	n.a.

Figure 5.8.2.1. HPLC spectrum of Methyl 2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)acetate (entry 17, Table 5.1.2); synthesized using current protocol ; run in chiral column (5 µm, 2.1×150 mm) (Isocratic, isopropanol-hexane solvent system)



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	12.02	208.9744	97.7065256	165.6574	n.a.
2	2	14.53	4.905	2.293474401	6.075	n.a.

Figure 5.8.2.2. HPLC spectrum of (S)-methyl 2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)acetate (entry 16, Table 5.1.2); synthesized using thionyl chloride in the absence of Oxyma; run in chiral column (5 µm, 2.1×150 mm) (Isocratic, isopropanol-hexane solvent system)



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	11.94	307.189	99.85641239	240.8398	n.a.
2	2	14.23	0.442	0.1435876139	0.003	n.a.

Figure 5.8.2.3. HPLC spectrum of (S)-methyl 2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)acetate (entry 16, Table 5.1.2); synthesized using current protocol; run in chiral column (5 µm, 2.1×150 mm) (Isocratic, isopropanol-hexane solvent system)

5.8.3. Mechanism study

^{13}C NMR Spectra

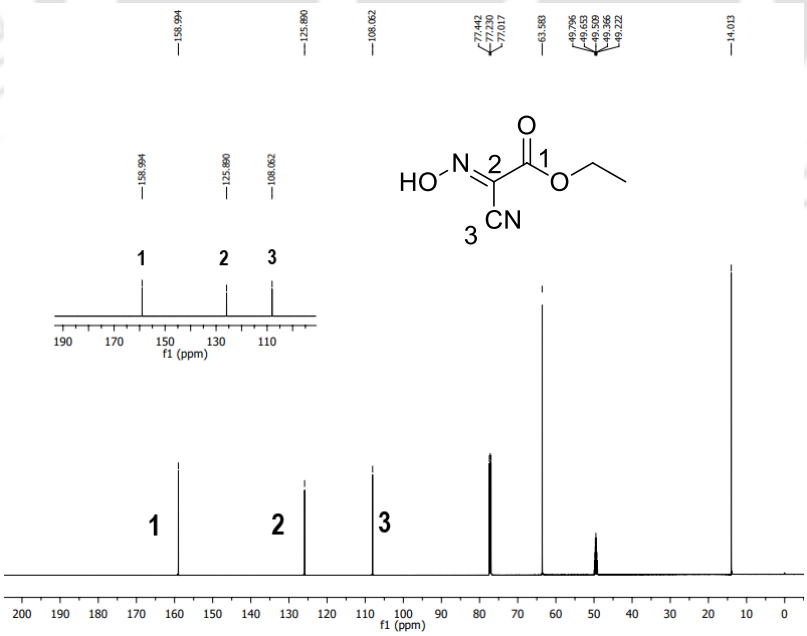


Figure 5.8.3.1. ^{13}C-NMR spectrum of Oxyma

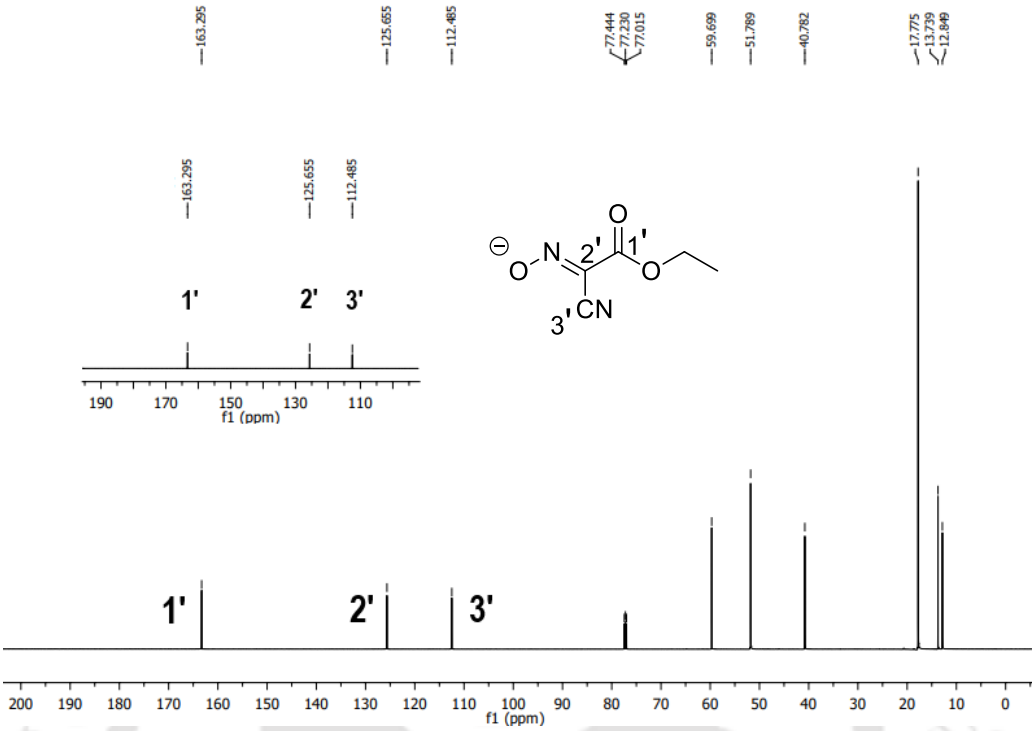


Figure 5.8.3.2. ^{13}C-NMR spectrum of Oxyma in the presence of DIPEA as base

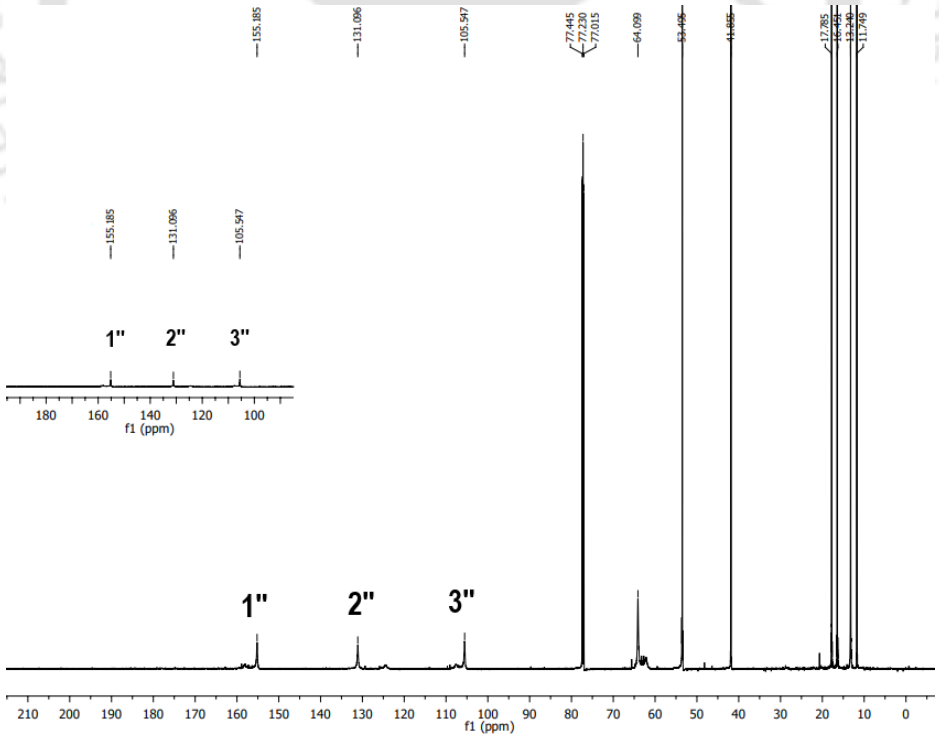


Figure 5.8.3.3. ^{13}C-NMR spectrum of the reaction mixture **(II)** [30 min after the addition of $SOCl_2$ to Oxyma in the presence of DIPEA as a base (equiv ratio of Oxyma and thionyl chloride is 1:1)]

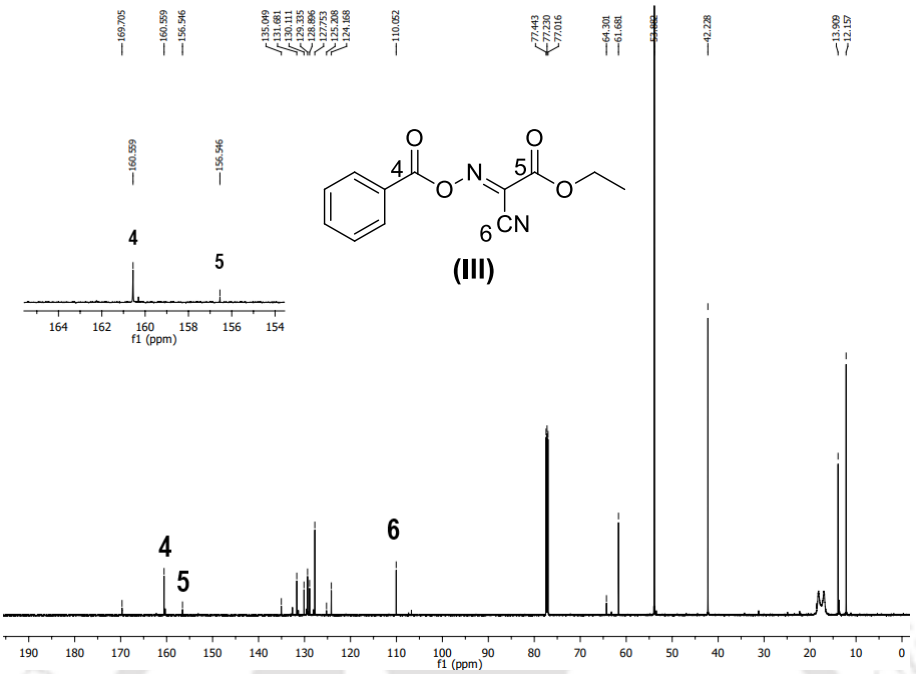


Figure 5.8.3.4. ^{13}C-NMR spectrum of reaction [10 min after the addition of benzoic acid to **II** in the presence of DIPEA as a base]

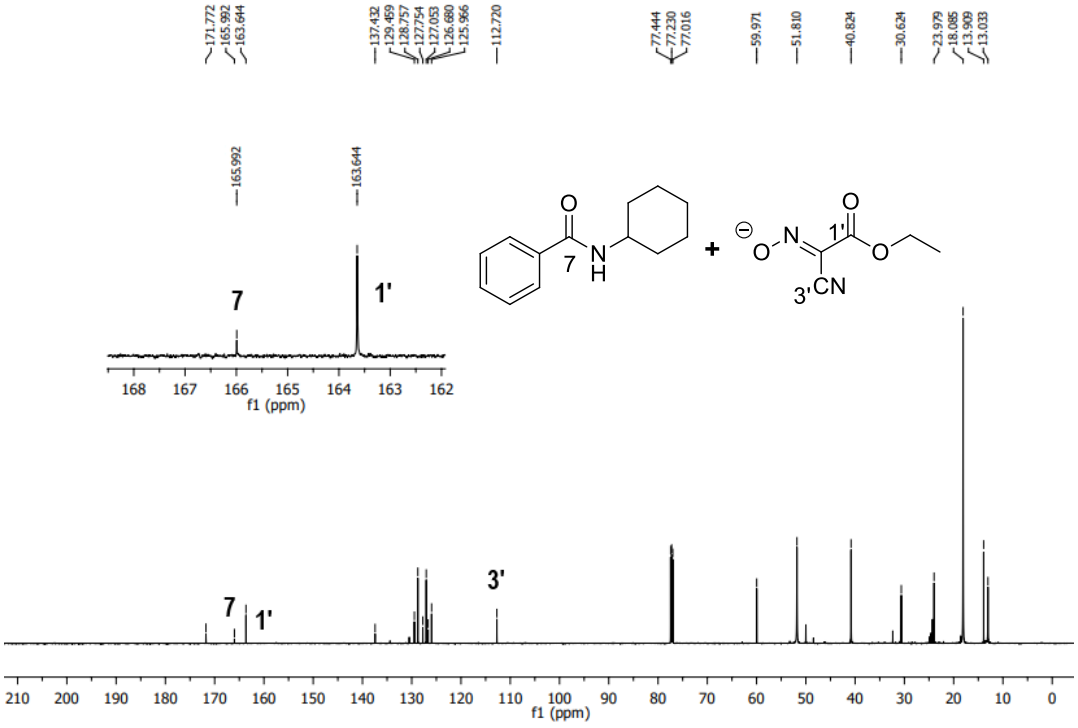


Figure 5.8.3.5. ^{13}C-NMR spectrum of reaction, after 80 min from the addition of cyclohexylamine

5.8.4. ^{1}H and ^{13}C-NMR spectrum of the reaction mixture of 2 equiv of Oxyma and 1 equiv of thionyl chloride

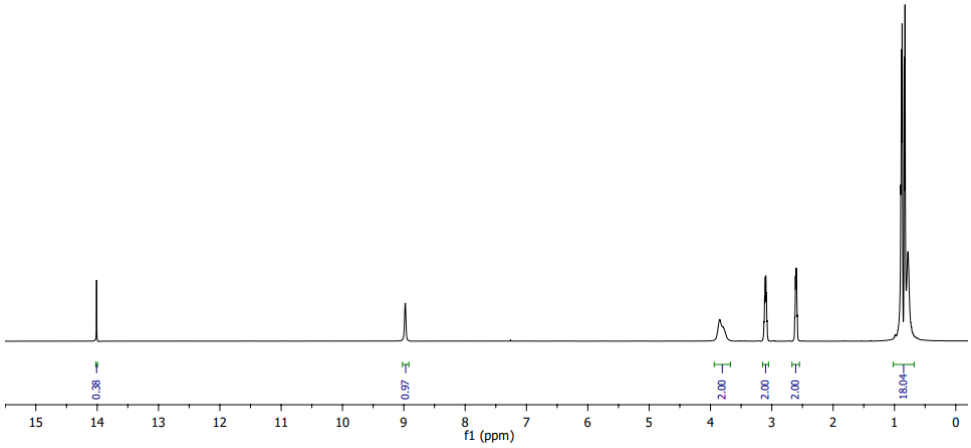


Figure 5.8.4.1. ^{1}H -NMR spectrum of the reaction mixture of 2 equiv of Oxyma and 1 equiv of $SOCl_2$ (reaction time 30 min)

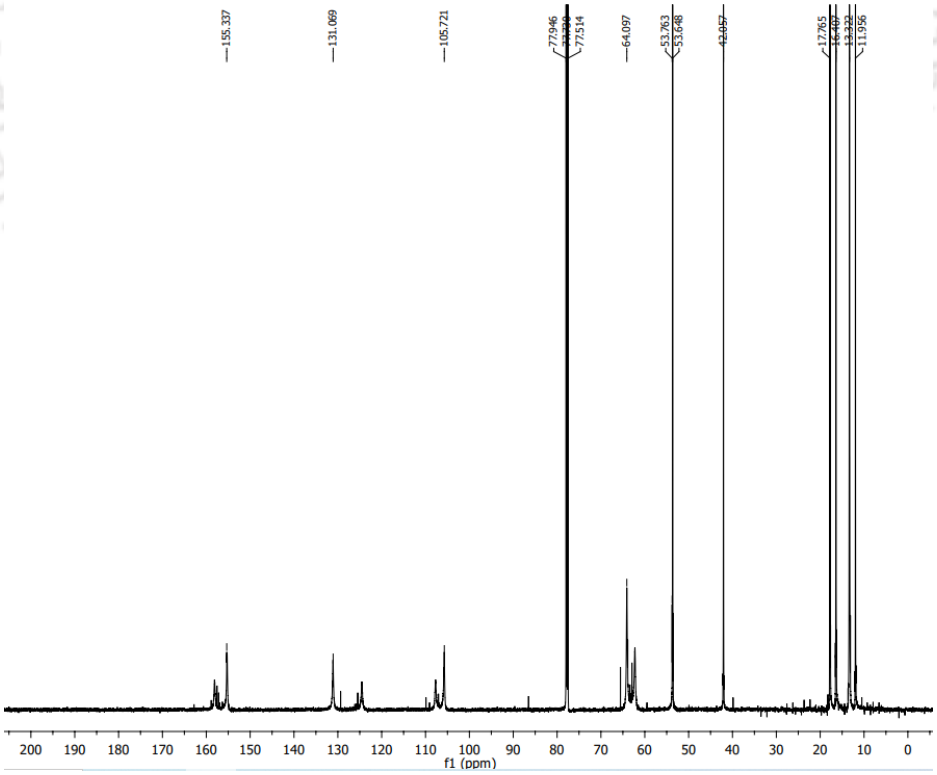
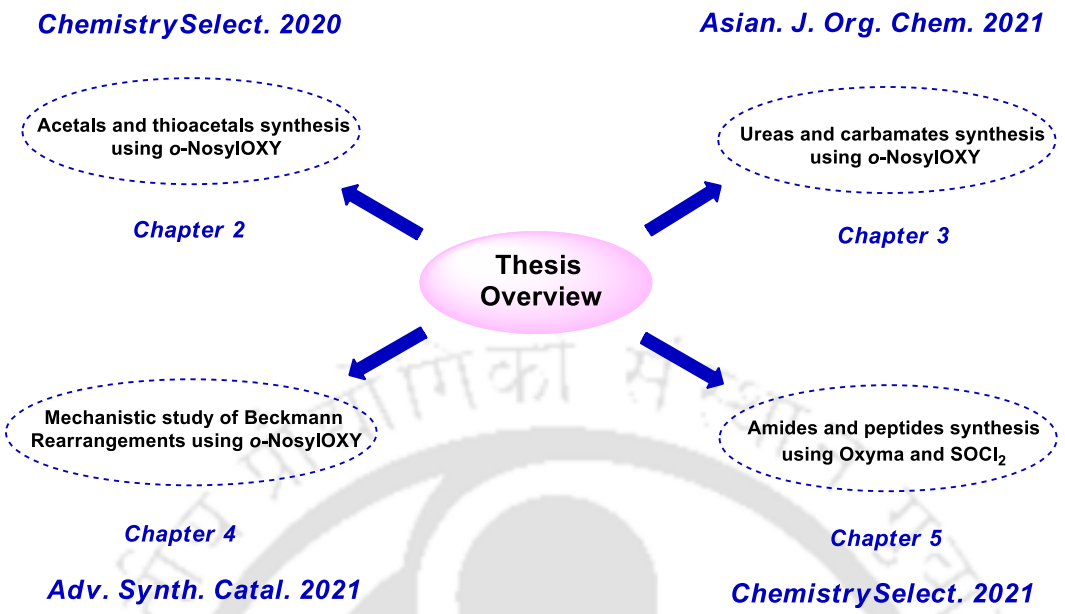


Figure 5.8.4.2. ^{13}C-NMR spectrum of the reaction mixture of 2 equiv of Oxyma and 1 equiv of $SOCl_2$ (reaction time 30 min)

Conclusions and Future Directions

Conclusions

The work presented in this thesis is mainly focused on the different applications of the coupling reagent *ortho*-NosylOXY (**I**) to synthesize acetals, thioacetals, ureas, carbamates, and thiocarbamates. A newer methodology is also described to convert carboxylic acids into amides, dipeptides, esters, and hydroxamates. The whole structure of the thesis is depicted in scheme 1. In chapter 1, we have discussed the importance of the compounds mentioned above, their existing methodologies, and their drawbacks. We have described the synthesis of acetals and thioacetals from aldehydes using *ortho*-NosylOXY in chapter 2. In chapter 3, we have demonstrated the racemization-free synthesis of ureas, carbamates, and thiocarbamates from carboxylic acids via Curtius rearrangement using *o*-NosylOXY. We have extended the mechanism study of the Beckmann rearrangement from ketoxime to amide using *o*-NosylOXY in chapter 4. Finally, in chapter 5, we have proposed a one-pot protocol to synthesize amides, peptides, esters, and hydroxamates using Oxyma and thionyl chloride with minimal racemization.

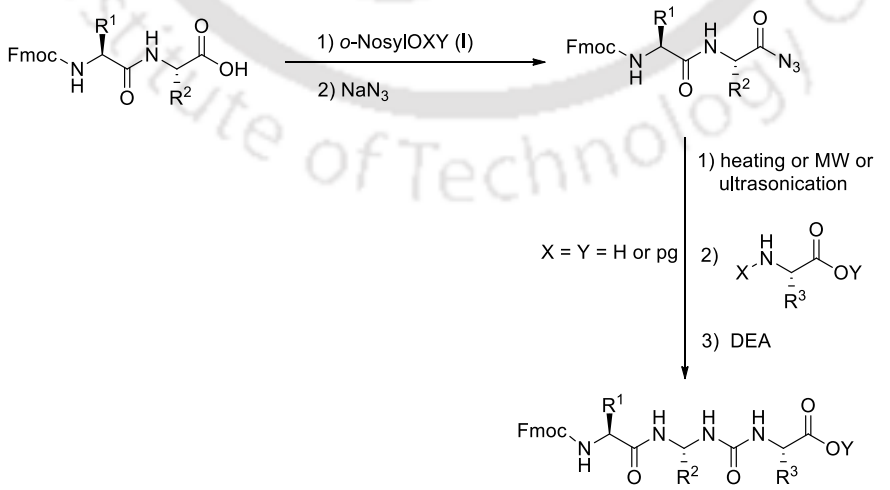


Scheme 1. Thesis Overview

Future directions

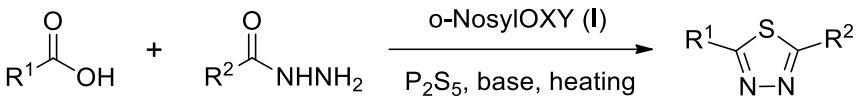
In the future, we can further use *o*-NosylOXY for other conversions. Some possible applications of *o*-NosylOXY are shown below.

1) Synthesis of oligo-α-peptidyl ureas from Fmoc protected peptides:



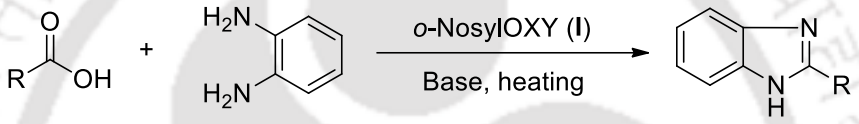
Scheme 2. Synthesis of oligo-α-peptidyl ureas using *o*-NosylOXY

2) Synthesis of thiadiazoles from carboxylic acids:



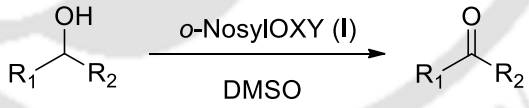
Scheme 3. Synthesis of thiadiazoles using *o*-NosylOXY

3) Synthesis of benzimidazoles from carboxylic acids:



Scheme 4. Synthesis of benzimidazoles using *o*-NosylOXY

4) Oxidation of alcohols to carbonyl compounds:



Scheme 5. Synthesis of ketone from secondary alcohol using *o*-NosylOXY

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Research Outcome

Publications:

1. **Kalita, T.**; Mandal, B. One-pot synthesis of amide, dipeptide, ester and hydroxamate using oxyma and thionyl chloride ($SOCl_2$). *ChemistrySelect*. **2021**, *6*, 1-8.
2. **Kalita, T.**; Dev, D.; Mondal, S.; Giri, R. S.; Mandal, B. Ethyl-2-cyano-2-(2-nitrophenylsulfonyloximino)acetate (*ortho*-NosylOXY) mediated one-pot racemization free synthesis of ureas, carbamates, and thiocarbamates via curtius rearrangement. *Asian J. Org. Chem*. DOI: 10.1002/ajoc.202100198.
3. Dev, D.;[#] **Kalita, T.**;[#] Mondal, T.; Mandal, B. Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*ortho*-NosylOXY)-mediated double beckmann rearrangement of ketoximes under microwave irradiation: a mechanistic perception. *Adv. Synth. Catal*. **2021**, *363*, 1427-1435.
4. **Kalita, T.**; Manne, S. R.; Mandal, B. Ethyl-2-cyano-2-(2-nitrophenylsulfonyloximino)acetate (*ortho*-NosylOXY) mediated acetalization and thioacetalization of aldehydes. *ChemistrySelect*. **2020**, *5*, 1-5.
5. Manne, S. R.; Chandra, J.; Giri, R. S.; **Kalita, T.**; Mandal, B. Synthesis of β-amino alcohols using ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY). *ChemistrySelect*. **2018**, *3*, 992-996.
6. Giri, R. S.; Manne, S. R.; Dolai, G.; Paul, A.; **Kalita, T.**; Mandal, B. $FeCl_3$ mediated side chain modification of aspartic acid- and glutamic acid- containing peptides on a solid support. *ACS Omega*, **2017**, *2*, 6586-6597.
7. Dev, D.; Chandra, J.; Palakurthy, N. B.; Thalluri, K.; **Kalita, T.**; Mandal, B. Benzoxazole and benzothiazole synthesis from carboxylic acid in solution and on resin by ethyl 2-cyano-2-(2-nitro-benzenesulfonyloxyimino)acetate and *para*-toluenesulfonic acid. *Asian J. Org. Chem.* **2016**, *5*, 663–675.

Poster presentation in conferences:

1. **Kalita, T**.; Mandal, B. Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY) mediated Curtius Rearrangement: one pot racemization free synthesis of ureas and carbamates. *International Conference on Sophisticated facility*, 30th June, **2017**, Central instruments facility, IIT Guwahati. (**Poster**)
2. **Kalita, T**.; Dev, D.; Mandal, B. Synthesis of benzoxazole and benzothiazole from carboxylic acid by Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloximino)acetate and para-toluenesulfonic acid. *Frontier in Chemical Sciences*, 8th December, **2016**, Department of Chemistry, IIT Guwahati. (**Poster**)

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Qualifications

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2012 to 2014	**M.Sc in Chemistry (First Class)** Tezpur University, Tezpur, India
2009 to 2012	**B.Sc in Chemistry (First Class)** Ramjas College, Delhi University, India

honour

- Secured first rank in M.Sc from Tezpur University (Gold medalist)
- Qualified State Eligibility Test For Lecturership (SET) held on 15/11/2015 in the subject Chemical Science, accredited by University Grants Commission, New Delhi.

Research Experiences

- **Dec, 2014-Present: Research Fellow** at the department of Chemistry, IIT Guwahati, India.

Academic and Professional Skills

- **Laboratory and Instrumentation:** Familiar with Synthetic Organic Chemistry, execution of organic reactions from milligram to gram scale, handling moisture sensitive compounds using protective atmosphere, peptide synthesis (solution phase), NMR Spectroscopy (1D), HPLC, Mass Spectrometry (ESI), FT-IR spectroscopy.
- **Software:** Chem Draw, MS-Office, MestRenova.
- **Operating Systems:** Windows
- **Teaching Experience:** Worked as Teaching Assistant (TA) in B.Tech and M.Sc Laboratory at IIT Guwahati, India since 2015.
- **Language:** Hindi, English and Assamese.

Research Interests

- Peptide Chemistry.
- Synthetic Organic Chemistry.
- Heterocyclic Synthesis.