New Applications of Boc-Oxyma, *o*-NosylOXY and Nitrobenzene Sulfonic Acids in Organic Synthesis

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Doctor of Philosophy in Chemistry

Submitted by

Srinivasa Rao Manne

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati-781039, Assam, India

Dedicated To My Family

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "**New Applications of Boc-Oxyma, *o*-NosylOXY and Nitrobenzene Sulfonic Acids in Organic Synthesis**" is the result of experiments carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the guidance of Dr. Bhubaneswar Mandal. All these results are also properly mentioned in my lab notebook.

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.

Date: 22nd October 2018
Place: IIT Guwahati

Srinivasa Rao Manne

Indian Institute of Technology Guwahati
Department of Chemistry
North Guwahati, Guwahati-781039, India
Phone: +91 (361) 258 2319 (O); Fax: +91 (361) 258 2349
e-mail: **bmandal@iitg.ac.in**

CERTIFICATE

This is to certify that **Mr. Srinivasa Rao Manne** has been working under my supervision since July 2013 as a regular registered Ph.D. student. I am forwarding his thesis entitled "**New Applications of Boc-Oxyma, *o*-NosylOXY and Nitrobenzene Sulfonic Acids in Organic Synthesis**" to be submitted for the Ph.D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Date: 22nd October 2018
Place: IIT Guwahati

Dr. Bhubaneswar Mandal
Thesis Supervisor

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Srinivasa Rao Manne

List of abbreviations

Boc	*tert*-Butyloxycarbonyl
Boc-Oxyma	Ethyl 2-(*tert*-butoxycarbonyloxyimino)-2-cyanoacetate
BOP	Benzotriazol-1-yloxy-tris(dimethylamino) phosphoniumhexafluorophosphate
Bz	Benzoyl
Bzl	Benzyl
Cbz	Benzyloxycarbonyl
CDI	*N*,*N*-Carbonyldiimidazole
DCM	Dichloromethane
EDC	1-Ethyl-3-(3-(dimethylamino)propyl)carbodiimide
DABCO	1,4-Diazabicyclo[2.2.2]octane
DIPEA	Diisopropylethyl amine
DMAP	*N*,*N*-Dimethylpyridin-4-amine
DMF	*N*,*N*-Dimethylformamide
ESI MS	Electrospray Ionization Mass Spectrometry
EtOAc	Ethyl Acetate
Fmoc	9-Fluorenylmethoxycarbonyl
FT-IR	Fourier Transformation Infra-red Spectroscopy
HATU	*N*-[(Dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl-methylene)-*N*-methylmethanaminiumhexafluorophosphate *N*-oxide
HBTU	*N*-[(1*H*-Benzotriazol-1-yl)(dimethylamino)-methylene]*N*-methylmethanaminiumhexafluorophosphate *N*-oxide
HDMA	1-((Dimethylamino)-(morpholino)methylene)-1*H*-[1,2,3]triazolo[4,5-*b*]pyridiniumhexafluorophosphate-3-oxide

HDMB	1-((Dimethylamino)(morpholino)methylene)-1*H*-benzotriazoliumhexafluorophosphate-3-oxide
HOBt	1-Hydroxy Benzotriazole
HPLC	High Pressure Liquid Chromatography
i-Pr	Isopropyl
LC-MS	Liquid Chromatography Mass Spectrometry
mL	Milli Liter
MW	Microwave
NMI	*N*-Methylimidazole
NMP	*N*-Methyl-2- pyrrolidone
NMR	Nuclear Magnetic Resonance
o-NosylOXY	Ethyl 2-cyano-2-(2-nitrophenylsulfonyloxyimino)
Oxyma	Ethyl 2-cyano-2-(hydroxyimino)acetate
PyBOP	Benzotriazole-1-yl-oxy-tris-pyrolidine-phosphonium Hexafluorophosphate
RP	Reverse Phase
SAHA	Suberoylanilide Hydroxamic Acid
SPPS	Solid Phase Peptide Synthesis
tBu	*tert*-Butyl
TCT	Cyanuric Chloride
TFA	Trifluoroacetic Acid
TFFH/PTF	Tetramethylfluoroformamidinium hexafluorophosph-ate/benzyl triphenylphosphonium dihydrogen trifluoride
THF	Tetrahydrofuran

Amino Acids

Name	3-Letter code	1-Letter code
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic acid	Glu	E
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

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

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

Abstract

The research work presented in this thesis has been divided into five chapters based on the results of the experimental work performed during the complete course of the doctoral studies. Chapter 1 contains the introduction. Chapter 2 describes the enantioselective synthesis of hydroxamic acids using Ethyl 2-(*tert*-butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma). Chapter 3 demonstrates the Ethyl 2-(*tert*-butoxycarbonyloxy-imino)-2-cyanoacetate (Boc-Oxyma) as an efficient promoter for the Lossen rearrangement of the hydroxamic acid into ureas, carbamates and thiocarbamates. Chapter 4 focuses on the mild efficient method for the reduction of carboxylic acid to alcohols using Ethyl 2-Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*ortho*-NosylOXY). Chapter 5 illustrates the enantioselective *N*-arylation of amines *via* ipso-nucleophilic aryl substitution on nitrobenzene sulfonic acid.

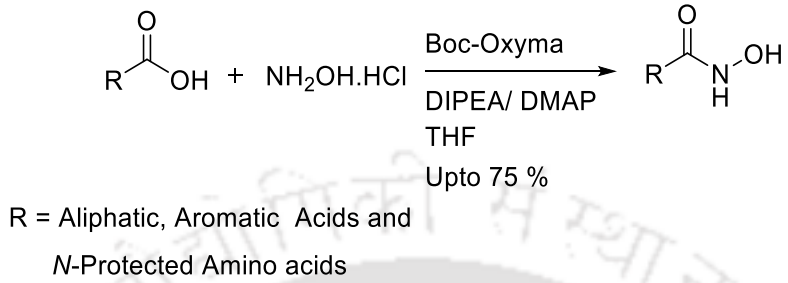
Chapter 1: Introduction

The thesis describes the novel methodologies for the synthesis of hydroxamic acids, ureas, carbamates, thiocarbamates, alcohols and arylamines. These functionalities exhibit a broad range of applications in pharmaceuticals, natural products, agrochemicals, dyes, and polymers. The introductory chapter briefly focuses on the importance of the above mention compounds, their existing synthetic protocols and drawbacks associated with the existing methods.

Chapter 2: Enantioselective Synthesis of Hydroxamic Acids Using Boc-Oxyma

The hydroxamic acids play vital roles as active pharmaceutical ingredients (APIs) and in the medicinal chemistry. Also, hydroxamic acid based compounds are entering into clinical trials as potential antibacterial, antifungal, anti-inflammatory, anti-asthmatic, anticancer and ant arthritis drugs. There are several methods reported in the literature for the synthesis of hydroxamic acids, but those methods suffer from various drawbacks. To overcome these drawbacks, we developed a simple efficient racemization-free synthesis of hydroxamic acids using Ethyl 2-(*tert*-butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma). Boc-Oxyma was added to a stirred solution of a carboxylic acid or *N*-protected

amino acids, DIPEA and a catalytic amount of DMAP in THF at 0-5 °C. The reaction mixture was stirred for 30 min for preactivation followed by the addition of hydroxylamine hydrochloride. Then we continued the reaction for more 2 h at room temperature.



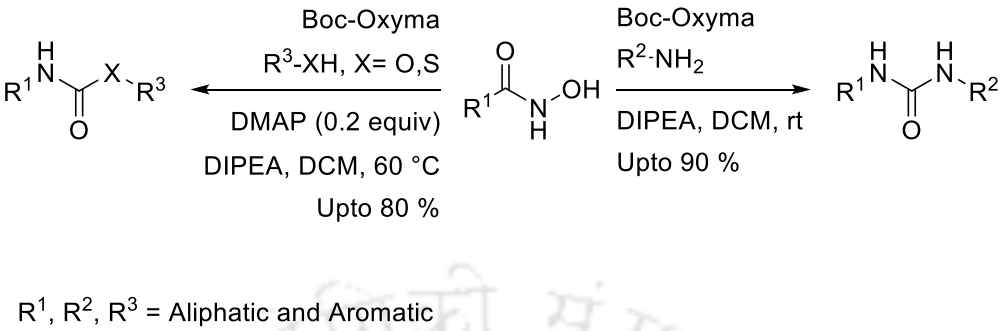
Scheme 1. *Synthesis of hydroxamic acids using the Boc-Oxyma*

A variety of carboxylic acids such as aromatic carboxylic acids, aliphatic carboxylic acids and *N*-protected amino acids were converted into the corresponding hydroxamic acid, respectively, with good yields. The method showed compatibility with various side chain protecting groups including, *tert*-butyl, trityl, and benzyl. To explore the utility of these methodologies in medicinal chemistry we synthesized some biologically important compound, SAHA (suberoylanilide hydroxamic acid) and their derivatives. These compounds were used as anticancer agents. Also, we successfully synthesized long-chain *N*-terminal peptide hydroxamic acids on resin using Fmoc based Solid Phase Peptide Synthesis protocol.

Chapter 3: Boc-Oxyma: An Efficient Promoter for the Lossen Rearrangement of the Hydroxamic Acids to Ureas, Carbamates and Thiocarbamates

In the previous chapter, we described the enantioselective synthesis of hydroxamic acids. In continuation of these syntheses, we developed a versatile synthetic methodology for the racemization free synthesis of ureas using these hydroxamic acids as starting material via Lossen rearrangement. The construction of urea linkages has got tremendous interest in recent years due to their broad biological activity and a diverse pharmacological profile. Initially, the hydroxamic acids react with Boc-Oxyma in the presence of DIPEA to form *O*-acylated hydroxamic acid at 0 °C. It further gets converted into the corresponding isocyanate via Lossen rearrangement which subsequently reacts with nucleophiles, such

as amines or alcohols or thiols to generate ureas, carbamates or thiocarbamates, respectively.

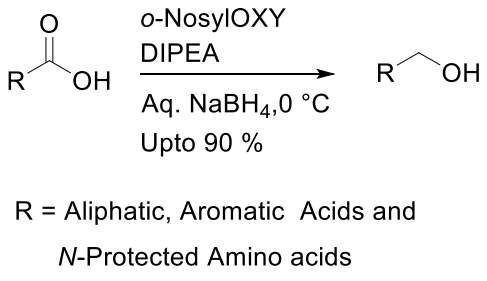


Scheme 2. *Synthesis of ureas, carbamates and thiocarbamates using the Boc-Oxyma*

We successfully synthesized simple and racemization free di- and tri-peptidyl ureas, carbamates and thiocarbamates with good yield. A rigorous mechanistic investigation was also carried out.

Chapter 4: Mild and Efficient Method for the Reduction of Carboxylic Acid to Alcohol using *ortho*-NosylOXY

Alcohols are the key synthons in synthetic organic chemistry, which can be used for the synthesis of some other important building blocks, such as aldehydes, acids, ligands, long chain of diamines and tetramines. Alcohols are also widely used in medicinal chemistry as antibiotics, anticancer drugs as well as perfumes, hair dyes, and photo developers. In this chapter, we described a simple and efficient method for the reduction of carboxylic acids and *N*-protected amino acids into corresponding alcohols using Ethyl 2-Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*ortho*-NosylOXY) as an activating reagent and $NaBH_4$ as a reductant.

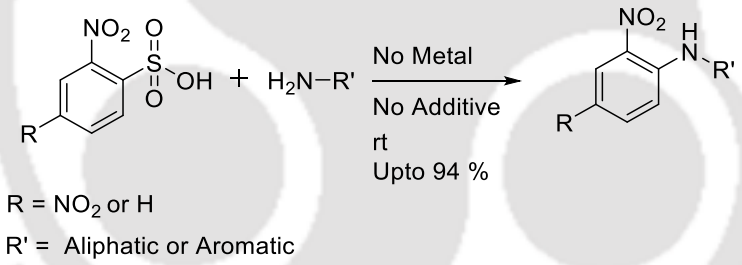


Scheme 3. *Reduction of carboxylic acid to alcohol using ortho-NosylOXY*

The reaction worked well with both aromatic or aliphatic carboxylic acids and *N*-protected amino acids in good to high yield. We also performed racemization study of the current protocol by HPLC. No racemization could be detected.

Chapter 5: Enantioselective *N*-Arylation of Amines *via* ipso-Nucleophilic Aryl Substitution on Nitrobenzene Sulfonic Acid

The arylamines are very often found in medicinal chemistry and natural products. These arylamines also drew considerable attention in many commercial fine chemicals industries, polymer and dye sectors. Traditionally arylamines are prepared by palladium or copper-catalyzed cross-coupling of aryl halides with amines. But these protocols have few drawbacks such as the use of expensive palladium complexes, high temperatures, longer reaction time and sensitivity towards air and moisture. To overcome these drawbacks, we developed a novel and efficient method for the synthesis of arylamines directly by the reaction of nitrobenzene sulfonic acid with amines *via* ipso nucleophilic aryl substitution (^{i}SNAr) process.



Scheme 4. *Synthesis of arylamines*

To the best of our knowledge, this is the first approach to the transformation of benzene sulfonic acid to the corresponding aminated products at room temperature. The salient features of this method are (a) aminated products are obtained in short time with good to excellent yields in high purity at room temperature, (b) does not require any metals, activating agents, halogenated agents, and toxic oxidants. We also investigated the racemization probability of the current protocol that indicates no racemization during amination reaction with chiral amino acids, which in turn allows enantioselective syntheses.

Contents

Chapter 1

Introduction

1.1. Introduction

Amide or peptide functionality is present in natural products, agrochemicals, polymers, and pharmaceuticals.[1] Generally, activation of carboxylic acid is the key step in amide bond formation and is usually carried out using coupling reagents. Synthesis of these reagents has a long history. The era began in 1955 by the introduction of dicyclohexylcarbodiimide (DCC).[2] Later, HOBt,[3] HOAt[4,] and 6-Cl-HOBt[5] were introduced as an additive with coupling reagents to increase its efficiency during peptide synthesis and prevent the racemization. Since then, significant efforts were made on the upgradation of the existing and also bringing out new coupling reagents. Accordingly, a broad spectrum, ranging from carbodiimides to oximes were developed and proved to be very effective in peptide synthesis.

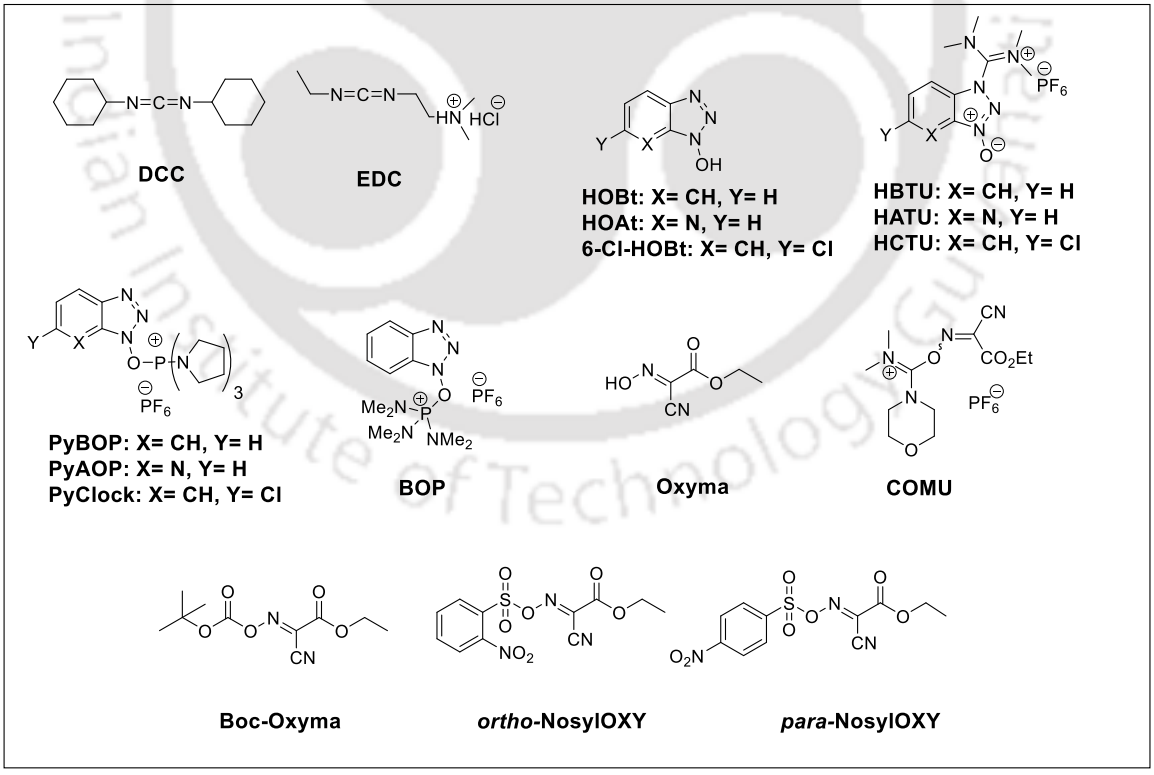


Figure 1.1 *Some important coupling reagents*

The benzotriazole based additives were expanded, and more efficient coupling reagents such as HBTU,[6] HATU,[7] HCTU[8] (as ammonium salts), BOP,[9] PyBOP,[10] and PyAOP[11] (as phosphonium salts) were developed. However, these benzotriazole derivatives are restricted due to their explosive nature.[12] In replacing these benzotriazoles, El-Faham and Albericio have introduced a phosphonium salt of Oxyma, O-[(cyano-(ethoxycarbonyl) methylidene)-amino]yloxytri-pyrrolidinophosphonium hexafluorophosphate (PyOxm)[13] as an efficient coupling reagent for peptides synthesis. Oxyma as a good racemization suppressant performs better than classical benzotriazole. Similarly, the recently introduced uronium salt, COMU[14] also renders a higher percentage of cyclic peptides than known phosphonium salts in cyclization models. Also, our group developed Oxyma based coupling reagents such as Boc-Oxyma,[15] *ortho*-NosylOXY[16,] and *para*-NosylOXY.[17] These coupling reagents successfully achieved various organic transformations such as the conversion of the carboxylic acids to amides, peptides, esters, thioesters, hydroxamates, ureas and heterocyclic compounds, such as benzoxazoles and benzothiazoles, ketones to amides and aldoximes to nitriles. The salient features of these coupling reagents include excellent racemization suppression capability and ease of synthesis. After the reaction, it generates only Oxyma as a solid byproduct that can be recovered easily and can be recycled for the synthesis of the same reagent. Given these interesting features and various applications of Oxyma based coupling reagents, the present thesis focus on the exploration of these coupling reagents for various organic transformations, such as synthesis of hydroxamic acids, ureas, carbamates, thiocarbamates, alcohols, and arylamines. The importance of these compounds is briefly discussed below.

1.2. Importance of Hydroxamic Acids, Ureas, Carbamates, Thiocarbamates, Alcohols, and Arylamines

1.2.1. Importance of Hydroxamic Acids

Hydroxamic acids are class of organic compounds with chemical formula RC(O)N(OH)R′, having a carbonyl group and R, R′ as organic residues. The structural formula is similar to amides, the only difference being the hydrogen atom is replaced by a hydroxyl group at the NH center. The hydroxamic acids exhibit a broad range of biological activities in pharmaceutical ingredients and medicinal chemistry.[18] Clinical trials on hydroxamic acid

compounds are in progress to check for potential antibacterial, anticancer, antifungal, anti-asthmatic, anti-inflammatory, and anti-arthritic properties.[19] Trichostatin A[20] was the first reported naturally occurring compound having a hydroxamic acid moiety and it is a mammalian histone deacetylase inhibitor (HDI), antifungal, antibiotic and anticancer drug. It also inhibits the growth of the eukaryotic cell cycle at the beginning stage and was shown to be selective and reversible towards inhibiting class I, II and IV types of HDAC without affecting class III. The IC_{50} value of 20 nM for Trichostatin A falls in a normal range. Suberoylanilide hydroxamic acid (SAHA)[21] is another hydroxamic acid-based drug, marketed under the trade name of Zolinza by Merck Company. It is used for the treatment of advanced cutaneous T-cell lymphoma, a type of skin cancer and treating patients having a tumor characterized by proliferation of neoplastic cells. Panobinostat[22] is a non-selective histone deacetylase inhibitor, developed by Novartis and sold in the market with the brand name of Farydak. It is used for the treatment of plasma cell myeloma cancer in adults after completing two earlier treatments. Hydroxamic acids also have strong chelating properties with metal ions, especially with transition metals, thus act as inhibitors of metalloenzymes and matrix metalloproteinase.[23]

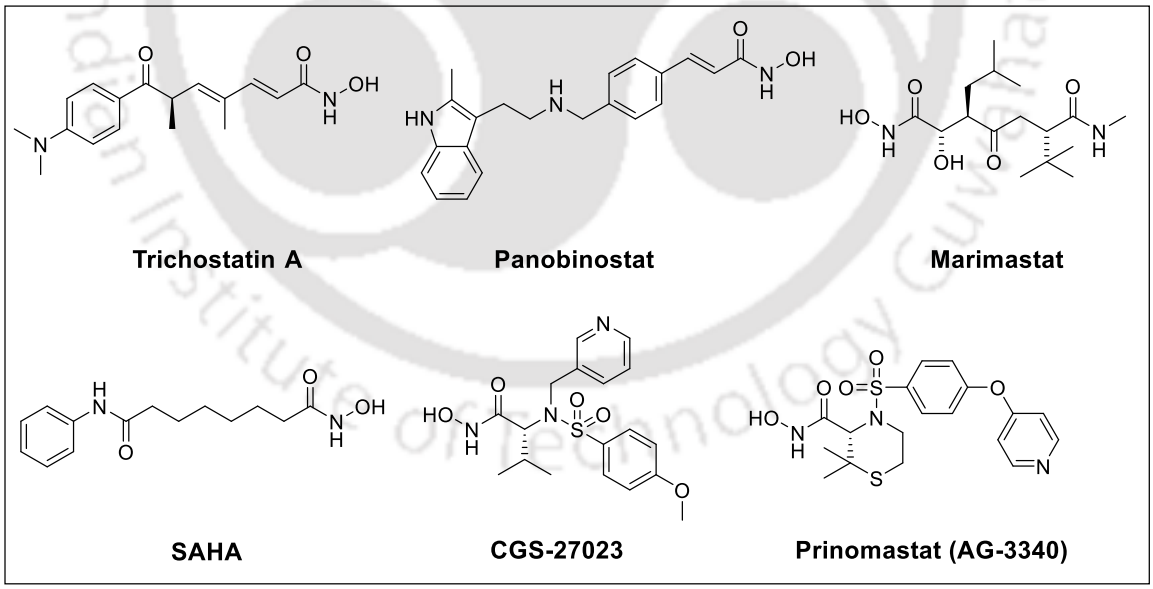


Figure 1.2.1.1 *Examples of some biologically active compounds*

1.2.2. Importance of Ureas

The compounds containing urea motifs have got large applications in pharmaceutical, polymers and material sciences.[24] Barbital[25] (diethylmalonyl urea), also known as veronal, was the first used commercially available barbiturate (sleep aid/hypnotic) from 1903 to mid-1950s. Sorafenib[26] is an inhibitor of tyrosine protein and Raf family kinases and is commercially available in the market for the treatment of primary kidney cancer and advanced primary liver cancer. Recently, it is also approved by FDA for the treatment of advanced thyroid carcinoma. Cariprazine[27] is a type of antipsychotic medication and is sold in the market with brand names Vraylar and Reagila. It is used for the treatment of schizophrenia, bipolar mania, and depression. Below given the list of scaffolds of urea which exhibit several other pharmacological activities such as antibiotics (acylampicillins),[28] anti-asthma (zileuton).[29] Sulfonylureas[30] are used to treat diabetes and nitrosoureas[31] serve as DNA alkylating agents for the treatment of cancer.

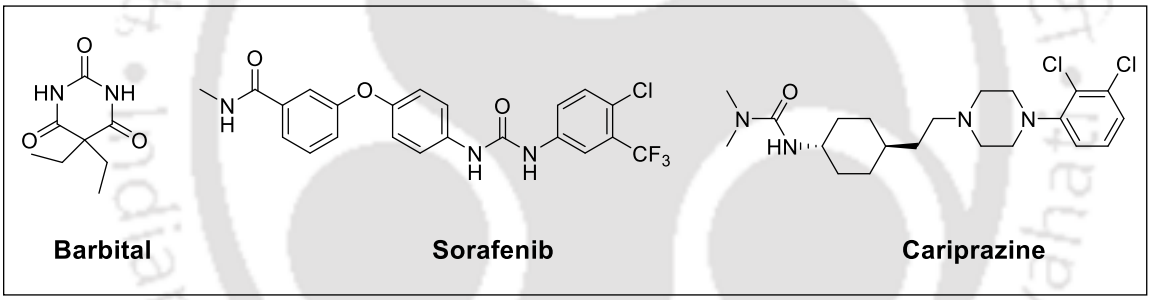


Figure 1.2.2.1. *Urea linkage containing biologically active compounds*

1.2.3. Importance of Carbamates and Thiocarbamates

The chemistry of carbamates is interesting because they are part of many natural products, medicinal and agrochemical-based products.[32] For example, Eszopiclone[33] is a cyclopyrrolone class of nonbenzodiazepine hypnotic agent used for the treatment of insomnia. Physostigmine[34] is a highly toxic parasympathomimetic alkaloid, naturally obtained from Manchineel tree and Calabar beans. It acts as a reversible cholinesterase inhibitor. Solifenacin,[35] a class of antimuscarinic agent used for the treatment of overactive bladder. Carbaryl, also known as carbaryl, is a largely used insecticide.

Similarly, thiocarbamates are widely distributed in nature and also part of many industrially and synthetically derived pharmaceuticals.[36] These compounds possess a broad range of

biological activities such as anesthetics, fungicides, antivirals, bactericides, pesticides and as antifertility agents. These compounds are most noted for their use as commercial herbicides. Some of the potent herbicides such as Molinate,[37] Thiobencarb[38,] and Orbencarb[39] are well-known examples.

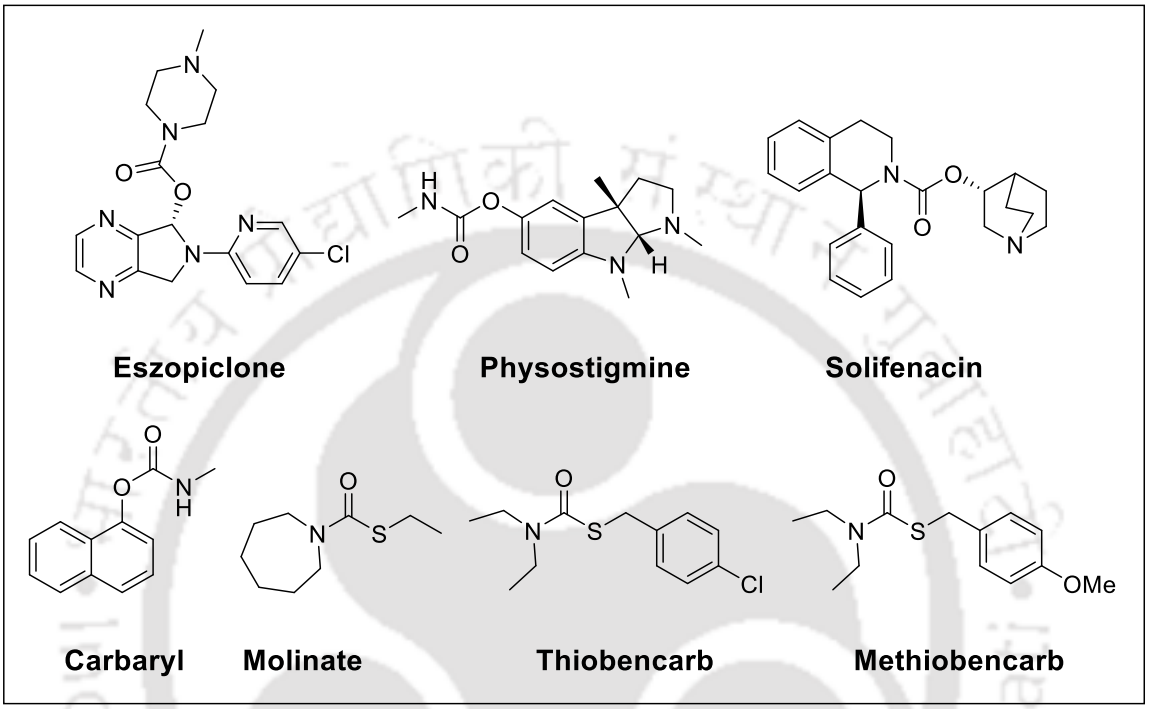


Figure 1.2.3.1. *Examples of some biologically active carbamates and thiocarbamates*

1.2.4. Importance of Alcohols

Synthetic chemists are alluded to *β*-amino alcohols due to their versatile applications in the synthesis of many important scaffolds. They serve as key synthons for the synthesis of *β*-amino acids,[41] long chain diamines and tetramines,[42] several insecticides,[43] ligands and chiral auxiliaries in asymmetric synthesis.[44] Especially, *β*-amino alcohols are important precursors for the synthesis of aldehydes,[45] which have diverse applications in synthetic and medicinal chemistry. Furthermore, the commercial importance of *β*-amino alcohol is evident from its presence in many known drugs and drug intermediates. For example, sphingosines[46] is a type of sphingolipids and is present in cell signaling processes. Similarly, symbioramide[47] is a class of bioactive ceramide compound, and it shows antileukemic activity against L-1210 murine leukemia cells. It was isolated by Kobayashi *et al.*[48] from the laboratory-cultured dinoflagellate Symbiodium sp, obtained from the insides of gill cells of an Okinawan bivalve Fragum sp. Thiamphenicol[49] is an antibiotic

compound and is widely used for the treatment of pelvic inflammatory disease and sexually transmitted infections. Gramicidin[50] also an antibiotic compound, it is a mixture of three polypeptides containing alternating L- and D-amino acids. Gramicidin is active against gram-positive bacteria as well as selective gram-negative bacteria. In addition to the above-stated advantages, *β*-amino alcohol also acts as a pharmacophoric group in several drugs as antiretroviral protease inhibitors (PIs).[51] *β*-amino alcohols also have considerable interest in the synthesis of perfumes, hair dyes, and photo developers.[52]

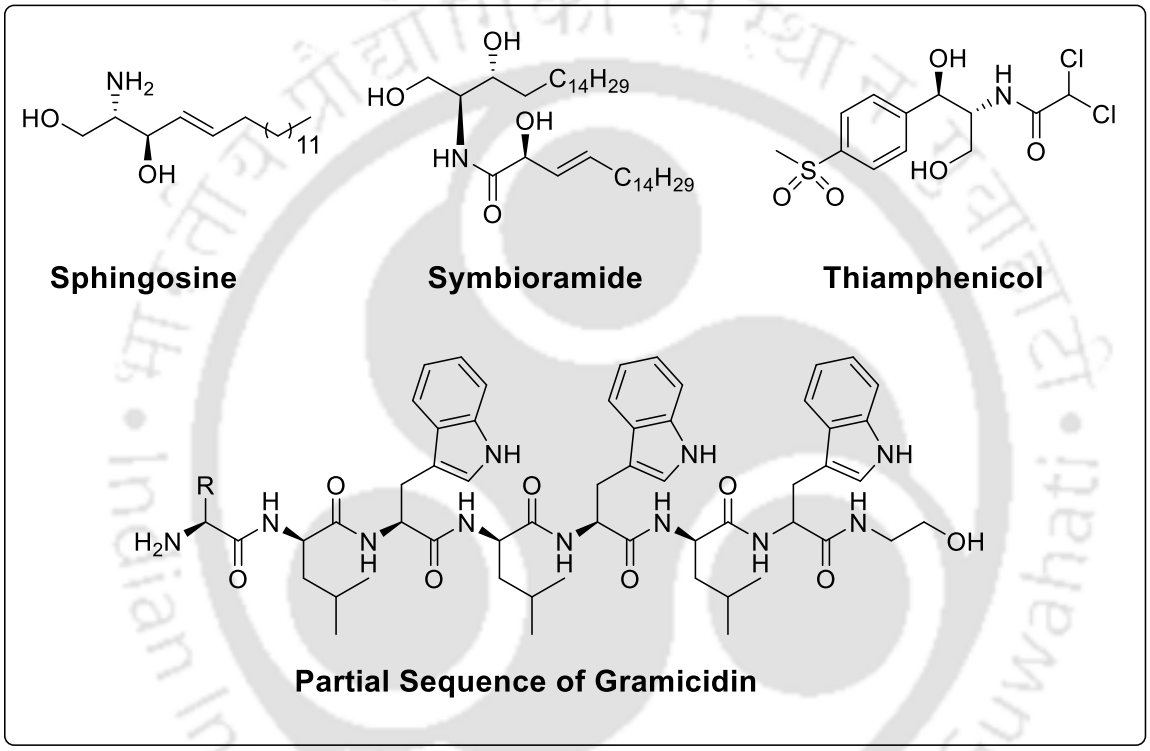


Figure 1.2.4.1. *Examples of some biologically active compounds*

1.2.5. Importance of Arylamines

The compounds containing arylamine moiety are of great interest because of their potential applications in many natural products, having unique and wide-ranging biological activities and useful electrical and mechanical properties.[53-55] These motifs are also widely used in the synthesis of fine chemicals, dyes and polymers.[56] Several synthetic and naturally occurring arylamines are found in many known drugs. For example, Folic[57] acid also known as vitamin B9, is essential for daily human body functions. Especially, it is essential for pregnant women to prevent miscarriage, congenital disabilities of the baby brain and spinal cord.[58] Norfloxacin[59] is an important member of the quinolone family and is an

antibacterial used for the treatment of urinary tract infection and inflammation of the prostate gland. It also shows high activity against gram-positive and gram-negative bacteria. Furthermore, arylamines are also found in pharmacological drugs such as vortioxetine[60]-an antidepressant, tolfenamic acid[61]-an anti-inflammatory agent and linezolid[62]-an antibiotic.

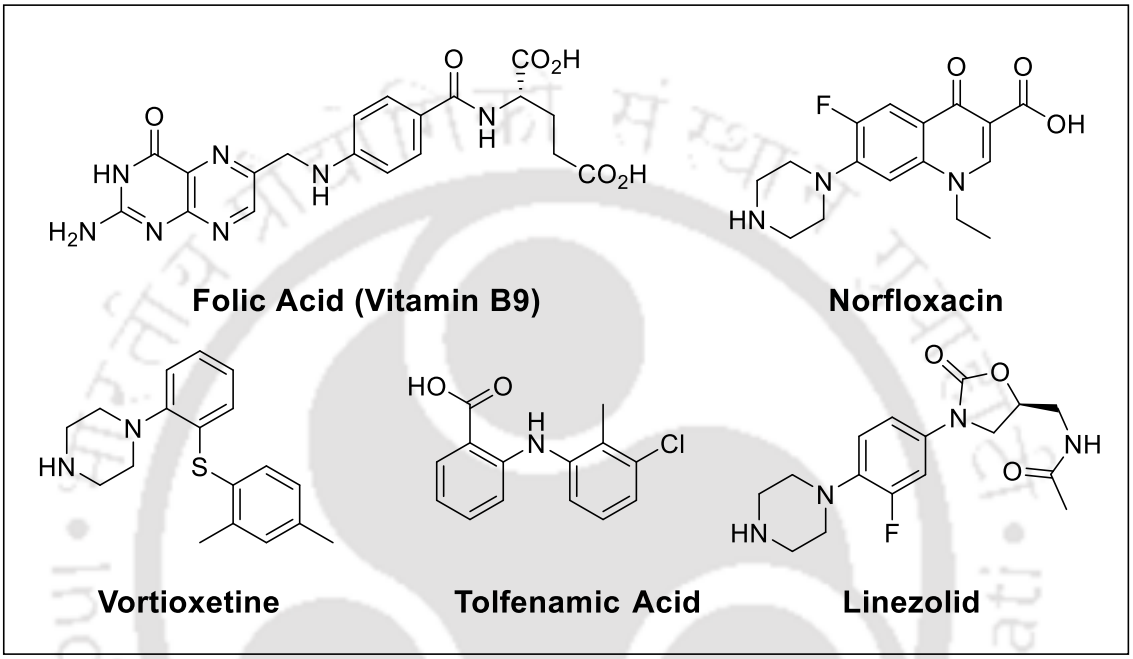


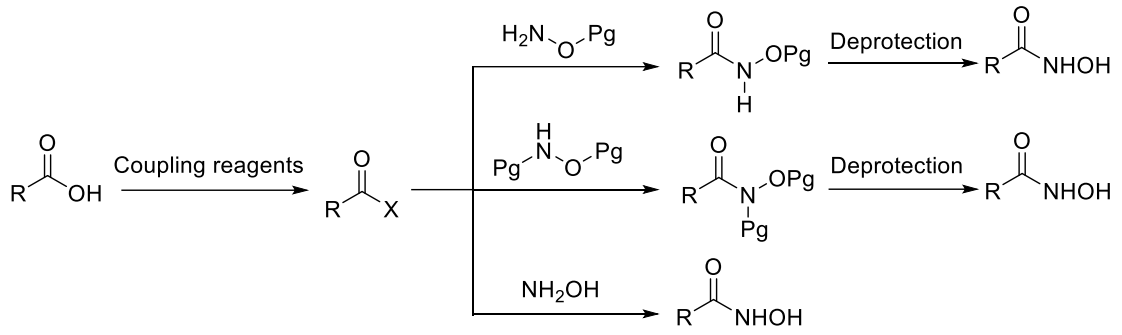
Figure 1.2.5.1. *Examples of some biologically active compounds*

1.3. Existing Methods for Synthesis of Hydroxamic Acids, Ureas, Carbamates, Thiocarbamates, Alcohols, and Arylamines

1.3.1. Existing Strategies for the Synthesis of Hydroxamic acids

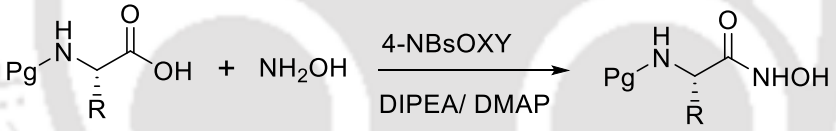
1.3.1.1. Classical Methods

Several methods have been developed for the synthesis of the hydroxamic acids, over the years. Generally, hydroxamic acids are synthesized by the activation of carboxylic acids with various coupling reagents such as, 2,4,6-trichloro[1,3,5]triazine (cyanuric chloride),[63] alkyl chloroformate,[64] cyclic phosphonic anhydride,[65] TFFH/PTF,[66] CDI,[67] followed by the reaction with *O*-protected or *N*,*O*-protected or unprotected hydroxylamine and finally deprotection, wherever necessary. (Scheme 1.3.1.1.1).



Scheme 1.3.1.1.1. *Classical approaches for the synthesis of hydroxamic acid*

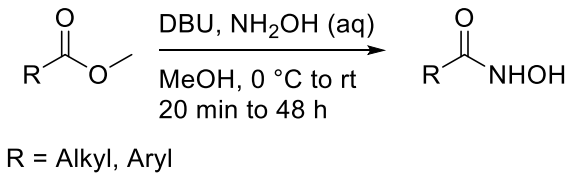
Our group has illustrated a mild efficient method for the racemization free synthesis of hydroxamic acids by using a novel and recyclable coupling reagent ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate (4-NBsOXY). The products are obtained in good to excellent yield under the mild conditions, without using any acid chlorides or strong bases. The main advantage of this reaction is that the byproducts, Oxyma (Ethyl 2-cyano-2-(hydroxyimino)acetate) and 4-nitrobenzenesulfonic acid, can not only be recovered easily but also be recycled to prepare the same reagent (Scheme 1.3.1.1.2) easily.[68]



Scheme 1.3.1.1.2. *Synthesis of hydroxamic acids using 4-NBsOXY*

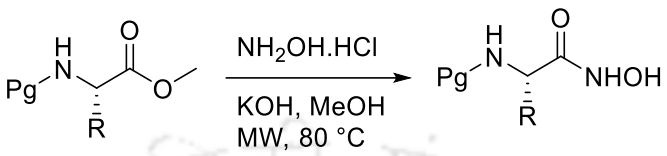
1.3.1.2. Synthesis of Hydroxamic Acids from Esters

A general, mild and efficient procedure to prepare a library of hydroxamic acids from esters was described by Tomas and co-workers using DBU or polymer-supported DBU as a base. The substrate scope of the reaction only limited to methyl esters (Scheme 1.3.1.2.1).[69]



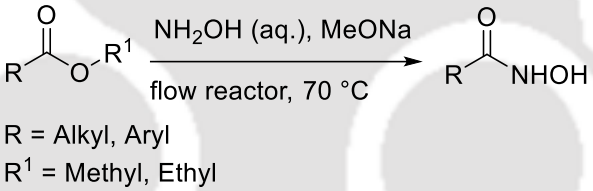
Scheme 1.3.1.2.1. *Base mediated hydroxamic acid synthesis*

Massaro *et al.* reported a microwave-assisted transformation of methyl esters into corresponding hydroxamic acids in the presence of hydroxylamine and a strong base. The method has been successfully applied to synthesize enantiomerically pure esters without loss of stereochemical integrity (Scheme 1.3.1.2.2).[70]



Scheme 1.3.1.2.2. *Synthesis of hydroxamic acid under microwave irradiation*

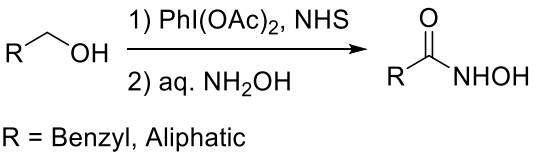
Martinelli and co-workers have demonstrated efficient, continuous flow synthesis of hydroxamic acids directly from inactive esters (methyl or ethyl esters). In this method, a mixture of ester and hydroxylamine (1:10 ratio, 0.5 M in MeOH) was simultaneously pumped into the flow reactor with a solution of sodium methoxide (0.5 M in MeOH). A constant flow rate was maintained at 70 °C temperature (Scheme 1.3.1.2.3).[71]



Scheme 1.3.1.2.3. *Continuous flow method for the synthesis of hydroxamic acids*

1.3.1.3. Synthesis of Hydroxamic acids from Alcohols

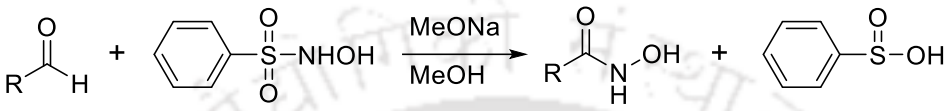
Luca and co-workers proposed a novel route for the oxidative synthesis of hydroxamic acids from benzylic and aliphatic alcohols in a one-pot manner. At first, alcohols are oxidized in the presence of hypervalent iodine (III) reagent and *N*-hydroxysuccinimide (NHS), followed by nucleophilic addition of the hydroxylamine to afford the hydroxamic acids (Scheme 1.3.1.3.1).[72]



Scheme 1.3.1.3.1. *Oxidative synthesis of hydroxamic acids*

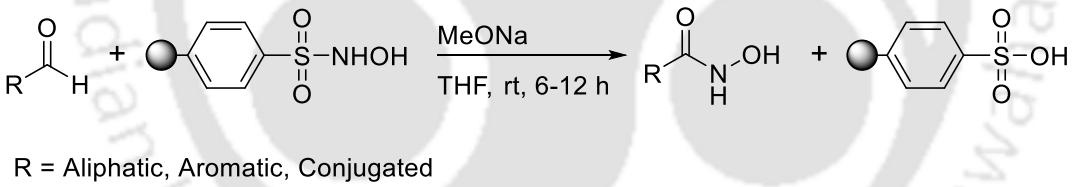
1.3.1.4. Synthesis of Hydroxamic Acids from Aldehydes

Angeli and Rimini reported the synthesis of hydroxamic acids from aldehydes in the presence of *N*-hydroxybenzenesulfonamide and sodium methoxide with good yield. After completion of the reaction, acidic workup gives the hydroxamic acid. The disadvantage of this method is the formation of a benzenesulfinic acid by-product, which is difficult to separate from the intended product (Scheme 1.3.1.4.1).[73]



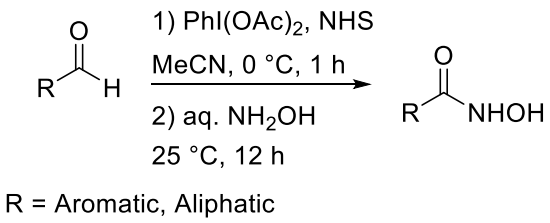
Scheme 1.3.1.4.1. *Angeli-Rimini's reaction*

Later, Porcheddu and Giacomelli modified Angeli-Rimini's protocol, and they reported a convenient procedure for the preparation of resin-bound *N*-hydroxybenzenesulfonamide. This resin was successfully employed to convert aldehydes into corresponding hydroxamic acids using 5.4 N solution of sodium methoxide in MeOH in THF solvent at room temperature (Scheme 1.3.1.4.2).[74]



Scheme 1.3.1.4.2. *Modified Angeli-Rimini's reaction*

Recently, Dettori *et al.* have demonstrated the one-pot oxidative transformation of aldehydes into hydroxamic acids by the use of hypervalent iodine (III) reagent and an aqueous solution of hydroxylamine. The reaction worked well for both aliphatic and aromatic aldehydes with good to excellent yields (Scheme 1.3.1.4.3).[75]



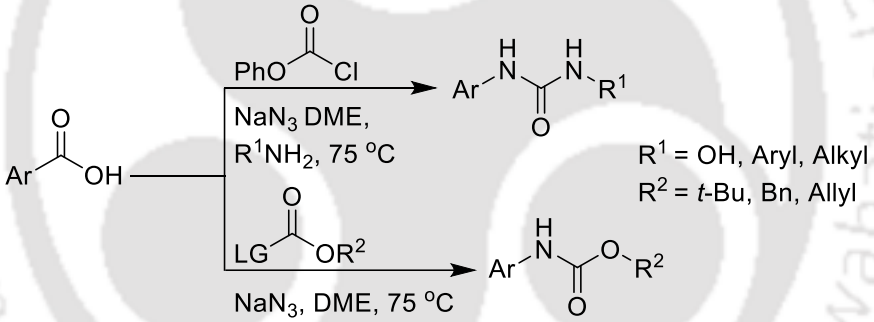
Scheme 1.3.1.4.3. *Oxidative synthesis of hydroxamic acids from aldehydes*

1.3.2. Existing Methods for the Synthesis of Ureas, Carbamates, and Thiocarbamates

Over the years many strategies have been developed for the synthesis of ureas, carbamates, and thiocarbamates, which include Curtius rearrangement, Hofmann rearrangement, Lossen rearrangement, and cross-coupling reactions.

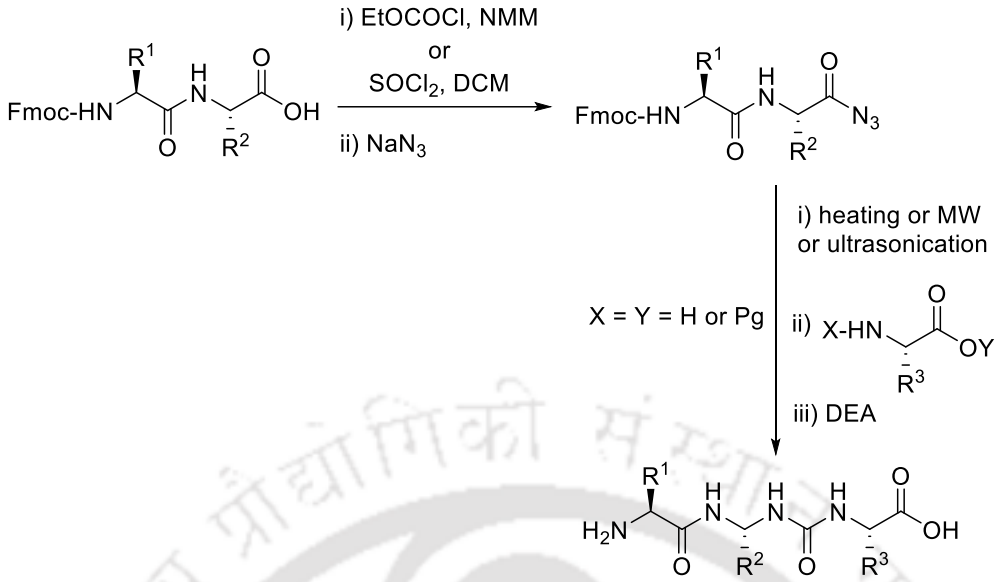
1.3.2.1. Curtius Rearrangement

The Curtius rearrangement was a well-established method for the preparation of isocyanate from acyl azide. Lebel *et al.* have described an efficient method for obtaining carbamates or ureas from aromatic carboxylic acids. The reaction of chloroformate or di-*tert*-butyl dicarbonate and sodium azide with acid gives azidoformate intermediate, which then undergoes a Curtius rearrangement to form isocyanate. The isocyanate is made to react with either an alkoxide or an amine to form the corresponding aromatic carbamate or urea (Scheme 1.3.2.1.1).[76]



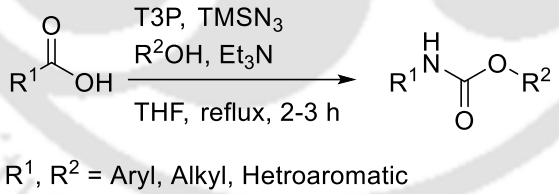
Scheme 1.3.2.1.1. *Preparation of aromatic ureas and carbamates*

Sureshbabu and co-workers synthesized oligo-α-peptidyl ureas from Fmoc protected peptide acids *via* peptide isocyanate intermediates. The Fmoc-peptide isocyanates were prepared by the Curtius rearrangement of Fmoc-peptide acid azides under thermal, microwave, and ultrasonic conditions. All the isocyanate intermediates were successfully isolated in stable crystalline solid forms with good to excellent yields (Scheme 1.3.2.1.2).[77]



Scheme 1.3.2.1.2. *Synthesis of the oligopeptidyl ureas.*

A system of propylphosphonic anhydride (T3P), azidotrimethylsilane and alcohol was studied for one-pot conversion of a carboxylic acid into carbamates through Curtius rearrangement. The reaction is viable with aromatic, heterocyclic and aliphatic carboxylic acids and a variety of alcohols. The formation of water-soluble byproducts and nontoxic nature, low epimerization tendency of T3P has made this protocol strategically crucial for large-scale applications (Scheme 1.3.2.1.3).[78]

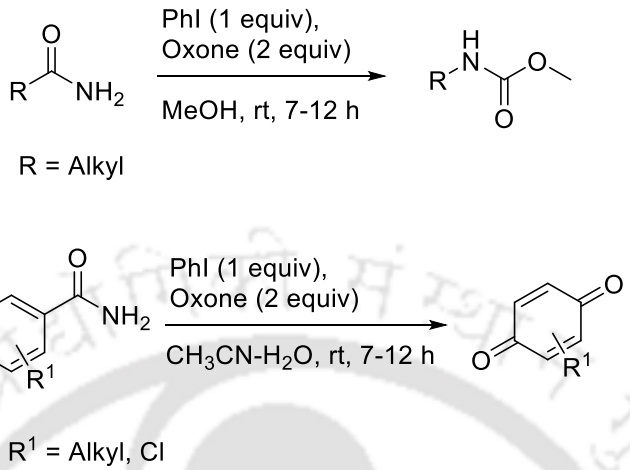


Scheme 1.3.2.1.3. *T3P mediated synthesis of carbamates.*

1.3.2.2. Hofmann Rearrangement

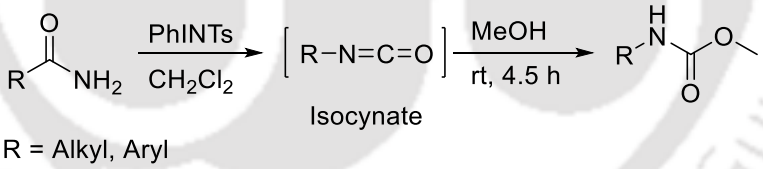
The Hofmann rearrangement of amide to an amine is relatively more useful in preparing the titled compounds. Zhdankin and co-workers have developed a convenient procedure for the preparation of methyl carbamates from alkyl carboxamides *via* Hofmann rearrangement using hypervalent iodine species. Here, in this reaction, iodine (III) is generated *in situ* from iodobenzene and Oxone in methanol solvent. This method has shown

compatibility with alkyl carboxamides, while substituted benzamides resulted in respective quinones (Scheme 1.3.2.2.1).[79]



Scheme 1.3.2.2.1. *Synthesis of alkyl carbamates via Hofmann rearrangement.*

Later, they have modified the procedure to obtain carbamates starting from both aliphatic and aromatic carboxamides. The modification involves the use of mild and highly selective (tosylimino)-phenyl-λ^3-iodane, PhINTs, as a reagent. This method allows the preparation of a variety of methyl carbamates with good functional group tolerance (Scheme 3.2.2.2).[80]

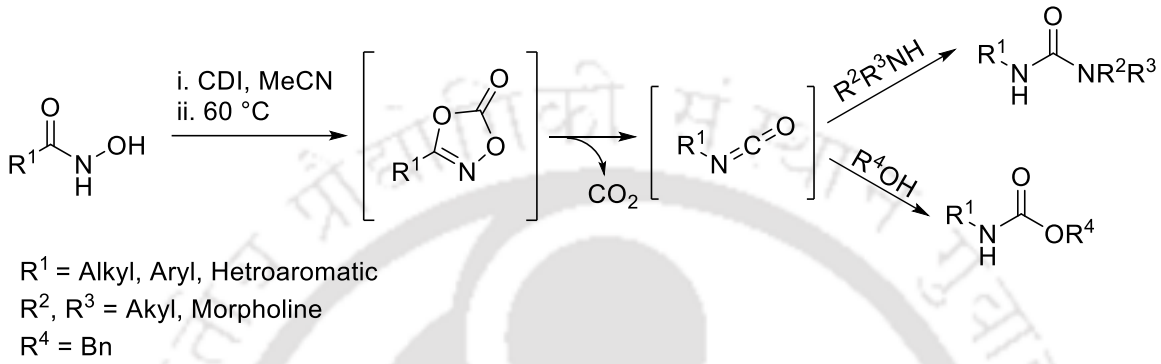


Scheme 1.3.2.2.2. *Synthesis of aryl and alkyl carbamates via Hofmann rearrangement.*

1.3.2.3. Lossen Rearrangement

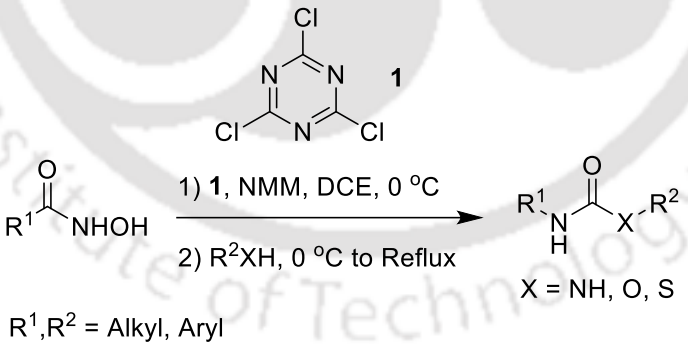
The use of potentially explosive azides in Curtius rearrangement and strong hypervalent iodine reagents in Hofmann rearrangement limit the practical utility for large-scale synthesis as well as for the preparation of complex natural products. The Lossen rearrangement is a valid alternative route to access the isocyanates. This rearrangement involves the transformation of activated hydroxamic acid into the corresponding isocyanate. Over the years, several methodologies are reported for the activation of hydroxamic acid to promote the Lossen rearrangement.

Hardink and co-workers have implemented Lossen rearrangement for the synthesis of unsymmetrical ureas and carbamates. carbonyldiimidazole (CDI) was found to mediate the rearrangement of hydroxamic acids to isocyanates. With imidazole and CO_2 being the sole stoichiometric byproducts and also not using any hazardous reagents, this reaction has the potential to be applied for large-scale synthesis (Scheme 1.3.2.3.1).[81]



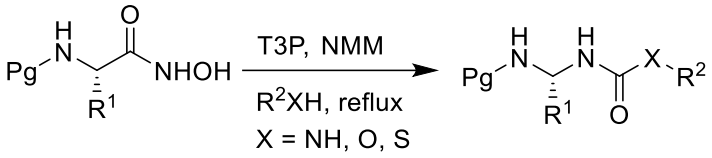
Scheme 1.3.2.3.1. *CDI mediate Lossen rearrangement*

In a similar approach, Hamon *et al*. showed the effective use of Cyanuric chloride (TCT) as an efficient promoter to activate hydroxamic acids. The so formed isocyanates were treated with suitable nucleophiles to afford the corresponding ureas, carbamates, and thiocarbamates (Scheme 1.3.2.3.2).[82]



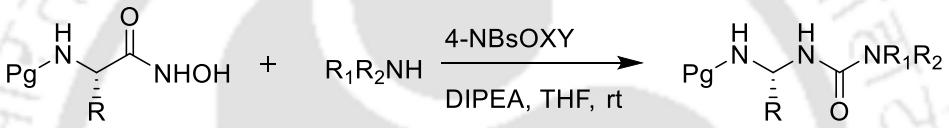
Scheme 1.3.2.3.2. *Preparation of ureas, carbamates and thiocarbamates using TCT*

Sureshbabu and co-workers have accomplished the activation of hydroxamic acids using 1-propanephosphonic acid cyclic anhydride (T3P) as a promoter. Ultrasonification has accelerated this conversion, furnishing the desired ureas and carbamates in good yields (Scheme 1.3.2.3.3).[83]



Scheme 1.3.2.3.3. *Synthesis of ureas, carbamates and thiocarbamates using T3P*

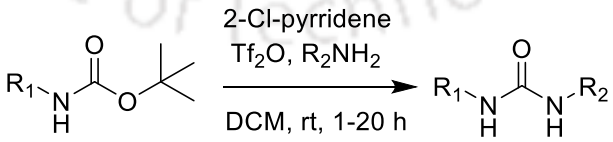
Our group reported the use of ethyl 2-cyno-2-(4-nitrophenylsulfonyloxyimino)acetate (4-NBsOXY) as a promoter in the racemization free synthesis of hydroxamic acids and ureas from carboxylic acids. The hydroxamic acids for the Lossen rearrangements were prepared from carboxylic acids using the same reagent. The reaction worked well with aliphatic, aromatic and long chain *N*-protected amino acids containing hydroxamic acids without racemization in good yields (Scheme 1.3.2.3.4).[68]



Scheme 1.3.2.3.4. *Synthesis of ureas using 4-NBsOXY*

1.3.2.4. Some Other Methodologies

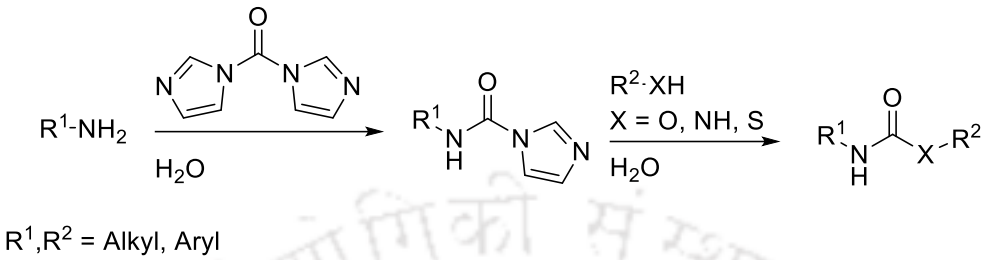
Spyropoulos and Kokotos have developed a practical, one-pot process for the synthesis of ureas from Boc-protected amines *via* isocyanate intermediates in the presence of 2-chloropyridine and trifluoromethanesulfonyl anhydride. This protocol is very effective in accessing a library of ureas from aliphatic primary and secondary amines, aniline and *C*-protected amino acids and no epimerization was observed with chiral substrates (Scheme 1.3.2.4.1).[84]



Scheme 1.3.2.4.1. *Preparation of ureas from Boc-protected amines*

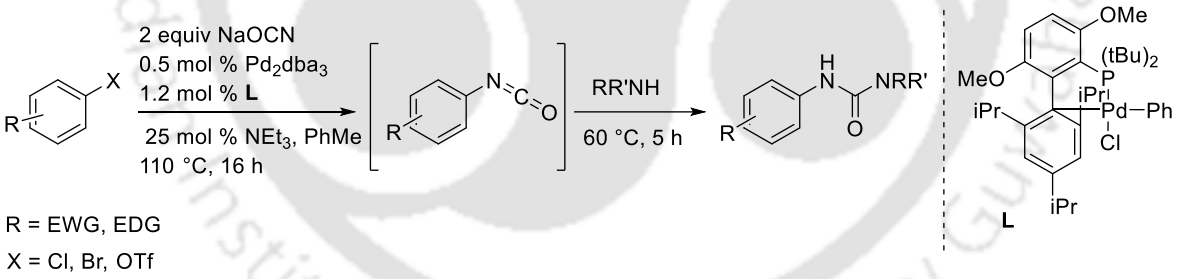
A safe and versatile “in water” imidazole carbonylation reaction was developed towards the synthesis of symmetrical and unsymmetrical ureas, thiocarbamates and carbamates using 1,1′-carbonyldiimidazole (CDI) in water solvent. The noteworthy feature of the

protocol is it essentially avoids the usage of inert and anhydrous conditions, and the product precipitated out from the reaction mixture can be obtained in pure form by filtration (Scheme 1.3.2.4.2).[85]



Scheme 1.3.2.4.2. *CDI mediate the synthesis of ureas, thiocarbamates, and carbamates*

Buchwald and co-workers have developed a one pot, palladium-catalyzed synthesis of aryl isocyanate, followed by the attack of amines to yield unsymmetrical *N,N′*-di- and *N,N,N′*-trisubstituted ureas. The reaction proceeds by cross-coupling of aryl chlorides and triflates with sodium cyanate in the presence of palladium catalyst. In this reaction, it was noted that the addition of phenol facilitated the reaction with more sterically hindered and heterocyclic substrates (Scheme 1.3.2.4.3).[86]

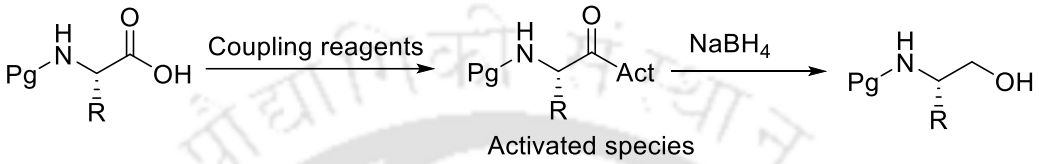


Scheme 1.3.2.4.3. *Preparation of ureas using Pd Catalyst.*

1.3.3. Strategies for the Synthesis of Alcohols

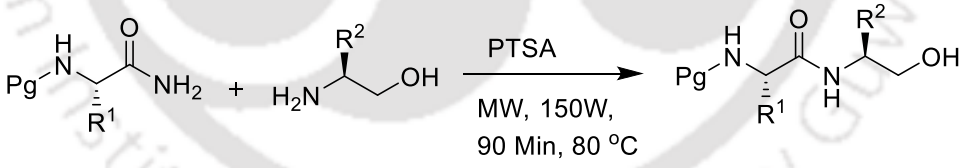
The reduction of carboxylic acids to alcohols is an important functional group transformation in organic synthesis. There are several methods in the literature for this reduction, and the most generally used method involves the conversion of a carboxylic acid into an activated species, which then can be reduced with a mild reducing agent, e.g., sodium borohydride as shown in Scheme 1.3.3.1. $NaBH_4$ is a well-known reagent for mild reductions in organic chemistry.[87] Low cost, high stability and ease of handling makes this

reagent more attractive in the laboratory as well as in the industry compared to other reducing agents. In the last two decades, numerous coupling reagents are used as acid activators such as EDC/HOBt,[88] $SOCl_2$/HOBt,[89] DCC/HOSu,[90] (BOP),[91] TFFH/PTF,[92] 2,4,6-trichloro-1,3,5-triazine (TCT),[93] cyanuric fluoride,[94] 1,1-carbonyldiimidazole,[95] sulfonylbenzotriazole derivatives,[96] and 1-propanephosphonic acid cyclic anhydride[97] as shown in Scheme 1.3.3.1.



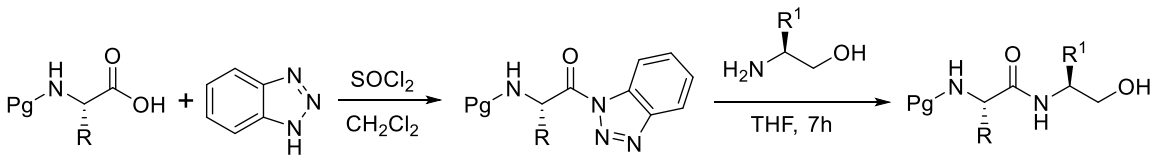
Scheme 1.3.3.1. *Synthesis of β-amino-alcohols using coupling reagents*

A summary of the work displaying the use of coupling reagents in the reduction of carboxylic acids to alcohols as reported in the literature is presented below. Our group has developed a simple and efficient method for the chemoselective synthesis of peptide alcohol from amide and *β*-amino alcohols *via* transamidation using readily available inexpensive PTSA (*para*-toluenesulfonic acid) under microwave irradiation. We utilized this protocol for the synthesis of the biologically important compounds: the fragment of gramicidin A and its derivatives (Scheme 1.3.3.2).[98]



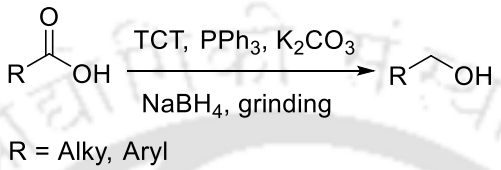
Scheme 1.3.3.2. *Synthesis of peptide alcohols*

Abdel-Samii group have demonstrated a convenient and efficient protocol for the synthesis of di- and tri-peptide alcohols by the reaction of *N*-protected amino acids with amino alcohols in the presence of $SOCl_2$ and benzotriazole. This protocol furnishes products in good yields with no detectable racemization for chiral compounds (Scheme 1.3.3.3).[99]



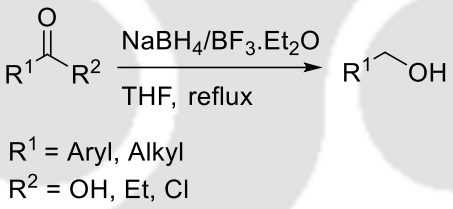
Scheme 1.3.3.3. *Synthesis of peptide alcohols using thionyl chloride*

Pattarawarapan and co-workers have described a new solvent-free reduction of carboxylic acids into corresponding alcohols in good to excellent yield using $NaBH_4$ as a reductant. Here, a combination of 2,4,6-trichloro-1,3,5-triazine (TCT), triphenylphosphine, K_2CO_3, and $NaBH_4$ in 1.0:0.2:1.5:2.0 mole ratio was very effectively used for reduction of carboxylic acids including aromatic acids, aliphatic acids, and *N*-protected α-amino acids (Scheme 1.3.3.4).[100]



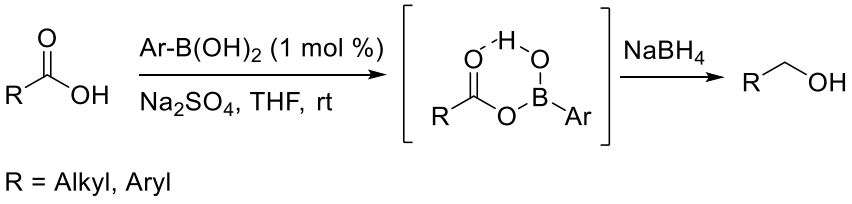
Scheme 1.3.3.4. *Solvent-free synthesis of alcohols*

Cho *et al.* described an interesting reactivity of $NaBH_4/BF_3{\cdot}Et_2O$ system towards reduction of carbonyls, acid chlorides, carboxylic acids, esters, amides and nitriles to alcohols. However, this method was not suitable for the synthesis peptide alcohols because of the cleavage of protecting groups (Scheme 1.3.3.5).[101]



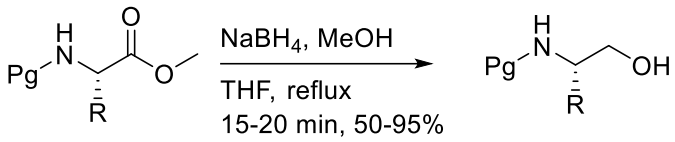
Scheme 1.3.3.5. *Synthesis of alcohols using $NaBH_4/BF_3{\cdot}Et_2O$*

Dapurkar and co-workers have demonstrated boronic acid catalyzed reduction of carboxylic acids to corresponding alcohols. The reaction of carboxylic acids with 3,4,5-trifluorophenylboronic acids in the presence of sodium sulfate generates acyloxyboron intermediates, which was further reduced with sodium borohydride resulting in alcohols in good to excellent yields (Scheme 1.3.3.6).[102]



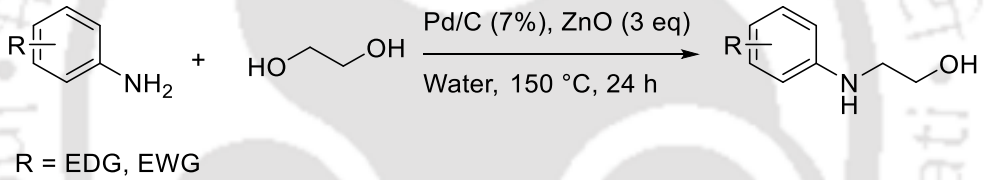
Scheme 1.3.3.6. *Reduction of amino acid esters using $NaBH_4$*

Souza and co-workers demonstrated a straightforward, one-pot reduction of amino acids esters to corresponding amino alcohols with NaBH4 in the presence of methanol. Reactions occurred in short time and without any racemization (Scheme 1.3.3.7).[103]



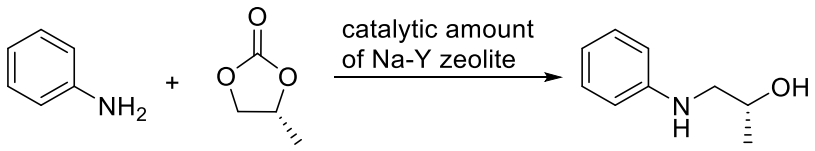
Scheme 1.3.3.7. *Reduction of amino acid esters using $NaBH_4$*

Llabres-Campaner et al. applied the concept of Borrowing Hydrogen (BH), also called Hydrogen Autotransfer (HA). in synthesizing *β*-amino alcohols from aromatic amines and glycols using Pd/C and ZnO as a heterogeneous catalyst. The chemistry appears here is the activation of ethylene glycol by ZnO, while Pd/C is involved in BH/HA cycle, giving mono-functionalized ethylene glycol (Scheme 1.3.3.8).[104]



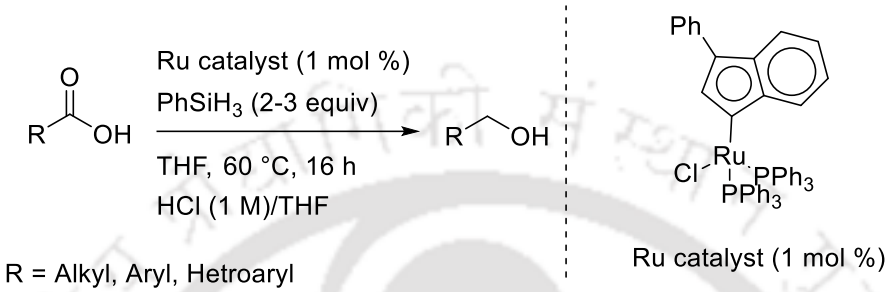
Scheme 1.3.3.8. *Synthesis of β-amino alcohols using Pd/C and ZnO as heterogeneous catalyst*

Gupte and co-workers reported the development of the Na-Y zeolite catalyzed the synthesis of *β*-amino alcohols. This methodology involves the reaction between aniline and propylene carbonate in the presence of Large Pore Zeolite Catalyst without using any solvent. The main advantages of this protocol: the use of propylene carbonates are alternate to epoxides, less hazardous materials, safe for handling and act as self-solvent System (Scheme 1.3.3.9).[105]



Scheme 1.3.3.9. *Na-Y Zeolite catalyzed synthesis of β-amino alcohols*

Nolan and co-workers described a versatile approach for the reduction of carboxylic acids into corresponding alcohols using 1 mol % of ruthenium catalyst and 2-3 equiv of $PhSiH_3$ in THF solvent at 60 °C. This reaction selectively reduced carboxylic acid functionality even in the presence of other potentially reducible functional moieties such as nitriles and other carbonyl-containing groups (Scheme 1.3.3.10).[106]

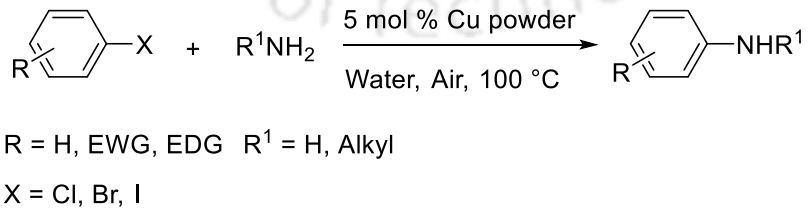


Scheme 1.3.3.10. *Solvent-free synthesis of alcohols*

1.3.4. Existing Methods for Synthesis of Arylamines

1.3.4.1. Copper-Catalyzed Synthesis of Arylamines

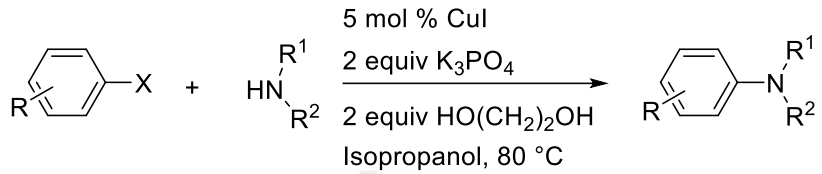
Transition metal catalyzed cross-coupling reactions are well-established methods for the formation of carbon-nitrogen bonds. The most traditional and widely used metals in C-N cross-coupling reactions are palladium, copper, and Rhodium, Nickel and Cobalt. Chen and co-workers have developed a facile and practical method for the Ullmann amination of aryl halides using water as a solvent, which makes this methodology highly valuable from both environmental and economic points of view. The reaction obviates the use of an organic solvent and complicated ligand, and it was best carried out in 5 mol % of copper powder and water, taken in a sealed tube and heated to 100 °C (Scheme 1.3.4.1.1).[107]



Scheme 1.3.4.1.1. *Copper powder catalyzed amination of aryl halide*

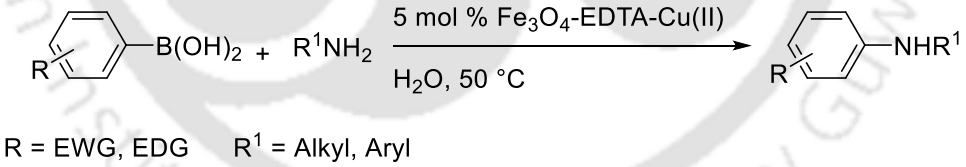
Buchwald and co-workers demonstrated copper-catalyzed amination of aryl bromides and aryl iodides using 5 mol % of copper iodide and ethylene glycol as ligand under mild

reaction conditions. This amination protocol can be successfully applied to a variety of substituted aryl halides as well as various amines and even carried out under open air without affecting the yield. (Scheme 1.3.4.1.2).[108]



Scheme 1.3.4.1.2. *Copper iodide catalyzed synthesis of arylamines*

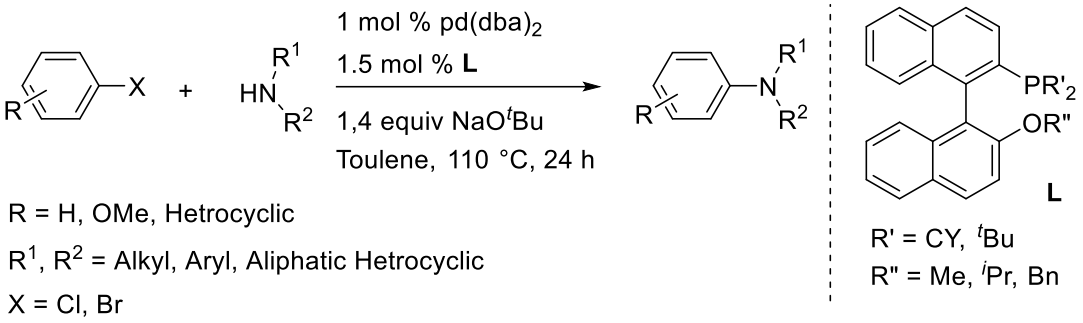
Yokomatsu and co-workers have described a convenient method for the synthesis of arylamines *via* C-N cross-coupling reaction. This protocol involves the reaction of aryl boronic acids with amines in the presence of Fe_3O_4 magnetic nanoparticles-supported EDTA–copper (II) complex in water solvent at 50 °C. This protocol is very effective in accessing a library of *N*-aryl compounds, and the catalyst can be recovered easily and reused up to eight times without significant loss of its catalytic activity (Scheme 1.3.4.1.3).[109]



Scheme 1.3.4.1.3. *Synthesis of arylamines using organic boranes*

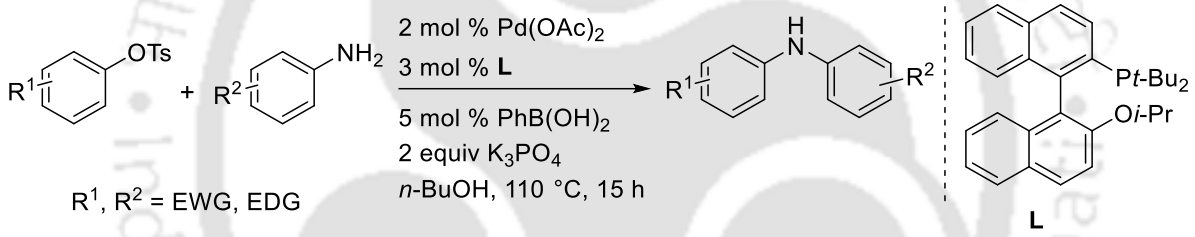
1.3.4.2. Palladium-Catalyzed Synthesis of Arylamines

Xie *et al.* described a palladium-catalyzed cross-coupling reaction of aryl halides with amines in the presence of electron-rich MOP-type phosphine ligands in toluene at 110 °C. These ligands are highly stable towards air and moisture and afforded good to excellent yield of arylated products with both primary and secondary amines (Scheme 1.3.4.2.1).[110]



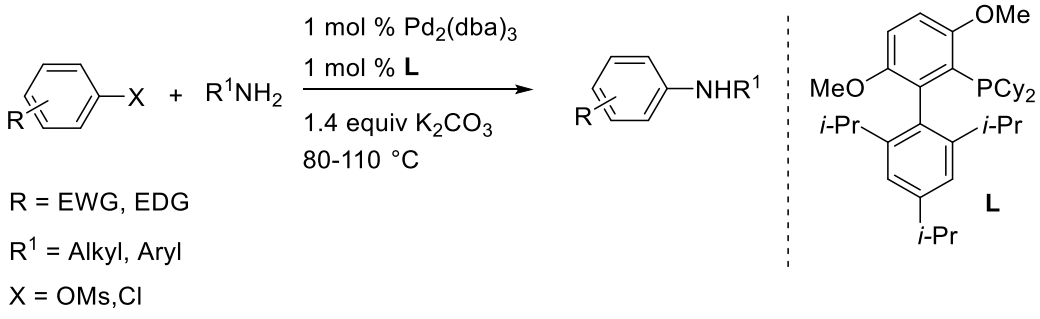
Scheme 1.3.4.2.1. *Palladium-catalyzed synthesis of arylamines from aryl halides*

The same group has also reported a palladium-catalyzed monoarylation of arylamines with aryl tosylates using the same MOP-type phosphine ligand. This reaction was accomplished using $PhB(OH)_2$ as an additive and K_3PO_4 as a base in *n*-BuOH solvent at 110 °C. The reaction is compatible with substrates having both electron-donating and electron-releasing groups to give the desired product in high yields (Scheme 1.3.4.2.2).[111]



Scheme 1.3.4.2.2. *Palladium-catalyzed synthesis of arylamines from aryl tosylate*

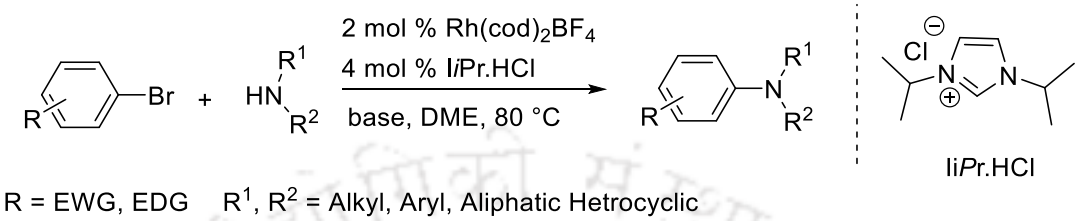
Buchwald and co-workers have developed a ligand termed BrettPhos, composed of biaryldialkylphosphine groups and used in conjunction with Palladium catalyst for the synthesis of arylamines. The reaction of aryl mesylates and aryl chloride with aromatic amines or methylamine in the presence of 1 mol % $Pd_2(dba)_3$ and 1 mol % brettphos ligand produced arylamines in good yields (Scheme 1.3.4.2.3).[112]



Scheme 1.3.4.2.3. *Palladium-catalyzed synthesis of arylamines*

1.3.4.3. Rhodium-Catalyzed Synthesis of Arylamines

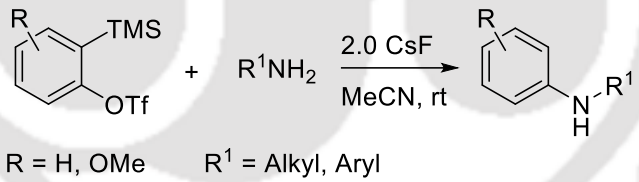
Direct amination of aryl bromides *via* a C-N cross coupling reaction was accomplished by the reaction of aryl bromides and amines using $Rh(cod)_2BF_4$ catalyst and *N*-heterocyclic carbene (NHC) as a ligand (Scheme 1.3.4.3.1).[113]



Scheme 1.3.4.3.1. *Rhodium-catalyzed synthesis arylamines*

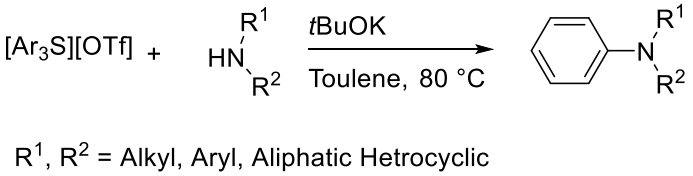
1.3.4.4. Transition-Metal-Free Synthesis of Arylamines

Liu and Larock reported a general and mild transition-metal-free method for the synthesis of arylamines by the reaction of *o*-silylaryl triflates with amines in the presence of CsF in acetonitrile at room temperature. Selective mono-arylation and diarylation of primary amines were achieved by using appropriate amounts of silylaryl triflate. In this reaction, methoxy-substituted silylaryl triflate displayed excellent regioselectivity compared to unsubstituted analog (Scheme 1.3.4.4.1).[114]



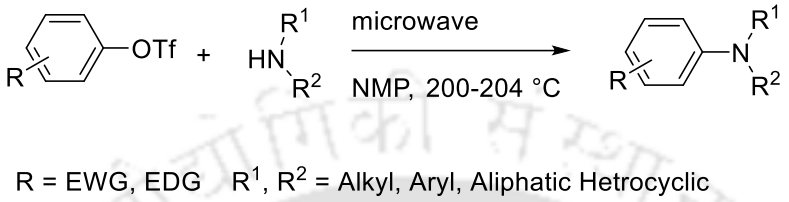
Scheme 1.3.4.4.1. *Synthesis of arylamines using o-silylaryl triflates*

Tian *et al.* have disclosed a transition metal free *N*-arylation of amines using triarylsulfonium triflates in the presence of *t*BuOK or KOH in toluene solvent at 80 °C. The reaction worked well for both aliphatic and aromatic amines in good to excellent yields (Scheme 1.3.4.4.2).[115]



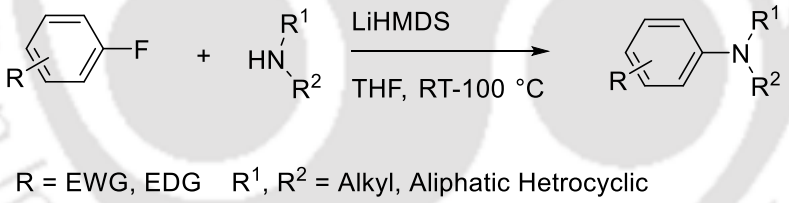
Scheme 1.3.4.4.2. *Reduction of amino acid esters using $NaBH_4$*

Xu and Wang described the microwave-assisted synthesis of arylamines using aryl triflates as an arylated agent without any base and catalyst in 1-methyl-2-pyridone (NMP) solvent. This transformation featured good functional group compatibility such as alkyl, halo, methoxy and nitro substituents on aryl triflates and proceeds smoothly to give the arylated products (Scheme 1.3.4.4.3).[116]



Scheme 1.3.4.4.3. *Microwave-assisted synthesis of arylamines*

Diness and co-workers reported the use of lithium bis(trimethylsilyl)amide as a base in controlled transition metal-free *N*-arylation of amines with less activated fluorobenzene. In addition to fluorobenzene, substrates having a range of additional substituents including alkyl, aryl, alkoxy, amine, azolyl, thioethers, and chlorine have also shown good reactivity (Scheme 1.3.4.4.4).[117]



Scheme 1.3.4.4.4. *Synthesis of arylamines from inactivated fluorobenzene*

1.4. Drawbacks of the Existing Methods

The literature reports reveal that the hydroxamic acids are usually prepared from hydroxylamine hydrochloride and previously activated carboxylic acids. However, most of these methods have some limitations such as involvement of expensive and less available coupling reagents. Furthermore, these coupling reagents are often very difficult to synthesize and involve multi-step synthesis comprising of harsh reaction conditions. Another well-established method, the reaction of hydroxylamine hydrochloride with methyl esters substrates under alkaline conditions leads to the formation of carboxylic acids as a by-product. Likewise, most of the solid support based methods are limited to

compounds with relatively low molecular mass. Also, many of these methods cause racemization. The classical methods such as Hofmann, Curtius and Lossen rearrangement are proven to be the practical methods for the synthesis of diverse ureas. However, use of strong hypervalent iodine reagents in Hofmann and potentially explosive azides in Curtius rearrangement limit the practical utility for large-scale synthesis as well as in the preparation of complex natural products. Alternatively, the Lossen rearrangement provides access to isocyanates under relatively mild conditions. To date, several synthetic methods have been developed for the synthesis of ureas through Lossen rearrangement. For example, phosgene and its derivatives such as triphosgene are widely used reagents for synthesis of ureas; together with chloroformates, cyanuric chloride, 1,1'-carbonyldiimidazole, 1-propanephosphonic acid cyclic anhydride (T3P), *N*,*N*′ – dicyclohexylcarbodiimide, *N*-benzyl-*N*′-(3-dimethylaminopropyl)carbodiimide, Zr(IV)-catalyst, Pd-catalyzed and 2-chloro-1-methylpyridinuim iodide. However, a major disadvantage of most of these coupling reagents developed to date is the generation of undesired byproducts and chemical waste as well as racemization. Also, the phosgene and its derivatives are toxic and very difficult to handle. Because of the diverse interest in *β*-amino-alcohols, versatile methods for their synthesis have been developed. But the existing coupling reagents are not good in suppressing the racemization and also they cannot be reused. Other methods required high temperature, longer reaction time, metal catalyst, which makes the various protecting groups of the amino acids incompatible. Traditionally, arylamines are prepared by palladium or copper-catalyzed cross-coupling of aryl halides with amines. But these protocols have few drawbacks such as the use of expensive palladium complexes, high temperatures, longer reaction time and sensitivity towards air and moisture.

1.5. Objectives of the Thesis

Based on the above observations, we proposed the following objectives to overcome the mentioned problems.

1. Synthesis of hydroxamic acids from carboxylic acid using Ethyl 2-(*tert*-butoxycarbonyl oxyimino)-2-cyanoacetate (Boc-Oxyma).
2. Synthesis of ureas, carbamates, and thiocarbamates of the hydroxamic acids using Boc-Oxyma *via* Lossen rearrangement.
3. Synthesis of alcohols from carboxylic acids using Ethyl 2-Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*ortho*-NosylOXY).
4. Synthesis of arylamines from *via* ipso-nucleophilic aryl substitution on nitrobenzene sulfonic acid.

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Chapter 2

Racemization Free Synthesis of Hydroxamic Acids Using Boc-Oxyma

The hydroxamic acid derivatives are found in many biologically active compounds and organic synthesis with a broad spectrum of applications (Chapter 1, section 1.2.1). There are many protocols published for the synthesis of hydroxamic acids (Chapter 1, section 1.3.1). However, most of these methods have some limitations, including involvement of expensive and less available coupling reagents. Furthermore, these coupling reagents are often very difficult to synthesize and involve multi-step synthesis that requires harsh reaction conditions. Another well-established method is the reaction of esters with hydroxylamine hydrochloride under alkaline conditions leads to the formation of carboxylic acids as a by-product. Likewise, most of the solid support based methods are limited to compounds with relatively low molecular mass. Also, many of these methods cause racemization. Recently our group reported a novel and efficient reagent, ethyl 2-(*tert*-butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma **I**, Figure 2.1) for coupling reactions. It readily activates the carboxylic acid group during the synthesis of amides, peptides, esters, and thioesters.[1] The main advantage of Boc-Oxyma is its excellent racemization suppression capability and ease of synthesis. After the reaction, it generates only Oxyma as a solid byproduct that can be recovered easily and can be recycled for the synthesis of the same reagent. In this chapter, a simple efficient racemization free synthesis of hydroxamic acids using Boc-Oxyma as a coupling reagent is described.

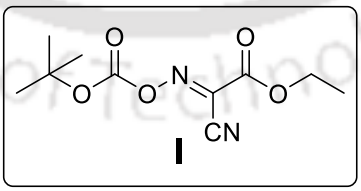
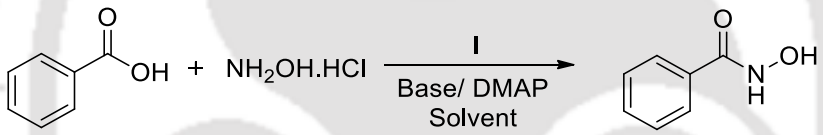


Figure 2.1. *Ethyl 2-(tert-Butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma)*

2.1 Optimization and Substrates Scope for the Synthesis Hydroxamic Acids

Initially, we commenced the optimization studies using benzoic acid as a model substrate (Table 2.1.1). For that, we added the coupling reagent **I** to a stirred solution of benzoic acid and DIPEA in THF solvent and continued for 30 min at 0-5 °C for pre-activation. Next, pre-dissolved hydroxylamine hydrochloride in DMF was added to the reaction mixture, stirring was continued at room temperature for 2 h and generated moderate yield (52%) of the desired product. When we used the catalytic amount of DMAP along with DIPEA the yield of the desired product enhanced up to 75%, hence we used 0.1 equiv of DMAP as a catalyst and 2.5 equiv of DIPEA as a base for further exploration. On the other hand, we screened various solvents and solvent combinations. THF/DMF solvent mixture were accepted as best solvent among them.

Table 2.1.1. Optimization of the reaction conditions[a]



Entry	Base	DMAP	Solvent	Yield (%)[b]
1	DIPEA	-	THF/DMF	52
2	**DIPEA**	**0.1 mmol**	**THF/DMF**	**75**
3	NMM	-	THF/DMF	50
4	NMM	0.1 mmol	THF/DMF	70
5	Et_3N	0.1 mmol	THF/DMF	69
6	DBU	-	THF/DMF	40
7	DIPEA	0.1 mmol	THF/H_2O	52

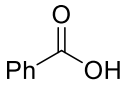
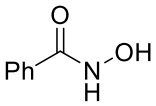
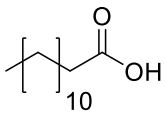
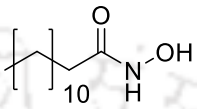
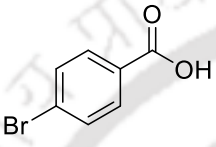
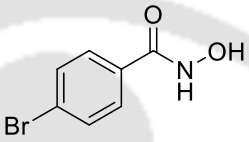
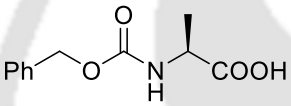
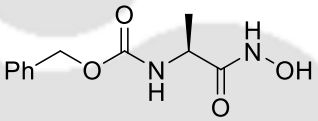
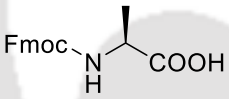
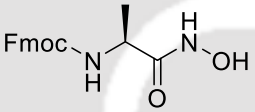
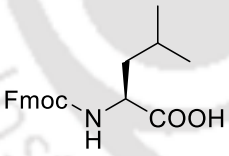
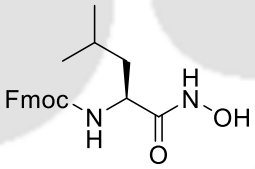
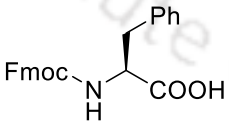
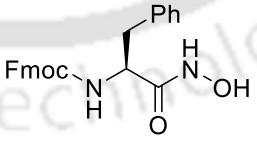
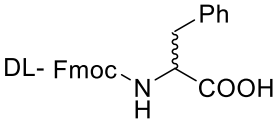
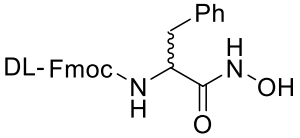
Continued……

Entry	Base	DMAP	Solvent	Yield (%)[b]
8	DIPEA	0.1 mmol	THF/MeOH	55
9	DIPEA	0.1 mmol	MeOH	60
10	DIPEA	0.1 mmol	H_2O	0
11	DIPEA	0.1 mmol	THF	56
12	DIPEA	0.1 mmol	DMF	53
13	DIPEA	0.1 mmol	MeOH/H_2O	38

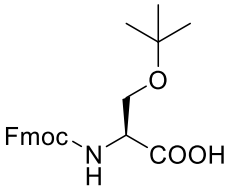
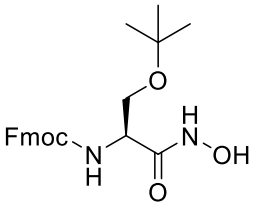
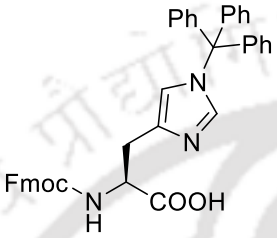
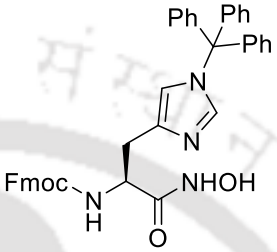
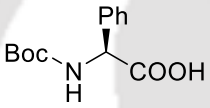
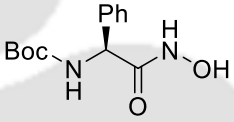
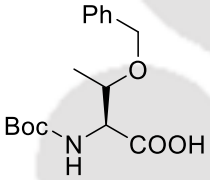
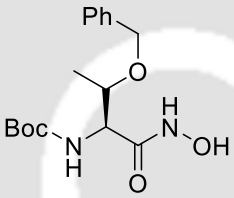
[a] Reaction conditions: Benzoic acid (1 mmol), Boc-Oxyma (1 mmol.), DMAP (as indicated), Base (2.5 mmol), hydroxylamine hydrochloride (1.5 mmol), room temperature, 2.5 h. THF/DMF ratio was 4:1 (entries 1-6). [b] Isolated yield.

The initial success of this methodology prompted us to explore the synthesis of a wide variety of peptide hydroxamic acids with various *N*-protected amino acids and carboxylic acids under the optimized reaction condition. All the reactions proceeded with good to excellent yield. The results are summarized in table 2.1.2. The reactions worked well with aromatic carboxylic acids (entry 1 and 2), aliphatic carboxylic acid (entry 3) and amino acids (entries 4-12). The method was compatible with common *N*-terminal protecting groups such as Cbz (entry 4), Fmoc (entries 5-10) and Boc (entries 11 and 12). The reactions also proceeded smoothly with various side chain protecting groups including, *tert*-butyl (entry 9), trityl (entry 10), and benzyl (entry 12).

Table 2.1.2. Synthesis of various hydroxamic acids using **I**[a]

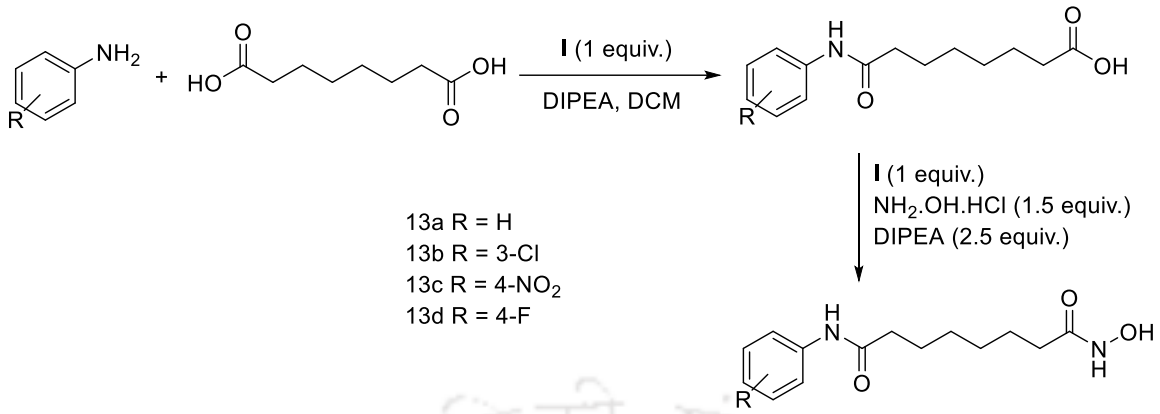
Entry	Acid	Product		
		Structure	Id	Yield[a]
1			**1a**	75
2			**2a**	72
3			**3a**	70
4			**4a**	72
5			**5a**	71
6			**6a**	69
7			**7a**	70
8			**8a**	69

Continued……

Entry	Acid	Product		
		Structure	Id	Yield[a]
9			**9a**	75
10			**10a**	71
11			**11a**	68
12			**12a**	70

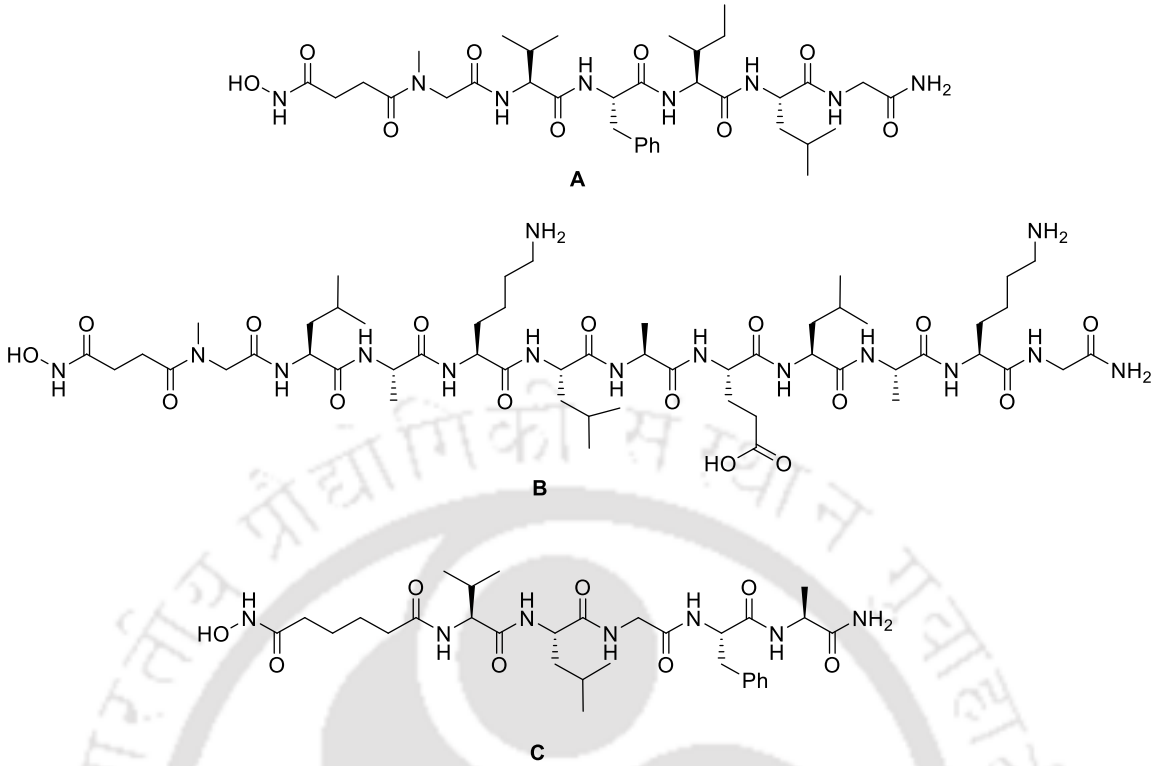
[a] Reaction condition: Carboxylic acid (1 mmol), Boc-Oxyma (1 mmol.), DMAP (0.1 mmol), DIPEA (2.5 mmol), hydroxylamine hydrochloride (1.5 mmol), stirred 2.5 h at room temperature. THF/DMF ratio was 4:1. [b] Isolated

Further, we demonstrated the utility of the current protocol in medicinal chemistry by synthesizing biologically active compounds suberoylanilide hydroxamic acid (SAHA)[2] and its derivatives (Scheme 2.1.1). In the first step, mono acylated product was obtained selectively and in the second step, reaction was performed using the current method. The added advantage of our method over the other reported methods[3] was of two-fold. Firstly, both steps could be achieved using the same reagent (**I**). Secondly, prior selective protection of the starting di-carboxylic acid was not necessary. Thus, one step was reduced and the reaction could be performed in a one-pot manner.



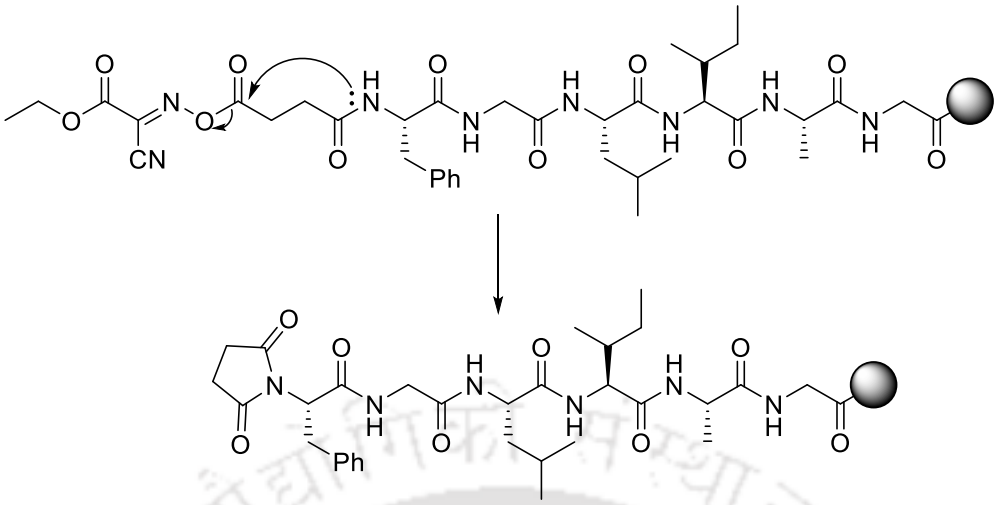
Scheme 2.1.1 *Synthesis of SAHA and its derivatives*

The methodology was further extended to the synthesis of peptide hydroxamic acids using solid phase peptide synthesis (SPPS) protocol.[4] Stepwise coupling of amino acids were performed on Rink amide MBHA resin following Fmoc/*t*-Bu orthogonal protection strategy using (benzotriazol-1-yloxy)tris(dimethylamino)phosphoniumhexafluorophosphate (BOP) as a coupling reagent. Then, succinylation was performed using succinic anhydride on the *N*-terminal amino acid of the peptide on solid resin. After that, hydroxamidation was performed by our method on a solid support using hydroxylamine hydrochloride (3 equiv), Boc-Oxyma (3 equiv), and DIPEA (5 equiv). DMF was used as a solvent for all the reactions on a solid support. Hydroxamidated peptides were finally cleaved using TFA/DCM (85:15) solvent mixture, precipitated with cold ether, and purified using semi-preparative HPLC. We selected hydrophobic peptide sequences for our exploratory studies, as these are known as "difficult sequences" for synthesis (**A** and **C,** Scheme 2.1.2). The amino acid sequence of peptide **B** (Scheme 2.1.2) is based on the amphiphilic peptides, applied by Mutter in designing TASP molecules.[5] Solid-phase synthesis of *C*-terminal hydroxamates of such peptides using modified resin is described recently.[6] But, we focused on the formation of *N*-terminal hydroxamates of such large peptides on the resin. Succinylation at the *N*-terminal was preferred, as many metalloprotein inhibitors bear succinylated hydroxamic acid derivatives at the *N*-terminal.[7]



***Scheme 2.1.2**. Long chain N-terminal peptide hydroxamic acids that were synthesized on solid support; peptide sequences: (A) GVFILG-NH_2 and (B) GLAKLAELAKG-NH_2, (C) VLGFA-NH_2; N-terminal Gly is N-methylated in A & B.*

However, when we tried to perform hydroxamidation on the succinylated *N*-terminal amino acid of a peptide (sequence: FGLIAG, Scheme 2.1.3) on solid support, almost quantitative conversion to the succinimide derivative of the peptide was observed. Such succinimide formation is highly probable as five-membered ring formations are preferable.[8] To avoid such five membered ring formation, two other peptides were synthesized by SPPS, where *N*-methylated glycine was used at the *N*-terminal (**A** and **B**, Scheme 2.1.2). On resin, hydroxamidation was successful for both of these peptides. However, to demonstrate that *N*-methylation, which is often not easy to perform and also *N*-methylated amino acid derivatives are costly, is not always necessary, another peptide hydroxamate was synthesized using adipic acid at the *N*-terminal (**C**, Scheme 2.1.2). We successfully synthesized three peptide hydroxamic acids **A**, **B** and **C** (Scheme 2.1.2) with an overall yield of 25%, 22% and 19%, respectively. Yields were calculated with respect to the reported resin loading by the supplier after purification by semi-preparative HPLC.



Scheme 2.1.3*. Undesired succinimide formation while hydroxamidation on solid support*

2.2 Racemization Study

We also examined the stereochemical aspects of this protocol using HPLC. All the hydroxamic acids that were synthesized from L-amino acids (entries 4a–7a and 9a–11a) exhibited single peak corresponding to single enantiomeric product when passed through a chiral HPLC column, whereas, that of a DL-amino acid derived hydroxamic acid (entry 8) exhibited two distinct peaks corresponding to two enantiomers, one was for L and the other one was for D enantiomer (Figure 2.2.1) in same experimental condition and same gradient. These results indicated that the current method of hydroxamic acid synthesis does not cause detectable racemization.

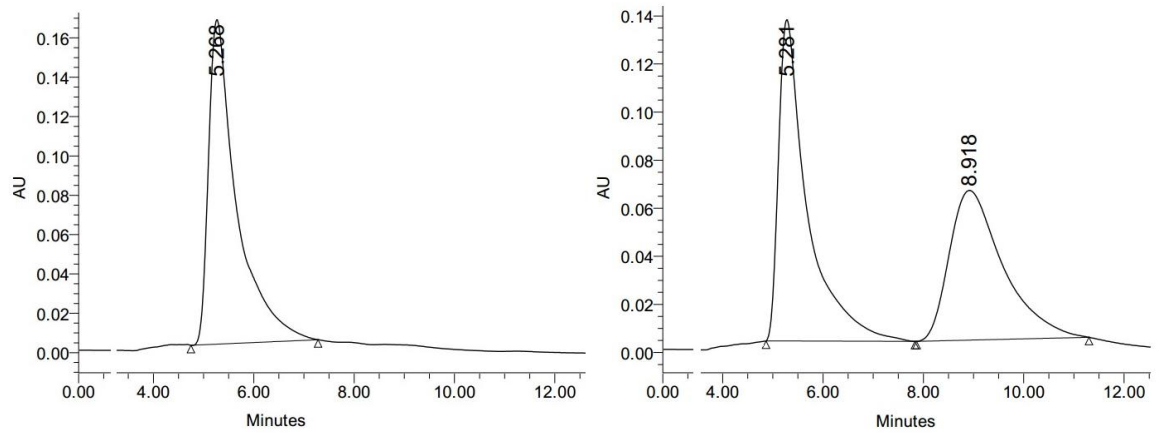
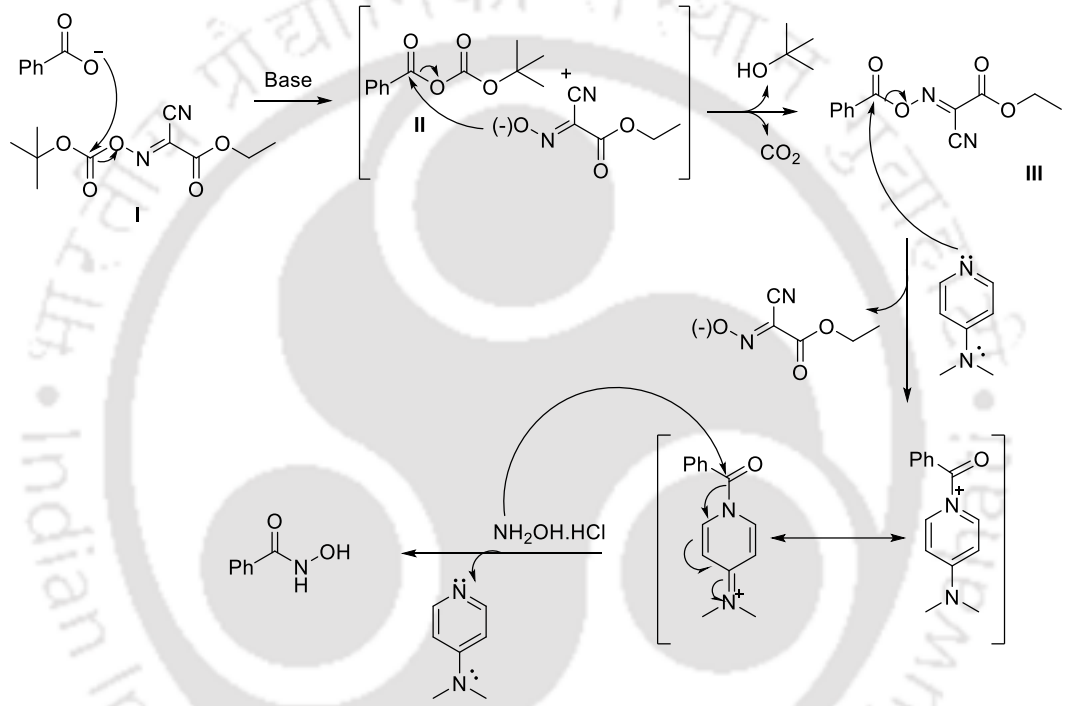


Figure 2.2.1. *HPLC profiles of products* ***7a*** *(left) and* ***8a*** *(right).*

2.3 Plausible Mechanism

On the basis of previous studies, a plausible reaction mechanism depicted in scheme 2.3.1. Initially, the carboxylic acid group reacts with Boc-Oxyma to form the corresponding ester of Oxyma, **III** via anhydride **II**.[1] In the second step, **III** reacts with hydroxylamine hydrochloride in the presence of DMAP[9] to form the desired product. However, hydroxylamine can also react directly with either intermediate **II** or the intermediate **III** and may generate the desired product.



Scheme 2.3.1. *The plausible reaction mechanism for the synthesis of hydroxamic acids by* ***I.***

2.4 Conclusion

In conclusion, a simple efficient racemization free method for the conversion of carboxylic acids to the corresponding hydroxamic acids with hydroxylamine hydrochloride in presence of DIPEA/DMAP under mild reaction conditions using Boc-Oxyma as a coupling reagent has been discussed. This method is compatible with Fmoc based SPPS as well as various acid or base labile protecting groups. Further, we demonstrated the utility of the current protocol for synthesizing biologically important SAHA derivatives. Thus, this method can be useful for the synthesis of various long chain MMP/ADAM inhibitors and other biologically important hydroxamates.

2.5 Experimental Section

2.5.1 Materials and Instrumentation

All chemicals were purchased from commercial sources and used without purification. All amino acids used are L-amino acids except glycine unless otherwise noted. Reactions were monitored using thin layer chromatography with silica gel G and silica gel GF254 using EtOAc/Hexane as a solvent system. Purification of the reaction products was carried out by column chromatography using silica gel (60-120 mesh) using eluent EtOAc/Hexane. Solvents were removed under reduced pressure using a Buchi rotary evaporator. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on 600 MHz and 400 MHz using $CDCl_3$ and CD_3OD as solvent and tetramethylsilane (TMS) as an internal standard. FT-IR spectra were recorded on Perkin Elmer FT-IR Spectrometer. Melting points were recorded on Buchi melting point apparatus and were uncorrected. High-resolution mass spectra (HRMS) were recorded on Agilent Q-TOF ESI-MS instrument. HPLC analysis was carried out in Waters HPLC system using a Symmetry C_8 column (5 µm, 3.5 × 150 mm, for peptide analysis) and Chiralpack-ASH column (5 µm, 2.1× 150 mm, for racemization studies) coupled to a PDA detector. HPLC grade solvents were used for HPLC analysis.

2.5.2 General procedure for the synthesis of hydroxamic acids

Ethyl 2-(*tert*-butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma, I) (1 mmol) was added to a stirred solution of carboxylic acid (1 mmol), DIPEA (1 mmol) and DMAP (0.1 mmol) in THF (2 mL) at 0-5 °C. Then the reaction mixture was stirred for 30 min followed by the addition of hydroxylamine hydrochloride in DMF (0.5 mL), DIPEA (1.5 mmol). The progress of the reaction was monitored by TLC at room temperature. After completion of the reaction, the reaction mixture was concentrated using rotary evaporator and then diluted with 15 mL of ethyl acetate and washed with 5% HCl (2×10 mL), 5% $NaHCO_3$ (2×10 mL), saturated NaCl solution (2×10 mL) and dried over anhydrous Na_2SO_4 and the evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate.

2.5.3 General procedure for the synthesis of SAHA and its derivatives

Ethyl 2-(*tert*-butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma, I) (1 mmol) was added to a stirred solution of suberic acid (2 mmol) and DIPEA in DCM (2 mL) at 0-5 °C

temperature. Then the reaction mixture was stirred for 1 h followed by the addition of aniline (1 mmol). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was acidified with 5% HCl and extracted with dichloromethane (2×15 mL) and dried under anhydrous $CaCl_2$ and the evaporation of the solvent gave a solid powder.

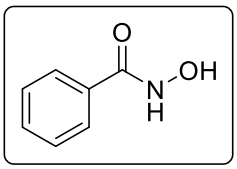
Ethyl 2-(*tert*-butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma, I) (1 mmol) was added to a stirred solution of previous carboxylic acid derivative (1 mmol), DIPEA (1 mmol) and DMAP (0.1 mmol) in THF (2 mL) at room temperature. Then the reaction mixture was stirred for 30 min followed by the addition of hydroxylamine hydrochloride in DMF (0.5 mL), DIPEA (1.5 mmol). The progress of the reaction was monitored by TLC at room temperature. After completion of the reaction, the reaction mixture was concentrated using rotary evaporator and then diluted with 15 mL of ethyl acetate and washed with 5% HCl (2×10 mL), 5% $NaHCO_3$ (2×10 mL), saturated NaCl solution (2×10 mL) and dried over anhydrous Na_2SO_4 and the evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate.

2.5.4 General procedure for the synthesis of peptide hydroxamic acids.

Peptides were synthesized by using standard Fmoc/*t*Bu solid phase peptide synthesis method on MBHA-Rink amide resin (loading 0.8. mmol/g). The syntheses were performed manually on a Stuart blood tube rotator. The Resin added into a 5 ml frit-fitted plastic syringe and swollen in dichloromethane (DCM) for 2 h followed by DMF for 1 h. The coupling of amino acid was achieved using 2 equiv of Fmoc amino acids, 2.5 equiv of a coupling reagent (BOP), and 5 equiv of the base (DIPEA). Each coupling steps were monitored by Kaiser's test. In cases of incomplete coupling, the cycles were repeated, followed by capping with acetic anhydride (2 equiv) and *N*-methyl imidazole (3 equiv). Fmoc deprotection was performed with 20% piperidine in DMF mixture for 21 min (7 min × 3). Hydroxamic acid attached after succinylation or adipoylation by using Boc-Oxyma (3 equiv.), hydroxylamine hydrochloride (3 equiv) and DIPEA (5 equiv) in DMF. The final peptides were cleaved from the resin using a cleavage cocktail (85% TFA and 15% DCM) for 3 h then precipitation with cold diethyl ether. The crude peptides were purified by semi-preparative HPLC followed by lyophilization. The yields of the peptides after purification are mentioned above.

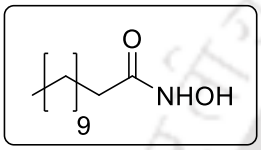
2.6 Characterization Data

_N_-Hydroxybenzamide 1a.



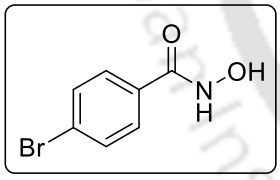
White solid; (102 mg, 75%), mp 125-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.63 (d, *J* = 6.8 Hz, 2H), 7.42-7.38 (t, *J* = 7.6 Hz, 1H), 7.33-7.30 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 166.7, 131.8, 131.5, 128.6, 127.0; FT-IR (KBr) 3296, 3058, 2758, 1643, 1612, 1573, cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_7H_8NO_2$ 138.0555, found 138.0554.

_N_-Hydroxydodecanamide 2a.



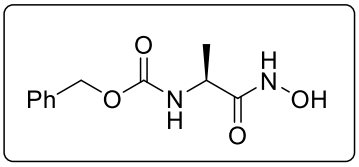
White solid; (174 mg, 81%), mp 75-77 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.46-2.44 (t, *J* = 7.8 Hz, 2H), 1.61-1.57 (m, 2H), 1.28-1.23 (m, 16H), 0.86-0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 33.1, 32.0, 29.7, 29.6, 29.4, 29.4, 29.3, 25.6, 22.7, 14.1; FT-IR (KBr) 3258, 2915, 2847, 1663, 1623, 1469, 1423, 720, 649 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{26}NO_2$ 216.1964, found 216.1964.

4-Bromo-_N_-hydroxybenzamide 3a.



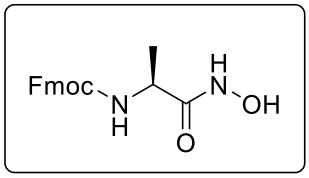
White solid; (149 mg, 70%), mp 181-183 °C; ^{1}H NMR (600 MHz, $CDCl_3$, few drops of CD_3OD, & DMSO-d_6 for solubility) δ 7.71-7.70 (d, *J* = 6.6 Hz, 2H), 7.57-7.56 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD, & DMSO-d_6 for solubility) δ 163.3, 130.4, 127.8, 124.5; FT-IR (KBr) 3296, 3063, 2779, 1649, 1614, 1591,1559 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_7H_7BrNO_2$ 215.9660, found 215.9663.

(*S*)-Benzyl (1-(hydroxyamino)-1-oxopropan-2-yl)carbamate 4a.



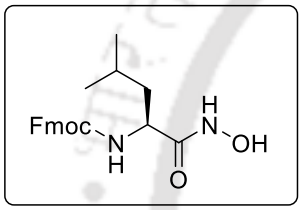
White solid; (171 mg, 72%), mp 106-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 5H), 6.00-5.98 (d, *J* = 6.8 Hz, 1H), 5.08-4.92 (m, 1H), 4.21(s, 2H), 1.27-1.26 (d, *J* = 6.4Hz 3H); ^{13}C NMR (100 MHz, $CDCl_3$, & few drops of CD_3OD for solubility) δ 170.5, 156.4, 136.1, 128.5, 128.2, 128.0, 67.1, 18.3; FT-IR (KBr) 3339, 3283, 2878, 1715, 1689, 1549, 1266 ,738 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{15}N_2O_4$ 239.1032, found 239.1034.

(*S*)-(9*H*-Fluoren-9-yl)methyl (1-(hydroxyamino)-1-oxopropan-2-yl)carbamate 5a.



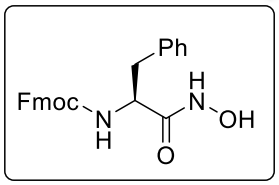
White solid; (231 mg, 71%), mp 128-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD) δ 7.77-7.75 (d, *J* = 7.6 Hz, 2H), 7.59-7.57 (d, *J* = 7.2 Hz, 2H), 7.42-7.38 (t, *J* = 7.2 Hz, 2H), 7.33-7.29 (t, *J* = 7.2 Hz, 2H), 4.39-4.37 (m, 2H), 4.21 (m, 1H), 4.13 (m, 1H), 1.36-1.34 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD, & DMSO-d_6 for solubility) δ 169.6, 156.9, 143.2, 140.4, 126.9, 126.3, 124.4, 119.1, 65.8, 48.1, 46.3, 17.5; FT-IR (KBr) 3429, 3320, 2921, 1685, 1616, 1532, 739 cm^{-1}; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{18}H_{17}N_2O_4Na$ 349.1164, found 349.1155.

(*S*)-(9*H*-Fluoren-9-yl)methyl (1-(hydroxyamino)-4-methyl-1-oxopentan-2-yl)carbamate 6a.



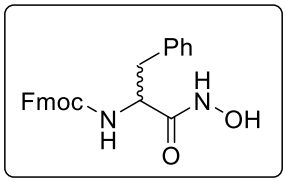
White solid; (254 mg, 69%), mp 133-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.77-7.75 (d, *J* = 7.6 Hz, 2H), 7.60-7.58 (d, *J* = 7.2 Hz, 2H), 7.42-7.38 (t, *J*= 7.2 Hz, 2H), 7.33-7.29 (t, *J* = 6.8 Hz, 2H), 6.13 (brs, 1H), 4.41-4.35 (m, 2H), 4.21-4.20 (m, 1H), 4.05 (s, 1H), 1.56 (s, 2H), 1.25 (s, 1H), 0.94-0.92 (d, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 169.7, 156.7, 143.7, 141.4, 127.9, 127.2, 125.1, 120.1, 67.2, 50.8, 47.2, 41.1, 24.7, 22.7; FT-IR (KBr) 3300, 3063, 2958, 1686, 1638, 1532, 737 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{25}N_2O_4$ 369.1814. found 369.1812.

(*S*)-(9*H*-Fluoren-9-yl)methyl(1-(hydroxyamino)-1-oxo-3-phenylpropan-2-yl)carbamate 7a.



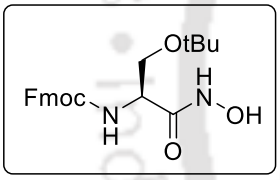
White solid; (281 mg, 70%), mp 171-173 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.78-7.76 (d, *J* = 7.6 Hz, 2H), 7.55-7.54 (d, *J* = 4.4 Hz, 2H), 7.42-7.39 (t, *J* = 7.2, 2H), 7.33-7.26 (m, 4H), 7.24-7.19 (t, *J* = 7.6 Hz, 3H), 4.40-4.36 (t, *J* = 7.2 Hz, 1H), 4.25-4.23 (d, *J* = 7.6 Hz, 2H), 4.17-4.14 (t, *J* = 7.2 Hz, 1H), 3.07-3.04 (m, 1H), 2.97-2.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ few drops of CD_3OD, & DMSO-d_6 for solubility) δ 167.8., 155.1, 142.8, 140.0, 136.2, 128.3, 127.3, 126.7, 126.1, 125.5, 124.1, 118.8, 65.5, 53.2, 45.9, 37.1; FT-IR (KBr) 3306, 3062, 2922, 1684, 1629, 1540, 741 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_4$ 403.1658,found 403.1656.

(*R/S*)-(9*H*-Fluoren-9-yl)methyl(1-(hydroxyamino)-1-oxo-3-phenylpropan-2-yl)carbamate 8a.



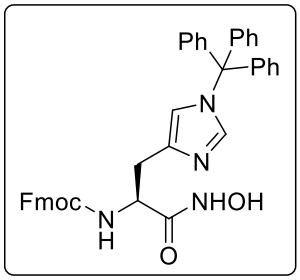
White solid; (277 mg, 69%), mp 172-174 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.78-7.76 (d, *J* = 7.6 Hz, 2H), 7.55-7.54 (d, *J* = 4.4 Hz, 2H), 7.42-7.39 (t, *J* = 7.2, 2H), 7.33-7.26 (m, 4H), 7.24-7.19 (t, *J* = 7.6 Hz, 3H), 4.40-4.36 (t, *J* = 7.2 Hz, 1H), 4.25-4.23 (d, *J* = 7.6 Hz, 2H), 4.17-4.14 (t, *J* = 7.2 Hz, 1H), 3.07-3.04 (m, 1H), 2.97-2.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ few drops of CD_3OD, & DMSO-d_6 for solubility) δ 167.8., 155.1, 142.8, 140.0, 136.2, 128.3, 127.3, 126.7, 126.1, 125.5, 124.1, 118.8, 65.5, 53.2, 45.9, 37.1; FT-IR (KBr) 3306, 3062, 2922, 1684, 1629, 1540, 741 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_4$ 403.1658, found 403.1656.

(*S*)-(9*H*-Fluoren-9-yl)methyl(3-(tert-butoxy)-1-(hydroxyamino)-1-oxopropan-2-yl) carbamate 9a.



White solid; (298 mg, 75%), mp 133-135 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76-7.74 (d, *J* = 7.8 Hz, 2H), 7.57 (s, 2H), 7.40-7.39 (t, *J* = 7.2 Hz, 2H), 7.31-7.29 (t, *J* = 7.2 Hz, 2H), 5.70 (s, 1H), 4.41 (s, 2H), 4.29 (s, 1H), 4.21-4.19 (t, *J* = 6.0 Hz, 1H), 3.74 (s, 1H), 3.41-3.39 (t, *J* = 7.2 Hz, 1H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 156.4, 143.8, 141.4, 127.9, 127.2, 125.2, 120.1, 74.6, 67.4, 61.5, 53.2, 47.2, 27.4; FT-IR (KBr) 3304, 3066, 2971, 1696, 1644, 1536, 738 cm^{-1}; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{22}H_{26}N_2O_5Na$ 421.1739, found 421.1740.

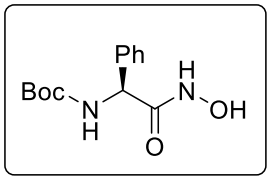
(9*H*-Fluoren-9-yl)methyl(1-(hydroxyamino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl)carbamate 10a.



White solid; (225 mg, 71%), mp 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.70 (d, *J* = 6.4 Hz, 2H), 7.52-7.50 (d, *J* = 6 Hz, 2H), 7.37-7.24 (m, 17H), 7.07-7.04 (m, 5H), 6.61 (s, 1H), 4.52-4.49 (m, 1H), 4.23-4.21 (d, *J* = 6.4 Hz, 2H), 4.08-4.06 (t, *J* = 7.2, 1H), 2.95-2.93 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 168.6, 156.4, 143.9, 142.0, 141.3, 138.6, 135.7, 129.8, 128.4, 128.3, 127.8, 127.2, 127.2, 125.4, 120.3, 120.0, 75.8, 66.0, 53.3, 47.2, 31.4; FT-IR

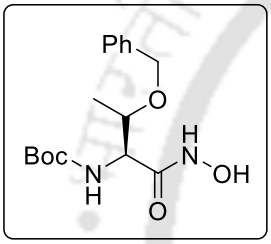
(KBr) 3406, 3061, 2923, 1672, 1493, 1447, 742 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{40}H_{35}N_4O_4$ 635.2658, found 635.2668.

(*S*)-*tert*-Butyl (2-(hydroxyamino)-2-oxo-1-phenylethyl)carbamate 11a.



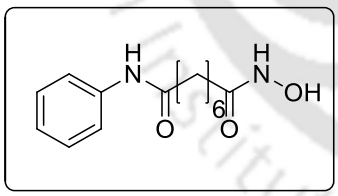
White solid; (180 mg, 68%), mp 127-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.30 (m, 5H), 5.1 (s, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 168.2, 155.7, 137.4, 128.8, 128.3, 127.1, 80.7, 55.6, 28.3; FT-IR (KBr) 3319, 3236, 2980, 2925, 1685, 1648, 1514 cm^{-1}; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{18}N_2O_4Na$ 289.1164, found 289.1161.

***tert*-Butyl (2*S*,3*S*)-3-(benzyloxy)-1-(hydroxyamino)-1-oxobutan-2-yl)carbamate 12a.**



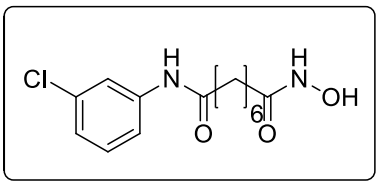
White solid; (226 mg, 70%), mp 168-169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.29 (m, 5H), 5.41-5.40 (d, *J* = 7.2 Hz, 1H) 4.59-4.49 (m, 1H), 4.29 (br, 1H), 4.10 (m, 1H), 1.44 (s, 9H), 1.17-1.15 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 156.0, 137.8, 128.6, 128.4, 128.0, 80.7, 74.4, 71.8, 56.5, 28.4, 15.8; FT-IR (KBr) 3331, 3260, 2969, 1679, 1637, 1525, 735 cm^{-1}; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{16}H_{24}N_2O_5Na$ 347.1583, found 347.1576.

***N*^{1}-Hydroxy-*N*^{8}-phenyloctanediamide 13a.**



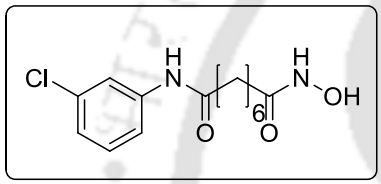
White solid; (90 mg, 68%), mp 158-159 °C; ^{1}H NMR (600 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.49-7.48 (d, *J* = 7.8 Hz, 2H), 7.32-7.30 (t, *J* = 7.8 Hz, 2H), 7.13-7.10 (t, *J* = 7.2 Hz, 2H), 2.38-2.34 (m, 4H), 1.74-1.63 (m, 4H), 1.42-1.37 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 172.4, 171.4, 138.1, 129.0, 124.2, 120.1, 120.1, 120.0, 37.3, 34.0, 32.6, 28.6, 25.4, 24.6; FT-IR (KBr) 3239, 2934, 2852, 1656, 1628, 1598, 1499, 1598, 1499, 1466, 758, 691 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{21}N_2O_3$ 265.1552, found 265.1540.

N^1-(3-Chlorophenyl)-N^8-hydroxyoctanediamide 13b.



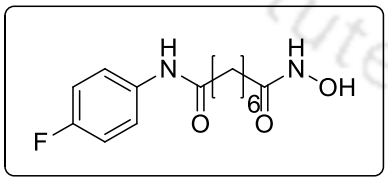
White solid; (106 mg, 71%), mp 141-142 °C; ^{1}H NMR (600 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.64-7.62 (d, *J* = 9 Hz, 1H), 7.37-7.34 (t, *J* = 7.8 Hz, 1H), 7.27 (s, 1H), 7.19-7.14 (m, 1H), 7.02-6.99 (t, *J* = 9 Hz, 1H), 2.29-2.22 (m, 2H), 2.07-2.03 (m, 2H), 1.64-1.56 (m, 4H), 1.23-1.20 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 173.0, 171.6, 139.6, 134.5, 129.9, 124.0, 120.0, 119.9, 117.9, 36.9, 34.0, 32.6, 28.7, 28.6, 25.3; FT-IR (KBr) 3266, 2933, 2851, 1670, 1591, 1537, 1426, 974, 780, 691, 676 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{20}ClN_2O_3$ 299.1162, found 299.1143.

N^1-Hydroxy-N^8-(4-nitrophenyl)octanediamide 13c.



Pale yellow solid; (115 mg, 74%), mp 108-109 °C; ^{1}H NMR (600 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 8.09-8.08 (d, *J* = 7.8 Hz, 2H), 7.70-7.68 (d, *J* = 7.8 Hz, 2H), 2.31-2.30 (m, 2H), 2.21-2.18 (m, 1H), 2.02-2.00 (m, 1H), 1.63-1.53 (m, 4H), 1.31-1.29 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 173.5, 171.3, 144.8, 143.0, 124.9, 119.1, 119.0, 36.9, 34.5, 32.6, 28.6, 28.6, 25.1; FT-IR (KBr) 3342, 2932, 2863, 1720, 1704, 1613, 1498, 1110, 864, 853, 753 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{20}N_3O_5$ 310.1403, found 310.1403.

N^1-(4-Fluorophenyl)-N^8-hydroxyoctanediamide 13d.



White solid; (97 mg, 69%), mp 160-162 °C; ^{1}H NMR (600 MHz, DMSO-d_6,) δ 8.69 (s, 1H), 7.58-7.56 (m, 2H), 7.12-7.09 (m, 2H), 2.27-2.24 (t, *J* = 7.8 Hz, 2H), 1.94-1.91 (t, *J* = 7.8 Hz, 2H), 1.56-1.46 (m, 4H), 1.25-1.22 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD & DMSO-d_6 for solubility) δ 172.5, 171.0, 134.4, 121.5, 115.1, 36.5, 32.4, 29.4, 28.2, 28.2, 25.1; FT-IR (KBr) 3331, 2969, 2847, 1679, 1640, 1525, 1424, 824, 793, 735 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{20}FN_2O_3$ 283.1458, found 283.1447.

2.7 References

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2.8 Selected Spectra

2.8.1 NMR (^{1}H and ^{13}C) spectra of compounds

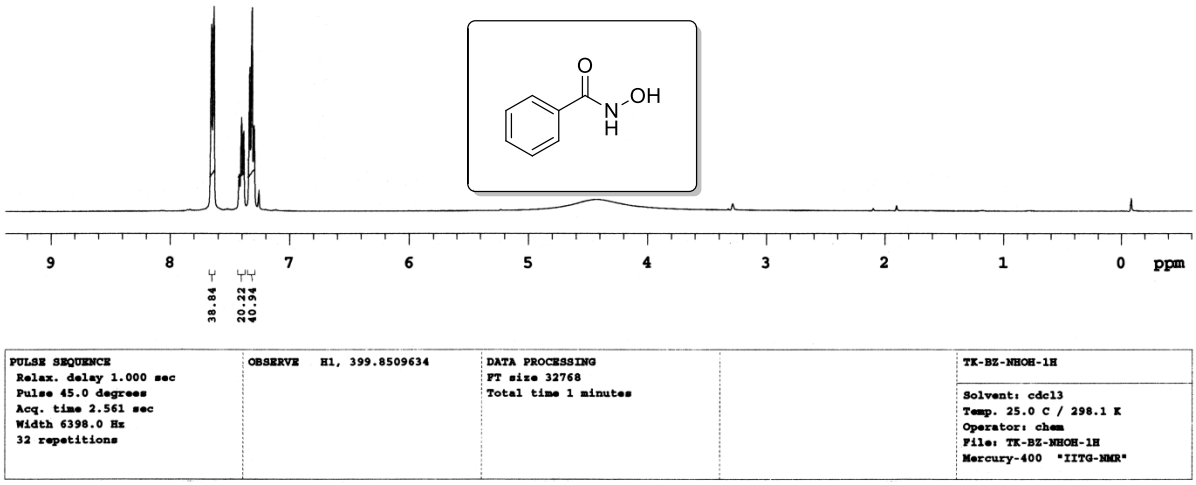


Figure 2.8.1.1. *^{1}H NMR Spectra of compound* ***1a***

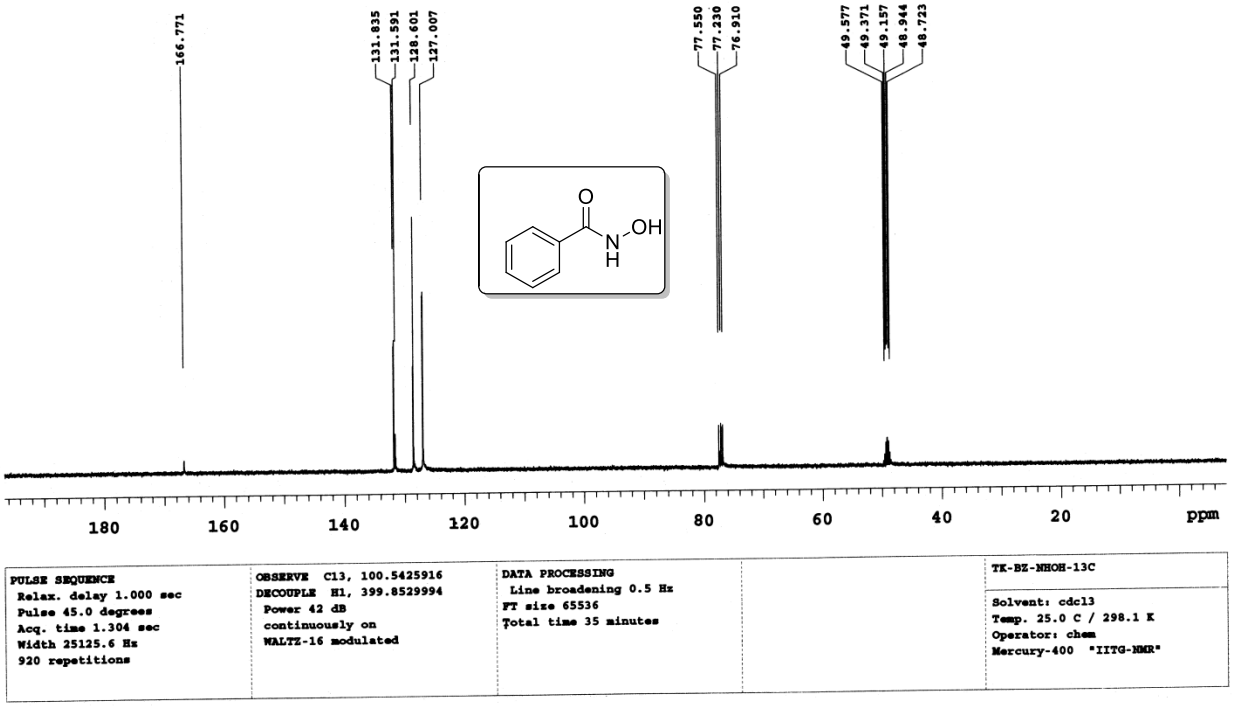


Figure 2.8.1.2. *^{13}C NMR spectra of compound* ***1a***

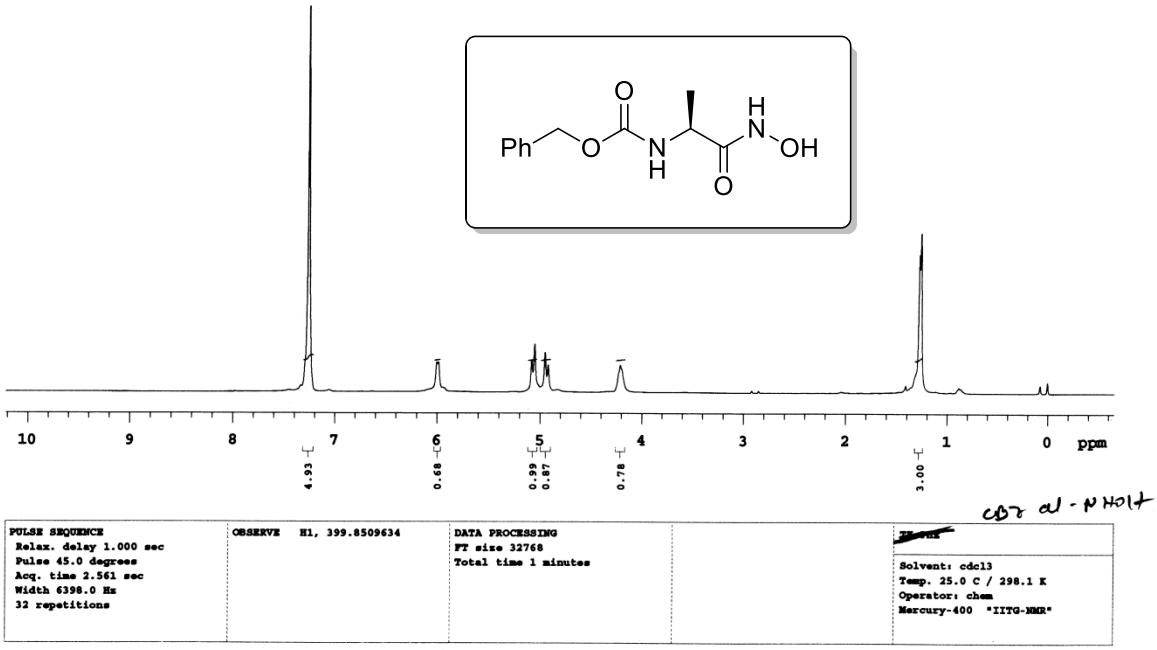


Figure 2.8.1.3. *^{1}H NMR spectra of compound* ***4a***

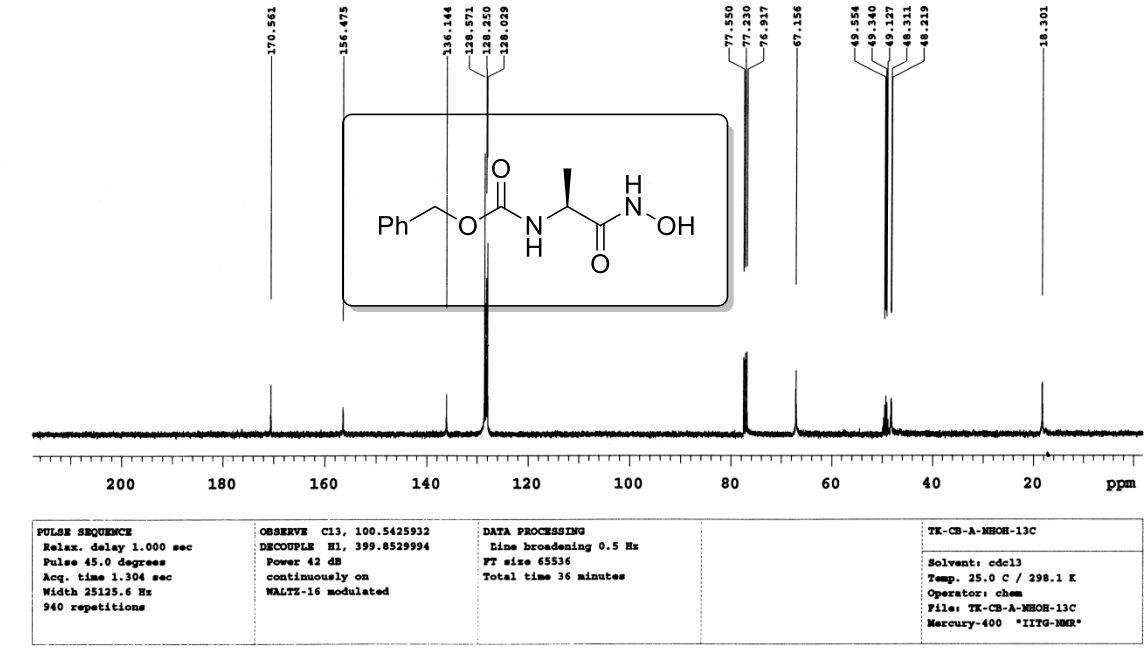


Figure 2.8.1.4. *^{13}C NMR spectra of compound* ***4a***

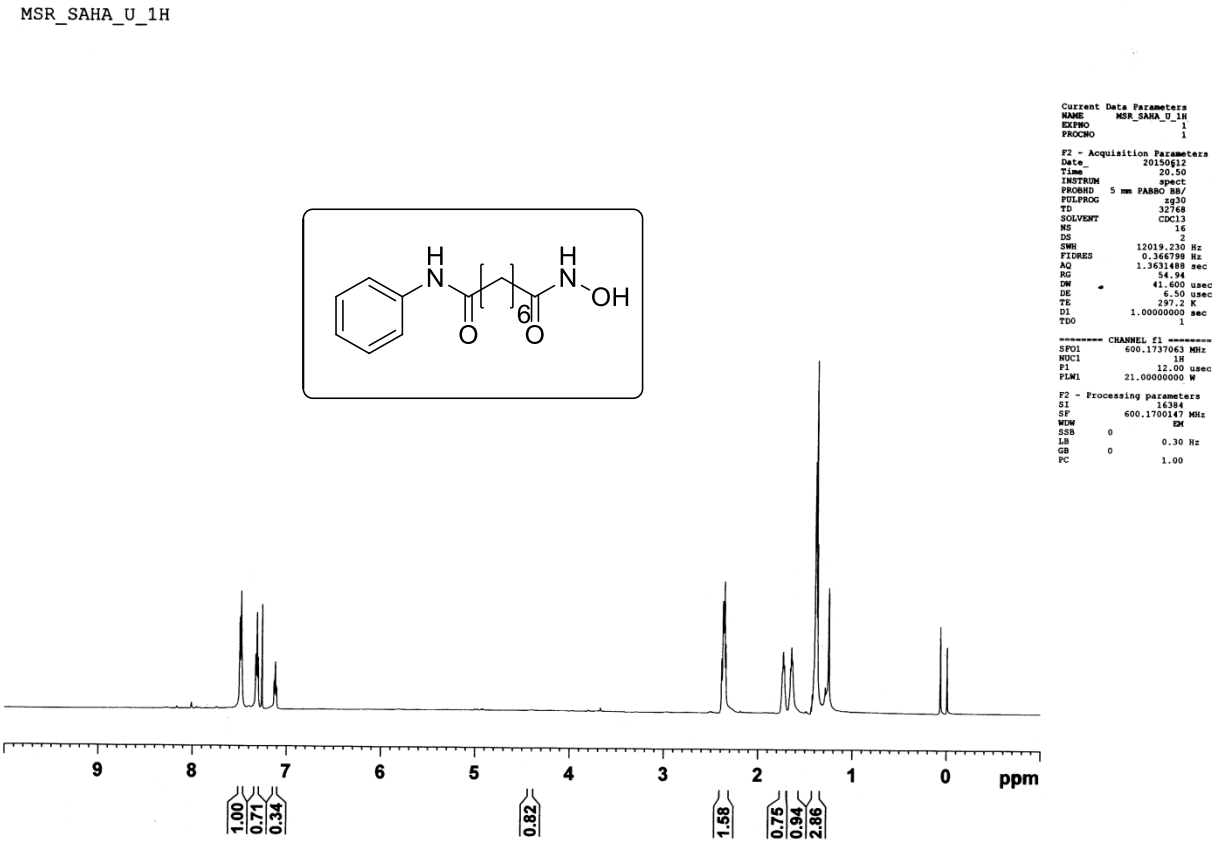


Figure 2.8.1.5. *^{1}H NMR spectra of **SAHA** compound*

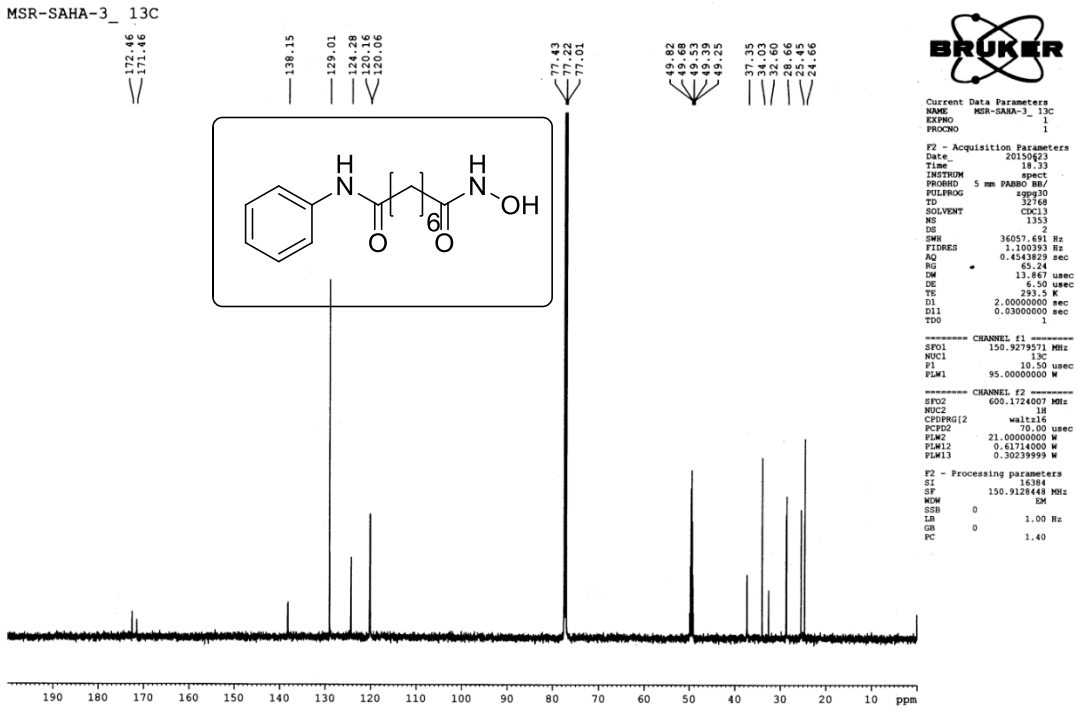


Figure 2.8.1.6. *^{13}C NMR spectra of **SAHA** compound*

2.8.2 Mass and HPLC spectra of A, B, C & undesired peptide succinimide

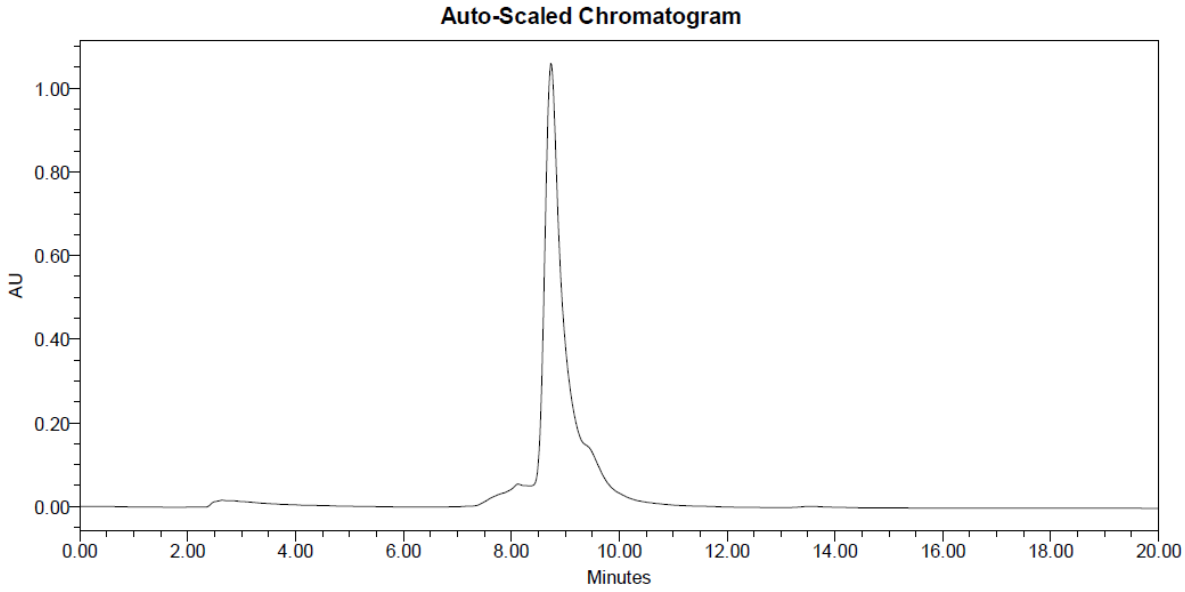


Figure 2.8.2.1. *HPLC spectra of compound* ***(A) HOHN-SU-Sar-VFILG-NH₂***

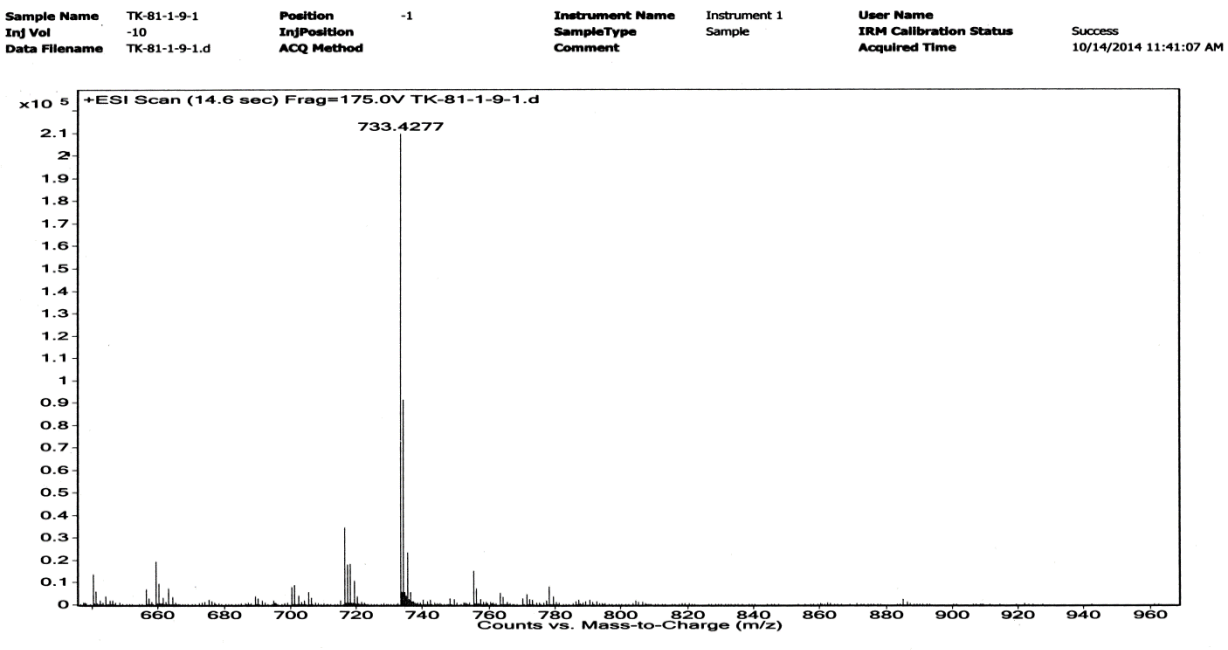


Figure 2.8.2.2. *HRMS spectra of compound* ***(A) HOHN-SU-Sar-VFILG-NH₂***

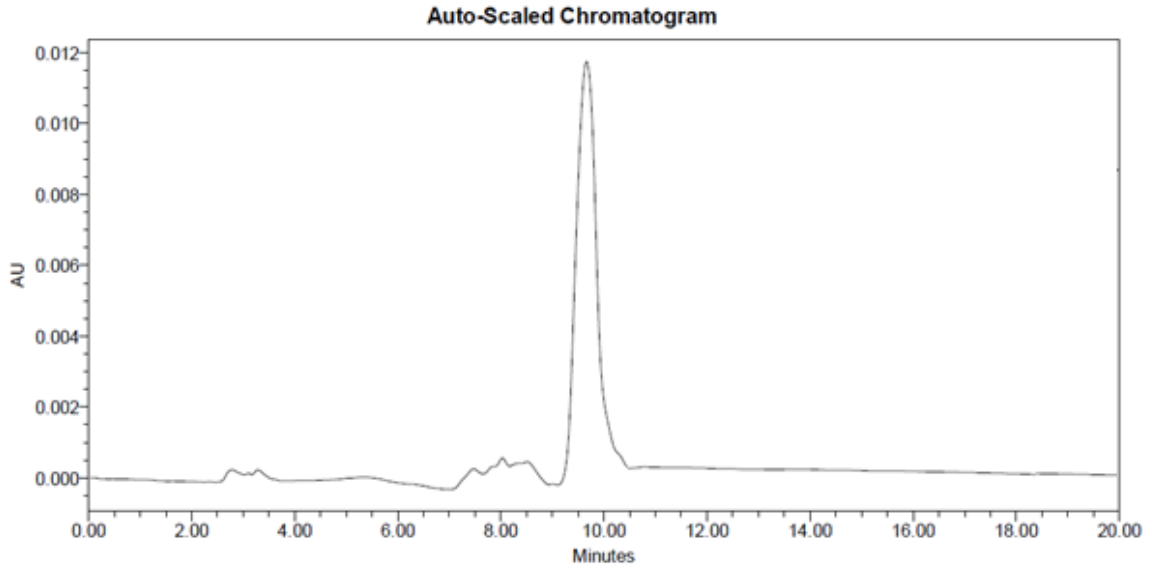


Figure 2.8.2.3. *HPLC spectra of compound* ***(B) HOHN-SU-Sar-LAKLAELAKG-NH₂***

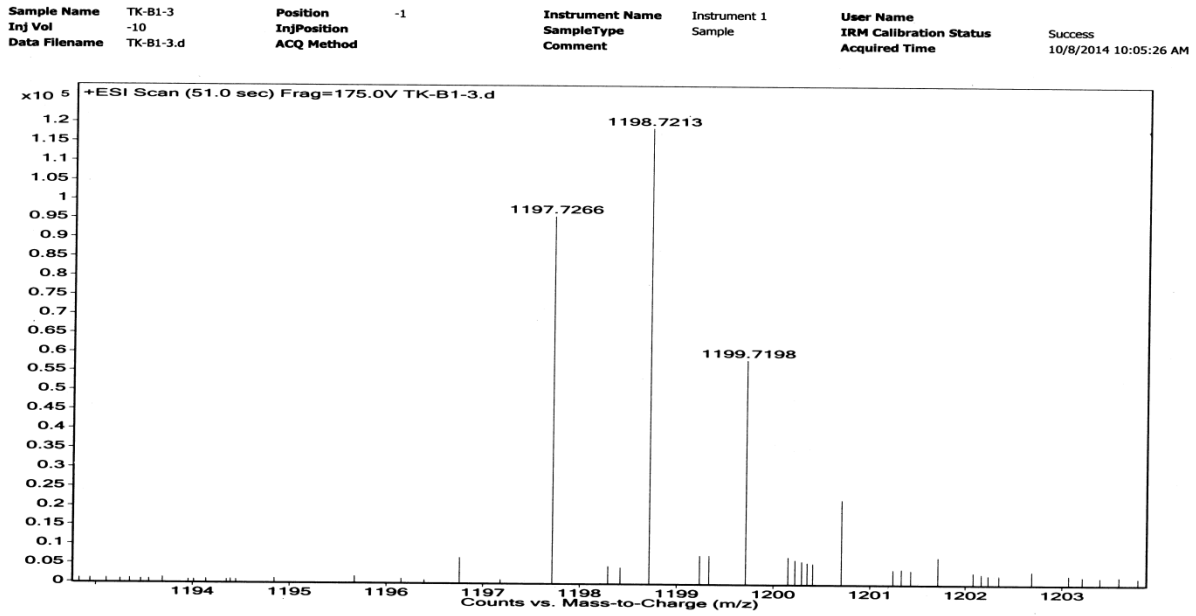


Figure 2.8.2.4. *HRMS spectra of compound* ***(B) HOHN-SU-Sar-LAKLAELAKG-NH₂***

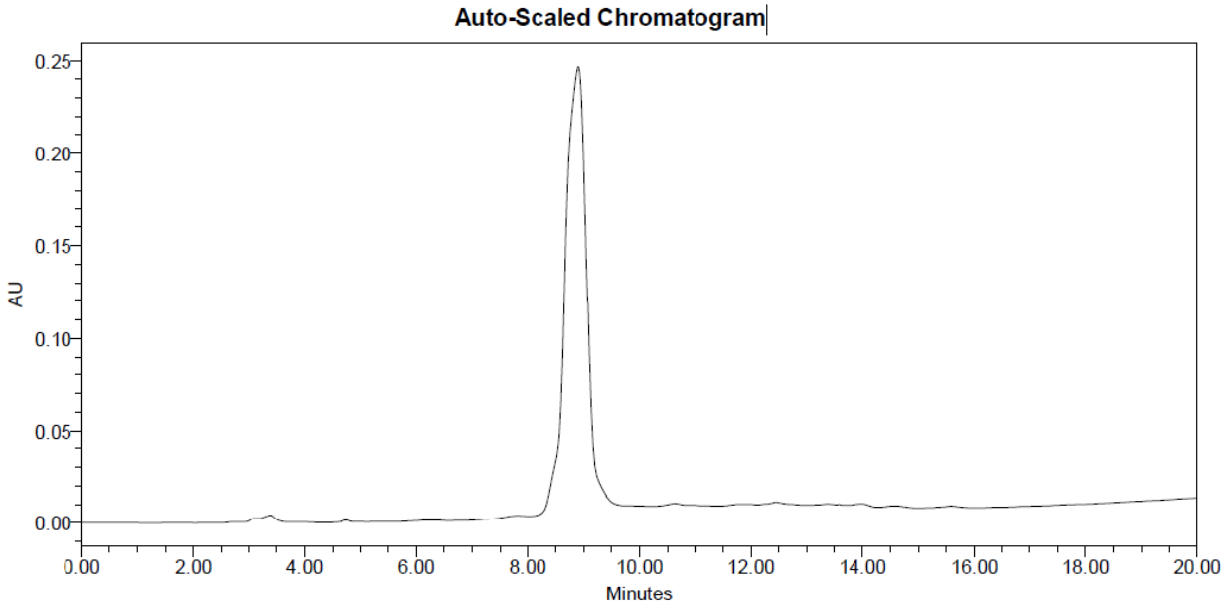


Figure 2.8.2.5. *HPLC spectra of compound* ***(C) HOHN-AD-VLGFA-NH₂***

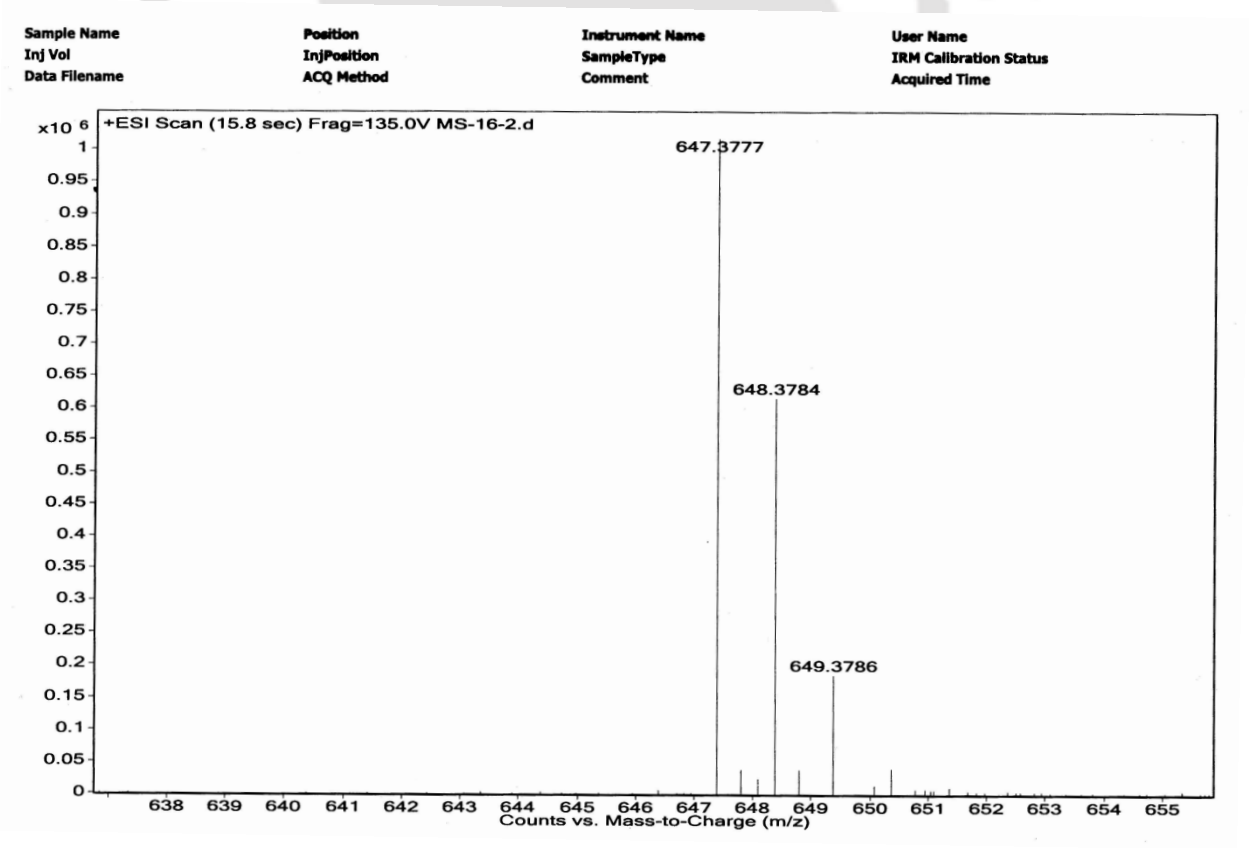


Figure 2.8.2.6. *HRMS spectra of compound* ***(C) HOHN-AD-VLGFA-NH₂***

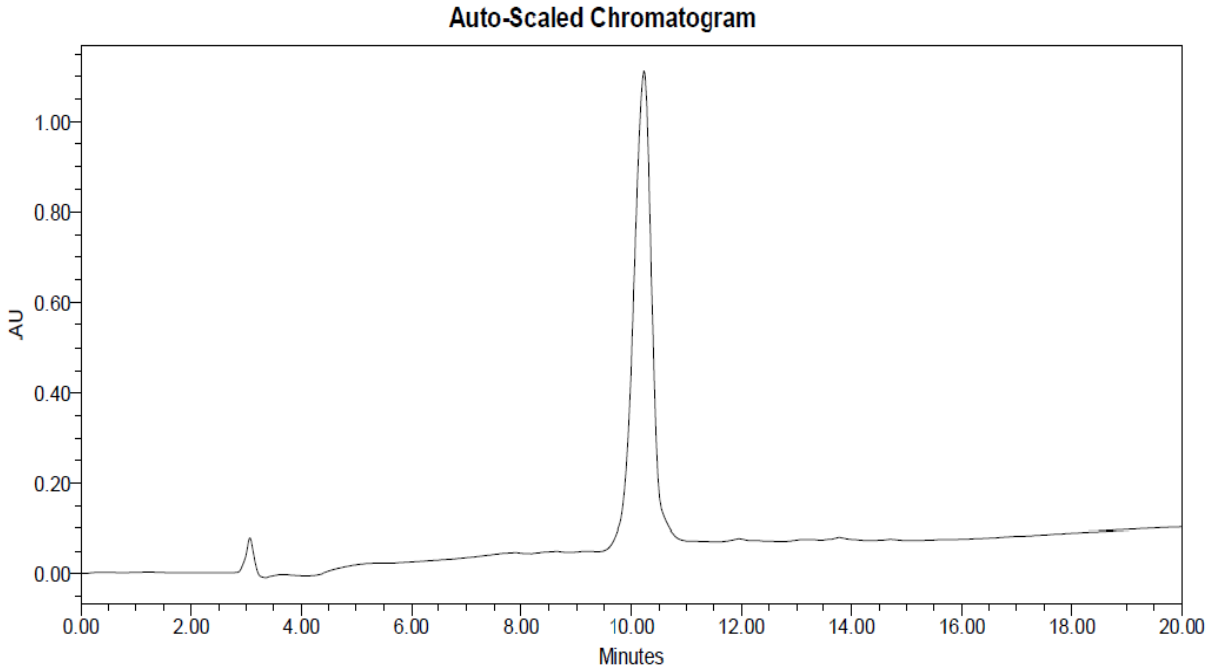


Figure 2.8.2.7. *HPLC spectra of the undesired peptide succinimide*

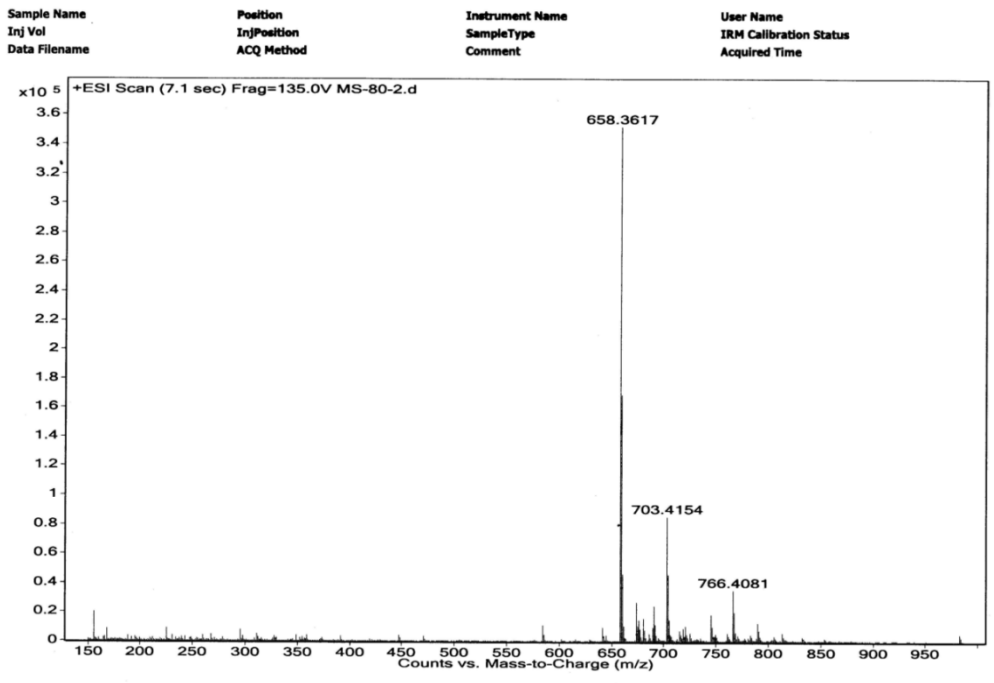


Figure 2.8.2.8. *HRMS spectra of the undesired peptide succinimide*

2.8.3 HPLC Data for racemization study

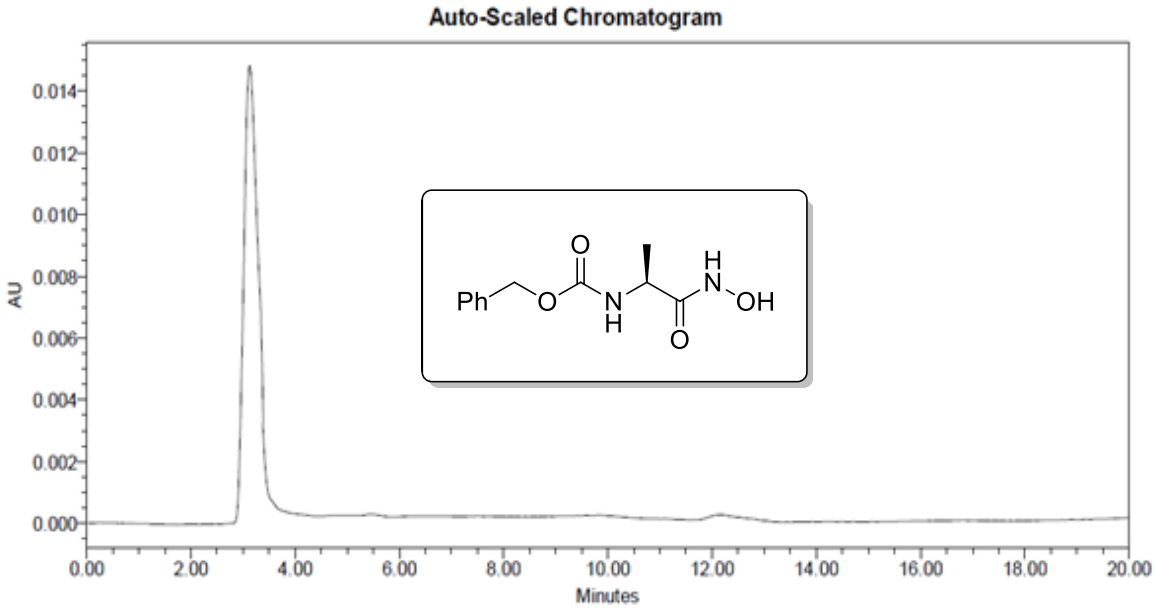


Figure 2.8.3.1. *HPLC spectra of compound* ***4a***

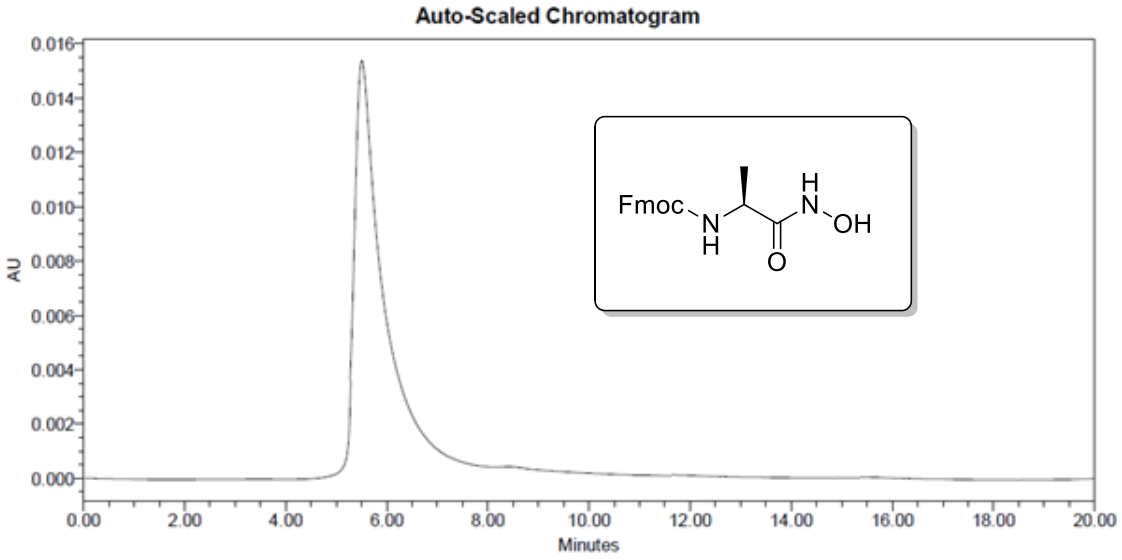


Figure 2.8.3.2. *HPLC spectra of compound* ***5a***

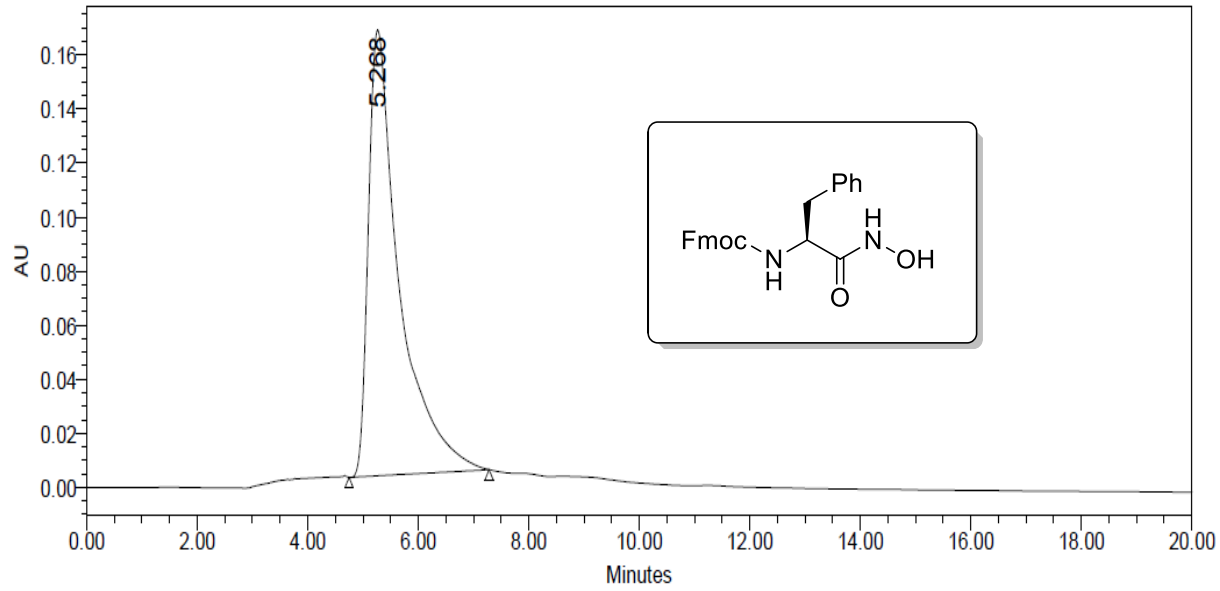


Figure 2.8.3.3. *HPLC spectra of compound* ***7a***

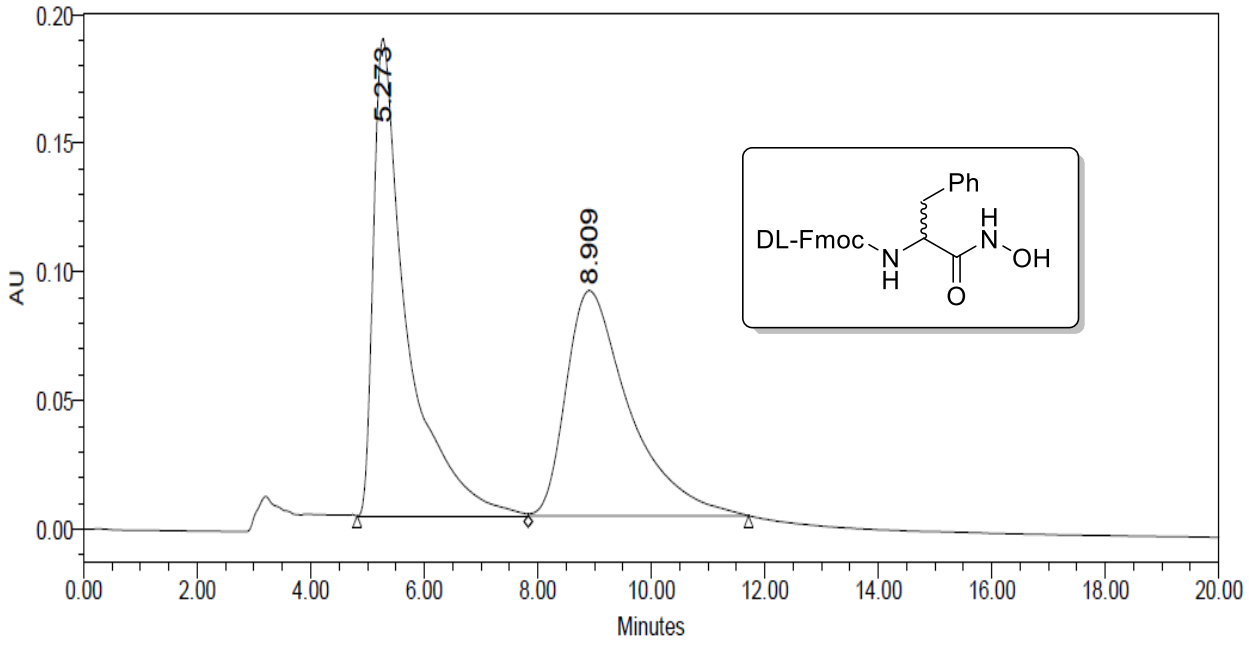


Figure 2.8.3.4. *HPLC spectra of compound* ***8a***

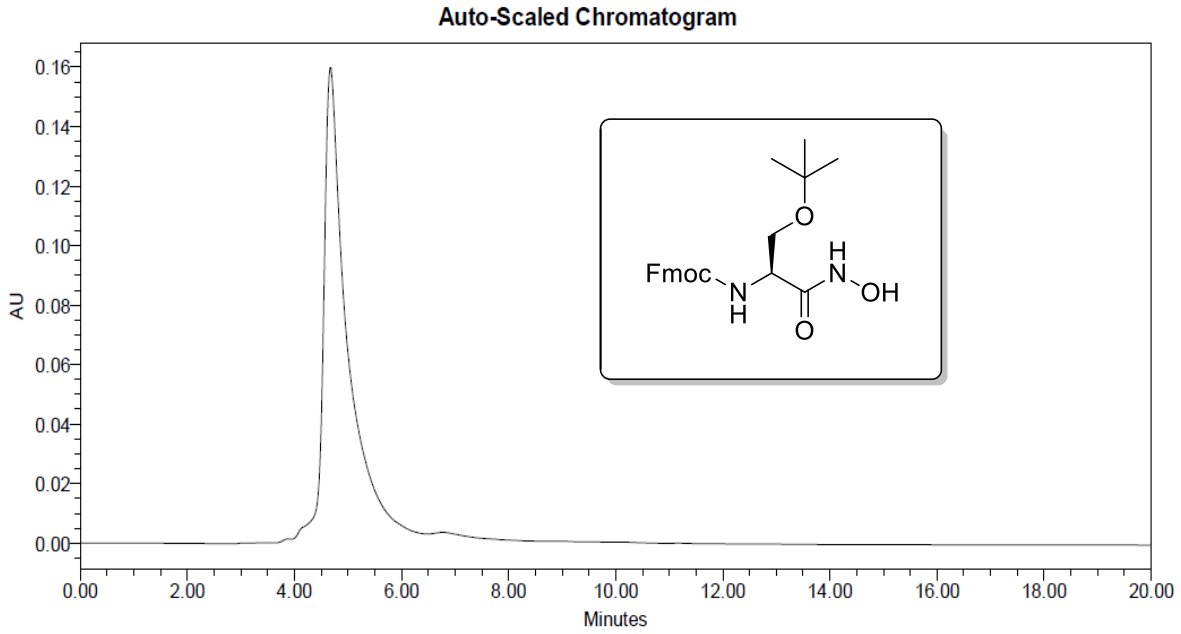


Figure 2.8.3.5. *HPLC spectra of compound* ***10a***

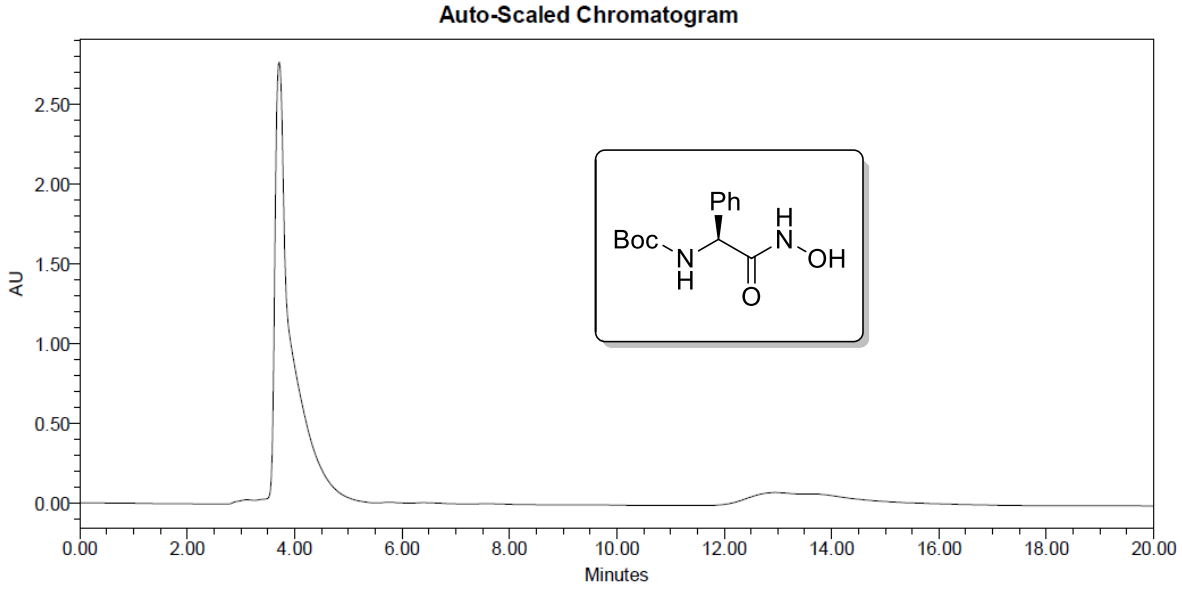


Figure 2.8.3.6. *HPLC spectra of compound* ***11a***

Chapter 3

Boc-Oxyma: An Efficient Promoter for the Lossen Rearrangement of the Hydroxamic Acids into Ureas, Carbamates and Thiocarbamates

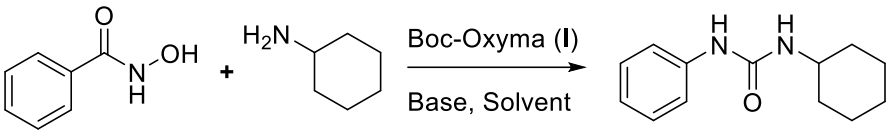
In our previous chapter, we have described the racemization free synthesis of hydroxamic acids using Boc-Oxyma (**I**) as a coupling reagent. Based on the existing methods (Chapter 1, section 1.3.2) and previous reports from our group, we hypothesized hydroxamic acids could be O-activated by **I** in the presence of base, and then could be converted into the corresponding isocyanate via Lossen rearrangement. Further, these isocyanates react with nucleophiles such as amines, alcohols and thiols to generate corresponding ureas, carbamates and thiocarbamates. In this chapter, we described the racemizaton free synthesis of ureas, carbamates and thiocarbamates using Boc-Oxyma *via* Lossen rearrangement of the hydroxamic acids that were described in the previous chapter.

3.1. Optimization and substrates scope

Initially, we optimized the reaction condition using benzhydroxamic acid **1a** as a model substrate. We treated benzhydroxamic acid with Boc-Oxyma and Cyclohexylamine in the presence of DBU in DCM and the reaction proceeds smoothly to afford desired product **3a** in 71% yield. With this result in hand, we started optimization of the reaction as depicted in Table 3.3.1. To increase the yield of product, we optimized the reaction condition with various bases such as NMM (*N*-methylmorpholine), Et_3N, NMI (*N*-methylimidazole), DMAP (4-Dimethylaminopyridine) and DABCO (1, 4-diazabicyclo [2.2.2] octane) and solvents such as DCM, $CHCl_3$, THF, CH_3CN, EtOAc, CH_3OH, and DMF. Among them, the presence of DIPEA as base and DCM as solvent were found to be the best optimal condition in terms of yield.

With the optimized condition in hand, the scope of the reaction was investigated with variety of amines such as aliphatic, aromatic and *C*-protected amines (Table 3.1.2). It was observed that all the reactions produced moderate to excellent yield. The conversion of various *para*-substituted phenyl hydroxamic acid into corresponding ureas also generated good yield (entry 3g-3h).

Table 3.1.1. Optimization of the reaction conditions[a]

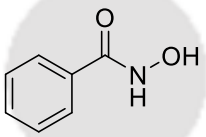
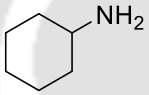
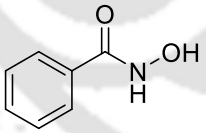
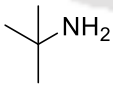
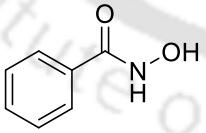
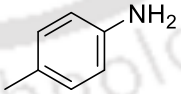
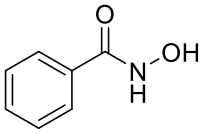
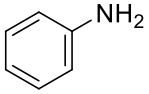
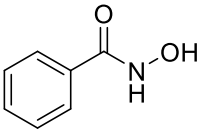
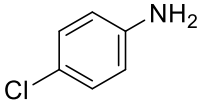


Entry	Base	Solvent	Yield (%)[b]
1	DBU	DCM	71
2	NMM	DCM	74
3	DABCO	DCM	55
4	NMI	DCM	54
5	DMAP	DCM	77
6	NEt_3	DCM	75
7	**DIPEA**	**DCM**	**90**
8	DIPEA	$CHCl_3$	85
9	DIPEA	THF	83
10	DIPEA	CH_3CN	81
11	DIPEA	EtOAc	87
12	DIPEA	CH_3OH	79
13	DIPEA	DMF	82
14	DIPEA	H_2O	45

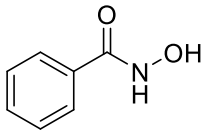
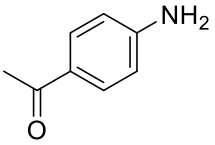
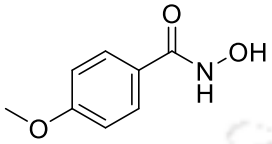
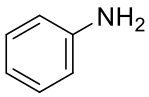
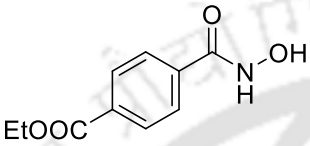
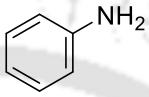
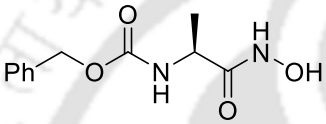
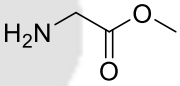
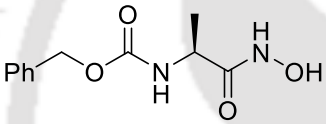
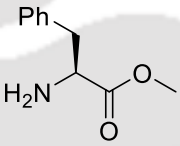
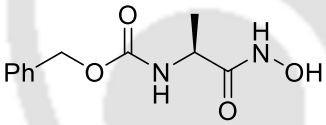
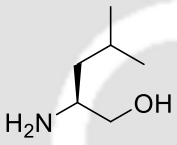
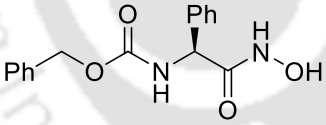
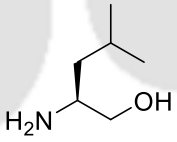
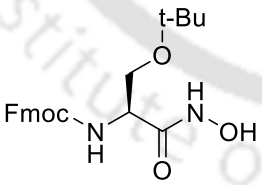
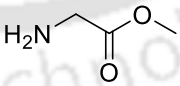
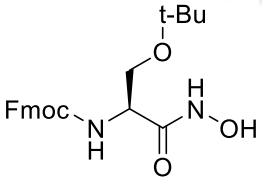
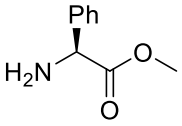
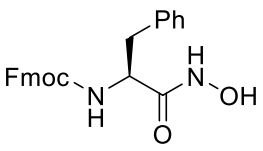
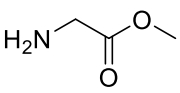
[a] Reaction conditions: benzhydroxamic acid (1 mmol), Boc-Oxyma (1 mmol), base (2.5 mmol), cyclohexylamine (1 mmol), solvent (2 mL), temperature: first 15 min at 0 °C, and then 6 h at room temperature after addition of amine, total reaction time 6-7 h. [b] Isolated yield.

A systematic investigation of the electronic effect of the substituents revealed that the electron withdrawing substituents hindered the reaction to a certain extent. The reaction worked well for amino acid derivatives with common amine protecting groups, such as Boc, Fmoc, CBz, and Bz (benzoyl), as well as various side-chain protecting groups of amino acids, such as tBu and Bzl. The yields were found to be good to excellent in all the cases including the sterically hindered amino acids, e.g., leucine, isoleucine, phenylalanine, and phenylglycine. The reaction worked well with aliphatic β-amino alcohols as a nucleophile. Usually, carbamates are formed in presence of hydroxyl group in Lossen rearrangement. Interestingly, although tertiary butanol was present as a byproduct in the reaction mixture, no trace of hydroxyl addition was observed. Also, when we used β-amino alcohols, chemoselective addition of amine occurred resulting in peptidyl ureas with free hydroxyl group (entries 11, 12, 16 and 19) as sole products. These ureas are very important intermediates for preparing anticancer agents.[1]

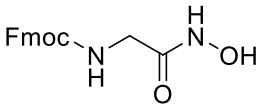
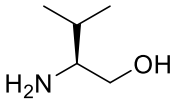
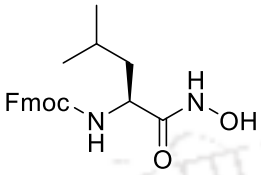
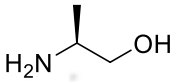
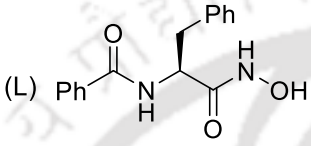
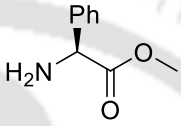
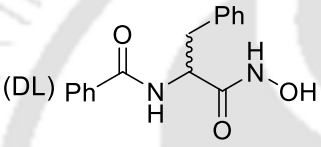
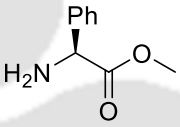
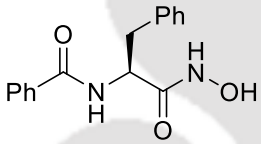
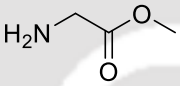
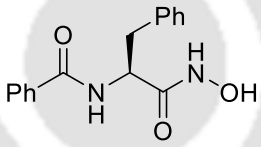
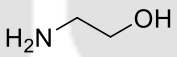
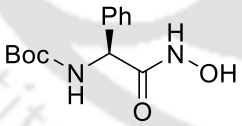
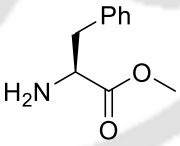
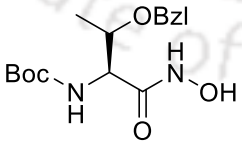
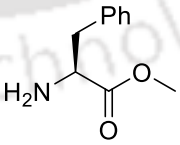
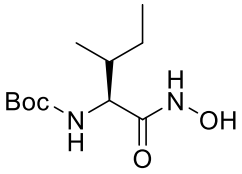
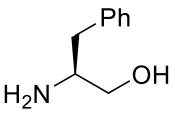
Table 3.1.2. Wide scope of the synthesis of ureas by using **I**[a]

Entry	Hydroxamic acid	Amine	Product	
			id	Yield(%)[b]
1			**3a**	90
2			**3b**	89
3			**3c**	90
4			**3d**	82
5			**3e**	76

Continued…….

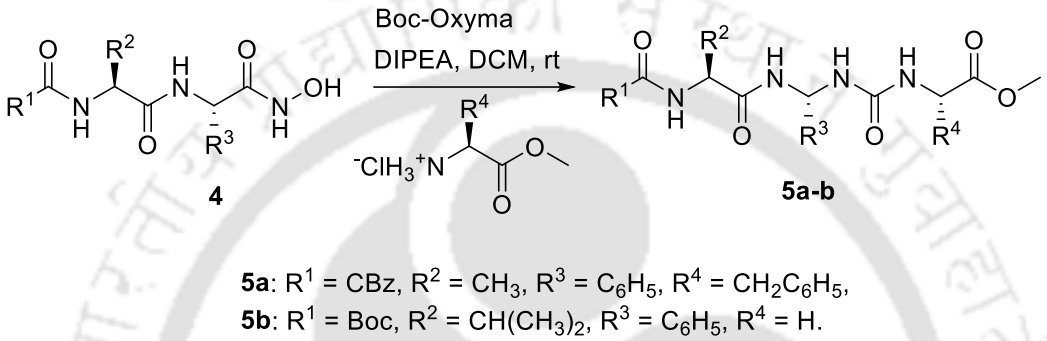
Entry	Hydroxamic acid	Amine	Product	
			id	Yield(%)[b]
6			**3f**	73
7			**3g**	87
8			**3h**	70
9			**3i**	85
10			**3j**	81
11			**3k**	83
12			**3l**	78
13			**3m**	82
14			**3n**	80
15			**3o**	77

Continued…….

Entry	Hydroxamic acid	Amine	Product	
			id	Yield(%)[b]
16			**3p**	83
17			**3q**	75
18			**3r**	83
19			**3s**	81
20			**3t**	80
21			**3u**	84
22			**3v**	85
23			**3w**	74
24			**3x**	79

[a] Reaction conditions: hydroxamic acid (1 mmol), Boc-Oxyma (1 mmol.), DIPEA (2.5 mmol), amine (1 mmol), DCM (2 mL), temperature: first 15 min at 0 °C and then 6 h at room temperature after addition of amine, total reaction time 6-7 h. [b] Isolated

Design of peptidomimetics often helps to obtain better active pharmaceutical ingredients, and replacement of peptide bond by peptidyl urea is a common technique for peptidomimetic design as it allows generation of H-bond donor and acceptors at desired sites. Moreover, some naturally occurring small peptidyl ureas have been isolated that have been demonstrated to inhibit HIV proteases[2] and microbial alkaline proteases.[3] Here, to extend the scope of our methodology, we synthesized tripeptidyl ureas from hydroxamic acid of dipeptides using methyl ester of amino acids in good yield (Scheme 3.1.1)



Scheme 3.1.1 *Synthesis of tripeptidyl ureas from hydroxamic acid derivatives of dipeptides by* ***I***

Finally, we extended this protocol for the synthesis of carbamates and thiocarbamates (Table 3.1.3) also, but the addition of DMAP and refluxing condition was required. The requirement of such harsher condition may be accounted for the relatively lower nucleophilicity of the alcohol and thiol group than the amine functional group. To a chilled solution of hydroxamic in DCM, Boc-Oxyma, DIPEA and 0.2 equiv of DMAP were added, and the mixture was stirred for 15 minutes. Then, the nucleophile (alcohol or thiol) was added, and the reaction mixture was refluxed for more five hours to obtain the desired product.

All the products were purified by column chromatography and characterized using various spectroscopic tools. The chemical structure of **3b** (Table 3.1.2) was further confirmed by X-ray crystallographic analysis (Figure 3.1.1).

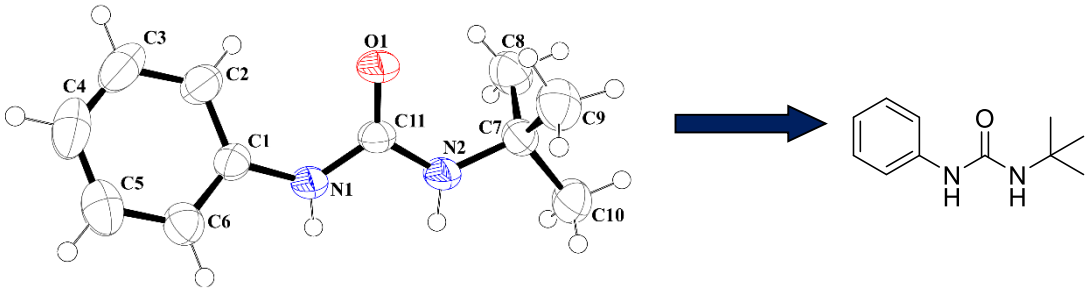
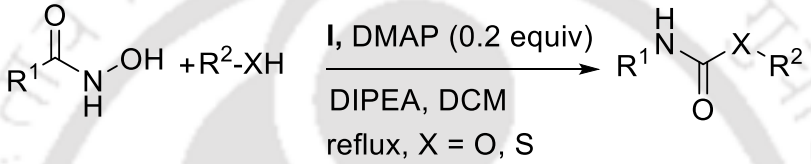
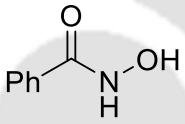
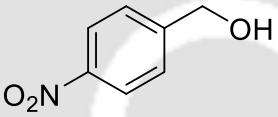
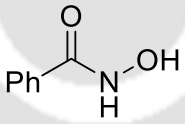
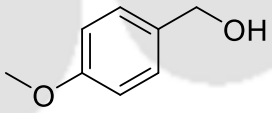
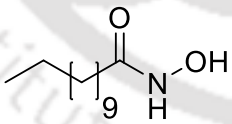
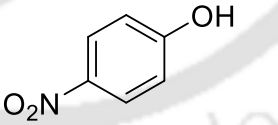
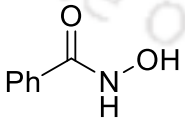
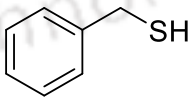
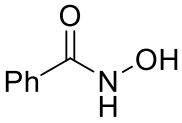
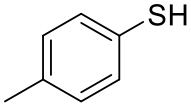


Figure 3.1.1. *X-ray crystallographic structure of 3b in table 3.1.2 (ORTEP diagram with ellipsoid of 50% probability, CCDC No. 1484427.)*

Table 3.1.3. Synthesis of carbamates and thiocarbamates by using **I**[a]



Entry	$R^1CONHOH$	R^2-XH	Product id	Yield(%)[b]
1			**6a**	77
2			**6b**	80
3			**6c**	76
4			**6d**	71
5			**6d**	74

[a] Reaction conditions: Hydroxamic acid (1 mmol), Boc-Oxyma (1 mmol), DIPEA (2.5 mmol), DMAP (0.2 mmol) alcohol or thiol (1 mmol), DCM (2 mL), temperature: first 15 min at 0 °C and then 5 h at reflux after addition of the nucleophile, total reaction time 5-6 h. [b] Isolated yield

3.2. Racemization Study

We have examined the racemization in this protocol. For that, we synthesized two peptidyl ureas Bz-L-Phe-L-Phg-OMe and Bz-DL-Phe-L-Phg-OMe by using **I** from L and DL form of Bz-phenylalanine hydroxamic acid, respectively, with methyl ester of phenylglycine. We compared HPLC profiles of the products (Figure 3.2.1). Single peak appeared at 70.5 in the HPLC profile of the L-isomer indicating the presence of single stereoisomeric product. On the other hand, distinct twin peaks appeared at 70.5 and 73.5 in the HPLC profile of the DL analog in the same gradient indicating the presence of two diastereomers (Figure 3.8.2.4 and 3.8.2.5). These results imply that no detectable racemization occurred during the conversion executed by the current protocol.

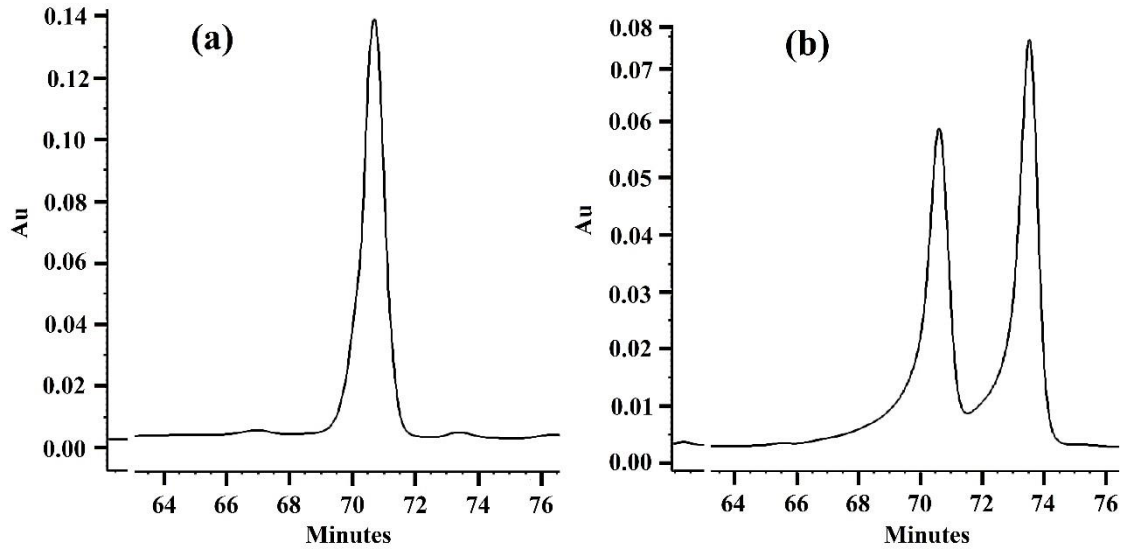


Figure 3.2.1. *HPLC profiles of products (a) L & (b) DL form of Bz-Phe-Phg-OMe dipeptidyl ureas*

3.3. Plausible mechanism

The plausible reaction mechanism is depicted in Figure 3.3.1. We performed the reaction between hydroxamic acid and Boc-Oxyma in the presence of DIPEA in an NMR tube using $CDCl_3$ as a solvent. ^{13}C and $^{1}HNMR$ spectra were recorded at the specified time intervals. Initially, the hydroxamic acid reacted with Boc-Oxyma and formed a stable intermediate **II** quickly within 15 minutes (Figure 3.3.1 and Figures 3.8.3.1−3.8.3.15), evident by the appearance of the peaks at 164.2 (A'), 136.4 (B') from 166.8 ppm (A) and 131.9 (B) corresponding to the carbonyl carbon and the adjacent aromatic carbon of the hydroxamic

acid, respectively. The signals of the carbonyl carbons of Boc-Oxyma 157.1 (C), 148.7 (D) were converted into 163.7 (C'), 153.2 (D') corresponding to the intermediate **II**, respectively. Presence of the intermediate **II** and Oxyma could be verified by ESI (-Ve mode, Figure 3.8.3.6 and +Ve mode, Figure 3.8.3.7) and ^{1}H NMR spectra (Figure 3.8.3.13) recorded till 5 min before addition of amine. Finally, two new peaks appeared slowly at 155.5 ppm (A") and 140.3 ppm (B"), after the addition of the tertiarybutyl amine, which corresponds to the carbonyl carbon of urea and the aromatic carbon, respectively. Now, if the reaction progress via a classical Lossen rearrangement mechanism, then the intermediate **II** should rearrange directly to the isocyanate **IV** and nucleophilic amine addition may take place then. But, unlike our previous work on Lossen rearrangement,[4] all our efforts to isolate the isocyanate went in vain, rather intermediate **II** could be isolated. Possibility of the formation of the cyclic intermediate **III** from **II** and its conversion to **IV** as reported by Pascal Dubé and co-workers[5] was also considered (Figure 3.3.1), but no characteristic peak of **III** was observed either in ^{1}H NMR or in ^{13}C NMR spectra (Figure 3.8.3.8, 3.8.3.9 and 3.8.3.15).

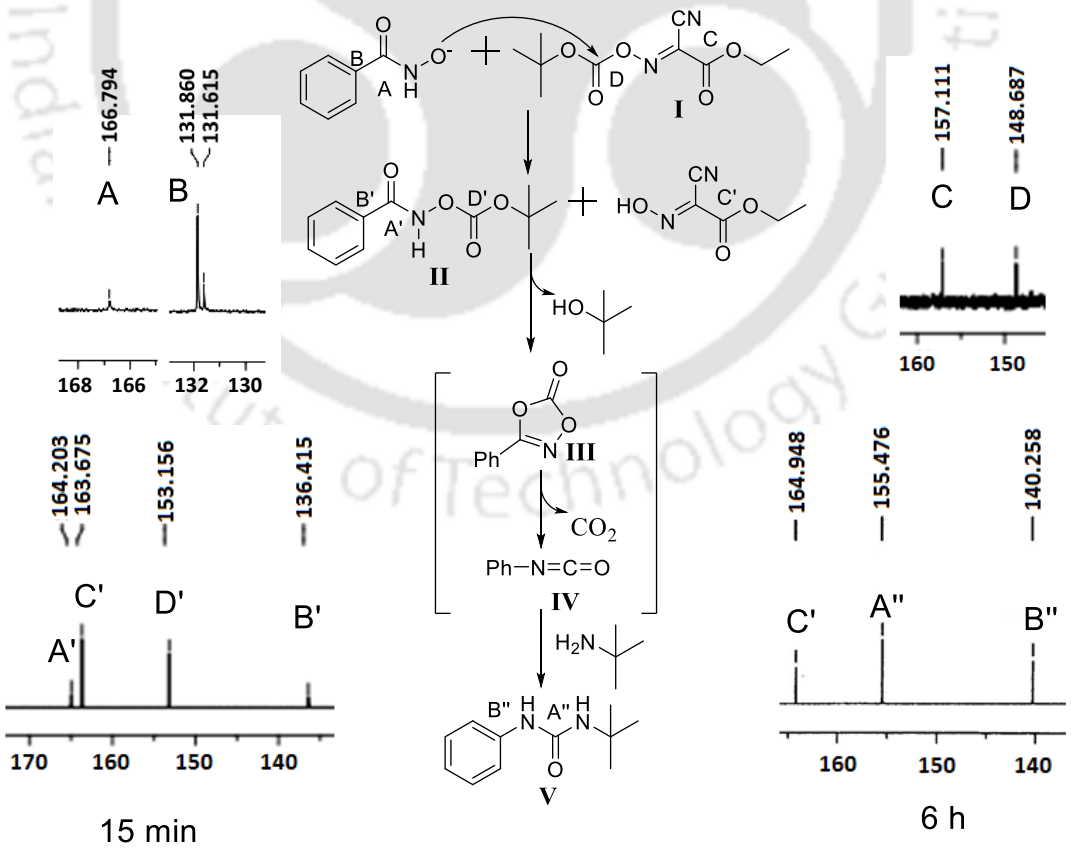


Figure 3.3.1. *Plausible reaction mechanism*

Furthermore, the characteristic quartet of the Oxyma that appeared within 5 min remained unchanged during the whole course of the reaction eliminating any possibility of further reaction of Oxyma with **II**. Also, the time resolved conversion of ^{13}C NMR peaks (Figure 3.8.3.8 and 3.8.3.9) as well as ^{1}H NMR peaks (Figure 3.8.3.15) indicated the absence of any further intermediate(s). Therefore, it was inferred that either direct attack of amine on the intermediate **II** resulted in urea, CO_2 and *tert*-butanol formation via a rearrangement that occurred in a concerted manner or the conversion of **II** to **III** or **IV** and subsequent attack by amine was so fast that it was impossible to get a trace of the intermediates III and **IV**.

3.4. Conclusion

In conclusion, we have demonstrated highly efficient and general method for the Lossen rearrangement of hydroxamic acid into ureas, carbamates and thiocarbamates in one-pot manner using Boc-Oxyma as a promoter. The main advantages of this methodology are: (a) All the hydroxamic acid substrates used in this article were obtained from the corresponding carboxylic acids using the same reagent, Boc-Oxyma. (b) Also, it is worth mention that Boc-Oxyma produces only Oxyma as a solid byproduct in the reaction that can be easily recovered and reused for the synthesis of the same reagent. (c) A wide reaction scope, with reactions that are clean and provide high yields without any racemization. Therefore, it seems that our protocol could be used as a valuable alternative to other known procedures.

3.5. Experimental Section

3.5.1. Materials and Instrumentation

As described in chapter 2 section 2.5.1

3.5.2. General procedure for the synthesis of ureas

Ethyl 2-(*tert*-butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma, I) (1 mmol) was added to a stirred solution of hydroxamic acid (1 mmol) and DIPEA (1 mmol) in DCM (2 mL) at 0-5 °C. Then the reaction mixture was stirred for 15 min followed by the addition of amine in DIPEA (1.5 mmol). The progress of the reaction was monitored by TLC at room temperature. After completion of the reaction, the reaction mixture was diluted with

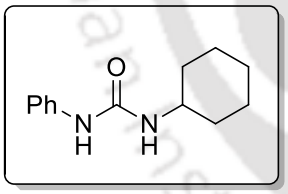
15 mL of DCM and washed with 5% HCl (2×10 mL), 5% $NaHCO_3$ (2×10 mL), saturated NaCl solution (2×10 mL) and dried over anhydrous $CaCl_2$ and the evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate.

3.5.3. General procedure for the synthesis of carbamates and thiocarbamates

Boc-Oxyma (1 mmol) was added to a stirred solution of hydroxamic acid (1 mmol), DIPEA (1.5 mmol) and DMAP (0.2 mmol) in 2 mL of DCM at 0 ˚C. Then the reaction mixture was stirred at the same temperature for 15 min followed by the addition of alcohols or thiols (1 mmol) and stirring at 60 °c temperature for more 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with 15 mL of DCM and washed with 5% HCl (2×10 mL), 5% $NaHCO_3$ (2×10 mL), saturated NaCl solution (2×10 mL) and dried over anhydrous $CaCl_2$ and the evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate.

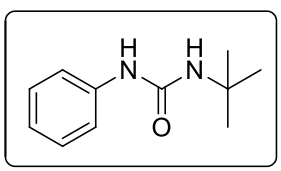
3.6. Characterization Data

Cyclohexyl-3-phenylurea 3a.



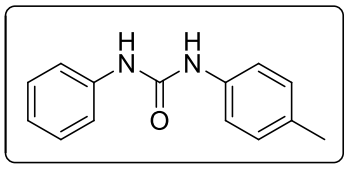
White solid; (98 mg, 90%), mp 125-127 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27-7.26 (m, 4H), 7.05-7.03 (m, 1H), 6.77 (s, 1H), 4.99 (s, 1H), 3.65-3.63 (m, 1H), 1.94-1.91 (m, 2H), 1.68-1.64 (m, 3H), 1.35-1.31 (s, 2H), 1.12-1.06 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 155.7, 139.5, 129.1, 122.8, 120.0, 48.8, 33.7, 25.6, 25.0; FT-IR (KBr) 3328, 2932, 2853, 1680, 1629, 1558, 1317 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{19}N_2O$ 219.1497, found 219.1486.

1-(*tert*-Butyl)-3-phenylurea 3b.



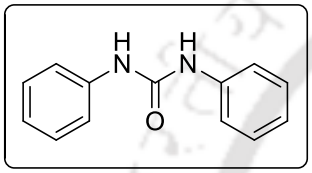
White solid; (170 mg, 89%), mp 166-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.26 (m, 4H), 7.05-7.02 (m, 1H), 6.63 (s, 1H), 4.96 (s, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 155.4, 139.2, 129.3, 123.4, 120.7, 120.6, 50.8, 29.5; FT-IR (KBr) 3361, 2924, 2853, 1647, 1539, 1211 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{17}N_2O$ 193.1341, found 193.1347.

1-Phenyl-3-(p-tolyl)urea 3c



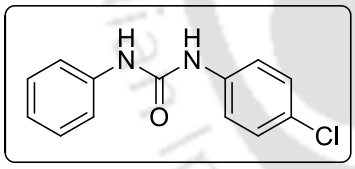
White solid; (101 mg, 90 %), mp 196-198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.55 (s, 1H) 7.44-7.42 (d, *J* = 7.6 Hz, 2H), 7.34-7.32 (d, *J* = 8.4 Hz, 2H) 7.28-7.24 (t, *J* = 7.6 Hz, 2H), 7.08-7.06 (d, *J* = 8.4 Hz, 2H) 6.96-6.93 (t, *J* = 7.2 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6,) δ 152.6, 139.8, 137.1, 130.6, 129.2, 128.8, 121.7, 118.3, 118.1, 20.3; FT-IR (KBr) 3301, 2922, 2852, 1789, 1635, 1535 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{15}N_2O$ 227.1184, found 227.1185.

1,3-Diphenylurea 3d



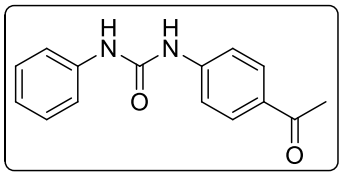
White solid; (86 mg, 82 %), mp 225-227 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 2H), 7.45-7.43 (d, *J* = 8 Hz, 4H), 7.28-7.24 (t, *J* = 7.6 Hz, 4H) 6.97-6.93 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6,) δ 152.6, 139.7, 128.8, 121.8, 118.2; FT-IR (KBr) 3328, 2924, 2845, 1790, 1662, 1552 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{13}N_2O$ 213.1028, found 213.1024.

1-(4-Chlorophenyl)-3-phenylurea 3e



White solid; (93 mg, 76 %), mp 238-240 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.70 (s, 1H), 7.49-7.43 (m, 4H), 7.33-7.25 (m, 4H), 6.99-6.95 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6,) δ 152.5, 139.5, 138.7, 128.8, 128.6, 127.3, 125.3, 122.0, 119.7, 118.3; FT-IR (KBr) 3440, 2922, 2852, 1636, 1594, 1563 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{12}ClN_2O$ 247.0638, found 247.0640.

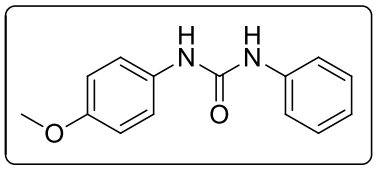
1-(4-Acetylphenyl)-3-phenylurea 3f



White solid; (92 mg, 73 %), mp 190-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 8.36 (br s, 1H), 8.03 (br s, 1H), 7.86-7.84 (d, *J* = 8.4 Hz, 2H), 7.49-7.47 (d, *J* = 8.8 Hz, 2H), 7.40-7.38 (d, *J* = 8 Hz, 2H), 7.30-7.27 (m, 2H), 7.06-7.03 (t, *J* = 7.2 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 153.3, 144.1, 138.4, 131.1, 130.0, 129.1, 123.4, 119.6, 117.8, 26.4; FT-IR (KBr)

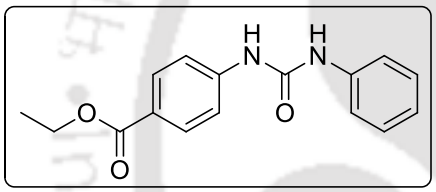
3440, 2921, 2848, 16631, 1638, 1598 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{15}N_2O_2$ 255.1134, found 255.1129.

1-(4-Methoxyphenyl)-3-phenylurea 3g



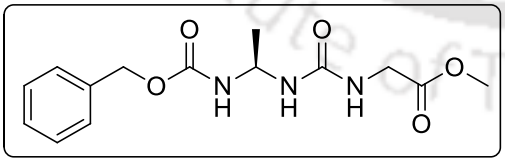
White solid; (105 mg, 87 %), mp 191-193 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.46 (s, 1H), 7.44-7.42 (d, *J* = 7.6 Hz, 2H), 7.36-7.34 (d, *J* = 9.2 Hz, 2H), 7.28-7.24 (t, *J* = 7.6 Hz, 2H), 6.96-6.92 (t, *J* = 7.6 Hz, 1H), 6.87-6.85 (d, *J* = 9.2 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.5, 152.8, 139.9, 132.7, 128.8, 121.6, 120.0, 118.1, 114.0, 55.1; FT-IR (KBr) 3298, 2923, 2853, 1720, 1560, 1246 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{15}N_2O_2$ 243.1134, found 243.1131.

Ethyl 4-(3-phenylureido)benzoate 3h



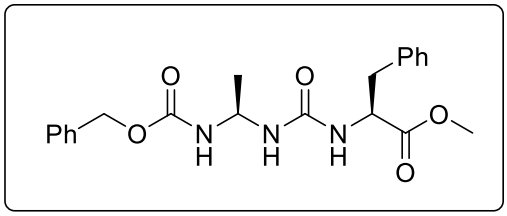
White solid; (99 mg, 70 %), mp 170-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.95 (s, 1H) 7.81-7.78 (d, *J* = 8.4 Hz, 2H), 7.23- 7.21 (d, *J* = 8.8 Hz, 2H), 7.18-7.13 (m, 4H), 6.99-6.98 (m, 1H), 4.33-4.28 (q, *J* = 7.2 Hz, 2H) 1.36-1.32 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 154.0, 143.1, 137.7, 130.8, 129.2, 124.6, 124.3, 121.2, 118.9, 61.1, 14.4; FT-IR (KBr) 3441, 2922, 2842, 1708, 1600, 1542 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{17}N_2O_3$ 285.1239, found 285.1241.

(*S*)-Methyl 5-methyl-3,7-dioxo-1-phenyl-2-oxa-4,6,8-triazadecan-10-oate 3i.



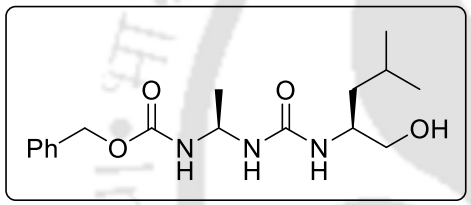
White solid; (131 mg, 85%), mp 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.37-7.30 (m, 5H), 5.18 (br, 1H), 5.08 (s, 2H), 3.93 (s, 2H), 3.72 (s, 3H), 1.47-1.45 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 171.8, 157.9, 156.5, 136.2, 128.6, 128.2, 128.0, 66.9, 56.0, 52.3, 41.8, 21.3; FT-IR (KBr) 3367, 2964, 2926, 1723, 1697, 1626, 1276 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{20}N_3O_5$ 310.1404, found 310.1403.

(5*S*,9*S*)-Methyl9-benzyl-5-methyl-3,7-dioxo-1-phenyl-2-oxa-4,6,8-triazadecan-10-oate 3j.



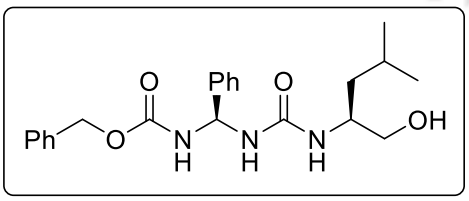
White solid; (161 mg, 81%), mp 141-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 5H), 7.23-7.18 (m, 3H), 7.12-7.10 (d, *J* = 7.2 Hz, 2H), 5.64 (br, 2H), 5.17 (br, 1H), 5.03 (s, 2H), 4.73-4.68 (m, 1H), 3.65 (s, 3H), 3.11-3.06 (m, 1H), 3.02-2.96 (m, 1H), 1.42-1.41 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 156.8, 156.1, 136.6, 136.3, 129.4, 128.6, 128.5, 128.2, 128.1, 126.9, 66.9, 56.1, 54.3, 52.2, 38.5, 21.5; FT-IR (KBr) 3298, 2924, 2849, 1737, 1697, 1640, 1502, 1267 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{26}N_3O_5$ 400.1872, found 400.1869.

Benzyl ((*S*)-1-(3-((S)-1-hydroxy-4-methylpentan-2-yl)ureido)ethyl)carbamate 3k.



White solid; (140 mg, 83%), mp 151-153 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 5.91 (br, 1H), 5.73 (br, 1H), 5.58 (br, 1H), 5.20 (br, 1H), 5.08 (s, 2H), 3.84 (s, 1H), 3.64-3.61 (m, 1H), 3.46-3.43 (m, 1H), 1.64-1.51 (m, 1H), 1.43-1.42 (d, *J* = 5.4 Hz, 3H), 1.39-1.23 (m, 2H), 0.90-0.88 (t, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 156.3, 136.0, 128.4, 128.1, 127.8, 66.8, 66.6, 55.8, 50.6, 40.3, 24.7, 23.0, 22.1, 21.3; FT-IR (KBr) 3447, 2953, 2921, 2849, 1697, 1645, 1539, 1263 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{28}N_3O_4$ 338.2080, found 338.2077.

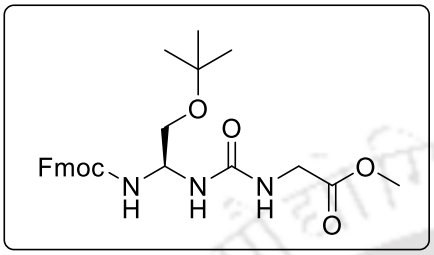
Benzyl((S)-(3-((S)-1-hydroxy-4-methylpentan-2-yl)ureido)(phenyl)methyl)carbamate 3l.



White solid; (155 mg, 78%), mp 192-194 °C; ^{1}H NMR (600 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.35-7.24 (m, 10H), 6.16 (br, 1H), 5.03 (s, 2H), 3.77 (s, 1H), 3.56-3.54 (m, 1H), 3.34 (br, 1H), 1.60-1.58 (m, 1H), 1.24 (br, 2H), 0.87-0.85 (t, *J* = 6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 158.2, 156.2, 136.1, 128.4, 128.3, 127.9, 127.8, 127.7, 125.7, 66.7, 65.6, 60.9, 50.0, 40.4, 24.6, 22.8, 21.8; FT-IR (KBr) 3311, 2954,

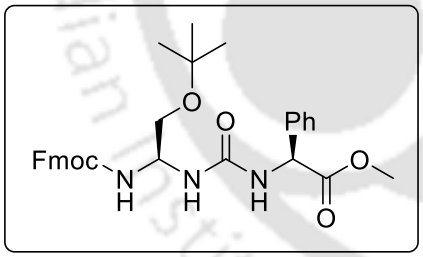
2924, 2853, 1679, 1618, 1438, 1259 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{22}H_{30}N_3O_4$ 400.2236, found 400.2230.

(*S*)-Methyl5-(*tert*-butoxymethyl)-1-(9H-fluoren-9-yl)-3,7-dioxo-2-oxa-4,6,8-triaza-decan-10-oate 3m.



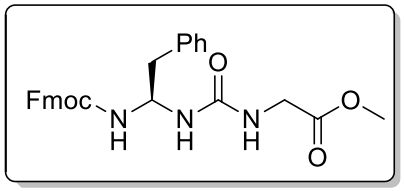
White solid; (192 mg, 82%), mp 135-137 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77-7.75 (d, *J* = 7.6 Hz, 2H), 7.60-7.58 (d, *J* = 7.2 Hz, 2H), 7.42-7.38 (t, *J* = 7.2 Hz, 2H), 7.33-7.29 (t, *J* = 7.2 Hz, 2H), 5.87-5.85 (d, *J* = 8 Hz, 1H), 5.52-5.50 (d, *J* = 7.6 Hz, 1H), 5.33 (br, 1H), 4.43-4.39 (m, 2H), 4.25-4.22 (t, *J* = 7.2 Hz, 1H), 3.98-3.97 (d, *J* = 5.2 Hz, 2H), 3.68 (s, 3H), 3.59-3.51 (m, 2H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 157.5, 156.8, 143.9, 141.4, 127.9, 127.2, 125.2, 120.1, 67.4, 63.9, 58.9, 52.2, 47.2, 42.2, 27.5; FT-IR (KBr) 3328, 2974, 2924, 1698, 1644, 1539, 1245 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{32}N_3O_6$ 470.2291, found 470.2286.

(5*S*,9*S*)-Methyl 5-(*tert*-butoxymethyl)-1-(9H-fluoren-9-yl)-3,7-dioxo-9-phenyl-2-oxa-4,6,8-triazadecan-10-oate 3n.



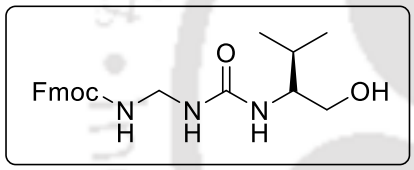
White solid; (218 mg, 80%), mp 162-164 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.77-7.75 (d, *J* = 7.8 Hz, 2H), 7.53-7.48 (m, 2H), 7.41-7.39 (t, *J* = 7.2 Hz, 2H), 7.34-7.28 (m, 4H), 7.19 (br, 3H), 5.79-5.77 (d, *J* = 8.4 Hz, 2H), 5.50-5.47 (m, 2H), 5.40 (br, 1H), 4.30-4.24 (m, 2H), 4.08 (br, 1H), 3.69 (s, 3H), 3.60-3.54 (m, 2H), 1.19 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.2, 156.6, 156.3, 144.0, 143.8, 141.4, 137.1, 128.8, 128.4, 127.9, 127.5, 127.2, 125.2, 120.1, 67.5, 63.9, 58.9, 57.5, 52.7, 47.1, 27.5; FT-IR (KBr) 3321, 2974, 2934, 1698, 1644, 1536, 1243 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{31}H_{36}N_3O_6$ 546.2604, found 546.2600.

(*S*)-Methyl 5-benzyl-1-(9H-fluoren-9-yl)-3,7-dioxo-2-oxa-4,6,8-triazadecan-10-oate 3o.



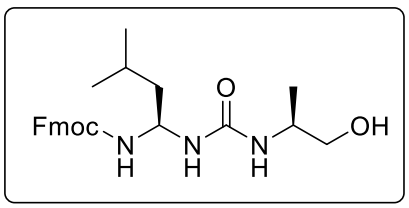
White solid; (182 mg, 77%), mp 160-162 °C; ^{1}H NMR (600 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.76-7.75 (d, *J* = 7.2 Hz, 2H), 7.53-7.52 (d, *J* = 6 Hz, 2H), 7.40-7.38 (t, *J* = 7.2 Hz, 2H), 7.28 (br, 4H), 7.23-7.21 (m, 3H), 5.16 (br, 1H), 4.32 (br, 2H), 4.17 (br, 1H), 3.94 (s, 2H), 3.70 (s, 3H), 3.15 (br, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 171.6, 157.9, 156.4, 143.8, 141.2, 136.8, 129.2, 128.4, 127.6, 127.0, 126.7, 125.0, 119.8, 66.7, 60.4, 52.0, 47.0, 41.6, 40.2; FT-IR (KBr) 3299, 2922, 2852, 1692, 1649, 1536, 1259 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{27}H_{28}N_3O_5$ 474.2029, found 474.2028.

(*S*)-(9*H*-Fluoren-9-yl) methyl((3-(1-hydroxy-3-methylbutan-2-yl)ureido)methyl)carbamate 3p.



White solid; (165 mg, 83 %), mp 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.77-7.75 (d, *J* = 7.6 Hz, 2H), 7.58-7.57 (d, *J* = 7.2 Hz, 2H), 7.41-7.38 (t, *J* = 7.6 Hz, 2H), 7.32-7.28 (m, 2H), 4.46 (s, 2H), 4.34-4.33 (d, *J* = 6 Hz, 2H), 4.22-4.20 (t, *J* = 8 Hz, 1H), 3.66-3.64 (m, 1H), 3.52-3.50 (d, *J* = 7.6 Hz, 2H), 1.79-1.82 (m, 1H), 0.94-0.89 (m, 6H); ^{13}C NMR (150 MHz, DMSO-D_6) δ 157.6, 156.6, 143.8, 140.7, 127.7, 127.1, 125.3, 120.1, 65.7, 61.8, 61.3, 55.7, 46.6, 28.1, 19.7; FT-IR (KBr) 3315, 2955, 2923, 2852, 1692, 1647, 1532, 1260 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{22}H_{27}N_3O_4$ 398.2080, found 398.2085.

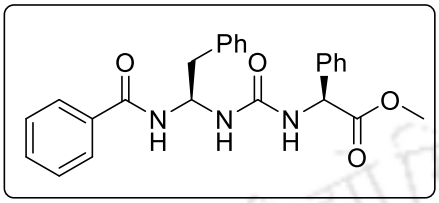
(9*H*-Fluoren-9-yl) methyl((S)-1-(3-((S)-1-hydroxypropan-2-yl)ureido)-3-methylbutyl) carbamate 3q.



White solid; (159 mg, 75 %), mp 157-159 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.77-7.75 (d, *J* = 6.8 Hz, 2H), 7.59-7.57 (d, *J* = 6.4 Hz, 2H), 7.42-7.38 (t, *J* = 7.6 Hz, 2H), 7.33-7.30 (t, *J* = 7.2 Hz, 2H), 4.97 (br, 1H), 4.37-4.35 (d, *J* = 7.6 Hz, 2H), 4.20 (br, 1H), 3.80 (br, 1H), 3.53-3.39 (m, 2H), 1.62 (br, 1H), 1.25 (br, 3H), 1.14-1.06 (m, 1H), 0.92 (br, 6H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 158.4, 156.8, 143.6, 141.2, 127.6,

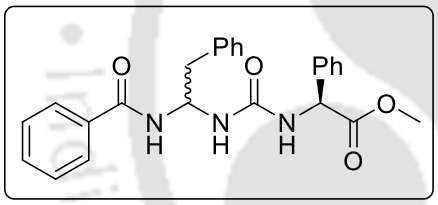
127.0, 124.9, 119.8, 66.7, 57.8, 57.7, 47.8, 47.0, 43.2, 24.7, 22.1, 21.9, 17.1; FT-IR (KBr) 3328, 2959, 2923, 2851, 1694, 1634, 1534, 1235 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{32}N_3O_4$ 426.2393, found 426.2393.

Methyl 2-(3-((R)-1-benzamido-2-phenylethyl)ureido)-2-phenylacetate 3r.



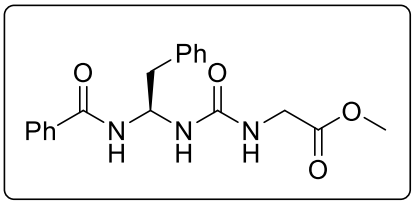
White solid; (179 mg, 83 %), mp 137-139 °C; ^1H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.74-7.09 (m, 15H), 5.37 (br, 1H), 5.32 (s, 1H), 3.55 (s, 3H), 3.21-3.16 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 172.3, 168.5, 157.2, 136.7, 134.6, 131.8, 129.4, 129.3, 128.9, 128.8, 128.58, 128.53, 128.46, 128.40, 127.3, 127.2, 127.1, 126.8, 59.9, 57.3, 52.6, 39.9; FT-IR (KBr) 3372, 2923, 2852, 1738, 1641, 1559, 1166 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{26}N_3O_4$ 432.1923, found 432.1913.

***Methyl ((1-benzamido-2-phenylethyl)carbamoyl)glycinate 3s.**



White solid; (174 mg, 81 %), 137-139 °C; ^1H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.63-7.13 (m, 15H), 5.38 (br, 1H), 5.30 (s, 1H), 3.62 (s, 3H), 3.57 (s, 3H), 3.28-3.27. (m, 2H), 3.19-3.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 172.2, 168.6, 168.5, 157.4, 157.2, 137.1, 136.8, 136.7, 133.9, 133.8, 131.8, 129.4, 129.3, 128.9, 128.8, 128.57, 128.55, 128.4, 128.3, 127.3, 127.26, 127.24, 126.7, 59.9, 57.4, 57.3, 52.66, 52.62, 39.8; FT-IR (KBr) 3372, 2923, 2852, 1738, 1641, 1559, 1166 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{26}N_3O_4$ 432.1923, found 432.1913.

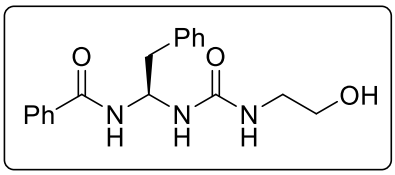
Methyl (*R*)-((1-benzamido-2-phenylethyl)carbamoyl)glycinate 3t.



White solid; (142 mg, 80 %), mp 166-168 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.66-7.65 (d, J = 7.2 Hz, 2H), 7.42-7.39 (t, J = 7.2 Hz, 1H), 7.27-7.25 (m, 2H), 7.21-7.16 (m, 4H), 7.13-7.10 (t, J = 7.2 Hz, 1H), 5.91 (br, 1H), 3.98-3.94 (m, 2H), 3.61 (s, 3H), 3.18-3.16 (d, J = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 171.5, 168.6, 158.2, 137.0, 133.8, 131.8, 129.3, 128.5, 128.4, 127.1, 126.7, 59.7, 52.0, 41.7, 39.9; (KBr) 3340, 2925, 2853, 1751,

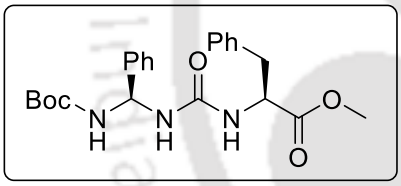
1640, 1578, 1207 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{21}N_3O_4$ 356.1610, found 356.1617.

(*R*)-*N*-(1-(3-(2-Hydroxyethyl)ureido)-2-phenylethyl)benzamide 3u.



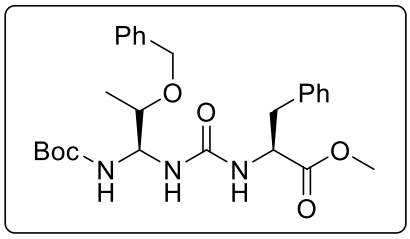
White solid; (137 mg, 84 %), mp 190-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.71-7.69 (d, *J* = 7.2 Hz, 2H), 7.52-7.48 (t, *J* = 7.2 Hz, 1H), 7.43-7.37 (m, 2H), 7.31-7.22 (m, 5H), 5.51-5.47 (t, *J* = 6.8 Hz, 1H), 3.61-3.58 (t, *J* = 5.2 Hz, 2H), 3.27-3.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, few drops of CD_3OD and DMSO- D_6 for solubility) δ 169.5, 159.8, 138.6, 135.6, 132.7, 130.5, 129.57, 129.5, 128.4, 127.7, 62.4, 60.7, 43.4, 41.7, 40.0; (KBr) 3361, 3251, 2926, 2852, 1647, 1622, 1573, 1276 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{21}N_3O_4$ 328.1661, found 328.1670.

Methyl(((*S*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)carbamoyl)phenyl alaninate 3v.



White solid; (181 mg, 85 %), mp 171-173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.22 (m, 8H), 7.12-7.10 (d, *J* = 6.8 Hz, 2H), 6.15-6.11 (m, 1H), 5.82-5.74 (m, 2H), 4.74-4.72 (m, 1H), 3.62 (s, 3H), 3.12-2.98 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 173.3, 157.0, 155.6, 139.9, 136.4, 129.3, 128.5, 128.4, 127.8, 126.9, 125.8, 80.3, 60.8, 54.1, 52.1, 38.4, 28.3; FT-IR (KBr) 3368, 3328, 2926, 1744, 1677, 1620, 1211 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{30}N_3O_5$ 428.2185, found 428.2193.

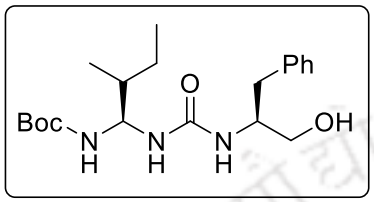
(2*S*,6*S*)-Methyl 2-benzyl-6-((*S*)-1-(benzyloxy)ethyl)-10,10-dimethyl-4,8-dioxo-9-oxa-3,5,7-triazaundecan-1-oate 3w.



White solid; (179 mg, 74 %), mp 161-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.16 (m, 10H), 5.35, (br, 1H), 5.18, (br, 1H), 5.03, (br, 1H), 4.71-4.67 (m, 1H), 4.64-4.62 (d, *J* = 6 Hz, 2H), 4.37-4.35 (d, *J* = 11.4 Hz, 1H), 3.63 (s, 3H), 3.11-3.00 (m, 2H), 1.42 (s, 9H), 1.23-1.22 (d, *J* = 6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 156.7, 156.6, 137.6,

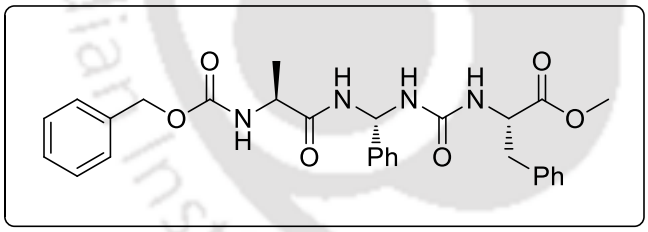
136.8, 127.5, 127.4, 128.8, 128.5, 128.3, 128.1, 126.9, 80.7, 76.4, 71.2, 62.2, 54.8, 52.2, 38.6, 28.5, 16.1; FT-IR (KBr) 3328, 2925, 2845, 1732, 1689, 1641, 1250 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{26}H_{35}N_3O_6$ 486.2604, found 486.2608.

tert-Butyl((1*S*,2*R*)-1-(3-(1-hydroxy-3-phenylpropan-2-yl)ureido)-2-methylbutyl) carbamate 3x.



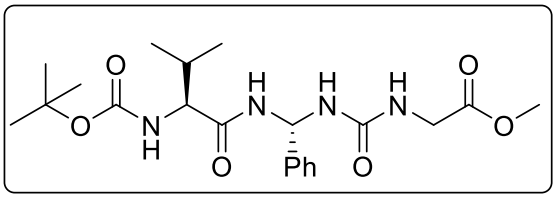
White solid; (150 mg, 79 %), mp 155-157 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 7.22-7.12 (m, 5H), 6.85 (br, 1H), 6.01 (br, 1H), 4.88 (br, 1H), 4.75 (br, 1H), 3.7 (br, 1H), 3.31-3.24 (m, 2H), 2.77-2.58 (m, 2H), 1.56 (br, 1H), 3.81 (br, 1H), 1.35 (s, 9H), 1.03-1.00 (m, 2H), 0.81-0.791 (tr, *J* = 4.8 Hz, 1H), 0.75-0.744 (d, *J* = 4.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 158.7, 156.4, 138.4, 129.3, 128.4, 126.4, 80.2, 64.5, 62.8, 53.7, 38.7, 37.6, 28.4, 25.3, 14.7, 11.1; FT-IR (KBr) 3344, 2964, 2920, 2872, 1686, 1638, 1571, 1248 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{34}N_3O_4$ 380.2549, found 380.2552.

(5*S*,8*R*,12*S*)-Methyl 12-benzyl-5-methyl-3,6,10-trioxo-1,8-diphenyl-2-oxa-4,7,9,11-tetraazatridecan-13-oate 5a.



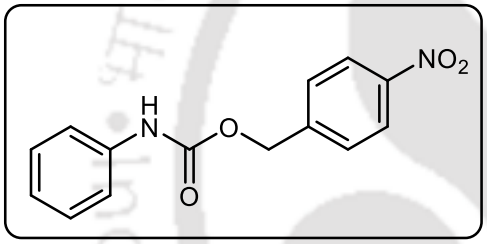
White solid; (100 mg, 75 %), mp 193-195 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 8.33-8.31 (d, *J* = 7.6 Hz, 1H), 7.38-7.13 (m, 15H), 6.36-6.35 (d, *J* = 6.8 Hz, 1H), 5.08-5.07 (d, *J* = 5.2 Hz, 2H), 4.68-4.65 (t, *J* = 6.4 Hz, 1H), 4.20- 4.18 (m, 1H), 3.68 (s, 3H), 3.13-2.98 (m, 2H), 1.34-1.32 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-D_6) δ 173.3, 172.5, 156.6, 156.2, 141.3, 137.2, 129.6, 128.8, 128.79, 128.7, 128.3, 128.1, 127.9, 127.1, 126.3, 65.9, 58.4, 54.3, 52.3, 50.5, 49.0, 38.1, 18.3; FT-IR (KBr) 3302, 3020, 2925, 1735, 1682, 1558, 1260 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{33}N_4O_6$ 533.2400, found 533.2407.

(6*R*,9*S*)-Methyl 9-isopropyl-13,13-dimethyl-4,8,11-trioxo-6-phenyl-12-oxa-3,5,7,10-tetraazatetradecan-1-oate 5b.



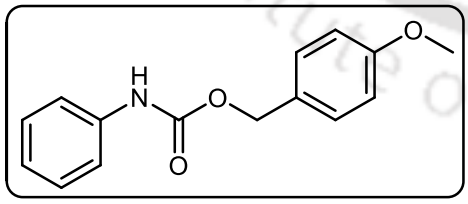
White solid; (156 mg, 72 %), mp 180-183 °C; ^{1}H NMR (400 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 7.31-7.18 (m, 5H), 6.53-6.49 (m, 2H), 5.65 (br, 1H), 3.96-3.77 (m, 3H), dt3.65 (s, 3H), 1.99-1.97 (m, 1H), 1.38 (s, 9H); 0.85-0.84 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 171.7, 157.8, 156.1, 139.4, 128.5, 128.4, 127.5, 126.19, 126.13, 79.8, 60.8, 58.6, 52.3, 42.1, 29.8, 28.5, 19.2, 18.3 cm^{-1}; FT-IR (KBr) 3340, 3271, 2964, 2917, 2870, 1703, 1657, 1558, 1206 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{33}N_4O_6$ 437.2400, found 437.2404.

4-Nitrobenzyl phenylcarbamate 6a.



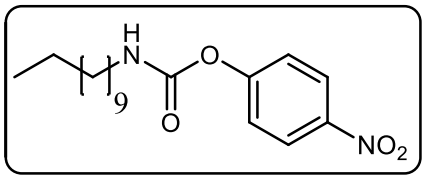
Light yellow solid; (105 mg, 77 %), mp 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.22 (d, *J* = 8 Hz, 2H), 7.56-7.54 (d, *J* = 8 Hz, 2H), 7.40-7.38 (d, *J* = 7.6 Hz, 2H), 7.34-7.30 (t, *J* = 7.6 Hz, 2H), 7.11-7.07 (t, *J* = 7.2 Hz, 1H), 6.81 (br, 1H), 5.29 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.0, 147.8, 143.6, 137.5, 129.3, 128.4, 124.0, 123.9, 119.2, 65.5 cm^{-1}; FT-IR (KBr) 3343, 2932, 1705, 1535, 1511, 1235 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{13}N_2O_4$ 273.0875, found 273.0888.

4-Methoxybenzyl phenylcarbamate 6b.



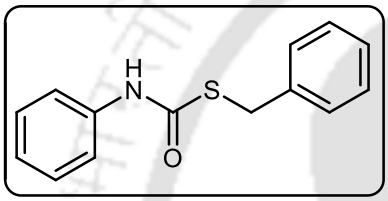
White solid; (102 mg, 80 %), mp 87-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.25 (m, 6H), 7.07-7.03 (t, *J* = 7.6 Hz, 1H), 6.91-6.89 (d, *J* = 7.2 Hz, 2H), 6.67 (br, 1H) 5.13 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.8, 153.6, 137.9, 130.3, 129.1, 128.2, 123.5, 118.8, 114.1, 66.9, 55.4 cm^{-1}; FT-IR (KBr) 3315, 2945, 2828, 1701, 1533, 1236 cm^{-1}; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{15}H_{15}NO_3Na$ 280.0950, found 280.0964.

4-Nitrophenyl undecylcarbamate 6c.



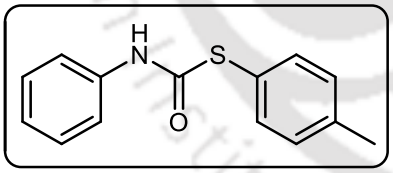
Pale yellow solid; (128 mg, 76 %), mp 83-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.23 (d, *J* = 9.2 Hz, 2H), 7.32-7.30 (d, *J* = 8.8 Hz, 2H), 3.30-3.25 (m, 2H), 1.60-1.55 (m, 4H), 1.26-1.25 (m, 14H), 0.89-0.86 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 156.1, 153.3, 144.8, 125.3, 122.1, 41.6, 32.0, 29.8, 29.79, 29.77, 29.72, 29.5, 29.4, 26.9, 22.8, 14.3 cm^{-1}; FT-IR (KBr) 3342, 2922, 2852, 1703, 1542, 1352, 1217 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{29}N_2O_4$ 337.2127, found 337.2148.

***S*-Benzyl phenylcarbamothioate 6d.**



White solid; (87 mg, 71 %), mp 84-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.39 (d, *J* = 5.6 Hz, 2H), 7.36-7.35 (d, *J* = 4.8 Hz, 2H), 7.31-7.29 (m, 4H), 7.25-7.24 (t, *J* = 2.4 Hz, 1H), 7.12-7.09 (t, *J* = 4.8 Hz, 1H), 4.22 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 165.6, 138.0, 137.7, 129.2, 129.0, 128.7, 127.4, 124.7, 120.0, 34.6 cm^{-1}; FT-IR (KBr) 3243, 3038, 2925, 1653, 1535, 1242, 1165, 751, 701 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{14}NOS$ 244.0796, found 244.0796.

***S*-*p*-Tolyl phenylcarbamothioate 6e.**



White solid; (90 mg, 74 %), mp 129-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.49 (d, *J* = 8 Hz, 2H), 7.37-7.35 (d, *J* = 8 Hz, 2H), 7.30-7.25 (m, 4H), 7.15 (br, 1H), 7.11-7.09 (t, *J* = 2.4 Hz, 1H), 7.12-7.09 (d, *J* = 7.2 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 165.0, 140.6, 137.7, 135.8, 130.6, 129.2, 124.7, 124.6, 119.6, 21.5 cm^{-1}; FT-IR (KBr) 3258, 3012, 2976, 1662, 1541, 1233, 1196, 784, 695 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{14}NOS$ 244.0796, found 244.0818.

3.7. References

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3.8. Selected Spectra

3.8.1 NMR (^{1}H and ^{13}C) spectra of compounds

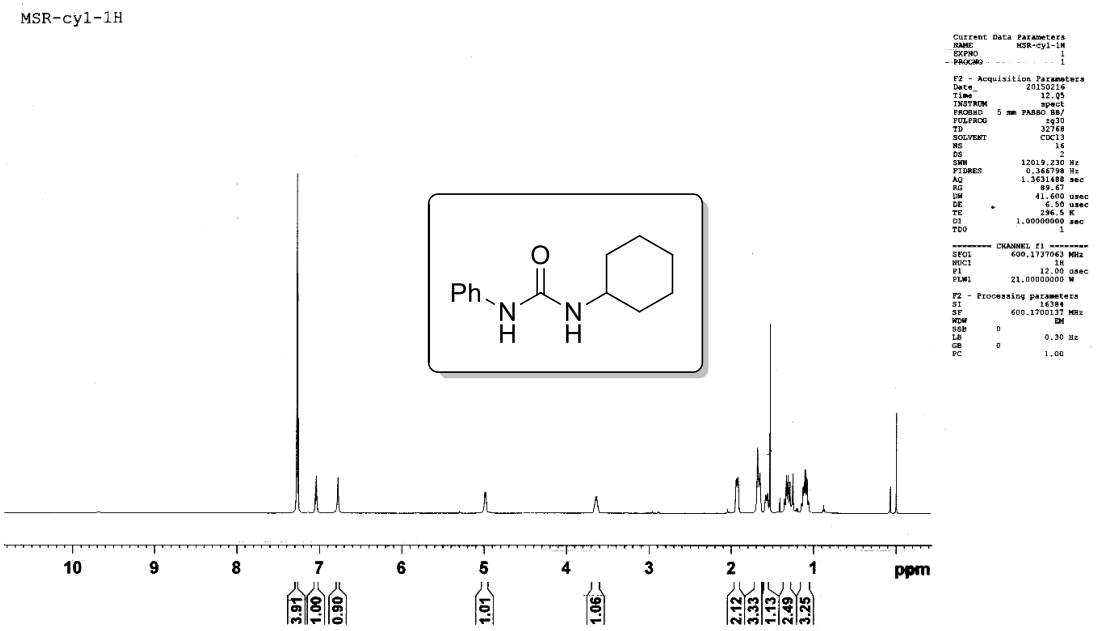


Figure 3.8.1.1. *^{1}H NMR spectra of compound* ***3a***

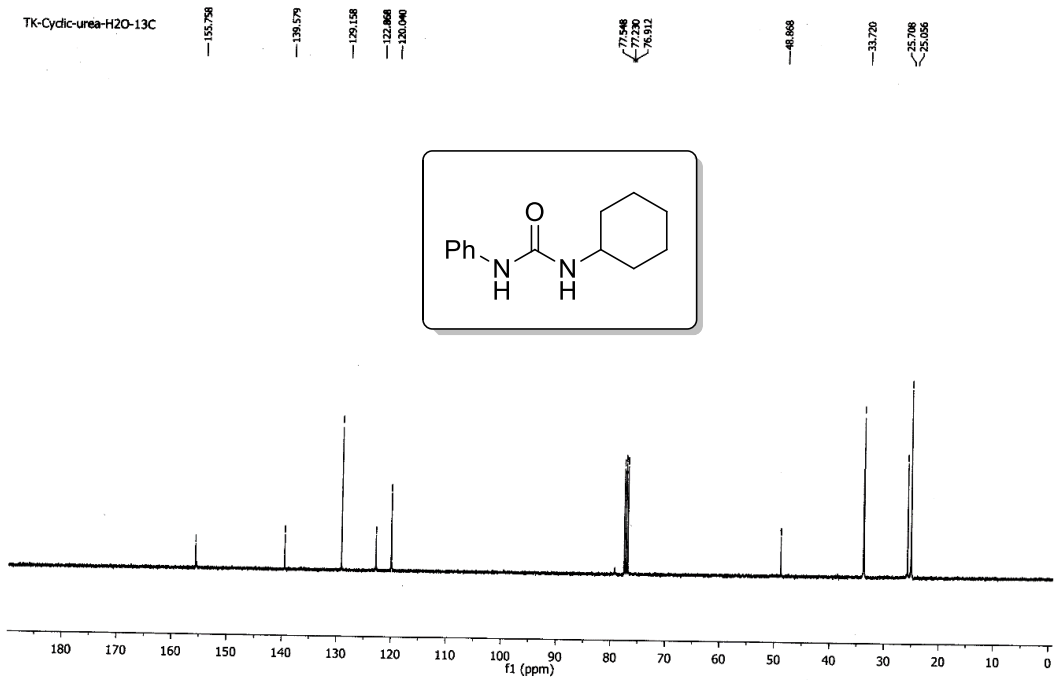


Figure 3.8.1.2. *^{13}C NMR spectra of compound* ***3a***

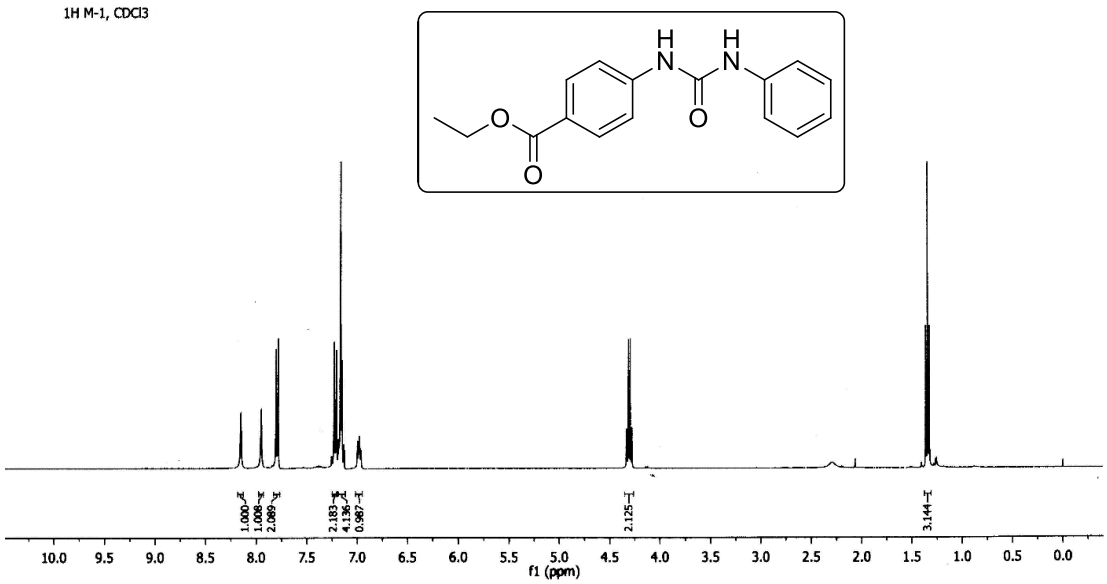


Figure 3.8.1.3. *^{1}H NMR spectra of compound* ***3h***

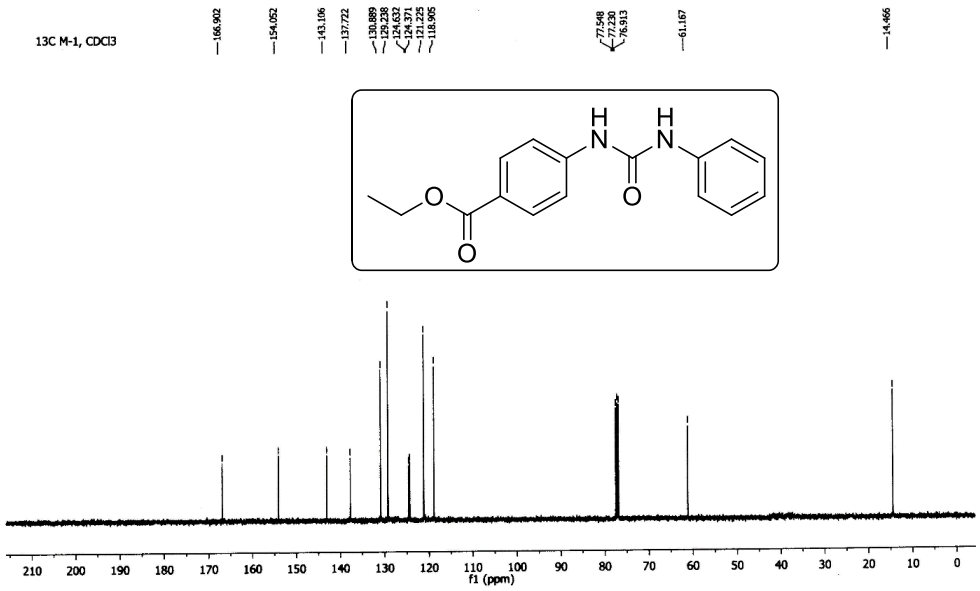


Figure 3.8.1.4. *^{13}C NMR spectra of compound* ***3h***

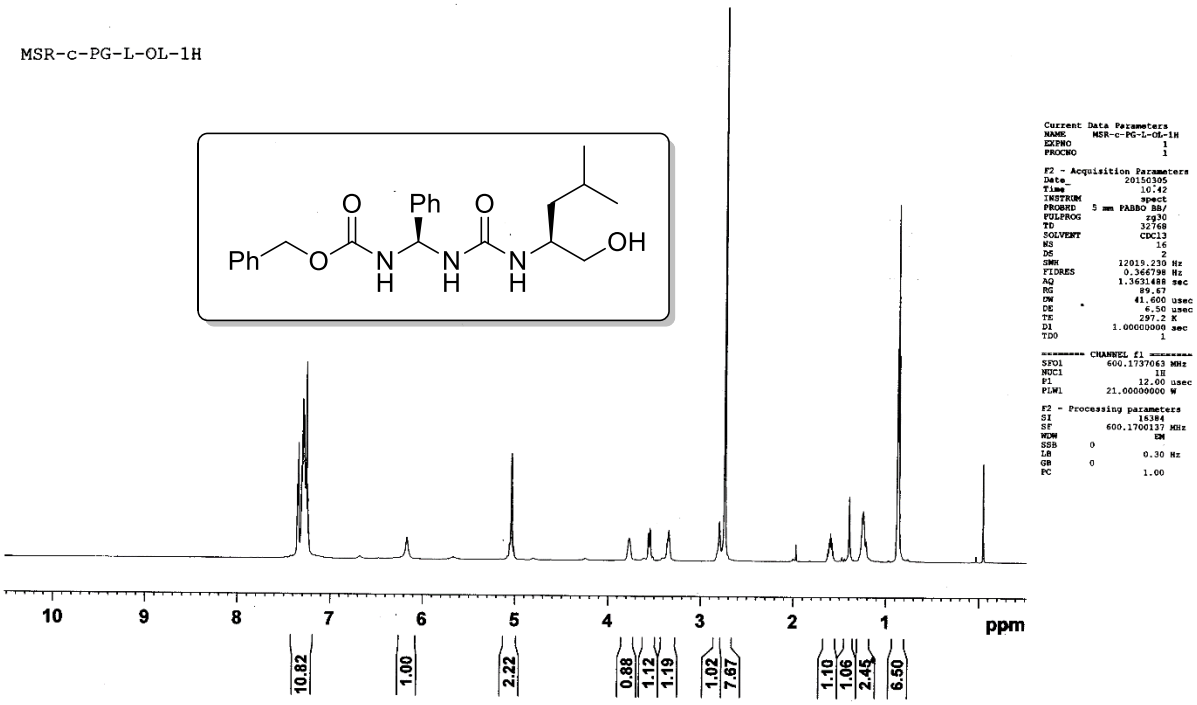


Figure 3.8.1.5. *^{1}H NMR spectra of compound **3l***

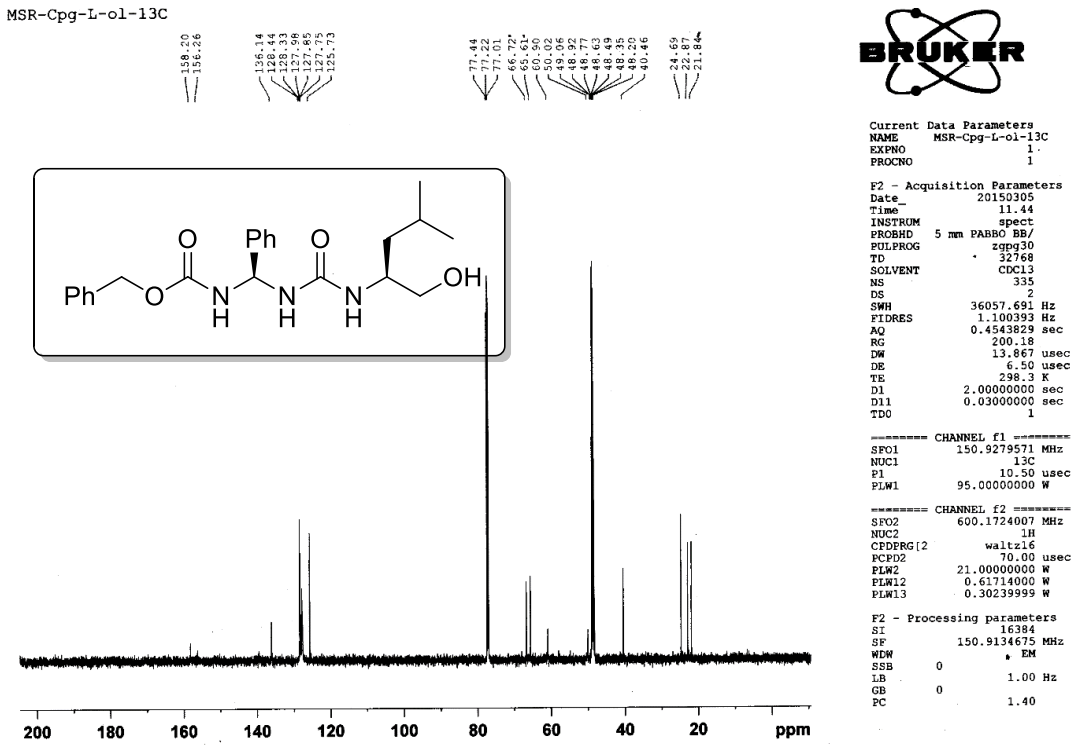


Figure 3.8.1.3. *^{13}C NMR spectra of compound **3l***

3.8.2 HPLC Data for racemization study

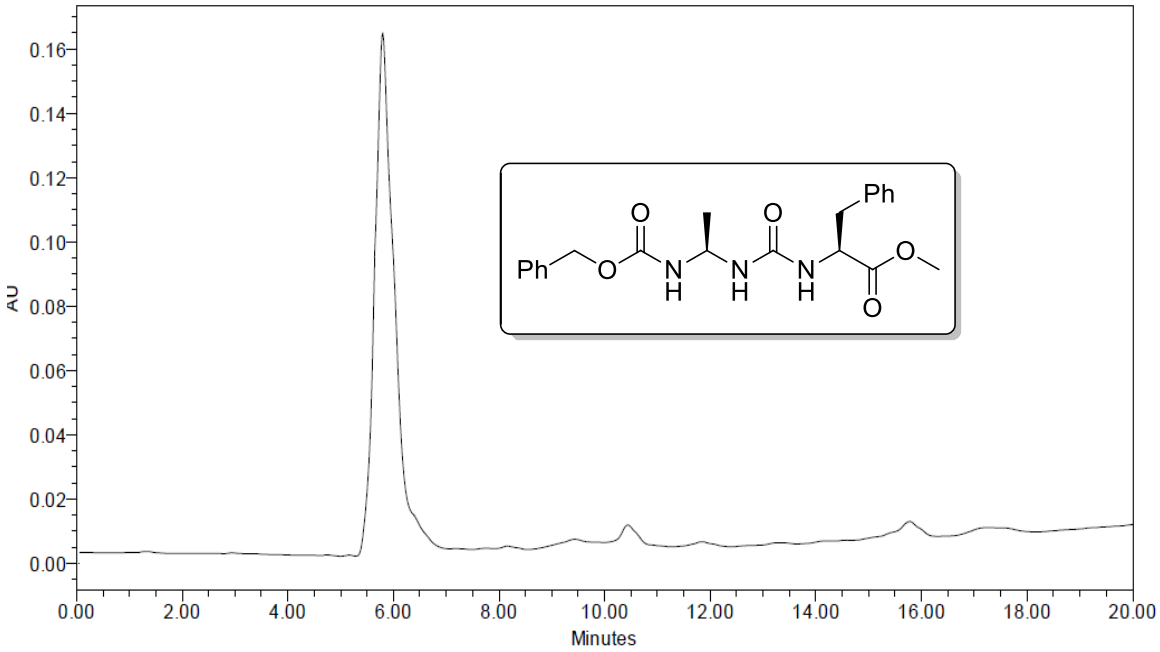


Figure 3.8.2.1. *HPLC spectra of compound* ***3j***

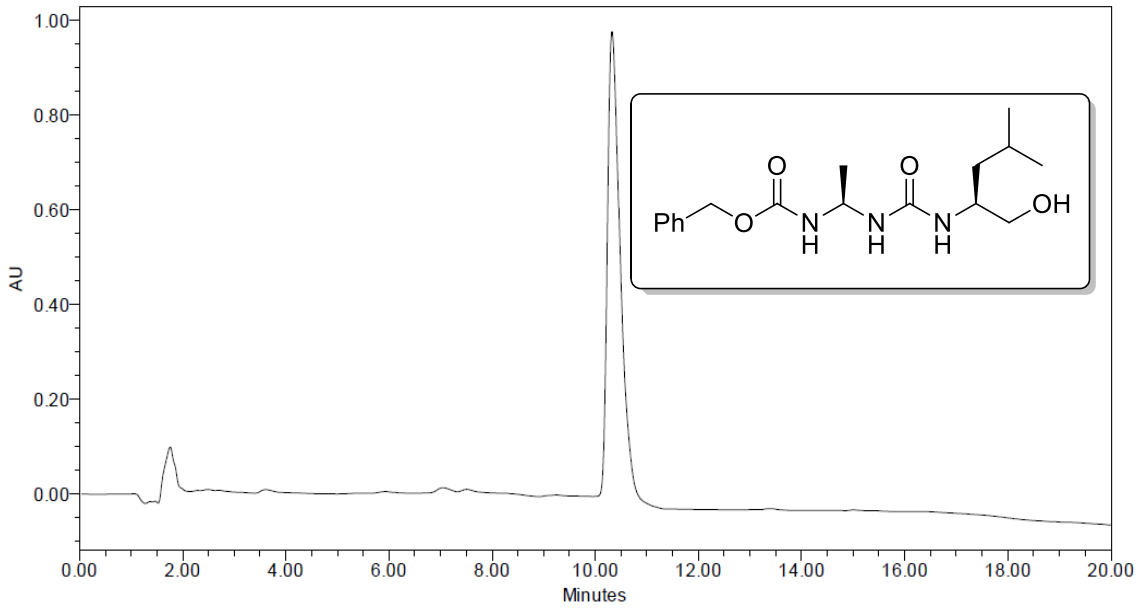


Figure 3.8.2.2. *HPLC spectra of compound* ***3k***

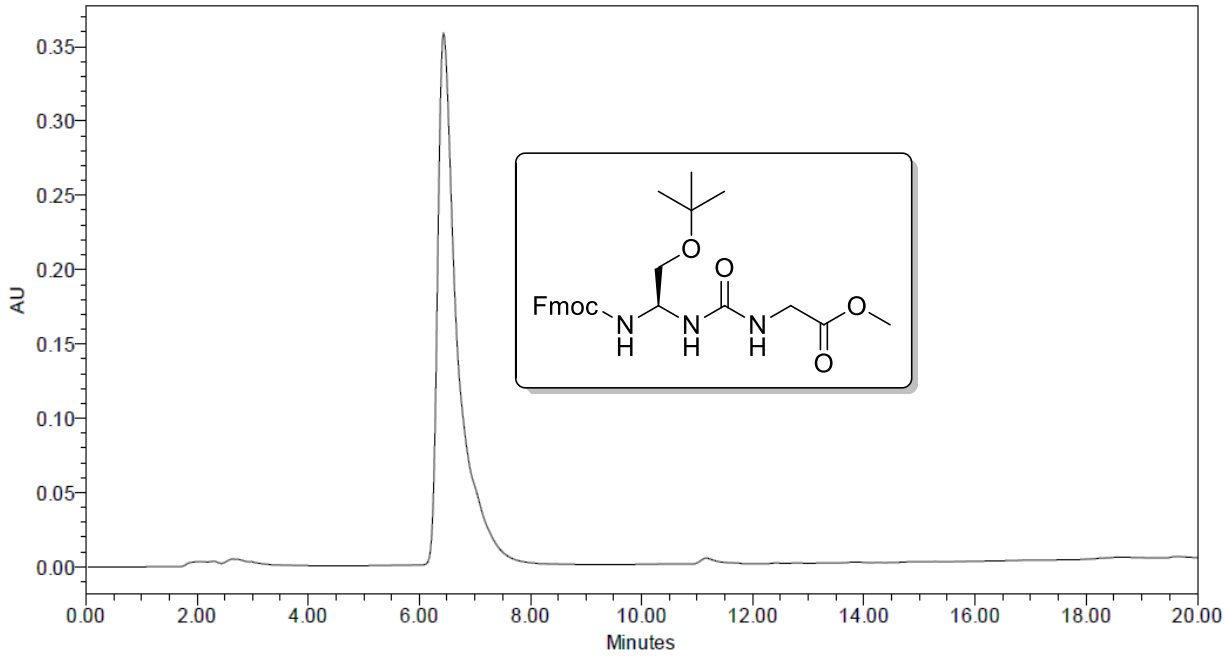


Figure 3.8.2.3. *HPLC spectra of compound* ***3m***

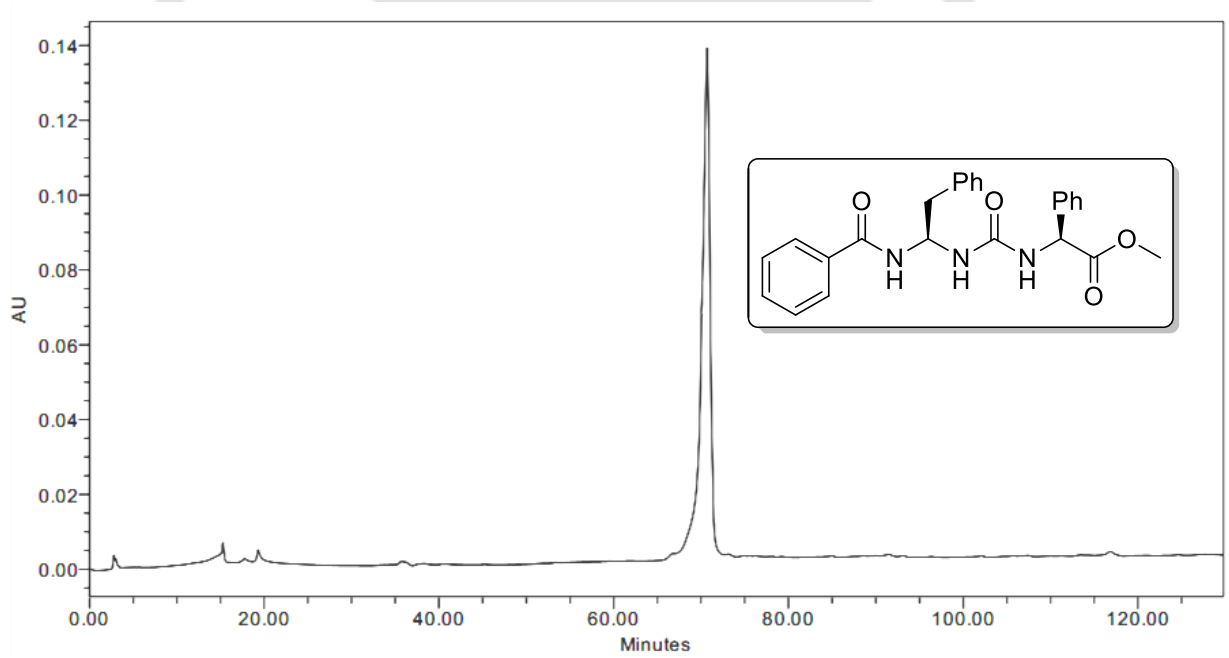


Figure 3.8.2.4. *HPLC spectra of compound* ***3r.*** *(C18 analytical column, and a gradient of 5% to 30% acetonitrile in water during first 20 min, then increasing amount of acetonitrile from 30% to 70% till 200 min was used for proper separation)*

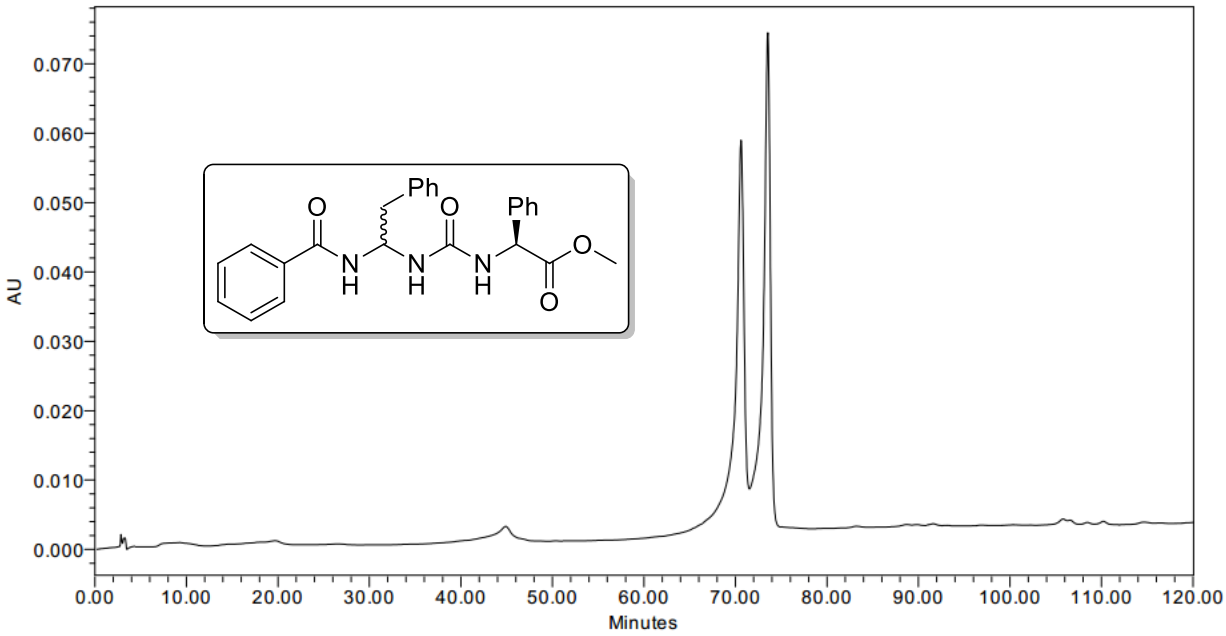


Figure 3.8.2.5.. *HPLC spectra of compound* ***3s.*** *(C18 analytical column, and a gradient of 5% to 30% acetonitrile in water during first 20 min, then increasing amount of acetonitrile from 30% to 70% till 200 min was used for proper separation. Run stopped at 120 min.)*

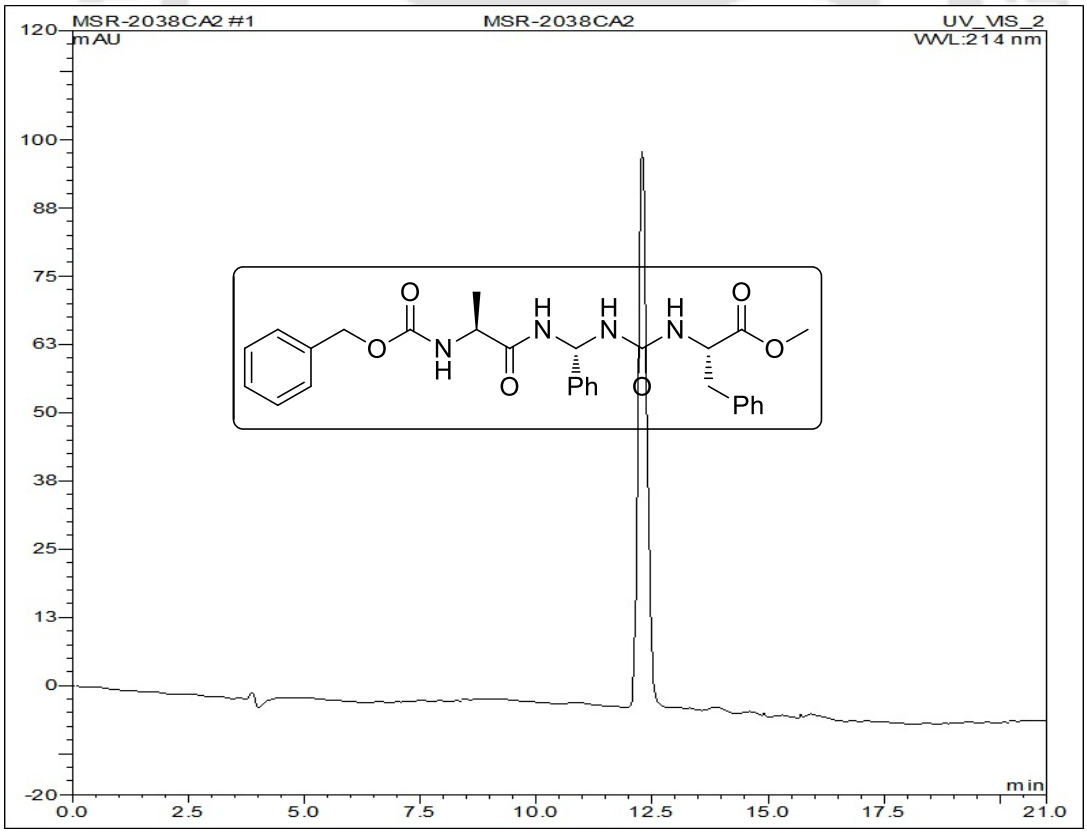


Figure 3.8.2.6. *HPLC spectra of compound* ***5a***

3.8.3 Mechanism Studies

^{13}C NMR Spectrum

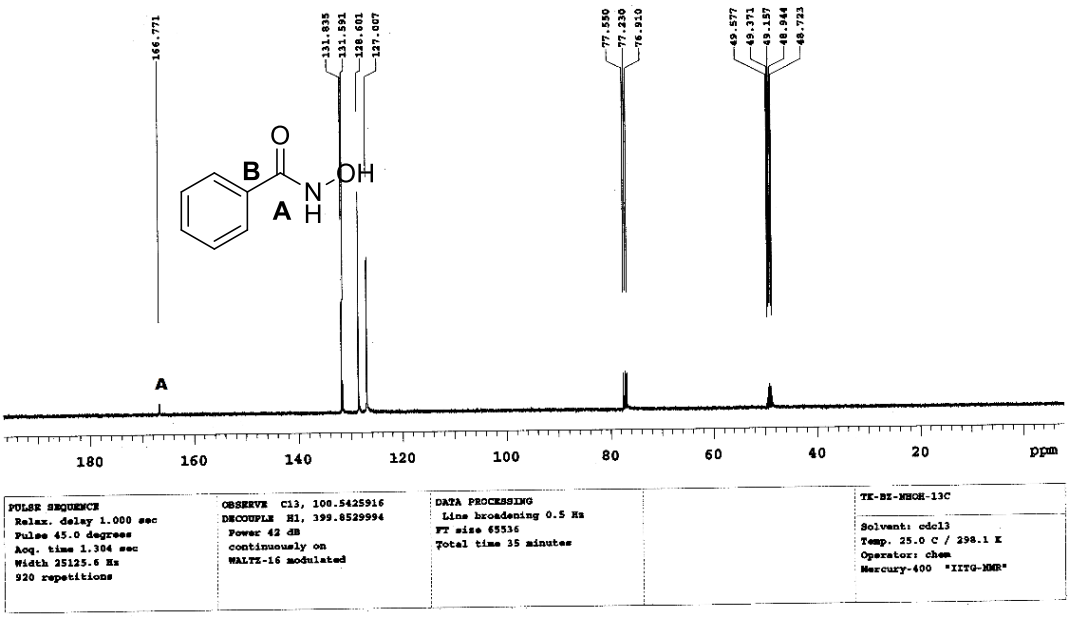


Figure 3.8.3.1. *^{13}C NMR spectra of benzhydroxamic acid*

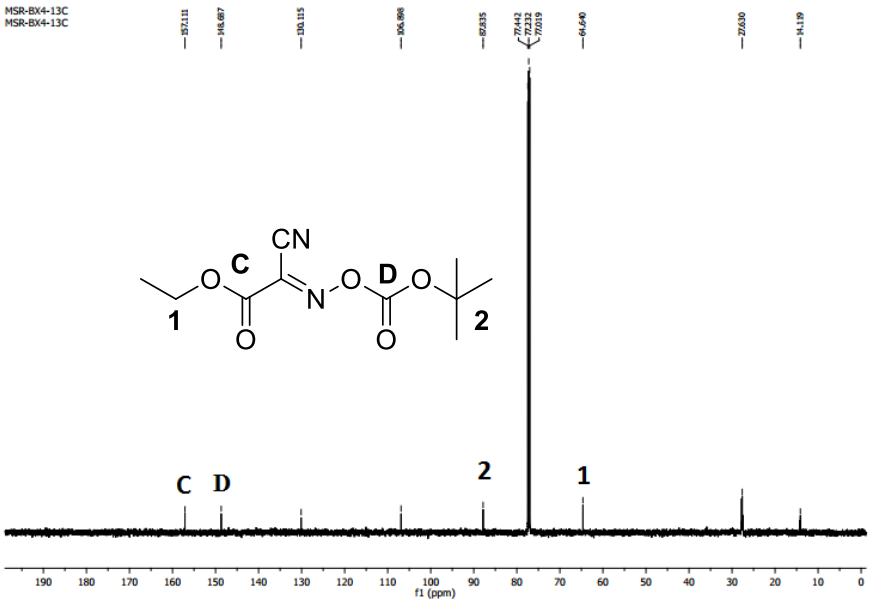


Figure 3.8.3.2. *^{13}C NMR spectra of Boc-Oxyma*

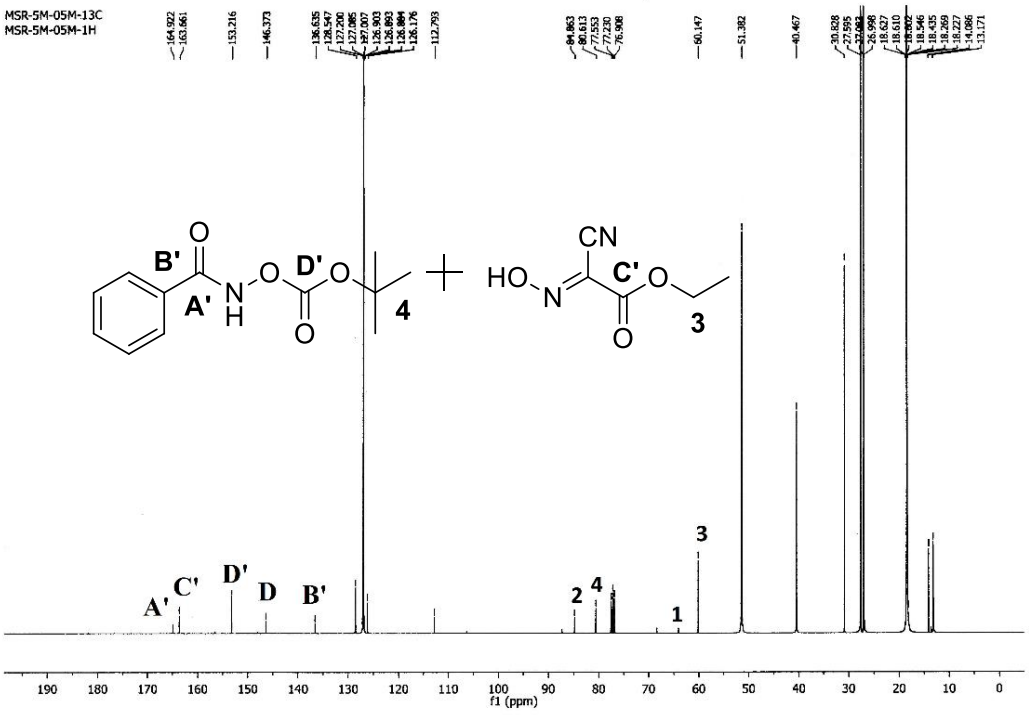


Figure 3.8.3.3. *^{13}C NMR spectra of reaction intermediates after 5 min*

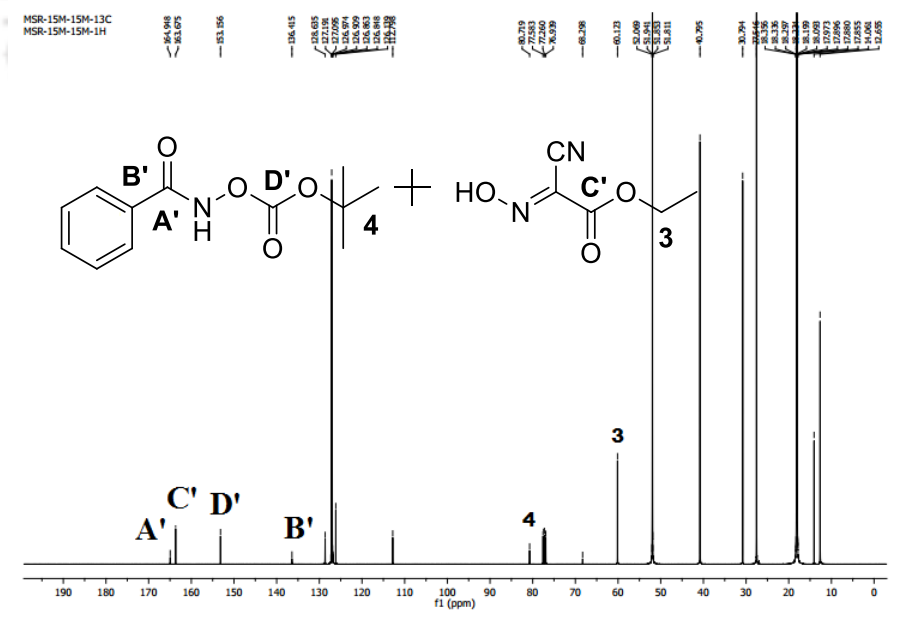


Figure 3.8.3.4. *^{13}C NMR spectra of reaction intermediates after 15 min*

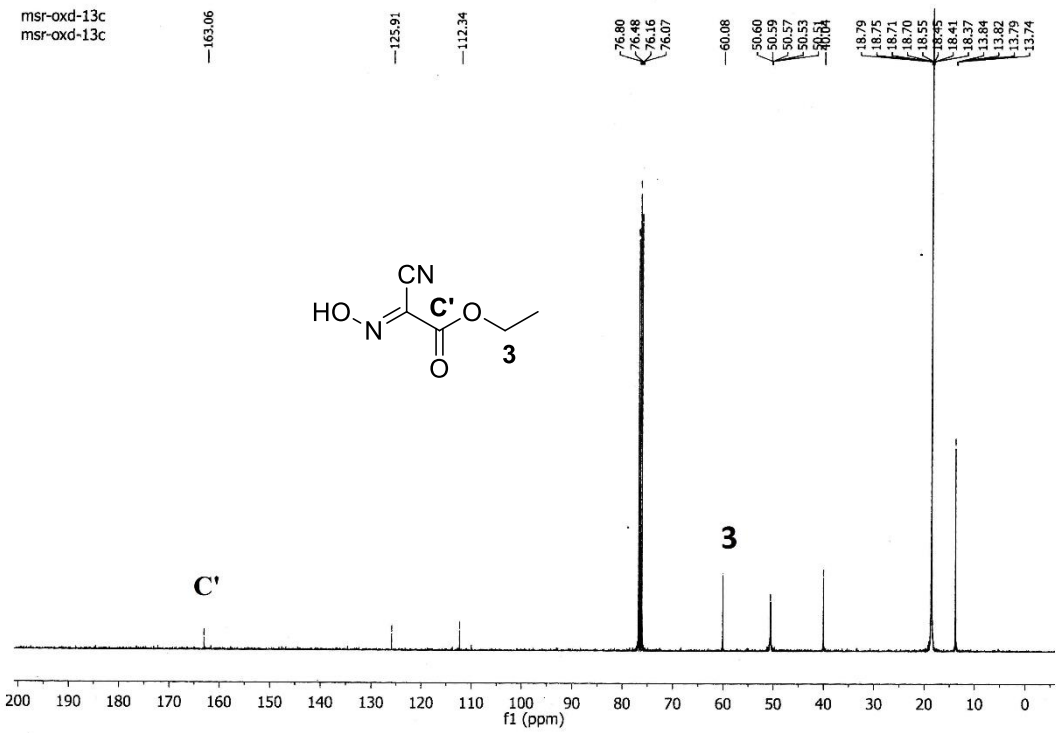


Figure 3.8.3.5. *^{13}C NMR spectra of Oxyma in the presence of base*

Sample Name	MSR-WR-VE	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Some Ions Missed
Data Filename	MSR-WR-VE.d	**ACQ Method**		**Comment**		**Acquired Time**	2/23/2016 12:20:38 PM

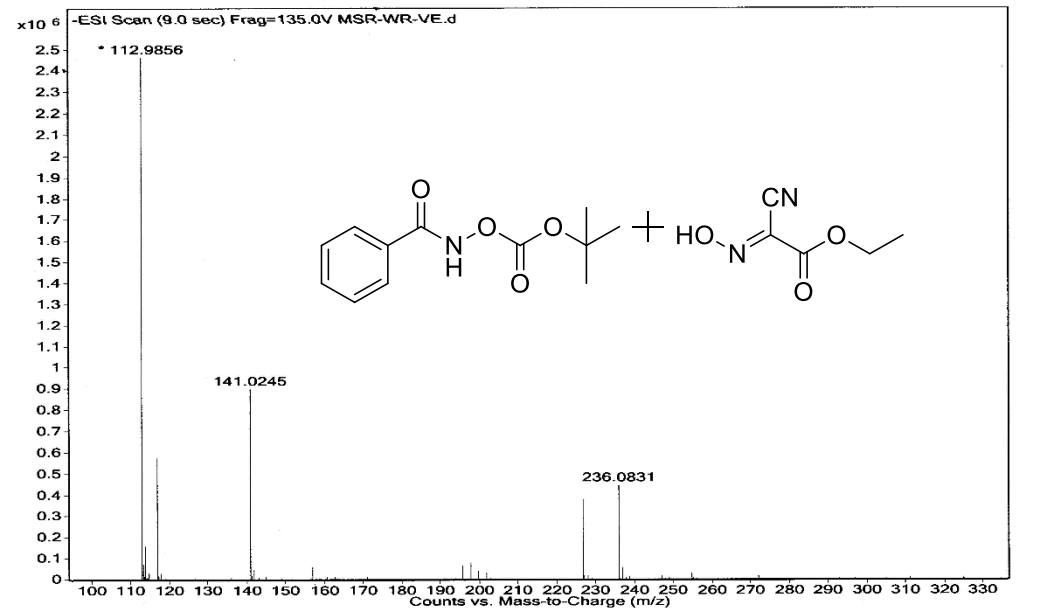


Figure 3.8.3.6. *ESI Mass spectra reaction after 15 min (-Ve mode)*

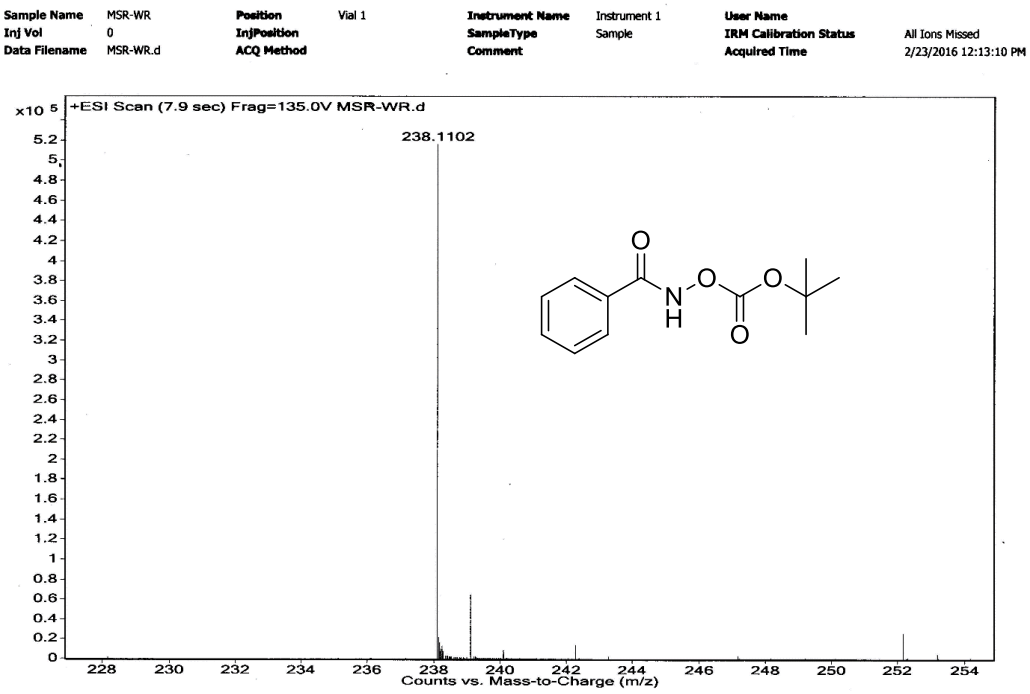


Figure 3.8.3.7. *ESI Mass spectra reaction after 15 min (+Ve mode)*

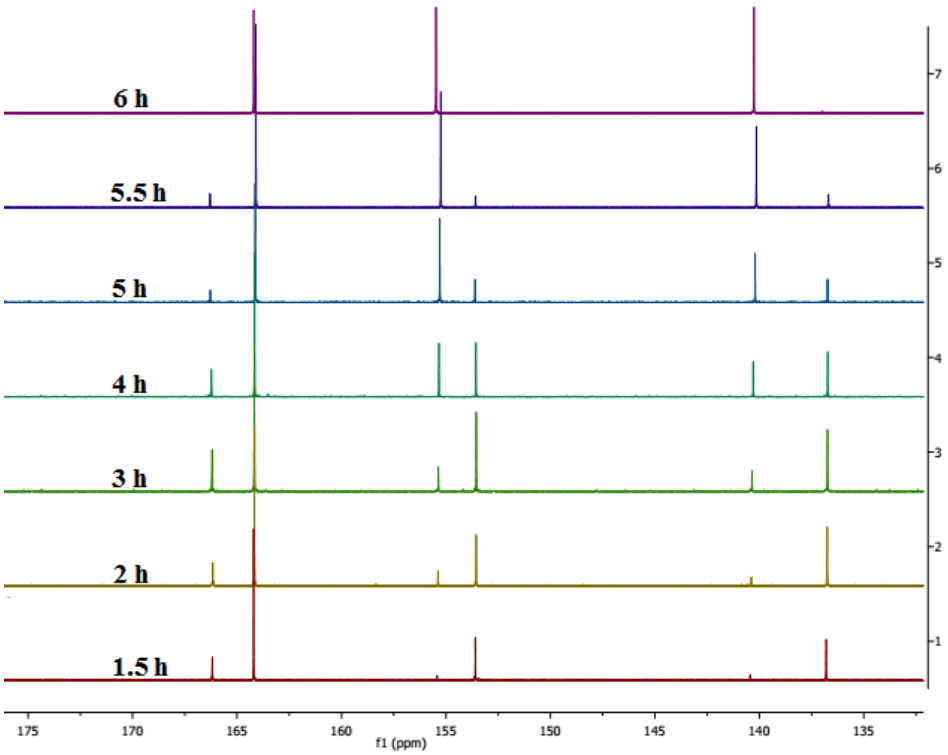


Figure *3.8.3.8.* ^{13}C NMR strack spectra of reaction 90 min to 6 h

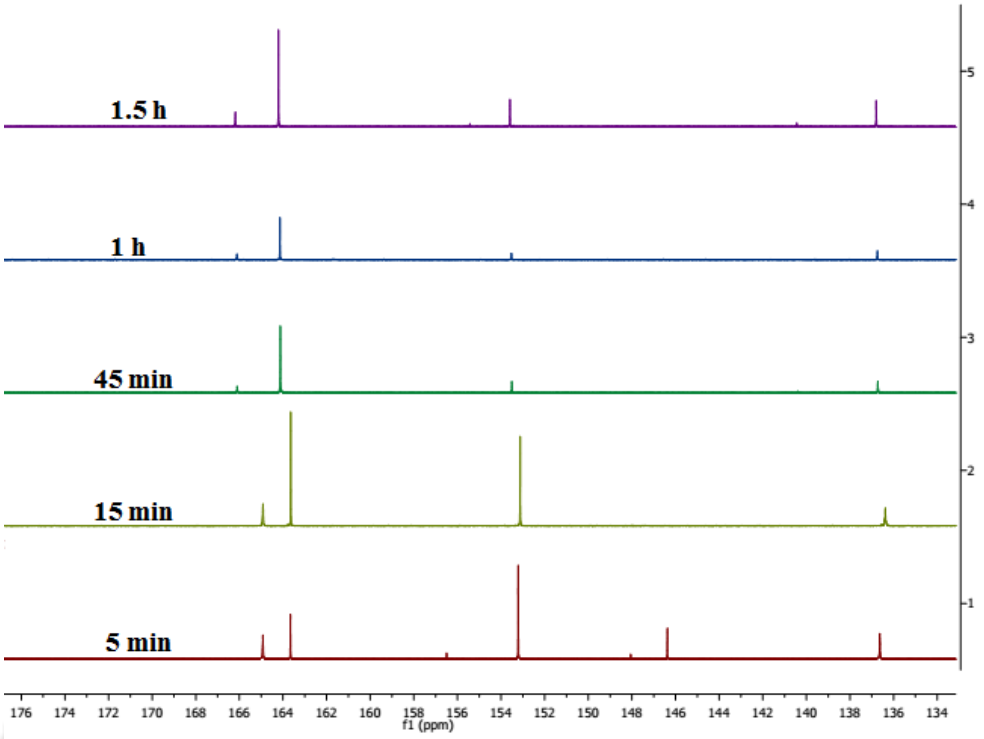


Figure 3.8.3.9. *^{13}C NMR strack spectra of reaction 5 min to 90 mint*

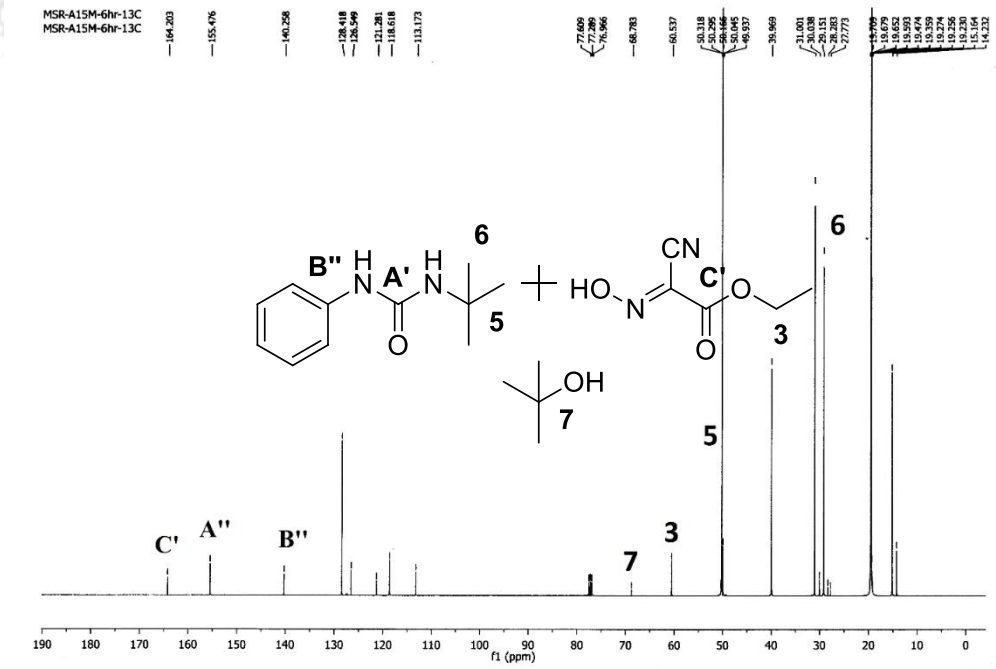


Figure 3.8.3.10. *^{13}C NMR spectra of reaction after 6 h*

^{1}H NMR Spectrum

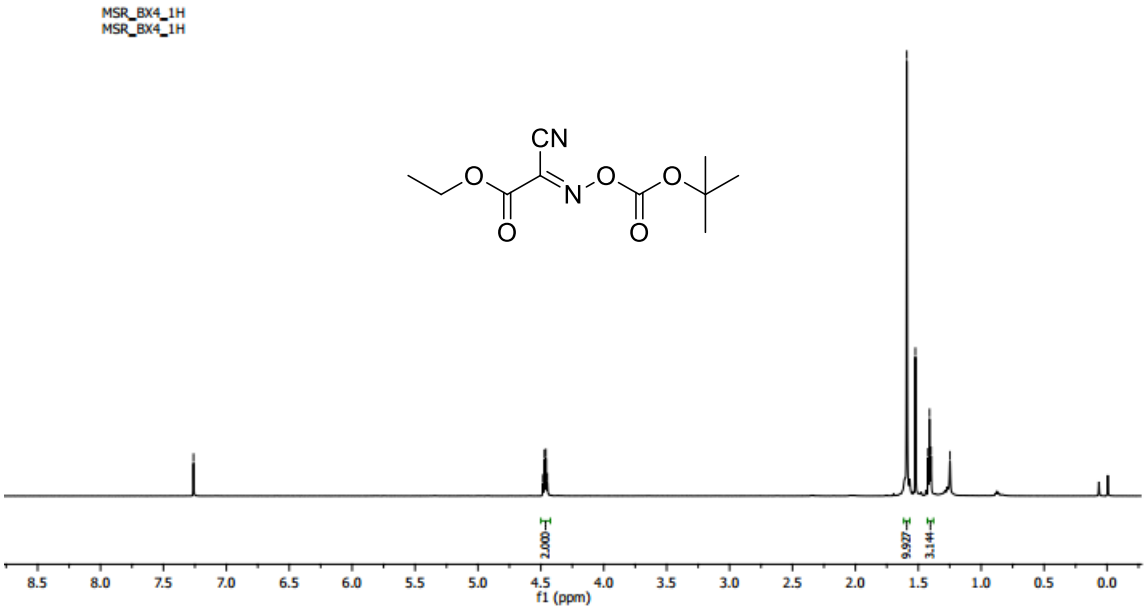


Figure 3.8.3.11. *^{1}H NMR spectra of Boc-Oxyma*

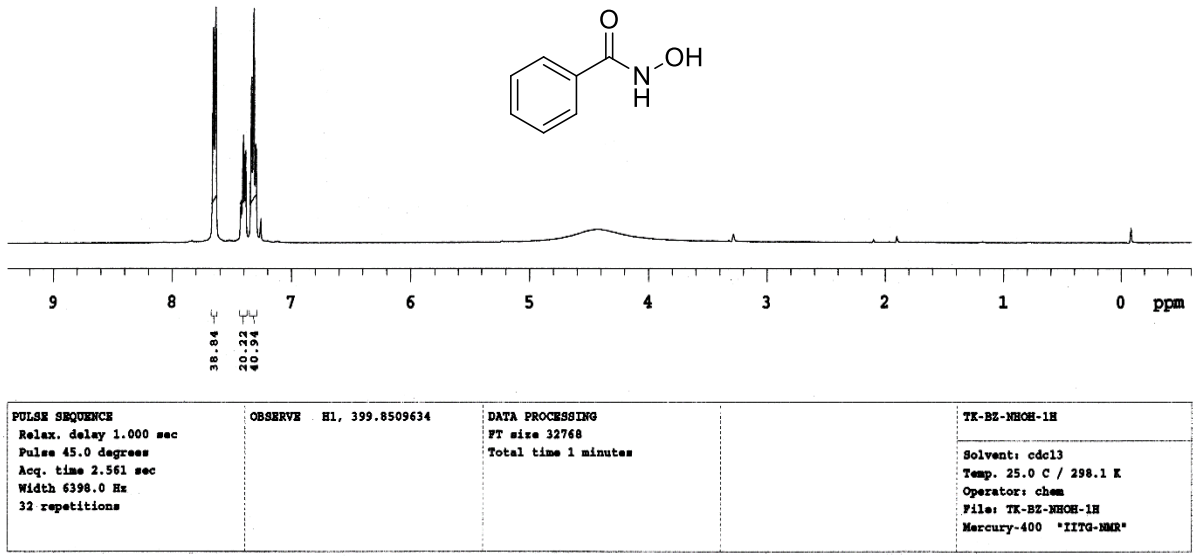


Figure 3.8.3.12. *^{1}H NMR spectra of benzhydroxamic acid*

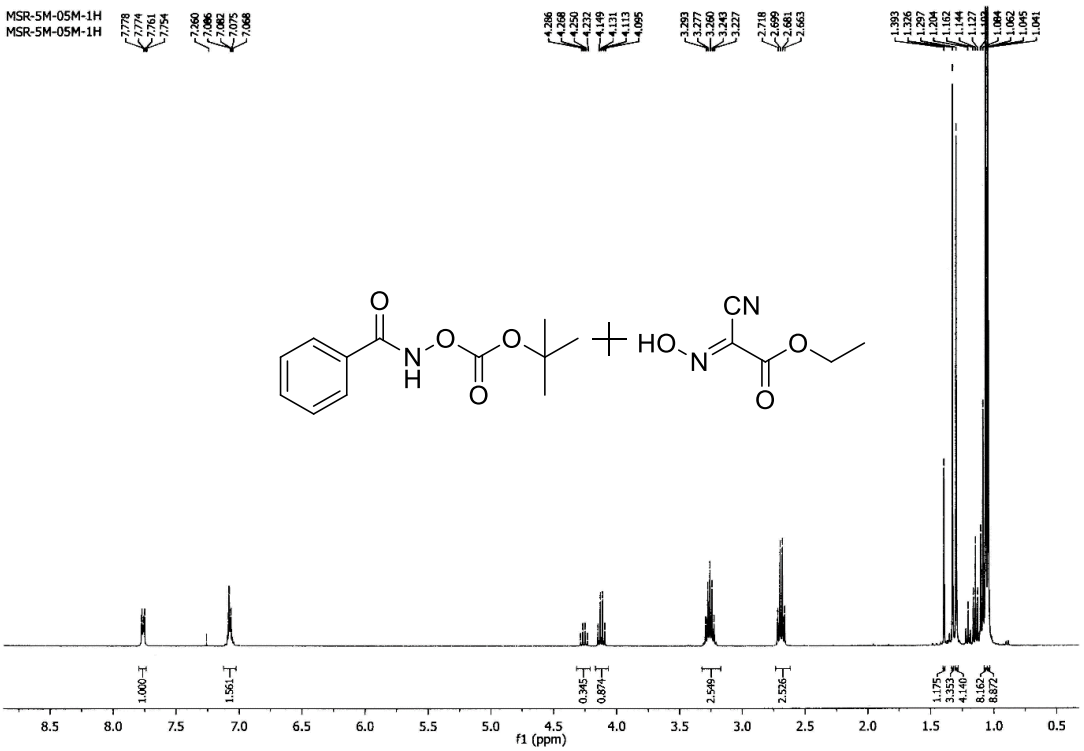


Figure 3.8.3.13.. *^{1}H NMR spectra reaction after 5 min*

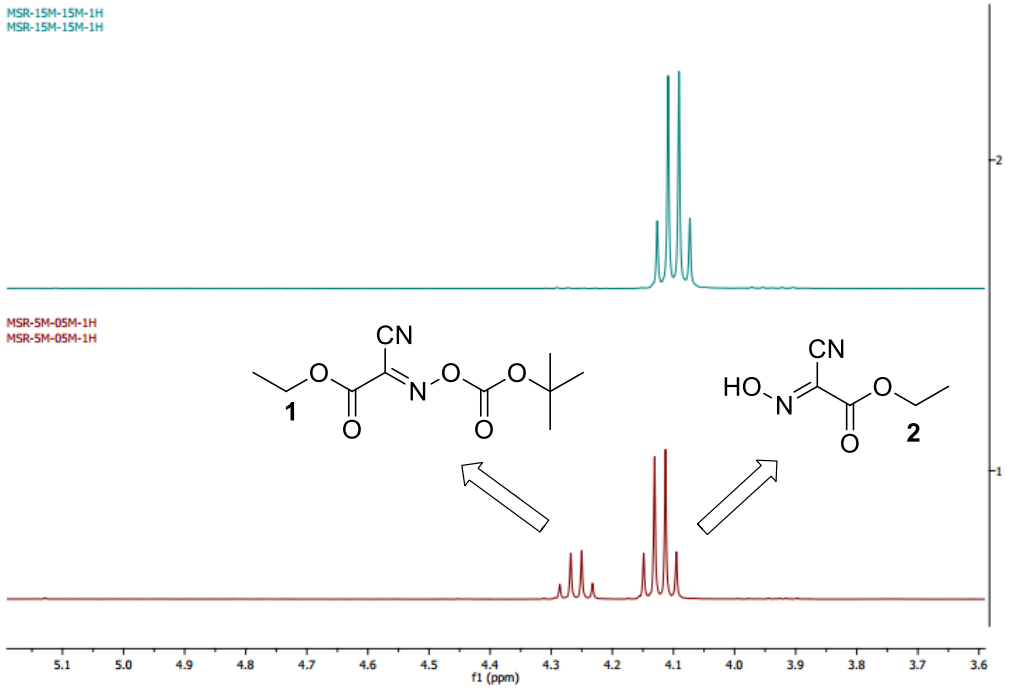


Figure 3.8.3.14. *^{1}H NMR spectra of reaction 5 min to 15 min*

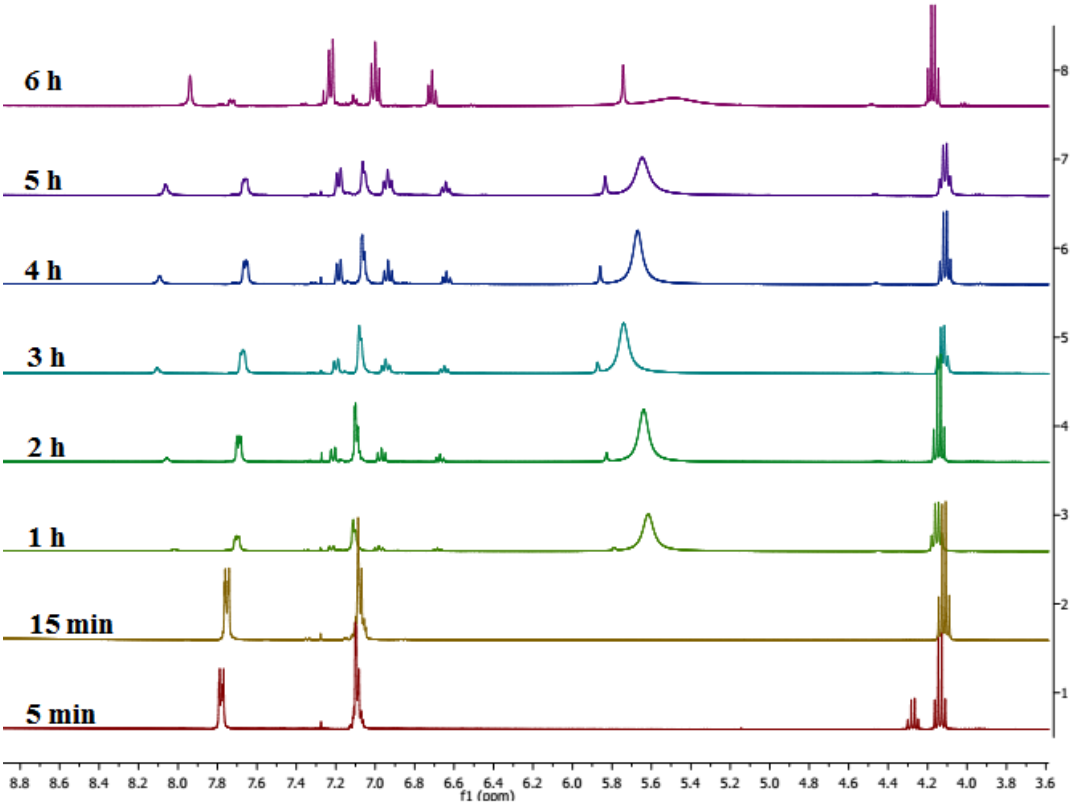


Figure 3.8.3.15. *^{1}H NMR stracked spectra of reaction 5 min to 6 h*

3.8.4. Crystal data

Table 3.8.4.1. Crystallographic parameters of 1-(*tert*-Butyl)-3-phenylurea **3b**

Compound No.	**3b**
Formulae	$C_9H_{10}O_3N_2$
CCDC NO	1484427
Formula. wt.	192.26
Crystal system	orthorhombic
Space group	Pbca
a (Å)	11.9658(5)
b (Å)	9.4934(4)
c (Å)	19.0906(8)
α(°)	90.00

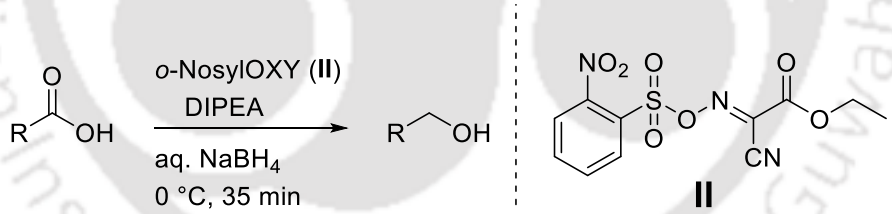
β(°)	90.00
γ(°)	90.00
V/ Å^3	2168.62(16)
Z	8
Density/Mgm^{-3}	1.178
Abs. Coeff. /mm^{-1}	0.077
F(000)	832
Total no. of reflections	16740
Reflections, $I > 2\sigma(I)$	0.0298
Max. 2θ/°	25.25
Ranges (h, k, l)	$-14 \leq h \leq 13$ $-11 \leq k \leq 11$ $-22 \leq l \leq 22$
Complete to 2θ (%)	25.25
Data/ Restraints/Parameters	0.0985/0/130
Goof (F^2)	1.063
R indices [$I > 2\sigma(I)$]	0.0491
R indices (all data)	0.0634

Chapter 4

Mild and Efficient Method for the Reduction of Carboxylic Acid to Alcohol using *Ortho*-NosylOXY

β-Amino alcohols are very useful and versatile class of organic compounds, widely spread in medicinal and synthetic organic chemistry (Chapter 1, section 1.2.4). There are many synthetic methods reported for the synthesis of *β*-amino alcohols (we have discussed few methodologies in Chapter 1, section 1.3.3).

However, the reported methodologies have some drawbacks such as the existing coupling reagents (2,4,6-trichloro-1,3,5-triazine, cyanuric fluoride, Boronic acid, BOP, *etc*.) are difficult to handle, hazardous and expensive, and they generate a substantial amount of undesired by-products. These reagents require harsh reaction conditions and toxic chemicals for their preparation. Non-recyclability and inability in suppressing the racemization are additional problems associated with the existing reagents. Furthermore, the existing methods require metal catalysts, high temperature, relatively longer reaction time, and incompatible with other functionalities in the substrate.



Scheme 4.1. *A general scheme for the reduction of carboxylic acids using o-NosylOXY and $NaBH_4$ system*

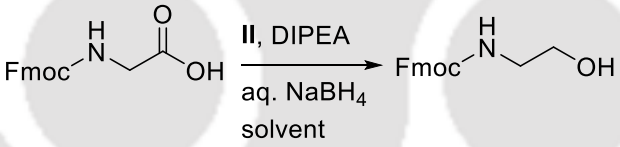
To tackle the drawbacks mentioned above, we have developed a mild, efficient and chemoselective approach for the synthesis of *β*-amino alcohols from the corresponding carboxylic acids using ethyl-2-cyano-2-(2-nitrobenzenesulfonyloxyimino) acetate (*o*-NosylOXY, **II**) as an acid activator and $NaBH_4$ as mild reductant (Scheme 4.1). Recently, our group reported *o*-NosylOXY, which is an efficient coupling reagent for the conversion of the carboxylic acids to amides, peptides, esters, thioesters, hydroxamates,[1] ureas,[2] and heterocyclic compounds[3] such as benzoxazoles and benzothiazoles as well as the conversion of aldoximes to nitriles.[4] The significant advantages of this reagent (**II)** are ease of preparation, excellent racemization suppression capability, and recyclable nature. *o*-

NosylOXY (**II)** was synthesized simply by the reaction of Oxyma (ethyl 2-hydroxyimino 2-cyanoacetate) with *ortho*-nitrobenzenesulfonyl chloride in the presence of diisopropyl-ethylamine (DIPEA) under the nitrogen atmosphere at 0 °C for 2 h.

4.1. Optimization and substrates scope for the synthesis alcohols

The reduction of the carboxylic acid was optimized using Fmoc-Gly-OH as a model substrate. Initially, we screened various solvents such as DCM, THF, CH_3CN, EtOAc, CH_3OH, H_2O, and DMF with one equivalent of $NaBH_4$ (Table 4.1.1). Among them, acetonitrile was found to be efficient and produced the highest yield (entry 4). Methanol also gave the desired product in 30% (entry 1). In this case, 62% of the methylated product was isolated. Next, we screened the equivalence of $NaBH_4$ using same model substrate in CH_3CN. The desired product was obtained in 90% yield (entry 4) with the stoichiometric amount of $NaBH_4$, and the yield of desired product was reduced to 75% (entry 8) when the amount of $NaBH_4$ was reduced to 0.5 equiv. No significant increment in the yield was observed using an excess of $NaBH_4$ (entries 9 and 10).

Table 4.1.1. Optimization of the reaction conditions[a]



Entry	$NaBH_4$ (eqiuv)	Solvent	Yield (%)[b]
1	1	MeOH	30
2	1	DCM	85
3	1	EtOAc	82
4	**1**	**ACN**	**90**
5	1	THF	74
6	1	DMF	43

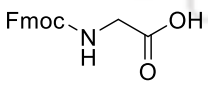
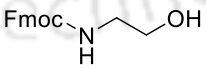
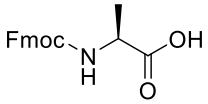
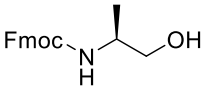
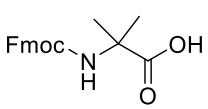
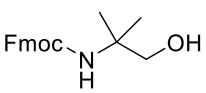
Continued……

Entry	$NaBH_4$ (eqiuv)	Solvent	Yield (%)[b]
7	1	H_2O	0
8	0.5	ACN	75
9	1.5	ACN	90
10	2	ACN	90

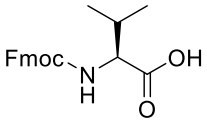
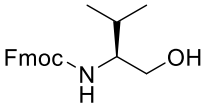
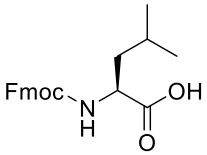
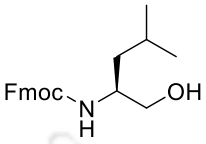
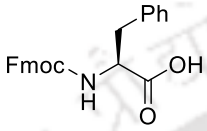
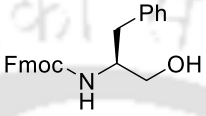
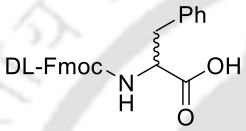
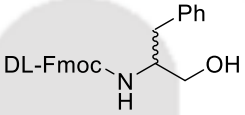
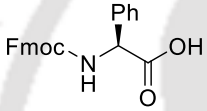
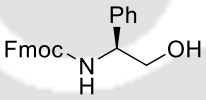
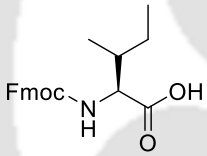
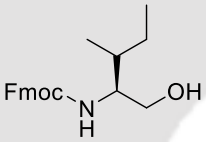
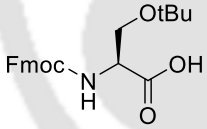
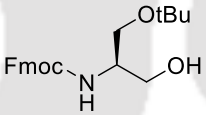
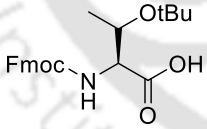
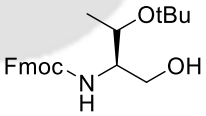
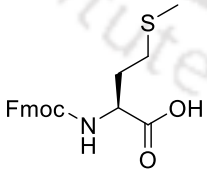
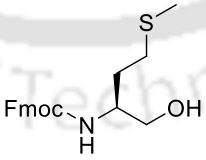
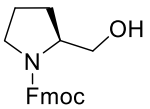
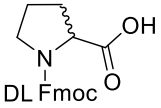
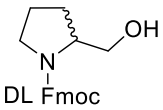
[a] Reaction conditions: Fmoc-Gly-OH (0.5 mmol), *o*-NosylOXY (0.5 mmol), DIPEA (0.5 mmol), $NaBH_4$ (varied amount) and various solvents (3 mL) at 0 °C. Reaction time is 35 min. [b] Yields refer to the isolated yield.

With the established optimal reaction conditions in hand, the scope of the reaction was investigated with a wide variety of carboxylic acids, and the results were summarized in table 4.1.2. The reaction worked well with the standard *N*-protecting groups of amino acids, such as Fmoc (entries 1-18), Boc (entries 19-20), and Cbz (entries 21-22), and also compatible with various side chain protecting groups, such as ^{t}Bu (entries 10,11 and15), Pbf (entry 16), Boc (entry 17) and Trt (entries 18). The yields were also found to be good to excellent in the case of sterically hindered amino acids, such as leucine, isoleucine, phenylalanine, Aib, proline, valine and phenylglycine (Table 4.1.2).

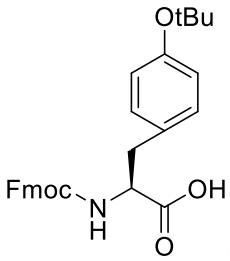
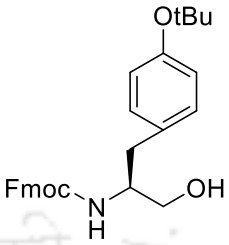
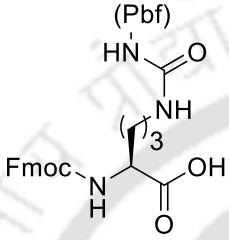
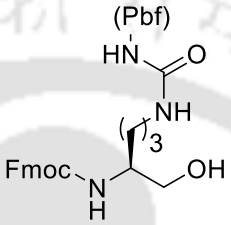
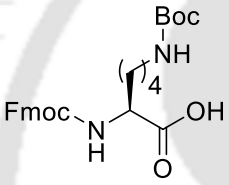
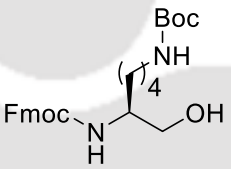
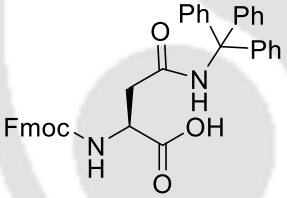
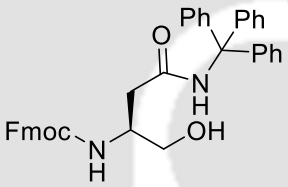
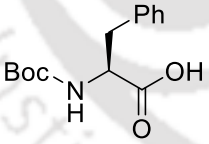
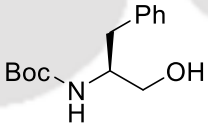
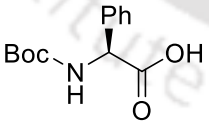
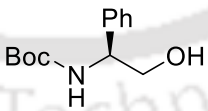
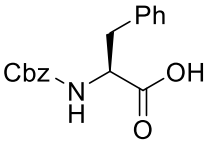
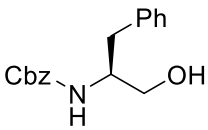
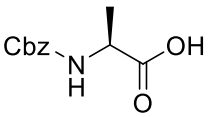
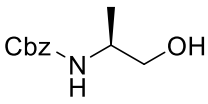
Table 4.1.2. The wide scope of the synthesis of the *β*-amino alcohols from the *N*-protected amino acids by using **II**[a]

Entry	Acid	Product		
		Structure	Id	Yield (%)[b]
1			**2a**	90
2			**2b**	85
3			**2c**	72

Continued……

Entry	Acid	Product		
		Structure	Id	Yield (%)[b]
4			**2d**	81
5			**2e**	84
6			**2f**	79
7			**2g**	77
8			**2h**	80
9			**2i**	83
10			**2j**	76
11			**2k**	72
12			**2l**	78
13			**2m**	69
14			**2n**	69

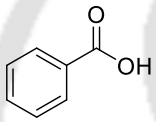
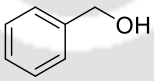
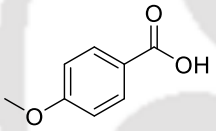
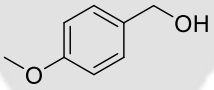
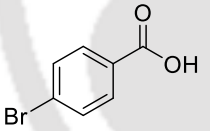
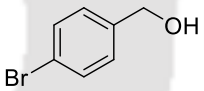
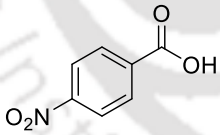
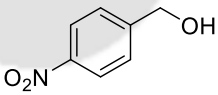
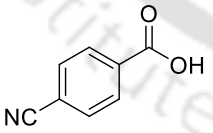
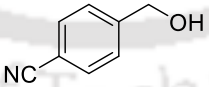
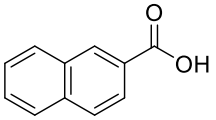
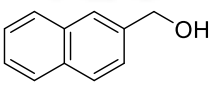
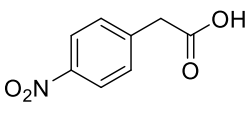
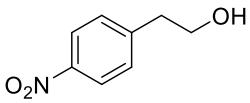
Continued……

Entry	Acid	Product		
		Structure	Id	Yield (%)[b]
15			**2o**	65
16			**2p**	63
17			**2q**	68
18			**2r**	62
19			**2s**	78
20			**2t**	76
21			**2u**	80
22			**2v**	83

[a] Reaction conditions: Acid (0.5 mmol), *o*-NosylOXY (0.5 mmol), DIPEA (0.5 mmol), $NaBH_4$ (0.5 mmol) and CH_3CN (3 mL) stirred for 35 min at 0 °C. [b] Isolated yield

Further, the efficiency of this protocol was studied by reducing a series of aromatic carboxylic acids (entries 1-6, Table 4.1.3) and an aliphatic carboxylic acid (entry 7) to corresponding alcohols. The functional groups, such as methoxy (entry 2), bromo (entry 3), nitro (entry 4) and cyano (entry 5) were tolerated in this method. Substrates having electron-withdrawing groups, like the nitro group and bromo group gave higher yields compared to the electron-donating groups, such as the methoxy group. The yields with the aliphatic acids (entry 7) were remarkably good. All the reactions were clean, and all the desired products were fully characterized.

Table 4.1.3. The reduction of the carboxylic acids into corresponding alcohols by using **II**[a]

Entry	Acid	Product		
		Structure	Id	Yield (%)[b]
1			**4a**	81
2			**4b**	84
3			**4c**	86
4			**4d**	89
5			**4e**	80
6			**4f**	70
7			**4g**	79

[a] Reaction conditions: Acid (1 mmol), *o*-NosylOXY (1 mmol), DIPEA (1 mmol), $NaBH_4$ (1 mmol) and CH_3CN (3 mL) stirred for 35 min at 0 °C. [b] Isolated yield

4.2. Racemization study

We also have investigated the racemization probability during the synthesis of *β*-amino alcohols. For that, we synthesized L-Fmoc-*β*-amino alcohols and DL-Fmoc-*β*-amino alcohols of phenylalanine using our protocol. These amino alcohols were directly loaded on a chiral HPLC column (Diacel, Chiral pack-ASH). In the case of L-amino alcohols, we observed one peak at 16 min corresponding to the single enantiomer, whereas, DL-amino alcohols exhibited two distinct peaks at 15 min and 17 min corresponding to two enantiomers (Figure 4.2.1, Figure 4.8.2.5 and Figure 4.8.2.6). To confirm, we have tested one more set of L and DL- *β*-amino alcohols of proline and observed similar results (Figure 4.8.2.8 and Figure 4.8.2.9). Remaining all L-*β*-amino alcohols exhibited single peaks corresponding to single enantiomers in respective HPLC profiles using similar eluent. These results confirm that the current protocol does not cause detectable racemization.

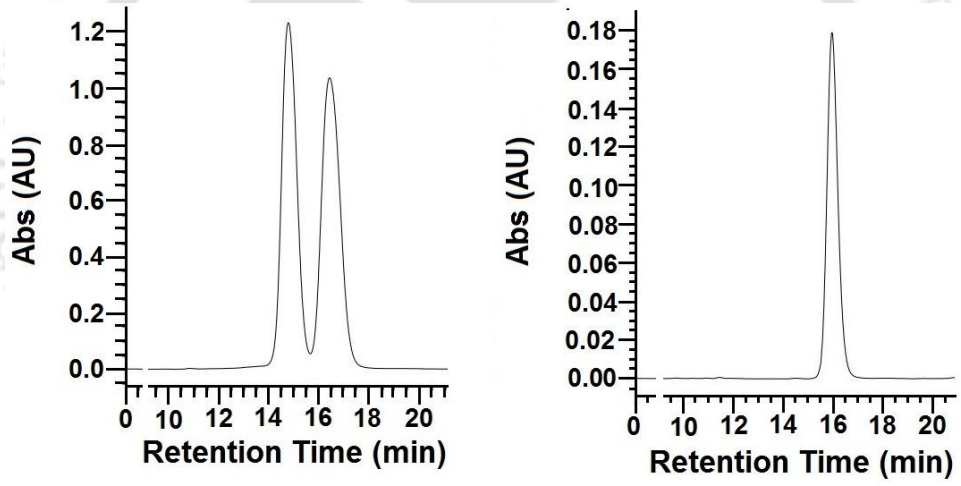
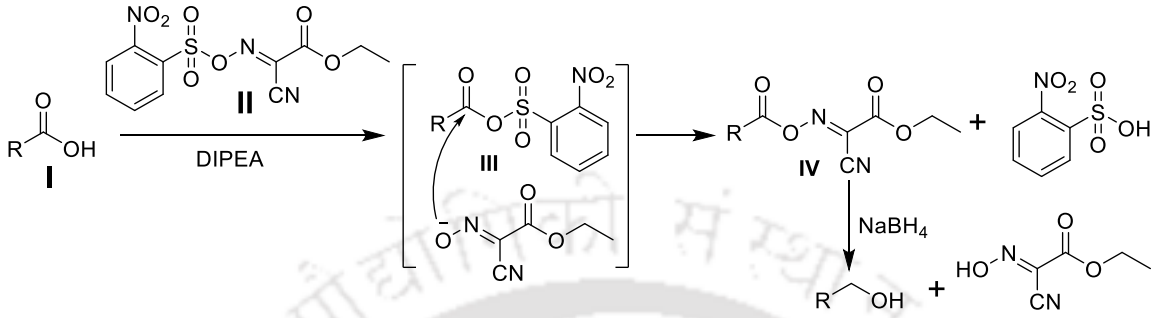


Figure 4.2.1. *HPLC profiles of L and DL-Fmoc-Phe-ol.*

4.3. Plausible Mechanism

Having demonstrated the substrate scope of *β*-amino alcohols, we turned our attention to the reaction mechanism. A probable mechanism is depicted in Scheme 4.3.1 based on existing literature.[5] Initially, the carboxylic acid (**I**) attacks the sulfonyl center of *o*-NosylOXY (**II**), resulting in activated sulphonate ester (**III**) and Oxyma anion. Further this anionic Oxyma attacks on the carbonyl carbon of **III** and results in the formation of the intermediate **IV**[3] with concomitant release of the sulfonic acid. Finally, the activated

Oxyma ester of the carboxylic acid (**IV**) reduced to the corresponding alcohols by $NaBH_4$. The intermediate **IV** in the reaction mixture was well characterized.[1]



Scheme 4.3.1. *A plausible mechanism for the reduction of carboxylic acids using o-NosylOXY and $NaBH_4$*

4.4. Conclusion

In conclusion, we have developed a convenient method for the converson of carboxylic acids into corresponding alcohols using *o*-NosylOXY as acid activator and $NaBH_4$ as a mild reductant. We have successfully applied this methodology with various carboxylic acids that included aromatic, aliphatic, and *N*-protected amino acids with excellent yield. The reactions were compatible with common *N*-protecting groups, e.g. Cbz, Fmoc, and Boc as well as side chain protected amino acids. The reagent **II** is an excellent racemization suppressant and easily recyclable reagent, makes the method environment-friendly.

4.5. Experimental Section

4.5.1. Materials and Instrumentations

As described in chapter 2 section 2.5.1

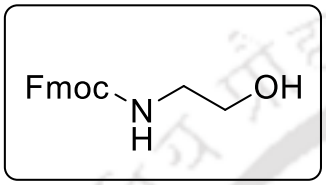
4.5.2. General procedure for the synthesis of alcohols

Ethyl-2-cyano-2-(2-nitrobenzenesulfonyloxyimino) acetate (*o*-NosylOXY, **I**) (1 mmol) was added to a stirred solution of carboxylic acid (1 mmol) and DIPEA (1 mmol) in CH_3CN (3 mL) at room temperature. After that, the reaction mixture was stirred for 5 min followed by the addition of sodium borohydride (1 mmol) in H_2O (0.5 mL) at 0 °C. The progress of the reaction was monitored by TLC at room temperature. After completion of the reaction, the reaction mixture was concentrated using rotary evaporator and then diluted with 15 mL

of ethyl acetate and washed with 5% HCl (2×5 mL), 5% $NaHCO_3$ (2×5 mL), saturated NaCl solution (2×5 mL) and dried over anhydrous Na_2SO_4. The evaporation of the solvent gave a residue that was purified by silica gel column chromatography using the mixture of hexane and ethyl acetate as eluent.

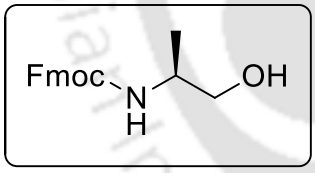
4.6. Characterization Data

(9H-Fluoren-9-yl)methyl (2-hydroxyethyl)carbamate 2a.



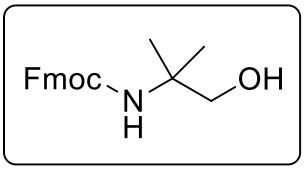
White solid (125 mg, 89%), mp 141-143 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76-7.75 (d, *J* = 7.2 Hz, 2H), 7.59-7.57 (d, *J* = 7.2 Hz, 2H), 7.41-7.38 (t, *J* = 7.2 Hz, 2H), 7.32-7.29 (t, *J* = 7.2 Hz, 2H), 4.42-4.41 (d, *J* = 6.6 Hz, 2H), 4.21-4.19 (t, *J* = 6.6 Hz, 1H), 3.70-3.68 (t, *J* = 4.8 Hz, 2H), 3.34-3.32 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.3, 144.0, 141.4, 127.8, 127.2, 125.1, 120.1, 66.8, 62.2, 47.3, 43.5; FT-IR (KBr) 3328, 2859, 1675, 1541, 1277, 1071, 739 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}NO_3$ 284.1287, found 284.1264.

(9H-Fluoren-9-yl)methyl (1-hydroxypropan-2-yl)carbamate 2b.



White solid (126 mg, 85%), mp 153-155 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77-7.76 (d, *J* = 7.2 Hz, 2H), 7.60-7.58 (d, *J* = 7.8 Hz, 2H), 7.41-7.39 (t, *J* = 7.2 Hz, 2H), 7.33-7.30 (t, *J* = 6.6 Hz, 2H), 4.42-4.41 (d, *J* = 6.6 Hz, 2H), 4.22-4.20 (t, *J* = 6.6 Hz, 1H), 3.83 (br s, 1H), 3.67 (br s, 1H), 3.53 (br s, 1H), 1.18-1.17 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.7, 144.08, 141.5, 127.8, 127.2, 125.1, 120.1, 66.9, 66.8, 49.1, 47.4, 17.4; FT-IR (KBr) 3324, 2926, 1686, 1545, 1268, 1043, 736 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{20}NO_3$ 298.1443, found 298.1437.

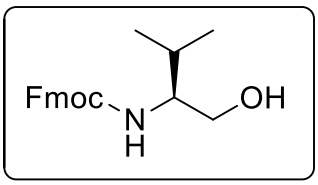
(9H-Fluoren-9-yl)methyl (1-hydroxypropan-2-yl)carbamate 2c.



Semi-solid (112 mg, 72%), ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77-7.76 (d, *J* = 7.8 Hz, 2H), 7.59-7.58 (d, *J* = 7.8 Hz, 2H), 7.42-7.39 (t, *J* = 7.8 Hz, 2H), 7.33-7.31 (t, *J* = 7.8 Hz, 2H), 4.86 (br s, 1H), 4.40 (br s, 2H), 4.20-4.18 (t, *J* = 6.6 Hz, 1H), 3.59 (s, 2H), 1.26 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.3, 144.0, 141.5, 127.9, 127.2, 125.1, 120.2, 70.3, 66.4, 54.7, 47.5, 24.7;

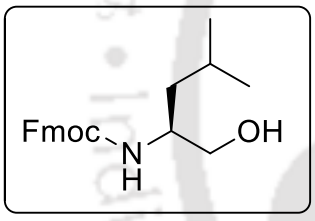
FT-IR (KBr) 3419, 2969, 2928, 1703, 1535, 1091, 740 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{22}NO_3$ 312.1600, found 312.1592.

(9H-Fluoren-9-yl)methyl (1-hydroxypropan-2-yl)carbamate 2d.



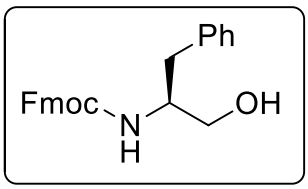
White solid (132 mg, 81%), mp 130-132 °C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77-7.76 (d, *J* = 7.2 Hz, 2H), 7.60-7.59 (d, *J* = 7.2 Hz, 2H), 7.41-7.39 (t, *J* = 7.2 Hz, 2H), 7.33-7.30 (t, *J* = 7.2 Hz, 2H), 4.88 (br s, 1H), 4.48-41 (m, 2H), 4.23-4.21 (t, *J* = 6.6 Hz, 1H), 3.71-3.62 (m, 2H), 3.47 (br s, 1H), 1.87-1.83 (m, 1H), 0.96-0.92 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.3, 144.0, 141.5, 127.8, 127.2, 125.1, 120.1, 66.7, 63.8, 58.7, 47.5, 29.3, 19.6, 18.7; FT-IR (KBr) 3443, 2923, 2848, 1637, 1020, 738 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{24}NO_3$ 326.1756, found 326.1762.

(S)-(9H-Fluoren-9-yl)methyl (1-hydroxy-4-methylpentan-2-yl)carbamate 2e.



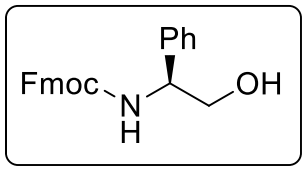
White solid (142 mg, 84%), mp 126-128 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77-7.76 (d, *J* = 7.2 Hz, 2H), 7.59-7.58 (d, *J* = 7.2 Hz, 2H), 7.41-7.39 (t, *J* = 7.2 Hz, 2H), 7.33-7.30 (t, *J* = 7.2 Hz, 2H), 4.77-4.76 (d, *J* = 7.8 Hz, 1H), 4.45-4.44 (d, *J* = 6.6 Hz, 2H), 4.22-4.20 (t, *J* = 6.6 Hz, 1H), 3.77 (br s, 1H), 3.67-3.66 (m, 1H), 3.53-3.50 (m, 1H), 1.63 (br, s,1H), 1.37-1.31 (m, 2H), 0.93-0.92 (d, *J* = 4.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.9, 144.0, 141.5, 127.8, 127.2, 125.2, 120.1, 66.7, 66.1, 51.5, 47.5, 40.5, 24.9, 23.2, 22.3; FT-IR (KBr) 3393, 2952, 1687, 1576, 1267, 739 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{26}NO_3$ 340.1913, found 340.1926.

(S)-(9H-Fluoren-9-yl)methyl (1-hydroxy-4-methylpentan-2-yl)carbamate 2f.



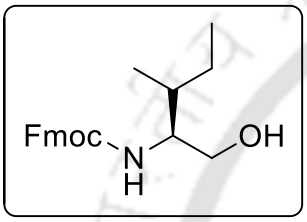
White solid (147 mg, 79%), mp 163-165 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76-7.75 (d, *J* = 7.8 Hz, 2H), 7.55-7.52 (t, *J* = 7.8 Hz, 2H), 7.41-7.38 (t, *J* = 7.2 Hz, 2H), 7.31-7.20 (m, 7H), 4.96 (br s, 1H), 4.41-4.37 (m, 2H), 4.19-4.17 (t, *J* = 6.6 Hz, 1H), 3.92 (br s, 1H), 3.67-3.58 (m, 2H), 2.85 (br s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.6, 144.0, 141.4, 137.7, 129.4, 128.7, 127.8, 127.2, 126.7, 125.1, 120.1, 66.7, 64.0, 54.2, 47.3, 37.4; FT-IR (KBr) 3443, 2924, 2852, 1632, 1024, 740 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{24}NO_3$ 374.1756, found 374.1760.

(S)-(9H-Fluoren-9-yl)methyl (1-hydroxy-4-methylpentan-2-yl)carbamate 2h.



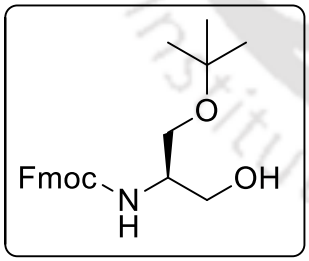
White solid (144 mg, 80%), mp 129-131 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76-7.26 (m, 13H), 5.51 (br s, 1H), 4.84 (br s, 1H), 4.44-4.43 (d, *J* = 5.4 Hz, 2H), 4.21 (br s, 1H), 3.88 (br s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.6, 144.0, 141.5, 139.2, 129.0, 128.0, 127.8, 127.2, 126.7, 125.2, 120.1, 66.9, 66.5, 57.2, 47.4; FT-IR (KBr) 3344, 2923, 2853, 1687, 1540, 1018, 736 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{22}NO_3$ 360.1600, found 360.1608.

(S)-(9H-Fluoren-9-yl)methyl (1-hydroxy-4-methylpentan-2-yl)carbamate 2i.



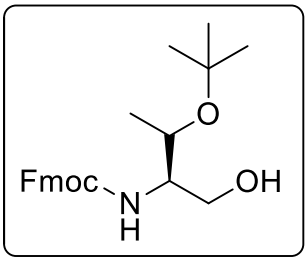
White solid (142 mg, 83%), mp 120-122 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77-7.76 (d, *J* = 7.8 Hz, 2H), 7.60-7.58 (d, *J* = 7.8 Hz, 2H), 7.41-7.39 (t, *J* = 7.8 Hz, 2H), 7.33-7.30 (t, *J* = 7.2 Hz, 2H), 4.91 (br s, 1H), 4.47-4.43 (m, 2H), 4.23-4.20 (t, *J* = 6.6 Hz, 1H), 3.73-3.62 (m, 2H), 3.54 (br s, 1H), 1.51-1.47 (m, 2H), 1.15-1.10 (m, 1H), 0.92-0.90 (t, *J* = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.2, 144.1, 141.5, 127.8, 127.2, 125.1, 120.1, 66.7, 63.7, 57.6, 47.5, 36.1, 25.6, 15.7, 11.5; FT-IR (KBr) 3480, 2924, 2854, 1671, 1541, 1045, 736 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{26}NO_3$ 340.1913, found 340.1903.

(R)-(9H-Fluoren-9-yl)methyl (1-(*tert*-butoxy)-3-hydroxypropan-2-yl)carbamate 2j.



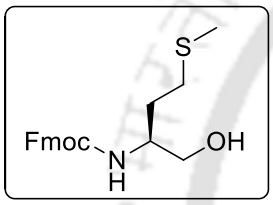
White solid (140 mg, 76%), mp 95-97 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77-7.76 (d, *J* = 7.8 Hz, 2H), 7.61-7.60 (d, *J* = 7.2 Hz, 2H), 7.41-7.39 (t, *J* = 6.6 Hz, 2H), 7.33-7.30 (t, *J* = 7.2 Hz, 2H), 5.57 (br s, 1H), 4.40-4.39 (d, *J* = 7.2 Hz, 2H), 4.24-4.22 (t, *J* = 6.6 Hz, 1H), 3.89-3.87 (m, 1H), 3.81-3.80 (m, 1H), 3.74-3.71 (m, 1H), 3.618-3.613 (d, *J* = 3 Hz, 2H), 1.20 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.5, 143.9, 141.3, 127.7, 127.1, 125.1, 120.0, 66.8, 64.1, 63.1, 51.9, 47.2, 27.4; FT-IR (KBr) 3339, 2926, 1668, 1540, 1089, 739 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{22}H_{28}NO_4$ 370.2018, found 370.2033.

(R)-(9H-Fluoren-9-yl)methyl (1-(*tert*-butoxy)-3-hydroxypropan-2-yl)carbamate 2k.



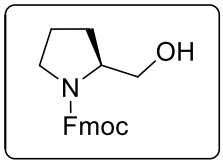
Semi solid (137 mg, 72%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77-7.76 (d, *J* = 7.2 Hz, 2H), 7.61-7.60 (d, *J* = 7.2 Hz, 2H), 7.41-7.39 (t, *J* = 7.2 Hz, 2H), 7.33-7.30 (t, *J* = 7.2 Hz, 2H), 5.29 (br s, 1H), 4.43-4.39 (m, 2H), 4.24-4.22 (t, *J* = 7.2 Hz, 1H), 3.96-3.94 (m, 1H), 3.72-3.61 (m, 3H), 1.21 (s, 9H), 1.17-1.16 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.2, 144.1, 141.5, 127.8, 127.2, 125.2, 120.1, 67.4, 67.0, 63.9, 57.3, 47.4, 28.8, 20.3; FT-IR (KBr) 3438, 2976, 2925, 1727, 1518, 1068, 738 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{30}NO_4$ 384.2175, found 384.2190.

(R)-(9H-Fluoren-9-yl)methyl (1-(*tert*-butoxy)-3-hydroxypropan-2-yl)carbamate 2l.



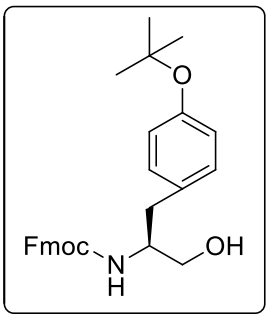
White solid (139 mg, 78%), mp 137-139 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77-7.76 (d, *J* = 7.8 Hz, 2H), 7.60-7.58 (d, *J* = 7.8 Hz, 2H), 7.41-7.39 (t, *J* = 7.8 Hz, 2H), 7.33-7.31 (t, *J* = 7.8 Hz, 2H), 5.01 (br s, 1H), 4.45-4.44 (d, *J* = 4.2 Hz, 2H), 4.22-4.20 (t, *J* = 6.6 Hz, 1H), 3.80-3.79 (m, 1H), 3.70-3.62 (m, 2H), 2.54-2.51 (m, 2H), 2.10(s, 3H), 1.87-1.76 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.8, 144.0, 141.5, 127.9, 127.2, 125.1, 120.1, 66.7, 65.0, 53.6, 52.5, 47.4, 30.8, 15.7; FT-IR (KBr) 3321, 2921, 2838, 1690, 1542, 1284,1037 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{24}NO_3S$ 358.1477, found 358.1469.

(R)-(9H-Fluoren-9-yl)methyl (1-(*tert*-butoxy)-3-hydroxypropan-2-yl)carbamate 2m.



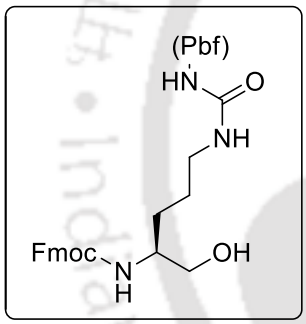
White solid (111 mg, 69%), mp 79-81 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77-7.76 (d, *J* = 7.2 Hz, 2H), 7.60-7.59 (d, *J* = 7.2 Hz, 2H), 7.42-7.39 (t, *J* = 7.2 Hz, 2H), 7.33-7.30 (t, *J* = 7.2 Hz, 2H), 4.46-4.38 (m, 2H), 4.26-4.23 (t, *J* = 7.2 Hz, 1H), 4.00-3.99 (m, 1H), 3.69-3.59 (m, 2H), 3.54-3.50 (m, 1H), 3.40-3.36 (m, 1H), 2.06-2.01 (m, 1H), 1.91-1.87 (m, 1H), 1.84-1.80 (m, 1H), 1.63-1.59 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.3, 144.1, 141.5, 127.9, 127.2, 125.1, 120.1, 67.7, 67.1, 60.9, 53.6, 47.5, 28.7, 24.2; FT-IR (KBr) 3442, 2925, 1677, 1422, 1107, 739 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{22}NO_3$ 324.1600, found 324.1628.

(R)-(9H-Fluoren-9-yl)methyl (1-(*tert*-butoxy)-3-hydroxypropan-2-yl)carbamate 2o.



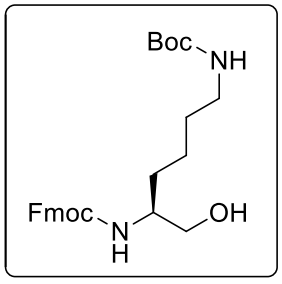
White solid (144 mg, 65%), mp 111-113 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76-7.75 (d, *J* = 7.8 Hz, 2H), 7.56-7.55 (d, *J* = 7.8 Hz, 2H), 7.41-7.38 (t, *J* = 7.8 Hz, 2H), 7.32-7.29 (t, *J* = 7.8 Hz, 2H), 7.06-7.07 (d, *J* = 7.8 Hz, 2H), 6.91-6.90 (d, *J* = 7.8 Hz, 2H), 5.01 (br s, 1H), 4.25-4.36 (m, 2H), 4.19-4.17 (t, *J* = 7.2 Hz, 1H), 3.89 (br s, 1H), 3.67-3.55 (m, 2H), 2.81-2.80 (d, *J* = 6.6 Hz, 2H), 1.31 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.6, 154.1, 144.0, 141.4, 132.5, 129.8, 127.8, 127.2, 125.1, 124.4, 120.1, 78.5, 66.7, 63.9, 54.2, 47.4, 36.7, 28.9; FT-IR (KBr) 3332, 2974, 2927, 1689, 1539, 1023, 737 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{31}NO_4$ 446.2331, found 446.2353.

(R)-(9H-Fluoren-9-yl)methyl (1-(*tert*-butoxy)-3-hydroxypropan-2-yl)carbamate 2p.



White solid (199 mg, 63%), mp 82-84 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73-7.72 (d, *J* = 7.2 Hz, 2H), 7.56-7.55 (d, *J* = 7.2 Hz, 2H), 7.36-7.34 (t, *J* = 7.2 Hz, 2H), 7.26-7.24 (m, 2H), 6.18 (br s, 2H), 5.57 (br s, 1H), 4.36-4.35 (d, *J* = 7.2 Hz, 2H), 4.14-4.10 (m, 2H), 3.64-3.55 (m, 3H), 3.21 (br s, 2H), 2.89 (br s, 1H), 2.56 (s, 1H), 2.49 (s, 1H), 2.06 (s, 1H), 1.57-1.52 (br s, 4H), 1.42 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 157.2, 156.5, 143.9, 141.4, 138.5, 132.7, 132.4, 127.8, 127.2, 125.3, 124.9, 120.1, 117.8, 86.6, 66.9, 64.8, 47.3, 43.3, 29.9, 28.7, 25.7, 22.9, 19.5, 18.1, 14.3,12.6; FT-IR (KBr) 3444, 2924, 2854, 1708, 1548, 1451, 1255, 1101, 738 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{34}H_{42}N_3O_4S$ 635.2903, found 635.2921.

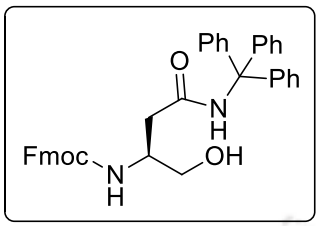
(S)-(9H-Fluoren-9-yl)methyl *tert*-butyl (6-hydroxyhexane-1,5-diyl)dicarbamate 2q.



White solid (154 mg, 68%), mp 139-141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76-7.75 (d, *J* = 7.8 Hz, 2H), 7.60-7.58 (d, *J* = 7.8 Hz, 2H), 7.41-7.38 (t, *J* = 7.8 Hz, 2H), 7.32-7.30 (t, *J* = 7.8 Hz, 2H), 5.09 (br s, 1H), 4.41 (br s, 1H),4.42-4.41 (d, *J* = 4.2 Hz, 2H), 4.22-4.19 (t, *J* = 6.6 Hz, 1H), 3.64-3.60 (m, 3H), 3.17-3.06 (m, 2H), 1.72-1.47 (m, 4H), 1.42 (s, 9H), 1.38-1.33 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.9, 156.5, 144.0, 141.4, 127.8, 127.2, 125.2, 120.1, 79.4,

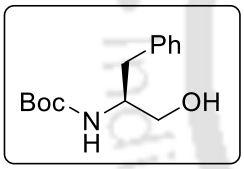
66.7, 64.8, 53.0, 47.4, 39.8, 30.6, 30.0, 28.5, 22.8; FT-IR (KBr) 3362, 2927, 2855, 1687, 1533, 1036, 737 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{26}H_{35}N_2O_5$ 455.2546, found 455.2560.

(R)-(9H-Fluoren-9-yl)methyl (1-(*tert*-butoxy)-3-hydroxypropan-2-yl)carbamate 2r.



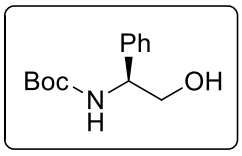
White solid (180 mg, 62%), mp 110-112 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76-7.74 (t, *J* = 7.2 Hz, 2H), 7.58-7.56 (d, *J* = 7.8 Hz, 2H), 7.42-7.20 (m, 19H), 4.84 (br s, 1H), 4.39-4.38 (d, *J* = 6.6 Hz, 1H), 4.20-4.18 (t, *J* = 6 Hz, 1H), 3.52-3.48 (m, 3H), 2.50-2.42 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 156.0, 143.7, 141.9, 141.4, 128.6, 127.9, 127.7, 127.2, 126.8, 125.1, 120.1, 74.3, 67.3, 50.4, 47.1, 36.3, 29.8; FT-IR (KBr) 3445, 2854, 1642, 1031, 739, 698 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{38}H_{35}N_2O_4$ 583.2597, found 583.2605.

(S)-*tert*-Butyl (1-hydroxy-3-phenylpropan-2-yl)carbamate 2s.



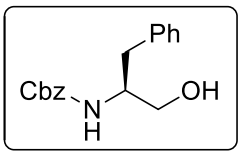
White solid (106 mg, 78%), mp 91-93 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.23 (m, 5H), 4.80-4.79 (d, *J* = 5.4 Hz, 1H), 3.89 (br, s, 1H), 3.69 (br, s, 1H) , 3.58 (br, s, 1H), 2.86-2.85 (d, *J* = 6.0 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.3, 137.9, 129.4, 128.7, 126.7, 79.9, 64.5, 53.9, 37.6, 28.5; FT-IR (KBr) 3356, 2925, 1687, 1528, 1170, 1006 cm^{-1}; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{14}H_{22}NO_3Na$ 274.1419, found 274.1421.

(S)-*tert*-Butyl (1-hydroxy-3-phenylpropan-2-yl)carbamate 2t.



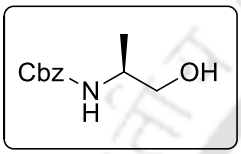
White solid (90 mg, 76%), mp 128-130 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 5.32 (br, s, 1H), 4.77 (br, s, 1H) , 3.82 (br, s, 2H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.3, 139.6, 128.9, 127.9, 126.7, 80.1, 67.0, 57.0, 28.5; FT-IR (KBr) 3247, 2976, 1672, 1552, 1054, 702 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{19}NO_3Na$ 260.1263, found 260.1273.

(S)-Benzyl (1-hydroxypropan-2-yl)carbamate 2u.



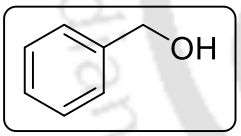
White solid (114 mg, 80%), mp 86-88 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.15 (m, 10H), 5.07 (s, 2H), 5.01 (br s, 1H), 3.96 (br s, 1H), 3.70-3.58 (m, 2H) , 2.87-2.86 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.7, 137.7, 136.4, 129.4, 128.7, 128.6, 128.2, 128.1, 66.9, 63.8, 54.2, 37.4; FT-IR (KBr) 3479, 2927, 2869, 1691, 1538, 1256, 1015, cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{20}NO_3$ 286.1443, found 286.1462.

(S)-Benzyl (1-hydroxypropan-2-yl)carbamate 2v.



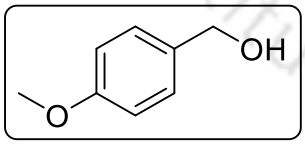
White solid (86 mg, 83%), mp 79-81 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (s, 5H), 5.08 (s, 2H), 3.82 (br, s, 1H), 3.64 (br, s, 1H) , 3.51 (br, s, 1H), 1.15-1.14 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.7, 136.5, 128.6, 128.29, 128.25, 66.9, 66.6, 49.0, 17.3; FT-IR (KBr) 3310, 2971, 1687, 1539, 1076, 693 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{16}NO_3$ 210.1130, found 210.1126.

Phenylmethanol 4a.



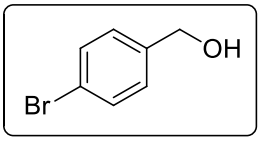
Liquid (88 mg, 81%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.29 (m, 5H), 4.67 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.8, 128.3, 127.3, 126.9, 64.6; FT-IR (KBr) 3443, 2927, 1613, 1247, 1031, 736 cm^{-1}.

(4-Methoxyphenyl)methanol 4b.



White solid (127 mg, 84%), mp 72-74 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28-7.27 (d, *J* = 7.2 Hz, 2H), 6.89-6.88 (d, *J* = 7.8 Hz, 2H), 4.59 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.9, 133.2, 128.6, 113.8, 64.5, 55.2; FT-IR (KBr) 3432, 2923, 1636, 1021, 737 cm^{-1}

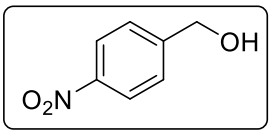
(4-Bromophenyl)methanol 4c.



White solid (160 mg, 86%), mp 72-74 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48-7.47 (d, *J* = 8.4 Hz, 2H), 7.23-7.22 (d, *J* = 8.4 Hz, 2H), 4.64 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.9, 131.7,

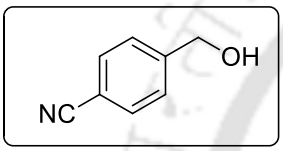
128.7, 121.6, 64.7; FT-IR (KBr) 3480, 2923, 2854, 1639, 1009, 504 cm^{-1}; LRMS (ESI) m/z: $[M+H]^+$ calcd for C_7H_8BrO 186.9759, found 186.2207.

(4-Nitrophenyl)methanol 4d.



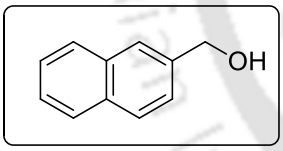
Yellow solid (155 mg, 89%), mp 93-95 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.22-8.21 (d, *J* = 8.4 Hz, 2H), 7.54-7.53 (d, *J* = 8.4 Hz, 2H), 4.84 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.4, 147.4, 127.1, 123.9, 64.1; FT-IR (KBr) 3476, 2924, 1640, 1515, 1345, 1055, 736 cm^{-1}; LRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_7H_8NO_3Na$ 176.0324, found 176.0097.

4-(Hydroxymethyl)benzonitrile 4e.



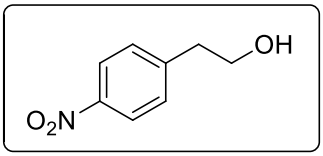
Semi-solid (109 mg, 80%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.22-8.21 (d, *J* = 8.4 Hz, 2H), 7.54-7.53 (d, *J* = 8.4 Hz, 2H), 4.84 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.6, 132.4, 127.1, 119.0, 111.0, 64.1; FT-IR (KBr) 3442, 2923, 2855, 2230, 1047, 816 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for C_8H_8NO 134.0606, found 138.0602.

Naphthalen-2-ylmethanol 4f.



White solid (111 mg, 70%), mp 68-70 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84-7.80 (m, 4H), 7.49-7.47 (m, 3H), 4.84 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.51, 133.57, 133.1, 128.5, 128.0, 127.9, 126.3, 126.1, 125.6, 125.3, 65.6; FT-IR (KBr) 3380, 2923, 2853, 1632, 1041, 818 cm^{-1}; LRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{11}O$ 159.0810, found 159.0319.

2-(4-Nitrophenyl)ethanol 4g.



Semi solid (133 mg, 79%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.16-8.14 (d, *J* = 8.4 Hz, 2H), 7.40-7.39 (d, *J* = 9.6 Hz, 2H), 3.93-3.90 (t, *J* = 6.6 Hz, 2H), 2.98-2.96 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.8, 146.7, 129.8, 123.6, 62.8, 38.8; FT-IR (KBr) 3441, 2923, 2853, 1640, 1517, 1346 cm^{-1}.

4.7. References

1. Dev, D.; Palakurthy, N. B.; Thalluri, K.; Chandra, J.; Mandal, B. Ethyl 2-cyano-2-(2-nitrobenzene sulfonyloxyimino)acetate (*o*-NosylOXY): A recyclable coupling reagent for racemization free synthesis of peptide, amide, hydroxamate and ester. *J. Org. Chem*. **2014**, *79*, 5420-5431.
2. Thalluri, K.; Manne, S. R.; Dev, D.; Mandal, B. Ethyl 2-Cyano-2-(4-nitrophenylsulfonyloxyimino) acetate-mediated lossen rearrangement: single-pot racemization-free synthesis of hydroxamic acids and ureas from carboxylic acids. *J. Org. Chem*. **2014**, *79*, 3765-3775.
3. 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.
4. Dev, D.; Palakurthy, N. B.; Kumar, N.; Mandal, B. An unexpected involvement of ethyl-2-cyano-2-(hydroxyimino)acetate cleaved product in the promotion of the synthesis of nitriles from aldoximes: a mechanistic perception. *Tetrahedron Lett.* **2013**, *54*, 4397-4400.
5. Morales-Serna, J. A.; Garcia-Rios, E.; Bernal, J.; Paleo, E.; Gavino, R.; Cardenas, J. Reduction of carboxylic acids using esters of benzotriazole as high-reactivity intermediates. *Synthesis*. **2011**, *9*, 1375-1382.

4.8. Selected Spectra

4.8.1. NMR (^{1}H and ^{13}C) spectra of compounds

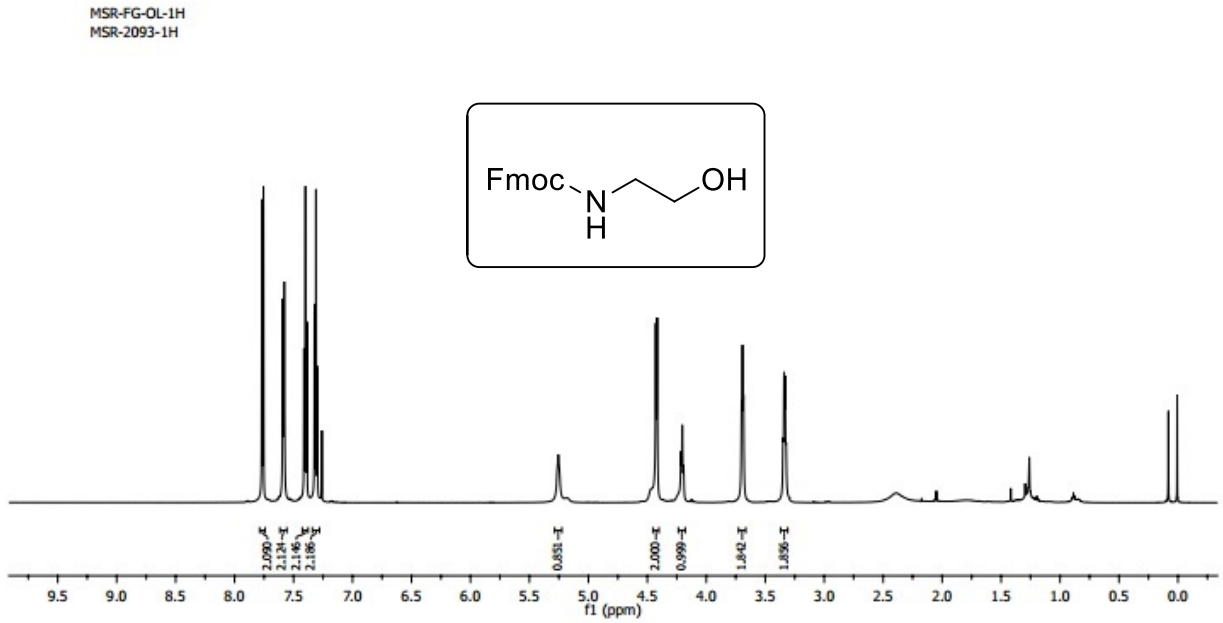


Figure 4.8.1.1. *^{1}H NMR spectrum of compound* ***2a***

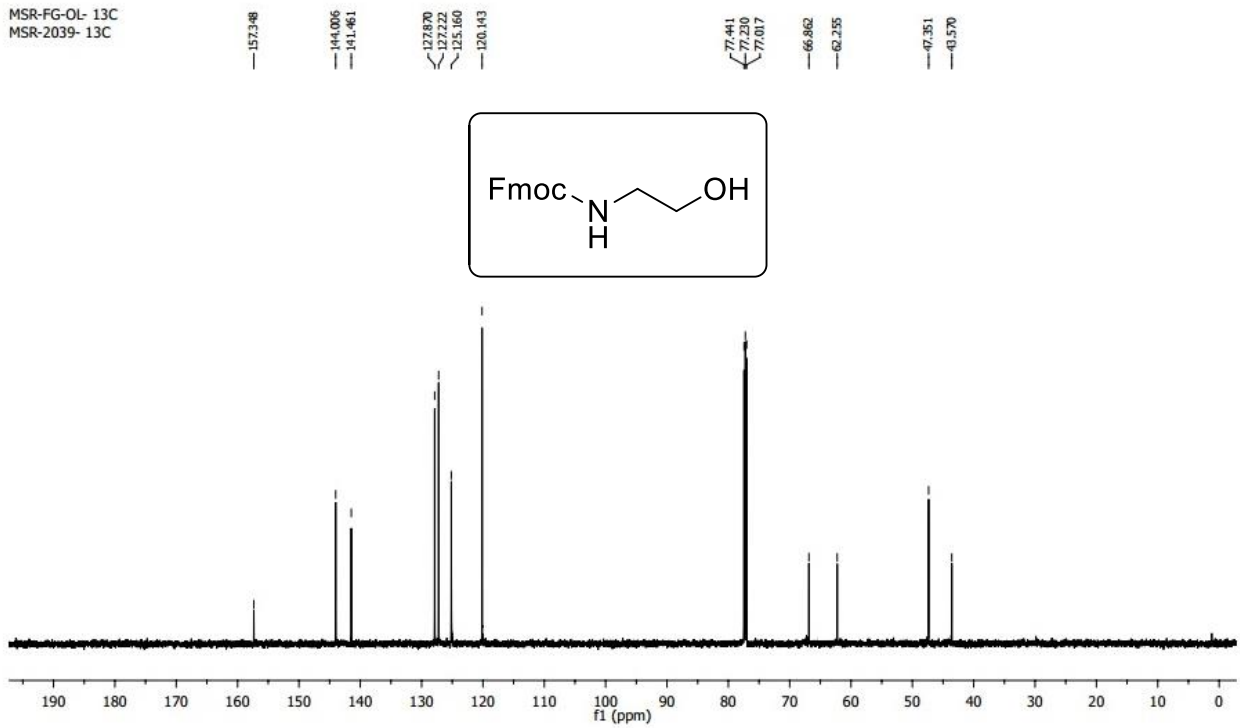


Figure 4.8.1.2. *^{13}C NMR spectrum of compound* ***2a***

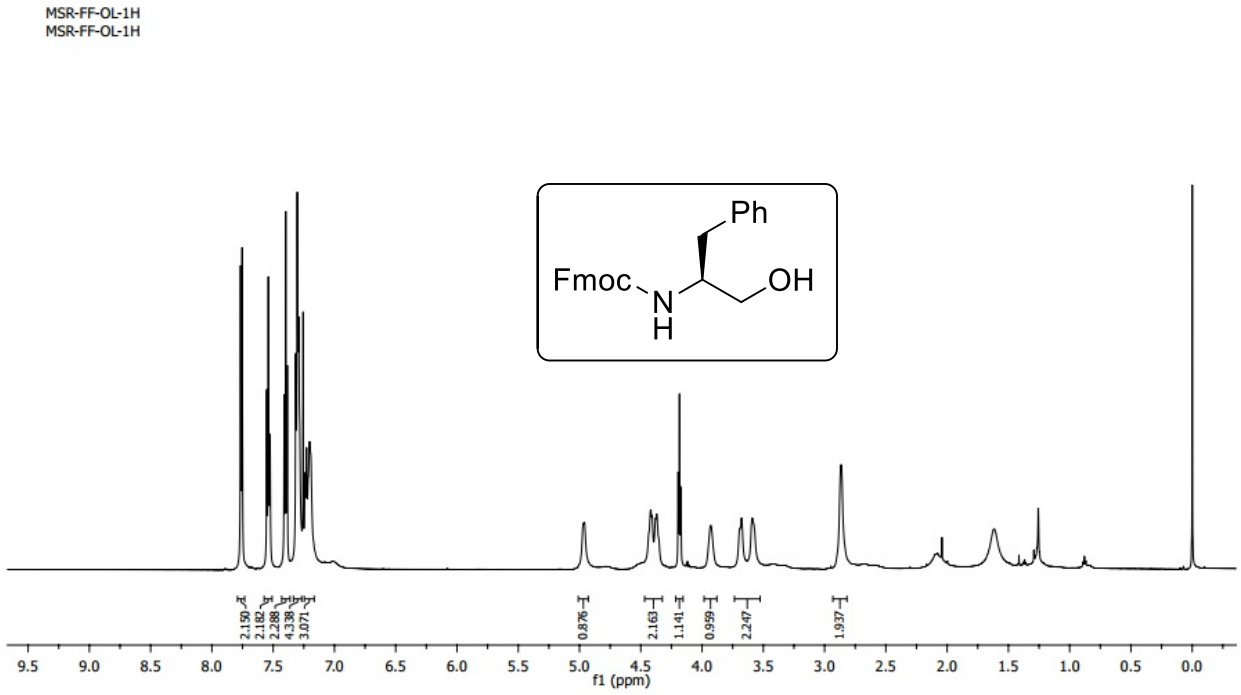


Figure 4.8.1.3. *^{1}H NMR spectrum of compound* ***2f***

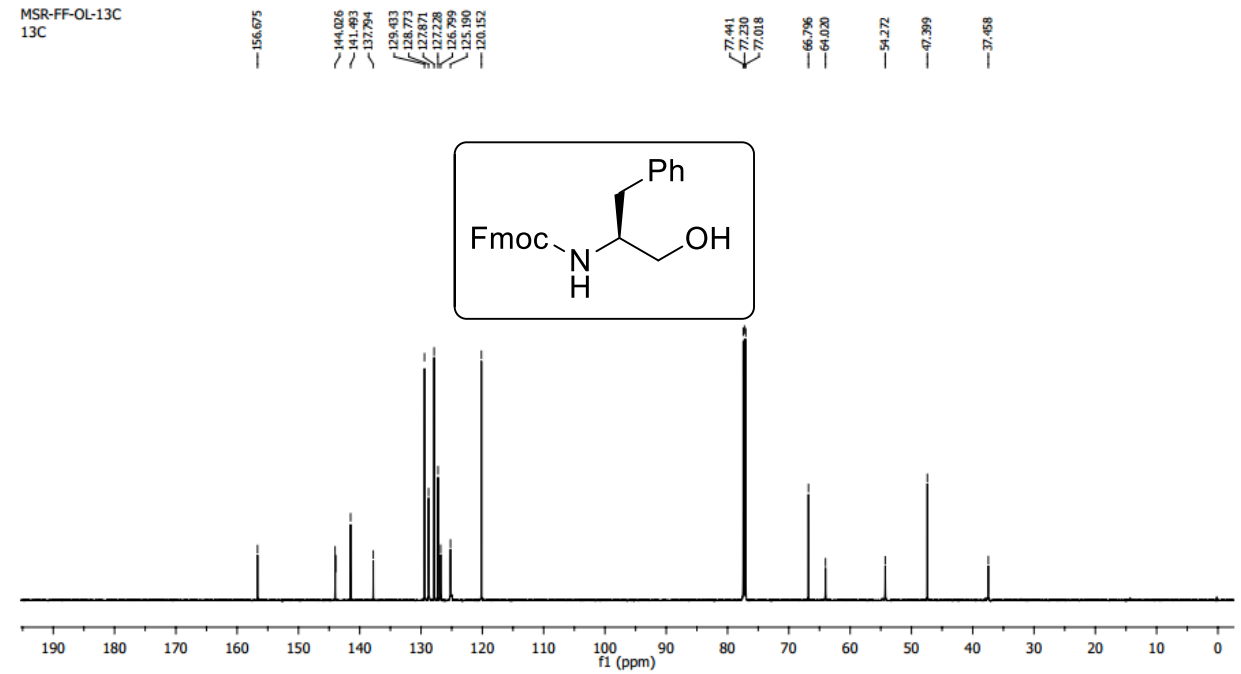


Figure 4.8.1.4. *^{13}C NMR spectrum of compound* ***2f***

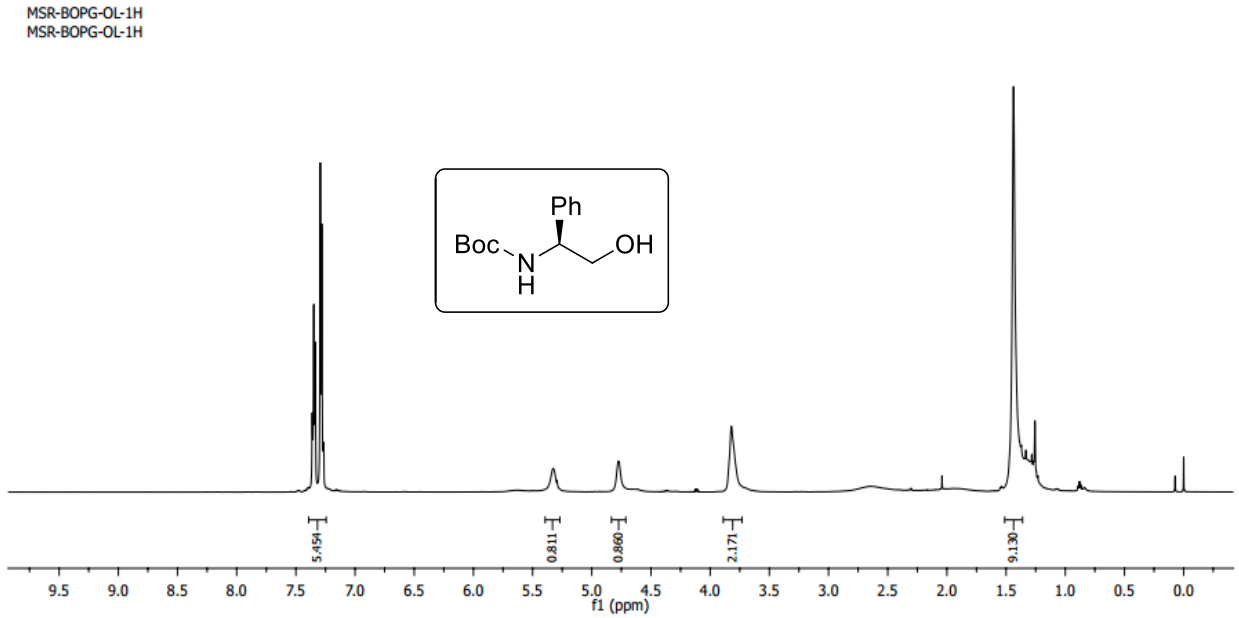


Figure* 4.8.1.5.** *^{1}H NMR spectrum of compound* ***2t

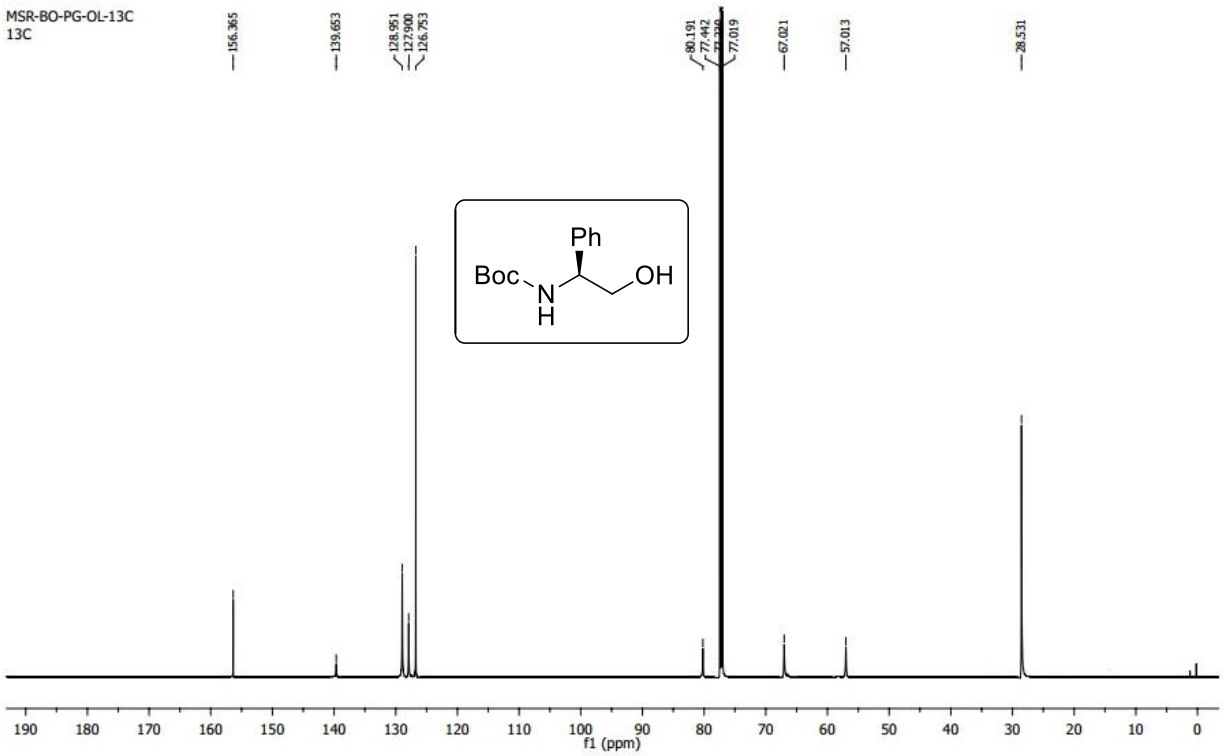


Figure 4.8.1.6. ^{13}C NMR spectrum of compound **2t**

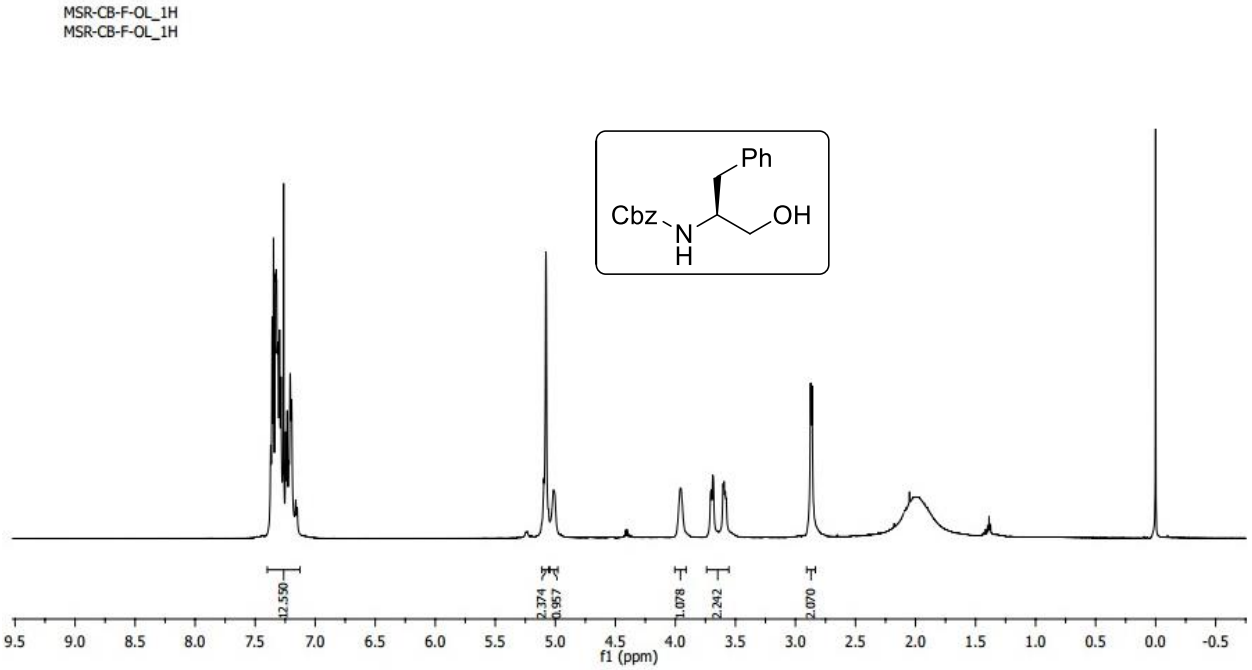


Figure 4.8.1.7. *^{1}H NMR spectrum of compound* ***2u***

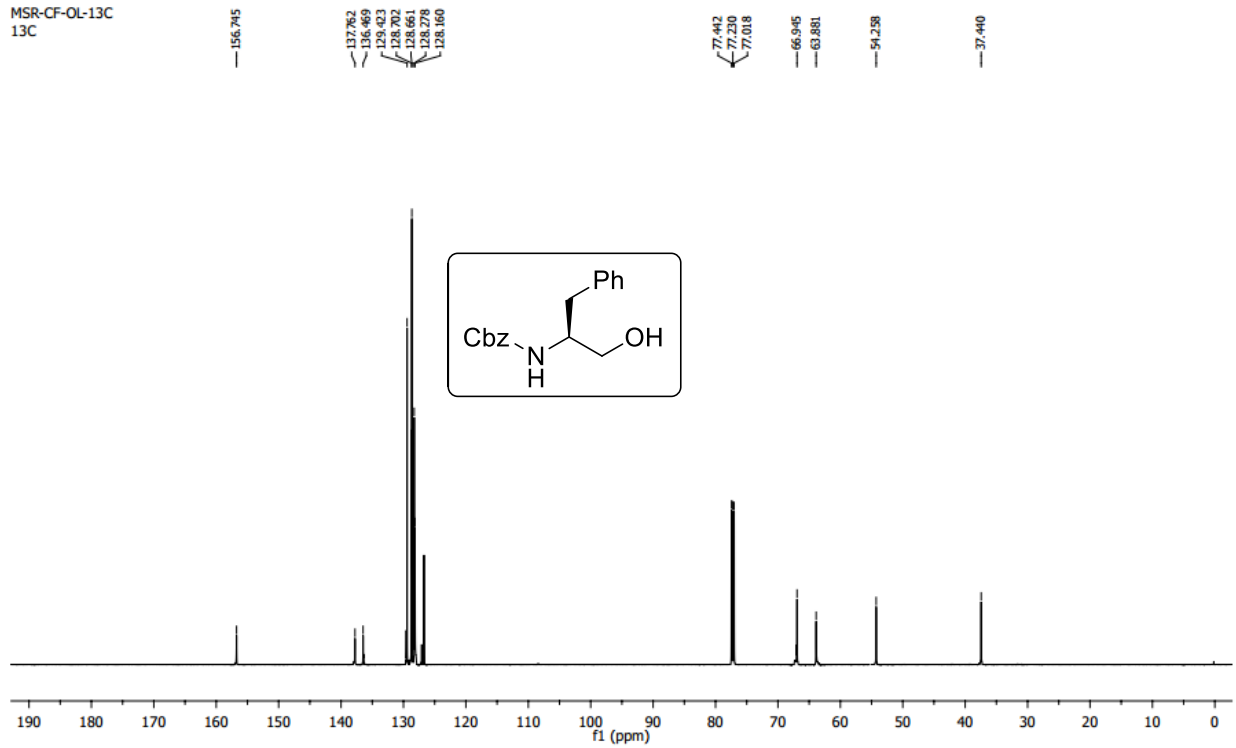


Figure 4.8.1.8. *^{13}C NMR spectrum of compound* ***2u***

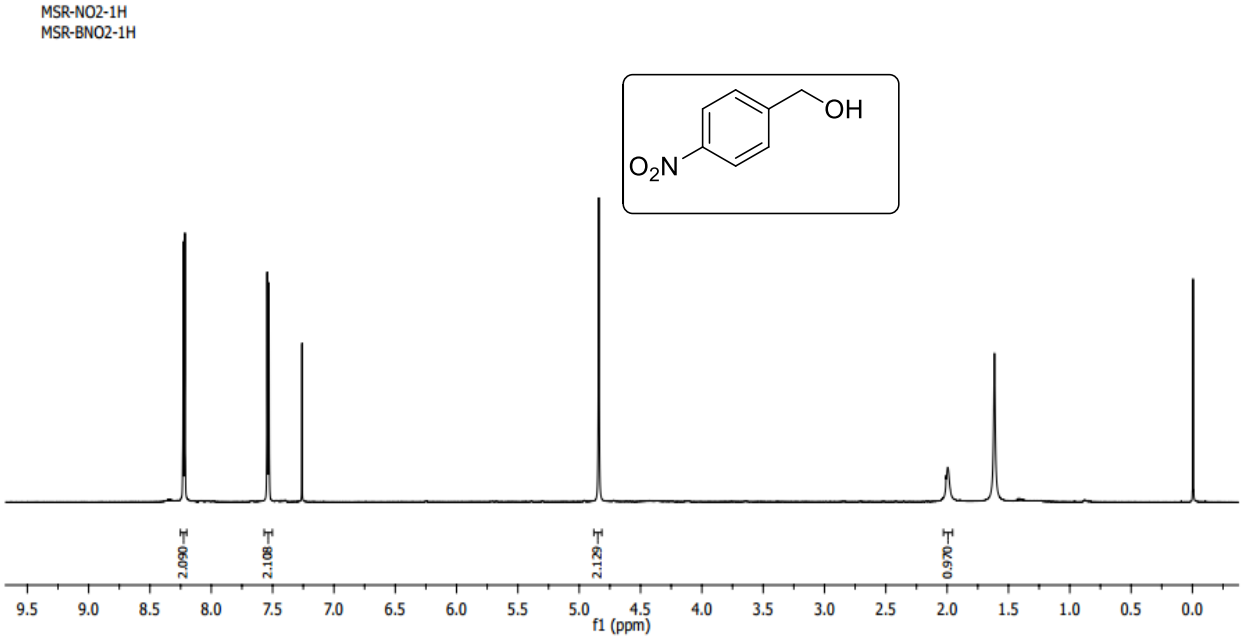


Figure 4.8.1.9. *^{1}H NMR spectrum of compound* ***4d***

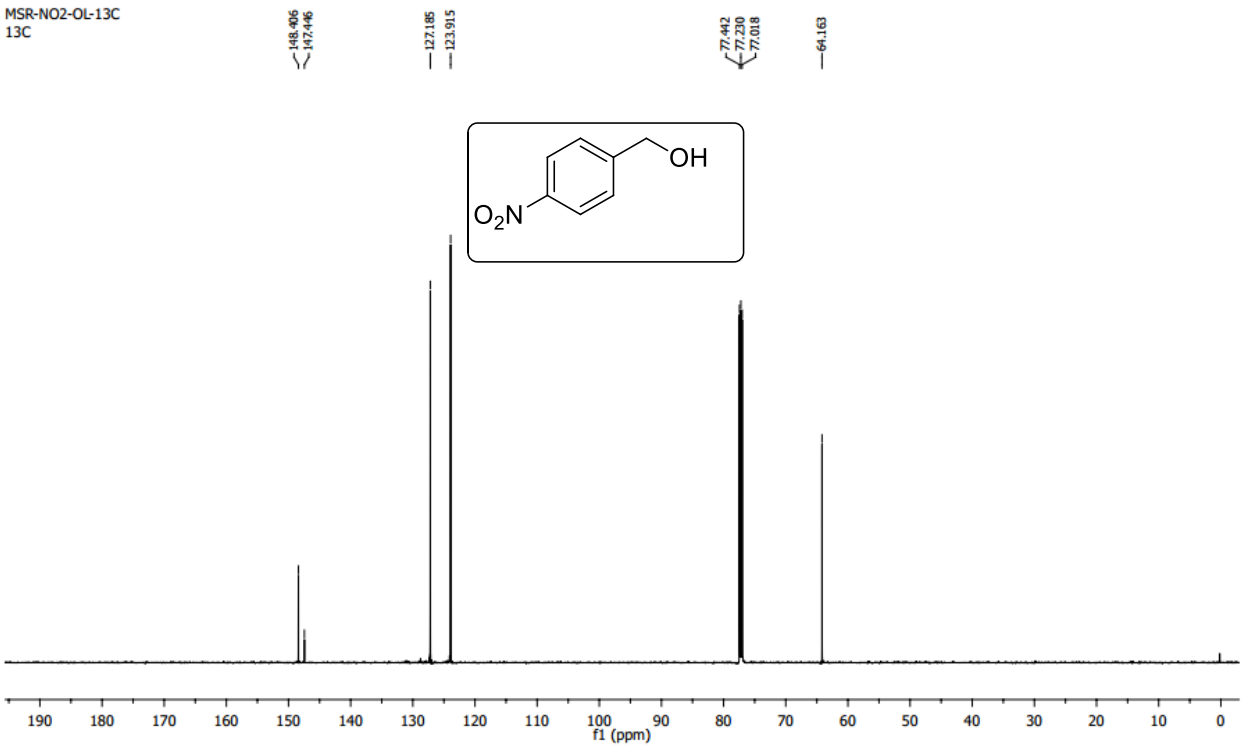


Figure 4.8.1.9. *^{13}C NMR spectrum of compound* ***4d***

4.8.2. HPLC Data for racemization study

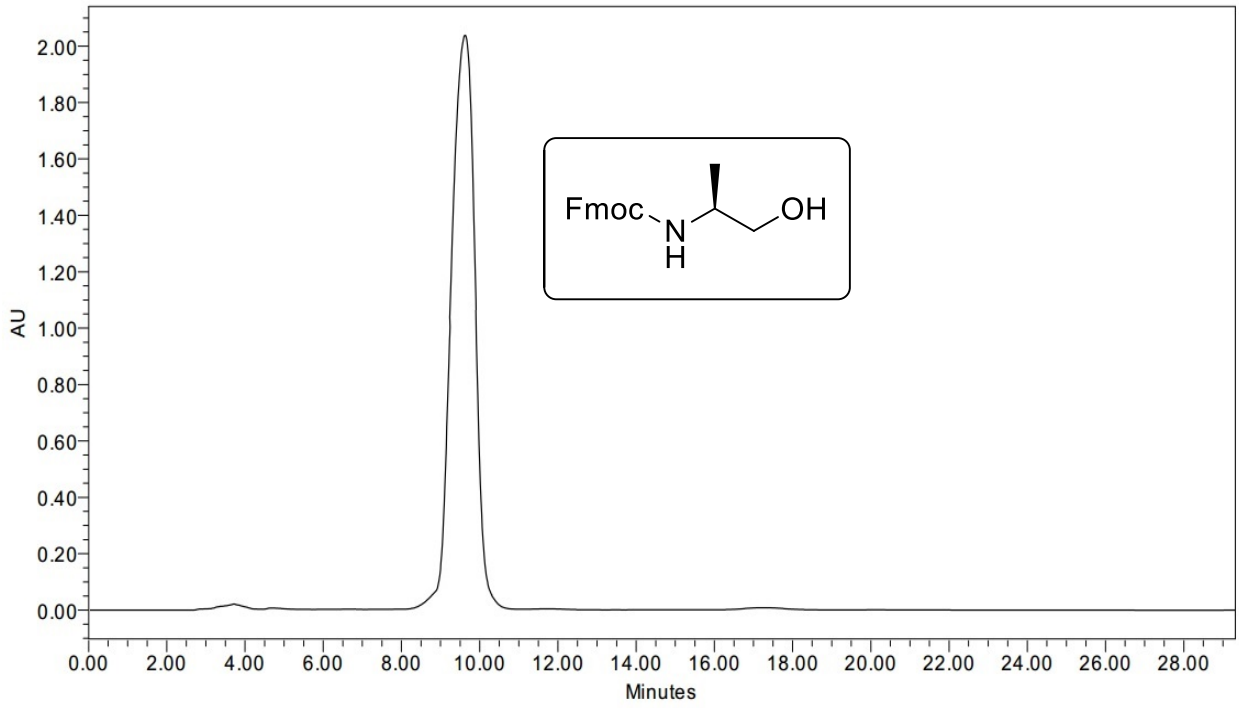


Figure 4.8.2.1. *HPLC spectra of compound* ***2b***

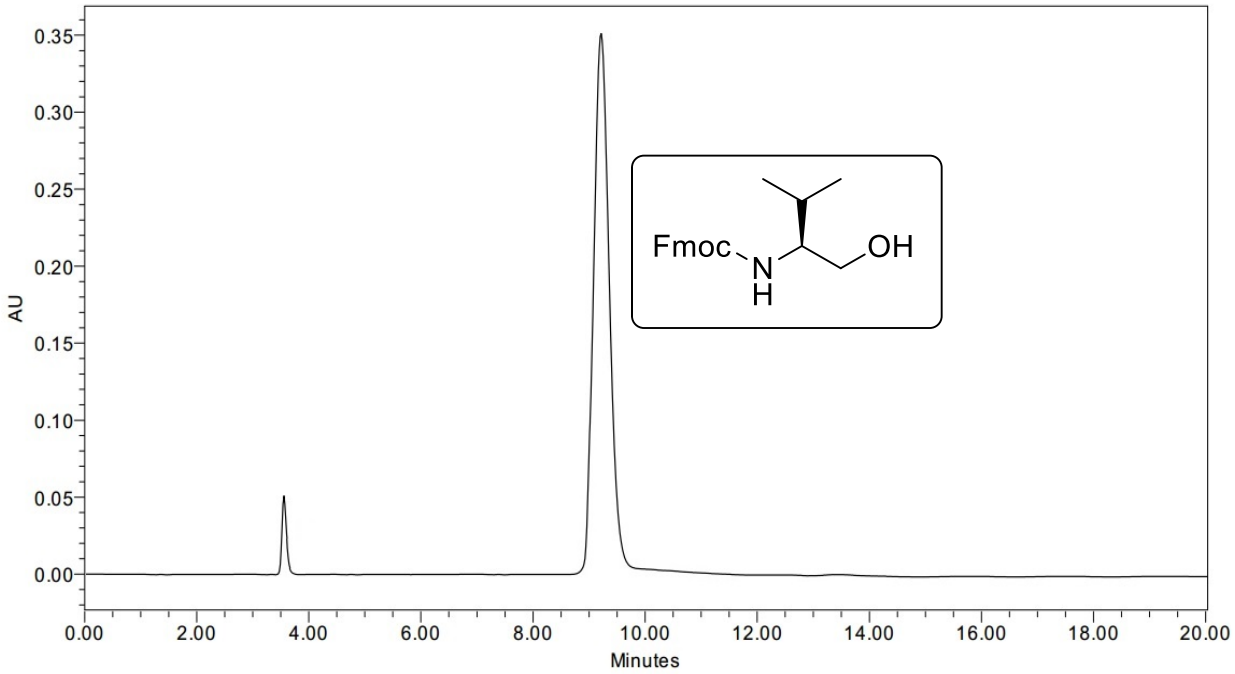


Figure 4.8.2.2. *HPLC spectra of compound* ***2d***

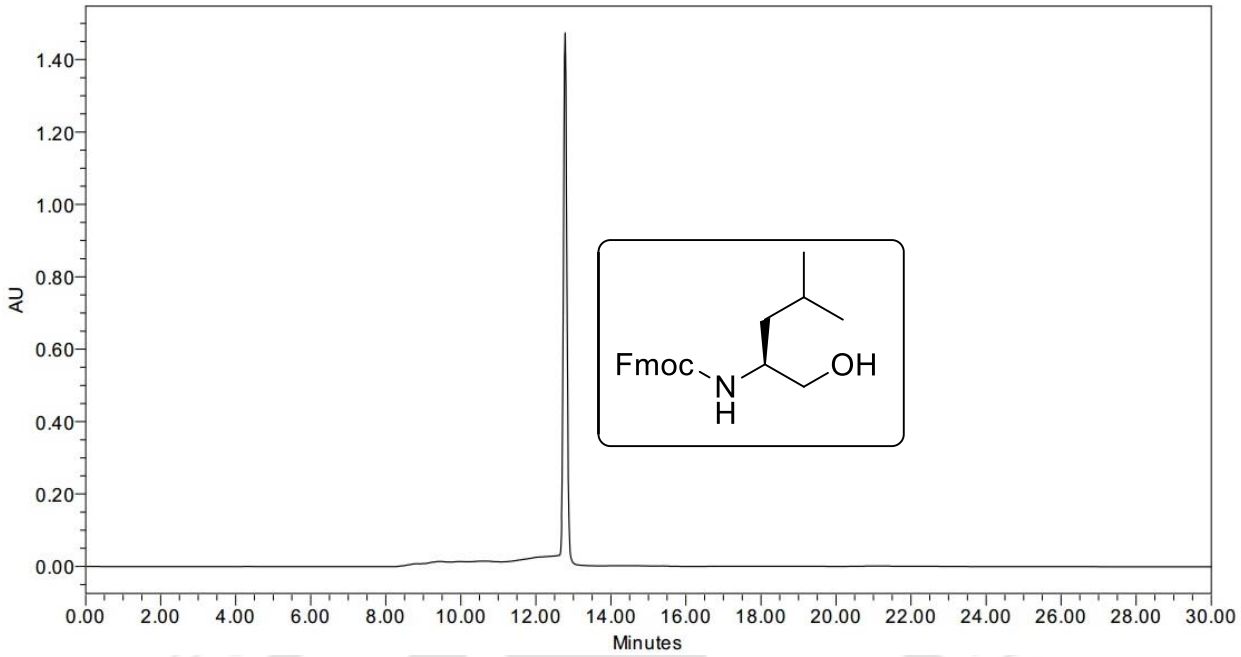


Figure 4.8.2.3. *HPLC spectra of compound* ***2e***

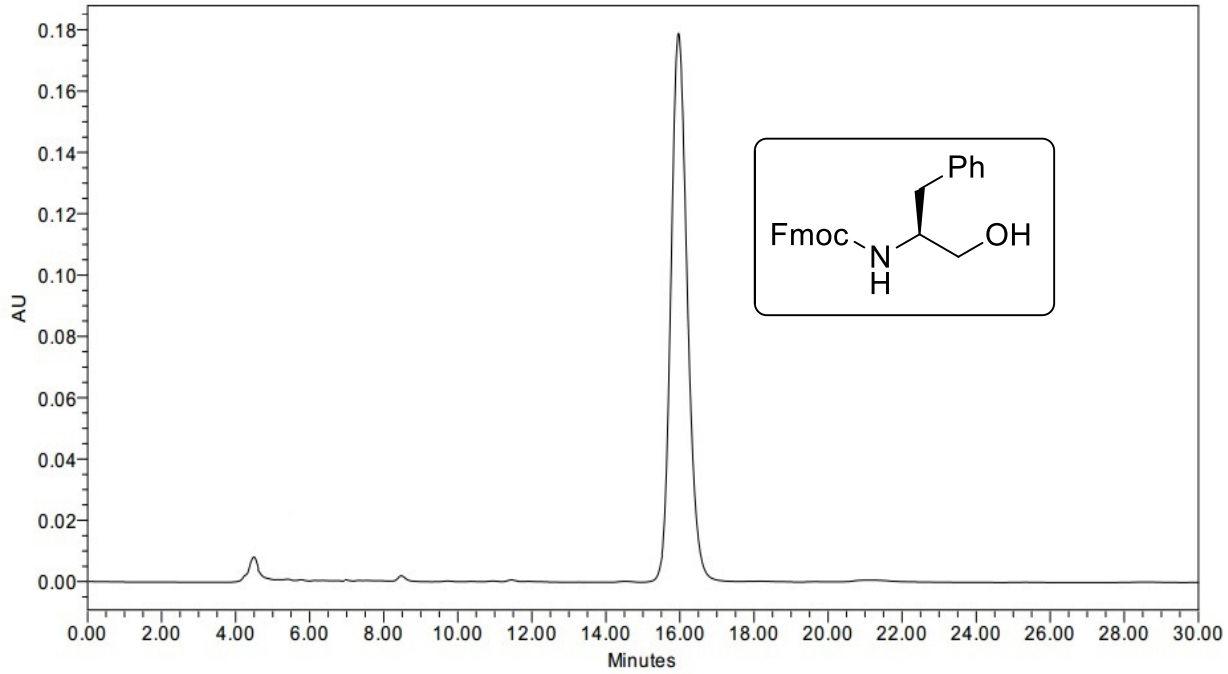


Figure 4.8.2.4. *HPLC spectra of* ***L*** *compound* ***2f***

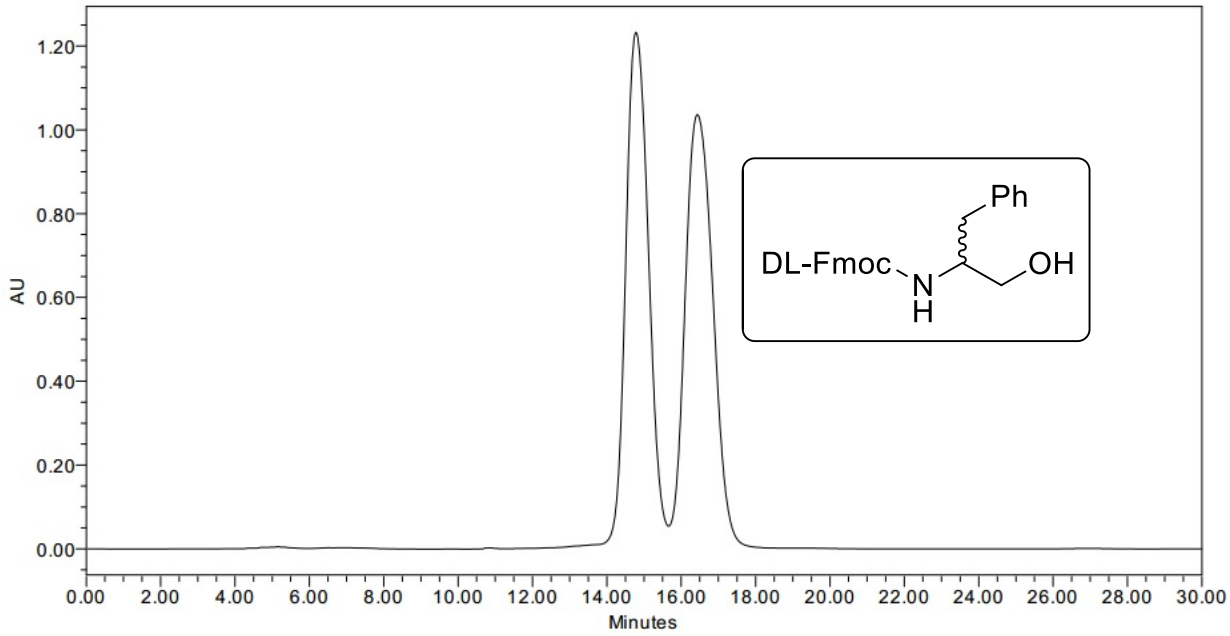


Figure 4.8.2.5. *HPLC spectra of* ***DL*** *compound* ***2g***

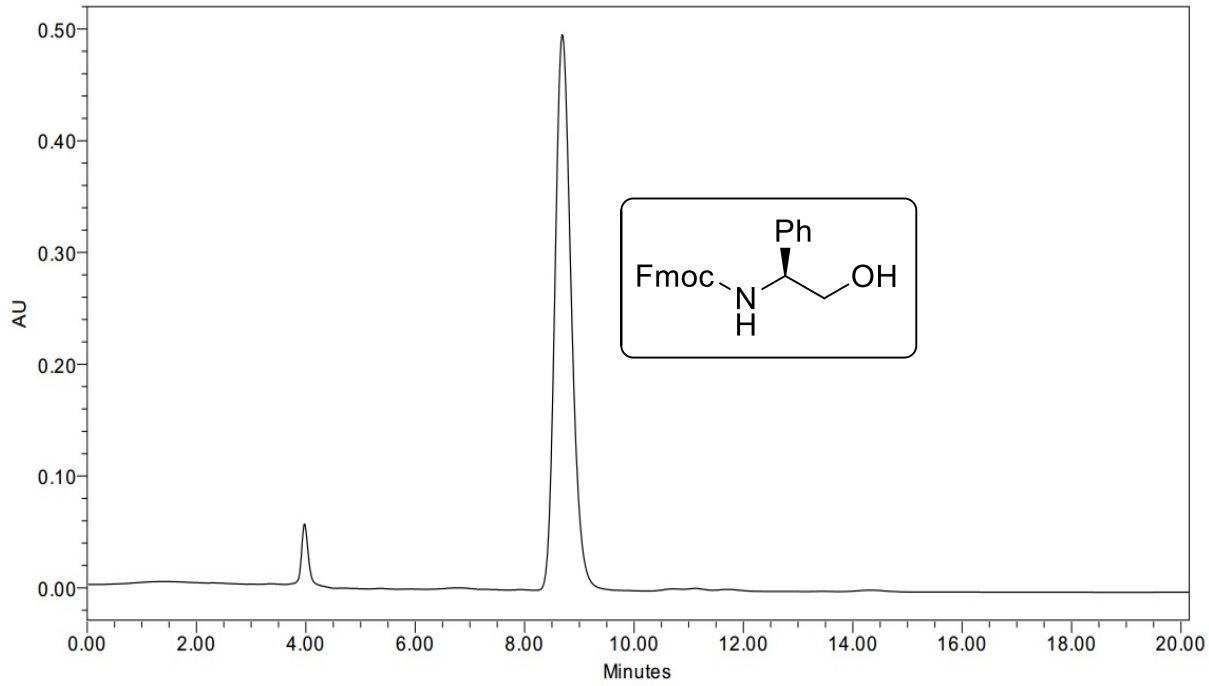


Figure 4.8.2.6. *HPLC spectra of compound* ***2h***

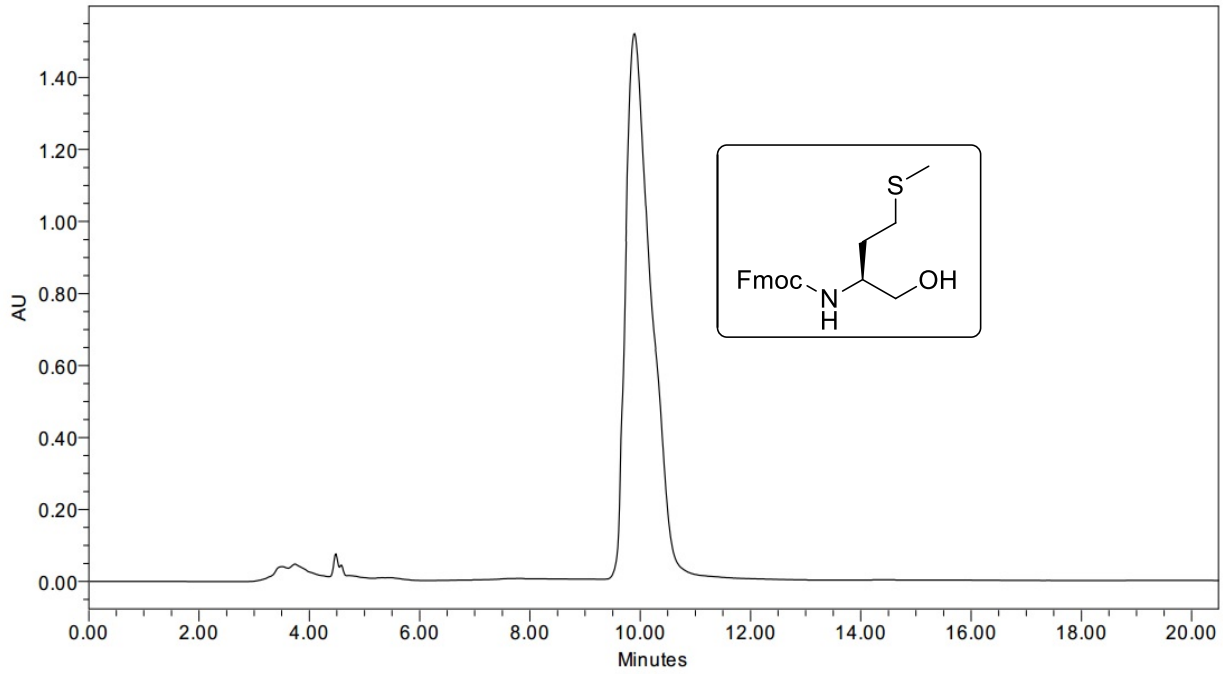


Figure 4.8.2.7. *HPLC spectra of compound* ***2l***

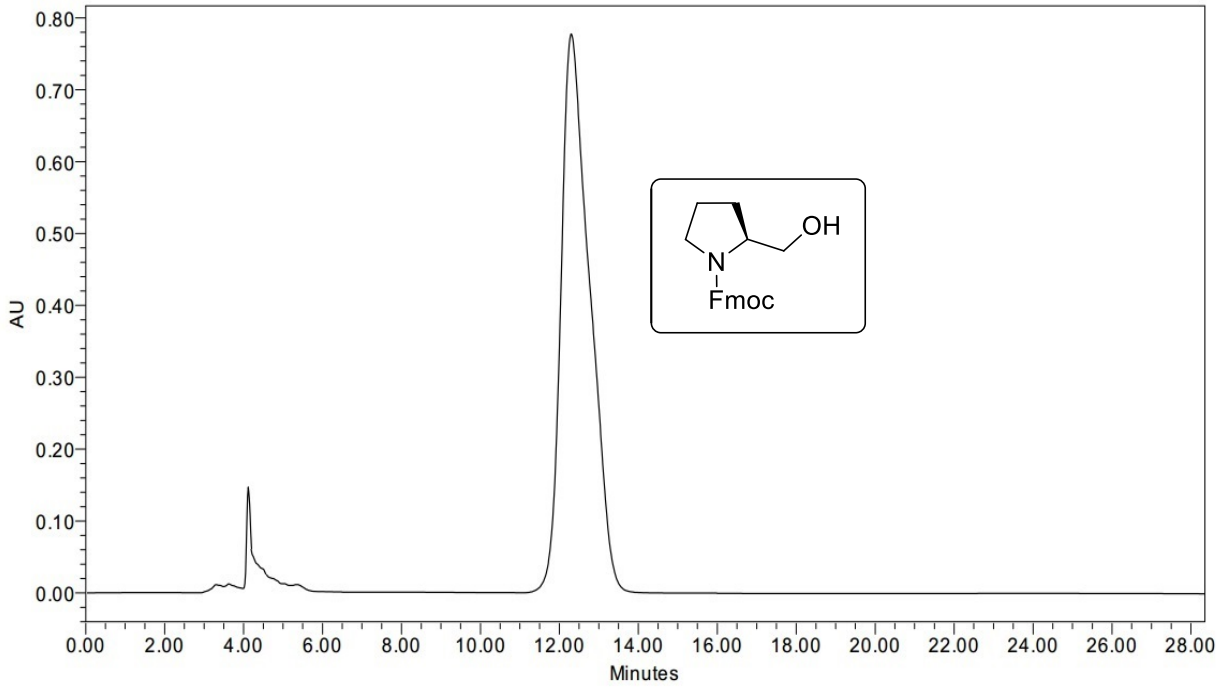


Figure 4.8.2.8. *HPLC spectra of compound* ***L 2l***

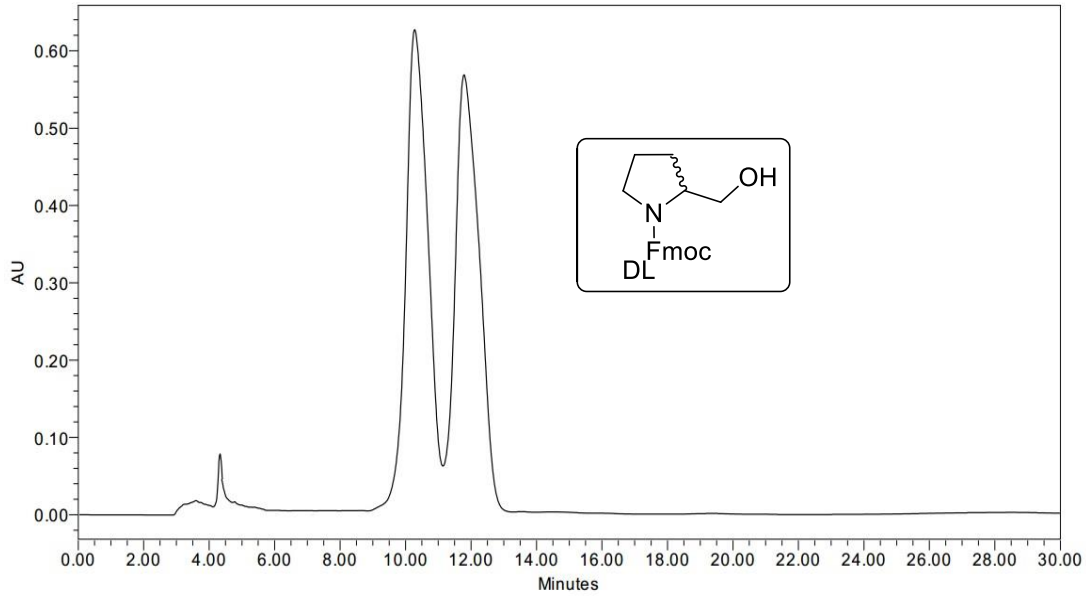


Figure 4.8.2.9. *HPLC spectra of compound* ***DL 2n***

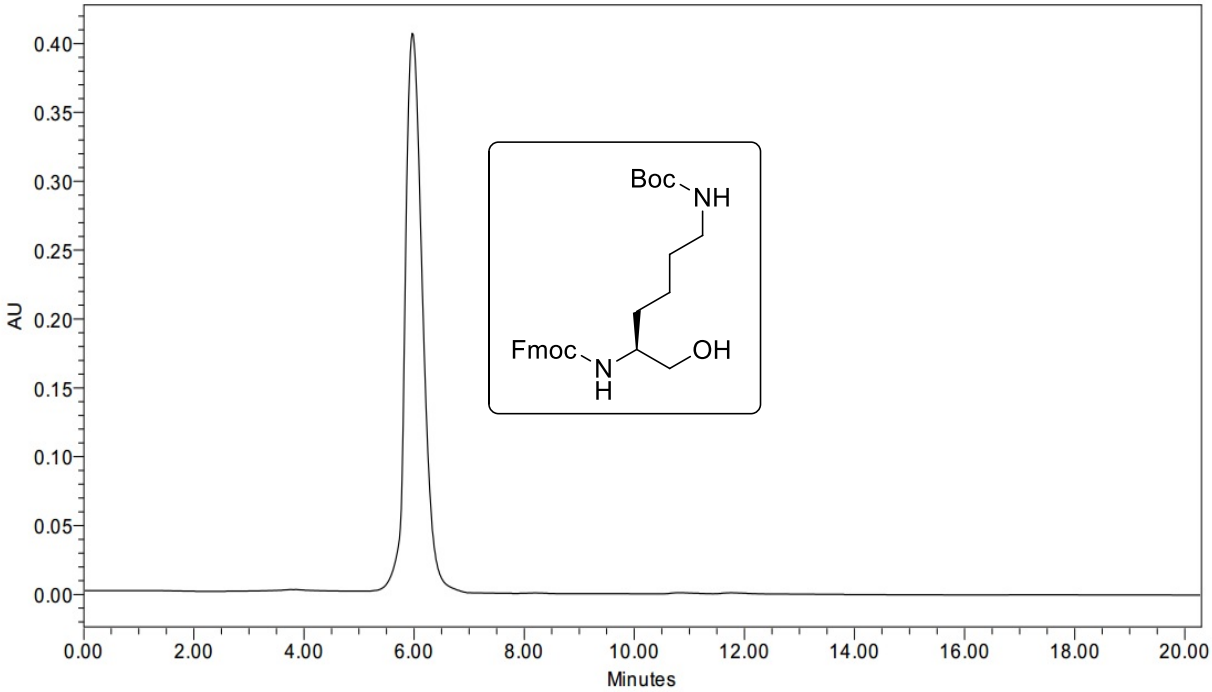


Figure 4.8.2.10. *HPLC spectra of compound* ***2q***

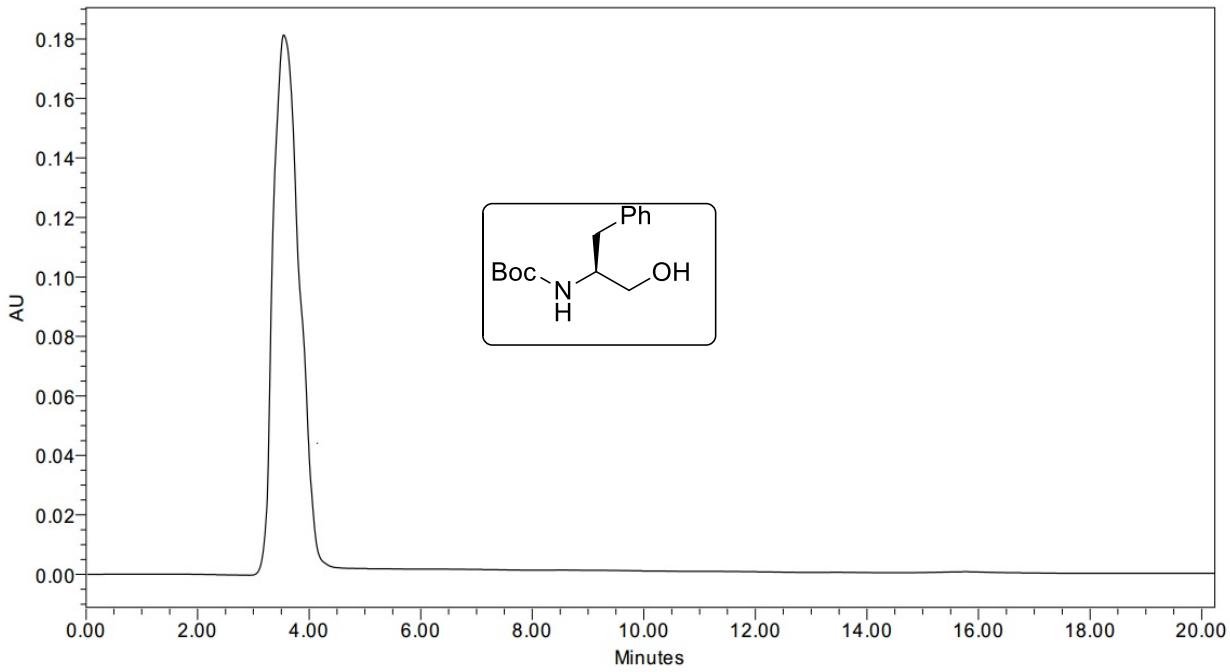


Figure 4.8.2.11. *HPLC spectra of compound* ***2s***

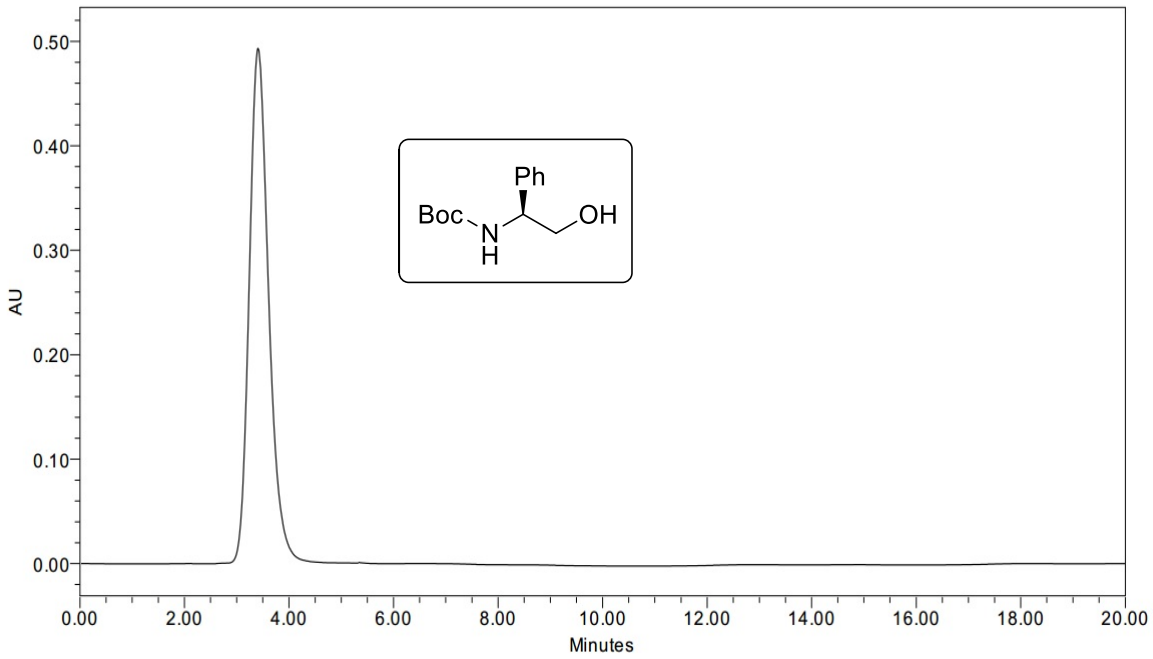


Figure 4.8.2.12. *HPLC spectra of compound* ***2t***

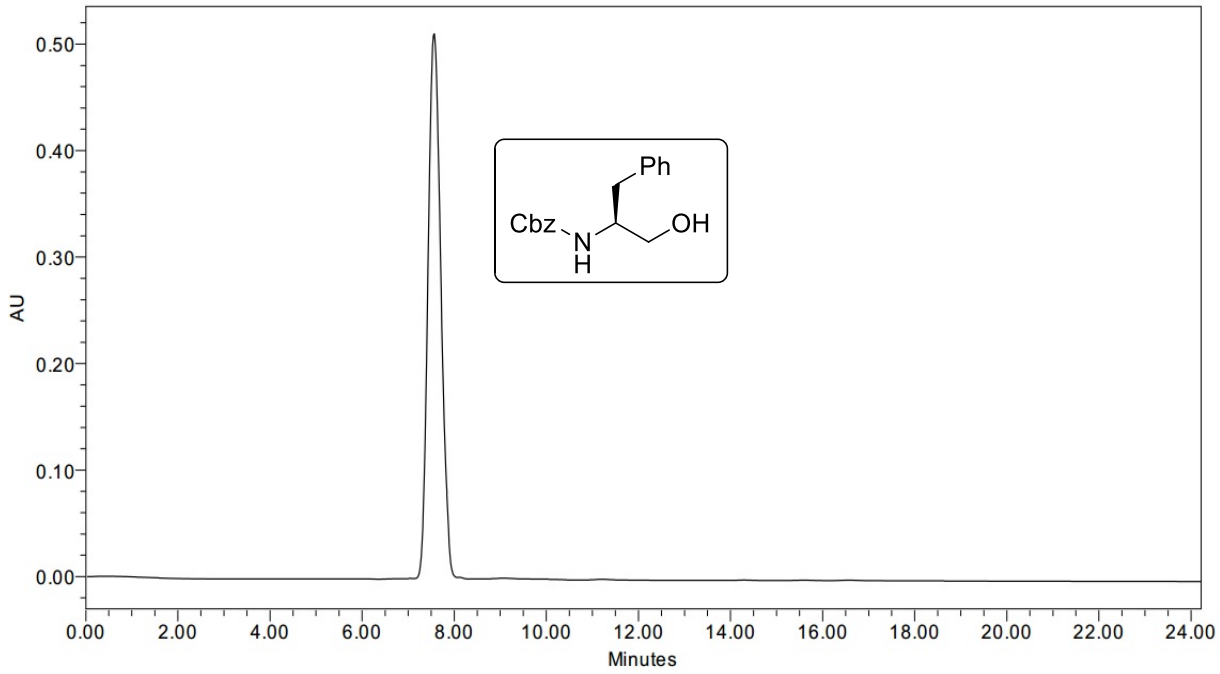


Figure 4.8.2.13. *HPLC spectra of compound* ***2u***

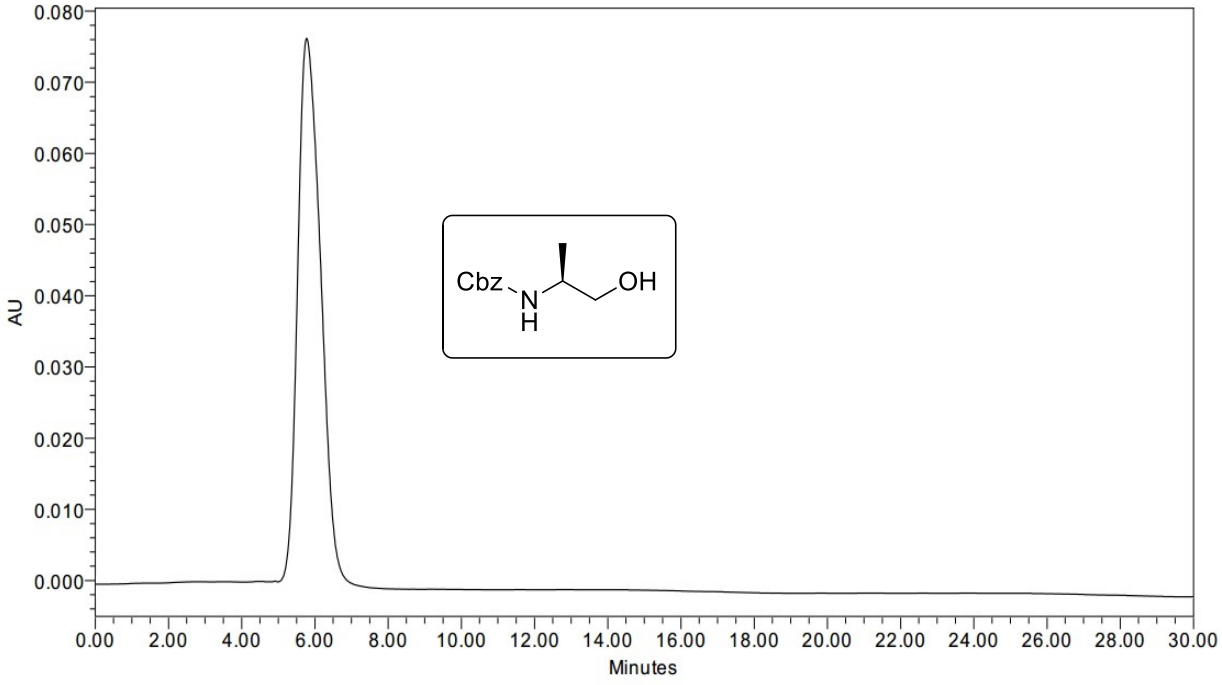


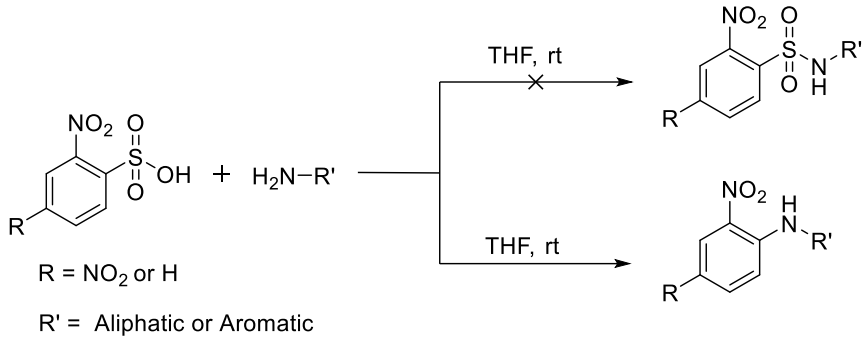
Figure 4.8.2.14. *HPLC spectra of compound* ***2v***

Chapter 5

Unprecedented *N*-Arylation of Amines *via* ipso-Nucleophilic Substitution on Nitrobenzene Sulfonic Acids

Arylamine compounds are versatile building blocks commonly encountered in many natural products, pharmaceuticals, photographic materials, agrochemicals, dyes, and polymers (Chapter 1, section 1.2.5). Because of the diverse interest of arylamines, several methods have been developed for the synthesis of arylamines (Chapter 1, section 1.3.4). The literature survey reveals that palladium-catalyzed cross-coupling reactions are most convenient approaches for the synthesis of arylamines. However, these reactions have some limitations such as a) use of expensive palladium complexes and their sensitivity towards exogenous oxygen and moisture, b) protocols leading to higher cost and c) poor substrate scope.[1] Alternatively, copper-mediated aryl coupling reactions are widely used in industrial scale, due to inexpensive copper salts and straight-forward approach. However, these protocols also suffer from some drawbacks: a) requirement of the stoichiometric or large amount of copper salts, which are insoluble in most organic solvents, b) the yields are not reproducible, c) high temperature and longer reaction time.[2] Therefore, it is always desirable to adopt a transition-metal-free method for the synthesis of arylamines. In this connection, few reports described the transition-metal-free couplings between primary or secondary amines and aryl halides.[3] However, usage of strong bases, lack of regioselectivity and modest yields makes this approach unattractive for most purposes.

For our research on medicinal chemistry, we wanted to convert aromatic sulfonic acid to the corresponding sulfonamide, which was achieved by our group previously by activating sulfonic acids,[4] but now by direct coupling. In an attempt to do so, we reacted aromatic sulfonic acids with an amine in THF at room temperature; unexpectedly we obtained an arylamine instead of the desired sulphonamide. In this chapter, we studied a simple and efficient methodology for the synthesis of arylamine directly from nitrobenzene sulfonic acid and amines without using any metal and additives (Scheme 5.1). This protocol neither requires heat nor expensive and air-sensitive metals and ligands that are often required in transition-metal catalyzed cross-coupling reactions.

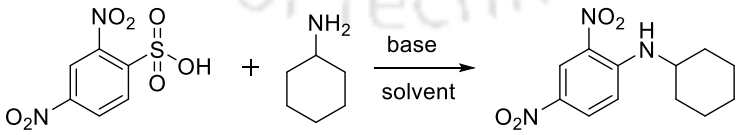


Scheme 5.1. *Unprecedented N-arylation of amines*

5.1. Optimization and substrates scope for the synthesis of arylamines

As a starting point for the development of our direct amination, we first examined the coupling reaction between 2,4-dinitrobenzene sulfonic acid and cyclohexylamine for optimizing reaction conditions, and the results are outlined in Table 5.1.1. We screened a variety of solvents, e.g., CH_3CN, H_2O, DCM, $CHCl_3$ EtOAc, DMF, MeOH, and THF. In the case of THF, we observed moderate yield (entry 8). In order to improve the yield, we used various bases such as DMAP, DBU, DABCO, and DIPEA. However, no change in the yield (entries 9-12) was noted. After that, we increased the equivalence of base (DIPEA) up to 4 fold, the same results were observed (Entries 13-15). These results indicated that there was no effect of bases on the reaction. Furthermore, we increased the equivalence of amine; surprisingly we noticed the enhancement in the yield of the desired product. We observed 74%, 94% and 96% yield for 2, 3 and 4 equiv of the amine (Entries 16-18), respectively. Therefore, 3 equivalents of amine and THF as a solvent were kept as the optimal condition.

Table 5.1.1. Optimization of the reaction conditions[a]



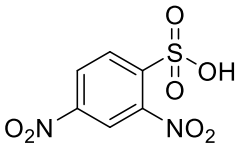
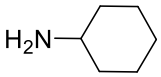
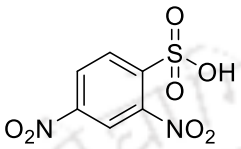
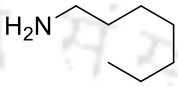
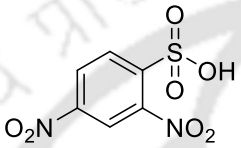
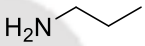
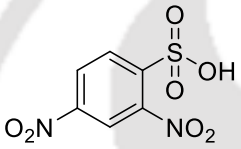
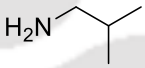
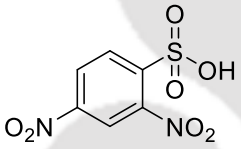
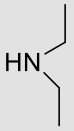
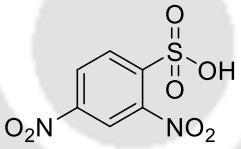
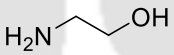
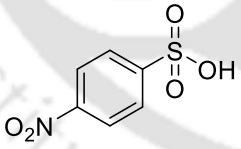
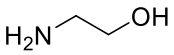
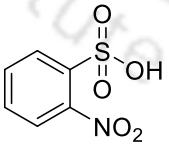
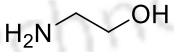
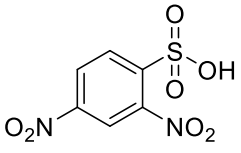
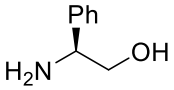
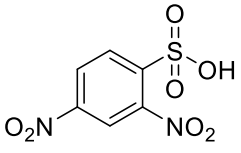
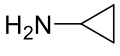
Entry	Solvents	Amine (equiv)	Base (equiv)	Yield (%)[b]
1	CH_3CN	1	-	22
2	H_2O	1	-	20

3	DCM	1	-	25
4	$CHCl_3$	1	-	26
5	EtOAC	1	-	24
6	DMF	1	-	21
7	MeOH	1	-	23
8	THF	1	-	44
9	THF	1	DMAP (1)	42
10	THF	1	DBU (1)	45
11	THF	1	DABCO (1)	44
12	THF	1	DIPEA (1)	45
13	THF	1	DIPEA (2)	44
14	THF	1	DIPEA (3)	44
15	THF	1	DIPEA (4)	42
16	THF	2	-	73
17	**THF**	**3**	**-**	**94**
18	THF	4	-	96

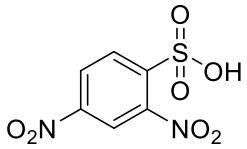
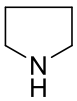
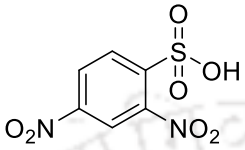
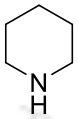
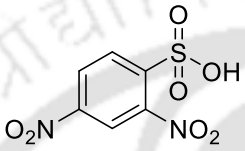
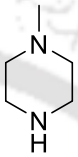
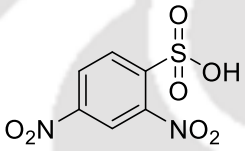
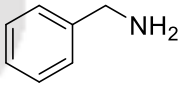
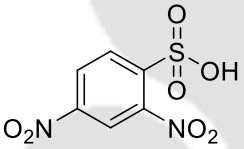
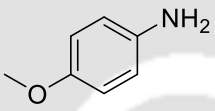
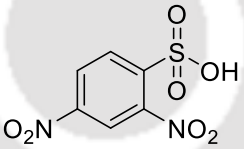
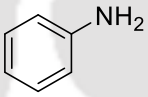
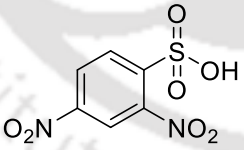
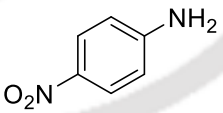
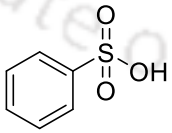
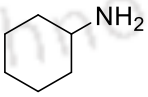
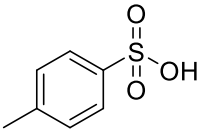
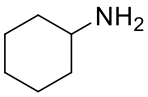
[a] Reaction conditions: 2,4-Dinitrobenzene sulfonic acid (0.5 mmol), Cyclohexylamine (Varied amount), DIPEA (different amount) stirred 30 min at room temperature. [b] Isolated yield.

With the optimal conditions in hand, we examined the scope of the reaction by using various substituted benzene sulfonic acids and common amines (Table 5.1.2). As shown in Table 5.1.2, both primary and secondary amines worked well in good to excellent yields (entries 1-5). Also, the reaction worked well with *β*-amino alcohols (entries 6-9). In case of *β*-amino alcohols, amine group was found to be arylated selectively, and hydroxyl group remained unreacted. Next, we extended the scope of reaction to the amination on heterocyclic compounds such as pyrrolidine, piperidine, and 1-methylpiperazine (entries 11-13).

Table 5.1.2. Facile *N*-arylation of simple amines[a]

Entry	Sulphonic acid	Amine	Product	
			Id	Yield (%)[b]
1			**3a**	94
2			**3b**	92
3			**3c**	93
4			**3d**	88
5			**3e**	83
6			**3f**	87
7			**3g**	n.d
8			**3h**	74
9			**3i**	83
10			**3j**	92

Continued……

Entry	Sulphonic acid	Amine	Product	
			Id	Yield (%)[b]
11			**3k**	84
12			**3l**	81
13			**3m**	88
14			**3n**	82
15			**3o**	79
16			**3p**	n.d
17			**3q**	n.d
18			**3r**	n.d
19			**3s**	n.d

[a] Reaction conditions: Sulfonic acid (0.5 mmol), Amine (1.5 mmol), Reaction time 30 min. [b]Isolated yield with respect to the sulfonic acid.

The electron-rich aromatic aniline, 4-methoxyaniline (entry 15) efficiently reacted with 2,4-dinitrobenzene sulfonic acid and gave the desired product in 79% yield. On the other hand, neutral and electron deficient aromatic anilines such as aniline and 4-nitroaniline (entries 16-17) failed to produce the desired product. Also, we could not observe arylation reaction with electron-rich benzene sulfonic acids (entries 18-19).

We next studied the scope of this methodology with various *C*-protected amino acids and 2, 4-dinitrobenzene sulfonic acid. All the substrates including the sterically hindered *C*-protected methyl esters of amino acids, e.g., leucine, valine, serine and phenylalanine (entries 1-8, Table 5.1.3) produced arylation products in moderate to high yields with high purity. Also, the reaction worked very well with *C*-protected *tert*-butyl esters of alanine, phenylalanine, and proline (entries 9-13). This methodology is compatible with *C*-terminus unprotected amino acid (entry 14) and the side chain amino group of amino acids (entry 15). Also, we successfully achieved arylation on dipeptides with good yield (entry 17).

All the products were very pure without any column chromatography and characterized by using various spectroscopic tools. The chemical structure of the compound **3d** and **5f** was further confirmed by X-ray crystallographic analysis (Figure 5.1.1).

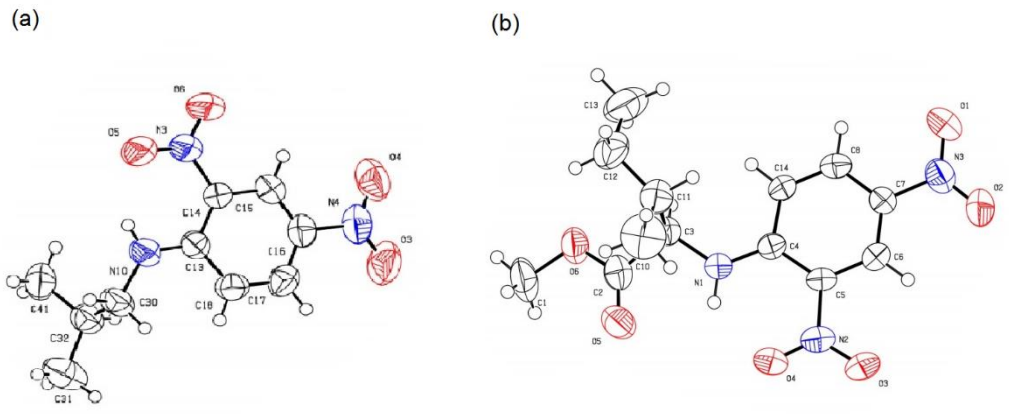
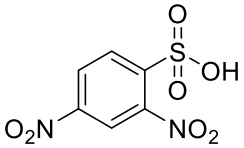
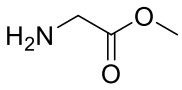
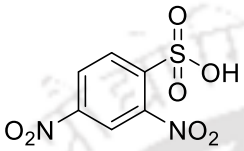
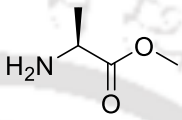
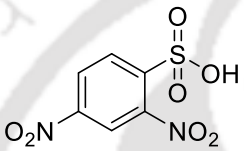
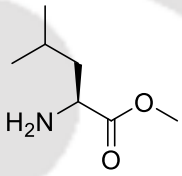
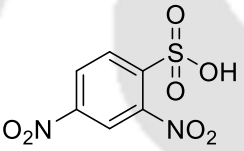
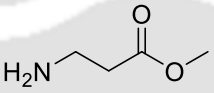
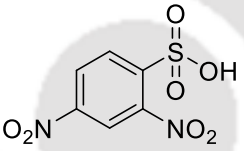
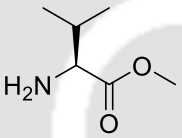
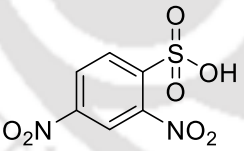
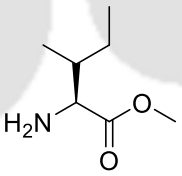
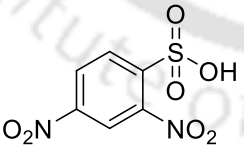
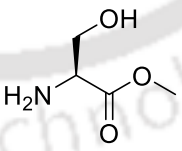
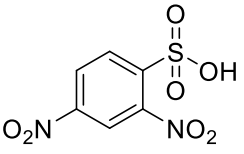
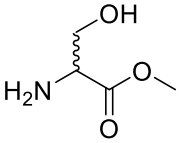
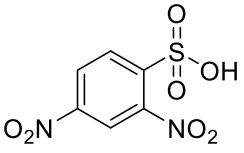
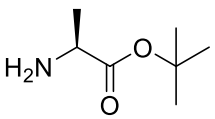
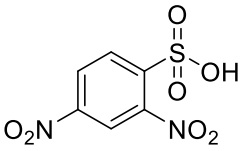
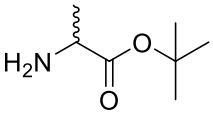
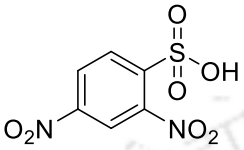
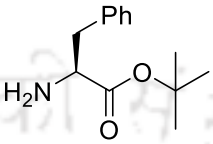
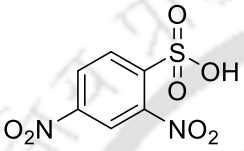
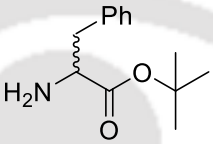
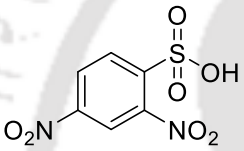
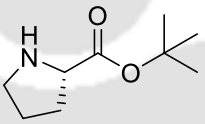
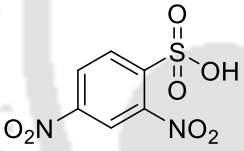
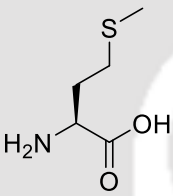
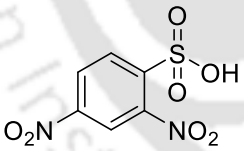
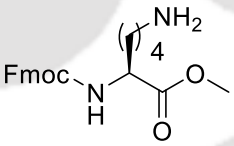
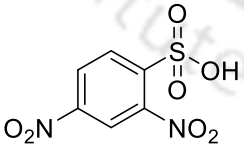
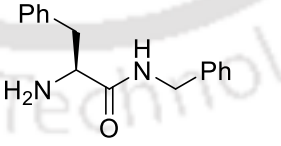
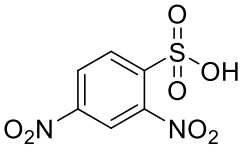
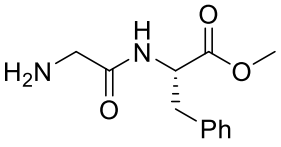


Figure 5.1.1. *X-ray crystallographic structure of (a) 3d and (b) 5f (ORTEP diagram with ellipsoid of 50% probability, CCDC No. (a) 1580047 (b) 1586476)*

Table 5.1.3. Facile *N*-arylation of the amino acids[a]

Entry	Sulphonic acid	Amino acid	Product	
			Id	Yield (%)[b]
1			**5a**	90
2			**5b**	86
3			**5c**	79
4			**5d**	85
5			**5e**	76
6			**5f**	72
7			**5g**	70
8			**5h**	70
9			**5i**	76

Continued……

Entry	Sulphonic acid	Amino acid	Product	
			Id	Yield (%)[b]
10			**5j**	75
11			**5k**	72
12			**5l**	73
13			**5m**	68
14			**5n**	62
15			**5o**	66
16			**5p**	69
17			**5q**	64

[a] Reaction conditions: 2,4-Dinitrobenzenesulfonic acid (0.5 mmol), amino acid (1.5 mmol), DIPEA (1.5 mmol), Reaction time 3 h. [b]Isolated yield with respect to sulfonic acid.

5.2. Racemization study

Racemization is a crucial factor in the synthesis of the pharmaceutical molecules, but we could not find any report for the racemization studies for such an amination reaction. At first, we performed arylation with *C*-protected methyl esters of DL- and L-serine using our protocol (entries 7-8, Figures 5.8.2.4 and 5.8.2.5). In the chiral HPLC profile, two peaks appeared at 18.5 and 21.5 for the DL compound, and only one peak appeared at 20.5 for the L compound (Figure 5.2.1). There was no signal of racemization for L-isomer in the HPLC profile. The HPLC profile of the DL-isomer helped as a reference. Furthermore, we synthesized another two sets of L and DL compounds (entries 9-12, Figures 5.8.2.6-5.8.2.9) and found the same results confirming no detectable racemization during the amination reaction. Therefore, this method can be used for amino acid and peptide derivatization without detectable racemization.

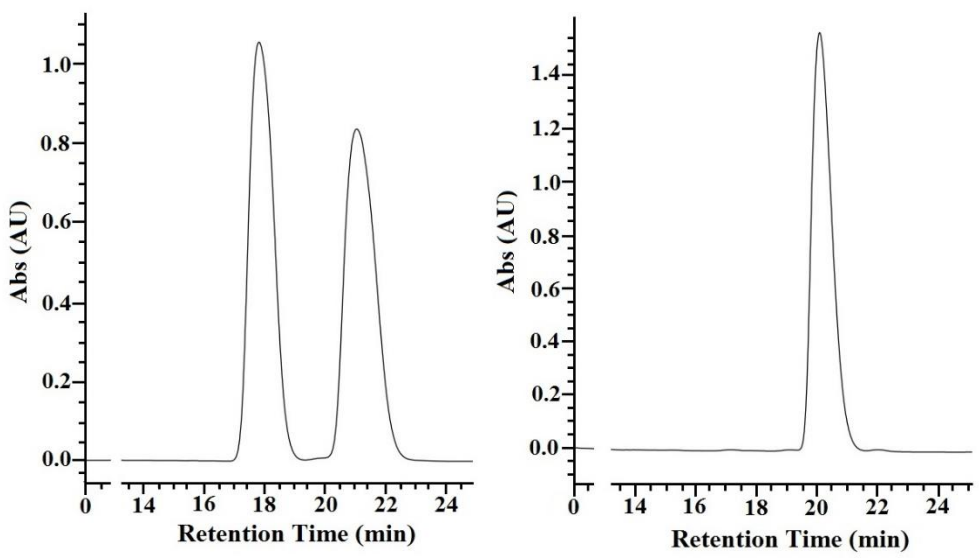
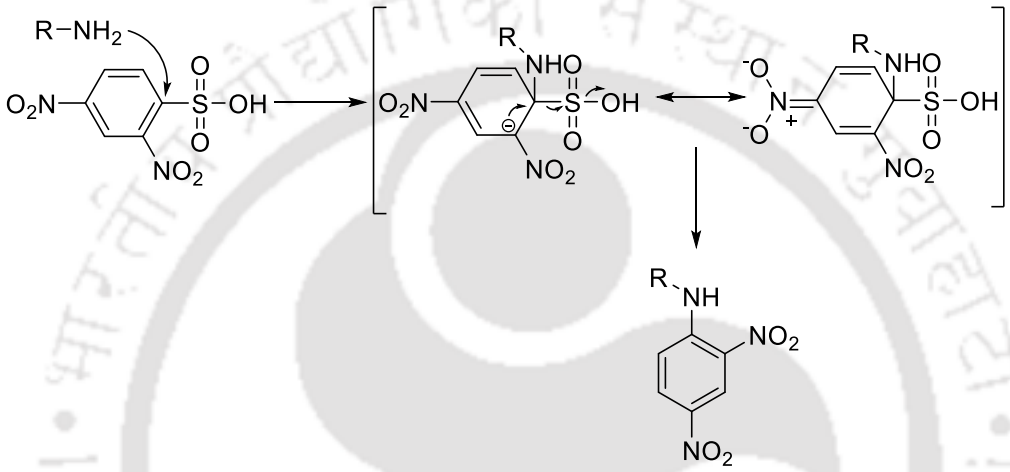


Figure 5.2.1. *HPLC profiles of DL and L of arylated serine compounds*

5.3. Plausible mechanism

A plausible mechanism is drawn based on the existing literature (Scheme 5.3.1).[5] When there are electron-withdrawing substituents on the benzene ring of the aromatic sulfonic acid, the benzene ring became relatively electron deficient, and the reaction proceeded smoothly. On the other hand, when we used unsubstituted benzene sulfonic acid or the same substituted by electron donating groups or any aliphatic sulfonic acid, we did not

observe the desired product. Therefore, we concluded that the reaction proceeded *via* ipso nucleophilic aromatic substitution ($^{i}S_NAr$, Scheme 5.3.1) by the formation of a Meisenheimer complex. The Meisenheimer complex was stabilized by the presence of the electron withdrawing groups. Furthermore, comparison of the reactions in entries 6, 7 and 8 in Table 5.1.2 suggests no reaction in the absence of the ortho-nitro group, which can be accounted for the higher rate of the reactions with ortho substituted aromatic sulfonic acids by stabilization of the Meisenheimer complex via ortho effect.[5b]



Scheme 5.3.1. *A plausible mechanism for the formation of arylamines*

5.4. Conclusion

A mild, efficient and eco-friendly method for the synthesis of arylamine from aryl sulfonic acid *via* ipso nucleophilic aryl substitution (^{i}SNAr) by an amine has been discussed in this chapter. To the best of our knowledge, this is the first report for the transformation of benzene sulfonic acid to the corresponding aminated products at room temperature without the assistance of any metals, activating agents, halogenated agents, and toxic oxidant. Main advantages of this method involve short reaction time with good to excellent yields in high purity, as well as convenient operation. Also, we disclosed the racemization study that indicated no racemization during amination reaction with chiral amino acids. Therefore, our method is new, environmentally friendly and it applies to the synthesis of amino acid and peptide derivatives.

5.5. Experimental Section

5.5.1. Materials and Instrumentation

As described in chapter 2 section 2.5.1

5.5.2. General procedure for the synthesis of arylamine from simple amines

Sulfonic acid (0.5 mmol) was added to the amine (1.5 mmol) in THF (2 mL) solvent at room temperature and stirred for 30 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated using rotary evaporator and then diluted with 15 mL of ethyl acetate, washed with 5% HCl (2×10 mL), 5% $NaHCO_3$ (2×10 mL), saturated NaCl solution (2×10 mL) and dried over anhydrous Na_2SO_4. The obtained residue was pure, and any further purification by column chromatography was not required.

5.5.3. General procedure for the synthesis of arylamine from *C*-protected amino acid

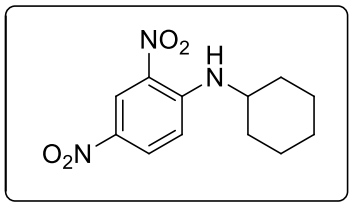
A mixture of the methyl ester of amino acid (3 mmol) and DIPEA (1 mmol) was added to sulfonic acid (1 mmol) in THF (2 mL) solvent at room temperature and stirred 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated using rotary evaporator and then diluted with 15 mL of ethyl acetate, washed with 5% HCl (2×10 mL), 5% $NaHCO_3$ (2×10 mL), saturated NaCl solution (2×10 mL) and dried over anhydrous Na_2SO_4. The obtained residue is very pure and no need any further column purification.

5.5.4. General procedure for the synthesis of arylamine from amino acid

Amino acid (3 mmol) was dissolved in THF and NaOH (aq.) solution. Then sulfonic acid (1 mmol) was added and stirred 3 h at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated using a rotary evaporator and acidified with 5% HCl then extracted with ethyl acetate (3×10 mL) and dried over anhydrous Na_2SO_4. The obtained residue was very pure, and any further purification by column chromatography was not required.

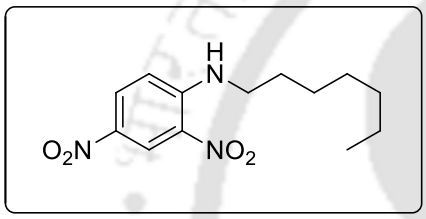
5.6. Characterization Data

_N_-Cyclohexyl-2,4-dinitroaniline 3a.



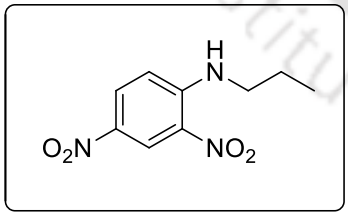
Yellow solid; (124 mg, 94%); mp 157-159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.127-9.120 (d, *J* = 2.8 Hz, 1H), 8.62-8.60 (d, *J* = 6.4 Hz, 1H), 8.23-8.20 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz,1H), 6.94-6.92 (d, *J* = 9.6 Hz, 1H), 3.62-3.60 (m, 1H), 2.08-1.23 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 130.3, 124.8, 114.4, 52.0, 32.5, 25.4, 24.5; FT-IR (KBr) 3350, 3109, 2942, 1619, 1586, 1516, 1330 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$, calcd for $C_{12}H_{16}N_3O_4$, 266.1141; found, 266.1130.

_N_-Heptyl-2,4-dinitroaniline 3b.



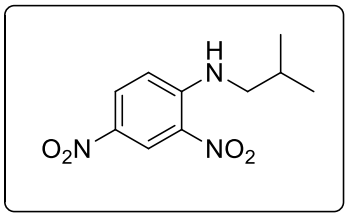
Yellow liquid; (129 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07-9.06 (d, *J* = 2.4 Hz, 1H), 8.55 (br, 1H), 8.24-8.21 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.93-6.90 (d, *J* = 9.6 Hz, 1H), 3.42-3.37 (m, 2H), 1.80-1.72 (m, 2H), 1.46-1.25 (m, 10H), 0.88-0.84 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 130.4, 124.3, 114.1, 43.7, 31.7, 28.9, 28.7, 27.0, 22.6, 14.1; FT-IR (KBr) 3367, 3106, 2929, 1622, 1590, 1524, 1336 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$, calcd for $C_{13}H_{20}N_3O_4$, 282.1454; found, 282.1451.

2,4-Dinitro-_N_-propylaniline 3c.



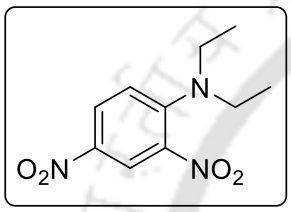
Yellow solid; (104 mg, 93%); mp 98-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.148-9.141 (d, *J* = 2.4 Hz, 1H), 8.58 (br, 1H), 8.28-8.25 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.93-6.91 (d, *J* = 9.6 Hz, 1H), 3.41-3.36 (m, 2H), 1.86-1.77 (m, 2H), 1.10-1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 130.4, 124.3, 114.1, 45.3, 22.1, 11.5; FT-IR (KBr) 3368, 3107, 2927, 1622, 1583, 1520, 1421, 1336 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_9H_{12}N_3O_4$ 226.0828, found 226.0818.

_N_-Isobutyl-2,4-dinitroaniline 3d.



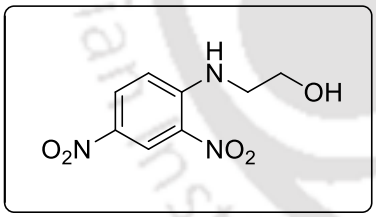
Yellow solid; (105 mg, 88%); mp 82-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.119-9.112 (d, *J* = 2.8 Hz, 1H), 8.65 (br, 1H), 8.26-8.22 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.92-6.90 (d, *J* = 9.2 Hz, 1H), 3.25-3.22 (tr, *J* = 5.6 Hz, 2H), 2.11-2.01 (m, 1H), 1.065-1.068 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 130.4, 124.5, 114.1, 51.2, 28.1, 20.4; FT-IR (KBr) 3357, 2921, 1621, 1585, 1521, 1311, 1233 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{10}H_{14}N_3O_4$ 240.0984, found 240.0969.

_N,N_-Diethyl-2,4-dinitroaniline 3e.



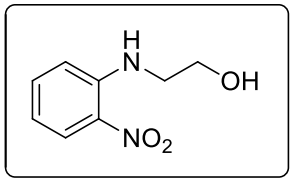
Brown oil; (99 mg, 83%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.155-9.151 (d, *J* = 2.4 Hz, 1H), 8.29-8.27 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.92-6.91 (d, *J* = 9.6 Hz, 1H), 3.49-3.45 (m, 4H), 1.44-1.42 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.4, 136.2, 130.6, 124.6, 114.0, 38.5, 14.3; FT-IR (KBr) 3435, 2921, 1621, 1585, 1525, 1335 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{10}H_{14}N_3O_4$ 240.0984, found 240.0968.

2-((2,4-Dinitrophenyl)amino)ethanol 3f.



Yellow solid; (98 mg, 87%); mp 88-90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.047-9.041 (d, *J* = 2.4 Hz, 1H), 8.81 (br, 1H), 8.23-8.20 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.98-6.96 (d, *J* = 9.6 Hz, 1H), 4.01-3.98 (t, *J* = 5.2 Hz, 2H), 3.62-3.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 130.4, 124.4, 114.3, 60.4, 45.4; FT-IR (KBr) 3350, 3333, 2923, 1622, 1584, 1498, 1335, 1039 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_8H_{10}N_3O_5$ 228.0620, found 228.0604.

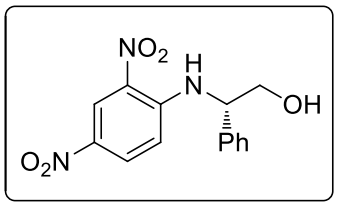
2-((2-Nitrophenyl)amino)ethanol 3h.



Red oil; (102 mg, 74%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (br, 1H), 8.18-8.17 (d, *J* = 7.2 Hz, 1H), 7.45-7.42 (t, *J* = 7.2 Hz, 1H), 6.90-6.88 (d, *J* = 7.8 Hz, 1H), 6.67-6.65 (t, *J* = 7.2 Hz, 1H), 3.95-3.93 (t, *J* = 6 Hz, 2H), 3.52-3.49 (m, 2H); 2.62 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.4, 127.1, 115.8, 113.9, 61.1, 45.1; FT-IR (KBr) 3378, 2920, 2851,

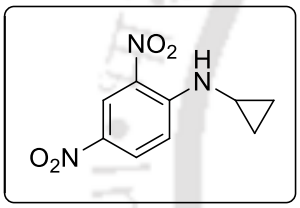
1619, 1572, 1511, 1259, 1036 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_8H_{11}N_2O_3$ 183.0770, found 183.0756.

(S)-2-((2-Dinitrophenyl)amino)-2-phenylethan-1-ol 3i.



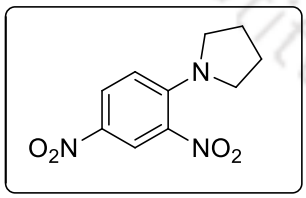
Yellow liquid; (102 mg, 83%); ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (br, 1H), 9.14-9.13 (d, *J* = 2.8 Hz, 1H), 8.10-8.07 (dd, *J* = 2.4 Hz, *J* = 2.8 Hz, 1H), 7.40-7.33 (m, 5H), 6.70-6.68 (d, *J* = 9.6 Hz, 1H), 4.81-4.77 (m, 1H), 4.13-3.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 137.4, 136.7, 131.2, 130.3, 129.6, 128.9, 126.6, 124.3, 115.5, 66.7, 59.7; FT-IR (KBr) 3435, 3358, 2923, 1618, 1522, 1334 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{14}N_3O_5$ 304.0933, found 304.0959.

***N*-Cyclopropyl-2,4-dinitroaniline 3j**.



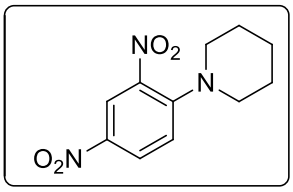
Yellow solid; (112 mg, 92%); mp 120-122 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 9.10-9.07 (d, *J* = 2.4 Hz, 1H), 8.54 (br, 1H), 8.30-8.28 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 7.40-7.39 (d, *J* = 9.0 Hz, 1H), 2.72-2.68 (m, 1H), 1.06-1.02 (m, 2H), 0.76-0.73 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.6, 136.9, 130.7, 130.2, 124.0, 115.7, 25.1, 8.2; FT-IR (KBr) 3364, 3103, 1618, 1515, 1422, 1303 cm^{-1}; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_9H_9N_3NaO_4$ 246.0491, found 246.0473.

1-(2,4-Dinitrophenyl)pyrrolidine 3k.



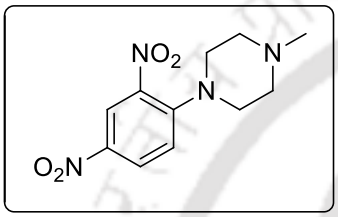
Light brown solid; (100mg, 84%); mp 93-95 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.64-8.63 (d, *J* = 2.4 Hz, 1H), 8.18-8.15 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.90-6.88 (d, *J* = 9.2 Hz, 1H), 3.35-3.32 (t, *J* = 6.4 Hz, 4H), 2.07-2.04 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 135.6, 135.1, 127.7, 124.0, 115.6, 51.2, 25.7; FT-IR (KBr) 3435, 2926, 1611, 1501, 1326 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{10}H_{12}N_3O_4$ 238.0828, found 238.0858.

1-(2,4-Dinitrophenyl)piperidine 3l.



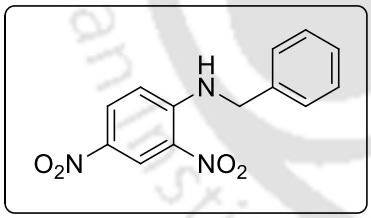
Yellow solid; (101 mg, 81%); mp 93-95 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.636-8.631 (d, *J* = 3.0 Hz, 1H), 8.17-8.15 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 7.05-7.04 (d, *J* = 9.0 Hz, 1H), 3.22-3.20 (t, *J* = 4.8 Hz, 4H), 1.72-1.64 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.6, 137.5, 128.2, 124.2, 119.2, 52.0, 25.6, 23.7; FT-IR (KBr) 2925, 1605, 1582, 1526, 1503, 1331 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_4N_3O_4$ 252.0984, found 252.0966.

1-(2,4-Dinitrophenyl)-4-methylpiperazine 3m.



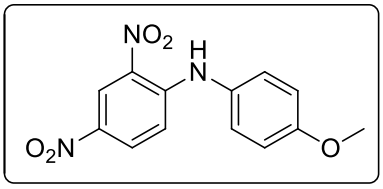
Dark brown oil; (117 mg, 88%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.686-8.681 (d, *J* = 3.0 Hz, 1H), 8.25-8.23 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 7.10-7.09 (d, *J* = 9.6 Hz, 1H), 3.30-3.29 (t, *J* = 4.8 Hz, 4H), 2.58-2.57 (t, *J* = 4.8 Hz, 4H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.5, 138.6, 128.4, 123.9, 119.5, 54.4, 50.7, 46.0; FT-IR (KBr) 2923, 1604, 1528, 1505, 1333 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{15}N_4O_4$ 267.1093, found 267.1095.

***N*-Benzyl-2,4-dinitroaniline 3n**.



Yellow solid; (112 mg, 82%); mp 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15-9.14 (d, *J* = 2.8 Hz, 1H), 8.91 (br, 1H), 8.23-8.20 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 7.42-7.33 (m, 5H), 6.92-6.90 (d, *J* = 9.2 Hz, 1H), 4.66-4.64 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 136.4, 135.7, 130.8, 130.4, 129.3, 128.4, 127.2, 124.2, 114.6, 47.6; FT-IR (KBr) 3374, 2924, 1618, 1334, 1264 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{12}N_3O_4$ 274.0828, found 274.0856.

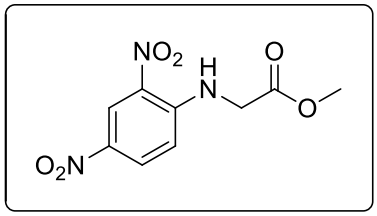
***N*-(4-Methoxyphenyl)-2,4-dinitroaniline 3o**.



Black solid; (114 mg, 79%); mp 136-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (br, 1H), 9.169-9.162 (d, *J* = 2.8 Hz, 1H), 8.14-8.11 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 7.22-7.21 (d, *J* = 8.8 Hz, 2H), 7.02-7.00 (m, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 148.1, 137.1, 130.8, 130.0, 129.3, 127.6, 124.2,

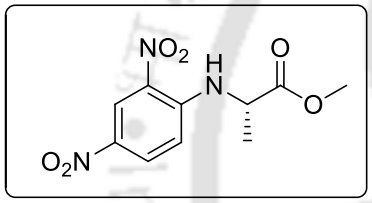
116.1, 115.5, 55.7; FT-IR (KBr) 3323, 2924, 1617, 1511, 1246 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{12}N_3O_5$ 290.0777, found 290.0802.

Methyl 2-((2,4-dinitrophenyl)amino)acetate 5a.



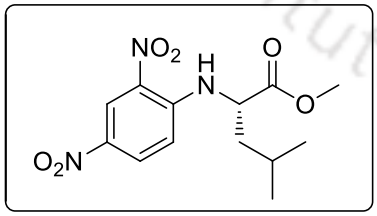
Yellow solid; (115 mg, 90%); mp 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12-9.11 (d, *J* = 2.4 Hz, 1H), 8.93 (br, 1H), 8.30-8.27 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.80-6.78 (d, *J* = 9.6 Hz, 1H), 4.22-4.20 (d, *J* = 5.2 Hz, 2H), 3.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 147.4, 137.0, 131.2, 130.6, 124.2, 114.1, 53.2, 44.9; FT-IR (KBr) 3347, 3112, 1755, 1622, 1331, 1238 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_9H_{10}N_3O_6$ 256.0570, found 256.0587.

(S)-Methyl 2-((2,4-dinitrophenyl)amino)propanoate 5b.



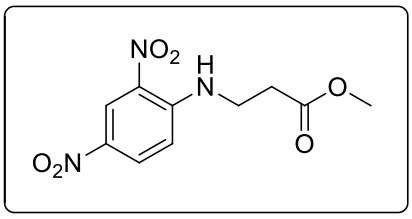
Light yellow solid; (115 mg, 86%); mp 72-74 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.155-9.151 (d, *J* = 2.4 Hz, 1H), 8.89 (br, 1H), 8.29-8.27 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.80-6.79 (d, *J* = 9.6 Hz, 1H), 4.43-4.38 (m, 1H), 3.82 (s, 3H), 1.66-1.65 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 147.1, 136.9, 130.6, 124.5, 114.0, 53.3, 51.7, 18.5; FT-IR (KBr) 3326, 2922, 1742, 1623, 1587, 1514, 1418, 1338, 1228 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{10}H_{12}N_3O_6$ 270.0726, found 270.0716.

(S)-Methyl 2-((2,4-dinitrophenyl)amino)-4-methylpentanoate 5c.



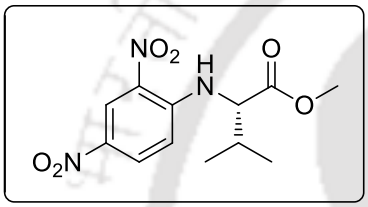
Brown oil; (123 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.166-9.162 (d, *J* = 2.4 Hz, 1H), 8.73 (br, 1H), 8.29-8.27 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.81-6.80 (d, *J* = 9.6 Hz, 1H), 4.34-4.30 (m, 1H), 3.79 (s, 3H), 1.89-1.86 (m, 2H), 1.81-1.75 (m, 1H), 1.04-1.03 (d, *J* = 6.0 Hz, 3H), 0.96-0.95 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 147.4, 136.8, 130.5, 124.3, 113.8, 54.8, 52.9, 41.3, 24.9, 22.6, 21.9; FT-IR (KBr) 3364, 2917, 1743, 1619, 1591, 1523, 1336 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{18}N_3O_6$ 312.1196, found 312.1196.

Methyl 3-((2,4-dinitrophenyl)amino)propanoate 5d.



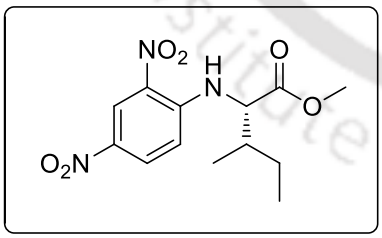
Brown solid; (114 mg, 85%); mp 96-98 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.049-9.045 (d, *J* = 2.4 Hz, 1H), 8.78 (br, 1H), 8.25-8.23 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.98-6.96 (d, *J* = 9.0 Hz, 1H), 3.76-3.73 (m, 2H), 3.72 (s, 3H), 2.78-2.76 (t, *J* = 6.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 148.1, 136.2, 130.5, 124.3, 113.8, 52.3, 39.0, 33.2; FT-IR (KBr) 3340, 3122, 2958, 1723, 1625, 1425, 1312, 1208 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{10}H_{12}N_3O_6$ 270.0726, found 270.0725.

Methyl 2-((2,4-dinitrophenyl)amino)-3-methylbutanoate 5e.



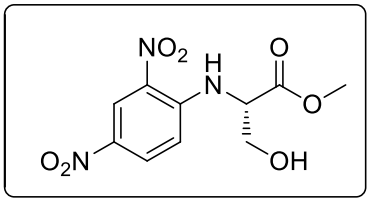
Brown oil; (112 mg, 76%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.166-9.162 (d, *J* = 2.4 Hz, 1H), 8.93 (br, 1H), 8.28-8.26 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.81-6.79 (d, *J* = 9.6 Hz, 1H), 4.17-4.15 (m, 1H), 3.79 (s, 3H), 2.39-2.36 (m, 1H), 1.13-1.12 (d, *J* = 7.2 Hz, 3H), 1.08-1.07 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 147.9, 136.9, 130.7, 124.5, 114.0, 62.0, 52.9, 31.6, 19.2, 18.5; FT-IR (KBr) 3360, 3106, 2923, 1741, 1619, 1591, 1523, 1338 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{16}N_3O_6$ 298.1039, found 298.1036.

(2S,3R)-Methyl 2-((2,4-dinitrophenyl)amino)-3-methylpentanoate 5f.



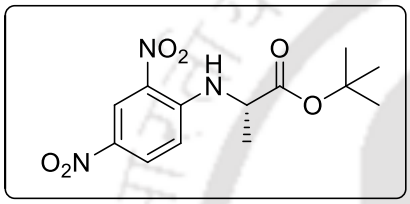
Yellow solid; (112 mg, 72%); mp 88-90 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.167-9.163 (d, *J* = 2.4 Hz, 1H), 8.96 (br, 1H), 8.28-8.26 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.80-6.79 (d, *J* = 9.6 Hz, 1H), 4.24-4.22 (m, 1H), 3.79 (s, 3H), 2.12-2.07 (m, 1H), 1.42-1.37 (m, 2H), 1.06-1.04 (d, *J* = 13.2 Hz, 3H), 1.02-0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 147.7, 136.8, 130.7, 124.5, 113.9, 60.8, 52.9, 38.0, 25.7, 15.8, 11.7; FT-IR (KBr) 3360, 2923, 1740, 1619, 1591, 1523, 1336, 1288 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{18}N_3O_6$ 312.1196, found 312.1192.

(S)-Methyl 2-((2,4-dinitrophenyl)amino)-3-hydroxypropanoate 5g.



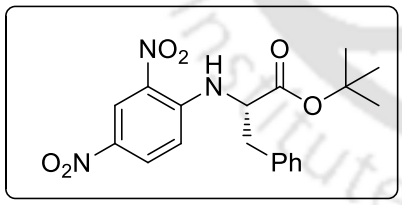
Yellow oil; (100 mg, 70%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.18 (br, 1H), 9.17-9.16 (d, *J* = 3.0 Hz, 1H), 8.29-8.27 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.87-6.86 (d, *J* = 9.6 Hz, 1H), 4.48-4.46 (m, 1H), 4.22-4.09 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 147.5, 137.1, 130.5, 124.4, 114.3, 62.6, 57.9, 53.5; FT-IR (KBr) 3424, 2922, 1742, 1620, 1589, 1337, 1155 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{10}H_{12}N_3O_7$ 286.0675, found 286.0660.

(S)-*tert*-Butyl 2-((2,4-dinitrophenyl)amino)propanoate 5i.



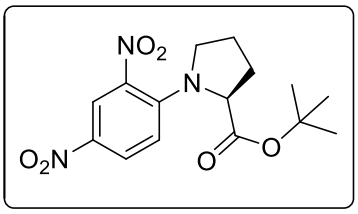
Light yellow solid; (118 mg, 76%); mp 117-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16-9.15 (d, *J* = 2.8 Hz, 1H), 8.97 (br, 1H), 8.29-8.26 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.80-6.78 (d, *J* = 9.6 Hz, 1H), 4.31-4.24 (m, 1H), 1.61-1.60 (d, *J* = 7.2 Hz, 3H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 147.0, 136.5, 131.0, 130.4, 124.3, 114.1, 83.5, 52.2, 28.0, 18.3; FT-IR (KBr) 3326, 2986, 1730, 1626, 1338, 1152 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{18}N_3O_6$ 312.1196, found 312.1199.

(S)-*tert*-Butyl 2-((2,4-dinitrophenyl)amino)-3-phenylpropanoate 5k.



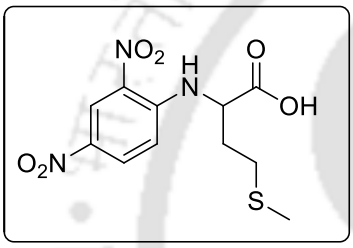
Yellow solid; (139 mg, 72%); mp 97-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11-9.10 (d, *J* = 3.0 Hz, 1H), 8.96 (br, 1H), 8.19-8.16 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 7.33-7.20 (m, 5H), 6.69-6.67 (d, *J* = 9.0 Hz, 1H), 4.49-4.44 (m, 1H), 3.33-3.17 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 146.6, 135.9, 134.7, 130.3, 129.7, 129.0, 128.2, 126.9, 123.5, 116.4, 114.2, 82.9, 57.0, 37.5, 27.2; FT-IR (KBr) 3434, 2925, 1727, 1618, 1335, 1147 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{22}N_3O_6$ 388.1509, found 388.1517.

(S)-*tert*-Butyl 1-(2,4-dinitrophenyl)pyrrolidine-2-carboxylate 5m.



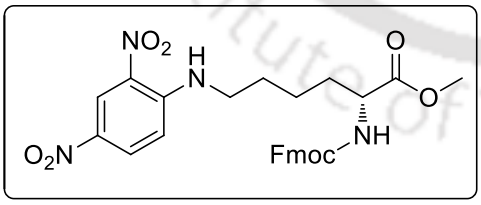
Brown liquid; (114 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62-8.61 (d, *J* = 2.4 Hz, 1H), 8.19-8.16 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 6.83-6.81 (d, *J* = 9.6 Hz, 1H), 4.41-4.38 (t, *J* = 6.4 Hz, 1H), 3.53-3.28 (m, 2H), 2.50-2.43 (m, 1H), 2.15-1.94 (m, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 145.2, 136.5, 136.1, 127.5, 123.7, 116.4, 83.1, 63.4, 52.0, 30.9, 27.9, 24.6; FT-IR (KBr) 3091, 2979, 1735, 1604, 1509, 1329 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{20}N_3O_6$ 338.1352, found 338.1375.

2-((2,4-Dinitrophenyl)amino)-4-(methylthio)butanoic acid 5n.



Brown liquid; (98 mg, 62%); ^{1}H NMR (600 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 8.98 (s, 1H), 8.86-8.85 (d, *J* = 7.2 Hz, 1H), 8.21-8.19 (d, *J* = 8.4 Hz, 1H), 7.63 (br, 1H) 6.98-6.97 (d, *J* = 9.6 Hz, 1H), 4.63-4.62 (m, 1H), 2.69-2.56 (m, 2H), 2.33-2.19 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, few drops of CD_3OD for solubility) δ 174.1, 147.2, 136.5, 130.9, 130.4, 124.0, 114.3, 67.8, 31.1, 29.7, 15.3; FT-IR (KBr) 3435, 2923, 2853, 1737, 1518, 1336 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{14}N_3O_6S$ 316.0603, found 316.0574.

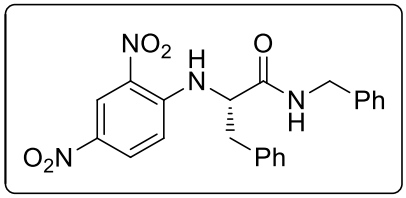
(S)-Methyl2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-6-((2,4-dinitrophenyl) amino)hexaneate 5o.



Yellow solid; (180 mg, 66%); mp 66-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.119-9.113 (d, *J* = 2.4 Hz, 1H), 8.52 (br, 1H), 8.26-8.23 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 7.77-7.75 (d, *J* = 7.6 Hz, 2H), 7.60-7.57 (t, *J* = 6.4 Hz, 2H), 7.42-7.38 (t, *J* = 7.6 Hz, 2H), 7.33-7.29 (t, *J* = 7.6 Hz, 2H), 6.89-6.87 (d, *J* = 9.6 Hz, 1H), 5.37-5.35 (t, *J* = 9.6 Hz, 1H), 4.42-4.40 (d, *J* = 8 Hz, 2H), 4.22-4.19 (t, *J* = 7.2 Hz, 1H), 3.77 (s, 3H), 3.42-3.37 (m, 2H), 1.96-1.49 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 156.1, 148.4, 143.9, 143.8, 141.5, 136.2, 130.5, 127.9, 127.2, 125.2, 124.5, 120.2, 113.9, 67.2, 53.5, 52.8, 47.3, 43.4, 32.6, 29.8, 28.2, 22.8; FT-IR (KBr)

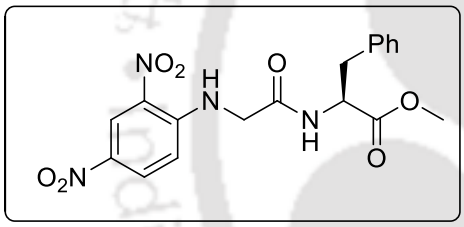
3370, 2924, 1720, 1620, 1523, 1335 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{29}N_4O_8$ 549.1985, found 549.2004.

(S)-*N*-Benzyl-2-((2,4-dinitrophenyl)amino)-3-phenylpropanamide 5p.



Light yellow solid; (145 mg, 69%); mp 126-128 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.096-9.091 (d, *J* = 3.0 Hz, 1H), 8.79 (br, 1H), 8.22-8.20 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 7.33-7.24 (m, 8H), 7.10-7.09 (m, 2H), 6.77-6.75 (d, *J* = 9.6 Hz, 1H), 6.07 (br, 1H), 4.40-4.32 (m, 3H), 3.34-3.27 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 147.1, 137.6, 137.2, 135.0, 131.7, 130.6, 129.5, 129.4, 129.0, 128.15, 128.12, 114.7, 60.2, 44.0, 39.1; FT-IR (KBr) 3432, 2923, 1653, 1624, 1456, 1341 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{22}H_{21}N_4O_5$ 421.1512, found 421.1499.

(S)-Methyl 2-(2-((2,4-dinitrophenyl)amino)acetamido)-3-phenylpropanoate 5q.



Light yellow solid; (129 mg, 64%); mp 125-127 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.13-9.12 (d, *J* = 3.0 Hz, 1H), 8.90 (br, 1H), 8.22-8.20 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz,1H), 7.21-7.20 (m, 3H), 7.01-6.99 (m, 2H), 6.67-6.66 (d, *J* = 9.6 Hz, 1H), 6.36 (br, 1H), 4.93-4.90 (m, 1H), 4.06-4.05 (d, *J* = 4.8 Hz, 2H), 3.77 (s, 3H), 3.21-3.06 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 166.7, 147.4, 137.3, 135.3, 131.5, 130.6, 129.1, 128.9, 127.6, 124.2, 53.2, 52.9, 46.7, 37.6; FT-IR (KBr) 3371, 2923, 1738, 1647, 1621, 1591, 1337, 1023 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{19}N_4O_7$ 403.1254, found 403.1244.

5.7. References

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5.8. Selected Spectra

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

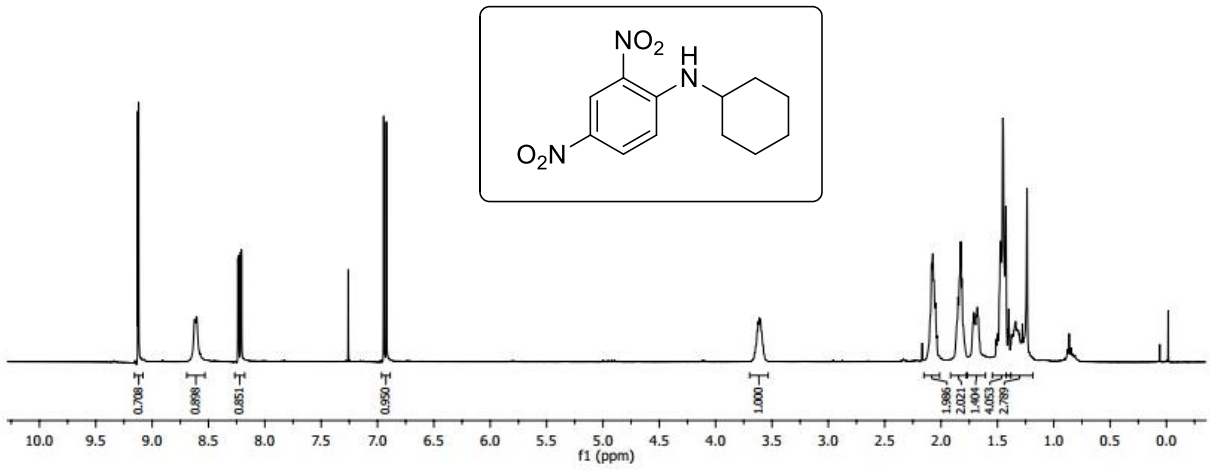


Figure 5.8.1.1. *^{1}H NMR Spectra of compound* ***3a***

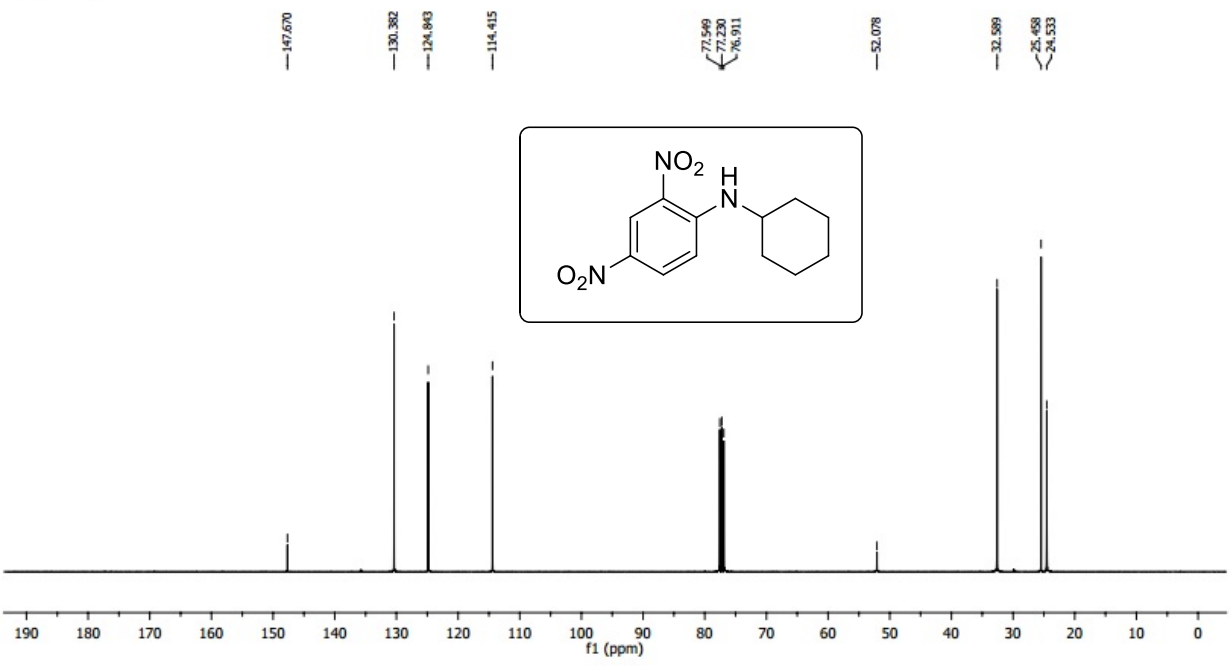


Figure 5.8.1.2. *^{13}C NMR spectra of compound* ***3a***

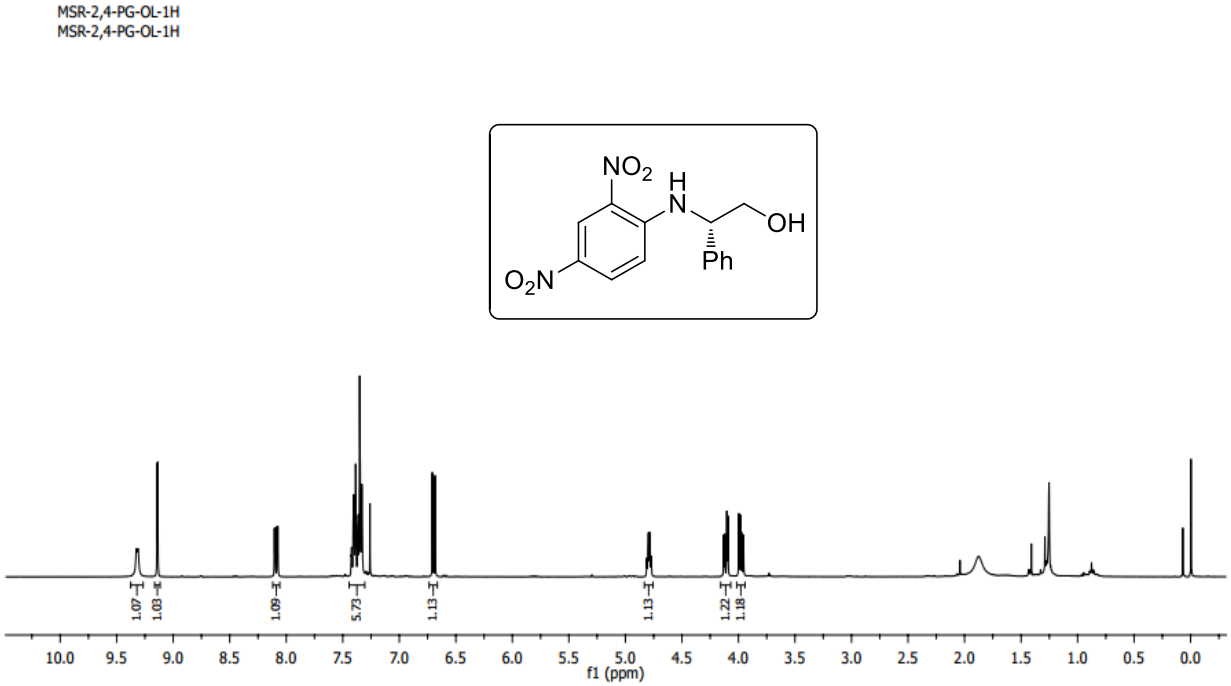


Figure 5.8.1.3. *^{1}H NMR Spectra of compound **3i***

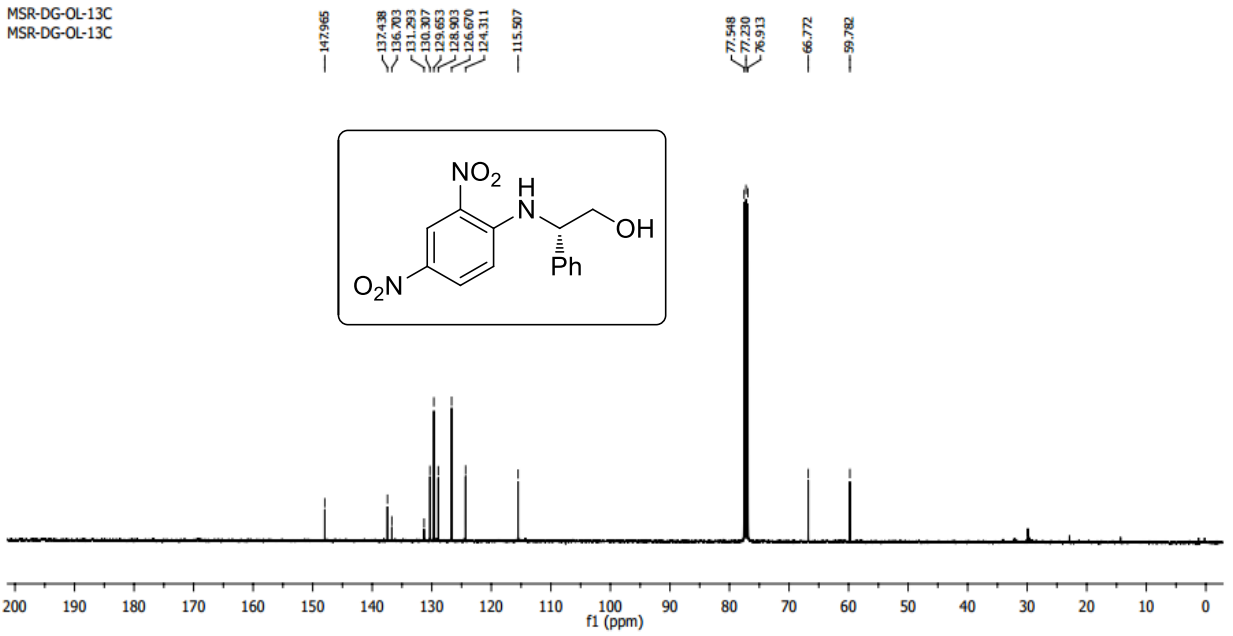


Figure 5.8.1.4. ^{13}C NMR spectra of compound **3i**

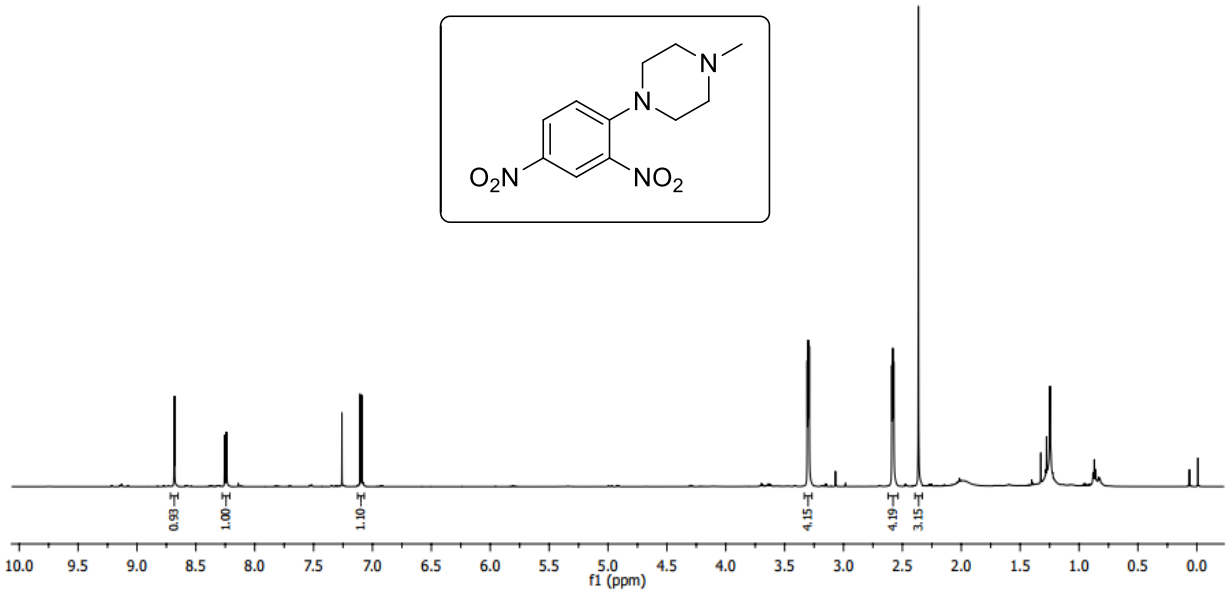


Figure 5.8.1.5. *^{1}H NMR spectra of compound* ***3m***

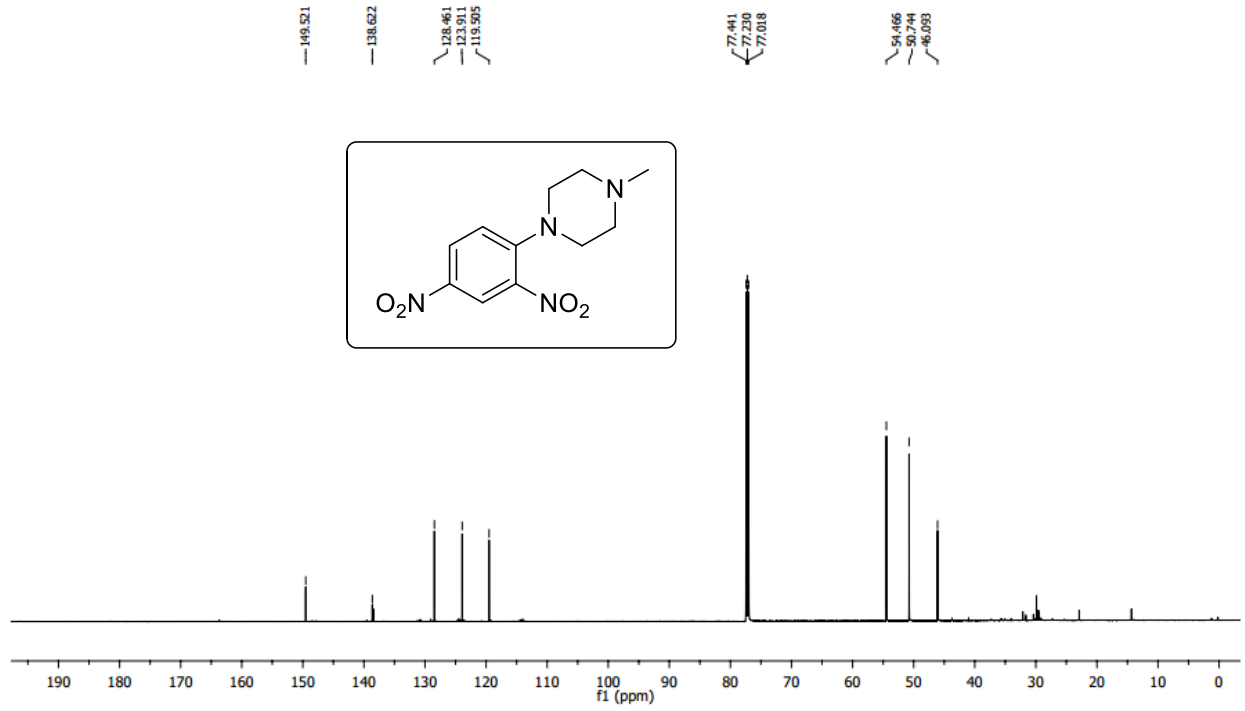


Figure 5.8.1.6. *^{13}C NMR spectra of compound* ***3m***

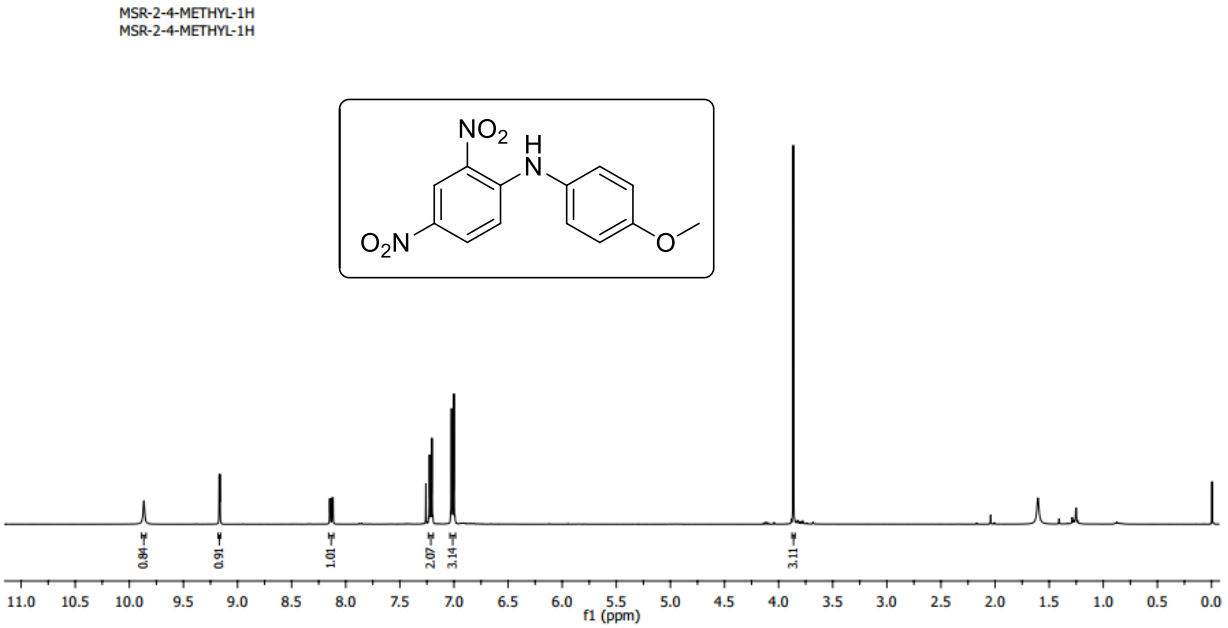


Figure 5.8.1.7. *^{1}H NMR Spectra of compound* ***3o***

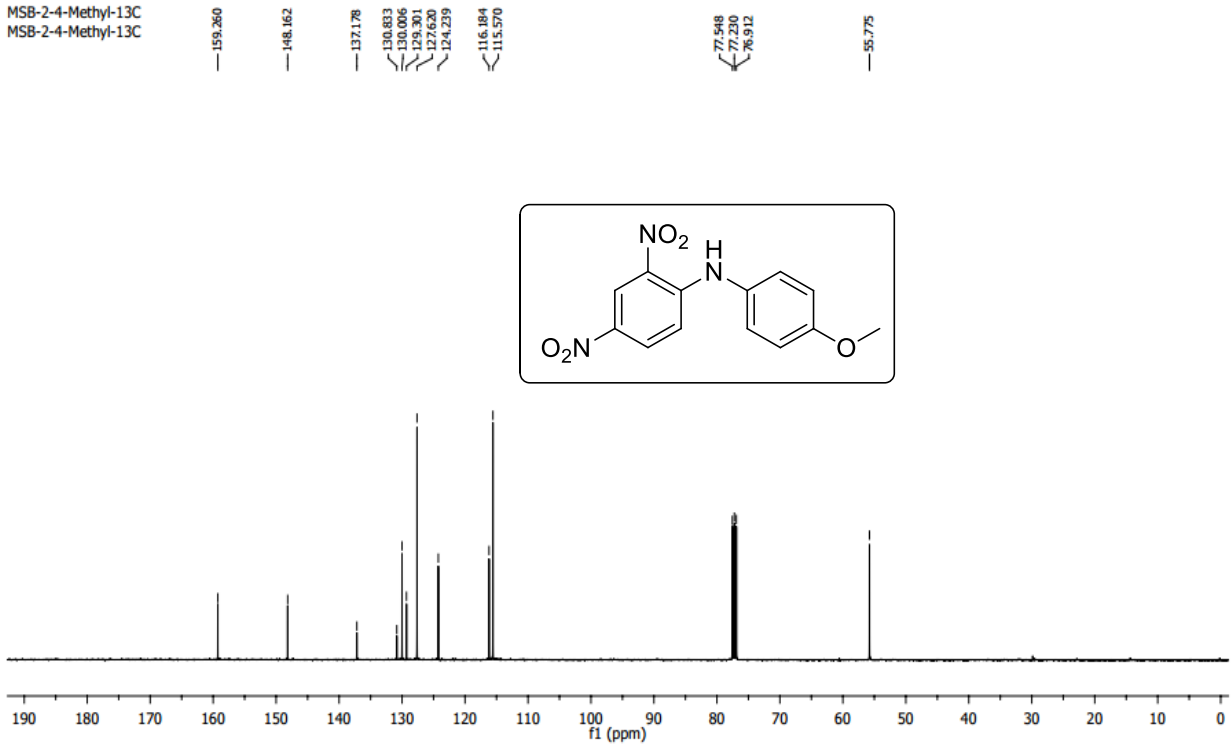


Figure 5.8.1.8. *^{13}C NMR spectra of compound* ***3o***

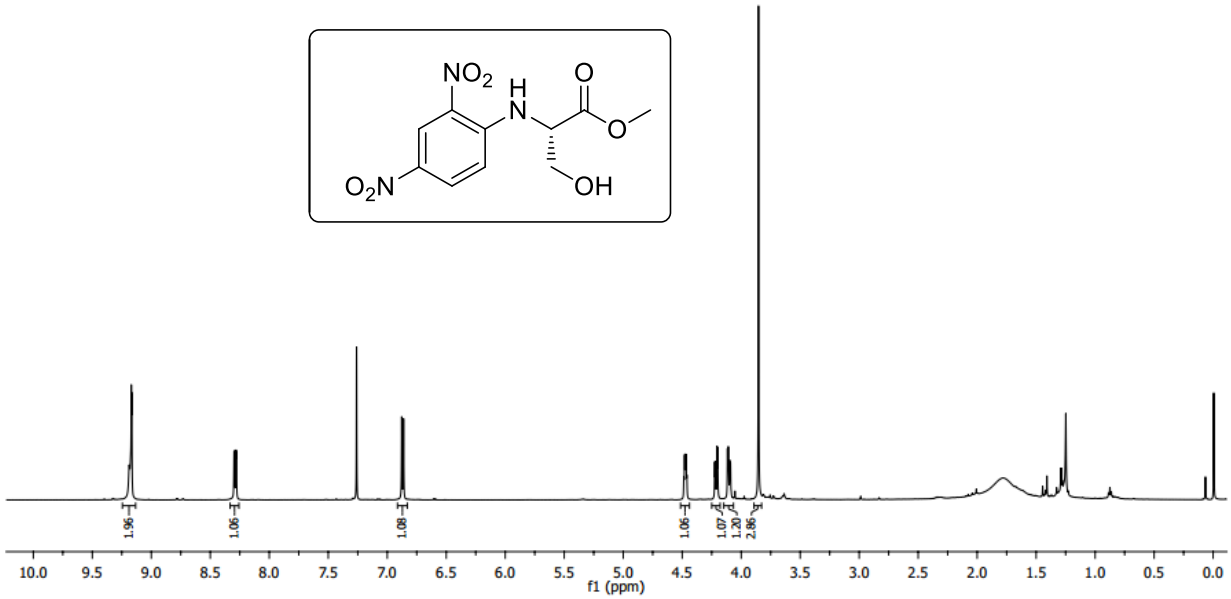


Figure 5.8.1.9. *^{1}H NMR spectra of compound* ***5g***

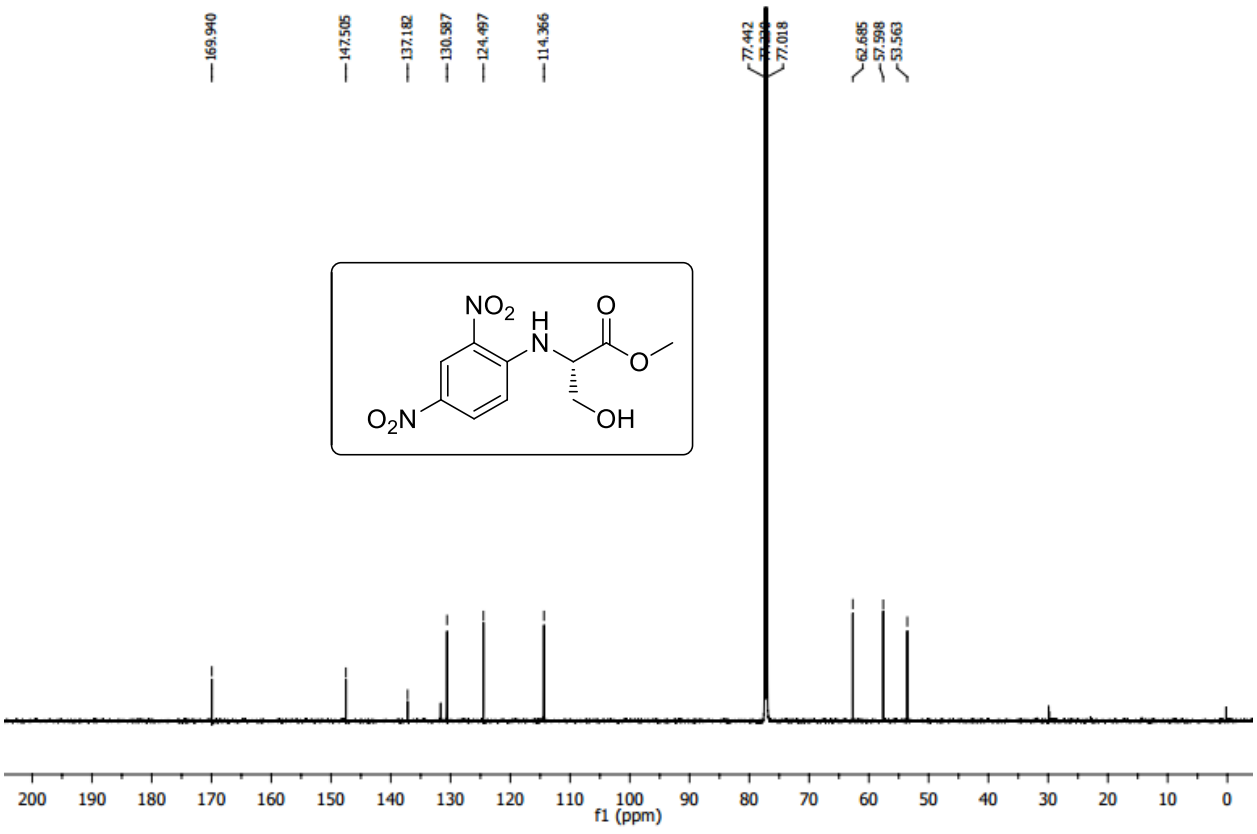


Figure 5.8.1.10. *^{13}C NMR spectra of compound* ***5g***

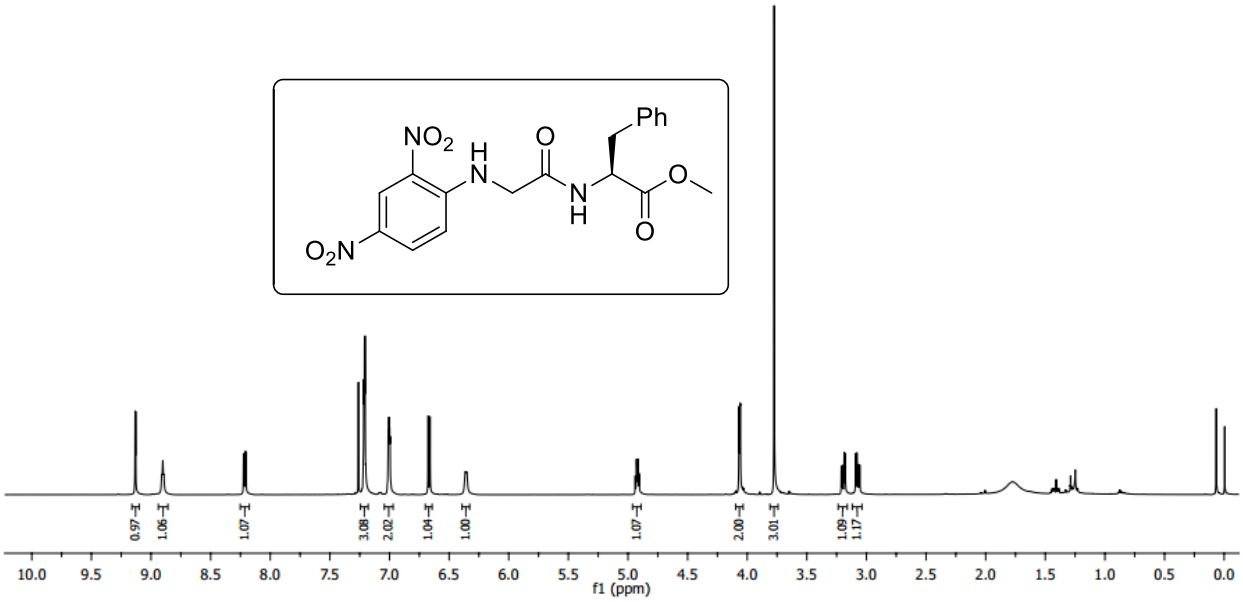


Figure 5.8.1.11. *^{1}H NMR spectra of compound* ***5q***

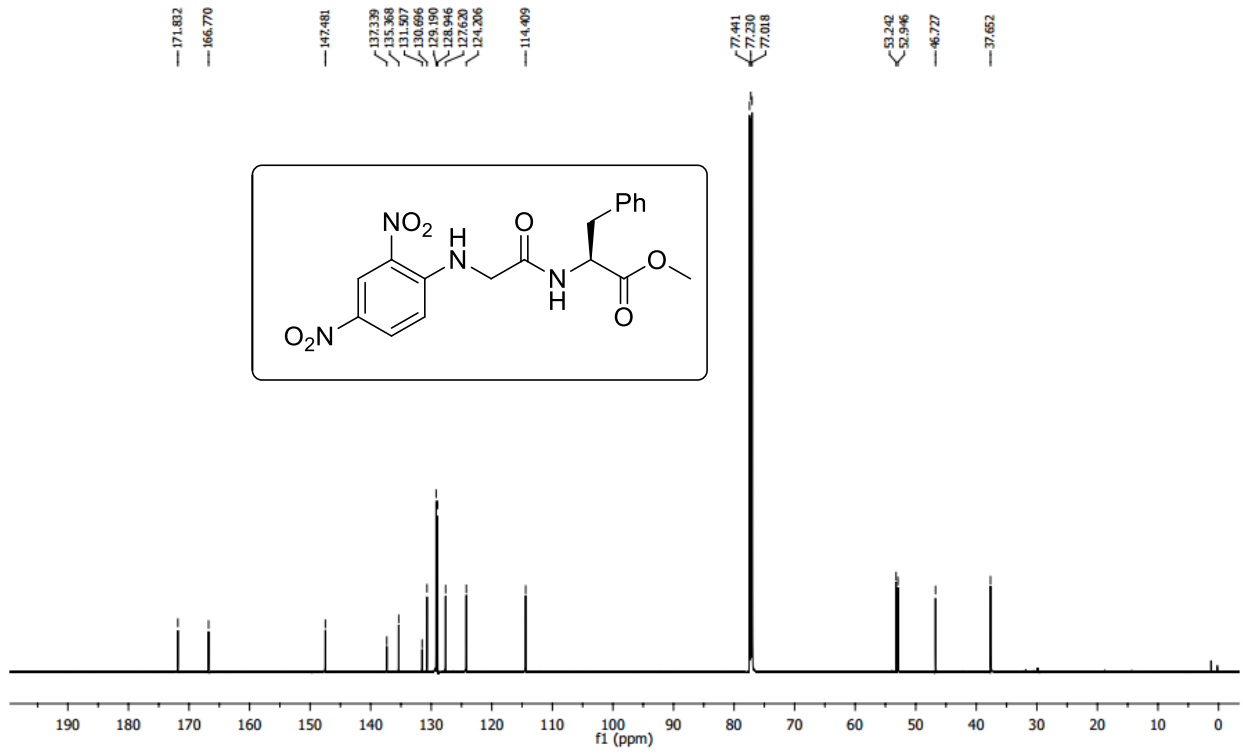


Figure 5.8.1.12. *^{13}C NMR spectra of compound* ***5q***

5.8.2. HPLC Data for racemization study

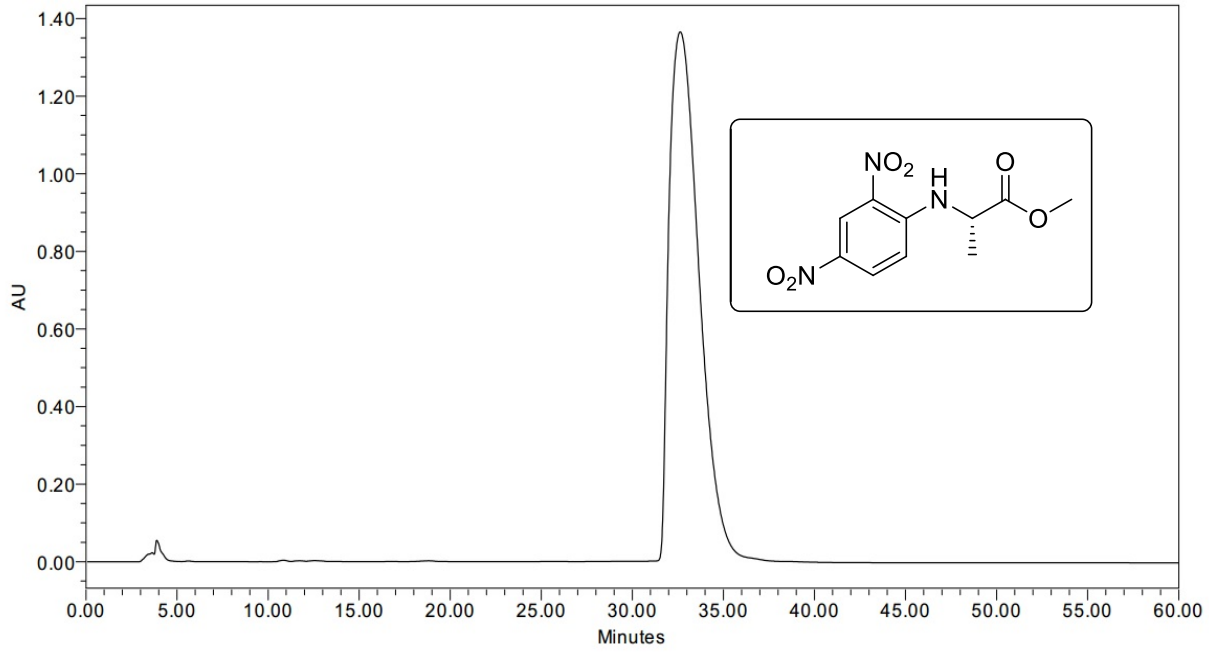


Figure 5.8.2.1. *HPLC spectra of compound* ***5b***

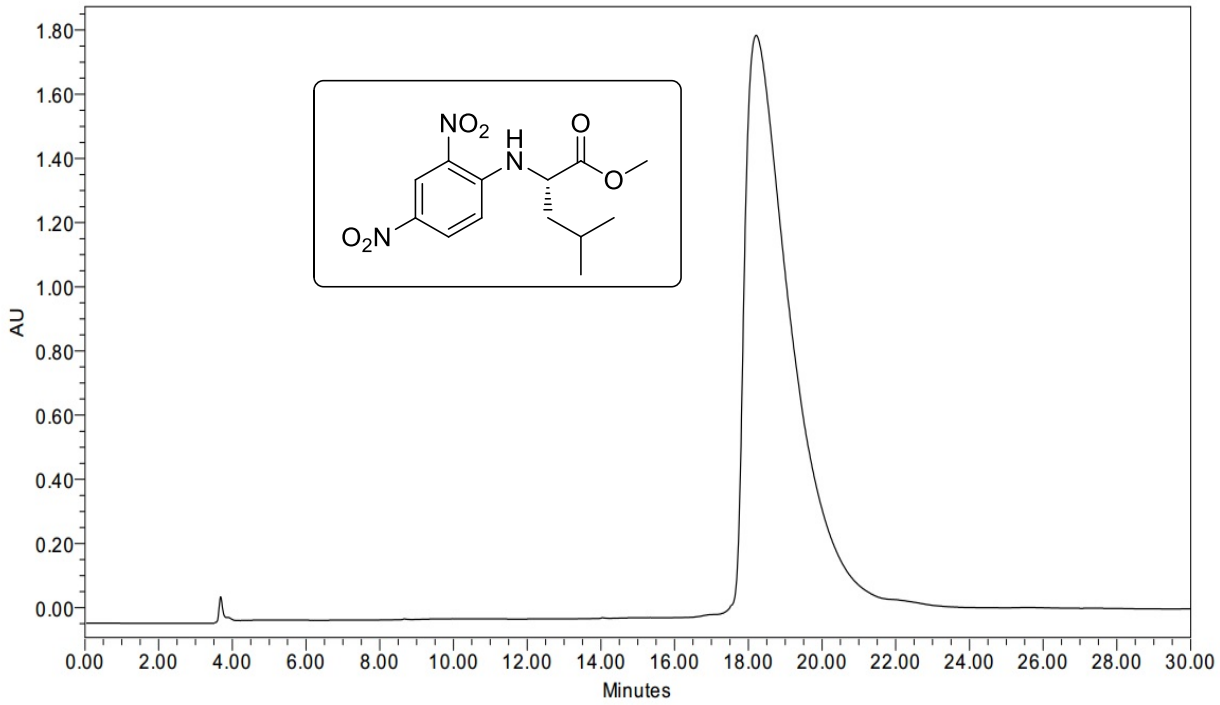


Figure 5.8.2.2. *HPLC spectra of compound* ***5c***

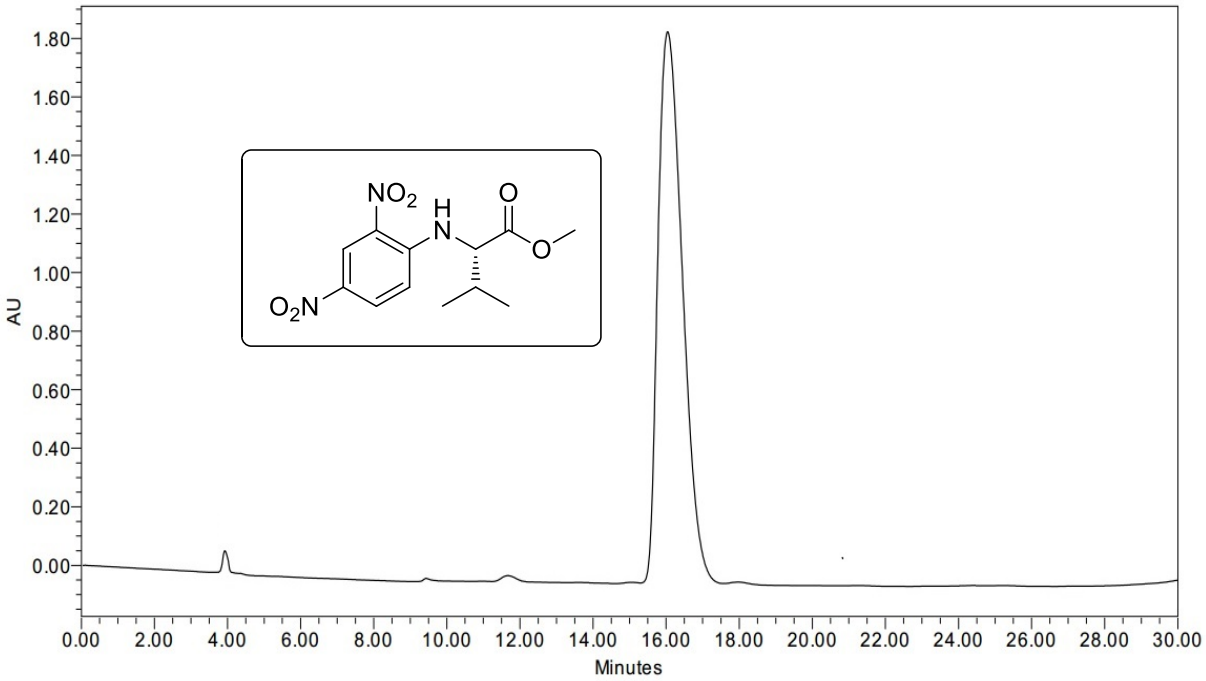


Figure 5.8.2.3. *HPLC spectra of compound* ***5e***

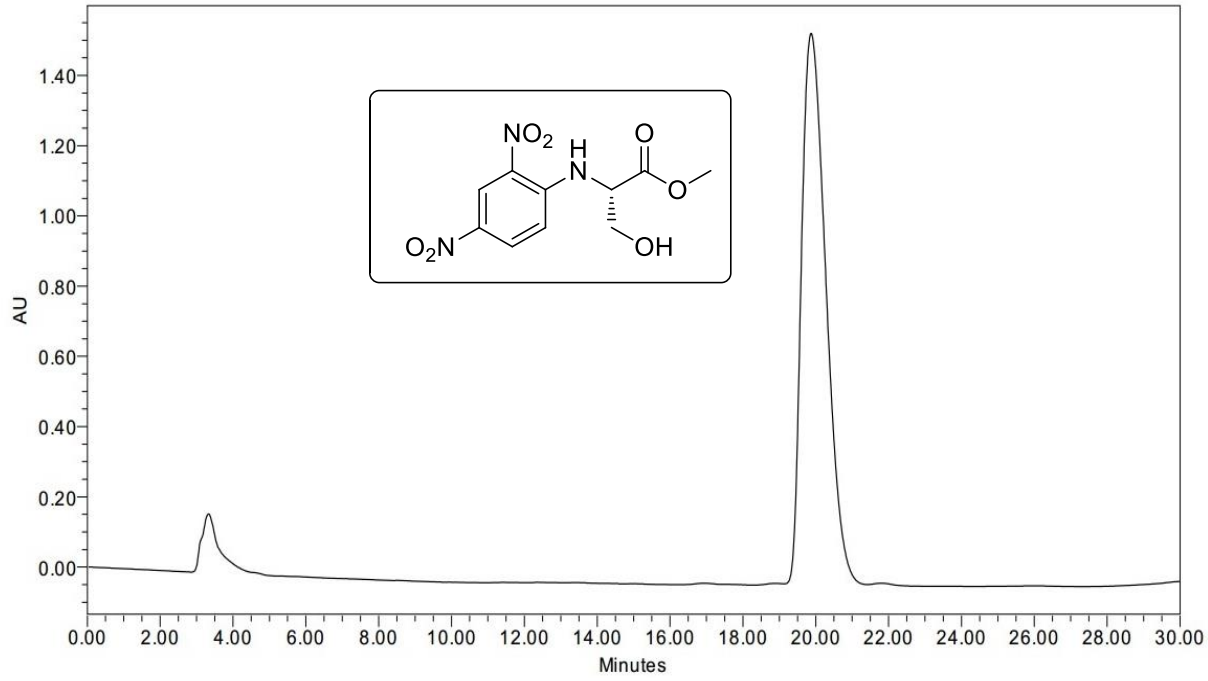


Figure 5.8.2.4. *HPLC spectra of* ***L*** *compound* ***5g***

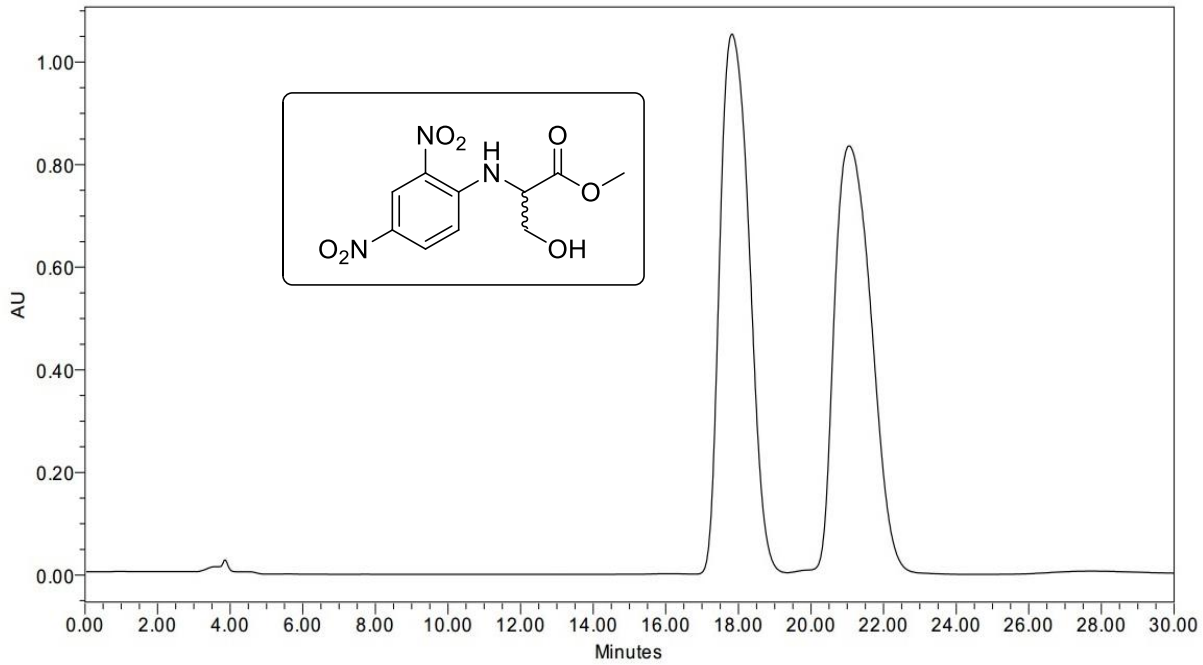


Figure 5.8.2.5. *HPLC spectra of* ***DL*** *compound* ***5h***

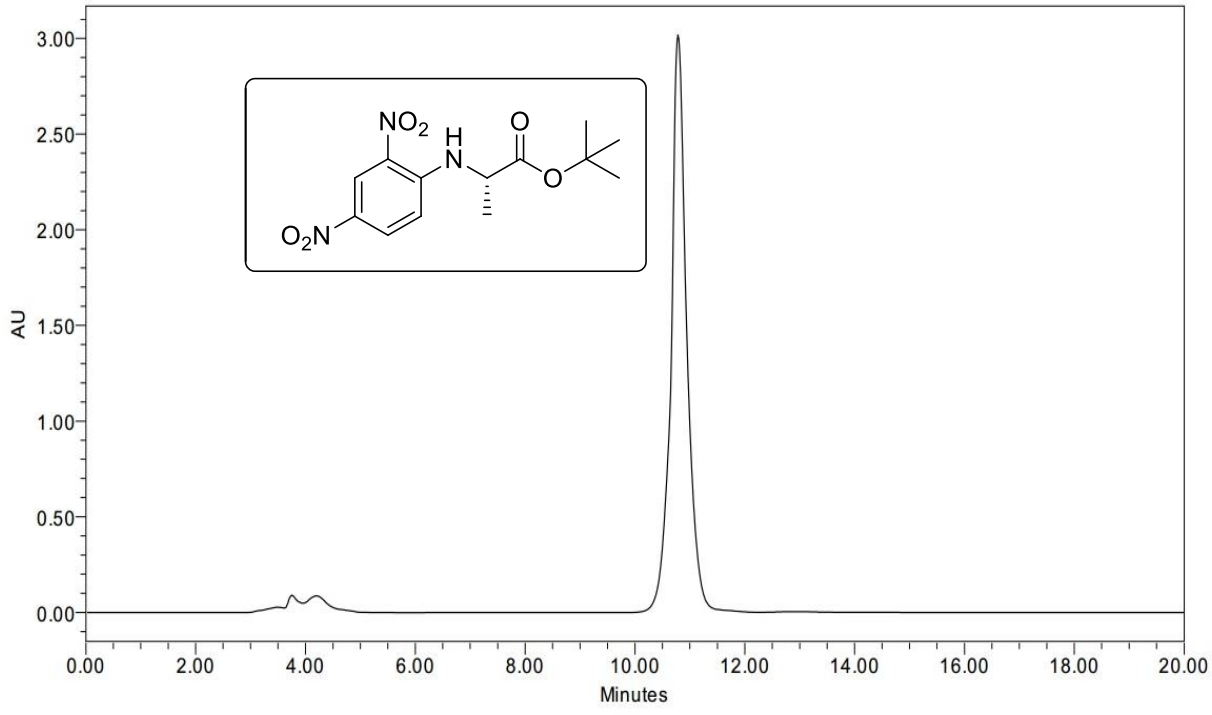


Figure 5.8.2.6. *HPLC spectra of* ***L*** *compound* ***5i***

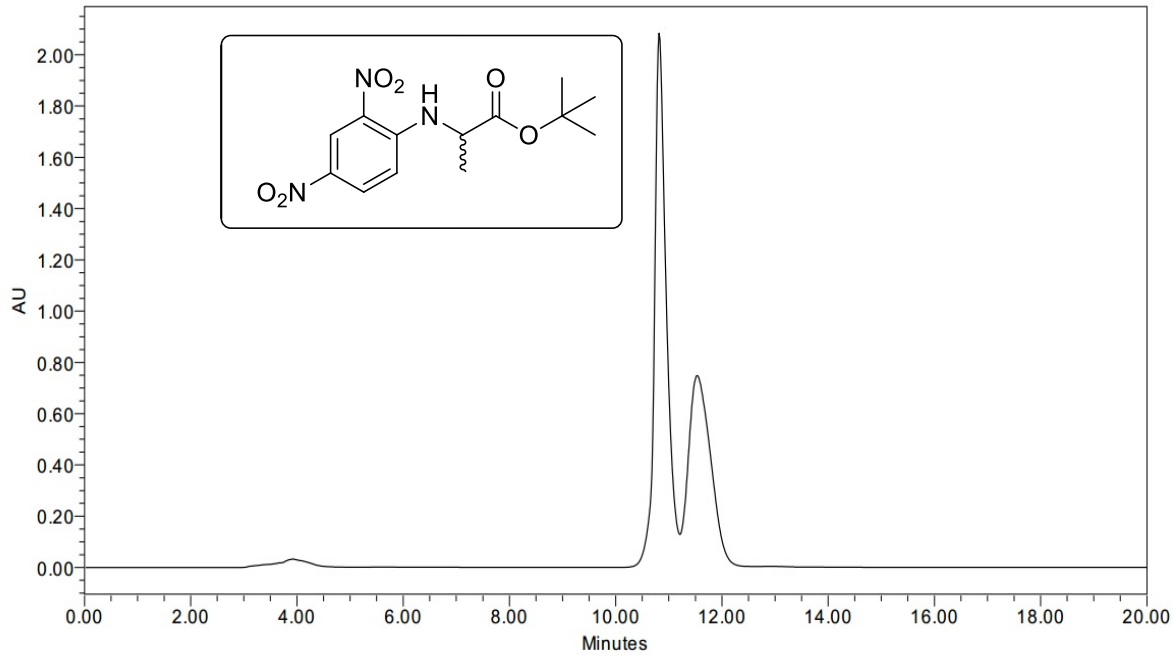


Figure 5.8.2.7. *HPLC spectra of* ***DL*** *compound* ***5j***

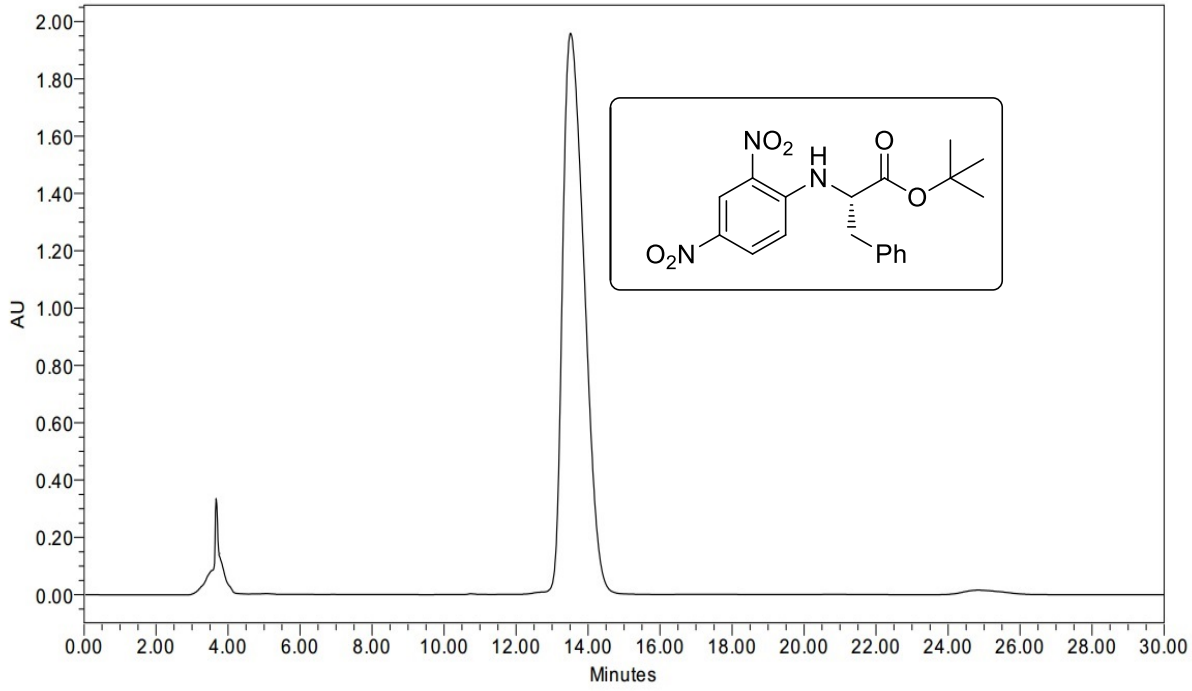


Figure 5.8.2.8. *HPLC spectra of* ***L*** *compound* ***5k***

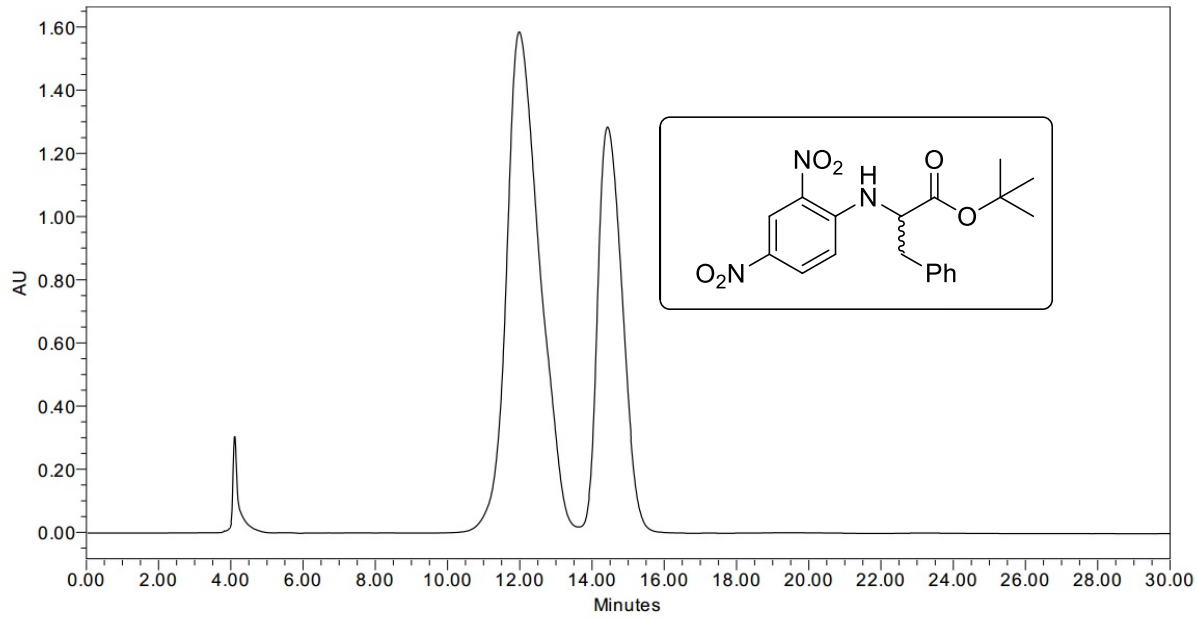


Figure 5.8.2.9. *HPLC spectra of* ***DL*** *compound* ***5l***

5.8.3. Crystal data

Table 5.8.3.1. Crystallographic parameters of *N*-isobutyl-2,4-dinitroaniline **3d**

Compound No.	**3d**
Formulae	$C_{10}H_{13}N_3O_4$
CCDC NO	1580047
Formula. wt.	239.23
Crystal system	Monoclinic
Space group	P 21
a (Å)	4.6727(3)
b (Å)	26.2700(14)
c (Å)	9.3667(5)
α(°)	90.00
β(°)	95.029(4)
γ(°)	90.00
V/ $Å^3$	1145.35(11)

Z	4
Density/Mgm^{-3}	1.387
Abs. Coeff. /mm^{-1}	0.109
F(000)	504
Total no. of reflections	11753
Reflections, $I > 2\sigma(I)$	0.0305
Max. 2θ/°	25.04
Ranges (h, k, l)	-5 ≤ h ≤ 5 -31 ≤ k ≤ 28 -10 ≤ l ≤ 11
Complete to 2θ (%)	25.04
Data/ Restraints/Parameters	0.0916/1/312
Goof (F^2)	1.050
R indices [$I > 2\sigma(I)$]	0.0412
R indices (all data)	0.0655

Table 5.8.3.2. Crystallographic parameters of (2S,3R)-methyl 2-((2,4-dinitrophenyl)amino)-3-methylpent-anoate **5f**

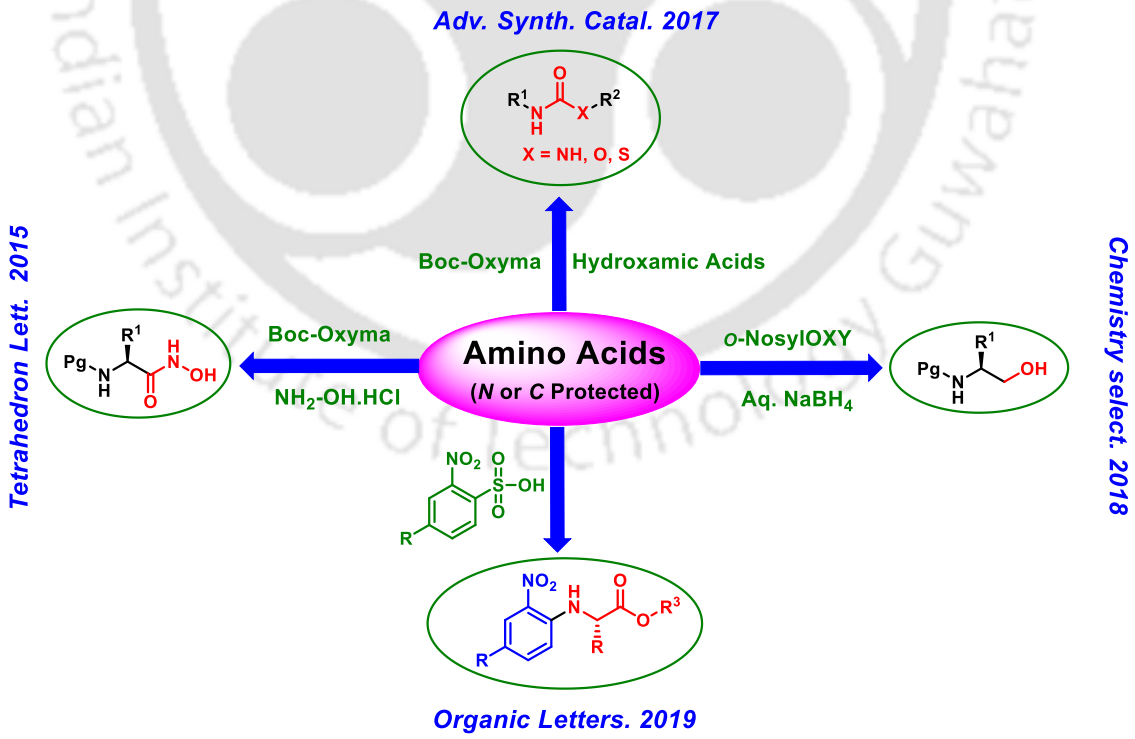
Compound No.	**5f**
Formulae	$C_{13}H_{17}N_3O_6$
CCDC NO	1586476
Formula. wt.	311.30
Crystal system	orthorhombic
Space group	P 21 21 21
a (Å)	27.653(3)
b (Å)	8.1173(9)

c(Å)	6.7660(7)
α(°)	90.00
β(°)	90.00
γ(°)	90.00
V/ $Å^3$	1518.7(3)
Z	1
Density/Mgm^{-3}	1.361
Abs. Coeff. /mm^{-1}	0.109
F(000)	656
Total no. of reflections	10053
Reflections, $I > 2\sigma(I)$	0.0455
Max. 2θ/°	24.74
Ranges (h, k, l)	$-32 \leq h \leq 26$ $-8 \leq k \leq 9$ $-7 \leq l \leq 7$
Complete to 2θ (%)	24.74
Data/ Restraints/Parameters	0.0964 /0/202
Goof (F^2)	1.174
R indices [$I > 2\sigma(I)$]	0.0461
R indices (all data)	0.0764

Conclusions and Future Directions

Conclusions

The works presented in this thesis are mainly focused on the development of new methodologies for the synthesis of hydroxamic acids, ureas, carbamates, thiocarbamates, alcohols, and arylamines. The whole structure of the thesis is depicted in Scheme 1. The importance of the compounds mentioned above, their existing synthetic methods, and drawbacks associated with the existing methods are briefly discussed in chapter 1. Boc-Oxyma mediated racemization-free synthesis of hydroxamic acids from carboxylic acids is described in chapter 2. In chapter 3, we described a simple and efficient method for the synthesis of ureas, carbamates, and thiocarbamates *via* Lossen rearrangement of the hydroxamic acids using Boc-Oxyma. In chapter 4, we described a versatile synthetic methodology for the racemization free synthesis of *β*-amino alcohols directly from carboxylic acids using *ortho*-NosylOXY. In chapter 5, we described the development of a new protocol for the synthesis of arylamines directly by the reaction of nitrobenzene sulfonic acid with amines *via* ipso nucleophilic aryl substitution (^{i}SNAr) process.



Scheme 1. *Thesis overview*

Future Directions

Some new methods have been developed for the synthesis of hydroxamic acids and ureas using Boc-Oxyma, alcohols with *ortho*-NosylOXY and arylamines with nitrobenzene sulfonic acids in my Ph.D. tenure. We can further explore the scope of these coupling reagents for various organic transformations such as hydroxamic acid to amine, oxidation of alcohols to aldehyde, controlled reduction of acid to an aldehyde. Also, nitrobenzene sulfonic acids can further be used for the ipso nucleophilic aryl substitution (^{i}SNAr) with carbon nucleophiles for C-C bond formation.

Research Outcome

Patent:

1. Mandal, B.; Chandra, J.; **Manne, S. R.**; Mondal, S. "A novel coupling reagent for esterification, thioesterification, amidation and peptide synthesis" New Indian Patent Application No. 201731045011 (complete application filed on the 14th Dec **2017)**

Book Chapter:

1. Thalluri, K.; Dev, D.; Palakurthy, N. B.; **Manne, S. R.;** Chandra, J.; Mandal, B "The coupling reagents the world in need indeed." in *Proceedings of International Conference on New Dimensions in Chemistry & Chemical Technologies – Applications in Pharma Industry, NDCT-2014*, 23th-25th June, 2014, JNTU Hyderabad. Prof. K. Mukkanti (Editor-in-Chief), Spectrum Publications, Hyderabad-500038, A. P. India. (ISBN 978-93-82829-90-4) 2014, p 348-351**.**

Publications:

1. **Manne, S. R.;** Chandra, J.; Mandal, B. "Synthesis of arylamines via ipso nucleophilic substitution of sulfonic acid." *Org. Lett***. 2019**, *21*, 636-639.
2. Chandra, J.; **Manne, S. R.;** Mondal, S., Mandal, B. "**(***E*)-Ethyl-2-cyano-2-(((2,4,6-trichlorobenzoyl)oxy)imino)acetate: A modified Yamaguchi reagent for racemization free esterification, thioesterification, amidation and peptide synthesis." *ACS Omega***. 2018**, *3*, 6120-6133.
3. **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**, *1*, 1–6.
4. 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.
5. Chaudhuri, R., **Manne, S. R.;** Mondal, S., Mandal, B. "Direct synthesis of sulphonates of alcohol, Oxyma-*o*-sulphonates and oxime-*o*-sulphonates under microwave irradiation." *ChemistrySelect.* **2017**, *2*, 8471–8477.

6. **Manne, S. R.;** Thalluri, K.; Giri, R. S.; Chandra, J.; Mandal, B. "Ethyl 2-(tert-Butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma): An efficient reagent for the racemization free synthesis of ureas, carbamates and thiocarbamates via lossen rearrangement." *Adv. Synth. Catal.* **2017**, *359*, 168–176.
7. **Manne, S. R.;** Thalluri, K.; Giri, R. S.; Paul, A.; Mandal, B. "Racemization free longer *N*-terminal peptide hydroxamate synthesis on solid support using Ethyl 2-(*tert*-butoxycarbonyloxyimino)-2- cyanoacetate." *Tetrahedron Lett.* **2015**, *56*, 6108-6111.
8. Thalluri, K.; **Manne, S. R.;** Dev, D.; Mandal, B**.** "Ethyl 2-Cyano-2-(4-nitrophenylsulfonyloxyimino)acetate-mediated Lossen rearrangement: single-pot racemization-free synthesis of hydroxamic acids and ureas from carboxylic acids." *J. Org. Chem*, 2014, *79*, 3765-3775.
9. Thalluri, K.; Paul, A.; **Manne, S. R.;** Dev, D.; Mandal, B. "Microwave assisted chemoselective organocatalytic peptide alcohol synthesis from *C*-terminal amide." *RSC Ad*v. **2014**, *4*, 47841–47847.

Conferences:

1. **Manne, S. R.;** Mandal, B. "A new generation of an efficient coupling reagent, 'Boc-Oxyma'- one more step towards the coupling reagents." Research Conclave-2018, 8th March 2018, Student Academic Board (SAB), Indian Institute of Technology Guwahati, Guwahati, India. (**Oral**)
2. **Manne, S. R.;** Mandal, B. "Ethyl 2-(tert-butoxycarbonyloxyimino)-2-Cyanoacetate (Boc-Oxyma), a novel coupling reagent for peptide synthesis and relevant organic transformation." XIII J-NOST Conference for Research Scholars (J-NOST-2017), 9th November 2017, Department of Chemistry, Banaras Hindu University, Varanasi. (**Oral**)
3. **Manne, S. R.;** Mandal, B. "One-pot reduction of amino acids to corresponding amino alcohols." ChemConvene-2017, 25th July 2017, Department of Chemistry, IIT Guwahati. (**Poster**)
4. **Manne, S. R.;** Mandal, B. "Synthesis of hydroxamic acids and ureas by using Ethyl 2-(tert-butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma) as a reagent and its racemization and mechanistic study by HPLC and NMR." International Conference

on Sophisticated Instruments in Modern Research 2017, 30th June 2017, Central instruments facility, IIT Guwahati, Page 67. (**Poster**)

5. **Manne, S. R.;** Mandal, B. "Synthesis of peptide hydroxamic acids directly from carboxylic acid using Ethyl 2-(tert-Butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma)." Frontiers in Chemical Sciences 2016, 8th December 2016, Department of Chemistry, IIT Guwahati, Page 106. (**Poster**)
6. **Manne, S. R.;** Mandal, B. "Peptide hydroxamic acids synthesis from carboxylic acid using Ethyl 2-(tert-Butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma)." 19th CRSI National Symposium in Chemistry, 14th July 2016, Department of Chemistry, University of North Bengal. (**Poster**)
7. **Manne, S. R.;** Thalluri, K.; Mandal, B. "Ethyl 2-Cyano-2-(4-nitrophenylsulfonyl oxyimino) acetate (4-NBsOXY) as a reagent for racemization free hydroxamic acids and ureas synthesis from acids." International Conference on Nascent Developments in Chemical Sciences: Opportunities for Academia-Industry Collaboration, 16th October 2015, Department of Chemistry, Birla Institute of Technology and Science, Pilani; Page-316. (**Poster**)
8. **Manne, S. R.;** Thalluri, K.; Giri, R. S.; Mandal, B. "Microwave assisted chemo-selective and stereoselective synthesis of peptide alcohols from amides via transamidation." ChemConvene-2015, 8th April 2015, Department of Chemistry, IIT Guwahati. (**Poster**)

Srinivasa Rao Manne

Present Address:

Mr. Srinivasa Rao Manne
Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati, Assam-781039, India.
Phone: +91-9085295924
Email: s.mannemsc@gmail.com
s.manne@iitg.ac.in

Permanent Address:

Mr. Srinivasa Rao Manne
D. No.15-103, Gollagudem Village
Mogalturu (Mandal), Westgodavari District
Andhra Pradesh-534281, India.
Phone: +91-9701710029

Education:

2013–Present **Ph.D. in Chemistry (CPI 8.57 out of 10)**
Indian Institute of Technology Guwahati, Assam, India

2008–2010 **M.Sc. in Organic Chemistry (First Class)**
Andhra University, Andhra Pradesh, India

2005–2008 **B.Sc. in Mathematics, Physics and Chemistry (First Class)**
Andhra University, Andhra Pradesh, India

Ph.D. Thesis:

Thesis Title: **"New Applications of Boc-Oxyma, *o*-NosylOXY and Nitrobenzene Sulfonic Acids in Organic Synthesis"**

Supervisor: **Dr. Bhubaneswar Mandal**

Achievements and Awards:

- Received best poster award in International Conference on Sophisticated Instruments in Modern Research, 30th June 2017, Central instruments facility, IIT Guwahati, India.

- Qualified National Eligibility Test (NET-JRF) June-2012 and (CSIR-rank 50) June-2013 in Chemical Science, Organized by The Council of Scientific and Industrial Research (CSIR), India.
- Qualified Graduate Aptitude Test (GATE) held on March 2012 in Chemistry, organized by Ministry of Human Resource Development, Government of India.

Research Experience:

- **2015-Present**: **Senior Research Fellow** at the Department of Chemistry, Indian Institute of Technology Guwahati, India.
- **2013-15**: **Junior Research Fellow** at the Department of Chemistry, Indian Institute of Technology Guwahati, India.
- **2012-2013**: **Project Assistant** at the Fluoro Organic Division, Indian Institute of Chemical Technology, Hyderabad, India.
- **2011**: **Tr. Research Chemist** at Research and development, Laxai-Avanti Life Science PVT LTD, Hyderabad, India.

Research and Instrumental skills:

- Expertise design and execution of multistep organic reactions from milligram to gram scale, handling air and moisture sensitive compounds using a protective atmosphere and Crystallization techniques.
- Peptide synthesis by both solution and solid phase.
- Conformational analysis of chiral compounds by 2D-NMR (COSY, NOESY), time-dependent NMR, HPLC, polarimeter, FT-IR spectroscopy, mass spectrometry (MS/LC-MS (kinetic study)), Gas Chromatography, *etc*.

Main Skills:

Teaching Experiences:

- **Since 2013**: Both Tutorial and Teaching Assistantship at IIT Guwahati, India (B.Tech and M.Sc.).

Languages:

- **Telugu:** Native (fluent)
- **English:** Very good level of spoken and written
- **Hindi:** Five years of study – good level of spoken and written

Computer Skills:

- **Operating Systems:** Windows
- **Softwares Familiar:** MS-Office, Chemoffice, ISIS draw, Origin, Adobe Illustrator.

Research interests:

- Peptide Chemistry and Chemical biology
- Metal-Catalyzed C-C and C-Heteroatom Bond Formations
- Asymmetric synthesis
- Heterocyclic Synthesis and Multicomponent Synthesis