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BOLU ABANT İZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
Department of Chemistry

SYNTHESIS OF AROMATIC AZO-BICYCLIC COMPOUNDS VIA RING-CLOSING METATHESIS (RCM)

MASTER OF SCİENCE

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BOLU, TEMMUZ - 2023

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SAMIRA SAID ALI ELSANOSI

ABSTRACT

SYNTHESIS OF AROMATIC AZO-BICYCLIC COMPOUNDS VIA RING-CLOSING METATHESIS (RCM)
MSC THESIS
SAMIRA SAID ALI ELSANOSI
BOLU ABANT IZZET BAYSAL UNIVERSITY
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DEPARTMENT OF CHEMISTRY
(SUPERVISOR: PROF. DR. F. DEVRİM ÖZDEMİRHAN)

BOLU, JULY 2023
(xiii +47)

Heterocyclic chemistry is the largest section of organic chemistry, which has made a great contribution to the development and improvement of many important areas of life. Among the heterocycles, Azahetero cyclic is the cyclic compound that contains a nitrogen atom in the ring. It is critical to almost every life process and a large percentage of the transformations that lead to the creation of increasingly sophisticated products. Azahetero cyclic compounds are abundant in many areas and are essential to life in a variety of ways. Several azahetero cyclic compounds are well recognized and are expanding quickly, holding a unique position among both natural products and synthesized compounds with significant pharmacological applications. The majority of medications and agricultural compounds that are biologically active are azahetero cyclic.

Examples of azahetero cyclic systems include alkaloids, antibiotics, vitamins, hemoglobin, hormones, many synthetic drugs, and dyes, to name a few.

In this context, benzyl 3,3',4,6'-tetrahydro-1'H,2H-spiro[naphthalene-1,2'-pyridine]-1'-carboxylate and benzyl allyl(1-vinyl-2,3-dihydro-1H-inden-1-yl) carbamate precursor of benzyl 2,3-dihydrospiro [Indyne-1,2'-pyrrole]-1'(5'H)-carboxylate were synthesized. Initially, 1-tetralone is converted to corresponding *N*-allylamine in the presence of a molecular sieve followed by a Grignard addition reaction in the presence of allyl magnesium bromide yields corresponding diene protected by benzyl chloroformate result benzyl allyl(1-allyl-1,2,3,4-tetrahydronaphthalen-1-yl) carbamate. Tetrahydropyridine was prepared by the Ring-Closing Metathesis using Grubbs 2nd generation catalyst. Moreover, 1-indanone is subjected to *N*-allylamine with a molecular sieve, in the same manner following benzyl chloroformate tandem reaction with vinyl magnesium bromide yielded corresponding diene precursor of dihydro spiro pyrrole; benzyl 2,3-dihydrospiro[indene-1,2'-pyrrole]-1'(5'H)-carboxylate.

KEYWORDS: Heterocyclic, Spirocyclic, Ring Closing Metathesis (RCM), Grubbs Catalyst

ÖZET

HALKA KAPAMA METATEZİ REAKSİYONU YOLUYLA AROMATİK AZO-BİSİKLO BİLEŞİKLERİNİN SENTEZİ
YÜKSEK LİSANS TEZİ
SAMIRA SAID ALI ELSANOSI
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LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ
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BOLU, TEMMUZ - 2023
(xiii +47)

Heterosiklik kimya, yaşamın birçok önemli alanının gelişmesine ve iyileştirilmesine büyük katkı sağlayan organik kimyanın en büyük dalıdır. Heterosiklller arasında Azaheterosiklik, halkada bir nitrojen atomu içeren siklik bileşiklerdir. Neredeyse her yaşam süreci ve giderek daha sofistike ürünlerin yaratılmasına yol açan dönüşümlerin büyük bir yüzdesi için kritik öneme sahiptir. Azaheterosiklik bileşikler doğada bol miktarda bulunur ve yaşam için çeşitli şekillerde gereklidir. Pek çok azaheterosiklik bileşik, hem doğal ürünler hem de farmasötik açıdan önemli sentetik bileşikler arasında özel bir yer işgal ederek iyi bilinmektedir ve hızla artmaktadır. Biyolojik olarak aktif farmasötiklerin ve tarım kimyasallarının çoğu Azaheterosikliktir.
Azaheterosiklik sistemlerin örnekleri arasında alkaloidler, antibiyotikler, vitaminler, hemoglobin, hormonlar, birçok sentetik ilaç ve boyalar sayılabilir.
Bu bağlamda benzil 3,3',4,6'-tetrahidro-1'H,2H-spiro[naftalin-1,2'-piridin]-1'-karboksilat ve benzil allil(1-vinil-2,3-dihidro-1H-inden-1-il)karbamat öncüsü olan benzil 2,3-dihidrospiro [Indyne-1 ,2'-pirol]-1'(5'H)-karboksilat sentezlenmiştir.
İlk olarak 1-tetralon moleküler elek eşliğinde *N*-allilimin türevine çevrilmiş; akabinde allil magnezyum bromür varlığında elde edilen ilgili dien benzil kloroformat ile korunmuş; benzilallil(1-allil-1,2,3,4-tetrahidronaftalen-1-il)karbamat eldeedlmiştir. Akabinde, Grubbs 2nd Jenerasyon varlığında Halka Kapama Metatez reaksiyon ukullanılar akil gili tetrahidropridin eldeedilmiştir. Aynışekilde 1-indanon moleküler elekvarlığında *N*-allilamin ile muamele edilerek akabinde benzil kloroformat ve vinil magnezyumbromür ile dihidro spiro pirol öncüsü benzil allil(1-vinil-2,3-dihidro-1H-inden-1-il) karbamat elde edilmiştir.

ANAHTAR KELİMELER: Heterosiklik, Spirosiklik, Halka Kapama Metatezi (RCM), Grubbs Katalizörü

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LIST OF ABBREVIATIONS AND SYMBOLS

°C	: Degree Celsius
^{13}C-NMR	: Carbon- 13 Nuclear Magnetic Resonance
^{1}H-NMR	: Proton Nuclear Magnetic Resonance
ADMET	: Acyclic diene Metathesis .
Cbz	: Carboxy benzyl
$CDCl_3$	: Deuterated chloroform
d	: Doublet (in NMR)
DCM	: Dichloromethane
eq.	: Equivalent weight
Et_3N	: Triethylamine
EtOAc	: Ethyl acetate
Hz	: Hertz
IR	: Infra-red
J	: Coupling Constants (in NMR)
$K2CO_3$	: Potassium carbonate
mg	: Milligram
$MgSO_4$	: Magnesium Sulfate
ml	: Milliliter
mmol	: Mili mole
N	: Nitrogen
Nacl	: Sodium chloride
$NaHCO_3$	: Sodium bicarbonate
NH_4CL	: Ammonium chloride
NMR	: Nuclear magnetic resonance
O	: Oxygen
ppm	: Parts per million
RCM	: Ring Closing Metathesis
ROM	: Ring-Opening Metathesis
ROMP	: Ring Opening Metathesis Polymerization
rt	: Room temperature

THF : Tetra hydro furan

TLC : Thin-layer chromatography

δ : Chemical shift in ppm (in NMR)

π : Pi

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my supervisor, Prof. Dr. Devrim Özdemirhan, for guidance, advice, criticism, encouragement, patience, understanding, insight during the research, and her constant support during this study.

I would like also to thank Prof. Dr. Özdemir ÖZARSLAN and Prof. Dr. İzzet MORKAN for their continuous support and advice.

I would like to thank my husband Ali MATHKOUR and my children Sirajaldeen and Malk very much for their support and love for me. With all my love and apologies.

I express a lot of thanks to my teachers with all respect.

I also express my thanks to my friends.

Finally, I would like to thank everyone who taught me and helped me reach my dream.

This study was partially supported by the …117Z412…., Grant No: ……

1. INTRODUCTION

Heterocyclic compounds are very important groups of organic compounds, used in many fields biological and comprise, the most and largest diverse class in organic compounds.

They are found in medicines, vitamins, and dyes as well as many natural products, biomolecules such as DNA and RNA, and bioactive compounds such as antineoplastics and antibiotics. Most modern and advanced manufacturing methods for pharmaceuticals, pesticides, dyes, and plastics are directly based on the synthesis of scaffolds from these compounds.

Many organic chemists are interested in these compounds because of their unusual composition and interactions, as well as the fact that they could be used to treat a range of conditions, including coronary heart disease, Alzheimer's disease, and others (1).

1.1 Heterocyclic compounds.

Include compounds organic, and cyclic that contain at least a single heteroatom in their ring structure (such as (O), (N), or (S)) (2–4).
These compounds have significant roles in nature, the food web, and thereby in human life. Based on such roles, heterocyclic compounds can be categorized based on several criteria, one of which is saturation level or degree of aromaticity. This criterion is based on the structural and electronic arrangement of the compound, and it includes saturated, partially saturated (5), and non-saturated heterocyclic compounds. Regarding aromaticity, it involves aromatic and non-aromatic heterocyclic compounds. Figure (1.1) shows some examples of Heterocyclic compounds.

Furan Pyrrole Thiophene Pyridine

Figure 1.1. Examples of heterocyclic compounds.

1.1.1 Saturated heterocyclic compounds.

Completely saturated heterocyclic compounds, also known as aliphatic heterocycles, contain no double bonds. Their properties are mainly determined and therefore affected by their ring strain. Examples of these compounds include oxiranes (Ethylene oxide), aziridine, thiirane, and tetrahydrofuran (6,7) as shown in Figure (1.2). During the construction of saturated heterocycles, a saturated hetero atom is added to the ring structure, responsible for the major properties of the compound, including added flexibility, enhanced hybridization, and ease of reconstruction in the laboratory via ring-closing metathesis, as well as ease of catalysis (i.e., ring-opening reaction) (8).

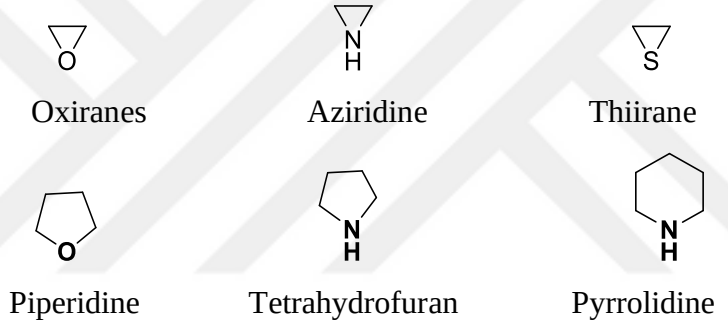


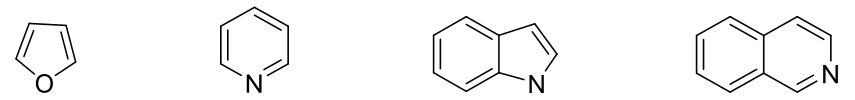
Figure 1.2. Examples of saturated heterocyclic compounds.

1.1.2 Aromatic heterocyclic compounds.

Huckel's rule, according to which a compound must be cyclic to be classified as aromatic, must be followed for a heterocyclic compound to be classified as such., it should have a planar geometry and should possess (4n+2) π– electrons (9).

This delocalized electron cloud differentiates aromatic from non-aromatic heterocycles. In addition, the heteroatom should be part of the aromatic ring in the compound. Aromatic heterocycles are available in two major classes, one includes single-ring heterocyclic compounds like furan and pyridine, and the other includes fused-ring heterocyclic compounds, like indole and Isoquinoline.

These aromatic compounds are also known as analogous to benzene, as shown in Figure (1.3) (10–12).



furan pyridine Indol Isoquinoline

Figure 1.3. Examples of aromatic heterocyclic compounds.

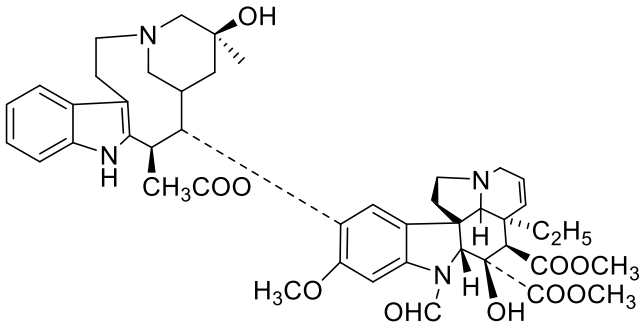
1.2 Importance of heterocyclic compounds.

Around 75% of the drugs the FDA's (Food and Drug Administration) approval contain heterocyclic compounds (13), specifically small nitrogen-containing heterocycles. Over the past few years, the focus on developing medically important drugs from such compounds has increased dramatically. The structure of natural products, antifungal, antibacterial, and antiviral medications, as well as many other physiologically significant chemicals and enzymes all contain heterocyclic compounds as essential structural elements (14).

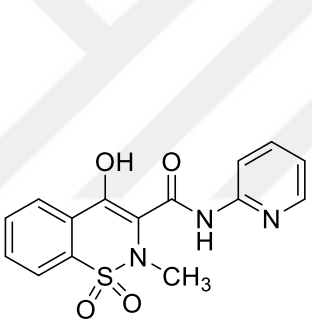
Many of the naturally occurring and synthesized heterocycles have been addressed to exhibit important medical importance, for instance Ezetimibe as a Cholesterol absorption inhibitor (15), Clavulanic acid as a potential inhibitor for ß-lactamase (16), quinolone-based anticancer drugs (17), Gefitinib as an inhibitor for EGFR (Growth factor receptor) tyrosine kinase (18).

Regarding naturally occurring heterocycles, they comprise the most important biological molecules, which are RNA and DNA, as heterocycles comprise the pyrimidine skeleton for thymine and Cytosine in DNA and uracil in RNA. Also, there is a large array of naturally occurring yet medically important heterocycles. These include nitrogen containing heterocycles like vincristine is utilized along with additional chemotherapy medications to treat some forms of leukemia (cancer of the white blood cells), and piperine. Oxygen containing heterocycles like Quercetin and Kaempferol. Sulfur containing heterocycles like Fucoidan (19). Thus, one can state that heterocyclic compounds have a significant presence in our life, both structurally and medically important.

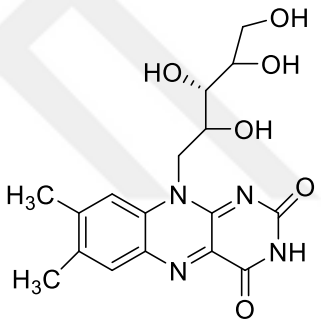
Piroxicam and Riboflavin B2 can be exemplified as benzene analogous. (Figure 1.4) shows some examples of drugs containing heterocyclic moieties.



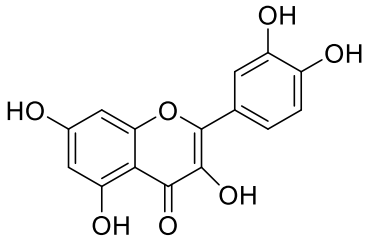
Vincristine



Piroxicam



Riboflavin B2



Quercetin

Figure 1.4. Examples of drugs containing heterocyclic moieties.

1.3 Bicyclic compounds

Bicyclic compounds include those featuring two cycles being joined together. If the molecule is structurally only composed of carbon atoms, it is named as carbocyclic compound. However, if one or more heteroatom is added to one or both ring structures, it is called a bicyclic heterocycle. Such heterocyclic compounds with bicyclic features have been found to exhibit important antibacterial roles. Such as Bicozamycin (a Bicyclomycin), a broad spectrum gram-negative anti-bacterial drug, active against Kelbsiella sp., Salmonella sp., and Escherichia coli (20), as shown in Figure (1.5).

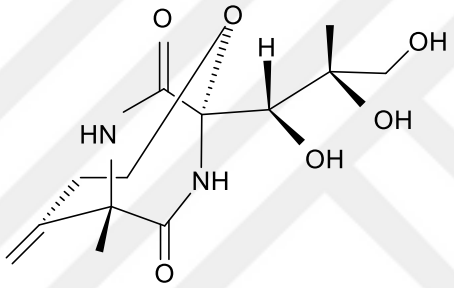


Figure 1.5. Bicyclomycin structure.

The fashion in which the two rings are linked determines the type of bicycle. It could be via a connection of two successive atoms, the compound is termed a fused bicycle such as Caffeine. It could also be via two non-succeeding atoms, in this case, it is termed a bridged bicycle, such as Cocaine. However, if the connection is established via a single atom, it is called a spiro-bicyclic compound as in Acorenone (21) as shown in Figure (1.6).

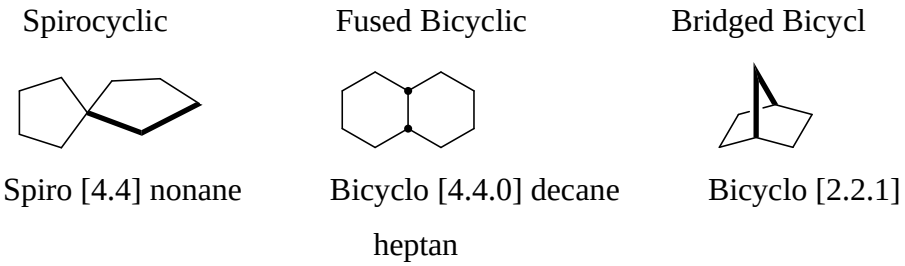
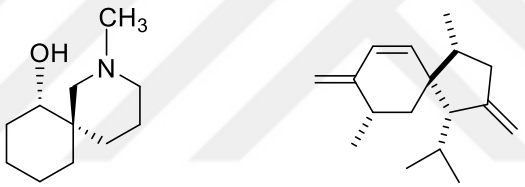


Figure 1.6. Spiro, Fused, Bridged Bicyclic compounds.

1.3.1 Spirocyclic compounds

In the previous two decades, spirocyclic compounds have a great deal of research attraction, these compounds include bicycles that are joined by a single tetrahedral carbon atom, making them active at binding to other structures and pharmacophores easily.

Spirocyclic are abundant in nature, first obtained by their isolation from plant and animal origins (22). They are also present in the structure of many other natural products including nankakurine, (-)-sibirine, and Shizuca-acordienol (23) as shown in Figure (1.7). Spirocyclic compounds have also been used in many pharmacological applications, as they have been used in major antimicrobial drug production.

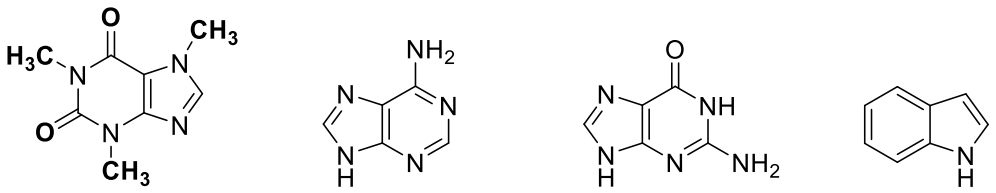


- (-) Sibirine Shizuka-acordienol

Figure 1.7. Examples of spirocyclic compounds.

1.3.2 Fused bicyclic compounds.

The construction of these compounds happens due to the fusion (i.e., condensation) of two rings sharing a bond. Examples of such compounds include Caffeine, Purines (Adenine and Guanine), and Indole as shown in Figure (1.8). They can be synthesized via a tandem ring-closing metathesis reaction utilizing ruthenium as a catalyst. Smaller rings are enclosed using fast ring-closure and larger ones are carried out via slow ring-closure (24).



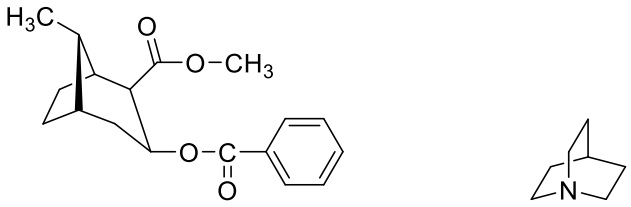
Caffeine Adenine Guanine Indole

Figure 1.8. Examples of fused bicyclic compounds.

1.3.3 Bridged bicyclic compounds.

This type of bicyclic compounds forms when an atom or an unbranched atom chain links two other bridgehead atoms.

These can be any atom other than hydrogen and should be part of the molecular skeletal framework being bonded to a triplet (or even more) atom (25). In this fashion, an atom bridge is thrown across the two sides of the ring, this could be from the left to the right side, or from the left side to the atom below (non-adjacent atoms). These compounds are non-planar, and examples of such bridged bicyclic compounds include Quinuclidine (26), and Cocaine (27) as shown in Figure (1.9). A distinct feature of this type of compounds is that it is rigid and no π–bonds form at the bridgehead atom.



Cocaine Quinuclidine

Figure 1.9. Examples of bridged bicyclic compounds.

1.4 Methods of Synthesizing Heterocyclic Compounds.

Synthesis of heterocyclic compounds can be carried out from oxides, halides, sulfides, and metal complexes, using various numbers of reducing agents. Particularly, it can be done via reducing amides, sulfoxides, imines, and sulfones. There is an array of methods by which heterocyclic compounds can be made, which includes nucleophilic substitution as in Azulene (28), ring closing metathesis (29), and various types of rings opening metathesis like substitution, rearrangement, and polymerization (30).

1.4.1 Synthesis Methods for Spirocyclic Compounds.

In recent decades, many different synthetic methodologies there have developed to construct spirocyclic compounds. This is due to the fact that spirocyclic have two major properties that made their synthesis available, these features include reduced lipophilicity, and having a three-dimensional structure that offers more coverage space to position exit vectors as well as chemical space. Recent synthetic approaches for these compounds include aerobic oxidative dearomatization by Katsuki and Oguma in 2014(31), Michael/Povarov domino approach, in the presence of an organocatalyst in a one-pot reaction strategy, developed by Wu and Wang (32). Zeng et al. used enantioselective method to synthesize spirocyclic with decent outputs using either the Michael addition reaction with a squaramide catalyst derivative or the thio [3+2] cyclization with Takemoto's catalyst (33).

Furthermore, Olefinic oxindole-based stereoselective reactions to synthesize spirocyclic compounds have been used different derivatives, but a cycloaddition reaction is needed to yield better results with this method (34). Other methods to synthesis these compounds include Pauson-Khand reaction, metathesis, and radical cyclization reactions (35).

1.4.2 Olefin Metathesis

The best way to describe the olefin metathesis reaction is as a reaction that forms carbon-carbon bonds. This metathesis was established in the mid-50 s of the last century, it has been used as one of the methods of choice to synthesize spirocyclic compounds. Two olefins react in this process, in which their alkylidene moieties are redistributed to create a new functioning olefin. As the method name indicates, it is a transposition process, in which two reacting olefins form three products. The olefin of interest is obtained by a cross-metathesis process and the other unwanted two products are formed from self-metathesis of the starting materials (36). The cross-metathesis process control is crucial to synthesize the desired olefin. as shown in figure (1.10) mechanism of olefine metathesis.

Olefin metathesis can be classified as; (ROM)-(RCM) - (ROMP) -(ADMET).

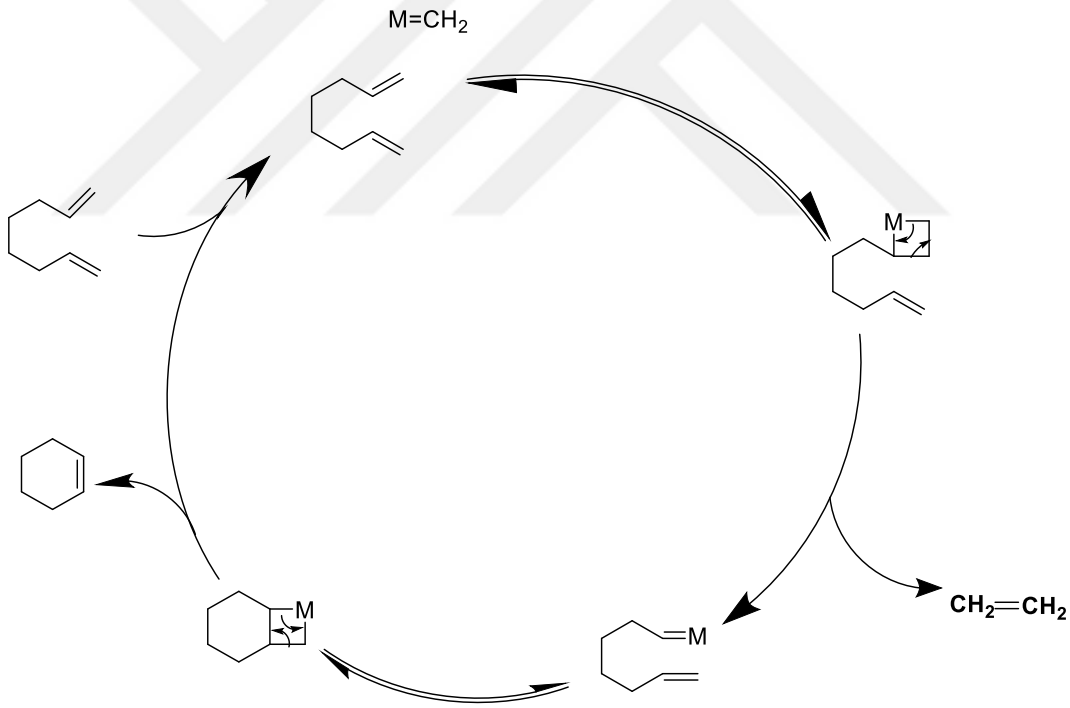


Figure 1.10. Mechanism of olefin metathesis.

1.4.3 Ring-closing metathesis.

Ring-closing metathesis reactions (RCM), a form of olefin metathesis, are frequently used to synthesize a variety of unsaturated heterocycles by using intramolecular metathesis of terminal alkenes in the reactive compounds. An ethylene and cycloalkane are the final products. as shown in Figure (1.11) The reaction is metal-catalyzed via a metallacyclobutane intermediate, which makes the reaction highly favorable by organic chemists because the byproduct is ethylene, and economically more suitable to produce ring-closed heterocycles. Historically, Didier Villemin first produced Exaltolide precursor using this method in 1980(37). Thene Jiro Tsuji used the same reaction to produce a macrolide. This was used a basis for later research in 1987, during which macrocyclic compounds were synthesized (38). After that, Grubbs et.al., in 1993, ruthenium carbene was utilized in the metathesis processes to create Grubbs' first-generation ring closure metathesis catalysts.

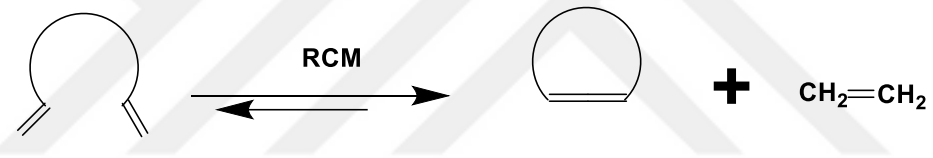


Figure 1.11. Ring-closing metathesis.

1.5 The Grubbs' catalyzed Metathesis Reaction

Metathesis reaction: exchanging the groups that are attached to any of the double bonds in alkenes. Here, the two involved alkenes in the reaction exchange partners in order for them to provide synthesized products, under the condition where neither of the products are reduced nor oxidized. Thus, defined as a metathesis reaction (39). As shown in Figure (1.12).

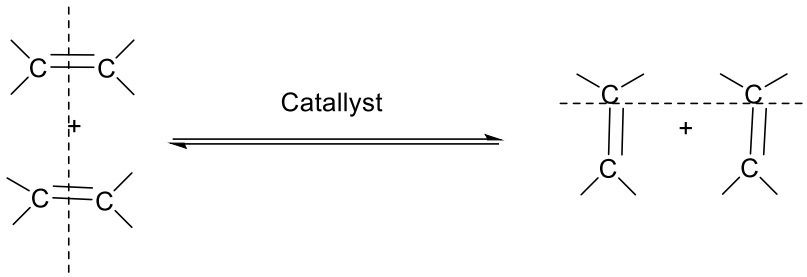


Figure 1.12. A metathesis reaction.

Reactants of the Grubbs reaction are almost always terminal alkenes. When such alkenes react, they tend to exchange a methyl group (CH_3), yielding an ethene. Ethene can easily escape the solution because it is a gas, which in turn makes the process irreversible (39), Figure (1.13) below.

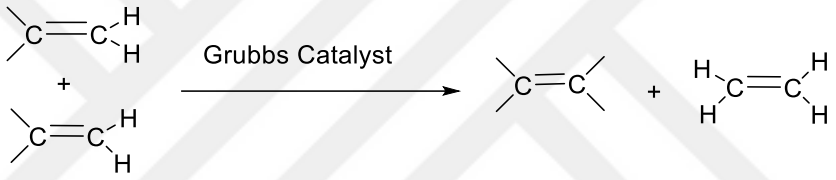


Figure 1.13. Ethene Escapes as a gas from the Grubb's reaction.

The example of Grubbs reaction, the synthesis of (E)-2-heptene and ethene from the reaction of l-butene and l-propene, as shown in figure (1.14).

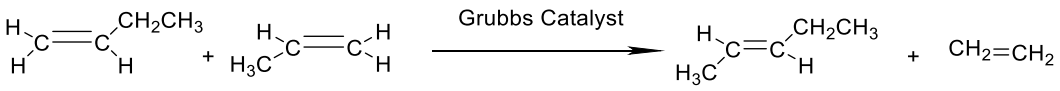


Figure 1.14. An example of Grubb's metathesis reaction.

1.5.1 The Grubbs Catalyst

During Grubbs reaction an organoruthenium complex serves as a Grubbs catalyst as shown in Figure (1.15) It is important to observe that the catalysis occurs at the center, where the π–bond between the ruthenium atom and the carbon atom is located, where the catalysis takes place. Since this catalyst is quite efficient for

the reaction, the Grubbs reaction can be used in many ways, with alkenes possessing several functional groups. Consequently, one of the most significant reactions in organic chemistry is Grubbs. (39). Due to its importance and the innovative approach of this reaction, Robert H. Grubbs and his colleagues received a Nobel prize in 2005; named a synthetic and mechanistic tour de force.

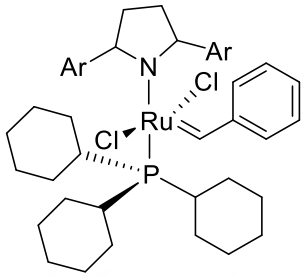


Figure 1.15. Grubb's catalyst(organoruthenium)

1.5.2 Grubbs' first-generation catalysts

An olefin metathesis-active ruthenium complex (Alkylidene complexes) first appeared as the Grubbs first-generation catalytic process in the early 1990s. This has enhanced the polymer chemistry as well as catalytic reactions used in organic chemistry. Historically, in this procedure, ruthenium trichloride was used to open the cyclobutene ring via a ring-opening polymerization reaction. Then, Grubbs et al., utilized Carbene-metal catalysts to be used in various synthesis applications, later the phenyl group was exchanged to a cyclohexyl group. The stable complex was then termed the first-Generation catalyst of Grubbs. Reactions of this generation of Grubbs' catalyst have enabled complete isolation as well as characterization of specimens of the so-called Grubbs-type complexes such as ancillary ligands (trans-[RuCl2(CHPh)(L^1)$_2$]) (40). Figure (1.16) left panel shows Grubbs I.

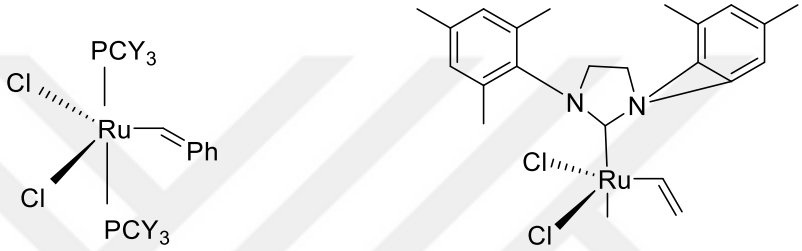
1.5.3 Grubbs' second-generation catalysts.

Grubb's second-generation catalyst was improved upon by the addition of an N-heterocyclic carbene (NHC) ligand in place of one phosphine ligand in the first generation. The features of this catalyst include improved strength in the electron-

donor capacity as well as possessing a much higher steric bulk of the ligands (i.e., the NHC ligand).

The latter means that the ligand is more tightly bound to the metal atom in the reaction, thereby providing better steric protection when compared to the phosphine ligand counterpart.

Consequently, the π -accepting alkene substrates' affinity to unsaturated ruthenium intermediates is greatly enhanced (41). Thus, comparing this catalyst to the Grubbs first-generation catalyst, it can be said that it is significantly more reactive and yield-enhancing.



Grubbs I Grubbs II

Figure 1.16. Grubb's first- and second-generation catalysts.

1.6 Aza-bicyclic compounds.

An aza-bicyclic compound is one of a kind of organic compound that contains a nitrogen atom in a bicyclic structure. The term "aza" refers to the presence of nitrogen, and "bicyclic" refers to the structure of the compound, which has two rings connected by a shared bond in its molecular structure.

Aza-bicyclic compounds can be classified depending on the size and structure of the rings involved.

A common example of an aza-bicyclic compound is indole, indoline, indolizidine, and quinolizidine, as shown in Figure (1.17).

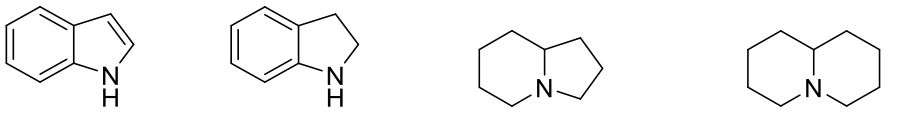
These compounds have diverse chemical and physical properties, and their structures can be modified by introducing different functional groups. aza-bicyclic can also be fused together to form more complex structures, which can lead to new and interesting properties. (42).

Aza-bicyclic compounds are important in medicinal chemistry, as they often exhibit biological activity, these are potential drugs or drug precursors. also, can be used as building blocks in organic synthesis, allowing the creation of more complex molecules. They can be applied in the synthesis of pharmaceuticals, pharmaceuticals and natural products.

The properties and reactivity of aza-bicyclic compounds can vary greatly depending on their specific structure and functional groups attached to the rings. For example, the nitrogen atom can participate in various chemical reactions, such as nucleophilic substitution, protonation, or coordination to metal ions.

Aza-bicyclic compounds can also exhibit stereoisomerism, where the spatial arrangement of atoms around the bicyclic structure can differ, resulting in different chemical and physical properties. This is particularly relevant in drug design, as different stereoisomers can have different pharmacological profiles. (43)

Bicyclic heterocycles are highly abundant both in nature and can be produced in the laboratory. Examples of aza-bicycles include pyridines, diazines, and hexazine, each of which possesses different number of nitrogen atoms in their composition. Synthesis of Derivatives of aza-bicyclic compounds has been, with great interest, to be used as certain enzyme blockers. For instance, Indolizidine iminosugars like swains nine and castanospermine (as well as quinolizidine alkaloids) have been used as potent glycosidase inhibitors (44), which were produced from sugar allytins.

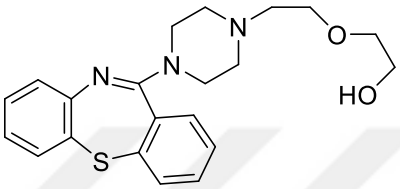


Indole Idoline Indolizidine quinolizidine

Figure 1.17. Examples of Aza-bicyclic compounds.

1.6.1 Examples of some drugs that contain aza-bicyclic structure.

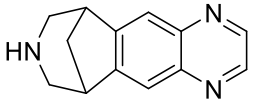
In medicine aza bi-cyclic containing structures can also be exemplified: Quetiapine is an antipsychotic drug that contains an aza bi-cyclic structure known as a dibenzo thiazepine ring. It's utilized to treat schizophrenia, bipolar disorder, and major depressive disorder (45).



Quetiapine

Figure 1.18. Structure of Quetiapine.

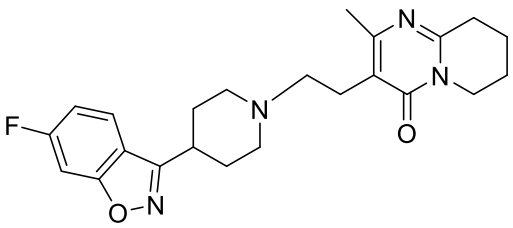
Varenicline is a smoking cessation drug that contains an aza bi-cyclic structure known as a pyrazine ring. helps to decrease desires and withdrawal symptoms the works by activating the brain's same receptors that nicotine does.



Varenicline

Figure 1.19. Structure of Varenicline.

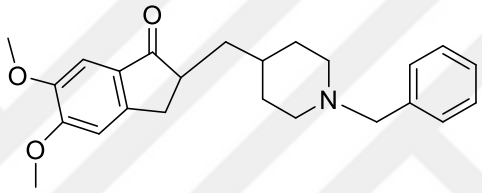
Risperidone is an antipsychotic drug that contains an aza bi-cyclic structure known as a benzisoxazole ring. It's utilized for treat bipolar disorder, schizophrenia, and autism-related irritability. (47).



Risperidone

Figure 1.20. Structure of Risperidone.

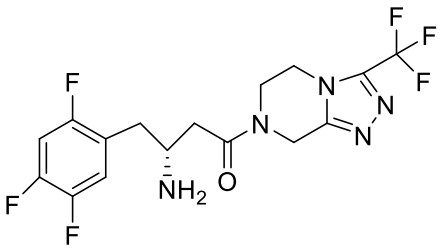
Donepezil is used to treat Alzheimer's disease and contains an aza-bicyclic structure known as a piperidine ring by inhibiting the enzyme acetylcholinesterase That causes the brain's neurotransmitter to be broken down. (48).



Donepezil

Figure 1.21. Structure of Donepezil.

Sitagliptin is another kind of drug used to treat type 2 diabetes that contains an aza-bicyclic structure known as a pyrazine ring.by inhibiting the enzyme dipeptidyl peptidase-4 (DPP-4), which helps to increase the levels of the hormone GLP-1 and stimulate insulin release (49).



Sitagliptin

Figure 1.22. Structure of Sitagliptin.

These are just a few examples of medicines that contain an aza bi-cyclic structure in their composition. The aza-bicyclic structure can impart specific

properties to the drug molecule, such as increased selectivity, improved pharmacokinetics, or enhanced biological activity.

2. AIM AND SCOPE OF THE STUDY

The aim of this work is to synthesize benzyl 3,3',4,6'-tetrahydro-1'H,2H-spiro[naphthalene-1,2'-pyridine]-1'-carboxylate and benzyl 2,3-dihydrospiro[indene] -1,2'-pyrrole] -1'(5'H) - carboxylic compounds starting with 1-tetralone (3,4-dihydronaphthalen-1(2H)-one) and 1-indanone (2,3-dihydro -1H -inden-1-one) via (RCM) using a Grubbs 2nd Second Generation catalyst.

Heterocyclic compounds containing nitrogen atom were selected for their biological and pharmacological importance. We also chose RCM React for several reasons… including does not require difficult conditions to perform, additionally to the fact that there are not many scaffolds prepared by this reaction (RCM).

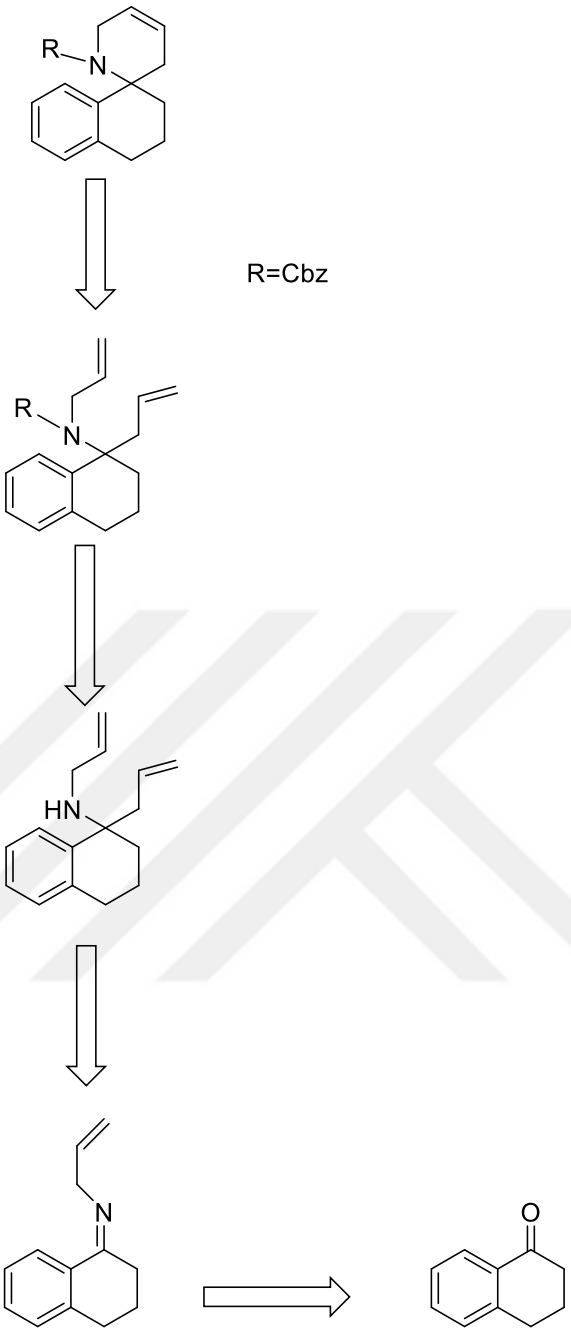


Figure 2.1. Retrosynthesis of the thesis study I**.**

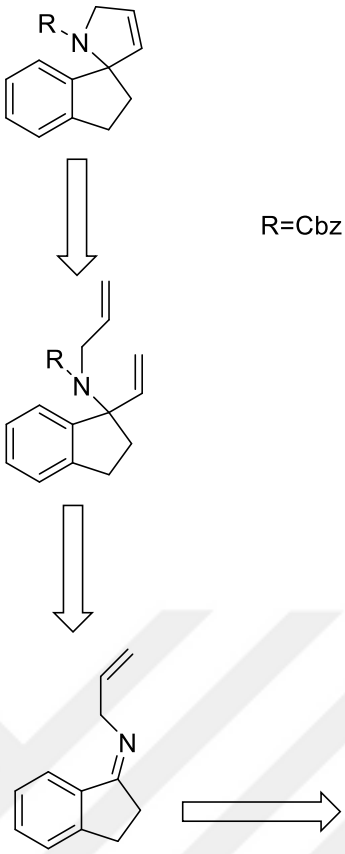


Figure 2.2. Retrosynthesis of the thesis study II.

3. MATERIALS AND METHODS

All the experiments were conducted in pre-dried glassware at 150 °C for 1 hour in an inert argon environment. Tetrahydrofuran (sodium benzophenone) and dichloromethane (P_2O_5) were extracted from the listed drying agents as reaction solvents.

^{1}H-NMR and ^{13}C-NMR spectra were captured using a JEOL ECS-400 spectrometer in $CDCl_3$.

The chemical shift was expressed in ppm as the internal standard relative to $CDCl_3$ for ^{1}H (400 MHz) and ^{13}C-NMR measurements in $CDCl_3$ (7.26 and 77.0 for ^{1}H and ^{13}C-NMR, respectively). Using a Thermo Nicolet IS10 ATR-FT-IR spectrophotometer, infrared spectra were captured**.**

Using a Rudolph research analytical, autopol II automatic polarimeter, optical rotations were measured.

Flash column chromatography was performed using thick-walled glass columns with a flash grade (Merc Silica Gel 60).

Thin-layer chromatography TLC, using plates precoated silica gel 60-F254, was used to properly monitor the reactions.

Poly molybdat phosphoric acid in ethanol and UV light was used to visualize the results.

A rotary evaporator was used to concentrate the solutions under

a vacuum, and all extracts were dried over ($MgSO_4$) aq.

Homoallylic imines **2a, 2b** were prepared by reported procedure (50). Also, *N*-homoallylic carbamates **4a, 3b** were synthesized according to the modified literature procedure.

3.1 General scheme synthesis of benzyl 3,3',4,6'-tetrahydro-1'H,2H-spiro[naphthalene-1,2'-pyridine]-1'-carboxylate via Ring-closing metathesis RCM.

3.1.1 Synthesis of (Z)-*N*-allyl-3,4-dihydronaphthalen-1(2H)-imine.

A 0.5 M solution of the cyclic ketone; α-tetralone (10.2 mmol) in benzene (20 mL) was added to a sealable tube. In the present of molecular sieves and allylamine (20.4 mmol) (1/1 ratio, w/w) were then added, the tube sealed, and the reaction mixture at (55–60) °C. After stirring overnight, the solution was filtered after being diluted with ether. Vacuum evaporation at low temperatures was used to carefully remove the ether. Benzene was removed by blowing nitrogen gas over the solution to give the pure imine product as a yellow-brown oil directly, used in the next step (50).

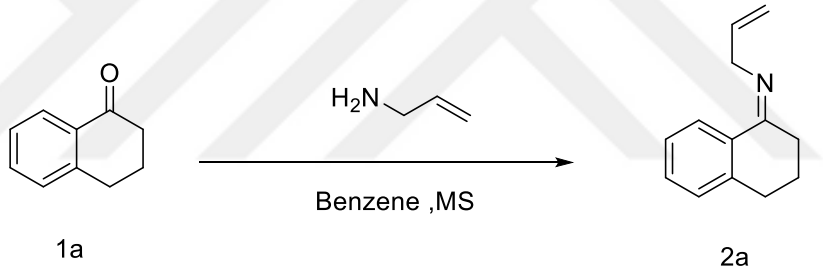


Figure 3.1. Synthesis of (Z)-*N*-allyl-3,4-dihydronaphthalen-1(2H)-imine.

3.1.2 Synthesis of *N*,1-diallyl-1,2,3,4-tetrahydronaphthalen-1-amine.

A mixture of allyl bromide (11 mmol) in anhydrous diethyl ether (7 mL) was dropped into a stirred Mg turnings solution (15 mmol) in dry diethyl ether (15 mL) at rt equipped with a reflux graham condenser. was allowed to reflux the mixture /for 25 min. after cooling to 0 °C, was add drop by drop the equivalent imine **2a** (10 mmol) in dry diethyl ether (5 mL), then stirred the mixture for 4 hours. With 20 mL of a saturated solution of ammonium chloride, the mixture of reaction was hydrolyzed. Diethyl ether (3x30 mL) was used to extract the combination that

resulted. The mixed organic phase was dried over $MgSO_4$ and evaporated by vacuum after being washed with brine (20 mL).

By using a solution of ethyl acetate/hexane and triethylamine in the proper ratios, by flash column chromatography, the crude products were purified.

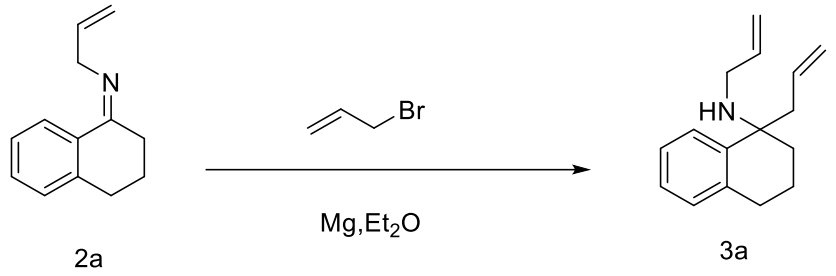


Figure 3.2. Synthesis of *N*,1-diallyl-1,2,3,4-tetrahydronaphthalen-1-amine.

3.1.3 Synthesis of benzyl allyl(1-allyl-1,2,3,4-tetrahydronaphthalen-1-yl) carbamate.

THF (3 mL) was used to dissolve 0.25 mmol of corresponding enyne **3a**. (0.28) mmol of benzyl chloroformate was then added, and at 60 °C for 1 hour the mixture was then heated. The mixture was divided into (20 mL) of water and (20 mL) of Et_2O, and the organic layers were separated, then washed with a saturated solution of $NaHCO_3$ and brine, dried over (MgSO4) and concentrated via filtration at lower pressure. by using a solution of ethyl acetate/hexane and triethylamine in the proper ratios, by use of flash column chromatography, the crude product was purified (51).

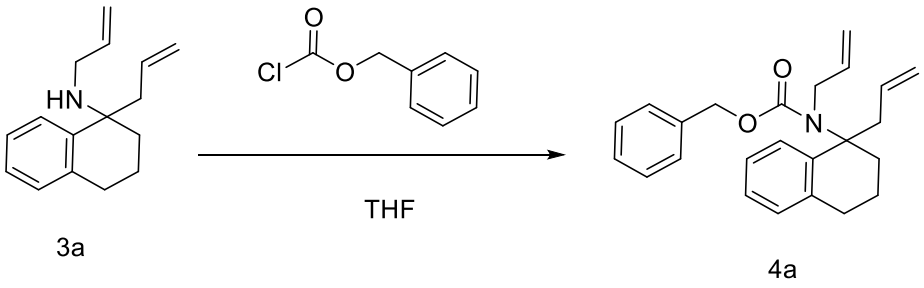


Figure 3.3 Synthesis of benzyl allyl(1-allyl-1,2,3,4-tetrahydronaphthalen-1-yl) carbamate.

3.1.4 Synthesis of benzyl 3,3',4,6'-tetrahydro-1'H,2H-spiro[naphthalene-1,2'-pyridine]-1'-carboxylate.

N-homoallylic diene (1.26 mmol) **4a** was dissolved in DCM (15 mL) and heat for 30 min at reflux. When the mixture had cooled to rt was added Grubbs' 2nd-generation catalyst (5 mol%), for an additional 2 hours it was heated at reflux. Used TLC to observe the reaction. After the reaction was complete, via a vacuum was concentrated the crude product, and the residue was then mixed with an aqueous solution of $NaHCO_3$. The organic components were extracted with CH_2Cl_2 after the solution was made basic with the addition of solid K_2CO_3. To obtain the crude product, the organic solution was concentrated and dried over ($MgSO_4$). Through the use of appropriate ethyl acetate/hexane and triethylamine as the eluent, it was purified using flash column chromatography.

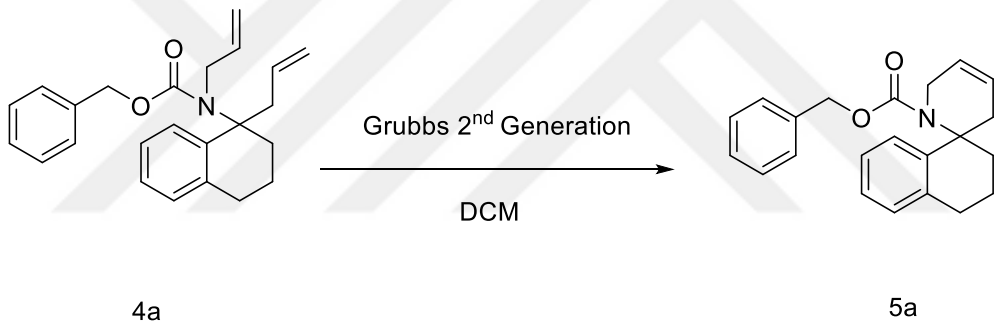


Figure 3.4. Synthesis of benzyl 3,3',4,6'-tetrahydro-1'H,2H-spiro[naphthalene-1,2'-pyridine]-1'-carboxylate.

3.2 General scheme synthesis of benzyl 2,3-dihydrospiro[indene-1,2'-pyrrole]-1'(5'H)-carboxylate via Ring-closing metathesis RCM.

3.2.1 Synthesis of (Z)-*N*-allyl-2,3-dihydro-1H-inden-1-imine.

A 0.5 M solution of the cyclic ketone;1-indanone; (2g) in benzene (25 mL) was added to a sealable tube. In the presence of molecular sieves (2.5g), and allylamine (2.32 mmol) (1/1 ratio, w/w) were then added, the tube sealed, and the

reaction mixture at (55–60) °C. The solution was diluted (after stirring overnight) with ether and filtered. Vacuum evaporation at low temperatures was used to carefully remove the ether. Benzene was removed by blowing nitrogen gas over the solution to give the pure imine product as a yellow-brawn oil used directly in the next step (50).

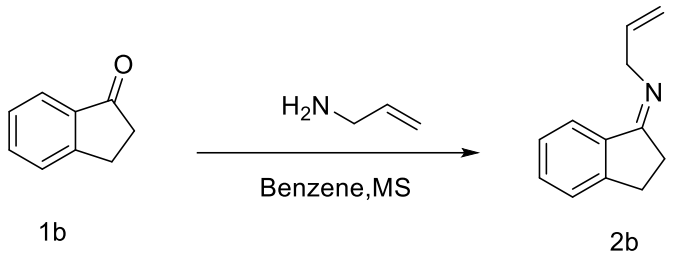


Figure 3.5. Synthesis of (Z)-*N*-allyl-2,3-dihydro-1H-inden-1-imine.

3.2.2 Synthesis of benzyl allyl(1-vinyl-2,3-dihydro-1H-inden-1-yl) carbamate.

A portion of (0.25 mmol) corresponding homoallylic **2b** amines in THF (3 mL) was dissolved, then benzyl chloroformate (0.28 mmol) was added, and at 60 °C for 1 hour the mixture was then heated, then the mixture was cooled to -78 °C was accomplished by using a mix of acetone and liquid nitrogen. and was add a solution of vinyl magnesium bromide in THF (1.04 M, 0.30 mmol). at rt \1.5 h, the mixture was stirred after the cooling bath was removed. Then add saturated aqueous NH_4Cl (0.5 mL), The mixture was divided into (20 mL) of water and (20 mL) of Et_2O, and the organic layers were separated, then washed with a saturated solution of $NaHCO_3$ and brine, dried over ($MgSO_4$) and concentrated via filtration at lower pressure. by using a solution of ethyl acetate/hexane and triethylamine in the proper ratios, by use of flash column chromatography, the crude product was purified (51).

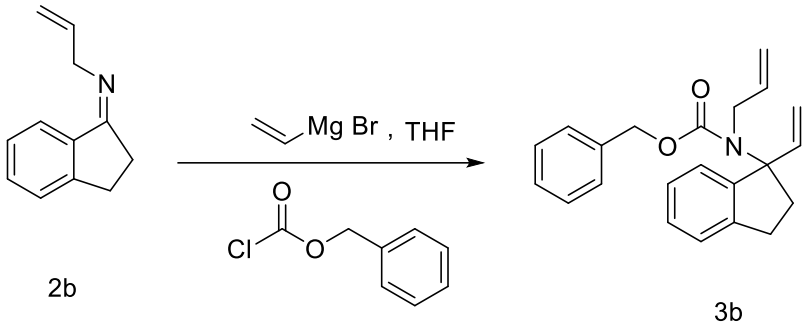


Figure 3.6. Synthesis of benzyl allyl(1-vinyl-2,3-dihydro-1H-inden-1-yl) carbamate.

3.2.3 Synthesis of benzyl 2,3-dihydrospiro[indene-1,2'-pyrrole]-1'(5'H)-carboxylate.

N-homoallylic diene (1.26 mmol) **3b** was dissolved in DCM (15 mL) and heated for 30 min at reflux. When the mixture had cooled to rt was added Grubbs' 2nd-generation catalyst (5 mol%), and it was then heated at reflux for an additional 2 hours. TLC was used to observe the reaction. When the reaction finished, the crude product was concentrated in a vacuum, and the residue was then mixed with an aqueous solution of $NaHCO_3$. The organic components were extracted with CH_2Cl_2 after a solution was made basic with the addition of solid K_2CO_3. To obtain the crude product. Through the use of appropriate ethyl acetate/hexane and triethylamine as the eluent, it was purified using flash column chromatography.

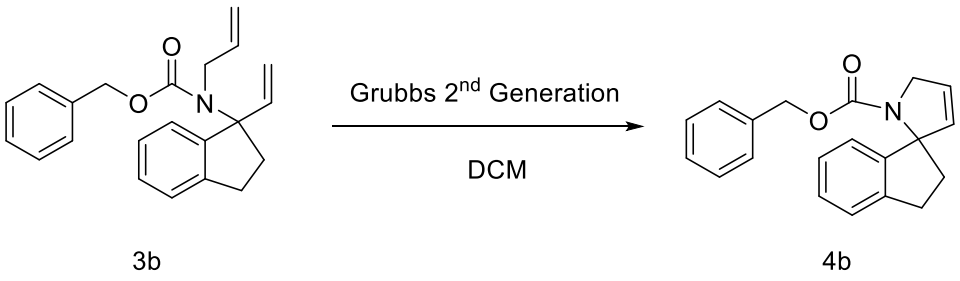


Figure 3.7. Synthesis of benzyl 2,3-dihydrospiro[indene-1,2'-pyrrole]-1'(5'H)-carboxylate.

4. RESULTS -AND DISCUSSION

4.1 General scheme synthesis of benzyl 3,3',4,6'-tetrahydro-1'H,2H-spiro[naphthalene-1,2'-pyridine]-1'-carboxylate via Ring-closing metathesis RCM.

4.1.1 Synthesis of (Z)-*N*-allyl-3,4-dihydronaphthalen-1(2H)-imine.

(Z)-*N*-allyl-3,4-dihydronaphthalen-1(2H)-imine was prepared from α-tetralone and allylamine with the presence of a molecular sieve in benzene. After workup, was obtained (Z)-*N*-allyl-3,4-dihydronaphthalen-1(2H)-imine as yellow oil with 97% chemical yield.

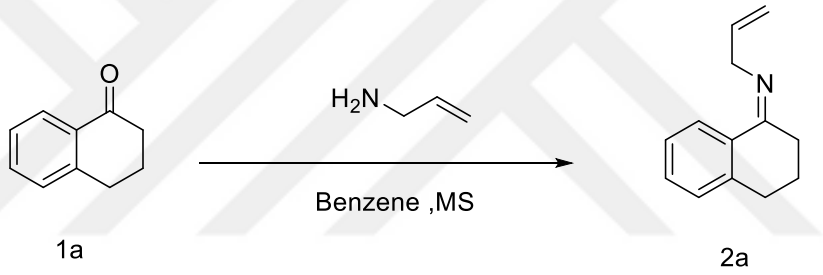


Figure 4.1. Synthesis of (Z)-*N*-allyl-3,4-dihydronaphthalen-1(2H)-imine.

Column chromatography was used to purify the product, and the system solvent was (EtOAc: Hexane: Et_3N) (1:7:1%).

^{1}H-NMR spectrum of the compound (Z)-*N*-allyl-3,4-dihydronaphthalen-1(2H) -imine shows doublet at 4.12 ppm.. with *J* =5.0 Hz belong to the allylic methylene protons directly attached to N atom. Between (6.07- 6.15) ppm multiplet belonged to the internal vinylic proton. One of the internal vinylic protons shows a quartet of a doublet at 5.15 ppm with *J* = 1.0,8 Hz due to one of the terminal vinylic protons. Other terminal vinylic proton exhibits a quartet of a doublet at 5.23 ppm with *J* =1.0 and 13.5 Hz. Multiplet between (7.33-7.26) ppm belongs to two of the aromatic ring protons the quartet 7.37 ppm with *J* =1.6 Hz belonged to one in the aromatic ring protons.

The signal 7.86 ppm doublet with J = 6 Hz is responsible from the methine proton in the aromatic ring. One couple of the methylene protons of the cyclohexane ring shows at 3.03 ppm triplet with J = 0.4 Hz. At 2.66 ppm triplet with J = 5 Hz is for the other couple methylene protons in the cyclohexane ring. 2.63-2.67 ppm multiplet for the last couple of methylene protons in the cyclohexane ring. at 3.09 ppm triplet with J = 9 Hz is due to the methylene protons in the cyclohexane ring of α-tetralone.

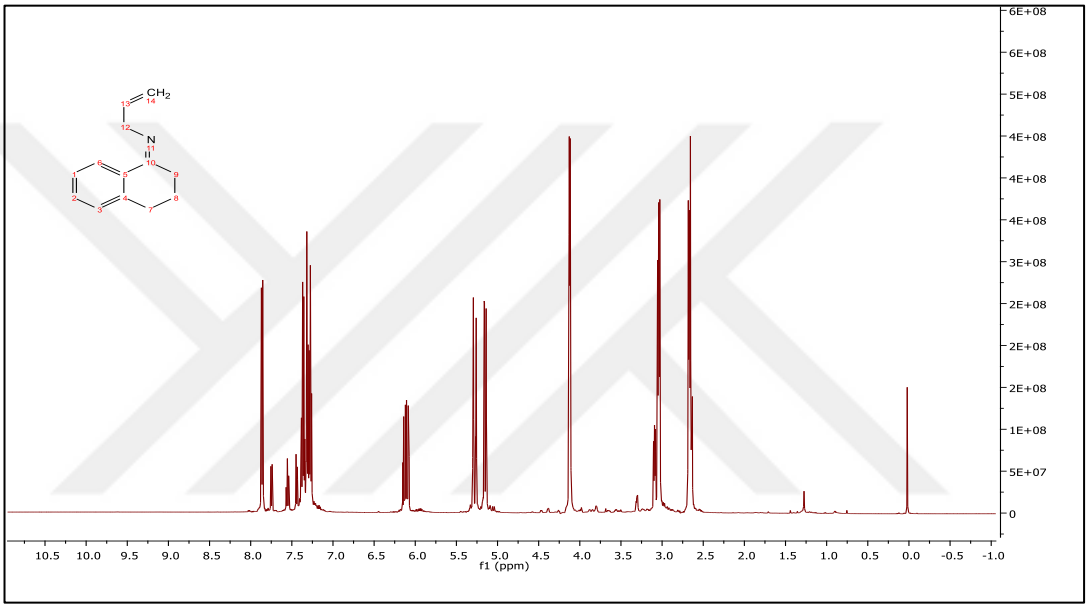


Figure 4.2. ^{1}H spectrum of (Z)-*N*-allyl-3,4-dihydronaphthalen-1(2H)-imine.

^{13}C-NMR spectrum of (Z)-*N*-allyl-3,4-dihydronaphthalen-1(2H)-imine exhibit signals at 21.1, 25.7, and 28.0 ppm due to the methylene carbons in cyclohexane ring respectively. A signal at 36.2 ppm belongs to one of the methylene carbons in a ring of cyclohexanone ring of α-tetralone. Allylic methylene carbon exhibits a signal at 56.2 ppm. Signals at 115.4, and 131.2 ppm belonged to allylic methylene and methine carbons. Furthermore, the signals at 127.2, and 139.7 ppm belong to quaternary carbon in the aromatic ring.

Methine carbons in the aromatic ring show signals at 122.4, 125.6, 126.9, and 136.0 ppm respectively. Finally, a signal at 155.1 ppm is back to quaternary imine carbon.

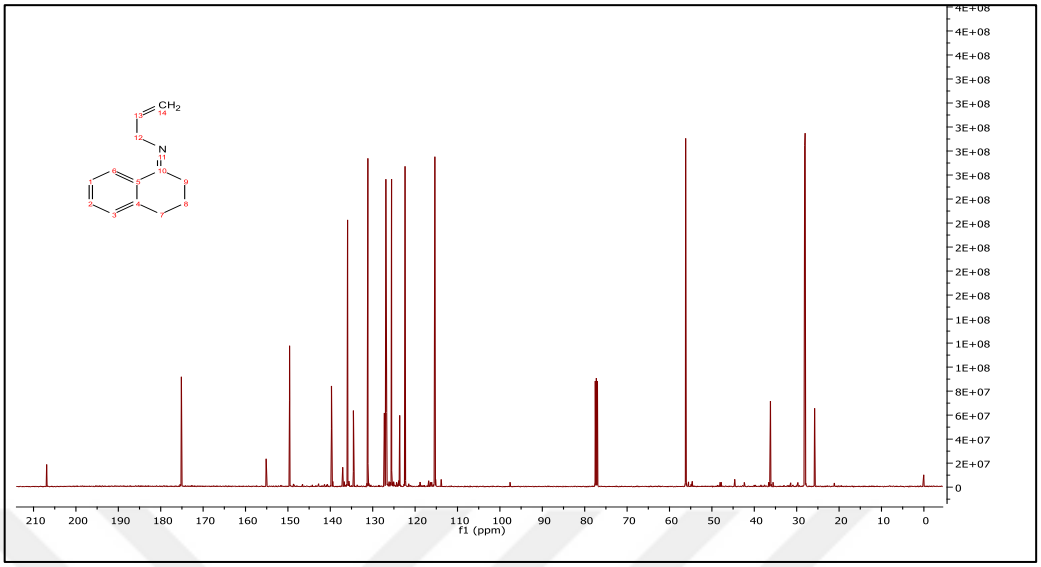


Figure 4.3. ^{13}C spectrum of (Z)-*N*-allyl-3,4-dihydronaphthalen-1(2H)-imine.

4.1.2 Synthesis of *N*,1-diallyl-1,2,3,4-tetrahydronaphthalen-1-amine.

N,1-diallyl-1,2,3,4-tetrahydronaphthalen-1-amine was prepared from (Z)-*N*-allyl-3,4-dihydronaphthalen-1(2H)-imine by Grignard reaction with the presence of allyl magnesium bromide in diethyl ether. The product was 74% chemical yield as a dark yellow oil.

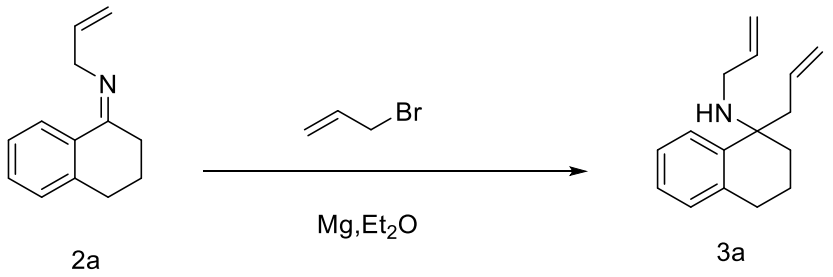


Figure 4.4. Synthesis of *N*,1-diallyl-1,2,3,4-tetrahydronaphthalen-1-amine.

Column chromatography was used to purify the product, and the system solvent was (EtOAc: Hexane: Et_3N) (1:7:1%).

^{1}H-NMR spectrum *N*,1-diallyl-1,2,3,4-tetrahydronaphthalen-1-amine exhibits a doublet at 7.25 ppm... with *J* =1.0 Hz due to the methine protons in aromatic ring. the other methine protons of the aromatic ring show multiplet between (7.20-7.29) ppm. between (5.74-5.82) ppm and (5.89-5.98) ppm show Multiplet are due to both allylic methine protons of the allyl side chains respectively.

One of the allylic methine protons shows a doublet of a doublet at 5.07 ppm... with *J* =1.2 and 9.6 Hz. At 5.12 ppm... with *J* = 1.2 and 9.8 Hz a doublet of a doublet are belong to other protons allylic methylene of the allyl side chain. The other methylene proton of the allyl side chain shows a doublet of a doublet at 5.19 ppm... with *J* = 1.6 and 6.9 Hz. The final one the allylic methylene protons of the allyl side chain shows a doublet of a doublet at 5.18 ppm... with *J* = 1.2 and 10.0 Hz.

At 3.14 ppm with *J* = 4.8 and 10.8 Hz doublet of a doublet belongs to one of the methylene protons attached to the nitrogen atom. the other methylene exhibits doublet of a doublet at 3.00 ppm with *J* = 4.8 and 10.9 Hz.

Both a doublet of a doublet at 2.95 ppm with *J* = 2.4 and 6.6 Hz ppm and a quartet at 2.91 ppm... with *J* = 6 .0 Hz are due to the diastereotopic methylene protons of the other allyl side chain. One of the diasterotopic methylene protons of the cyclohexane ring shows a doublet of a doublet at 2.58 ppm... with *J* = 6.0 and 9.2 Hz. The other one exhibits doublet of a doublet at 2.49 ppm... with *J* =5.6 and 11.4 Hz.

Doublet of a doublet at 2.15 ppm... with *J* = 3.6 and 6.8 Hz, and triplet at 2.12 ppm... with *J* =2.8 Hz are to the other methylene protons of the cyclohexane ring.

Finally, multiplet between 2.19 and 2.25 ppm belong to two of the proton's methylene in the cyclohexane ring.

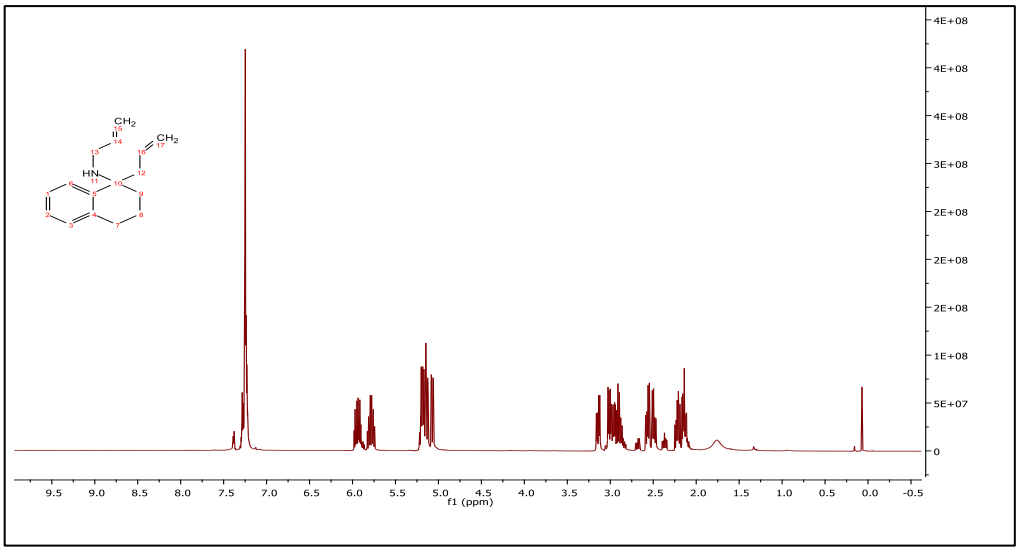


Figure 4.5. ^{1}H spectrum of *N*,1-diallyl-1,2,3,4-tetrahydronaphthalen-1-amine.

^{13}C-NMR spectrum of (*N*,1-diallyl-1,2,3,4-tetrahydronaphthalen-1-amine). A signal at 115.3 and 118.3 ppm belong to the terminal vinylic carbons of two allyl side chains. Internal vinylic ones exhibit signals at 143.6 and 146.4 ppm respectively of the two-allyl side chains.

The signals at 134.4, and 137.3 ppm respectively are responsible for the quaternary carbon of the aromatic ring.

The signals at 127.4, 126.2, 124.9, and 123.7 ppm are due to the methine carbon of the aromatic ring respectively. The signal at 68.4 ppm is responsible for the quaternary carbon. The signals at 44.0, and 45.9 ppm are due to the allylic methylene carbons directly attached to the nitrogen atom and the other methylene carbon of the allyl side chain.

Finally, the cyclohexane ring methylene carbon exhibit signals at 29.9, and 35.3 ppm respectively.

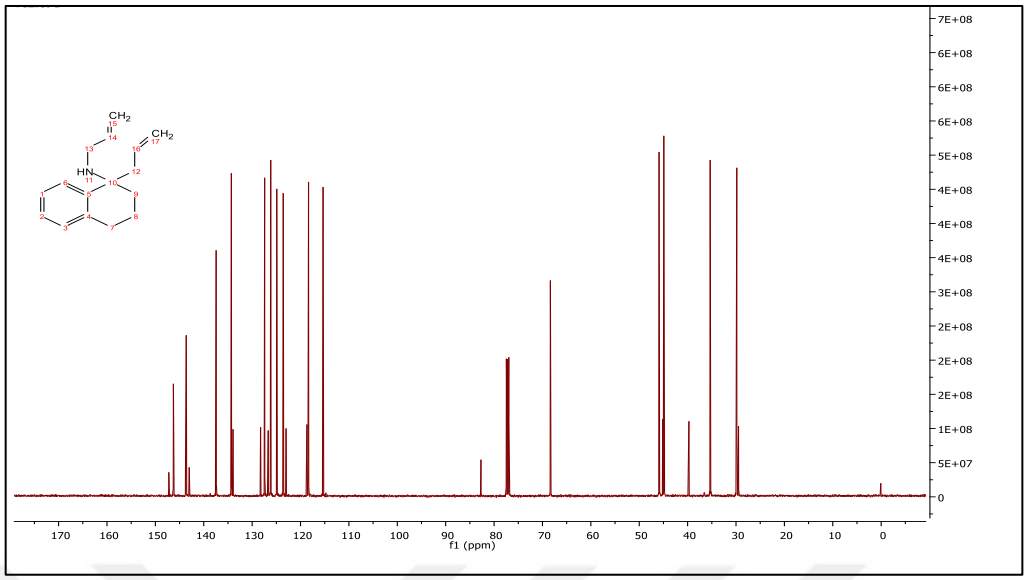


Figure 4.6. ^{13}C spectrum of *N*,1-diallyl-1,2,3,4-tetrahydronaphthalen-1-amine.

4.1.3 Synthesis of benzyl allyl(1-allyl-1,2,3,4-tetrahydronaphthalen-1-yl) carbamate.

Benzyl allyl(1-allyl-1,2,3,4-tetrahydronaphthalen-1-yl) carbamate 4a was prepared from *N*,1-diallyl-1,2,3,4-tetrahydronaphthalen-1-amine by benzyl chloro format-cbz-in Tetrahydrofuran obtained as dark yellow oil with 72% yield. Shows in Figure (4.7).

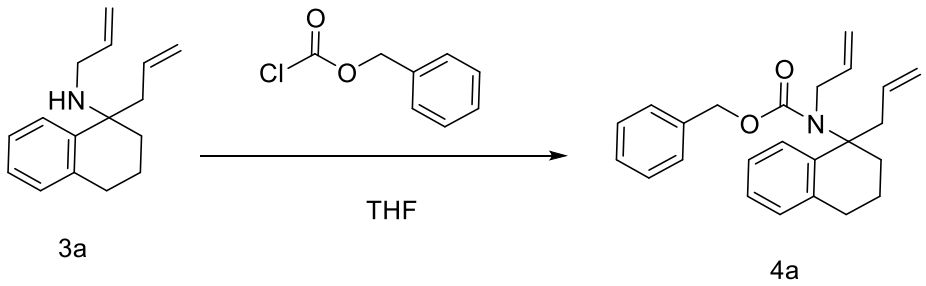


Figure 4.7. Synthesis of benzyl allyl(1-allyl-1,2,3,4-tetrahydronaphthalen-1-yl) carbamate.

Column chromatography was used to purify the product, and the system solvent was (EtOAc: Hexane: Et_3N) (1:7:1%).

^{1}H-NMR spectrum of benzyl allyl(1-allyl-1,2,3,4-tetrahydronaphthalen-1-yl) carbamate. Multiplet between (7.30-7.42) ppm belongs to four of the protons in the phenyl ring of the benzoyl group. Multiplet, between (7.23-7.26) ppm is responsible for one of the methyl protons in the phenyl ring of the benzoyl group. Three methine protons of the other fused benzene ring exhibit multiplet between (7.14-7.19) ppm. The last methine proton of the benzene ring shows a multiplet between 7.06-7.09 ppm.

Multiplet between (5.76-5.86) belongs to the internal vinylic proton of the allyl group attached to the nitrogen atom directly. Another internal vinylic proton exhibit multiplet between (5.49-5.60) ppm. The doublet of a doublet at 5.05 ppm… with J =1.6 and J = 11.6 Hz is belonging to one of the terminal vinylic protons of the allyl side chain attached to the nitrogen atom directly. One of the terminal vinylic protons of the other allyl side chain shows a doublet of a doublet at 5.09 ppm with J = 1.6 and J = 17.6 Hz. The doublet of a doublet at 5 .00 ppm... with J = 1.2 and J =9.0 Hz is due to the other terminal vinylic proton of the allyl group directly attached to the nitrogen atom. The other terminal vinylic proton of the other allylic side chain also shows a doublet of a doublet at 4.94 ppm... with J = 17.4 and J =1.6 Hz. The singlet at 5.07 ppm belongs to the methylene protons of the benzyl group. One of the allylic methylene protons directly attached to the nitrogen atom exhibits a doublet of doublet at 4.03 ppm... with J = 5.6 and 16.8 Hz.

The doublet of a doublet at 3.74 ppm... with J = 5.2 and 16.6 Hz belongs to the other allylic protons methylene directly attached to a nitrogen atom. The allylic methylene protons fused with the benzene ring show doublet of a doublet at 3.25 ppm with J = 14.4 and 8.0 Hz.

The doublet of a doublet at 2.98 ppm... with J = 6.0 and 14.4 Hz belongs to one of the allylic methylene protons of the other allyl side chain. The other one exhibits a multiplet between 2.66 and 2.78 ppm. The multiplet between 1.86-1.94 ppm belongs to the methylene protons of the cyclohexane ring. Multiplet between (1.74-1.85) ppm of other protons methylene of the ring's cyclohexane.

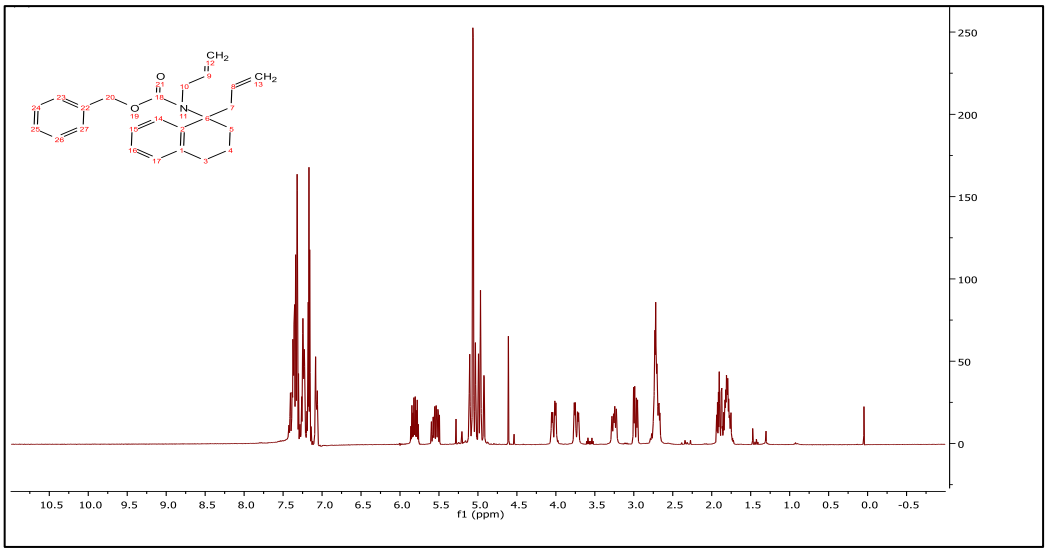


Figure 4.8. ^{1}H spectrum of benzyl allyl(1-allyl-1,2,3,4-tetrahydronaphthalen-1-yl) carbamate.

^{13}C-NMR spectrum of benzyl allyl(1-allyl-1,2,3,4-tetrahydronaphthalen-1-yl) carbamate a signal at 155.8 ppm for the ester carbonyl carbons. The signals at 117.8 and 115.6 ppm are for the terminal vinylic carbons of the allyl side chains. Internal vinylic carbons exhibit

signals at 129.2 and 138.0 ppm respectively. signals at 136.3, and 135.1 ppm are responsible for the quaternary carbons of the fused connection. One of the ring carbons exhibits signals at 128.4, 127.8, and 127.9 ppm respectively with the other ring methine carbons at 125.6, 126.9 with 127.4 ppm in turn.

The benzylic carbon and quaternary carbon directly attached to the nitrogen atom show signals at 66.9, and 63.6 ppm respectively. The signals at 49.1 and 44.9 ppm are responsible for the allylic methylene carbons.

Finally, the cyclohexane ring methylene carbons exhibit signals at 32.9, 29.4, and 19.5 ppm respectively.

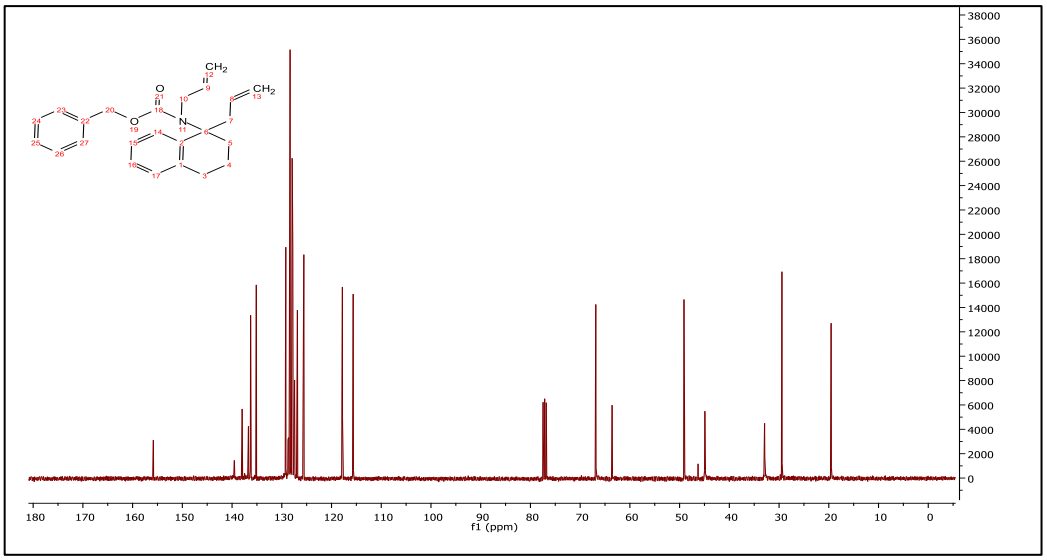


Figure 4.9. ^{13}C spectrum of benzyl allyl(1-allyl-1,2,3,4-tetrahydronaphthalen-1-yl) carbamate.

4.1.4 Synthesis of benzyl 3,3',4,6'-tetrahydro-1'H,2H-spiro[naphthalene-1,2'-pyridine]-1'-carboxylate.

Benzyl 3,3',4,6'-tetrahydro-1'H,2H-spiro[naphthalene-1,2'-pyridine]-1'-carboxylate was prepared from benzyl allyl(1-allyl-1,2,3,4-tetrahydronaphthalen-1-yl) carbamate by Grubbs 2nd generation in di chloro methane DCM. Figure (4.10) as shown, was obtained as dark oil with 80% yield.

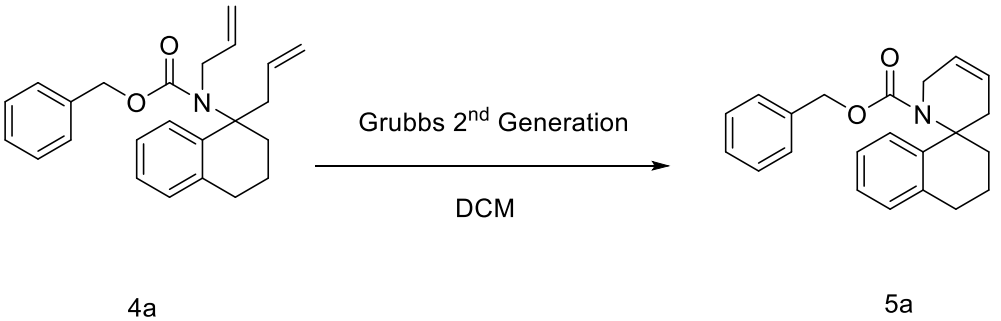


Figure 4.10. Synthesis of benzyl 3,3',4,6'-tetrahydro-1'H,2H-spiro[naphthalene-1,2'-pyridine]-1'-carboxylate.

Column chromatography was used to purify the product, and the system solvent was (EtOAc: Hexane: Et_3N) (1:7:1%).

^{1}H-NMR spectrum of benzyl 3,3',4,6'-tetrahydro-1'H,2H-spiro[naphthalene-1,2'-pyridine]-1'-carboxylate. Two doublets at 4.79 and 4.89 ppm with *J* = 12 Hz belong to the methylene protons of the benzoyl group.

One of the methylene protons directly attached to the nitrogen exhibits doublet of a doublet at 4.29 ppm with *J* = 5.0 and 18.0 Hz and the quartet of doublet at 4.18 ppm.. with *J* = 3.00 and 17.0 Hz are responsible for the methylene protons directly attached to the nitrogen atom. Multiplet between 1.69-1.87 ppm belongs to two of the methylene protons of the cyclohexane ring.

Furthermore, one of another methylene protons of the cyclohexane ring exhibits a triplet of a doublet at 1.97 ppm with *J* = 2.0 and 13.0 Hz besides a doublet of triplet at 2.19 ppm with *J* = 13.0 and 3.0 Hz belongs to the other methylene proton of the cyclohexane ring. One of the allylic methylene protons of the tetrahydropyridine ring shows a quartet of a doublet at 2.41 ppm with *J* =2.0 and 26.0 Hz. Doublet at 2.54 ppm with *J* = 7.0 Hz is responsible for the other allylic methylene protons of the tetrahydropyridine ring.

Moreover, one of the other allylic methylene protons fused with the benzene ring shows a doublet at 2.59 ppm.. with *J* = 7.0 Hz. A doublet at 2.63 ppm ..with *J* = 12.0 Hz belongs to another allylic methylene fused with of benzene ring. One of the olefinic protons of the tetrahydropyridine ring shows a quartet of triplet at 5.92 ppm with *J* = 3.0 and 6.0 Hz. The quartet of triplets at 6.06 ppm.. with *J* = 3.0 and 7.0 Hz is due to the other olefinic proton of the tetrahydropyridine ring. Multiplet between 6.89-6.95 ppm and a doublet at 6.96 ppm with *J* = 8.0 Hz belongs to the two of the benzene ring protons of the naphthalene. Furthermore, doublet of a doublet at 7.08 ppm with *J* =1.0 and 7.0 Hz with a triplet at 7.11 ppm.. with *J* =1.0 Hz belong to the other protons of the ring. One of the protons of the phenyl ring of the benzyl group exhibits doublet of a doublet at 7.14 ppm ,with *J* = 1.0 and 7.0 Hz. The other two show doublet of a doublet at 7.24 ppm, with *J* =1.0 and 5.0 Hz. The Finally at 7.29 ppm, with *J* =1.0 and 8.0 Hz exhibits doublet of a doublet.

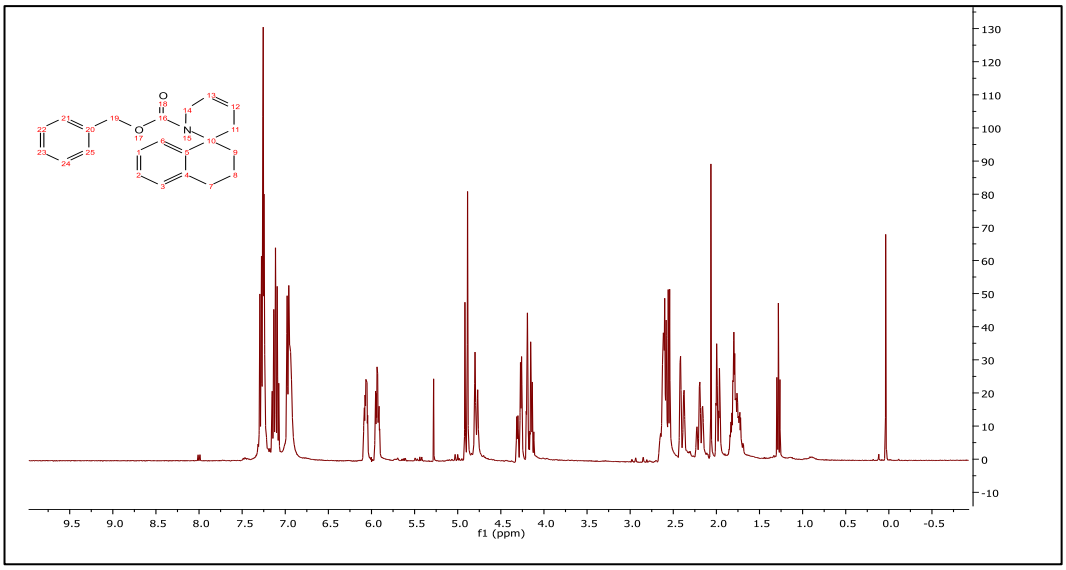


Figure 4.11. ^{1}H spectrum of benzyl 3,3',4,6'-tetrahydro-1'H,2H-spiro[naphthalene-1,2'-pyridine]-1'-carboxylate.

^{13}C-NMR spectrum of benzyl 3,3',4,6'-tetrahydro-1'H,2H-spiro[naphthalene-1,2'-pyridine]-1'-carboxylate the ester carbonyl exhibits a signal at 155.7 ppm. A signal at 144.0, 136.4, 128.5, and 128.1 ppm are due to quaternary carbons of one of the aromatic rings. Moreover, quaternary carbons of the other aromatic ring exhibit at 128.0, 127.7, 126.1, 125.7, and 125.4 ppm respectively. A signal at 67.0 and 59.3 ppm belong to the quaternary carbon directly attached to the Nitrogen atom and methylene carbon of the benzoyl group respectively. The allylic methylene carbon directly attached to the nitrogen atom shows a signal of 44.2 ppm. Furthermore, a signal at 39.4 ppm belongs to the other allylic methylene carbon of the tetrahydropyridine ring. Finally, the methylene carbons of the spirocyclic ring exhibit signals at 32.5, 29.6, and 21.3 ppm successively.

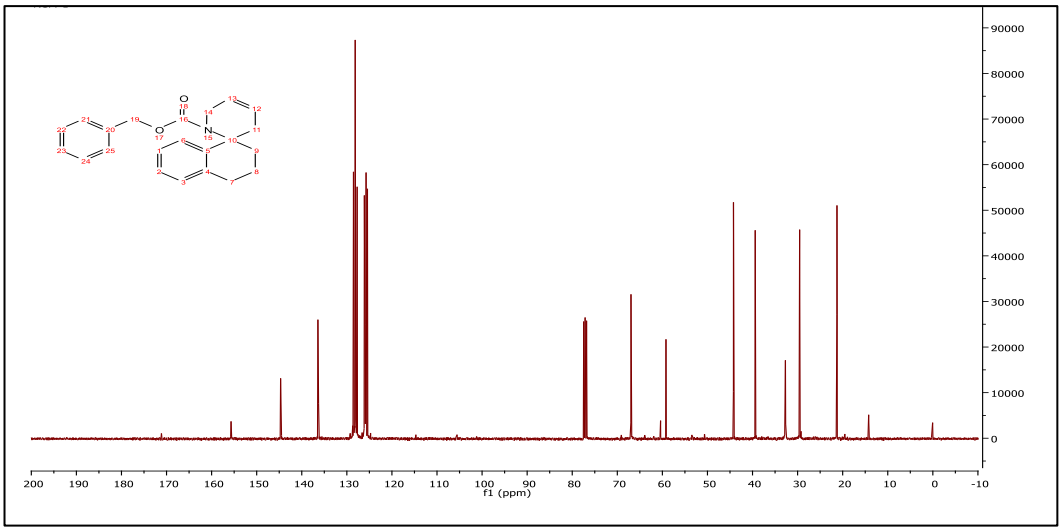


Figure 4.12. ^{13}C spectrum of benzyl 3,3',4,6'-tetrahydro-1'H,2H-spiro[naphthalene-1,2'-pyridine]-1'-carboxylate.

4.2 General scheme synthesis of benzyl 2,3-dihydrospiro[indene-1,2'-pyrrole]-1'(5'H)-carboxylate via Ring-closing metathesis RCM.

4.2.1 Synthesis of (Z)-*N*-allyl-2,3-dihydro-1H-inden-1-imine.

(Z)-*N*-allyl-2,3-dihydro-1H-inden-1-imine was prepared from 1-indanone and allylamine with the presence of molecular sieve in benzene shows as in the Figure (4.13). After work up, (Z)-*N*-allyl-2,3-dihydro-1H-inden-1-imine was obtained 82% chemical yield as dark brown oil.

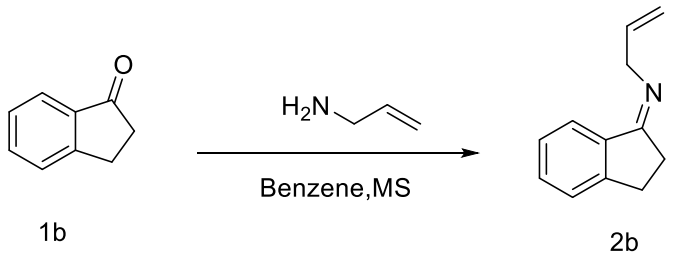


Figure 4.13. Synthesis of (Z)-N-allyl-2,3-dihydro-1H-inden-1-imine.

Column chromatography was used to purify the product, and the system solvent was (EtOAc: Hexane: Et_3N) (1:1:1%).

^{1}H-NMR spectrum of (Z)-*N*-allyl-2,3-dihydro-1H-inden-1-imine exhibits two triplets at 2.07 and 3.09 ppm with *J* = 4.6 and 5.2 Hz for the two methylene protons of the cyclopentane ring. A doublet at 4.17 ppm with *J* =15.6 Hz is responsible for the allylic methylene protons directly attached to the Nitrogen atom. One of the terminal vinylic protons shows a quartet of a doublet at 5.29 ppm with *J* = 1.2 and *J* =13.2 Hz and the other one exhibits another quartet of a doublet at 5.18 ppm with *J* = 1.2 Hz and 2.0 Hz. The internal vinylic proton is responsible for the multiplet between 6.09 and 6.17 ppm. Furthermore, one of the aromatic ring protons shows a doublet at 7.88 ppm with *J* =6 Hz. The triplet at 7.40 ppm with *J* = 6 Hz is for other aromatic methylene protons followed by at 7.35 ppm with *J* =6.0 Hz by the other aromatic methylene protons.

Finally, triplet at 7.30 ppm with *J* = 15 Hz is for the last aromatic ring proton.

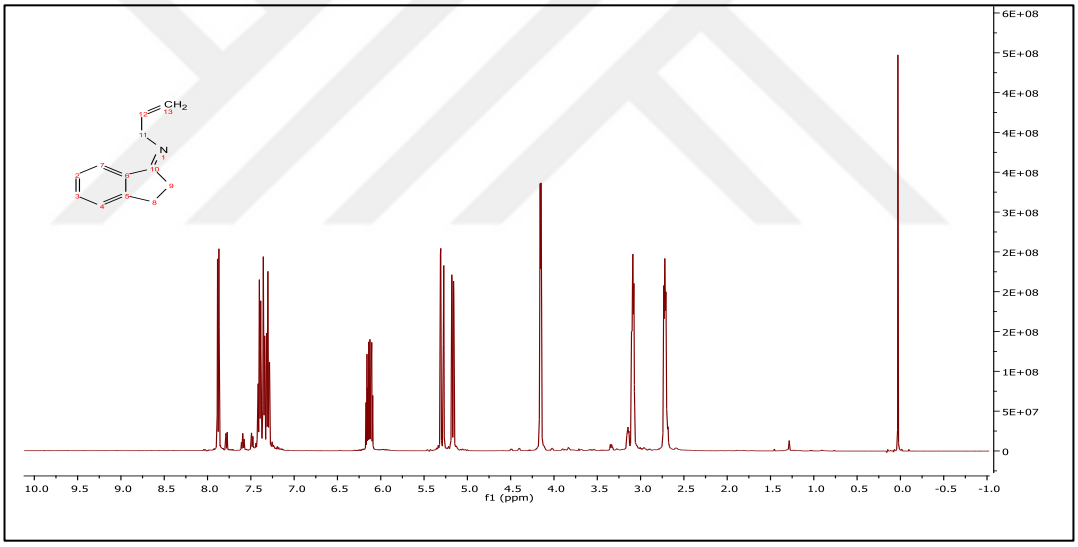


Figure 4.14. ^{1}H spectrum of (Z)-*N*-allyl-2,3-dihydro-1H-inden-1-imine.

^{13}C-NMR spectrum of (Z)-*N*-allyl-2,3-dihydro-1H-inden-1-imine the signals at 28.0 and 28.1 ppm are due to the methylene carbons of the cyclopentane ring. Allylic methylene carbon directly attached to the Nitrogen atom exhibits signal at 56.2 ppm.

Moreover, the internal vinylic carbon and terminal vinylic carbon show signals at 131.1 and 115.3 ppm respectively. The signals at 136.0-139.8 ppm belong

to the fused part's quaternary carbons. Finally, the other aromatic ring methine carbons show signals at 122.3, 125.5,126.9 ppm respectively.

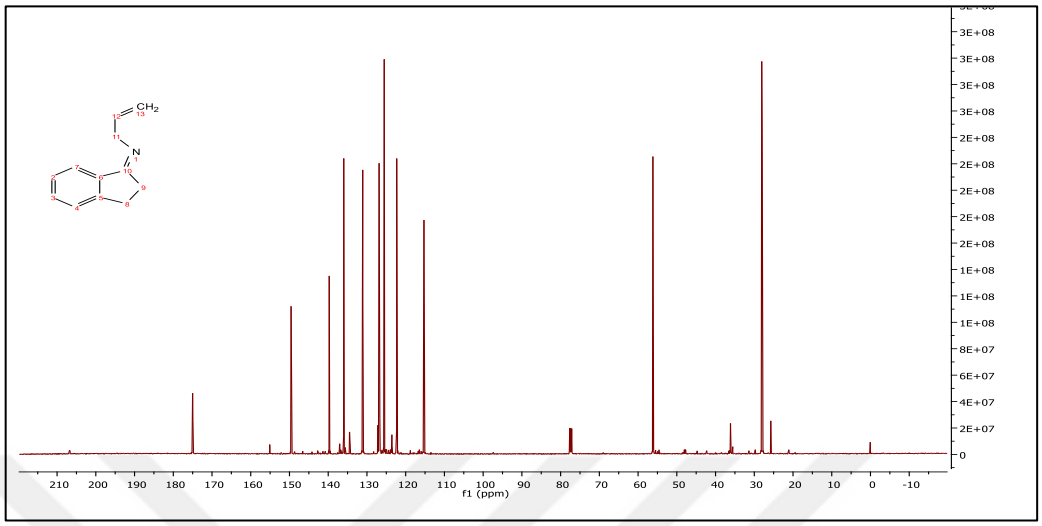


Figure 4.15. ^{13}C spectrum of (Z)-*N*-allyl-2,3-dihydro-1H-inden-1-imine.

4.2.2 Synthesis of benzyl allyl(1-vinyl-2,3-dihydro-1H-inden-1-yl) carbamate.

Benzyl allyl(1-vinyl-2,3-dihydro-1H-inden-1-yl) carbamate was prepared from (Z)-*N*-allyl-2,3-dihydro-1H-inden-1-imine by benzyl chloroformate and vinyl magnesium bromide in tetrahydrofuran shown in Figure (4.16), benzyl allyl(1-vinyl-2,3-dihydro-1H-inden-1-yl) carbamate was obtained as dark brown oil with 94% chemical yield as dark brown oil .

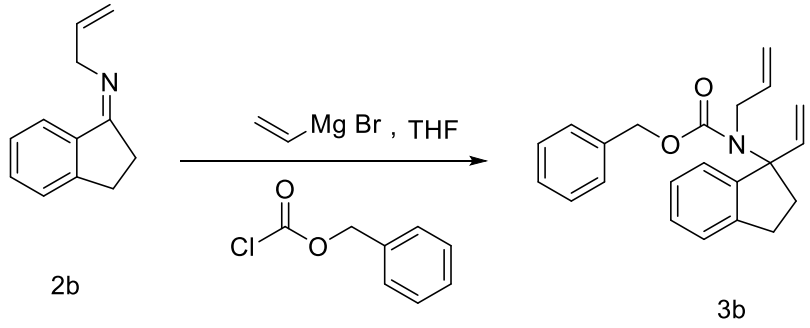


Figure 4.16. Synthesis of benzyl allyl(1-vinyl-2,3-dihydro-1H-inden-1-yl) carbamate.

Column chromatography was used to purify the product, and the system solvent was (EtOAc: Hexane: Et_3N) (1:1:1%).

^{1}H-NMR spectrum of benzyl allyl(1-vinyl-2,3-dihydro-1H-inden-1-yl) carbamate One of the internal vinylic protons exhibits a multiplet between 5.81-5.95 ppm, and the other one exhibits a multiplet between 5.68-5.78 ppm. Additionally, the singlet for the benzylic methylene protons is at 5.30 ppm. One of the terminal vinylic protons is responsible for the doublet of a doublet at 5.19 ppm with J = 7.6 and 16.9 Hz. The doublet of the doublet is present in the other two terminal vinylic protons at 5.14 ppm with J = 10.8 and 20.2 Hz. For the final terminal vinylic proton, the doublet of a doublet at 5.08 ppm with J = 10.0 and 34.0 Hz is appropriate.

The cyclopentane ring's methylene protons exhibit multiplet between 2.06-2.15 ppm in one case and 2.17-2.22 ppm in the other. Doublet of a doublet at 2.50 ppm with J = 7.2 and 16.2 Hz is for the other one of the methylene protons in the cyclopentane ring.

Multiplet between 2.79-2.92 ppm is for the other methylene proton of the cyclopentane ring.

Doublet of a doublet at 3.10 ppm with J = 6 Hz and 15.4 Hz is responsible for one of the allylic methylene protons directly attached to the Nitrogen atom. The other allylic methylene proton exhibit doublet of a doublet at 2.96 ppm with J = 6 Hz and 14 Hz. Doublet at 7.37 ppm with J = 4.2 Hz is responsible for one of the methine protons of the aromatic ring. The triplet at 7. 22 ppm with J = 8.0 Hz is for the other two methine protons of the aromatic ring.

Finally, the methine proton of the aromatic ring is represented by the multiplet between 7.25 and 7.27 ppm.

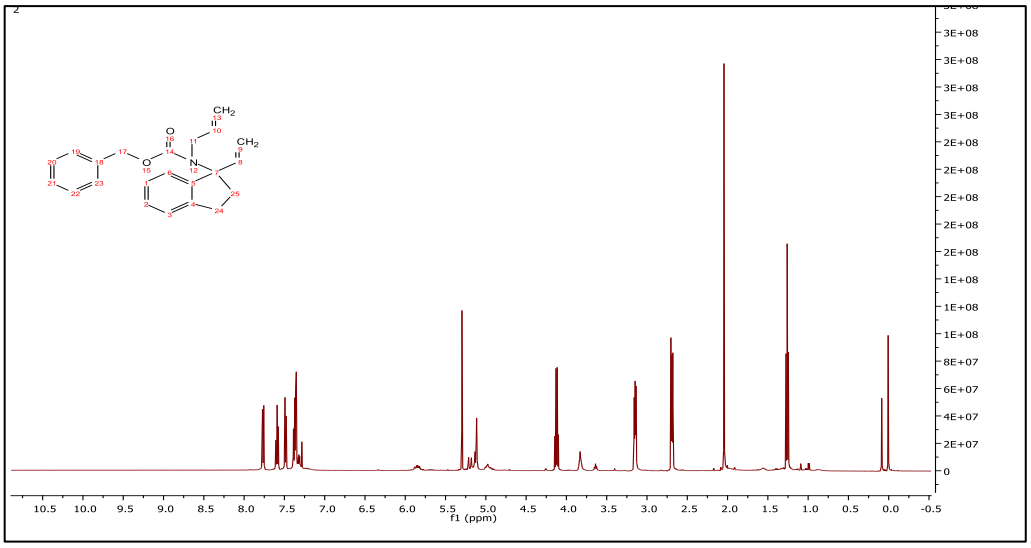


Figure 4.17. ^{1}H spectrum of benzyl allyl(1-vinyl-2,3-dihydro-1H-inden-1-yl) carbamate.

^{13}C-NMR spectrum of benzyl allyl(1-vinyl-2,3-dihydro-1H-inden-1-yl) carbamate the ester carbonyl carbon shows at 146.9 ppm. The signals at 115.5 and 118.4 ppm are for the one of the terminal vinylic carbons of the allylic side chain. Internal vinylic-carbons exhibit signals at 134.5 and 143.1 ppm respectively. The signals at 134.5, 126.7, 126.1 ,124.9, 123.6, and 122.8 ppm are responsible for one the aromatic ring carbons. The signals at 143.7 ppm with 137.3 ppm are for the quaternary carbons of the fused part. The signals at 128.1, 128.3, 128.5, and 133.8 ppm belong to the other aromatic ring carbons.

The quaternary carbon directly attached to the nitrogen show signal at 82.8 ppm with the methylene carbon at 67.8 ppm directly attached to the nitrogen atom.

Finally, the signals at 39.8 and 30.2 ppm are for the methylene carbons in the cyclopentane.

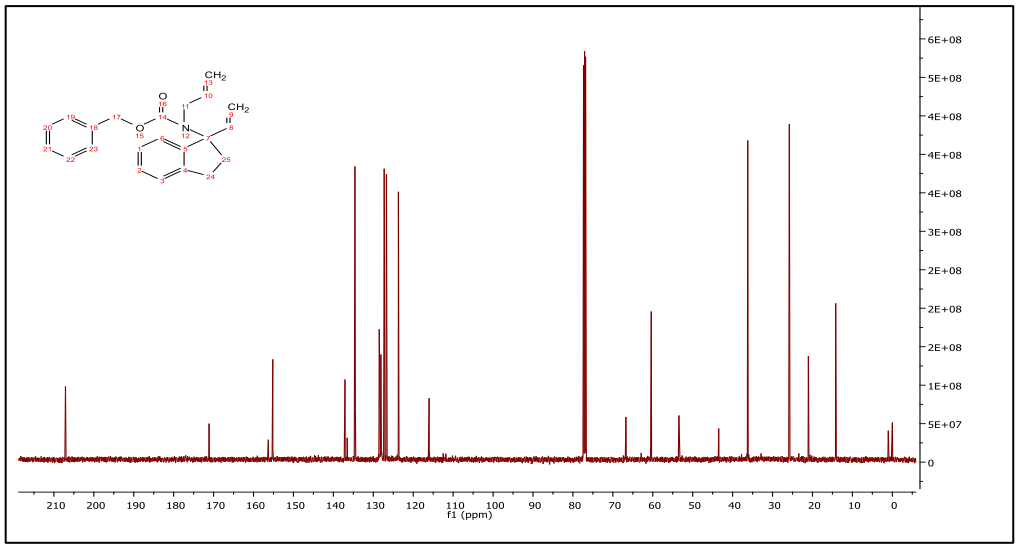


Figure 4.18. ^{13}C spectrum of benzyl allyl(1-vinyl-2,3-dihydro-1H-inden-1-yl) carbamate.

4.2.3 Synthesis of benzyl 2,3-dihydrospiro[indene-1,2'-pyrrole]-1'(5'H)-carboxylate.

Benzyl 2,3-dihydrospiro[indene-1,2'-pyrrole]-1'(5'H)-carboxylate was prepared from benzyl allyl(1-vinyl-2,3-dihydro-1H-inden-1-yl) carbamate by Grubbs 2nd generation in di chloromethane DCM shows in Figure (4.19), was obtained 79% chemical yield as dark brown.

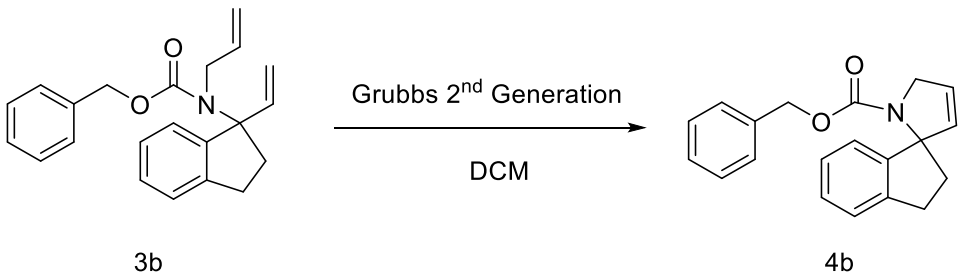


Figure 4.19. Synthesis of benzyl 2,3-dihydrospiro[indene-1,2'-pyrrole]-1'(5'H)-carboxylate.

Column chromatography was used to purify the product, and the system solvent was (EtOAc: Hexane: Et_3N) (1:1:1%).

The ^{1}H-NMR and ^{13}C-NMR spectra of the product are not clear enough for identification.

5. CONCLUSIONS AND RECOMMENDATIONS

In this study benzyl 3,3',4,6'-tetrahydro-1'H,2H-spiro[naphthalene-1,2'-pyridine]-1'-carboxylate and precursor of benzyl 2,3-dihydrospiro[indene-1,2'-pyrrole]-1'(5'H) carboxylate; benzyl allyl(1-vinyl-2,3-dihydro-1H-inden-1-yl) carbamate obtained 80% and 79% overall chemical yield respectively. Benzyl 3,3’,4,6’-tetrahydro-1’H,2H-spiro[naphthalene-1,2’-pyridine]-1’-carboxylate synthesized using Grubbs 2nd generation catalyst via (RCM), a technique that is regularly employed to create heterocyclic units in literature; as well as benzyl 2,3-dihydrospiro[indene-1,2'-pyrrole]-1'(5'H)-carboxylate constitute the skeleton of natural products having biological activities.

6. REFERENCES

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