T.R.
BOLU ABANT İZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES

SYNTHESIS OF CYCLOHEXENE SUBSTITUTED AZASPIRODIEN COMPOUNDS BY RCM AND CORRESPONDING TETRAHYDROSPIROCYCLOPENTA [C]PYROLIDINONE COMPOUNDS VIA PKR

DOKTOR OF PHİLOSOPHY

SHAFEEK BUHLAK

BOLU, OCAK - 2021

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DOKTORA TEZİ

SHAFEEK BUHLAK

ACADEMIC SUPERVISOR
PROF. DR. F. DEVRİM ÖZDEMİRHAN

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APPROVAL OF THE THESIS

SYNTHESIS OF CYCLOHEXENE SUBSTITUTED AZASPIRO-DIEN COMPOUNDS BY RCM AND CORRESPONDING TETRA HYDROSPIROCYCLOPENTA[C]PYROLIDINONE COMPOUNDS VIA PKR submitted by **Shafeek BUHLAK** and defended before the Examining Committe Members listed below in partial fulfillment of the requirements for the degree of **Doctor of Philosophy** in **Department of Chemistry, Institute of Graduate Studies of Bolu Abant Izzet Baysal University in 28.01.2021** by

Examining Committee Members	**Signature**
Supervisor Prof. Dr. Devrim ÖZDEMİRHAN Bolu Abant Izzet Baysal University	.....
Member Prof. Dr. Ayşe MORKAN Bolu Abant Izzet Baysal University	.....
Member Prof. Dr. Özdemir ÖZARSLAN Bolu Abant Izzet Baysal University	.....
Member Assoc. Prof. Dr. Bahadır ALTINTAŞ Bolu Abant Izzet Baysal University	.....
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In this thesis dissertation that was properly prepared according to the Thesis Writing Rules of Bolu Abant İzzet Baysal University of the Institute of Graduates Studies, I hereby declare that;

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SHAFEEK BUHLAK

ABSTRACT

SYNTHESIS OF CYCLOHEXENE SUBSTITUTED AZASPIRODIEN COMPOUNDS BY RCM AND CORRESPONDING TETRAHYDROSPIROCYCLOPENTA[C]PYROLIDINONE COMPOUNDS VIA PKR
PHD THESIS
SHAFEEK BUHLAK
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BOLU ABANT IZZET BAYSAL UNIVERSITY
DEPARTMENT OF CHEMISTRY
(SUPERVISOR: PROF. DR. F. DEVRİM ÖZDEMİRHAN)

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xv + 129

The coverage of this context is related to the synthesis of several novel spirocyclic scaffolds containing nitrogen atom due to their importance in organic medicinal and pharmaceutical chemistry. Cyclohexenone and its derivatives were selected as starting materials due to the presence of these compounds in highly functionalized and important chiral bioactive compounds. First, cyclohexenone was reacted with allylamine or propargyl amine to form N-allyl imine and N-propargyl imine derivatives. Followed by the Grignard addition reaction with/without the protection of nitrogen atom to attain the corresponding diene and enyne structures. Ring Closing Metathesis (RCM) was applied on diene structures to finally attain the corresponding azaspiroundecadiene and azaspirodecadiene carboxylate with 81% and 78% respectively. On the other hand, Pauson-Khand reaction (PKR) was applied on enyne structures in the presence of cobalt carbonyl $Co_2(CO)_8$ and N-methyl morpholine N-oxide (NMO) to obtain cyclopenta[c]pyridinenone, cyclopenta[c]pyridinene carboxylate and cyclopenta[c]pyrroline carboxylate skeletons with 67%, 75% and 65% chemical yields respectively. Finally, all compounds obtained in this context are novel from Imine to spirocyclic compounds and all reactions were carried out under nitrogen atmosphere (N_2).

KEYWORDS: RCM, Ring Closing Metathesis, PKR, Pauson-Khand reaction, Heterocyclic compounds, Chiral, Grubbs Catalyst

ÖZET

SİKLOHEKSEN İÇEREN AZASPİRODİEN BİLEŞİKLERİNİN HKM YÖNTEMİ İLE VE İLGİLİ TETRAHİDROSPİROSİKLOPENTA[C]PİROLİDİNON BİLEŞİKLERİNİN PKR İLE SENTEZİ
DOKTORA TEZİ
SHAFEEK BUHLAK
BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ
LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ
KİMYA ANABİLİM DALI

(TEZ DANIŞMANI: PROF. DR. DEVRİM ÖZDEMİRHAN)

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Bu bağlamın kapsamı, organik tıbbi ve farmasötik kimyadaki önemi nedeniyle nitrojen atomu içeren birkaç yeni spirosiklik iskelet yapılı bileşiklerin senteziyle ilgilidir. Sikloheksenon ve onun türevleri yüksek miktarda fonksiyonlaştırılmış ayrıca kiral bioaktif önemi nedeniyle başlangıç maddeleri olarak seçilmiştir. İlk olarak sikloheksenon N-allylimin ve N-propargylimin oluşturmak için allylamin veya propargylamin ile reaksiyona sokulur. Daha sonra karşılık gelen dien ve enyne yapıları elde etmek için azot atomu koruma veya korumasız Grinard reaksiyonu yapılır. Sonunda karşılık gelen azaspiroundekadien ve azaspirodekdien karboksilat 81%, 78% sırasıyla elde etmek için halka kapanışı metatezi (HKM) dien yapılarına uygulandı. Diğer taraftan enin yapılarına kobalt karbonil $Co_2(CO)_8$ ve N-metil morfolin N-oksit (NMO) varlığında siklopenta[c]peridienon, siklopenta[c]piridienin karboksilat, ve siklopenta[c]pyrolin karboksilat iskeletleri sırasıyla 67%, 75% ve 65% verimlerle elde etmek için Pauson-Khand reaksiyonu (PKR) uygulandı. Son olarak bu bağlamdaki elde edilen tüm bileşikler iminden spirosiklik bileşiklere kadar yenidir ve tüm reaksiyonlar nitrojen atmosferi (N_2) altında gerçekleştirilmiştir.

ANAHTAR KELİMELER: Halka Kapama Metatezi, Heterosiklik Bilesikler, Pauson-Khand reaksiyonu, Grubbs Katalizörü

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LIST OF ABBREVIATIONS AND SYMBOLS

NMO	: 4-methyl-morpholine N-oxide
NH_4Cl	: Ammonium Chloride
Atm	: Atmosphere
b.p.	: Boiling Point
bs	: Broad Singlet
Cbz	: Carboxybenzyl
δ	: Chemical shift in ppm (in NMR)
J	: Coupling Constants (in NMR)
DNA	: Deoxyribonucleic Acid
$CDCl_3$	: Deuterated Chloroform
CH_2Cl_2	: Dichloromethane
DCM	: Dichloromethane
$Co_2(CO)_6$	: Dicobalt Hexacarbonyl
$Co_2(CO)_8$	: Dicobalt Octacarbonyl
DME	: Dimethyl Ethane
dd	: Doublet of Doublet (in NMR)
ddd	: Doublet of Doublet of Doublet (in NMR)
d	: Doublet (in NMR)
ee	: Enantiomeric excess
EtOAc	: Ethyl Acetate
Hz	: Hertz
HRMS	: High Resolution Mass Spectrometry
HTX	: Histrionicotoxin
IR	: Infra-Red
IUPAC	: International Union of Pure and Applied Chemistry
mL	: Milliliter
mmol	: Millimole
MO	: Molecular Orbital
m	: Multiplet (in NMR)
NPS	: N- (phenylseleno)phthalimide
DMF	: N,N-Dimethylformamide

^{13}C-NMR : Nuclear Magnetic Resonance of Carbon ^{13}

^{1}H-NMR : Nuclear Magnetic Resonance of Proton

ppm : Parts Per Million

PKR : Pauson-Khand Reaction

Ph : Phenyl Group

q : Quartet (in NMR)

qd : Quartet of Doublet (in NMR)

Rf : Retardation Factor

RNA : Ribonucleic Acid

RCM : Ring Closing Metathesis

SiO_2 : Silicon dioxide

s : Singlet (in NMR)

$NaBH_4$: Sodium Tetrahydroborate

THF : Tetrahydrofouran

Ts : Tosyl

Et_3N : Triethylamine

TMANO : Trimethylamine-N-oxide

t : Triplet (in NMR)

tdd : Triplet of Doublet of Doublet (in NMR)

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1. INTRODUCTION

1.1 Heterocyclic Compounds

All organic compounds with ring structure should be, either aromatic or non-aromatic, and containing carbons with one element or more other than carbon as (Oxygen 'O', Nitrogen 'N', Boron 'B', Phosphorus 'P', or Sulfur 'S') are called heterocyclic compound (1).

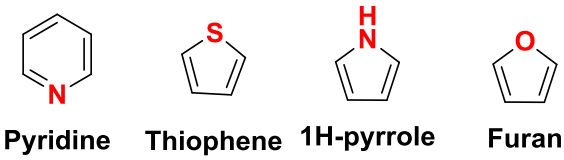


Figure 1.1. Examples of heterocyclic compounds.

1.1.1 Saturated Heterocyclic Compounds

When we add a saturated atom (sp^3 atom) to the ring, this ring will be more flexible, more possibility of stereoisomerisms (sp^3 hybridization) and have special chemical properties, such as; it make ring easy to create by ring closing (RC) reaction, or easy to break by ring opening reaction. In addition, the heteroatom adjust the orientation of the ring (2). Most of these compounds react as similar as open-chain compound or non-heterocyclic compounds, however the strain energy (that comes from the cyclic formula) induce the reactivity of these compounds. Due to that, some of them used as solvents like tetrahydrofouran (THF) and dioxane. In addition, saturated and partially saturated heterocyclic compounds reside abundantly in natural products.

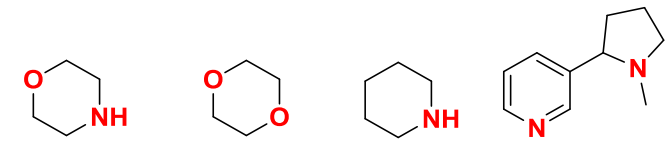


Figure 1.2. Examples of saturated heterocyclic compounds.

1.1.2 Aromatic Heterocyclic Compounds

Hückel rule is the general rule described the aromaticity state that to say the cyclic compound is aromatic, it must follow cyclic conjugation systems with (4n+2) electrons, that means (2, 6, 10, 14 …) π – electrons. The experts in organic chemistry know that more than 50% of all organic compounds include heterocyclic aromatic compounds, and there are many compounds for human beings that made from this kind of compounds (3).

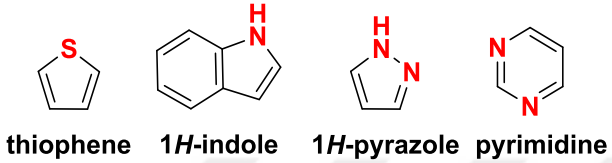


Figure 1.3. Example of aromatic heterocyclic.

1.1.3 Heterocycles in Our Life

Huge amounts of heterocyclic compounds are occurring in nature, and many of these compounds are artificial. Some of them having an important application in agriculture, medicine, industrial chemicals and in other day-technological fields.

Although the heterocyclic compounds have various application in our life, we must mention the hazards and toxicity of certain kind of heterocycles. Such as, Tetrachlorodioxin, consider as the responsible of inflammatory in immune system (4). However, the chemist must be aware of many substances that seem not toxic, but it observe toxic effects. For example CR gas, (it is not a gas and use as riot control agent) lachrymator substance, and skin irritant; the first known of these effects by the first chemist who made it (5).

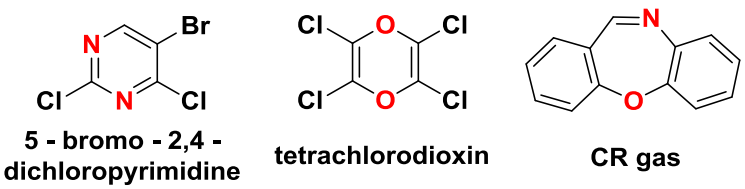


Figure 1.4. Example of toxic heterocyclic compounds

1.1.4 Medicinal Applications of Heterocyclic Compounds

Heterocyclic compounds have attractive properties to use in drugs and medicine. For example, Ifosfamide (Phosphorus-Heteroatom) used to slow down cancer cells growth as alkylating utilities (6). Other example, Piroxicam used as anti-inflammatory to cut the arthritis pain symptoms (7). In addition, Ebselen (selenium-Heteroatom) used as hydro-peroxide scavenger (8). Furthermore, Diazaborine, showed anti-bacterial utilities and Silavenlafaxine, serotonin analog, as nerve system cure and antidepressant (9). Oxalatrunculin B anticancer activity and antifungal utilities (10). Finally, nitrogen-heteroatom compound such as Fluconazole has antifungal and properties (11).

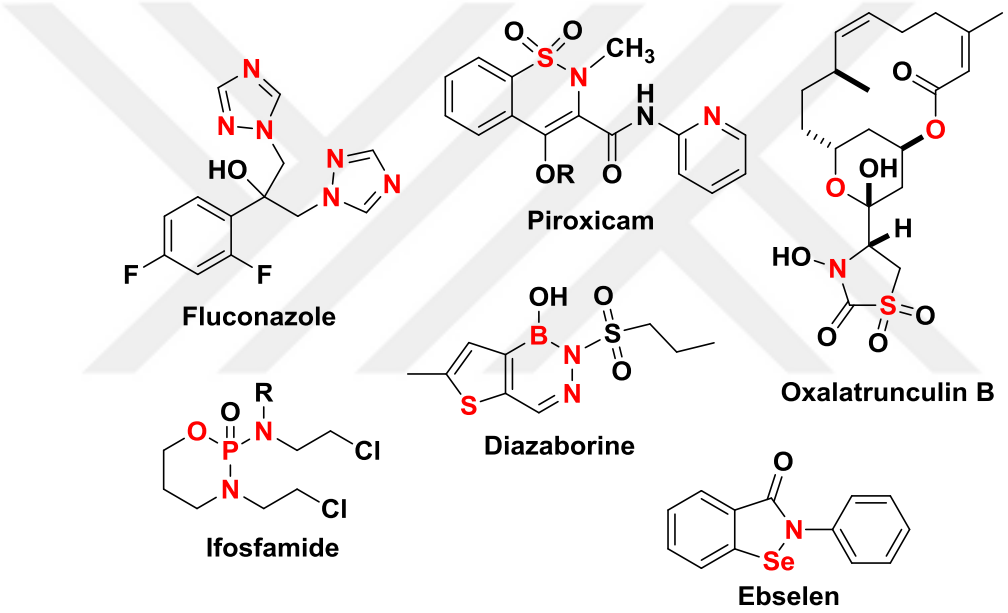


Figure 1.5. Medicine heterocyclic

1.2 Bicyclic Compounds

Bicyclic compounds, consist of two (Bi), rings (Cyclic) connecting to each other by one of the following three choices: either fused bicyclic compounds (connected with two consecutive atoms), or bridged bicyclic compounds (connected with two non-consecutive atoms), or spiro bicyclic compound (connected with one atom) (12).

1.2.1 Fused Bicyclic Compounds

Two rings have one or more common bond. One of the important fused ring is purine; this compound is part of the RNA and DNA, in addition, caffeine is one of the purine derivative. Moreover, pyrazine a roast meat or cracker-popcorn aroma (13) is another example of fused compound. Indole is the most important compound for lives. Formed from pyrrole that fused with benzene. This biological important compound form one of the essential amino acid called Tryptophan that is important for making protein and survive the living cells (14).

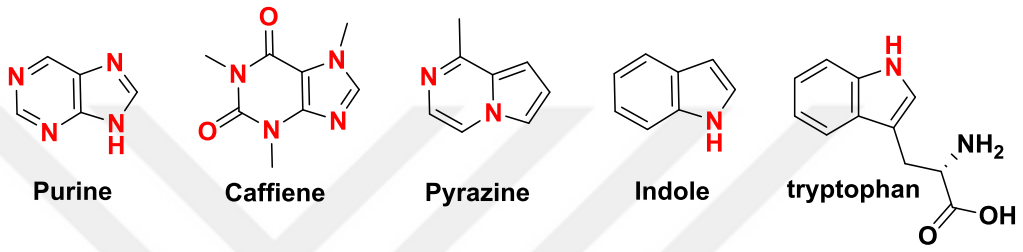


Figure 1.6. Examples of some fused compounds

1.2.2 Bridged Bicyclic Compounds

These compounds can occur when one or more atoms tether across from one side of the ring to the other side. This structure is very rough and the reaction always occur on the direction of one-atom-bridge instead of two atoms. In addition, there is no π bonds at the bridgehead of these compounds, because it cannot be formed at this place, unless the rings (or one of it) is larger than eight carbons. This rule is known as Bredt's rule (15).

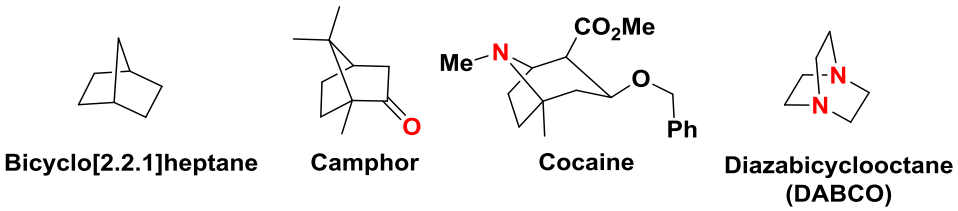


Figure 1.7. Example of bridge bicyclic compounds

1.2.3 Spirocyclic Compounds

Von Baeyer is the first chemist describes the spirane skeleton in 1900. Spirane have two rings connected to each other by one mutual atom (16). These compounds have attractive structure due to the common carbon atom (spiro-atom) has a tetrahedral nature and make its ring-planes perpendicular to each other (17). Because of this unique asymmetric chiral structure, and the presence of spiro structure in natural products due to its biological activity (18), these compounds will be target of our project.

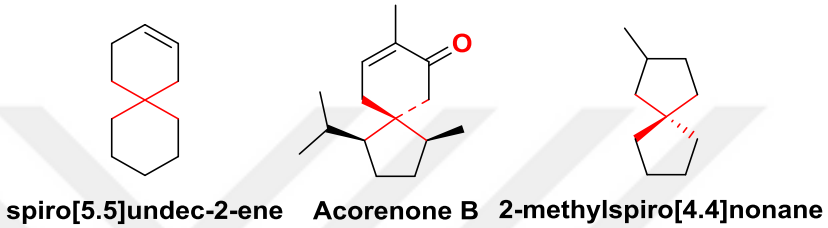


Figure 1.8. Example of spiro cyclic compounds

1.3 Introduction on Spirocyclic Concept

Spirocyclic rings meet at one single atom. This means that two rings are orthogonal on the tetrahedral atom that is common to both of these two rings (2).

These unique compounds has attracted the chemist as scaffolds (priviliged structure) in drugs and natural product chemistry, because of thier rigid and cyclic (usually bi or poly) structure in addition to thier capability to bind wide range of pharmacophore and/or lipophilic structures (19). Moreover, researcher approved that spirocyclic scaffolds can be used in thermotropic liquid crystals as in LCD (20).

1.3.1 Nomenclature of Spiro-cyclic compounds

When there are two ring systems with one common atom (this atom called spiro atom), these two rings are named by the prefix ***spiro***, and in square bracket write the number of atoms in each ring except the spiro atom (in ascending order) separated by a full stop, followed by the name of the parent-hydrocarbon by the total number of skeletal atoms (including the heteroatom$_s$) (16). Heteroatom$_s$ indicated by their prefixes. **Aza** for ***N***, **Oxa** for ***O***, **Thia** for ***S***, **Phospha** for ***P*** and

Sila for ***Si***...etc. If there are two of same heteroatom, suffix the prefix of heteroatom by 'di'. Finally, the heteroatom number must have the smallest number. For example if there is (N, O, S) in the compound, the writing of hetero atoms must be (#-Oxa-#Thia-#-Aza) (21).

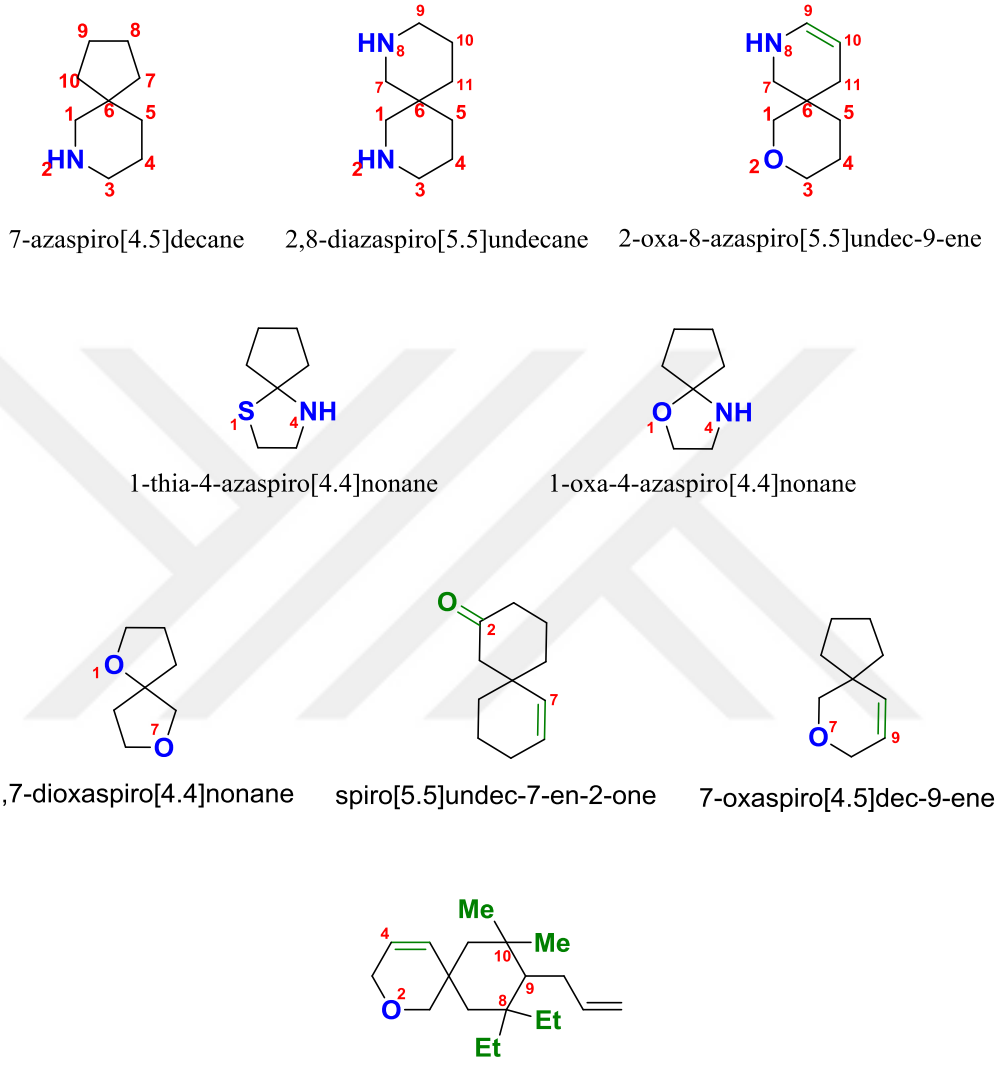


Figure 1.9. Example of spirocyclic compounds

1.3.2 Spirocyclic in Natural Products and Pharmaceuticals

Natural products are organic compounds that made by living-organisms by primary or secondary metabolisms. Some of these products (mostly come from plants) have pharmaceutical activity to treat wide range of diseases or infections (22). The biological activities of numerous plants have been studied along with the

expansion of organic chemistry, and large percent of medicine drugs have the origins from natural products (23).

Matteo Aldeghi and his colleagues studied the characters of drugs by the molecules aspect; they found that 95% of drugs include cyclic compounds. In addition, the drugs of three-dimensional structure (molecule that have sp^3 and saturated carbon atoms) make up to three quarters of drugs that have aromatic flat or planner scaffolds. Beside spiro-rings, bicyclic rings are the most frequent motifs of 3-D structure of drugs (24).

Spiro-rings containing compounds are prevailing in natural products isolated from frogs, insect, plants, or marine organisms.

Histrionic toxin (HTX) is family of eleven compounds differ by the side chain and one of the most toxic poison was extracted from skin of small shining colored frogs "Dendrobates" found at 1971 in Columbia (25). In addition, alkaloids (HTX) also isolated from the ant in Panama called "Carebarella bicolor" (26). These compounds are very effective antagonist for nicotinic receptor; they can block the response to acetylcholine. Due to that, it reduces both the conductivity of channels and the time needed to open these channels (27).

Alkaloids: are compounds synthesized naturally by plants or animals, containing nitrogen in its skeletons as heteroatom and having biological activities. (28).

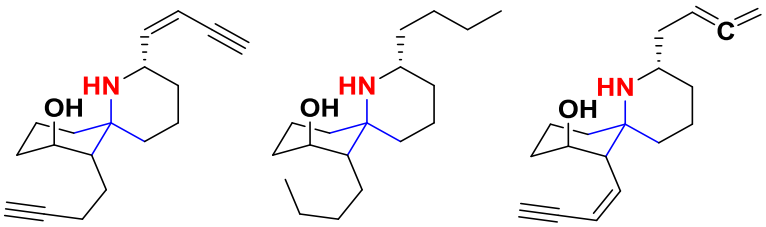


Figure 1.10. Three examples of histrionicotoxin moiety

Another example of spirocyclic natural-containing products is Griseusins A, isolated from Streptomyces Griseus, which collected from soil samples in 1976 in Peru. This compound shows active against (positive-gram) bacteria (29), and anti-

cancer feature. In 2013 Naysmith B.R. synthesized it with high enantiomeric excess (ee) synthetic route (30).

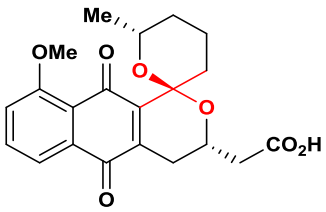


Figure 1.11. Griseusine, spiroketal product

Halichlorine isolated from Halichondria okadai Kadota (marine sponge) in 1998. It demonstrate inhibitory activity of the VCAM-1 (vascular cell adhesion molecule-1), that used for treatment of coronary heart disease and inflammation (31). Pinnaic acid, another marine product was isolated at 1996 from Pinna muricata, which resembles the skeleton of Halichlorine and has the medical properties to treat the inflammatory disease (32).

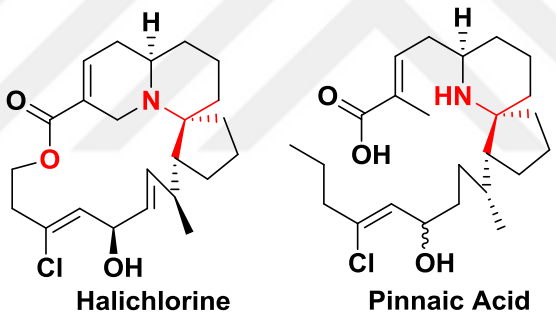


Figure 1.12 Halichlorine and Pinnaic acid as Natural Spirocyclic Products

Spirocurcasone is natural product found in Jatropha curcas roots in small amount in 2011. After that in 2014 Qin and his research group synthesize this product in high yield from other natural product (Curcasones A) found and isolated from the same Jatropha curcas roots in a one-pot method. This compound exhibits high cytotoxicity. Thus, can be used as anti-cancer drug that decrease the tumor cell growth in vitro (33) (34).

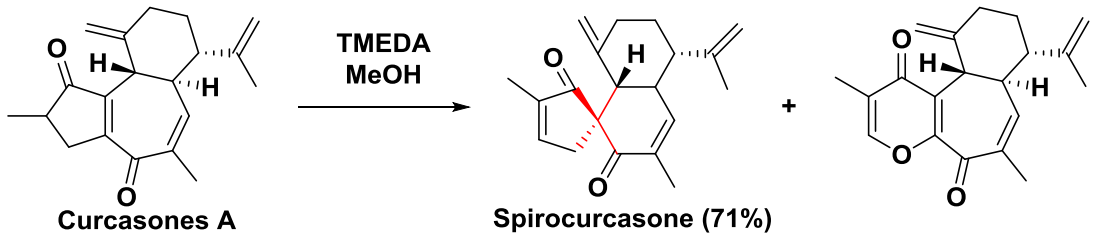


Figure 1.13. Synthesis of spirocurcasone

By looking to the diversity of spirocyclic skeletons that reported in the scientific literature, one can find how these scaffolds are omnipresent in natural products. Therefore, the last ten years show the rise of isolating from natural products and synthesize more new significant spirocyclic scaffolds for library development and pharmaceutical drugs marketing. The following compounds are a few examples of these drugs. Spirooxindoles like Horsfiline isolated from a tree live in Malaysia called 'Horsfieldia superba',used in local therapeutic (35). In addition, spirofornabuxine that isolated from buxussempervirens plant (adi şimşir) exhibit activity against fungal and leishmanial disease (36). Oliceridine analgesic medicine approved in 2020 in USA that treating pain as an intravenous injection (37). Other example is azaspirocyclic compound that used as stabilizer for the metabolism and (38). Finally, spiroazatidine derivatives that can be used as antidiabetic drugs (39).

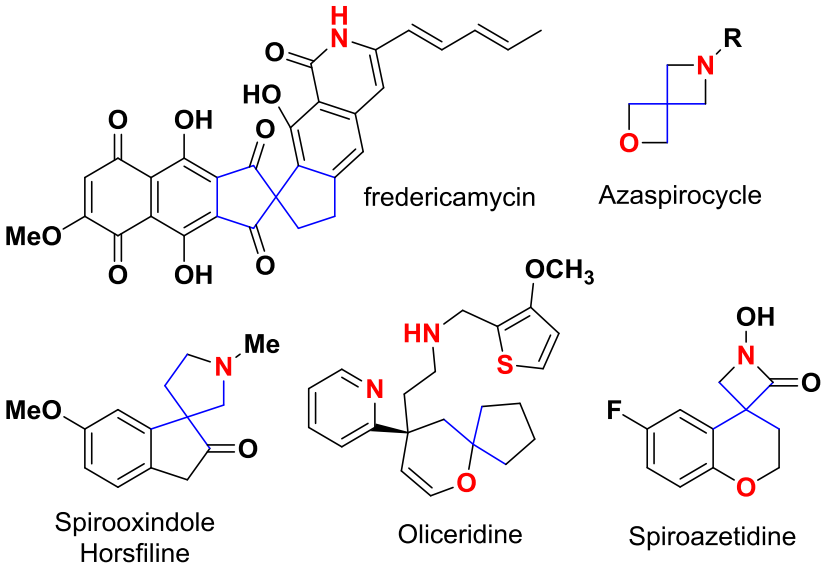


Figure 1.14. Some spirocyclic natural products

1.4 Methods for Synthesis Spirocyclic Structure

There are many methods used to create spirocyclic center involve: alkylation process, rearrangement approaches, radical cyclization process (40), photochemical reactions, transition metal based reactions, metathesis methods, ring expansion tactics, and Pauson-Khand reaction approaches (41).

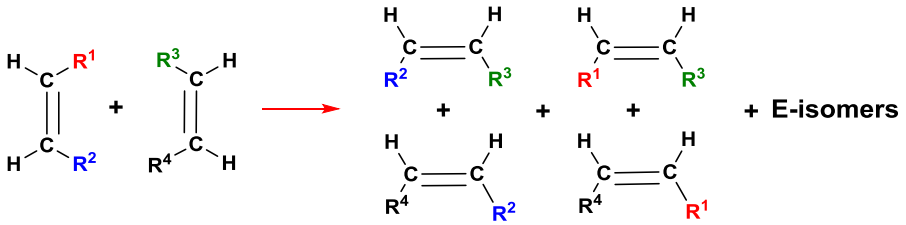
In this study, our interest will be on the most important methods, ring closing metathesis (42) and Pauson-Khand reaction (43).

1.4.1 Olefin Metathesis

Meta (change) and Thesis (position), two Greek words were made up to make the term "Metathesis" to express the reaction between two substituent groups (perhaps H or alkyl groups) that attached to carbon-carbon double bonds (C=C) of alkenes either similar or dissimilar to each other. This reaction can also be expressed as olefin metathesis or π-bond metathesis (44).

There are many types of metathesis like **R**ing **C**losing **M**etathesis (**RCM**), the opposite of this reaction called "**R**ing **O**pening **M**etathesis" (**ROM**), as shown in (Equation 1.1), "**C**ross **M**etathesis" (**CM**) (Equation 1.2), **R**ing-**C**losing **E**nyne **M**etathesis (**RCEM**) which is the same as RCM except the reaction will be between double bonds and triple bonds (45).

Equation 1.1. Ring closing and ring opening metathesis



Equation 1.2. Cross metathesis

Olefin metathesis is a useful reaction on the commercial side. It utilized in agricultural chemistry, polymer industries, drugs, and produced new materials with special and beneficial properties.

Our concern study will be on ring closing metathesis (RCM). This kind of metathesis is important to make different size of rings.

This metathesis is useful approach to make five and six membered cyclic-rings (46). However, it is more difficult to create ten or more membered macro-cycles-rings. It needs high temperature, low stable vacuum and (most important condition) high-dilution reaction medium (47)(48).

The first reported ring closing metathesis (RCM) was in 1980 by Villemin, through reacting metal catalyst (Tungsten complex) with a diene (49).

After that in 1990, molybdenum complex [Mo]-I metathesis was discovered by Schrock to use it by Grubbs research group in the earliest catalyzed RCM to make cyclic ether from diene in 1992. Three years later Grubbs and his colleague synthesized more active and stable (to moisture and air) catalyst called it "Grubbs first Generation (G-I)" and after that further active catalyst "Grubbs second generation (G-II)" (50). These catalysts (Figure 1.15) and the reactions that made by Grubbs R.H, Schrock R.R., and ChauvinY. allow metathesis reactions to be more efficient, easy, and take place in mild conditions. Therefore, "the olefin metathesis became the most important reaction in Organic Chemistry". Due to that, these three names deserve, in 1995, Nobel prize in chemistry (51).

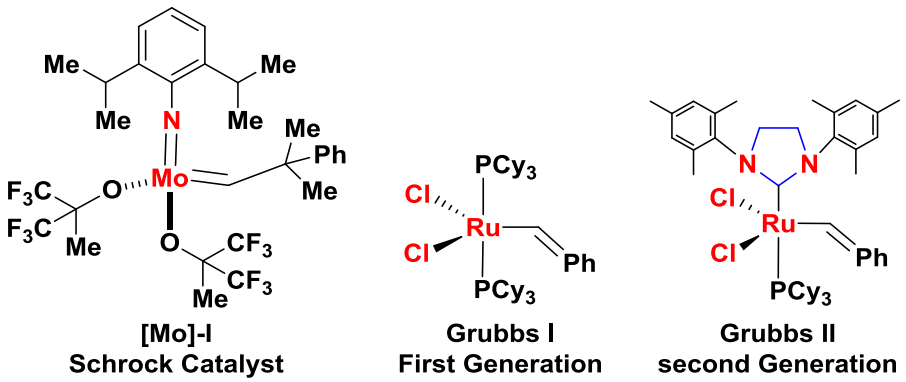


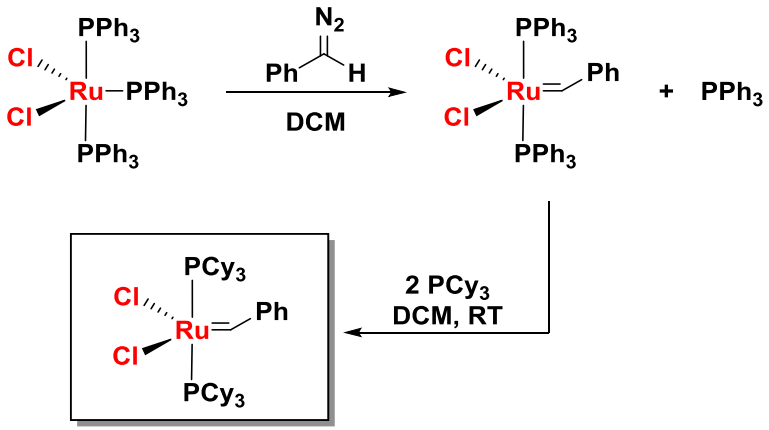
Figure 1.15. Schrock and grubbs catalysts.

1.4.1.1 Grubbs 1st Generation

Ruthenium-trichloride is the catalyst that used by Natta for Ring-Opening Polymerization of cyclobutene (52). This catalyst was attracted Grubbs and his colleagues and started to develop Carbene-Metal catalysts that used in organic synthesis application. In 1992, their research gained the first "ruthenium-carbene complex" that can be used with good stability in protic solvents. This vinylidene-Ru complex has the formula of $[RuCl_2(PR_3)(=CH\text{-}CH=CPh_2)]$ and (R) here is phenyl group. This Ruthenium-complex-catalyst known in IUPAC as'(3,3-diphenylallylidene)-bis(triphenylphosphine)dichlororuthenium'(53). After that, the phenyl group changed with 'cyclohexyl group' this exchange increased the activity of the complex and allowed it to use in unstrained-olefin polymerization reaction (54).

Equation 1.3. Vinylidene-Ru complex

After that, Grubbs and his co-workers developed the benzylidene-ruthenium complexes that reported in 1995 with the formula of '$[Ru\ Cl_2\ (PR_3)_2(=CHPh)]$' (R) here is phenyl or cyclohexyl group. The complex with cyclohexyl group known commercially as Grubbs First Generation (Grubbs 1st Generation). With IUPAC name of 'benzylidene- bis(tricyclohexyl-phosphine)dichlororuthenium' (55). This catalyst has good air-stability in addition of the compatibility and good reactivity purposes with wide range of moieties of organic compounds.



Equation 1.4. Synthesis of grubbs 1st generation.

1.4.1.2 Grubbs 2nd Generation

Low loading catalyst, high reactivity to create reactive intermediate-complex and making high yield products, all these properties, lead Grubbs research group to develop their 1st. Grubbs catalyst by changing one of phosphine group with bis-amino carbene cyclic group. This creates more reactivity and higher yield of products. The catalyst was synthesized by reacting Grubbs 1st generation with 2-Alkoxy-4,5-dihydroimidazoles in presence of potassium tert-butoxide. This catalyst has the formula '[$RuCl_2\{C(N(mesityl)CH_2)_2\}(PCy_3)(=CHPh)$]' ($C_{43}H_{72}Cl_2P_2Ru$). Named as Grubbs second generation (G-II) or (Grubbs 2nd generation) and the IUPAC name is '(Z)-benzylidene(1,3-dimesitylimidazolidin-2-yl)(tricyclohexyl-phosphaneyl)ruth-enium(II)chloride' and has Purple color with molar mass of (822.97 g/mol) (56). This catalyst have higher stability to air, moisture and temperature. Moreover, it does not need any special procedure or equipment (57). After this succeed many researcher group had developed catalysts based on these two catalysts. However, Grubbs 1st and 2nd generations still, until now, the most useful and efficient catalysts for the mostly of metathesis reactions.

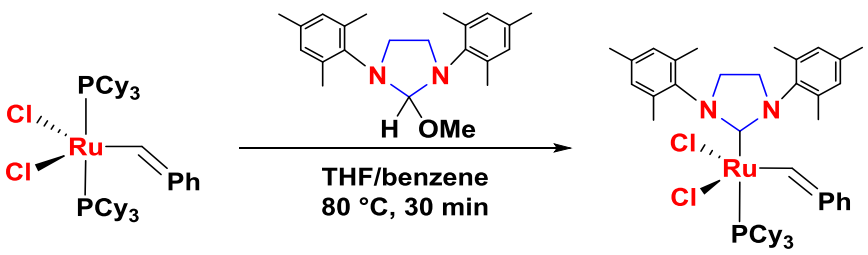
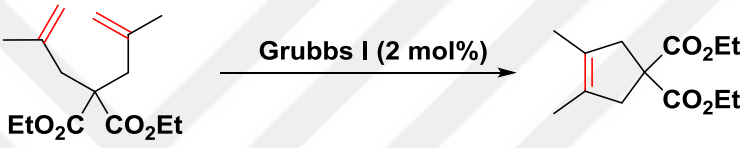


Figure 1.16. Synthesis of grubbs 2nd catalyst

1.4.1.3 Effect of Solvents on Grubbs Catalysts

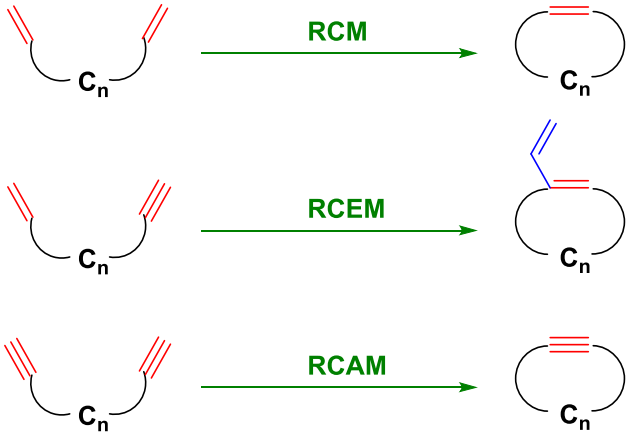
Solvent effect on Grubbs catalysts studied by many researcher due to wide applications of this kind of important reaction. In general, solvent have small effect of the initiation rate of Grubbs catalysts. The most effective solvent for this reaction with high enantioselectivity is fluoroaromatic solvents. However, the disadvantage of this solvent is the high toxicity and the low-solubility of wide range of polar compound in it (58) (59). Dichloromethane (CH_2Cl_2) or 1,2-dichloroethane (Cl-CH_2-CH_2-Cl) are the most favorable, polar and aprotic solvents that initiate the Grubbs catalyst in high yield with mediate-reflux temperature (60). However, toluene preferred when the reaction needs high temperature conditions (61).



Solvent	C_2H_4Cl	$C_6H_5CH_3$	C_6F_6	$C_6F_5CF_3$
Yield %	38	56	74	85

Figure 1.17. Effect of solvents on grubbs catalysts

As we mentioned above, our concern will be on RCM that has three types of metathesis: (1) Ring-Closing-Diene (RCM). (2) Ring-Closing-Enyne (RCEM). (3) Ring-Closing-Alkyne (RCAM).



Equation 1.5. Different types of RCM.

1.4.1.4 Ring-Closing-Diene-Metathesis (RCM)

We can understand this reaction by explaining the mechanism of it. First the Carbene (from the catalyst) bind with one (C=C) double bonds of the diene to make **[2+2] Cycloaddition** of metallacyclobutane ring. After that, a cleavage of the last ring would form a "new carbene complex". Now this complex has the same reactivity of the catalyst, so it reacts with the other (C=C) double bonds of the diene to make ring fused with other metallacyclobutane ring. And the same as before, the cleavage will happen to make the desired ring with new carbene complex that attacks another molecule and the same reaction pathway with one different that the losing of (ethene) as gas (2).

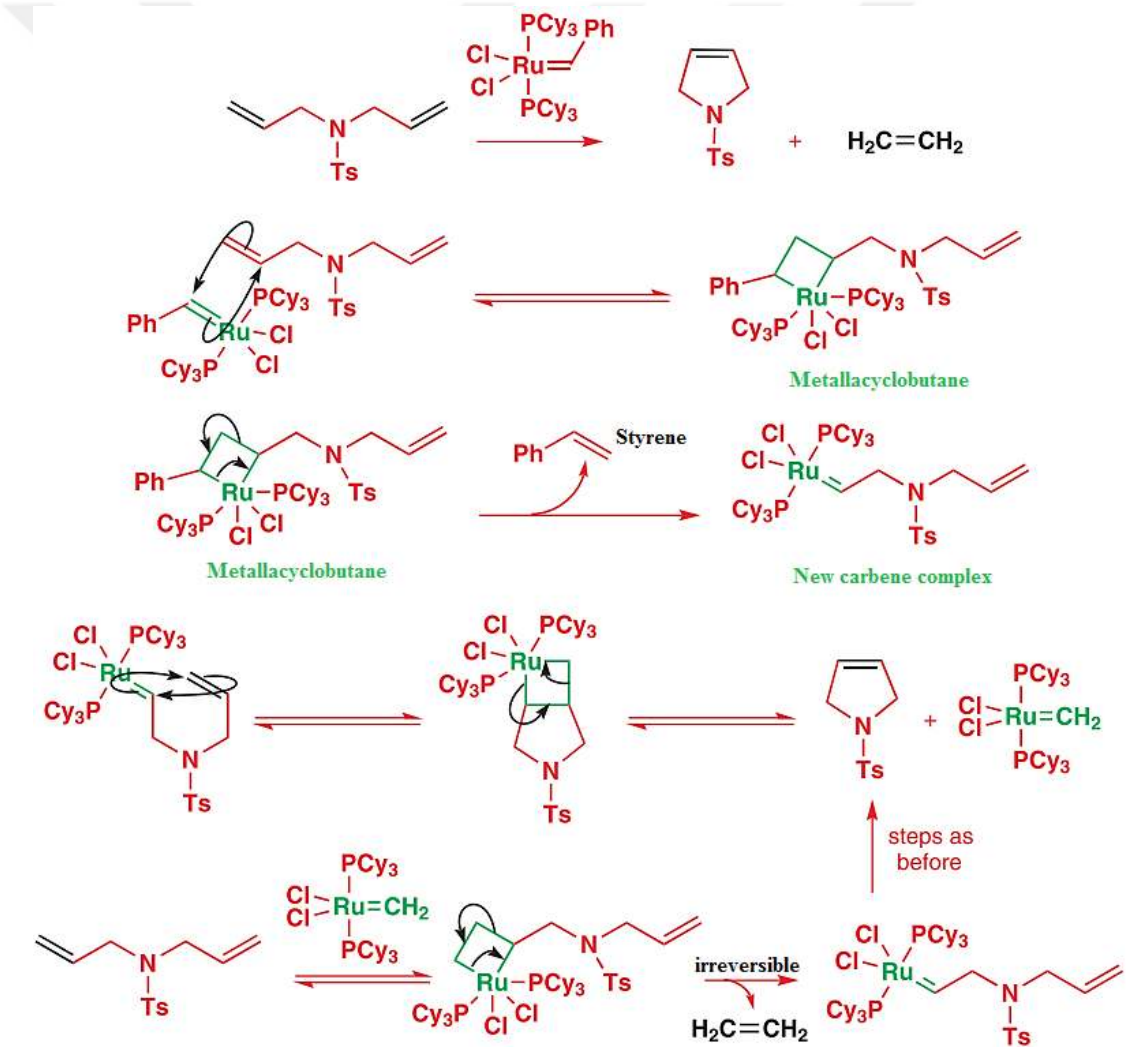
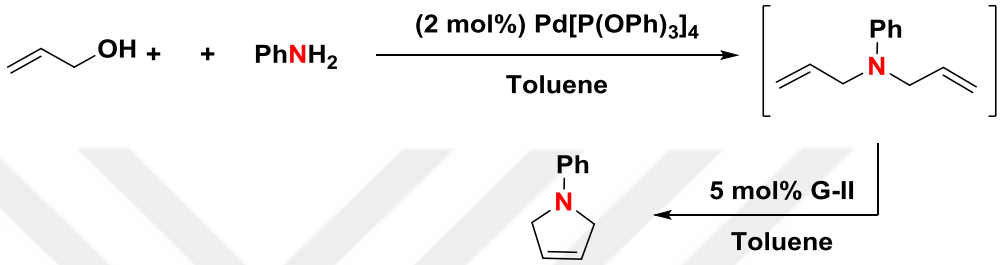


Figure 1.18. Mechanism of ring closing metathesis reaction

We can confirm from the previous mechanism that the entropy is making the RCM reactions. Due to, one molecule forms two molecules one of them is gas (Ethylene), thus the equilibrium goes to head toward the cyclization (62).

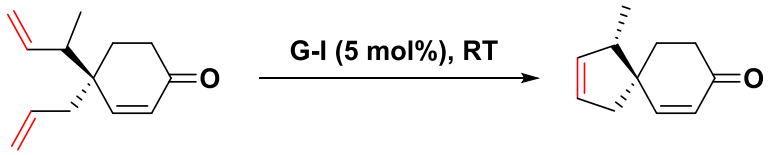
In 2011 Sawadjoon and Samec synthesized pyrroline derivatives in one-pot procedure from allyl-alcohol and amine by using palladium complex as catalyst to form diallylamine which is transformed to corresponding pyrroline by RCM with Grubbs second generation catalyst. (63).



Equation 1.6. Synthesis of pyrroline

1.4.1.4.1 Ring-Closing-Metathesis in Spiro Cyclic Compound

Spirocyclohexenone and cyclopentene derivatives synthesized in 1998 by Meyers and his colleagues. They used Grubbs first generation with diallyl compound in mild condition (at RT. in 3 h.) (64).



Equation 1.7. RCM of spirocyclohexenone

Nitrogen-containing spiro-cycles, according to the lots of articles, unsaturated amines are unreactive to the metathesis in general. The reason of this fact is in the electron pair of the nitrogen-atom makes coordination with metal complex of the catalyst. To prevent that, we need to protect amino group by turned it to hindered tertiary amines or crowded secondary-amines (65). This protection group would be either electron-withdrawing, aryl, or any sterically hindered group (66). In addition, if there is N-H the *trans*-conformation is more preferable than *cis*-conformation to minimize the repulsion between groups that we need in RCM

reaction. However, if there is a bulky group, the *cis*- conformation would preferable on *trans*-conf. to prevent steric hindrance with bulky group (67) (Figure 1.19). As we can see in the following literature studies.

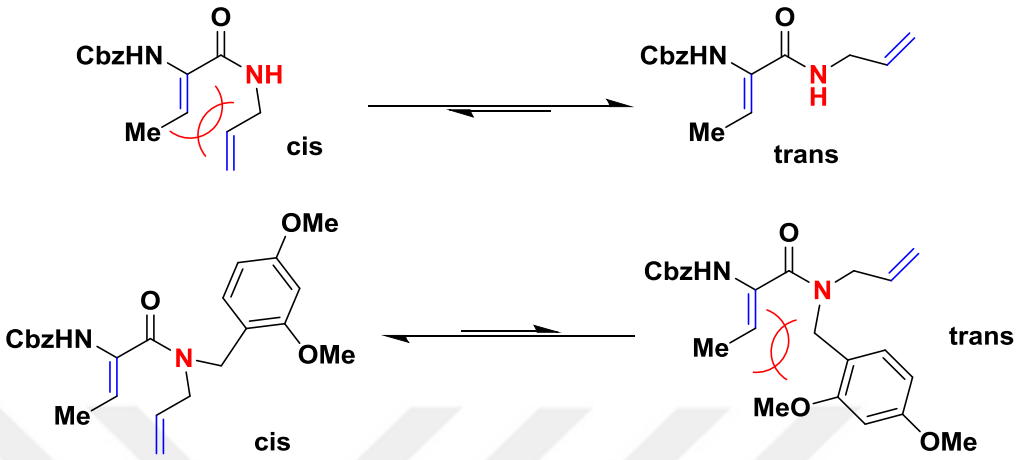


Figure 1.19. Effect of conformation of substitutes

David Tanner and his group, in 1999, face many problems to synthesize neurotoxic spirocyclic alkaloids Depentylperhydrohistrionicotoxin (12H-HTX) from 2,3-epoxycyclohexan-1-one in nine steps to form final product. These steps involve making amine group by (NPS), converting amine group to tosylamide, allylation, and finally cyclization by Grubbs-I generation which face another problem by loading large amount of catalyst and high temperature reaction (68).

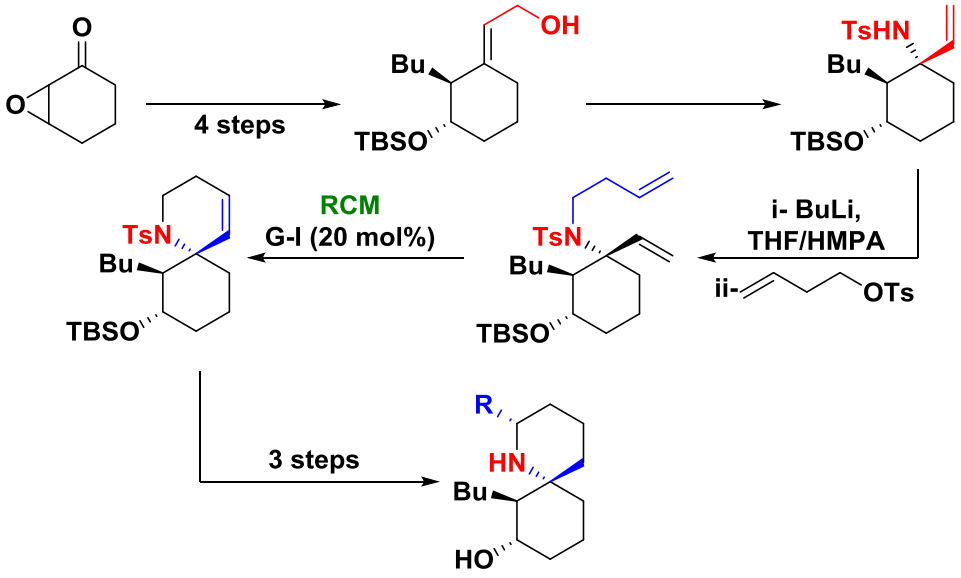
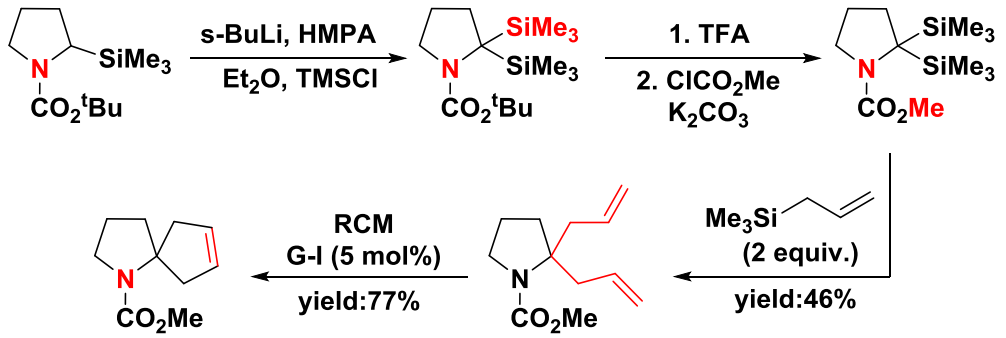


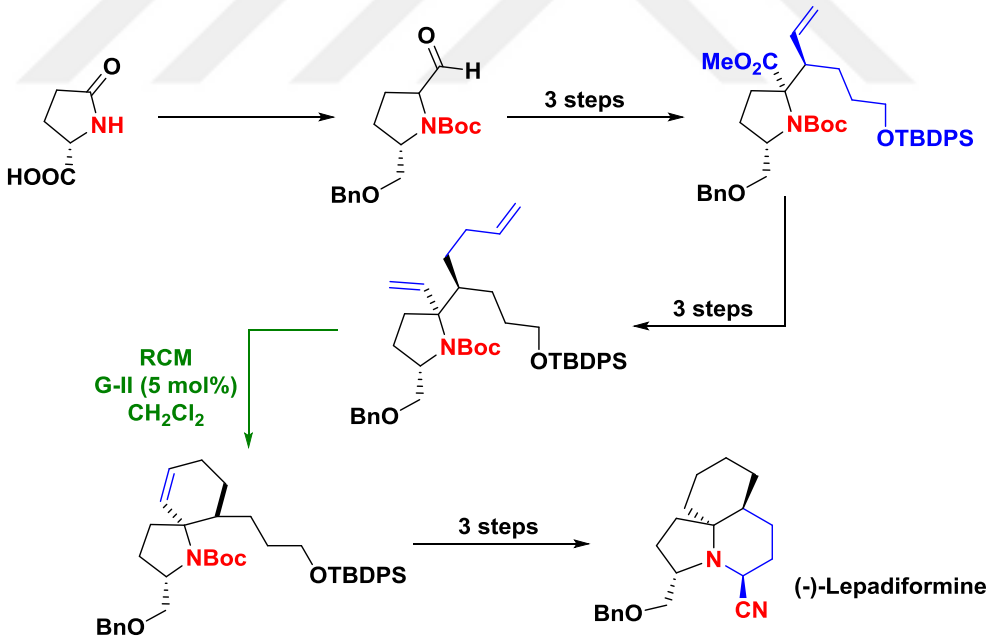
Figure 1.20. Synthesis of 12H-HTX

In 2002, azaspiro compound was synthesized by Suga research group through the skeleton of pyrrolidine by sequential reactions to dialkylated precursor of RCM spiro-product (69).



Equation 1.8. Synthesis of aza-spiro compound

Sanghee Kim and his colleagues, synthesized alkaloid compound have called (–)-lepadiformine that has azaspirocyclic core starting from (S)-pyro-glutamic acid by sequence of reactions involving RCM reaction to form azaspirocyclic compound (the precursor of the final (–)-lepadiformine) (70).



Equation 1.9. Scheme of (–)-lepadiformine synthesis

Nankakurines A, was synthesized from Luciduline. By treating the last compound with allylamine followed by Grignard reaction with allyl-magnesium-bromide. The ring closing metathesis occurred by adding Grubbs second-generation

catalyst after protecting the secondary amine by p-toluensulfonic (p-TSOH). The last step is the hydrogenation of the only double bonds in the compound (71).

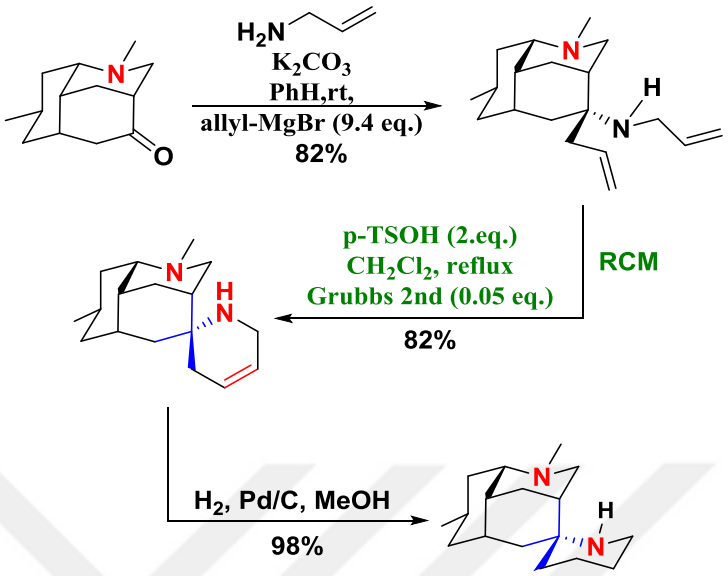


Figure 1.21. Synthesis of Nankakurines by RCM

In 2015 research group in chemical department in Wuhan University synthesized chiral benzo-fused-spirocyclic cyclopentenone. This kind of molecules can investigate the tumescence in DNA (NCSi-gb Analogue). In one of synthesis steps they use Grubbs 1st generation (G-I) catalyst to convert dienone to spirocyclopentenone skeleton (72).

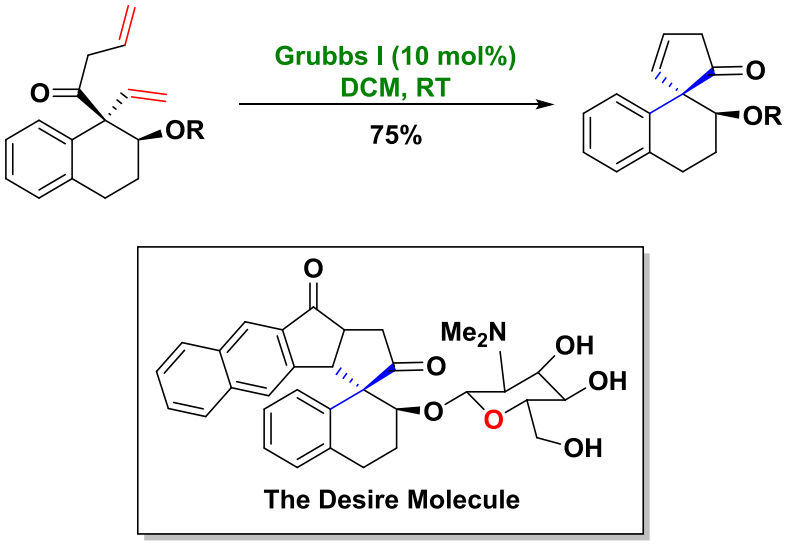


Figure 1.22. RCM step in synthesize (NCSi-gb) analogue.

1.4.1.5 Ring-Closing-Enyne-Metathesis (RCEM)

Enyne is a function group containing alkyne and alkene group. In this reaction the catalyst reacts with compound that has (C=C) double bonds and (C≡C) triple bonds to form 1,3-butadiene by the same mechanism of (RCM) and reaction starts with [2+2] cycloaddition between the metal complex and alkyne. However, ring closing enyne metathesis has two differents of RCM. First, the (RCEM) driven by stability of product due to diene conjugation (in RCM the reaction driven by entropy). Second, the reaction here is irreversible. Because 1,3-butadiene is less reactive toward the catalyst than starting material due to the conjugation (73) (62).

There is an issue about, is this will be ***exo*** or ***endo*** product?

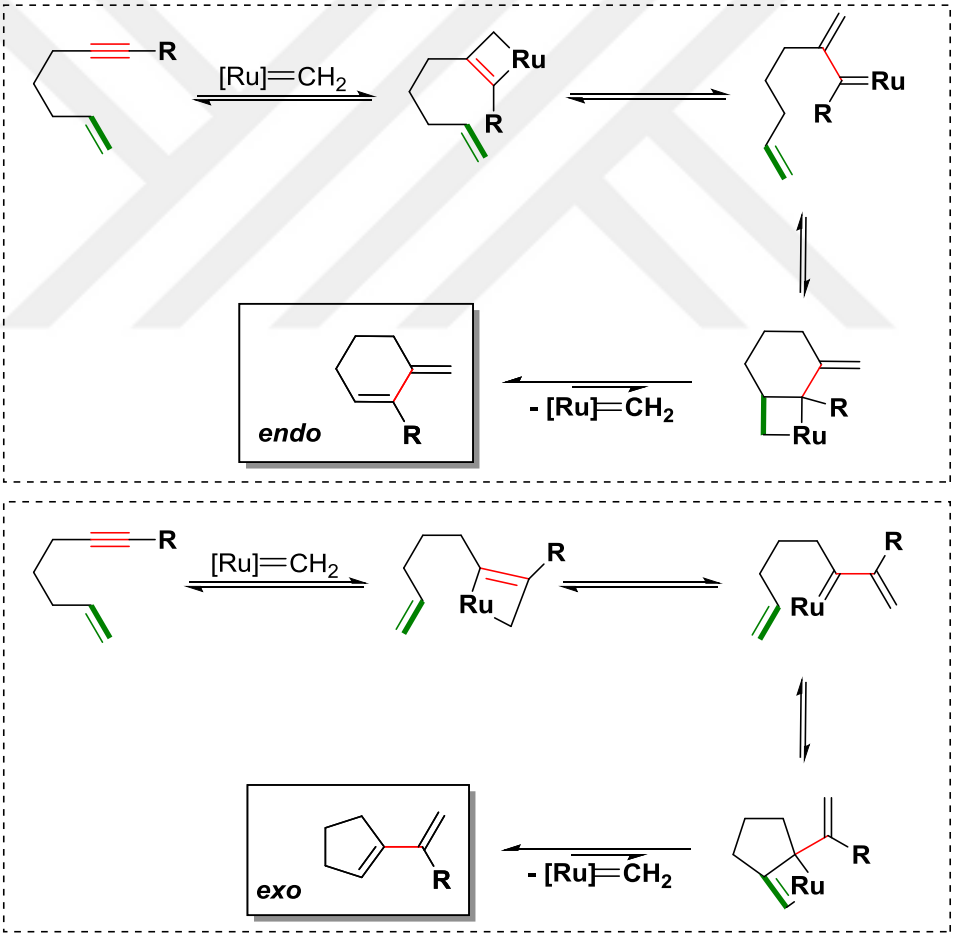
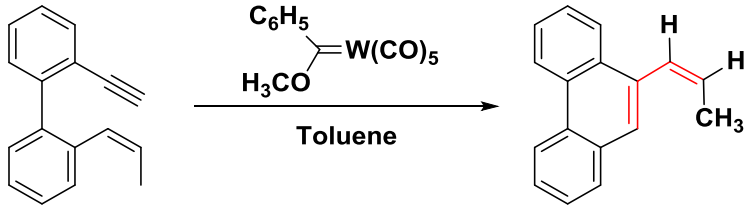


Figure 1.23. Mechanisms of endo or exo product

The selectivity of the catalyst (toward the bonding with enyne) issue was solved by Hansen and co-workers. They found that if the reaction produces less than nine member cyclic then *exo* would be more favorable (for medium and small

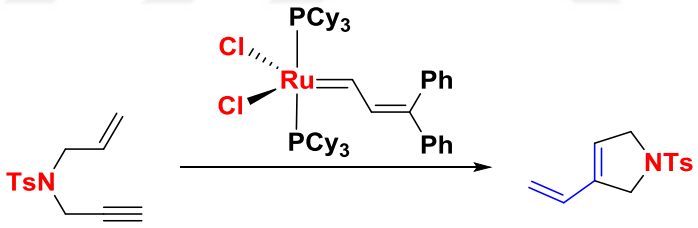
cyclic product). However, if the product has more than eight member, then *endo* will be more favorable (for macrocyclic product) (74) (75)

Katz T.J. research group reported first Enyne metathesis reaction in 1985. They use "carbene-tungsten carbonyls" complex as catalyst (76).



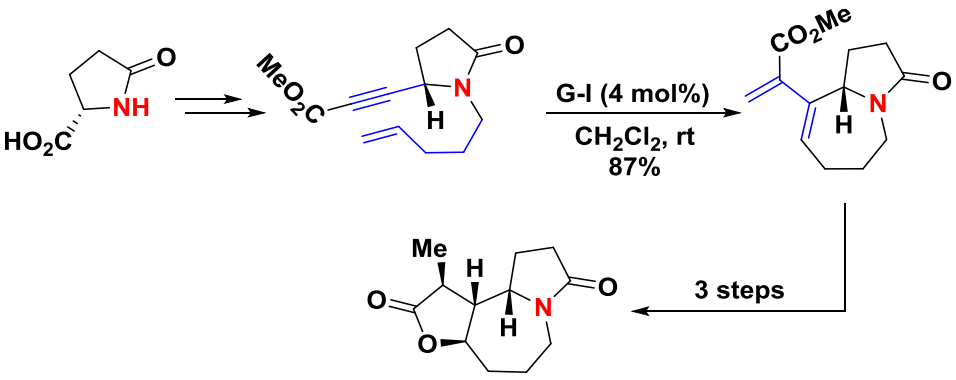
Equation 1.10. First reaction of enyne metathesis

In 1994 Miwako Mori. use Fischer complex (chromium carbene) catalyst for the Enyne metathesis by (36%) yield (77). The reason of low yield that if there is a terminal alkyne, the alkene part of the Ru-intermediate product may coordinate with the ruthenium carbene. Thus decreasing the activity of the catalyst. In 1998, Mori found that we could increase the product yield to 90% by doing the reaction in ethylene atmosphere (78).



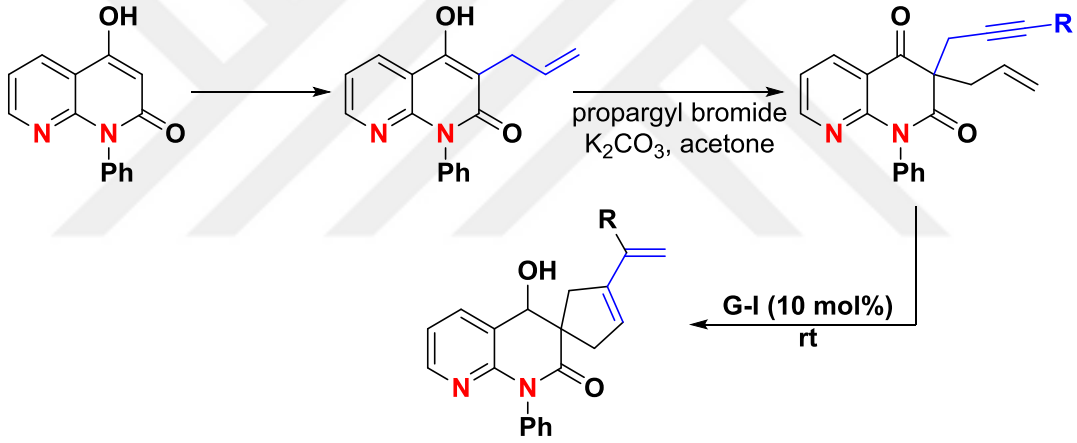
Equation 1.11. Enyne metathesis by ru complex.

The first synthesis of natural product by RCEM was in 1996 starting from (−)-pyroglutamic acid to form ene–yne compound. Then convert the last one by RCEM reaction to bicyclic compound by G-1 catalyst followed by to reactions to finish with the desire compound "(−)-stemoamide" (79).



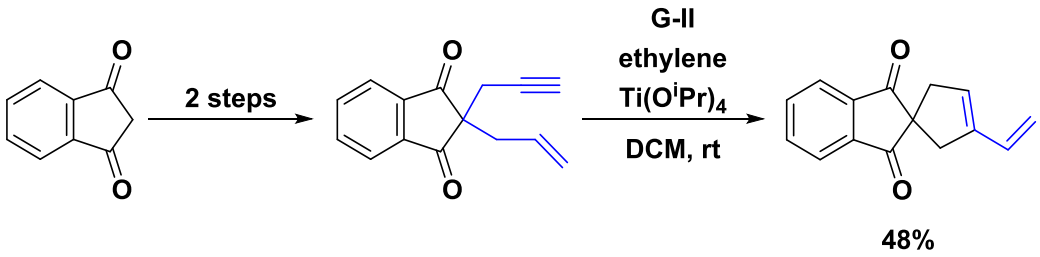
Equation 1.12. Synthesis of (−)-Stemoamide

Majumdar and his colleague synthesized spironaphthyridinone (Pyridopyridine) derivatives that used in some Alzheimer for memory loss curing. The reaction is made by using Grubbs first generation under N_2 atmosphere at room temperature (80).



Equation 1.13. Synthesis of spironaphthyridinone

Kotha S. with his research group found, in 2013, a novel spirocyclic scaffold approach for fredericamycin (**Error! Reference source not found.**) by allylation nd propargylation of indane-1,3-dione. After that they used (Grubbs 2nd) to convert it to spirocyclic compound (81).

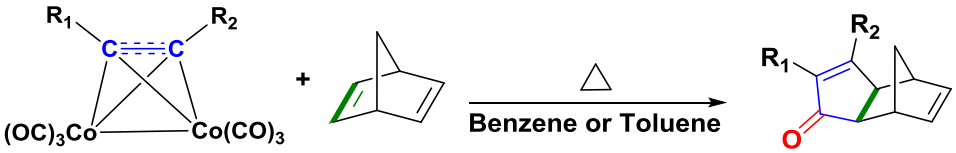


Equation 1.14. Synthesis of spirocyclic diene by RCEM

RCEM is a useful tool to construct complex molecules that could utilize in wide range of medicine and material applications.

1.4.2 Pauson-Khand Approach

The association of metal complex catalysts in organic chemistry accelerate the preparation of new organic compound from 1950s. One of the new organic cyclization approach in this relation the reaction that called Pauson-Khand reaction is the [2+2+1] cycloaddition reaction due to the three different π systems between alkyne, alkene, (both of them associated with two atoms), and one molecule of carbon monoxide that came from cobalt complex (which associated with one atom). The first mention of this reaction in a very brief article in 1971 (82). This reaction had discovered accidentally. Pauson research group aimed to synthesize cobalt-containing molecules from norbornene but the main product was cyclopentenone compound. They demonstrate this reaction in 1973 as hexacarbonylalkynedicobalt complex reacted with norbornadiene and the product was cyclopentenone derivative (83).



Equation 1.15. First Pauson-Khand reaction

1.4.2.1 Dicobalt Octacarbonyl ($Co_2(CO)_8$)

This compound has red-orange crystal with melting point of 51°C. If this compound exposed to air, it change its color to dark violet. Soluble in ether and alcohols. Prepared by combination of cobalt metal with carbon monoxide at 200°C,

100 atm. (84). The structure of this compound presents by two isomers. In solid state and in the solution at low temperature, bridge state is predominate. However, in solution at room temperature, the non-bridge state is predominate. In non-bridge state the cobalt has hybridizing of dsp^3 (each of cobalt has 5 hybrid orbitals, one half-filled orbital overlapped with other Co half-filled orbital, and four orbital gain lone pair electron from carbon monoxide (CO). thus, four coordinate bond Co ← CO). However, the hybridization of the bridge state is d^2sp^3. First, the two half-filled hybridize orbital overlapped to each other on the cobalt atoms to make Co-Co bond. Moreover, the three hybridize orbitals accepting the lone pair electrons from Carbon monoxide (three molecules) and forming CO→Co coordinate bonds (6 bond). Finally, the bridge formed by the last two half-filled orbitals that overlapped with carbon atom of the remaining carbonyl. (85).

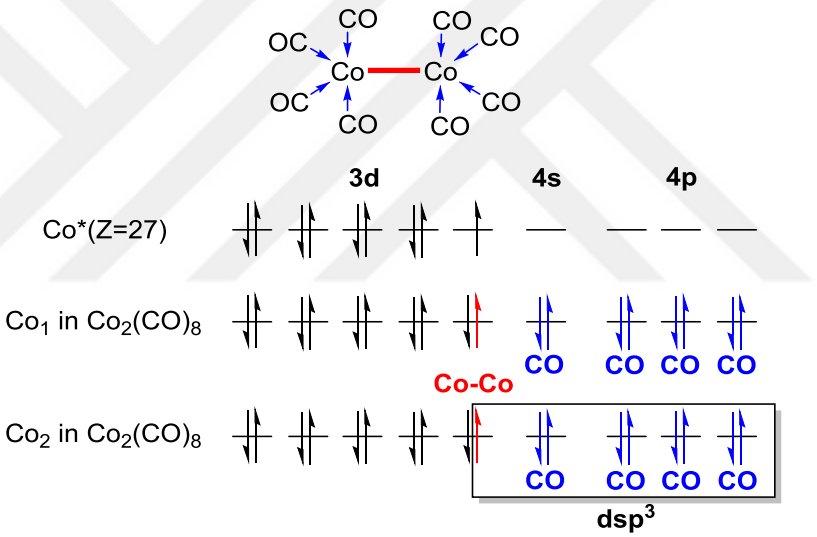


Figure 1.24. Non-bridge dicobalt octacarbonyl hybridization

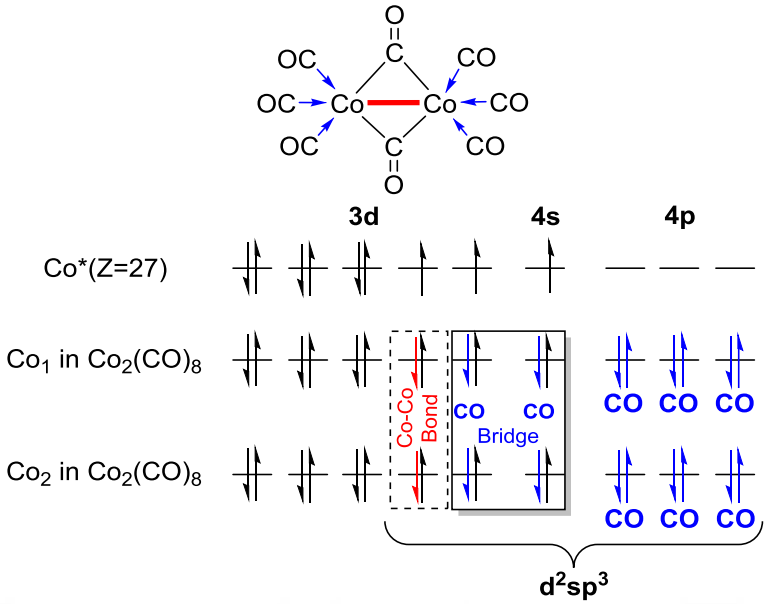


Figure 1.25. Bridge dicobalt octacarbonyl hybridization

1.4.2.2 Mechanism of Pauson-Khand Reaction

Philip Magnus suggested the mechanism of Pauson-Khand reaction in 1985, this method accepted by the other researchers. He suggested (as shown in Figure 1.26) that the alkyne-hexacarbonyldicobalt with 18-electron (I) suffered one carbon monoxide ligand to be alkyne-bentacarbonyldicobalt complex with 16-electron. The last complex coordinate with the olefin to be 18-electron complex (II). That allow the insertion of olefin to form cyclo-cobalt complex (III). The cobalt atom that lost (IV) is coordinating with new carbon monoxide (CO) to insert with cyclo-cobalt complex. After that, reduction would occur to form (VII) and finally elimination process to form cyclopentenone (VIII) and Hexacarbonyldicobalt (86).

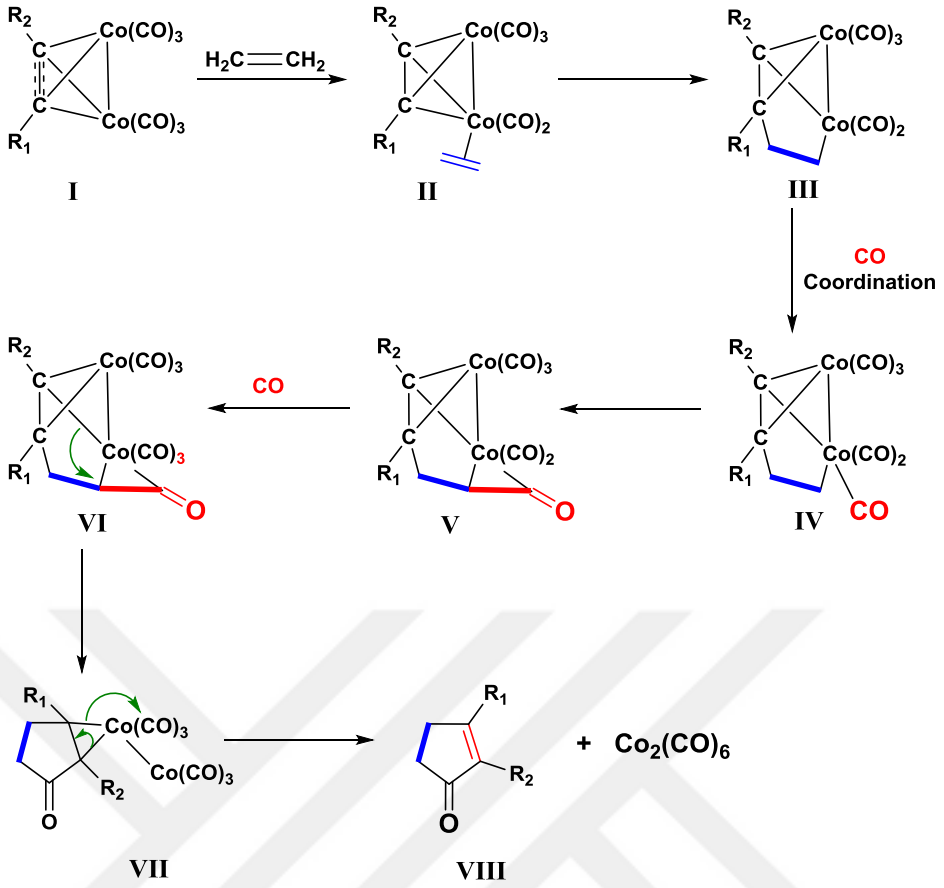
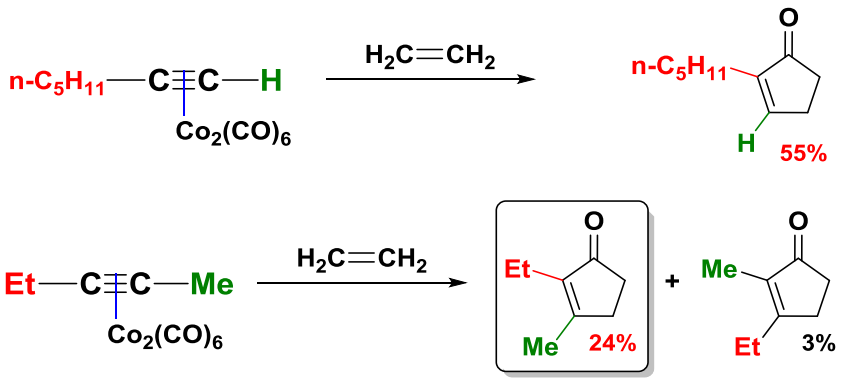


Figure 1.26. Mechanism of Pauson-Khand reaction

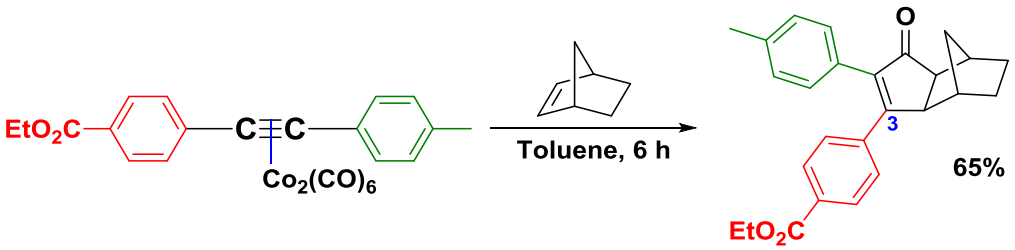
1.4.2.3 Regioselectivity of Pauson-Khand Reaction

There are two kinds of regioselectivity in this reaction. First, **for the Alkyne**, it based on the steric hindrance of the substituent. The larger components the closer to C=O double bonds (second position of cyclopentenone product) (87)(88).



Equation 1.16. Example of regioselectivity of Pauson-Khand

In 2001, Gimbert and Greene have approved by (DFT) that if there is internal alkyne conjugated with (EWG) electron withdrawing group, this group would be in 3-position of the cyclopentenone product (89).



Equation 1.17. Effect of electron difference in Pauson-Khand reaction

The second factor effect the regioselectivity is **the alkene insertion**, which is less expected one. For instance, if there is acyclic alkene, it will be no position control (of alkene substituent). However, when the substituent has heteroatom it would be efficiency in regioselectivity. This because of the heteroatom may treat as ligand for cobalt that turn to minimize the flexibility of the complex. Thus, more selectivity. For example, when alkyne-cobalt complex react with homallylic amine (or sulfide) or with diethyl allylphosphonate (Figure 1.27). These functional units acting as ligand-donors along the reaction so it restricted the rotation. Hence, it connect on 5-position of cyclopentenone (90) (91).

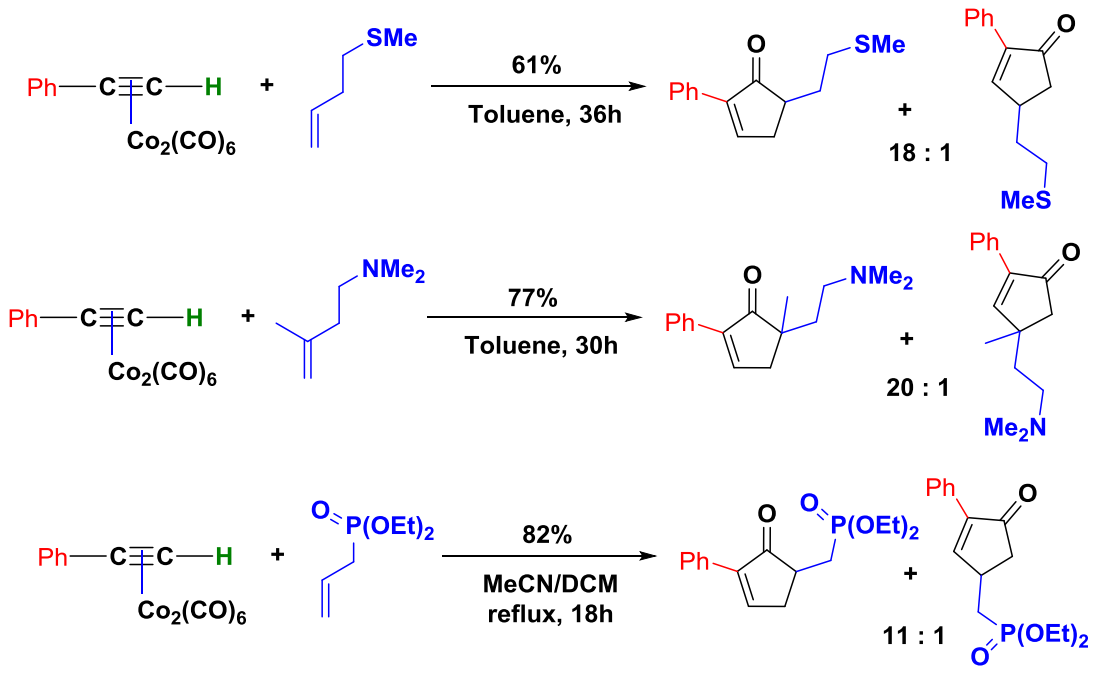


Figure 1.27. Different heteroatom and regioselectivity.

1.4.2.4 Pauson-Khand Reaction (Intramolecular)

All the examples that shown above are "Intermolecular Pauson-Khand reaction". N. E. Schore performed the first intramolecular Pauson Khand reaction in 1981. This approach allowed the metal-complex-mediate synthesis to prepare many important natural or unnatural products. In (Figure 1.28) we can see the first acyclic compound (hept-6-en-1-ynes and oct-7-en-1-ynes) that converted to bicyclic compound (92).

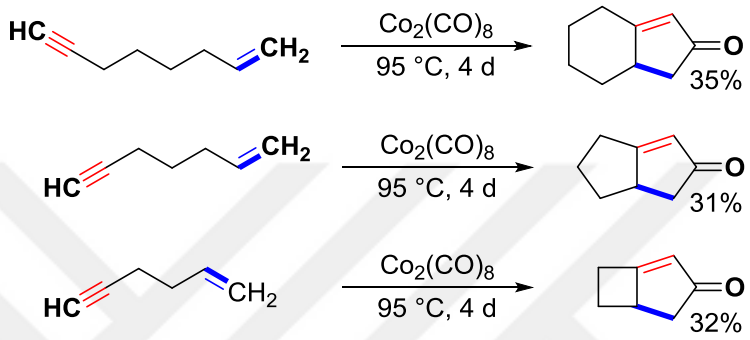


Figure 1.28. The first Pauson-Khand intramolecular reaction

Another example occur by Magnus concentrated on stereoselectivity (that is important when synthesis natural product) of intramolecular reaction by synthesized natural products called Hirsutic acid and Coriolin. When there is a bulky substituent on (C-3) of propargyl or on (C-5) of it (allylic position). In addition, we can improve the selectivity, if there are other bulky group on the (C-1) of propargyl (on terminal alkyl carbon atom) (86) (93).

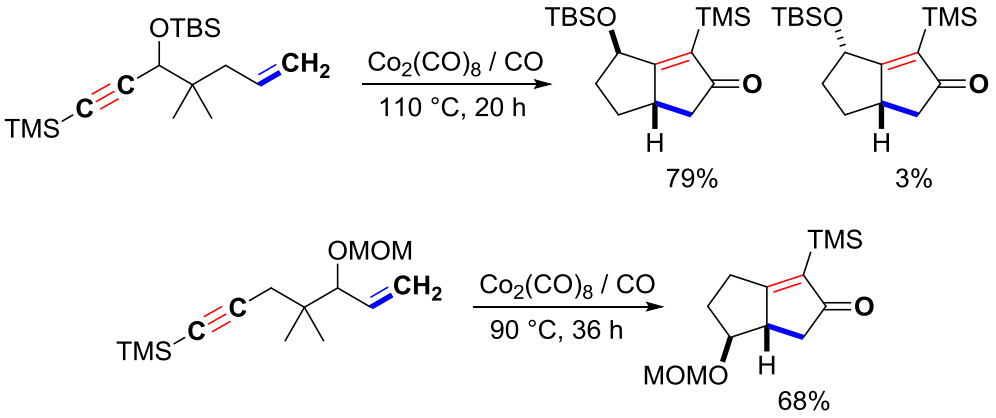


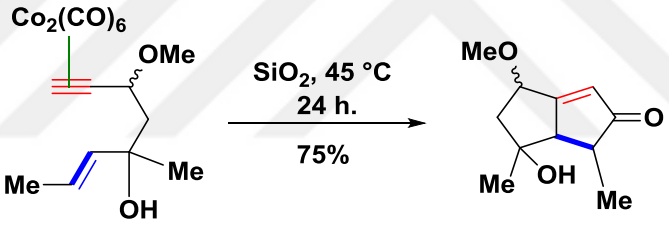
Figure 1.29. Effect of bulky group on stereoselectivity

1.4.2.5 Pauson-Khand annulation Promoting

As we can see above, all Pauson-Khand reaction promoted by high temperature (60 – 120)°C (and/or pressures) not mention to by-product that presence more difficulties. Moreover, the low (or mediate) yield of the desire products. Due to that, the researchers do huge efforts to enhance and promote this kind of reaction. The researchers found some techniques involving dry-state-supporting adsorption, ultrasound effect, microwave promotion, and N-oxides.

1.4.2.5.1 Dry-State-Supporting Adsorption

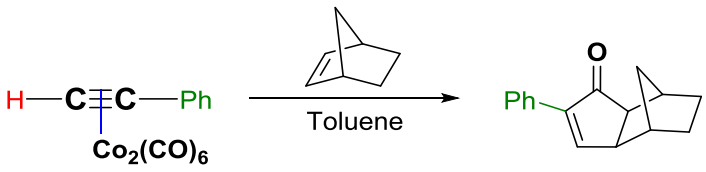
Smit and co-worker reported this technique in 1986 based on finding support (silica or alumina) and adsorbing the alkyne complex on it. This can enhance the exchanging of decarbonylative ligand. Furthermore, when the substrate adsorbing on the support it restrict the movement of conformation of the substrate. Therefore, increase the yield of the product in low temperature (94).



Equation 1.18. Dry supporting addsorbant effect

1.4.2.5.2 Ultrasound Effect

Billington and co-workers found that using low-powered sonication. Although decrease the reaction time it had low effect of product yield (95). However, according to Torres R., Using high-powered sonication can improve the reaction efficiency (good yield with mild reaction conditions as short time and low temperature) if combined with another Pauson-Khand promoter. For example, the reaction of norbornene with alkyne-cobalt complex had improved from (75% yield in 4 h. at 60 – 70 °C) in thermal condition to (84% yield in 10 min.) in high-powered Ultrasonication. However, when N-oxide promoter added with high powered Ultrasonication, yield raised to (95% in 6 min.) (96).



Equation 1.19. Reaction of Norbornene by different conditions

1.4.2.5.3 Microwave For Pauson-Khand Enhancing

The first employed of microwave approach in Pauson-Khand reaction by Evans and his group was in 2002. (Intra and Inter) molecular Pauson-Khand reaction had been occurred in microwave. They found that it accelerate, enhance and reduce time of the reaction, as well as improve the yield of the desired product. (from 16 hours with yield 70% to 20 minutes with yield 75% for the first reaction) (97).

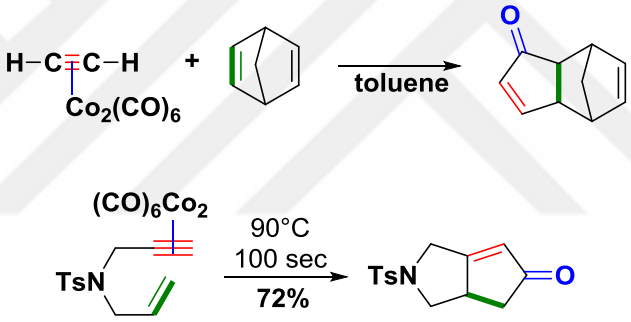


Figure 1.30. Effect of microwave on PKR

1.4.2.5.4 N-Oxide as Pauson-Khand Reaction Promoter

Schreiber and his colleagues was the first researcher that use N-Oxide in Pauson-Khand reaction. They found that these tertiary (3^{o}) amine-oxides enhance the reaction by reacting with one of carbon monoxide (CO) ligand and oxidize it to CO_2 (weak ligand that coordinates to the Cobalt). Thus employed as a free site that help the olefin to coordinates to the Cobalt atom (98).

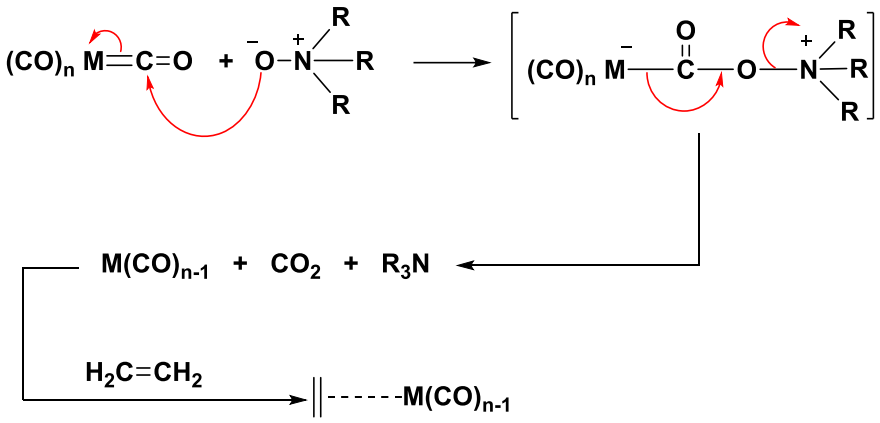


Figure 1.31. Effect of N-oxide on the Pauson-Khand catalyst.

The yield clearly increase, for example the first equation in (Figure 1.32), when comparing between the ultrasonic Pauson-Khand reaction (45% yield at 45°C) with the addition of NMO to Pauson-Khand reaction (68% yield at RT) (99).

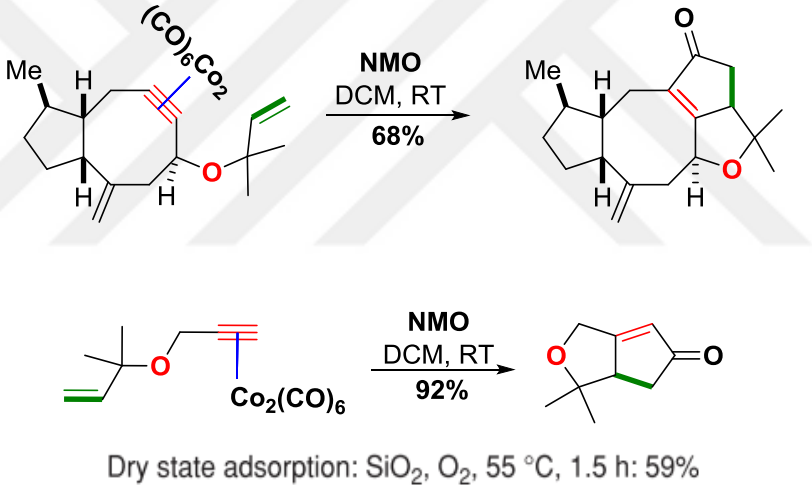
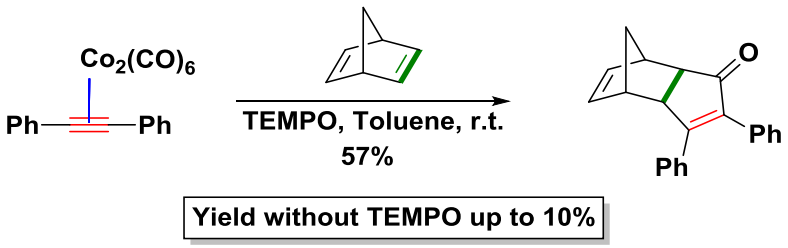


Figure 1.32. Effect of NMO on Pauson-Khand reaction

Here we will count some amine-oxides compounds that used as promoter for PKR. N-Methylmorpholine-N-oxide (NMO) (99), Trimethylamine-N-oxide (TMANO) (100), Quinine-N-oxide especially for enantioselective reactions (101), Sparteine N-oxides (102), 2,2,6,6-tetramethylpiperidine N-oxide-free radical (TEMPO) particularly in reaction that have stearic alkyne (Equation 1.20) (103), and Burcine N-oxide (104).



Equation 1.20. TEMPO as promoter in Pauson-Khand reaction

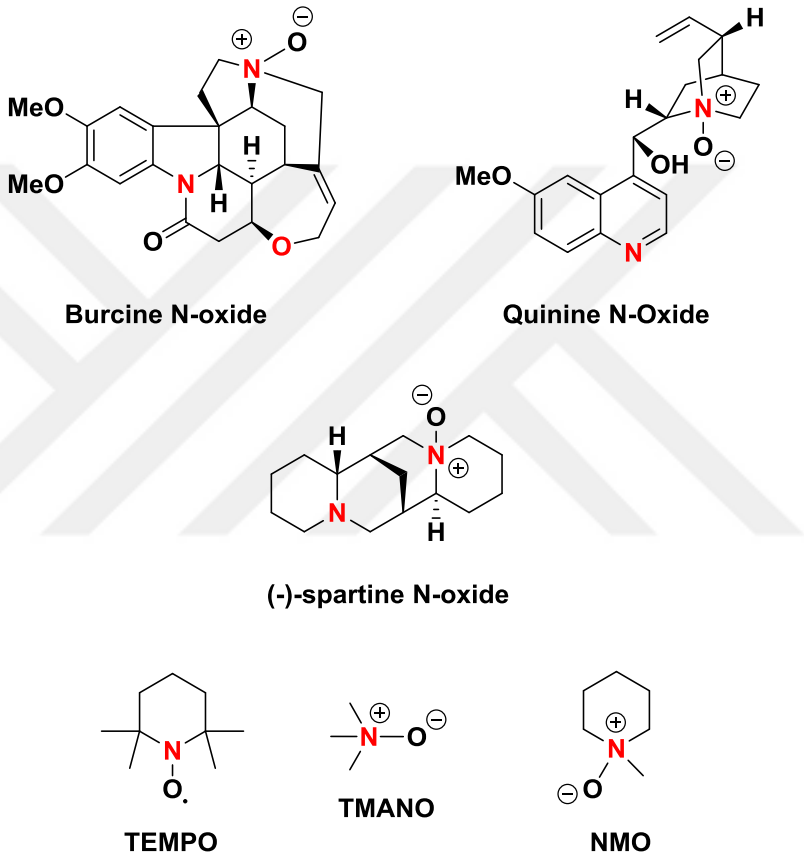


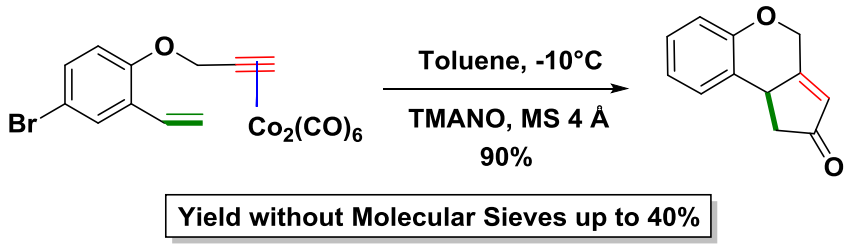
Figure 1.33. Examples of amine-Oxide compound

These amine-oxides allowed the reaction to occur in mild condition (in room temperature with decreasing in reaction Time). In contrast, the disadvantage of these compounds require excess of N-oxide that needs more filtration and purification.

1.4.2.5.5 Other Pauson-Khand Reaction's Promoter

Molecular Sieves is another promoter that make an effect with N-oxide by inducing the reaction by increasing the yield. This efficiency was investigated by

Castells J. and his colleagues. They use TMANO with powder molecular sieves (by eight time of starting material mass) (105).



Equation 1.21. Molecular sieves effect in Pauson-Khand reaction

Alkyl sulfide and other sulfide containing compounds used as Pauson-Khand reaction promoter. These promoters accelerate the reaction in presence of carbon monoxide (CO) and with increasing of the temperature. Some examples, tetramethylthiourea (TMTU) (106) (107) (Figure 1.40), n-butyl methyl sulfide (n-BuSMe) (108), tri-n-butylphosphine sulfide (nBu_3PS) (109), dimethyl sulfoxide (DMSO) (110)

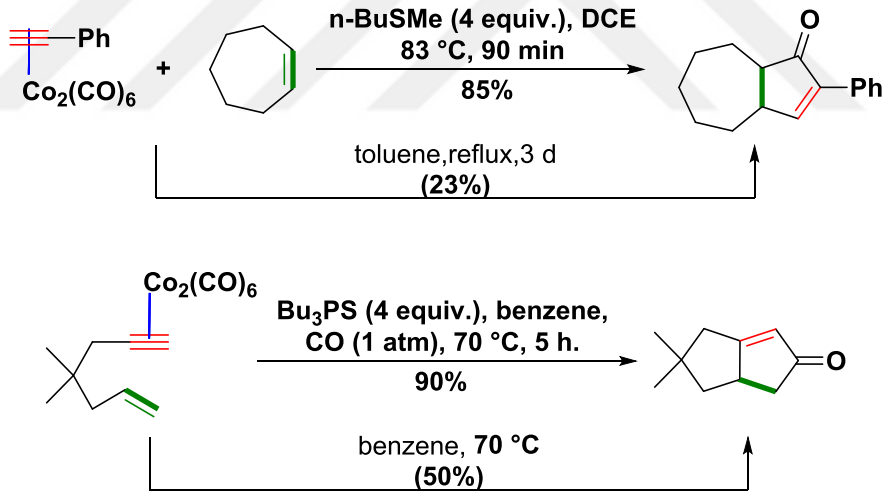


Figure 1.34. Effect of sulfide containing promoter

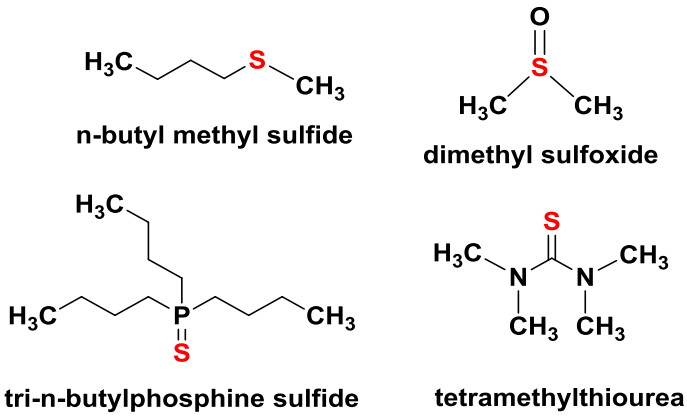
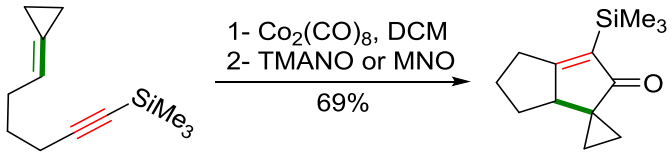


Figure 1.35. Examples of sulfide containing compounds

We must mention that NMO monohydrate or TMANO dehydrate exhibit good promoter to give good yield in most case (111). However, for NMO anhydrous, William J. Kerr found that it gave a good yield if the alkyne not active. Unless that, it decrease the yield of the product because it decompose the alkyne or alkyne complex (112).

1.4.2.6 Pauson-Khand Reaction in Spiro-Cyclic Compound

Armin de Meijere synthesized Spiro (cyclopropanebicyclo[n.3.0]alkenones) moieties. Starting from Trimethylsilyl-protected enynes and made the complex with $Co_2(CO)_8$ followed by adding trimethyl-amine N-oxide at -78°C under O_2 gas (113).



Equation 1.22. Synthesis of spirocyclopropanated moiety

Hotha S. used hexose/pentose enyne scaffolds as starting materials to synthesized spirocyclic compounds. He used silica gel as dry state promoter after the complex of enyne-cobalt was occur, (43).

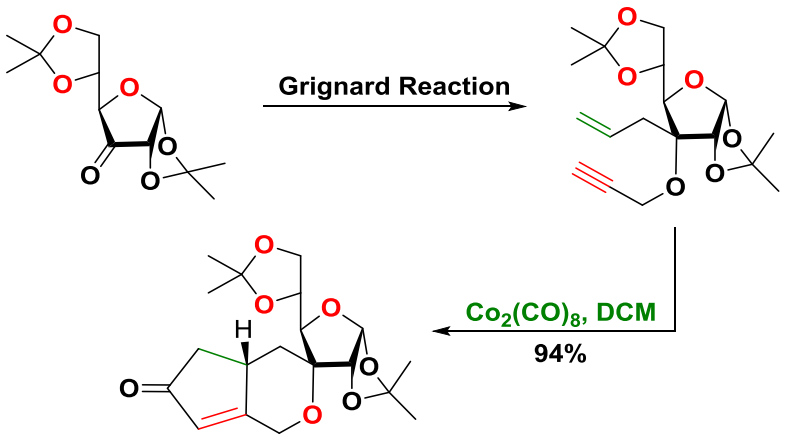


Figure 1.36. Spirocyclic compound from pentose enyne moieties

Aquariane synthesized in 2006 by Burnell D. Thornton P. from Tricycle-spirocyclic compound that performed by Pauson-Khand reaction of enyne with cobalt complex in addition with TMANO as promoter at 30°C with good yield between 65% - 70% (114).

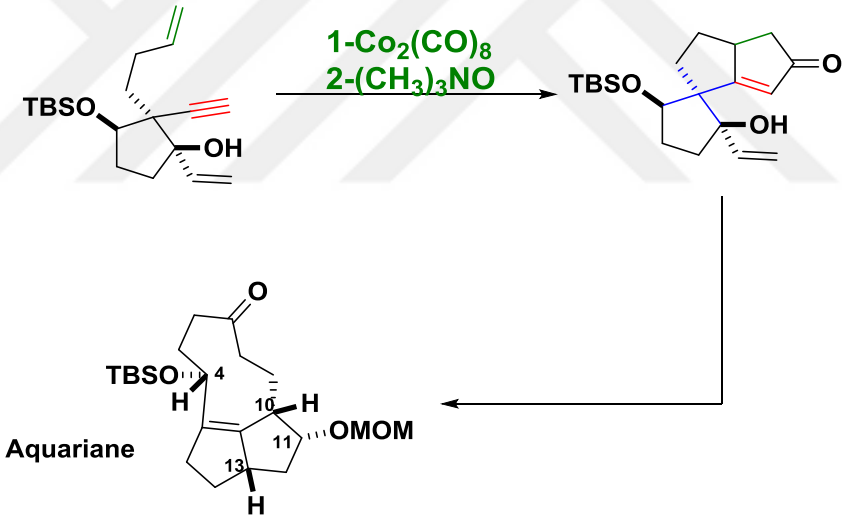
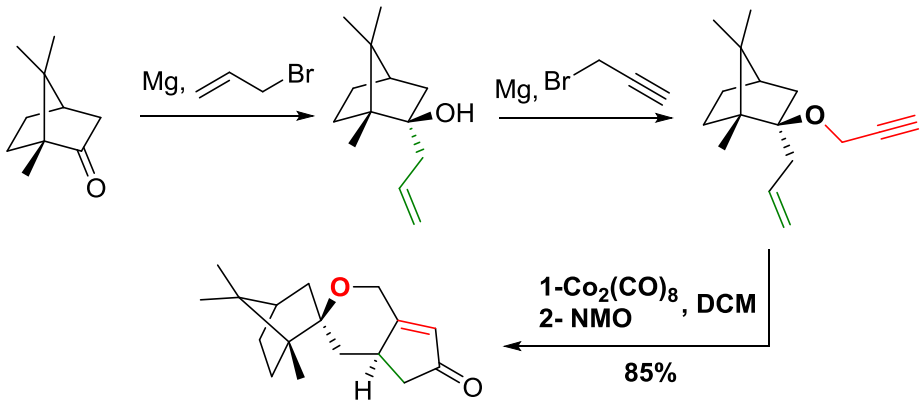


Figure 1.37. Synthesis of Aquariane.

C. Tanyeli and his co-workers had made a stereoselective reaction by intramolecular Pauson-Khand reaction of Enyne moieties starting from (1R)-(+)-camphor that followed by two steps of Grignard reaction. This approach shown good conformation directing of the stereo-center of the spirocyclic product (115).



Equation 1.23. Synthesis of spirocyclopentenone-pyran moieties

Burnell D. and Thornton P. were started from six-member ring ketone to make Enyne-Cobalt complex after that, adding TMANO to make the desired compound with good enantiomeric excess (ee) (116).

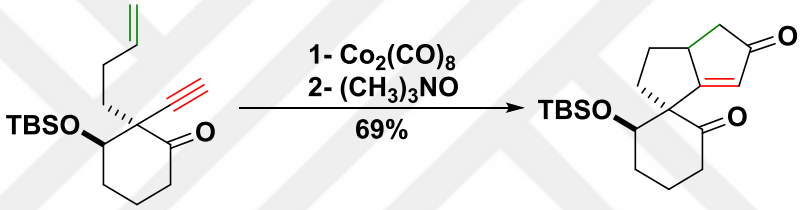


Figure 1.38. Synthesis of spirocyclic product from ketone derivative

Homoallylic alcohols were used to synthesize the desired enynes hired to produce spirocyclic (oxygen heteroatom) compound in 2014 by using Pauson-Khand reaction with NMO as promoter (117).

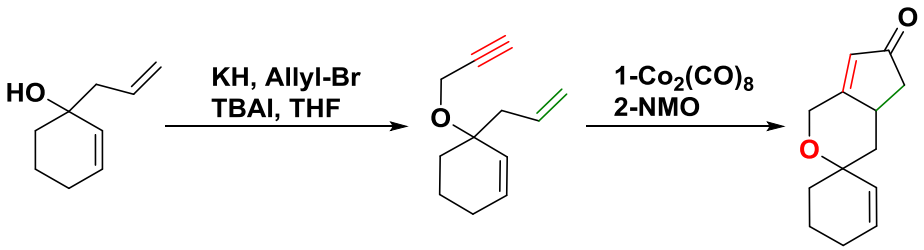


Figure 1.39. Synthesis of spirocyclic (oxygen heteroatom) compound

In 2020, Innocenti, R and his research group synthesized "pyrrolocyclopentenone spirocyclic compound" by using microwave approach to produce enyne compound. After adding $Co_2(CO)_8$ with TMTU as promoter to synthesize their desired product (118).

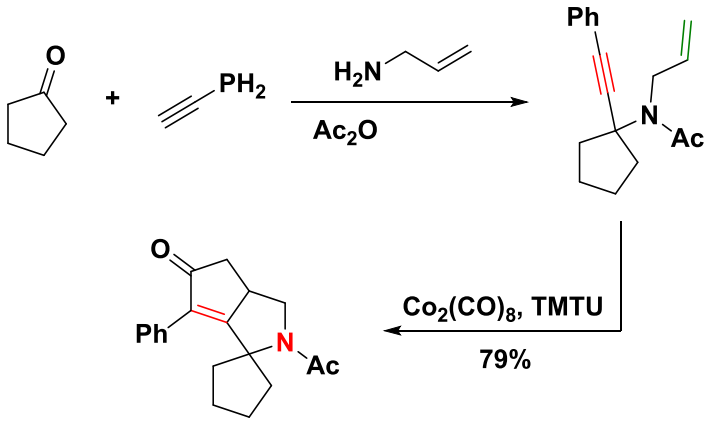


Figure 1.40. Synthesis of "pyrrolocyclopentenone spirocyclic compound"

1.5 Aza-Spiro-Compounds

Aza spiro Compounds that have Nitrogen atom in at least on cycle of their spirocyclic system. These skeletons observed in numerous of natural products (Alkaloids). The chemists and pharmacists have interest this kind of compounds because of the properties in drug discoveries, and can be used as building blocks and scaffolds in medicinal compounds (119).

An examination of pK_a values usually trend that the amine of these compounds are more basic, polar than corresponding monocyclic system. However, less oxidative degraded in liver of both mice and human (120). Hereafter some azaspiro compounds have interesting biological activities or pharmaceutical utilities.

(±)-pandamarine (has azaspiro[4.5]- decane) isolated from Pandanus. That used for treatment of rheumatism and epilepsy (121). azaspiro[4,5]decane structure (NK-1 receptor antagonist) that has three chiral centers that used in treatment of inflammation, anxiety, and emesis (122). Azaspiro[3.3]heptane derivatives are also important scaffolds for drugs manufacturing due to low metabolic clearance average like anti-bacterial agent or anti-vasopressin agent (treatment for hyponatremia in patients with heart failure congestive) (123) (124).

The Pyrrolidine (A-366) is another spiro compound that has biological activity as strong, special selective inhibitor of Histone Methyltransferase (HMTs) especially (G9a). there is a connection between (HMTs) and leukemia, lung cancer,

and cancer cells of prostate) (125). Pteropodine is a compound that isolated from Cat's claw plant exhibit anti-inflammatory, protective impact of DNA damage and anti-proliferative action to ovarian carcinoma and lymphoblastic leukemia cells (126). In azaspirone species there is a compound that commercial called Buspirone. This drug has anti-anxiety purpose by doing a physiological agonist reaction toward serotonin receptor (127). In conclusion we can see that the predominance of the spirocyclic skeleton that used in drug utility are five, and six member ring and less for three and four membered rings.

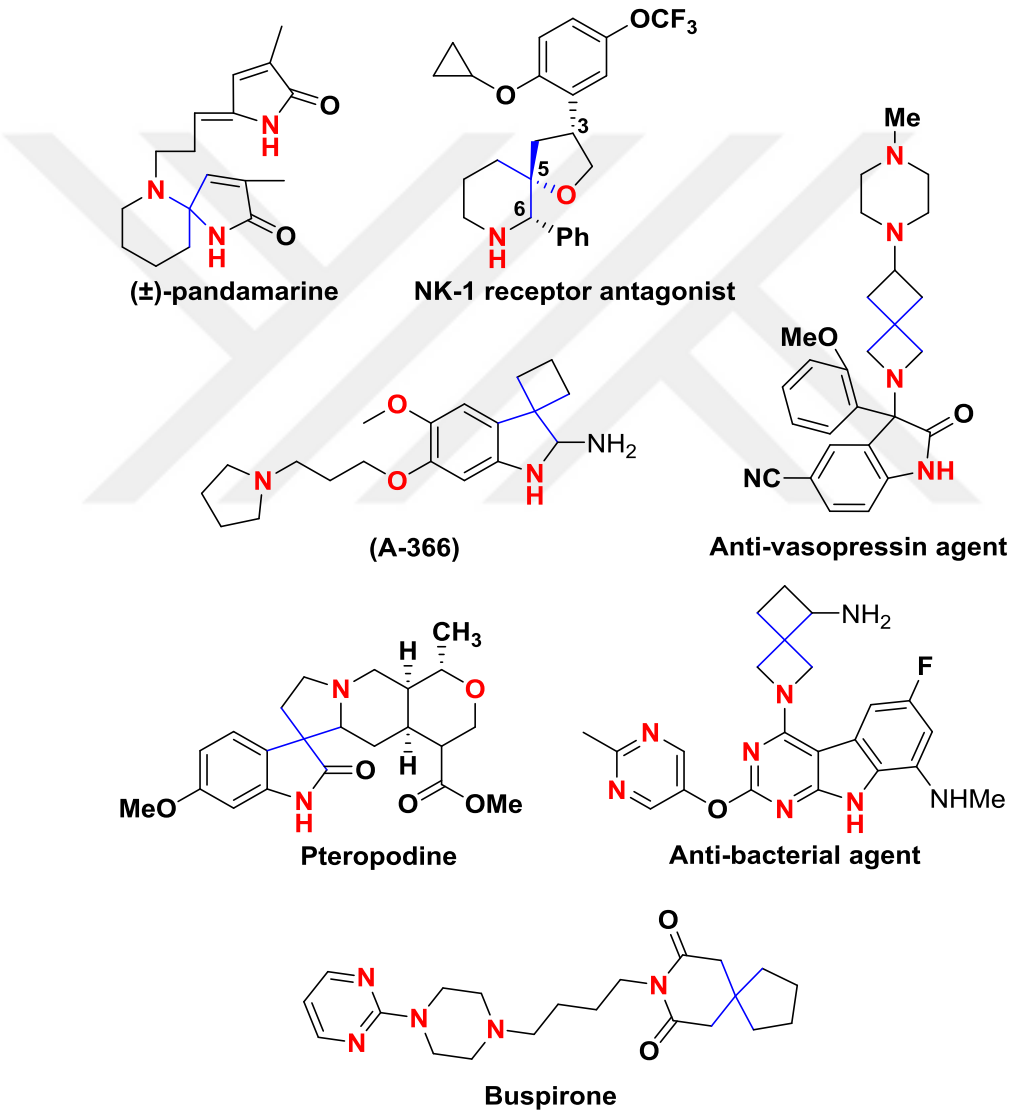


Figure 1.41. Examples of Aza-Spiro compounds

2. AIM AND SCOPE OF THE STUDY

The aim of this study is to produce a derivation of related unique spirocyclic substructures that would provide the chance to influence incremental modifications in the molecular planning of different compound archives.

In addition, spirocyclic compounds that containing nitrogen heteroatom was selected because of their biological and pharmaceutical features. Moreover we chose RCM and PKR reaction for the following reasons:

- The procedure of this reaction require mild conditions. Moreover, it could take various functional group.
- There are just a few examples of scaffold that prepared via RCM reaction. Due to that, our purpose in this project was to fill the gap by synthesis heterocyclic compounds derived from simple reactions.

These important reasons have promoted us to synthesize novel azaspirodien compounds by ring closing metathesis and tetrahydrospirocyclopenta[c] pyrolidinone compounds via Pauson-Khand reaction by this retrosynthesis.

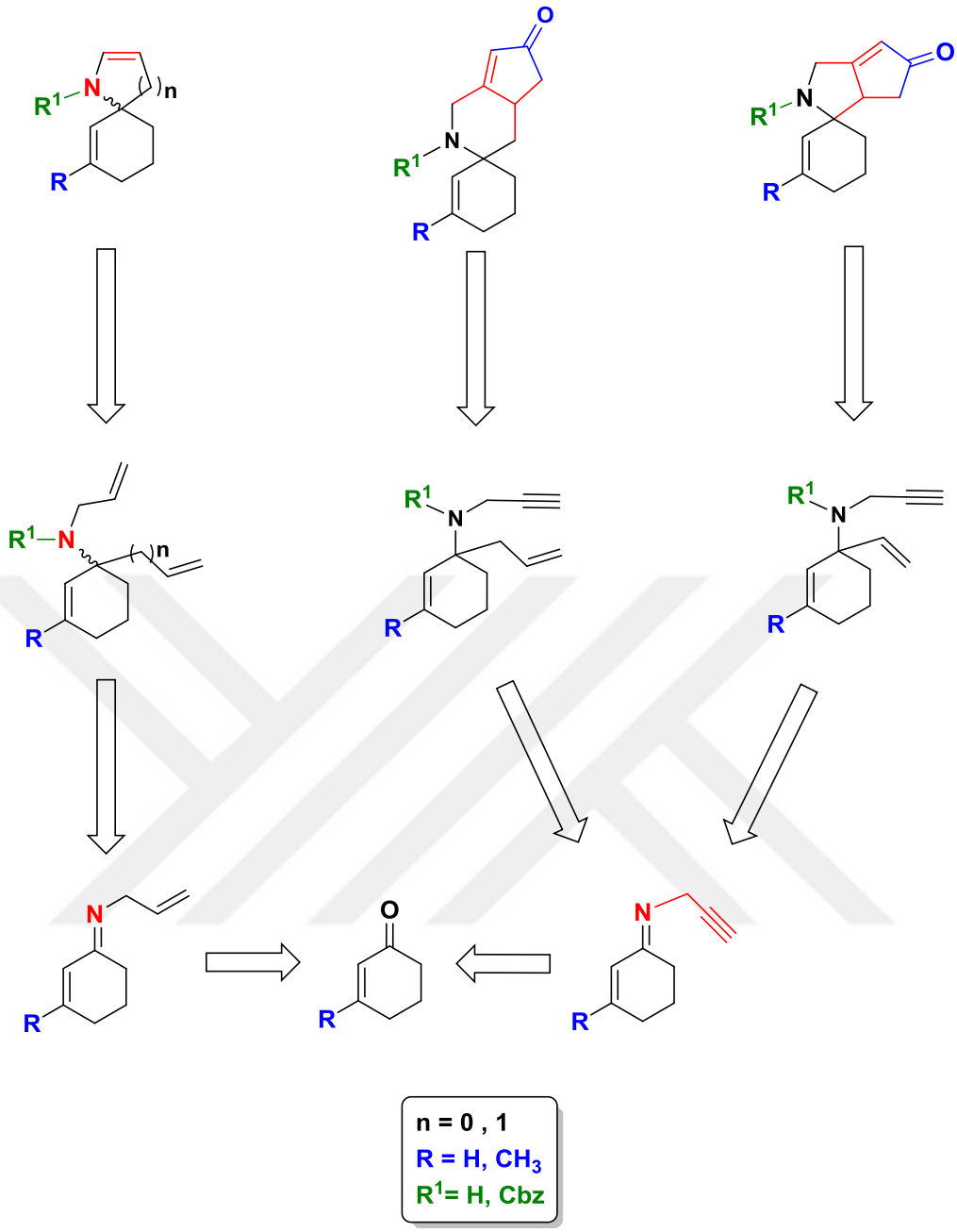


Figure 2.1. Retrosynthesis of the thesis study

3. MATERIALS AND METHODS

3.1 General Remarks for Chemicals, Workup, and Analytical Techniques

Solvents (Dichloromethane, Tetrahydrofouran, Benzene, Hexane, Ethyl acetate, Triethylamine, Diethyl ether, Ethanol...), Molecular sieves, Dicopaltoctamonoxide catalyst and other reagents (Allyl Amine, vinyl amine, propargylamine, p-toluensulfonic acid monohydrate, N-methylmorpholine N-oxide, Grignard reagents...) are commercial purchased from either Aldrich, Merck, or Acros.

Cyclohexenone and its derivatives, was selected due to the presence of these compounds in highly functionalized, important chiral-bioactive components (128).

All reactions were fulfilled under a nitrogen atmosphere, unless mentioned and all chemicals, that air or water sensitive, were stored under (N_2) "inert atmosphere".

Flash column chromatography was accomplished using "Silica gel" from J.T. Baker (70-230 mesh ASTM). Thin layer chromatography (TLC) was used to monitor reactions using (Silica gel 60 F_{254}) from Merck. In addition, TLC was monitored by UV light (UV-Leuchte 254 nm) (or/and) molybdatophosphoric acid hydrate (Merck) dye solved in ethanol heating with hot gun.

Infrared (IR) Spectra was recorded on "FTIR 8400-S SHIMADZU". In addition, absorption frequency of bands were reported in cm^{-1}.

Mass spectra was recorded at Central Laboratory in Middle East Technique University (METU) on "Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS".

Nuclear Magnetic Resonance (NMR) spectra was measured by using 'JEOL ECS-400 spectrometer'. The chemical shift was expressed in parts per million (ppm) and correlated to the residual proton and carbon resonance of the solvent $CDCl_3$ at 295 K (δ 7.26 for ^{1}H-NMR and 77.0 for ^{13}C-NMR). Chemical shift (multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet, dt = doublet of

triplet, ddd = doublet of doublet of doublet, td = triplet of doublet, br = broadened, J = coupling constant (Hz).

Anhydrous magnesium sulphate ($MgSO_4$) (Merck) was used to dried all the desire extractions before concentrate them be rotary evaporator (under vacuum).

All reactions were made in '**Reaction System'** consisting of round bottomed flask (two-necked) equipped with water-cooled condenser (Graham condenser), rubber septum fitted with nitrogen inlet gas (as an inert gas) and (2.5 cm) magnetic stir bar (balık).

Grignard reaction with vinyl magnesium bromide needs medium temperature of (−78) °C that achieved by using mixture of liquid nitrogen with acetone.

All the filtration of the crude mixture (after reaction had made) made by vacuumed Büchner funnel fitted with Whatman-1 filter paper, 120 mm. (unless we mentioned it).

All imine products were used directly without any purification due to high sensitivity of imine compound that it might broke down when purified it. (129) (130)

3.2 Research Plan of Ring-Closing Metathesis (RCM)

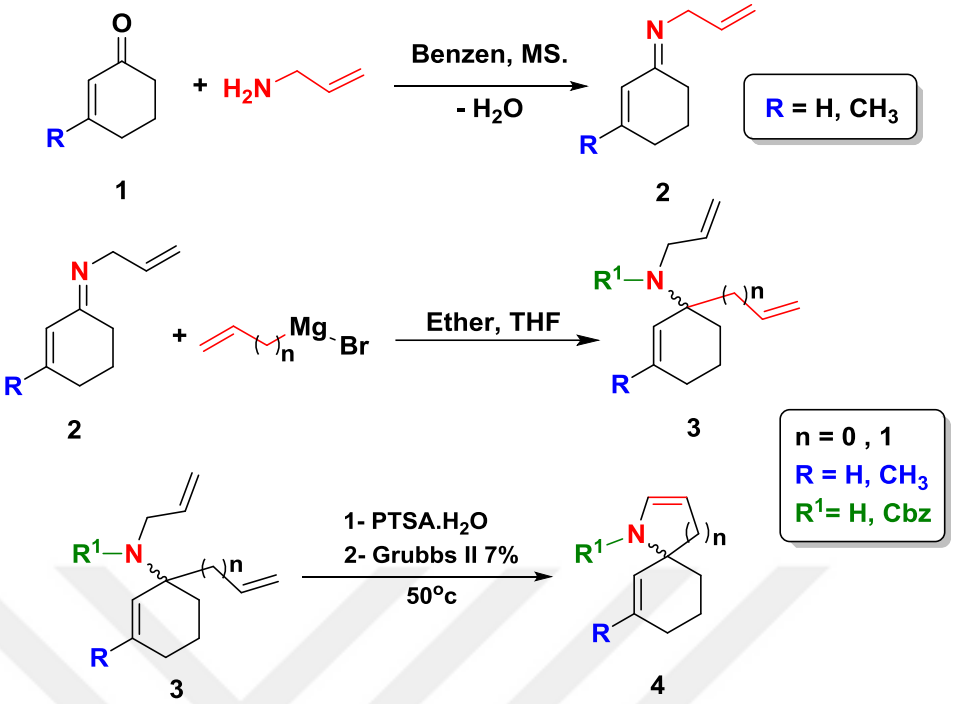
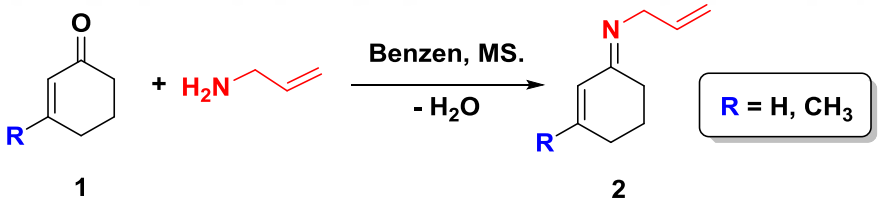


Figure 3.1. Research plane for synthesis of spirocyclic compound

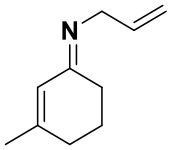
3.2.1 General procedure for Imine formation (2)



Equation 3.1. Synthesis of imine for RCM

A 100-ml flask equipped with water-cooled condenser (Graham condenser), rubber septum equipped with nitrogen inlet gas (as an inert gas) and 2.5 cm magnetic stir bar is charged with cyclohexenone derivatives **1** (1.5 g, 1 equiv.), allylamine (2 equiv.), molecular sieves (2.5 g.) in presence of 30 mL benzene as solvent. The reaction mixture heated and allowed to stir in oil bath 45 °C for 3 days (131). The resulting brown slurry was filtered and washed by diethyl ether. The solvent was removed by vacuum. After that, blowing the solution by nitrogen gas on the residue for removing benzene to give crude imine product **2** that used directly without any purification.

3.2.1.1 (E)-N-allyl-3-methylcyclohex-2-en-1-imine (2a)



2a

(E)-N-allyl-3-methylcyclohex-2-en-1-imine was obtained as orange yellow oil. Chemical Formula ($C_{10}H_{15}N$), molecular weight: (149.24).

IR (neat): 3025, 2890, 1680, 720 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm (Figure 4.1)

1.79 – 1.68 (m, 2H, for the diastereotopic methylene protons at position I)

1.81 (d, J = 1.4 Hz, 3H, for the methyl protons at position H)

2.16 – 2.04 (m, 2H, for the diastereotopic methylene protons at position G)

2.28 – 2.31 (m, 2H, for methylene protons at position F)

3.98 (dd, J = 5.7, 20.6 Hz, 2H, for allylic methylene protons at position E)

5.03 (dd, J = 1.4, 10.3 Hz, 1H, for terminal vinylic proton at position C)

5.09 (dd, J = 1.7, 17.2 Hz, 1H, for terminal vinylic proton at position B)

6.02 – 5.91 (m, 1H, for internal vinylic proton)

6.13 (d, J = 1.4 Hz, 1H, for olefinic methine proton at position A)

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm (Figure 4.2)

167.89 (for imine carbon at position A)

148.72 (for quaternary carbon at position B)

127.4 (for terminal vinylic carbon)

136.36 (for internal vinylic carbon)

116.1 (for olefinic methine carbon at position E)

53.2 (for allylic methylene carbon at position F)

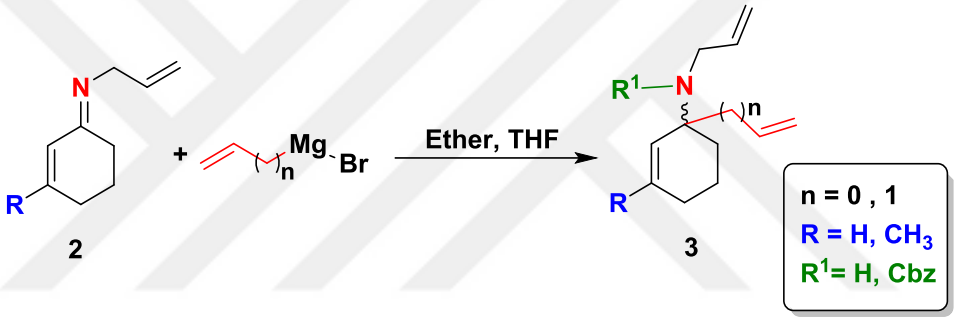
35.0 (for the methylene carbon at position G)

30.4 (for the methylene carbon at position H)

25.7 (for the methylene carbon at position I)

22.1 (for methyl carbon at position J)

3.2.2 Synthesis of Dienes (3) by Grignard Reaction



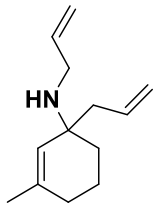
Equation 3.2. Grignard reaction for diene synthesis

General procedure for Grignard reaction with allyl magnesium bromide:

A 100-ml flask was charged with magnesium turnings (2.5 equiv.) with 25 ml of anhydrous diethyl ether the system was closed condenser (Graham condenser) and rubber septum fitted with nitrogen inlet gas (as an inert gas). Allyl bromide (2 equiv.) was added to it. The mixture was allowed to stir for 1.5 hour (Since the reaction start vigorously) at room temperature. After that, the system was cooled down to (0 °C) by putting it in ice bath and imine **2** (1 equiv.) was added drop-wise to it. The mixture was allowed to stir overnight at room temperature. The reaction mixture was hydrolyzed by saturated solution of ammonium chloride (NH_4Cl) followed by extraction the organic phase by diethyl ether (3X) (129). The resulting organic mixture was dried by anhydrous magnesium sulfate ($MgSO_4$) and filtered it. The solvent was removed under vacuum. Column chromatography was used to

purify the crude product using system solvent of (ethyl acetate, hexane and triethylamine) (EtOAc: Hexane: Et_3N) in suitable ratios.

3.2.2.1 N,1-diallyl-3-methylcyclohex-2-en-1-amine (3a)



3a

N,1-diallyl-3-methylcyclohex-2-en-1-amine was obtained as yellow thick oil (1.55 gr) with 75% chemical yield. Chemical formula ($C_{13}H_{21}N$), Molecular Weight: (191.32). The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

Rf = 0.8 (silica gel), (EtOAc: Hexane: Et_3N) (1:1:1%)

IR (neat): 3319, 3074, 2931, 2829, 1639, 1075 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm (Figure 4.3)

5.98 – 5.89 (m, 1H, for internal vinylic proton 1)

5.87 – 5.75 (m, 1H, for internal vinylic proton 2)

5.25 (s, 1H, for the olefinic methine proton 3)

5.18 (dd, J = 1.6, 17.1 Hz, 1H for one of terminal vinylic protons 4)

5.12 (dd, J_1 = 1.6, J_2 = 9.7 Hz, 1H, for the other terminal vinylic proton 4`)

5.05 (dd, J_1 = 1.7, J_2 = 9.7 Hz, 2H for the other terminal vinylic protons 5)

3.11 – 3.3 (m, 2H, for methylene allylic protons at position 6)

2.24 – 2.26 (m, 2H, for methylene allylic protons at position 7)

1.85 – 1.87 (m, 2H, for methylene protons at position 8)

1.56 (s, 3H, for methyl protons 9)

1.63 – 1.50 (m, 4H methylene protons at position 10 and 11)

1.71 (br, for the amine proton)

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm (Figure 4.4)

137.6 (for vinylic carbon at position 1)

136.4 (for vinylic carbon at position 2),

134.6 (for olefinic methine carbon at position 3)

127.6 (for olefinic methine carbon at position 4)

117.9 (for terminal vinylic carbon at position 6)

115.4 (for terminal vinylic carbon at position 5)

77.2 (for the quaternary carbon at position 7)

54.7 (for allylic methylene carbon at position 8)

45.2 (for allylic methylene carbon at position 9)

31.8 (for methylene carbon at position 10)

30.10 (for methylene carbon at position 11)

23.9 (for methylene carbon at position 12)

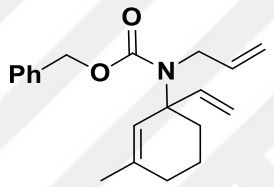
19.7 (for methyl carbon 13)

General procedure for Grignard reaction with vinyl magnesium bromide:

Crude imine **2** was putted in 100-mL flask with 30 mL THF the system was closed with 'Graham condenser' and rubber septum fitted with nitrogen inlet gas.

Benzyl chloroformate (1.5 equiv.) was added to it. The reaction mixture was heated to 60 °C for 2.5 hour (controlled by TLC). Then the crude product was cooled to -78 °C and vinyl magnesium bromide (1 M in THF) was added to it. After that the system was wormed to room temperature with stirring overnight (130). Then the reaction mixture was hydrolyzed by saturated solution of ammonium chloride (NH_4Cl). The organic phase was extracted by ethyl acetate (EtOAc) after that washing it by 20 ml solution of sodium bicarbonate ($NaHCO_3$) and 20 ml brine. Magnesium sulfate was used to dry the final organic mixture and filtered it. The solvent was evaporated by vacuum and the crude product was purified by flash chromatography using system solvent of (EtOAc: Hexane: Et_3N) in suitable ratios.

3.2.2.2 Benzyl allyl(3-methyl-1-vinylcyclohex-2-en-1-yl)carbamate (3b)



3b

Benzyl allyl(3-methyl-1-vinylcyclohex-2-en-1-yl)carbamate was obtained as brown thick oil (1.73 gr) with 69% chemical yield. Chemical formula: ($C_{20}H_{25}NO_2$), Molecular weight: (311.43). The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

Rf = 0.54 (silica gel), (EtOAc: Hexane: Et_3N) (1:5:1%)

IR (neat): 3031, 2930, 2982, 1703, 1641, 1264, 1190 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm (Figure 4.5)

1.15 – 1.95 (m, 2H, for methylene protons 11)

1.71 (s, 3H, for methyl protons)

2.17 – 2.19 (m, 2H, for methylene protons 10)

2.51 – 2.59 (m, 2H, for methylene protons 9)

4.09 (dd, J_1 = 5.0, J_2 = 15.0 Hz, 1H, for one of allylic methylene proton 8)

4.01 (dd, J_1 = 5.1, J_2 = 12.1 Hz, 1H, for the other allylic methylene proton)

4.51 (s, 2H, for benzylic methylene protons 7)

5.10 – 5.13 (m, 2H, for terminal vinylic protons 6 and 6`)

5.12 – 5.35 (m, 1H, for one of terminal vinylic proton 4)

5.16 (dd, J_1 = 4.2, J_2 = 7.3 Hz, 1H, for the other terminal vinylic proton 4`)

5.14 (s, 1H, for the olefinic methine protons 5)

5.48 – 5.53 (m, 1H, for internal vinylic protons 3)

5.65 – 5.89 (m, 1H, for internal vinylic protons 2)

7.34 - 7.41 (m, 5H, for phenyl ring protons)

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm (Figure 4.6)

23.7 (for methylene carbon 18 in cyclohexene ring)

27.4 (for methyl carbon)

29.8 (for methylene carbon at position 16 in cyclohexene ring)

46.1 (for methylene carbon 15 in cyclohexene ring)

52.5 (for allylic carbon at position 14)

66.8 (for quaternary carbon at position 13)

67.2 (for benzylic methylene carbon 12)

116.8 (for terminal vinylic carbon 11)

117.3 (for terminal vinylic carbon 10)

118.7 (for olefinic methine carbon 9)

127.6 (for methine carbon at position 8 of the phenyl ring)

124.4 (for methine carbon at position 8` of the phenyl ring)

127.7 (for methine carbon at position 7 of the phenyl ring)

128.5 (for methine carbon at position 6 of the phenyl ring)

128.3 (for methine carbon at position 6` of the phenyl ring)

128.6 (for internal vinylic carbon 5)

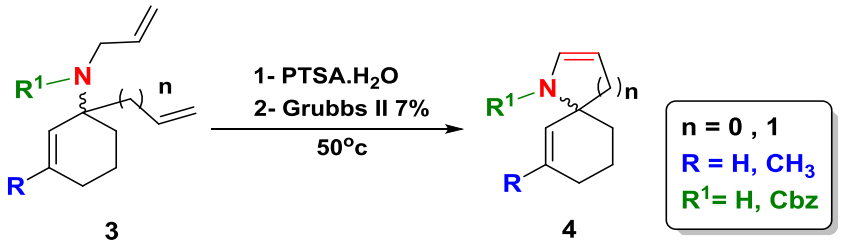
131.0 (for internal vinylic carbon 4)

133.9 (for the quaternary carbon at position 3)

137.4 (for the quaternary carbon at position 2)

154.5 (for ester carbon 1)

3.2.3 Ring Closing Reaction (4)

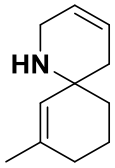


3 4

Equation 3.3. Spirocyclic synthesis by RCM of diene

A diene **3** was putted in 50-ml flask with 30 mL DCM. p-toluensulfonic acid monohydrate (1.1 equiv.) was added to it. The system was closed with rubber septum fitted with nitrogen inlet gas and condenser. The mixture allowed stirring in oil bath at 50 °C for 2 hours. After that, the mixture was cooled down to room temperature and Grubbs 2nd (0.07 equiv.) was added to it. The reaction allowed to stir at room temperature for 48 hours (132). Then 20-30 mL saturated solution of sodium bicarbonate was added followed by solid potassium carbonate (K_2CO_3) until pH = 11. Organic phase was extracted from base solution using DCM. In addition, the organic layer was dried by anhydrous magnesium sulfate ($MgSO_4$) and the solvent was evaporated by vacuum. The desire product was isolated from the crude mixture using column chromatography filled by Silica gel using system solvent of (EtOAc: Hexane: Et_3N) in suitable ratios.

3.2.3.1 8-methyl-1-azaspiro[5.5]undeca-3,7-diene (4a)



4a

8-methyl-1-azaspiro[5.5]undeca-3,7-diene was obtained as dark brown thick oil (1.04 gr) with 81% chemical yield. Chemical formula ($C_{11}H_{17}N$). Molecular weight: (163.26). The product was identified by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy and HRMS.

Rf = 0.11 (silica gel), (EtOAc: Hexane: Et_3N) (1:1:1%)

IR (neat): 3305, 3074, 2901, 2971, 1639, 1075 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm (Figure 4.7)

5.63 (d, J = 11.1 Hz, 1H, for methine proton 1)

5.58 (dt, J_1 = 1.65, J_2 =11.1 Hz, 1H, for olefinic methine proton 2)

5.29 (s, 1H, for olefinic methine proton 3)

3.33 – 3.23 (m, 2H, for diastereotopic methylene protons 4)

1.91 – 1.85 (m, 2H, for methylene protons 5)

1.83 (d, J = 5.3 Hz, 1H, for one of diastereotopic methylene proton 6)

1.80 (d, J = 5.8 Hz, 1H, for the other diastereotopic methylene proton 6)

1.56 (s, 3H, for methyl protons)

1.45 (dd, J_1 = 4.2, J_2 = 8.5 Hz, 2H, for the methylene protons 8)

1.12 – 1.81 (m, 2H, for methylene protons 9)

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm (Figure 4.8)

135.6 (for olefinic methine carbon 1)

127.4 (for olefinic methine carbon 2)

125.4 (for olefinic methine carbon 3)

124.2 (for olefinic methine carbon 4)

49.4 (for the quaternary carbon)

41.3 (for methylene carbon 6)

37.1 (for methylene carbon at position 7)

33.4 (for methylene carbon at position 8)

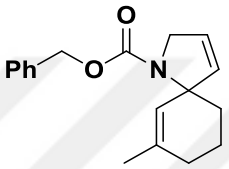
30.5 (for methylene carbon at position 9)

23.9 (for the methyl carbon 10)

19.25 (for the other methylene carbon at position 11)

HRMS: (ESI-TOF)m/z: calculated for $C_{11}H_{18}N$ $[M+H]^+$: 164.1439 and it was found 164.1459.

3.2.3.2 Benzyl 7-methyl-1-azaspiro[4.5]deca-3,6-diene-1-carboxylate (4b)



4b

Benzyl 7-methyl-1-azaspiro[4.5]deca-3,6-diene-1-carboxylate was obtained as dark green thick oil (1.1 gr) with 70% chemical yield. Chemical formula ($C_{18}H_{21}NO_2$). Molecular weight: (238.37). The product was identified by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy:

Rf = 0.7 (silica gel), (EtOAc: Hexane: Et_3N) (1:5:1%)

IR (neat): 3029, 2933, 2989, 1693, 1648, 1252, 1184 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm (Figure 4.9)

1.61 (s, 3H, for methyl protons)

1.62 – 1.68 (m, 2H, for methylene protons 9 in cyclohexene ring)

1.89 – 1.98 (m, 2H, for methylene protons 8 in cyclohexene ring)

2.71 – 2.76 (m, 2H, for methylene protons 7 in cyclohexene ring)

4.64 – 4.6 (m, 2H, for diastereotopic methylene protons 6)

5.21 (s, 2H, for benzylic methylene protons in position 5)

5.71 – 5.81 (m, 1H, for olefinic methine proton 4)

5.99 (t, J = 2.1 Hz, 1H, for the other methine proton 3)

7.15 (ddd, J_1 = 1.2, J_2 = 2.2, J_3 = 8.3 Hz, 1H, for methine proton 2)

7.21 – 7.32 (m, 5H, for phenyl ring protons)

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm (Figure 4.10)

22.5 (for methylene carbon 16 in cyclohexene ring)

26.8 (for the methyl carbon)

27.3 (for methylene carbon 14 in cyclohexene ring)

28.3 (for methylene carbon 13 in cyclohexene ring)

37.5 (for methylene carbon 12)

46.3 (for benzylic methylene carbon 11)

68.6 (for quaternary carbon 10)

120.7 (for methine carbon 9 in cyclohexene ring)

126.6 (for methine carbon 8)

128.5 (for methine carbon 7 in phenyl ring)

128.6 (for methine carbon 7` in phenyl ring)

128.7 (for methine carbon 6 in phenyl ring)

128.8 (for methine carbon 5 in phenyl ring)

128.8 (for methine carbon 5` in phenyl ring)

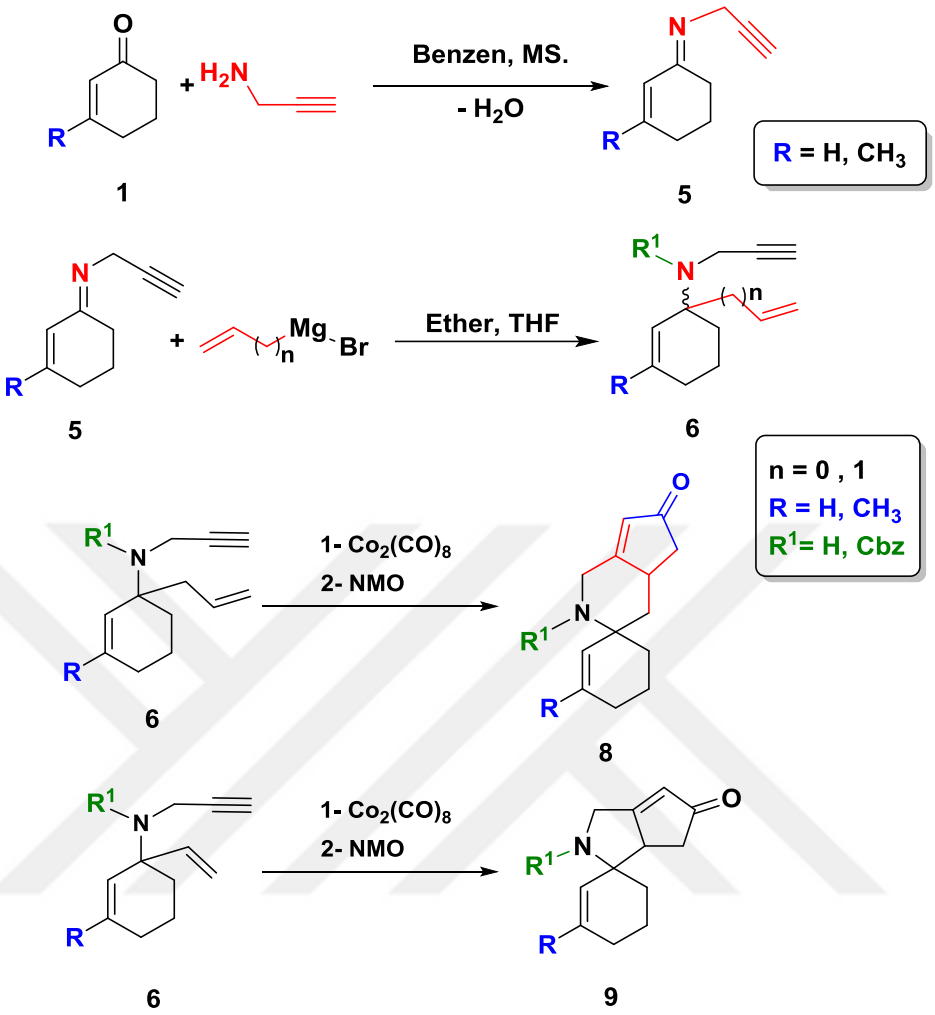
135.1 (for quaternary carbons 4)

136.7 (for quaternary carbons 3)

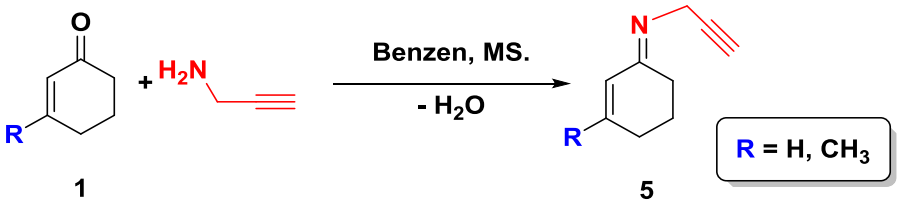
145.7 (for olefinic methine carbon 2)

150.7 (for ester carbon at position 1)

3.3 Research Plan of Pausond-Khand Reaction (PKR)



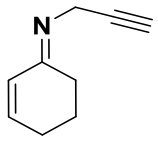
3.3.1 General Procedure for Imine Formation



A 100-ml flask equipped with condenser (Graham condenser), 2.5 cm magnetic stir bar and rubber septum fitted with nitrogen inlet gas is charged with cyclohexenone derivatives **1** (1.5 g., 1 equiv.), propargylamine (2 equiv.), molecular sieves (2.5 g.) and 30 mL benzene. The reaction mixture was heated to 45°C and allowed to stir for 3 days. The resulting brown slurry was filtered and washed by diethyl ether. The solvent removed by vacuum. After that blowing

nitrogen gas on the residue for removing benzene to give crude imine product that used directly without any purification.

3.3.1.1 (*E*)-N-(prop-2-yn-1-yl)cyclohex-2-en-1-imine (5a)



5a

(E)-N-(prop-2-yn-1-yl)cyclohex-2-en-1-imine was obtained as yellow oil. Chemical formula: ($C_9H_{11}N$). Molecular weight: (133.19). The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

IR (neat): 3305, 3041, 2910, 2982, 2130, 1670, 1630, 1072 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm

2.15 (t, J = 2.0 Hz, 1H, for acetylenic proton)

2.29 (dd, J_1 = 2.1, J_2 = 7.9 Hz, 1H, for one of propargylic methylene proton)

2.24 (dd, J_1 = 1.9, J_2 = 7.5 Hz, 1H, for the other propargylic methylene proton)

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm

169.7 (for imine carbon)

130.8 (for methine carbon in cyclohexene ring)

117.0 (for methine carbon in cyclohexene ring)

41.4 (for the propargylic carbon)

80.8 (for internal acetylenic carbon)

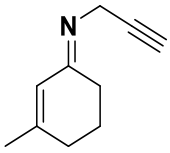
72.3 (for terminal acetylenic carbons)

30.1 (the methylene carbons in the cyclohexene ring)

25.5 (the methylene carbons in the cyclohexene ring)

21.6 (the methylene carbons in the cyclohexene ring)

3.3.1.2 *(E)*-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-imine (5b)



5b

(E)-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-imine was obtained as orange yellow oil, Chemical formula: ($C_{10}H_{13}N$). Molecular weight: (147.22). The product was identified without any purification by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

IR (neat): 3302, 3052, 2900, 2986, 2125, 1661, 1625, 1066 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm (Figure 4.11)

1.81 (d, J = 1.3 Hz, 3H, for methyl protons)

2.10 – 2.14 (m, 2H, for diastereotopic methylene protons at position 6)

2.18 (t, J = 4.6 Hz, 1H, for the acetylenic proton at position 5)

2.21 – 2.23 (m, 2H, for methylene protons at position 4)

2.24 – 2.31 (m, 2H, for methylene protons at position 3)

4.00 (d, J = 2.2 Hz, 2H, for methyl protons)

5.90 (q, J = 1.3 Hz, 1H, for the olefinic methine proton 1)

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm (Figure 4.12)

169.6 (for imine carbon)

149.4 (for the quaternary carbon next to methyl carbon)

115.4 (for olefinic methine carbon at position 3)

70.2 (for the terminal acetylenic carbon)

72.1 (for the internal acetylenic carbon)

36.6 (for the propargylic methylene carbon at position 6)

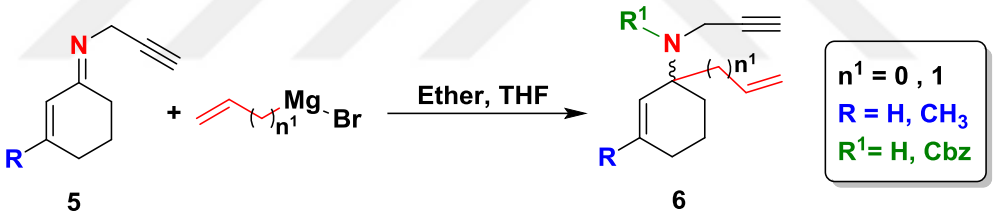
30.5 (for methylene carbons at position 7)

25.4 (for methylene carbons at position 8)

24.1 (for methylene carbons at position 9)

22.1 (for the methyl carbon)

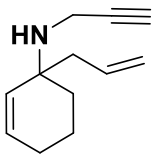
3.3.2 Grignard Reaction



General procedure for Grignard reaction with allyl magnesium bromide:

Grignard reagent was made by adding allyl bromide (2 equiv.) to magnesium turnings (2.5 equiv.) in 25 ml of anhydrous diethyl ether. After that, the system was cooled down to 0 °C. Imine **5** (1 equiv.) was added drop-wise to it. The mixture was allowed to stir overnight at room temperature. Then the reaction mixture was hydrolyzed by saturated solution of ammonium chloride followed by extraction the organic phase by diethyl ether (3X). The resulting organic mixture was dried by anhydrous magnesium sulfate ($MgSO_4$) and filtered it. The solvent was removed under vacuum. Column chromatography was used to purify the crude product using system solvent of (ethyl acetate, hexane and triethylamine) (EtOAc: Hexane: Et_3N) in suitable ratios.

3.3.2.1 1-allyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine (6a)



6a

1-allyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine was obtained as yellow thick oil with 72% chemical yield. Chemical formula ($C_{12}H_{17}N$). Molecular weight: (175.28). The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

Rf = 0.82 (silica gel), (EtOAc: Hexane: Et_3N) (1:1:1%)

IR (neat): 3305, 3074, 2901, 2971, 1639, 1075 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm (Figure 4.13)

1.55 – 1.50 (m, 2H, methylene protons at position 10)

1.70 (ddd, J = 3.7, 7.7 and 8.9 Hz, 2H, for the methylene protons 9)

1.96 (m, 2H, for the methylene protons 8)

2.18 (t, J = 2.5 Hz, 1H, for the acetylenic proton 7)

2.25 – 2.32 (m, 1H, for one of allylic methylene proton 6)

2.22 (dd, J = 4.1 and 8.6 Hz, 1H, for the other allylic methylene proton 6`)

3.34 (dd, J = 0.7 and 2.4 Hz, 2H, for the propargylic methylene protons 5)

5.14 (dddd, J = 1.0, 1.2, 2.0, 15.1 Hz, 1H, for one of terminal vinylic proton 4)

5.05 – 5.09 (m, 1H, for the other terminal vinylic proton 4`)

5.47 (ddd, J = 1.8, 4.8 and 8.1 Hz, 1H, for the other olefinic methine proton 3)

5.75 – 5.81 (m, 1H, for olefinic methine proton 2)

5.87 – 5.82 (m, 1H, for the internal vinylic proton 1)

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm (Figure 4.14)

136.5 (for internal vinylic carbon 1)

133.6 (for olefinic methine carbon 2)

126.5 (for olefinic methine carbon 3)

117.5 (for terminal vinylic carbon 4)

83.0 (for internal acetylenic carbon)

70.1 (for terminal acetylenic carbon 6)

54.5 (for the quaternary carbon)

44.4 (for the allylic methylene carbon 8)

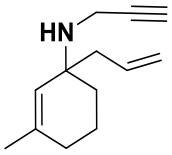
34.7 (for the methylene carbon 9)

31.2 (for the methylene carbon 11)

29.4 (for propargylic methylene carbon)

19.1 (for the methylene carbon 12)

3.3.2.2 1-allyl-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine (6b)



6b

1-allyl-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine was obtained as yellow thick oil with 77% chemical yield. Chemical formula ($C_{13}H_{19}N$). Molecular weight: (189.30). The product was identified by IR, ^{1}H-NMR ^{13}C-NMR spectroscopy and HRMS.

Rf = 0.80 (silica gel), (EtOAc: Hexane: Et_3N) (1:1:1%)

IR (neat): 3311, 3238, 3052, 2901, 2971, 2050, 1102 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm (Figure 4.15)

1.42 – 1.36 (m, 2H, for methylene protons at position 10)

1.49 – 1.51 (m, 2H, for methylene protons at position 9)

1.55 (s, 3H, for methyl protons)

1.72 – 1.77 (m, 2H, for methylene protons at position 7)

2.05 (t, J = 2.4 Hz, 1H, for the acetylenic proton at position 6)

2.10 – 2.15 (m, 2H, for allylic methylene protons at position 5)

3.19 (d, J = 2.5 Hz, 2H, for methylene protons at position 4)

4.95 (dd, J = 1.6 and 7.1 Hz, 1H, for one of terminal vinylic proton 3`)

4.96 – 5.00 (m, 1H, for the other terminal vinylic proton 3)

5.09 (s, 1H, for olefinic methine proton 2)

5.78 – 5.68 (m, 1H, for the internal vinylic proton 1)

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm (Figure 4.16)

136.8 (for internal vinylic carbon at position 1)

133.9 (for olefinic methine carbon at position 2)

126.8 (for olefinic methine carbon at position 3)

117.8 (for terminal vinylic carbon at position 4)

88.3 (for internal acetylenic carbon)

70.4 (for Terminal acetylenic carbon)

54.8 (for quaternary carbon at position 7)

44.4 (for allylic methylene carbon at position 8)

35.0 (for the methylene carbon at position 9)

31.5 (for propargylic methylene carbon 10)

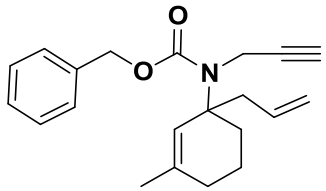
29.8 (for the methylene carbon at position 11)

23.6 (for methyl carbon)

19.5 (for the methylene carbon at position 13)

HRMS: (ESI-TOF)m/z: calculated for $C_{13}H_{20}N$ $[M+H]^+$: (190.1596) found: (190.1613).

3.3.2.3 Benzyl (1-allyl-3-methylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate (Protection) (6c)



6c

Benzyl (1-allyl-3-methylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate was obtained as yellow thick oil with 72% chemical yield. Chemical formula ($C_{21}H_{25}NO_2$). Molecular weight: (323.44). The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR and HRMS.

Rf = 0.54 (silica gel), (EtOAc: Hexane: Et_3N) (1:3:1%)

IR (neat): 3310, 3025, 2911, 2942, 2050, 1699, 1652, 1241 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm (Figure 4.17)

1.21 - 1.30 (m, 2H, for methylene protons at position 12)

1.77 - 1.84 (m, 2H, for methylene protons at position 9)

2.08 (dd, J_1 = 4.8 and J_2 = 8.5 Hz, 2H, for methylene protons 11)

1.72 (s, 3H, for methyl protons)

1.87 – 1.92 (m, 2H, for allylic methylene protons 8)

1.99 – 2.05 (m, 1H, for acetylenic proton 7)

3.94 – 4.14(m, 2H, for propargylic methylene protons 6)

5.00 (d, J = 9.5 Hz, 1H, for one of the benzylic methylene proton 5)

4.97 – 5.00 (m, 1H, for the other benzylic methylene proton 5`)

5.08 (dd, J_1 = 3.3 and J_2 = 9.2 Hz, 1H, for the terminal vinylic proton 4)

5.16 (dd, J_1 = 4.0 and J_2 = 9.2 Hz, 1H, for other terminal vinylic proton 4`)

5.52 (s, 1H, for methine proton 3)

5.67 – 5.78 (m, 1H, for internal vinylic proton 2)

7.41–7.25 (m, 5H, for phenyl ring protons)

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm (Figure 4.18)

18.5 (for methylene carbon at position 19 in cyclohexene ring)

25.5 (for the methyl carbon)

30.4 (for methylene carbon at position 17 in cyclohexene ring)

31.9 (for propargylic methylene carbon at position 16)

36.8 (for allylic methylene carbon at position 15)

38.8 (for methylene carbon at position 14 in cyclohexene ring)

60.8 (for the stereogenic carbon at position 13)

64.1 (for benzylic methylene carbon at position 12)

69.8 (for terminal acetylenic carbon)

70.7 (for internal acetylenic carbon)

81.8 (for terminal vinylic carbon)

118.1 (for olefinic methine carbon at position 8)

127.9 (for the methine carbon at 7 position of the phenyl ring)

128.4 (for the methine carbon at 7` position of the phenyl ring)

128.5 (for the methine carbon at position 6 of the phenyl ring)

128.6 (for the methine carbon at position 6` of the phenyl ring)

128.7 (for the methine carbon at position 5 of the phenyl ring)

129.3 (for internal vinylic carbon)

131.9 (for the quaternary carbon at position 3)

134.2 (for the quaternary carbon at position 2)

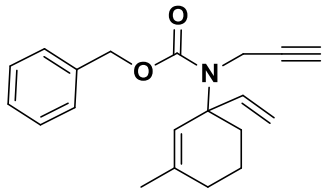
155.2 (for the ester carbon 1)

HRMS: (ESI-TOF)m/z: calculated for $C_{21}H_{26}NO_2$ $[M+H]^+$: (324.1964), and it found (324.1971).

General procedure for Grignard reaction with vinyl magnesium bromide:

Crude imine was putted in 100-mL flask with 30 mL THF the system was closed with 'Graham condenser' and rubber septum fitted with nitrogen inlet gas. Benzyl chloroformate (1.5 equiv.) was added to it. The reaction mixture was heated to 60 °C for 2.5 hours (controlled by TLC). Then the crude product was cooled to -78 °C and vinyl magnesium bromide (1 M in THF) was added to it. After that, the system was wormed to room temperature and allowed to stir overnight. Then the reaction mixture was hydrolyzed by saturated solution of ammonium chloride (NH_4Cl). The organic phase was extracted by (EtOAc). after that washing it by 20 ml solution of sodium bicarbonate ($NaHCO_3$) and 20 ml brine (130)**.** Magnesium sulfate was used to dry the final organic mixture and filtered it by. The solvent was evaporated under vacuum. Column chromatography was used to purify the crude product using system solvent of (EtOAc: Hexane: Et_3N) in suitable ratios.

3.3.2.4 Benzyl (3-methyl-1-vinylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate (6d)



6d

Using system solvent of (EtOAc: Hexane: Et_3N) (1:5:1%). Rf = 0.49

Benzyl (3-methyl-1-vinylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate was obtained as brown oil with 75% chemical yield. Chemical formula: ($C_{20}H_{23}NO_2$), Molecular weight: (309.41). The product was identified by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

Rf = 0.49 (silica gel), (EtOAc: Hexane: Et_3N) (1:5:1%)

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm (Figure 4.19)

1.63 – 1.72 (m, 2H, for methylene protons at position 11)

1.76 (d, J = 1.7 Hz, 3H, for methyl protons)

2.27 (t, J = 2.3 Hz, 1H, for the acetylenic proton)

2.32 – 2.35 (m, 2H, for methylene protons 7)

2.25 – 2.16 (m, 2H, for methylene protons 9)

4.28 (dd, J_1 = 2.4, J_2 = 8.15 Hz, 1H, for one of propargylic methylene proton)

4.20 – 4.25 (m, 1H, for the other propargylic methylene proton 6`)

5.18 (d, J = 2.3 Hz, 2H, for benzylic methylene protons at position 5)

5.38 (dd, J_1 = 2.6 and J_2 = 15.8 Hz, 1H, for one of terminal vinylic proton 4)

5.27 – 5.31 (m, 1H, for the other terminal vinylic proton 4`)

5.82 (s, 1H, for olefinic methine proton 2)

5.69 – 5.52 (m, 1H, for internal vinylic proton)

7.39 – 7.33 (m, 5H, for phenyl ring protons)

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm (Figure 4.20)

21.4 (for methylene carbon at position 18 in cyclohexene ring)

23.8 (for methyl carbon 17)

26.9 (for methylene carbon at position 16 in cyclohexene ring)

29.9 (for methylene carbon at position 15 in cyclohexene ring)

39.6 (for propargylic methylene carbon 14)

67.4 (for stereogenic carbon at position 13)

67.7 (for benzylic methylene carbon at position 12)

72.0 (for terminal acetylenic carbon at position 11)

79.8 (for internal acetylenic carbon at position 10)

112.2 (for terminal vinylic carbon at position 9)

119.4 (for olefinic methine carbon at position 8)

127.8 (for methine carbon at position 7 of the phenyl ring)

127.9 (for methine carbon at position 7` of the phenyl ring)

128.2 (for methine carbon at position 6 of the phenyl ring)

128.6 (for methine carbons at position 5 and 5` of the phenyl ring)

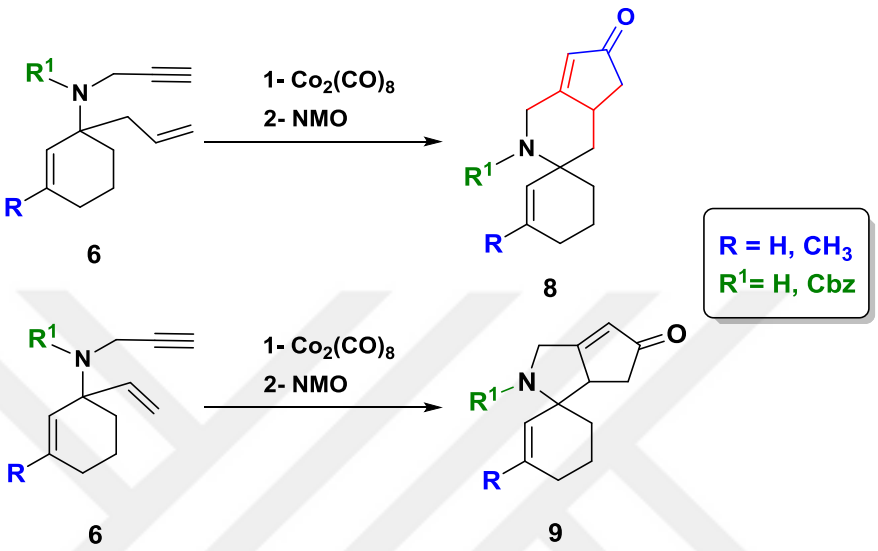
131.2 (for internal vinylic carbon at position 4)

136.3 (for the quaternary carbon at position 3)

142.5 (for the quaternary carbon at position 2)

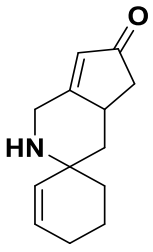
154.5 (for ester carbon at position 1)

3.3.3 General Procedure for Pauson-Khand Reaction



In 50 mL flask, **6** (1 equiv.) was putted in presence of CH_2Cl_2. Dicobalt Octacarbonyl $Co_2(CO)_8$ (1.8 equiv.) with 5 ml DCM was added to it. The reaction mixture allowed stirring for 2.5 h. (controlled by TLC). After that, NMO (10 equiv.) was added to it and the reaction mixture allowed to stir overnight (133). The final product was purified by flash column chromatography used (EtOAc: Hexane: Et_3N) as eluent in suitable ratios.

3.3.3.1 1',2',4a',5'-tetrahydrospiro[cyclohexane-1,3'-cyclopenta [c]pyr-idin]-2-en-6'(4'H)-one (8a)



8a

1',2',4a',5'-tetrahydrospiro[cyclohexane-1,3'-cyclopenta[c]pyr-idin]-2-en-6'(4'H)-one was obtained as dark red thick oil with 67% chemical yield. Chemical

formula ($C_{13}H_{17}NO$). Molecular weight: (203.29). The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

Rf = 0.49 (silica gel), (EtOAc: Hexane: Et_3N) (1:1:1%)

IR (neat): 3310, 3074, 2915, 2929, 1637, 1677, 1075, 1241 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm

0.85 – 0.94 (m, 2H, for methylene protons at position 10)

1.09 – 1.15 (m, 2H, for methylene protons at position 9)

1.62 (dd, J_1 = 3.8, J_2 = 9.2 Hz, 1H, for one of diastereotopic methylene proton at position 8 in tetrahydropyridine ring)

1.53 (dd, J_1 = 3.6, J_2 = 8.9 Hz, 1H, for the other diastereotopic methylene proton at position 8` in tetrahydropyridine ring)

1.85 – 1.91 (m, 2H, for methylene protons at position 7)

2.01 – 2.28 (m, 2H, for methylene protons at position 6)

2.85 – 3.02 (m, 1H, for methine proton at position 5)

3.75 (d, J = 3.2 Hz, 1H, for one of methylene proton at position 4 in tetrahydropyridine ring)

3.90 (d, J = 3.1 Hz, 1H, for the other methylene proton at position 4` in tetrahydropyridine ring)

5.05 (d, J = 7.3 Hz, 1H, for olefinic methine proton 3 in cyclohexene ring)

5.65 – 5.85 (m, 1H, for the other olefinic methine proton 2)

5.99 (s, 1H, for methine proton 1)

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm

26.9 (for the methylene carbon at position 13 in cyclohexene ring)

32.7 (for the methylene carbon at position 12 in cyclohexene ring)

42.1 (for the methylene carbon at position 11 in cyclohexene ring)

43.3 (for the stereogenic carbon at position 10)

50.8 (for methylene carbons at position 8 in tetrahydropyridine ring)

55.2 (for methylene carbons at position 7 in tetrahydropyridine ring)

47.4 (for methylene carbon at position 9)

62.3 (for quaternary carbon at the position 6)

120.3 (for methine carbons at position 5 in cyclohexene ring)

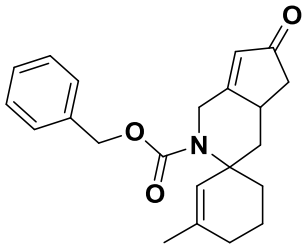
135.2 (for methine carbons at position 4 in cyclohexene ring)

137.2 (for methine carbon at position 3)

172.2 (for the quaternary carbons at positions 2)

201.5 (for carbonyl carbon 1)

3.3.3.2 Benzyl 3-methyl-6'-oxo-4',4a',5',6'-tetrahydrospiro[cyclohexane-1,3'-cyclopenta[c]pyridin]-2-ene-2'(1'H)-carboxylate (8b)



8b

Benzyl 3-methyl-6'-oxo-4',4a',5',6'-tetrahydrospiro[cyclohexane-1,3'-cyclopenta[c]pyridin]-2-ene-2'(1'H)-carboxylate was obtained as yellow thick oil with

75% chemical yield. Chemical formula ($C_{22}H_{25}NO_3$). Molecular weight: (351.45). The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

Rf = 0.64 (silica gel), (EtOAc: Hexane: Et_3N) (1:1:1%)

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm (Figure 4.21)

1.80 – 1.82 (m, 2H, for methylene protons 12 in cyclohexene ring)

1.92 - 1.94 (m, 2H, for methylene protons 11 in cyclohexene ring)

1.96 (s, 3H, for the methyl protons)

2.29 (dd, J_1 = 2.4, J_2 = 4.7 Hz, 2H, for methylene protons at position 9 in tetrahydropyridine ring)

2.33 (dd, J_1 = 2.9, J_2 = 4.1 Hz, 2H, for methylene protons at position 8)

2.36 (d, J = 4.3 Hz, 2H, for methylene protons at position 7)

2.39 – 2.41 (m, 1H, for the methine proton at position 6)

4.12 (d, J = 3.5 Hz, 1H, for one of methylene proton 5)

4.10 (d, J = 3.5 Hz, 1H, for the other methylene proton 5`)

4.86 (s, 2H, for benzylic methylene protons 4)

5.22 (s, 1H, for olefinic methine proton at position 3)

5.87 (s, 1H, for methine proton at position 2)

7.27 – 7.41 (m, 5H, for phenyl ring protons)

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm (Figure 4.22)

18.6 (for the methylene carbon at position 20 in cyclohexene ring)

24.0 (for the methyl carbon)

24.3 (for the methylene carbon at position 18 in cyclohexene ring)

30.2 (for the methylene carbon at position 17 in cyclohexene ring)

30.4 (for the stereogenic carbon at position 16)

31.7 (for the methylene carbon at position 15 of the tetrahydropyridine ring)

37.1 (for methylene carbon at position 14)

53.7 (for the methylene carbon at position 13 of the tetrahydropyridine ring)

54.5 (for quaternary carbon at the position 12)

72.4 (for benzylic methylene carbon 11)

125.8 (for olefinic methine carbon at position 10)

126.7 (for methine carbon at position 9 of the phenyl ring)

126.8 (for methine carbon at position 9` of the phenyl ring)

127.8 (for methine carbon at position 8 of the phenyl ring)

127.6 (for methine carbon at position 7)

128.7 (for methine carbon at position 6 of the phenyl ring)

128.5 (for methine carbon at position 6` of the phenyl ring)

134.5 (for the quaternary carbon at position 5)

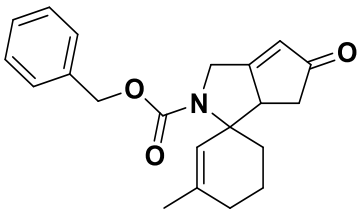
136.7 (for the quaternary carbon at position 4 of cyclohexene ring)

139.9 (for the quaternary carbon at position 3)

163.8 (for ester carbon at position 2)

203.5 (for carbonyl carbon at position 1)

3.3.3.3 Benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'H-spiro[cyclohe-xane-1,1'-cyclopenta[c]pyrrol]-2-ene-2'-carboxylate (9a)



9a

Benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'H-spiro[cyclohe-xane-1,1'-cyclopenta[c]pyrrol]-2-ene-2'-carboxylate was obtained as dark brown thick oil with 65% chemical yield. Chemical formula ($C_{21}H_{23}NO_3$). Molecular weight: (337.42). The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR and HRMS.

Rf = 0.49 (silica gel), (EtOAc: Hexane: Et_3N) (1:2:1%)

IR (neat): 3010, 2924, 2968, 1697, 1645, 1278, 1213 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm (Figure 4.23)

0.9 – 1.45 (m, 2H, for methylene protons at position 11)

1.97 – 2.14 (m, 2H, for methylene protons at position 9)

1.22 (s, 3H, for methyl protons at position 10)

1.68 – 1.76 (m, 1H, for one of diastereotopic methylene proton at position 8 in tetrahydropyridine ring)

1.62 (ddd, J_1 = 2.8, J_2 = 7.1, J_3 = 11.5 Hz, 1H, for the other diastereotopic methylene proton at position 8 in tetrahydropyridine ring)

2.23 (dd, J_1 = 10.9, J_2 = 5.7 Hz, 1H, for one of the diastereotopic methylene proton at position 7)

2.48 (dd, J_1 = 2.8, J_2 = 10.0 Hz, 1H, for the other diastereotopic methylene proton at position 7)

3.70 – 4.12 (m, 1H, for the methine proton at position 6)

4.46 (d, J = 3.9 Hz, 1H, for one of the diastereotopic proton at position 5)

4.8 (d, J = 2.0 Hz, 1H, for the other diastereotopic proton at position 5)

5.15 (d, J = 16.2 Hz, 2H, for benzylic methylene protons at position 4)

5.74 – 5.37 (m, 1H, for olefinic methine proton at position 3)

6.04 (d, J = 2.9 Hz, 1H, for methine proton at position 2)

7.57 – 7.06 (m, 1H, for phenylic ring protons)

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm (Figure 4.24)

21.1 (for methylene carbon at position 19 of the cyclohexene ring)

24.0 (for the methyl carbon)

27.5 (for methylene carbon at position 17 of the cyclohexene ring)

29.7 (for methylene carbon at position 16 of the cyclohexene ring)

31.1 (for methylene carbon at position 15)

46.9 (for the stereogenic carbon at position 14)

49.1 (for methylene carbon at position 13)

54.6 (for the quaternary carbon at position 12)

67.3 (for benzylic methylene carbon at position 11)

123.7 (for methine carbon at position 10 of the cyclohexene ring)

128.2 (for methine carbon at position 9 of the phenyl ring)

128.1 (for methine carbon at position 9` of the phenyl ring)

128.3 (for methine carbon at position 8 of the phenyl ring)

128.5 (for methine carbon at position 7 of the phenyl ring)

128.4 (for methine carbon at position 7` of the phenyl ring)

128.7 (for methine carbon at position 6)

136.5 (for the quaternary carbon at position 5 of the cyclohexene ring)

142.3 (for the quaternary carbon at position 4 of the phenyl ring)

171.7 (for ester carbon at position 3)

152.6 (for the quaternary carbon at position 2)

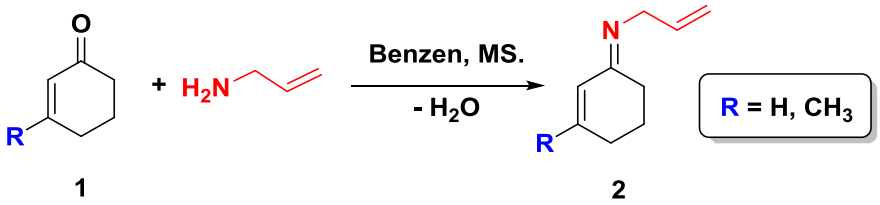
213.2 (for carbonyl carbon at position 1)

HRMS: (ESITOF)m/z: was calculated for $C_{21}H_{24}NO_3$ $[M+H]^+$: (338.1756) was found as (338.1784).

4. RESULTS AND DISCUSSION

4.1 Result and discussion for RCM product

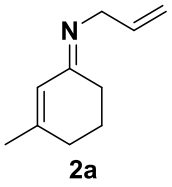
4.1.1 General procedure for imine formation (2)



Equation 4.1. Synthesis of imine for RCM

Ketones can react very slowly with amine to form imines. This reaction can occur in high temperature, long reaction time, removing water, and in presence of acidic catalyst (pH 4 – 6) to dehydrate carbinolamine as intermediate to form imine (134) (135). Molecular sieves were added to the reaction for water retention and react as acid catalysts to facilitate the carbonyl compound for the nucleophilic attack (136). Thus, cyclohexene derivatives (**1**), was reacted with allylamine in presence of molecular and benzene. The reaction mixture heated to 45 °C and allowed to stir for 3 days. The resulting brown slurry was vacuum filtered and washed with diethyl ether. The solvent removed by vacuum. After that blowing the solution by nitrogen gas on the residue for benzene removing to give crude imine product that used directly without any purification.

4.1.1.1 (*E*)-N-allyl-3-methylcyclohex-2-en-1-imine (2a)



(E)-N-allyl-3-methylcyclohex-2-en-1-imine (**2a**) was obtained as orange yellow oil, Chemical Formula ($C_{10}H_{15}N$), molecular weight: (149.24). The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

When we compared IR spectra of Cyclohexenone and our desire product it showed that there is a new peak at (1680) cm^{-1} for C=N instead of the C=O at (1710) cm^{-1}.

^{1}H-NMR: In the spectrum of (*E*)-N-allyl-3-methylcyclohex-2-en-1-imine there is difficulty in identification of the signals because the imine product is not pure (crude imine). However, the spectrum shows multiplet between 1.79 – 1.68 ppm due to the diastereotopic methylene protons at I position. Methyl protons at H position show doublet at 1.81 ppm with J = 1.4 Hz. Furthermore, the diastereotopic methylene protons at G position show multiplet between 2.16 – 2.04 ppm. Multiplet between 2.28 – 2.31 ppm for methylene protons at F position. At 3.98 ppm there is doublet of doublets for allylic methylene protons at E position with J_1 = 5.7 and J_2 =20.6 Hz. In addition, each of terminal vinylic protons at position C and B show doublet of doublets at 5.03 ppm with J_1 = 1.4, J_2 =10.3 Hz and at 5.09 ppm with J_1 = 1.7, J_2 = 17.2 Hz respectively. The internal vinylic proton shows multiplet between 5.91 - 6.02 ppm. Finally, olefinic methine proton A exhibits doublet at 6.13 ppm with J = 1.4 Hz.

^{13}C-NMR: The spectrum of (*E*)-N-allyl-3-methylcyclohex-2-en-1-imine shows signal at 167.8 ppm for imine carbon A. The quaternary carbon B shows signal at 148.7 ppm. Moreover, terminal and internal vinylic carbons show signals at 127.4, and 136.4 ppm respectively. The olefinic methine carbon (position E) gives signal at 116.1 ppm. In addition, allylic methylene carbon in position F shows signal at 53.2 ppm. Furthermore, the methylene carbons in position I, H and G show signals at 25.7 ppm 30.4 ppm and 35.0 ppm respectively. Finally, methyl carbon J shows signal at 22.1 ppm.

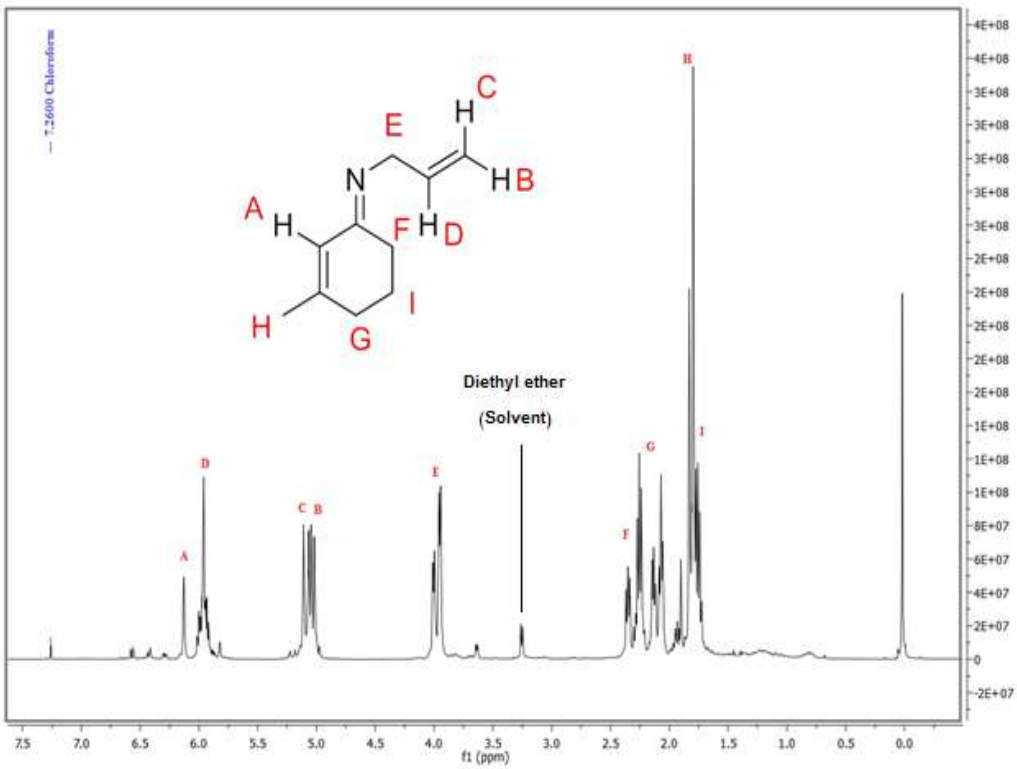


Figure 4.1. ^{1}H-NMR spectrum of (*E*)-N-allyl-3-methylcyclohex-2-en-1-imine

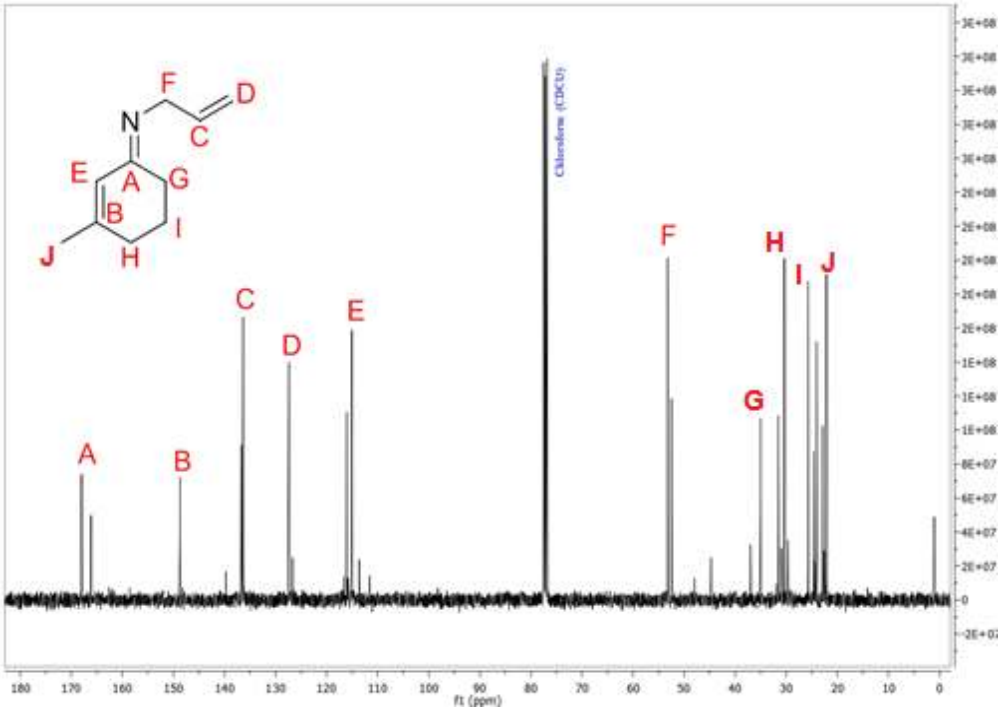
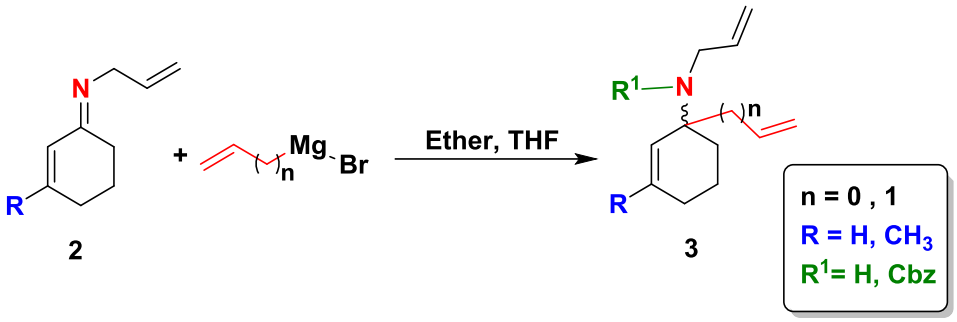


Figure 4.2. ^{13}C-NMR spectrum of (*E*)-N-allyl-3-methylcyclohex-2-en-1-imine

4.1.2 Synthesis of Dienes (3) by Grignard Reaction



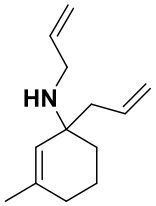
Equation 4.2. Grignard Reaction for Diene Synthesis

General procedure for Grignard reaction with Allyl magnesium bromide:

Imine can react with allyl magnesium bromide (Grignard reagent) by nucleophilic attack on the carbon (C=N) double bonds. This reaction has low yield but very good selectivity due to the poor electrophilicity of imine-carbon (137). This problem relatively solved by adding excess amount of magnesium when making Grignard reagent this amount can react directly with releasing bromide to produce Lewis acid that activate nucleophilic addition of imine carbon (138). Ether and THF were used as aprotic solvent in these reactions because they can solvate the Mg ion that coordinate to the ether lone-pair electrons (139).

Grignard reagent was made by adding allyl bromide to Magnesium turnings in presence of anhydrous diethyl ether. After that, the system was cooled down to (0 °C) and imine (crude) (**2**) was added drop-wise to it. The mixture was allowed to stir overnight at room temperature. After workup, crude product was purified by flash chromatography with mixture of (ethyl acetate, hexane and triethylamine) in suitable ratios.

4.1.2.1 N,1-diallyl-3-methylcyclohex-2-en-1-amine (3a)



3a

The product was purified by column chromatography using system solvent of (EtOAc: Hexane: Et_3N) (1:1:1%). Rf = 0.8

N,1-diallyl-3-methylcyclohex-2-en-1-amine 3a was obtained as yellow thick oil with 75% chemical yield. Chemical formula ($C_{13}H_{21}N$). Molecular weight: (191.32). The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. Spectrum of N,1-diallyl-3-methylcyclohex-2-en-1-amine, shows new double bonds on position 2,5, and 5` with new allylic group at position 7 in addition of the allyl group from imine compound and the broad signal at 1.71 ppm for (>N-H). The imine carbon signal disappear and instead of it, the quaternary carbon signal appeared. All these approve that the imine compound had changed to diene.

IR: (3319) cm^{-1} for >N-H, (3074) cm^{-1} for C_{SP}^2 –H, (2931) cm^{-1} for C_{SP}^3 –H, (2829) cm^{-1} for -CH_3, (1639) cm^{-1} for >C=CH_2, and at (1075) cm^{-1} for C_{SP}^3 –N<

^{1}H-NMR: The spectrum of N,1-diallyl-3-methylcyclohex-2-en-1-amine shows multiplet between 5.98 – 5.89 ppm for internal vinylic proton 1. In addition, there is multiplet between 5.87 – 5.75 ppm for internal vinylic proton 2. Singlet at 5.25 ppm for the olefinic methine proton 3. One of terminal vinylic protons 4 exhibits doublet of doublet, at 5.18 ppm with J_1 = 1.6 Hz and J_2 = 17.1 Hz. The other terminal vinylic proton exhibits doublet of doublet at 5.12 ppm with J_1 = 1.6 Hz and J_2 = 9.7 Hz. The other terminal vinylic protons 5 and 5` exhibit doublet of doublet at 5.05 ppm with J_1 = 1.7 and J_2 = 9.7 Hz. Methylene allylic protons at position 6 and 7 show multiplet between 3.11 – 3.3 ppm and between 2.24 – 2.26 ppm respectively. Furthermore, multiplet between 1.85 – 1.87 ppm is due to methylene protons at position 8. Singlet at 1.56 ppm for methyl protons 9. Finally, methylene protons at position 10 and 11 overlapped between 1.63 – 1.50 ppm (two protons each of them).

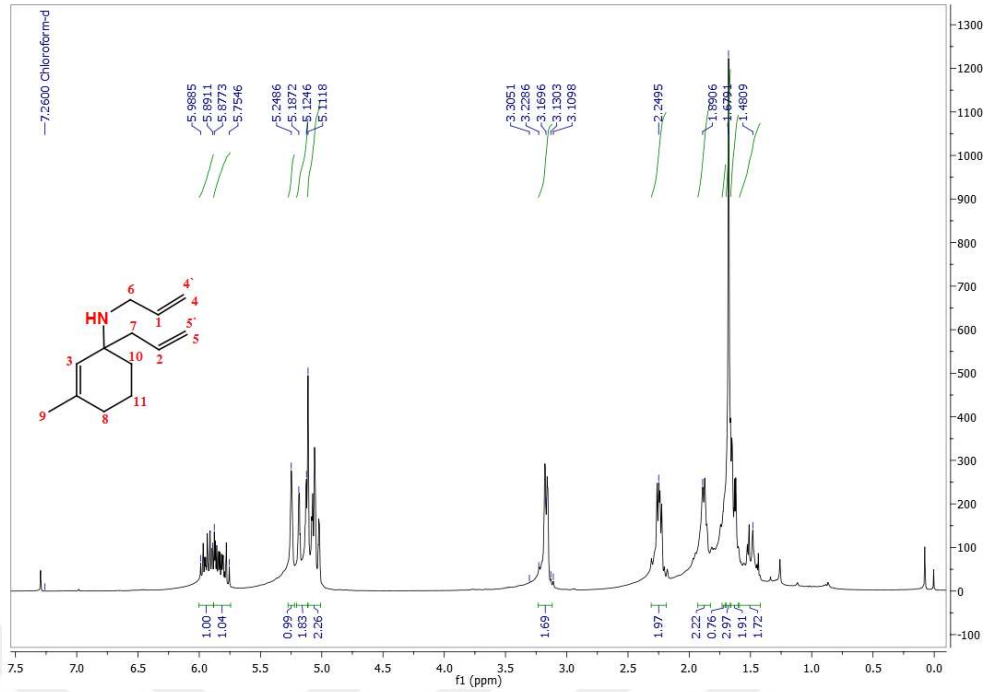


Figure 4.3. ^{1}H-NMR spectrum of N,1-diallyl-3-methylcyclohex-2-en-1-amine

^{13}C-NMR: The spectrum of N,1-diallyl-3-methylcyclohex-2-en-1-amine shows signals at 137.6, 136.4, 134.6, and 127.6 ppm for vinylic carbons 1, 2, olefinic methine carbons 3 and 4 respectively. Terminal vinylic carbon 6 and 5 exhibit signals at 117.9 ppm and at 115.4 ppm respectively. Furthermore, the quaternary carbon 7 shows signal at 77.2 ppm. The allylic methylene carbons 8 and 9 show signals at 54.7 ppm and 45.2 ppm respectively. Moreover, methylene carbons at position 10, 11, and 12 show signals at 31.8 ppm, 30.1 ppm and 23.9 ppm respectively. Finally, methyl carbon 13 shows signal at 19.7 ppm.

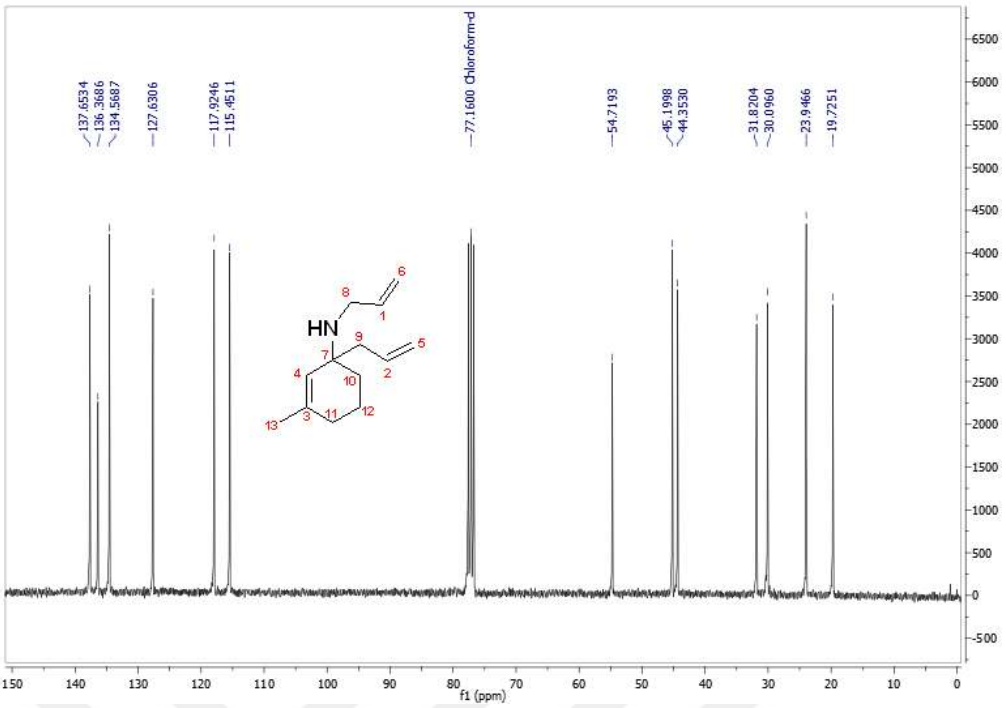


Figure 4.4. ^{13}C-NMR spectrum of N,1-diallyl-3-methylcyclohex-2-en-1-amine

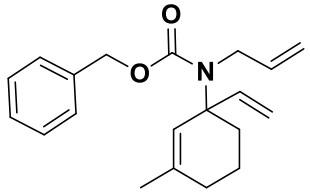
General procedure for Grignard reaction with vinyl magnesium bromide

Crude imine was added with THF to benzyl chloroformate. The reaction mixture was heated to 60 °C for 2.5 h (controlled by TLC). Then the crude product was cooled to -78 °C and vinyl magnesium bromide was added to it. After that, the system was wormed to room temperature with stirring overnight. Then the reaction mixture was hydrolyzed by saturated solution of ammonium chloride (NH_4Cl). The organic phase was extracted by ethyl acetate (EtOAc). After that washing it by solution of sodium bicarbonate ($NaHCO_3$) and brine. The organic phase was extracted and dried by magnesium sulfate and filtered it (130). The solvent was removed under vacuum and the crude product was purified by column Chromatography (Silica gel, eluent: EtOAc: Hexane: Et_3N) in suitable ratios.

The Following compounds that obtained by this reaction were performed and approved by showing new signal around ~1690 cm^{-1} for new carbonyl group in IR spectra. Moreover, signal between 150 – 160 ppm owned to carbonyl carbon. Imine carbon signal disappear and instead of it, the quaternary carbon signal

appeared in ^{13}C-NMR. Finally, in ^{1}H-NMR new phenyl signals around 7-ppm region and new two vinylic protons around 5 – 5.5 ppm with new methylene protons due to benzyl group. All these approve that the imine compound had changed to diene.

4.1.2.2 Benzyl allyl(3-methyl-1-vinylcyclohex-2-en-1-yl)carbamate (3b)



3b

The product was purified by column chromatography using system solvent of (EtOAc: Hexane: Et_3N) (1:5:1%). (Rf = 0.55).

Benzyl allyl(3-methyl-1-vinylcyclohex-2-en-1-yl)carbamate **3c** was obtained as brown thick oil with 69% chemical yield. Chemical formula: ($C_{20}H_{25}NO_2$), Molecular weight: (311.43). The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

IR: (3031) cm^{-1} for C_{SP}^2 –H, (2930) cm^{-1} for C_{SP}^3 –H, (2982) cm^{-1} for -CH_3, (1703) cm^{-1} for >C=O, (1641) cm^{-1} for >C=CH_2, C_{SP}^2 –O at (1264) cm^{-1}. Finally, at (1190) cm^{-1} for C_{SP}^3 –N<.

^{1}H-NMR: The spectrum of benzyl allyl(3-methyl-1-vinylcyclohex-2-enyl) carbamate shows multiplet between 1.15 – 1.95 ppm for methylene protons 11. The methyl protons show singlet at 1.71 ppm. Moreover, methylene protons 10 show multiplet between 2.17 – 2.19 ppm. The same with methylene protons 9 show multiplet between 2.51 – 2.59. In addition, one of allylic methylene proton 8 shows doublet of doublet at 4.09 ppm with J_1 = 5.0, J_2 = 15.0 Hz, and the other allylic methylene proton shows doublet of doublet at 4.01 ppm with J_1 = 5.1, J_2 = 12.1 Hz. Benzylic methylene protons 7 show singlet at 4.51 ppm. Furthermore, terminal vinylic protons 6 and 6` are overlapped between 5.10 – 5.13 ppm. One of terminal vinylic proton 4 exhibits multiplet between 5.12 – 5.35 ppm, and the other one exhibits doublet of doublet at 5.16 ppm with J = 4.2 and 7.3 Hz. Moreover, singlet

at 5.14 ppm is due to olefinic methine protons 5. Each of internal vinylic protons 3 and 2 show multiplet between 5.48 – 5.53 ppm, and 5.65 – 5.89 ppm respectively. Finally, phenyl ring protons show multiplet between 7.34 - 7.41 ppm.

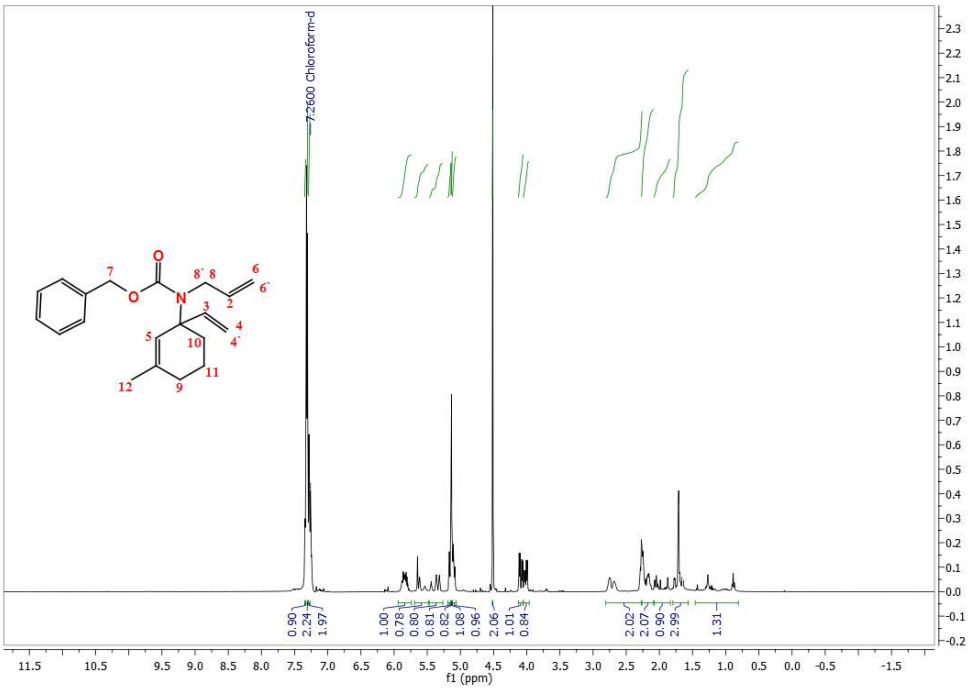


Figure 4.5. ^{1}H-NMR spectrum of benzyl allyl(3-methyl-1-vinylcyclohex-2-en-1-yl) carbamate

^{13}C-NMR: The spectrum of benzyl allyl(3-methyl-1-vinylcyclohex-2-en-1-yl)carbamate shows signals at 23.7, 29.8 and 46.1 ppm are due to the methylene carbons 18, 16 and 15 in cyclohexene ring respectively. The methyl carbon 17 shows signal at 27.4 ppm. The signal at 52.5 ppm for allylic carbon 14. The quaternary carbons 13 shows signal at 66.8 ppm. In addition, signal at 67.2 ppm due to benzylic methylene carbon 12. Terminal vinylic carbons 11 and 10, exhibit signals at 116.8 and 117.3 ppm respectively. Moreover, signal at 118.7 ppm due to the olefinic methine carbon 9. Methine carbons 8, 8`, 7, 6 and 6` of the phenyl ring exhibit signals at 127.6, 124.4, 127.7, 128.5, and 128.3 ppm respectively. Furthermore, internal vinylic carbons 5 and 4 show signals at 128.6 and 131.0 ppm respectively. The quaternary carbons 3 and 2 exhibit signals at 133.9 and 137.4 ppm. Finally, the signal at 154.5 ppm is due to ester carbon 1.

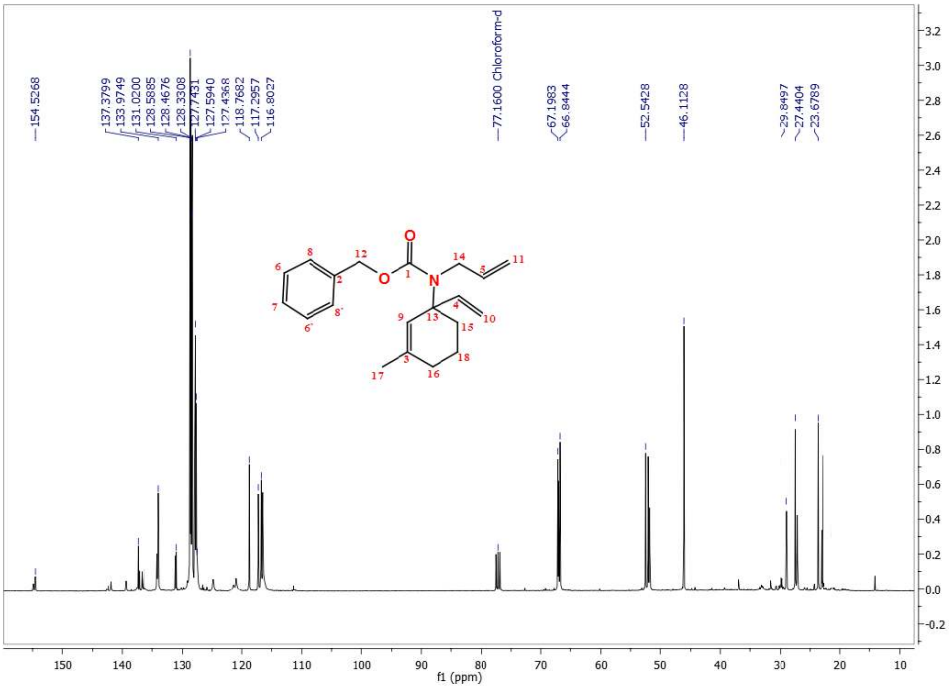
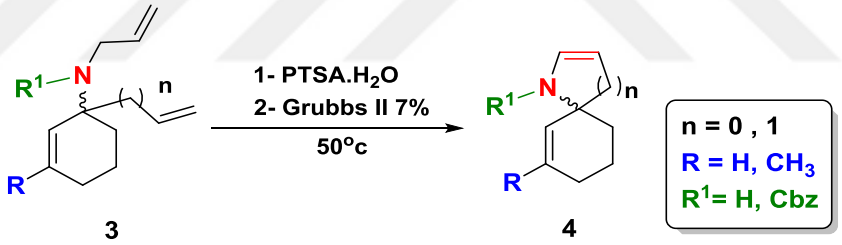


Figure 4.6. ^{13}C-NMR spectrum of Benzyl allyl(3-methyl-1-vinylcyclohex-2-en-1-yl) carbamate

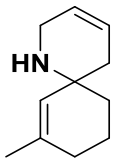
4.1.3 General procedure for Ring Closing Reaction (4)



Equation 4.3. Spirocyclic Synthesis by RCM of Diene

A diene **3** was reacted with p-toluensulfonic acid monohydrate in DCM. The mixture allowed to stirring for 2 hour at 50 °C. After that, the mixture was cooled down to room temperature and Grubbs 2nd was added to it. The reaction mixture was allowed stirring at room temperature for 48 hour. Then saturated solution of sodium bicarbonate ($NaHCO_3$) was added followed by solid potassium carbonate (K_2CO_3) until pH = 11. Organic phase was extracted from base solution and dried by anhydrous magnesium sulfate. The solvent was evaporated under vacuum. Finally, the desire product was isolated from the crude mixture using column chromatography filled by Silica gel and the mobile phase is (EtOAc: Hexane: Et_3N) in suitable ratios.

4.1.3.1 8-methyl-1-azaspiro[5.5]undeca-3,7-diene (4a)



4a

The product was purified by column chromatography using system solvent of (EtOAc: Hexane: Et_3N) (1:1:1%). Rf = 0.11.

8-methyl-1-azaspiro[5.5]undeca-3,7-diene was obtained as dark brown thick oil with 81% chemical yield. Chemical formula ($C_{11}H_{17}N$). Molecular weight: (163.26).

The product was identified by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy and HRMS. It shows three olefinic methine position instead of three C=C double bond position in diene in addition of the same number of allylic positions comparing with diene starting material.

IR: (3305) cm^{-1} for >N-H, (3074) cm^{-1} for C_{SP}^2 –H, (2901) cm^{-1} for C_{SP}^3 – H, (2971) cm^{-1} for -CH_3, (1639) cm^{-1} for >C=CH_2, and at (1075) cm^{-1} for C_{SP}^3 –N<.

^{1}H-NMR: The spectrum of 8-methyl-1-azaspiro[5.5]undeca-3,7-diene shows doublet at 5.63 ppm with J = 11.1 Hz for methine proton 1. In addition, there is doublet of triplets at 5.58 ppm for olefinic methine proton 2 with J_1 = 1.65, J_2 =11.1 Hz. Singlet at 5.29 ppm due to olefinic methine proton 3. Diastereotopic methylene protons 4 show multiplet between 3.33 – 3.23 ppm. Moreover, multiplet between 1.91 – 1.85 ppm for methylene protons 5. One of diastereotopic methylene proton 6 exhibits doublet at 1.83 ppm with J = 5.3 Hz, and the other one shows doublet at 1.80 ppm with J = 5.8 Hz. Furthermore, singlet at 1.56 ppm due to methyl protons. Finally, doublet of doublets at 1.45 ppm with J_1 = 4.2 and J_2 = 8.5 Hz for the methylene protons 8, and multiplet between 1.12 – 1.81 ppm due to methylene protons 9.

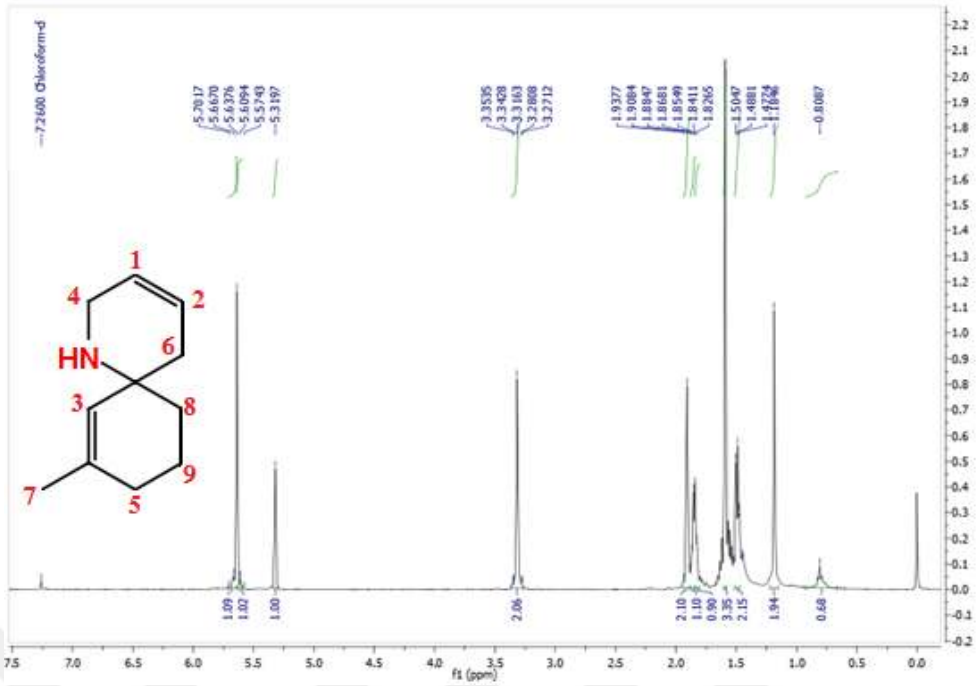


Figure 4.7. ^{1}H-NMR spectrum of 8-methyl-1-azaspiro[5.5]undeca-3,7-diene

^{13}C-NMR: The spectrum of 8-methyl-1-azaspiro[5.5]undeca-3,7-diene shows signals at 135.6, 127.4, 125.4, and 124.2 ppm for olefinic methine carbons 1, 2, 3, and 4 respectively. The quaternary carbon shows signal at 49.4 ppm. Moreover, methylene carbons 6, 8 and 9 show signals at 41.3, 33.4 and 30.5 ppm. The methylene carbon at position 7 shows signal at 37.1 ppm. The other methylene carbon 11 shows signal at 19.25 ppm. Finally, the methyl carbon 10 shows signal at 23.9 ppm.

HRMS: (ESI-TOF)m/z: calculated for $C_{11}H_{18}N$ $[M+H]^+$: 164.1439 and it was found 164.1459.

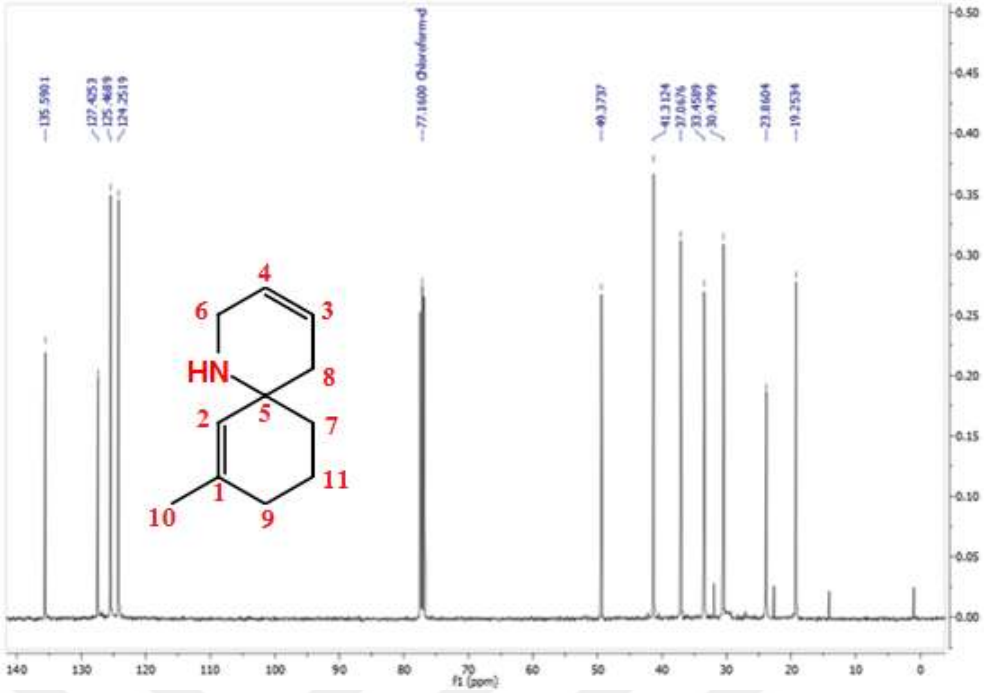
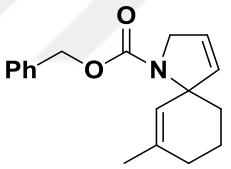


Figure 4.8. ^{13}C-NMR spectrum of 8-methyl-1-azaspiro[5.5]undeca-3,7-diene

4.1.3.2 Benzyl 7-methyl-1-azaspiro[4.5]deca-3,6-diene-1-carboxylate (4b)



4b

The product was purified by column chromatography using system solvent of (EtOAc: Hexane: Et_3N) (1:5:1%). Rf = 0.7

Benzyl 7-methyl-1-azaspiro[4.5]deca-3,6-diene-1-carboxylate was obtained as dark green thick oil with 81% chemical yield. Chemical formula ($C_{18}H_{21}NO_2$). Molecular weight: (238.37).

The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR and HRMS.

IR: (3029) cm^{-1} for C_{SP}^2 –H, (2933) cm^{-1} for C_{SP}^3 –H, (2989) cm^{-1} for -CH_3, (1693) cm^{-1} for >C=O, (1648) cm^{-1} for >C=CH_2, C_{SP}^2 –O at (1252) cm^{-1}. Finally, at (1184) cm^{-1} for C_{SP}^3 –N<.

^{1}H-NMR: The spectrum of benzyl 7-methyl-1-azaspiro[4.5]deca-3,6-diene-1-carboxylate shows singlet for methyl protons at 1.61 ppm. Each of methylene protons 7, 8 and 9 in cyclohexene ring exhibit multiplet between 2.71 – 2.76 ppm, 1.89 – 1.98 ppm, and 1.61 – 1.68 ppm respectively. Diastereotopic methylene protons 6 show multiplet between 4.64 – 4.6 ppm. Moreover, singlet at 5.21 ppm is due to benzylic methylene protons in position 5. Furthermore, olefinic methine proton 4 exhibits multiplet 5.71 – 5.81 ppm. The other methine proton 3 shows triplet at 5.99 ppm with J = 2.1 Hz. On the other hand, methine proton 2 shows doublet of doublet of doublet at 7.15 ppm with J_1 = 1.2 Hz, J_2 = 2.2 and J_3 = 8.3 Hz. Finally, phenyl ring protons exhibit multiplet between 7.21 – 7.32 ppm.

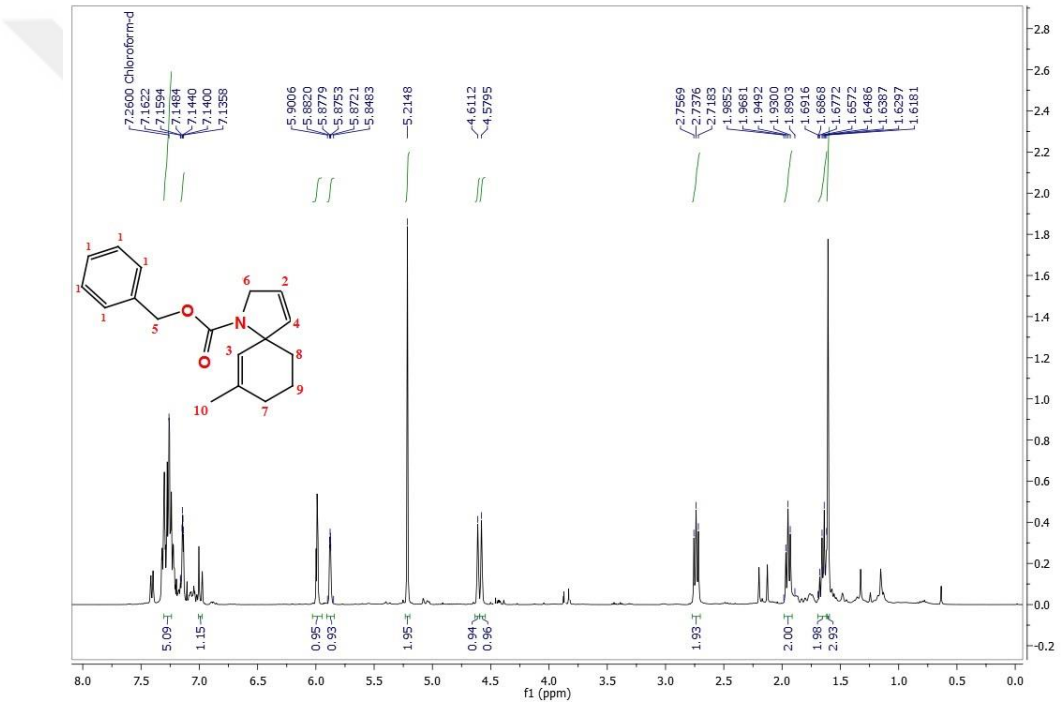


Figure 4.9. ^{1}H-NMR spectrum of benzyl 7-methyl-1-azaspiro[4.5]deca-3,6-diene-1-carboxylate

^{13}C-NMR: The spectrum of benzyl 7-methyl-1-azaspiro[4.5]deca-3,6-diene-1-carboxylate shows signals at 22.5, 27.3, and 28.3 ppm for methylene carbons 16, 14 and 13 in cyclohexene ring respectively. The methyl carbon exhibits signal at 26.8 ppm. Methylene carbon 12 shows signal at 37.5 ppm. In addition, benzylic methylene carbon 11 shows signal at 46.3 ppm. Quaternary carbon 10 exhibits signal at 68.6 ppm. Moreover, methine carbons 9 and 8 show signals at 120.7 and 126.6 ppm. Furthermore, methine carbons in phenyl ring 7, 7`, 6, 5 and 5` show signals at 128.5, 128.6, 128.7, 128.8, and 128.8 ppm respectively.

Quaternary carbons 4 and 3 show signals at 135.1, 136.7 ppm respectively. Olefinic methine carbon 2 shows signal at 145.7 ppm. Finally, the ester carbon shows signal at 150.7 ppm.

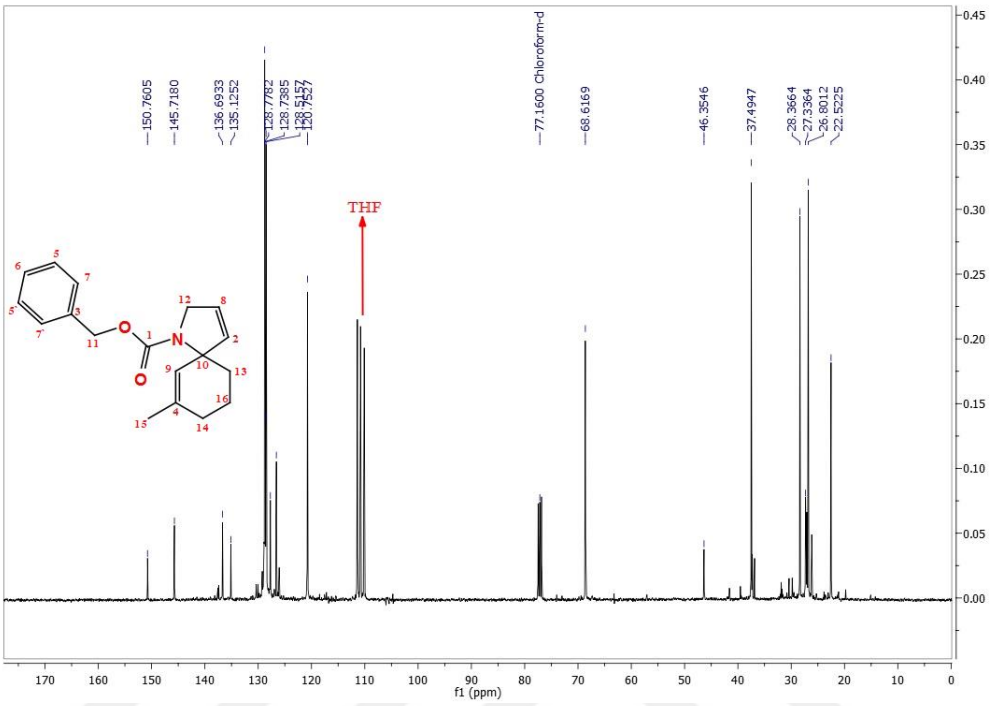
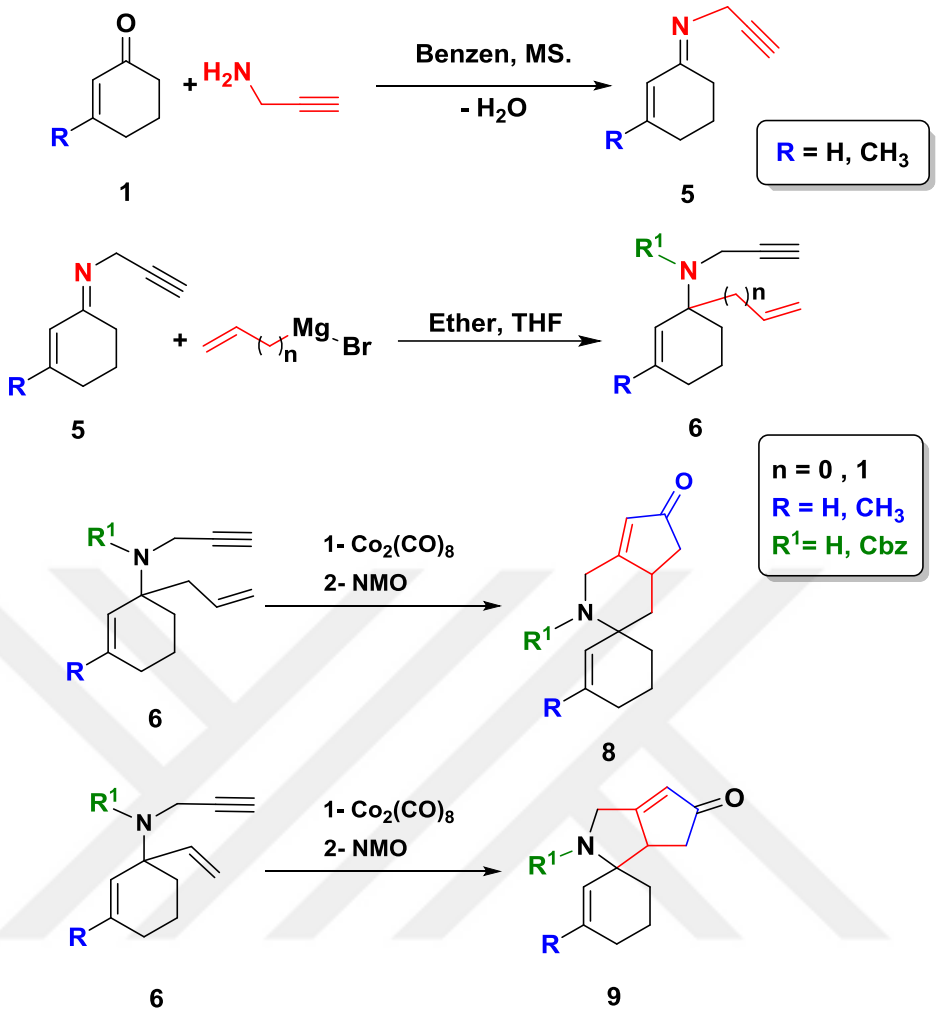


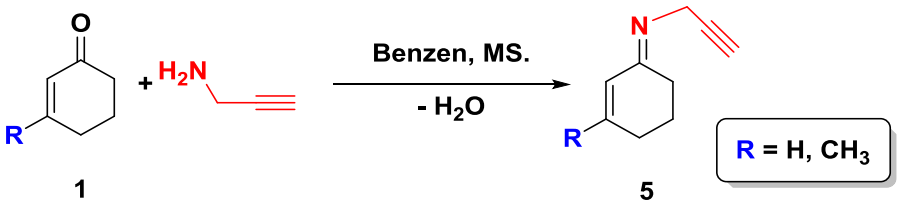
Figure 4.10. ^{13}C-NMR spectrum of Benzyl 7-methyl-1-azaspiro[4.5]deca-3,6-diene-1-carboxylate

4.2 Result and discussion for PKR product



1 5 5 6 6 8 6 9

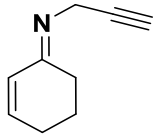
4.2.1 General procedure for Imine formation



1 5

Imine **5** was prepared from cyclohexene derivative **1** and allylamine in presence of molecular sieves in presence of benzene. The reaction mixture heated to 45°C and allowed to stir for 3 days. The resulting slurry was vacuum filtered and washed by diethyl ether. The solvent removed under vacuum. After that blowing the solution by nitrogen gas on the residue for benzene removing to give crude imine product that used directly without any purification.

4.2.1.1 (*E*)-N-(prop-2-yn-1-yl)cyclohex-2-en-1-imine (5a)



5a

(*E*)-N-(prop-2-yn-1-yl)cyclohex-2-en-1-imine was obtained as crude woody brown oil, Chemical formula: ($C_9H_{11}N$). Molecular weight: (133.19). The product was identified without any purification by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

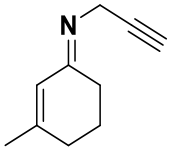
There is a new signal at (1670) cm^{-1} for C=N in new desire product instead of the C=O at (1710) cm^{-1} in cyclohexenone.

IR: (3305) cm^{-1} for C_{SP} –H, (3041) cm^{-1} for C_{SP}^2 –H , (2910) cm^{-1} for C_{SP}^3 –H, (2982) cm^{-1} for CH_3, (2130) cm^{-1} for -C≡C-, (1670) cm^{-1} for >C=N-, (1630) cm^{-1} for >C=C<, (1072) cm^{-1} for C_{SP}^3 –N<.

^{1}H-NMR: The spectrum of (*E*)-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-imine shows new triplet at 2.15 ppm with J = 2.0 Hz for the acetylenic proton. In addition, One of propargylic methylene proton shows doublet of doublet at 2.29 ppm with J = 2.1 and J = 7.9 Hz. The other propargylic methylene proton exhibits doublet of doublet at 2.24 ppm with J = 1.9 Hz and J = 7.5 Hz.

^{13}C-NMR: The spectrum shows new signal at 169.7 ppm for imine carbon. In addition of two new signals at 80.8 ppm and 72.3 ppm for internal and terminal acetylenic carbons. Moreover, signals at 130.3 and 117.0 ppm are due to methine carbons in cyclohexene ring. The propargylic carbon exhibits signal at 41.4 ppm. Finally the methylene carbons in the cyclohexene ring show signals at 30.1, 25.5, 21.6 ppm.

4.2.1.2 (*E*)-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-imine (5b)



5b

(*E*)-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-imine was obtained as crude orange yellow oil, Chemical formula: ($C_{10}H_{13}N$). Molecular weight: (147.22). The product was identified without any purification by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

When we compared IR spectra of Cyclohexenone and our desire product it showed that there is a new signal at (1625) cm^{-1} for C=N instead of the C=O at (1710) cm^{-1}.

IR: (3302) cm^{-1} for C_{SP} –H, (3052) cm^{-1} for C_{SP}^{2} –H , (2900) cm^{-1} for C_{SP}^{3} –H, (2986) cm^{-1} for CH_3, (2125) cm^{-1} for -C≡C-, (1661) cm^{-1} for >C=N-, (1625) cm^{-1} for >C=C<, (1066) cm^{-1} for C_{SP}^{3} –N<.

^{1}H-NMR: The spectrum of (*E*)-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-imine shows difficulty in identification of the signals because the imine product is not pure (crude imine). However the signal shows doublet at 1.81 ppm with J = 1.3 Hz for methyl protons. Multiplet between 2.10 – 2.14 ppm is due to the diastereotopic methylene protons at position 6. Moreover, the acetylenic proton at position 5 shows triplet at 2.18 ppm with J = 4.6 Hz. Multiplet between 2.21 – 2.23 ppm for methylene protons at position 4. Furthermore, methylene protons 3 show multiplet between 2.24 – 2.31 ppm. The other methylene protons at position 2 exhibit doublet at 4.00 ppm with J = 2.2 Hz. Finally, the olefinic methine proton 1 shows quartet at 5.90 ppm with J = 1.3 Hz.

^{13}C-NMR: The spectrum of (*E*)-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-imine shows signal at 169.6 ppm for imine carbon. The quaternary carbon (next to methyl carbon) shows signal at 149.4 ppm. The signal at 115.4 ppm is due to methine carbon 3. The terminal and internal acetylenic carbons show signals at 70.2, 72.1 ppm respectively. The propargylic methylene carbon at position 6 shows signal at 36.6 ppm. Furthermore, signals at 30.5 ppm 25.4 ppm and 24.1 ppm are due to methylene carbons at position 7, 8 and 9 respectively. Finally, the methyl carbon shows signal at 22.1 ppm.

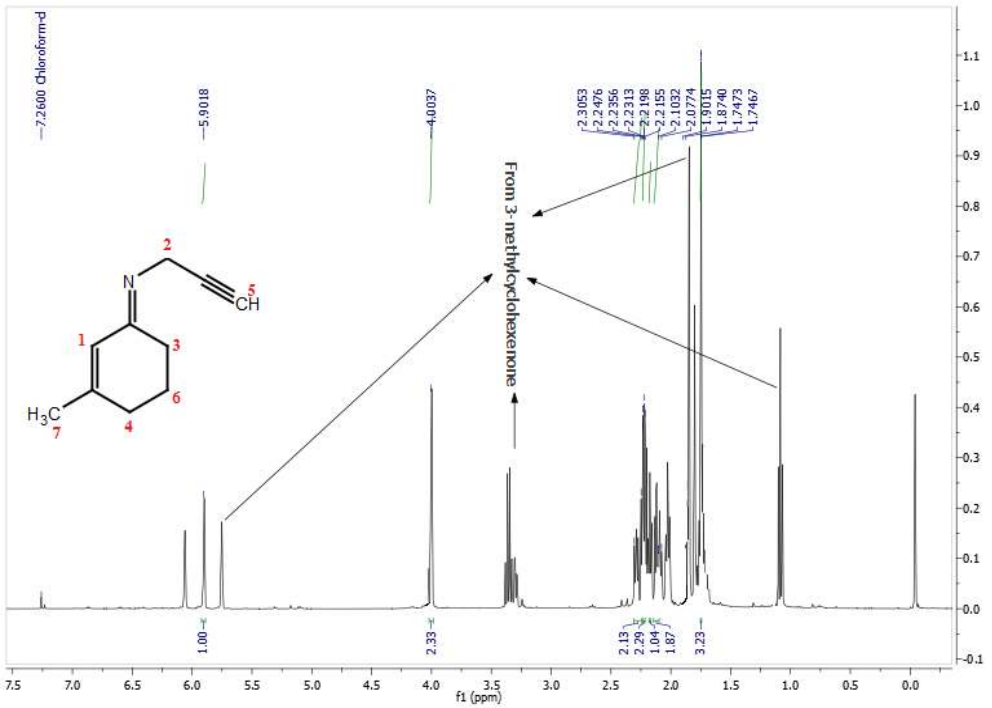


Figure 4.11. [1]H-NMR spectrum of (*E*)-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-imine

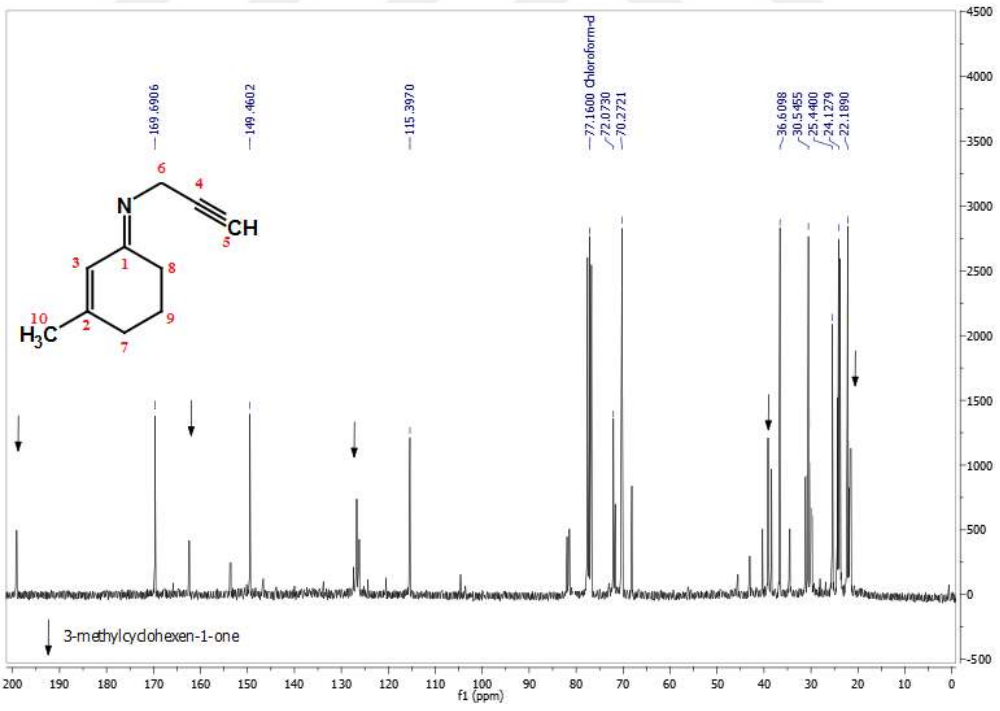
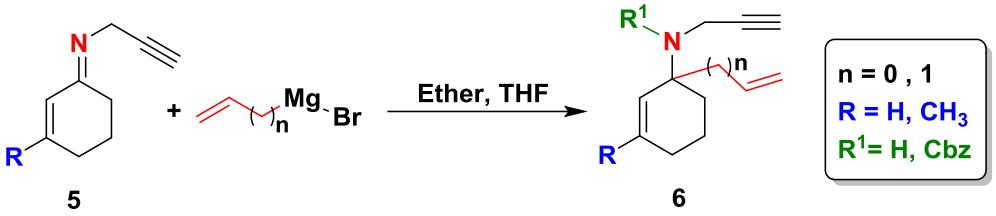


Figure 4.12. [13]C-NMR spectrum of (*E*)-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-imine

4.2.2 Grignard Reaction

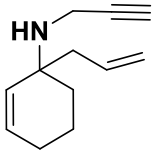


General procedure for Grignard reaction with allyl magnesium bromide:

Imine can react with allyl magnesium bromide (Grignard reagent) by nucleophilic attack on the carbon (C=N) double bonds. This reaction has low yield but very good selectivity due to the poor electrophilicity of imine-carbon (137). This problem relatively solved by adding excess amount of magnesium when making Grignard reagent this amount can react directly with releasing bromide to produce Lewis acid that activate nucleophilic addition of imine carbon (138). ether and THF were used as aprotic solvent in these reactions because they can solvate the Mg ion that coordinate to the ether lone-pair electrons (139).

Grignard reagent, (140), was made by adding allyl bromide (2 equiv.) to magnesium turnings (2.5 equiv.) in 25 ml of anhydrous diethyl ether. After that, the system was cooled down to 0 °C by putting it in ice bath and imine (crude) **5** (1 equiv.) was added drop wise to it. The mixture was allowed to stir overnight at room temperature. After workup, solvent was removed, and the crude product was purified by column chromatography with mixture of (ethyl acetate, hexane and triethylamine) in suitable ratios.

4.2.2.1 1-allyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine (6a)



6a

The product was purified by column chromatography using system solvent of (EtOAc: Hexane: Et_3N) (1:1:1%), Rf = 0.82.

1-allyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine obtained as yellow thick oil with 72% chemical yield. Chemical formula ($C_{12}H_{17}N$). Molecular weight: (175.28). The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

IR: (3305) cm^{-1} for >N-H, (3074) cm^{-1} for C_{SP}^{2} –H, (2901) cm^{-1} for C_{SP}^{3} – H, (2971) cm^{-1} for -CH_3, (1639) cm^{-1} for >C=CH_2, and at (1075) cm^{-1} for C_{SP}^{3} –N<

^{1}H-NMR: the spectrum of 1-allyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine shows the multiplet between 1.55 – 1.50 ppm for methylene protons 10. The methylene protons 9 show doublet of doublet of doublet at 1.70 ppm with J = 3.7, 7.7 and 8.9 Hz. The methylene protons 8 exhibit multiplet at 1.96 ppm. The acetylenic proton 7 shows triplet at 2.18 ppm with J = 2.5 Hz. Moreover, one of allylic methylene proton 6 shows multiplet between 2.25 – 2.32 ppm. The other allylic methylene proton 6` shows doublet of doublet at 2.22 ppm with J = 4.1 and 8.6 Hz. The propargylic methylene protons 5 show doublet of doublet at 3.34 ppm with J = 0.7, and 2.4 Hz. Furthermore, doublet of doublet of doublet of doublet at 5.14 ppm for one of terminal vinylic proton 4 with J = 1.0, 1.2, 2.0 and 15.1 Hz. The other terminal vinylic proton 4` shows multiplet between 5.05 – 5.09 ppm. Methine proton 2 shows multiplet between 5.75 – 5.81 ppm, and the other methine proton 3 shows doublet of doublet of doublet at 5.47 ppm with J = 1.8, 4.8 and 8.1 Hz. Finally, the internal vinylic proton 1 exhibits multiplet between 5.87 – 5.82 ppm.

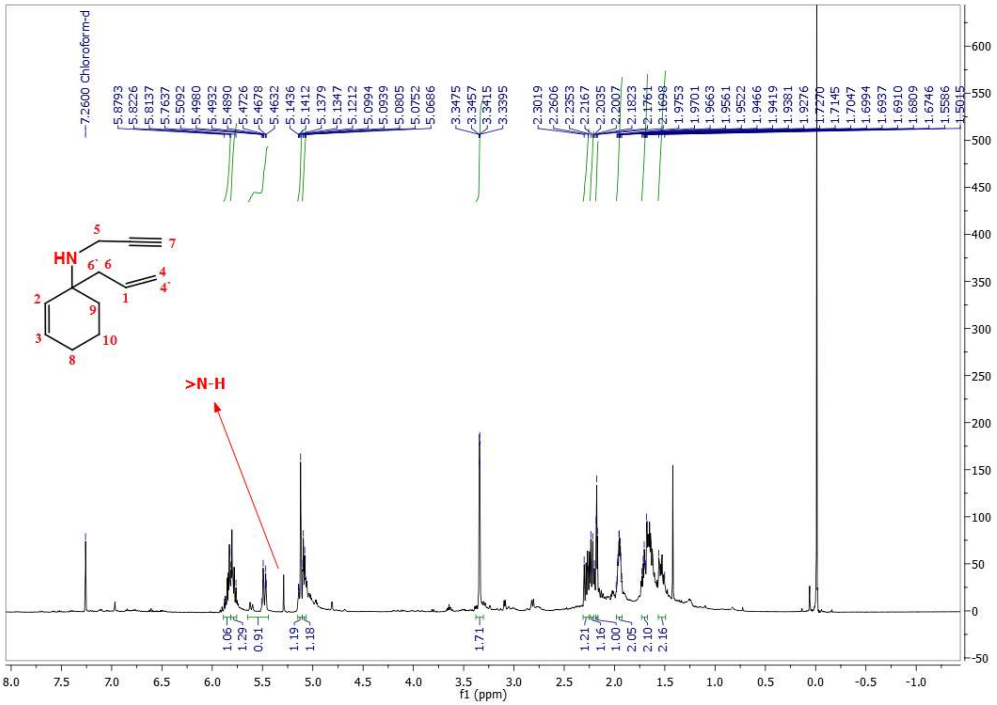


Figure 4.13. ^{1}H-NMR spectrum of 1-allyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine

^{13}C-NMR: The spectrum of 1-allyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine shows signals at 136.5, 133.6 and 126.5 ppm for internal vinylic carbon 1, olefinic methine carbons 2, and 3 respectively. Signal at 117.5 ppm is due to terminal vinylic carbon 4. Followed by internal acetylenic carbon at 83.0 ppm. Terminal acetylenic carbon 6 shows signal at 70.1 ppm. The quaternary carbon shows signal at 54.5 ppm. Moreover, the allylic methylene carbon 8 shows signal at 44.4 ppm. Signal at 29.4 is due to propargylic methylene carbon. Finally, the methylene carbons 9, 11, and 12 show signals at 34.7 ppm 31.2 ppm and 19.1 ppm respectively.

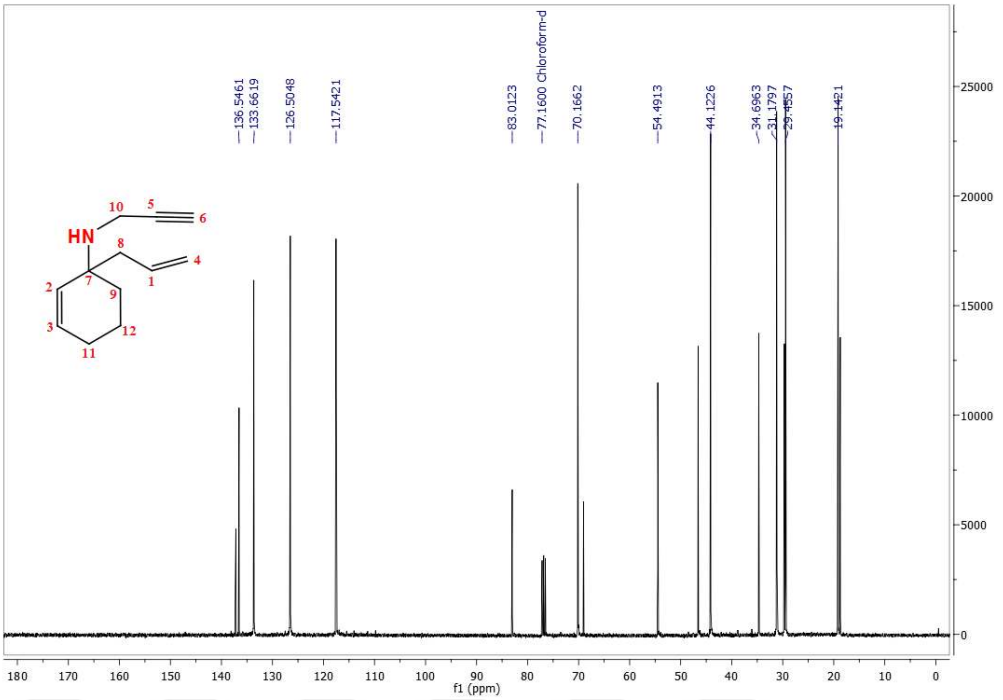
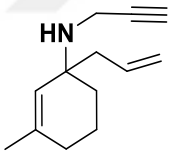


Figure 4.14. ^{13}C-NMR spectrum of 1-allyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine

4.2.2.2 1-allyl-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine (6b)



6b

The product was purified by column chromatography using system solvent of (EtOAc: Hexane: Et_3N) (1:1:1%). Rf = 0.80.

1-allyl-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine was obtained as yellow thick oil with 77% chemical yield. Chemical formula ($C_{13}H_{19}N$). Molecular weight: (189.30). The product was identified by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy and HRMS.

IR: (3311) cm^{-1} for C_{SP} –H, (3238) cm^{-1} for >N-H (3052) cm^{-1} for C_{SP}^2 –H , (2901) cm^{-1} for C_{SP}^3 –H, (2971) cm^{-1} for -CH_3, (2050) cm^{-1} for -C≡C-, (1102) cm^{-1} for C_{SP}^3 –N<.

^{1}H-NMR: The spectrum of 1-allyl-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine shows multiplet for each of methylene protons at position 10, 9 and 7 between 1.42 – 1.36, 1.49 – 1.51 and 1.72 – 1.77 ppm. Methyl protons show singlet at 1.55 ppm. The acetylenic proton 6 shows triplet at 2.05 ppm with J = 2.4 Hz. Moreover, multiplet between 2.10 – 2.15 ppm for allylic methylene protons 5. Methylene protons 4 show doublet at 3.19 ppm with J = 2.5 Hz. Doublet of doublet at 4.95 ppm due to one of terminal vinylic proton 3` with J = 1.6 and 7.1 Hz. The other terminal vinylic proton 3 shows multiplet between 4.96 – 5.00 ppm. Furthermore, olefinic methine proton 2 shows singlet at 5.09 ppm. Finally, the internal vinylic proton 1 exhibits multiplet between 5.78 – 5.68 ppm.

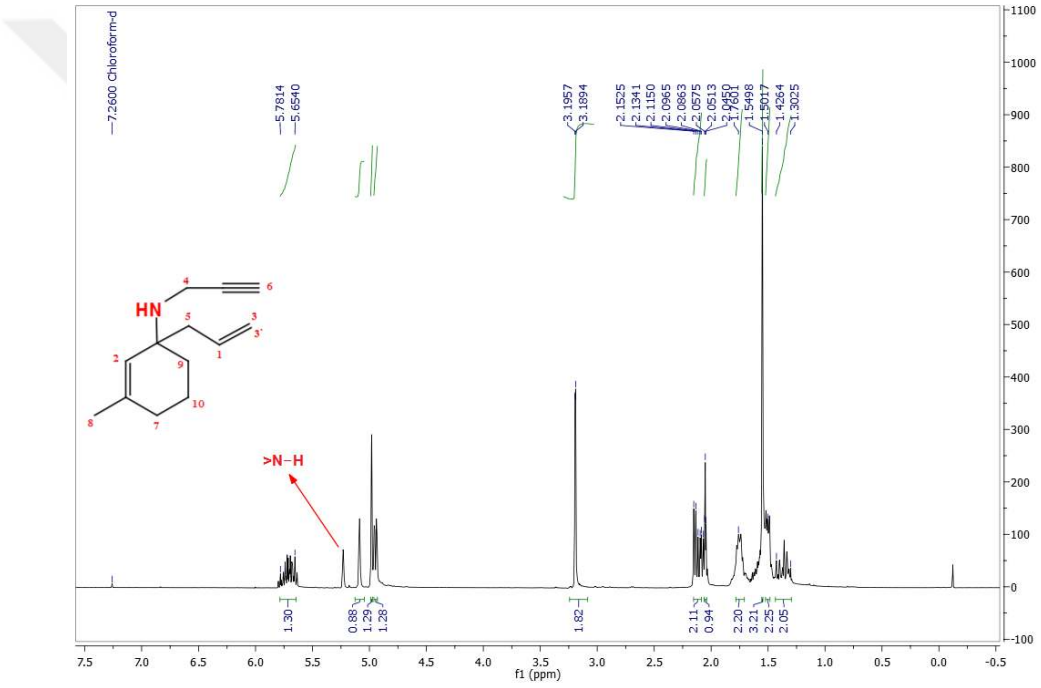


Figure 4.15. ^{1}H-NMR spectrum of 1-allyl-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine

^{13}C-NMR: The spectrum of 1-allyl-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine shows signals at 136.8, 133.9 and 126.8 ppm for internal vinylic carbon 1, olefinic carbons 2 and 3 respectively. Terminal vinylic carbon 4 exhibits signal at 117.8 ppm. Internal acetylenic carbon shows signal at 88.3 ppm. Terminal acetylenic carbon 6 shows signal at 70.4 ppm. Moreover, the quaternary carbon shows signal at 54.8 ppm. The allylic methylene carbon 8 shows signal at 44.4 ppm. Furthermore, signal at 31.5 ppm is due to propargylic methylene carbon 10. The

methylene carbons 9, 11, and 13 show signals at 35.0, 29.8 and 19.5 ppm respectively. Finally, methyl carbon shows signal at 23.6 ppm.

HRMS: (ESI-TOF)m/z: calculated for $C_{13}H_{20}N$ $[M+H]^+$: (190.1596) found: (190.1613).

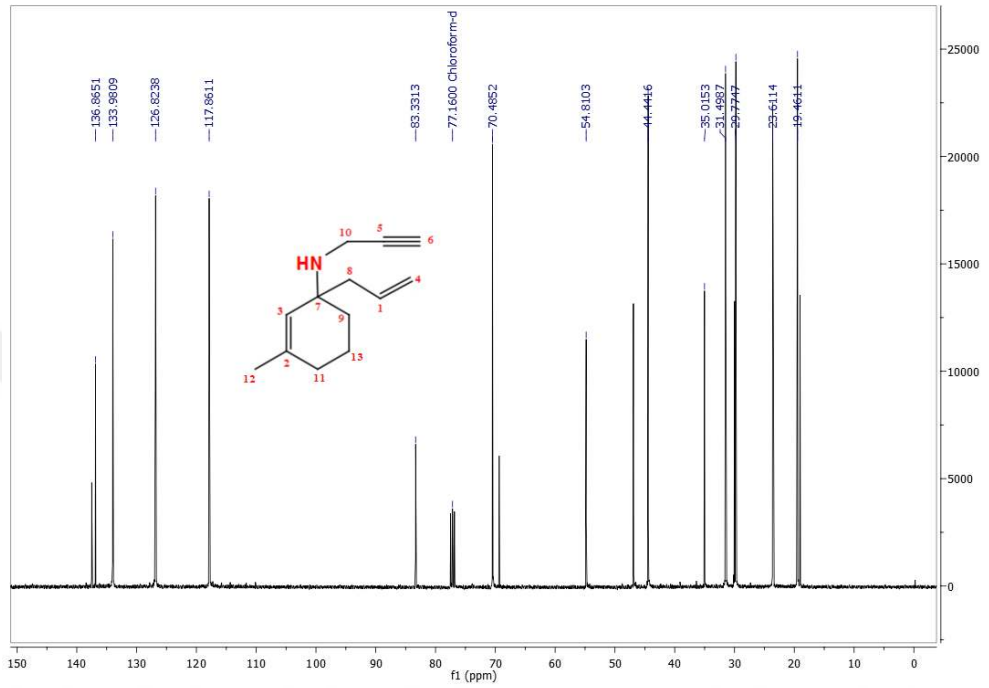
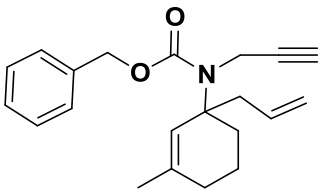


Figure 4.16. ^{13}C-NMR spectrum of 1-allyl-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine

4.2.2.3 Benzyl (1-allyl-3-methylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate (Protection) (6c)



6c

The product was purified by column chromatography using system solvent of (EtOAc: Hexane: Et_3N) (1:3:1%). Rf = 0.54.

Benzyl (1-allyl-3-methylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate was obtained as yellow thick oil with 72% chemical yield. Chemical formula

($C_{21}H_{25}NO_2$). Molecular weight: (323.44). This product was identified by IR, ^{1}H-NMR ^{13}C-NMR and HRMS.

IR: (3310) cm^{-1} for C_{SP} –H, (3025) cm^{-1} for C_{SP^2} –H , (2911) cm^{-1} for C_{SP^3} –H, (2942) cm^{-1} for -CH_3, (2050) cm^{-1} for -C≡C-, (1699) cm^{-1} for >C=O, (1652) cm^{-1} for >C=CH_2, (1241) cm^{-1} for C_{SP^3} –N<

^{1}H-NMR: the spectrum of benzyl (1-allyl-3-methylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate shows multiplet between 1.21 - 1.30 ppm and 1.77 - 1.84 ppm are due to methylene protons at position 12 and 9 respectively. Methylene protons 11 show doublet of doublet at 2.08 ppm with J_1 = 4.8 and J_2 = 8.5 Hz. The methyl protons show singlet at 1.72 ppm. Moreover, allylic methylene protons 8 exhibit multiplet between 1.87 – 1.92 ppm. Followed by multiplet between 1.99 – 2.05 ppm due to acetylenic proton 7. Propargylic methylene protons 6 exhibit multiplet between 3.94 – 4.14 ppm. One of the benzylic methylene proton 5 shows doublet at 5.00 ppm with J = 9.5 Hz. The other benzylic methylene proton 5` shows multiplet between 4.97 – 5.00 ppm. The terminal vinylic proton 4 shows doublet of doublet at 5.08 ppm with J = 3.3 Hz and J = 9.2 Hz. The other terminal vinylic proton 4` shows doublet of doublet at 5.16 ppm with J = 4.0 Hz and J = 9.2 Hz. Furthermore, methine proton 3 exhibits singlet at 5.52 ppm. The multiplet between 5.67 – 5.78 ppm is due to internal vinylic proton 2. Finally, Phenyl ring protons show multiplet between 7.41–7.25 ppm.

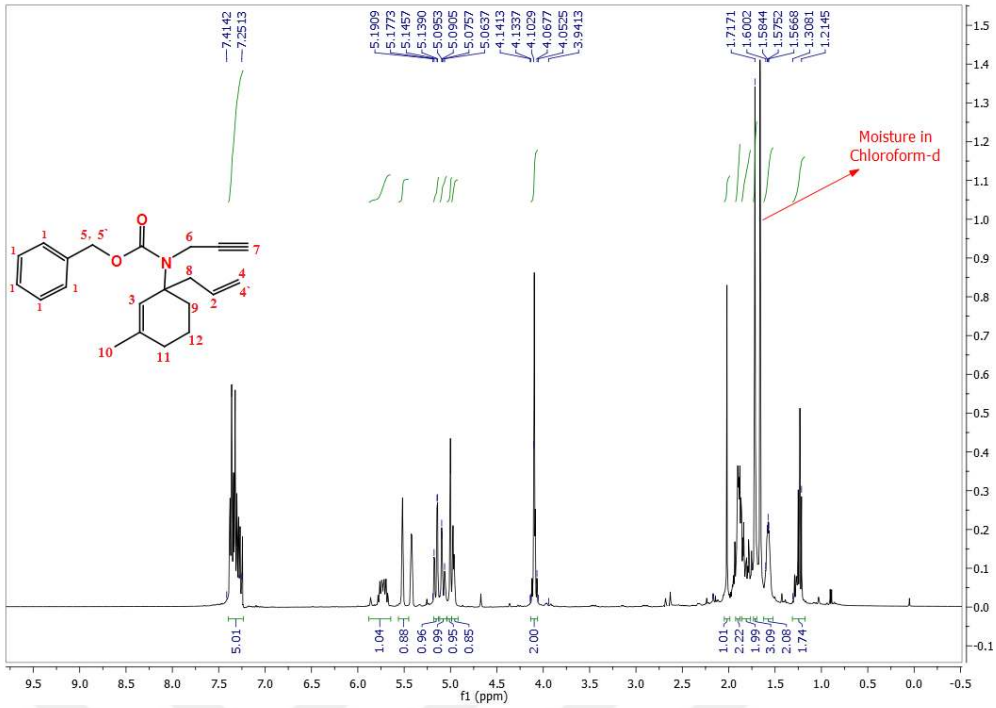


Figure 4.17. ^{1}H-NMR spectrum of Benzyl (1-allyl-3-methylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate

^{13}C-NMR: The spectrum of benzyl (1-allyl-3-methylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate shows signals at 18.5, 30.4 and 38.8 ppm are due to methylene carbons 19, 17 and 14 in cyclohexene ring respectively. The methyl carbon shows signal at 25.5 ppm. Moreover, the stereogenic carbon 13 shows signal at 60.8 ppm. The methine carbons 7, 7`, 6, 6` and 5 positions of the phenyl ring exhibit signals at 127.9, 128.4, 128.5, 128.6, and 128.7 ppm respectively. The ester carbon 1 exhibit signal at 155.2 ppm. In addition, allylic and propargyl positions show signals at 36.8 and 31.9 ppm respectively. Moreover, terminal and internal acetylenic carbons show signals at 69.8 and 70.7 ppm respectively. Olefinic methine carbon 8 shows signal at 118.1 ppm. Furthermore, there are two signals at 129.3 and 81.8 ppm for internal and terminal vinylic carbons. The quaternary carbons 2 and 3 show signals at 134.2 and 131.9 ppm respectively. Finally, benzylic methylene carbon 12 exhibits signal at 64.1 ppm.

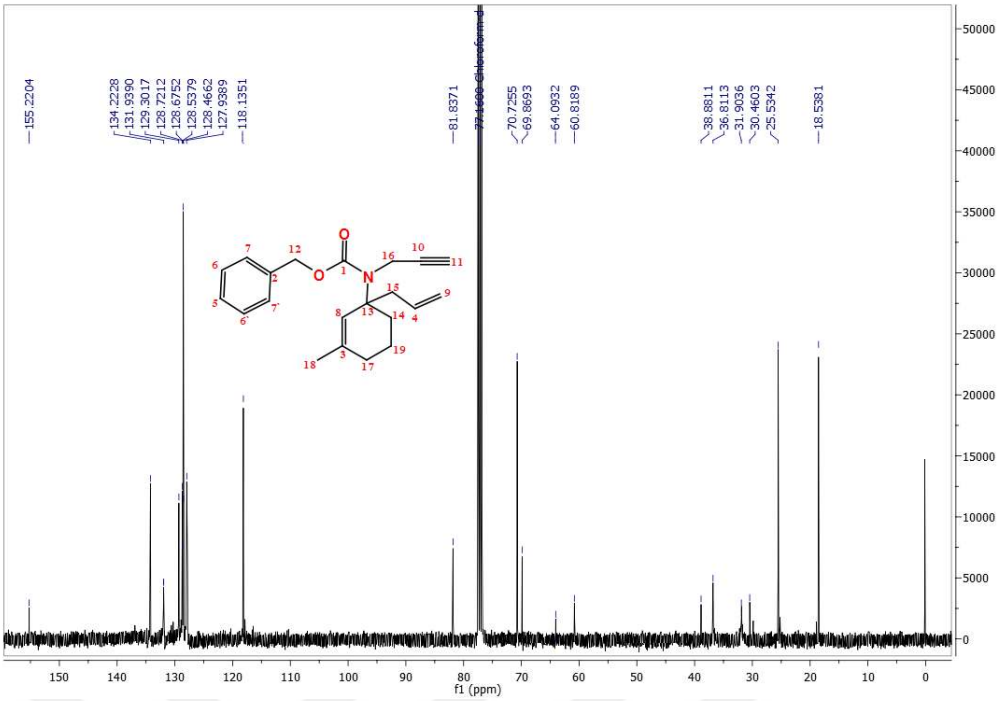
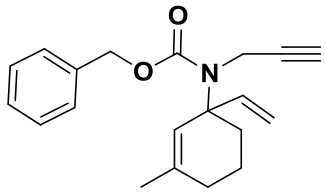


Figure 4.18. ^{13}C-NMR spectroscopy for Benzyl (1-allyl-3-methylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate

Grignard reaction with vinyl magnesium bromide

Crude imine was react with benzyl chloroformate (1.5 equiv.) in 30 mL THF the system was closed with 'Graham condenser' with nitrogen inlet gas. The reaction mixture was heated to 60 °C for 2.5 h (controlled by TLC). Then the crude product was cooled to -78 °C then vinyl magnesium bromide (1 M in THF) was added to it. After that, the system was wormed to room temperature and stirring overnight. Then the reaction mixture was hydrolyzed by saturated ammonium chloride solution (NH_4Cl). The organic phase was separated by adding ethyl acetate (EtOAc) after that washing it by 20 ml sodium bicarbonate solution ($NaHCO_3$) followed by 20 ml brine. Magnesium sulfate was used to dry the final organic mixture and filtered (130). Finally, the solvent was evaporated under vacuum and the crude product was purified by flash column chromatography (Silica gel, eluent: EtOAc: Hexane: Et_3N) in suitable ratios.

4.2.2.4 Benzyl (3-methyl-1-vinylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate (6d)



6d

The product was purified by column chromatography using system solvent of (EtOAc: Hexane: Et_3N) (1:5:1%). (Rf = 0.49).

Benzyl (3-methyl-1-vinylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate was obtained as brown oil with 75% chemical yield. Chemical formula: ($C_{20}H_{23}NO_2$), Molecular weight: (309.41). The product was identified by ^{1}H-NMR, ^{13}C-NMR spectroscopy and HRMS.

^{1}H-NMR: The spectrum of benzyl (3-methyl-1-vinylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate shows new multiplet in aromatic area due to phenyl ring protons between 7.39 – 7.33 ppm. Internal vinylic proton shows multiplet between 5.69 – 5.52 ppm. Moreover, singlet at 5.82 ppm for olefinic methine proton 2. One of terminal vinylic proton 4 shows doublet of doublet at 5.38 ppm with J_1 = 2.6 and J_2 = 15.8 Hz. The other proton 4` exhibits multiplet between 5.27 – 5.31 ppm. Benzylic methylene protons show doublet at 5.18 ppm with J = 2.3 Hz. One of propargylic methylene proton 6 shows doublet of doublet at 4.28 ppm with J = 2.4 Hz and J = 8.15 Hz. The other proton 6` shows multiplet between 4.20 – 4.25 ppm. The multiplet for each of methylene protons 7 and 9 between 2.32 – 2.35 ppm and 2.25 – 2.16 ppm respectively. The other multiplet between 1.63 – 1.72 ppm is due to methylene protons 11. The acetylenic proton shows triplet at 2.27 ppm with J = 2.3 Hz. Finally, methyl protons show doublet at 1.76 ppm with J = 1.7 Hz.

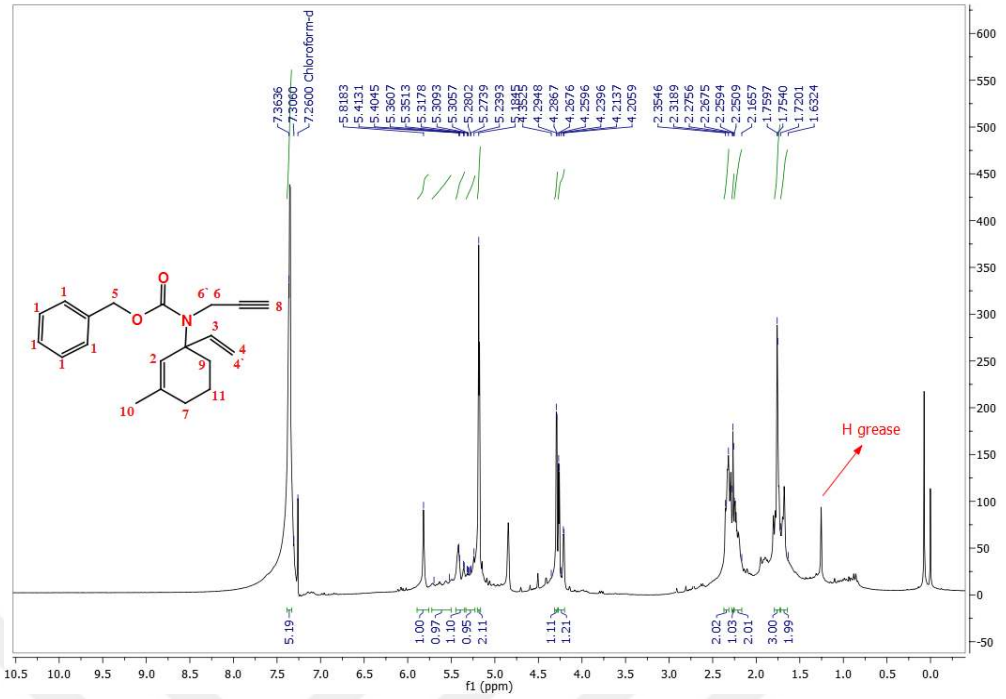


Figure 4.19. ^{1}H-NMR spectrum of benzyl (3-methyl-1-vinylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate

^{13}C-NMR: the spectrum of benzyl (3-methyl-1-vinylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate shows signals at 21.4, 26.9 and 29.9 ppm due to methylene carbons 18, 16 and 15 in cyclohexene ring. The methyl carbon 17 shows signal at 23.8 ppm. The signal at 39.6 ppm for propargylic methylene carbon 14. The stereogenic carbon 13 shows signal at 67.4 ppm. Furthermore, signal at 67.7 ppm due to benzylic methylene carbon 12. Internal and terminal acetylenic carbons 10 and 11 show signals at 79.8 and 72.0 ppm respectively. Terminal vinylic carbon 9 exhibits signal at 112.2 ppm. In addition, signal at 119.4 ppm belongs to the olefinic methine carbon 8. Moreover, methine carbons 7, 7`, 6, and 5 of the phenyl ring exhibit signals at 127.8 , 127.9, 128.2, and 128.6 ppm respectively. Internal vinylic carbon 4 shows signal at 131.2 ppm. The quaternary carbons 3 and 2 exhibit signals at 136.3 and 142.5 ppm. Ester carbon 1 shows signal at 154.5 ppm.

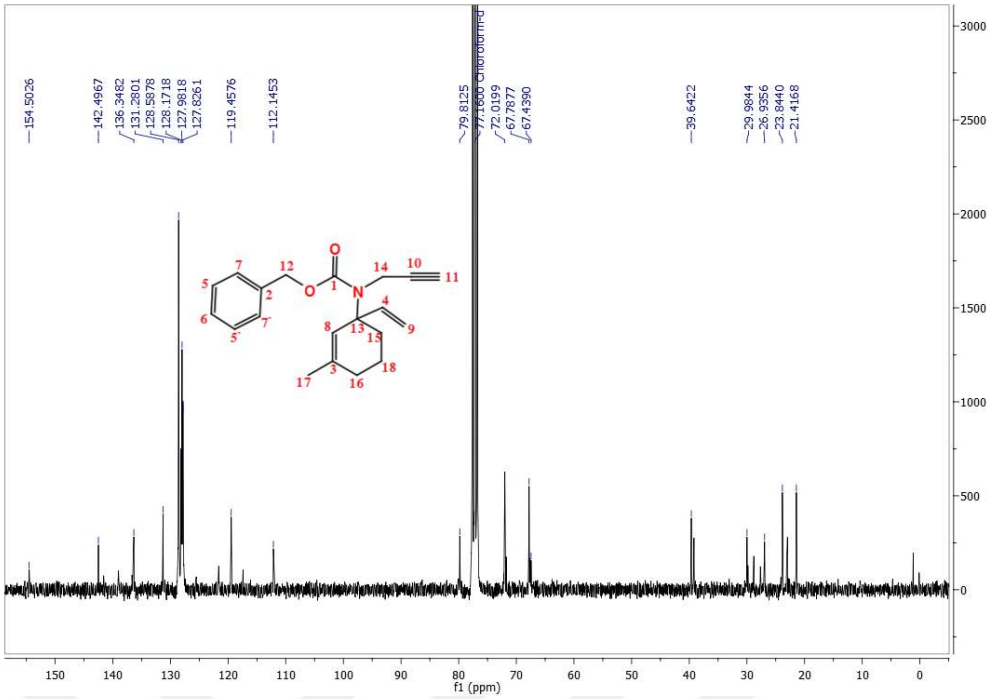
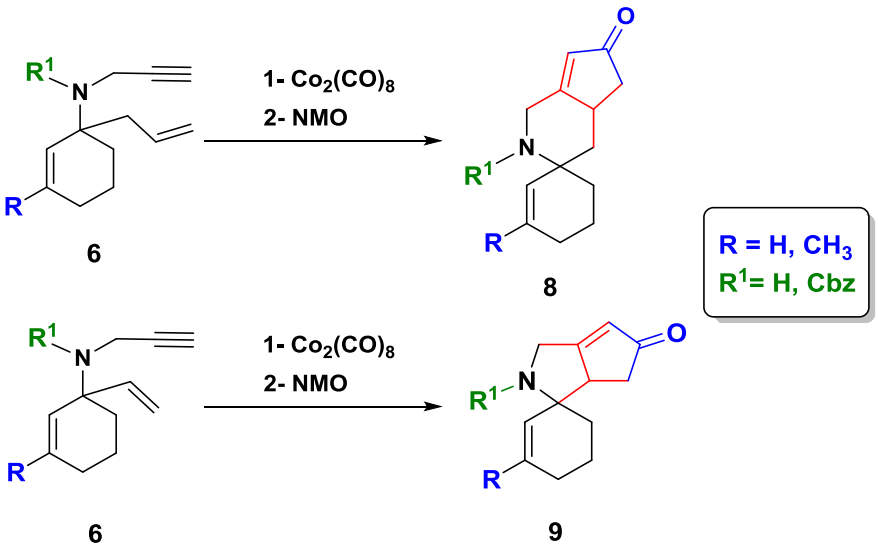


Figure 4.20. ^{13}C-NMR spectroscopy for benzyl (3-methyl-1-vinylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate

HRMS: (ESI-TOF)m/z: calculated for $C_{20}H_{24}NO_2$ $[M+H]^+$: (310.1807) and was found as (310.1821).

4.2.3 General Procedure for Pauson-Khand Reaction (8, 9)

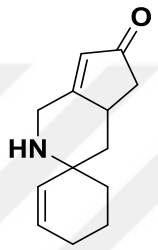


A solution of **6** (1 equiv.) in DCM was react with dicobaltoctacarbonyl ($Co_2(CO)_8$) (1.8 equiv.) in 5 ml DCM. The reaction mixture allowed to stir 2.5 h. (controlled by TLC). After that, NMO (10 equiv.) was added to it and the reaction

mixture allowed to stir overnight. The final product was purified by flash column chromatography used (Silica gel, eluent: EtOAc: Hexane: Et_3N) in suitable ratios.

Upon the IR spectra of all PKR products we can found that the C_{SP} –H had disappear in (~3300) cm^{-1} range and emersion the carbonyl signal at around (1680-1720) cm^{-1}. We can support this evidence by disappearance of signals of acetylenic protons around 2.2 - 2.6 ppm in ^{1}H-NMR spectra. In addition, the appearance of carbonyl signal at around (~200) ppm in ^{13}C-NMR.

4.2.3.1 1',2',4a',5'-tetrahydrospiro[cyclohexane-1,3'-cyclopenta [c]-pyridin]-2-en-6'(4'H)-one (8a)



8a

The product was purified by column chromatography using system solvent of (EtOAc: Hexane: Et_3N) (1:1:1%). Rf = 0.49.

1',2',4a',5'-tetrahydrospiro[cyclohexane-1,3'-cyclopenta-[c]pyridin]-2-en-6'(4'H)-one was obtained as dark red thick oil with 67% chemical yield. Chemical formula ($C_{13}H_{17}NO$). Molecular weight: (203.29). The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

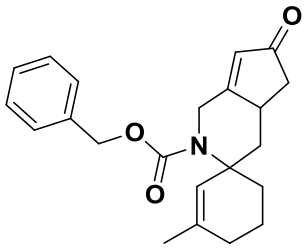
IR: (3310) cm^{-1} for >N-H, (3074) cm^{-1} for C_{SP}^2 –H, (2915) cm^{-1} for C_{SP}^3 –H, (2929) cm^{-1} for -CH_3, (1637) cm^{-1} for >C=CH_2, (1677) for >C=O and at (1075) cm^{-1} for C_{SP}^3 –N<

^{1}H-NMR: The spectrum of 1',2',4a',5'-tetrahydrospiro[cyclohexane-1,3'-cyclopenta-[c]pyridin]-2-en-6'(4'H)-one shows multiplet between 0.85 – 0.94 ppm for methylene protons 10. Followed by multiplet between 1.09 – 1.15 ppm due to methylene protons 9. Moreover, one of diastereotopic methylene proton 8 in tetrahydropyridine ring shows doublet of doublet at 1.62 ppm with J_1 = 3.8, J_2 = 9.2 Hz. The other methylene proton 8` exhibits doublet of doublet at 1.53 ppm with J_1

= 3.6, J_2 = 8.9 Hz. Methylene protons 7 show multiplet between 1.85 – 1.91 ppm. Multiplet between 2.01 – 2.28 ppm due to methylene protons 6. The methine proton at position 5 shows multiplet between 2.85 – 3.02 ppm. One of methylene proton 4 in tetrahydropyridine ring shows doublet at 3.75 ppm with J = 3.2 Hz and the other methylene proton 4` exhibits doublet at 3.90 ppm with J = 3.1 Hz. Furthermore, olefinic methine proton 3 shows doublet at 5.05 ppm with J = 7.3 Hz and the other olefinic methine proton 2 shows multiplet between 5.65 – 5.85 ppm. Finally, methine proton 1 shows singlet at 5.99 ppm.

^{13}C-NMR: The spectrum of 1',2',4a',5'-tetrahydrospiro[cyclohexane-1,3'-cyclopenta-[c]pyridin]-2-en-6'(4'H)-one shows signals at 26.9, 32.7 and 42.1 ppm are due to the methylene carbons at positions 13, 12 and 11 of cyclohexene ring respectively. The stereogenic carbon 10 shows signal at 43.3 ppm. Moreover, Signals at 50.8 and 55.2 ppm are due to methylene carbons 8 and 7 of the of the tetrahydropyridine ring respectively. The signal at 47.4 ppm is due to methylene carbon at position 9. The quaternary carbon at the position 6 exhibits signal at 62.3 ppm. Signals at 120.3 and 135.2 ppm belong to methine carbons at position 5 and 4 respectively. Furthermore, methine carbon 3 exhibits signal at 137.2 ppm. The quaternary carbon at positions 2 shows signal at 172.2 ppm. Finally, carbonyl carbon 1 exhibits signal at 201.5 ppm.

4.2.3.2 Benzyl 3-methyl-6'-oxo-4',4a',5',6'-tetrahydrospiro[cyclohexane-1,3'-cyclopenta[c]pyridin]-2-ene-2'(1'H)-carboxylate (8b)



8b

The product was purified by column chromatography using system solvent of (EtOAc: Hexane: Et_3N) (1:1:1%). (Rf = 0.64).

Benzyl3-methyl-6'-oxo-4',4a',5',6'-tetrahydrospiro[cyclohexane-1,3'-cyclope-nta[c]pyridin]-2-ene-2'(1'H)-carboxylate was obtained as yellow thick oil with 75% chemical yield. Chemical formula ($C_{22}H_{25}NO_3$). Molecular weight: (351.45). The product was identified by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

^{1}H-NMR: The spectrum of benzyl 3-methyl-6'-oxo-4',4a',5',6'-tetrahydrospiro [cyclohexane-1,3'-cyclopenta[c]pyridin]-2-ene-2'(1'H)-carboxylate shows multiplet between 1.80 – 1.82 ppm for methylene protons 12 in cyclohexene ring. Followed by multiplet between 1.92 - 1.94 ppm due to methylene protons 11. The methyl protons show singlet at 1.96 ppm. Moreover, methylene protons 9 in tetrahydropyridine ring show doublet of doublet at 2.29 ppm with J_1 = 2.4, J_2 = 4.7 Hz. Doublet of doublet at 2.33 ppm for methylene protons 8 with J_1 = 2.9, J_2 = 4.1 Hz. Moreover, methylene protons 7 show doublet at 2.36 ppm with J = 4.3 Hz. The methine proton at position 6 shows multiplet between 2.39 – 2.41 ppm. One of methylene proton 5 shows doublet at 4.12 ppm with J = 3.5 Hz and the other methylene proton 5` exhibits doublet at 4.10 ppm with J = 3.5 Hz. Furthermore, methylene protons 4, olefinic methine proton 3 and methine proton 2 show singlet to each of them at 4.86, 5.22, and 5.87 ppm respectively. Finally, phenyl ring protons show multiplet between 7.27 – 7.41 ppm.

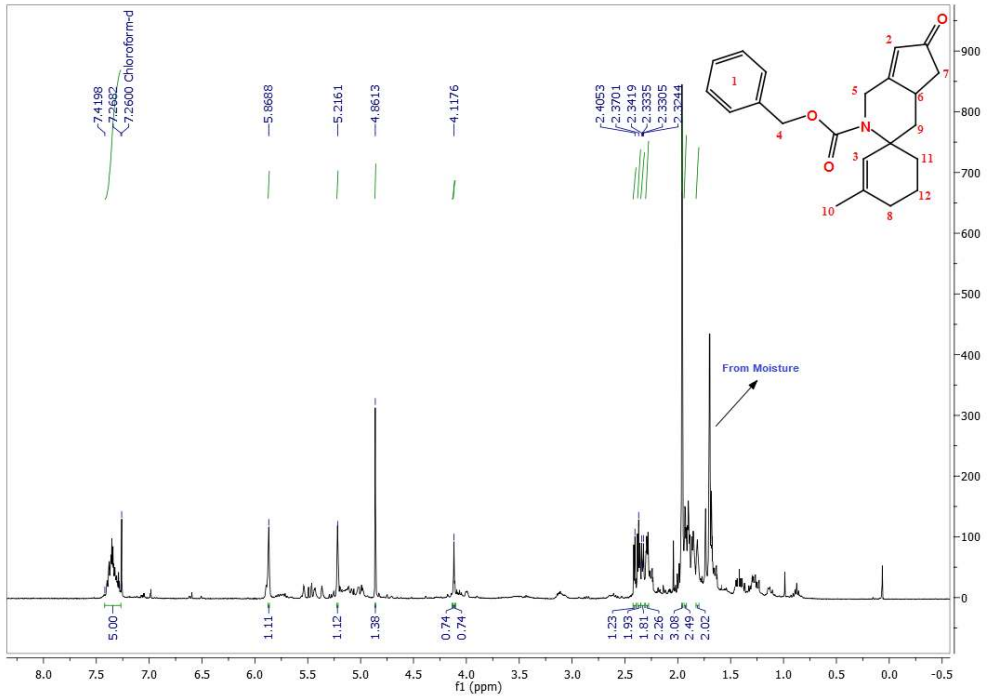


Figure 4.21. [1]H-NMR spectrum of benzyl 3-methyl-6'-oxo-4',4a',5',6'-tetrahydro spiro[cyclohexane-1,3'-cyclopenta[c]pyridin]-2-ene-2'(1'H)-carboxylate

[13]C-NMR: The spectrum of benzyl 3-methyl-6'-oxo-4',4a',5',6'-tetrahydrospiro [cyclohexane-1,3'-cyclopenta[c]pyridin]-2-ene-2'(1'H)-carboxylate shows signals at 18.6, 24.3 and 30.2 ppm are due to the methylene carbons at positions 20, 18 and 17 of cyclohexene ring respectively. The methyl carbon 19 shows signal at 24.0 ppm. The stereogenic carbon 16 shows signal at 30.4 ppm. Moreover, the signals at 31.7 and 53.7 ppm are due to methylene carbons 15 and 13 of the of the tetrahydropyridine ring respectively. The signal at 37.1 ppm is due to methylene carbon at position 14. The quaternary carbon at the position 12 exhibits signal at 54.5 ppm. Followed by signal at 72.4 ppm for benzylic methylene carbon 11. The signals at 125.8 and 127.6 ppm belong to methine carbons at position 10 and 7 respectively. Furthermore, methine carbons 9, 9`, 8, 6, and 6` of the phenyl ring exhibit signals at 126.8, 126.7, 127.8 and 128.7, 128.5 ppm respectively. The quaternary carbons at positions 5, 4, and 3, show signals at 134.5, 136.7, and 139.9 ppm respectively. Finally, carbonyl carbon 1 and ester carbon 2 exhibit signals at 203.5 and 163.8 ppm respectively.

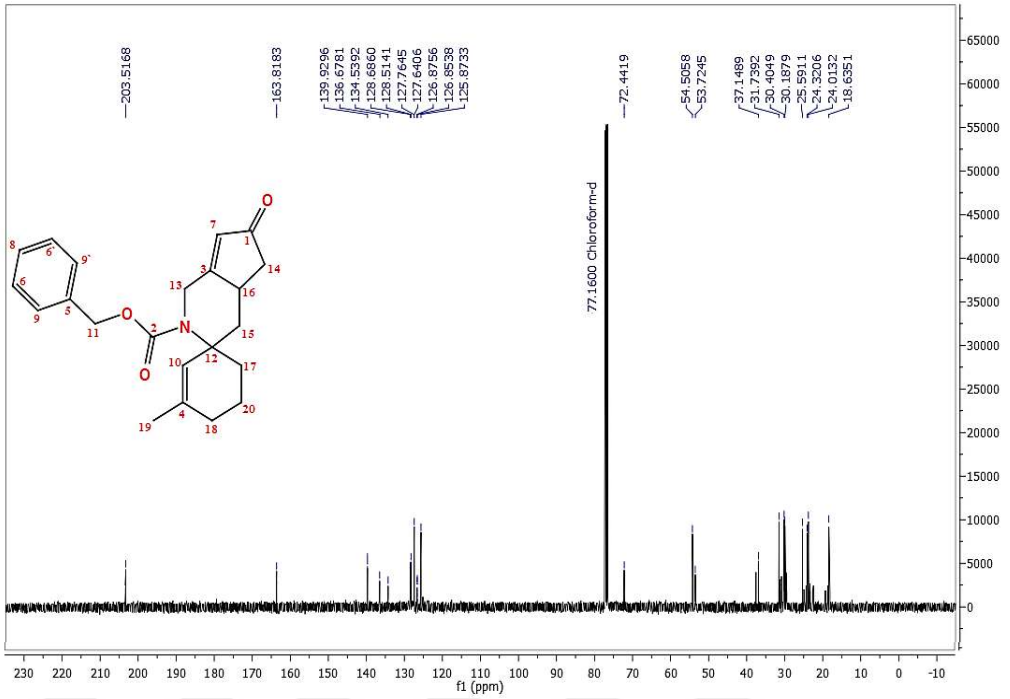
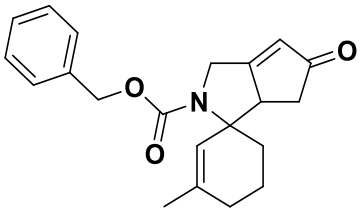


Figure 4.22. ^{13}C-NMR spectrum of benzyl 3-methyl-6'-oxo-4',4a',5',6'-tetrahydro-spiro[cyclohexane-1,3'-cyclopenta[c]pyridin]-2-ene-2'(1'H)-carboxylate

4.2.3.3 Benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'H-spiro [cyclohe-xane-1,1'-cyclopenta[c]pyrrol]-2-ene-2'-carboxylate (9a)



9a

The product was purified by column chromatography using system solvent of (EtOAc: Hexane: Et_3N) (1:2:1%). (Rf = 0.49).

Benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'H-spiro[cyclohe-xane-1,1'-cyclopenta[c]pyrrol]-2-ene-2'-carboxylate was obtained as dark brown thick oil with 65% chemical yield. Chemical formula ($C_{21}H_{23}NO_3$). Molecular weight: (337.42). The product was identified by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

IR: (3010) cm^{-1} for C_{SP}^2 –H, (2924) cm^{-1} for C_{SP}^3 –H, (2968) cm^{-1} for -CH_3, (1697) cm^{-1} for >C=O, (1645) cm^{-1} for >C=CH_2, C_{SP}^2 –O at (1278) cm^{-1}. Finally, at (1213) cm^{-1} for C_{SP}^3 –N<.

^{1}H-NMR: The spectrum of benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'H-spiro[cyclohexane-1,1'-cyclopenta[c]pyrrol]-2-ene-2'-carboxylate shows multiplet between 0.9 – 1.45 ppm and between 1.97 – 2.14 ppm for methylene protons 11 and 9 respectively. The methyl protons 10 show singlet at 1.22 ppm. One of diastereotopic methylene proton 8 shows multiplet between 1.68 – 1.76 ppm, and the other one exhibits doublet of doublet of doublet at 1.62 ppm with J_1 = 2.8, J_2 = 7.1 and J_3 = 11.5 Hz. Moreover, one of the diastereotopic methylene proton 7 shows doublet of doublet at 2.23 ppm with J_1 = 10.9, J_2 = 5.7 Hz, and the other one shows doublet of doublet at 2.48 ppm with J = 2.8 and 10.0 Hz. The methine proton 6 shows multiplet between 3.70 – 4.12 ppm. One of the diastereotopic proton 5 shows doublet at 4.46 ppm with J = 3.9 Hz and the other one shows doublet at 4.8 ppm with J = 2.0 Hz. Furthermore, benzylic methylene protons 4 show doublet at 5.15 ppm with J = 16.2 Hz. In addition, multiplet between 5.74 – 5.37 ppm due to olefinic methine proton 3, doublet for methine proton 2 at 6.04 ppm with J = 2.9 Hz. Finally, phenyl ring protons show multiplet between 7.57 – 7.06 ppm.

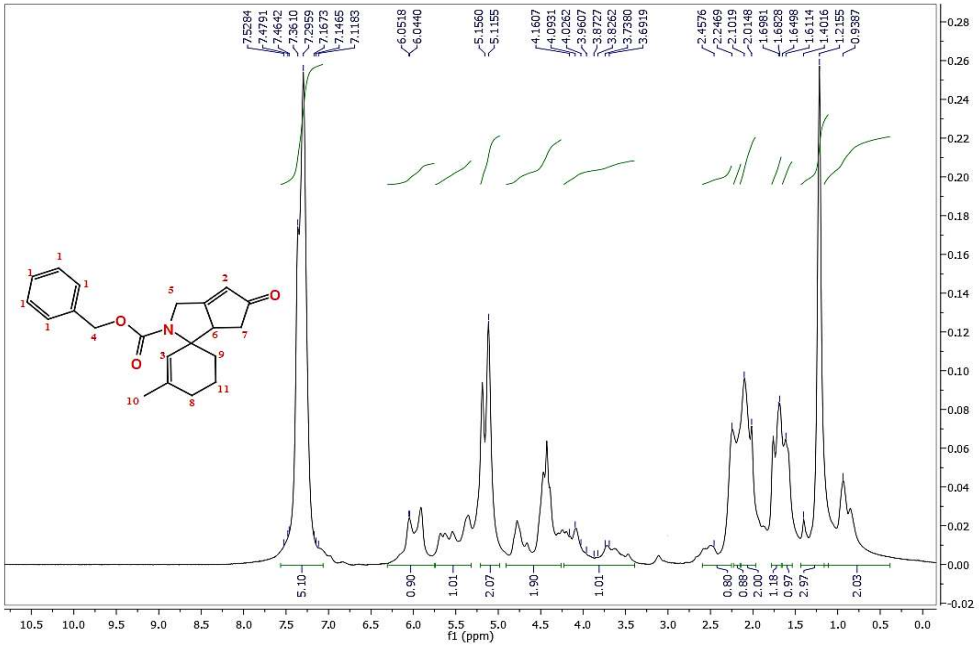


Figure 4.23. ^{1}H-NMR spectrum of benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'H-spiro[cyclohexane-1,1'-cyclopenta[c]pyrrol]-2-ene-2'-carboxylate

^{13}C-NMR: The spectrum of benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'H-spiro[cyclohexane-1,1'-cyclopenta[c]pyrrol]-2-ene-2'-carboxylate shows signals at 21.1, 27.5 and 29.7 ppm due to methylene carbons 19, 17 and 16 in cyclohexene ring respectively. The methyl carbon shows signal at 24.0 ppm. The signal at 31.1 ppm due to methylene carbon 15. The stereogenic carbon 14 shows signal at 46.9 ppm. Furthermore, the signal at 49.1 ppm for methylene carbon 13. The quaternary carbon at position 12 exhibits signal at 54.6 ppm. In addition, signal at 67.3 ppm for benzylic methylene carbon 11. Signals at 123.7 and 128.7 ppm belong to methine carbons at positions 10 and 6 respectively. Moreover, methine carbons 9, 9`, 8, 7 and 7` of the phenylic ring exhibit signals at 128.2, 128.1, 128.3 128.5 and 128.4 ppm respectively. The quaternary carbons 5, 4, and 2 show signals at 136.5, 142.3 and 152.6 ppm respectively. Ester carbon and carbonyl carbon 3 and 1 exhibit signals at 171.7 and 213.2 ppm.

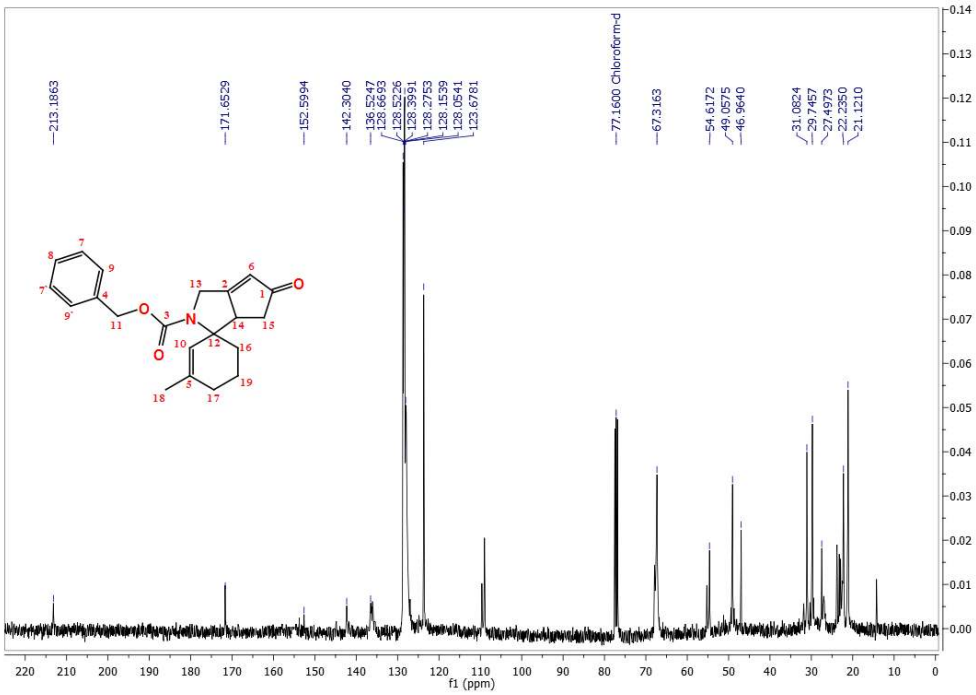


Figure 4.24. ^{13}C-NMR spectrum of benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'H-spiro[cyclohexane-1,1'-cyclopenta[c]pyrrol]-2-ene-2'-carboxylate

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6. APPENDICES

Appendix 1: IR Spectrum of Some Products

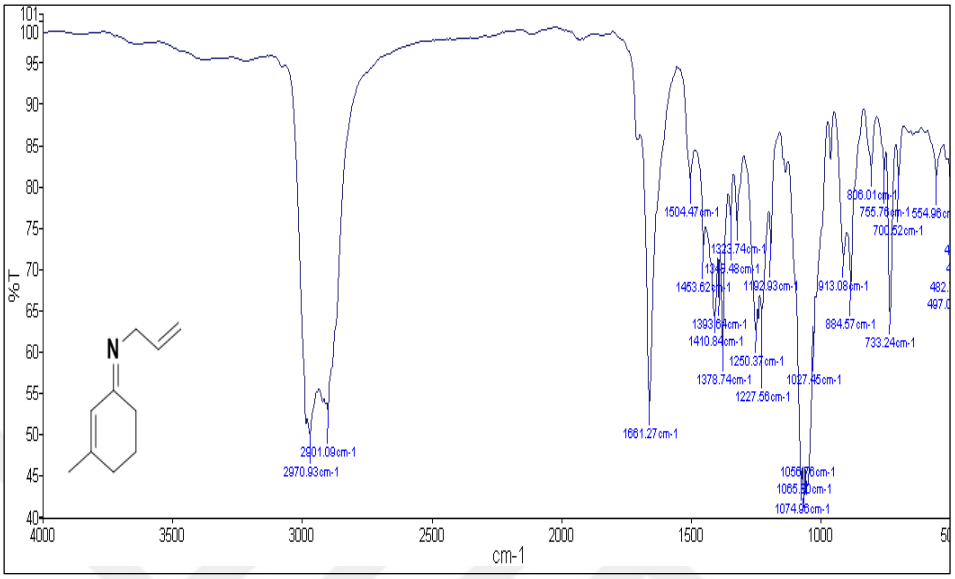

Figure 6.1. IR spectrum of *(E)*-N-allyl-3-methylcyclohex-2-en-1-imine

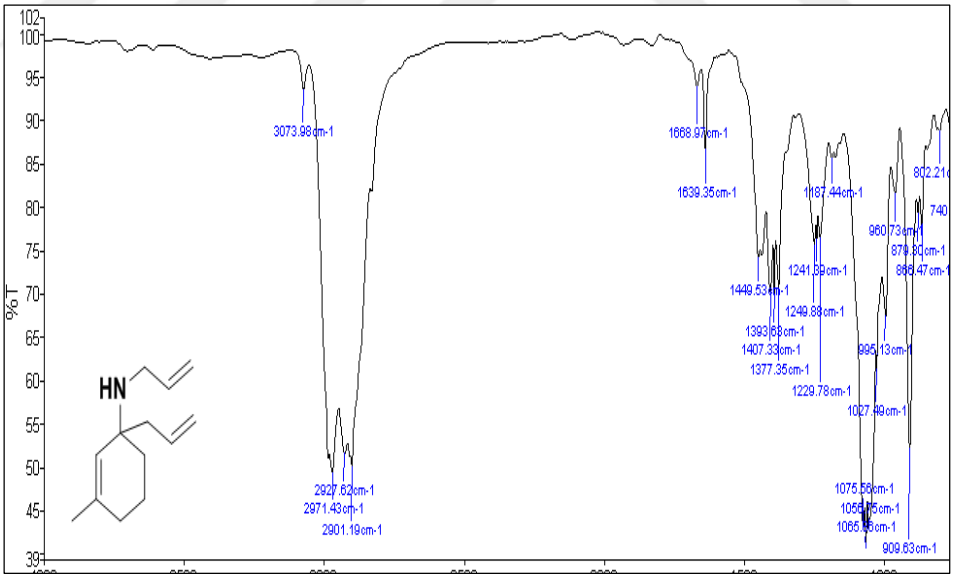

Figure 6.2. IR spectrum of N,1-diallyl-3-methylcyclohex-2-en-1-amine

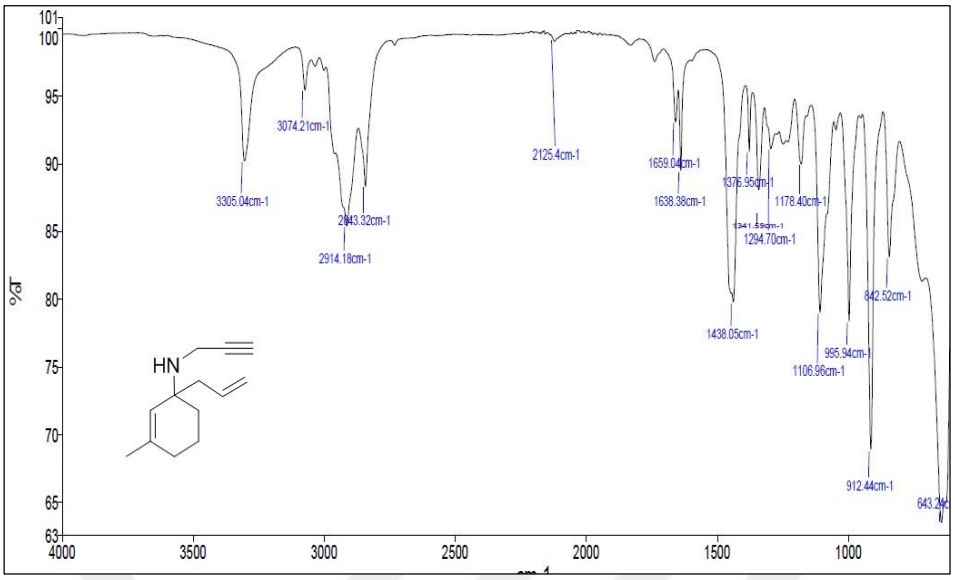

Figure 6.3. IR spectrum of 1-allyl-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-amine

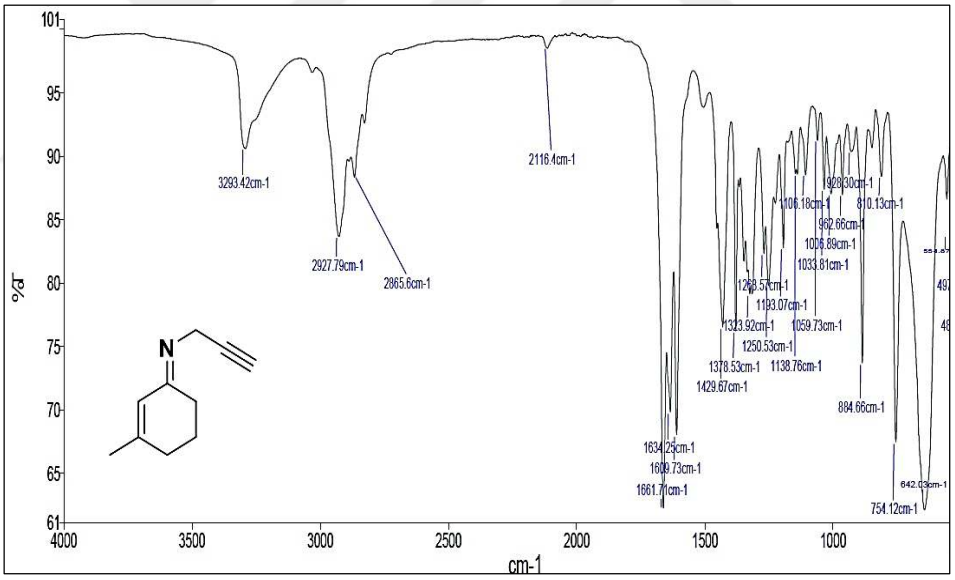

Figure 6.4. IR spectrum of (*E*)-3-methyl-N-(prop-2-yn-1-yl)cyclohex-2-en-1-imine

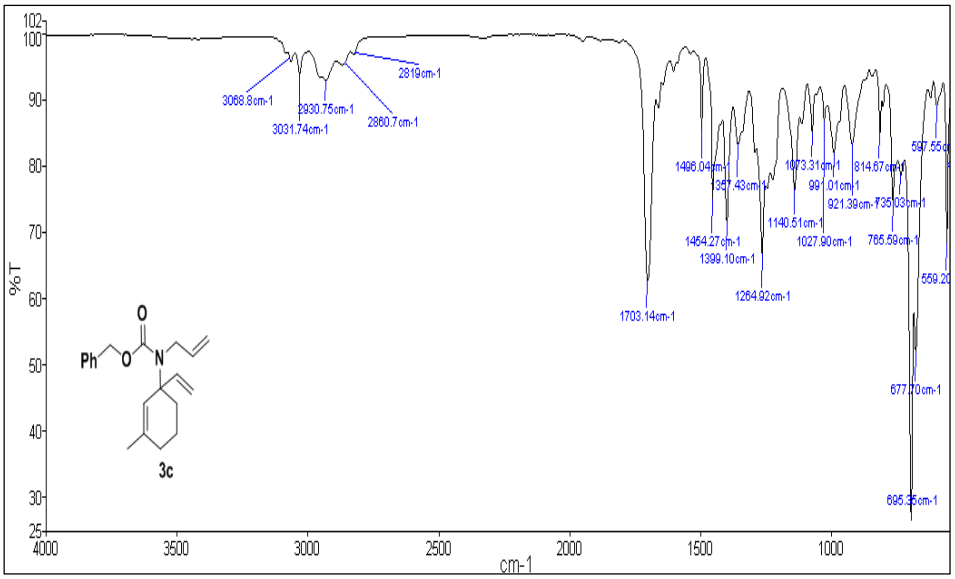

Figure 6.5. IR spectrum of benzyl allyl(3-methyl-1-vinylcyclohex-2-en-1-yl) carbamate

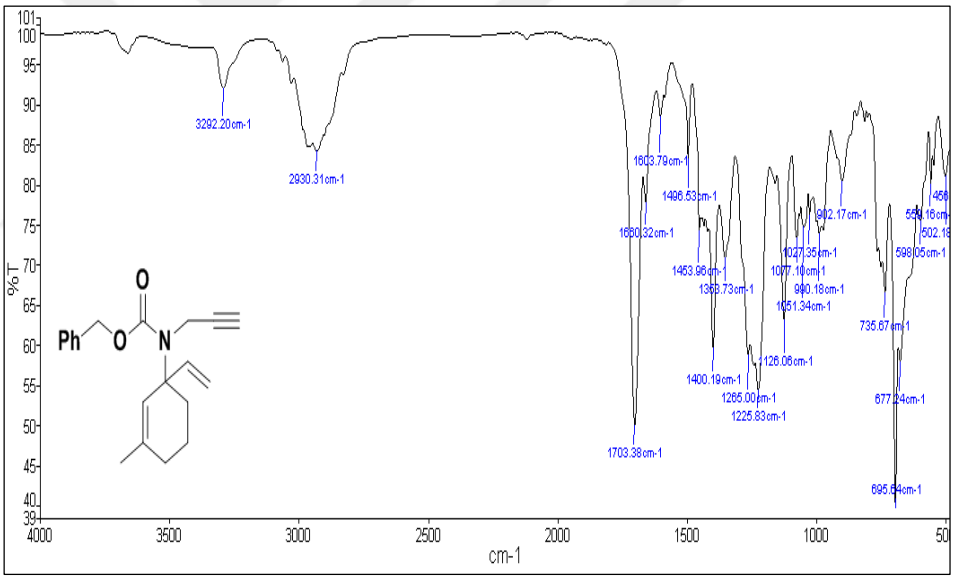

Figure 6.6. IR spectrum of benzyl (3-methyl-1-vinylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate

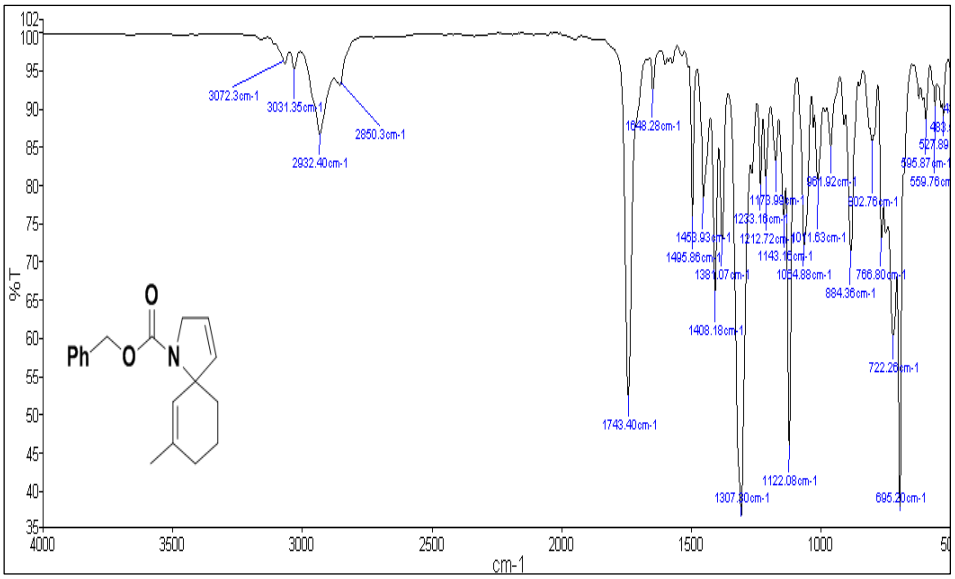

Figure 6.7. IR spectrum of benzyl 7-methyl-1-azaspiro[4.5]deca-3,6-diene-1-carboxylate

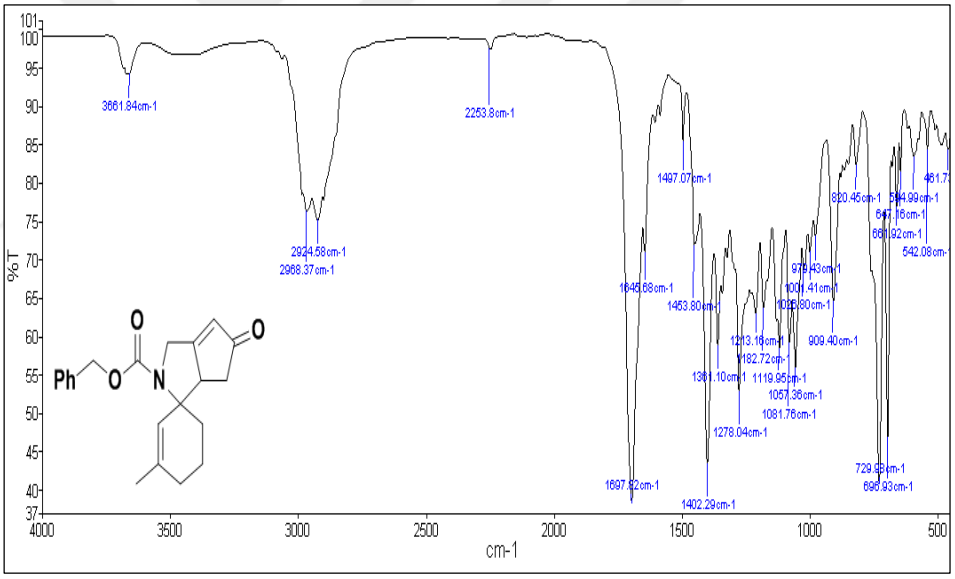

Figure 6.8. IR spectrum of benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'H-spiro[cyclohe-xane-1,1'-cyclopenta[c]pyrrol]-2-ene-2'-carboxylate

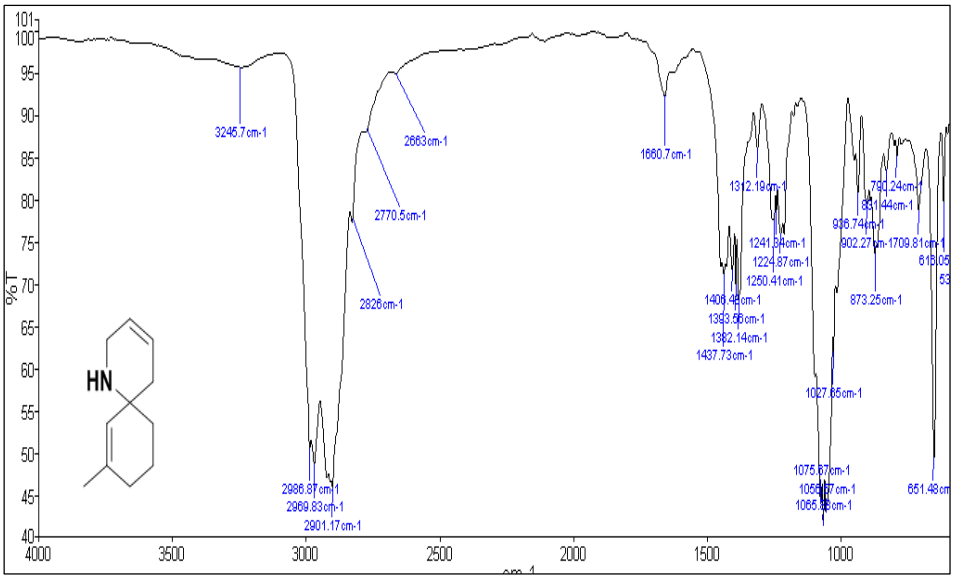

Figure 6.9. IR spectrum of 8-methyl-1-azaspiro[5.5]undeca-3,7-diene

7. CURRICULUM VITAE

Name SURNAME :

Place and Date of Birth :

Universities

Bachelor's Degree :

MSc Degree

e-mail :

Address

List of Publications :

[1] Buhlak S., Ibrahim B., Alhamoui M., (2014) "Manufacturing Mixed Lubricant Grease Based on Syrian Base Oil and studying Its Properties", International Journal of ChemTech Research, 6 (4): 2247-2254.

8. ORIGANILITY REPORT

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DIRECTORATE OF INSTITUTE OF GRADUATE STUDIES

STUDENT & SUPERVISOR PLAGIARISM DECLARATION FORM

Department	Chemistry		
Name and surname	Shafeek BUHLAK		
Student number	99919468858		
Postgraduate program	MSc with thesis ☐	PhD ☑	
Academic year and semester of thesis examination	2020 / 2021	Autumn ☑	Spring ☐
Thesis defence date	28 / 01 / 2021		
Number of pages	146		
Thesis title (Tr)	Sikloheksen içeren azaspirodien bileşiklerinin HKM yöntemi ile ve ilgili tetrahidrospirosiklopenta[c]pirolidinon bileşiklerinin PKR ile sentezi.		
Thesis title (Eng)	Synthesis of Cyclohexene Substituted Azaspirodien Compounds By RCM and Corresponding Tetrahydrospirocyclopenta[c]pyrolidinone Compound via PKR.		

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