ABANT IZZET BAYSAL UNIVERSITY

THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

SYNTHESIS OF VARIOUS TETRAHYDROPYRIDINE DERIVATIVES

MASTER OF SCIENCE

DURUKAN KOÇ

BOLU, JANUARY 2017

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APPROVAL OF THE THESIS

SYNTHESIS OF VARIOUS TETRAHYDROPYRIDINE DERIVATIVES submitted by **DURUKAN KOÇ** in partial fulfillment of the requirements for the degree of Master of Science in **Department of Chemistry, Abant Izzet Baysal University** by,

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January 25, 2017

Prof. Dr. Duran KARAKAS .....

Director, **Graduate School of Natural and Applied Sciences**

To the Unforgettable Memories of,

My grandmother Zehra KOÇ and my grandfather Esma GÜÇLÜ

My Parents, İsmil KOÇ and Adile KOÇ

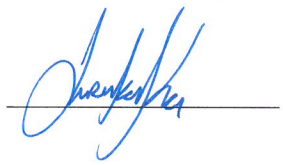
And

My big brother, Doğacan KOÇ

DECLARATION

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Durukan KOÇ



ABSTRACT

SYNTHESIS OF VARIOUS TETRAHYDROPYRIDINE DERIVATIVES
MSC THESIS
DURUKAN KOÇ
ABANT IZZET BAYSAL UNIVERSITY GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
DEPARTMENT OF CHEMISTRY
(SUPERVISOR: ASSOC. PROF. DR. F. DEVRİM ÖZDEMİRHAN)

BOLU, JANUARY 2017

In this context it is intended to obtain corresponding tetrahyropyridine frameworks for this *N*-allylimine compounds; building blocks for nitrogen containing dien structures which are Ring Closing Methatesis (RCM) precursors were synthesized from *p*-chlorophenyl and furyl substituted carboxaldehydes in the presence of allylamine and magnesium sulfate. Then in the second step, *N*-allylimine compounds obtained will be converted to corresponding dien structures; RCM precursors by Grignard type reaction. Then the dien structures will be converted to corresponding *p*-chlorophenyl substituted tetrahydropyridine skeleton, 2-(4-chlorophenyl)-1,2,3,6 tetrahydropyridine with 87% chemical yield, and furyl substituted tetrahydropyridine derivative; (2-furan-2-yl)-1,2,3,6 tetrahydropyridine skeleton isolated by 93% chemical yield by Ring Closing Methatesis reaction in the presence of Grubbs' II nd generation catalyst.

Corresponding *N*-propargylimine structure were obtained in the presence of propargylamine and $MgSO_4$ by using *p*-chlorophenyl, and furyl-substituted carboxaldehydes as starting compounds. *N*-propargylamine compounds were converted to corresponding nitrogen containing enyne skeletons by Grignard type reaction in the presence of Mg and allylbromide in diethyl ether. From the corresponding nitrogen containing enyne skeletons; *p*-chlorophenyl substituted cyclopenta[c]piperidine framework;3-4-(chlorophenyl)3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridine-6-(2*H*)-one by 81% chemical yield and >96% diastereomeric excess. Then furyl substituted cyclopenta[c]piperidine unit; 3-(furan-2-yl)-3,4,4a, 5-tetrahydro-1*H*-cyclopenta[c]pyridine-6(2*H*)-one isolated by 79% chemical yield with 86% diastereoselectivty by PKR in the presence of cobalt carbonyl and *N*-methyl morpholine *N*-oxide.

KEYWORDS: Ring Closing Metathesis, Pauson-Khand reaction, Heterocylic compounds, Grubbs Catalyst

ÖZET

ÇEŞİTLİ TETRAHİDROPİRİDİN TÜREVLERİNİN SENTEZİ
YÜKSEK LİSANS TEZİ
DURUKAN KOÇ
ABANT İZZET BAYSAL ÜNİVERSİTESİ FEN BİLİMLERİ ENSTİTÜSÜ
KİMYA ANABİLİM DALI
(TEZ DANIŞMANI: DOC. DR. DEVRİM ÖZDEMİRHAN)

BOLU, OCAK - 2017

Sözkonusu tetrahidropiridin iskeletlerinin rasemik olarak eldesi hedeflenmiş, bunun için ilk olarak, Halka Kapama Metatezi (HKM) habercisi olan azot içeren dien yapıların sentezlenmesinde önemli yapıtaşları olan ilgili N-alilimin bileşikleri *p*-klorofenil ve furil substituentli karboksi aldehitlerden alilamin ve magnezyum sülfat eşliğinde elde edilmiştir. Daha sonra elde edilen N-alilimin bileşikleri Grignard tipi reaksiyon ile HKM habercisi olan ilgili dien yapılara dönüştürülmüşler en önemli aşama ise dien yapılar Halka Kapama Yöntemi ile Grubbs' II katalizörü yardımı ile kapatılarak ilgili p-klorofenil substituentli tetrahidropridin iskeleti; 2-(4-klorofenil)-1,2,3,6 tetrahidropiridin, %87 ve furanil substituentli tetrahidropiridin türevi olan (2-furan-2-il)-1,2,3,6 tetrahidropiridin iskeleti %903 kimyasal verimle izole edilmiştir.

Siklopenta[c]piperidin iskeletinin önemi projenin ikinci yarısındaki hedefimizi belirlemiş bu açıdan sözkonusu iskeletin eldesi için ilk olarak PKR habercisi, azot içeren enin yapılarının sentezi gerçekleştirilmiştir. Bunun için ilk olarak *p*-klorofenil ve furil substituentli karboksaldehitlerden proparjilamin ve MgSO4 varlığında ilgili *N*-proparjilimin yapılar elde edilmiştirtir. *N*-proparjilimin bileşikleri Grignard tipi reaksiyon ile Mg ve alilbromür varlığında dietileter içerisinde sözkonusu azot içeren enin iskeletine dönüştürülmüşlerdir. Enin yapılardan PKR ile kobaltkarbonil ve *N*-metilmorfolin-*N*-oksit varlığında p-klorofenil substituentli siklopenta[c]piperidin 3-4-(klorofenil)-3,4,4a,5-tetrahidro-1*H*-siklopenta[c]pridin-6(2*H*)-on %81 kimyasal verim ve >%96 %de değeriyle izole edilmiştir. Daha sonra siklopenta[c]piperidin iskeleti, furil substituentli siklopenta[c]piperidin yapıtaşı 3-(furan-2-il)-3,4,4a,5-tetrahidro-1H-siklopenta[c]piridin-6(2*H*)-on, %79 kimyasal verim ve >% 86 % de değeriyle izole edilmişlerdir.

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

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LIST OF ABBREVIATIONS AND SYMBOLS

Acac : Acetylacetone

Atm : Atmosphere

BuSMe : Butyl methyl sulphide

Cbz : Carboxybenzyl

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

$CDCl_3$: Chloroform-d

CH_2Cl_2 : Dichloromethane

$Co_2(CO)_6$: Dicobalt hekzacarbonil

$Co_2(CO)_8$: Dicobalt octacarbonil

$Co(acac)_2$: Cobalt (II) acetylacetonate

cod : 1,5-cyclooctandienyl

$Cy(NH_2)$: Cyclohexylamine

DCM : Dicholoromethane

DME : Dimethylethane

DMAC : Dimethylacetamide

EtOAc : Ethyl acetate

Glu : Glutamic acid

Hz : Heartz

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

IR : Infra Red

Ind : Indenyl

Me_3SiCN : Trimethylsilanecarbonitrile

ml : Milliliter

mmol : Millimole

NMO : 4-methyl-morpholine N-oxide

$NaBH_4$: Sodium tetrahydroborate

NH_4Cl : Ammonium Chloride

mCPBA : Meta-chloroperbenzoic acid

PD : Parkinson's Disease

Ph : Phenyl

$P(OPh)_3$: Triphenyl phosphite

PKR : Pauson-Khand Reaction

SN	**:** Substantia Nigra
SEM	**:** 2-(tri-methylsilyl)ethoxymethyl
SiO_2	**:** Silicon dioxide
t-BuLi	**:** Tersiyer butyllithium
TASF	**:** Tris- (dimethylamino)sulfonium difluorotrimethylsilicate
TBS	**:** Tert-Butyldimethylsilyl ethers
THP	**:** Tetrahydropyranyl ethers
TMANO	**:** Trimethylamine-N-oxide
TMS	**:** 3-Bromo-1-(trimethylsilyl)-1-propyne
TPAP	**:** Tetrapropylammonium perruthenate
Ts	**:** Tosil
ppm	**:** Parts per million
s	**:** Singlet
bs	**:** Broad singlet
d	**:** Doublet
dd	**:** Doublet of doubletq
ddd	**:** Doublet of doublet of doublet
t	**:** Triplet
tdd	**:** Triplet of doublet of doublet
qd	**:** Quartet of doublet
pd	**:** Pentet of doublet

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I devote this thesis to my grandfather Zehra KOÇ, my grandmother Esma GÜÇLÜ, my parents İsmail KOÇ and Adile KOÇ and finaly my big brother Doğacan KOÇ to their unforgettable memories.

1. INTRODUCTION

1.1 Heterocyclic Compound

Fused ring system where each bond is part of a ring; where each ring is ortho-fused or ortho- and peri-fused to at least one other ring; and where no bond is common to more than two rings is termed a fused ring system (Moss, 1998).

Ortho-fused **1**

Ortho- and peri-fused **2**

Figure 1.1. Type of fused ring system

It is known that fused heterocyclic compounds indicate a variety of biological properties and many of them have found application as chemotherapeutic agents in the curations of Parkinson's Disease.

Parkinson's disease (PD) which is a neurodegenerative, slowly progressive disorder, mainly characterized by the selective loss of dopaminergic neurons of the substantia nigra (SN) It has been suggested that neuroinflammation, oxidative stress, protein degradation, mitochondrial dysfunction, disturbed autophagy and aging are associated with this pathology (Al-Harbi, 2013).

Moreover by hyperglycemia resulting from defects in insulin secretion, insulin action or both the large number of antibiotics and chemotherapeutics, the emergence of old and new antibiotic resistant bacterial strains constitutes a substantial need for the new class of potent antimicrobial agents. Heterocyclic compounds play an important role in designing a new class of structural entities of medicinal importance with new mechanisms of action (Al-Harbi, 2013).

Followed by "Hercampuri", has been used since ancient times as a remedy against hepatitis, diabetes, and hypertension. Investigations into its chemical constituents have revealed a variety of bitter phenolic compounds that occur together with a limited number of terpenoids. Nitidasin is one of the example of these (Daniel et al, 2014).

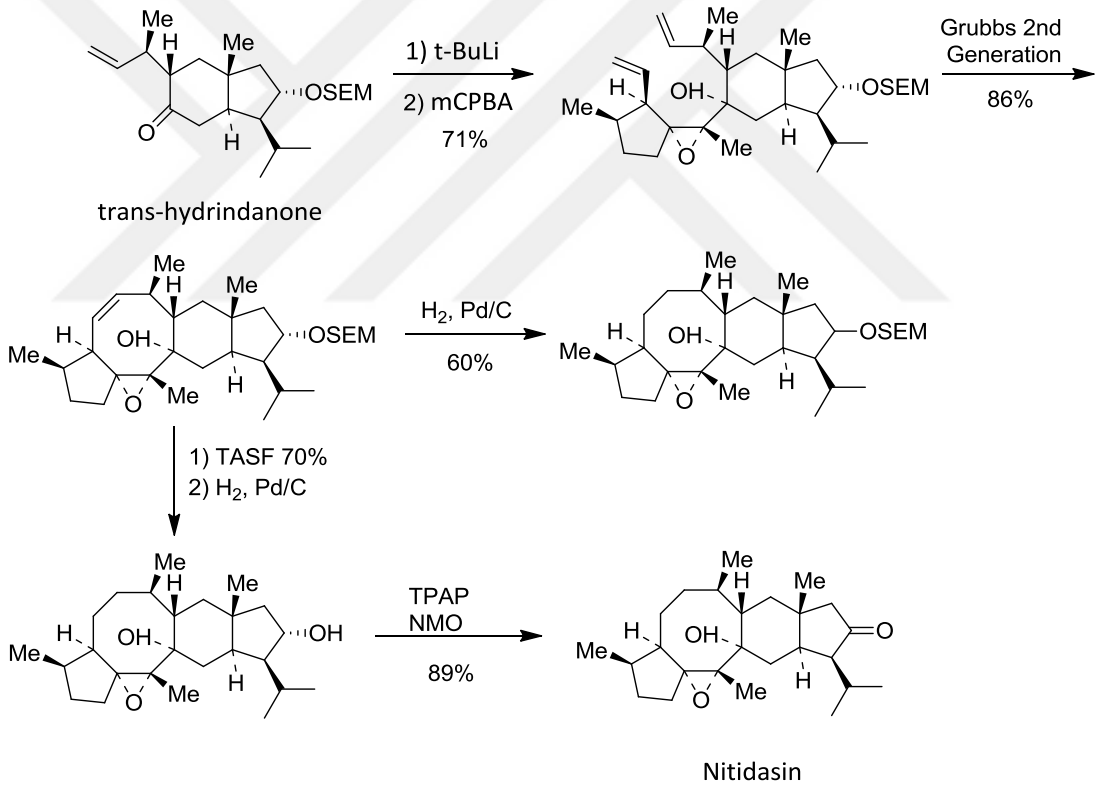

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Figure 1.2. Synthesis of Nitidasin

Highly oxynated fused cyclopenta[c]piperidine ring skeleton obtain via Pauson Khand reaction. Can be a building block for the construction of İridoid skeleton which are large family of natural products having biological activities ranging from sedative to antimicrobial to antileukemic effects or as specionin, have shown potent antifeedant activity for some common insect pests (Jose, 1998).

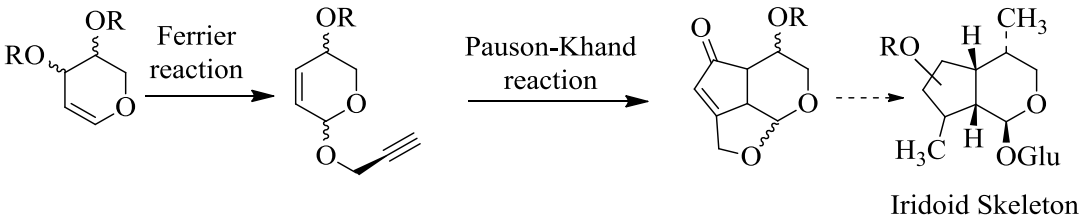

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Figure 1.3. General strategy for Iridoid skeleton

Heterocycle-fused quinolinones having wide biological activities has attracted a great deal of attention in the field of medicinal chemistry. Indeed, it has recently been reported that selected heterocycle-fused quinolinone derivatives can act as 1) microsomal prostagrandin E synthase- 1 (mPGES-1) inhibitors 2) serine protease dipeptidyl peptidase 4 (DPP-4) inhibitors 3) Hedgehog (Hh) signal pathway inhibitors 4) M4 muscarinic ACh receptors positive allosteric modulators (mAChR PAMs) 5) cyclic nucleotide phosphodiesterase 9A (PDE9A) inhibitors 6) and (S)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)-propionic acid (AMPA) antagonists (Tomoyo et al, 2015).

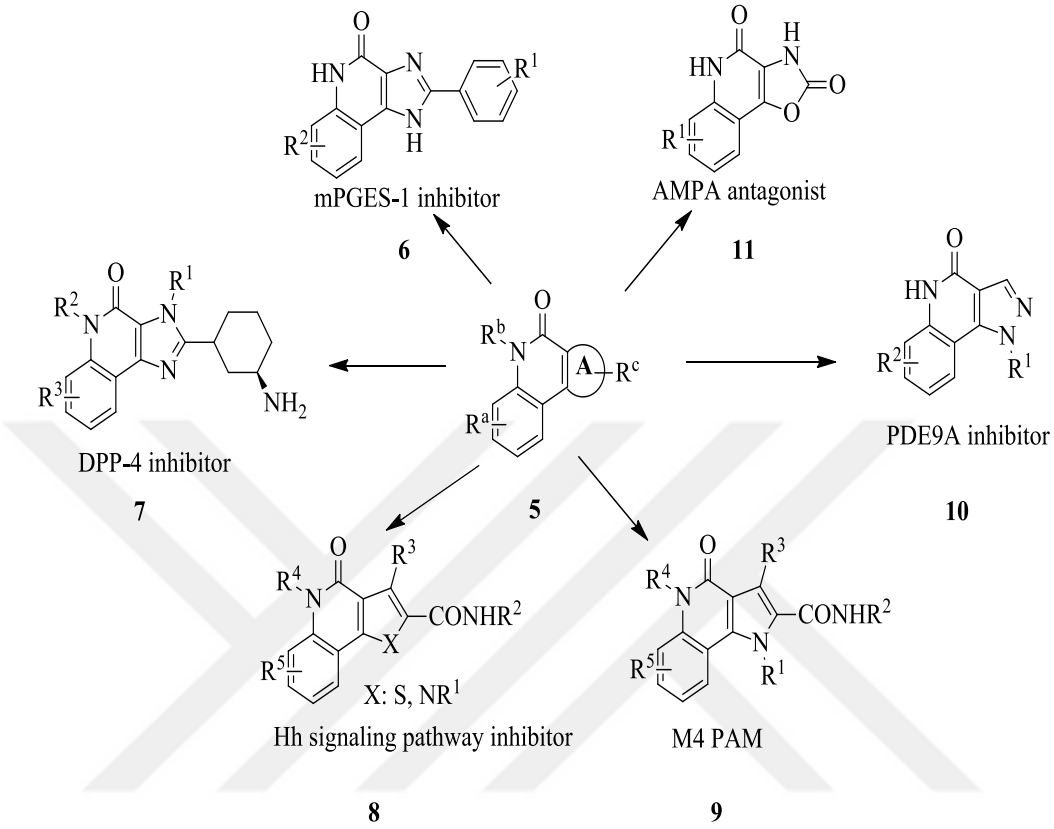


Figure 1.4. The heterocycle-fused quinoline scaffold.

Dienyne metathesis is a useful method for the synthesis of fused bicyclic or polycyclic compounds in one step and many bond fissions and bond formations occur during the process. In the total synthesis of natural products using dienyne metathesis, retro-synthetic analyses are completely different from those of the methods reported previously, and the reaction process was generally shortened. Fused polycyclic compounds can be also dienyne metathesis demonstrated by Grubbs (Grubbs et al, 1998).

1.2 Pauson-Khand Cycloaddition Reaction

1.2.1 Introduction to the Pauson-Khand Reaction

Catalysis and metal-mediated transformations play an important role in addressing the atom economy issue (Gibson and Stevenazzi, 2003). The issue of atom economy raised by Trost, "an ideal chemical reaction must be not only selective, but also a simple addition in which the other reactants are required only in catalytic amounts" (Trost, 1995).

There is surely no match for the Pauson–Khand reaction in terms of potential flexibility and atom economy for the synthesis of five membered rings (Gibson and Mainolfi, 2005). In 1971 Pauson and Khand pioneered [2+2+1] carbonylative cyclization reaction which is one of the earliest examples (Pauson and Khand, 1971).

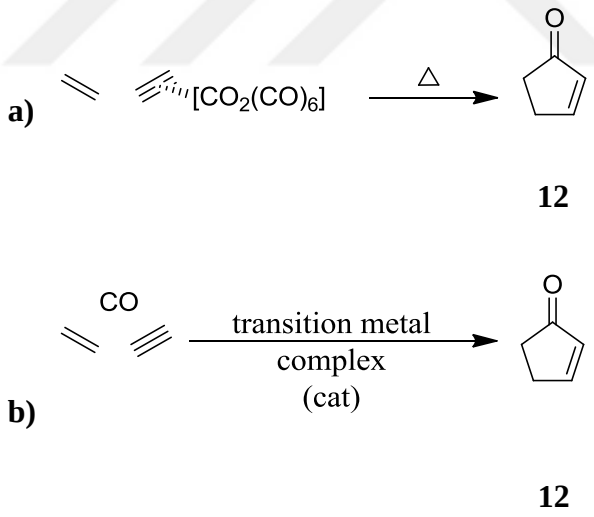
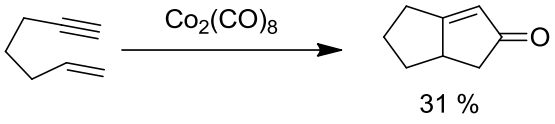


Figure 1.5. The PKR: a) The stoichiometric approach; b) The catalytic version

The comprehensive process is a formal three-component, incorporating the alkene p-bond, [2+2+1] cycloaddition, an alkyne p-bond, and the carbon atom of CO into the new five-membered ring (Chung, 1999).

Schore and Croudace (1981) expanded the synthetic utility of this reaction considerably by attaching the alkene to the alkyne via a carbon tether and demonstrating the first intramolecular Pauson-Khand cycloaddition reaction in 1981.

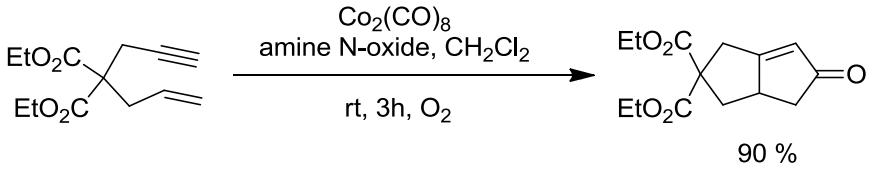


13 **14**

Figure 1.6. First intramolecular Pauson-Khand reaction

Now the reaction has been known as an important methodological approach to the challenging cyclopentenone ring system and has been used in many synthetic applications (Meijere and Tom Dieck, 1988).

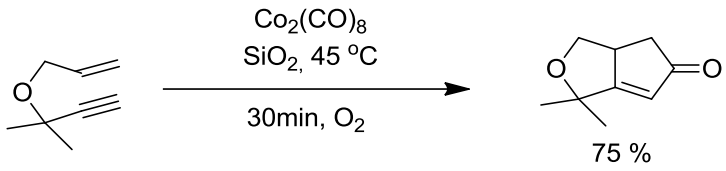
The Pauson-Khand reaction, (PKR) often has encountered some limitations because of its intrinsic problems in reaction conditions such as requiring high temperature (usually 60–120°C) and long reaction time (6h–4 days) despite its versatility and tolerance of a number of reactive functional groups (Chung, 1999). Initially, the necessity of the severe conditions and the resulting low yields compromised the synthetic utility of the process. However, the addition of a number of additives or promoters increases the reaction (Chung, 1999).



15 **16**

Figure 1.7. Effect of additives to the Pauson-Khand reaction

Adsorption of the cyclization precursor onto silica gel or alumina was the first demonstrated by Smit and Caple. To allow the reactions to be carried out at lower temperatures with shorter reaction times. (Smit and Caple et al, 1986)



17 **18**

Figure 1.8. The intramolecular Pauson-Khand cycloaddition reactions

Krafft (1988) attached a directing/accelerating ligand to an undeformed olefin and acquired both high levels of regiocontrol and high yields in the intermolecular PKR.

The promotion of the PKR at room temperature using N-methylmorpholine N-oxide and trimethylamine N-oxide, respectively were reported by Schreiber and Jeong independently.

1.2.2 Cyclopentanone Ring

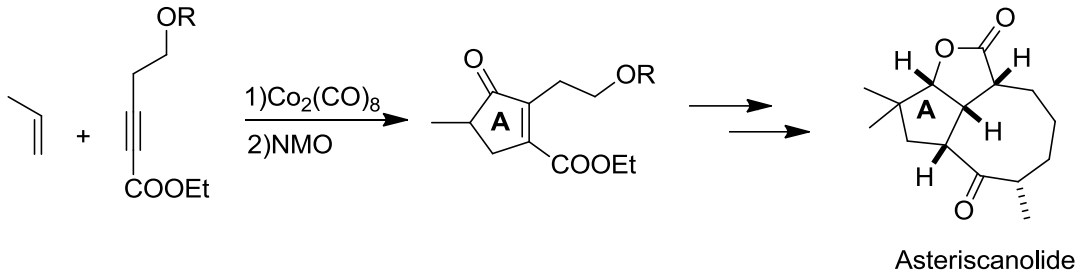
For the synthesis of the cyclopentenone ring, the Pauson-Khand reaction (PKR) has been established as a powerful method.

Many natural products contain a cyclopentane ring as one of their structural property. For the synthesis of cyclopentanes, one of the primary methods the Pauson-Khand cycloaddition has seen widespread use in a kind of approaches to natural product synthesis (Brummond and Kent, 2000).

This contain the synthesis of prostaglandins, different triquinanes and polyquinanes such as ceratopicanol, furanether B, kainic acid, hirsutene, fenestranes, brefeldine A, epoxidictimene, loganine, xestobergsterol, spatane, daphane, iridomirmecin, dendrobin, kalmanol and b-cuparenone (Perez-Castells et al, 2004).

Kraft reported the total synthesis of asteriscanolide, a sesquiterpene structurally connected epoxidictimene. The synthesis depends on a regioselective intermolecular

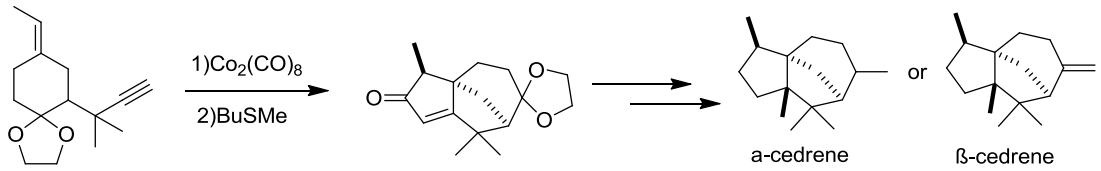
PKR with propene. Means of a ring closing metathesis reaction accomplished the formation of the cyclooctane ring in the final stages (Krafft et al,2001).



19 **20** **21** **22**

Figure 1.9. The total synthesis of Asteriscanolide

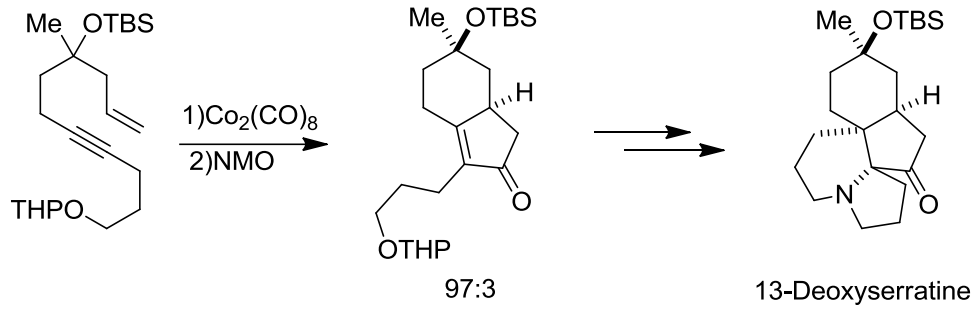
For the synthesis of the cedrene skeleton, an intermolecular PKR has been used as a key step. A monocyclic enyne with an exocyclic olefin fragment was the starting material. In high yield, a bridged adduct is obtained. It is further modulated to supply a total synthesis of α- and β-cedrene (Kerr et al, 2001).



23 **24** **25** **26**

Figure 1.10. The synthesis of the Cedrene skeleton

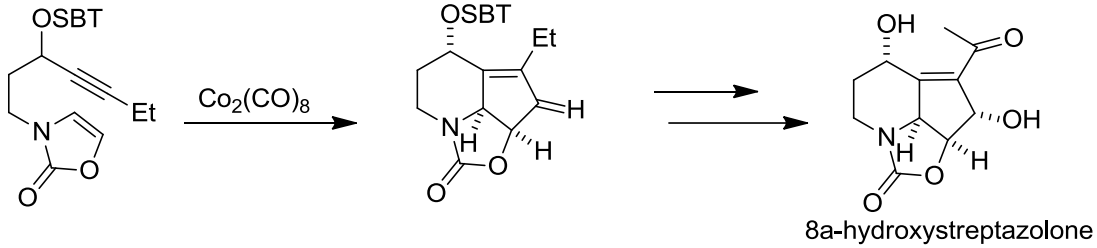
Zard has reported a total synthesis of 13-deoxyserratine recently. A highly diastereoselective Pauson-Khand reaction and a radical cyclisatin cascade were the key steps in this synthesis (Cassayre, 2002).



27 **28** **29**

Figure 1.11. The total synthesis of 13-Deoxyserratine

Mukai has impressed a total synthesis of 8a-hydroxystreptazolone in which the key step is an intramolecular Pauson-Khand reaction fulfilled on a 2-oxazolone derivative which is a natural product possessing antifungal and antibiotic activities (Nomura and Mukai, 2002).



30 **31** **32**

Figure 1.12. The total synthesis of 8α-Hydroxystreptazolone

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(+)-Fusarisetin A stand for an emerging class of anticancer agents. It structurally coupled with the members of the cytochalasin family of fungalmetabolites. The PKR has shown up as a powerful method for the synthesis of cyclopentenones, during the course of the past two decades. The reaction has been successfully applied

to the total syntheses of complex natural products. Herein, using the PKR as a key step reported last accomplishment of the total synthesis of (+)-fusarisetin A (Huang et al, 2013).

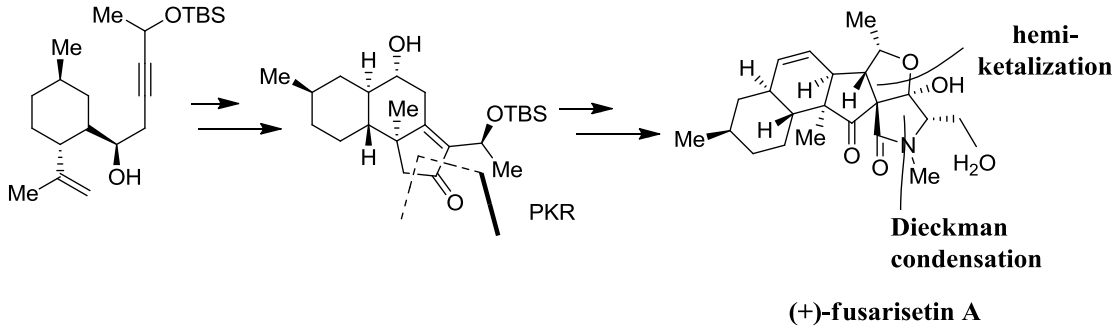


Figure 1.13. The total synthesis of (+)-Fusarisetin A

Tecomanine a substance with strong hypoglycemic activity, is one of a number of naturally-occurring alkaloids with cyclopentanopyridine- or cyclopentanopiperidinebased structures (Cordell, 1977). Hammouda and Motawi synthesized first isolated tecomanine in several ways (Hammouda and Motawi, 1959). They chose to find out the possibility that tecomanine might be efficiently accessed through Pauson–Khand cyclization of a suitably substituted alkenylalkynylamine precursor without the need to present the methyl groups ensuing to cycloaddition. (Ockey et al, 2003).

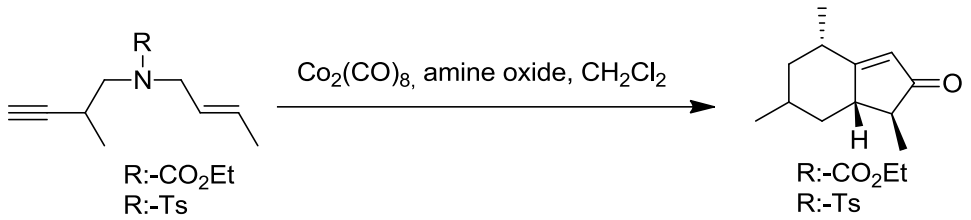
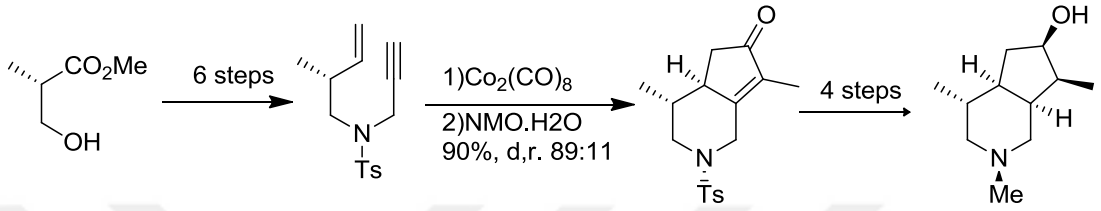


Figure 1.14. The total synthesis of Tecomanine

In a more general perception, since many natural products and pharmaceutically active agents have substituted piperidine ring systems the synthesis

of this class of functionalised heterocyclic compound remains of interest to the general synthetic chemistry community (Buffat, 2003; Watson, 2000).

A new class of monoterpene alkaloids, which is called as the kinabalurines, was isolated from Kopsia pauciflora in 1997 (Kam et al, 1997). These compounds isolated from different plant sources class, which display analgesic properties, have hypoglycaemic features.



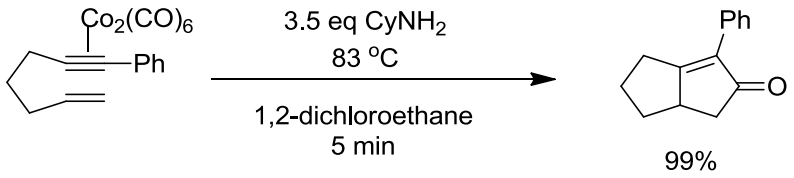
38 **39** **40** **41**

Figure 1.15. The total synthesis of Kinabalurines

1.2.3 Stoichiometric the Pauson-Khand Cycloaddition

A few advances of this reaction have been reported in recent years. Methods for generation of alkyne-$Co_2(CO)_6$ complexes in different solvents were used and reported their synthetic applications were developed. There have been several reports describing the use of cobalt, titanium and rhodium complexes in catalytic amounts, along with CO, in Pauson-Khand reaction cyclopentenone synthesis in recent years (Rajesh and Periasamy, 1999).

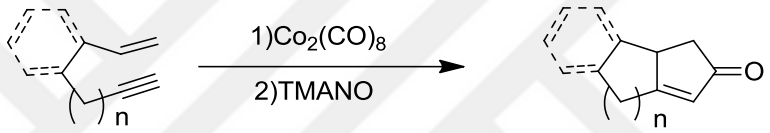
Sugihara and Yamaguchi reported several sulfides can be used to promote the stoichiometric Pauson-Khand reaction. Sugihara and co-workers reported the use of primary amine in the rate enhancement of the PKR (Sugihara et al, 1997). Sugihara attributes this finding to Krafft's demonstration that a properly positioned sulfur halve tethered to the Pauson-Khand precursor increases the reaction efficiency (Krafft, 1988).



42 **43**

Figure 1.16. Sugihara and co-workers cycloadduct

PeÂrez-Castells has shown that the addition of molecular filter to the N-oxide promoted cycloaddition results in improved yields of cycloadduct (PerArez-Castells et al, 1999).



44 **45**

Figure 1.17. Peârez-Castells cycloadduct

The moderately hindered primary amines, such as the ones containing secondary alkyl groups, promote the PKR most effectively.

1.2.4 Catalytic Pauson-Khand Reaction

There has been important interest in developing catalytic kind of the P-K cycloaddition. Recently there have been remarkable advances toward this end using sub-stoichiometric amounts of a kind of early and late transition metals such as cobalt, titanium, ruthenium and rhodium (Brummond and Kent, 2000).

1.2.5 Cobalt Catalyzed Cycloadditions

Indeed, Pauson and co-workers reported the first examples of the catalytic cycloaddition with octacarbonyldicobalt in 1973 (Pauson et al, 1973).

Previos examples contained only forced reactive alkenes like norbornene and were fulfilled with a continuous supply of ethyne. All the reactions were handled within a narrow thermal window (60–70 ^{o}C), and a range of pressures of carbon monoxide were employed (Gibson and Stevenazzi, 2003).

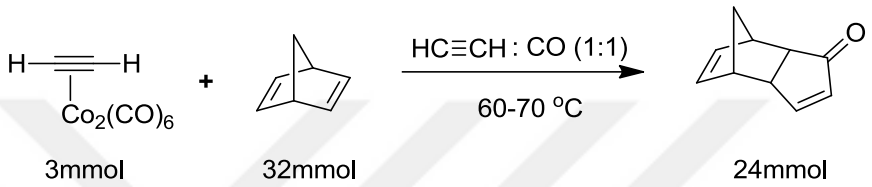


Figure 1.18 Cobalt catalyst cycloaddition

Following the work of Pauson and co-workers, to catalyse cycloadditions of nonforced alkenes (Pauson et al, 1974). Rautenstrauch and coworkers employed 0. 0022 equiv. of [$Co_2(CO)_8$] (Rautenstrauch et al, 1990).

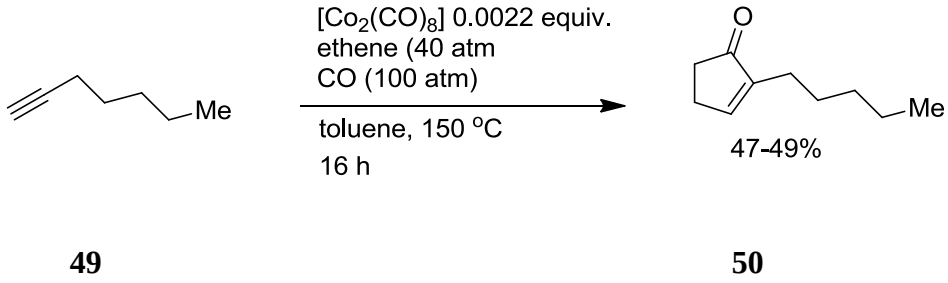
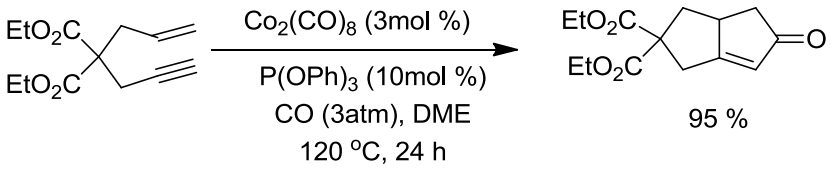


Figure 1.19. Rautenstrauch and coworkers catalyse cycloaddition

Jeong and Chung et al reported a catalytic conversion of enynes into cyclopentenones employing phosphites as coligands (Jeong and Chung et al, 1994).



51 **52**

Figure 1.20. Cobalt-catalyzed with triphenylphosphite as an additive

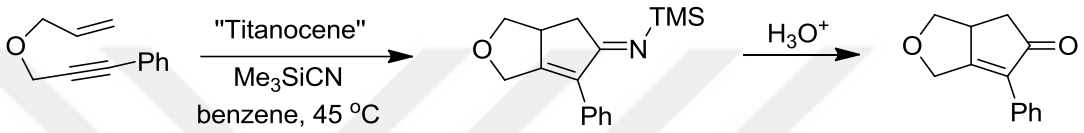
Table 1.1. A summary of cobalt catalysts activities

A Decade of Advancements in Pauosn-Khand Type Reaction			
A summary of cobalt catalysts activities			
Entry	Inter-PKR	Intra-PKR	Catalyst Sysytem
1	+	+	$[Co_2(CO)_8]+R_3PS$
2	+	+	$[Co_2(CO)_7PPh_3]$
3	+	–	$[Co_2(CO)_6(PPh_3)_2]$
4	+	+	$[Co_2(CO)_8$+S-BINAP]
5	–	+	$[Co_2(CO)_8+P(OPh)_3]$
6	–	+	$[Co_2(CO)_8$+biphosphite ligand]
7	–	+	$[Co_2(CO)_8$+hv]
8	–	+	$[Co_2(CO)_8+CyNH_2]$
9	–	+	$[Co_2(CO)_8$+DME]
10	+	+	$[Co_3CO)_9(\mu^3$-CH)]
11	+	–	$[Co_4(CO)_{12}]$
12	–	+	Stabilized Co nanoparticle
13	+	+	PEG-stabilized Co nanoparticle
14	+	+	Raney cobalt
15	+	+	$[Co_2Rh_2]$
16	+	+	$[Ru_3(CO)_{12}$/CNC]
17	+	–	$[Co_4(CO)_{11}P(OPh)_3]$
18	+	+	$[Co(acac)_2+NaBH_4]$
19	+	+	Indenyl cobalt (I)
20	+	–	$[Co_2(CO)_8$+PuPHOS/CamPHOS]
21	–	+	$[Co_2(CO)_8$+CTAB]
22	+	+	$[Co_2(CO)_8]$

1.2.6 Titanium Catalyzed Cycloaddition

Recently the use of other metals to contribute the catalytic Pauson-Khand cycloaddition has attracted much attention.

Buchwald and co-workers reported the development of a titanium catalyzed Pauson-Khand reaction. In a series of reports, Buchwald highlights a catalytic Pauson-Khand reaction equivalent that utilizes a titanocene as the catalyst to contribute cycloaddition between an enyne and an isocyanide (Buckwald et al, 1993, 1994; Hicks et al, 1996).

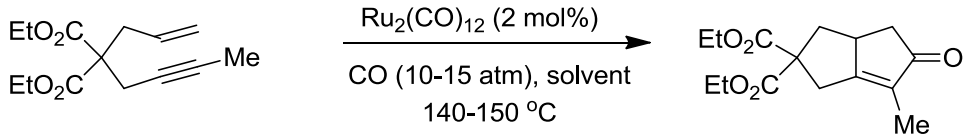


53 **54** **55**

Figure 1.21. Titanium catalyzed Pauson-Khand reaction

1.2.7 Ruthenium and Rhodium Catalyzed Cycloaddition

First one was Murwasai and Mitsudo et.al work, reported almost contemporaneously that $Ru_3(CO)_{12}$ effectively catalyzed the intramolecular cycloaddition of enynes to form cyclopentenones (Moritimo et al, 1997; Kondo et al, 1997).



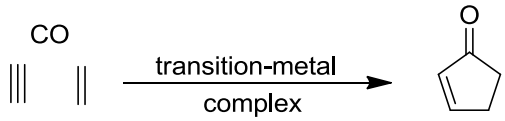
56 **57**

	solvent	yield
Murai	dioxane	86%
Mitsudo	DMAc	76%

Figure 1.22. Ruthenium catalyzed Pauson-Khand reaction

1.2.8 The Intermolecular Pauson–Khand Reaction

This reaction, explored in 1971 by Pauson and Khand (1971) constitutes potential flexibility and atom economy.



58

Figure 1.23. The first intermolecular Pauson-Khand reaction

The scope of the intermolecular pkr reaction in has always been limited, having poor reactivity and selectivity of simple alkenes (Gibson and Mainolfi, 2005).

The mechanism of the Pauson–Khand reaction;

Magnus and coworkers offered a mechanism for the stoichiometric reaction in 1985, is still being accepted working mechanism (Magnus, 1985a, 1985b).

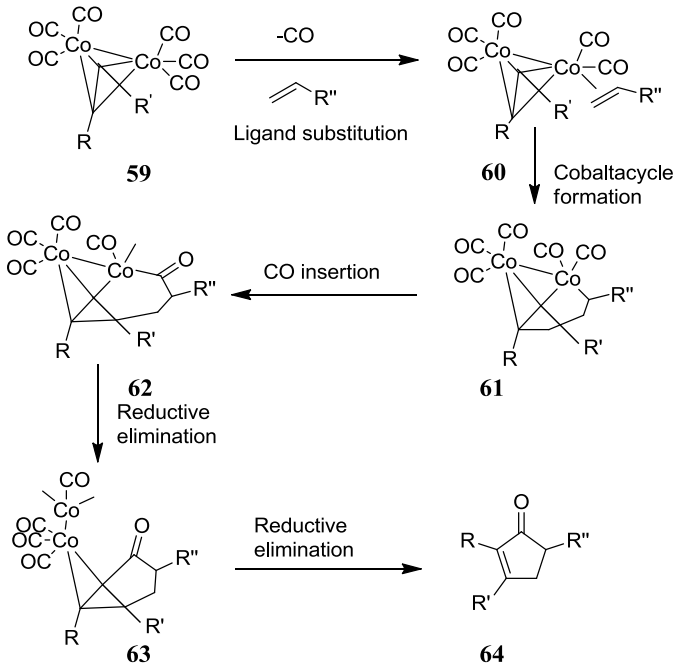
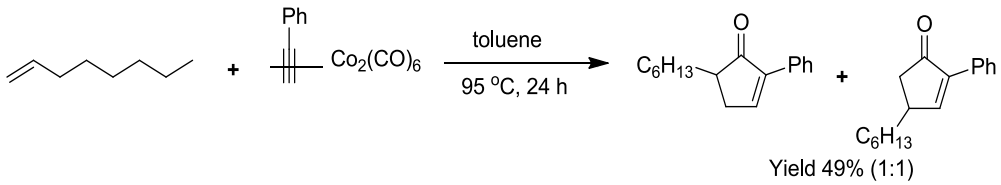


Figure 1.24. Proposed mechanism of the intermolecular Pauson-Khand reaction

Starting from the initial hexacarbonyl complex; The first step contains the loss of one CO ligand exceedingly endothermic, creates a vacant coordination site in intermediate (Gordon et al, 1998). Then coordination of the alkene with the cobalt and then inserts into a cobalt–carbon bond to form the cobaltcycle in which the regiochemical and stereochemical outcome is definite and is thought to be the rate-determining step. The groups of Peric's, Nakamura, and Gimbert have all performed great theoretical calculations on the role of the alkene in cobaltacycle formation. Followed by insertion of CO and reductive elimination to form the cyclopentenone (Gibson and Mainolfi, 2005); building blocks for the construction of complex biologically active molecules (Marks and Furstenberger, 1999; Straus and Glass, 2001).

The development of efficient, environmentally friendly, comprehensive and possibly asymmetric catalytic intermolecular systems would maximize the synthetic attractiveness of the Pauson–Khand reaction to promote this powerful reaction; a method in the synthetic planning of complex biologically active molecules (Bernandes et al, 1995; Chan and Jamison, 2003, 2004).

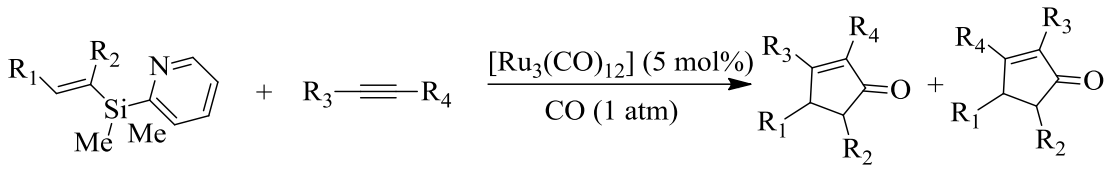
First application of intermolecular Pauson–Khand reaction performed by Krafft in 1988 (Krafft, 1988).



65 **66** **67** **68**

Figure 1.25. An intermolecular Pauson-Khand reaction of terminal alkene

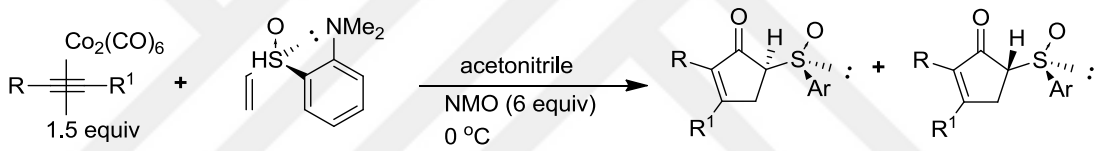
In 2002, Itami and Yoshida reported the pyrid,ylsilyl-directed Pauson-Khand reaction (Itami and Yoshida, 2002).



69 **70** **71** **72**

Figure 1.26. The pyridiylsilyl-directed Pauson-Khand reaction

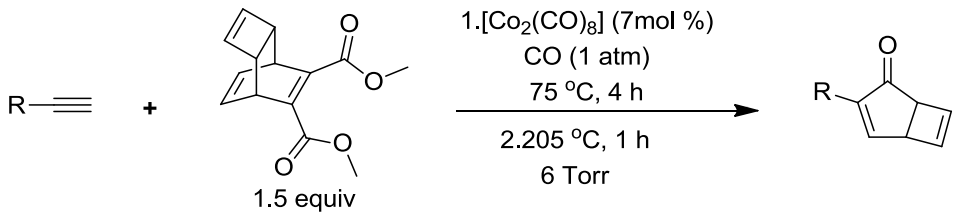
Furthhermore, Carretero and co-workers accomplished the use of nonracemic chiral 2-(N,N-dimethylamino)-phenyl vinyl sulfoxide as a substrate-directing the stoichiometric asymmetric intermolecular Pauson–Khand reaction (Carretero et al, 2003, 2004).



73 **74** **75** **76**

Figure 1.27. The (o-dimethylamino)phenylsulfinyl-directed intermolecular Pauson-Khand reaction

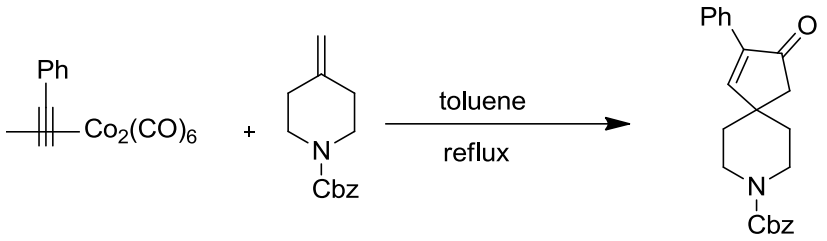
The catalytic intermolecular PKR with cyclobutadiene equivalent Gibson and Mainolfi (Gibson et al, 2004).



77 **78** **79**

Figure 1.28. The catalytic intermolecular Pauson-Khand reaction with cyclobutadiene

Intermolecular PKR of methylene piperidines (Ishizaki et al, 2001, 2003).



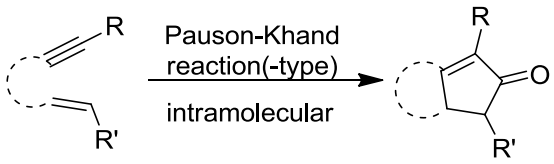
80 **81** **82**

Figure 1.29. The intermolecular Pauson-Khand reaction of methylene piperidines

1.2.9 Intramolecular Pauson-Khand Reaction

The intramolecular version of this reaction has an advantage of having high regioselectiviy thus to give only one type of bicyclic cyclopentenones (Lee and Kwonk, 2010).

In the first intramolecular version reported by Schore in 1981 (Schore and Croudace, 1981), demonstrated the synthetic potential inherent in an intramolecular Pauson-Khand cyclization, which allows for the formation of two rings and three new carbon-carbon bonds (Hicks et al, 1999).



83 **84**

Figure 1.30. The first intramolecular Pauson-Khand reaction

The mechanism of intramolecular Pauson-Khand reaction is also so similiar to the mechanism of intermolecular Pauson-Khand reaction.

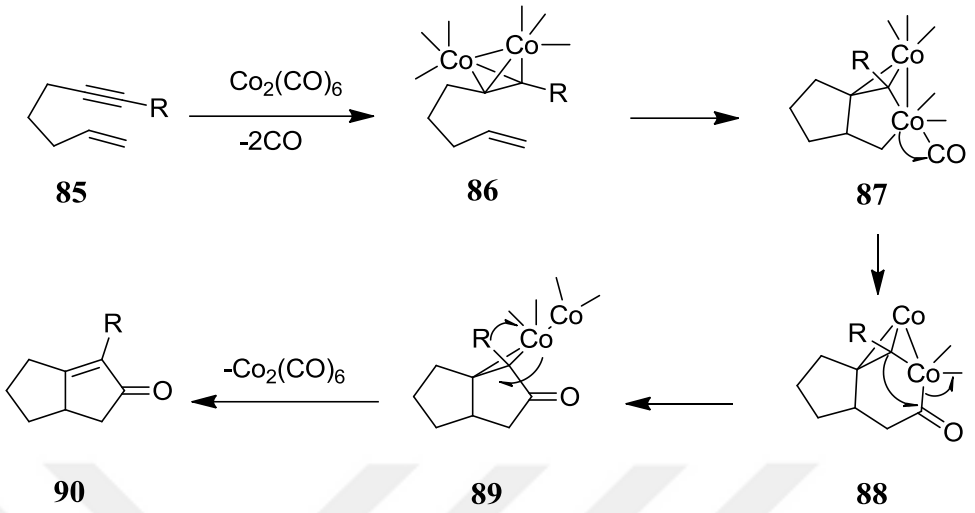
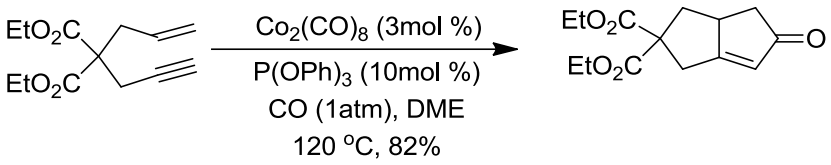


Figure 1.31. The mechanism of intramolecular Pauson-Khand reaction

Smit et al. (1986) reported the adsorption of the cobalt-complexed enynes onto any of a variety of chromatographic supports (silica gel, alumina, zeolites, etc.) facilitates enormously the intramolecular Pauson–Khand cycloaddition reaction allows the usage of lower temperatures and shorter reaction times.

During this period a number of many catalytic intramolecular Pauson-Khand cyclizations have been developed. Modifications to the reaction conditions and/or the cobalt metal catalyst have proven to be effective in increasing the yields of the cycloaddition reaction.

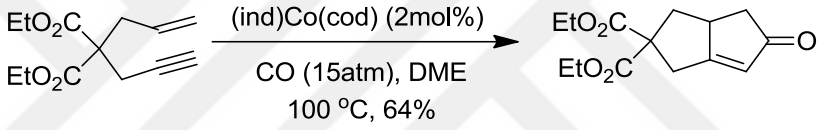
Jeong reports that one of the main obstacles to overcome in the development of a catalytic process is the formation of metal clusters or other inactive cobalt carbonyl species so modification of the ligands might stablize the active cobalt intermediates Jeong et al, 1994). Use of triphenylphosphite (10 mol%) as a coligand with dicobaltoctacarbonyl (3 mol%) gave 51-94% yields in seven examples of intramolecular cycloadditions (Brummond and Kent, 2000).



51 **52**

Figure 1.20. Cobalt-catalyst. with triphenyl phosphite as an additive

In a second communication, Jeong reports the usage of a 1,5-cyclooctadiene(indenyl)cobalt(I) complex to catalyse both inter- and intramolecular cycloadditions. 64 and 94% chemical yields respectively were reported (Jeong et al, 1994).

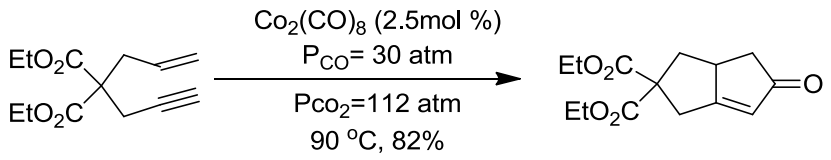


51 **52**

Figure 1.32. 1,5-cyclooctadiene (indenyl)cobalt(I) complex-catalyzed under CO

In a later report, Livinghouse determined the cobalt catalyzed intramolecular Pauson-Khand reaction can also be promoted thermally (Livinghouse et al, 1998).

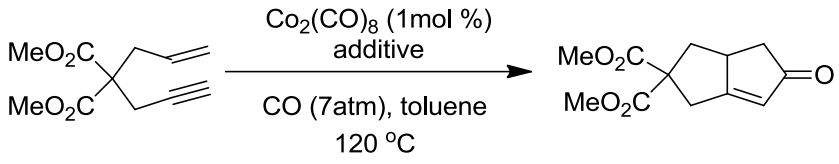
Jeong has demonstrated that super critical fluids can promote the Pauson-Khand cycloaddition process (Jeong et al, 1997). Yields of cycloadduct were between 51-91%.



51 **52**

Figure 1.33. Jeong et.al. Pauson-Khand cycloaddition process

Sugihara has reported that both the inter- and intramolecular catalytic Pauson-Khand cycloaddition of enynes can also be promoted using `hard' Lewis bases. Sugihara utilizes the fact that `hard' Lewis bases are known to labilize the ligands of low-valent organotransition metal complexes (Sigihara and Yamaguchi, 1998).



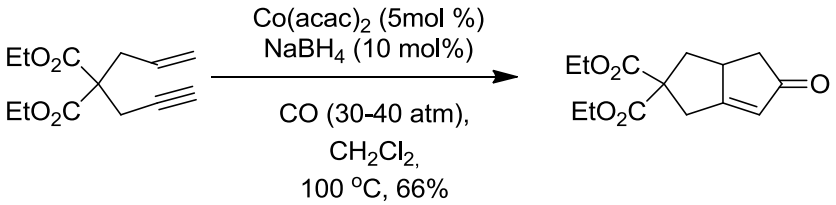
91 **92**

additive	yield
DME (4 mol%)	94%
H_2O (4ml)	97%

Figure 1.34. Pauson-Khand reaction cycloaddition of enynes using Lewis bases

Chung reports two different variants utilizing alternative cobalt catalysts.

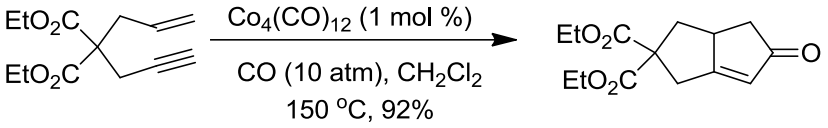
In the first one, both $Co(acac)_2$ and $NaBH_4$ in catalytic amounts was found to effectively promote either the inter- or intramolecular cycloaddition (Lee and Chung, 1996).



51 **52**

Figure 1.35. Alternative cobalt catalyst, $Co(acac)_2$

In a second one Chung utilizes the cobalt cluster compound $Co_4(CO)_{12}$ as the cobalt source between 73-96% chemical yield (Shambayati et al, 1990; Chung et al, 1991).



51 **52**

Figure 1.36. Alternative cobalt catalyst, $Co_4(CO)_{12}$

Followed by the usage of amine N-oxides, independently introduced by Jeong and Schreiber, has become the most popular way to promote the PKR (Krafft et al, 2002). The N-oxides act by oxidizing one CO ligand, which is transformed into CO_2, thus forming a vacant site in the cobalt cluster (Perez-Castells, 2004).

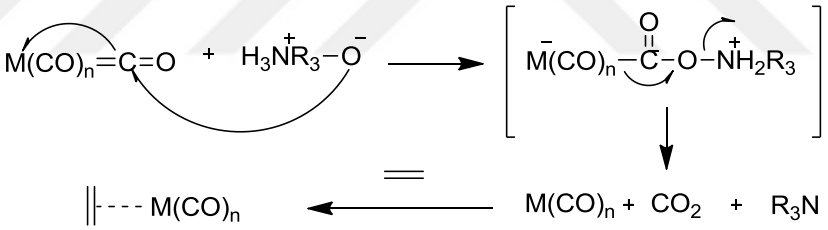
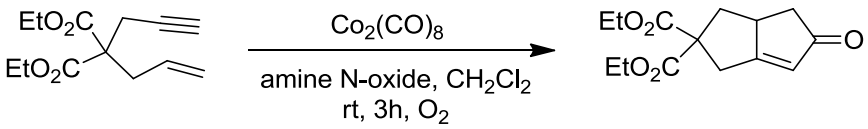


Figure 1.37. The mechanism of formation of N-oxides

The addition a number of additives or promoters increases the reaction (Chung, 1999).



15 **16**

Figure 1.38. Effect of additives to the Pauson-Khand reaction

Krafft has shown that modifications of the reaction conditions can lead to variations in the result of the intramolecular PKR (Krafft et al, 2002).

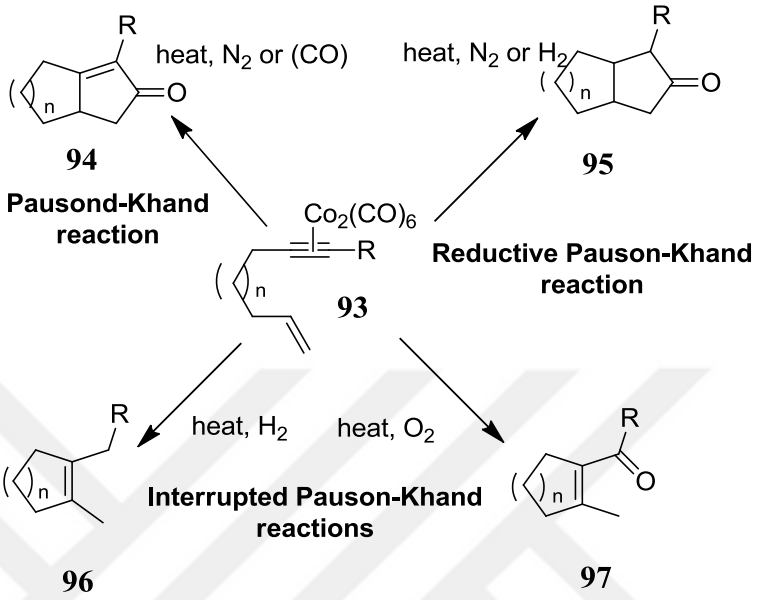


Figure 1.39.Krafft reported intramolecular Pauson-Khand reaction variations

Bolton reported the only intramolecular version of PKR performed on a solid support (Bolton, 1996; Bolton et al, 1997).

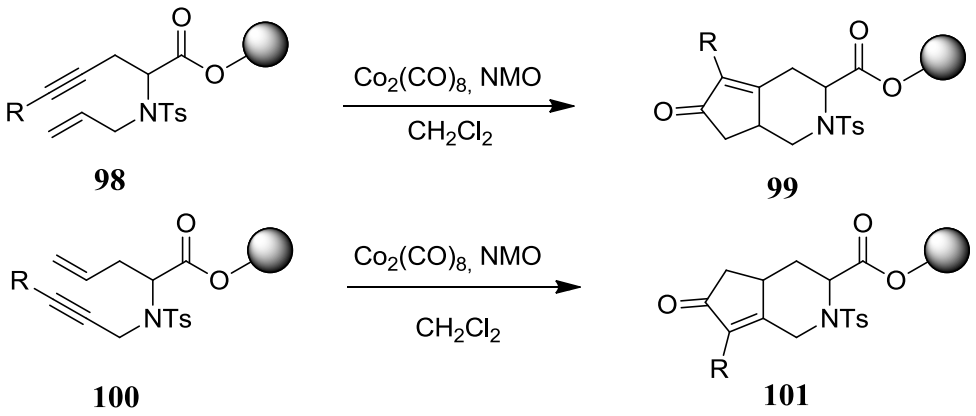


Figure 1.40. Esterification of acid afforded Pauson-Khand cycloadduct

1.3 Olefin Metathesis

1.3.1 Introduction

Olefin metathesis is an unique carbon skeleton reorganization in which unsaturated carbon-carbon bonds are rearranged in the presence of metal carbene complexes (Trost et al, 1991). This reaction is a powerful tool for the formation of C-C bonds in chemistry. The number of applications of this reaction has dramatically increased in the past few years. Of particular significance, metathesis utilizes no additional reagents beyond a catalytic amount of metal carbene and the product from the reaction is, in most cases, a volatile olefin such as ethylene. The broad applicability of olefin metathesis has attracted attention from both academic and industrial scientists (Grubbs and Chang, 1998).

The fascinating story of olefin metathesis began almost five decades ago, when Anderson and Merckling reported the first carbon-carbon double-bond rearrangement reaction in the titanium-catalyzed polymerization of norbornene (Banks and Bailey, 1964).

In 1967, Calderon and co-workers named this metal-catalyzed redistribution of carbon-carbon double bonds olefin metathesis, from the Greek Word "μετR΄ θεση", which means change of position. (Calderon et al, 1967). In fact, the first observation of the metathesis of propene at high temperature was reported in 1931 (Calderon, 1972).

Figure 1.41. Metathesis of two olefinic bonds

The reaction was firstly observed by the Ziegler-Natta in 1950's (Katz, 2005). The first catalyzed metathesis reactions were found in the 1950's when industrial chemists at Du Pont, reported that propene led to ethylene and 2-butenes when it was

heated with molybdenum in the form of the metal, oxide or [$Mo(CO)_6$] on alümina (Truett, 1960; Eleuterio, 1991).

1.3.2 Mechanism of Olefin Metathesis

The generally accepted mechanism for olefin metathesis was originally proposed by Chauvin and Herisson in 1970 (Herisson and Chauvin, 1970). According to this mechanism, olefin metathesis proceeds through metallacyclobutane intermediates, generated by the coordination of the olefin(s) to a metal alkylidene, series of alternating [2 + 2]-cycloadditions and cycloreversions . Attaching of an olefin to a metal alkylidene species (I -II), forming metallacyclobutane complexes (III) and then subsequent releasing of a dissimilar olefin, resulting in the formation of new metal alkylidene (IV). show figure 1.42. (Katz and McGinnis, 1975, 1976, 1977; Grubbs et al, 1975, 1976).

Because of the reversibility of all individual steps in the catalytic cycle, an equilibrium mixture of olefins is obtained. For the metathesis to be productive and useful. It is necessary to shift the equilibrium in one direction. These mechanistic explanation, followed by highly sophisticated attempts to synthesize metal alkylidenes and metallacyclobutanes, eventually led to the synthesis of the first well-defined olefin metathesis catalysts.

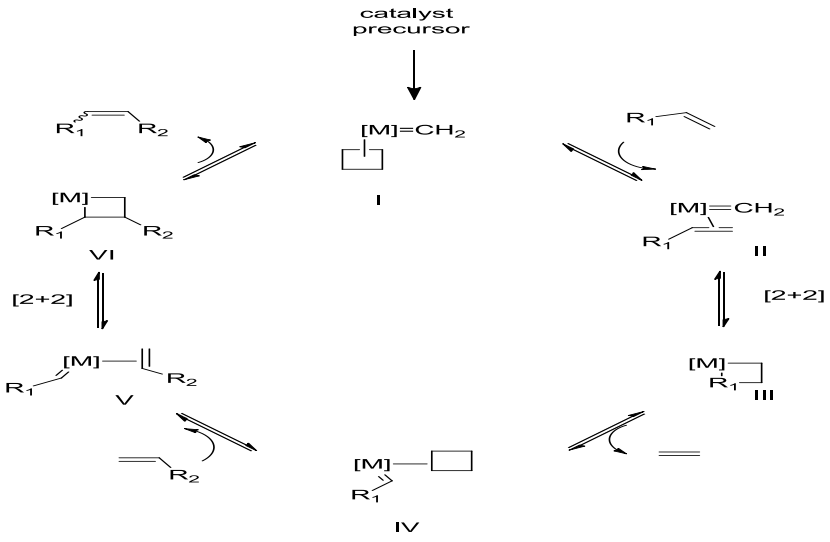


Figure 1.42. Mechanism of transiton metal-catalized olefin metathesis

1.3.3 Well-Defined Catalytic Systems in Olefin Metathesis Reaction

Catalyst systems begin olefin metathesis is very large (Ivin and Mol, 1997). However, exploiting ill-defined multicomponent catalyst system done by most early work in olefin metathesis (Warwel and Siekermann, 1983; Leymet et al, 1989; Liaw and Lin, 1993). Chauvin's mechanism present some new ideas. First, it proposed the inference of a metal carbene complex to commence the catalysis of the metathesis reaction. This idea first present that one could just synthesize metal-alkylidene complexes and allow them react as catalysts with olefins to fulfill the metathesis reaction.

Casey and Burkhardt who showed which $[W(CO)_5(QCPh_2)]$ reacts with isobutene to form 1,10-diphenylethylene published the first result of this kind of catalysts **(**Figure 1.43). Chauvin himself reported in that even some Fischer-type carbene could promote metathesis in 1976 (Casey and Burkhardt, 1974).

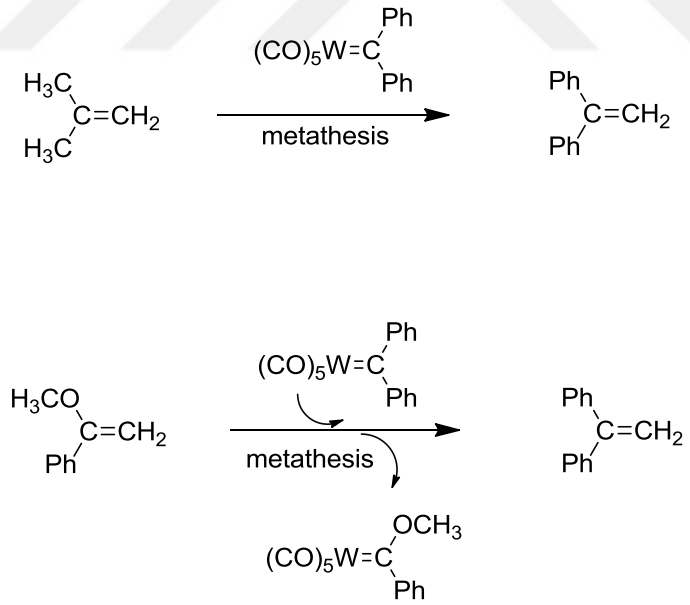


Figure 1.43. Casey and Burkhardt catalyst with olefin metathesis reaction

Katz, whose work led to the familarization of the Chauvin mechanism, carried out many experiments going on via this mechanism. (Katz, 1978; Katz and Lee, 1980).

Moreover Dick Schrock's group reported a tantalum-alkylidene complex, [Ta(QCH–t-Bu)Cl(PMe_3)(O– t-Bu)$_2$] 1980 (Schrock.1979; Schrock et al, 1980).

Schrock et al. quite increased their efforts in the promoted researh for stable molecular alkylidene and alkylidyne complexes of metals. Catalyze the metathesis of unsaturated hydrocarbons.

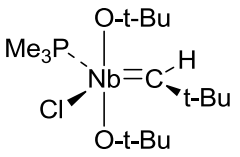
This was successful (Wengrovius and Schrock, 1980) and generated whole family of molybdenum and tungsten-alkylidene complexes of the general formula [M(QCHCMe_2Ph)(QN–Ar) (OR_2], R being bulky groups. These are the most active alkene metathesis catalysts (Schrock, 1990; Bazan et al, 1990, 1991).

Followed by Osborn et al. reported well-defined W(VI) (Tungsten) alkylidene metathesis catalysts (Kress and Osborn et al, 1983).

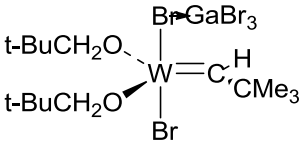
Moreover Basset et al. reported aryloxoalkoxoalkylidene W(VI) (Tungsten) and Lewis acid catalysts free initiators that let the polymerization of norbornenes following (Basset et al, 1985).

Schrock's catalysts offer many advantage even though being highly active, commercially available that can be used without additives which can also be applied in asymmetric reaction (Tsang et al, 2003).

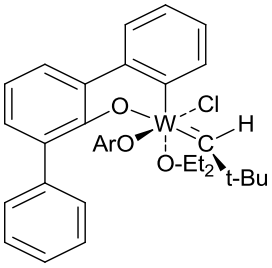
Schrock's closely relevant Mo-alkylidyne complexes do not react with olefins, but they selectively and productively metathesize alkynes without the necessity for a co-catalyst (Astruc, 2005). For example, the [W($CCMe_3$)(O–t-Bu)$_3$] effects some hundred indorsement per minute under mild conditions.



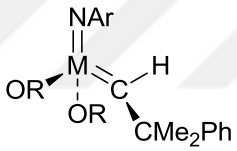
1st unimolecular metal-alkylidene metathesis catalyst (cis-pentene)
Schrock R.R.J, Mol, Catal, 1980



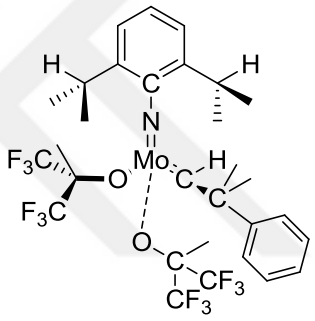
Osborn's catalyst, 1983



Basset's catalyst, 1985



General formula of the family of Schrock's metathesis catalyst
(M= Mo or W, R and Ar bulky substituents)
1990
see the prototype on the right



Commercial prototype of the family of Schrock's metathesis catalyst (can achieve RCM of tri and tetrasubstituted olefins

Figure 1.44. First Nb molecular catalyst and main families of molecular Mo and W metathesis catalyst

Grubbs had been interested in the metathesis reaction for a long time, as indicated by his mechanistic proposal of a metallocyclopentane intermediate early on (Grubbs, 1972).

After a while, he showed, in the course of the same reaction, the formation of a Rualkylidene intermediate. Then the polymerization of cyclooctene, an olefin with little constraints, when the alkylidene ligand source was ethyl diazoacetate added to the aqueous solution of $[Ru(H_2O)_6]$ $(OTs)_2$ (Novak and Grubbs, 1988).

Followed by Grubbs reported the first molecularly well-defined ruthenium-carbene complex which promoted the ROMP of low-strain olefins. The catalytic RCM of functionalized dienes in 1992. Showed these vinylidene complexes $[RuCl_2(PR_3)(QCH–CHQCPh_2)]$ (R = Ph or Cy) were efficient molecular catalysts for these polymerization reactions and other metathesis reactions such as those subsuming ring closing of terminal diolefins (Grubbs et al, 1993).

Moreover In 1995, the new molecularly well-defined catalysts $[Ru(QCHPh)Cl_2(PR_3)_2]$, R = Ph or Cy, whose structures are closely related to the vinylidene, appeared and were commercially avaliable with R = Cy. $[Ru(QCHPh)Cl_2(PCy_3)_2]$ is now known as the first generation Grubbs catalyst (Demonceau et al, 1992).

Then In Grubbs first generation catalysts containing only one such ligand, increase the electron density at the ruthenium center, however, their trans effect labilizes the ruthenium-phosphine bond, favoring phosphine dissociation. Thus, the second generation of ‘‘Grubbs catalysts ’’ $[RuCl_2\{C(N(mesityl)CH_2)_2\}(PCy_3)(QCHPh)]$ and its catalytic activity in metathesis were successively proposed by the groups of Nolan, Grubbs, (Grubbs et al, 1999) and Furstner and Herrmann (Furstner and Hermann, 1999).

Lastly Hoveyda, (Hoveyda et al, 1999) Hofmann, (Hofmann et al, 1999a, 1999b, 2004) Grela (Grela et al, 2004) and Blechert (Blechert, 2002a, 2002b, 2002c) reported other related, very active, stable and functional- ruthenium metathesis catalysts.

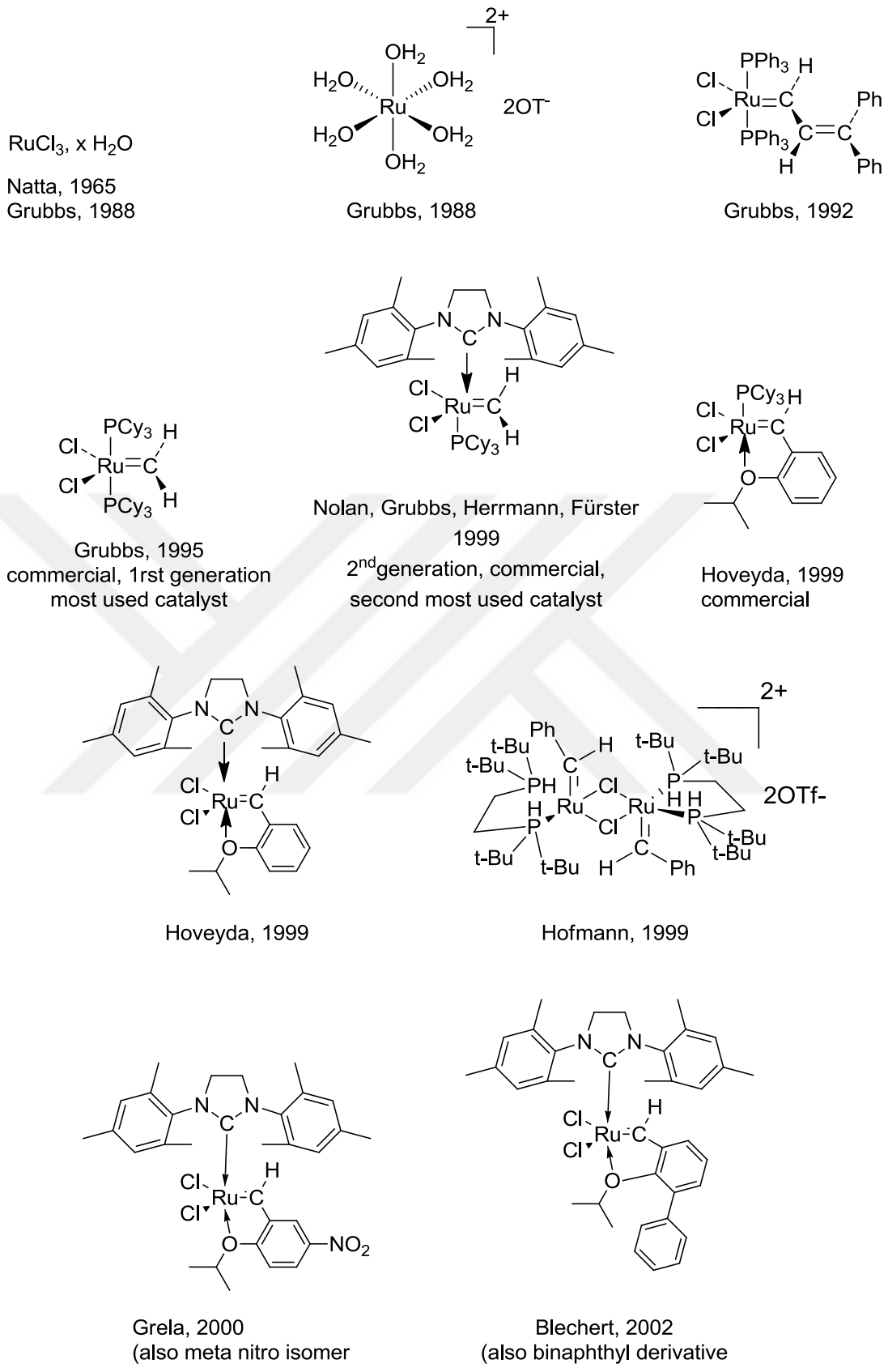


Figure 1.45. Main families of Ru catalyst

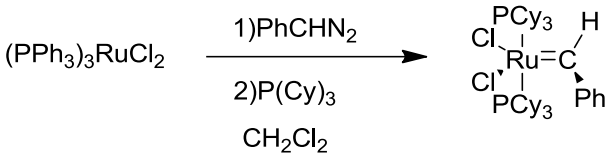
1.3.4 Grubbs Catalysts

In recent years, The First and Second Generation Grubbs catalyst have been used in commercially available in industry and research laboratories used in olefin metathesis reactions. In 2005, the revolutions in this area resulted by using of metathesis catalyst were recognized by the Royal Swedish Academy Of Sciences, awarding the Nobel Prize in chemistry to Chauvin, Schrock and Grubbs.

1.3.4.1 First Generation Grubbs Catalysts

Ru-carbene systems have drawn a lot of attention, not only because exhibiting high reactivity in a variety of ROMP, RCM and CM processes under mild conditions, but also because of their remarkable accepting of many different organic functional groups (Nguyen and Grubbs, 1993).

Catalytic activity is not reduced significantly in the presence of air, moisture or minor impurities in solvents. They can be conveniently stored even under an air atmosphere without severe decomposition for several weeks (Grubbs and Chang, 1998). Although the Ru-carbene system often exhibits relatively lower propagation rates (Nguyen and Grubbs, 1997), especially with sterically bulky substrates when compared to the Mo-catalyst system, and also their availability and ease of use make it preferable (Grubbs and Chang, 1998).



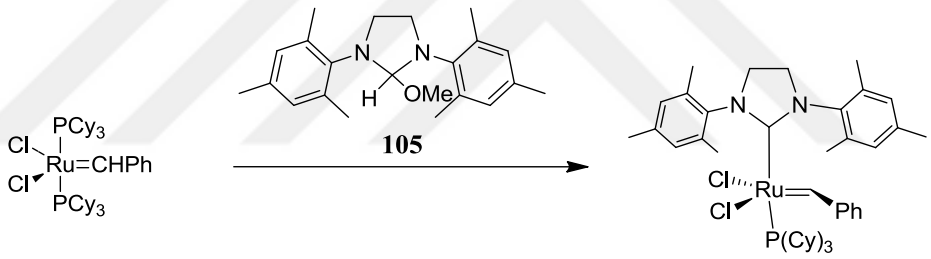
102 **103**

Figure 1.46. Synthesis of Grubbs first generation

The First Generation Grubbs catalyst IUPAC name 'benzylidene-bis(tricylohexynlphosphine)-dichlororuthenium' is obtained synthesising from $RuCl_2(PPh_3)_3$ phenyldiazomethane and tricyclohexylphosphine in one step synthesis (Schwab and Grubbs, 1995).

1.3.4.2 Second Generation Grubbs Catalysts

The "second-generation" catalyst UIPAC name 'benzylidene[1,3-bis-(2,4,6 trimethylphenyl)imidazolidine)' engenders metathesis reactions with particularly high levels of activity in certain cases similarities the Schrock system (Grubbs et al, 1999). Despite these advances, the search for increasingly efficient and selective metathesis catalysts continues unabated (Blechert et al, 2002). On the contrary, this new, commercially available, catalyst also more thermally stable than the first one. In Grubbs first generation catalysts containing only one such ligand, increase the electron density at the ruthenium center, however, and their trans effect labilizes the ruthenium-phosphine bond, favoring phosphine dissociation (Astruc, 2005). This catalyst has sensitivity to air and water so that it was put to use with under a nitrogen or argon atmosphere.



104 **106**

Figure 1.47. Synthesis of Grubbs second generation

The one of the second generation catalysts was made in 1999 (shown the figure 1.47) (Furstner and Hermann, 1999). One of the first and significant adaptations of Grubbs second generation catalyst (Hoveyda et al, 1999, 2000) was reported by the group Hoveyda in 2000 (Nguyen and Grubbs, 1997). After that modification, many of modifications was reported and worth examples of that phosphine-free complex by Grubbs (Grubbs et al, 2001, 2002) and the 14 electron complex by Piers (Piers et al, 2004).

1.3.5 Types of Olefin Metathesis Process

Last attention has been documented for olefin metathesis, particularly in the past 20 years. which resulted in discovery of more efficient catalysts and their applications. Several classes of olefin metathesis including;

- Cross Metathesis (CM)- Ring-Opening Metathesis (ROM)- Ring-Closing Metathesis (RCM)- Ring Opening Metathesis Polymerisation (ROMP)- Acyclic Diene Metathesis (ADMET)

1.3.5.1 Cross Metathesis (CM)

Cross metathesis is metal carbene catalyzed intermolecular coupling between two different olefins potentially yields 3 new types of alkenes as depicted in (Figure 1. 48) (Grubbs and Chang, 1998).

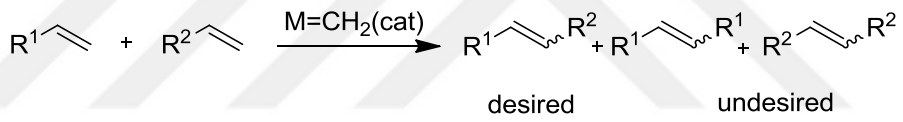


Figure 1.48. Metal carbene catalyzed Cross Metathesis

There are three main variations on this theme a) cross-metathesis, b) ring-opening cross-metathesis, and c) intermolecular enyne metathesis (Herisson and Chauvin, 1971).

Efficiency of the cross metathesis depends on the selectivity observed in the couplings. Minimization of unproductive alkenes from "self-metathesis" and consequently maximization of productive cross-metathized alkenes is a crucial issue to be optimized. In addition to the regioselecfivity, stereocontrol of the newly formed double bonds is another important consideration in this chemistry (Grubbs and Chang, 1998).

1.3.5.2 Ring-Opening Metathesis (ROM)

Ring-opening metathesis (ROM) in which a cyclic olefin and an acyclic olefin produce a new cyclic olefin (Mehta and Nandakumar, 2002).

Ring opening metathesis of is applied strained ring systems and subsequent coupling with acyclic alkenes provides new types of diene products. Recently reported a combination of ring-opening metathesis and selective cross-coupling (Schneider and Blechert, 1996). Strained norbornenes were treated with a symmetrically disubstituted olefin, which was present in large excess to suppress the self-metathesis of the norbornenes. Surprisingly, the self-metathesis hardly occurred with monosubstituted olefins, and high selectivities and yields could be achieved even with a 1 : 1 ratio of the two olefins. To the best of our knowledge, selective cross-couplings with the easily accessible and relatively stable ruthenium catalyst have not beenreported (Blechert and Schneider 1997).

This is, as far as we are aware, the highest turnover number ever reported for Grubb's ruthenium catalyst. This atom-efficient synthesis is also remarkable for its regioselectivity. According to the Chauvin mechanism, cycloaddition of a carbene complex to an olefin results in the formation of a metallocyclobutane, whose cycloreversion leads to ring opening. The regioselectivity is thus presumably due to steric effects in the cycloaddition. (Trost, 1995)

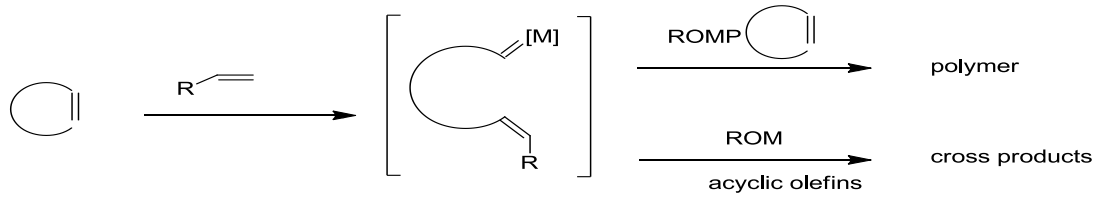


Figure 1.49. General Ring-Opening Metathesis reaction

1.3.5.3 Ring-Opening Metathesis Polymerization (ROMP)

ROMP of cyclic olefins has become a valuable tool for the polymer chemist (Piotti, 1999). Ring-opening metathesis polymerization (ROMP) has emerged as a powerful and broadly applicable method for synthesizing macromolecular materials (Bielawski and Grubbs, 2007).

The discovery of olefin metathesis, a process where the carbon–carbon double bond of an olefin is broken and reformed in the presence of an organometallic catalyst, leading to the equilibration of the alkylidene units (Pariya et al, 1998).

Then Ring-opening metathesis polymerization (ROMP) is a chain growth polymerization process where a mixture of cyclic olefins is converted to a polymeric material (Wagener et al 1991, 2003, 2005).

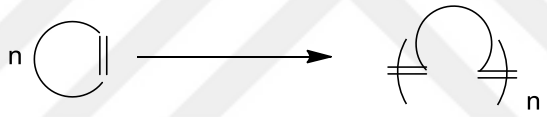


Figure 1.50. A generalized example of a ring-opening metathesis polymerization (ROMP) reaction.

Moreover, the ROMP systems are living processes, having high level of structure and molecular weight control, with very low polydispersities. The importance of this polymerization technique is shown by the fact that it is used industrially for the production of useful polymers such as polydicyclopentadiene, polycyclooctene and poly- norbornene (Piotti, 1999).

1.3.5.4 Acyclic Diene Metathesis (ADMET)

Two decades have passed since the metathesis polymerisation of α,ω-dienes was successfully demonstrated by the group of Wagener and the term acyclic diene metathesis (ADMET)polymerisation was coined. Since then, the advances of metathesis chemistry have allowed to expand the scope of this versatile polymerisation reaction that nowadays finds applications in different fields, such as polymer, material, or medicinal chemistry.

Acyclic diene metathesis polymerization (ADMET) represents an equilibrium step condensation reaction where the continuous production and removal of a small alkene, typically ethylene, provides the necessary driving force to obtain high polymer (Wagener et al, 1991). During the reactions new double bonds can be formed in cis- or trans- configuration depends upon the ratio of monomer and the catalysts used. Ring opening metathesis polymerization is chaing growth addition polymerization inspite of being acyclic diene metathesis is step growth polymerization process (Mutlu et al, 2011).

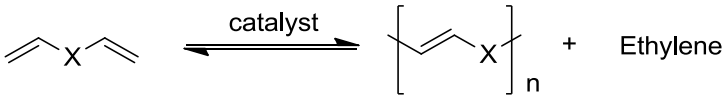


Figure 1.51. Acyclic diene metathesis (ADMET) polymerization

ADMET polymerization has become a frequetly used method for producing linear unsaturated polyalkenylenes, as a result of the synthesis of highly active Schrock alkylidenes, and the variety of monomer systems which are accesible. Unsaturated polymers of this class can be depolymerized, yielding well-defined olefin-terminated" and functionalized oligomers (Portmess, 1996).

1.3.5.5 Ring Closing Metathesis (RCM)

Recently ring-closing olefin metathesis (RCM) has received a great deal of attention for the synthesis of medium or large sized rings from acyclic diene precursors. This intensive study is primarily due to the development of well-defined metathesis catalysts which are tolerant to many functional groups as well as reactive towards a diverse range of substrates (Grubbs and Chang, 1998).

The first example was reported in 1980 by Tsuji, catalytic ring-closing metathesis (RCM) has only recently emerged as an effective strategy in organic synthesis (Tsuji and Hashiguchi, 1980).

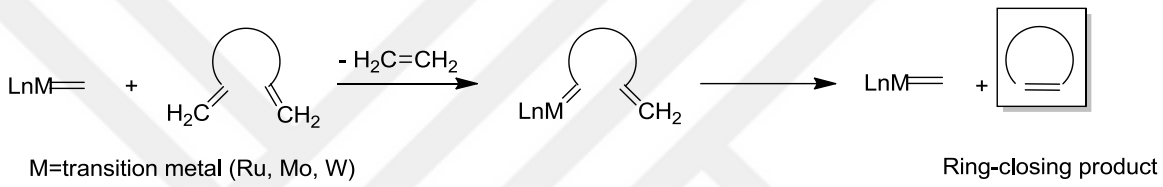


Figure 1.52. The first example catalytic Ring Closing Metathesis

A suitable alkene (diene, enyne etc.) is covalently attached to the resin because metathesis can be employed as a tool for the elaboration of immobilized compounds. Metathesis is carried out, and the products formed are cleaved off by conventional methodology figure 1.53-a. Followed by release it simultaneously from the solid support figure 1.53-b.

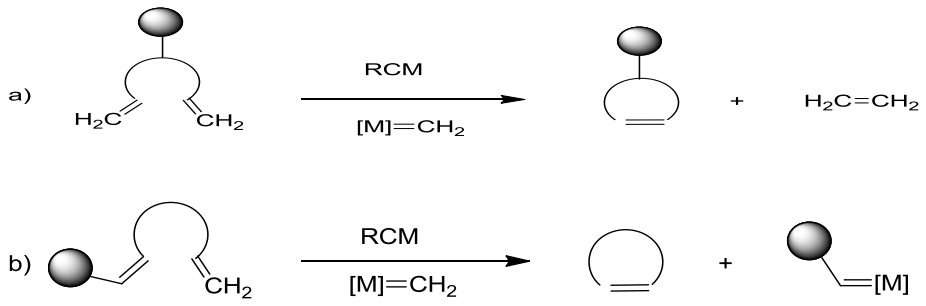
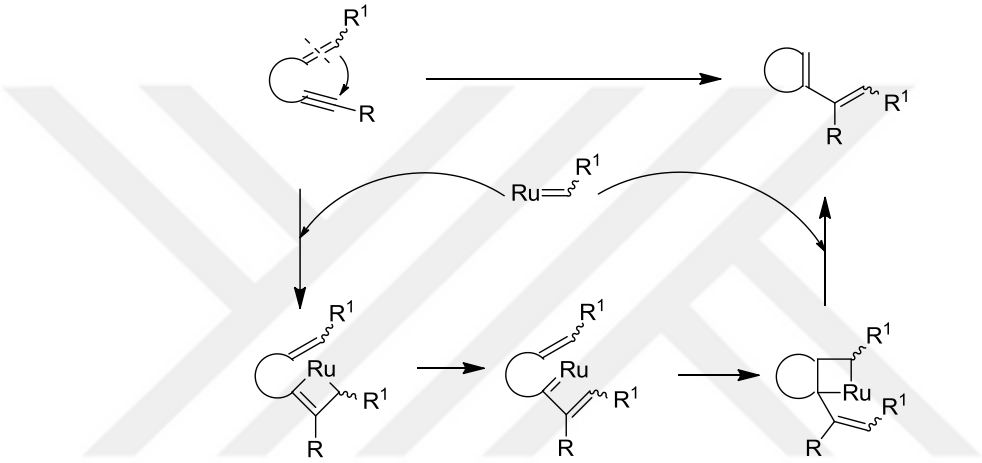


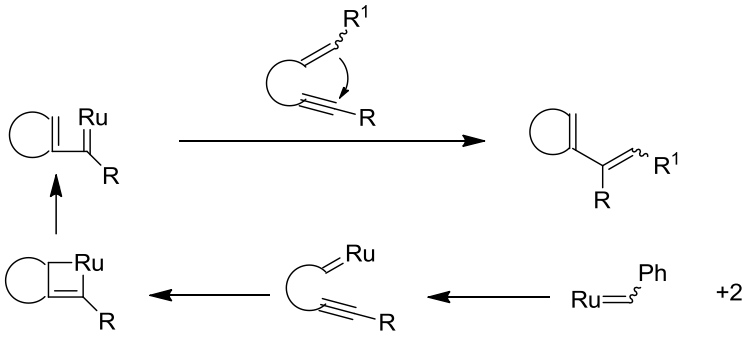
Figure 1.53. a)The product is cleaved from the resin after the metathesis reaction.
b)The product is released by the metathesis reaction.

1.3.5.5.1 Ring Closing Enyn Metathesis

The metathesis of enynes having alkene and alkyne moieties in the molecule is an extremely interesting reaction. The first enyne metathesis was reported by Katz (Katz et al, 1985, 1989, 1991) who used a Fischer tungsten carbene complex. Mori group has reported a chromium-catalyzed.In this reaction, the double bond is cleaved, a carbon-carbon bond is formed between the double and triple bonds, and the cleaved alkylidene part of the double bond migrates onto the alkyne carbon to produce a cyclic compound having a diene moiety (Figure 1. 54) (Mori et al, 2007).



Route 1



Route 2

Figure 1.54. Ring Closing Enyn Metathesis

The first example of the total synthesis of a natural product using enyne metathesis is the synthesis of (-)-stemoamide (Kinoshita and Mori, 1996). (-)-Pyroglutamic acid was converted into enyne **107** having an ester group on the alkyne, and RCM of enyne **107** was carried out in the presence of ruthenium carbene complex to afford bicyclic compound **108**, which was converted into **109** and then halolactonization was carried out to give **110** from this compound **110**, (-)-stemoamide could be synthesized.

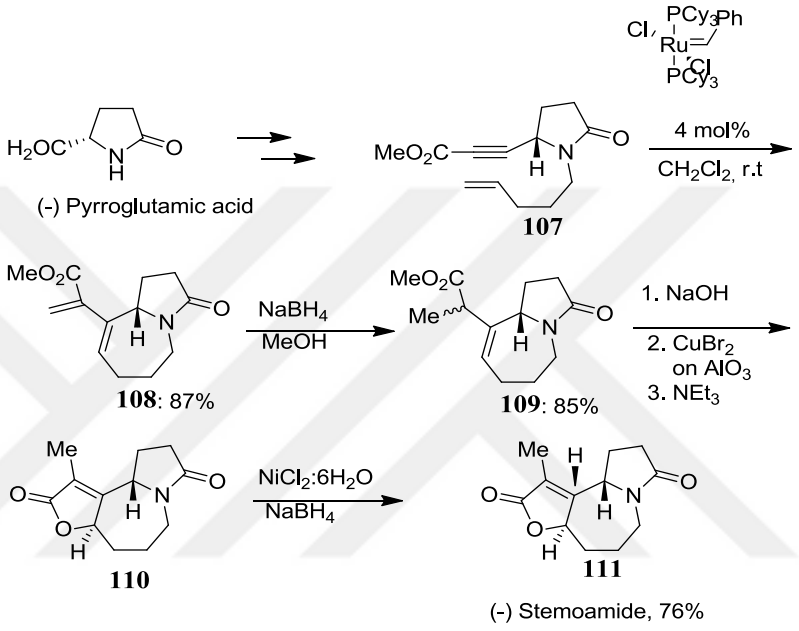


Figure 1.55. The synthesis of (-)-Stemoamide

(±)-Differolide **114** could be easily synthesized by enyne metathesis.(Mori et al, 2007). Enyne **112** was reacted with to give lactone **113**, which spontaneously dimerized to afford (±)-differolide. (Figure 1. 56)

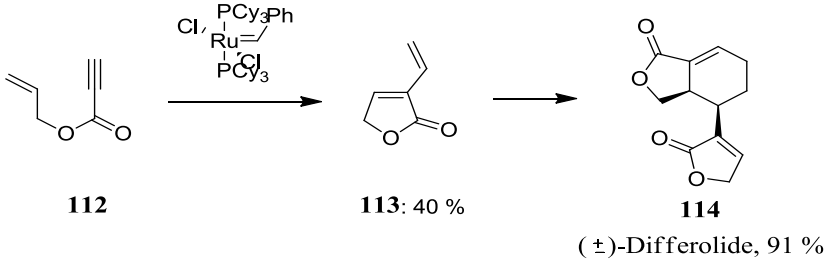


Figure 1.56. Synthesis of (±)-Differolide

1.3.5.5.2 Ring Closing Dyne Metathesis

Dienyne metathesis is a useful method for the synthesis of fused bicyclic or polycyclic compounds in one step, and many bond fissions and bond formations occur during the process. In the total synthesis of natural products using dienyne metathesis, retro-synthetic analyses are completely different from those of the methods reported previously, and the reaction process was generally shortened. Grubbs demonstrated the synthesis of various fused polycyclic compounds using dienyne metathesis. Double and triple bonds are placed at the appropriate positions in the carbon chain. A steroidal skeleton could be synthesized from polyenyne in high yield in one step, although many processes were involved in this reaction (Mori et al, 2007).

Another example reported by Grubbs group. Examples of enantioselective RCM reaction are becoming numerous for instance, the synthesis of (+) – brevomicin **(**Burke et al, 1999).

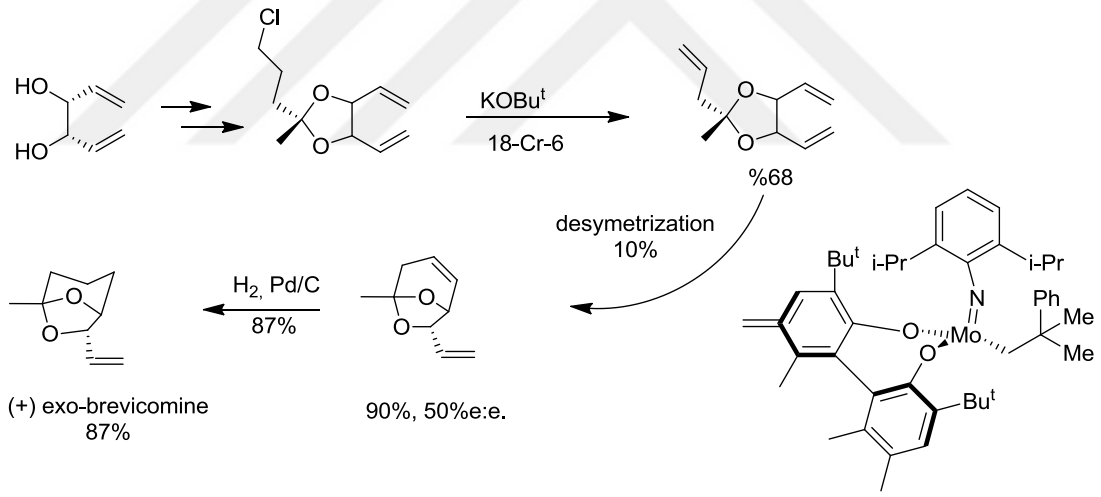


Figure 1.57. The synthesis of (+) – Brevomicin

2. AIM AND SCOPE OF THE STUDY

The aim of this work is to synthesize 2-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine **118** and 2-(furan-2-yl)-1,2,3,6-tetrahydropyridine **125** compounds were obtained via Ring Closing Metathesis by using Grubbs Second Generation catalyst also to obtain 3-(4-chlorophenyl)-3,4,4a,5-tetrahydro-1H-cyclopenta[c]pyridin-6(2H)-one **121** and 1-(furan-2-yl)-N-(prop-2-yn-1-yl)but-3-en-1-amine **128** compounds via Pauson-Khand cycloaddition reaction in the presence of NMO and $Co_2(CO)_8$, cyclopenta[c]pyridin compounds which are valuable building blocks in the synthesis of natural product skeleton.

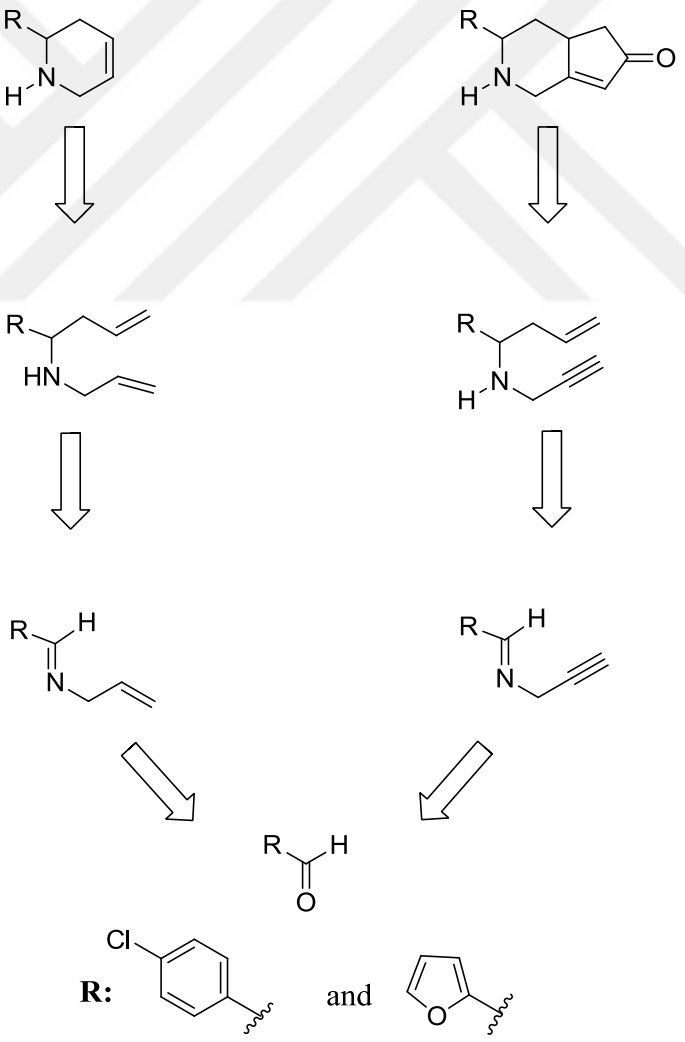
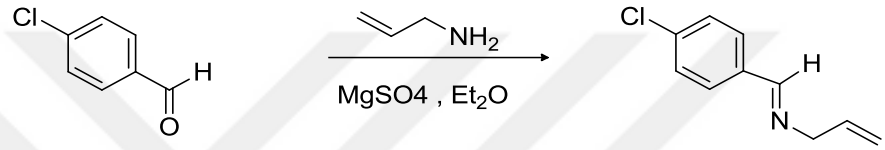


Figure 2.1. Retrosynthesis of the work

3. RESULT AND DISCUSSION

3.1 Synthesis of (E)-*N*-(4-chlorobenzylidene)prop-2-en-1-amine 116

(E)-*N*-(4-chlorobenzylidene)prop-2-en-1-amine **116** was prepared from p-cholorobenzaldeyde **115** and allylamine in the presence of dry ether and anyhydrous magnesium sulfate shown in Figure 2.1. After work up, (E)-*N*-(4-chlorobenzylidene)prop-2-en-1-amine **116** was obtained as yellow oil with 92% chemical yield.



115 **116**

Figure 3.1. Synthesis of (E)-*N*-(4-chlorobenzylidene)prop-2-en-1-amine **116**

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

^{1}H-NMR spectrum of (E)-*N*-(4-chlorobenzylidene)prop-2-en-1-amine **116** shows a doublet of doublet at 4.17 ppm with J_1=5.8, J_2=1.4 Hz of the allylic methylene protons. Terminal vinylic protons; Ha and Hb exhibit quartet of doublet at 5.08 ppm with J_1=10.4, J_2=1.2 Hz and quartet of doublet at 5.15 ppm with J_1=17.2, J_2=1.6 Hz respectively. The multiplet between 5.90-6.04 ppm is due to the internal vinylic protons. Methine proton at third position of the ring shows doublet at 7.30 ppm with J=8.4 Hz values. Doublet at 7.43 ppm with J=8.4 Hz belongs to the methine proton at fifth position of the ring. The signal shows doublet at 7.60 ppm with J=8.4 Hz is due to the methine proton at sixth position of the ring. The methine proton at second position of the ring exhibits doublet at 7.73 ppm with J=8.4 Hz. Finally, the singlet peak at 8.16 ppm is due to imine proton.

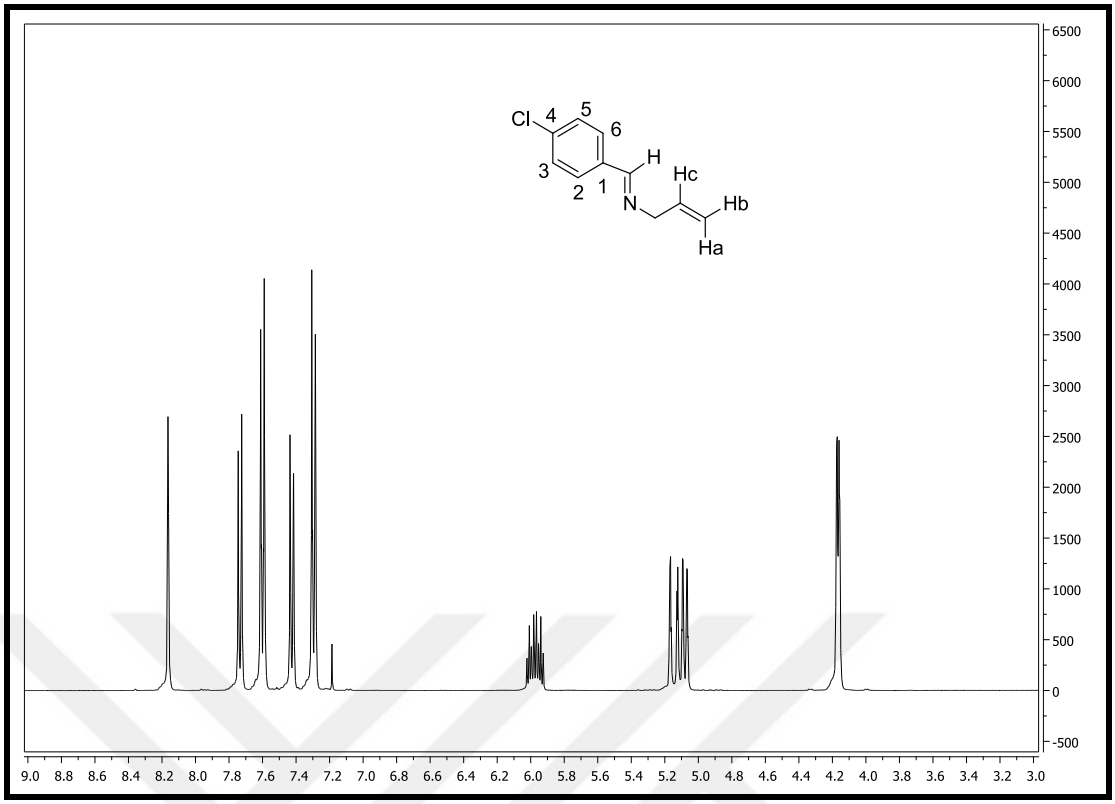


Figure 3.2. ^{1}H-NMR spectrum of (E)-*N*-(4-chlorobenzylidene)prop-2-en-1-amine **116**

^{13}C-NMR spectrum of (E)-*N*-(4-chlorobenzylidene)prop-2-en-1-amine **116** shows a signal at 63.4 ppm for the allylic methylene carbon. The signals at 116.3 ppm and 130.9 ppm are due to the vinylic carbons. Methine carbon at third position of the ring shows 128.9 ppm. The signal at 129.3 ppm belongs to the methine carbons at fifth position of the ring. Furthermore, the methine carbons at second and sixth position of the ring show signal at 134.6 and 135.7 ppm respectively. The signal at 136.7 ppm is due to the methine carbon at first position of the ring and the methine carbon at fourth position of the ring exhibits signal at 141.0 ppm. Finally, the imine carbon shows signal at 160.6 ppm.

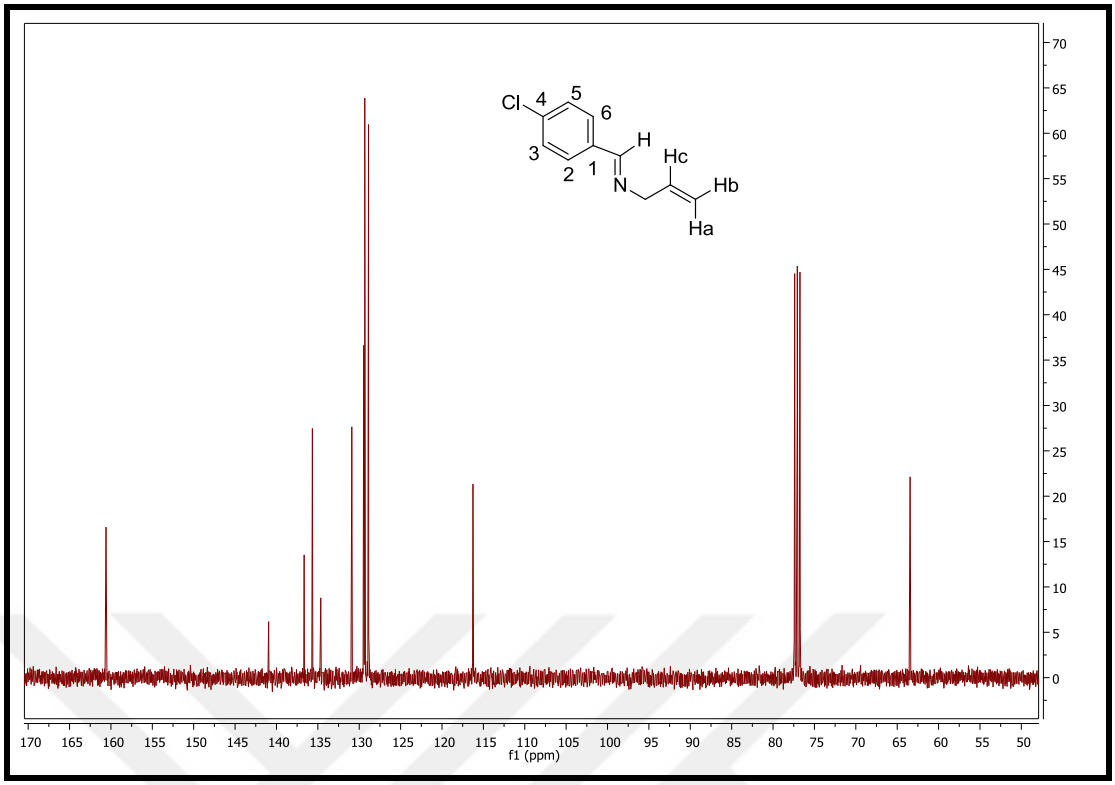
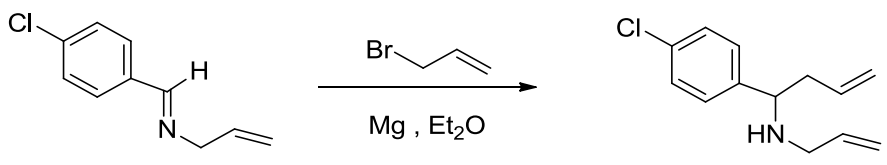


Figure 3.3. ^{13}C-NMR spectrum of (E)-*N*-(4-chlorobenzylidene)prop-2-en-1-amine **116**

3.2 Synthesis of *N*-allyl-1-(4-chlorophenyl)but-3-en-1-amine 117 : (Diastereomeric Mixture)

N-allyl-1-(4-chlorophenyl)but-3-en-1-amine **117** was prepared from (E)-*N*-(4-chlorobenzylidene)prop-2-en-1-amine **116** and allyl bromide in the presence of diethyl ether by a Grignard reaction shown in Figure 2.4. After work up, *N*-allyl-1-(4-chlorophenyl)but-3-en-1-amine **117** was obtained as yellow oil with 84% chemical yield.



116 **117**

Figure 3.4. Synthesis of *N*-allyl-1-(4-chlorophenyl)but-3-en-1-amine **117**

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

^{1}H-NMR spectrum of *N*-allyl-1-(4-chlorophenyl)but-3-en-1-amine **117** shows broad singlet at 2.29 ppm is due to N-*H* proton. One of the diastereotopic allylic methylene protons exhibit multiplet between 2.43-2.35 ppm. Other one show multiplet between 2.53-2.44 ppm. Triplet of doublet of doublet at 2.99 ppm with J_1=14.1, J_2=6.7, J_3=1.2 Hz are due to one of the diastereotopic allylic methylene protons. Other one exhibits triplet of doublet of doublet at 3.10 ppm with J_1=14.1, J_2=5.4, J_3=1.5 Hz. The stereogenic methine proton shows triplet at 3.69 ppm with J=8.8 Hz. The terminal vinylic protons; Ha and Hb exhibit multipet between 5.04-5.08 ppm and multiplet between 5.08-5.15 ppm. Other terminal vinylic protons; Ha' and Hb' show multiplet between 5.11-5.16 and multiplet between 5.16-5.21 ppm respectively. One of the internal vinylic proton exhibits multiplet between 5.78-5.61 ppm. The multiplet at 5.91-5.78 ppm is due to other internal vinylic proton. The multiplet between 7.25-7.28 ppm is due to the methine proton at third position of the ring. The multiplet between 7.28-7.30 ppm belongs the methine proton at fifth position of the ring respectively. Finally, the methine protons at second and sixth position of the ring show multiplet between 7.30-7.33 ppm.

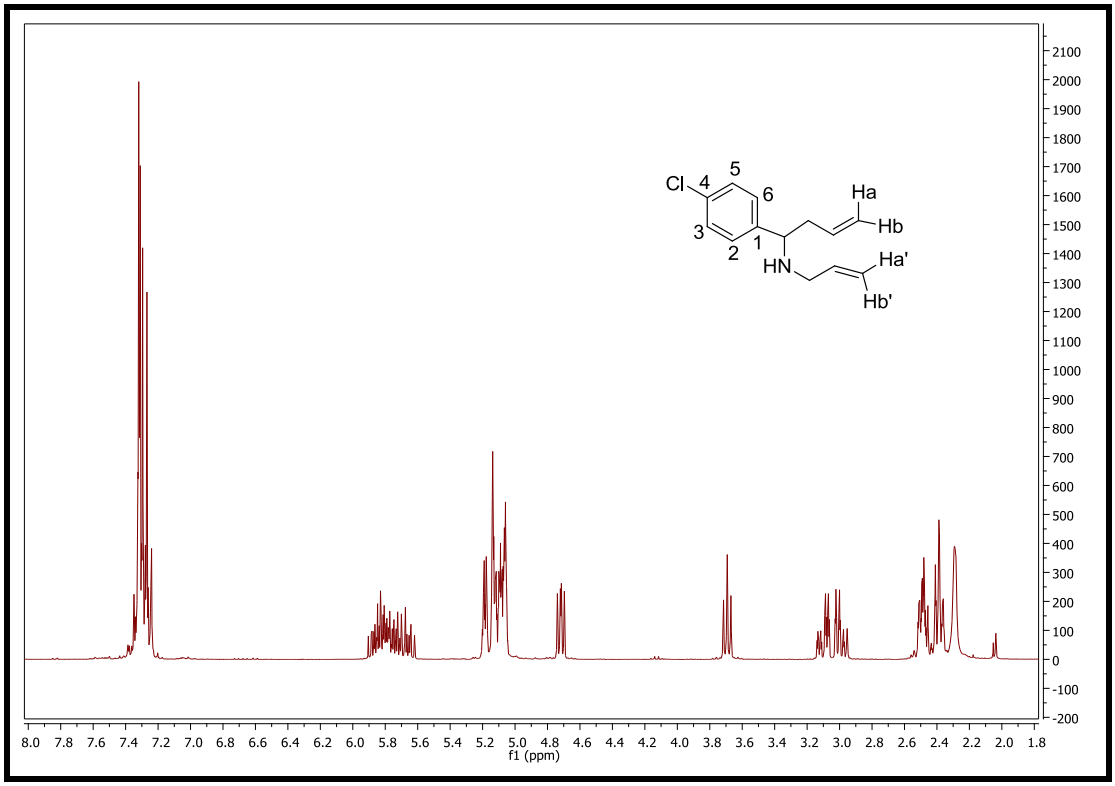


Figure 3.5. ^{1}H-NMR spectrum of *N*-allyl-1-(4-chlorophenyl)but-3-en-1-amine **117**

^{13}C-NMR spectrum of *N*-allyl-1-(4-chlorophenyl)but-3-en-1-amine **117** shows a signals at 42.9 and 43.9 ppm belongs to the allylic carbon atom. Other allylic carbon atom shows a signal at 49.9 ppm. The signals at 61.0 and 72.5 ppm belongs to the quaternary carbon atom. Terminal vinylic carbons exhibit signals at 116.2, 118.1 and 118.8 ppm. The methine carbons at the second and sixth position exhibit a signals at 127.3 and 128.5 ppm. The other methine carbon at the third and fifth position exhibit a signals at 128.6 and 128.7 ppm respectively. Internal vinylic carbon shows signals at 132.6 and 133.1 ppm. Other internal vinylic carbon exhibit a signal at 134.1 and 134.9 ppm. The signal at 136.5 ppm is due to the methine carbon at fourth position of the ring. Finally the methine carbon at first position of the ring exhibit signals at 142.0 and 142.5 ppm.

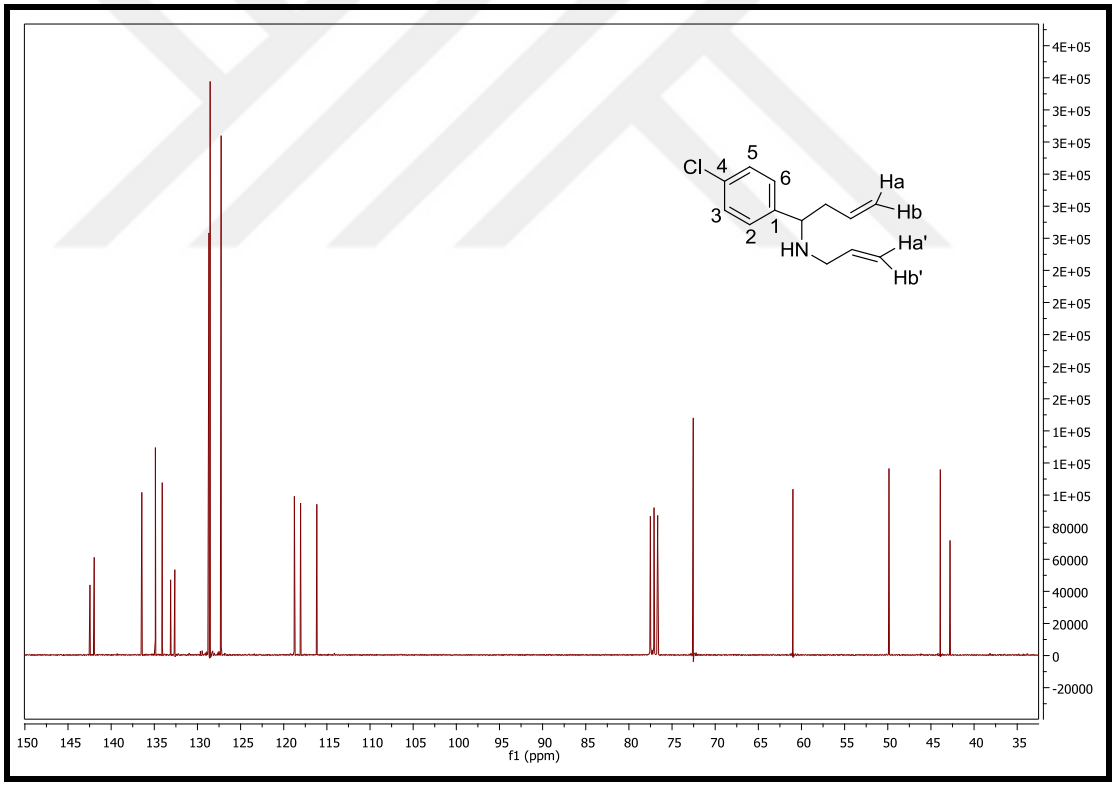
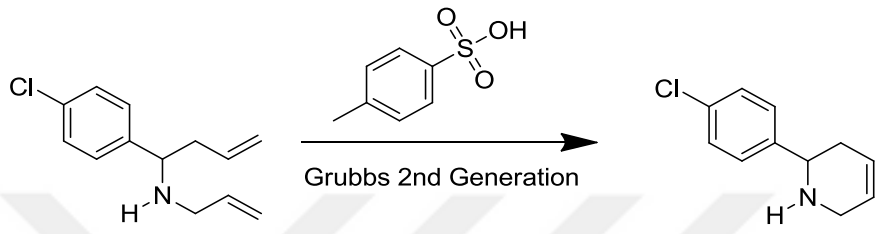


Figure 3.6. ^{13}C-NMR spectrum of *N*-allyl-1-(4-chlorophenyl)but-3-en-1-amine **117**

3.3 Synthesis of 2-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine 118

2-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine **118** was synthesized from *N*-allyl-1-(4-chlorophenyl)but-3-en-1-amine **117** in the presence of p-toluenesulfonic acid monohydrate in DCM by using Grubbs Second Generation catalyst with Ring Closing Metathesis shown in Figure 2.7. After work up, 2-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine **118** was obtained as yellow oil with 87% chemical yield.



117 **118**

Figure 3.7. Synthesis of 2-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine **118**

The product was identified by ^{1}H-NMR and ^{13}C-NMR spectroscopy

^{1}H-NMR spectrum of 2-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine **118** shows broad singlet at 2.28 ppm is due to N-*H* proton. The diastereotopic methylene protons at fifth position of the tetrahydropyridine ring show quartet of doublet at 2.40 ppm with J_1=4.4, J_2=2.0 Hz. One of the methylene protons at second position of the tetrahydropyridine ring shows pentet of doublet at 3.60 ppm with J_1=3.5, J_2=2.4 Hz and other methylene protons exhibit pentet of doublet at 3.65 ppm with J_1=3.4, J_2=2.0 Hz respectively. The triplet at 3.84 ppm with J=9.2 Hz is due to the stereogenic methine proton at sixth position of the tetrahyroypyridine ring. One of the methine proton at third position of the tetrahydropyridine ring show pentet of doublet at 5.78 ppm with J_1=3.4, J_2=2.4 Hz. Other methine proton at fourth position of the tetrahydropyridine ring show quartet of doublet at 5.87 ppm with J_1=13.1, J_2=2.0 Hz. The doublet at 7.28 ppm with J=0.8 Hz are due to the methine protons at 3' and 5' position of the p-chlorophenyl ring. Other methine protons 2' and 6' prime position of *p*-chlorophenyl ring show doublet at 7.32 ppm with J=1.6 Hz.

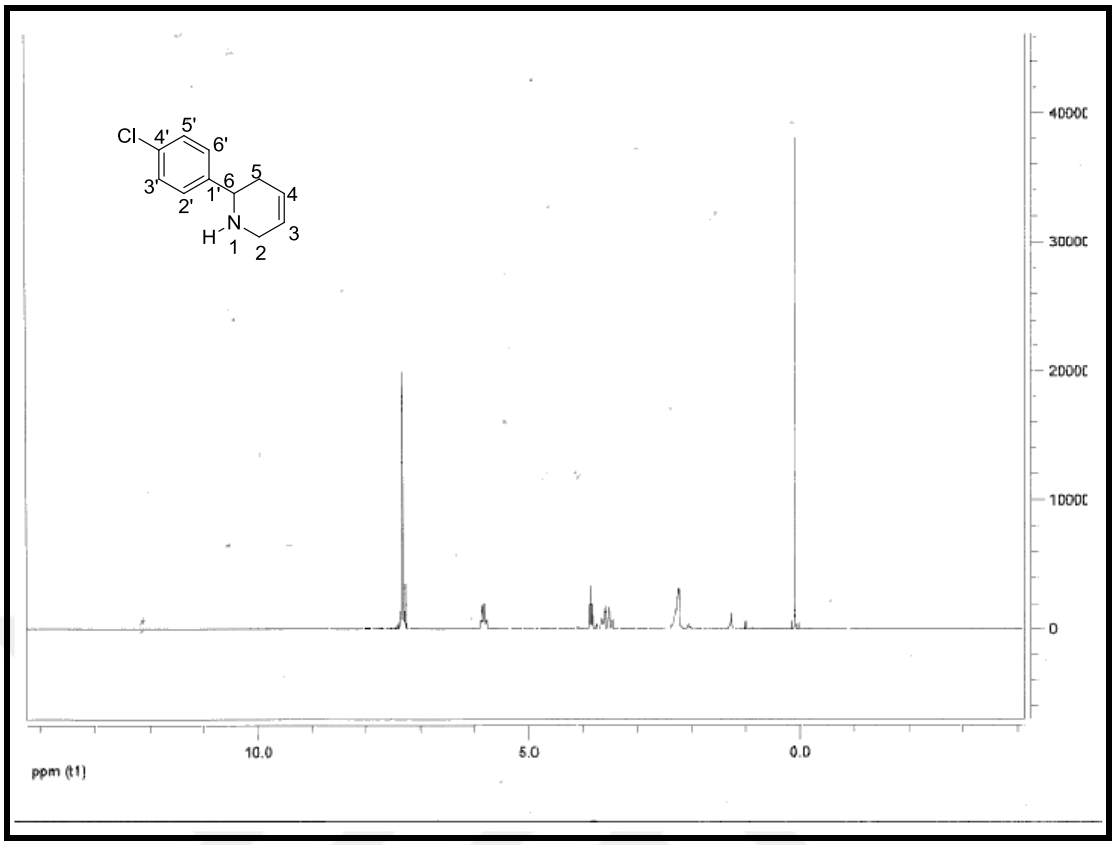


Figure 3.8. ^{1}H-NMR spectrum of 2-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine **118**

^{13}C-NMR spectrum of 2-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine **118** shows a signal at 33.7 ppm is due to the allylic methylene carbon at fifth position of tetrahydropyridine ring. Other allylic methylene carbon at second position of the tetrahydropyridine ring shows a signal at 46.2 ppm. The methine carbon at the sixth position of tetrahydropyridine exhibits signal at 57.4 ppm. The methine carbon at fourth position of tetrahydropyridine shows signal at 125.3 ppm. The signal at 126.0 ppm is due to the other methine carbon at third position of the tetrahydropyridine. The methine carbons at 2' and 6' position of the *p*-chlorophenyl ring exhibit signal at 127.7 ppm. The signal at 128.4 ppm belong to the other methine carbons at 3' and 5' position of the p-chlorophenyl ring. The signal at 133.0 ppm is due to the methine carbon at 4' position of the p-chlorophenyl ring. Finally, the methine carbon at 1' position of the p-chlorophenyl ring show signal at 143.0 ppm.

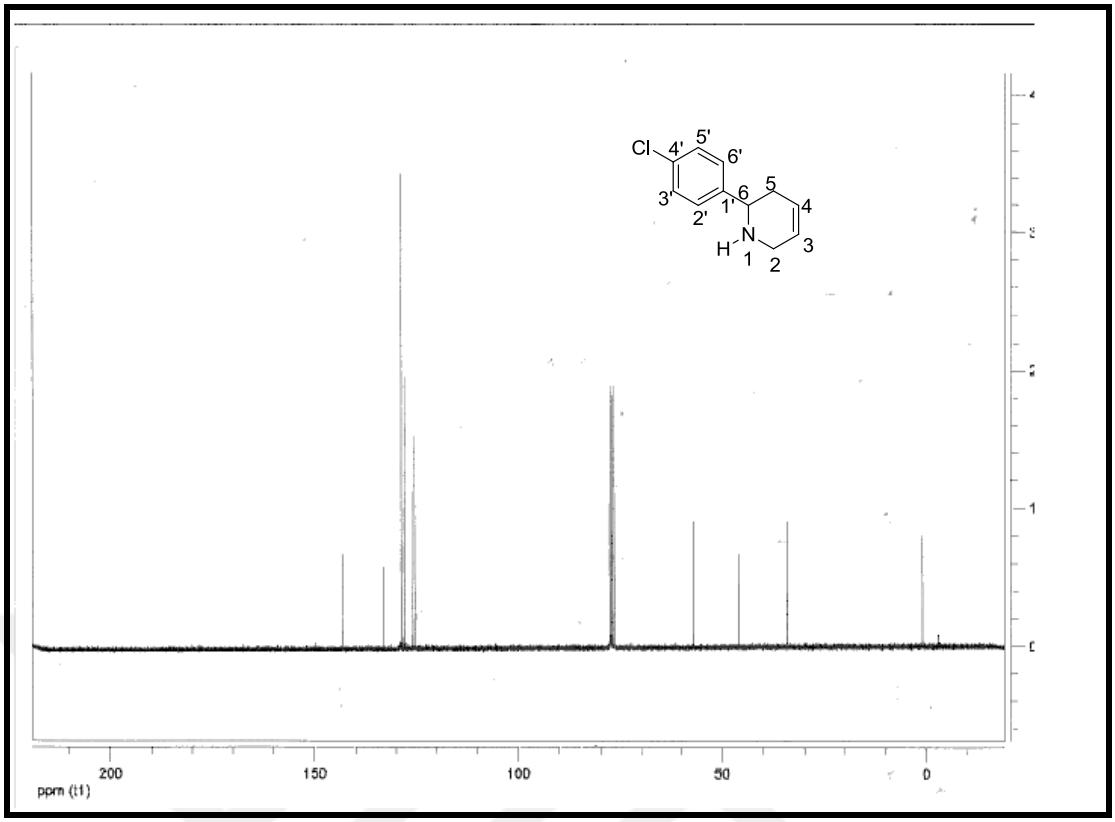
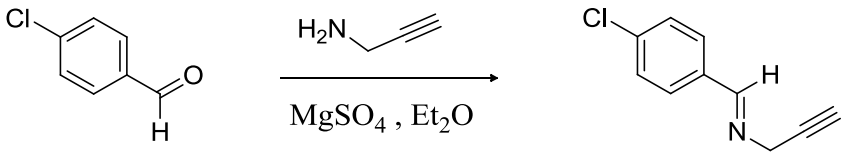


Figure 3.9. ^{13}C-NMR spectrum of 2-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine **118**

3.4 Synthesis of (E)-*N*-(4-chlorobenzylidene)prop-2-yn-1-amine 119

(E)-*N*-(4-chlorobenzylidene)prop-2-yn-1-amine **119** was prepared from p-cholorobenzaldeyde **115** and propargylamine in the presence of dry ether and anyhydrous magnesium sulfate shown in Figure 2.10. After work up, (E)-*N*-(4-chlorobenzylidene)prop-2-yn-1-amine **119** was obtained as yellow oil with 88% chemical yield.



115 **119**

Figure 3.10. Synthesis of (E)-*N*-(4-chlorobenzylidene)prop-2-yn-1-amine **119**

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

^{1}H-NMR spectrum of (E)-*N*-(4-chlorobenzylidene)prop-2-yn-1-amine **119** shows triplet at 2.46 ppm with J = 2.4 Hz belongs to the acetylenic proton. The diasterotopic methylene protons of the propargyl group exhibit triplet 4.42 ppm with J=2.2 Hz. The signal at 7.29 ppm with J_1=8.4 Hz shows doublet for the methine proton at third position of the ring. Doublet at 7.40 ppm with J_1=8.4 Hz belongs to methine proton at fifth position of the ring. The methine proton at sixth position of the ring show doublet at 7.59 ppm with J_1=8.8 Hz values. The last methine proton at second position of the ring exhibits doublet at 7.71 ppm with J_1=8.8 Hz. Finally, the singlet at 8.16 ppm is due to imine proton.

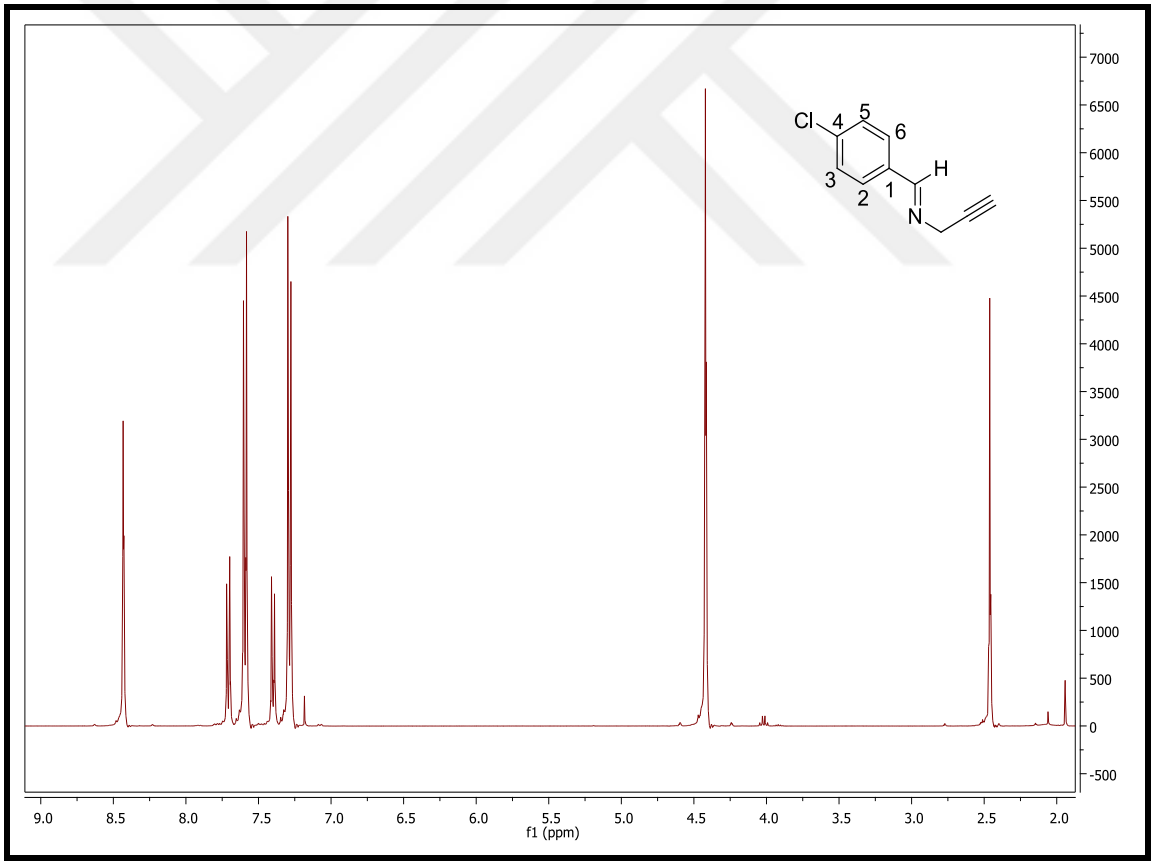


Figure 3.11. ^{1}H-NMR spectrum of (E)-*N*-(4-chlorobenzylidene)prop-2-yn-1-amine **119**

^{13}C-NMR spectrum of (E)-*N*-(4-chlorobenzylidene)prop-2-yn-1-amine **119** shows signals at 47.1 ppm for the allylic methylene carbon of the propargyl group. The signals at 75.83 ppm and 78.8 ppm are due to the methine and quaternary carbon of the propargyl group. The methine carbons fifth and third position of the ring show signals at 128.9 and 129.4 ppm respectively. Moreover, the signals at 129.5 and 130.9 ppm belong to the methine carbons at sixth and second position of the ring. The signal at 134.3 ppm belongs to the methine carbon at first position of the ring. The other methine carbon at fourth position of the ring exhibits signal at 136.9 ppm. Finally, the signal at 161.0 for the imine carbon.

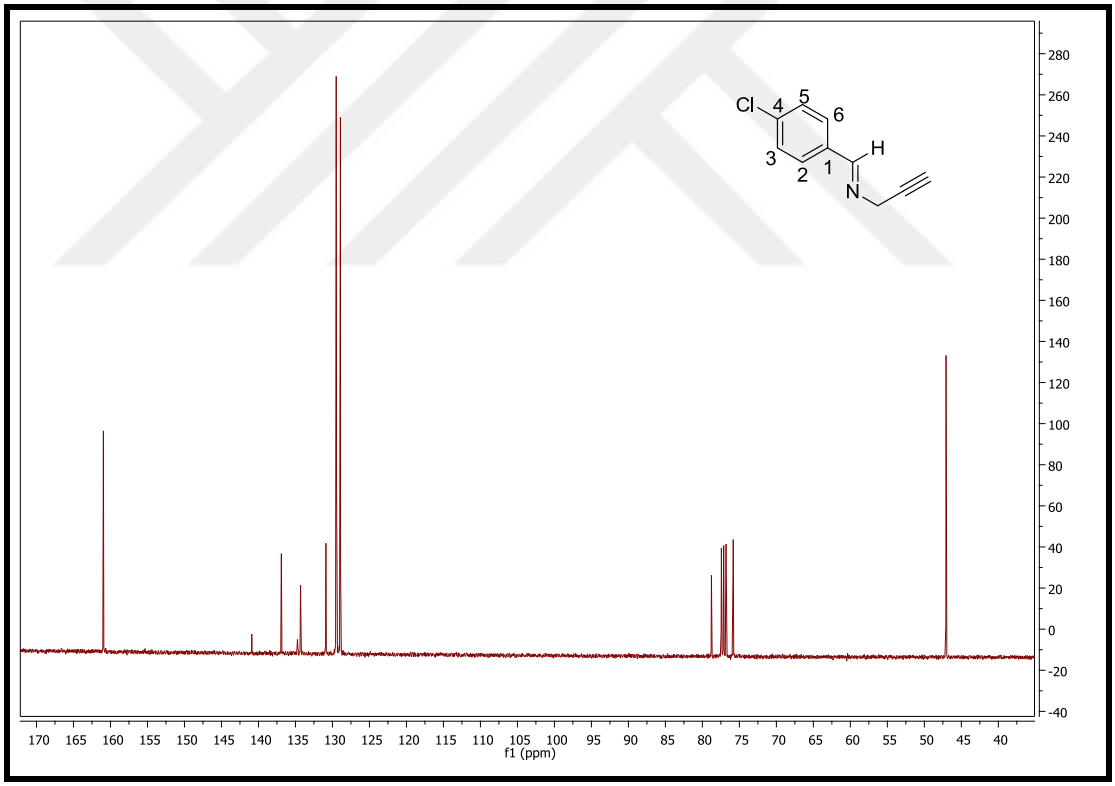
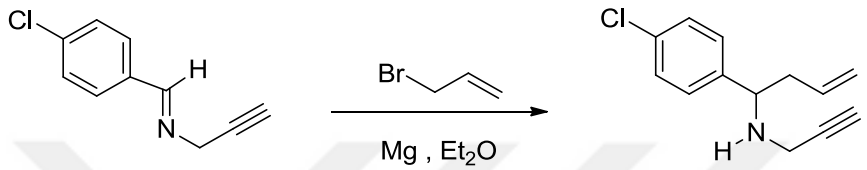


Figure 3.12. ^{13}C-NMR spectrum of (E)-*N*-(4-chlorobenzylidene)prop-2-yn-1-amine **119**

3.5 Synthesis of 1-(4-chlorophenyl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine 120 : (Diastereomeric Mixture)

1-(4-chlorophenyl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **120** was prepared from (E)-*N*-(4-chlorobenzylidene)prop-2-yn-1-amine **119** and allyl bromide in the presence of di ethyl ether by a Grignard reaction shown in Figure 2.13. After work up, 1-(4-chlorophenyl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **120** was obtained as yellow oil with 82% chemical yield.



119 **120**

Figure 3.13.Synthesis of 1-(4-chlorophenyl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **120**

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

^{1}H-NMR spectrum of 1-(4-chlorophenyl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **120** shows broad singlet at 1.97 ppm is due to N-*H* proton. Triplet at 2.13 ppm with *J*=2.4 Hz is due to the acetylenic proton. The allylic methylene protons of the allyl group show multiplet between 2.21-2.37 ppm. One of the diastereotopic methylene proton of the propargyl group exhibits doublet of doublet at 2.98 ppm with J_1=17.6, J_2=2.4 Hz and other one doublet of doubet at 3.28 ppm with J_1=17.6 J_2=2.4 Hz respectively. The doublet of doublet at 3.84 ppm with J_1=6.8 J_2=5.0 Hz belongs to the sterogenic methine proton. Furthermore terminal vinylic protons show multiplet between 5.07-4.98 ppm. The multiplet between 5.55-5.70 ppm are due to internal vinylic protons. The methine proton of the ring shows singlet at 7.21 ppm. Other methine protons of the ring show multiplet between 7.35-7.23 ppm.

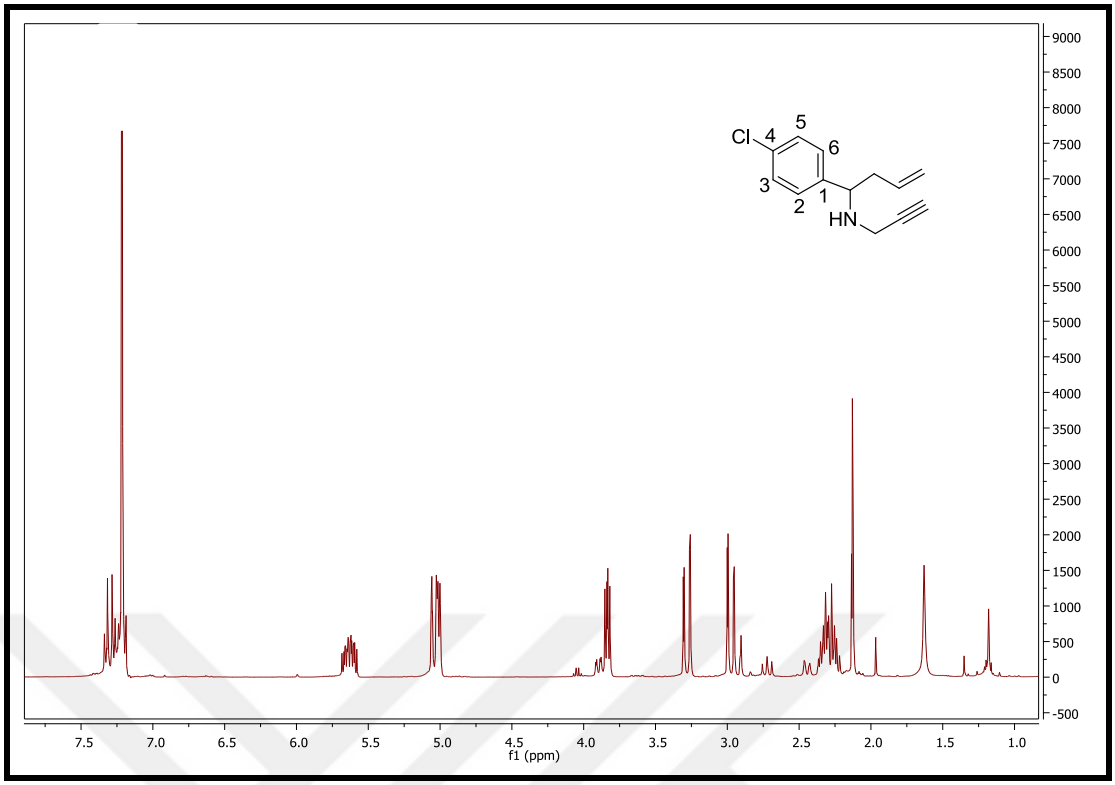


Figure 3.14. ^{1}H-NMR spectrum of 1-(4-chlorophenyl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **120**

^{13}C-NMR spectrum of 1-(4-chlorophenyl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **120** shows signals at 35.7 and 39.4 ppm belongs to the allylic carbon atom of the propargyl group. Other allylic carbon atom of the allyl group shows a signals at 42.7 and 50.0 ppm. The signals at 59.6 and 63.8 ppm belongs to the steregenic carbon atom. The methine and quaternary carbon of the propargyl unit exhibit signal at 71.5 ppm and 82.0 ppm respectively. Moreover, vinylic carbons of allyl group exhibit signals at 118.2 ppm and 134.8 ppm. The signals at 128.6 and 128.7 ppm are due to the methine carbons at the sixth and second position of the ring respectively. The other methine carbons at the third and fifth position of the ring exhibit a signals at 128.8 and 128.9 ppm. The signals at 132.9 and 133.8 ppm belongs to the methine carbon at fourth position of the ring. Finally the methine carbon at first position of the ring exhibits signals at 140.0 and 141.2 ppm.

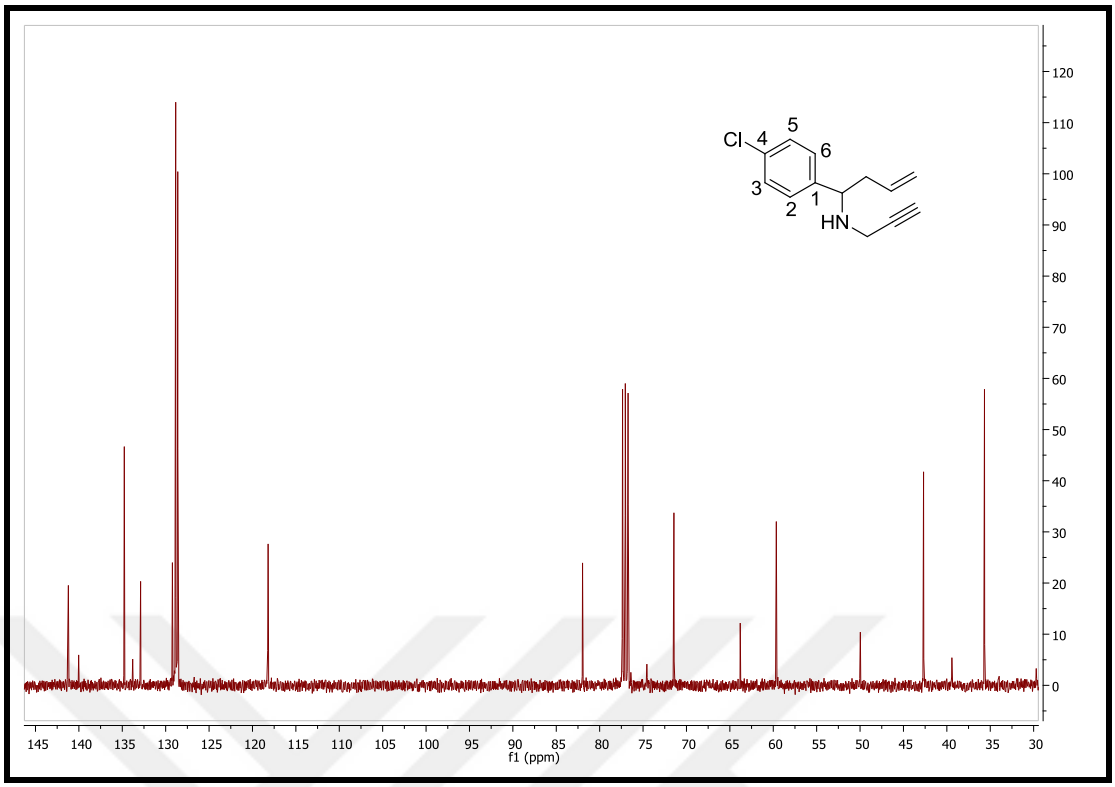
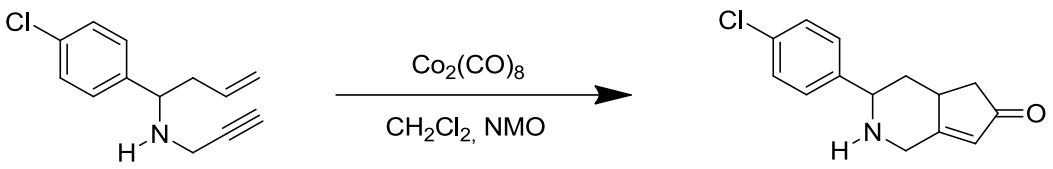


Figure 3.15. ^{13}C-NMR spectrum of 1-(4-chlorophenyl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **120**

3.6 Synthesis of 3-(4-chlorophenyl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one 121 : (Diastereomeric Mixture)

3-(4-chlorophenyl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one-**121** was synthesized by using the Pauson-Khand cycloaddition reaction. 1-(4-chlorophenyl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **120** was reacted with dicobalt octacarbonyl in the presence of NMO as a promoter to obtain 3-(4-chlorophenyl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **121** in CH_2Cl_2 via Pauson-Khand cycloaddition reaction as shown in figure 2.16. After work up, 3-(4-chlorophenyl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **121** was obtained as yellow oil with 81% chemical yield.



120 **121**

Figure 3.16. Synthesis of 3-(4-chlorophenyl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **121**

The product was identified by ^{1}H-NMR and ^{13}C-NMR spectroscopy

^{1}H-NMR spectrum of 3-(4-chlorophenyl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **121** broad singlet at 2.04 ppm is due to the N-*H* proton. The multiplet between 1.87-2.19 ppm belong to the diastereotopic methylene protons at sixth position of tetrahydro ring and other diastereotopic methylene protons at fifth position and finally, the stereogenic methine proton at 6a position. The multiplet between 4.10-4.27 ppm are due to the diastereotopic methylene protons at second position and the other stereogenic methine proton at seventh position. The singlet at 7.28 ppm is due to the olefinic proton that is found at the third position Triplet at 7.51 ppm with J=4.0 Hz belong to methine protons at 2' and 6' position of the *p*-chlorophenyl ring. The methine protons at 3' and 5' position of the *p*-chlorophenyl ring show doublet at 7.83 ppm with *J*=8 Hz.

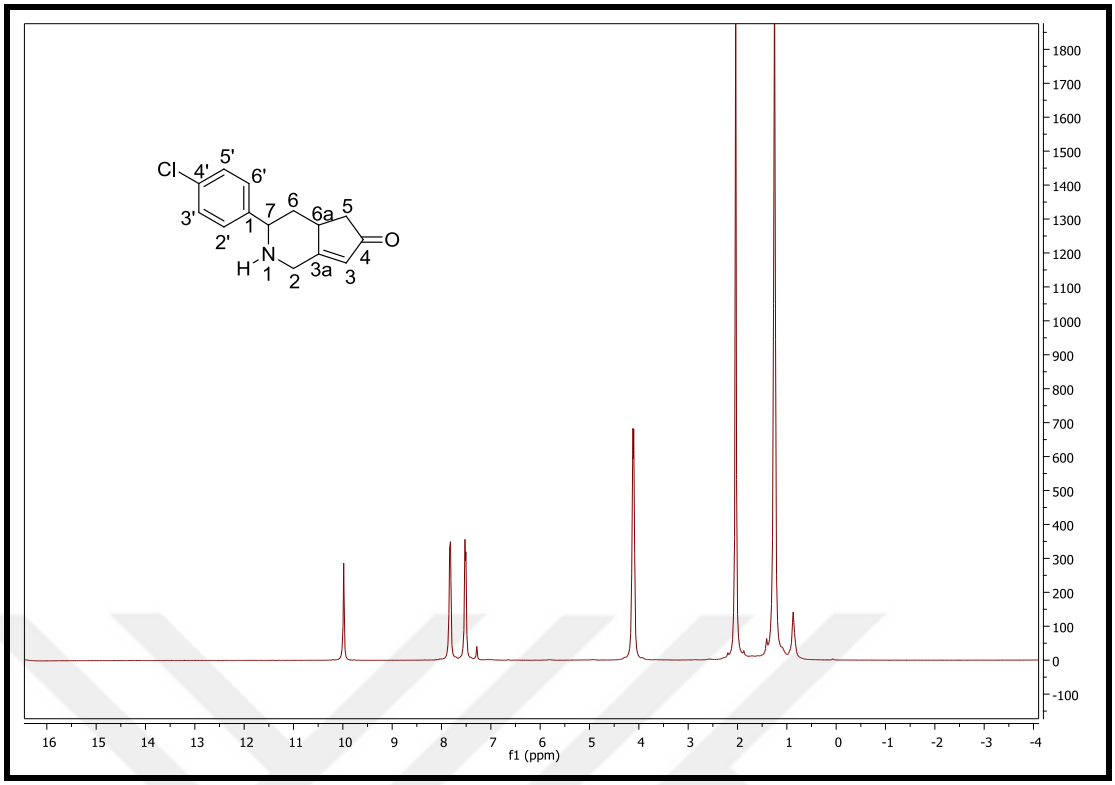


Figure 3.17. ^{1}H-NMR spectrum of 3-(4-chlorophenyl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **121**

^{13}C-NMR spectrum of 3-(4-chlorophenyl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **121** a signal at 14.2 ppm is due to the methylene carbon at sixth position of tetrahydro ring of two diastereomers. The methylene carbon at fifth position of the cyclopenta[c]pyridine ring of two diastereomers shows signals at 21.0 and 23.0 ppm. The signals at 29.7 and 31.8 ppm is due to methylene carbon at second position of the tetrahydro ring of two diastereomers. The stereogenic methine carbon at 6a position exhibits a signal at 49.2 ppm. The signal at 60.3 ppm belongs to the stereogenic methine at the seventh position. The methine carbons of the *p*-chlorophenyl ring show signals at 129.2, 130.9 and 134.8 ppm of diastereotopic mixture. The signal at 140.7 ppm is due to the olefenic carbon at third position of cyclopenta[c]pyridine ring. The quarternary methine carbon at 3a position exhibits a signal 171.0 ppm. Finally, the carbonyl carbon of the cyclopenta[c]pyridine ring exhibits signal at 210.6 ppm.

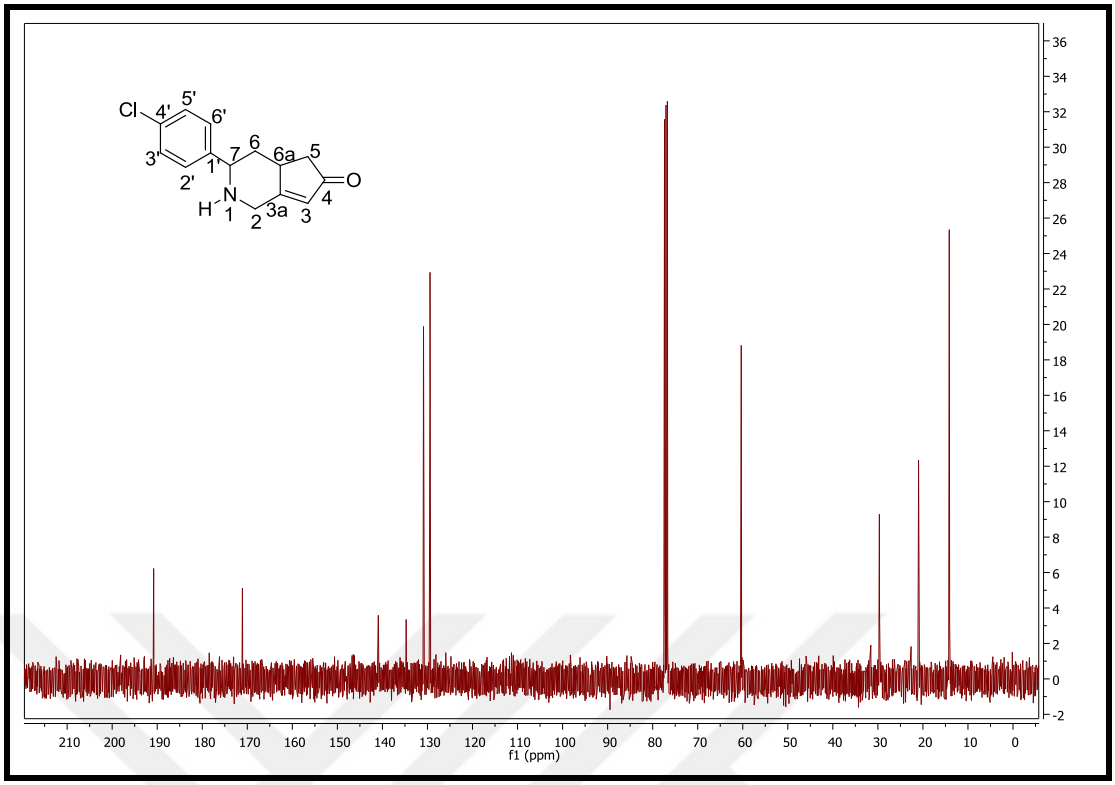
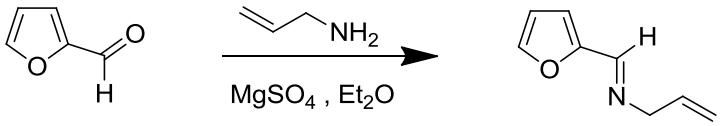


Figure 3.18. ^{13}C-NMR spectrum of 3-(4-chlorophenyl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **121**

3.7 Synthesis of (E)-*N*-(furan-2-ylmethylene)prop-2-en-1-amine 123

(E)-*N*-(furan-2-ylmethylene)prop-2-en-1-amine **123** was prepared from furan-2-carbaldehyde **122** and allylamine in the presence of dry ether and anyhydrous magnesium sulfate shown in Figure 2.19. After work up, (E)-*N*-(furan-2-ylmethylene)prop-2-en-1-amine **123** was obtained as colourless oil with 96% chemical yield.



122 **123**

Figure 3.19. Synthesis of (E)-*N*-(furan-2-ylmethylene)prop-2-en-1-amine **123**

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

^{1}H-NMR spectrum of (E)-*N*-(furan-2-ylmethylene)prop-2-en-1-amine **123** shows doublet of doublet at 4.15 ppm with J_1= 6, J_2=1.6 Hz are due to the allylic methylene protons. Terminal vinylic protons; Ha and Hb exhibit doublet of quartet at 5.08 ppm with J_1=2.9, J_2=1.3 Hz and doublet of quartet at 5.14 ppm with J_1=3.3, J_2=1.3 Hz respectively. The multiplet between 5.89-6.09 ppm is due to the internal vinylic proton; Hc of the allyl group. The methine proton third position of the ring show doublet of doublet at 6.40 ppm with J_1=3.5, J_2=1.8 Hz values. Other methine proton at fourth position of the ring shows doublet at 6.68 ppm with J=3. 2 Hz values. The doublet at 7.44 ppm with J=1.6 Hz is due to methine proton at second position of the ring. Finally, the singlet at 8.03 ppm is due to the imine proton.

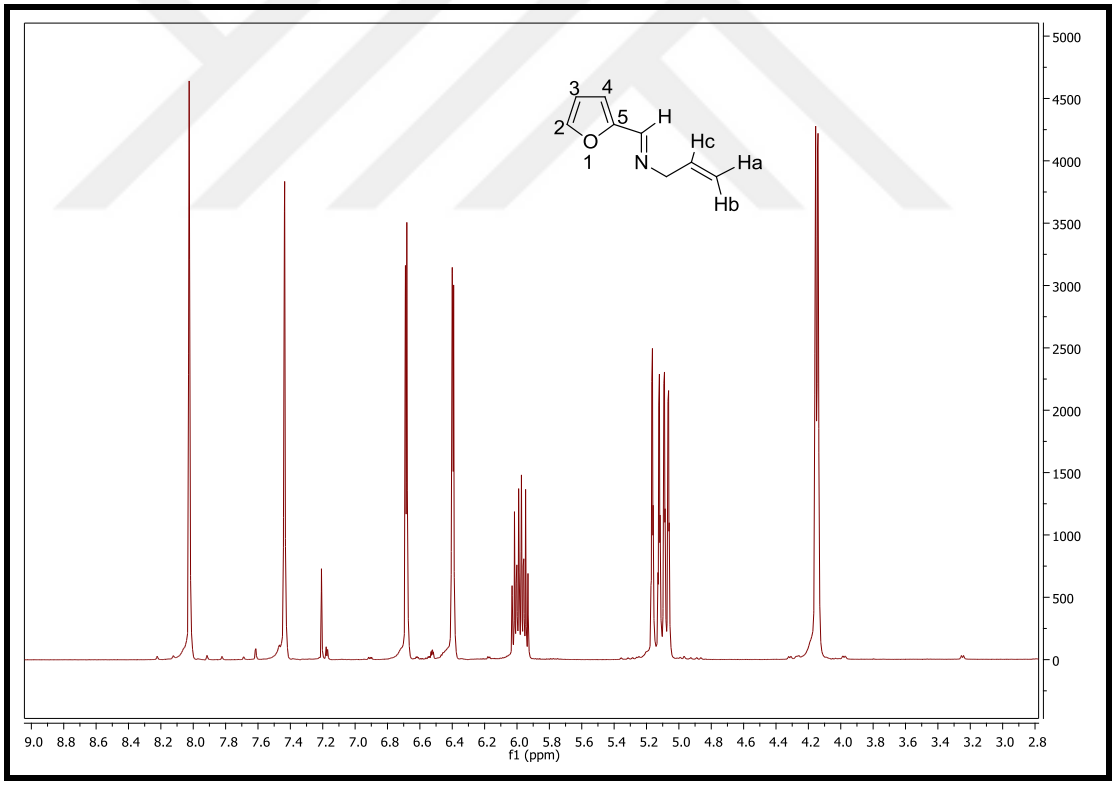


Figure 3.20. ^{1}H-NMR spectrum of (E)-*N*-(furan-2-ylmethylene)prop-2-en-1-amine **123**

^{13}C-NMR spectrum (E)-*N*-(furan-2-ylmethylene)prop-2-en-1-amine **123** of shows signals at 63.6 ppm for the allylic methylene carbon. The methine carbons at third and fourth position of the ring exhibit signals at 111.6 and 113.9 ppm respectively. The signals at 116.4 and 135.6 ppm are due to the vinylic carbons. The methine carbon at second position of the ring exhibits signal at 144.7 ppm. The imine carbon shows signal at 150.4ppm. Finally, the signal at 151.6 ppm belongs to the methine carbon at fifth position of the ring.

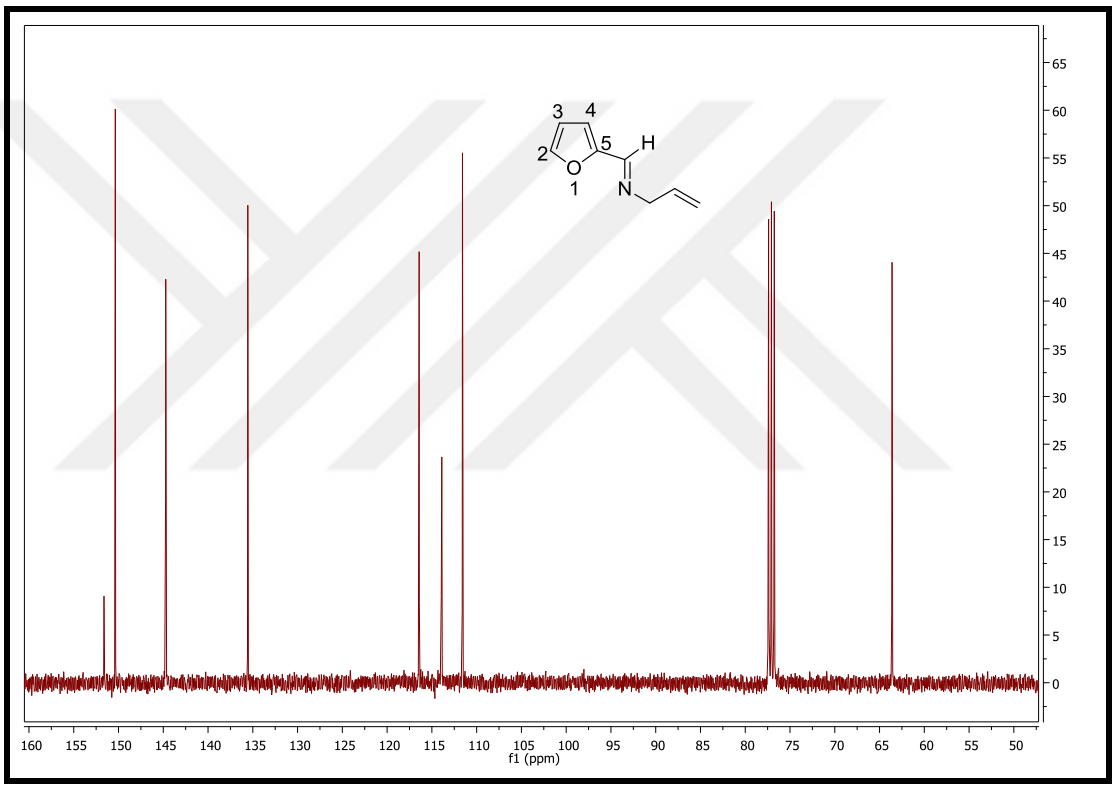
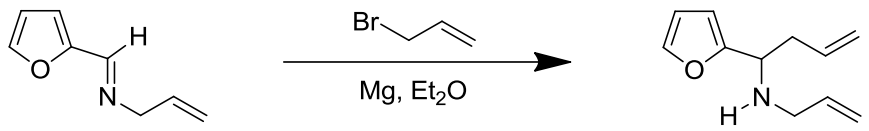


Figure 3.21. ^{13}C-NMR spectrum of (E)-*N*-(furan-2-ylmethylene)prop-2-en-1-amine **123**

3.8 Synthesis of *N*-allyl-1-(furan-2-yl)but-3-en-1-amine 124 : (Diastereomeric Mixture)

N-allyl-1-(furan-2-yl)but-3-en-1-amine **124** was prepared from (E)-*N*-(furan-2-ylmethylene)prop-2-en-1-amine **123** and allyl bromide in the presence of di ethyl ether by a Grignard reaction shown in Figure 2.22. After work up, *N*-allyl-1-(furan-2-yl)but-3-en-1-amine **124** was obtained as colourless oil with 87% chemical yield.



123 **124**

Figure 3.22. Synthesis of *N*-allyl-1-(furan-2-yl)but-3-en-1-amine **124**

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

^{1}H-NMR spectrum of *N*-allyl-1-(furan-2-yl)but-3-en-1-amine **124** shows broad singlet at 1.92 ppm is due to N-*H* proton. One of the diastreotopic allylic methylene protons exhibit multiplet between 2.41-2.49 ppm. Other one show multiplet between 2.53-2.59 ppm. The triplet of doublet of doublet at 3.02 ppm with J_1= 14.0, J_2=6.4, J_3=1.2 Hz belong to one of the diastereotopic allylic methylene proton. Other one exhibits triplet of doublet of doublet at 3.12 ppm with J_1=13.8, J_2=5.6, J_3=1.5 Hz. The stereogenic methine proton shows triplet at 3.72 ppm with *J*= 7 Hz. The terminal vinylic protons; Ha and Hb exhibit multipet between 4.96-5.00 ppm and multiplet between 5.00-5.03 ppm. Other terminal vinylic protons; Ha' and Hb' show multiplet between 5.03-5.07 and multiplet between 5.07-5.17 ppm respectively. One of the internal vinylic proton of allyl group exhibit multiplet between 5.58-5.71 ppm. The multiplet between 5.72-5.84 ppm is due to other internal vinylic proton of allyl group. The methine proton fourth position of the ring shows doublet of doublet at 6.13 ppm with J_1=38.2, J_2=3.0 Hz values. Other methine proton at third position of the ring shows doublet of doublet of doublet at 6.68 ppm with J_1 =11.2, J_2=3.2, J_3=2 Hz values. The doublet of doublet at 7.30 ppm with J_1=7.6, J_2=1.2 Hz is due to methine proton at second position of the ring.

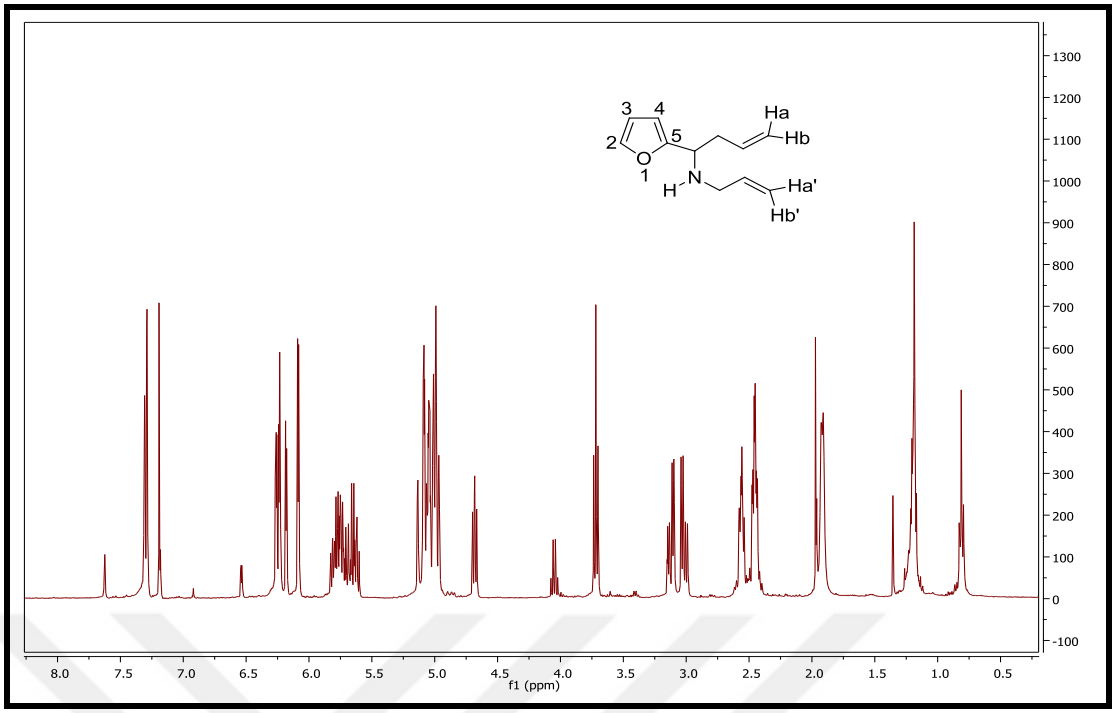


Figure 3.23. ^{1}H-NMR spectrum of *N*-allyl-1-(furan-2-yl)but-3-en-1-amine **124**

^{13}C-NMR spectrum of *N*-allyl-1-(furan-2-yl)but-3-en-1-amine **124** show signals at 39.2 and 40.1 ppm belong to the allylic carbon atom of the allyl group of two diastereomers. The other allylic carbon atom of the *N*-allyl group of two diastereomers show a signals at 49.8 and 54.9 ppm. The signal at 66.9 ppm belongs to the quaternary carbon atom. The methine carbon at fourth position of the ring of two diastereomers exhibit signals at 106.1 and 106.6 ppm. The signals at 109.8 and 110.1 ppm are due to the methine carbon of two diastereomers at third position of the ring. Terminal vinylic carbons of the allyl and *N*-allyl group exhibit signals at 116.1, 117.5 and 118.5 ppm of diastereotopic mixture. The signals at 133.7, 134.7 and 136.5 ppm belong to the internal vinylic carbons of allyl and *N*-allyl groups. Furthermore, the methine carbon at second position of the ring of two diastereomers exhibit signals at 141.5 and 142.0 ppm. Finally, the signal at 156.0 ppm belongs to the methine carbon at fifth position of the ring.

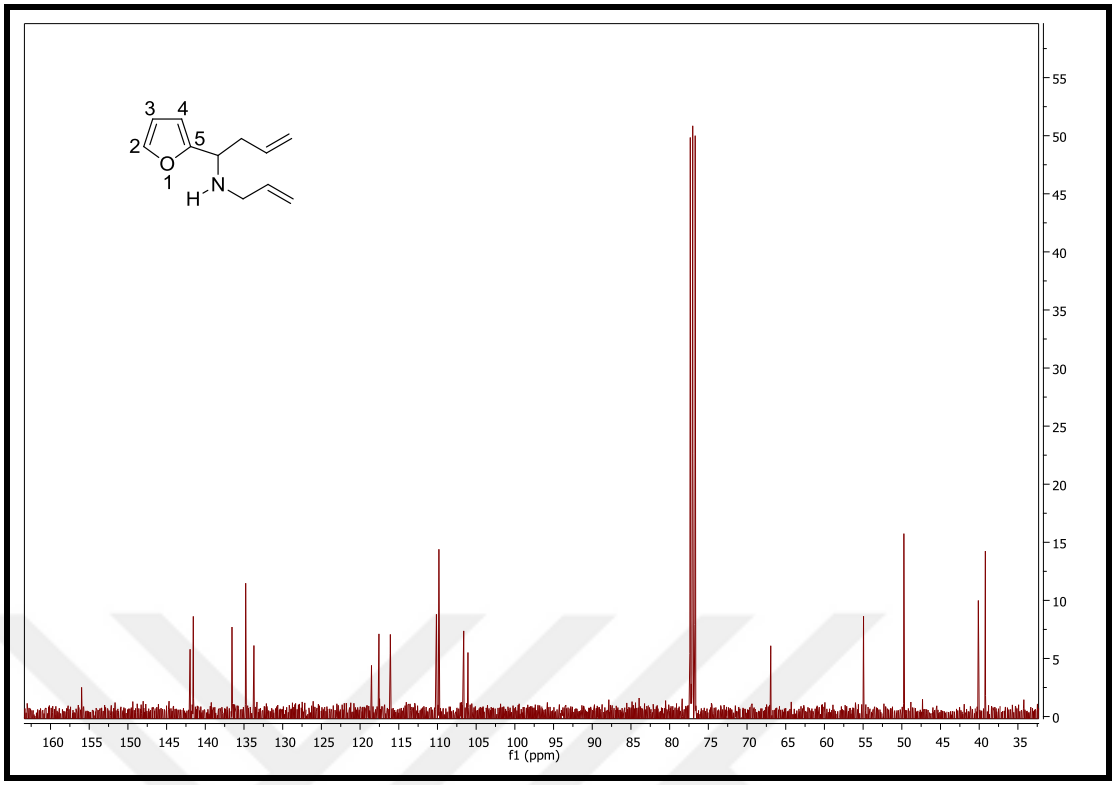
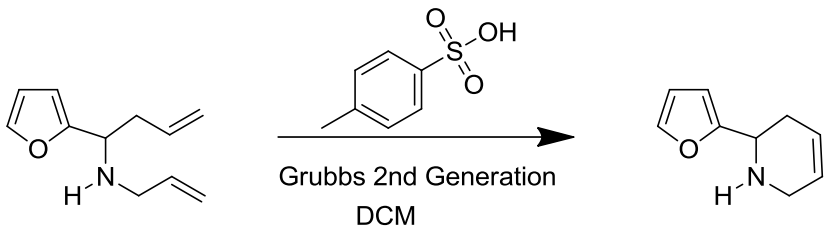


Figure 3.24. ^{13}C-NMR spectrum of *N*-allyl-1-(furan-2-yl)but-3-en-1-amine **124**

3.9 Synthesis of 2-(furan-2-yl)-1,2,3,6-tetrahydropyridine 125

2-(furan-2-yl)-1,2,3,6-tetrahydropyridine **125** was synthesized from *N*-allyl-1-(furan-2-yl)but-3-en-1-amine **124** in the presence of p-toluenesulfonic acid monohydrate in DCM by using Grubbs Second Generation catalyst with Ring Closing Metathesis shown in Figure 2.25. After work up, 2-(furan-2-yl)-1,2,3,6-tetrahydropyridine **125** was obtained as colourless oil with 93% chemical yield.



124 **125**

Figure 3.25. Synthesis of 2-(furan-2-yl)-1,2,3,6-tetrahydropyridine **125**

The product was identified by ^{1}H-NMR and ^{13}C-NMR spectroscopy

^{1}H-NMR spectrum of 2-(furan-2-yl)-1,2,3,6-tetrahydropyridine **125** shows broad singlet at 2.19 ppm is due to N-*H* proton. The diastereotopic methylene protons at fifth position of the tetrahydropyridine ring show multiplet between 2.25-2.28 ppm. One of the methylene proton at second position of the tetrahydropyridine ring shows doublet of doublet at 3.30 ppm with J_1=17, J_2=1.8 Hz and other methylene proton exhibits doublet of doublet at 3.44 ppm with J_1=17.2, J_2=2 Hz. The triplet at 3.91 ppm with J=7 Hz is due to the stereogenic methine proton at sixth position of the tetrahyroypyridine ring. The methine protons at third and fourth position of the tetrahydropyridine ring show multiplet between 5.64–5.71 ppm and 5.71 – 5.78 ppm respectively. The doublet of triplet at 6.10 ppm with J_1=2.4, J_2=0.8 Hz belongs to the methine proton at 3' position of the furyl ring. Other methine protons at 4' position of the furyl ring shows doublet of doublet at 6.23 ppm with J_1=3.2, J_2=1.6 Hz values. Finally, the doublet of doublet at 7.27 ppm with J_1=1.8, J_2=0.8 Hz is due to methine proton at 5' position of the furyl ring.

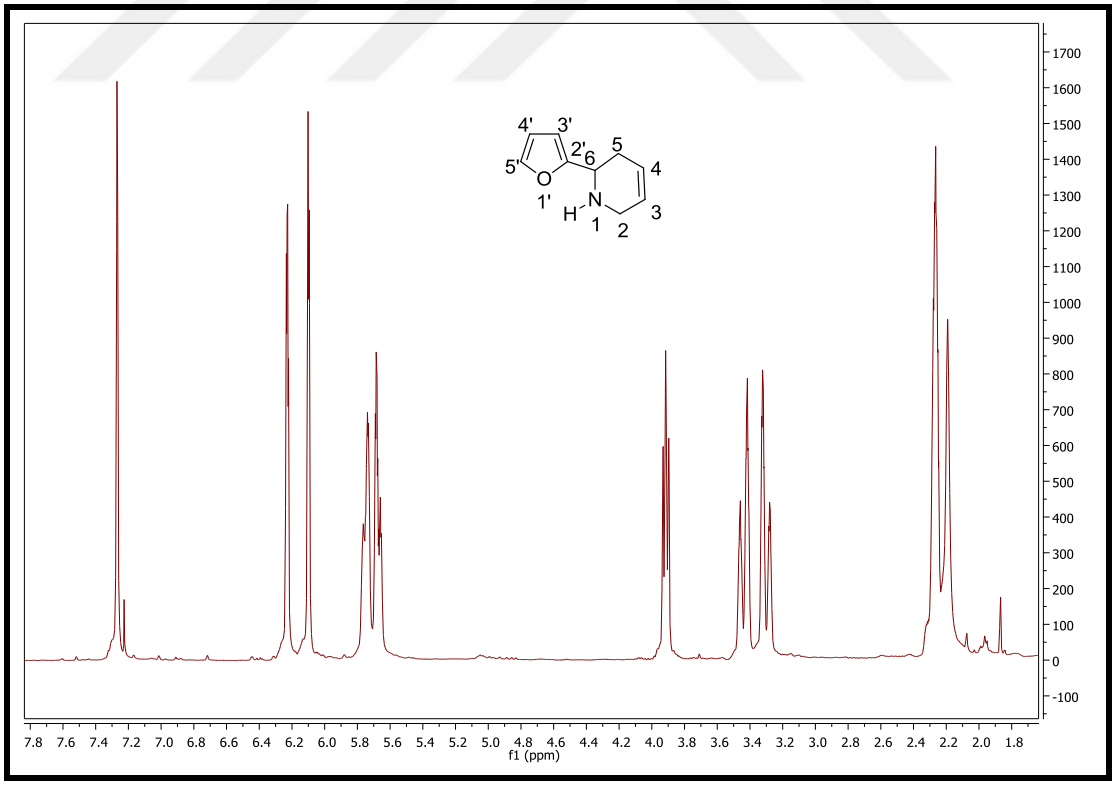


Figure 3.26. ^{1}H-NMR spectrum of 2-(furan-2-yl)-1,2,3,6-tetrahydropyridine **125**

^{13}C-NMR spectrum of 2-(furan-2-yl)-1,2,3,6-tetrahydropyridine **125** shows signal at 29.8 ppm is due to the allylic methylene carbon at fifth position of tetrahydropyridine ring. The signal at 44.8 ppm is due to other allylic methylene carbon at second position. The stereogenic methine carbon at sixth position of tetrahydropyridine exhibits signal at 50.4 ppm. The methine carbons at 4' and 3' position of the furyl ring exhibit signals at 104.5 and 110.0 ppm. The signal at 124.5 ppm belongs to the methine carbon third position of tetrahydropyridine ring. The signal at 126.5 ppm is due to the other methine carbon at fourth position of tetrahydropyridine ring. The methine carbon at 4' position of the furyl ring exhibits signal at 141.5 ppm. Finally, the signal at 156.9 ppm belongs to the methine carbon at 1' position of the furyl ring.

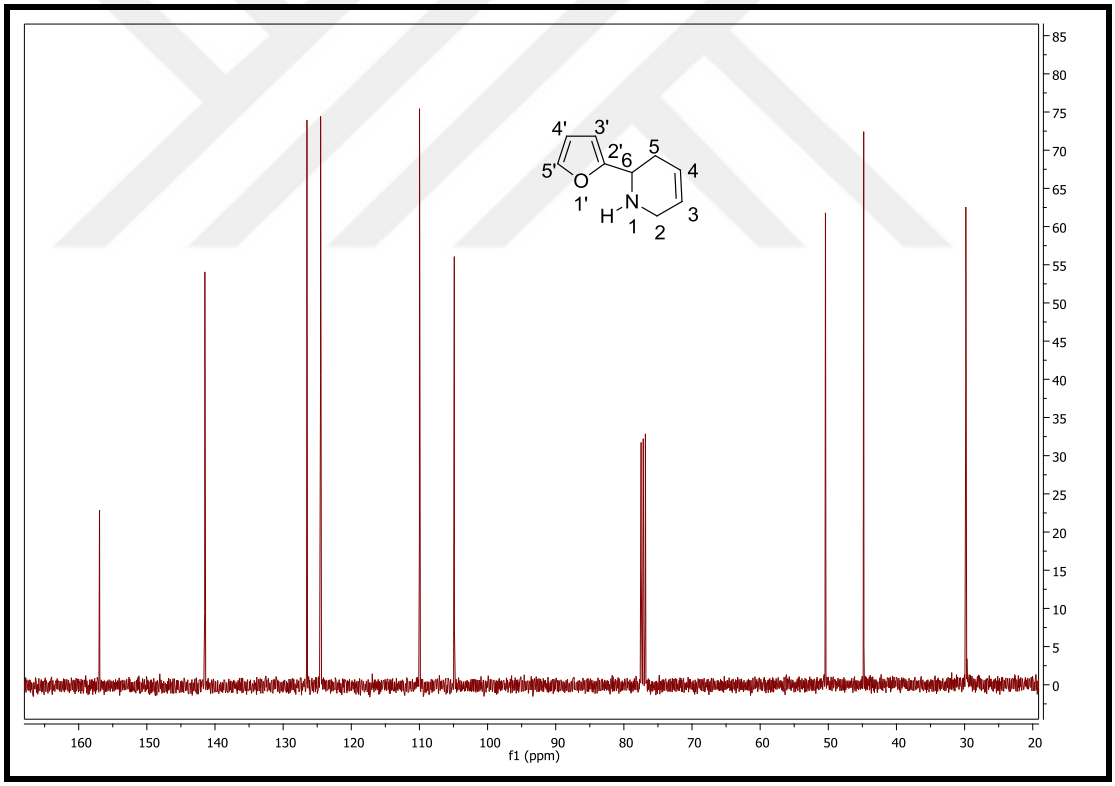
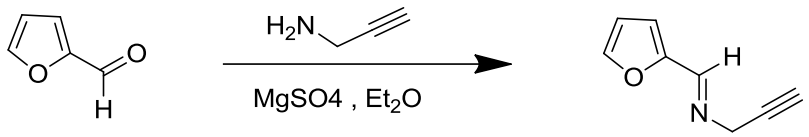


Figure 3.27. ^{13}C-NMR spectrum of 2-(furan-2-yl)-1,2,3,6-tetrahydropyridine **125**

3.10 Synthesis of (E)-*N*-(furan-2-ylmethylene)prop-2-yn-1-amine 126

(E)-*N*-(furan-2-ylmethylene)prop-2-yn-1-amine **126** was prepared from furan-2-carbaldehyde **122** and properglamine in the presence of dry ether and anyhydrous magnesium sulfate shown in Figure 2.28. After work up, (E)-*N*-(furan-2-ylmethylene)prop-2-yn-1-amine **126** was obtained as colourless oil with 84% chemical yield.



122 **126**

Figure 3.28. Synthesis of (E)-*N*-(furan-2-ylmethylene)prop-2-yn-1-amine **126**

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

^{1}H-NMR spectrum of (E)-*N*-(furan-2-ylmethylene)prop-2-yn-1-amine **126** shows a triplet at 2.48 ppm with J=2.4 Hz is belongs to the acetylenic proton. The diasterotopic methylene protons of the propargyl group exhibit triplet at 4.45 ppm with J=2 Hz. Doublet of doublet at 6.40 ppm with J_1=3.4, J_2=1.8 Hz belongs to the methine proton at third position of the ring. Other methine proton at fourth position of the ring shows doublet at 6.73 ppm with J=3.2 Hz values. The doublet at 7.45 ppm with J=1.2 Hz is due to methine proton at second position of the ring. Finally, imine proton shows a singlet at 8.35 ppm.

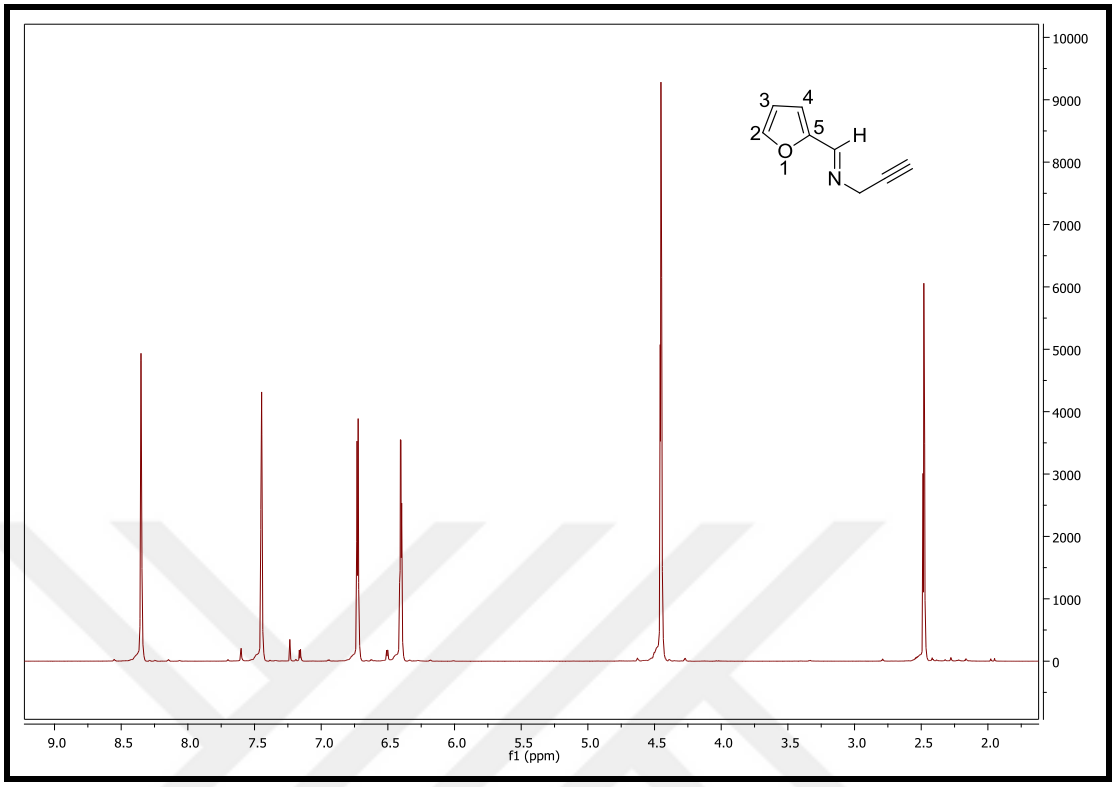


Figure 3.29. ^{1}H-NMR spectrum of (E)-*N*-(furan-2-ylmethylene)prop-2-yn-1-amine **126**

^{13}C-NMR spectrum of (E)-*N*-(furan-2-ylmethylene)prop-2-yn-1-amine **126** shows signal at 46.7 ppm for the allylic methylene carbon of the propargyl group. The signals at 76.4 ppm and 78.3 ppm are due to the methine and quaternary carbons of the propargyl group. The methine carbons of the ring at third and fourth position of the furan ring exhibit signals at 111.7 and 114.6 ppm respectively. The signal at 145.0 ppm belongs to the methine carbon at second position of the ring. The imine carbon shows signal at 150.5 ppm. Finally, the signal at 151.6 ppm is due to the methine carbon at fifth position of the ring.

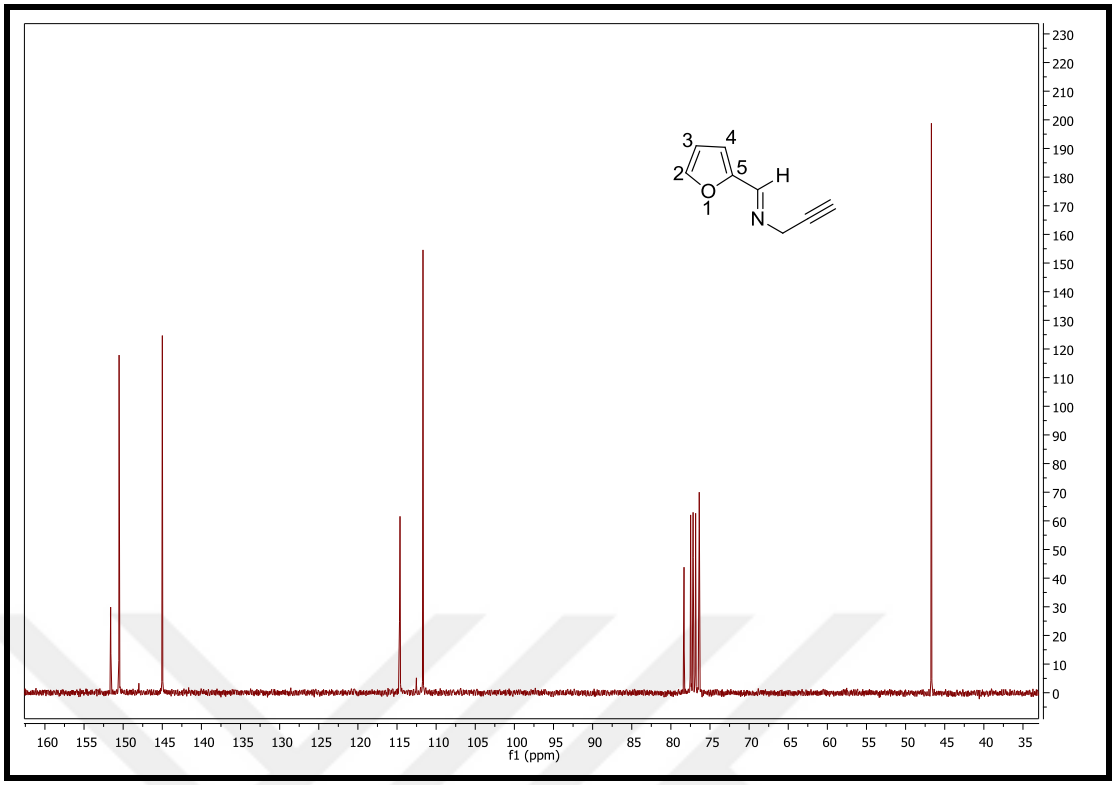
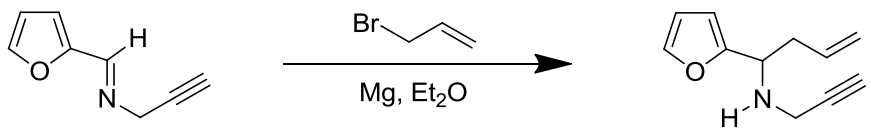


Figure 3.30. ^{13}C-NMR spectrum of (E)-*N*-(furan-2-ylmethylene)prop-2-yn-1-amine **126**

3.11 Synthesis of 1-(furan-2-yl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine 127 : (Diastereomeric Mixture)

Synthesis of 1-(furan-2-yl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **127** was prepared from E)-*N*-(furan-2-ylmethylene)prop-2-yn-1-amine **126** and allyl bromide in the presence of di ethyl ether by a Grignard reaction shown in Figure 2.22. After work up, synthesis of 1-(furan-2-yl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **127** was obtained as colourless oil with 81% chemical yield.



126 **127**

Figure 3.31. Synthesis of 1-(furan-2-yl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **127**

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

^{1}H-NMR spectrum of 1-(furan-2-yl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **127** shows broad singlet at 1.73 ppm is due to the N-*H* proton. The triplet at 2.13 ppm with *J*=2.4 Hz is due to one of diastereotopic acetylenic proton. The multiplet between 2.21-2.37 ppm belong to the allylic methylene protons of the allyl group. Other diastereotopic acetylenic proton exhibits a signal at 2.48 ppm with *J*=2 Hz. One of the diastereotpic methylene proton of the propargyl group exhibits doublet of doublet at 3.14 with J_1= 17.2, J_2=2.4 Hz and other one shows a signal at 3.34 ppm with J_1=17.0, J_2=2.6 Hz. The triplet at 3.93 ppm with *J*= 6.8 Hz is due to one of the stereogenic methine proton. Other stereogenic methine proton exhibits a signal at 4.47 ppm with *J*=2 Hz. Doublet of doublet at 5.01 ppm with J_1=10.0, J_2=0.8 Hz is due to the terminal vinylic proton. Other terminal vinylic proton shows a doublet of doublet at 5.06 ppm with J_1=17.2, J_2=1.2 Hz. The multiplet between 5.61-5.72 ppm belongs to the internal vinylic proton. One of the diastereotopic methine proton third position of the ring show doublet at 6.13 ppm with *J*=3.2 Hz and other one doublet of doublet at 6.23 ppm with J_1=3.2, J_2=2 Hz. Doublet of doublet at 6.42 ppm with J_1=3.2, J_2=1.6 Hz and doublet at 6.74 ppm with J=3.6 Hz belong distereotopic methine protons at fourth position of the ring, respectively. Finally one of the diastereotopic methine proton at second position of the ring shows quartet at 7.23 ppm with *J*=0.8 Hz values.The signlet at 7.46 ppm is due to other diastereotopic methine proton at second position of the ring.

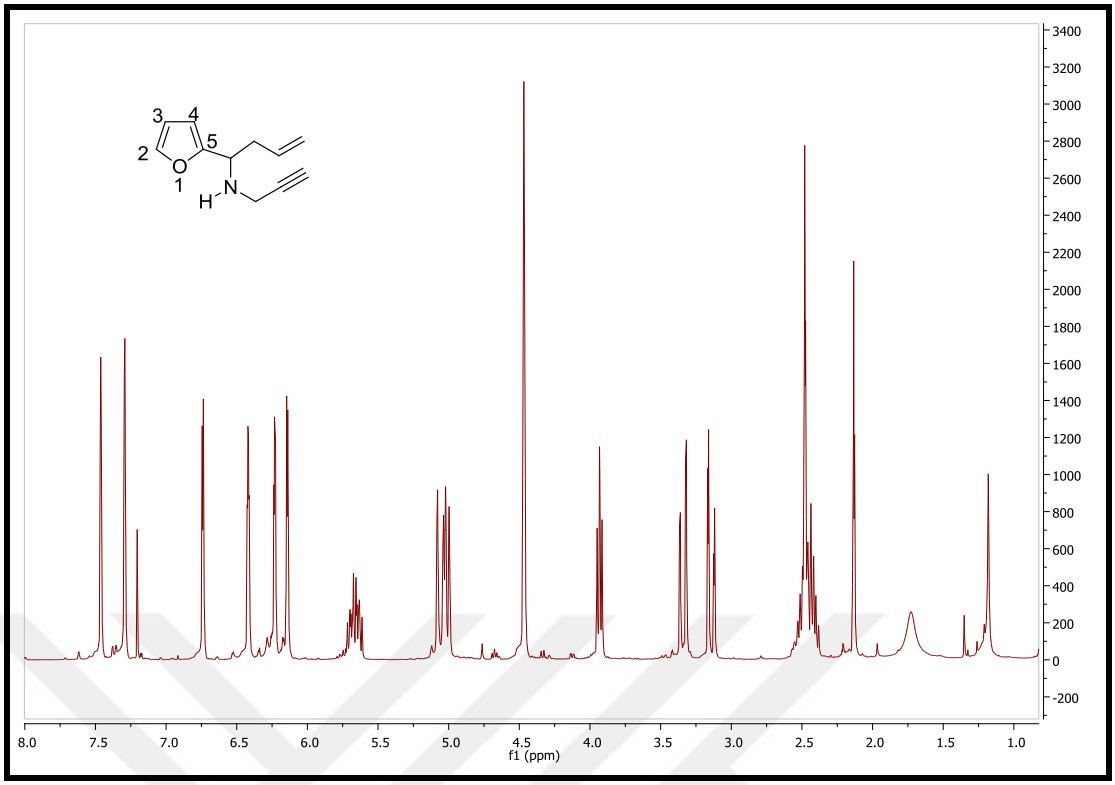


Figure 3.32. ^{1}H-NMR spectrum of 1-(furan-2-yl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **127**

^{13}C-NMR spectrum of 1-(furan-2-yl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **127** shows signals at 29.7 and 35.7 ppm belong to the allylic carbon atom of the propargyl group of two diastereomers. The other allylic carbon atom of the allyl group of two diastereomers show a signals at 39.1 and 46.7 ppm. The signal at 54.0 belongs to the stereogenic carbon atom. The acetylenic carbon exhibit signals at 71.4 and 76.4 ppm. Furthermore, quaternary carbon of the propargyl unit of two diastereomers exhibit signals at 78.3 and 81.9 ppm. The methine carbon at fourth position of the furyl ring of two diastereomers exhibit signals at 107.2 and 109.8 ppm. The signal at 111.7 ppm belongs to the methine carbon at third position of the furyl ring. Terminal vinylic carbon of two diastereomers exhibit signals at 114.6 and 117.9 ppm. The signals at 134.5 and 141.9 ppm is due to the internal vinylic carbon of two diastereomers. The methine carbon of the ring at second position of the ring of two diastereomers exhibit signals at 145.0 and 150.6 ppm. Finally, the methine carbon at fifth position of the furyl ring of two diastereomers show a signals 151.6 and 155.0 ppm.

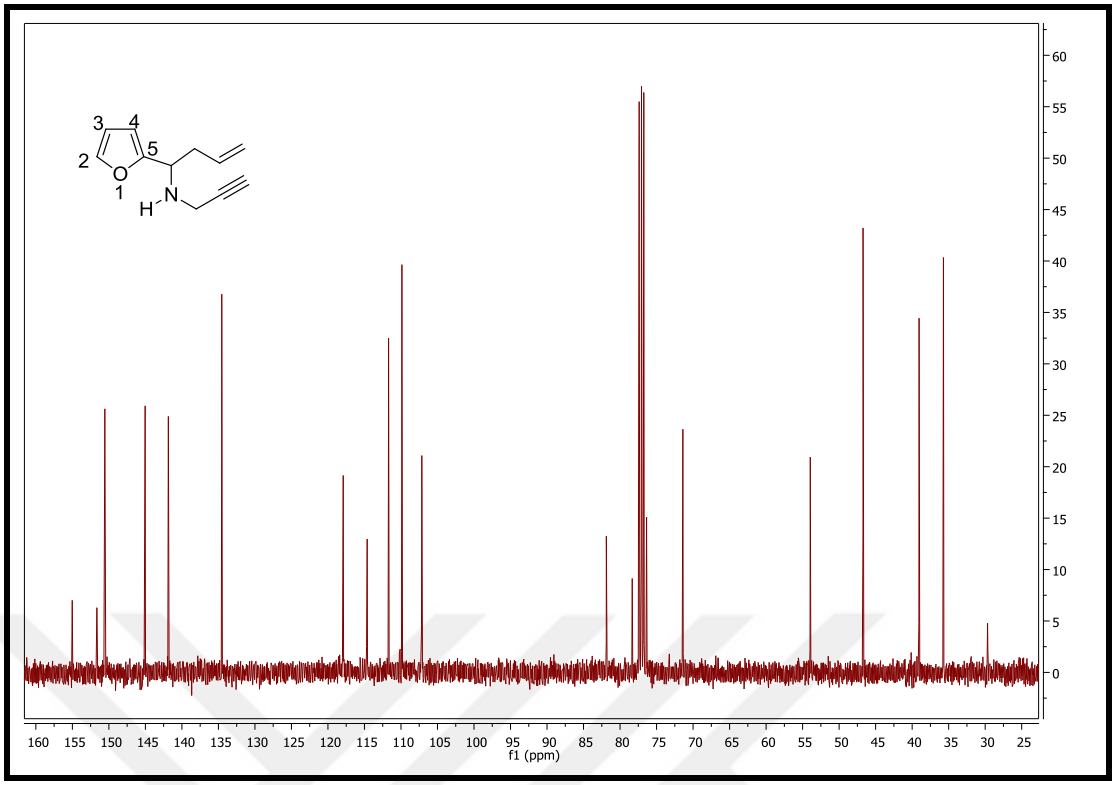
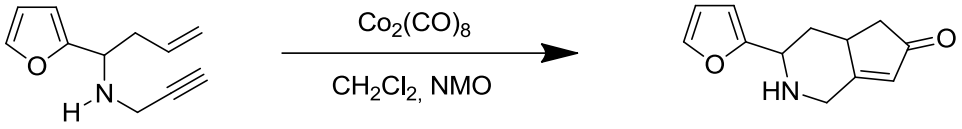


Figure 3.33. ^{13}C-NMR spectrum of 1-(furan-2-yl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **127**

3.12 Synthesis of 3-(furan-2-yl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one 128 : (Diastereomeric Mixture)

3-(furan-2-yl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **128** was synthesized by using the Pauson-Khand cycloaddition reaction. 1-(furan-2-yl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **127** was reacted with dicobalt octacarbonyl in the presence of NMO as a promoter to obtain 3-(furan-2-yl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **128** in CH_2Cl_2 via Pauson-Khand cycloaddition reaction as shown in Figure 2.34. After work up, 3-(furan-2-yl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **128** was obtained as yellow oil with 79% chemical yield.



127 **128**

Figure 3.34. Synthesis of 3-(furan-2-yl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **128**

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

^{1}H-NMR spectrum of 3-(furan-2-yl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **128** shows singlet peak at 1.98 ppm is due to the N-*H* proton. The doublet of doublet at 1.28 ppm with J_1=5.4, J_2=4.8 Hz are due to methylene proton at sixth position of the tetrahydro ring. The stereogenic proton at 6a position shows multiplet between 1.15-1.26 ppm. The multiplet between 1.97-2.13 ppm belong to the methylene protons at fifth position of the cyclopenta[c]pyridin ring. Other stereogenic methine proton at seventh position shows triplet at 3.99 ppm with *J*=5.6 Hz. The quartet at 4.05 ppm with *J*=7.2 Hz are due to methylene protons at second position of the tetrahdyro ring. The olefinic proton at third position of the cyclopenta[c]pyridin ring shows quartet at 6.44 ppm with *J*=1.6 Hz. The doublet at 7.06 ppm with *J*=3.2 Hz is due to methine proton at 4' position of the furyl ring. The methine proton at 3' position of the furyl ring shows singlet at 7.20 ppm. Finally the singlet at 7.37 ppm belongs to the methine proton 2' position of the furyl ring.

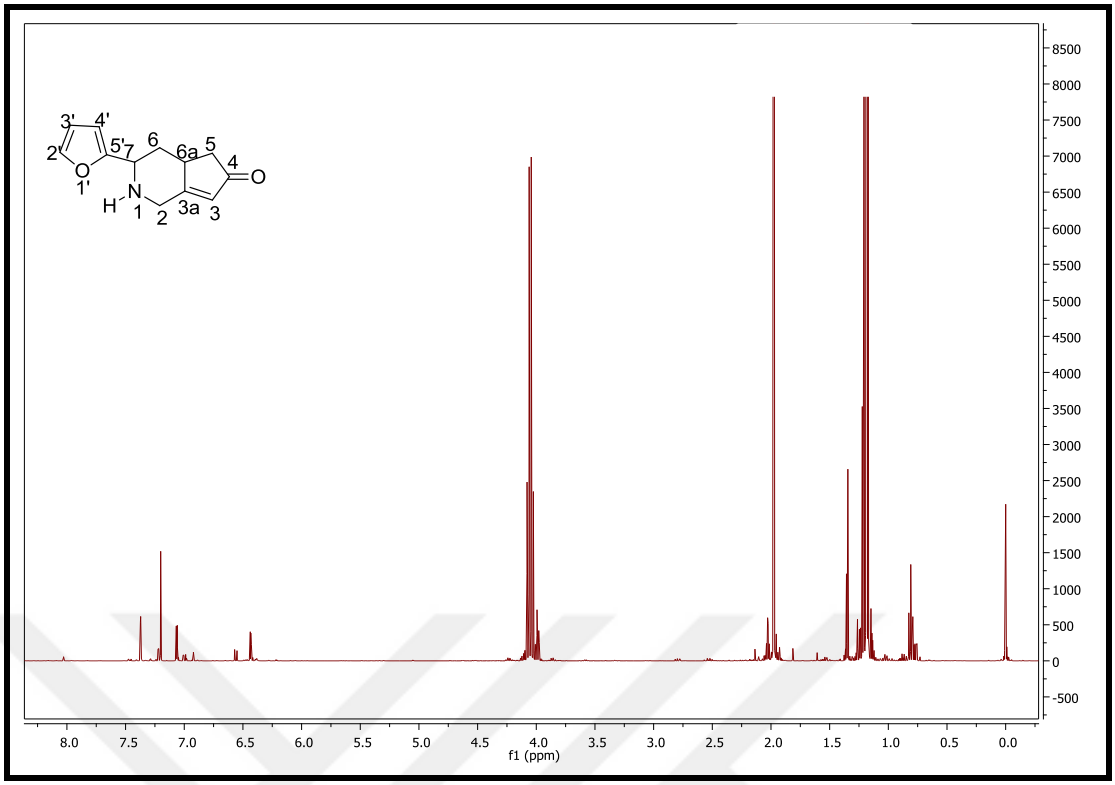


Figure 3.35. ^{1}H-NMR spectrum of 3-(furan-2-yl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **128**

^{13}C-NMR sprektrum of 3-(furan-2-yl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **128** shows a signal at 14.1 and 14.2 ppm is due to the methylene carbon of two diastereomers at sixth position of tetrahydro ring. The stereogenic methine carbon of two diastereomers at 6a position shows signals at 21.4 and 22.7 ppm. The signals at 29.4 and 29.7 ppm is due to methylene carbon at fifth position of the cyclopenta[c]pyridine of two diastereomers. The signal at 41.5 ppm is due to other methylene carbon at second position of the tetrahydro ring. The stereogenic methine carbon at the seventh position exhibits a signal at 60.4 ppm. The signals at 101.8 and 104.7 ppm belong to the methine carbon of the ring at 4' position of the furyl ring of two diastereomers. The methine carbon at 3' position of the furyl ring of two diastereomers exhibits signals at 112.2 and 116.7 ppm. Furthermore, olefinic methine carbons at third position of cyclopenta[c]pyridine ring show signals at 135.8 ppm. The signal at 136.6 ppm is due to the other methine carbon at 2' position furyl ring. The methine carbon at 5' position of the furyl ring of two diastereomers exhibit signals at

149.5 and 149.9 ppm. The signal at 171.2 ppm belongs to the quarternary carbon at 3a position. Finally, the carbonyl carbon of the cyclopenta[c]pyridine ring exhibits signal at 214.9 ppm.

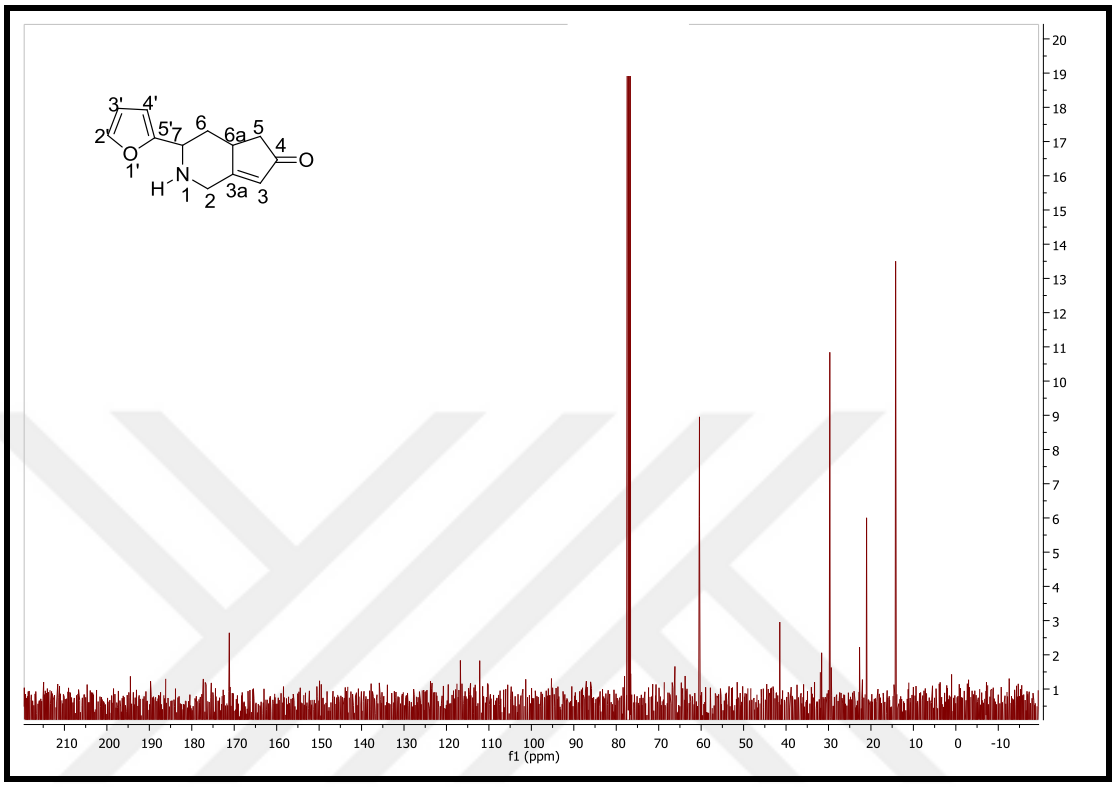


Figure 3.36. ^{13}C-NMR spectrum of 3-(furan-2-yl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **128**

4. MATERIAL AND METHOD

In this study, the instruments which are written below for the structure characterization of the compounds were used. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker Spectrospin Avance DPX 400 spectrometer, 400 MHz High Performance Digital FT-NMR Spectrometer, and Bruker AC 80 MHz FT-NMR Spectrometer by using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as internal standard. Chemical Shifts are given parts per million (from internal standard tetramethylsilane). Spin multiplicities are mentioned as: s (singlet), ss (strong singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), dt (doublet of triplet), pd (pentet of doublet), t (triplet), td (triplet of doublet), tdd (triplet of doublet of doublet), ddd (doublet of doublet of doublet), m (multiplet).

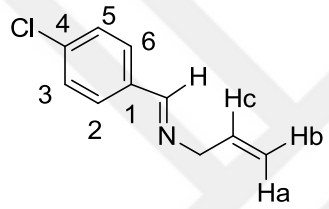
IR spectra were recorded on SHIMADZU FTIR 8400-S instrument. Bond positions were reported in reciprocal centimetres. (cm-1).

Flash column chromatography was performed by using thick-walled glass columns with a flash grade (Merck Silica Gel 60). Reactions were monitored by thin layer chromatography using precoated silica gel plates (Merck Silica Gel PF70 254), visualized with UV-light and polymolbyden phosphoric acid in ethanol as appropriate.

All extracts were dried over anhydrous magnesium sulphate ($MgSO_4$) and the solutions were concentrated under vacuum by performing rotary evaporator.

4.1 Synthesis of (E)-*N*-(4-chlorobenzylidene)prop-2-en-1-amine 116

To solution of p-cholorobenzaldeyde (2g, 14.23 mmol) in dry ether and anyhydrous $MgSO_4$, (2.23g, 18.50 mmol) equipped with a reflux condenser. The mixture was cooled down to 0°C and the allylamine (1.60 ml, 21.34 mmol) in dry ether was added dropwise with a injection syringe at under the argon atmosphere. The mixture was allowed to wait two hours and than resultant mixture was stirred three days. After stirred three days, the solution was filtered with dry ether and the solvent was removed in vacuo. The crude product was purified by flash column chromatography by using EtOAc/Hexane at the ratio of 1:8 as the eluent to obtain (E)-*N*-(4-chlorobenzylidene)prop-2-en-1-amine **116** as 92% chemical yield.



Rf=0.89 (silica gel – (EtOAc-Hexane), (1:8)

IR(neat): 3025, 2890, 2735, 1695, 1650, 1195, 736 cm^{-1}

^{1}H-NMR ($CDCl_3$) δ ppm

4.17 (dd, J_1=5.8, J_2=1.4 Hz, 2H, for the allylic methylene protons)

5.08 (qd, J_1=10.4, J_2=1.2 Hz, 1H, for one of the terminal vinylic proton Ha)

5.15 (qd, J_1=17.2, J_2=1.6 Hz, 1H, for other terminal vinylic proton Hb)

5.90-6.04 (m, 1H, for the internal vinylic proton of allyl group Hc)

7.30 (d, J=8.4 Hz, 1H, for the methine proton at third position of the ring

7.43 (d, J=8.4 Hz, 1H, for the methine proton at fifth position of the ring)

7.60 (d, J=8.4 Hz, 1H, for the methine proton at sixth position of the ring)

7.73 (d, *J*=8.4 Hz, 1H, for the methine proton at second position of the ring)

8.16 (s, 1H, for the imine proton)

^{13}C-NMR ($CDCl_3$) δ ppm

63.4 (for the allylic methylene carbon)

116.3 (for one of the vinylic carbon)

128.9 (for the methine carbon at third position of the ring)

129.3 (for the methine carbon at fifth position of the ring)

130.9 (for other vinylic carbon)

134.6 (for the methine carbon at sixth position of the ring)

135.7 (for the methine carbon at second position of the ring)

136.7 (for the methine carbon at first position of the ring)

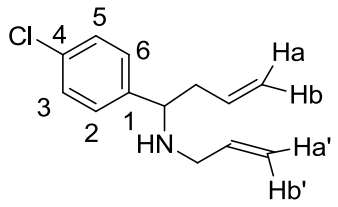
141.0 (for the methine carbon at fourth position of the ring)

160.6 (for the imine carbon)

4.2 Synthesis of *N*-allyl-1-(4-chlorophenyl)but-3-en-1-amine 117

To a stirred solution of Mg turnings (0.47g, 19.62 mmol) and iodine turning (2 pieces) in minimum amount of dry ethyl ether at 25^{o}C equipped with a reflux condenser. The mixture was added dropwise into a mixture of allyl bromide (1.25 mL, 14.39 mmol) in anhydrous diethyl ether with a injection syringe until the reaction begins. The mixture was allowed to reflux 45 minutes. The mixture was cooled down to 0^{o}C and (E)-*N*-(4-chlorobenzylidene)prop-2-en-1-amine (2.35g 13.08 mmol) in diethyl ether was added dropwise. The resultant mixture was stirred 24 hours. The reaction mixture was hydrolyzed with saturated NH_4Cl solution (10 mL). The resultant mixture was extracted with diethyl ether (4x30mL) and dried over anhydrous $MgSO_4$

and evaporated in vacuum. The crude product was purified by flash column chromatography by using EtOAc / Hexane at the ratio of 1:8 as the eluent to obtain *N*-allyl-1-(4-chlorophenyl)but-3-en-1-amine **117**as 84% chemical yield.



Rf=0.80 (silica gel – (EtOAc-Hexane), (1 : 8)

IR (Neat): 3425, 1664, 1236, 736 cm^{-1}

^{1}H-NMR($CDCl_3$) δ ppm

2.29 (s, 1H, for the N-H proton)

2.35-2.43 (m, 1H, for the one of the diastreotopic allylic methylene protons)

2.44-2.53 (m, 1H, for the other diastreotopic allylic methylene protons)

2.99 (tdd, J_1=14.1, J_2=6.7, J_3=1.2 Hz, 1H, for one of the diastereotopic allylic methylene proton)

3.10 (tdd, J_1=14.1, J_2=5.4, J_3=1.5 Hz, 1H, for other diastereotopic allylic methylene proton)

3.69 (t, J=8.8 Hz, 1H, for the stereogenic methine proton)

5.08-5.15 (m, 1H, for the terminal vinylic proton; Ha)

5.04-5.08 (m, 1H, for the terminal vinylc proton; Hb)

5.11-5.16 (m, 1H, for the terminal vinylc proton; Ha')

5.16-5.21 (m, 1H, for the terminal vinylc proton; Hb')

5.61-5.78 (m, 1H, for one of the internal vinylc proton)

5.78-5.91 (m, 1H, for other internal vinylc proton)

7.25-7.28 (m, 1H, for the methine proton at third position of the ring)

7.28-7.30 (m, 1H, for the methine proton at fifth position of the ring)

7.30-7.33 (m, 2H, for the methine proton at second and sixth position of the ring)

^{13}C-NMR ($CDCl_3$) δ ppm

42.9 (for the allylic carbon one of diastereomers)

43.9 (for the allylic carbon of the other diastereomers)

49.9 (for the allylic carbon of *N*-allyl group)

61.0 (for the quaternary carbon atom of one diastereomers)

72.5 (for the quaternary carbon atom of other diastereomers)

116.2 (for the terminal vinylic carbons of one of diastereomers

118.1 (for the terminal vinylic carbons of other diastereomers)

118.8 (for the terminal vinylic carbon atom of last diastereomers)

127.3 (for the methine carbon at second position of the ring)

128.5 (for the methine carbon at sixth position of the ring)

128.6 (for the methine carbon at third position of the ring)

128.7 (for the methine carbon at fifth position of the ring)

132.6 (for internal vinylic carbon of one of diastereomers)

133.1 (for internal vinylic carbon of the other diastereomers)

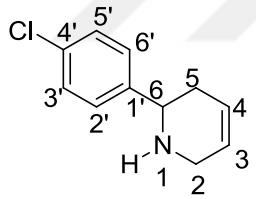
136.5 (for the methine carbon at fourth position of the ring)

142.0 (for the methine carbon at first position of the ring of one of diastereomers)

142.5 (for the methine carbon at first position of the ring of the other diastereomers)

4.3 Synthesis of 2-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine 118

N-allyl-1-(4-chlorophenyl)but-3-en-1-amine (2.43g, 10.96 mmol) in CH_2Cl_2 (10 mL) and p-toluensulfonic acid was added in a flask. The mixture was stirred in oil bath at 55^oC for 2h. Grubbs second generation catalyst (0.46g, 0.54 mmol) was added and theresulting mixture was stirred room temperature for one hour. (TLC monitoring). After this process, mixture was stirred in oil bath for 1h. And than $NaHCO_3$ was added in a mixture until Ph:12. The resultant product was extracted with diethylether and dried over anyhydrous $MgSO_4$ and concentrated in a vacuo. The product 2-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine **118** (1.84g, 9.53mmol) was obtained as yellow coloured oil purified by flash column chromatography by using EtOAc/Hexane/Et_3N at the ratio of 1:1:1% as in 87% chemical yield.



Rf=0.75 (silica gel – (EtOAc / Hexane / Et_3N), (1:1:1%))

IR (neat): 3057, 3015, 1659, 735 cm^{-1}

^{1}H-NMR($CDCl_3$) δ ppm

2.28 (bs, 1H, for the N-*H* proton)

2.40 (qd, J_1=4.4, J_2=2.0 Hz, 2H, for the diastereotopic methylene protons at fifth position of the tetrahydropyridine ring)

3.60 (pd, J_1=3.5, J_2=2.4 Hz, 1H, for one of the methylene proton at second position of the tetrahydropyridine ring)

3.65 (pd, J_1=3.4, J_2=2.0 Hz, 1H, for the other methylene proton at second position of the tetrahydropyridine ring)

3.84 (t, J=9.2 Hz, 1H, for the stereogenic methine proton at sixth position of the tetrahyroypyridine ring)

5.78 (pd, J_1=3.4, J_2=2.4 Hz 1H, for one of the methine proton at third position of the tetrahydropyridine ring)

5.87 (pd, J_1=13.1, J_2=2.0 Hz 1H, for the other methine proton at fourth position of the tetrahydropyridine ring)

7.28 (d, J=0.8 Hz, 2H, for one of the methine protons at 3' and 5'position of the p-chlorophenyl ring)

7.32 (d, J=1.6 Hz, 2H, for the other methine protons at 2' and 6' position of the p-chlorophenyl ring)

^{13}C-NMR ($CDCl_3$) δ ppm

33.7 (for the allylic methylene carbon at fifth position of tetrahydropyridine ring)

46.2 (for other allylic methylene carbon at second position of tetrahydropyridine ring)

57.4 (for the methine carbon at sixth position of tetrahydropyridine ring)

125.3 (for the methine carbon at fourth position of tetrahydropyridine ring)

126.0 (for the other methine carbon at third position tetrahydropyridine ring)

127.7 (for the methine carbons at 2ˈ and 6ˈ position of the p-chlorophenyl ring)

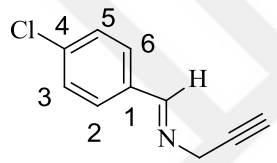
128.4 (for the methine carbons at 3ˈand 5ˈ position of the p-chlorophenyl ring)

133.0 (for the methine carbon at 4ˈ position of the p-chlorophenyl ring)

143.0 (for the methine carbon at 1ˈ position of the p-chlorophenyl ring)

4.4 Synthesis of (E)-*N*-(4-chlorobenzylidene)prop-2-yn-1-amine 119

To solution of p-cholorobenzaldeyde (2g, 14.23 mmol) in dry ether and anyhydrous $MgSO_4$ (2.05g, 18.5 mmol) equipped with a reflux condenser. The mixture was cooled down to 0°C and the propargylamine (1.36 ml, 21.34mmol) in dry ether was added dropwise with a injection syringe at under the argon atmosphere. The mixture was allowed to wait two hours and than resultant mixture was stirred three days. After stirred three days the solution was filtered with dry ether and the solvent was removed in vacuo. The crude product was purified by flash column chromatography by using EtOAc Hexane at the ratio of 1:8 as the eluent to obtain (E)-*N*-(4-chlorobenzylidene)prop-2-yn-1-amine **119** (2.22 g, 12.50 mmol) as 88% chemical yield.



Rf=0.90 (silica gel), (EtOAc/Hexane), (1:8)

IR (neat): 3315, 1675, 2252, 740 cm^{-1}

^{1}H-NMR($CDCl_3$) δ ppm

2.46 (t, *J*=2.4 Hz, 1H, for the acetylenic proton)

4.2 (t, *J*=2.2 Hz, 2H, for the diasterotopic methylene protons of the propargyl group)

7.29 (d, *J*=8.4 Hz, 1H, for the methine proton at third position of the ring)

7.40 (d, *J*=8.4 Hz, 1H, for the methine proton at fifth position of the ring)

7.59 (d, *J*=8.4 Hz, 1H, for the methine proton at sixth position of the ring)

7.71 (d, *J*=8.8 Hz, 1H, for the methine proton at second position of the ring)

8.16 (s, 1H, for the imine proton)

^{13}C-NMR ($CDCl_3$) δ ppm

47.1 (for the allylic methylene carbon of the propargyl group)

75.8 (for the methine carbon of propargyl group)

78.8 (for the quaternary carbon of the propargyl group)

128.9 (for the methine carbon at third position of the ring)

129.4 (for the methine carbon at fifth position of the ring)

129.5 (for the methine carbon at sixth position of the ring)

130.9 (for the methine carbon at second position of the ring)

134.3 (for the methine carbon at first position of the ring)

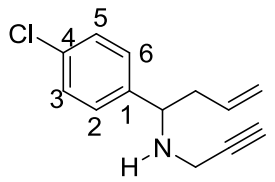
136.9 (for the other methine carbon at fourth position of the ring)

161.0 (for the imine carbon)

4.5 Synthesis of 1-(4-chlorophenyl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine 120

To a stirred solution of Mg turnings (0,147g, 18.7 mmol) and iodine turning (2 pieces) in minimum amount of dry ethyl ether at 25ºC equipped with a reflux condenser was added dropwise into a mixture of allyl bromide (1.19 ml, 13.7 mmol) in anhydrous diethyl ether with a injection syringe until the reaction begins. The mixture was allowed to reflux 45 minutes. The mixture was cooled down to 0ºC and (E)-*N*-(4-chlorobenzylidene)prop-2-yn-1-amine **119** (2.22g, 12.49 mmol) in diethyl ether was added dropwise. The resultant mixture was stirred 24 hours. The reaction mixture was hydrolyzed with saturated NH_4Cl solution (10 mL). The resultant mixture was extracted with diethyl ether (4x30 mL) and dried over anhydrous $MgSO_4$ and evaporated in vacuum. The crude product was purified by flash column chromatography by using EtOAc/Hexane at the ratio of 1:8 as the eluent to obtain 1-

(4-chlorophenyl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **120** (2.25g, 10.25 mmol) as 82% chemical yield.



Rf=0.51 (silica gel), (EtOAc/Hexane), (1:8)

IR (neat): 3418, 2422, 1674, 725 cm^{-1}

^{1}H-NMR($CDCl_3$) δ ppm

1.97 (s, 1H, for the N-*H* proton)

2.13 (t, *J*=2.4 Hz, 1H, for the acetylenic proton)

2.21-2.37 (m, 2H, for the allylic methylene protons of the allyl group)

2.98 (dd, J_1=17.6 J_2=2.4 Hz, 1H, for one of the diastereotopic methylene proton of the propargyl group)

3.28 (dd, J_1=17.6 J_2=2.4 Hz, 1H, for the other diastereotopic methylene proton of the propargyl group)

3.84 (dd, J_1=5 J_2=6.8 Hz, 1H, for the stereogenic methine proton)

4.98-5.07 (m, 2H, for the terminal vinylic protons of allyl group)

5.55-5.70 (m, 1H, for the internal vinylic protons of allyl group)

7.21 (s, 1H, for the methine proton of the ring)

7.23-7.35 (m, 3H, for the other methine protons of the ring)

^{13}C-NMR ($CDCl_3$) δ ppm

35.7 (for the allylic carbon atom of the one of diastereomer of the propargyl group)

39.4 (for the allylic carbon atom of the other diastereomer of the propargyl group)

42.7 (for the allylic carbon atom of one of diastereomer of the allyl group)

50.0 (for the allylic carbon atom of the other diastereomer of the allyl group)

59.6 (for the steregenic carbon atom of one of diastereomer)

63.8 (for the steregenic carbon atom of the other diastereomer)

71.5 (for the methine carbon of the propargyl unit)

82.0 (for the quaternary carbon of the propargyl unit)

118.2 (for one of the vinylic carbon)

128.6 (for the methine carbon at sixth position of the ring)

128.7 (for the methine carbon at second position of the ring)

128.8 (for the methine carbon at third position of the ring)

128.9 (for the methine carbon at fifth position of the ring)

132.9 (for the methine carbon of one of diastereomer at fourth position of the ring)

133.8 (for the methine carbon of other diastereomer at fourth position of the ring)

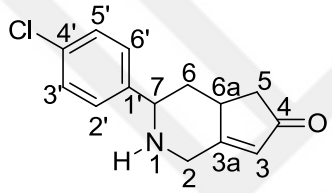
134.8 (for the other vinylic carbon)

140.0 (for the methine carbon of one of diastereomers at first position of the ring)

141.2 (for the methine carbon of the other diastereomer at first position of the ring)

4.6 Syntheesis of 3-(4-chlorophenyl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one 121

1-(4-chlorophenyl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **120** (2.25g, 10.2 mmol) in CH_2Cl_2 (10 mL) was added $Co_2(CO)_8$ (0.17g, 0.51 mmol), and stirred for half past two hours (TLC monitoring) under argon atmosphere. Then, NMO (2.40g, 21.02 mmol) was added and stirred for 24h. The crude 3-(4-chlorophenyl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2H)-one was purified by flash column chromatography by using EtOAc/Hexane at the ratio of 1:1 as the eluent to obtain in 3-(4-chlorophenyl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2H)-one **121** (2.05 g, 8.3 mmol) 81% chemical yield.



Rf=0.59 (silica gel), (EtOAc/Hexane), (1:1)

IR (neat): 3977, 3341, 3079, 3012, 2869, 1675, 1609, 1487, 720 cm^{-1}

^{1}H-NMR($CDCl_3$) δ ppm

2.04 (bs, 1H*2, for the N-*H* diastereomeric mixture)

1.87-2.19 (m, 4H*2, for the diastereotopic methylene protons at sixth position of tetrahydropyridine ring and other methylene protons at fifth position of the cyclopenta[c]pyridin ring and finally the stereogenic methine proton at 6a position, diastereomeric mixture)

4.10-4.27 (m, 3H, for the diastereotopic methylene protons at second position of the tetrahydropyridine ring and the other stereogeni cmethine proton at seventh position)

7.28 (s, 1H, for the olefinic methine proton at third position of the furan ring)

7.51 (t, *J*=4 Hz, 2H, for the methine protons at 2' and 6' position of the p-chlorophenyl ring)

7.83 (d, *J*=8 Hz, 2H, for the methine protons at 3' and 5' position of the p-chlorophenyl ring)

^{13}C-NMR ($CDCl_3$) δ ppm

14.2 (for the methylene carbon at sixth position of tetrahydropyridine)

21.0 (for the methylene carbon of one of diastereomer at fifth position of tetrahydropyridine)

23.0 (for the methylene carbon of the other diastereomer at fifth position of tetrahydropyridine)

29.7 (for the methylene carbon of one of diastereomers at second position of tetrahydropyridine)

31.8 (for the methylene carbon of the other diastereomers at second position of tetrahydropyridine)

47.5 (for the stereogenic methine carbon of one of diastereomer at 6a position)

49.2 (for the stereogenic methine carbon of the other diastereomer at 6a position)

60.3 (for the methine carbon at the seventh position of tetrahydropyridine ring)

129.2 (for the methine carbon of diastereomers of the p-chlorophenyl ring)

130.9 (for the methine carbon of diastereomers of the p-chlorophenyl ring)

134.8 (for the methine carbon of diastereomers of the p-chlorophenyl ring))

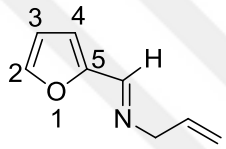
140.7 (for the olefenic methine carbon at third position of the cyclopenta[c]pyridine ring)

171.0 (for the quarternary methine carbon at second position)

210.6 (for the carbonyl carbon of the cyclopenta[c]pyridine ring).

4.7 Synthesis of (E)-*N*-(furan-2-ylmethylene)prop-2-en-1-amine 123

To solution of furfural (1.73ml, 20.82 mmol) in dry ether and anyhydrous $MgSO_4$ (3.25g, 27.06 mmol) equipped with a reflux condenser. The mixture was cooled down to 0°C and the allylamine (2.34 ml, 31.22 mmol) in dry ether was added dropwise with an injection syringe at under the argon atmosphere. The mixture was allowed to wait two hours and than resultant mixture was stirred three days. After stirred three days the solution was filtered with dry ether and the solvent was removed in vacuo. The crude product was purified by flash column chromatography by using EtOAc/Hexane at the ratio of 1:6 as the eluent to obtain (E)-*N*-(furan-2-ylmethylene)prop-2-en-1-amine **123** (2.70 g, 19.98 mmol) as 96% chemical yield.



Rf=0.86 (silica gel), (EtOAc/Hexane), (1:6)

IR (neat): 3155, 3086, 2885, 1690, 1651, 1199, 1210 cm^{-1}

^{1}H-NMR ($CDCl_3$) δ ppm

4.15 (dd, J_1=6.0, J_2=1.6 Hz, 2H, for the allylic methylene protons)

5.08 (qd, J_1=3.3, J_2=1.7 Hz, 1H, for one of the terminal vinylic proton Ha)

5.14 (qd, J_1=3.3, J_2=1.3 Hz, 1H, for the other terminal vinylic proton Hb)

5.89-6.09 (m, 1H, for the internal vinylic proton of allyl group Hc)

6.40 (dd, J_1=3.5. J_2=1.8 Hz, 1H, for methine proton at third position of the ring)

6.68 (d, J=3.2 Hz, 1H, for methine proton at fourth position of the ring)

7.44 (d, J=1.6 Hz, 1H, for methine proton at second position of the ring)

8.03 (s, 1H, for the imine proton)

^{13}C-NMR ($CDCl_3$) δ ppm

63.6 (for the allylic methylene carbon)

111.6 (for the methine carbon at third position of the ring)

113.9 (for the methine carbon at fourth position of the ring)

116.4 (for one of the vinylic carbon)

135.6 (for the other vinylic carbon)

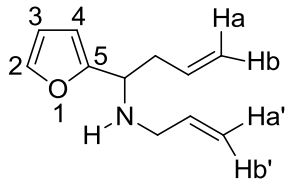
144.7 (for the methine carbon at second position of the ring)

150.4 (for the imine carbon)

151.6 (for the methine carbon at fifth position of the ring)

4.8 Synthesis of *N*-allyl-1-(furan-2-yl)but-3-en-1-amine 124

To a stirred solution of Mg turnings (0.72 g, 29.97 mmol) and iodine turning (2 pieces) in minimum amount of dry ethyl ether at 25^{o}C equipped with a reflux condenser. The mixture was added dropwise into a mixture of allyl bromide (1.90 mL, 21.98 mmol) in anhydrous diethyl ether with a injection syringe until the reaction begins. The mixture was allowed to reflux 45 minutes. The mixture was cooled down to 0^{o}C and (E)-N-(furan-2-ylmethylene)prop-2-en-1-amine 2.70 g (19.98 mmol) in diethyl ether was added dropwise. The resultant mixture was stirred 24 hours. The reaction mixture was hydrolyzed with saturated NH_4Cl solution (10 mL). The resultant mixture was extracted with diethyl ether (3x30 mL) and dried over anhydrous $MgSO_4$ and evaporated in vacuum. The crude product was purified by flash column chromatography by using EtOAc/Hexane at the ratio of 1:6 as the eluent to obtain *N*-allyl-1-(furan-2-yl)but-3-en-1-amine **124** (3.08 g, 17.38 mmol) as 87% chemical yield.



Rf=0.66 (silica gel), (EtOAc/Hexane), (1:6)

IR (neat): 3433, 3150, 3055, 2880, 1658, 1235, 1225 cm^{-1}

^{1}H-NMR($CDCl_3$) δ ppm

1.92 (s, 1H, for the N-H proton)

2.41-2.49 (m, 1H, for the one of the diastreotopic allylic methylene proton of allyl group)

2.53-2.59 (m, 1H, for the other diastreotopic allylic methylene proton of allyl group)

3.02 (tdd, J_1=14.0, J_2=6.4, J_3=1.2 Hz, 1H, for one of the diastereotopic allylic methylene proton of *N*-allyl group)

3.12 (tdd, J_1=13.8, J_2=5.6, J_3=1.5 Hz, 1H, for the other diastereotopic allylic methylene proton of *N*-allyl group)

3.72 (t, J=7.0 Hz, 1H, for the stereogenic methine proton)

4.96-5.00 (m, 1H, for the terminal vinylic proton; Ha)

5.00-5.03 (m, 1H, for other terminal vinylic proton; Hb)

5.03-5.07 (m, 1H, for other one terminal vinylic proton; Ha')

5.07-5.15 (m, 1H, for other one terminal vinylic proton; Hb')

5.58-5.71 (m, 1H, for the one of the internal vinylic proton of allyl group)

5.72-5.84 (m, 1H, for the other internal vinylic proton of *N*-allyl group)

6.13 (dd, J_1=38.2, J_2=3.0 Hz, 1H, for the methine proton at fourth position of the ring)

6.68 (ddd, J_1=11.2, J_2=3.2, J_3=2.0 Hz, 1H, for the methine proton at third position of the ring)

7.30 (dd, J_1=7.6, J_2=1.2 Hz, 1H, for the methine proton at second position of the ring)

^{13}C-NMR ($CDCl_3$) δ ppm

39.2 (for the allylic carbon atom of one of diastereomer)

40.1 (for the allylic carbon atom of the other diastereomer)

49.8 (for the allylic carbon atom one of diastereomers of the *N*-allyl group)

54.9 (for the allylic carbon atom of the other of the *N*-allyl group)

66.9 (for the quaternary carbon atom)

106.1 (for the methine carbon of one of diastereomers at fourth position of the ring)

106.6 (for the methine carbon of the other diastereomer at fourth position of the ring)

109.8 (for the methine carbon of one of diastereomer at third position of the ring)

110.1 (for the methine carbon of one of diastereomer at third position of the ring)

116.1 (for terminal vinylic carbons atom of diastereomer)

117.5 (for terminal vinylic carbons atom of diastereomer)

118.5 (for terminal vinylic carbons atom of diastereomer)

133.7 (for internal vinylic carbon atom of diastereomer)

134.7 (for internal vinylic carbon atom of diastereomer)

136.5 (for ınternal vinylic carbon atom of diastereomer)

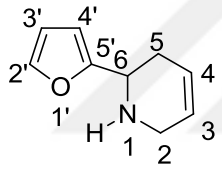
141.5 (for the methine carbon of one of diastereomers at second position of the ring)

142.0 (for the methine carbon of the other diastereomer at second position of the ring)

156.0 (for the methine carbon at fifth position of the ring)

4.9 Synthesis of 2-(furan-2-yl)-1,2,3,6-tetrahydropyridine 125

N-allyl-1-(furan-2-yl)but-3-en-1-amine (3.08 g, 17.38 mmol) in CH_2Cl_2 (10 mL) and p-toluensulfonic acid (3.60 g, 19.11 mmol) was added in a flask. The mixture was stirred in oil bath at 55°C for 2h. Grubbs second generation catalyst (0.73g, 0.87 mmol) was added and theresulting mixture was stirred room temperature for one hour. (TLC monitoring). After this process, mixture was stirred in oil bath for 1h. And than $NaHCO_3$ was added in a mixture until Ph:12. The resultant product was extracted with diethylether and dried over anyhydrous $MgSO_4$ and concentrated in a vacuo. The product 2-(furan-2-yl)-1,2,3,6-tetrahydropyridine (2.42 g, 16.16 mmol) was obtained as dark coloured oil purified by flash column chromatography by using EtOAc/Hexane/Et_3N at the ratio of 1:1:1% as in 93% chemical yield.



Rf=0.70 (silica gel), (EtOAc / Hexane / Et_3N), (1:1:1%)

IR (neat): 3320, 1648, 1336, 1220 cm^{-1}

^{1}H-NMR (CDCl3) δ ppm

2.19 (s, 1H, for the N-*H* proton)

2.25-2.28 (m, 2H, for the diastereotopic methylene protons at fifth position of the tetrahydropyridine ring)

3.30 (dd, J_1=17, J_2=1.8 Hz, 1H, for one of the methylene proton at second position of the tetrahydropyridine ring)

3.44 (dd, J_1=17.2, J_2=2.0 Hz, 1H, for the other methylene proton at second position of the tetrahydropyridine ring)

3.91 (t, *J*=7 Hz, 1H, for the stereogenic methine proton at sixth position)

5.64-5.71 (m, 1H, for one of the methine proton at third position of the tetrahydropyridine ring)

5.71-5.78 (m, 1H, for the other methine proton at fourth position of the tetrahydropyridine ring)

6.10 (dt, J_1= 2.4, J_2=0.8 Hz 1H, for the methine proton at 4' position of the furyl ring)

6.23 (dd, J_1= 3.2, J_2=1.6 Hz 1H, for the methine proton at 3' position of the furyl ring)

7.27 (dd, J_1=1.8, J_2=0.8 Hz, 1H, for the methine proton at 2' position of the furyl ring)

^{13}C-NMR (CDCl3) δ ppm

29.8 (for the allylic methylene carbon at fifth position of the tetrahydropyridine ring)

44.8 (for other allylic methylene carbon the second position of the tetrahydropyridine ring)

50.4 (for the stereogenic methine carbon at the sixth position)

104.5 (for the methine carbon at 4' position of the furyl ring)

110.0 (for the methine carbon at 3' position of the furyl ring)

124.5 (for the methine carbon at third position of tetrahydropyridine ring)

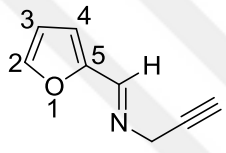
126.5 (for the methine carbon at fourth position tetrahydropyridine ring)

141.5 (for the methine carbon at 2' position of the furyl ring)

156.9 (for the methine carbon at 5' position of the furyl ring)

4.10 Synthesis of (E)-*N*-(furan-2-ylmethylene)prop-2-yn-1-amine 126

To solution of furfural (1.73ml, 20.82 mmol) in dry ether and anyhydrous $MgSO_4$ (3.25g, 27.06 mmol) equipped with a reflux condenser. The mixture was cooled down to 0ºC and the propargylamine (1.99 ml, 31.22 mmol) in dry ether was added dropwise with an injection syringe at under the argon atmosphere. The mixture was allowed to wait two hours and than resultant mixture was stirred three days. After stirred three days the solution was filtered with dry ether and the solvent was removed in vacuo. The crude product was purified by flash column chromatography by using EtOAc/Hexane at the ratio of 1:6 as the eluent to obtain (E)-*N*-(furan-2-ylmethylene)prop-2-yn-1-amine **126 (**2.3 g, 17.42 mmol) as 84% chemical yield.



Rf= 0.78 (silica gel), (EtOAc/Hexane), (1:6)

IR (neat): 3300, 3010, 2890, 2245, 1670, 1240, 1150 cm^{-1}

^{1}H-NMR (CDCl3) δ ppm

2.48 (t, *J*=2.4 Hz, 1H, for the acetylenic proton)

4.45 (t, *J*=2.0 Hz, 2H, for the methylene protons of the propargyl group)

6.40 (dd, J_1=3.4, J_2=1.8 Hz, 1H, for the methine proton at third position of the ring)

6.73 (d, *J*=3.2 Hz, 1H, for the methine proton at fourth position of the ring)

7.45 (d, *J*=1.2, Hz, 1H, for the methine proton at second position of the ring)

8.35 (s, 1H, for the imine proton)

^{13}C-NMR (CDCl3) δ ppm

46.7 (for the allylic methylene carbon of the propargyl group)

76.4 (for the methine carbon of propargyl group)

78.3 (for the quaternary carbon of the propargyl group.

111.7 (for the methine carbon at third position of the ring)

114.6 (for the methine carbon at fourth position of the ring)

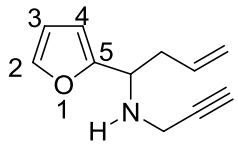
145.0 (for the methine carbon at second position of the ring)

150.5 (for the imine carbon)

151.6 (for the methine carbon at fifth position of the ring)

4.11 Synthesis of 1-(furan-2-yl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine 127

To a stirred solution of Mg turnings (0.62 g, 26.13 mmol) and iodine turning (2 pieces) in minimum amount of dry ethyl ether at 25^{o}C equipped with a reflux condenser. The mixture was added dropwise into a mixture of allyl bromide 1.66 mL (19.16 mmol) in anhydrous diethyl ether with an injection syringe until the reaction begins. The mixture was allowed to reflux 45 minutes. The mixture was cooled down to 0^{o}C and (E)-*N*-(furan-2-ylmethylene)prop-2-yn-1-amine (2.32 g, 17.42 mmol) in diethyl ether was added dropwise. The resultant mixture was stirred 24 hours. The reaction mixture was hydrolyzed with saturated NH_4Cl solution (10 mL). The resultant mixture was extracted with diethyl ether (3x30 mL) and dried over anhydrous $MgSO_4$ and evaporated in vacuum. The crude product was purified by flash column chromatography by using EtOAc/Hexane at the ratio of 1:6 as the eluent to obtain 1-(furan-2-yl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine (2.47 g, 14.09 mmol) as 81% chemical yield.



Rf=0.87 (silica gel), (EtOAc/Hexane), (1:6)

IR (neat) : 3545, 3323, 3095, 2988, 2774, 2260, 1674 cm^{-1}

^{1}H-NMR (CDCl3) δ ppm

1.73 (s, 1H, for the N-*H* proton)

2.13 (t, *J*=2.4 Hz, 1H*2, for one of the acetylenic proton)

2.21-2.37 (m, 2H, for the allylic methylene protons of the allyl group)

2.48 (t, *J*=2.0 Hz, 1H*2, for the other acetylenic proton)

3.14 (dd, J_1=17.2 J_2=2.4 Hz, 1H, for one of the methylene proton of the propargyl group)

3.34 (dd, J_1=17.0 J_2=2.6 Hz, 1H, for the other methylene proton of the propargyl group)

3.93 (t, *J*=6.8 Hz, 1H*2, for one of the diastereotopic stereogenic methine proton)

4.47 (t, *J*=2.0 Hz, 1H*2, for the other diastereotopic stereogenic methine proton)

5.01 (dd, J_1=10.0 J_2=0.8 Hz 1H, for one of the terminal vinylic proton of allyl group)

5.06 (dd, J_1=17.2 J_2=1.2 Hz 1H, for the other terminal vinylic proton of allyl group)

5.61-5.72 (m, 1H, for the internal vinylic protons of allyl group)

6.13 (d, *J*=3.2 Hz, 1H*2, for the methine proton of one of diastereomer at third position of the ring)

6.23 (dd, J_1=3.2, J_2=2.0 Hz, 1H*2, for the methine proton of the other diastereomer at third position of the ring)

6.42 (dd, J_1=3.2, J_2=1.6 Hz, 1H*2, for methine proton of one of diastereomer at fourth position of the ring)

6.74 (d, J=3.6 Hz, 1H*2, for the methine proton of the other diastereomer at fourth position of the ring)

7.23 (q, J=0.8 Hz, 1H*2, for the methine proton of one of diastereomer at second position of the ring)

7.46 (s, 1H*2, for the methine proton of the other diastereomers at second position of the ring)

^{13}C-NMR (CDCl3) δ ppm

29.7 (for the allylic carbon atom of one of diastereomer of the propargyl group)

35.7 (for the allylic carbon atom of the other diastereomer of the propargyl group)

39.1 (for the allylic carbon atom of one of diastereomer of the allyl group)

46.7 (for the allylic carbon atom of the other diastereomer of the allyl group)

54.0 (for the stereogenic carbon atom)

71.4 (for the acetylenic methine carbon of one of diastereomer of the propargyl unit)

76.4 (for the acetylenic methine carbon of the other diastereomer of the propargyl unit)

78.3 (for the quaternary carbon of one of diastereomer of the propargyl unit)

81.9 (for the quaternary carbon of the other diastereomer of the propargyl unit)

107.2 (for the methine carbon of one of diastereomer at fourth position of the furyl ring)

109.8 (for the methine carbon of the other diastereomer at fourth position of the furyl ring)

114.6 (for the terminal vinylic carbon of one of diastereomer of allyl group)

117.9 (for the terminal vinylic carbon of the other diastereomer of allyl group)

134.5 (for the internal vinylic carbon of one of diastereomer of allyl group)

141.9 (for the internal vinylic carbon of the other diastereomer of allyl group)

145.0 (for the methine carbon of one of diastereomer at second position of the ring)

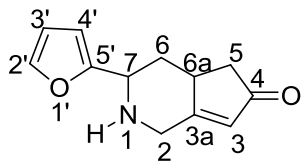
150.6 (for the methine carbon of the other diastereomer at second position of the ring)

151.6 (for the methine carbon of one of diastereomer at first position of the ring)

155.0 (for the methine carbon of the other diastereomer at first position of the ring)

4.12 Synthesis of 3-(furan-2-yl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one 128

1-(furan-2-yl)-*N*-(prop-2-yn-1-yl)but-3-en-1-amine **127** (2.47 g, 14.09 mmol) in CH_2Cl_2 (10 mL) was added $Co_2(CO)_8$ (4.82 g,24.33 mmol) and stirred for half past two hours (TLC monitoring) under argon atmosphere. Then, NMO (16.52 g, 141.08 mmol) was added and stirred for 24h. The crude product 3-(furan-2-yl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **128** was purified by flash column chromatographyby using EtOAc/Hexane at the ratio of 1:1 as the eluent to obtain in 3-(furan-2-yl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **128** (2.26 g, 11.12 mmol) 79% chemical yield.



Rf=0.76 (silica gel), (EtOAc/Hexane), (1:1)

IR (neat) : 3210, 3125, 1681, 1092 cm^{-1}

^{1}H-NMR (CDCl3) δ ppm

1.98 (s. 1H, for the N-*H* proton)

1.28 (dd, J_1=4.8, J_2=5.4 Hz, 2H, for the methylene protons at sixth position of the cyclopenta[c]pyridine ring)

1.15-1.26 (m, 2H, for the stereogenic proton at 6a positon)

1.97-2.13 (m, 1H, for the methylene protons at fifth position of the cyclopenta[c]pyridine ring)

3.99 (t, *J*=5.6 1H, for the other stereogenic methine proton at seventh position of the tetrahdyro ring)

4.05 (q, *J*=7.2 Hz, 2H, for the methylene protons at seventh position of the tetrahdyro ring)

6.44 (q, *J*=1.6 Hz 1H, for the olefinic methine proton third position of the cyclopenta[c]pyridine ring)

7.06 (d, *J*=3.2 Hz, 1H, for the methine proton at 4' position of the furyl ring)

7.20 (s, 1H, for the methine proton at 3' position of the furyl ring)

7.37 (s, 1H, for the methine proton 2' position of the furyl ring)

^{13}C-NMR (CDCl3) δ pppm

14.1 (for the methylene carbon of one of diastereomer at sixth position of the tetrahydropyridine ring)

14.2 (for the methylene carbon of the other diastereomer at sixth position of the tetrahydropyridine ring)

21.4 (for the methine carbon of one diastereomer at 6a position of the cyclopenta[c]pyridine ring)

22.7 (for the methine carbon of the other diastereomer at 6a position of the cyclopenta[c]pyridine ring)

29.4 (for the methylene carbon of one of diastereomer at fifth position of the cyclopenta[c]pyridine ring)

29.7 (for the methylene carbon of the other diastereomer at fifth position of the cyclopenta[c]pyridine ring)

41.5 (for the methylene carbon at second position of the tetrahydropyridine ring)

60.4 (for the stereogenic methine carbon at seventh position)

101.8 (for the methine carbon of one of diastereomer at 4′ position of the furyl ring)

104.7 (for the methine carbon of the other diastereomer at 4′ position of the furyl ring)

112.2 (for the methine carbon of one of diastereomer at 3′ position of the furyl ring)

116.7 (for the methine carbon of the other diastereomer at 3′ position of the furyl ring)

135.8 (for the olefenic methine carbon at third position of the cyclopenta[c]pyridine ring)

136.6 (for the methine carbon at 2′ position of the furyl ring)

149.5 (for the methine carbon of one of diastereomer at 5′ position of the furan ring)

149.9 (for the methine carbon of the other diastereomer at 5′ position of the furan ring)

158.7 (for the methine carbon at fifth position of the furan ring)

171.2 (for the quarternary methine carbon at 3a position)

214.9 (for the carbonyl carbon)

5. CONCLUSIONS AND RECOMMENDATIONS

In this study 2-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine **118** and 2-(furan-2-yl)-1,2,3,6-tetrahydropyridine **125** obtained by using Grubbs Second Generation Catalyst with 93% and 87% overall chemical yield respectively. Then, 3-(4-chlorophenyl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **121** was synthesized via Pauson-Khand reaction in the presence of NMO as a promoter and $Co_2(CO)_8$ with respect to 81% overall chemical yield. In the same manner 3-(furan-2-yl)-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(2*H*)-one **128** obtained with 79% overall chemical yield. Tetrahydropyridine and cyclopenta[c]piperidine compounds found in the structure of natural products that has biological activities, were synthesized by Ring Closing Metathesis and Pauson-Khand reaction which are frequently used methods in the literature for the synthesize of heterocyclic units.

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