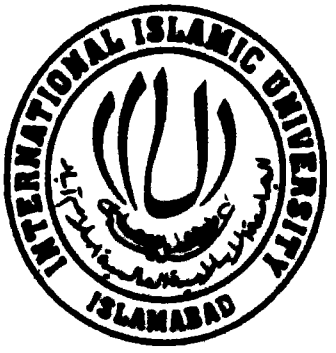
Synthesis and characterization of *N*-thiourea propargylamine

By A^3-Coupling



By

Aamir Rameez

127-FBAS/MSCHM/F21

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Faculty of Sciences

International Islamic University, Islamabad

(2021-2023)

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بسم الله الرحمن الرحيم

Final Approval

It is certified that we have read the thesis submitted by Aamir Rameez and it is our judgment that this project is of sufficient standard to warrant its acceptance by the International Islamic University, Islamabad for the MS degree in Chemistry.

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DECLARATION

I Aamir Rameez, hereby declare, that I am aware of consequences of a deliberately or negligently wrongly submitted affidavit. The work presented in the following thesis is my own effort, except where otherwise acknowledged and that the thesis is my own composition. No part of the thesis has been previously presented for any other degree.

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Aamir Rameez

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List of Abbreviations

βAP	Beta Amyloig Plaques
MAO	Mono amino oxidase
L-DOPA	L-3.4-dihydroxyphenyl alanine
FAD	Flavin adenine dinucleotide
EFV	Efavirenz
HIV	Human Immunodeficiency virus
DMA	Dimethylacetamide
THF	Tetrahydrofuran
PTSA	p-toluene sulfonic acid monohyderate
DMF	Dimethyl formamide
NaOH	Sodium hydroxide
Cbz	Carboxy benzyl group
BOC	tert-Butyloxy carbonyl group
DCM	Dichloromethane
MCRs	Multi-component reactions
DIPEA	N,N-Diisopropylethyl amine
Sp	Senile plaques
NFT	Neurofibrillary tangles
FAD	Familiar Alzheimer disease
SAD	Sporadic Alzheimer disease
PD	Parkinson disease
DNA	Deoxyribonucleic acid
CNS	Central nervous system
EP	Epinephrine
DA	Dopamine
NE	Nor epinephrine
5-HT	5-hydroxy tryptamine
TMS	Tetra methyl silane
DCE	1,2-Dichloroc ethane

Abstract

Medicinal Chemistry lies mainly on the shoulders of organic synthesis. Small synthetic organic molecules are considered more emerging molecules in medicinal chemistry. A^3- coupling, which is a three-component reaction, has proved to be prominent in the organic synthesis due to formation of propargylamines which are converted into diverse array of heterocyclic compounds. Considering the importance of A^3-Coupling, the present study focuses on the development of a new methodology for the synthesis of *N*-thiourea propargylamines using the A^3-coupling mechanism. For this purpose, thiosemicarbazide, benzaldehyde and aniline were reacted together using different catalysts, solvents, and reaction conditions for the synthesis of *N*-thiourea propargylamine. Firstly, thiosemicarbazide as amine, benzaldehyde, and phenylacetylene as alkyne were used to synthesize *N*-thiourea propargylamine but only intermediate imine was obtained as final product ad no alkynylation of thiosemicarbazone was observed. Different catalysts such as $ZnCl_2$, CuCl, $FeCl_3$, $NiCl_2.5H_2O$, $CuCl_2$, $ZnBr_2$, $AlCl_3$, and $ZrCl_4$ were used for the alkynylation of thiosemicarbazone, but no desired product was obtained. At this stage, a different synthetic strategy was adopted to accomplish the alkynylation of this imine; for this purpose, initially, simple propargylamine was synthesized using benzaldehyde, benzylamine, and phenylacetylene in the presence of $ZnCl_2$ as catalyst and toluene as solvent at 110 °C for 24 hours. Then synthesized propargylamine was then reacted with phenyl isothiosyanate which gave *N*-thiourea propargylamine. Using this strategy three *N*-thiourea propargylamine derivatives were synthesized. The structures was confirmed using IR and NMR spectroscopic techniques.

Chapter no. 1

Introduction

Introduction

1.1 Organic chemistry

Organic Chemistry is the chemistry of compounds containing carbon as essential element. Organic Chemistry deals with the study of hydrocarbons and their derivatives. There are exceptions in the definition of organic chemistry because there are many compounds that exist in nature that contain carbon but are not included in organic chemistry, such as CO, CO_2, CS_2, CO_3^{-2}, $HSCN^-$ and HCO_3^- [1]. Major sources of organic compounds are natural products like coal, petroleum, and natural gas. Organic compounds can be synthesized by partial synthesis or total synthesis. The importance of organic chemistry rests not only in its relevance to the advancement of science but also in its close relationship to daily life. Organic substances play a crucial role in influencing our daily lives, from the food we consume to the clothes we wear. Organic compounds have a wide range of uses in pharmaceuticals, agriculture, Food and drink, petrochemicals, plastics and polymers, dyes and pigments, environmental cleanup, etc. In synthetic chemistry, organic compounds have a lot of uses in the field of pharmaceuticals where many organic compounds are used as intermediates and building blocks for the drug discovery process. There is a wide range of history of organic compounds in the field of pharmaceuticals starting from ancient medicinal practices to rational drug design.

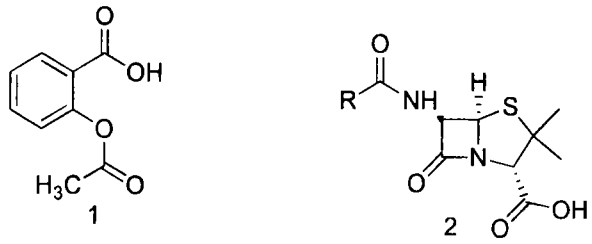
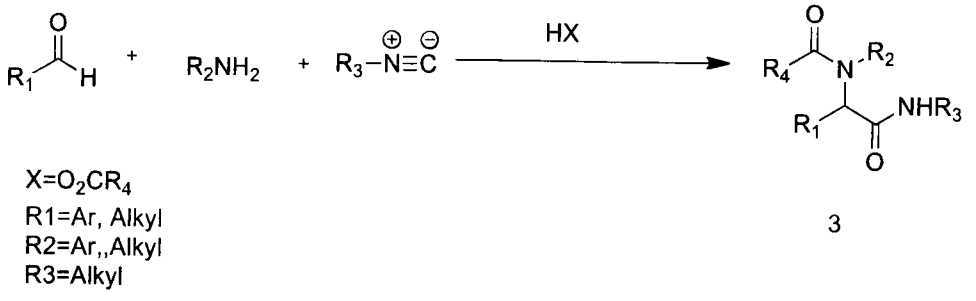


Figure 1.1: Drugs discovered from the natural product.

In the 20th century, many organic compounds were used in the development process of drug, such as paracetamol (acetaminophen), ibuprofen, and antipyretics. Nowadays, rational drug designs have been developed in which computer-aided drug design and structure-activity relationships have facilitated the target development of organic compounds in the field of pharmaceuticals.

1.2 Multicomponent reaction (MCR)

Organic synthesis has played a major role in the field of many medicinal chemistry. The length of synthesis depends upon the number of bonds being synthesized. In research, many types of reactions have been devised, but devising multiple bond formations in one operation has become a prominent method in synthetic chemistry. In the Multiple component reaction (MCR) process, three or more components of reactants are combined to form a targeted product. Besides region-, chemo-, and stereo-selective processes, multiple component reactions have been more beneficial because of their readily available starting material, operational simplicity, resource-effectiveness, and environmental friendliness. Due to inherent convergence and high productivity, multicomponent reactions have become more significant in academic and industrial research. MCR has become an integral part of medicinal research because of its usage in the drug discovery process, from lead discovery to lead optimization. Mannich and click reactions are the types of multicomponent reactions. A^3-coupling is one of the multicomponent reactions in which different derivatives of aldehyde, alkyne, and amines react with each other in different conditions, synthesizing the target product propargylamine, which is a biologically active compound. One of the key developments in this sector is the Ugi four-component reaction (Ugi 4CR), and significant resources had invested in the study of this transformation's potential. In this unique reaction, a primary amine, a carbonyl molecule, a carboxylic acid, and isocyanides react to produce a-amide amides as shown in **scheme 1** (Pan, S. C., *et al* 2008)



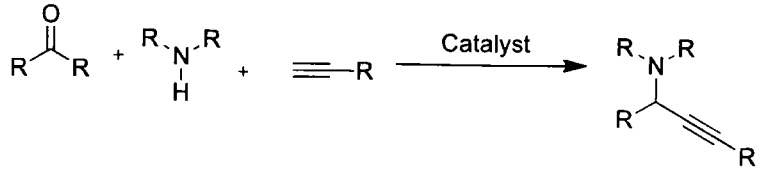
Scheme 1: Ugi four-component reaction for the synthesis of amides.

1.2.1 A^3-coupling:

The A^3-coupling reaction is an important type of MCR. The streamlined assembly of complex molecules has been made possible by this ground-breaking reaction, pushing the boundaries of

chemical synthesis, and opening new vistas for scientific inquiry. Gourmont published the first study on the three-component coupling of a terminal alkyne, secondary amine, and formaldehyde to produce propargylamine in 1953. Aldehydes, secondary amines, and alkynes were coupled in solid phase in the presence of excess CuCl (2 equiv.). In 1998, Dax *et al.* and Li *et al.* first used the name "A^3-coupling" in 2002 to describe the formalin creation of propargylamine derivatives employing a variety of Cu- and Ru-catalysts. Since then, numerous catalysts the A^3-coupling reactions have been utilized using a variety of catalysts, including bimetallic, Cu-/Ru- salts and transition metals such as Cu, Au, Ag, Ni, Fe, and Zn.

A^3-coupling reaction, is a useful tool that makes it possible to form a variety of molecular structures quickly and effectively from straightforward starting components. The reactants such as aldehyde, amine, and alkyne often abbreviated as A, A', and A"—that make up the reaction are where the term "A^3-coupling" comes from which is used for the synthesis of propargylamine as shown in **scheme 2**.



Scheme 2: Synthesis of propargylamine by A^3-coupling.

The A^3-coupling reaction's atom economy and ease of operation are two of its most enticing features. The A^3-coupling streamlines the synthesis process, greatly lowering time, cost, and waste generation, in contrast to conventional multistep synthesis, which may necessitate several reaction steps and purification methods. Synthetic chemists from all over the world have been drawn to this efficiency because it provides a sustainable method of reaching complicated chemical structures with great yields and no negative environmental impact.

The A^3-coupling's broad substrate range and tolerance of various functional groups make it a useful tool in lead optimization and drug discovery campaigns, where quick access to libraries with a variety of structural compositions is crucial in the hunt for novel therapeutic agents.

1.3 Thiosemicarbazide

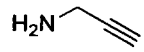
Thiosemicarbazide is an important compound to access variety of heterocyclic compounds. New compounds that can have impact on the body can be discovered using variety of molecules. Molecules that include the elements nitrogen and sulphur are the main focus of synthetic, analytical, and medicinal chemistry. Some nitrogen and sulphur containing molecules, such as triazole, thiadiazole and oxadiazole may offer therapeutic benefits, including the ability to combat cancer, relieve pain, kill germs, stop seizures, and reduce inflammation (Varvaresou *et al.,* 1998). Large libraries of small drugs like compounds have been created through the use of combinatorial chemistry and have been tested for certain biological activities. Numerous studies on the synthesis and biological assessment of tiny bioactive heterocyclic compounds with aryls in them, such as thiosemicarbazide and thiosemicarbazones, which have been studied after their therapeutic values (Siwek, D *et al*,.2012). Thiosemicarbazides are important in the pharmaceutical industry. Using such compounds in organic chemistry has become a common approach for creating various types of ring-shaped molecules. Their interactions with substances containing C=O and C=N groups are a significant way to create biologically active compounds, like triazoles and thiadiazoles (Del Corso, Cappiello, & Mura, 1994).

1.3.1 Synthetic and medicinal Importance of thiosemicarbazide

Semicarbazide and thiosemicarbazide have comparable chemical properties. However, the thione group in thiosemicarbazide is more adaptable than the keto group in semicarbazide. Thiosemicarbazide exhibits a larger variety of behaviors as a result. Investigations are being done on notable thiosemicarbazide derivatives give the synthesis of heterocycles using TSC. (Cardia *et al.,* 2006)

1.4 Propargylamine

A unique and useful substance, propargylamine plays a key role in the fields of organic chemistry and medicinal sciences. Its distinctive molecular structure, which includes a terminal alkyne and an amine functional group, endows it with a variety of intriguing features that have drawn the interest of both industry and researchers. Propargylamine appears to be a fascinating research topic with far-reaching consequences, from its crucial function as a fundamental component in synthetic chemistry to its biological activities and therapeutic possibilities.



Propargylamine

Figure 1.3: Structure of propargylamine.

The ability of propargylamine to take part in several chemical transformations is at the core of its relevance. A variety of fascinating reactions, such as copper-catalyzed click chemistry, Sonogashira coupling, and numerous multicomponent reactions, can occur when an alkyne and an amine moiety are present in the same molecule. Propargylamine is a key tool in the synthesis of new materials and bioactive substances because these adaptable synthetic techniques enable scientists to rapidly access complicated molecular structures. Propargylamine, which is synthesized by A^3-coupling, is an important class of organic compounds because of the importance of the amine group at β-position to an alkyne moiety. Propargylamine acts as a key intermediate for the synthesis of different Nitrogen-containing compound derivatives. Propargylamine is used for the synthesis of many *N*-heterocyclic organic compounds such as pyrroles, thiazole 2-diones, Quinolones, triazolo 1,4-diaazepanes, 1,4-oxazipanes, substituted imidazole, and 2-oxazolidinones (Manujyothi, R. *et al.*, 2021) as shown in **figure 1.4**.

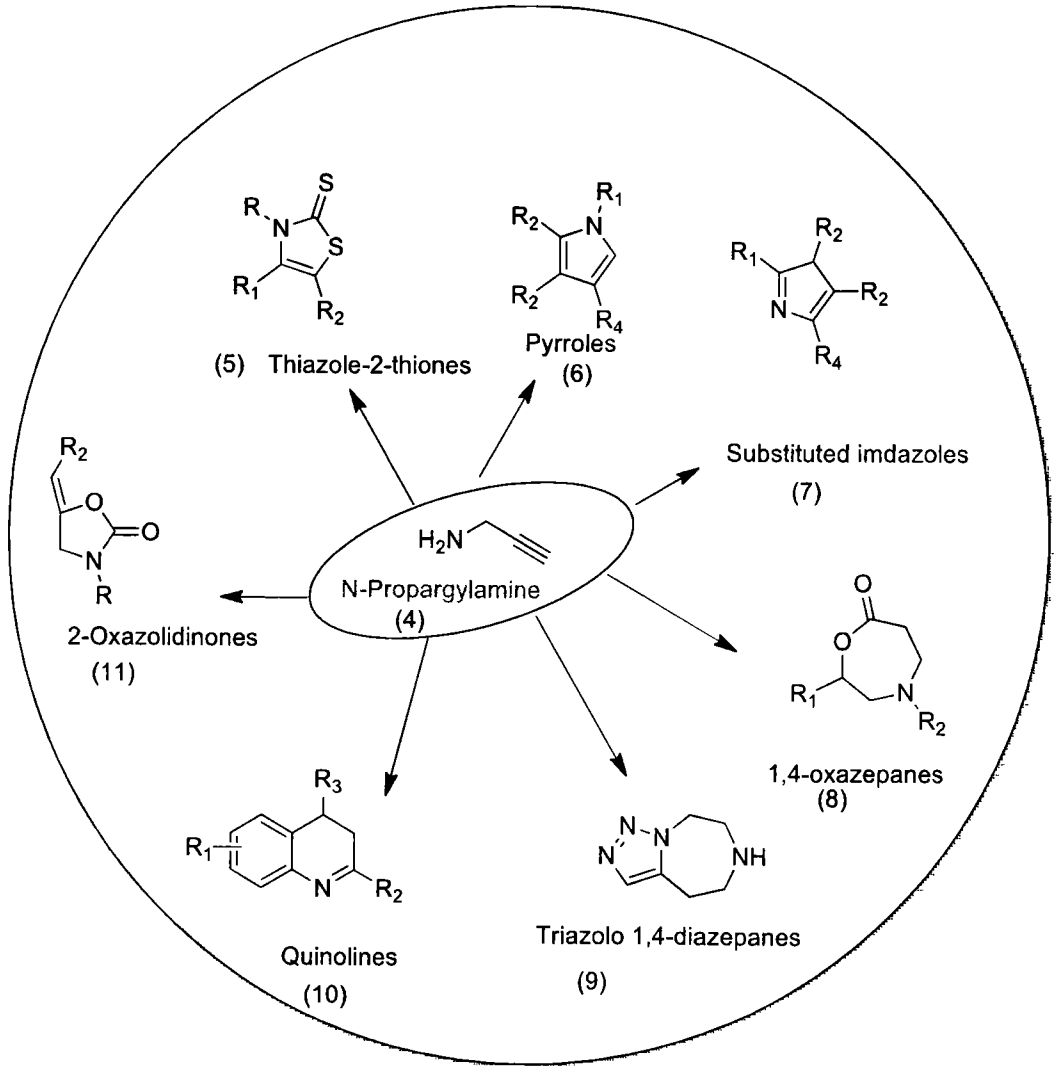


Figure 1.4: Synthesis of important heterocyclic compounds using Propargylamine (Manujyothi, R. *et al.*, 2021).

Propargylamine has unusual reactivity that goes beyond that of a synthetic intermediate. This substance has attracted a lot of interest recently in the field of medical chemistry. Its scaffold is frequently present in numerous medications and biologically active compounds, making it a sought-after component in the development of new drugs. It's potential for treating neurological disorders, cancer, infectious diseases, and inflammation has been studied by researchers. The creation of innovative therapeutic medicines with improved efficacy and selectivity has been made possible because of the propargylamine moiety's demonstrated potential for influencing important biological processes and enzymes.

The role of propargylamine as the structural foundation for monoamine oxidase (MAO) inhibitors is one significant illustration of the substance's pharmacological significance. By controlling the concentrations of neurotransmitters in the brain, these inhibitors are essential in the treatment of depression and neurodegenerative diseases. Psychopharmacology has been transformed by the discovery and development of propargylamine-based MAO inhibitors, which offer more effective and secure substitutes for conventional antidepressants.

The adaptability of propargylamine also extends to the field of materials science, where its inclusion in polymers and nano materials has produced sophisticated functional materials with distinctive characteristics. Its use in click chemistry as a molecular linker has made it easier to create custom materials with exact control over their structure and characteristics. These propargylamine-based compounds show enormous potential for tackling a variety of technological difficulties, from medication delivery systems to sensors and catalysts.

1.5 Pharmaceutical importance of propargylamine

1.5.1 Alzheimer's disease (AD)

Millions of people worldwide live with the dreadful neurological ailment known as Alzheimer's disease. It has an irreparable impact on both patients and their families because it is a progressive and irreversible disorder that robs people of their cognitive ability, memories, and independence. Numerous research initiatives and partnerships have been launched in the areas of neurology, medicine, and pharmaceutical sciences as a result of this complicated disease's emergence as a significant public health issue.

This extensive investigation attempts to elucidate the structural features and functional characteristics of propargylamine derivatives in order to identify their underlying mechanisms of action in the context of AD pathogenesis. The major goal is to research the synthesis and biological assessment of propargylamine derivatives through the skillful application of A^3-coupling. The examination of their potential as therapeutic agents for Alzheimer's disease is the subject of great attention. This research aspires to make considerable contributions to the constantly increasing field of AD research by employing the principles of organic chemistry and utilizing the adaptability of the A^3-coupling reaction, while also giving new insights into the potential development of AD therapeutics. The systematic and rigorous investigation of these compounds

has the potential to make major advancements in both organic chemistry and our understanding of the etiology and course of AD.

AD is characterized by neurotic plaques and neurofibrillary tangles due to amyloid-beta accumulation. Risk factors encompass age, genetics, head injuries, vascular diseases, infections, and environmental factors. The exact cause remains unknown, though the cholinergic and amyloid-beta hypotheses are prominent. AD prevalence is increasing globally, with limited treatment options. Propargylamine-modified pyrimidinylthiourea derivatives were synthesized by A^3- coupling and used as multifunctional agents for Alzheimer's disease. It was evaluated that propargylamine derivatives have good inhibitory activity against AChE (vs. BuCHE, IC_{50}=10.324μM, SI>123)) and MAO-B (vs MAO-A, IC_{50} =1.427 μM, SI>35) as shown in **Figure 1.5** (Sinth S. *et al.*, 2021.)

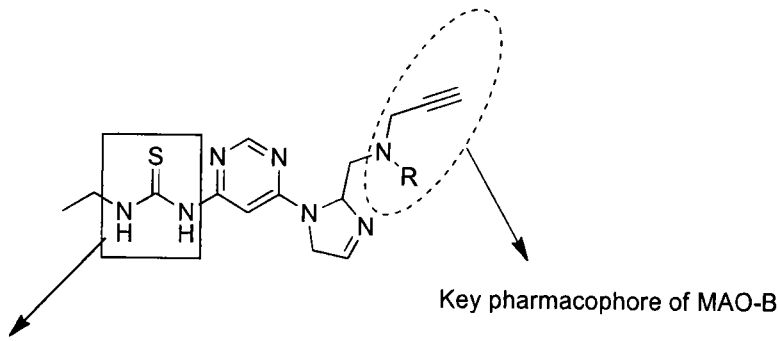


Figure 1.5: Uses of Propargylamine derivatives against Alzheimer's disease (yi-xiang xu *et al.*, 2018).

1.5.2 Parkinson's disease (PD)

Parkinson's disease, initially recognized for its motor symptoms, such as bradykinesia, rigidity, and tremors, was first described by James Parkinson in 1817. However, disturbances in sleep were later noted, with patients experiencing disrupted sleep patterns, tremulous movements during sleep, and increasing sleepiness. Over time, awareness of sleep-related issues in PD has grown, revealing their significant impact on patients and their caregivers. Sleep disturbances encompass a range of problems, including excessive daytime sleepiness (EDS) and rapid eye movement

(REM) sleep behavior disorder (RBD). These sleep issues not only affect the quality of life but can also serve as early markers of PD.

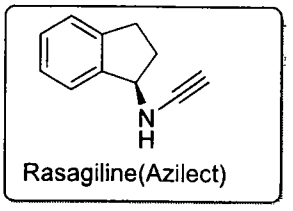
Considering the increased presence of brain MAO and iron in conditions like Alzheimer's disease, Parkinson's disease, and aging, which can contribute to iron-dependent oxidative stress and neuro degeneration, a series of multifunctional drugs known as the M30 HLA-20 series has been developed. These drugs function as brain-permeable iron chelators and brain-selective MAO inhibitors, all while carrying the propargyl neuroprotective moiety. Selegiline and rasagiline are propargylamine-type MAO inhibitors that have neuroprotective effects. Selegiline shields neurons from oxidative stress and neurotoxins, slowing disease progression. Rasagiline, without neurotoxic metabolites, shows stronger neuroprotection and neurorescue, improving motor function and reducing stroke incidence. This is attributed to interactions at mitochondrial sites regulating BCl-2 proteins and activating specific pathways.

Selegiline's anti-Parkinson effects prompted exploration of inhibitors targeting MAO-A and B, catechol-O-methyltransferase, and cholinesterase for Parkinson's and Alzheimer's therapies. Cholinesterase inhibitor drugs for Alzheimer's have limited efficacy. The complex nature of neurodegenerative disorders requires a multifunctional approach, such as Rasagiline, which combines cholinesterase and MAO inhibitory activities with a neuroprotective propargyl moiety. Brain MAO and iron level increase in conditions like Alzheimer's and Parkinson's, leading to brain-permeable iron chelators and MAO inhibitors.

Rasagiline, derived from Selegiline, is presented as a novel multifunctional neuroprotective drug. It combines cholinesterase and brain-selective monoamine-oxidase (MAO) A and B inhibitory activities with a neuroprotective propargyl moiety, potentially treating Alzheimer's, dementia with Lewy bodies, and Parkinson's disease with dementia.

Both Selegiline and Rasagiline are explored for their neuroprotective activities. Selegiline protects neuronal cells from oxidative stress and neurotoxins, contributing to its potential to slow Parkinson's and possibly Alzheimer's progression. In contrast, Rasagiline, without neurotoxic metabolites, shows superior neuroprotective and neurorescue effects, promoting motor function recovery and reducing stroke incidence in animal models. The mechanism involves interactions at mitochondrial sites that regulate BCl-2 family proteins and activate specific pathways.

Current drug classes for neurodegenerative diseases are limited, so a new approach is proposed, involving careful polypharmacology or multifunctional drugs targeting various CNS aspects. Multifunctional drugs like ladostigil and M30 aim to address dementia-related features while considering the novel α- secretase pathway for Alzheimer's therapy.



Rasagiline(Azilect)

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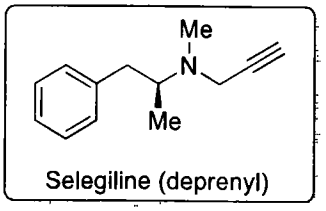

Selegiline (deprenyl)

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Figure 1.6: MAO inhibitors containing propargylamine moiety.

1.6 Problem statement

FDA databases and a literature survey revealed the structural importance of *N*-heterocycles compounds in drug design and development. *N*-thiourea propargylamine has biological activity because of its propargyl group. Several propargylamine derivatives synthesized by A^3- coupling have been moved into clinical trials, but there is still a need to develop N-thiourea propargylamine with high selectivity, low toxicity, biological activity, and the ability to target many diseases.

1.7 Aim and objectives

General aim of this research is to synthesize *N*-thiourea propargylamine derivatives

Specific objectives to achieve this aim include:

- To develop methodology for the alkynylation of thiosemicarbazone
- To synthesize *N*-thiourea propargylamine by A^3-coupling using aldehyde thiosemicarbazide
- To purify N-thiourea propargylamine
- To characterize *N*-thiourea propargylamine by M.P, FT-IR, GC-MS, and ^{1}HNMR.

Chapter no. 2

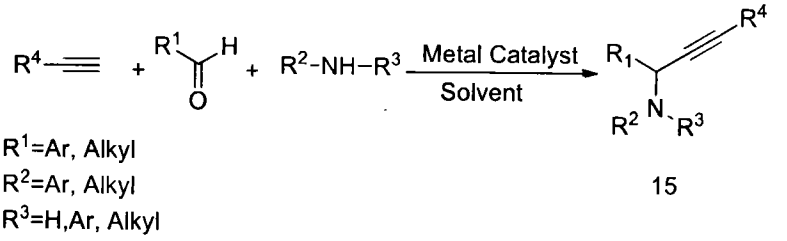
Literature Review

Literature Review

An extensive survey of the Literature shows that a variability of Propargylamine, which was synthesized by A^3-coupling in different reaction condition has gained the attention of scientists recently. Propargylamine had been synthesized by A^3-coupling using different transition metal salt catalysts and different solvents. This chapter includes the different methods of synthesis of propargylamine and its biological importance.

2.1 Synthesis of propargylamine by A^3-coupling

A^3-Coupling had been the most prevalent method for the synthesis of propargylamine which acts as a key intermediate in the synthesis of *N*-heterocyclic compounds. In a general way propargylamine have been synthesized by using aldehyde, alkyne, and amine in the presence of different metal catalysts and different solvent as shown in **scheme 2** (Gupta 2019).



R^1=Ar, Alkyl
R^2=Ar, Alkyl
R^3=H,Ar, Alkyl

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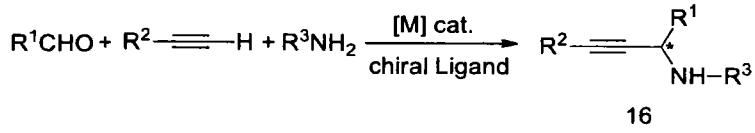
Scheme 2: General scheme of Propargylamine synthesis (A^3-coupling).

In 2022, Farhi, J. *et al.* described a method for the synthesis of propargylamine by using a metal catalyst and using different chiral ligand. A^3-coupling was thought to work via late transition metals activating the C-H atom. The transition metals were considered as well recognized for joining with terminal alkynes to produce a "metal-complex," which increased the acidity of the alkyne proton to facilitate further abstraction. The terminal alkynes could be deprotonated by the amines present in the reaction medium as the weak base after the C-H bond has been activated, producing the required organometallic alkynyl nucleophile. The metal catalyst is simultaneously renewed for use in another reaction cycle as a result of the imine or iminium ion's reaction with the metal acetylide to produce propargylamines as shown in **scheme 3.** The use of chiral ligands in this technique frequently results in good stereo selectivity (Farhi, J *et al.*, 2022).



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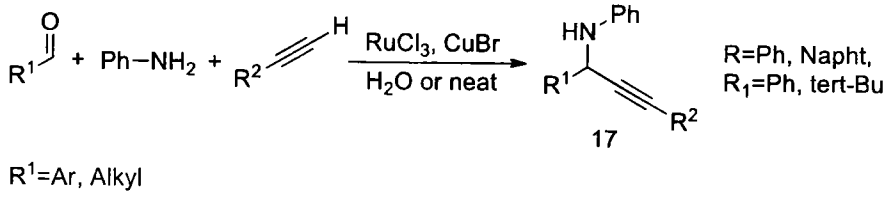
Scheme 3: Asymmetric synthesis of Propargylamine.

Different catalysts were used for the synthesis of propargylamine but Copper was best catalyst and used in different copper salts form such as $CuCl_2$, CuBr, CuBr, CuI, and CuCl as catalysts by using H_2O as solvent. Propargylamine was also synthesized under the solvent free conditions as shown in **scheme** 4 (Li, C. J., *et al* 2002).



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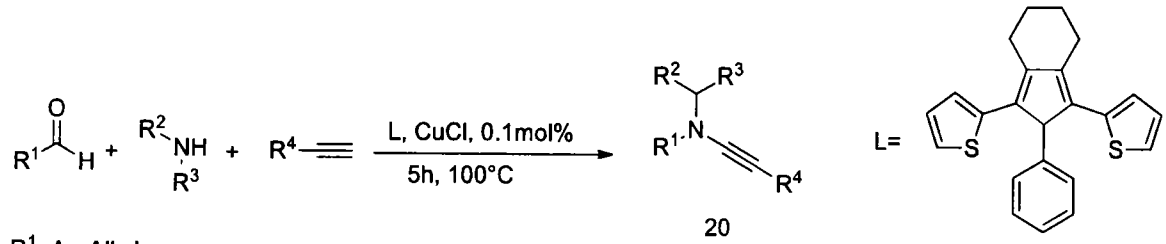
Scheme 4: Synthesis of propargylamine using $RuCl_3$ and CuBr (A^3-Coupling).

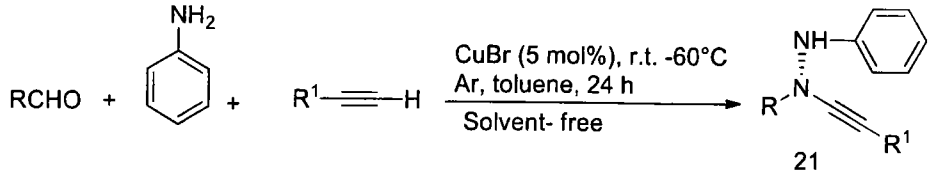
Camarata *et al* described the use of Copper complex catalyst for the high yield of propargylamine. Complex copper catalysts such as L= [$CuCl_2$, 5-bis (2-thienyl)-1-phenylphosphole] (19) an air stable copper (I)-phosphole complex, was used as catalyst in single and double A^3-coupling processes to produce mono- and bi-propargylamines (20). Numerous aldehydes, amines, and terminal alkynes were examined. Most of these reactions produced the anticipated propargylamine with good yield as shown in **scheme 6** (Cammarata, J. R et al., 2017).



R^1=Ar, Alkyl
R^2=Alkyl
R^3=H
R^4 =Ph

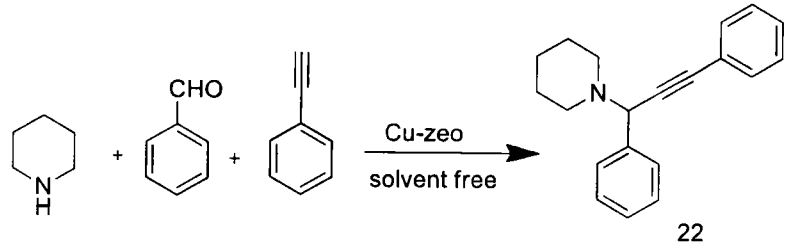
Scheme 6: Synthesis of propargylamine catalyzed by an air stable copper (I)-phosphole complex.

Scheme 7 represented another method where Li *et al* combined CuBr and $RuCl_3$ metal sources to add phenylacetylene to an imine made from aniline and derivatives of aromatic or aliphatic aldehydes. They noted that the reaction required the addition of an acetylide to an imine, a more difficult substrate than the more electronegative iminium produced by secondary amines. The imine reacts with the hypothesized in situ produced Cu-acetylide intermediate, resulting in the synthesis of the appropriate Propargylamine.



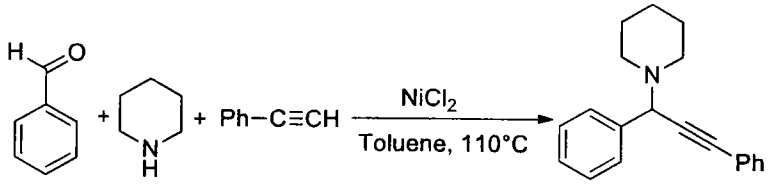
Scheme 7: Synthesis of propargylamine in the presence CuBr.

Scheme 8 represented the synthesis of propargylamine (22) using Cu-zeolite as catalyst. For the synthesis of proparglamine, piperidine was used as an amine, benzaldehyde as aldehyde and the phenylacetylene was used under the solvent-free method in the presence of Cu-zeolite as a catalyst and Cu-zeolite was recycled at the end of reaction. (Patil, M. K *et al.*, 2008).



Scheme 8: Synthesis of propargylamine by using piperidine as amine in the presence of Cu-zeo catalyst.

In different literature, it was found that different transition metal salts can be used as catalyst for the synthesis of propargylamine (23) by A^3-Coupling. However, literature showed that among transition metal salts, nickel chloride proved to be more economical and potent catalyst to produce an impressive quantitative yield of propargylamines as described in **Scheme 9**. This reaction had remarkable results in the absence of any co-catalyst or activator (Samai *et al,* 2010).

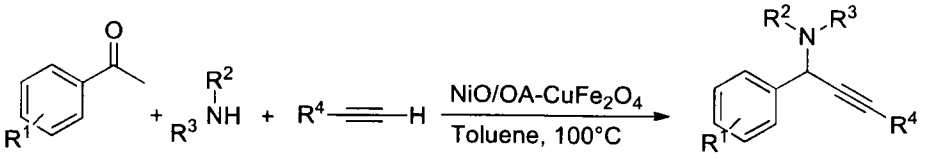


72%

(23)

Scheme 9: Nickel chloride ($NiCl_2$) catalyzed synthesis of propargylamines (A^3-coupling)

Ni/Cu/Fe catalyst had an affordable and efficient approach for the A^3-coupling reaction of aldehydes, amines, and terminal alkynes to produce the appropriate propargylamines (24) as demonstrated by this Nano catalyst. The complex of nickel catalyst NiO\OA-$CuFe_2O_4$ was prepared, which was further used for the synthesis of propargylamine by A^3-coupling as evaluated in **Scheme 10**. (Daryanavard, M *et al.*, 2020).



24

Scheme 10: Ni/Cu/Fe Termetallic Nano catalyst for the Synthesis of Propargylamines (24) through the A^3-Coupling.

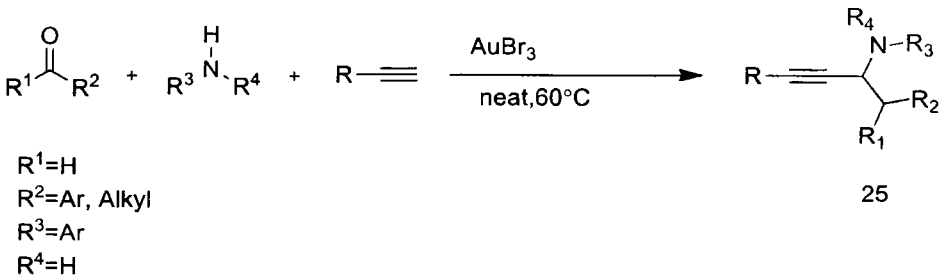
2.1.2 Solvent free synthesis of propargylamine

The majority of synthetic techniques made extensive use of volatile organic solvents. Additionally, many of the standard solvents were flammable, poisonous, or corrosive. Solvents were widely used for a variety of tasks, including controlling temperature, cleaning clothing and equipment, isolating

and purifying organic compounds through recrystallization, etc. It was impossible to ignore how solvents contribute to the waste load in the manufacturing of fine chemicals and pharmaceuticals. Green chemistry strived to reduce environmental issues by removing the inherent risk of specific goods and processes. Green chemistry enhanced product selectivity, resource and energy efficiency, operational simplicity, environmental safety and health, and operational ease to improve chemical synthesis. Green chemistry offers a new synthetic method by reducing the risks and wastes connected to the traditional method and making research sustainable (Manujyothi, R., et al. 2021).

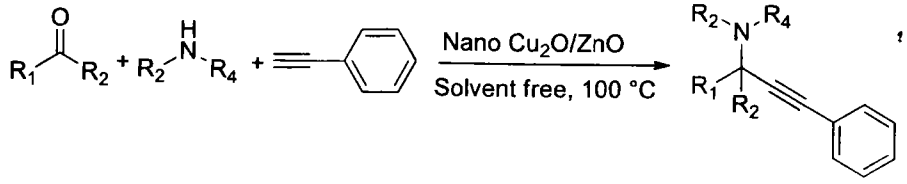
In this case, a solvent-free synthesis offers a more environmentally friendly synthetic option. Only a very small percentage of the synthesis of propargylamines has been reported to be metal-free. Long reaction times and high temperatures are two difficulties that come with metal-free synthesis. These reactions offer a smaller range of substrates, and it has yet to be proven that they can react smoothly with aliphatic alkynes.

Due to its biocompatibility, gold offers environmentally beneficial metal catalysis. A unique method was developed by Cheng and his colleagues for synthesizing propargylamines containing quaternary carbon centers. Through the direct intermolecular interaction of ketones, secondary amines, and alkynes, gold was used to create propargylamines. Model substrates such as cyclohexanone, Morpholine, and phenylacetylene were used, and the best results were obtained using 4 mol % $AuBr_3$ in neat conditions at 60 °C. The substrate scope studies displayed the inability of aromatic ketones to give the desired products. This might be due to the special stability of conjugated aromatic ketones, which may result in difficulty in the formation of the intermediate as shown in **scheme 11.** (Wei, C., & Li, C. J. 2003).



Scheme 11: Synthesis of propargylamine by $AuBr_3$ under solvent free condition.

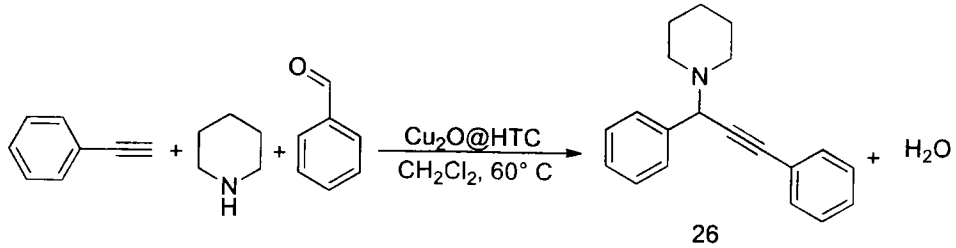
Sarvari *et al* has showed through a one-pot, three-component coupling reaction of terminal alkynes, aldehydes, or ketones, and secondary amines in excellent isolated yields under solvent-free conditions, using a catalytic amount of Nano Cu_2O-ZnO as the recyclable, heterogeneous catalyst, a straightforward, effective method for producing propargylamines **(26) as observed in Scheme 12** has been described. The catalyst could be reused in further catalytic reactions, and it was found that its activity remained largely unchanged for ten successive runs. The catalyst was characterized by using powder X-ray diffraction (XRD), transmission electron microscopy (TEM), scanning electron microscopy (SEM), BET surface area measurement, and FT-IR spectroscopy (Hosseini-Sarvari *et al.*, 2014).



26

Scheme 12: Synthesis of propargylamine by using Cu_2O\ZnO nano catalyst (A^3-coupling).

Nakhate *et al* has represented that the three-component coupling of phenylacetylene, aldehyde, and amine was carried out using a copper oxide-supported carbon microsphere, which was synthesized, described, and used. Cu_2O@HTC was produced utilizing a straightforward hydrothermal procedure, glucose as the carbon source, and water as the solvent. (Nakhate, A.V., *et al.* 2018).

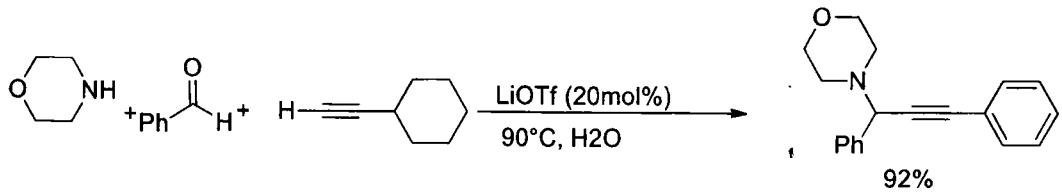


26

Scheme 13: Cu_2O nanoparticles supported hydrothermal carbon microspheres as catalyst for propargylamine (26) synthesis.

2.2 Synthesis of propargylamine by using secondary amine

The three-component A^3-coupling reaction, which produces propargylamine, has been successfully carried out in the presence of the more effective and environmentally friendly catalyst lithium tiflate (LioTf). No solvent of any type was used to perform this reaction. Because of the conditions that were used, including the absence of solvent, the ease with which the catalyst could be recovered, its eco-friendliness, the method's simplicity, and the excellent yield that was anticipated, this synthetic scheme was more acceptable, charming, and valid (D Dindulkar, 2013).



92%

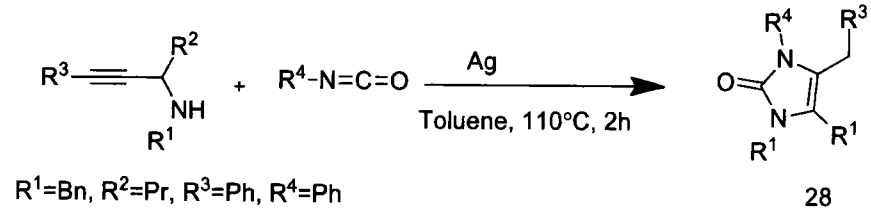
27

Scheme 14: Synthesis of Propargylamine by using morpholine as amine (A^3-coupling).

2.3 Synthetic importance of propargylamine

Due to their distinctive chemical structure, which consists of a nucleophilic amine and an acetylene moiety on the same backbone, propargylamines have been used as versatile building blocks for the synthesis of a wide range of different aromatic nitrogen heterocycles. Because of this special quality, propargylamine molecules can function as both electrophilic and nucleophilic substrates in chemical reactions. There were numerous ways to make heterocyclic organic compounds from propargylamines, and these procedures are usually made easier by transition metals like Au, Cu, and Pd (Lauder, Toscani., et al. 2017).

Secondary propargylamine has been synthesized by using A^3-coupling mechanism. The production of 2-imidazolone was achieved via a one-pot procedure based on the cycloisomerization of propargylic ureas, which were produced from secondary propargylamines and isocyanates as shown in **Scheme 12** (Peshkov, V. A et al., 2011).

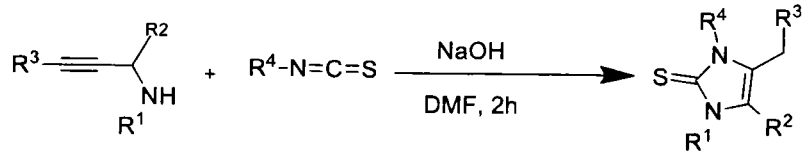


R^1=Bn, R^2=Pr, R^3=Ph, R^4=Ph

28

Scheme 15: Synthesis of 2-imidazolone by propargylamine.

It had been accomplished to hydroaminate propargylamine with isothiocyanates intramolecularly and without the need for a transition metal. Imidazole-2-thione and Spiro-cyclic imidazolidine-2-thione were both synthesized in a single pot using an atom-efficient, regioselective intramolecular 5-exo-dig cycloisomerization. Propargylthiourea allows the process to be completed at room temperature, and isolated yields of 65–97% were achieved as observed in **Scheme 16** (Ranjan, A., *et al.* 2014).



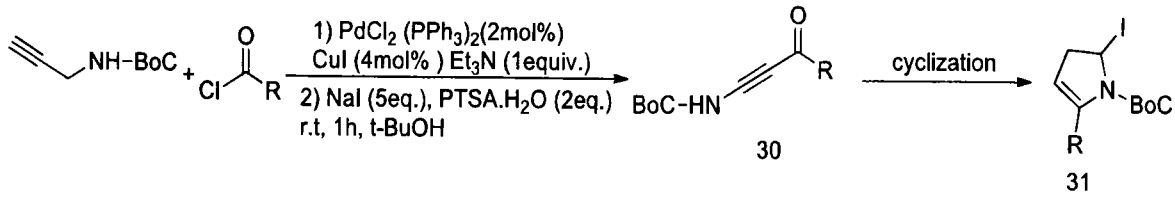
R_1=Bn, R_2=Pr, R_3=Ph, R_4=Ph

29

Scheme 16: Synthesis of Imidazole-2-thione by propargylamine.

2.3.1 Synthesis of pyrroles by propargylamine

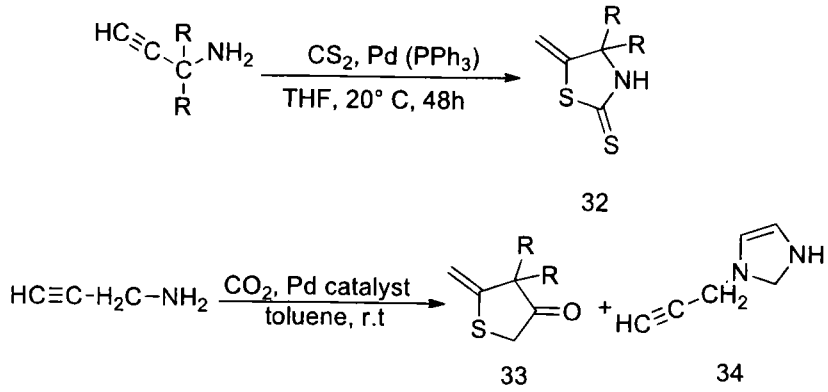
Müller *et* al. used $PdCl_2(PPh_3)_2$ and CuI. As an appealing catalytic system for the production of 2, 4-substituted pyrroles with high yields. To standardize the reaction conditions, the impact of catalyst loading, base, solvent type, and temperature have been assessed. Sonogashira cross-coupling reaction of N-Boc-4-iodopyrroles and acyl chloride in the presence of $PdCl_2(PPh_3)_2$ and CuI occurred, leading to the formation of a propargylamine as an intermediate as shown in **Scheme 17**, which then followed by conversion to 2-substituted *N*-Boc-4-iodopyrroles through reaction with NaI in the presence of p-toluene sulfonic acid (Liu, Pan et al., 2012).



Scheme 17: Synthesis of propargylamine using Pd complex catalyst

2.3.2 Propargyamine reaction with CO_2 and CS_2

The reactions of propargylamine derivatives with carbon dioxide and carbon disulfide have been systematically examined in the presence of transition-metal catalysts. $Pd(OAc)_2$ is the best catalyst for the formation of the corresponding oxazolidinones. In addition, we found that, in the reaction of propargylamine with carbon dioxide catalyzed by a palladium(0) metal catalyst in toluene, both oxazolidinone 33 and imidazolidinone 34 could be obtained under mild reaction conditions at the same time as described in **scheme 18** (Shi and Shen 2002).

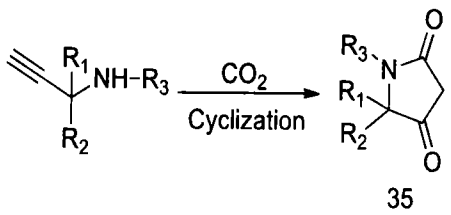


Scheme 18: Synthesis of oxazolidinone and imidazolidinone by propargylmine.

2.3.3 Reaction of propargylamine with CO_2

Fossil fuels were being consumed quickly due to the recent expansion of the global economy, which has resulted in a steady rise in carbon dioxide (CO_2) emissions and causes serious environmental issues. To overcome the environmental issue of CO_2 it is used in the synthetic process by reacting with propargylamine to form 2-oxazolidone. Therefore, it was vital to discover strategies for limiting the rise in atmospheric CO_2.The carboxylative cyclization of propargylamine with CO_2 which occurred by solvent free method could produce structural units of 2-oxazolidone for numerous significant organic molecules that are widely used in the chemical

industry, as well as the fields of materials and medicine. Additionally, 2-oxazolidone comprises polar ester groups and a double bond, both of which have the potential to be further modified as shown in **Scheme 19**(Wu, Guo., et al.2022) .

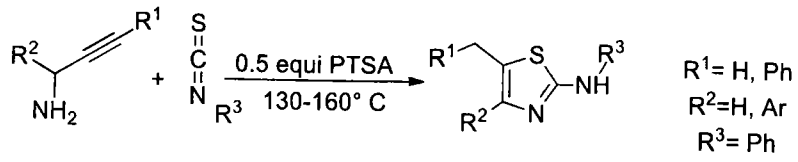


35

Scheme 19: Carboxylic cyclization of CO_2 of propargylamine.

2.3.4 Reaction of propargylamine with isothiocyanate

For the synthesis of 2-aminothiazoles, a straightforward and adaptable microwave-assisted technique had been adopted. At temperatures above 130 °C and within a short period of time, the selective synthesis of 2-aminothiazoles was accomplished by the domino reaction of propargylamines and isothiocyanates in the presence of catalytic PTSA. The tautomeric 2-amino-4-methylenethiazolines were synthesized by the same reaction when carried out at lower temperatures as observed in **Scheme 20** (Scalacci, Pelloja et al., 2016).



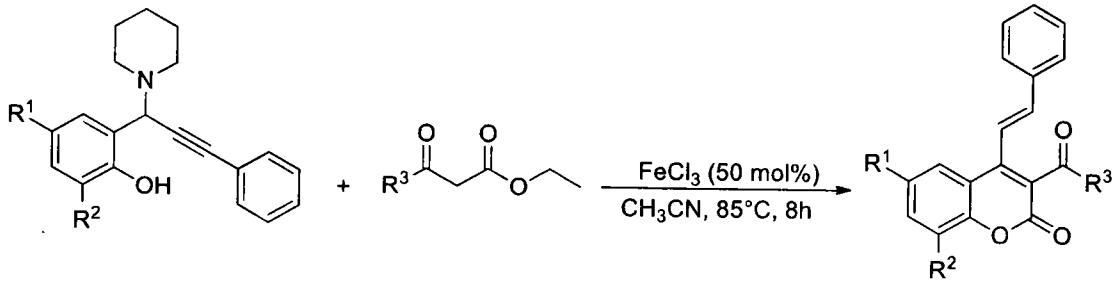
36

Scheme 20: Propargylamine reaction with isothiocyanate.

2.3.5 Synthesis of 4-styrylcoumarins by reactions of propargylamines with β-keto esters

Coumarins, also referred to as 2H-chromen-2-ones, are important structural motifs that are present in many biologically active synthetic molecules2,3 as well as natural products. These molecules have demonstrated biological activities such as antibacterial, anti-inflammatory, antimicrobial, anti-HIV, antioxidant, and anticancer properties. By using a cascade reaction involving propargylamines and -keto esters via 1,4-conjugate addition, alkyne-allene isomerization, intramolecular trans esterification, and isomerization, it was possible to synthesize 4-styryl-2H-chromen-2-ones in a unique and highly regioselective manner. This one-pot, one-step technique

worked as a versatile and effective way to create 4-styryl-2H-chromen-2-one derivatives when it came to the accessibility of the raw ingredients and the catalytic systems. Notably, this reaction revealed the increased reactivity of propargylamines as well as a new pathway to the isocoumarin skeletons as observed in **Scheme 21** (Yan, Cai et al., 2019).

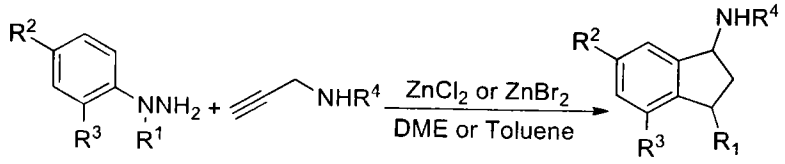


37

Scheme 21: Synthesis of 4-styryl-2H-chromen-2-ones via $FeCl_3$-promoted cascade reactions of propargylamines with β-keto esters.

2.3.6 Synthesis of indole from propargylamine

Beller indicated an effective one-pot method for synthesizing 3-amidoindoles 552 from arylhydrazines and propargylamines that were readily accessible on the market. With up to 94% yields and high regioselectivity, indoles were produced. Depending on the substrate, either $ZnCl_2$ or $ZnBr_2$ were utilized as catalysts. Finally, the indoles synthesized by this method were assessed as possible GSK-3 inhibitors as described in **Scheme 22** (Reddy, Nallapati et al., 2018).

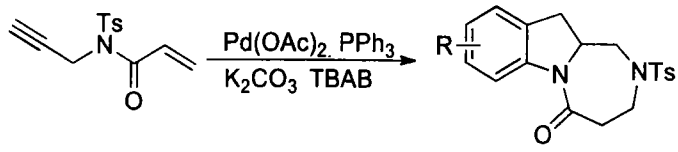


38

Scheme 22: Synthesis of indole by propargylamine

In order to synthesize indoline derivatives from propargylamines, Wang and associates described a fascinating Pd-catalyzed domino cyclization reaction. Good to excellent yields of up to 99% Indolines were produced. The authors also explored the mechanism of the reaction and

hypothesized that a Pd-catalyzed Sonogashira coupling should take place initially, followed by indole cyclization, regio-, and chemoselective *N*-1-acylation, and ultimately a 1,4- Michael addition reaction as evaluated in **Scheme 23** (Gharpure and Shelke 2017).

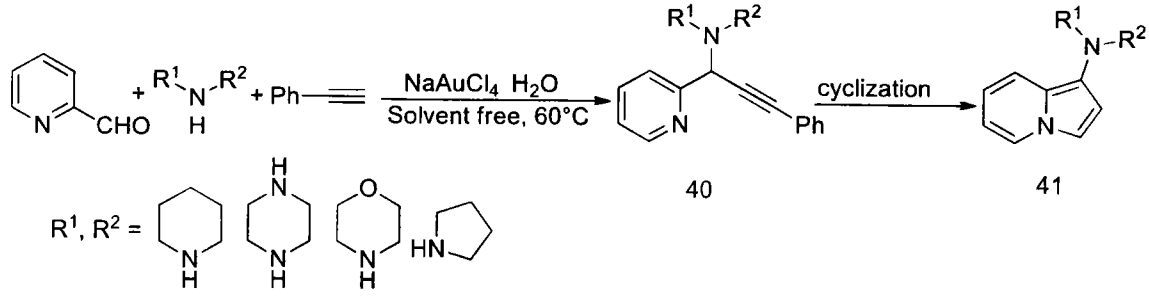


39

Scheme 23: Synthesis of indole catalyzed by Pd complex from propargylamine.

2.3.7 Synthesis of aminoindolizine by propargylamine

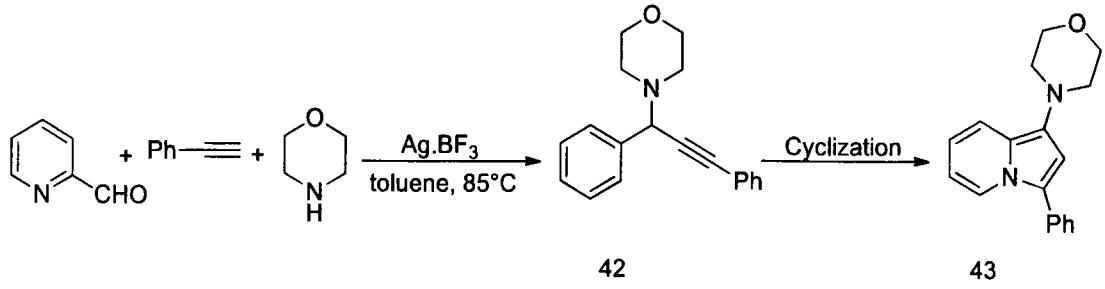
The heterocyclic compound aminoindolizine was synthesized by propargyamine by cyclization. Indolizine was found to be an effective drug that could act against bacteria, viruses, and inflammation as well. By the A^3-coupling mechanism propargylamine had been synthesized which was catalyzed by gold and act as an intermediate for the synthesis of aminoindolizine. The reactions were performed by solvent free method at 60 °C temperature as evaluated in **Scheme 24** (Liu, Song et al. 2007).



40 41

Scheme 24: Synthesis of aminoindolizine in the presence of a gold complex.

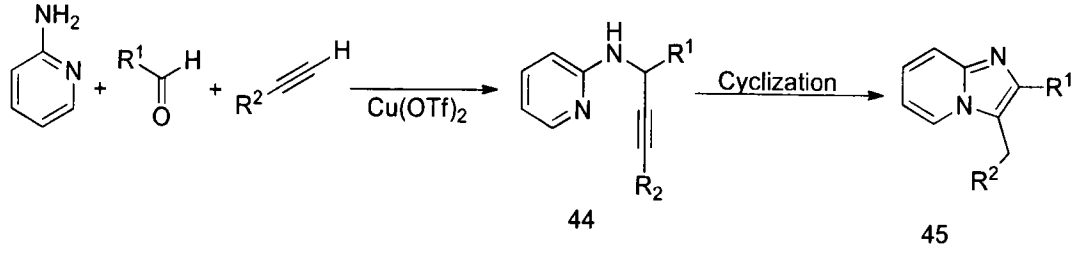
1-aminoindolizine had been synthesized by the direct A^3-coupling of heteroaryl aldehyde , secondary amine and terminal alkyne in the presence of silver catalyst as evaluated in **Scheme 24** (Mishra, Bagdi et al., 2014).



Scheme 25: Synthesis of aminoindolizine in the presence of silver complex catalyst.

2.3.8 Synthesis of imidazopyridine by propargylamine

As a vital pharmacophore, imidazopyridine could be detected in a wide range of biologically active synthetic substances. A key ingredient found in pharmacologically significant compounds, such as multiple anxyolytic medicines, is imidazo [1, 2-a] pyridine. An imidazopyridine was also important in the synthesis of many heterocyclic compounds. In a tandem one-pot, three-component coupling reaction, 2-aminopyridine, an aldehyde, and a terminal alkyne could be reacted to produce imidazopyridines, which results in the synthesis of an intermediate propargylamine and the subsequent 5-exo-dig cyclization as evaluated in **Scheme 26** (Chernyak and Gevorgyan 2010).

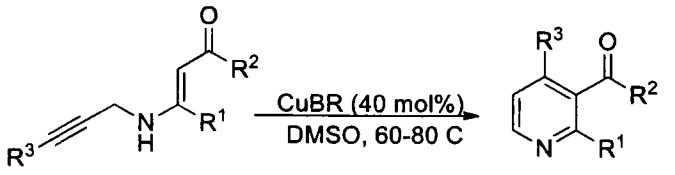


Scheme 26: Synthesis of imidazopyrides by propargylamine.

2.3.9 Synthesis of pyridine and piperidines derivative by Propargylamine

Pyridine is considered most important *N*- heterocyclic organic compound which has been used in the synthesis of more than 100 drugs. Pyridine derivatives has been synthesized by using an expensive catalyst and in low yield under the harsh conditions in the organic synthesis. Propargylamine was used as intermediate for the synthesis of pyridine derivatives as evaluated in **Scheme 27**. *N*-propargyl *β*-enaminones was used as a starting material by using CuBr as catalyst

for the synthesis of pyridine because β-enaminones have both electrophilic and nucleophilic natures (Mandlimath and Sathiyanarayanan 2016).



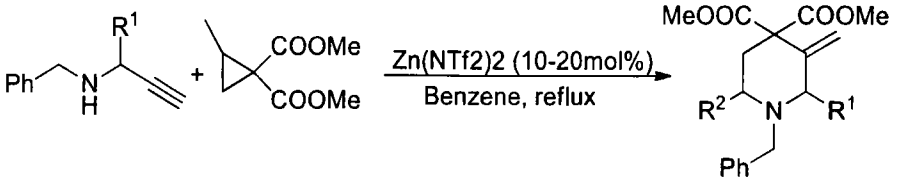
R^1= Ph, C_5H_{11}
R^2= Me, Ph, 4-CN-Ph
R^3= H, Ph, 4-Me-Ph, 4-OMe-Ph

46

Scheme 27: Synthesis of pyridine derivative by propargylamine.

2.3.10 Synthesis of benzofuran by propargylamine

Only two examples of this type of reaction were documented in the literature, and little research has been done on the use of *N*-propargylamines as starting substrates in the synthesis of piperidines. The chemistry and use of benzyl protected propargylamines were studied by Leblod, Leduc, and Kerr in 2009, who found that they came into contact with 1,1-cyclopropane diesters in the presence of $Zn(NTf2)_2$ as a catalyst to form highly substituted piperidines in good to exceptional yields . The key processes of the reaction, according to the suggested mechanism, comprise a cyclopropane ring-opening and a Conia-ene cyclization as evaluated in **Scheme 28** (Vessally, Hosseinian et al., 2016).

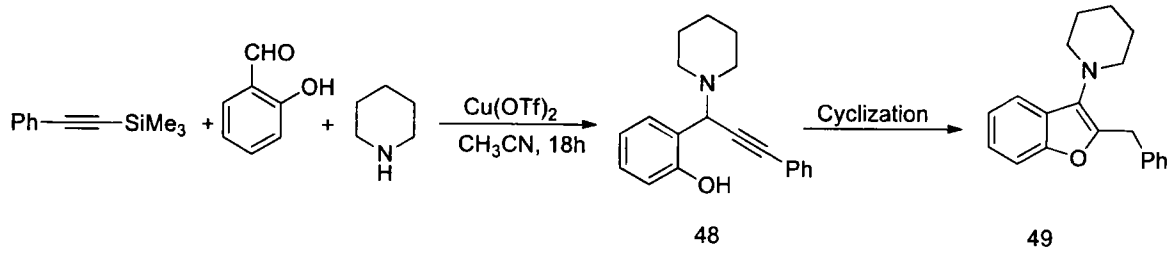


47

Scheme 28: Synthesis of benzofuran by propargylamine.

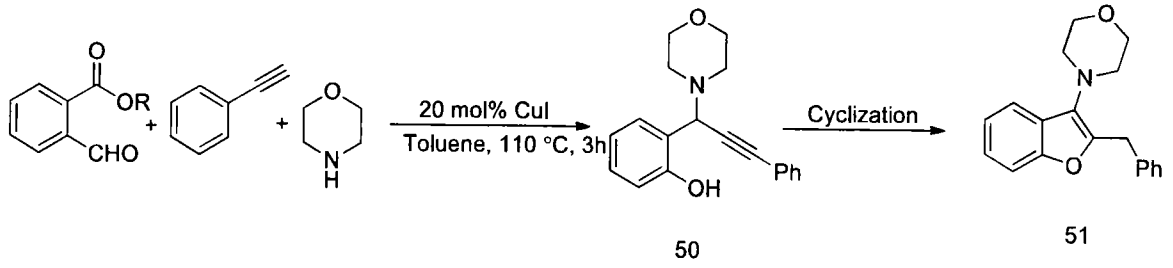
Multicomponent reactions have played an important role in organic chemistry due to their importance in the synthesis of various types of *N*- heterocyclic compounds, which have a lot of importance in drug discovery in medicinal chemistry. Benzofuran have been considered as biologically active compound. Sakai and his coworkers synthesize benzofuran by using

propargylamine as intermediate which is synthesized by A^3-coupling in the presence of $Cu(OTf)_2$ as a catalyst as evaluated in **Scheme 29** (Sakai, Uchida et al. 2008).



Scheme 29: Synthesis of benzofuran by propargylamine.

Benzofuran derivatives had been synthesized by using morphaline as an amine, salicylaldehyde as aldehyde and phenylacetylene as alkyne. Benzofuran derivative was synthesized by A^3 coupling in the presence of copper iodide catalyst and toluene as a solvent at 110 °C as seen in **Scheme 30** (Cruz-Hernández, Landeros et al., 2019).

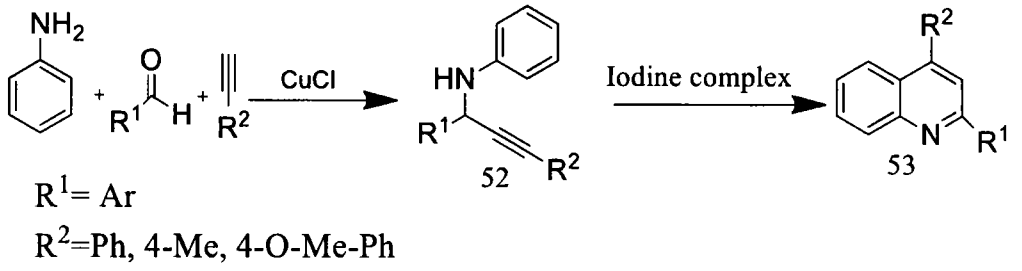


Scheme 30: Synthesis of benzofuran derivative by Propargylamine.

2.3.11 Synthesis of Quinoline by propargylamine

Quinoline had been synthesized by N-propargylamine in the presence of CuCl as a catalyst which allowed it to reflux into tetrahydrofuran (THF) by A^3 coupling. Quinoline had played a significant role in the pharmaceutical application and in the bioactive heterocyclic compounds. Qunioline has antibiotic, anti-inflammatory anti-tuberculosis and anti-HIV properties. (Lie *et al.*, 2012). Quinoline had been synthesized by A^3-coupling mechanism, in which propargylamine is first synthesized as an intermediate by using different catalyst and different reaction conditions. This

propargylamine was further used for the synthesis of quinolone in the presence of iodine as catalyst as seen in **Scheme 31** (Vessally, Edjlali et al., 2016).



Scheme 31: Synthesis of Quinoline by propargylamine

2.4 Biological Significance of propargylamines

For the first time Dr. Alios Alzheimer (German neuropathologist and psychiatrist) had specified a dementing condition that later became known as AD. Alzheimer had reported the case of Auguste D a 51 year old woman in his conference lecture in 1906 and in his article that had been published in 1907. It has been identified that Auguste D had suffered with a particular disease of cerebral cortex with the indication of progressive memory loss declination of intellectual abilities behavioral imbalance and psychosocial ruination as well. Surprisingly Alzheimer had described this disease more than a century ago and still there was a need to explore AD and its treatment for the betterment of people's future.

Clinical diagnosis has shown that Alzheimer disease is actually a progressive loss of memory. Many God gifted expertise can be busted including language, decision making power, focus, visual consideration. Nutritional deficiencies (vitamin B 12) metabolic and endocrine disorders (hypothyroidism) are also main causes of dementia. Within 5 to 10 years, the symptoms began to worsen. In neuropathology significant loss of synaptic neurons has been found in patient suffered from AD, leading towards brain atrophy. The formation of neurofibrillary tangles (NFT) and senile plaques (SP) has been found as the basis of brain atrophy. There were two types of Alzheimer disease: familiar AD and sporadic AD. Familiar AD (fAD) was due to a mutation in one presenilin gene located on chromosome 21. It has been identified that the epsilon four allete of apolipoprotein located on chromosome 19 is susceptible to Sporadic AD (SAD) (Korolev *et al.*, 2014).

Aging was a major factor in Alzheimer disease. Other factors include loss of consciousness and hypertension. Brain stroke stress surrounding toxins arteriosclerosis smoking alcohol consumption cerebrovavacular disease gene mutations and arteriosclerosis were also more contributing factors towards Alzheimer disease (Lindsay *et al,*. 2002).

The percentage of neurodegenerative disease had been elevated approximately all around the world and the suffering patients could have prolonged life assurance that was brought about by preventive health measures. Despite high frequency of neurodegenerative disease there has been little enhancement in introduction of disease modifying therapies to prevent neurological disorders. Neurodegenerative disease include Alzheimer s disease (AD), Parkinson disease (PD) and Huntington disease (HD) as well. Neurological disorders also arise from acute traumatic neurological lacerations and stroke. Multiple factors had been found to be responsible for brain disorders, including environmental, genetic and endogenous factors. These disorders share a common feature i.e. selective damage to a particular cluster of neurons. Each disease has its own molecular mechanism, but some general pathways have been investigated in neurological disorders that include altered phosphorylation of proteins, Mitochondrial dysfunction, oxidation stress, metal dyshomeostasis and protein assembly and aggregation have also been involved (jellinger *et al* ,. 2003).

2.4.1 MAO & cholinesterase inhibition

The pathogenesis of NDs had also been hypothesized to be significantly influenced by low levels of acetylcholine (Goedert, M., *et al* 2006). A loss of function had been observed as these diseases advanced. In the specific brain regions that govern learning and memory activities, cholinergic neurons caused a deficiency of acetylcholine (ACh) (Shih, J. C., *et* al 1999). Consequently, AChEIs like Acetyl cholinesterase inhibitors, Tacrine (**a**), Rivastigmine (**b**), Donepezil (**c**) & Galanthamine (**d**) the multifunctional monoamine oxidase and ChE inhibitors ladostigil (**e**) and PF9601N (**f**) are acetylcholinesterase inhibitors. By decreasing AChE and increasing the amounts of ACh in the synaptic cleft, these medications have been known to reduce the symptoms of AD (Scarpini E et al., 2003). Additionally, AChE had been linked to the accelerated development of amyloid fibrils in the brain and the creation of stable complexes with amyloid-(A) (Inestrosa NC, Álvarez A, Pérez CA *et al,* . 1999). By delaying the production of these amyloid fibrils and A complexes, which were expected to play a significant part in the

pathophysiology of ND decreasing, the activity of AChE has been found to show neuroprotective effects. Galanthamines (d) are the cornerstone of currently accessible therapy (Scarpini E et al ,. 2003). AD treatment is possible by using a propargylamine-containing moiety. These substances have been known to block AChE, which could lessen AD symptoms. The synaptic cleft by increasing AChE levels. AChE have also been thought to speed up the development of amyloid fibrils in the brain and create stable complexes containing amyloid-(A) as shown in **Figure 2.1**.

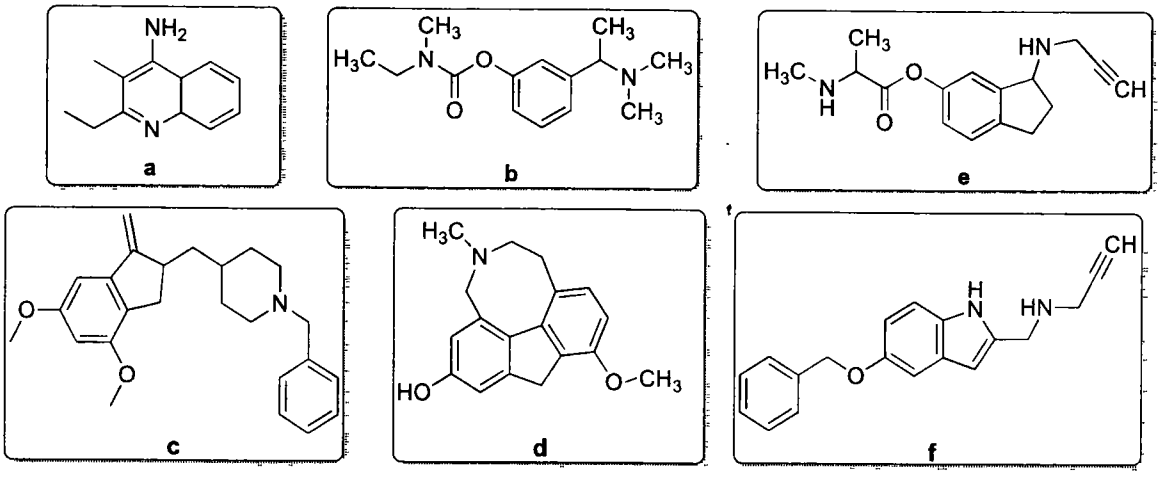


Figure 2.1: Acetylcholinesterase inhibitors Tacrine (**a**), rivastigmine (**b**), donepezil (**c**) & galanthamine (**d**); the multifunctional monoamine oxidase and ChE inhibitors ladostigil (**e**) and PF9601N (**f**).

The Propargylamine moiety had been logically included in the structures of numerous drug-like compounds created for neuroprotection in order to produce molecules with broader therapeutic psotential that may one day be able to treat multifactorial NDs. MAO enzyme has two forms MAO-A and MAO-B but MAO- B enzyme is affected by neurodegenerative disorders. Samadi et al. (2011) synthesized multitarget-directed MAO and AChE inhibitors. By joining the N-benzyl piperidine and propargylamine moieties found in the well-known MAO-I PF9601N (e) and the AChEI donepezil (b) through the proper linker by hybrid drug design as evaluated in **Figure 2.2** (Samadi A .*et al.*, 2012).

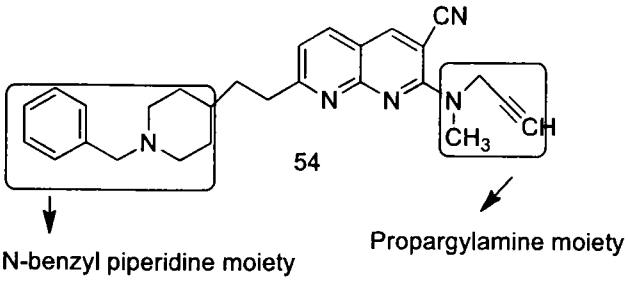


Figure 2.2: Compound 54 containing N-benzyl piperidine moiety and propargylamine moiety.

Chapter no. 3

Experimental Section

3. Experimental Section

3.1 Chemicals used

Chemicals and reagents were purchased from different chemical sources such as Toluene, benzaldehyde, aniline, phenylacetylene, and different aldehyde's derivatives, thiosemicarbazide, benzylamine, phenylisothiocyanate, different transition metal catalysts such as $ZnCl_2$, CuCL, $CuCl_2$, $FeCl_3$, $ZnBr_2$, $ZrCl_4$, $NiCl_2.5H_2O$, $AlCl_3$, $MgCl_2.6H_2O$, Ethylacetate, n-Hexane, DCM, DMF, Methanol, Ethanol, Acetic Acid, Acetone, Ethanol, methanol, anhydrous magnesium sulphate were purchased from sigma Aldrich.

3.2 Instruments used

3.2.1 Melting point apparatus

The melting point of synthesized compounds was measured using the Gallen kamp melting point instrument. The capillary was filled with a small amount of sample, which was injected into the devise. The temperature began to rise and was examined with the digital thermometer provided. The temperature was detected when the sample began to liquefy.

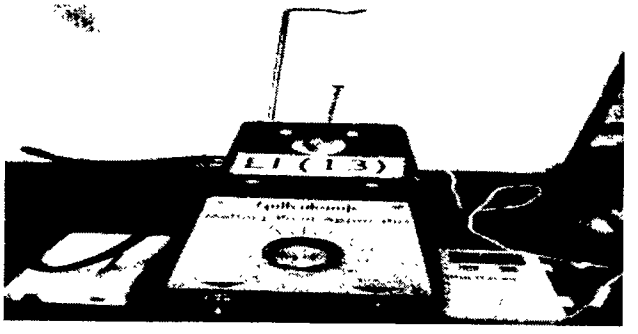


Figure 3.1: Melting point apparatus

3.2.2: FT-IR spectrophotometer

PerkinElmer UATR 2, USA, version 10.6.2, was used to record FT-IR spectra in the 450-4000 cm^{-1} range. In order to identify functional groups like C=O, CH, or NH, FT-IR spectroscopy is frequently employed to analyze organic molecules. It primarily produces two types of modifications in molecules: stretching vibration changes bond length and bending vibration changes bond angle. The fingerprint region, which is exclusive to different compounds and is typically in the range of 700 to 400 cm, is used to identify functional properties. (Khan *et al.*, 2018)

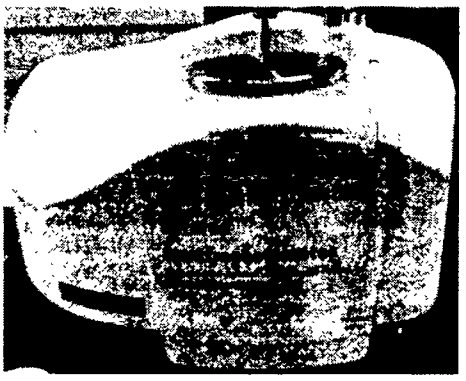


Figure 3.2: FT-IR spectrophotometer

3.3.1 Thin layer chromatography

TLC was performed on pre coated sheets of alumina (MERCK) with a thickness of 0.25 mm was pre-lined with silica gel (60 F - 254) and modified into a usable size of 2 cm with visibility below UV (254 nm).

3.3.2 Chromatogram detection

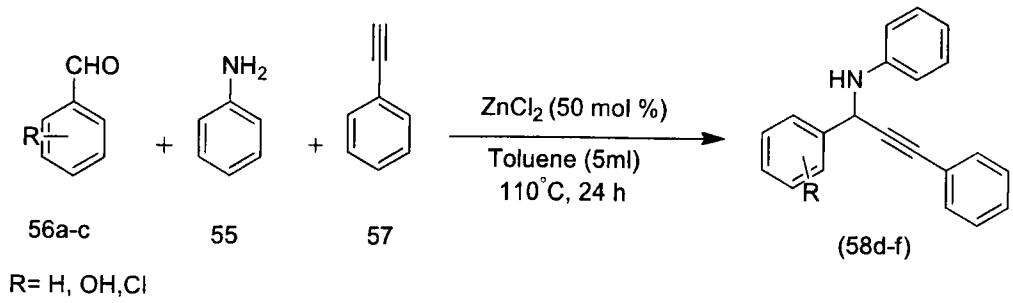
Chromatograms were developed using n-hexane: EtOAc as the mobile phase. The chromatogram was carried out using a UV lamp with a wavelength of 254 nm. The retention factor was the ratio of the distance traveled by the components and the solvent.

$$R_f \frac{(\text{Distance traveled by component})}{(\text{Distance traveled by solvent})}$$

3.4 General procedure for the synthesis of Propargylamine (58d-f)

Primitive study was performed was performed by using Benzaldehyde **(56a)** (1mmol) as a source of Aldehyde, aniline **(55)** (1mmol) as a source of amine and phenyl acetylene **(57)** as a source of alkyne. First of all, benzaldehyde and aniline were dissolved in toluene (5ml) used as solvent in a round bottom flask. After stirring for 30 minutes was performed, imine was synthesized, after that phenyl acetylene (1mmol) and $ZnCl_2$ (50 mol %) as catalyst were added to a reaction mixture. After 10 minutes of stirring heating plate was switched on to start refluxing at 110 °C. The progress of reaction was monitored by TLC by making 100% of the solvent *n*-hexane. After that, a solvent mixture of *n*-hexane: EtOAc (9:1) was used. After monitoring the TLC, working of reaction mixture was performed using solvent extraction technique. For that purpose, reaction mixture was diluted with ethyl acetate (5ml) and poured in separating funnel. Then 10 ml of water was dissolved

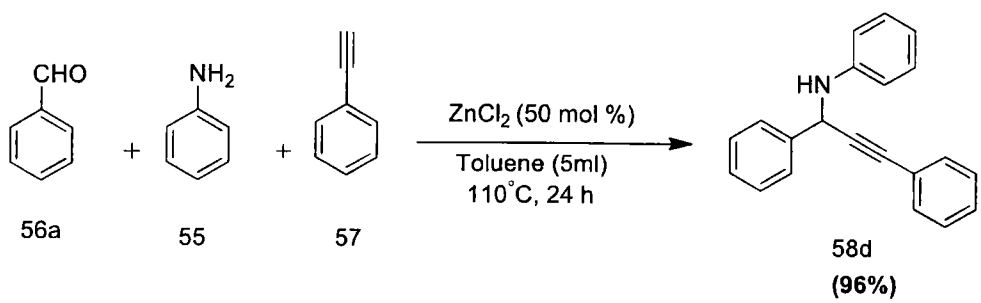
in a separating funnel, after shaking two layers i.e. organic layer and aqueous layer were formed. These layers were separated into two labeled beakers. Solvent extraction was performed three times. After that organic layer was dried with anhydrous magnesium sulphate and filtered. When organic was dried and the organic layer was filtered. The filtrate contained our desired product. The solvent was removed under vacuum to get a pure product **(58d)** in yellow oil form of in 96% yield as shown in **scheme 3.1**.



Scheme 3.1: General scheme of propargylamine **(58d-f)** synthesis

3.4.1 Synthesis of *N*-(1, 3-diphenylprop-2-yn-1-yl) aniline by benzaldehyde (58d)

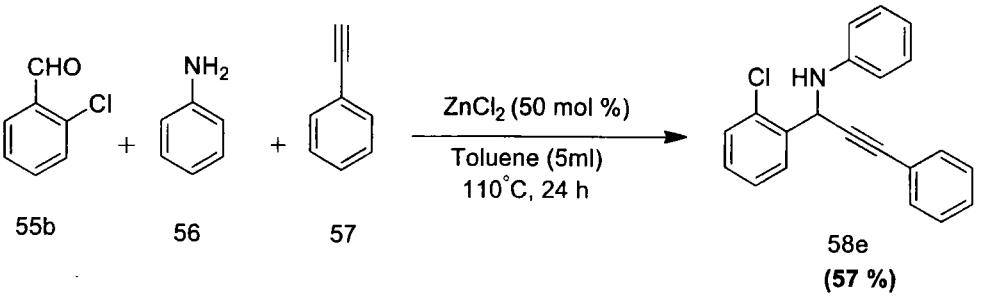
For the synthesis 58d, General procedure was followed by dissolving for the synthesis of propargylamine (58d-f) was followed by dissolving benzaldehyde **(56a)** (1mmol) as an aldehyde, aniline **(55)** (1mmol) as amine, and phenylacetylene **(57)** (1mmol) in toluene as solvent in the presence of $ZnCl_2$ (50 mol%) as shown in scheme 3.2. The reaction was monitored by TLC. After completion solvent extraction was performed, organic layer was separated, dried with anhydrous magnesium sulphate, filtered out, and solvent was evaporated under the in solvent in a fuming hood. Then the final product, *N*-(1, 3-diphenylprop-2-yn-1-yl) aniline (58d) was obtained as yellow oil in 96% yield. After that, the compound was characterized by FTIR and GCMS.



Scheme 3.2: Synthesis of *N*-(1, 3-diphenylprop-2-yn-1-yl) aniline (58d) using A^3-coupling

3.4.2: Synthesis of *N*-(1-(2-chlorophenyl)-3-phenylprop-2-yn-1-yl) aniline (58e)

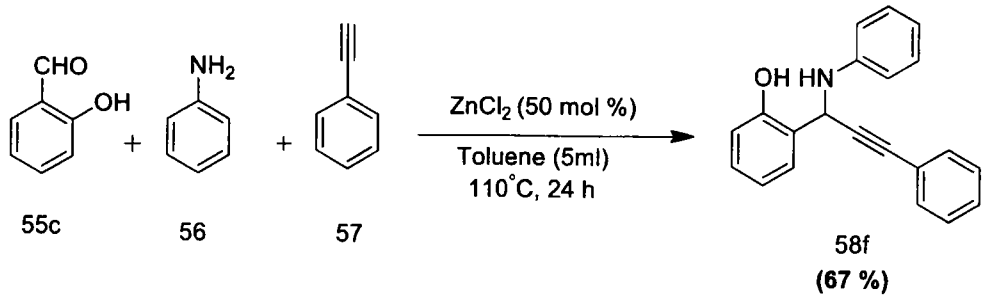
A general procedure was used to synthesize propargylamine **(58e)** by using 2-chlorobenzaldehyde **(55b)** (1 mmol) as a source of aldehyde, aniline **(56)** (1 mmol), and phenyl acetylene **(57)** (1 mmol) in the presence of $Zncl_2$ as catalyst and toluene as solvent. After refluxing for 24 hour at 110 °C the reaction mixture was monitored by TLC using the solvent mixture n-hexane: EtOAc (7:3). After optimizing, the general procedure was followed to get the final product **(58e)** in a light yellow color of yield **(57%)** as shown in **scheme 3.3**.



Scheme 3.3: Synthesis of *N*-(1-(2-chlorophenyl)-3-phenylprop-2-yn-1-yl) aniline **(58e)** by 2-chlorobenzaldehyde (A3-Coupling)

3.4.3: Synthesis of 2-(3-Phenyl-1-(phenylamino) prop-2-yn-1-yl) phenol (58f)

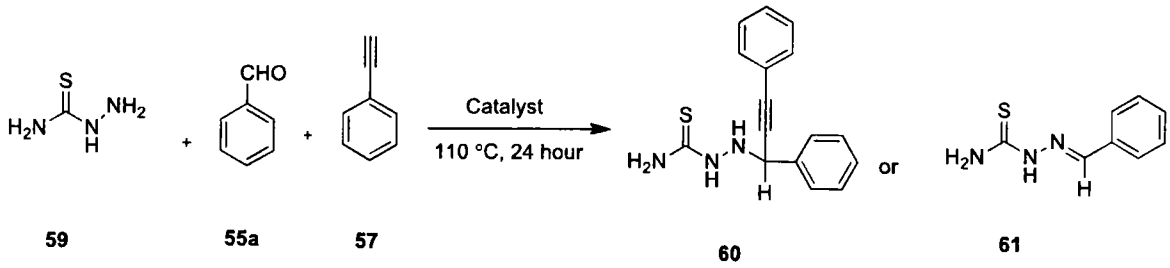
General procedure was used to synthesize **(58f)** by dissolving 2-hydroxyenzaldehyde (1mmol) **(55c)** as an aldehyde, aniline **(56)** as an amine and phenylacetylene **(57)** (1mmol) as alkyne in toluene (10 ml) as a solvent in the presence of ZnCl2 (50mol %) as a catalyst as shown in scheme 3.4. After 24 hours of refluxing, the reaction mixture was monitored by TLC using the solvent mixture DCM: EtOAc (9:1). After completion, solvent extraction was done using DCM and water, organic layer was separated dried with anhydrous magnesium sulphate and filtered out. The solvent was evaporated by rotary evaporation and our final product, 2-(3-Phenyl-1-(phenylamino) prop-2-yn-1-yl) phenol **(58f),** was obtained in a black oily form with yield **(67 %)** and further characterized by FTIR and GCMS.



Scheme 3.4: Synthesis of 2-(3-Phenyl-1-(phenyl amino) prop-2-yn-1-yl) phenol **(58f)** by 2-hydroxyenzaldehyde (A^3-coupling)

3.5 Synthesis of *N*-thiourea propargylamine by using different catalysts

In this series, the main focus was to discover the best catalyst that gave the highest yield for the synthesis of *N*-thiourea propargylamine **(60).** General scheme of methodology was followed, with thiosemicarbazide **(59)** as source of amine, benzaldehyde **(56a)** as an aldehyde, and phenylacetylene **(57)** as an alkyne. According to general scheme for synthesizing the main product, thiosemicarbazide (1mmol) and benzaldehyde (1mmol) were dissolved in toluene (10 ml) and continued stirring for 30 minutes. After 30 minutes, phenylacetylene **(57)** (1mmol) and different catalysts in different mol % were used to form metal acetylide. Then, the temperature was adjusted to 110 °C to reflux the reaction mixture for 24 hours. After refluxing for 24 hours, reaction mixture was monitored by TLC, by using different solvent mixtures. After optimizing the reaction mixtures solvent extraction is done by using ethyl acetate as an organic solvent and water as an aqueous media. After extracting three times, the organic layer was separated and is then dried with anhydrous magnesium sulphate, which absorbs the water. After that organic layer was filtered out, the filtrate containing solvent was evaporated using a rotary evaporator. The pure product was obtained as shown in **scheme 3.5,** which was further characterized by using FTIR, GCMS.

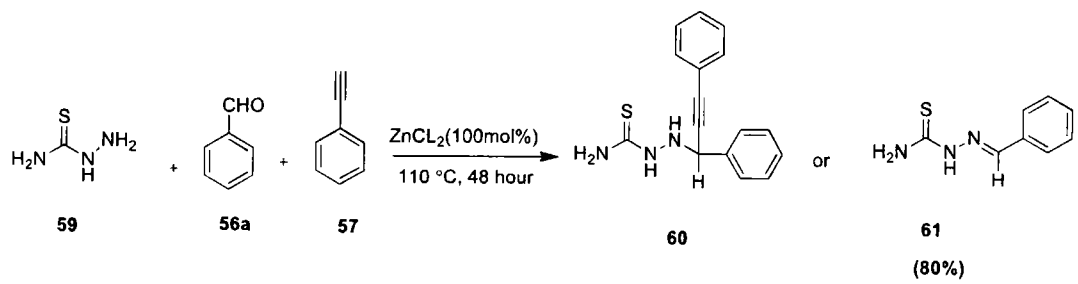


59 55a 57 60 61

Scheme 3.5: General scheme of synthesis of hydrazine carbothioamide **(61)** product

3.5.2 Synthesis of N-thiourea propargylamine by using $ZnCl_2$

General scheme of reaction was followed for the synthesis of *N*-thiourea propargylamine by using thiosemicarbazide **(59)** benzaldehyde, and phenylacetylene **(57)** in the presence of $ZnCl_2$ as catalyst in toluene (10ml). First of all, thiosemicarbazide (1mmol) and benzaldehyde were dissolved in toluene and stirred for half an hour. After half an hour of stirring, phenylacetylene **(57)** (1mmol) was added in the presence of $ZnCl_2$ as catalyst to form the zinc acetylide. Then temperature was adjusted to 110 °C to reflux the reaction mixture for 48 hours. After refluxing for 48 hours, reaction mixture was monitored by TLC, by using different solvent mixture. After optimizing the reaction mixtures solvent extraction was done by using ethyl acetate as organic solvent and water as aqueous media. After extracting for three times, the organic layer was separated and dried with anhydrous magnesium sulphate which absorbs the water. After that organic layer was filtered out, the filtrate containing solvent was evaporated using a rotary evaporator. The pure product **(61)** of **(80%)** yield is obtained as shown in **scheme 3.5**, which is further characterized by using FTIR as IR peaks 3390 cm^{-1} (N-H), 2923 cm^{-1} C-H, 1598 (C=N), 1450 cm^{-1} C=C aromatic, 1097 cm^{-1} (C=S).

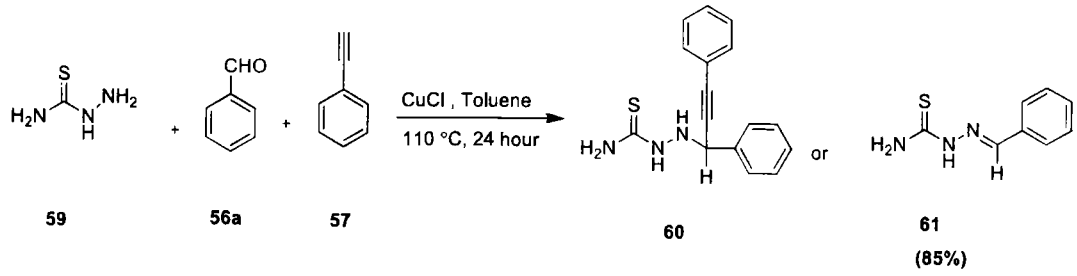


59 56a 57 60 61 (80%)

Scheme 3.5: General Synthesis of hydrazine carbothioamide **(61)** in the presence of $ZnCl_2$.

3.5.3 Synthesis of *N*-thiourea propargylamine by using CuCl

The *N*-thiourea propargylamine was synthesized by using general procedure of A^3-coupling with the help of thiosemicarbazide **(59)** (1 mmol), benzaldehyde **(56a)** (1 mmol), and phenylacetylene **(57)** (1 mmol) in toluene (10 ml). Toluene was first used to dissolve thiosemicarbazide (1 mmol) and benzaldehyde, which was then stirred for 30 minutes. After 30 minutes of stirring, phenylacetylene **(57)** (1 mmol) was added with CuCl (50 mol %) acting as a catalyst to synthesize copper acetylide. The reaction mixture was then refluxed for 24 hours at a temperature adjustment of 110 °C. TLC was used to monitor the reaction mixture after it had been refluxed for 24 hours. After optimizing the reaction mixture, Ethyl acetate, an organic solvent, and water, an aqueous medium, were used in solvent extraction. After three extractions, the organic layer was separated and dried using anhydrous magnesium sulphate. Following the extraction of the organic layer, the filtrate containing solvent was evaporated using a rotary evaporator. One gets the pure product **(61)** of **(85%)** yield as shown in **scheme 3.6**, further characterized by spectroscopic techniques such as FTIR, GCMS, ^{1}HNMR.



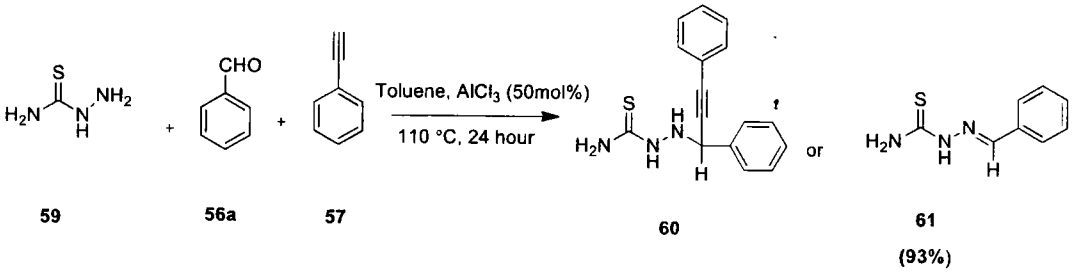
59 56a 57 60 61 (85%)

Scheme 3.6: General Synthesis of imine hydrazine carbothioamide in the presence of CuCl (A^3-Coupling)

3.5.4 Synthesis of N-thiourea propargylamine by using $AlCl_3$

The general scheme was followed to synthesize *N*-thiourea propargylamine **(60)** in toluene (10ml) utilizing thiosemicarbazide **(59)**, benzaldehyde **(56a)**, and phenylacetylene **(57)** in the presence of $AlCl_3$ as a catalyst. Toluene was initially utilized to dissolve thiosemicarbazide (1 mmol) and benzaldehyde, which follows by stirring for 30 minutes. Phenylacetyle **(57)** (1 mmol) was added after 30 minutes of stirring, and $AlCl_3$ (50 mol %) acts as a catalyst to synthesize acetylide. The

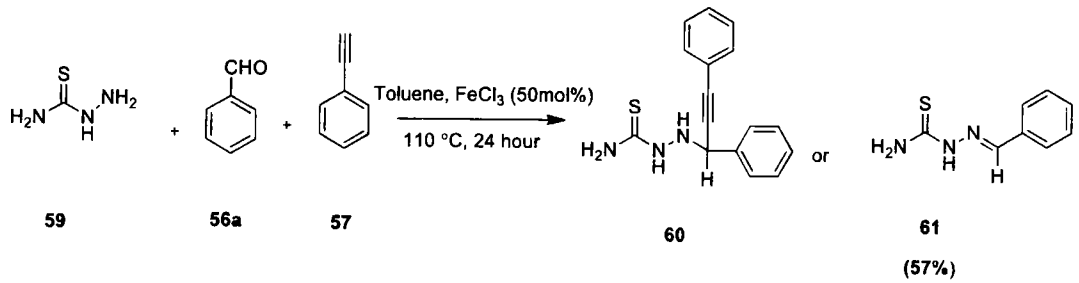
reaction mixture was then refluxed for 48 hours at a temperature of 110 °C. After being reheated for 24 hours, the reaction mixture was TLC-monitored while being used with various solvent mixtures. Using ethyl acetate as an organic solvent and water as an aqueous medium, solvent extraction was carried out once the reaction mixture had been optimized. The organic layer is separated and dried with anhydrous magnesium sulphate after three extraction cycles. The solvent-containing filtrate was evaporated using a rotary evaporator after the organic layer had been removed. It was possible to produce the pure product **(61)** of **(93%)** as shown in **scheme 3.6**, which was then further examined using FTIR and GCMS.



Scheme 3.6 General Synthesis of hydrazine carbothioamide **(61)** in the presence of $AlCl_3$.

3.5.5: Synthesis of N-thiourea propargylamine by using $FeCL_3$

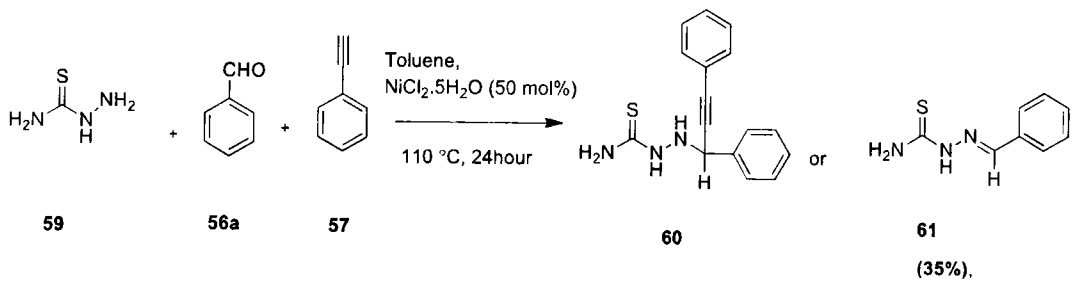
General scheme was followed for the synthesis of *N*-thiourea propargylamine **(60)** by using thiosemicarbazide **(59)**, benzaldehyde **(56a)**, and phenylacetylene **(57)** in the presence of $FeCl_3$ as catalyst in toluene (10ml). First of all, thiosemicarbazide (1mmol) and benzaldehyde were dissolved in toluene, and stirred for half an hour. After half an hour of stirring, phenylacetylene **(57)** (1mmol) was added in the presence of $FeCl_3$ (50 mol %) as a catalyst to form the acetylide. Then temprature was adjusted to 110 °C to reflux the reaction mixture for 48 hours. After refluxing for 48 hours, the reaction mixture was monitored by TLC, by using different solvent mixtures. After optimizing the reaction mixture solvent extraction was done by using ethyl acetate as an organic solvent and water as aqueous media. After extracting for 3 times, the organic layer was separated and dried with anhydrous magnesium sulphate which absorbs the water. After that organic layer was filtered out, the filtrate containing solvent was evaporated by using rotary evaporator. The pure product with **(57 %)** yield was obtained as shown in **scheme 3.7**, which was further characterized by using FTIR, GCMS.



Scheme 3.7: General Synthesis of hydrazine carbothioamide **(61)** in the presence of $FeCl_3$.

3.5.6: Synthesis of N-thiourea propargylamine by using $NiCl_2.6H_2O$

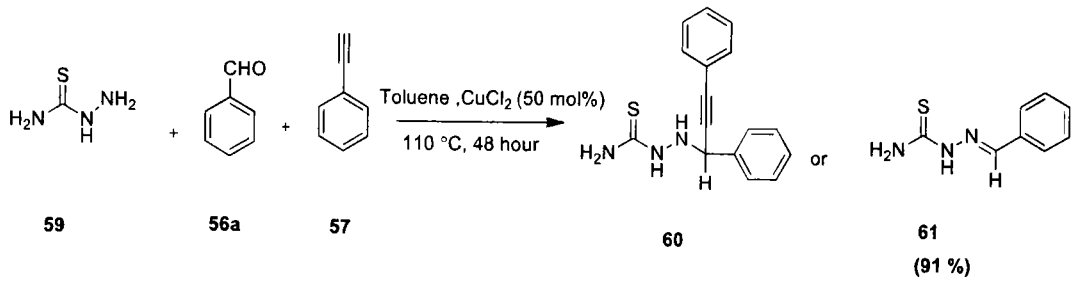
General scheme was followed for the synthesis of *N*-thiourea propargylamine by using thiosemicarbazide **(59)**, benzaldehyde **(56a)**, and, phenylacetylene **(57)** in the presence of $NiCl_2.6H_2O$ as catalyst in toluene (10ml). First of all, thiosemicarbazide (1mmol) and benzaldehyde (1mmol) were dissolved in toluene and stirred for half an hour. After half an hour of stirring, phenylacetylene **(57)** (1mmol) was added in the presence of $NiCl_2.6H_2O$ (50 mol %) as a catalyst to form the copper acetylide. Then the temperature was adjusted to 110 °C to reflux the reaction mixture for 24 hours. After refluxing for 24 hours, the reaction mixture was monitored by TLC, by using different solvent mixture. After optimizing the reaction mixture, solvent extraction was done by using ethyl acetate as organic solvent and water as aqueous media. After extracting for 3 times, the organic layer was separated and dried with anhydrous magnesium sulphate which absorbed the water. After that organic layer was filtered out, the filtrate containing solvent was evaporated using a rotary evaporator. The pure product **61** of **(35%)** yield was obtained as shown in **scheme 3.8** but the trace amount of product can't be further characterized.



Scheme 3.8: General Synthesis of hydrazine carbothioamide **(61)** in the presence of $NiCl_2.6H_2O$ (A^3-Coupling)

3.5.7: Synthesis of N-thiourea propargylamine by using $CuCl_2$

General scheme was followed for the synthesis of *N*-thiourea propargylamine **(60)** by using thiosemicarbazide **(59)**, benzaldehyde **(56a)**, and phenylacetylene **(57)** in the presence of $CuCl_2$ as catalyst in toluene (10ml). First of all, thiosemicarbazide (1mmol) and benzaldehyde was dissolved in toluene and stirred for half hour. After half an hour of stirring phenylacetylene **(57)** (1mmol) was added in the presence of $CuCl_2$ (50 mol %) as catalyst to form the copper acetylide. Then temperature was adjusted to 110 °C to reflux the reaction mixture for 24 hour. After refluxing for 48 hours, the reaction mixture is monitored by TLC, by using different solvent mixture. After optimizing the reaction mixture solvent extraction was done by using ethyl acetate as organic solvent and water as aqueous media. After extracting for 3 times, the organic layer was separated then was dried with anhydrous magnesium sulphate, which absorbs the water. After that organic layer is filtered out, the filtrate containing solvent was evaporated using a rotary evaporator. The pure product **(61)** was obtained **(91%)**, which was further characterized by using FTIR, GCMS. By spectroscopic techniques, it was confirmed that hydrazine carbothioamide **(61)** was formed as shown in **scheme 3.9** but **(60)** was not observed.

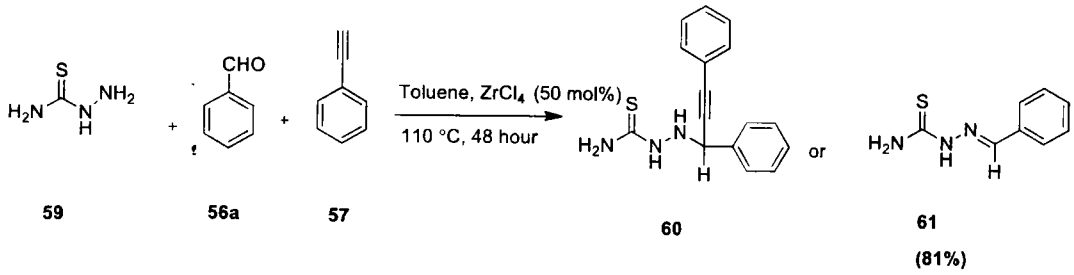


Scheme 3.9: General Synthesis of hydrazine carbothioamide **(61)** in the presence of $CuCl_2$.

3.5.8: Synthesis of N-thiourea propargylamine by using $ZrCl_4$

General scheme was followed for the synthesizes of *N*-thiourea propargylamine **(60)**, by using thiosemicarbazide **(59)**, benzaldehyde **(56a)**, and phenylacetylene **(57)** in the presence of $ZrCl_4$ as catalyst in toluene (10ml). First of all, thiosemicarbazide (1mmol) and benzaldehyde were dissolved in toluene to stir for half hour. After half an hour of stirring, phenylacetylene **(57)** (1mmol) was added in the presence of $ZrCl_4$ (50 mol %) as catalyst to form the acetylide. Then temprature was adjusted to 110 °C to reflux the reaction mixture for 48 hours. After refluxing for 48 hours, the reaction mixture was monitored by TLC, by using different solvent mixture. After

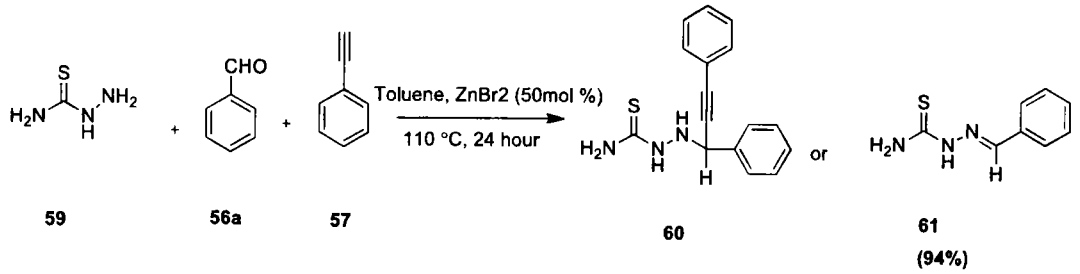
optimizing the reaction mixture, solvent extraction was done by using ethyl acetate as organic solvent and water as aqueous media. After extracting for three times, the organic layer was separated and then was dried with anhydrous magnesium sulphate which absorbs the water. After that organic layer was filtered out, the filtrate containing solvent was evaporated using a rotary evaporator. The pure product **(61)** is obtained, which was further characterized by using FTIR, GCMS. It was found that *N*-thiourea propargylamine (60) was not confirmed but hydrazine carbothioamide **(61)** of yield **(81%)** was formed as shown in **scheme 3.10**.



Scheme 3.10: General Synthesis of hydrazine carbothioamide **(61)** in the presence of $ZrCl_2$.

3.5.9: Synthesis of N-thiourea propargylamine by using $ZnBr_2$

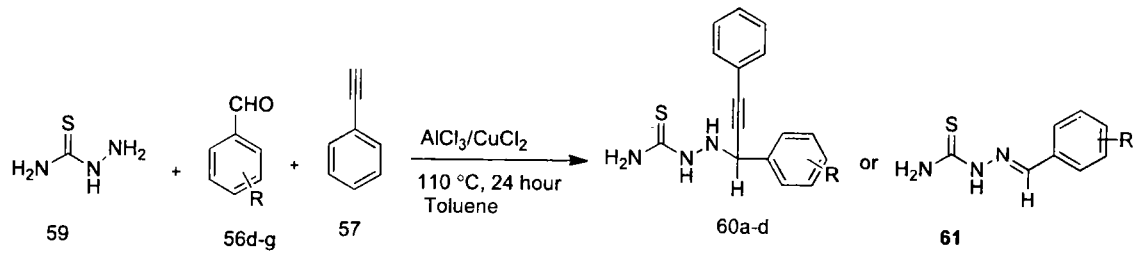
General scheme was followed for the synthesizes of *N*-thiourea propargylamine **(60)**, by using thiosemicarbazide **(59)**, benzaldehyde **(56a)**, and phenylacetylene **(57)** in the presence of $ZnBr_2$ as catalyst in toluene (10ml). First of all, thiosemicarbazide (1mmol) and benzaldehyde were dissolved in toluene to stir for half hour. After half an hour of stirring, phenylacetylene **(57)** (1mmol) was added in the presence of $ZnBr_2$ (50 mol %) as catalyst to form the zinc acetylide. Then temperature was adjusted to 110 °C to reflux the reaction mixture for 24 hours. After refluxing for 24 hours, the reaction mixture was monitored by TLC, by using different solvent mixture. After optimizing the reaction mixture solvent extraction was done by using ethyl acetate as organic solvent and water as aqueous media. After extracting for 3 times, the organic layer was separated then is dried with anhydrous magnesium sulphate which absorb the water. After that organic layer was filtered out, the filtrate containing solvent was evaporated using a rotary evaporator. The pure product **(61)** of **94%** yield as shown in **scheme 3.11**, which is further characterized by using FTIR, GCMS.



Scheme 3.11: General Synthesis of hydrazine carbothioamide **(61)** in the presence of $ZnBr_2$.

3.6 Synthesis of *N*-thiourea propargylamine by using different benzaldehye derivatives

In this series different benzaldehyde derivatives were used for the synthesis of propargylamine derivatives. General methodology was followed for the synthesis of propargylamine derivative 60a-d as shown in **Scheme 3.11**.

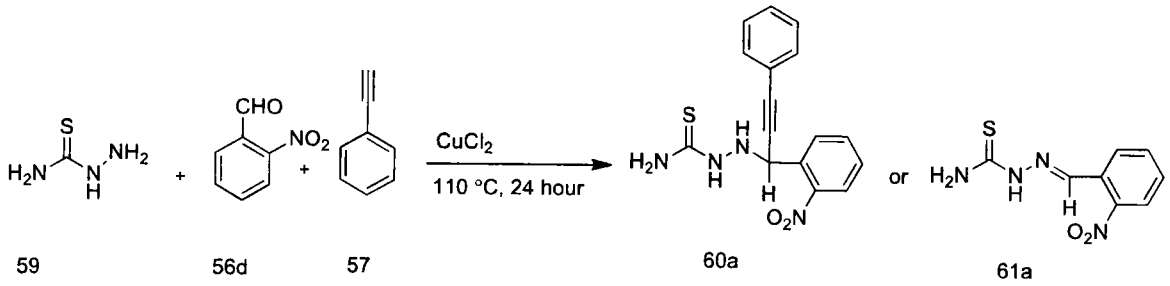


Scheme 3.11: General Synthesis of *N*-thiourea propargylamine synthesis by Aldehyde derivatives

3.6.1 Synthesis of *N*-thiourea propargylamine by 2-Nitrobenzaldehyde

First of all, 3-Nitrobenzaldehyde and thiosemicarbazide were dissolved in toluene (10ml) and stirred for 30 minutes. After stirring, phenylacetylene **(57)** (1mmol) and $CuCl_2$ (50 mol %) added to the reaction mixture and started refluxing for 24 hours. After refluxing for 24 hours, the reaction mixture was monitored by TLC DCM: EtOAc in 9:1. After optimizing, solvent extraction was done by using ethyl acetate and H_2O, organic layer was separated and dried using anhydrous magnesium sulphate. After filtration, the solvent was evaporated under vacuum so pure product as shown in **Scheme 3.12**is obtained which was characterized by FTIR had IR peaks 3424 cm^{-1} (N-

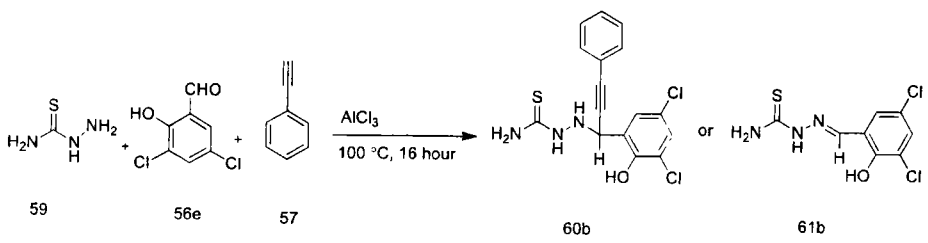
H), 3244 cm-1 N-H, 3154 cm-1 C-H Ar, 2979 cm-1 C-H, 1514 cm-1 (C=N), 1541 cm-1 and 1329 cm-1 NO_2, 1602 cm-1 and 1471 cm-1 C=C aromatic, 1102 cm-1 (C=S).



Scheme 3.12: Synthesis of compound **(61a)** by 3-Nitrobenzaldehyde (A^3-Coupling).

3.6.2 Synthesis of *N*-thiourea propargylamine by 3, 5-Dichlorosalicylaldehyde

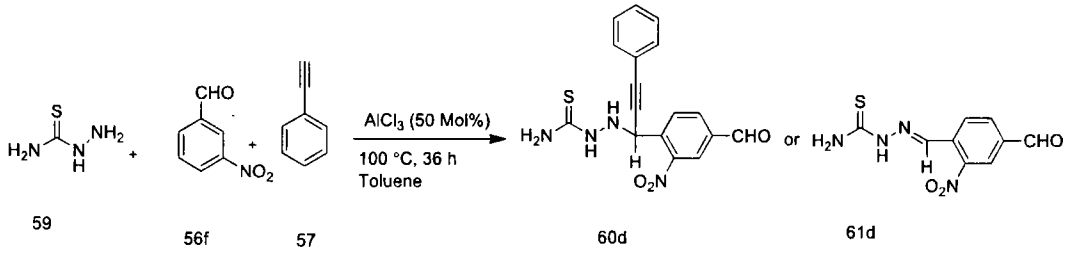
First of all, 3, 5-Dichlorosalicylaldehyde and thiosemicarbazide were dissolved in toluene (10ml) and stirred for 30 minutes. After stirring, phenyl acetylene **(57)** (1mmol) and $AlCl_3$ (50 mol %) added to reaction mixture and started refluxing for 16 hours. After refluxing for 16 hours, the reaction mixture was monitored by TLC n-Hexane: EtOAc in 7:3. After optimizing, solvent extraction was done by using ethyl acetate and H_2O. Organic layer was separated and dried using anhydrous magnesium sulphate. After filtration, the solvent was evaporated under vacuum so pure product was obtained which is characterized by FTIR had IR Peaks 3454 cm^{-1} (O-H), 3349 cm^{-1} N-H, 1595 cm^{-1} (C=N), 1527 cm^{-1} C=C aromatic, 1219 cm^{-1} C-O, 1150 cm^{-1} (C=S), 732 cm^{-1} C-Cl.



Scheme 3.13: Synthesis of compound **(61b)** by 3, 5-Dichlorosalicylaldehyde.

3.6.3 Synthesis of *N*-thiourea propargylamine by 3-Nitrobenzaldehyde

First of all, 3-Nitrobenzaldehyde and thiosemicarbazide were dissolved in DCM (10ml) and stirred for 30 minutes. After stirring, phenylacetylene **(57)** (1mmol) and $AlCl_3$ (50 mol %) were added to reaction mixture and started refluxing for 24 hours at 50 °C. After refluxing for 16 hours, the reaction mixture was monitored by TLC n-Hexane: EtOAc in 7:3. After optimizing, the solvent extraction was done by using ethyl acetate and H_2O, organic layer was separated and dried using anhydrous magnesium sulphate. After filtration, the solvent was evaporated under vacuum so pure product is obtained which was characterized by FTIR following IR peaks 3424 cm^{-1} (N-H), 3244 cm^{-1} N-H, 3154 cm^{-1} C-H Ar, 2979 cm^{-1} C-H, 1514 cm^{-1} (C=N), 1541 cm^{-1} and 1329 cm^{-1} NO_2, 1602 cm^{-1} and 1471 cm^{-1} C=C aromatic, 1102 cm^{-1} (C=S).

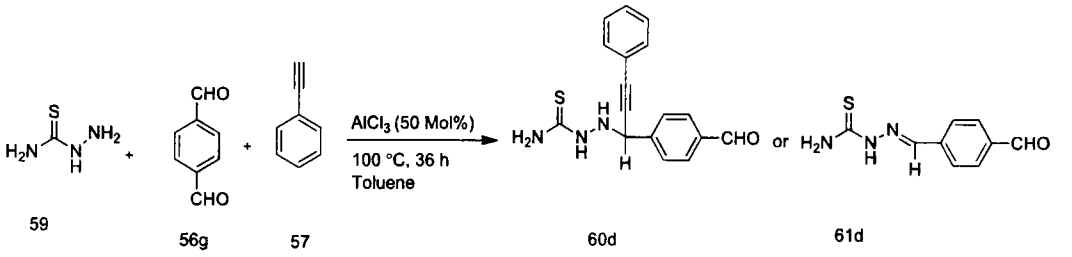


59 56f 57 60d 61d

Scheme 3.14: Synthesis of compound **(61c)** by 3-Nitrobenzaldehyde

3.6.4 Synthesis of *N*-thiourea propargylamine by Terptaldehyde

First of all, Terptaldehyde and thiosemicarbazide were dissolved in DCM (10ml) and stirred for 30 minutes. After stirring, phenylacetylene **(57)** (1mmol) and $AlCl_3$ (50 mol %) added in reaction mixture and started refluxing for 36 hours at 50°C. After refluxing for 16 hours, the reaction mixture was monitored by TLC n-Hexane: EtcOAc in 7:3. After optimizing, solvent extraction was done by using ethyl acetate and H_2O, organic layer was separated and dried using anhydrous magnesium sulphate. After filtration, the solvent was evaporated under vacuum so pure product was obtained which was characterized by GCMS, FTIR. It was confirmed by characterization that imine **(61d)** which is formed by **(56d)** and **(60d)** was observed.



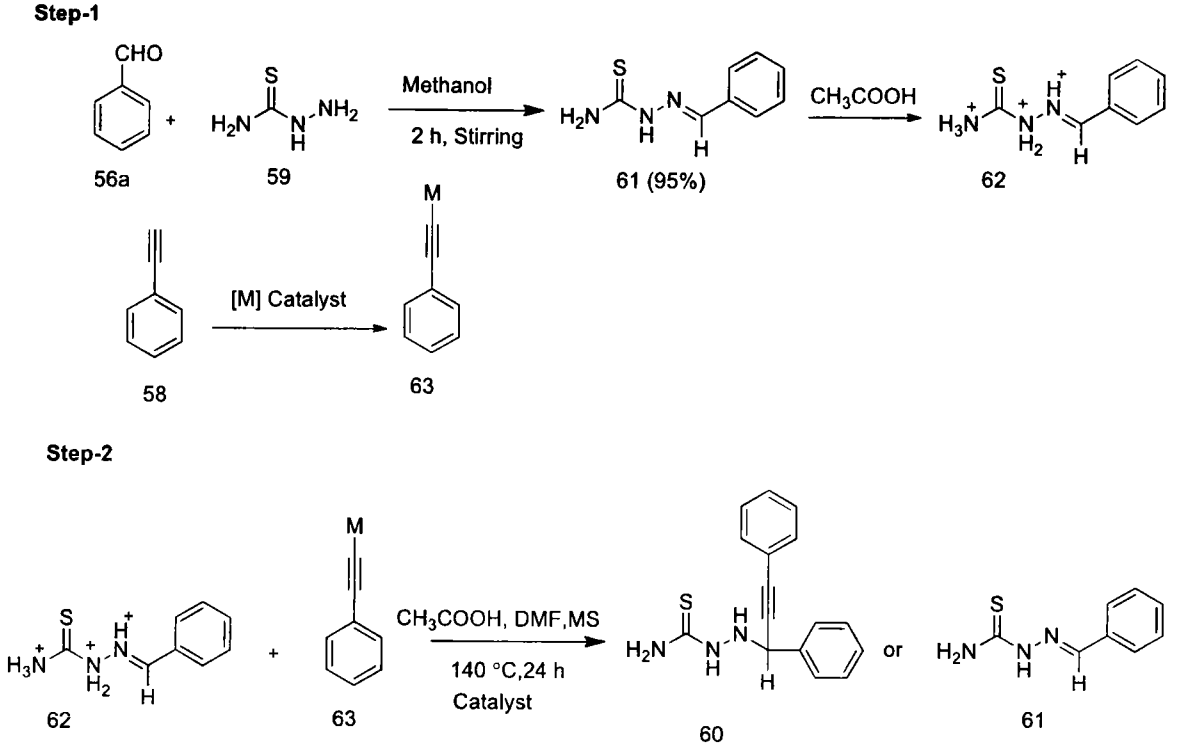
Scheme 3.15: Synthesizes of compound **(61d)** by Terptaldehyde.

3.7: Synthesis of *N*-thiourea propargylamine by modified method

After the XRD techniques, it was shown that imine was synthesized which was more stable to react with phenylacetylene **(57)**. In this series, the main focus was to remove hindrance and back donation by the protonation of thiosemicarbazone. For the back donate, acetic acid is used. Methodology was changed, first of all benzaldehyde (1mmol), and thiosemicarbazide (1mmol) dissolved in ethanol and stirring was continued for 1hour. After that, reaction mixture was monitored by TLC n-Hexane: EtOAc in 7:3. After optimization, imine was formed by comparing the TLC spot of this series product with series-ii. The reaction mixture was dissolved in ethylacetate, the solvent was evaporated and pure imine was synthesized. After imine synthesis, the reaction proceeds in two steps. In step-a, imine was dissolved in dry DMF (5ml) and 3 drops of acetic acid were added to the DMF. Acetic acid was used for protonation so that the iminium ion was formed. In separate round bottom flask, phenylacetylene **(57)** (1mmol) and $ZnBr_2$ and continue stirring for 30 minutes to synthesize zinc acetylide. After 30 minutes, step-b is proceed reaction mixture of iminium ion is poured down into zinc acetylide for refluxing 48 hours at 160 °C. After refluxing for 48 hour, the reaction mixture was monitored by TLC n-Hexane: EtOAc in in 7:3 ratio.

After optimization, the working was done by solvent extraction using ethylacetate and water. After 3 times of extraction, the organic layer was separated, dried with anhydrous magnesium sulphate and filtered. The filtrate contains the pure product. The solvent was evaporated using rotary evaporator. After solvent evaporation, the pure product was obtained which was characterized by FTIR, GCMS.

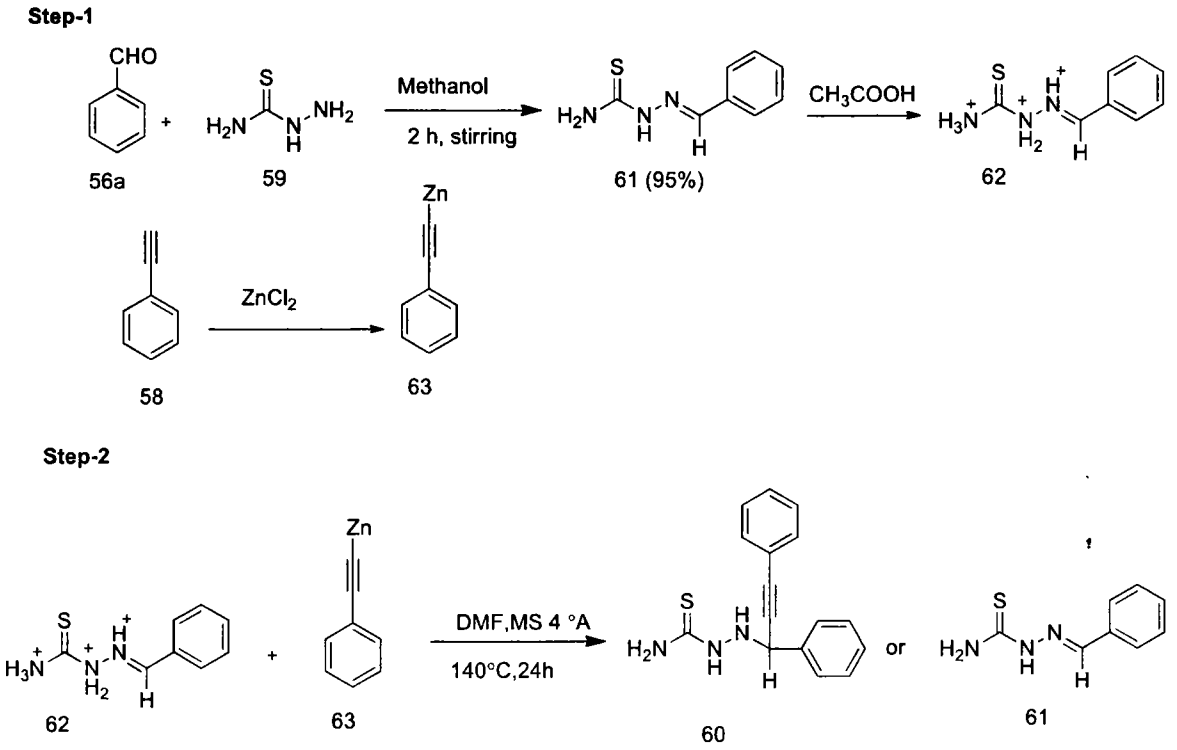
After characterization, it was confirmed that imine was present in final product but *N*-thiourea propargylamine was not observed.



Scheme 3.16 General scheme of Synthesis of *N*-thiourea propargylamine by hydrazine carbothioamide

3.7.1 Synthesis of *N*-thiourea propargylamine using preformed thiosemicarbazone and $ZnCl_2$

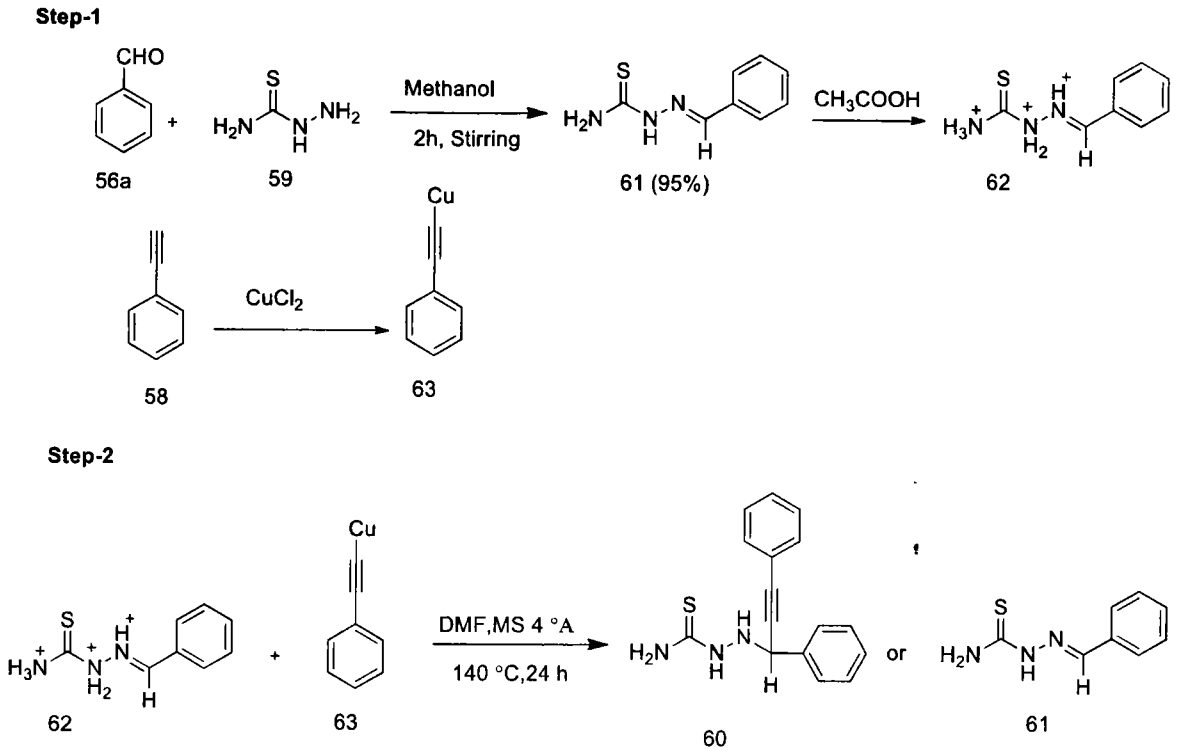
General methodology of series-iv was followed but in this reaction $ZnCl_2$ was used as catalyst for the synthesis of zinc acetylide. Zinc acetylide reacted with iminium ion to form the desired product **(60).** The pure product was further characterized by GCMS, FTIR which showed the presence of imine. After characterization, it was confirmed imine is present as final product **(61).**



Scheme 3.17: Synthesis of *N*-thiourea propargylamine by hydrazine carbothioamide in the presence of $ZnCl_2$

3.7.2: Synthesis of *N*-thiourea propargylamine by thiosemicarbazone in the presence of $CuCl_2$

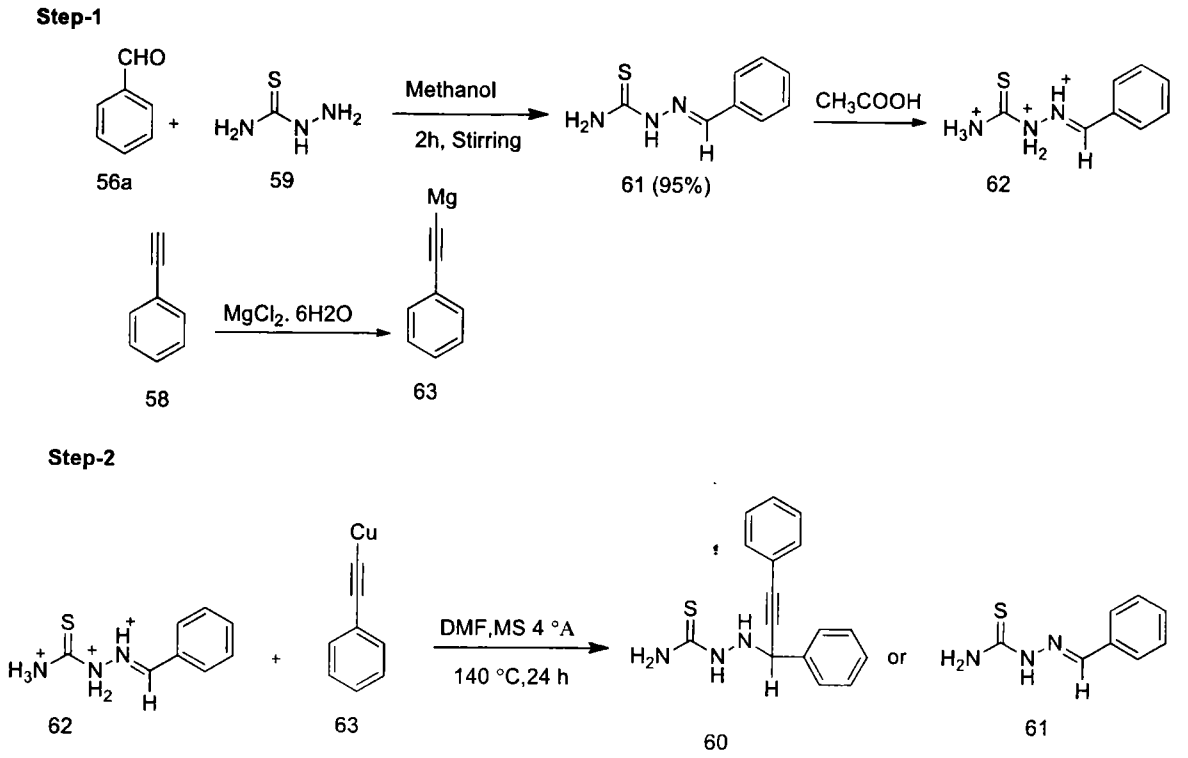
General methodology of series-iv was followed but in this reaction $CuCl_2$ was used as catalyst for the reaction with phenylacetylene **(57)** for the synthesis of copper acetylide. Copper acetylide reacted with iminium ion to form the desired product. The pure product was further characterized by GCMS, FTIR.



Scheme 3.18: Synthesis of hydrazine carbothioamide **(61)** in the presence of $CuCl_2$

3.7.3: Synthesis of *N*-thiourea propargylamine by thiosemicarbazone in the presence of $MgCl_2.6H_2O$

Grignard reagents was also used for the synthesis of metal acetylide. In step-a, $MgCl_2.6H_2O$ (50 mol %) and phenylacetylene **(57)** (1mmol) dissolved in DMF for the synthesis of magnesium acetylide. In this step imine was dissolved in DMF and 2 drops of acetic acid were add to make iminium ion. After step-a, the reaction mixture of iminium ion was dissolved in the magnesium acetylide for refluxing 24h. After refluxing, General methodology was followed for working to obtain pure product **(60)** but in this reaction also imine **(61)** was formed.

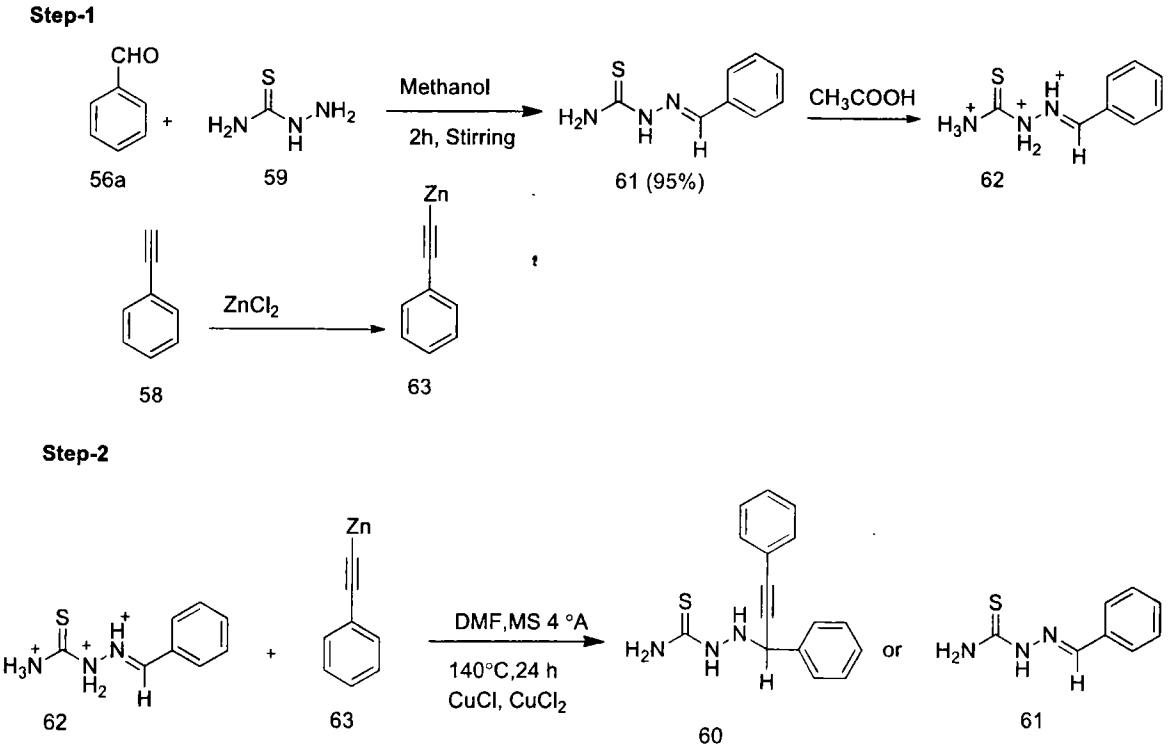


Scheme 3.19: Synthesis of Imine hydrazine carbothioamide **(61)** by In the presence of $MgCl_2.6H_2O$.

3.7.4 Synthesis of *N*-thiourea propargylamine by thiosemicarbazone in the presence of hybrid catalyst

In this method *N*-thiourea propargylamine was synthesized by using hybrid transition metal catalyst such as CuCl. $ZnCl_2$, $CuCl_2$. In step-1, the imine was prepared by using benzaldehyde (1mmol) and thiosemicarbazide (1mmol) in ethanol. After the imine synthesizing, imine was dissolved in Toluene (10ml) and 2 drops of sulphuric acid were added for the protonation of imine into iminium ion. After that phenylacetylene **(57)** (1mmol) and $ZnCl_2$ (10 m0l %) in toluene (5 ml) and continue stirring for 30 minutes. After stirring for 30 minutes, reaction mixture of iminium ion dissolved in the reaction mixture of zinc acetylide and continue refluxing for 48h. During refluxing other catalyst CuCl (10 mol %) and $CuCl_2$ (10mol %) were added and continue refluxing for 48h. After refluxing for 48h, reaction mixture was monitored by TLC in solvent mixture of n-hexane: EtOAc 7:3. After optimizing, solvent extraction was done by mixing 10 ml of ethyl acetate

and 20 ml of water in reaction mixture in separating funnel. After separation of organic layer, organic layer was dried by using anhydrous magnesium sulphate. After 10 minutes, filtration were done, the filtrate were poured down in china dish to evaporate the solvent. The solvent was evaporated under vacuum. After evaporation pure product was obtained which was further characterized by GCMS, FTIR.

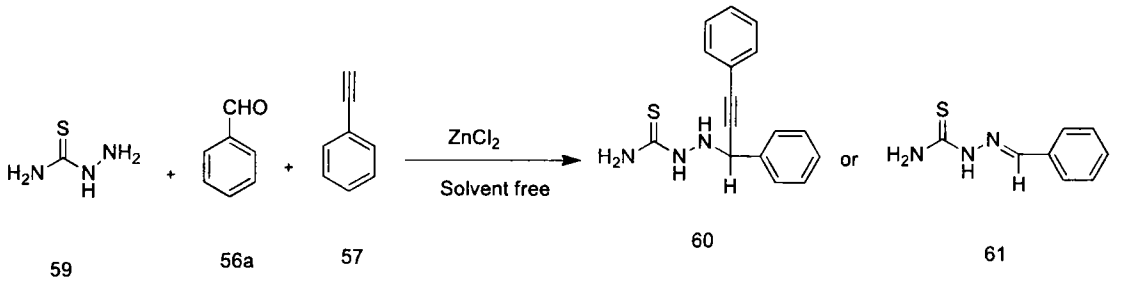


Scheme 3.20: Synthesis of hydrazine carbothioamide **(61)** In the presence of hybrid catalyst.

3.8 Synthesis of *N*-thiourea propargylamine under solvent free condition

N-thiourea propargylamine was synthesized under solvent free condition. First of all thiosemicarbazide (1mmol) and benzaldehyde (1mmol) were grinded. Phenlyacetylene **(57)** (1mmol) and $ZnCl_2$ (10 mol %) are grinded for 30 minutes. After that a paste of reaction mixture was obtained, which was monitored by TLC in solvent mixture of n-hexane: EtOAc 9:1. After optimizing, the solvent extraction was done by using ethyl acetate and water. Organic layer was separated and dried with anhydrous magnesium sulphate. After that, filtration was done and

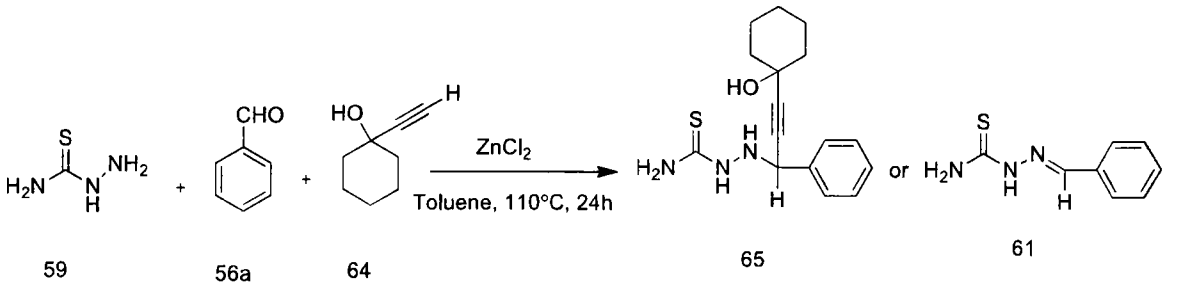
reaction mixture was taken in china dish, so that solvent is evaporated. After evaporation, pure product is obtained as shown in **scheme 3.21** which was characterized by GCMS, FTIR. After characterization, it was confirmed that imine **(61)** but desired product **(60)** was not obtained.



Scheme 3.21: Synthesis of hydrazine carbothioamide **(61)** under solvent free condition.

3.9 Synthesis of *N*-thiourea propargylamine by 1-ethynyl-1-cyclohexanol

In previous methodologies, we used phenylacetylene (57) as alkyne but unable to alkylation of imine, therefore we tried another alkyne, 1-ethynyl-1-cyclohexanol as alkyne. General scheme of mythology was followed for the synthesis of *N*-thiourea propargylamine by the reaction of thiosemicarbazide (59), benzaldehyde (56a), and 1-ethynyl-1-cyclohexanol (64) but just like previous one we obtained hydrazine carbothioamide **(61)** as evaluated in **Scheme 3.22**.

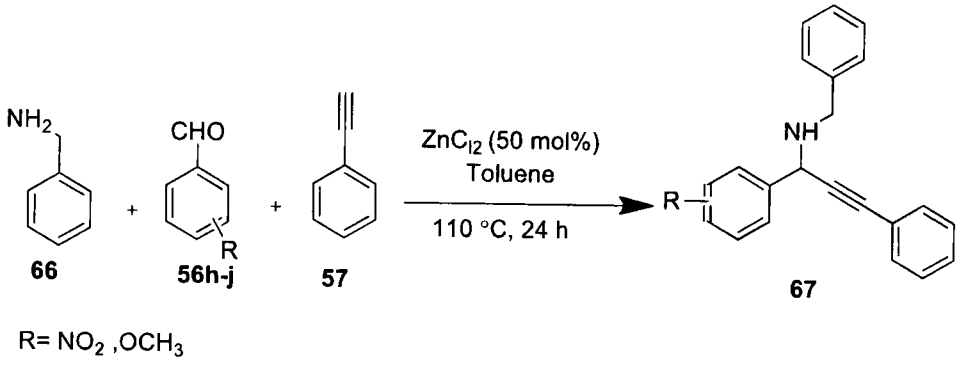


Scheme 3.22: Synthesis of hydrazine carbothioamide (61) by 1-ethynyl-1-cyclohexanol.

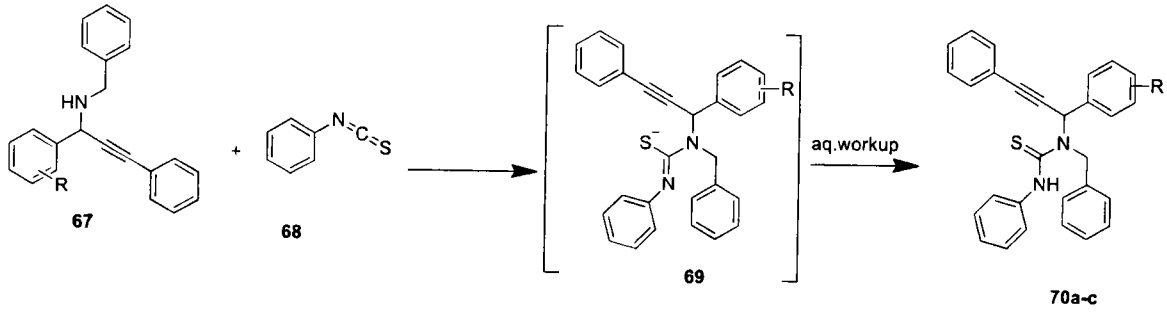
3.10 Synthesis of *N*-thiourea propargylamine by using phenylisothiocyanate

To get desired product a different strategy was adopted. In this synthetic pathway benzylamine **(66)** was used as primary amine First in this sequence, benzylamine **(66)** (1mmol), benzaldehyde **(56)** (1mmol), and phenylacetylene **(57)** (1mmol) were dissolved in toluene (10 ml) and allowed to reflux for 24 hours to produce propargylamine **(67)** as shown in scheme 3.22. The reaction

mixture was refluxed for 24 hours while being monitored by TLC in a solvent mixture of 9:1 n-hexane: EtOAc. For workup, EtoAc and H_2O were used to do the solvent extraction. The organic layer was separated and dried with anhydrous magnesium sulphate following the three times extraction. After filtration, the reaction mixture was placed in a china dish to allow the solvent to evaporate slowly. After evaporation, pure product propargylamine **(67)** was obtained. After obtaining pure propargylamine 65, was dissolved in toluene (15 ml) and stirred for 15 minutes. After that, 1 mmol of phenylisothiocyanate **(68)** was added to the reaction mixture, and the mixture was then allowed to reflux for 24 hours at 110 °C as shown in scheme 3.23. After refluxing, the reaction progress was monitored by TLC using an n-hexane: EtOAc (9:1) solvent mixture. After workup, the organic layer was separated and solvent was evaporated under a vacuum. The result was a pure substance that was further examined using FTIR. The resulting product was characterized by FTIR having IR peaks such as C≡C on 2052 cm^{-1}, Ar C=C 1602 cm^{-1}, C-H (2854 cm^{-1}) (Secondary amines N-H (2923and 2856 cm^{-1}), C-N (1274 cm^{-1}), C=S (1071 cm^{-1}).



Scheme 3.22: Synthesis of propargylamine 65 using benzylamine



Scheme 3.23 Synthesis of *N*-thiourea propargylamine using phenylisothiocyanate.

Chapter 4

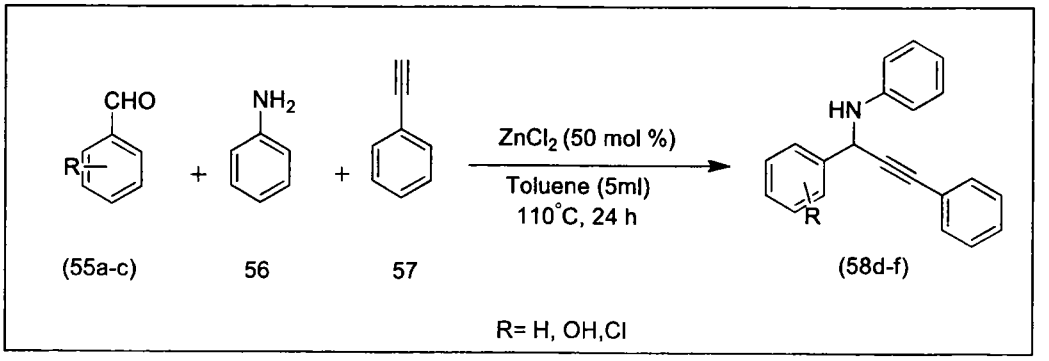
Results and Discussion

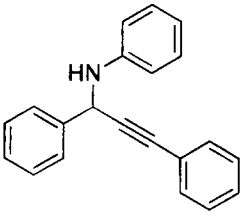
Results and Discussion

Present work is an attempt for the synthesis of *N*- thiourea propargylamine by A^3-coupling. A^3-coupling basically involves the one-pot condensation of aldehyde, amine, and alkyne. Synthesis of *N*-thiourea propargylamine was tried by using different catalysts and different solvents.

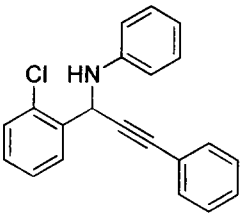
4.1 Synthesis of simple Propargylamine using Aniline (58d-f)

In Series-I, propargylamine was synthesized by using aniline (55) as amine, Aldehyde derivatives (56 a-c) and phenylacetylene 57 as alkyne. In this series propargylamine derivatives (58d-f) were synthesized by using three aldehydes derivatives (55a-c) such as 2-chlorobenzaldehyde, 2-hydroxybenzaldehyde, aniline (56) and phenylacetylene **(57)** in the presence of $ZnCl_2$ as catalyst and toluene as solvent under different reaction conditions as shown in scheme 4.1. All these reagents were refluxed for 5-24 h. The progress of the reaction was continuously monitored by TLC (on pre-coated aluminium sheets) using solvent system, n-hexane: ethylacetate (9:1) as mobile phase. After the completion of the reaction, the solvent extraction was performed by using ethylacetate as organic solvent and distilled water for the aqueous media. After solvent extraction, organic layer was separated and dried with anhydrous magnesium sulphate, filtered and solvent was evaporated under the under reduced pressure to afford a pure product. Different aldehydes were used in first synthetic series of propargylamine as substituted benzaldehye, 2-chlorobenzaldehyde, and 2-hydroxybenzaldehyde as given below in **scheme 4.1**.

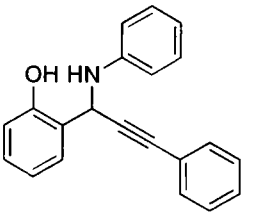




58d



58e



58f

Scheme 4.1: Synthesis of simple propargylamine by using aniline.

Table 4.1: Physical data of Propargylamine **(58d-f).**

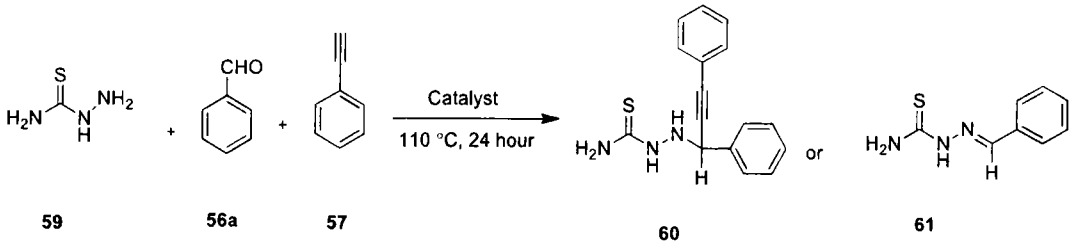
Compound	Physical state	Molecular Formula	Molecular Weight (g/mol)	R (*n*-hexane:EtOAc (9:1)	Y.ield (%)
58d	Yellow Oil	$C_{21}H_{17}N$	283	0.56	96
58e	Light yellow Oil	$C_{21}H_{16}ClN$	317	0.58	57
58f	Black Oil	$C_{21}H_{17}NO$	299	0.61	67

4.2 Synthesis of *N*-thiourea propargylamine using thiosemicarbazide as amine partner

The synthesis of previous series was performed to get handy expertise for such compound. The original aim of this research was the synthesis of propargylamine using thiosemicarbazide as amine partner. For this purpose, extensive optimization was performed.

4.2.1 Optimization of catalyst and reaction condition for alkynylation of thiosemicarbazone

The major goal of this series was to identify the optimum catalyst that would produce the maximum yield of *N*-thiourea propargylamine using thiosemicarbazide. However, the thiosemicarbazide **(59)** as source of amine, benzaldehyde **(56a)** as the aldehyde, and phenylacetylene **(57)** as the alkyne were used according to A^3-mechanism as shown in **table 4.2**. Thiosemicarbazide **(59)** (1 mmol) and benzaldehyde **(56a)** (1 mmol) were dissolved in a toluene solution (10 ml) and stirred continuously for 30 minutes to produce imine. After 30 minutes, metal acetylide was synthesized using phenylacetylene **(57)** (1 mmol) and various catalysts at various mol%. The reaction mixture was then refluxed for 24 hours at a temperature of 110 °C. Following a 24-hour reflux, the reaction mixture was then TLC-monitored using various solvent mixtures. After the completion of reaction, solvent extraction was performed by using ethyl acetate as an organic solvent and water as an aqueous medium. The organic layer was separated after three extractions and dried with anhydrous magnesium sulfate. The filtrate containing solvent was evaporated using a rotary evaporator. After removal of solvent white fine crystals were obtained, which after single crystal X-ray diffraction study revealed the presence of thiosemicarbazone (61) as imine or Schiff base. While no alkynylation was observed. After that variety of catalysts were tested e.g. $ZnCl_2$ (Table 4.2, entry 1), CuCl (Table 4.2 entry, 2) in 50 mol% but TLC comparison showed presence of imine (61). Further $AlCl_3$ (100 mol %), $FeCl_3$ (50 mol %), $NiCl_2.6H_2O$ (50 mol %), $CuCl_2$ (50 mol %), $ZrCl_4$ (50 mol %), $ZnBr_2$ (50 mol %) were also tried.



Scheme 4.2: Synthesis of hydrazine carbothioamide 61 compound.

Table 4.2: Optimization using different catalyst

Entry	Catalyst (mol %)	Time (h)	Yield (%) 60/61
1	$ZnCl_2$ (50 mol %)	48	0/80
2	CuCl (50 mol %)	24	0/85
3	$AlCl_3$ (100 mol %)	24	0/93
4	$FeCl_3$ (50 mol %)	24	0/57
5	$NiCl_2.6H_2O$ (50 mol %)	24	0/35
6	$CuCl_2$ (50 mol %)	24	0/91
7	$ZrCl_4$ (50 mol %)	48	0/81
8	$ZnBr_2$ (50 mol %)	24	0/94

Different catalyst was utilized to obtain the *N*- Thiourea propargylamine but when the obtained product was characterized by spectroscopic techniques it was examined that imine was synthesized. It was then realized that no one catalyst was able to form *N*-thiourea propargylamine **(60)** but formed intermediate imine **(61)** of fine crystal. The imine **(61)** which was synthesized using different catalyst was characterized by IR ν_{max} (cm^{-1}): have N-H stretching on 3390 cm^{-1} which indicate the primary amine is present in final compound and C-H peak observed on 2923 cm^{-1} which showed the presence of C-H in the final compound, 1450 cm^{-1} indicated C=C aromatic which showed the presence of benzene ring in the final compound, C=S peak observed on 1097 cm^{-1} which showed that thio group in the final compound. C=N peak observed on 1598 cm^{-1} indicate the presence of imine in the final product which showed that final product imine **(61)** is synthesized as shown **figure 4.1.**

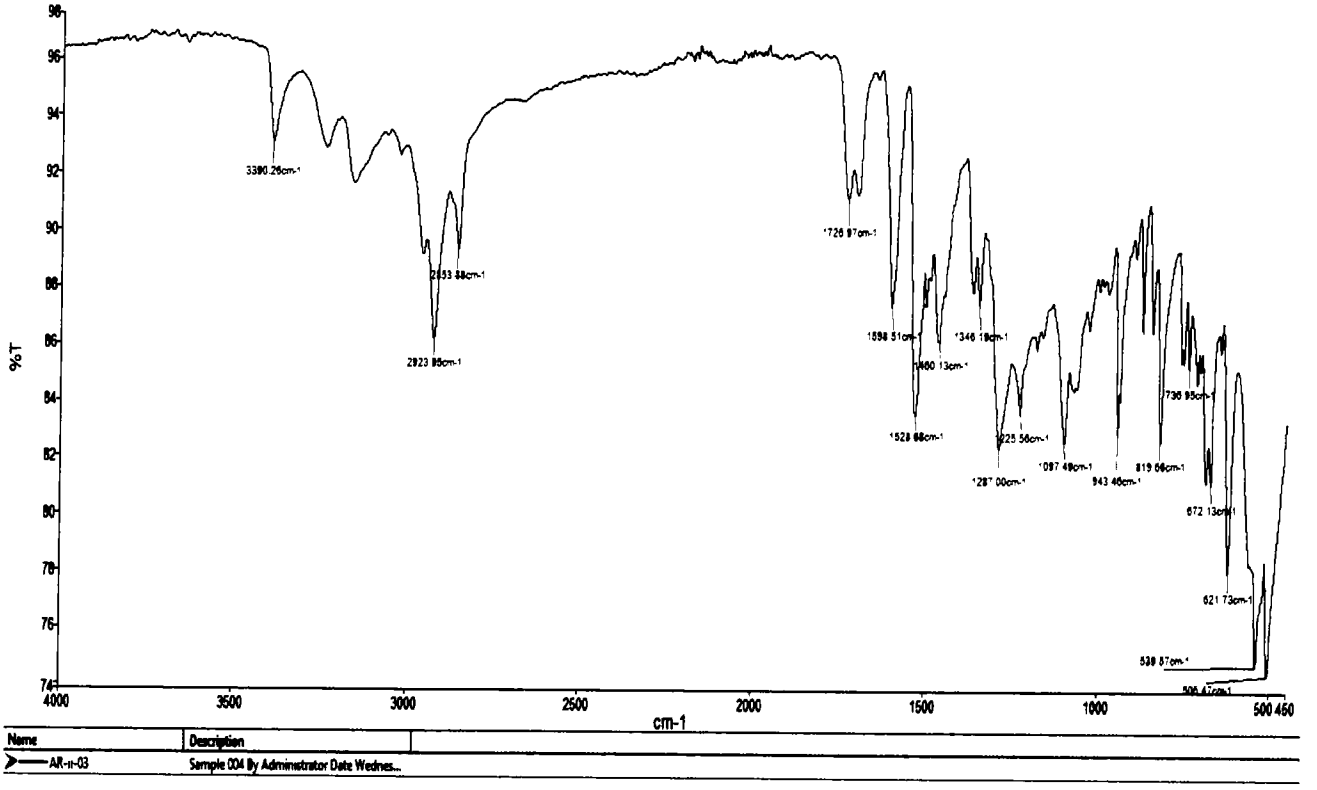


Figure 4.1: FTIR spectra of hydrazine carbothioamide **(61).**

Pure product was characterized by single crystal XRD which provide data about internal lattice of crystalline substance including bond length, bond angle, torsion angle, anisotropic atomic displacement, hydrogen bond distance. By observing the internal lattice of pure compound it's confirmed that hydrazine carbothioamide **(61)** was synthesized.

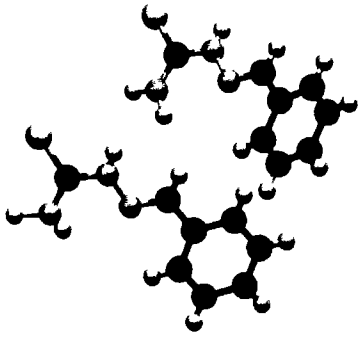
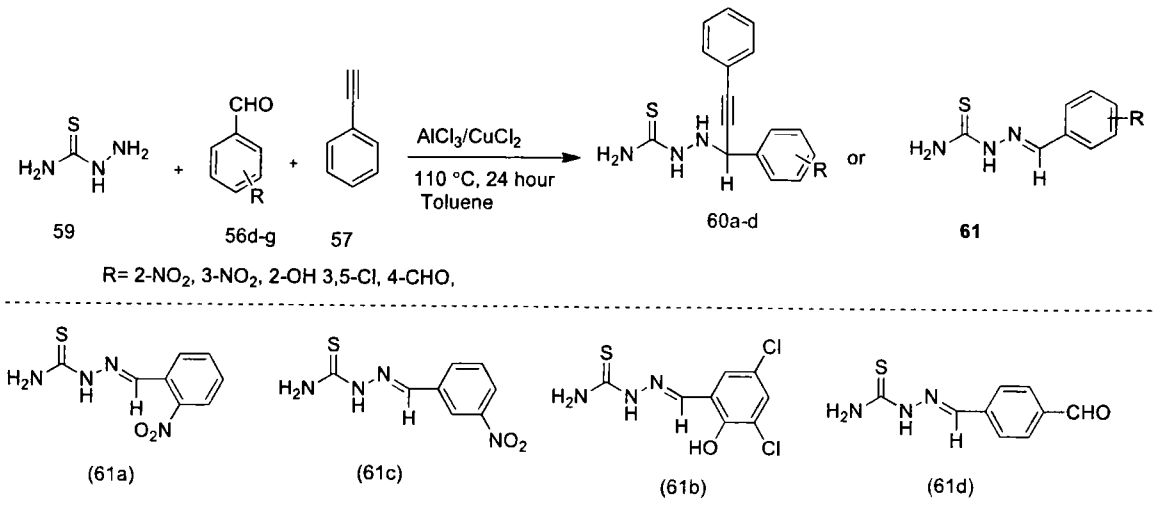


Figure 4.2: Structure of compound **(61)** by single crystal XRD.

4.3 *N*-thiourea Propargylamine synthesis using different aldehydes

In previous attempt different catalysts were utilized but no one able to form desired product **(61)**. In this series instead of benzaldehyde derivatives were used to obtain *N*-thiourea propargylamine derivatives using A^3-coupling mechanism as shown in scheme 4.3. For the synthesis of propargylamine derivatives in this series, several aldehyde derivatives (56d-g) were used according to A^3-coupling mechanism. General methodology of A^3-coupling mechanism was used in this series. Different *N*-thiourea propargylamine **(60a-d)** derivatives which are synthesized by single-pot condensation later characterized by GCMS, FTIR, ^{1}HNMR. After characterization, it was also confirmed by using different aldehydes was not beneficial for the desired product **(60a-d)** but liked previous work imine **(61a-d)** were formed because alkyne was not attached to the thiosemicarbazones **(61a-d)** as observed in **Scheme 4.3.**



Scheme 4.3: Synthesis of hydrazine carbothioamide hydrazine carbothioamide *derivatives* by using different aldehydes.

Table 4.3: Physical data of imine derivatives obtained using different aldehydes

Compound	Physical appearance	Molecular Weight (g/mol)	R_f *n*-hexane:EtOAC (9:1)	Yield imine (%)
61a	Yellow Solid	224	0.48	95
62b	Brick red Solid	262	0.54	85
62c	Yellow Solid	224	0.59	92
61d	Light Yellow	207	0.54	79

The presence of imine derivatives **(61a-d)** was confirmed by the FT-IR spectroscopic technique. Pure product **(61a)** was characterized by IR. have following peaks such as N-H peak on 3424 cm^{-1} which denote the presence of primary amine in our final product , Aromatic C-H peak observed on 3154 cm^{-1} which showed the presence of C-H in the benzene ring, C=C peak observed on 1471 cm^{-1} which showed the presence of benzene ring, C=N peak observed on the 1514 cm^{-1} which indicated the imine was synthesized in final compound, C=S peak observed on 1102 cm^{-1} which showed thio group on the basis of this it was synthesized by thiosemicarbazide as shown **Figure 4.3**.

By observing the following peaks, the peak 1514 cm^{-1} (C=N) indicate that imine (61a) was synthesized and peak at 1329 cm^{-1} indicate that imine was NO_2-substituted because it was synthesized by 3-nitrobenzaldehyde **(56d)**.

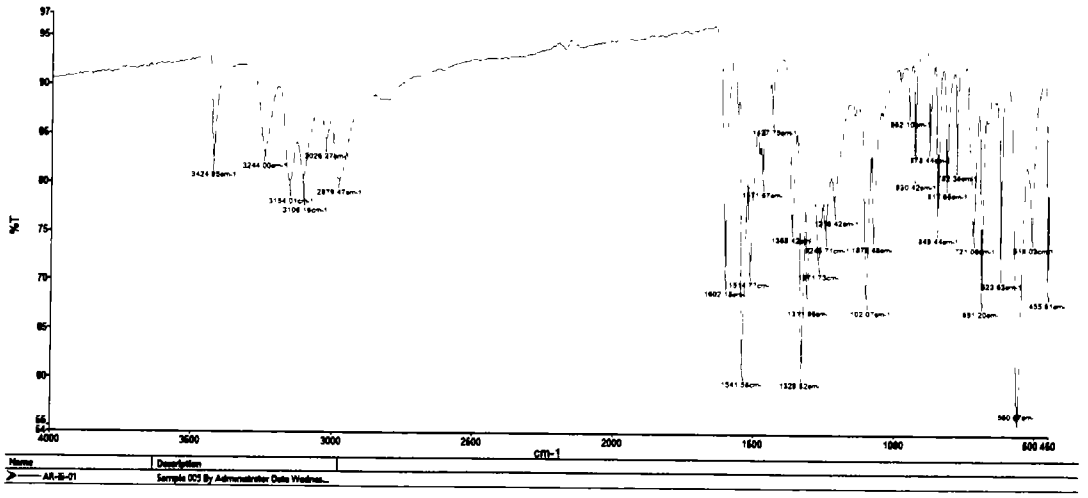


Figure 4.3: FTIR spectra of compound **61a**

The pure product **(61b)** which was synthesized by using 3, 5-dichloro salicylaldehyde was characterized by IR, v_{max} (cm^{-1}) contains following peaks O-H peak was observed on 3454 cm^{-1}, N-H peak observed on 3349 cm^{-1} which indicate that primary amine in the final compound, C=N peak observed on 1595 cm^{-1} which showed that imine was synthesized in final product, aromatic C=C observed on 1219 cm^{-1} showed benzene ring presence.

By observing the following peaks, the peak 1595 cm^{-1} (C=N) indicated that imine **(61b)** was synthesized and peaks at 3454 cm^{-1} (O-H), and 732 cm^{-1} (C-Cl). Indicated that imine **(61b)** was synthesized by 3, 5-dichloro salicylaldehyde **(56e)**.

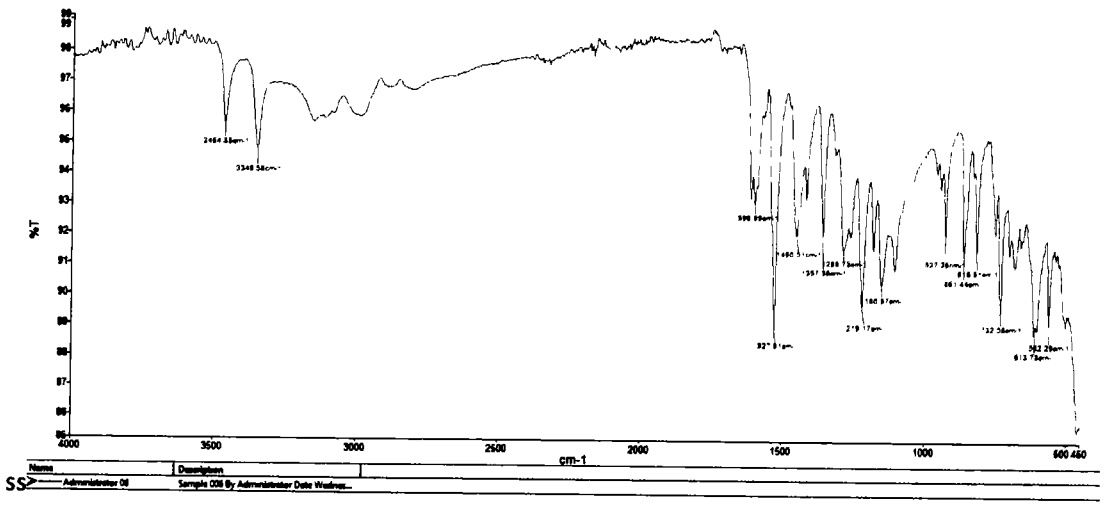
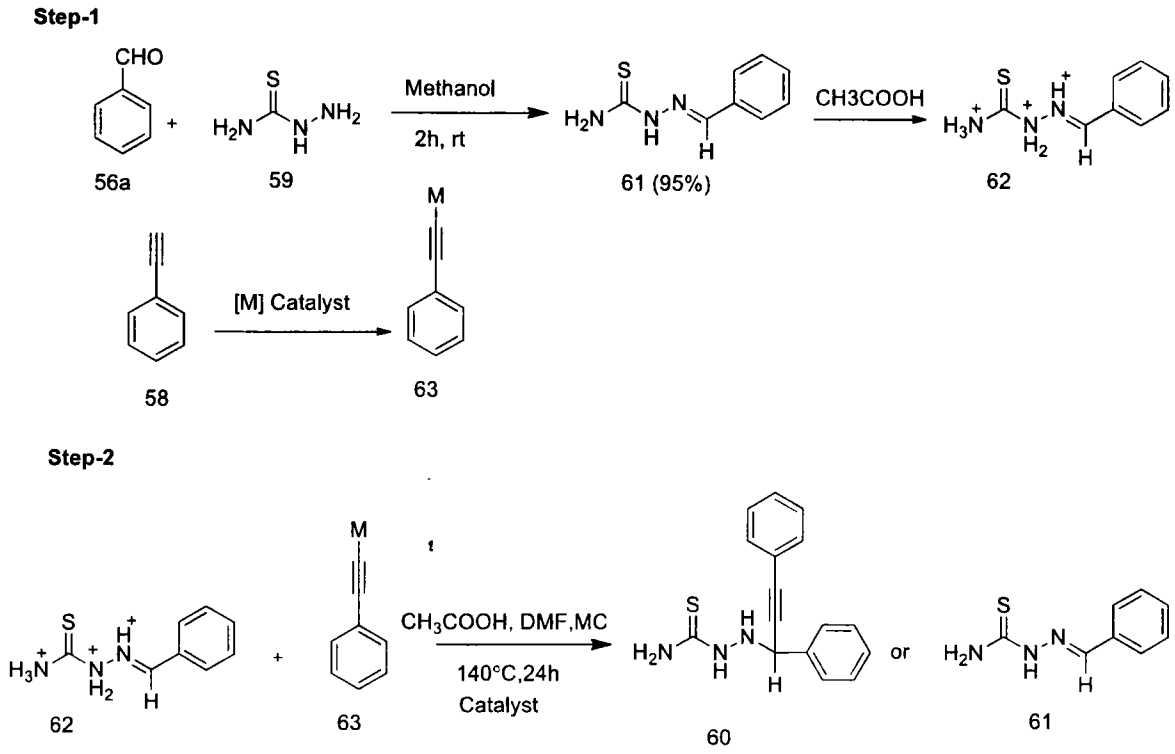


Figure 4.4: FTIR spectrum of compound **(61b).**

4.4 Modification in the synthetic method for *N*-thioureapropargylamine

In previous work, optimization of catalyst and different aldehydes derivatives was utilized by using one pot condensation mechanism of A^3-coupling but unable to obtained desired product N-thiourea propargylamine but by previous method stable imine **(61)** was formed because steric hindrance and back donation prevent phenylacetylene to attach to imine. In further working, synthetic method was modified by doing experiment in two steps.

The primary goal of this modification was to eliminate steric hindrance and back donation by thiosemicarbazone protonation. Acetic acid was utilized for the back donate. First, benzaldehyde (1 mmol) and thiosemicarbazide (1 mmol) were mixed in ethanol and stirred for an additional hour. After that, the reaction mixture was optimized using TLC with a 7:3 n-Hexane: EtOAc ratio. By comparing the TLC spot of this product with the previous imine **(61)** it was confirmed hat, imine **(61)** was synthesized in step-1. The pure imine **(61)** was dissolved in dry DMF (5ml), and the DMF was then mixed with 3 drops of acetic acid in order to form an iminium ion. In this step, $ZnBr_2$ (50 mol %) and phenylacetylene (1 mmol) were combined in a separate round-bottom flask, and the mixture was stirred for 30 minutes to synthesize zinc acetylide (63). Following step-2, iminium ion reaction mixture was put into zinc acetylide and allowed to reflux for 48 hours at 160 °C. The reaction mixture was monitored by TLC using a 7:3 n-Hexane: EtOAc ratio after refluxing for 48 hours. Solvent extraction was used to complete the process after optimization. Three repetitions of extraction result in the separation of the organic layer, which was then dried with anhydrous magnesium sulphate and filtered, resulting in the filtrate which contains the pure product. Rotary evaporators were used to evaporate the solvent. The pure product was collected and identified by FTIR and GCMS.



Scheme 4.4 General scheme of synthesis by imine **(61).**

Table 4.4: Physical data of *N*- thiourea propargylamine.

Entry	Catalyst	Solvent	Temperature °C	Time (h)	Yield (%) 60/61
1	$ZnCl_2$	DMF	140	24h	0/85
2	$CuCl_2$	DMF	140	24h	0/81
3	$MgCl_2.6H_2O$	Toluene	110	24h	0/67
4	$ZnCl_2$, CuCl2, CuCl	DMF	140	24h	0/91

After work up, obtained product was characterized by IR , ν_{max} (cm^{-1}): N-H peak obtained on 2921 cm^{-1} showed the presence of primary amine in the final product .C-H peak on 2852 cm^{-1} and C=C peak on 1451 cm^{-1} showed the presence of benzene ring in final product. C=S peak was observed

on 1097 cm^{-1} which showed that final product synthesized by thiosemicarbazide as shown in **Figure 4.5**.

After observing FTIR, the peak of C=N on 1598 cm^{-1} indicates that after modification of synthetic scheme desired product **(60)** was not obtained but just like above methodology intermediate **(61)** obtained.

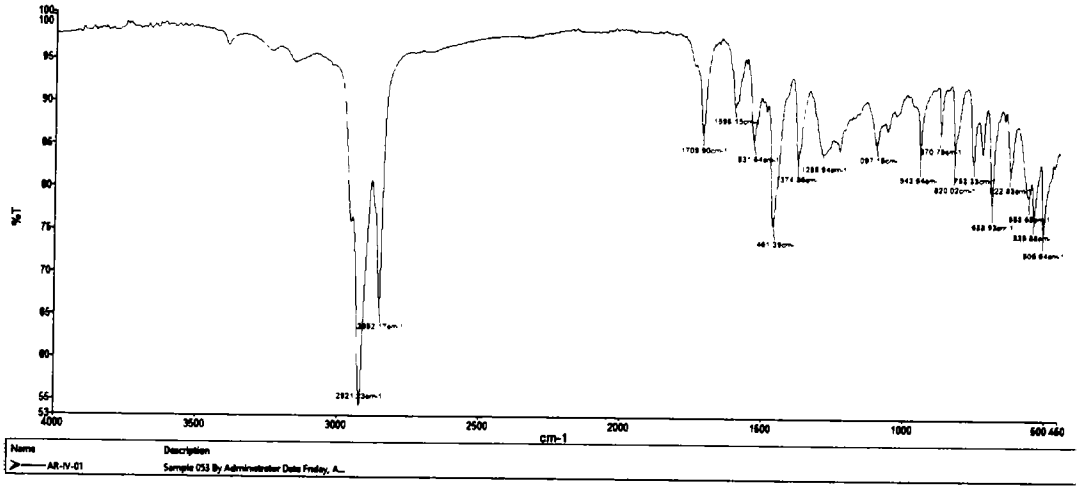
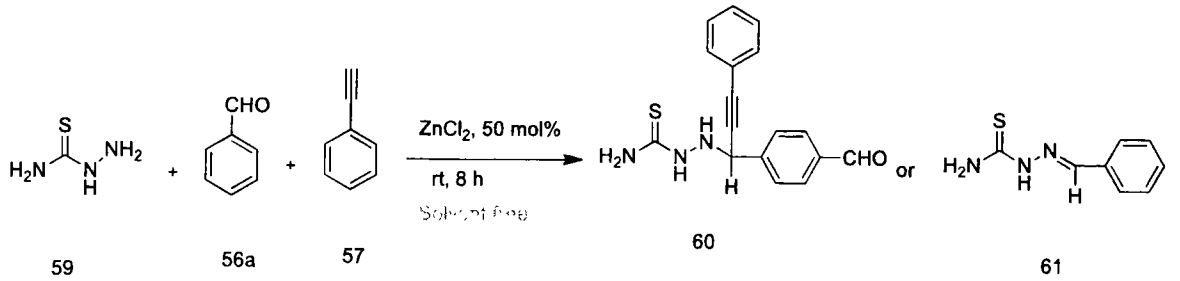


Figure 4.5: FT-IR characterization of **(61b)**

4.5 Synthesis of *N*-thiourea propargylamine under solvent free condition

Furthur methodology was changed toward solvent free condition to synthesize the desired product *N*-thiourea propargylame. Firstly, thiosemicarbazide **(59)** (1mmol) and benzaldehyde **(56a)** (1mmol) were grinded together. $ZnCl_2$ (10 mol %) and phenlyacetylene **(57)** (1 mmol) were ground for 30 minutes. A paste of the reaction mixture was then produced, and it was TLC-analyzed in a 9:1 mixture of n-hexane and ethylacetate solvent. Following optimization, ethylacetate and water were used to do the solvent extraction. Anhydrous magnesium sulphate was used dry the organic layer. Following filtering, the reaction mixture was placed in a china dish to allow the solvent to evaporate.

After obtaining pure product, TLC of this obtained product with imine **(61)** was analyzed in a 9:1 mixture of n-hexane and ethyl acetate solvent. It was optimized that in a solvent free mechanism: also imine (61) was obtained as observed in **Scheme 4.5**.

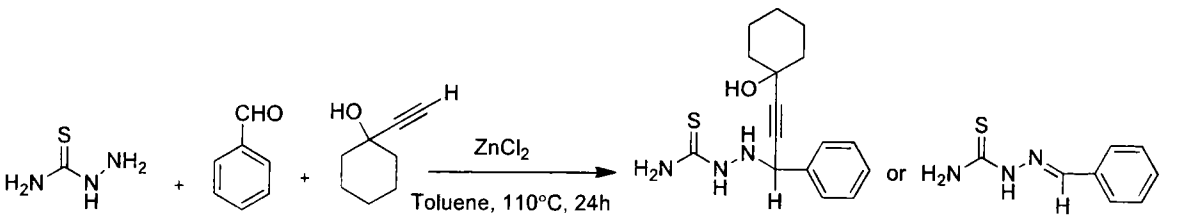


59 56a 57 60 61

Scheme 4.5: Synthesis of propargylamine by using solvent free conditions.

4.6 Synthesis of *N*-thiourea propargylamine by 1-ethynyl-1-cyclohexanol

In previous methodologies, we used phenylacetylene (57) as alkyne but unable to alkylation of imine, therefore we tried another alkyne, 1-ethynyl-1-cyclohexanol as alkyne. General scheme of mythology was followed for the synthesis of *N*-thiourea propargylamine as shown **Scheme 4.6** by the reaction of thiosemicarbazide (59), benzaldehyde (56a), and 1-ethynyl-1-cyclohexanol (64) in toluene for 24h. After working, pure compound was obtained which was further characterized by FTIR.



59 56a 64 65 61

Scheme 4.6: Synthesis of hydrazine carbothioamide (61) by 1-ethynyl-1-cyclohexanol

The pure product **(61)** which was synthesized by using 1-ethynyl-1-cyclohexanol was characterized by IR ν_{max} (cm^{-1}) have O-H peak on 3454 cm^{-1} which showed the hydroxyl group in the final product. N-H stretching was observed on 3349 cm^{-1} which indicated the presence of primary amine in the final compound, C-O stretching observed on 1219 cm^{-1}, C=S peak observed on 1150 cm^{-1}, C=N stretching observed on 1595 cm^{-1} which showed the presence of imine in the final product as shown in **Figure 4.6** .

By observing the following peaks, the peak 1595 cm^{-1} (C=N) indicate that imine **(61)** was synthesized because no peak of alkyne was obtained.

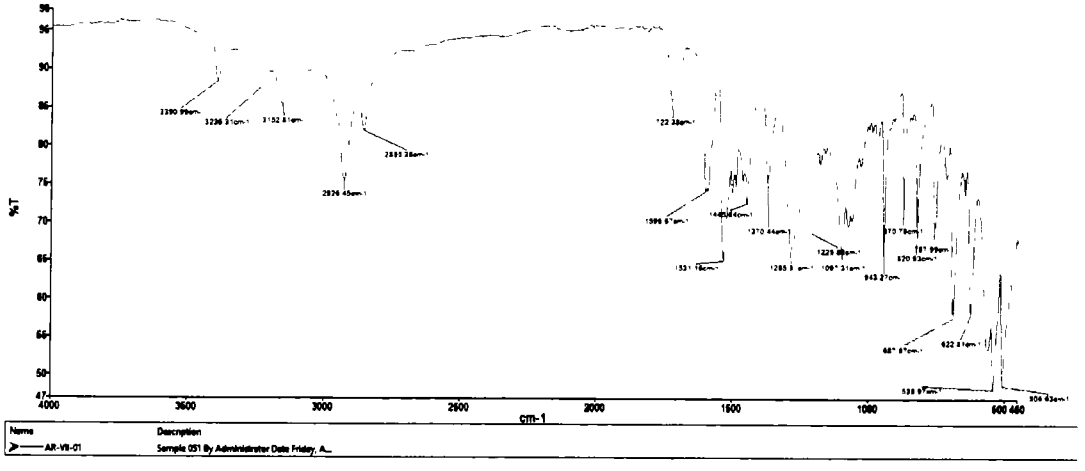
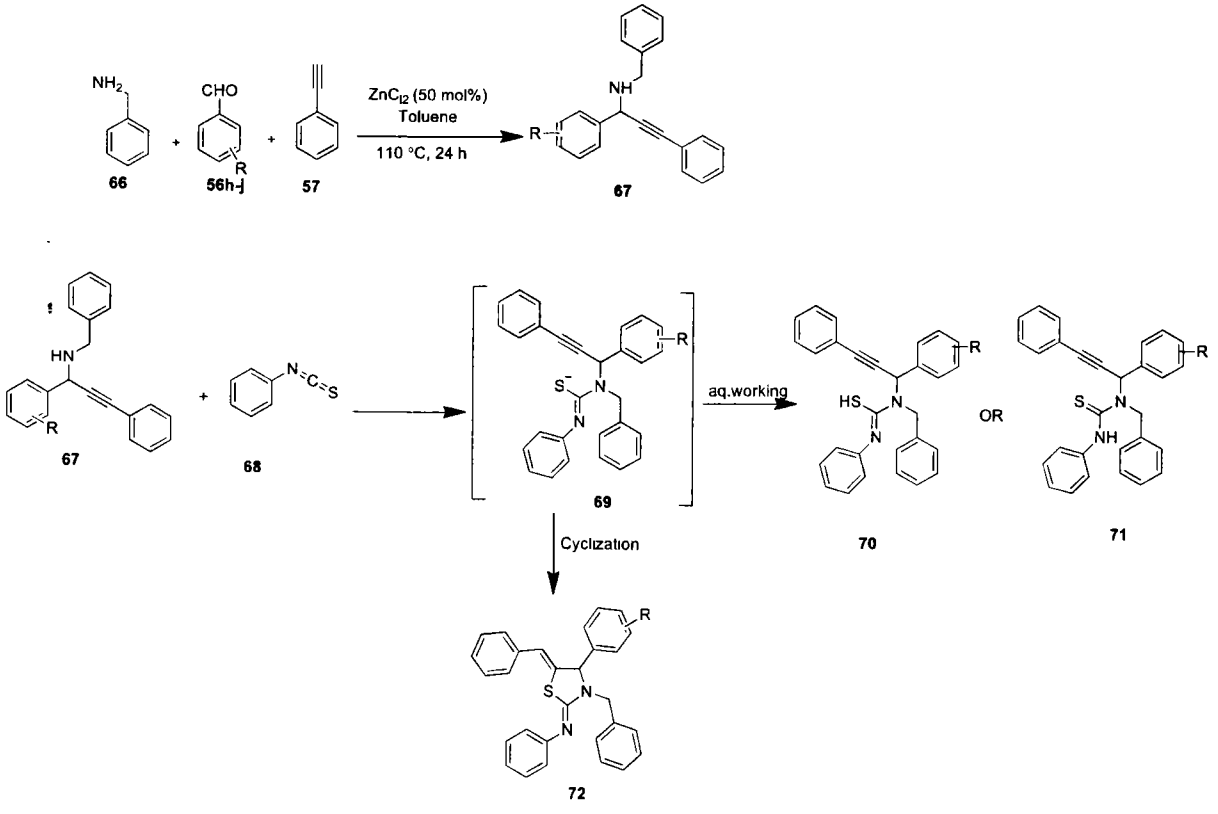


Figure 4.6: FT-IR spectra of **(61)**

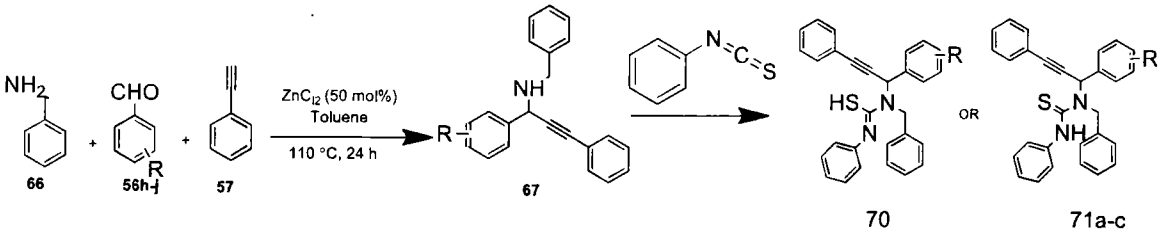
4.7 Use of phenylisothiocyanate for the synthesis of *N*- thiourea propargylamine

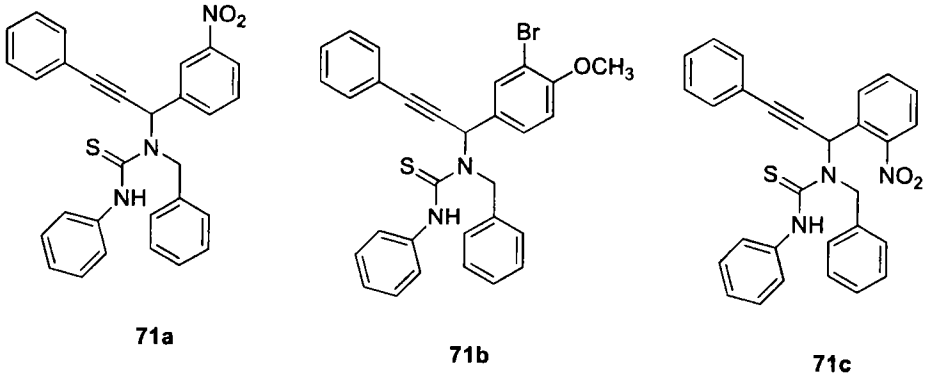
To get desired product a different strategy was adopted. In this synthetic pathway benzylamine **(66)** was used as primary amine First in this sequence, benzylamine **(66)** (1mmol), benzaldehyde **(56)** (1mmol), and phenylacetylene **(57)** (1mmol) were dissolved in toluene (10 ml) and allowed to reflux for 24 hours to produce propargylamine **(67)** as shown in scheme 3.22. The reaction mixture was refluxed for 24 hours while being monitored by TLC in a solvent mixture of 9:1 n-hexane: EtOAc. For workup, EtOAc and H_2O were used to do the solvent extraction. The organic layer was separated and dried with anhydrous magnesium sulphate following the three times extraction. After filtration, the reaction mixture was placed in a china dish to allow the solvent to evaporate slowly. After evaporation, pure product propargylamine **(67)** was obtained. After obtaining pure propargylamine **(65)**, was dissolved in toluene (15 ml) and stirred for 15 minutes. After that, 1 mmol of phenylisothiocyanate **(68)** was added to the reaction mixture, and the mixture was then allowed to reflux for 24 hours at 110 °C as shown in scheme 3.23. After refluxing, the reaction progress was monitored by TLC using an n-hexane: EtOAc (9:1) solvent mixture. After workup, the organic layer was separated and solvent was evaporated under a vacuum. The pure compound was characterized by FTIR. After characterization, it was confirmed that compound (71) was synthesized. Then by using this route, benzaldehyde derivatives such as 3-Nitrobenzaldehyde, 3-bromo-4methoxy benzaldehyde were used to synthesize derivatives of *N*-

thioamide propargylamine as shown in **scheme 4.7**. Propargylamine when reacted with phenylisothiocyante intermediate compound **(69)** was obtained which can further cyclize to compound **(72) or** open chain compound **(70)** and **(71).** But according to FTIR spectra, it was observed that compound **(71)** was synthesized as shown in **scheme 4.6.**



Scheme 4.6: Propargylamine synthesis using phenylisothiocyanate





71a 71b 71c

Scheme 4.7: Propargylamine synthesis benzaldehyde derivatives.

According to FTIR spectra, the free N-H peak was observed at 2923and 2856 cm^{-1} which showed the presence of secondary amine if compound **(72)** or **(70)** was present then no free N-H peak should be observed, C≡C peak was observed at 2062 cm^{-1} which showed the presence of alkyne but C-N peak at 1274 cm^{-1} and C=S peak at 1071 cm^{-1} confirmed that compound **(71)** was synthesized because C=N peak and C-S peaks were not present it showed that **(70)** and **(72)** were not observed as shown in **Figure 4.7** .

By observing the following peaks of FTIR, it was confirmed that *N*-thiourea propargylamine **(71)** was major compound that was formed.

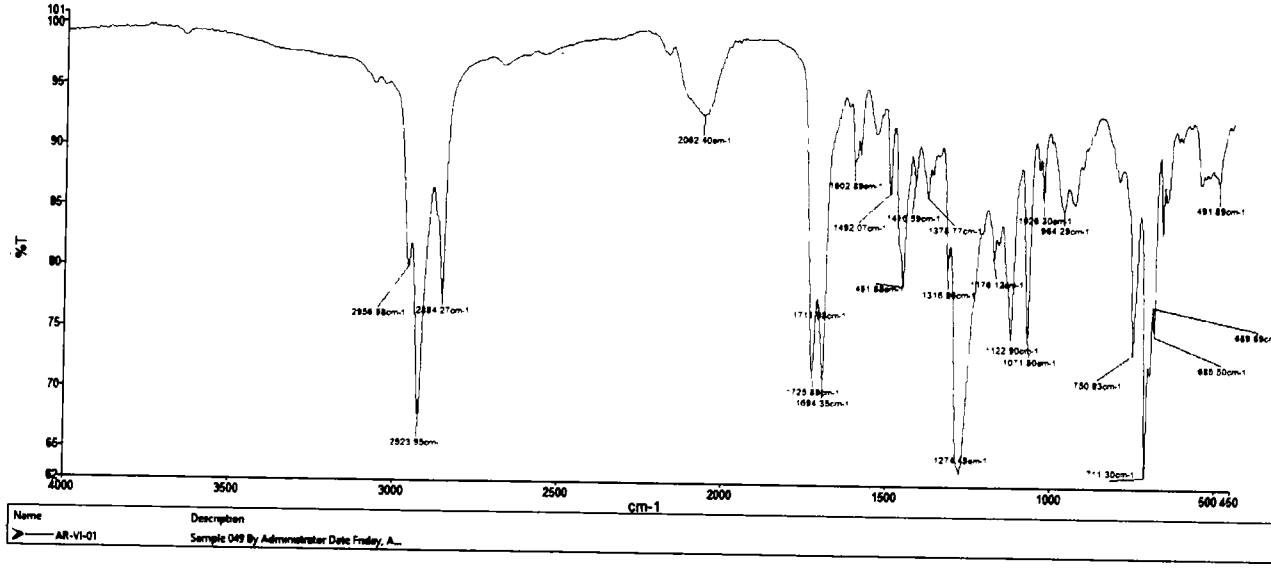


Figure 4.7: FTIR characterization of compound (**71**)

Conclusion

Synthesis of *N*-thiourea propargylamine have been successfully synthesized by the reaction of different amines, aldehyde derivatives, and alkyne by adopting A^3-coupling mechanism. Different synthetic schemes were adopted to synthesize the *N*-thiourea propargylamine by using A^3-coupling mechanism. First of all, available catalyst such as $ZnCl_2$, CuCl, $FeCl_3$, $NiCl_2.5H_2O$, $CuCl_2$, $ZnBr_2$, $AlCl_3$, and $ZrCl_4$ and different solvents such as methanol, ethanol, DCM, and toluene tried to obtained *N*-thiourea propargylamine but no one catalyst to able to synthesize *N*-thiourea propargylamine but imine was formed as major product. Then different aldehydes derivatives were used but no one able to synthesize *N*-thiourea propargylamine. The modification synthetic route was adopted in which benzylamine, different aldehydes, and phenylacetylene were used to synthesize propargylamine. The synthesized propargylamine reacted with phenylisothiosyanate to synthesize *N*-thiourea propargylamine. The synthesized compounds further characterized by spectroscopic techniques such as FTIR, GCMS, and ^{1}HNMR. After characterization, it was examined that our target compound *N*-thiourea propargylamine was obtained.

Chapter 5

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