T. C.
VAN YUZUNCU YIL UNIVERSITY
INSTITUTE OF NATURAL AND APPLIED SCIENCES
DEPARTMENT OF CHEMISTRY

SYNTHESIS OF BIOLOGICALLY IMPORTANT NEW INDOLE DERIVATIVES

M.Sc. THESIS

PREPARED BY: Ali Rasw HAMAD
SUPERVISOR: Prof. Dr. Arif KIVRAK

VAN-2021

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ACCEPTANCE and APPROVAL PAGE

This thesis entitled "**SYNTHESIS OF BIOLOGICALLY IMPORTANT NEW INDOLE DERIVATIVES**" presented by Ali Rasw Hamad undergo supervision of Prof. Dr. Arif KIVRAK in the Department of Chemistry has been accepted as a M. Sc. thesis according to Legislations of Graduate Higher Education on 07/01/2021 with majority of votes members of jury.

Chair: Prof. Dr. Adnan BULUT	Signature:
Member: Prof. Dr. Arif KIVRAK	Signature:
Member: Doç. Dr. Murat RAKAP	Signature:

This thesis has been approved by the committee of The Institute of Natural and Applied Science on...……../...../…...….. with decision number.....

Signature
Prof. Dr. Suat ŞENSOY
Director of Institute

THESIS STATEMENT

All information presented in the thesis obtained in the frame of ethical behavior and academic rules. In addition all kinds of information that does not belong to me have been cited appropriately in the thesis prepared by the thesis writing rules.

Signature

Ali Rasw HAMAD

ABSTRACT

SYNTHESIS OF BIOLOGICALLY IMPORTANT NEW INDOLE DERIVATIVES

HAMAD, Ali Rasw
M.Sc. Thesis, Department of Chemistry
Supervisor: Prof. Dr. Arif KIVRAK
January 2021, 61 Pages

Indole derivatives are the most important class in heterocyclic compounds. There is a variety of indole based heterocyclic, and they are used for the treatments of different diseases. They have been used as anti-bacterial, anti-parasitic, anti-cancer, anti-inflammatory and anti-tumor agents. In the present study, novel indole derivatives are designed, synthesized. Initially, one-pot cyclization reaction was used for the formation of 3-thiophenyl-indole, and then electrophilic aromatic substitution reaction was applied to synthesis of iodo-substituted indoles. Before condensation reaction, Suzuki-Miyaura coupling reactions were performed for the synthesis of corresponding aldehyde derivatives. All synthesized compounds were characterized by using spectroscopic methods.

Keyword: Cyclization reaction, Condensation reaction, Indole, Suzuki-Miyaura coupling reaction.

ÖZET

BİYOLOJİK ÖNEME SAHİP YENİ İNDOL TÜREVLERİNİN SENTEZİ

HAMAD, Ali Rasw
Yüksek Lisans Tezi, Kimya Anabilim Dalı
Danışman: Prof. Dr. Arif KIVRAK
Ocak 2021, 61 Sayfa

İndol türevleri, heterosiklik bileşiklerin en önemli üyeleridir. İndol içeren çok önemli ve farklı heterosiklikler vardır ve bunlar farklı hastalıkların tedavisinde kullanılmaktadır. Anti-bakteriyel, anti-parazitik, anti-kanser, anti-enflamatuarve anti-tümör olarak kullanılan indol türevleri söz konusudur. Bu çalışmada, yeni indol türevleri tasarlanmış ve sentezlenmiştir. İlk olarak, 3-tiyofenil-indol sentezi için one-pot halkalaşma tepkimesi kullanılmış, ardından iyodo içeren indollerin sentezi için elektrofilik aromatik yerdeğiştirme tepkimeleri uygulanmıştır. Kondenzasyon tepkimesinden önce, aldehit türevlerinin sentezi için Suzuki-Miyaura kenetlenme tepkimesi kullanılmıştır. Sentezlenen tüm bileşiklerin yapısal karakterizasyonları spektroskopik yöntemler kullanılarak tamamlanmıştır.

Anahtar kelimeler: Halkalaşma tepkimeleri, Kondenzasyon tepkimesi, Indol, Suzuki-Miyaura kenetlenme tepkimesi.

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At the beginning, I want to thank and remember the almighty God (Allah), the Lord of all the worlds, with blessing and peace be upon his Prophet Mohammed. That empowers me to complete my studies and my research work for the degree of Master of Science in Chemistry department at Van Yuzuncu Yil University.

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I am grateful to my mother and father and sister for their enduring sacrifice, blessings, notion and encouragement which pave the way of mine in this university. Also, I would like to categorical my one-of-a-kind gratitude to my love Dedan and my son Kardin.

I take this possibility to express my regard and deepest feel of perception to all of the group workers of laboratory chemistry for their help and cooperation at some points of the direction of my study. Without their assist, it would no longer be feasible to be successful in this realistic work. My heartfelt thanks to all my classmates and friends for giving me ethical guide and motivation at some points of my studies.

2021
Ali Rasw HAMAD

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SYMBOLS AND ABBREVIATIONS

Some symbols and abbreviations used in this study are presented below, along with descriptions.

Symbols	Description
Bs	Broad Singlet
s	Singlet (NMR spectroscopy)
d	Doublet (NMR spectroscopy)
dd	Doublet of Doublets (NMR spectroscopy)
t	Triplet (NMR spectroscopy)
q	Quartet (NMR spectroscopy)
p	Pentet (NMR spectroscopy)
m	Multiplet (NMR spectroscopy)
δ	Chemical Shift
Brs	Broad Strong
ppm	Parts Per Million (in NMR)
MHz	Megahertz
KHz	Kilohertz
Hz	Hertz
J	Coupling Constant
r.t	Room Temperature
h	Hour
Hr	Hour (s)
^{o}C	Degree Celcius
equiv.	Equivalent
R	Alkyl Group
Me	Methyl Group

Symbols	Description
Ar	Aryl group
mg	Milligram
kg	Kilogram
mL	Milliliter
mmol	Millimole
min	Minute
mg	Milligram
kg	Kilogram
mL	Milliliter
$CDCl_3$	Deuterochloroform
DCM	Dichloromethane
DMF	N, N-dimethylformamide
EtOAc	Ethyl acetate
Et_3N	Triethylamine
MeOH	Methanol
NIS	N-iodosuccinicimide
THF	Tetrahydrofuran
TMS	Tetramethylsilane
K_2CO_3	Potassium Carbonate
$LiCO_3$	Lithium Carbonate
$MgSO_4$	Magnesium Sulfate Anhydrous
Al_2O_3	Aluminiumtryioxide
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine) Palladium (0)
$PdCl_2(PPh_3)_2$	Bis(triphenylphosphine) Palladium (II)chloride
TLC	Thin-layer Chromatography

Abbreviations	Description
IR	Infrared
HRMS	High Resolution Mass Spectrometry
NMR	Nuclear Magnetic Resonance
^{1}H NMR	Proton Nuclear Magnetic Resonance Spectroscopy
^{13}C NMR	Carbon 13 Nuclear Magnetic Resonance Spectroscopy
UV	Ultraviolet

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1. INRODUCTION

Heteroaromatic structures have critical roles in our life's due to extensive variety of applications such as antiseptics, pharmaceuticals and antioxidant compounds, dye stuff, inhibitors, polymers, and as main motifs in the synthesis of organic compounds and natural products. They are cyclic molecules, and contain heteroatoms like sulfur, oxygen and nitrogen on their structure.

Indole derivatives are the most important class in heterocyclic compounds. There is a variety of indole based heterocyclic, and they are used for the treatments of different diseases. They have been used as anti-bacterial, anti-parasitic, anti-cancer, anti-inflammatory and anti-tumor agents.

2. LITERATURE REVIEW

2.1. Heterocyclic Compounds

Heteroaromatic structures have critical roles in our life's due to extensive variety of applications such as antiseptics, pharmaceuticals and antioxidant compounds, dye stuff, inhibitors, polymers, and as main motifs in the synthesis of organic compounds and natural products. They are cyclic molecules, and contain heteroatoms like sulfur, oxygen and nitrogen on their structure. There are a variety of aromatic and non-aromatic heterocyclic compounds in nature. In addition, heterocyclic compounds can be classified as oxygen, nitrogen or sulfur based, and could be organized by using size of the ring structure. Chemical and physical properties are depended on the type and numbers of heteroatoms in the rings, and number of the cycles (Broughton and Watson, 2004; Eicher et al., 2012; Gomtsyan, 2012).

As seen in (Figure 2.1), there are well-known heterocyclic organic compounds. Three, four, five- or six-membered rings are the most common, and containing heteroatoms of oxygen (O), nitrogen (N) and sulfur (S). Pyridine, pyrrole, furan and thiophene could be best examples for the well-known heteroaromatic compounds in literature. Pyridine is six membered rings (six atoms-five carbon atoms and one nitrogen atom). Pyrrole, furan and thiophene structures are consisting of four atoms of carbon and one atom of nitrogen, oxygen and sulfur, respectively (Kunied and Mutsanga, 2002). Heterocyclic compounds play very critical roles for the treatments of diseases, many of them have higher biological activities due to heteroatoms increase the biological properties (Dua et al., 2011; Pozharskii et al., 2011; Taylor et al., 2014).

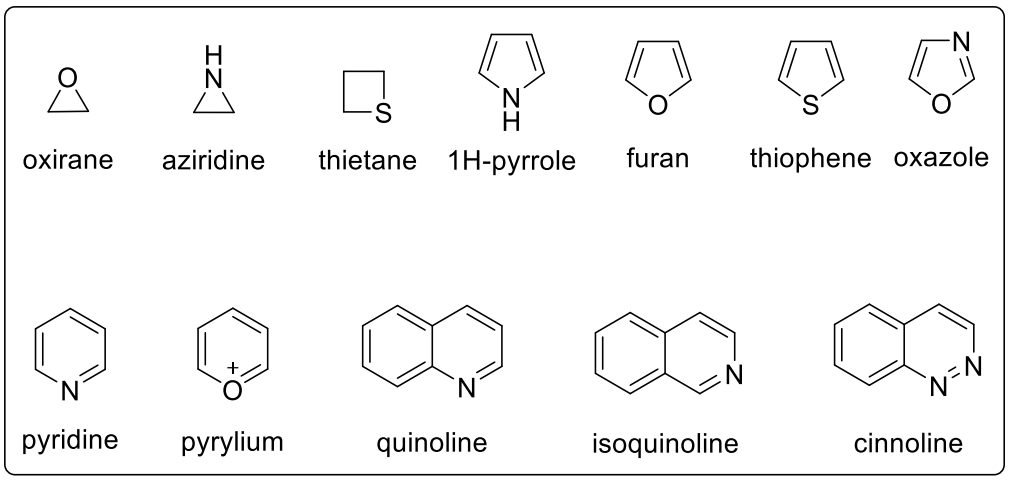


Figure 2.1. Examples of heterocyclic compounds.

Penicillin is fused-heterocyclic compounds including nitrogen, sulfur and oxygen hetero atoms on its structure. Penicillin, member of β-lactams ring, are the best antibiotic to treat a variety of diseases (Bansal, 1999). Other β-lactams are also used as anti-bacterial, anti-fungal in medicine (Figure 2.2).

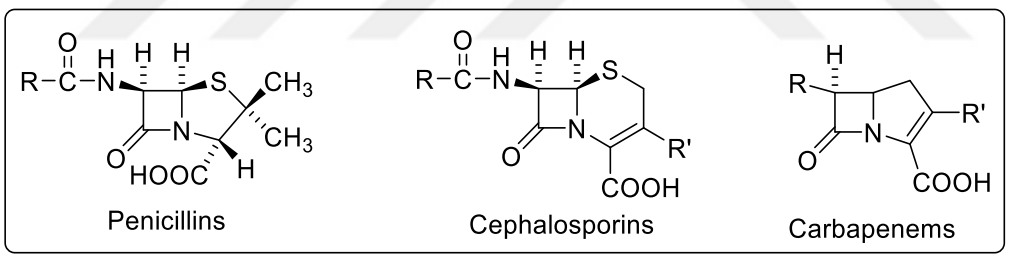


Figure 2.2. β-Lactam heterocyclic derivatives.

Nucleic acids (DNA and RNA) are the key building blocks of our lives. DNA and RNA are the main information-carrying molecules of the cell, they determine the inherited characteristics of every living thing. There are two main classes of nucleic acids; deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Adenine (A), guanine (G), cytosine (C), thymine (T), and uracil (U) heterocyclic compounds are the main structures for DNA and RNA (Figure 2.3) (De Proft and Geerlings, 2014; Brahmachari, 2015; Lodish et al., 2016).

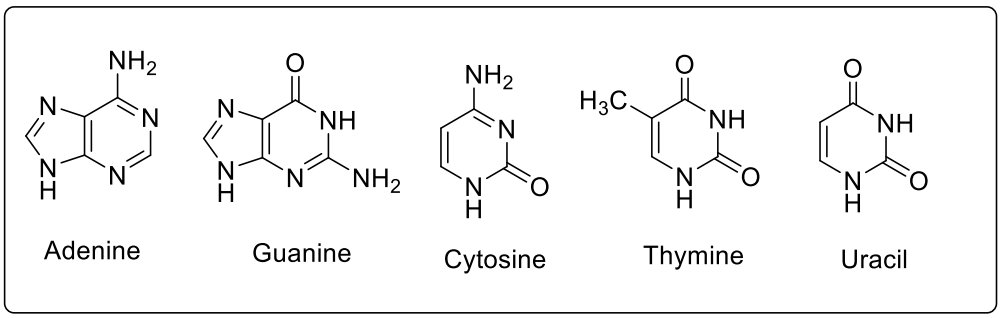


Figure 2.3. Nucleic acids.

2.2. Indole

Indole derivatives are important for the development of new compounds of pharmaceutical interest. The indole structure is a poly heterocyclic compound which easily participates in chemical reactions. Its bonding sites are analogous to pyrrole. The indole name came from indigo and oleum, and a bicyclic structure consists of a six-membrane ring of benzene bonded to a five-membrane pyrrole ring (Biswal et al., 2012). Indoles are aromatic organic compounds with planer conjugate system with 10 π-electrons (Figure 2.4) (Sharma et al., 2010).

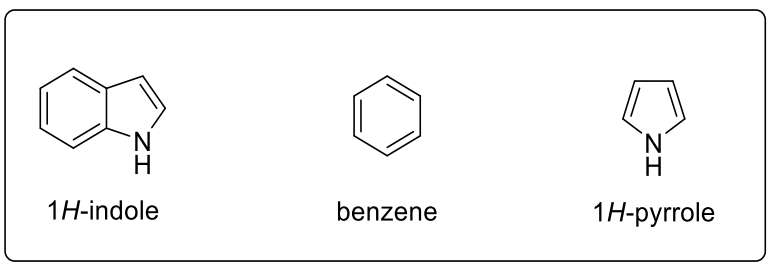


Figure 2.4. Indole, benzene and pyrrole.

Indole is reactive at four different positions, so they give the reactions from the carbon atom 3, nitrogen atom, the C2–C3 π-bond and the C2–N sigma bond. Moreover, cycloaddition reactions of the C2–N sigma bond are investigated. The resonance of indole is shown in (Figure 2.5), this delocalization of electrons gives the more reactivity in electrophilic substitution reactions at 3 positions.

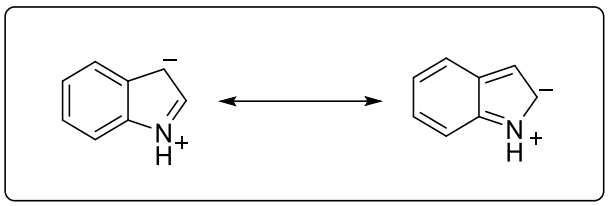


Figure 2.5. Resonance of indole.

Actually, there are different indole isomers such as; 3H-indole, 2H-indole and 1H-isoindole in organic chemistry (Figure 2.6).1*H*-Indole structure is the most common and well-known indole isomer due to higher reactivity (Shelke, 2016).

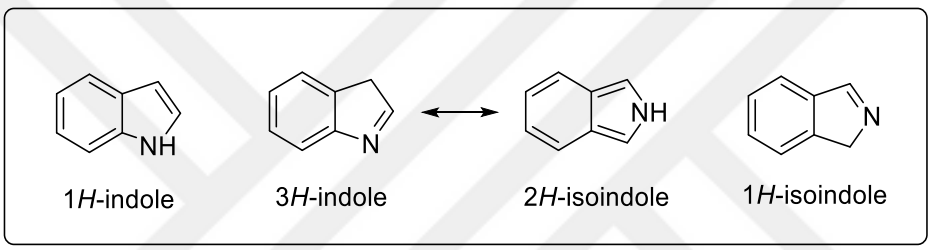


Figure 2.6. Indole isomers.

Indole natural products, alkaloids, are used for the treatments of many diseases. There are more than 1,500 indole alkaloids including the simple and more complex in literature (Hesse, 2002). Some of natural indoles is the very essential to continue our life's and many of them are extensively used for the investigation of new drugs in pharmacology. There are different kinds of naturally occurring alkaloids, for example amino acid tryptophan is a part of human nutrition. It also regulates plant growth in the form of hormone indole-3-acetic acid. Moreover, Serotonin (5-hydroxytryptamine) is a critical neurotransmitter in the central nervous system. They have roles in sleep and memory, as well as metabolism and emotional well-being (Figure 2.7) (Lednicer, 2009; Kaushik et al., 2013).

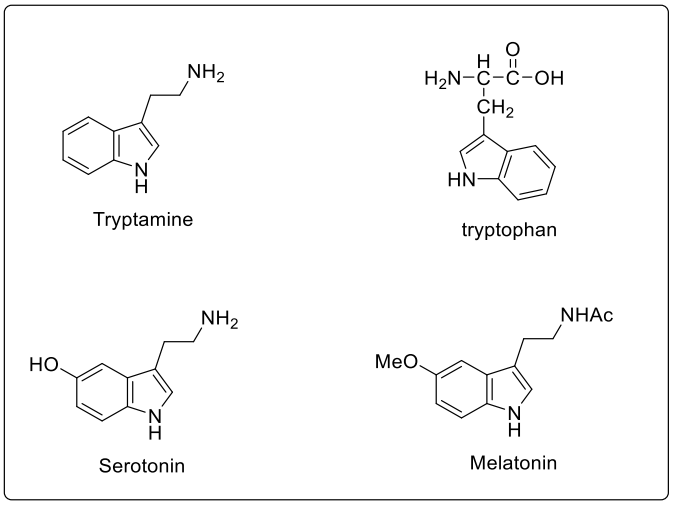


Figure 2.7. Some natural indole derivatives.

Last decades, indole based organic molecules have been gained big importance due to unexpected biological properties. A variety of indole based novel heteroaromatic compounds were synthesized and reported. Discovery of new drug molecules requires exploration of different structural motifs, and indole ring system represents one of the most important structural subunits in drug discovery. Molecules containing indole nucleus as a part of their structure, further called indoles, possess diverse biological activities securing their use as drugs (Figure 2.8) and (Figure 2.9). This is expressed by the diverse use of indoles as antimicrobial (Ma et al., 2018), anti-cancer (Darehkordi et al., 2013), anti-HIV (Karaaslan and Suzen, 2011), anti-fungal (Sinha et al., 2008), anti-parkinsonian (Sravanthi and Manju, 2016), anti-tumor (Zhang and Demain, 2005), antimalarial (Agarwal et al., 2005), antioxidant (Buemi et al., 2013), anti-bacterial (Lakshmi et al., 2010), anti-diabetic (Dhuguru and Skouta, 2020), anticonvulsant (Singh and Singh, 2018).

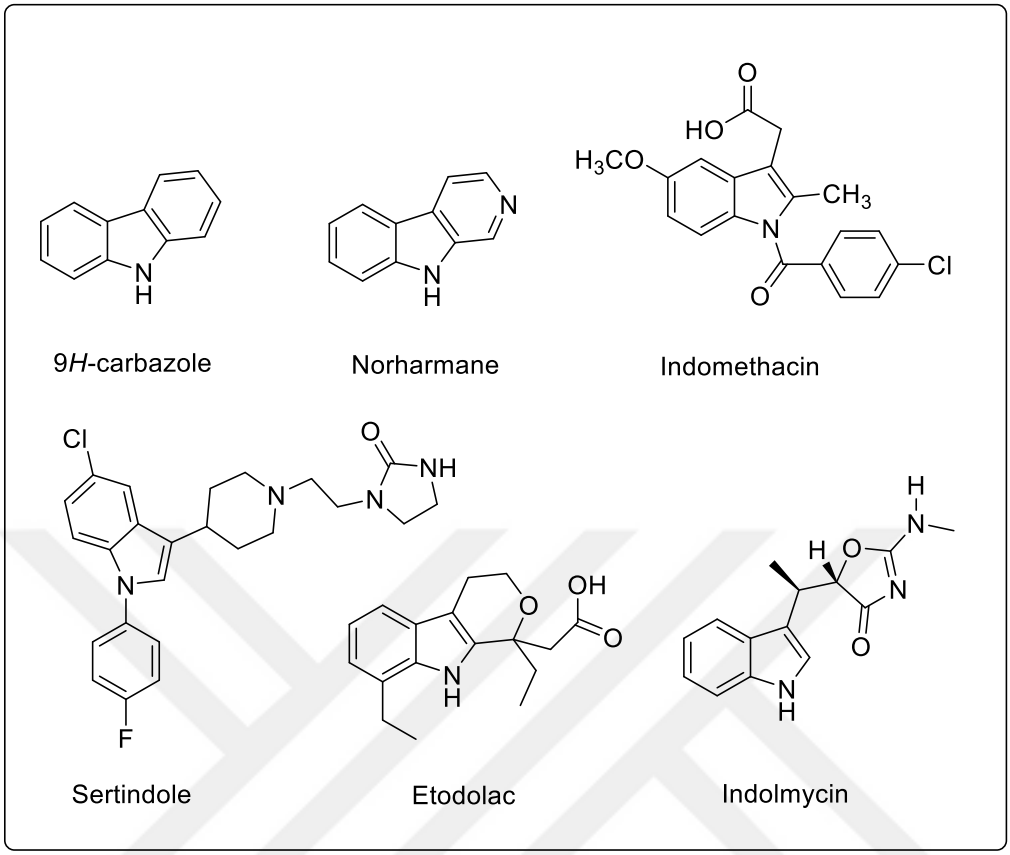


Figure 2.8. Biologically active indole derivatives.

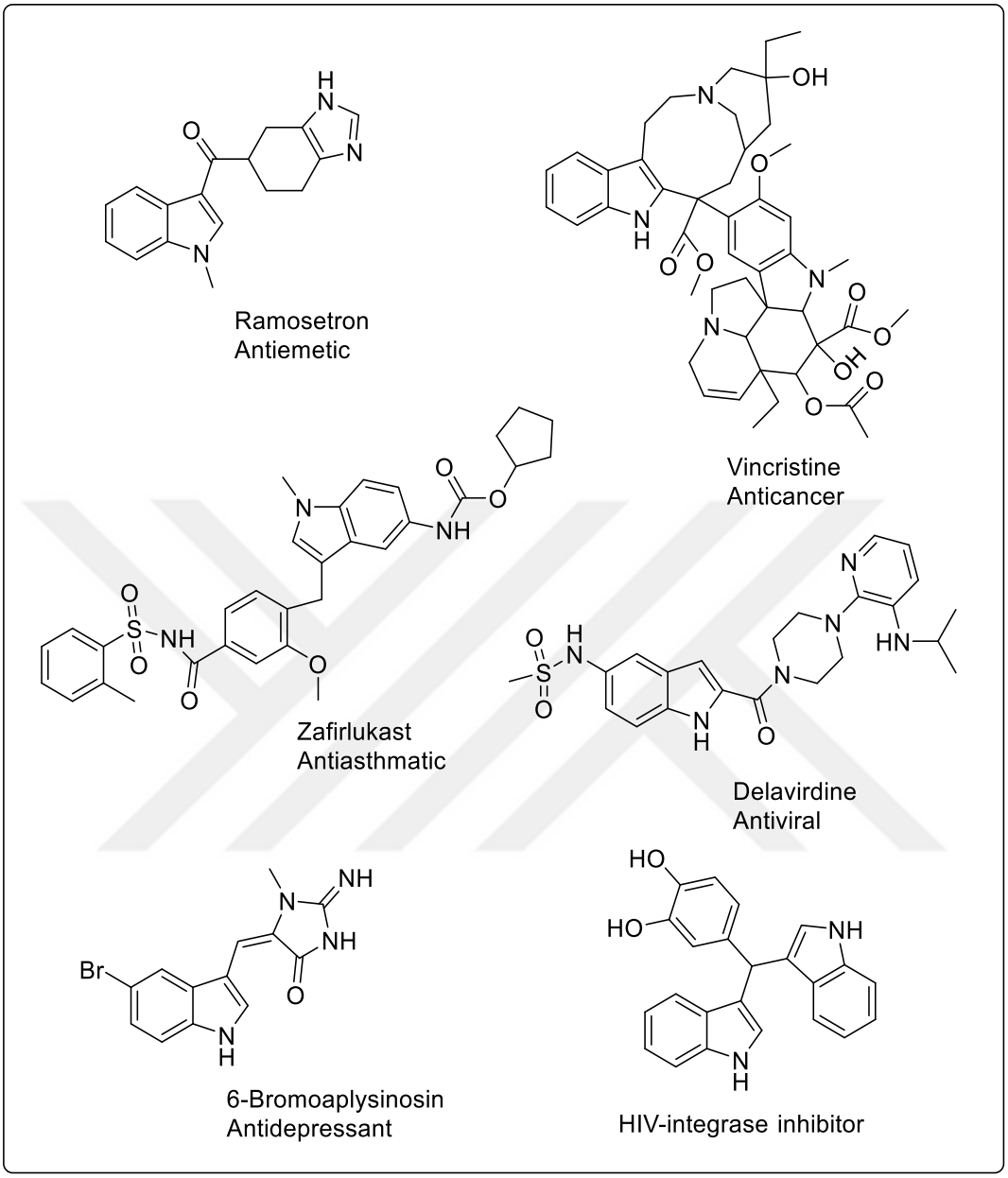


Figure 2.9. Indole based commercial drugs.

2.2.1. Synthesis of Indole

Natural indoles may be isolated from plants by using extraction procedure. On the other hand, researchers tried to find novel synthetic pathways for the synthesis of biologically active indole compounds. In literature, a variety of methodologies were reported for the formation of indoles by using i) Transition-metal catalysis, ii) C-C bond

formation or C-N bond formation reactions (Inman and Moody, 2013, Kerzare and Khedekar, 2016; Chadha and Silakari, 2017). Some methodologies were summarized as below (Figure 2.10).

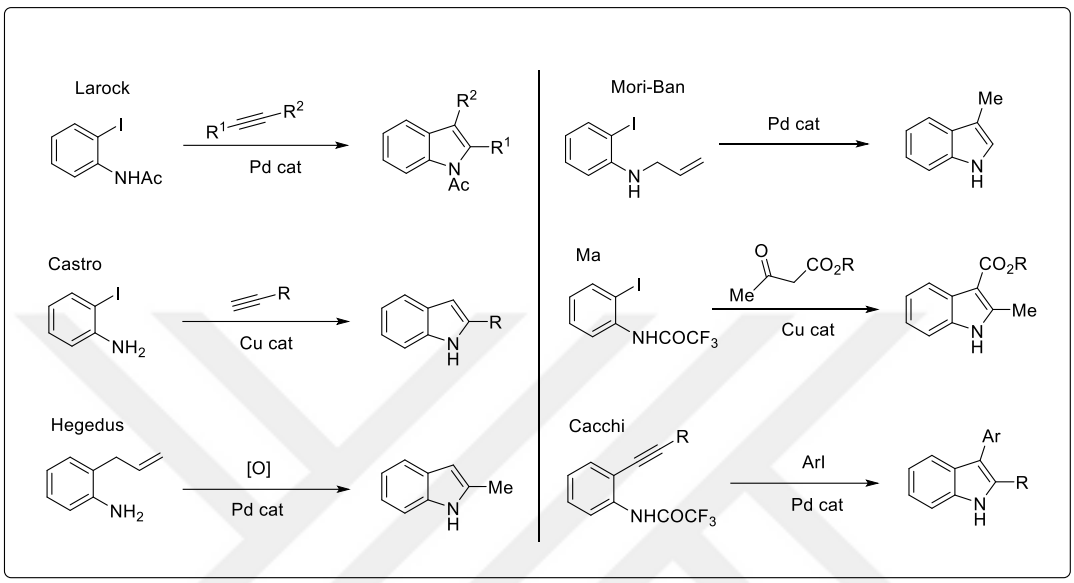


Figure 2.10. Synthesis indole from *o*-substituted anilines mediated via transition-metal catalysis.

Larock Indole Synthesis;

A new method was established for the synthesis of 2,3-disubstituted indoles by Larock et al (Figure 2.11). They investigated that a palladium-catalyzed annulation of o-iodoaniline with alkynes gave the indoles in moderate to excellent yields (Larock and Yum, 1991; Larock et al., 1998; Li, 2011).

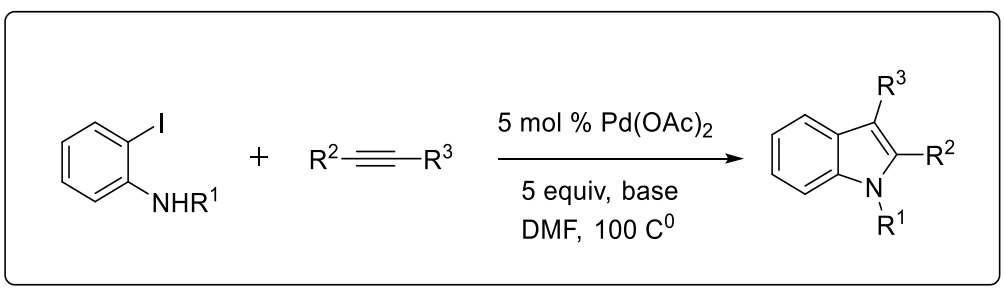


Figure 2.11. 2, 3-Disubstituted indole synthesis by Larock.

Castro Indole Synthesis;

2-Aryl-indole derivatives could be synthesized from the reaction between 2-iodoaniline and terminal alkynes in the presence of copper catalyst. This reaction was called as Castro indole reaction (Figure 2.12) (Castro et al., 1966; Krüger et al., 2008).

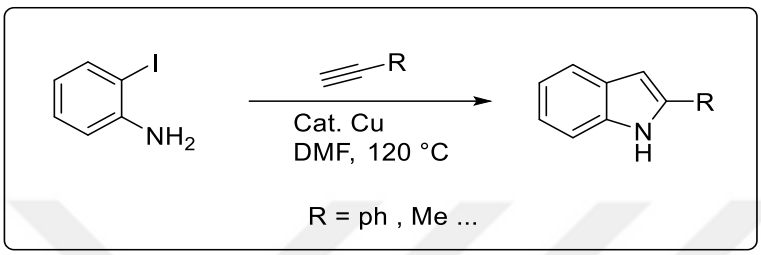


Figure 2.12. Castro indole synthesis.

Hegedus Indole Reaction;

Hegedus et al. were reported that the cyclization reaction of cyclization o-allylaniline catalyzed by palladium (II) complex was form the 2-methylindole structure (Hegedus et al., 1978; Hegedus, 1988; Wang, 2009). This cyclization reaction was carried out in triethylamine and THF solvent mixture (Figure 2.13). On the other hand, Hegedus indole reaction is not efficient to preparing indole derivatives.

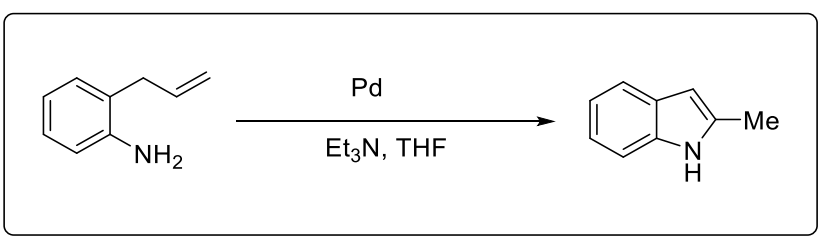


Figure 2.13. Hegedus indole synthesis.

Ma Indole Reaction;

The reaction of 2-halotrifluoroacetanilides with β-keto esters and amides formed 2,3-disubstitutedindoles (Figure 2.14) (Chen et al., 2007).

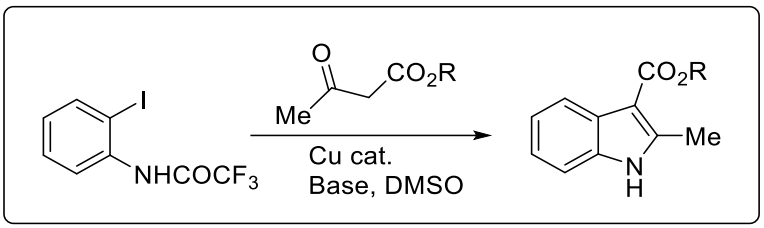


Figure 2.14. Coupling-condensation2,3-disubstituted indoles.

Cacchi indole reaction;

2,3-Disubstituted indoles could be produced from o-alkynyltrifluoroacetanilides and aryl iodide (Figure 2.15). In the first step, 2-alkynyl trifluoroacetanilides was prepared from 2-iodoaniline via Sonogashira coupling reaction. Then, Palladium catalyzed cyclization reaction produced the corresponding indoles. This method may be more convenient to selectively synthesis of 3-aryl-indole derivatives (Cacchi and Fabrizi, 2005).

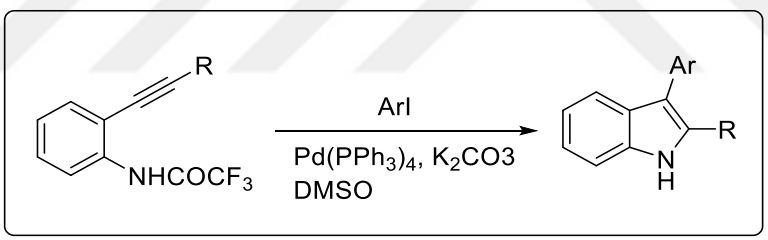


Figure 2.15. Cacchi indole synthesis.

Fischer indole synthesis;

First Indole was synthesized by Hermann Emil Fischer in 1883. Fischer synthesized indoles by starting from arylhydrazones in the presence of an acid catalyst. For Fischer indole reaction, arylhydrazones are formed from a condensation reaction between an arylhydrazine and an aldehyde or ketone. Then [3,3] sigmatropic shift gives an intermediate before ring closing. Finally, rearrangement gave the desired indole compounds (Figure 2.16) (Robinson, 1969; Sajjadifar et al., 2010; Shaikh et al., 2013).

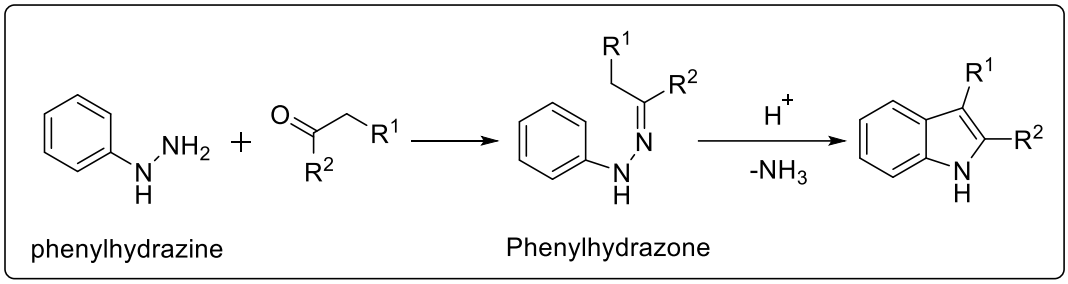


Figure 2.16. Fischer indole synthesis.

Bartoli Indole Synthesis;

Bartoli found a new reaction for the formation of indoles (Figure 2.17). When o-substituted nitrobenzene was react with 3 moles of the vinyl magnesium halide, 7-methyl-indole was obtained as the major product (Bartoli et al., 1989; Knepper and Bräse, 2003; Li, 2005).

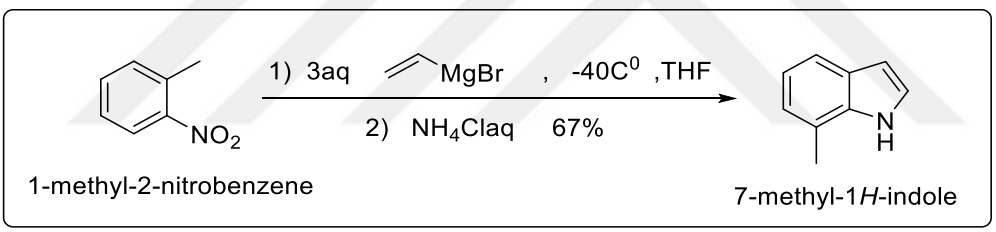


Figure 2.17. Bartoli indole reaction.

Madelung indole synthesis;

Madelung reported that *N*-benzoyl-*o*-toluidine was converted to the corresponding 2-phenylindole of (Figure 2.18) when heated with two equivalents of sodium ethoxide at high temperatures (Hassner and Stumer, 2002; Kürti and Czakó, 2005).

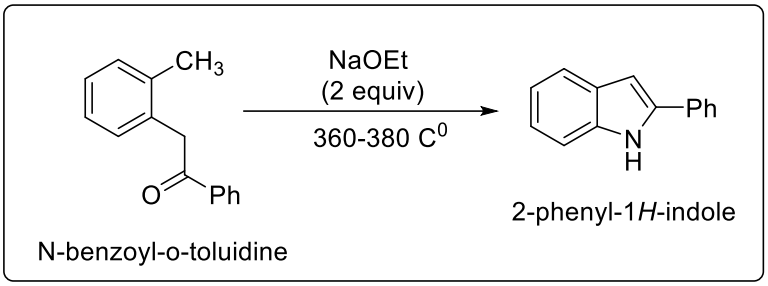


Figure 2.18. Indole synthesis via Madelung.

Reissert indole synthesis;

Reissert was also investigated that a condensation reaction between o-nitrotoluene and diethyl oxalate produced o-nitrophenyl pyruvate (Figure 2.19). After reduction of nitro groups, they gave the cyclization reaction in the presence of Zn catalyst in acetic acid to afford the indole-2-carboxylic ester (Colombo et al., 2011).

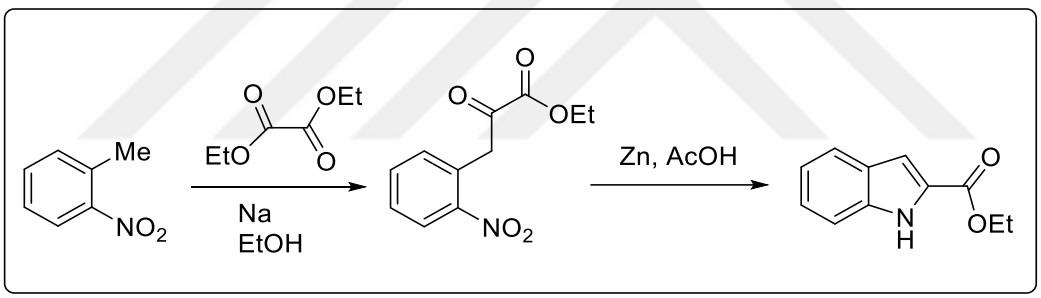


Figure 2.19. Reissert indole synthesis.

2.3. Palladium-Catalyzed Cross-Coupling Reactions

2.3.1. Sonogashira coupling reaction

The Sonogashira coupling reaction is the most popular for the formation of new carbon-carbon bond (Figure 2.20). In general, when halo-aryl structures are reacted with terminal alkyne in the presence of Pd and Cu, this reaction gave new C-C bond between alkynes and halo-aryls. In literature, there are varieties of modified Sonogashira coupling procedure. Sonogashira coupling reactions are very important for the synthesis of biologically active compounds. Moreover, they have been used for library studies to

increase the active derivatives. Sonogashira couplings reaction needs mild reaction conditions, have high region-selectivity at room temperature, give high yields (Chouzier et al., 2004; Nishihara, 2013).

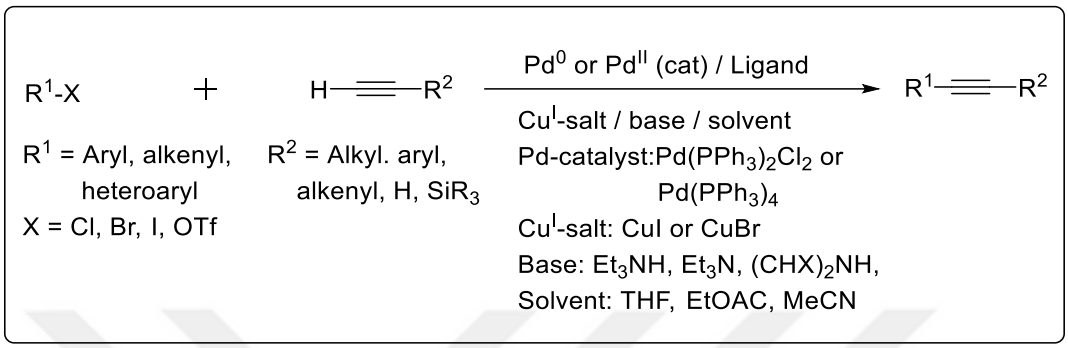


Figure 2.20. Sonogashira coupling reactions.

As seen (Figure 2.21), Sonogashira coupling reaction includes two catalytic cycle; palladium cycle and cupper cycle. Initially, the Pd(0) active catalyst gave the oxidative addition into an Ar-X bond. The terminal acetylide is deprotonated and then metallated to form a copper acetylide, which is used to transmetallation to palladium. Reductive elimination form the disubstituted acetylene and regenerates a Pd(0) species, which can facilitate another catalytic cycle (Chinchilla and Nájera, 2007; Wang et al., 2011).

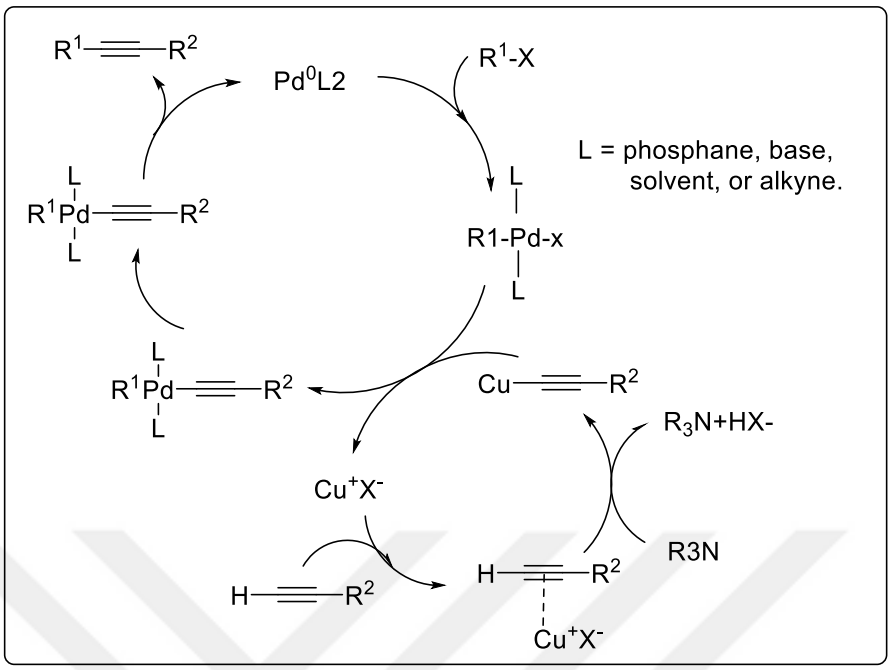


Figure 2.21. Sonogashira reaction mechanism.

2.3.2. Suzuki coupling reactions

The Suzuki-Miyaura reaction involves the coupling of a boronic acids with various of organic halide as Pd-catalyzed coupling reactions (Figure 2.22). Suzuki-Miyaura cross-coupling reaction is typically mild, tolerates a variety of organic groups and typical non-toxic boron by-products of boric acid. The reactivity depends on the types of halogens. Variety of biaryl compounds have been synthesized by using these methodologies, which are important intermediary in the syntheses of organic products, functionalized polymers, and pharmaceuticals (Bringmann and Menche, 2001; Roberts et al., 2007; Bringmann et al., 2008).

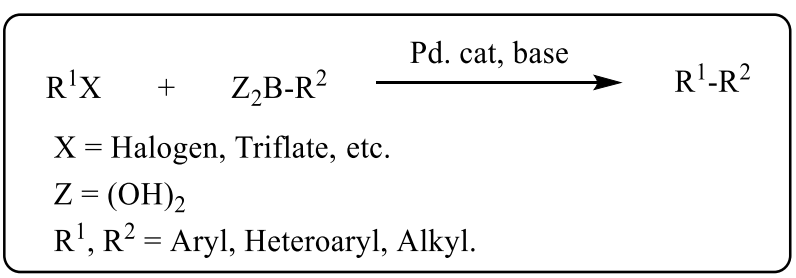


Figure 2.22. General Suzuki coupling reaction.

The proposed mechanism for Suzuki-Miyaura is carried out in three stages; oxidative addition, trans-metalation, with reductive elimination (Figure 2.23) (Wu et al., 2010; Melchor, 2013).

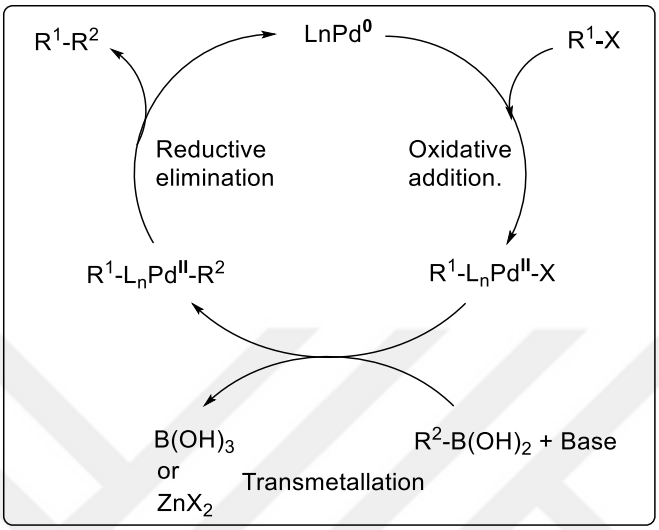


Figure 2.23. Mechanism of Suzuki-Miyaura coupling reaction.

2.4. Electrophilic Cyclization

Last decades, the electrophilic cyclization reaction has been gained critical roles for the synthesis of heterocyclic compounds due to its advantages. Electrophilic cyclization reactions give the highest yield under mil reaction conditions. Moreover, these reactions need very shorter time to conversion. They have been applied not only synthesis of biologically active compounds in medicine, but also synthesis of new conductive organic compounds in material chemistry. Recently, electrophilic cyclization of alkynes using halogen, sulfur and selenium electrophiles was reported as new pathways for the preparation of a wide variety of new heterocyclic compounds such as indoles (Yue and Larock, 2004; Yue et al., 2006a), isoindolinones (Yao and Larock, 2005), quinolines, isoquinolines (Huang et al., 2001; Zhang et al., 2005), isocoumarins (Ma et al., 2014), chromones (Zhou et al., 2006; Vanguru et al., 2018), isochromenes (Yue et al., 2006b), furans (Sniady et al., 2005; Okitsu et al., 2008), benzofurans (Yue et al., 2005), furanones (Larock, 2008), furopyridines (Arcadi et al., 2002), thiophenes (Flynn et al., 2001a), benzothiophenes (Flynn et al., 2001b; Larock and Yue, 2001), selenophenes (Alves et al.,

2007), benzoselenophenes (Kesharwani et al., 2006), naphthalenes (Barluenga et al., 2003), isoxazoles (Waldo and Larock, 2007; He et al., 2014), bicyclic β-lactams (Ren et al., 1998; Schulz et al., 2014), cyclic carbonates (Marshall and Yanik, 1999; North and Pasquale, 2009), spiro[4.5]trienones (Zhang and Larock, 2005; Hua et al., 2020), coumestrol and coumestans (Yao et al., 2005), benzothiazine-1,1-dioxides (Barange et al., 2007), 2*H*-benzopyrans (Worlikar et al., 2007), α-pyrones (Yao and Larock, 2003), pyrroles, etc. (Chen et al., 2009).

Different kind of electrophiles are used for these cyclization reactions, for example I_2, ICl, $IPyBF_4$, Br_2, NBS and PhSeBr are the most popular electrophiles. These cycle reactions are affected by nucleophilicity, the polarity of the carbon-carbon triple bond, the geometrical orientation of the functional groups, and the existence of the electrophile (Figure 2.24) (Kesharwani, 2013).

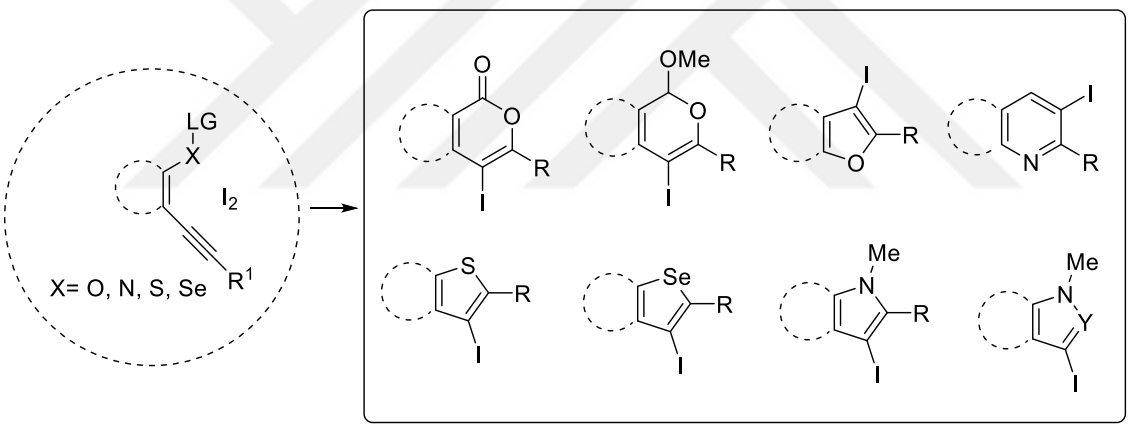


Figure 2.24. Electrophilic cyclization reactions.

2.5. Condensation Reactions

In organic chemistry, Knoevenagel, Claisen-Schmidt, Michael and aldol condensations are well-known condensation reactions for the formation of new product. Knoevenagel condensation is a nucleophilic addition of an activated methylene compound to an aldehyde or ketone using an amine base as a catalyst (Figure 2.25). Then, a molecule of water is eliminated (condensation) via by a dehydration reaction. The product is often an α, β-unsaturated carbonyl compound (enone). The Knoevenagel reaction is a particular variant of the aldol reaction with subsequent elimination of water. It is widely used in organic chemistry for C=C bond formation. The activated methylene compound should be of the form EWG-CH_2-EWG, where EWG is an electron-withdrawing group like diethyl malonate, malonic acid and malononitrile etc. Condensation reactions mostly formed the only product with higher yields (Ren et al., 2002; Jadhav and Yadav, 2019; Zanin et al., 2018).

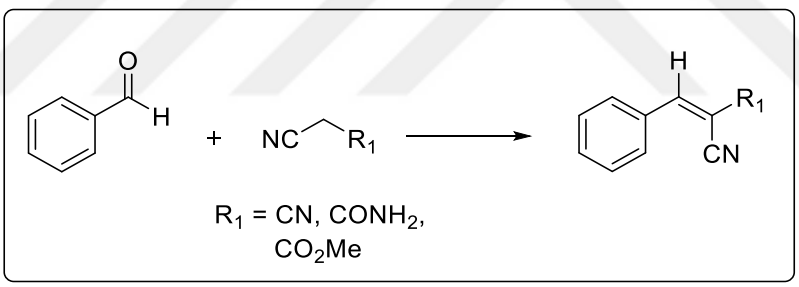


Figure 2.25. Condensation reactions.

2.6. The Aim of Project

Herein, we developed a new synthetic pathway for synthesis of EWG-substituted indoles including thiophene and furan. Firstly, one-pot two step cyclization reaction was applied for the preparation of 2-phenyl-3-thiophenyl-indoles by starting from *N, N*-dimethyl-o-iodoaniline. Then, electrophilic aromatic substitution reaction was performed to synthesis of iodo-substituted indoles. Before condensation reaction, Suzuki-Miyaura coupling reactions were used for the formation of aldehyde functionalized indoles (Figure 2.26).

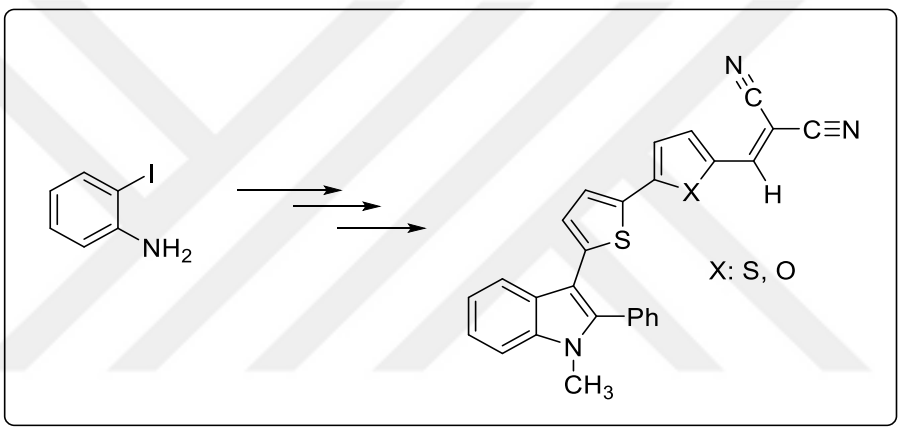


Figure 2.26. Synthesis indole derivatives.

3. MATERIALS AND METHODS

The design and biological active properties synthesis of novel benzo[b]pyrrole derivatives were studied. Characterization of the molecules was carried out by infrared, mass, and nuclear magnetic resonance spectra ^{1}H and ^{13}C-NMR spectroscopy. 1H and ^{13}C NMR spectra were recorded on an Agilent NMR (400 MHz) Spectrometer using $CDCl_3$ as solvent. In addition, using tetramethylsilane (TMS) as an internal reference and the chemical shift values (δ) are given in parts per million (ppm). The 1H NMR data are reported different spin multiplicity were showed by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sext (sextet) m (multiplet), brs (broad singlet), coupling constants (J), were reported in hertz (Hz) and number of protons. The ^{13}C NMR data are reported types of carbon that includes: C, CH, CH_2, and CH_3. All reactions were monitored by thin layer chromatography (TLC) coated with (0.25 mm) silica gel plates, and visualization was achieved using UV light flash chromatography was performed by using silica gel (Merck 230-400 mesh), using the mobile phase indicated. Separation and Purification of compounds were checked by TLC after that by column chromatography. All of the organic solvents used were dried over appropriate drying agents and distilled prior to use. Unless otherwise noted, organic extracts were dried with $MgSO_4$.

3.1. Synthesis of 2-Iodo-N, N-Dimethylaniline (ARH1)

To a solution of 2-iodoaniline (4 g, 18.2 mmole), K_2CO_3 (5.047 g, 36.5 mmole) in DMF (10 mL) were added iodomethane (7.77 g, 54.7 mmole) in a round bottom flask. Then, the mixture was stirred for 12 hours at room temperature. When starting compound was gone, mixture was extracted with EtOAc (30 mL x 3), then washed with satd. NaCl and organic phase was dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using Hexane/EtOAc (100:1) to give ARH1 (4 g, 88%) as a light-yellow liquid (Figure 3.1). ^{1}H NMR (400 MHz, CDCl3) δ 7.85 (dd, *J* = 7.84, 1.48 Hz), 7.31 (m, 1H), 7.1 (dd, *J* = 8.04, 1.56 Hz, 1H), 6.77 (m, 1H), 2.77 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.95, 140.19, 129.08, 125.01, 120.5, 97.21, 45.03.

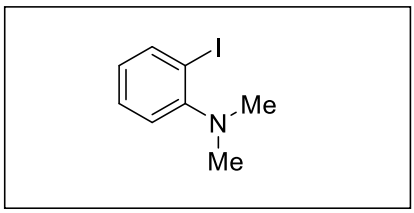


Figure 3.1. Synthesis of ARH1.

3.2. Synthesis of 1-Methyl-2-Phenyl-3-(thiophen-2-yl)-1H-indole (ARH3)

The solution of *N*, *N*-dimethyl-2-iodoaniline (2 g, 8.1 mmole), phenyl acetylene (911.1 mg, 8.9 mmole) and CuI (77.1 mg, 0.41 mmole) in Et_3N (6 mL) was added $PdCl_2(PPh_3)_2$ (284.1 mg, 0.405 mmole) in the microwave vial. Then, the mixture was stirred under MW irradiation at 65 ^oC for 30 min. After coupling reaction (ARH2), 2-iodothiophene (5.671 g, 27.1 mmole) in acetonitrile (3 mL) was poured into reaction vials, and the reaction was mixed under MW irradiation for additional 30 min at 90 ^oC. When starting compound was gone, mixture was extracted with EtOAc (30 mL x 3), then washed with satd. NaCl and organic phase was dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using Hexane/EtOAc (100:1) to give ARH3 (1.887 g, 72%) as a solid light-yellow (Figure 3.2). ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 4.2 Hz, 1H), 7.47 (d, *J* = 13.9 Hz, 6H), 7.36 (d, *J* = 1.4 Hz, 1H), 7.28 (s, 1H), 7.17 (s, 1H), 6.99 (dd, *J* = 11.5, 5.5 Hz, 2H), 3.65 (s, 3H) (Figure 3.3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.31, 137.23, 137.03, 131.69, 131.24, 128.63, 128.52, 126.84, 124.76, 123.31, 122.40, 120.49, 119.91, 109.58, 108.49, 77.38, 77.06, 76.74, 30.89 (Figure 3.4).

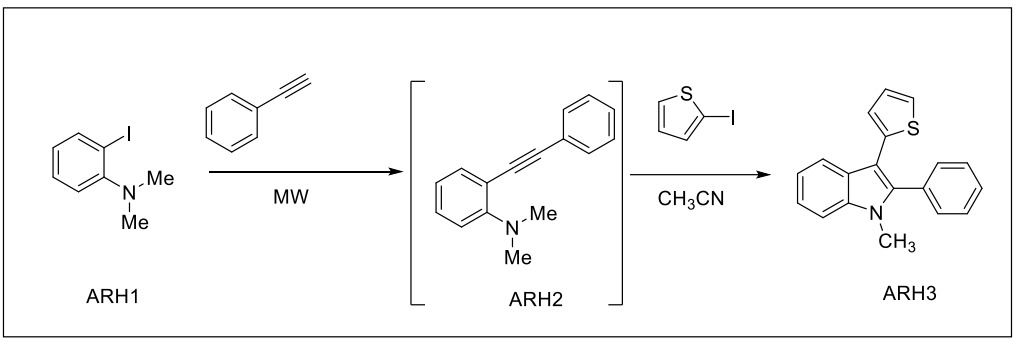


Figure 3.2. Synthesis of ARH3.

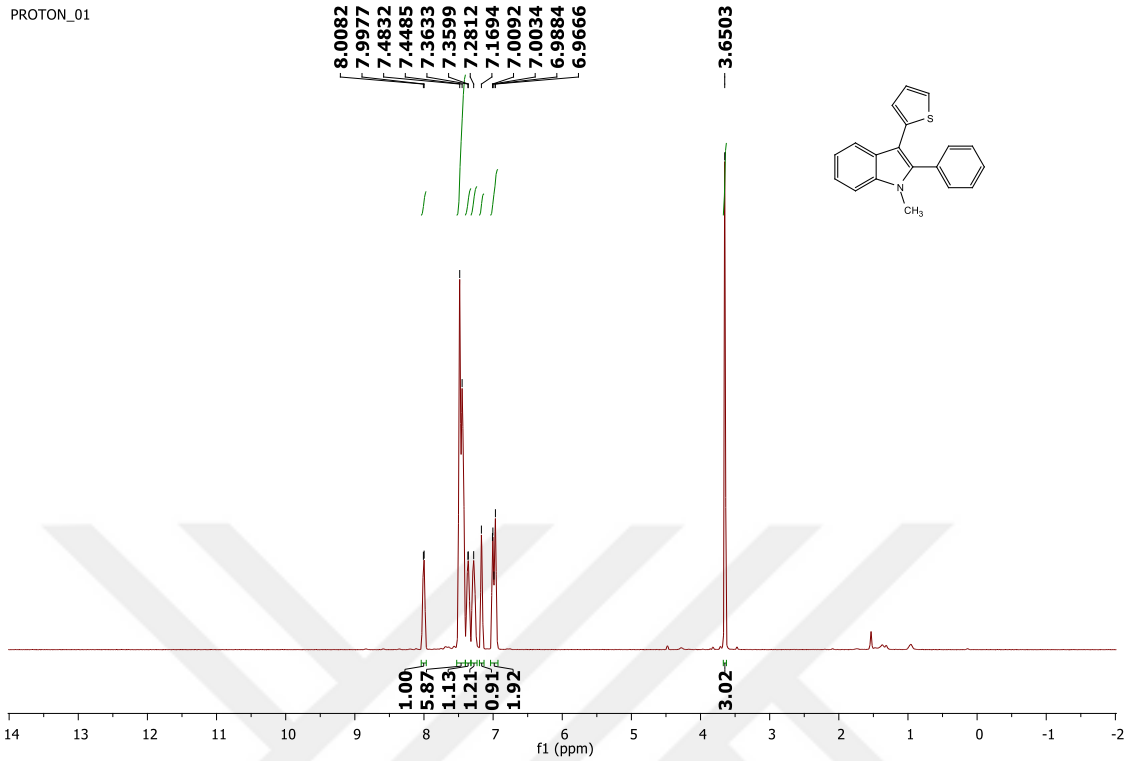


Figure 3.3. [1]HNMR spectra ARH3.

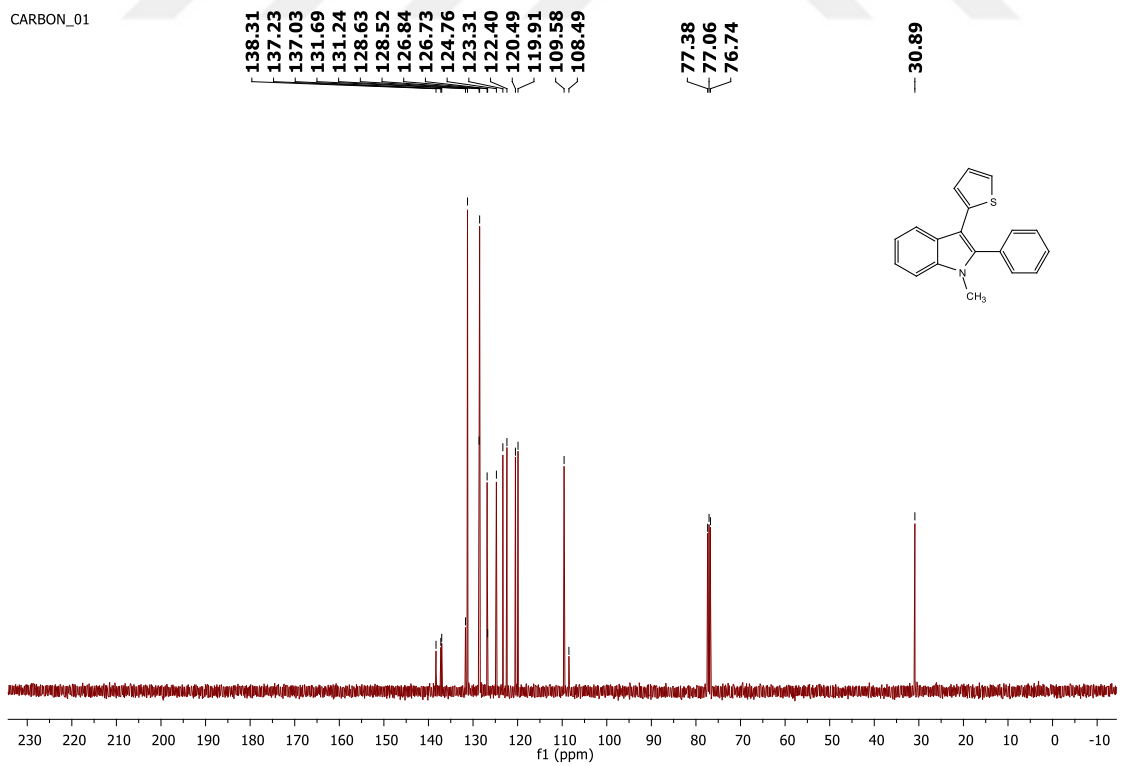
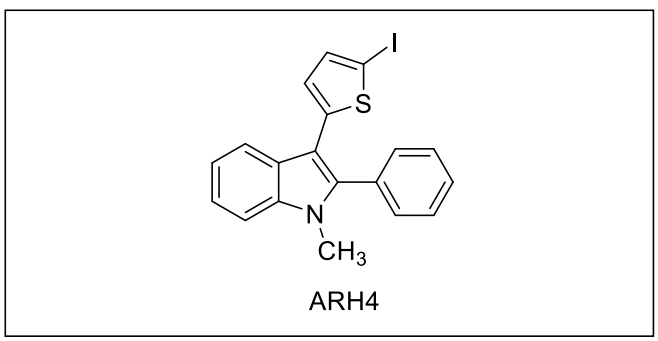


Figure 3.4. [13]C NMR spectra ARH3.

3.3. Synthesis of 3-(5-Iodothiophen-2-yl)-1-Methyl-2-Phenyl-1H-indole (ARH4)

To a solution of 1-methyl-2-phenyl-3-(thiophen-2-yl)-1H-indole ARH3 (200 mg, 0.7 mmole) in chloroform (5 mL) were added N-Iodo succinimide (NIS) (171.2 mg, 0.7 mmol) under inert atmosphere. Then, the mixture was stirred at room temperature for 12 hours. When starting compound was gone, mixture was extracted with EtOAc (30 mL x 3), then washed with satd. NaCl and organic phase was dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using Hexane/EtOAc (100:1) to give ARH4 (200 g, 69%) as a white solid (Figure 3.5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (ddd, *J* = 12.1, 7.3, 4.8 Hz, 1H), 7.49 (m, 3H), 7.41 (m, 3H), 7.34 (ddd, *J* = 9.0, 1.8, 0.9 Hz, 1H), 7.26 (s, 1H), 7.10 (ddd, *J* = 3.0, 2.5, 0.7 Hz, 1H), 6.60 (m,1H), 3.62 (m, 3H) (Figure 3.6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.60, 138.55, 136.93, 136.85, 131.23, 131.08, 128.89, 128.66, 126.42, 126.34, 122.55, 120.70, 119.65 109.67, 107.87, 77.35, 77.04, 76.72, 70.43, 30.89 (Figure 3.7). FT-IR (ATR) 2987.74, 2970.38, 2900.94 (C-H), 1932.67, 1797.66, 1668.43 (C-H).



ARH4

Figure 3.5.Synthesis of ARH4.

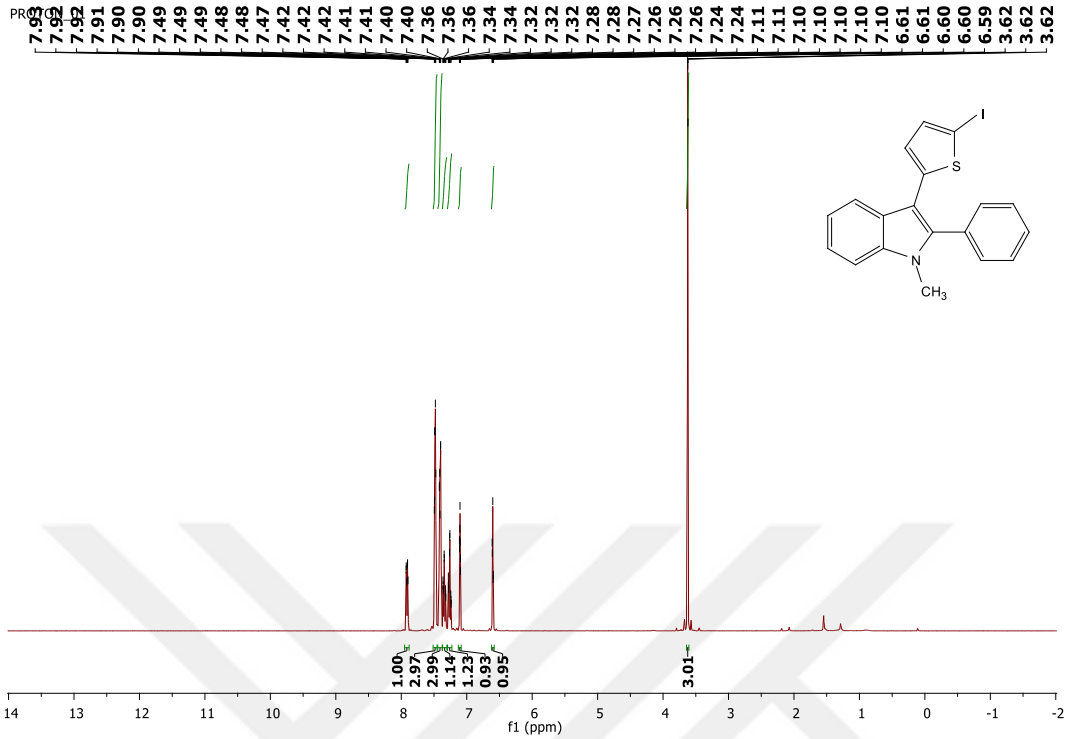


Figure 3.6. ^{1}H NMR spectra ARH4.

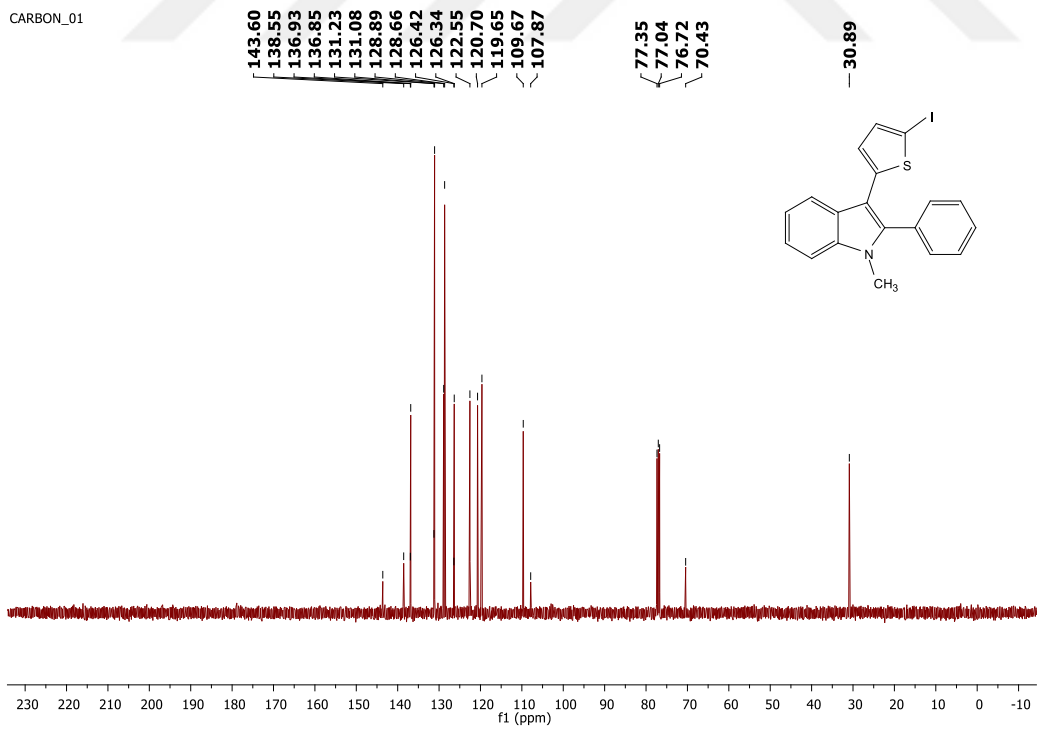


Figure 3.7. ^{13}C NMR spectra ARH4.

3.4. Synthesis of 5-(5-(1-Methyl-2-Phenyl-1H-indol-3-yl) thiophen-2-yl) Furan-2-Carbaldehyde (ARH5) via Suzuki-Miyaura Coupling Reaction

To a solution of 3-(5-iodothiophen-2-yl)-1-methyl-2-phenyl-1H-indole ARH4 (80 mg, 0.19 mmole), 5-formylfuran-2-boronicacid (40.5 mg, 0.29 mmole) in methanol (6 mL) were added $Pd(PPh_3)_4$ (44.60 mg, 0.04mmole) and $LiCO_3$ (28.48 mg, 0.39 mmol) under inert atmosphere. Then, the mixture was stirred under MW irradiation at 70 ^{0}C for 30 min. When starting compound was gone, mixture was extracted with EtOAc (30 mL x 3), washed with satd. NaCl and organic phase was dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using Hexane/EtOAc (100:1) to give ARH5 (52 g, 70%) as a yellow solid (Figure 3.8).

^{1}H NMR (400 MHz$CDCl_3$) δ 9.55 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.50 (m, 3H), 7.42 (m, 3H), 7.31 (m, 5H), 6.83 (d, *J* = 3.9 Hz, 1H), 6.55 (d, *J* = 3.7 Hz, 1H), 3.63 (s, 3H) (Figure 3.9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.20, 146.83, 140.70, 138.98, 137.06, 131.23, 131.03, 129.06, 128.79, 126.61, 125.49, 122.70, 120.92, 119.76, 109.77, 106.75, 77.32, 77.00, 76.68, 30.89, 29.69 (Figure 3.10). FT-IR (ATR) 2922.16, 2900.91, 2854.65 (C-H, aldehyde), 1726.29, 1666.5 (C=O).

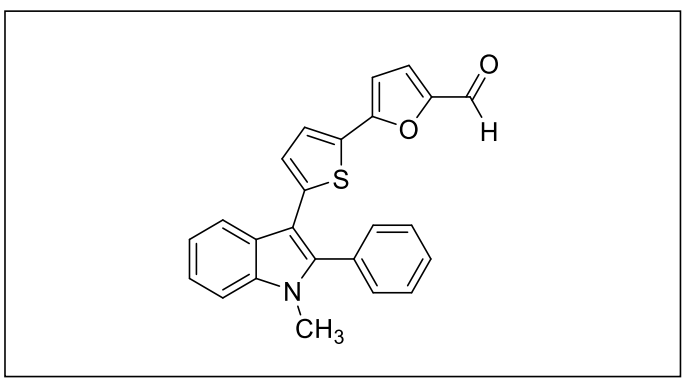


Figure 3.8. Synthesis of ARH5.

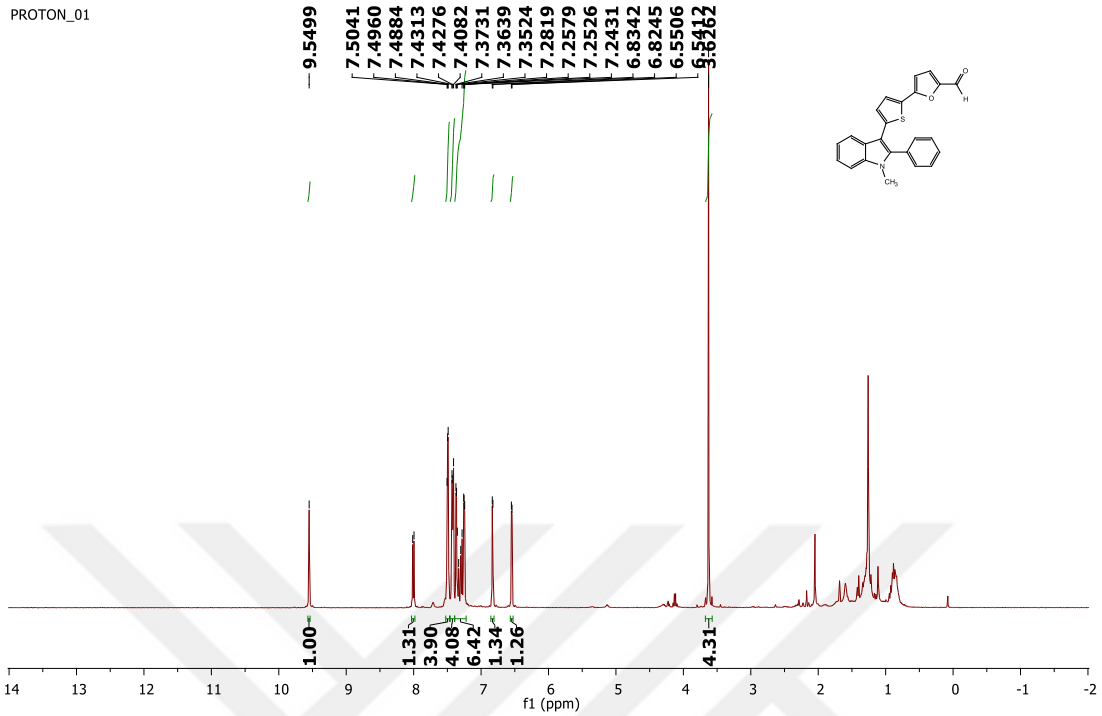


Figure 3.9. ^{1}H NMR spectra ARH5.

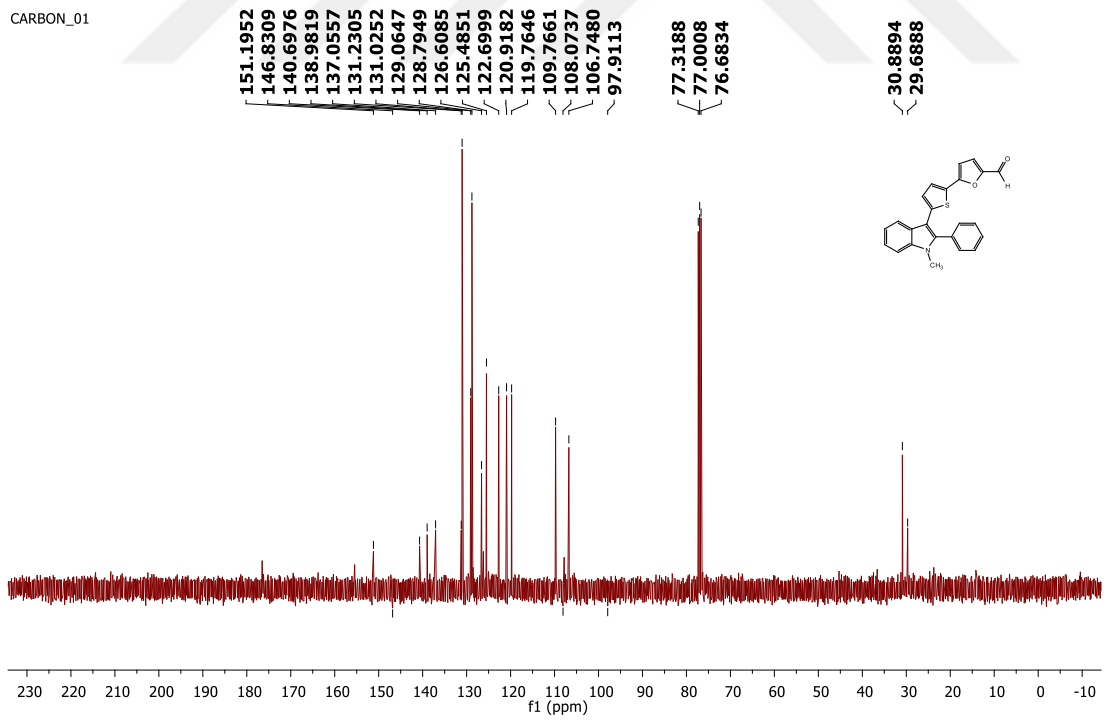


Figure 3.10. ^{13}C NMR spectra ARH5.

3.5. Synthesis of 5'-(1-Methyl-2-Phenyl-1H-indol-3-yl)-[2,2'-bithiophene]-5-Carbaldehyde (ARH7)

To a solution of 3-(5-iodothiophen-2-yl)-1-methyl-2-phenyl-1H-indole (100 mg, 0.24 mmole), 5-formylthiophin-2-boronicacid (56.5 mg, 0.36 mmole) in methanol (6 mL) were added $Pd(PPh_3)_4$ (55.7 mg, 0.05 mmole) and $LiCO_3$ (35.6 mg, 0.48 mmole) under inert atmosphere. Then, the mixture was stirred under MW irradiation at 70 ^{0}C for 30 min. When starting compound was gone, mixture was extracted with EtOAc (30 mL x 3), washed with satd. NaCl and organic phase was dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using Hexane/EtOAc (100:1) to give ARH7 (84 g, 84%) as a yellow solid (Figure 3.11).

^{1}H NMR (400 MHz, $CDCI_3$) δ 9.81 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 3.9 Hz, 1H), 7.34 (m, 11H), 6.81 (d, *J* = 3.8 Hz, 1H), 3.63 (s, 3H) (Figure 3.12). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.32, 140.24, 138.95, 137.48, 137.05, 131.26, 131.05, 129.09, 128.79, 126.42, 125.54, 123.22, 122.69, 120.91, 119.74, 109.78, 30.88 (Figure 3.13). FT-IR (ATR) 2848.86 (C-H, aldehyde), 1726.29, 1656.85, 1535.34 (C=O).

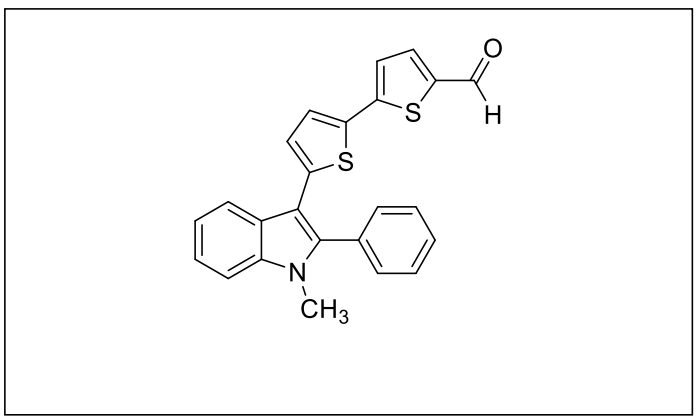


Figure 3.11. Synthesis of ARH7.

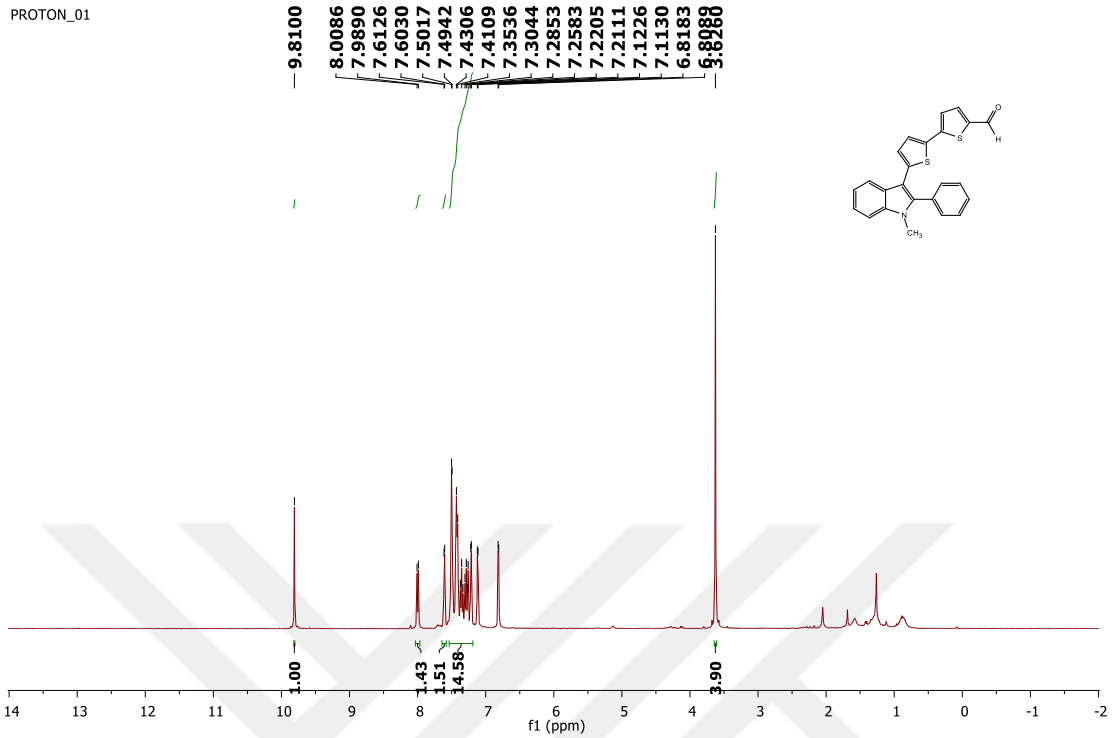


Figure 3.12. ^{1}H NMR spectra ARH7.

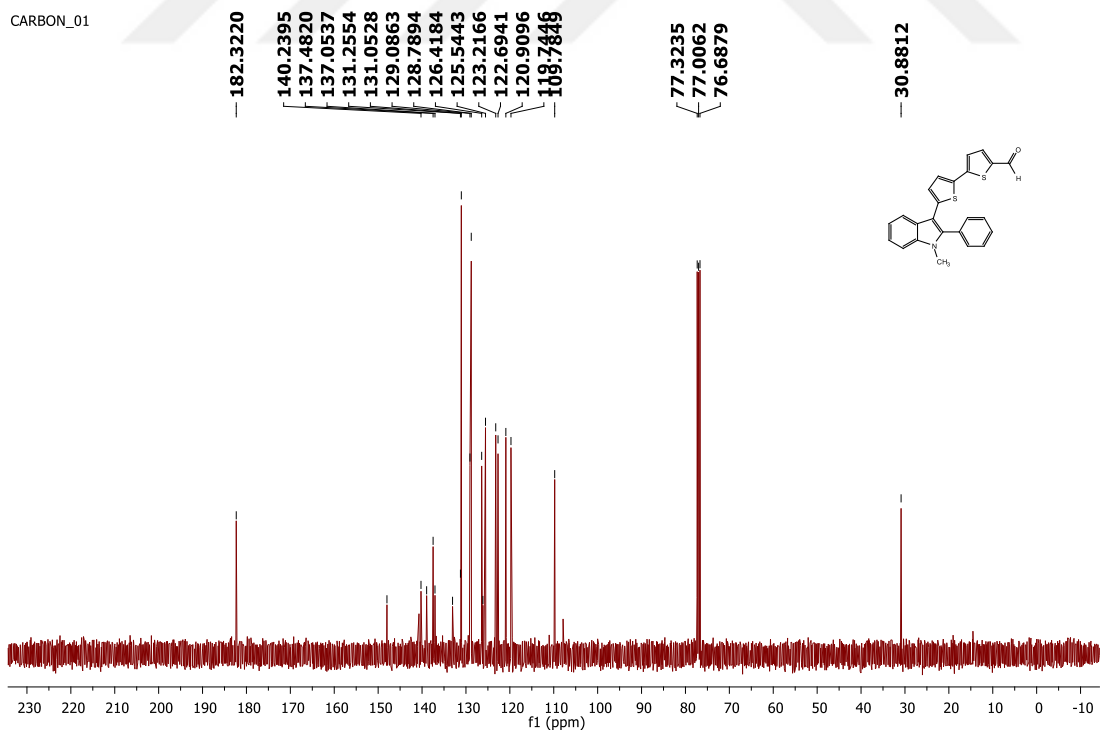


Figure 3.13. ^{13}C NMR spectra ARH7.

3.6. Condensation Reaction, 2-((5-(5-(1-Methyl-2-Phenyl-1H-indol-3-yl) Thiophen-2-yl) Furan-2-yl) Methylene) Malononitrile (ARH8)

To a solution of 5-(5-(1-methyl-2-phenyl-1H-indol-3-yl) thiophen-2-yl) furan-2-carbaldehyde (30 mg, 0.078 mmole) and malononitrile (20.7 mg, 0.31 mmole) in toluene (5 mL) were added Al_2O_3 (87.8 mg, 0.86 mmole) under inert atmosphere. Then, the mixture was stirred under MW irradiation at 120 ^{0}C for 4 hours. When starting compound was gone, mixture was extracted with EtOAc (30 mL x 3), washed with satd. NaCl and organic phase was dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using Hexane/EtOAc (100:1) to give ARH8 (26 g, 76%) as a pink solid (Figure 3.14).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 1H), 7.47 (m, 7H), 7.36 (m, 1H), 7.29 (m, 3H), 6.84 (d, *J* = 3.9 Hz, 1H), 6.62 (d, *J* = 3.9 Hz, 1H), 3.62 (s, 3H) (Figure 3.15). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.53, 142.83, 139.42, 137.07, 131.08, 130.95, 129.28, 128.92, 125.85, 122.84, 121.15, 119.71, 113.76, 109.89, 108.83, 77.33, 77.01, 76.70, 68.14 (Figure 3.16). FT-IR (ATR) 2900.94, 2220.07 (CN).

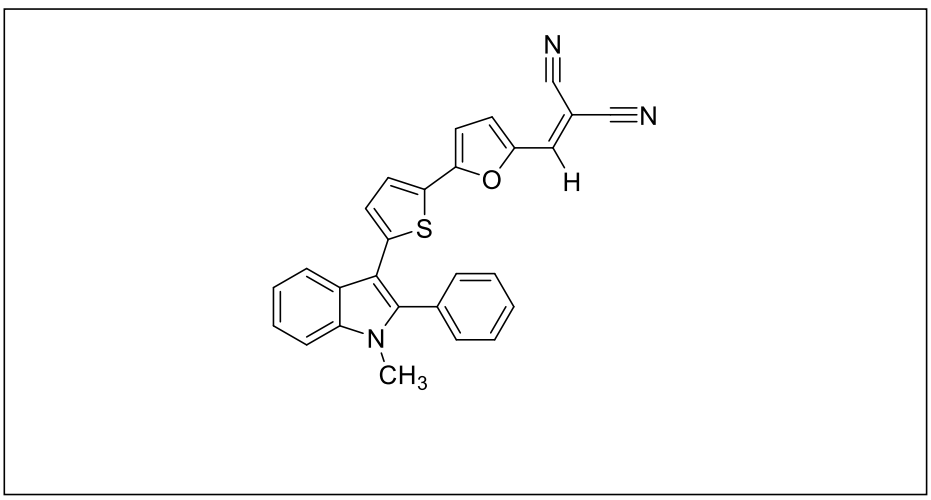


Figure 3.14. Synthesis of ARH8.

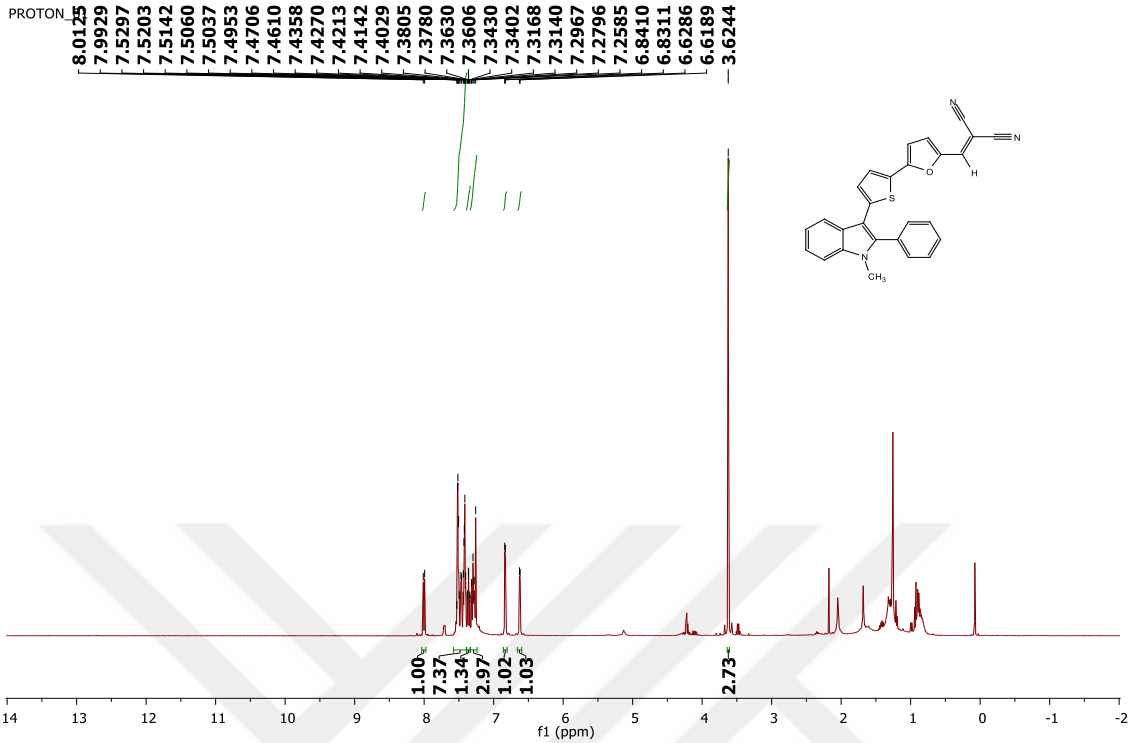


Figure 3.15. ^{1}H NMR spectra ARH8.

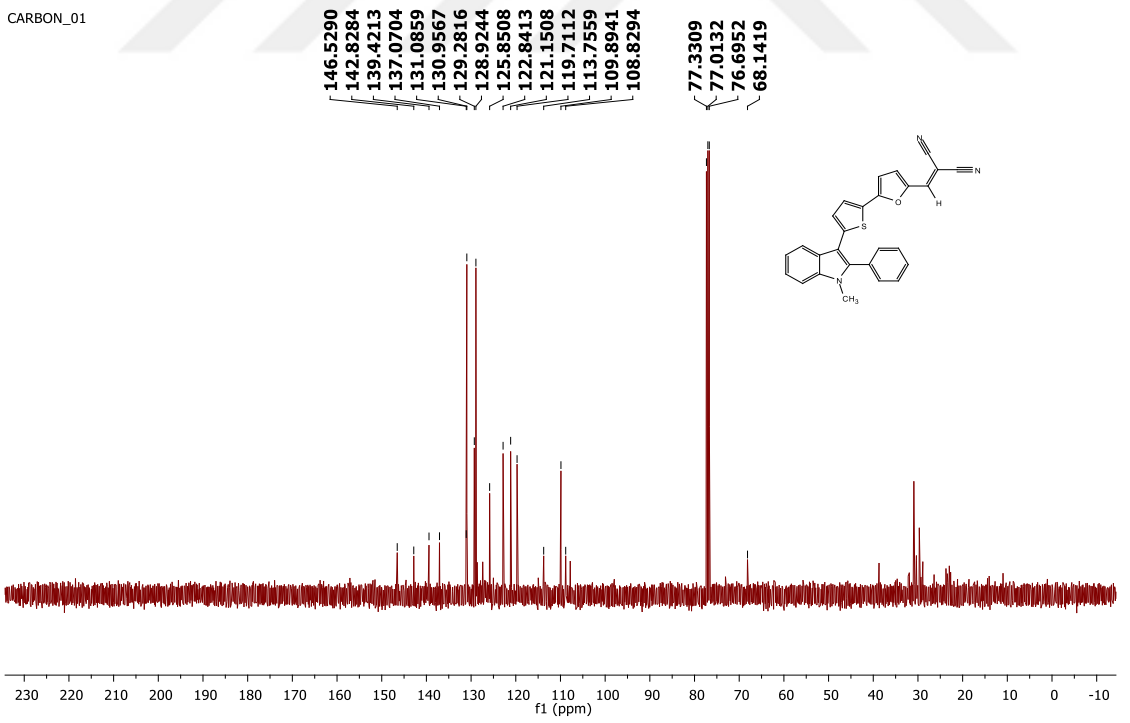


Figure 3.16. ^{13}C NMR spectra ARH8.

3.7. Synthesis of 2-((5'-(1-Methyl-2-Phenyl-1H-indol-3-yl)-[2,2'-bithiophen]-5-yl) Methylene) Malononitrile (ARH10)

To a solution of 5'-(1-methyl-2-phenyl-1H-indol-3-yl)-[2,2'-bithiophene]-5-carbaldehyde (40 mg, 0.10 mmole), malononitril (26.4 mg, 0.4 mmole) in toluene (5 mL) were added Al_2O_3 (112.156 mg, 1.1 mmol) under inert atmosphere. Then, the mixture was stirred under MW irradiation at 120 ^{0}C for 4 hours. When starting compound was gone, mixture was extracted with EtOAc (30 mL x 3), washed with satd. NaCl and organic phase was dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using Hexane/EtOAc (100:1) to give ARH10 (27 g, 60%) as a pink solid (Figure 3.17). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.64 (m, 1H), 7.52 (m, 4H), 7.42 (m, 3H), 7.36 (ddd, *J* = 11.4, 6.3, 2.8 Hz, 1H), 7.29 (m, 2H), 7.11 (d, *J* = 4.2 Hz, 1H), 6.79 (d, *J* = 3.9 Hz, 1H), 3.62 (m, 3H) (Figure 3.18). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.45, 149.86, 142.19, 140.34, 139.33, 137.08, 132.51, 131.99, 131.13, 129.27, 128.93, 127.80, 125.90, 125.74, 123.58, 122.87, 121.14, 119.74, 114.63, 113.74, 109.93, 107.76, 77.34, 77.02, 76.71, 74.48, 30.92 (Figure 3.19). FT-IR (ATR) 2924.09, 2220.07 (CN).

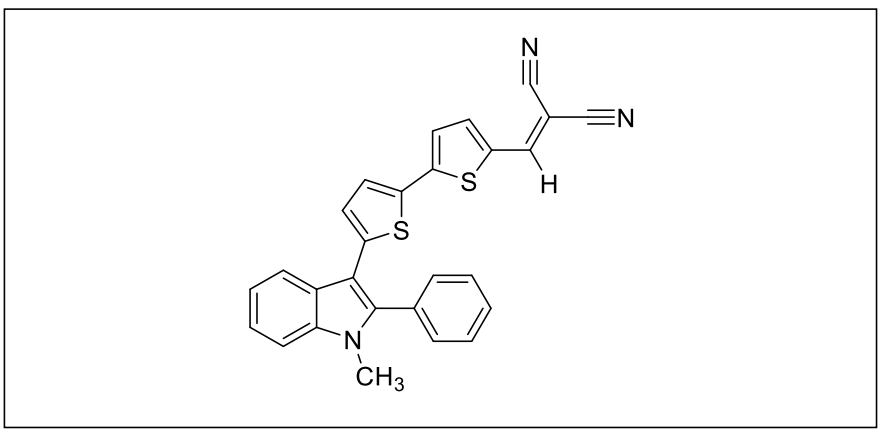


Figure 3.17. Synthesis of ARH10.

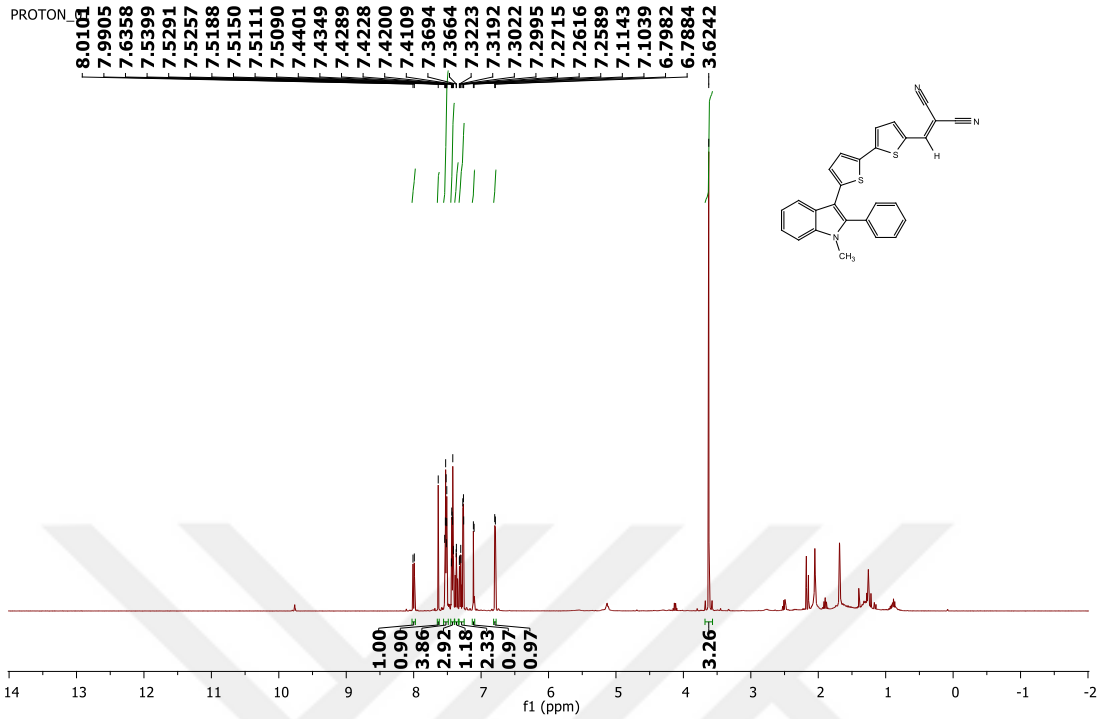


Figure 3.18. ^{1}H NMR spectra ARH10.

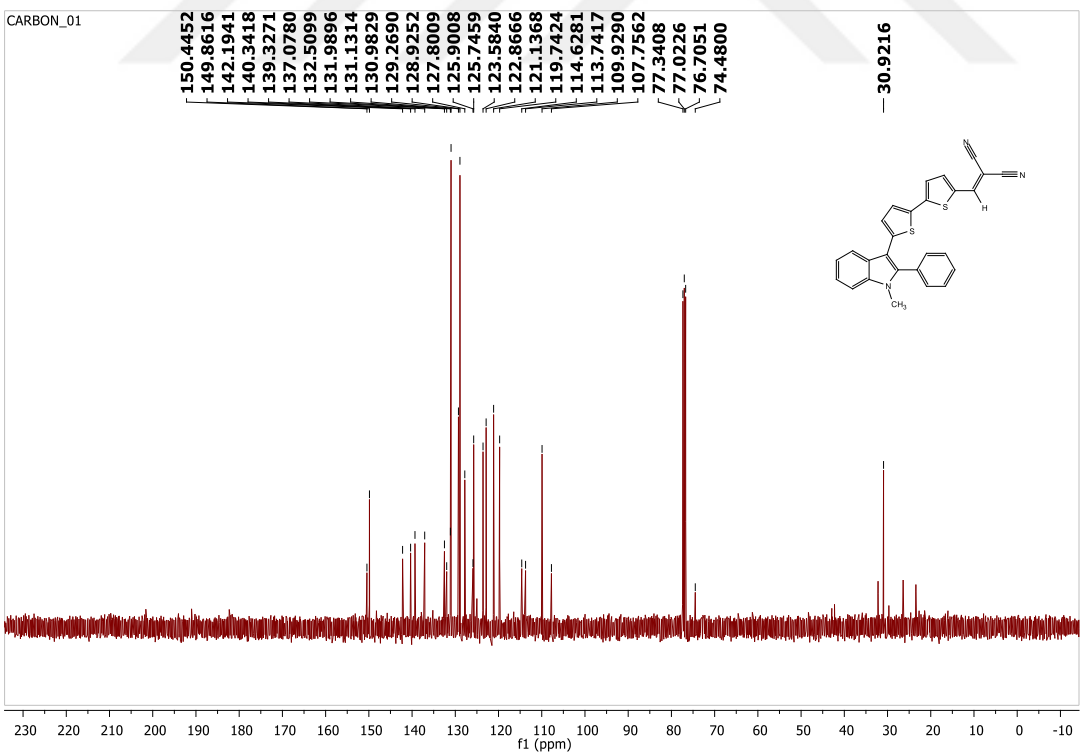


Figure 3.19. ^{13}C NMR spectra ARH10.

4. RESULTS AND DISCUSSION

In the present study, novel indole derivatives including strong electron withdrawing groups were designed and synthesized by using following reaction methodologies;

1. One-pot two step electrophilic cyclization reaction,
2. Electrophilic aromatic substitution reaction,
3. Pd-catalyzed Suzuki-Miyaura coupling reactions,
4. Condensation reactions.

4.1. One-pot Two Step Electrophilic Cyclization Reaction

Recently Larock et al. were reported a new synthetic pathway for the preparation of indole derivatives. They found one-pot, three-component coupling reaction for the synthesis of indoles under the microwave irradiations. By using standard Sonogashira coupling conditions, 3-aryl-indoles was obtained in two steps reaction. In our study, we used modified Larocks methodology for the formation of ARH3 (Yue and Larock, 2004; Yue et al., 2006a). Firstly, ARH1 was prepared as a starting compound. When the ARH1 was allowed to react with phenyl acetylene in the presence of Pd/Cu catalyst system in triethyl amine under MW irradiation at 65 ^{o}C for 30 min., ARH2 intermediate was formed. Then, acetonitrile and a 2-iodothiophene was added for electrophilic cyclization reaction. ARH3 was formed after 30 min at 90 ^{o}C under MW irradiation. After purification procedure, we isolated in 72% yield of ARH3 (Figure 4.1).

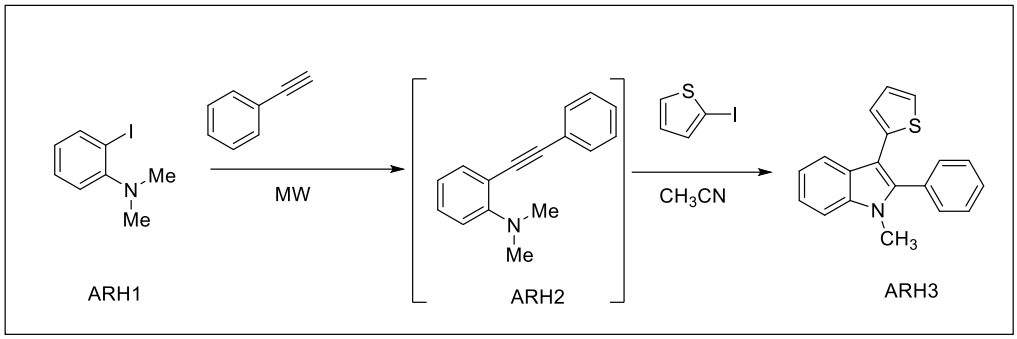


Figure 4.1. One-Pot synthesis of ARH3.

As seen in (Figure 4.2) and (Figure 4.3), the possible reaction mechanism was proposed. Sonogashira coupling mechanism was occurred in the first cycle. Then, iodothiophene activated with Pd catalyst to give the intermediate. Nitrogen's lone pair electrons make a bond with alkyne to form the carbocation intermediates. Finally, reductive elimination produces the expected product ARH3.

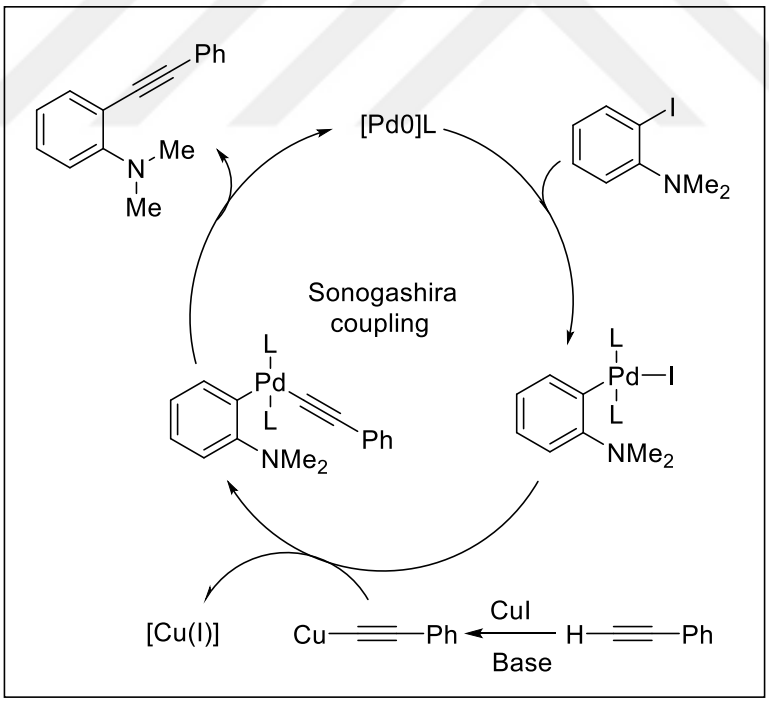


Figure 4.2. First cycle for the formation of o-alkynyl-N, N-dimethylaniline.

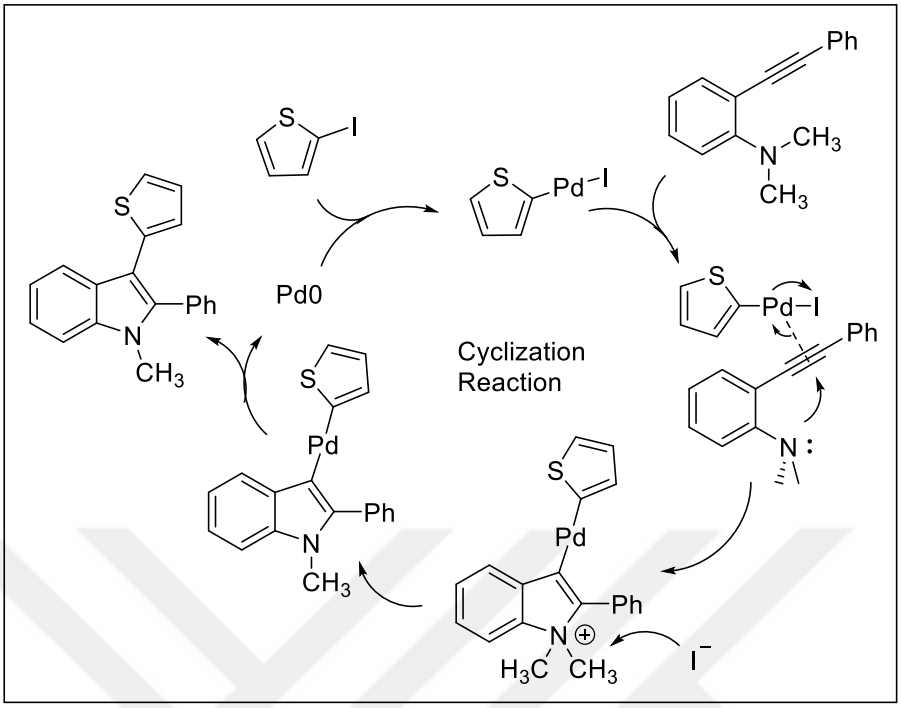


Figure 4.3. Second cycle for the formation of ARH3.

4.2. Synthesis 3-(5-Iodothiophen-2-yl)-1-Methyl-2-Phenyl-1H-indole (ARH4) via Electrophilic Aromatic Substitution Reaction

3-(5-Iodothiophen-2-yl)-1-methyl-2-phenyl-1H-indole (ARH4) was synthesized by using electrophilic aromatic substitution reaction. In literature, there are a variety of synthetic procedure for the formation of halo-substituted aromatic compounds. Bromide, iodide is used as an electrophile, and this type reactions need Lewis acids as a catalyst. On the other hand, NIS or NBS give the similar reactions. In the present study, we used NIS for the synthesis of 3-(5-iodothiophen-2-yl)-1-methyl-2-phenyl-1H-indole (ARH4), (Figure 4.4). If 1-methyl-2-phenyl-3-(thiophen-2-yl)-1H-indole (ARH3) was allowed to react with NIS in chloroform at room temperature, 3-(5-iodothiophen-2-yl)-1-methyl-2-phenyl-1H-indole (ARH4) was isolated in 69% yield.

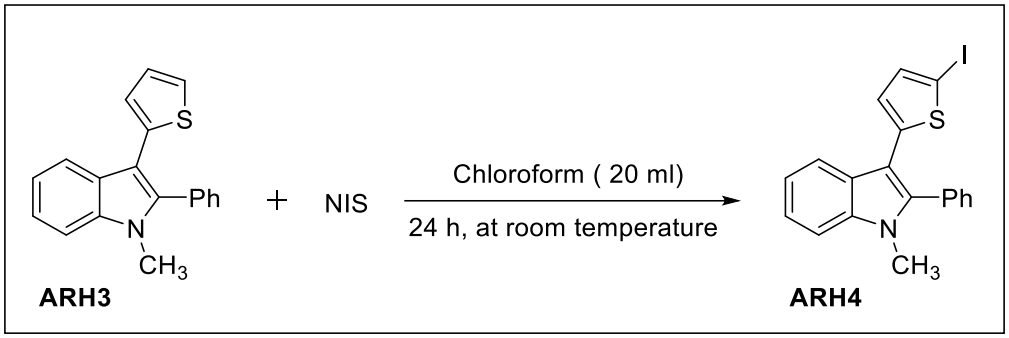


Figure 4.4. Synthesis of 3-(5-iodothiophen-2-yl)-1-methyl-2-phenyl-1H-indole (ARH4).

4.3. Pd-Catalyzed Suzuki-Miyaura Coupling Reactions

After isolation of 3-(5-iodothiophen-2-yl)-1-methyl-2-phenyl-1H-indole (ARH4), we were focused on the synthesis of aldehyde substituted indole derivatives via coupling reactions. Suzuki-Miyaura is the well-known coupling reaction to form the new carbon-carbon bonds between halo-aryl compounds and aryl boronic acids (Bringmann and Menche, 2001; Roberts et al., 2007; Bringmann et al., 2008). Suzuki-Miyaura coupling reaction needs a palladium catalyst like $Pd(PPh_3)_4$, and boronic acid derivatives. There are a variety of modified Suzuki-Miyaura coupling reactions using for the preparation of organic compounds. Some of procedures gave the high yields of heteroaromatics, others did not form the coupling reactions. In the lights of our knowledge, we applied our best Suzuki-Miyaura procedure for the synthesis of ARH5 (Figure 4.5). When ARH 4 was reacted with 5-formylfuran-2-boronicacid in methanol with Li_2CO_3under MW irradiation, desired product ARH5 was formed in 70% yield. The ARH5 was characterized by using spectroscopic methods including ^{1}H NMR, ^{13}C NMR, FT-IR and Mass. As seen in ^{1}H NMR spectra, there is a singlet at 9.5 ppm belonging to aldehyde's proton peak. Aromatic protons are shifted between 6.5 ppm and 8.2 ppm. Moreover, carbonyl's carbon shifted at 175 ppm in ^{13}C NMR. Carbonyl groups also gave a sharp peak in FT-IR spectra.

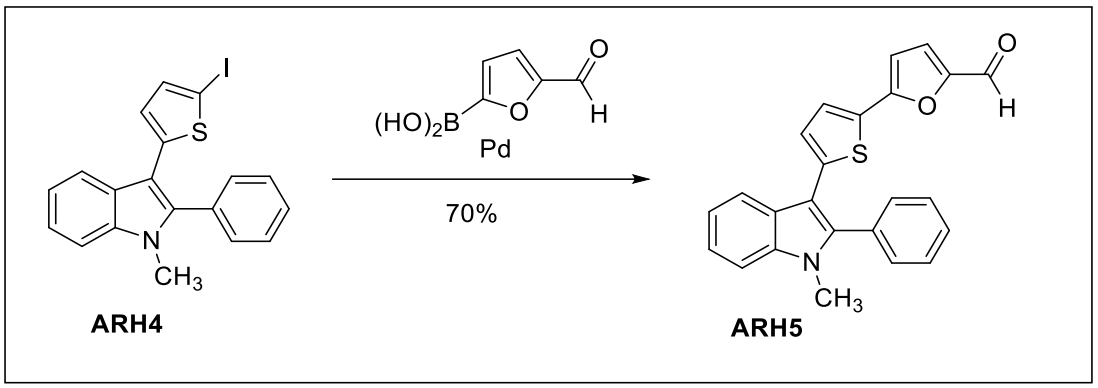


Figure 4.5. Synthesis5-(5-(1-methyl-2-phenyl-1H-indol-3-yl) thiophen-2-yl) furan-2-carbaldehyde (ARH5).

Next, we synthesized ARH7 by starting from the ARH4 (Figure 4.6). Thiophene and its derivatives have very critical roles not only biological applications, but also material applications. Thiophenes have been used as a building block in drugs. In addition, they are important key structures for the formation of polymers. Therefore, thiophene based new indoles may be displayed higher activities than currents, or may be creates new activities. In our study, the reaction between ARH4 and 5-formylthiophin-2-boronic acid in the presence of Pd-catalyzed gave the corresponding aldehyde functionalized indole ARH7. The isolated yield was found as 84% yield. We also characterized ARH7 by using spectroscopic methods.

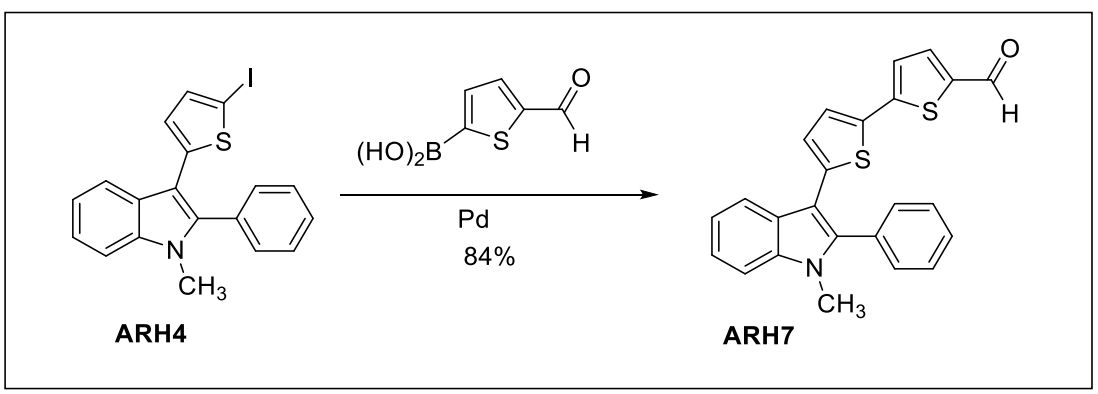


Figure 4.6. Synthesis of compound (ARH7).

4.4. Condensation Reactions

Condensation reactions have been used for the formation of a larger molecule from two smaller ones. Last parts of our study, Knoevenagel condensation reactions was applied for the synthesis of strong electron withdrawing group substituted indoles (Zanin et al., 2018). There are different kinds of condensation reaction in organic chemistry. These reactions need to basic medium, mostly form the one product with excellent yields. Last years, we synthesized novel heteroaromatic compounds by using condensation reactions. When ARH5 was allowed to react with malononitrile in the presence of aluminum oxide in toluene under MW irradiation, condensation reaction gave the ARH8 (76%) as only product. The same reaction condition was employed for the formation of ARH10, we obtained in 60% yield of desired product. After isolation, ARH8 and ARH10 were characterized by using NMR, FT-IR and mass spectrometers. As seen (Figure 4.7) and (Figure 4.8).

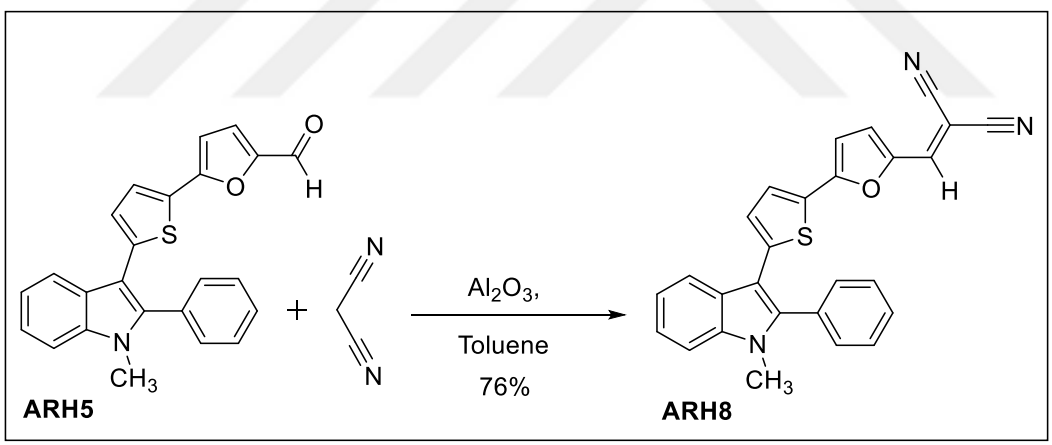


Figure 4.7. Synthesis of compound ARH8.

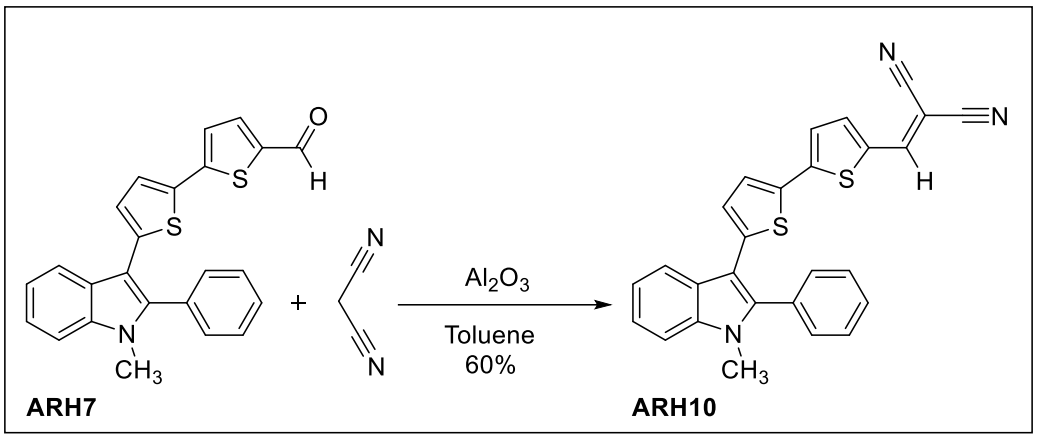


Figure 4.8. Syntheses of compound ARH10.

There are some characteristic groups like cyano on the structures. After condensation reaction, aldehyde functional groups were gone. In addition, FT-IR spectra improved that there is a sharp CN peaks at 2220 cm^{-1}. Reaction mechanism for condensation reactions is seen in (Figure 4.9).

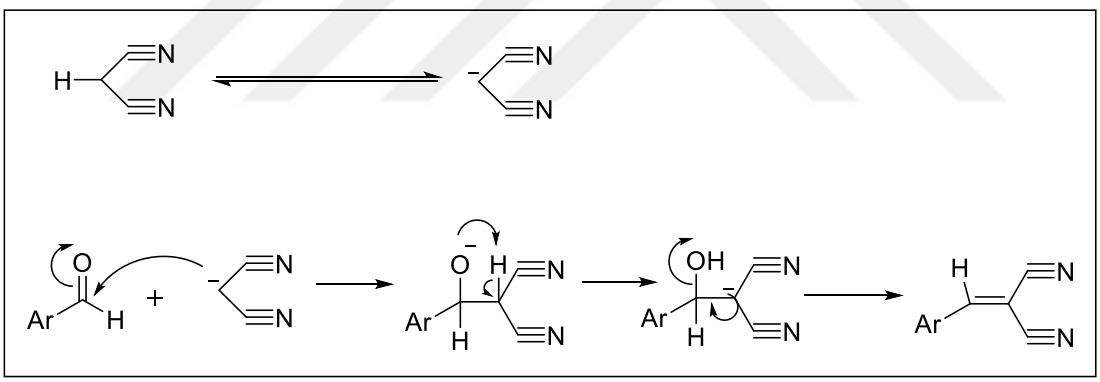


Figure 4.9. Mechanism for condensation reaction.

5. CONCLUSION

In the present study, novel indole derivatives including strong electron withdrawing groups were synthesized and characterized. Firstly, one pot two step cyclization reaction was used for the synthesis of 1-methyl-2-phenyl-3-(thiophen-2-yl)-1H-indole (ARH3). The cyclization reaction formed the desired compounds with 72% yield. Then halogenation reaction was applied to formation of 3-(5-iodothiophen-2-yl)-1-methyl-2-phenyl-1H-indole (ARH4) (69%). Suzuki-Miyaura coupling reactions were carried out for the synthesis of 5-(5-(1-methyl-2-phenyl-1H-indol-3-yl) thiophen-2-yl) furan-2-carbaldehyde (ARH5) and 5'-(1-methyl-2-phenyl-1H-indol-3-yl)-[2,2'-bithiophene]-5-carbaldehyde (ARH7). ARH5 and ARH7 were obtained in 70% and 84% yields, respectively. Finally, condensation reactions were employed for the synthesis of ARH8 (76%) and ARH10 (60%). New indoles may be new candidates not only biological applications but also material applications.

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EXTENDED TURKISH SUMMARY
(GENİŞLETİLMİŞ TÜRKÇE ÖZET)

BİYOLOJİK ÖNEME SAHİP YENİ İNDOL TÜREVLERİNİN SENTEZİ

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Yüksek Lisans Tezi, Kimya Anabilim Dalı
Danışman: Prof. Dr. Arif KIVRAK
Ocak 2021, 61 Sayfa

ÖZ

İndol türevleri, heterosiklik bileşiklerin en önemli üyeleridir. İndol içeren çok önemli ve farklı heterosiklikler vardır ve bunlar farklı hastalıkların tedavisinde kullanılmaktadır. Anti-bakteriyel, anti-parazitik, anti-kanser, anti-enflamatuarve anti-tümör olarak kullanılan indol türevleri söz konusudur. Bu çalışmada, yeni indol türevleri tasarlanmış ve sentezlenmiştir. İlk olarak, 3-tiyofenil-indol sentezi için one-pot halkalaşma tepkimesi kullanılmış, ardından iyodo içeren indollerin sentezi için elektrofilik aromatik yerdeğiştirme tepkimeleri uygulanmıştır. Kondenzasyon tepkimesinden önce, aldehit türevlerinin sentezi için Suzuki-Miyaura kenetlenme tepkimesi kullanılmıştır. Sentezlenen tüm bileşiklerin yapısal karakterizasyonları spektroskopik yöntemler kullanılarak tamamlanmıştır.

Anahtar kelimeler: Halkalaşma tepkimeleri, Kondenzasyon tepkimesi, Indol, Suzuki-Miyaura kenetlenme tepkimesi.

1. GİRİŞ

Son yüzyılda farklı hastalıkların tedavisi için yeni heterosiklik maddelerin sentezi ve izolasyonu çok önem kazanmıştır. İlaç ARGE çalışmalarında ana yapıya farklı gruplar bağlanarak temel yapının biyolojik özelliği artırılmakta veya tamamen yeni bir özelliğe sahip yeni bir molekül elde edilmektedir. Ticari olarak kullandığımız ilaçların yapılarına bakıldığında çoğunlukla yapısında en az bir hetero atom bulunan organik maddeler

olduğu görülmektedir. Bir organik yapının ilaç olabilmesi için belli kuralları söz konusudur. İlk olarak heteroaromatik moleküllerin tasarımı, sentezi, saflaştırılması ve karakterizasyonudur. Tasarım aşamasında ilaç potansiyeli olabilmesi için Lipinskii Kuralına (belli sayıda heteroatom, çözünürlük, moleküler ağırlığının 500 g/mol den az olması vb.) uyması gereklidir. İkinci aşamada ise hedeflenen heteroaromatik bileşiğin yüksek verimler ve uygulanabilir yöntemler ile sentezlenmesi gerekmektedir. İlaç uygulamaları için sentezlenen bileşiğin saf olması doğru sonuçların elde edilmesi için büyük önem arz etmektedir. Ayrıca yapıların farklı sübstitüentlere sahip olması veya türevlendirilebilir olması ilaç araştırmaları için kritiktir. Son yıllarda kanser başta olmak üzere farklı hastalıkların tedavisinde kullanılabilecek yeni heteroaromatik moleküllerin sentezi ve biyolojik özellikleri üzerine oldukça yoğun çalışmalar devam etmektedir. Günümüzde doğada bulunan organik yapılardan bazılarını ilaç olarak kullanmaktayız. Ancak doğada bulunan ve keşfedilmeyi bekleyen ne kadar madde olduğu büyük bir soru işaretidir. Keşfedilmiş yapıların sentetik olarak elde edilmesi kadar henüz doğada olup olmadığını bilmediğimiz yeni hetero- veya karbo- organik maddelerin elde edilmesi de çok önemlidir.

Son çalışmalar da indol ve yapısında indole içeren yeni nesil türevlerinin üzerine önemli sonuçlar elde edilmiştir. Literatüre bakıldığında hayati sistemimin için kritik öneme sahip. Indoller olduğu kadar farklı hastalıkalrın tedavisinde kullanılan indol türevleride söz konusudur. Biyolojik önemi henüz bilinmeyen ve hastalıklara karşı çok yeni ve farklı davranımlar gösterebilecek yeni indol türevlerin sentezlenmesi ilaç araştırmaları için çok önemlidir. Bu çalışmada geliştirdiğimiz yeni yöntemler ile yeni indol türevleri sentezlenmiştir.

2. BULGULAR VE TARTIŞMA

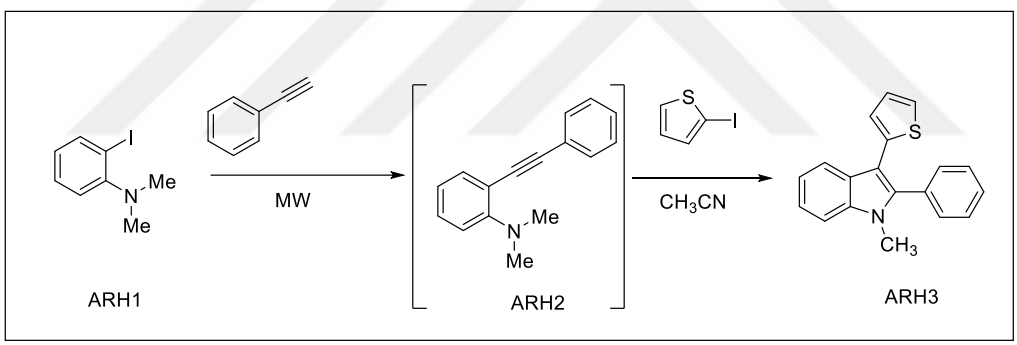
Bu çalışmada, güçlü elektron çekme grupları içeren yeni indol türevleri aşağıdaki tepkimeler kullanılarak sentezlenmiştir.

1. Tek kapta iki aşamalı elektrofilik Halkalaşma tepkimesi,
2. Halojenlenme Tepkimesi,
3. Pd katalizörlü Suzuki-Miyaura kenetlenme tepkimeleri,

4. Kondenzasyon tepkimeleri.

3.1. Tek Kapta iki Aşamalı Elektrofilik Halkalaşma Tepkimesi,

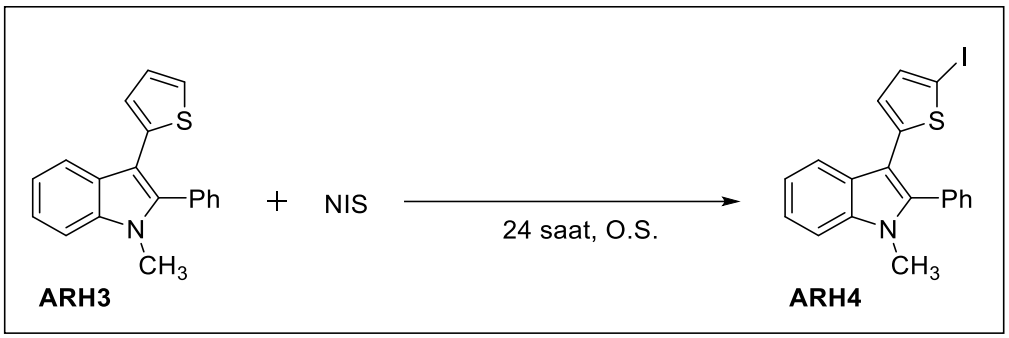
Larock ve ark. indol türevlerinin hazırlanması için yeni bir metot bulmuşlardır. Mikrodalga altında indollerin sentezi için tek kapta ve üç bileşenli tepkime kullanılarak 3-aril indollerin sentezini başarmışlardır. Çalışmamızda, ARH3 oluşumu için modifiye edilmiş Larock metodolojisi kullanılmıştır. İlk olarak, ARH1 başlangıç maddesi hazırlandı. ARH1'in, trietil amin içinde Pd /Cu katalizör sistemi varlığında, 65 ºC' de 30 dakika süreyle mikrodalga altında fenil asetilen ile tepkimeye girmesine izin verildiğinde, ARH2 ara maddesi oluşmuştur. Daha sonra elektrofilik halkalaşma reaksiyonu için asetonitril ve 2-iyodotiyofen eklenmiştir. ARH3, mikrodalga altında 90 ºC'de 30 dakika sonra oluşturuldu. Saflaştırma işleminden sonra %72 verimle ARH3 sentezlenmiştir.



Şekil E1. Tek Kapta ARH3 sentezi.

3.2. Halojenlenme Tepkimesi

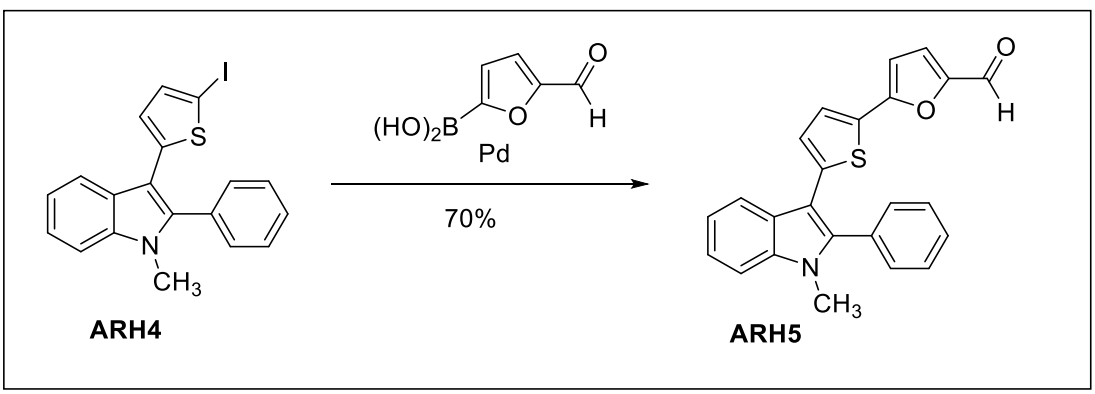
3- (5-İyodotiyofen-2-il) -1-metil-2-fenil-1 H-indol (ARH4) halojenlenme tepkimesi ile sentezlendi. Bu çalışmada, 3- (5-iyodotiyofen-2-il) -1-metil-2-fenil-1H-indol (ARH4) sentezi için NIS kullandık. 1-Metil-2-fenil-3-(tiofen-2-il)-1-H-indol (ARH3) oda sıcaklığında kloroform içinde NIS ile tepkimeye bırakıldığında, 3-(5-iyodotiofen-2-il)-1-metil-2-fenil-1H-indol (ARH4), % 69 verimle izole edildi.



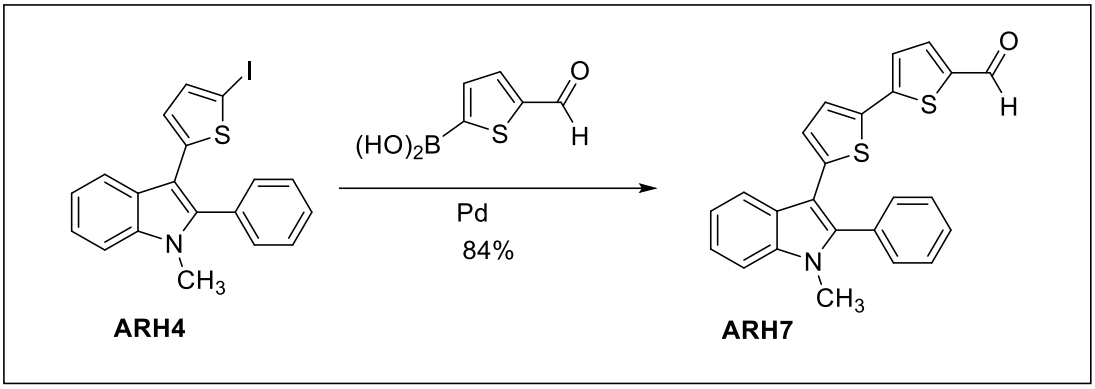
Şekil E2. ARH4 sentezi.

3.3. Pd Katalizörlü Suzuki-Miyaura Kenetlenme Tepkimeleri

3-(5-iyodotiyofen-2-il)-1-metil-2-fenil-1H-indol (ARH4) izolasyonundan sonra, yapısında aldehit fonksiyonel grubu içeren indollerin sentezi gerçekleştirilmiştir. Suzuki-Miyaura kenetlenme tepkimesi yeni karbon-karbon bağları oluşturmak için en iyi bilinen tepkimelerdendir. Bu çalışmada, ARH5 sentezi için mikrodalga altında gerçekleşen Suzuki-Miyaura tepkimesi kullanılmıştır. Tepkime sonucunda % 70 verimle hedeflenen ürün ARH5 elde edilmiştir. İzole edilen ARH5 spektroskobik yöntemler (NMR, FT-IR ve Kütle) kullanılarak karakterize edilmiştir. Aynı sentez yöntemi kullanılarak ARH7 aldehit içeren indol türevide sentezlenmiştir. Bu tepkime sonucunda %84 verim ile istenilen türev izole edilmiş ve karakterizasyonu yapılmıştır.



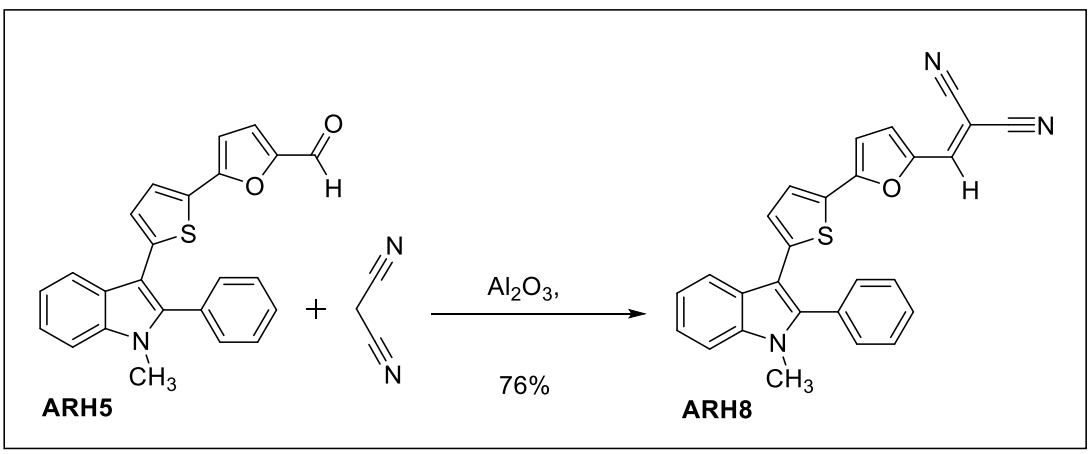
Şekil E3. ARH5 sentezi.



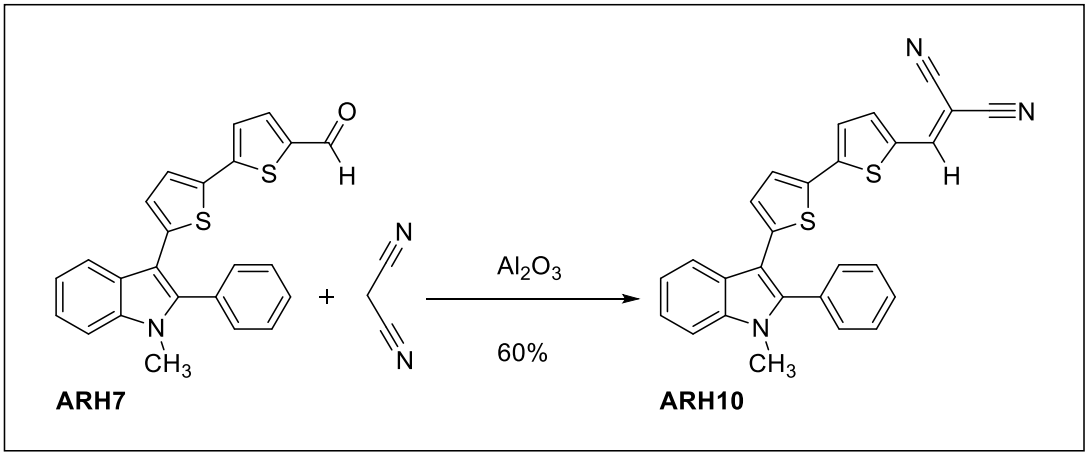
Şekil E4. ARH7 sentezi.

3.4. Kondensazyon Tepkimeleri

Çalışmamızın son bölümünde, Knoevenagel kondenzasyon tepkimesi kullanılmıştır. ARH5' in mikrodalga altında toluen içinde alüminyum oksit varlığında malononitril ile tepkimeye girmesine izin verildiğinde, kondenzasyon tepkimesi gerçekleşerek ARH8 (% 76) elde edilmiştir. ARH10 oluşumu için aynı tepkime koşulu kullanılmış ve % 60 verimle istenen ürün elde edilmiştir. ARH8 ve ARH10 yapılarının yapısal karakterizasyonlar spektroskobik yöntemler kullanılarak kesin olarak belirlenmiştir.



Şekil E5. ARH8 sentezi.

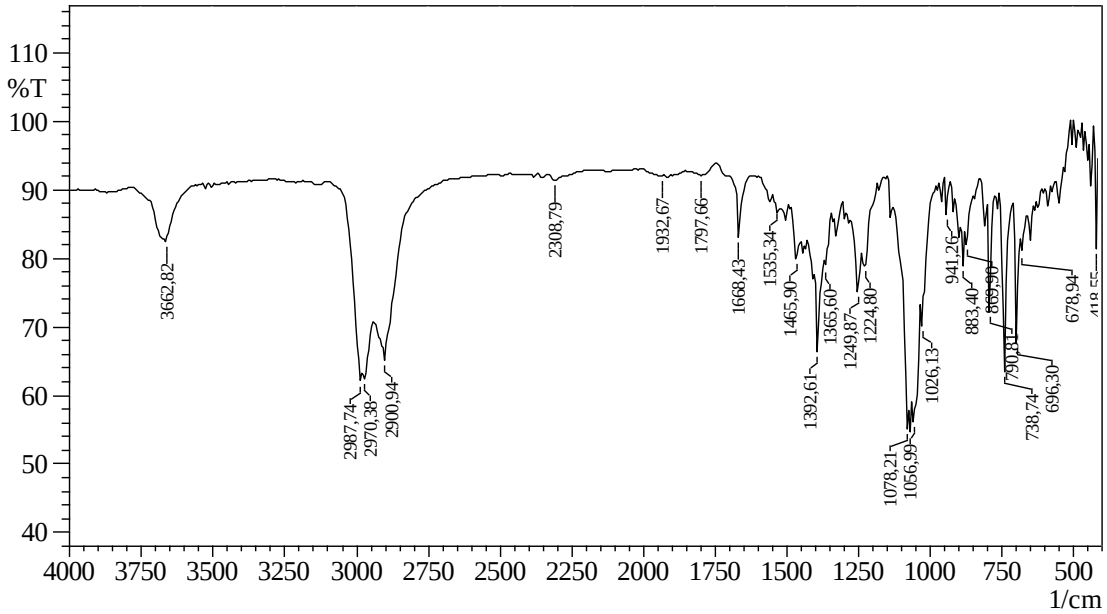


Şekil E6. ARH10 sentezi.

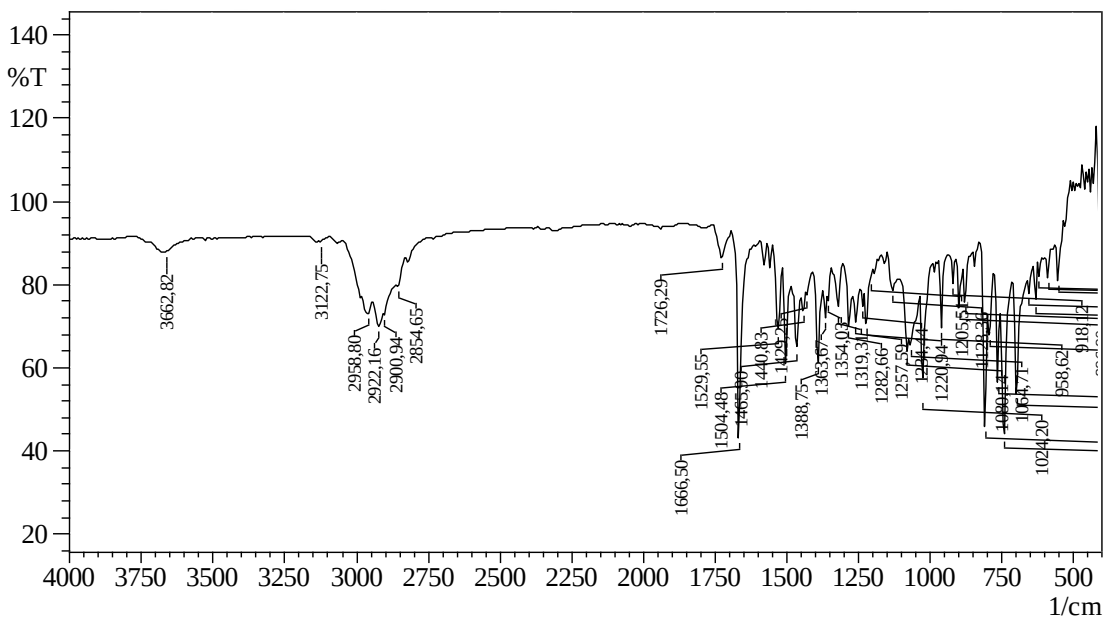
3. SONUÇ

Bu çalışmada, güçlü elektron çekme grupları içeren yeni indol türevleri sentezlenmiş ve karakterize edilmiştir. İlk olarak, 1-metil-2-fenil-3- (tiofen-2-il) -1 H-indol (ARH3) sentezi için bir kap iki aşamalı halkalaşma tepkimesi kullanılmıştır. Halkalaşma tepkimesi ile % 72 verimle ara ürün elde edilmiştir. Daha sonra halojenlenme tepkimesi ile 3- (5-iyodotiyofen-2-il) -1-metil-2-fenil-1H-indol (ARH4) (% 69) elde edildikten sonra Suzuki-Miyaura kenetlenme tepkimeleri ile ARH5 ve ARH7 sentezlenmiştir. ARH5 ve ARH7 sırasıyla %70 ve %84 verimle elde edildi. Son basamakta ise, ARH8 (% 76) ve ARH10 (% 60) kondenzasyon tepkimeleri ile sentezlenmiştir.

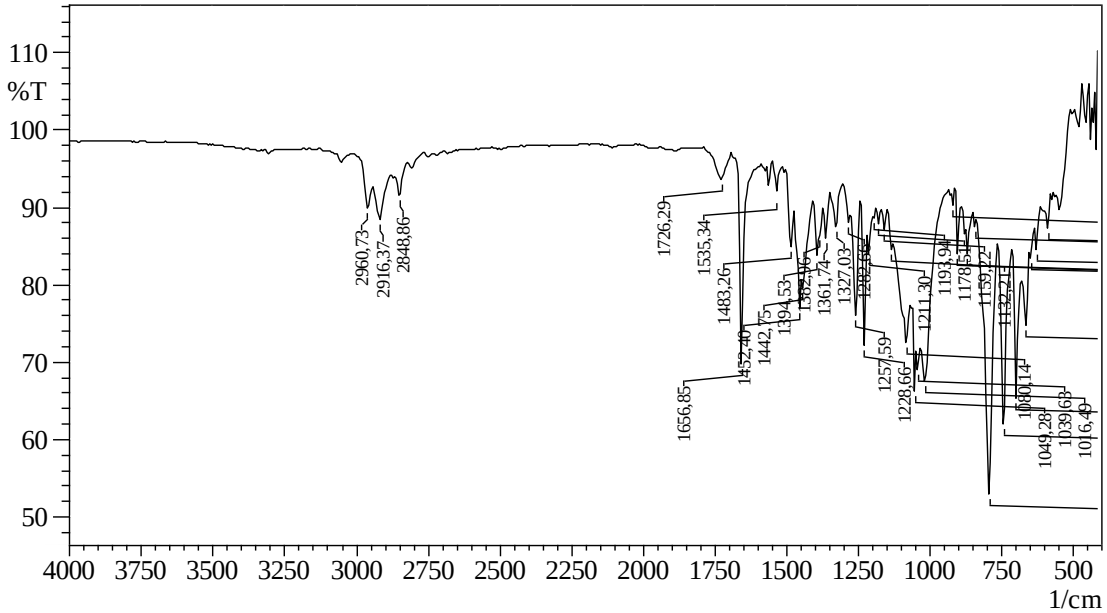
APPENDIX A: FT-IR DATA



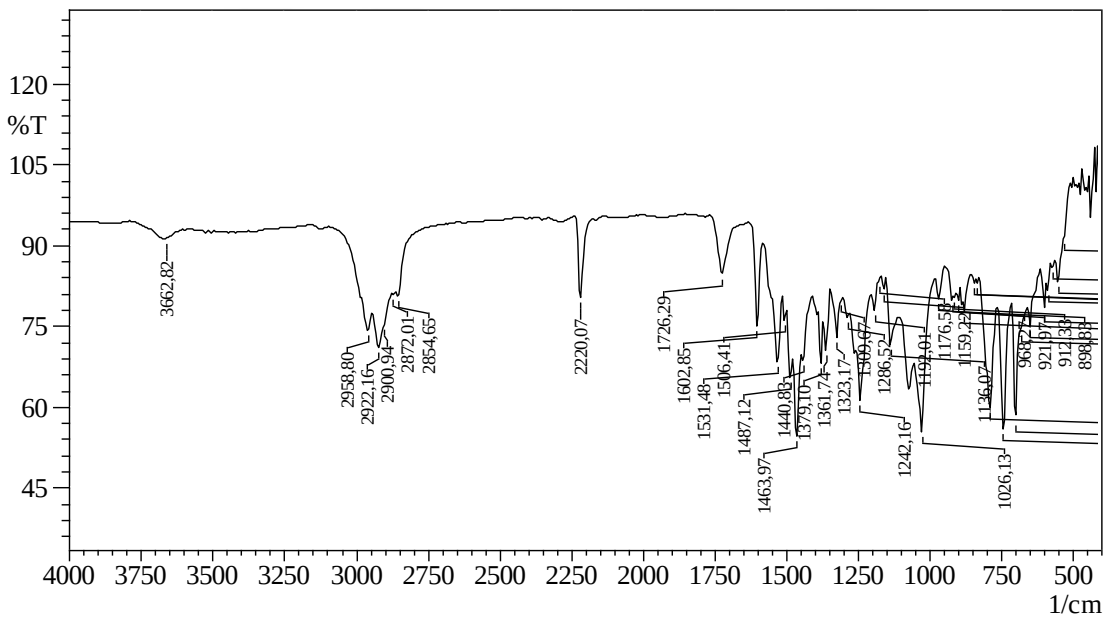
Appendix A 1. IR-FT analysis of 4AR.



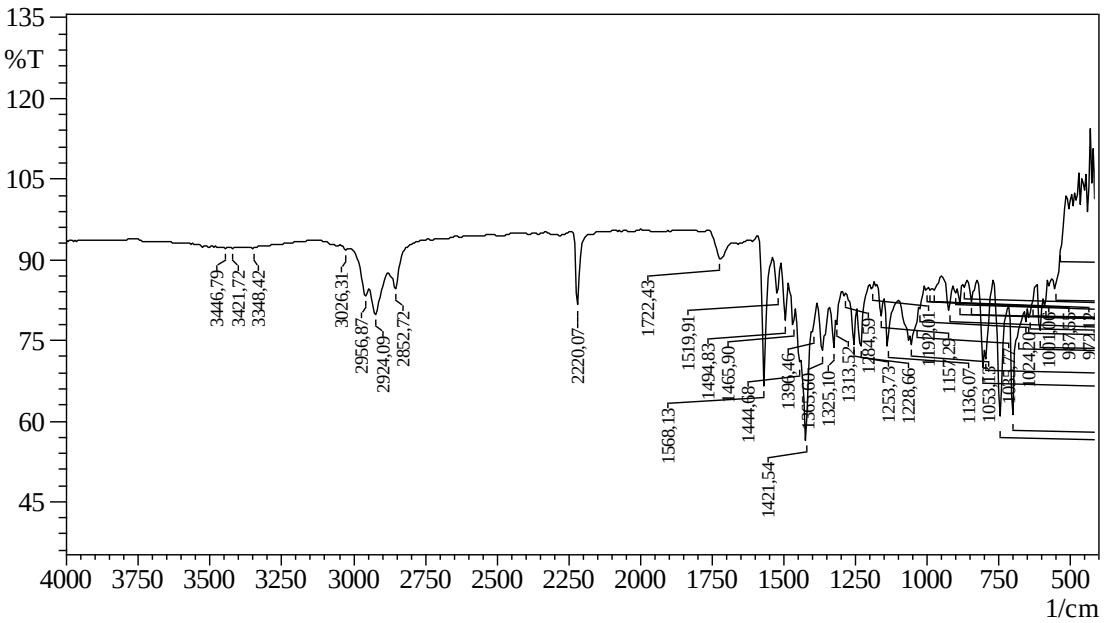
Appendix A 2. IR-FT analysis of 5AR.



Appendix A 3. IR-FT analysis of 7AR.



Appendix A 4. IR-FT analysis of 8AR.



Appendix A 5. IR-FT analysis of 10AR.

CURRRICULUM VITAE

Ali Rasw Hamad, was born in 1987, in Sulaymaniyah-Iraq. He completed primary, secondary and high school education in Zharawa-Sulaymaniya. He studies from Department of chemistry, College of Faculty of Science and Health at koya University in 2010. He graduated from the mentioned Department in 2014. He was working at Koya University as an assistance chemist since 2015. Later in 2019, he has been accepted to study M.Sc. in Van-Turkey. He has been completed his M.Sc. in Department of Chemistry, The Institute of Natural and Applied Sciences, Van Yuzuncu Yil University in Van -Turkey on January 2021.

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