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MICROWAVE-ASSISTED SONOGASHIRA-TYPE COUPLING OF TERMINAL ALKYNES AND ARYL BORONIC ACID

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สุทธิเกียรติ พืชมงคล: การใช้ไมโครเวฟช่วยในปฏิกิริยาคู่ควบแบบโซโนกาชิระของเทอร์มินัลอัลไคน์และกรดแอริลโบโรนิค. (MICROWAVE-ASSISTED SONOGASHIRA-TYPE COUPLING OF TERMINAL ALKYNES AND ARYL BORONIC ACID) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ.ดร.วรวรรณ พันธุมนาวิน, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: ผศ.ดร.บุญโชติ เผ่าสวัสดิ์ยรรยง, 85 หน้า.

ในงานวิจัยนี้ได้ออกแบบและสร้างเตาไมโครเวฟสำหรับสังเคราะห์ปฏิกิริยาเคมี การให้ความร้อนแก่ปฏิกิริยาเคมีโดยใช้ไมโครเวฟช่วยนั้นสามารถเพิ่มร้อยละผลผลิตและอัตราการเกิดของปฏิกิริยาเคมีได้ การใช้คลื่นไมโครเวฟช่วยในการเร่งปฏิกิริยาจะให้ความร้อนอย่างเฉพาะเจาะจง ข้อดีหลักของการใช้ไมโครเวฟช่วงเร่งปฏิกิริยาคือ ช่วงเร่งอัตราการเกิดของปฏิกิริยาเพิ่มร้อยละผลผลิตและมีความปลอดภัย นอกจากนั้นยังสามารถนำไปประยุกต์ใช้ได้อย่างหลากหลายสำหรับปฏิกิริยาเคมีอินทรีย์อื่นๆ การใช้ไมโครเวฟช่วยในปฏิกิริยาคู่ควบแบบโซโนกาชิระของเทอร์มินัลอัลไคน์ที่ขาดแคลนอิเล็กตรอนและกรดแอริลโบโรนิคในระบบที่ปราศจากลิแกนด์ภายใต้บรรยากาศปกตินั้นเป็นวิธีที่ง่ายและรวดเร็ว ช่วยให้ใช้ตัวเร่งปฏิกิริยาแพลเลเดียมในปริมาณที่น้อยในระบบที่ใช้เงินเป็นตัวช่วย ใช้โพแทสเซียมคาร์บอเนตเป็นเบสและเตตระไฮโดรฟิวแรนเป็นตัวทำละลายและใช้กำลังของเครื่องไมโครเวฟเพียง 100 วัตต์ เป็นเวลา 20 นาที สามารถให้ร้อยละผลผลิตที่ดีซึ่งการใช้ไมโครเวฟช่วยในปฏิกิริยาคู่ควบแบบโซกาชิระนี้เป็นวิธีที่ไม่ยุ่งยากและง่ายเพื่อจะเป็นทางเลือกแทนการให้ความร้อนแบบปกติ

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SUTTIKIAT PUECHMONGKOL: MICROWAVE-ASSISTED SONOGASHIRA-TYPE COUPLING OF TERMINAL ALKYNES AND ARYL BORONIC ACID. ADVISOR: ASST. PROF. WORAWAN BHANTHUMNAVIN, Ph.D., CO-ADVISOR: ASST. PROF. BOONCHOAT PAOSAWATYANYONG, Ph.D., 85 pp.

A microwave reactor for chemical synthesis have been designed and constructed. Microwave irradiation provided a selective heating to the reaction mixture. The main advantage of use microwave-assisted is reaction acceleration, yield improvement, and safe. An easy, rapid methodology for microwave-assisted Sonogashira-type coupling reactions of arylboronic acids with electron-deficient terminal alkynes in absence of ligand under ambient atmosphere is described. The reactions used low loading palladium-catalyzed in silver-assisted system, K_2CO_3 as base, and THF as solvent to afford the corresponding product in moderate-high yield in 20 min with only 100 Watt microwave power. Thus, it represents a simple and alternative method for conventional heating.

Field of Study : Petrochemistry and Polymer Science	Student's Signature :
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LIST OF ABBREVATIONS

Ar	aryl or aromatic group
br	broad (NMR)
Bu	butyl
^{o}C	degree celsius
cm	centimeter
d	doublet (NMR)
dd	doublet of doublet (NMR)
DBU	1,8-Diazabicycloundec-7-ene
DIEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
eq	equivalence
Et	ethyl
f_c	cutoff frequency
g	gram
h	hour
Hz	hertz
IR	infrared
J	coupling constant
m	multiplet (NMR)
m-	meta
M	molar
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mmol	millimole
mol	mole
nm	nanometer

NMR	Nuclear Magnetic Resonance
o-	ortho
OAc	acetate
OTf	Trifluoromethanesulfonate
p-	para
Ph	phenyl
ppm	part per million
Pr	propyl
py	pyridine
rt	room temperature
s	second
s	singlet (NMR)
S	Siemens
t	triplet (NMR)
t-	tertiary
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilane or trimethylsilyl
UV	ultraviolet
λ	wavelength
δ	chemical shift
π	pi
%	percent

CHAPTER I

INTRODUCTION

1.1 Statement of the problem

The Sonogashira cross-coupling reaction is well-known as being one of the most important and powerful methods for the construction of C(*sp*) – C(*sp*^{2}) bonds to give aromatic alkynes and conjugated enynes [1, 2]. Since these are important precursors to a large number of compounds, the reaction has been widely applied to the synthesis of natural products, pharmaceuticals, and a wide variety of organic materials [3]. The most commonly used catalytic systems is $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ [4-7] together with CuI [8,9] as a co-catalyst in the presence of stoichiometric amount of base. The reaction is usually carried out in organic solvents such as benzene, toluene, THF, DMF in N_2 atmosphere and take a long period of reaction time. In recent years a variety of modifications have been reported for this reaction. Efforts have been put by some researchers try to eliminate the use of copper [10] amine by using a specific ligand or support palladium catalyst [11-14]. However, the high costs and multistep processes to prepare the phosphine ligands and supported palladium catalyst complexes have made it unpopular, particularly for large scale reactions. So the used of a very simple of palladium catalyst in ambient atmospheres were interested. The traditional Sonogashira reaction of terminal alkynes with aryl halides is known for being well established as a powerful method for C-C bond formation, but known not to work well with electron-deficient alkynes [15]. In order to overcome the drawbacks, the Sonogashira-type of terminal alkynes and arylboronic acids or aryl trimethoxysilanes by palladium-silver system under mild conditions has been reported recently [16].

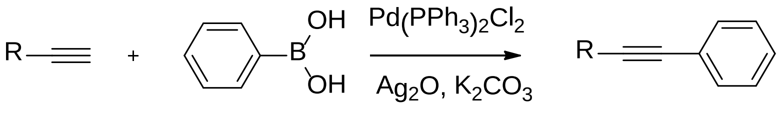


Figure 1.1 Sonogashira-type coupling reaction with arylboronic acid and terminal alkynes.

Microwave (MW) irradiation technique of organic reaction has gained higher popularity in the past decades and has been proven useful for the enhancement of the reaction rates and conversions under milder conditions as reported in many publications [17-19]. In general, its cleaner system, low energy usage, safe application and eco-friendly attributes make microwave-assisted organic transformation very attractive provided that the reaction mixture is adequately polar to suffer absorption of microwave energy. Herein, we focused on a mild condition and a very simple and low loading catalytic system of microwave-assisted Sonogashira-type cross-coupling reaction with arylboronic acid and electron-deficient alkynes.

1.2 Research objectives

The main objectives of this research are as follows

1. To design and construct a microwave reactor system for chemical reactions. The reactor consists of large chamber with connect to condenser and stirrer, rectangular waveguide, and microwave energy source.
2. To study a microwave-assisted Sonogashira-type coupling reaction of terminal alkynes and arylboronic acids

1.3 Scope of investigation

The stepwise investigation was carried out as follows:

1. Literature survey on related research work.
2. Design and construction of a microwave oven for chemical reactions.
3. Investigate the model reaction of Sonogashira reaction with trimethylsilylacetylene and 1-bromo-4-nitrobenzene in conventional heating method and microwave irradiation heating method for optimization the reaction time and microwave power.
4. Use the optimization condition to varieties of terminal alkynes and aryl halide.
5. Investigate the Sonogashira-type coupling reaction with phenylboronic acid and ethyl propiolate, electron-deficient alkynes, for optimization the reaction time and microwave power.
6. Application of the optimized condition in varieties of arylboronic acids.
7. Discussion the results and summary.

CHAPTER II

THEORY AND LITERATURE REVIEW

In this chapter, important background in this work will be presented. The chapter begins with the detail of coupling reactions and their limitations. Next, microwave background and mechanism will be described. In the last section of this chapter, microwave-assisted chemical reactions of interest will be discussed.

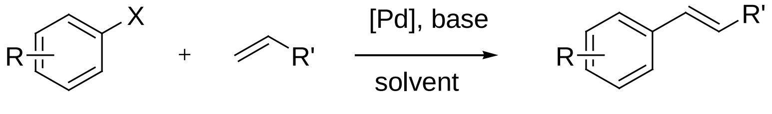
2.1 Coupling reactions

The formation of carbon-carbon bonds represents probably the most important synthetic step in organic chemistry and carbon-carbon cross-coupling has received much attention in the past decades for the preparation of variety of target compounds. The cross-coupling reaction of organometallic reagents with organic electrophiles in the presence of metal catalysts, such as nickel and palladium complexes, is the method for a wide range of C-C, C-H, C-N, C-O, C-S, and C-P bond forming processes. These reactions provide a common class of synthetic transformation, commonly referred to as “cross-coupling reaction”. In a large number of the carbon-carbon bond forming reactions, we will review some of the major and important reactions that similarly reagent, reaction condition, and catalytic system. Heck coupling reaction, Suzuki coupling reaction, and Sonogashira coupling reaction will be described.

In the 1960s to 1970s, the reaction of Li/Mg reagents in the presence of stoichiometric amount of copper halide catalyst has been studied extensively [20, 21]. The utilization of the reaction was very limited until the discovery of the transition metal catalyzed cross coupling reaction of Grignard reagents [22, 23]. Although the simple reaction using phosphine-free metal halides resulted in extensive homocoupling, a selective reaction at the sp^2-carbon was achieved in the presence of phosphine complex. After those discoveries, a lot of modification of the transition metal complex and organometallic reagents to be highly useful as catalysts or nucleophiles. Although the reaction of Li/Mg has been studies extensively, the use of reactive reagents is unfortunately complicated and limited by a lack of functional group compatibility. The nickel-catalyzed cross-coupling reactions of vinyl halides with Grignard reagents were found to proceed highly efficiently by Corriu and co-workers [24], and Kumada and Tamao [25] in 1972. Nickel catalysts are unfortunately not applicable to the reaction with organolithium compounds, which are highly versatile reagents and have some drawback from stereochemical scrambling of the starting alkenyl halides and metals. Thus, palladium-catalyzed have proven to be a more attractive, first demonstrated in 1973 by Murahashi in the reaction of vinyl halide with aryllithiums [26, 27]. In 1975, Cassar [28] and Heck [29] reported a palladium-catalyzed cross-coupling reaction of acetylides between terminal alkynes with aryl halides and in the same year, it was found that the of use copper co-catalyst exhibits a significant accelerating effect in the presence of triethylamine. The procedure called Sonogashira or Sonogashira-Hagihara reaction is now accepted as the most practical method for alkynylation of aryl and alkenyl halides [30].

2.1.1 Heck coupling reactions

The palladium catalyzed arylation of alkenes with an organic halide was first reported in the early 1970’s by Mizoroki and Heck [29, 31]. As the reaction is very versatile and can be applied to a wide range of aryl and vinyl substrates in a single step under mild conditions, it has become one of the cornerstones of palladium chemistry from both research and industrial points of view. Numerous homogeneous palladium catalysts have been used and an extensive literature is available on the topic. A wide range of solvents can be used for the reactions, but polar solvents such as DMF, THF, acetonitrile, and 1,4-dioxane are particularly [32, 33].

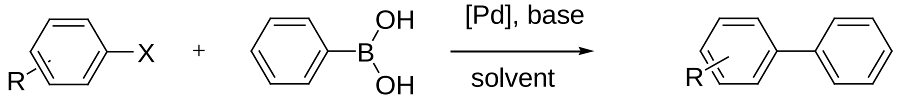


R = H, alkyl, CHO, NO_2, halide ...
R' = Ph, OR, $COOR_1$, $CONR_2$, CN ...
X = halide, OSO_2CF_3, COCl, ...

Figure 2.1 Heck coupling reactions [29].

2.1.2 Suzuki coupling reactions

The Suzuki reaction is perceived to be one of the most environmentally benign methods. First published by Akira Suzuki in 1979, in many publications this reaction is also called the name Suzuki-Miyaura reaction [34-36]. It is also often referred to as "Suzuki coupling". The reaction is a cross-coupling of an aryl halide with an organoboronic acids and uses a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) to affect part of the transformation. This is a versatile and widely utilized reaction for selective formation of carbon (*sp*^{2}) – carbon (*sp*^{2}) bonds. Commercially available ligands have been used extensively for the reaction; however, it requires elevated reaction temperatures. It is widely used to synthesize poly-olefins, styrene, and substituted biphenyls, and has been extended to incorporate alkyl bromides.

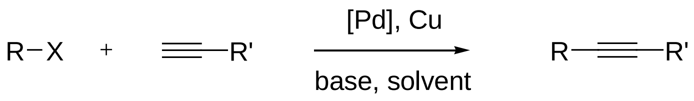


R = H, CN, NO_2, CH_3, ...
X = halide

Figure 2.2 Suzuki coupling reactions [36].

2.1.3 Sonogashira coupling reactions

The important and powerful method for the synthesis of substituted alkynes via the cross-coupling of aryl halide and terminal alkynes was first reported by Kenkichi Sonogashira and Nobue Hagihara in 1975 [30]. The Sonogashira-Hagihara more often known as Sonogashira coupling reaction for the construction of carbon (*sp*) - carbon (*sp*^{2}) bond is widely used to give aromatic alkynes and conjugated enynes. Typically, the reaction requires anhydrous and anaerobic conditions, but newer procedures have been developed where these restrictions are not important.



R = aryl, heteroaryl, vinyl
R' = aryl, hetaryl, alkenyl, alkyl, SiR_3
X = I, Br, Cl, OTf

Figure 2.3 Sonogashira coupling reactions [1].

The general reactivity order of the *sp*^{2} species is vinyl iodide ≥ vinyl triflate ≥ vinyl bromide > vinyl chloride > aryl iodide > aryl triflate ≥ aryl bromide >> aryl chloride. Therefore, the Sonogashira process usually runs smoothly when the more expensive and unstable aryl or vinyl iodides are used. The exact mechanism of the homogeneous copper co-catalyzed Sonogashira reaction is unknown, but believed to take place through two independent catalytic cycles as shown in **Figure 2.4** where a tertiary amine is represented as a base, with other amines or inorganic base performing similarly. The generally accepted catalytic cycle for the palladium catalysis (Pd-cycle) is based on a usually fast oxidative addition of R^1-X (R = aryl, heteroaryl, vinyl; X = I, Br, Cl, OTf) to the real catalyst generated from the initial palladium complex.

The transition metal-catalyzed cross-coupling reaction that forms and cleaves the bond of two organic molecules proceeds by a sequence of oxidative addition – transmetalation (alkylation) – reductive elimination. The palladium complexes are highly effective in catalyzing cross-coupling reactions; all these steps are well known processes in homogeneous catalysis; however a combination of the processes has provided a very powerful and traditional catalytic method. Various phosphine ligands are effective in stabilizing for the palladium, but the stoichiometry, size, and electronic effect of the phosphine contribute to the reactivity of catalysts toward oxidative addition and reductive elimination. However, a number of new ligands have been designed and synthesized to attain high catalyst efficiency or selectivity and to expand the scope of the reaction.

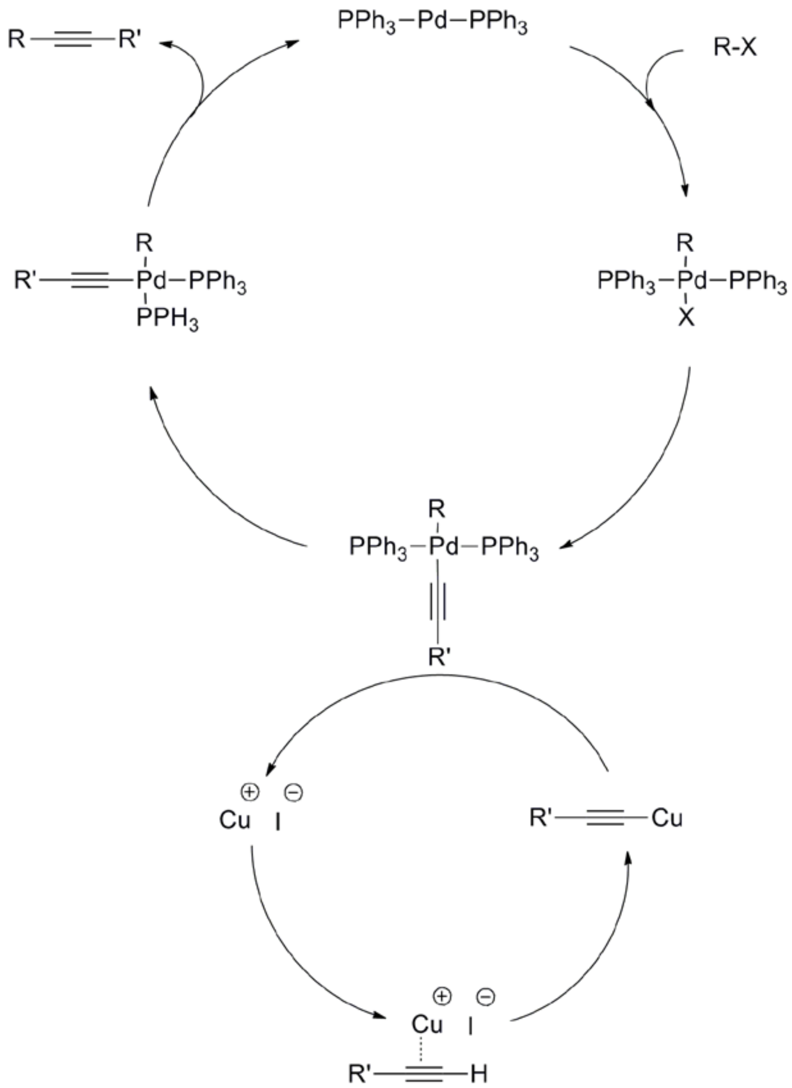
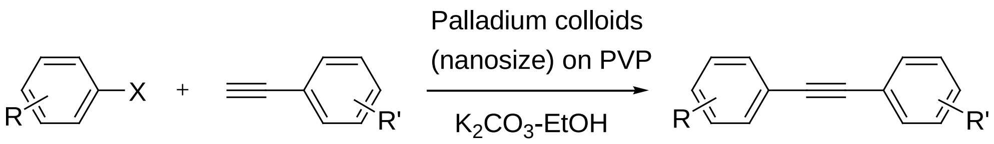


Figure 2.4 Sonogashira coupling reactions mechanism [1].

In the past there have been reports on Sonogashira coupling reaction in an aqueous-organic solvent mixture using palladium-ligand catalyst with water soluble sulfonated phosphines, but no reported in pure water was observed. Driven by environmental concerns, using water as solvent for organic reaction is much more attractive. In 2004, Sengupta and Bhattacharya reported that the Sonogashira cross-coupling reactions of aryl iodides and bromides can be carried out in pure water without any organic co-solvent, additives, or phase transfer catalysts [6]. The optimized condition using $Pd(PPh_3)_4$ as catalyst, CuI as co-catalyst, DIEA or pyrrolidine as base in water and heating by oil bath at 70 °C for 30 min to give a good yield.

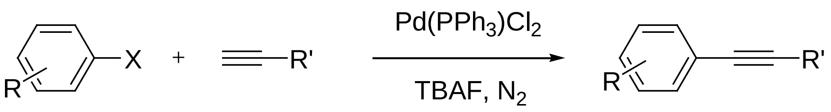
In 2005, Li and co-workers reported poly(vinylpyrrolidone) supported nanoparticle palladium metal catalyst in Sonogashira coupling reaction of aryl iodides and aryl bromides with terminal alkynes by using ethanol as the solvent, and potassium carbonate as base 80 °C for 6 hours this gave excellent yield [37]. The palladium metal was recovered and recycled by simple decantation of the reaction solution, the reaction yield were slightly decreased after eight repetitive cycles.



R = H, CH_3, OCH_3, NO_2, CF_3, CN   R' = H, Br, F, CH_3, CH_2CH_3
X = I, Br

Figure 2.5 PVP-support nanosized palladium(0) catalyst in Sonogashira coupling reaction [37].

In 2006, Liang and co-worker reported a general method for the fast Sonogashira cross-coupling reactions under copper-, amine-, and solvent-free condition [38]. Recently, tetrabutylammonium fluoride (TBAF) has been reported as useful promoter for amine-free palladium-catalyzed Sonogashira coupling reaction. Although the effect of TBAF was not clear, TBAF acted as base and phase-transfer catalysis (PTS). In particular, this protocol could be applied to the reaction of aryl iodides, bromides, and inactivate chlorides. The reaction carried out in 3 eq of TBAF with 3 mol% of $Pd(PPh_3)_2Cl_2$ as catalyst gave moderate to excellent yields.



R = CHO, NO_2, $COCH_3$, CH_3 R' = Ph, OH, Ph-OCH_3
X = I, Br

Figure 2.6 Palladium-catalyzed Sonogashira coupling reaction under copper-, amine- and solvent-free conditions [38].

In 2007, Guan and co-workers reported $PdCl_2/PPh_3$-catalyzed Sonogashira coupling reaction of aryl bromides with terminal alkynes in water [39]. The reaction works very well with $PdCl_2/PPh_3$ catalytic system and pyrrolidine are used as base which allows the coupling reaction to proceed at 120 °C in moderate to excellent yields. However, $PdCl_2$ itself without added phosphine ligand was much less effective for this transformation. In 2010, Sawant and co-workers reported $FeCl_3/PPh_3$-catalyzed Sonogashira coupling reaction of aryl iodides with terminal alkynes [40]. The reaction was conducted for 48 hours at 135 °C to give excellent yield. The utility of different phosphine ligands was investigated. Most of the ligands were found to be ineffective, with only PPh_3 giving good yields. From the reported above that means the phosphine ligands is still need in some Sonogashira coupling reaction.

Despite numerous reports on the use of coupling reactions by polymer-supported palladium catalysts, they have not been widely applied to the Sonogashira reaction. In 2010, Bakherad and co-workers reported copper- and phosphine-free Sonogashira coupling reactions by *N*,*N*-bis(naphthylideneimino)diethylenetriamine complex a polystyrene resin supported palladium(II) of aryl iodides with terminal alkynes [41]. The main advantages are the highly active, easily separated, and easily reusable immobilized catalyst. The reactions is carried out in Et_3N as base and DMF as solvent at room temperature for 3-5 hours to give the desired products in good yields from aryl iodides with electron-withdrawing groups. The yields slightly decrease for aryl iodides possessing electron-donating groups. The catalyst was recovered and reused 10 times with only marginal loss in catalytic activity. In the same year, Suzuka and co-workers reported polystyrene-poly(ethylene glycol) (PS-PEG) resin supported palladium phosphine complex Sonogashira coupling reaction in water [42]. One of the major problems were the use of both a palladium catalyst and a copper reagent as co-catalyst resulting in contaminate of the coupling products with metal residue. Moreover, the coupling often suffers from the Glaser-type oxidative dimerization of alkynes substrate as side reaction in the Cu(I) co-catalyst system. The coupling reaction of various aryl halides with terminal acetylene carried out in water by using Et_3N as base in the presence of PS-PEG resin supported triarylphosphine ligand under copper-free condition at 40 °C for 6 hours gave a good yield with iodobenzene bearing electron-donating groups in para positions. Iodobenzene having electron deficient aromatic ring also underwent under similar reaction conditions and yields slightly decrease in the coupling of meta- and ortho-substituted iodobenzene. The bromoarenes were carried out at higher reaction temperature to give moderated yield and chloroarenes was much lower than iodo and bromo. Finally, PS-PEG resin supported palladium catalyst was recovered by simple filtration and reused four times without any loss efficiency. Some drawback of the polymer supported resin palladium complex is that it is difficult and takes a long reaction time to prepare, moreover this is limited by narrow choice of base and solvent.

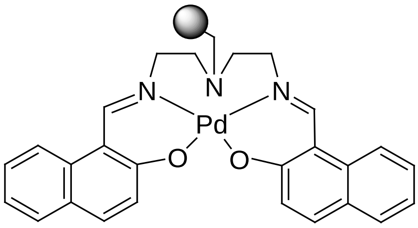


Figure 2.7 Polystyrene resin supported Pd(II) complex [42].

In another recent study, describing the copper co-catalyzed cross-coupling of terminal alkynes and aryl halide or triflates, it can concluded that catalytic amounts of copper are required for a coupling reaction to take place. Regarding the use of microwave, it has recently been reported that trimethlysilylacetylenes and aryl halide can be prepared efficiently by using standard Sonogashira cross-coupling condition and microwave irradiation with much reduced reaction times.

2.1.4 Sonogashira-type coupling reactions

Recently, numerous groups of researchers have tried to modify the Sonogashira cross-coupling reaction, although various modifications have been carried out, but some limitations still remain. The reaction similar to Sonogashira coupling reaction but changing the starting material to fix some problem of the reactions is also known as Sonogashira-type coupling reactions. A possible mechanism of Sonogashira-type coupling reaction with silver-assisted is shown in **Figure 2.8.** Initially, the reaction between Pd(II) and alkynylsilver or alkyne with the aid of base affords intermediate **1**. Transmetalation of intermediate **1** with arylboronic acid takes place leading to intermediate **2**. Finally, reductive elimination of intermediate **2** gives the corresponding desired product **3** and Pd(0) species. Pd(0) species can be readily oxidized by Ag_2O to the active Pd(II) species. Ag_2O is play important key roles in the reaction.

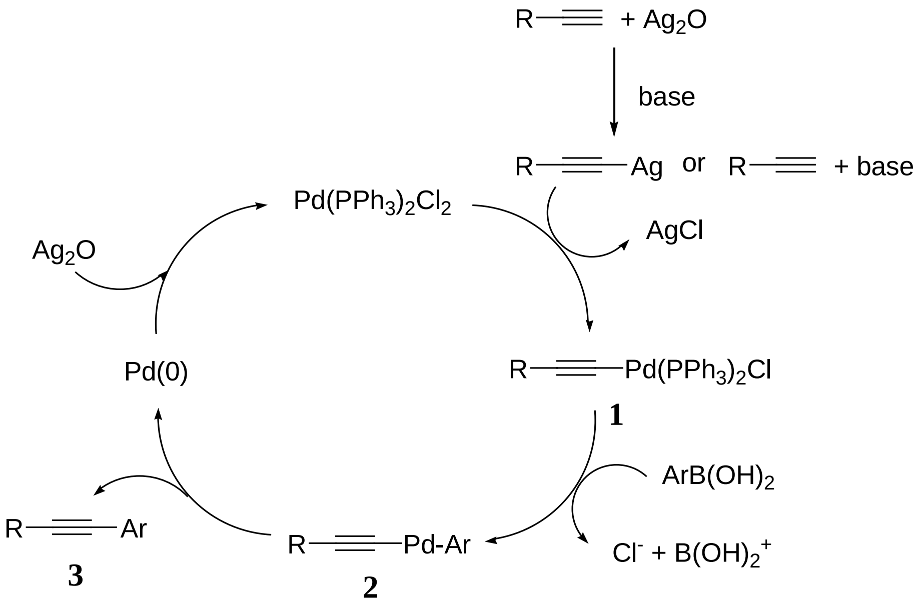
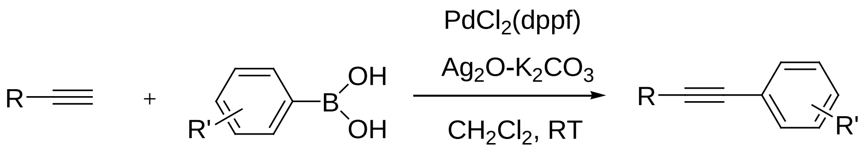


Figure 2.8 Sonogashira-type coupling reaction mechanism [43].

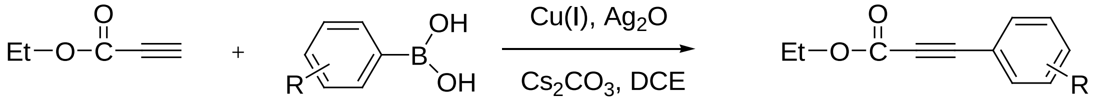
According, the Sonogashira coupling reaction has a serious problem when coupling with the electron-deficient terminal alkynes. The coupling desired products were not formed but the homocoupling were formed instead. To overcome this limitation, Zou and co-workers reported the palladium-catalyzed, silver-assisted procedure for constructing aryl alkynes by direct cross-coupling of boronic acids with terminal alkynes in 2003 [44]. After extensive optimization, a combination of 5% eq $PdCl_2$(dppf), 2 eq Ag_2O and 5 eq K_2CO_3 was found to gave the good yield in air atmosphere. Silver(I) oxide has been known to activate C-B bond thus accelerating the transmetylation between $RB(OH)_2$ and palladium complex. Typical electron-donating or electron withdrawing groups on the arylboronic acid have been shown to have a little effect on the cross-coupling reaction. The electron-deficient alkyne also gave the desired coupling product in good yields.



R = C_6H_{13}, CH_2OBn, $CO_2CH_2CH_3$, Ph
R' = H, $CO_2CH_2CH_3$, OCH_3, C_4H_9

Figure 2.9 Sonogashira-type coupling reactions of terminal alkynes with arylboronic acids catalyzed by a palladium-silver system under mild conditions [44].

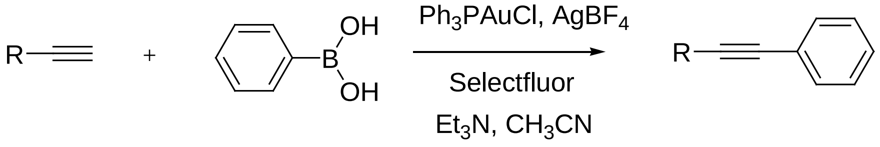
In 2009, Pan and co-workers reported the ligand-free Sonogashira-type coupling reaction of arylboronic acids with terminal alkynes by use of copper(I)-catalyzed in the presence of silver oxide system under mild reaction conditions [45]. Copper(I)-catalyst is less expensive and more sustainable. The catalyst has remained a highly desirable goal, instant palladium and phosphine ligand complex that is often expensive and difficult to prepare. Silver(I) oxide was applied as the promoter in the presence of Cs_2CO_3 as base and 1,2-dichloroethane (DCE) as solvent to afford the coupling product in a good yield. No product was formed in the absence of CuI or Ag_2O and the absence of any base only 25% of the coupling product was isolated. Finally, the optimized reaction conditions were tested with a series of arylboronic acids and electron-deficient terminal alkynes resulting in moderate-high yield. However, the steric hindrance of the arylboronic acids has significant effect on the reaction that was sharply decreased in yields. Although under these conditions the reaction seem to run smoothly, but it still requires a very long reaction time of at least 36 hours at room temperature.



R = H, $CO_2CH_2CH_3$, CH_3, Cl, F, CF_3, CO_2CH_3

Figure 2.10 Ligand-free copper(I)-catalyzed Sonogashira-type coupling reactions of terminal alkynes with arylboronic acids [45].

In 2011, Qian and Zhang reported the Au(I)/Au(III) catalyzed Sonogashira-type reactions of terminal alkynes with arylboronic acids under mild conditions. Because Au(I) has the same electronic group, and has the ability to undergo the Au(I)/Au(III) redox cycle [46]. The optimized reaction was carried out by using $Ph_3PAuCl/AgBF_4$ as catalyst, selectfluor® as oxidant, Et_3N as base and CH_3CN as solvent under N_2 atmosphere to give high yield. By using the optimized conditions, various arylboronic acids were tested. Arylboronic acids with electron-withdrawing groups afforded moderate to good yields. On the other hand, the electron-rich arylboronic acids produced the lowest yields. It should be noted that the reaction requires temperature at 50 °C and 10-24 hours of reaction time.

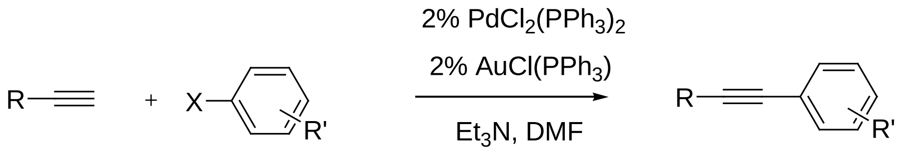


R = NHTs, NBocTs, OBn, OTs
R' = H, F, Cl, CH_3, OCH_3, CO_2CH_3

Figure 2.11 Au(I)/Au(III)-catalyzed Sonogashira-type coupling reaction of functionalized alkynes with arylboronic acids under mild conditions [46].

Another published on the gold catalyst has been reported by Panda and Sarkar in the topic of “On the catalytic duo $PdCl_2(PPh_3)_2/AuCl(PPh_3)$ that cannot effect a Sonogashira-type reaction” [47]. Due to the traditional Sonogashira experimental procedure involves CuI as a co-catalyst in a solution containing amine bases have been reported that homocoupling problem as a side reaction. The development of new co-catalyst other than CuI which will not allow homocoupling is desirable. The combination of $PdCl_2(PPh_3)_2$ and $AuCl(PPh_3)$ makes a unique catalytic system that allows Sonogashira-type cross-coupling of both aryl and alkyl alkynes with aryl halides in excellent yields. The reaction carried out by using gold-catalyzed in the silver-assisted system in the presence of Selectfluor® that a source of electrophilic fluorine was used to oxidize the resulting Au(I) intermediate to Au(III) species, Et_3N

as base, CH_3CN as solvent at room temperature. Even the highly sterically hindered aryl halides couple with alkynes without any difficulties. Furthermore, Independent experiments were carried out to see the role of palladium and gold separately. While the gold complex $AuCl(PPh_3)$ was found to be totally inactive in the absence of the palladium complex $PdCl_2(PPh_3)_2$.



R= Ph, CH_2OH,CH_2CH_2OH
X= I, Br

R' = 4-$COCH_3$, 4-CH_3, 2,6-CH_3
2-OCH_3, 3-OCH_3, 4-OCH_3
3,5-OCH_3, 2,4-OCH_3, 2-NH_2
2-F, 2-Br

Figure 2.12 Catalyst duo $PdCl_2(PPh_3)_2$/$AuCl(PPh_3)$ on Sonogashira-type reaction [47].

2.2 Microwave background

Microwave is electromagnetic spectrum between infrared waves and radio waves with the wavelength between 1 nm to 30 cm. It covers a frequency range between 0.3 and 30 GHz and it is an ultrahigh frequency waves used for television broadcasting [48-51]. The lower microwave frequency ranges (L band) are used for purpose of communication and the higher frequency ranges (W band) are reserved for analytical techniques such as spectroscopies. Cellular telephone operate in two bands, one from about 800 to 900 MHz and another one around 1.8 to 1.95 GHz. Although there is no formal definition of frequency range for “microwave”, because some text books will define all frequencies above 300 MHz as microwave.

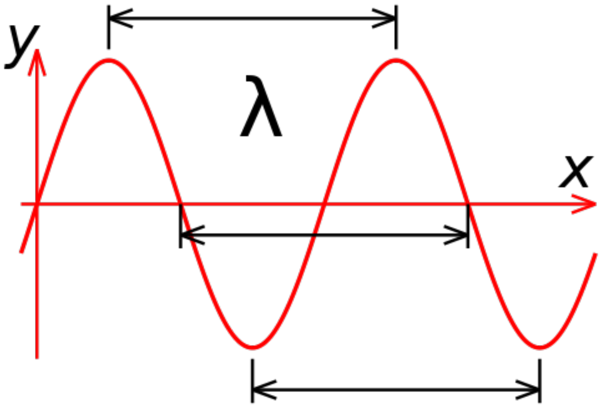


Figure 2.13 Wavelength of a sine wave, λ, can be measured between any two points with the same phase.

In physics, a wave is a disturbance that travels through space and time, usually accompanied by the transfer of energy. Waves travel and the wave motion transfers energy from one point to another, often with no permanent displacement of the particles of the medium that is with little or no associated mass transport. They consist, instead, of oscillations or vibrations around almost fixed locations. The wavelength of a sinusoidal wave is the spatial period of the wave, the distance over which the wave's shape repeats. It is usually determined by considering the distance between consecutive corresponding points of the same phase (**Figure 2.12**) and it is a characteristic of both traveling waves and standing waves, as well as other spatial wave patterns. Wavelength is commonly designated by the Greek letter *lambda* (λ). The concept can also be applied to periodic waves of non-sinusoidal shape. The term wavelength is also sometimes applied to modulated waves, and to the sinusoidal envelopes of modulated waves or waves formed by interference of several sinusoids. The SI unit of wavelength is the meter.

One type of wave is a mechanical wave, which propagates through a medium in which the substance of this medium is deformed. Another type of wave can travel through a vacuum, *e.g.* electromagnetic radiation (including visible light, ultraviolet radiation, infrared radiation, gamma rays, X-rays, and radio waves). This type of wave consists of periodic oscillations in electrical and magnetic fields. Electromagnetic radiation is a wave that combines electric and magnetic fields

(**Figure 2.13**), where the properties of the radiation depend on the wavelength, frequency, and other parameters of the wave.

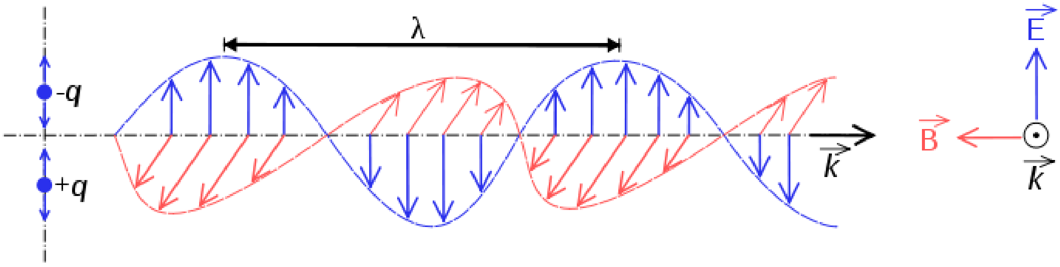


Figure 2.14 Electromagnetic radiations.

These waves are produced by several types of microwave generators, *e.g.*, magnetrons, klystrons, and gyrotrons. The most common are magnetrons, the last two generators being used for generating ultrahigh frequency microwave. In the commercial ovens the microwave are produced by magnetrons and have the frequency of 2.45 GHz (**Figure 2.14**), the corresponding for space wavelength being 12.25 cm. The microwave produced by generator is guided through metallic channel called waveguide, which reflects the microwave towards the reaction cavity, where the processing sample is placed.

The electromagnetic spectrum (**Figure 2.15**) covers a wide range of wavelengths and photon energies. Light used to "see" an object must have a wavelength about the same size as or smaller than the object. Generally, electromagnetic radiation is classified by wavelength into radio, microwave, infrared, the visible region also known as light, ultraviolet, X-rays, and gamma-rays. All waves of electromagnetic radiation travel at the speed of light, different types of waves have differing wavelengths, frequencies, and energies. The behavior of electromagnetic radiation depend on its wavelength, the shorter wavelength of the radiation has the greater the frequency and the larger the energy. The electromagnetic spectrum ranges from gamma (γ) radiation, which has the shortest wavelength, highest frequency, and greatest energy, to radio waves, which has the longest wavelength and lowest frequency and energy.

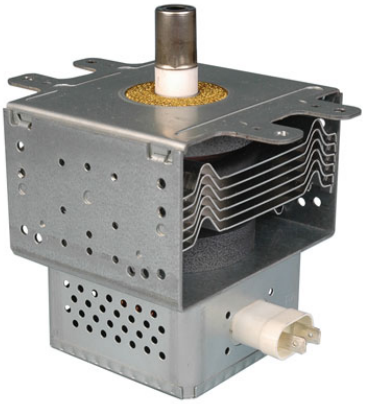


Figure 2.15 Original Panasonic magnetron 2M261-M32F.

Waves of a very long wavelength, such as thousands of meters, tend to travel along the surface of the earth and can penetrate into the water that are useful for communication with submarines, and for broadcasting time signals. Broadcast radio, short wave radio, television, cellular telephones, and other communication/broadcast system all use electromagnetic radiation, or “radio frequency waves”. Each communication service uses just a part of the spectrum that is suitable for its needs.

Light, infrared heat, ultraviolet, and even X-rays and gamma-rays are all forms of electromagnetic waves. All of these are thousands times shorter wavelengths than the shortest wavelengths of microwave.

Electromagnetic waves are typically described by any of the following three physical properties: the frequency f, wavelength λ, or photon energy E. Frequencies range from 2.4×10^{23} Hz. Wavelength is inversely proportional to the wave frequency. Photon energy is directly proportional to the wave frequency. These relations are illustrated by the following equations:

$$f = \frac{c}{\lambda}\text{, or } f = \frac{E}{h}\text{, or } E = \frac{hc}{\lambda}$$

Where

c = the speed of light in vacuum = 299,792,458 m/s

h = Planck's constant = $6.62606896(33)\times10^{-34}$ J s = $4.13566733(10)\times10^{-15}$ eV s [52].

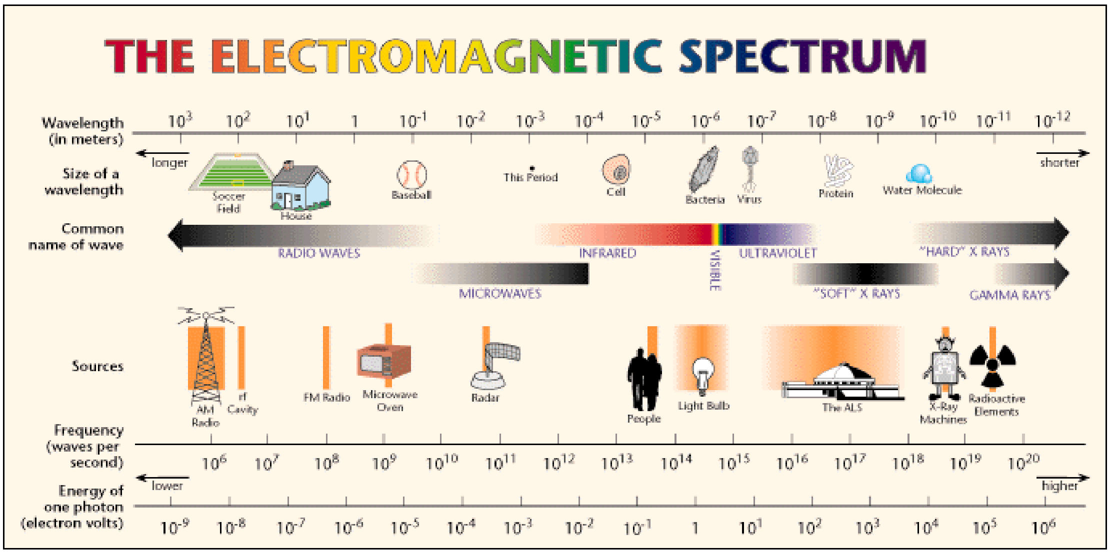


Figure 2.16 The electromagnetic wave spectrum.

2.3 Microwave activation for chemical reactions.

Robert Bunsen was invented the burner in 1855, the energy form this heat source could be applied to a reaction vessel in a focused manner. The Bunsen burner was superseded by the isomantle, oil bath, or hot plate as a source to applying heat to a chemical reaction. In the past decades, Microwave irradiation of organic reaction has gained higher popularity in the scientific community. Since the first published reports in the use of microwave irradiation to carry out organic chemical transformations by the groups of Gedye and Giguere/Majetich in 1986 [48]. After that, more than 3500 articles have been published in this fast moving and exciting field, nowadays referred to as microwave-assisted organic synthesis (MAOS) [53]. A long reaction time and a high temperature required for the reaction to proceed well as reported by other researchers have accelerated the use of microwave as an alternative means to carry out the reactions. Reaction rate improvement could be explained considering the higher and more rapid temperature homogeneity reached employing microwave than using conventional heating method. The higher product yields can be frequently observed. In microwave assisted reactions molecules are directly kinetically/thermally activated, conversely in conventional heating method vessel is heated and then transfers the heat to molecules by convection. In many of the publications, microwave heating has been shown to dramatically reduce the reaction time, enhance the reaction rates and conversions under milder conditions compared to conventional heating methods. In principle, any chemical reaction that requires heat can be performed under microwave conditions. The short reaction times provided by microwave synthesis make it rapid reaction scouting and optimization of reaction conditions.

In the initial of microwave synthesis, the experiments were typically carried out in sealed Teflon or glass vessels in a domestic household microwave oven without any temperature or pressure measurements. The typical microwave ovens are not designed for the chemical reaction usage; acids and solvents corrode the interiors quickly and there are no safety controls. The rapid uncontrolled heating of organic solvents under closed vessel conditions can cause the violent explosions. In the 1990s, the several groups started to use solvent-free microwave chemistry, which eliminated the danger of explosions. Particularly in the beginning of MAOS, the solvent-free was very popular since it allowed the safe use for typical microwave ovens and standard open vessel technology. In contrast, technical difficulties relates to non-uniform heating, mixing, and control the reaction temperature.

The microwave reactor for chemical synthesis design will be presented, for a large chamber and can apply to varieties of chemical reaction. Alternatively, microwave-assisted synthesis was often carried out using standard organic solvents under open vessel conditions. If the solvent are heated at ambient pressure in an open vessel by microwave irradiation, the boiling point of the solvent typically limits the reaction temperature that can be achieved. Nonetheless, high reaction rates, high-boiling microwave absorbing solvents were frequently used in open vessel microwave synthesis. In addition, the risk with the flammability of organic solvents in a microwave reactor and the lack of available temperature and pressure control were major concerns.

The main attraction of using microwave is short reaction times in cleaner systems. In addition, presently, there is no doubt that there is particular microwave effect. Microwave irradiation is just a simple, rapid and effective way of energy transfer to reaction medium provide if it is polar enough to suffer the absorption of microwave energy. More advantages are microwave generate higher power densities, enabling increased production speeds and decreased production costs.

Microwave energy is selectively absorbed by areas of greater moisture. This results in more uniform temperature and moisture profiles, improved yields and enhanced performance. Precisely controllable and can be turned on and off instantly, no need to warm-up and cool-down. The use of industrial microwave system avoids combustible gaseous by-products, eliminating the need for environmental permits and improving working conditions.

2.3.1 Microwave chemistry

Microwave heating in the laboratory began to gain wide acceptance following papers in 1980s. Microwave chemistry is the science of applying microwave irradiation to chemical reactions. Microwave act as high frequency electric fields and will generally heat any material containing mobile electric charges, such as polar molecules in a solvent or conducting ions in a solid.

The generally accepted advantages of microwave-assisted organic synthesis compared to conventional heating method are speed, convenience, and energy efficiency. Because at least one component from the reaction mixtures can interact with microwave, a very high heating rate can be accomplished. Presently, thermally driven organic transformation take place by either of two ways; conventional heating or microwave accelerated heating. In the former, reactants are slowly activated by a conventional external heat source. Heat will transfer into the substance, passing through the walls of the vessel in order to reach the solvent and reactants resulting in a slow and inefficient method for transfer energy into the system. The temperature gradient created can lead to so-called wall effects. In the latter, microwave couple directly with the molecules of the entire reaction mixture, leading to a very rapid rise in temperature. Since the process is not limited by the thermal conductivity of the vessel, the result is an instantaneous superheating of any substance that will respond to either dipole rotation or ionic conduction. The direct bulk heating generated by microwave irradiation is an energy-efficient and uniform heating of the whole reaction system. It is clear that microwave chemistry can provide access to synthetic transformations, which may be take a very long period reaction time and low yielding using conventional heating

2.3.1.1 Dipolar polarization mechanism

For a molecule in a polar liquid such as water (methanol, acetonitrile, DMF, THF, etc.) commonly employed in microwave enhanced reaction, there are intermolecular forces which give any motion of the molecule some inertia. The dipole is sensitive to external electric fields, and will attempt to align with them by rotation. When the field direction changes (this occurs 4.9 billion times per second at 2450 MHz), the molecules return the alignment energy to the field. This realignment is rapid for a free molecule, but in liquids instantaneous alignment is prohibited by the presence of other molecules. A limit is therefore placed on the ability of the dipole to respond to a field, which affects the behavior of the molecule with different frequencies of electric field. Under low frequency irradiation, the dipole may react by aligning itself in phase with the electric field. Some energy is gained by this behavior, and some is also lost in collisions, the overall heating effect is small. If the high frequency, on the other hand, they do not align with the field caused no energy transfer takes place, and therefore, no heating. Between these two extremes case, at the approximately frequencies which are the response times for dipoles can respond to the alternating field, and therefore to rotate, but high enough that the rotation does not precisely follow the field. As the dipole re-orientates to align itself with the field, the field is already changing; the phase difference exists between the orientation of the field and that of the dipole. It causes energy to be lost from the dipole in random collisions, and to give rise to dielectric heating.

Table 2.1 List of Dielectric constant and loss tangent of solvent [49].

Solvent	Dielectric constant	Loss tangent
Hexane	1.9	-
Benzene	2.3	-
Carbon tetrachloride	2.2	-
Chloroform	4.8	0.091
Acetic acid	6.1	0.174
Ethyl acetate	6.2	0.059
THF	7.6	0.047
Methylene chloride	9.1	0.042
Acetone	20.6	0.054
Ethanol	24.6	0.941
Methanol	32.7	0.659
Acetonitrile	36.0	0.062
Dimethyl formamide	36.7	0.161
Dimethyl sulfoxide	47.0	0.825
Formic acid	58.0	0.722
Water	80.4	0.123

2.3.1.2 Ionic conduction mechanism

A solution which containing ions or even a single isolate ion with a hydrogen bonded cluster in the sample oscillate back and forth through the solution under the influence of an electric field, colliding with neighboring molecules or atoms cause agitation or motion resulting in an increased collision rate and creating heat. The conduction mechanism is a much stronger than dipolar mechanism with regards to heat generating capacity. The ionic conductivity mechanism is very importance when considering heating ionic liquids within a microwave.

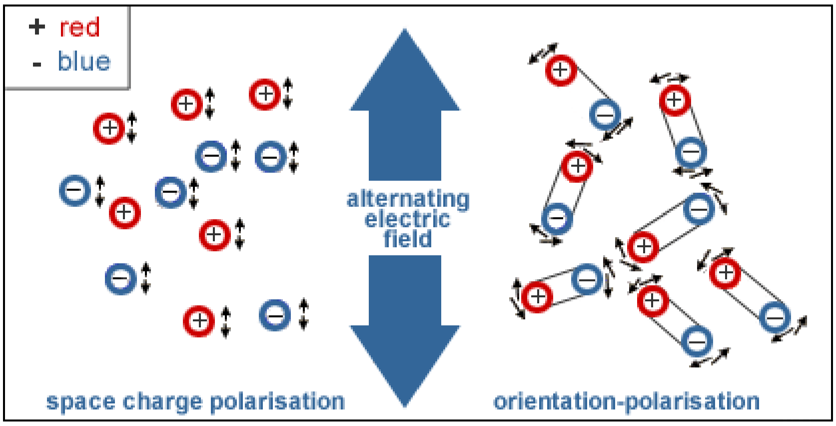


Figure 2.17 Microwave heating mechanism.

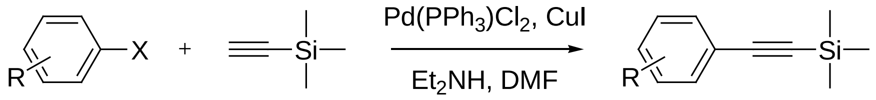
In conclusion, the process time of conventional heating is limited by the rate of heat flow into the body of the material from the surface as determined by specific heat, thermal conductivity, density and viscosity. Surface heating is very slow and non-uniform, edges and corners being much hotter than the inside of material. Large oven are slow to respond to needed temperature changes, take a long time to warm up, difficult to control, radiant losses, difficult to control, expensive, and have high heat capacities. Conversely, microwave heating the volume of material at the same rate is possible also known as volumetric heating. Volumetric heating is not depending on heat transfer by conduction or convection, energy is transferring though the material electromagnetically. The rate of heating is not limited and uniformity of heat distribution is greatly improved. The heating times can be reduced to less than one percent of that required using the conventional heating method.

2.3.2 Microwave advantages

Because volumetric heating is not dependent on heat transfer by conduction or convection, it is possible to use microwave heating instant conventional heat transfer is inadequate. Microwave can generate higher power densities and enabling increased production speeds, and decreased production costs. Microwave energy is selectively absorbed by area of greater moisture results in more uniform temperature and moisture profiles to improved yields and enhanced product performance. Microwave is precisely controllable and can be turned on and off instantly, no need to warm up and cool down. And the use of industrial microwave system avoids combustible gaseous by-products, eliminating the need for environmental permits and improving working conditions.

In 2000, Kabalka and co-worker reported rapid microwave-enhanced, solventless Sonogashira coupling reaction on alumina. From the soluble palladium reagents tend to expensive and difficult to recover, the solvent also recycle ability problems [54]. Since alumina is a particularly useful reagent in organic synthesis because it can be modified to enhance the reactivity and utilized for solve some of the environmental problem. The palladium-doped alumina in the presence of triphenylphosphine and cuprous iodide has been developing. Under microwave irradiation in solvent-free condition, the coupling occurs smoothly between a variety of aryl iodides and vinyl iodides with terminal alkynes. An electron-donating group on the aromatic ring leads to the desired product in excellent yield. Strong electron-withdrawing group leads to more moderate yield and the yield slightly decrease when the benzene ring have bulky group on the ortho-position. However, the reaction condition does not work with aryl bromides and aryl chlorides, the starting material are fully recovered. Next, in 2001, they reported a solventless, microwave-enhance Sonogashira coupling reaction of aromatic iodides with terminal alkynes on potassium fluoride dope alumina in the presence of palladium powder, cuprous iodide, and triphenylphospgine [55]. A number of reaction parameters such as base concentration, temperature, and the reaction time were evaluated to effort the maximum yield of the coupling reaction. The reaction requires the presence of a base, potassium fluride was the most effective. The palladium powder, triphenylphosphine and cuprous iodide are all essential to the reaction. A variety of aromatic terminal alkynes and aliphatic terminal alkynes were successfully with aromatic iodides in excellent yields. Internal alkynes were not reactive. Aryl bromides, aryl chlorides, aryl fluorides and aryl triflates were also not reactive and were recovered unchanged. The trimethylsilylated alkynes react readily with iodobenzene, *p*-methyliodobenzne, *p*-acetyliodobenzene and 2-iodothiophene to afford the corresponding coupling products in excellent yields.

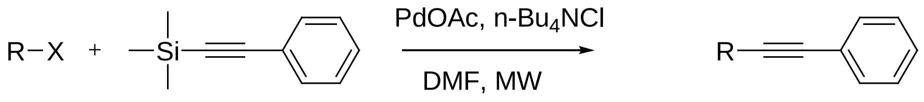
In 2001, Erdélyi and Gogoll reported a microwave-enhance, rapid, and efficient homogeneous-phase of the Sonogashira coupling reaction by applied to the coupling of aryl iodides, bromides, triflates, and aryl chlorides with trimethylsilylacetelene [56]. Several procedures were published describing the Sonogashira coupling is less reactive aryl bromides and triflates involving take long period of reaction times and limited choice of reaction medium. From the weakness, microwave irradiation heating has emerged as a versatile method to speed up many of chemical reactions that can deliver high yields in a few minutes. The optimized reaction conditions gave excellent yields for aryl halides containing a large variety of substitutions in different positions. The single mode microwave irradiations were performed under controlled conditions with monitoring of temperature, pressure, and irradiation power that make the procedure highly safe.



R = H, 4-CF_3, 2-CO_2CH_3, 3-CO_2CH_3, 4-CO_2CH_3
2-OCH_3, 3-OCH_3, 4-OCH_3, 2-NH_2, 3-NH_2, 4-NH_2
3-pyridine, 3-thiophene

Figure 2.18 Homogeneous-phase Sonogashira coupling reactions using controlled microwave heating [56].

In 2005, Sørensen and co-worker reported copper-free palladium-catalyzed sonogashira-type coupling of aryl halides and 1-aryl-2-(trimethylsilyl)acetylenes [57]. A procedure for diarylacetylene synthesis via the direct coupling of activated aryl- and heteroaryl bromides and iodides with 1-aryl-2-trimethylsilylacetylenes has been developed to avoids the use of a copper(I) iodide as co-catalyst. Improvement in reaction yields has been obtained by replacing conventional oil bath heating with the use of microwave dielectric heating to give short reaction times at elevated temperature. The reaction to be highly reproducible when using a microwave instrument that allows for control and monitoring of temperature. For the most of experiments was used DMF as solvent, with its high polarity it absorbs microwaves well, resulting in very rapid heating. The reaction mixture in a hot oil bath results in much slower heating and conversion rates, and the rapid heating when applying microwave may be the explanation for the higher isolated yields.



R = pyridine, 2-methylpyridine, 3-hydroxypyridine
X = I, Br

Figure 2.19 Homogeneous-phase Sonogashira coupling reactions using controlled microwave heating [57].

In 2008, Huang and co-worker reported a rapid and efficient palladium-catalyzed Sonogashira coupling reaction of aryl chlorides [58]. Typically, Sonogashira coupling reaction is inefficient with umreactive aryl chlorides. The optimized reaction conditions is 2% $Pd(PPh_3)_2Cl_2$, 4% $PtBu_3$, 10% DBU, and 1 equiv Cs_2CO_3 in DMF with microwave irradiation at 150 °C to give excellent yield in 10 min. the catalytic system is also effective for Suzuki coupling reaction, Buchwald-Hartwig animation, and Heck coupling reaction with inactivate aryl chlorides.

In 2009, Shook and co-worker reported microwave-assisted, palladium-catalyzed Sonogashira-type coupling of terminal alkynes with a variety of heteroaryl thiomethylethers [59]. The reaction have been successfully coupled with organozinc reagents in the absence of the Cu(I) additive. But there are limited reports using thioethers as coupling partners. Because palladium insertion into the carbon-sulfur bond is quite facile. The coupling of alkynes and heteroaromatic thioethers. phenylacetylene was used initially Various Cu(I) salts such as CuI, CuOTf, and CuTC (copper(I) 2-thiophene carboxylate) were used in combination with a palladium(II) catalyst to carry out. The reactions were run in refluxing THF using conventional heating conditions in the hood with $Pd(dppf)Cl_2$ as the palladium source, only starting materials were recovered from the reactions as no desired coupling products were formed after 16 hours. Then, tried running the reactions in the microwave at 100 °C for 0.5 hours and the coupling product was formed in 24% yield. Increasing reaction time to 1 hour resulted in only a slight increase in yield. Using a more common palladium catalyst, $Pd(PPh_3)Cl_2$, for Sonogashira reactions gave lower yield of the desired product. Next, increasing the reaction time to 2 hours, but it did not increase the conversion. This represents a significant increase in yield which has the same reaction time and reagents equivalents, but the addition of reagents at the beginning and halfway through the reaction resulted in higher yield of product than that obtained from adding all the reagents at the beginning of the reaction. This suggests that the catalyst decomposes under the reaction conditions, and that it is somewhat overcome when the reagents are added portionwise. With a better understanding of the reaction conditions and which protocol, the scope of the reaction using various heteroaromatic thiomethylethers and substituted alkynes were explored. The electron- donating group did not increase reactivity. The higher temperature and microwave, or both are required to form product in appreciable yields. Using phenylacetylenes that contain electron-withdrawing groups gave lower yields. An additional, the fluoro analog gave a good yield but the yield of cyano derivative only slightly increased.

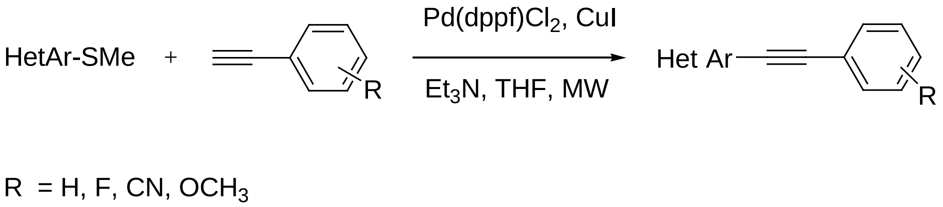
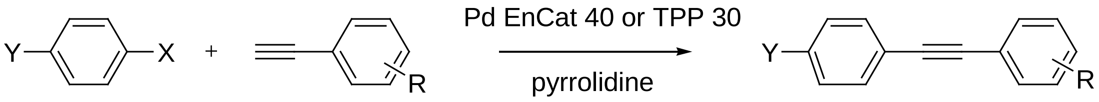


Figure 2.20 Microwave-assisted, palladium-catalyzed Sonogashira-type coupling of terminal alkynes with a variety of heteroaryl thiomethylethers [59].

In 2009, Carpita and co-worker reported convenient copper- and solvent-free Sonogashira-type alkynylation of aryl iodides and bromides using Pd EnCat^{TM} [60]. The copper- and solvent-free alkynylations of aryl iodides and bromides using 0.1–0.01 mol % of Pd as Pd EnCat^{TM} 40 or TPP30. The high yielding reactions can be achieved under aerobic conditions for a variety of activated and deactivated aryl iodides. Microwave irradiation is able to enhance yields and rates of the reactions. The commercially available Pd EnCat^{TM} catalysts have been reported as using a low loading and as being easily removed and recycled. The catalysts consist of Pd(II) acetate microencapsulated in a polyurea matrix are air and moisture stable and can be easily removed by filtration. The optimization condition was conducted in order to improve the yield by applying a lower Pd loading and working under solvent and ligand free conditions without tetrabuthylammonium bromides (TBAB) and with pyrrolidine as the base. The results are reported show that the solvent free conditions allow for the isolation in higher yields even with much lower catalyst loadings. Therefore, a selecting aryl iodides bearing electron-withdrawing and donating groups and a few examples of aryl bromides. In particular, Pd EnCat 40 gave good to excellent yields with 0.01 mol % of Pd when iodobenzene or aryl iodides bearing electron- withdrawing groups were employed, whereas electron-rich aryl iodides gave better results with 0.1 mol % of Pd. Moreover, Pd EnCat 40 allowed excellent results even with ortho-substituted phenylethynes and triisopropylsilylethyne. On the other hand, less reactive ortho-substituted iodides afforded higher yields when Pd EnCat TPP30 was used.



X = I, Br
Y = H, $NH_{2,}$ Cl, Br, CF_3, CH_3, OCH_3, $COCH_3C$
R = H, NH_2, OCH_3

Figure 2.21 Copper-free Sonogashira-type coupling reaction by PdEnCat 40 or TPP30 [60].

CHAPTER III

METHOD AND MATERIALS

In this chapter, our microwave reactor design, chemical reagents and method details will be presented. The first section of this chapter describes the microwave chamber design and microwave guiding component including rectangular waveguide. Next, the chemical reagents for Sonogashira coupling reaction and experimental set up method will be described.

3.1 Microwave chamber design

The basic design of a microwave reactor is simple. The main body of microwave chamber is constructed from small hole perforated sheet stainless steel with the dimension of 30×30×30 cm^3. The adjustable stand height of 10 cm has been designed to be place underneath the chamber to accommodate a magnetic stirrer. The whole reactor is basically a stainless steel box that has an opening in the front fitted with a door. The door is made from stainless steel with a 20×20 cm^2 size and is equipped with hinges on the right hand side, while the latch is placed on the other side. This can easily accommodate various customary chemical reaction setups. The top plate and bottom plate are also made from stainless steel with a reclosable circle opening at the top of a 10 cm diameter. This enables an assembly of extended reaction setup such as a connection of a condenser, a gas inlet, inlet-outlet cooling water, or a mechanical stirrer. The air is blown out of the electric blower form T.C.P. Industry Co., Ltd. through the cooling fins of the magnetron, an electronic tube that produces high-frequency microwave oscillations which is the microwave generating device. The magnetron subassembly includes several important parts. The simulation photo from computer program (Solid work) is shown in appendix A.1. The photograph is shown in **Figure 3.1**. The details each of flanges are described clearly in appendix B.1.

Figure 3.1 The photograph of microwave reactor.

3.2 Microwave guiding component

3.2.1 A rectangular waveguide

A traditional microwave reactor for chemical synthesis mostly utilizes a 2450 MHz (2.45 GHz) [46] microwave magnetron generator which is the same as in ordinary commercial microwave ovens. The common transmission line in this frequency is a hollow-pipe waveguide. The dimension of the waveguide is depending on the specified frequency range of which its electromagnetic wave can undergo propagate and relate to the cut off frequency ($f_{c_{mn}}$) [61]. The lowest frequency of electromagnetic wave that can propagation is called a cut off frequency. Rectangular waveguides are one of the earliest types of the transmission lines that are used in many applications. A transmission line is a device designed to guide electrical energy from one point to another. Rectangular waveguide is used for high frequency and high power microwave irradiation to reduce attenuation loss. The mode theory is used to describe the propagation of wave along a rectangular waveguide [62, 63]. A transverse mode of wave of electromagnetic radiation is a particular electromagnetic field pattern of radiation measured in a plane perpendicular to propagation direction of the wave. Transverse modes occur in radio waves and microwaves confined to a waveguide, and also in light waves in an optical fiber and in a laser's optical resonator. Transverse modes occur because of boundary conditions imposed on the wave by waveguide. For example, microwaves in a hollow metal waveguide must have zero tangential electric field amplitude at the walls of the waveguide, and so the transverse pattern of the electric field of the wave is restricted to those which fit between the walls. For this reason, the allowed modes can be found by solving Maxwell's equations for the boundary conditions of a given waveguide. A rectangular waveguide supports transverse magnetic (TM) mode and transverse electric (TE) modes but not transverse electromagnetic (TEM) mode because we can not define a unique voltage since there is only one conductor in a rectangular wave guide. TM mode is a normal mode in which the longitudinal components that have no magnetic field in the direction of propagation, the magnetic lines of flux are perpendicular to the axis of the waveguide. TE modes have no electric field in the direction of propagation. In TE mode, the electric lines of flux are perpendicular to the axis of the waveguide. WR340 standard waveguide is designed and used, due to this dimension, only TE_{10} mode can be propagated [64]. The mode theory uses electromagnetic wave behavior to describe the propagation of wave along a rectangular waveguide. Furthermore, the high conductivity of aluminum (3.816×10^{7} S/m) is caused for low skin depth for microwave.

For the WR340, the cut off frequency is 1.72 GHz (inside width (a) = 86.4 mm, and inside height (b) = 43.2 mm). This is less than the 2.45 GHz mean that the electromagnetic wave can propagate.

$$f_{c10} = \frac{c}{2\pi}\sqrt{\left(\frac{m\pi}{a}\right)^{2} + \left(\frac{n\pi}{b}\right)^{2}}$$

The wavelength within waveguide (λ_g) also relates to the free space wavelength (λ_0 = 121.6 mm), follows by this equation;

$$\lambda_g = \frac{\lambda_0}{\sqrt{\left(1-\left(f_c/f\right)^2\right)}}$$

For f_c is 1.72 GHz and f is 2.45 GHz, the value of λ_g become 170 mm. Rectangular waveguide is designed with the length of 340 mm. The simulation photo of rectangular waveguide is shown in appendix B.2. The photograph is shown in **Figure 3.2**. The magnetron head is coupled via the waveguide at a distance of 22 mm from end cap, which is used as a standard coupling.

The rectangular waveguide is connecting to the microwave chamber with waveguide flange, for rectangular waveguide there exist a number of competing standard flanges which are not entirely mutually compatible. The rectangular waveguide WR340 is used a standard 10 hole flange CPR340F. A waveguide flange is connector for joining sections of waveguide, being a hollow metal conduit for microwave energy. The connection between a pair of flange is made with 10 bolts. Outer dimension is 1,382 × 952 mm^2 with 9.65 mm thin. The photograph is shown in **Figure 3.3**.

Figure 3.2 The photograph of WR340 rectangular waveguide.

Figure 3.3 The photograph of rectangular waveguide flange CPR340F.

3.2.2 Magnetron power supply

A power supply is a device that supplies electrical energy to electric loads. The reactor is fed with 2.45 GHz for the standard magnetron, microwave radiation arriving to the processing chamber through the WR340 rectangular waveguide from the microwave magnetron generator. The power supply can control the output of microwave power manually with the maximum effective output power of 500 Watt. In this work, we vary the microwave power around 10-30% of the maximum power. Most of the reaction conditions performed smoothly at 100 Watt (20% of the maximum power). **Figure 3.4** shows the photograph of the simple microwave power supply.

Figure 3.4 The photograph of microwave power supply.

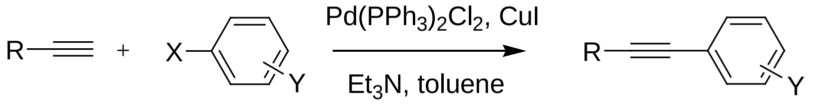
3.3 Chemical reagents

Chemicals were reagent grade and were used without further purification. They were purchased from the following vendors:

- Aldrich Chemical Co., Inc.: silver(I) oxide (Ag_2O), tetrabutylammonium fluoride (TBAF), tetrakis(triphenylphosphine)palladium(0), magnesium sulfate
- Tokyo Chemical Industry Co., Ltd.: trimethylsilyacetylene (TMS), bis(triphenylphosphine)palladium(II) dichloride, phenylboronic acid, 4-bromophenylboronic acid, 3-bromophenylboronic acid, 2-bromophenylboronic acid, 4-chlorophenylboronic acid, 4-nitrophenylboronic acid, and 4-methoxyphenylboronic acid, ethyl propiolate
- Fluka Chemical Corp.: phenylacetylene , *N*,*N*-dimethylformamide (DMF), 1-bromo-4nitrobenzene, 4-bromobenzonitrile, 4-bromobenzaldehyde, bromobenzene , 4-bromoanisole, 4-methyliodobenzene, 3-methyliodobenzene, 2- methyliodobenzene, copper(I) iodides
- Carlo Erba Reagent: triethylamine (TEA)
- Merck Co., Ltd.: diethyl ether, benzene, toluene

Acetonitrile (ACN) and tetrahydrofuran (THF) purchased from Labscan Asia Co., Ltd. as solvent for the synthesis was reagent grade and was purified by standard method prior to use. Solvents for column chromatography including dichloromethane, hexanes, ethyl acetate, and methanol were commercial grade and were distilled before use. All reactions were performed in a microwave reactor with a 30×30×30 cm^3 reaction chamber which was originally designed and constructed. A 2.45 GHz microwave generator and a 500 W microwave power supply are connected to the reaction chamber through a WR340 rectangular waveguide. The progress of the reaction was followed by thin layer chromatography (TLC) performed on Merck D.C. silica gel 60 F_{254} 0.2 mm precoated aluminium plates. Reaction mixtures were purified by column chromatography using 70-230 mesh silica gel. ^1H NMR spectra were recorded in $CDCl_3$ on a Varian Mercury-400 Plus operating at 400 MHz and a Bruker Avance 400, operating at 400 MHz. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) or using the residual protonated solvent signal as a reference ($CDCl_3$ δ 7.27). Coupling constants (*J*) are proton-proton coupling unless otherwise noted and reported in Hertz (Hz). Multiplicities were abbreviated as followed: singlet (s), doublet (d), triplet (t), and quartet (q). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br). All reported reaction yields are isolated yields.

3.4 Sonogashira coupling reaction



1a: R = $Si(CH_3)_3$
1b: R = Ph
1c: R = $CO_2CH_2CH_3$

2a: X = Br
2b: X = Br, Y = 4-NO_2
2c: X = Br, Y = 4-CN
2d: X = Br, Y = 4-CHO
2e: X = Br, Y = 4-OCH_3

2f: X = I, Y = 4-CH_3
2g: X = I, Y = 3-CH_3
2h: X = I, Y = 2-CH_3

3.4.1 General procedure for palladium (II)-catalyzed Sonogashira coupling reaction with conventional heating.

The method by Erdélyi and Gogoll [56] was follwed with a slightly modification. A mixture of an aryl halide (2.00 mmol), a terminal alkyne (3.00 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.05 mmol), CuI (19.0 mg , 0.10 mmol), and Et_3N (4 mL) in 4 mL of solvent was stirred and heated with an oil bath at 80 °C under N_2 for 24 hours. The reaction mixture was then allowed to cool to room temperature. The mixture was subjected to filtration and the filtrate was washed with diethyl ether (2×10 mL). Subsequently, the solution was extracted three times with water and twice with saturated NaCl. Portions of the organic phase were combined and dried over $MgSO_4$. Solvent was then evaporated under reduced pressure. The crude product was purified by column chromatography (hexanes/CH_2Cl_2) to give the desired coupled products.

trimethyl((4-nitrophenyl)ethynyl)silane 3a

Purifications by column chromatography (hexane/CH_2Cl_2 8:1) to afforded product as a yellow crystal. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 0.27 (s, 9H), 7.60 (d, *J* = 7.49 Hz, 2H), 8.17 (d, *J* = 7.72 Hz, 2H).

4-((trimethylsilyl)ethynyl)benzonitrile 3b

Purifications by column chromatography (hexane/CH_2Cl_2 8:1) to afforded product as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 0.26 (s, 9H), 7.53 (d, *J* = 7.89 Hz, 2H), 7.59 (d, *J* = 8.15 Hz, 2H).

trimethyl(p-tolylethynyl)silane 3c

Purifications by column chromatography (hexane/CH_2Cl_2 8:1) to afforded product as a light yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 0.27 (s, 9H), 2.37 (s, 3H), 7.13 (d, *J* = 7.39 Hz, 2H), 7.38 (d, *J* = 7.03 Hz, 2H).

trimethyl(m-tolylethynyl)silane 3d

Purifications by column chromatography (hexane/CH_2Cl_2 8:1) to afforded product as a light yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 0.27 (s, 9H), 2.34 (s, 3H), 7.35-7.26 (m, 1H), 7.21 (t, *J* = 7.56 Hz, 1H), 7.15 (d, *J* = 7.52 Hz, 1H).

trimethyl(o-tolylethynyl)silane 3e

Purifications by column chromatography (hexane/CH_2Cl_2 8:1) to afforded product as a light yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 0.07 (s, 9H), 2.24 (s, 3H), 6.92 (t, *J* = 6.98 Hz, 1H), 7.10-6.96 (m, 2H), 7.23 (d, *J* = 7.56 Hz, 1H).

4-((trimethylsilyl)ethynyl)benzaldehyde 3f

Purifications by column chromatography (hexane/CH_2Cl_2 5:1) to afforded product as a brown solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 0.29 (s, 9H), 7.63 (d, *J* = 7.23 Hz, 2H), 7.84 (d, *J* = 7.17 Hz, 2H), 10.02 (s, 1H).

((4-methoxyphenyl)ethynyl)trimethylsilane 3g

Purifications by column chromatography (hexane/CH_2Cl_2 5:1) to afforded product as a brown solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 0.24 (s, 9H), 3.81 (s, 3H), 6.81 (d, *J* = 7.29 Hz, 2H), 7.40 (d, *J* = 7.71 Hz, 2H).

1-nitro-4-(phenylethynyl)benzene 4b

Purifications by column chromatography (hexane/CH_2Cl_2 5:1) to afforded product as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.38-7.40 (m, *J* = 4.90 Hz, 3H), 7.54-7.60 (m, *J* = 3.51 Hz, 2H), 7.67 (d, *J* = 8.08 Hz, 2H), 8.23 (d, *J* = 8.38 Hz, 2H).

4-(phenylethynyl)benzonitrile 4c

Purifications by column chromatography (hexane/CH_2Cl_2 5:1) to afforded product as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.35-7.38 (m, 3H)**,** 7.52-7.57 (m, 2H), 7.60-7.67 (m, 4H).

1-methyl-4-(phenylethynyl)benzene 4e

Purifications by column chromatography (hexane/CH_2Cl_2 5:1) to afforded product as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 2.37 (s, 3H)**,** 7.16 (d, *J* = 7.53 Hz, 2H), 7.33-7.40 (m, 3H), 7.43-7.45 (m, 2H), 7.51-7.53 (m, 2H).

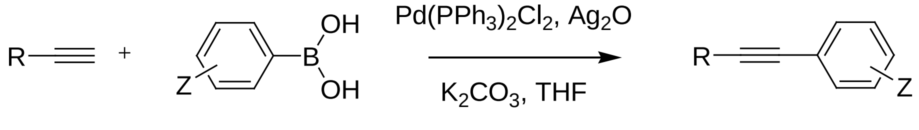
1,2-bis(4-nitrophenyl)ethyne 4f

Purifications by column chromatography (hexane/CH_2Cl_2 5:1) to afforded product as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.72 (d, *J* = 8.29 Hz, 4H), 8.27 (d, *J* = 8.03 Hz, 4H).

3.4.2 General procedure for Palladium (II)-catalyzed Sonogashira coupling reaction with microwave heating.

The procedure outlined above was followed but the reaction was carried out in a microwave assembly instead of an oil bath under ambient atmosphere. The microwave power and the reaction time were varied to optimize reaction conditions. Work up procedure was similarly conducted.

3.5 Sonogashira-type coupling reaction



1b: R = Ph
1c: R = $CO_2CH_2CH_3$

2j: Z = 4-Br
2k: Z = 3-Br
2l: Z = 2-Br

2m: Z = 4-Cl
2n: Z = 4-NO_2
2o: Z = 4-OCH_3

3.5.1 General procedure for Palladium (II)-catalyzed Sonogashira-type coupling reaction with microwave heating.

A 50 mL round bottom flask was charged with a mixture of aryl boronic acid (1.00 mmol), alkynes (1.10 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg , 0.05 mmol), K_2CO_3 (692.0 mg, 5.00 mmol), Ag_2O (580.0 mg, 2.50 mmol), and TBAF (5 mL). After that the mixture was stirred and heated with microwave irradiations at 100 Watt for 20 min in the microwave reactor under ambient atmosphere. The reaction mixture was allowed to cool to room temperature. The mixture was then subjected to filtration and the filtrate was washed with diethyl ether (2×10 mL). Then the solvent was evaporated on rotary evaporator under reduced pressure and the crude product was purified by column chromatography (hexanes/CH_2Cl_2) to give the desired coupled products.

1,2-diphenylethyne 4a

Purifications by column chromatography (hexane) to afforded product as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.36-7.38 (m, *J* = 7.58 Hz, 6H), 7.52-7.56 (m, *J* = 6.52 Hz, 4H).

1-bromo-4-(phenylethynyl)benzene 4h

Purifications by column chromatography (hexane) to afforded product as a yellow power. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.38 (m, *J* = 6.65, 6.36 Hz, 5H), 7.56 (m, *J* = 7.18 Hz, 4H).

1-chloro-4-(phenylethynyl)benzene 4k

Purifications by column chromatography (hexane) to afforded product as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.36 (m, 5H), 7.49 (d, *J* = 8.33 Hz, 2H), 7.55 (d, *J* = 3.33 Hz, 2H).

ethyl 3-phenylpropiolate 5a

Purifications by column chromatography (hexane/CH_2Cl_2 8:1) to afforded product as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.38 (t, *J* = 7.01 Hz, 3H), 4.32 (q, *J* = 7.01 Hz, 2H), 7.61 (m, *J* = 7.45 Hz, 2H), 7.39-7.47 (m, 3H).

ethyl 3-(4-bromophenyl)propiolate 5b

Purifications by column chromatography (hexane/CH_2Cl_2 8:1) to afforded product as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.38 (t, *J* = 6.99 Hz, 3H), 4.32 (q, *J* = 6.99 Hz, 2H), 7.46 (d, *J* = 7.20 Hz, 2H), 7.54 (d, *J* = 8.17 Hz, 2H).

ethyl 3-(3-bromophenyl)propiolate 5c

Purifications by column chromatography (hexane/CH_2Cl_2 8:1) to afforded product as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.38 (t, *J* = 6.93 Hz, 3H), 4.32 (q, *J* = 6.78 Hz, 2H), 7.33-7.23 (m, 1H), 7.53 (d, *J* = 7.62 Hz, 1H), 7.60 (d, *J* = 8.03 Hz, 1H), 7.75 (s, 1H).

ethyl 3-(4-chlorophenyl)propiolate 5e

Purifications by column chromatography (hexane/CH_2Cl_2 8:1) to afforded product as a brown oil. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.38 (t, *J* = 7.13 Hz, 3H), 4.32 (q, *J* = 6.97 Hz, 2H), 7.38 (d, *J* = 7.24 Hz, 2H), 7.54 (d, *J* = 8.21 Hz, 2H).

ethyl 3-(4-nitrophenyl)propiolate 5f

Purifications by column chromatography (hexane/CH_2Cl_2 5:1) to afforded product as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.40 (t, *J* = 7.01 Hz, 3H), 4.35 (q, *J* = 7.08 Hz, 2H), 7.77 (d, *J* = 7.92 Hz, 2H), 8.28 (d, *J* = 7.83 Hz, 2H)

ethyl 3-(4-methoxyphenyl)propiolate 5g

Purifications by column chromatography (hexane/CH_2Cl_2 6:1) to afforded product as a brown oil. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.37 (t, *J* = 7.10 Hz, 3H), 3.86 (s, 3H), 4.31 (q, *J* = 7.01 Hz, 2H), 6.91 (d, *J* = 8.11 Hz, 2H), 7.56 (d, *J* = 7.91 Hz, 2H).

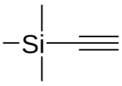
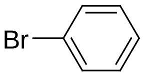
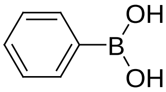
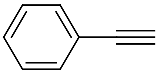
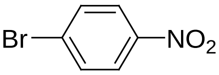
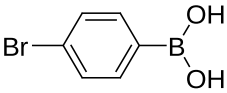
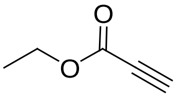
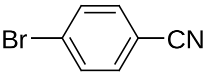
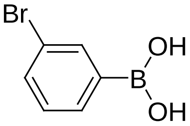
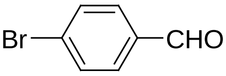
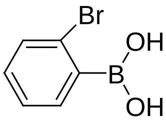
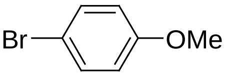
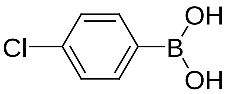
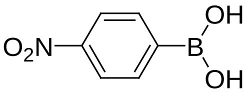
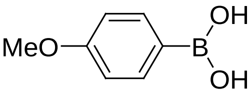
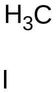
3.5.2 General procedure for Copper(I)-catalyzed Sonogashira-Ttype coupling reaction with conventional heating.

A mixture of aryl boronic acid (0.50 mmol), alkynes (0.75 mmol), CuI (14.5 mg , 0.075 mmol), Ag_2O (232.0 mg, 1.00 mmol), base (2.00 mmol), and 4 mL of solvent was stirred and heated with an oil bath at 80 °C under air atmosphere for 30 hours. The reaction mixture was allowed to cool to room temperature. The mixture was then subjected to filtration and the filtrate was washed with diethyl ether (2×10 mL). Subsequently, the solution was extracted three times with water and twice with saturated NaCl. Portions of the organic phase were combined and dried over $MgSO_4$. Solvent was then evaporated under reduced pressure. The crude product was purified by column chromatography (hexanes/CH_2Cl_2, 8:1) to give the desired coupled products.

3.5.3 General procedure for Copper(I)-catalyzed Sonogashira-type coupling reaction with microwave heating.

The procedure outlined above was followed but the reaction was carried out in a microwave assembly under air atmosphere instead of an oil bath. The base and solvent were varied to optimize reaction conditions. Work up procedure was similarly conducted.

Table 3.1 List of Sonogashira and Sonogashira-type coupling reagents.

Terminal alkynes		Aryl halides		Arylboronic acids	
	**1a**		**2a**		**2i**
	**1b**		**2b**		**2j**
	**1c**		**2c**		**2k**
			**2d**		**2l**
			**2e**		**2m**
			**2f**		**2n**
			**2g**		**2o**
			**2h**		

CHAPTER IV

RESULTS AND DISCUSSION

This chapter is divided into three parts. The first part covers palladium-catalyzed Sonogashira coupling reaction with and without microwave activation. The second part, copper-catalyzed Sonogashira coupling reaction will be demonstrated. Finally, the palladium-catalyzed, silver-assisted Sonogashira-type coupling reaction will be described in the last section.

4.1 Palladium-catalyzed Sonogashira coupling reaction

4.1.1 Palladium-catalyzed Sonogashira coupling reaction with conventional heating method

At the beginning of this research, we investigated the traditional Sonogashira coupling reaction following the literature procedure [65]. The coupling reaction (**Figure 4.1**) between trimethylsilylacetylene **(1a)** and 1-bromo-4-nitrobenzene **(2b)** has been performed. In the presence of 10 mol% of $Pd(PPh_3)_2Cl_2$, 0.1 mol% of CuI co-catalyst, Et_3N as base, and benzene as solvent under a N_2 atmosphere at 60 °C *via* an oil bath for 24 hours, trimethyl((4-nitrophenyl)ethynyl)silane **(3a)** was formed in a moderate 64 % yield. This is a little bit lower than the yield of 78% reported in the literature [65]. The expected mechanism is as previously shown in **Figure 2.4**. The reaction took place in 2 catalytic cycles of palladium catalyst and copper co-catalyst, by forming a complex with palladium in the initial step. Transmetallations is usually the rate-determining step, and as we have seen in other traditional Sonogashira coupling reaction, this generally takes a long period of reaction time.

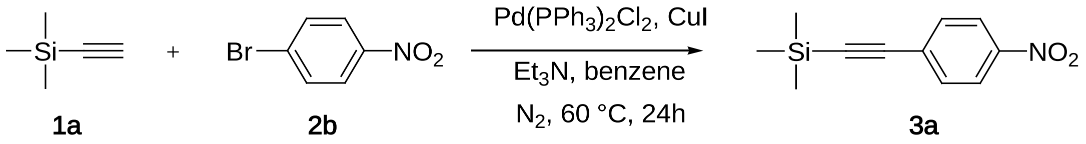


Figure 4.1 Sonogashira coupling reaction between **(1a)** and (**2b)** with conventional heating.

Following the above conditions, another aryl halide bearing an electron withdrawing group 4-bromobenzonitrile **(2c)** has been subjected to the reaction to give 4-((trimethylsilyl)ethylnyl)benzonitrile **(3b)** in moderate 64 % yield (**Figure 4.2**). This is comparable the yield of 72% reported in the literature [64].

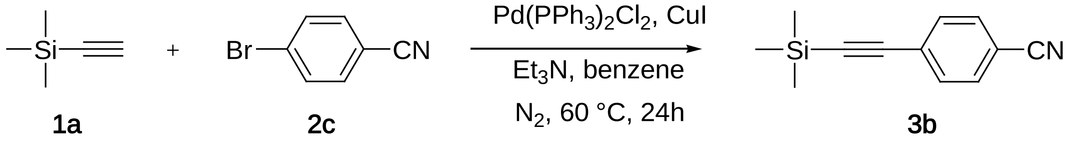


Figure 4.2 Sonogashira coupling reaction between **(1a)** and (**2c)** with conventional heating.

On the other hand, an aromatic halide with an electron donating methoxy group, 4-bromoanisole **(2e)** yielded no desired coupling product after 24 hours under the same reaction condition (**Figure 4.3**). In general, aryl halides bearing electron-donating substituents afforded lower yields than aryl halides with electron-withdrawing group because of lower reactivity [6].

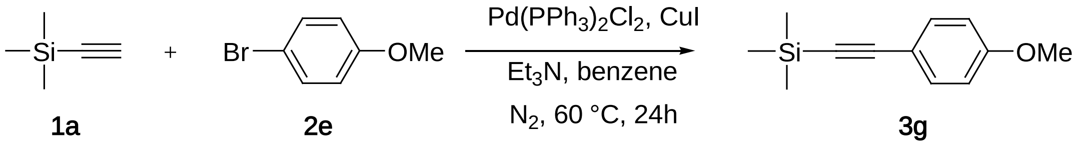


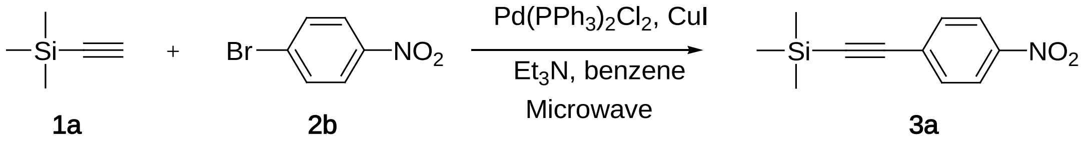
Figure 4.3 Sonogashira coupling reaction between **(1a)** and (**2e)** with conventional heating.

Next, the palladium-catalyzed Sonogashira coupling reaction of **(1a)** with **(2b)** under microwave irradiation was studied as a model reaction to identify the optimal reaction conditions for comparison purposes. Bromoarenes are cheaper and more readily available than iodoarenes, hence synthetically more useful. Therefore, they will be substrates of choice. The reaction was carried out under ambient atmosphere in the presence of 10 mol% of $Pd(PPh_3)_2Cl_2$ catalyst together with 0.1 mol% of CuI co-catalyst in Et_3N as base and benzene as solvent. The reaction was performed under controlled microwave irradiation conditions that make this procedure highly safe, reliable, and reproducible. The data are compiled in **Table 4.1**.

4.1.2 Palladium-catalyzed Sonogashira coupling reaction with microwave heating method

With conventional heating in an oil bath the reaction proceeded with a much slower heating and conversion rates. In contrast, when the reaction was activated in a microwave chamber under an ambient atmosphere using 50 Watt of microwave for an arbitrary 10 minutes, the product was afforded to 75 % yield. The rapid heating when applying microwave may be the explanation for the higher isolated yields obtained in the cases where comparable experiments were carried out. In order to find an optimum power of microwave to apply on the systems, reactions were carried out while microwave generator was adjusted to vary microwave power from 50, 100, to 150 Watt (**Table 4.1**, entries 2-4).

Table 4.1 Effect of microwave power and reaction time on the outcome of microwave-assisted Sonogashira reaction.



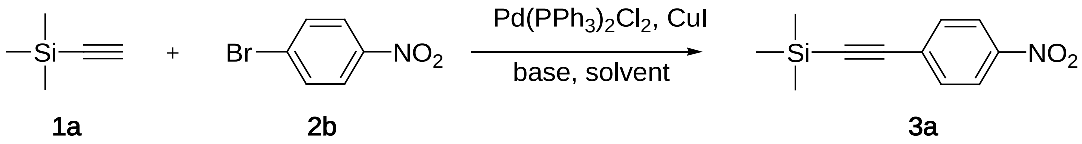
Entry	Heating method	MW Power (W)	Time	Yield[a] (%)
1	Conventional	N/A	24 h	64[b]
2	MW irradiation	50	10 min	75
3	MW irradiation	100	10 min	90
4	MW irradiation	150	10 min	87
5	MW irradiation	100	5 min	66
6	MW irradiation	100	15 min	86

[a] Isolated yield. [b] heated with oil bath under N_2 at 60° C.

It was found that at 100 and 150 Watt, product yields are observed in comparable amounts (90 % and 87 % yield) so a 100 Watt microwave power was considered best for this reaction condition because no significant yield improvement was observed when the microwave power was increased to 150 Watt. Subsequently, the reaction time was varied at 5, 10, and 15 minutes at 100 Watt microwave power (**Table 4.1**, entries 5, 3, and 6, respectively) to find an optimal period required for highest conversion. It was observed that the reaction with 10 minute reaction time gave the highest product yields. In 5 minutes of reaction times, only 66 % yield was isolated from the reaction due to the reaction was not completed in short reaction times. At 15 minutes of reaction times 86 % and not a significantly higher yield was observed after 10 minutes. To prevent a fast decomposition of palladium catalyst at higher temperatures, the microwave of 100 watt and a 10 minute reaction time have been used throughout. The reaction was found to be highly reproducible when using a microwave equipment upon which or a control and monitoring of temperature as well as efficient stirring can be achieved. Solvent with high polarity will absorb microwaves well, resulting in very rapid heating.

Further investigation revealed that the base and solvent used have played a significant role in this reaction. The effects of different organic and inorganic base were tested and the date are tabulated in **Table 4.2**.

Table 4.2 Effect of base and solvent on Sonogashira coupling reaction.



Entry	Base	Solvent	Heating	Yield (%)
1	Et_3N	benzene	MW	90
2	Et_3N	Toluene	MW	95
3	Et_3N	DMF	MW	85
4	Et_3N	H_2O	MW	50
5	K_2CO_3	Toluene	MW	-
6	TBAF	-	Oil bath	54
7	TBAF	-	Heating block	64
8	TBAF	-	MW	85

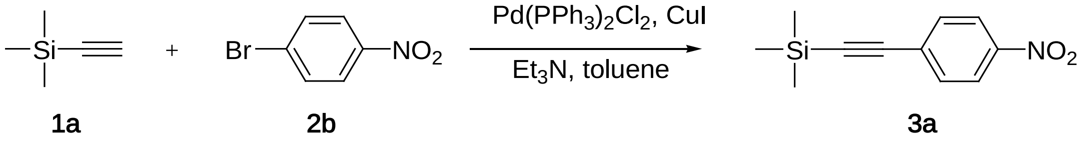
Apparently, Et_3N was the most effective among the tested bases and no desired product was isolated in the presence of inorganic base K_2CO_3 (**Table 4.2**, entry 5). In the solvent tests, it was observed that the reaction gave excellent yield in 90 in benzene (**Table 4.2**, entry 1) and 93 % in toluene (**Table 4.2**, entry 2). The yield was slightly decreased to 85 % (**Table 4.2**, entry 3) in presence of DMF. Finally, the use of water as a solvent gave only 50% yield of the product. This is because water has a very high electric constant and can absorb microwave as well. Due to cost considerations and environmental aspects, toluene was the best choice in the procedure. Moreover, toluene is easier to remove from the reaction mixture than DMF. In addition, solventless

Sonogashira coupling reactions in TBAF as base were also examined. Conventional heating method *via* oil bath and heating block gave only moderate 54 % and 64 % yield (**Table 4.2**, entries 5 and 6) of the isolated product. In the cases where solvents have high points, a water condenser was connected to the set up. As shown in entry 8, a high 85 % yield was observed.

4.1.3 The effect of palladium loading on Sonogashira reaction.

Palladium catalyst loading effect on the reaction with microwave activation was also determined by decreasing the amount of catalyst used in the reactions from the usual amount of 10 to 5.0, 2.5, 1.0 mol%, and none, respectively. The data are summarized in **Table 4.3**.

Table 4.3 Effect of Palladium catalyst loading on Sonogashira reaction.



Entry	Catalyst	Pd loading (mol%)	Heating	Yield [a] (%)
1	$Pd(PPh_3)_2Cl_2$	10.0	Oil bath	64[b]
2	$Pd(PPh_3)_2Cl_2$	10.0	MW	90
3	$Pd(PPh_3)_2Cl_2$	5.0	MW	93
4	$Pd(PPh_3)_2Cl_2$	2.5	MW	95
5	$Pd(PPh_3)_2Cl_2$	2.5	MW	79[c]
6	$Pd(PPh_3)_2Cl_2$	1.0	MW	74
7	$Pd(PPh_3)_2Cl_2$	0.0	MW	0
8	$Pd(PPh3)_4$	2.5	MW	90
9	$Pd(PPh3)_4$	1.0	MW	79
10	$Pd(PPh3)_4$	0.0	MW	0

[a] Isolated yield. [b] heated with oil bath under N_2 at 60° C for 24 h. [c] without CuI.

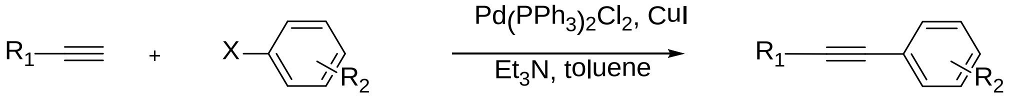
Two palladium catalysts, Pd(II) and Pd(0) were used for comparison. Traditional Sonogashira coupling reaction with conventional heating was carried out with 10 mol% of $Pd(PPh_3)_2Cl_2$ to give moderate 64% yields (**Table 4.3**, entry 1) as previously reported. In contrary, when microwaves is used at 100 Watt microwave power for 10 minutes reaction time, catalyst loading 10.0, 5.0, and only 2.5 mol% of $Pd(PPh_3)_2Cl_2$ can catalyze the reaction to give the desired coupling product over 90% yield (**Table 4.3**, entry 2-4). Interestingly, the coupling reaction between **1a** and **2b** can also be carried out without CuI. In the absence of CuI co-catalyst, the reaction resulted in a reduced product yield of 79% (**Table 4.3**, entry 5). It is known that a small amount of CuI in the reaction mixture results in a faster reaction. As the amount of $Pd(PPh_3)_2Cl_2$ decreased to 1.0 mol%, the reaction proceeded with desired coupling product in 74% yield (**Table 4.3**, entry 6). However, in the absence of the crucial palladium catalyst, no product was detected (**Table 4.3**, entry 7). $Pd(PPh_3)_4$ catalyst also resulted in highly comparable amounts of product at each catalyst loading as can be seen in entries 8-10. Again, the presence of palladium catalyst is proven necessary. Among these, $Pd(PPh_3)_2Cl_2$ was used further because of its lower sensitivity to air. However, it should be noted that increased catalyst loading above 2.5 mol% did not affect the reaction yields.

4.1.4 The effect of aryl halides and terminal alkynes on Sonogashira reaction.

The optimized reaction conditions for microwave-assisted Sonogashira coupling reaction compiled from preliminary tests mentioned earlier led us to use 2.5 mol% of $Pd(PPh_3)_2Cl_2$ as catalyst, 0.1 mol% of CuI as co-catalyst, Et_3N as base and toluene as solvent at 100 Watt microwave power for 10 minutes for the reactions that follow. These reaction conditions were applied to a coupling of (**1a)** with a range of aryl aromatic halides bearing electron-withdrawing and electron-donating groups. The data are compiled in **Table 4.4**. From the literature reviews, generally, aryl halides bearing electron-withdrawing groups are more reactive than those with electron-donating groups. The more reactive iodobenzene was also used in comparison with bromobenzene. The reaction of **(1a)** with 4-methyliodobenzene (**2f**) gave an excellent 91 % yield (**Table 4.4**, entry 1) due to reactivity of iodobenzene and not too strong of an electron-donating group like methyl group. Meta-substituted group on iodobenzene gave slightly decreased yield of 87 % (**Table 4.4**, entry 2), and ortho-substituted group gave a sharply decrease to a moderate 57 % yield. The influence of steric hindrance was not significantly observed in the cases of meta- and para-substituted halides. However, in the ortho-substituted compound, the reaction showed lower reactivity which might be a contribution from steric effects. This resulted in a large decrease in yields. Bromobenzene which bears electron-withdrawing groups (**2b)** and (**2c)** gave excellent 93 % and 94 % yield (**Table 4.4**, entries 4 and 5) since electron-withdrawing group on aromatic halides makes them highly reactive. An exceptional case, however, was observed on 4-bromobenzaldehyde (**2d**), where the coupling reaction gave only moderate 51 % (**Table 4.4**, entry 6) isolated yield after 20 minutes. It may be because it is not stable so that leads to decreased yields. An aromatic halide with a strong electron-donating group such as 4-bromoanisole (**2e**) gave only very low 10 % yield (**Table 4.4**, entry 7).

The reaction between phenylacetylene **(1b)** with bromobenzene (**2a)** gave 71 % yield (**Table 4.4**, entry 8) because bromobenzene is less reactive than iodobenzene. The coupling reaction between phenylacetylene **(1b)** with aryl halides was also investigated by using the optimized reaction conditions. As we expected, aryl halides with electron-withdrawing group such as (**2b)** and (**2c)** gave high 85 % and 79 % yield (**Table 4.4**, entries 9 and 10). Moreover, no desired product was isolated from the reaction of aromatic halides bearing electron-donating group (**Table 4.4**, entry 11).

Table 4.4 Effect of aryl halide and terminal alkynes on Sonogashira coupling reaction.



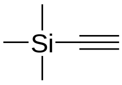
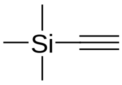
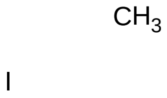
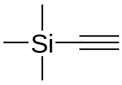
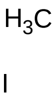
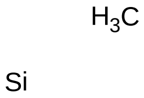
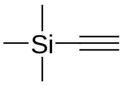
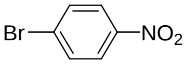
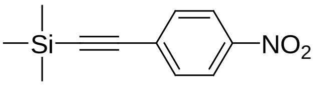
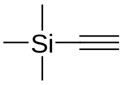
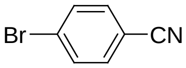
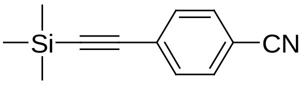
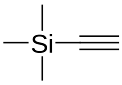
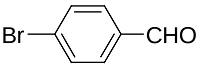
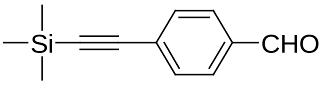
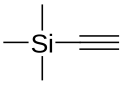
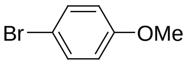
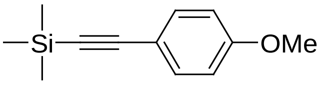
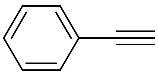
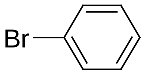
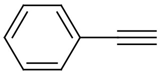
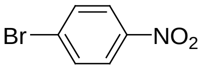
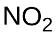
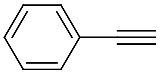
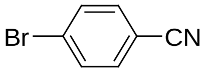
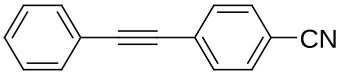
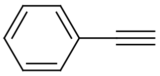
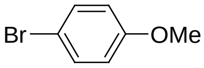
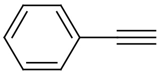
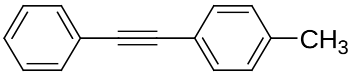
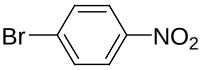
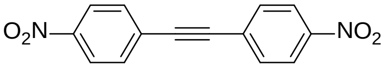
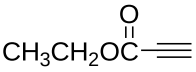
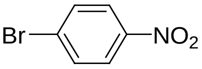
Entry	Terminal alkynes	Aryl halide	Coupling product		Yield (%)
1				**3c**	91
2				**3d**	87
3				**3e**	57
4				**3a**	95
5				**3b**	94
6				**3f**	51
7				**3g**	10
8				**4a**	71
9				**4b**	85
10				**4c**	79
11				**4d**	0

Table 4.4 (cont.)

Entry	Terminal alkynes	Aryl halide	Coupling product		Yield (%)
12		I CH$_3$		**4e**	90
13	O_2N			**4f**	30
14	 $CH_3CH_2O\overset{O}{C}-\equiv$		O CH_3CH_2OC NO_2	**4g**	0

In comparison with literature procedure that reported that by Erdélyi and Gogoll [56], the Sonogashira coupling reaction of aryl iodides and aryl bromides containing electron-withdrawing group and electron-donating group gave excellent yields (over 90%). The reaction using commonly $Pd(PPh_3)_2Cl_2$ as catalyst, CuI as co-catalyst, Et_2NH as base, and DMF as solvent with 120 °C microwave irradiation in 5 minutes. All reaction in literature procedure were conducted under nitrogen atmosphere in heavy-walled glass Smith process vial sealed with aluminum crimp cap fitted with silicon septum that the inner diameter height 2 cm. The microwave reactor that was used was from Smith Synthesizer single-mode microwave cavity producing continuous irradiation at 2450 MHz with monitoring of temperature, pressure, and irradiation power *vs.* time. It is noteworthy that electron-donating group on the aromatic bromides such as 2-bromoanisole, 3-bromoanisole, and 4-bromoanisole gave high 80-90% yield in the presence of triphenylphosphine as ligand with microwave irradiation in 25 minutes. In light of this, we tried to use the same condition with our own-designed microwave reactor in ambient atmosphere. Unfortunately, comparable product yields were not observed. This may be due to the fact that commercial microwave reactor for synthesis can monitor the pressure that provides the efficiency of heat transfer process in the reaction mixtures and nitrogen atmosphere make the palladium-catalyst decompose more slowly.

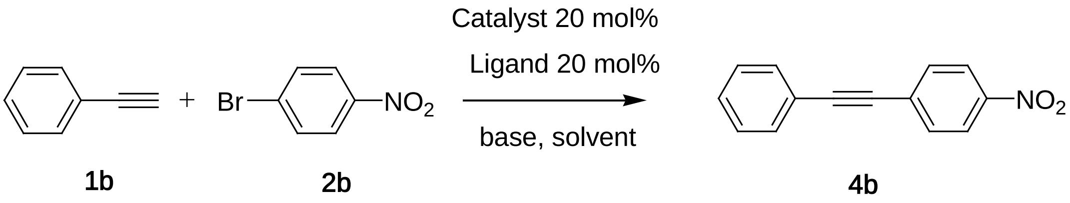
4.2 Copper-catalyzed Sonogashira coupling reaction

Next, phenylacetylene was used as starting material, the traditional Sonogashira that used palladium supported complex as catalyst, Et_3N as base, and DMF as solvent have been reported by Bakherad and co-workers [41]. The reaction was also carried out under nitrogen atmosphere for 4-8 hours to give **4a**, **4b**, and **4d** in high 90% yield. Due to the palladium supported complex have more selectivity and are more stable than the commonly palladium-catalyst. In the same way of microwave heating method reported by Huang and co-workers [56]. The reaction that used $Pd(PPh_3)_2Cl_2$ as catalyst, 4% $PtBu_3$, 10% DBU, Cs_2CO_3 as base, and DMF as solvent run smoothly with **2d**, aromatic bromides containing electron-donating group gave moderate 58% yield under pressure and nitrogen atmosphere.

In addition, we investigated electron-deficient terminal alkynes such as ethyl propiolate (**1c**) with reactive aryl bromides (**2b)** but no desired product were formed. This confirmed that the traditional Sonogashira coupling reaction does not worked with electron-deficient terminal alkynes even though microwave-assisted method was employed.

In several modifications of Sonogashira coupling reactions, copper-catalyzed Sonogashira has been reported. Palladium-catalyzed protocols have limitation due to the use of expensive Pd metal and phosphine ligand palladium complex. Next, the test experiments of copper-catalyst Sonogashira coupling reaction were carried out in the variation of copper-catalyzed, ligand, and base as shown in **Table 4.5**. However, only a low amount coupling desired product was formed by with both conventional and microwave heating method. The ligand, salicylic acid and, triphenylphosphine (PPh_3), gave only low yield but in the absence of ligand no coupling desired product were observed.

Table 4.5 Effect of copper-catalyzst and ligands on Sonogashira coupling reaction.



Entry	Catalyst	Ligand	Base	Solvent	Heating	Time	Yield(%)
1	$CuCl_2$	Salicylic acid	Cs_2CO_3	DMF	Oil bath	24 h	12
2	$CuCl_2$	Salicylic acid	K_2CO_3	DMF	Oil bath	24 h	9
3	$CuCl_2$	PPh_3	K_2CO_3	DMF	Oil bath	24 h	11
4	$CuCl_2$	PPh_3	K_2CO_3	DMF	MW	10 min	10
5	$CuCl_2$	-	K_2CO_3	DMF	MW	10 min	-
6	CuI	Salicylic acid	K_2CO_3	DMF	MW	10 min	0
7	CuI	Salicylic acid	K_2CO_3	DMF	MW	20 min	0

4.3 Sonogashira-type of terminal alkynes with arylboronic acids coupling reaction.

To overcome the limitations, we had turned our focus to one of Sonogashira coupling reaction variant, namely, the Sonogashira-type coupling reaction. Phenylboronic acid (**2i**) has been used for the Sonogashira-type coupling reaction to give a moderate-high yield from the literature. To make it easy and simple Sonogashira-type, we tried to use phenylboronic acid with the optimized reaction conditions (**Figure 4.4**). However, even after 20 minutes of microwave-assisted conditions, no desired product was detected.

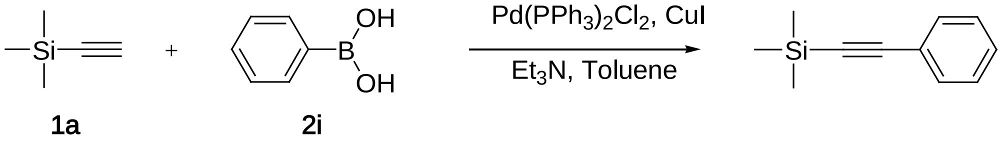
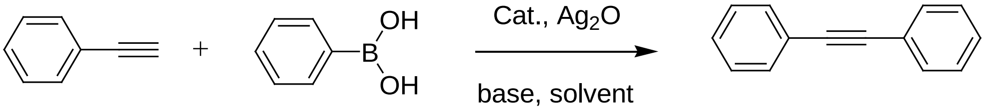


Figure 4.4 Sonogashira-type coupling reaction between **1a** and **2i** with microwave heating.

Initial studies of Sonogashira-type coupling reaction were performed by using phenylacetylene (**1b**) and phenylboronic acid (**2i**) as model substrates. Silver-assisted condition has played an important role in this reaction because it was reported to facilitate the C-B bond activation, and hence, applied as the promoter. First, we tried to use palladium catalyst in silver-assisted system, K_2CO_3 as base, and CH_2Cl_2 as solvent under inert N_2 atmosphere at room temperature for 36 hours, no desired product were formed (**Table 4.6**, entry 1). Next, we used other base and solvent but it did not work. Only CuI catalyst in silver-assisted system, K_2CO_3 as base, and DCE as solvent by used conventional heating at 80 °C for 36 hours would give the desired product in 3 % yield (**Table 4.6**, entry 2). DCE and toluene did not work on this reaction because of lower electric constant of both solvents. Therefore, they are not efficient in microwave-assisted conditions (**Table 4.6**, entry 3 and 6) even though more reactive base such Cs_2CO_3 (**Table 4.6**, entry 5) was used. DMF with high electric constant, can be heated very well by microwave but no desired product was isolated due to copper-catalyzed is not reactive enough (**Table 4.6**, entry 7).

The observe of palladium-catalyzed, silver-assisted system reaction conditions gain a moderate 48 % yield (**Table 4.6**, entry 8) when the reaction used 5 mol% of $Pd(PPh_3)_2Cl_2$ catalyst, 2 eq Ag_2O as promoter, 2 eq K_2CO_3 as base and 1.0M TBAF solution in THF as solvent. The reaction tend to increase yield to 63 % when used THF as solvent (**Table 4.6**, entry 9), and 50 % yield with ACN as solvent (**Table 4.6**, entry 10).

Table 4.6 Effect of catalyst, base, and solvent on Sonogashira-type coupling reaction.



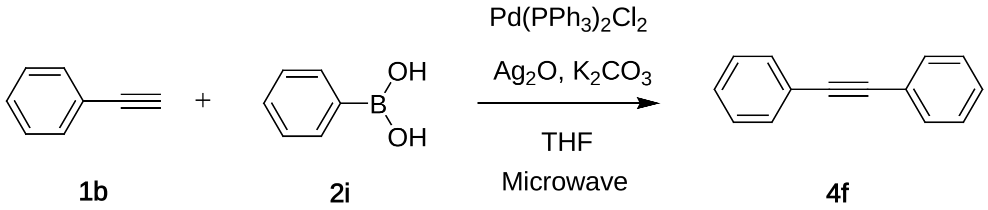
1b **2i** **4f**

Entry	Catalyzed	Base	Solvent	Heating	Time	Yield (%)
1	$Pd(PPh_3)_4$	K_2CO_3	CH_2Cl_2	-	36 h	0
2	CuI	K_2CO_3	DCE	Oil bath	36 h	3
3	CuI	K_2CO_3	DCE	MW	10 min	0
4	CuI	Et3N	DCE	MW	10 min	0
5	CuI	Cs_2CO_3	DCE	MW	10 min	0
6	CuI	K_2CO_3	Toluene	MW	10 min	0
7	CuI	K_2CO_3	DMF	MW	10 min	0
8	$PdPPh_3)_2Cl_2$	K_2CO_3	TBAF	MW	10 min	48
9	$Pd(PPh_3)_2Cl_2$	K_2CO_3	THF	MW	10 min	63
10	$Pd(PPh_3)_2Cl_2$	K_2CO_3	ACN	MW	10 min	50

4.3.1 Effect of phenylacetylene with arylboronic acids.

To evaluate the effects of the amount palladium catalyst, silver(I) oxide-assisted (Ag_2O), microwave power, and period of reaction time on the outcome of the Sonogashira-type reaction, a series of reactions have been carried out. The results are summarized in **Table 4.7**. In 5 mol% palladium-catalyzed loading, 2 equivalents of Ag_2O, 100 Watt microwave power for 10 minutes, only 9 % yield (**Table 4.7**, entry 1) product was isolated. It was found that the yield of **(4f)** was enhanced to 63 % yield (**Table 4.7**, entry 2) when 2 eq of K_2CO_3 was added. It was investigated to observe that the yield of **(4f)** was slightly decreased to 56 % yield (**Table 4.7**, entry 3) in the present of 2.5 mol% palladium-catalyzed loading. In the absence of Ag_2O at same condition, no desired coupling product was isolated (**Table 4.7**, entry 4). In addition, decreasing silver(I) oxide from 2 eq to 1 eq sharply decrease coupling product to 13 % yield (**Table 4.7**, entry 5).

Table 4.7 Effect of Palladium-catalyzed, silver-assisted system on Sonogashira-type coupling reaction.



Entry	Pd loading	Ag_2O	K_2CO_3	Microwave power	Time	Yield (%)
1	5.0 mol%	2 eq	-	100	10	9
2	5.0 mol%	2 eq	2 eq	100	10	63
3	2.5 mol%	2 eq	2 eq	100	10	56
4	2.5 mol%	-	2 eq	100	10	-
5	2.5 mol%	1 eq	2 eq	100	10	13
6	2.5 mol%	2 eq	2 eq	150	10	67
7	2.5 mol%	2 eq	2 eq	100	15	76
8	2.5 mol%	2 eq	2 eq	100	20	84
9	2.5 mol%	2 eq	2 eq	100	25	79

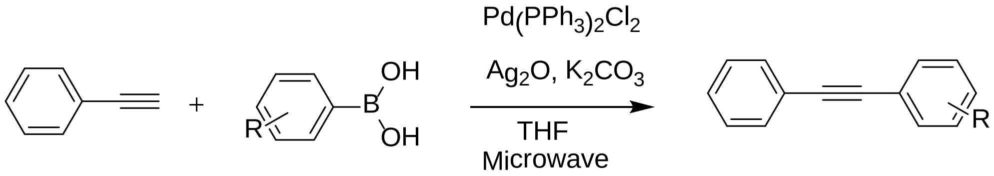
In parallel, to compare reaction times, and microwave power was also varied (**Table 4.7**, entries 6-9). Using typically palladium-catalyzed, silver-assisted system and irradiation at 150 Watt microwave power, the corresponding product was found in 67 % yield (**Table 4.7**, entry 6). When compared with result in entry 3 it can be seen that the yield was slightly increased. On the other hand, using 100 Watt microwave power for 15, 20, and 25 minutes the corresponding coupling product yield were increased to 76 %, 84 %, and 79 % isolated yields (**Table 4.7**, entries 7, 8, and 9). From above, the optimized reaction condition is 2.5 mol% of $Pd(PPh_3)_2Cl_2$, 2 eq of Ag_2O, 2 eq of

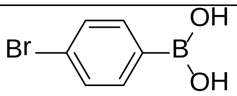
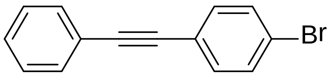
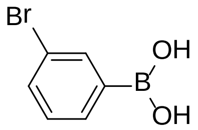
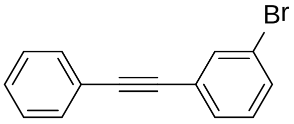
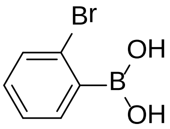
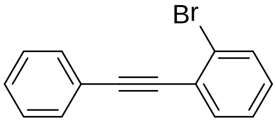
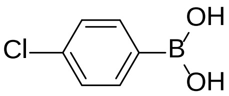
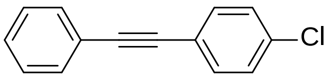
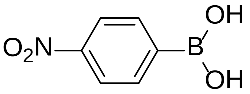
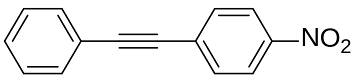
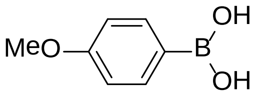
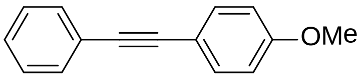
K_2CO_3 as base, and THF as solvent under 100 watt microwave power for 20 minute reaction times.

4.3.2 Effect of electron-deficient terminal alkynes with arylboronic acids.

The Sonogashira-type coupling reaction between a wide range of arylboronic acids was explored to see the general effectiveness of the palladium-catalyzed, silver-assisted system (**Table 4.8**) under the above optimized reaction conditions.

Table 4.8 Effect of arylboronic acids on Sonogashira-type coupling reaction.



Entry	Aryl boronic acid	Coupling product		Yield (%)
1			**4h**	72
2			**4i**	72
3			**4j**	-
4			**4k**	68
5			**4b**	30
6			**4d**	-

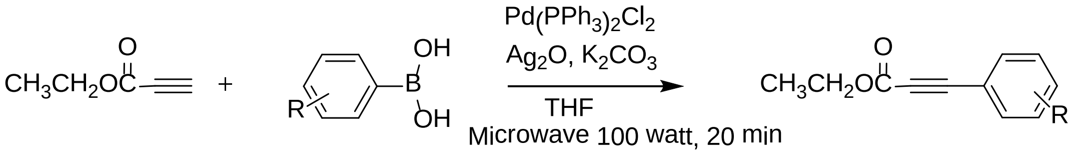
4-bromoboronic acid **(2j)**, 3-bromoboronic acid (**2k)**, and 4-chloroboronic (**2m)** acid worked well with this reaction system to give a desired coupling product in high

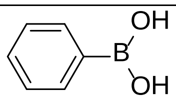
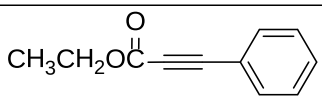
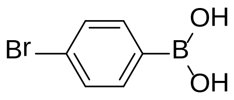
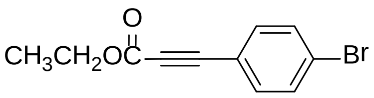
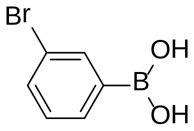
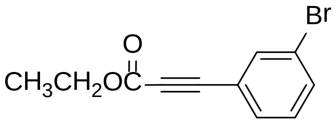
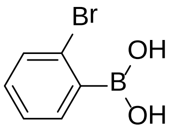
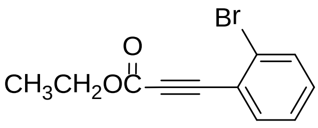
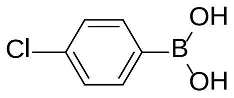
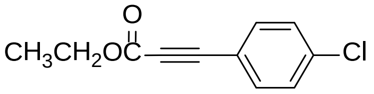
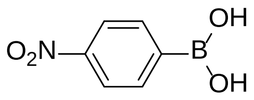
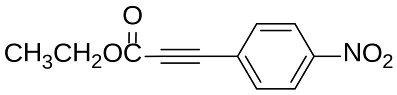
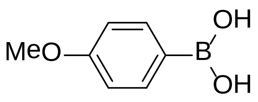
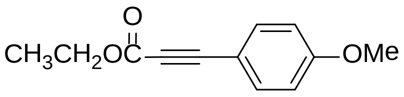
72 % yield for **4h** and **(4i**) and 68 % yield for **(4k)** (**Table 4.8**, entries 1, 2, and 4). On the other hand, an arylboronic acid with an ortho-substitution gave no isolated coupling product. The arylboronic acid bearing electron-withdrawing group such 4-nitrophenylboronic acid **(2n)** gave only 30 % yield (**Table 4.8**, entry 5) of the corresponding product. Moreover, electron-donating substituents on arylboronic acid such as 4-methoxyphenylboronic acid (**2o)** did not yield coupling product.

Attempts to obtain products from a Sonogashira coupling reaction between electron-deficient terminal alkynes and aryl halides have failed. Finally, the experimental procedure for the Sonogashira-type coupling reaction of electron-deficient terminal alkynes with arylboronic acids is carried out in the palladium-catalyzed, silver-assisted system. In the presence of K_2CO_3 as base and THF as solvent with 100 Watt microwave power 20 minutes. Phenylboronic acid (**2i**) gave high 75% yield (**Table 4.9**, entry 1) with electron-deficient alkynes ethyl propionate (**1c**). In comparison with the results shown in entry 14 of **Table 4.4**, no product yield was obtained. Thus, arylboronic acid has been shown to work well with electron-deficient terminal alkynes.

The reactions of 4-bromophenylboronic acid (**2j**) and 3-bromophenylboronic acid (**2k**) proceeded smoothly to give moderated 52% and 50% yield, respectively (**Table 4.9**, entries 2, 3). It is noteworthy that no corresponding desired product was isolated in the presence of 2-bromophenylboronic acid **2l** (**Table 4.9**, entry 4) due to the steric hindrance effect that difficult to react with the ortho-substituted of boronic acids. In the same as above, 4-chlorophenylboronic **2m** acid gave moderated 50% yield (**Table 4.9**, entry 5) mean in the para-substituted, bromo and chloro have no effect with the coupling reaction. Next, 4-nitrophenylboronic acid **2n** is the electron-withdrawing group on the boronic acid gave moderated 63% yield. And the last 4-methoxyphenylboronic acid **2o** that is the electron-donating group on boronic acid gave only low 32% yield. From the study, the used of arylboronic acids can react with the electron-deficient terminal alkynes in the present of palladium-catalyzed and silver-assisted system in the moderate-high yield.

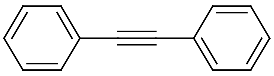
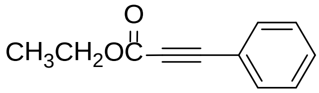
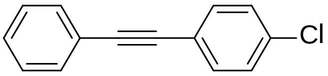
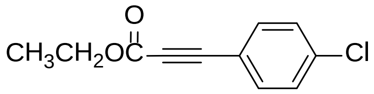
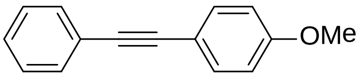
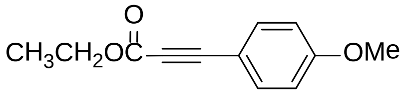
Table 4.9 Effect of arylboronic acids with electron-deficient terminal alkynes on Sonogashira-type coupling reaction.



Entry	Aryl boronic acid	Coupling product		Yield (%)
1			**5a**	75
2			**5b**	52
3			**5c**	50
4			**5d**	-
5			**5e**	50
6			**5f**	63
7			**5g**	32

From the literature procedure of copper-catalyzed Sonogashira-type coupling reaction of arylboronic acids with terminal alkynes that have been reported by Pan and co-workers [45]. The reaction carried out with CuI as catalyst in silver-assisted system, used of strong inorganic base Cs_2CO_3 and DCE as solvent at 80 °C for 36 hours to give moderate 63% yield of **4a** and high 80% yield of **5a**. Compare with ours microwave procedure that gave high 84% yield of 4a and 75% yield of 5a, respectively. It noteworthy, arylboronic acids that baring electron-donating group **2o**, in the literature procedure gave moderate 63% yield of **4d** and high 88% yield of **5h**. In contract with this study, arylboronic acids that baring electron-donating group gave only low 32% yield of **5h** and no product observed of **4d** as shown in **Table 4.10**.

Table 4.10 Sonogashira-type coupling reaction compare between ours microwave procedure and literature procedure.

Entry	Product		Literature		This work	
			Condition	Yield	Condition	Yield
1		**4a**	80°C,36h	63	MW, 20 min	84
2		**5a**	80°C,36h	80	MW, 20 min	75
3		**4i**	80°C,36h	36	MW, 20 min	68
4		**5f**	80°C,36h	88	MW, 20 min	50
5		**4d**	80°C,36h	63	MW, 20 min	-
6		**5h**	80°C,36h	67	MW, 20 min	32

In the same way, the literature procedure that used gold-catalyzed has been reported by Qian and co-workers [46]. The reaction carried out under room temperature for 24 hours with selectfluro®, a source of electronphile fluorine that was used to oxidize the resulting Au(I) intermediate to Au(III) species. The starting material is propagyl tosylamide and phenylboronic acid **2i** that gave only moderate yield and the product could not be separated from the unreacted starting material.

CHAPTER V

CONCLUSION AND SUGGESTIONS

An easy and simple Sonogashira coupling reaction using microwave irradiation compare with conventional heating method with a variety of aryl halides as coupling partners under ambient atmosphere were reported. The reaction was optimized with amount of palladium-catalyzed loading, base, solvent, microwave power, and reaction time. Electron-withdrawing groups containing aryl halides react with terminal alkynes gave desired product in good to excellent yields within a few minutes as compared to hours or days when used conventional heating method because the microwave equipment can provides heating efficiency to the reaction. However, strong electron-donating groups containing aryl bromides gave only low yields for this reaction condition. Moreover, we have demonstrated the Sonogashira-type coupling reaction of electron-deficient terminal alkynes with arylbornonic acids in palladium-catalyzed, silver-assisted system under ambient atmosphere by used microwave irradiations was successfully employed to give good yields in short reaction times. However, ortho-substituted phenylboronic acid was not reacting in this reaction system.

Palladium-supported polymers catalyst in heterogeneous phase has been reported that can recover the catalyst and used 5-8 times with no significant yield decrease. But polymer-supported catalyst is complicated and difficult to prepare, moreover it also takes a long reaction time. The suggestion for future work is to use recovered catalyst, because palladium-catalyzed is quite expensive. Nowadays a few publications reported about recovering the catalyst. Recovering palladium-catalyzed system from our reaction condition was tested. In the perliminary study, we can recover the palladium-catalyzed in 1-2 times but yield was sharply decreased because unsupported palladium was decomposed with air. Improvement of the catalyst system is now interest. It can subsequently save a lot of cost in a large scale reaction.

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APPENDICES

APPENDIX A

MICROWAVE CHAMBER

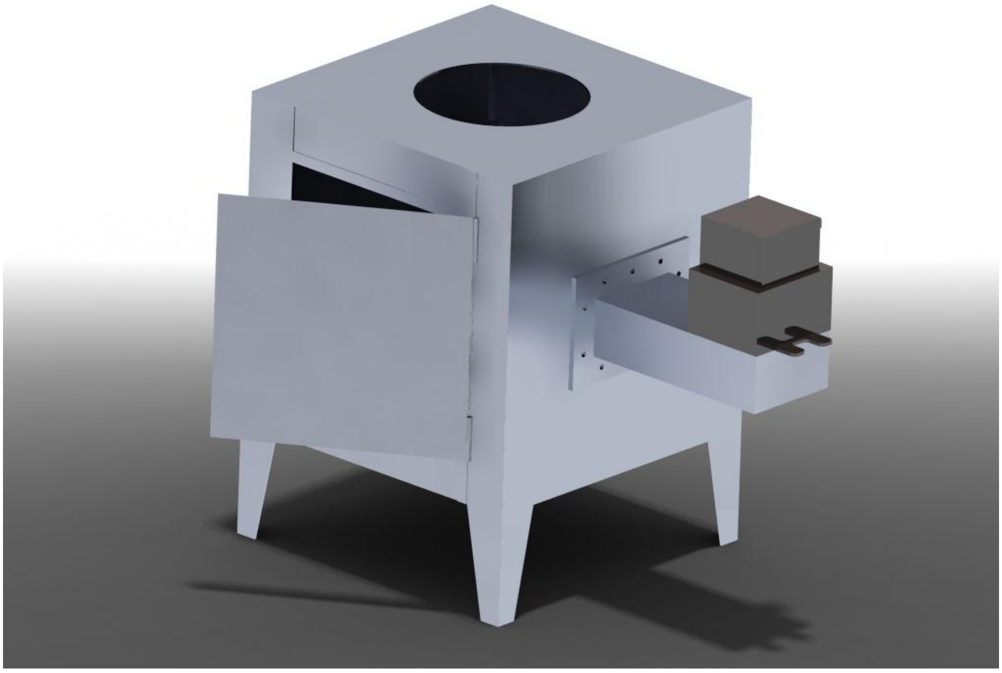
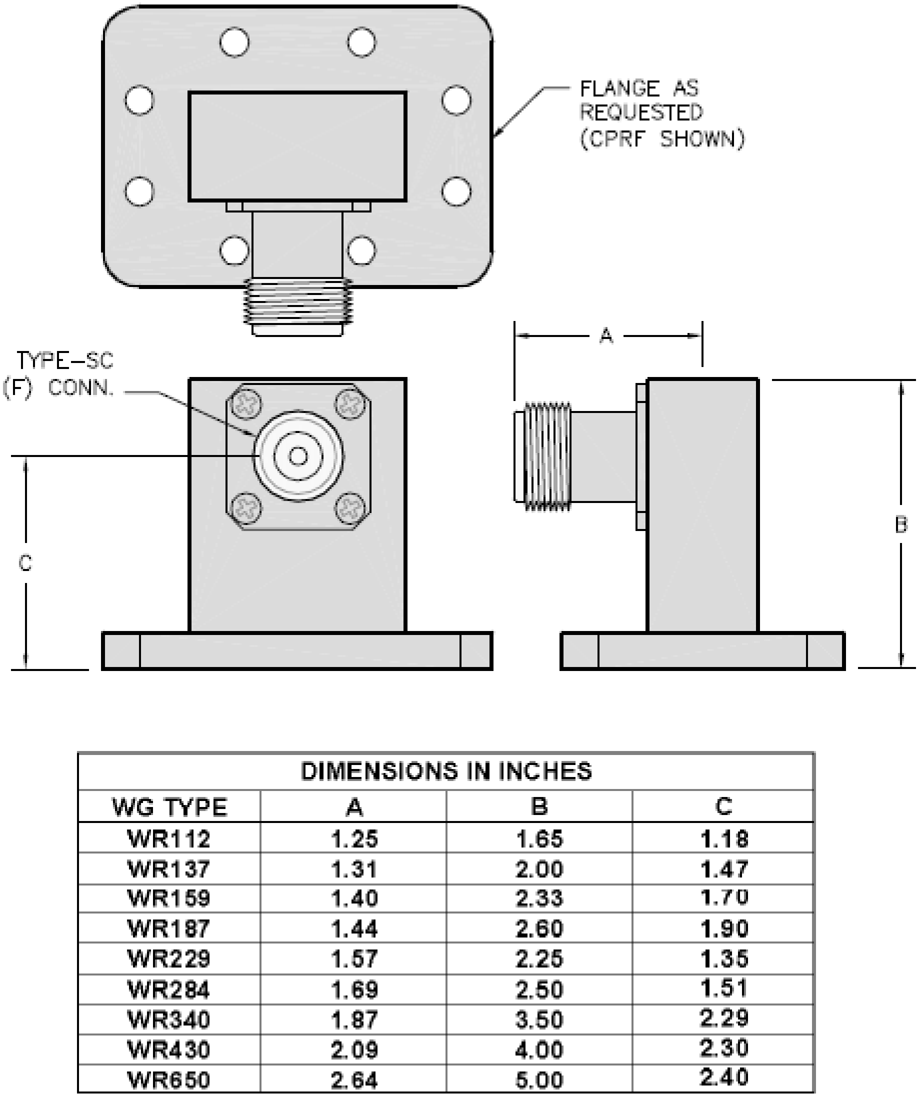


Figure A-1 The simulation of microwave chamber equipped with WR340 rectangular waveguide.

APPENDIX B

RECTANGULAR WAVEGUIDE



DIMENSIONS IN INCHES			
WG TYPE	A	B	C
WR112	1.25	1.65	1.18
WR137	1.31	2.00	1.47
WR159	1.40	2.33	1.70
WR187	1.44	2.60	1.90
WR229	1.57	2.25	1.35
WR284	1.69	2.50	1.51
WR340	1.87	3.50	2.29
WR430	2.09	4.00	2.30
WR650	2.64	5.00	2.40

Figure B-1 Rectangular waveguide standard.

.

Figure B-2 The simulation of rectangular waveguide from Solid work.

APPENDIX C

MAGNETRON HEAD

Table C-1 Magnetron type: MB2422A-130CF**.**

Characteristic	Specification	Typical
Frequency of operation:	2470 MHz	2460 MHz
Frequency variations:		+/- 10 MHz
CW Power Output:	1400 W	1260 W
Anode voltage current	4.7 kV	4.5 kV
Filament voltage (standby):	4.8 V	4.4 V
Filament current:	15.5 A	14 A
RF launch type:	Rectangular or oven cavity	
Efficiency:	approx: 70 %	
Basis type:	2M137 (Panasonic)	
Net weight:	Approx: 800 mg	

APPENDIX D

NMR SPECTRUM

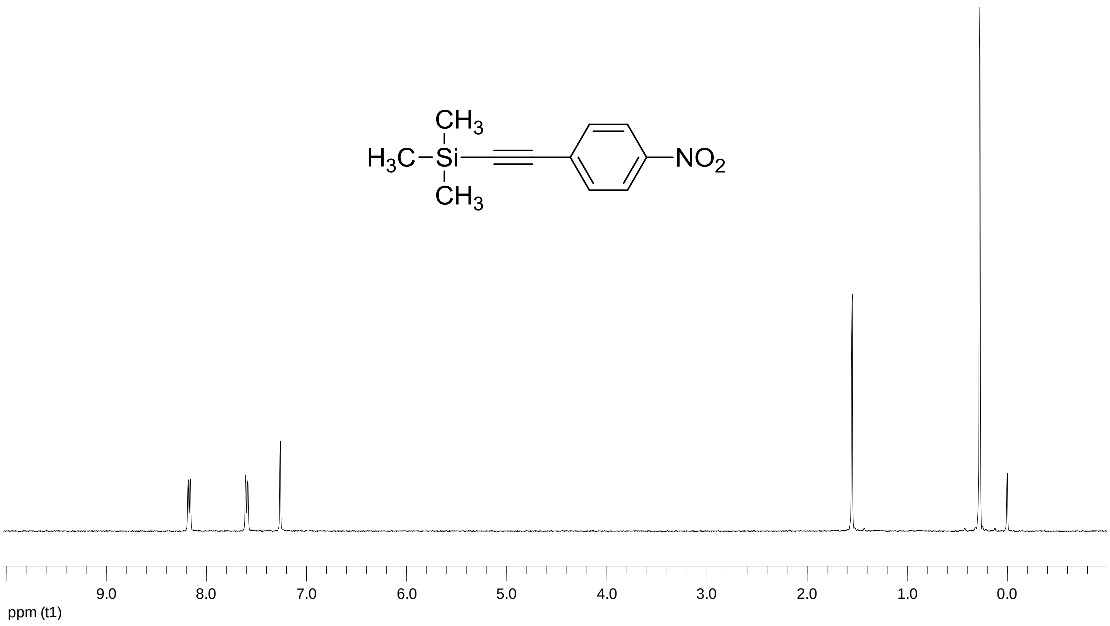


Figure D-1 The ^{1}H NMR spectrum of trimethyl((4-nitrophenyl)ethynyl)silane (**3a**)

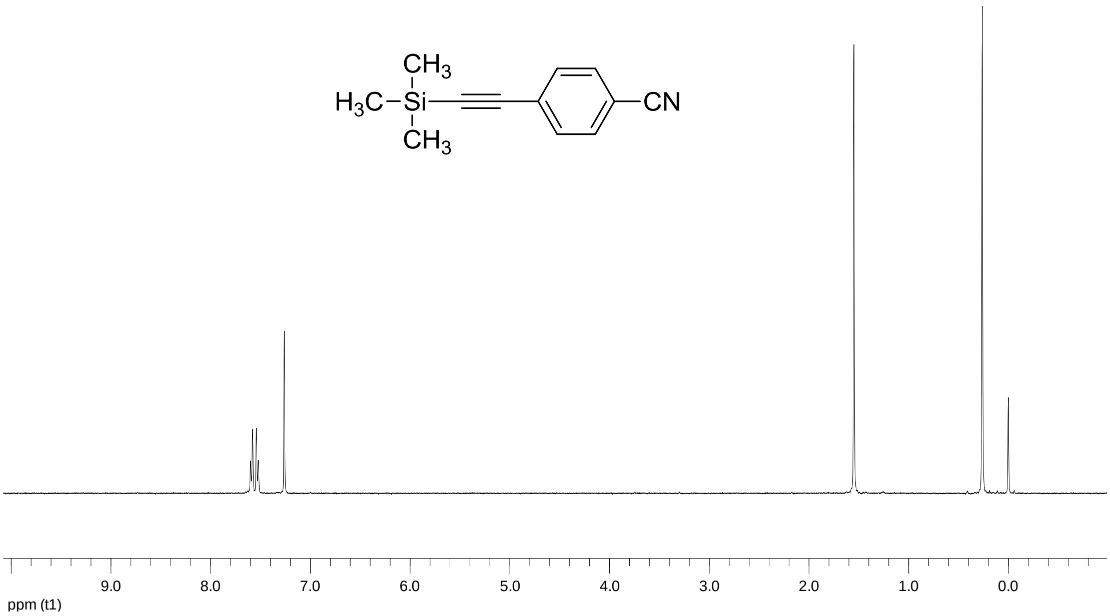


Figure D-2 The ^{1}H NMR spectrum of 4-((trimethylsilyl)ethynyl)benzonitrile (**3b**)

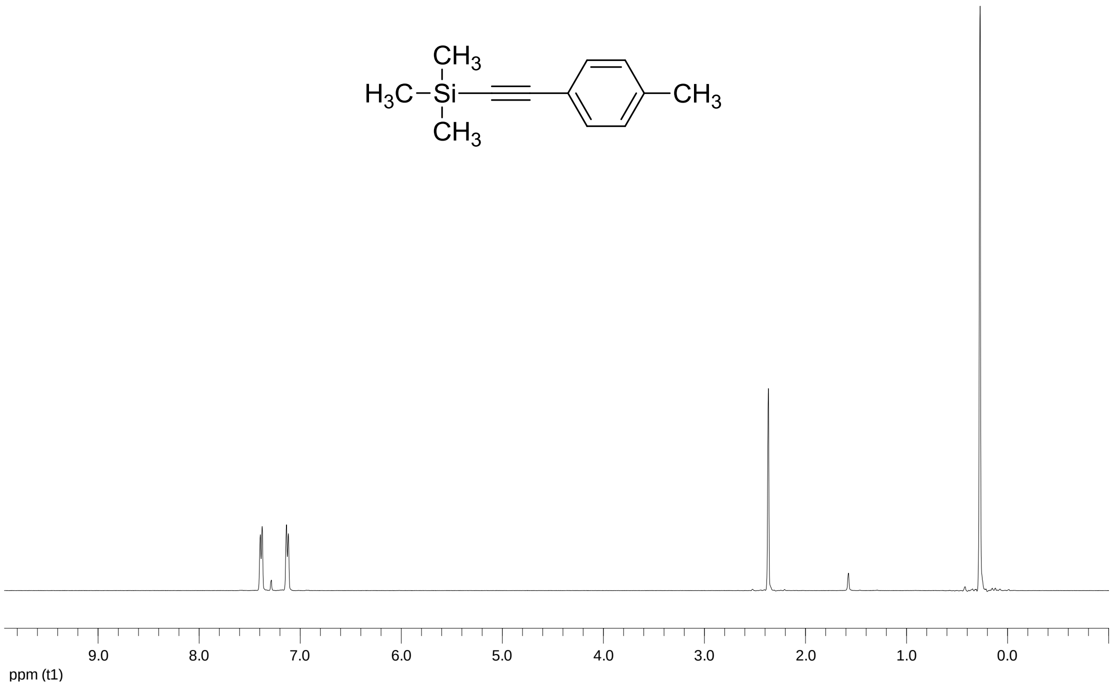


Figure D-3 The ^{1}H NMR spectrum of trimethyl(p-tolylethynyl)silane (**3c**)

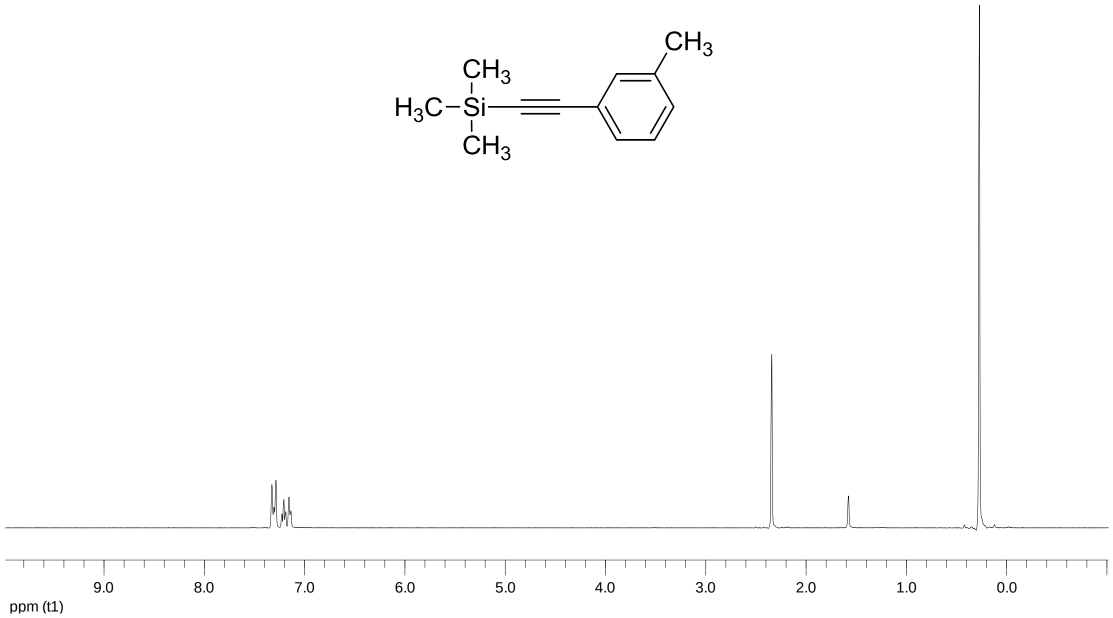


Figure D-4 The ^{1}H NMR spectrum of trimethyl(m-tolylethynyl)silane (**3d**)

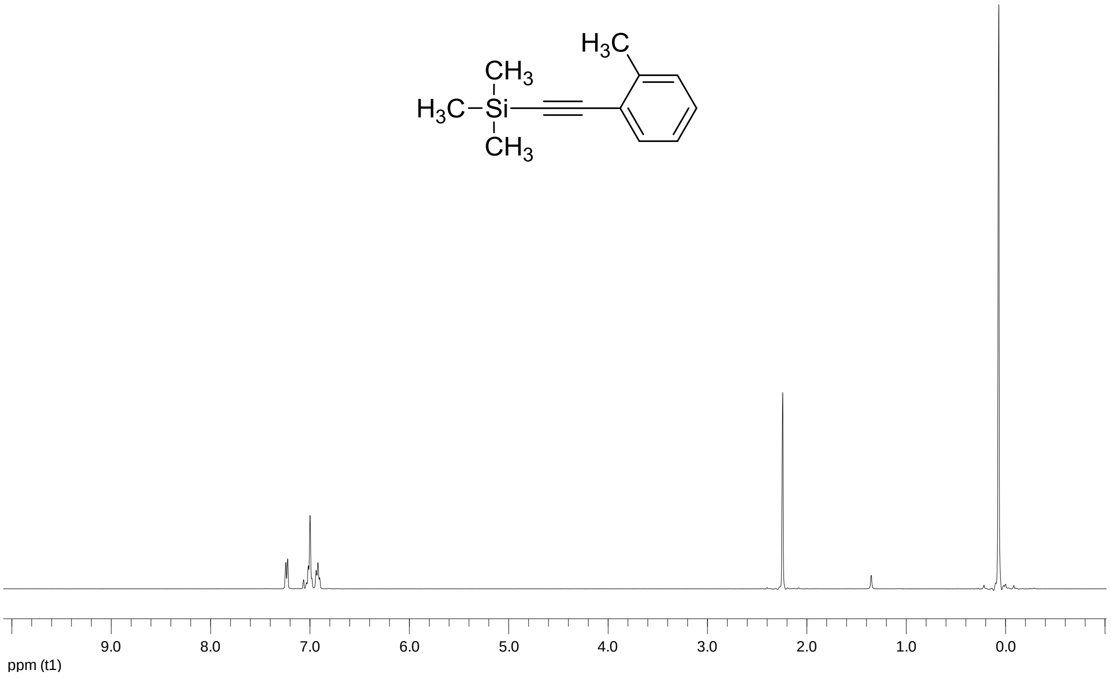


Figure D-5 The ^{1}H NMR spectrum of trimethyl(o-tolylethynyl)silane (**3e**)

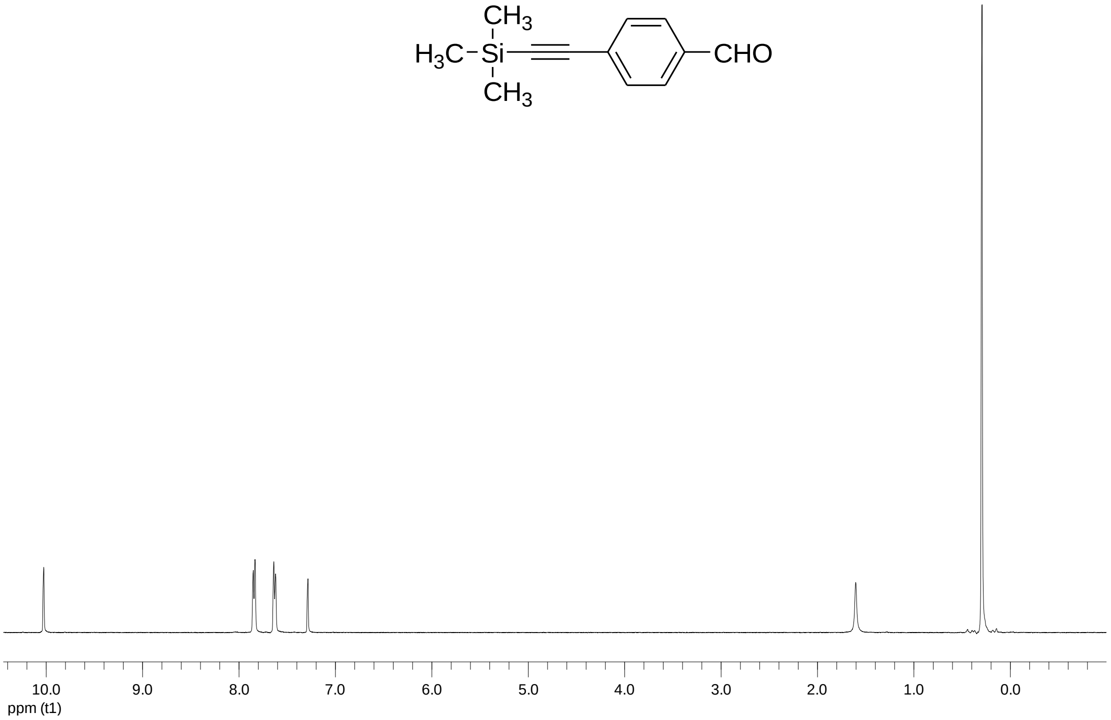


Figure D-6 The ^{1}H NMR spectrum of 4-((trimethylsilyl)ethynyl)benzaldehyde (**3f**)

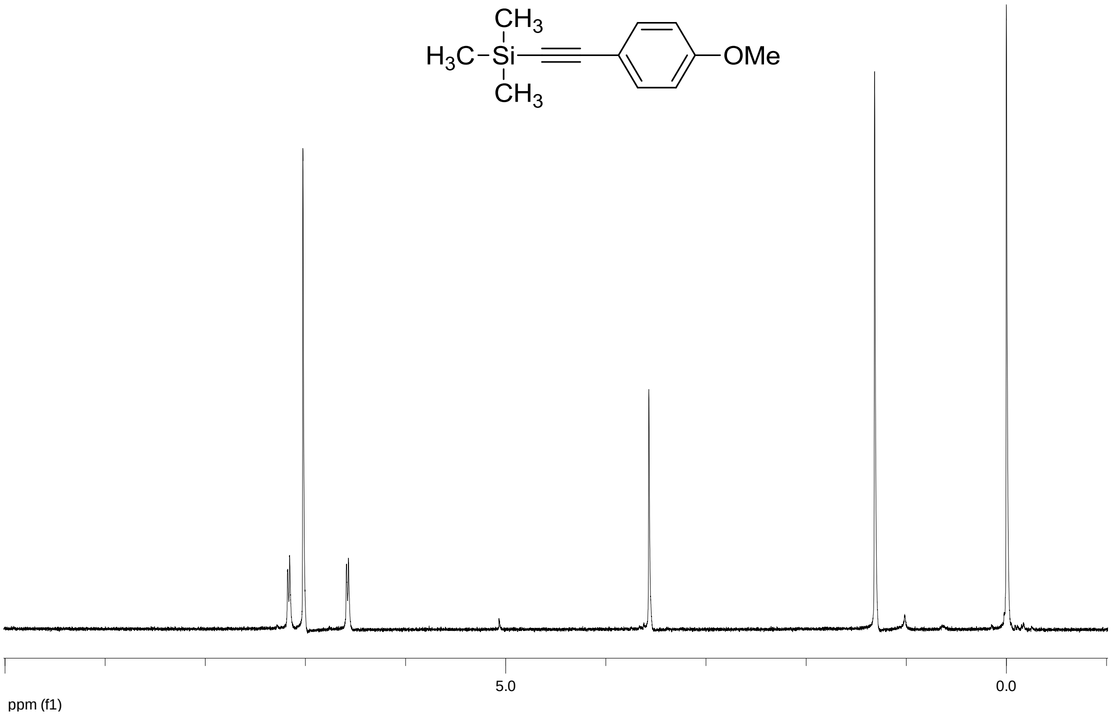


Figure D-7 The ^{1}H NMR spectrum of ((4-methoxyphenyl)ethynyl)trimethylsilane (**3g**)

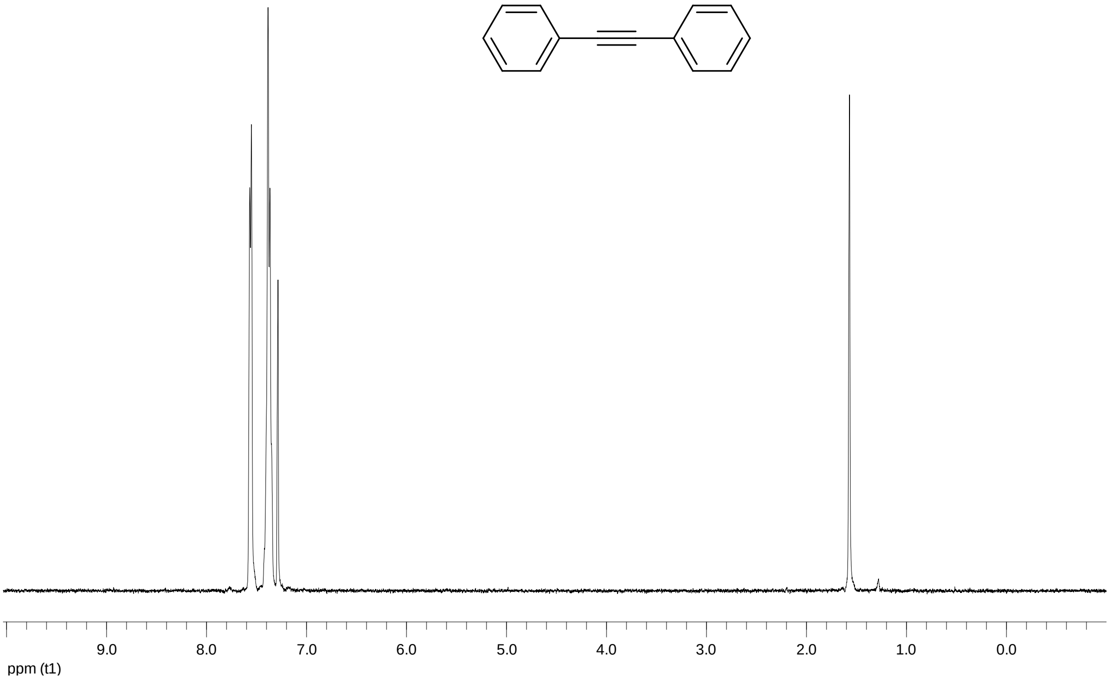


Figure D-8 The ^{1}H NMR spectrum of 1,2-diphenylethyne (**4a**)

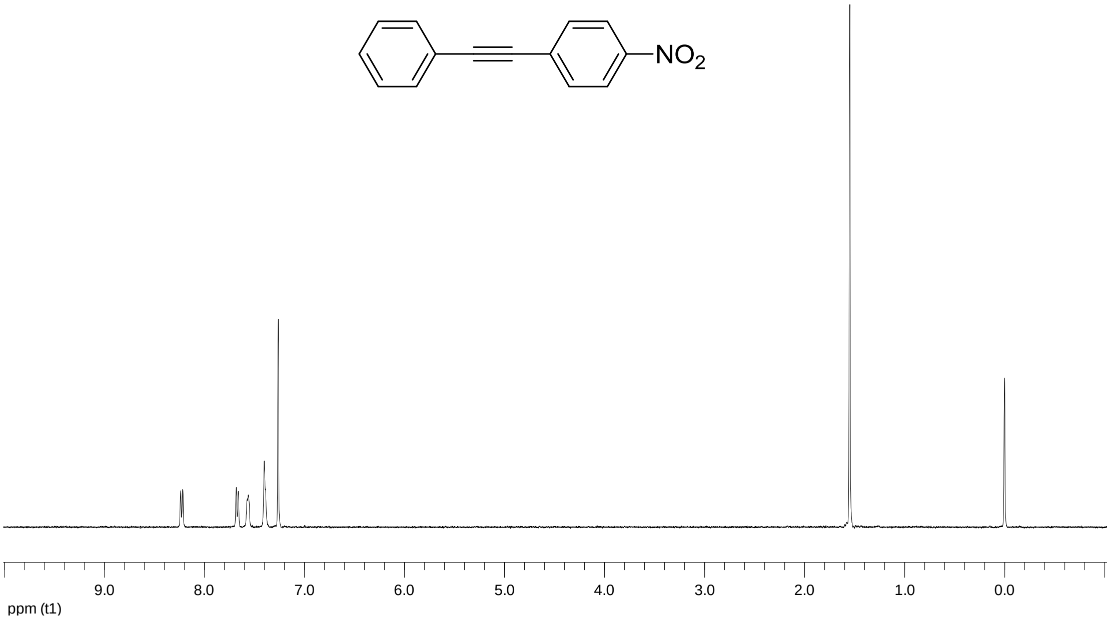


Figure D-9 The ^{1}H NMR spectrum of 1-nitro-4-(phenylethynyl)benzene (**4b**)

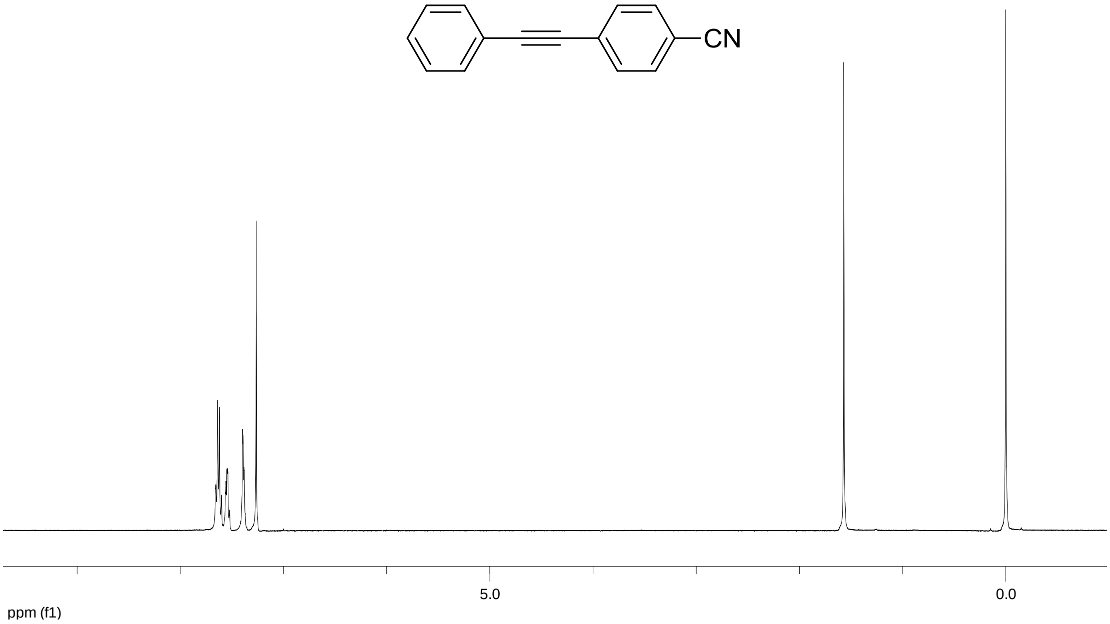


Figure D-10 The ^{1}H NMR spectrum of 4-(phenylethynyl)benzonitrile (**4c**)

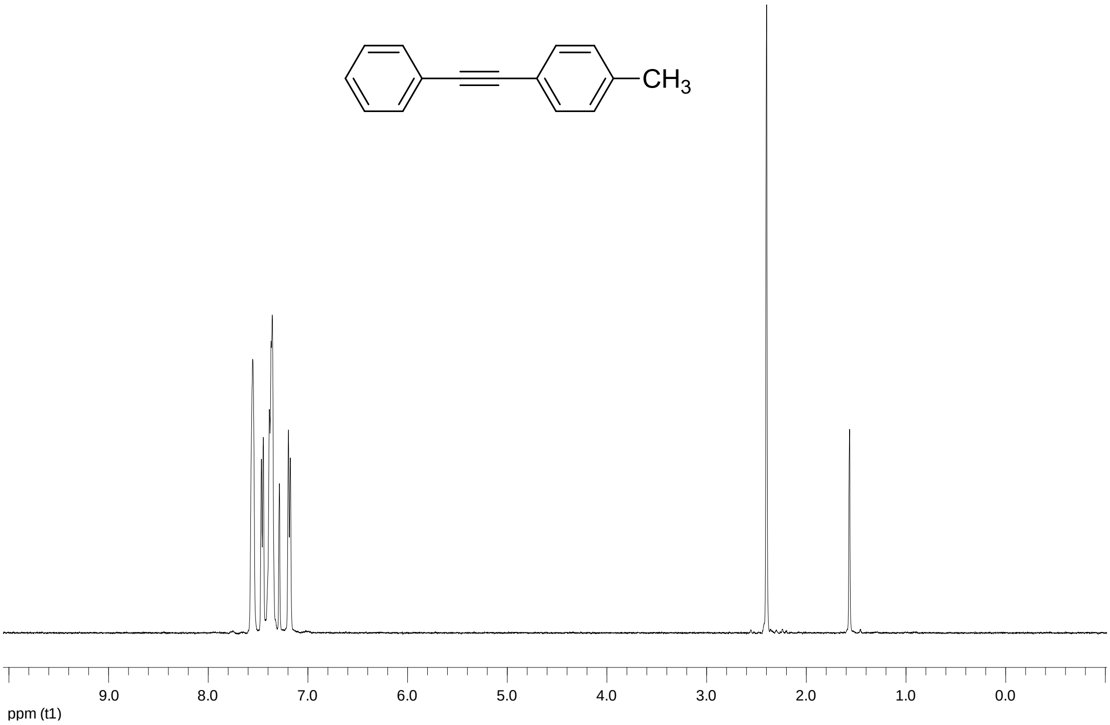


Figure D-11 The ^{1}H NMR spectrum of 1-methyl-4-(phenylethynyl)benzene (**4e**)

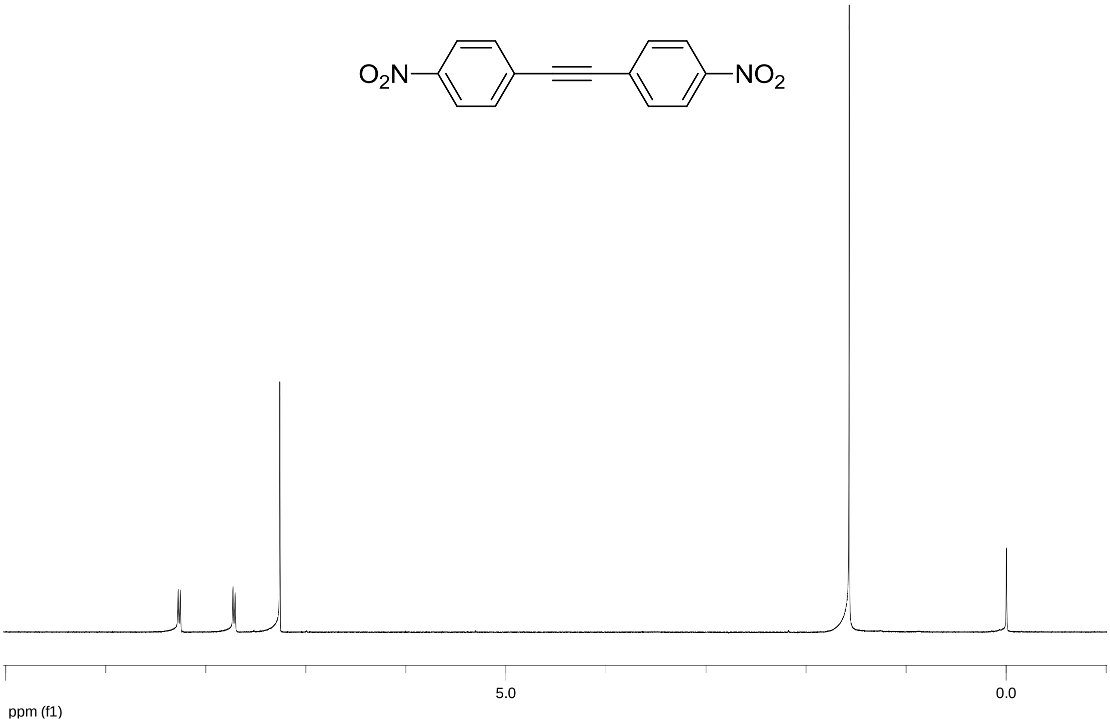


Figure D-12 The ^{1}H NMR spectrum of 1,2-bis(4-nitrophenyl)ethyne (**4f**)

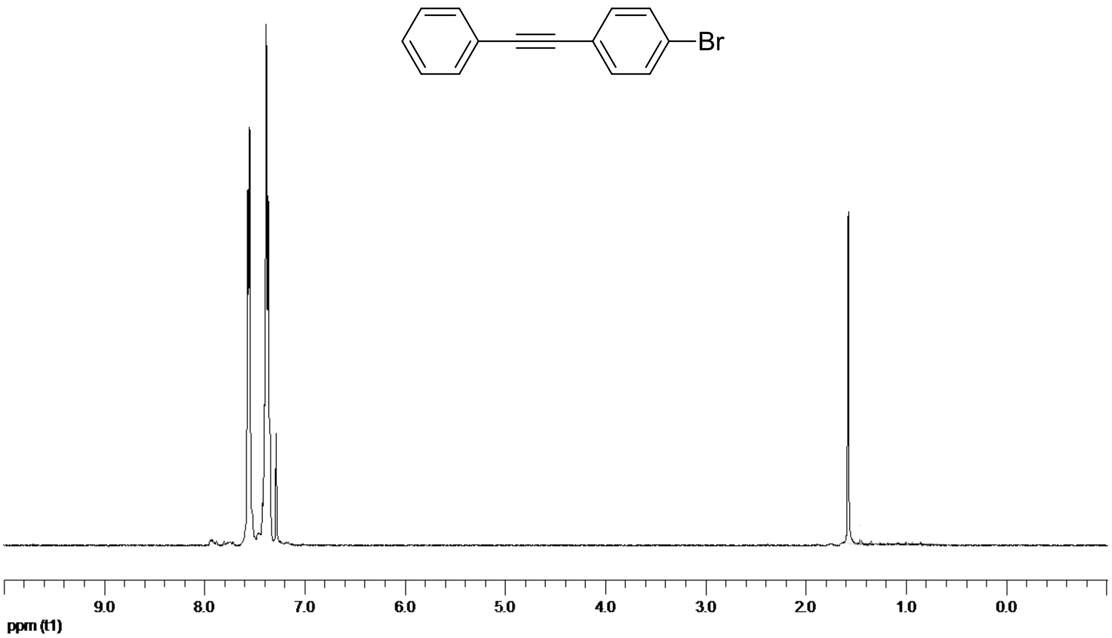


Figure D-13 The ^{1}H NMR spectrum of 1-bromo-4-(phenylethynyl)benzene (**4h**)

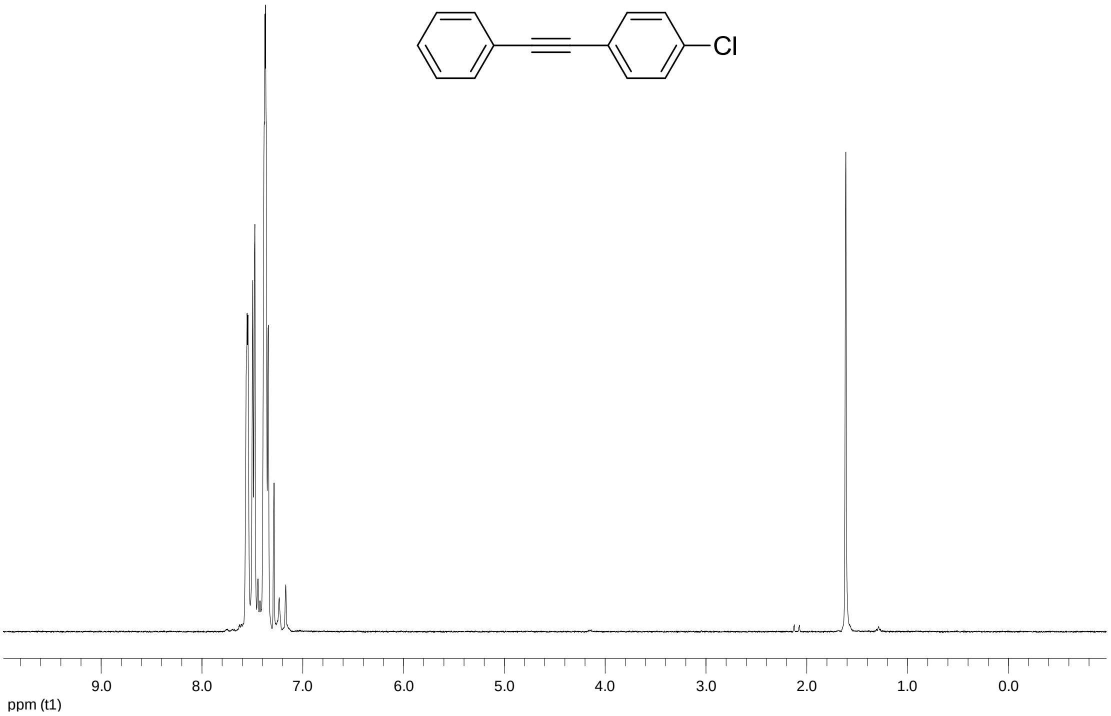


Figure D-14 The ^{1}H NMR spectrum of 1-chloro-4-(phenylethynyl)benzene (**5k**)

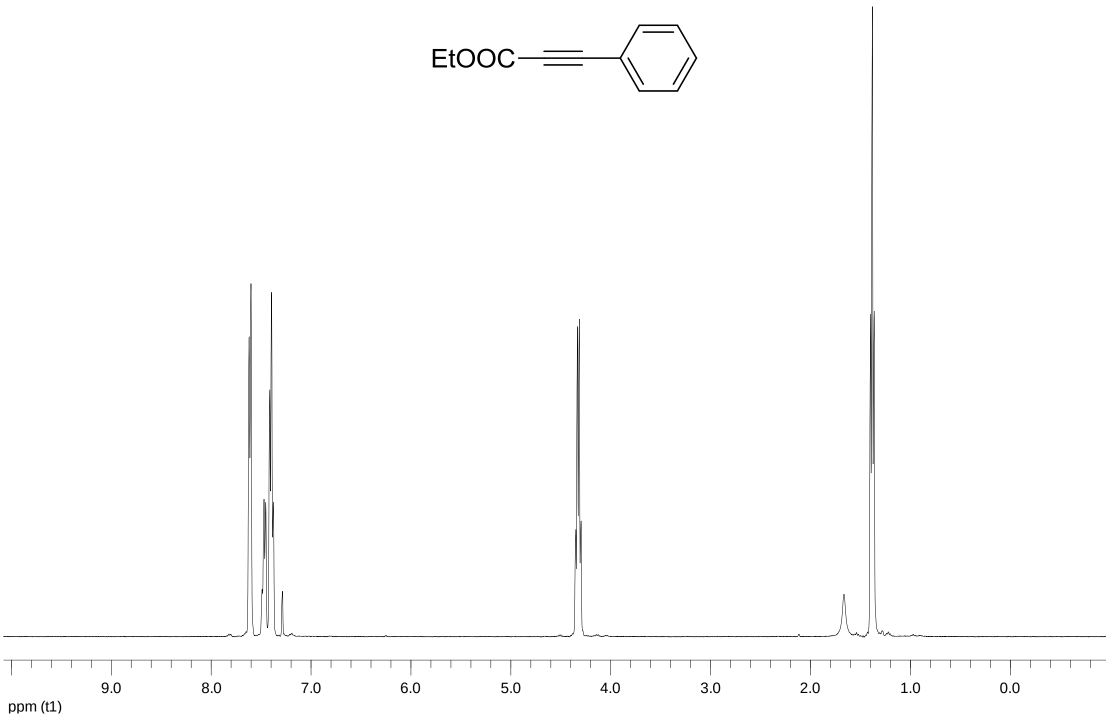


Figure D-15 The ^{1}H NMR spectrum of ethyl 3-phenylpropiolate (**5a**)

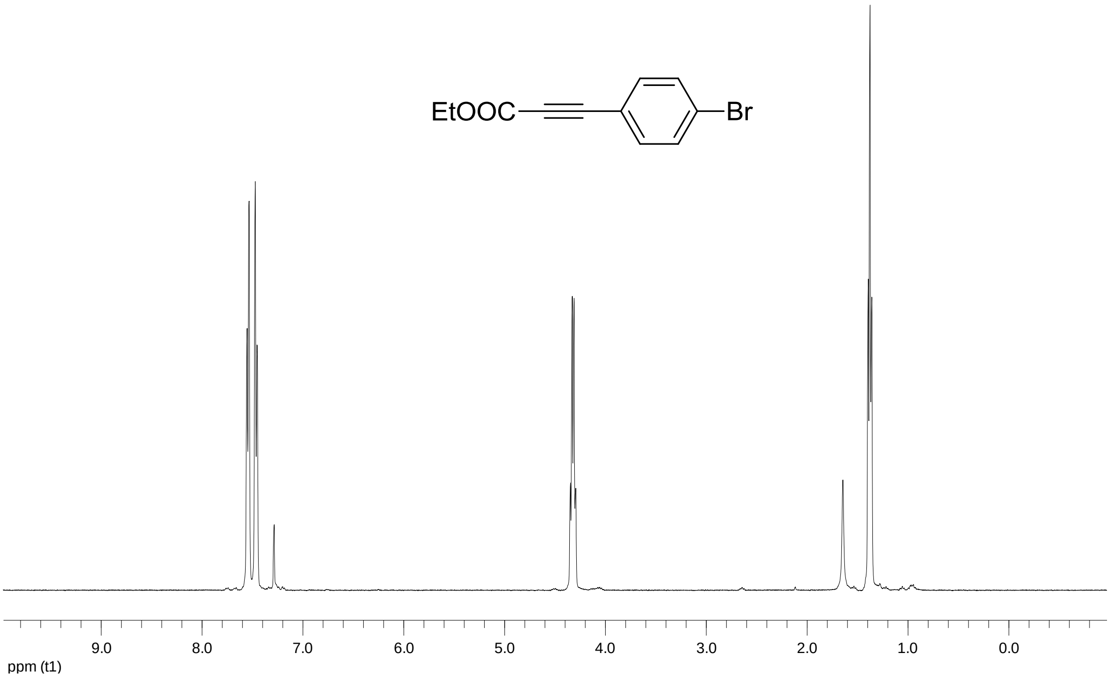


Figure D-16 The ^{1}H NMR spectrum of ethyl 3-(4-bromophenyl)propiolate (**5b**)

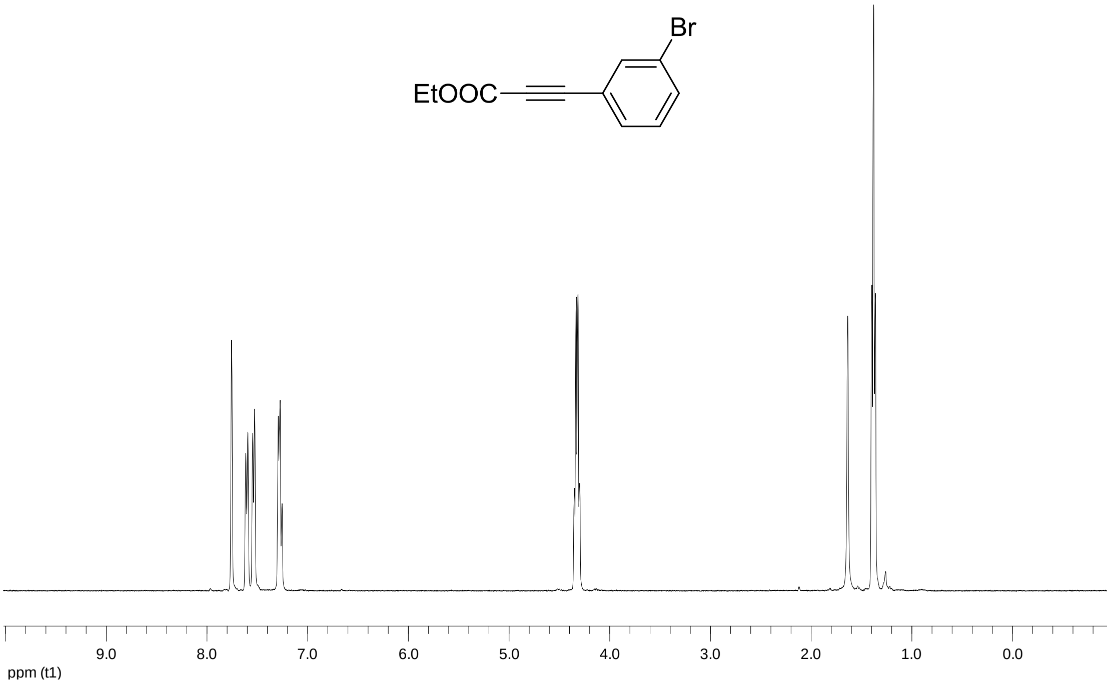


Figure D-17 The ^{1}H NMR spectrum of ethyl 3-(3-bromophenyl)propiolate (**5c**)

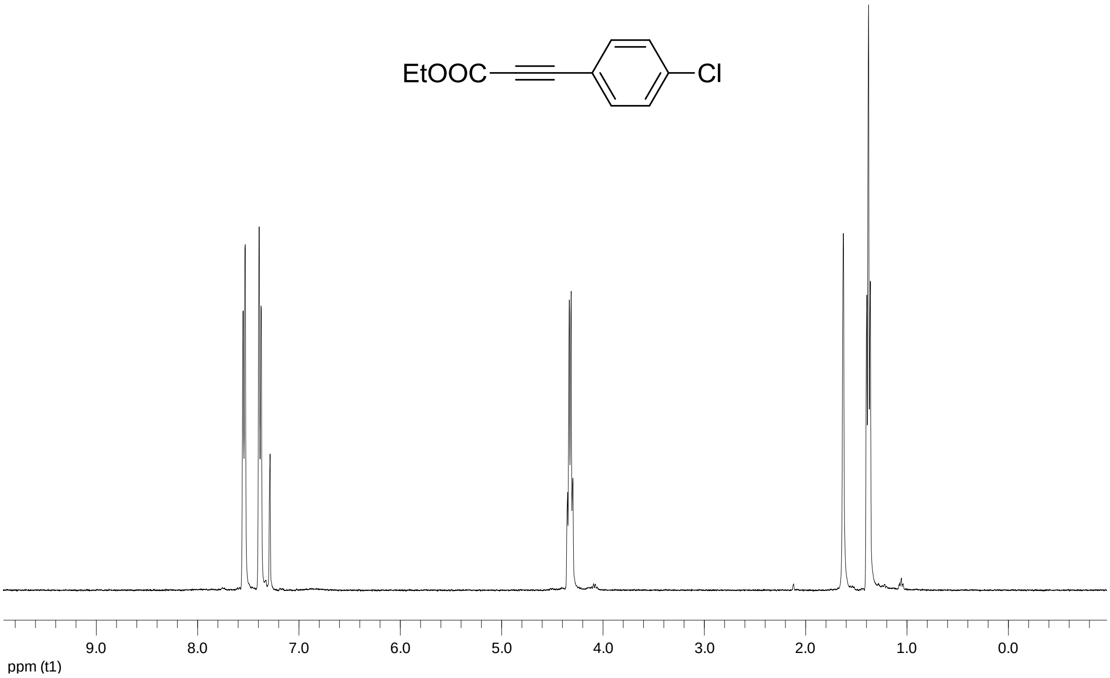


Figure D-18 The ^{1}H NMR spectrum of ethyl 3-(4-chlorophenyl)propiolate (**5e**)

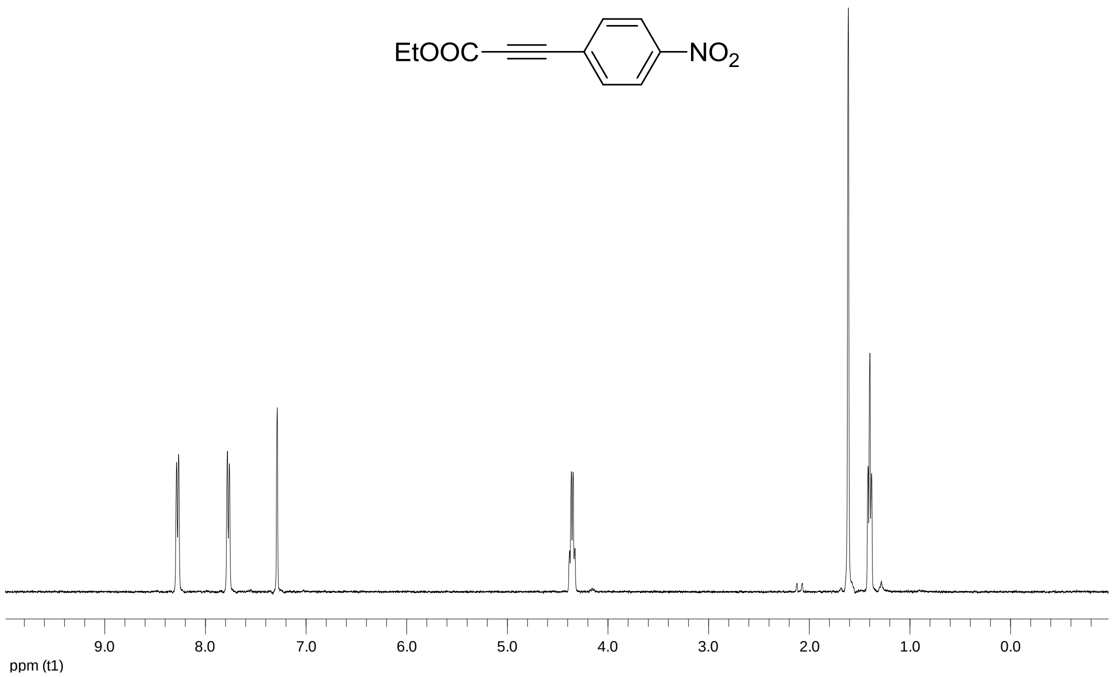


Figure D-19 The ^{1}H NMR spectrum of ethyl 3-(4-nitrophenyl)propiolate (**5f**)

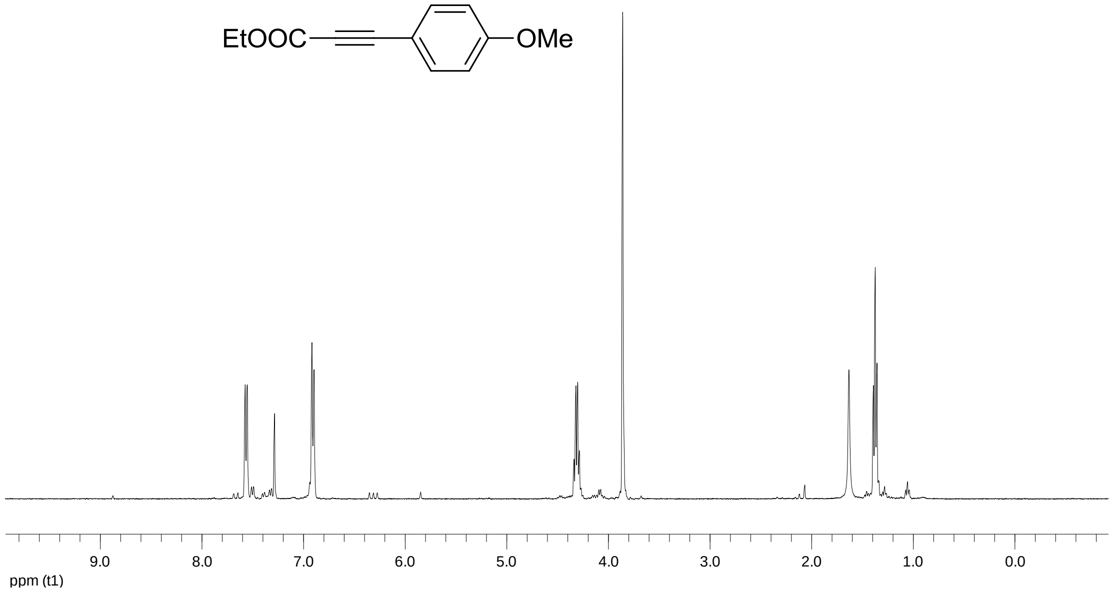


Figure D-20 The ^{1}H NMR spectrum of ethyl 3-(4-methoxyphenyl)propiolate (**5g**)

VITAE

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Presentation in Conference:

January 2011	The 12th anniversary of the International Symposium on Eco-Material Processing and Design (ISEPD 2011), Empress Hotel, Chiang mai, Thailand.
Publication:	"Environmentally Benign Microwave-Assisted Sonogashira Preparation of Aromatic Compound" *Material Science Forum* 695 (2011): 113-116.