

**ONE-POT SYNTHESIS OF THIAZOLE HYDRAZONES IN WATER**

**By**

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## ABSTRACT

In this project, a total of eight thiazole hydrazone derivatives had been successfully synthesized and characterized. One-pot synthesis of thiazole hydrazones were carried out by using water as solvent. This reaction provide the advantages of high product yield, low-cost, simple experimental design, as well as environmental benign. The structures of eight different compounds were characterized by using IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, HMQC, HMBC and melting point apparatus.

## **ABSTRAK**

Dalam kajian ini, lapan thiazole hydrazone derivatif telah berjaya disintesis dan dicirikan. Satu langkah sintesis thiazole hydrazone telah dijalankan dengan menggunakan air sebagai pelarut. Tindakbalas kimia ini telah menyumbang kelebihan dari segi tinggi hasil, murah kos, reka bentuk eksperimen yang mudah dan mesra alam sekitar. Struktur bagi lapan thiazole hydrazone derivatif telah dicirikan dengan menggunakan IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, HMQC, HMBC dan alat pengukur takat lebur.

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This project is not my individual achievement instead it is the result of support and help from many people all of this while. First and foremost, I would like to express my sincere gratitude to my supervisor, Dr. Sim Kooi Mow for his patient guidance and encouragement throughout this Final Year Project. He is willing sacrifice his precious time to point out my mistakes and advise me on various expects so that I could improve and grow as an individual.

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Last but not least, I owe a deep sense of gratitude to my family and all my friends who always cheer me up during my hardships and provide me the moral support and all kinds of encouragement towards the success of this project.

## DECLARATION

I hereby declare that the project report is based on my original work except for quotations and citations which have been duly acknowledge. I also declare that it has not been previously or concurrently submitted for any other degree at UTAR or other institutions.

---

TAN KIT LIN

## APPROVAL SHEET

This thesis entitled **“ONE-POT SYNTHESIS OF THIAZOLE HYDRAZONE  
IN WATER”** was prepared by TAN KIT LIN and submitted as partial fulfillment of the requirements for the degree of Bachelor of Science (Hons) Chemistry at Universiti Tunku Abdul Rahman.

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It is hereby certified that **TAN KIT LIN** (ID no: **15ADB07445**) has completed this Final Year Project entitled “ONE-POT SYNTHESIS OF THIAZOLE HYDRAZONE IN WATER” under supervision of Associate Professor Dr. SIM KOOI MOW from the Department of Chemical Science, Faculty of Science.

I hereby give permission to my supervisor to write and prepare a manuscript of these research findings for publishing in any form, I did not prepare it within six (6) months’ time from this date, provided, that my name is included as one of the authors for this article. Arrangement of name will depend on my supervisor.

Yours truly,

\_\_\_\_\_

(TAN KIT LIN)

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## LIST OF ABBREVIATIONS

Acetone- $d_6$	Deuterated acetone
$d$	Doublet
$dd$	Doublet of doublets
DMSO- $d_6$	Deuterated dimethyl sulfoxide
FTIR	Fourier Transform Infrared
HMBC	Heteronuclear Multiple Bond Coherence
HMQC	Heteronuclear Multiple Quantum Coherence
Hz	Hertz
$J$	Coupling constant in Hz
$m$	Multiplet
mmol	milimole
mL	millilitre
NMR	Nuclear magnetic resonance
$R_f$	Retention factor
$s$	Singlet
$t$	Triplet
TLC	Thin Layer Chromatography
$\delta$	Chemical shift in ppm
$\delta_C$	Chemical shift of carbon
$\delta_H$	Chemical shift of proton

## CHAPTER 1

### INTRODUCTION

#### 1. Introduction of thiazole hydrazones

Thiazole or 1,3-thiazole is a five-membered heterocyclic organic compound which composed of a sulfur (S) atom , a nitrogen (N) atom and three carbon atoms, with a molecular formula of  $C_3H_3NS$ . It is an aromatic compound.

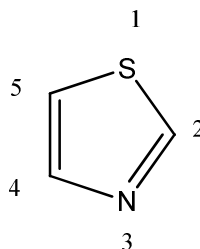


Figure 1.1: Structure of thiazole

Hydrazone is an organic compound similar to ketone or aldehyde, with the difference of oxygen atom of carbonyl group is being replaced by  $-NNR_3R_4$  group. The structure of hydrazone is  $R_1R_2C=NNR_3R_4$ .

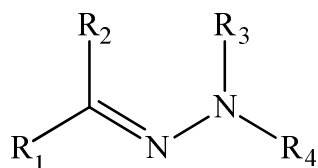


Figure 1.2: Structure of hydrazone

Hydrazone can be synthesized through the reaction between hydrazine ( $\text{NH}_2=\text{NH}_2$ ) and carbonyl group ( $\text{C}=\text{O}$ ). The presence of adjacent nitrogen in hydrazine make it more nucleophilic than regular amine. The lone pair electrons in hydrazine attack the carbonyl carbon via nucleophilic addition. As a result, the carbonyl oxygen will be replaced by the  $-\text{NNH}_2$  group which is contributed by the hydrazine molecule.

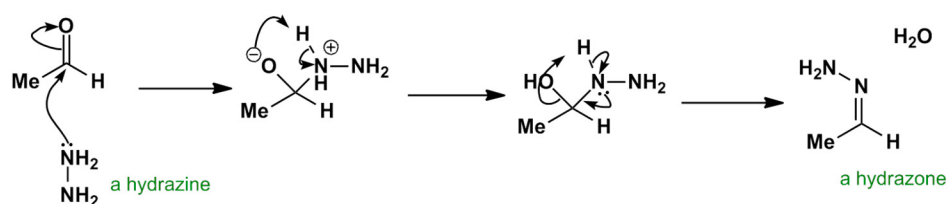


Figure 1.3: Synthesis of hydrazone

Thiazole hydrazone is the combination of thiazole and hydrazone structure in a single compound molecule. Thiazole hydrazone compound can be easily synthesized via the condensation reaction between aromatic aldehydes or ketones and thiosemicarbazide. The intermediate - thiosemicarbazone is obtained which subsequently react with the n-bromoacetophenone to yield the final product which is thiazole hydrazone via Hantzsch cyclization reaction (Zhang et al., 2012).

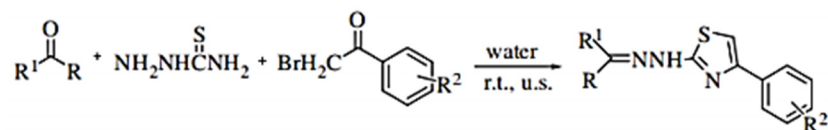


Figure 1.4: Synthesis of thiazole hydrazine by Zhang et al. (2012)

## 2. Application of thiazole hydrazones

Thiazole is found to be pharmacologically active and subjected to varied biological activities and drug development such as antioxidant, anti-allergy, inflammation and HIV infection. In addition, hydrazone also exhibit diverse pharmacological and biological properties including antimicrobial, anti-inflammatory, analgesic, antifungal, anti-cancer and others. Hence, both active thiazole and hydrazone moiety are combined into the thiazole hydrazone derivatives which have an advance potential in drug and medicine field (Anbazhagan and Sankaran, 2013). For an example, 4-(chloromethyl)-2-(2- cyclohexylidenehydrazinyl) thiazole exhibited a good antibacterial activity against Escherichia coli bacteria. Next, imidazo [2,1-*b*] thiazole acetohydrazone exhibited a good diuretic activity (Andreani et al., 1987). Moreover, 2-(2-benzyliden-hydrazinyl)-4- methylthiazole shows an excellent anti-proliferative activity against gastric carcinoma cells (Grozav et al., 2014).

## 3. One pot synthesis

In synthetic organic chemistry, one-pot synthesis of more than two molecules in the same reaction flask is generally considered to be a practical method. It is

practical because bond-forming steps and several synthetic transformations can be done in a single flask, while circumventing several purification procedures at the same time. A one-pot approach can thus reduce chemical waste, time saving, and simplify practical aspects (Hayashi, 2016). This kind of synthesis is a greener fashion owing to the lesser work-up procedures and purification steps compared to a conventional method (Sydnes, 2014). The common examples for one-pot multicomponent reaction are Biginelli and Hantzsch reactions.

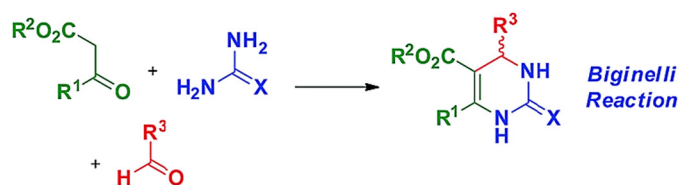


Figure 1.5: Biginelli reaction (Alvim, da Silva Júnior and Neto, 2014)

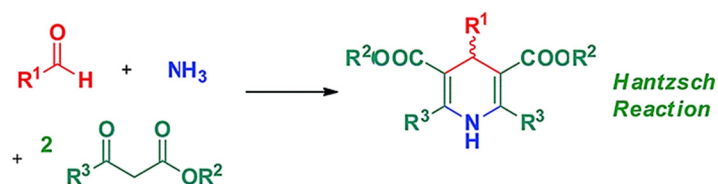


Figure 1.6: Hantzsch reactions (Alvim, da Silva Júnior and Neto, 2014)

#### 4. Distilled water as green solvent

Solvent defined as a substance which able to dissolve another substances, and it is commonly used in laboratory, manufacturing processes and often essential for



many applications such as cleaning, synthetic chemistry and others. Many of these solvents are volatile organic compound (VOCs) which will give negative impacts to environment such as depleting the ozone layer as well as form the tropospheric smog. In addition, some of these volatile solvents may harmful to human health and carcinogenic. As the awareness and realization of how volatile organic solvents affect the environment and human health gradually increase, alternative solvents are currently being used to overcome these problems. One of the desired alternative solvent is distilled water and it is considered as green solvent due to its characteristics of non-flammability, ease of availability from natural sources, cheap and non-toxicity. However, the utilization of water as green solvent is limited due to the organic compounds unable to dissolve well in water, which show a poor solubility in water (Chattopadhyay, 2015).

### **1.5 Objectives:**

The objectives of this final year project are:

1. To synthesize a series of thiazole hydrazone derivatives by utilize the water as solvent through one pot synthesis.
2. To study the effect of various solvents on the product yield in one-pot synthesis.
3. To compare the product yield obtained from one-pot synthesis with two-steps synthesis.

4. To characterize the structures of thiazole hydrazone derivatives by using melting point apparatus, Fourier-Transform Infrared Spectroscopy (FTIR), Thin Layer Chromatography (TLC) and Nuclear Magnetic Resonance Spectroscopy (NMR).

## CHAPTER 2

### LITERATURE REVIEW

#### 1. One pot synthesis

##### 2.1.1 Synthesis of novel Naphtho[1,8-gh]quinazoline-7,10-dione derivatives with CuCl<sub>2</sub> via one pot under solvent free condition

According to K. Mohammadi (2018), a short times of reaction and simple methodology was used to synthesis naphtho[1,8-gh]quinazoline-7,10-diones in excellent yield. In the presence of catalyst which is CuCl<sub>2</sub>, the Biginelli-type reaction of phenalen-1,3-dione with the benzaldehyde derivatives and urea were used for the synthesis of naphtho[1,8-gh]quinazoline-7,10-diones in a solvent free condition had carried out.

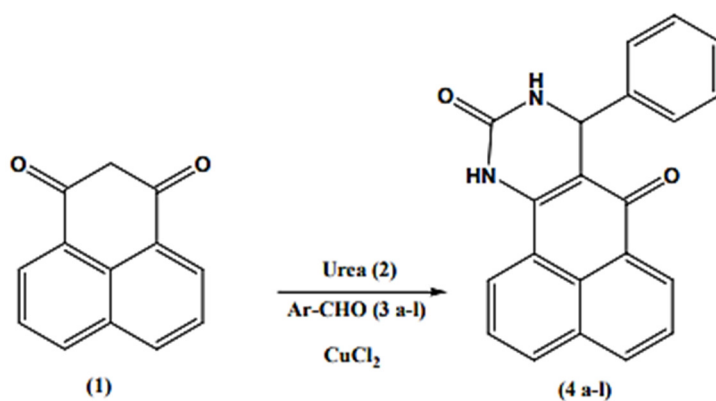


Figure 2.1: Synthesis of novel naphtho[1,8-gh]quinazoline-7,10-diones in solvent free condition by K. Mohammadi (2018)

### 2.1.2 Synthesis of *N*-arylsulfonyl-2-iminocoumarins via one-pot three-component

Mandal and Kumar (2018) had carried out a feasible transition metal-free protocol to synthesis *N*-arylsulfonyl-2-iminocoumarins derivative. In this reaction, 2-hydroxybenzaldehydes, aryl sulfonyl chlorides and arylacetonitriles were reacted together with 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base in a bio-mass-derived green solvent 2-methyltetrahydrofuran. The 2*H*-chromen-2-imines was formed when 2-hydroxybenzaldehyde condensed with arylacetonitriles. Then, the 2*H*-chromen-2-imines was further reacted with aryl sulfonyl chlorides via a one-pot method to yield the final product. This methodology yield the 3-aryl-*N*-arylsulfonyl-2-iminocoumarins in an environmentally friendly and effective route by preventing cumbersome intermediate syntheses and purifications steps.

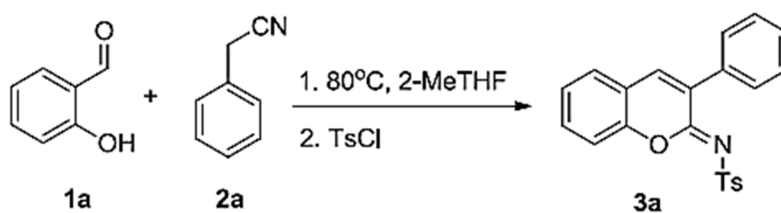


Figure 2.2: Synthesis of 3-aryl-*N*-arylsulfonyl-2-iminocoumarins by Mandal and Kumar (2018)

### 2.1.3 Synthesis of polyhydroquinoline derivatives through Hantzsch reaction catalysed by Gadolinium triflate via one-pot multi component

According to Sheik Mansoor et al. (2017), in the presence of catalyst which is Gadolinium(III) trifluoromethanesulfonate (Gadolinium triflate)  $Gd(OTf)_3$ , polyhydroquinoline derivatives can be successfully prepared at ambient temperature by reacting different aromatic aldehydes, dimedone, ethyl acetoacetate and ammonium acetate via Hantzsch reaction. The protocol is environmentally benign, operationally simple and the good yield of polyhydroquinoline was obtained. Furthermore, the recovery and reuse of catalyst – Gadolinium triflate in this reaction is available. The overall reaction pathway is shown below:

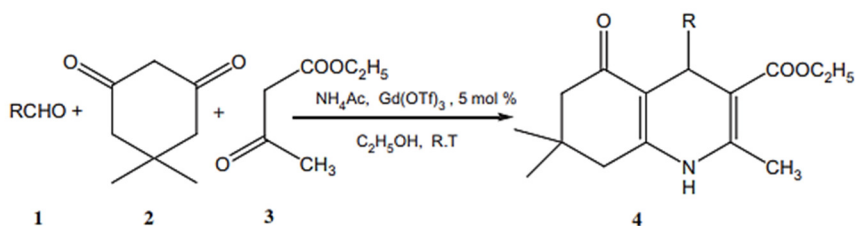


Figure 2.3:  $Gd(OTf)_3$  catalyzed synthesis of polyhydroquinoline derivatives via Hantzsch reaction by Sheik Mansoor et al. (2017)

### 2.1.4 Synthesis of hydrazinyl thiazole derivatives through one-pot reaction under catalyst and solvent free with microwave assisted

In this reaction, the equal molar amount of aryl ketones, thiosemicarbazide and substituted phenacyl bromide were reacted together to synthesis the hydrazinyl thiazole. Then, the starting materials were subjected to the microwave irradiation for a short period of time around 30 to 175 seconds at a heating of 300 W. Once the reaction was completed, the solid crude product was recrystallized by using ethanol and a pure hydrazinyl thiazole derivative compound is obtained (Chinnaraja and Rajalakshmi, 2015). This was an efficient and environmentally benign protocol since it is solvent and catalyst free as shown in the reaction scheme below:

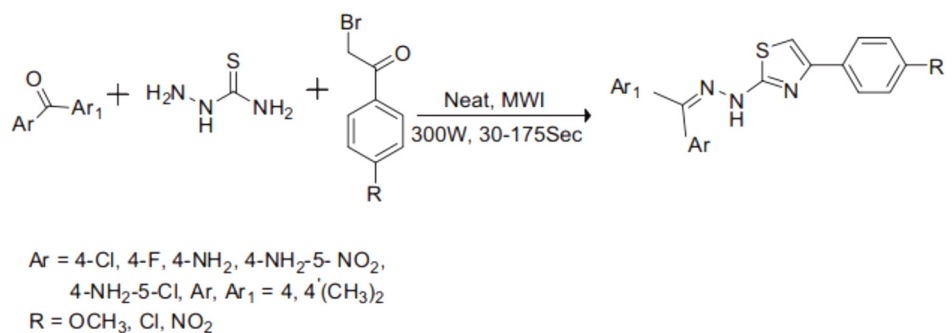
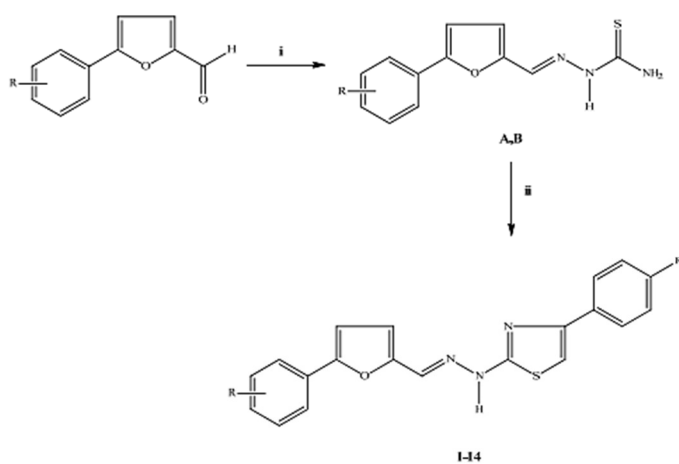


Figure 2.4: Synthesis of hydrazinyl thiazole by Chinnaraja and Rajalakshmi (2015)

## 2. Synthesis of thiazole hydrazone derivatives

### 2.2.1 Synthesis of new nitro-substituted thiazolyl hydrazone derivatives

According to Altıntop et al. (2014), thiazolyl hydrazone can be synthesized through two steps reaction. Firstly, 5-arylfurfural thiosemicarbazones were synthesized by reacting the 5-arylfurfurals with thiosemicarbazide in 40 mL ethanol and refluxed for about 12 hours. Next, the 5-arylfurfural thiosemicarbazones was mixed with 2-bromoacetophenone derivatives in 20 mL ethanol and refluxed again for another 8 hours. Then, the 5-arylfurfural thiosemicarbazones undergo the ring closure and finally produced the new thiazolyl hydrazone derivatives. The reaction was carried out according to the steps shown in Figure 2.5.



*Reagents and conditions:* (i)  $\text{NH}_2\text{CSNHNH}_2$ , ethanol, reflux, 12 h; (ii)  $\text{ArCOCH}_2\text{Br}$ , ethanol, reflux, 8 h.

Figure 2.5: Synthesis of thiazolyl hydrazone derivatives by Altıntop et al. (2014)

## 2.2.2 Synthesis of 2-hydrazino-1,3-thiazole derivatives

According to Maillard et al. (2013), thiazole hydrazone derivatives can be synthesized via two steps reaction easily. In initial step, a series of carbonyl compound were reacted with thiosemicarbazide in ethanol under reflux condition. Then, the intermediate thiosemicarbazone was obtained and it subsequently reacted with 2-chloro-1-(2-hydroxy-5-methoxyphenyl)-ethanone. Lastly, the desired product- thiazolyhydrazones was obtained and the reaction equation was shown in Figure 2.6:

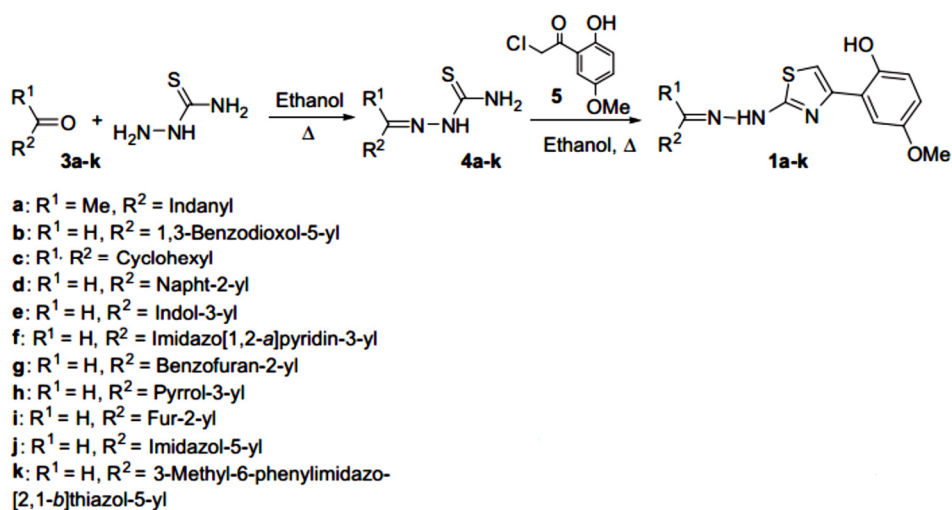


Figure 2.6: Synthesis of 2-hydrazino-1,3-thiazole derivatives by Maillard et al. (2013)



### 2.2.3 Synthesis of 2-thiazolyl hydrazones

4'-(2-methylpropyl)acetophenone (0.01 mol), thiosemicarbazide (0.01 mol) and 1 mL of concentrated hydrochloric acid, HCl were mixed together in 15 mL methanol. After refluxed the reaction for 2 hours, the mixture was cooled to room temperature led to the formation of 1-(1-(4-isobutylphenyl) ethylidene) thiosemicarbazide as an intermediate. After that, the intermediate 1-(1-(4-isobutylphenyl)ethylidene) thiosemicarbazide reacted with phenacyl bromide/substituted phenacyl bromide in 50 mL isopropanol and it was refluxed for 2–4 hours. Then, the crude product – 2-thiazolyl hydrazones produced were filtered and purification was carry out by utilizing silica gel column chromatography (Anbazhagan and Sankaran, 2015).

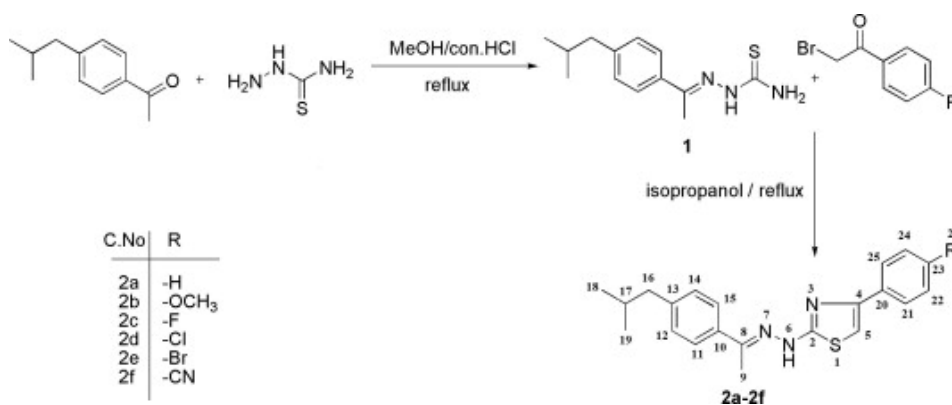


Figure 2.7: Synthesis of 2-thiazolyl hydrazones by Anbazhagan and

Sankaran (2015).

#### **2.2.4 Synthesis of thiazolyldrazone derivatives via one-pot multicomponent reaction**

A series of thiazolyldrazones derivatives were synthesized in a good yield through one-pot multicomponent condensation of 1,3-indandione (**1**), thiosemicarbazide (**2**), and 3-(2-bromoacetyl)-2H-chromen-2-ones (**3a-f**) or 2-bromo-1-(4-substituted-phenyl)ethanone (**5a-f**) by adding small amount of acetic acid and refluxed for 1 to 3 hours with ethanol. The reaction was monitored by Thin Layer Chromatography (TLC) plate. Once the TLC plate shown the reaction completed, the crude solid was filtered out followed by washed with hot ethanol, which able to form a pure product without recrystallization (Rajitha et al., 2015). The overall reaction pathway is shown below:

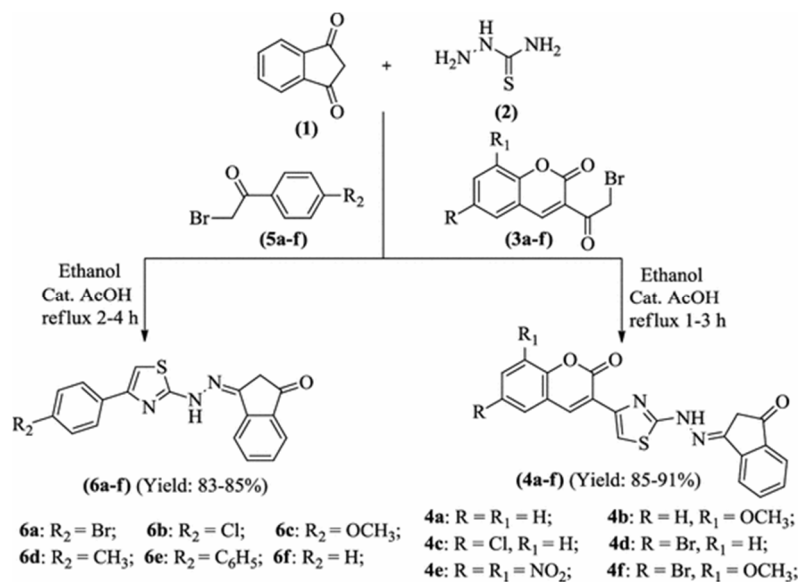


Figure 2.8: Synthesis of thiazolylhydrazone derivatives by Rajitha et al. (2015)

## 2.2.5 Synthesis of hydrazones containing 4-methylbenzo[*d*]thiazole moiety

Weng, Tan and Liu (2012) had reported on the synthesis of hydrazone derivatives series containing 4-methylbenzo[*d*]thiazole moiety. This reaction was performed in four steps as shown in Figure 2.9 below. Firstly, *o*-toluidine (**1**) reacted with ammonium thiocyanate and the reaction mixture refluxed at 100–110°C for 8 hours and let it vaporized to below the 50% of the total volume. The precipitate of *o*-tolylthiourea (**2**) was obtained after the mixture is cooled. Next, thionyl chloride, SOCl<sub>2</sub> solution and dry powdered *o*-tolylthiourea was heated at 20°C for 10 hours. 2-Amino-4-methylbenzo[*d*]thiazole (**3**) will formed and it reacted with hydrazine hydrate refluxed while stirring for 4 hours. After that, acetone was mixed with the solution of 2-hydrazino-4-methylbenzothiazole (**4**) in ethanol and 1 M hydrochloric acid and the reaction mixture was agitated for 15 min at room temperature. The precipitate was finally filtered and recrystallized from ethanol to give a good yield of white solid 2-hydrazino-4-methylbenzo[*d*]thiazole.

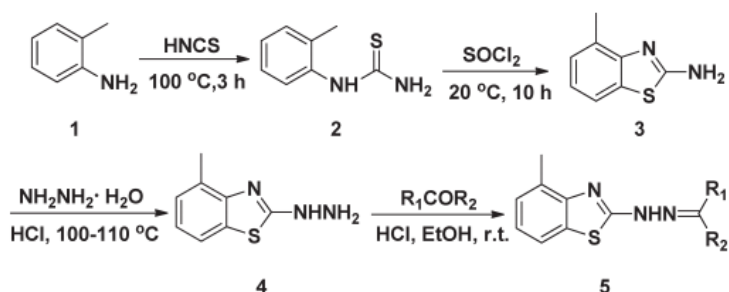


Figure 2.9: Synthesis of 2-Hydrazino-4-methylbenzo[*d*]thiazole by Weng, Tan and Liu (2012)

## 2.2.6 Synthesis of phenyl thiazole hydrazone

Phenyl thiazole hydrazone can be easily synthesized by reacting the equal molar amount of 2-hydrazino-4-phenyl thiazole and appropriate aromatic aldehydes in absolute ethanol or methanol, followed by refluxing for 3 hours. In this reaction, acetic acid was added as a catalyst in order to obtain an ideal yield. A pure thiazole hydrazone derivatives can be obtained by evaporated the excess solvent through vacuum and recrystallized from ethanol (Khan et al., 2015). The overall reaction pathway is illustrated below:

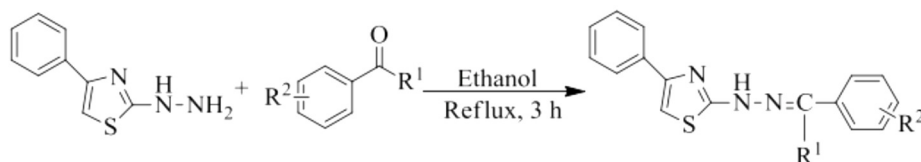


Figure 2.10: Synthesis of phenyl thiazole hydrazone derivatives by Khan et al. (2015)

## 2.2.7 Synthesis of arylidene-hydrazinyl-thiazole derivatives

Grozav et al. (2014) had successfully synthesized the arylidene-hydrazinyl-thiazole derivatives by an appropriate Hantzsch condensation reaction. In the presence of solvent which is ethanol, a series of aromatic aldehyde were condensed with hydrazinecarbothioamide and followed by the cyclization process with  $\alpha$ -halocarbonyl derivatives produced the arylidene-hydrazinyl-thiazole derivatives. An excellent yield of product can be obtained in this reaction.

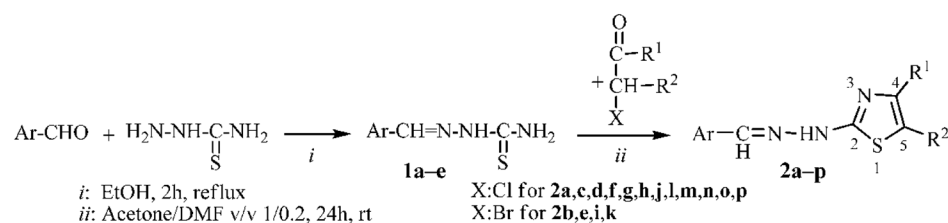


Figure 2.11: Synthesis of arylidene-hydrazinyl-thiazole derivatives by Grozav et al. (2014)

## 2.3 Use of water as green solvent in synthesis

### 2.3.1 Synthesis of 4-*H*-Benzo[*b*]pyrans in water at ambient temperature

In the study of Mosaddegh, Hassankhani and Mansouri (2010), a several solvents were chosen to test their efficiency in synthesis of 4-*H*-benzo[*b*]pyrans at room temperature. It had proven that the polar solvent will tend to give a high yields compare to non-polar solvent in mild reaction conditions. Besides the excellent yields, a very short experimental time of the reaction can be achieved when using water as a green solvent. The result in Table 2.1 shown that water is the better reaction medium at room temperature condition compare to the organic solvents media.

Table 2.1: Solvent effects on synthesis of 4-*H*-benzo[*b*]pyrans at room temperature

<b>Solvent</b>	<b>Time</b>	<b>Yield (%)</b>
Distilled water	5 minutes	94
Ethanol	18 hours	82
Dichloromethane	24 hours	Trace
Ethylacetate	24 hours	Trace
1,2-Dichloroethane	24 hours	Trace

### 2.3.2 Synthesis of bioactive pyrimido[4,5-*b*]quinoline derivatives as antibacterial agents in water

An effective and environmentally friendly one-pot method of pyrimido[4,5-*b*]quinoline derivatives has been developed using water as a green solvent. Water is non-poisonous, non-flammable, non-corrosive and is easily accessible at low cost in comparison with organic solvents. These properties make it both cost-effective and benign to environment and thus widely known as a green solvent (Tabatabaeian et al., 2014). The reaction was carried out in different temperature and using different solvent in order to find the optimum reaction condition. Finally, it was found that water afforded the highest yield at 85°C as presented in Table 2.2.

Table 2.2: Influence of the solvents on the synthesis of pyrimido[4,5-*b*]quinolone

Solvent	Temperature (°C)	Yield (%)
Water	85	95
Water	100	92
Water/ethanol (1:1)	90	85
Methanol	Reflux	80
Ethanol	Reflux	78



Acetonitrile	Reflux	60
<i>n</i> -Hexane	Reflux	Trace

### 2.3.3 Synthesis of 2-amino-4,6-diphenylnicotinonitriles in water without catalyst

2-amino-4,6-diphenylnicotinonitriles can be successfully synthesized by reacting the benzaldehyde, acetophenone, malononitrile, and ammonium acetate in a different reaction condition by changing the solvent system and performing the ultrasonic irradiation. In this study, it found that when the water was used as solvent in both condition with sonication and without sonication, an excellent yield was obtained (Safari, Banitaba and Khalili, 2012). The result was tabulated in Table 2.3 below:

Table 2.3: Effect of solvents and reaction condition in synthesizing 2-amino-4,6-diphenylnicotinonitriles at 30 ° C

Solvent	Product yield (%)	
	With sonication	Without sonication
Water	87	77
Ethanol	70	57
Methanol	65	55

THF	40	25
Acetonitrile	35	Trace
Dichloromethane	30	Trace
Solvent free	60	35

## CHAPTER 3

### MATERIALS AND METHODOLOGY

#### 3.1 The chemicals used

The chemicals used in this project are shown in table below:

Table 3.1: The chemicals used

<b>Chemicals</b>	<b>Manufacturer</b>	<b>Country</b>
Absolute ethanol	Fischer Scientific	Malaysia
Methanol	Merck	Germany
Chloroform	Merck	Malaysia
Acetonitrile	Fischer Scientific	UK
Dimethylformamide (DMF)	Lab-Scan	Thailand
Acetone	Fischer Scientific	UK
<i>n</i> -Hexane	Merck	Germany
Ethyl acetate	Lab-Scan	Thailand
DMSO- <i>d</i> <sub>6</sub>	Merck	Germany

### **3.2 The instruments used**

The instruments including Stuart SMP10 melting point apparatus, Perkin-Elmer Spectrum RX1 FT-IR spectrophotometer and JEOL ECX-400 FT-NMR spectrometer are used in this project.

### **3.3 Methodology**

#### **3.3.1 Synthesis of thiazole hydrazones derivatives through one-pot reaction**

2 mmol of starting material were mixed in a 50 mL of round bottom flask. A magnetic stirrer bar and a few boiling chips were also added into the flask, followed by 15 mL of distilled water. The flask was brought to reflux for certain hours and the reaction was monitored by Thin Layer Chromatography (TLC) plate. Once the TLC plate shown the completion of the reaction, the round bottom flask was allowed to cool to room temperature and the mixture was then poured into a beaker that containing some crushed ice. The beaker was leave undisturbed for a certain period usually overnight for maximize the precipitation of product. After that, the solid product was filtered by using a vacuum suction filtration with cold distilled water during rinsing process. The solid product was further dried in oven.

### **3.3.2 Synthesis of thiazole hydrazone through two-steps reaction**

2 mmol of mixture were mixed in a 50 mL round bottom flask. Magnetic stirrer bar and a few boiling chips were added into the flask, followed by 15 mL of distilled water and refluxed the mixture. Thin Layer Chromatography (TLC) plate was used to monitor the reaction. After the completion of reaction, the flask was cooled to room temperature first and the content was poured into a beaker that containing crushed ice. In order to maximize the precipitation of product, the beaker was leave undisturbed and overnight. The product was filtered by using a vacuum suction filtration with cold distilled water and dried in oven.

### **3.4 Purification – Recrystallization**

Recrystallization is a technique that used to purify an impure compound by using a suitable solvent. In this project, ethanol was chosen as a solvent because it is volatile and it do not react with the solute – desired compound. First of all, a small number of boiling chips were added into ethanol and boiled it by using a hot plate. The crude product that required to purify was placed in a beaker and hot ethanol was added and swirled until the crude product was completely dissolved. Before proceed to the hot filtration, a piece of filter paper was folded into a cone shape and placed into a glass funnel. Then, the solution mixture was filtered through the paper and the filtrate was concentrated to a volume around 20 mL. The solution was then

covered with aluminum foil to prevent dust falling into solution and leave the beaker undisturbed at fumehood. The aluminum foil was pierced with a few small holes to allow the solvent evaporate and a pure compound was obtained.

### **3.5 Characterization of thiazole hydrazone derivatives**

#### **3.5.1 Infrared spectroscopy (IR)**

Infrared spectroscopy is widely used to identify and determine a compound based on the functional groups presence in that compound. This technique is mainly use in organic and inorganic chemistry. This is the analysis of infrared radiation interacting with interested molecule. When an infrared radiation is directed to a compound, the specific bonds in the compound will absorb the radiation at specific frequencies. Hence, the functional groups present in the compound can be identified. The model of instrument used in this project was Perkin-Elmer Spectrum RX1 FT-IR spectrophotometer. The compounds were analyzed in the frequencies range between  $4000\text{ cm}^{-1}$  and  $400\text{ cm}^{-1}$ .

#### **3.5.2 Nuclear Magnetic Resonance (NMR)**

Nuclear Magnetic Resonance (NMR) spectroscopy is an analytical technique that used for determining the content, purity and the molecular structure of sample. The principle of NMR is based upon the spins of atomic nuclei. The magnetic effect that caused by the spin of neutrons and protons is measure by NMR. The physical, electronic, chemical and structural information of a compound can be attained by analyzing the peaks of NMR

spectra. For the NMR sample preparation, the sample was first dissolved in deuterated solvents such as dimethyl sulfoxide (DMSO) or mixture of DMSO- $d_6$  and acetone- $d_6$  which depend on the sample solubility in particular solvent. The sample solution was introduced in a NMR tube to an approximately 4 cm height. In order to prevent evaporation of solvent, the NMR tube was sealed and subjected to NMR analysis. Since the solvent amount is larger than the sample that being analyzed, it is necessary to ensure that the solvent do not dominate in the spectra. In this project, the JEOL ECX-400 FT-NMR spectrometer was performed to get one- and two-dimensional NMR which including  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, Heteronuclear Multiple Quantum Coherence (HMQC), and Heteronuclear Multiple Bond Coherence (HMBC).

### **3.5.3 Thin Layer Chromatography (TLC)**

Thin-layer chromatography (TLC) is a very common chromatographic technique that used in synthetic chemistry to identify compounds, monitor the progress of a reaction and also determine the purity of a compound. The advantages of TLC are relative low cost, simple, speed of separation and high sensitivity. The surface of TLC plate is coated with polar absorbent, usually silica which act as stationary phase. In this project, the mixture of ethyl acetate and *n*-hexane in a ratio of 1: 1 act as mobile phase. A small portion of sample was dissolved in the mixture of ethanol and chloroform at 1:1 ratio and spotted the sample on the baseline of plate. After that, the



plate was slowly placed in a developing chamber and allowed the mobile phase to travel through the plate via capillary action. The plate was leave undisturbed in the chamber until the mobile phase reached 1 cm from the top. The plate was carefully taken out from chamber and it was visualized under short-wavelength UV light. The completion of reaction was shown by observing a single spot of the compound and it does not appear as same level with reagents used.

#### **3.5.4 Melting point apparatus**

Melting point of a compound is determined by using Stuart SMP10 melting point apparatus in this project. This is one way to determine the purity of a compound. A sharp melting range of one or two degree can be obtained if the compound is pure. The melting range is defined as the temperature where the sample begin to melt and the temperature where melting process is completed. A one-end sealed capillary tube that contained a small portion of the sample was inserted into the melting point apparatus and heated. The melting range of sample was observed and recorded.

## CHAPTER 5

### CONCLSION

#### 5.1 Conclusion

In this project, a total of eight thiazole hydrazones were successfully synthesized in good yield by using the water as solvent via one-pot synthesis. Solvent test was carried out and the water was selected as solvent in this project due to it give the highest yield compare to rest of solvent. The yields of products in one-pot synthesis and two-steps reaction were compared. However, the one-pot synthesis was selected because it gave high product yield, time saving as well as cost saving. All the thiazole hydrazones compounds were elucidated and characterized by using IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, HMQC, HMBC, and melting point apparatus.

#### 5.2 Future perspective

In future, one-pot synthesis of thiazole hydrazone derivatives can be done by the aid of microwave irradiation to shorten the reaction time. Besides, bioactivities such as antioxidant, antifungal, antibacterial and anticancer can be carried out in order to discover the potential usage of thiazole hydrazones.

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