แฮโลจิเนชันของสารประกอบเอ็น-เฮเทอโรแอโรแมติกไฮดรอกซีด้วยไทรเฟนิลฟอสฟีน/แฮโลจิเนทิงเอเจนต์

นางสาววรณัน กิจรุ่งไพบูลย์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์
คณะวิทยาศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2554

HALOGENATION OF *N*-HETEROAROMATIC HYDROXY COMPOUNDS WITH PPh_3/HALOGENATING AGENT

Miss Woranun Kijrungphaiboon

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Petrochemistry and Polymer Science
Faculty of Science
Chulalongkorn University
Academic Year 2011

Thesis Title	Halogenation of *N*-Heteroaromatic Hydroxy Compounds with PPh_3/Halogenating Agent
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Field of Study	Petrochemistry and Polymer Science
Thesis Advisor	Assistant Professor Warinthorn Chavasiri, Ph.D.

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วรณัน กิจรุ่งไพบูลย์ : แฮโลจิเนชันของสารประกอบเอ็น-เฮเทอโรแอโรแมติกไฮดรอกซีด้วยไทรเฟนิลฟอสฟีน/แฮโลจิเนทิงเอเจนต์ (HALOGENATION OF *N*-HETEROAROMATIC HYDROXY COMPOUNDS WITH PPh_3/HALOGENATING AGENT) อ. ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ.ดร.วรินทร ชวศิริ, 63 หน้า.

ได้พัฒนาปฏิกิริยาแฮโลจิเนชันของสารประกอบเอ็น-เฮเทอโรแอโรแมติกไฮดรอกซีโดยใช้ไทรเฟนิลฟอสฟีน/แฮโลจิเนทิงเอเจนต์ 2 วิธีคือการให้ความร้อนแบบธรรมดาและไมโครเวฟ ได้หาภาวะที่เหมาะสมสำหรับการสังเคราะห์เอ็น-เฮเทอโรแมติกแฮไลด์ เช่น ชนิดของแฮโลจิเนทิงเอเจนต์ ปริมาณรีเอเจนต์ เวลาและตัวทำละลาย ในกรณีของการให้ความร้อนแบบธรรมดา ไทรคลอโรแอซิโทไนไทรล์ (Cl_3CCN) หรือ คาร์บอนเททระโบรไมด์ (CBr_4) กับไทรเฟนิลฟอสฟีนเป็นรีเอเจนต์ที่มีประสิทธิภาพสูงสำหรับการเปลี่ยนสารประกอบเอ็น-เฮเทอโรแอโรแมติกไฮดรอกซีเป็นแฮไลด์ที่อุณหภูมิรีฟลักซ์ของทอลูอีนเป็นระยะเวลา 4 ชั่วโมง ในทางกลับกันไทรคลอโรแอซิโทไนไทรล์ เฮกซะคลอโรแอซิโทน และ คาร์บอนเททระโบรไมด์กับไทรเฟนิลฟอสฟีนสามารถเปลี่ยนสารประกอบเอ็น-เฮเทอโรแอโรแมติกไฮดรอกซีและอนุพันธ์ของคูมารินเป็นแฮไลด์ที่ต้องการในปริมาณสูงที่อุณหภูมิ 150 °C 20 นาที ภายใต้สภาวะไมโครเวฟ

สาขาวิชา ปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์ ลายมือชื่อนิสิต .....

ปีการศึกษา 2554 ลายมือชื่อ อ. ที่ปรึกษาวิทยานิพนธ์หลัก .....

5272653223: MAJOR PETROCHEMISTRY AND POLYMER SCIENCE
KEYWORDS: HALOGENATION / *N*-HETEROAROMATIC HYDROXY COMPOUND / MICROWAVE

WORANUN KIJRUNGPHAIBOON: HALOGENATION OF *N*-HETEROAROMATIC HYDROXY COMPOUNDS WITH PPh_3/HALOGENATING AGENT. ADVISOR: ASST. PROF WARINTHORN CHAVASIRI, Ph.D., 63 pp.

Two new methodologies utilizing conventional heating and microwave (MW) heating for halogenation of *N*-heteroaromatic hydroxy compounds using PPh_3 and halogenating agent have been developed. The optimal conditions for the synthesis of *N*-heteroaromatic halides including type of halogenating agent, amount of reagents, reaction time and solvent were explored. In the case of conventional heating, Cl_3CCN or CBr_4 in combination with PPh_3 approved to be a highly reactive reagent for the conversion of *N*-heteroaromatic hydroxy compounds to the corresponding halides in refluxing toluene for 4 h. On the other hand, Cl_3CCN, $Cl_3CCOCCl_3$ and CBr_4 with PPh_3 could convert *N*-heteroaromatic hydroxy compounds and coumarin derivatives to desired halides in high yields at 150^{o}C for 20 min under MW irradiation.

Field of Study: Petrochemistry and Polymer Science Student's Signature .....
Academic Year: 2011 Advisor's Signature .....

ACKNOWLEDGEMENTS

The author would like to express her highest appreciation to her advisor, Assistant Professor Dr. Warinthorn Chavasiri for his valuable instructions, very kind assistance, generous guidance and encouragement throughout the course of this research. Furthermore, sincere thanks are extended to Natural Products Research Unit, Department of Chemistry, Faculty of Science, Chulalongkorn University, for the support of chemicals and laboratory facilities. I would like to thank the Graduate school, Chulalongkorn University, for financial support.

The greatest thanks are also extended to Professor Dr. Pattarapan Prasassarakich, Associate Professor Dr. Mongkol Sukwattanasinitt and Dr. Wanchai Pluempanupat for their suggestion, comments, correction and helps as thesis examiners.

Moreover, thanks are extended to Center for Petroleum, Petrochemicals and Advanced Materials, Chulalongkorn University, Program in Petrochemistry and Polymer Science, Faculty of Science, Chulalongkorn University, the Thailand Research Fund (TRF-MAG) and the 90th Anniversary of Chulalongkorn University Fund (Ratchadaphiseksomphot Endowment Fund) for granting financial support to fulfill this study and provision of experimental facilities.

Further acknowledgment is extended to her friends for friendship and helps throughout the entire of study. Especially, the author very appreciate to her family members whose names are not mentioned for their love, assistance, understanding, encouragement and social support throughout her entire education. Without them, the author would never have been able to achieve this goal.

CONTENTS

page

CHAPTER **page**

CHAPTER **page**

CHAPTER **page**

LIST OF TABLES

Table **page**

LIST OF FIGURES

Figure **page**

LIST OF FIGURES

Figure **page**

LIST OF SCHEME

Scheme **page**

LIST OF ABBREVIATIONS

conc.	concentrated
d	doublet (NMR)
dd	doublet of doublet (NMR)
equiv.	equivalent
g	gram (s)
h	hour (s)
HPLC	high performance liquid chromatography
Hz	hertz
J	coupling constant (NMR)
m	multiplet (NMR)
MB	mass balance
min	minute (s)
mL	milliliter (s)
mmol	millimole (s)
µL	microliter
MW	microwave
NMR	nuclear magnetic resonance
ppm	part per million
q	quartet (NMR)
RT	room temperature
s	singlet (NMR)
TLC	thin layer chromatography
t	triplet (NMR)
td	triplet of doublet (NMR)
UV	ultraviolet
W	watt
%	percent
^{o}C	degree Celsius
δ	chemical shift

CHAPTER I

INTRODUCTION

Heteroaromatics have been reported as versatile synthetic precursor to synthesize catalysis polymerization [1] or use as a monomer to increase average molecular weight of polymer [2]. Although heteroaromatic have many valuable structures, there are still demands of nucleophilic substitution to prepare other classes of organic compounds such as amines and ethers.

Nucleophilic substitutions of haloaromatics or haloheteroaromatics are in fact not facile comparing with those of saturated analogues. Nonetheless, those processes can be achieved by a wide range of nucleophiles *via* an addition-elimination mechanism, particularly simple in the presence of (i) electron withdrawing substituent and (ii) the good leaving group (*e.g.* halide).

N-Heteroaromatic halides are known as one of useful intermediates in organic synthesis and pharmaceutical interest [3-5], for instance, as a phase transfer agent, an important intermediate for the manufacture of pyrithione-based biocides in cosmetics and a starting material in the production of various pharmaceutical products such as antihistamine drug, phemiramine [6].

1.1 Introduction of *N*-Heteroaromatic Halides

The nucleophilic displacement of haloheteroaromatics is an important reaction resulting in the generation of many other functional groups such as *N*-heteroaromatic amines, ethers and so on (Fig 1.1).

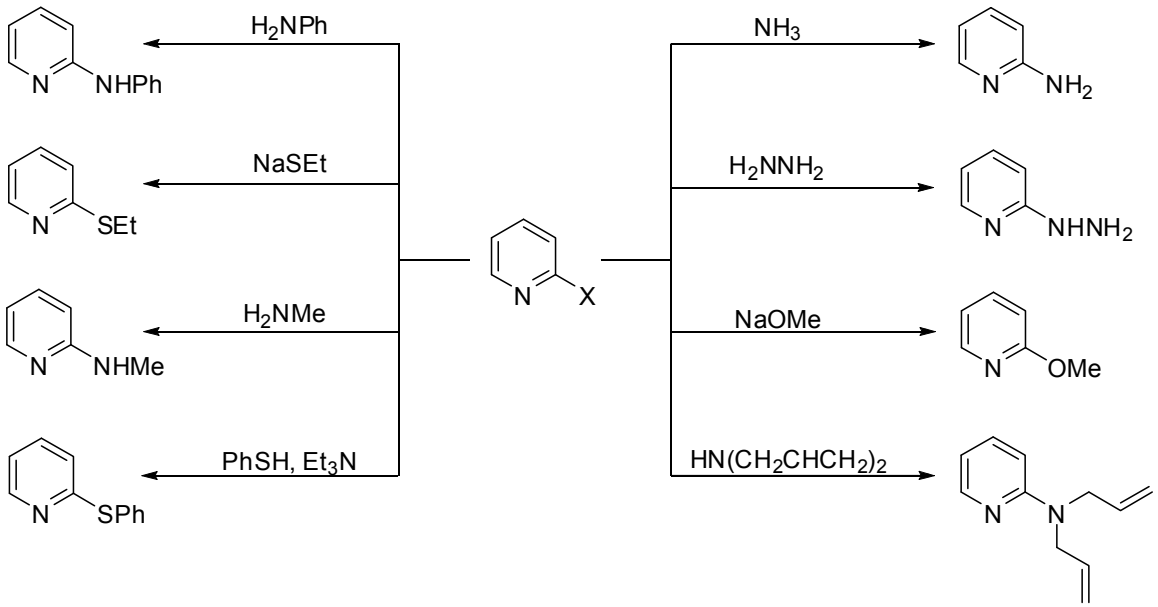


Figure 1.1 Conversion of *N*-heteroaromatic halides tother organic compounds

N-Heteroaromatic halides can be prepared by several means, for example, halogenations of *N*-heteroaromatics in the vapor phase at over 300^{o}C [7]. The most common protocols stem from the conversion of *N*-heteroaromatic hydroxy compounds because of their commercial availability and easy transformation processes.

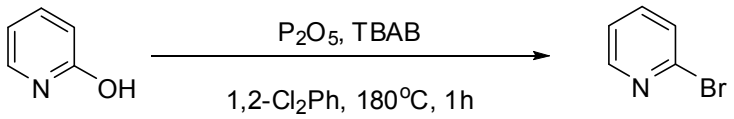
1.2 Literature Reviews of *N*-Heteroaromatic Halides from *N*-Heteroaromatic Hydroxy Compounds

The general method for the preparation of *N*-heteroaromatic halides has been addressed by the use of phosphorus oxyhalide (POX_3, X = Cl or Br), phosphorus pentachloride (PCl_5), and triphenylphosphine (PPh_3) with halogenating agent such as *N*-chlorosuccinimide (NCS).

1.2.1 Common Reagents

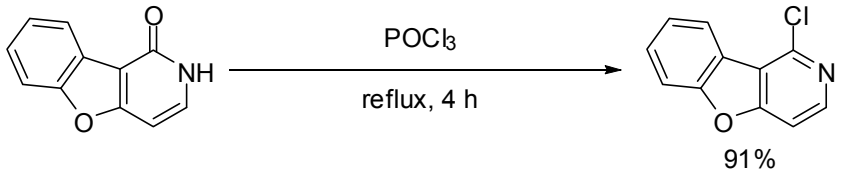
The methodologies for the preparation of *N*-heteroaromatic halides utilizing halogenating agents have been extensively investigated. For instance, Kato and co-workers [8] reported the use of P_2O_5 and a quaternary ammonium bromide for the conversion of hydroxyheteroaromatics to the corresponding bromoheteroaromatics.

Hydroxyheteroaromatics containing an electron-withdrawing group furnished high yields of bromoheteroaromatics at 100°C within 1-10 h. However, under this particular conditions studied, this method was not successful in the preparation of 2-bromopyridine. More severe conditions were required.

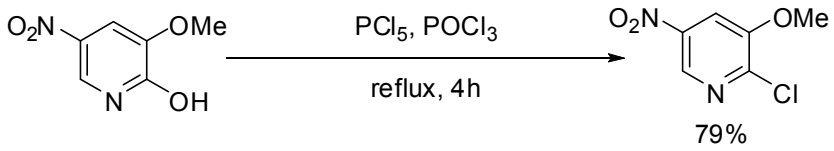


In 2009, O'Shea and co-workers [9] addressed the bromination of 5-bromo-3-nitropyridin-2-ol using *N*-bromosuccinamide (NBS)/Ph_3P, P_2O_5/Bu_4NBr or $POBr_3$. Treatment of the mentioned substrate with NBS/Ph_3P or P_2O_5/Bu_4NBr did not lead to good yields of product. Interestingly, the bromination using $POBr_3$ provided high yield (80-92%).

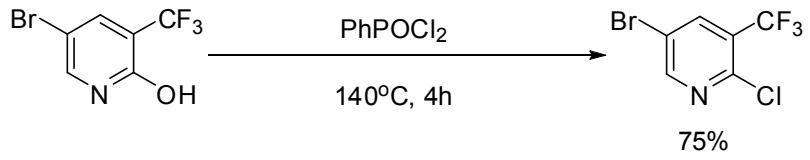
In the same year, Mojumdar and co-workers [10] converted *N*-heteroaromatic hydroxy compounds to the corresponding *N*-heteroaromatic chlorides using $POCl_3$ under reflux conditions for 4 h.



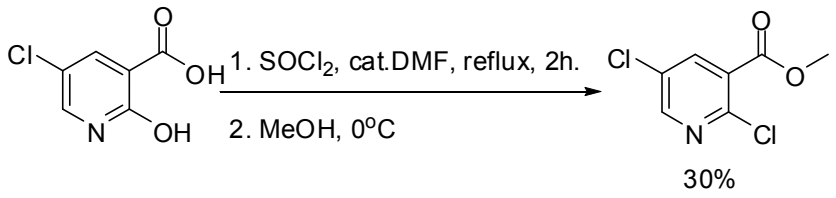
Later, Morgentin and co-workers [11] explored the effect of PCl_5 and $POCl_3$ in the nucleophilic substitution of 2-hydroxypyridine derivatives. A strong electron-withdrawing group was required at C-3 and C-5 of starting material.



In 2009, Gleave and co-workers [12] reported the use of $PhPOCl_2$ for the conversion of hydroxyl group in heteroaromatics to the corresponding chlorides.



In 2009, Vanlaer and co-workers [13] demonstrated the conversion of hydroxyl and carboxyl groups to chloride and acyl chloride, respectively using $SOCl_2$, with low yields.



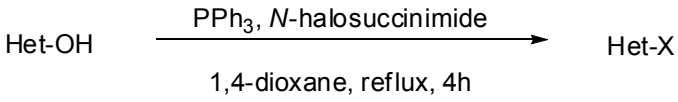
As previous reports, brominating and chlorinating agents used are quite harmful, difficult to handle or in some cases generate by-products such as HCl or SO_2 gases during the reaction, which cause those reagents not be applicable to the acid-sensitive molecules.

1.2.2 Phosphorus Compounds with Halogenating Agents

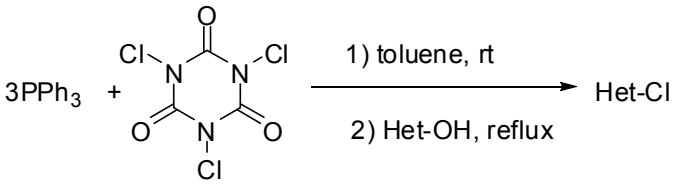
Although several synthetic methods for *N*-heteroaromatic halides have been developed, there remains a need for facile and general methods towards accessing *N*-heteroaromatic halides. There are a few reports describing the preparation of *N*-heteroaromatic halides from *N*-heteroaromatic hydroxy compounds using PPh_3/ halogenating agent, together with the use of *N*-halosuccinimide or trichloroisocyanuric acid (TCICA).

In 1999, Sugimoto and co-workers [14] developed the methodology to prepare *N*-heteroaromatic halide by treating *N*-heteroaromatic hydroxy compounds with PPh_3 and *N*-halosuccimide in 5:5 mole ratio (base on substrate). The corresponding *N*-heteroaromatic chloride and bromide were obtained in moderate to high yield. Later, in 2001, Sugimoto and coworkers [15] reported the optimum conditions for this reagent. Variable parameters studied were solvent, amount of reagent and reaction time using 2-hydroxyquinoline as a model compound. The developed reaction worked

well to achieve *N*-heteroaromatic halides in the range of 43-89% yield. However, 4-bromoquinazoline was produced in low yield because of the instability of product.



In 2005, Sugimoto and Tenji [16] addressed the methodology for the synthesis of *N*-heteroaromatic chloride using PPh_3 and TCICA at reflux temperature of toluene. This method provided a viable procedure using low amount of reagent required. However, this method required long reaction time (23-49 h).



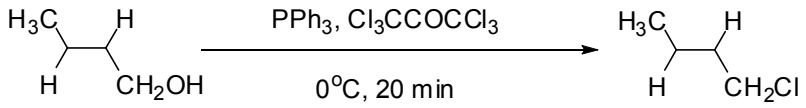
Despite the fact that PPh_3/*N*-halosuccinimide has been documented for the halogenations of *N*-heteroaromatic hydroxy compounds, the method still have its own disadvantage such as large amount of reagent, long reaction time, low efficiency or severe reaction conditions required.

1.3 Literature Reviews on Organic Transformation Using PPh_3/Halogenating Agent

The convenient methodology for the preparation of halides using comparatively facile under mild conditions has been constantly investigated, for example, a combination of PPh_3 and halogenating agent such as Cl_3CCN, Cl_3CCONH_2 or $Br_3CCOCBr_3$ [17-19]. These systems are attractive since the reaction can be performed under mild and acid-free conditions with good yield.

1.3.1 Alcohol

In 1977, Magid and co-workers [20] reported the use of PPh_3/$Cl_3CCOCCl_3$ for the transformation of allylic alcohols into chlorides. This method revealed high reactivity, regiospecificity and stereoselectivity.



In 1983, Bringmann and Schneider [21] reported the method for the preparation of alkyl chloride using phosphorus compounds and chlorinating agents. The reaction was carried out under mild and neutral conditions. This method could be employed to synthesize alkyl chlorides from alcohols using PPh_3/Cl_3CCCl_3 in high yields.

In 2006, Pluempanupat and Chavasiri [18] reported the mild and efficient procedure for the chlorination of alcohols using PPh_3/Cl_3CCONH_2. Although, this reagent is less reactive compared with Cl_3CCN, a mild and cost effective alternative of Cl_3CCONH_2 was prompted to apply this reagent to synthesize chlorides.

In 2008, Tongkate and co-workers [19] developed an alternative method for the preparation the corresponding alkyl bromides from alcohols by the combination use of $PPh_3/Br_3CCOCBr_3$ or $PPh_3/Br_3CCOOEt$. This protocol can be applied for the synthesis of all primary and secondary alkyl and cyclic alcohols.

1.3.2 Carboxylic Acid

In 1997, Villeneuve and Chan [22] addressed the method for the synthesis of acyl chloride by the reaction of carboxylic acid with $PPh_3/Cl_3CCOCCl_3$ at -78°C in CH_2Cl_2. The advantage for this method was high efficient protocol under very mild condition. The suitable molar ratio of PPh_3:Cl_3CCOCl_3 was 1:0.5.

In 1999, Jang and co-workers [17] described the conversion of acid chlorides from carboxylic acids with PPh_3/Cl_3CCN at RT under neutral condition. Various carboxylic acids could be transformed to the corresponding acid chlorides in high yields.

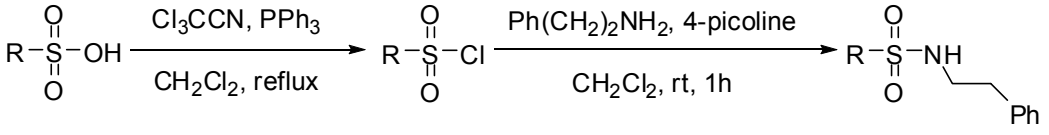
In 2009, Chaysripongkul and co-workers [23] introduced PPh_3/Cl_3CCONH_2 as another alternative reagent for the transformation of carboxylic acids to their analogous amides and esters *via* acid chlorides as reactive intermediate.

In 2009, Kang and co-workers [24] investigated the bromination of carboxylic acids using $PPh_3/Br_3CCOOEt$ under mild conditions and acid-free conditions. Aromatic carboxylic acids gave the corresponding acid bromides in high yields. However, aliphatic acid bromides were obtained in low to moderate yields. The usefulness of this method was easy to perform and neutral reaction condition could be employed.

In the same year, Menezes and co-workers [25] demonstrated the bromination of carboxylic acid by $PPh_3/Br_3CCOCBr_3$. Aromatic acids were smoothly converted to the corresponding aromatic acid bromides in high yields, whereas aliphatic acids did not work well.

1.3.3 Sulfonic Acid

From the literature review, only one report using PPh_3/halogenating agent as a reagent was addressed. In 2006, Chantarasriwong and co-wokers [26] showed the facile method for the preparation of sulfonamides from various sulfonic acids *via* sulfonyl chlorides in good yield. The optimum conditions were reported. The suitable halogenated reagent was Cl_3CCN with the ratio of sulfonic acid, Cl_3CCN and PPh_3 of 1:3:3. The reaction was carried out under refluxing CH_2Cl_2 for approximately 1 h.



These aforementioned PPh_3/halogenating agent systems are attractive since the reaction can perform to produce the desired products in excellent yields under mild condition with short reaction time. The combination of PPh_3 with halogenating agents has nonetheless not been applied to *N*-heteroaromatic hydroxy compounds. Thus, to examine the scope of this developed methodology for this class of compounds should be worth considering.

1.4 Halogenation under Microwave Irradiation

Conventional heating techniques such as using oil bath, sand bath or heating mentle are commonly used in organic synthesis. This is a conventional way to have an outside heat source on transferring and conducting heat to the middle of the vessel. Microwave (MW) heating directs activation of molecules in the solution, not the reaction vessel itself (Fig 1.2) [27].

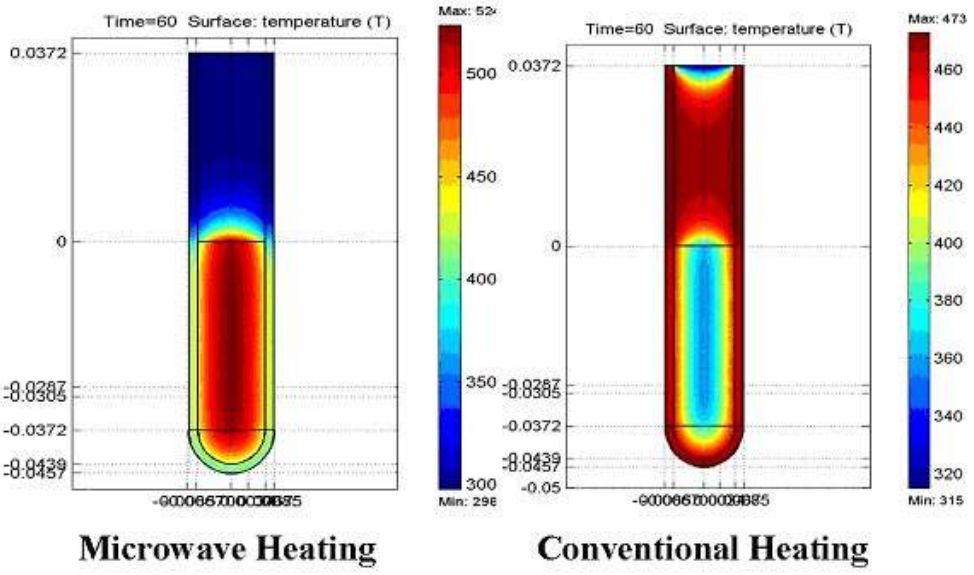


Figure 1.2 Surface temperature of microwave and conventional heating

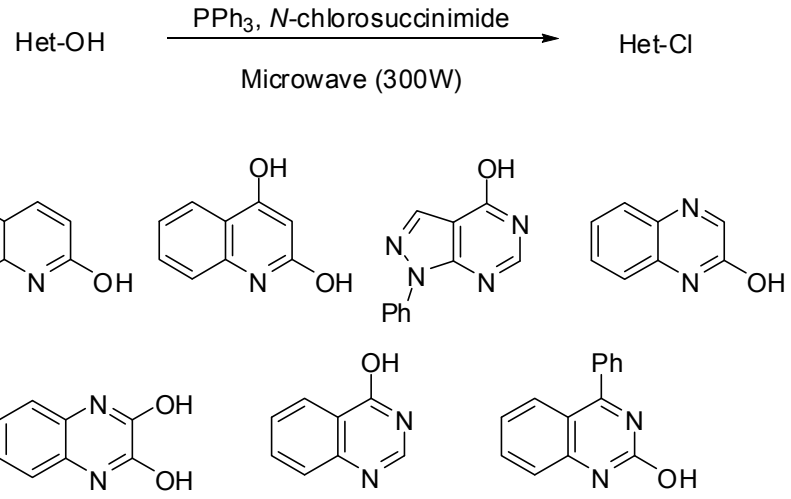
MW heating is a type of electro-heat technique designed to heat electrically-insulating (dielectric) materials. This energy transfer can be achieved *via* electrical conduction and dipole rotation (Fig 1.3) [28].

(a) (b)

Figure 1.3 (a) Polar molecule will follow the applied electric field (b) Dipolar molecules which try to align with an oscillating electric field

In general, heating reaction with conventional energy source is a valuable technique for organic synthesis. The use of MW in organic synthesis has dramatically increased the interest in recent years. Some papers reported that the reaction time for the chlorination of *N*-heteroaromatic hydroxy compounds prepared by MW heating could dramatically decrease compared with conventional heating.

In 2005, Tenji and co-workers [29] developed an efficient method for the chlorination of *N*-heteroaromatic hydroxy compounds using PPh_3/NCS under solvent-free MW assisted conditions using only 2.5-6 min. *N*-Heteroaromatic hydroxy compounds were carried out to give the corresponding chlorides in variable yields (0-64%). Some *N*-heteroaromatic chlorides such as 2-chloro-4-phenylquinazoline were decomposed under microwave irradiation.



In 2006, Takahashi and co-workers [30] showed that PPh_3/NCS could convert *N*-heteroaromatic hydroxy compounds to *N*-heteroaromatic chlorides under solvent-free conditions by MW irradiation or conventional heating in low to high yield. The advantages of both methods were solvent-free and low amount of PPh_3 and NCS (2 or 4 equiv for conventional heating and MW irradiation, respectively). Although the advantages of the method using MW irradiation were short reaction time, this method cannot be applied to unstable substrates at higher temperature.

1.5 Goal of The Research

The objective of this research is to develop facile halogenations of *N*-heteroaromatic hydroxy compounds utilizing PPh_3/halogenating agent by varying type and amount of halogenating agents, solvent system and reaction time, and to investigate the scope and limitation of this developed method by two protocols: conventional heating method, and a MW assisted synthesis.

CHAPTER II

EXPERIMENTAL

2.1 Instruments and Equipment

Thin layer chromatography (TLC) was performed on aluminium sheets pre-coated with silica gel (Merck's, Kieselgel 60 PF_{254}). Column chromatography was performed on silica gel (Merck's silica gel 60 G Art 7734 (70-230 mesh)). Chromatotron (model 7924 T, Harrison Research) on silica gel plate of 1 mm thickness was used for centrifugal thin layer chromatography.

The ^{1}H and ^{13}C NMR spectra were performed in $CDCl_3$ with tetramethylsilane (TMS) as an internal reference on Varian nuclear magnetic resonance spectrometer, model Mercury plus 400 NMR spectrometer which operated at 399.84 MHz for ^{1}H and 100.54 MHz for ^{13}C nuclei. The chemical shifts (δ) are assigned by comparison with residue solvent protons.

The MW assisted reactions were conducted on CEM Discover 300W single-mode microwave instrument. The vessels used were special glass tubes with self-sealing septa to control pressure with appropriate sensors on the top.

HPLC was conducted on Waters 600 controller equipped with a waters 2996 photodiode array detector (USA). Alltima C18 4.6 x 250 mm I.D., 5 μm column was used for separation purpose.

2.2 Chemicals

All solvents used in this research were purified prior to use by standard methodology. The reagents used for synthesis were purchased from Fluka chemical company or otherwise stated and were used without further purification.

2.3 Preparation of Brominating Agents

Ethyl tribromoacetate [31]

One mL of concentrated H_2SO_4 was cautiously added to the mixture of Br_3CCO_2H (11.87 g, 40 mmol, 1 equiv) and EtOH 4.5 mL. The mixture was refluxed for 6 h and then poured into 100 mL of water in a separatory funnel. The upper layer of crude ester was removed and washed with 50 mL of water, saturated aqueous $NaHCO_3$ and water, respectively, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*.

Ethyl tribromoacetate: colorless oil (80%). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.42 (3H, t, J = 7.1 Hz) and 4.45 (2H, q, J = 7.1 Hz), ^{13}C NMR ($CDCl_3$) δ (ppm): 13.7, 29.5, 65.7 and 161.9.

Hexabromoacetone [32]

Anhydrous NaOAc 7 g was mixed with 20 mL of glacial CH_3CO_2H. The reaction mixture was stirred and heated to 60^{o}C. Acetone 1.4 mL was added and followed by dropwise addition of Br_2 5 mL over a 10 min period with stirring. The mixture was then heated to 95^{o}C for 2 h. After, it was cooled to RT and mixed with 100 mL of water to precipitate the desired product as a white solid. After air drying, the pure product was obtained upon recrystallization from *n*-hexane.

Hexabromoacetone: white solid (60%), ^{13}C NMR ($CDCl_3$) δ (ppm): 24.5 and 173.5.

2.4 Synthesis of *N*-Heteroaromatic Halides by Conventional Heating

2.4.1 General Procedure for the Synthesis *N*-Heteroaromatic Chlorides

A stirred solution of *N*-heteroaromatic hydroxy compound 0.25 mmol (1 equiv.) and PPh_3 0.75 mmol (0.1967 g, 3 equiv.) in toluene was successively added a selected chlorinating agent 0.375 mmol (1.5 equiv.) at reflux temperature. After stirring for 4 h, the reaction mixture was stopped. The reaction mixture was purified

by chromatotron or quantified by HPLC using isocratic water/MeOH (90:10) as mobile phase, flow rate 1.0 mL/min for 20 min, and injection volume 10 μL.

2.4.2 Optimum Conditions for the Conversion of *N*-Heteroaromatic Hydroxy Compounds to *N*-Heteroaromatic Chlorides

2-Hydroxypyridine was used as a model compound. Several factors including type of chlorinating agent, mole ratio of PPh_3 and chlorinating agent, reaction time and solvent were varied to explore the efficiency of the reaction.

2.4.2.1 Effect of Type of Chlorinating Agents

The conversion of 2-hydroxypyridine to 2-chloropyridine was carried out using the reaction conditions as described in the general procedure. Seven different chlorinating agents including Cl_3CCN, $Cl_3CCOCCl_3$, Cl_3CCO_2Et, Cl_3CCCl_3, CCl_4, Cl_3CCONH_2, and NCS were utilized.

2.4.2.2 Effect of Mole Ratio of PPh_3 and Chlorinating Agents

The ratios of $PPh_3/Cl_3CCOCCl_3$ and PPh_3/Cl_3CCN for the synthesis of *N*-heteroaromatic cholides were varied: 3:0, 2:2, 3:2, 3:1, 3:1.5 and 3:3. The yield of *N*-heteroaromatic chorides was determined in the crude mixture by HPLC.

2.4.2.3 Effect of Reaction Time

According to the general procedure, variation of reaction time as 1-8 h was conducted to observe the effect of reaction time.

2.4.2.4 Effect of Solvents

The general reaction was carried out using four different extra solvents (2.5 mL): CH_2Cl_2, CH_3CN, tolune and *p*-xylene at reflux temperature for 4 h.

2.4.3 General Procedure for the Synthesis *N*-Heteroaromatic Bromides

A stirred solution of *N*-heteroaromatic hydroxy compound 0.25 mmol (1 equiv.) and PPh_3 0.75 mmol (0.1967 g, 3 equiv.) in toluene was successively added

selected brominating agent 0.25 mmol (1 equiv.) at reflux temperature. After stirring for 8 h, the reaction mixture was stopped. The quantity of 2-bromopyridine in the crude mixture was determined by HPLC using isocratic water/methanol (90:10) as mobile phase, flow rate 1.0 mL/min for 20 min, and injection volume 10 μL or isolated by chromatotron.

2.4.4 Optimum Conditions for the Conversion of *N*-Heteroaromatic Hydroxy Compounds to *N*-Heteraromatic Bromides

2.4.4.1 Effect of Type of Brominating Agents

According to the general procedure, four types of brominating agents: CBr_4, Br_3CCO_2Et, $Br_3CCOCBr_3$ and NBS were selected to compare their effects on the reaction efficiency.

2.4.4.2 Effects of Mole Ratio of PPh_3 and CBr_4

The selected brominating agent was added to the mixture of 2-hydroxypyridine and PPh_3 in toluene. The ratio of PPh_3 and brominating agent examined were as follows: 1:1, 2:1, 2:1.5, 3:1 and 3:1.5. The quantity of 2-bromopyridine in the crude mixture was determined by HPLC.

2.4.4.2 Effects of Reaction Time

The reaction time was varied as follows: 4, 6 and 8 h. 2-bromopyridine occurred in the reaction mixture was quantified by HPLC.

2.4.5 The Synthesis of *N*-Heteroaromatic Halides

The halogenation of *N*-heteroaromatic hydroxy compounds using a suitable ratio of PPh_3 and selected halogenating agent at reflux temperature was conducted. Eight different *N*-heteroaromatic hydroxy compounds including 2-, 3-, 4-hydroxypyridines, 2- and 8-hydroxyquinolines, 4-hydroxy, 4-hydroxy-6-nitro and 4-hydroxy-6,7-dimethoxyquinazoline were examined. The quantity of *N*-heteroaromatic halides in the crude mixture was determined by HPLC or purified by chromatotron.

2-Chloropyridine: colorless oil. ^{1}H NMR ($CDCl_3$) δ_H (ppm): 7.16-7.19 (1H, m), 7.28 (1H, d, J = 8.0 Hz), 7.61 (1H, td, J = 8.0 and 2.0 Hz) and 8.33-8.35 (1H, m).

2-Bromopyridine: colorless oil. ^{1}H NMR ($CDCl_3$) δ_H (ppm): 7.22-7.25 (1H, m), 7.46-7.56 (2H, m) and 8.35-8.36 (1H, m).

4-Chloropyridine: colorless oil. ^{1}H NMR ($CDCl_3$) δ_H (ppm): 7.29 (2H, d, J = 4.8 Hz), 8.50 (2H, d, J = 4.8 Hz).

2-Chloroquinoline: colorless oil. ^{1}H NMR ($CDCl_3$) δ_H (ppm): 7.34 (1H, d, J = 8.6 Hz), 7.50-7.55 (1H, m), 7.68-7.73 (1H, m), 7.77 (1H, d, J = 8.1 Hz), 7.99 (1H, d, J = 8.8 Hz) and 8.06 (1H, d, J = 8.6 Hz).

2-Bromoquinoline: yellow oil. ^{1}H NMR ($CDCl_3$) δ_H (ppm): 7.53 (1H, d, J = 8.4 Hz), 7.59 (1H, t, J = 7.5 Hz), 7.75 (1H, t J = 7.7 Hz), 7.82 (1H, d, J = 8.0 Hz), 8.00 (1H, d, J = 8.0 Hz) and 8.06 (1H, d, J = 8.5 Hz).

4-Chloroquinazoline: white solid. ^{1}H NMR ($CDCl_3$) δ_H (ppm): 7.76 (1H, dd, J = 8.0 Hz), 7.99 (1H, dd, J = 8.0 Hz), 8.09 (1H, d, J = 8.0 Hz), 8.29 (1H, d, J = 8.0 Hz) and 9.06 (1H, s).

4-Bromoquinazoline: white solid. ^{1}H NMR ($CDCl_3$) δ_H (ppm): 7.73 (1H, dd, J = 8.0 Hz), 7.95 (1H, dd, J = 8.0 Hz), 8.04 (1H, d, J = 8.0 Hz), 8.20 (1H, d, J = 8.0 Hz) and 8.97 (1H, s).

4-Chloro-6-nitroquinazoline: yellow solid. ^{1}H NMR ($CDCl_3$) δ_H (ppm): 7.86 (1H, d, J = 8.8 Hz), 8.34 (1H, s), 8.54 (1H, dd, J = 8.8, 2.8 Hz) and 8.78 (1H, d, J = 2.8 Hz).

4-Bromo-6-nitroquinazoline: white solid. ^{1}H NMR ($CDCl_3$) δ_H (ppm): 7.85 (1H, d, J = 8.8 Hz), 8.38 (1H, s), 8.53 (1H, dd, J = 8.8, 2.4 Hz) and 8.77 (1H, d, J = 2.4 Hz). ^{13}C NMR ($CDCl_3$) δ_C (ppm): 122.4, 123.0, 128.9, 129.0, 145.5, 149.5, 152.5 and 160.4.

4-Chloro-6,7-dimethoxyquinazoline: white solid. ^{1}H NMR ($CDCl_3$) δ_H (ppm): 4,05 (6H, s), 7.30 (1H, s), 7.35 (1H, s) and 8.84 (1H, s).

4-Bromo-6,7-dimethoxyquinazoline: white solid. ^{1}H NMR ($CDCl_3$) δ_H (ppm): 4,08 (6H, d, J = 3.6 Hz), 7.32 (1H, s), 7.36 (1H, s) and 8.80 (1H, s). ^{13}C NMR ($CDCl_3$) δ_C (ppm): 56.5, 56.7, 105.0, 106.9, 122.1, 148.3, 151.6, 152.3, 153.4 and 156.8.

2.5 Synthesis of *N*-Heteroaromatic Halides with the aids of MW irradiation

2.5.1 General Procedure for the Synthesis *N*-Heteroaromatic Chlorides

A selected chlorinating agent 0.25 mmol (1 equiv.) in toluene 1.0 mL was added to the mixture of *N*-heteroaromatic hydroxy compound 0.25 mmol (1 equiv.) and PPh_3 0.5 mmol (0.1311 g, 2 equiv.) in toluene 1.5 mL. The reaction mixture was heated at 150^{o}C for 20 min in a MW reactor, cooled and diluted with MeOH. The sample solution was analyzed by HPLC using isocratic water/MeOH (90:10) as mobile phase, flow rate 1.0 mL/min for 20 min and injection volume 10 μL or isolated by chromatotron.

2.5.2 Optimum Conditions for the Conversion of *N*-Heteroaromatic Hydroxy Compounds to *N*-Heteroaromatic Chlorides

2-Hydroxypyridine was used as a model compound. Several parameters including mole ratio of PPh_3 and chlorinating agent, reaction time, temperature and type of chlorinating agent was investigated.

2.5.2.1 Effect of Mole Ratio of PPh_3 and Chlorinating Agents, Reaction Time and Temperature

The general synthesis procedure of 2-chloropyridine using PPh_3 and Cl_3CCN was carried out using different mole ratios (1:1, 2:1, 2:2 and 3:3), reaction time (10 and 20 min) and temperature (100, 120, 150 and 180^{o}C).

2.5.2.2 Effect of Type of Chlorinating Agents

The conversion of 2-hydroxypyridine into 2-chloropyridine was carried out using the reaction condition descried in the general procedure using seven different chlorinating agents: Cl_3CCN, $Cl_3CCOCCl_3$, Cl_3CCCl_3, Cl_3CCO_2Et, Cl_3CCONH_2, CCl_4 and NCS.

2.5.3 General Procedure for the Synthesis *N*-Heteroaromatic Bromides

A typical procedure involved the reaction of 2-hydroxypyridine 0.25 mmol (0.238 g, 1 equiv.), PPh_3 0.50 mmol (0.1311 g, 2 equiv.) and CBr_4 0.25 mmol (0.0829 g, 1 equiv.) in toluene 2.5 mL at 150^{o}C for 20 min. The product was separated by chromatotron or quantified by HPLC using isocratic water/MeOH (90:10) as mobile phase, flow rate 1.0 mL/min for 20 min, injection volume 10 μL.

2.5.4 Optimum Conditions for the Conversion of *N*-Heteroaromatic Hydroxy Compounds to *N*-Heteroaromatic Bromides

2.5.4.1 Condition Optimization of Bromination of *N*-Heteroaromatic Hydroxy Compounds

According to the general procedure, the variation of mole ratio of PPh_3 and brominating agent as 1:1 and 2:1, reaction time as 10 and 20 min and temperature of 110, 150 and 180^{o}C was explored to observe those effects on the bromination of 2-hydroxyquinoline by MW assisted technique. The quantity of 2-bromopyridine in the crude mixture was determined by HPLC.

2.5.4.2 Effects of Type of Brominating Agents

The suitable condition using MW assisted heating was carried out using different brominating agents: CBr_4, Br_3CCO_2Et, $Br_3CCOCBr_3$ and NBS.

2.5.5 The Synthesis of Other *N*-Heteroaromatic Halides and related compounds

The reaction of PPh_3 0.5 mmol (0.1311 g, 2 equiv.) and selected halogenating agent 0.25 mmol (1 equiv.) with various heteroaromatic hydroxy compounds (0.25 mmol, 1 equiv.): 2-, 3-, 4-hydroxypyridines, 2- and 8-hydroxyquinolines, 4-hydroxy,

4-hydroxy-6-nitro and 4-hydroxy-6,7-dimethoxyquinazoline and 2-, 7-hydroxycoumarin in toluene were heated in a MW reactor. The reaction mixture was analyzed by HPLC or purified by chromatotron.

4-Chlorocoumarin: white solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 6.56 (1H, s), 7.31-7.38 (2H, m), 7.57-7.61 (1H, m) and 7.83 (1H, d, J = 8.0 Hz)**.**

4-Bromocoumarin: white solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 6.81 (1H, s), 7.27-7.34 (2H, m), 7.54-7.58 (1H, m) and 7.79 (1H, d, J = 8.0 Hz)**.**

7-Chlorocoumarin: white solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 6.42 (1H, d, J = 9.6 Hz), 7.26-7.28 (1H, m), 7.35 (1H, s), 7.42 (1H, d, J = 8.0 Hz) and 7.67 (1H, d, J = 9.6 Hz)**.**

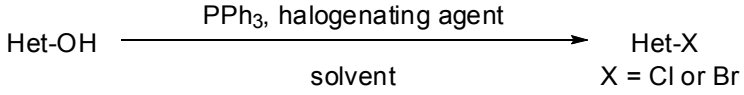
7-Bromocoumarin: white solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 6.44 (1H, d, J = 9.6 Hz), 7.34 (1H, d, J = 8.0 Hz), 7.41 (1H, d, J = 8.0 Hz), 7.51 (1H, s), and 7.66 (1H, d, J = 9.6 Hz)**.**

CHAPTER III

RESULTS AND DISCUSSION

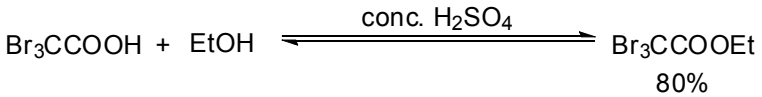
The conversion of *N*-heteroaromatic hydroxy compounds into *N*-hetero-aromatic halides is a useful protocol since the derived products are important intermediates which can further be transformed to other more valuable compounds. For instance, (κ^2-N,O)-salicylaldiminato nickel(II)-methyl pyridine complexes are known useful for the catalysts of polymerization of polyethylene [1-2]. The common methods have been addressed using a variety of reagents such as $POCl_3$, $POBr_3$, PCl_5 and $SOCl_2$ [12, 33-34]. Nevertheless, there are still several drawbacks of employing such common reagents, for instance, sensitivity to moisture, difficulty to handle and in some cases HCl or SO_2 gases generated.

The purposes of this research are to explore a new, efficient and convenient method for the chlorination and bromination of *N*-heteroaromatic hydroxy compounds using PPh_3/chlorinating or brominating agents under acid-free conditions. The general equation can be simplified as shown below.



3.1 Preparation of Authentic Samples and Reagents

Two brominating agents: Br_3CCO_2Et and $Br_3CCOCBr_3$ used in this research were synthesized. The first brominating agent can be accomplished by the esterification of Br_3CCO_2H with EtOH in the presence of conc H_2SO_4 as a catalyst affording Br_3CCO_2Et in 80%.



The ^{1}H NMR spectrum of Br_3CCO_2Et (Fig 3.1) revealed two peaks of a methyl group at δ_H 1.40 (t, J = 7.2 Hz, 3H) and a methylene group at δ_H 4.43 (q, J = 7.2 Hz, 2H).

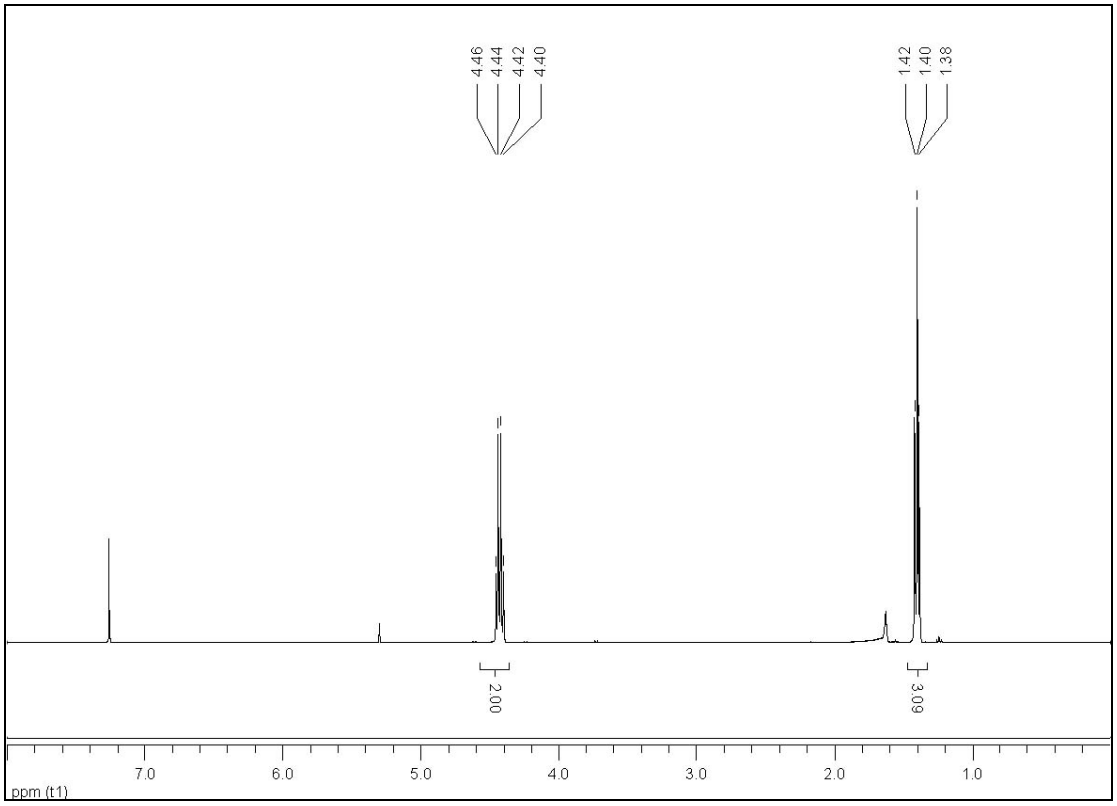
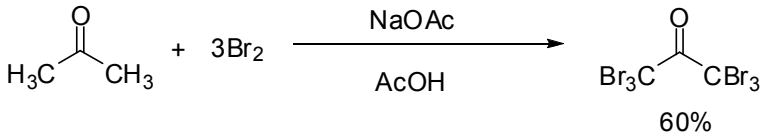


Figure 3.1 The ^{1}H NMR spectrum of Br_3CCO_2Et

The synthesis of $Br_3CCOCBr_3$ could be achieved by the reaction of acetone, Br_2 and NaOAc in glacial CH_3CO_2H as previously described [19]. The ^{13}C NMR spectrum (Fig 3.2) displays a carbonyl carbon peak at δ_C 173.5 while the peak at δ_C 24.5 can be referred to a carbon bearing three bromine atoms.



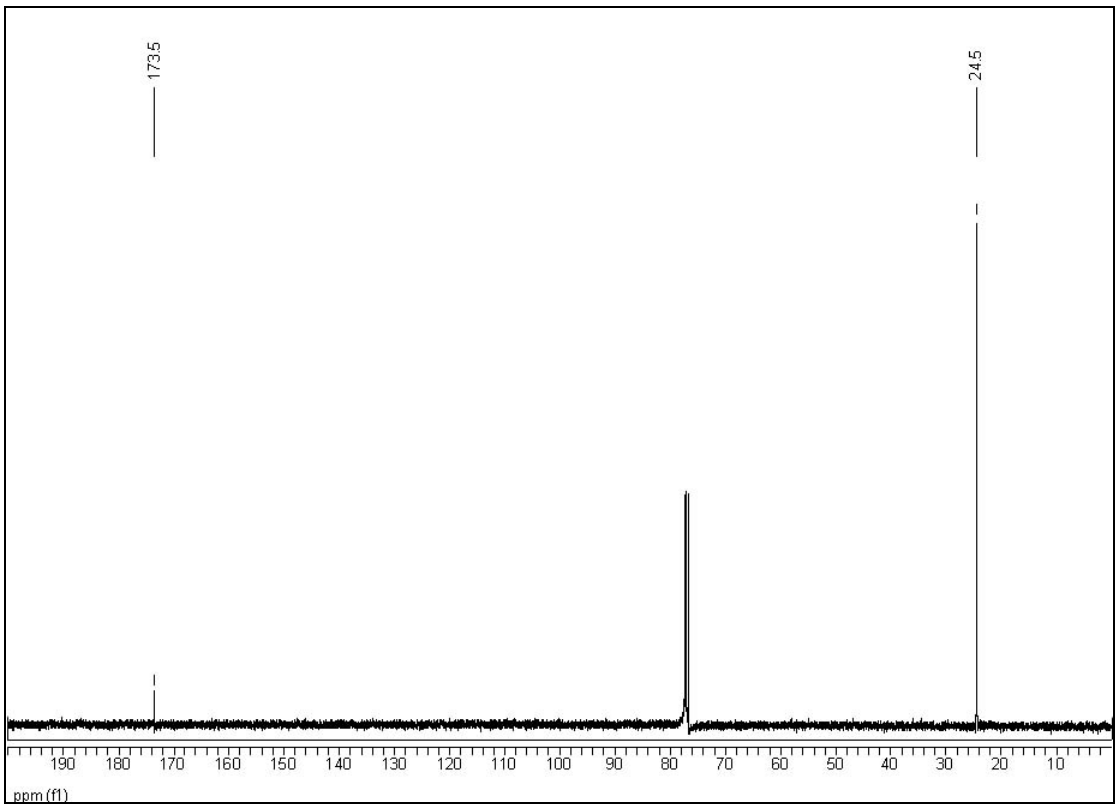


Figure 3.2 The ^{13}C NMR spectrum of $Br_3CCOCBr_3$

3.2 Synthesis of *N*-Heteroaromatic Halides by Conventional Heating

3.2.1 Optimum Conditions for the Conversion of *N*-Heteroaromatic Hydroxy Compounds to *N*-Heteroaromatic Chlorides

To search for optimum conditions for the chlorination of *N*-heteroaromatic hydroxy compounds, the effects of type of chlorinating agent, mole ratio of PPh_3 and chlorinating agent, reaction time and solvent were investigated. 2-Hydroxypyridine was selected as a model substrate and %yield of the target compound, 2-chloropyridine was quantified by HPLC in the crude mixture. An example of the HPLC chromatogram of the reaction mixture from the chlorination of 2-hydroxypyridine with PPh_3/CCl_4 is presented in Fig 3.3.

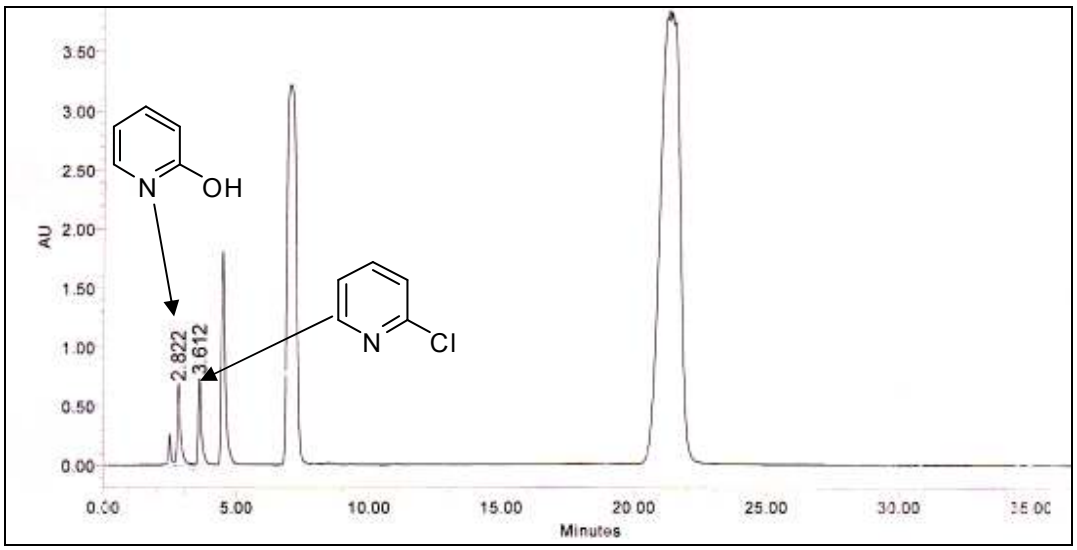


Figure 3.3 HPLC chromatogram of the crude mixture from the reaction between 2-hydroxypyridine and PPh_3/CCl_4

From Fig 3.3, the HPLC chromatogram displays the peaks of 2-hydroxypyridine and 2-chloropyridine at 2.82 and 3.61 min, respectively. The peak areas were taken to calculate for the percentage yield of product by calibration curve method. Linear calibration curves of 2-chloropyridine and 2-hydroxypyridine were constructed using five different concentrations. The calibration curves of standard compounds are shown in Figs 3.4 and 3.5.

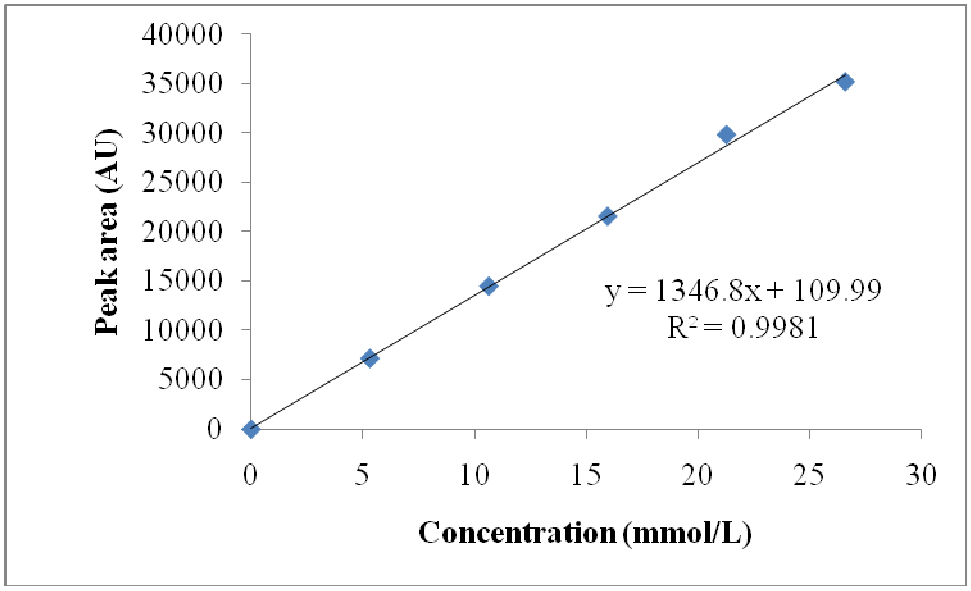


Figure 3.4 The calibration curve of 2-chloropyridine

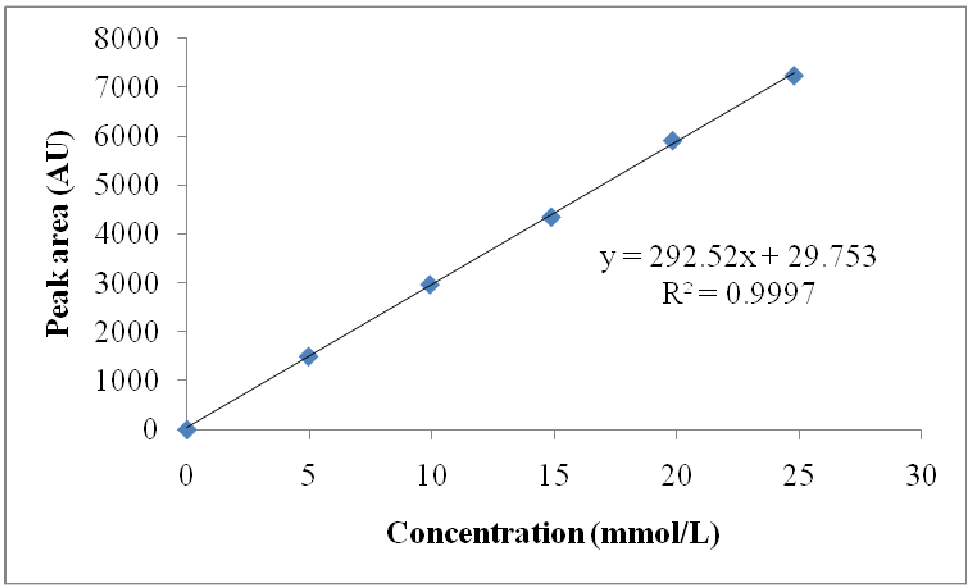


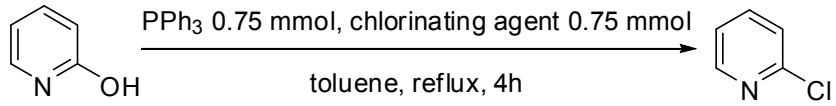
Figure 3.5 The calibration curve of 2-hydroxypyridine

Figures 3.4 and 3.5 show the correlation coefficient (R^2) value approaching 1.00 indicating very high linear relationship within this concentration range.

3.2.1.1 Effect of Type of Chlorinating Agents

According to the literature reviews, the efficiency of chlorinating agent greatly depended on type of chlorinating agent [18]. Thus, seven selected chlorinating agents (0.75 mmol) was treated with 2-hydroxypyridine (0.25 mmol) in the presence of PPh_3 (0.75 mmol) in refluxing toluene for 4 h. The results are summarized in Table 3.1.

Table 3.1 Effects of type of chlorinating agents on the chlorination of 2-hydroxypyridine



0.25 mmol

Entry	Chlorinating agent	%Recovery Het-OH	%Yield Het-Cl	MB (%)
1	none	100	-	100
2	Cl_3CCN	-	101	101
3	$Cl_3CCOCCl_3$	4	99	103
4	Cl_3CCO_2Et	31	63	94
5	Cl_3CCCl_3	58	46	104
6	CCl_4	80	22	102
7	Cl_3CCONH_2	95	7	102
8	NCS	31	41	72

When the reaction was carried out in the absence of chlorinating agent, no reaction took place (entry 1). Cl_3CCN and $Cl_3CCOCCl_3$, reagents bearing an electron-withdrawing group were found to be the most reactive reagents affording the corresponding chlorides in quantitative yields (entries 2 and 3). On the other hand, other chlorinating agents including Cl_3CCO_2Et, Cl_3CCCl_3, CCl_4, Cl_3CCONH_2 and NCS provided 2-chloropyridine in low to moderate yields (entries 4-8).

According to previous literature, several methods for the conversion of *N*-heteroaromatic hydroxy compounds into *N*-heteroaromatic chlorides has been

addressed. In the case of chlorination of 2-hydroxypyridine, the use of PPh_3 and NCS in ratio 5:5 (based on substrate) furnished 2-chloropyridine in only 43% yield. Cl_3CCN and $Cl_3CCOCCl_3$ could completely proceed for the conversion of 2-hydroxypyridine. Those reagents were commercial reagents and new chlorinating agent for chlorination of *N*-heteroaromatic hydroxy compound.

In addition, 2-hydroxypyridine reacted smoothly with PPh_3/Cl_3CCN provided 2-chloropyridine in quantitative yield (entry 2). After 4 h, the reaction mixture was purified by chromatotron eluting with hexane/EtOAc (9:1). The corresponding 2-chloropyridine was fully characterized its identity by ^{1}H NMR spectrum. The ^{1}H NMR spectrum of 2-chloropyridine (Fig 3.6) showed a multiplet signal at δ_H 7.16-7.19 of a proton on a C-5. A doublet signal at δ_H 7.28 (J = 8.0 Hz) was ascribed to H-3. The triplet of doublet signal (J = 8.0 and 2.0 Hz) at δ_H 7.61 was assigned to a proton of C-4. A multiplet at δ_H 8.33-8.35 was due to a proton on a carbon connecting with nitrogen atom.

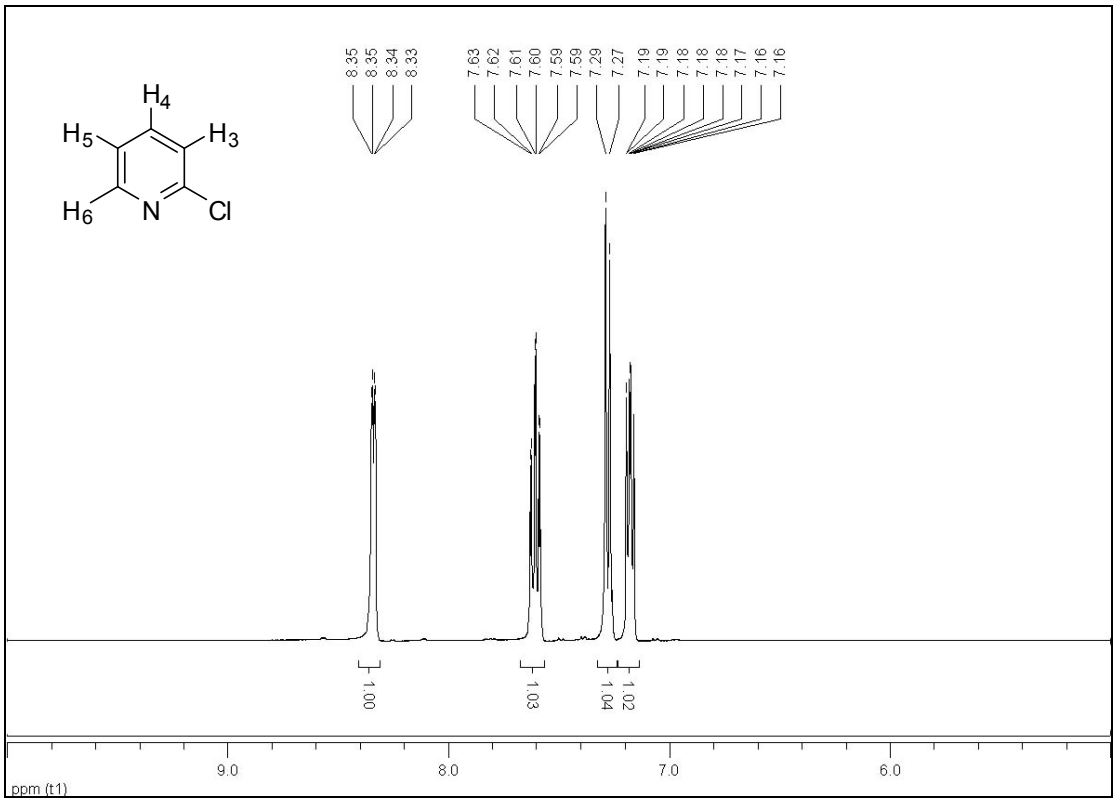
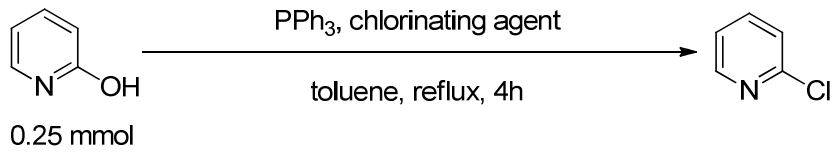


Figure 3.6 The ^{1}H NMR spectrum of 2-chloropyridine

3.2.1.2 Effect of Mole Ratio of PPh_3 and Chlorinating Agents

The ratios of PPh_3 and chlorinating agents were varied to search for the most suitable ratio that provided the maximum yield of 2-chloropyridine. $Cl_3CCOCCl_3$ and Cl_3CCN were selected as chlorinating agents and the results are demonstrated in Table 3.2.

Table 3.2 Effects of mole ratio of PPh_3 and chlorinating agent on the chlorination of 2-hydroxypyridine



Entry	Chlorinating agent	Mole ratio[a]		%Recovery Het-OH	%Yield Het-Cl	MB (%)
		PPh_3	Chlorinating agent			
1	$Cl_3CCOCCl_3$	3	0	99	NR	99
2		2	2	47	58	105
3		3	2	14	89	103
4		3	3	4	99	103
5	Cl_3CCN	1	0.5	96	5	101
6		3	1	31 (12)[b]	60 (92)[b]	91 (104)[b]
7		3	1.5	-	99	99
8		2	1.5	35	64	99
9		3	3	-	101	101

[a] Based on 2-hydroxypyridine

[b] 8 h was used

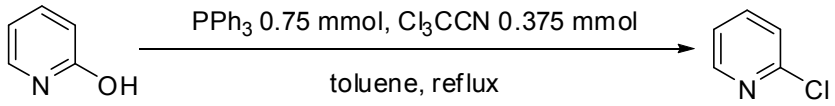
Table 3.2 reveals that when the reaction was performed in the absence of PPh_3, none of 2-chloropyridine was obtained (entry 1). This was clearly demonstrated that PPh_3 was important for this reaction. Using PPh_3:$Cl_3CCOCCl_3$ 3:3, the target compound could be achieved in almost quantitative yield (entry 4). Decreasing the ratio of PPh_3:$Cl_3CCOCCl_3$ to 2:2 and 3:2, the yield of the desired product was significantly decreased (entries 2 and 3). In the case of Cl_3CCN, only 3:1.5 mole ratio

of PPh_3:Cl_3CCN was enough to successfully convert 2-hydroxypyridine to 2-chloropyridine quantitatively (entry 7). Decreasing the amount of PPh_3 or Cl_3CCN significantly altered the yield of desired product (entries 5, 6 and 8). Nonetheless, the use of PPh_3 and Cl_3CCN in 3:1 could eventually provided the quantitative yield of the desired product when the reaction was prolonged to 8 h (entry 6). Between these two chlorinating agents, cyano group had much more electron-withdrawing effect than chloroketo group. Thus, the amount of Cl_3CCN could be used in less than that of $Cl_3CCOCCl_3$.

3.2.1.3 Effect of Reaction Time

The reaction time for the chlorination of 2-hydroxypyridine was quested for the optimized conditions. The results are presented in Table 3.3.

Table 3.3 Effects of reaction time on the chlorination of 2-hydroxypyridine



0.25 mmol

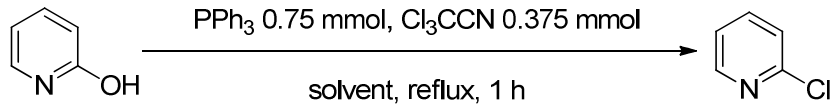
Entry	Reaction time (h)	%Recovery Het-OH	%Yield Het-Cl	MB (%)
1	1	75	44	119
2	3	20	91	111
3	4	-	99	99
4	8	-	102	102

From Table 3.3, increasing the reaction time from 4 to 8 h seemed not to reveal a significant effect on the yield of target molecule (entries 3 and 4). Forty-four and 91% yield of 2-chloropyridine was obtained when the reaction time was reduced to 1 and 3 h, respectively (entries 1 and 2).

3.2.1.4 Effect of Solvents

Various solvents were employed to observe their effects on the outcome of the reaction. The main criteria for the solvents selected included those that could make the reaction mixture at reflux temperature homogeneously. The results are displayed in Table 3.4.

Table 3.4 Effect of solvents on the chlorination of 2-hydroxypyridine



0.25 mmol

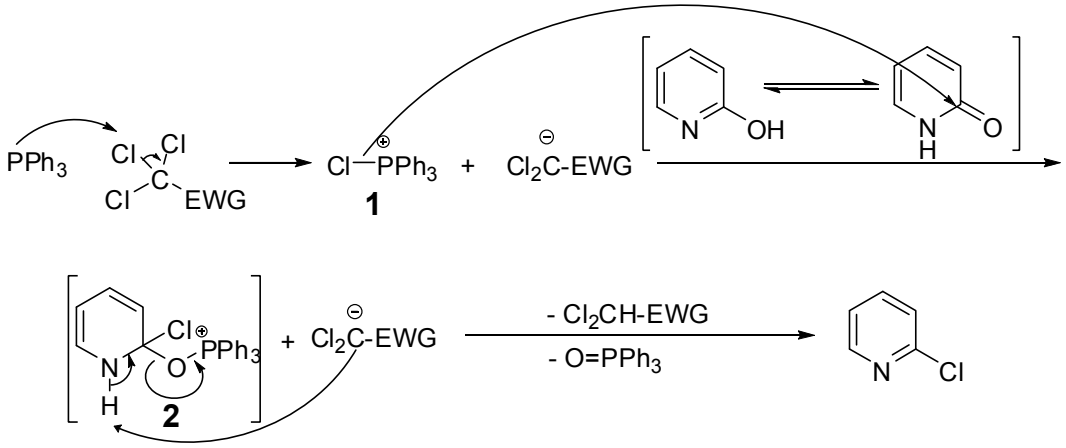
Entry	Solvent (2.5 mL)	Boiling point (°C)	%Recovery Het-OH	%Yield Het-Cl	MB (%)
1	CH_2Cl_2	40	105	NR	105
2	CH_3CN	82	100	NR	100
3	toluene	110	75	44	119
4	*p*-xylene	140	-	102	102

As the results presented in Table 3.4, no reaction occurred when CH_2Cl_2 and CH_3CN were used (entries 1 and 2). Only 44% yield of the desired product was achieved within 1 h at reflux temperature of toluene (entry 3). 2-Hydroxypyridine could be transformed to 2-chloropyridine in quantitative yield in *p*-xylene (entry 4). Because of the high boiling point of *p*-xylene, it is difficult to remove from the reaction mixture, which made the work-up process of the reaction inconvenient. After screening a number of solvents, toluene was found to suit the need for the chlorination of 2-hydroxypyridine.

3.2.1.5 The Proposed Mechanism

The mechanism for the chlorination of organic compounds such as alcohols and carboxylic acids using PPh_3/chlorinating agent has been addressed [18]. The chlorination of *N*-heteroaromatic hydroxy compounds using PPh_3/chlorinating agent was believed to operate *via* a similar mechanism (Scheme 3.1). PPh_3 reacts with Cl_3C-

EWG to generate intermediate **1**, which then reacts with *N*-heteroaromatic hydroxy compound to yield aryloxyphosphonium salt **2**. This salt eventually decomposes to give the desired *N*-heteroaromatic halide and triphenylphosphine oxide. Thus, the reactive chlorinating agent should contain an electron-withdrawing group (EWG) connecting to $–CCl_3$ to stabilize the negative charge presented in intermediate **1**.



Scheme 3.1 Proposed mechanism for the chlorination of *N*-heteroaromatic hydroxy compound using PPh_3/chlorinating agent

3.2.2 Optimum Conditions for the Conversion of *N*-Heteroaromatic Hydroxy Compounds to *N*-Heteroaromatic Bromides

Generally, *N*-heteroaromatic bromides had a better reactivity than *N*-heteroaromatic chlorides as a result of a good leaving group of bromide ion. Various factors including type of brominating agent, mole ratio of PPh_3:brominating agent and reaction time were scrutinized to evaluate for the optimal conditions for the conversion of *N*-heteroaromatic hydroxy compounds to *N*-heteroaromatic bromides. In this study, 2-hydroxypyridine was used as a model substrate and the percentage yield of 2-bromopyridine and 2-hydroxypyridine was quantified by HPLC technique from the crude mixture.

An example of HPLC chromatogram of the crude mixture of 2-hydroxypyridine with PPh_3/CBr_4 is presented in Fig 3.7.

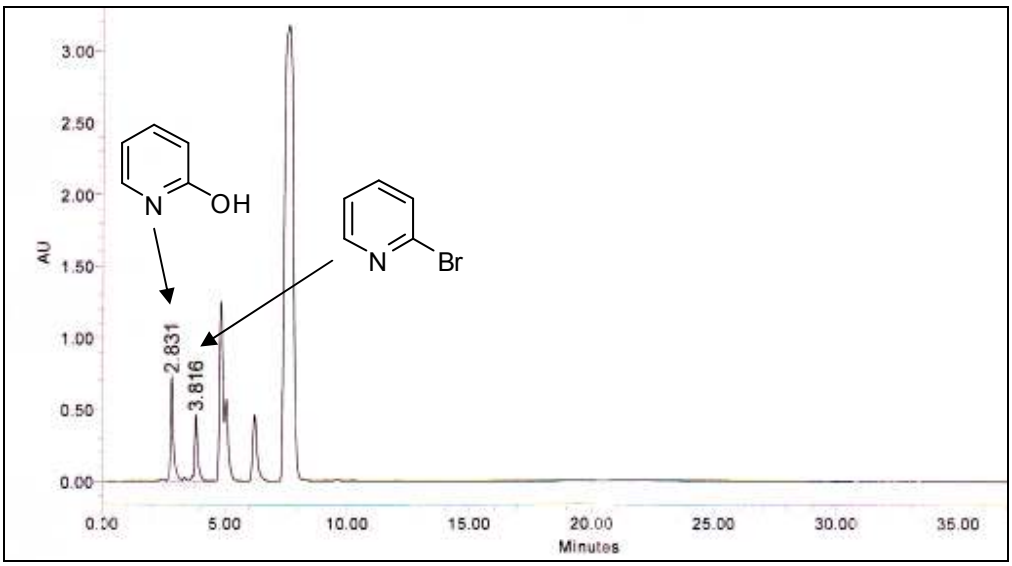


Figure 3.7 HPLC chromatogram of the reaction mixture of 2-hydroxypyridine with PPh_3/CBr_4

The HPLC chromatogram of the crude mixture displays the peak of 2-hydroxypyridine and 2-bromopyridine with sufficient resolution. The peak areas at 2.83 and 3.82 min were used to determine the percentage yields of 2-hydroxypyridine and 2-bromopyridine by comparison of the integration of the peak areas in reaction mixture with linear calibration curve of standards.

2-Bromopyridine calibration curve (Fig 3.8) was constructed using five different concentrations in the range of 10-25 mmol/L. The linear plot was obtained with excellent linear coefficient (>0.9990). This relationship confident showed that the analytical procedure can be accurately determined the amount of desired product in the reaction mixture.

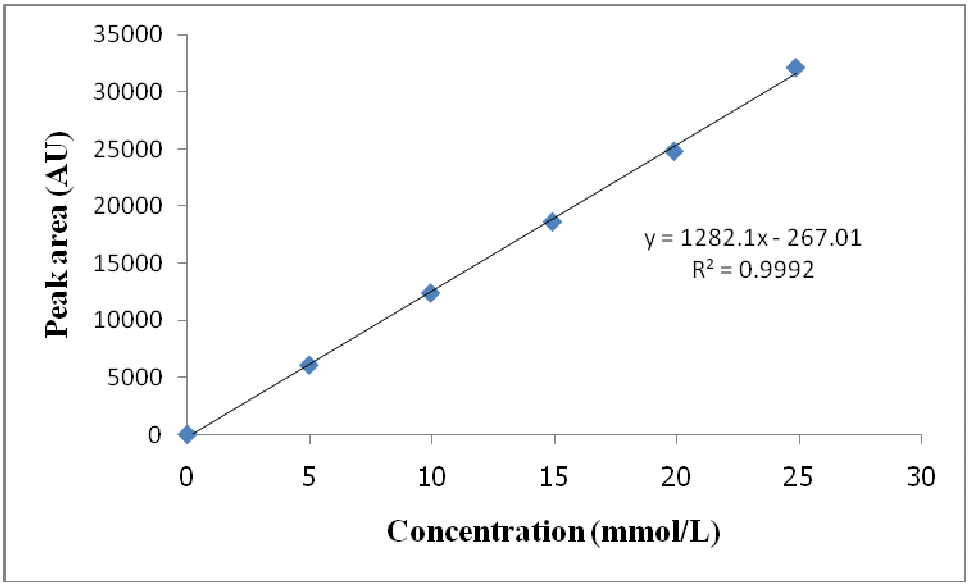
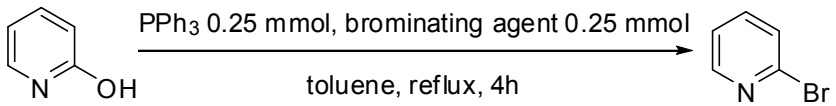


Figure 3.8 The calibration curve of 2-bromopyridine

3.2.2.1 Effect of Type of Brominating Agents

Four brominating agents: CBr_4, Br_3CCO_2Et, $Br_3CCOCBr_3$ and NBS were used in this research. The effects of types of brominating agents on the bromination of *N*-heteroaromatic hydroxy compounds were examined and the results are presented in Table 3.5.

Table 3.5 Effect of type of brominating agents on the bromination of 2-hydroxypyridine



0.25 mmol

Entry	Brominating agent	%Recovery Het-OH	%Yield Het-Br	MB (%)
1	CBr_4	81	15	96
2	Br_3CCO_2Et	97	3	100
3	$Br_3CCOCBr_3$	14	45	59
4	NBS	76	25	101

From the above results, Br_3CCO_2Et provided the desired product in low yield (entry 2). CBr_4, $Br_3CCOCBr_3$ and NBS were three promising candidates for the preparation of *N*-heteroaromatic bromide (entries 1, 3 and 4). CBr_4 and $Br_3CCOCBr_3$ can be designated as new brominating agents for bromination of *N*-heteroaromatic hydroxy compounds. Although, the combination of PPh_3 and $Br_3CCOCBr_3$ could be smoothly converted to 2-bromopyridine in high yield, several by-products were also obtained (monitoring by TLC). On the other hand, CBr_4 gave only the desired bromide. Thus, CBr_4 was chosen for further investigation.

The reaction using CBr_4 as a brominating agent provided the desired product in 15%. 2-Bromopyridine could be separated from the crude mixture by chromatotron eluting with hexane/EtOAc (9:1). This compound was characterized its identity by ^{1}H NMR spectrum. ^{1}H NMR spectrum (Fig 3.9) clearly presented a multiplet signal of H-5 at δ_H 7.22-7.25. The multiplet signal at δ_H 7.46-7.56 was due to two protons of C-3 and C-4. Another proton could be identified from the presence of a multiplet signal at δ_H 8.35.

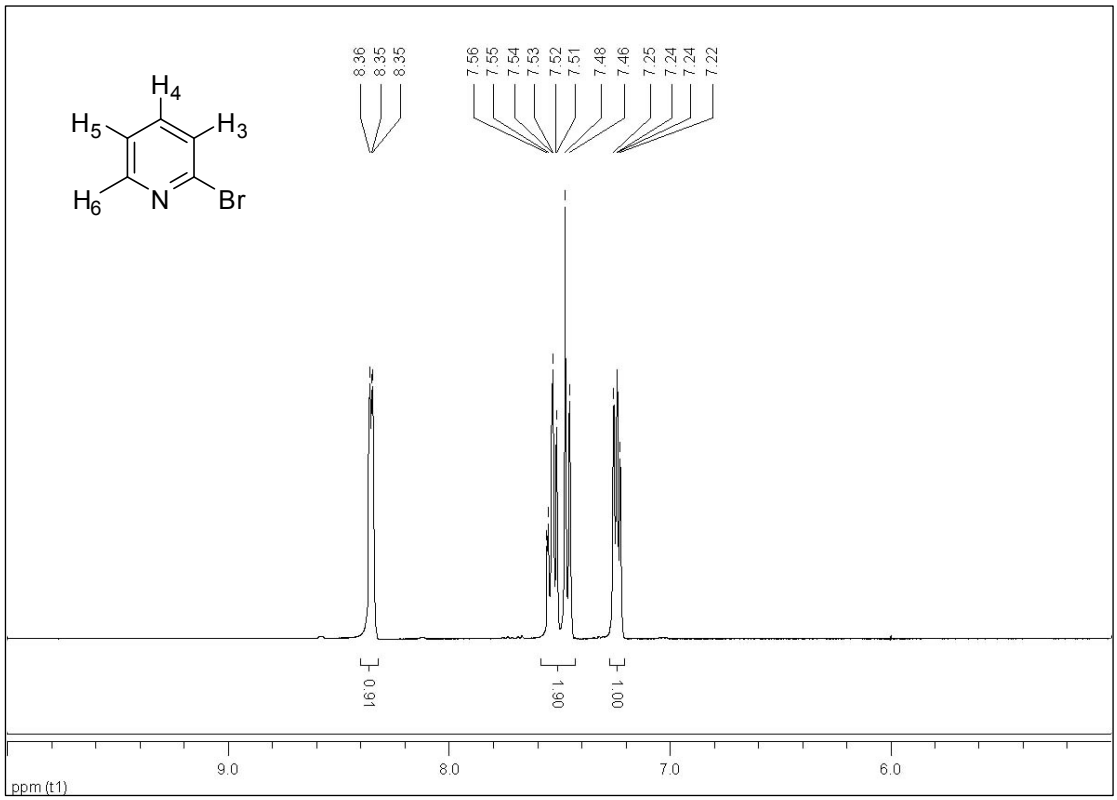
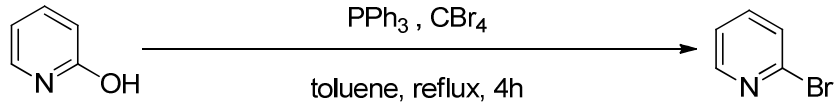


Figure 3.9 The ^{1}H NMR spectrum of 2-bromopyridine

3.2.2.2 Effect of Mole Ratio of PPh_3 and CBr_4

Two parameters: mole ratio of PPh_3 and brominating agents was investigated with the aim to attain the most appropriate conditions. The results are presented in Table 3.6.

Table 3.6 Effect of the amount of PPh_3:CBr_4 on the bromination of 2-hydroxy-pyridine



0.25 mmol

Entry	Mole ratio[a]		%Recovery	%Yield	MB
	PPh_3	CBr_4	Het-OH	Het-Br	(%)
1	1	1	81	15	96
2	2	1	31	69	100
3	2	1.5	48	61	109
4	3	1	69	30	99
5	3	1.5	69	30	99

[a] Based on 2-hydroxypyridine

From Table 3.6, several ratios of PPh_3 and CBr_4 were examined to compare the outcome of the reaction. When the ratio of PPh_3 and CBr_4 was increased from 1:1 to 2:1 and 2:1.5, the yield of the corresponding bromide increased (entries 1-3). In contrast, the yield of the desired product decreased when the ratio of PPh_3 and CBr_4 increased to 3:1 and 3:1.5 (entries 4 and 5).

Comparing the peak integration of phosphonium salt ($BrP^+Ph_3Br_3C^-$) in the reaction mixture using the mole ratio of PPh_3:CBr_4 2:1 at 2.52 min with 3:1 at 2.53 min indicated that the quantity of phosphonium salt increased in the case of the mole ratio of PPh_3:CBr_4 being 3:1 (Fig 3.10, b and c). The signal of phosphonium salt was nearly corresponded to that derived from the combination of PPh_3 and CBr_4 at 2.54 min (Fig 3.8, a). From these results, the use of PPh_3:CBr_4 in the ratio of 3:1 was selected for further examination.

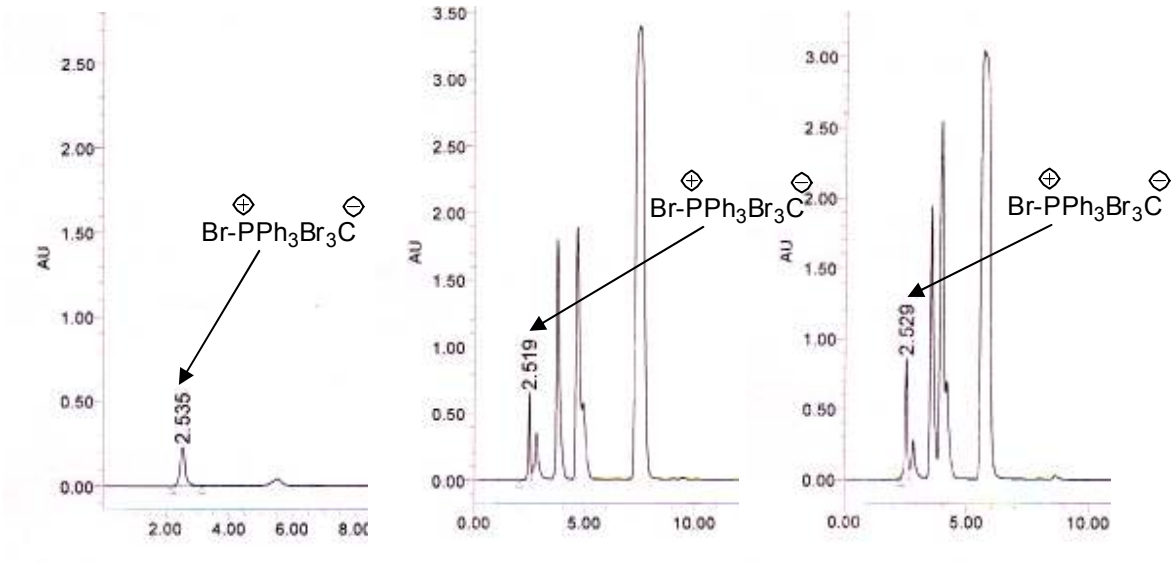
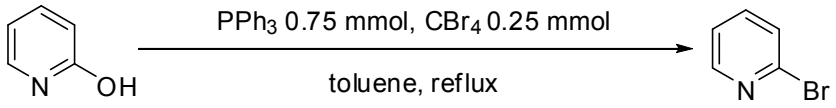


Figure 3.10 HPLC chromatograms (a) a combination of PPh_3 and CBr_4 (b) the reaction mixture using 2:1 PPh_3/CBr_4 (c) using 3:1 PPh_3/CBr_4

3.2.2.3 Effect of Reaction Time

The reaction time for the bromination of 2-hydroxypyridine was quested for the optimized conditions. The results are described in Table 3.7.

Table 3.7 Effect of reaction time on the bromination of 2-hydroxypyridine



0.25 mmol

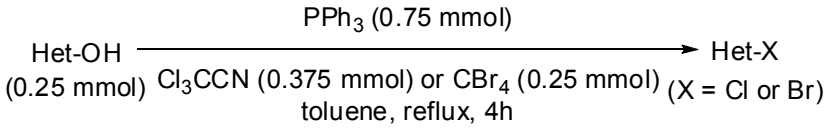
Entry	Reaction time (h)	%Recovery Het-OH	%Yield Het-Br	MB (%)
1	4	69	30	99
2	6	22	70	92
3	8	-	104	104

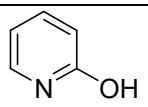
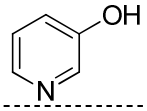
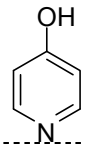
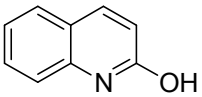
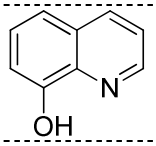
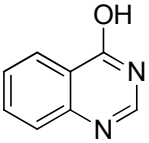
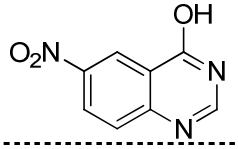
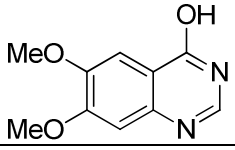
Table 3.7 shows that the reaction time had a profound effect on the yield of the target product. The synthesis of 2-bromopyridine could be quantitatively achieved by performing at refluxing toluene for 8 h.

3.2.3 The Synthesis of *N*-Heteroaromatic Halides

To investigate the generality and scope of this developed method, the preparation of *N*-heteroaromatic halides was carried out using a variety of *N*-heteroaromatic hydroxy compounds. The results are summarized in Table 3.8.

Table 3.8 The conversion of *N*-heteroaromatic hydroxy compounds to *N*-heteroaromatic halides using conventional heating



Entry	Substrate	Halogenating agent	Isolated yield (%)
1		Cl_3CCN	99[a]
2		CBr_4	104[a]
3		Cl_3CCN	NR
4		Cl_3CCN	94
5		CBr_4	-[b]
6		Cl_3CCN	95
7		CBr_4	90
8		Cl_3CCN	NR
9		Cl_3CCN	42 (87)[c] (75)[e]
10		CBr_4	37[c]
11		Cl_3CCN	31[c] (52)[e] (61)[f]
12		CBr_4	31[d] (11)[f]
13		Cl_3CCN	84[e]
14		CBr_4	61[e]

[a] quantified by HPLC
[b] product could not separate from reaction mixture
[c] 20 min was used
[d] 30 min was used
[e] 1 h was used
[f] 2 h was used

In the case of hydroxypyridines (entries 1-5), 2- and 4-hydroxypyridines could be converted into the corresponding halopyridines in high yield while 4-bromopyridine is difficult to separate from the reaction mixture because it is quickly decomposed [35]. However, 3-hydroxypyridine was not reactive enough under this condition. This may be because the nitrogen atom could not stabilize the negative charge of aryloxyphosphonium salt. Similarly, for the quinoline derivatives (entries 6-8), the halogenations of 2-hydroxyquinoline afforded 2-haloquinoline in high yield (90-95%) while 8-haloquinoline could not be formed under this condition.

The ^{1}H NMR spectrum of 4-chloropyridine (Fig 3.11) presented a doublet signal (J = 4.8 Hz) of H-3 and H-5 at δ_H 7.29 and doublet signal (J = 4.8 Hz) of H-2 and H-6 at δ_H 8.50.

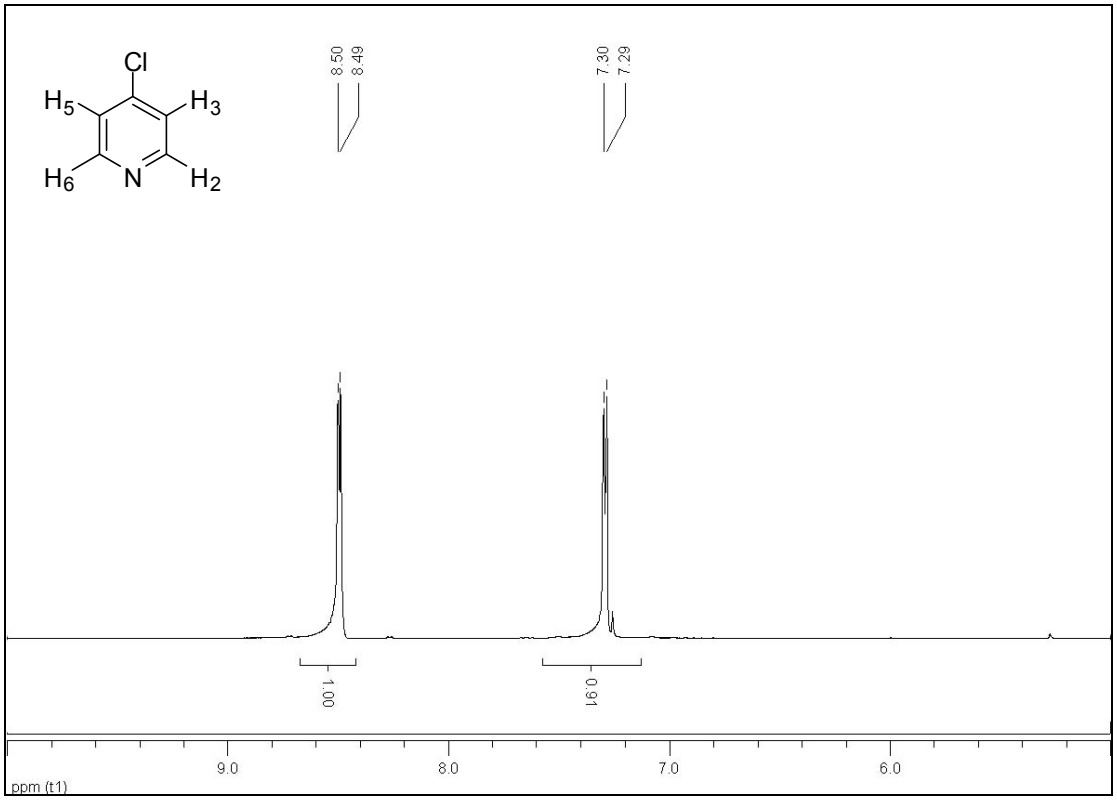


Figure 3.11 The ^{1}H NMR spectrum of 4-chloropyridine

The ^{1}H NMR spectrum of 2-chloroquinoline (Fig 3.12) displays a doublet signal (J = 8.6 Hz) of H-3 at δ_H 7.34. The signals around δ_H 7.50-7.55 were typical for H-5 to H-8. The doublet signal (J = 8.6 Hz) at δ_H 8.05 was belonged to a proton of C-4. In addition, the ^{1}H NMR spectrum of 2-bromoquinoline (Fig 3.13) contained the doublet signal (J = 8.4 Hz) at δ_H 7.53, which was indicative of H-3. The signals around δ_H 7.57-8.01 were belonged to four protons at C-5 to C-8. The doublet signal (J = 8.5 Hz) at δ_H 8.06 could be assigned for H-4.

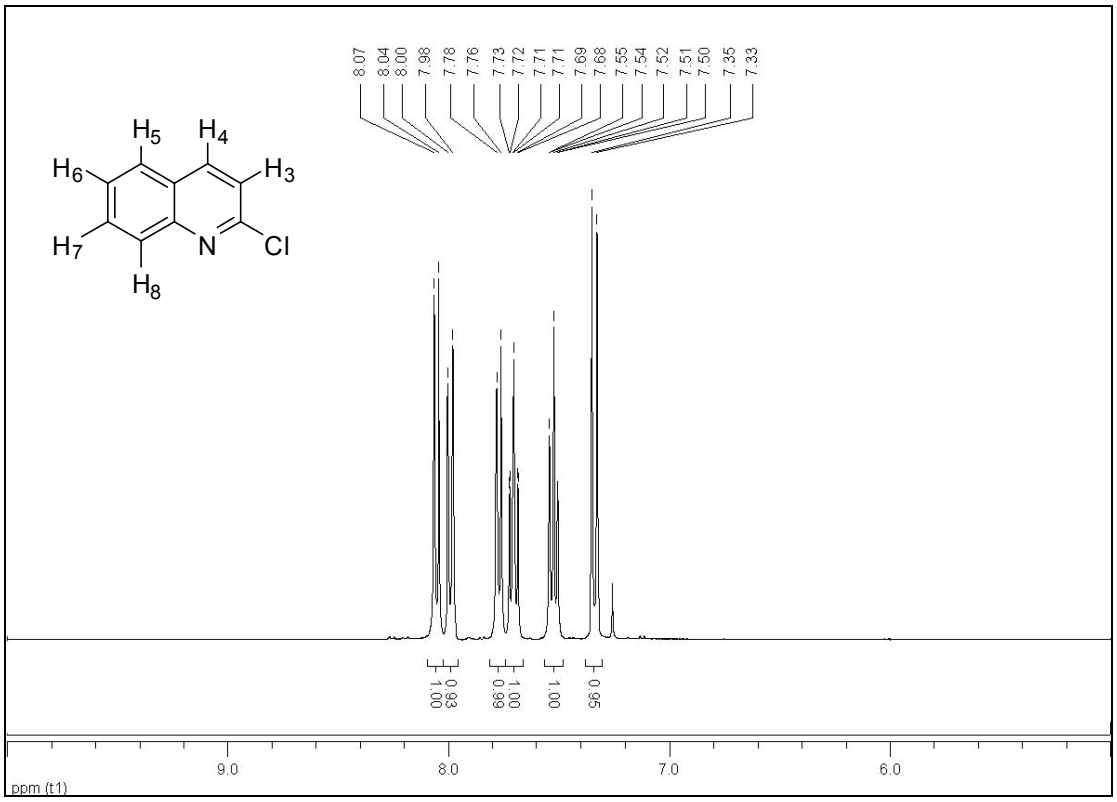


Figure 3.12 The ^{1}H NMR spectrum of 2-chloroquinoline

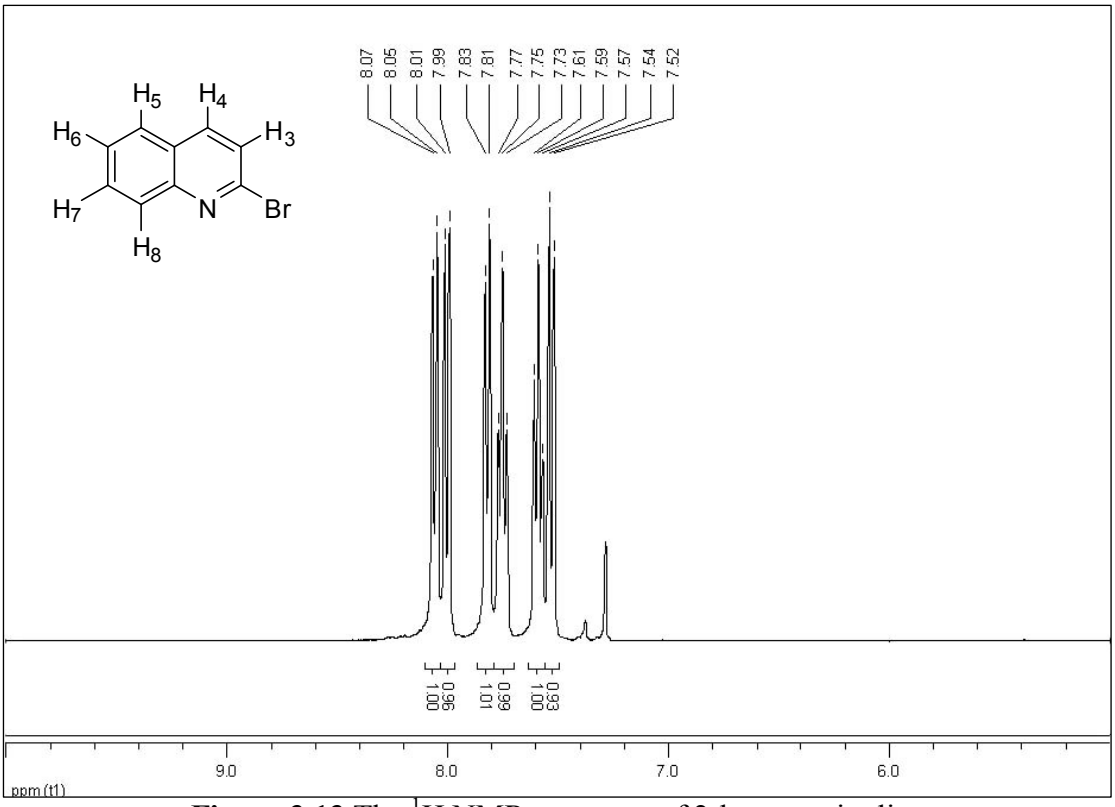


Figure 3.13 The ^{1}H NMR spectrum of 2-bromoquinoline

Two nitrogen atoms in heteroaromatic hydroxy compounds in the case of quinazoline derivetives were examined. At 4 h, the desired chloride was obtained in only 42%, several by-products were also obtained (monitoring by TLC). Because, more nitrogen atom at N-1 and N-4 exhibited high reactivity towords the nucleophilic substitution at C-4 [36]. Hence, decreasing reaction time from 4 h to 20 min and 1 h offering 4-chloroquinazoline in high yield (entry 9). Similarly, 4-hydroxyquinazoline proceeded to the corresponding bromide in 37% within 20 min (entry 10). The ^{1}H NMR spectrum of 4-chloroquinazoline (Fig 3.14) showed a pair of doublet of doublet signals (J = 8.0 Hz) at δ_H 7.76 and 7.99 of H-6 and H-7, respectively. Doublet signals at δ_H 8.09 (J = 8.0 Hz) and 8.29 (J = 8.0 Hz) were due to H-5 and H-8, respectively. The proton on carbon between two nitrogen atoms was observed from a singlet signal at δ_H 9.06. The ^{1}H NMR spectrum of 4-bromoquinazoline (Fig 3.15) displayed doublet of doublet signals (J = 8.0 Hz) at δ_H 7.73 and 7.95 of H-6 and H-7, respectively. Two doublets at δ_H 8.04 (J = 8.0 Hz) and 8.20 (J = 8.0 Hz) were assigned to H-5 and H-8, respectively. A singlet signal at δ_H 8.97 was due to a proton of carbon connecting with two nitrogen atoms.

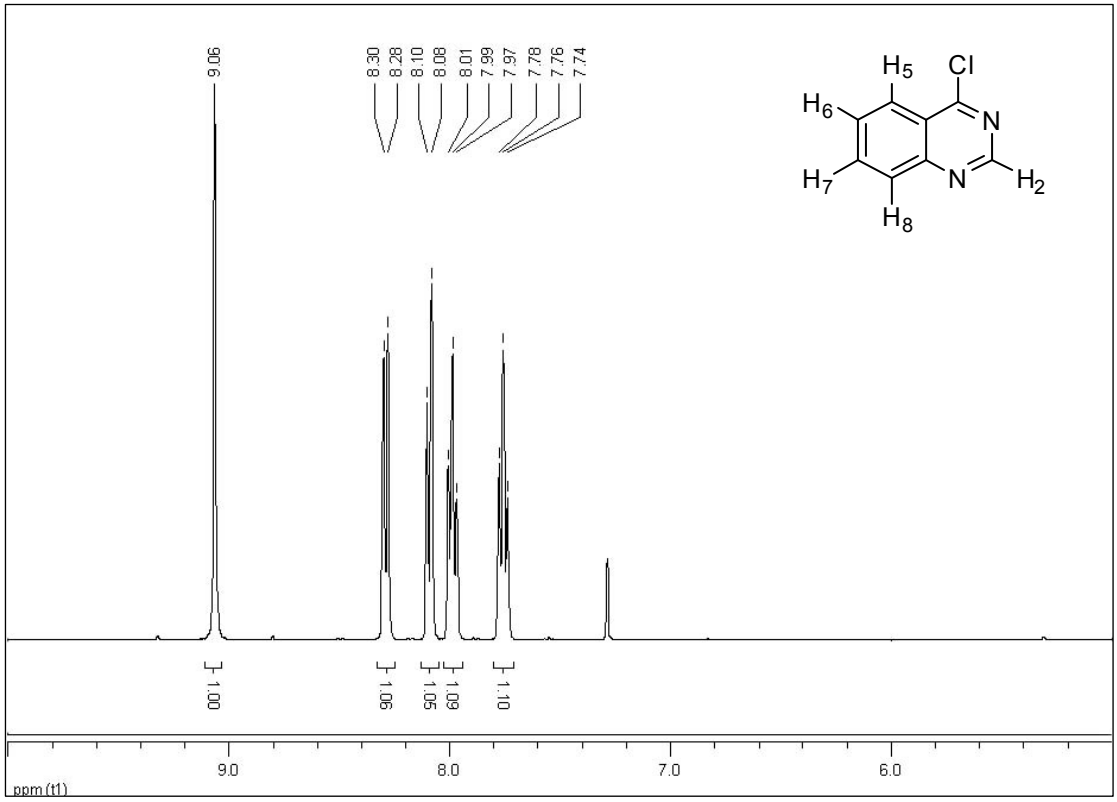


Figure 3.14 The ^{1}H NMR spectrum of 4-chloroquinazoline

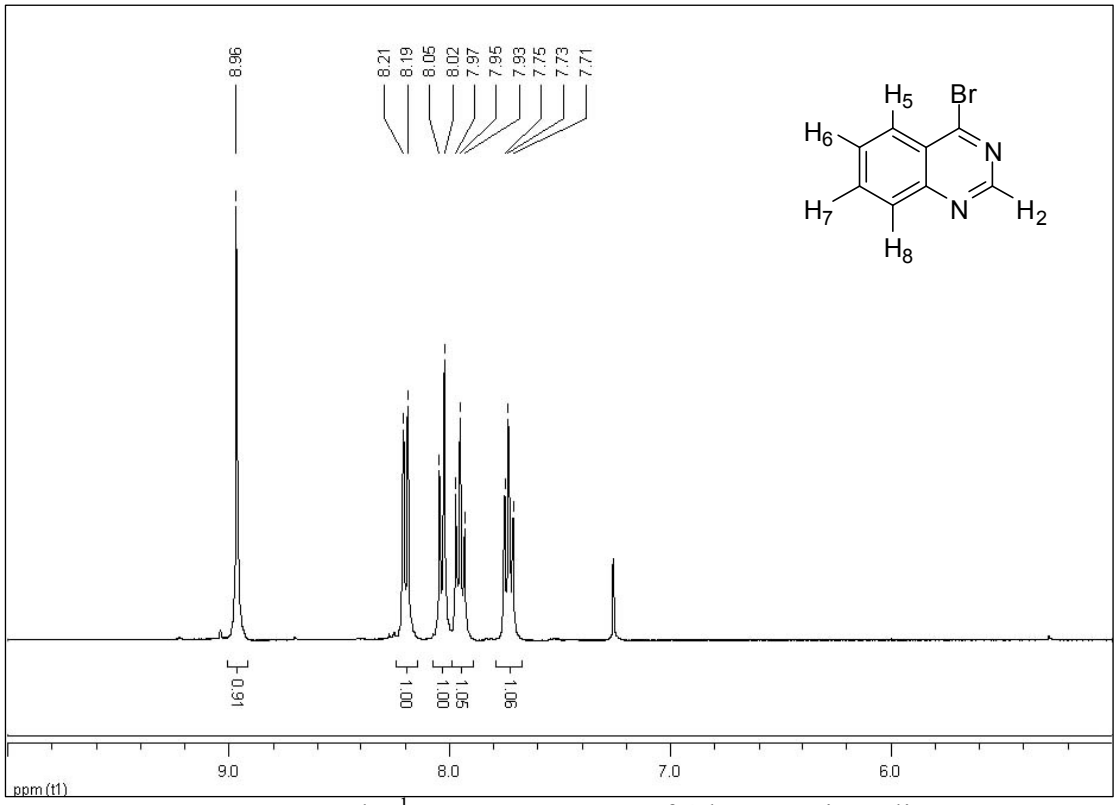


Figure 3.15 The ^{1}H NMR spectrum of 4-bromoquinazoline

4-Hydroxy-6-nitroquinazoline and 4-hydroxy-6,7-dimethoxyquinazoline were chosen to compare the effect of electron withdrawing group and electron donating group on quinazoline. At 1 h, the chlorination of 4-hydroxyquinazoline, 4-hydroxy-6-nitroquinazoline and 4-hydroxy-6,7-dimethoxyquinazoline gave desired chlorides in 75, 52 and 84% yield, respectively (entries 9, 11 and 13). From these results, it was clearly seen that the substrate bearing electron withdrawing group rendered the reactivity of the reaction [37].

In the case of 4-hydroxy-6-nitroquinazoline, 4-chloro-6-nitroquinazoline was obtained in 31% yield at 20 min. To prolong the reaction time to 1 and 2 h gave a desired bromide in 52 and 61%, respectively (entry 11). Bromination of 4-hydroxy-6-nitroquinazoline provided 31 and 11% yield of 4-bromo-6-nitroquinazoline within 20 min and 1 h, respectively (entry 12). The ^{1}H NMR spectrum of 4-chloro-6-nitroquinazoline (Fig 3.16) showed a doublet signal (J = 8.8 Hz) at δ_H 7.86 of H-8. A proton on carbon between two nitrogen atoms was observed from a singlet signal at δ_H 8.34. The doublet of doublet signal (J = 8.8 and 2.8 Hz) at δ_H 8.54 belonged to H-7. The doublet signal (J = 2.8 Hz) at δ_H 8.78 could be assigned to proton at 5-position. Moreover, there was no report on 4-bromo-6-nitroquinazoline, thus this compound is the new compound synthesized in haloheteroaromatic class. The ^{1}H NMR spectrum (Fig 3.17) of this compound presented a doublet signal (J = 8.8 Hz) at δ_H 7.85, which was indicative of H-8. A singlet signal at δ_H 8.38 could be assigned for a proton on carbon connecting with both nitrogen atoms. The doublet of doublet signal (J = 8.8 and 2.4 Hz) at δ_H 8.53 was typical of H-7. The doublet signal (J = 2.4 Hz) at δ_H 8.77 was assigned for H-5. The ^{13}C NMR spectrum (Fig 3.18) contained eight signals at δ_C 122.4, 123.0, 128.9, 129.0, 145.5, 152.5 and 160.4.

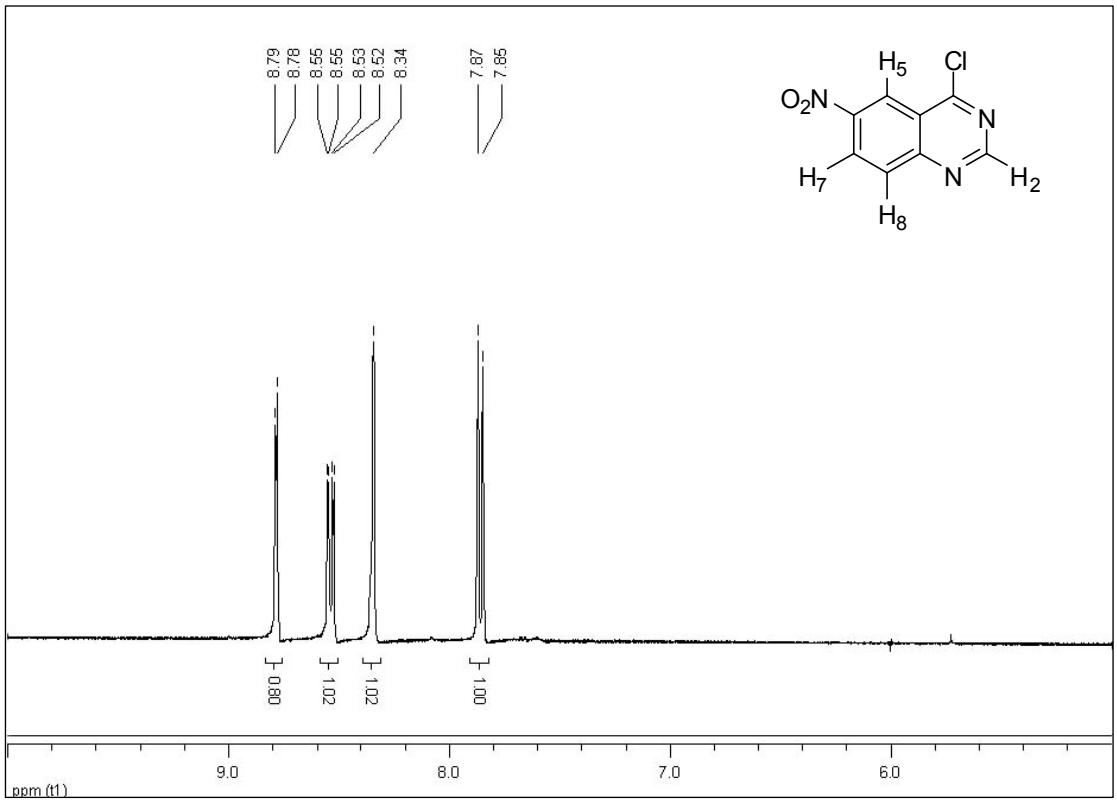


Figure 3.16 The ^{1}H NMR spectrum of 4-chloro-6-nitroquinazoline

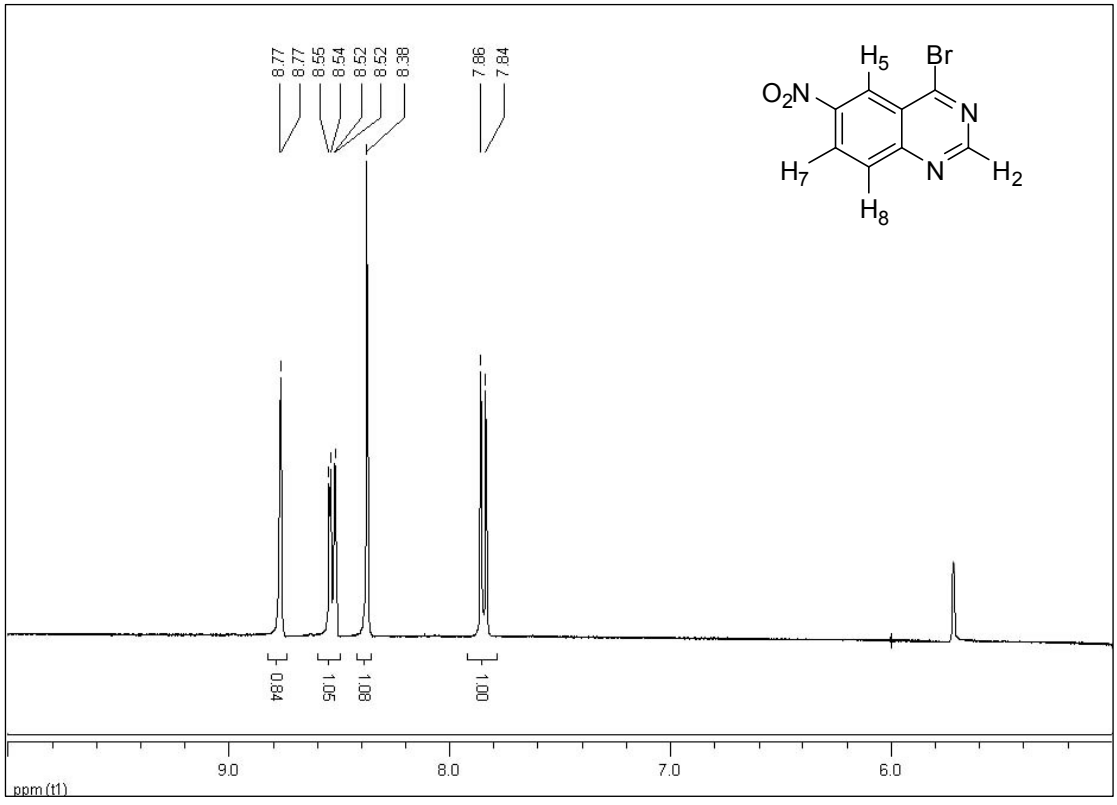


Figure 3.17 The ^{1}H NMR spectrum of 4-bromo-6-nitroquinazoline

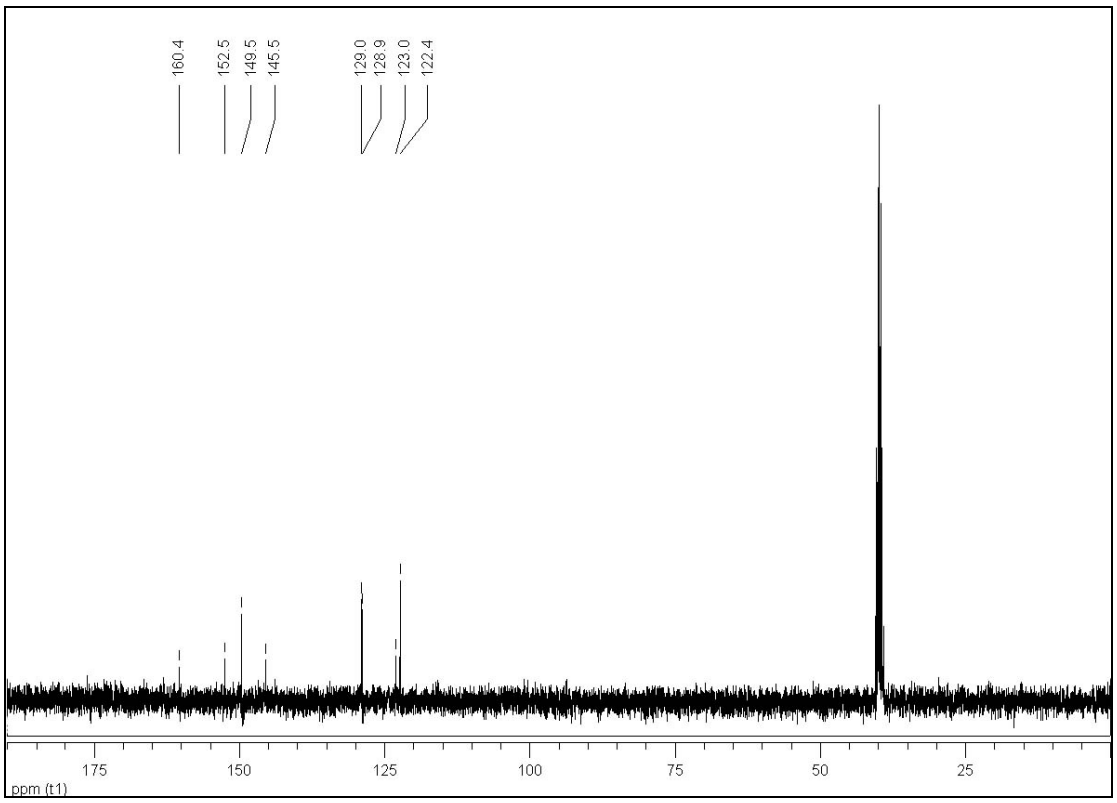


Figure 3.18 The ^{13}C NMR spectrum of 4-bromo-6-nitroquinazoline

In addition, 4-halo-6,7-dimethoxyquinazoline furnished the corresponding chloride and bromide in 84 and 61% yields, respectively (entries 13-14). The ^{1}H NMR spectrum of 4-chloro-6,7-dimethoxyquinazoline (Fig 3.19) showed a signal of six protons of methoxy group at δ_H 4.05. Three singlet signals of aromatic protons appeared at δ_H 7.30, 7.35 and 8.84. The ^{1}H NMR spectrum of 4-bromo-6,7-dimethoxyquinazoline (Fig 3.20) exhibited a doublet signal (J = 3.6 Hz) at δ_H 4.08, indicating the presence of six methoxy protons. Three singlet signals at δ_H 7.32, 7.36 and 8.80 were ascribed for three aromatic protons. The ^{13}C NMR spectrum of this compound (Fig 3.21) displayed two peaks at δ_H 56.5 and 56.7, indicating the presence of methoxy carbons. The signals around δ_C 105.0, 106.9, 122.1, 148.3, 151.6, 152.3, 153.4 and 156.8 were assigned for eight aromatic carbons.

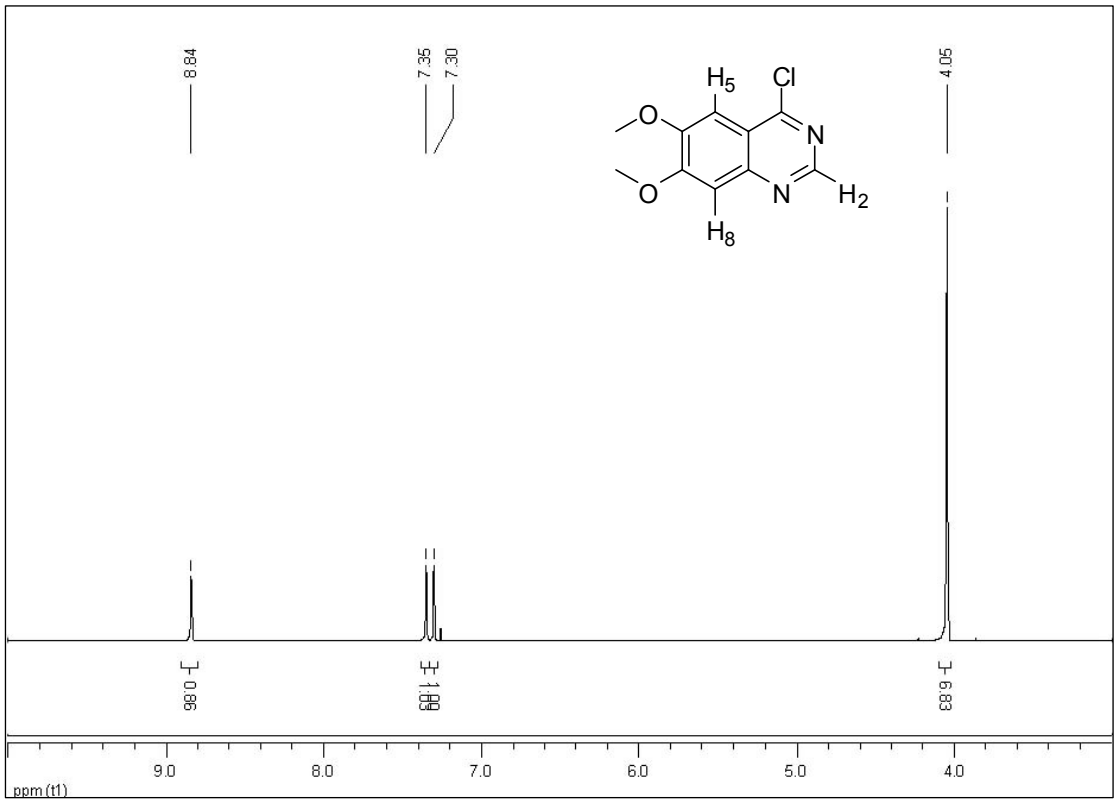


Figure 3.19 The ^{1}H NMR spectrum of 4-chloro-6,7-dimethoxyquinazoline

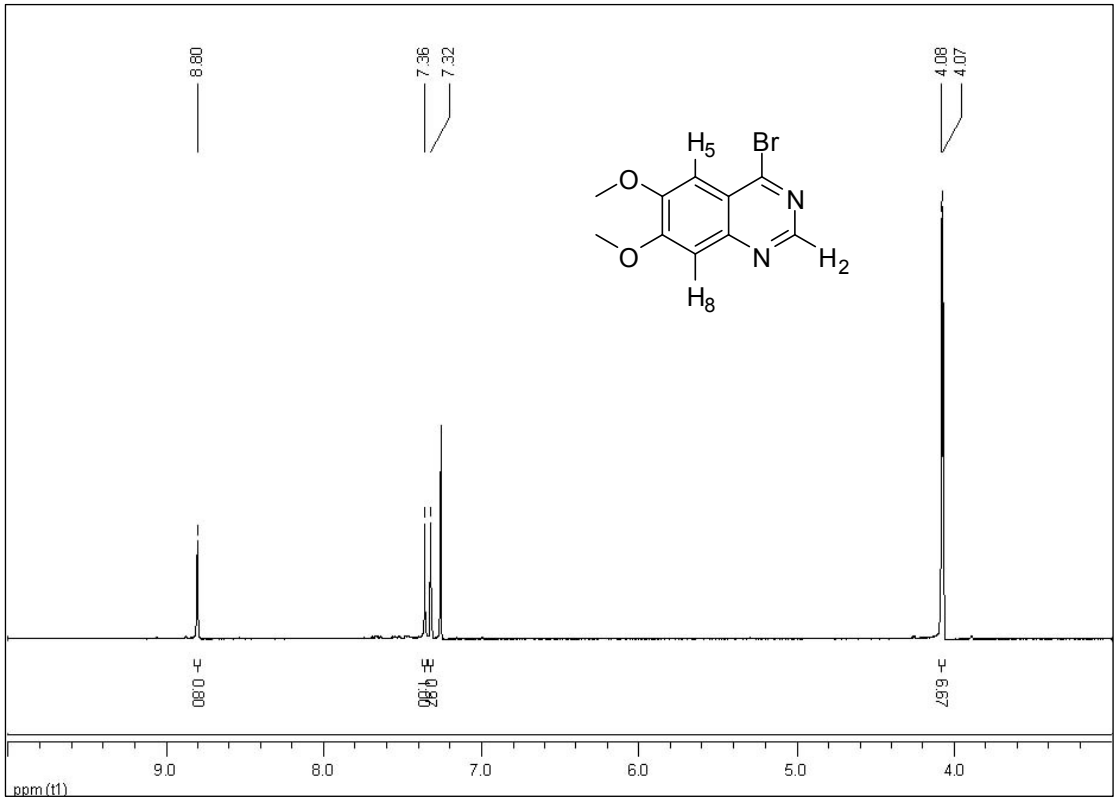


Figure 3.20 The ^{1}H NMR spectrum of 4-bromo-6,7-dimethoxyquinazoline

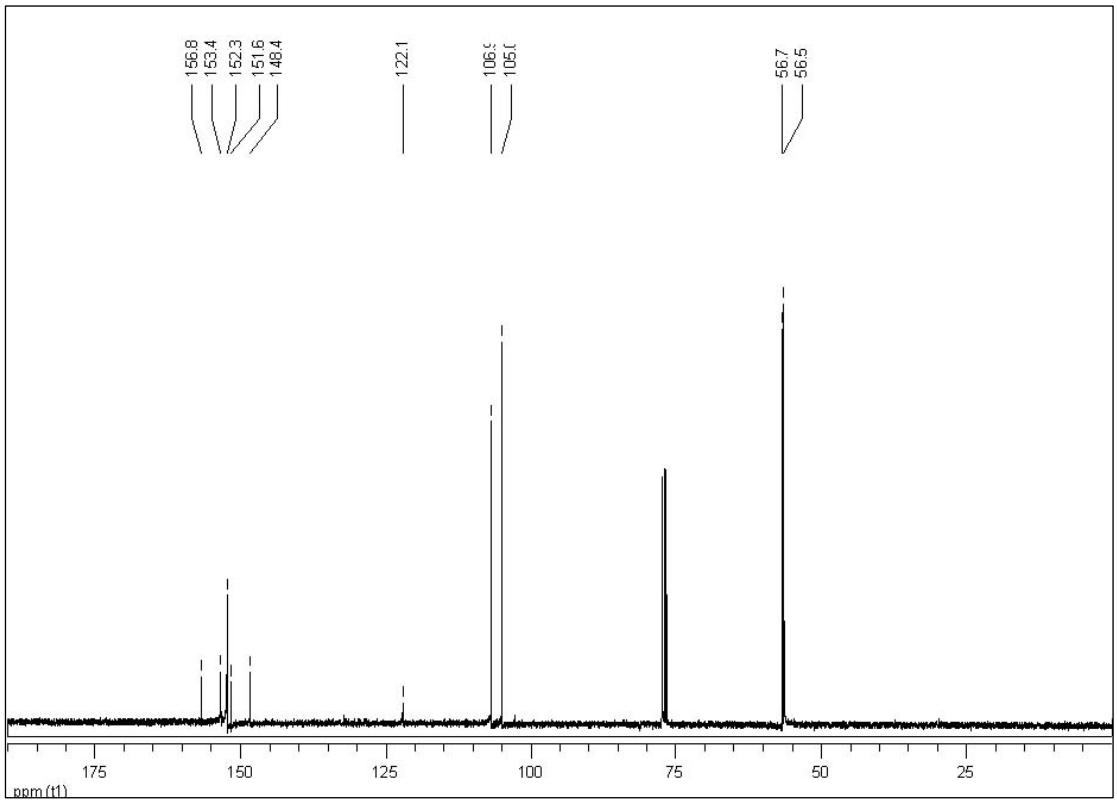


Figure 3.21 The ^{13}C NMR spectrum of 4-bromo-6,7-dimethoxyquinazoline

3.3 Synthesis of *N*-Heteroaromatic Halides by MW Irradiation

3.3.1 Optimum Conditions for the Conversion of *N*-Heteroaromatic Hydroxy Compounds to *N*-Heteroaromatic Chlorides Using MW Irradiation

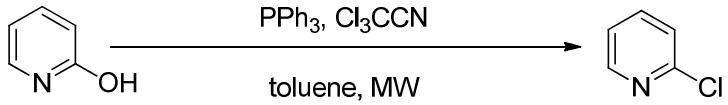
In order to reach optimum conditions for the chlorination of *N*-heteroaromatic hydroxy compounds, 2-hydroxypyridine was selected as a chemical model. Various factors including type of chlorinating agent, mole ratio of PPh_3 and chlorinating agents, reaction time and temperature were scrutinized to evaluate for the optimal conditions.

3.3.1.1 Effect of Mole Ratio of PPh_3/Cl_3CCN, Reaction Time and Temperature

From the optimum conditions for the chlorination of *N*-heteroaromatic hydroxy compounds by conventional heating, a combination of PPh_3 and Cl_3CCN was an efficient reagent for the preparation of *N*-heteroaromatic chlorides. Therefore, mole

ratio of PPh_3/Cl_3CCN and various parameters including reaction time and temperature were investigated to search for a suitable condition for the preparation of 2-chloropyridine from 2-hydroxypyridine with the aids of MW irradiation. The results are presented in Table 3.9.

Table 3.9 Effect of mole ratio of PPh_3/Cl_3CCN, reaction time and temperature on the chlorination of 2-hydroxypyridine



Entry	Temperature (^oC)	Time (min)	Mole ratio[a]		%Recovery	%Yield	MB
			PPh_3	Cl_3CCN	Het-OH	Het-Cl	(%)
1[b]	110		3	3	108	6	114
2	150	10	3	3	-	105	105
3	180		3	3	-	104	104
4			2	1	16	79	95
5		10	2	2	16	86	102
6	150		2	2	4	100	104
7		20	2	1	-	106	106
8			1	1	48	50	98

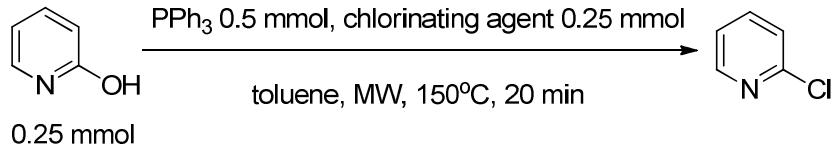
[a] based on 2-hydroxypyridine

The effect of temperature was examined to find out the most suitable ratio that produced the maximum yield of target product (entries 1-3). The temperature of 150^oC was enough to furnish 2-chloropyridine in quantitative yield (entry 2). The exploration on the mole ratio of PPh_3/Cl_3CCN was performed. The yield of 2-chloropyridine was decreased when the amounts of PPh_3:Cl_3CCN were decreased to 2:1 and 2:2 at 150^oC for 10 min (entries 4 and 5). Nevertheless, the complete reaction could be accomplished from prolonging the reaction to 20 min (entries 6 and 7). The yield of product was reduced when mole ratio of PPh_3:Cl_3CCN was 1:1 . Therefore, 2-hydroxypyridine:PPh_3:Cl_3CCN in the ratio of 1:2:1 at 150^oC for 20 min was considered as the most proper condition for the chlorination of 2-hydroxypyridine.

3.3.1.2 Effect of Type of Chlorinating Agents

The effect of type of chlorinating agents (Cl_3CCN, Cl_3CCCl_3, CCl_4, Cl_3CCO_2Et, Cl_3CCONH_2 and $Cl_3CCOCCl_3$) was investigated. The results are reported in Table 3.10.

Table 3.10 Effect of type of chlorinating agent on the chlorination of 2-hydroxypyridine



Entry	Chlorinating agent	%Recovery Het-OH	%Yield Het-Cl	MB (%)
1	Cl_3CCN	-	106	106
2	$Cl_3CCOCCl_3$	-	106	106
3	Cl_3CCCl_3	12	93	105
4	Cl_3CCO_2Et	32	72	104
5	Cl_3CCONH_2	96	2	98
6	CCl_4	92	NR	92

The efficiency of the chlorinating agent greatly depended on the type of substituent on the chlorinating agent. Under the specified conditions, reagents bearing a strong electron-withdrawing group such as Cl_3CCN, $Cl_3CCOCCl_3$ and Cl_3CCCl_3 gave the desired products in high yields (entries 1-3). Cl_3CCO_2Et and Cl_3CCONH_2, reagents having a weak electron-withdrawing group furnished 2-chloropyridine in low to moderate yield (entries 4 and 5). For CCl_4, none of the desired chloride was obtained (entry 6).

From the aforementioned results, Cl_3CCN and $Cl_3CCOCCl_3$ displayed as the highest efficient reagent to prepare 2-chloropyridine than various chlorinating agents screened. Hence, those reagents were considered as the most proper chlorinating agents for chlorination of hydroxyheteroaromatics.

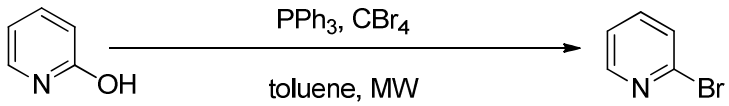
3.3.2 Optimum Conditions for the Conversion of *N*-Heteroaromatic Hydroxy Compounds to *N*-Heteroaromatic Bromides

Several parameters including temperature, reaction time, the amount of PPh_3/ brominating agent and type of brominating agent were investigated to optimize the reaction conditions for the conversion of *N*-heteroaromatic hydroxy compounds to *N*-heteroaromatic bromides. 2-Hydroxypyridine was selected as a model.

3.3.2.1 Condition Optimization for Bromination of *N*-Heteroaromatic Hydroxy Compounds

Several factors including temperature, reaction time and mole ratio of PPh_3/ CBr_4 were explored and the results are exhibited in Table 3.11.

Table 3.11 Effect of mole ratio of PPh_3/CBr_4, reaction time and temperature on the bromination of 2-hydroxypyridine



Entry	Temperature (^oC)	Time (min)	Mole ratio[a]		%Recovery	%Yield	MB
			PPh_3	CBr_4	Het-OH	Het-Br	(%)
1	110	10	2	1	94	10	104
2	150	10	2	1	11	94	105
3	180	10	2	1	-	104	104
4	150	10	1	1	43	60	103
5		20	2	1	3	99	102

[a] based on 2-hydroxypyridine

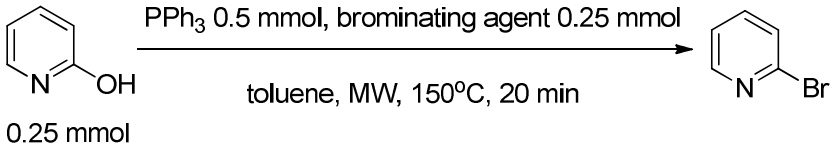
Table 3.11 demonstrates that when the reaction was heated at 110^oC by MW, 10% of 2-bromopyridine was obtained (entry 1). Hence, increasing the reaction temperature to 150 and 180^oC, 94 and 104% of the desired product were attained (entries 2 and 3). Decreasing the mole ratio of PPh_3 and CBr_4 from 2:1 to 1:1 furnished *N*-heteroaromatic chloride in moderate yield (entry 4). At 150^oC, more yield

of desired product could be lifted up from 94 to 99% when the reaction was carried out for 10 to 20 min, respectively (entry 5).

3.3.2.2 Effect of Type of Brominating Agents

A commercially available brominating agent, CBr_4 was used in this research. The other two brominating agents as mentioned above, Br_3CCO_2Et and $Br_3CCOCBr_3$ were synthesized. Furthermore, NBS has been previously utilized for the conversion of *N*-heteroaromatic hydroxy compounds into *N*-heteroaromatic bromides [29]. To explore the effect of type of brominating agents for this particular reaction, four brominating agents were selected and the results are presented in Table 3.12.

Table 3.12 Effect of types of brominating agents



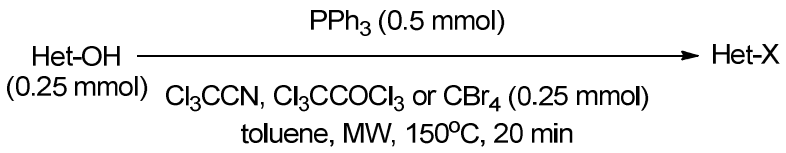
Entry	Brominating agent	%Recovery Het-OH	%Yield Het-Br	MB (%)
1	CBr_4	3	99	102
2	Br_3CCO_2Et	8	93	101
3	$Br_3CCOCBr_3$	-	79	79
4	NBS	15	70	85

Under the specified conditions, the desired product was obtained in high yield in the case of CBr_4 and Br_3CCO_2Et (entries 1 and 2). Although, $Br_3CCOCBr_3$ provided alkyl bromides from alcohols in high yields at RT [19], it was unstable at high temperature. Hence, $Br_3CCOCBr_3$ could not completely convert 2-hydroxypyridine into 2-bromopyridine at 150°C (entry 3). Using NBS, 2-bromopyridine was also attained in moderate yield (entry 4). It is an interesting to mention that CBr_4 was cheaper than Br_3CCO_2Et. Therefore, CBr_4 was found to be the best choice for the preparation of bromoheteroaromatics.

3.3.3 The Synthesis of *N*-Heteroaromatic Halides and Related Compounds

Since the optimized conditions could be obtained as previously discussed, the application of this developed protocol to convert various *N*-heteroaromatic hydroxy compounds and related compounds into their corresponding haloheteroaromatics using the combination of PPh_3 and Cl_3CCN, $Cl_3CCOCCl_3$ or CBr_4 were further investigated. The results are shown in Table 3.13.

Table 3.13 The synthesis of *N*-heteroaromatic halides and related compounds from hydroxyheteroaromatic using PPh_3/halogenating agent with the aids of MW irradiation



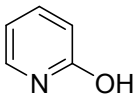
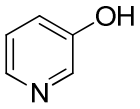
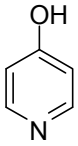
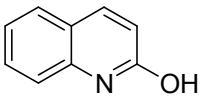
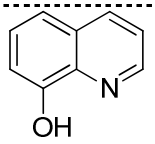
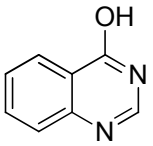
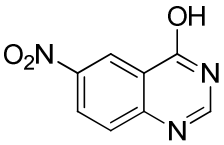
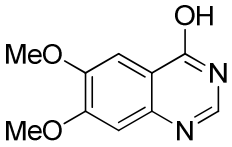
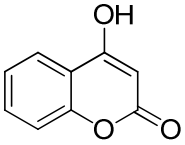
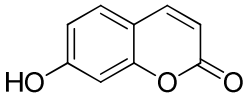
Entry	Substrate	Halogenating agent	Isolated yield (%)
1		Cl_3CCN	106[a]
2		$Cl_3CCOCCl_3$	106[a]
3		CBr_4	99[a]
4		Cl_3CCN	NR
5		Cl_3CCN	38
6		Cl_3CCN	83
7		$Cl_3CCOCCl_3$	94
8		CBr_4	97
9		Cl_3CCN	NR

Table 3.13 (continued)

Entry	Substrate	Halogenating agent	Isolated yield (%)
10		Cl_3CCN	7 (64)[b]
11		$Cl_3CCOCCl_3$	76[b]
12		CBr_4	38 (50)[b]
13		Cl_3CCN	65[b]
14		CBr_4	17[b,d]
15		Cl_3CCN	37[b]
16		CBr_4	37[b]
17		Cl_3CCN	81
18		$Cl_3CCOCCl_3$	78
19		CBr_4	85
20		Cl_3CCN	3 (42)[c] (51)[c,g]
21		CBr_4	34[c,g] (48)[c,e] (56)[c,f]

a) quantified by HPLC, b) at 100°C, c) at 180°C, d) 5 min, e) 25 min, f) 30 min, g) 40 min

The attempts to utilize this developed procedure for the synthesis of haloheteroaromatic were carried out. Under various conditions, 2-hydroxypyridine and 2-hydroxyquinazoline could be converted to the corresponding haloheteroaromatic in high to quantitative yield (entries 1-3 and 6-8). 4-Hydroxypyridine could be transformed to the corresponding desired chloride in low yield (entry 5). The conversion of 3-hydroxypyridine and 8-hydroxyquinazoline to the corresponding desired products could not be achieved because the charge in the intermediate was not rest on nitrogen (entries 4 and 9). In the case of 4-hydroxyquinazoline, the corresponding chloride and bromide were afforded in 7 and 38%, respectively (entries 10 and 12). Since 4-haloquinazolines are unstable at higher temperature, the temperature of the reaction of 4-hydroxyquinazoline was decreased from 150 to 100°C with the expectation to lift up the yield of 4-haloquinazoline. The desired product was increased to 50-76% (entries 10-12). In addition, 4-hydroxy-6-

nitroquinazoline and 4-hydroxy-6,7-dimethoxyquinazoline were employed, the desired halides were obtained in low to moderate yields (17-65%, entries 13-16). Moreover, this method could be applied for preparing halocoumarin. The comparative reactivity of each position of hydroxycoumarin was carried out by competing 4- and 7-hydroxycoumarins. 7-Hydroxycoumarin showed less reactivity than 4-hydroxycoumarin under the developed system (81 and 3%, entries 17 and 20). In the case of 4-hydroxycoumarin, it was readily reacted to give the corresponding halocoumarin in high yields (78-85%, entries 17-19). However, in order to improve the yield of 7-chlorocoumarin, the system needed some modification such as the increment of temperature and reaction time (entry 20). For the synthesis of 7-bromocoumarin (entry 21), The reaction gave 34% yield of desired bromide at 180^{o}C for 40 min. Because of high reactivity of desired bromide, unwanted product could be formed when using long reaction time. Therefore, the reaction time was decreased to 25 and 30 min, 48 and 56% yield of 7-bromocoumarin were achieved.

The ^{1}H NMR spectrum of 4-chlorocoumarin (Fig 3.22) presented a single signal of the proton on a carbon connecting with carbonyl at 6.56. The multiplet signals at δ_H 7.31-7.38 belonged to H-6 and H-8. The signal around δ_H 7.57-7.61 could be assigned for H-7. The doublet signal (J = 8.0 Hz) at δ_H 7.83 could be ascribed for H-5. The ^{1}H NMR spectrum of 4-bromocoumarin (Fig 3.23) showed a single signal of proton on carbon connecting with carbonyl at δ_H 6.81. The multiplet signals of H-6 to H-8 were revealed at δ_H 7.27-7.58. A signal of H-5 was observed from the presence of a doublet signal (J = 8.0 Hz) at δ_H 7.79.

The ^{1}H NMR spectrum of 7-chlorocoumarin (Fig 3.24) displayed two double signals (J = 9.6 Hz) of H-3 and H-4 at δ_H 6.42 and 7.67, respectively. The multiplet signal around δ_H 7.26-7.28 was ascribed to H-6. A singlet signal at δ_H 7.35 was indicated to H-8. The doublet signal (J = 8.0 Hz) around δ_H 7.42 was typical of H-5. The ^{1}H NMR spectrum of 7-bromocoumarin (Fig 3.25) showed two doublet signals (J = 9.6 Hz) of H-3 and H-4 at δ_H 6.44 and 7.66, respectively. Two doublet signals (J = 8.0 Hz) around δ_H 7.34 and 7.41 were due to H-5 and H-6, respectively. A singlet signal at δ_H 7.51 was ascribed to H-8.

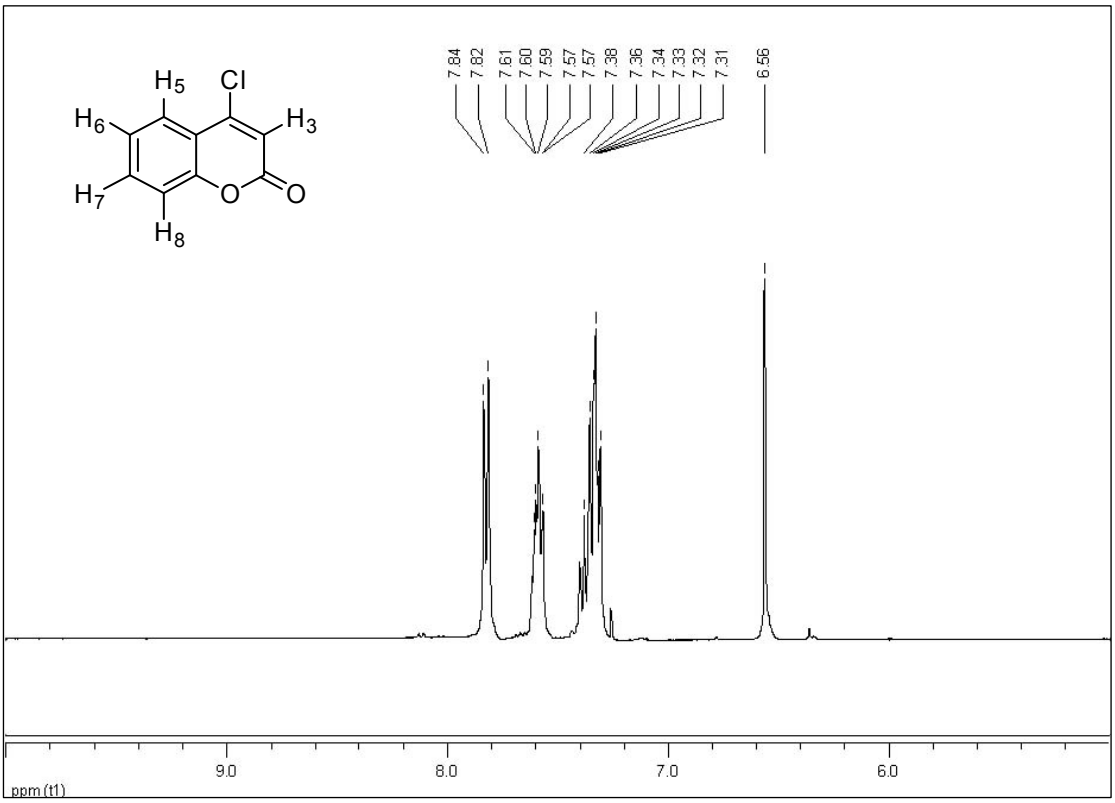


Figure 3.22 The ^{1}H NMR spectrum of 4-chlorocoumarin

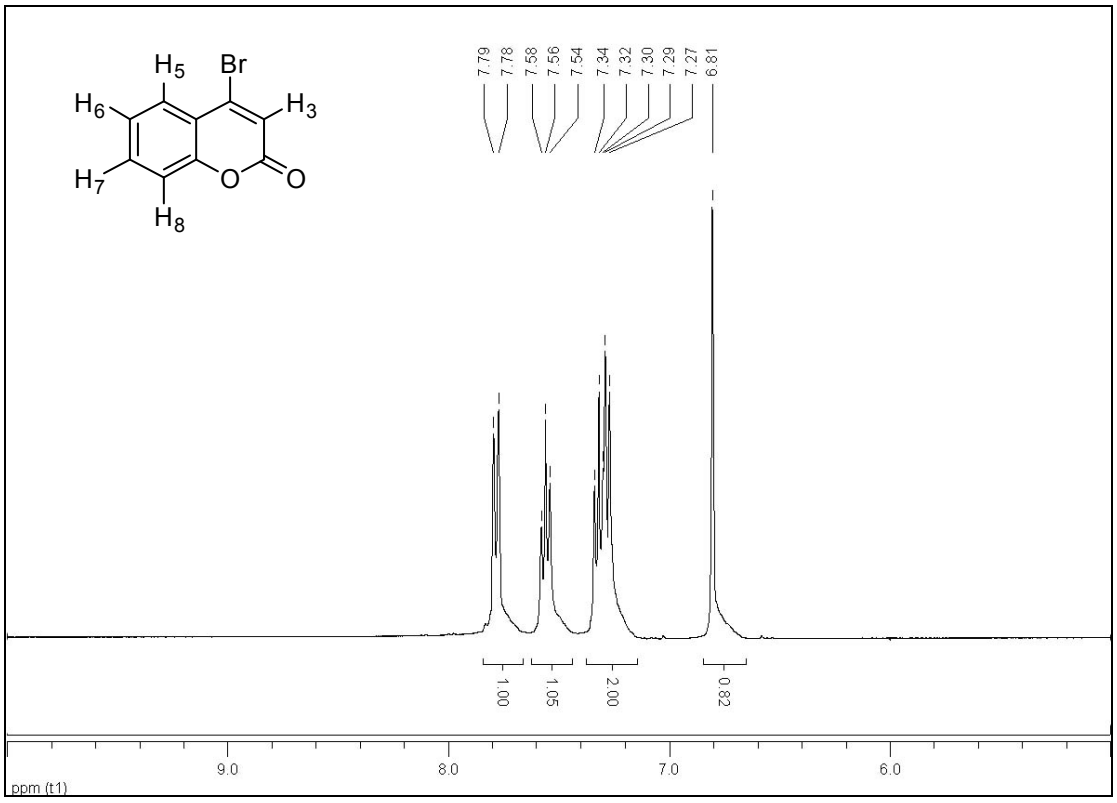


Figure 3.23 The ^{1}H NMR spectrum of 4-bromocoumarin

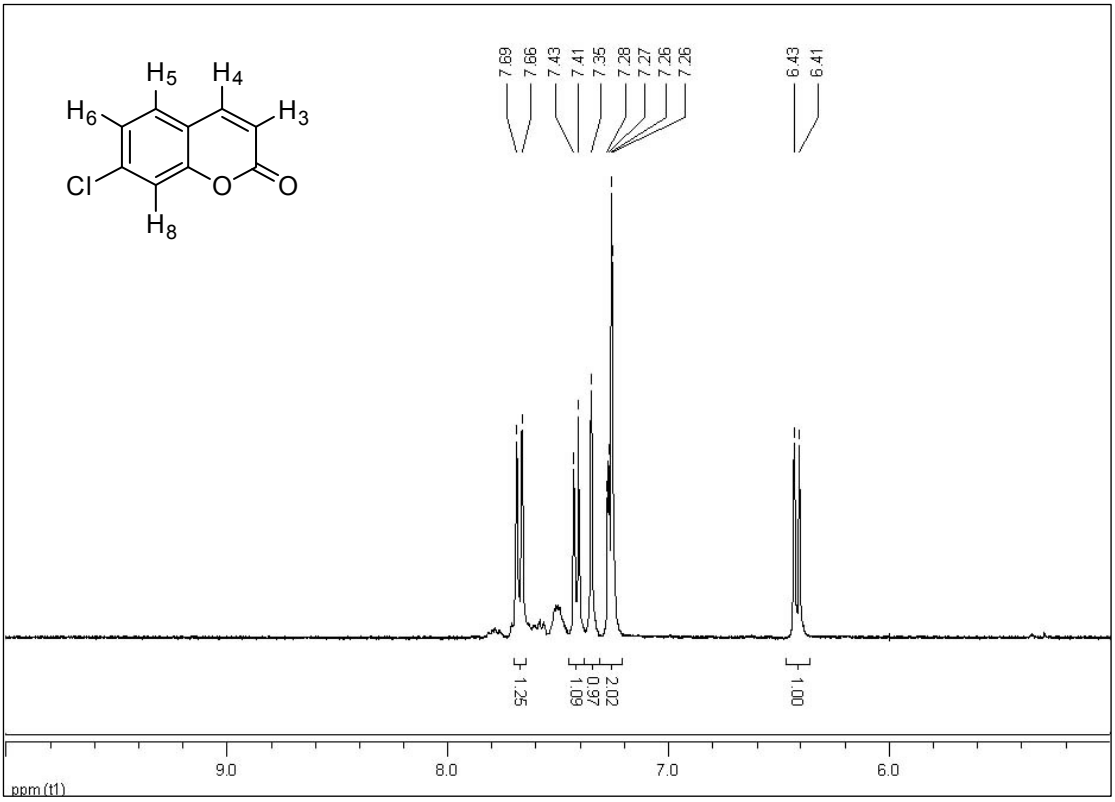


Figure 3.24 The ^{1}H NMR spectrum of 7-chlorocoumarin

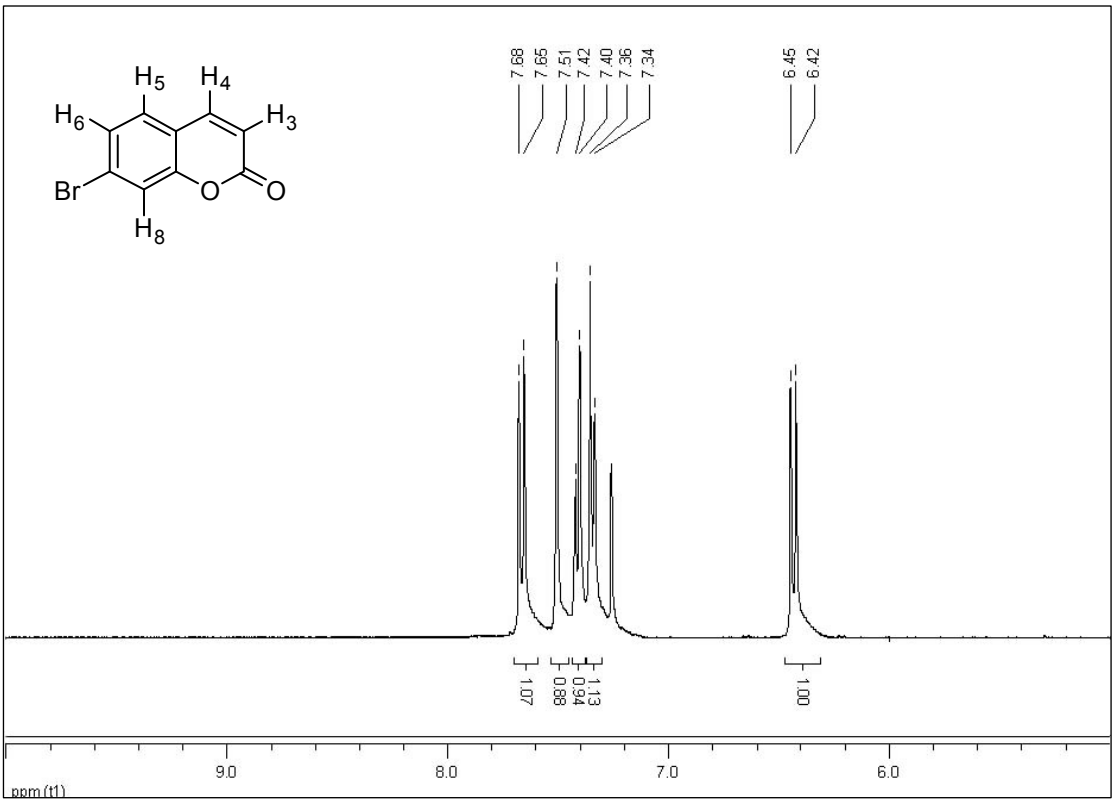


Figure 3.25 The ^{1}H NMR spectrum of 7-bromocoumarin

3.4 A Comparative Study on the Use of Conventional Heating and MW Assisting Reaction for the Synthesis of Haloheteroaromatic

Haloheteroaromatics were accomplishedly obtained by heating the reaction mixture of hydroxyheteroaromatics, PPh_3/halogenating agent such as Cl_3CCN and CBr_4. Two methodologies involving the use of conventional heating and microwave irradiation have been developed. To summarize, the optimized condition for halogenations of hydroxyheteroaromatics can be concluded in Table 3.14.

Table 3.14 Conditions optimization for halogenations of *N*-heteroaromatic hydroxy compounds

Condition	Convention heating		MW Irradiation	
	Chlorination	Bromination	Chlorination	Bromination
Halogenating agent	Cl_3CCN	CBr_4	Cl_3CCN or $Cl_3CCOCCl_3$	CBr_4
PPh_3:halogenating agent	3:1.5	3:1	2:1	2:1
Time	4 h	8 h	20 min	20 min
Solvent	toluene	toluene	toluene	toluene
Temperature	~110 °C	~110 °C	150 °C	150 °C

It was clearly found that MW irradiation is a convenient way to gain desired products in very short reaction time compared with conventional heating. Due to the fact that in the case of conventional heating, the energy must be conducted through the walls of vessel of reaction mixture. However, microwave radiation passes through the walls of the vessel to directly the reaction mixture. In the case of MW irradiation using closed vessels, the reaction mixture could heated above boiling point of solvent. The higher temperatures achieved in the closed system give the MW irradiation an advantage over the conventional heating under refluxing temperature.

CHAPTER IV

CONCLUSION

Two new and convenient methods for the preparation of *N*-heteroaromatic halides from *N*-heteroaromatic hydroxy compounds using PPh_3/ halogenating agent have been explored. Those include the system using conventional heating and microwave irradiation. This research is to search for optimal condition for this developed protocol which could be provided the high yields under mild conditions.

The first system, using conventional heating could be performed the chlorination of *N*-heteroaromatic hydroxy compounds utilizing the combination of PPh_3/Cl_3CCN in refluxing toluene (~110^oC) within 4 h. The preparation of *N*-heteroaromatic bromides was carried out employing the same conditions as that of chlorination of *N*-heteroaromatic hydroxyl compounds but using CBr_4 instead of Cl_3CCN within 8 h. Furthermore, microwave-assisted halogenations could perfectly be exploited to prepare *N*-heteroaromatic halides using PPh_3/Cl_3CCN, $Cl_3CCOCCl_3$ or CBr_4 at 150^oC for 20 min.

Various *N*-heteroaromatic hydroxy compounds were examined on the halogenations effect of their *N*-heteroaromatic hydroxy compounds under developed conditions. Treating of PPh_3/Cl_3CCN, $Cl_3CCOCCl_3$ or CBr_4 with 2-, 4-hydroxypyridines or 2-hydroxyquinoline could generate the corresponding chlorides or bromides in high yield. Unfortunately, the developed method could not convert 3-hydroxypyridine and 8-hydroxypyridine to the desired halides. The study on the effect of electron withdrawing and electron donating group substituents on 4-hydroxyquinazoline, 4-hydroxyquinazoline beared with an electron withdrawing group, the desired halides were detected in lower yield than 4-hydroxyquinazoline and 4-hydroxy-6,7-dimethoxyquinazoline. In addition, hydroxycoumarin could be efficiently reacted under the developed methodology.

A comparative study of halogenation of *N*-heteroaromatic hydroxy compounds by conventional heating and MW irradiation was conducted, it was observed that halogenation of *N*-heteroaromatic hydroxy compounds yielding *N*-heteroaromatic halides with the aids of MW irradiation took place faster than the conventional heating. However, the MW promoted reactions were not suitable for unstable compound at high temperature such as haloquinazoline derivertives.

Proposal for the Further Work

The developed methodology can be applied to prepare heteroaromatic halides. Therefore, it may be extended to prepare bromopyridine derivatives from hydroxypyridine. For instance, 2-bromo-4-methoxy-5-nitropyridine, a key intermediate for the preparation of AKT inhibitor may be synthesized by halogenation of 4-methoxy-5-nitropyridin-2-ol.

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