โบรมิเนชันของแอโรแมติกโดยใช้เฮกซะโบรโมแอซิโทน

นายณัฐ โต๊ะสัมฤทธิ์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาเคมี ภาควิชาเคมี
คณะวิทยาศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2557

BROMINATION OF AROMATICS USING HEXABROMOACETONE

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A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Science Program in Chemistry

Department of Chemistry

Faculty of Science

Chulalongkorn University

Academic Year 2014

Thesis Title	BROMINATION OF AROMATICS USING HEXABROMOACETONE
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Field of Study	Chemistry
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ณัฐ โต๊ะสัมฤทธิ์ : โบรมิเนชันของแอโรแมติกโดยใช้เฮกซะโบรโมแอซิโทน (BROMINATION OF AROMATICS USING HEXABROMOACETONE) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ดร.วรินทร ชวศิริ, 73 หน้า.

ได้ค้นพบวิธีสังเคราะห์ใหม่ภายใต้ภาวะที่ไม่รุนแรงและให้ผลผลิตสูงสำหรับโบรมิเนชันของแอโรแมติกโดยใช้เฮกซะโบรโมแอซิโทน (เอชบีเอ) เมื่อใช้แอนิโซลเป็นสารต้นแบบสำหรับศึกษาภาวะและปัจจัยที่เหมาะสม ได้แก่ การใช้รังสียูวี อุณหภูมิ เวลา ความเข้มข้นของสารตั้งต้น อัตราส่วนโดยโมลระหว่างแอนิโซลต่อเอชบีเอ และสารเติมแต่ง พบว่าสามารถเตรียม 4-โบรโมแอนิโซลได้ในปริมาณที่สูง ภายในระยะเวลาสั้น ได้ศึกษาแอโรแมติกชนิดอื่นเพิ่มเติมอีก 12 ชนิด พบว่า แอโรแมติกที่มีหมู่ให้อิเล็กตรอนจะมีความว่องไวในการเกิดปฏิกิริยามาก และเกิดผลิตภัณฑ์แทนที่ 2 และ 3 ตำแหน่งบนวงแอโรแมติก การเลือกเกิดของปฏิกิริยาสามารถควบคุมได้ โดยการใช้อัตราส่วนโดยโมลระหว่างสารตั้งต้นต่อเอชบีเอที่แตกต่างกัน ตัวทำละลาย เวลาที่ใช้ทำปฏิกิริยา หรือการเติมเอชบีเอแบบแบ่งส่วน ได้ศึกษาขอบเขตของการเกิดปฏิกิริยาสำหรับแอโรแมติกบางชนิดได้แก่ แอลลิลเบนซีน แซฟรอล 4′-คลอโรฟลาวาโนน ฟลาโวนและพิโนสโทรบิน พบว่า แนวโน้มของความว่องไวในการเกิดปฏิกิริยาได้แก่ การเกิดปฏิกิริยาที่พันธะคู่ > แอโรมาติกที่มีหมู่แทนที่ที่ว่องไวต่อปฏิกิริยา > แอลฟา-คาร์บอนิล ตามลำดับ เชื่อว่ากลไกการเกิดปฏิกิริยาจะเกิดผ่านโบรมีนที่เกิดขึ้นในปฏิกิริยาจากเอชบีเอ

ภาควิชา เคมี ลายมือชื่อนิสิต .....

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ปีการศึกษา 2557

5571968023 : MAJOR CHEMISTRY

KEYWORDS: BROMINATION / AROMATICS / HEXABROMOACETONE

NAT TOHSAMRIT: BROMINATION OF AROMATICS USING HEXABROMOACETONE. ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., 73 pp.

A novel, mild and high yielding synthetic method for the bromination of aromatics using hexabromoacetone (HBA) is disclosed. Using anisole as a template, various parameters including UV radiation, temperature, time, the substrate concentration, molar ratio of anisole: HBA and additives were explored to search for optimum conditions which led to the selective production of the corresponding 4-bromoanisole in high yield in short reaction time. Twelve aromatics were examined and found that aromatics with electron-donating group were very reactive forming di- or tri-substituted products. The regioselectivity of the reaction could be controlled by using different ratios of substrate to HBA, solvent, reaction time, or adding HBA in small portion. Several chemical probes including allylbenzene, safrole, 4′-chloroflavanone, flavone and pinostrobin were selected to investigate the scope of this reaction. The trend of the reactivity could be observed in order for the bromination towards unsaturated portion > aromatic with activating group > **α**-carbonyl group. The reaction pathway was believed to occur *via* Br_2 generated *in situ* from HBA.

Department: Chemistry
Field of Study: Chemistry
Academic Year: 2014

Student's Signature .....

Advisor's Signature .....

ACKNOWLEDGEMENTS

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

The greatest thanks are also extended to Associate Professor Dr. Vudhichai Parasuk, Dr. Panuwat Padungros and Assistant Professor Dr. Wanchai Pluempanupat for their suggestion, comments, correction and helps as thesis examiners.

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

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LIST OF ABBREVIATIONS

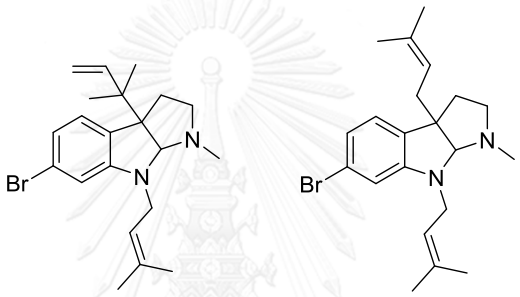
Ar-H	Aromatic proton (s)
br	broad (NMR)
Calc	Calculated
conc	concentrated
d	doublet (NMR)
DCE	1,2-dichloroethane
dd	doublet of doublet
ddd	doublet of doublet of doublet
g	gram (s)
GC	Gas chromatography
h	hour (s)
HBA	hexabromoacetone
Hz	hertz
J	coupling comstant (NMR)
kJ	kilojoule (s)
m	multiplet (NMR)
MB	mass balance
min	minute (s)
mL	milliliter (s)
mM	millimolar (s)
mmol	milimole (s)
mol	mole (s)

NBS	*N*-bromosuccinimide
nm	namometer (s)
NMR	nuclear magnetic resonance
ppm	part per million
q	quartet (NMR)
quant	quantitative
RT	room temperature
R_t	retention time (s)
s	singlet (NMR)
t	triplet (NMR)
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultra violet
W	watt
%	percent
α	alpha
β	beta
δ	chemical shift (NMR)

CHAPTER I

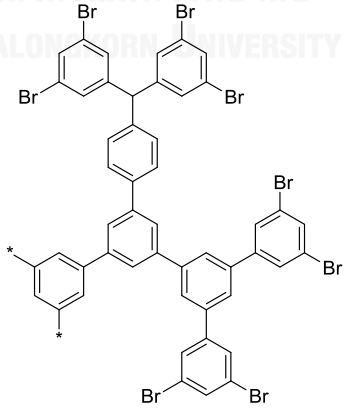
INTRODUCTION

Bromoarenes are fundamentally important compounds in organic synthesis since they are used as intermediates in both pharmaceutical and agrochemical aspects, some organometallic compounds and biologically active substrates as antitumor, antifungal, antibacterial, antineoplastic and antiviral compounds [1-3]. For example, Chrisophersen and co-workers investigated flustramine from marine bryozoans [4].



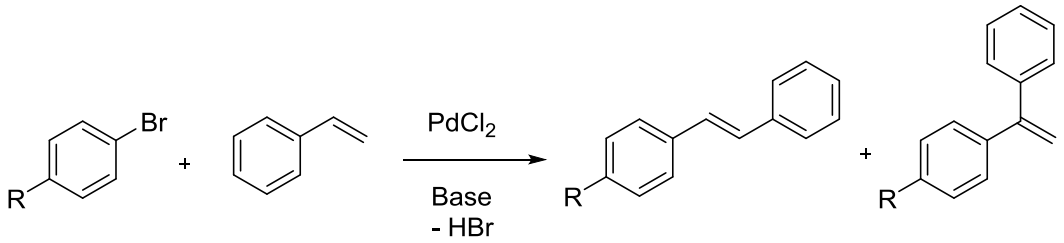
Flustramines A and B

Miyamura synthesized a hyperbranched polyphenylene from brominated aromatics and used as a precursor of palladium-catalyzed cross–coupling reaction [5].



Hyperbranched polyphenylene

Moreover, Schmidt *et al.* used an unactivate bromoarene as a phenylating agent in Heck coupling reaction with ligand free palladium catalyst [6].

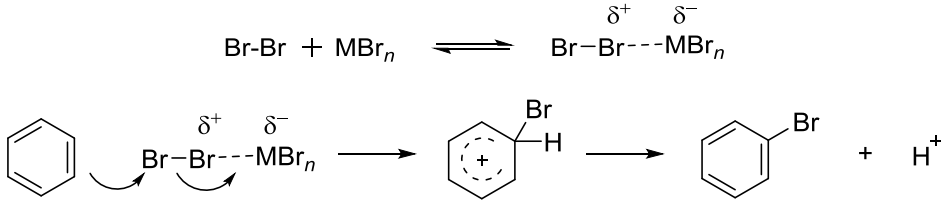


Heck coupling of bromoarene with styrene

According to many advantages and applications of bromoarenes, there is a need to search for an alternative protocol to synthesize bromoarenes with better yield and selectivity.

1.1 Classical methods for the bromination of aromatics

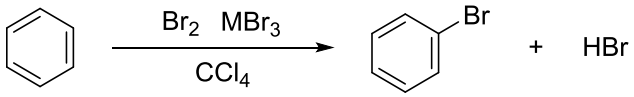
The bromination of aromatics belongs to electrophilic aromatic substitution. The mechanism was proceeded through the arenium ion [7]. Bromoarenes can be prepared from various methods employing a variety of bromine sources; for example, by adding the reagent containing bromine and co-reagent to generate active bromine species, electrolysis a bromine alkaline salt to get an active bromine species [8] or bromination through other substrates then converting the product to an aromatic [9]. The most basic method is the addition of liquid bromine directly into aromatics; nonetheless, benzene and other unactivated aromatics do not react with bromine at cold or RT. In the presence of halogen carriers or aromatic halogenating catalyst such as metal halide those reactions can take place readily. The aromatic halogenating catalysts are usually all electrophilic reagents. Their function appears to increase the electrophilic reactivity of halogen. The mechanism for the bromination of benzene can be represented by Scheme 1.1 [10].



Scheme 1.1 The bromination of benzene catalyzed by Lewis acid

The classical method for bromination of aromatics involves the addition of liquid bromine directly to aromatic compounds. For example, the bromination of

benzene, benzene and $FeBr_3$ were placed in the round bottom flask and dissolved in CCl_4. Then, the liquid bromine was carefully added into the mixture. The reaction was refluxed in benzene for 1 h or longer (Scheme 1.2).



Scheme 1.2 Classical method for the bromination of benzene

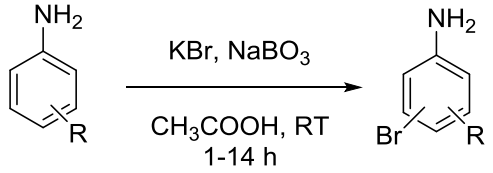
Another method for bromination of unreactive substrate such as nitrobenzene or cyanobenzene is using mercuric acetate or trifluoroacetate. These conditions generate acyl hypohalites, which are the active halogenating agents. The trifluoroacetyl hypohalites are very reactive reagents. Even nitrobenzene, for example, is readily brominated by trifluoroacetyl hypobromite.

However, Br_2 and other halogenation catalysts are corrosive to human tissue in liquid state and its vapors irritate eyes and throat. Bromine vapors are very toxic with inhalation. Thus, with highly corrosive and oxidative properties, Br_2 is very hazardous and handle with difficulty for performing a chemical reaction. Moreover, according to the classical reactions using liquid Br_2, those reactions suffered with a corrosive by-product, not perform at ambient conditions, some required transition metal catalysts which were expensive and could not control regioselectivity with poly-brominated compounds, especially for some aromatics bearing electron donating groups. Liquid bromine must thus be avoided to use, a new brominating agent needs to be explored.

1.2 The development of brominating agents

The attempts to avoid employing liquid Br_2 led to the development of new methods for bromination of aromatics. In 2000, Roche *et al.* used KBr as a brominating agent with $NaBO_3$ to generate active bromonium ion. This method was reported to use for the bromination of aniline leading to the product in high yield, and the reaction could readily take place at RT. However, this reaction took a long

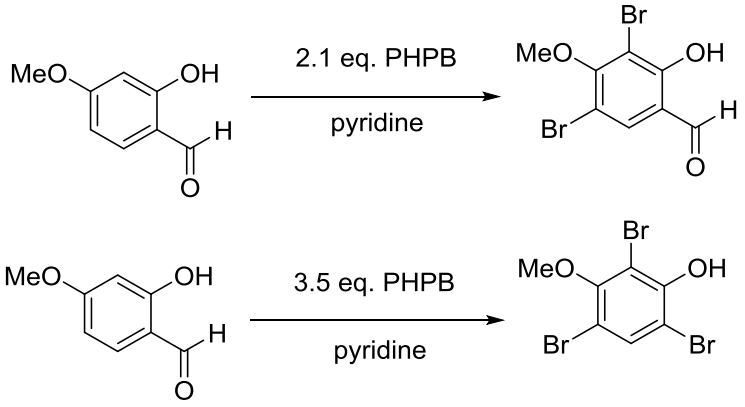
time and the regioselectivity of the reaction was still a problem that could not be solved [11].



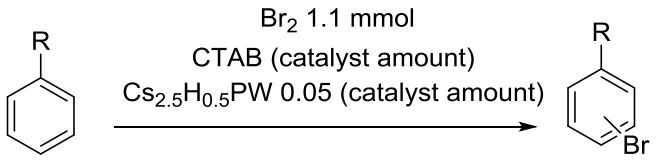
In the same year, Munir and Dordick utilized soybean peroxidase (SBP) as halogenation catalyst for the oxidation of KBr with H_2O_2. SBP is the natural enzyme isolating from soybean seed coat. These reactions could perform under mild and green conditions. However, many factors were needed to be controlled. In addition, the yield of products was poor and the reaction took a long time [12].

In 2001, Chandra *et al.* reported a new method for bromination of aromatics using LiBr. Ceric ammonium nitrate was a powerful one-electron oxidant, this chemical was used as a co-reagent for generating active species, bromonium ion. The yield of product was moderate to high and these methods could proceed under mild conditions. However, a long time was required to perform these reactions [13].

In 2002, C′ordoba and Plumet used pyridinium hydrobromide perbromide (PHBH) as a brominating agent and pyridine as a co-reagent to brominate aromatics. This method could be used for bromination of aromatics containing electron withdrawing group such as aldehyde. This reaction, nevertheless could not control the regioselectivity of mono- or di-brominated products [14].



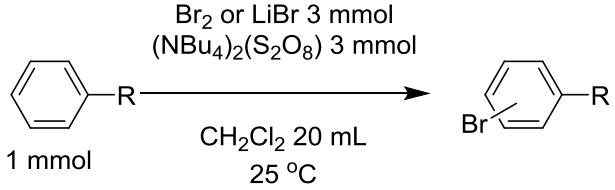
In 2003, Firouzabadi and co-workers addressed the heterogeneous system for the bromination of aromatics using Br_2 and cetyltrimethyl ammonium bromide (CTAB) with heteropoly acid cesium salt as co-reagent and catalyst. This reaction provided the target product very fast with high yield. Nevertheless, this catalyst and co-reagent were suitable with aromatics bearing a high electron donating group [15].



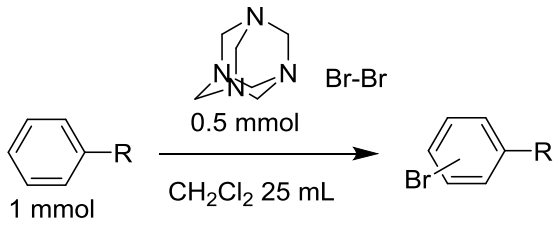
In the same year, Narender et al. expressed the bromination of aromatics with NH_4Br and oxone as co-reagent which was believed to generate Br^+. The advantages of this procedure were that the reactions could perform at ambient conditions and produced the desired molecules in high yield. On the other hand, the disadvantages were that the regioselectivity of reaction could not be controlled since it depended mainly on the nature of substrate and the reaction took a long time [16].

In 2004, Rajagopal *et al.* used *N*-bromosuccinimide (NBS) and phosphotungstic acid supported on zirconia catalyst. The isolated yields of products were very high. However, the reaction took a long time and could not brominate aromatics containing poor electron donating group [17].

Park and co-workers reported the bromination of aromatics using Br_2 or LiBr as brominating agent together with tetrabutylamonium peroxydisulfate as co-reagent. This method produced high yield and could control the selectivity of mono- or di-substituted products when a suitable brominating agent was used. However, this method took a long time [18].

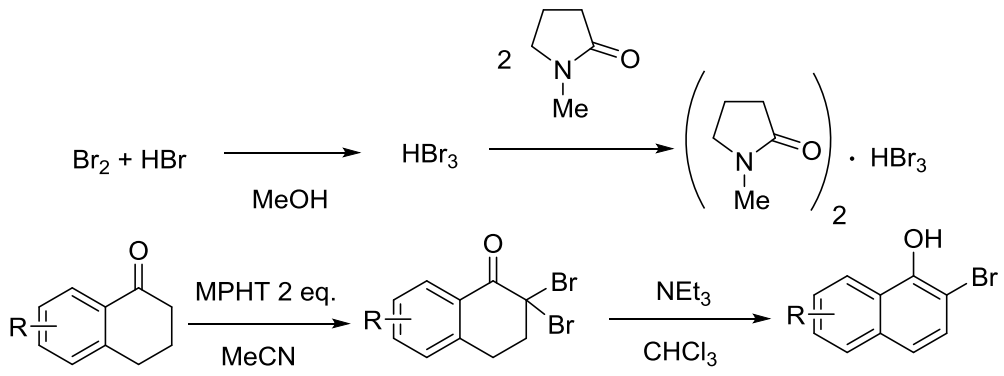


In 2005, Heravi *et al.* used hexamethylenetetramine bromine for bromination of aromatics. The reaction could perform in short time to gain a high yield of products. Nevertheless, the reaction could not perform at RT, not compatible with some substrates and must prepare the brominating agent with a support prior to use [19].



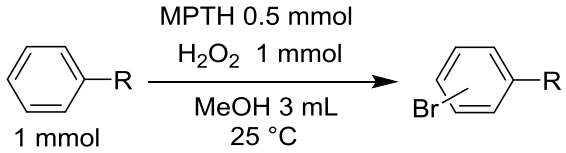
In the same year, Gnaim and co-workers used Br_2, SO_2Cl_2 and supporting microporous catalysts. The catalyst must be varied to obtain the high potency for selectivity and conversion. With this method, the unreactive aromatics such as chlorobenzene could be brominated and the target product was obtained in high yield [20].

Bekaert *et al.* used *N*-methylpyrrollidine-2-one hydrotribromide (MPHT) with H_2O_2 as brominating agent to synthesize brominated naphthols. The bromination took place at **α**-carbonyl position, and then converted to naphthol by adding NEt_3. The advantage of this method was a short time to brominate a carbonyl and got the good overall yield of naphthol. However, long reaction time was needed to convert **α,α´**-dibromo compound to naphthol [9].



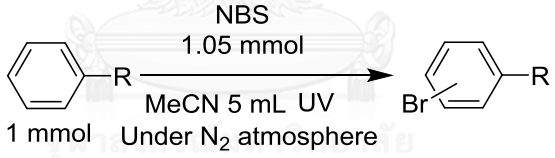
Another research employing MPHT was reported in 2006, Singhal *et al.* reported the use of MPHT and H_2O_2 as co-reagent in aromatic bromination. This

reaction was occurred readily at RT and provided a high yield of product. Nonetheless, the reaction was not compatible with some substrates such as benzaldehyde. H_2O_2 would oxidize an aldehyde group to be a carboxyl group [21].

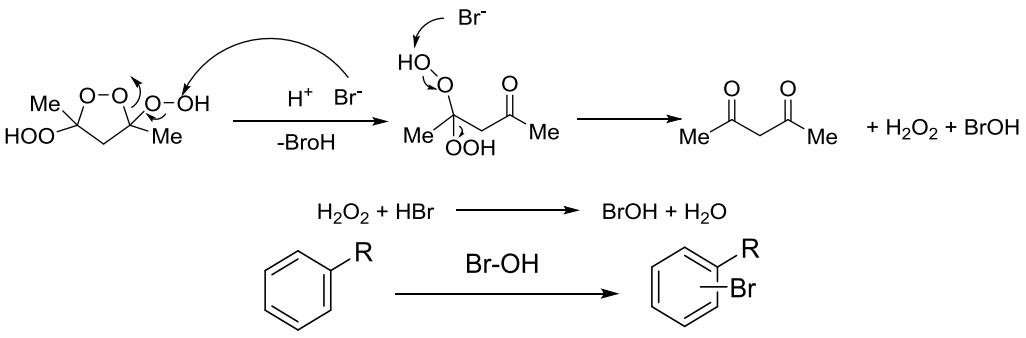


Another research in 2006, Guo *et al.* addressed the bromination of aromatics with alkyl bromide and NaH. This method could brominate aniline with complete conversion. However, it could not perform at ambient conditions and took a very long time [22].

In 2008, Chhattise *et al.* used NBS as a brominating agent without co-reagent. This method was the first report as a photochemical bromination of aromatics using UV radiator. This reaction generated a high yield of products and the reaction took place very fast. The disadvantage of this condition was the reaction was limited to certain substrates containing electron withdrawing group [23].

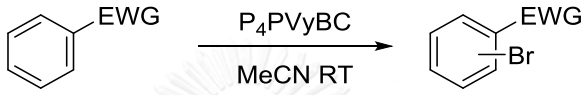


In 2012, Khosravi brominated aromatics using HBr with *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalone. The prominent points of this reaction were a new method to generate a bromine active species, and the reaction could perform at RT with short time [24].



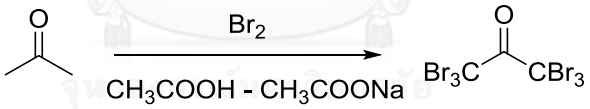
In 2012, Ghorbani-Vaghei used a *N,N,N´,N´*-tetrabromobenzene-1,3-disulfonamide as a brominating agent to brominate unreactive aromatics. The reaction could carry out at RT, but taking very long time; the products were obtained in poor to moderate yield [25].

In 2013, Albadi and co-worker used a poly(4-vinylpyridinium bromochromate) (P_4PVyBC) for the synthesis of bromoarenes. This brominating agent could be used at ambient conditions with short time. The products were obtained in high yield and could react with substrates containing electron withdrawing group [26].

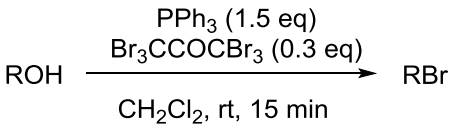


1.3 Hexabromoacetone

Hexabromoacetone (HBA) was first synthesized by bromination of acetone in 1969 to study the formation of perhaloacetone. This method was carried out by treating acetone with Br_2 in a buffer AcOH-NaOAc. HBA was obtained in 80% yield. Since then, there was no report of the use of this reagent in organic synthesis [27].

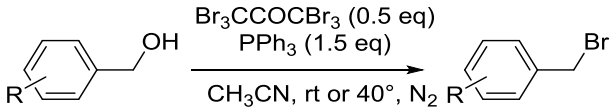


The first report on the utilization of HBA coupled with triphenylphosphine (PPh_3) was published in 2008 for the efficient synthesis of alkyl bromide form alcohol. The reaction could be perfomed in short time and produced alkyl bromide in high yield [28].



Another research was reported in 2011, Joseph *et al*. used this reagent with PPh_3 to synthesize benzyl halide form benzyl alcohol. High yield of benzyl bromide

was obtained and the reaction was performed in short time. The researchers used this method for the synthesis of an omeprazole's precursor [29].



Moreover, HBA has been investigated as a brominating agent for various reactions such as bromination of alkanes, deprotection of acetals and ketals, bromination of hydrosilane, ring opening of epoxide and preparation of allyl bromide [30, 31]. Thus, this reagent has been proved as a versatile brominating agent. However, to our best knowledge, there was no report on utilizing this reagent for bromination of aromatics. The goal of this research is to use HBA as the brominating agent for bromination of aromatics, to explore the scope of this developed protocol and to propose the mechanistic pathway of this reaction.

Chapter II

EXPERIMENTAL

2.1 Instruments and Equipment

Thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica (Merck Kieselgel 60 PF_{254}). Column chromatography was carried out on silica gel (Merck Kieselgel 60, 70-230 mesh).

The ^{1}H and ^{13}C NMR spectra were performed in deuterated chloroform ($CDCl_3$) or otherwise stated with tetramethylsilane (TMS) as an internal reference on the 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.

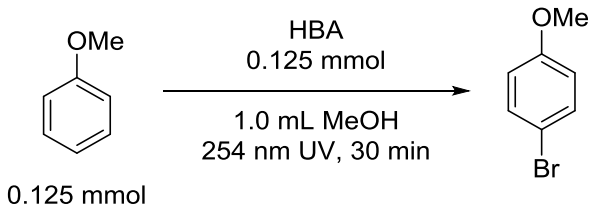
The gas chromatography (GC) was performed using Varian CP-3800 gas chromatograph instrument equipped with a flame ionization detector (FID) with N_2 as a carrier gas using 30-m long CP sil5 or SGE BP1 column (0.25-mm outer diameter, 0.25 μm film thickness).

2.2 Chemicals

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

2.3 Optimized conditions study for the bromination of anisole

General procedure



The mixture of anisole (13.5 mg, 0.125 mmol) and HBA (66.5 mg, 0.125 mmol) was dissolved in MeOH 1.0 mL in quartz cells. The mixture was stirred for 30 min upon the irradiation of UV (254 nm) at RT. After being completed, the reaction was quenched by $NaHCO_3$ 0.5 mL. The reaction mixture was then extracted with Et_2O and dried over anhydrous Na_2SO_4. The quantification of 4-bromoanisole was carried out by GC using biphenyl as an internal standard.

2.3.1 The effect of temperature and UV radiation

Four sets of experiments were performed to explore the optimized conditions. The first experiment was conducted without irradiating the reaction by UV, while the second reaction was the same as the former except for adding $AlCl_3$ (5% molar of anisole) to the reaction. The third and the forth reactions were performed to observe the effect of reaction temperature at 0°C and at refluxed temperature of the reaction, respectively.

2.3.2 The effect of solvent

The reaction was carried out following the general protocol except for five diverse solvents: 1,2-dichloroethane (DCE), tetrahydrofuran (THF), ethyl acetate (EtOAc), Et_2O and MeCN being used instead of MeOH.

2.3.3 The effect of reaction time

The reaction was carried out using the reaction conditions described in the general procedure except for varying reaction time as 1, 5, 15, 30 and 60 min.

2.3.4 The effect of the concentration of anisole

The reaction was performed according to the general procedure except for the concentration of anisole being altered as 0.03, 0.06, 0.13, 0.25 and 0.50 mM. The concentrations of anisole were controlled by adjusting the volume of the solution using MeOH.

2.3.5 The effect of the molar ratio of anisole: HBA

The reaction was carried out following the general procedure except for the molar ratio of anisole: HBA being changed: 1:0.5, 1:0.12 and 1:0.25.

2.3.6 The effect of additives

The reaction was performed according to the general procedure except for adding selected additives. The following additives (5% mol of anisole) including $CrBr_3$, $InCl_3$, $AlCl_3$, $NiCl_2$ and $FeCl_3$ were added into each reaction. The reaction time at 15 and 30 min were investigated.

2.4 The effect of brominating agents: a comparative study

2.4.1 Comparative study on the bromination of anisole with different brominating agents

The reaction was carried out following the general protocol except for five different brominating agents including HBA, NBS, Br_2, bromine water and HBr being employed. 2,4-Dibromoanisole was synthesized to use as an authentic sample by dissolving anisole (27.0 mg, 0.25 mmol) in MeOH 2 mL and treated with Br_2. The reaction mixture was stirred for overnight at RT to obtain the quantitative yield of 2,4-dibromoanisole. The obtained product was characterized by ^{1}H NMR.

2,4-dibromoanisole: colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.87 (*s*, 3H, C<u>H</u>$_3$-Ar), 6.78 (*d*, *J* = 8.8 Hz, 1H, Ar-<u>H</u>), 7.04 *(dd, J* = 2.4 Hz, 1H, Ar-<u>H</u>) and 7.39 (*dd, J* = 2.4 Hz, 1H, Ar-<u>H</u>) [32].

2.4.2 Comparative study on the molar ratio of anisole:brominating agent

The reaction was described in the general procedure except for the molar ratio of anisole:HBA and anisole:NBS being employed as 1:1, 2:1 and 4:1.

2.5 The bromination of selected aromatics

2.5.1 Preparation of aromatics

Flavone [33]

Conc sulfuric acid (2.45 g, 25.0 mmol) was added to a suspension of 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione (6.00 g, 25.0 mmol) in 30 mL of glacial acetic acid, and refluxed for 1 h. The color of the mixture changed from yellow to beige. The mixture was cooled to RT, poured over 160 g of ice, allowed to stand for 30 min, and filtered. The solid was washed with H_2O 300 mL until the filtrate aws acid-free and was recrystallized from acetone.

Flavone: yellowish solid (80%), ^{1}H NMR ($CDCl_3$) δ (ppm): 6.85 (*s*, 1H, COC<u>H</u>C-Ar), 7.45 (*t*, *J* = 7.6 Hz, 1H, Ar-<u>H</u>), 7.51-7.55 (*m*, 3H, Ar-<u>H</u>), 7.58 (*dd*, *J* = 8.4, 1.1 Hz, 1H, Ar-<u>H</u>), 7.73 (*ddd*, *J* = 8.3, 6.8, 1.7 Hz, 1H, Ar-<u>H</u>), 7.90-7.97 (*m*, 2H, Ar-<u>H</u>) and 8.23 (*dd*, *J* = 8.0, 1.7 Hz, 1H, Ar-<u>H</u>).

4′-chloroflavanone [34]

A mixture of 2′-hydroxyacetophenone (2.72 g, 0.02 mol) and 4-chlorobenzaldehyde (2.8 g, 0.02 mol) in EtOH 30 mL, 1 mL of 50% NaOH aqueous solution was added and the reaction was stirred overnight at RT. The precipitated solid was filtered and recrystallized from hot EtOH to obtain the pure product.

(E)-3-(3-chlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one: yellow needle crystal (90%), ^{1}H NMR ($CDCl_3$) δ (ppm): 6.96 (*m*, 1H, Ar-<u>H</u>), 7.03 (*dd*, *J* = 8.4, 1.4 Hz, 1H, Ar-<u>H</u>), 7.41 (*dd*, *J* = 8.5, 1.4 Hz, 2H, Ar-<u>H</u>), 7.48-7.55 (*m*, 1H, Ar), 7.60-7.65 (*m*, 2H, CH=C<u>H</u>-Ar), 7.84 (*d*, *J* = 1.2 Hz, 1H, C<u>H</u>=CH-Ar), 7.87 – 7.96 (*m*, 1H, Ar-<u>H</u>) and 12.76 (*s*, 1H, O<u>H</u>).

(*E*)-3-(3-chlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (2.58 g, 10 mmol) was mixed with sodium acetate (5 g) in 30 mL of MeOH. 3 Drops of water were

added in reaction and refluxed overnight. The reaction mixture was poured into cold water and extracted with EtOAc. The organic phase was washed with saturated NaCl solution and dried over anhydrous Na_2SO_4. After removing solvent, the residue was purified by silica gel column using 10% EtOAc in hexane to obtain the pure product.

4′-chloroflavanone: green solid (52%), ^{1}H NMR ($CDCl_3$) **δ** (ppm): 2.61-3.33 (*m*, 2H, COC$\underline{H}_2$), 5.47 (*dd*, *J* = 13.2, 3.0 Hz, 1H, C$\underline{H}$-Ar), 7.10 – 7.03 (*m*, 2H, Ar-$\underline{H}$), 7.42 (*m*, 4H, Ar-$\underline{H}$), 7.48–7.56 (*m*, 1H, Ar-$\underline{H}$) and 7.93 (*dd*, *J* = 7.7, 1.7 Hz, 1H, Ar-$\underline{H}$).

2.5.2 General procedure

The following aromatics: phenol, *o*-ethylphenol, aniline, allylbenzene, safrole, thymol, ethylbenzene, *p*-dichlorobenzene, **α**-naphthol, flavone, 4′-chloroflavanone and pinostrobin (0.125 mmol) was mixed with HBA (66.5 mg, 0.125 mmol) in quartz cells. 0.5 mL of MeCN was added. The mixture was stirred for 30 min under UV (254 nm). After the reaction was completed, it was quenched with cold water and extracted with Et_2O. The organic phase was washed with water, dried over anhydrous Na_2SO_4. The crude products were purified by silica gel column (eluent: hexane and EtOAc). The yield of the desired products was determined by GC using biphenyl as an internal standard. All purified products were confirmed their identities by ^{1}H NMR.

4-bromo-2-ethylphenol: yellowish solid. ^{1}H NMR ($CDCl_3$) **δ** (ppm): 1.14 (*t*, *J* = 7.6 Hz, 3H, Ar-CH_2-C$\underline{H}_3$), 2.52 (*q*, *J* = 7.6 Hz, 2H, Ar-C$\underline{H}_2$-CH_3), 6.56 (*d*, *J* = 8.5 Hz, 1H, Ar-$\underline{H}$) and 6.93 – 7.31 (*m*, 2H, Ar-$\underline{H}$) [35].

4-bromoaniline: brown oil. ^{1}H NMR ($CDCl_3$) **δ** (ppm): 3.55 (*s*, 2H, -Ar-N$\underline{H}_2$), 6.30 – 6.78 (*d*, *J* = 6.21 Hz, 2H, Ar-$\underline{H}$) and 7.11 – 7.64 (*d*, *J* = 6.67 Hz, 2H, Ar-$\underline{H}$) [36].

4-bromo-1-naphthol: brown solid. ^{1}H NMR ($CDCl_3$) **δ** (ppm): 5.46 (*br, s,* 1H, Ar-O$\underline{H}$), 6.71 (*d*, *J* = 8.0 Hz, 1H, Ar-$\underline{H}$), 7.36 – 7.82 (*m*, 3H, Ar-$\underline{H}$) and 8.04 – 8.37 (*m*, 2H, Ar-$\underline{H}$) [37].

2.6 The regioselectivity study

2.6.1 Bromination of phenol

The preparation of 2,4,6-tribromophenol was operated by treating phenol (23.5 mg , 0.25 mmol) with excess of Br_2 in water (2.0 mL) to yield white solid and recrystallized with EtOH. Product was characterized with ^{1}H NMR.*2,4,6-tribromophenol:* white solid. ^{1}H NMR ($CDCl_3$) **δ** (ppm): 7.58 (*s*, 2H, Ar-H) [38].

2.6.1.1 Effect of reaction time

The reaction was carried out using the reaction conditions described in the general procedure except for different reaction times being monitored: 5, 15, 30 min.

2.6.1.2 Effect of solvent

Phenol (11.7 mg, 0.125 mmol) and HBA (66.5 mg, 0.125 mmol) were allowed to react according to the general procedure except for the solvent: hexane, and hexane:MeCN (1:1) being used instead of MeCN.

2.6.2 Bromination of thymol

Thymol (18.7 mg, 0.125 mmol) was dissolved in MeCN (0.5 mL). NBS (22.3 mg, 0.125 mmol) or HBA (66.5 mg, 0.125 mmol) was added. The reaction was performed under UV at RT. Water (0.5 mL) was added to quench the reaction. Two products were separated with silica gel column using 10% EtOAc in hexane and characterized with ^{1}H NMR. The yield of all products (4-bromothymol and 4,6-dibromothymol) were analyzed by GC.

4-bromo-6-isopropyl-3-methylphenol: white solid. ^{1}H NMR ($CDCl_3$) **δ** (ppm): 1.26 (*d*, *J* = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.33 (*s*, 3H, Ar-CH_3), 3.17 (*m,* 1H, $CH(CH_3)_2$), 6.66 (*s*, 1H, Ar-H) and 7.31 (*s*, 1H, Ar-H) [39].

2,4-dibromo-6-isopropyl-3-methylphenol: white solid. ^{1}H NMR ($CDCl_3$) **δ** (ppm): 1.21 (*d*, *J* = 6.8 Hz, 6H, $CH(CH_3)_2$), 2.52 (*s*, 3H, Ar-CH_3), 3.25 (*m*, 1H, $CH(CH_3)_2$), and 7.31 (*s*, 1H, Ar-H) [40].

2.6.3 Bromination of pinostrobin

Pinostrobin (33.7 mg, 0.125 mmol) was dissolved in MeCN (0.5 mL) and HBA (66.5 mg, 0.125 mmol) was added. The reaction was performed under UV radiation at RT. Water (0.5 mL) was added to quench the reaction. Three products were separated by silica gel column using 10% EtOAc in hexane and characterized with ^{1}H NMR. Yields of all products were analyzed by using GC.

6-bromo-5-hydroxy-7-methoxy-2-phenylchroman-4-one: yellow solid. ^{1}H NMR ($CDCl_3$) **δ** (ppm): 2.87 (*dd*, *J* = 17.3, 3.1 Hz, 1H, COC$\underline{H}_2$CH), 3.13 (*dd*, *J* = 17.3, 4.0 Hz, 1H, COC$\underline{H}_2$CH), 3.92 (*s*, 3H, Ar-OC$\underline{H}_3$), 5.46 (*dd*, *J* = 13.2, 3.1 Hz, 1H, COCH$_2$C$\underline{H}$), 6.18 (*s*, 1H, Ar-$\underline{H}$), 7.40–7.56 (*m*, 5H, Ar-$\underline{H}$) and 12.61 (*s*, 1H, Ar-O$\underline{H}$).

8-bromo-5-hydroxy-7-methoxy-2-phenylchroman-4-one: yellow solid. ^{1}H NMR ($CDCl_3$) **δ** (ppm): 3.05 (*m*, 2H, COC$\underline{H}_2$CH), 3.92 (*s*, 3H, Ar-OC$\underline{H}_3$), 5.58 (*dd*, *J* = 12.0, 3.5 Hz, 1H, COCH$_2$C$\underline{H}$), 6.17 (s, 1H, Ar-$\underline{H}$), 7.34-7.66 (*m*, 5H, Ar-$\underline{H}$) and 12.16 (*s*, 1H, Ar-O$\underline{H}$).

6,8-dibromo-5-hydroxy-7-methoxy-2-phenylchroman-4-one: yellow solid. ^{1}H NMR ($CDCl_3$) **δ** (ppm): 3.02 – 3.25 (*m*, 2H, COC$\underline{H}_2$CH), 3.99 (*s*, 3H, Ar-OC$\underline{H}_3$), 5.61 (*dd*, *J* = 12.2, 3.5 Hz, 1H, COCH$_2$C$\underline{H}$), 7.40 – 7.56 (*m*, 5H, Ar-$\underline{H}$) and 12.61 (*s*, 1H, Ar-O$\underline{H}$).

2.6.3.1 Effect of solvent

The reaction was carried out following the general protocol except for three diverse solvents: MeOH, hexane, MeCN: hexane (1:1) and MeCN: hexane (1:4) being used instead of MeCN.

2.6.3.2 Effect of reaction time

The reaction was carried out using the reaction conditions described in the general procedure except for different reaction time being monitored: 5, 10, 15 min.

2.6.4 Bromination of flavone and 4′-chloroflavanone

Flavone (27.7 mg, 0.125 mmol) was dissolved in 0.5 mL of MeCN. HBA (66.5 mg, 0.125 mmol) was added. The reaction was performed under UV at RT for 30 min. Water 0.5 mL was added to quench the reaction and extract the organic phase with 5.0 mL of Et_2O.

The bromination of 4′-chloroflavanone was operated by mixing 4′-chloroflavanone (32.3 mg, 0.125 mmol) with HBA (66.5 mg, 0.125 mmol). The mixture was dissolved in MeCN 0.5 mL and stirred under UV at RT for 30 min. The reaction was quenched with water 0.5 mL and extracted with Et_2O 5.0 mL. The crude mixture was separated by silica gel column using 10% EtOAc in hexane. The yield of the product that obtained was quantified by ^{1}H NMR.

3,3′-dibromo-2-(4-chlorophenyl)chroman-4-one: yellow solid. ^{1}H NMR ($CDCl_3$) **δ** (ppm): 5.28 (*s*, 1H, $COCBr_2C\underline{H}$), 7.11 (*dd*, *J* = 8.4, 1.1 Hz, 1H, Ar-<u>H</u>), 7.21 (*ddd*, *J* = 8.1, 7.2, 1.1 Hz, 1H, Ar-<u>H</u>), 7.45 (*d*, *J* = 8.6 Hz, 2H, Ar-<u>H</u>), 7.62 (*ddd*, *J* = 8.7, 7.2, 1.7 Hz, 1H, Ar-<u>H</u>), 7.70 (*d*, *J* = 8.5 Hz, 2H, Ar-<u>H</u>) and 8.09 (*dd*, *J* = 8.0, 1.7 Hz, 1H, Ar-<u>H</u>).

2.6.5 Bromination of allylbenzene and safrole

The bromination of allylbenzene was explored under two different conditions. The mixture of allylbenzene (118.2 mg, 1 mmol) and two diverse brominating agents: HBA or NBS (1 mmol) was dissolved in CCl_4 (6 mL). The reaction was refluxed vigorously in the presence of light for 24 h. In the case of NBS, the solid formed during the reaction was filtered off and the crude product was chromatographed over silica gel and eluted with 5% EtOAc in hexane.

The other condition, allylbenzene (14.7 mg, 0.125 mmol) was dissolved in MeCN (0.5 mL) in 2 quartz cells. NBS (22.3 mg, 0.125 mmol) or HBA (66.5 mg, 0.125 mmol) was added. The reaction was performed under UV at RT. Adding 0.5 mL of water to quench the reaction. The yield of all products were quantified by GC.

(2,3-dibromopropyl)benzene: yellowish oil. ^{1}H NMR ($CDCl_3$) **δ** (ppm): 3.15 (*dd*, *J* = 14.5, 7.8 Hz, 1H, Ar-C<u>H</u>$_2$CHBrCH_2Br), 3.50 (*d*, *J* = 7.0 Hz, 1H, Ar-C<u>H</u>$_2$CHBrCH_2Br), 3.65 (*dd*, *J* = 10.5 Hz, 1H, Ar-CH_2CHBrC<u>H</u>$_2$Br), 3.85 (*dd*, *J* = 10.5, 4.2 Hz, 1H, Ar-CH_2CHBrC<u>H</u>$_2$Br), 4.38 (*m*, 1H, Ar-CH_2C<u>H</u>BrCH_2Br) and 7.50 – 7.15 (*m*, 5H, Ar-<u>H</u>) [41].

(1-bromoallyl)benzene: colorless oil. ^{1}H NMR ($CDCl_3$) **δ** (ppm): 3.97 (*dd*, *J* = 11.4, 4.1 Hz, 1H, Ar-CBrHCH=C<u>H</u>$_2$), 4.29 (*dd*, *J* = 11.4, 4.2 Hz, 1H, Ar-CBrHCH=C<u>H</u>$_2$), 4.77 (*dt*, *J* = 9.5, 4.2 Hz, 1H, Ar-CBrHC<u>H</u>=CH_2), 5.34 (*d*, *J* = 9.5 Hz, 1H, Ar-CBr<u>H</u>CH=CH_2) and 7.34 – 7.56 (*m*, 5H, Ar-<u>H</u>) [42].

The bromination of safrole was operated by mixing safrole (20.2 mg, 0.125 mmol) with HBA (66.5 mg, 0.125 mmol) and dissolved the mixture in MeCN 0.5 mL. The reaction was operated under the UV at RT for 30 min. Adding 0.5 mL of water to quench the reaction and extracted with Et_2O. The mixture of safrole and product was separated with 5% EtOAc in hexane. The product was characterized with ^{1}H NMR. The yield of product was quantified by GC.

5-(2,3-dibromopropyl)benzo[d][1,3]dioxole: yellowish solid. ^{1}H NMR ($CDCl_3$) **δ** (ppm): 3.06 (*dd*, *J* = 14.6, 7.5 Hz, 1H, Ar-CH_2CHBrC$\underline{H}_2$Br), 3.39 (*dd*, *J* = 14.6, 4.8 Hz, 1H, Ar-CH_2CHBrC$\underline{H}_2$Br), 3.54-3.65 (m, 1H, Ar-C$\underline{H}_2$CHBrCH_2Br), 3.81 (*dd*, *J* = 10.5, 4.1 Hz, 1H, Ar-C$\underline{H}_2$CHBrCH_2Br), 4.25-4.35 (*m*, 1H, Ar-CH_2C$\underline{H}$BrCH_2Br), 5.96 (*dd*, *J* = 5.0, 1.2 Hz, 2H, O-C$\underline{H}_2$-O) and 6.71-6.82 (*m*, 3H, Ar-$\underline{H}$) [43].

2.6.5.1 Effect of reaction time on the bromination of safrole

The reaction was carried out using the reaction conditions described in the general procedure except for reaction time at 2 h being monitored. The yields of product in crude mixture were quantified with ^{1}H NMR.

2.7 Competitive study on the bromination of phenol and allylbenzene

Phenol (11.7 mg, 0.125 mmol), allylbenzene (14.7 mg, 0.125 mmol) and HBA (66.5 mg, 0.125 mmol) were mixed. Other conditions were followed the general protocol. The molar ratio of phenol: allylbenzene: HBA was varied as 2:2:1, 4:4:1 and 8:8:1

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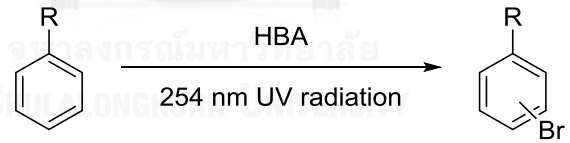
Chapter III

RESULTS AND DISCUSSION

Haloarenes have been utilized as versatile intermediates in organic synthesis. The systematic studies for the manipulation of haloarenes, especially chloroarenes have widely been addressed whereas those for bromination of aromatics still have not been verified since usable brominating agents are limited. The classical bromination of aromatics normally used liquid bromine (Br_2) and toxic or expensive halogenating catalyst such as mercuric acetate, trifluoroacetate or other Lewis acids [10]. Side products from the reaction were high acidic and high corrosion. Thus, the main aim of this research is to explore the utilization of a new brominating agent (HBA) for aromatic bromination. HBA has been used as a brominating agent for many reactions such as bromination of alcohols [28], ring opening of epoxides [30] and bromination of benzyl and allyl alcohols [31]. However, HBA has not been reported as a brominating agent for aromatics. The exploration of optimum conditions utilizing this developed HBA for the synthesis of bromoarenes was additionally carried out. The general equation can be simplified as shown below.



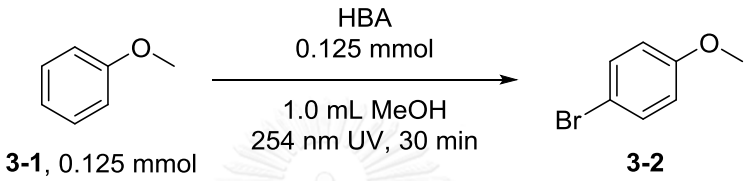
R = EDG and EWG group

3.1 Conditions optimization for the bromination of anisole

For conditions optimization, anisole **(3-1)** was chosen as a template. Many factors concerning the bromination of anisole **(3-1)** such as effect of temperature and UV radiation, solvents, reaction time, concentration of anisole, molar ratio of anisole: HBA, and additives are needed to be scrutinized. This section was aimed to screen for appropriate conditions and will use for the bromination of other aromatics.

General procedure

The mixture of anisole **(3-1)** and HBA was dissolved in MeOH and placed in quartz cells. The mixture was stirred for 30 min upon the irradiation of UV (254 nm) at RT. After being completed, the reaction was quenched by saturated $NaHCO_3$. The reaction mixture was then extracted with Et_2O and dried over anhydrous Na_2SO_4. The quantification of 4-bromoanisole **(3-2)** was carried out by GC using biphenyl as an internal standard.



4-Bromoanisole **(3-2)** was a commercially available compound using as the standard for GC, while 2,4-dibromoanisole **(3-3)** was synthesized by treating anisole **(3-1)** with Br_2 in MeOH and stirred at RT overnight, the product was obtained in 89.3 % yield with R_t 8.53 min by SGE-BP1. The derived product was characterized with ^{1}H NMR. The ^{1}H NMR spectrum displays the methoxy protons at **δ** 3.87 (*s*, 3H) and the aromatic protons at **δ** 6.76 (*d*, *J* = 8.7 Hz, 1H), 7.36 (*dd*, *J* = 8.7, 2.5 Hz, 1H) and 7.65 *(d, J* = 2.4 Hz, 1H).

3.1.1 Effect of temperature and UV radiation

Four sets of experiments were performed to explore the optimized conditions. The first reaction was conducted without irradiating the reaction by UV, while the second reaction was the same as the former except for adding $AlCl_3$ (5% mole of anisole) to the reaction. The third and the forth reactions were performed to observe the effect of reaction temperature at 0°C and at refluxed temperature of the reaction, respectively. The results are presented in Table 3.1.

Table 3.1 The effects of temperature and UV radiation on the bromination of anisole **(3-1)**

Entry	Conditions	%Recovery	%Yield	MB (%)
1	Without UV, RT	79	12	91
2	Without UV, RT, 5% $AlCl_3$	99	4	103
3	Without UV, 0°C	100	0	100
4	Without UV, refluxing MeOH	71	16	87
5	UV, RT	34	73	107

Reaction conditions: anisole **(3-1)** (0.125 mmol), HBA (0.125 mmol), MeOH (1.0 mL) for 30 min

According to the effect of UV radiation and temperature on the formation of 4-bromoanisole **(3-2)**, the reaction in the absence of UV (entry 1) generated the target product in poor yield. The addition of Lewis acid as $AlCl_3$ (5% mole) (entry 2) did not improve the yield of target product. This was clearly demonstrated that a radiation of UV was important for this reaction. When the reaction was performed at 0°C and refluxing MeOH, the former could not produce 4-bromoanisole **(3-2)** (entry 3), while the latter (entry 4) generated the product in poor yield. Therefore, the reaction must perform at RT with UV radiation.

3.1.2 Effect of solvents

The effect of solvent on the bromination of anisole **(3-1)** was carried out following the general protocol except for five diverse solvents (DCE, THF, EtOAc, Et_2O and MeCN) being used instead of MeOH. The results are presented in Table 3.2.

Table 3.2 The effects of solvent on the bromination of anisole **(3-1)**

Entry	Solvent	%Recovery	%Yield	MB (%)
1	DCE	88	10	98
2	THF	98	5	103
3	EtOAc	77	20	97
4	Et_2O	91	3	94
5	MeCN	55	49	104
6	MeOH	30	69	99

Reaction conditions: anisole **(3-1)** (0.125 mmol), HBA (0.125 mmol), solvent (1.0 mL), UV RT for 30 min

Table 3.2 reveals that when the reaction was performed in different media, the yields of product were increased in the order of using MeOH> MeCN > EtOAc > DCE > THF > Et_2O. This observation suggests that more polar solvent would stabilize an active bromine species forming in the reaction.

3.1.3 Effect of reaction time

The third parameter for optimization is reaction time. The reactions were carried out as described in the general procedure except for reaction time being varied: 1, 5, 15, 30 and 60 min. The results are accumulated in Table 3.3.

Table 3.3 The effects of reaction time on the bromination of anisole **(3-1)**

Entry	Time (min)	%Recovery	%Yield	MB (%)
1	1	91	9	100
2	5	69	25	94
3	15	21	59	80
4	30	30	69	99
5	60	0	87	87

Reaction conditions: anisole **(3-1)** (0.125 mmol), HBA (0.125 mmol), MeOH (1.0 mL), UV RT

From the aforementioned results, the yield of products increased when the reaction was performed for longer time. At 1-30 min, the reactions were not completed and anisole **(3-1)** could still be detected in every reaction. The reaction seemed to complete within 60 min. Though the reaction for 60 min could make the reaction complete, it was too long. Therefore, other factors that affected on the reaction have to be determined.

3.1.4 Effect of anisole concentrations

The reaction was performed according to the general procedure except for the concentration of anisole **(3-1)** being altered as 0.03, 0.06, 0.13, 0.25 and 0.50 mM. The concentrations of anisole were controlled by adjusting the volume of the solution using MeOH. The results are described in Table 3.4.

Table 3.4 The effects of the concentration of anisole

Entry	Concentration (mM)	%Recovery	%Yield	MB (%)
1	0.03	51	47	99
2	0.06	32	65	97
3	0.12	27	72	99
4	0.25	8	91	99
5	0.50	39	47	86

Reaction conditions: anisole **(3-1)** (0.125 mmol), HBA (0.125 mmol), MeOH, UV RT for 30 min

Form Table 3.4, the yield of the target product was increased when high concentration of anisole was used. However, using 0.50 mM of anisole, the yield of target product was lower than 0.25 mM (entries 4 and 5). This may indicate the using 0.25 mL of MeOH was too little volume for the reaction. Thus, the best concentration to optimize conditions was 0.25 mM anisole or using MeOH 0.5 mL.

3.1.5 Effect of molar ratio of anisole: HBA

The fifth parameter is the molar ratio of anisole to HBA. The reaction was carried out following the general procedure except for the molar ratio of anisole: HBA being altered: 1.00: 1.00, 1.00: 0.50, 1.00: 0.25 and 1.00: 0.12. The results are described in Table 3.5.

Table 3.5 The effect of the molar ratio of anisole: HBA

Entry	Molar ratio of anisole: HBA	%Recovery	%Yield		MB (%)
			Based on anisole	Based on HBA	
1	1.00: 1.00	29	78	78	108
2	1.00: 0.50	71	47	98	118
3	1.00: 0.25	68	38	130	106
4	1.00: 0.12	84	21	171	105

Reaction conditions: anisole **(3-1)** (0.125 mmol), HBA, MeOH 1.0 mL, UV RT for 30 min

From the above table, when the ratio of anisole: HBA increased or using less HBA, the formation of 4-bromoanisole **(3-2)** was decreased. This was clearly demonstrated that the amount of HBA was essential for this reaction. Considering the yield of target product based on the amount of HBA, the formation of 4-bromoanisole **(3-2)** was increased when less amount of HBA was employed. This experiment was additionally set up to observe the efficiency of HBA. In entry 4, with the molar ratio of anisole: HBA 8:1, the target product was attained in very high yield based on the mole of brominating agent used. These results displayed a good efficiency of HBA as the brominating agent for aromatic bromination. However, this result must be compared with other brominating agents used.

3.1.6 Effect of additives

The last variation examined was the effects of additives. The reaction was performed according to the general procedure except for adding selected additives.

The following additives (5% mol of anisole) including $CrBr_3$, $InCl_3$, $AlCl_3$, $NiCl_2$ and $FeCl_3$ were added in the reaction. Two molar ratios of anisole: HBA (1:1) and reaction time at 15 and 30 min were investigated. The additive was chosen depended on the literature review that Lewis acid is well known as a good catalyst for aromatic bromination [10]. The results are presented in Table 3.6.

Table 3.6 The effect of additives on the bromination of anisole **(3-1)** at 1:1 molar ratio of anisole: HBA

Entry	Time (min)	Additive	%Recovery	%Yield	MB (%)
1	15	$InCl_3$	35	53	88
2		$AlCl_3$	59	45	104
3		$NiCl_2$	52	56	108
4		no additive	48	52	100
5	30	$CrBr_3$	44	59	103
6		$InCl_3$	37	58	95
7		$AlCl_3$	40	66	106
8		$NiCl_2$	34	56	90
9		$FeCl_3$	43	34	77
10		no additive	38	62	100

Reaction conditions: anisole **(3-1)** (0.125 mmol), HBA (0.125 mmol), MeOH 1.0 mL, UV RT for 30 min

From the aforementioned results, at 30 min (entries 5-10), all additives did not assist the improvement for the formation of 4-bromoanisole **(3-2)**, except $AlCl_3$ (entry 7) was slightly enhanced the activation process of the reaction. The reactions were then tried to conduct in shorter time (15 min). Nonetheless, similar results were observed. These results indicated that additive had a slight or none effect to enhance the performance of this reaction.

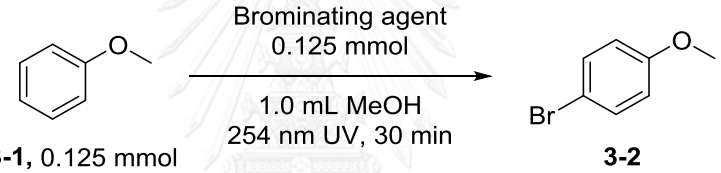
According to all observation and condition optimization for the bromination of anisole **(3-1)**, the optimum conditions could be drawn as anisole (0.125 mmol, 0.25 mM), 1:1 molar ratio of anisole: HBA in MeOH at RT under UV irradiation.

3.2 The effect of brominating agents: a comparative study

3.2.1 Comparative study on the bromination of anisole with selected brominating agents

Various brominating agents used in this research: HBr, liquid Br_2, bromine water and NBS are commercially available. The effects of type of brominating agents on the bromination of anisole **(3-1)** were examined and the results are presented in Table 3.7.

Table 3.7 The effects of brominating agents on the bromination of anisole **(3-1)**



Entry	Brominating agent	%Recovery	%Yield	MB (%)
1	HBA	29	78	107
2	NBS	14	82	96
3	Br_2	0	62 (42)[a]	104
4	Bromine water	35	63	98
5	HBr	92	0	92

[a] 2,4-dibromoanisole **(3-3)**

The yields of 4-bromoanisole **(3-2)** from the reaction of anisole with 5 different brominating agents under optimum conditions were compared. HBA and NBS were reacted with anisole **(3-1)** to yield 4-bromoanisole **(3-2)** in high yield (entries 1-2). The reaction with Br_2 (entry 3) yielded two products; one was the target 4-bromoanisole **(3-2)**, while the other was characterized as 2,4-dibromoanisole **(3-3)** by comparing with an authentic sample using GC. Under this particular conditions

explored, the reaction with Br_2 seemed to undergo further bromination of the first product, 4-bromoanisole **(3-2)**. Thus, another experiment was carried out by reducing the molar equivalent of anisole: Br_2 to 2:1, the quantitative yield of the target molecule could be achieved with no sign of 2,4-dibromoanisole **(3-3)**. The reaction utilizing bromine water produced 4-bromoanisole **(3-2)** in moderate yield, while using HBr (48% w/w in H_2O) did not generate any product (entries 4-5). From entry 5, the mechanistic pathway of this reaction was suggested not to take place *via* Br^- as the normal mechanism when HBr was used [10].

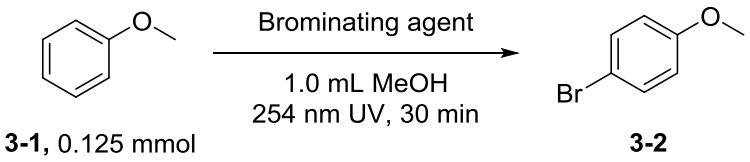
From the above results, Br_2 was found to be the best brominating agent. The regioselectivity of the reaction could be controlled by adjusting the molar equivalence of substrate and Br_2. Nevertheless, Br_2 is very hazardous liquid and hard to handle in formal reaction. Especially for Thailand where there is an extremely strict regulation not allow to import Br_2 to the kingdom or even with special permission to order, its prize is quite high and takes a long process to get the reagent. HBA was a reagent of choice that could provide the target product in high yield with ease of handle. Thus, HBA was selected for further study.

Based upon the aforementioned results, HBA and NBS were efficient brominating agents. NBS has been known as a good brominating agent for synthesis of many brominated compounds [44]. Comparing the yield of 4-bromoanisole **(3-2)** form HBA and NBS under optimum conditions, the yield derived from using NBS was slightly higher than that from HBA. Since this reaction was performed through UV irradiating which should generate bromine radical. The bond strength of N-Br (243 kJ/mol) is weaker than that of C-Br (276 kJ/mol) [45]; thus, NBS should generate bromine radical easier than HBA.

3.2.2 Comparative study on the molar ratio of anisole: brominating agents

The ratios of anisole **(3-1)** and selected brominating agents (HBA or NBS) were varied with the aim to study the efficiency of the brominating agent for the bromination of anisole **(3-1)**. The results are demonstrated in Table 3.8.

Table 3.8 The effects of molar ratio of anisole: brominating agent on the bromination of anisole



3-1, 0.125 mmol **3-2**

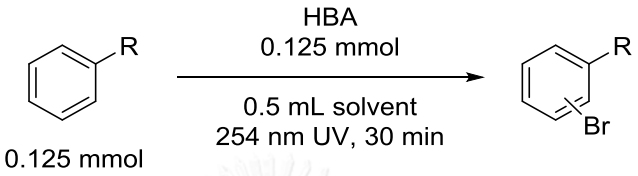
Entry	Brominating agent	Molar ratio of anisole: brominating agent	%Recovery	%Yield		MB (%)
				Based on anisole	Based on HBA	
1	HBA	1.00: 1.00	29	78	78	107
2		1.00: 0.25	68	38	129	106
3	NBS	1.00: 1.00	14	82	82	96
4		1.00: 0.25	82	8	37	90

From the above results, the suitable molar ratio of anisole **(3-1)**: brominating agent for the formation of 4-bromoanisole **(3-2)** was anisole: brominating agents (1:1) (entries 1 and 3). The yield of target product from the reaction using NBS was still higher than HBA. However, at lower molar ratio of anisole: brominating agents (1:0.25) (entries 2 and 4), the product yield in the case of HBA was significantly higher than NBS. These results pointed out that HBA was more efficient than NBS at lower concentration. Considering the yield of products based the amount of brominating agent employed, HBA revealed much more efficient than NBS with 129%, while that for NBS was only 37%.

3.3 Bromination of selected aromatics

Under the optimum conditions for the bromination of anisole **(3-1)**, other twelve aromatics were selected as substrates to explore the scope of this new protocol. In certain cases, when the yields of products were not good, MeCN was tried to use instead of MeOH. The results are collected as shown in Table 3.9.

Table 3.9 The bromination of selected aromatics with HBA



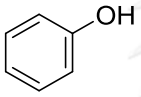
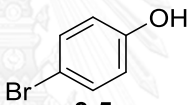
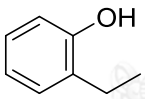
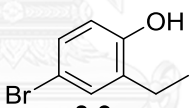
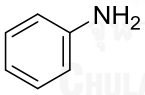
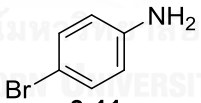
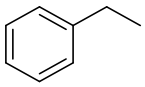
Entry	Solvent	Aromatic	Product	%Recovery	%Yield	MB (%)
1	MeOH	 **3-4**	 **3-5**	19	53	72
2		 **3-8**	 **3-9**	48	37	85
3		 **3-10**	 **3-11**	61	9	70
4		 **3-12**	no reaction	91	-	91

Table 3.9 (Continued)

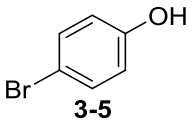
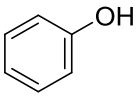
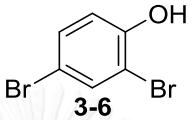
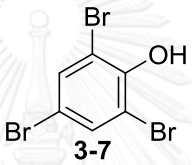
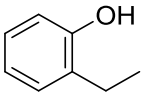
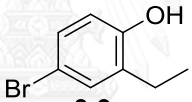
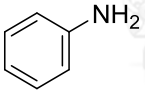
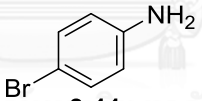
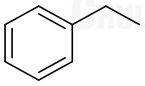
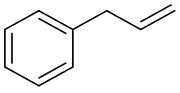
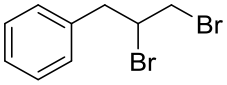
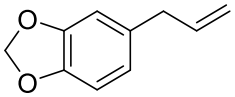
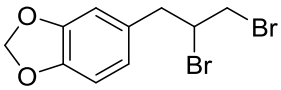
Entry	Solvent	Aromatic	Product	%Recovery	%Yield	MB (%)
			 **3-5**		80	
5		 **3-4**	 **3-6**	0	17	102
			 **3-7**		5	
6	MeCN	 **3-8**	 **3-9**	0	75	75
7		 **3-10**	 **3-11**	47	43	90
8		 **3-12**	no reaction	87	0	87
9		 **3-13**	 **3-14**	0	quant	100
10		 **3-15**	 **3-16**	56	36	92

Table 3.9 (Continued)

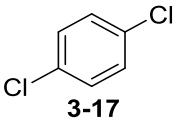
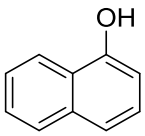
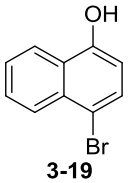
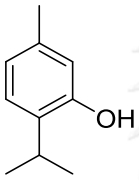
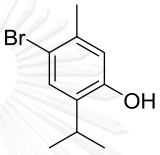
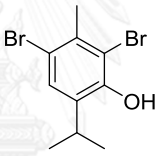
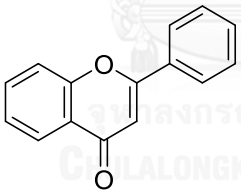
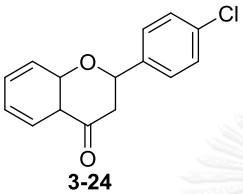
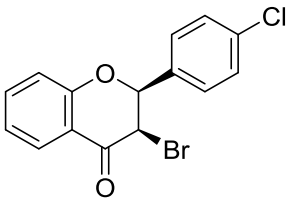
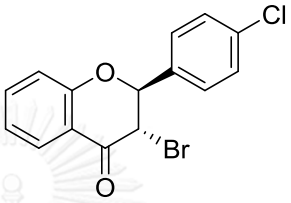
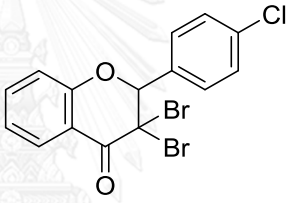
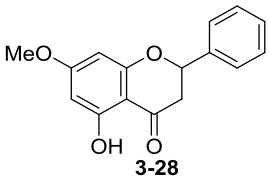
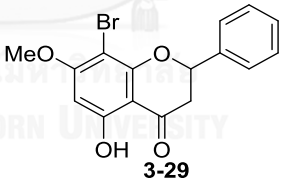
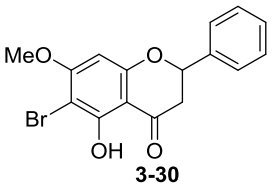
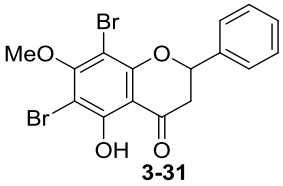
Entry	Solvent	Aromatic	Product	%Recovery	%Yield	MB (%)
11		 **3-17**	no reaction	95	0	95
12		 **3-18**	 **3-19**	0	79	79
13	MeCN	 **3-20**	 **3-21**  **3-22**	0	80 17	97
14		 **3-23**	no reaction	97	0	97

Table 3.9 (Continued)

Entry	Solvent	Aromatic	Product	%Recovery	%Yield	MB (%)
15	MeCN	 **3-24**	 **3-25** *cis*	0	27	96
			 **3-26** *trans*		37	
			 **3-27**		32	
16		 **3-28**	 **3-29**	0	31	106
			 **3-30**		47	
			 **3-31**		29	

Phenol **(3-4)** and aniline **(3-10)** (entries 5 and 7) were chosen to observe the effect of electron donating group containing in aromatic ring. The bromination of phenol **(3-4)** gave three products which were identified by comparison with authentic samples as 4-bromophenol **(3-5)**, 2,4-dibromophenol **(3-6)** and 2,4,6-tribromophenol **(3-7)**. For aniline **(3-10)**, Br_2 was *in situ* generated in reaction, and then reacted with aniline to give, low to moderate yield of 4-bromoaniline **(3-11)**. The ^{1}H NMR of compound (**3-11)** is presented in Fig 3.1.

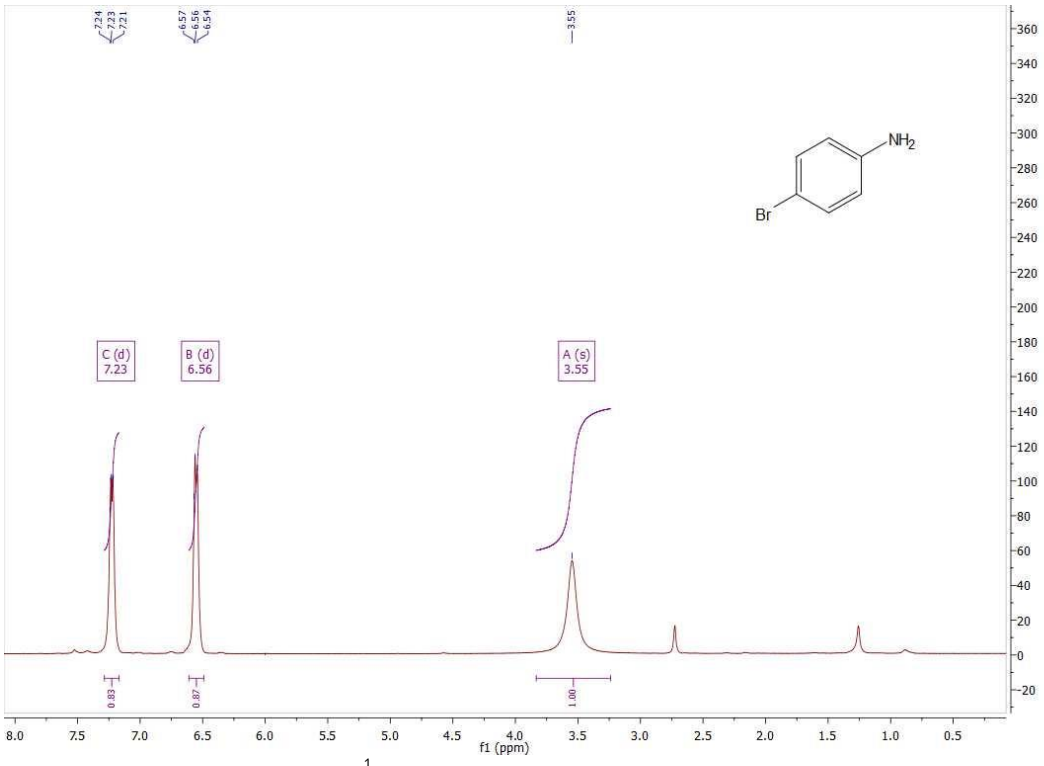


Figure 3.1 The ^{1}H NMR spectrum of 4-bromoaniline **(3-11)**

The next two selected compounds: ethyl benzene **(3-12)** and *p*-dichlorobenzene **(3-17)** (entries 8 and 11) were used as substrates. With HBA under the conditions studied, there was no brominated product observed. *p*-dichlorobenzne **(3-17)** was categorized as electron withdrawing group, so the bromination should not be taken place. Nonetheless, the weak electron donating group as ethyl still could not activate the aromatic ring. This caused no reaction being taken place with ethylbenzene **(3-12)**.

The regioselectivity study towards the bromination either at benzylic or aromatic positions was evaluated using *o*-ethylphenol **(3-8)** as a template (entry 6). It

was observed that the aromatic was more reactive than that at benzylic position since the sole brominated product taking place on aromatic could be detected. However, it was reported that this reaction also depended on polarity of solvent. With nonpolar solvent such as CCl_4 under reflux, the activation process may occur at the benzylic position [46].

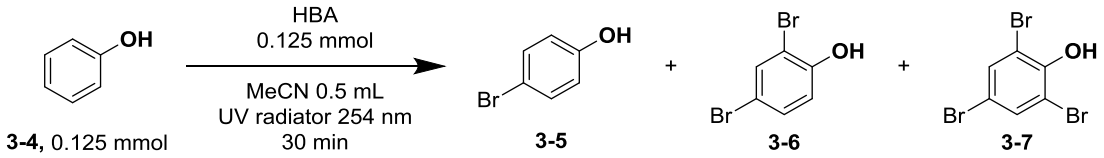
For allylbenzene **(3-13)** and safrole **(3-15)** (entries 9 and 10), these compounds were a good template since the bromination could take place at three plausible positions: benzylic, allylic, aromatic or unsaturation positions. The sole product of allylbenzene **(3-13)** with quantitative yield was characterized as a dibromo compound derived from the bromination at unsaturated portion of allylbenzene. The yield of the product from the bromination of safrole **(3-15)** (entry 10) was moderate; but still selectively yield the addition product.

For **α**-naphthol **(3-18)** and thymol **(3-20)** (entries 12-13), when **α**-naphthol **(3-18)** was reacted with HBA, only one product was observed at the *p*-position of phenolic ring. Thymol **(3-20)** produced mono- and di-substituted products. The mono-substituted product was formed by the bromination at *para*-position of phenolic OH, while di-substituted product was formed by bromination at the *para* and *ortho*-positions of phenolic OH. Due to the complication of compounds in entries 14-16, the details of those compounds were described in regioselective study section.

3.4 The regioselectivity study

3.4.1 Bromination of phenol (3-4)

Phenol **(3-4)** was chosen as the first substrate to explore the regioselectivity of the developed system. From preliminary study (Table 3.9), the bromination of phenol yielded three products- 4-bromophenol **(3-5)**, 2,4-dibromophenol **(3-6)** and 2,4,6-tribromophenol **(3-7)** with different extent.



4-Bromophenol (**3-5**) and 2,4-dibromophenol (**3-6**) are commercial available compounds, thus can be used as authentic samples to compare the behaviors on TLC and GC. 2,4,6-Tribromophenol (**3-7**) was prepared by treating phenol with bromine water to yield white precipitate. After recrystallization with EtOH, the white product with R_t 7.13 min (SGE-BP1) was characterized by ^{1}H NMR. The ^{1}H NMR spectrum reveals the signal at **δ** 7.58 (*s,* 2H) which could be assigned for two aromatic protons. With attempts trying to control the regioselectivity of this reaction, a series of experiments was carried out.

3.4.1.1 The effect of reaction time

The effect of reaction time was examined by carrying out the reaction as described in the general procedure except for different reaction time being monitored: 5, 15 and 30 min. The results are presented in Table 3.10.

Table 3.10 The effects of reaction time on the bromination of phenol **(3-4)** using HBA

Entry	Time (min)	%Recovery	%Yield			MB (%)
			3-5	3-6	3-7	
1	5	52	26	0	0	78
2	10	38	34	0	0	73
3	15	30	70	0	0	100
4	30	0	80	17	5	102
5	30[a]	0	59	11	8	78

Reaction conditions: phenol **(3-4)** (0.125 mmol), HBA (0.125 mmol), MeCN 0.5 mL, UV RT

[a] adding HBA 0.125 mmol in 4 portions

When the reaction was performed for short time (entries 1-3), both di- **(3-6)** and tri-substituted **(3-7)** products could not be detected. This manifestly exhibited that those products should derive from further bromination of 4-bromophenol **(3-5)**. Although the regioselectivity of these products was controlled by reaction time, the yield of the target product was still moderate with remained substrate. At 30 min, all phenols were converted, three products (**3-5** – **3-7**) were obtained although the addition of HBA was divided into 4 portions.

3.4.1.2 The effects of solvent

According to the literature, phenol could be brominated very rapidly yielding 2,4,6-tribromophenol **(3-8)** due to its high reactivity. The regioselectivity of the reaction could nevertheless be controlled by adjusting solvent. The polar solvent could stabilize the active bromine species (Br^+) well and generate a poly-substituted product. Therefore, a set of experiments was conducted according to the general procedure except for changing the solvent from MeCN to hexane and hexane:MeCN (1:1). The results are shown in Table 3.11.

Table 3.11 The effects of solvent on the bromination of phenol **(3-4)** using HBA

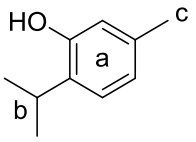
Entry	Solvent	%Recovery	%Yield			MB (%)
			3-5	3-6	3-7	
1	MeCN	0	80	17	5	102
2	Hexane	67	20	0	0	87
3	MeCN: Hexane (1:1)	0	85	0	0	85

Reaction conditions: phenol **(3-4)** (0.125 mmol), HBA (0.125 mmol), solvent 0.5 mL, 30 min, UV RT

Using less polarity solvent such as hexane (entry 2), none of di- **(3-6)** or tri-substituted **(3-7)** products were obtained. This result was well agreed with previous studies that less polarity solvent could control the regioselectivity of the reaction [23]. However, the yield of product obtained was low. The combination of different

polarity of solvent was thus tried. When the mixture of MeCN and hexane (1:1) was used instead of MeCN, 4-bromophenol **(3-5)** was detected in high yield. Remaining phenol, di- **(3-6)** and tri-substituted **(3-7)** products were not found. Thus, it could be concluded that the regioselectivity of the reaction could be controlled by performing the reaction in short time using a mixed solvent.

3.4.2 Bromination of thymol (3-20)



Thymol **(3-20)** is a monoterpene distributed in plant kingdom [47]. Considering the structure of this compound, it has 3 different positions that could be brominated, *i.e.*, (a) aromatic ring, (b) *iso*-propyl group and (c) methyl group. The reaction of thymol **(3-20)** with HBA under optimized conditions provided only the brominated product at aromatic ring. Mono- and di-substituted products were identified by separation from the reaction mixture with silica gel column using 10% EtOAc in hexane.

4-Bromo-6-*iso*propyl-3-methylphenol **(3-21)** was obtained as white solid (79.5% yield, R_t 7.47 min by SGE-BP1). The ^{1}H NMR spectrum (Fig 3.2) displays the methyl protons at **δ** 1.26 (*d*, *J* = 6.9 Hz, 6H) and that of the methine proton and at **δ** 3.17 (*m*, 1H) for *iso*propyl group. The methyl protons on aromatic ring were visualized at **δ** 2.33 (*s*, 3H) while two singlet signals with intensity of 1H each at **δ** 6.66 and 7.31 could be assigned for two protons of aromatic ring.

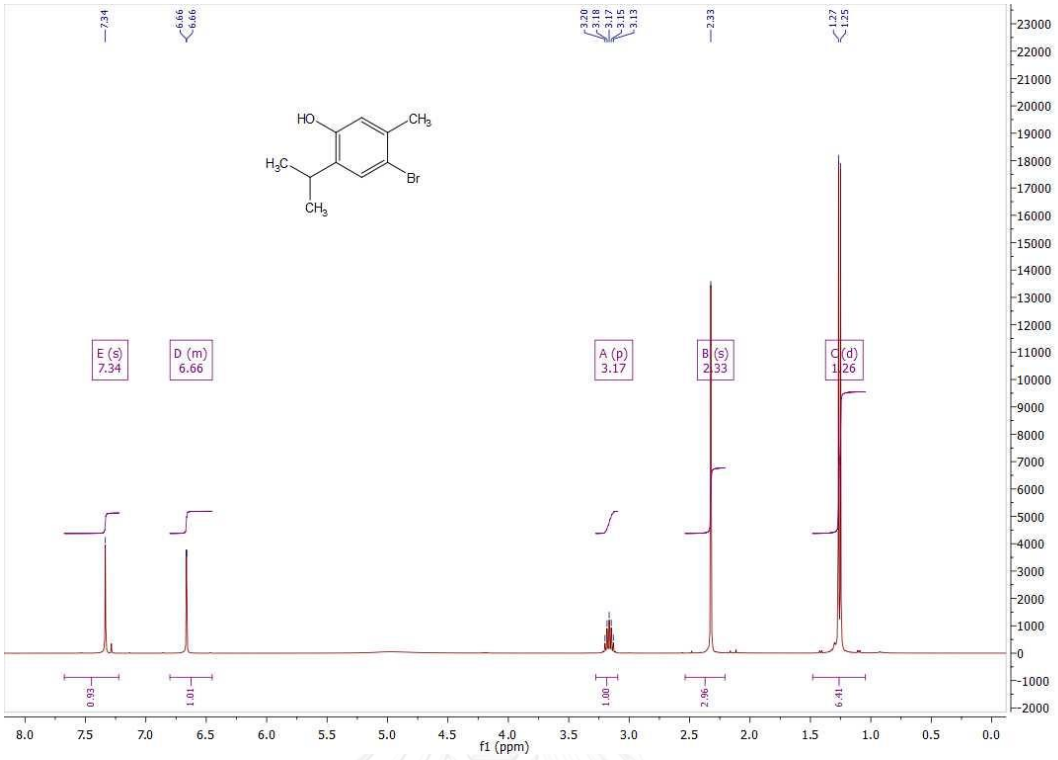


Figure 3.2 The ^{1}H NMR spectrum of 4-bromo-6-isopropyl-3-methylphenol **(3-21)**

The other isolated compound was obtained as white solid (16.6% yield, R_t 8.13 min SGE-BP1). The ^{1}H NMR spectrum (Fig 3.3) shows the proton signal of methyl protons at **δ** 1.21 (*d*, *J* = 6.8 Hz, 6H) and that of the methine proton at **δ** 3.25 (*m*, 1H) in *iso*propyl group. The methyl protons on aromatic ring ($C\underline{H}_3$-Ar) could be observed at **δ** 2.52 (s, 3H), while the hydroxyl group was detected at **δ** 5.68 (*s*, 1H). The rest singlet signal with 1H intensity at **δ** 7.31 (*s*, 1H) could be attributed to an aromatic proton. In addition, this spectrum was found to be different from Fig 3.3 and could be used to confirm the structure of dibromo compound since the proton signal at **δ** 6.66 was disappeared. This compound was thus identified as 2,4-dibromo-6-*iso*propyl-3-methylphenol **(3-22)**.

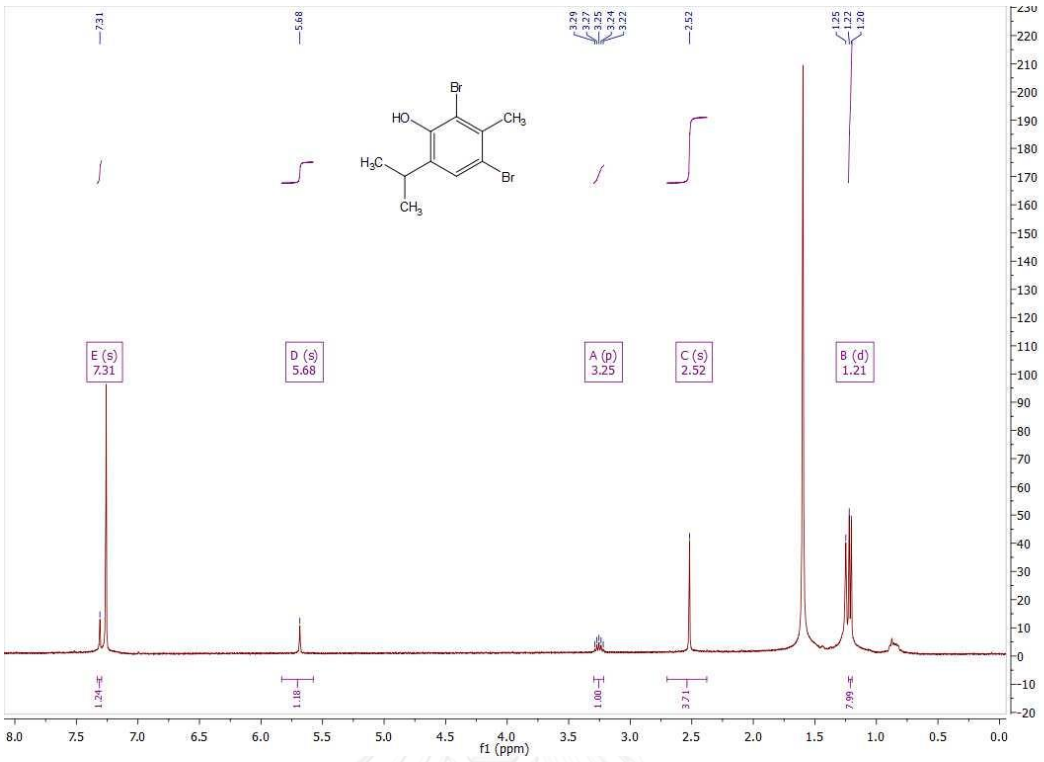
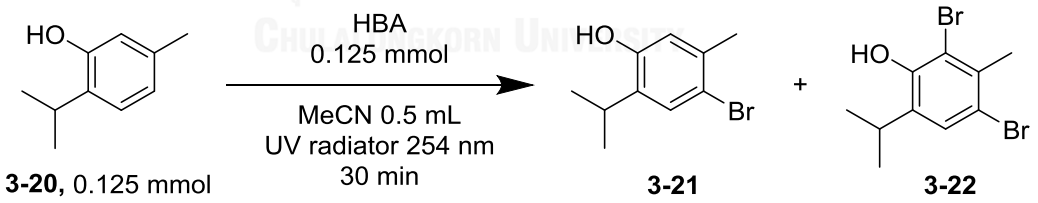


Figure 3.3 The ^{1}H NMR spectrum of 2,4-dibromo-6-isopropyl-3-methylphenol **(3-22)**

With the aim to make the developed system more selective, another experiment was carried out following the general protocol except for the slow addition of HBA into 4 portions. The results are described in Table 3.12.

Table 3.12 The effects of slow addition of HBA on the bromination of thymol **(3-20)**

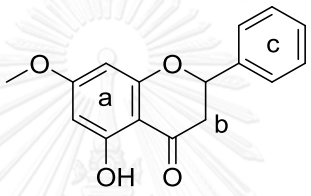


3-20, 0.125 mmol **3-21** **3-22**

Entry	Portion of HBA	%Recovery	%Yield		MB (%)
			3-21	3-22	
1	1	0	80	17	97
2	4	0	95	0	95

It could be seen that thymol **(3-20)** was a reactive compound that could react completely with HBA under optimum conditions yielding two products as mono- and dibromo compounds. For the molar ratio of anisole: HBA as 1.00: 0.25, 38% of 4-bromoanisole **(3-2)** was obtained (Table 3.5). This could speculate that using small amount of HBA may assist the formation of target product in high quantity. Attempting to gain a single monobromo compound **(3-21)** was accomplished by slow adding HBA in 4 portions to the reaction every 8 min. 95% of the target compound could be obtained.

3.4.3 Bromination of pinostrobin (3-28)



Pinostrobin (configuration *S*) **(3-28)**, a natural flavanone was isolated from the rhizomes of *Boesenbergia rotunda* (fingerroot) [48]. This molecule contained many functional groups such as carbonyl, methoxy and phenolic hydroxyl group. Thus, it should be a good probe to study the selectivity of this reaction. Three positions in pinostrobin **(3-28)** could be brominated, *i.e.*, (a) aromatic ring A bearing both methoxy and hydroxyl groups, (b) **α**-position of carbonyl group in ring B, and (c) the unsubstituted aromatic ring C.

After 30 min, the reaction of pinostrobin and HBA under optimized conditions was completed (followed by TLC) and worked up. The crude mixture was analyzed by GC (SGE-BP1) and displayed three signals at R_t 6.41, 6.80, and 7.16 min. The crude mixture was further analyzed by GC-MS to look for the information of the molecular weights of three brominated compounds. The GC-MS analysis results are presented in Figs 3.4 - 3.6.

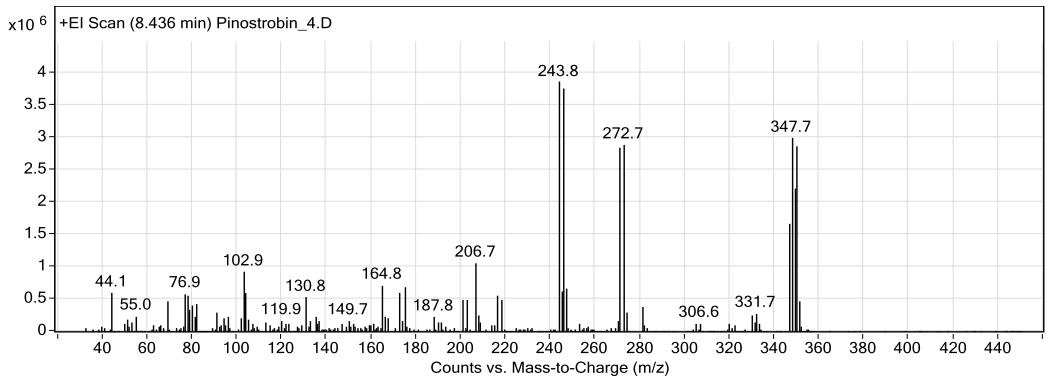


Figure 3.4 The mass spectrum of the compound at Rt 6.41 min

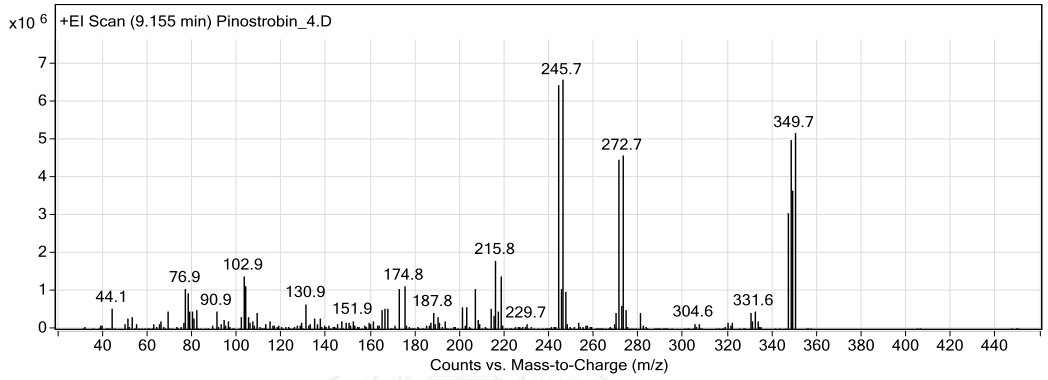


Figure 3.5 The mass spectrum of the compound at Rt 6.80 min

Two compounds at Rt 6.41 and 6.80 min exhibited the same molecular ion peak at m/z 348 (M+) together with another important peak at m/z 350 (M+2)+ as isotopic clusters separated by two mass units and the expected ratio 1:1 for one bromine atom present as a substituent on aromatic. Thus, these two compounds should be mono-substituted pinostrobin [49].

For the compound with Rt 7.16 min, the mass spectrum (Figure 3.5) clearly revealed the molecular ion peak at m/z 428 which was well-matched with the molecular weight of 6,8-dibromopinostrobin (3-31). The spectrum exhibited three important peaks at m/z 426 (M+), 428 (M+2)+ and 430 (M+4)+ with 1:2:1 ratio at two mass units difference, thus reflecting the presence of the two bromine atoms [49].

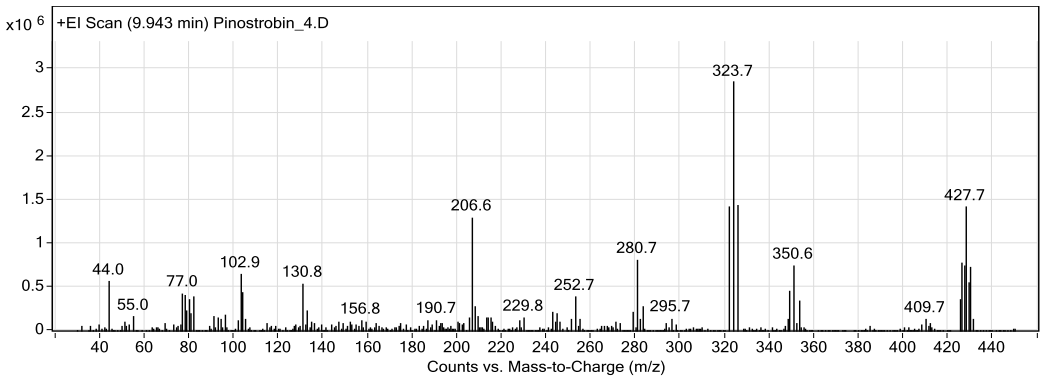


Figure 3.6 The mass spectrum of the compound at Rt 7.16 min

In order to gain an authentic sample, the separation of the crude mixture was performed by silica gel column using 10% EtOAc in hexane as an eluent. The first isolated compound as yellow solid (30.5% yield) was identified as 8-bromo-5-hydroxy-7-methoxy-2-phenylchroman-4-one or 8-bromopinostrobin (**3-29)** which revealing as a single peak at R_t 6.41 min. The ^{1}H NMR of this compound is presented in Fig 3.7.

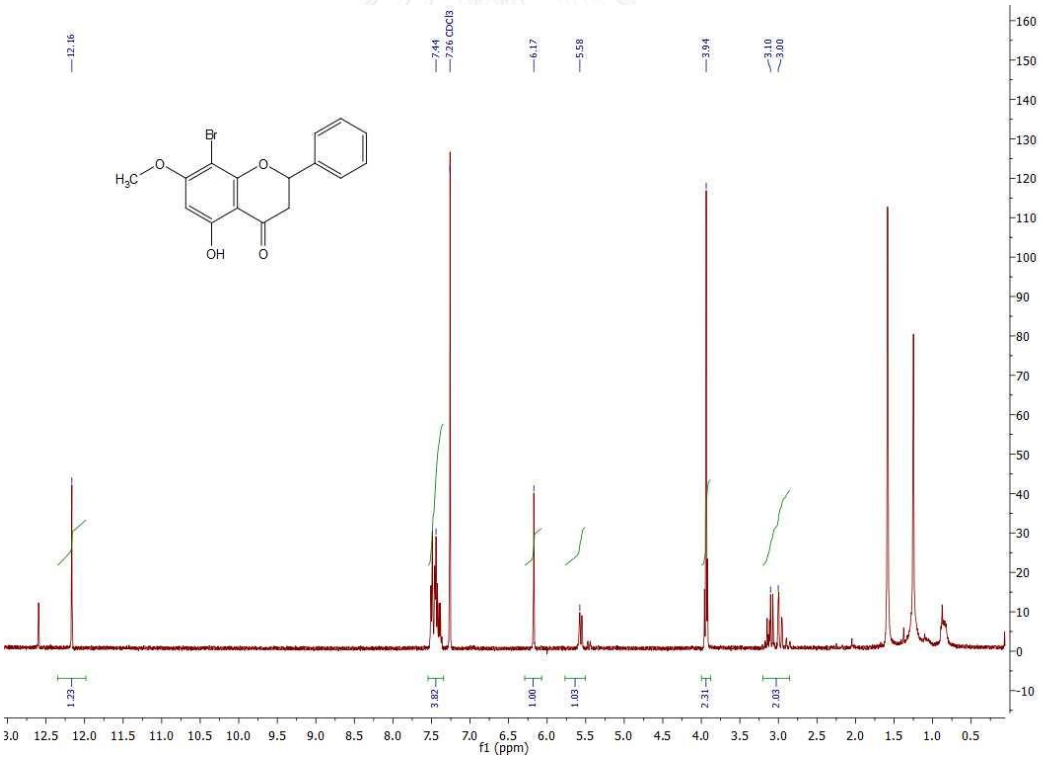


Figure 3.7 The ^{1}H NMR spectrum of the compound at R_t 6.41 min (8-bromo-5-hydroxy-7-methoxy-2-phenylchroman-4-one, **3-29**)

The ^{1}H NMR spectrum (Fig 3.7) reveals the signals at **δ** 3.05 (*m*, 2H) and 3.92 (*s*, 3H) of **α**-carbonyl and methoxy protons, respectively. The benzylic proton could be observed at **δ** 5.58 (*dd*, *J* = 12.0, 3.5 Hz, 1H). In addition, the aromatic protons could be visualized at **δ** 6.17 (*s*, 1H) and 7.34–7.66 (*m*, 5H). The phenolic proton was detected at **δ** 12.16 (*s*, 1H).

The second isolated compound as yellow solid (46.9% yield) which revealed a single peak at R_t 6.80 min was identified as 6-bromo-5-hydroxy-7-methoxy-2-phenylchroman-4-one (6-bromopinostrobin), **3-30**. Its ^{1}H NMR spectrum is shown in Fig 3.8.

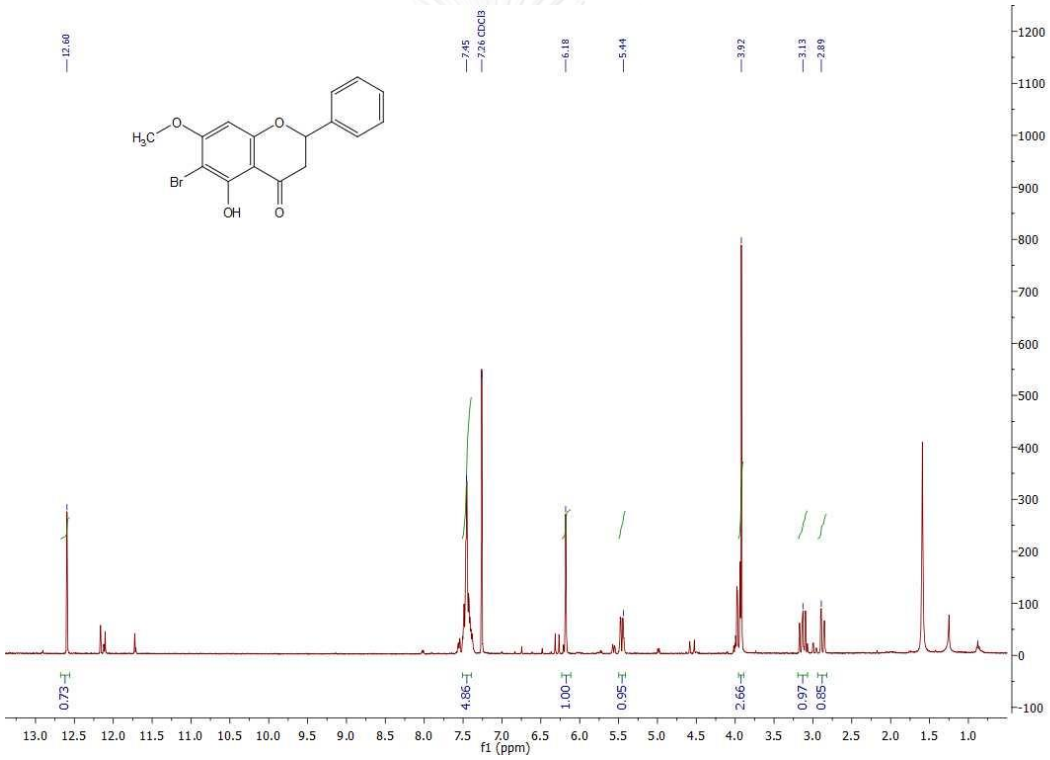


Figure 3.8 The ^{1}H NMR spectrum of the compound at R_t 6.80 min (6-bromo-5-hydroxy-7-methoxy-2-phenylchroman-4-one, **3-30**)

The ^{1}H NMR spectrum reveals the signals at **δ** 2.87 (*dd*, *J* = 17.3, 3.1 Hz, 1H), 3.13 (*dd*, *J* = 17.3, 4.0 Hz, 1H) of **α**-carbonyl protons, and that of methoxy protons at **δ** at 3.92 (*s*, 3H). The benzylic proton could be observed at **δ** 5.46 (*dd*, *J* = 12.0, 3.5

Hz, 1H).The signals attributing to aromatic protons at **δ** 6.18 (*s*, 1H) and 7.40–7.56 (*m*, 5H), and the phenolic proton was visualized at **δ** 12.61 (*s*, 1H).

The last compound as yellow solid (28.6% yield) exhibited a single peak at R_t 7.16 min was characterized as 6,8-dibromo-5-hydroxy-7-methoxy-2-phenylchroman-4-one (6,8-dibromopinostrobin), **3-31**. The ^{1}H NMR spectrum of this compound is presented in Fig 3.9.

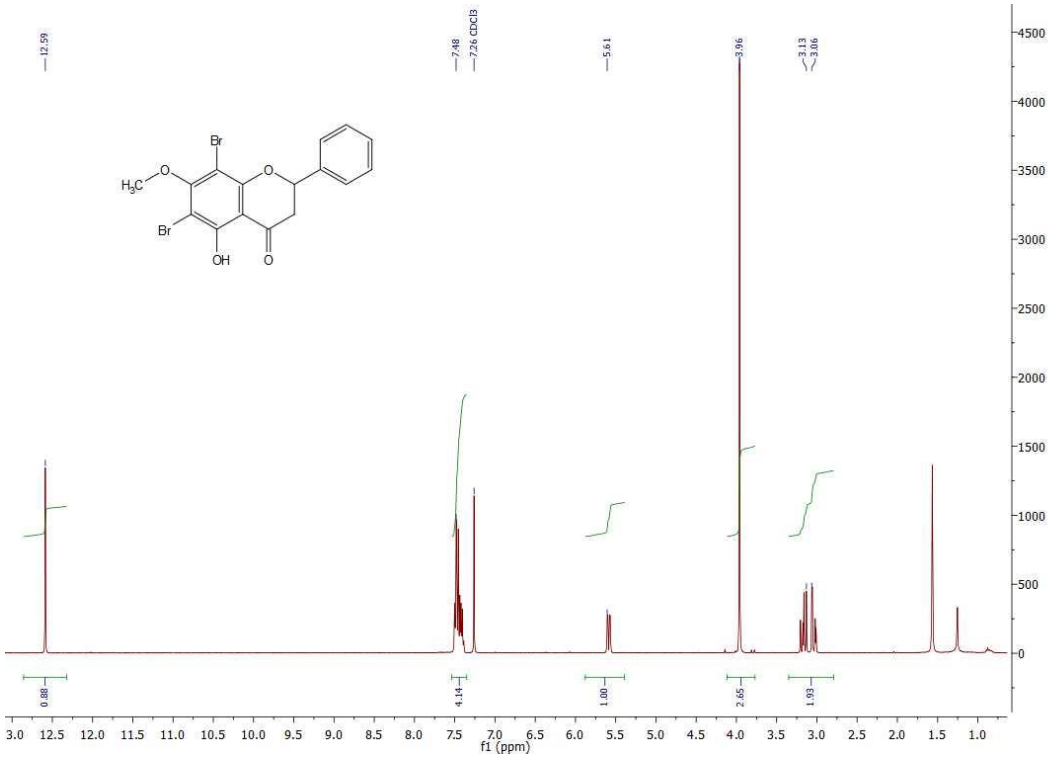


Figure 3.9 The ^{1}H NMR spectrum of the compound with R_t 7.16 min (6,8-dibromo-5-hydroxy-7-methoxy-2-phenylchroman-4-one, **3-31**)

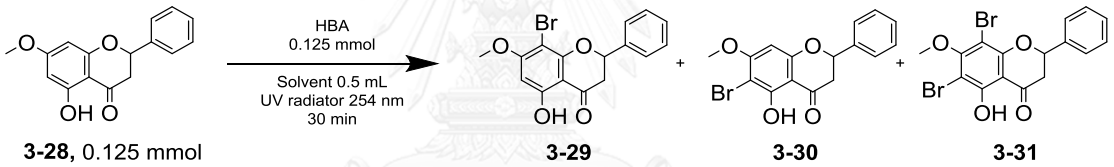
The ^{1}H NMR spectrum reveals the signals at **δ** 3.02-3.25 (*m*, 2H) of **α**-carbonyl protons and that of methoxy protons at **δ** 3.99 (*s*, 3H). The benzylic proton could be observed at **δ** 5.61 (*dd*, *J* = 12.2, 3.5 Hz, 1H). Additionally, the spectrum displayed the aromatic proton signals at **δ** 7.40–7.56 (*m*, 5H), while the phenolic proton was detected at **δ** 12.61 (*s*, 1H).

Moreover, this compound was analyzed with HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{12}Br_2O_4Na$ 450.89741; Found: 450.89967.

From the bromination of pinostronbin (**3-28**), three compounds with 46.9, 30.5 and 28.8 %yield, respectively were obtained. These compounds were fully characterized by means of spectroscopic methods as 8-bromo-5-hydroxy-7-methoxy-2-phenylchroman-4-one (**3-29**), 6-bromo-5-hydroxy-7-methoxy-2-phenylchroman-4-one (**3-30**) and 6,8-dibromo-5-hydroxy-7-methoxy-2-phenylchroman-4-one (**3-31**). It should be noted here that to the best knowledge, these compounds have never been reported in chemical literatures. Compound **3-30**, the major product from this reaction was derived from the bromination at the position *ortho* to hydroxy and methoxy groups.

The effects of solvent on the product distribution were investigated. Hexane, MeOH and MeCN: hexane (1:1) were used to replace MeCN. The results are described in Table 3.13.

Table 3.13 The effects of solvent on the bromination of pinostrobin **(3-28)**

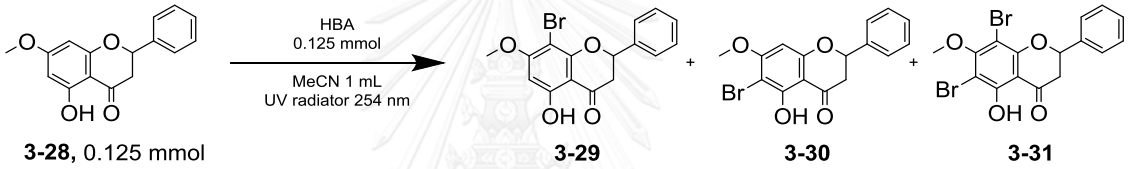


Entry	Solvent	%Recovery	%Yield			MB (%)
			3-29	3-30	3-31	
1	MeCN	0	31	47	29	106
2	MeOH	68	20	15	0	103
3	Hexane	69	11	11	0	91
4	MeCN: Hexane (1:1)	0	20	33	50	103
5	MeCN:Hexane (1:4)	0	32	46	26	104

According to Table 3.13, when using MeOH or hexane (entries 2-3), none of di-substituted product could be detected. However, the yield of products (mono-brominated products) was low with around 70% of remained pinostrobin. When MeCN and hexane in 1:1 ratio was used instead of MeCN, di-substituted product was observed (entry 4).The use of the combination of MeCN: hexane in 1:4, yielded compound **3-30** as the major product. This result is conformable with those of the bromination of phenols (3.4.1.2).

The effect of reaction time was examined by performing the reaction under optimized conditions and varied the reaction time (5, 10 and 15 min). The results are presented in Table 3.14.

Table 3.14 The effect of reaction time on the bromination of pinostrobin **(3-28)**

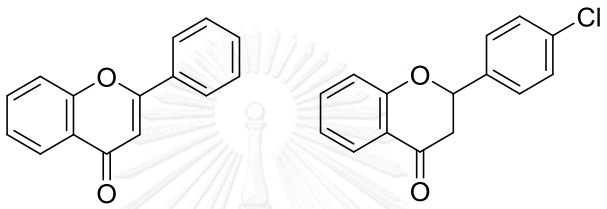


Entry	Time (min)	%Recovery	%Yield			MB (%)
			3-29	3-30	3-31	
1	5	40	22	35	0	97
2	10	0	33	58	0	91
3	15	0	25	58	21	104

The results revealed that when the reaction was performed for 5 min, di-substituted product **(3-31)** was not formed. Even the reaction was left longer for 10 min, none of di-substituted product was found and pinostrobin (**3-28**) was all converted to mono-substituted products. When the reaction was conducted for 15 min, the dibromo compound (**3-31**) was attained, presumably derived from further bromination of mono-substituted products (**3-29** and **3-30**).

3.4.4 Bromination of flavone (3-23) and 4′-chloroflavanone (3-24)

According to the results from the bromination of pinostrobin **(3-28)**, the bromination took place prevailing at the aromatic ring containing activating groups such as phenolic and methoxy groups. This section aims to investigate the scope of the bromination with HBA towards other aromatics. 2-(4-Chlorophenyl)chroman-4-one or 4′-chloroflavanone **(3-24)** and flavone **(3-23)** were chosen as chemical proves. Since both compounds are not commercial available, they were thus needed to synthesize.



flavone **(3-23)** 4'-chloroflavanone **(3-24)**

The synthesis of flavone **(3-23)** was operated through the esterification of 2-hydroxyacetophenone and benzoyl chloride. The attained ester was treated with KOH and pyridine at 50°C for the Baker-Venkataraman rearrangement and cyclization by treated with conc H_2SO_4 [33]. The product (79.8% yield) was recrystallized with acetone, R_t: 5.50 min in SGE-BP1.

The ^{1}H NMR spectrum (Fig 3.10) reveals an olefinic proton signal at **δ** 6.85 (*s*, 1H). The protons belonging to the phenyl group could be observed at **δ** 7.51-7.55 (*m*, 3H) and 7.90-7.97 (*m*, 2H). Another set of the 4*H*-chromen-4-one protons was detected at **δ** 7.45 (*t*, *J* = 7.6 Hz, 1H), 7.58 (*dd*, *J* = 8.4, 1.1 Hz, 1H), 7.73 (*ddd*, *J* = 8.3, 6.8, 1.7 Hz, 1H), and 8.23 (*dd*, *J* = 8.0, 1.7 Hz, 1H).

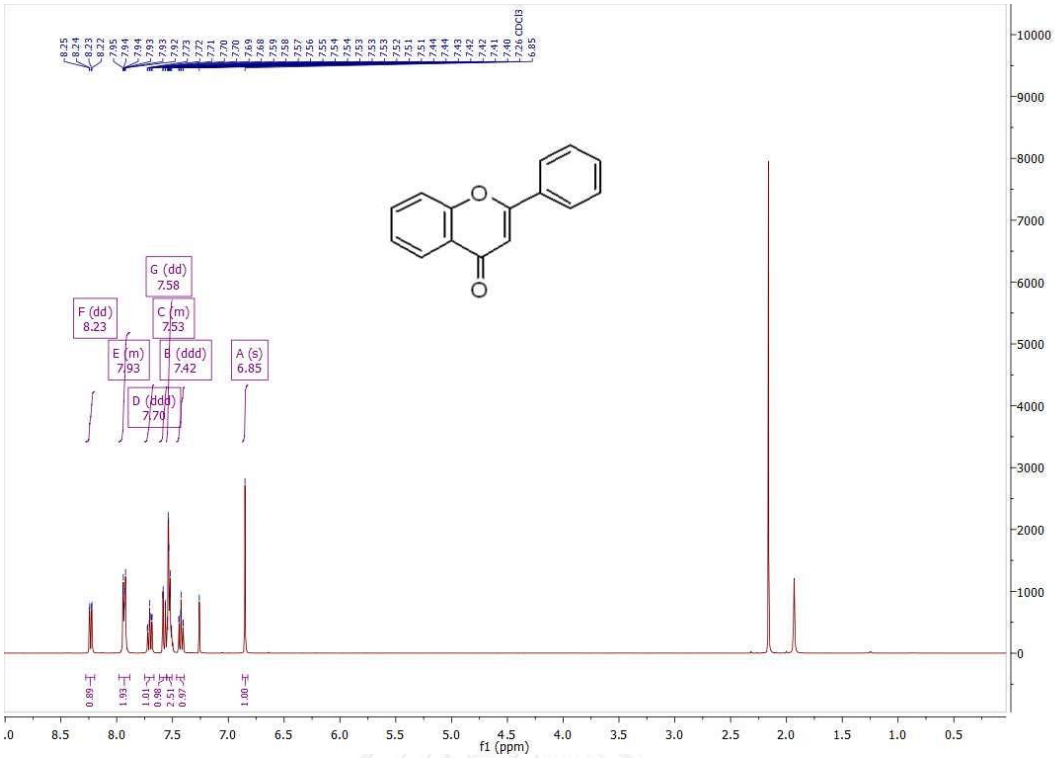


Figure 3.10 The ^{1}H NMR spectrum of flavone **(3-23)**

4′-Chloroflavanone (racemic mixture) (**3-24)**, was synthesized from the reaction of 2-hydroxyacetophenone and 4-chlorobenzaldehyde to generate chalcone. The obtained chalcone was cyclized upon treating with NaOAc under reflux for overnight [34]. The product as light green solid was purified by silica gel column using 10% EtOAc in hexane to furnish the target molecule 51.8% yield, R_t: 5.43 min in SGE-BP1. The ^{1}H NMR spectrum of this compound was presented in Fig 3.11.

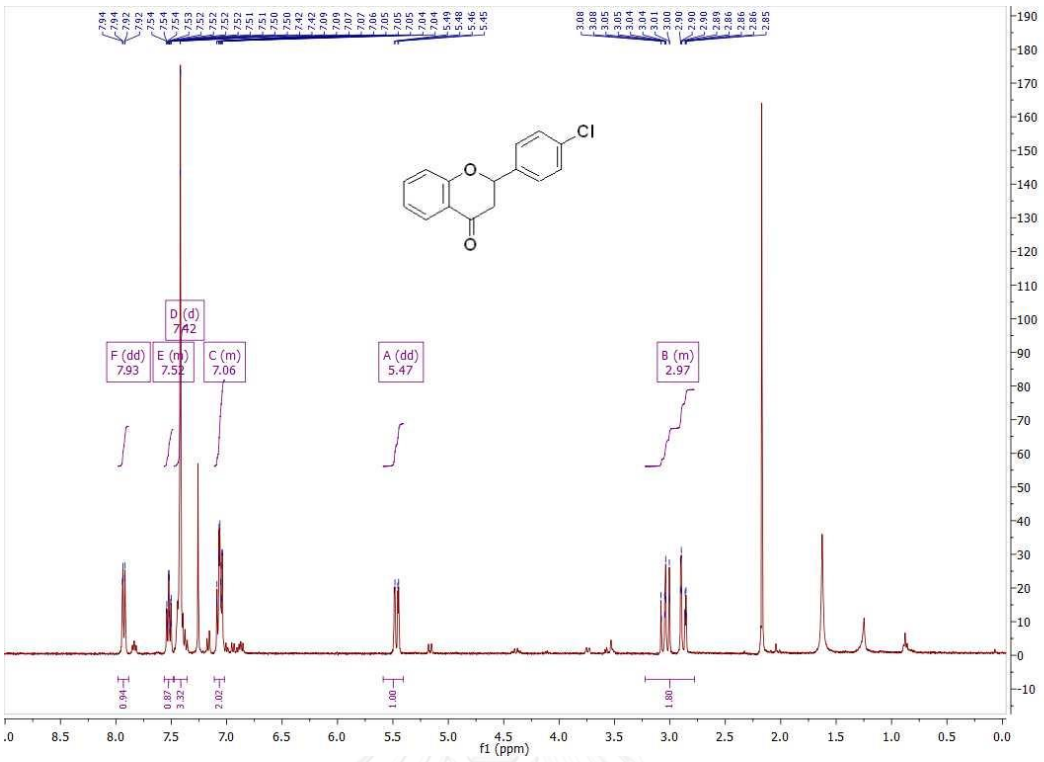


Figure 3.11 The ^{1}H NMR spectrum of 4′-chloroflavanone **(3-24)**

The ^{1}H NMR spectrum of 4′-chloroflavanone **(3-24)** (Fig 3.11) reveals the signals of **α**-carbonyl protons at **δ** 2.61-3.33 (*m*, 2H) and a benzylic proton could be observed at **δ** 5.47 (*dd*, *J* = 13.2, 3.0 Hz, 1H). Another set of the chroman-4-one protons was detected at **δ** 7.10 – 7.03 (*m*, 2H), 7.48 – 7.56 (*m*, 1H) and 7.93 (*dd*, *J* = 7.7, 1.7 Hz, 1H). In addition, the phenyl protons could be observed at **δ** 7.42 (*m*, 4H).

Under the optimized conditions examined, none of the product was obtained from the reaction of flavone **(3-23)** with HBA, while that of 4′-chloroflavanone **(3-24)** and HBA yielded complicated products observing from GC. Three new compounds could be detected from GC: two signals were overlapped at R_t 5.90 min and the other was at R_t 6.34 min. Thus, the crude mixture was separated by silica gel column (10% EtOAc in hexane) to furnish the product at R_t 6.34 min which was further characterized by ^{1}H NMR. The ^{1}H NMR spectrum of this compound was presented in Fig 3.12.

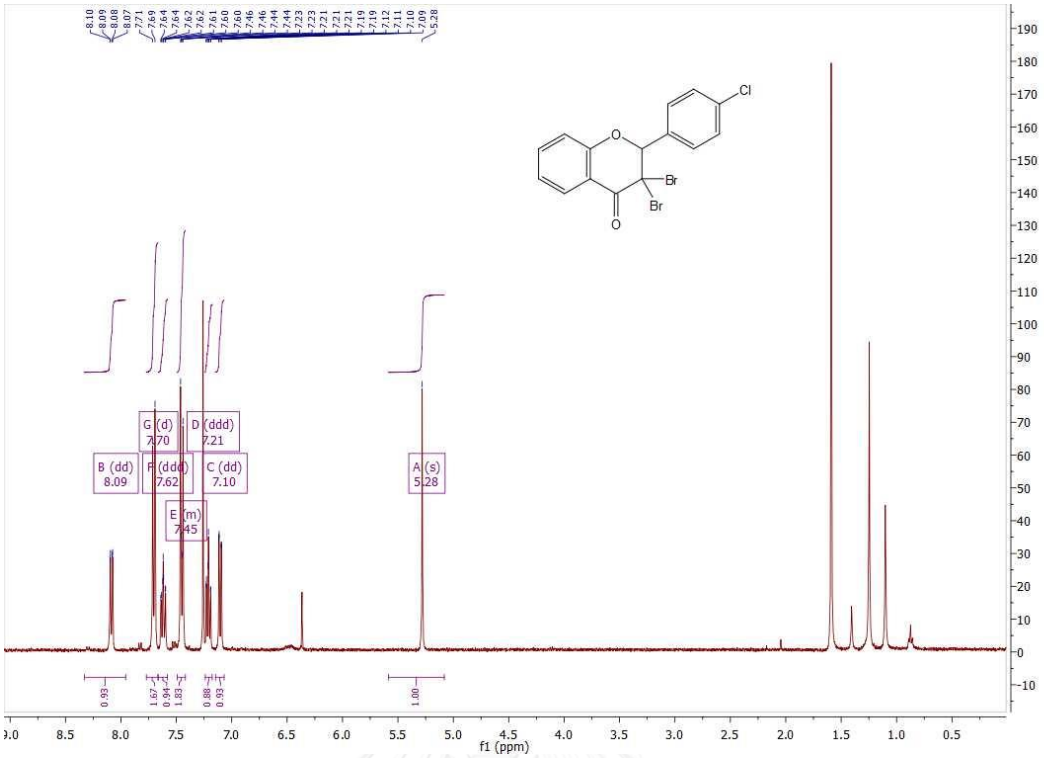


Figure 3.12 The ^{1}H NMR spectrum of the product at Rt 6.34 min

The ^{1}H NMR spectrum (Fig 3.12) displays the benzylic proton signal at **δ** 5.28 (*s*, 1H) and those at **δ** 7.10 (*dd*, *J* = 8.4, 1.1 Hz, 1H), 7.21 (*ddd*, *J* = 8.1, 7.2, 1.1 Hz, 1H), 7.45 (*d*, *J* = 8.6 Hz, 2H), 7.62 (*ddd*, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.70 (*d*, *J* = 8.5 Hz, 2H) and 8.09 (*dd*, *J* = 8.0, 1.7 Hz, 1H) belonging to the protons of chroman-4-one and phenyl group. This spectrum was clearly endorsed the structure of this product as 3,3′-dibromo-2-(4-chlorophenyl)chroman-4-one **(3-27)**.

The remaining two products were still in the mixture and could not separate. The reaction mixture was further analyzed by ^{1}H NMR (Fig 3.13). The crude mixture displayed the proton signals at **δ** 4.53 (*d*, *J* = 1.8 Hz, 1H) and 5.44 (*d*, *J* = 1.7 Hz, 1H) which was well-matched with two protons of (2*S*,3*R*)-3-bromo-2-(4-chlorophenyl)chroman-4-one (*cis*-isomer) **(3-25)**. Another two signals appeared at **δ** 4.98 (*d*, *J* = 9.1 Hz, 1H) and 5.55 (*d*, *J* = 9.1 Hz, 1H) were coincided with the 2 protons of (2*S*,3*S*)-3-bromo-2-(4-chlorophenyl)chroman-4-one (*trans*-isomer) **(3-26)** which contained 2 proton signals at **δ** 4.98 (*d*, *J* = 8.0 Hz, 1H, **β**-H) and 5.56 (*d*, *J* = 8.0 Hz, 1H, **α**-H) [50]. In addition, the spectrum displayed the signal at **δ** 5.30 (*s*, 1H)

belonging to the benzylic proton of 3,3′-dibromo-2-(4-chlorophenyl)chroman-4-one. The yields of these three products were determined on the basic of ^{1}H NMR using toluene as an internal standard.

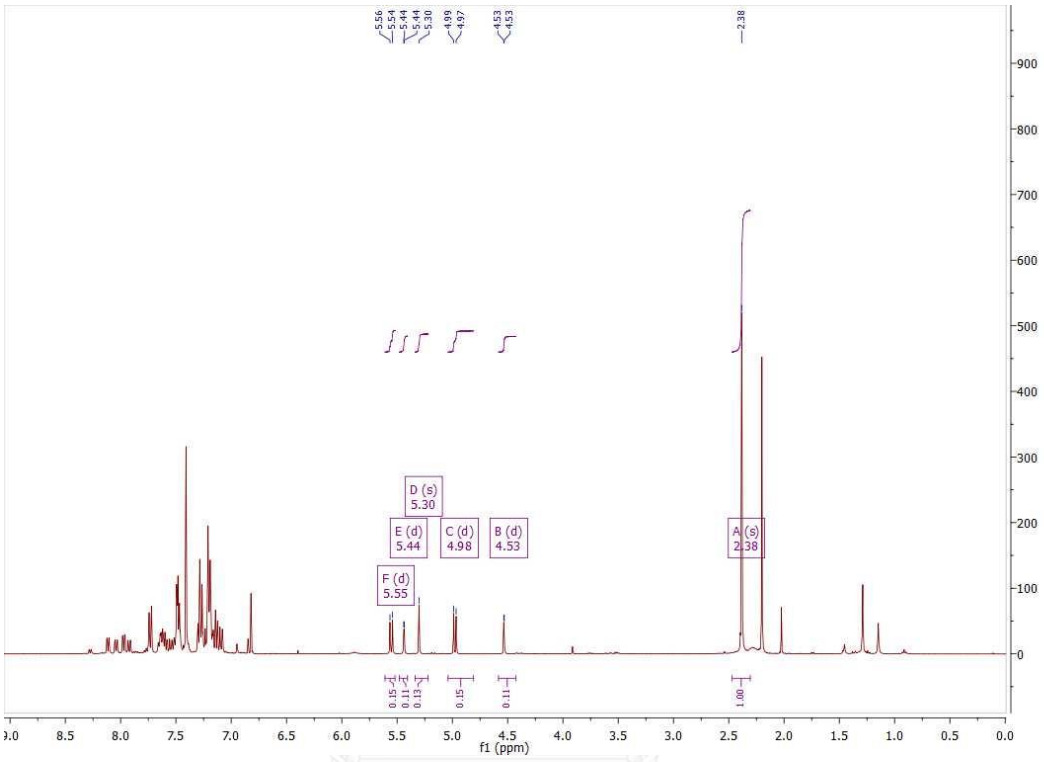


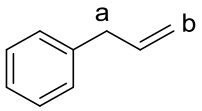
Figure 3.13 The ^{1}H NMR spectrum of the crude mixture from the bromination of 4′-chloroflavanone **(3-24)**

From the results of the bromination of selected aromatics (table 3.9), there was no reaction between flavone **(3-23)** and HBA, while the 4′-chloroflavanone **(3-24)** reacted completely yielding three bromo compounds. Considering the structure of flavone **(3-23)**, the bromination should be taken place at unsaturation part. Nonetheless, this unsaturation was a α, β-unsaturated carbonyl compound, which rendered the electron density at this position. Thus, no addition was occurred.

The bromination of 4′-chloroflavanone **(3-24)** was clearly observed at the α-carbonyl position with no sign of bromination being occurred at the aromatic. This was mainly because there was no activating group present in the aromatic ring, thus the bromination at α-position of carbonyl group was prevailed. Accumulated from the results of the bromination of pinostrobin **(3-28)**, flavone **(3-23)** and 4′-

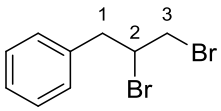
chloroflavanone **(3-24)**, it could be concluded that the bromination using HBA was preferentially in the order of unsaturation group > aromatic with activating group > **α**- position of carbonyl group. The efficiency of the addition to the unsaturation part was greatly depended the structure of substrate.

3.4.5 Bromination of allylbenzene (3-13) and safrole (3-15)



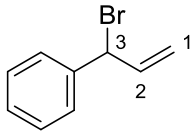
The next selected aromatic is allylbenzene **(3-13)** which contained another two active sites, *i.e.*, benzylic and allylic position (a) and unsaturated position (b). Allylbenzene **(3-13)** is a good probe to rationalize the mechanism of the reaction. If the main product was derived from the allylic bromination at position a, the active species may involve bromine radical, while if the addition was prevailed, the active bromine species generated should be Br_2.

When allylbenzene **(3-13)** reacted with HBA under the optimum conditions, the only product obtained was (2,3-dibromopropyl)benzene **(3-14)**, two bromine atoms added to the double bond. No brominated product stemmed from the bromination at either aromatic ring or allylic position was detected. This implied that the active species generated from HBA should be Br_2. Another experiment was thus set up to compare the bromination of allylbenzene **(3-13)** using HBA and NBS.



(2,3-Dibromopropyl)benzene **(3-14)** was synthesized following the general procedure. Allylbenzene **(3-13)** was treated with HBA and stirred at RT under UV radiation for 30 min, only (2,3-dibromopropyl)benzene **(3-14)** was obtained with quantitative yield (R_t 7.05 min by SGE-BP1). The product was characterized by ^{1}H NMR, the spectrum revealed two benzylic protons at **δ** 3.15 (*dd, J* = 14.5, 7.8 Hz, 1H) and 3.50 (*d*, *J* = 7.0 Hz, 1H). Two protons at terminal carbon were detected at **δ** 3.65 (*dd*, *J* = 10.5 Hz, 1H) and 3.85 (*dd*, *J* = 10.5, 4.2 Hz, 1H). The proton signal at **δ** 4.38

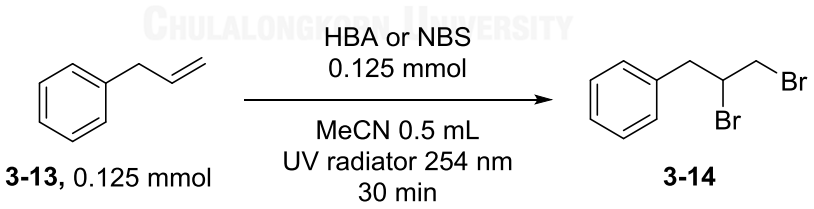
(*m*, 1H) could be assigned for the proton of the carbon at position 2, while the signals at **δ** 7.15-7.50 (*m*, 5H) belonged to aromatic protons.



(1-Bromoallyl)benzene **(3-32)** was synthesized by mixing allylbenzene **(3-13)** and NBS in CCl_4 and refluxed overnight [42]. After purification by 5% EtOAc in hexane, the product was obtained with 76.3% yield (R_t 8.54 min by SGE-BP1) and characterized by ^{1}H NMR. Its spectrum displayed the signals of the protons on terminal carbon at **δ** 3.97 (*dd*, *J* = 11.4, 4.1 Hz, 1H) and 4.29 (*dd*, *J* = 11.4, 4.2 Hz, 1H). The benzylic proton was visualized at **δ** 5.34 (*d*, *J* = 9.5 Hz, 1H) and the proton on C-2 was obtained at **δ** 4.77 (*dt*, *J* = 9.5, 4.2 Hz, 1H) and the signals at **δ** 7.34-7.56 (*m*, 5H) belonged to the aromatic protons.

The effects of brominating agent were studied by perfoming the reaction under optimized conditions except for varying brominating agents. The results are presented in Table 3.15.

Table 3.15 The bromination of allybenzene **(3-13)** using HBA and NBS in MeCN under UV radiation for 30 min



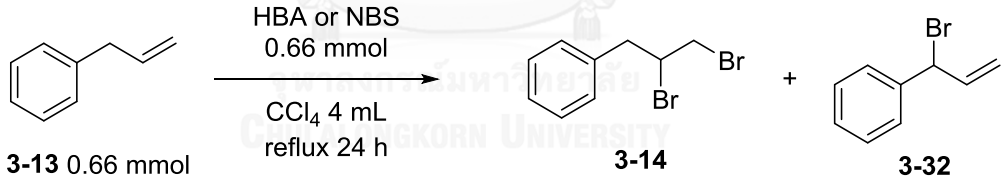
Entry	Brominating agent	%Recovery	%Yield	MB (%)
1	HBA	0	107	107
2	NBS	12	48	60

Table 3.15 reveals that the reaction with NBS (entry 2) produced only (2,3-dibromopropyl)benzene **(3-28)** as the major product (48%). This clearly showed that

the mechanism for this reaction involved the addition of Br_2. Since, NBS contained only 1 bromine atom, thus Br_2 would at maximum be generated only 0.5 equivalent compared with starting material. So, the yield of **3-14** that obtained in 47.8% was almost quantitative. While HBA was comprised of 6 bromine atoms which could generate the excess of Br_2 in the reaction. Thus, using the same equivalent of brominating agent, HBA could provide the quantitative yield of the target product (entry 1). In conclusion, when the reaction was performed in polar solvent under UV radiation, both HBA and NBS were *in situ* generated a Br_2 in the reaction.

To study and confirm the mechanism of the reaction with HBA, another experiment was set up using the reported reaction conditions which believed to operate *via* bromine radical [42]. That reaction involved the reaction of substrate and NBS under refluxing CCl_4 in the presence of light for 24 h. The same procedure was repeatedly carried out using HBA instead of NBS. After the reaction was completed, the product was analyzed by GC. The results are shown in Table 3.16.

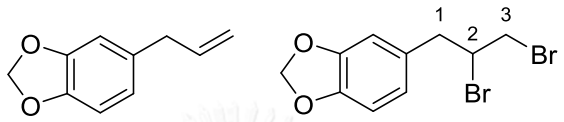
Table 3.16 The brominations of allylbenzene **(3-13)** using NBS and HBA in CCl4 at reflux for 24 h



Entry	Brominating agent	%Recovery	%Yield		MB (%)
			3-14	3-32	
1	HBA	82	18	0	100
2	NBS	0	0	72	72

From the aforementioned results, only the reaction using NBS generated (1-bromoallyl)benzene **(3-32)**. This reaction was thought to occur through Br• which was taken place at allylic position. With HBA, only (2,3-dibromopropyl)benzene **(3-28)**

was detected with remaining starting material. This clearly demonstrated that the active species of HBA was not a free Br•, but possibly that the generated Br• was combined instantly to produce Br_2 and rapidly added to the unsaturated portion. Under this particular condition, the applied energy was not enough to break C-Br of HBA, whereas it was enough to break N-Br of NBS [45] generating bromine radical to allow the reaction taking place at allylic position. That caused the high yield of (1-bromoallyl)benzene (**3-32**) from the reaction with NBS.



3-15 **3-16**

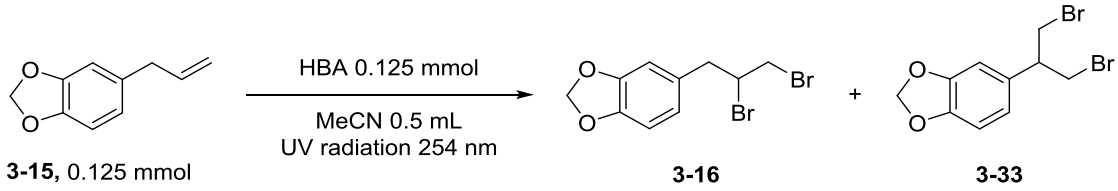
The other selected compound was safrole **(3-15)** which was obtained from hydrodistillation of the root-bark of *Cinnamomum porrectum* by Ms. Suekanya Jarupinthusophon. This compound was chosen to investigate the competitive reactions between the aromatic substitution and the addition to the double bond, both present in the same molecule.

The bromination of safrole **(3-15)** was performed by reacting the substrate with HBA for 2 h. 5-(2,3-Dibromopropyl)benzo[*d*][1,3]dioxole **(3-16)** was obtained in 49.2% yield (R_t 9.0 min by SGE-BP1). The product was separated with 5% EtOAc in hexane and characterized by ^{1}H NMR. Two proton signals on terminal carbon were detected at **δ** 3.06 (*dd*, *J* = 14.6, 7.5 Hz, 1H) and 3.39 (*dd*, *J* = 14.6, 4.8 Hz, 1H). The signals at **δ** 3.54-3.65 (*m*, 1H) and 3.81 (*dd*, *J* = 10.5, 4.1 Hz, 1H) could be assigned for benzylic protons. The proton of C-2 was visualized at **δ** 4.25-4.35 (*m*, 1H). The protons observed at **δ** 5.96 (*dd*, *J* = 5.0, 1.2 Hz, 2H) were attributed to the proton of acetal group and at **δ** 6.71-6.82 (*m*, 3H) were aromatic protons.

3.4.5.1 Effect of reaction time on bromination of safrole

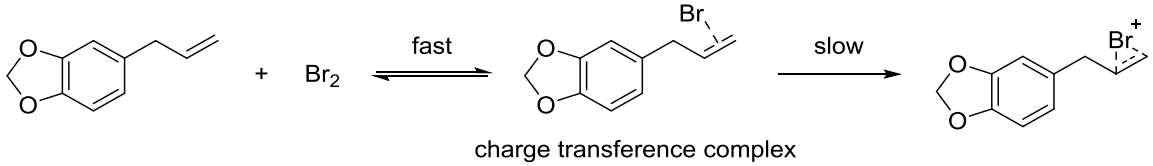
The effects of reaction time on the bromination of safrole **(3-15)** were carried out and the results are reported as shown in Table 3.17.

Table 3.17 The effects of reaction time on the bromination of safrole **(3-15)**

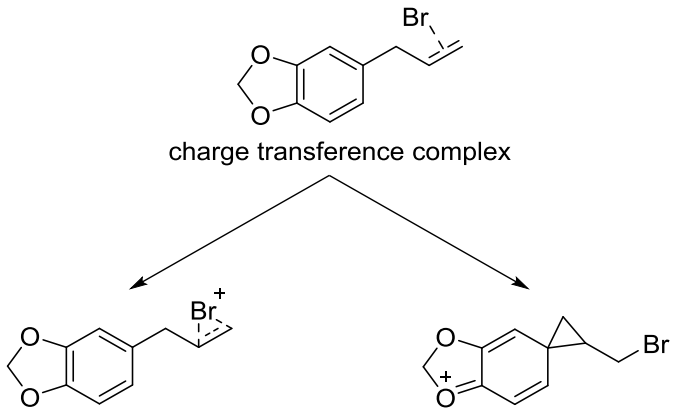


Entry	Time (min)	%Recovery	%Yield		MB (%)
			3-16	3-33	
1	30	56.5	35.3	0	91.8
2	120	20.3	49.2	18.6	88.1

The attempt to increase the yield of target product was performed by prolonging the reaction time from 30 min to 2 h. Surprising that compound **3-33** (5-(1,3-dibromopropan-2-yl)benzo[*d*][1,3] dioxole) was detected as another product from the reaction besides the desired product (**3-16**). The formation of the minor product was thought to occur *via* the transition state (charge transfer complex) leading to bromonium ion which was formed slower than the bond breaking in transition state (Scheme 3.1). Acetal group was known to stabilize the aromatic ring by forming the phenonium ion in polar solvent [51]. Thus, the competition was taken place towards the formation of 2 intermediates (Scheme 3.2). That caused when comparing with allylbenzene (**3-13**), the addition to the double bond of safrole **(3-15)** was slower.



Scheme 3.1 Formation of charge transference complex



Scheme 3.2 Competition of bromonium ion and phenonium ion towards to compound **3-16** and **3-33** respectively

5-(1,3-Dibromopropan-2-yl)benzo[*d*][1,3] dioxole **(3-33)** was co-occurred with the main product 5-(2,3-Dibromopropyl)benzo[*d*][1,3]dioxole **(3-16)**. Thus, the reaction mixture analyzed by ^{1}H NMR is shown in Fig 3.14.

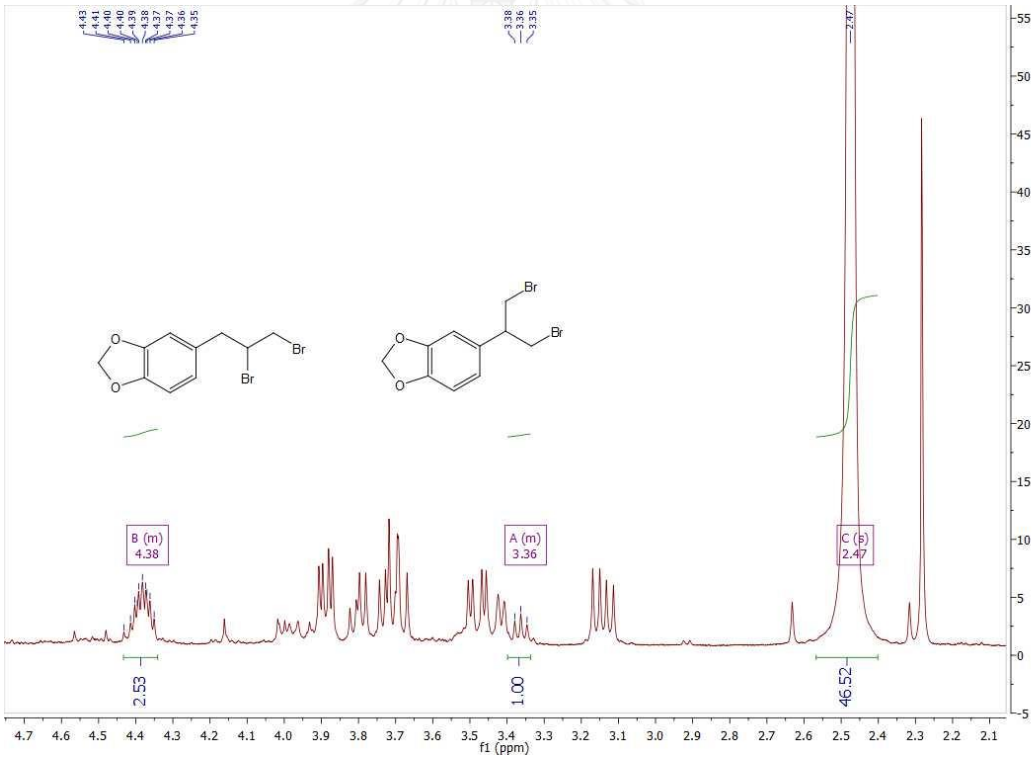


Figure 3.14 The ^{1}H NMR of the crude mixture from the bromination of safrole **(3-15)**

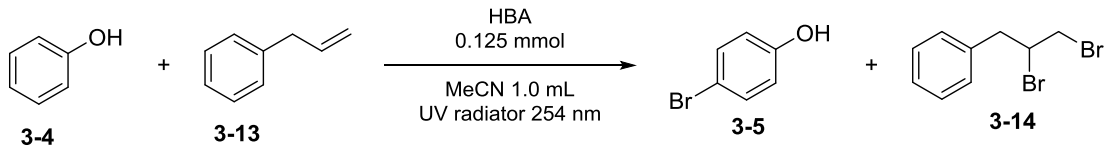
The ^{1}H NMR of the crude mixture displayed the proton signals at **δ** 4.38 (*m*, 1H) which well-matched with the proton on C-2 of 5-(2,3-dibromopropyl)benzo[*d*][1,3]dioxole **(3-16)**. Another signal appeared at **δ** 3.36 (*m*, 1H) was coincided with the methine proton of 5-(1,3-dibromopropan-2-yl)benzo[*d*][1,3]dioxole **(3-33)** [52]. The yield of these two products were determined on the basic of ^{1}H NMR using toluene as an internal standard, while the recovery of safrole **(3-15)** in the reaction was determined by GC.

From the result of the bromination of allylbenzene **(3-13)** and safrole **(3-15)**, HBA preferred the addition to the double bond to the aromatic bromination. This clue could endorse that the reaction using HBA was taken place *via* the generation of Br_2 and then the bromination took place relied on the functional group present in the substrate molecule.

3.5 Competitive study on the bromination of phenol and allylbenzene

From previous results, both phenol **(3-4)** and allylbenzene **(3-13)** were highly reactive towards the bromination with HBA, nonetheless with different pathway. A set of experiment was set up to examine the reactivity of both substrates. The reaction was carried out under the reaction conditions described in the general procedure, HBA was added into the reaction in the ratio of phenol: allylbenzene: HBA in 1:1:1, 2:2:1, 4:4:1 and 8:8:1. The yields of two expected products are shown in Table 3.18.

Table 3.18 The competitive study on the bromination of phenol **(3-4)** and allylbenzene **(3-13)** with HBA



Entry	Molar ratio of Allylbenzene: phenol: HBA	Phenol (3-4) reaction			Allylbenzene (3-13) reaction		
		%Recovery	%Yield	MB	%Recovery	%Yield	MB
1	1:1:1	30	40	70	0	quant	100
2	2:2:1	58	17	75	33	65	97
3	4:4:1	67.3	12	79	61	35	96
4	8:8:1	83.0	0	83	85	0	85

From the aforementioned results, at all molar ratios, the amount of the product derived from allylbenzene (**3-13**) was higher than that from phenol (**3-4**). This demonstrated that the active bromine species in reaction was reactive with the addition to the double bond more than the bromination (substitution) on aromatic. The yield of both target products was decreased at lower molar ratio of substrate: HBA. At the ratio of 8:8:1, none of the product was obtained. This experiment strongly implied that the active bromine species produced from HBA should be Br_2. The reactivity towards the function groups was in the order of unsaturated group > reactive aromatics > allylic and benzylic group.

3.6 The proposed mechanism for the bromination of aromatics using HBA

According to the outcome in topic 3.1, under the optimized conditions for the bromination of anisole **(3-1)**, HBA displayed a high efficiency when the molar ratio of anisole:HBA (8:1) was used. 4-Bromoanisole **(3-2)** was attained in very high yield based on the mole of HBA. The new experiment was designed and carried out to

observe the efficiency of HBA per bromine atom in the molecule. The results are collected in Table 3.19.

Table 3.19 Calculation of provided bromine atom from HBA.

Entry	Molar ratio of anisole: HBA	%Yield based on HBA	%Efficiency per bromine atom	Expected yield of product	Provided bromine atom
1	6: 1	161	27	100	1.6
2	8: 1	171	29	75	2.3

HBA was allowed to react with anisole (**3-1**) using less equivalent of substrate to HBA, *i.e.*, 6:1 and 8:1. In the case of using 6:1 ratio, if all HBA was transformed to Br_2, the expected yield based on HBA must be 600%. However, the actual yield was 161%. The efficiency of HBA per bromine atoms could be calculated as 27% form the equation shown below:

$$\frac{\%\,Yield\ based\ on\ HBA}{Expected\ yield\ (600)} \times 100 = \%Efficiency\ per\ bromine\ atom$$

(Equation 3.1)

The calculation of provided bromine atom from HBA was conducted to observe the efficiency per bromine atom. If all bromine atoms were decomposed from 6 bromine atoms of HBA, the expected efficiency per bromine atoms must be 100%. The actual efficiency was observed is 27%, thus, the actual provided bromine from the calculation on the Eq 3.2 was 1.6 atoms.

$$\frac{\%Efficiency\ per\ bromine\ atom}{\%Expected\ efficiency\ per\ bromine\ atom} \times Expected\ provided\ bromine = \ Actual\ provided\ bromine$$

(Equation 3.2)

Considering for 8:1 equivalent of anisole:HBA, the yield of 4-bromoanisole **(3-2)** based on HBA was 171%. The actual efficiency per bromine atom was 29%. The expected efficiency must be 75% (from 600/800) and the actual provided bromine

that calculated from Eq 3.2 was observed in 2.3. From the bromination at 6: 1 and 8: 1 equivalent of anisole: HBA, the calculation of provided bromine atom by HBA were observed in 1.6 and 2.3 respectively. So, it could assume that HBA provided 2 Br atoms per molecule at RT.

Moreover, the crude reaction mixture was recorded by ^{1}H NMR (Fig 3.15), the proton signals at **δ** 6.36 could be assigned for the signal of $Br_2C\underline{H}COC\underline{H}Br_2$ or tetrabromoacetone [53]. This signal was derived from the by-product of the reaction showing that not all bromine atoms of HBA were used in the reaction.

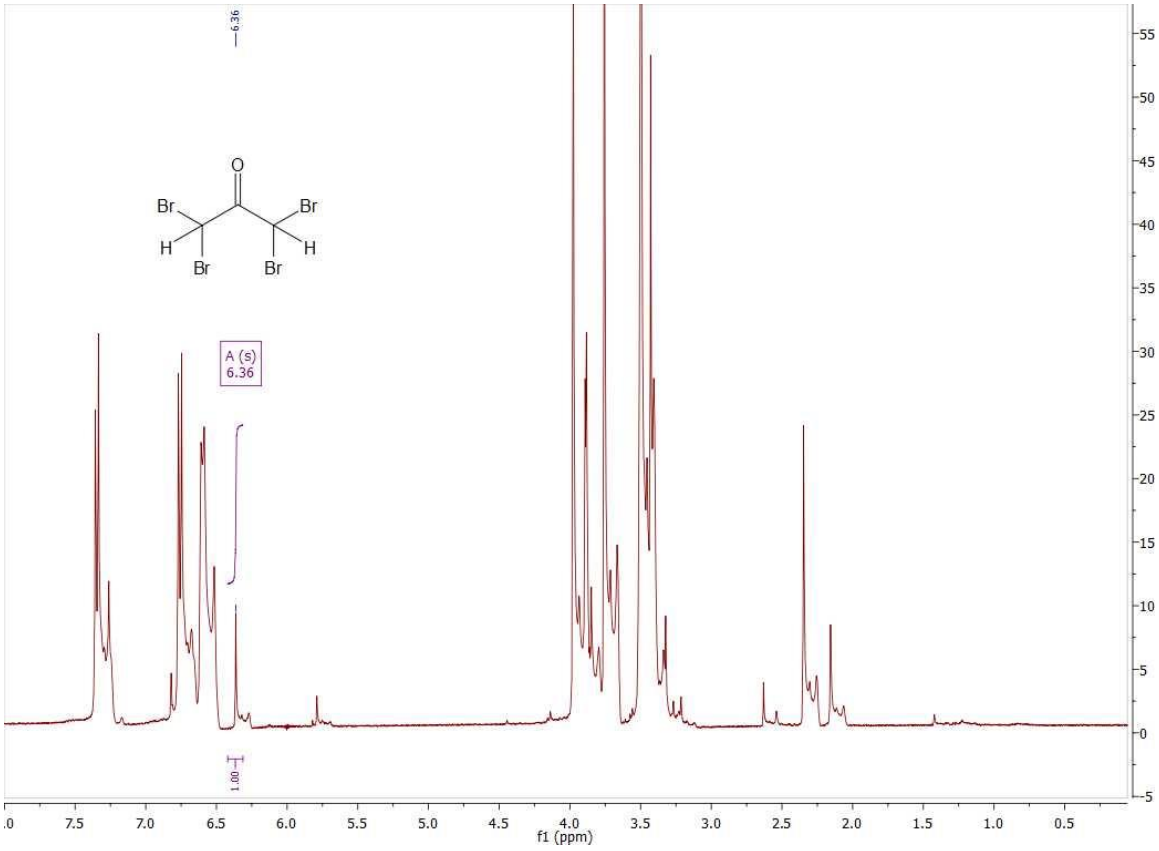


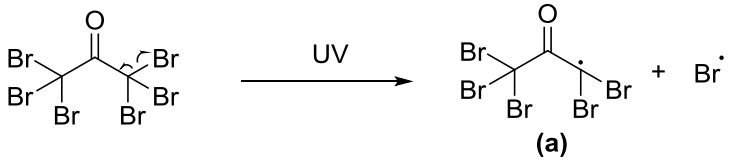
Figure 3.15 The ^{1}H NMR spectrum of the reaction mixture from the bromination of anisole **(3-1)**

The mechanism for the bromination of aromatics using HBA has never been reported. It was believed that the mechanism should initially take place *via* a radical process. While HBA in solid state is white, the solution containing HBA gave yellow-orange color. This was assumed that HBA could generate Br• and two Br• instantly

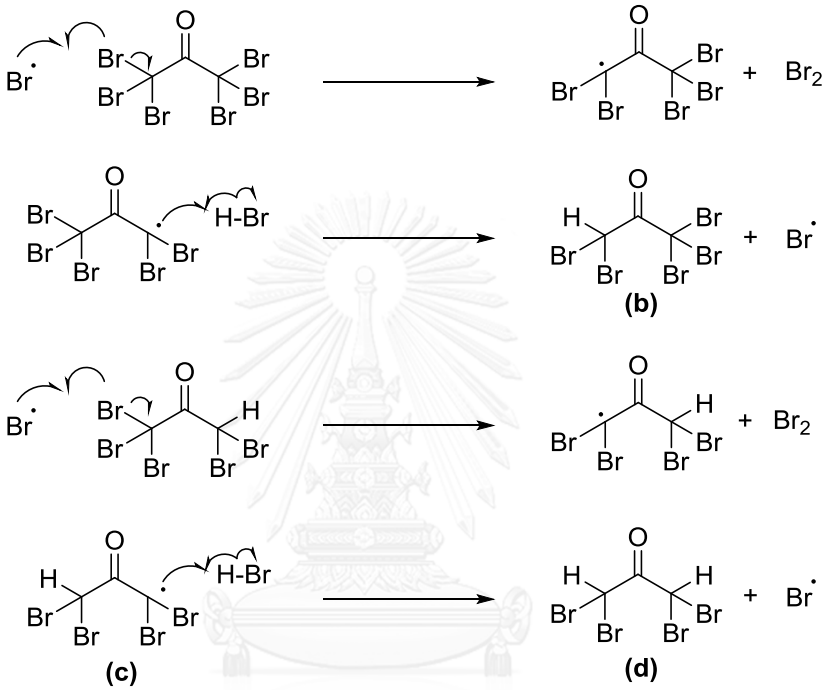
combined to become Br_2. Thus, the first step of the mechanism was believed to involve the homolytical C-Br bond breaking of HBA to generate Br•.

The proposed mechanism is displayed in Scheme 3.3. In the initiation step, homolysis of HBA to form Br• and C• **(a)** was initiated by UV. A bromine atom had an unpaired electron and acted as a free radical. In the next step, the propagation, Br• induced the cleavage of C-Br bond into C• **(a),** Br_2 was generated and reacted with anisole. C• **(a)** reacted with HBr that acquired from the by-product of anisole bromination to form **(b)** and another Br•. This Br• radical would then go on to take part in another propagation reaction of the HBA or **(b)**. Resulting of the **(b)** C-Br bond cleavage, C• **(c)** and Br_2 were formed. Then C• **(c)** reacted with HBr to acquire the tetrabromoacetone **(d).** The termination step, free Br• was reacted with another Br• to form the Br_2.

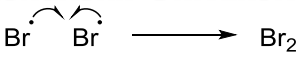
Step I (Initiation)



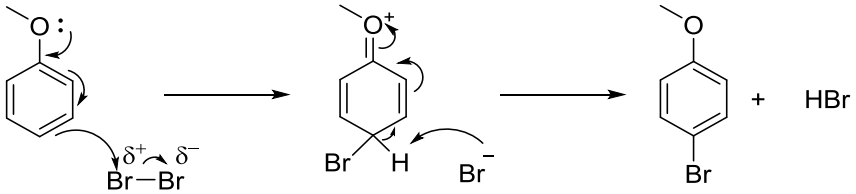
Step II (Propogation)



Step III (Termination)



Bromination of anisole



Scheme 3.3 The proposed mechanistic pathway for the bromination of anisole using HBA

CHAPTER IV
CONCLUSION

The main aim of the research is to search for the method to brominate aromatics using HBA. The new developed protocol was disclosed as a novel method for the bromination of aromaitcs under mild conditions to obtain products in high yield.

Anisole was used as the template for optimizing the conditions. Various effects were investigated. The optimized conditions were that anisole was treated with HBA with the ratio of 1:1 at RT under UV for 30 min in MeOH 0.5 mL to furnish the high yield of 4-bromoanisole. Various aromatics were chosen for investigating the regioselectivity of the reaction

The regioselectivity study revealed that aromatics with electron donating group such as phenol were very reactive forming di- or tri-substituted products. The regioselectivity of the reaction could be controlled by using different ratios of substrate to HBA, the combination of MeCN: hexane, shorter reaction time or adding HBA in 4 small portions.

The scope of reaction was uncovered by studying several probes including allylbenzene, safrole, 4′-chloroflavanone and pinostrobin. The trend of the reactivity could be observed in order for the bromination towards olefinic moiety > aromatic with activating group > α-carbonyl group. It could also assume that the reaction was operated *via* Br_2 which was believed that occur *via* radical pathway.

Proposal for the future work

This methodology can be used to prepare the desired bromoarenes in high yield. Therefore, the utilization of HBA may be extended to prepare the unreactive-aromatics such as benzaldehyde, benzoic acid or nitrobenzene. The combination of using HBA with some reagent such as BF_3-H_2O or other halogenating catalyst to brominate unreactive aromatics should be explored.

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APPENDIX

Calculation method of % yield of product

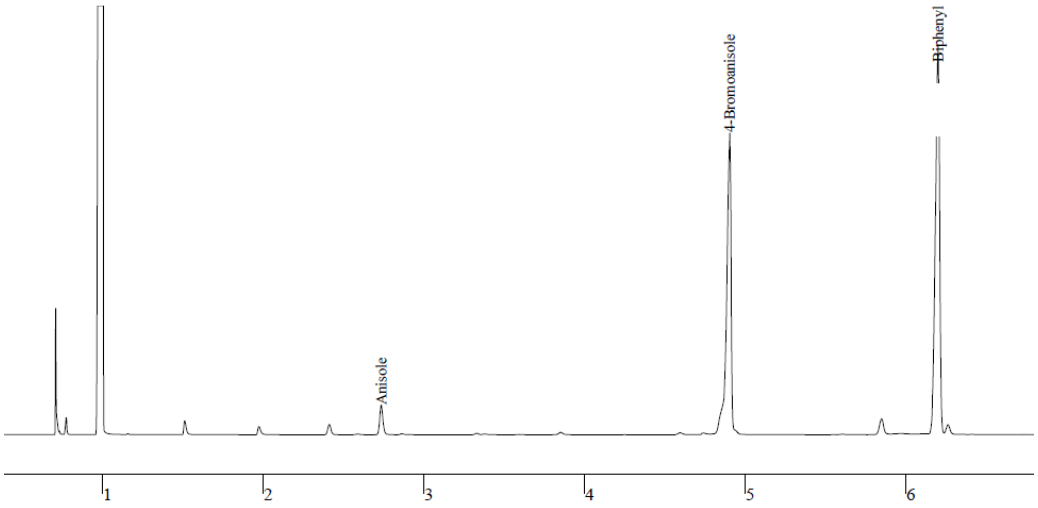

Figure A-1 Chromatogram of the crude mixture for bromination of anisole

$$\frac{Area\ of\ Internal\ standard}{Area\ of\ Sample} \times \frac{Mol.of\ Sample}{Mol.of\ Internal\ standard} = IRF$$

$$\frac{Actual\ mole\ of\ product}{Expect\ mole\ of\ product} \times 100 = \%\ Yield$$

VITA

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