การพัฒนาโบรมิเนทิงเอเจนต์สำหรับการสังเคราะห์แอลคิลโบรไมด์และแอซิดโบรไมด์

นางสาว ประทุมรัตน์ ทองเกตุ

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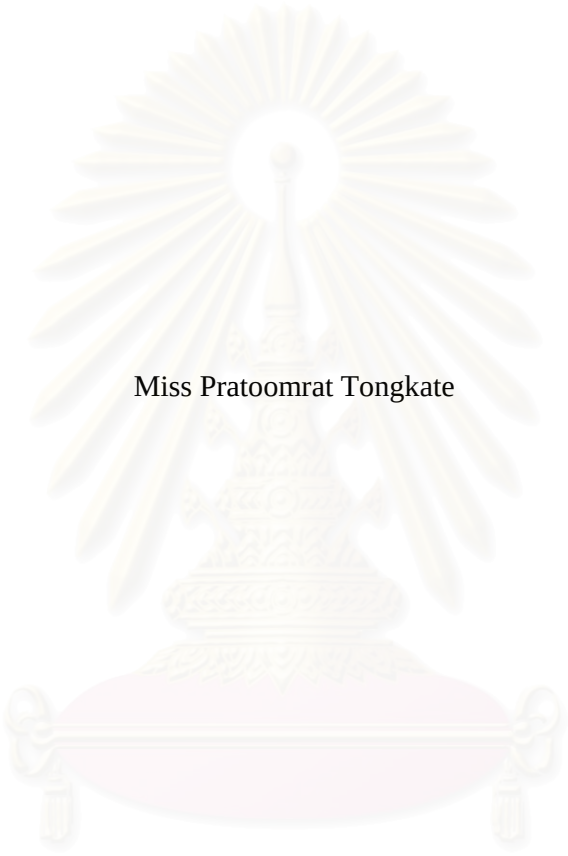
จุฬาลงกรณ์มหาวิทยาลัย

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาเคมี ภาควิชาเคมี
คณะวิทยาศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2550
ลิขสิทธิ์ของจุฬาลงกรณ์มหาวิทยาลัย

DEVELOPMENT OF BROMINATING AGENTS FOR SYNTHESES OF ALKYL BROMIDES AND ACID BROMIDES

Miss Pratoomrat Tongkate



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จุฬาลงกรณ์มหาวิทยาลัย

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 2007

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Thesis Title	Development of Brominating Agents for Syntheses of Alkyl Bromides and Acid Bromides
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Field of Study	Chemistry
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ประทุมรัตน์ ทองเกตุ: การพัฒนาโบรมิเนทิงเอเจนต์สำหรับการสังเคราะห์แอลคิลโบรไมด์และแอซิดโบรไมด์ (DEVELOPMENT OF BROMINATING AGENTS FOR SYNTHESES OF ALKYL BROMIDES AND ACID BROMIDES) อ. ที่ปรึกษา: ผศ.ดร.วรินทร ชวศิริ, 60 หน้า.

ได้พัฒนาโบรมิเนทิงเอเจนต์ใหม่สองชนิด ได้แก่ เอทิลไทรโบรโมแอซิเทต (Br_3CCO_2Et) และเฮกซะโบรโมแอซิโทน ($Br_3CCOCBr_3$) ใช้ร่วมกับไทรเฟนิลฟอสฟีน(PPh_3) เพื่อเปลี่ยนไพรมารีและเซกันดารีแอลกอฮอล์เป็นแอลคิลโบรไมด์ที่สอดคล้องกันในปริมาณสูงภายใต้ภาวะที่ไม่รุนแรงในระยะเวลาสั้น เชื่อว่ากลไกการเกิดปฏิกิริยาเกิดผ่านปฏิกิริยาแทนที่แบบ S_N2 โดยมีหลักฐานสนับสนุนจากการเปลี่ยนคอนฟิกุเรชันแบบอินเวอร์ชันของผลิตภัณฑ์แอลคิลโบรไมด์ นอกจากนี้ $Br_3CCOCBr_3/PPh_3$ สามารถใช้เป็นรีเอเจนต์ที่มีประสิทธิภาพเพื่อเตรียมแอซิดโบรไมด์โดยตรงจากกรดคาร์บอกซิลิก สามารถประยุกต์วิธีการที่พัฒนาขึ้นได้อย่างมีประสิทธิภาพสำหรับการสังเคราะห์อนุพันธ์กรดคาร์บอกซิลิก เช่น เอมีด เอสเทอร์ แอซิดแอนไฮไดรด์และไทโอเอสเทอร์โดยปฏิกิริยาแบบวันพอต ได้ศึกษาความเสถียรของ $Br_3CCOCBr_3$ ที่ 80°C และภายใต้รังสี UV โดยละเอียดและพบว่ารีเอเจนต์นี้เสถียรและว่องไวด้วยความเลือกจำเพาะต่อการทำปฏิกิริยาเฉพาะหมู่ฟังก์ชันสูง

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ภาควิชา.....เคมี..... ลายมือชื่อนิสิต.....ประทุมรัตน์ ทองเกตุ.....

สาขาวิชา.....เคมี..... ลายมือชื่ออาจารย์ที่ปรึกษา.....

ปีการศึกษา.....2550.....

4872352623: MAJOR CHEMISTRY
KEY WORD: BROMINATING AGENT/ ALKYL BROMIDE/ ACID BROMIDE/ SYNTHETIC METHODOLOGY

PRATOOMRAT TONGKATE : DEVELOPMENT OF BROMINATING AGENTS FOR SYNTHESES OF ALKYL BROMIDES AND ACID BROMIDES: THESIS ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., 60 pp.

Two new brominating agents, ethyl tribromoacetate (Br_3CCO_2Et) and hexabromoacetone ($Br_3CCOCBr_3$) have been developed and utilized in combination with triphenylphosphine (PPh_3) for conversion of primary and secondary alcohols into the corresponding alkyl bromides in high yield under mild conditions within short reaction time. The general mechanism was believed to occur *via* S_N2 supporting by the evidence of the inversion of configuration of the analogous alkyl bromide. In addition, $Br_3CCOCBr_3/PPh_3$ could be utilized as an efficient reagent to prepare acid bromides form carboxylic acid. This developed methodology was efficiently applied for the synthesis of carboxylic acid derivatives such as amides, esters, acid anhydrides and thioesters in one-pot reaction. The stability of $Br_3CCOCBr_3$ at 80°C and under UV irradiation was thoroughly studied and it was found that this reagent was quite stable and reactive with high chemoselectivity.

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

Department.....Chemistry..... Student's signature.....Pratoomrat Tongkate
Field of study.....Chemistry..... Advisor's signature.....Warinthorn Chavasiri
Academic year.....2007.....

ACKNOWLEDGEMENTS

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

The greatest thanks are also extent to Professor Dr. Udom Kokpol, Associate Professor Dr. Pipat Karntiang, Associate Professor Dr. Thawatchai Tuntulani and Dr. Anawat Ajavakom for their suggestions, comments, corrections and helps as thesis examiners.

Moreover, thanks are extended to the Department of Chemistry, Faculty of Science, Chulalongkorn University for granting financial support to fulfill this study and provision of experimental facilities.

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

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LIST OF ABBREVIATIONS

%	percent
°C	degree of Celsius
∑	mass balance
br s	broad singlet (NMR)
δ	chemical shift
J	coupling constant (NMR)
d	doublet (NMR)
dd	doublet of doublet (NMR)
eq	equivalent (s)
g	gram (s)
h	hour (s)
HPLC	High performance liquid chromatography
Hz	hertz
m.p.	melting point
mmol	millimole (s)
min	minute (s)
m	multiplet (NMR)
nm	nanometer
NMR	nuclear magnetic resonance
ppm	part per million
q	quartet (NMR)
RT	room temperature
s	singlet (NMR)
t	triplet (NMR)
TLC	thin layer chromatography
UV	ultra violet
W	watt
α	alpha

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CHAPTER I

INTRODUCTION

The conversion of alcohols and carboxylic acids into their corresponding alkyl and acyl halides is useful because the derived products are important intermediates in chemical industry [1] and pharmaceutical science [2]. Alkyl chlorides and acid chlorides are well known and useful. Their preparation has been widely studied, thus various reagents for this propose are consistency developed and hence available. However, comparing between chloride and bromide compounds, alkyl and acid bromides reveal higher reactivity than the corresponding alkyl and acid chlorides. Nonetheless, relatively few methods have been reported on preparing and not many brominating agents are readily available [3-5].

The desire of this research is to develop reliable brominating agents, which non-toxic, reactive and handy, for preparing alkyl and acid bromides under mild conditions. This procedure will further apply to manipulate carboxylic acid derivatives such as amides, esters, acid anhydrides and thioesters.

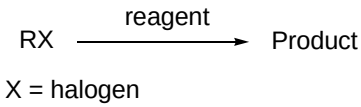
1.1 Introduction of Alkyl Halides

Alkyl halides are important intermediates which can convert to many other functional groups such as ethers, esters, nitriles, amines and sulfides. The conversions of alkyl halides to other organic compounds are illustrated as shown in Table 1.1.

1.2 Classical Method for the Preparation of Alkyl Halides from Alcohols

Alkyl halides can be manipulated from various sources of starting materials, for example alkanes, alkenes, alcohols and epoxides. The general and simple protocols mostly stem from the conversion of alcohols. The main reason is owing to the uncomplicated process of the conversion, the variety and easy procreation and commercial availability of alcohols.

Table 1.1 The conversion of alkyl halides to other organic compounds [6]

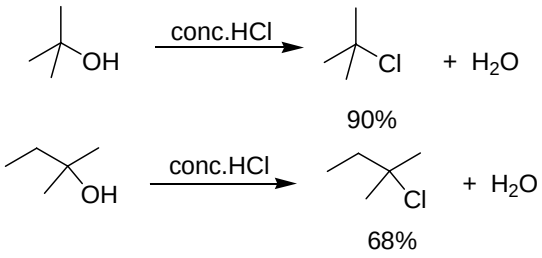


Reagent	Product	Functional group
HO^-	ROH	alcohol
H_2O	ROH	alcohol
$R'O^-$	ROR'	ether (Williamson synthesis)
$R'C\equiv C^-$	$RC\equiv CR'$	alkyne
R'-Metal	RR'	alkane (Coupling)
I^-	RI	alkyl iodide
NC^-	RCN	nitrile
$R'COO^-$	R'COOR	ester
NH_3	RNH_2	primary amine
NH_2R'	RNHR'	secondary amine
NHR'R''	RNR'R''	tertiary amine
PPh_3	$R\overset{+}{P}Ph_3,\ X^-$	phosphonium salt
HS^-	RSH	thiol (mercaptan)
RS^-	RSR	thioether (sulfide)
$ArH + AlCl_3$	ArR	alkylbenzene (Friedel-Crafts)
Base	C=C	alkene
Mg, dry ether	RMgCl	Grignard reagent
Metal, H^+	RH	alkane

1.2.1 The Synthesis of Alkyl Chlorides by Common Reagents

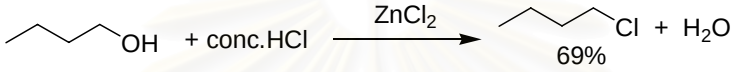
a) HCl [7]

The reaction between alcohols with HCl yields alkyl chlorides and water. This reaction is suitable for conversion of tertiary alcohols into the corresponding alkyl chlorides. On the contrary, primary and secondary alcohols react very slowly giving poor yield and rearrangement often occurs.

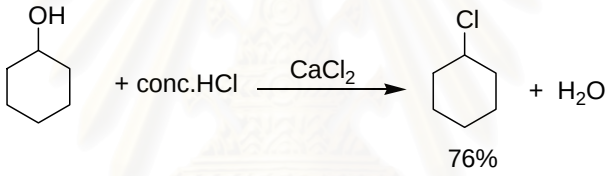


b) $ZnCl_2$, $CaCl_2$ and CuCl [7]

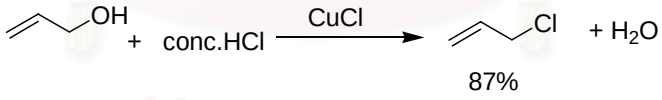
Anhydrous $ZnCl_2$ is a common reagent for the preparation of alkyl chlorides from primary and secondary alcohols.



In the case of alicyclic secondary alcohols anhydrous $CaCl_2$ is recommended.

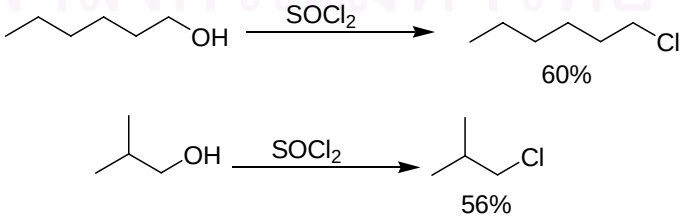


The conversion of unsaturated alcohols and alkyl alcohols into the corresponding chlorides by HCl and $ZnCl_2$ gives poor yield, but using CuCl as a catalyst has proved to be more satisfactory.



c) $SOCl_2$ [7]

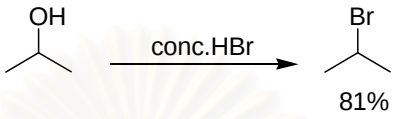
$SOCl_2$ is another well known reagent for preparing alkyl chlorides from alcohols.



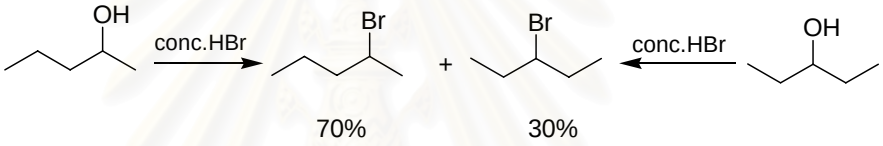
1.2.2 The Synthesis of Alkyl Bromides by Common Reagents

a) HBr [7]

The preparation of alkyl bromide is more readily than that of alkyl chlorides. Secondary and tertiary bromides can be prepared directly from the reaction of corresponding alcohols by heating with constant boiling HBr.

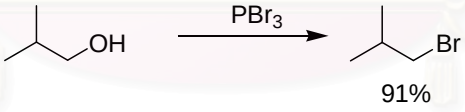


This method is however not highly regioselective, for example in the case of 2- and 3-pentanol, the same mixed products, 2- and 3-bromopentanes in 70 : 30 ratio were obtained.



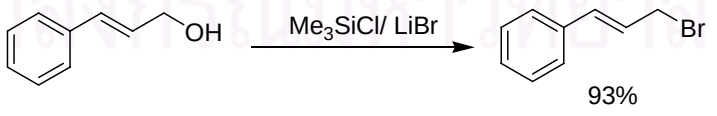
b) PBr_3 [7]

One of common reagents for preparation of alkyl bromides from alcohols is PBr_3. This reagent was generated *in situ*; however it was considered as an hazardous reagent.



c) $Me_3SiCl/LiBr$ [7]

$Me_3SiCl/LiBr$ is another highly regioselective brominating agent for preparation of alkyl bromides.



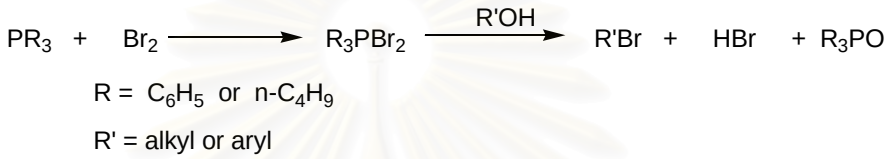
1.3 Literature Reviews on the Conversion of Alcohols into Alkyl Halides by Organophosphorus/Halogenating Agent

The combination of phosphorus compounds and halogenating agents such as PR_3/CCl_4, PPh_3/Cl_3COCCl_3, PR_3/Br_2, PR_3/CBr_4 systems is another choice of reagents

to prepare alkyl halides. These reagents are efficient since the reaction could be performed under mild and acid-free conditions with good yield.

Burn and Cadogan [8] reported the reactions between $(RO)_3P$ and CCl_4 or $BrCCl_3$ with alcohols yielding the corresponding alkyl halides, trialkyl phosphate and chloroform.

Wiley and co-workers [9] described the conversion of alcohols and phenols to the corresponding alkyl and aryl bromides using phosphorus reagents and bromine. The reaction delivered HBr as by-product.

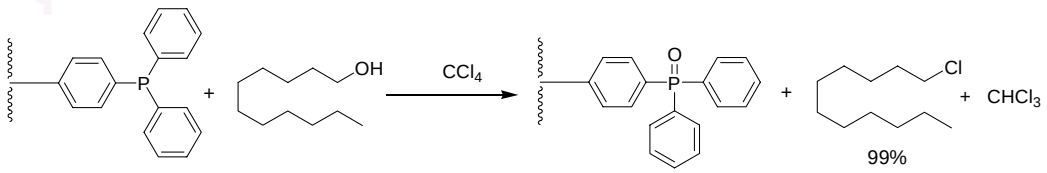


This method could be used to prepare alkyl and aryl chlorides by using CCl_4 replacing Br_2.

Lee and Nolan [10] developed methods for the preparation of chloro sugars and chloropolyols using phosphorus compounds and halogenating agents. The reaction was still acted rapidly under mild and neutral conditions. Moreover, this method could be possible for the preparation of chloroesters from hydroxyl-ester using PPh_3 and CCl_4. The reaction proceeded with inversion of configuration at the reacting center and neighboring optical centers are not affected.

Hozz and Gilani [11] reported the transformation of alcohols to alkyl chlorides and alkyl bromides using tri-*n*-octylphosphine (TOP) with CCl_4 or CBr_4, respectively. Primary and secondary alkyl chlorides could be obtained in high yield in the same as for primary alkyl bromides. Tertiary alkyl chlorides however gave low yield.

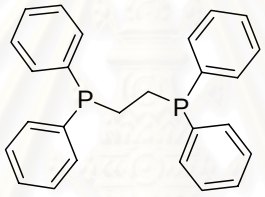
Steven and Dan [12] demonstrated the modification of filterable reagent, polystyryl-diphenylphosphine resin. The use of this reagent with CCl_4 was accomplished for conversion of primary and secondary alcohols to alkyl chlorides.



Magid and co-workers [13] addressed the reaction of allylic alcohols with PPh_3- CCl_3COCCl_3 complex affording the corresponding alkyl chlorides. This method was regio- and stereoselective conversion of allylic alcohols at low temperature (0ºC).

Sugimoto and co-workers [14] exhibited the conversion of hydroxylheterocycles into the corresponding bromo and chloroheterocycles using PPh_3/*N*-bromosuccinimide and *N*-chlorosuccinimide, respectively. However, the use of excess of halogenating agents was necessary to obtain good yield of product.

Pollastri and co-workers [15] developed the filterable phosphine source, 1,2-bis(diphenylphosphino)ethane or diphos, to avoid the problems of phosphine-oxide by-product isolation. The reaction of primary and secondary alcohols with diphos and CCl_4 or CBr_4 led to the formation of alkyl chlorides and bromides in moderate or high stereoselective yield.



diphos

Iranpoor and co-workers [16] reported the preparation of alkyl bromides from alcohols using a mixture of PPh_3, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and tetrabutylammonium bromide as a brominating agent. Thiols and selenols could be converted into alkyl bromides under the same conditions. Moreover, this method could be used to prepare alkyl chloride and iodide.

$$RYH \xrightarrow[CH_2Cl_2]{PPh_3/DDQ/R'_4N^+X^-} RX$$

Y = O, S, Se X = Cl, Br, I

Desmaris and co-workers [17] described the conversion of alcohols into the corresponding alkyl bromides employing furious phosphine CBr_4 complex. This method had the advantage because the fluorous-phosphine oxide by-product in the reaction could be separated by liquid-liquid extraction.

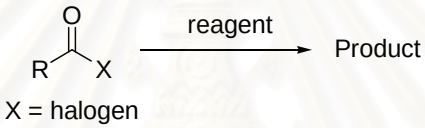
Iranpoor and co-workers [18] developed the filterable phosphorus reagent, silicaphosphine (Silphos): $[P(Cl)_{3-n}(SiO_2)_n]$, which converted alcohols and thiols to

their corresponding bromide in the presence of Br_2. In addition, alkyl iodides could be prepared by reaction between silphos and I_2.

1.4 Introduction of Acid Halides

Acid halides are also known as acyl halides, which are important as intermediates to transform into other derivatives of carboxylic acids such as amides, esters, thioesters and acid anhydrides. These derivatives are usually bioactive compounds [2] or intermediates in industry [1]. Therefore the conversion of carboxylic acids into acid halides is frequently encountered transformation in organic synthesis. The conversions of acid halides to other organic compounds are illustrated as shown in Table 1.4.

Table 1.2 The conversion of acid halides to other organic compounds [19-23]



Reagent	Product	Functional group
HO^-	RCO_2H	carboxylic acid
H_2O	RCO_2H	carboxylic acid
R' MgX	R'_3COH	3^oalcohol
R'_2CuLi	RCOR'	ketone
R'OH	RCO_2R'	ester
R'SH	RCOSR'	thiol ester
NH_2R'	RCONHR'	amide
NHR'R''	RCONR'R''	amide
$R'CO_2H$	$R'CO_2COR$	acid anhydride
C_6H_6, $AlCl_3$	ArCOR	Friedel-Crafts Acylation
$LiAl(Ot\text{-}Bu)_3H$	RCHO	aldehyde
H_2/Pd	RCHO	aldehyde
$LiAlH_4$, H_2O	RH	1^oalcohol

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1.5 Preparation of Acid Halides

Acid halides can be prepared from various starting materials and methods. Generally, they are prepared from carboxylic acids. The common acid halides in organic synthesis are acid chlorides and acid bromides. Though acid bromides are known to be much more reactive than acid chlorides, the latter are more available. That is because the methods and reagents for preparation of acid chlorides are readily known and frequently employed.

1.5.1 Literature Reviews on the Transformation of Carbonyl Compounds to Acid Bromides

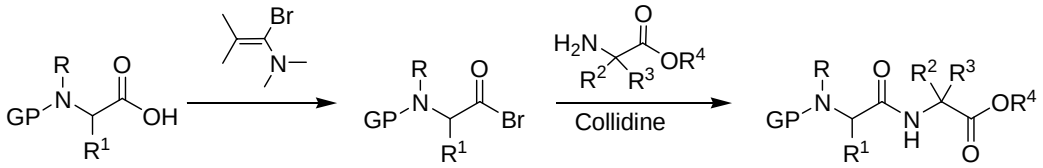
Adams and Ulich [24] reported the conversion of carboxylic acid and sodium salts of organic acid to acid bromides by treatment with oxalyl bromide. The reaction between the salts of organic acid and oxalyl bromide ran smoothly and such a small excess of the oxalyl bromide was required. Oxalyl bromide may be generated by the action of HBr upon oxalyl chloride.

Burton and Degering [25] described the preparation of acetyl bromide from the reaction of glacial acetic acid with PBr_3 generated *in situ* from a mixture of Br_2 and phosphorus. This method gave acetyl bromide in excellent yield.

Aizpurua and Palomo [26] addressed the preparation of carboxylic acid bromides by treatment carboxylic acid with phenylphosphine dibromide as a brominating agent at room or high temperature.

Bains and co-workers [4] developed the new method to prepare acid bromides. The procedure involved treating carboxylic acid with BBr_3 onto alumina. This method gave moderate to excellent yield of products.

DalPozzo and co-workers [27] demonstrated the synthesis of peptides using *N*-protected amino acid bromide as intermediates, generated *in situ* by treatment *N*-protected carboxylic acid with 1-bromo-*N*,*N*-1-trimethyl-1-propenylamine under mild and neutral conditions. This amino acid bromide was treated with other amino acids for synthesis of peptides.



Jang and co-workers [5] reported the preparation of acid bromides from carboxylic acids with PPh_3 and ethyl tribromoacetate (Br_3CCO_2Et) at room temperature under neutral conditions. The acid bromides generated were trapped into amides in one-step.

Jang and co-workers [28] described the conversion of aromatic aldehydes into acid bromides by treatment aldehydes with Br_3CCO_2Et under radical conditions. The acid bromides generated may convert to amides in one-step. Aromatic aldehydes with electron-donating group were found to be more reactive than aromatic aldehydes with electron-withdrawing groups and aliphatic aldehydes under reaction conditions examined.

1.6 Literature Reviews on the Synthesis of Carboxylic Acid Derivatives

Acid halides were not so stable especially in humid environment. Normally, the acid halides generated were converted to more stable carboxylic acid derivatives.

1.6.1 Amides

Amides are important in organic and biological chemistry and can be prepared from various starting materials with many synthetic routes.

Venkataraman and Wagle [29] demonstrated the conversion of carboxylic acids to acid chlorides, amides and peptides using carboxylic acid with cyanuric chloride and then amine was added to convert the intermediate formed into amide.

Harison and co-workers [30] described the conversion of carboxylic acids to acid chlorides by treatment acids with CCl_4 and polymer-support phosphine. A mixture of acid chlorides and amines was then converted into amides.

Jang and co-workers [31] displayed the conversion of carboxylic acids to acid chlorides by treatment carboxylic acid with CCl_3CN and PPh_3 in CH_2Cl_2. The reaction took place under mild and acid free conditions.

Khalafi-Nezhad and co-workers [32] developed the solvent-free procedure for transformation aliphatic and aromatic carboxylic acids to amides. This method utilized the direct reaction of carboxylic acids and silica-supported ammonium salts, NEt_3 and TsCl as condensing agents. The reaction proceeded rapidly with high yields at room temperature.

Kangani and Kelley [33] addressed one pot synthesis of amides from the corresponding carboxylic acids using Deoxo-Fluor [$(CH_3OCH_2CH_2)_2NSF_3$] as reagent. The reaction proceeded rapidly in CH_2Cl_2 at 0°C.

Heuser and co-workers [34] reported two-step synthesis of oxazolopyridines. The synthesis involving amide formation between *o*-aminopyridinols and aliphatic or aromatic carboxylic acids followed by using CCl_3COCCl_3/PPh_3 combination at room temperature.

1.6.2 Esters

Esters could be synthesized directly from an acid and an alcohol in the presence of strong acid such as H_2SO_4 and HCl. However, the interaction between a carboxylic acid and an alcohol was a reversible process. Therefore, the development of a better process was conferred.

Liu and co-workers [35] described two closely related methods for the condensation of carboxylic acids with alcohols to esters. Two methods differed from each other only in the reagent involved for the activation of carboxylic acids. In one case, *N*,*N*-dimethylphosphoramidic dichloride [$(CH_3)_2NPOCl_2$)] was used as a reagent, and in the other, phenyl dichlorophosphate [$C_6H_5OPOCl_2$] was used. The reaction proceeded smoothly at room temperature under neutral conditions.

Sucheta and co-workers [36] addressed the general method for the convenient conversion of carboxylic acids to the corresponding acid halides using PPh_3 and *N*-bromo/iodosuccinimides. Several acids were smoothly esterified with alcohol to furnish esters in high yield.

Kawabata and co-workers [37] displayed the esterification of carboxylic acids with alcohols using the system of heterogeneous catalysts at high temperature. Montmorillonite-enwrapped titanium catalyst was found to efficiently promote the esterification of carboxylic acids with alcohols.

1.6.3 Carboxylic Acid Anhydrides

Carboxylic acid anhydrides are commonly used as reactive intermediates in organic synthesis for preparing many other functional groups, due to their enhanced electrophilic character of the carbonyl groups.

Fife and Zhang [38] addressed the new methodology for the preparation of asymmetric acid anhydrides by treating a mixture of carboxylic acid with one-half equivalent of $SOCl_2$ in CH_2Cl_2 with a solid-state copolymer of 4-vinylpyridine.

Kim and Jang [39] described the preparation of symmetrical acid anhydrides from the corresponding carboxylic acids by treating acids with Cl_3CCN and PPh_3 in the presence of NEt_3 at room temperature.

1.6.4 Thioesters

Thioesters are of great interest carboxylic acid derivatives because of their close relation to many biomolecules such as coenzyme A.

Weber [40] described the preparation of peptide thioesters under prebiotic conditions by condensation of amino acid thioesters generated by the reaction of small sugars with ammonia and thiols.

Weber [41] developed the method for the synthesis of peptide thioesters from free amino acids and thiols in water. Using this one-pot reaction, the synthesis began by reacting amino acid with 1,1-carbonyldiimidazole to give an amino acid carboxyanhydride intermediate that condensed to both peptides and peptide thioesters in the presence of added thiol.

1.7 The Objective of This Research

The objective of this research is to develop brominating agents to utilize in combination with PPh_3 and to explore the optimum conditions for the preparation of alkyl bromides and acid bromides under mild conditions. The application of the developed methodology for the synthesis of carboxylic acid derivatives such as amides, esters, acid anhydrides and thioesters was also examined.

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CHAPTER II

EXPERIMENTAL

2.1 Instruments and Equipment

Melting points were determined with a Fisher-Johns melting point apparatus. Thin layer chromatography (TLC) was performed on aluminium sheets pre-coated with silica gel (Merck's, Kieselgel 60 PF_{254}) and column chromatography was performed on silica gel (Merck's silica gel 60 G Art 7734 (70-230 mesh).

The ^{1}H- and ^{13}C-NMR spectra were performed in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6) 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.

HPLC was performed on Water® 600 controllers equipped with a Water® 2996 dual UV wavelength detector (USA) using Econosphere 5 Cl8-ARII(25X250 mm) reversed phase column (Alltech Associates, IL, USA).

Specific rotations were measured on a Jasco P-1010 polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg $\cdot$ cm^2 $\cdot$ g^{-1}.

2.2 Chemicals

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

2.3 Preparation of Brominating Agents

Ethyl tribromoacetate [7, 42]

One mL of conc. H_2SO_4 was cautiously added to the mixture of Br_3CCO_2H 1 eq (40 mmol, 11.87 g) and EtOH 4.5 mL. The mixture was refluxed for 3-6 h and then poured into 100 mL of water in a separatory funnel. The upper layer of crude ester was removed and washed with 50 mL of water, saturated aqueous $NaHCO_3$ and water respectively then dried over anhydrous Na_2SO_4.

Ethyl tribromoacetate: colorless oil (82%). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.36 (3H, t, *J* = 7.20 Hz, $CH_2C\underline{H}_3$) and 4.46 (2H, q, *J* = 7.20 Hz, $C\underline{H}_2CH_3$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.7, 29.5, 65.7 and 161.9.

***N,N*-Diethyltribromoacetamide and *N,N*-phenyltribromoacetamide** [24,42]

In a round bottom flask was placed 1 eq (15 mmol, 4.45 g) of Br_3CCO_2H, 2.62 mL of oxalyl chloride and 1-2 drops of DMF. The reaction was proceeded spontaneously for 15-20 min and refluxed for 2 h. The excess of oxalyl chloride was evaporated *in vacuo.* The mixture was added dropwise to well stirred, aqueous diethylamine or aniline and stirred for another 1 h at RT. When the reaction was completed, *N,N*-diethyltribromoacetamide was extracted with 10% HCl, saturated aqueous $NaHCO_3$ and H_2O, respectively, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. In the case of the preparation of phenyltribromoacetamide, the solid was collected upon filtration and air-dried.

N,N-diethyltribromoacetamide: yellow oil (68%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.28 (3H, br s, $CH_2C\underline{H}_3$), 1.36 (3H, br s, $CH_2C\underline{H}_3$), 3.45 (2H, br s, $C\underline{H}_2CH_3$) and 3.79 (2H, br s, $C\underline{H}_2CH_3$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 11.8, 13.0, 37.2, 43.4, 45.2 and 159.3.

Phenyltribromoacetamide: yellow needle (81 %), ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.15 (1H, t, *J* = 7.32 Hz, Ar-$\underline{H}$), 7.75 (2H, m, Ar-$\underline{H}$), 7.85 (2H, d, *J* = 8.03 Hz, Ar-$\underline{H}$) and 10.92 (1H, s, N$\underline{H}$). ^{13}C-NMR (DMSO-d_6) δ (ppm): 120.1, 125.1, 129.2, 138.1 and 159.0.

Hexabromoacetone [43]

Anhydrous NaOAc 7 g was mixed with 20 mL of glacial acetic acid. The reaction mixture was stirred and heated to 60°C, acetone 1.4 mL was added and followed by dropwise addition of Br_2 5 mL over a 10 min period with stirring. The

mixture was then heated to 95°C for 2 h. After which it was cooled to RT and mixed with 100 mL of water to precipitate the desired product as white solid. After air drying, the pure product was obtained upon recrystallization from hexane.

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

2.4 General Procedure for Conversion of Alcohols to Alkyl Bromides

A stirred solution of alcohol 1 eq (0.25 mmol) and PPh_3 1.5 eq (0.375 mmol, 0.098 g) in dry CH_2Cl_2 (0.5 mL) was successively added selected halogenated reagent 2 eq (0.5 mmol) at RT (30 °C) under N_2 atmosphere. After stirring for 30 min, the crude mixture was analyzed by ^{1}H-NMR with the addition of toluene as an internal standard or purified by silica gel column.

2.5 Study on Optimum Conditions for Conversion of Alcohols to Alkyl Bromides

2.5.1 Effect of Brominating Agents

The conversion of 2-phenylethyl alcohol to 2-phenylethyl bromide was carried out using the reaction conditions described in the general procedure. Six different brominating reagents including 1,2-dibromoethane ($BrCH_2CH_2Br$), bromotrichloromethane (Cl_3CBr), tribromoacetic acid (Br_3CCO_2H), tetrabromo methane (CBr_4), ethyl tribromoacetate (Br_3CCO_2Et) and hexabromoacetone ($Br_3CCOCBr_3$) were utilized.

2.5.2 Effect of PPh_3 and Brominating Agents Ratio

The ratios of PPh_3 and brominating agent for the synthesis of 2-phenylethyl bromide utilizing the general procedure were varied (based on 2-phenylethyl alcohol 1 eq). After 30 min, the yield of 2-phenylethyl bromide in the crude mixture was determined by ^{1}H-NMR with the addition of toluene as an internal standard. Brominating agents: Br_3CO_2Et, $Br_3CCOCBr_3$, CBr_4 were selected.

2.5.3 Effect of Reaction Time

According to the general procedure, the reaction time for each brominating agent can procure using suitable ratios of the PPh_3 and brominating agent as follows: 1.5:1 eq, 1.5:0.3 eq and 1.5:1.5 eq in the case of utilizing Br_3CCO_2Et, $Br_3CCOCBr_3$ and CBr_4, respectively. The time variations are as follows: 5, 15 and 30 min at RT (30

°C). 2-Phenylethyl bromide occurred in the reaction mixture was quantified by ^{1}H-NMR with the addition of toluene as an internal standard.

2.6 The Synthesis of Alkyl Bromides

The bromination of alcohol using a suitable ratio of PPh_3/Br_3CCO_2Et and $PPh_3/Br_3CCOCBr_3$ at RT for 15 min was conducted. Different chosen alcohols including primary, secondary and tertiary alcohols were examined. The quantity of alkyl bromide in the crude mixture was determined by ^{1}H-NMR using toluene as an internal standard or purified by silica gel column.

2-Phenethyl bromide: colorless oil (82%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.20 (2H, t, *J* = 7.70 Hz, $PhCH_2C\underline{H}_2Br$), 3.61 (2H, t, *J* = 7.70 Hz, $PhC\underline{H}_2CH_2Br$) and 7.24-7.37 (5H, m, Ar-<u>H</u>). ^{13}C-NMR ($CDCl_3$) δ (ppm): 33.3, 39.6, 127.1, 128.8 and 139.1.

Nopyl bromide: colorless oil (78%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.77 (3H, s, $CC\underline{H}_3$), 1.10 (H, d, *J* = 8.58 Hz, $CC\underline{H}(CH_2)_2$), 1.20 (3H, s, $CC\underline{H}_3$), 1.19-2.45 (7H, m, alkyl groups), 3.28 (2H, m, $C\underline{H}_2Br$) and 5.25 (H, s, $C=C\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.2, 26.2, 30.8, 31.3, 31.6, 38.0, 40.4, 40.6, 45.4, 119.1 and 145.1.

1-Adamantyl bromide: white needle (36%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72 (6H, s, alkyl groups), 2.09 (3H, s, alkyl groups) and 2.36 (6H, s, alkyl groups). ^{13}C-NMR ($CDCl_3$) δ (ppm): 32.6, 35.5, 48.3 and 66.8.

1,5-Dibromopentane: colorless oil (86%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.60 (2H, m, $CH_2C\underline{H}_2CH_2$), 1.88 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$) and 3.41(4H, t, *J* = 6.64 Hz, $BrC\underline{H}_2$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 26.8, 31.8 and 33.2.

1,10-dibromodecane: colorless oil (87%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.29 (8H, s, alkyl groups), 1.40 (4H, br s, alkyl groups) and 3.39 (4H, t, *J* = 6.88 Hz, $BrC\underline{H}_2$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 28.1, 28.7, 29.3, 32.8 and 34.0.

2.7 Stereoselectivity Study

To a stirred solution of (-)-cholesterol 1 eq (3 mmol, 1.16 g) or (-)-(R)-2-octanol (3 mmol, 0.3907 g) and PPh_3 1.5 eq (4.5 mmol, 1.18 g) in dry CH_2Cl_2 4 mL was successively added selected Br_3CCO_2Et 1 eq (3 mmol, 0.9651 g) at room temperature (30 °C) under N_2 atmosphere. After stirring for 15 min, the crude mixture was purified by silica gel column using hexane as eluent. The optical rotation of the

starting material alcohol and bromide product were measured on polarimeter using $CHCl_3$ as solvent.

Cholesteryl bromide: white needle (82%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.67-2.53 (43H, m, alkyl groups), 3.92 (1H, m, BrC<u>H</u>) and 5.36 (1H, br s, C=C<u>H</u>). ^{13}C-NMR ($CDCl_3$) δ (ppm): 11.8, 18.7, 19.2, 20.9, 22.6, 22.8, 23.8, 24.3, 28.0, 28.2, 31.7, 31.8, 34.3, 35.7, 36.2, 36.4, 39.5, 39.6, 40.3, 42.3, 44.3, 50.1, 52.6, 56.1, 56.6, 112.3 and 141.5.

*(+)-(S)-2-octyl bromide***:** colorless oil (84%)**,** ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.88 (3H, m, C<u>H</u>$_3$), 1.28-1.53 (8H, m, alkyl groups), 1.70 (3H, d, *J* =6.71 Hz, BrCHC<u>H</u>$_3$), 1.78 (2H, m, BrCHC<u>H</u>$_2$)**,** 4.12 (1H, m, BrC<u>H</u>)**.** NMR ($CDCl_3$) δ (ppm): 14.1, 22.6, 26.5, 27.7, 28.6, 31.7, 41.2 and 52.0.

2.8 Comparative Reactivity Study of Brominating Agents for Conversion of Alcohols to Alkyl Bromides

The reactivity of Br_3CCO_2Et, $Br_3CCOCBr_3$ and other brominating agents was investigated using a competitive reaction between brominated and chlorinated reagents towards alcohol. The reactivity of selected chlorinating agent was rationalized by the obtained yield ratio of alkyl bromide and chloride.

2-Phenylethyl alcohol 1 eq (0.25 mmol, 0.03 g) was added to a mixture of Cl_3CCN 0.75 eq (0.19 mmol, 0.05 mL) and selected brominating agent 0.75 eq (0.19 mmol) in dry CH_2Cl_2 (0.5 mL). The mixture was treated with PPh_3 1.5 eq (0.375 mmol, 0.098 g) under the developed system. After 15 min, the crude mixture was evaporated to dryness and both alkyl halides were determined by ^{1}H-NMR with the addition of toluene as an internal standard.

2.9 General Procedure for the Synthesis of Carboxylic Acid Derivatives

Step 1: PPh_3 2 eq (6 mmol, 1.57 g) in CH_2Cl_2 3 mL was added to a mixture of carboxylic acid 1 eq (3 mmol) and $Br_3CCOBr_3$1 eq (3 mmol) in dry CH_2Cl_2 3 mL at reflux temperature. The mixture was stirred for approximately 1 h.

Step 2: A mixture of amine or other nucleophiles (alcohol and thiol) 1 eq (3 mmol) and 4-picoline 3 eq (9 mmol) was added to the above mixture. The reaction was continued stirring for another 20 min or followed by TLC at selected temperatures. When the reaction was completed, the organic layer was extracted with 10% HCl and saturated aqueous $NaHCO_3$, respectively, dried over anhydrous Na_2SO_4

and evaporated *in vacuo*. The mixture was separated with silica gel column eluting with 4:1 hexane/EtOAc. Purification by recrystallization with a mixture of CH_2Cl_2 and hexane or another appropriate solvent was conducted to achieve the desired amide or ester and thioester products.

2.10 Study on the Optimum Conditions for Preparing Acid Bromides

2.10.1 Effect of PPh_3 and $Br_3CCOCBr_3$ Ratio

The suitable ratio of $PPh_3/Br_3CCOCBr_3$ was determined using the reaction conditions described in the general procedure (carboxylic acid: benzoic acid, amine: 2-phenylethyl amine). The variation of PPh_3 and $Br_3CCOCBr_3$ ratios was as follows: 2:1, 2:0.5, 2:0.3 and 2:0.2, respectively.

2.10.2 Effect of Temperature and Reaction Time

The general synthesis of *N*-phenethylbenzamide using the ratio of PPh_3/Br_3CCOBr_3 2:0.3 eq was performed using different reaction time and temperature in steps 1 and 2.

2.11 Synthesis of Carboxylic Acid Derivatives

2.11.1 The Synthesis of Amides, Esters and Thioesters

According to the general procedure using $PPh_3/Br_3CCOCBr_3$ 2:0.3, after 5 min a mixture of amine (or alcohol or thiol) and 4-picoline 3 eq (9 mmol, 0.88 mL) was added to the above mixture at RT and stirred for approximately 5 min or followed by TLC at selected temperatures.

N-phenethylbenzamide: white needle (88%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.94 (2H, t, *J* = 6.79 Hz, $CH_2C\underline{H}_2Ph$), 3.72 (2H, dd, *J* = 6.79 and 12.87 Hz, $NHC\underline{H}_2CH_2$), 6.19 (H, br s, N<u>H</u>), 7.25-7.48 (8H, m, Ar-<u>H</u>) and 7.84 (2H, d, *J* = 7.37 Hz, Ar-<u>H</u>). ^{13}C-NMR ($CDCl_3$) δ (ppm): 36.7, 41.2, 126.6, 126.8, 128.5, 128.7, 128.8, 131.4, 134.6, 139.9 and 167.5.

N-phenethylstearamide: white needle (89%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.88 (3H, m, $CH_2C\underline{H}_3$), 1.25 (28H, br s, alkyl groups), 1.52 (2H, m, alkyl groups), 2.11 (2H, t, *J* = 7.45 Hz, $CO_2C\underline{H}_2$), 2.81(2H, t, *J* = 6.88 Hz, $CH_2C\underline{H}_2Ph$), 3.52 (2H, dd, *J* = 6.88 and 12.95 Hz, $NHC\underline{H}_2CH_2$), 5.44 (H, br s, N<u>H</u>) and 7.18-7.33 (5H, m, Ar-<u>H</u>) .^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1, 22.7, 25.8, 29.2-29.7, 31.9, 36.7, 36.9, 40.4, 126.5, 128.6, 128.6, 139.9 and 173.1.

N,N-diethyl-3-methylbenzamide: yellow oil (73%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.05 (3H, br s,$CH_2C\underline{H}_3$), 1.19 (3H, br s, $CH_2C\underline{H}_3$), 2.31 (3H, s, $ArC\underline{H}_3$), 3.20 (2H, br s, $N(CH\underline{H}CH_3)_2$), 3.43 (2H, br s, $N(C\underline{H}HCH_3)_2$) and 7.08-7.23 (4H, m, Ar-H).^{13}C-NMR ($CDCl_3$) δ (ppm): 13.1, 14.4, 21.5, 39.4, 43.4, 127.0, 128.4, 129.9, 137.4, 138.4, and 171.7.

N,N-diethyl-2-methylbenzamide: yellow oil (42%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.95 (3H, t, *J* = 7.13 Hz, $CH_2C\underline{H}_3$), 1.18 (3H, t, *J* = 7.13 Hz, $CH_2C\underline{H}_3$), 2.21 (3H, s, $ArC\underline{H}_3$), 3.04 (2H, m, $N(CH\underline{H}CH_3)_2$), 3.34-3.61 (2H, br s, $N(C\underline{H}HCH_3)_2$) and 7.05-7.13 (4H, m, Ar-H).^{13}C-NMR ($CDCl_3$) δ (ppm): 12.8, 13.9, 18.6, 38.6, 42.6, 125.3, 125.7, 128.5, 130.2, 133.7, 136.9 and 170.8.

N,N-diethyl-4-methylbenzamide: yellow oil (78%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.05 (3H, br s,$CH_2C\underline{H}_3$), 1.16 (3H, br s, $CH_2C\underline{H}_3$), 2.29 (3H, s, $ArC\underline{H}_3$), 3.21 (2H, br s, $N(CH\underline{H}CH_3)_2$), 3.44 (2H, br s, $N(C\underline{H}HCH_3)_2$), 7.12 (2H, d, *J* = 7.87 Hz Ar-H) and 7.20 (2H, d, *J* = 7.87 Hz Ar-H).^{13}C-NMR ($CDCl_3$) δ (ppm): 12.8, 14.1, 21.3, 39.2, 43.3, 126.3, 129.9, 134.2, 139.0 and 171.4.

N,N-diethyl-4-nitrobenzamide: white needle (67%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.07 (3H, br s,$CH_2C\underline{H}_3$), 1.22 (3H, br s, $CH_2C\underline{H}_3$), 3.17 (3H, d, *J* = 6.62 Hz, $N(CH\underline{H}CH_3)_2$), 3.53 (2H, *J* = 6.62 Hz, $N(C\underline{H}HCH_3)_2$), 7.51 (2H, d, *J* = 8.46 Hz, Ar-H) and 8.21 (2H, d, *J* = 8.46 Hz, Ar-H).^{13}C-NMR ($CDCl_3$) δ (ppm): 12.7, 14.2, 39.4, 43.2, 123.8, 127.3, 143.3, 147.9 and 168.9.

Piperidin-1-yl-o-tolyl-methanone: white needle (78%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.42 (2H, br s, alkyl groups), 1.63 (4H, br s, alkyl groups), 2.27 (3H, s, $ArC\underline{H}_3$), 3.14 (2H, br s, alkyl groups), 3.67(H, br s, alkyl groups), 3.76 (H, br s, alkyl groups)and 7.10-7.22 (4H, m, Ar-H).^{13}C-NMR ($CDCl_3$) δ (ppm): 18.9, 24.5, 25.7, 26.5, 42.3, 47.8, 125.5, 125.8, 128.6, 130.3, 133.9, 136.7 and 170.0

1-(3, 4-Methylendioxy-cinnamoyl)-piperidin: white needle (95%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.59-1.65 (6H, m, alkyl groups), 3.60 (4H, br s, alkyl groups), 5.97 (2H, s, $OC\underline{H}_2O$), 6.72 (H, d, *J* = 15.33 Hz, C=C\underline{H}), 6.78 (H, d, *J* = 7.91 Hz, Ar-H), 6.97 (H, d, *J* = 7.91 Hz, Ar-H), 7.00(H, s, Ar-H), and 7.56(H, d, *J* = 15.33 Hz, C=C\underline{H}). ^{13}C-NMR ($CDCl_3$) δ (ppm): 24.9, 25.8, 26.9, 43.5, 47.2, 101.6, 106.5, 108.6, 115.8, 123.8, 130.1, 142.2, 148.4, 149.0 and 165.6.

1-Piperonyloyl-piperidine: white needle (86%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.49-1.59 (6H, m, alkyl groups), 3.39-3.80 (4H, br s, alkyl groups), 5.90 (2H, s,

$OC\underline{H}_2O$), 6.72 (H, d, *J* = 15.33 Hz, C=C$\underline{H}$), 6.72 (H, d, *J* = 7.82 Hz, Ar-$\underline{H}$) and 6.82 (2H, m, Ar-$\underline{H}$).^{13}C-NMR ($CDCl_3$) δ (ppm): 24.5, 25.9, 43.3, 48.5, 101.3, 107.8, 108.0, 121.1, 129.9,147.4, 148.4 and 169.7.

Phenethyl benzoate: colorless oil (86%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.10 (2H, t, *J* = 7.00 Hz, $CH_2C\underline{H}_2Ph$), 4.56 (2H, t, *J* = 7.00, $OC\underline{H}_2CH_2$), 7.24-7.57 (8H, m, Ar-$\underline{H}$) and 8.05 (2H, d, *J* = 7.06 Hz, Ar-$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 35.2, 65.5, 126.6, 128.4, 128.6, 128.9, 129.6, 130.3, 132.9, 137.9 and 165.5.

Octyl 2-(2,4-dichlorophenoxy)acetate: colorless oil (90%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.88 (3H, t, *J* = 6.74 Hz, $CH_2C\underline{H}_3$), 1.26 (12H, br s, alkyl groups), 1.62 (2H, m, alkyl groups), 4.18 (2H, t, *J* = 6.67 Hz, $CO_2C\underline{H}_2R$), 4.69 (2H, s, $OC\underline{H}_2CO_2$), 6.78 (H, d, *J* = 8.81 Hz, Ar-$\underline{H}$), 7.15 (H, dd, *J* = 2.48 and 8.81 Hz, Ar-$\underline{H}$) and 7.40(H, d, *J* = 2.48 Hz, Ar-$\underline{H}$).^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1, 22.6, 25.7, 28.4, 29.1, 29.2, 31.7, 35.7, 36.3, 114.5, 124.2, 126.9, 127.4, 130.2, 152.3 and 168.2.

O-benzoyl-cholesterol: white needle (70%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.69-2.01 (41H, m, alkyl groups), 2.46 (2H, d, *J* = 7.72 Hz, alkyl groups), 4.86 (H, m, $CO_2C\underline{H}$), 5.43 (H, m, C=C$\underline{H}$), 7.43 (2H, t, *J* = 7.43 Hz, Ar-$\underline{H}$), 7.54 (H, t, *J* = 7.43 Hz, Ar-$\underline{H}$) and 8.04 (2H, d, *J* = 7.43 Hz, Ar-$\underline{H}$).^{13}C-NMR ($CDCl_3$) δ (ppm): 11.8, 18.7, 19.3, 21.0, 22.5, 22.7, 22.8, 23.8, 24.2, 27.8, 28.0, 28.1, 28.2, 31.8, 31.9, 35.8, 36.1, 36.6, 37.0, 38.1, 39.5, 39.7, 42.3, 50.0, 56.1, 56.5, 56.6, 74.5, 122.8, 128.2, 129.5, 132.7, 139.6 and 166.0.

Phenethyl stearate: white needle (91%) ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.89 (3H, t, *J* = 6.58 Hz, $CH_2C\underline{H}_3$), 1.25 (28H, br s, alkyl groups), 1.58 (2H, m, alkyl groups), 2.22 (2H, t, *J* = 7.46 Hz, $CO_2C\underline{H}_2$), 2.93 (2H, t, *J* = 7.05 Hz, $CH_2C\underline{H}_2Ph$), 4.28 (2H, t, *J* = 7.05 Hz, $OC\underline{H}_2CH_2$) and 7.21-7.32 (5H, m, Ar-$\underline{H}$) .^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1, 22.7, 24.9, 29.1, 29.2, 29.3, 29.4, 29.6, 29.7, 31.9, 34.3, 35.1, 64.7, 126.5, 128.4, 128.8, 137.9 and 173.8.

S-phenethyl benzothioate: colorless oil (95%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.20 (2H, t, *J* = 7.42 Hz, $CH_2C\underline{H}_2Ph$), 3.34 (2H, t, *J* = 7.42, $SC\underline{H}_2CH_2$), 7.31-7.49 (7H, m, Ar-$\underline{H}$), 7.59 (H, t, *J* = 7.45, Ar-$\underline{H}$) and 8.02 (2H, d, *J* = 7.82 Hz, Ar-$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 30.5, 36.0, 126.6, 127.2, 128.5, 128.6, 128.7, 133.4, 137.1 and 191.8.

S-octyl 2-(2,4-dichlorophenoxy)ethanethioate: colorless oil (92%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.87 (3H, t, *J* = 6.59 Hz, $CH_2C\underline{H}_3$), 1.25 (12H, m, alkyl groups),

1.58 (2H, m, alkyl groups), 2.93 (2H, t, *J* = 7.33 Hz, SC<u>H</u>$_2$R), 4.70 (2H, s, OC<u>H</u>$_2$COS), 6.77 (H, d, *J* = 8.78 Hz, Ar-<u>H</u>), 7.17 (H, dd, *J* = 2.42 and 8.78 Hz, Ar-<u>H</u>) and 7.40(H, d, *J* = 2.42 Hz, Ar-<u>H</u>).^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1, 22.6, 28.2, 28.8, 29.0, 29.1, 29.2, 31.7, 73.5, 114.5, 124.1, 127.2, 127.6, 130.3, 152.1 and 197.2.

2.11.2 The Synthesis of Acid Anhydrides

A mixture of carboxylic acid 2 eq (6 mmol) and hexabromoacetone 0.3 eq (0.9 mmol, 0.479 g) in dry CH_2Cl_2 3 mL were added PPh_3 2 eq (6 mmol, 1.57 g) in dry CH_2Cl_2 3 mL and 4-picoline 3 eq (9 mmol, 0.88 mL) dropwise at room temperature. The reaction mixture was allowed to react for 10 minutes. When the reaction was completed, the organic layer was extracted with 10% HCl and saturated aqueous $NaHCO_3$, respectively, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The mixture was separated with silica gel column chromatography eluting with 4:1 hexane/EtOAc.

Benzoic anhydride: white needle (89%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.53 (4H, t, *J* = 8.15 Hz, Ar-<u>H</u>), 7.68 (2H, m, Ar-<u>H</u>), 8.16 (4H, d, *J* = 8.15 Hz, Ar-<u>H</u>).^{13}C-NMR ($CDCl_3$) δ (ppm): 128.9, 130.5, 134.6 and 162.4.

2-Naphthoic anhydride: white needle (81%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.57 (4H, m, Ar-<u>H</u>), 7.71 (2H, t, *J* = 7.42 Hz, Ar-<u>H</u>), 7.94 (2H, d, *J* = 8.18 Hz, Ar-<u>H</u>), 8.14 (2H, d, *J* = 8.18 Hz, Ar-<u>H</u>), 8.44 (2H, d, *J* = 7.29 Hz, Ar-<u>H</u>) and 9.16 (2H, t, *J* = 8.71 Hz, Ar-<u>H</u>).^{13}C-NMR ($CDCl_3$) δ (ppm): 124.5, 124.8, 125.6, 126.8, 128.8, 131.9, 132.2, 133.9, 135.6 and 162.9.

Stearic anhydride: white needle (78%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.87 (6H, t, *J* = 6.52 Hz, CH_2C<u>H</u>$_3$), 1.25 (56H, br s, alkyl groups), 1.65 (4H, m, alkyl groups) and 2.43 (4H, t, *J* = 7.42 Hz, CO_2C<u>H</u>$_2$).^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1, 22.7, 24.2, 28.8, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 35.3 and 169.6.

2.12 Chemoselectivity Study

A stirred solution of benzoic acid 0.5 eq (1.5 mmol, 0.183 g) and benzenesulfonic acid (1.5 mmol, 0.237) in dry CH_2Cl_2 3 mL was added a solution of PPh_3 2 eq (6 mmol, 1.57 g) in CH_2Cl_2 3 mL. A mixture of 2-phenylethyl amine 1 eq (3 mmol, 0.38 mL) and 4-picoline (9 mmol, 0.88 mL) was then added to the above mixture dropwise at RT. When the reaction was completed, the organic layer was extracted with 10% HCl and saturated aqueous $NaHCO_3$, respectively, dried over

anhydrous Na_2SO_4 and evaporated *in vacuo*. The mixture was separated with silica gel column eluting with 4:1 hexane/EtOAc.

N-phenethylbenzenesulfonamide: white needle (11%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.76 (2H, t, *J* = 6.93 Hz, $CH_2C\underline{H}_2Ph$), 3.23 (2H, dd, *J* = 6.39 and 13.35 Hz, $NHC\underline{H}_2CH_2$), 4.49 (H, br s, N<u>H</u>), 7.09 (2H, d, *J* = 7.99 Hz, Ar-<u>H</u>), 7.25 (3H, m, Ar-<u>H</u>), 7.47-7.57 (3H, m, Ar-<u>H</u>) and 7.81 (2H, d, *J* = 7.81 Hz, Ar-<u>H</u>). ^{13}C-NMR ($CDCl_3$) δ (ppm): 35.8, 44.2, 126.8, 127.0, 128.6, 128.7, 129.1, 132.6, 137.5 and 139.9.

2.13 Comparative Reactivity Study on Brominating Agents for the Formation of Acid Bromide

2,2-Diphenylacetic acid 1 eq (0.25 mmol, 0.053 g) was added to a mixture of Cl_3CCONH_2 0.75 eq (0.19 mmol, 0.031 g) and selected brominating agents 0.75 eq in NMR tube. The mixture was treated with a solution of PPh_3 1.5 eq (0.375 mmol, 0.098 g) in $CDCl_3$. After 15 min, the crude mixture was determined both acid bromide and chloride by ^{1}H-NMR with the addition of toluene as an internal standard.

2.14 Stability of $Br_3CCOCBr_3$

2.14.1 Stability at 80 °C

Eight vials containing $Br_3CCOCBr_3$ 0.3 eq (0.075 mmol, 0.0399 g) were kept in sand bath at 80 °C for 1, 2, 3, 4, 5, 6, 24 and 48 h. Each vial was then taken and used as a brominating agent for transformation 2-phenylethyl alcohol to 2-phenylethyl bromide under standard conditions. The product was determined by ^{1}H-NMR with the addition of toluene as an internal standard.

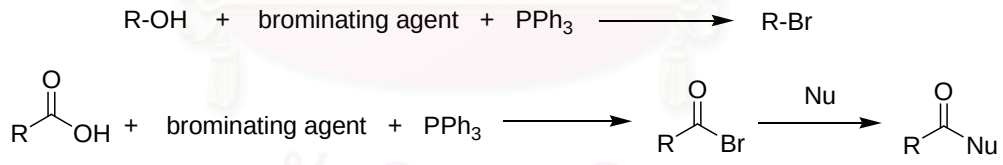
2.14.2 Stability under UV Light

The same procedure was carried out, but the samples were kept under UV light (234 nm, 6 W). The UV irradiation time was 1, 3, 5, and 7 h. Each vial containing $Br_3CCOCBr_3$ was used for conversion of 2-phenylethyl alcohol into 2-phenylethyl bromide under standard conditions. The product was determined by ^{1}H-NMR with the addition of toluene as an internal standard.

CHAPTER III

RESULTS AND DISCUSSION

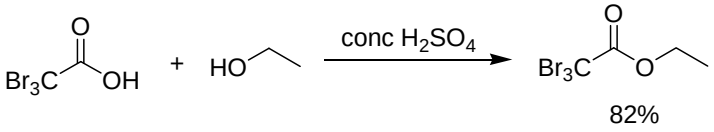
Alkyl and acyl halides have been utilized as one of versatile intermediates in organic chemistry since they can undergo diverse transformations to other compounds [44]. The formations of acyl halides are an efficient route to transform carboxylic acids to their derivatives such as amides, esters and so on. Although alkyl and acyl chlorides have widely been used in organic synthesis for a few decades, the corresponding chlorides are generally less reactive compared with those of bromides. Moreover, brominating agents that required for that kind of preparation are normally not readily available. In this research, two new brominating agents have been developed and introduced. The exploration of optimum conditions utilizing these developed reagents and PPh_3 for the preparation of alkyl and acid bromides from alcohols and carboxylic acids respectively was carried out. The general equation can be simplified as shown below.



3.1 Synthesis of Brominating Agents

Two new brominating agents developed in this research are ethyl tribromoacetate (Br_3CCO_2Et) and hexabromoacetone ($Br_3CCOCBr_3$) which could be prepared by the following methods.

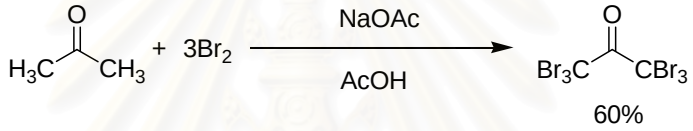
Br_3CCO_2Et could be fruitfully prepared by esterification of tribromoacetic acid, ethanol and concentrated sulfuric acid as a catalyst by conventional fashion [42-43].



Br_3CCO_2Et coupled with PPh_3 has been recently introduced for the preparation of amides *via* acid bromide [5]; nevertheless it has never been reported as a brominating agent for the conversion of alcohols into alkyl bromides.

The ^{1}H-NMR spectrum of Br_3CCO_2Et (Fig 3.1) reveals two peaks of a methylene group resonating at δ_H 4.46 (q, J = 7.20 Hz) and a methyl group at δ_H 1.36 (t, J = 7.20 Hz). The ^{13}C-NMR spectrum (Fig 3.2) exhibits a carbonyl carbon at δ_C 161.9, the carbon atom bearing three bromine atoms at δ_C 65.7 and two peaks at 29.5 and 13.7 belonging to methylene and methyl carbons, respectively.

The synthesis of $Br_3CCOCBr_3$ could be achieved by the reaction of acetone, bromine and sodium acetate in glacial acetic acid as previously described [44].



Although $Br_3CCOCBr_3$ was prepared in 1969 [43], only two reports involving the synthesis of bioactive compounds have been addressed [45-46].

The ^{13}C-NMR spectrum (Fig 3.3) exhibits a carbonyl carbon at δ_C 173.5 and the other peak of the carbon bearing bromine atoms at δ_C 24.5.

Since these two prepared brominating agents are new, the purity of these reagents were thoroughly checked by HPLC column (Nova-Pak normal phase) using hexane: isopropanol 95:5, expressing 100% purity (Fig 3.4).

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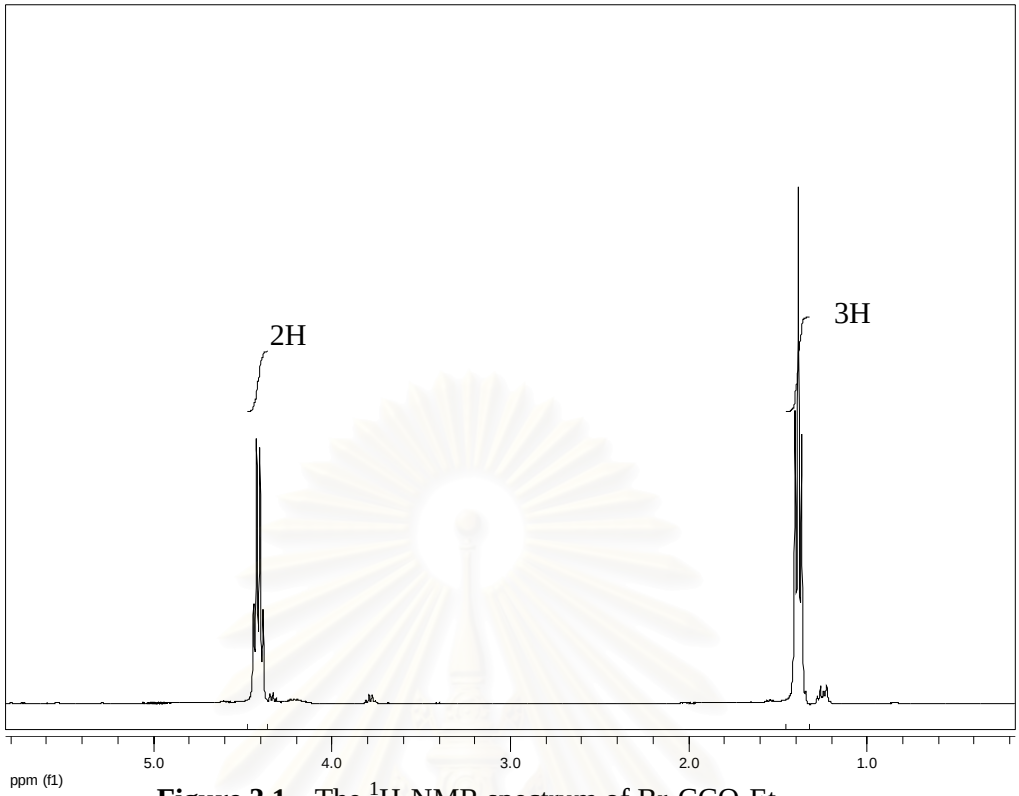

Figure 3.1 The ^{1}H-NMR spectrum of Br_3CCO_2Et

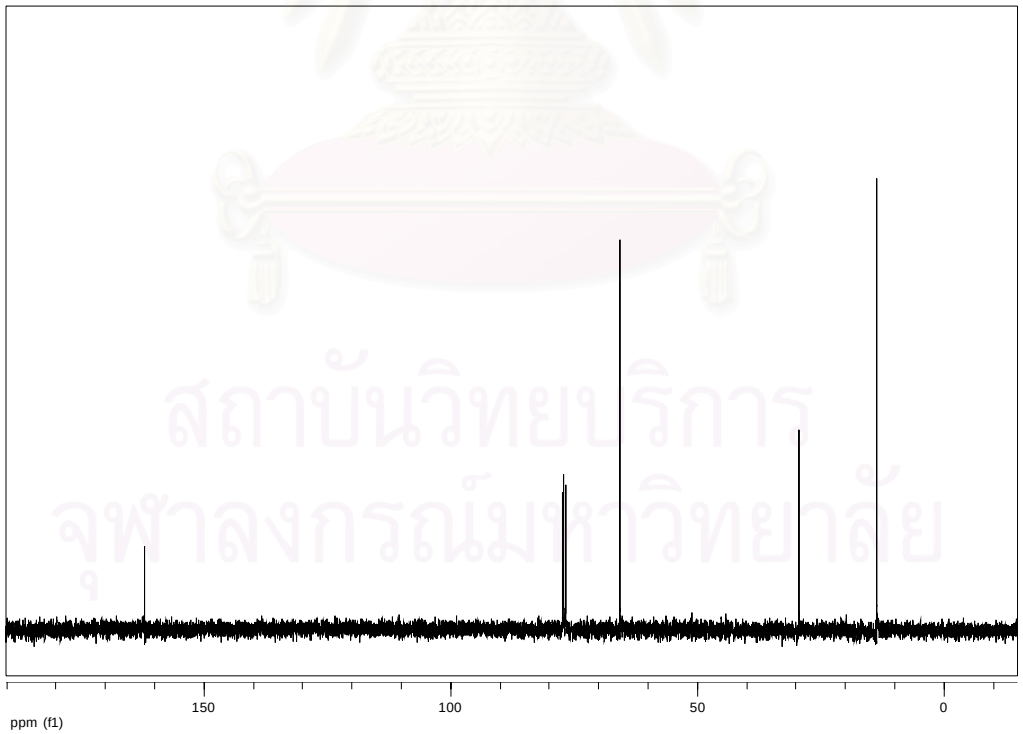

Figure 3.2 The ^{13}C-NMR spectrum of Br_3CCO_2Et

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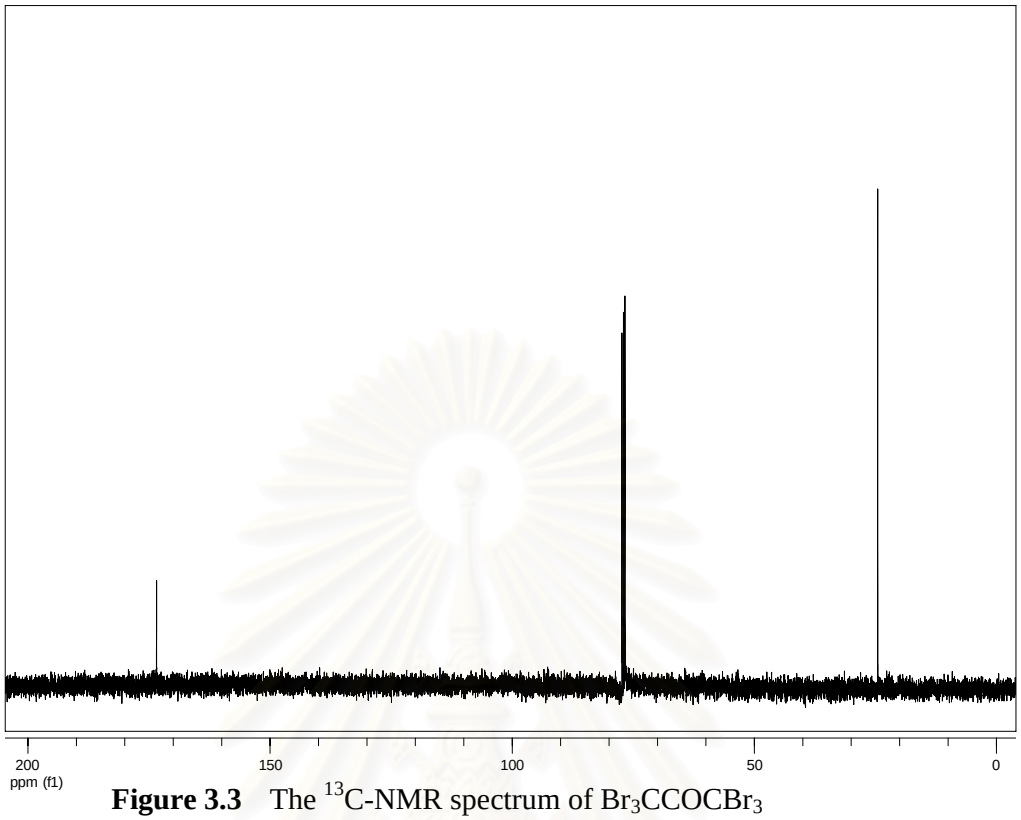
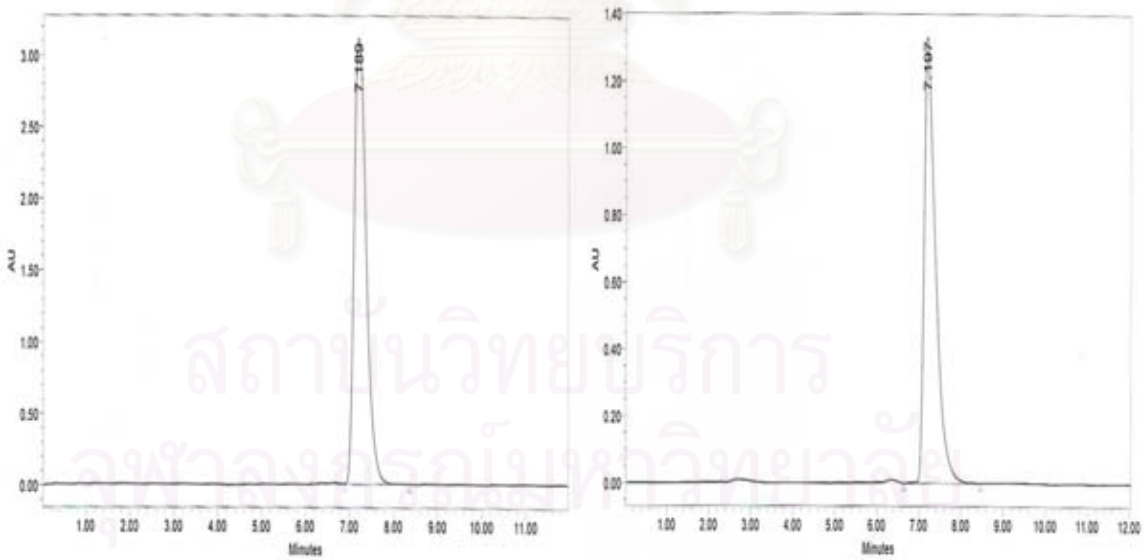


Figure 3.3 The ^{13}C-NMR spectrum of $Br_3CCOCBr_3$



(A) (B)

Figure 3.4 HPLC chromatogram of (A) Br_3CCO_2Et and (B) $Br_3CCOCBr_3$

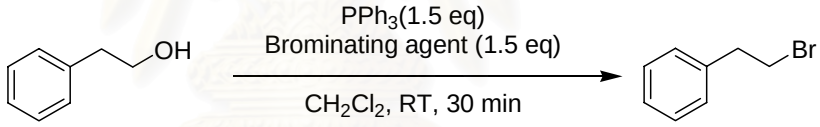
3.2 Conditions Optimization for the Preparation of Alkyl Bromides

Various factors including types of brominating agent, molar ratio of PPh_3 to brominating agent, reaction time and temperature were scrutinized to search for new appropriate brominating agents and to evaluate for the optimal conditions for the conversion of alcohols to alkyl bromides. 2-Phenethyl alcohol was selected as a chemical model.

3.2.1 Effects of Types of Brominating Agents

Certain brominating agents used in this research are commercial available, *i.e.*, 1,2-dibromoethane ($BrCH_2CH_2Br$), bromotrichloromethane ($BrCCl_3$), tribromoacetic acid (Br_3CCO_2H) and tetrabromomethane (CBr_4). The other two, Br_3CCO_2Et and $Br_3CCOCBr_3$ were obtained from the synthesis as described in 3.1. The effect of types of brominating agents was carefully examined and the results are presented in Table 3.1.

Table 3.1 The effects of brominating agents on the conversion of 2-phenethyl alcohol to 2-phenethyl bromide



0.25 mmol

Entry	Brominating agent	% yield *			Σ
		2-Phenethyl bromide	Recovered alcohol	Other	
1	none	trace	98	trace	98
2	$BrCH_2CH_2Br$	trace	100	trace	100
3	$BrCCl_3$	21	41	40[a]	102
4	Br_3CCO_2H	82	trace	16[b]	98
5	CBr_4	96	trace	trace	96
6	Br_3CCO_2Et	95	trace	trace	95
7	$Br_3CCOCBr_3$	98	trace	trace	98

* % yield is determined by ^{1}H-NMR using toluene as an internal standard

[a] % Yield of $PhCH_2CH_2Cl$

[b] % Yield of $Br_3CCO_2CH_2CH_2Ph$

% Yield of 2-phenethyl bromide was determined by ^{1}H-NMR from the crude reaction mixture with the addition of toluene as an internal standard. The example of the crude reaction mixture using $BrCCl_3$ is presented in Fig 3.5.

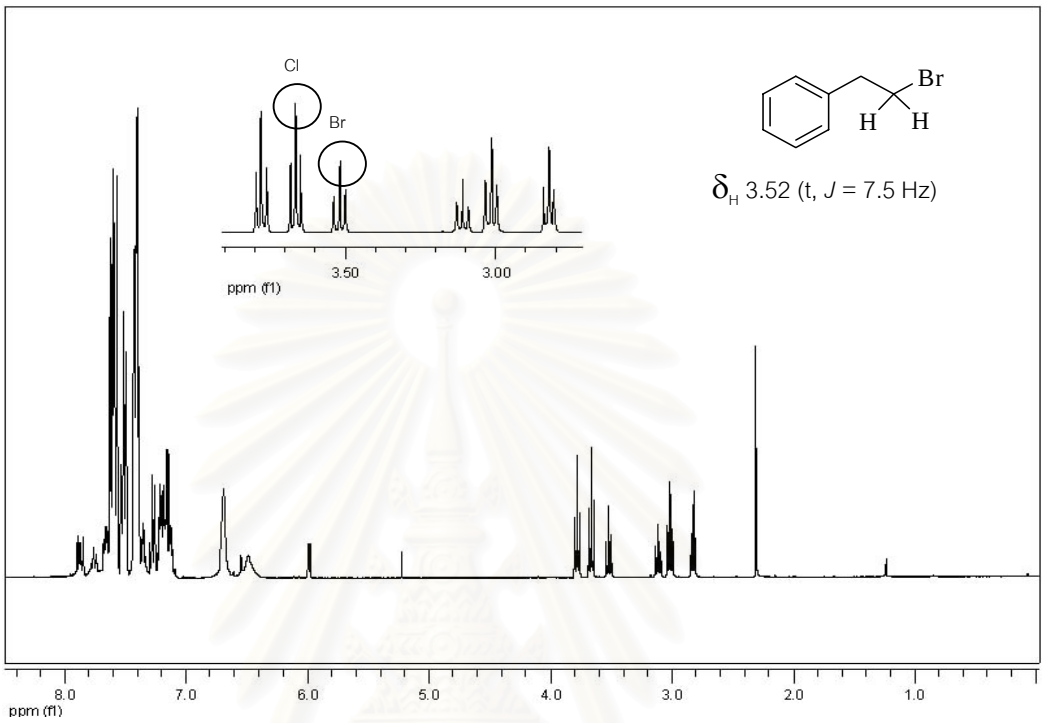
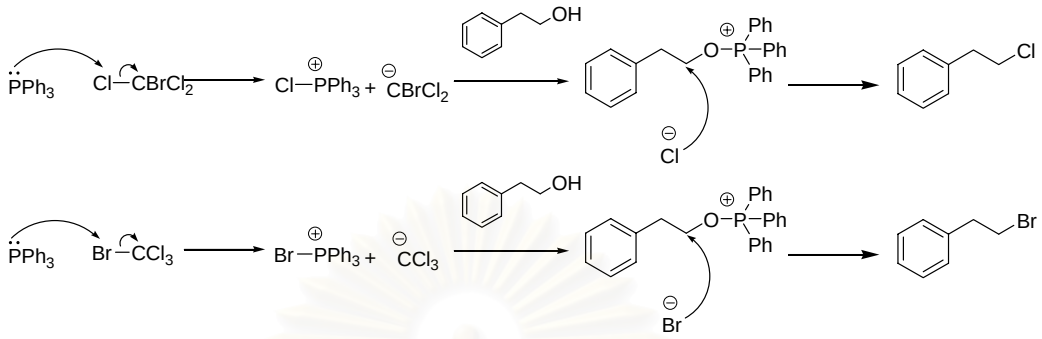


Figure 3.5 The ^{1}H-NMR spectrum of 2-phenylethyl alcohol, 2-phenylethyl chloride and 2-phenethyl bromide in the crude reaction mixture

Considering the effect of brominating agents on the conversion of 2-phenethyl alcohol to 2-phenethyl bromide, it was observed that when the reaction was carried out in the absence of brominating agent (entry 1), no reaction took place. The reaction using $BrCH_2CH_2Br$ (entry 2) provided the desired product only in trace amount. Interestingly, two corresponding alkyl bromide and alkyl chloride were detected in 21% and 40% yield, respectively when $BrCCl_3$ was used (entry 3). This observation could be explained that PPh_3 reacted with either chlorine or bromine atoms in $BrCCl_3$ to generate phosphonium salt intermediate. The intermediate formed was then converted to the corresponding alkyl bromide or chloride. Although bromine was a more reactive species than chlorine, the yield of 2-phenethyl bromide was obtained in lower yield than that of 2-phenethyl chloride. It was therefore conceivable that the yield of the desired product from these two competitive pathways was depended on

the amount of chlorine/bromine as 3/1 present in the reagent. The chance for PPh_3 to react with chlorine could be statistically three folds more than bromine atom.



Comparing the results in entry 2 with those in entries 4-7, it was clearly seen that the structure of brominating agent was greatly affected on the reactivity of the reaction. The brominating agent bearing more affinity electron-withdrawing group, for instance, entry 4 (Br_3CCO_2H) provided the desired product in higher yield. This was also observed for the case of entries 5-7 using CBr_4, Br_3CCO_2Et and $Br_3CCOCBr_3$, respectively. In the case of using Br_3CCO_2H (entry 4), the reaction still gave good yield of 2-phenethyl bromide (82%), however the side-reaction product as 2-phenethyl tribromoaceate ($Br_3CCO_2CH_2CH_2Ph$) was also detected. The occurrence of the latter was confirmed by comparing with authentic specimen obtained from the synthesis [42-43].

Regarding to the efficiency of brominating agents investigated, it could be arranged as shown below.

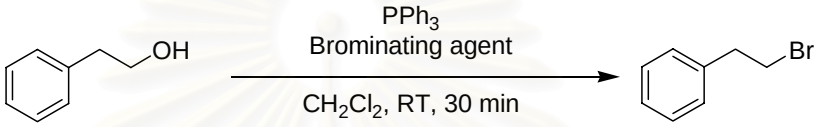
$$Br_3CCO_2Et \sim Br_3CCOCBr_3 \sim CBr_4 > Br_3CCO_2H > \quad BrCCl_3 > BrCH_2CH_2Br$$

Based upon the results attained, Br_3CCO_2Et, $Br_3CCOCBr_3$ and CBr_4 are potent brominating agents. CBr_4 has been reported as a brominating agent in literature for decades [11, 17 and 47]. On the other hand, Br_3CCO_2Et and $Br_3CCOCBr_3$ are new brominating agents which have not been reported elsewhere. Thus, it is justified to work on these two brominating agents in more details.

3.2.2 Effects of Molar Ratio of PPh_3:Brominating Agent

The effect of molar ratio of PPh_3 and brominating agents was investigated with the aim to attain the most appropriate ratio of the combination. Br_3CCO_2Et, $Br_3CCOCBr_3$ and CBr_4 were selected as brominating agents. The results are demonstrated in Table 3.2.

Table 3.2 Effects of molar ratio of PPh_3:brominating agent on the conversion of 2-phenethyl alcohol to 2-phenethyl bromide



0.25 mmol

Entry	Brominating agent	Molar ratio of PPh_3 : Brominating agent	yield*		Σ
			2-Phenethyl bromide	Recovered alcohol	
1		1.0 : 1.0	78	21	99
2		1.5 : 1.5	95	-	95
3	Br_3CCO_2Et	1.5 : 1.0	96	-	96
4		1.5 : 1.0	98[a]	-	98
5		1.5 : 0.5	78	28	105
6		2.0 : 0.5	67	34	101
7		1.0 : 1.0	77	24	101
8		1.5 : 1.5	98	-	98
9	$Br_3CCOCBr_3$	1.5 : 1.0	99	-	99
10		1.5 : 0.5	99	-	99
11		1.5 : 0.3	98	-	98
12		1.5 : 0.3	98[a]	-	98

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Table 3.2 (continued)

Entry	Brominating agent	Molar ratio of PPh_3 : Brominating agent	yield*		Σ
			2-Phenethyl bromide	Recovered alcohol	
13		1.5 : 0.25	74	27	101
14		1.0 : 1.0	77	23	100
15	CBr_4	1.5 : 1.5	96	-	96
16		1.5 : 1.5	97[a]	-	97
17		1.5 : 1.0	90	11	101
18		1.5 : 0.5	42	57	99

* Determined by ^{1}H-NMR using toluene as an internal standard

[a] 5 min at RT

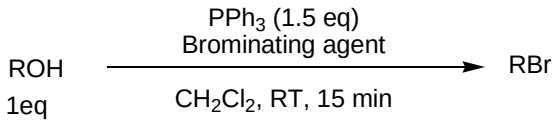
As the results presented in Table 3.2, it was found that the suitable ratio of PPh_3:brominating agent for conversion of 2-phenethyl alcohol to 2-phenethyl bromide was 1.5:1 (entry 3) in case of using Br_3CCO_2Et, whereas for $Br_3CCOCBr_3$ and CBr_4, they were 1.5:0.3 equivalent (entry 11) and 1.5:1.5 equivalent (entry 15), respectively. This result showed that the required amount of brominating agent was relied on type of brominating agent. To illustrate this, the reagents bearing electron-withdrawing groups enhanced the reactivity. When $Br_3CCOCBr_3$ was employed, only 0.3 equivalent was necessary.

It should be also mentioned at this point that the conversion of 2-phenethyl alcohol to 2-phenethyl bromide under these particular conditions requires the short reaction time as 15 min. Further experiments to lessen the reaction time clearly revealed that only 5 min was enough to convert 2-phenethyl alcohol to 2-phenethyl bromide almost quantitatively (entries 4, 12 and 16).

3.3 Application of Developed Procedures for the Synthesis of Alkyl Bromides

Since the optimized reaction conditions such as types of brominating agents, ratio of PPh_3:brominating agent and reaction time could be achieved as previously discussed. The scope of the reaction to convert various alcohols into their corresponding bromides using two selected brominating agents, Br_3CCO_2Et and $Br_3CCOCBr_3$ was further explored and the results are displayed in Table 3.3.

Table 3.3 Conversion of alcohols to alkyl bromides using Br_3CCO_2Et/PPh_3 and $PPh_3/Br_3CCOCBr_3$ systems



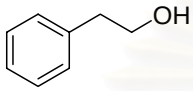
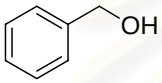
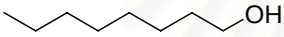
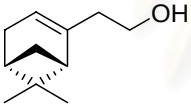
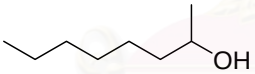
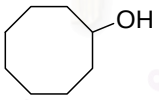
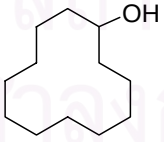
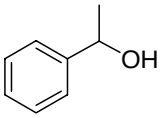
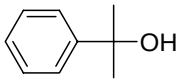
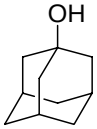
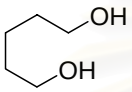
Entry	ROH	Brominating agent	% yield*		Σ
			Alkyl bromide	Olefin	
1		Br_3CCO_2Et	98	-	98
		Br_3CCO_2Et	82[a]		
		$Br_3CCOCBr_3$	98	-	98
2		Br_3CCO_2Et	98	-	98
3		Br_3CCO_2Et	quant	-	quant
		$Br_3CCOCBr_3$	97	-	97
4		Br_3CCO_2Et	78[a]		
5		Br_3CCO_2Et	97	-	97
		$Br_3CCOCBr_3$	quant	-	quant
6		Br_3CCO_2Et	72	26	98
		$Br_3CCOCBr_3$	84	15	99
7		Br_3CCO_2Et	74	27	101
		$Br_3CCOCBr_3$	80	19	99
8		Br_3CCO_2Et	98	-	98

Table 3.3 (continued)

Entry	ROH	Brominating agent	% yield*		Σ
			Alkyl bromide	Olefin	
9		Br_3CCO_2Et	46	48	94
		$Br_3CCOCBr_3$	67	30	97
10		Br_3CCO_2Et	36[a]		
11		Br_3CCO_2Et	51[a]		
			86[a,b]		
12		Br_3CCO_2Et	52[a]		
			87[a,b]		

* Determined by ^{1}H-NMR using toluene as an internal standard

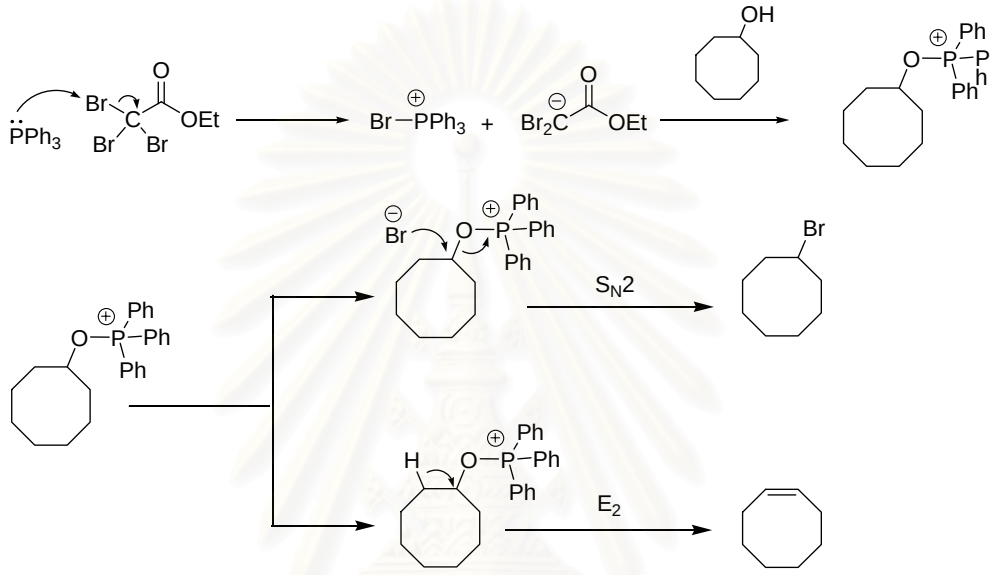
[a] Isolated yield

[b] Molar ratio of PPh_3:Br_3CCO_2Et is 3:2

According to the results presented in Table 3.3, all primary alcohols (entries 1-4) and an aliphatic secondary alcohol (entry 5) could be completely converted to the corresponding alkyl bromides in excellent yields within 15 min. Secondary benzylic alcohol could be converted into the corresponding bromide in excellent yield (entry 8). The transformation of 1-adamantanol to alkyl bromide could be achieved in moderate yield (entry 10) together with a recovered alcohol substance. Interestingly, the amount of reagent, temperature and reaction time had very little influence on the product yield. The reaction of diols and brominating agent was carried out (entries 11-12), only dibromoalkanes were detected. Although, the amount of Br_3CCO_2Et was decreased from 6 to 3 eq with the aim to produce monobromoalkanes, the recovered alcohol was observed and the formation of dibromoalkanes was still detected in moderate yield.

In the case of cyclic alcohols (entries 6-7), besides the main product as bromides, the corresponding alkenes derived from β-elimination could be detected. Pluempanupat and coworkers [49] reported that using PPh_3/chlorinating agent for the

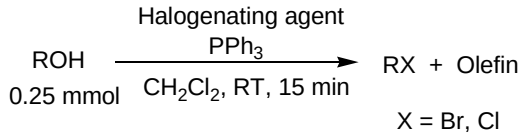
conversion of cyclooctanol and cyclododecanol (Table 3.4, entries 1-2) to the corresponding chlorides provided the ratio of alkyl chloride to alkene approximately 1:1. The substitution and elimination reactions often occurred competitively. Which reaction was favored would depend on several factors such as nucleophile (or base), substrate and solvent [19, 49**]**. Two competitive mechanistic pathways towards the formation of alkyl bromide and alkene are depicted in Scheme 3.1.

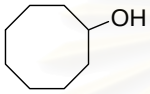
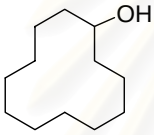
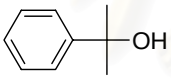


Scheme 3.1 Two mechanistic pathways towards the formation bromocyclooctane and cyclooctene

Both chloride and bromide ions generated could undergo concomitantly substitution and elimination reactions. The bromide ion is more nucleophilic than chloride. In the case of using brominating agent, alkyl bromides as major products and alkenes as minor ones were observed. This clearly supported the concept of the nucleophilicity in the substitution reaction. In the event that using poor nucleophile, competitive elimination reactions also took place.

Table 3.4 The comparison of the conversion of cyclic and tertiary alcohols to the corresponding chloride or bromide



Entry	ROH	Halogenating agent	% yield*		Σ
			Alkyl halide	Olefin	
1		Cl_3CCONH_2[a]	56	40	96
		Br_3CCO_2Et	72	26	98
		$Br_3CCOCBr_3$	84	15	99
2		Cl_3CCONH_2[a,b]	42	57	99
		Br_3CCO_2Et	74	27	101
		$Br_3CCOCBr_3$	80	19	99
3		Cl_3CCONH_2[c]	71	28	99
		Br_3CCO_2Et	58	48	106
		$Br_3CCOCBr_3$	67	35	102

* Determined by ^{1}H-NMR using toluene as internal standard

[a] The previous work addressed by Pluempanupat [49]

[b] Reaction time was 60 min

From the results in Table 3.4, it was observed that the conversion cyclic alcohols into alkyl bromides afforded olefins lass than in case of the formation alkyl chlorides (entries 1-2). While tertiary alcohol such as phenyl-2-propanol which can generate a stable carbocation provided an olefinic product in 28% yield. But olefin were found significantly increased when formation of alkyl bromide.

The conversion of a tertiary alcohol as 2-phenyl-2-propanol into its corresponding bromide was accomplished in moderate yield with equal amount of the elimination product (entry 9). This may arise from the influence of phenyl substituent at the tertiary carbon atom which may enhance the competition between S_N1 and E_1. While in the case of conversion into chloride using chlorinating agent, the elimination

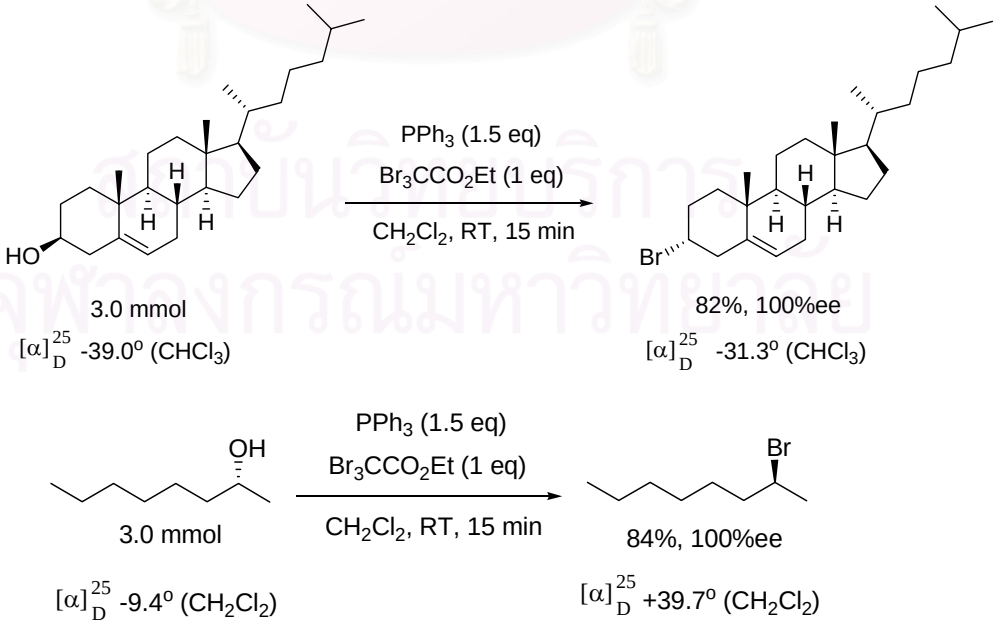
product was obtained less than in the case of bromide (Table 3.4, entry 3). In addition, bromide is both a good nucleophile and a good leaving group than chloride, thus once alcohol was converted into alkyl bromide, it may rapidly transform to olefin by E_1 mechanism.

The capability of this developed brominating agents, Br_3CCO_2Et and $Br_3CCOCBr_3$, can be applied for the conversion of structurally different alcohols to their bromides under mild conditions. These reagents would act rapidly and requires short reaction time consuming than other brominating agents which were reported such as PPh_3/ *N*-bromoacetamide [50], PPh_3/ $ZnBr_2$ [51] and PPh_3/ CBr_4 [15]. Moreover, this process could not generate by-product that is corrosive chemicals and invariably makes the conditions become acidic such as HBr gas in system of PPh_3/*N*-bromosuccinimide [52] and PPh_3/Br_2[9].

3.4 Stereoselectivity Study

Stereoselectivity study of this developed method was performed by using optically active substrates, (-)-cholesterol and (-)-(*R*)-2-octanol.

A stirred solution of (-)-cholesterol (1 eq) or (-)-(*R*)-2-octanol (1 eq) and PPh_3 (1.5 eq) in dry CH_2Cl_2 (4 mL) was successively added Br_3CCO_2Et (1 eq) at RT (30°C) under N_2 atmosphere. After 15 min, the reaction mixture was evaporated to dryness and was purified by silica gel column using hexane as an eluent to yield the (-)-cholesteryl bromide in 82% and (+)-(*S*)-2-octyl bromide in 84% yield.



Under the standard protocol, a chiral alcohol [(-)-cholesterol $[\alpha]_D^{25}$ -39.0°, *c* = 1.03, $CHCl_3$ and (-)-(*R*)-2-octanol $[\alpha]_D^{25}$ -9.4°, *c* = 1.03, CH_2Cl_2] could be successfully transformed into the enantiomerically pure cholesteryl bromide ($[\alpha]_D^{25}$ -31.3°, *c* = 1.11, $CHCl_3$) and (+)-(*S*)-2-octyl bromide ($[\alpha]_D^{25}$ +39.7°, *c* = 1.04, CH_2Cl_2) in good isolated yield with perfectly complete inversion of configuration.

To illustrate this, the conversion of (-)-(*R*)-2-octanol into (+)-(*S*)-2-octyl bromide was clearly supported by the optical rotation value change from -9.4° to +39.7°. While the sign of the optical rotation of cholesterol did not change. This phenomena was, however, in good agreement with the conversion of cholesterol ($[\alpha]_D^{25}$ -40.2°, *c* = 2.00, $CHCl_3$) to cholesteryl chloride ($[\alpha]_D^{25}$ -31.5°, *c* = 1.00, $CHCl_3$) reported in literature [53]. This result showed that the configuration of (-)-cholesterol was completely converted to that of cholesteryl bromide. These two instances manifestly confirmed that the conversion of alcohols to the corresponding alkyl bromides using the combination of PPh_3/Br_3CCO_2Et occurred *via* S_N2 mechanism.

3.5 Relative Reactivity of Brominating Agents on the Formation of Alkyl Bromide

The conversion of alcohols to the corresponding bromides with various reagents has widely been studied [9, 15 and 50-52]. The reactivity of these brominating agents has nevertheless not yet been reported in literatures.

The relative reactivity of brominating agents could be investigated using a competitive reaction between brominating and chlorinating agents towards alcohol. The reactivity of selected brominating agents was rationalized by the ratio of the yield of alkyl bromide and chloride obtained.

2-Phenethyl alcohol (1 eq) was added to a mixture of Cl_3CCN (0.75 eq) and a selected brominating agent (0.75 eq) in dry CH_2Cl_2 (0.5 mL). The mixture was treated with PPh_3 (1.5 eq) under the developed system. After 15 min, the crude mixture was evaporated to dryness and both alkyl halides were determined by ^{1}H-NMR with the addition of toluene as an internal standard. The example of the crude reaction mixture using Cl_3CCN and Br_3CCO_2Et is depicted in Fig 3.6.

The comparative study on a relative reactivity of various brominating agents towards the conversion of alcohols to alkyl bromides is described in Table 3.5.

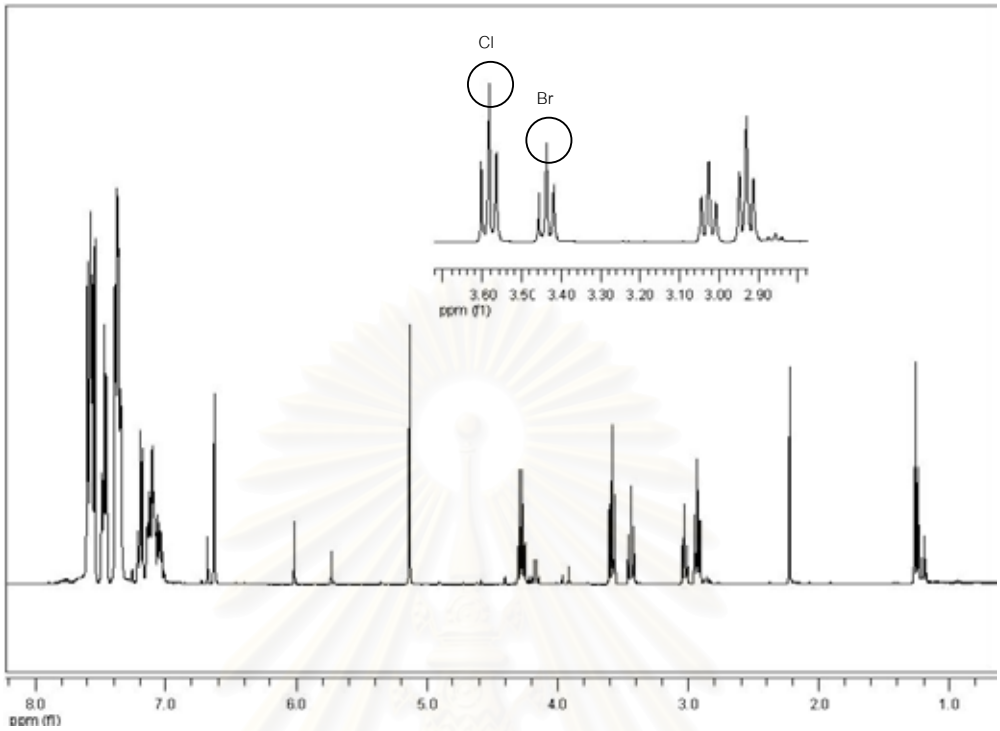
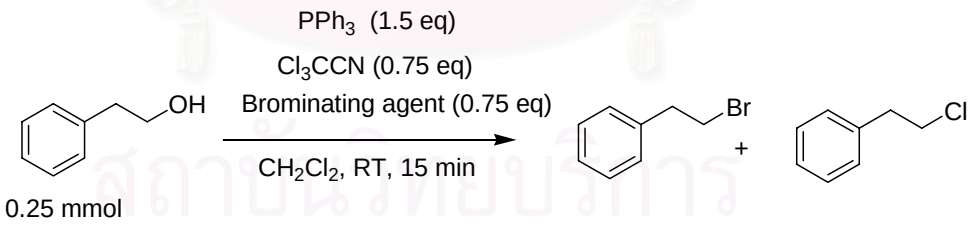


Figure 3.6 The ^{1}H-NMR spectrum of 2-phenylethyl chloride and 2-phenylethyl bromide in the crude mixture from the competitive reaction of Cl_3CCN and Br_3CCO_2Et

Table 3.5 Relative reactivity of selected brominating agents on the bromination of 2-phenethyl alcohol



0.25 mmol

Entry	Brominating agent	%yield*		RBr/RCl	Reactivity[a]
		RBr	RCl		
1	CBr_4	51	50	1.02	1.55
2	Br_3CCO_2Et	41	62	0.66	1
3	$Br_3CCOCBr_3$	80	18	4.44	6.73
4	$Br_3CCONEt_2$	47	52	0.90	1.36

* Determined by ^{1}H-NMR using toluene as an internal standard

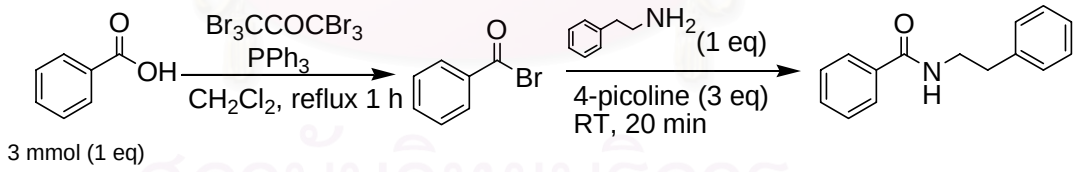
[a] Based on Br_3CCO_2Et

Considering the reactivity of brominating agents on the formation of alkyl bromides compared with Cl_3CCN as a reference, it could be concluded that the reagent bearing strong electron-withdrawing group as $Br_3CCOCBr_3$ revealed the highest reactivity**.** Other reagents: CBr_4, $Br_3CCONEt_2$ and Br_3CCO_2Et, displayed the same level of reactivity.

3.6 Conditions Optimization for Preparing Acid Bromides

The search for suitable conditions for the preparation of acid bromide is the main purpose of this section. $Br_3CCOCBr_3$ was selected as a brominating agent since it was discovered as a new reagent, thus there was no information on this regards. Nevertheless, several parameters are indeed necessary to explore prior to reach the optimal conditions. It should be noted at this point that the acid bromide formed is quite unstable, in this study it was thus designed to transform the acid bromide generated in the reaction into a more stable product such as amide. The selected amide in this study was 2-phenylethylamine to afford *N*-phenethylbenzamide. The effect of molar ratio of PPh_3:$Br_3CCOCBr_3$ on the formation of acid bromide is examined as presented in Table 3.6.

Table 3.6 Effect of the molar ratio of PPh_3:$Br_3CCOCBr_3$ on the preparation of acid bromide



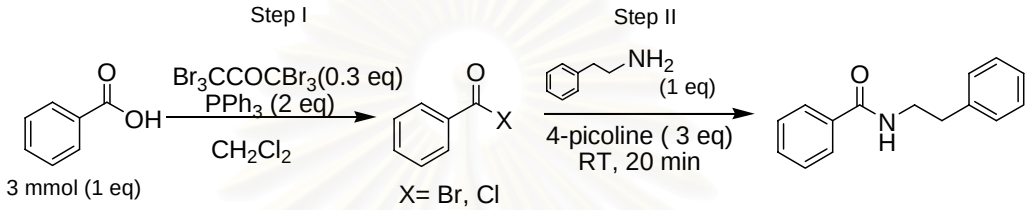
3 mmol (1 eq)

Entry	PPh_3 : $Br_3CCOCBr_3$	% Isolated yield
1	2.0 : 1.0	83
2	2.0 : 0.5	81
3	2.0 : 0.3	89
4	2.0 : 0.2	80

Table 3.6 shows the effect of the molar ratio of PPh_3:$Br_3CCOCBr_3$ for the generation of acid bromide. Interestingly, $Br_3CCOCBr_3$ could be employed as 0.3 equivalent based on starting benzoic acid. The suitable molar ratio of PPh_3:$Br_3CCOCBr_3$ found was 2.0:0.3 equivalent (entry 3).

Two parameters: temperature and reaction time for the production of acid bromides were next examined. The results are collected as shown in Table 3.7.

Table 3.7 Effects of temperature and reaction time on the synthesis of acid bromide



Entry	Reaction temperature	Reaction time of step I (min)	% Isolated yield
1	reflux (38-40^oC)	60	89
2	RT (28-30^oC)	60	88
3	RT (28-30^oC)	30	88
4	RT (28-30^oC)	15	88
5	RT (28-30^oC)	5	87
6	RT (28-30^oC)	15	6[a]
7	RT (28-30^oC)	15	40[b]

[a] PPh_3 : Cl_3CCONH_2 2 : 0.3 was used

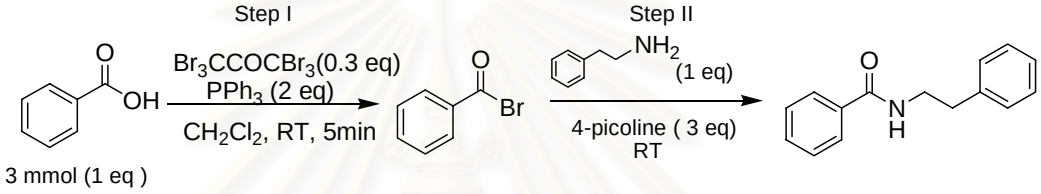
[b] PPh_3 : Cl_3CCONH_2 2 : 2 was used

Table 3.7 exhibits the effect of various temperatures and reaction time of step I while that of step II was fixed for 20 min at RT. The results clearly displayed that the reaction temperature was not the main influence on the reaction. Whether the reaction was performed at reflux or RT, the same extent of the product was achieved (entries 1-2). The reaction time in step I was then varied for 5, 15, 30 and 60 min, it was quite interesting that this transformation is very efficient since the time required is only 5 min (entries 3-5). Other independent experiments were carried out using Cl_3CCONH_2 replacing $Br_3CCOCBr_3$, the reactions could take place but poor yield of the desired product was obtained (entries 6-7). This implied that this new brominating agent is

effective to generate acid bromide which has already known to be more reactive than acid chlorides [5]. Moreover, the acid bromide formed could transform into the desired amide in only 20 min at RT.

The question that the reaction time of 20 min was really needed for the transformation of the acid bromide intermediate to the desired amide was raised. A series of experiment was designed to answer this question and the results are presented in Table 3.8.

Table 3.8 Effect of reaction time in step II on the conversion acid bromide to amide



Entry	Reaction temperature	Reaction time of step II (min)	% Isolated yield
1	RT (28-30°C)	20	87
2	RT (28-30°C)	10	89
3	RT (28-30 °C)	5	88
4	RT (28-30°C)	5	72[a]

[a] 4-picoline was not used

Table 3.8 manifestly shows that under the standard conditions performed, the real reaction required for step II was only 5 min at RT (entries 1-3). Therefore, the standard condition for the synthesis of amide acid *via* acid bromide was totally 10 min at RT. This new procedure is notably quite efficient and effective. In addition, the experiment performed to check the importance of 4-picoline in the reaction was carried out and it was found that without 4-picoline, the yield of the desired product was significantly decreased (entry 4). This result implied that the method required base as 4-picoline for activating the reaction process. In addition, the advantages of the present method and reagent reported over other reagents such as TsCl [32], $SOCl_2$ [7, 54], and $(COCl)_2$ [24, 43] are 1) a few amount of brominating agent was required.

2) the reaction could perform smoothly and rapidly under mild conditions at RT and 3) this reaction did not generate toxic gases as byproduct.

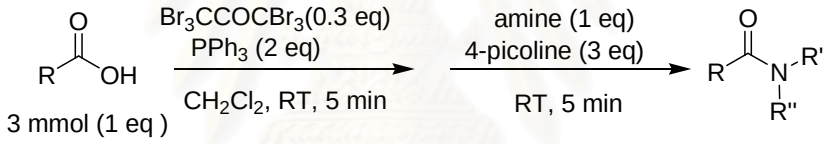
3.7 Application of the Developed Procedures for the Synthesis of Carboxylic Acid Derivatives

Stemmed from the successfulness of using this developed methodology to synthesize the desired amides, this general procedure was further extended to investigate the one-pot conversion of carboxylic acid into their derivatives including amides, esters, acid anhydrides and thioesters.

3.7.1 Synthesis of Amides

Utilizing the optimal conditions as previously described, various carboxylic acids and amines were chosen. The results of the synthesis of amides using this methodology are collected as tabulated in Table 3.9.

Table 3.9 The synthesis of amides using $PPh_3/Br_3CCOCBr_3$ system



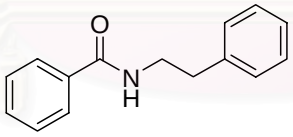
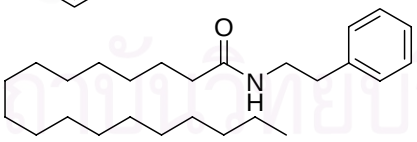
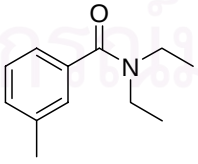
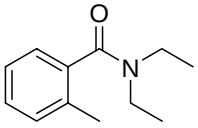
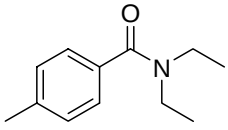
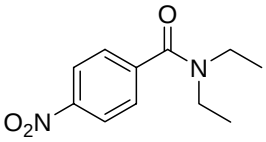
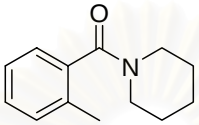
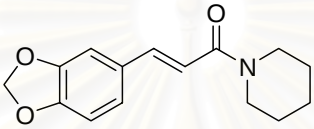
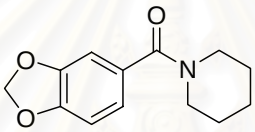
Entry	Target amides	Isolated yield(%)
1		88
2		89[a]
3		73
4		42
5		78

Table 3.9 (continued)

Entry	Target amides	Isolated yield(%)
6		67
7		78
8		95
9		86

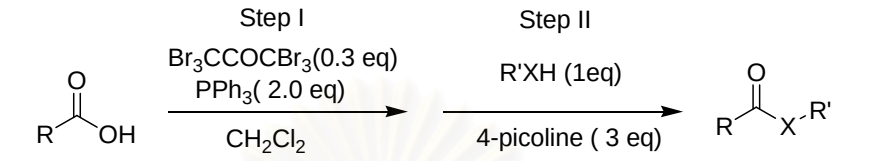
[a] 30 min at reflux in step I

Both aliphatic and aromatic carboxylic acids could be transformed into their amides in quantitative yield using 2-phenylethanamine (entries 1-2). In the case of secondary amine such as diethylamine being employed, the decreasing of the amount of products was observed, possibly because steric hindrance of nucleophile (entries 3-6). Interestingly, when *o*-toluoic acid was used as a substrate, the amide product was obtained in poor yield (entry 4). While employing piperidine, a less sterically hindered nucleophile, the reaction proceeded to furnish the desired amide in 78% yield (entry 7). On the other hand, when *p*-nitrobenzoic acid, an aromatic carboxylic acid containing electron withdrawing group was used, the desired amide was slightly decreased (entry 6) comparing with *o*-toluoic acid bearing electron donating group (entry 5). The overall results showed slight effects of the substituents on aromatic carboxylic acid either electron donating or withdrawing groups. This implied that the steric effect was more important for this reaction. In addition, when piperidine was employed, the desired amides were afforded in high yield (entries 7-9).

3.7.2 Synthesis of Esters and Thioesters

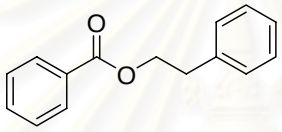
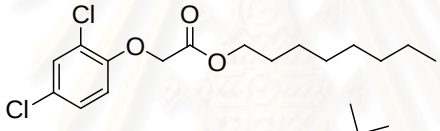
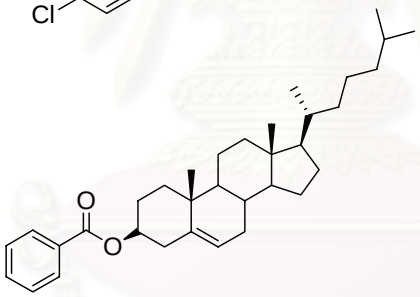
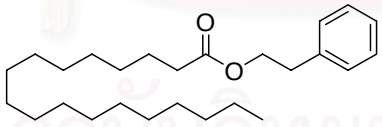
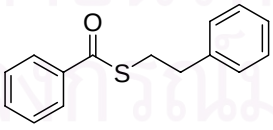
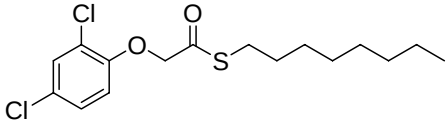
Further applications of this methodology were extended for the synthesis of carboxylic esters and thioesters. The results are presented in Table 3.10.

Table 3.10 Synthesis of esters and thioesters using $PPh_3/Br_3CCOCBr_3$ system



3 mmol (1 eq)

X= O, S

Entry	Products	Isolated yield(%)
1		86[a]
2		90[a]
3		47[a] 70[b]
4		trace[a] 91[c]
5		95[a]
6		92[a]

[a] 5 min at RT in step I and 5 min at RT in step II

[b] 5 min at RT in step I and 30 min at reflux in step II

[c] 30 min at reflux in step I and 5 min at RT in step II

Carboxylic esters and thioesters could be prepared under similar conditions used for that of amides, but changing nucleophile to alcohols and thiols, respectively. Table 3.10 reveals the effect of substrate and nucleophile (alcohol and thiol). It was observed that in the case of simple carboxylic acids under standard conditions, the corresponding esters and thioesters could accomplishly attained (entries 1-2 and 5-6). A steric nucleophile such as cholesterol (entry 3) gave low yield at RT. With the aim to lift up the yield of the target molecule, increasing temperature in step II successfully increased % yield of the desired product. On the other hand, aliphatic carboxylic acid with long chain hydrocarbons such as stearic acid also needed to prolong the reaction time and temperature in step I to achieve the high yield of the desired product (entry 4). The synthesis of esters and thioesters using the same starting material revealed that the yield of thioesters was higher than that of esters. This was undoubtful because of the better nucleophilic activity of thiol [23, 49].

Although, the yields of the desired products were not significant differences between the developed method and previous reported methods: using Ph_3PBr_2 [26], $AgBF_4$ [55] and PPh_3/Cl_3CCONH_2 [56]. The advantages of the present method are quite easy procedure, short reaction time and in many cases the reaction can be performed at RT.

3.7.3 Synthesis of Acid Anhydrides

Carboxylic acid anhydride is another important carboxylic acid derivative. Generally it can be prepared by reacting a carboxylic acid with an acyl halide [5, 7, 28]. Under standard conditions, using this developed methodology, symmetrical acid anhydride could fruitfully be prepared. In addition some anhydrides are prepared by dehydrating two carboxylic acid molecules [57]. The results are tabulated in Table 3.11.

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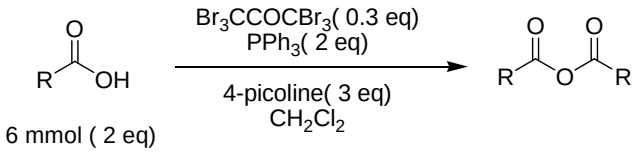
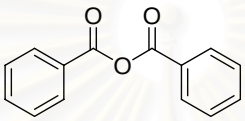
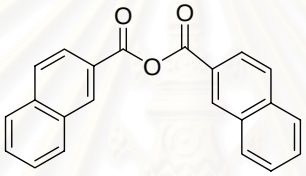
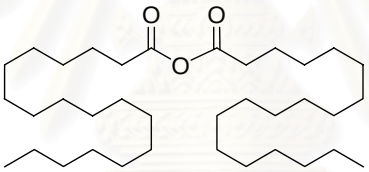
Table 3.11 Synthesis of symmetrical acid anhydrides from carboxylic acids using $PPh_3/Br_3CCOCBr_3$ system



Entry	Acid anhydrides	Isolated yield(%)
1		89[a]
2		81[a]
3		78[b]

[a] 10 min at RT

[b] 30 min at reflux

It could be clearly seen from the above results that this general protocol could be applied for the synthesis of symmetrical acid anhydrides from carboxylic acid. The stoichiometry of the reaction needs however to be considered. Half of carboxylic acid was converted to acid bromide, while the rest carboxylic acids would act as a nucleophile attacking the acid bromide previously formed. Under the standard conditions: only 10 min at RT was still needed with the results of high yield of the target products for aromatic carboxylic acid such as benzoic acid and 2-naphthoic acid. On the other hand, poor nucleophile such as stearic acid, aliphatic carboxylic acid with long chain hydrocarbon, the reflux temperature was necessary. However, the synthesis of stearic anhydride under reflux condition gave a high yield.

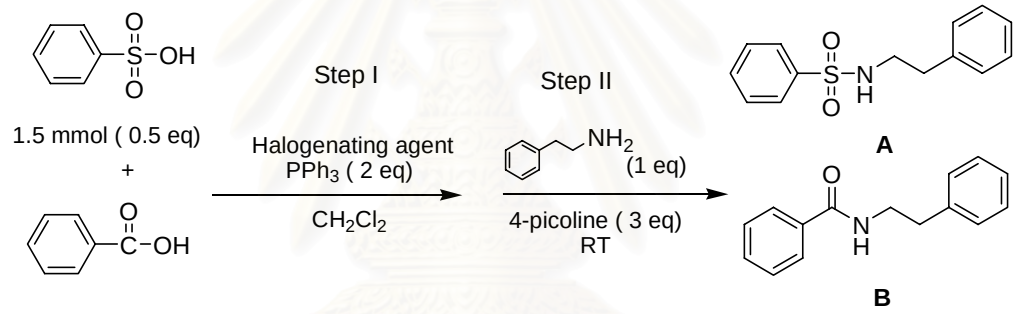
The present method has an advantage over the preparation of aromatic carboxylic acid anhydride by thermal dehydration. That was because this reaction

could be performed at RT. Moreover, this developed reagent, $Br_3CCOCBr_3$ required short reaction time consuming than other brominating agents which was afored reported such as PPh_3/Br_3CCO_2Et [39]. In addition this method did not generate corrosive by-product and toxic chemicals such as HCl and SO_2 gas in the reaction using $SOCl_2$ [38].

3.8 Chemoselectivity Study

The selection of good and reliable method or reagent is crucial in organic synthesis. The chemoselectivity of four selected halogenating agents: $Br_3CCOCBr_3$, Cl_3CCN, Cl_3CCONH_2 and $Cl_3CCOCCl_3$ towards aromatic carboxylic acid using benzoic acid as a model and aromatic sulfonic acid using benzenesulfonic acid as a model was studied. The results are demonstrated in Table 3.12.

Table 3.12 The chemoselectivity study of halogenating agents



Entry	Halogenating agent	Molar ratio of PPh_3 : Halogenating agent	% yield	
			A	B
1	$Br_3CCOCBr_3$	2.0 : 0.3[a]	trace	90
2	Cl_3CCN	2.0 : 2.0[b]	11	89
3	Cl_3CCONH_2	2.0 : 2.0[b]	trace	92
4	$Cl_3CCOCCl_3$	2.0 : 2.0[b]	trace	36
5	$Cl_3CCOCCl_3$	2.0 : 0.3[a]	trace	86

[a] 5 min at RT in step I and 5 min at RT in step II

[b] 30 min at reflux in step I and 20 min at RT in step II

The competitive reactions were performed between benzoic acid and benzenesulfonic acid. The results showed high selectivity in the case of using $Br_3CCOCBr_3$, Cl_3CCONH_2 and Cl_3CCOCl_3 (entries 1, 3-4) to yield only sulfonamide (product B). Both Cl_3CCONH_2 and Cl_3CCOCl_3 however displayed lower reactivity than $Br_3CCOCBr_3$. The reactivity comparison of chlorinating agents was studied and reported by Pluempanupat *et al*. [58]. Both Cl_3CCONH_2 and Cl_3CCOCl_3 exhibited lower reactivity than Cl_3CCN. In this research, the reactivity of $Br_3CCOCBr_3$ was studied and revealed the highest reactivity as presented in Table 3.5. Recent study has shown that $Br_3CCOCBr_3$ is more reactive than Cl_3CCN [58]. In addition, the use of Cl_3CCN with the substrates containing both carboxylic acid and sulfonic acid was not chemoselective since a mixture of products A and B was detected (entry 2).

3.9 Reactivity of Brominating Agents on the Formation of Acid Bromide

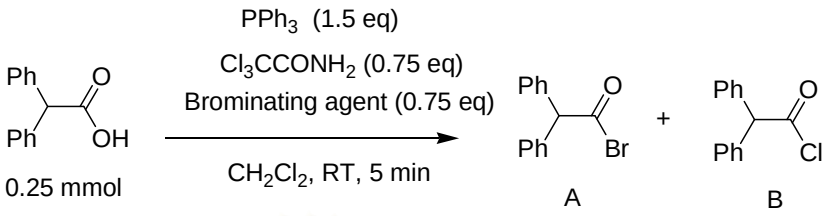
The reactivity of brominating agents for the conversion of alcohols into the bromides was previously studied. In this part the reactivity of various brominating agents for transforming carboxylic acids to acid bromides was studied. The same trend of reactivity of brominating agents for the formation of alkyl bromides was observed. The reactivity of brominating agents for conversion carboxylic acids into acid bromides in addition has nevertheless not yet been reported in literatures.

The reactivity of brominating agents was investigated using a competitive reaction between brominating and chlorinating agents towards carboxylic acid. The reactivity of selected brominating agents was rationalized by the ratio of the yield ratio of acid bromide and chloride obtained.

2,2-Diphenylacetic acid (1 eq) was added to a mixture of Cl_3CCONH_2 (0.75 eq) and selected brominating agents (0.75 eq) in an NMR tube. The mixture was treated with the solution of PPh_3 (1.5 eq) in $CDCl_3$. After 15 min, the crude mixture was determined both acid bromide and chloride by ^{1}H-NMR in the crude mixture with the addition of toluene as an internal standard.

The study of a relative reactivity of various brominating agents towards the formation of acid bromide is described in Table 3.13.

Table 3.13 Relative reactivity of selected brominating agents on the bromination of 2,2-diphenylacetic acid



Entry	Brominating agent	% yield*		A/B	Reactivity[a]
		A	B		
1	none	-	44	-	-
2	CBr_4	54	52	1.04	1
3	Br_3CCO_2Et	84	14	6.00	5.77
4	$Br_3CCOCBr_3$	95	6	15.83	15.22

* Determined by ^{1}H-NMR using toluene as an internal standard

[a] Based on CBr_4

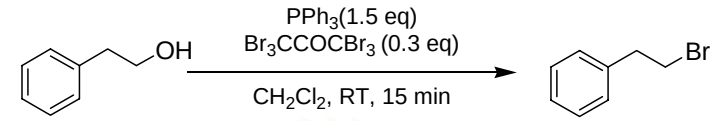
Considering the reactivity of brominating agents on the formation of acid bromides compared with Cl_3CCONH_2 as a reference, $Br_3CCOCBr_3$ displayed the highest reactivity among all brominating agents. The reactivity of brominating agents on the preparation of acid bromides could be arranged in order from the highest reactivity to the lowest as: $Br_3CCOCBr_3$ > Br_3CCO_2Et > CBr_4. It should also be mentioned that the reactivity of brominating agents on the bromination of alcohol could be arranged not in the same trend as those observed for acid bromide as $Br_3CCOCBr_3$ > CBr_4. > Br_3CCO_2Et. This result indicated the reactivity of brominating agents markedly depended on type of substantes.

3.10 Stability of $Br_3CCOCBr_3$

The information about $Br_3CCOCBr_3$ reported in literature involved only its preparation and m.p. [44]. No other information is available. Since $Br_3CCOCBr_3$ was disclosed in this study as a new brominating agent, the stability of this reagent should therefore be studied. Two parameters were selected to test for the efficacy of $Br_3CCOCBr_3$ including the stability of this reagent under UV radiation and the temperature of 80 °C during its storage. The sample which kept under the environments studied was used as a brominating agent to convert 1-phenylethanol to

1-phenylethyl bromide compared with the standard one kept in a dessicator. The results are accumulated as shown in Tables 3.14-3.15.

Table 3.14 Stability of $Br_3CCOCBr_3$ at 80°C



0.25 mmol

Entry	Time (h)	yield*
1	1	96
2	2	99
3	3	quant
4	4	quant
5	5	96
6	6	99
7	24	quant
8	48	quant

* Determined by ^{1}H-NMR using toluene as an internal standard

Table 3.15 Stability of $Br_3CCOCBr_3$ under UV radiation

Entry	Time (h)	yield*
1	1	96
2	3	quant
3	5	95
4	7	97

* Determined by ^{1}H-NMR using toluene as an internal standard

Tables 3.14-3.15 show the stability of $Br_3CCOCBr_3$ which was kept at 80°C for different durations. 1-Phenethyl bromide was still obtained in an excellent yield,

even though $Br_3CCOCBr_3$ was kept under that condition for a long time. In the case of UV radiation, the same results were obtained.

This study disclosed the efficient procedure for the preparation of acid bromides using $PPh_3/Br_3CCOCBr_3$ under mild conditions. The method can be fruitfully applied for the synthesis of various carboxylic acid derivatives such as amides, esters, acid anhydrides and thioesters in one-step. Moreover, the chemical property of $Br_3CCOCBr_3$ such as reactivity, stability and chemoselectivity was indeed thoroughly studied.

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CHAPTER IV

CONCLUSION

The purpose of this research is to investigate and to develop the new brominating agent to utilize in combination with PPh_3 and to explore the optimum conditions for the formation of alkyl bromides and acid bromides under mild conditions. The application of the developed methodology for the synthesis of carboxylic acid derivatives such as amides, esters, acid anhydrides and thioesters was also carefully explored.

The conversion of alcohols into their alkyl bromides utilizing a combination of PPh_3/Br_3CCO_2Et and $PPh_3/Br_3CCOCBr_3$ could be smoothly converted to the corresponding alkyl bromides in high yield under mild conditions at RT within short reaction time. Primary and secondary alcohols appeared to be the most reactive substrates yielding the corresponding bromides *via* S_N2 displacement. Although olefinic products were obtained from the reaction of secondary cyclic alcohols, this method produced olefins less than in the case of using PPh_3/Cl_3CCONH_2. The steric hindrance of tertiary alcohols strongly affected to afford low yield of desired bromides and consequently to a large production of olefin.

$PPh_3/Br_3CCOCBr_3$ could also use to prepare acid bromides which then possible to transform to carboxylic acid derivatives. This developed protocol was indeed disclosed to be an efficient system to synthesize amides under mild and rapid conditions. In addition this study demonstrated slight effects of the substituents on aromatic carboxylic acid either donating and electron-withdrawing groups and implied that steric effect revealed more important for this reaction. Esters and thioesters could be prepared under similar conditions for those of amides. In the case of steric nucleophile, step II was required longer time and high temperature. On the other hand, the reaction with long chain carboxylic acid needed to prolong the reaction time and high temperature in step I. In addition, the synthesis of esters and thioesters using the same starting material revealed that the yield of thioesters was higher than that of esters.

This general protocol could also be applied for the synthesis of symmetrical acid anhydrides directly from carboxylic acid. The aromatic carboxylic acid could transform into the desired acid anhydrides in only 10 min at RT. However, the long chain carboxylic acid anhydride needed to synthesize under reflux condition giving quantitative yield.

The chemical property of brominating agents such as the reactivity, chemoselectivity and stability were studied. The reactivity for the conversion of alcohols to corresponding alkyl bromides showed the same reactivity as the formation of acid bromides. $Br_3CCOCBr_3$ displayed the highest reactivity over all brominating agents. Moreover, $Br_3CCOCBr_3$ demonstrated high chemoselectivity in the case of carboxamide and sulfonamide formation that only carboxamide was obtained. For stability study, it was found that $Br_3CCOCBr_3$ which was kept at 80°C for a long time was still behave as a good brominating agent. In case of UV radiation, the same results were obtained.

Proposal for the Further Work

This research concerns with the development of brominating agents and methodology for the synthesis of alkyl and acyl bromides. This outcome opened many possibilities to deal with further exploration. 1) This methodology should be applied with Friedel-Crafts reaction and developed the new combination reaction for one pot synthesis. 2) The developed method should be used to prepare alkyl and acyl bromides in coupling reactions such as Suzuki coupling and 3) the utilization of $Br_3CCOCBr_3$ for the synthesis of acid bromides from aromatic aldehydes should be verified.

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REFFERENCES

1. (a) Fillon, H.; Gosmini, C.; Pe´richon, J. A Convenient Method for the Preparation of Aromatic Ketones from Acyl Chlorides and Arylzinc Bromides using a Cobalt Catalysis. *Tetrahedron*, **2003**, *59*, 8199–8202; (b) Bertrand, M. B.; Wolfe, J. P. Stereoselective Synthesis of *N*-Protected Pyrrolidines via Pd-Catalyzed Reactions of γ-(*N*-Acylamino) Alkenes and γ-(*N*-Boc-amino) Alkenes with Aryl bromides. *Tetrahedron*, **2005**, *61*, 6447–6459; (c) Gonza´lez-Bobes, F.; Fu, G. C. Amino Alcohols as Ligands for Nickel Catalyzed Suzuki Reactions of Unactivated Alkyl Halides, Including Secondary Alkyl Chlorides, with Arylboronic Acids *J. Am. Chem. Soc*. **2006**, *128*, 5360-5361.
2. (a) Bourguignon, J.; De´saubry, L.; Raboisson, P.; Wermuth, C.; Lugnier, C. 9-Benzyladenines: Potent and Selective cAMP Phosphodiesterase Inhibitors. *J. Med. Chem*. **1997**, *40*, 1768-1770; (b) Oiry, J.; Puy, J.; Mialocq, P.; Clayette, P.; Fretier, P.; Jaccard, P.; Dereuddre-Bosquet, N.; Dormont, D.; Imbach, H. Synthesis and in Vitro Anti-HIV Activity in Human Monocyte-Derived Macrophages of 2-Oxothiazolidine-4(*R*)-carboxylic Acid Derivatives. *J. Med. Chem*. **1999**, *40*, 4733-4740; (c) Gaspari, P.; Banerjee, T.; Malachowski, W. P.; Muller, A. J.; Prendergast, G. C.; DuHadaway, J.; Bennett, S.; Donovan, A. M. Structure-Activity Study of Brassinin Derivatives as Indoleamine 2,3-Dioxygenase Inhibitors. *J. Med. Chem.* **2006**, *49*, 684-692 (d) Hayakawa, M.; Kaizawa, H.; Moritomo, H.; Koizumi, T.; Ohishi, T.; Yamano, M.; Okada, M.; Ohta, M.; Tsukamoto, S.; Raynaud ,F. I.; Workman, P.; Waterfieldc M. D.; Parkerd, P. Synthesis and Biological Evaluation of Pyrido[3´,2´: 4,5]furo3,2-*d*]pyrimidine Derivatives as Novel PI3 Kinase p110α Inhibitors. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 2438–2442; (e) Shiradkar, M. R.; Murahari, K. K.; Gangadasu, H. R.; Suresh, T.; Kalyan, C. A.; Panchal, D.; Kaur, R. Burange, P.; Ghogare, J.; Mokalec, V.; Raut, M. Synthesis of New S-derivatives of

Clubbed Triazolyl Thiazole as Anti-Mycobacterium Tuberculosis Agents. *Bioorg. Med. Chem*. **2007**, *15*, 3997–4008.

3. Devos, A.; Reanine, J.; Frisque-Hesbain, A.; Colens, A.; Ghosez, L. Synthesis of Acyl Halides under very Mild Condition. *J. Chem. Soc., Chem. Commun*. **1979**, 1180-1181.
4. Bains, S.; Green, J.; Tan, L. C.; Pagni, R. M.; Kabalka, G. W. The Conversion of Carboxylic Acids into Acid Bromides on BBr_3-Modified Alumina. *Tetrahedron Lett.* **1992**, *33*, 7475-7476.
5. Jang, D. H.; Joo, Y. Y.; Lee, E. H.; Chaysripongkul, S. A Mild and Efficient Reaction for Conversion of Carboxylic Acids into Acid Bromides with Ethyl tribromoacetate/Triphenylphosphine under Acid-free Conditions. *Tetrahedron Lett*. **2006**, *47*, 5693-5696.
6. Mcmurry, *J. Organic Chemistry*. California: Brooks/Cole Publishing Company, **1996**.
7. Vogel, A. I. *A Textbook of Practical Organic Chemistry*. London: Longman Group, **1989**.
8. Burn, A. J.; Cadogan J. I. G. The Reactivity of Organophosphorus Compounds. Part XVIIX a Novel Oxidation of Some Tervalent Compounds: Reduction of Carbon Tetrachloride to Chloroform by Trialkyl Phosphites. *J.Chem.Soc*. **1963**, 5788-5796.
9. Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. Studies in Organophosphorus Chemistry. I. Conversion of Alcohols and Phenols to Halides by Tertiary Phosphine Dihalides. *J.Chem.Soc*. **1964**, *86*, 964-965.
10. (a) Lee, J. B.; Nolan, T. J. Sugar Esters III New Reagent for Deoxyhalo Sugar Preparation. *Can. J. Chem*. **1966**, *44*, 86-87. (b) Lee, J. B.; Nolan, T. J. Sugar Esters IV The Preparation of Chloroesters under Essentially Neutral Conditions. *Tetrahedron* **1967**, *23*, 359-363.
11. Hooz, J.; Gilani, S. S. A Rapid, Mild Procedure for the Preparation Alkyl Chlorides and Bromides. *Can. J. Chem.* **1968**, *46*, 86-87.
12. Steven, L. R.; Dan, P. L. Solid Phase Phosphorus Reagents Conversion of Alcohols to Alkyl Chlorides. *J. Org. Chem.* **1975**, *40*, 1669-1670.
13. Magid, R. M.; Fruchey, O. S.; Johnson, W. L. Hexachloroacetone/ Triphenylphosphine : a Reagent for the Regio- and Stereoselective conversion of Allylic Alcohols into Chlorides. *Tetrahedron Lett.* **1977**, *18*, 2999-3002.

14. Sugimoto, O.; Mori, M.; Tanji, K. A Facile Halogenation of Same Hydroxyheterocycles using Triphenylphosphine and *N*-halosuccinimide. *Tetrahedron Lett.* **1999**, *40*, 7477-7478.

15. Pollastri, M. P.; Sagal, J. F.; Chang, G. The Conversion of Alcohols to Halides using a Filterable Phosphine Source. *Tetrahedron Lett.* **2001**, *42*, 2459-2460.

16. Iranpoor, N.; Firouzabadi, H.; Aghapour, G.; Vaez Zadeh, A. R. Triphenylphosphine/2,3-Dichloro-5,6-dicyanobenzoquinone as a New, Selective and Neutral System for the Facile Conversion of Alcohols, Thiols and Selenols to Alkyl Halides in the Presence of Halide ions. *Tetrahedron,* **2002**,*58*, 8689-8693.

17. Desmaris, L.; Percina N.; Cottier, L.; Sinou, D. Conversion of Alcohols to Bromides using a Fluorous Phosphine. *Tetrahedron Lett.* **2003**, *44*, 7589-7591.

18. Iranpoor, N.; Firouzabadi, H.; Jamalian, A.; Kazemi, F. Silicaphosphine (Silphos): a Filterable Reagent for the Conversion of Alcohols and Thiols to Alkyl Bromides and Iodides. *Tetrahedron* **2003**, *61*, 5699-5704.

19. Wade, L.G. *Organic Chemistry*. New Jersey: Prentice-Hall International, **1995**, 1014-1016.

20. Morrison, R.T. and Boyd, R.N. *Organic Chemistry*. New Jersey: Prentice-Hall International, **1992**, 760-762.

21. Meakins, G.D. *Oxford Chemistry Primers. Functional Groups: Characteristics and Interconversion.* New York: Oxford University Press, **1996**, 78-79.

22. Norman, R.O.C. *Principles of Organic Synthesis*. London: Chapman and Hall, 1**978**.

23. March, J. *Advanced Organic Chemistry*. New York: John Wiley & Sons, **1992**.

24. Adams, R.; Ulich, L. H. The use of Oxalyl Chloride and Bromide for Producing Acid Chlorides, Acid Bromides or Acid Anhydrides. III. *J. Am Chem. Soc.* **1920**, *42*, 599-611.

25. Burton, T. M.; Degering ED. F. The Preparation of Acetyl Bromide. *J. Am Chem. Soc*. **1940**, *62*, 227.

26. Aizpurua, J. M.; Palomo, C. Reagents and Synthetic Methods 14. A Facile Synthesis of Carboxylic Acid Bromides and Esters under Neutral Conditions via Reaction of the Trimethylsilyl Esters with Triphenylphosphine Dibromide. *Synthesis*. **1982**, 684-687.

27. DalPozzo, A.; Bergonzi, R.; Ni, M. *N*-Protected Amino Acid Bromides: Efficient Reagents for the Incorporation into Peptides of Extremely Hindered α,α-Dialkyl- and α-Fluoroalkyl-Amino Acids. *Tetrahedron Lett*. **2001**, *42*, 3925-3927.

28. Kang, D. H.; Joo, T. Y.; Chavasiric, W.; Jang, D. O. Radical Mediated-Direct Conversion of Aldehydes into Acid Bromides. *Tetrahedron Lett*. **200**7, *48*, 285-287.

29. Venkataraman, K. and Wagle, D.R. Cyanuric Chloride: A useful Reagent for Converting Carboxylic Acids into Chlorides, Esters, Amides and Peptides. *Tetrahedron Lett.*, **1979**, *32*, 3037-3040.

30. Harrison, C. R.; Hodge, P.; Hunt, B. J.; Khoshdel, E.; Richarson, G. Preparation of Alkyl Chlorides, Acid Chlorides, and Amides using Polymer-Supported Phosphines and Carbontetrachloride: Mechanism of These Reaction. *J. Org. Chem*. **1983**, *48*, 3721-3728.

31. Jang, D.O.; Park, D.J. and Kim, J. A Mild and Efficient Procedure for the Preparation of Acid Chlorides from Carboxylic Acids. *Tetrahedron Lett.* **1999**, *40*, 5323-5326.

32. Khalafi-Nezhad, A.; Parhami, A.; Soltani Rad, M. N.; Zarea, A. Efficient Method for the Direct Preparation of Amides from Carboxylic Acids using Tosyl Chloride under Solvent-Free Conditions. *Tetrahedron Lett.* **2005**, *46*, 6879–6882.

33. Kangani, C. O.; Kelley, D. E. One Pot Direct Synthesis of Amides or Oxazolines from Carboxylic Acids using Deoxo-Fluor Reagent. *Tetrahedron Lett*. **2005**, *46*, 8917-8920.

34. Heuser, S.; Keenanb, M.; Weichert, A. G. New Facile and Mild Synthesis of 2-Substituted Oxazolopyridines. *Tetrahedron Lett*. **2005**, *46*, 9001-9004.

35. Liu, H.; Chan, W. H.; Lee, S. P. Convenient Procedures for Esterification of Carboxylic Acids. *Tetrahedron Lett.* **1978**, *19*, 4461-4464.

36. Sucheta, K.; Reddy, G.S.R.; Ravi, D.; Rama Rao.; N. A Novel, General Route to the Synthesis of a Carboxylic Acid Esters and Thiolesters. *Tetrahedron Lett.* **1994**, *35*, 4415-4416.

37. Kawabata, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. Highly Efficient Eesterification of Carboxylic Acids with Alcohols by Montmorillonite-

Enwrapped Titanium as a Heterogeneous Acid Catalyst. *Tetrahedron Let.* **2003**, *44*, 9205–9208.

38. Fife, W. K.; Zhang, Z. Phase Managed Organic Synthesis 3. Symmetrical Anhydrides from Carboxylic Acids via Polymer Assisted Reaction. *Tetrahedron Let.* **1986**, *27*, 4937-4940.
39. Kim, J.; Jang, D. O. A. Convenient Method for Synthesis of Symmetrical Acid Anhydrides from Carboxylic Acids With Trichloroacetonitrile and Triphenylphosphine. *Synth. Commun*. **2001**, *31*, 395-399.
40. Weber, A. L. Prebiotic Amino Acid Thioester Synthesis: Thiol-Dependent Amino Acid Synthesis from Formose Substrates (Formaldehyde and Glycolaldehyde) and Ammonia. *Orig. Life Evol. Biosphere*, **1998**, *28*, 259–270.
41. Weber, A. L. Aqueous Synthsis of Peptide Thioesters from Amino Acids and a Thiol using 1,1-Carbonyldiimidazole. *Orig. Life Evol. Biosphere*, **2005**, *35*, 421-427.
42. Tietze, L. F.; Eicher, T. H. *Reactions and Syntheses in the Organic Chemistry Laboratory*. California: University Science Book, **1988**, 110.
43. Gilbert, E. E. Perhaloketones. XVII. Hexabromoacetone and The Bromochloro perhaloacetones. *Tetrahedron*, **1969**, *25*, 1801-1806.
44. (a) Krief, A.; Laval, A. M. Coupling of Organic Halides with Carbonyl Compounds Promoted by SmI_2, The Kagan Reagent. *Chem. Rev.* **1999,** *99,* 745-777. (b) Fillon, H.; Gosmini, C.; Pe´richon, J. A Convenient Method for the Preparation of Aromatic Ketones from Acyl Chlorides and Arylzinc bromides Using a Cobalt Catalysis. *Tetrahedron* **2003**, *59*, 8199–8202. (c) Bertrand, M. B.; Wolfe J. P. Stereoselective Synthesis of *N*-protected Pyrrolidines via Pd-catalyzed Reactions of γ-(*N*-acylamino) Alkenes and γ -(*N*-Boc-amino) Alkenes with Aryl Bromides. *Tetrahedron* **2005**, *61*, 6447–6459. (d) Gonza´lez-Bobes, F.; Fu, G. F. Amino Alcohols as Ligands for Nickel-Catalyzed Suzuki Reactions of Unactivated Alkyl Halides, Including Secondary Alkyl Chlorides, with Arylboronic Acids. *J. Am. Chem. Soc.* **2006**, *128*, 5360-5361. (e) Sonntag, N. O. V. The Reactions of Aliphatic Acid Chlorides. *Chem. Rev.* **1953**, *52*, 237-416.
45. Sato, A.; Sugano, M.; Horikoshi, H.; Yoshioka, S.; Nagaki, H. Pentabromopropenyl Bromoacetates as Aldose Reductase Inhibitors. J.P. 02,145,541, 1990; through *Chem. Abstr*. **1990**, 113, 178250.

46. Bollyky, L. J. Chemiluminescence from Tetracyanoethylene and Perhalocarbonyl Compounds, a Polycyclic Aromatic Hydrocarbon, and a Peroxide. U.S. 3,442,816, 1969; through *Chem. Abstr*. **1969**, 71, 16976.

47. Kocienski, P. J.; Cernigliaro, G.; Feldstein, G. A Síntesis of (±)-Methyl *n*-Tetradeca-trans-2,4,5-trienoate, an Allenic Ester Produced by the Male Dried Bean Beetle *Acanthoscelides obtectus*. *J. Org. Chem.* **1977**, *42*, 353-355.

48. (a) Pluempanupat, W. Synthetic Method for Carbon-Carbon and Carbon-Heteroatom Bonds using Phosporus Reagents, Doctor of Philosophy's Dissertation, Department of Chemistry, Chulalongkorn University, **2005**. (b) Pluempanupat, W.; Chavasiri, W. An efficient Method for Chlorination of Alcohols using PPh_3/Cl_3CCONH_2. *Tetrahedron Lett.* **2006**, *47*, 6821-6823.

49. Solomons, G.; Fryhly, C. *Organic Chemistry*, New York: John Wiley & Sons, New York, **2000**, 230-280.

50. Bose, A. K.; Lal, B. A Facile Replacement of Hydroxyl by Halogen with Inversion. *Tetrahedron Lett.* **1973**, *40*, 3937–3940.

51. Ho, P.; Davies, N. Reaction of Alcohols with Zinc Halide, Diethyl Azodicarboxylate, and Triphenylphosphine. A Effective Method for the Preparation of Halides. *J. Org. Chem*. **1984**, *49*, 3027-329.

52. Trippet, S. A New Synthesis of Acetylenes. Part II The Reaction of Triphenylphosphine with ∝-Halogeno-carbonyl Compounds. *J. Chem. Soc*. *1962*, 2337–2340.

53. Drabowicz, J.; Luczak. J.; Mikolajczyk, M. Triphenylphosphine/ Dichloroselenurane: A New Reagent for a Selective Conversion of Alcohols into Alkyl Chlorides. *J. Org. Chem.* **1998**, *63*, 9565-9568.

54. Li, D.; Zhu, S.; Pelton, R., H. Preparation and Characterization of Graft Copolymers of Polyacrylamide and Polyethylenimine. *Eur. Polym. J.* **1998**, *8*, 1199-1205.

55. Fukuoka, S.; Takimoto, S.; Katsuki, t.; Yamaguchi, M. Activation of Mixed Carboxylic α-Bromotoluoyl Anhydrides by Sinvertetrafluoroborate Synthesis of Esters and Thiol esters. *Tetrahedron Lett*. **1987**, *28*, 4711-4712.

56. (a) Chayaripongkal, S. Reagent Development for the Preparation of Acid chloride for Synthesis of Bioactive Compounds, Master's thesis, Department of Chemistry, Chulalongkorn University, **2003**. (b) Chantarasruwong,

Halogenated Reagents and Triphenylphosphine for the Syntheses of Amides, Esters and Sulfonamides, Master's thesis, Department of Chemistry, Chulalongkorn University, **2005**.

57. Noller, R. C. *Textbook of Organic Chemistry*. W. B. Saunders Company, **1966**.
58. Pluempanupat, W.; Chantarasriwong, O; Taboonpong, P.; Jang, O. H.; Chavasiri, W. Reactivity of Chlorinating Agents/PPh_3 for the Chlorination of Alcohols and Carboxylic Acids: a Comparative Study. *Tetrahedron Lett*. **2007**, *48*, 223–226.

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