



CHAPTER I

INTRODUCTION

Organohalogenes are organic compounds which their carbons are directly bonded to at least one halogen atom. They can be divided into alkyl, vinylic, aryl, and acyl halides. An alkyl halide which all the carbon single bonds bearing to the halogen can also be further subdivided into alkyl, allylic and benzylic halides [1].

Alkyl halides, especially alkyl chlorides, are important industrial chemicals as solvents, inhaled anesthetics in medicine, refrigerants, pesticides and fumigating agents [2]. In addition, they are generally used as both synthetically useful precursors and valuable end products in chemical and pharmaceutical industries [3]. Therefore, many researches try to develop more efficient methodologies to synthesize this class of compounds. The optimum conditions in each newly developed reaction are still essentially needed to be considered to achieve a maximum yield.

1.1 Introduction of Alkyl Halides

Alkyl halides are important precursors which can be converted to many other functional groups such as ethers, esters, nitriles, amines and sulfides [4]. The transformation of alkyl halides to other organic compounds are illustrated as shown in Table 1.1.

Table 1.1 Conversion of alkyl halides to other organic compounds [4]
$$\text{RX} \xrightarrow{\text{reagent}} \text{Product}$$

X = halogen

Reagent	Product	Functional group
HO^-	ROH	alcohol
H_2O	ROH	alcohol
$\text{R}'\text{O}^-$	ROR'	ether (Williamson synthesis)
$\text{R}'\text{C}\equiv\text{C}^-$	$\text{RC}\equiv\text{CR}'$	alkyne
R'-Metal	RR'	alkane (Coupling)
I^-	RI	alkyl iodide
NC^-	RCN	nitrile
$\text{R}'\text{COO}^-$	R'COOR	ester
NH_3	RNH ₂	primary amine
$\text{NH}_2\text{R}'$	RNHR'	secondary amine
$\text{NHR}'\text{R}''$	RNR'R''	tertiary amine
PPh_3	$\text{RPPH}_3^+ \text{X}^-$	phosphonium salt
HS^-	RSH	thiol (mercaptan)
RS^-	RSR	thioether (sulfide)
$\text{ArH} + \text{AlCl}_3$	ArR	alkylbenzene (Friedel-Crafts)
Base	C=C	alkene
Mg, dry ether	RMgX	Grignard reagent
Metal, H^+	RH	alkane

1.2 Classical Methods for the Preparation of Alkyl Halides from Alcohols [4]

Alkyl halides can be prepared from various sources of starting materials, for example halogenation of alkanes, addition of alkenes, substitution of alcohols and ring opening of epoxides [6]. The general and simple protocols mostly stem from the

conversion of alcohols. It was due to the easy transformation process, the variety and commercial availability.

The preparation of alkyl halides from alcohols using common reagents (such as HCl, SOCl_2) has been reported for decades. The reaction of alcohols with HCl or HBr produced the corresponding alkyl halides, especially tertiary alkyl halides, in excellent yield, whereas other alcohols could be slowly converted or not react with the reagents. In the case of using SOCl_2 for chlorination, the reaction was only occurred in severe conditions, and HCl and SO_2 gas as by-products are invariably produced. Moreover, there are certain reports using phosphorus reagents such as PCl_3 , PBr_3 and POCl_3 , as halogenating agents for the preparation of alkyl halides [4]. In addition, chlorotrimethylsilane (Me_3SiCl) coupled with lithium bromide in CH_3CN was chosen as a reagent system to treat with alcohols in order to transform the alcohols into the desired bromides in high yield. This reaction was equally applicable not only to primary, secondary and tertiary alcohols, but also to allylic and benzylic alcohols [7].

According to the outcomes derived from such common reagents, some problems still remained. For example, the use of HCl and HBr often causes undesired side reactions, especially rearrangement products that occurred when the reagent reacted with some secondary alcohols. Other common reagents such as SOCl_2 , PCl_3 and PBr_3 are known as harmful reagents and produce corrosive by-products. From the aforementioned reasons, many researchers have attempted to improve the synthesis of halides using non-toxic reagents under mild conditions. Therefore, the controllable and selective methodology is still called for further study for the preparation of halides.

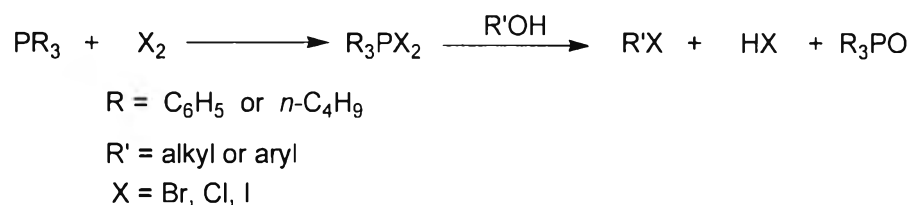
1.3 Literature Reviews on the Conversion of Alcohols into Halides by Organophosphorus/Halogenating Agent

Numerous methodologies for the preparation of alkyl halides using phosphorus compounds/halogenating agent such as $\text{PPh}_3/\text{CCl}_4$, $\text{PPh}_3/\text{Cl}_3\text{CCCl}_3$, $\text{PPh}_3/\text{Cl}_3\text{CCN}$, PR_3/Br_2 , PR_3/CBr_4 systems are alternatively attractive methods. That is

because those reactions could be performed under mild and acid-free conditions. Moreover, most halogenating agents are commercially available.

Burn and Cadogan [8] exhibited the conversion of alcohols using the combination of $(RO)_3P$ and CCl_4 or $BrCCl_3$ yielding the corresponding alkyl halides, trialkyl phosphites and chloroform.

Wiley and co-workers [9] reported the preparation of a variety of alkyl and aryl chlorides in high yields using phosphorus reagents of the type R_3PX_2 ($X = Br, Cl, I$) prepared by halogenation of PPh_3 in carbon tetrahalide followed by exhaustive evaporation of the solvent. The reaction produced HX gas as a by-product.

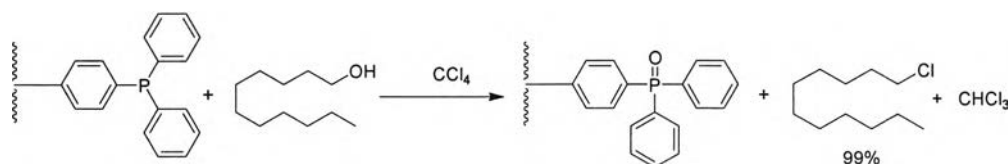


Lee and Nolan [10] developed the method for the preparation of chloro sugars and chloropolyols using phosphorus compounds and halogenating agents. The reaction acted rapidly under mild and neutral conditions. In addition, this method could be possible for the preparation of chloroesters from hydroxyl-ester using PPh_3/CCl_4 .

Weiss and Snyder [11] described the transformation of either alcohols or thiols into their corresponding alkyl chlorides using PPh_3/CCl_4 under mild conditions yielding 27% of the desired alkyl chlorides.

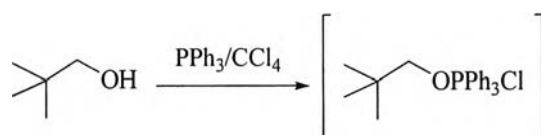
Hozz and Gilani [12] reported the transformation of alcohols to alkyl chlorides and alkyl bromides using tri-*n*-octylphosphine (TOP) with CCl_4 or CBr_4 , respectively. Primary and secondary alkyl chlorides could be obtained in high yield. The same trend could be observed for primary alkyl bromides. Tertiary alkyl chlorides however gave low yield.

Steven and Dan [13] developed the formation of alkyl chlorides from primary, and secondary alcohols using CCl_4 with the modification of filterable reagent, polystyryl-diphenylphosphine resin.



Miyano and co-workers [14] described the use of the combination of PPh_3 and CuCl_2 for the chlorination of alcohols. The reaction worked well to achieve alkyl chlorides in the range of 42-95% yield. The reactions using cyclohexanol and methanol as starting materials gave poor yields of alkyl chlorides and alkene was generated as by-products. When CuBr_2 was used in place of CuCl_2 , the reaction yielded alkyl bromides.

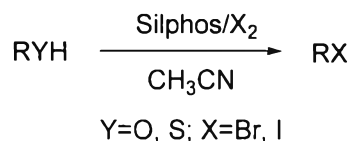
Jones and co-workers [15] exhibited the rate of formation of phosphorylated intermediate formed by reacting PPh_3 , CCl_4 and an alcohol. This combination was only slightly influenced by steric effects. The relative rates of intermediate formation were primary > secondary > neopentyl. The neopentyl alcohol reacted with the phosphorylating agent at room temperature (RT) to form an intermediate without concomitant decomposition to neopentyl chloride. The structure of the intermediate was elucidated by $^1\text{H-NMR}$ and ^{31}P decoupling.



Matveeva and co-workers [16] reported that certain alcohols such as 2-decanol, 2-methyl-3-octanol and 2,4-dimethyl-3-pentanol could be converted into the desired alkyl chlorides by using $\text{PPh}_3/\text{Cl}_3\text{CCN}$. They also demonstrated that alkyl chlorides were only the products formed, although another nucleophile such as iodide was added to the reaction.

Schlama and co-workers [17] studied the preparation of alkyl chlorides and alkyl bromides from tetrahydropyran (THP) derivatives of alcohols using dimethyl-

Iranpoor and co-workers [22] reported that alcohols and thiols could be converted to the desired bromides and iodides using silicaphosphine (Silphos): $[P(Cl)_{3-n}(SiO_2)_n]$ as the filterable phosphorus reagent with Br_2 and I_2 in refluxing CH_3CN .



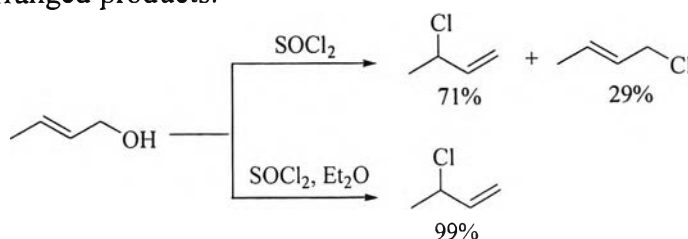
Pluempanupat and Chavasiri [23] demonstrated that alcohols could be converted into their desired chlorides in excellent yield using PPh_3/Cl_3CCONH_2 as a new reagent system. Various alcohols, especially primary alcohols, could smoothly be converted into chlorides under mild conditions.

Tongkate and co-workers [24] reported the comparative study of the bromination of alcohols with various brominating agents to achieve the corresponding alkyl bromides. The order of the reactivity of the reagent was $PPh_3/Br_3CCOCBr_3$, PPh_3/Br_3CCO_2Et and PPh_3/CBr_4 , respectively.

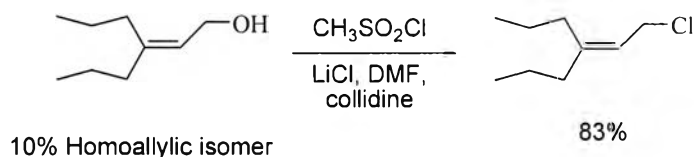
According to the literatures using common reagents or the combination of phosphorus compound/halogenating agent, several methods for the conversion of alcohols into their corresponding halides have been addressed; however, those methods mainly reported for the preparation of alkyl halides rather than allylic and benzylic halides.

1.4 Literature Reviews on the Conversion of Benzylic and Allylic Alcohols

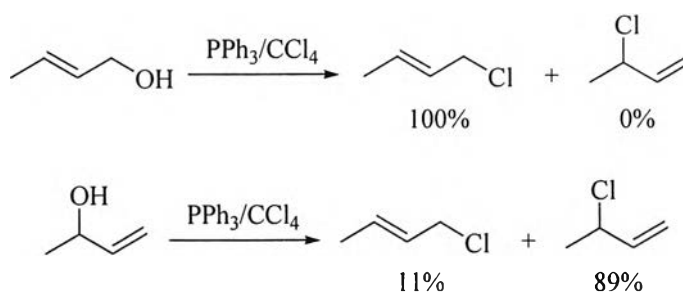
Not many literatures addressed the conversion of benzylic and allylic alcohols into benzylic and allylic halides. For example, Caserio and co-workers [25] reported that the chlorination of certain allylic alcohols using $SOCl_2$ in Et_2O produced the undesired rearranged products.



Collington and Meyer [26] investigated the conversion of allylic alcohols to their corresponding halides without allylic rearrangement using methanesulfonyl chloride ($\text{CH}_3\text{SO}_2\text{Cl}$) and a mixture of LiCl , DMF and collidine at $0\text{ }^\circ\text{C}$. The unrearranged allylic chlorides were formed in excellent yield.



Snyder [27] reported that the combination of $\text{PPh}_3/\text{CCl}_4$ was of a potential in chlorination of allylic alcohols. That system could convert primary and secondary allylic alcohols into their corresponding chlorides without the formation of the rearranged products, whereas allylic alcohols containing terminal double-bond carbon, 3-buten-2-ol did not produce the desired product.



Ronald and co-workers [28] explored a regio- and stereoselectivity for the conversion of allylic alcohols into allylic chlorides using $\text{PPh}_3/\text{CCl}_3\text{COCCl}_3$. The similar results to those of Snyder were reported.

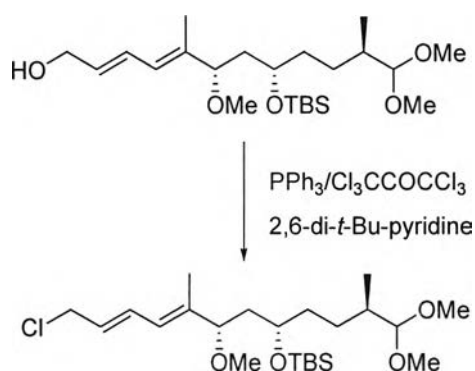
Nicolaou and co-workers [29] showed the preparation of allylic bromides using phosphorus tribromide (PBr_3) and $\text{PPh}_3/\text{CBr}_4$ from tertiary alcohols being terminal double-bond carbon and primary allylic alcohols, respectively. Tertiary alcohols reacting with PBr_3 yielded their allylic bromides in 95% whereas primary allylic alcohols treating with $\text{PPh}_3/\text{CBr}_4$ yielded 70%.

Matveeva and co-workers [30] investigated a regio- and stereoselective halogenation of allylic alcohols. Mixing *cis*- and *trans*- $\text{RCH}=\text{CHCH}_2\text{OH}$ ($\text{R} = \text{CH}_3, n\text{-C}_5\text{H}_{11}$) with CCl_3R_1 ($\text{R}_1 = \text{-CN, -CO}_2\text{Et, -COCCl}_3$) in CH_3CN and PPh_3 gave the

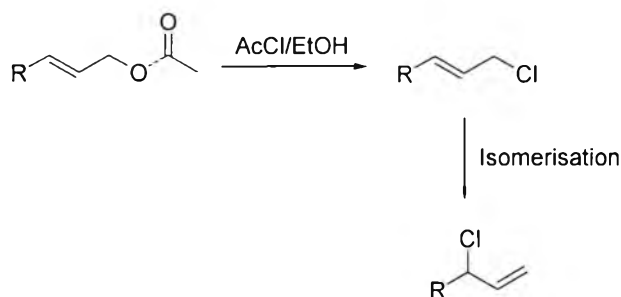
corresponding allylic chlorides with $\geq 95\%$ regio- and stereoselectivity. The selectivity for analogous reactions of *cis*- and *trans*-HOCHRCH=CH₂ was 81-92% while CH₂=CHCHDOH gave 53% CH₂=CHCHDCl.

Munyemans and co-workers [31] studied the reaction of tetramethyl- α -halogenoenamines for the conversion of alcohols into halides. Primary and secondary alcohols were smoothly converted into their corresponding alkyl halides in excellent yield while secondary allylic and propargyl alcohols gave some rearranged halides generated after the formation of the desired halides.

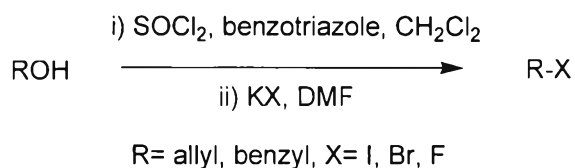
Meyer and co-workers [32] addressed the synthetic investigations of rapamycin. In the chlorination step, dienallylic alcohol was treated with PPh₃/Cl₃CCOCCl₃ in the presence of 2,6-di-*tert*-butylpyridine at -40 °C within 15 min.



Vejendra and Ganesh [33] reported that AcCl/EtOH could rapidly transform secondary allylic alcohols, primary and secondary allylic acetates into allylic chlorides which still retained the olefinic bond in the more stable position. The reaction with primary allylic alcohols containing 1,2-disubstituted alkene was however very slow.



Bandgar and Bettigeri [34] demonstrated that a combination of SOCl_2 , benzotriazole, and potassium halides in DMF reacting with allylic and benzylic alcohols could generate allylic and benzylic halides in high to excellent yield. However, this reagent system was unreactive with primary, secondary and tertiary alcohols.



Sanchita and co-workers [35] reported the synthesis of unsymmetrical allylic chlorides using 2,4,6-trichloro-1,3,5-triazine (TCT) in combination with DMF. The reaction showed that electronic and steric properties of the allylic alcohol starting materials have an effect on the formation of their allylic chlorides.

The previously reported procedures for the preparation of benzylic and allylic halides generally suffer from one or other disadvantages, such as low yields, long reaction time, use of expensive reagents, requirement of severe reaction conditions or complicate work-up procedures. The investigation for a new, selective and efficient halogenation method using inexpensive, safe and easily available reagent is thus promising.

1.5 Goal of The Research

The objective of this research is to develop an efficient and selective protocol for halogenation of benzylic and allylic alcohols utilizing PPh_3 /halogenating agent under mild conditions.