CHAPTER III

CARBON-CHLORINE BOND FORMATION USING PHOSPHORUS AND HALOGENATED REAGENTS

3.1 Introduction

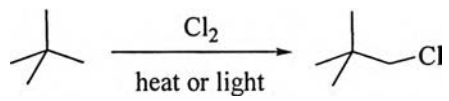
It would be difficult to study organic chemistry without becoming aware of halo-substituted alkanes. Among their many uses, alkyl halides are employed as industrial solvents, as inhaled anesthetics in medicine, as refrigerants, and as pesticides and fumigating agents [50].

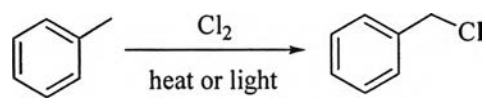
Alkyl chlorides are generally used as both synthetically useful intermediates and valuable end products in chemical industry and pharmaceutical science [51]. Therefore, over the past century, there has been copious evidence for the development of many methodologies to synthesize this class of compounds. Moreover, the optimum conditions in each nearly developed reaction are still essentially needed to be considered to achieve a maximum yield.

3.1.1 The Synthesis of Alkyl Chlorides

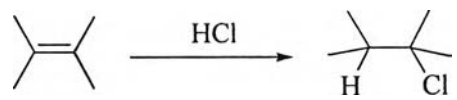
In the laboratory, alkyl chlorides are most often prepared from various starting materials with many manners.

- From chlorination of certain hydrocarbons [52]

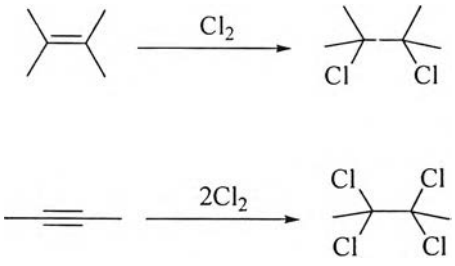




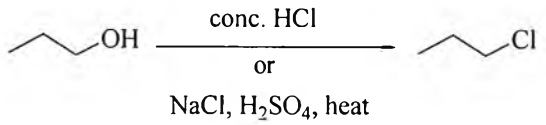
- From addition of hydrogen chloride to alkenes [52]

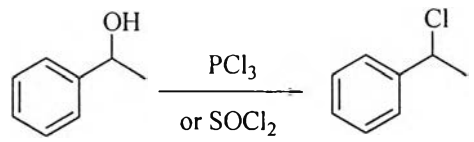


- From addition of chlorine to alkenes and alkynes [52]

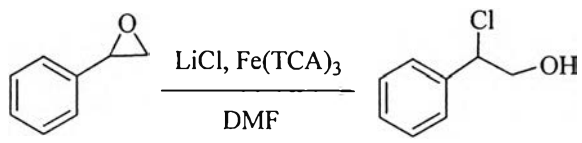


- From alcohols [52]





- From ring opening of epoxides [53]



Although alkyl chlorides can be manipulated from various sources of starting materials, 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 available of alcohols [54]. From these reasons, alcohols were chosen to study the efficiency towards chlorinating reagents.

3.1.2 The Importance of Alkyl Chlorides

Alkyl chlorides are of importance as intermediates to convert into many other functional groups such as ethers, esters, nitriles, amines and sulfides. The conversions of alkyl chlorides to other organic compounds are illustrated as shown in Table 3.1.

Table 3.1 The conversion of alkyl chlorides to other organic compounds [52]

$$RCl \xrightarrow{\text{reagent}} \text{Product}$$

Type of Reaction	Reagent	Product	Functional group
Nucleophilic substitution	HO^-	ROH	alcohol
	H_2O	ROH	alcohol
	$R'O^-$	ROR′	ether (Williamson synthesis)
	$R'C{\equiv}C^-$	RC≡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	$RPPh_3^+ X^-$	phosphonium salt
	HS^-	RSH	thiol (Mercaptan)
	RS^-	RSR	thioether (Sulfide)
	$ArH + AlCl_3$	ArR	alkylbenzene (Friedel-Crafts)
Dehydrohalogenation	Base	C=C	alkene
Preparation of Grignard reagent	Mg, dry ether	RMgCl	Grignard reagent
Reduction	Metal, H^+	RH	alkane

3.2 Literature Reviews on Alkyl Chloride Synthesis from Alcohols

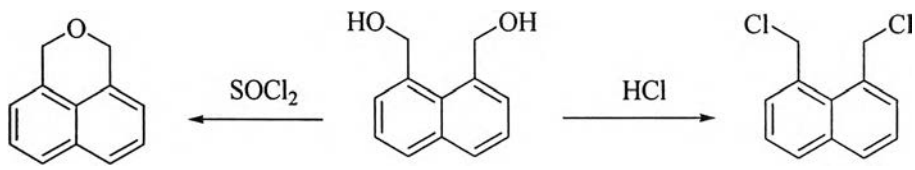
Conversion of alcohols into alkyl chlorides can be accomplished by several approaches. Reaction of an alcohol with common reagents such as HCl gas, thionyl chloride ($SOCl_2$), oxalyl chloride ($(COCl)_2$), phosphorus trichloride (PCl_3), phosphorus pentachloride (PCl_5) and phosphorus oxychloride ($POCl_3$) to give alkyl chloride are among classical methods. Some newer methods have also appeared such as the use of triphenylphosphine (PPh_3) and tetrachloromethane (CCl_4) complex and the reagent of PPh_3 and *N*-chlorosuccinamide (NCS).

3.2.1 Reaction of Alcohols with Common Reagents

3.2.1.1 HCl

Alcohols react readily with HCl to yield alkyl chlorides and water. The reaction is carried out either by passing dry HCl gas into alcohol, or by heating alcohol with concentrated aqueous acid.

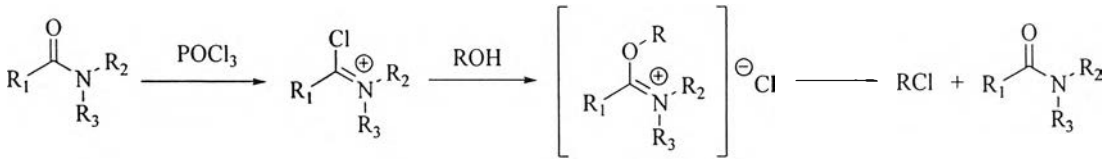
Boekelhel and co-workers addressed the conversion of 1-8-naphthalene-dimethanol to 1,8-*bis*-(chloromethyl)naphthalene by using HCl. When the diol was treated in the usual fashion with $SOCl_2$ to effect replacement of the hydroxyl groups by chlorine, concomitant formation of the corresponding cyclic ether occurred. By the use of concentrated HCl at 0°C, the side reaction was avoided and the desired chloride resulted in 93% yield [55].



3.2.1.2 PCl_3, PCl_5 and $POCl_3$

In the early stage, the preparation of alkyl chlorides could be accomplished by treating with common reagents such as PCl_3, PCl_5 and $POCl_3$.

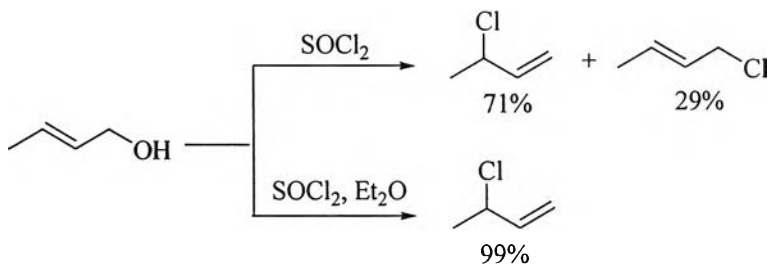
In 1980, Yoshihara and co-workers reported the synthesis of several iminium salts and their use in the preparation of alkyl halides from alcohols. The yields of alkyl chlorides obtained by this method are generally high. Moreover, the use of iminium salts afforded far better yields of alkyl chlorides than the use of $POCl_3$ [56].



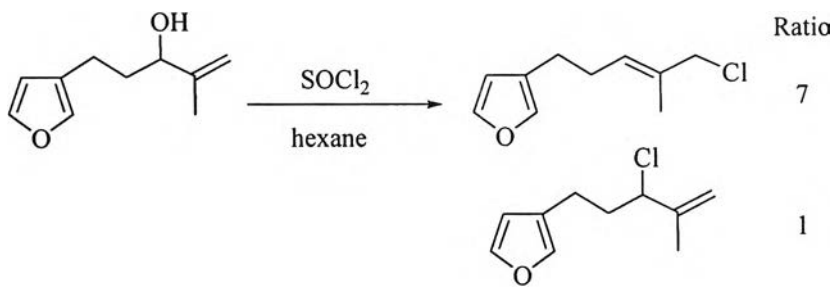
3.2.1.3 $SOCl_2$

Generally, tertiary alcohols are readily converted into alkyl chlorides by treatment with HCl at 0°C. Primary and secondary alcohols are much more resistant to acid, however, and are best converted into alkyl halides by treatment with $SOCl_2$.

Caserio and co-workers reported the chlorination of allylic alcohols by using $SOCl_2$ in the presence of dilute ether solution [57].



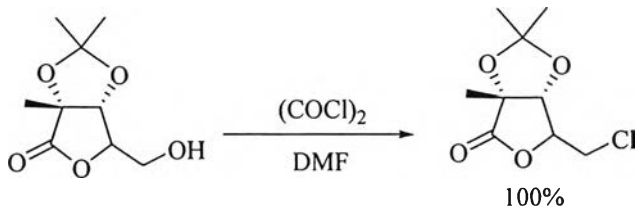
Foland and co-workers reported the total synthesis of isoarnebifuranone. One of all steps was the treatment of allylic alcohol with $SOCl_2$ in hexane yielding allylic chloride in 65% isolated yield as the major isomer of a 7:1 mixture of regioisomers [58].



However, alcohols could be converted to alkyl chlorides on treatment with two or three times of redistilled $SOCl_2$. In some cases, the reactions took place immediately but usually the mixture has to be refluxed with stirring at the boiling point of $SOCl_2$. Since the by-products of the reaction were gaseous, they were readily removed and any excess $SOCl_2$ was distilled off. These by-products are harmfully corrosive chemicals and invariably make the conditions become acidic.

3.2.1.4 $(COCl)_2$

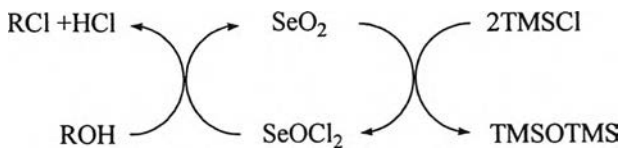
Ireland and co-workers addressed an approach to the synthesis of the monensin tetrahydropyran-*bis*(tetrahydrofuran) *via* the ester enolate Claisen rearrangement and reductive decarboxylation. In the chlorination step, α-D-glucosaccharinic acid γ-lactone was converted to the corresponding chloride in quantitative yield using $(COCl)_2$ [59].



3.2.1.5 TMSCl

It has been well established that alcohols can be converted to their corresponding iodides or bromides by the action of trimethylsilyl halides, TMSI [60] or TMSBr [61], respectively. The same reaction does not occur with the less reactive TMSCl alone.

However, Lee and Kang reported that this transformation could be accomplished with TMSCl when a catalytic quantity of SeO_2 was employed. In the presence of a catalytic amount of SeO_2, TMSCl served as an efficient chlorinating reagent for a wide variety of alcohols. Selenium oxychloride ($SeOCl_2$) generated *in situ* seemed to react with alcohols forming unstable alkyl selenites, which rapidly decomposed to alkyl chlorides [62].



This reagent was superior to $SOCl_2$ and other chlorinating agents not only in terms of the yield and mildness of the reaction conditions but also because the competing side reactions were greatly suppressed.

Snyder reported that both primary and tertiary alcohols could be readily converted to alkyl chlorides by TMSCl and a catalytic quantity of DMSO. The facile,

high yield reaction was postulated to take place through a mechanism similar to that proposed for TMSI and TMSBr [63].

3.2.1.6 $InCl_3$/$HSiMe_2Cl$

Yasuda and co-workers reported the $InCl_3$-catalyzed reaction of alcohols with chlorodimethylsilane ($HSiMe_2Cl$) in the presence of benzil to give the corresponding chlorides under mild conditions. Benzil significantly changed the reaction course because the reducing product through dehydroxyhydration was obtained in the absence of benzil. The secondary or tertiary alcohols and benzylic alcohols were effectively chlorinated. The substrates bearing acid-sensitive functional groups were found to be compatible with this system. The highly selective chlorination of the tertiary site was observed in the competitive reaction between tertiary and primary alcohols. The highly coordinated hydrosilane generated from benzil and $HSiMe_2Cl$ was an important intermediate [64].

The outcomes derived from utilizing common reagents revealed that a challenging problem still remained. For example, 1) the co-regeneration of HCl often causes undesired side reactions [65]. The reaction can be used to prepare primary, secondary or tertiary halides with aforementioned reagents; nevertheless the alcohols of isobutyl or neopentyl type often gave large amounts of rearrangement products. Moreover, tertiary chlorides are easily made with concentrated HCl, but primary and secondary alcohols react with HCl so slowly that a catalyst, usually zinc chloride, is required.

2) A number of such methods which accomplish this conversion are known, most require either harmful reagents (such as $SOCl_2$ and $(COCl)_2$), the application of heat or sometimes extremely produce corrosive by-products (such as strong acids and SO_2). Besides, if a starting material acid contains acid sensitive functional groups, under acidic conditions it is likely that the desired alkyl chloride may be obtained in low yield or not at all. Consequently, many more convenient methods that can be conducted by using harmless reagents, moderate degree of heat or milder conditions are desirable. The new methodology with controllable selectivity is therefore still called for and be a responsible task for organic chemists.

3.2.2 Phosphorus Compounds with Halogenated Reagents

The convenient methodology for the preparation of alkyl chlorides using comparatively non-toxic reagents under mild conditions has been constantly studied such as a combination of organophosphorus reagent and halogenated reagent such as PPh_3/Cl_2 [66], PPh_3/CCl_4 [67-69], PPh_3/Cl_3CCCl_3 [70-71], PPh_3/Cl_3COCCl_3 [72-73] or PPh_3/Cl_3CCN [74-77] systems. These reagents are attractive since the reaction could be performed under mild and acid-free conditions with good yield.

3.2.2.1 PPh_3/Cl_2

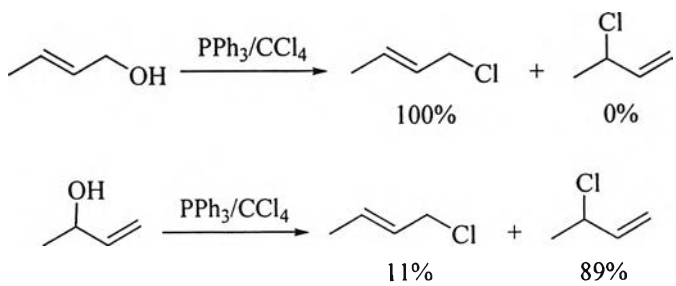
Wiley and co-workers reported that an important characteristic of PPh_3/Cl_2 system is its tendency to induce substitution without elimination or rearrangement. The cyclic halide preparations best illustrate the former point. The conversions of secondary pentyl and neopentyl alcohols to halides without rearrangement illustrate the latter. Phenols are converted at elevated temperatures without position isomers being formed [66].

$$PPh_3 \xrightarrow{Cl_2} Cl_2PPh_3 \xrightarrow{ROH} RCl + POPh_3 + HCl$$

3.2.2.2 PPh_3/CCl_4

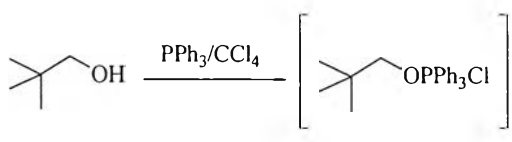
Alkyl chlorides could be prepared from alcohols with the combination of PPh_3/CCl_4 under mild and neutral conditions. The reaction took place rapidly to produce the desired product, triphenylphosphine oxide and chloroform. This reaction did not generate any strong acidic material, thus it is suitable for the preparation of alkyl chloride containing acid sensitive functional group [67].

Snyder reported the conversion of allylic alcohols to the corresponding chlorides without rearrangement [68].



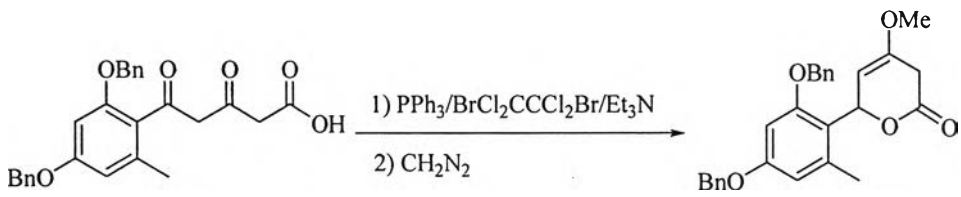
Jones and co-workers reported the rate of formation of phosphorylated intermediate formed by reacting PPh_3, CCl_4 and an alcohol. This combination was

only slightly influenced by steric effects. The relative rates of intermediate formation were primary > secondary > neopentyl. The relative rates of intermediate decomposition followed the order of primary > secondary > neopentyl. Thus neopentyl alcohol reacted with the phosphorylating agent at room temperature to form an intermediate without concomitant decomposition to neopentyl chloride. The structure of the intermediate was elucidated by ^{1}H NMR and ^{31}P decoupling [69].

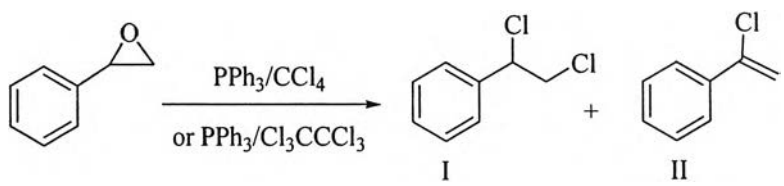


3.2.2.3 PPh_3/Cl_3CCCl_3

Bringmann and co-workers converted alcohols to alkyl chlorides by using the combination of PPh_3/Cl_3CCCl_3 and $PPh_3/BrCl_2CCCl_2Br$ in high yield. Moreover, this reagent could also be demonstrated in the course of the biomimetric synthesis of the aglycon of the biologically active bitter glucoside aloenin [70].



Hashimoto and co-workers addressed the reaction of PPh_3-trichloromethyl compounds such as CCl_4 and CCl_3CCl_3 with styrene oxide to give I and II.



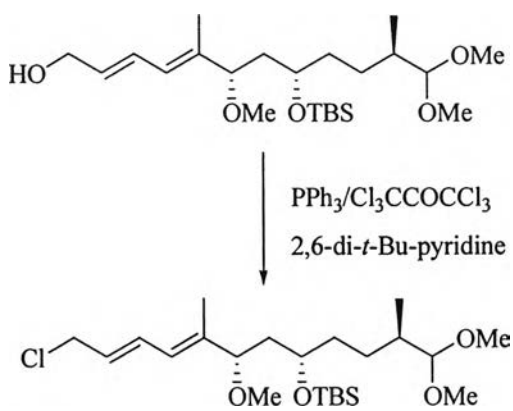
The reaction was accelerated in polar solvents such as MeCN. I was quantitative formed when excess PPh_3 was used. II was formed in high yield when phenols were added to the reaction mixture. The reactions using other Cl_3C-compounds (except Cl_3CCCl_3) gave products analogous to those of CCl_4. Cl_3C-compounds having more electron withdrawing groups other than Cl gave higher I and II ratios than did CCl_4. The reaction with Cl_3CCCl_3 gave I quantitatively at room temperature [71].

However, the conversion of alcohols to the desired alkyl chlorides by using above combinations cannot be proceeded within short reaction time at room temperature. Later, the combination of Ph_3P/Cl_3COCCl_3 or Ph_3P/Cl_3CCN systems has been addressed as another viable route for the preparation of alkyl chloride with high efficiency.

3.2.2.4 $PPh_3/Cl_3CCOCCl_3$

Magid and co-workers reported a mild reagent for the regioselective and stereospecific production of chlorination. Allylic alcohols reacted with $PPh_3/Cl_3CCOCCl_3$ in less than 20 min at 10-15 °C to produce excellent yields of the corresponding alkyl chlorides. Isolation was accomplished simply by flash distillation. The conversion occurred with total preservation of double bond geometry and with >99% inversion of configuration for optically active alcohol. All primary and secondary alcohols gave predominantly the unrearranged alkyl chloride whereas tertiary alcohols furnished mostly rearranged product. With more highly substituted systems, elimination to diene became an important side reaction [72].

Meyer and co-workers addressed the synthetic investigations of rapamycin. In the chlorination step, dienallylic alcohol was treated with $PPh_3/Cl_3CCOCCl_3$ in the presence of 2,6-di-*tert*-butylpyridine at -40 °C within 15 min [73].



3.2.2.4 PPh_3/Cl_3CCN

Matveeva and co-workers reported that the conversion of alcohols such as 2-decanol, 2-methyl-3-octanol, 2,4-dimethyl-3-pentanol, into the corresponding alkyl chlorides with Cl_3CCN in the presence of PPh_3 was regiospecific. If an external nucleophile such as iodide and rhodanide was introduced to the reaction, the alkyl chloride was still a predominant product [74].

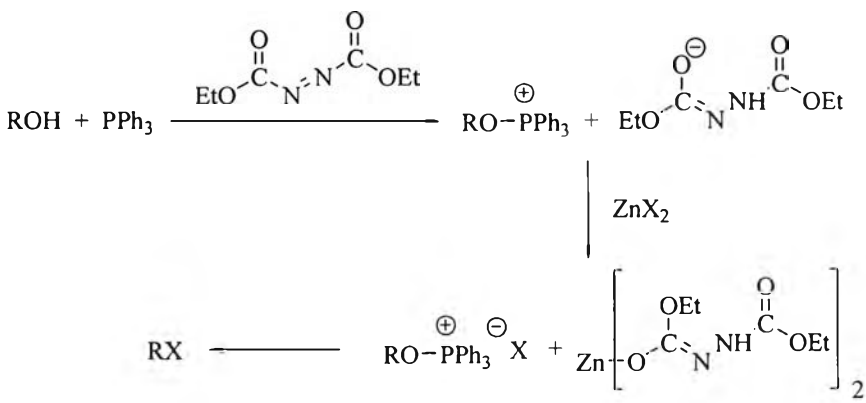
Later, Matveeva and co-workers investigated continually a regio- and stereoselective substitution of halide for hydroxyl groups in allylic alcohols. Treating *cis*- and *trans*-RCH=CHCH$_2$OH (R = Me, *n*-C$_5$H$_{11}$) with CCl$_3$R$_1$ (R$_1$ = CN, CO$_2$Et, COCCl$_3$) in MeCN and PPh$_3$ gave the corresponding alkyl chloride with ≥ 95% regio- and stereoselectivity. The selectivity for analogous reactions of *cis*- and *trans*-HOCHRCH=CH$_2$ was 81-92%, while CH$_2$=CHCHDOH gave 53% CH$_2$=CHCHDCl [75].

Furthermore, the combination of PPh$_3$/Cl$_3$CCN could be used for the preparation of acid chlorides from carboxylic acids. For example, Jang and co-workers reported the transformation of carboxylic acids to the corresponding acid chlorides by treatment carboxylic acid with Cl$_3$CCN and PPh$_3$ in CH$_2$Cl$_2$ [76]. This method could be performed under a mild reaction and acid free conditions. Later, Jang and Kim further developed the aforementioned conditions for the synthesis of symmetrical acid anhydride [77].

3.2.2.5 PPh$_3$/CuCl$_2$ or ZnCl$_2$

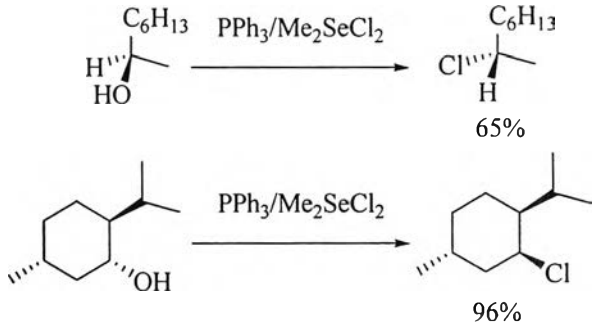
Miyano and co-workers reported the chlorination of alcohols with PPh$_3$/CuCl$_2$. Aliphatic alcohols were converted to the corresponding alkyl chlorides in 42-95% yields while cyclohexanol and menthol gave poor results because of the olefin-forming side reaction. However, phenol was not chlorinated under the reaction conditions. (-)-(R)-2-octanol gave (+)-(S)-2-chlorooctane with 81% net inversion. Furthermore, bromides were also obtained by using CuBr$_2$ instead of CuCl$_2$ [78].

Ho and Davies reported the reaction of alcohols with the combination of zinc halide, DEAD and PPh$_3$ for the preparation of alkyl halides. Primary, secondary, and allylic alcohols under the same conditions have been converted in good yields into the corresponding alkyl halides. The reaction was generally completed in minutes at room temperature [79].



3.2.2.5 PPh_3/Me_2SeCl_2 or Ph_2SeCl_2

Drabowicz and co-workers reported a very efficient, stereoselective synthesis of alkyl chlorides from alcohols using a mixture of PPh_3 and dimethyl- or diphenyldichloroselenurane (Me_2SeCl_2 or Ph_2SeCl_2) as a combination reagent. The usefulness of this method for conversion of alcohols into alkyl chlorides was demonstrated by experiments with optically active substrates such as enantiomers of 2-octanol and (-)-menthol. In the case of acyclic, chiral alcohols, both enantiomers of 2-octanol and (-)-menthol were converted to the corresponding chlorides and with essentially full inversion of configuration [67].



These reagents are attractive since the reaction could be preformed under mild and acid-free conditions with good yields. This evidence could be postulated for its importance. Nonetheless, the development for the high yield and chemoselective reaction with selective reagents under mild and neutral conditions are still called for consideration.

Recently, trichloroacetamide (Cl_3CCONH_2) as an alternative halogenated reagent for conversion of carboxylic acids to their analogous amides and esters upon the combination with PPh_3 was introduced by Chaysripongkul [80]. This reagent, eventhough a bit less reactive compared with CCl_3CN [81], its cost and the ease of work-up make this reagent far more conceivable to be employed. This chapter devoted for the extended study of the use of this new combination of PPh_3/Cl_3CCONH_2 for the conversion of alcohols to the corresponding alkyl chlorides.

3.3 Scope of This Work

The methodology for the preparation of alkyl chloride using comparatively non-toxic reagents under mild and neutral conditions will be focused. The objective of the research described in this chapter is to develop a new combination of phosphorus and halogenated reagents for chlorination of alcohols and to explore the optimum

conditions for the preparation of alkyl chloride. Moreover, the comparative study on the reactivity of developed reagent in the chlorination of various primary, secondary, tertiary, benzylic and allylic alcohols would be taken into the serious consideration.

3.4 Experimental

3.4.1 Instruments and Equipment

Melting points were determined with a Fisher-Johns melting point apparatus or Electrothermal digital melting point apparatus model IA 9100 and are uncorrected. Column chromatography was carried out on silica gel (Merck Kieselgel 60, 70-230 mesh). Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck Kieselgel 60 PF_{254}). The FT-IR spectra were recorded on a Nicolet Fourier Transform Infrared Spectrophotometer model Impact 410: solid samples were incorporated to potassium bromide to form a pellet. 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. 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}.

3.4.2 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 otherwises stated and were used without further purification.

3.4.3 Preparation of Halogenated Reagents

3.4.3.1 Ethyl dichloroacetate, ethyl chloroacetate, ethyl tribromoacetate and *i*propyl trichloroacetate [82-83]

1 mL of concentrated sulfuric acid was cautiously added to the mixture of dichloroacetic acid, chloroacetic acid or tribromoacetic acid (20 mmol) and ethanol or *i*-propanol (40 mmol). The mixture in the round bottom flask fitted by a condenser was refluxed for 6 hours 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, and dried over anhydrous Na_2SO_4.

Ethyl dichloroacetate: colorless oil (80%); ^{1}H-NMR ($CDCl_3$) δ 5.91 (s, 1H), 4.28 (q, J = 7.2 Hz, 2H) and 1.31 (t, J = 7.1 Hz, 3H).

Ethyl chloroacetate: colorless oil (70%); ^{1}H-NMR ($CDCl_3$) δ 4.18 (q, J = 7.1 Hz, 2H), 4.00 (s, 2H) and 1.24 (t, J = 7.1 Hz, 3H).

Ethyl tribromoacetate: colorless oil (72%); ^{1}H-NMR ($CDCl_3$) δ 4.46 (q, J = 7.2 Hz, 2H) and 1.44 (t, J = 7.2 Hz, 3H).

^{i}Propyl trichloroacetate: colorless oil (69%); ^{1}H-NMR ($CDCl_3$) δ 5.18 (sep, J = 6.3 Hz, 1H) and 1.41 (d, J = 6.3 Hz, 6H).

3.4.3.2 Trichloroacetanilide [84]

Into a three-necked flask was placed a solution of hexachloroacetone (100 mmol) in 40 mL of hexane. To the stirred solution was added, dropwise, aniline (100 mmol) over a period of 35-40 minutes. During this time, the temperature was raised to about 55 °C. After the addition was completed, stirring was continued at 65-70 °C for another 45 minutes. The hot solution was poured into a beaker and then cooled to 0-5 °C. The solid was collected upon filtration and air-dried. Recrystallization from 90% ethanol to obtain white crystal (73%); ^{1}H-NMR ($CDCl_3$) δ 8.31 (br s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.41 (t, J = 8.4 Hz, 2H) and 7.24 (t, J = 8.4 Hz, 1H).

3.4.4 General Procedure

3.4.4.1 Synthesis of Alkyl Chlorides

A stirred solution of alcohol 1 eq (0.25 mmol) and PPh_3 2 eq (0.5 mmol) in dry CH_2Cl_2 (0.5 mL) was successively added selected halogenated reagent 2 eq (0.5 mmol) at room temperature (30 °C) under N_2 atmosphere. After 15 min, the reaction was quenched by cold water and the corresponding product was determined by ^{1}H-NMR on the crude mixture with toluene as an internal standard or purified by column chromatography on silica gel (eluent: hexane).

2-Phenylethyl chloride: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.20-7.25 (m, 5H), 3.62 (t, J = 7.4 Hz, 2H) and 3.02 (t, J = 7.4 Hz, 2H).

(+)-(S)-2-Octyl chloride: colorless oil; $[\alpha]_D^{25}$ +26.9, c = 0.58, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 4.01 (sex, J = 6.5 Hz, 1H), 1.69 (m, 2H), 1.28-1.50 (m, 11H) and 0.89 (t, J = 6.7 Hz, 3H).

(-)-Nopyl chloride: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 5.33 (br s, 1H), 3.46-3.54 (m, 2H), 2.35-2.44, (m, 3H), 2.18-2.30 (m, 2H), 2.10 (br s, 1H), 2.03 (t, J = 4.6 Hz, 1H), 1.28 (s, 3H), 1.18 (d, J = 8.5 Hz, 1H) and 0.84 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 144.4, 119.2, 45.5, 42.5, 40.7, 40.2, 38.0, 31.6, 31.3, 26.3 and 21.2.

2-Chloro-2-phenylacetophenone: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.96 (d, J = 8.0 Hz, 2H), 7.32-7.55 (m, 8H) and 6.35 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 191.5, 135.9, 134.3, 132.1, 129.5, 129.4, 129.3, 129.2, 129.1, 128.8, 128.7, 128.6, 128.5 and 62.3.

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl chloride: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.17-7.41 (m, 20H), 6.11 (br s, 1H), 5.02 (d, J = 10.8 Hz, 1H), 4.85-4.95 (m, 2H), 4.75 (s, 2H), 4.61 (d, J = 12.1 Hz, 1H), 4.54, (d, J = 10.7 Hz, 1H), 4.50 (d, J = 12.1 Hz, 1H), 4.05-4.14 (m, 2H), 3.76-3.83, (m, 3H) and 3.68 (d, J = 10.9 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 138.5, 138.0, 137.6, 137.4, 128.6, 128.5, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 93.5, 81.4, 79.8, 76.4, 75.9, 75.3, 73.5, 73.4, 73.0 and 67.7.

3.4.4.2 Reactivity Study of Alcohols

A stirred solution of two selected alcohols 1 eq (0.25 mmol each) in dry CH_2Cl_2 (0.5 mL) were successively added PPh_3 1 eq (0.25 mmol) and Cl_3CCONH_2 1 eq (0.25 mmol) at room temperature (30 °C) under N_2 atmosphere. After 15 min, CH_2Cl_2 was removed by evaporation and alkyl chlorides in the crude mixture were determined by ^{1}H-NMR with the addition of toluene as an internal standard.

3.4.4.3 Reactivity Study of Halogenated Reagents

2-Phenylethanol 1 eq (0.25 mmol) was added to a mixture of Br_3CCO_2Et 0.75 eq and a chlorinated reagent 0.75 eq (0.188 mmol each) in dry CH_2Cl_2 (0.5 mL). The mixture was treated with PPh_3 1.5 eq (0.375 mmol) at RT (30 °C) under N_2 atmosphere. After 15 min, the crude mixture was evaporated to dryness and both alkyl halides were determined by ^{1}H-NMR in the crude mixture with the addition of toluene as an internal standard.

3.4.5 Optimum Conditions Study

3.4.5.1 Effect of Halogenated Reagents

1) The synthesis of 2-phenylethyl chloride was carried out using the reaction conditions described in the general procedure. Sixteen different chlorinated reagents:

CCl_4, $CHCl_3$, Cl_3CCCl_3, trichlorofluoromethane (Cl_3CF), trichlorobromomethane (Cl_3CBr), 2,2,2-trichloroethanol (Cl_3CCH_2OH), Cl_3CCN, hexachloro-2-propanone ($Cl_3CCOCCl_3$), trichloroacetic acid (Cl_3CCO_2H), Cl_3CCO_2Et, $Cl_3CCO_2CH(CH_3)_2$, 2,2,2-trichloroethyl acetate ($Cl_3CCH_2O_2CCH_3$), trichloroacetic anhydride $(Cl_3CCO)_2O$, Cl_3CCONH_2, $Cl_3CCONHPh$ and ferric chloride ($FeCl_3$) were utilized.

2) The synthesis of 2-phenethyl halide such as fluoride, bromide and iodide was carried out using the reaction conditions described in the general procedure. Five different halogenated reagents: ethyl trifluoroacetate (F_3CCO_2Et), tribromoacetic acid (Br_3CCO_2H), ethyl tribromoacetate (Br_3CCO_2Et), iodomethane (CH_3I) and iodoform (CHI_3) were employed.

3.4.5.2 Effect of PPh_3 and Cl_3CCONH_2 Ratio and Reaction Time

The ratios of PPh_3 and Cl_3CCONH_2 for the synthesis of 2-phenylethyl chloride utilizing the general procedure were varied (based on 2-phenylethanol 1 eq). The variations of the PPh_3 and Cl_3CCONH_2 ratios are as follows: 0.5:0.5, 1:1, 1.25:1.25, 1.5:1.5, 2:2 and 3:3, respectively. Determine the yield of 2-phenylethyl chloride by ^{1}H-NMR in the crude mixture with toluene as an internal standard. Furthermore, employing the above-mentioned reaction conditions, the reaction was operated by altering reaction time at room temperature (30 °C).

3.4.5.3 Effect of Type of Alcohol

The chlorination of alcohol using the combination of PPh_3/Cl_3CCONH_2 at room temperature within 15 min was conducted. Different alcohols including primary, secondary and tertiary alcohols were examined. In addition, some of these alcohols containing benzylic position, alkene, allylic, cyclic, ketone, ester, ether and bulky group were used as substrate.

3.5 Results and Discussion

In this chapter, the development of a chlorinated reagent and the exploration of optimum conditions for the preparation of alkyl chloride from alcohol, PPh_3 and halogenated reagent were thoroughly examined.

3.5.1 Conditions Optimization

Optimum conditions for the preparation of alkyl chlorides from alcohols utilizing various chlorinated reagents coupled with PPh_3 were examined. Variable

parameters studied included types of chlorinated reagent, ratio of PPh_3 and halogenated reagent, and reaction time. 1-Phenylethanol was chosen as a model compound to avoid a benzylic effect. Typical reaction involved the reaction of alcohol (1 eq), halogenated reagent (1.5 eq) and PPh_3 (1.5 eq) in CH_2Cl_2 at room temperature (30 °C) for 30 min. The desired alkyl chloride was determined by ^{1}H-NMR in the crude mixture utilizing toluene as an internal standard.

2-Phenylethyl chloride in the crude mixture as the ultimate target molecule was confirmed its identity by ^{1}H-NMR spectroscopic technique. The spectrum displayed two triplet signals of methylene protons connecting with chlorine atom at δ_H 3.62 and methylene protons next to a phenyl group at δ_H 2.97 (lit. δ_H 3.63 and 3.01 [85]). The ^{1}H-NMR spectrum of 2-phenylethyl chloride in the crude mixture is shown in Figure 3.1.

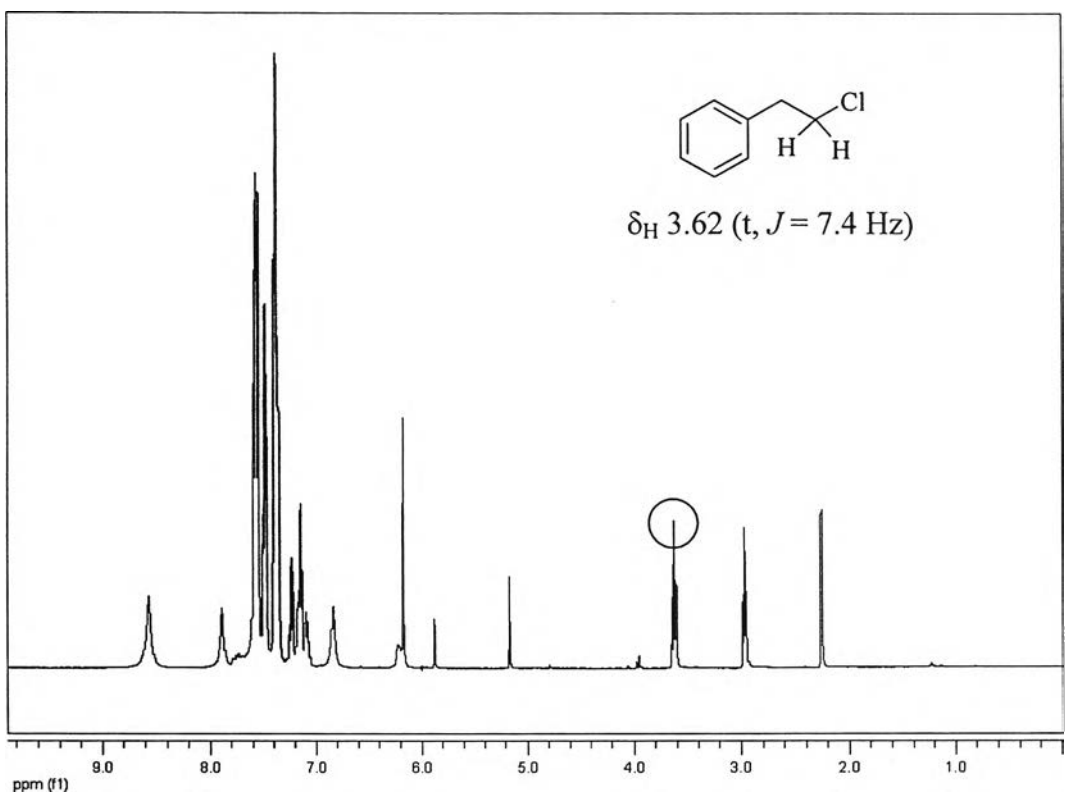
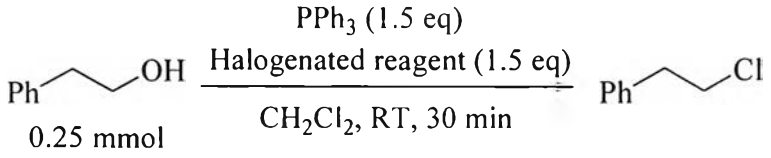


Figure 3.1 ^{1}H-NMR spectrum of 2-phenylethyl chloride in the crude mixture

3.5.1.1 Effect of Halogenated Reagents

Significant differences in the reactivities of alkyl chloride were mainly caused from halogenated reagent. To observe this assumption, the variation of diverse twenty two halogenated reagents was explored and the results are described in Table 3.2.

Table 3.2 Effect of halogenated reagents



Entry	Halogenated reagent	% Yield	Recovered alcohol (%)	Σ (%)
1	-	0	95	95
2	CCl_4	trace	99	99
3	$CHCl_3$	0	100	100
4	Cl_3CCCl_3	quant	-	100
5	Cl_3CF	0	100	100
6	Cl_3CBr	40 (25)[a]	35	100
7	Cl_3CCH_2OH	0	95	95
8	$Cl_3CCH_2O_2CCH_3$	0	100	100
9	Cl_3CCN	quant	-	100
10	$Cl_3CCOCCl_3$	95	-	95
11	$(Cl_3CCO)_2O$	0 (49)[b]	53	102
12	Cl_3CCO_2H	35	56	91
13	Cl_3CCO_2Et	82	21	103
14	$Cl_3CCO_2{}^iPr$	71	29	100
15	Cl_3CCONH_2	81	24	105
16	$Cl_3CCONHPh$	80	23	103
17	$FeCl_3$	0	100	100
18	F_3CCO_2Et	(RF) 0	98	98
19	Br_3CCO_2H	(RBr) 65	-	99[c]
20	Br_3CCO_2Et	(RBr) 99	-	99
21	CH_3I	(RI) 0	100	100
22	CHI_3	(RI) 0	100	100

a) %Yield of $PhCH_2CH_2Br$

b) %Yield of $PhCH_2CH_2O_2CCCl_3$

c) %Yield of unidentified product was obtained in 34%

Considering the effect of halogenated reagents on the formation of alkyl halide, it was observed that when the reaction was carried out in the absence of halogenated reagent (entry 1), the desired alkyl chloride was not obtained. This was clearly demonstrated that the halogenated reagent was crucial for this reaction. The efficiency of chlorinating agent was greatly depended on type of the substituent. The reagents in entries 2-4 were previously utilized for the conversion of alcohols into alkyl chlorides. Nonetheless, under this specific conditions low yield of the desired product was found except for the case of Cl_3CCCl_3 providing the target molecule with quantitative yield. The poor result was also attained with a chlorinated reagent containing alkyl group or fluorine or bromine atom at trichloromethyl group (Cl_3C-) (entries 5-8). Interestingly, two corresponding alkyl chloride and bromide products were found in 40% and 25% yields, respectively when Cl_3CBr was used (entry 6). The ^{1}H-NMR spectrum of 2-phenylethyl chloride and 2-phenylethyl bromide [86] in the crude mixture is shown in Figure 3.2.

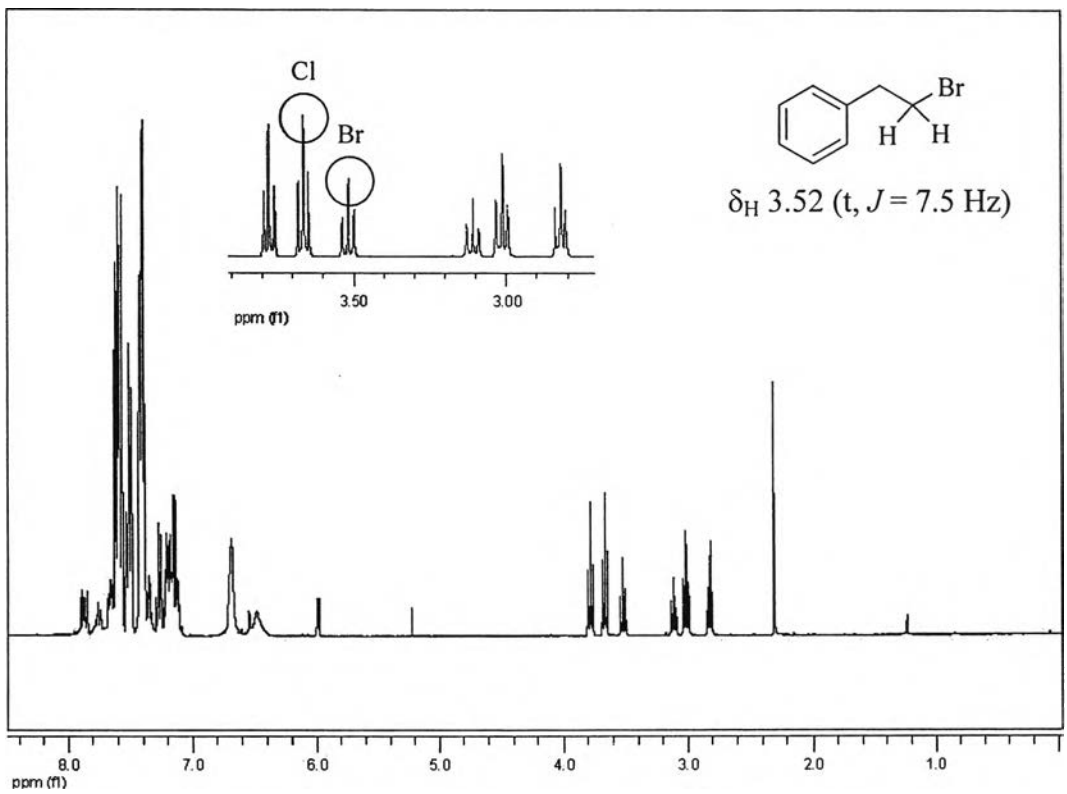
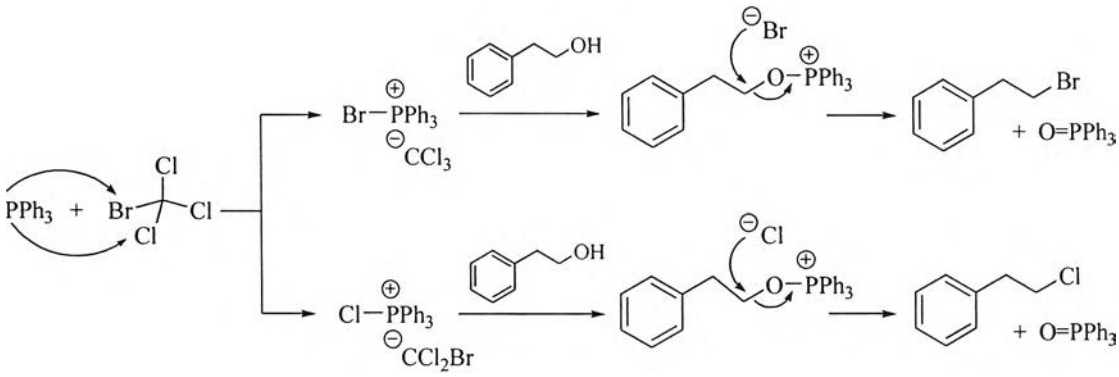


Figure 3.2 ^{1}H-NMR spectrum of 2-phenylethyl chloride and 2-phenylethyl bromide in the crude mixture

It was considered that this proceeding reaction took place *via* competitive substitution between chloride and bromide as shown below.



PPh_3 could be reacted with either chlorine or bromine atoms to generate phosphonium salt intermediate as presented. Then the formed intermediates were converted to the corresponding alkyl chloride or bromide. Although bromine atom of Cl_3CBr was a more reactive group with PPh_3 than chlorine atom, the yield of 2-phenylethyl bromide was obtained in lower yield than 2-phenylethyl chloride. It was therefore conceivable that the yield of the desired product from two competitive pathways was depended on amount of chlorine/bromine atoms as 3/1. The chance of PPh_3 to react with chlorine atom could be occurred statistically more than bromine atom in three fold.

Cl_3CCN and $Cl_3CCOCCl_3$ (entries 9-10), a reagent bearing electron-withdrawing group furnished the desired product in quantitative yield, while $(Cl_3CCO)_2O$ did not lead to the desired alkyl chloride. $PhCH_2CH_2O_2CCl_3$ was instead obtained as a major product in 49% yield. It was rationally considered that the anhydride bond of this halogenated reagent was significantly reactive for alcohol to generate the attained ester. This postulation was confirmed by the reaction of 2-phenylethanol 1 eq and $(Cl_3CCO)_2O$ 2 eq without PPh_3 under the same reaction conditions. The same ester was obtained in 72% yield. The ^{1}H-NMR spectrum of isolated ester (Fig 3.3) displayed five aromatic protons at δ_H 7.25-7.34. Two triplet signals at δ_H 4.49 (J = 7.0 Hz) and δ_H 3.04 (J = 7.0 Hz) was ascribed for four protons of two methylene groups connecting with $-O_2CCCl_3$ and phenyl group, respectively. The ^{13}C-NMR spectrum (Fig 3.4) displayed three peaks at δ_C 34.7, 64.2 and 67.8 indicating two methylene carbons and Cl_3C- groups, respectively. Four signals of aromatic carbons were observed at δ_C 126.9, 128.7, 129.0 and 136.8. The peak at δ_C 164.5 appropriated for a carbonyl carbon was clearly observed [87].

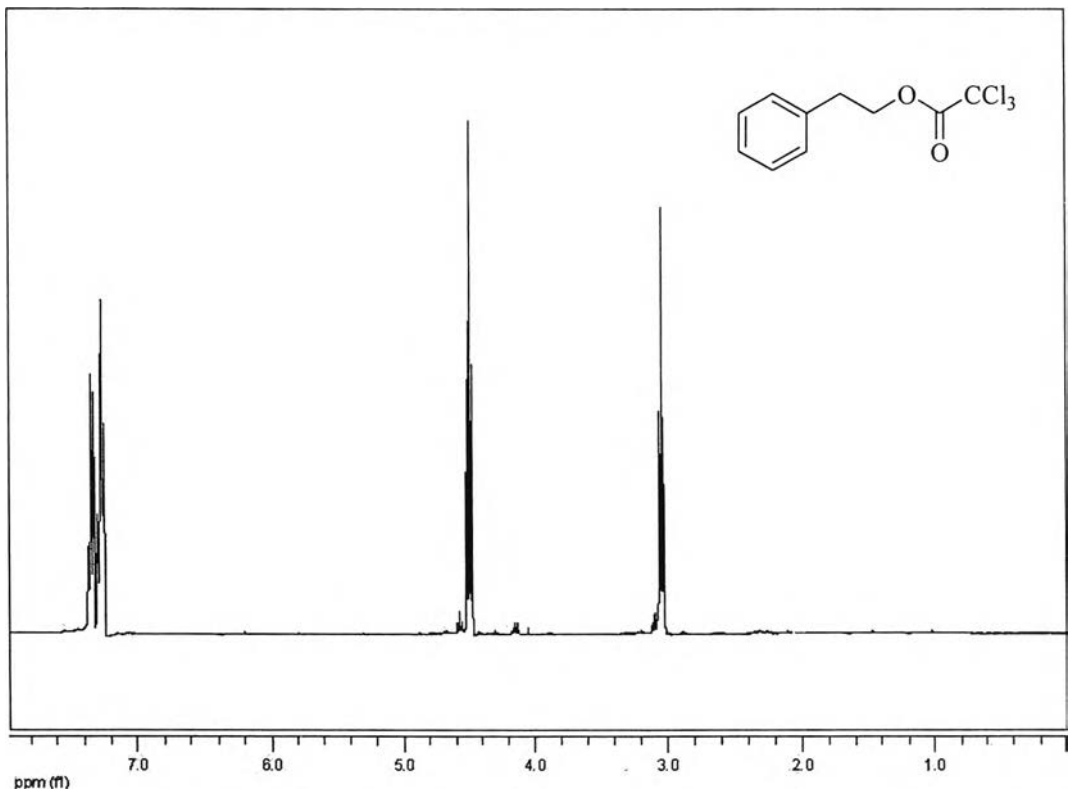


Figure 3.3 ^{1}H-NMR spectrum of $PhCH_2CH_2O_2CCl_3$

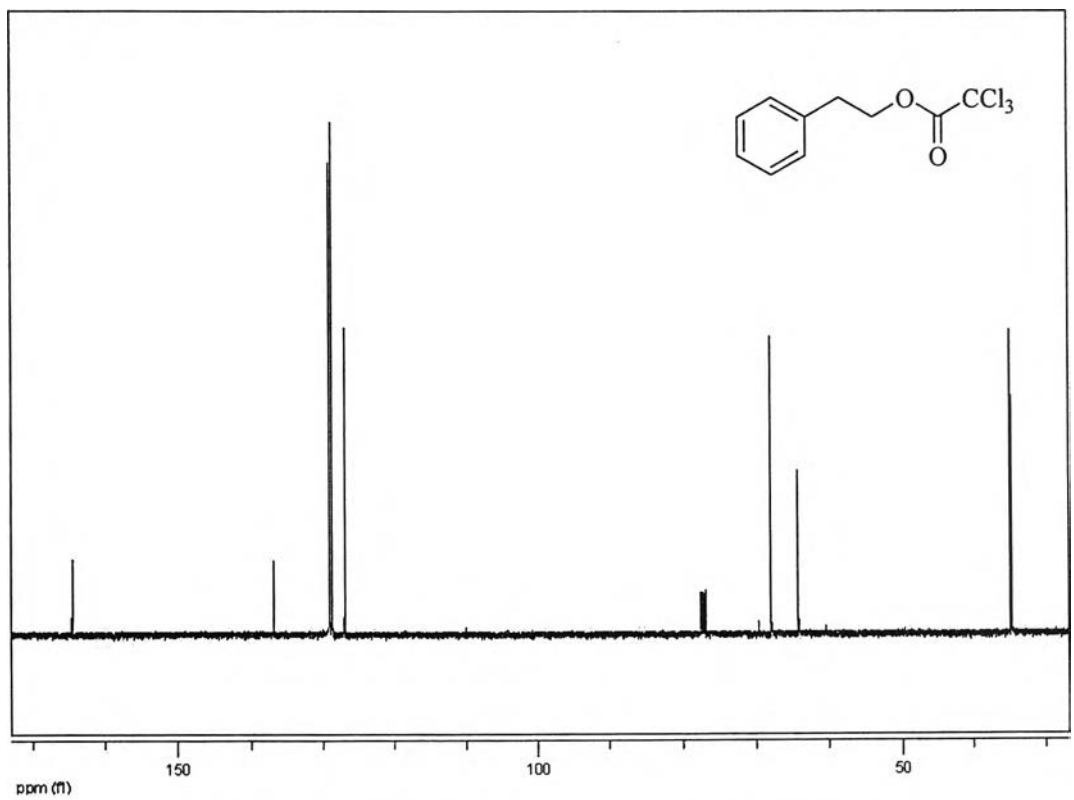


Figure 3.4 ^{13}C-NMR spectrum of $PhCH_2CH_2O_2CCl_3$

Cl_3CCO_2H (entry 12) did not provide good yield of the desired alkyl chloride. This was probably because of its acidity that may make the reaction become acidic and thus not appropriate for further reaction to take place. Other electron-withdrawing group containing reagents (entries 13-16) were chosen to prove this assumption. For instance, the utilization of Cl_3CCO_2Et, Cl_3CCONH_2 and $Cl_3CCONHPh$ (entries 13, 15 and 16) furnished the target product in comparable yield to that obtained from Cl_3CCN. Nonetheless, the use of $FeCl_3$ for this reaction could not convert 2-phenylethanol to the corresponding chloride. It was believed that the insolubility of $FeCl_3$ in CH_2Cl_2 would render the ability of this reagent (entry 17).

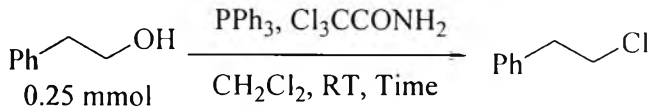
Based on the results obtained, Cl_3CCONH_2 was considered as the most proper halogenated reagent for further investigation because it has not been addressed, commercially available reagent with cheap price and indeed the ease of work-up procedure.

In addition, fluorinated, brominated and iodinated reagents were chosen to explore whether they could be utilized for the preparation of corresponding halides under above conditions. Fluorination of 2-phenylethanol using F_3CCO_2Et was not possible to convert into its analogues alkyl fluoride (entry 18). The use of Br_3CCO_2Et (entry 20) gave 2-phenylethyl bromide in excellent yield more than that of Br_3CCO_2H (entry 19). The formation of alkyl iodide was also not possible when CH_3I or CHI_3 were used as iodinating reagent.

3.5.1.2 Effect of PPh_3 and Cl_3CCONH_2 Ratio and Reaction Time

The ratios of PPh_3 and Cl_3CCONH_2 were varied to find out for the most suitable ratio that provided the maximum yield of alkyl chloride. The results are shown in Table 3.3.

Table 3.3 Effect of PPh_3 and Cl_3CCONH_2 ratio and reaction time



Entry	PPh_3 (eq)	Cl_3CCONH_2 (eq)	Time (min)	% Yield	Recovered alcohol (%)	Σ (%)
1	0.5	0.5	15	15	85	100
2	1.0	1.0	15	53	50	103
3	1.25	1.25	15	73	29	102
4	1.5	1.5	15	75	25	100
5	1.5	1.5	30	81	24	105
6	2.0	2.0	15	quant	-	100
7	2.0	2.0	30	quant	-	100
8	3.0	3.0	15	quant	-	100

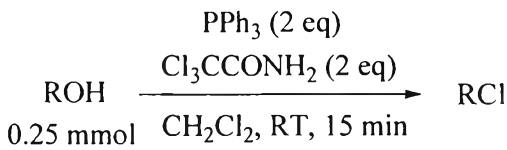
The use of PPh_3 and Cl_3CCONH_2 in 0.5:0.5 and 1:1 eq (based on alcohol) furnished alkyl chloride in poor and moderate yields, respectively (entries 1-2). Increasing the amount of PPh_3 and Cl_3CCONH_2 over one eq significantly elevated the yield of the target product compared with the former cases (entries 3-8). From this results, the quantitative yield was gained when two eq of PPh_3 and Cl_3CCONH_2 were used. Especially, the short reaction time could also be possible for the production of alkyl chloride in quantitative yield within 15 min (entry 6).

3.5.2 Chlorination of Selected Alcohols

3.5.2.1 Primary, Secondary and Tertiary Alcohols

This disclosed reaction conditions were extended to investigate the conversion of various alcohols including primary, secondary and tertiary alcohols into their analogous alkyl chlorides. The generality of this chlorination methodology is summarized in Table 3.4.

Table 3.4 Chlorination of selected alcohols



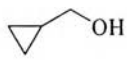
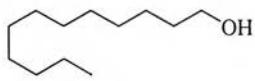
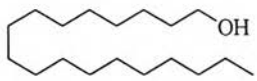
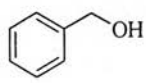
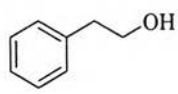
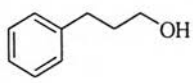
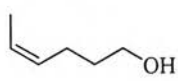
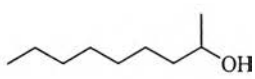
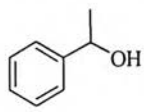
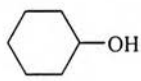
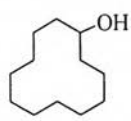
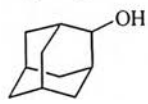
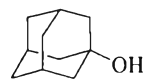
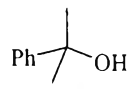
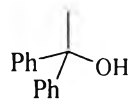
Entry	ROH	% Yield	Olefin (%)	Σ (%)
1		82	-	82
2		96	-	96
3		98	-	98
4		96	-	96
5		74 (27)[a]	-	101
6		quant	-	100
7		92	-	92
8		94	-	94
9		quant	-	100
10		83 (17)[a]	-	100
11		37	15	52
12[b]		42	57	99
13		quant	-	100

Table 3.4 (continued)

Entry	ROH	% Yield	Olefin (%)	Σ (%)
14		68 (33)[c]	-	101
15		72	14	102
16		11	88	99

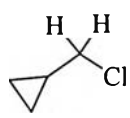
a) %Yield of alkyl phosphonium salt

b) The reaction time was 60 min

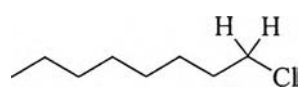
c) %Yield of recovered 1-adamantanol

All of the desired alkyl chlorides were quantified by ^{1}H-NMR spectroscopic technique. The selected ^{1}H-NMR spectral assignments of various alkyl chlorides and detected olefins for structural determination compared with the literatures are shown below.

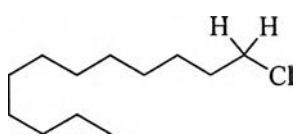
- Primary alkyl chlorides



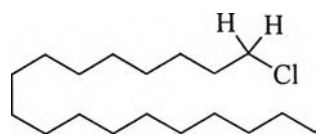
δ_H 3.09 (d, J = 7.4 Hz) [88]



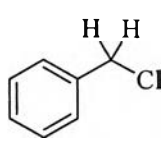
δ_H 3.40 (t, J = 6.7 Hz) [89]



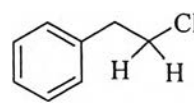
δ_H 3.40 (t, J = 6.7 Hz) [90]



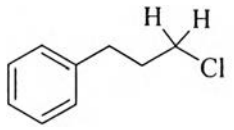
δ_H 3.40 (J = 6.7 Hz) [91]



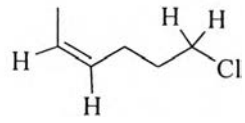
δ_H 4.42 (s) [91]



δ_H 3.62 (t, J = 7.4 Hz) [85]



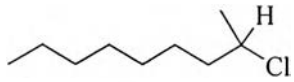
δ_H 3.32 (t, J = 6.5 Hz) [92]



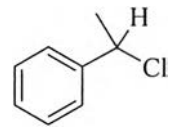
δ_H 3.37 (t, J = 6.6 Hz)

δ_H 6.90-7.10 (m) [93]

- Secondary alkyl chlorides

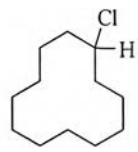


δ_H 3.92 (sex, J = 6.5 Hz) [96]

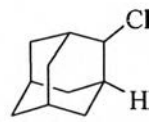


δ_H 5.00 (q, J = 6.8 Hz) [67]

δ_H 3.90 (m) [94]

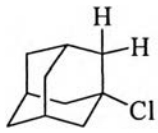


δ_H 4.01 (m) [95]

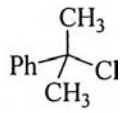


δ_H 4.56 (br t, J = 4.0 Hz) [64]

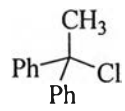
- Tertiary alkyl chlorides



δ_H 1.97 (s) [64]

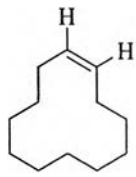


δ_H 1.84 (s) [96]

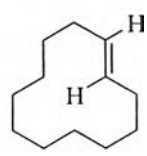


δ_H 2.18 (s) [97]

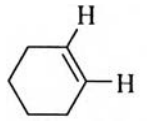
- Olefin products



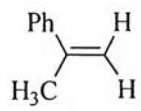
δ_H 5.17 (t, J = 5.0 Hz) [98]



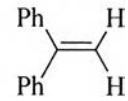
δ_H 5.22 (m) [98]



δ_H 5.58 (br s) [99]



δ_H 1.99 (s) [100]



δ_H 5.34 (s) [101]

Various primary alcohols could be completely converted to the corresponding alkyl chlorides in high to quantitative yield (entries 1-8). The chlorination carried out with (hydroxymethyl)cyclopropane was a discrete reaction and provided a mechanistic clue (entry 1). To illustrate this, due to the cyclopropane ring was not cleaved; this could confirm that the reaction mechanism was not taken place *via* a radical pathway [102]. In the case of long chain aliphatic alcohols including 1-octanol, 1-dodecanol and 1-octadecanol, the carbon chain length, perhaps being considered as steric hindrance, did not affect this reaction (entries 2-4). However, the effective transformation was observed in the reaction with benzyl alcohol. It was found that the chlorination at benzylic position did not proceed completely and gave alkyl phosphonium compound (Fig 3.5) as another product in 27% yield. The benzylic effect on the chlorination of alcohol under this particular conditions was carefully investigated and will discuss in the next topic.

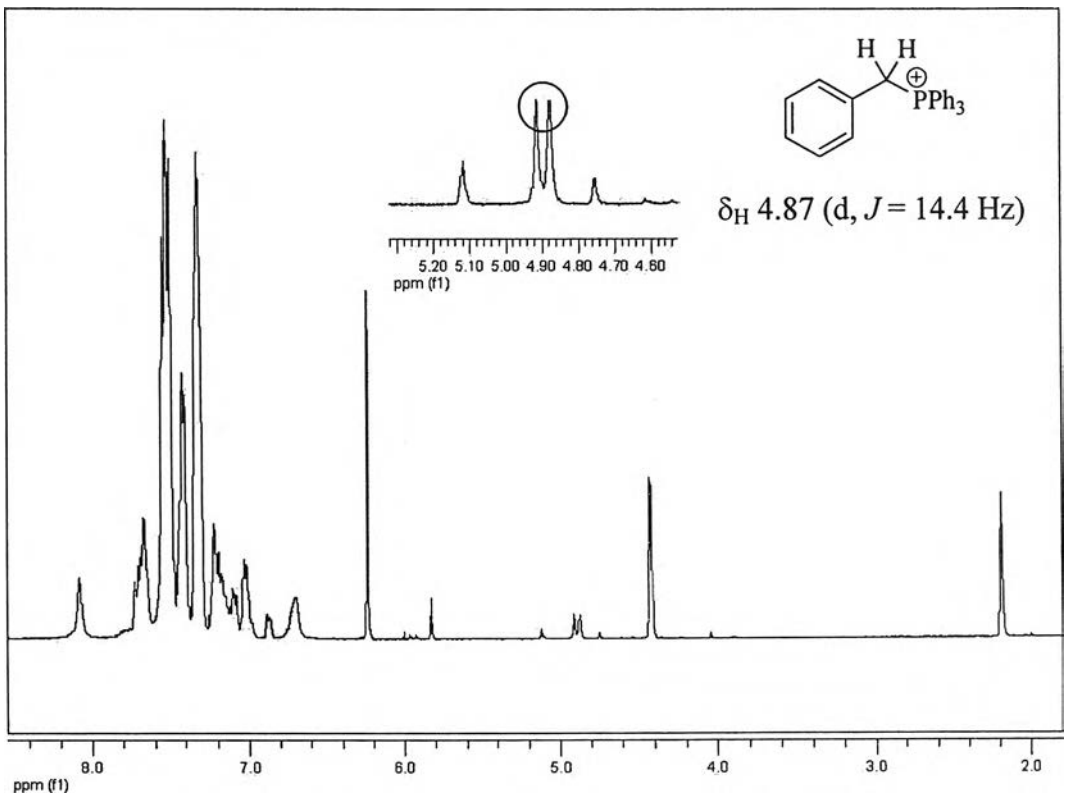


Figure 3.5 ^{1}H-NMR spectrum of phosphonium salt in the crude mixture

Alcohols containing two or three carbon linkages between phenyl ring and hydroxy group could be converted to the corresponding chlorides in excellent yields (entries 6-7). This result confirmed that the benzylic position had a profound effect to the chlorination under this developed system. In addition, alcohol containing C=C smoothly transformed only to the desired alkyl chloride whereas alkene moiety was not intact (entry 8). It can thus be concluded that the combination of PPh_3/Cl_3CCONH_2 disclosed as the chemoselective chlorination of alcohol.

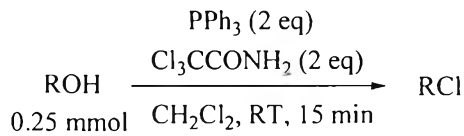
For secondary alcohol, (±)-2-octanol could be converted to the corresponding chloride in high yield (entry 9). The effect of benzylic position was predominant the same as previous result (benzyl alcohol) when (±)-1-phenylethanol was examined. The desired alkyl chloride and alkyl phosphonium salt were obtained in 83% and 17% yields, respectively (entry 10). Cyclic compounds such as cyclohexanol and cyclododecanol; on the other hand, were converted into cyclic alkyl chlorides upon treatment with PPh_3/Cl_3CCONH_2 in low to moderate yield (entries 11-12) except for 2-adamantanol (entry 13). The olefinic product was additionally detected in this reaction with almost equal amount to the alkyl chloride present. This implied that the reaction may competitively proceeded *via* two major pathways possibly as substitution *vs* elimination.

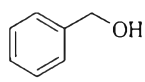
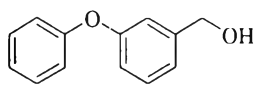
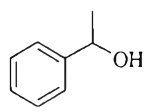
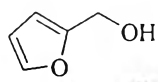
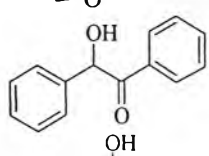
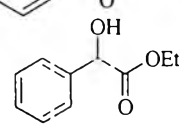
The conversion of 1-adamantanol and 2-phenylpropanol to the corresponding alkyl chlorides could also be achieved in high yield (entries 14-15). In the case of 1,1-diphenylethanol with two phenyl substituents at tertiary carbon atom, diphenylethyl chloride was detected in low yield. Peradventure, this alcohol which was considered to proceed *via* E2 reaction, also gave 1,1-diphenylethylene as a main product (entry 16).

3.5.2.2 Benzylic Alcohols

From the above results, undesired product as alkyl phosphonium compound was detected when benzyl alcohol and (±)-1-phenylethanol were converted to the corresponding alkyl chlorides by using the combination of PPh_3/Cl_3CCONH_2. In this topic, the effect of benzylic position on chlorination of alcohols under this developed system was focused. The chlorination results of various benzylic alcohols are tabulated in Table 3.5.

Table 3.5 Chlorination of selected benzylic alcohols

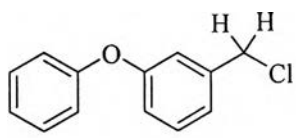


Entry	ROH	% Yield		Σ
		RCl	R^+PPh_3	(%)
1		74	27	101
2		72	27	99
3		83	16	99
4		65	32	97
5		92	-	92
6		69 (24)[a]	-	103

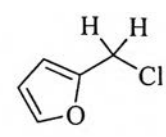
a) %Yield of recovered ethyl mandelate

The characteristic ^{1}H-NMR spectral assignment of the desired chlorides and the corresponding phosphonium compounds of the crude mixture is presented below.

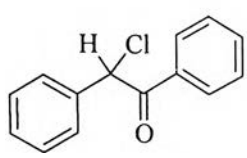
- Alkyl chlorides



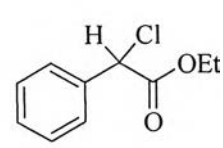
δ_H 4.36 (s) [103]



δ_H 4.47 (s) [104]

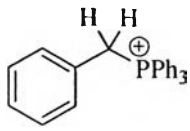


δ_H 6.33 (s) [105]

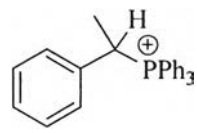


δ_H 5.30 (s) [106]

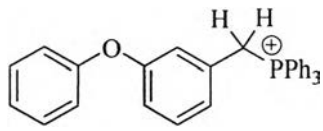
- Alkyl phosphonium compounds



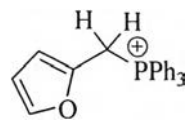
δ_H 4.87 (d, J = 14.4 Hz) [107]



δ_H 5.14 (m) [108]



δ_H 4.91 (d, J = 14.5 Hz)

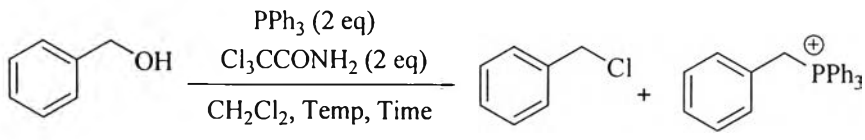


δ_H 5.00 (d, J = 13.3 Hz) [109]

Upon treating with PPh_3/Cl_3CCONH_2, (3-phenoxy)benzyl alcohol containing benzylic position still yielded the corresponding chloride and phosphonium compound in 72% and 24% yields, respectively (entry 2). The similar result was obtained when furfuryl alcohol was converted to the desired product (entry 4). It was confirmed that benzylic effect should be influenced by S_N1 to generate benzylic carbocation which was further converted to phosphonium compound by nucleophilic substitution of PPh_3. Surprisingly, the chlorination of benzil and ethyl mandelate gave only the corresponding chloride in good to excellent yields (entries 5-6) whereas the corresponding phosphonium compound could not be detected. This observation gave informative clues that the benzylic carbocation of this type was generated with difficulty since the destabilization of benzylic carbocation by electron-withdrawing carbonyl group mainly occurred.

In addition, it was observed that the formation of alkyl chloride in the case of benzylic alcohols, *e.g.* benzyl alcohol did not completely proceed under standard conditions. With the aim to improve the yield of the desired alkyl chloride using benzyl alcohol as model, a series of experiments was carefully explored and the results are tabulated in Table 3.6.

Table 3.6 Chlorination of benzyl alcohol

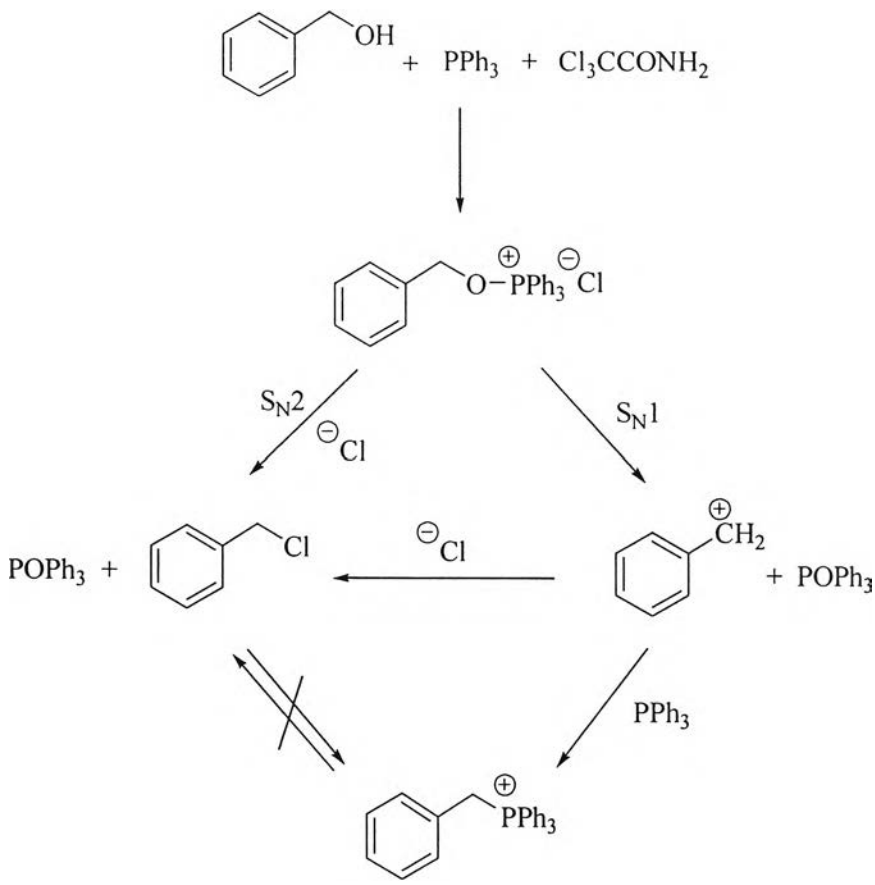


0.25 mmol

Entry	Temp (°C)	Time (min)	% Yield		Σ (%)
			RCl	$PhCH_2{}^+PPh_3$	
1	0	5	76	19	95
2	RT	15	74	27	101
3	RT	30	77	21	98
4	RT	60	80	18	98
5	40	30	86	14	100
6	40	60	86	13	99
7	RT	24 h	78	22	100

Benzyl alcohol could transform to the desired benzyl chloride in higher yield if the reaction conditions were a bit altered. This could be seen from the outcome of the experiment. Factors that controlled the yield of the desired product included the reaction temperature (entries 3 *vs* 5 and 4 *vs* 6). However, the need of higher temperature for the reaction had little effect on the selectivity to produce the corresponding chloride more than phosphonium compound for S_N2 pathway.

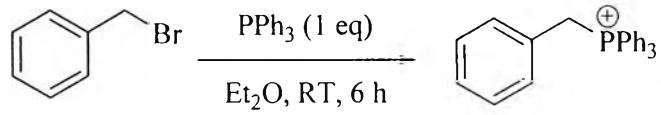
These results clearly supported that the pathway of chlorination of benzylic alcohols possibly took place competitively by two pathways between S_N1 and S_N2 following the decomposition of intermediate RO^+PPh_3. A proposed mechanistic pathway of chlorination of benzyl alcohol to benzyl chloride and benzyl phosphonium salt is displayed in Scheme 3.1.



Scheme 3.1 The proposed mechanistic pathway for chlorination of benzyl alcohol

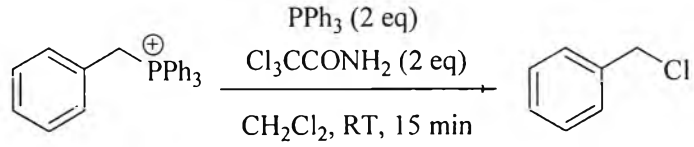
In principle, the chlorination of alcohol with the combination of PPh_3 and Cl_3CCONH_2 probably involved the formation of an intermediate phosphonium salt (RO^+PPh_3) [20]. This intermediate was believed to easily decompose to triphenylphosphine oxide ($POPh_3$), the formation of which is thermodynamic driving force for the reaction, which suffer nucleophilic attacked by chloride. The resulting benzyl chloride was obtained *via* S_N2 mechanism. On the other postulation, that intermediate could be decomposed *via* S_N1 pathway, particularly in the case of benzylic alcohols. This phenomenon can occur due to the stability of generated benzyl carbocation ($PhCH_2^+$) and $POPh_3$ and subsequently that carbocation was converted to benzyl chloride. Concomitantly, the competitive substitution could be taken place where PPh_3 reacted with benzylic carbocation formed to produce the stable phosphonium compound ($PhCH_2^+PPh_3$). In addition, this phosphonium compound was checked whether it can be converted to benzyl chloride under this developed conditions. Thus, a model substrate, $PhCH_2^+PPh_3$ was synthesized by nucleophilic substitution between benzyl bromide and PPh_3 [110]. The ^{1}H-NMR spectrum of

isolated phosphonium compound displayed multiplet signals of twenty aromatic protons at δ_H 7.00-7.76 and a doublet signal at δ_H 4.90 (J = 14.3 Hz).



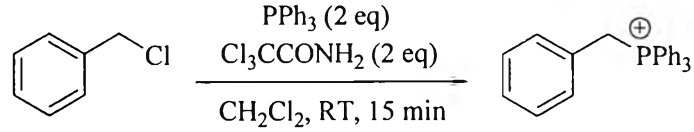
(1 eq)

The synthesized phosphonium compound was subjected to the standard chlorination (PPh_3/Cl_3CCONH_2). It was clearly found that benzyl chloride did not occur under the developed conditions (recovered benzyl phosphonium 96%, $\sum$ = 96%). It was therefore confirmed that the phosphonium compound could not be converted to benzyl chloride under this developed conditions.

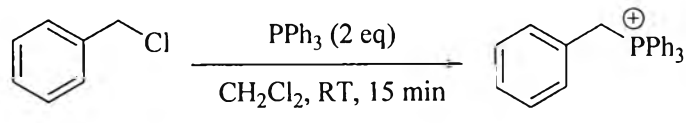


(0.25 mmol) Not detect

In addition, the conversion of benzyl chloride to benzyl phosphonium salt was also studied. Benzyl phosphonium salt was obtained in only trace amount with this developed reagent (recovered benzyl chloride 91%, $\sum$ = 93%). On the other hand, the product was not detected (recovered benzyl chloride 87%, $\sum$ = 87%) when the reaction in the absence of Cl_3CCONH_2 was examined.



(0.25 mmol) Trace



(0.25 mmol) Not detect

According to the aforementioned results, almost selected benzylic alcohols gave predominantly the desired alkyl chloride. The ratio of alkyl chloride and phosphonium product was obtained around >73 : <27, except for those alcohols having electron-withdrawing group at benzylic position. The main reason was that

this proceeding chlorination rendered to S_N2 more than S_N1 because of the destabilization of benzylic carbocation by electron-withdrawing carbonyl group. The benzylic effect should therefore be considered as one of crucial factors to be justified.

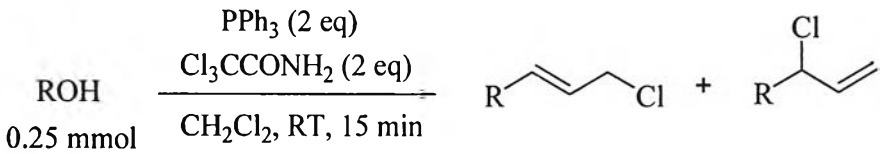
3.5.2.3 Allylic Alcohols

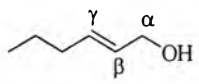
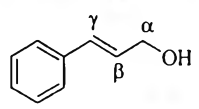
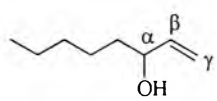
The synthesis of an allylic chloride from its alcohol presents regio- and stereochemical problems not encountered with saturated compounds with two main aspects.

1) The transformation should be regiospecific, leading exclusively to the α-substituted (or γ-substituted) product. 2) The conditions must be such that stereochemistry at the β, γ double bond is not lost.

In this present work, the chlorination of three allylic alcohols including *trans*-2-hexen-1-ol, cinnamyl alcohol and 1-octen-3-ol was examined on the effect of allylic rearrangement with PPh_3/Cl_3CCONH_2. The results are displayed in Table 3.7.

Table 3.7 Chlorination of selected allylic alcohols

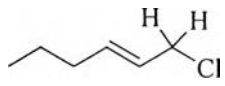


Entry	ROH	% Yield		Σ (%)
		α-Cl	γ-Cl	
1		72	-	92[a]
2		73	-	100[b]
3		69	30	99

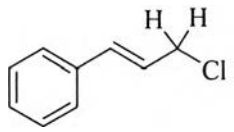
a) Unidentified product was obtained in 20%

b) Alkyl phosphonium salt was obtained in 27%

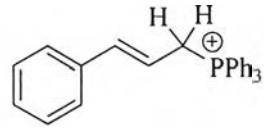
The presence of allylic chlorides and alkyl phosphonium salts was determined by ^{1}H-NMR spectroscopic technique of the crude mixture. The selected ^{1}H-NMR spectral assignment of these compounds is shown below.



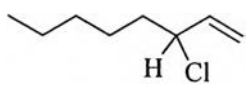
δ_H 3.84 (t, J = 7.0 Hz) [111]



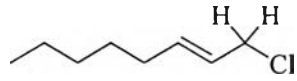
δ_H 4.07 (d, J = 5.2 Hz) [112]



δ_H 4.52 (dd, J = 15.3 Hz) [113]

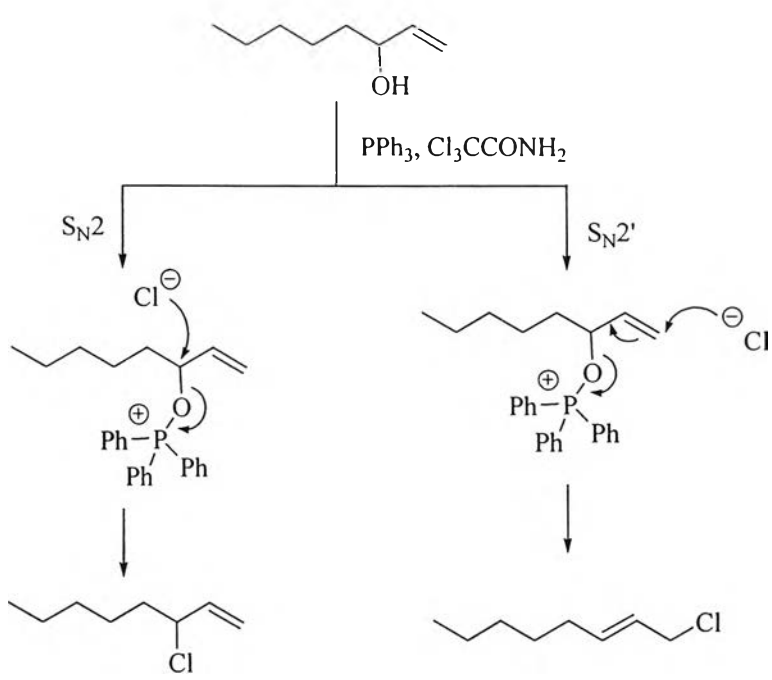


δ_H 4.33 (q, J = 7.3 Hz) [114]



δ_H 4.03 (d, J = 7.1 Hz) [115]

From the attained results, the high regioselectivity of the system was disclosed. For *trans*-2-hexen-1-ol and cinnamyl alcohol, the corresponding allylic chlorides were obtained in high yields without the rearrangement of carbon skeleton (entries 1-2). This was considered that the proceeding chlorination of these allylic alcohols was transformed to more stable alkene (S_N2). Therefore, the competitive pathway (S_N2') to generate the rearranged product was difficultly occurred. The same trend could be seen in the case of 1-octen-3-ol (entry 3). The unrearranged allylic chloride was predominated (S_N2), although γ-substituent which produced more stable alkene allowed substantial quantity of rearranged product to form (S_N2'). This chlorination was considered to proceed through two competitive pathways between S_N2 and S_N2' as shown below.



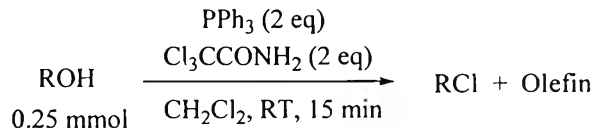
Generally, the desired allylic chloride was obtained from the decomposition of the intermediate phosphonium salt *via* S_N2 displacement. Concomitantly, this intermediate could competitively be decomposed by chloride attack to furnish the formation of more stable allylic chloride *via* S_N2' displacement. However, the α-Cl/γ-Cl ratio was found to be 3/1. It was therefore concluded that the use of developed reagent still proceeded *via* S_N2 prevailly (not depended on the stability of alkene group).

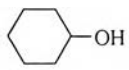
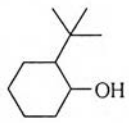
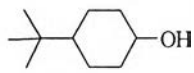
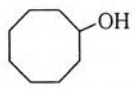
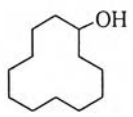
Several procedures have been described for the conversion of allylic alcohols into allylic chlorides with predictable stereo- and regiochemistry, but none is generally applicable to all types of substitution patterns [116]. This combination of PPh_3/Cl_3CCONH_2 provided a partial solution to this synthetic problem 1) allylic alcohols afforded good yields of largely unrearranged chloride. 2) the geometry of the β-γ double bond was preserved.

3.5.2.4 Cyclic Alcohols

The chlorination of cyclic alcohols such as cyclohexanol and cyclododecanol (Table 3.4) seemed to be superseded by the formation of alkene products together with the corresponding alkyl chloride. Thus, the reagent role played by PPh_3/Cl_3CCONH_2 in the elimination reaction was also confirmed by examining the reaction of cyclic alcohols. The results are accumulated in Table 3.8.

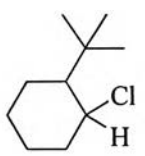
Table 3.8 Chlorination of selected cyclic alcohols



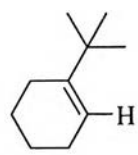
Entry	ROH	% Yield		Σ
		RCl	Olefin	(%)
1		37	15	52
2		26	78	104
3		76	28	104
4		56	40	96
5[a]		42	57	104

a) Reaction time 60 min was used

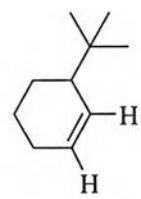
All cyclic chlorides and corresponding olefins were quantified by ^{1}H-NMR spectroscopy from the crude mixture. The selected ^{1}H-NMR spectral assignment of these compounds is shown below.



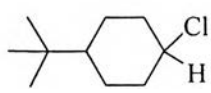
δ_H 4.20 (br) [117]



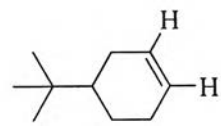
δ_H 5.31 (br) [118]



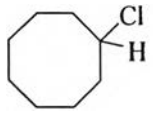
δ_H 5.56 (br) [119]

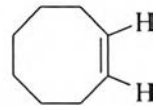


δ_H 4.25 (m) [120]



δ_H 5.45 (br) [121]



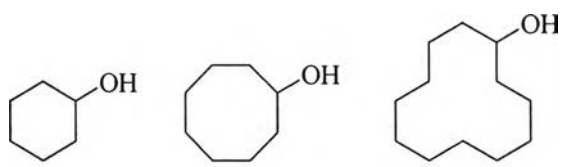


δ_H 4.03-4.08 (m) [122]

δ_H 5.43-5.46 (m) [123]

The olefinic products were detected in the chlorination of cyclic alcohols with almost equal amount to the alkyl chloride present (entries 1-5). This implied that the reaction may competitively proceeded *via* two major pathways as substitution *vs* elimination. The α-bulky substituent of cyclohexanol yielded the corresponding cyclic chloride in low yield, whereas cyclohexanol containing γ-bulky substituent could be transformed to the corresponding cyclic alkyl chloride in high yield (entries 2-3). This was clearly explained that the steric hindrance of substituent affected on the rate of the substitution by chloride ion. In the other words, elimination to olefin could be predominantly competed.

Furthermore, the reactivity of the chlorination of cyclic alcohols on ring size was examined. It was found that cyclohexanol could be converted to the corresponding cyclohexyl chloride in higher yield than cyclooctanol and cyclododecanol, respectively (entries 1, 4 and 5). This result could be seen from by the ratio of S_N2/E_2 as shown below.

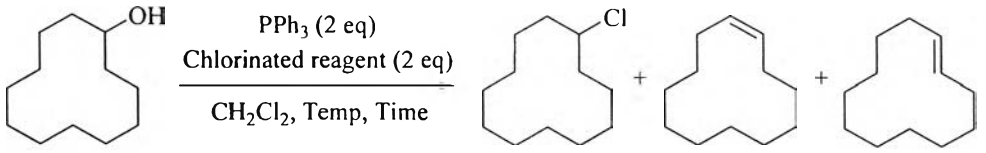


S_N2/E_2 2.47 1.40 0.74

From the above results, it could be disclosed that the chlorination of cyclic alcohols with developed reagent depended greatly on steric hindrance of substituent group and ring size.

The competitive reaction between chlorination (S_N2) and elimination (E_2) of cyclic alcohol was further examined by using cyclododecanol as a probe. The reaction conditions such as reaction times and temperatures, type of halogenated reagents and bases were varied to gain some information of this competitive pathway. The results are tabulated in Table 3.9.

Table 3.9 Chlorination of cyclododecanol



0.25 mmol

Entry	Chlorinated reagent	Temp (°C)	Time (min)	% Yield			Σ (%)
				RCl	Olefin	RO^+PPh_3	
1		0	60	26	39	38	103
2		RT	15	26	43	31	100
3	Cl_3CCONH_2	RT	60	42	57	-	99
4		40	30	32	44	24	100
5		40	60	44	56	-	100
6[a]		RT	60	46	54	-	100
7		0	15	45	54	-	100
8	Cl_3CCN	RT	15	50	55	-	105
9		RT	60	48	53	-	101
10		40	60	47	53	-	100
11	$Cl_3CCONHPh$	RT	60	40	66	-	106
12	Cl_3CCCl_3	RT	60	49	52	-	101

a) Pyridine 2 eq was added after the reaction progressed for 15 min

Cyclododecyl chloride was obtained in slightly lower yield than the olefinic products (*cis*, δ_H 5.17 & *trans*, δ_H 5.22) (entries 1-2). Low temperature did not affect on this competitive pathway. The chlorination of cyclododecanol was not proceeded completely when the reaction was examined within short reaction time. This result could be checked from the ^{1}H-NMR spectrum of the crude mixture. It was found that the ^{1}H-NMR signal of phosphonium salt intermediate was manifestly detected at δ 4.45 (Fig 3.6).

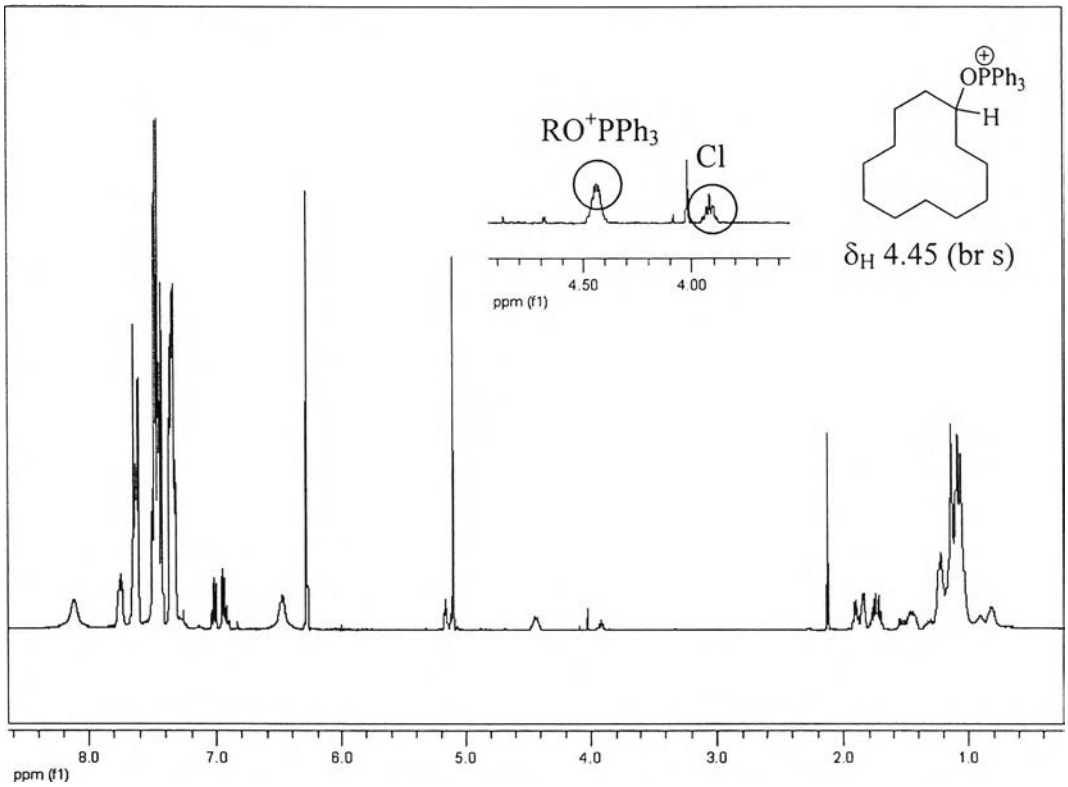


Figure 3.6 ^{1}H-NMR spectrum of the reaction mixture from the chlorination of cyclododecanol at 15 min

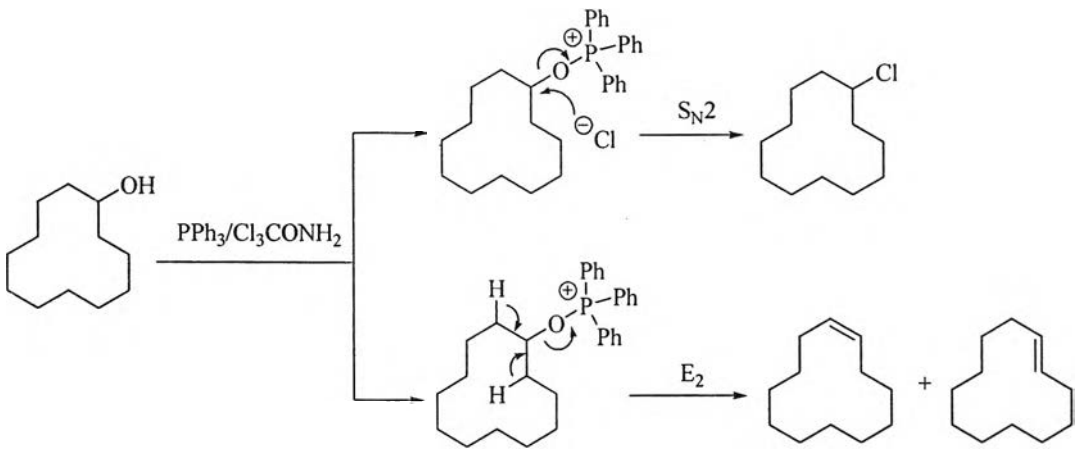
However, this signal disappeared when the longer period of the reaction was used such as 60 min (entry 3). Surprisingly, the use of Cl_3CCN instead of Cl_3CCONH_2, the phosphonium salt intermediate was not detected even the reaction time of 15 min was examined (entries 1 *vs* 7 and 2 *vs* 8). This implied that the chlorination of cyclododecanol with PPh_3/Cl_3CCN could be taken place readily and yielded to cyclododecyl chloride faster than the use of PPh_3/Cl_3CCONH_2. The reactivity of this chlorination reagent was carefully studied and will discuss in the next topic.

Cyclododecanol could be completely transformed to cyclododecyl chloride and *cis*- and *trans*-cyclododecene if the reaction conditions were a bit altered. The parameter influenced the formation of cyclododecyl chloride in this particular case was greatly depended upon the need of longer period of time for the reaction between the phosphonium salt generated and chloride anion. The yield of cyclododecyl chloride could therefore increase from 26% (entry 2) to 42% under modified reaction conditions (entry 3). However, the complete reaction still yielded olefinic products higher than cyclododecyl chloride. The outcome suggested that the cyclic

phosphonium salt proceed with E_2 more easily than S_N2 pathway. In addition, the more reactive halogenated reagent as PPh_3/Cl_3CCN was separately studied and found that no selectivity was still observed (entries 7-10).

Moreover, other three factors studied did not control the selectivity of S_N2 and E2: 1) refluxing temperature (40 °C) (entry 5) 2) Cl_3CCN, Cl_3CCCl_3 or $Cl_3CCONHPh$ as halogenated reagent (entries 7-12) and 3) the addition of pyridine (entry 6).

According to the aforementioned results, it could be concluded that two competitive pathways to generate cyclododecyl chloride and olefin not depend on reaction temperature, halogenated reagents and base. From this postulation, the selectivity of the reaction was rationally controlled by steric hindrance of phosphonium salt intermediate. The bulky intermediate was decomposed to the olefin by E2 pathway easier than the formation of alkyl chloride by S_N2 pathway. The proposed competitive pathway is shown below.



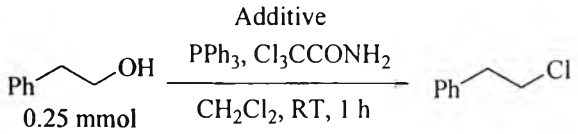
Ratio *cis-* / *trans-* = 37/73

3.5.3 Mechanistic Study

3.5.3.1 Effect of External Nucleophile

The effect of external nucleophiles such as sodium chloride (NaCl) and trimethylsilyl azide ($TMSN_3$) was carefully examined. The results are displayed in Table 3.10.

Table 3.10 Effect of external nucleophile



Entry	Ratio[a] (eq)	Additive (eq)	Temp (°C)	% Yield	Recovered alcohol (%)	Σ (%)
1[b]	1:1	-	RT	53	50	103
2	1:1	NaCl (5)	RT	51	44	95
3	1:1	NaCl (5)	40	60	36	96
4[b]	2:2	-	RT	quant	-	100
5[c]	2:2	$TMSN_3$ (1.5)	40	93	trace	93
6	2:2	$TMSN_3$ (1.5)	40	12	86	100

a) Ratio of PPh_3/Cl_3CCONH_2

b) The reaction time was 15 min

c) $TMSN_3$ was added after the reaction progressed for 15 min

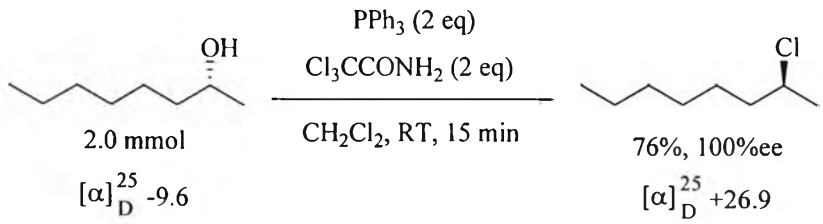
Surprisingly, NaCl as external chloride could not assist the increment of %yield of the corresponding alkyl chloride at both reaction temperatures (entries 2-3). Similarly, the alkyl chloride is still a predominant product without concomitant formation of alkyl azide when $TMSN_3$ as external azide was added (entries 5-6). This strongly implies that the ion pair intermediate formed is so tight that it could not react with added nucleophile [124]. Nonetheless, the desired alkyl chloride was obtained in low yield when $TMSN_3$ was added before the started reaction (entry 6). Probably, the intermediate derived from the combination of PPh_3/Cl_3CCONH_2 may react with $TMSN_3$ rapidly and destroyed the reactivity of the active species generated.

3.5.3.2 Stereochemistry Study

Stereochemistry study of this developed method was performed by using an optically active substrate, (-)-(R)-2-octanol.

A stirred solution of (-)-(R)-2-octanol (1 eq) and PPh_3 (2 eq) in dry CH_2Cl_2 (4 mL) was successively added selected halogenated reagent (2 eq) at room temperature (30 °C) under N_2 atmosphere. After 15 min, the reaction was quenched

by cold water and purified by quick column chromatography on silica gel (eluent: hexane) to give (+)-(S)-2-octyl chloride in 76% yield.



The ^{1}H-NMR spectrum (Fig 3.7) of isolated (+)-(S)-2-octyl chloride displayed a sextet signal of methine proton at δ_H 4.01 (J = 6.5 Hz) and two multiplet signals around δ_H 1.69 and 1.28-1.50 of thirteen protons. A triplet signal of methyl group occurred at δ_H 0.89 (J = 6.7 Hz).

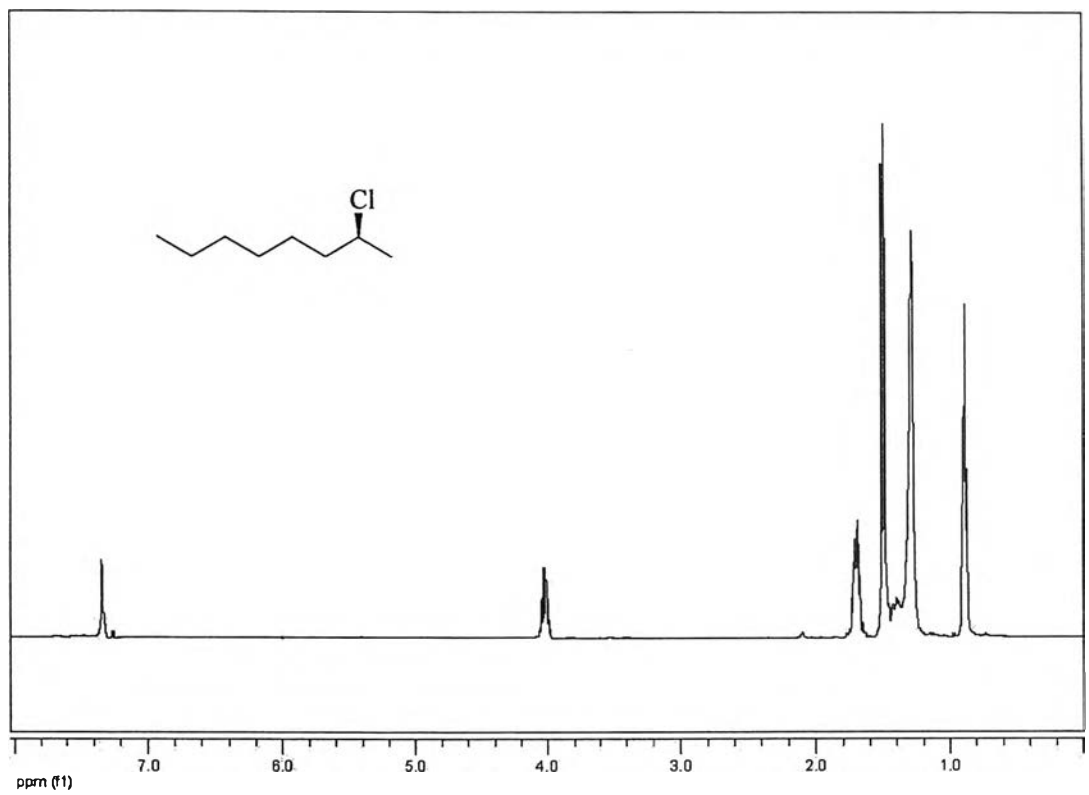


Figure 3.7 ^{1}H-NMR spectrum of (+)-(S)-2-octyl chloride

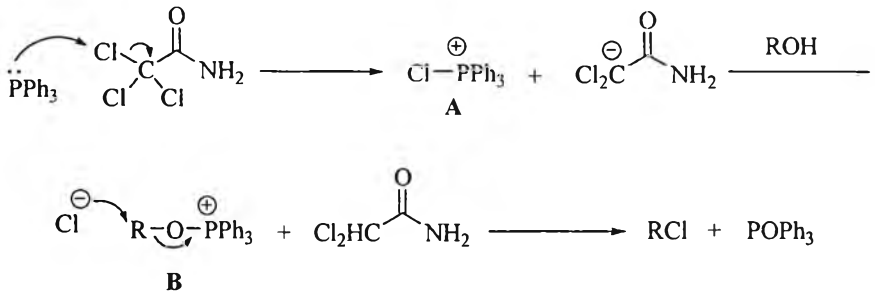
Under the standard protocol, a chiral alcohol ($[\alpha]_D^{25}$ -9.6, c = 0.97, $CHCl_3$) could be successfully transformed into the enantiomerically enriched (+)-(S)-2-octyl chloride ($[\alpha]_D^{25}$ +26.9, c = 0.58, $CHCl_3$) in good isolated yield with perfectly complete inversion of configuration. Moreover, the stereochemistry of the chlorination product was also determined by HPLC using commercially available

chiral column (cyclobond I 2000). Only one isomer of (+)-(S)-2-octyl chloride was detected. The HPLC result was confirmed by comparison with (-)-(R)-2-octyl chloride derived from the chlorination of (-)-(R)-2-octanol using $SOCl_2$, which is a well-known method to furnish alkyl chloride with retention of configuration.

From above results, it was clearly considered that the chlorination of (-)-(R)-2-octanol using the combination of PPh_3/Cl_3CCONH_2 occurs by S_N2 mechanism.

3.5.3.3 Proposed Mechanism

It has been addressed that the mechanism for PPh_3/CCl_4 reagent to convert alcohols into alkyl chlorides involved the formation and the decomposition of the alkoxyphosphonium intermediate. The use of combination of PPh_3/Cl_3CCONH_2 was also believed to proceed in a similar manner. The proposed mechanism is shown below.



PPh_3 reacts with Cl_3CCONH_2 to give **A** which then reacts with alcohol to give alkoxyphosphonium salt (**B**), the formation of which is thermodynamic driving force for the reaction, which suffer nucleophilic attack by the chloride. In the last step, that intermediate eventually decomposes to give alkyl chloride and phosphine oxide *via* inversion of configuration by S_N2 displacement. However, in some specific cases the mechanism of chlorination of alcohol still depends on types of alcohols. For example, the competitive reaction between S_N2 *vs* S_N1 and S_N2 *vs* E_2 were manifestly observed when benzylic and cyclic alcohols were used, respectively.

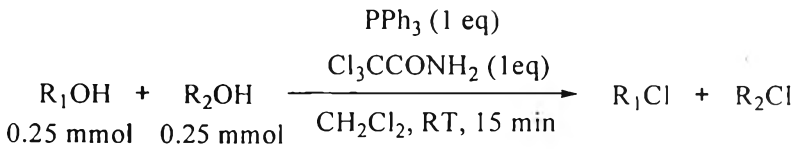
3.5.4 Reactivity Study

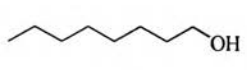
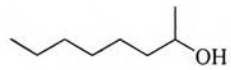
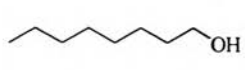
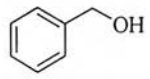
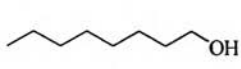
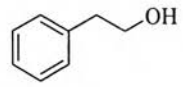
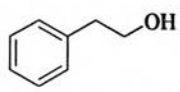
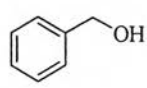
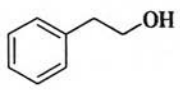
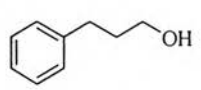
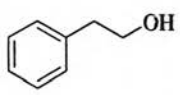
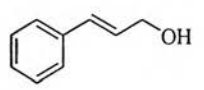
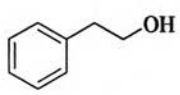
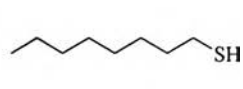
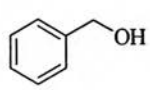
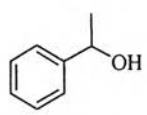
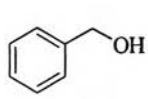
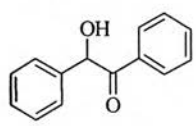
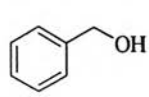
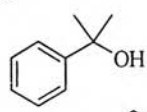
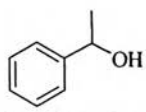
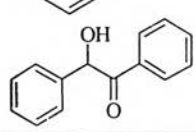
3.5.4.1 Alcohols

The relative reactivity of PPh_3/Cl_3CCONH_2 with various alcohols was further studied by competing two selected alcohols in the same reaction vessel.

A stirred solution of two selected alcohols (1 eq each) in dry CH_2Cl_2 (0.5 mL) were successively added PPh_3 (1 eq) and Cl_3CCONH_2 (1 eq) under standard conditions. The results are accumulated in Table 3.11.

Table 3.11 Reactivity study of selected alcohols



Entry	R_1OH	R_2OH	% Yield R_1Cl/R_2Cl	Recovered alcohol (%) R_1OH/R_2OH	Σ (%)
1			43/0	56/84	100/84
2			36/12	64/78	100/90
3			27/17	70/83	97/100
4			25/2	75/97	100/99
5			15/21	77/77	92/98
6			26/36	77/64	103/100
7			39/0	61/96	100/96
8			35/0	65/99	100/99
9			32/0	61/97	93/97
10			17/6	57/23	91[a]/87[a,b]
11			44/0	49/98	93/98

a) Unidentified product was obtained in 17% yield

b) Olefin product was obtained in 38% yield

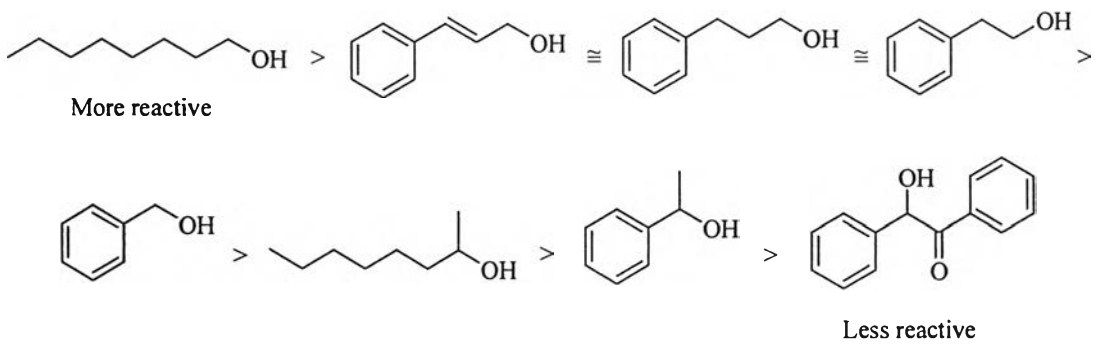
Long chain aliphatic primary and secondary alcohols (1-octanol *vs* 2-octanol) were first chosen to examine the reactivity study towards PPh_3/Cl_3CCONH_2. 1-Octyl chloride was obtained in 43% yield whereas 2-octyl chloride was not detected (entry 1). This result gave an informative clue that the chlorination of primary alcohol was more reactive than that of secondary alcohol under developed system. Furthermore, long chain aliphatic alcohol as 1-octanol could still be converted to the desired 1-octyl chloride in predominant yield compared with benzyl alcohol and 2-phenylethanol (entries 2-3). These results clearly supported that the mechanism of chlorination under developed conditions took place *via* S_N2 displacement.

The comparative reactivity study of primary alcohols containing various functional groups such as carbon chain length, benzylic and C=C was also conducted using 2-phenylethanol as a model. It was clearly found that the carbon chain length did not affect on the reaction since the competitive chlorination between 2-phenylethyl and 3-phenylpropyl chlorides furnishing in approximate yields (entry 5). The same result was also obtained in the case of C=C present (entry 6). On the other hand, benzylic alcohol showed less reactivity than 2-phenylethanol under developed system (entry 4). In addition, the reactivity study of alcohol was extended to compare with 1-octanethiol. Surprisingly, only 2-phenylethyl chloride was produced while 1-octyl chloride was not detected. Thus, under this particular conditions, alcohol was reacted with PPh_3/Cl_3CCONH_2 more readily than thiol.

The chlorination of primary, secondary and tertiary benzylic alcohols was also examined to compare the reactivity of these alcohols under developed conditions. Only benzyl alcohol was smoothly transformed to benzyl chloride whereas the corresponding alkyl chlorides from 1-phenylethanol and benzoin were not detected (entries 8-9). The high reactivity of benzyl alcohol was again observed when the competitive chlorination between benzyl alcohol and 2-phenyl-2-propanol was examined (entry 10). It was clearly confirmed that the chlorination of primary benzylic alcohol yielded the desired chloride more than secondary and tertiary ones. Moreover, the reactivity comparison of both unreactive secondary benzylic alcohols in entries 8 and 9 was reexamined to explore the effect of α-substituent. 1-Phenylethanol could readily proceed to give 1-phenylethyl chloride while 2-chloro-2-phenylacetophenone did not detect under this competitive condition (entry 11). This was considered that the alcohol containing electron donating group (methyl) at

α-position assisted the conversion to the corresponding alkyl chloride faster than that bearing electron-withdrawing group (carbonyl). Although, the two competitive pathways between S_N1 and S_N2 were occurred in the case of benzylic alcohols, the predominant reaction still proceeded *via* S_N2 mechanism.

According to the aforementioned results, the reactivity of alcohols with PPh_3/Cl_3CCONH_2 could clearly be concluded: 1) primary alcohols appear to be the most reactive under developed system supporting the S_N2 mechanism 2) aliphatic alcohols are more reactive than benzylic alcohols and 3) compounds containing electron donating substituent at benzylic position are more reactive than those with electron-withdrawing substituent. The order of reactivity of alcohols is displayed below.



3.5.4.2 Halogenated Reagents

The reactivity of Cl_3CCONH_2 and other chlorinated reagents was also investigated using a competitive reaction between brominated and chlorinated reagents towards alcohol. The reactivity of selected chlorinated reagents was rationalized by the obtained yield ratio of alkyl bromide and chloride.

2-Phenylethanol (1 eq) was added to a mixture of Br_3CCO_2Et (0.75 eq) and selected chlorinated reagent (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 in the crude mixture with the addition of toluene as an internal standard. The example of the competitive reaction between Br_3CCO_2Et and $Cl_3CCOCCl_3$ for 2-phenylethanol is presented in Fig 3.8. The comparative reactivity results of chlorinated reagents are shown in Table 3.12.

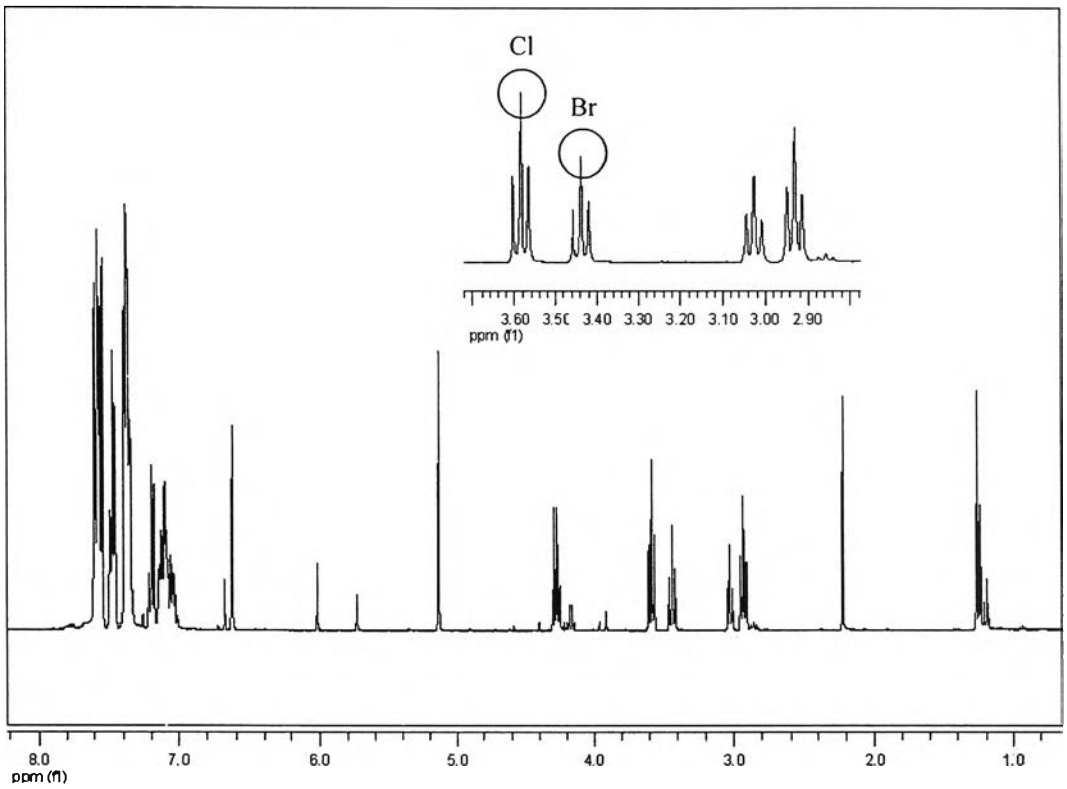
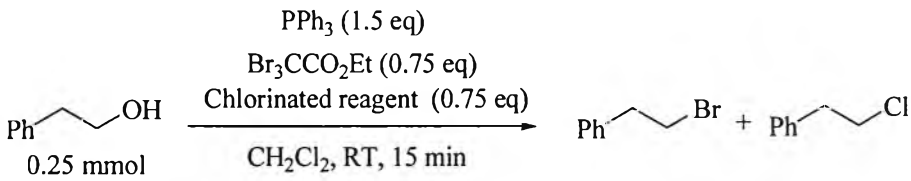


Figure 3.8 ^{1}H-NMR spectrum of 2-phenylethyl chloride and 2-phenylethyl bromide in the crude mixture from the competitive reaction of $Cl_3CCOCCl_3$ and Br_3CCO_2Et

Table 3.12 Reactivity comparison of selected halogenated reagent



Entry	Chlorinated reagent	% Yield		RCl/RBr	Reactivity[a]
		RCl	RBr		
1	Cl_3CCCl_3	2	98	0.02	2
2	$Cl_3CCOCCl_3$	62	38	1.63	163
3	Cl_3CCN	48	52	0.92	92
4	Cl_3CCO_2Et	2	98	0.02	2
5	Cl_3CCONH_2	1	99	0.01	1
6	$Cl_3CCONHPh$	1	99	0.01	1

a) Based on Cl_3CCONH_2

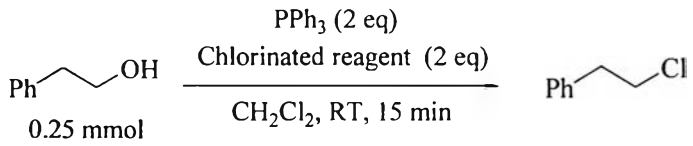
The reagents in entries 1-4 have been previously utilized for conversion of alcohols into alkyl chlorides; nevertheless no data cited on the relative reactivities of these reagents. $Cl_3CCOCCl_3$ and Cl_3CCN (entries 2 and 3), a reagent bearing strongly electron-withdrawing group showed the high reactivity of 163 and 92 fold over Cl_3CCONH_2, respectively. On the other hand, Cl_3CCONH_2, a developed reagent displayed the same level of reactivity Cl_3CCCl_3, Cl_3CCO_2Et and $Cl_3CCONHPh$ (entries 1 and 4-6).

Considering the reactivity of chlorinated reagents on the formation of alkyl chloride, it was observed that the reactivity of chlorinating agent was greatly depended on type of the electron-withdrawing substituent on chlorinated reagents as $-COCCl_3 > -CN > -CCl_3 \cong -CO_2Et > -CONH_2 \cong -CONHPh$. This postulation can be used as a fundamental concept for the development of new efficient halogenated reagents.

Nowadays, the cost of reagent is one of the important factors to be seriously considered in organic synthesis. The practical synthetic reaction must offer high yield of the desired product using non-toxic and inexpensive reagents. Although, Cl_3CCONH_2 showed relatively lowest reactivity compared with other chlorinated reagents, it was still recognized as a new suitable chlorinated reagent judging from both cheap price and high %yield of the desired chloride achieved.

In addition, ethyl tri-, di- and mono-chloroacetates were chosen to explore their reactivities as chlorinated reagent models for the chlorination of 2-phenylethanol under optimized conditions. The results are shown in Table 3.13.

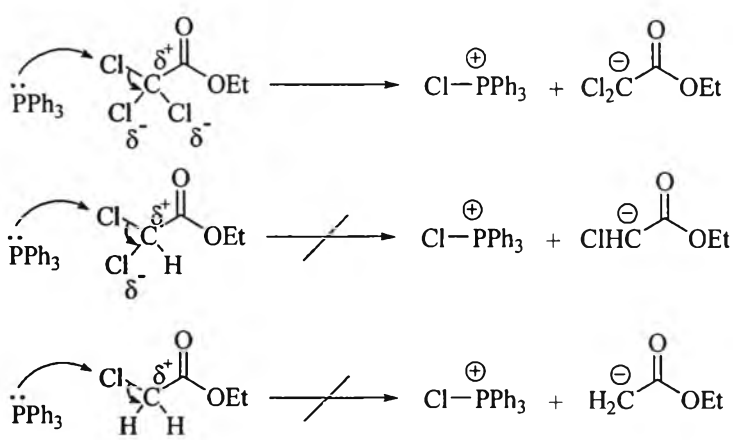
Table 3.13 Effect of ethyl tri-, di- and mono-chloroacetates for the chlorination of 2-phenylethanol



Entry	Chlorinated reagent	% Yield	Recovered alcohol (%)	Σ (%)
1	Cl_3CCO_2Et	quant	-	100
2	Cl_2CHCO_2Et	0	98	98
3	$ClCH_2CO_2Et$	0	99	99

Normally, Cl_3CCO_2Et containing three chlorine atoms could convert 2-phenylethanol to the corresponding chloride in quantitative yield (entry 1). The desired product nonetheless did not obtain when Cl_2CHCO_2Et or $ClCH_2CO_2Et$ having two and one chlorine atom, respectively were used as chlorinated reagents (entries 2-3).

From this result, it was found that PPh_3 rarely reacts with both unreactive chlorinated reagents in first step because the one and two electronegative chlorine atoms possibly did not strongly polarize the carbon atom as shown below.

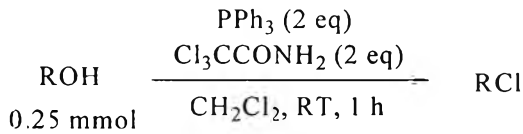


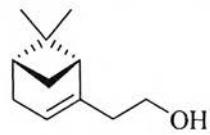
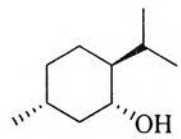
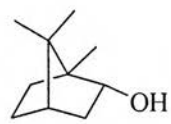
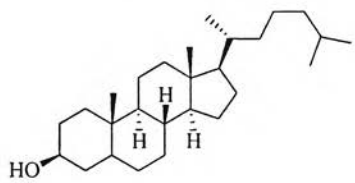
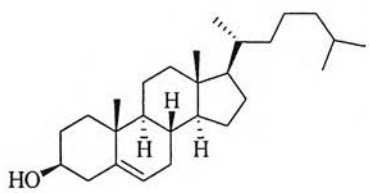
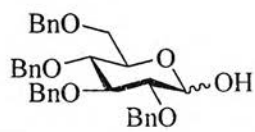
3.5.5 Applications of Developed Reagent for Chlorination of Selected Alcohols

Several naturally occurring alcohols such as (-)-nopol, (-)-menthol, (-)-borneol, (D)-glucose derivatives, cholesterol and cholestanol could be used as a good raw material. These substrates were chosen to observe whether this developed

system could be employed to convert the more complicated molecules to the corresponding alkyl chlorides. The results are presented in Table 3.14.

Table 3.14 Chlorination of natural occurring alcohols



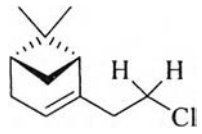
Entry	ROH	% Yield		Σ (%)
		RCl	Olefin	
1		99	-	99
2		62	43	105
3		55	45	100
4		87	-	100[a]
5		80	-	95[b]
6		88	-	88[c]

a) Unidentified product was obtained in 13% yield

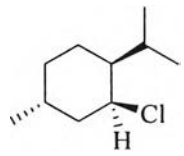
b) Unidentified product was obtained in <15% yield

c) Recovered 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose was obtained in trace amount

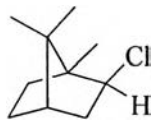
The characteristic ^{1}H-NMR spectral assignment of the corresponding alkyl chlorides in the crude mixture is presented below.



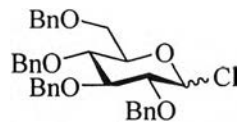
δ_H 3.37 (m) [125]



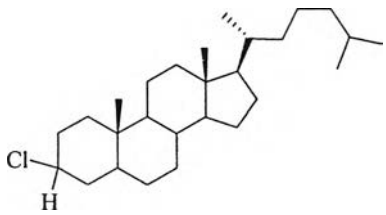
δ_H 4.51 (br s) [67]



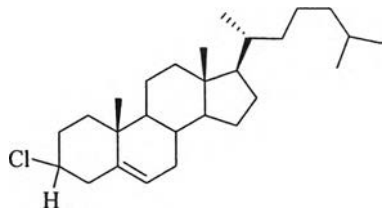
δ_H 3.95 (dd, J = 8.3, 4.6 Hz) [126]



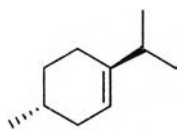
δ_H 6.11 (d, J = 3.6 Hz) [127]



δ_H 4.50 (br s) [128]



δ_H 3.76 (m), 5.37 (br) [129]



δ_H 5.52 (br s) [130]

δ_H 4.49 (s), 4.71 (s) [131]

(-)-Nopol was converted to the desired chloride in excellent yield without the rearrangement of carbon skeleton (entry 1). Natural occurring alcohols containing cyclic moiety could be transformed to the corresponding chloride in moderate to high yields (4-5). However, the elimination products were still obtained in low to moderate yields. It was hypothesized that elimination was taken place where the steric hindered at 2-position present. The product distributions of menthol and borneol were confirmed that above postulation. Moreover, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose could be easily converted to the corresponding alkyl chloride in high yield (entry 6).

In addition, three selected alcohols including (-)-nopol, benzoin and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose were reexamined for up-scale conditions (alcohol 2 mmol, PPh_3 and Cl_3CCONH_2 4 mmol each). The isolation procedure successfully furnished (-)-nopyl chloride, 2-chloro-2-phenylacetophenone and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl chloride in 74%, 50% and 51% yield, respectively.

The ^{1}H-NMR spectrum of **(-)**-nopyl chloride (Fig 3.9) displayed one broad singlet of olefin proton at δ_H 5.33. The multiplet signal at δ_H 3.46-3.54 was due to one proton adjacent to chlorine. The presence of eight protons of alkyl groups was inferred from the presence of two multiplets, one broad singlet, one triplet and one doublet at δ_H 2.35-2.44, 2.35-2.44, 2.10, 2.03 and 1.18, respectively. Two singlet signals at δ_H 1.28 and 0.84 was assigned to six protons of two methyl groups. The ^{13}C-NMR spectrum (Fig 3.10) displayed two peaks at δ_C 114.4 and 119.2 indicating two olefin carbons. Nine signals of aliphatic carbon were observed at δ_C 45.5, 42.5, 40.7, 40.2, 38.0, 31.6, 31.3, 26.3 and 21.2.

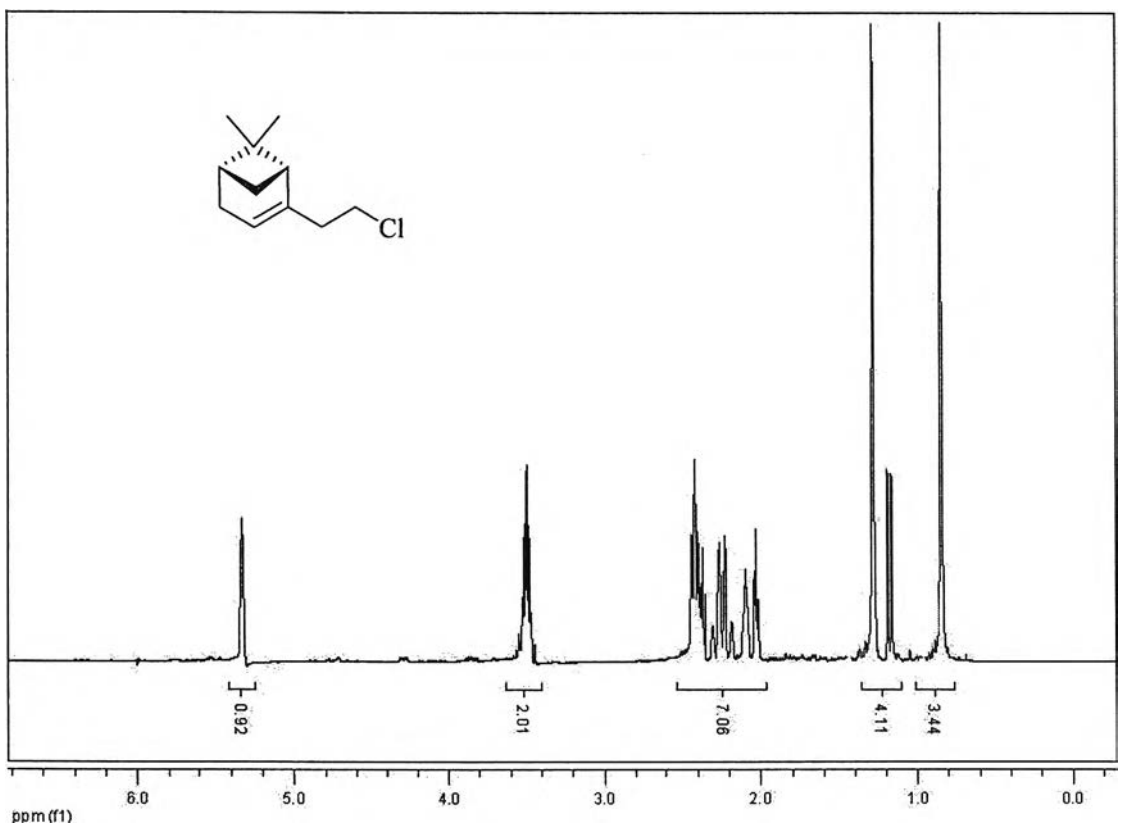


Figure 3.9 ^{1}H-NMR spectrum of **(-)**-nopyl chloride

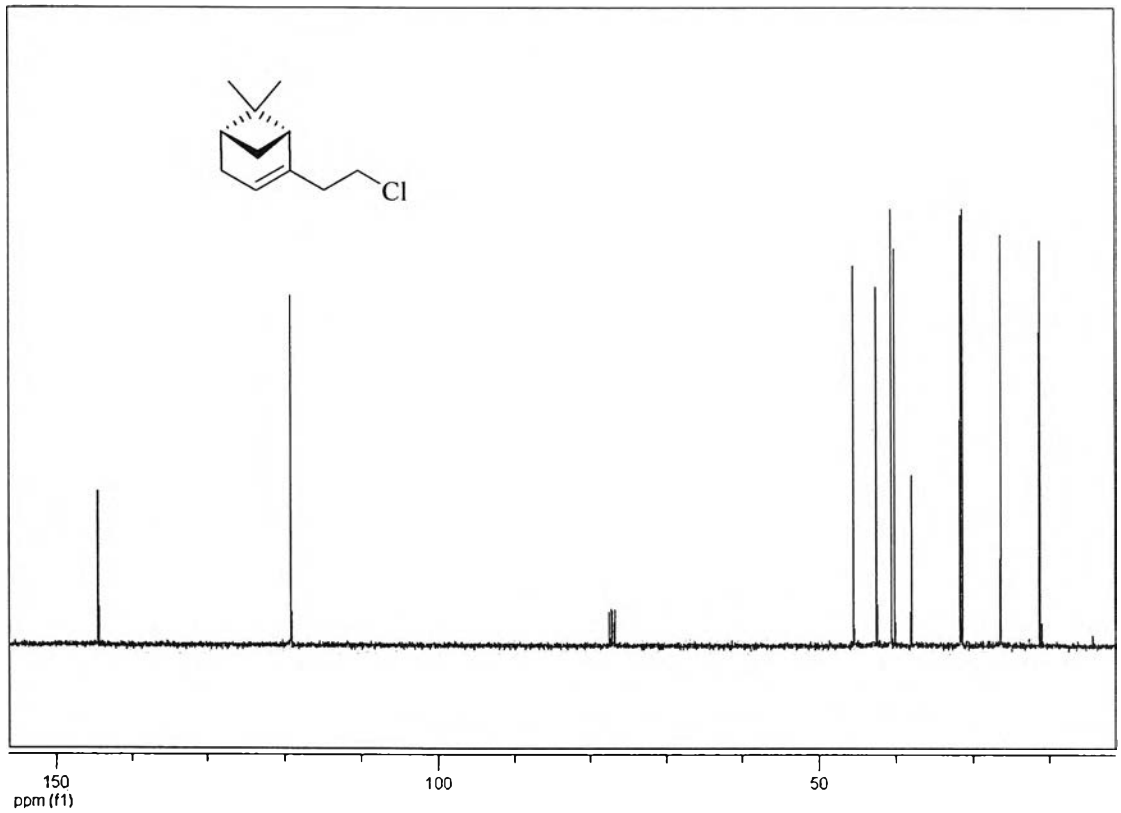


Figure 3.10 ^{13}C-NMR spectrum of (-)-nopyl chloride

The ^{1}H-NMR spectrum of 2-chloro-2-phenylacetophenone (Fig 3.11) contained a doublet signal at δ_H 7.96 of two aromatic protons. The signals around δ_H 7.32-7.55 belonged to eight aromatic protons. The singlet signal at δ_H 6.35 was ascribed to one proton connecting to chlorine atom and a carbonyl group. The ^{13}C-NMR spectrum (Fig 3.12) signified a carbonyl carbon at δ_C 191.5 and twelve aromatic carbons at δ_C 135.9, 134.3, 132.1, 129.5, 129.4, 129.3, 129.2, 129.1, 128.8, 128.7, 128.6 and 128.5. Besides, only one aliphatic carbon at δ_C 62.3 was observed.

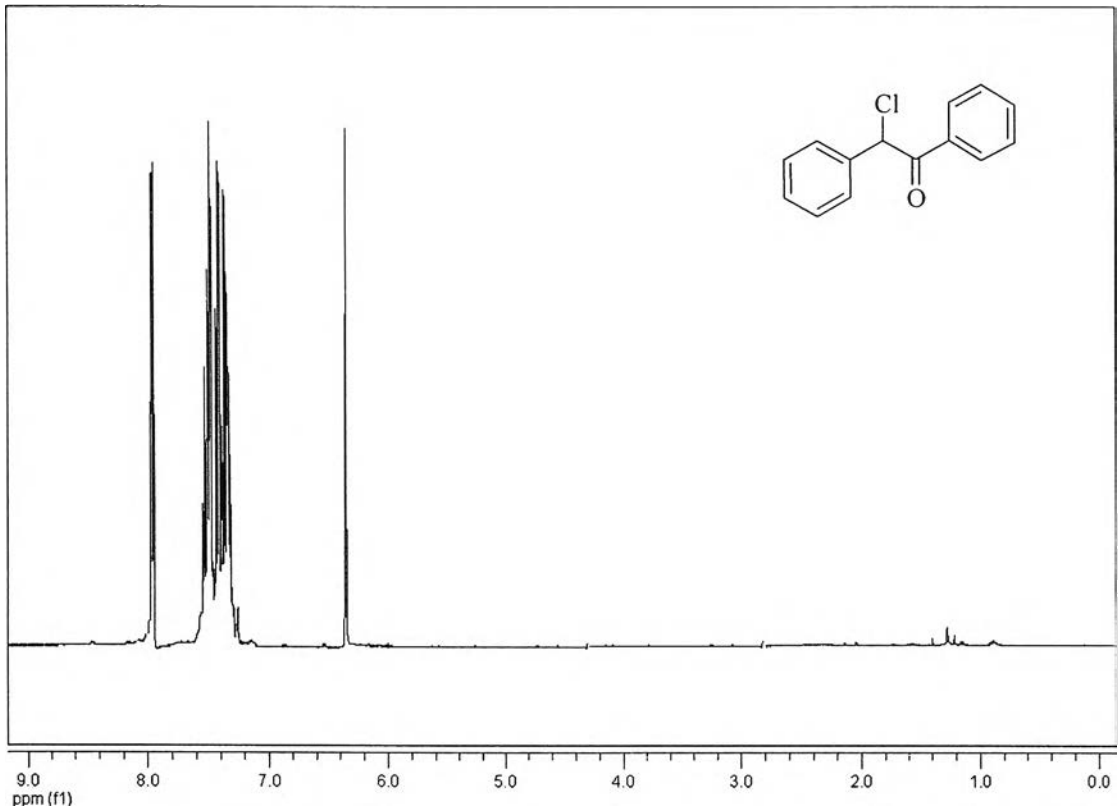


Figure 3.11 ^{1}H-NMR spectrum of 2-chloro-2-phenylacetophenone

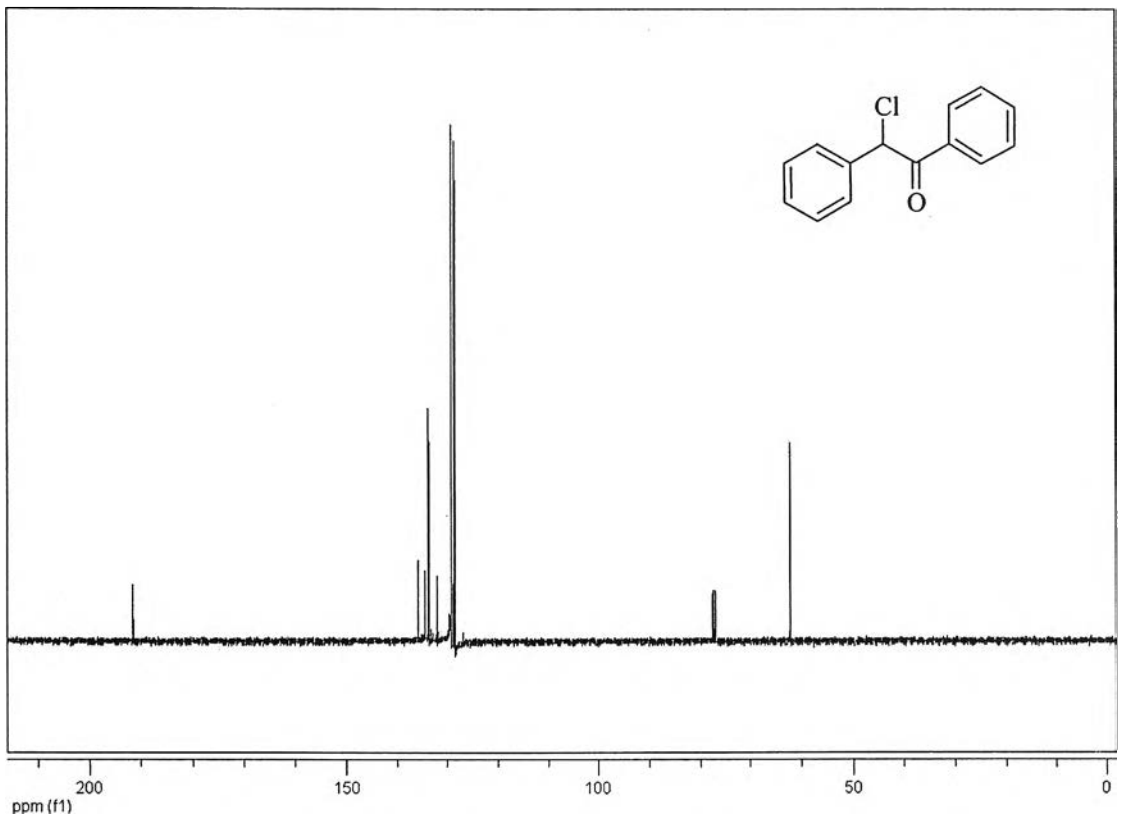


Figure 3.12 ^{13}C-NMR spectrum of 2-chloro-2-phenylacetophenone

The ^{1}H-NMR spectrum of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl chloride (Fig 3.13) displayed twenty aromatic protons as multiplet around δ_H 7.17-7.41. The signal belonging to anomeric proton was observed as broad singlet at δ_H 6.11. Four methylene protons of benzyl group of glucose derivative were detected as multiplet around δ_H 4.50-5.02. The remaining proton signals of glucose were visualized as multiplet around δ_H 3.68-4.05. The ^{13}C-NMR spectrum (Fig 3.14) showed the aromatic carbons of benzyl protecting groups around δ_C 127.7-138.5. For anomeric carbon, it was observed at δ_C 93.5. The other carbons of glucose derivative and methylene carbons could be seen around δ_C 67.7-81.4.

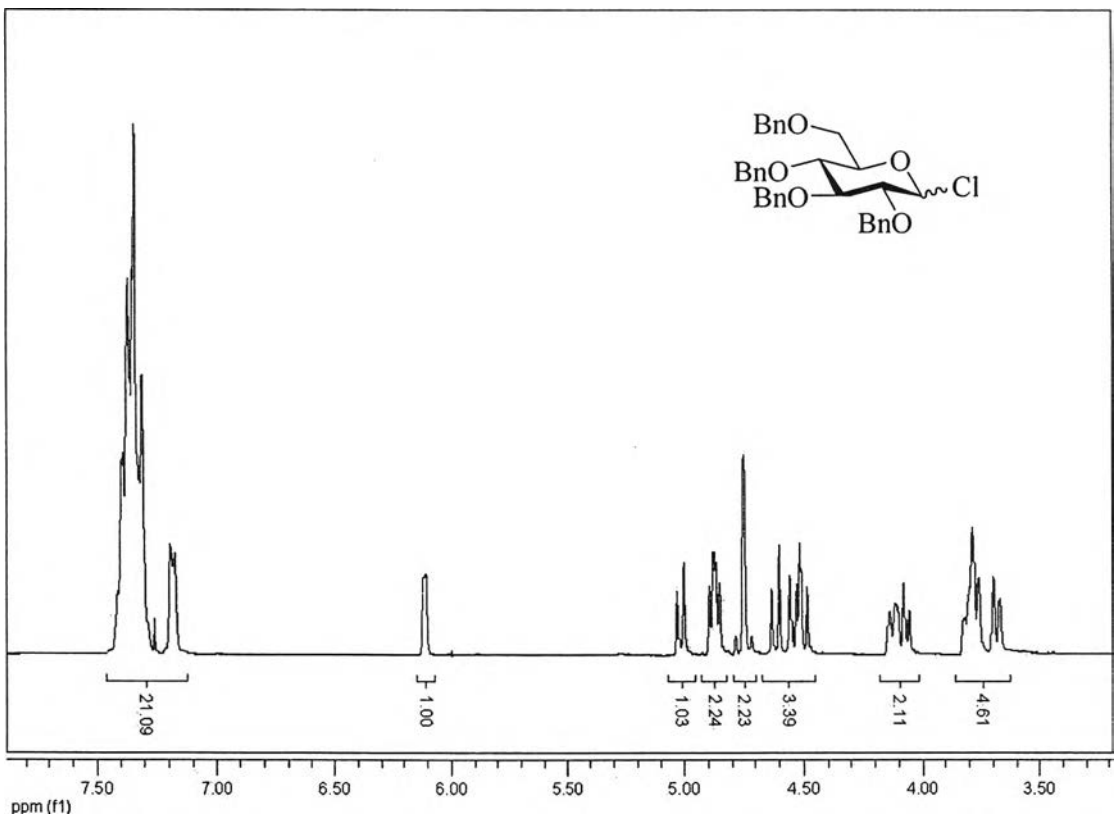


Figure 3.13 ^{1}H-NMR spectrum of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl chloride

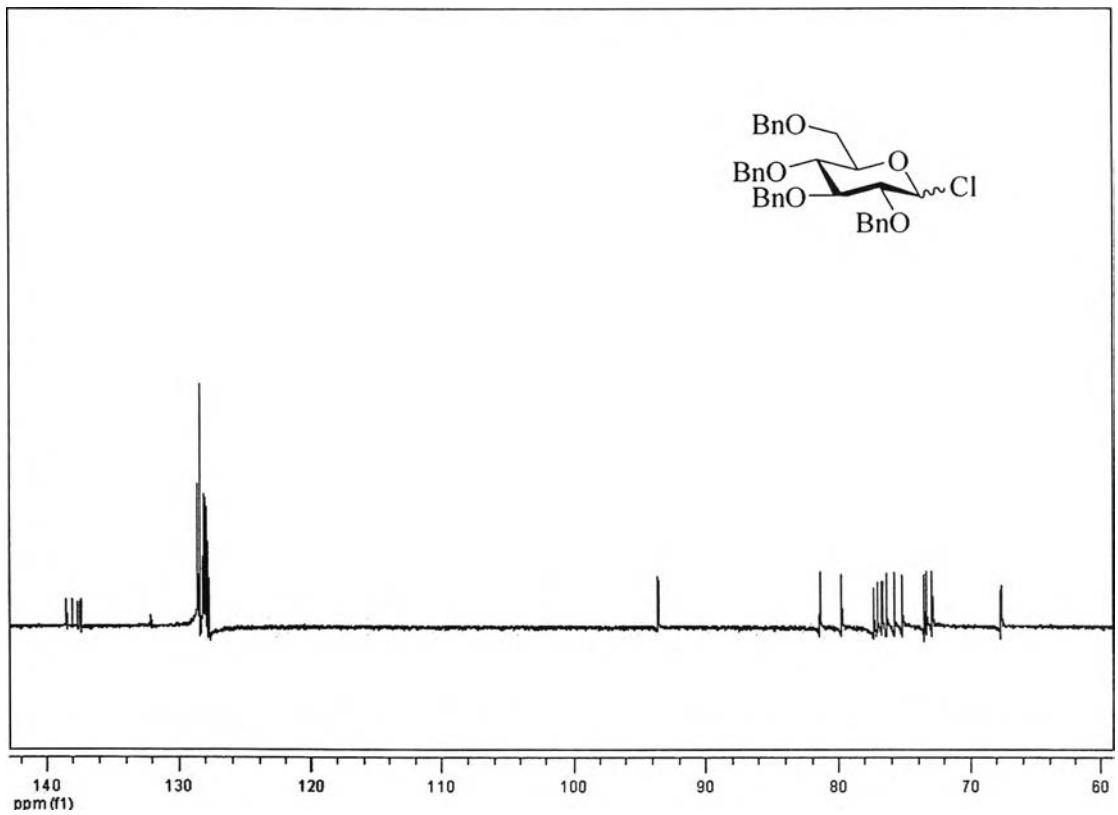


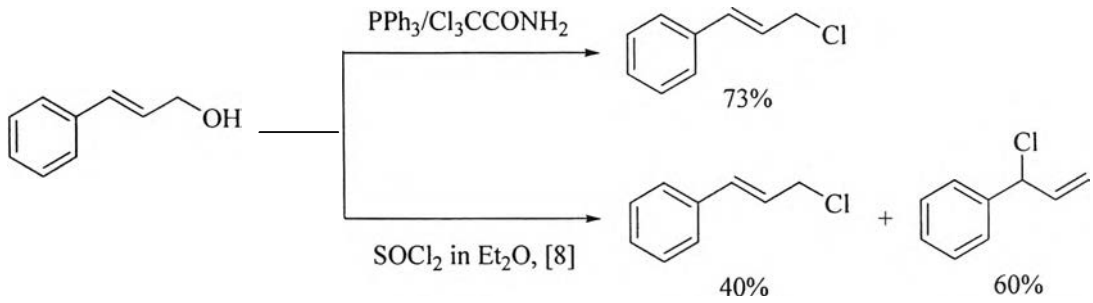
Figure 3.14 ^{13}C-NMR spectrum of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl chloride

3.5.6 Comparison of PPh_3/Cl_3CCONH_2 with Common Reagents

Even though alkyl chlorides could be prepared in high to excellent yields by cited methods using common reagents, the experimental conditions required were not very appreciated in practical sense. For instance:

3.5.6.1 $SOCl_2$

$SOCl_2$ which is one of common reagents used made the reaction conditions become acidic and required high temperature. By the consequence, by-products such as SO_2 and HCl are harmfully corrosive gases derived directly from the reaction while this developed method could be carried out under mild conditions. The complicated process of the classical procedure is the re-distillation of $SOCl_2$ every time before using. Moreover, the rearranged carbon skeleton product was observed when allylic alcohols were treated with $SOCl_2$ whereas that problem was not found utilizing the developed reagent. Cinnamyl alcohol could be used as an exampler.

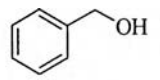
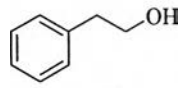
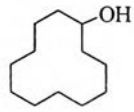
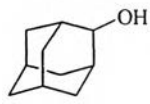
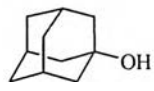


Another intriguing point is that the developed reagent is carried out under acid free conditions, thus it can produce alkyl chloride from alcohol starting material containing acid sensitive functional groups such as 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose. Nevertheless, the developed procedure has the complicated process in the purification to get rid of $POPh_3$. This disadvantage should be seriously considered and may be solved by using supported phosphine backbone [132].

3.5.6.2 $InCl_3/HSiMe_2Cl$

From the literature review, Yasuda and co-workers reported $InCl_3$-catalyzed reaction of alcohols with $HSiMe_2Cl$ in the presence of benzil. However, this chlorination still required long reaction time to completely convert alcohol to alkyl chloride in high yields. This comparative data of both reagents on the chlorination of alcohols is displayed in Table 3.15.

Table 3.15 The comparative data on the chlorination of PPh_3/Cl_3CCONH_2 and $InCl_3/HSiMe_2Cl$

Entry	ROH	PPh_3/Cl_3CCONH_2		$InCl_3/HSiMe_2Cl$ [15]	
		Time	% Yield	Time	% Yield
1		15 min	74	1 h	80
2		15 min	quant	21 h	0
3		1 h	42	15 h	59
4		15 min	quant	91 h	98
5		15 min	68	82 h	93

The developed reagent (PPh_3/Cl_3CCONH_2) could be rapidly converted primary, secondary and tertiary alcohols to the corresponding alkyl chlorides in the same or better yields with very short reaction time compared with the reported reagents (entries 1-5). Moreover, PPh_3/Cl_3CCONH_2 was clearly confirmed as the efficient chlorinated reagent more than $InCl_3/HSiMe_2Cl$, for instance in the case of 2-phenylethanol being transformed to 2-phenylethyl chloride (entry 2).

3.6 Conclusion

The objective of this present work is to search for a suitable halogenated reagent capable of transforming alcohols to its analogous chlorides. At the same time optimal conditions of this developed protocol was cautiously scrutinized. This developed methodology was indeed disclosed to be an efficient and convenient system for chlorination of alcohols under mild conditions, and provided the high yield of desired product. The cost of the reagent used was found to be superior to other related methods cited in the literature.

From this research, the optimum conditions for carbon-chlorine bond formation were disclosed: alcohol 1eq as a substrate, Cl_3CCONH_2 2 eq and PPh_3 2 eq as a combination reagent, CH_2Cl_2 0.5 mL as a solvent at room temperature within 15 min.

Various alcohols were examined to study on the chlorination effects of their alcohols under developed conditions. The characteristic of the developed system is summarized below:

1) Primary alcohols appear to be the most reactive substrate towards PPh_3/Cl_3CCONH_2 yielding exclusively the corresponding chlorides within short reaction time.
2) Aliphatic alcohols are more reactive than benzylic alcohols and alcohols containing electron donating substituent at benzylic position are more reactive than those bearing electron-withdrawing substituent.
3) The steric hindrance of secondary or tertiary alcohols affects strongly on the outcome of the reaction: a large steric interference leads to a low desired chloride and consequently to a large production of olefin.
4) Benzylic effect is possible to take place for the chlorination depending on the competitive reactions of S_N1 and S_N2.

5) Allylic alcohols afforded good yields of largely unrearranged allylic chloride except the case of terminal allylic alcohols proceeded *via* S_N2 and S_N2'.
6) Alkyl chloride is still a predominant product when the external nucleophile such as extra chloride or azide ions was introduced into the reaction.
7) The proposed mechanism for chlorination of alcohol was proceeded mainly *via* S_N2 pathway.