การเตรียมแอลคิลแฮไลด์และสารประกอบที่เกี่ยวข้องจากแอลคิลไดเฟนิลฟอสฟีไนท์แบบวันพอต

นางสาวกนกพร ฤชามณี

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

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ONE-POT PREPARATION OF ALKYL HALIDES AND RELATED COMPOUNDS FROM ALKYL DIPHENYLPHOSPHINITES

Miss Kanokporn Ruchamanee

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กนกพร ฤชามณี : การเตรียมแอลคิลแฮไลด์และสารประกอบที่เกี่ยวข้องจากแอลคิลไดเฟนิลฟอสฟีไนท์แบบวันพอต (ONE-POT PREPARATION OF ALKYL HALIDES AND RELATED COMPOUNDS FROM ALKYL DIPHENYLPHOSPHINITES) อ. ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ.ดร.วรินทร ชวศิริ, 57 หน้า.

ได้พัฒนาวิธีการเตรียมแอลคิลแฮไลด์จากแอลกอฮอล์แบบวันพอตที่มีประสิทธิภาพภายใต้ภาวะการทดลองที่ไม่รุนแรง ในกรณีของการเตรียมแอลคิลไอโอไดด์และโบรไมด์ ใช้ระบบรีเอเจนต์ผสมระหว่างคลอโรไดเฟนิลฟอสฟีนและเกลือแฮไลด์ ที่อุณภูมิห้อง 30 นาที พบว่าแอลกอฮอล์ปฐมภูมิให้ปริมาณผลิตภัณฑ์เป้าหมายในปริมาณสูงที่สุด (96-100%) รองลงมาคือทุติยภูมิ (72%) และตติยภูมิ (18-20%) ตามลำดับ สำหรับการเตรียมแอลคิลคลอไรด์ ใช้คลอโรไดเฟนิลฟอสฟีนเป็นรีเอเจนต์ ที่อุณภูมิห้อง 45 นาที พบว่า แอลกอฮอล์ปฐมภูมิให้ปริมาณผลิตภัณฑ์ในปริมาณสูงที่สุด (86-90%) รองลงมาคือทุติยภูมิ (55%) และตติยภูมิ (10%) ตามลำดับ นอกจากนี้ได้ประยุกต์วิธีสังเคราะห์แอลคิลแฮไลด์จากแอลกอออล์ในการสังเคราะห์แอลคิลไทโอไซยาเนตและแอลคิลเอไซด์แบบวันพอต พบว่าสามารถสังเคราะห์แอลคิลไทโอไซยาเนตได้ปริมาณสูง (77-80%) โดยสังเคราะห์ผ่านแอลคิลโบรไมด์จากแอลกอฮอล์ตามวิธีข้างต้น จากนั้นเติมแอมโมเนียมไทโอไซยาเนตลงในปฏิกิริยา อย่างไรก็ตามไม่ประสบความสำเร็จในการสังเคราะห์แอลคิลเอไซด์จากแอลกอฮอล์

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A mild and efficient one-pot protocol for preparing alkyl halides from alcohols was developed. In the case of the synthesis of alkyl iodides and bromides, a combination of chlorodiphenylphosphine and alkali metal salt at room temperature for 30 min was utilized. Primary alcohols yielded the target product (96-100%), secondary (72%) and tertiary alcohols (18-20%), respectively. For the preparation of alkyl chlorides, chlorodiphenylphosphine at room temperature for 45 min could be used to transform primary alcohols in the highest yield (86-90%), followed by secondary (55%) and tertiary alcohols (10%), respectively. Furthermore, this disclosed methodology for the preparation of alkyl halide from alcohol was applied for a one-pot synthesis of alkyl thiocyanates and azides. The synthesis of alkyl thiocyanates could be accomplished in high yield (77-80%) *via* alkyl bromide from alcohols as described above, followed by the addition of ammonium thiocyanate. However, the attempts to synthesize alkyl azides from alcohol were not successful.

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LIST OF ABBREVIATIONS

br s	broad singlet (NMR)
conc.	concentrated
d	doublet (NMR)
dd	doublet of doublet (NMR)
equiv.	equivalent (s)
g	gram (s)
h	hour (s)
HPLC	high performance liquid chromatography
Hz	hertz
J	coupling constant (NMR)
m	multiplet (NMR)
m.p.	melting point
MB	mass balance
min	minute (s)
mL	milliliter (s)
mmol	millimole (s)
N	normal
nm	nanometer
NMR	nuclear magnetic resonance
^{o}C	degree of Celsius
ppm	part per million
q	quartet (NMR)
quant	quantitative
RT	room temperature
s	singlet (NMR)
t	triplet (NMR)
TLC	thin layer chromatography
UV	ultraviolet
W	watt
#	amount

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%	percent
α	alpha
δ	chemical shift

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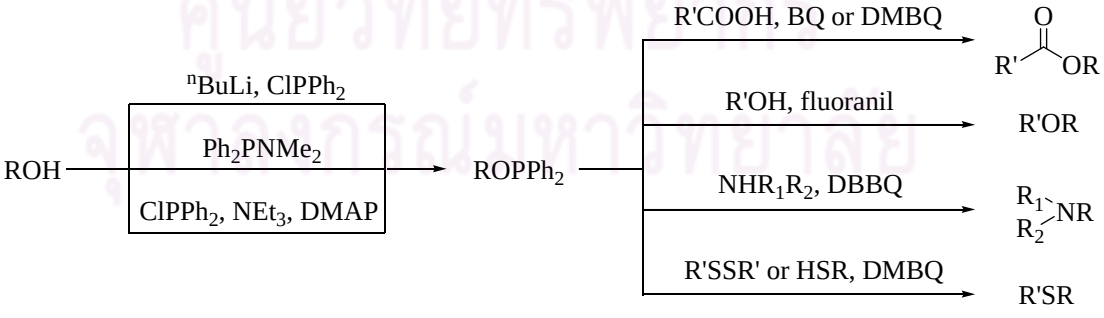
CHAPTER I

INTRODUCTION

1.1 Introduction of alkyl diphenylphosphinites

Oxidation-reduction condensation is known as one of very convenient and useful synthetic reactions for the preparation of C-O bond such as esters and ethers [1]. The fundamental concept of oxidation-reduction condensation is to perform dehydration condensation by eliminating H_2O as two H-atoms and one O-atom by a combination of a weak reductant and an oxidant. The most characteristic feature of this reaction is that it proceeds under mild and neutral conditions without any assistance of acidic or basic promoters.

Mukaiyama reported the preparation of alkyl cyanides, sulfides, amide, esters and ethers from alcohols using two-step process which involves prior conversion of alcohols into alkyl diphenylphosphinites followed by the substitution with various nucleophiles and benzoquinone. The preparation protocols for alkyl esters [2], ethers [3], amide [4] and sulfides [5] from alcohol are illustrated in Scheme 1.1.



Scheme 1.1 The conversion of alcohols to alkyl esters, ethers, amide and sulfides.

In 1972, Hudson and coworkers reported the synthesis of alkyl halide from alcohols, alkyl diphenylphosphenite and HX or X_2 at 20°C. This method gave alkyl halide in low to high yield [6].

$$Ph_2POR \xrightarrow{XY} RY + Ph_2P(O)X$$

X = H or Y; Y = I, Br, Cl

However, up till now there has been no report on the conversion of alcohols to alkyl halides or related compounds *via* alkyl diphenylphosphenite in a single step.

1.2 Introduction of alkyl halides

A current functional group interconversion is important in the chemical industry. Alkyl halides are important intermediates in organic reaction such as coupling reactions [7] and olefin synthesis [8]. In addition alkyl halides are valuable in pharmaceutical [9], biological [10], and agricultural science [11].

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

There are many ways to synthesize alkyl halides from alcohols such as

1) Reaction of alcohol with common reagents such as HX, $SOCl_2$ and PX_3.

2) Preparation of alkyl halides from organophosphorus, halogenating agents and alcohol.

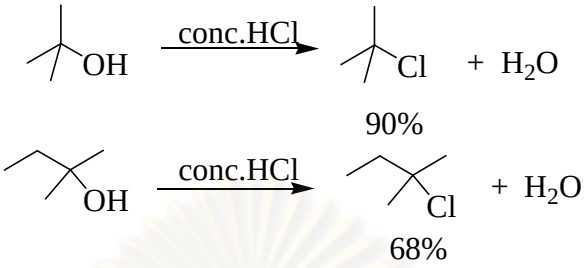
3) Synthesis of alkyl halides from alcohols, acids or Lewis acids and halide salts.

1.2.1 Reaction of alcohol with common reagents

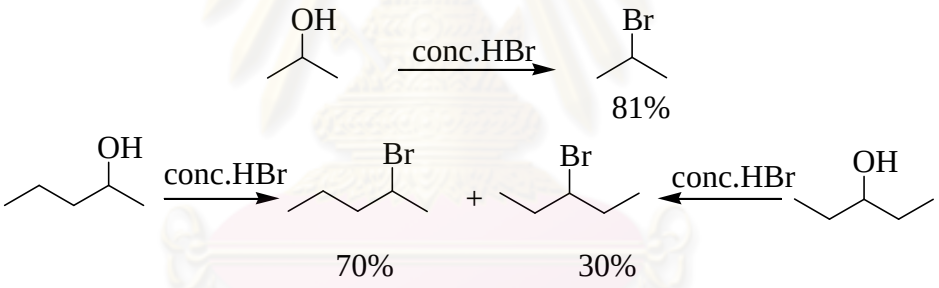
1.2.1.1 HX

The conversion of alcohols to alkyl chlorides using conc. HCl could be achieved in moderate to high yields. Tertiary alcohols proceeded smoothly to give the

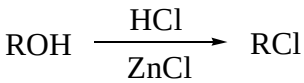
corresponding chloride in excellent yield (90%). However, primary and secondary alcohols proceeded slowly giving the desired chlorides in moderate yield (68%) and a common side-rearrangement often occurred.



The preparation of alkyl bromides is more readily than that of alkyl chlorides. Secondary and tertiary bromides can be prepared directly from the reaction of the corresponding alcohols by heating with constant boiling HBr. This method is not highly regioselective, for example in the case of 2- and 3-pentanol, the same ratio of products, 2- and 3-bromopentanes were obtained in 70:30 [12].

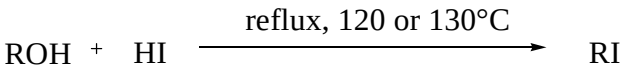


In 1924, Norris and Taylor reported the synthesis of alkyl chlorides from the reaction of primary saturated alcohols with conc. HCl in the presence of $ZnCl_2$. Methyl, ethyl, *n*-propyl, *iso*propyl, *n*-butyl, *sec*-butyl, *iso*amyl, cetyl, *β*-phenylethyl, *γ*-phenylpropyl, *m*-nitrobenzyl, *p*-nitrobenzyl alcohols and 2-pentanol could be used to form the desired chlorides in 60-70% yields. On the other hand, *iso*butyl alcohol was converted into alkyl chloride in 15% yield at a high temperature due to the problem of the competing elimination [13].



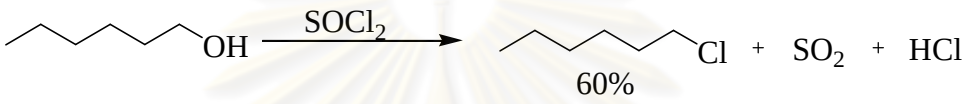
In 2008, Klein and co-workers investigated the transformation of alcohols to alkyl bromides and HI. The desired products could be obtained in moderate to high

yield. The product was further applied to synthesize biologically relevant 3,7-dimethyladenine and 9-butyladenine [14].

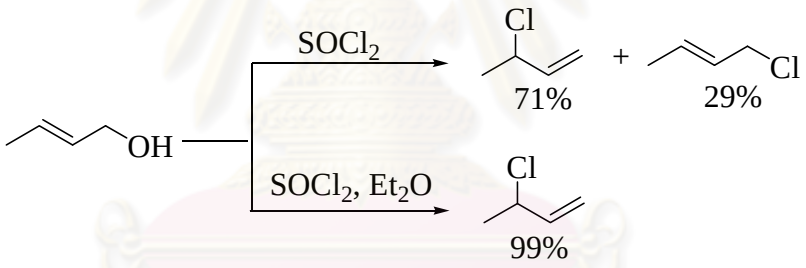


1.2.1.2 $SOCl_2$

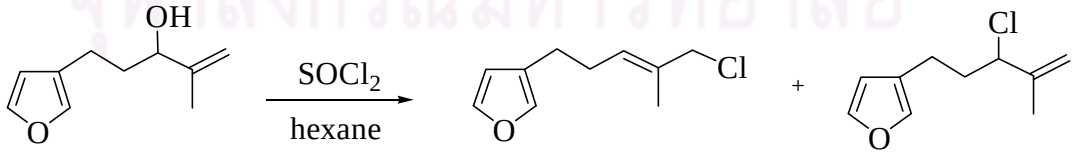
One of common reagents for the preparation of alkyl chlorides from alcohols is $SOCl_2$. This reaction did not give rearrangement product, but toxic by-products [12].



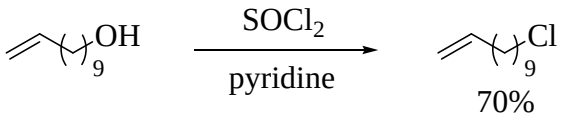
In 1955, Caserio and co-workers demonstrated the transformation of allylic alcohols to alkyl chlorides using $SOCl_2$ in the presence of dilute ether solution [15].



In 1989, Foland and co-workers described the total synthesis of isoarnebifuranone. One of all steps involved 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 [16].

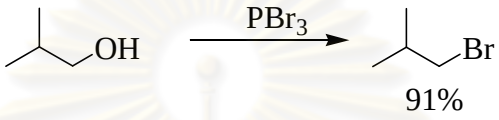


In 2004, Baughman and co-workers addressed the preparation of α-alkenyl halide metathesis synthons. One of all steps was the synthesis of alkenyl chloride from alkenyl alcohol using $SOCl_2$ and pyridine [17].



1.2.1.3 PX_3

PBr_3 is another well known reagent for preparing alkyl bromides from alcohols. This reagent was generated *in situ*; however, it was considered as a hazardous reagent [12].



In 1965, Coulson and co-workers reported the evidence to show that the first two dealkylations, for X = C1 or Br, gave isomerically and optically pure (if ROH was a optically pure) straight-chain alkyl halides, whereas the third let to some rearrangement in 2- or 3-pentyl or 2-octyl, but not in *n*-alkyl, isopropyl, *t*-butyl, and *s*-butyl groups. There was some loss in optical purity for the 2-octyl system in the third step. Similar results were obtained when X = I, except that 2-octyl iodide lose some optical purity in all three steps. For the *iso*butyl system (X = C1 or Br) some rearrangement occurred in each step, but not when X = I; for then, *t*-butyl iodide (< 1%) was isolated only from the third step [18].

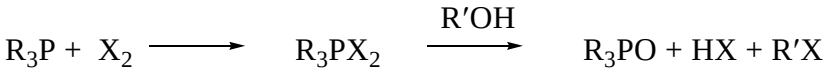
$$3ROH + PCl_3 \longrightarrow [ROPCl_2,(RO)_2PCl] \longrightarrow (RO)_3P + 3HCl$$

$$\longrightarrow RCl + (RO)_2P(O)H \longrightarrow RCl + ROP(O)HOH \longrightarrow RCl + P(OH)_3$$

Besides the reactions quoted above, there have several limitations such as using hazardous reagent, the generation of toxic by-products and rearranged products.

1.2.2 Preparation of alkyl halides from organophosphorus, halogenating agents and alcohol.

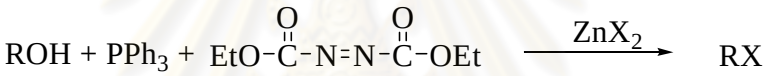
In 1964, Wiley and co-workers explored the synthesis of alkyl and aryl halides in high yields using phosphorus reagents of the type R_3PX_2. This reagent gave alkyl halide in high yields but did not give elimination or rearrangement product [19].



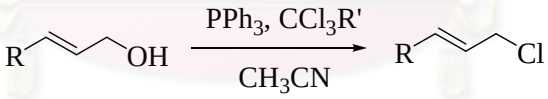
In 1968, Weiss and co-workers reported the conversion of alcohols to alkyl chlorides using PPh_3 and CCl_4. This reaction gave the corresponding chlorides in 27% yield [20].

In 1978, Miyano and co-workers addressed the reactions between PPh_3 and $CuCl_2$ or $CuBr_2$ with alcohols. The corresponding alkyl halides were obtained in moderate to high yield. Nonetheless, using cyclohexanol and menthol as a substrate gave low yields due to the formation of alkene by-product [21].

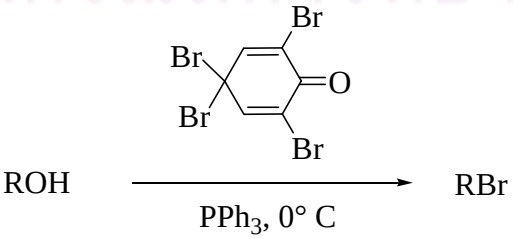
In 1984, Ho and Davies demonstrated the use of diethyl azodicarboxylate, PPh_3 and zinc halide for the preparation of alkyl halide. The desired products could be obtained in high yield under very mild condition [22].



In 1989, Matveeva and co-workers studied a regio-stereoselectivity of allylic alcohol, PPh_3, and derivatives of trichloroacitic acid. This reaction can perform to give alkyl chlorides in high yield [23].

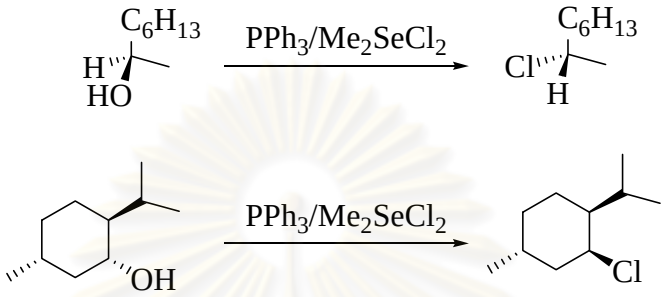


In 1998, Matveeva and co-workers reported the transformation of alcohols to alkyl bromides using 2,4,4,6-tetrabromocyclohexa-2,5-dienone. This method presented the high reactivity, regiospecificity and stereoselectivity [24].

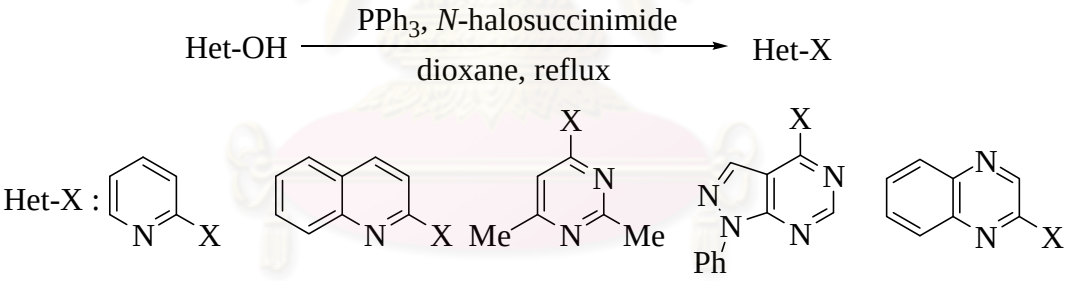


In the same year, Drabowicz and co-workers presented the new reagent system, dimethyl- or diphenyldichloroselenurane for converting alcohol into

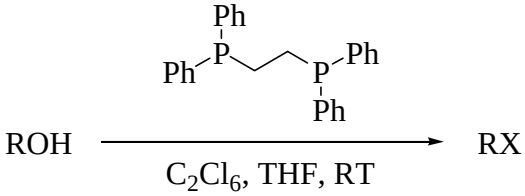
chlorides. The usefulness of this method was demonstrated by experiments with optically active substrates such as enantiomers of 2-octanol and (-)-menthol. In the case of acyclic, chiral alcohols, both enantiomers of 2-octanol and (-)-menthol were converted to the corresponding chlorides and with essentially full inversion of configuration [25].



In 1999, Sugimoto and co-workers explored a conversion of hydroxyheterocycles to haloheterocycles using PPh_3 and *N*-halosuccinimide. The corresponding chloroheterocycles and bromoheterocycles were obtained in moderate to high yield [26].



In 2001, Pollastri and co-workers addressed the conversion of alcohols to halides using 1,2-*bis*(diphenylphosphino)ethane (diphos). Various alcohols could be transformed to the corresponding chlorides and bromides in moderate to high yields [27].



X = Cl, Br

In 2002, Firouzabadi and co-workers proposed the new methodology for halogenation of alcohol using PPh_3, 2,3-dichloro-5,6-dicyanobenzoquinone in the presence of R_4NX. This method could be employed to generate the desired products in high yield, whereas no excellent selectivity between the different types of alcohols was obtained [28].

$$RYH \xrightarrow[CH_2Cl_2,\ 0°C \text{ or } RT]{PPh_3/DDQ/R'_4NX} RX$$

Y = O, S, Se; X = Cl, Br, I; and R' = H, *n*-butyl, *n*-hexyl

In 2003, Desmaris and co-workers investigated the reaction of alcohol with the fluorous phosphine-CBr_4 complex in toluene or in two-phase toluene-FC-72 (FC-72 being a mixture of fluorous hexanes) system afforded the corresponding bromide in good yields. The separation of bromides from the phosphine oxide could be simply carried out by a simple liquid–liquid extraction. This fluorous phosphine oxide could also be recycled after reduction [29].

$$ROH + P(C_6H_4\text{-}p\text{-}(OCH_2C_7F_{15})_3 \xrightarrow{CBr_4} RBr + OP(C_6H_4\text{-}p\text{-}(OCH_2C_7F_{15})_3$$

$$OP(C_6H_4\text{-}p\text{-}(OCH_2C_7F_{15})_3 \xrightarrow{HSiCl_3} P(C_6H_4\text{-}p\text{-}(OCH_2C_7F_{15})_3$$

In 2005, Iranpoor and co-workers developed a new heterogeneous reagent, silicaphosphine $[PCl)_{3-n}(SiO_2)_n]$ which could be prepared from the reaction of silica gel and PCl_3, for the transformation of alcohols and thiols into bromides and iodides. Various alcohols and thiols could be converted into their corresponding alkyl bromides and iodides in high yields [30].

$$ROH \xrightarrow[CH_3CN,\ \text{reflux}]{\text{Silphos},\ X_2} RX$$

In 2006, Pluempanupat and Chavasiri reported the preparation of alkyl halides from alcohol by using PPh_3 and CCl_3CONH_2. Primary alcohols could be performed to give the corresponding chlorides in excellent yields *via* S_N2 pathway [31].

$$ROH \xrightarrow[CH_2Cl_2,\ RT,\ 15\ min]{Cl_3CCONH_2,\ PPh_3} RCl$$

In the same year, Hajipour and co-workers demonstrated the procedure for the conversion of benzylic, allylic and aliphatic alcohols to the corresponding iodides using PPh_3/I_2 under solvent-free conditions using microwave irradiation. The desired products could be obtained in high yield under mild condition [32].

$$ROH \xrightarrow[microwave]{I_2,\ PPh_3,\ solvent\text{-}free} RI$$

In the same year, Firouzabadi and co-workers presented the conversion of alcohol into their bromides and iodides using *N*-bromo and *N*-iodosaccharins, respectively in the presence of PPh_3 at RT in CH_2Cl_2. Aliphatic, allylic and benzylic alcohols were smoothly converted to the corresponding bromides or iodides in high yields. In the case of cyclic alcohol, the bromination of cyclohexanol gave cyclohexyl bromide and cyclohexene and the iodination of cyclohexanol gave only cyclohexene [33].

$$ROH \xrightarrow[CH_2Cl_2,\ RT]{NXSac/PPh_3} RX$$

X=Br, I

In 2008, Tongkate and co-workers investigated the bromination of alcohols using Br_3CCOBr_3/PPh_3 and Br_3CCO_2Et/PPh_3 under mild conditions with short reaction times. Primary, secondary and cyclic alcohols gave the corresponding bromides in high yields. However, tertiary alcohols gave the corresponding alkyl bromides in lower yields [34].

$$ROH \xrightarrow[CH_2Cl_2,\ RT,\ 15\ min]{\substack{PPh_3 \\ Brominating\ agent}} RBr$$

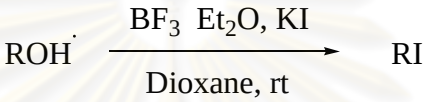
Brominating agent = $Br_3CCOCBr_3$, Br_3CCO_2Et

According to the aforementioned results, many efficient methods for the synthesis of alkyl halide have been disclosed. Nevertheless, some reactions have

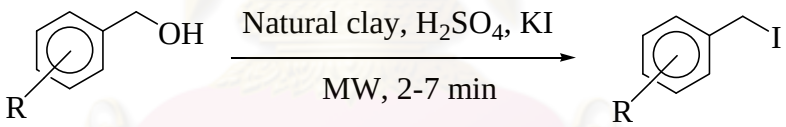
limitations such as long reaction times and harsh conditions. In addition, there is no report on the synthesis of alkyl halides from alcohols using $ClPPh_2$.

1.2.3 Synthesis of alkyl halides from alcohols, acids or Lewis acids and halide salts

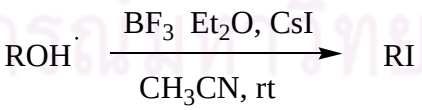
In 2001, Bandger and coworkers described the conversion of alcohols to the corresponding alkyl iodides using KI and $BF_3{\cdot}Et_2O$. Allylic and benzylic iodides could be obtained in high yields, whereas saturated aliphatic alcohols did not work well [35].



In 2002, Bandger and coworkers presented an efficient method for iodination of alcohol using KI/H_2SO_4 supported on natural kaolinitic clay under microwave irradiation. The conversion of benzylic alcohols into benzylic iodides was achieved in high yields and short reaction times [36].



In 2003, Hayat and coworkers proposed the new system using CsI and $BF_3{\cdot}Et_2O$. Benzylic, allyic and secondary alcohols could also be performed well by this technique; however, saturated aliphatic alcohols did not yield iodides even after prolonged time [37].



In 2006, Tajik and coworkers demonstrated the iodination of benzylic and aliphatic alcohols by $Al(HSO_4)_3$/KI. Aliphatic alcohols were smoothly converted to the corresponding iodides in high yields. In the case of benzylic alcohols, the rate of reaction was slower when the ring containing an electron-withdrawing group was used [38].

$$ROH \xrightarrow[n\text{-hexane}]{Al(H_2SO_4)_3,\ KI} RI$$

In the same year, Hajipour *et al.* investigated the iodination of alcohols under heterogeneous condition using KI and silica sulfuric acid (SiO_2-H_2SO_4) which generated chlorosulfonic acid and HCl (g). Allylic and benzylic alcohols were smoothly converted to the corresponding iodides in high yields [39].

$$ROH \xrightarrow[CH_3CN,\ rt]{\text{Silica sulfuric acid, KI}} RI$$

These methods have some advantages such as cheaper and commercially available halide salts.

As all mentioned above, the intention of this work is to develop an efficient one-pot synthesis of alkyl halides directly from alcohols using the combined reagents of chlorodiphenylphosphine and halide salts. The reactions were carried out under mild conditions, short reaction time and high yield of products.

1.3 Related compounds

1.3.1 Alkyl thiocyanates

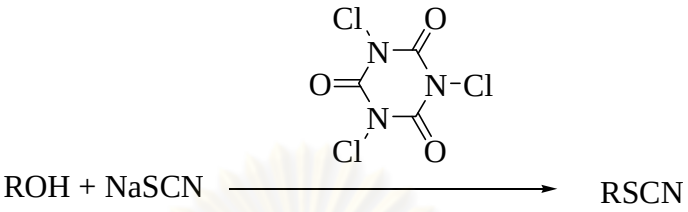
Thiocyanates are useful intermediates in organic synthesis, and for their biological activities. There are a few reports on the conversion of alkyl alcohols to azides using organophosphorus reagent.

In 2003, Iranpoor and co-workers reported the conversion of alcohols, thiols, carboxylic acids, trimethylsilyl ethers and carboxylates to thiocyanates using PPh_3/DEAD/NH_4SCN. This method provided a simple and general method for the conversion of different functionalities into their corresponding thiocyanates. The excellent chemoselectivity of the method is also advantageous [40].

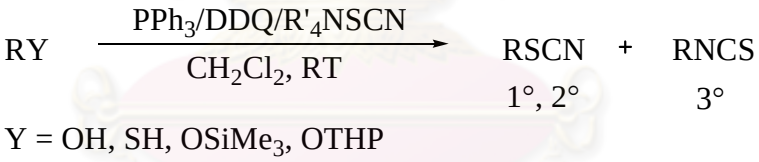
$$RXH \xrightarrow[CH_2Cl_2,\ RT]{PPh_3/DDQ/R'_4NSCN} \underset{1°,\ 2° = 100\%}{RSCN} + \underset{3° = 100\%}{RNCS}$$

X= O, S

In 2004, Hiegel and co-workers investigated the preparation of alkyl nitrates, nitrites, and thiocyanates form alcohols using trichloroisocyanuric acid with PPh_3. Primary, secondary and benzyl alcohols gave high yields of thiocyanates. However, cyclic alcohols did not give the corresponding thiocyanates [41].



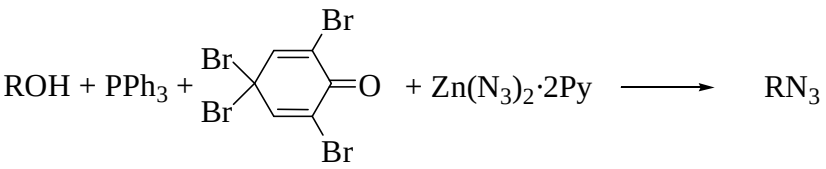
In 2006, Iranpoor and co-workers addressed the preparation of thiocyanates and isothiocyanates from alcohols, thiols, trimethylsiyl-, and tetrahydropyranyl ethers using PPh_3/2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)/n-Bu_4NSCN. Primary alcohols were converted to their coresponding alkyl thiocyanates without the formation of any isothiocyanates, but secondary alcohols gave also some minor amounts of isothiocyanates as a side-product. In the case of tertiary alcohol, the isothiocyanate was formed as the major product together with small amounts of eliminated product [42].



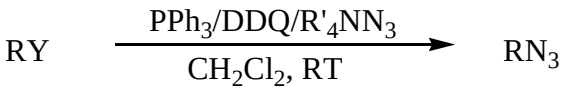
1.3.2 Alkyl azides

Azides are important functional groups in organic synthesis for many purposes and have been extensively used for the introduction of amino groups and construction of heterocycles.

In 1997, Saito and co-workers developed the method for the conversion of alcohols to azides with 2,4,4,6-tetrabromo-2,5-cyclohaxadienone/PPh_3/$Zn(N_3)_2$·2Py in mixed CH_3CN/toluene [43].



In 2004, Iranpoor and co-workers reported the synthesis of alkyl azides with PPh_3/DDQ/*n*-$BuNN_3$ system. Primary, secondary and tertiary azides were proceeded to form the desired products in high yields. However, secondary and tertiary azides required longer time to complete the reaction [44].



Y = OH, SH, $OSiMe_3$

In 2007, Kuroda and co-workers presented the conversion of *tert*-alcohol to *tert*-alkyl azides by way of oxidation-reduction condensation using alkyl diphenylphosphinites with trimethylsilyl azide ($TMSN_3$) in the presence of methoxy-benzoquinine (MBQ). The corresponding *tert*-alkyl azides with inverted configuration were also achieved in high yield [45].

1.4 Objective of this research

The objectives of this research are to explore and develop the optimized conditions for the one-pot conversion of alkyl alcohol to alkyl halide using $ClPPh_2$ under mild conditions, short reaction time and high yield of products. The application of this developed methodology for the preparation of related compounds is also examined.

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

CHAPTER II

EXPERIMENTAL

2.1 Instruments and equipment

All reactions were carried out under an atmosphere of N_2. Reactants and products were identified by several spectroscopic techniques. ^{1}H- and ^{13}C-NMR spectroscopy was performed in $CDCl_3$ with tetramethylsilane (TMS) as an internal reference on a Varian nuclear magnetic resonance spectrometer, model Mercury plus 400, 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. Yields of products were determined by ^{1}H-NMR technique using toluene as an internal standard. Thin layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel (Merck, Kieselgel 60 PF254). Column chromatography was performed on silica gel (Merck, Kieselgel 60G Art 7734, 70-230 mesh; or Art 9385, 230-400 mesh) and aluminium oxide 90 active neutral (70-230 mesh).

2.2 Chemical reagents

Substrates and reagents used for synthesis were purchased from Fluka chemical company or otherwises stated and were used without further purification.

All solvents used in this research were purified prior to use by standard methodology except for those which were reagent grades.

2.3 Alkyl iodides

2.3.1 General procedure for conversion of alcohols to alkyl iodide

A stirred solution of alcohol 1 equiv. (0.25 mmol), NaI 3 equiv. (0.75 mmol) and Bu_4NI 0.8 equiv. (0.4mmol) in dry CH_3CN (1 mL) was successively added $ClPPh_2$ 3.45

equiv. (0.86 mmol, 0.16 mL) at RT (30-32°C) under N_2 atmosphere. After 3 h, the crude mixture was analyzed by ^{1}H-NMR spectroscopy with the addition of toluene as an internal standard or purified by silica gel column.

2.3.2 Study on optimum conditions for conversion of alcohols to alkyl iodide

2.3.2.1 Effect of alkali metal salts

The conversion of 1-octanol into 1-octyl iodide was carried out using the reaction conditions described in the general procedure. Three different alkali metal salts including sodium iodide (NaI), potassium iodide (KI) and lithium iodide (LiI) were utilized.

2.3.2.2 Effect of the amounts of NaI

According to the general procedure, the amount variation of NaI as 0.15, 0.25, 0.28, 0.30 and 0.35 equiv. was explored to observe the effect of the amount of NaI on the iodination of 1-octanol.

2.3.2.3 Effect of the amounts of Bu_4NI and reaction time

The general reaction performed using the amount variation of Bu_4NI as 0.3, 0.5 and 0.8 equiv. and different reaction time.

2.3.2.4 Effect of solvents

The general reaction was carried out using five different solvents: benzene, toluene, THF, CH_3CN and CH_2Cl_2 at room temperature for 30 min under N_2.

2.3.3 The synthesis of alkyl iodides

$$\underset{1\ \text{equiv.}}{ROH} + \underset{3.4\ \text{equiv.}}{ClPPh_2} + \underset{3\ \text{equiv.}}{NaI} + \underset{0.8\ \text{equiv.}}{Bu_4NI} \xrightarrow[CH_3CN\ 1\ mL]{RT,\ 30\ min} RI$$

The iodination of different alcohols (0.25 mmol) using NaI (0.75 mmol), $ClPPh_2$ (0.86 mmol) and Bu_4NI (0.4 mmol) in CH_3CN at room temperature for 30 min was conducted. The quantity of alkyl iodide in the crude mixture was determined by ^{1}H-NMR using toluene as an internal standard or purified by silica gel column.

1-Octyl iodide: Colorless oil (61%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.88 (3H, t, *J* = 6.65, CH_3), 1.26-1.40 (10H, m, 5×CH_2), 1.82 (2H, m, *J* = 7.28 Hz, CH_2) and 3.19 (2H, t, *J* = 7.03 Hz, CH_2); ^{13}C-NMR ($CDCl_3$) δ (ppm): 7.4, 14.1, 22.6, 28.5, 29.1, 30.5, 31.8 and 33.6.

1-Adamantyl iodide: white solid (18%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.81 (6H, t, *J* = 14.34 Hz, 3×CH_2), 1.96 (3H, s, CH) and 2.64 (6H, s, 3×CH_2); ^{13}C-NMR ($CDCl_3$) δ (ppm): 33.1 (3C), 35.6 (3C), 51.2 and 52.5 (3C).

2.4 Alkyl bromides

2.4.1 General procedure for conversion of alcohols to alkyl bromide

A stirred solution of alcohol 1 equiv. (0.25 mmol) and LiBr 3 equiv. (0.75 mmol, 0.0651 g) in dry CH_3CN (1 mL) was successively added $ClPPh_2$ 3.45 equiv. (0.86 mmol, 0.16 mL) at RT (30-32°C) under N_2 atmosphere. After 30 min, the crude mixture was analyzed by ^{1}H-NMR with the addition of toluene as an internal standard or purified by silica gel column.

2.4.2 Study on optimum conditions for conversion of alcohols to alkyl bromide

2.4.2.1 Effect of alkali metal salts

According to the general procedure, variation of alkali metal salts as sodium bromide (NaBr), potassium bromide (KBr) and lithium bromide (LiBr) was explored to observe the effect of alkali metal salts on the bromination of 2-phenylethanol.

2.4.2.2 Effect of the amounts of LiBr

The general reaction performed using the amount variation of LiBr as 1, 2 and 3 equiv. was explored to observe the effect of the amount of brominating agent on the bromination of alcohol.

2.4.2.3 Effect of the amounts of Bu_4NBr and reaction time

The reaction of alcohol with various amounts of Bu_4NBr: 0.15 and 0.3 equiv. in dry CH_3CN (1 mL) was stirred under N_2 at room temperatures at the reaction time: 15 and 30 min.

2.4.2.4 Effect of solvents

The general reaction performed using various solvents (1 mL): benzene, toluene, THF, CH_3CN and CH_2Cl_2 at room temperature for 30 min under N_2.

2.4.3 The synthesis of alkyl bromides

$$\underset{1\text{ equiv.}}{ROH} + \underset{3.4\text{ equiv.}}{ClPPh_2} + \underset{3\text{ equiv.}}{LiBr} \xrightarrow[CH_3CN\ 1\text{ mL}]{RT,\ 30\text{ min}} RBr$$

The reaction of variation of alcohol (0.25 mmol), $ClPPh_2$ (0.86 mmol) and LiBr (0.75 mmol) in CH_3CN (1 mL) was stirred at room temperature for 30 min under N_2. After evaporation, the corresponding products were analyzed by ^{1}H-NMR based on a standard toluene 10 µL or purified by silica gel column.

2-Phenethyl bromide: colorless oil (80%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.20 (2H, t, J = 7.70 Hz, $PhCH_2C\underline{H}_2Br$), 3.61 (2H, t, J = 7.70 Hz, $PhC\underline{H}_2CH_2Br$) and 7.24-7.37 (5H, m, Ar-H), ^{13}C-NMR ($CDCl_3$) δ (ppm): 33.3, 39.6, 127.1, 128.8 and 139.1.

1-Adamantyl bromide: white solid (20%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72 (6H, s, alkyl groups), 2.09 (3H, s, alkyl groups) and 2.36 (6H, s, alkyl groups). ^{13}C-NMR ($CDCl_3$) δ (ppm): 32.6, 35.5, 48.3 and 66.8.

2.5 Alkyl chlorides

2.5.1 General procedure for conversion of alcohols to alkyl chloride

A stirred solution of alcohol 1 equiv. (0.25 mmol) in dry CH_3CN (1 mL) was successively added $ClPPh_2$ 3.45 equiv. (0.86 mmol, 0.16 mL) at RT (30-32°C) under N_2 atmosphere. After 45 min, the crude mixture was analyzed by ^{1}H-NMR with the addition of toluene as an internal standard or purified by silica gel column.

2.5.2 Study on optimum conditions for conversion of alcohols to alkyl chloride

According to the general procedure, the variation of reaction time as 30 and 45 min and solvent as CH_3CN and CH_2Cl_2 was explored to observe the effect of reaction time and solvent on the chlorination of 2-phenylethanol.

2.5.3 The synthesis of alkyl chlorides

$$\underset{1\ \text{equiv.}}{ROH} + \underset{3.4\ \text{equiv.}}{ClPPh_2} \xrightarrow[CH_2Cl_2\ 1\ mL]{RT,\ 45\ min} RCl$$

The reaction of variation of alcohol (0.25 mmol) and $ClPPh_2$ (0.86 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 45 min under N_2. After evaporation, the corresponding products were analyzed by ^{1}H-NMR based on a standard toluene 10 µL or purified by silica gel column.

2.6 Related compounds

2.6.1 Alkyl thiocyanates

2.6.1.1 General procedure for conversion of alcohols to alkyl thiocyanate

A stirred solution of alcohol 1 equiv. (0.25 mmol) and LiBr (0.75 mmol, 0.065 g) in dry CH_3CN (1 mL) was successively added $ClPPh_2$ 3.45 equiv. (0.86 mmol, 0.16 mL) at RT (30-32°C) under N_2 atmosphere for 30 min. When the reaction was completed, the reaction mixture was added NH_4SCN 3 equiv. (0.75 mmol) at reflux temperature under N_2 atmosphere. After 8 h, the crude mixture was analyzed by ^{1}H-NMR spectroscopy with the addition of toluene as an internal standard or purified by silica gel column.

2.6.1.2 Study on optimum conditions for conversion of alcohols to alkyl thiocyanate

1-Octhanol was used to synthesize alkyl thiocyanate. Several factors including thiocyanate reagents, phase transfers and reaction time were varied to explore the efficiency of the reaction. In addition, using the same technique with 1-octanol as a substrate to verify the optimized condition was carried out.

2.6.2 Alkyl azides

2-Phenylethanol was used as a model compound. Several parameters including type of azide reagents, the amounts of azide reagents, temperature, reaction time, and solvents were investigated to optimize the reaction conditions for conversion of alcohols to alkyl azide. In this optimizing study, the obtained product was characterized by ^{1}H-NMR spectroscopy based on a standard toluene 10 µL.

CHAPTER III

RESULTS AND DISCUSSION

The transformation of alcohols into the corresponding halides represents an important functional group interconversion in organic synthesis. They are usually prepared from the corresponding alcohols by the action of a great variety of reagents. However, some reactions have several limitations such as using hazardous reagent, generate toxic by-products, rearranged products, long reaction times and harsh conditions. There is no report for synthesis alkyl halide from alcohol using $ClPPh_2$ and alkali metal salts in 1 step.

In this research, the development and exploration of optimum conditions for the one-pot synthesis of alkyl halide from alkyl alcohol using $ClPPh_2$ under mild conditions, short reaction time and high yield of products. The application of this developed methodology for the preparation of related compounds is also examined.

3.1 Alkyl iodide

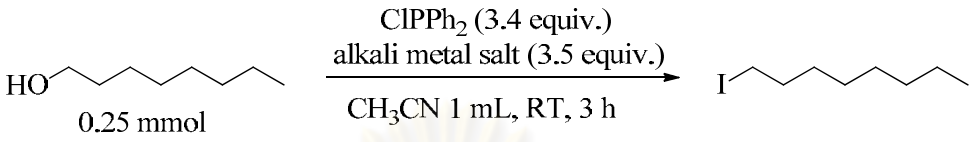
3.1.1 Study on optimum conditions for conversion of alcohols to alkyl iodides

To search for an optimized condition for the iodination of alcohol, the effects of alkali metal salts, the amount of NaI, and Bu_4NI, reaction time and solvents were investigated. 1-Octanol was selected as a model substrate for these examinations. In this optimizing study, the obtained product was characterized by ^{1}H-NMR based on a standard toluene 10 μL.

3.1.1.1 Effect of alkali metal salts

The reactions of 1-octanol (1 equiv.) with three alkali metal salts were performed to quest for the optimized conditions. The results are described in table 3.1.

Table 3.1 Effect of alkali metal salts in the synthesis of 1-iodooctane



Entry	Alkali metal salt	Yield[a]			Σ (%)
		1-iodooctane	Recovered Alcohol	Other[b]	
1	LiI	84	-	16	100
2	NaI	96 (61[c])	-	-	96
3	KI	90	-	-	90

[a] analyzed by ^{1}H-NMR based on toluene 10 μL
[b] %yield of 1-octyl diphenylphosphinite and 1-octyl diphenylphosphinite oxide
[c] isolated yield

As the results presented in table 3.1, the reaction using LiI (entry 1) provided the desired product in 84% and by products as 1-octyl diphenylphosphinite and 1-octyl diphenylphosphinite oxide in 16%. Entries 2 and 3 gave only 1-iodooctane in 96 and 90%, respectively. The reaction using NaI gave the best yield of 1-iodooctane. Consequently, NaI was appropriate to be used as iodinating agent.

The corresponding 1-octyl iodide was fully characterized its identity by NMR spectroscopy. The ^{1}H- and ^{13}C-NMR spectra of 1-octyl iodide are illustrated in Figs 3.2 and 3.3, respectively. The ^{1}H-NMR spectrum displayed the triplet signal of methylene protons adjacent to iodide at δ_H 3.19. The ^{13}C-NMR revealed the signal at δ_C 33.4 assigned to the carbon connecting to iodine. Seven remaining signals were seven carbons on an aliphatic chain.

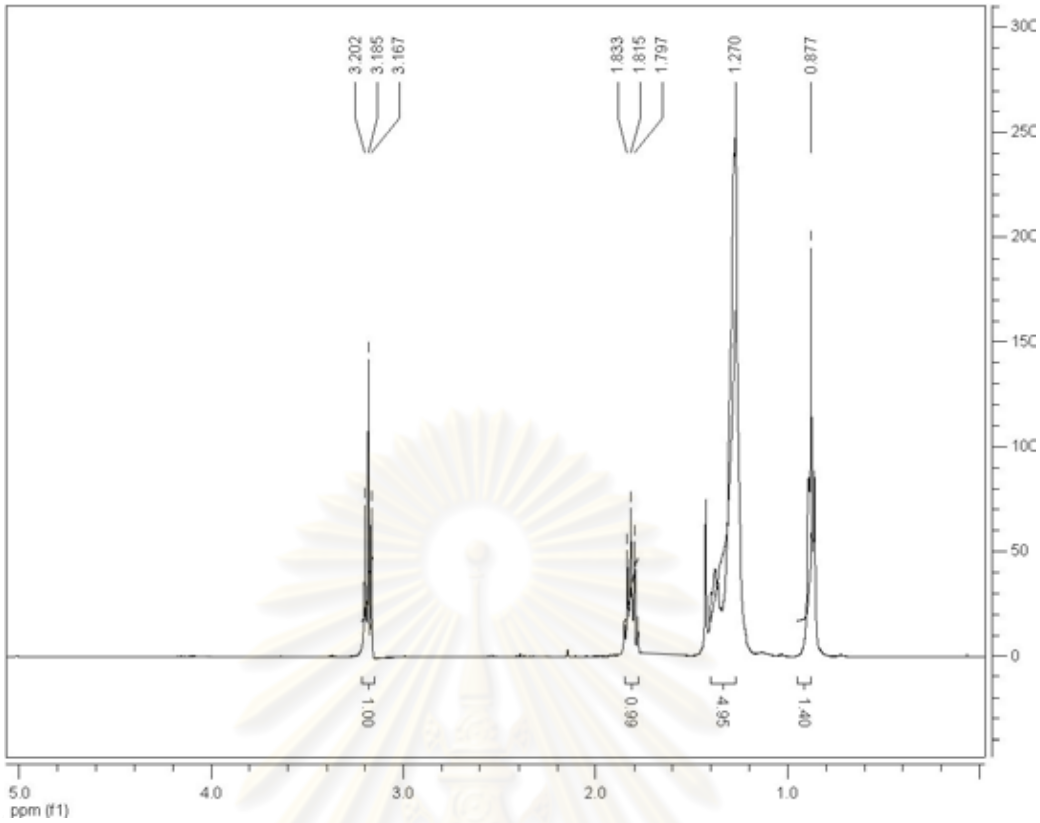


Figure 3.1 The ^{1}H-NMR spectrum of 1-octanol iodide

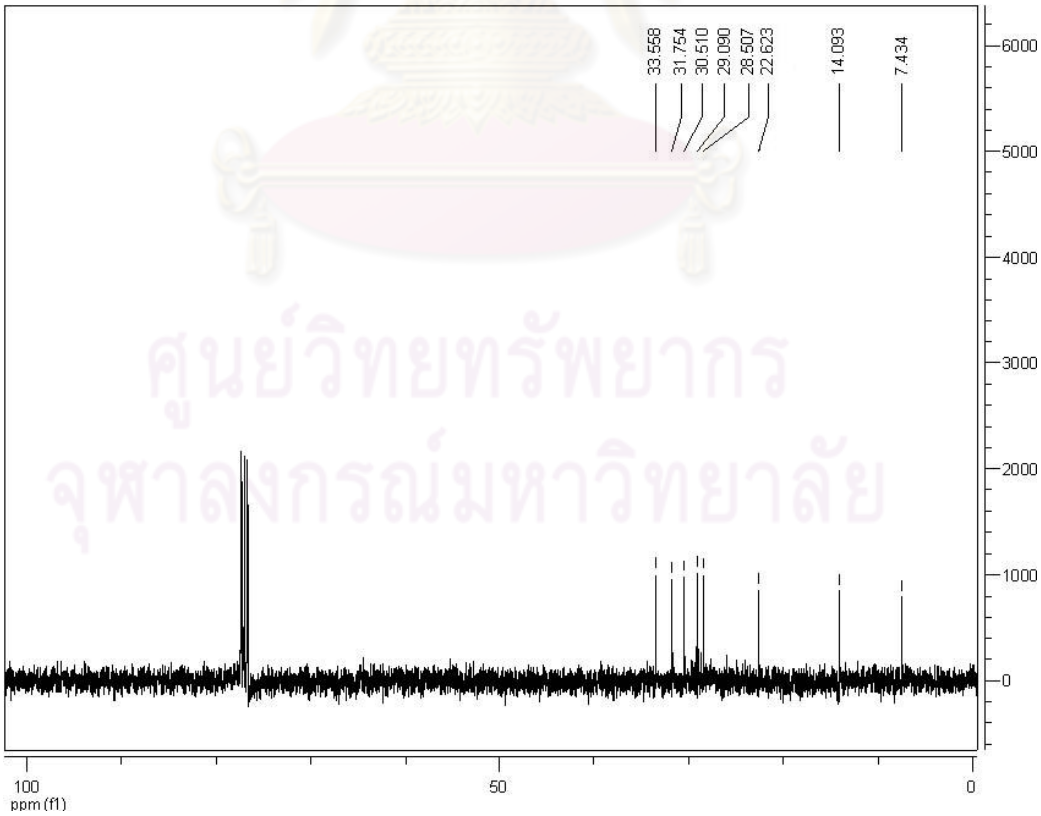


Figure 3.2 The ^{13}C-NMR spectrum of 1-octanol iodide

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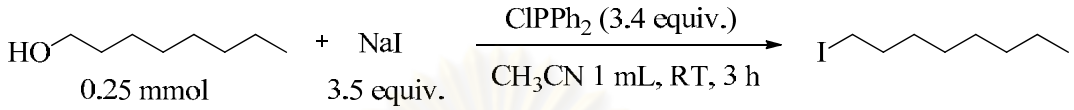
3.1.1.2 Effect of the amounts of NaI

Preliminary results revealed that using NaI, the transformation of 1-octanol to 1-iodooctane could be achieved in excellent yield. The amount of NaI was thus investigated to search for optimum conditions as presented in Table 3.2.

Table 3.2 Effect of the amounts of NaI in the synthesis of 1-iodooctane



Entry	NaI (equiv.)	% Yield[a]			Σ (%)
		1-iodooctane	Recovered alcohol	Other[b]	
1	1.5	53	-	37	90
2	2.5	72	-	18	90
3	3.0	96	-	-	96
4	3.5	96	-	-	96

[a] analyzed by ^{1}H-NMR based on toluene 10 μL
[b] %yield of 1-octyl diphenylphosphinite and 1-octyl diphenylphosphinite oxide

Table 3.2 reveals that the yield of product was increased when the amounts of NaI were increased (entries 1-4). Moreover, it should be mentioned that the conversion of 1-octanol to 1-iodooctane using NaI 3.0 and 3.5 equiv. (entries 3 and 4) gave almost the same yield. However, NaI 3.0 equiv. was considered as the most proper amount for further investigation.

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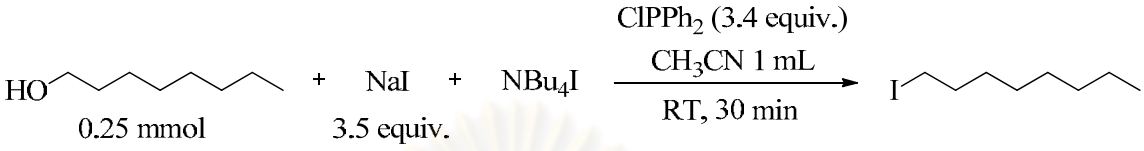
3.1.1.3 Effect of the amounts of Bu_4NI and reaction time

The effect of the amounts of Bu_4NI and reaction time was investigated and the results are accumulated in Table 3.3.

Table 3.3 Effect of the amounts of Bu_4NI and reaction time



Entry	Bu_4NI (equiv.)	Reaction time (h)	% Yield[a]			Σ (%)
			1-iodooctane	Recovered alcohol	Other[b]	
1	-	0.5	76	-	14	90
2	-	1	81	-	9	90
3	-	1.5	84	-	8	92
4	-	2	92	-	-	92
5	-	3	96	-	-	96
6	0.3	0.5	78	-	12	90
7	0.5	0.5	88	-	8	96
8	0.8	0.5	96	-	-	96

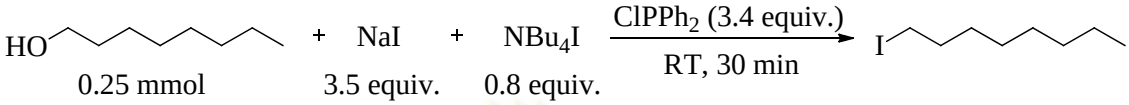
[a] analyzed by ^{1}H-NMR based on toluene 10 μL
[b] %yield of 1-octyl diphenylphosphinite and 1-octyl diphenylphosphinite oxide

Iodonation of 1-octanol was performed using the reaction time ranging form 0.5 to 3 h (entries 1–5). The reaction gave the highest yield within 3 h was employed (entry 5). When the reaction time was lessened to 0.5 h, 1-iodooctane was merely obtained in 76% yield, whereas employing the same reaction condition, but adding Bu_4NI from 0.3 to 0.8 equiv. (entries 6-8) yielded the desired product in high yield. When 0.8 equiv. was used, 1-iodooctane was obtained in the highest yield (entry 8). From the above results, the optimal amounts of Bu_4NI and reaction time for the synthesis of 1-iodooctane was 0.8 equiv. and 0.5 h, respectively.

3.1.1.4 Effect of solvents

Solvent was another important factor for iodination of 1-octanol. In this study, five diverse solvents were examined. The results are shown in Table 3.4.

Table 3.4 Effect of solvents



Entry	Solvent	% Yield[a]
1	CH_3CN	96
2	toluene	58
3	THF	73
4	benzene	62
5	CH_2Cl_2	75

[a] analyzed by ^{1}H-NMR based on toluene 10 μL

The treatment of 1-octanol (1 equiv.), $ClPPh_2$ (3.4 equiv.) , NaI (3 equiv.) and Bu_4NI (0.8 equiv.) was performed in various solvents at RT for 30 min. Common solvents which were not expensive and commercially available such as toluene, THF, benzene and CH_2Cl_2 provided the desired product in moderate yields (entries 2-5). When CH_3CN was used, 1-iodooctane was obtained in excellent yield (entry 1). Therefore, the reaction of alcohol (1 equiv.), $ClPPh_2$ (3.4 equiv.), NaI (3 equiv.) and Bu_4NI (0.8 equiv.) in CH_3CN at RT for 30 min was applied to be the optimized condition for screening substrates.

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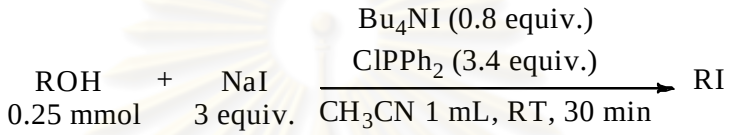
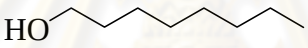
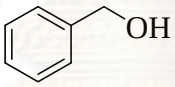
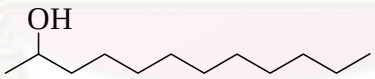
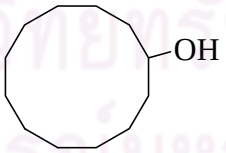
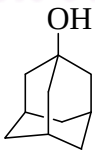
3.1.2 The synthesis of alkyl iodides

Since the optimized reaction conditions such as alkali metal salts, the amounts of NaI, the amounts of Bu_4NI, reaction time and solvents could be achieved as previously discussed. The scope of the preparation of alkyl iodide from alcohols using $ClPPh_2$/NaI/Bu_4NI in CH_3CN at RT was further explored and the results are displayed in Table 3.5.

Table 3.5 The synthesis of alkyl iodide from alcohols using $ClPPh_2$/NaI/Bu_4NI in CH_3CN at RT



Entry	Substrate	Product[a] (%yield)
1		96
2		100
3		72
4		61
5		18[b]

[a]analyzed by ^{1}H-NMR based on toluene 10 μL
[b]isolated yield

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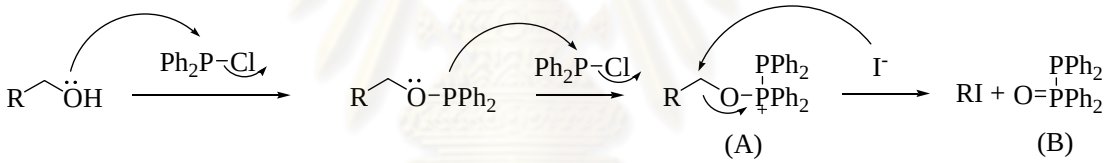
Primary alkyl iodide: 1-iodooctane underwent a clean reaction providing the corresponding alkyl iodide in an excellent yield (entry 1). Similarly, the preparation of benzyl iodide was also achieved using benzyl alcohol in quantitative yield (entry 2). On the contrary, 2-dodectyl and 1-adamentyl iodides were obtained only in moderate and low yield as the reaction was not completed within this optimized time (entries 3 and 5). Steric hindrance of substrate might cause this incomplete reaction. In the case of cyclic secondary iodide, the reaction did not smoothly proceed (entry 4). It suffered from the elimination of alkyl iodide to its corresponding alkene.

3.1.3 The proposed mechanism

The reaction pathway for the formation of alkyl iodides was proposed as illustrated in Scheme 3.1. In the first step, alcohol initially reacted with $ClPPh_2$ to generate alkyl diphenylphosphinite. Then alkyl diphenylphosphinite was reacted with $ClPPh_2$ to generate intermediate **A** and then the reaction of the intermediate with iodide anion formed alkyl iodide and by-product **B**.



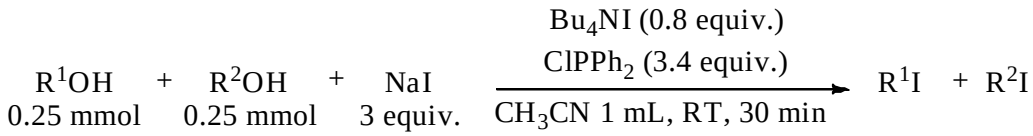
Scheme 3.1 Proposed mechanism for iodination of alcohol.

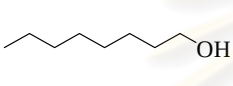
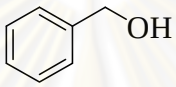
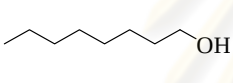
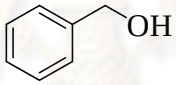
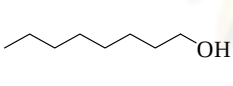
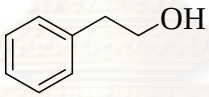
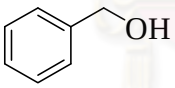
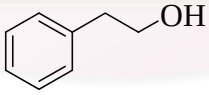
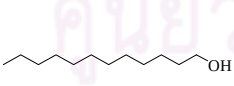
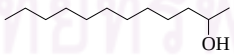
3.1.4 Reactivity studies of selected alcohols

The relative reactivity of $ClPPh_2$/NaI/Bu_4NI with various alcohols was further studied by competing two selected alcohols in the same reaction vessel.

Two selected alcohols (1 equiv. each), $ClPPh_2$ (3.4 equiv.), NaI (3 equiv.) and Bu_4NI (0.8 equiv.) in dry CH_3CN (1 mL) were stirred under standard conditions. The results are accumulated in Table 3.6.

Table 3.6 Reactivity studies of selected alcohols



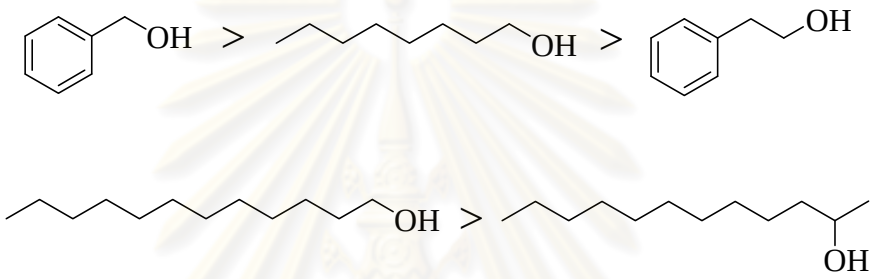
Entry	R^1OH	R^2OH	% Yield[a] R^1I/R^2I	Recovered alcohol[a] (%) R^1OH/R^2OH	Σ (%)
1			96/95	0/0	96/95
2[b]			36/95	60/0	96/95
3			95/22	3/75	98/97
4			99/36	0/56	99/92
5			86/12	9/81	95/93

[a] analyzed by ^{1}H-NMR based on toluene 10 μL
[b] 15 min

For the experimental time around 30 min, the amount of the products gained from 1-octanol and benzyl alcohol (long chain primary alcohol *vs* benzylic primary alcohol) was not different (entry 1); nevertheless, in 15 min benzyl alcohol gave the designated product more than 1-octanol (entry 2). 1-Octanol and benzyl alcohol could still be converted to the desired alkyl iodide in predominant yield compared with 2-phenylethanol (entries 3 and 4). 1-Iodododecane was obtained in 86% yield whereas

2-iododododecane was obtained in 12% yield (entry 5). This result gave an informative clue that the iodination of primary alcohol was more reactive than that of secondary alcohol under developed system.

According to the aforementioned results, the reactivity of alcohols with $ClPPh_2$/NaI/Bu_4NI could clearly be concluded: 1) benzyl alcohols appear to be the most reactive under this developed system supporting the S_N2 mechanism 2) long chain primary alcohols are more reactive than steric primary alcohols. 3) primary alcohols are more reactive than secondary alcohols. The order of reactivity of alcohols is displayed below.



3.2 Alkyl bromide

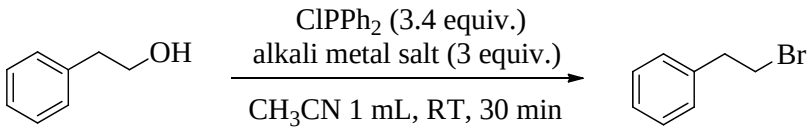
3.2.1 Study on optimum conditions for conversion of alcohols to alkyl bromides

Several parameters including type of alkali metal salts, the amount of LiBr, and Bu_4NBr, reaction time, and solvents were investigated to optimize the reaction conditions for conversion of alcohols to alkyl bromides. For optimizing the reaction conditions, 2-phenylethanol was used as a model substrate. In this optimizing study, the obtained product was characterized by ^{1}H-NMR based on a standard toluene 10 µL.

3.2.1.1 Effect of alkali metal salts

Significant differences in the reactivities of alkyl bromide were mainly caused from types of alkali metal salts. The results of the effect of halogenating agent on the formation of 1-octadecyl benzoate are collected in Table 3.7.

Table 3.7 Effect of alkali metal salts in the synthesis of 2-phenylethyl bromide



0.25 mmol

Entry	Alkali metal salt	Yield[a]				Σ (%)
		2-Phenylethyl bromide	2-Phenylethyl chloride	Recovered alcohol	Other[b]	
1	LiBr	~100	-	-	trace	100
2	NaBr	46	17	17	17	97
3	KBr	69	-	23	11	104

[a] analyzed by ^{1}H-NMR based on toluene 10 μL
[b] %yield of 2-phenylethyl diphenylphosphinite and 2-phenylethyl diphenylphosphinite oxide

The effect of alkali metal salts on the synthesis of alkyl bromides was manifestly observed when using NaBr (entry 2), the desired product was obtained only 46% yield. NaBr was less soluble in CH_3CN, thus causing the competition between Cl^- from $ClPPh_2$ and Br^- from NaBr. The reaction using LiBr (entry 1) gave the desired product in quantitative yield. Accordingly, LiBr was a suitable brominating agent and was used for further exploration.

3.2.1.2 Effect of the amounts of LiBr

In order to find out the optimized conditions, the amount of LiBr was one of crucial parameters for the reaction that needed to examine. The outcome is presented in Table 3.8.

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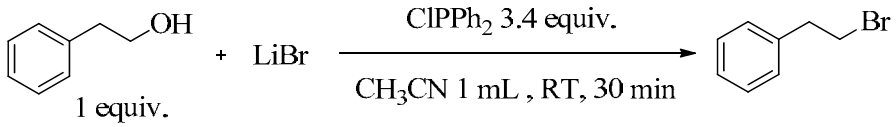
Table 3.8 Effect of the amounts of LiBr in the synthesis of 2-phenylethyl bromide



Entry	LiBr (equiv.)	% Yield[a]			Σ (%)
		2-Phenylethyl bromide	Recovered Alcohol	Other[b]	
1	1	30	64	4	98
2	2	58	29	3	90
3	2.5	83	17	3	103
4	3	100	-	trace	100

[a] analyzed by ^{1}H-NMR based on toluene 10 μL
[b] %yield of 2-phenylethyl diphenylphosphinite and 2-phenylethyl diphenylphosphinite oxide

The yield of 2-phenyl bromide was increased from 30 to 100% upon raising the amount of LiBr from 1 to 3 equiv.. The use of LiBr 3 equiv. gave a quantitative yield of the desired product.

3.2.1.3 Effect of the amount of Bu_4NBr and reaction time

The amount of Bu_4NBr and reaction time were important factor for bromination of 2-phenylethanol. The results are shown in Table 3.9.

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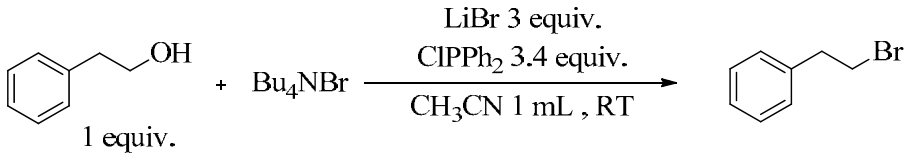
Table 3.9 Effect of the amounts of Bu_4NBr and reaction time



Entry	Bu_4NBr (equiv.)	Reaction time (min)	% Yield[a]			Σ (%)
			2-Phenylethyl bromide	Recovered alcohol	Other[b]	
1	-	15	80	16	3	99
2	-	30	100	-	-	100
3	0.15	15	86	-	-	86
4	0.3	15	92	-	-	92

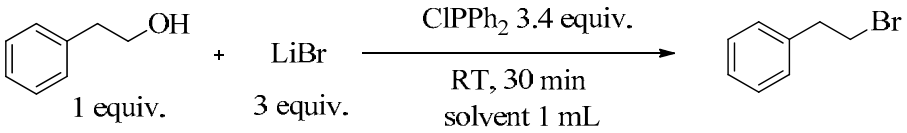
[a] analyzed by ^{1}H-NMR based on toluene 10 μL
[b] %yield of 2-phenylethyl diphenylphosphinite and 2-phenylethyl diphenylphosphinite oxide

Table 3.9 reveals that when the reaction was carried out in the absence of Bu_4NBr at 30 min (entry 2), the desired product was obtained in 100% yield. The reaction using Bu_4NBr 0.15 equiv. at 15 min gave 2-phenylethyl bromide in 86% yield (entry 3). Comparing the effect of Bu_4NBr at the reaction time of 15 min, without the addition of this bromide salt, 2-phenylethyl bromide was merely obtained in 80% yield (entry 1), whereas the addition of Bu_4NBr 0.3 equiv. yielded the target product in 92% yield (entry 4). However, Bu_4NBr is rather expensive. To prolong the reaction time to 30 min was determined as the most proper optimized conditions (entry 2).

3.2.1.4 Effect of solvents

2-Phenylethanol was selected as a model substrate to explore the solvent effect on this reaction. The treatments of 2-phenylethanol (1 equiv.), $ClPPh_2$ and LiBr in four diverse solvents were displayed in Table 3.10.

Table 3.10 Effect of solvents



Entry	Solvent	% Yield[a]
1	CH_3CN	100
2	Toluene	62
3	THF	58
4	Benzene	56
5	CH_2Cl_2	91

[a] analyzed by ^{1}H-NMR based on toluene 10 μL

From Table 3.10, toluene, THF and benzene provided the desired product in moderate yields (entries 2-4). When CH_3CN and CH_2Cl_2 were used, 2-phenylethyl bromide was obtained in high yield (entries 1 and 5). Nevertheless, when CH_2Cl_2 was employed in this reaction (entry 5), the solubility of LiBr in this solvent was poor. After screening a number of solvents, CH_3CN was found to suit the need for this reaction.

3.2.2 The synthesis of alkyl bromide

Since the optimized conditions could be obtained as previously discussed, the scope of the reaction to convert various alcohols into their corresponding alkyl bromide was further investigated. The results are displayed in Table 3.11.

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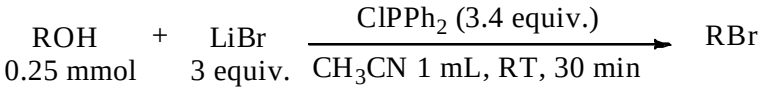
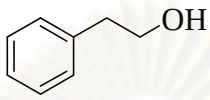
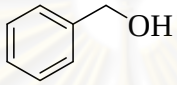
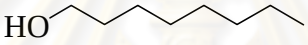
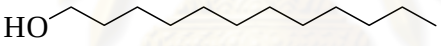
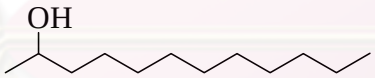
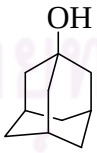
Table 3.11 The synthesis of alkyl bromide from alcohols using $ClPPh_2$/LiBr in CH_3CN at RT



Entry	Substrate	Product[a] (%yield)
1		100
2		99
3		98
4		99
5		72
6		20[b]

[a] analyzed by ^{1}H-NMR based on toluene 10 μL
[b] isolated yield

Various primary alcohols could be completely converted to the corresponding alkyl bromides in high to quantitative yield (entries 1-4). Alcohols containing two or three carbon linkages between phenyl ring and hydroxy group could be converted to the corresponding chlorides in excellent yields (entry 1). Similarly, the preparation of benzyl bromide was also achieved using benzyl alcohol in a quantitative yield (entry 2). In the case of long chain aliphatic alcohols including 1-octanol and 1-dodecanol,

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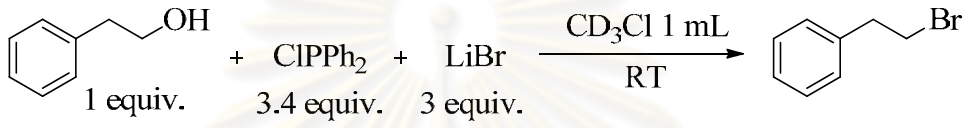
the carbon chain length, perhaps being considered as steric hindrance, did not affect this reaction (entries 3-4). For secondary alcohol, 2-dodecanol could be converted to the corresponding bromide in moderated yield (entry 5). The conversion of 1-adamantanol to the corresponding alkyl bromide could also be achieved in low yield (entry 6) because steric hindrance.

3.2.3 Kinetic study

The kinetic study of the bromination of 2-phenylethanol under the optimized conditions was explored. The results are presented as shown in Figure 3.3.



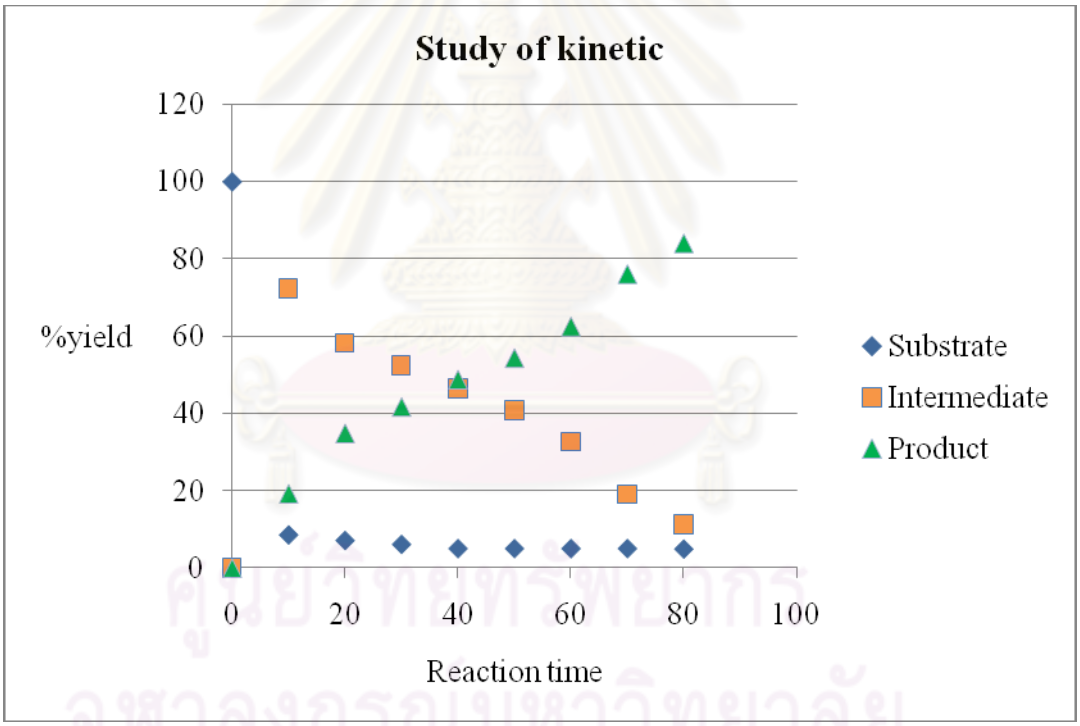


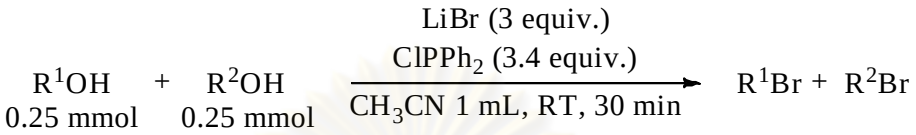
Figure 3.3 Kinetic study of the bromination of 2-phenylethanol under the optimized conditions

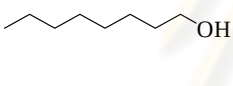
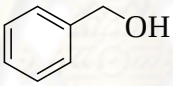
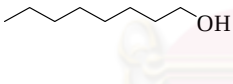
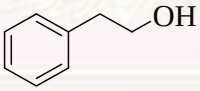
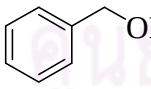
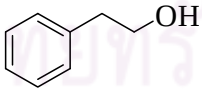
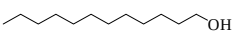
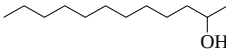
With the aids of ^{1}H-NMR spectroscopy, it was clearly seen that the reaction produced alkyl diphenylphosphinite as a detected intermediate in the early stage. The maximum amount was around 10 min and then gradually reduced. The formation of the product could be observed after 10 min and the maximum yield was found around 80 min.

3.2.4 Reactivity study of selected alcohols

The relative reactivity of various alcohols with $ClPPh_2$/LiBr was further studied by competing two selected alcohols under the optimum reaction conditions. The outcome is presented in Table 3.12.

Table 3.12 Reactivity study of selected alcohols

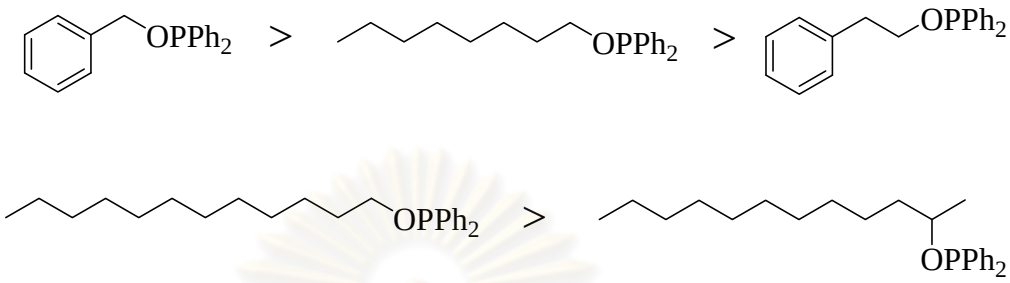


Entry	R^1OH	R^2OH	% Yield[a] R^1Br/R^2Br	Recovered alcohol[a] (%) R^1OH/R^2OH	Σ (%)
1			0/98	93/0	93/98
2			98/1	2/96	100/97
3			38/3	58/93	96/96
4			38/0	61/93	95/93

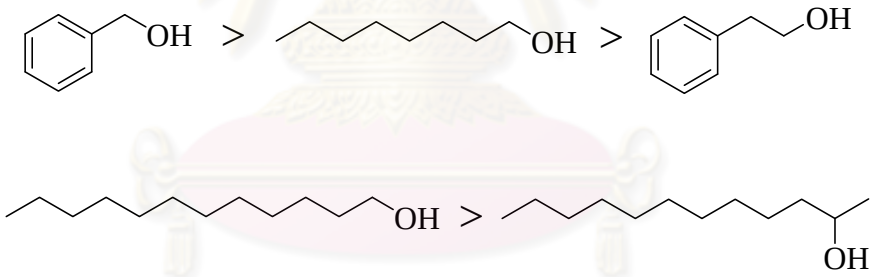
[a] analyzed by ^{1}H-NMR based on toluene 10 μL

The results of reactivity of alcohols with $ClPPh_2$/LiBr exhibited the same trend as those with $ClPPh_2$/NaI/Bu_4NI. In addition, kinetic studies indicated that alcohols quickly reacted to $ClPPh_2$, producing alkyldiphenylphosphenite intermediate in the

first step. On the other hand, the transformation of these resulting intermediates into alkyl bromides slowly preformed *via* S_N2 mechanism, which suggests that the first step is the rate-determining step. Therefore, the order of reactivity of alkyl diphenylphosphenite is displayed below.

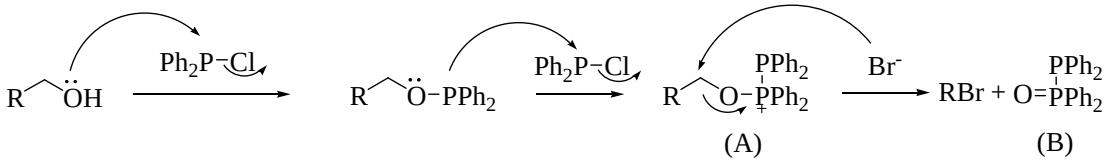


According to the aforementioned results, the reactivity of alcohols with $ClPPh_2$/LiBr could clearly be concluded: 1) benzyl alcohols appear to be the most reactive under this developed system supporting the S_N2 mechanism 2) long chain primary alcohols are more reactive than steric primary alcohols. 3) primary alcohols are more reactive than secondary alcohols. The order of reactivity of alcohol is displayed below.



3.2.5 The proposed mechanism

The reaction pathway for the formation of alkyl iodides was proposed as illustrated in Scheme 3.2. In the first step, alcohol initially reacted with $ClPPh_2$ to generate alkyl diphenylphosphinite. Then alkyl diphenylphosphinite was reacted with $ClPPh_2$ to generate intermediate **A** and then the reaction of the intermediate with iodide anion formed alkyl iodide and by-product **B**.



Scheme 3.2 Proposed mechanism for bromination of alcohol.

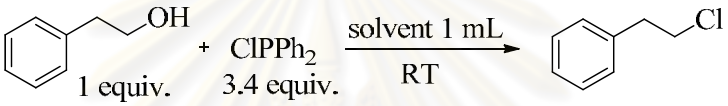
3.3 Alkyl chloride

3.3.1 Study on optimum conditions for conversion of alcohols to alkyl chlorides

Various factors including reaction time and solvents were scrutinized to evaluate for the optimal conditions for the conversion of alcohols to alkyl chlorides. 2-Phenethyl alcohol was selected as a chemical model. In this optimizing study, the obtained product was characterized by ^{1}H-NMR based on a standard toluene 10 μL.

The effect of reaction time and solvents was investigated and the results are accumulated in Table 3.13.

Table 3.13 Effect of reaction time and solvents



Entry	Solvent (mL)	Reaction time (min)	% Yield[a]			Σ (%)
			2-Phenylethyl chloride	Recovered alcohol	Other[b]	
1	CH_3CN	30	17	71	9	97
2		45	20	70	8	98
3	CH_2Cl_2	30	76	17	8	101
4		45	90	-	10	100

[a] analyzed by ^{1}H-NMR based on toluene 10 μL

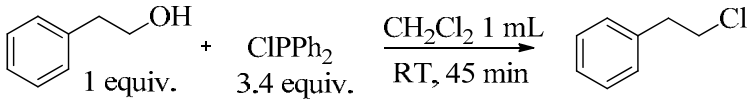
[b] %yield of 2-phenylethyl diphenylphosphinite and 2-phenylethyl diphenylphosphinite oxide

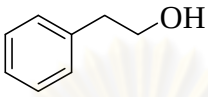
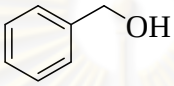
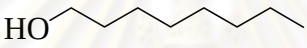
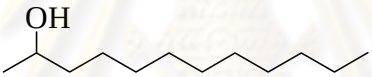
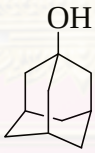
From Table 3.13, CH_3CN provided the desired product in low yields (entries 1-2). When CH_2Cl_2 was used, 2-phenylethyl chloride was obtained in high yield (entries 3-4). After screening a number of solvents, CH_2Cl_2 was found to suit the need for this reaction.

3.3.2 The synthesis of alkyl chloride

In order to explore the scope and limitations of this methodology, the treatment of various alcohols (1 equiv.) with $ClPPh_2$ (3.4 equiv.) in CH_2Cl_2 at RT afforded a wide range of alkyl chlorides as summarized in Table 3.14.

Table 3.14 The synthesis of alkyl chloride from alcohols using $ClPPh_2$ in CH_2Cl_2 at RT



Entry	Substrate	Product[a] (%yield)
1		90
2		89
3		86
4		55
5		10[b]

[a] analyzed by ^{1}H-NMR based on toluene 10 μL
[b] isolated yield

Primary alkyl alcohols (2-phenylethanol and 1-octanol) and benzyl alcohol underwent a clean reaction providing the corresponding alkyl chlorides in excellent yields (entries 1-3). The conversion of 2-dodecanol and 1-adamantanol to the corresponding alkyl chlorides could also be achieved in moderate and low yields (entries 4-5). Steric hindrance of substrate might cause incomplete reaction.

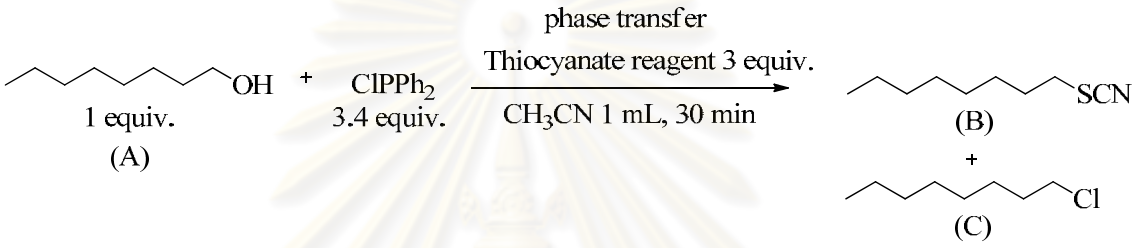
3.4 Related compounds

This disclosed methodology for the preparation of alkyl halide directly from alcohol was further applied for one-pot synthesis of alkyl thiocyanate and azide.

3.4.1 Alkyl thiocyanate

From the success of using the optimum reaction conditions to synthesize the desired alkyl halides, this general procedure was further investigated. The conversion of alcohol into alkyl thiocyanate was first explored. 1-Octanol was selected as a model substrate to search for an optimized condition. The reactions of 1-octanol (1 equiv.) and $ClPPh_2$ (3.4 equiv.) with various thiocyanate reagents and phase transfers in CH_3CN were carried out at RT for 30 min. The outcomes are shown in Table 3.15.

Table 3.15 Effect of thiocyanate reagents and phase transfers

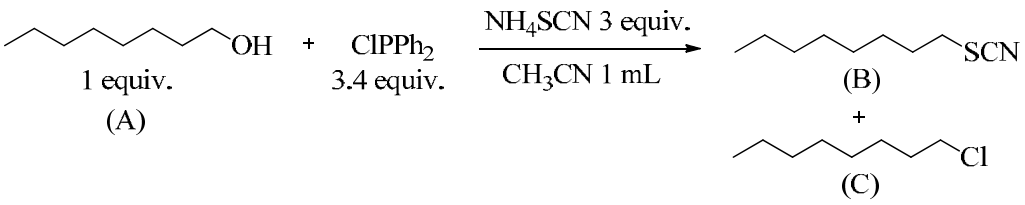


Entry	Thiocyanate reagent	phase transfer		Product[a] (%yield)				Σ (%)
		Type	equiv.	A	B	C	Other[b]	
1		-	-	10	28	22	44	94
2	KSCN	Bu_4NSCN	0.8	15	30	4	46	95
3		Bu_4NBr	0.09	10	27	14	43 (3)[c]	97
4		-	-	25	32	trace	46	103
5	NH_4SCN	Bu_4NSCN	0.8	10	32	15	38	95
6		Bu_4NBr	0.09	12	33	10	44 (4)[c]	103

[a] analyzed by ^{1}H-NMR based on toluene 10 μL
[b] %yield of 1-octyl diphenylphosphinite and 1-octyl diphenylphosphinite oxide
[c] 1-octyl bromide

From Table 3.15, the reaction using KSCN gave 1-thiocyanatooctane in 27-30% yield (entries 1-3). On the other hand, the similar reactions in the presence of NH_4SCN afforded the desired product around 30% yield (entries 4-6). NH_4SCN was selected as the optimal reagent. The reaction time for the production of 1-thiocyanatooctane was next examined. The results are collected as shown in Table 3.16.

Table 3.16 Effect of reaction times



Entry	Phase transfer	Reaction time (h)	Product[a] (%yield)				Σ (%)
			A	B	C	Other[b]	
1	-	0.5	25	32	trace	46	103
2		1	11	35	15	38	99
3		2	trace	36	11	44	91
4[c]		2	-	45	15	30	90
5		8	-	37	17	40	94
6[c]		8	-	50	15	30	90
7	Bu_4NSCN	0.5	10	32	15	38	95
8		1	-	34	14	43	91
9		2	-	36	15	40	91
10		8	-	40	10	42	92
11[c]		8	-	52	10	31	93

[a] analyzed by ^{1}H-NMR based on toluene 10 μL
[b] %yield of 1-octyl diphenylphosphinite and 1-octyl diphenylphosphinite oxide
[c] reflux temperature

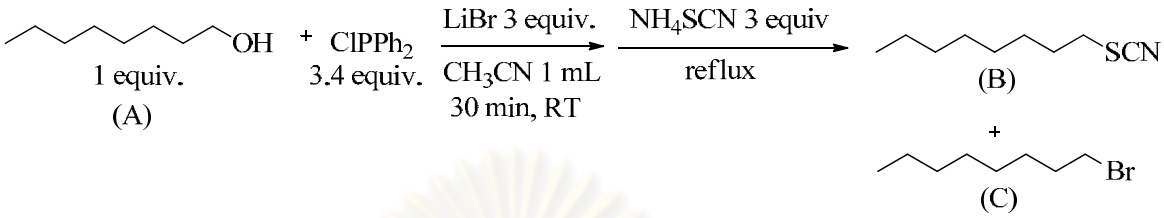
As shown in Table 3.16, the reaction in the presence or absence of Bu_4NSCN did not show the difference in the production of 1-thiocyanatooctane (entries 1-11). The reaction at reflux yielded the desired product in higher yield than that obtained at RT; however, only 50% (entries 6 and 11). From the above observations, the amount of the desired product was unsatisfactory. Therefore, more studies are carried out by two-step procedure.

Step I: The preparation of alkyl bromide using 1-octanol 1 equiv. (0.25 mmol) as a substrate, LiBr 3 equiv. (0.75 mmol), $ClPPh_2$ 3.4 equiv. (0.85 mmol) for 30 min at RT.

Step II: The synthesis of thiocyanate was completed from the reaction of the received alkyl bromide with NH_4SCN 3 equiv. (0.75 mmol).

The reaction time for the production of 1-thiocyanatooctane was next examined. The results are described in Table 3.17.

Table 3.17 Effect of reaction times in two-step synthesis



Entry	Reaction time (h)	Product[a] (%yield)				Σ (%)
		A	B	C	Other[b]	
1	0.5	-	20	76	-	96
2	2	-	36	59	-	95
3	5	-	49	48	-	97
4	8	-	77	18	-	95

[a] analyzed by ^{1}H-NMR based on toluene 10 μL
[b] %yield of 1-octyl diphenylphosphinite and 1-octyl diphenylphosphinite oxide

As show in Table 3.17, the synthesis of 1-thiocyanatooctane was performed at reflux using reaction time from 0.5 to 8 h (entries 1-4). The reaction gave the highest yield of products within 8 h. In addition, using the same protocol for other alcohols to verify the optimized condition was carried out. The outcomes are presented in Table 3.18.

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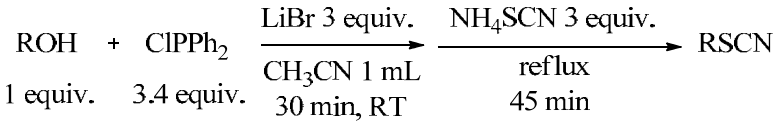
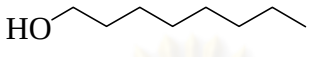
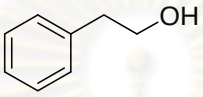
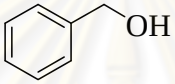
Table 3.18 The synthesis of alkyl thiocyanate from alcohols



Entry	Substrate	Product[a] (%yield)
1		77
2		78
3		80

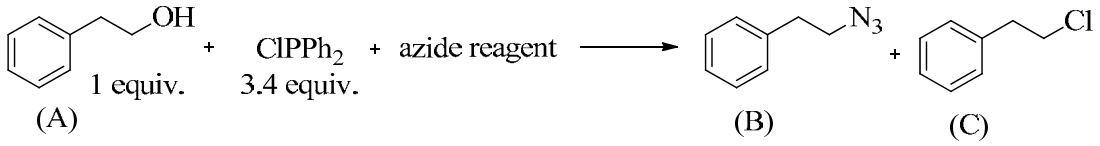
[a] analyzed by ^{1}H-NMR based on toluene 10 μL

By utilizing the two-step protocol, primary alkyl alcohols (entries 1 and 2) and benzyl alcohol (entry 3) could be transformed to the corresponding alkyl thiocyanates in high yields.

3.3.2 Alkyl azide

2-Phenylethanol was used as a model compound. Several parameters including type of azide reagents, the amount of azide reagents, temperature, reaction time, and solvents were investigated to optimize the reaction conditions for conversion of alcohols to alkyl azides. The obtained product was characterized by ^{1}H-NMR based on a standard toluene 10 μL. The results are presented in Table 3.19.

Table 3.19 The synthesis of alkyl azide from alcohols



Entry	Azide reagent		Reaction time (h)	Solvent		Temp. (°C)	Product[a] (%yield)				MB
	Type	Equiv.		Type	mL		A	B	C	Other[b]	
1				CH_2Cl_2	1	rt	20	-	62	10	92
2				CH_3CN	1	rt	80	-	10	8	98
3			0.25	THF	1	rt	82	-	8	8	98
4		1		DMSO	1	rt	90	-	-	-	90
5				CH_2Cl_2	1	rt	-	-	93	-	93
6	Me_3SiN_3		0.5	THF	1	rt	51	-	32	12	95
7				CH_3CN	1	rt	63	-	17	10	93
8				CH_2Cl_2	1	rt	-	-	95	-	95
9		2	0.5	THF	1	rt	55	-	31	10	96
10				CH_3CN	1	rt	59	-	20	12	91
11					1	rt	-	-	93	-	93
12				CH_2Cl_2	1	0	-	-	90	-	90
13					2	rt	15	-	80	-	95
14					1	rt	56	-	30	10	96
15					1	0	55	-	33	8	96
16	Me_3SiN_3	3	0.5	THF	1	reflux	30	-	55	10	95
17					2	rt	67	-	15	10	92
18					1	rt	69	-	15	6	90
19					1	0	70	-	20	2	92
20				CH_3CN	1	reflux	38	-	50	5	93
21					2	rt	80	-	9	5	94

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Table 3.19 (Continued)

Entry	Azide reagent		Reaction time (h)	Solvent		Temp. (°C)	Product[a] (%yield)				MB
	Type	Equiv.		Type	mL		A	B	C	Other[b]	
22					1	rt	-	-	95	-	95
23				CH_2Cl_2	1	0	-	-	90	-	90
24					2	rt	14	-	83	-	97
25					1	rt	54	-	35	10	99
26					1	0	55	-	35	8	98
27	Me_3SiN_3	3	2	THF	1	reflux	28	-	55	9	92
28					2	rt	65	-	20	10	95
29					1	rt	65	-	20	6	91
30					1	0	70	-	22	2	94
31				CH_3CN	1	reflux	28	-	60	5	93
32					2	rt	75	-	15	3	93

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Table 3.19 (Continued)

Entry	Azide reagent		Reaction time (h)	Solvent		Temp. (°C)	Product[a] (%yield)				MB
	Type	Equiv.		Type	mL		A	B	C	Other[b]	
33				CH_2Cl_2	1	rt	-	-	90	-	90
34		1	0.5	THF	1	rt	20	-	35	40	95
35				CH_3CN	1	rt	14	-	30	50	94
36				CH_2Cl_2	1	rt	-	-	92	-	92
37		2	0.5	THF	1	rt	20	-	38	38	96
38				CH_3CN	1	rt	13	-	32	45	90
39				CH_2Cl_2	1	rt	-	-	95	-	95
40			0.5		1	rt	18	-	39	40	97
41	NaN_3			THF	1	reflux	10	-	50	30	90
42					1	rt	18	-	31	43	92
43				CH_3CN	1	reflux	15	-	51	32	98
44		3		CH_2Cl_2	1	rt	-	-	95	-	95
45			2		1	rt	15	-	43	35	93
46				THF	1	reflux	15	-	43	30	90
47					1	rt	17	-	40	33	90
48				CH_3CN	1	reflux	10	-	60	25	95

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Table 3.19 (Continued)

Entry	Azide reagent		Reaction time (h)	Solvent		Temp. (°C)	Product[a] (%yield)				MB
	Type	Equiv.		Type	mL		A	B	C	Other[b]	
49				CH_2Cl_2	1	rt	-	-	93	-	93
50		1	0.5	THF	1	rt	25	-	30	37	92
51				CH_3CN	1	rt	16	-	30	50	96
52				CH_2Cl_2	1	rt	-	-	95	-	95
53		2	0.5	THF	1	rt	22	-	40	35	97
54				CH_3CN	1	rt	15	-	35	40	90
55				CH_2Cl_2	1	rt	-	-	95	-	95
56			0.5		1	rt	15	-	38	40	93
57	Bu_4NN_3			THF	1	reflux	13	-	51	30	94
58					1	rt	20	-	38	38	96
59				CH_3CN	1	reflux	15	-	45	32	92
60		3		CH_2Cl_2	1	rt	-	-	95	-	95
61			2		1	rt	20	-	45	30	95
62				THF	1	reflux	15	-	47	28	90
63					1	rt	19	-	42	33	94
64				CH_3CN	1	reflux	19	-	56	20	95

[a] analyzed by ^{1}H-NMR based on toluene 10 μL
[b] %yield of 2-phenyletyl diphenylphosphinite and 2-phenyletyl diphenylphosphinite oxide

The attempts to utilize this developed procedure for the synthesis of alkyl azide were carried out. Under various conditions, the alkyl chloride was detected as a product without formation of alkyl azide. After several attempts, it was rationally thought that the reagent $ClPPh_2$ may react with azide reagent. Based on previous

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literature, the reaction using $ClPPh_2$ and excess LiN_3 provided N_3PPh_2 as a colorless solid which decomposed at 13.6-13.8°C [46].

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CHAPTER IV

CONCLUSION

The objective of this research is to explore and develop the optimized conditions for the one-pot conversion of alkyl alcohol to alkyl halide using $ClPPh_2$ under mild conditions, short reaction time and high yield of products. The application of this developed methodology for the preparation of related compounds is also explored.

From this research, the optimum conditions for the conversion of alkyl alcohols into halides were disclosed. The outcome of the optimum conditions for the iodination of alcohols was that alcohol (1 equiv.) as substrate, $ClPPh_2$ (3.45 equiv.), NaI (3 equiv.) and Bu_4NI (0.8 equiv.) were recommended to carry out in CH_3CN under RT for 30 min. The preparation of alkyl bromide was carried out employing the same conditions as that of alkyl iodide but using LiBr instead of NaI and not using Bu_4NI. In synthesis of alkyl chloride, the optimal condition was using alcohol (1 equiv.) as substrate and $ClPPh_2$ (3.45 equiv.) in CH_2Cl_2 under RT for 45 min.

Various alcohols were examined to study on the halogenation effects of their alcohols under developed conditions. The characteristics of the developed system can be summarized below:

1) Primary alcohols appear to be the most reactive substrate in this reaction within short reaction time.
2) The steric hindrance of secondary or tertiary alcohols affects on the outcome of the reaction: a large steric interference leads to a low desired halides.

The application of this developed methodology to the synthesis of various thiocyanate was also fruitfully achieved. Therefore, the optimum conditions were synthesized by one-pot synthesis in two steps.

Step I: The preparation of alkyl bromide using 1-octanol 1 equiv. (0.25 mmol) as a substrate, LiBr 3 equiv. (0.75 mmol), $ClPPh_2$ 3.4 equiv. (0.85 mmol) for 30 min at RT.

Step II: The synthesis of thiocyanate was completed from the reaction of the received alkyl bromide with NH_4SCN 3 equiv. (0.75 mmol**)** for 8 h at reflux temperature.

However, the conversion of alcohols into azides is not possible mainly because the azide reagent reacted with $ClPPh_2$.

Proposal for the further work

This research distinctly revealed the successful methodology development for the preparation of alkyl halides and alkyl thiocyanate from alcohols *via* alkyl diphenyl- phosphinites in one-pot synthesis. This outcome opened many possibilities to deal with further exploration. This methodology should be applied with other related compound as amide, amine and ester.

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REFERENCES

[1] Mukaiyama, T.; Kuwajima, I.; Suzuki, Z. Novel Method for the Preparation of Acid Anhydrides by Means of Diphenylmercury and Tertiary Phosphine. J. Org. Chem. 28 (1963) : 2024-2027.

[2] Shinto, T.; Mukaiyama, T. Efficient Method for the Preparation of Primary, Inverted Secondary and Tertiary Alkyl Carboxylates from Alcohols and Carboxylic Acids by a New Type of Oxidation-Reduction Condensation Using Simple 1,4-Benzoquinone. Chem. Lett. 12 (2003) : 1100-1101.

[3] Shinto, T.; Kikuchi, W.; Mukaiyama, T. Efficient Method for the Preparation of Carboxylic Acid Alkyl Esters or Alkyl Phenyl Ethers by a New-Type of Oxidation–Reduction Condensation Using 2,6-Dimethyl-1,4-benzoquinone and Alkoxydiphenylphosphines. Bull. Chem. Soc. Jpn. 76 (2003) : 1645-1667.

[4] Mukaiyama, T.; Aoki, H. *N*-Alkylation of Phthalimide, Carboxamide, and Sulfonamides by Oxidation-Reduction Condensation Using Di-*tert*-butyl-1,4-benzoquinone and Alkyl Diphenylphosphinite. Chem. Lett. 2 (2005) : 142-143.

[5] Mukaiyama, T.; Ikegai, K. A New Method for the Preparation of Alkyl Sulfides from Alcohols *via* Alkoxydiphenylphosphines by Oxidation-Reduction Condensation. Chem. Lett. 33 (2004) : 1522-1523.

[6] Hudson, H. R.; Qureshi, A. R.; Ragoonanan, D. Factors in the Formation of Isomerically and Optically Pure Alkyl Halides. Part IX. Reactions of (1-Substituted *n*-Alkyl) Diphenylphosphinites with Hydrogen Halides and with Halogens. J. Chem. Soc. Perkin I (1972) : 1595-1597.

[7] Altenhoff, G.; Wurtz, S.; Gloriusb, F. The First Palladium-Catalyzed Sonogashira Coupling of Unactivated Secondary Alkyl Bromides. Tetrahedron Lett. 47 (2006) : 2925-2928.

[8] Huanga, X.; Xua, W. Polystyrene-Supported Benzyl Selenide: an Efficient Reagent for Highly Stereocontrolled Synthesis of Olefins and Allylic Alcohols. Tetrahedron Lett. 43 (2002) : 5495-5497.

[9] Pathak, A. K.; Pathak, V.; Seitz, L. E.; Suling, W. J.; Reynolds, R. C. Antimycobacterial Agents. 1. Thio Analogues of Purine. J. Med. Chem. 47 (2004) : 273-276.

[10] Munbunjong, W.; Lee, E. H.; Ngernmaneerat, P.; Kim, S. J.; Singh, G.; Chavasiri, W.; Jang, D. O. Indium-Mediated Cleavage of Diphenyl Diselenide and Diphenyl Disulfide: Efficient One-Pot Synthesis of Unsymmetrical Diorganyl Selenides, Sulfides, and Selenoesters. Tetrahedron 65 **(**2009) : 2467-2471.

[11] Grodnitzky, J. A.; Coats, J. R. QSAR Evaluation of Monoterpenoids' Insecticidal Activity. J. Agric. Food Chem. 50 (2002) : 4576-4580.

[12] Vogel, A. I. A Textbook of Practical Organic Chemistry. London: Longman Group, 1989.

[13] Norris, J. F.; Taylor, H. B. The Preparation of Alkyl Chlorides. J. Am. Chem. Soc. 46 (1924) : 753-757.

[14] Klein, S.M.; Zhang, C.; Jiang, Y.L. Simple Synthesis of Fresh Alkyl Iodides Using Alcohols and Hydriodic Acid. Tetrahedron Lett. 49 (2008) : 2638-2641.

[15] Caserio, F. C.; Dennis, G. E.; Dewolfe, R. H.; Young, W. G. The Reaction of Thionyl Chloride with Allylic Alcohols. J. Am. Chem. Soc. 77 (1955) : 4182-4783.

[16] Foland, L. D.; Decker, O. H.W.; Moore, H. W. Synthesis of Isoarnebifuranone, Nanaomycin, and Deoxyfrenolin. Structure Elucidation of Arenebifuranone. J. Am. Chem. Soc. 111 (1989) : 989-995.

[17] Baughman, T. W.; Sworen, C. J.; Wagener, B. K. The Facile Preparation of Alkenyl Metathesis Synthons. Tetrahedron 60 (2004) : 10943-10948.

[18] Coulson, E. J.; Gerrard, W.; Hudson, H. R. Factors in the Formation of Isomerically and Optically Pure Alkyl Halides. Part IV. The Tree Dealkylation Steps in Phosphorus Trihalide(Cl, Br, I)-alcohol Systems. J. Chem. Soc. (1965) : 2364-2369.

[19] Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. Studies in Organophosphorus Chemistry. I. Conversion of Alcohols and Phenols to Halides by Tertiary Phosphine Dihalides. J. Chem. Soc. 86 (1964) : 964-965.

[20] Weiss, R. G.; Snyder, E. I. Stereochemistry of Chloride Formation from Alcohols and Thiols by Use of Triphenylphosphine and Carbon Tetrachloride. J. Chem. Soc; Chem. Commun. 21 (1968) : 1358-1359.

[21] Miyano, S.; Watanabe, H.; Ushiyama, H.; Yamada, Y.; Hashimoto, H. Chlorination of Alcohols with Copper(II) Chloride and Triphenylphosphine. Nippon Kagaku Kaishi. 1 (1978) : 138-140.

[22] Ho, P.; Davies, N. Reaction of Alcohols with Zinc Halide, Diethyl Azodicarboxylate, and Triphenylphosphine. A Effective Method for the Preparation of Halides. J. Org. Chem. 61 (1984) : 3027-3029.

[23] Matveeva, E. D.; Kurts, A. L.; Yalovskaya, A. I.; Nikishova, N. G.; Bundel, Y. G. Regio- and Stereospecific Substitution of the Hydroxyl of Aliphatic Alcohols with Halogen J. Org. Chem. Russia 25 (1989) : 716-721.

[24] Matveeva, E. D.; Podrugina, T. A.; Zefirov, N. S. 2,4,4,6-Tetrabromocyclohexa-2,5-dienone in the Presence of Triphenylphosphine as a Regiospecific and Stereoselective Reagent for the Nucleophilic Substitution of Bromine for Hydroxyl. Mendeleev Commun. 8 (1998) : 21-22.

[25] Drabowicz, J.; Luczak. J.; Mikolajczyk, M. Triphenylphosphine /Dichloroselenurane: A New Reagent for a Selective Conversion of Alcohols into Alkyl Chlorides. J. Org. Chem. 37 (1972) : 1466.

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

[27] Pollastri, M. P.; Sagal, J. F.; Chang, G. The Conversion of Alcohols to Halides using a Filterable Phosphine Source. Tetrahedron Lett. 42 (2001) : 2459-2460.

[28] Iranpoor, N.; Firouzabadi, H.; Aghapour, G.; Zadeh, A. R. V. Triphenylphosphine/2,3-Dichloro-5,6-dicyanobenzoquinone as a New, Selective and Neutral System for the Facile Conversion of Alcohols, Thiols and Selenols to Alkyl Halides in the Presence of Halide Ions. Tetrahedron 58 (2002) : 8689-8693.

[29] Desmaris, L.; Percina N.; Cottier, L.; Sinou, D. Conversion of Alcohols to Bromides Using a Fluorous Phosphine. Tetrahedron Lett. 44 (2003) : 7589-7591.

[30] Iranpoor, N.; Firouzabadi, H.; Jamalian, A.; Kazemi, F. Silicaphosphine (Silphos): a Filterable Reagent for the Conversion of Alcohols and Thiols to Alkyl Bromides and Iodides. Tetrahedron Lett. 61 (2005) : 5699-5704.

[31] Pluempanupat, W.; Chavasiri, W. An efficient Method for Chlorination of Alcohols Using PPh_3/Cl_3CCONH_2. Tetrahedron Lett. 47 (2006) : 6821-6823.

[32] Hajipour, A. R.; Falahati, A. R.; Ruoho, A. E. Iodination of Alcohols Using Triphenylphosphine/Iodine Under Solvent-Free Conditions Using Microwave Irradiation. Tetrahedron Lett. 47 (2006) : 4191-4196.

[33] Firouzabadi, H.; Iranpoor, N.; Ebrahimzadeh, F. Facile Conversion of Alcohols into Their Bromides and Iodides by *N*-bromo and *N*-iodosaccharins/triphenylphosphine under neutral conditions. Tetrahedron Lett. 47 (2006) : 1771-1775.

[34] Tongkate, P.; Pleumpanupat, W.; Chavasiri, W. Hexabromoacetone and Ethyl Tribromoacetate: A Highly Efficient Reagent for Bromination of Alcohols. Tetrahedron Lett. 49 (2008) : 1146-1148.

[35] Bandgar, B. P.; Sadavarte, V. S.; Uppalla, L. S. An Expedient and Highly Seletive Iodination of Alcohols Using a $KI/BF_3{\cdot}Et_2O$ System. Tetrahedron Lett. 42 (2001) : 951-953.

[36] Bandgar, B. P.; Sadavarte, V. S.; Bettigeri, S. V. Selective Iodination of Benzylic Alcohols with KI/H_2SO_4 Supported on Natural Kaolinitic Clay Under Microwave Irradiation. Monatshefte für Chemie 133 (2002) : 345-348.

[37] Hayat, S.; Rahman, A. U.; Khan, K. M.; Choudhary, M. I.; Maharvi, G. M.; Ullah, Z.; Bayer, E. An Alternative Method for the Highly Seletive Iodination of alcohols Using a CsI/ $BF_3{\cdot}Et_2O$ System. Synth. Commun. 14 (2003) : 2531-2540.

[38] Tajik, H.; Shirini, F.; Zolfigol, M. A.; Samimi, F. Convenient and Efficient Method for the Iodination of Benzylic and Aliphatic Alcohols by Using $Al(HSO_4)_3$/KI in Nonaqueous Solution. Synth. Commun. 36 (2006) : 91-95.

[39] Hajipour, A. R.; Zarei, A.; Ruoho, A. E. Efficient Method for Iodination of Alcohols Using KI/Silica Sulfuric Acid (SSA). Synth. Commun. 36 (2006) : 1039-1050.

[40] Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Azadi, R. Conversion of Alcohols, Thiols, Carboxylic Acids, Trimethylsilyl Eters, and Carboxylates to Thiocyanates with Triphenylphosphine/Diethylazodicarboxylate/NH_4SCN. Synthesis 1 (2004) : 92-96.

[41] Hiegel, G. A.; Nguyen, J.; Zhou, Y. Preparation of Alkyl Nitrates, Nitriles and Thiocyanates from Alcohols Utilizing Trichloroisocyanuric Acid with Triphenylphosphine. Synth. Commun. 34 (2004) : 3449-3453.

[42] Iranpoor, N.; Firouzabadi, H.; Nowrouzi, N. Preparation of Thiocyanates and Isothiocyanates from Alcohol, Thiols, Trimethylsilyl-, and Tetrahydropyranyl Ethers Using Triphenylphosphine/2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)/n-Bu4NSCN system. Tetrahedron 62 (2006) : 5498-5501.

[43] Saito, A.; Saito, K.; Tanaka, A.; Oritani, T. An efficient method for converting Alcohols to Azide with 2,4,4,6-tetrabromo-2,5-cyclohexadienone/PPh_3 /$Zn(N_3)_2 \cdot 2Py$. Tetrahedron Lett. 38 (1997) : 3955-3958.

[44] Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Nowrouzi, N. A Novel and Highly Selective Conversion of Alcohol, Thiols, and Silyl Ethers to Using the Triphenylphosphine/2,3-dichloro-5,6-dicyanobenzoquinone(DDQ)/n-Bu_4NN_3 system. Tetrahedron Lett. 45 (2004) : 3291-3294.

[45] Kuroda, K.; Hayashi, Y.; Mukaiyama, T. Conversion of Tertiary Alcohols to tert-Alkyl Azides by Way of Quinone-Mediated Oxidation-Reduction Condensation Using Alkyl Diphenylphosphinites. J. Org. Chem. 63 (2007) : 6358-6364.

[46] Paciorek, K. L.; Kratzer, R. Preparation of Diphenylphosphinous Azide and Syntheses of Phosphonitriles. Inorg. Chem. 3 (1964) : 594-595.

APPENDIX

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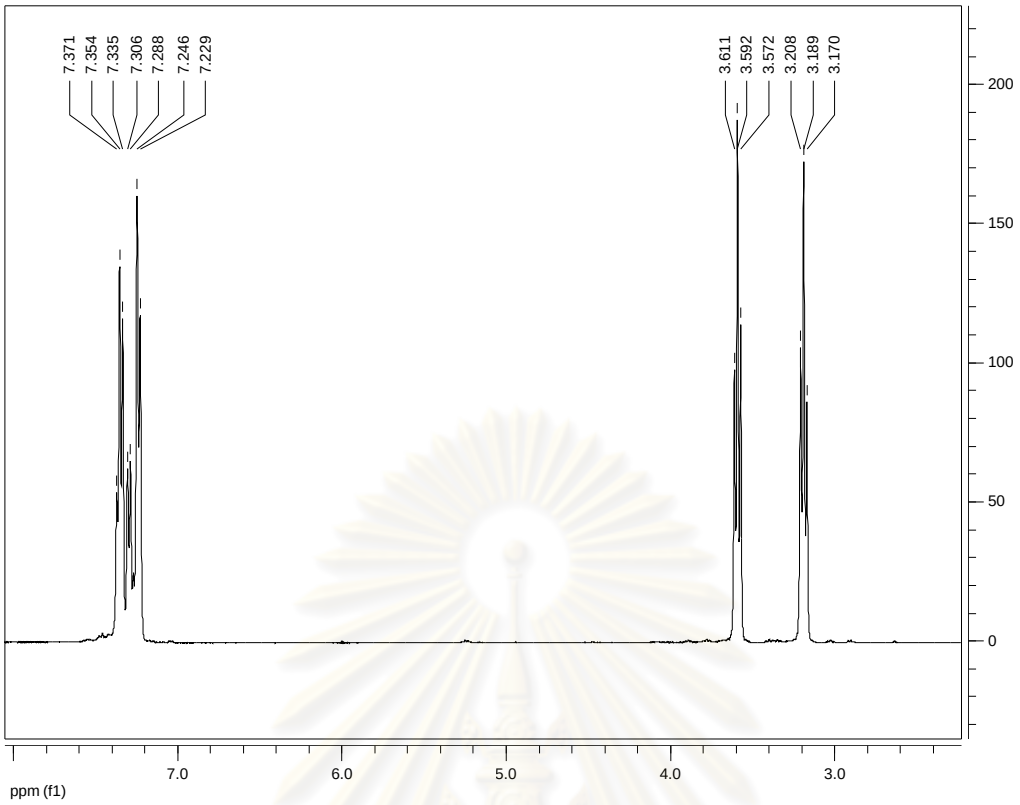

Figure A-1 The ^{1}H-NMR spectrum of 2-phenylethyl bromide

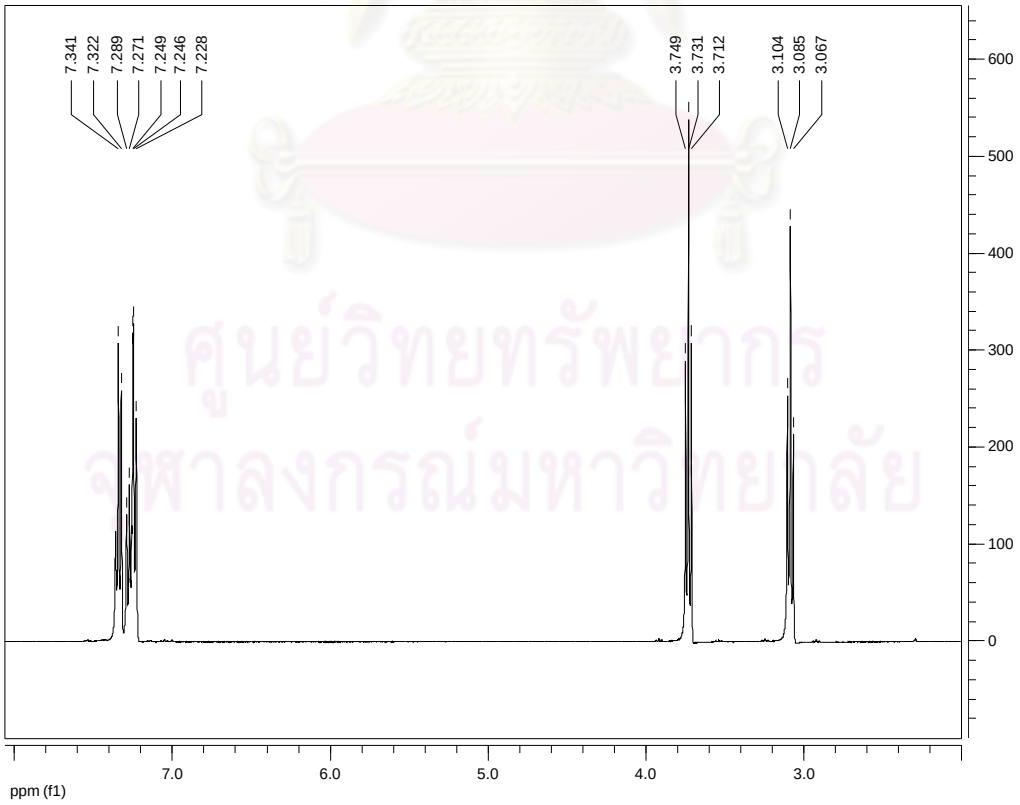

Figure A-2 The ^{1}H-NMR spectrum of 2-phenylethyl chloride

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