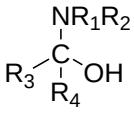
# CHAPTER 1

# SYNTHESIS OF AMINO ALCOHOLS AND ESTERS

# 1. Introduction

## 1.1 Amino Alcohol

In general amino alcohols are organic compounds that contain both an amine functional group (–N-$R_1R_2$) and an alcohol functional group (-OH) and may be considered as a derivative of amine or as a derivative of alcohol. Both of these groups can play a role in the reaction depending upon the nature of the reactions. The biological activities associated with this functional group have attracted intense interests among organic, physical and medicinal chemists. In general amino alcohol was named by referring to the orientation of amino group and hydroxyl group. Generally substituted amino alcohols always known in simple term as 1,1-amino alcohol (**1**), 1,2- amino alcohol (**2**), 1,3- amino alcohol (**3**), 1,4- amino alcohol (**4**) and etc. The orientation and arrangement of these functional groups indicate the type of amino alcohol: they are aliphatic, alicyclic, cyclic or aromatic divalent.

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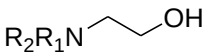


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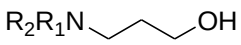


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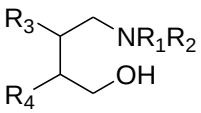



**4**

$R_1$, $R_2$, $R_3$, $R_4$ = H, alkyl, aryl

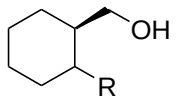
### 1.1.1 Importance of Amino Alcohols

Amino alcohols are an important class of compounds. These types of compounds have been used widely in many parts of chemistry especially in organic chemistry,[1] biochemistry,[2,3] medicinal chemistry,[4-8] physical organic chemistry[9-14] and applied chemistry.[15] Their special abilities were contributed by amine and alcohol

functional groups. The presence of amino and hydroxyl group can play great role in mimic the enzyme-like catalysts reaction. The protonated amino group might recruit a negatively charged side chain in the antibody. The hydroxy group, which mimics part of the postulated tetrahedral transition state, might recruit hydrogen bonding donor/acceptor system. One example of the type of catalytic system envisaged is the carboxylate/carboxylic acid couple of the aspartic proteinases.[15,16]

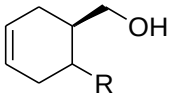
Amino alcohols were widely used to studies the activity of active esters especially *p*-nitrophenyl acetate.[9-14] Reactions of active esters played a great importance as the models the mechanism of action of "serine enzymes".[17] Werber and Shalitin studied the reaction of tertiary amino alcohols with active ester such as *p*-nitrophenyl acetate.[13,14] Meanwhile, Hine and Khan studied the reaction of 1,4-amino alcohol with *p*-nitrophenyl acetate.[9-12] These types of studies allowed chemists to understand the reaction occurred in enzymes systems due to the reaction of amino alcohol at carbonyl carbon active esters. This can be classified into two classes; first class contains nucleophiles which efficiently attack at active ester substrates to form stable acylated compounds. These reactions can serve as models for the enzymes-acylation step. In the other class a catalytic group is built into the substrate molecule in a favorable steric position and it intramolecularly catalyzes the hydrolysis of the susceptible group, thus imitating the deacylation step of the enzymatic mechanism.[13,14] The mechanisms have similarity with the action of acetylcholine esterase, α-chymotrypsin, and several other enzymes apparently involves attack on the substrate carbonyl carbon group by serine hydroxyl group that is hydrogen bonded to an imidazole nitrogen atom from a histidine residue.[17,18]

Several example of 1,3- amino alcohol (**5-8**) with adjacent stereogenic centers find noteworthy applicability in synthetics and medicinal chemistry. Homochiral **5-8** can serve as building blocks of pharmacology active fused saturated 1,3-heterocycles.[19]




R = **5** = 

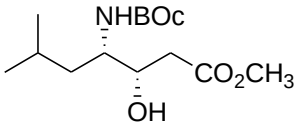
**6** = 




R = **7** = 

**8** = 

The biological activities of amino alcohol associated with this functional group have attracted intense interests among organic and medicinal chemists in these compounds. For example, statine (**9**), the key component of the naturally occurring pepstatin, which is the prototype of the amino alcohols with the protease inhibitory activities.[20] A number of reported syntheses of statine attest the importance of amino alcohol compounds. β-Amino alcohol derivative is one of the moiety present in a number of potent antimalarial,[4-8] drug exemplied by quinine (**10**) and mefloquine (**11**). Moreover, structural requirements for antiplasmodial activity of amino alcohol antiplasmodial agents include the presence of an aromatic portion and amino alcohol portion in such a way that the amino and alcohol groups are separated by two to three carbon atoms.[5] Paclitaxel[21] (**12)**, is used as antibacterial agent and chlorampenicol[22] (**13)** is used as anti-cancer.

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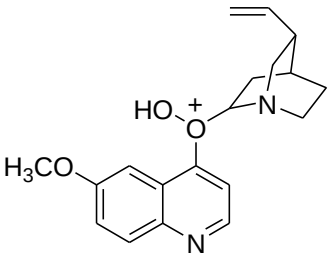


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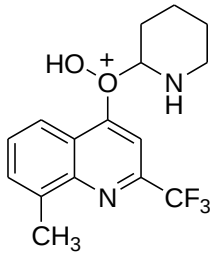


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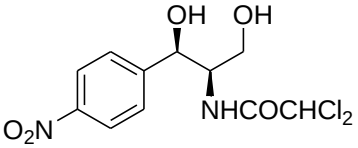


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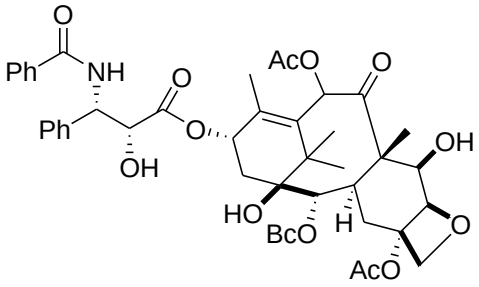
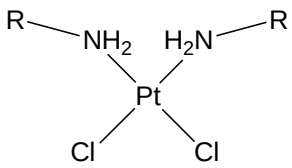



**13**

Nowadays, the central targets of anticancer drug have successfully discovery and developed compounds which have a higher stability in blood and enforce their tumour-inhibiting capability in the cancer cell.[23] A further important features of amino alcohol platinum complexes (**14**) are the ability of the ligand hydroxyl group, as well as of the alcoholato oxygen atom in the ring closed species, to form hydrogen bonds with nucleobases. This hydrogen bonding is expected to play a crucial role in the binding of the platinum compound to DNA.[24]



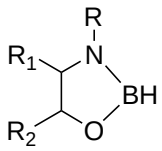

**14**

R = -$CH_2CH_2OH$, -$(CH_2)_2OH$, -$(CH_2)_4OH$

The major reported application of amino alcohol derivatives in organic synthesis were in the asymmetry synthesis. Oguni and Omi reported the ability of chiral 2-amino alcohols to catalyze the enantioselective addition of diethylzinc to benzaldehyde.[25] After that report, a wide variety of related reactions have been described in the literature and excellent levels of enantioselection have been achieved. In particular, $R_2Zn$ modified with chiral amino alcohol shows a high ability to promote the asymmetric alkylation prochiral aldehyde and ketone. The reaction was based on the enantioselective addition of organomettalic reagents to prochiral aldehydes and ketone. The addition of carbon-nucleophiles to this carbonyl compound to give secondary alcohols is one of the basic reactions of organic synthesis. Enantiomerically pure alcohols are particularly useful as building blocks for the synthesis of natural products and pharmaceutical chemicals since a large number of synthetic methods have been developed to transform this functionality into other organic functions like amines, halogens etc.[26]

Asymmetric reduction of prochiral ketones using oxazaborolidines[27-29] (**15**) has become one of the standard tools for the synthetic chemist, allowing access to enantiomerically enriched secondary alcohols with excellent enantiomeric excesses that may serve as the chiral ligands for enantioselective synthesis and highly useful intermediates in the synthesis of bioactive compounds and natural products. Since the introduction of this catalyst by Itsuno[30] and subsequent developments by Corey et al.[31] the studies on mechanistic investigations, substrate applicability, and catalyst optimization have never stopped and many interesting results have been obtained. Oxazaborolidines (**15**) was prepared by the reaction of borane with amino alcohol. Amino alcohols not only bind with zinc and borane to form complexes, they also bind

with other metal such as $LiAlH_4$,[32] titanium[33] and Ruthenium (II)[34] to form organic-metal complexes with later were used in synthesis of alcohol from ketone derivatives.



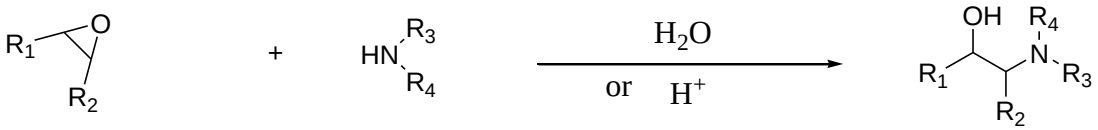

**15**

### 1.1.2 Methods of Synthesis of Amino Alcohol Derivatives

The wide applicability of amino alcohol derivatives have attracted attention of synthetic chemists to synthesize compound having amino alcohol moiety and evaluate their biological activities as well as their applications in industries.

#### 1.1.2.1 Amino Alcohol from Epoxides

The most convenient method to synthesis 1,2-amino alcohol is reaction between epoxides (**16**) with amines (**17**). These type of reactions involving nucleophilic attacking the epoxides which lead to ring opening of epoxides. These reactions are usually performed in water or alcohols as solvents, and the alkoxide ion intermediate is rapidly transformed to an alcohol by proton transfer. The regiochemistry of ring-opening reactions of epoxides depending on the nature of reaction conditions.[6,35-38]




**16** **17** **18**

$R_1$,$R_2$,$R_3$,$R_4$ = H, alkyl, aryl

**Scheme 1-1**

### 1.1.2.2 Reaction of Grignard Reagent with Amino Carbonyl Compounds

The development of new stereoselective methods for the synthesis of amino alcohols is of great interest. One of the most straightforward methods for the stereoselective synthesis of amino alcohols involves the nucleophilic addition of organometallics to chiral amino carbonyl compounds either under chelation or non-chelation control. These types of reaction involved the Grignard reagents (**20**). [26,35,39-41]


**19** **20** **21**

R' = -$NR_1R_2$
C-$NR_1R_2$
C-C-$NR_1R_2$

R'', R''' = alkyl, aryl

**Scheme 1-2**

### 1.2.2.3 Amino Alcohol from Reduction of Carbonyl Group

Most reported methods to synthesis of amino alcohol involved the reduction step.[26,35,42-46] There are various types of reducing agent available. For examples, sodium borohydride, lithium aluminum hydride, borane-methyl sulfide and etc.. Lithium

aluminum hydride is the most powerful reducing agent. It can reduce almost all the functional group. For the amino alcohol the most common used was lithium aluminum hydride. These were due to the presence of two functional groups which are amide/amine and carbonyl compound. Borane-dimethyl sulfide was also a good reducing agent.[44] The used of sodium borohydride as reducing agent in the present of iodine was reported by McKennon and Meyer.[45] Most common solvent that been used are ether and tetrahydrofuran (THF).


**19** **22**

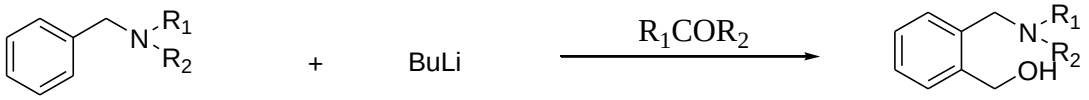
R' = $NR_1R_2$
C-$NR_1R_2$
C-C-$NR_1R_2$
R" = alkyl,aryl

X = $LiAlH_4$
$BH_3$.DMS
$NaBH_4$

**Scheme 1-3**

### 1.2.2.4 Lithiation of Substituted Benzylamine

These reactions occur via ortho-lithiation of substituted benzylamine (**23**) by BuLi, followed by addition of paraformaldehyde or other carbonyl compounds. [47,48]



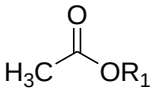

**23** **24**

R1,R2 = H, alkyl,aryl

**Scheme 1-4**

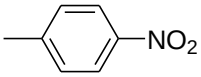
## 1.2 Acetates

Esters are classified according to which acids and alcohols are produced by hydrolysis. Esters having an acetic acid or vinegar base are called acetates (**25**).[49] It are used extensively as solvents, due to their ability to dissolve various greases. As for our substrate, *p*-nitrophenyl acetate (**26**) is widely used in kinetic studies.[15-17,50-54]




**25**

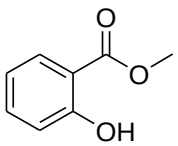
$R_1$ = alkyl, aryl

**26** = $R_1$ = 


### 1.2.1 Importance of Acetates

Esters having an acetic acid or vinegar base are called acetates. They are used extensively as solvents, due to their ability to dissolve various greases. For examples, methyl acetate and ethyl acetate were widely used in the laboratory as a solvent or as an extraction solvent. Their usage not only limited as a solvent but also as a substance in many chemistry reactions such reaction with Grignard reagents and lithium aluminum hydride to synthesis of an alcohol.[26,35]

In pharmaceutical industries, the acetate was used not only as an extraction solvent. Their derivatives were also useful drug. For example, salicylic acid acetate (**27**) is used in the treatment of rheumatic arthritis.[55]




**27**

Polyester is a category of polymer which contained the ester functional group in their main chain. Polyester is the most widely used man-made fiber in the world. Polyester are used to make bottles, films, tarpaulin, reinforcement of plastics for SF6 switches, canoes, liquid crystal displays hologram, filters, dielectric film and capacitors, film instruction for wire and insulating tapes. For examples polyvinylacetate (PVA) (**28**).[56]

$H_2C=CHCOOCH_3$

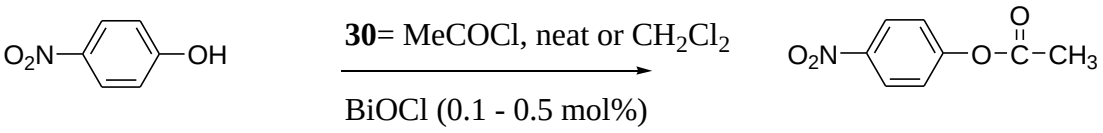
**28**

Ester hydrolysis is an important and prevalent reaction in both organic and biological chemistry.[9-14,17,50-54] This reaction is the best understood of all nucleophilic acyl substitution. The studies of the hydrolysis of active esters have been a great importance in attempts to understand the mechanism of enzyme action. The mechanism of the hydrolysis ester can be classified in a few terms. It depends on the attacking compound on the carbon carbonyl, but the general acid and general base catalysis (GA-GB) is of particular interest from the viewpoint of enzymatic hydrolysis.[17] For examples, the study of hydrolysis of **26** by chymotrypsin.

### 1.2.2 Synthesis of *p*-Nitrophenyl Acetate

There are various reported procedures to synthesis **26**. The most common procedures are acylation[57,58] and acetylation.[59,60]

### 1.2.2.1 Acylation




**29** **26**

**Scheme 1-5**

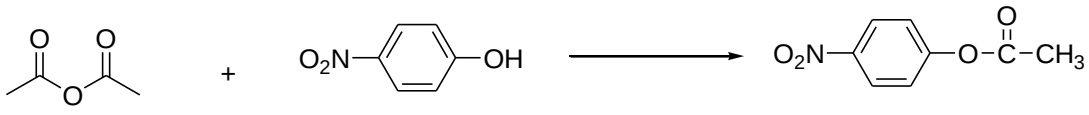
Facile catalyzed acylation of heteroatoms using $BiCl_3$ were generated in situ from the procatalyst BiOCl and acetyl chloride (**30**). This method can be done in a solvent (method A) or under solventless (method B) conditions, furnishing the corresponding acylated derivatives in very good to excellent yields. Compared to method A, method B is more favorable because using lower amount of BiOCl and required shorter time thus making the acylation procedure environmentally friendly. Highly efficient acylation of alcohol, amines and thiols under solvent-free and catalyst-free conditions.

### 1.2.2.2 Acetylation

#### 1.2.2.2.1 Acetylations in Solvent-free Conditions Under Microwave Irradiation

**Using Ac2O-Py/basic Alumina (power = 300 W).**

This method is inexpensive and the support can be reused several times after washing and drying. This method can also be applied in N- and S-acetylation.




**31** **29** **26**

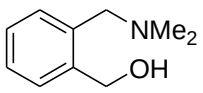
**Scheme 1-6**

#### 1.2.2.2.2 Catalytic Acetylation of Alcohol with Zeolite H-FER Under Solventless Condition.

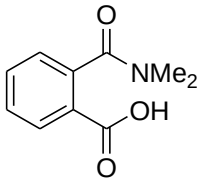
The catalyst (zeolite H-FER) used in this method can be synthesized according to reported procedure. The zeolite can be reused several times without any loss of activity, simply by filtering the catalyst, washing with acetone, drying and reused immediately.

## 1.3 Results and Discussions

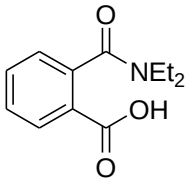
At the first place, our main compound is *N*,*N*-(dimethylphenylamino)benzyl alcohol (**32**). We tried to synthesize by reduction of *N*,*N*-dimethylphthalamic acid (**33**) with lithium aluminum hydride. As cited in references, the reaction required reflux for 3 days to make sure reaction complete and using 7 equivalent $LiAlH_4$.[12]



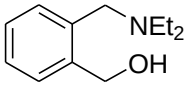

**32**




**33**

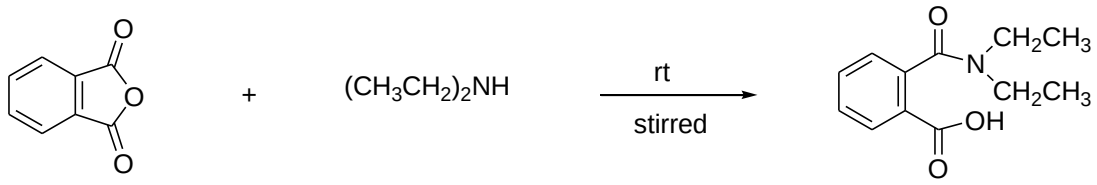



**34**




**35**

However, we are unable to get the product that we wanted. After several attempts, we decided to change the reaction condition. Instead of reflux, we carried out the reaction at room temperature. The percentage of yields were too small and because of the limiting of starting material we decided to change to *N*,*N*-diethylphthalamic acid (**34)**.

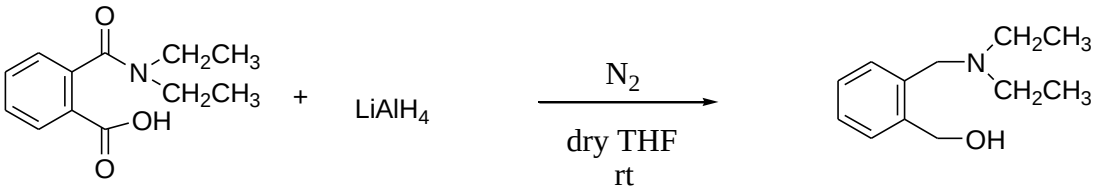



**36** **37** **34**

**Scheme 1-7**

Starting material, compound **34** was synthesized by reacting the phthalic anhydride (**36**) with *N*,*N*-diethylamine (**37**) in THF.[61,62] The reaction mixture was stirred at room temperature until white precipitate appeared, **34** as shown in Scheme 1-7. The completion of the reaction was check by TLC.

Compound **34** was reduced to the desired amino alcohol using $LiAlH_4$ as demonstrated in Scheme 1-8. The result was quite impressive compare to the reduction of compound **33.** The reduction of **34** to **35** was believed to follow the mechanism as demonstrated in Fig. 1-1.




**34** **35**

**Scheme 1-8**

Other than using $LiAlH_4$, we also tried to obtain compound **35** from **34** by using Borane-DMS as the reducing agents. The reaction was carried out as demonstrated in Scheme 1-9.

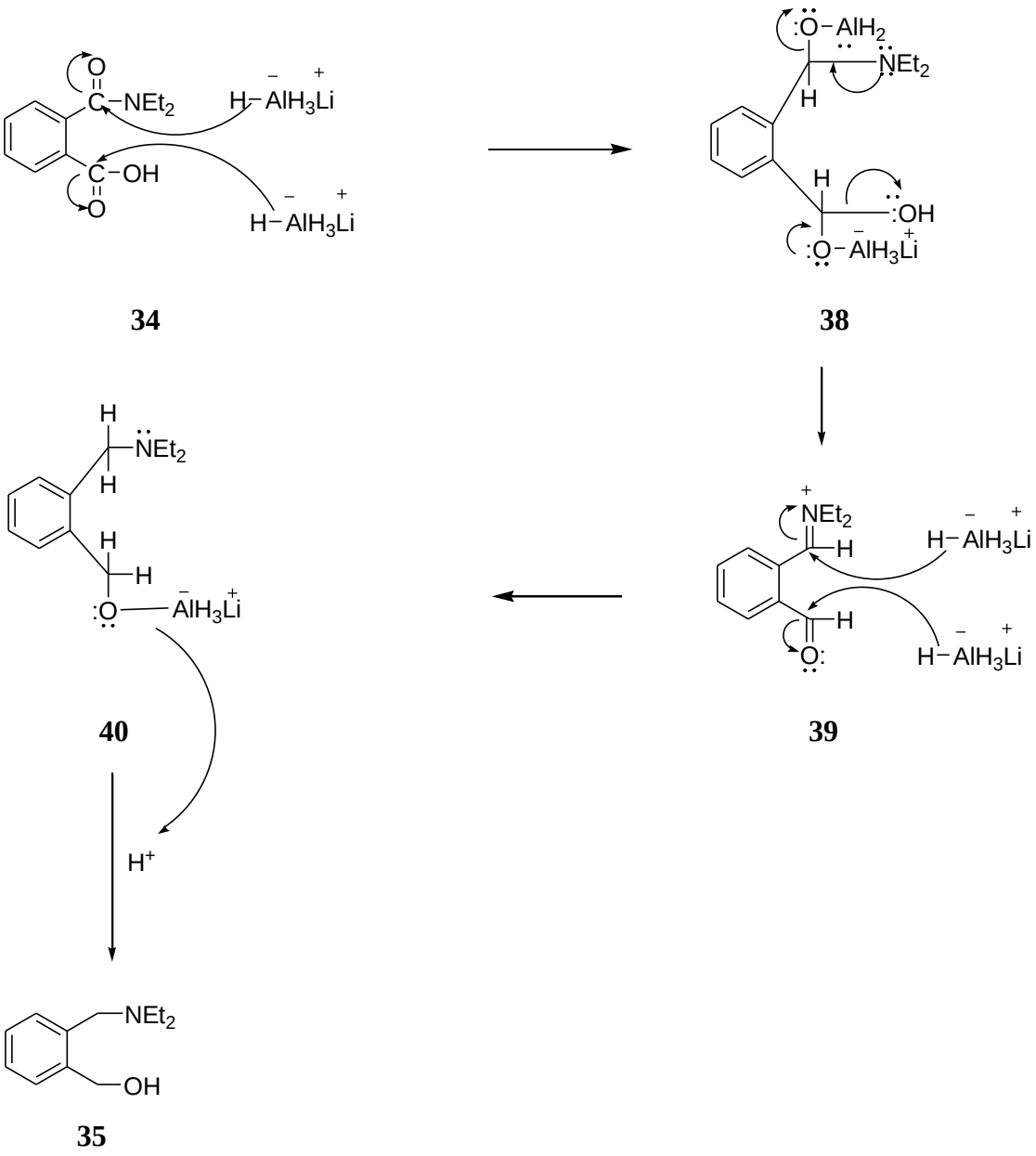
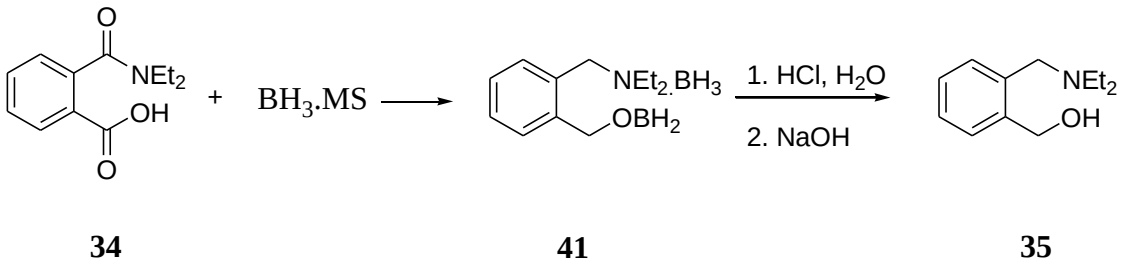
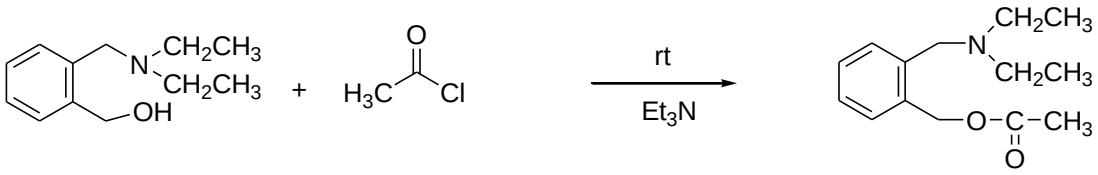



**Figure 1-1**



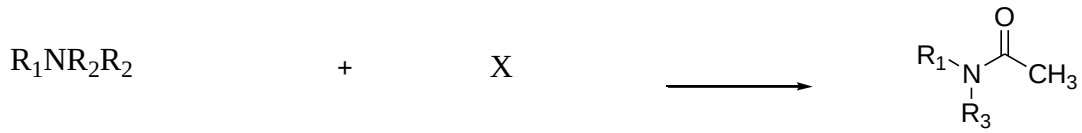

**Scheme 1-9**

The synthesis of esters derivatives were carried out using acylation and acetylation method.[44-46] Two different types of acylating agent were used. Compound **42** was synthesized using acetyl chloride as shown in Scheme 1-10, while compound **44** and **45** were synthesized using acetic anhydride Scheme 1-11. Both reactions were carried out at room temperature under inert atmosphere using dry diethyl ether as solvent as shown in Scheme 1-10 and Scheme 1-11.[26]




**35** **30** **42**

**Scheme 1-10**




**43 =** $R_1$,$R_2$ = H, $R_3$ =Bz
**37 =** $R_1$, = H
$R_2$,$R_3$ = $CH_2CH_3$

X = **30**, **31**

**44, 45**

**Scheme 1-11**

The outlines of the reaction were shown in Fig. 1-2. The reaction involved addition and elimination process.[26] The synthesized compounds are summarized in Table 1-1. The detailed synthesis procedures are described in Chapter 2.

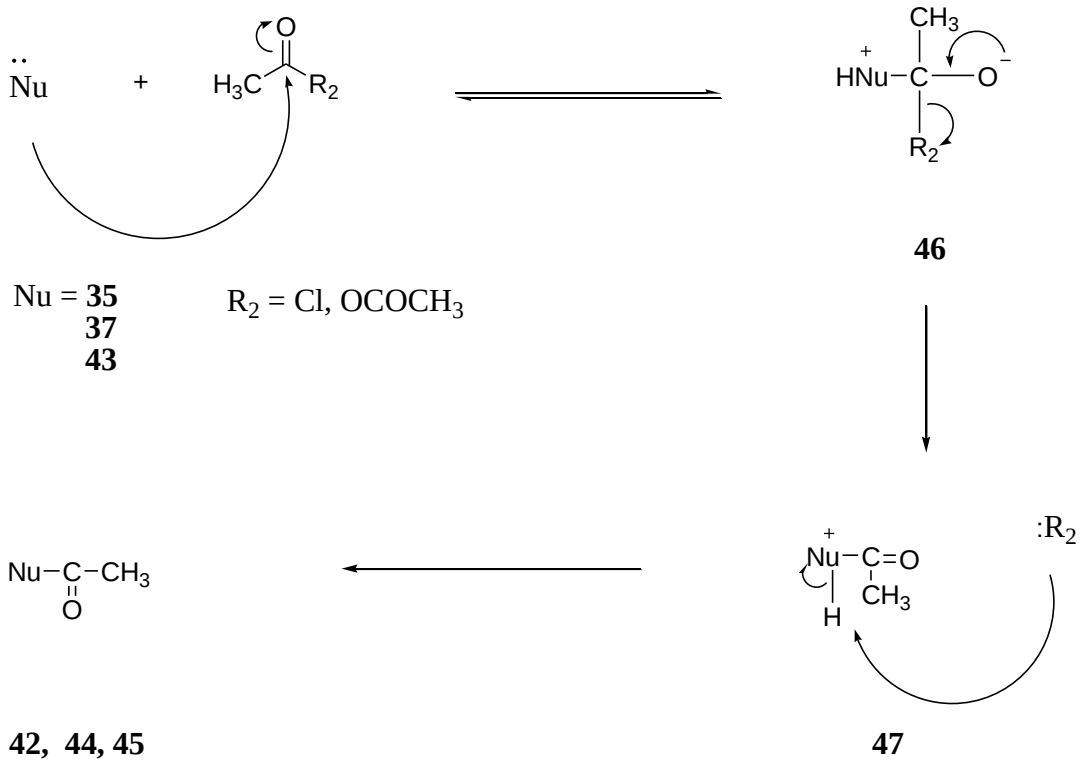
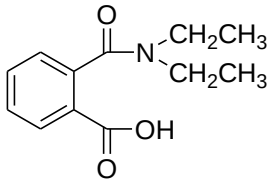
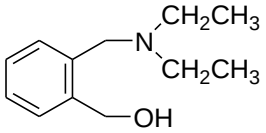
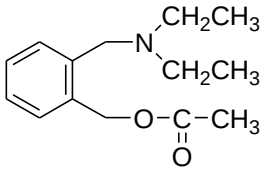
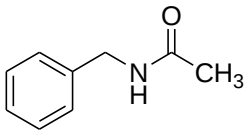
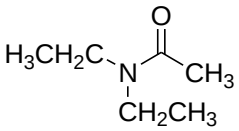

Nu
+
H3C
R2
CH3
HNu
C
O
R2
46
Nu = 35
37
43
R2 = Cl, OCOCH3
:R2
Nu
C
O
CH3
H
Nu
C
CH3
O
42, 44, 45
47

**Figure 1-2**

**Table 1-1: Summary of Synthesized Compounds *N,N*-Disubstituted Phthalamic Acid, *N,N*-disubstituted Amino Alcohol and *N,N*-disubstituted Acetamide**.

| Compounds | % Yields | bp./mp.($^{o}$C) (lit.bp./mp.) |
|---|---|---|
| *N,N*-Diethylphthalamic Acid  **34** | 64.0 [a] | 161-162 (149-151) [b] |
| *N,N*-(Diethylaminomethyl)benzyl Alcohol  **35** | 85.1 [c] 74.7 [e] | 234-236 [d] (70-75) [f,g] |
| 2-((diethylamino)methyl)benzyl Acetate  **42** | 74.2 [h] | 158-160 [d] |
| *N*-Benzylacetamide  **44** | 51.7 [h] | - [i] (220-230) [j] |
| *N*, *N*-Diethylacetamide  **45** | 19.8 [k] | - [i] (185.5) [l] |

[a] Purify by washing with several portions of diethyl ether.
[b] Hoesch L., *Helvetica Chimica Acta*, **1981**, *64(3)*, 890-904.
[c] Percentage yield of reduction with lithium aluminum hydride.

[d] Boiling point measured by air bath distillation
[e] Percentage yield of reduction with borane-dimethyl sulfide.
[f] Mayer K. K., Archieve der Pharmazie, **1981**, *314(8)*, 669-774.
[g] bp. at pressure : 0.3 Torr.
[h] Purify by column chromatography.
[i] b.p was not measured due to limited volume of compound.
[j] Dehn W. M., *J. A. Chem. Soc*., **1913**, *34*, 1399-1409.
[k] Yields after extraction
[l] "Hazardous Substance Data Bank" data are provided by National Library of Medicine, US

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