CHAPTER I

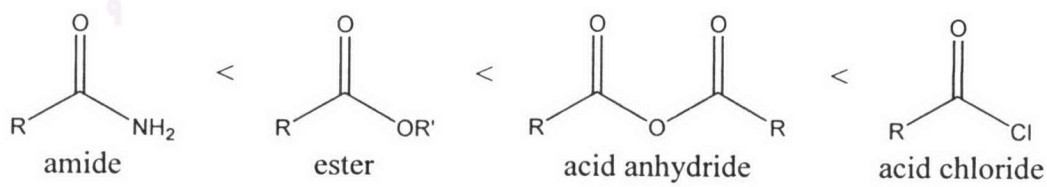
INTRODUCTION

Nowadays, there is a trend for synthetic substances to replace natural compounds. Some examples including ephedrine, salicylates, vitamins, and xanthines are mostly synthetic and steroids are often semisynthetic. Most bioactive compounds are usually found as various simple derivatives such as amides and esters. Therefore, over the past century, there has been copious evidence for the development of many methodologies to synthesize these classes of compounds. Moreover, the optimum conditions in each reaction are essentially needed to be considered to achieve a maximum yield.

The convenient methodology for the preparation of acid chloride using comparatively non-toxic reagents under mild conditions will be mainly focused in this research. The application of this procedure will further be manipulated for certain bioactive compounds.

1.1 Introduction of Acid Chlorides

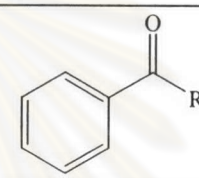
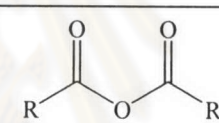
Acid chlorides are also known as acyl chlorides. Acid chlorides are among important derivatives of carboxylic acids (*e.g.* acid anhydride, ester and amide). Comparing the reactivity of different acyl derivatives, acid chlorides are the most reactive compounds. This is because the electronegative chlorine atom strongly polarizes the carbonyl group, whereas amides are the least reactive compounds.



Acid chlorides are of importance as intermediates to convert into many other functional groups[1-5], such as aldehydes, ketones, esters, acid anhydrides and amides.

The conversions of acid chlorides to other organic compounds are illustrated as shown in Table 1.1.

Table 1.1 The conversion of acid chlorides to other organic compounds.[1-5]

substrate	reagent	product
acid chloride **RCOCl**	$LiAl(Ot\text{-}Bu)_3H$	RCHO (aldehyde)
	H_2/Pd	RCHO (aldehyde)
	$LiAlH_4$, H_2O	RCH_2OH (1° alcohol)
	R′MgX	R'_3COH (3° alcohol)
	R'_2CuLi	RCOR′ (ketone)
	C_6H_6, $AlCl_3$	 (aromatic ketone)
	H_2O	RCOOH (carboxylic acid)
	R′COOH	 (acid anhydride)
	R′OH	RCOOR′ (ester)
	$R'NH_2$	RCONHR′ (amide)
	R′SH	RCOSR′ (thiol ester)

1.2 Synthesis of Acid Chlorides

Acid chlorides can be prepared from various starting materials with many manners. Generally, they are prepared from carboxylic acids.

1.2.1 From Carboxylic Acids

- Reaction with Thionyl Chloride[6]

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

The rate of acid chloride formation depends on the nature of carboxylic acids, thionyl chloride was also suitable reagent for aliphatic carboxylic acid.

- **Reaction with Phosphorus Chloride Compounds**[2,6]

The preparation of acid chloride can be achieved by treating carboxylic acids with phosphorus compounds such as phosphorus trichloride (PCl_3) and phosphorus pentachloride (PCl_5). However, these methods are not popular because they cannot be used to prepare an acid chloride of an aminobenzoic acid since it attacks the amino group and their use was largely restricted to aromatic carboxylic acids.

- **Reaction with Oxalyl Chloride**[7]

The general procedure by which acid chlorides are produced from acids by means of excess oxalyl chloride ($(COCl)_2$). If the amount of oxalyl chloride used is not enough, the acid anhydride will be obtained as the final product instead of acid chlorides. This procedure also requires high temperature and produces corrosive by-products such as hydrogen chloride gas.

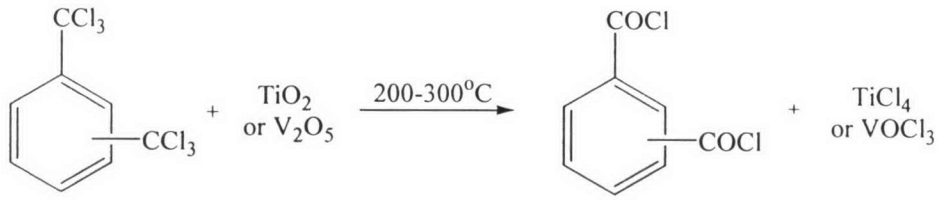
1.2.2 From Aldehydes[5]

Aldehydes can be converted to acid chlorides by treatment with chlorine (Cl_2). However, the reaction operates only when the aldehyde does not contain an α-hydrogen and even then this reactions is unpracticed. If an aldehyde reactant bears an α-hydrogen, α-halogenation will occur instead.

1.2.3 From Aryl *1,1,1*-Trichloromethanes

- **Reaction with Metal Oxide**[8]

Trichloromethylated aromatic compounds can be converted to aromatic acid chlorides by treatment with metal oxides. The reaction was carried out by heating a mixture of the reactants to 200-300 °C. Examples of metal oxides such as titanium dioxide (TiO_2) and vanadium pentoxide (V_2O_5) gave high yield, while other oxides such as those of arsenic, zirconium and antimony were operable but gave lower yields. This reaction could be activated *mono-* or *bis*-trichloromethyl groups equally well.



- **Reaction with Hexamethyldisiloxane**[9]

The aromatic acid chlorides were formed by treating with an organosilicon oxide, hexamethyldisiloxane, at room temperature. This reaction was an exothermic and the temperature increased to 65 °C. This process can be conducted under mild conditions since there are some advantages over inorganic oxides such as TiO_2 and V_2O_5.

- **Reaction with Sulfur Dioxide**[10]

This procedure requires high temperature to give high yield. The reaction can proceed at a lower temperature in the presence of antimony pentachloride ($SbCl_5$) or other Lewis acids. In the case of sulfur dioxide, a side raction that forms thionyl chloride as a by product, is irritation.

1.2.4 From Ketenes[11]

Hydogen chloride gas adds to ketene to give the corresponding acid chloride. This reaction requires an excess of hydogen chloride gas to give acid chloride. If the amount of HCl was not enough, an enol will be obtained as a final product.

1.3 Literature Reviews of Acid Chlorides Synthesis from Carboxylic Acids

The general methodologies for the preparation of acid chlorides are addressed by the use of commom reagents such as thionyl chloride[6], phosphorus chlorides[2,6], oxalyl chloride[7] and phosphorus reagents such as triphenylphosphine with halogenated reagent.

1.3.1 Common Reagents

In the early stage, the preparation of acid chlorides could be accomplished by treating with common reagents such as phosphorus trichloride (PCl_3) and phosphorus pentachloride (PCl_5). However, these methods were not successful in the preparation of some acid chlorides. As a result, a variety of other procedures for acid chloride synthesis has been developed.

R. Adams and L.H. Ulich[7] reported the use of oxalyl chloride ($(COCl)_2$) alone or in benzene as a solvent treated with carboxylic acids to furnish acid chlorides. In this communication, *p*-hydroxybenzoic acid and nitro-derivatives of benzoic acids could not be transformed into acid chlorides.

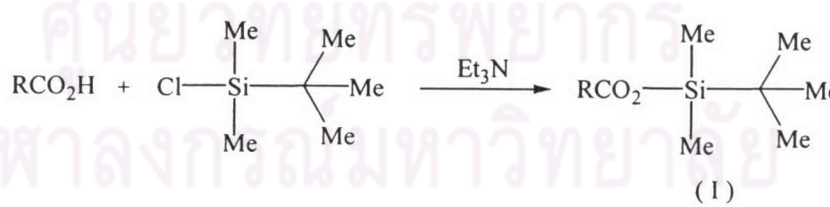
L. McMaster and F.F. Ahmann[6] addressed the reaction of excess thionyl chloride ($SOCl_2$) with carboxylic acid to acid chloride. The by-products of the reaction were harmfully corrosive chemicals and made conditions be acidic. These methods are not used with trichloro-acid, amino-acetic acids, some of dibasic acids and phthalic acids.

W. Gerrard and A.M. Thrush[12] developed the reaction of excess thionyl chloride ($SOCl_2$) with carboxylic acid to acid chloride by addition of pyridine. In the presence of pyridine, another reaction occurred concurrently with some acids, acid chloride reacting with unchanged acid to give anhydride. The rate of the formation of acid chlorides depended on the nature of the acid.

K. Rudolf and R. Joachim[13] reported the preparation of acid chlorides by heating carboxylic acids with $POCl_3$ in an inert solvent in the presence of at least 1.2 mole of tertiary amine such as pyridine.

I.N. Uspenskaya and G.V. Moksarev[14] addressed the use of $PhCCl_3$ reacting with carboxylic acid in the presence of catalytic amount of $FeCl_3$ to form acid chloride.

A. Wissner and C.V. Grudzinskas[15] prepared acid chloride by the conversion of carboxylic acids to *tert*-butyldimethylsilyl esters (TBMS) and then reacted with oxalyl chloride in the presence of DMF.

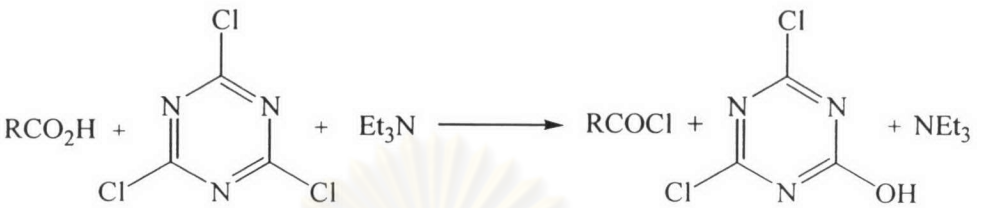


(I)

This method was particularly useful for the preparation of acid chlorides which were derived from hydroxy substituted carboxylic acids. This reaction was

accomplished as a new method for generating acid chlorides under neutral conditions. Furthermore, the side products (*tert*-butyldimethylchlorosilane, CO and CO_2) in this case are volatile compounds which could be removed with ease.

K. Venkataraman and D.R. Wagle[16] reported the preparation of acid chlorides by using carboxylic acid with cyanuric chloride (CC).



This method was carried out at room temperature and cyanuric chloride was separated as an insoluble product; the solution containing the acid chloride and any uncoverted acid could be used directly for further reactions.

C. Jeannine, S. Jean Pierre and W. Gary[17] prepared the acid chloride by using tetrachloroethylene carbonate and $(Bu_2N)_2CO$ as catalyst at 130 °C. Tetrachloro-ethylene carbonate has its own disadvantage, *i.e.*, the use at high temperature.

D. Martin and co-workers[18] reported the process for the manufacture of acid chloride comprising of the treatment of carboxylic acid with Cl_2CO in the presence of $HCON(CHMe_2)_2$.

1.3.2 Phosphorus Compounds with Halogenated Reagents

J.B. Lee[19] first described the preparation of acid chloride under mild conditions using the reaction of carboxylic acid with triphenylphosphine (PPh_3) and carbontetrachloride (CCl_4). The reaction took place rapidly to produce acid chloride, triphenylphosphine oxide and chloroform. This reaction did not generate any strong acidic material, therefore it is suitable for the preparation of acid chloride containing acid sensitive functional groups.

I. Tomoskozi, L. Gruber and L. Radics[20] developed the method of Lee *et al.* by increasing the amount of triphenylphosphine to substrate molar ratio from 1 to the value required by the stoichiometry of processes resulted in the increase of the yield.

K. Sucheta, G.S.R. Reddy and co-workers[21] reported the convenient method for the conversion of carboxylic acid to the corresponding acid halide by using triphenylphosphine and *N*-bromo/iodo succinimides.

G.B. Villeneuve and T.H. Chan[22] converted carboxylic acids by using hexachloroacetone and PPh_3 at –78 °C in dichloromethane to the corresponding acid chlorides. This method is a mild reaction which can be carried out under acid free conditions.

D.O. Jang *et al.*[23] reported the transformation of carboxylic acids to the corresponding acid chlorides by treatment the carboxylic acid with trichloroacetonitrile and PPh_3 in dichloromethane. This method is a mild reaction which can be carried out under acid free conditions. Later, D.O. Jang and J. Kim[24] further developed the aforementioned conditions for the synthesis of symmetrical acid anhydride.

I. Azumaya and colleagues[25] converted carboxylic acids by using dichloro-triphenylphosphorane in chloroform to the corresponding acid chlorides.

It can be clearly seen that the preparation of acid chloride has been continuously scrutinized. This evidence could be postulated for its importance. Nonetheless, the development for the high yield and chemoselective reaction with selective reagents under mild conditions are still called for consideration.

Acid chlorides were not so stable especially in humid environment, thus the acid chlorides generated in this study will be converted to more stable compounds such as amide and esters. Some amides and esters were also well known as an important class of organic compounds possessing biological activities.

1.4 Literature Reviews of Amides Synthesis

Amides can be prepared from various starting materials with many synthetic routes, commonly prepared from amines and carboxylic acid derivatives. Various methods for the preparations of amides are illustrated as shown in Fig 1.1.

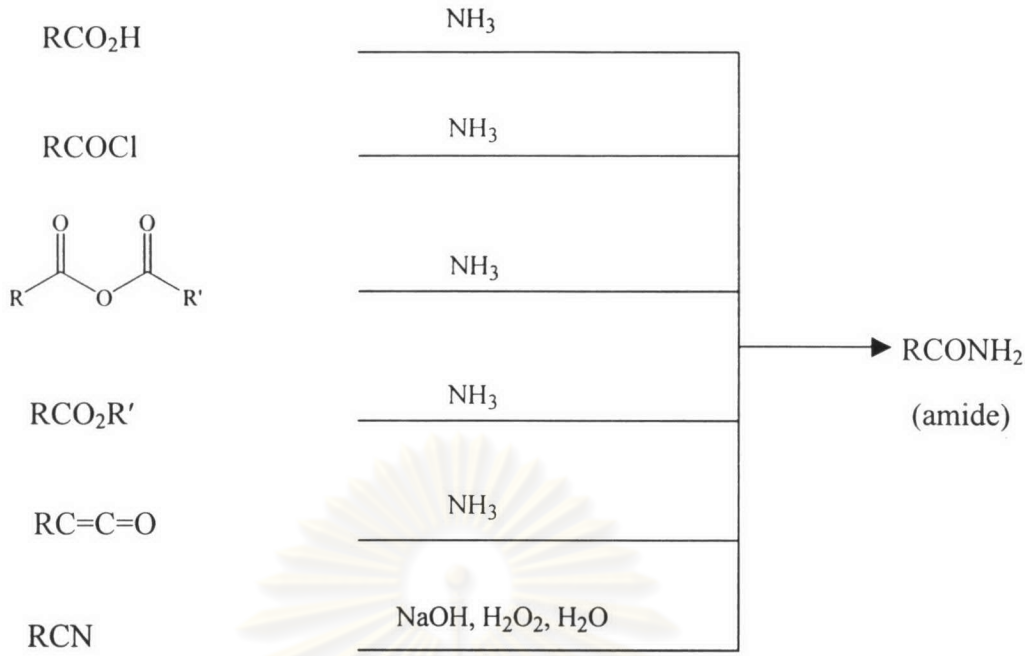


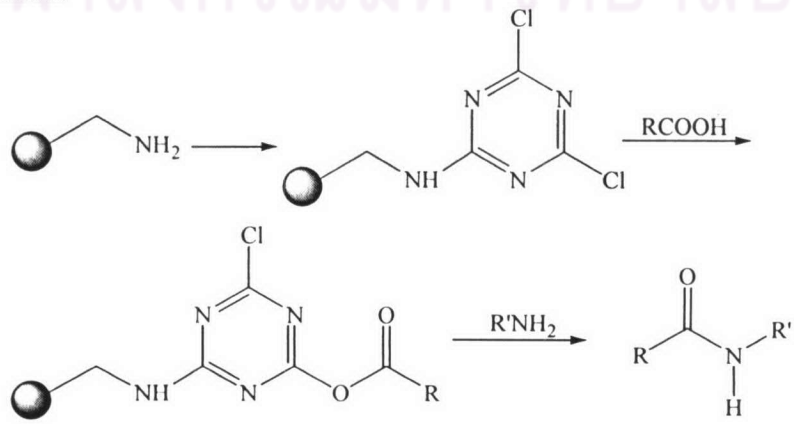
Figure 1.1 The conversion of organic compounds to amides.

1.4.1 Synthesis of Amide without Acid Chloride

T.H. Chan and L.T.L. Wong[26] reported the use of silicon tetrachloride in pyridine as a coupling reagent for the formation of an amide from a carboxylic acid and an amine. Under these conditions, aromatic amines reacted with both aliphatic and aromatic acids to give moderate to good yields of amides. Aliphatic amines, however, gave only poor yields of amides at room temperature. The yield could be substantially improved by raising the reaction temperature to reflux.

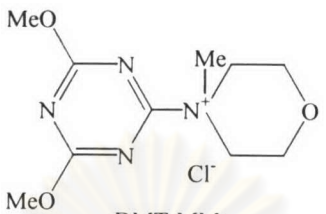
H.R. Seikaly and T.T. Tidwell[11] addressed the reaction of ketene with primary amines to give amides in good yield.

S. Masala and M. Taddei[27] speculated on the possibility of using a resin-bound triazine to activate a carboxylic acid for a nucleophilic substitution at the carbonyl to give an amide.



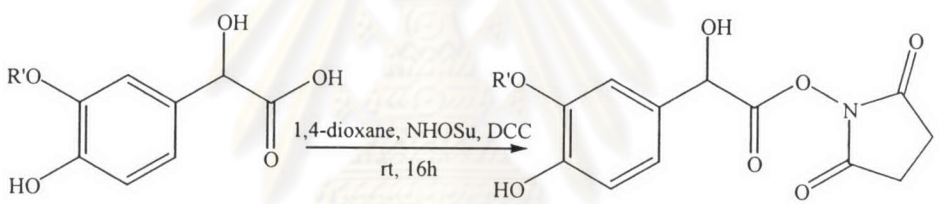
M. Kunishima *et al.*[28] reported the preparation of amide by using a condensing agent, *4*-(*4,6*-dimethoxy-*1,3,5*-triazin-*2*-yl)-*4*-methylmorpholinium chloride (DMT-MM) in the presence of amine and subsequent aminolysis of resulting acyloxytriazine in alcoholic solvents occurred selectively with excellent yield.

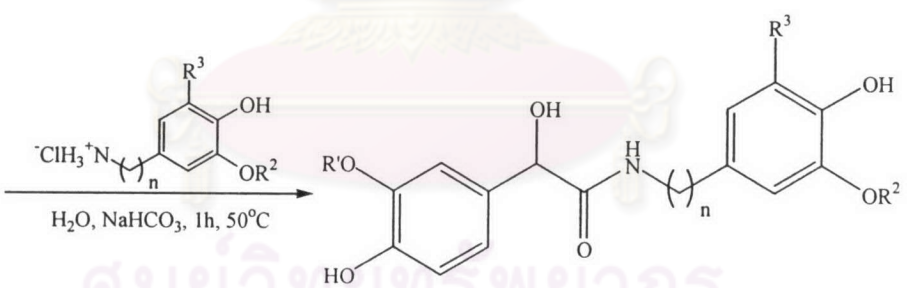
$$RCO_2H + RNH_2 + \text{DMT-MM} \xrightarrow{\text{EtOH, RT}} RCONHR$$



DMT-MM

J.P. Ley and H.J. Bertram[29] synthesized hydroxymandelic acid amides of phenolic amines by condensation of *3,4*-dihydroxymandelic or *4*-hydroxy-*3*-methoxymandelic acid *N*-succinimidyl esters and several phenolic benzylamino and phenethylamino hydrochlorides in moderate to good yield.





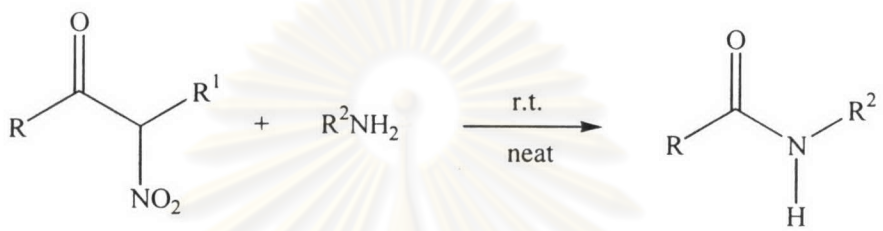
L. Perreux, A. Loupy and F. Volatron[30] reported the synthesis of amide *via* the pyrolysis of the salts obtained by mixing neat primary amines and carboxylic acids. This reaction was performed under solvent-free conditions within short times and appreciable yields under microwave activation.

$$RCO_2H + R'NH_2 \rightleftharpoons RCO_2^-, {}^+NH_3R' \xrightarrow{\Delta} RCONHR' + H_2O$$

H. Sharghi and M.H. Sarvari[31] described the efficient application of wet alumina in the synthesis of amides directly from aldehydes.

$$RCHO \xrightarrow[MeSO_2Cl,\ 100^oC]{wet\text{-}Al_2O_3,\ NH_2OH.HCl} RCONH_2$$

R. Ballini, G. Bosica and D. Fiorini[32] reported a new reactivity of α-nitro ketones with primary amines to the formation of amides. The reaction was performed at room temperature, without any catalyst and solvent.



J. Garcia, F. Urpi and J. Vilaeeasa[33] converted carboxylic acids using aryl or alkyl azides and PPh_3 in refluxing benzene to the corresponding amides. This method however had the limitation, especially for the utilization in lactam formation.

I. Bosch and co-workers[34] reported the preparation of amide by treating acid chloride or acid anhydride with trialkylphosphazene or triphenylphosphazene. In some case these unexpected *C*-phosphonium salts are the predominant products.

$$RCOCl + Ph_3P{=}NR \xrightarrow{C_6H_6} RCONHR$$

$$RCOOCOR + Ph_3P{=}NR \xrightarrow{C_6H_6} RCONHR$$

1.4.2 Synthesis of Amide *via* Acid Chloride

K. Venkataraman and D.R. Wagle[16] documented the conversion of carboxylic acids to acid chlorides, amides and peptides using carboxylic acid with cyanuric chloride (CC) and then amine was added to convert the intermediate formed into amide.

G.B. Villeneuve and T.H. Chan[22] addressed the reaction of carboxylic acids with hexachloroacetone and PPh_3 at –78 °C in dichloromethane to the desired acid chlorides and then amide after being treated with amines.

D.O. Jang *et al.*[23] displayed the conversion of carboxylic acids to acid chlorides by treatment the carboxylic acid with trichloroacetonitrile and PPh_3 in

dichloromethane. The methodology was a mild reaction which could be carried out under acid free conditions.

I. Azumaya and co-workers[25] synthesized amides by using dichloro-triphenylphosphorane in chloroform. This method is important, especially for the synthesis of cyclic compounds from *N*-alkyl-aminobenzoic acids, as a carboxylic acid and an amine can be mixed simultaneously.

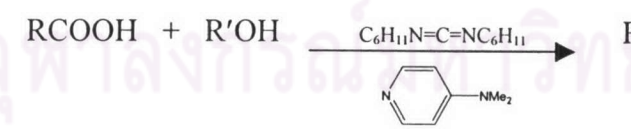
It was found that the methodology for the synthesis of amide has been continuously considered. This was stemmed from the importance of amides functional groups which occurred in many drugs, natural products and peptides. Therefore, it was still a great need to persue the development of many applicable methods for synthesizing this important functional group.

1.5 Literature Reviews of Esters Synthesis

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

K. Sucheta, G.S.R. Reddy and co-workers[21] reported the general method for the convenient conversion of carboxylic acids to the corresponding acid halides by using triphenylphosphine and *N*-bromo/iodo succinimides. Thus, several acids were smoothly esterified with alcohol to furnish esters in high yield.

B. Neises and W. Steglich[35] addressed the method for the esterification of carboxylic acids by treating with dicyclohexylcarbodiimide and *4*-dimethyl aminopyridine. The reaction could be applied to a variety of acids and alcohols, including polyols and even very acid labile alcohols such as vitamin A.



M. Kunishima *et al.*[28] reported the preparation of ester using a condensing agent, *4*-(*4,6*-dimethoxy-*1,3,5*-triazin-*2*-yl)-*4*-methylmorpholinium chloride (DMT-MM) and alcohol in the presence of NMM, the present condensation reaction was simple, easy and therefore very practical.

E.P. Boden and G.E. Keck[36] synthesized ester by using dicyclohexyl carbodiimide (DCC) and *4*-(dimethylamino)pyridine (DMAP). These reaction was available for formation of the large ring lactone.

It has an evidence for the exploration of the development of the preparation of esters. This was because, like amides, ester compounds were another functional group present in various biologically active compounds.

1.6 Biological Active Amide Compounds

Most amide compounds show a large number of biological activities both of pharmaceutical and agricultural activities. Some instance compounds (Figs 1.2-1.3) are reviewed as presented below.

1.6.1 Agricultural Activity

Fungicide such as carboxin **(I)**.[37] This compound is a well-established systemic fungicide. It is the active ingredient of several effective seed treatment fungicides that are commercially available and used worldwide to control smut and rust diseases agricultural crops.

Insecticide, for example niranin **(II)** and thalebanin **(III)**[38] which were isolated from lipophilic leaf extracts of *Glycosmis* cf. *mauritiana*, *G.* cf. *cyanocarpa* and *G.* crassifolia displayed pronounced antifungal and/or insecticidal activity against *Cladosporium herbarum* and *Spodoptera littoralis*, respectively.

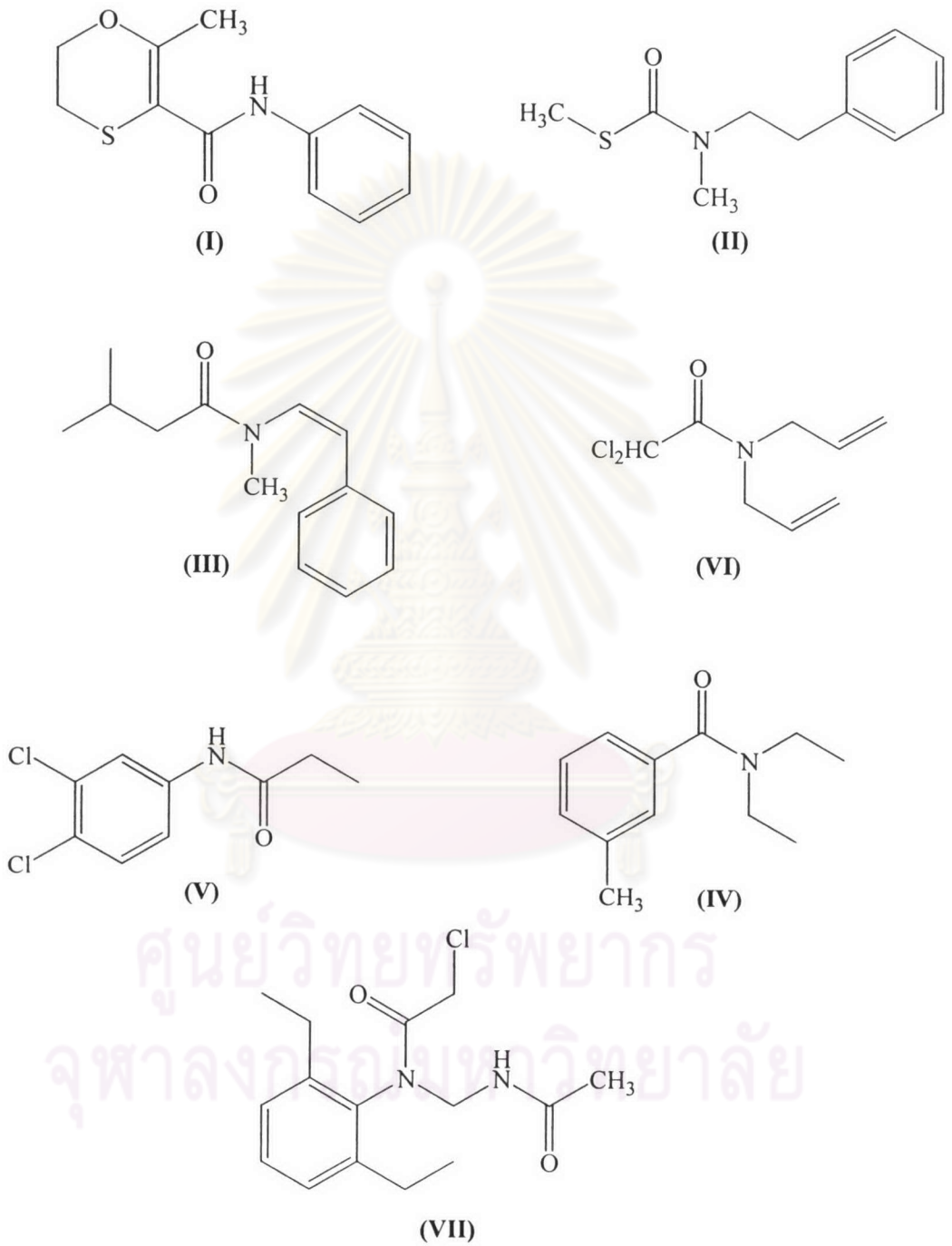
Insect repellent A wide used repellent is DEET **(IV)**[39] which is an effective against mosquitoes, fleas and many other insects. When the insect encounters an atmosphere filled with repellent, the signals from its receptors are distorted in some fashion and it has difficulty recognizing or finding the host.

Herbicide For example propanil **(V)**[40]. This compound is an anilide used as a post-emergence selective contact herbicide in a wide variety of economically important crops, including rice, cotton, potatoes and corns to control broad-leaved and grass weeds

Herbicide safener For example dichlomide **(VI)**[41] which is a failure herbicide safener. It increases the tolerance of herbicides by decrease rate of detoxification in plant.

Plant growth regulator such as amidochlor **(VII)**.[42] It is a retardation of vegetative growth chemical that causes a diminution of apical dominance leading to a shorter main stem and increased lateral branching. In many types of plants such as

silage crops, potatoes, sugar canes, beets, grapes, melons and fruit trees, the retardation of vegetative growth caused by this compound results in as increase in the carbohydrate content of the plants at harvest.



Figture 1.2 Structures of agricultural active amide compounds

1.6.2 Pharmaceutical Activity

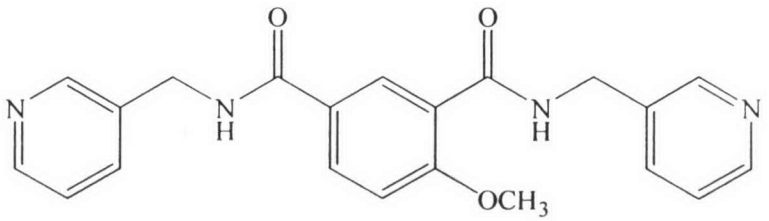
Anticoagulant for example picotamide **(VIII)**[43] which is an agent inhibiting blood plate aggregation. This compound is advisable to reduce the tendency to spontaneous aggregation of blood plates, as connected with thrombo and fibrinophilia.

Anticonvulsant such as cinromide **(IX)**.[44] This compound is used for the treatment or prophylaxis for convulsions of mammals such as mice, dog, cat and more importantly of man.

Antineoplastic for example fenretinide **(X)**[45] which is chemically related to vitamin A. This compound provides a chemo-preventative therapy for inhibiting local relapses or new localization of leukoplakia or development of squamous cell carcinoma. Besides, it reduces the risk of breast and ovarian cancer in women.

Free radical scavenger and antioxidant such as *N-trans*-caffeoyl-phenethylamine **(XI)**.[46] This compound is inhibiting effects on lipid peroxidation or the antioxidative activity of *2,2'*-azo*bis*(*2*-amidinopropane) dihydrochloride-induced lipid peroxidation.

Antimycobacterial For example *N,N'-bis*(*3,4*-dichlorophenyl)butanediamide **(XII)**[47] which is active against *Mycobacterium tuberculosis, M. fortuitum* and *M. kansasii*.



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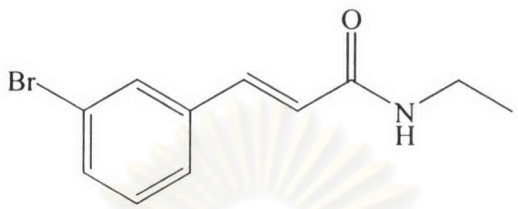

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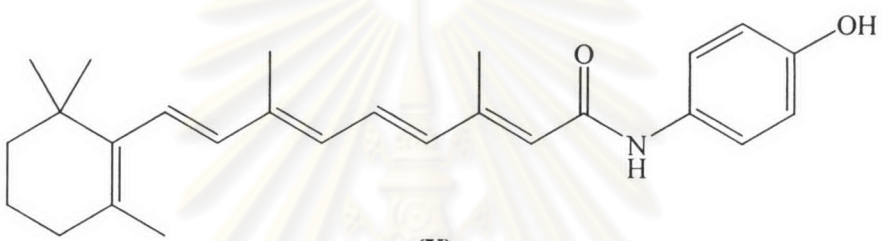

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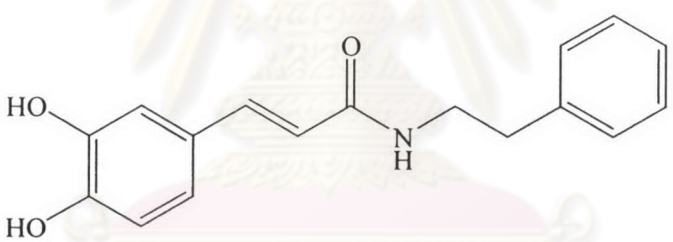

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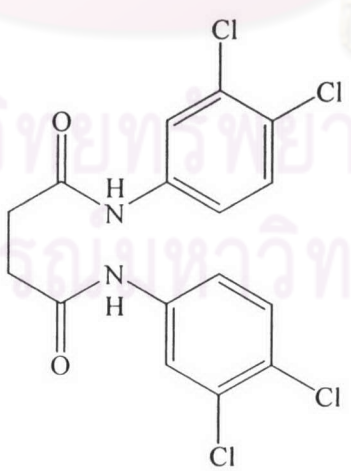


(XII)

Figture 1.3 Structures of pharmaceutical active amide compounds

As it could be clearly seen, amides have been widely used both in agricultural and pharmaceutical aspects. Biologically active amides could be viewed to derive from both synthesis and natural products. In some cases, compounds isolated from natural product resources were not enough. The synthesis becomes the indispensable task. Most amides are synthesized by the conversion of acid chlorides.

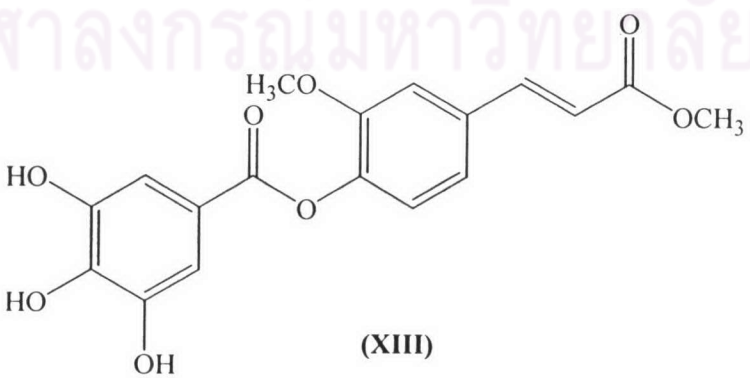
1.7 Biological Active Ester Compounds

Generally, esters have characteristically pleasant odors unlike the parent acids which were noted for their offensive smells. Many of them were widely used as ingredient of perfumes. Examples of fragrances of esters were listed in Table 1.2.

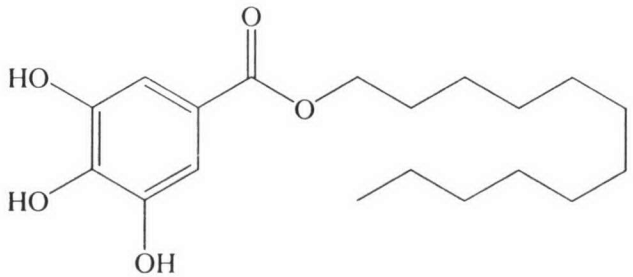
Table 1.2 Fragrances of esters

formula	fragrance	name
$HCOOCH_2CH(CH_3)_2$	raspberries	isobutyl formate
$CH_3COO(CH_2)_4CH_3$	bananas	amyl acetate
$CH_3COO(CH_2)_2CH(CH_3)_2$	pears	isoamyl acetate
$CH_3COO(CH_2)_7CH_3$	oranges	octyl acetate
$CH_3(CH_2)_2COOCH_2CH_3$	pineapples	ethyl butyrate
$CH_3(CH_2)_2COO(CH_2)_4CH_3$	apricots	amyl butyrate
$HOC_6H_4COOCH_3$	wintergreen	methyl salicylate

Certain esters displayed antioxidant activity. For example, methyl *4-o*-galloylferulate **(XIII)** and lauryl gallate **(XIV)**.[48] These compounds displayed inhibiting effects on the autoxidation of methyl linoeate in bulk system.



(XIII)



(XIV)

Cholesteryl esters were widely used for technical application such as liquid crystal display devices.[49] Moreover, fatty acid esters of sterols and steriods were well-known ingredients of cosmetic and pharmaceutical formulations. Recently, plant steryl and stanyl esters have been found to be effective in lowering plasma cholesterol concentration by inhibiting the adsorption of cholesterol from the small intestine.

1.8 The Objective of This Research

The objective of this research is to develop a chemical reagent and to explore the optimum conditions for the preparation of acid chloride under mild conditions and to apply the developed methodology for the synthesis of biological active amides or esters.