CHAPTER I
INTRODUCTION

Even though the major sources of biologically active compounds are derived from natural resources, the tiny amount of them was obviously realized to be one of the obstacles for further fully utilization. Therefore, the chemical manipulation becomes crucial tools to solve this limitation. In the synthesis, each reaction seems to have its own procedure because of the difference in its nature. Therefore, the optimum conditions in each reaction needed to be considered for obtaining a maximum yield. The analysis of the principles or procedure of inquiry in a particular field is called methodology, which is the investigation of the compositions in the reaction such as reagents, reaction times and solvent systems.

During the course of this research, the methodology for the preparation of acid chloride using comparatively non-toxic reagents under mild conditions will be focused. The synthesis of biological active amides will also be exemplified as the application of this developed procedure.

Introduction to Acid Chlorides

1. The Importance of Acid Chlorides

Acid chlorides, also called acyl chlorides, are among important derivatives of carboxylic acids as their versatility for the synthesis of other organic compounds[1-5] such as aldehydes, ketones, esters, acid anhydrides and amides, *etc.* The conversions of acid chlorides to other organic compounds are illustrated as shown in Fig. 1.1.

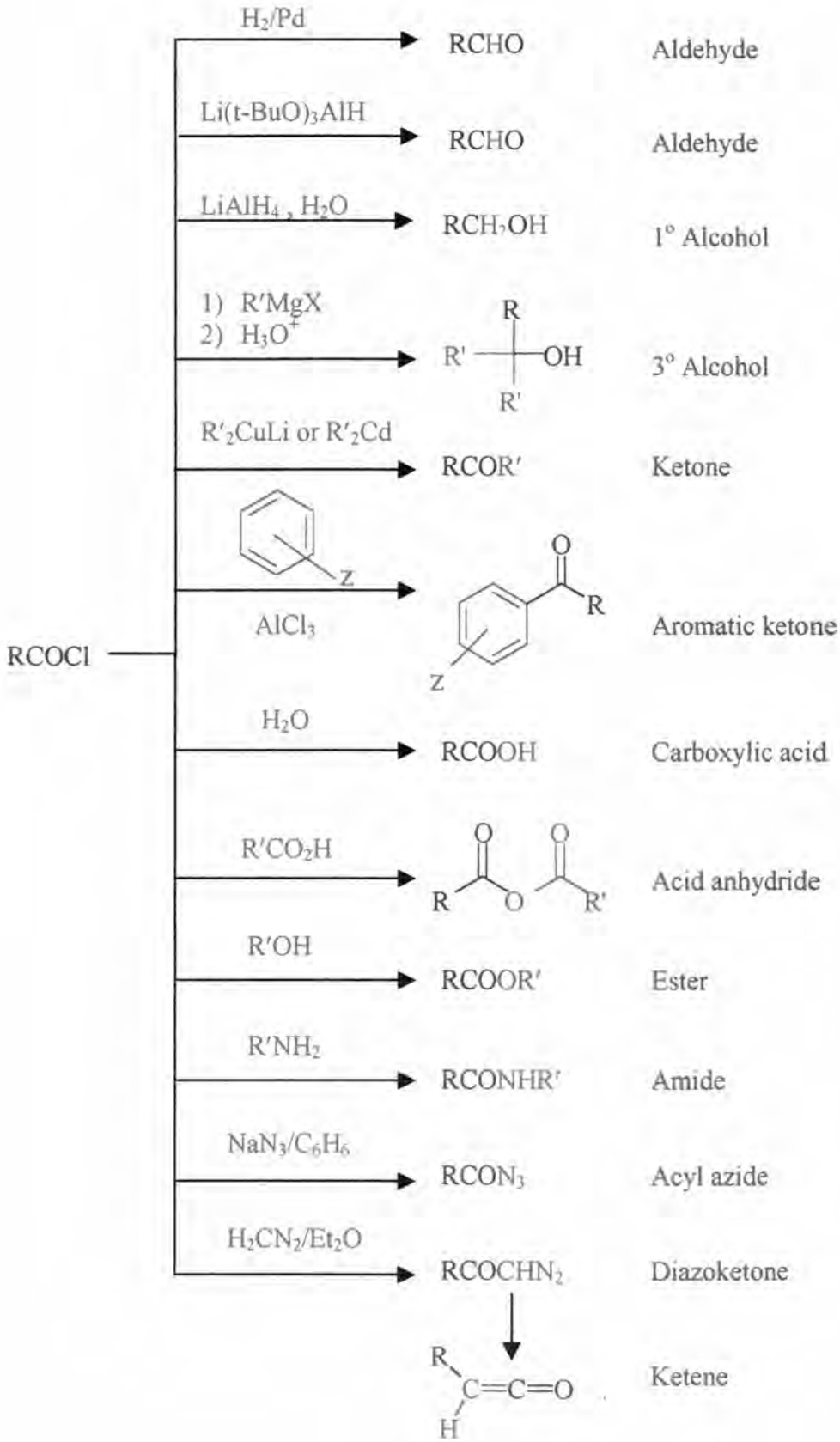


Figure 1.1 The conversions of acid chlorides to other organic compounds

As merits above, the methodology for the preparations of acid chlorides becomes the subject of scrutinized investigation and has been extensively studied from the past to the present time.

2. The Synthesis of Acid Chlorides

Acid chlorides can be prepared from various starting materials with many manners. For example,

2.1. From Carboxylic Acids

2.1.1. Reaction with Phosphorus Chloride Compounds[2,6,7]

At original period of the preparation of acid chloride, phosphorus chloride compounds such as phosphorus trichloride (PCl_3) and phosphorus pentachloride (PCl_5) were used as reagents for converting carboxylic acids to their corresponding acid chlorides. Nowadays, these methods are not popular because some acid chlorides such as animobenzoyl chloride and malonyl chloride were not able to synthesize by this methodology.

$$3RCO_2H + PCl_3 \longrightarrow 3RCOCl + H_3PO_3$$

$$RCO_2H + PCl_5 \longrightarrow RCOCl + POCl_3 + HCl$$

2.1.2. Reaction with Oxalyl Chloride[6]

Carboxylic acids are treated with excess oxalyl chloride ($(COCl)_2$) to give acid chlorides. If the amount of $(COCl)_2$ 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 produced corrosive by-products.

$$RCO_2H + (COCl)_2 \longrightarrow RCOCl + CO_2 + CO + HCl$$

2.1.3. Reaction with Thionyl Chloride[7]

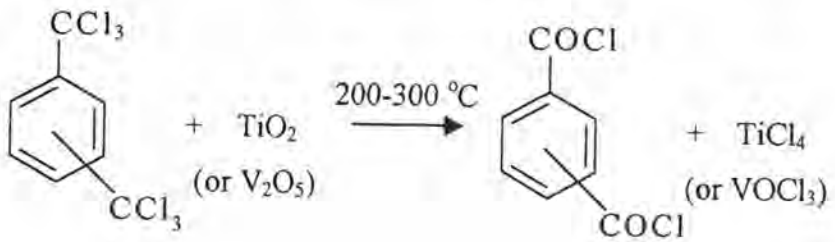
An acid is treated with two or three times of redistilled thionyl chloride. Usually the mixture has to be refluxed with stirring at boiling point of the thionyl chloride. In a few cases several days of refluxing are required. The rate of acid chloride formation depends on the nature of carboxylic acid. The advantage of this process is by-products of the reaction are gaseous, they are readily removed and any excess thionyl chloride needs to be distilled off. These by-products are harmfully corrosive chemicals and make conditions be acidic.

$$RCO_2H + SOCl_2 \longrightarrow RCOCl + SO_2 \quad HCl$$

2.2. From Aryl 1,1,1-trichloromethanes

2.2.1. Reaction with Metal Oxide[8]

The aromatic acid chlorides and metal chlorides are produced by a reaction of trichloromethylated aromatic compounds and metal oxides. The reaction is carried out by heating a mixture of the reactants to 200-300 °C. Metal oxides such as titanium dioxide (TiO_2) and vanadium pentoxide (V_2O_5) give the best yield, while other oxides such as those of arsenic, antimony and zirconium are operable but give lower yields. Aromatic compounds containing mono- or bis-trichloromethyl groups work equally well.



2.2.2. Reaction with Hexamethyldisiloxane[9]

The aromatic acid chlorides are formed by treated with an organosilicon oxide, hexamethyldisiloxane, at room temperature. This reaction is an exothermic and the temperature increased to 65°C. This process has an advantage over inorganic oxide such as TiO_2 and V_2O_5 in that the reaction can be conducted under mild conditions.

$$ArCCl_3 + (Me_3Si)_2O \longrightarrow ArCOCl + 2Me_3SiCl_2$$

2.2.3. Reaction with Sulfur Dioxide[10]

This fashion 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. Friedel-Crafts side reactions may reduce the yield of acid chloride unless the ring bears strongly electron-attracting substituents.

$$ArCCl_3 + SO_2 \xrightarrow{100\text{-}200\ ^\circ C} ArCOCl + SOCl_2$$

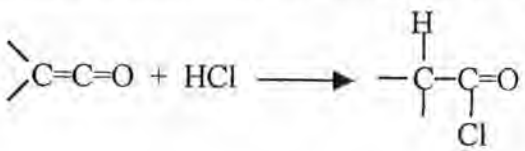
2.3. From Aldehydes[5]

Aldehydes can be directly 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 reaction is not very useful. If an aldehyde reactant bears an α hydrogen, α halogenation will occur instead.

$$RCHO + Cl_2 \longrightarrow RCOCl + HCl$$

2.4. From Ketenes[11]

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



3. The Problems of Acid Chloride Synthesis

Although acid chlorides can be produced from various sources of starting materials, the general procedure is the conversion of carboxylic acids. That is because of the uncomplicated process of the conversion, the variety and easy procuration of carboxylic acids. While a number of such methods which accomplish this conversion are known, most require either harmful reagents (such as $SOCl_2$, $(COCl)_2$), the application of heat or sometimes produce extremely corrosive by-products (such as strong acids, SO_2). Besides, if an acid starting material contains acid sensitive functional groups, under acidic conditions it is likely that the desired acid chloride may be obtained in low yield or not at all.[12] Consequently, many more convenient methods that can be conducted by using harmless reagents, moderate degree of heat or milder conditions are desirable.

Literature Reviews of Acid Chlorides Synthesis from Carboxylic Acids

About ten years before nineteenth century, carboxylic acids were converted to acid chlorides by using phosphorus chloride compounds such as phosphorus trichloride (PCl_3) and phosphorus pentachloride (PCl_5).

$$3RCO_2H + PCl_3 \longrightarrow 3RCOCl + H_3PO_3$$

$$RCO_2H + PCl_5 \longrightarrow RCOCl + POCl_3 + HCl$$

These methods are not successful in the preparation of some acid chlorides for example it cannot produce an acid chloride of an aminobenzoic acid since it attacks the amino group. As a result, a large variety of different procedures for acid chloride synthesis have been developed.

In 1920, R. Adams and L.H. Ulich[6] reported the use of oxalyl chloride ($(COCl)_2$) to react with carboxylic acids for the production of acid chlorides.

$$RCO_2H + \underset{\text{(excess)}}{(COCl)_2} \xrightarrow[2\text{ hr}]{\text{reflux}} RCOCl + CO_2 + CO + HCl$$

Under this particular conditions, *p*-hydroxybenzoic acid and nitro-derivatives of benzoic acids could not be transformed into acid chlorides. If the amount of oxalyl chloride used was not enough, the acid anhydride would be obtained as the final product instead of acid chlorides.

In the same year, H. Crompton and P.L. Vanderstichele[13] addressed the preparation of acid chlorides by using the reaction between carboxylic acids and α,β-dichlorovinyl ethyl ether. The yields were variable because of the side-reaction.

$$RCO_2H + ClCH{=}\overset{\displaystyle Cl}{\overset{|}{C}}{-}OEt \xrightarrow{\text{reflux}} RCOCl + ClCH_2{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}OEt$$

In 1927, R.E. Montanna[14] introduced the routes of acid chlorides preparation from carboxylic acids and silicon tetrachloride ($SiCl_4$) with C_6H_6 or $C_6H_4Me_2$ as solvents. After raising the temperature to about 50 °C, the acid chloride was distilled off through a fractionating column.

$$RCO_2H + SiCl_4 \xrightarrow[C_6H_6]{50\ ^\circ C} RCOCl + SiO_2 + HCl$$

Employing this methodology, however, dibasic acids, *o*-nitrobenzoic and pyruvic acids showed negative results.

In 1928, L. McMaster and F.F. Ahmann[7] reported the reaction of thionyl chloride ($SOCl_2$) with carboxylic acid to yield acid chloride. This method needed excess amount of $SOCl_2$. By-products are gaseous which readily removed and any excess $SOCl_2$ could be distilled off. These by-products are harmful which make vigorous acidic conditions.

$$RCO_2H + SOCl_2 \xrightarrow[\text{(excess)}]{\text{reflux}} RCOCl + SO_2 + HCl$$

R. Zubaowski[15] reported in 1929 the reaction of chlorinated aromatic hydrocarbons with carboxylic acids in the presence of catalyst ($ZnCl_2$) for acid chloride synthesis.

$$RCO_2H + ArCCl_3 \longrightarrow RCOCl + ArCOCl + HCl$$

In 1934, P. Carre and D. Liberrmann[16] showed that pyridine facilitated the reaction of thionyl chloride on carboxylic acids and permitted the preparation of certain acid chlorides.

$$RCO_2H + SOCl_2 \xrightarrow[\text{reflux}]{\text{pyridine}} RCOCl + SO_2 + HCl$$
(excess)

N. Gerrard and A.M. Thrush[17] reported in 1953 the reaction in carboxylic acid-thionyl chloride systems depended on the structure of acid.

In 1961, I.T. Strukov[18] passed chlorine gas through a mixture of PCl_3 and carboxylic acid to the completion of the reaction of acid chloride formation. The sufficiently purification was used to separate by-product, $POCl_3$.

$$RCO_2H + Cl_2 + PCl_3 \longrightarrow RCOCl + POCl_3$$

J.B. Lee[19] described in 1966 the preparation of acid chloride under mild conditions by using the reaction of carboxylic acid with triphenylphosphine (PPh_3) and carbontetrachloride (CCl_4).

$$RCO_2H + Ph_3P + CCl_4 \longrightarrow RCOCl + Ph_3PO + HCCl_3$$

This reaction does not generate any strong acidic material, therefore it is suitable for the preparation of acid chlorides which contains acid sensitive functional groups. However, this process required relatively long reaction time at room temperature and high temperature was needed for the shorter reaction time.

In 1968, Y. Iwakura and S. Kyo[20] described the production of acid chloride by the reaction of carboxylic acid with ethyl isocyanate (EtNCO) in the presence of saturated hydrochloride gas (HCl).

$$RCO_2H + EtNCO + \text{sat. HCl (g)} \xrightarrow[\text{over night}]{20\ ^\circ C} RCOCl$$

This method carried out with long reaction time under acidic conditions.

In the same year, K. Rudolf and R. Joachim[21] reported the preparation of acid chlorides by heating carboxylic acids with $POCl_3$ in an inert solvent in the presence of at least 0.2 mole tertiary amine (pyridine).

$$RCO_2H + POCl_3 \xrightarrow[\text{reflux}]{\text{pyridine}} RCOCl$$

In 1970, T. Yoshiyuki, M. Toshio and O. Hotuma[22] synthesized acid chlorides by utilizing the reaction of carboxylic acids with sulfur monochloride (S_2Cl_2) using iodine as a catalyst.

$$RCO_2H + S_2Cl_2 + I_2 \xrightarrow[5\ hr, 150\ ^\circ C]{\text{reflux}} RCOCl$$

Under this particular conditions, aromatic dicarboxylic acids and fatty acids however, gave no acid chlorides.

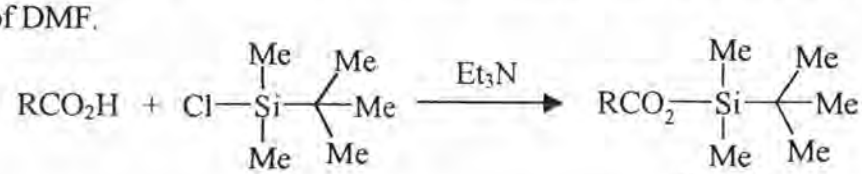
In 1971, I.N. Uspenskaya and G.V. Moksarev[23] addressed the use of $PhCCl_3$ reacted with carboxylic acid in the presence of catalytic amount of $FeCl_3$ to form acid chloride.

$$RCO_2H + PhCCl_3 \xrightarrow[2\ hr,\ 100\ ^\circ C]{FeCl_3} RCOCl$$

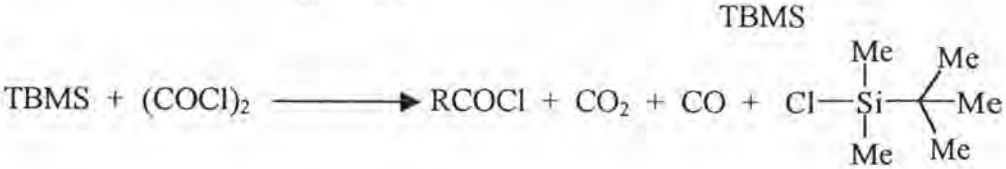
In 1977, E. Kichiji, F. Takeo and I. Haruo[24] prepared acid chloride by using the reaction of carboxylic acids with $ClCO_2CCl_3$ in the presence of dimethylformamide (DMF) as catalyst. However, $ClCO_2CCl_3$ is a very harmful reagent.

$$RCO_2H + ClCO_2CCl_3 \xrightarrow[1\ hr,\ 70\ ^\circ C]{DMF} \xrightarrow[30\ min,\ 100\ ^\circ C]{N_2\ bubbled} RCOCl$$

In 1978, A. Wissner and C.V. Grudzinskas[12] reported the preparation of acid chloride could be accomplished by the conversion of carboxylic acids to *tert*-butyldimethylsilyl esters (TBMS) and then reacted with oxalyl chloride in the presence of DMF.



TBMS

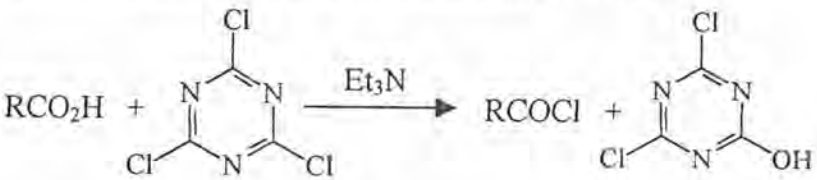


The advantages of this procedure are that it can be carried out under neutral conditions and by-products are volatile compounds which can be removed with ease. On the other hand, it possesses a complicated process that it requires converting carboxylic acid to TBMS.

In 1979, K. Yushin, I. Shojiro and N. Masahiro[25] treated carboxylic acid with chlorine in the presence of PCl_3 for acid chloride synthesis. By-product, PCl_5 was converted to $POCl_3$ by treatment with H_2O or a phosphorus compound such as H_3PO_4 or P_2O_5.

$$RCO_2H + Cl_2 + PCl_3 \longrightarrow RCOCl$$

In the same year, K. Venkataraman and D.R. Wagle[26] reported the formation of acid chloride by reacting carboxylic acid with cyanuric chloride (CC).



This fashion carried out at room temperature and CC could be separated as an insoluble product. The solution containing acid chloride and any unconverted acid can be used directly for further reactions. Nevertheless the reaction carried out with relatively long reaction time and CC which is a reagent for the manufacture of reactive dyes, fluorescent brightening agent is not commercially available.

Besides, A. Devos and co-worker[27] synthesized acid chloride by treated carboxylic acid with tetramethyl-α-chloroenamine at room temperature under mild conditions.

By-product is the inert amide, so the isolation of acid chloride for further reaction will often be unnecessary. The preparation of tetramethy-α-chloroenamine nevertheless requires the use of phosgene.

In 1980, D. Joachim and co-worker[28] converted α,β-unsaturated carboxylic acids to β-chloro acid chlorides by sequential treatment with HCl in DMF and phosgene (Cl_2CO); without HCl, the yield of acid chloride was decreased.

$$RCH{=}CHCO_2H \xrightarrow[DMF]{HCl} \xrightarrow{Cl_2CO} R{-}\overset{Cl}{\underset{|}{C}}H{-}\overset{O}{\overset{\|}{C}}CCl$$

In 1989, C. Jeannine, S. Jean Pierre and W. Gary[29] reported the preparation of acid chloride by using tetrachloroethylene carbonate and $(Bu_2N)_2CO$ as catalyst.

$$RCO_2H + \text{tetrachloroethylene carbonate} \xrightarrow[1\ hr,\ 130\ ^{O}C]{(Bu_2N)_2CO} RCOCl$$

In 1991, D. Martin and co-worker[30] reported the process for the manufacture of acid chlorides comprising of the treatment of carboxylic acids with Cl_2CO in the presence of $HCON(CHMe_2)_2$.

$$RCO_2H + Cl_2CO + HCON(CHMe_2)_2 \xrightarrow{75\ ^{o}C} RCOCl$$

Later on, in 1993 W. Thomas and co-worker[31] described a procedure for the preparation of acid chlorides comprising of the treatment of carboxylic acids with Cl_2CO in the presence of an unsaturated nitrogen compound e.g. isonitrile, RNC (R = cyclohexyl, CMe_3).

$$RCO_2H + Cl_2CO + RNC \longrightarrow RCOCl$$

In 1997, G.B. Villeneuve and T.H. Chan[32] converted carboxylic acids by using hexachloroacetone ($Cl_3CC(O)CCl_3$) and Ph_3P as reagents at –78 °C in methylene chloride to the corresponding acid chlorides. An acid chloride was converted to amide for characterization. This method is a mild reaction which can be carried out under acid free conditions. The side products occurred such as trichloroacetamide resulting the low yield of the reaction.

$$RCO_2H + Cl_3C{-}\overset{O}{\overset{\|}{C}}{-}CCl_3 + Ph_3P \xrightarrow[CH_2Cl_2]{-78\ ^{O}C} RCOCl$$

It can be seen that the preparation of acid chloride has been continuously scrutinized for a long time. That can postulate for its importance. Besides the development for the high yield, chemoselective, mild reagents and mild conditions are needed for consideration. Especially, reactions that can proceed under mild conditions become emphasized criteria during last twenty years ago.

Since it is not so stable especially in humid environment, presumably acid chlorides generated in this study will be converted to more stable and inert organic

compound such as amide. Besides acting as an acid chloride trap, some amides are also well known as an important class of organic compounds that possesses biological activities.

Biological Active Amide Compounds

Most amide compounds show a large number of biological activities both of pharmaceutical and agricultural activities.

1. Pharmaceutical Activity

1.1. ***Analgesic*** For example propiramide[33] (**I**) which is an orally administered opiate analgesic with partial morphine-like agonist and weak antagonist properties. Analgesic activity was demonstrated by preliminary examinations in human experimental pain model in 1970s.

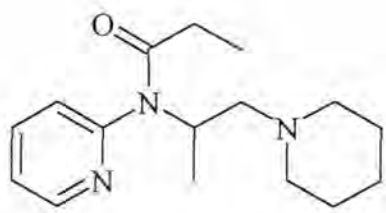
1.2. ***Antibacterial*** For example carfecillin sodium[34] (**II**) which is a non-toxic sodium salt of penicillin. This compound is active against Gram-positive and Gram-negative bacteria, which makes it useful as the therapeutic and prophylactic agent against bacterial infection in animal, including man and poultry. It is used in the form of food staffs such as flavoring agents, conventional vehicles and additives and capsules and other carriers in the form of unit dose containers.

1.3. ***Anticoagulant*** For example picotamide[35] (**III**) 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.

1.4. ***Anticonvulsant*** Such as cinromide (**IV**)[36]. This compound is used for the treatment or prophylaxis for convulsions of mammals such as mice, dogs and cats and more importantly of man.

1.5. ***Antifungal*** Such as crotamiton (**V**)[37]. This compound is an antifungal composition that used as an active ingredient of an external antifungal agent.

1.6. ***Antineoplastic*** For example fenretinide[38] (**VI**) which is a 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.



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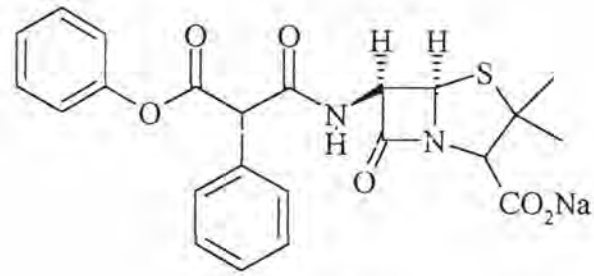

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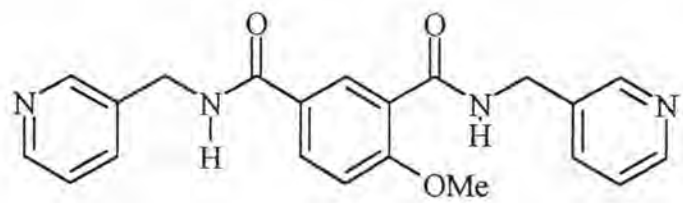

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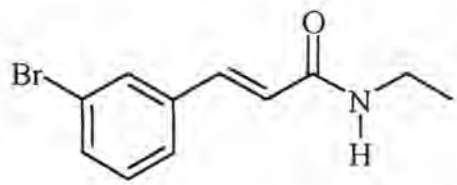

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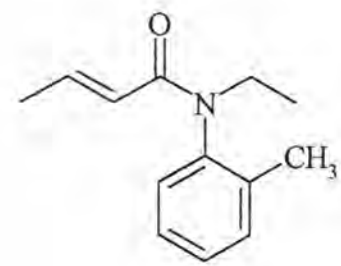

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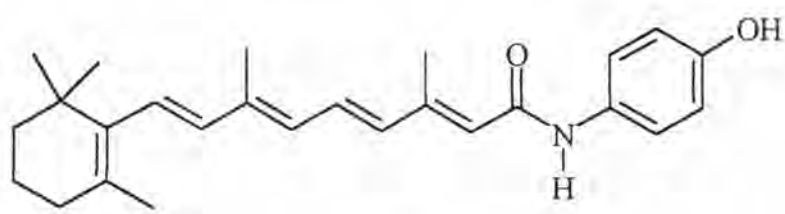


(VI)

Figure 1.2 Structures of selected pharmaceutical active amides

2. Agricultural activity

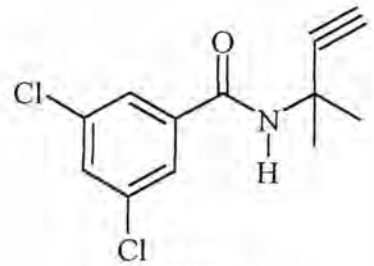
2.1. ***Herbicide*** For example pronamide[39] (**VII**) which is a herbicide used either before weeds emerge (preemergence), and/or after weeds come up (postemergence). It controls a wide range of annual and perennial grasses, as well as certain annual broadleaf weeds. Pronamide is usually incorporated into the soil by cultivation, irrigation, or rain immediately following application. The toxic action of this herbicide is selective, meaning that it kills specific target plants while sparing other desirable plants. It destroys plant by inhibits mitosis.

2.2. ***Herbicide safener*** For example dichlomide[40] (**VIII**) which is a failure herbicide safener. It increases the tolerance of herbicides by decrease rate of detoxification in plant.

2.3. ***Insect repellent*** A wide used repellent is DEET[41] (**IX**) which is an effective against mosquitoes, fleas, gnats, 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.

2.4. ***Insecticide*** For example affinin[42] (**X**) which was first isolated from *Heliopsis longipes* Blake. It is also possible to prepare combinations with other pesticidally active substances, fertilize and/or growth regulators.

2.5. ***Plant growth regulator*** Such as amidochlor (**XI**)[43]. 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.



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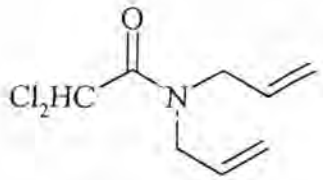

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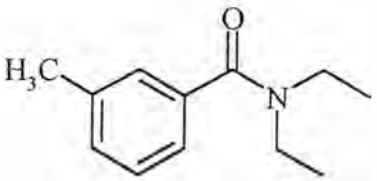

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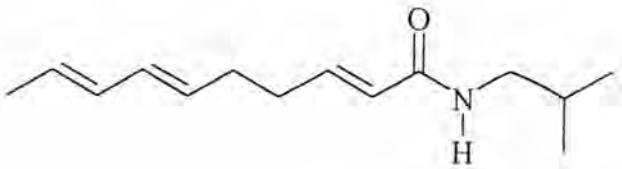

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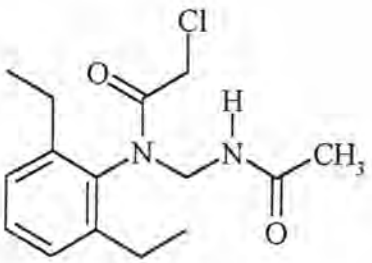

(XI)

Figure 1.3 Structures of selected agricultural active amides

It is clearly seen that amides are used widely both in pharmaceutical and agricultural aspects. Biologically active amides could be viewed to derive from both synthesis and isolation from natural products. In some cases, compounds insulated from natural product resources were not enough for further investigation and/or commerce. For this result, the synthesis becomes the indispensable task. Most amides are synthesized by the conversion of acid chlorides.

The Goal of This Research

The goals of this research are to find out optimum conditions for acid chloride preparation carried out under mild conditions and enable to synthesize biological active amides with the developed method.