การสังเคราะห์กรดไขมันเอมีด กรดไขมันเอสเทอร์และอนุพันธ์โดยใช้แฮโลจิเนทิงเอเจนต์และไทรเฟนิลฟอสฟีน

นางสาวปวีณา พงษ์พิพัฒน์

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SYNTHESIS OF FATTY ACID AMIDES, FATTY ACID ESTERS AND THEIR DERIVATIVES USING HALOGENATING AGENTS AND TRIPHENYLPHOSPHINE

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A Thesis Submitted in Partial Fulfillment of the Requirements
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ปวีณา พงษ์พิพัฒน์ : การสังเคราะห์กรดไขมันเอมีด กรดไขมันเอสเทอร์และอนุพันธ์โดยใช้แฮโลจิเนทิงเอเจนต์และไทรเฟนิลฟอสฟีน. (SYNTHESIS OF FATTY ACID AMIDES, FATTY ACID ESTERS AND THEIR DERIVATIVES USING HALOGENATING AGENTS AND TRIPHENYLPHOSPHINE) อ. ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ.ดร.วรินทร ชวศิริ, 40 หน้า.

ได้พัฒนาวิธีการสังเคราะห์กรดไขมันเอมีด กรดไขมันเอสเทอร์และอนุพันธ์ของกรดไขมันโดยใช้แฮโลจิเนทิงเอเจนต์และไทรเฟนิลฟอสฟีน พบว่าในระบบที่มีไทรคลอโรแอเซทามีดและไทรเฟนิลฟอสฟีนสามารถสังเคราะห์อนุพันธ์ของกรดไขมันได้อย่างมีประสิทธิภาพ ได้ศึกษาภาวะที่เหมาะสมในการสังเคราะห์อนุพันธ์ของกรดไขมันโดยศึกษาผลกระทบของชนิดของแฮโลจิเนทิงเอเจนต์และไทรเฟนิลฟอสฟีน เวลาและอุณหภูมิที่ใช้ นอกจากนี้ได้ใช้พอลิสไตรีนซัพพอร์ตไทรเฟนิลฟอสฟีนในปฏิกิริยาเพื่อทำสารผลิตภัณฑ์ให้บริสุทธิ์ได้ง่ายขึ้น พบว่าภาวะที่เหมาะสมคือสังเคราะห์ภายใต้อุณหภูมิรีฟลักซ์ของไดคลอโรมีเทนเป็นเวลา 30 นาทีทั้งในขั้นตอนของการเปลี่ยนกรดไขมันให้เป็นแอซิดคลอไรด์ และขั้นตอนในการทำปฏิกิริยาต่อกับนิวคลีโอไฟล์เพื่อให้ได้อนุพันธ์ของกรดไขมัน การใช้พอลิสไตรีนซัพพอร์ตไทรเฟนิลฟอสฟีนในการสังเคราะห์ให้ปริมาณผลผลิตที่เทียบเท่ากับการใช้ไทรเฟนิลฟอสฟีน วิธีการนี้สามารถประยุกต์ในการสังเคราะห์อนุพันธ์ของกรดไขมันเอมีด และกรดไขมันเอสเทอร์หลายประเภททั้งแอโรมาติก แอลิฟาติกสายสั้น แอลิฟาติกสายยาว นอกจากนี้ได้นำภาวะที่พัฒนาแล้วในการเตรียมอนุพันธ์ของกรดไขมัน โดยได้สังเคราะห์กรดไขมันไทโอเอสเทอร์และกรดไขมันแอนไฮไดรด์ซึ่งให้ผลเป็นที่น่าพอใจ

สาขาวิชา ปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์ ลายมือชื่อนิสิต ปวีณา พงษ์พิพัฒน์

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PAWEENA PONGPIPATT: SYNTHESIS OF FATTY ACID AMIDES, FATTY ACID ESTERS AND THEIR DERIVATIVES USING HALOGENATING AGENTS AND TRIPHENYLPHOSPHINE. THESIS ADVISOR: ASST.PROF. WARINTHORN CHAVASIRI, Ph.D., 40 pp.

The methodology for the synthesis of fatty acid amides, fatty acid esters and their derivatives utilizing halogenating agents and PPh_3 was developed. Trichloroacetamide coupled with PPh_3 was found to be an effective system for this kind of conversion. To optimize the reaction conditions, type of halogenating agents and PPh_3, reaction time and temperature were investigated. Polystyrene-supported PPh_3 was used in this reaction to simplify the purification of the product. The optimum condition for the fatty acid chloride preparation step and the nucleophilic attack step were achieved when refluxed both steps in CH_2Cl_2 for 30 min each. The use of polystyrene-supported PPh_3 also gave a comparable yield to that of PPh_3. This methodology was applied to synthesize aromatic, short chain and long chain aliphatic fatty acid amides and esters. Furthermore, the developed methodology for the preparation of fatty acid derivatives including fatty acid thioesters and fatty acid anhydrides was successfully achieved.

Field of Study: Petrochemistry and Polymer Science Student's Signature Paweena Pongpipatt
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LIST OF ABBREVIATIONS

%	percent
^{o}C	degree of Celsius
δ	chemical shift
eq	equivalent (s)
g	gram (s)
h	hour (s)
Hz	hertz
m.p.	melting point
mmol	millimole (s)
min	minute (s)
nm	nanometer
NMR	nuclear magnetic resonance
ppm	part per million
RT	room temperature
TLC	thin layer chromatography
UV	ultra violet
W	watt
conc.	concentration
mL	milliliter
quant	quantitative
N	normal

CHAPTER I

INTRODUCTION

Nowadays, there is a trend attempting to manipulate value-adding substances from industrial by-products. Fatty acids are by-products in biodiesel production and vegetable oil industries. The transformation of fatty acids to derived products can be used in various chemical industries with many benefits. For instance, fatty acid esters can be applied to use in drugs and cosmetics industries, whereas fatty acid amides could be utilized as lubricant in plastic industry [1-2]. Their preparations have been widely explored. There are certain reports that proposed the processes for fatty acid derivatives formation, but most of methodologies used enzyme as biocatalyst; thus it invariably requires special care conditions, long time to complete the reaction and to achieve the maximum yield.

The utilization of halogenating agents and triphenylphosphine (PPh_3) has been developed as a versatile reagent in organic synthesis. These reported systems can convert carboxylic acids to their derivatives under mild conditions, short reaction time and gave good yield [3-4]. Nonetheless, there is no report using this system with fatty acids. In this research, the use of halogenating agent combined with PPh_3 for fatty acid derivatives synthesis will be developed. The extension of the utilization of this convenient procedure will provide a new opportunity to prepare various fatty acid derivatives such as fatty acid esters, amides and thioesters.

1.1 Introduction of Acid Halides

Acid halides are important as intermediates to convert into many other functional groups such as esters, amides, acid anhydrides and thioesters. Acid chlorides, one of useful acid halides, are generally prepared by the reaction of carboxylic acids with certain reagents such as thionyl chloride ($SOCl_2$) [5-6], phosphorus chloride compounds (PCl_3, PCl_5) [7] and oxalyl chlorides ($COCl_2$) [8]. However, these methods were not successful in the preparation of some acid chlorides. Therefore, a variety of other procedures for acid chloride synthesis has been developed. The application of PPh_3 and halogenating agents has been exploited within

last decades. These reagents could be used to convert carboxylic acids into a more reactive functional group efficiently [9-13]. The conversions of acid halides to other organic compounds are illustrated as shown in Table 1.1.

Table 1.1 The conversion of acid halides to other organic compounds [9-13]

Substrate	Reagent	Product
Acid halide (RCOX) X=halogen	H_2O	carboxylic acid
	R'COOH	acid anhydride
	R'OH	ester
	$R'NH_2$	amide
	R'SH	thioester
	R'_2CuLi	ketone
	R'MgX	alcohol
	$LiAl(Ot\text{-}Bu)_3H$	aldehyde

1.2 Literature Reviews on Halogenating Agents and PPh_3

The methodologies for the preparation of carboxylic acid derivatives utilizing halogenating agents and PPh_3 have been extensively investigated in many research groups. For example, in 1999, Jang and co-workers [14] developed an alternative method for the preparation acid chlorides from carboxylic acids by using CCl_3CN and PPh_3. Subsequent addition of primary amines resulted in the corresponding secondary amides in high yield. Later, in 2003 Jang and co-workers [15] further applied that developed system to prepare various esters from carboxylic acids. Racemic α-tocopherol, clofibrate and flavoxate could be prepared in high yields using this method.

In 2000, Plubchang [16] described the synthesis of amides using CCl_3CN and PPh_3 at RT. This reaction proceeded efficiently with aromatic carboxylic acids. Bioactive amides such as *N,N*-Diethylbenzamide, *N,N*-diethyl-*m*-toluamide (DEET) and *2*-Chloro-*N,N*-diethylcinnamamide could be prepared according to this methodology.

In 2001, Kim and Jang [17] reported the preparation of symmetrical acid anhydrides from the corresponding carboxylic acids by treating with CCl_3CN and PPh_3 in the presence of NEt_3 at RT.

In 2002, Vago and Greiner [18] reported a novel acylation procedure using polymer supported synthesis, with *in situ* generated acyl chlorides using CCl_3CN and PPh_3.

In 2003, Chaysripongkul [19] addressed the methodology for the synthesis of amides and esters using various halogenating agents coupled with triphenylphosphine. She found that using CCl_3CONH_2 and PPh_3 in CH_2Cl_2 and refluxing the reaction provided a mild reaction condition and short reaction time. Moreover, this reagent could be applied to prepare bioactive ester compounds efficiently.

In 2005, Heuser and co-workers [20] displayed two-step synthesis of oxazolopyridines. The synthesis concerning amide formation between *o*-amino-pyridinols and aliphatic or aromatic carboxylic acids followed by using CCl_3COCCl_3 with PPh_3 at RT.

In 2005, Chantarasriwong [21] described the methodology for the syntheses of amides, esters and sulfonamides using halogenating agents and PPh_3. This developed system could be applied to many types of carboxylic derivatives. Moreover, the developed method could be applied to use in bioactive compound synthesis.

In 2006, Jang and co-workers [22] reported the preparation of acid bromides from carboxylic acids using PPh_3 coupled with Br_3CCO_2Et at room temperature under neutral conditions. The acid bromides generated were trapped into amides in one-step and gave good results in terms of %yield.

In 2007, Tongkate [23] addressed the preparation of carboxylic acid derivatives using Br_3CCO_2Et and $Br_3CCOCBr_3$ as new brominating agents for efficient conversion of alcohols to alkyl bromides and for carboxylic acids to acid bromides in the presence of PPh_3. Some reactions required only 10 minutes to complete the reaction and resulted in target molecules. This developed procedure proceeded rapidly under mild conditions and resulted in the desired products in high yield.

1.3 Literature Reviews on the Synthesis of Fatty Acid Derivatives

Fatty acids can be converted to many products such as fatty acid esters, fatty acid amides, fatty acid thioesters and fatty acid anhydrides. The fatty acid derivatives are very useful for industries and can be prepared from many synthetic routes.

1.3.1 Amides

Fatty acid amides are important in plastic industry. Most of them are used as lubricant and can be prepared from biocatalysis reaction [24]. The well known fatty acid amides used as lubricant is ethylene *bis*-stearamide (EBS) [25].

Jordan and Port [26] described the preparation of fatty acid amides using fatty acid esters and amines in the presence of NaOMe as catalyst. This procedure was fruitfully obtained in high yield of desired product. Aminolysis was found to be rapid at 30°C under anhydrous conditions. With primary amines under optimum conditions, the minimum reaction times necessary to obtain yields of amide over 90% were more than 16 h.

In 1992, Bilyk and co-workers [27] reported the direct amidation of triglyceride from fats or oils. The products were a mixture of glycerol and many different types of fatty acid amides. From the product mixtures, it had to be further separated to obtain the pure product of fatty acid amide. The reactions run to completion in 3–12 h at temperatures of 50–60°C, approximately 100°C lower than employed in present conventional practice. If the mixed amides produced from the various natural triglyceride mixtures of fats and oils were acceptable products, this synthetic method provided these products in satisfactory quality while conserving energy and avoiding the intermediate production of fatty acids or their esters.

In 1996, Zoete and co-workers [28] displayed the synthesis of *cis*-11-eicosenamide and erucamide (*cis*-13-docosenamide) by ammoniolysis reaction using lipase enzyme as catalyst. Ammoniolysis of triglycerides to the corresponding fatty acid amides was efficiently catalysed by *Candida antarctica* lipase (Novozym 435). Thus, this reaction gave desired products after 72 h at 60°C. The products could be used as lubricant in plastic industry. In the same year, Zoete and co-workers [29] developed an efficient enzymatic procedure, the one-pot conversion of carboxylic acids to the corresponding amides via *in situ* formation of the ester and subsequent

ammoniolysis. The resulting octanamide was isolated in 93% yield. The one-pot procedure was also applied to oleic acid, which resulted in the isolation of oleamide in 90% yield. This reaction took a long time because of using lipase enzyme as catalyst in reaction.

In 1996, Sugiura and co-workers [30] synthesized arachidonamide and oleamide using lipase enzyme as catalyst. This reaction proceeded with high yield (93%) but long reaction time required. This enzymatic synthesis was studied using rat brain subcellular fractions as enzyme sources. They found that oleamide was formed from oleic acid and ammonia on incubation with a brain homogenate. The enzyme activity catalyzing the formation of oleamide from oleic acid and ammonia was highest in the microsomal fraction among the subcellular fractions. Boiled microsomes did not exhibit appreciable enzyme activity. These results revealed that oleamide could be synthesized enzymatically in the brains of stimulated animals.

1.3.2 Esters

The synthesis of fatty acid esters could be prepared from fatty acid and alcohol in the presence of strong acid. This reaction was nevertheless a reversible process, so the better methodology for ester synthesis was still called for.

In 1996, Habulin and co-workers [31] reported lipase-catalyzed syntheses of oleic acid esters with various primary alcohols that performed in a batch stirred tank reactor in an almost nonaqueous medium without organic solvents. For all syntheses 50 °C was found to be the optimal temperature. Initial reaction rates were influenced by the alcohol chain length. The study of the pressure stability of the immobilized lipase from *Rhizomucor miehei* (lipozyme IM) showed that the lipase preparation is quite stable. Esterification rates at high pressure were determined, and it was found that they were higher than at atmospheric pressure. The highest rate and maximal conversion were near the critical point of carbon dioxide. Moreover, the synthesis of oleyl oleate using lipase enzyme was studied. This product could be used as jojoba oil because of the same property. Furthermore, oleyl oleate that prepared from this reaction could also be applied in pharmaceutical industry, cosmetics industry and as food additives in food industry.

In 2006, Laudani and co-workers addressed [32] the methodology for the synthesis of *n*-octyl oleate by esterification of fatty acids with 1-octanol using supercritical-CO_2 as reaction medium. This method was focused on organic solvent-free reaction. Due to the use of supercritical-CO_2, this reaction proceeded slowly. The products prepared from this method were used as additives in cosmetics and pharmaceutical industry, as polymer plasticizer and lubricant in plastic industry and material for oiling agent in textile industry.

In 2008, Park and co-workers [33] described the synthesis of methyl oleate that could be used as biodiesel. This fatty acid ester prepared from esterification of oleic acid in vegetable oils (VOs) with CH_3OH. In this work, a heterogeneous catalyst system was developed for the production of biodiesel from used VOs using a continuous process. The activities of several heterogeneous catalysts on the conversion of FFA were tested, with a WO_3/ZrO_2 catalyst finally being selected. A method for preparing pellet-type catalysts was also developed. The pellet-type WO_3/ZrO_2 catalyst showed highly active and durable catalytic activities in the continuous flow process. The reaction time was 140 h with 70% of desired product.

1.3.3 Acid Anhydrides

Most fatty acids could be converted to fatty acid amides and fatty acid esters. Other fatty acid derivatives are fatty acid anhydrides and thioesters. Acid anhydrides are normally used as reactive intermediates in organic synthesis for preparing many other functional groups. Fatty acid anhydrides were also used as lubricant in plastic industry.

Zelinger and Lapidot [34] described a simple method for the preparation of caprylic, palmitic, stearic, and oleic acid anhydrides. The influence of different solvents on the course of the reaction between dicyclohexylcarbodiimide (DCC) and several fatty acids was studied. Carbon tetrachloride was found to be the solvent in which the highest yield of anhydride was produced. Moreover, from the kinetics of the formation of oleic and palmitic anhydrides at 25^{o}C, it was concluded that the reaction completed after 40 min. This methodology gave the corresponding anhydrides in high yield (87-94%).

Rowe [35] reported the synthesis of palmitic acid anhydride and used it as slip and anti-blocking agents for polyolefin. Moreover, stearic acid anhydride can also be used but it was not gave good result when comparing with palmitic acid anhydride. This acid anhydride could be applied either in solid form or in solution. In addition, the acid anhydride used in polyolefin was only two parts by weight and gave a good result.

1.3.4 Thioesters

Thioesters are activated esters that are utilized as versatile intermediates in organic chemistry for the preparation of various compounds, *e.g.*, peptides, macrolide antibiotics, and other pharmaceuticals. Acyl thioesters are active acylation intermediates in biochemical and bioorganic nucleophilic reactions, having higher reactivity and selectivity than the corresponding oxygen analogs.

Weber and co-workers [36] reported solvent-free thioesterification of fatty acids with alkanethiols using immobilized lipases as catalysts and evacuated to remove water and CH_3OH. By using this method, fatty acids could convert to fatty acid thioesters in high yield (80-85%).

Later, in 2004 Weber and co-workers [37] described mono-thioesters and di-thioesters by lipase-catalyzed reactions of α,ω-alkanedithiols with palmitic acid or its methyl ester. 1-*S*-monopalmitoylhexanedithiol and 1-*S*-monopalmitoyl-octanedithiol were prepared in high yield (80–90%) by this method. Lipase-catalyzed transthioesterifications of methyl palmitate with α,ω -alkanedithiols using the same enzymes were less effective than thioesterification for the preparation of the corresponding 1-*S*-mono-palmitoyl thioesters. This procedure was good for environment because of using solvent-free reaction condition.

1.4 Introduction to Polymer-Supported Triphenylphosphine

In recent years, the use of polymer-supported reagents has become popular because of their ease of reaction purification. Polystyrene-supported PPh_3 is one of the most useful solid-supported reagents in organic synthesis. Using of polystyrene-supported PPh_3 can avoid problem of triphenylphosphine oxide removal. When using triphenylphosphine, triphenylphosphine oxide was invariably a by-product of the

reaction and could not be separated by simple procedure like liquid-liquid extraction. To separate this by-product, column chromatograph was required. In addition, certain cares, it took a long time to obtain the desired product. Therefore, the utilization of polystyrene-supported triphenylphosphine overcomes the difficulty of purification of target product. By filtration, it can separate the solid-supported reagent from reaction mixture so the catalyst can be recycled for the next reaction [38-39].

1.4.1 Literature Reviews on Polymer-Supported Triphenylphosphine

In 2000, Charette and co-workers [40] reported the synthesis of polystyrene-supported PPh_3 using non-cross-linked polystyrene. The polymer was synthesized in three steps from non-cross-linked polystyrene. Tin chloride-mediated chloromethylation of polystyrene followed by nucleophilic displacement with the cesium phenoxide derived from *p*-hydroxyphenyldiphenylphosphine oxide gave the phosphine oxide. A subsequent reduction of the phosphine oxide with trichlorosilane and *N*,*N*-dimethylaniline at 100 °C led to the phosphine in quantitative yield. Then, it was used in Staudinger/ Aza-Wittig reaction which involved imine synthesis.

In 2005, Zhao and co-workers [41] described the methodology for the preparation of polystyrene-supported PPh_3 using cross-linked polystyrene. A series of polar group functionalized polystyrene-supported phosphine reagents were examined as catalysts in the aza-Morita–Baylis–Hillman reactions. For these reactions polystyrene-PPh_3 (1 mmol PPh_3/g loading) resin in THF solvent provided the highest yield of all the catalyst/solvent combinations examined. Using this synthetic polystyrene-supported PPh_3, the desired product obtained in high yield.

In 2005, Thomas and co-workers [42] reported polystyrene-supported PPh_3 synthesis by using *co*-polymerized bromopolystyrene and then used the polystyrene-supported PPh_3 in amide synthesis. From the beginning, co-polymerised 4-bromopolystyrene had been converted to a range of polymer-supported reagents and scavengers by bromine–magnesium exchange using Oshima's trialkylmagnesate complex followed by quenching with a variety of electrophiles. When comparing with commercial polystyrene-supported PPh_3, it was found that %yield of desired products from both reactions are comparable.

1.5 Limitations of Previous Works

From literature reviews, most of fatty acid derivatives synthesis used enzyme as catalyst. However, these reactions proceeded very slowly, gave moderate conversion. Therefore, the limitations of those previous protocols could be summarized as:

1. Long reaction time
2. Use of hazardous materials
3. Moderate conversion
4. High pressure catalytic synthesis

1.6 The Objective of This Research

The objective of this research was divided into two parts:

1. To systematically study on the optimization conditions for the synthesis of fatty acid amides and fatty acid esters using halogenating agents and PPh_3.
2. To utilize the optimized conditions to synthesize fatty acid amides, fatty acid esters and their derivatives.

CHAPTER II

EXPERIMENTAL

2.1 Instruments and Equipment

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on aluminium sheets pre-coated with silica gel (Merck's, Kieselgel 60 PF_{254}) and column chromatography was performed on silica gel; Merck's silica gel 60 G Art 7734 (70-230 mesh) were used as adsorbents.

The ^{1}H- and ^{13}C-NMR spectra were performed in $CDCl_3$ or DMSO-d_6 with tetramethylsilane (TMS) as an internal reference on the 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.

2.2 Chemicals

All solvents used in this research were purified prior to use by standard methodology except for those which were reagent grades. The reagents used for synthesis were purchased from Fluka chemical company or otherwise stated and were used without further purification.

2.3 General Procedure for the Synthesis of Fatty Acid Amides and Esters

Step 1: PPh_3 2 eq (6 mmol, 1.57 g) in CH_2Cl_2 3 mL was added to a mixture of selected fatty acid 1 eq (3 mmol) and Cl_3CCONH_2 2 eq (6 mmol) in CH_2Cl_2 3 mL. The mixture was stirred and refluxed for approximately 1 h.

Step 2: A mixture of amine or other nucleophiles (alcohol or thiol) 1 eq (3 mmol) and 4-picoline 3 eq (9 mmol) was added to the above mixture. The reaction was continued stirring for another 30 min. When the reaction was completed, the organic layer was extracted with 1 N HCl and saturated aqueous $NaHCO_3$, respectively, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The mixture was

separated with silica gel column eluting with 4:1 hexane/EtOAc to achieve the desired amide, ester or thioester products.

2.4 Optimum Conditions Study

2.4.1 Effect of Molar Ratio of Halogenating Agents: PPh_3

The suitable ratio of Cl_3CCONH_2/PPh_3 was determined using the reaction conditions described in the general procedure (fatty acid: stearic acid, amine: propylamine, alcohol: octanol). The variation of Cl_3CCONH_2 and PPh_3 ratios were examined as follows: 1:1, 1:2 and 1:3, respectively.

2.4.2 Effect of Halogenating Agents

The synthesis of octyl stearate was carried out using the reaction conditions described in the general procedure, by using three different halogenating agents in the same manner: Cl_3CCN, Cl_3CCONH_2 and $Br_3CCOCBr_3$.

2.4.3 Effect of Temperature and Reaction Time

The general synthetic procedure of octyl stearate using the ratio of Cl_3CCONH_2/PPh_3 1:1 eq was performed at different reaction time and temperature of steps I and II.

2.5 Application of Developed Procedures for the Synthesis of Fatty Acid Amides and Esters

According to the general procedure using Cl_3CCONH_2/PPh_3 1:1 eq, after 30 min a mixture of amine (or alcohol or thiol) and 4-picoline 3 eq (9 mmol, 0.88 mL) was added at reflux temperature and stirred for approximately 30 min.

2.5.1 Variation of Fatty Acids

The general procedure using Cl_3CCONH_2, 4-picoline and CH_2Cl_2 as halogenating agent, base and solvent, respectively at reflux temperature for 1 h was conducted, but different fatty acids: palmitic acid, behenic acid and oleic acid were employed instead of stearic acid.

2.5.2 Variation of Amines

The reaction was carried out using reaction conditions described in 2.5.1, but different amines: ethylamine, cyclohexylamine, 1-octadecylamine instead of propylamine.

2.5.3 Variation of Alcohols

The reaction was carried out using reaction conditions described in 2.5.1, but different alcohols: ethanol, 1-propanol, 1-octadecanol instead of 1-octanol.

2.6 The Use of Polystyrene-Supported PPh_3

According to the general procedure (using Cl_3CCONH_2 with PPh_3), polystyrene-supported PPh_3 (purchased from Novabiochem, load capacity: 1 mmol/g, 100-200 mesh) was used to substitute PPh_3. When the reaction was completed, polystyrene-supported PPh_3 was filtered off. The organic layer was extracted with 1 N HCl and saturated aqueous $NaHCO_3$, respectively, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to achieve the desired product.

2.7 Synthesis of Target Molecules

2.7.1 The Synthesis of Fatty Acid Amides, Esters and Thioesters

According to the general procedure using Cl_3CCONH_2/PPh_3 1:1 eq, after 30 min a mixture of amine (or alcohol or thiol) and 4-picoline 3 eq (9 mmol, 0.88 mL) was added at reflux temperature and stirred further for another 30 min.

2.7.2 The Synthesis of Fatty Acid Anhydrides

A mixture of fatty acid 2 eq (6 mmol) and Cl_3CCONH_2 2 eq (6 mmol, 0.97 g) in dry CH_2Cl_2 3 mL were added PPh_3 2 eq (6 mmol, 1.57 g) in dry CH_2Cl_2 3 mL and 4-picoline 3 eq (9 mmol, 0.88 mL) dropwise at reflux temperature. The reaction mixture was allowed to react for 1 h. When the reaction was completed, the organic layer was extracted with 1 N HCl and saturated aqueous $NaHCO_3$, respectively, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The mixture was separated with silica gel column eluting with 4:1 hexane/EtOAc to achieve the desired acid anhydride.

CHAPTER III

RESULTS AND DISCUSSION

In this research, the development of a chemical reagent and the exploration of optimum conditions for the preparation of fatty acid halide from fatty acid using halogenating agent and PPh_3 were examined. The fatty acid halide formed was simultaneously converted to fatty acid derivatives for characterization by treating with interested nucleophiles in the presence of base.

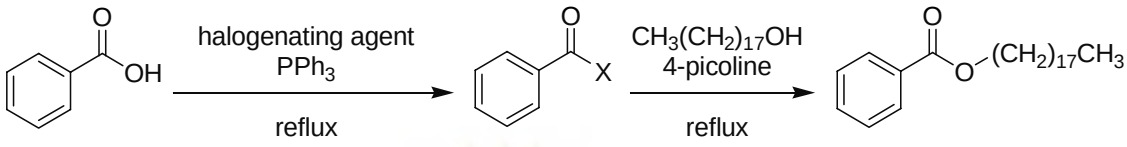
3.1 Optimum Conditions Study

Villeneuve and Chan [43] reported that the association of $Cl_3CCOCCl_3$ and PPh_3 could be used for the transformation of carboxylic acids to acid chlorides. In 1999 [14], an efficient procedure for the preparation of acid chlorides from carboxylic acids using Cl_3CCN combined with PPh_3 was investigated and disclosed to be a proficient reagent for the conversion of carboxylic acids to acid chlorides. However, most reported procedures mentioned on the limitation use for fatty acid, presumably because of steric hindrance of the long chain fatty acid.

Various factors were thus further studied to find out for suitable chemical agents and to determine the optimum conditions for the preparation of fatty acid halides from fatty acids. The parameters studied included types of halogenating agents, reaction time, temperature and molar ratio of the selected halogenating agent. Moreover, the optimized conditions would then be applied to the synthesis of fatty acid derivatives.

3.1.1 Effect of Halogenating Agents

Significant differences in the reactivities of acid halide intermediate formation were mainly caused from types of halogenating agent. The results of the effect of halogenating agent on the formation of 1-octadecyl benzoate are collected in Table 3.1.



X = Cl, Br

Table 3.1 Effects of halogenating agents on the formation of 1-octadecyl benzoate

Entry	Halogenating agent	%Yield of 1-octadecyl benzoate
1	none	trace
2	CCl_3CN	72
3	CCl_3CONH_2	88
4	$Br_3CCOCBr_3$	74

reaction conditions: benzoic acid (3 mmol), halogenating agent (6 mmol), PPh_3 (6 mmol), 1-octadecanol (6 mmol), 4-picoline (9 mmol), CH_2Cl_2 (6 mL) at reflux temperature.

reaction time: step I 30 min, step II 30 min.

The CCl_3CN and CCl_3CONH_2 employed in entries 2 and 3, respectively, were commercially available whereas $Br_3CCOCBr_3$ (entry 4) was conveniently synthesized by treating acetone with bromine following the procedure cited in previous work [23].

Considering the effect of halogenating agents on the formation of acid halide, it was observed that when the reaction was carried out in the absence of halogenating agent (entry 1), the desired product was obtained only in trace amount. This was clearly demonstrated that the halogenating agent was important for this reaction. The proficiency of halogenating agent depended on the halide group on the halogenating agents. To describe this, the use of CCl_3CONH_2 (entry 3) gave %yield of the desired product significantly more than that obtained from using Cl_3CCN and $Br_3CCOCBr_3$ (entries 2 and 4). Although, a bromide ion was a better leaving group and more nucleophilic than chloride ion, by this method for the preparation of long chain ester, CCl_3CONH_2 was more efficient than $Br_3CCOCBr_3$. In addition, a type of the substituent on halogenating agents also revealed the effect on the reactivity of the reaction, for example, CCl_3CONH_2 (entry 3) gave the ester product in higher yield than CCl_3CN (entry 2). Moreover, when consider the price of both reagents,

CCl_3CONH_2 and CCl_3CN, it was found that CCl_3CONH_2 (100 g/ 34.40 US dollar) is cheaper than CCl_3CN (100 mL/ 69.30 US dollar). It should be noted that using $Br_3CCOCBr_3$ as halogenating agent resulted in product with %yield as high as that by synthesized using CCl_3CN as halogenating agent, but CCl_3CN was commercially available reagent while $Br_3CCOCBr_3$ had to be synthesized from acetone and bromine [23].

The efficiency of halogenating agents providing octadecyl benzoate could be arranged as shown below.

$$CCl_3CONH_2 > Br_3CCOCBr_3 > CCl_3CN$$

From the above study, CCl_3CONH_2 was determined as the most proper halogenating agent for further investigation. This was considered from the price of the reagent, %yield of the desired product and the ease of work-up procedure. The ^{1}H-NMR spectrum of 1-octadecyl benzoate is presented in Fig 3.1.

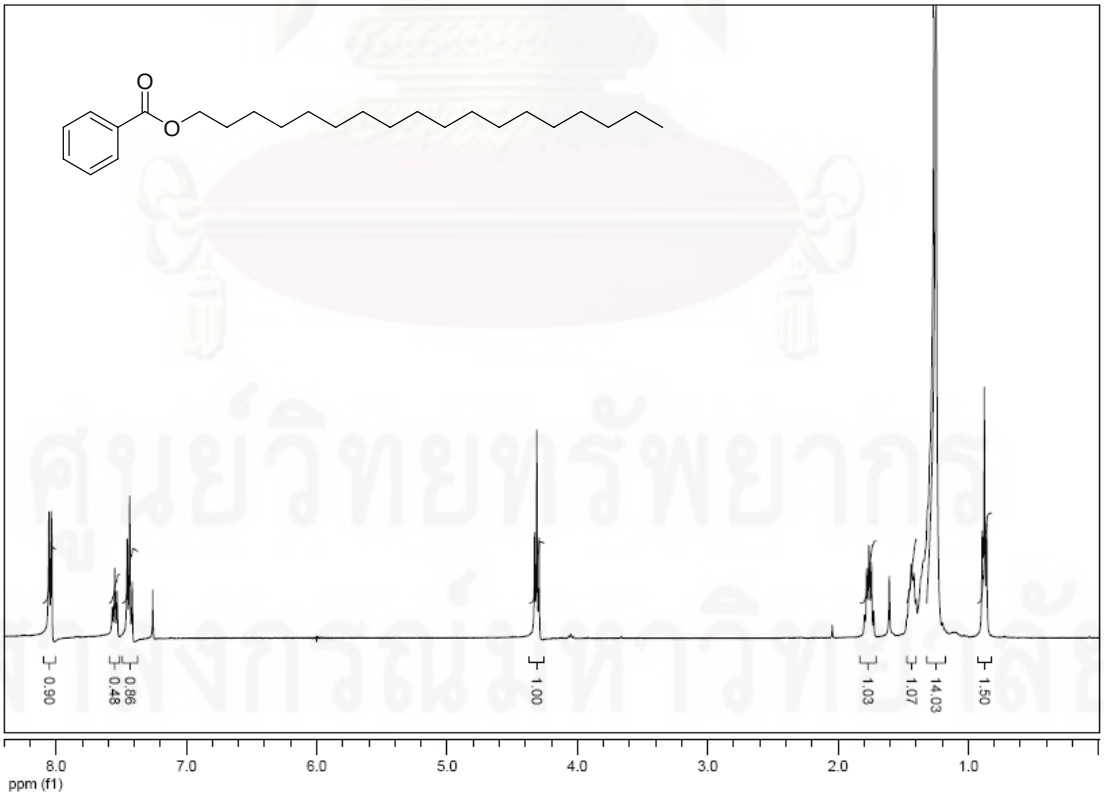


Figure 3.1 The ^{1}H-NMR spectrum of 1-octadecyl benzoate.

Octadecyl benzoate: (88%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.88 (3H, t, *J* = 6.48 Hz, $ArCOO(CH_2)_{17}C\underline{H}_3$), 1.20-1.34 (28H, m, $ArCOOCH_2CH_2CH_2(C\underline{H}_2)_{14}CH_3$), 1.40-1.47 (2H, m, $ArCOOCH_2CH_2C\underline{H}_2(CH_2)_{14}CH_3$), 1.76 (2H, quin, *J* = 6.74 Hz, $ArCOOCH_2C\underline{H}_2(CH_2)_{15}\ CH_3$), 4.31 (2H, t, *J* = 6.67 Hz, $ArCOOC\underline{H}_2(CH_2)_{16}CH_3$) and 7.42-8.05 (5H, m, Ar-<u>H</u>).

3.1.2 Effect of Molar Ratio of CCl_3CONH_2:PPh_3

For optimizing reaction conditions, stearic acid and 1-octanol were used as model substrates. When the former was treated with CCl_3CONH_2 and PPh_3 in CH_2Cl_2 at reflux temperature, followed by treating with 1-octanol in the presence of 4-picoline as a base, 1-octyl stearate was achieved as the desired product. The effect of molar ratio of CCl_3CONH_2:PPh_3 was explored and the results are shown in Table 3.2.

Table 3.2 Effects of molar ratio of CCl_3CONH_2:PPh_3 on the formation of 1-octyl stearate

Entry	Molar ratio of CCl_3CONH_2:PPh_3	%Yield of 1-octyl stearate
1	1 : 1	96
2	1 : 2	94
3	1 : 3	59

reaction conditions: stearic acid (3 mmol), octanol (6 mmol), 4-picoline (9 mmol), CH_2Cl_2 (6 mL) at reflux temperature.

reaction time: step I 1 h, step II 30 min.

As the results presented in Table 3.2, it was found that only 1:1 molar ratio of CCl_3CONH_2:PPh_3 (entry 1) was required to convert stearic acid to the corresponding 1-octyl stearate in high yield. Moreover, it should be mentioned that the conversion of stearic acid to 1-octyl stearate when using 1:2 molar ratio of CCl_3CONH_2:PPh_3 (entry 2) also gave high yield of the desired product. However, 1:1 molar ratio of CCl_3CONH_2:PPh_3 was considered as the most proper ratio for further investigation because this ratio could offer high yield of product using less amount of PPh_3 than

entry 2. In contrast, the yield of the desired product decreased when the ratio of CCl_3CONH_2 and PPh_3 were increased to 1:3 (entry 3). This may be due to the excess of PPh_3 could react with product and led to the formation of undesired products [19, 21].

3.1.3 Effect of the Amount of Nucleophile

According to the general procedure, the amount of the nucleophile used was in 1:1 ratio to the amount of carboxylic acid. With more steric hindered nucleophile such as long chain amine, it affected the %yield of the desired product. The percentage yields of benzoate esters achieved from general procedure when altering time and amount of nucleophile are described in Table 3.3.

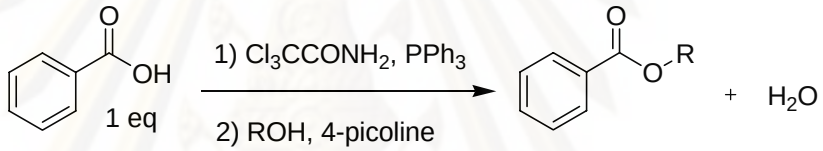


Table 3.3 Effects of the amount of nucleophile on the formation of benzoate esters

Entry	Type of nucleophile	Equivalent (eq)	Reaction time in step II (h)	%Yield of benzoate esters
1	1-octanol	1	1	79
2	1-octanol	1.5	1	89
3	1-octadecanol	1	1	56
4	1-octadecanol	1	3	60
5	1-octadecanol	1	5	55
6	1-octadecanol	1.5	1	80
7	1-octadecanol	l .5	3	81
8	1-octadecanol	2	1	87
9	1-octadecanol	3	1	88

reaction conditions: benzoic acid (3 mmol), CCl_3CONH_2 (6 mmol), PPh_3 (6 mmol), 4-picoline (9 mmol), CH_2Cl_2 (6 mL) at reflux temperature.

reaction time: step I 1 h.

It was clearly revealed that when alcohol with a short chain was used as a nucleophile (entries 1-2), benzoate esters were obtained in high yields. On the other hand, with a long chain alcohol (entries 3-9), the equivalence of alcohol greatly affected the %yield of the desired product. From the results of the synthesis of 1-octadecyl benzoate, the higher %yield was achieved when more nucleophile was added. The reason was probably due to the steric hindrance of nucleophile. In conclusion, the equivalence of nucleophile needed was less than 2 eq to attain high yield of desired product.

3.1.4 Effect of Reaction Time and Temperature

Reaction time and temperature in fatty acid chloride preparation step (step I) and step II that fatty acid chloride reacted further 30 min with nucleophile resulted in fatty acid derivatives in the general procedure were changed in order to find the relationship between reaction time and temperature which provided the desired product in high yield. The results are displayed in Table 3.4.

Table 3.4 Effects of reaction time on the formation of 1-octadecyl benzoate

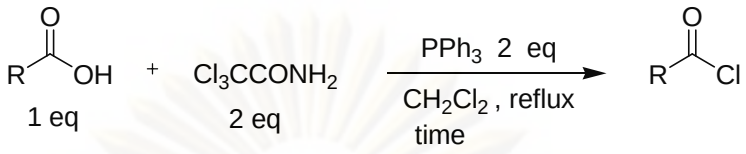
Entry	Reaction time (min)		%Yield of 1-octadecyl benzoate
	Step I	Step II	
1	60	30	84
2	60	60	87
3	30	60	83
4	30	30	88

reaction conditions: benzoic acid (3 mmol), CCl_3CONH_2 (6 mmol), PPh_3 (6 mmol), octadecanol (6 mmol), 4-picoline (9 mmol), CH_2Cl_2 (6 mL) at reflux temperature.

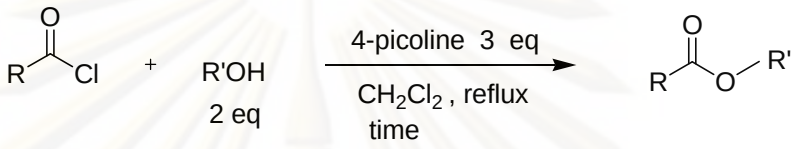
It was found that the reaction time could be minimized to 30 min in both steps I and II while the high yield of the desired product was still attained. Therefore, further investigation will apply this condition to long chain fatty acid.

3.2 The Preparation of Fatty Acid Esters

Step I



Step II



From the results in Table 3.4, the optimum reaction time can be decreased to 30 min in steps I and II. The reaction time and temperature on the formation of 1-octyl stearate was further investigated. The objective of this study was to apply the conditions to fatty acid so stearic acid was chosen as the acid and reacted with 1-octanol to prepare 1-octyl stearate. The results of the variation of reaction time and temperature were shown in Table 3.5.

Table 3.5 Effects of reaction time and temperature on the formation of 1-octyl stearate

Entry	Reaction time (min)		%Yield of 1-octyl stearate
	Step I	Step II	
1	60	30	94
2	30	30	96
3	15	30	88
4	30	15	33
5[a]	30	30	63

reaction conditions: stearic acid (3 mmol), CCl_3CONH_2 (6 mmol), PPh_3 (6 mmol), octanol (6 mmol), 4-picoline (9 mmol), CH_2Cl_2 (6 mL) at reflux temperature.

[a] The reaction was performed at RT (28-30^{o}C).

From the general procedure, the reaction times of steps I and II were 1 h and 30 min, respectively, it was found that the desired product was attained in high yield. Therefore, lower reaction time was investigated. It revealed that even if the reaction time was decreased to 30 min in both two steps, the product was achieved in high yield. It was noticed that %yield of the desired product decreased when reaction time was decreased to 15 min either in step I or II. For the reaction temperature, it was found that the desired product was obtained in low yield when reaction was taken place at room temperature. The increase of the reaction temperature provided the product in almost quantitative yield with short reaction time, only 30 min. Therefore, the appropriate temperature and time for this reaction are 30 min at refluxing CH_2Cl_2 temperature in both steps. In addition, by carrying out the reaction at elevated temperature the solubility for some fatty acid substrates was better. Some fatty acids were not completely dissolved at room temperature.

3.2.1 Variation of Fatty Acids

Since the optimized conditions could be obtained as previously discussed, the scope of the reaction to convert various fatty acids into their corresponding esters was further investigated. The results are displayed in Table 3.6.

Table 3.6 Effects of fatty acids on the formation of fatty acid esters

Entry	Acid	Time in step 1 (min)	Time in step 2 (min)	%Yield
1	Palmitic acid (C16)	30	30	96
2	Behenic acid (C22)	30	30	95
3	Stearic acid (C18)	30	30	96

reaction conditions: fatty acid (3 mmol), CCl_3CONH_2 (6 mmol), PPh_3 (6 mmol), octanol (6 mmol), 4-picoline (9 mmol), CH_2Cl_2 (6 mL) at reflux temperature.

According to the results displayed in Table 3.6, it was found that all entries gave good yield of desired products. The length of fatty acid did not affect on the conversion of fatty acid to the corresponding fatty acid esters. The high yield of the desired product still attained even though the amount of carbon increased to 22 atoms.

Therefore, this optimized reaction condition could be used to synthesize fatty acid esters efficiently. Furthermore, variation of alcohols was observed on the formation of fatty acid esters.

3.2.2 Variation of Alcohols

The results of the conversion of fatty acids to fatty acid esters employing different alcohols are presented in Table 3.7.

Table 3.7 Effects of alcohols on the formation of fatty acid esters

Entry	Alcohol	Time in step 1 (min)	Time in step 2 (min)	%Yield
1	1-propanol	30	30	96
2	1-octanol	30	30	96
3	1-octadecanol	30	30	95

reaction conditions: stearic acid (3 mmol), CCl_3CONH_2 (6 mmol), PPh_3 (6 mmol), alcohol (6 mmol), 4-picoline (9 mmol), CH_2Cl_2 (6 mL) at reflux temperature.

It was noticed that under the optimized reaction conditions, the transformation of fatty acids to fatty acid esters with diverse alcohols occurred efficiently with good yield. Although, the last entry was quite long chain alcohol (C18) but the reaction could furnish the desired product in high yield. Considering the extent of the reaction, this developed methodology has advantage to selected fatty acids and alcohols. The yield of the desired product was generally excellent yield. To our best knowledge, there was no report on the success of the preparation of fatty acid esters using long chain fatty acids and long chain fatty alcohols before. Thus, this developed protocol could be claimed as an efficient method for this specific purpose. The ^{1}H-NMR spectrum of 1-octadecyl stearate (entry 3) is presented in Fig 3.2. When comparing with %yield of desired product in other literatures, it should be mentioned that %yield of desired product was higher and reaction time was shorter than previous work.

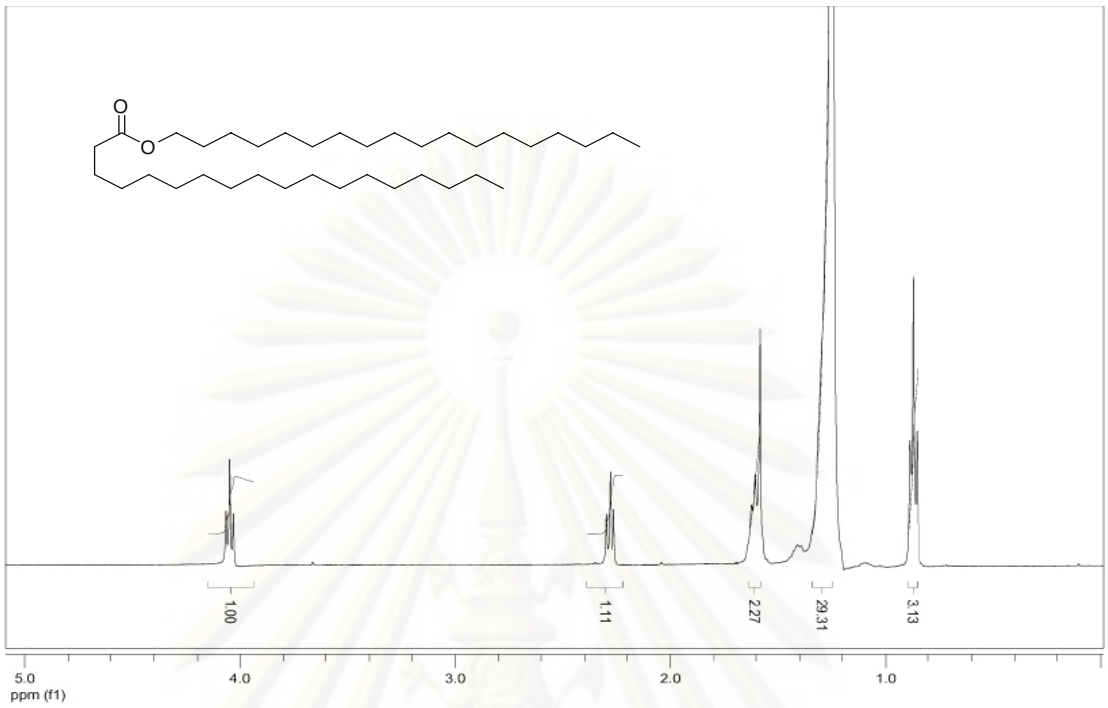
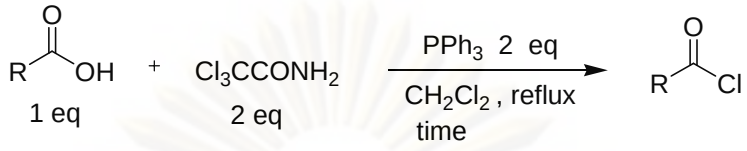


Figure 3.2 The ^{1}H-NMR spectrum of 1-octadecyl stearate.

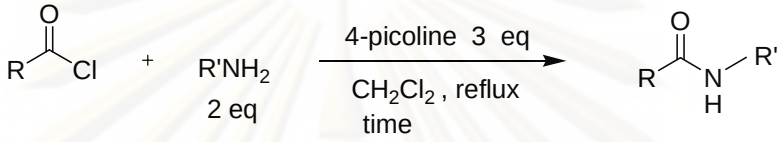
Octadecyl stearate: (95%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.87 (6H, t, *J* = 6.23 Hz, $C\underline{H}_3(CH_2)_{16}COO(CH_2)_{17}C\underline{H}_3$), 1.19-1.37 (58H, m, $CH_3(C\underline{H}_2)_{14}(CH_2)_2COO(CH_2)_2(C\underline{H}_2)_{15}CH_3$), 1.55-1.62 (4H, m, $CH_3(CH_2)_{14}C\underline{H}_2CH_2COOCH_2C\underline{H}_2(CH_2)_{15}CH_3$), 2.28 (2H, t, *J* = 7.53 Hz, $CH_3(CH_2)_{15}C\underline{H}_2COO(CH_2)_{17}CH_3$) and 4.05 (2H, t, *J* = 6.69 Hz, $CH_3(CH_2)_{16}COOC\underline{H}_2(CH_2)_{16}CH_3$).

3.3 The Preparation of Fatty Acid Amides

Step I



Step II



Gaining the information from the optimization of fatty acid ester synthesis, the preparation of fatty acid amides was investigated. Stearic acid and 1-propylamine were used as model substrates to furnish 1-propyl stearamide as the desired product. The results are presented in Table 3.8.

Table 3.8 Effects of reaction time and temperature on the formation of 1-propyl stearamide.

Entry	Reaction time (min)		%Yield of 1-propyl stearamide
	Step I	Step II	
1	60	30	90
2	30	30	90
3[a]	30	30	91

reaction conditions: stearic acid (3 mmol), CCl_3CONH_2 (6 mmol), PPh_3 (6 mmol), propylamine (6 mmol), 4-picoline (9 mmol), CH_2Cl_2 (6 mL) at reflux temperature.

[a] reaction occurred at room temperature (28-30^{o}C) in step II.

As presented in Table 3.8, all entries gave excellent yields of 1-propyl stearamide even though the reaction temperature carried out the reaction was at room temperature in step II (entry 3). This may be because the nitrogen nucleophile attacked to the corresponding acid chloride was stronger.

3.3.1 Variation of Amines

Because of excellent yields of 1-propyl stearamide, variation of amines was conducted. The results are shown in Table 3.9.

Table 3.9 Effects of amines on the formation of fatty acid amides

Entry	Amine	Equivalent (eq)	Time in step 1 (min)	Time in step 2 (min)	Yield (%)
1	1-Octadecylamine (C18)	1	30	30	2
2	1-Octadecylamine (C18)	2	30	30	3
3	Cyclohexylamine (C6)	1.5	30	30	88
4	Cyclohexylamine (C6)	2	30	30	93
5	1-Octadecylamine (C18)[a]	2	30	30	5
6	1-Octadecylamine (C18)[b]	2	30	30	3
7	1-Octadecylamine (C18)	2	30	4 h	47
8	1-Octadecylamine (C18)	1.5	30	2 h	32

reaction conditions: stearic acid (3 mmol), CCl_3CONH_2 (6 mmol), PPh_3 (6 mmol), amine (6 mmol), 4-picoline (9 mmol), CH_2Cl_2 (6 mL) at reflux temperature.

[a] Used $Br_3CCOCBr_3$ as halogenating agent.

[b] Used Cl_3CCN as halogenating agent.

From the study on the effect of amines, it was found that if amines were short chain or cyclic (entries 3-4), the desired product resulted in high yield. In case of 1-octadecyl stearamide, the amide product was detected in low yield. This is because of steric hindrance. Due to the low yield of desired product, reaction time in step II was increased to 2 and 4 h. It revealed that when the reaction time increased, the yield of fatty acid amide also increased (entries 7-8). Comparing the yield of target product, this optimized methodology was suitable for short chain and cyclic amines. If the structure of amine was longer, more reaction time may be required. The ^{1}H-NMR spectrum of 1-cyclohexyl stearamide is presented in Fig 3.3.

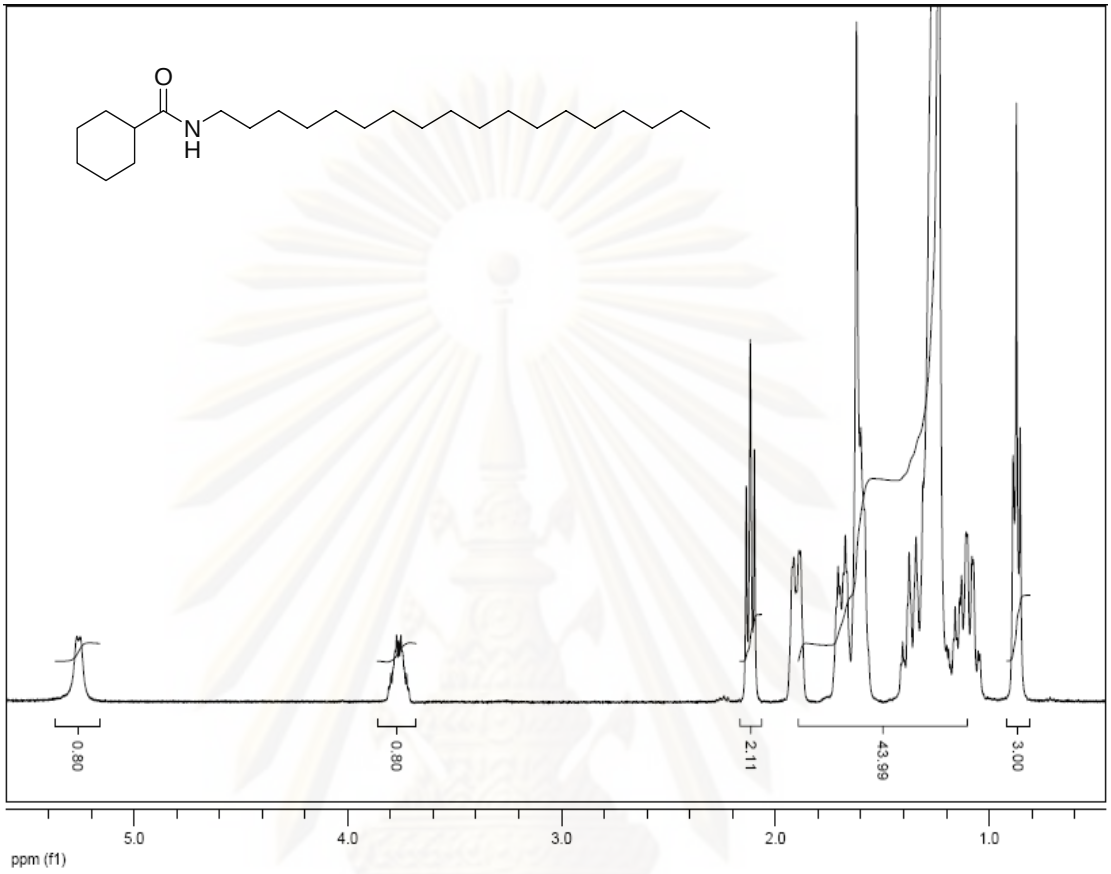


Figure 3.3 The ^{1}H-NMR spectrum of 1-cyclohexyl stearamide.

Cyclohexyl stearamide: (93%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.87 (3H, t, *J* = 6.39 Hz, $C\underline{H}_3(CH_2)_{16}CONHCH(CH_2)_5$), 1.04-1.92 (42H, m, $CH_3(C\underline{H}_2)_{15}CH_2CONHCH(C\underline{H}_2)_5$), 2.12 (2H, t, *J* = 7.46 Hz, $CH_3(CH_2)_{15}C\underline{H}_2CONHCH(CH_2)_5$), 3.71-3.81 (1H, m, $CH_3(CH_2)_{15}CH_2CONHC\underline{H}(CH_2)_5$) and 5.26 (1H, d, *J* = 7.72 Hz, $CH_3(CH_2)_{15}CH_2CON\underline{H}CH(CH_2)_5$).

Even though the product of 1-octadecylamine and stearic acid was not obtained in high yield, it gave a good result with benzoic acid and resulted in 89% yield of desired product. The ^{1}H-NMR spectrum of 1-octadecyl benzylamide is presented in Fig 3.4.

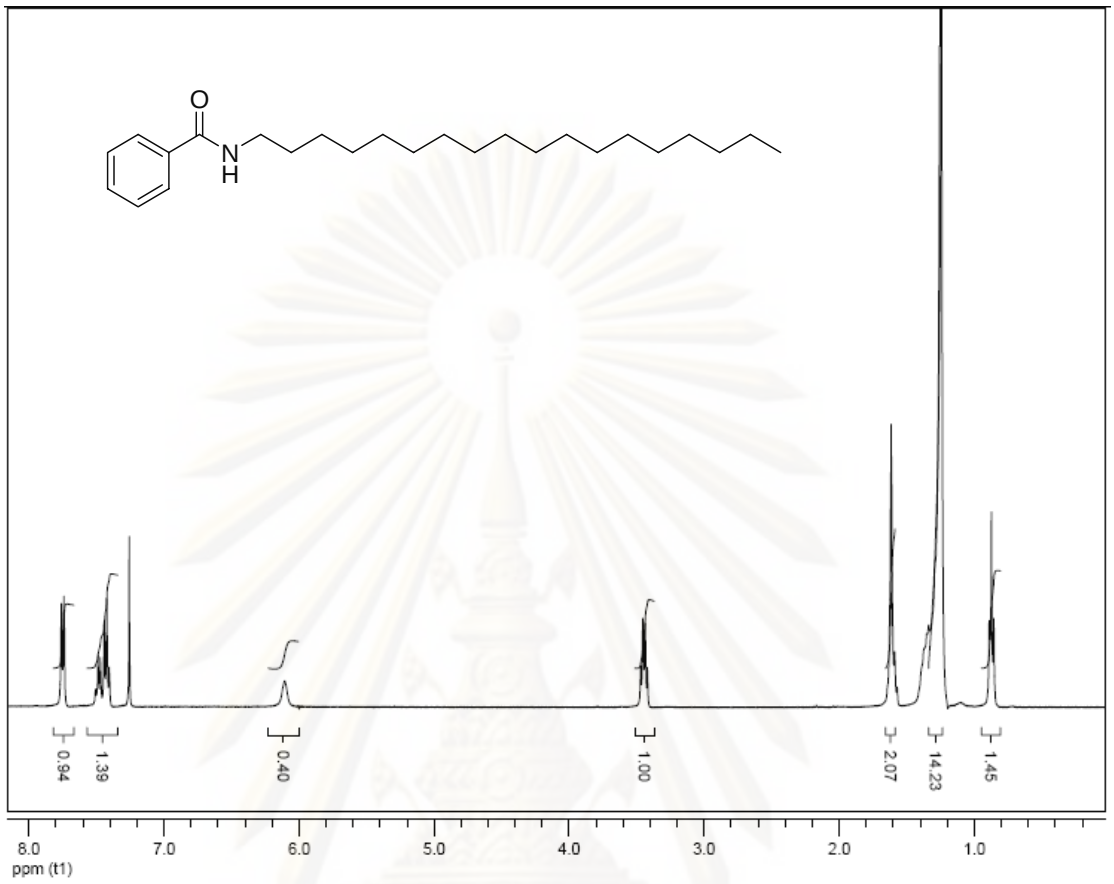


Figure 3.4 The ^{1}H-NMR spectrum of 1-octadecyl benzylamide.

Octadecyl benzylamide: (89%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.87 (3H, t, *J* = 7.06 Hz, $ArCONH(CH_2)_{17}C\underline{H}_3$), 1.20-1.43 (28H, m, $ArCONHCH_2CH_2CH_2(C\underline{H}_2)_{14}CH_3$), 1.57-1.66 (4H, m, $ArCONHCH_2C\underline{H}_2C\underline{H}_2(CH_2)_{14}CH_3$), 3.45 (2H, q, *J* = 7.00 Hz, $ArCONHC\underline{H}_2(CH_2)_{16}CH_3$), 6.11 (1H, bs, $ArCON\underline{H}(CH_2)_{17}CH_3$) and 7.41-7.76 (5H, m, Ar-$\underline{H}$).

3.4 The Use of Polystyrene-Supported PPh_3

Nowadays, polymer-supported reagent was well-known as recyclable and efficient reagent in organic synthesis. Due to the ease of work up procedure, polystyrene-supported PPh_3 was selected and explored in this study. The results of the synthesis of fatty acid esters using polystyrene-supported PPh_3 are demonstrated in Table 3.10.

Table 3.10 Synthesis of fatty acid esters using polystyrene-supported PPh_3

Entry	Starting carboxylic acid	Starting alcohol	% Yield
1	benzoic acid	1-octanol	85
2	benzoic acid	1-octadecanol	91
3	stearic acid	1-octanol	89
4	stearic acid	1-octadecanol	47

reaction conditions: carboxylic acid (3 mmol), polymer supported PPh_3 (6 mmol), CCl_3CONH_2 (6 mmol), alcohol (6 mmol), 4-picoline (9 mmol), CH_2Cl_2 (6 mL) at reflux temperature (38-40 ^oC).

reaction time: step I 30 min, step II 30 min.

Using of polystyrene-supported PPh_3 (load capacity 1 mmol/g, purchased from Novabiochem 5 g/ 5455 Baht) instead of PPh_3 still gave a good yield of desired product. This method was investigated to find the way to reduce problem of triphenylphosphine oxide removal. For the general procedure, triphenylphosphine oxide was removed by using column chromatograph that sometimes took a long time to purify the desired product. However, the cost of polystyrene-supported PPh_3 was much higher than PPh_3. If the desired product wanted in very large amount, polystyrene-supported PPh_3 needed should be in very big scale resulting in high cost. From entry 4, it should be mentioned that using stearic acid as starting material instead of benzoic acid, the %yield of desired product decreased to 47%. This may be because of steric hindrance of both fatty acid and nucleophile. Moreover, polystyrene-supported PPh_3 is solid supported reagent, so it cannot dissolve in reaction mixture resulted in the difficulty of nucleophilic attack.

The synthesis of other derivatives of stearic acid was also investigated and the resulted are displayed in Table 3.11.

Table 3.11 Synthesis of stearic acid derivatives using commercial polystyrene-supported PPh_3

Entry	Carboxylic acid	Nucleophile	Product	% Yield
1	stearic acid	1-octanol	1-octyl stearate	88
2	stearic acid	1-propylamine	1-propyl stearamide	89
3	stearic acid	1-octanethiol	1-octyl thiostearate	89

reaction conditions: carboxylic acid (3 mmol), polystyrene-supported PPh_3 (6 g, 6 mmol of PPh_3), CCl_3CONH_2 (6 mmol), neucleophile (6 mmol), 4-picoline (9 mmol), CH_2Cl_2 (6 mL) at reflux temperature (38-40^oC).

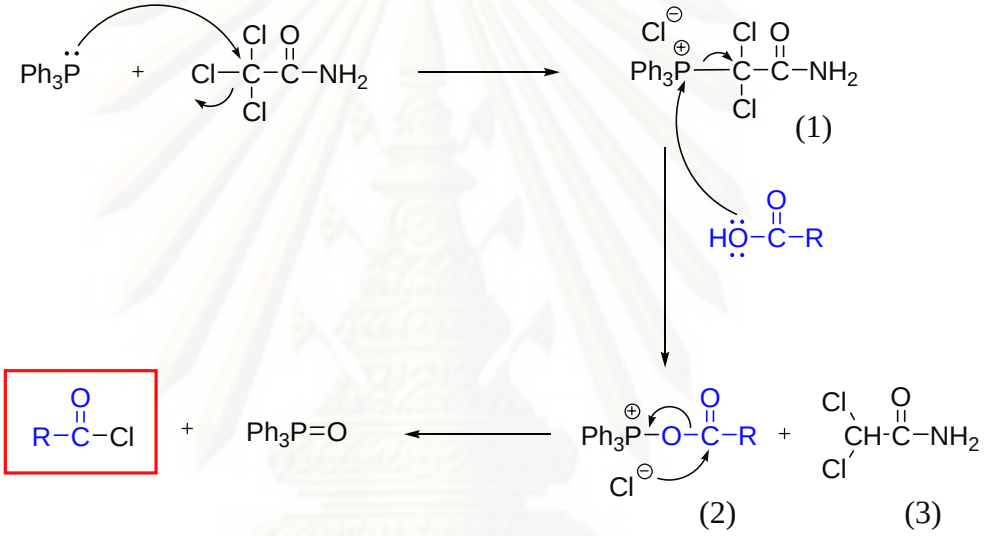
reaction time: step I 30 min, step II 30 min.

From the results in Table 3.11, it revealed that the synthesis of fatty acid derivatives using polystyrene-supported PPh_3 also gave good yield of desired products. By filtration, polystyrene-supported PPh_3 could be removed from the reaction mixture. Therefore, triphenylphosphine oxide was also removed. The desired product could be achieved without further purification. The aim of this applied method is to simplify the purification step but the cost of this method will increase from the general procedure. However, using polystyrene-supported PPh_3 could be an alternative choice for fatty acid derivatives synthesis if the cost of making polystyrene-supported PPh_3 is reduced in the future. From the result of %yield of desired product, it was noticed that using polystyrene-supported PPh_3 also gave good yield comparable to the %yield of desired product that synthesized from reaction using PPh_3 coupled with Cl_3CCONH_2.

3.5 The Proposed Mechanism

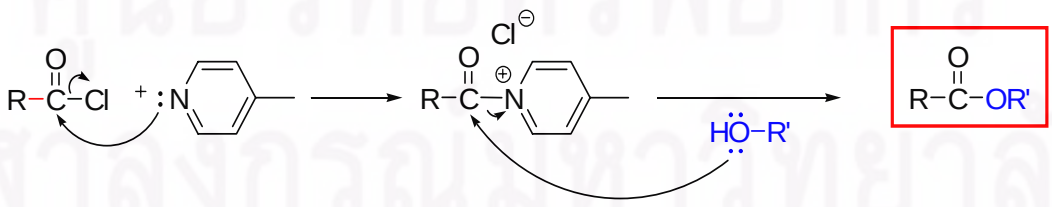
The mechanism of acid chloride formation in this research was believed to take place similar to that reported by Chaysripongkul [19]. The proposed mechanism is described as follows.

The reaction was obviously a multi-step process. Initially, species (1) occurred by a reaction between PPh_3 and Cl_3CCONH_2. Species (1) was reacted further with fatty acid yielding species (2) and (3). The mechanism is shown below.

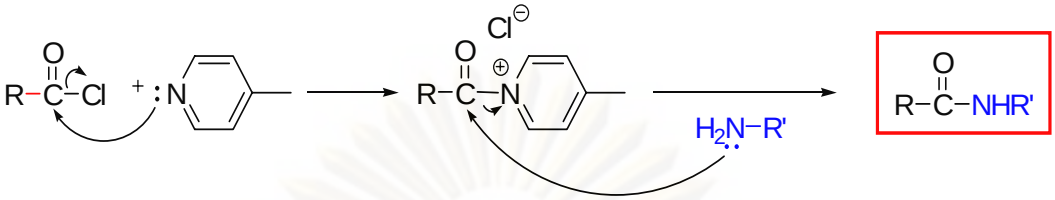


In the next step, nucleophile and 4-picoline in CH_2Cl_2 was added in reaction to reacted further and then resulted in fatty acid derivatives. The mechanism is shown below.

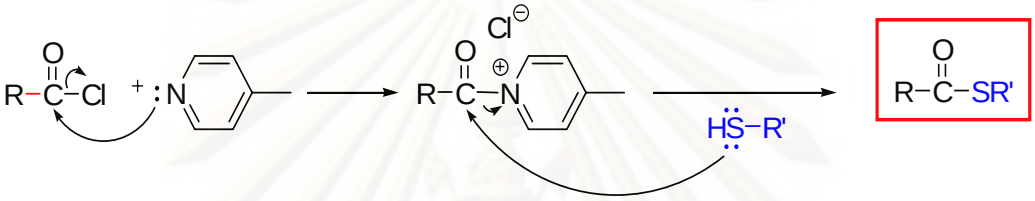
Fatty acid ester synthesis:



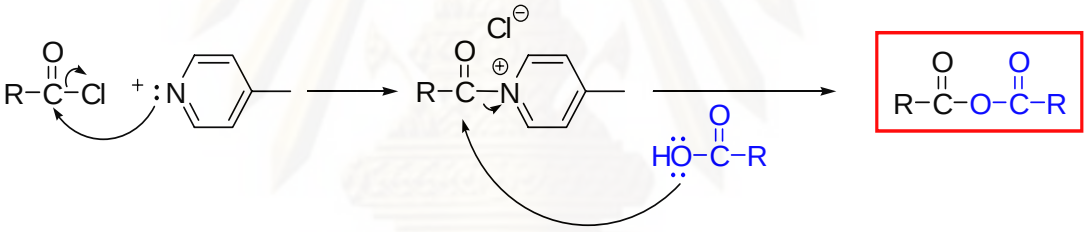
Fatty acid amide synthesis:



Fatty acid thioester synthesis:



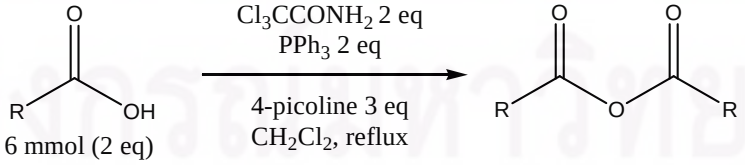
Fatty acid anhydride synthesis:



3.6 Synthesis of Fatty Acid Derivatives

From the success of using the optimum reaction conditions to synthesize the desired fatty acid esters and amides, this general procedure was further investigated. The conversion of fatty acid into their derivatives was studied in this part.

3.6.1 Synthesis of Fatty Acid Anhydrides



Further application of this developed procedure was extended for the synthesis of fatty acid anhydrides. The results are presented in Table 3.12.

Table 3.12 Synthesis of fatty acid anhydrides using developed methodology

Entry	Acid	Equivalent (eq)	Time (min)	Yield (%)
1	Stearic acid	2	60	25
2[a]	Stearic acid	2	60	22
3	Palmitic acid	2	60	23
4	Oleic acid	2	60	24
5	Benzoic acid	2	60	27
6[b]	Stearic acid	2	30	21
7[c]	Benzoic acid	2	60	65
8[c]	Stearic acid	2	60	26
9	Benzoic acid	2	30	28

[a] Reaction occurred in 2 steps

[b] Used $Br_3CCOCBr_3$ as halogenating agent

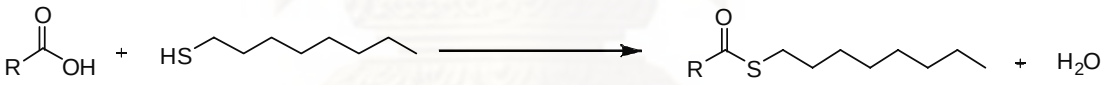
[c] Used Cl_3CCN as halogenating agent

From the results in Table 3.12, it was observed that in the case of fatty acids under standard conditions, the corresponding acid anhydrides resulted in low yield. To investigate the %yield of desired product, fatty acid anhydride synthesis in entry 2 was studied. In this study, the reaction occurred in 2 steps similar to other fatty acid derivative preparations. One equivalent of fatty acid (starting material) was added in step I to be converetd to fatty acid chloride, and then another equivalent of the same fatty acid was added in step II as nucleophile to react with fatty acid chloride resulted in target molecule. It revealed that even though the reaction occurred in 2 steps, the yield of desired product was not different from the procedure that occurring in 1 step. Thus, the 1-step and 2-step fatty acid anhydride preparation did not give different results in term of the % yield of the target product. With the aim to lift up the yield of desired product, other halogenating agents were used. In entries 6 and 8, using $Br_3CCOCBr_3$ and Cl_3CCN, respectively, as halogenating agents, it was revealed that even though different halogenating agents were used, the yield of target molecule was not significant differences from general method. To increase the yield of desired

product, reaction time was studied. By using general method and increasing reaction time, the same results still attained. On the other hand, in entry 7, if the starting acid was simple carboxylic acid like benzoic acid, the yield of desired acid anhydride was obtained in moderate yield. From the results of %yield obtained in all entries, it was noticed that the yields of desired product achieved in low yield comparing with previous studied including fatty acid esters and amides. This may be because the acid nucleophile that attacks the acid chloride in step II is weak nucleophile. Therefore, the amount of nucleophile that attacked the acid chloride occurred more difficult than strong nucleophile, amine and alcohol, and resulted in desired product was less than the others when comparing with nucleophile in fatty acid esters and amides synthesis.

3.6.2 Synthesis of Fatty Acid Thioesters

Fatty acid thioesters is another important fatty acid derivative. It could be prepared under similar conditions used for that of esters, changing nucleophile to thiols. Table 3.13 reveals the effect of substrate and the results are tabulated in this Table.



1-octanethiol

Table 3.13 Synthesis of fatty acid thioesters using developed methodology

Entry	Fatty acid	Time in step 1	Time in step 2	%Yield
1	benzoic acid	30	30	97
2	palmitic acid	30	30	95
3	stearic acid	30	30	91
4	behenic acid	30	30	94

reaction conditions: fatty acid (3 mmol), PPh_3 (6 mmol), CCl_3CONH_2 (6 mmol), 1-octanethiol (6 mmol), 4-picoline (9 mmol), CH_2Cl_2 (6 mL) at reflux temperature (38-40 ^oC).

The synthesis of fatty acid thioesters using the optimized methodology resulted in excellent yield. It was revealed that such simple carboxylic acid as benzoic acid and long chain acid like fatty acid also obtained the corresponding thioester in high yields. Furthermore, in the preparation of fatty acid esters and thioesters using the same starting material, the yield of fatty acid thioesters was higher than that of esters. This is because of the better nucleophilic activity of thiol.

CHAPTER IV

CONCLUSION

The objective of this research is to systematically study on the optimization conditions for the synthesis of fatty acid amides, fatty acid esters using halogenating agents and PPh_3. Moreover, this developed methodology could be used to synthesize fatty acid amides, fatty acid esters and fatty acid derivatives. The procedures could be carried out under mild conditions and provided the high yields of desired products.

The optimized reaction conditions were revealed: fatty acid 1 eq as a substrate, Cl_3CCONH_2 2 eq and PPh_3 2 eq as a combination reagent, CH_2Cl_2 6 mL as a solvent, 4-picoline 3 eq as a base and the reaction was recommended to carry out under refluxing CH_2Cl_2 for 30 min or followed by TLC. Moreover, Cl_3CCN, $Br_3CCOCBr_3$ could be used as an alternative halogenating agent instead of Cl_3CCONH_2. This developed methodology was effective to convert fatty acid to its derivatives such as amides and esters. The cost of the halogenating agent used was found to be more economical than other related methods in previous works.

To investigate the scope of the synthesis of fatty acid esters, various fatty acids and alcohols were examined to determine the limitation of this protocol. The outcome from the study on the effect of fatty acid illustrated that this method was suitable for various fatty acids from 16 to 22 carbon atoms and high yields of desired products were still obtained. From the variation of alcohol, the yields of desired product were still achieved even though the carbon atoms of alcohol were up to 18 atoms. Furthermore, various amines were examined to verify that this developed methodology can be applied. The results revealed that the yields of the target products depended on the length of amine chain.

The application of this developed methodology to the synthesis of various fatty acid amides and esters was also fruitfully achieved. In addition, this general protocol could also be applied for the synthesis of other derivatives including fatty acid thioesters and fatty acid anhydrides. The high yields of target molecules revealed that the developed procedure was an effective system for fatty acid derivatives synthesis.

The use of polystyrene-supported PPh_3 was an alternative reagent for the preparation of fatty acid derivatives. The yields of the desired product were still attained. The advantages of using polystyrene-supported PPh_3 as reagent are the ease of triphenylphosphine oxide removal and reusable reagent for organic synthesis. However, the cost of polystyrene-supported PPh_3 is much more than PPh_3.

Proposal for the Further Work

This research provided many guidelines for future work. For instance, other halogenating agents such as ethyl trichloroacetate (Cl_3CCO_2Et), ethyl tribromoacetate (Br_3CCO_2Et) and trichloroacetanilide ($Cl_3CCONHC_6H_5$) and PPh_3 should be carefully further examined. The application of this optimum system should be used to synthesize fatty acid amides, esters and their derivatives in large scale and compare with the product prepared by biocatalysis synthesis that uses lipase enzyme as catalyst in reaction which is being used in many industries. In addition, fatty acids that were by-products from biodiesel plants could be used to investigate the results of fatty acid mixtures and separation of fatty acids. Moreover, from a good trend of the results in terms of isolated yield of desired product in fatty acid derivatives synthesis using polystyrene-supported PPh_3 coupled with Cl_3CCONH_2, the further reaction using this reagent should be studied. Therefore, the utilization of polystyrene-supported PPh_3 in this kind of conversion should be verified to explore the result of reusable reagent.

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