CHAPTER III

RESULTS AND DISCUSSION

In this research, the development of a chemical reagent and the exploration of optimum conditions for the preparation of acid chloride from carboxylic acid, halogenated reagent and triphenylphosphine (PPh_3) were examined. The acid chloride formed was simultaneously converted to amide for characterization by treating with interested amine in the presence of base. The general equation can be simplified as shown below.

$$RCO_2H + \text{halogenated reagent} + PPh_3 \xrightarrow{\text{solvent}} RCOCl \qquad \text{(step 1)}$$

$$RCOCl + R'NH_2 \xrightarrow{\text{base}} RCONHR' \qquad \text{(step 2)}$$

3.1 Study on the Conditions Optimization

From previous literatures, it has been reported that the combination of hexachloroacetone and triphenylphosphine could be used for the conversion of carboxylic acids to acid chlorides.[22] Later, trichloroacetonitrile coupled with triphenylphosphine were disclosed to be an applicable reagent for this kind of transformation.[23,64]

In the present study, various factors were further scrutinized to search for new appropriate chemical reagents and to evaluate for the optimal conditions for the preparation of acid chloride. The standard chemical reaction involves the reaction of benzoic acid with halogenated reagent to form the acid chloride intermediate, which was consequently trapped with selected cyclohexylamine to furnish the desired product. Variable parameters studied included halogenated reagent, base, reaction time, temperature and solvent system. Moreover, under the optimized conditions, this protocol would then applied for the synthesis of potential bioactive compounds.

3.1.1 Effect of Halogenated Reagent

Significant differences in the reactivities of acid chloride intermediate formation were mainly caused from halogenated reagent. The results are described in Table 3.1.

Table 3.1 Effects of halogenated reagents on the formation of *N*-cyclohexyl benzamide

entry	halogenated reagent	%yield of *N*-cyclohexylbenzamide
1	none	trace
2	trichloroacetonitrile (Cl_3CCN)	64
3	trichloroacetamide (Cl_3CCONH_2)	62
4	ethyl trichloroacetate (Cl_3CCO_2Et)	62
5	ethyl tribromoacetate (Br_3CCO_2Et)	78
6	iodoacetic acid (ICH_2CO_2H)	13
7	trichloroacetic acid (Cl_3CCO_2H)	40
8	tribromoacetic acid (Br_3CCO_2H)	43
9	trichloroacetic anhydride ($(Cl_3CCO)_2O$)	12
10	*i*-propyl trichloroacetate ($Cl_3CCO_2CH(CH_3)_2$)	55
11	trichloroacetanilide ($Cl_3CCONHC_6H_5$)	69
12	*N,N*-diethyltrichloroacetamide ($Cl_3CCONEt_2$)	60
13	*N,N*-diethyltribromoacetamide ($Br_3CCONEt_2$)	72

reaction conditions: benzoic acid (3 mmol), halogenated reagent (6 mmol) PPh_3 (6 mmol), CH_2Cl_2 (6 mL), cyclohexylamine (3 mmol) Et_3N (9 mmol), room temperature (28-30 °C).

reaction time: step I 1 hour, step II 20 minutes.

The halogenated reagents employed in entries 2-3 and 6-9 are commercially available reagents whereas those in entries 4-5 and 10-13 were derived from the synthesis in this research.

The synthesis of ethyl trichloroacetate, ethyl tribromoacetate and *i*-propyl trichloroacetate (entries 4, 5 and 10) was achieved by esterification of the corresponding carboxylic acid, alcohol and concentrated sulfuric acid as a

catalyst.[50,51] The yield of the desired reagent was comparably high (69-75%). The IR spectrum of ethyl trichloroacetate and ethyl tribromoacetate exhibited the ester carbonyl absorption band at 1762 cm^{-1}. The presence of alkyl and C-O bond was inferred from the presence of bands at 2981 and 1240 cm^{-1}. The ^{1}H-NMR spectrum also clearly confirmed the identity of these compounds: three protons at δ_H 1.38 and two protons at δ_H 4.39 of an ethyl group.

The synthesis of trichloroacetanilide (entry 11) was fruitfully performed by treating hexachloroacetone with aniline following the procedure cited in literature.[52] The IR spectrum of trichloroacetanilide exhibited the amide carbonyl absorption band at 1699 cm^{-1}. The medium intensity bands at 1598 and 1443 cm^{-1} were the characteristic peaks of an aromatic ring. The presence of alkyl, N-H and C-N bonds was inferred from the presence of bands at 3054, 3307 and 1315 cm^{-1}. The ^{1}H-NMR spectrum displayed five aromatic protons at δ_H 7.24-7.57 and a broad singlet N-H proton at δ_H 8.31 with intensity of one proton.

N,N-Diethyltrichloroacetamide and *N,N*-diethyltribromoacetamide (entries 12 and 13) could be synthesized by conversion the corresponding carboxylic acids to their acid chlorides by using oxalyl chloride and a few drops of dimethylformamide. Then, the mixture was added to an aqueous diethylamine solution to yield the desired product.[7,50] This reaction could indeed be utilized to prepare tribromoacetamide.

N-Cyclohexylbenzamide as the ultimate target molecule was confirmed its identity by IR and ^{1}H-NMR spectra. The IR spectrum clearly exhibited the amide carbonyl absorption band at 1629 cm^{-1}. The medium intensity bands at 1562 and 1444 cm^{-1} were the characteristic peaks of an aromatic ring. The presence of alkyl, N-H and C-N bonds could be detected at 2924, 3242 and 1332 cm^{-1}, respectively. The ^{1}H-NMR spectrum displayed five aromatic protons at δ_H 7.24-7.75 and a broad singlet N-H proton at δ_H 6.03. The multiplet signals at δ_H 1.12-2.03 were typical of the protons of cyclohexyl ring and the methine proton of cyclohexyl ring was detected at δ_H 3.88-4.02. The IR and ^{1}H-NMR spectra of *N*-cyclohexylbenzamide are shown in Figures 3.1 and 3.2.

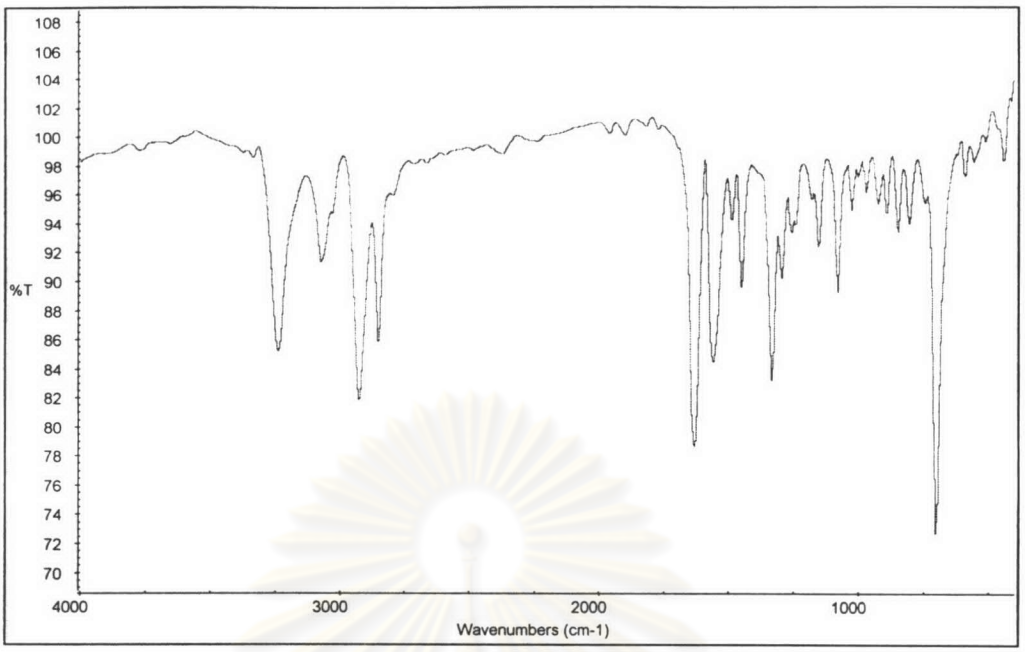


Figure 3.1 The IR spectrum of *N*-cyclohexylbenzamide

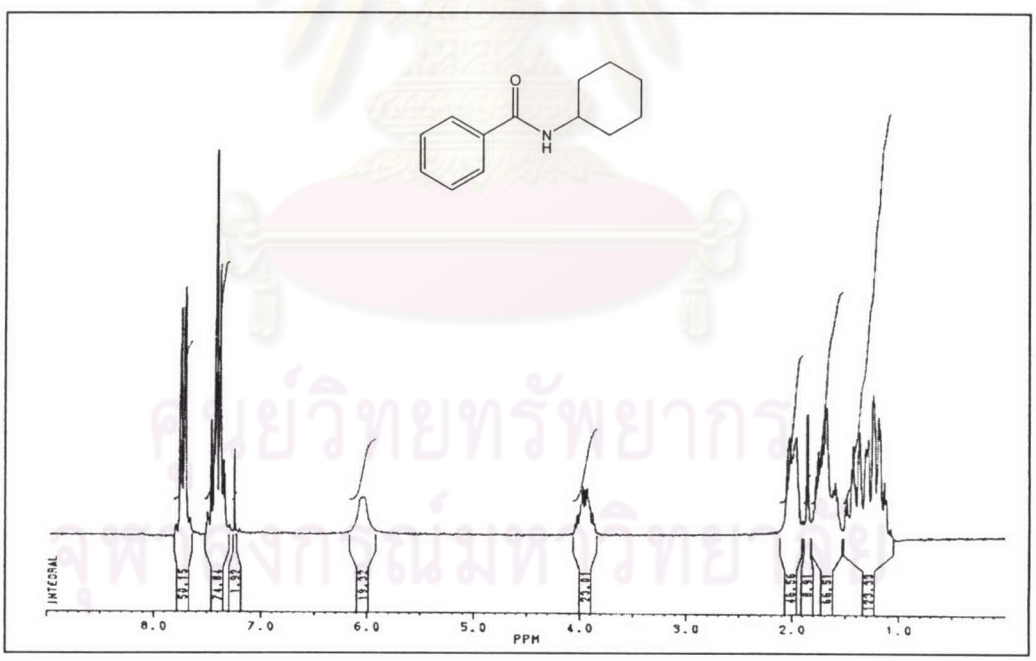


Figure 3.2 The ^{1}H-NMR spectrum of *N*-cyclohexylbenzamide

Considering the effect of halogenated reagents on the formation of acid chloride, it was observed that when the reaction was carried out in the absence of halogenated reagent (entry 1), the desired product was obtained only in a trace amount. This was clearly demonstrated that the halogenated reagent was crucial for this reaction. The efficiency of halogenated reagent was found to depend on a type of the halide group on halogenated reagents. To illustrate this, the use of Br_3CCO_2Et (entry 5) gave %yield of *N*-cyclohexylbenzamide more than that of Cl_3CCO_2Et (entry 4). This was perhaps derived from the fact that a bromide ion was a better leaving group and of more nucleophilic character than chloride ion.[2] In addition, a type of the substitutent on halogenated reagents also revealed the profound effect on the reactivity of the reaction, for example, Cl_3CCO_2H (entry 7) gave the amide product in moderate yield compared with Cl_3CCN (entry 2). The latter reagent bearing more affinity electron-withdrawing group that revealed the influence to provide the desired product in higher yield. Other reagents containing electron-withdrawing group were chosen to prove this assumption. For instance, Cl_3CCONH_2, Cl_3CCO_2Et, $Cl_3CCONHC_6H_5$ and $Cl_3CCONEt_2$ (entries 3, 4, 11 and 12) provided the yield of product comparable to that of Cl_3CCN. Either trichloroacetic acid or tribromoacetic acid (entries 7 and 8) did not give good yield of the desired product probably because of their acidity that may make the reaction become acidic and thus not appropriate for further reaction to take place.

The efficiency of halogenated reagents providing *N*-cyclohexylbenzamide could be arranged as shown below.

Br_3CCO_2Et > $Br_3CCONEt_2$ > $Cl_3CCONHC_6H_5$ ~ Cl_3CCN ~ Cl_3CCONH_2 ~ Cl_3CCO_2Et ~ $Cl_3CCONEt_2$ > $Cl_3CCO_2CH(CH_3)_2$ > Br_3CCO_2H > Cl_3CCO_2H > ICH_2CO_2H > $(Cl_3CCO)_2O$ > none

From the above study, Cl_3CCONH_2 was considered as the most proper halogenated reagents for further investigation. This was judged from the price of the reagent and the ease of work-up procedure. To illustrate this, the reaction employing Cl_3CCONH_2 could be easily performed and the work up procedure was more convenient than those using Br_3CCO_2Et or $Br_3CCONEt_2$ or $Cl_3CCONHC_6H_5$, $Cl_3CCONEt_2$ or Cl_3CCN, respectively.

3.1.2 Effect of Base

According to the literature review, it was observed that similar reported reactions to produce acid chloride normally used triethylamine as a base. Not many studies, nonetheless, paid much attention to the effect of base.[22-24] Therefore, another worth intriguing feature conducted in this study was the examination the effect of bases. Various bases were thus investigated and the results are tabulated in Table 3.2.

Table 3.2 Effects of bases on the formation of *N*-cyclohexylbenzamide

entry	base	pK_a	%yield of *N*-cyclohexylbenzamide
1	none	-	75
2	triethylamine	10.72	62
3	DMAP	9.70	57
4	pyridine	5.25	86
5	*4*-picoline	6.02	90
6	imidazole	6.95	63
7	quinaldine	5.87	82
8	*3*-cyanopyridine	3.71	55
9	pyridine-*N*-oxide	6.90	65
10	quinoline	4.94	90

reaction conditions: benzoic acid (3 mmol), Cl_3CCONH_2 (6 mmol) PPh_3 (6 mmol), CH_2Cl_2 (6 mL), cyclohexylamine (3 mmol) base (9 mmol), room temperature (28-30 °C).

reaction time: step I 1 hour, step II 20 minutes.

It was noticed that the quantity of *N*-cyclohexylbenzamide was significantly increased when the base used was a weak base. For example, pyridine, *4*-picoline, quinaldine and quinoline (entries 3, 4, 6 and 10) gave the desired product in high yield compared with the common base, triethylamine employed. Moreover, this reaction could be performed without using any extra base (entry 1) to yield the desired product in high yield. From the above information, the suitable base for this reaction should be of the structure analogous to pyridine such as *4*-picoline, quinoline and quinaldine.

From the studies on the effect of base described above, the bases which aid the reaction to provide desired products from the highest to the lowest, are shown below.

4-picoline ~ quinoline > pyridine > quinaldine > none > pyridine-*N*-oxide ~ imidazole ~ triethylamine > DMAP ~ *3*-cyanopyridine

It should be worth noting here that the use of *4*-picoline, quinoline, pyridine and quinaldine as an effective base for the aids of converting acid chlorides to amides has never addressed in the chemical literature.

3.1.3 Effect of Solvent System

The effect of solvent system was investigated. The main criteria for the solvents selected included those that could dissolve both carboxylic acid and reagents used homogeneously such as dichloromethane, chloroform, acetonitrile, ethyl acetate and tetrahydrofuran. The results are demonstrated in Table 3.3.

Table 3.3 Effects of solvent system on the formation of *N*-cyclohexylbenzamide

entry	solvent	%yield of *N*-cyclohexylbenzamide
1	CH_2Cl_2	90
2	$CHCl_3$	79
3	CH_3CN	60
4	EtOAc	49
5	THF	45

reaction conditions: benzoic acid (3 mmol), Cl_3CCONH_2 (6 mmol) PPh_3 (6 mmol), solvent (6 mL), cyclohexylamine (3 mmol) *4*-picoline (9 mmol), room temperature (28-30 °C).

reaction time: step I 1 hour, step II 20 minutes.

Four common solvents were selected to examine whether they could use to replace CH_2Cl_2 in this reaction. It was found that CH_2Cl_2 (entry 1) still gave *N*-cyclo hexylbenzamide in the highest yield. However, in some specific cases $CHCl_3$ (entry 2) may be another alternative use instead of CH_2Cl_2 in this kind of reaction.

3.1.4 Effect of Temperature and Reaction Time

Reaction time and temperature in step I of the general procedure were altered in order to find out the relationship between the reaction time and temperature which could provide *N*-cyclohexylbenzamide in the highest yield. The results of %yield of *N*-cyclohexylbenzamide when altering time and temperature are displayed in Table 3.4.

Table 3.4 Effects of temperature and reaction time on the formation of *N*-cyclohexyl benzamide

Entry	Reaction temperature (°C)	Reaction time of step I (minutes)	%yield of *N*-cyclohexylbenzamide
1	room temp. (28-30 °C)	60	90
2	0-5 °C	60	32
3	reflux (38-40 °C)	30	97
4	reflux (38-40 °C)	50	99

reaction conditions: benzoic acid (3 mmol), Cl_3CCONH_2 (6 mmol) PPh_3 (6 mmol), CH_2Cl_2 (6 mL), cyclohexylamine (3 mmol) *4*-picoline (9 mmol).

reaction time: step II 20 minutes.

For the duration of the reaction time of 1 hour at 0-5 °C, it was found that the desired product was attained in low yield. The increase of the reaction temperature provided the product in almost quantitative yield with short reaction time only 30 minutes. Therefore, the suitable temperature and time for this reaction are 30 minutes at refluxing dichloromethane temperature. In addition, the advantage of this reaction carried out at elevated temperature was the better solubility for some carboxylic acid substrates, which in some cases not totally dissolve at room temperature.

3.2 The General Consideration of Selected Halogenated Reagents and Bases

The cost of reagent is one of the important factors to be seriously considered in organic synthesis. The practical synthetic reaction must offer high yield of the desired product using non-toxic and inexpensive reagents. The costs of both

halogenated reagent and base are therefore considered as expressed in Tables 3.5 and 3.6.

Table 3.5 The comparison between %yield of *N*-cyclohexylbenzamide and the cost of some halogenated reagents

entry	halogenated reagent	cost* (amount / price)	%yield of *N*-cyclohexylbenzamide
1	Cl_3CCN	100 mL/ 69.30	64
2	Cl_3CCONH_2	100 g/ 34.40	62
3	Cl_3CCO_2Et	**	62
4	Br_3CCO_2Et	**	78
5	ICH_2CO_2H	100 g/ 96.10	13
6	Cl_3CCO_2H	100 g/ 19.00	40
7	Br_3CCO_2H	100 g/ 49.40	43
8	$(Cl_3CCO)_2O$	100 mL/ 137.30	12
9	$Cl_3CCO_2CH(CH_3)_2$	**	55
10	$Cl_3CCONHC_6H_5$	**	69
11	$Cl_3CCONEt_2$	**	60
12	$Br_3CCONEt_2$	**	72

* US dollar (from Fluka catalogue, 1997)

** halogenated reagents were derived from direct preparation in this research starting from Cl_3COOH (entry 6)

It was found that the suitable halogenated reagents judged from both price and %yield of *N*-cyclohexylbenzamide were trichloroacetamide and ethyl trichloroacetate (entries 2 and 3) which could be synthesized from trichloroacetic acid (entry 6). The repeat synthesis of *N*-cyclohexylbenzamide was carefully performed employing Cl_3CCONH_2 or Cl_3CCO_2Et under the best conditions (reaction conditions: benzoic acid (3 mmol), Cl_3CCONH_2 (6 mmol), PPh_3 (6 mmol), CH_2Cl_2 (6 mL), cyclohexylamine (3 mmol) and *4*-picoline (9 mmol) and reaction time: step I at reflux for 30 minutes, step II at room temperature for 20 minutes), it was ultimately observed that the reaction with Cl_3CCONH_2 gave the desired product (97%) higher than that utilizing Cl_3CCO_2Et (87%). It should however be noted that ClC_3CCN

(entry 1) and Br_3CCO_2Et (entry 4) also gave the desired product in good yield, but the costs of these reagents were rather expensive.

Table 3.6 The comparison between %yield of *N*-cyclohexylbenzamide and the cost of base

entry	base	cost* (amount / price)	%yield of *N*-cyclohexylbenzamide
1	triethylamine	250 mL/ 34.90	62
2	DMAP	250 g/ 224.50	57
3	pyridine	250 mL/ 23.30	86
4	*4*-picoline	250 mL/ 14.20	90
5	imidazole	250 g/ 157.10	63
6	quinaldine	250 mL/ 143.75	82
7	*3*-cyanopyridine	250 g/ 38.75	55
8	pyridine-*N*-oxide	250 g/ 96.25	65
9	quinoline	250mL/22.45	90

* US dollar (from Fluka catalogue, 1997)

It was found from Table 3.6 that the appropriate base which was suitable both price and %yield of the desired product, *N*-cyclohexylbenzamide was *4*-picoline (entry 4). Besides the affordable price of *4*-picoline, the work up procedure could be performed easily and the amide product was achieved in excellent yield.

From the outcome of variable factors studied as described above, it could be concluded that the optimum conditions for this reaction were as follows: step I; carboxylic acid 1 eq as a substrate, Cl_3CCONH_2 2 eq and PPh_3 2 eq as a combination of reagent, CH_2Cl_2 6 mL as a solvent and the reaction should be carried out at reflux for 30 minutes (or following by TLC), Step II; amine 1 eq as a trapping agent, *4*-picoline 3 eq as a base at room temperature and the appropriate reaction time could be followed by TLC.

It should indeed mention at this point that this research disclosed a new methodology to utilize the combination of inexpensive reagents: Cl_3CCONH_2 and *4*-picoline as a halogenated reagent and base, respectively. These reaction conditions

were thus kept as standard conditions for the synthesis of biological amides and esters.

3.3 The Mechanism of Acid Chloride Formation

The mechanism of acid chloride formation in this research was believed to take place similar to that reported by P.C. Crofts[65] and J.B. Lee.[19] The proposed mechanism is described as follows.

The reaction was obviously a multi-step process. Initially, species **(1)** occurred by an action between PPh_3 and Cl_3CCONH_2. Species **(1)** was reacted further with carboxylic acid yielding species **(2)** and **(3)**. Finally, acid chloride and triphenylphosphine oxide were produced by the transformation of species **(2)**. The evidence of the presence of triphenylphosphine oxide could be visualized by isolation of triphenylphosphine from the reaction procedure by column chromatography as white needle crystal, melting at 154-156 °C. The mechanism is shown below.

$$PPh_3 + Cl_3CCONH_2 \longrightarrow \underset{\textbf{(1)}}{Ph_3P^+CCl_2CONH_2Cl^-}$$

$$\textbf{(1)} + RCOOH \longrightarrow \underset{\textbf{(2)}}{RCOOP^+Ph_3Cl^-} + \underset{\textbf{(3)}}{Cl_2HCCONH_2}$$

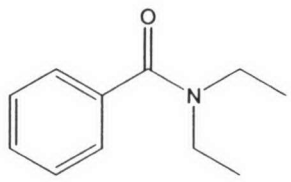
$$\textbf{(2)} \longrightarrow RCOCl + Ph_3P{=}O$$

3.4 Application of Developed Procedures for the Synthesis of Target Molecules

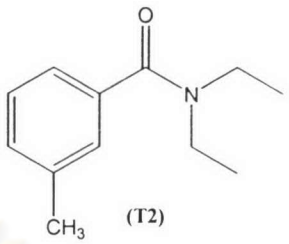
Most bioactive compounds usually found as simple derivatives of amides and esters.[66] The amide compounds generally showed a large number of biological activities both of pharmaceutical and agricultural activities. The ester compounds are also widely well-known active ingredient in cosmetics, nutraceuticals and pharmaceutical formulations. This developed acid chloride preparation protocol was therefore attempted to apply for the synthesis of those biological amides and esters.

3.4.1 Biologically Active Amides

***N,N*-Diethylbenzamide (T1) and *N,N*-diethyl-3-methylbenzamide or *N,N*-diethyl-*m*-toluamide or DEET (T2)**, an insect repellent, have been well-known to employ as mosquito, flea, gnat and many other insect repellents.[67]



(T1)



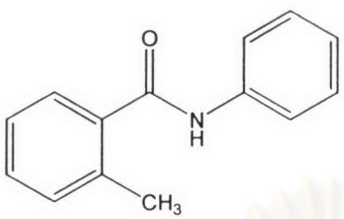
(T2)

The synthesis of these compounds[67] was previously reported by treating carboxylic acid with $SOCl_2$ under reflux, after that the amine was added into the mixture. The yield of **T1** was nevertheless not reported while that of **T2** was 94%. The drawback of this reaction however could manifestly be seen from the use of $SOCl_2$ which the by-products were harmfully corrosive chemicals and invariably make the conditions become acidic.

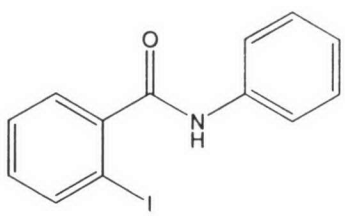
T1 could be achieved without any difficulty employing this developed protocol in 99%. The IR spectrum (Fig 1) exhibited a strong absorption band at 1629 cm^{-1}, indicating the presence of amide carbonyl. The medium intensity bands at 1524 and 1450 cm^{-1} were the characteristic peaks of an aromatic ring. The C-H and C-N bonds were inferred from the presence of bands at 2970 and 1372 cm^{-1}. The ^{1}H-NMR spectrum (Fig 2) displayed five aromatic protons at δ_H 7.38. Four broad singlets at δ_H 1.10, 1.25, 3.26 and 3.55 were typical of two ethyl groups.

By employing this developed methodology, DEET **(T2)** could also be achieved in 99%. The IR spectrum (Fig 3) of this derived amide clearly exhibited the amide carbonyl absorption band at 1619 cm^{-1}. The medium intensity bands at 1564 and 1460 cm^{-1} were the characteristic peaks of an aromatic ring. The presence of alkyl and C-N bonds could be observed from the bands at 2970 and 1367 cm^{-1}. The ^{1}H-NMR spectrum (Fig 4) displayed four aromatic protons at δ_H 7.15-7.28 and a methyl group substituted on an aromatic ring at δ_H 2.40 with 3H intensity. Four broad singlets at δ_H 1.10, 1.28, 3.25 and 3.58 were typical of two ethyl groups.

***2*-Methylbenzanilide or mebenil (T3) and *2*-iodobenzanilide or benodanil (T4).** **T3** possessed a fungicidal effect against *Rhizoctonia solani*[68] while benodanil **(T4)** exhibited good action on injurious fungi, especially from the class of *Basidiomycetes*, *e.g. Rhizoctonia, Coniophora, Tilletia, Puccinia,* and *Ustilago.*[59]



(T3)



(T4)

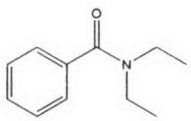
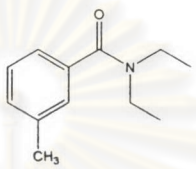
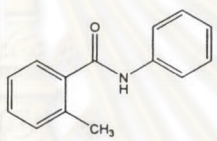
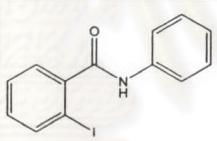
The reports of the synthesis of these compounds[68,69] were successfully performed by the reaction of *o*-MeC_6H_4COCl or *o*-IC_6H_4COCl with $PhNH_2$ in benzene at 10 °C to yield **T3** and **T4** in 97% and 90%, respectively. The drawback of this reaction could obviously be seen from the reaction temperature employed at 10 °C which was not easy to handle.

By employing this developed methodology, **T3** could be accomplished in 91%. The IR spectrum (Fig 5) exhibited a strong absorption band at 1645 cm^{-1}, indicating the presence of amide carbonyl. The medium intensity bands at 3119, 1594 and 1439 cm^{-1} were the characteristic peaks of an aromatic ring. The presence of N-H and C-N bonds was inferred from the presence of bands at 3227 and 1326 cm^{-1}. The ^{1}H-NMR spectrum (Fig 6) displayed a multiplet signal of nine aromatic protons at δ_H 7.18-7.67 and a singlet methyl proton substituted on an aromatic ring at δ_H 2.55.

This developed methodology could also accomplishly be successful to prepare **T4** in 88 %. The IR spectrum (Fig 7) displayed a strong absorption band at 1660 cm^{-1}, indicating the presence of amide carbonyl. The medium intensity bands at 3032, 1598 and 1439 cm^{-1} were the characteristic peaks of an aromatic ring. The presence of N-H and C-N bonds was inferred from the lucid bands at 3307 and 1322 cm^{-1}. The ^{1}H-NMR spectrum (Fig 8) showed a multiplet signal at 7.20-7.97 ppm with nine protons integration of indicating the presence of two aromatic rings.

To summarize, four bioactive amides were fruitfully prepared from this developed methodology with excellent yield as presented in Table 3.7. In addition, the information upon the preparation of those target molecules previously cited was included in this table.

Table 3.7 The summarization of selected synthesized biological active amides

entry	starting carboxylic acid	starting amine	amide product	%yield	lit.
1	benzoic acid	diethylamine		99	using thionyl chloride[67]
2	*m*-methyl benzoic acid	diethylamine		99	using thionyl chloride (94%)[67]
3	*o*-methyl benzoic acid	aniline		91	*o*-MeC_6H_4COCl and $PhNH_2$ (97%)[68]
4	*o*-iodo benzoic acid	aniline		88	*o*-IC_6H_4COCl and $PhNH_2$ (90%)[69]

Even though all target molecules could be prepared in excellent yield by cited methods, the experimental conditions required were not very appreciated in practical sense. For instance, $SOCl_2$ or acid chloride which made the reaction conditions become acidic and high temperature were unavoidably utilized. By the consequence, by-products such as SO_2 and HCl are harmfully corrosive gases derived directly from the reaction. Moreover, in some cases low temperature such as 10 °C or lower may mandatorily required. The present developed conditions were carried out under mild conditions, for example, the reaction temperature in step I at refluxing dichloromethane (38-40 °C) and step II at room temperature were easy to manage. The reaction conditions were in addition acid free.

To comprehend the scope of this developed system, a variety of amines including aliphatic and aromatic amines was selected to react with a model substrate, benzoic acid. The outcomes are tabulated in Table 3.8.

Table 3.8 Effect of amines on the synthesis of amides using this developed reaction

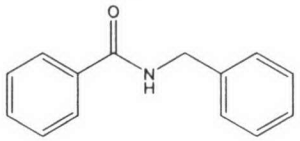
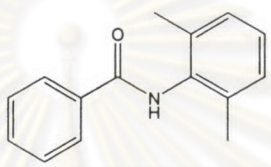
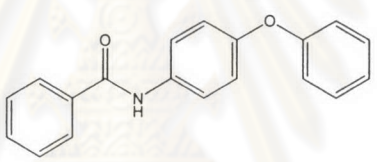
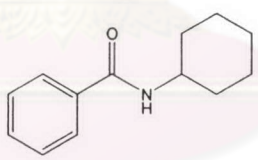
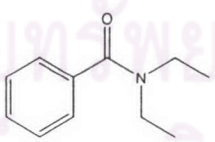
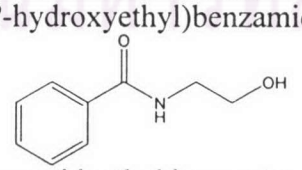
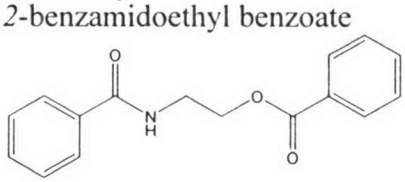
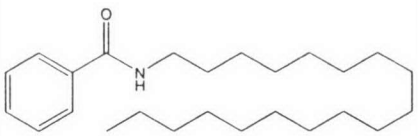
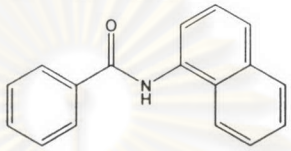
entry	starting amine	amide product	%yield	IR (C=O) (cm^{-1})
1	benzylamine	*N*-benzylbenzamide 	93	1641
2	*2,6*-dimethyl aniline	*N*-(*2,6*-dimethylphenyl) benzamide 	97	1642
3	*4*-phenoxyaniline	*N*-(*4*-phenoxyphenyl) benzamide 	84	1645
4	cyclohexylamine	*N*-cyclohexylbenzamide 	99	1629
5	diethylamine	*N,N*-diethylbenzamide **(T1)** 	99	1629
6	ethanolamine	*N*-(*2*-hydroxyethyl)benzamide  *2*-benzamidoethyl benzoate 	11 51	1637 1706, 1644

Table 3.8 (continued)

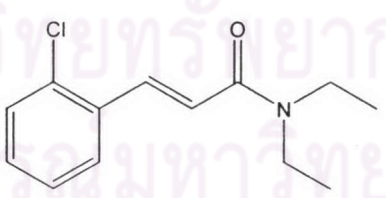
entry	starting amine	amide product	%yield	IR (C=O) (cm^{-1})
7	octadecylamine	*N*-octadecylbenzamide 	63	1634
8	α-naphthylamine	*N*-(*1*-naphthyl)benzamide 	62	1649

From the studies on the effect of amines, *N*-(*2,6*-dimethylphenyl)benzamide, *N*-(*4*-phenoxyphenyl)benzamide, *N*-octadecylbenzamide and *N*-(*1*-naphthyl)-benzamide (entries 2, 3, 7 and 8) could still be achieved in moderate to high yield, eventhough the structures of these amines were relatively steric. In the case of *N*-(*2*-hydroxyethyl)benzamide (entry 6), the amide product was detected in low yield. The main product was the one derived from the reaction of acid chloride produced with ambident nucleophiles. This major product was fully characterized by IR and ^{1}H-NMR spectra. To illustrate this, the IR spectrum (Fig 63) exhibited a strong absorption band at 1706 and 1644 cm^{-1}, indicating the presence of ester and amide carbonyl moiety. The medium intensity bands at 3017, 1537 and 1490 cm^{-1} were the characteristic peaks of an aromatic ring. The presence of N-H, C-N and C-O bonds was inferred from the observation of bands at 3334, 1388 and 1270 cm^{-1}. The ^{1}H-NMR spectrum (Fig 64) contained a singlet signal at δ_H 7.00 of N-H proton. The signals around δ_H 7.42-8.07 were belonged to ten aromatic protons of two benzene rings. Two triplet signals at δ_H 3.87 (J = 5.44 Hz) and 4.56 (J = 5.44 Hz) of aliphatic protons were ascribed to four protons of ethyl groups. In order to obtain only *N*-(*2*-hydroxyethyl)benzamide, protected oxygen functional group such as acetate or benzoate derivatives may be required.[50] Considering the extent of this reaction, this developed methodology has advantage to unlimited selected amines. Both aliphatic and aromatic amines could be employed for the synthesis of amides. The yield of the target molecules was generally moderate to excellent yield regardless of type of amine

used. For example, the aromatic compounds: benzylamine, *2,6*-dimethylaniline, *4*-phenoxyaniline and α-naphthylamine (entries 1, 2, 3 and 8) provided the desired products in excellent yield. Aliphatic amines such as cyclohexylamine and diethylamine (entries 4 and 5) gave the target molecules in superb yield. Octadecylamine (entry 7), a longer aliphatic amine yielded the amide product in moderate yield. It should be noted, nonetheless, at this point that with long chain aliphatic amines, the yield of the desired product got lesser, perhaps because of steric hindrance. Entries 4, 5 and 7 could be an instance. The moderate yield of the ultimate product may be enhanced if the reaction conditions may a bit alter as will examplify later. In addition, according to the literature reviews, *N*-(*4*-phenoxyphenyl)benzamide (entry 3) has not been reported. Thus, this compound is the new compound derived from the synthesis.

Cinnamamides, other biologically active compounds have always been wide-spread in nature.[70,71] Many attempts have been addressed to synthesize this class of compounds. For instance, the synthesis of pipernonaline isolated from *P. longum* L.[70], piperine and piperiline as constituents of *P. nigrum* L.[71] has been reported. Some cinnamamide target molecules were selected to evaluate the scope of this developed protocol.

***2*-Chloro-*N,N*-diethylcinnamamide (T5),** displayed the herbicidal activity[72] by a phytotoxic activity against variety of plants, including *Amaranthus retroflexus*, *Artemisia vulguris*, *Chenopodium album* and *Vicia sativa* through either foliar and root adsorption. The preparation of this compound was however not recorded.

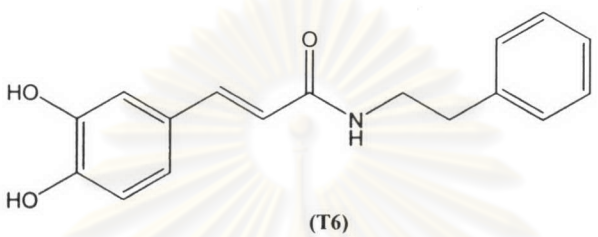


(T5)

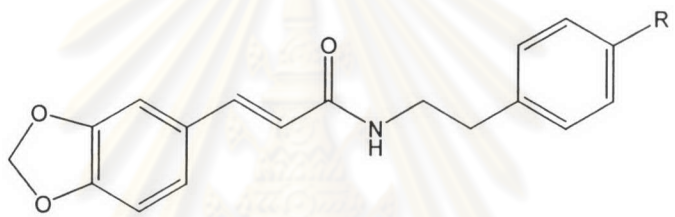
By employing this developed methodology, **T5** could be achieved in 79%. The IR spectrum (Fig 9) showed an amide carbonyl and α,β-unsaturated absorption bands at 1643 and 1601 cm^{-1}, respectively. The presence of Ar-Cl and C-N bonds were inferred from the presence of bands at 1046 and 1367 cm^{-1}. The absorption bands at 1564 and 1465 cm^{-1} were indicative of the presence of aromatic ring. The ^{1}H-NMR spectrum (Fig 10) showed a pair of doublet at δ_H 6.84 (J = 15.24 Hz) and δ_H 8.04 (J =

15.24 Hz) of two *trans*-olefinic protons.[83] A multiplet signal at δ_H 7.30-7.61 was due to four aromatic protons. Broad singlet (δ_H 1.26) and quartet (δ_H 3.55) of aliphatic protons were ascribed to ten protons of two ethyl groups.

***N-trans*-Caffeoyl-*β*-phenethylamine (T6)** is a potential natural antioxidant with multiple mechanisms involving free radical scavenging, metal ion chelation and inhibitory actions on specific enzymes that induce free radical and lipid hydroperoxide formation.[46]



(T6)



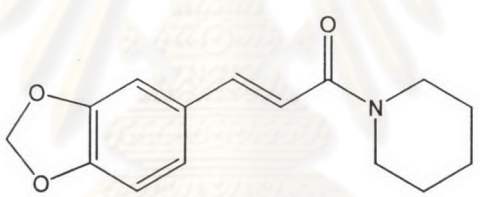
T6-1; R = H
armatamide; R = OCH_3

The preparation of **T6** was documented from caffeic acid and phenethylamine using benzotriazol-1-yloxy-*tris*(dimethylamino)phosphoniumhexafluorophosphate (BOP) as a coupling reagent to yield **T6** in 76%.[46] The synthesis of **T6-1** was achieved[60] from piperonal and phenethylamine by heating under reflux in toluene for 24 hours to yield **T6-1** in 45%.

Utilizing this developed methodology, the preparation of **T6** was planed to synthesize *via* *N*-(*3,4*-methylenedioxycinnamoyl)phenethylamide **T6-1** followed by the deprotection using boron trichloride.[73] **T6-1** could be successfully achieved in 79%. The IR spectrum (Fig 11) exhibited a strong absorption band at 1645 cm^{-1} indicating the presence of amide carbonyl. The absorption bands at 1495, 1321 and 1250 cm^{-1} were suggested for the presence of olefinic, C-N bonds and methylenedioxy group, respectively. The absorption bands at 3073, 1547 and 1439 cm^{-1} were typical characteristic of aromatic ring. The presence of an alkyl group was inferred from the detection of the band at 2904 cm^{-1}. The ^{1}H-NMR spectrum (Fig 12) displayed a triplet signal at δ_H 2.92 (J = 7.04 Hz) and a quartet at δ_H 3.69 (J = 7.04

Hz), indicating the presence of an alkyl group. The signals around δ_H 6.82-7.37 were assigned for eight aromatic protons. A pair of doublet at δ_H 6.17 (J = 15.24 Hz) and 7.57 (J = 15.24 Hz) was typical of *trans*-olefinic group.[83] The signal at δ_H 6.02 was ascribed for two protons of a methylenedioxy group. The broad singlet at δ_H 5.60 was assigned to one proton of N-H. In addition, according to the literature search, it was found that armatamide[74], isolated from the bark of *Zanthoxylum armatum*, was extensively used in the Indian system of medicines as a carminative, stomachic and anthelmintic. This compound was analogous with **T6-1** where a methoxy group was beared on a benzene ring at *para* position of phenethylamine. This present developed methodology can certainly be employed to synthesize armatamide with ease if *4*-methoxyphenethylamine is readily available.

***N*-(*3,4*-methylenedioxycinnamoyl)piperidide (T7)** was found for the first time from the wood of *Piper navae-hallandiae*.[75] This compound was employed as a synergist for pyrethrum.[76] Morover, it possessed an antiepilepsirnium activity.[60]



(T7)

Previously, the preparation of this compound[60] was addressed by heating piperonal and piperidine under reflux in THF for 36 hours to yield **T7** in 94%.

According to this developed protocol, **T7** could be fruitfully achieved in 79%. The IR spectrum (Fig 13) exhibited a strong absorption band at 1645 cm^{-1}, pointing out the presence of amide carbonyl. Other absorption bands at 1495, 1352 and 1245 cm^{-1} were indicated for the olefinic, C-N bond and methylenedioxy group, respectively. The absorption bands at 3001, 1593 and 1439 cm^{-1} were characteristic of aromatic ring. The presence of alkyl group was inferred from the observation of the absorption bands at 2934 and 2858 cm^{-1}. The ^{1}H-NMR spectrum (Fig 14) displayed two broad singlet signals at δ_H 1.63 and 3.68 belonging to the signal of a piperidine ring. The signals around δ_H 6.82-7.07 with three protons integration were assigned to three aromatic protons. In addition, a pair of *trans*-coupled doublet at δ_H 6.76 (J =

15.60 Hz) and 7.59 (J = 15.60 Hz) was manifestly detected.[83] The signal at δ_H 6.02 could be ascribed for two protons of a methylenedioxy group.

It was observed that moderate yield of this desired product, **T7** was achieved under standard conditions. With the aim to improve the yield of this target molecule, a series of experiments was carefully explored and the results are tabulated in Table 3.9.

Table 3.9 Comparative study for the synthesis of **T7**

entry	step I		step II		%yield
	Cl_3CCONH_2 (eq)	PPh_3 (eq)	piperidine (eq)	time (hour)	
1	2	2	1	1.5	79
2	2	2	1	3	84
3	3	3	1	1.5	99
4	2	2	2	1.5	66

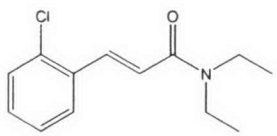
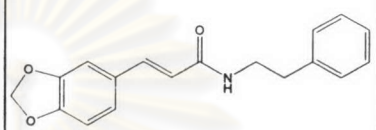
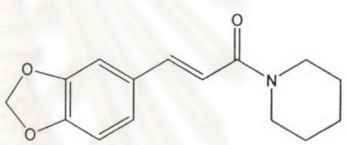
reaction conditions: *3,4*-methylenedioxycinnamic acid (1 eq), CH_2Cl_2 (6 mL), step I at reflux for 1 hour, step II at room temperature.

It was clearly found that cinnamic acid could be transformed to the desired amide in higher yield if the reaction conditions were a bit altered. This could be seen from the outcome of the experiment. Factors that controlled the yield of the desired product included the reaction time in step II (entry 2), and the amount of the halogenated reagents and PPh_3 (entry 3). Nevertheless, the amount of amine seemed not to reveal a significant effect on the yield of target molecule (entry 4). The first two parameters implied that the formation of acid chloride in this particular case was greatly depended upon the ratio of coupled reagents (Cl_3CCONH_2 and PPh_3) and the need of longer period for the reaction between the intermediate generated and amine should be seriously considered. The yield of **T7** could therefore increase from 79% in entry 1 to 84 and 99% under modified reaction conditions (entries 2 and 3).

According to the aforementioned results, it could be concluded that the ratio of halogenated reagent and PPh_3 had a profound effect on the efficiency of the reaction. This parameter should therefore be considered as one of crucial factors to be justified.

The synthesis of biological cinnamamides in this research was summarized as presented in Table 3.10.

Table 3.10 Summarization of selected synthesized biological cinnamamides

entry	starting carboxylic acid	starting amine	amide product	%yield	lit.
1	*2*-chloro cinnamic acid	diethylamine		79	-
2	*3,4*-methylene dioxycinnamic acid	phenethyl amine		79	piperonal and phenethyl-amine (45%)[60]
3	*3,4*-methylene dioxycinnamic acid	piperidine		99*	piperonal and piperidine (94%)[60]

* under modified reaction conditions

With the same synthetic concept to observe the scope of these reactions, various types of carboxylic acids were utilized as a chemical probe. The results are presented in Table 3.11.

Table 3.11 Effect of carboxylic acids on the synthesis of amides using the developed methodology

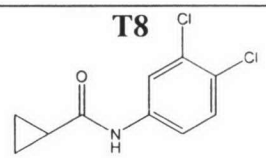
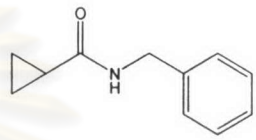
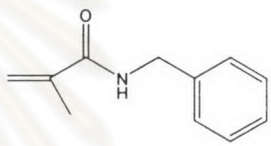
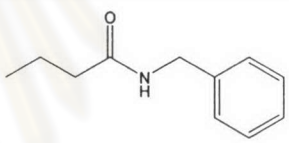
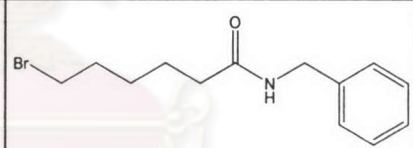
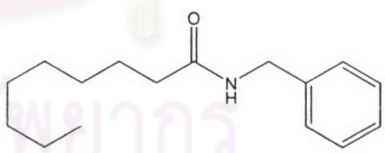
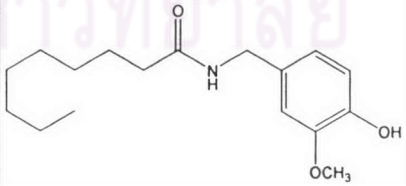
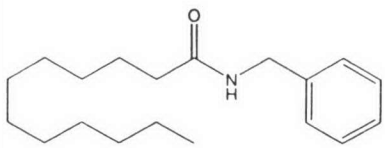
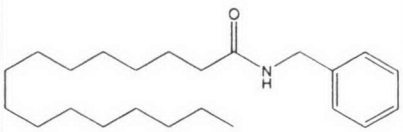
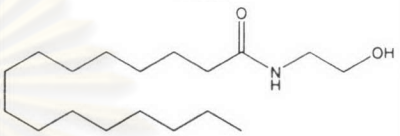
entry	starting carboxylic acid	starting amine	amide product	%yield
1	cyclopropane carboxylic acid	*3,4*-dichloro aniline	**T8** 	80
2	cyclopropane carboxylic acid	benzylamine		97
3	methacrylic acid	benzylamine		15
4	butyric acid (C_4)	benzylamine		94
5	*6*-bromo-caproic acid (C6-Br)	benzylamine		67
6	nonanoic acid (C_9)	benzylamine		89
7	nonanoic acid (C_9)	vanillylamine	**T9** 	28
8	lauric acid (C_{12})	benzylamine		83

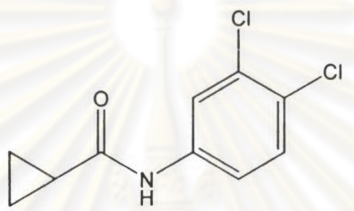
Table 3.11 (continued)

entry	starting carboxylic acid	starting amine	amide product	%yield
9	palmitic acid (C_{16})	benzylamine		44
10	palmitic acid (C_{16})	ethanolamine	**T10** 	31

The amides displayed in entries 1, 7 and 10 are biological amide target molecules. Those compounds displayed herbicidal activity[61], mutagenicity[53,77] and anti-inflammatory activity.[62] It was observed that the desired amides manipulated using short chain aliphatic carboxylic acids could be achieved in higher yield than those stemmed from long chain aliphatic carboxylic acids. For example, *N*-benzylcyclopropanecarboxamide, *N*-benzylbutanamide, *N*-benzyl-*6*-bromohexanamide, *N*-benzylnonanamide and *N*-benzyldodecanamide (entries 2, 4, 5, 6 and 8) could be gained in high yield whereas *N*-benzylhexadecanamide (entry 9) was received in relatively low yield along with large amount of acid starting material recovered. Although this reaction was not suitable with long chain aliphatic carboxylic acid, the desired product as *N*-benzyldodecanamide was still achieved in high yield. In the case of long chain carboxylic acid; the yield of *N*-benzylhexadecanamide (entry 9) could be improved by using the modified conditions (such as the amount of Cl_3CCONH_2 and PPh_3: 3:3 eq). The reaction carried out with cyclopropane carboxylic acid and benzylamine was a discrete reaction and provided a mechanistic clue. To illustrate this, due to the cyclopropane ring was not cleaved; this could confirm that the reaction mechanism was not taken place *via* a radical pathway. In the case of methacrylic acid (entry 3), the desired product was gained in poor yield, perhaps because of the steric effect of methyl group. The comparative study between the synthesis of *N*-benzylnonanamide and capsaicine synthetic (entries 6 and 7) were

conducted. It was observed that *N*-benzylnonanamide was obtained in higher yield than capsaicine synthetic. This was probably due to the fact that a hydroxy group on an aromatic ring of amine may react with acid chloride formed. This was also true for entry 10 that the desired product was gained in poor yield. To improve the yield of the target molecules, it was mandatory to protect a reactive hydroxy group or improve the optimum conditions as mentioned. In addition, it should be noted here that *N*-benzyl-cyclopropanecarboxamide (entry 2) has not been reported in chemical literature.

***3',4'*-Dichlorocyclopropanecarboxanilide or cypromid (T8)** (entry 1) was introduced for commercial use as a selective postemergence herbicide in corn.[61]



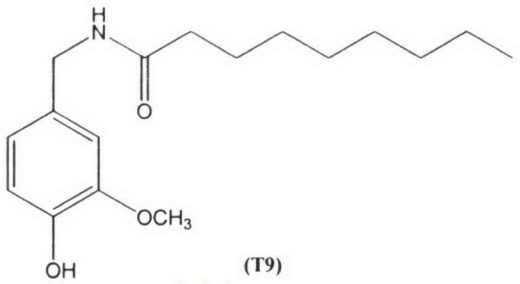
(T8)

The preparation of this compound was described[61] by cleavage of α-substituted butyrolactones with hydrogen chloride to produce γ-chlorobutyric acids which were esterified with methanol, then cyclized with base to the desired esters and then the mixture was added with *3,4*-dichloroaniline to yield **T8** in 90%.

By employing this simple developed methodology, **T8** could be successfully achieved in 80%. The IR spectrum (Fig 15) showed an amide carbonyl absorption band at 1665 cm^{-1}. The presence of N-H, alkyl and C-N bonds were inferred from the occurrence of bands at 3283, 3098 and 1398 cm^{-1}. The presence of aromatic ring was in good agreement from the detection of bands at 1588 and 1470 cm^{-1}. The ^{1}H-NMR spectrum (Fig 16) displayed three aromatic protons at δ_H 7.34-7.77. The broad singlet at δ_H 7.57 was assigned for N-H proton. The signal at δ_H 0.88-1.09 was ascribed to four protons of two methylene groups. The C-H proton of cyclopropane ring showed a multiplet signal at δ_H 1.50.

***N*-Vanillylpelargonamide or capsaicine synthetic (T9)** (entry 7) was an analogous of capsaicin, the principal pungent component in many *Capsaicums* being known to exhibit a variety of biological activities, including recent findings

concerning its mutagenicity.[53,77] *N*-Vanillylpelargonamide was prepared to use as a hyperemia including active, *e.g.* in plasters.[78]

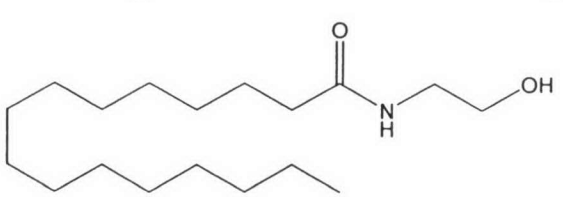


(T9)

Naturally occuring *cis*- and *trans*-capsaicins could be prepared from (*E*) or (*Z*)-acids by treating with $SOCl_2$ under reflux for 8 hours, after that the mixture was added with vanillylamine and continued stirring for another 2 hours and then refluxed for 2 hours to yield the target compounds in 53% and 66%, respectively.[53]

With the use of this developed methodology, **T9** was obtained only in 28%. The IR spectrum (Fig 17) showed an amide carbonyl absorption band at 1651 cm^{-1}. The broad band around 3158-3009 cm^{-1} was the characteristic peak of a hydroxy group. The presence of N-H, C-N bonds and alkyl group were inferred from the detection of the bands at 3311, 1377 and 2919 cm^{-1}. Two bands at 1278 and 1156 cm^{-1} were assigned to C-O bonds. The ^{1}H-NMR spectrum (Fig 18) displayed a broad singlet signal which was indicative of N-H proton at δ_H 5.70. The signals around δ_H 6.84-6.96 were typical of three aromatic protons, as well as methyl, methoxy and alkyl protons occurring around δ_H 0.88, 3.81 and 1.29-4.41, respectively. **T9** in fact was achieved in comparatively low yield. This was perhaps vanillylamine contained a hydroxy group which could concurrently compete the derived reaction to take place. Therefore, to avoid undesirable reaction a hydroxy group must be protected or the modified conditions were needed to be considered.

***N*-Palmitoylethanolamine or PEA (T10)** (entry 10) was reported to isolate from a phospholipid fraction of egg yolk and hexane extract of peanut meal. This compound was known to be responsible for its anti-inflammatory activity.[62]

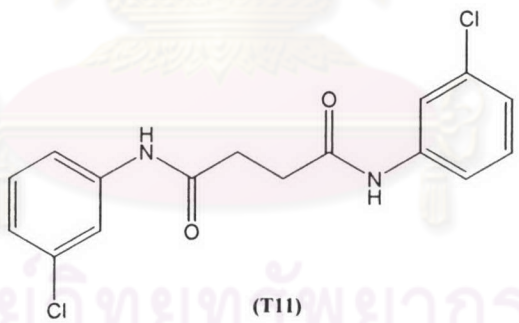


(T10)

The preparation of this compound was described[79,80] from palmitic acid and ethanolamine by heating these two compounds under reflux in THF for 2-6 hours. The yield of the desired product was nevertheless not mentioned.

By employing this developed methodology, **T10** could be achieved in 31%. The IR spectrum (Fig 19) showed an amide carbonyl absorption band at 1644 cm^{-1}. The broad band around 3631-3365 cm^{-1} was the characteristic of a hydroxy group. The presence of N-H, C-N bonds and alkyl group were inferred from the presence of bands at 3291, 1372 and 2909 cm^{-1}. The ^{1}H-NMR spectrum (Fig 20) contained two singlet signals at δ_H 7.78 and 2.55, which were indicative of N-H and O-H protons, respectively. The signals around δ_H 0.86-4.67 were belonged to thirty four aliphatic protons in an aliphatic chain. This developed reaction provided **T10** in low yield, due to the presence of a hydroxy group of ethanolamine and may be influenced from a long chain carboxylic acid as palmitic acid. It was also found that most starting material was still remained.

***N,N'-bis*(*3*-Chlorophenyl)butanediamide (T11)** was recorded for its antimycobacterial and antialgal activity.[47] This compound inhibited growth and chlorophyll production in *Chlorella vulgaris*.



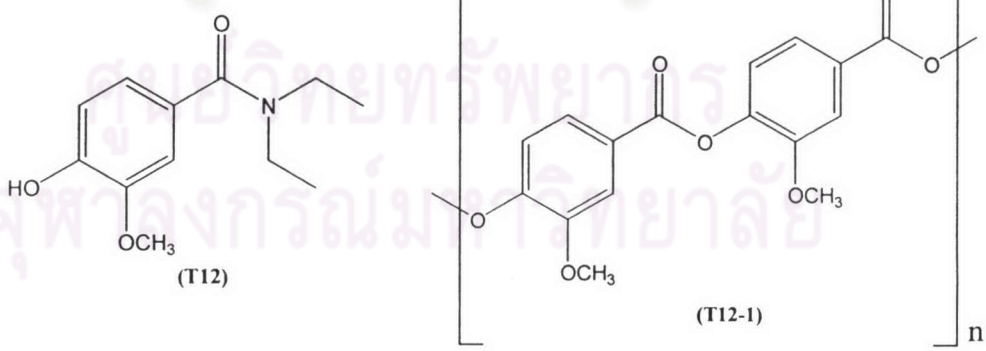
(T11)

The preparation of this compound was addressed by the use of succinic acid and phosphorus pentachloride upon heating at 120 °C for 5 hours, followed by the addition of *3*-chloroaniline in pyridine dropwise at 0 °C for 24 hours and then poured into water to yield **T11** in 92%.[47] The drawback of this reaction however could manifestly be seen from the temperature employed and the long reaction time required.

Employing this developed methodology, **T11** could be achieved in 25%. The IR spectrum (Fig 21) showed an amide carbonyl absorption band at 1668 cm^{-1}. The presence of N-H and C-N bonds were inferred from the occurence of bands at 3288

and 1321 cm^{-1}. The absorption bands at 1589 and 1410 cm^{-1} were indicative of the presence of an aromatic ring. The ^{1}H-NMR spectrum (Fig 22) showed a singlet signal at δ_H 2.68, indicating the presence of an alkyl group. The signals around δ_H 7.09-7.83 were typical of three aromatic protons. The broad singlet signal at δ_H 10.23 could be assigned for N-H proton. In the case of **T11** being achieved in poor yield, it will be helpful to improve the reaction conditions by increasing the amount of the coupled reagents.

***N,N*-Diethylvanillic acid amide (T12)** The abovementioned target molecule **(T12)** was planned to synthesize employing vanillic acid and *N,N*-diethylamine as a staring material. Under the usual conditions employed, a white crystalline solid 0.147 g, m.p. >350 °C was achieved. This compound was surprisingly not soluble in any common organic solvents. The IR spectrum (Fig 3.3) revealed a strong absorption peak at 1736 cm^{-1}, possibly the C=O stretching vibration of ester instead of a normal C=O absorption band of amide detected in other previously mentioned products. The medium intensity bands at 1605, 1414 cm^{-1} were the characteristic peaks of an aromatic ring. The presence of alkyl and C-O bond was inferred from the presence of bands at 2930 and 1291 cm^{-1}. From the spectroscopic data, it implied that the OH group present in the staring material must involve in this intramolecular nucleophilic subsitution as an internal nucleophile. The structure for the obtained product was therefore proposed as **T12-1**.



(T12) (T12-1)

To avoid an intramolecular reaction occurred as in the case of using vanillic acid, veratric acid was used instead. The expected product was *N,N*-diethylveratric acid amide. Unfortunately, this reaction could not provide the expected product at all; veratric acid was almost recovered. To confirm this observation, *3,4,5*-trimethoxy-

benzoic acid was employed as a starting material, the corresponding amide was still not possible to be achieved. This observation was therefore suggested that the electronic effect of substituents on the benzene ring plays a key role on the reactivity of the reaction.

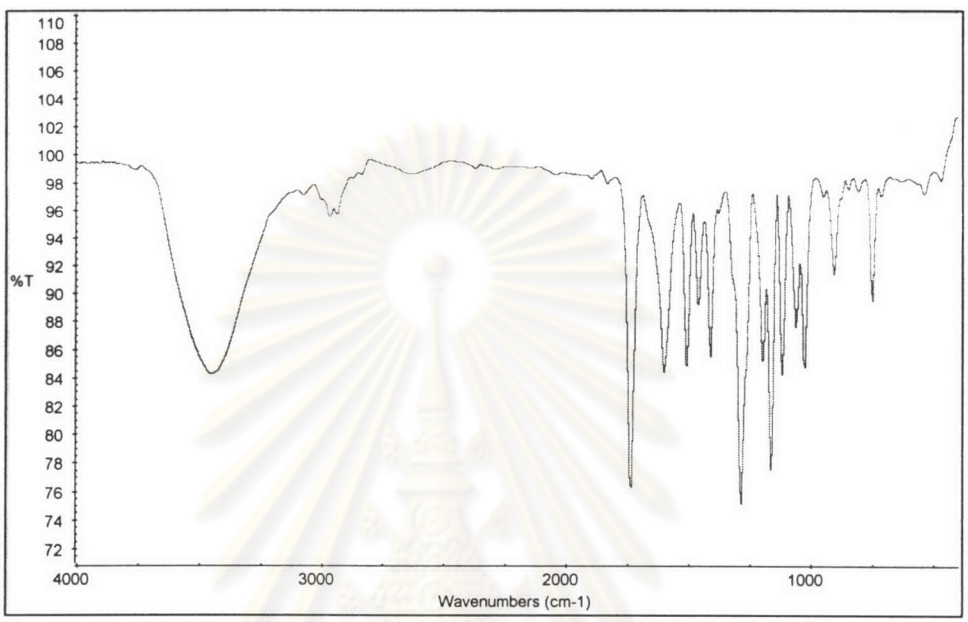


Figure 3.3 The IR spectrum of **T12-1**

To explore whether the substituent on an acid moiety had an effect on this reaction, two benzoic acids with different substituents at *para* position, *i.e.* an electron withdrawing group ($-NO_2$) and an electron donating group ($-OCH_3$) were used as a starting material and the reaction was performed in the usual manner. *4*-Nitro-*N*-cyclohexylbenzamide and *4*-methoxy-*N*-cyclohexylbenzamide were eventually achieved in good yield as presented in Table 3.12.

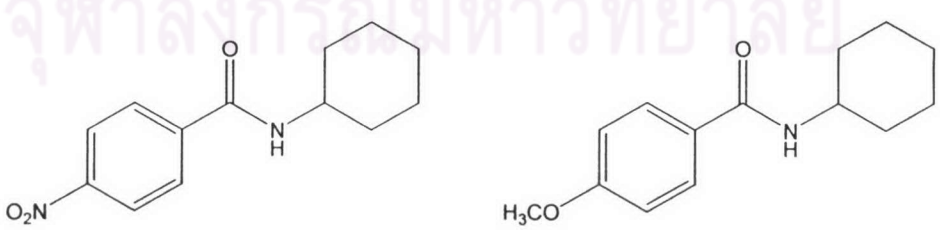


Table 3.12 Effects of substitutents on a benzoic acid ring on the yield of amide obtained

substituted group	%yield
4-H	90
4-NO_2	93
4-OCH_3	91

reaction conditions: carboxylic acid (3 mmol), Cl_3CCONH_2 (6 mmol) PPh_3 (6 mmol), CH_2Cl_2 (6 mL), cyclohexylamine (3 mmol) *4*-picoline (9 mmol), step I reflux (38-40 °C), step II room temperature (28-30 °C).

reaction time: step I 1 hour, step II 20 minutes.

From the study on the electronic effect, it was therefore found that the substitutents at *para* position of benzoic acid had no effect on the reaction. Thus, the substituent at *meta* position may influence on the reactivity. This result still reinforced that this methodology could be applied for various substitutents on benzoic acid except for those present at *meta* position, perhaps directly due to a withdrawing ability by an inductive effect.

The IR spectrum of *4*-nitro-*N*-cyclohexylbenzamide and *4*-methoxy-*N*-cyclohexylbenzamide exhibited a strong absorption bands at 1629 and 1624 cm^{-1}, indicating the presence of amide carbonyl. The presence of N-H, alkyl and C-N bonds were inferred from the occurence of bands at 3308, 2924, 1342 and 3298, 2934, 1332 cm^{-1}. Two bands at 1536 and 1326 cm^{-1} were assigned for a nitro group of N=O bond. The band at 1255 cm^{-1} was characteristic of a methoxy group of *4*-methoxy-*N*-cyclohexylbenzamide. The presence of an aromatic ring was ascertained from the presence of bands at 1593, 1449 and 1541, 1445 cm^{-1}. The ^{1}H-NMR spectrum of *4*-nitro-*N*-cyclohexylbenzamide displayed four aromatic protons at δ_H 8.30 (J = 8.78 Hz) and at δ_H 7.34 (J = 8.78 Hz). The broad singlet at δ_H 6.07 was assigned to one proton of N-H and a multiplet signal at δ_H 3.97-4.06 of NH-C*H* proton. The multiplet signal at δ_H 1.25-2.09 could be assigned to ten protons of the alkyl groups. The ^{1}H-NMR spectrum of *4*-methoxy-*N*-cyclohexylbenzamide exhibited four aromatic protons at δ_H 6.94 (J = 8.78 Hz) and at δ_H 7.74 (J = 8.78 Hz). The broad singlet at δ_H 5.91 was belonged to one proton of N-H proton and a NH-C*H* proton could be

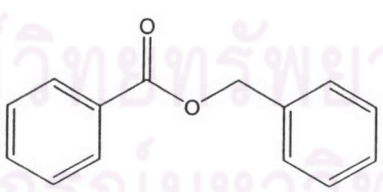
detected at δ_H 3.95-4.00 as a multiplet (1H). The multiplet at δ_H 1.64-2.07 of ten protons of the alkyl groups and the siglet at δ_H 3.87 of methoxy protons were clearly observed.

3.4.2 Biologically Active Esters

The synthetic biologically active esters are well-known as an ingredient in cosmetic, nutraceutical and pharmaceutical formulations.[3] Esters are generally formed by the reaction of a carboxylic acid with an alcohol in the presence of mineral acid such as sulfuric acid or dry hydrochloric acid. The disadvantage of this reaction is a reversible process and it proceeds very slowly. Other cited methodologies for the preparation of esters could be found in the literature. For example, inducing condensation of acid chloride with alcohol by the use of zinc as catalyst or by the action of acid chloride with sodium salt of the acid. Moreover, esters could be obtained by the Claisen method from benzaldehyde not sufficiently free from chlorine-substituted aldehydes.[82]

In this research, esters were synthesized *via* acid chloride by using the similar methodology to that for the preparation of amides, but the temperature used in step II was changed from room temperature to refluxing temperature of dichloromethane.

Benzyl benzoate (T13) was isolated from rhizomes of *Kaempferia rotunda*. This compound exhibited insecticidal activity towards neonate larvae of *S. littoralis* only when applied topically *via* the larval integument.[81]



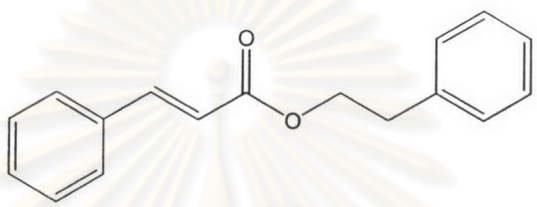
(T13)

The preparation of this compound was described from benzaldehyde and a small of sodium benzylate by stirring these compounds at room temperature for 1 hour and then warmed on the water bath for about 2 hours to yield **T13** in 90%.[82]

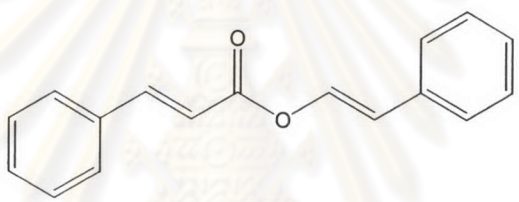
By employing this facile developed methodology, **T13** could be achieved in 85%. The IR spectrum (Fig 23) clearly showed an ester carbonyl absorption band at 1719 cm^{-1}. The medium intensity bands at 3063, 1598 and 1493 cm^{-1} were the

characteristic peaks of an aromatic ring. The presence of C-O bond was inferred from the detection of band at 1372 cm^{-1}. The ^{1}H-NMR spectrum (Fig 24) showed a multiplet at δ_H 7.35-8.12 with 10H intensity, indicating the presence of two aromatic rings. The singlet at δ_H 5.40 was assigned for two methylene protons.

Phenethyl cinnamate (T14) and cinnamoyl cinnamate (T15) were well-known ingredient of perfume. It has been reported that phenethyl cinnamate constitutes as one of the main odoriferous components, and used for cosmetic products. **T15** was performed in full compliance with food, drug and cosmetic act.



(T14)



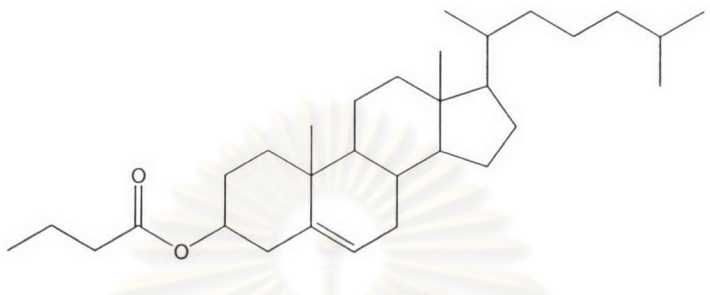
(T15)

T14 could be fruitfully achieved in 98%. The IR spectrum (Fig 25) showed an ester carbonyl absorption band at 1716 cm^{-1}. The medium intensity bands at 3057, 1634 and 1450 cm^{-1} were the characteristic peaks of an aromatic ring. The presence of C-O bond and α,β-unsaturated bond was inferred from the observation of bands at 1311 and 1501 cm^{-1}. The ^{1}H-NMR spectrum (Fig 26) showed a pair of doublet at δ_H 6.47 (J = 15.83 Hz) and δ_H 7.72 (J = 15.83 Hz) of two *trans*-olefinic protons. A multiplet signal at δ_H 7.29-7.57 was due to ten aromatic protons. A triplet signal at δ_H 3.07 (J = 7.04 Hz) and 4.46 (J = 7.04 Hz) of aliphatic protons were ascribed to four protons of ethyl groups.

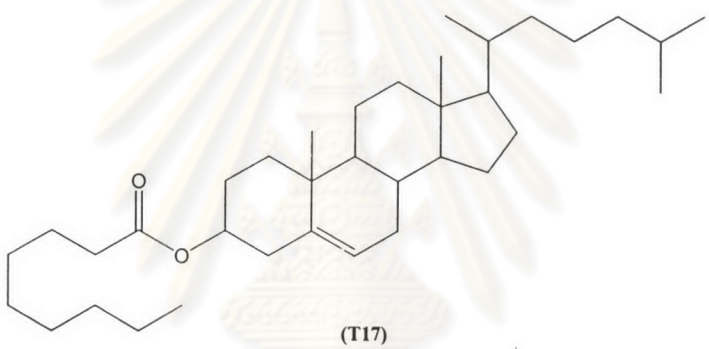
According to this developed methodology, **T15** could be achieved in 84 %. The IR spectrum (Fig 27) showed an ester carbonyl absorption band at 1710 cm^{-1}. The medium intensity bands at 3063, 1629 and 1450 cm^{-1} were the characteristic peaks of an aromatic ring. The presence of C-O bond and α,β-unsaturated bond was inferred from the presence of bands at 1301 and 1495 cm^{-1}. The ^{1}H-NMR spectrum (Fig 28) showed a pair of doublet at δ_H 6.42 (J = 15.83 Hz), 6.53 (J = 16.02 Hz), δ_H 6.75 (J =

15.83 Hz) and δ_H 7.78 (J = 16.02 Hz) of four *trans*-olefinic protons. A multiplet signal at δ_H 7.29-7.59 was due to ten aromatic protons.

Cholesteryl butyrate (T16) and cholesteryl nonanoate (T17), cholesteryl esters are widely used for technical applications such as liquid crystal display devices, ingredient of cosmetics, nutraceuticals and pharmaceutical formulations.[49,63]



(T16)



(T17)

The synthesis of **T16** was previously described by employing the enzymatic preparation of carboxylic acid esters, particularly fatty acid esters, of cholesterol in high yield by transesterification of acid, with cholesterol *in vacuo* at moderate temperature using immobilized lipase from *Candida rugosa* as the catalyst.[69] The synthesis of **T17** has not been reported.

Utilizing this developed methodology, **T16** and **T17** could be obtained in 78% and 79%. The IR spectrum (Figs 29 and 32) of **T16** and **T17** showed ester carbonyl absorption bands at 1734 and 1737 cm^{-1}. The presence of alkyl group, alkene and C-O bond were inferred from the notification of bands at 2939, 1475, 1189 and 2930, 1460, 1168 cm^{-1}. The ^{1}H-NMR spectrum (Fig 30) of **T16** showed a doublet at δ_H 5.41 of one olefinic proton. A multiplet signal at δ_H 4.65 was due to a proton on a carbon connecting with an ester group. A multiplet at δ_H 0.71-2.34 was ascribed to protons of cholesterol and propyl group. The ^{13}C-NMR spectrum (Fig 31) displayed twenty seven peaks at δ_C 11.9-73.7, indicated alkyl group of cholesteryl and propyl

group. The two signals of olefinic carbons was observed at δ_C 122.6 and 139.7. The peak at δ_C 173.2 appropriated for a carbonyl carbon was observed. The ^{1}H-NMR spectrum (Fig 33) of **T17** showed a doublet at δ_H 5.40 of one olefinic proton. A multiplet signal at δ_H 4.65 was due to a proton of carbon connecting with an ester group. A multiplet at δ_H 0.71-2.33 was assigned to protons of cholesterol and octyl group. The ^{13}C-NMR spectrum (Fig 34) displayed thirty one peaks at δ_C 11.9-73.7, indicating the presence of alkyl group of cholesteryl and octyl group. The two signals of olefinic carbons at δ_C 122.6 and 139.7 were detected. The peak at δ_C 173.3, coincided to a carbonyl carbon was manifestly revealed. **T17** has not been reported in literature; thus this compound is a new synthetic compound.

The synthesis of biologically active esters in this research could be summarized as demonstrated in Table 3.13.

Table 3.13 The summarization of selected synthesized biological active esters

target molecule	biological activity	%yield	lit.
benzyl benzoate **(T13)***	insecticide	85	benzaldehyde and sodium benzylate (90%)[82]
phenethyl cinnamate **(T14)***	perfume and cosmetic	98	-
cinnamoyl cinnamate **(T15)***	cosmetic and drug	84	-
cholesteryl butyrate **(T16)****	cosmetic and pharmaceutical formulation	78	using immobilized lipase from *Candida rugosa*[69]
cholesteryl nonanoate **(T17)****	cosmetic and pharmaceutical formulation	79	-

reaction conditions: carboxylic acid (3 mmol), Cl_3CCONH_2 (6 mmol) PPh_3 (6 mmol), CH_2Cl_2 (6 mL), amine (3 mmol) *4*-picoline (9 mmol), reflux (38-40 °C).

reaction time: step I 1 hour, step II 1 hour*

step I 1 hour, step II 3 hours**