CHAPTER III
RESULTS AND DISCUSSION

In this research, optimum conditions for the preparation of acid chloride from carboxylic acid reacting with chlorinated reagent (Cl_3CCN) and PPh_3 were examined. The acid chloride formed was simultaneously converted to amide for characterization by treating with an interested amine in the presence of Et_3N. The equation of both conversions was depicted below.

$$RCO_2H + Cl_3CCN + PPh_3 \xrightarrow[\text{Step I}]{} \xrightarrow[\text{Step II}]{R'NH_2,\ Et_3N} RCONHR'$$

Study on Condition Optimization

Various factors were needed to be cautiously evaluated to optimize the conditions for acid chloride preparation. Benzoic acid was the first chosen substrate as a chemical model. Benzoic acid was believed to transform to benzoyl chloride and then was converted to a known amide, benzanilide, when the reaction was allowed to react with aniline. The purpose to transform acid chloride to amide was primarily due to the unstability of acid chloride and also for the ease of characterization. Variable parameters studied are the ratio of Cl_3CCN and PPh_3, reaction time, temperature, solvent system and chlorinated reagent.

1. Influence of Ratio of Cl_3CCN and PPh_3

The ratios of Cl_3CCN (TCA) and PPh_3 (TPP) were varied to find out the suitable ratio to provide the maximum yield of benzanilide. The results of this variation are presented in Table 3.1.

Table 3.1 Effect of Cl_3CCN and PPh_3 ratio on % yield of benzanilide.*

Entry	Equivalent (eq)			% Yield of benzanilide
	Benzoic acid	Cl_3CCN	PPh_3	
1	1	1	1	51
2	1	1	2	76
3	1	1	3	46
4	1	1	4	38
5	1	1	5	33
6	1	2	0	0
7	1	2	1	51
8	1	2	2	75
9	1	2	3	50
10	1	2	4	43
11	1	2	5	37
12	1	3	1	51
13	1	4	1	48
14	1	5	1	50
15	1	0	2	trace
16	1	3	2	74
17	1	4	2	72
18	1	5	2	73

* reaction conditions : Benzoic acid (3 mmol), CH_2Cl_2 (6 mL), aniline (3 mmol), Et_3N (9 mmol), room temperature (28-30 °C), reaction time : step I (1 h), step II (20 min).

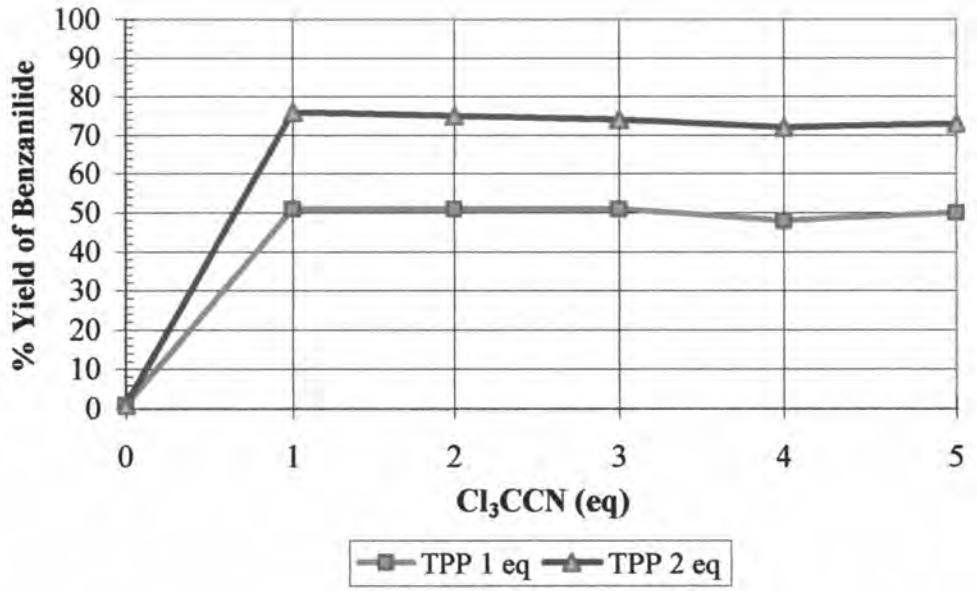


Figure 3.1 % yield of benzanilide with various ratios of Cl_3CCN

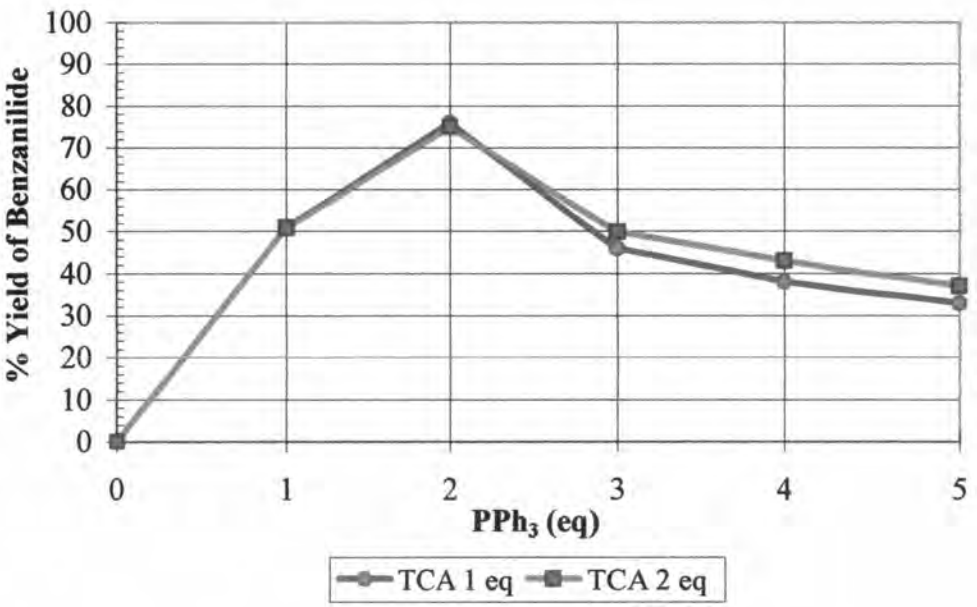


Figure 3.2 % yield of benzanilide with various ratios of PPh_3

When the reaction was carried out without Cl_3CCN, benzanilide was obtained only trace amount (see Table 3.1, entry 15). Furthermore, the reaction in the absence of PPh_3 did not provide a desirable product (entry 6). Therefore, it can conclude that PPh_3 and Cl_3CCN are very essential reagents for this reaction.

Effect of Cl_3CCN Ratio

At the beginning of study, the amount of PPh_3 was fixed at one equivalent (entries 1, 7 and 12-14) and two equivalents (entries 2, 8 and 16-18), while the amount of Cl_3CCN was varied. In the reactions that fixed the amount of PPh_3 at one equivalent (entries 1,7 and 12-14) when one equivalent of Cl_3CCN was utilized (entry 1), benzanilide was obtained in the highest yield. After increasing the amount of Cl_3CCN over one equivalent (entries 7 and 12-14), the yield of the desired product was a little change compared with the former case. Similar to the reactions which fixed the amount of PPh_3 at two equivalents (entries 2, 8 and 16-18), when the one equivalent of Cl_3CCN was used (entry 2), the reaction gave the maximum yield of benzanilide. Increasing the amount of Cl_3CCN over one equivalent (entries 8 and 16-18), the desired product acquired was altered only in a little change. Therefore, the suitable amount of Cl_3CCN was found to be one equivalent.

Effect on PPh_3 Ratio

Like the study on the effect of Cl_3CCN ratio, the amount of Cl_3CCN was first fixed at one (entries 1-5) and two (entries 7-11) equivalents, whereas the amount of PPh_3 was varied. In the reactions that fixed the amount of Cl_3CCN at one equivalent (entries 1-5), the maximum yield of benzanilide was earned when two equivalents of PPh_3 was used (entry 2). Increasing the amount of PPh_3 more than two equivalents (entries 3-5), the amount of the final product was decreased. This may be because the excess of PPh_3 could react with benzoyl chloride and benzanilide, which lead to the formation of unwanted products. The results from the reaction when the amount of Cl_3CCN was fixed at two equivalents (entries 7-11) were similar. The maximum yield was gained when two equivalents of PPh_3 were used (entry 8) and gradually decreased when the amount of PPh_3 was increased over two equivalents (entries 9-11). Thus, the appropriate amount of PPh_3 was disclosed to be two equivalents.

Therefore, the most suitable ratio of carboxylic acid : Cl_3CCN : PPh_3 under this optimization conditions was 1:1:2.

2. Influence of Time and Temperature

Reaction time and temperature in step I of the general procedure were altered in order to find out the relationship between time and temperature which provided benzanilide in high yield. The suitable time must give the highest yield of the desired product. The results of % yield of benzanilide when altering time and temperature are displayed in Table 3.2.

Table 3.2 Effects of time and temperature on % yield of benzanilide.*

Reaction time (h)	**% Yield of benzanilide**	
	Room temperature (28-30 °C)	**Low temperature (0-5 °C)**
0.5	41	27
1.0	75	44
1.5	74	64
2.0	73	82
3.0	76	80

* reaction conditions : Benzoic acid (3 mmol), Cl_3CCN (6 mmol), PPh_3 (6 mmol), CH_2Cl_2 (6 mL), aniline (3 mmol), Et_3N (9 mmol).

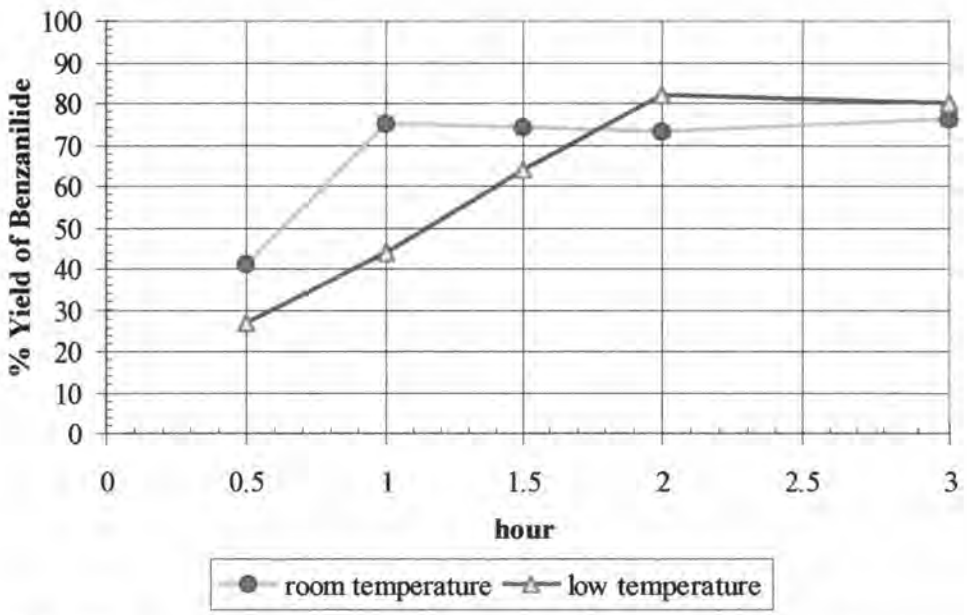


Figure 3.3 The results of % yield of benzanilide when altering time and temperature in step I of the general procedure

At room temperature (28-30 °C) when the reaction was treated for 1 h, the maximum yield of benzanilide was obtained. Increasing reaction time over 1 h produced invariable yield compared with the former. At lower temperature (0-5 °C) the maximum yield of product was acquired when the reaction was treated for 2 h. After increasing reaction time, the yield of product was consistent. Comparing the reactions carried out at room temperature and at low temperature, it was found that the reaction performed at lower temperature gave a little higher amount of benzanilide than that carried out at room tempeature. Therefore the suitable time and temperature for this reaction are 2 h at 0-5 °C.

3. Influence of Solvent System

As described in the general procedure, CH_2Cl_2 was used as a reaction medium because it can dissolve both carboxylic acid and reagents used. Other common solvents were chosen to examine whether they can be employed to substitute CH_2Cl_2 or can enhance the yield of desired products. The results are demonstrated in Table 3.3.

Table 3.3 Effects of solvent system on % yield of benzanilide.*

Entry	Solvents	% Yield of benzanilide
1	CH_2Cl_2	75
2	$CHCl_3$	81
3	CCl_4	59
4	1,2-DCE	32
5	Toluene	58
6	Ether	59
7	THF	63
8	EtOAc	66
9	Acetonitrile	73
10	Acetone	60

* reaction conditions : Benzoic acid (3 mmol), Cl_3CCN (6 mmol), PPh_3 (6 mmol), solvent (6 mL), aniline (3 mmol), Et_3N (9 mmol), room temperature (28-30 °C), reaction time : step I (1 h), step II (20 min).

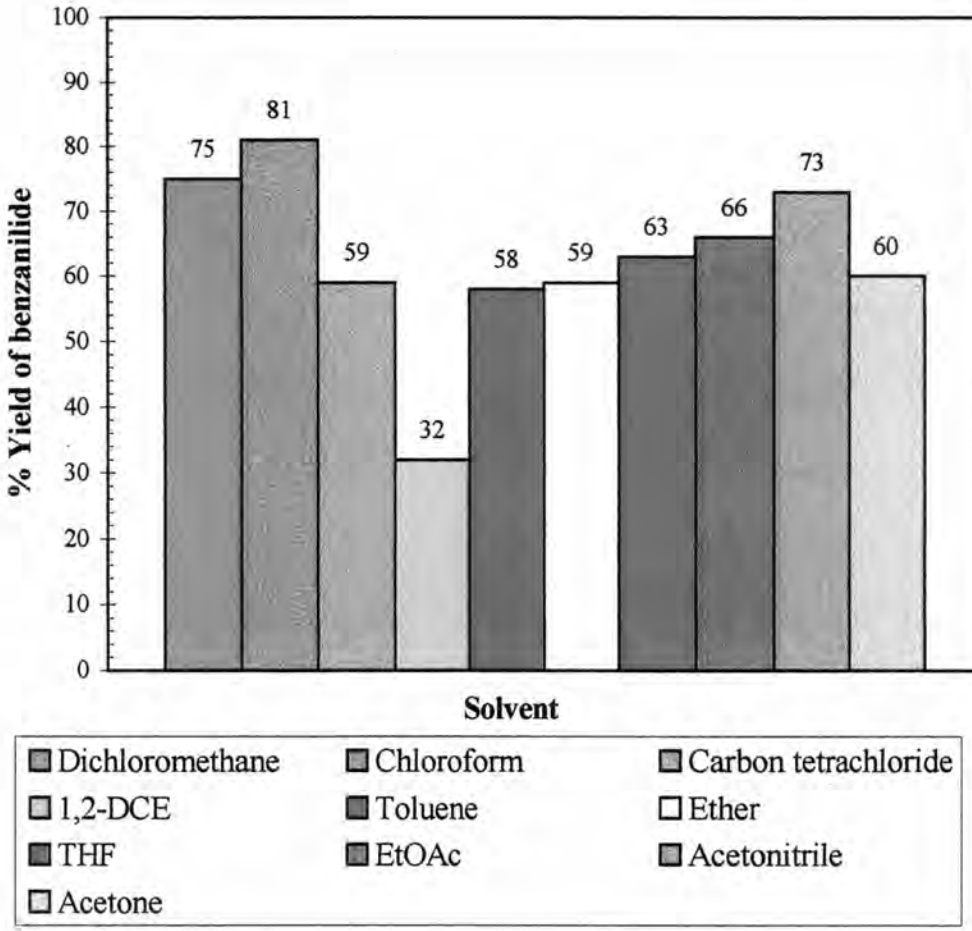


Figure 3.4 Effects of solvent system on benzanilide formation.

Nine common solvents including CH_2Cl_2, $CHCl_3$, CCl_4, 1,2-DCE, toluene, ether, THF, EtOAc, acetonitrile and acetone were examined whether they could use to replace CH_2Cl_2 in this reaction. It was found that, the quantity of desired product was significantly increased when the reaction media was altered from CH_2Cl_2 to $CHCl_3$ (entry 2) or acetonitrile (entry 9). On the other hand, when employing CCl_4, toluene, ether, THF, EtOAc and acetone (entries 3,5-8 and 10) as a solvent instead CH_2Cl_2, the amount of benzanilide was lessen. In the case of utilizing 1,2-DCE (entry 4), the reaction produced low yield of the desired product. From this study it was clearly seen that $CHCl_3$ and acetonitrile can be used instead CH_2Cl_2 in this reaction.

Notwithstanding, the high polarity of some carboxylic acid substrates make them not totally dissolve in CH_2Cl_2, $CHCl_3$ and acetonitrile. Besides, when employing the polar solvent such as THF or acetone, the reaction gave the desired product only in medium yield. To solve this bottle-necked matter, the attempts to employ a mixture of solvent were investigated. Various combinations of solvents were examined. It was

found that a mixture of chloroform with co-solvent provided another alternative solvent for carrying out this reaction. The results of the variation of co-solvent 3 mL and $CHCl_3$ 3 mL are described in Table 3.4.

Table 3.4 Effects of a mixed solvent system on % yield of benzanilide.*

Entry	Solvents (1:1 $CHCl_3$: co-solvent)	% Yield of benzanilide
1	1:1 $CHCl_3$: Ether	80
2	1:1 $CHCl_3$: THF	80
3	1:1 $CHCl_3$: acetone	78
4	1:1 $CHCl_3$: MeOH	trace

* reaction conditions : Benzoic acid (3 mmol), Cl_3CCN (6 mmol), PPh_3 (6 mmol), $CHCl_3$: co-solvent (3 mL : 3 mL), aniline (3 mmol), Et_3N (9 mmol), room temperature (28-30 °C), reaction time : step I (1 h), step II (20 min).

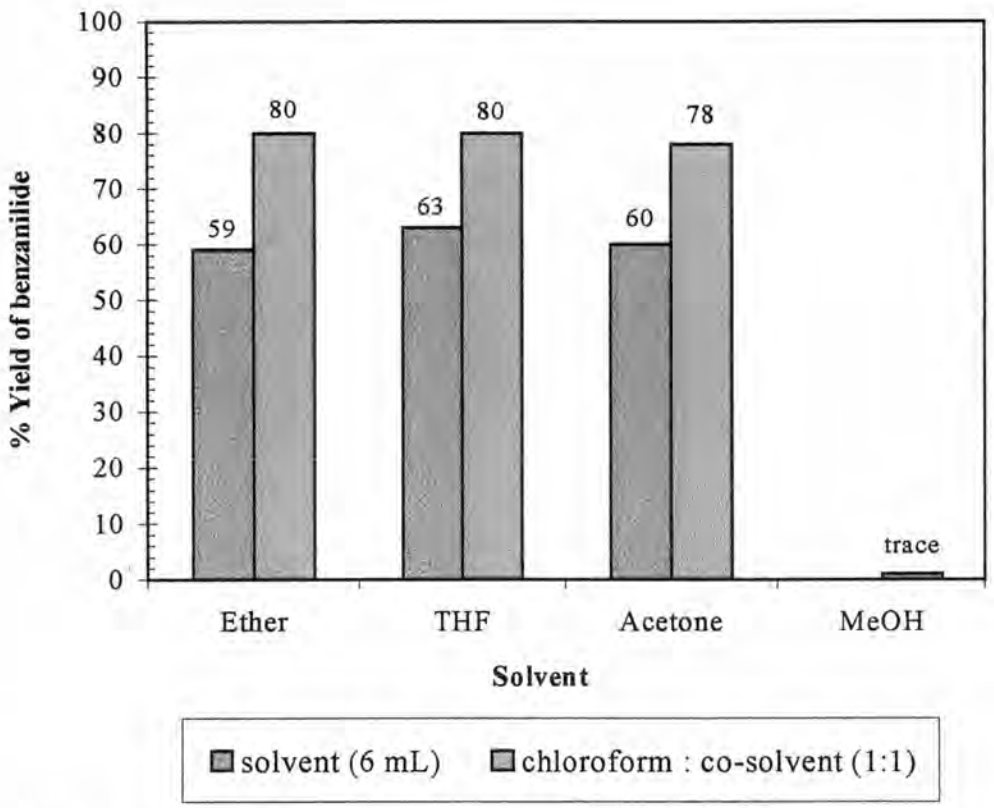


Figure 3.5 Comparative results on the production of benzanilide when using solvent and a mixture of chloroform : co-solvent (1:1)

It was found that when $CHCl_3$ was used as solvent with co-solvent such as ether, THF and acetonitrile, the amount of the desired product was increased compared with each original solvent used. On the contrary, when using MeOH as co-solvent with $CHCl_3$, the reaction presented only trace amount of benzanilide. This is probably because of an interaction between MeOH and anion by a solvation. Furthermore, unwanted side-reactions such as the decomposition of acid chloride may possibly be occurred.

The yield of the desired product is markedly depended on the solubility of the carboxylic acid and reagents. As the reaction progresses, the solvent interacts with any of other compounds such as substrates, nucleophile and intermediate, thereby influencing the yield of desired product.

From the studies on the effect of solvent system described above, the solvents which aid the reaction to provide desired products from the highest to the lowest, is shown below.

$CHCl_3$ ~ 1:1 THF-$CHCl_3$ = 1:1 ether-$CHCl_3$ > 1:1 acetone-$CHCl_3$ > CH_2Cl_2 > acetonitrile > EtOAc > THF > acetone ~ CCl_4 ~ toluene > 1,2-DCE > 1:1 methanol-$CHCl_3$

4. Influence of Chlorinated Reagents

Another worth investigating feature was chlorinated reagents. Various reagents were examined and the results are tabulated in Table 3.5

Table 3.5 Effects of chlorinated reagents on % yield of benzanilide.*

Entry	Chlorinated reagents	% Yield of benzanilide
1	Absence chlorinated reagent	trace
2	Chloroform ($CHCl_3$)	trace
3	Trichloroacetonitrile (Cl_3CCN)	75
4	Carbon tetrachloride (CCl_4)	trace
5	Bromotrichloromethane (Cl_3CBr)	62
6	2-Chloroacetamide ($ClCH_2CONH_2$)	trace
7	Trichloroacetamide (Cl_3CCONH_2)	73
8	Ethyl trichloroacetate (Cl_3CCO_2Et)	72
9	Trichloroacetic acid (Cl_3CCO_2H)	41
10	Trichloroethanol (Cl_3CCH_2OH)	trace
11	Hexachloro-2-propanone ($Cl_3CCOCCl_3$)	43
12	Hexachloroethane (Cl_3CCCl_3)	67
13	Trifluoroacetic acid (F_3CCO_2H)	trace

* reaction conditions : Benzoic acid (3 mmol), reagent (6 mmol), PPh_3 (6 mmol), CH_2Cl_2 (6 mL), aniline (3 mmol), Et_3N (9 mmol), room temperature (28-30 °C), reaction time : step I (1 h), step II (20 min).

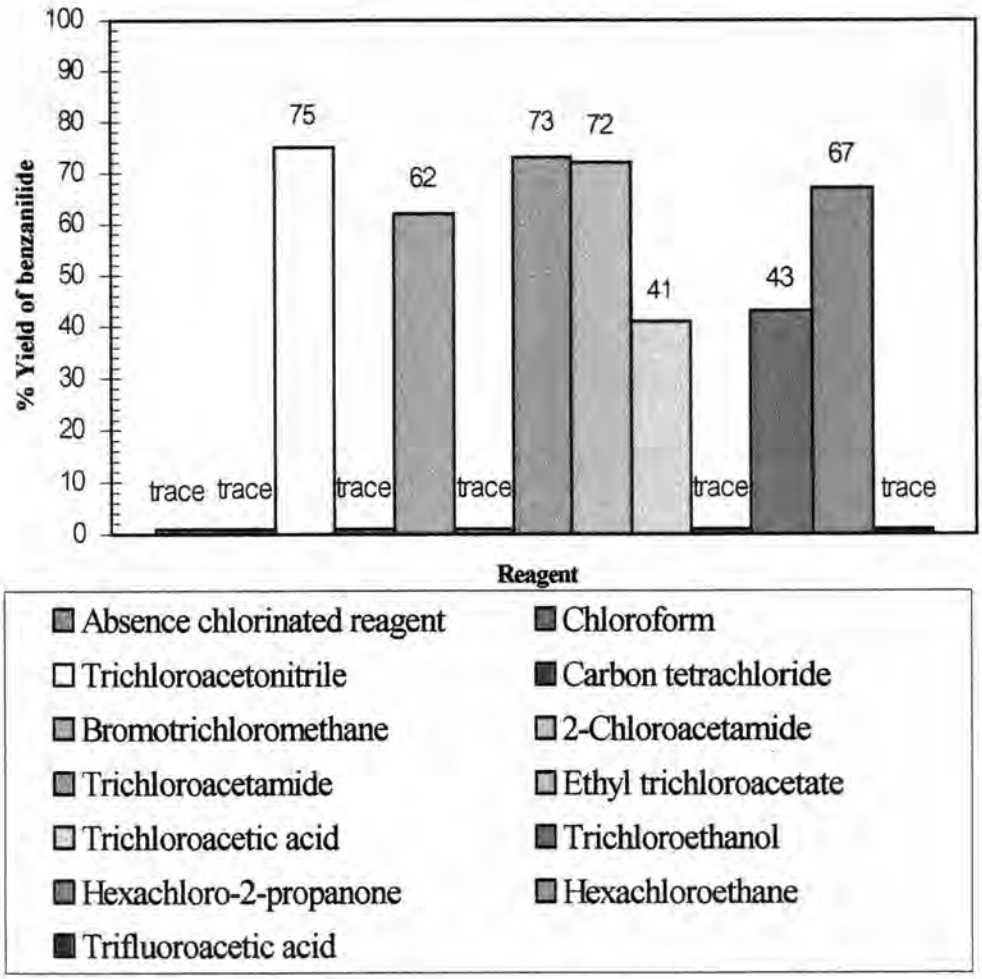


Figure 3.6 Effects of chlorinating agents for the production of benzanilide

The general tendency of reagent efficiency, which provided benzanilide is shown below.

$Cl_3CCN \sim Cl_3CCONH_2 \sim Cl_3CCOOEt > Cl_3CCCl_3 > Cl_3CBr > Cl_3CC(O)CCl_3 > Cl_3CCOOH >$ none $\sim CHCl_3 \sim CCl_4 \sim Cl_3CCH_2OH \sim ClCH_2CONH_2 \sim F_3CCOOH$

It was found that when the reaction was carried out in the absence of chlorinated reagent (entry 1), benzanilide was obtained only trace amount. This clearly demonstrated the chlorinated reagent is essential for this reaction. The efficiency of chlorinating agent was found to be greatly depended on a type of the substituted group on chlorinated reagents. For example, $CHCl_3$ (entry 2) gave benzanilide in trace amount while Cl_3CCN (entry 3) which is a reagent bearing electron-withdrawing groups gave the desired product in high yield. Other electron-withdrawing group reagents were chosen to prove the assumption. For instance, the

reagents such as Cl_3CCONH_2 and Cl_3CCO_2Et (entries 7 and 8) provided high yield of product. Some electron-withdrawing reagents such as $Cl_3CC(O)CCl_3$ and CCl_4 gave medium and poor yield, respectively. The chlorinated reagent as $Cl_3CC(O)CCl_3$ (entry 11) was reported to produce side-reactions[32] which abated the yield of benzanilide while CCl_4 (entry 4) required higher temperature or longer reaction time to give high yield.[19] Trichloroacetic acid (entry 9) and trifluoroacetic acid (entry 13) gave not good yield probably because of its acidity. When Cl_3CCH_2OH (entry 10) was used as a chlorinated reagent, benzanilide was acquired in trace amount. This is probably because an unwanted side-reaction taken place rapidly at a hydroxy group of Cl_3CCH_2OH. However, Cl_3CCN also provided desired product in the highest yield. Accordingly, Cl_3CCN was considered as the most fitting reagent for further investigation.

From the outcome of variable factors studied as described above, it should be concluded that the optimum conditions for this reaction are as follows: carboxylic acid 1 eq. as substrate, Cl_3CCN 1 eq. and PPh_3 2 eq. as reagents, $CHCl_3$ 6 mL as solvent and the reaction should be carried out at 0-5 °C for two hours. Under these conditions benzanilide was derived in maximum yield (87 %). These reaction conditions were then kept as standard conditions for biological amide synthesis. Nonetheless, in some case that $CHCl_3$ could not dissolve carboxylic acid, the solvent was changed to other solvents such as 1:1 THF-$CHCl_3$, 1:1 ether-$CHCl_3$, 1:1 acetone-$CHCl_3$, CH_2Cl_2 and acetonitrile.

Carboxylic Acid Variation

The conversion of various carboxylic acids into acid chlorides has been examined by using a similar manner to that described for the benzanilide (**C1**) synthesis. Other carboxylic acids were chosen to examine the effects of type of carboxylic acid on the yield of corresponding amides. Moreover, the substituted groups on carboxylic acid were meditated. The results are summarized in Table 3.6.

Table 3.6 Physical properties and % yield of amides from carboxylic acid variation.*

Amide (Cpd.)	Starting carboxylic acid	Physical properties		% Yield of amide
		Appearance	m.p. (°C)	
benzanilide (**C1**)	Benzoic acid	White needle crystals	164-165	75
2-hydroxy-*N*-phenyl benzamide (**C2a**)	Salicylic acid	White plate crystals	133-135	55
2-hydroxy-*N*-phenyl benzamide (**C2b**)	Acetylsalicylic acid	White plate crystals	134-135	49
4-methoxy-*N*-phenyl benzamide (**C3**)	4-methoxybenzoic acid	White needle crystals	171-173	66
4-nitro-*N*-phenyl benzamide (**C4**)	4-nitrobenzoic acid	White needle crystals	213-214	49
3,N-diphenyl-2-propenamide (**C5**)	Cinnamic acid	White needle crystals	154-156	68
N-phenyl-hexadecanamide (**C6**)	Palmitic acid	White needle crystals	88-89	68
3-bromo-*N*-phenyl propanamide (**C7**)	3-bromopropionic acid	White plate crystals	120-121	37
N,N'-diphenyl phthalamide (**C8**)**	Phthalic acid	Yellow needle crystals	251-253 (decomp.)	34

* reaction conditions : Carboxylic acid (3 mmol), Cl_3CCN (6 mmol), PPh_3 (6 mmol), CH_2Cl_2 or appropriate solvent (6 mL), aniline (3 mmol), Et_3N (9 mmol), room temperature (28-30 °C), reaction time : step I (1 h), step II (20 min).

** reaction conditions : Carboxylic acid (3 mmol), Cl_3CCN (12 mmol), PPh_3 (12 mmol), 1:1 THF-$CHCl_3$ (9 mL), aniline (6 mmol), Et_3N (18 mmol), room temperature (28-30 °C), reaction time : step I (1 h), step II (20 min).

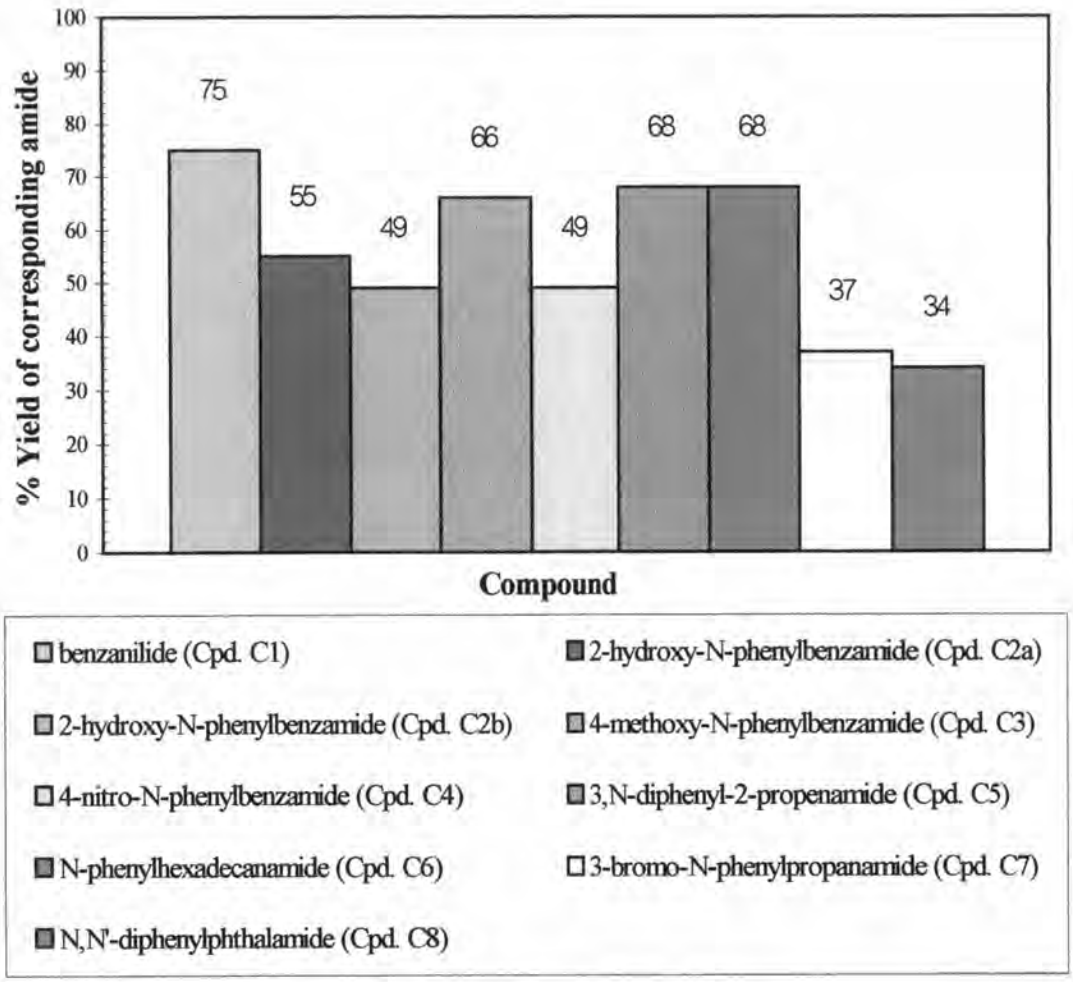


Figure 3.7 % yield of amide from carboxylic acid variation

It was observed that desirable amide product which was produced from unsubstituted aromatic carboxylic acids (**C1**) was obtained in higher yield than amide which was produced from unsubstituted aliphatic carboxylic acid (**C6**). An acid with electron-donating group such as 4-methoxybenzoic acid offered corresponding amide in significantly higher yield than an acid with electron-withdrawing group, 4-nitrobenzoic acid (amides **C3** and **C4**). In the case of salicylic acid which contained electron-donating group, its corresponding amide (**C2a**) was obtained in medium yield. This was probably due to the fact that a hydroxyl group could react with acid chloride and bestowed salicylanilide salicylate as side-product.[55] Acetylsalicylic acid was synthesized with the aim trying to solve this problem, nevertheless its analogue amide (**C2b**) was obtained in medium yield. This was probably because of the effect of acetyl group which is the electron-withdrawing group. Conjugated unsaturated carboxylic acid such as cinnamic acid provided corresponding amide (**C5**) in high

yield. The amide which was prepared from 3-bromopropionic acid (**C7**) also provided amide in low yield maybe because side-reaction was taken place. Dicarboxylic acid such as phthalic acid gave amide (**C8**) in low yield probably because of a steric effect.

It should be concluded that, this procedure is more suitable for aromatic carboxylic acid and acid with electron-donating group than aliphatic carboxylic acid and acid with electron-withdrawing group, respectively.

Amine Variation

Five amine-derived amides could be prepared from benzoic acid by utilizing a similar process to that mentioned for the preparation of benzanilide (**C1**) instead of aniline and confirmed their identities by comparison physical properties with those reported in literature. The results are presented in Table 3.7.

Table 3.7 Physical properties and % yield of amides from amine variation.*

Amide (Cpd.)	Amine	Physical properties		% Yield of amide
		Appearance	m.p. (°C)	
Benzanilide (**C1**)	Aniline	White needle crystals	164-165	75
N,*N*-diphenyl benzamide (**A1**)	*N*-phenylaniline	Yellow prism crystals	177-179	7
N-methylphenyl benzamide (**A2**)	Benzylamine	White needle crystals	103-104	77
N-cyclohexyl benzamide (**A3**)	Cyclohexylamine	White needle crystals	147-149	89
N-*i*-butylbenzamide (**A4**)	*N*-*i*-butylamine	Light yellow liquid	**	80
N-*n*-butylbenzamide (**A5**)	*N*-*n*-butylamine	Flaming yellow liquid	**	61

* reaction conditions : Benzoic acid (3 mmol), Cl_3CCN (6 mmol), PPh_3 (6 mmol) CH_2Cl_2 (6 mL), amine (3 mmol), Et_3N (9 mmol), room temperature, reaction time : step I (1 hr), step II (20 min).

** The boiling point did not examine.

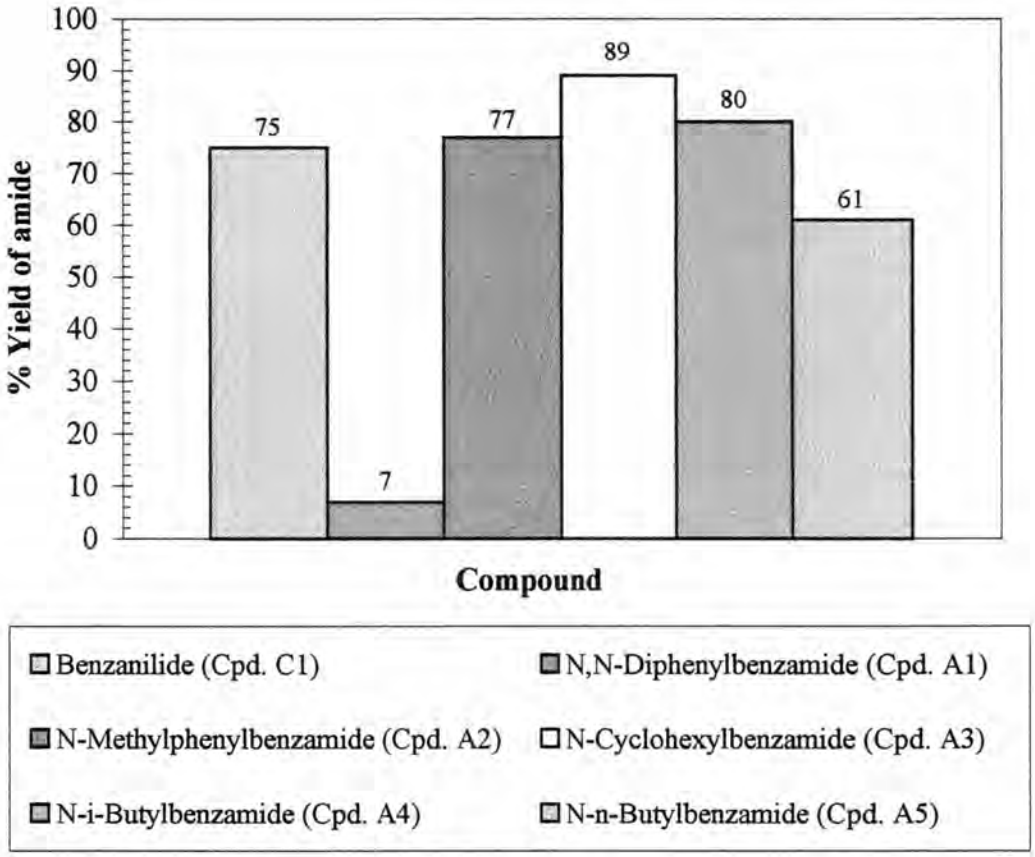


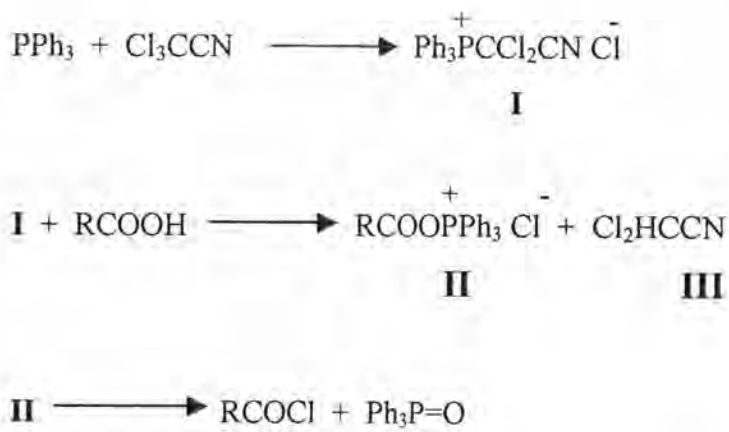
Figure 3.8 % yield of amide from amine variation

It was found that alicyclic amine such as cyclohexylamine provided the desired amide (**A3**) in excellent yield. Aliphatic amines such as *i*-butylamine and *n*-butylamine afforded the desired amides in high yield (amides **A4** and **A5**). The amine which is not of an aromatic ring connecting to amino group such as *N*-benzylamine gave amide in higher yield than aromatic amines such as aniline (amides **A2** and **C1**). This is because the nitrogen of aniline displayed less nucleophilic character than that of *N*-benzylamine due to the resonance effect. The conjugation of the nitrogen lone pair with the phenyl ring of aniline made electron be delocalized to the ring. Secondary amine such as diphenylamine provided amide in poor yield compared with primary aromatic amine such as aniline (amides **A1** and **C1**). Since diphenylamine has two phenyl rings conjugated with the nitrogen lone pair, it made electron very easy to delocalize. Besides, the steric effect from two crowded phenyl rings leaded diphenylamine not good nucleophile.

It should be concluded that the amount of the desired amides was depended on the efficiency of the nucleophilic nature of amine. The good nucleophilic amine provided amide in high yield.

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[56] and J.B. Lee[19]. The proposed mechanism is shown below.



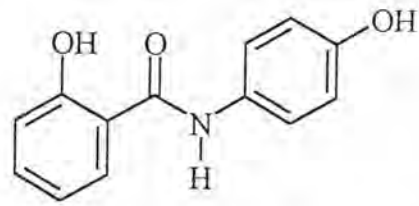
The reaction is obviously a multi-step process. Initially, species **I** (triphenyldichlorocyanomethylphosphonium chloride) occurred by an action between PPh_3 and Cl_3CCN. Species **I** was reacted further with carboxylic acid yielding species **II** and **III**. Finally, acid chloride and triphenylphosphine oxide were produced by the transformation of species **II**. The evidence of the presence of triphenylphosphine oxide could be visualized by isolation of triphenylphosphine from the reaction procedure by colum chromatography as white needle crystal, melting at 154-156°C (lit.[57] 152-157 °C).

Application of Developed Procedure for Synthesis of Target Molecules

The developed acid chloride procedure was applied for the synthesis of biological amides, focusing in benzamide and cinnamamide groups.

1. **Benzamide Group**

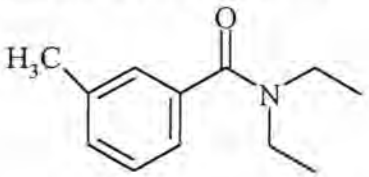
1.1 ***Osalmid*** **(T1)** This compound has been widely used for curing a chlera.[58]



The synthesis of this compound was reported[59] by treating the acid chloride of acetylsalicylic acid with amine at room temperature for 2 hours and finally at the boiling point of ether for 3 hours to give the amide acetate in 90 %. After that, the amide acetate was hydrolyzed by 0.1 N NaOH, then precipitated by 0.1 N HCl and crystallized by very dilute alcohol to give the desired product in quantitative yield.

By employing this developed methodology, Osalmid could be achieved in 47 %. The IR spectrum demonstrated amide carbonyl and C-N absorption bands at 1615 and 1331 cm^{-1}, respectively. The absorption band at 3298 cm^{-1} was due to N-H bond. The broad band around 3604-3352 cm^{-1} was a characteristic of a hydroxy group. The presence of aromatic ring was inferred from the presence of the absorption bands at 3039, 1550, 1505 and 1442 cm^{-1}. The ^{1}H-NMR spectrum displayed a singlet signal at δ_H 1.78 ppm, indicating the presence of N-H proton. Four doublets and two triplet aromatic signals were assigned to eight aromatic protons. The presence of a proton of hydroxy group was inferred from the presence of a singlet signal at δ_H 6.91 ppm. The singlet signal at δ_H 10.38 ppm was due to a hydroxy proton which has a H-bond bonding with a carbonyl group. The ^{13}C-NMR spectrum contained an amide carbonyl carbon at δ_C 167.9 ppm. The ten signals of aromatic carbons, appropriate for two aromatic rings at δ_C 115.2, 115.5, 121.0, 121.4, 121.9, 129.4, 130.3, 134.5, 148.2 and 155.4 ppm were observed.

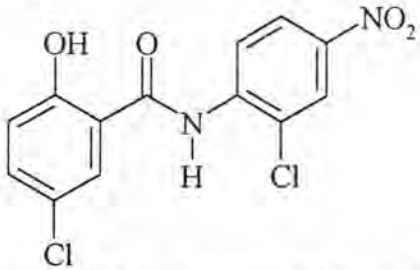
1.2 ***DEET*** (**T2**), an insect repellent compound, has been well-known to employ as mosquitoes, fleas, gnats and many other insects repellent [42].



The synthesis of this compound[60] was reported by treated carboxylic acid with $SOCl_2$ and refluxed for 8 hours, after that the mixture was added with amine and continued stirring for 1 hour to yield compound **T2** in 94%.

By employing this developed methodology, DEET could be achieved in 89 %. The IR spectrum of this derived amide exhibited amide carbonyl absorption band at 1629 cm^{-1}. The medium intensity bands at 3113, 1564 and 1428 cm^{-1} were the characteristic peaks of an aromatic ring. The presence of alkyl and C-N bond was inferred from the presence of bands at 2972 and 1357 cm^{-1}. The ^{1}H-NMR spectrum displayed four aromatic protons (δ_H 7.01-7.05) and a methyl group (δ_H 2.30) substituted on an aromatic ring. Four broad singlets at δ_H 1.08, 1.17, 3.21 and 3.46 ppm were typical of two ethyl groups. The ^{13}C-NMR spectrum revealed an amide carbonyl carbon (δ_C 171.3 ppm) and four aliphatic carbons (δ_C 12.8, 14.1, 39.1 and 43.2 ppm). In addition, six aromatic carbons (δ_C 123.0, 126.7, 128.1, 129.7, 137.1 and 138.0 ppm) and a methyl group (δ_C 21.2 ppm) substituted to one of the aromatic ring were observed.

1.3 ***Niclosamide*** (**T3**), a molluscicide, is utilized for control an amount of snail.[58]

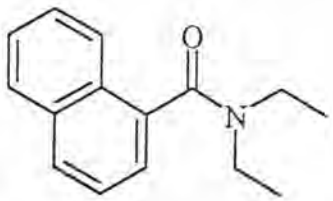


The synthesis of compound **T3** was reported[61] by refluxing carboxylic acid, PCl_3 and amine at 140 °C for 3 hours. The yield of the desired product was nevertheless not reported.

By employing this developed methodology, Niclosamide could be achieved in 39 %. The IR spectrum displayed the absorption bands at 3322 and 1349 cm^{-1}, indicating the presence of N-H and C-N bonds. The presence of hydroxy group was

inferred from the presence of the broad band around 3564-3279 cm^{-1}. The absorption band at 1649 cm^{-1} was attributed to an amide carbonyl group. Two bands at 1523 and 1315 cm^{-1} were assigned to nitro group. The presence of aromatic rings were inferred from the absorption bands at 3081, 1590 and 1431 cm^{-1}, as well as Ar-Cl bond at 1011 cm^{-1}. The ^{1}H-NMR spectrum displayed a singlet signal which was indicative of a proton of N-H bond at δ_H 1.57 ppm. Four doublets and two singlets aromatic signals were typical of six aromatic protons. The presence of a hydroxy proton with a H-bonding with a carbonyl group could be observed from the singlet signal at δ_H 10.42 ppm. The ^{13}C-NMR spectrum exhibited an amide carbonyl carbon at δ_C 164.8 ppm and twelve aromatic carbons at δ_C 113.7, 114.4, 117.7, 119.2, 122.5, 124.3, 125.9, 129.1, 135.1, 144.6, 148.7 and 159.6 ppm.

1.4 ***N,N-diethyl-1-naphthamide*** (**T4**), displays an antidotes for herbicide to sunflower.[62]

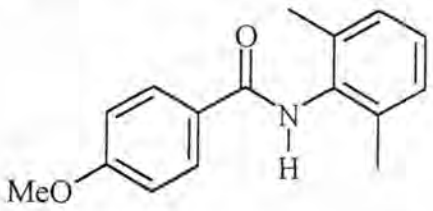


In the former report of compound **T4** synthesis[63], carboxylic acid was treated with $SOCl_2$ and refluxed for 2.5 hours. After reacting with amine at 0 °C for 45 min. and finally at room temperature for 2 hours, compound **T4** was obtained in 57 %.

By employing this developed one-pot methodology, compound **T4** could be achieved in 95 %. The IR spectrum exhibited several strong absorption band such as at 1629 cm^{-1}, indicating the presence of amide carbonyl. The absorption bands at 3052, 1627, 1509 and 1475 cm^{-1} were characteristic of an aromatic ring. The presence of an alkyl group was inferred from the presence of the absorption band at 2965 cm^{-1}. In addition, the peak indicative of C-N bond was detected at 1296 cm^{-1}. The ^{1}H-NMR spectrum demonstrated the signals around δ_H 7.35-7.85 ppm which indicated the presence of seven aromatic protons. Moreover, four peaks indicative of aliphatic protons at δ_H 0.97, 1.35, 3.08 and 3.54 ppm were observed. The ^{13}C-NMR spectrum signified an amide carbonyl carbon (δ_C 170.3 ppm) and ten aromatic carbons (δ_C 123.2, 124.7, 125.1, 126.4, 126.9, 128.3, 128.7, 129.6, 133.5 and 135.1 ppm),

appropriate for the 1-naphthamide structure. Besides, four aliphatic carbons at δ_C 13.1, 14.3, 39.1 and 43.1 ppm were observed.

1.5 ***N-(2,6-dimethylphenyl)-4-methoxybenzamide*** (**T5**), presents an anticonvulsive activity.[64]

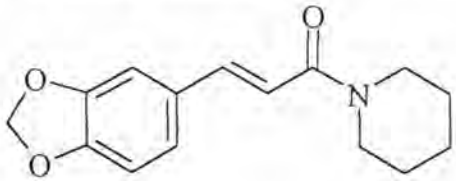


The preparation of this compound was reported[49] from the amidation of acid chloride and amine overnight at room temperature to give the desired product in 94 %.

By employing this developed methodology, compound **T5** could be achieved in 68 %. The IR spectrum displayed amide carbonyl absorption band at 1644 cm^{-1}, as well as a methoxy group at 2834 cm^{-1}. The absorption band at 3250 and 1306 cm^{-1}, were indicated the presence of N-H bond. The presence of aryl groups was inferred from the presence of the absorption bands at 3003, 1610, 1533 and 1494 cm^{-1}. The band at 2945 cm^{-1} was characteristic of alkyl group. The ^{1}H-NMR spectrum showed two methyl groups (δ_H 2.26) and a methoxy group (δ_H 3.86) substituted to the aromatic rings. The singlet signal at δ_H 1.58 ppm was typical of a N-H proton. One triplet and three doublets of aromatic protons at δ_H 6.45, 6.83, 6.96 and 7.84 ppm, indicating seven aromatic protons were observed. The ^{13}C-NMR spectrum displayed an amide carbonyl (δ_C 165.4 ppm) and a methoxy carbon (δ_C 55.5). The presence of two aromatic rings at δ_C 113.9, 123.7, 126.7, 127.3, 128.3, 129.1, 135.6 and 162.5 ppm was inferred from the presence of eight aromatic carbon signals. A signal of alkyl group δ_C 15.3 ppm was characteristic of two carbons substituted to the aromatic ring.

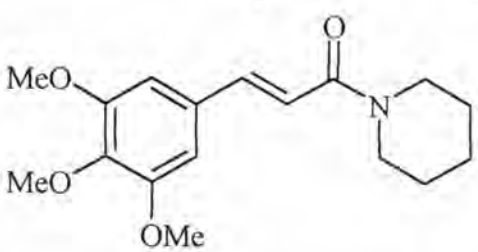
2. **Cinnamamide Group**

2.1 ***N-(3,4-Methylenedioxycinnamoyl)piperidide*** (**T6**) was found for the first time from wood of *Piper navae-hallandiae*.[50] This compound is employed as a synergist for pyrethrum.[65] Moreover, it possesses an antiepilepsirnium activity.[66] The preparation of this compound was not recorded.



By employing this developed methodology, compound **T6** could be achieved in 94 %. The IR spectrum showed an amide carbonyl absorption band at 1730 cm^{-1}, as well as a methylenendioxy group at 1250 cm^{-1}. The absorption bands at 1601 and 1359 cm^{-1} were indicated the presence of olefinic and C-N bond, respectively. The absorption bands at 3166, 1643 and 1495 cm^{-1} were characteristic of aromatic ring. The presence of alkyl group was inferred from the presence of bands at 2935 and 2857 cm^{-1}. The ^{1}H-NMR spectrum displayed two broad singlet signals at δ_H 1.61 and 3.59 ppm, indicating the presence of a piperidine ring. The signals around δ_H 6.71-6.77 ppm were assigned to three aromatic protons. A pair of *trans*-coupled doublet at δ_H 6.98 (J = 14.93 Hz) and 7.54 (J = 15.33 Hz) was typical of a *trans*-olefin group. The signal at δ_H 5.93 ppm was ascribed to two protons of methylenedioxy group. The ^{13}C-NMR spectrum demonstrated five signals of aliphatic at δ_C 24.5, 25.5, 26.6, 43.2 and 46.8 ppm, appropriate for the piperidine structure. Moreover, ten signals of 3,4-methylenedioxycinnamoyl structure were observed at δ_C 101.3, 106.2, 108.2, 115.6, 123.4, 129.7, 141.7, 148.1, 148.7 and 165.2 ppm.

2.2 ***N-(3,4,5-Trimethoxycinnamoyl)piperidide*** (**T7**) was reported the posses an anticonvulsive activity.[67] It was found firstly from stems of *Piper longum*.[68]

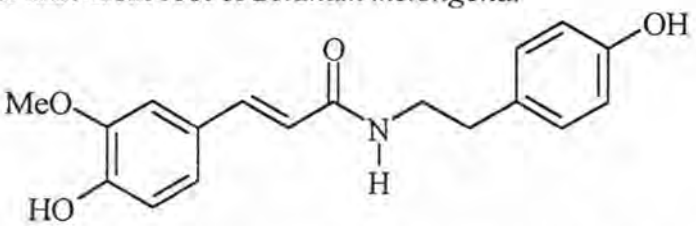


The preparation of compound **T7** was reported[69] by reacting carboxylic acid with $SOCl_2$ to give the corresponding acid chloride. Then, it was treated with pyridine

in 10% NaOH at 0-5 °C for 1 hour and finally overnight at room temperature to give the desired product. The notification of the amount of the desired product was not observed.

By employing this developed methodology, compound **T7** could be achieved in 89 %. The IR spectrum demonstrated amide carbonyl and α,β-unsaturated group at 1717 and 1639 cm^{-1}, respectively. The absorption bands at 2844 and 2931cm^{-1} were characteristic of methoxy and alkyl groups. The presence of aromatic ring was inferred from the presence of bands at 3061, 1581 and 1436 cm^{-1}. The absorption band at 1344 cm^{-1} was attributed to C-N band. The ^{1}H-NMR spectrum showed two broad singlets at δ_H 1.57 and 3.50 ppm, indicating the presence of a piperidine ring. The signal at δ_H 6.74 ppm was assigned to the two same aromatic protons, as well as three methoxy groups at δ_H 3.86 ppm. The doublets at δ_H 6.93 (J = 15.81 Hz) and 7.65 (J = 15.95 Hz) were due to two *trans*-olefin protons adjacent to a carbonyl. The ^{13}C-NMR spectrum displayed nine peaks at δ_C 56.2, 60.4, 104.8, 116.9, 131.1, 133.4, 142.3, 153.3 and 165.3 ppm, indicative of cinnamoyl structure and three methoxy groups substituted to an aromatic ring. The five signals of aliphatic carbons at δ_C 24.5, 25.6, 26.8, 43.4 and 47.0 ppm, appropriated for piperidine structure were observed.

2.3 ***N-Feruloyltyramine*** (**T8**) presents an inhibition on human platelet aggregation.[52] In addition, it was reported about termite antifeedant.[70] This compound was found for first time from root of *Solanum melongena.*[71]

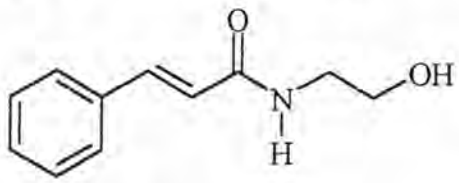


The preparation of this compound[52] was reported by the reaction between carboxylic acid, tyramine and DCC (N,N'-dicyclohexylcarbodiimide). The mixture was carried out overnight at room temperature. The amount of the desired product was however not notified.

By employing this developed methodology, compound **T8** could be achieved in 52 %. The IR spectrum exhibited an amide carbonyl and α,β-unsaturated bonds at 1726 and 1630 cm^{-1}, respectively. The absorption bands at 3329 and 1267 cm^{-1} were attributed to N-H and C-N bonds. The presence of hydroxy groups was inferred from

the presence of the broad band around 3656-3284 cm^{-1}. The absorption bands at 3090, 1596, 1509, 1465 and 1417 cm^{-1} were assigned to aromatic rings, as well as alkyl and methoxy group at 2940 and 2848 cm^{-1}, respectively. The ^{1}H-NMR spectrum displayed triplet signal which was indicative of an N-H proton at δ_H 1.17 ppm. The singlet at δ_H 3.78 ppm was assigned to three protons of the methoxy group. Two doublets at δ_H 6.34 (J = 15.88 Hz) and 7.45 (J = 15.92 Hz) were due to two *trans*-olefin protons adjacent of a carbonyl. The presence of four aliphatic protons was inferred from the presence of one triplet and one quartet at δ_H 2.75 and 3.01 ppm, respectively. Four doublets and one singlet aromatic signals were attributed to seven aromatic protons. Two protons of two hydroxy groups were not observed. The ^{13}C-NMR spectrum signified ten signals at δ_C 55.6, 111.0, 116.2, 122.6, 125.8, 127.3, 144.0, 147.9, 149.0 and 168.3 ppm, appropriate for the feruloyl structure. Moreover, two aliphatic (δ_C 32.1 and 45.3 ppm) and four aromatic (δ_C 115.3, 129.5, 143.5 and 156.1 ppm) signals of tyramine structure were observed.

2.4 ***Idrocilamide*** (**T9**) that is used as a muscle relaxant in mammal[58] was found firstly from leaves of *Erythrophleum chlorostruchys*.[72]

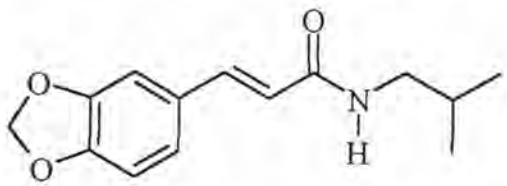


The preparation of this compound was reported[73] from cinnamic acid by esterification with EtOH and then reacted with ethanolamine at 120°C for 18 hours to give the amide product in 53 % or by direct reaction between carboxylic acid and ethanolamine to give the desired amide in 68.5%.

By employing this developed methodology, Idrocilamide could be achieved in 33 %. The IR spectrum showed an amide carbonyl absorption band at 1728 cm^{-1}, as well as an olefinic bond at 1637 cm^{-1}. The broad band around 3644-3285 cm^{-1} was characteristic of a hydroxy group. The presence of N-H and C-N bonds were inferred from the presence of bands at 3230 and 1346 cm^{-1}. The absorption bands at 3057, 1532 and 1437 cm^{-1} were indicated the presence of aromatic ring. The absorption at 2916 cm^{-1} was assigned to alkyl group. The ^{1}H-NMR spectrum contained two singlet signals which was indicative of the N-H and O-H protons at δ_H 1.22 and 3.95 ppm,

respectively. A pair of *trans*-coupled doublet at δ_H 7.72 (J = 16.16 Hz) and 7.17 (J = 16.53 Hz) was assigned to a *trans*-olefin group. The signals around δ_H 7.32-7.76 ppm were typical of five aromatic protons, as well as four aliphatic protons around δ_H 3.35-3.48 ppm. The ^{13}C-NMR spectrum demonstrated seven signals (δ_C 120.6, 127.8, 128.7, 129.3, 135.4, 142.4 and 165.2 ppm), appropriate for the cinnamoyl structure. Moreover, two signals of aliphatic carbons at δ_C 46.0 and 64.5 ppm were observed.

2.5 ***Fagaramide*** (**T10**) shows anti-inflammatory activity[74] *via* inhibition of prostaglandin synthesis. Moreover, it displays the molluscicide against *Biomphalaria glabratus*.[75] This compound was found firstly from stem and root barks of *Fagara xanthoxyloides*.[76]

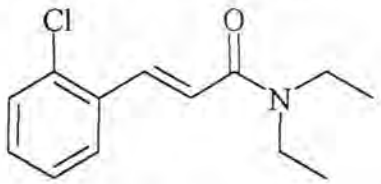


The synthesis of this compound was reported[77] by refluxing carboxylic acid and $SOCl_2$ to gain acid chloride. After that acid chloride was converted to 3-acylthiazolidine-2-thione by treating with thallium (I) salt of thiazolidine-2-thione. 3-Acylthiazolidine-2-thione was treated with amine to give the desired amide in 78 %.

By employing this developed methodology, Fagaramide could be achieved in 69 %. The IR spectrum showed amide carbonyl absorption band at 16447 cm^{-1}, as well as a methylenendioxy group at 1243 cm^{-1}. The absorption band indicative of N-H bond was detected at 3289 cm^{-1}. The absorption bands at 1615 and 1330 cm^{-1} were indicated the presence of olefinic and C-N bond, respectively. The absorption bands at 3076, 1547 and 1494 cm^{-1} were characteristic of aromatic ring. The presence of alkyl group was inferred from the presence of bands at 2965 cm^{-1}. The ^{1}H-NMR spectrum displayed three signals including doublet (δ_H 0.93), multiplet (δ_H 1.75-1.88) and triplet (δ_H 3.19), appropriate for the *i*-butyl structure. The singlet at δ_H 1.57 ppm was assigned to the proton at N-H bond. Two doublets (δ_H 6.19 and 6.77) and a singlet (δ_H 6.99) aromatic signals were assigned to three aromatic protons. A pair of *trans*-coupled doublet at δ_H 6.19 (J = 15.49 Hz) and 7.51 (J = 15.56 Hz) was typical of a *trans*-olefinic group. The signal at δ_H 5.97 ppm was ascribed to two protons of methylenedioxy group. The ^{13}C-NMR spectrum exhibited three signals of alkyl carbons (δ_C 20.2, 28.6 and 47.1 ppm), appropriate for *i*-butyl structure. Moreover, ten

signals of 3,4-methylenedioxycinnamoyl structure were observed at δ_C 101.4, 106.3, 108.5, 118.8, 123.8, 129.3, 140.6, 148.2, 148.9 and 166.1 ppm.

2.6 ***2-Chloro-N,N-diethyl-cinnamamide*** (**T11**) displays the herbicidal activity[78] by a phytotoxic activity against variety of plants, including *Amaranthus retroflexus, Artemisia vulguris, Chenopodium album and Vicia sativa* through either foliar and root absorption. The preparation of this compound was not recorded.



By employing this developed methodology, compound **T11** could be achieved in 70 %. The IR spectrum exhibited absorption bands at 1639 and 1601 cm^{-1} which were indicated the presence of amide carbonyl and α,β-unsaturated groups. The absorption bands at 3601, 1564 and 1465 cm^{-1} were characteristic of aromatic ring. The presence of C-N and Ar-Cl bonds were inferred from the presence of the absorption bands at 1364 and 1046 cm^{-1}. ^{1}H-NMR spectrum showed a pair of doublet at δ_H 7.13 (J = 15.34 Hz) and 7.79 (J = 15.32 Hz) of two *trans*-olefin protons. Two triplets (δ_H 1.06 and 1.13) and two quartets (δ_H 3.43 and 3.54) of aliphatic proton were ascribed to ten protons of two ethyl groups. Multiplet signal at δ_H 7.35-7.52 was due to four aromatic protons. The ^{13}C-NMR spectrum contained nine signals (δ_C 126.9, 132.7, 133.4, 134.9, 136.0, 138.1, 138.5, 141.3 and 169.3 ppm), indicative of 2-chlorocinnamoyl structure. Four aliphatic carbons at δ_C 18.3, 20.4, 45.6 and 46.7 ppm were appropriated to two same ethyl groups.

Eleven target molecules in benzamide and cinnamamide groups were exemplified for the applicably developed procedure. The desired products were obtained in high to excellent yield. Nevertheless some compounds such as **T1**, **T3**, **T8** and **T9** provided the desired product in medium yield. This is probably because the unwanted reactions were occurred from the hydroxy group of carboxylic acid moiety, particularly in compounds **T1**, **T3**, **T8** and amine moiety in compound **T9**. In addition, the amount of the amide products were depended on other effects such as the efficiency of the nucleophilic amine and the type and substituted of carboxylic acid. The good nucleophilic amine gave amide in high yield, as well as the carboxylic acids

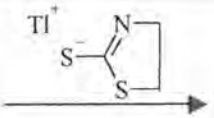
with electron-donating group gave the higher yield than those with electron-withdrawing group. This effect was previously observed as already discussed in carboxylic acid and amine variation section.

Some target molecules were reported by using other procedures. The comparison of target molecule preparation between the reported procedure and the developed procedure are demonstrated in Table 3.8.

Table 3.8 The comparison of target molecule preparation between the reported procedure and the developed procedure*.

Cpd	The reported procedure		% Yield from this procedure
	Procedure	% Yield	
T1	Acid chloride acetate + amine $\xrightarrow[2\text{ h}]{\text{room temp.}}$ $\xrightarrow[3\text{ h}]{\downarrow\uparrow}$ Amide acetate $\xrightarrow[2)\ 0.1\text{ N HCl}]{1)\ 0.1\text{ N NaOH}}$ **T1**	90	47
T2	Acid + $SOCl_2$ $\xrightarrow[8\text{ h}]{\downarrow\uparrow}$ $\xrightarrow[1\text{ h}]{\text{Amine}}$ **T2**	94	89
T3	Acid + PCl_3 + amine $\xrightarrow[3\text{ h}]{140\ ^\circ\text{C}}$ **T3**	-	39
T4	Acid + $SOCl_2$ $\xrightarrow[2.5\text{ h}]{\downarrow\uparrow}$ $\xrightarrow[0\ ^\circ\text{C, 45 min}]{\text{Amine}}$ $\xrightarrow[2\text{ h}]{\text{room temp.}}$ **T4**	57	95
T5	Acid chloride + amine $\xrightarrow[\text{overnight}]{\text{room temp.}}$ **T5**	94	68
T6	Compound from natural extract.	-	94
T7	Acid + $SOCl_2$ $\xrightarrow{\downarrow\uparrow}$ $\xrightarrow[0\text{-}5\ ^\circ\text{C, 1 h}]{\text{Amine, 10 \% NaOH}}$ $\xrightarrow[\text{overnight}]{\text{room temp.}}$ **T7**	-	89
T8	Acid + amine + DCC $\xrightarrow[\text{overnight}]{\text{room temp.}}$ **T8**	-	52

Table 3.8 (cont.)

Cpd	The reported procedure		% Yield from this procedure
	Procedure	% Yield	
T9	I : Acid + EtOH ⟶ ester $\xrightarrow[120\ ^{\circ}C,\ 18\ h]{\text{Amine}}$ **T9**	53	33
	II : Acid + amine ⟶ **T9**	68.5	
T10	Acid + $SOCl_2$ ⟶  ⟶ 3-acylthiazolidine-2-thione $\xrightarrow{\text{Amine}}$ **T10**	78	69
T11	-	-	70

* The developed procedure :

acid + PPh_3 + Cl_3CCN $\xrightarrow[2\ h]{0\text{-}5\ ^{\circ}C}$ $\xrightarrow[\text{room temp., 2 h}]{\text{Amine}}$ amide product

- The detail was not reported.

It was seen that the syntheses of the target molecules could be accomplished by using many procedures. However, the classical procedure is the preparation of acid chloride from the reaction between carboxylic acid and $SOCl_2$ and treated the acid chloride with amine to give the desired amide product. When compared the classical procedure ($SOCl_2$) with this developed procedure, it was found that the developed procedure provided the amount of the desired product both higher (**T4**) and lower (**T2** and **T10**) than the classical procedure. However, the developed procedure was carried out under mild conditions which were easy to control and handled, and used less time than the others. Therefore, another advantage of the developed procedure over classical procedures is the energy saving. Besides, unlike the classical manner, this manner does not produce extremely corrosive by-product. Finally, because this method is carried out under acid free condition then it can produce acid chloride from an acid starting material containing acid sensitive functional groups. Nevertheless, this developed procedure has the complicated process in the purification, while the

complicated process of the classical procedure is the re-distillation of $SOCl_2$ ever time before using.