การสังเคราะห์แอริลคีโทนจากกรดคาร์บอกซิลิกแบบวันพอตผ่านฟรีเดล-คราฟต์แอซิเลชัน

นายอรรถพล เกษมสุขนิมิต

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ONE-POT SYNTHESIS OF ARYL KETONE FROM CARBOXYLIC ACID VIA FRIEDEL-CRAFT ACYLATION

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A Thesis Submitted in Partial Fulfillment of the Requirements
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Thesis Title	ONE-POT SYNTHESIS OF ARYL KETONE FROM CARBOXYLIC ACID VIA FRIEDEL-CRAFT ACYLATION
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อรรถพล เกษมสุขนิมิต : การสังเคราะห์แอริลคีโทนจากกรดคาร์บอกซิลิกแบบวันพอตผ่านฟรีเดล-คราฟต์แอซิเลชัน (ONE-POT SYNTHESIS OF ARYL KETONE FROM CARBOXYLIC ACID VIA FRIDEL-CRAFT ACYLATION) อ. ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ดร. วรินทร ชวศิริ, 53 หน้า.

ได้พัฒนาวิธีการสังเคราะห์แอลริลคีโทนจากกรดคาร์บอกซิลิกที่มีประสิทธิภาพภายใต้ภาวะที่ไม่รุนแรง สามารถสังเคราะห์แอลริลคีโทนโดยปฏิกิริยาฟรีเดล-คราฟต์แอซิเลชันของสารประกอบแอโรมาติกด้วยแอซิดแฮไลด์ที่เกิดจากแฮโลจิเนทิงเอเจนต์และ PPh_3 แบบอินซิทู ศึกษาภาวะที่เหมาะสมในการสังเคราะห์ 4-เมทอกซีเบนโซฟีโนนซึ่งเป็นปฏิกิริยาต้นแบบ ปฏิกิริยาประกอบด้วยสองขั้นตอน ขั้นแรกเป็นการเปลี่ยนกรดเบนโซอิกเป็นเบนโซอิลคลอไรด์โดยการใช้ Cl_3CCN แงละ PPh_3 ร่วมกัน ขั้นต่อมาเป็นปฏิกิริยาฟรีเดล-คราฟต์แอซิเลชันระหว่างแอนิโซลกับแอซิลเลทิงเอเจนต์ที่เกิดจากวิธีอินซิทูโดยที่มีอะลูมิเนียมไทรคลอไรด์อยู่ด้วย วิธีแบบวันพอตนี้ยังไม่มีรายงานในเอกสารอ้างอิงทางเคมี สามารถทำได้ภายใต้ภาวะที่ไม่รุนแรง ใช้เวลาสั้น ให้ผลิตภัณฑ์ในปริมาณดีถึงดีมากโดยเฉพาะอย่างยิ่งสำหรับสารประกอบแอโรมาติกที่มีหมู่แอคทิเวต

ภาควิชา.....เคมี.....ลายมือชื่อนิสิต.....

ปีการศึกษา.....2551.....ลายมือชื่ออ.ที่ปรึกษาวิทยานิพนธ์หลัก.....

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ATTHAPOL KASEMSUKNIMIT: ONE-POT SYNTHESIS OF ARYL KETONE FROM CARBOXYLIC ACID VIA FRIEDEL-CRAFT ACYLATION. ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., 53 pp.

The mild and efficient approach for aryl ketones synthesis from carboxylic acids has been developed. Aryl ketones can be synthesized by Friedel-Crafts acylation of aromatic compounds with acid halides *in situ* generated from halogenating agent and PPh_3. The optimal conditions for the synthesis of 4-methoxybenzophenone as a model reaction are thoroughly scrutinized. The reaction is composed of two steps: the first step is the conversion of benzoic acid to benzoyl chloride by combination of Cl_3CCN and PPh_3, while the second step is Friedel-Craft acylation between anisole and the *in situ* generated acylating agent in the presence of $AlCl_3$. This developed one-pot protocol which has never been reported in chemical literatures can be efficiently performed under mild conditions with short reaction time furnishing good to excellent yields of the desired aryl ketone, particularly for activated aromatic compounds.

Department.....Chemistry.....Student's Signature Atthapol Kasemsuknimit
Academic year.....2008..... Advisor's Signature W. Chavasiri

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LIST OF ABBREVIATIONS

δ	chemical shift (NMR)
J	coupling constant (NMR)
cm^{-1}	wave number (IR)
ºC	degree Celsius
CH_3CN	acetonitrile
Ar	aryl
CH_2Cl_2	dichloromethane
$CDCl_3$	deuterated chloroform
d	doublet (NMR)
dd	doublets of doublet (NMR)
EtOH	ethanol
EtOAc	ethyl acetate
g	gram(s)
Hz	hertz
h	hour
IR	infrared
lit	literature
KBr	potassium bromide
Me	methyl group
m.p.	melting point
mL	milliliter(s)
mmol	millimole(s)
m	multiplet (NMR)
NMR	nuclear magnetic resonance
q	quartet (NMR)
rt	room temperature
s	singlet (NMR)
THF	tetrahydrofuran

TLC	thin layer chromatography
OTf	triflate
NTf	(trifluoromethanesulfonyl)amide
t	triplet (NMR)
Ts	tosyl group

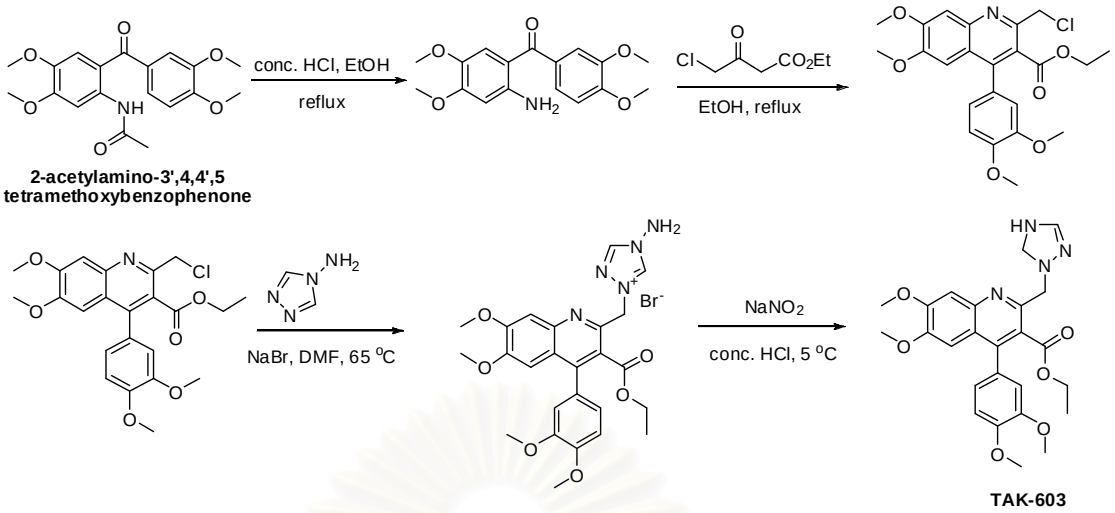
CHAPTER I

INTRODUCTION

The knowledge of functional group interconversion from large quantity chemicals such as aryl ketones to their intermediates is indispensable in laboratory and industrial point of view. Intermediates play an important role as the media for synthesis of diverse products in organic synthesis especially in the case of severity or tedious procedures required for the direct transformation of substrates. Aryl ketones are among those examples of appealing substrates which have abundant utilities. Due to their similar skeleton to natural products, they have thus gained considerable interest as precursors in synthetic bioactive compounds.

1.1 Introduction of aryl ketone

Aryl ketone represented as Ar(CO)R is one of the most important fine chemicals widely used in cosmetics, pharmaceuticals, agrochemicals and dyes [1]. For instance, 2-acetylamino-3′,4,4′,5-tetramethoxybenzophenone was produced in large quantity as a starting material to prepare ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (TAK-603) identified as a disease-modifying antirheumatic drug [2].



Scheme 1.1 Synthesis of ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (TAK-603)

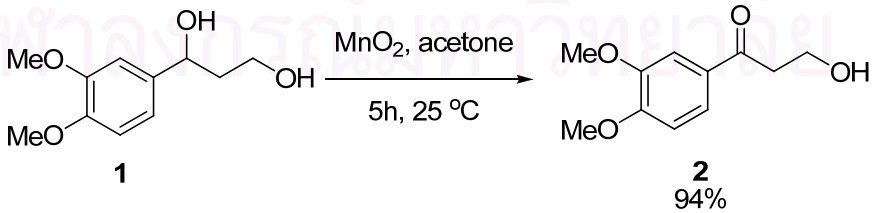
1.2 Synthesis of aryl ketones

There are many procedures for the preparation of aryl ketones from various starting materials, for example;

- by oxidation with MnO_2;
- by the reaction of acid chlorides with organocadmium;
- by Fukuyama coupling; and
- by Friedel-Crafts acylation.

1.2.1 By oxidation with MnO_2

Secondary alcohols can be oxidized to aryl ketones with MnO_2 in neutral media. The reaction proceeds *via* a radical intermediate, producing MnO as byproduct. The secondary benzylic alcohol **1** was oxidized to aryl ketone **2** in preference to the reaction at the primary aliphatic hydroxyl [3].

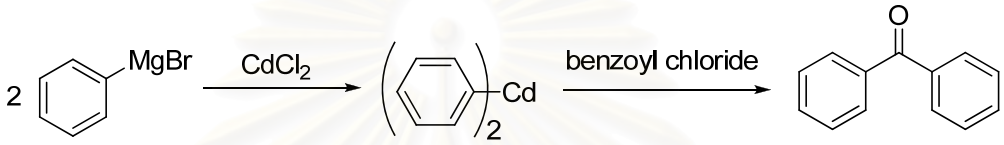


1 **2** 94%

Although the oxidation of allylic and benzylic alcohols is faster, saturated alcohols do react with MnO_2. Their oxidation requires a neutral medium, freshly prepared and activated MnO_2, the proper solvent and long reaction times.

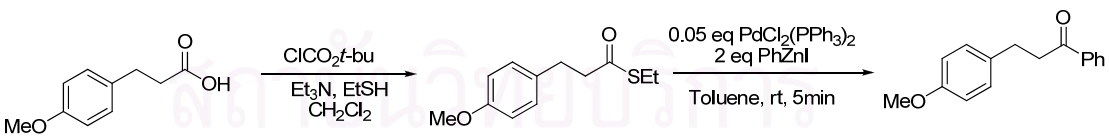
1.2.2 By the reaction of acid chlorides with organocadmium compounds

Another important method for synthesis of aryl ketones was nucleophilic substitution of carbonyl derivatives with organocadmium reagent (R_2Cd) [4]. Organocadmium reagents are readily formed from primary Grignard reagents but secondary and tertiary organocadmium reagents are relatively unstable, and the likely decomposition pathway is dissociation to radicals, which disproportionate to give alkanes and alkenes. Organocadmium reagents such as dibenzylcadmium are formed by reaction of a Grignard reagent (benzylmagnesium bromide) and anhydrous cadmium chloride ($CdCl_2$) [5].



1.2.3 By Fukuyama coupling

This reaction was discovered by Fukuyama *et al.* in 1998 [6]. The Fukuyama coupling is a coupling reaction taking place between a thioester and an organozinc halide in the presence of palladium catalyst. The advantages of this reaction are high chemoselectivity, mild reaction conditions and the use of less-toxic reagents [7]. An advantage of this method is that the reaction stops at the ketone and does not proceed to a tertiary alcohol. In addition, the protocol is compatible with functional groups such as ketones, acetates, sulfides, aromatic bromides, chlorides and aldehydes.



1.2.4 By Friedel-Crafts acylation

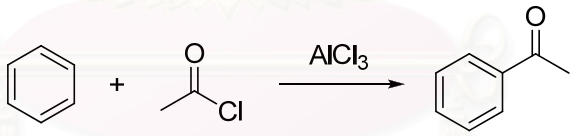
The Friedel-Crafts acylation is typically more popular method than others for preparation of aryl ketones since the synthesis of aryl ketones using organometallic reagents, though well-established, sometimes suffers from drawback such as tedious purification and competition between nucleophilic addition and nucleophilic substitution [8].

Friedel-Crafts acylation is affected by the formation of an acylium ion as an active electrophilic species. The reactive acylium ion is generated from an acyl halide or anhydride by treatment with Lewis acid such as commonly used $AlCl_3$. Although $AlCl_3$ could potentially affect the catalysis of Friedel-Crafts acylation, the product ketone is sufficiently basic to interact strongly with $AlCl_3$, so that in fact more than one equivalent of $AlCl_3$ is required. $AlCl_3$ can be removed in an aqueous work-up step, which hydrolyzes to HCl and $Al(OH)_3$. The carbonyl group in aryl ketone is polarized (δ^+) and is attacked directly to the aromatic ring. The aryl ketone is deactivated relative to the starting material (aromatic compound) and further reaction given a polyacylated deactivative is not a major problem since acylium ion is less reactive than aromatic compound.

1.3 Literature reviews of aryl ketone synthesis from Friedel-Crafts acylation

The stimulus to study on Friedel-Crafts acylation has resulted from several factors. One of the foremost actuating influences has been the development of various acylating agents such as acid halides, esters, acid anhydrides and carboxylic acids.

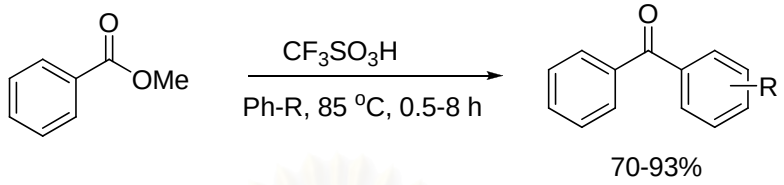
The general reaction was simply formulated using aromatic compound, $AlCl_3$ and acid halide. The electrophilic aromatic substitution of acetyl chloride with benzene in the presence of $AlCl_3$ would furnish ketones in good yields [9].



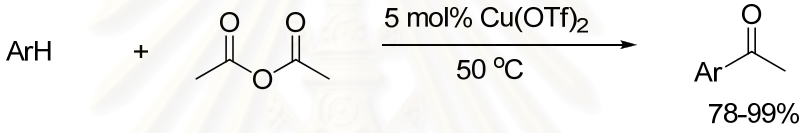
Nevertheless, the use of acid chloride as acylating agent conduces towards limitations such as sensitive to moisture and not many substrate diversities. Several recent new methods have been developed trying to overcome these disadvantages. Among important alternatives, the replacement of acid chlorides by acid anhydrides or esters is a good example.

In 2000, Hwang *et al.* reported that the new route to synthesize aryl ketones using a highly reactive benzoylating reagent produced by activating methyl benzoate with trifluromethanesulfonic acid (F_3CSO_3H). Benzophenone derivatives could be obtained in good to excellent yields. Two and a half molars of F_3CSO_3H compared to methyl benzoate was necessary to achieve suitable reaction which involves

superelectrophilic activation. On the other hand, aliphatic esters, under the same conditions, are less reactive than benzoic acid esters. For example, methyl phenyl acetate reacted with benzene under prolonged reflux for three days in the presence of F_3CSO_3H giving deoxybenzoin as a major product in 54% yield [10].



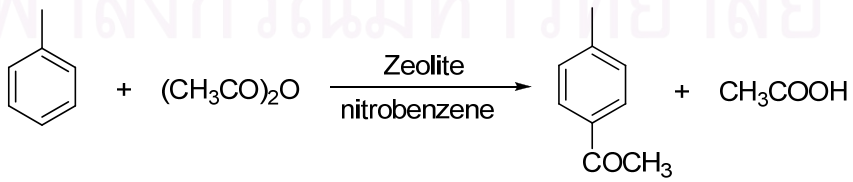
In 2000, Singh *et al.* studied the preparation of aryl ketones using Ac_2O as an acylating agent. $Cu(OTf)_2$ catalyzed the Friedel-Crafts acylation required an excess of Ac_2O. However, there were many drawbacks for this method such as the excess solvent, Ac_2O required and by-product, carboxylic acid, produced [11].



In 2003, Sheemol *et al.* addressed that rare earth cations exchanged zeolite β catalysts were active for the liquid phase acylation of toluene with Ac_2O in nitrobenzene solvent with >95% selectivity towards the *p*-isomer of the product. The order of activity of various rare earth cations exchanged β is as follows:

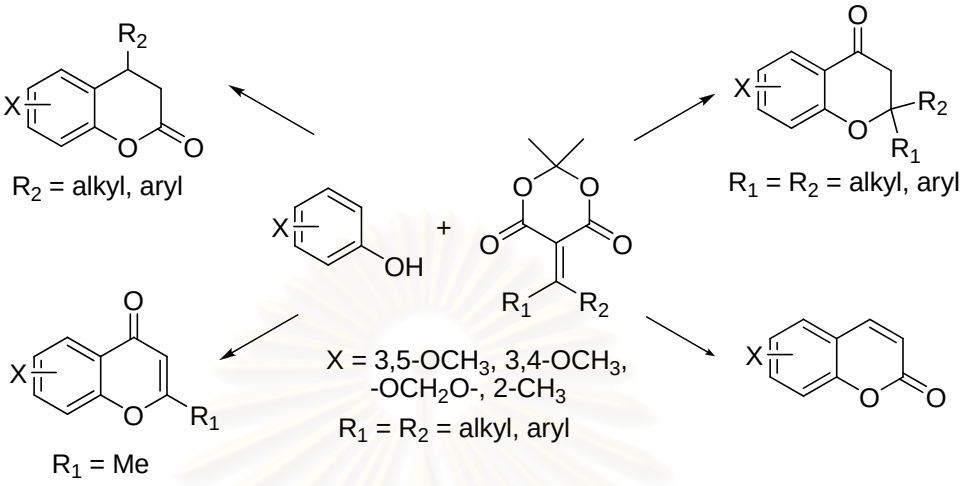
La-β>H-β=Ce-β>Dy-β>Eu-β>Sm-β>Gd-β>Nd-β>Pr-β

It was further shown that acylation of toluene is Brönsted acid catalyzed reaction. Among various solvents studied namely nitrobenzene, *o*-dichlorobenzene, ethylene dichloride, it was observed that nitrobenzene was the most efficient solvent for acylation of toluene with Ac_2O.



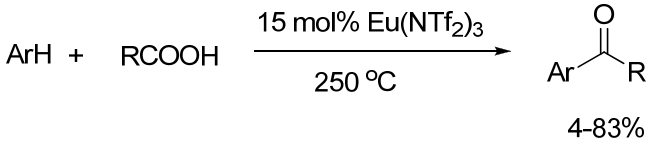
In 2005, Fillion *et al.* investigated $Yb(OTf)_3$ catalyzed intramolecule Friedel-Crafts acylation of 5-alkylidene with Meldrum's acid as acylating agent. Meldrum's acid derivatives are powerful acylating agents in metal triflate catalyzed

intramolecular Friedel-Crafts acylation. This approach was applied to the synthesis of benzocyclic ketones, such as 3,4-dihydrocoumarins, 4-chromanones, coumarins, and chromones [12].

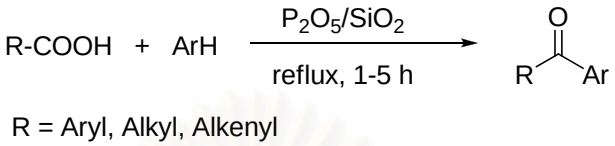


However, the use of acid anhydrides necessarily yields 1 equiv of carboxylic acids as by-products. Methyl esters could be employed in the presence of excess amount of F_3CSO_3H. Meldrum's acids are also used as acylating agents in Lewis acid-catalyzed acylations. However, the most desirable acylating agents are probably carboxylic acids which are common precursors of acid chlorides and anhydrides, because the reaction produces water as the only by-product.

In 2006, Kawamura *et al.* explored dehydrative Friedel-Crafts acylation reaction of aromatic compounds using carboxylic acids as acylating agent. The Friedel-Crafts acylation of *p*-xylene with hexanoic and heptanoic acids was selected as a model reaction. Nevertheless, the reaction required high temperature in the presence of Lewis acid or Brønsted acid. Various metal triflate and *bis*(trifluoromethanesulfonyl)amide showed catalytic activity at high temperature, among which $Eu(NTf_2)_3$ proved to be the most effective and efficiently catalyzed the acylation reaction of alkyl and alkoxybenzenes with aliphatic and aromatic carboxylic acids at 250°C [13].



In 2008, Zarei *et al.* reported the conversion of carboxylic acids to the corresponding aryl ketones in the presence of P_2O_5/SiO_2. The acylation reactions were carried out by heating a stirred mixture of the carboxylic acid, excess aromatic compound and P_2O_5/SiO_2 at reflux. The P_2O_5/SiO_2 was prepared by mixing P_2O_5 and dried silica gel 60, previously heated at 120°C for 24 h [14].



According to the aforementioned results, many efficient methods for Friedel-Crafts acylation with carboxylic acids have been disclosed. Nevertheless, some reactions still suffered from drawbacks such as low yields, long reaction time, drastic and tedious work-up procedures. Therefore, the new methodologies which could solve these problems are still called for.

1.4 Literature reviews of acid halides synthesis from carboxylic acids

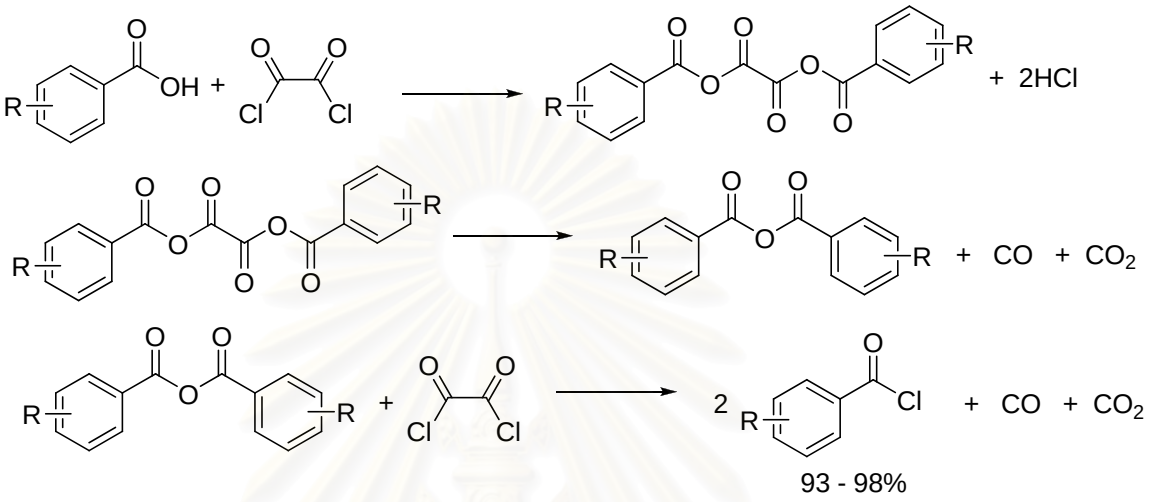
Halide ions are excellent leaving group for Friedel-Crafts acylation; therefore, acid halides are useful intermediates for manipulating aryl ketones. In particular, acid halides are easily prepared and commonly used as an activated form of a carboxylic acid; consequently, various procedures for acid halide synthesis have been developed.

1.4.1 Common reagents

In the early stage, the preparation of acid chlorides could be accomplished by treating with common reagents such as PCl_3 and PCl_5. However, these methods were not successful in the preparation of some acid chlorides for example it could not produce an acid chloride of an aminobenzoic acid since it attacked the amino group. As a result, a variety of other procedures for acid chloride synthesis has been developed.

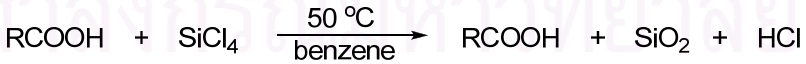
In 1920, Adams *et al.* reported the preparation of acid chlorides and bromides with oxalyl chloride and bromide, respectively. The reactions could convert carboxylic acid to furnish acid halides, whereas *p*-hydroxybenzoic acid and nitro derivatives of benzoic acids could not be transformed into acid chlorides. Certain

nitro-derivatives of benzoic acids reacted very peculiarly with oxalyl chloride; thus *p*-nitrobenzoic, 1,3-dinitrobenzoic, 2,4,6-trinitrobenzoic acids when chlorination with oxalyl chloride, all gave the corresponding double anhydride of 2 moles of aromatic acid and 1 mole of oxalic acid. Even on refluxing for several hours with excess of oxalyl chloride, no decomposition of these double anhydride was taken place [15].



In the same year, Crompton *et al.* studied the use *α,β*-dichlorovinyl ethyl ether to react with carboxylic acids for the production of acid chlorides. The yields were variable because of the side-reaction [16].

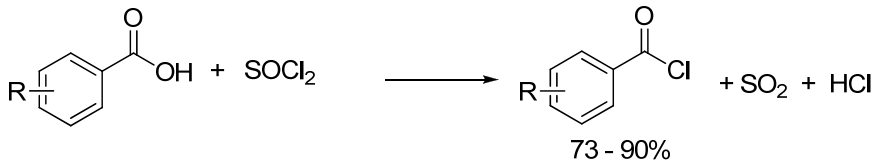
In 1927, Montanna *et al*. introduced the routes of acid chloride preparation from carboxylic acids and silicon tetrachloride with benzene or xylene as solvents. After raising the temperature to about 50°C, the acid chloride was distilled off through a fractionating column.



Employing this methodology, however, dibasic acids, *o*-nitrobenzoic acid and pyruvic acids showed negative results [17].

In 1928, McMaster *et al.* studied the action of thionyl chloride ($SOCl_2$) on carboxylic acids. The transformations of carboxylic acid into acid chlorides were

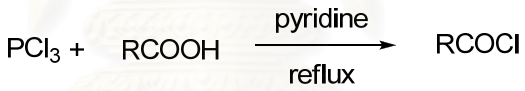
achieved in high yields, whereas using $SOCl_2$ produced harmfully corrosive chemicals and made acidic conditions [18].



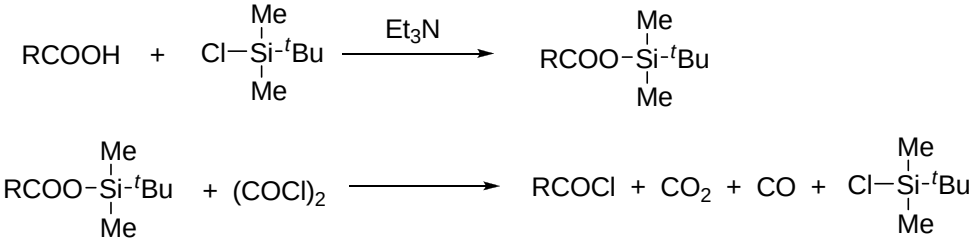
R = *o*-NO_2, *m*-NO_2, *p*-NO_2, *p*-NH_2 and *m*-NH_2

In 1953, Gerrard *et al.* developed the chlorination of carboxylic acid with $SOCl_2$ by addition of pyridine. In the presence of pyridine, another reaction occurred concurrently with some acids, acid chloride reacting with unchanged acid to give anhydride. The reactivity for the conversion of acid chloride depended on the nature of acid [19].

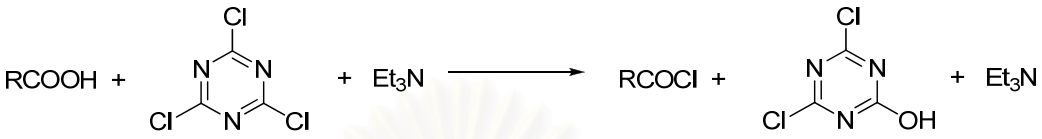
In 1968, Rudolf *et al.* reported the preparation of acid chlorides by heating carboxylic acids with $POCl_3$ in an inert solvent in the presence of at least 1.2 moles of tertiary amine such as pyridine [20].



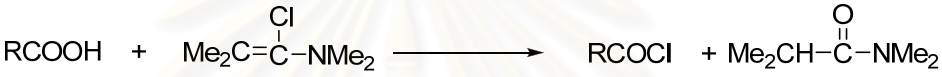
In 1978, Wissner *et al.* prepared acid chloride by the conversion of carboxylic acid to *tert*-butyldimethylsilyl ester (TBMS) and then reacted with oxalyl chloride in the presence of DMF. This method was particularly useful for the preparation of acid chlorides derived from hydroxy substituted carboxylic acids. This reaction was accomplished as a new method for generating acid chlorides under neutral conditions. Furthermore, the side products (*tert*-butyldimethylchlorosilane, CO and CO_2) in this case are volatile compounds which could be removed with ease [21].



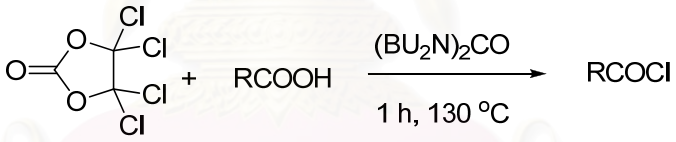
In 1979, Venkataraman *et al.* reported the preparation of acid chlorides by using carboxylic acid with cyanuric chloride. This method was carried out at RT and cyanuric chloride was separated as an insoluble product; the solution containing the acid chloride and any unconverted acid could be used directly for further reactions [22].



Besides, Devos *et al.* addressed the preparation of acid chloride by treated carboxylic acid with tetramethyl-α-chloroenamine at RT under mild conditions [23].



In 1989, Jeannine *et al.* prepared the acid chloride using tetrachloroethylene carbonate and $(Bu_2N)_2CO$ as catalyst at 130°C. Tetrachloroethylene carbonate has its own disadvantage, *i.e.*, the use at high temperature [24].

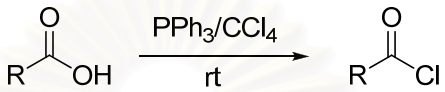


In 1991, Martin *et al.* reported the process for the manufacture of acid chloride comprising of the treatment of carboxylic acid with Cl_2CO in the presence of $HCON(CHMe_2)_2$ [25].

1.4.2 Phosphorus compounds with halogenating agents

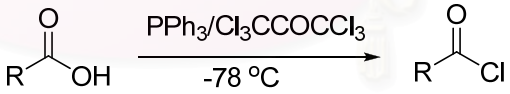
The common reagents such as $SOCl_2$, phosphorus chlorides and oxalyl chloride which are used generally for the preparation of acid chlorides from carboxylic acids cannot be applied to acid-sensitive substrates due to the generation of strong acidic conditions during the reaction. As a result, a variety of other procedures for acid halide synthesis has been developed.

In 1966, Lee first reported the new methodology for synthesis of acid chloride under mild conditions using the reaction of carboxylic acid with PPh_3 and CCl_4. The reaction could be rapidly converted to acid chloride with no generation of any strongly acidic material; therefore, it is suitable for the preparation of acid chloride containing acid sensitive functional groups. This process nonetheless required relatively long time at RT and high temperature was needed for shortening reaction time [26].

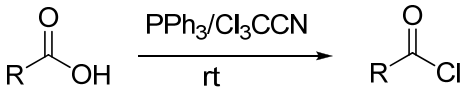


In 1994, Sucheta *et al.* exhibited the convenient method for the conversion of carboxylic acid to the corresponding acid halide by using PPh_3 and *N*-bromo/iodo succinimides [27].

In 1997, Villeneuve *et al.* presented that carboxylic acids could be converted by hexachloroacetone and PPh_3 at -78°C in CH_2Cl_2 to the corresponding acyl chlorides. This method is acid free condition which can be carried out under mild conditions. The side products occurred such as trichloroacetamide which generated from combination of pentachloracetone counteranion of the triarylphosphonium chloride species with a free amine. resulting the low yield of the reaction [28].

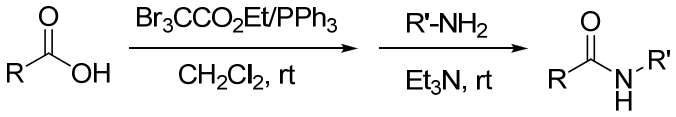


In 1999, Jang *et al.* demonstrated the transformation of carboxylic acids to the corresponding acid chlorides by treatment carboxylic acid with CCl_3CCN and PPh_3 in CH_2Cl_2. This method is a mild reaction which can be carried out under acid free conditions [29].



In 2006, Kang *et al*. developed a method of preparing acid bromides from carboxylic acids with readily available Br_3CCO_2Et and PPh_3 under mild and neutral

conditions. The present process is not only easy to perform but also has other advantages such as neutral reaction conditions and low toxicity of the reagents [30].



1.5 Application of aryl ketones as biological active compounds

Most aryl ketones show a large number of biological activities both in pharmaceutical and agricultural aspects. Some instance compounds are reviewed as presented in Tables 1.1-1.2.

Table 1.1 Some synthesized aryl ketones as biological active compounds

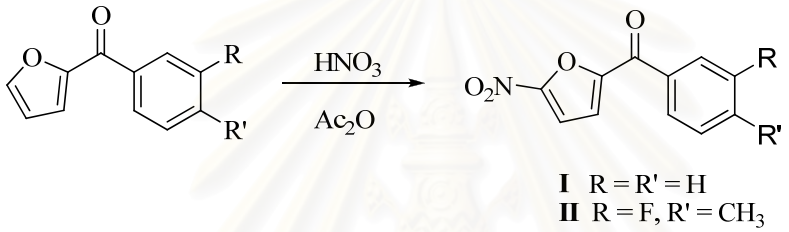
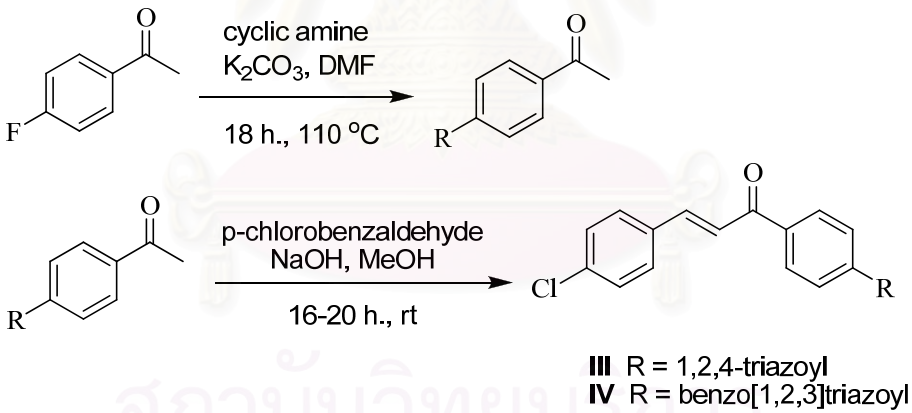
Name	Synthesis	Biological Activity
5-nitro-2-furyl phenyl ketone **(I)** and 3-fluoro-4-methyl phenyl 5-nitro-2-furyl ketone **(II)**		Antifungal [31]
1-(4-(1H-1,2,4-Triazol-1-yl) phenyl)-3-(4-chlorophenyl) prop-2-en-1-one **(III)** and 1-(4-(1H-Benzo[d][1,2,3] triazol-1-yl)phenyl)-3-(4-chlorophenyl) prop-2-en-1-one **(IV)**		Antimalarial [32]

Table 1.1 (cont)

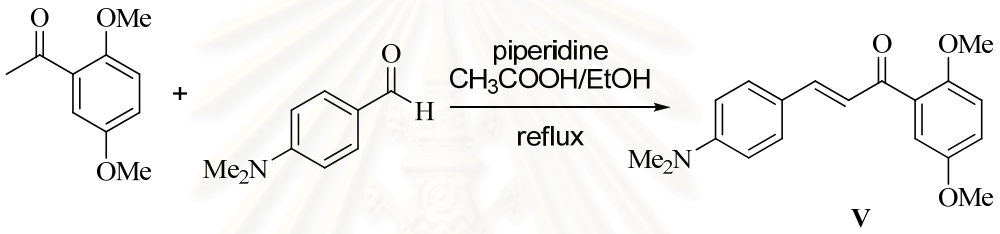
Name	Synthesis	Biological Activity
(*E*)-l-(2,5-dimethoxyhenyl)-3-[4-(dimethylamino)phenyl]-2-methyl-2-propen-l-one) **(V)**	 **V**	Antimitotic [33]

Table 1.2 Some aryl ketones as biological active compounds derived from natural products

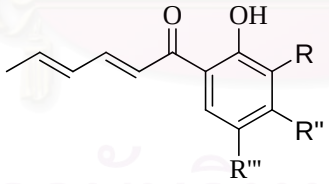
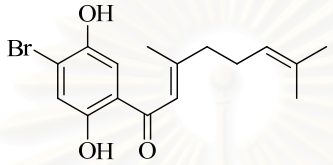
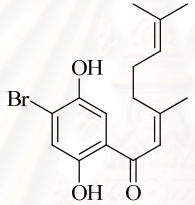
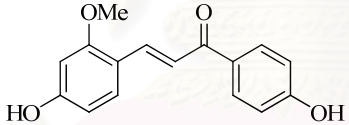
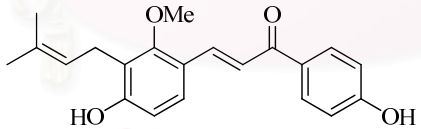
Name	Structure	Source	Biological activities
1-(2´-hydroxy-4´,5´-dimethoxyphenyl)-*E*,*E*-2,4-hexadien-1-one **(VI)**, 1-(2´-hydroxy-4´-methoxy-5´-methylphenyl)-*E*,*E*-2,4-hexadien-1-one **(VII)** and 1-(2´,4´-dihydroxy-5´,3´-dimethylphenyl)-*E*,*E*-2,4-hexadien-1-one **(VIII)**	 **VI** R = H, R' = OCH_3, R" = CHO **VII** R = H, R' = OCH_3, R" = CH_3 **VIII** R = CH_3, R' = OH, R" = CH_3	*Phaeoacremonium* (NRRL32148)	Antifungal [34]

Table 1.2 (cont)

(4-bromo-2,5-dihydroxyphenyl)-*E*-(2,6-dimethylhepta-1,5-dienyl) ketone **(IX)** and (4-bromo-2,5-dihydroxyphenyl) –Z-(2,6dimethylhepta-1,5-dienyl) ketone **(X)**	 **IX**  **X**	*Cymopolia barbata*	Antifeedant properties [35]
echinatin **(XI)** and licochalcone A **(XIII)**	 **XI**  **XII**	Roots of *Glycyrrhizae inflate*	Antileishmanial [36]

As it could be clearly seen, aryl ketones have been widely used both in agricultural and pharmaceutical aspects. Biologically active aryl ketones could be viewed to derive from both synthesis and natural products. In some cases, compounds isolated from natural product resources were in trace amount and not enough for further application. The synthesis becomes thus the indispensable task.

1.6 The objective of this research

The objective of this research is to explore and develop the optimized conditions for the preparation of aryl ketones directly from carboxylic acids *via* Friedel-Crafts acylation.

CHAPTER II

EXPERIMENTAL

2.1 General procedure

The reactants and products were identified by several spectroscopic techniques. Chromatography: Thin layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel (Merck, Kieselgel 60 PF_{254}). Column chromatography was performed on silica gel (Merck, Kieselgel 60G Art 7734, 70-230 mesh; or Art 9385, 230-400 mesh) and aluminium oxide 90 active neutral (70-230 mesh). Spectrometer: The ^{1}H and ^{13}C-NMR spectra were obtained in deuterated chloroform ($CDCl_3$) or dimethylsulfoxide (DMSO-d_6), with Fourier transform nuclear magnetic resonance spectrometer of Varian model Mercury+400 spectrometer which was operated at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei, or Bruker model AC-100F spectrometer which was operated at 100 MHz for ^{1}H. Gas chromatography-mass spectrometric analysis was recorded on Agilent Technologies G1530N instrument (6890N Network GC system-5973 mass selective detector, EI, 70 eV).

2.2 Chemical reagents

All solvents used in this research were purified, except for reagent grades, and dried prior to use by standard methodology. The substrates and reagents for synthesizing the precursors and products employed in this work were purchased from Fluka and Sigma-Aldrich Co., Ltd. and were used without further purification.

2.3 Preparation of substrates

2.3.1 Halogenating agents

Ethyl tribromoacetate [37, 38]

1 mL of concentrated sulfuric acid was cautiously added to the mixture of 20 mmol of trichloroacetic acid or tribromoacetic acid and 25 mmol of ethanol. The mixture in the rounded bottom flask fitted by a condenser was refluxed for 3-6 hours and then poured into 100 mL of water in a separatory funnel. The upper layer of crude ester was removed and washed with 50 mL of water, saturated aqueous $NaHCO_3$ and water, respectively, and dried over Na_2SO_4. The product is colorless oil 4.67 g (72%). IR (neat): 2981, 1750, 1469, 1361, 1233 and 1021 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.44 (3H, t, J = 7.20 Hz, CH_2CH_3) and 4.46 (2H, q, J = 7.20 Hz, CH_2CH_3).

Hexabromoacetone [39]

Anhydride sodium acetate (7.00 g) was mixed with 20 mL of glacial acetic acid in the rounded bottom flask equipped with reflux condenser, thermometer and heater. The mixture was heated to 60 ^{o}C, and 1 mL of acetone was added, followed by the dropwise addition of 7 mL of liquid Br_2 over a 10 min period with stirring. The liquid Br_2 reacted immediately, and the reaction was mildly exothermic such that no external cooling was needed to maintain a temperature of 60-70 ^{o}C. The mixture was then heated to 95 ^{o}C and held there for 6-8 hours, after which it was cooled to room temperature and mixed with cool water to precipitate the desired product as white solid. Recrystallization from hexane to obtain white crystal 5.27 g (73%), m.p. 122-123 ^{o}C. ^{13}C-NMR ($CDCl_3$) δ (ppm): 173.5 and 24.5.

2.3.2 Protecting of pyrrole and indole with *p*-toluenesulfonic acid or methyl iodide

***N*-*p*-Toluenesulfonylpyrrole** [40]

A solution of pyrrole (0.625 g, 0.93 mmol), KOH (1.05 g, 0.02 mmol) and tosyl chloride (1.67 g, 0.88 mmol) in THF (25 mL) was prepared. The solution was refluxed for 4 h, cooled to room temperature, whereupon diethyl ether was added and the reaction mixture transferred to a separatory funnel. The reaction mixture was washed with copious amounts of water followed by a saturated NaCl solution. The organic layer was separated, dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The resulting grey solid was recrystallised from methanol to

yield thedesired product as a fine white powder (1.63 g, 80%); mp 100–102 ^{o}C; ^{1}H-NMR ($CDCl_3$) 2.38 (3H, s, C*H*$_3$), 6.26 (2H, t, *J* 2.2 Hz, Py), 7.14 (2H, t, *J* 2.0 Hz, Py), 7.26 (2H, d, *J* 9.4 Hz, Ar*H*), 7.74 (2H, d, *J* 8.4 Hz, Ar*H*); ^{13}C-NMR ($CDCl_3$) 21.7, 113.6, 120.8, 126.9, 130.1, 136.1, 145.1.

***N*-*p*-Toluenesulfonylindole** [41]

Indole (1.172 g, 10 mmol) was dissolved in THF, and powdered KOH (2.806 g, 50 mmol) was added. The mixture was stirred at room temperature and tosyl chloride (2.100 g, 11 mmol) was added. The reaction mixture was left to stir at room temperature for 19 h. Then the solid was collected by filtration and washed with CH_2Cl_2 (20 mL). The liquid phase was concentrated in vacuo and the yellowish oily residue was recrystallized from MeOH; this gave *N*-*p*-toluenesulfonylindole as white crystals. Yield: 1.80 g (72%); white crystals; m.p. 83–85 °C. ^{1}H NMR ($CDCl_3$): 2.33 (3H, s, C*H*$_3$), 6.65 (1H, dd, *J* = 8.4, 0.9 Hz, Ar*H*), 7.17–7.25 (3H, m, Ar*H* and 2H, Ph*H*), 7.30 (1H, dd, *J* = 8.4, 0.9 Hz, Ar*H*), 7.50–7.55 (1H , m, Ar*H*), 7.56 (1H, d, *J* = 3.6 Hz, Ar*H*), 7.71–7.80 (2H, m, Ph*H*), 7.99 (1H, dd, *J* = 8.4, 0.9 Hz, Ar*H*).

1-methylindole [42]

In small portions, just sufficient to maintain the blue color, 5.0 g of clean, metallic sodium was added with vigorous stirring. After dissolution was complete, a solution of 0.23 g (2 mmol) of indole in 5 mL of anhydrous ether was added slowly and then, after an additional 10 min, a solution of 0.31 g (2 mmol) of methyl iodide in an equal volume of anhydrous ether was added dropwise. Stirring is continued for a further 15 min. The ammonia was allowed to evaporate, 20 mL of water was added, followed by 20 mL of ether. The ether layer was separated, the aqueous phase was extracted with an additional 20 mL of ether, and the combined ether extracts were washed with three 15 mL-portions of water and dried over anhydrous sodium sulfate. The solvent were removed at atmospheric pressure, and the crude oil is purified by distillation under reduced pressure. 1-Methylindole was obtained as colorless oil. In several runs the yield is 20.1 g (75%); colorless oil; ^{1}H NMR ($CDCl_3$): 3.81 (3H, s, *N*-C*H*$_3$), 6.50 (1H, m, Ar*H*), 7.07 (1H, m, Ar*H*), 7.12 (1H, m, Ar*H*) , 7.23 (1H, m, Ar*H*) , 7.33 (1H, m, Ar*H*) , 7.64 (1H, m, Ar*H*).

2.3.3 Synthesis of *trans*-substituted cinnamic acids [43]

3-nitrocinnamic acid

Malonic acid 3.12 g (0.03 mol) and 3-nitrocinnamic acid (0.03 mol) were dissolved in 5.20 mL of anhydrous pyridine and 0.28 mL of piperidine. The mixture was refluxed for 1.5 hour, and then cooled to room temperate and poured into 10.0 g of ice containing 8 mL of conc HCl and 26 mL of water. The white solid was precipitated, filtered and washed with ice-water and recrystallized with 95%EtOH. ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.57 (1H, d, *J* = 16.20 Hz, ArCH=C*H*), 7.60 (1H, t, *J* = 8.40 Hz, Ar*H*), 7.86 (2H, m, Ar*H* and ArC*H*=CH), 8.26 (1H, d, *J* = 7.96 Hz, Ar*H*), 8.40 (1H, s, *J* = 7.96 Hz, Ar*H*)**.**

2.4 General procedure for the synthesis of aryl ketones

Step 1: Triphenylphosphine 2 eq (1.57 g, 6 mmol) in 3 mL of CH_2Cl_2 was added to a mixture of carboxylic acid 1 eq (3 mmol) and selected halogenating agent 2 eq (6 mmol) in 1 mL of CH_2Cl_2 at selected temperature. The mixture was stirred and followed by TLC (hexane: EtOAc, 1:1) until no detection of carboxylic acid presence in the reaction mixture at selected temperature.

Step 2: Selected Lewis acid 4 eq (12 mmol) and selected aromatic compound 1 eq (3 mmol) was added to the above mixture. The reaction was continued stirring and followed by TLC at selected temperature. When the reaction was completed, the mixture was then quenched with ice and extracted with CH_2Cl_2 and $NaHCO_3$. The organic layer was extracted with brine and saturated aqueous $NaHCO_3$, respectively, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The mixture was separated by silica gel column chromatograph eluting with hexane and EtOAc to give the corresponding aryl ketone. The aryl ketones are mostly well known in literature and were identified by comparison of their physical and spectral data.

2.5 Study on the optimum conditions

2.5.1 Effect of halogenating agents

The synthesis of (4-methoxyphenyl)(phenyl)methanone was carried out using the reaction condition described in the general procedure at room temperature (carboxylic acid: benzoic acid, aromatic compound: anisole), by using six different halogenating agents in the same manner: trichloroacetonitrile (Cl_3CCN),

trichloroacetamide (Cl_3CCONH_2), ethyl trichloroacetate (Cl_3CCO_2Et), ethyl tribromoacetate (Br_3CCO_2Et), hexachloroacetone ($Cl_3CCOCCl_3$) and hexabromoacetone ($Br_3CCOCBr_3$).

2.5.2 Effect of amounts of PPh_3 and halogenating agents to carboxylic acid

The synthesis of (4-methoxyphenyl)(phenyl)methanone was carried out using the reaction conditions described in the general procedure at room temperature. Various ratios of carboxylic acid : Cl_3CCN : PPh_3 studied were 1:1:1, 1:1:2, 1:2:1, 1:2:2, 1:2:3, 1:2:4, 1:3:2 and 1:4:2 eq.

2.5.3 Effect of solvent systems

Solvents for the synthesis of (4-methoxyphenyl)(phenyl)methanone according to the general procedure at room temperature (carboxylic acid: benzoic acid, halogenating agent: Cl_3CCN, aromatic compound: anisole) were varied from CH_2Cl_2 to chloroform, acetonitrile, tetrahydrofuran and ethyl acetate.

2.5.4 Effect of Lewis acids

According to the general procedure (carboxylic acid: benzoic acid, halogenating agent: Cl_3CCN, aromatic compound: anisole), Lewis acid was altered from $AlCl_3$ to $FeCl_3$, $SnCl_2$ and $ZnCl_2$.

2.5.5 Effect of amounts of $AlCl_3$, temperature and reaction time in step II

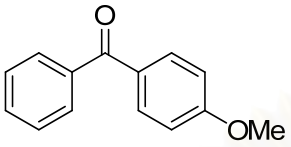
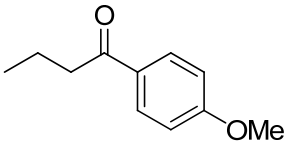
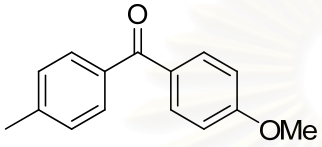
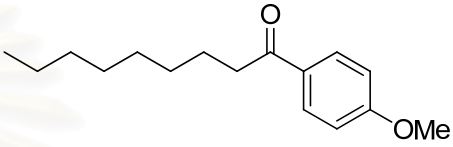
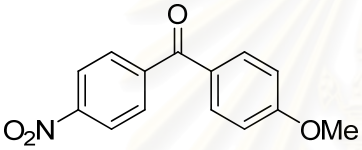
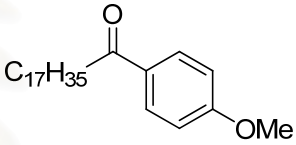
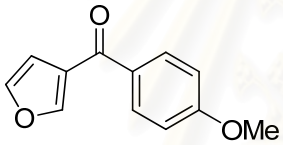
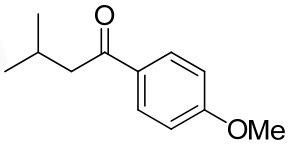
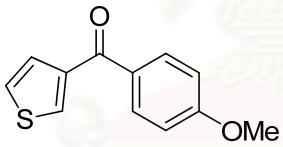
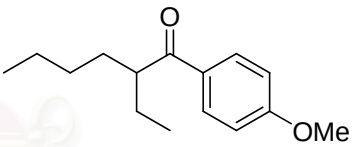
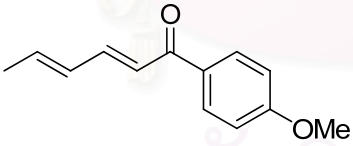
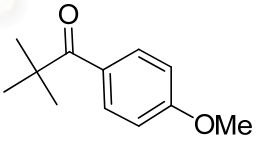
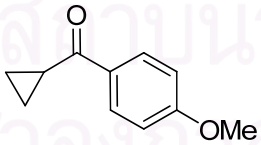
The general synthesis procedure of (4-methoxyphenyl) (phenyl)methanone using trichloro- acetamide, dichloromethane and anisole as halogenated reagent, solvent and aromatic compound, respectively was carried out at different reaction time and temperature: (1-3 hours) and (28-30 and 38-40 °C).

2.6 The screening of substrates

2.6.1 Type of carboxylic acids

The synthesis of aryl ketones was carried out using the reaction conditions described in the general procedure at room temperature. Various carboxylic acids were changed from benzoic acid to 4-nitrobenzoic acid, 4-methylbenzoic acid, furan-3-carboxylic acid, thiophen-3-carboxylic acid, sorbic acid, cyclopropanecarboxylic

acid, butyric acid, nanoic acid, stearic acid, isovaleic acid, 2-ethylhexanoic acid and pivalic acid. The mixture was separated with silica gel column eluting with hexane and EtOAc to give the corresponding aryl ketone.

	RCOR′		RCOR′
C1		**C8**	
C2		**C9**	
C3		**C10**	
C4		**C11**	
C5		**C12**	
C6		**C13**	
C7			

(4-methoxyphenyl)(phenyl)methanone (C1) (94%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.88 (3H, s, ArOC*H*$_3$), 6.96 (2H, d, *J* = 8.77 Hz, Ar*H*), 7.46 (2H, t, *J* = 7.39 Hz, Ar*H*), 7.56 (1H, t, *J* = 7.27 Hz, Ar*H*), 7.75 (2H, d, *J* = 7.58 Hz, Ar*H*), 7.83 (2H, d, *J* = 8.80 Hz, Ar*H*)**.**

(4-methoxyphenyl)(4-methylphenyl)methanone (C2) (93%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.44 (3H, s, ArC*H*$_3$), 3.88 (3H, s, ArOC*H*$_3$), 6.96 (2H, d, *J* = 8.43 Hz, Ar*H*), 7.27 (2H, d, *J* = 8.12 Hz, Ar*H*), 7.67 (2H, d, *J* = 7.45 Hz, Ar*H*), 7.81 (2H, d, *J* = 8.27 Hz, Ar*H*).

(4-methoxyphenyl)(4-nitrophenyl)methanone (C3) (91%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.91 (3H, s, ArOC*H*$_3$), 6.99 (2H, d, *J* = 8.71 Hz, Ar*H*), 7.81 (2H, d, *J* = 8.79 Hz, Ar*H*), 7.88 (2H, d, *J* = 8.69 Hz, Ar*H*), 8.33 (2H, d, *J* = 8.67 Hz, Ar*H*).

furan-3-yl(4-methoxyphenyl)methanone (C4) (90%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.89 (3H, s, ArOC*H*$_3$), 6.89 (1H, s, Ar*H*), 6.98 (2H, d, *J* = 8.70 Hz, Ar*H*), 7.50 (1H, s, Ar*H*), 7.89 (1H, d, *J* = 8.71 Hz, Ar*H*), 7.91 (1H, s, Ar*H*).

thiophen-3-yl(4-methoxyphenyl)methanone (C5) (96%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.89 (3H, s, ArOC*H*$_3$), 6.98 (2H, d, *J* = 8.74 Hz, Ar*H*), 7.38 (1H, m, Ar*H*), 7.56 (1H, d, *J* = 4.91 Hz, Ar*H*), 7.87 (1H, s, Ar*H*), 7.88 (2H, d, *J* = 8.86 Hz, Ar*H*).

(2*E*,4*E*)-1-(4-methoxyphenyl)hexa-2,4-dien-1-one (C6) (79%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.89 (3H, d, *J* = 6.02 Hz, CHC*H*$_3$), 3.87 (3H, s, ArOC*H*$_3$), 6.27 (2H, m, H_3CC*H*=C*H*CH), 6.88 (2H, d, *J* = 15.03 Hz, CH=C*H*-CH), 6.95 (2H, d, *J* = 8.83 Hz, Ar*H*), 6.88 (2H, d, *J* = 15.03 Hz, CH=C*H*-C=O), 7.39 (1H, dd, *J* = 14.94, 10.32 Hz, CH-C*H*=CH), 7.95 (2H, d, *J* = 8.90 Hz, Ar*H*).

cyclopropyl(4-methoxyphenyl)methanone (C7) (90%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.99 (2H, m, CH_2C*H*$_2$CH), 1.20 (2H, m, CH_2C*H*$_2$CH), 2.63 (1H, m, $(CH_2)_2$C*H*-C=O), 3.87 (3H, s, ArOC*H*$_3$), 6.95 (2H, d, *J* = 8.87 Hz, Ar*H*), 8.01 (2H, d, *J* = 8.87 Hz, Ar*H*).

1-(4-methoxyphenyl)butan-1-one (C8) (93%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.99 (3H, t, *J* = 7.40 Hz, CH_2C*H*$_3$), 1.75 (2H, q, *J* = 7.37 Hz, CH_2C*H*$_2$$CH_3$), 2.89 (2H, t, *J* = 7.33 Hz, CH_2C*H*$_2$C=O), 3.86 (3H, s, ArOC*H*$_3$), 6.93 (2H, d, *J* = 8.73 Hz, Ar*H*), 7.94 (2H, d, *J* = 8.72 Hz, Ar*H*).

1-(4-methoxyphenyl)nonan-1-one (C9) (89%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.87 (3H, t, *J* = 6.94 Hz, CH_2C*H*$_3$), 1.27 (10H, m, CH_2(C*H*$_2$)$_5$$CH_3$), 1.71 (2H, t, *J* = 7.00 Hz, CH_2C*H*$_2$$C_6H_{13}$), 2.90 (2H, t, *J* = 7.34 Hz, O=CC*H*$_2$$CH_2$), 3.87 (3H, s, ArOC*H*$_3$), 6.93 (2H, d, *J* = 8.88 Hz, Ar*H*), 7.94 (2H, d, *J* = 8.87 Hz, Ar*H*).

1-(4-methoxyphenyl)octadecan-1-one (C10) (85%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.87 (3H, t, *J* = 6.94 Hz, CH_2C*H*$_3$), 1.27 (28H, m, CH_2(C*H*$_2$)$_{14}$$CH_3$), 1.71 (2H,

t, *J* = 7.00 Hz, $CH_2CH_2C_6H_{13}$), 2.90 (2H, t, *J* = 7.34 Hz, O=CCH_2CH_2), 3.87 (3H, s, ArOCH_3), 6.93 (2H, d, *J* = 8.88 Hz, Ar*H*), 7.94 (2H, d, *J* = 8.87 Hz, Ar*H*).

1-(4-methoxyphenyl)-3-methylbutan-1-one (C11) (87%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.98 (6H, d, *J* = 6.66 Hz, CHCH_3), 2.27 (1H, m, $CH_2CH(CH_3)_2$), 2.77 (2H, d, *J* = 6.92 Hz, O=CCH_2CH), 3.86 (3H, s, ArOCH_3), 6.93 (2H, d, *J* = 8.88 Hz, Ar*H*), 7.93 (2H, d, *J* = 8.91 Hz, Ar*H*).

2-ethyl-1-(4-methoxyphenyl)hexan-1-one (C12) (89%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.83 (3H, d, *J* = 6.93 Hz, CHCH_3), 1.25 (4H, m, $CH_2(CH_2)_2CH_3$), 1.51 (3H, m, $CHCH_2CH_3$), 1.74 (2H, m, $CHCH_2CH_3$), 3.30 (1H, d, *J* = 7.38 Hz, O=CC*H*$(CH_2)_2$), 3.87 (3H, s, ArOCH_3), 6.94 (2H, d, *J* = 8.68 Hz, Ar*H*), 7.95 (2H, d, *J* = 8.71 Hz, Ar*H*).

1-(4-methoxyphenyl)-2,2-dimethylpropan-1-one (C13) (13%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.26 (9H, s, $C(CH_3)_3$), 3.79 (3H, s, ArOCH_3), 6.85 (2H, d, *J* = 7.90 Hz, Ar*H*), 7.31 (2H, d, *J* = 7.88 Hz, Ar*H*).

2.6.2 Type of aromatic compounds

The synthesis of aryl ketones was carried out using the reaction conditions described in the general procedure at room temperature. The aromatic compounds were varied from anisole to 1,3-dimethoxybenzene, toluene, *p*-xylene, *o*-xylene, mesitylene, benzene, chlorobenzene, naphthalene, *N*-tosyl indole and *N*-tosyl pyrrole. The mixture was separated with silica gel column eluting with hexane and ethyl acetate to give the corresponding aryl ketone.

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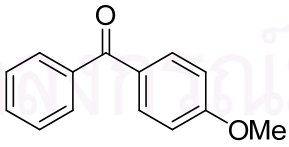
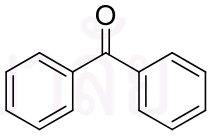
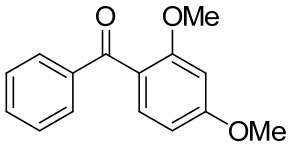
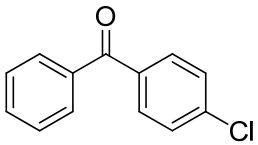
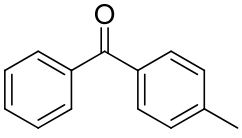
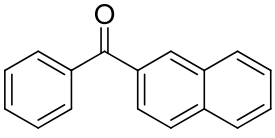
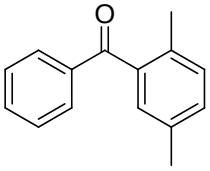
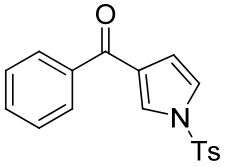
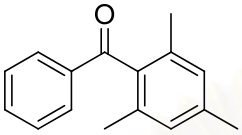
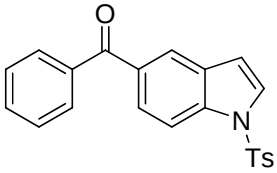
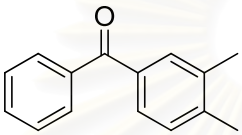
A1 = C1		**A7**	
A2		**A8**	
A3		**A9**	

	RCOR′		RCOR′
A4		**A10**	
A5		**A11**	
A6			

(2,4-dimethoxyphenyl)(phenyl)methanone (A2) (93%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.69 (3H, s, ArOC*H*$_3$), 3.86 (3H, s, ArOC*H*$_3$), 7.22 (2H, d, *J* = 7.80 Hz, Ar*H*), 7.47 (2H, t, *J* = 7.68 Hz, Ar*H*), 7.56 (2H, q, *J* = 7.37 Hz, Ar*H*), 7.62 (1H, s, Ar*H*), 7.79 (2H, d, *J* = 7.09 Hz, Ar*H*).

(4-methylphenyl)(phenyl)methanone (A3) (81%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.44 (3H, s, ArC*H*$_3$), 7.28 (2H, t, *J* = 7.90 Hz, Ar*H*), 7.47 (1H, t, *J* = 7.28 Hz, Ar*H*), 7.58 (2H, t, *J* = 7.40 Hz, Ar*H*), 7.72 (2H, d, *J* = 8.15 Hz, Ar*H*), 7.78 (2H, d, *J* = 6.97 Hz, Ar*H*).

(2,5-dimethylphenyl)(phenyl)methanone (A4) (88%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.33 (3H, s, ArC*H*$_3$), 2.38 (3H, s, ArC*H*$_3$), 7.05 (1H, d, *J* = 7.74 Hz, Ar*H*), 7.11 (1H, s, Ar*H*), 7.33 (1H, d, *J* = 7.74 Hz, Ar*H*), 7.45 (2H, m, Ar*H*), 7.57 (1H, m, Ar*H*) , 7.82 (2H, m, Ar*H*).

(2,4,6-dimethylphenyl)(phenyl)methanone (A5) (89%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.08 (6H, s, ArC*H*$_3$), 2.22 (3H, s, ArC*H*$_3$), 6.90 (2H, s, Ar*H*), 7.42 (2H, t, *J* = 7.28 Hz, Ar*H*), 7.55 (1H, t, *J* = 7.40 Hz, Ar*H*), 7.80 (2H, d, *J* = 8.15 Hz, Ar*H*).

(3,4-dimethylphenyl)(phenyl)methanone (A6) (90%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.32 (3H, s, ArC*H*$_3$), 2.34 (3H, s, ArC*H*$_3$), 7.22 (2H, d, *J* = 7.80 Hz, Ar*H*), 7.47 (2H, t, *J* = 7.68 Hz, Ar*H*), 7.56 (2H, q, *J* = 7.37 Hz, Ar*H*), 7.62 (1H, s, Ar*H*), 7.79 (2H, d, *J* = 7.09 Hz, Ar*H*).

(phenyl)(phenyl)methanone (A7) (76%)**;** ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.42 (2H, t, *J* = 7.02 Hz, Ar*H*), 7.53 (2H, t, *J* = 7.01 Hz, Ar*H*), 7.76 (4H, d, *J* = 7.04 Hz, Ar*H*).

(4-chlorophenyl)(phenyl)methanone (A8) (5%)**;** ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.36 (s, 3H, Ar*H*), 7.20–7.22 (d, 2H, *J*=7.8 Hz, Ar*H*), 7.36–7.39 (d, 2H, *J*=8.6 Hz, Ar*H*), 7.60–7.67 (m, 4H, Ar*H*)

naphthalen-2-yl(phenyl)methanone (A9) (89%) ; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.56 (7H, m, Ar*H*), 7.87 (2H, d, *J* = 7.01 Hz, Ar*H*), 7.92 (1H, d, *J* = 7.56 Hz, Ar*H*), 8.10 (1H, d, *J* = 8.10 Hz, Ar*H*), 8..10 (1H, d, *J* = 8.21 Hz, Ar*H*).

phenyl(1-tosyl-1*H*-pyrrol-3-yl)methanone (A10) (88%); ^{1}H-NMR ($CDCl_3$) δ (ppm): d 2.42 (3H, s, CH_3), 6.79 (1H, dd, *J*=1.5, 3.0 Hz, Ar*H*), 7.23 (1H, dd, *J*=2.3, 3.2 Hz, Ph*H*), 7.28 (2H, d, *J*=8.1 Hz, Ar*H*), 7.39-7.56 (3H, m, Ar*H*), 7.71 (1H, t, *J*=1.7 Hz, Ar*H*), 7.75-7.82 (4H, m, Ar*H*)

phenyl(1-tosyl-1*H*-indol-5-yl)methanone (A11) (73%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.36 (3H, s, CH_3), 7.26 (2H, d, *J* = 7.86 Hz, Ph*H*), 7.41 Hz (2H, m, Ar*H*), 7.54 (2H, m, Ar*H*), 7.54 (2H , m, Ar*H*), 7.64 (1H, m, Ar*H*), 7.80 (2H, d, *J* = 8.38 Ar*H*), 7.86 (2H, d, *J* = 7.39, Ph*H*), 7.98 (1H, s, Ar*H*), 8.02 (1H, s, Ar*H*), 8.31 (1H, d, *J* = *6.99*).

2.7 Applications of the developed procedure for the synthesis of biologically active ketones

The synthesis of biologically active ketones was carried out using the reaction conditions described in the general procedure at room temperature. (*E*)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one could be synthesized using *trans*-cinnamic acid as carboxylic acid and anisole as aromatic. 3-Nitrocinnamic acid and 1,3,5-trimethoxybenzene were selected for synthesis of (*E*)-3-phenyl-1-(2, 4, 6-trimethoxyphenyl)prop-2-en-1-one. The synthesis of chalcone was carried out using the reaction condition described in the general procedure but the 2nd step was modified by using excess benzene (3 mL) under reflux.

(*E*)-chalcone (63%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.98-8.10 (2H, m), 7.84 (1H, d, *J* = 15.6 Hz, ArC*H*=CH), 7.36-7.70 (9H, m).

(*E*)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (88%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.89 (3H, s, ArOCH_3), 6.99 (2H, d, *J* = 8.89 Hz, Ar*H*), 7.41 (3H, m,

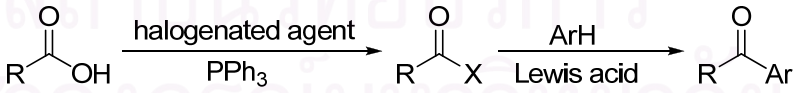
Ar*H*), 7.55 (1H, d, *J* = 15.66 Hz, ArCH=C*H*), 7.64 (2H, m, Ar*H*), 7.80 (1H, d, *J* = 15.66 Hz, ArC*H*=CH), 8.05 (2H, d, *J* = 8.88 Hz, Ar*H*).

(*E*)-3-phenyl-1-(2, 4, 6-trimethoxyphenyl)prop-2-en-1-one (53%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.79 (6H, s, ArOCH_3), 3.87 (3H, s, ArOCH_3), 6.18(2H, s, ArH), 7.06 (1H, d, *J*=16.00 Hz, ArCH=C*H*), 7.43 (1H, d, *J* = 16.00 Hz, ArC*H*=CH), 7.56 (1H, dd, *J* = 7.9, Ar*H*), 7.84 (1H, *J* = 7.7 Hz, Ar*H*), 8.20 (1H, d, *J* = 7.9, Ar*H*), 8.35 (1H, s, Ar*H*).

CHAPTER III

RESULTS AND DISCUSSION

The main purpose of this research is to develop a one-pot protocol to prepare aryl ketones directly from carboxylic acid *via* Friedel-Crafts acylation. This developed procedure is easily manipulated under mild conditions by treating aromatic compounds with acid halides *in situ* generated from the combination of halogenating agent and PPh_3. According to previous literatures, the reactions utilizing carboxylic acids as acylating agents normally required acid catalysts such as zeolite [44], clay [45], heteropoly acids and their salts [46] or Lewis acid [47]. These reactions, however, were invariably carried out under severe conditions and the catalytic efficiency and a limited applicable substrate range. Up till now, it was not withstanding that there was no report of the direct methodology for one-pot synthesis of aryl ketones from acid halide generated from carboxylic acid, halogenating agent and PPh_3. In fact, the reaction is composed of two steps. The first step is the conversion of carboxylic acids to acid halides, while the second step is Friedel-Craft acylation between aromatic compounds and acylating agent in the presence of common Lewis acids such as $SnCl_2$, $AlCl_3$, $FeCl_3$, *etc.* The general equation can be simplified as shown below.



3.1 Condition optimizations

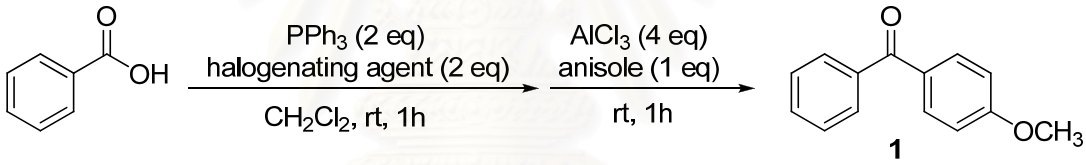
From previous reports for the preparation of acid halide, it has been reported that the combination of PPh_3 and halogenating agents such as Cl_3CCN, $Cl_3CCOCCl_3$, $Br_3CCOCBr_3$ and Br_3CCO_2Et could be successfully used for the conversion of carboxylic acids to acid halides in excellent yields [48-50].

In this research, various factors were carefully scrutinized to optimize the conditions for the preparation of aryl ketone. The typical procedure involves the reaction of benzoic acid with certain halogenating agents to form an acid halide intermediate, which was consequently trapped by a selected aromatic compound (for example, anisole) by Friedel-Craft acylation to furnish the desired product. Various parameters studied included types of halogenating agent, ratio of PPh_3 to halogenating agent, solvent system, Lewis acid, temperature and reaction time. Moreover, under the optimized conditions, this protocol was extended to apply for the synthesis of potential bioactive compounds.

3.1.1 Effect of halogenating agents

The reactions of benzoic acid with various halogenating agents were screened to quest for optimized conditions. The results are presented in Table 3.1.

Table 3.1 Effects of halogenating agents on the formation of (4-methoxyphenyl)(phenyl)methanone (**1**).



Entry	Halogenating agents	% Isolated yield
1	None	Trace
2	Cl_3CCN	94
3	Cl_3CCONH_2	81, 89[a]
4	Cl_3CCO_2Et	88
5	$Cl_3CCOCCl_3$	73, 80[b]
6	Br_3CCO_2Et	94, 92[c]
7	$Br_3CCOCBr_3$	54[b]

[a] The reaction was carried out under reflux in step I.

[b] One equiv of halogenating agent was used.

[c] The reaction was carried out for 15 min both in steps I and II.

The halogenating agents employed in entries 2-5 are commercially available whereas those in entries 6 and 7 were derived from the synthesis.[37-39]

The synthesis of Br_3CCO_2Et (entry 6) were achieved by esterification of the corresponding carboxylic acid, EtOH and conc H_2SO_4 as a catalyst. The yield of the desired reagent was moderate (69-75%). The IR spectrum of Br_3CCO_2Et exhibited the ester carbonyl absorption band at 1762 cm^{-1}. The presence of alkyl and C-O bond were inferred from the presence of bands at 2981 and 1240 cm^{-1}. The ^{1}H-NMR spectrum also clearly confirmed the identity of this compound: three protons at δ_H 1.38 and two protons at δ_H 4.39 of an ethyl group.

The synthesis of $Br_3CCOCBr_3$ (entry 7) was achieved by the bromination of acetone in AcOH in the presence of NaOAc as previously described. The yield of the desired reagent was moderate (70-80%). The ^{13}C-NMR spectrum displays a carbonyl carbon at δ_C 173.5 and the other peak of the carbon bearing bromine atoms at δ_C 24.5.

The ultimate molecule **1** was confirmed its identity by ^{1}H-NMR spectrum (Fig 3.1) which exhibited the singlet peak at δ_H 3.85 corresponding to the methoxy protons. Two doublet signals (2H each) at δ_H 6.95 and 7.83 (J = 8.78 Hz) represented the protons *ortho* to the methoxy group and the carbonyl group, respectively. Five protons at δ_H 7.45–7.78 were ascribed for aromatic protons.

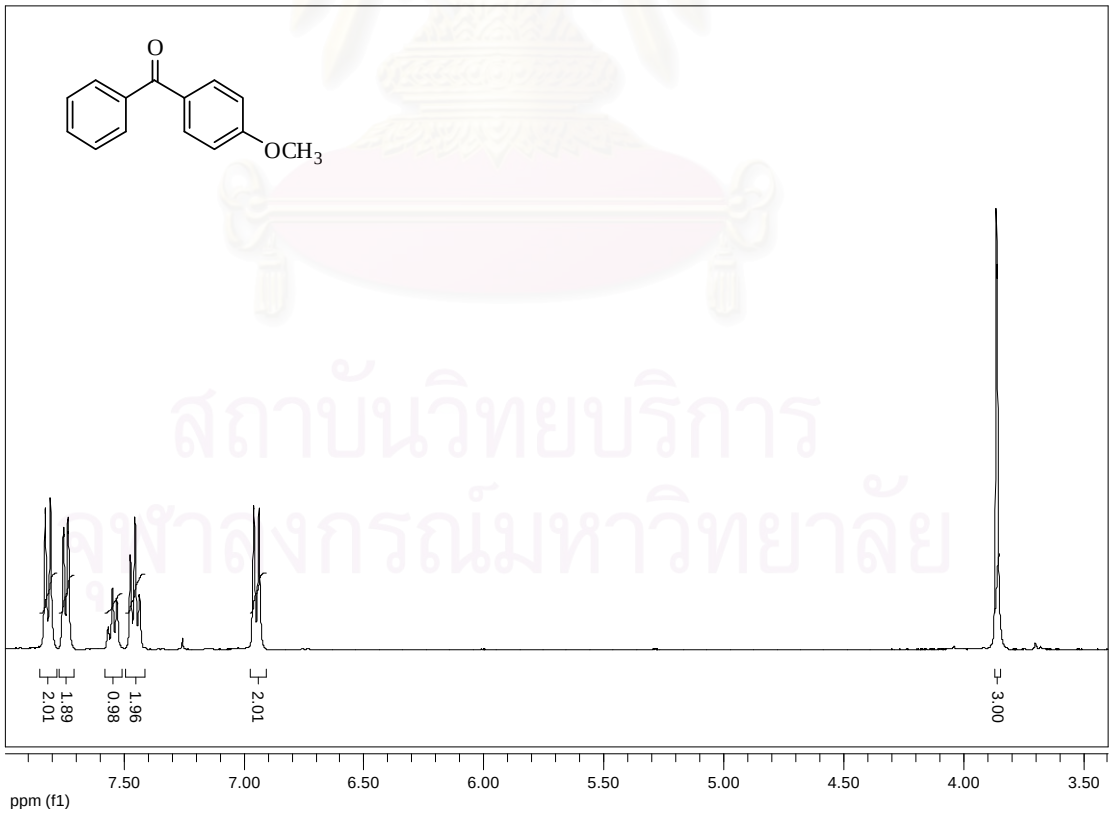


Figure 3.1 The ^{1}H-NMR spectrum of (4-methoxyphenyl) (phenyl)methanone (**1**)

Generally in Friedel-Crafts acylation, there were two main possible isomers produced: *o*- and *p*-isomers. Nonetheless, under this reaction condition, **1** was detected as the sole product from the reaction. No trace of the the *ortho* isomer was visualized.

Considering the effect of halogenating agents on this one-pot synthesis, when the reaction was carried out in the absence of halogenating agent (entry 1), the desired product was obtained only in trace amount. This was clearly demonstrated that the halogenating agent was crucial for this reaction. The efficiency of halogenating agent depended on type of substituents and halides on halogenating agents. For example, the use of Br_3CCO_2Et (entry 6) gave higher yield of the desired product than that of Cl_3CCO_2Et (entry 4). Interestingly, only short reaction time was required to complete the reaction for Br_3CCO_2Et (entry 6c). This was perhaps due to the fact that an acid bromide was better formed and the bromide ion was a better leaving group and of stronger nucleophile than chloride ion [51]. The chlorination of a carboxylic acid using Cl_3CCN/PPh_3 smoothly proceeded at room temperate while Cl_3CCONH_3/PPh_3 required reflux temperature. As -CN and $-CO_2Et$ substituted on a trichloromethyl group were more affinity electron-withdrawing group than that of $–CONH_2$, they thus exhibited more reactive than Cl_3CCONH_2 for converting benzoic acid to benzoyl chloride under the same condition. Perhaloacetones, $Br_3CCOCBr_3$ and $Cl_3CCOCCl_3$ (entries 5b and 7b), did not give good yield of the target molecule probably notwithstanding that $-COCX_3$ (X = Cl and Br) was good electron-withdrawing group. This problem may be caused from the perhaloacetones reacting with Lewis acid and thus not appropriate for further reaction to take place [28]. To prove this observation, the amount of $Cl_3CCOCCl_3$ was reduced to 1 equiv. Benzoic acid was still converted to benzoyl chloride in a quantitative manner and the final product was obtained in 80% yield (entry 5b).

The efficiency of halogenating agents for one-pot synthesis of aryl ketone could be arranged in sequence as shown below.

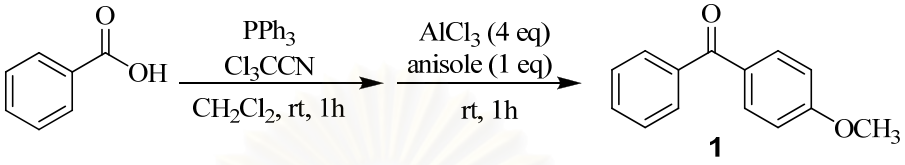
$$Br_3CCO_2Et \sim Cl_3CCN \sim Cl_3CCO_2Et > Cl_3CCONH_2 > Cl_3CCOCCl_3 > Br_3CCOCBr_3 > \text{none}$$

From the above outcome, Cl_3CCN was considered as the most proper halogenating agent for further investigation. This was judged from the yield of the target molecule, the reactivity of the reagent and the ease of work-up procedure.

3.1.2 Effect of the ratio of PPh_3 to Cl_3CCN

The reaction of benzoic acid with various ratios of PPh_3 to Cl_3CCN was tried to quest for the optimized conditions. The results are described in Table 3.2.

Table 3.2 Effect of the ratio of PPh_3 to Cl_3CCN on the formation of (4-methoxy phenyl)(phenyl)methanone (**1**)



Entry	Benzoic acid : Cl_3CCN : PPh_3	%Yield[a]
1	1 : 1 : 1	46
2	1 : 2 : 1	67
3	1 : 1 : 2	92
4	1 : 2 : 2	quant
5	1 : 2 : 3	94
6	1 : 2 : 4	31
7	1 : 3 : 2	quant
8	1 : 4 : 2	quant

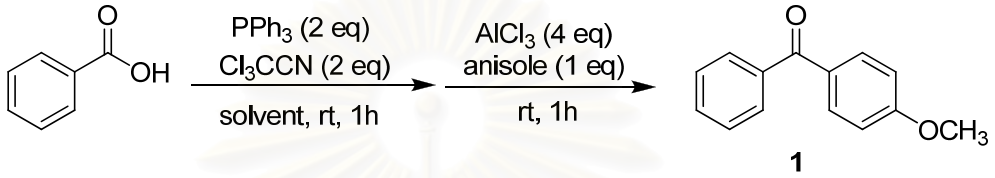
[a] The yield was quantified by ^{1}H-NMR using toluene as an internal standard.

From Table 3.2, the conditions for the one-pot synthesis of **1** in the presence of Cl_3CCN were optimized. The reaction in the presence of 1:1:1 and 1:2:1 ratios afforded the desired product in moderate yield. When the reactions were carried out using higher ratios of Cl_3CCN, the target aryl ketone could be achieved in good yields (entries 3-5, 7-8). On the other hand, using more PPh_3 rendered the efficiency of the reaction (entry 6). This was probably because $AlCl_3$ coordinated with the excess amount of PPh_3, hence deactivating the acidity of $AlCl_3$. The ratio of benzoic acid : Cl_3CCN : PPh_3 (1:2:2) was thus applied for further experiments.

3.1.3 Effect of solvent systems

Solvent was another important factor for the synthesis of aryl ketones. In order to explore on the effect of solvent system, various solvents that could dissolve both carboxylic acid and reagents homogeneously such as CH_2Cl_2, $CHCl_3$, CH_3CN, EtOAc and THF were selected. The results are demonstrated in Table 3.3.

Table 3.3 Effects of solvent on the formation of (4-methoxyphenyl)(phenyl) methanone (**1**)



1

Entry	Solvents	%Yield[a]
1	CH_2Cl_2	quant
2	$CHCl_3$	96
3	CH_3CN	67
4	EtOAc	31
5	THF	57

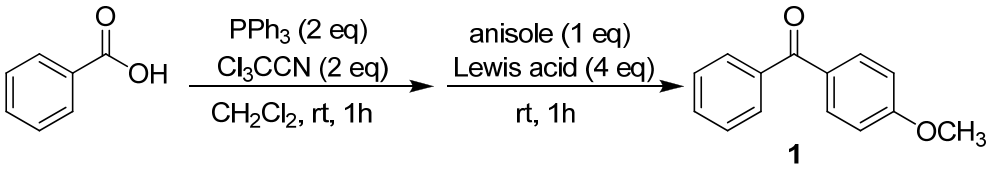
[a] The yield was quantified by ^{1}H-NMR using toluene as an internal standard.

As shown in Table 3.3, the one-pot synthesis of **1** was fruitfully performed in CH_2Cl_2 and $CHCl_3$ (entries 1 and 2). Especially, the reaction using CH_2Cl_2 as solvent gave quantitative yield of the desired product within 1 h. Other solvents: CH_3CN, EtOAc and THF gave **1** in low to moderate yields (entries 3-5). From the above results, the reaction of benzoic acid (1 equiv), Cl_3CCN (2 equiv) and PPh_3 (2 equiv) in CH_2Cl_2 at RT for 1 h was applied as the optimized conditions for step I.

3.1.4 Effect of Lewis acids

Under optimized conditions for step I, various Lewis acids were treated with anisole for Friedel-Crafts acylation. In this study, four common Lewis acids including $AlCl_3$, $FeCl_3$, $SnCl_2$, and $ZnCl_2$ were investigated. The results are demonstrated in Table 3.4.

Table 3.4 Effects of Lewis acids on the formation of (4-methoxyphenyl)(phenyl) methanone (**1**)



1

Entry	**Lewis acids**	**%Yield[a]**
1	$AlCl_3$	quant
2	$FeCl_3$	trace
3	$SnCl_2$	trace
4	$ZnCl_2$	trace

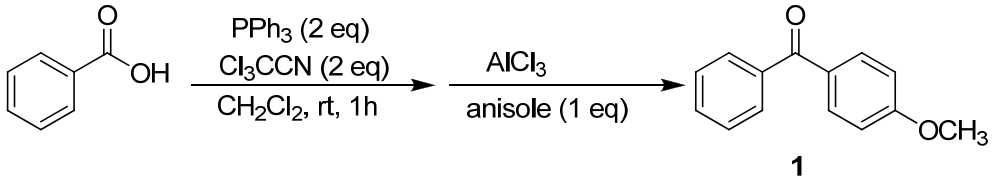
[a] The yield was quantified by ^{1}H-NMR using toluene as an internal standard.

The reactions were not proceeded when the following Lewis acids: $FeCl_3$, $SnCl_2$ and $ZnCl_2$ were employed (entries 2-4) under standard conditions, while using $AlCl_3$ as Lewis acid could activate this reaction to give the corresponding **1** in quantitative yield (entry 1). This was possibly due to the fact that $AlCl_3$ was stronger Lewis acid than other selected Lewis acids. Therefore, $AlCl_3$ was a suitable Lewis acid for further examination.

3.1.5 Effect of the amounts of $AlCl_3$, temperature and reaction time in step II

The reaction of benzoic acid with various amounts of $AlCl_3$, temperature and reaction time in step II was examined. The results are displayed in Table 3.5.

Table 3.5 Effects of the amounts of $AlCl_3$, temperature and reaction time in step II



1

Entry	$AlCl_3$ (equiv)	step II		% Isolated yield
		Temperature (°C)	Reaction time (h)	
1	1	Reflux	3	6
2	2	Reflux	3	16
3	3	Reflux	2	82
4	3	RT (28-30 °C)	2	89
5	4	RT (28-30 °C)	1	92

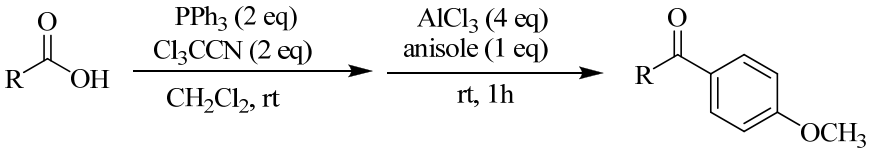
The amount of $AlCl_3$ profoundly affected the reaction yield. When the amount of $AlCl_3$ increased, %yield of **1** was significantly increased (entries 3-5). Using the amount of $AlCl_3$ less than 3 equiv, the reaction provided the product **1** in low yield (entries 1 and 2). On the other hand, using 3 equiv of $AlCl_3$ under reflux and RT gave the desired product in 82 and 89 %yield, respectively (entries 3 and 4). Under this optimal condition, it could be confirmed that Friedel-Crafts acylation of activated aromatics could be taken place using $AlCl_3$ as Lewis acid [51]. In addition, the amount of $AlCl_3$ more than 3 equiv furnished an excellent yield even at RT and short reaction time (entry 5). This was probably because the kinetic of Friedel-Crafts acylation using $AlCl_3$ depended on [RCOCl-$AlCl_3$]; thus upon increasing of $AlCl_3$, the reaction rate was increased [52].

3.2 The screening of substrates

3.2.1 Type of carboxylic acids

In order to explore the scope and limitations of this methodology, the treatment of various carboxylic acids (1 equiv) with anisole (1 equiv) in the presence of $AlCl_3$ (4 equiv) in CH_2Cl_2 at RT was carried out as summarized in Table 3.6.

Table 3.6 Synthesis of aryl ketones from various carboxylic acids under the optimal conditions



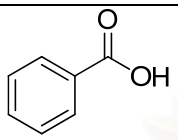
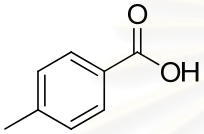
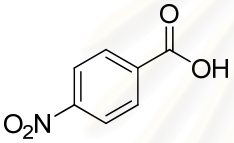
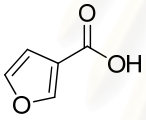
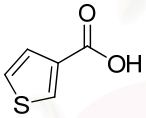
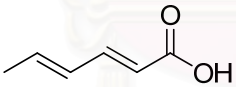
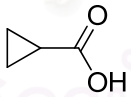
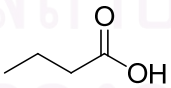
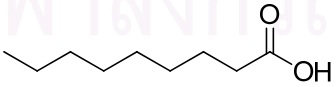
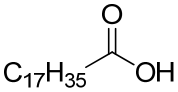
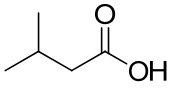
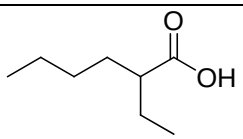
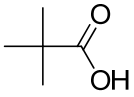
Entry	RCOOH	Reaction time in step I (h)	% Isolated yield
1		1	94
2		2	93
3		2	91
4		2	90
5		2	96
6		4	79
7		1	90
8		4	93
9		4	89
10		4	85
11		4	87

Table 3.6 (cont)

Entry	RCOOH	Reaction time in step I (h)	% Isolated yield
12		4	89
13		4	10

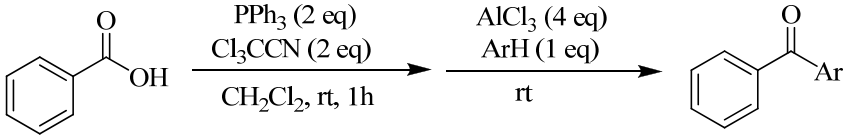
[a] The reaction was carried out under reflux temperature in step I.

Under this particular condition, using aromatic and substituted aromatic carboxylic acids as substrates could furnish the corresponding aryl ketones in excellent yields (entries 1-3). The substituent at *para* position of benzoic acid displayed the electronic effect on the outcome of the reaction. Heterocyclic aromatic compounds also underwent a clean reaction to provide the corresponding heterocyclic aromatic ketones in excellent yield (entries 4 and 5). Similarly, the preparation of unsaturated aryl ketones could be achieved (entry 6). Due to cyclopropanecarboxylic acid was not cleaved and gave excellent yield of the target molecule (entry 7), this could confirm that the reaction mechanism was not taken place *via* a radical pathway. Primary aliphatic carboxylic acids could completely be converted to aryl ketones in excellent yields (entries 8-11). In a similar fashion, the aryl ketone from secondary carboxylic acid could be attained in excellent yield (entry 12). Nonetheless, tertiary carboxylic acid could be transformed into its corresponding aryl ketone in only poor yield (entry 13). Steric hindrance might be the main cause.

3.2.2 Type of aromatic compounds

Under this optimized condition, various aromatic compounds (1 equiv) were treated with $AlCl_3$ (4 equiv) in CH_2Cl_2 to investigate the limitation and generality of this developed method. The results are summarized in Table 3.7.

Table 3.7 Synthesis of various aryl ketones from the corresponding aromatic compounds



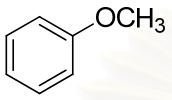
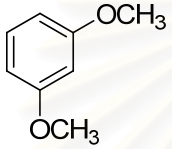
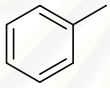
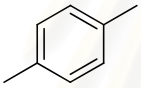
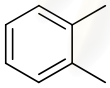
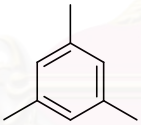
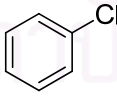
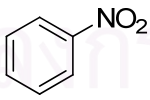
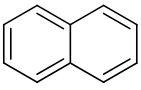
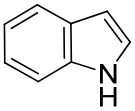
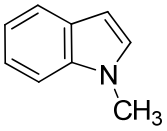
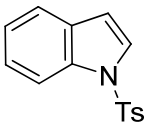
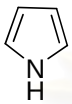
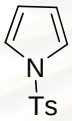
Entry	ArH	Reaction time in step II (h)	% Isolated yield
1		1	92
2		2	93
3		1	81
4		1	88
5		1	89
6		1	89
7		3	11, 51[a], 76[b]
8		6	5
9		24	0
10		1	89
11		1	0

Table 3.7 (cont)

Entry	ArH	Reaction time in step II (h)	% Isolated yield
12		1	0
13		1	73
14		3	0
15		1	88

[a] The reaction was carried out under reflux temperature in step II.

[b] The reaction was carried out under benzene as solvent.

The Friedel-Crafts acylation of benzoic acid with $AlCl_3$ and electron-donating groups such as anisole, 1,3-dimethoxybenzene, *p*-xylene, *o*-xylene, mesitylene and toluene gave high yields of the corresponding aryl ketones even at RT (entries 1–5). Anisole was more reactive than 1,3-dimethoxybenzene. The lower yield of the latter might be caused by its steric effect (entry 6). In the case of benzene with no activating group or containing electron withdrawing groups, the acylation was difficult to accomplish and led to the lower yield of the desired products. To illustrate this, benzene furnished the corresponding benzophenone in poor and moderate yield at RT and even under reflux, respectively (entry 7). However, this methodology could be successfully synthesized polycyclic ketone in high yield (entry 10). Deactivated benzenes such as chlorobenzene and nitrobenzene were inactive under these optimized reaction conditions (entries 8 and 9). These results stated that the reaction favored by activated benzene and polycyclic aromatic compounds such as alkylbenzene, alkoxybenzene or naphthalene whereas that was disfavored by deactivated benzenes such as halobenzene or nitrobenzene.

For *N*-heterocyclic compounds, the acylation of indole and methyl-*N*-indole was not accomplished since $AlCl_3$ may decompose and undesirable oligomerization of strong Lewis acid ($AlCl_3$) was occurred (entries 11 and 12) [53]. Similarly, the reaction of pyrrole was unsuccessful (entry 14). This may be because the immoderate

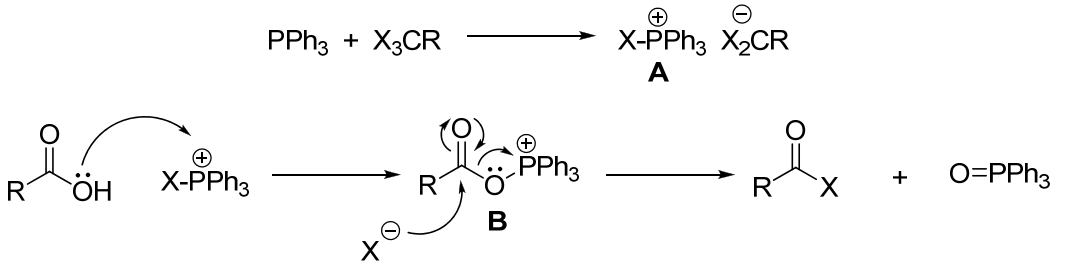
nucleophilicity of *N*-heterocyclic compounds induced oversubstitution and/or unwanted transformations; therefore the containment of nucleophilicity was needed [54]. Harnessing the reactivity of *N*-heterocyclics are often achieved by the use of *N*-protecting group for indole and pyrrole with tosyl groups. This chosen strategy would overcome the current formation of 1-tosyl derivatives and to limit polymerization which has not been observed when the indole and pyrrole systems were deactivated by the presence of electron-withdrawing groups on the ring [55]. The acylation of *N*-*p*-toluenesulfonyl-indole and -pyrrole could proceed successfully furnishing 3-acylated product in good and excellent yield, respectively (entries 13 and 15). In analogy, the steric effects invoked to explain the high regioselectivity of *N*-triisopropylsilylpyrrole. It would be anticipated that the rate of reaction of the 2-organoaluminum intermediate with an acyl chloride would be slower than the rate of reaction of the less sterically encumbered 3-isomer with acyl chloride. A combination of these factors provided a rationalization for the regioselective formation of the 3-acyl isomers in the acylation of *N*-*p*-toluenesulfonyl-pyrrole and indole using $AlCl_3$. Thus, the regioselective acylation of *N*-*p*-toluene-sulfonylpyrrole and indoles with $AlCl_3$ is not a Friedel-Crafts acylation, but is rather the reaction of an organoaluminum intermediate with an acyl chloride [56].

To compare this protocol with other previous methods, this method provided aryl ketones in excellent yield under mild conditions whereas most of prior reports presented the manipulation of aryl ketones under severe conditions. Additionally, this optimized condition required shorter reaction time to complete the reactions comparing with many procedures.

3.3 The mechanism of the one-pot synthesis of aryl ketone

3.3.1 The mechanism in step I

The mechanism in step I, the formation of acid halide was believed to take place similar to that reported by Crofts [57]. The proposed mechanism is shown in Scheme 3.1.

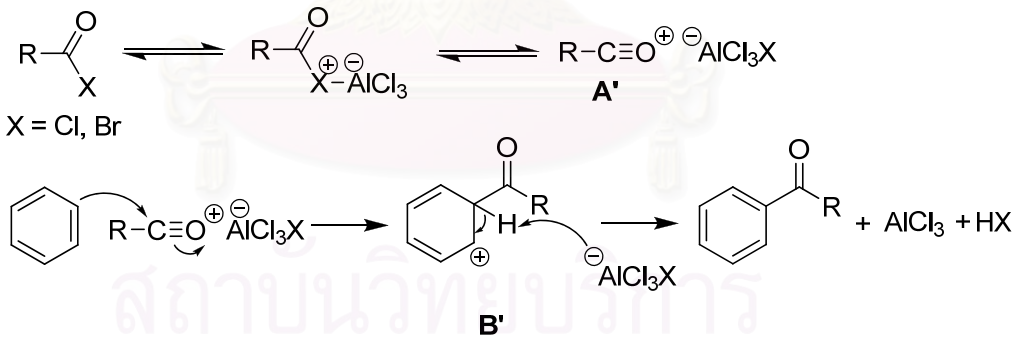


Scheme 3.1 The mechanism for the formation of acid halide

The conversion of carboxylic acid to acid chloride was obviously a multi-step process. The initially step involved the generation of intermediate **A** from PPh_3 and halogenated agent and then the substitution of **A** with carboxylic acid yielded an alkoxyphosphonium salt **B** which then transformed to the corresponding halide by S_N2 displacement.

3.3.2 The mechanism in the one-pot synthesis of aryl ketone in step II

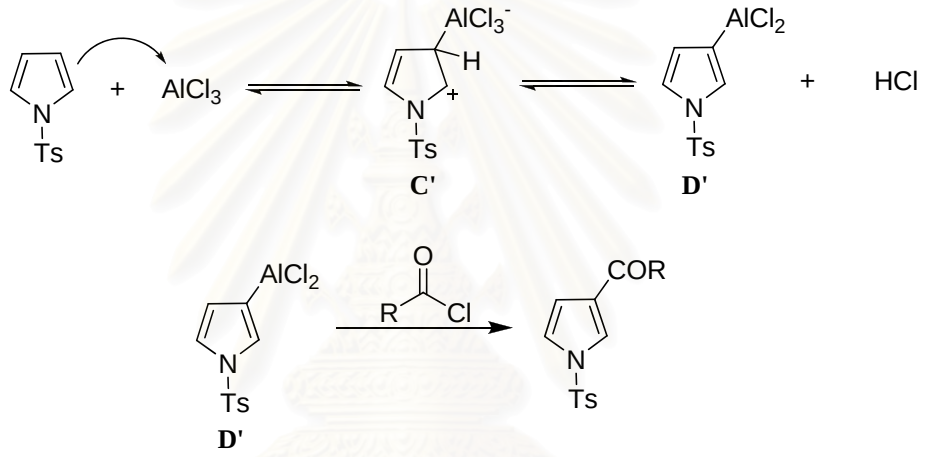
The mechanism in step II proceeded *via* Friedel-Crafts acylation. The mechanism of Friedel-Crafts acylation was the same as that previous reported [58]. The reaction pathway for the formation of aryl ketone is outlined in Scheme 3.2.



Scheme 3.2 The mechanism for Friedel-Crafts acylation

The first step, acyl halide reacted with Lewis acid to form a more electrophilic carbon, an acylium ion **A′**. The π electrons of the aromatic **C=C** acted as a nucleophile, attacking the electrophilic carbocation. This step destroyed the aromaticity giving the cyclohexadienyl cation intermediate **B′**. Removal of the proton from the sp^3 carbon bearing the acyl- group reformed the **C=C** and the aromatic system, generating HCl and regenerating the active catalyst.

The mechanism of acylation of tosyl-*N*-pyrrole with $AlCl_3$ for this methodology is probably similar to that proposed by Okauchi and Ottoni [53, 55]. In principle the path outlined in Scheme 3.3 would lead to 3-acylated products. The reaction of tosyl-*N*-pyrrole with $AlCl_3$ led reversibly to 3-organoaluminum **D′** species *via* cation **C′.** The acid catalyzed equilibrium of substituted pyrrole was exceedingly facile. Reaction of organoaluminum intermediate **D′** with the acyl chloride led to the 3-acylpyrrole. The reaction of organoaluminum compounds with acyl halides to provide ketones was a known reaction, which was facilitated in the presence of $AlCl_3$ or organoaluminum halides [56]. For acylation of tosyl-*N*-pyrrole case, the mechanism was probably similar to the acylation of tosyl-*N*-pyrrole mechanism.



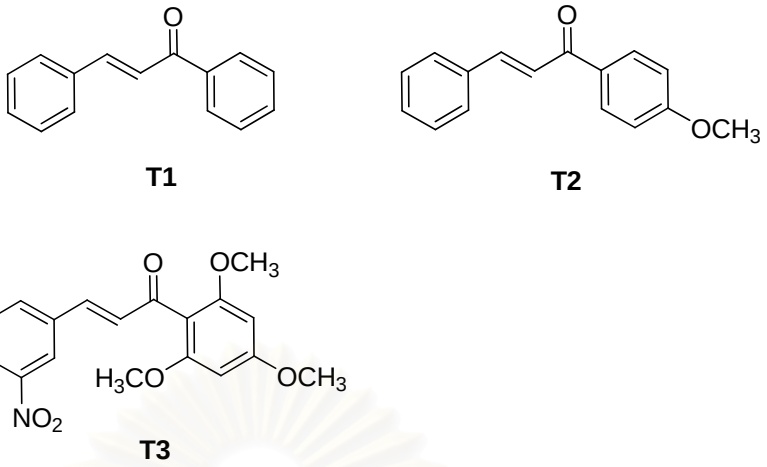
Scheme 3.3 The mechanism for acylation of tosyl-*N*-pyrrole

3.4 Applications of the developed procedure for the synthesis of biologically active ketones

The developed procedure for the synthesis of aryl ketones was further applied for the manipulation of biologically active ketones, focusing on chalcone derivative.

Chalcones are open-chain flavonoids with common skeleton of 1,3-diaryl-2 propen-1-one. Their wide-range biological properties, including antimicrobial activities, are largely attributed to the *α,β*-unsaturated ketone moiety. Introduction of various substituents into the two aryl rings is also a subject of interest because it leads to useful SAR conclusions and thus helps to synthesize pharmacologically active chalcones [60].

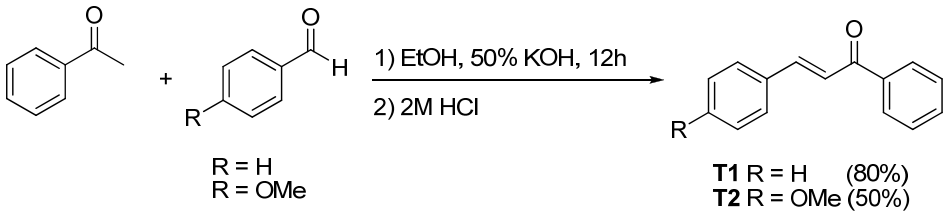
Chalcone and their derivatives could be synthesized by Claisen–Schmidt condensations between ketones and appropriate aryl aldehydes. The desired products were obtained in yields between 43-80% after purification, following procedures described previously [61, 62].



(*E*)-chalcone (T1) and (*E*)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (T2)

T1 and **T2** showed *in vitro* antiparasitic activity against *Giardia lamblia* [62]. Moreover, **T2** displayed antimalarial activity (*Plasmodium falciparum K1*) and antileishmanial activity against *Leishmania donovani* amastigotes [63]. The reports of the synthesis of these compounds were successfully performed by the reaction of benzaldehyde with acetophenone or *p*-methoxyacetophenone in 50%KOH/EtOH solution. The reaction mixture was stirred overnight at room temperate and gave **T1** 80% and **T2** 63%. By using this developed protocol, **T1** and **T2** could be achieved without any difficulty in 66 and 88%, respectively.

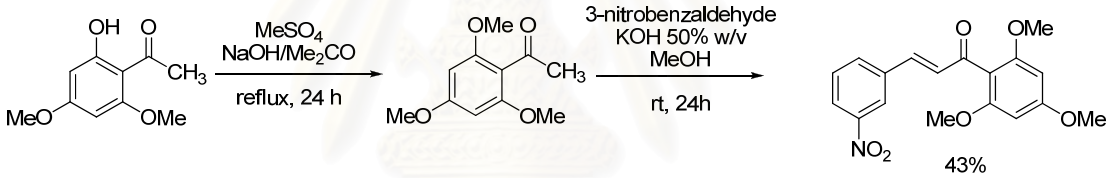
In Claisen-Schmidt condensation, the yields of the desired product were significantly depended on the electrophilicity of aldehyde. Meanwhile, for Friedel-Crafts acylation, the yields of the desired product were essentially depended on the nucleophilicity of aromatic. Hence, the synthesis of **T1** through Claisen-Schmidt condensation furnished better yield than that attained from Friedel-Crafts acylation. On the other hand, **T2** could be fruitfully prepared by Friedel-Crafts acylation rather than Claisen-Schmidt condensation.



(*E*)-3-phenyl-1-(2, 4, 6-trimethoxyphenyl) prop-2-en-1-one (T3)

T3 has been reported to inhibit induced nitric oxide synthase (iNOS) and also iNOS protein expression in RAW 264.7 cells (Mouse leukaemic monocyte macrophage cell line) [61]. Nitric oxide (NO) is a free radical gas produced from l-arginine and molecular oxygen by catalytic reaction of nitric oxide synthase (NOS). NO can react with superoxide derived from macrophages to generate highly cytotoxic peroxynitrite which destroys the invading microorganisms. In addition, **T3** has shown potent inhibition of interleukin-1 (IL-1) release from lipopolysaccharide (LPS)-stimulated human monocytes and a protein tyrosine phosphatase from *Mycobacterium tuberculosis* – PtpA [61, 64].

The synthesis of these compounds was previously reported by treating 2,4,6-trimethoxyacetophenone (TMA) with the corresponding aldehyde in KOH/MeOH. TMA was obtained by the reaction of xanthoxylin, NaOH, acetone and Me_2SO_4. The yield of **T3** was 43% yield [61]. By employing this developed methodology, **T3** could also be achieved in 53%.



CHAPTER IV

CONCLUSION

The objectives of this research are to search for optimized conditions for one-pot synthesis of aryl ketones from carboxylic acids *via* Friedel-Crafts acylation by halogenating agent and PPh_3. These developed methods could be performed under mild conditions, short reaction time and high yields of the desired products.

During the course of this research, the optimal conditions for the preparation of aryl ketones directly from carboxylic acids were disclosed: carboxylic acid (1 equiv), PPh_3 (2 equiv), Cl_3CCN (2 equiv), anisole (1 equiv), $AlCl_3$ in CH_2Cl_2 at RT for 1 h or followed by TLC. In addition, Br_3CCO_2Et, Cl_3CCO_2Et and Cl_3CCONH_2 could be utilized as an alternative halogenating agent instead of Cl_3CCN. From the variation of carboxylic acids, this method was suitable for all carboxylic acids that could dissolve in CH_2Cl_2. The substituents on an aromatic acid at *para* position were explicitly uneffected on the outcome of the reaction either being an electron-withdrawing or electron-donating group. Aliphatic carboxylic acids could be utilized to afford in high yield of the target products at longer reaction time. From the variation of aromatic compounds, the yields of the desired product were insignificantly depended on the nucleophilicity of aromatic compounds. The treatment of benzoic acid under this optimal condition revealed that the possible mechanism was proceeded *via* a nucleophilic substitution reaction in step I and electrophilic aromatic substitution reaction in step II.

Propose for the future work

This research distinctly revealed the successful methodology development for the preparation of aryl ketones directly from carboxylic acids. The outcome opened many possibilities to deal with future exploration. In the future, the further development of these new methods using catalytic reagents for Friedel-Crafts

acylation such as metal triflate ($M(OTf)_n$), metal bis(trifluoromethanesulfonyl)amide ($M(NTf_2)_n$) and trifluoromethanesulfonic acid (CF_3SO_3H) which are efficient catalyst in organic syntheses should be explored.

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