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SYNTHESIS OF COUMARINS CATALYZED BY METAL HALIDES

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A Thesis Submitted in Partial Fulfillment of the Requirements
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(SYNTHESIS OF COUMARINS CATALYZED BY METAL HALIDES)
อ. ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ดร. วรินทร ชวศิริ, 54 หน้า.

จากการทดสอบเพื่อคัดสรรสารประกอบโลหะเฮไลด์พบว่า คอปเปอร์(II)คลอไรด์สามารถเร่งปฏิกิริยาคอนเดนเซชันแบบเพคแมนน์ของรีซอร์ซินอลและเอทิลแอซิโทแอซิเทตได้ 7-ไฮดรอกซี-4-เมทิลคูมารินเป็นผลิตภัณฑ์หลัก และ 4-(2,4-ไดไฮดรอกซีเฟนิล)-7-ไฮดรอกซี-4-เมทิลโครมาน-2-โอนเป็นผลิตภัณฑ์รอง ในกรณีของสารประกอบโครเมียม(III)พบว่า โครเมียม(III)คลอไรด์เฮกซะไฮเดรตสามารถเร่งปฏิกิริยาคอนเดนเซชันแบบเพคแมนน์ของรีซอร์ซินอลและเอทิลแอซิโทแอซิเทตได้เป็น 7-ไฮดรอกซี-4-เมทิลคูมารินในปริมาณสูง ได้ศึกษาภาวะที่เหมาะสมสำหรับปฏิกิริยาคอนเดนเซชันของรีซอร์ซินอลและเอทิลแอซิโทแอซิเทต ได้แก่ ชนิดและปริมาณของตัวเร่งปฏิกิริยา เวลาและอุณหภูมิ ชนิดและปริมาณของตัวทำละลาย

จากภาวะที่เหมาะสมสำหรับปฏิกิริยาคอนเดนเซชันของรีซอร์ซินอลและเอทิลแอซิโทแอซิเทต ได้เลือกสารอื่นมาศึกษาได้แก่ ไพโรแกลลอล, 3-เมทอกซีฟีนอล, เมทา-ครีซอล, 2-แนฟทอล, 2-เมทิลรีซอร์ซินอล, ออร์ซินอล, และ 3-แอมิโนฟีนอล สามารถเปลี่ยนรูปไปเป็นคูมารินที่สอดคล้องกันได้ในปริมาณปานกลางถึงดีมาก

สาขาวิชา.....ปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์.....ลายมือชื่อนิสิต ลัดดาวรรณ เจริญศิริวัฒน์.....
ปีการศึกษา.....2551.....ลายมือชื่ออ.ที่ปรึกษาวิทยานิพนธ์หลัก.....

4872444723 : MAJOR PETROCHEMISTRY AND POLYMER SCIENCE
KEY WORD: PECHMANN CONDENSATION / CATALYST / PHENOLS / COUMARIN

LADDAWAN CHAREONSIRIWAT: SYNTHESIS OF COUMARINS CATALYZED BY METAL HALIDES. THESIS PRINCIPAL ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., 54 pp.

Screening for metal halides disclosed that copper(II) chloride could catalyze the Pechmann condensation of resorcinol with ethyl acetoacetate to afford 7-hydroxy-4-methylcoumarin as a major product and 4-(2,4-dihydroxyphenyl)-7-hydroxy-4-methylchroman-2-one as a minor product. In the case of chromium(III), chromium(III) chloride hexahydrate could catalyze Pechmann condensation of resorcinol with ethyl acetoacetate to obtain 7-hydroxy-4-methylcoumarin in high yield. The optimum conditions for the condensation of resorcinol with ethyl acetoacetate including amount and type of catalyst, reaction temperature, amount and type of solvent were conducted.

Utilizing the developed optimum conditions for the Pechmann condensation of resorcinol with ethyl acetoacetate, other selected chemical models: pyrogallol, 3-methoxyphenol, phloroglucinol, *m*-cresol, 2-naphthol, 2-methylresorcinol, orcinol and 3-aminophenol could be transformed to the corresponding coumarins in moderate to excellent yield.

Field of study Petrochemistry and Polymer Science Student's signature. Laddawan.....
Academic year.....2008.....Principal Advisor's signature .....W. Chavasiri

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δ	chemical shift (NMR)
J	coupling constant (NMR)
cm^{-1}	wave number (IR)
ºC	degree Celsius
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
COSY	correlated spectroscopy
$Cr(acac)_3$	chromium(III) acetylacetonate
$Cr(str)_3$	chromium(III) stearate
DMSO-d_6	deuterated dimethylsulfoxide
d	doublet (NMR)
dd	doublets of doublet (NMR)
EtOAc	ethyl acetate
EtOH	ethanol
g	gram(s)
HMBC	heteronuclear multiple bond correlation experiment
HSQC	heteronuclear single quantum coherence experiment
Hz	hertz
h	hour
IR	infrared
lit	literature
KBr	potassium bromide
MeOD-d_4	deuterated methanol
m	multiplet (NMR)
mL	milliliter(s)
mmol	millimole
m.p.	melting point

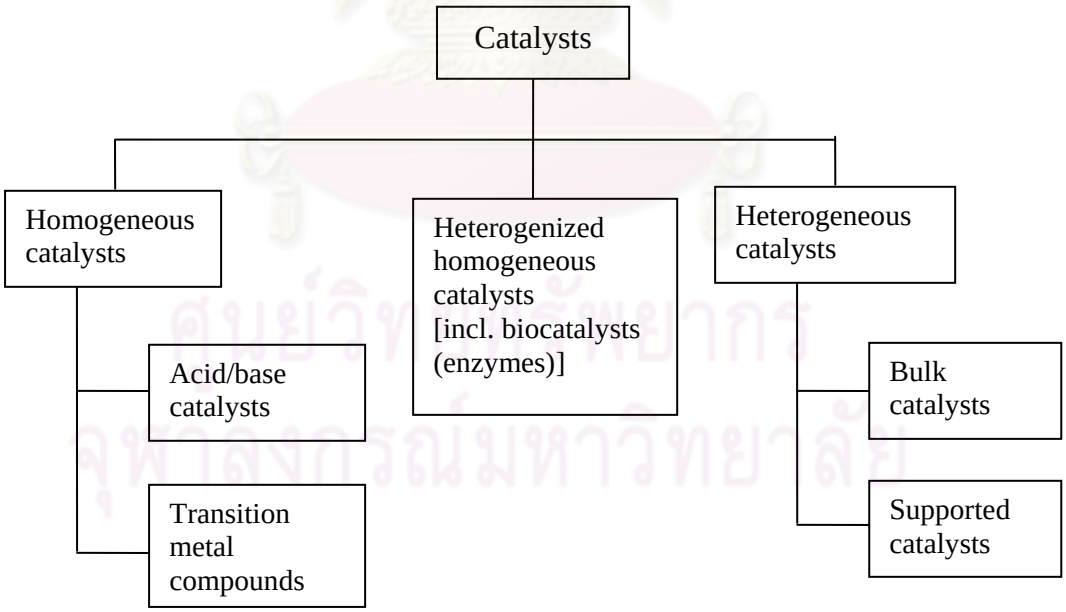
NMR	nuclear magnetic resonance
mol%	percent by mole
q	quartet (NMR)
R_f	retardation factor
s	singlet (NMR)
s	strong (IR)
THF	tetrahydrofuran
TLC	thin layer chromatography
t	triplet (NMR)
w	watt
w	weak (IR)

CHAPTER I

INTRODUCTION

1.1 Homogeneous catalysts [1]

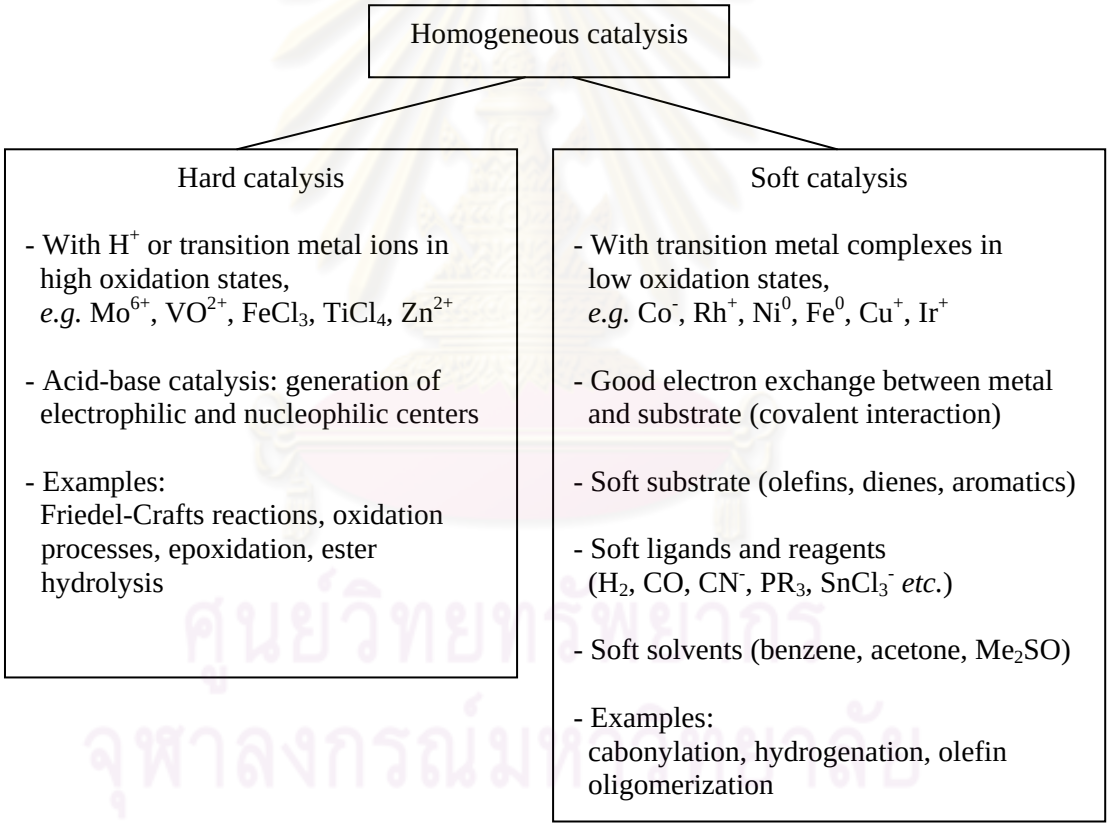
The numerous catalysts known today can be classified according to various criteria: structure, composition, area of application, or state of aggregation. Catalysts could be classified according to the state of aggregation in which they act. There are two large groups: heterogeneous catalysts (solid-state catalysts) and homogeneous catalysts (Scheme 1.1). There are also intermediate forms such as homogeneous catalysts attached to solids (support catalysts), also known as immobilized catalysts. The well-known biocatalysts (enzymes) also belong to this class.



Scheme 1.1 Classification of catalysts

Catalytic processes that take place in a uniform gas or liquid phase are classified as homogeneous catalysis. Homogeneous catalysts are generally well-defined as chemical compounds or coordination complexes, which, together with the reactants, are molecularly dispersed in the reaction medium.

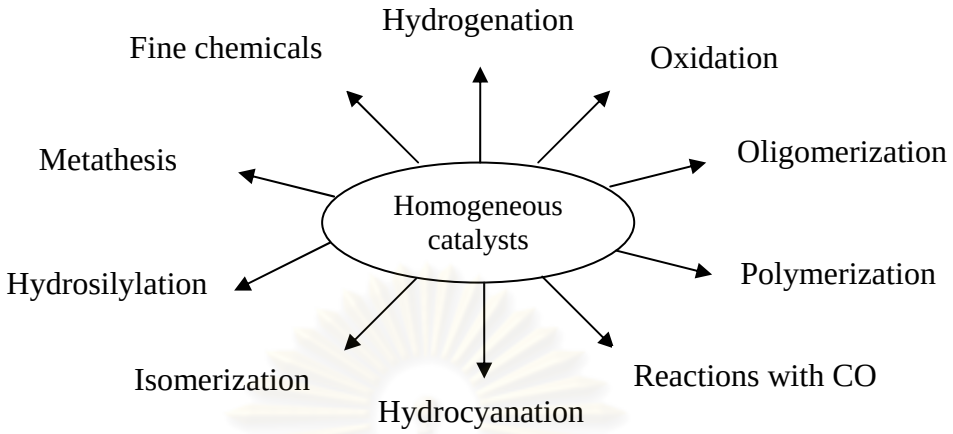
Catalytic processes generally consist of complicated series of reactions, whereby the activation of individual steps can place different demands on the catalyst. Previous reports have classified the homogeneous catalysis of organic reactions on the basis of the HSAB concept. If the first step of a reaction cycle is regarded as an acid-base reaction between the catalyst and the organic substrate, then a distinction can be made between “hard” and “soft” catalysts, providing a simple basis for understanding transition metal catalyzed processes. (Scheme 1.2).



Scheme 1.2 Hard and soft catalysis with transition metal compounds

In the last three decades homogeneous catalysis has undergone major growth. Many new processes with transition metal catalysts have been developed, and many new products have become available. Homogeneous transition metal catalyzed

reactions are now used in nearly all areas of the chemical industry, as shown in Scheme 1.3.

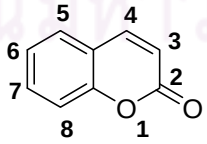


Scheme 1.3 Homogeneous transition metal catalyzed reactions carried out industrially

Nowadays the broad spectrum of catalytic processes would be inconceivable without homogeneous transition metal catalysts, importance of which could be expected to grow in future. In the case of basic chemicals the chances for new catalytic processes are small, but they are better for higher value chemicals such as fine and specialty chemicals. Pharmaceuticals and agrochemicals are two areas where homogeneous catalysts have advantages. Complex molecules can often be synthesized in single-step one pot reactions with the aid of transition metals.

1.2 What is coumarin? [2]

Coumarin, 2*H*-1-benzopyran-2-one or 1,2-benzopyrone, $C_9H_6O_2$ (**1**), is one of the most important aroma chemicals having unique characteristics not only because of its haylike bittersweet odor, but also because of its quality as a perfume fixative.



(**1**)

Coumarin is widely distributed in the plant kingdom, notably in high concentration in the tonka bean, woodruff, and bison grass. But most of it has been produced synthetically for many years for commercial uses. In addition to its use in the perfumery, cosmetic, and related industries, coumarin has several other industrial

applications. Formerly, large quantities of coumarin were used in food industry mostly associated with vanillin for flavoring chocolates, baked goods, and in the confection of cream soda flavored beverages.

1.2.1 The importance of coumarins

The synthesis of coumarins and their derivatives has attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products containing this heterocyclic nucleus. They are widely used as additives in manufacture of food, perfumes, cosmetics, pharmaceuticals [3] and in the preparation of insecticides, optical brighteners [4] and dispersed fluorescent and laser dyes [5]. Also, coumarins have varied bioactivities, for example, inhibition of platelet aggregation [6, 7], anticancer [8] and inhibition of steroid 5α-reductase [9].

A large number of coumarin derivatives have been identified in plants and many of them have been synthesized and studied for their physiological activity. Only a few are mentioned here because of their economic significance.

3,4-Dihydrocoumarin is prepared by catalytic hydrogenation of coumarin. It is also used in the perfumery industry for its haylike odor. It is less powerful than coumarin but its higher solubility in alcohol may make it preferable in some applications.

3- and 6-methylcoumarins have some use in the perfume industry. The 6-methyl derivative is permitted in flavor compositions.

4-Hydroxycoumarin can be synthesized by cyclization of acetyl methyl salicylate. It is a coumarin metabolite occurring in spoiled hay. Derivatives of 4-hydroxycoumarin for instance dicoumarol, warfarin, cyclocoumarol, ethyl *bis*–coumaracetate, and *bis*-4-hydroxycoumarin are synthetic blood anticoagulants.

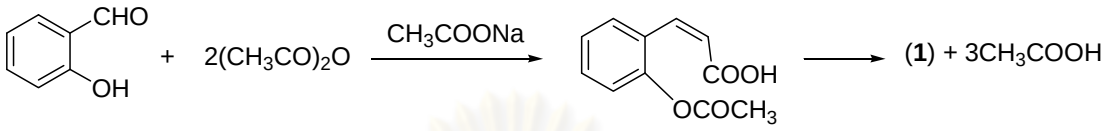
7-Hydroxycoumarin, known as umbelliferone, occurs naturally in gum resins of umbelliferae and is an important coumarin metabolite. It is readily manufactured from resorcinol and maleic or fumaric acid. Umbelliferone and *β*-methyl umbelliferone (7-hydroxy-4-methylcoumarin) are used as fluorescent brighteners.

1.3 Methods for the synthesis of coumarins

Coumarins have been synthesized by several routes including von Pechmann, Perkin, Knoevenagel, Reformatsky and Wittig reactions.

1.3.1 By Perkin reaction

Perkin first synthesized coumarin in 1868 by the reaction of sodium salt of salicylaldehyde with acetic anhydride and it was found later that the reaction could be made from salicylaldehyde itself by using NaOAc as a catalyst, through the intermediary of *cis*-*o*-acetoxycinnamic acid.



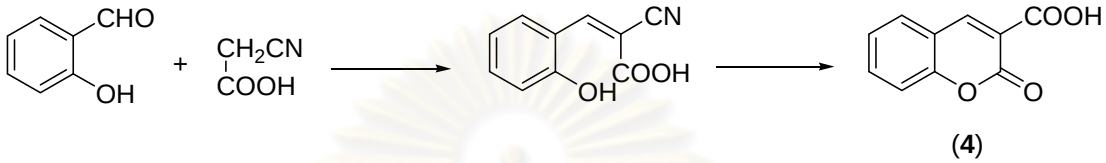
This reaction was also extended to other aromatic aldehydes for the preparation of *α*,*β*-unsaturated carboxylic acids. Several mechanisms of the reaction have been proposed. The most accepted mechanism involves the reaction of the aldehyde with the enol form of the acid anhydride which is promoted by the presence of the sodium salt or of another base. The resulting reaction product is then dehydrated into an unsaturated carboxylic acid.

The Perkin reaction is of importance for the industrial production of coumarin and a number of modifications have been studied to improve it, such as addition of a trace of iodine; addition of oxides or salts of metals such as iron, nickel, manganese, or cobalt [10]; addition of catalytic amounts of pyridine or piperidine; replacement of NaOAc by K_2CO_3 or by CsOAc [11]; and use of alkali metal biacetate [12].

1.3.2 By Knoevenagel reaction

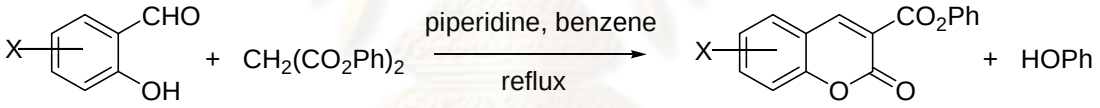
3-Substituted coumarins can be synthesized by Knoevenagel reaction, which involves the condensation of *o*-hydroxyaldehydes such as salicylaldehyde with acetic acid derivatives containing an active methylene group such as acetoacetic acid, malonic acid, cyanoacetic acid, and their esters. Ammonia or organic bases such as pyridine, piperidine, and primary and secondary amines are used as catalysts. Removal of the substituted group in the 3-position by heating or hydrolysis can produce coumarin. Thus coumarin 3-carboxylic acid obtained by the condensation of salicylaldehyde with malonic acid is decarboxylated into coumarin by heating to 290°C. The decarboxylation can be done at a lower temperature with a better yield in the presence of mercuric salts:

where R = H or C_2H_5. The coumarin 3-carboxylic acid (**4**) is also obtained by hydrolysis of the cyano group resulting from the condensation of salicylaldehyde with cyanoacetic acid.

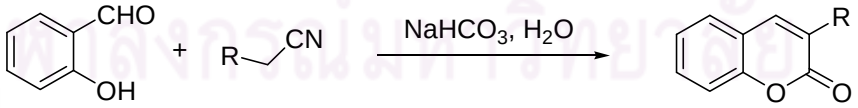


(**4**)

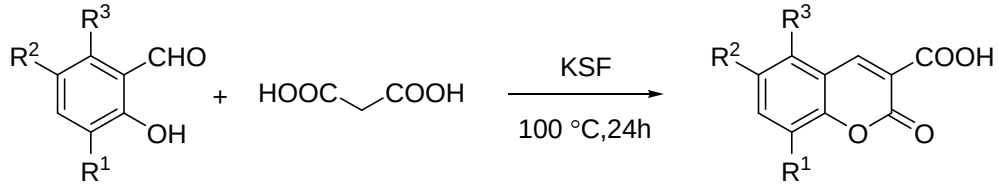
Hoogenboom and co-workers reported the condensation of salicylaldehydes with diphenyl malonate to give the corresponding coumarins [13]. The diphenyl malonate could be converted with the substituted salicylaldehydes to a series of 3-carbophenoxycoumarins in the present of piperidine, the usual Knoevenagel reaction catalyst, in benzene at reflux temperature.



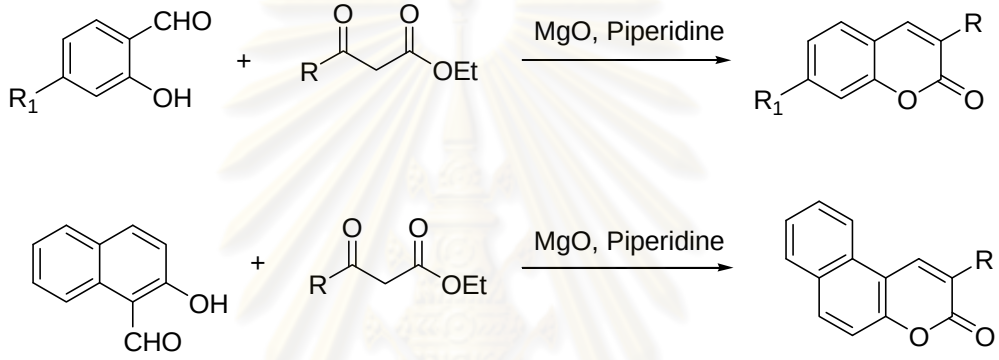
Brufola and co-workers addressed the preparation of 3-substituted coumarins by using salicylaldehyde and acetonitriles [14]. The reaction of salicylaldehyde with monosubstituted acetonitriles were executed in aqueous solution of $NaHCO_3$ and stirred at 20-90°C to yield 3-substituted coumarins.



Bigi and co-workers published the condensation of salicylaldehyde with malonic acid catalyzed by montmorillonite KSF [15]. The reaction of various salicylaldehydes with malonic acid was performed in the present of KSF catalyst in aqueous medium at reflux for 24 h to give the corresponding coumarin-3-carboxylic acids.

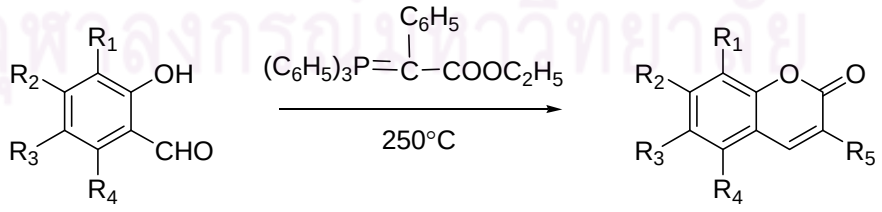


Shockravi and co-workers reported the the Knoevenagel type condensation of salicylaldehyde with β-ketoesters [16]. The condensation of salicylaldehyde and 2-hydroxy-1-naphtaldehyde with a variety of β-ketoesters supported onto MgO in the present of a drop of piperidine for the rapid synthesis of 3-substituted coumarins.



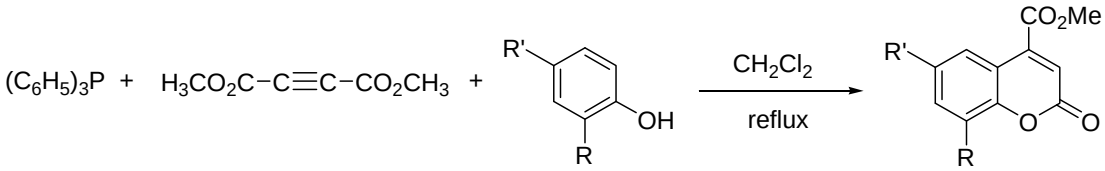
1.3.3 By Wittig reaction

Narasimhan and co-workers addressed the method of several methoxy- and benzo-coumarins and 3-phenylcoumarins synthesis [17]. The reaction of starting o-hydroxyaldehydes with α-ethoxycarbonylbenzylidenetriphenylphosphorane was heated at 250°C, under nitrogen for 2 h to afford 3-phenylcoumarins and their benzo derivatives.



Yavari and co-workers published the application of triphenylphosphine as a reagent for the reaction of phenol with dimethyl acetylenedicarboxylate (DMAD) [18]. By substituted phenols led to a vinyltriphenylphosphonium salt, which

undergoes with the phenolate conjugate base to produce 4-carboxymethylcoumarins in high yields.



1.3.4 By Pechmann reaction

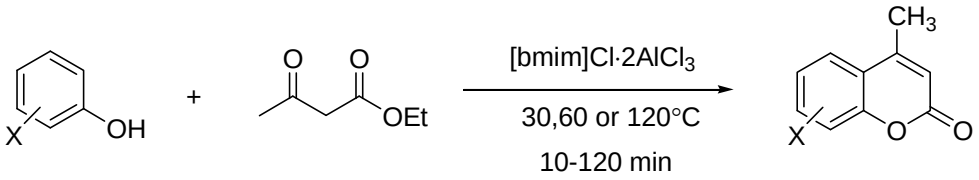
The von Pechmann reaction is a venerable reaction and it is one of the most simple and straightforward methods used to produce coumarins. Classically, the process consists of the condensation of phenols with β- ketoesters in the presence of a variety of reagents and gives good yields of 4-substituted coumarins.

Several acid catalysts have been used in the von Pechmann reaction including sulfuric acid [19, 20], aluminium chloride [21], phosphorus pentoxide [22], hyperchloric acid [23], trifluoroacetic acid [24], solid acid catalysts [25] and combination of solid acid catalysts and microwave irradiation [26, 27]. However, these catalysts have to be used in excess; for example, sulfuric acid in ten to twelve equivalents [19], trifluoroacetic acid in three to four equivalents [24] and phosphorous pentoxide is required in a five-fold excess.

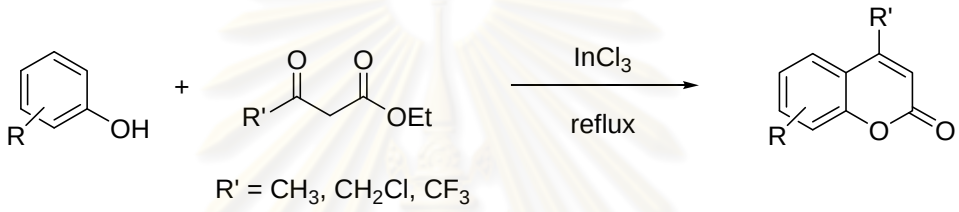
Moreover, in some cases, mixtures of substituted phenols, β-ketoesters and the acidic catalyst were allowed to stand overnight or for a number of days (depending on their reactivity) or were heated above 150°C, and undesired side-products such as chromones, in addition to coumarins were isolated. As a result, the disposal of excess acid waste leads to environmental pollution. In recent years, Lewis acids such as $InCl_3$ [29], $AlCl_3$-nBPC, $Sm(NO_3)_3$ [30], $ZrCl_4$ [31] and $Yb(OTf)_3$ [37] as well as acidic ionic liquid [28, 34] were employed to catalyze Pechmann reactions. However, some of these Lewis acids are moisture sensitive and require special care in handling and storage. Consequently, there is scope for further development of milder reaction conditions, increased variation of the substituents in both components and better yields.

Potdar and co-workers addressed the use of [bmim]Cl· $2AlCl_3$ ionic liquid as an acid catalyst in the condensation of phenols with ethyl acetoacetate [28]. The ionic liquid played the dual role of solvent and Lewis acid catalyst providing a quick route

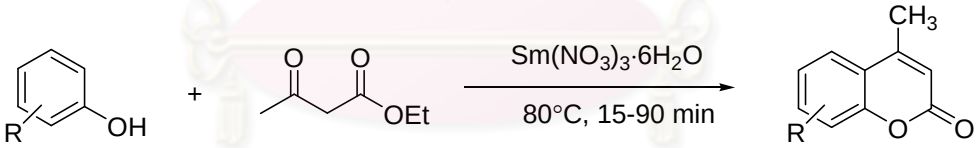
to syntheses of coumarins. Nevertheless, this acid catalyst was sensitive to moisture and all additions were carried out in an inert atmosphere.



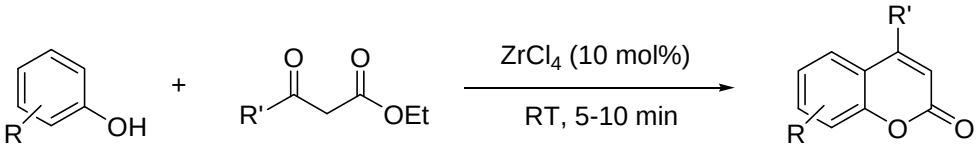
Bose and co-workers reported the utilization of $InCl_3$ catalyzed the coumarin derivatives synthesis [29]. The pechmann condensation was carried out in the present of 10 mol% of metal halide catalyst under nitrogen atmosphere at reflux temperature. 4-Substituted coumarins were furnished in good to excellent yield.



Bahekar and co-workers published the application of $Sm(NO_3)_3 \cdot 6H_2O$ in the Pechmann condensation leading to the formation of coumarins [30]. The reaction was performed under reflux temperature and nitrogen atmosphere to give the corresponding coumarin product in moderate to excellent yield.

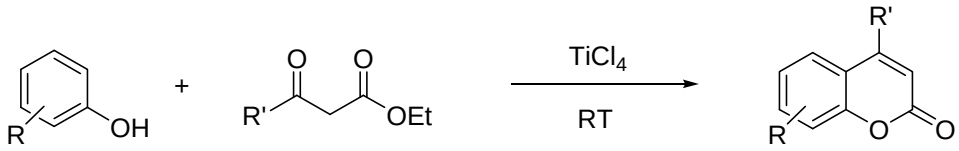


Sharma and co-workers reported the studies on a $ZrCl_4$ catalyzed one-pot protocol for the synthesis of 4-substituted coumarins [31]. The reaction was carried out at ambient temperature and found to be adaptable to a variety of substrates. The corresponding of coumarins product were acquired in high yield.

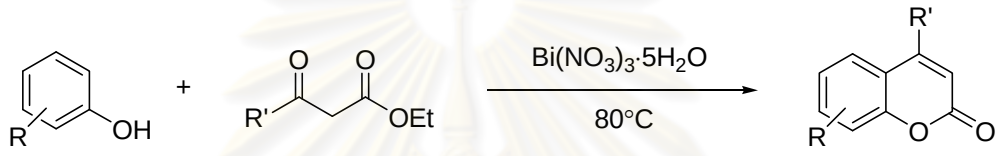


Valizadeh and co-workers published the utilizing of $TiCl_4$ as a reagent for coumarin synthesis [32]. This reaction condition employed a 1:1.5 ratio of the phenol

and the β-ketoester in the present of $TiCl_4$ 0.5 equivalent at room temperature for a few minutes. The coumarin derivatives were obtained in good to excellent yield.

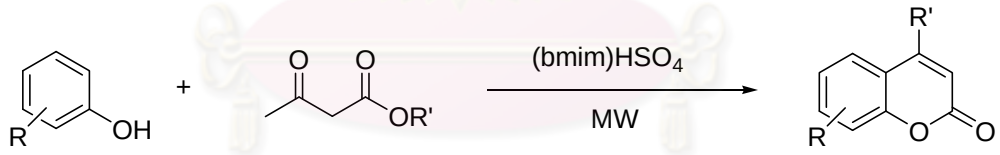


Alexander and co-workers addressed the Pechmann condensation of phenols and β-ketoesters [33]. $Bi(NO_3)_3 \cdot 5H_2O$ was used as catalyst. The reaction was carried out at 80°C under solvent free condition leading to the construction of the coumarin derivatives in good yield.



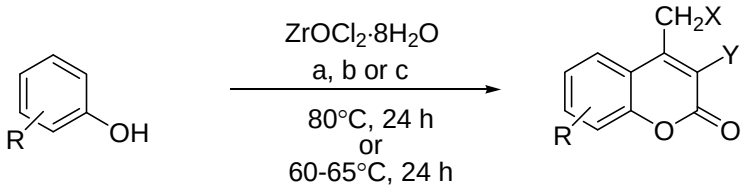
R' = CH_3, CH_2Cl, CF_3, Ph

Singh and co-workers reported the microwave accelerated preparation of [bmim][HSO_4] ionic liquid as an acid catalyst [34]. Pechmann reaction was carried out both by thermal heating and microwave irradiation (140 W) as well. The corresponding coumarin derivatives were obtained in high yield.



R' = CH_3, C_2H_5

Rodríguez-Domínguez and co-workers published the use of $ZrOCl_2 \cdot 8H_2O$ as an Pechmann catalyst [35]. The reaction was carried out at 80°C for 24 hours and, in some cases, a little ethanol was added as solvent. However, in the case of halogenated coumarins either at the 3- or 4-position, the reaction was performed at between 60 and 65°C in order to avoid formation of resins. The product was acquired in moderate to good yield.



Where X and Y are either H or Cl a) Ethyl acetoacetate; b) Ethyl 2-chloroacetoacetate; c) Ethyl 4-chloroacetoacetate

From the literature reviews, various methods could be successfully developed for the coumarin synthesis. A few reports involving the preparative procedure of these heterocyclic compounds employing metal halides as catalyst have ever been addressed. Nonetheless, the utilization of first row transition metal halides as catalyst for the coumarin synthesis has not been addressed much in chemical literatures. Due to its inexpensiveness, available and ease of preparation, this research is therefore focused on the development of some metal and first row transition metal halides for Pechmann condensation to furnish coumarin derivatives using resorcinol as a chemical model.

1.4 The goal of this research

The objective of this research can be summarized as follows:

1. To search for effective metal halide catalysts for the synthesis of coumarins.
2. To systematically study on the optimization conditions for the synthesis of coumarins catalyzed by metal halides under mild reaction conditions.
3. To utilize the optimized conditions to synthesize coumarin derivatives by condensing phenols with β-ketoesters.

CHAPTER II

EXPERIMENTAL

2.1 Instruments and equipments

Spectrometers: The IR spectra were recorded on Nicolet model Impact 410 FT/IR spectrophotometer. Solid samples were incorporated into a pellet of potassium bromide (KBr). Liquid samples were dropped on NaCl plates. The ^{1}H- and ^{13}C-NMR spectra were performed in $CDCl_3$ or DMSO-d_6 with tetramethylsilane (TMS) as an internal reference on Varian nuclear magnetic resonance spectrometer, model Mercury plus 400 NMR spectrometer which operated at 399.84 MHz for ^{1}H and 100.54 MHz for ^{13}C nuclei. The chemical shifts (δ) are assigned by comparison with residue solvent protons.

Chromatography: Thin layer chromatography (TLC) was performed on aluminium sheets pre-coated with silica gel (Merck's, Kieselgel 60 PF_{254}). Column chromatography was performed on silica gel (Merck's silica gel 60 G Art 7734 (70-230 mesh)).

Melting points (m.p.) were determined with a Fisher-Johns melting point apparatus and are uncorrected.

Elemental analysis (EA) was carried out on CHNS/O ANALYSER (Perkin Elmer PE2400 Series II) at Scientific and Technological Research Equipment Center Chulalongkorn University. Gaseous products freed by pyrolysis in high-purity oxygen 15 and were chromatographically separated by frontal analysis and quantitatively detected by thermal conductivity detector.

2.2 Chemicals

All solvents used in this research were purified prior to use by standard methodology. The reagents used for synthesis and all organic substrates were purchased from Fluka chemical company or otherwises stated and were used without further purification.

2.3 Syntheses

2.3.1 Preparation of $Cr(acac)_3$

Chromium(III) chloride hexahydrate (10 mmol, 2.66 g) was dissolved in distilled water (3 mL) and the mixture was heated until homogeneity. After that concentrated ammonium hydroxide solution (4.5 mL) was dropped slowly. The solution was stirred for about 15-20 min on a water bath (80°C) and brown solid was filtered off and washed with distilled water until no more chloride was detected. The precipitate was placed in Erlenmeyer flask, acetylacetone (10 mmol, 6 mL) was slowly dropped for 35 min on water bath and a precipitate of red solid was observed. The products were filtered and recrystallized by 95% ethanol. The blue gray solid of $Cr(acac)_3$ was obtained (75%), m.p. 209-215°C. IR (KBr, cm^{-1}): 1527-1578(s), 1381(s), 1277(s), 1018(s) and 927(m).

2.3.2 Preparation of $Cr(str)_3$

Stearic acid (22 mmol, 6.26 g) was dissolved into a solution of NaOH (0.88 g NaOH in 20 mL) at 80°C togive a 2 M solution. The solution was stirred until clear and homogeneity, $CrCl_3 \cdot 6H_2O$ (7.3 mmol) dissolve in 10 mL of distilled water was added giving a light purple precipitate. The reaction mixture was allowed to stir at the same temperature until the complex formed, then the precipitate was collected and dried in vacuo (75%), m.p. 100-103°C. IR (KBr, cm^{-1}): 1750(s), 1607(s), 1473(m), 1327(s), 1287(s), 1051(m), 864(m), 767(m), 475(s). (EA), %C = 48.35, %H = 3.27 and %N = 9.44.

2.4 General procedure for the synthesis of coumarin derivatives

To phenol (5 mmol) and β-ketoester (5 mmol), metal halide catalyst (5 mol%) was added and the mixture was stirred in a pre-heated oil-bath at 80°C. After completion of the reaction, the reaction mixture was cooled to RT, poured into ice-cold water and stirred for 10-15 min. The crystalline products were collected by filtration under suction, washed with ice-cold water and then recrystallized from hot EtOH to afford the desired product. The coumarin derivatives are mostly well known in literature and were identified by comparison of their physical and spectral data.

In case of other metal halides beside $CrCl_3 \cdot 6H_2O$ utilizing as catalyst in Pechmann condensation, the isolation procedure was necessary.

2.4.1 General isolation procedure

After the reaction was completed, the products were separated as follows: the crystalline products were collected according to the general procedure and were purified by silica gel column using a mixture of hexane-EtOAc as a mobile phase. The equivalent fractions monitored by TLC were combined and the solvent was completely evaporated. The residue was characterized by ^{1}H-NMR spectroscopy.

7-hydroxy-4-methylcoumarin: white solid, m.p. 184-185°C, R_f 0.32 (hexane-EtOAc (1:1)); ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.57 (d, *J* = 8.7 Hz, 1H), 6.78 (dd, *J* = 2.3, 8.7 Hz, 1H), 6.68 (d, *J* = 2.3 Hz, 1H), 6.11 (s, 1H) and 2.34 (s, 3H).

4-(2,4-dihydroxyphenyl)-7-hydroxy-4-methylchroman-2-one: light brown solid, R_f 0.22 (hexane-EtOAc (1:1)); ^{1}H-NMR (MeOD-d_4) δ (ppm): 7.02 (d, *J* = 8.4 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 6.48 (s, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 6.27 (s, 1H), 6.09 (d, *J* = 7.9 Hz, 1H), 3.98 (d, *J* = 15.4 Hz, 1H), 2.50 (d, *J* = 15.5 Hz, 1H) and 1.70 (s, 3H). ^{13}C-NMR (MeOD-d_4) δ (ppm): 170.3, 157.2, 157.1, 156.2, 151.6, 128.5, 126.9, 122.5, 121.0, 111.4, 105.5, 103.3, 103.2, 40.2, 39.4 and 24.5. (EA), %C = 65.74, %H = 4.70 and %O = 29.56.

2.5 $CuCl_2$ catalyzed Pechmann condensation

The Pechmann condensation was carried out in the same manner as described above utilizing $CuCl_2$ as a catalyst.

2.6 General procedure for the proof for the formation of Compound 2

The mixture of 7-hydroxy-4-methylcoumarin (0.2 mmol, 35.2 mg) with resorcinol (0.2 mmol, 22 mg) was carried out in the presence of $CuCl_2$ (5 mol%, 1.3 mg), using a little EtOH as solvent at reflux temperature for 2 h. After evaporation, the crudes were concentrated and analyzed by ^{1}H-NMR based on a standard CH_3CN 10 µL.

2.7 Study on the optimum conditions for Pechmann condensation of resorcinol with ethyl acetoacetate

2.7.1 Effect of metal halide on Pechmann condensation

The Pechmann condensation was carried out in the same manner as previously described employing various metal halides: $CrCl_3 \cdot 6H_2O$, $CrBr_3 \cdot 6H_2O$, $MnCl_2$, $CoCl_2$, $CuCl_2$, $SnCl_2 \cdot 2H_2O$, $NiCl_2$, $FeCl_3$ and $InCl_3 \cdot H_2O$ as a catalyst.

2.7.2 Effect of chromium(III) metal on Pechmann condensation

The Pechmann condensation was carried out in the same manner aforementioned, switching from $CrCl_3 \cdot 6H_2O$ to $CrBr_3 \cdot 6H_2O$, $Cr(NO_3)_3 \cdot 9H_2O$, $Cr(acac)_3$ and $Cr(str)_3$.

2.7.3 Effect of temperatures on Pechmann condensation

The Pechmann condensation was performed according to the general procedure mentioned earlier using $CrCl_3 \cdot 6H_2O$ as a catalyst, but different reaction temperatures were varied: RT (28-30°C) and reflux temperature.

2.7.4 Effect of solvent on Pechmann condensation

The Pechmann condensation was carried out in the same manner as described above except for EtOH, THF, CH_2Cl_2, toluene, CH_3CN, isooctane, xylene and water were used as a reaction medium. The amount of solvent used was 3 mL and reduced to 1 mL.

2.7.5 Effect of the amount of catalyst on Pechmann condensation

The Pechmann condensation was carried out as described in the general procedure, but the amount of catalyst was varied: 0, 1, 5, 10 and 20 mol%**.**

2.8 Synthesis of various coumarin derivatives *via* Pechmann condensation

2.8.1 Various phenolic compounds

Selected phenolic compounds, namely pyrogallol, 3-methoxyphenol, phloroglucinol, *m*-cresol, 2-naphthol, 2-methylresorcinol, orcinol and 3-aminophenol were reacted according to the general procedure as previously described. $CrCl_3 \cdot 6H_2O$ was utilized as catalyst. The crystalline products of coumarin derivatives were identified by comparison of their physical and spectral data with those reported in literature.

7-methoxy-4-methylcoumarin: light orange solid, 25% yield, m.p. 160–162°C, R_f 0.50 (hexane-EtOAc (1:1)); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.50 (d, *J* = 8.8 Hz, 1H), 6.86 (dd, *J* = 2.5, 8.7 Hz, 1H), 6.82 (s, 1H), 6.14 (s, 1H), 3.88 (s, 3H) and 2.40 (s, 3H).

5,7-dihydroxy-4-methylcoumarin: beige solid, 100% yield, m.p. 283–285°C, R_f 0.18 (hexane-EtOAc (1:1)); ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.22 (s, 1H), 6.14 (s, 1H), 5.81 (s, 1H) and 2.48 (s, 3H).

7,8-dihydroxy-4-methylcoumarin: gray solid, 91% yield, m.p. 241–243°C, R_f 0.20 (hexane-EtOAc (1:1)); ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.07 (d, *J* = 8.5 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.10 (s, 1H) and 2.33 (s, 3H).

7-hydroxy-4,8-dimethylcoumarin: white solid, 71% yield, m.p. 264–266°C, R_f 0.35 (hexane-EtOAc (1:1)); ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.37 (d, *J* = 8.6 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 1H), 6.05 (s, 1H), 2.30 (s, 3H) and 2.10 (s, 3H).

7-hydroxy-4,5-dimethylcoumarin: light gray solid, 23% yield, m.p. 258–259°C, R_f 0.40 (hexane-EtOAc (1:1)); ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.55 (d, *J* = 14.2 Hz, 2H), 6.00 (s, 1H), 2.50 (s, 3H) and 2.24 (s, 3H).

7-amino-4-methylcoumarin: yellow solid, 8% yield, m.p. 225–227°C, R_f 0.25 (hexane-EtOAc (1:1)); ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.37 (d, *J* = 8.6 Hz, 1H), 6.53 (dd, *J* = 2.0, 8.6 Hz, 1H), 6.38 (d, *J* = 1.9 Hz, 1H) 6.08 (s, 2H), 5.87 (s, 1H) and 2.27 (s, 3H).

2.8.2 Various β-ketoesters

Selected β-ketoesters, methyl acetoacetate and ethyl benzoylacetate were reacted according to the general procedure as previously described. $CrCl_3 \cdot 6H_2O$ was utilized as catalyst. The crystalline products of coumarin derivatives were identified by comparison of their physical and spectral data with those reported in literature.

7-hydroxy-4-phenylcoumarin: brown solid, 26% yield, m.p. 256-257°C, R_f 0.50 (hexane-EtOAc (1:1)); ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.46-7.52 (m, 5H), 7.24 (d, *J* = 8.7 Hz, 1H), 6.74-6.77 (m, 2H) and 6.11 (s, 1H).

5,7-dihydroxy-4-phenylcoumarin: beige solid, 15% yield, m.p. 243-245°C, R_f 0.28 (hexane-EtOAc (1:1)); ^{1}H-NMR (DMSO-d_6) δ (ppm): δ_H 7.31-7.33 (m, 5H), 6.24 (s, 1H), 6.14 (s, 1H) and 5.72 (s, 1H).

7-hydroxy-8-methyl-4-phenylcoumarin: light brown solid, 25% yield, m.p. 285-286°C, R_f 0.52 (hexane-EtOAc (1:1)); ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.46-7.52 (m, 5H), 7.09 (d, *J* = 8.7 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.11 (s, 1H) and 2.18 (s, 3H)

7,8-dihydroxy-4-phenylcoumarin: dark gray solid, 12% yield, m.p. 195-197°C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.48-7.51 (m, 5H), 6.72-6.76 (m, 2H) and 6.10 (1H).

2.9 Synthesis of coumarin *via* Knoevenagel condensation

Salicylaldehyde and diethyl malonate were reacted according to the general procedure as previously described. $CrCl_3 \cdot 6H_2O$ was utilized as catalyst. The crystalline product of corresponding coumarin was identified by comparison of its physical and spectral data with those reported in literature.

Ethyl 3-coumarincarboxylate: yellow solid, 14% yield, m.p. 92-94°C, R_f 0.42 (hexane-EtOAc (1:1)); ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.52 (s, 1H), 7.60-7.66 (m, 2H), 7.31-7.36 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

2.10 Synthesis of quinolinone

m-Phenylenediamine and ethyl acetoacetate were reacted according to the general procedure as previously described. $CrCl_3 \cdot 6H_2O$ was utilized as catalyst. The crystalline product of quinolinone was identified by comparison of its physical and spectral data with those reported in literature.

7-Amino-4-methylquinolin-2-one: gray solid, 22% yield, m.p. 278-280°C, R_f 0.20 (EtOAc); ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.30 (d, *J* = 8.6 Hz, 1H), 6.42 (d, *J* = 8.6 Hz, 1H), 6.33 (s, 1H) 5.91 (s, 1H), 5.71 (s, 2H) and 2.24 (s, 3H).

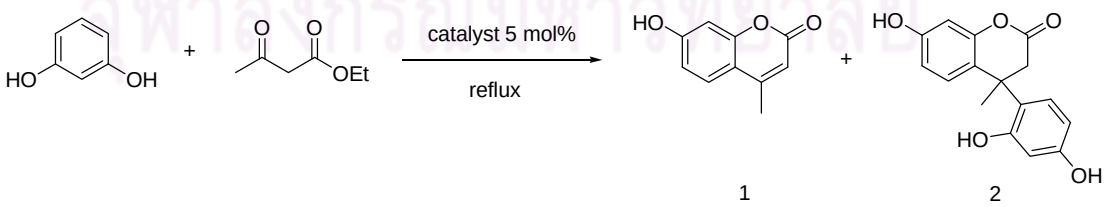
CHAPTER III

RESULTS AND DISCUSSION

Coumarins remain an important class of bioactive compounds. Chemists have shown keen interest in synthesizing coumarins in view of their applications range from additives in food, perfumes, cosmetics, pharmaceuticals and their use in the syntheses of insecticides and optical brighteners. Coumarins have also possessed variety of bioactivities, for example anticoagulant properties, anticancer and inhibition of steroid 5α-reductase. This research mainly focuses on the synthesis of coumarins *via* Pechmann condensation catalyzed by metal halides. The catalytic activity of metal halides has been explored and demonstrated to search for a new and efficient protocol for coumarin synthesis under several diverse conditions.

3.1 $CuCl_2$ catalyzed Pechmann condensation of resorcinol with ethyl acetoacetate

To examine on the use of $CuCl_2$ catalyzed Pechmann condensation, the reaction of a model compound, resorcinol and ethyl acetoacetate was carried out in the presence of 5 mol% $CuCl_2$ catalyst at reflux temperature (neat). After the reaction was completed (monitored by TLC), two new spots were observed. The separation of the reaction mixture was performed by silica gel column furnishing two products which were identified by ^{1}H-NMR.



1 2

Supporting by spectroscopic data, the major and minor products were 7-hydroxy-4-methylcoumarin (**1**) and 4-(2,4-dihydroxyphenyl)-7-hydroxy-4-methyl chroman-2-one (**2**) in 62 and 13% yield, respectively. According to the chemical literature, the minor product was found to be the new product.

The ^{1}H-NMR spectrum of **1** (Fig 3.1) revealed the significant signal of methyl group at δ_H 2.34 (s, 3H). Three signals belonging to aromatic protons were observed at δ_H 7.57 (d, *J* = 8.7 Hz, 1H), 6.78 (dd, *J* = 2.3, 8.7 Hz, 1H) and 6.68 (d, *J* = 2.3 Hz, 1H). The signal of olefinic proton was in addition detected at δ_H 6.11 (s, 1H).

The structure of the new product (**2**) was clearly proved by 2D-NMR spectroscopy. To illustrate this, the ^{1}H-NMR spectrum of **2** (Fig 3.2) revealed the singlet signal of methyl group at δ_H 1.70 (3H). The methylene protons displayed as two doublet signals at δ_H 3.98 (*J* = 15.4 Hz, 1H) and 2.50 (*J* = 15.5 Hz, 1H). The aromatic protons of coumarin detected at δ_H 7.02 (d, *J* = 8.4 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H) and 6.48 (s, 1H). The signals at δ_H 6.38 (d, *J* = 8.4 Hz, 1H), 6.27 (s, 1H) and 6.09 (d, *J* = 7.9 Hz, 1H) were assigned for aromatic protons of phenol.

The ^{13}C-NMR spectrum of this compound (Fig 3.3) displayed the signal at δ_C 24.5 for sp^3 carbon of alkyl group and that at δ_C 40.2 for β-carbon of the lactone ring. The signal at δ_C 39.4 could be assigned for α-carbon of the lactone ring. The six signals of aromatic carbons were observed at δ_C 103.2, 103.3, 105.5, 111.4, 126.9 and 128.5. The aromatic carbon connecting to the oxygen was detected at δ_C 151.6. The three carbons were next to hydroxyl groups displayed the signals at δ_C 156.2, 157.1 and 157.2. The peak at δ_C 170.3 appropriated for a carbonyl carbon was observed.

The assignment for ^{1}H, ^{13}C NMR, ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC correlations of (**2**) is tabulated in Table 3.1.

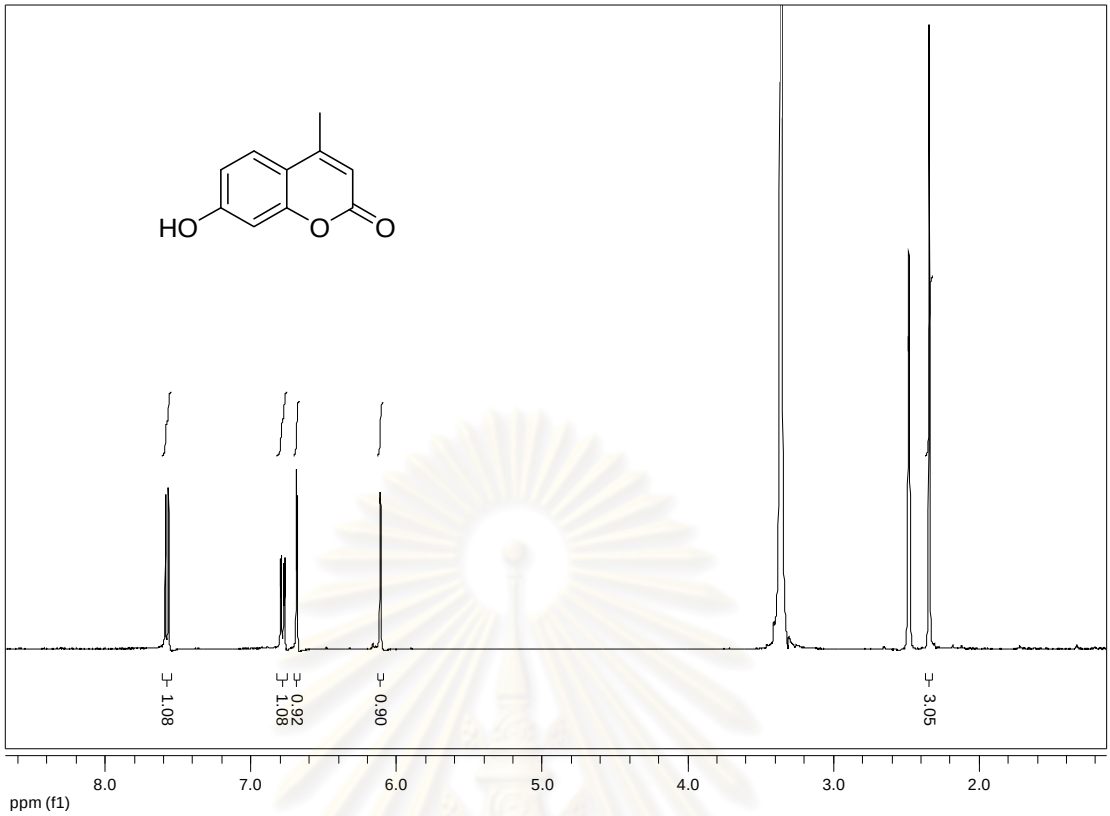


Figure 3.1 The ^{1}H-NMR spectrum of 7-hydroxy-4-methylcoumarin (**1**)

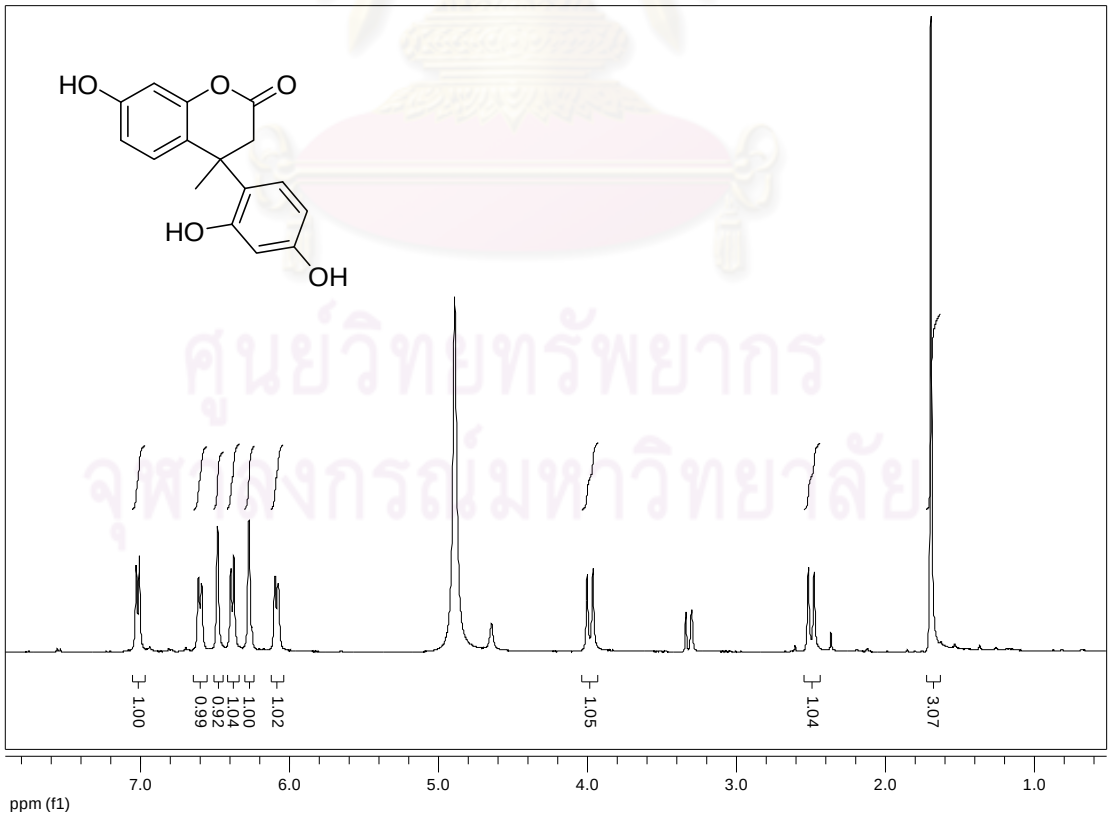


Figure 3.2 The ^{1}H-NMR spectrum of 4-(2,4-dihydroxyphenyl)-7-hydroxy-4-methylchroman-2-one (**2**)

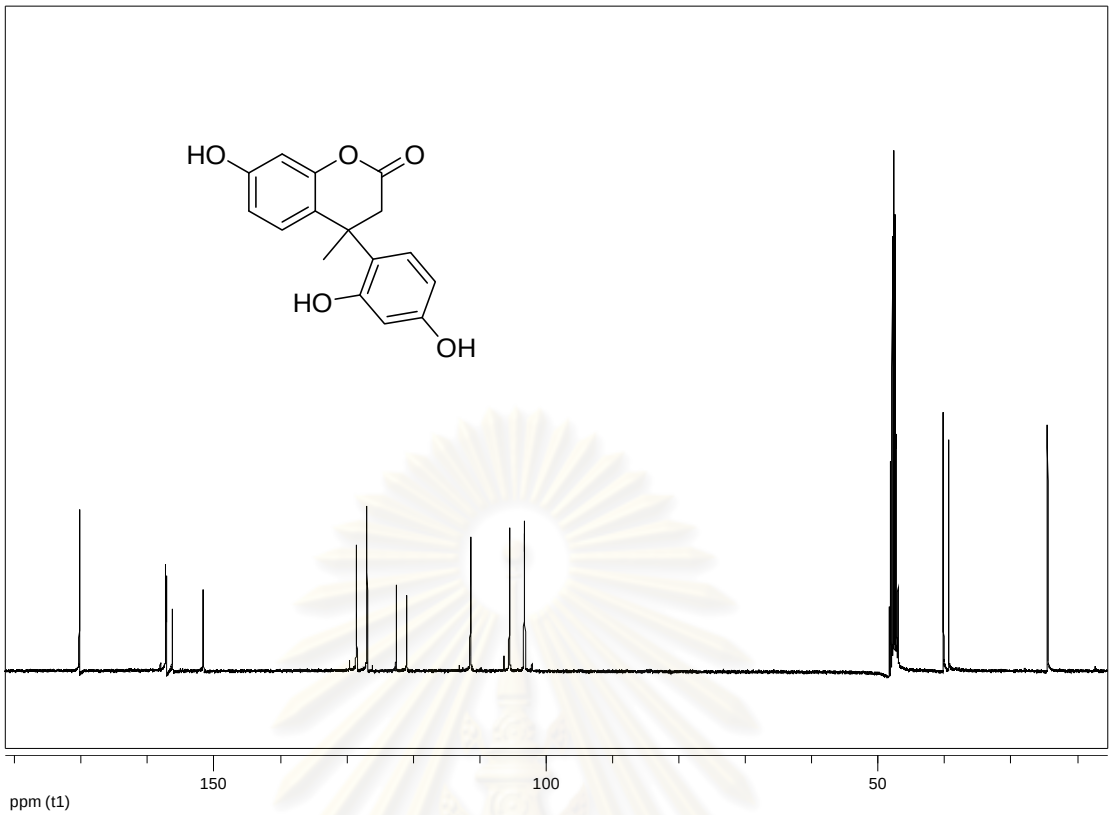


Figure 3.3 The ^{13}C-NMR spectrum of (**2**)

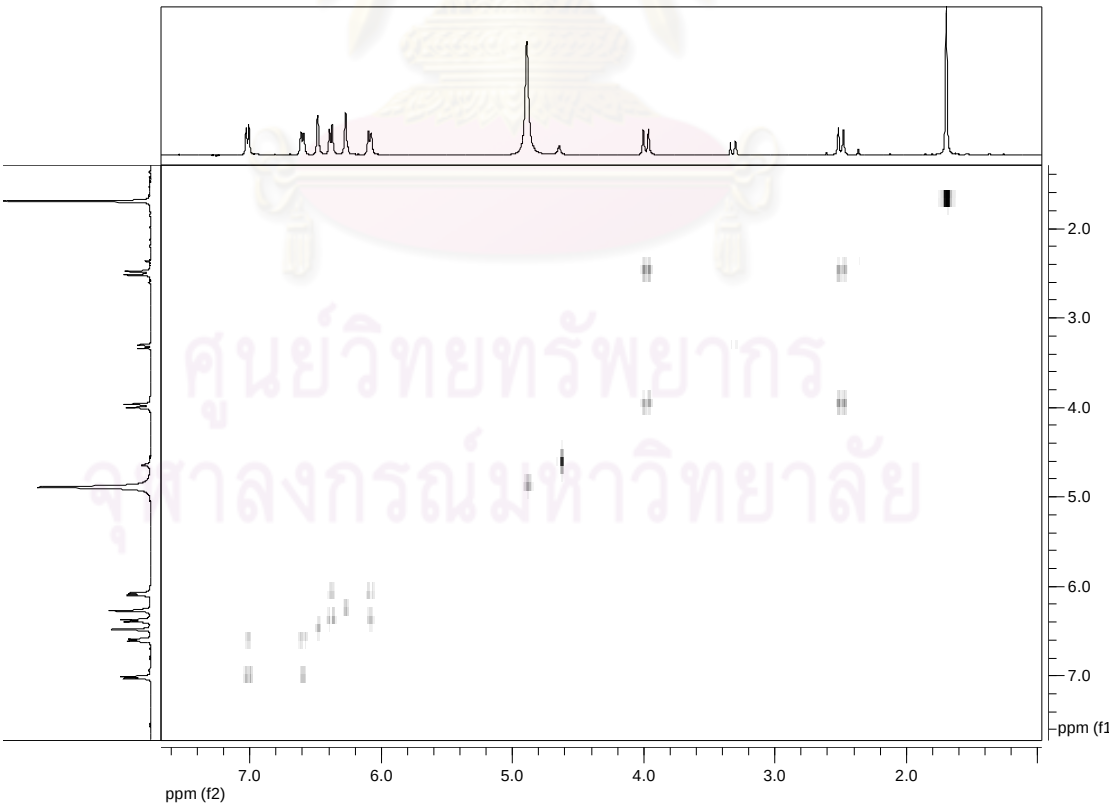


Figure 3.4 The ^{1}H–^{1}H COSY spectrum of (**2**)

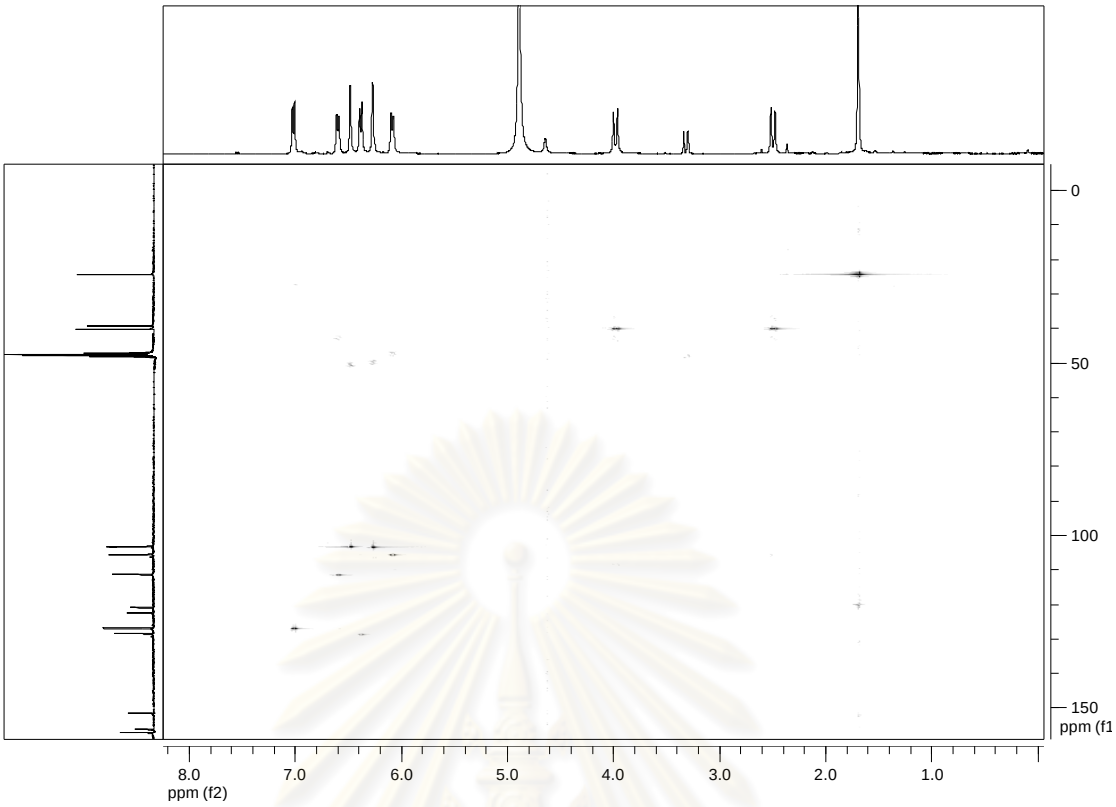


Figure 3.5 The ^{1}H–^{13}C HSQC spectrum of (**2**)

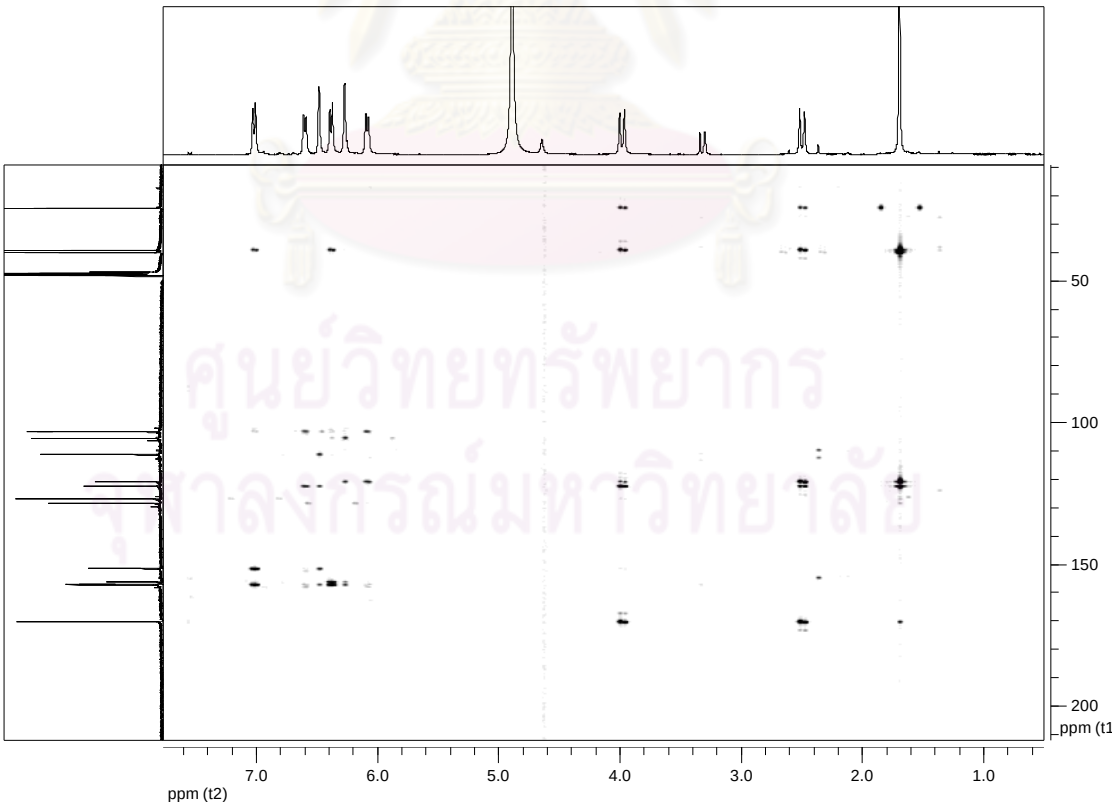


Figure 3.6 The ^{1}H–^{13}C HMBC spectrum of (**2**)

Table 3.1 ^{1}H and ^{13}C NMR data, and ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC correlations of (**2**)

Carbon number	Chemical shift (δ, ppm)		^{1}H–^{1}H COSY	^{1}H–^{13}C HMBC
	δ_C	^{1}H–^{13}C HSQC δ_H		
CH_3	24.5	1.70 s		2, 3, 4, 10, 1′
2	170.3	-		
3	39.4	2.50 d (*J* = 15.5 Hz) ,	3	CH_3, 2, 4, 10, 1′;
		3.98 d (*J* = 15.4 Hz)		CH_3, 2, 4, 10, 1′;
4	40.2	-		
5	126.9	7.02 d (*J* = 8.4 Hz)	6	
6	111.4	6.60 d (*J* = 8.1 Hz)	5	7, 8, 10
7	157.2	-		
8	103.2	6.48 (s)		6, 7, 9, 10
9	151.6	-		
10	122.5	-		
1′	121.0	-		
2′	128.5	6.38 d (*J* = 8.4 Hz)	3′	4, 6′
3′	105.5	6.09 d (*J* = 7.9 Hz)	2′	1′, 4′, 5′
4′	157.1	-		
5′	103.3	6.27 (s)		1′, 3′, 4′, 6′
6′	156.2	-		

400 MHz, coupling constant *J* in Hz in parentheses

Spectra taken in MeOD-d_4

The proton sequences of this compound were established from ^{1}H–^{1}H COSY: the aromatic proton of coumarin moiety at δ_H 7.02 (H-5) showed correlations with the signal at δ_H 6.60 (H-6). The aromatic signal at δ_H 6.38 (H-2′) showed further correlations with the proton resonances at δ_H 6.09 (H-3′). In the HMBC experiment, one methyl proton resonanceing at δ_H 1.70 showed clear correlations with the carbon signals at δ_C 170.3 (C-2), 39.4 (C-3), 40.2 (C-4), 122.5 (C-10) and 121.0 (C-1′). Long

range correlations from two protons at δ_H 2.50 and 3.98 of methylene group to four carbon signals at δ_C 24.5 (CH_3), 170.3 (C-2), 40.2 (C-4), 122.5 (C-10), 121.0 (C-1′). The correlation from the aromatic proton at δ_H 6.60 (H-6) to four carbon signals at δ_C 157.2 (C-7), 103.2 (C-8) and 122.5 (C-10). The carbon signal at δ_C 40.2 (C-4), 157.2 (C-7) and 151.6 (C-9) showed correlation with δ_H 7.02 (H-5). Correlation was observed between the aromatic signal at δ_H 6.48 (H-8) and the carbon signals at δ_C 111.4 (C-6), 157.2 (C-7), 151.6 (C-9) and 122.5 (C-10). Other important correlations was showed between the aromatic signal at δ_H 6.38 (H-2′) and the carbon resonances at δ_C 40.2 (C-4) and 156.2 (C-6′); the proton signal at 6.09 (H-3′) showed correlation with δ_C 121.0 (C-1′), 157.1 (C-4′) and 103.3 (C-5′); and the proton signal at 6.09 (H-5′) showed correlation with δ_C 121.0 (C-1′), 105.5 (C-3′), 157.1 (C-4′) and 156.2 (C-6′).

For the interpretation of minor product from 2D-NMR spectroscopy, could obtain the structure of new product. The key interactions observed in the $^{1}H–^{13}C$ HMBC spectrum of (**2**) as shown in Fig 3.7.

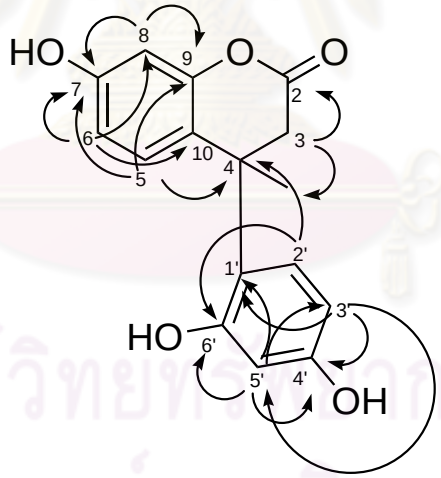


Figure 3.7 Key interactions observed in the $^{1}H–^{13}C$ HMBC spectrum of **2**.

Percent composition of carbon, hydrogen and oxygen for the new product (**2**) was analyzed by elemental analysis technique (EA). The result is presented in Table 3.2.

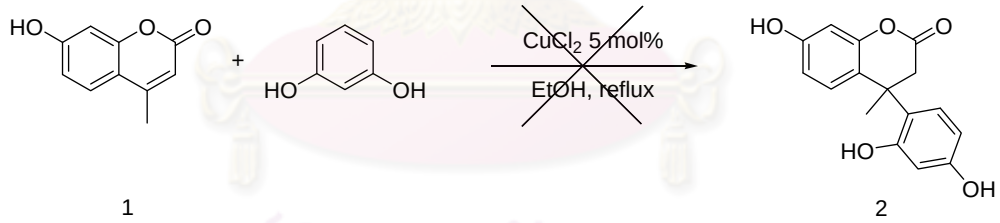
Table 3.2 Elemental analysis of 4-(2,4-dihydroxyphenyl)-7-hydroxy-4-methyl chroman-2-one (**2**)

Value	%C	%H	%O
Theoretical	65.08	5.12	29.80
Experimental	65.74	4.70	29.56

Table 3.2 indicates that compound **2** contains 65.74, 4.70 and 29.56% of carbon, hydrogen and oxygen, respectively *vs* the theoretical value of 65.08 for carbon, 5.12 for hydrogen and 29.80 for oxygen. The theoretical and experimental values for carbon, hydrogen and oxygen were acceptable to claim the structure of this new product.

3.2 The proof for the formation of Compound 2

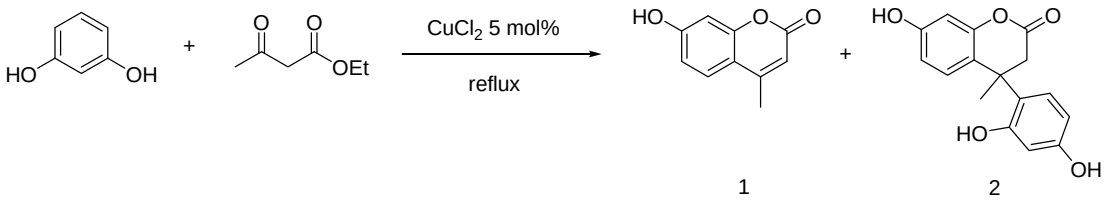
For better understanding of the formation of the new coumarin product (**2**), the treatment of 7-hydroxy-4-methylcoumarin (**1**, 1 equiv) with resorcinol (1 equiv) was carried out in the presence of $CuCl_2$ 5 mol%, using a little EtOH as solvent at reflux temperature for 2 h.



1 2

The new coumarin product (**2**) did not form while **1** was recovered more than 90%. This revealed that Pechmann condensation of resorcinol with ethyl acetoacetate furnishing **1** which could not further react with resorcinol to afford **2**.

The kinetic study on the Pechmann condensation of resorcinol (1 equiv) and ethyl acetoacetate (1 equiv) was investigated to proof the formation of the new coumarin product (**2**). The reaction was carried out in the presence of 5 mol% $CuCl_2$ catalyst at reflux temperature for 2 h and was analyzed by ^{1}H-NMR based on a standard CH_3CN 10 µL. The results are shown in Figure 3.8.



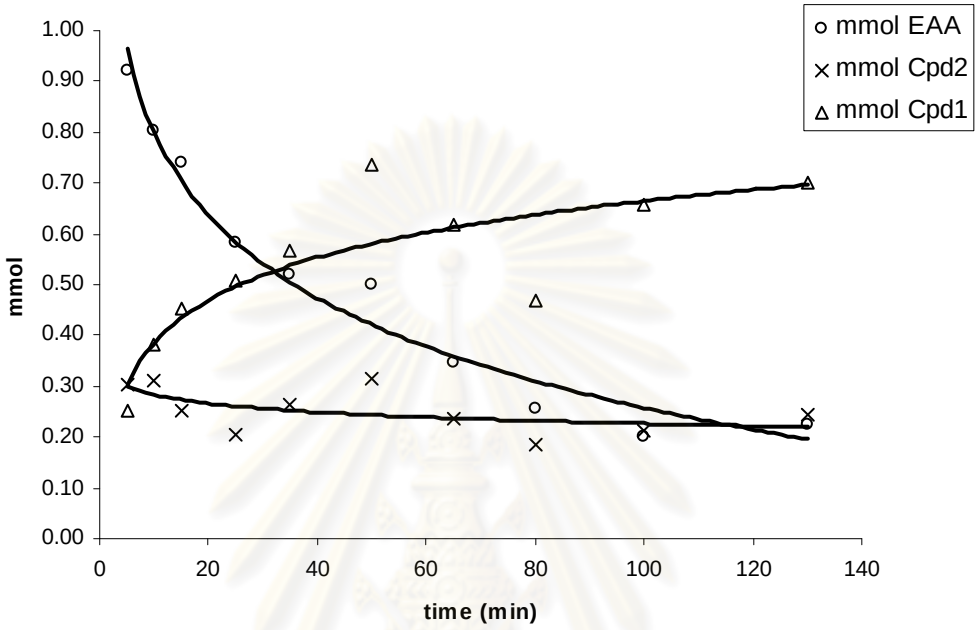
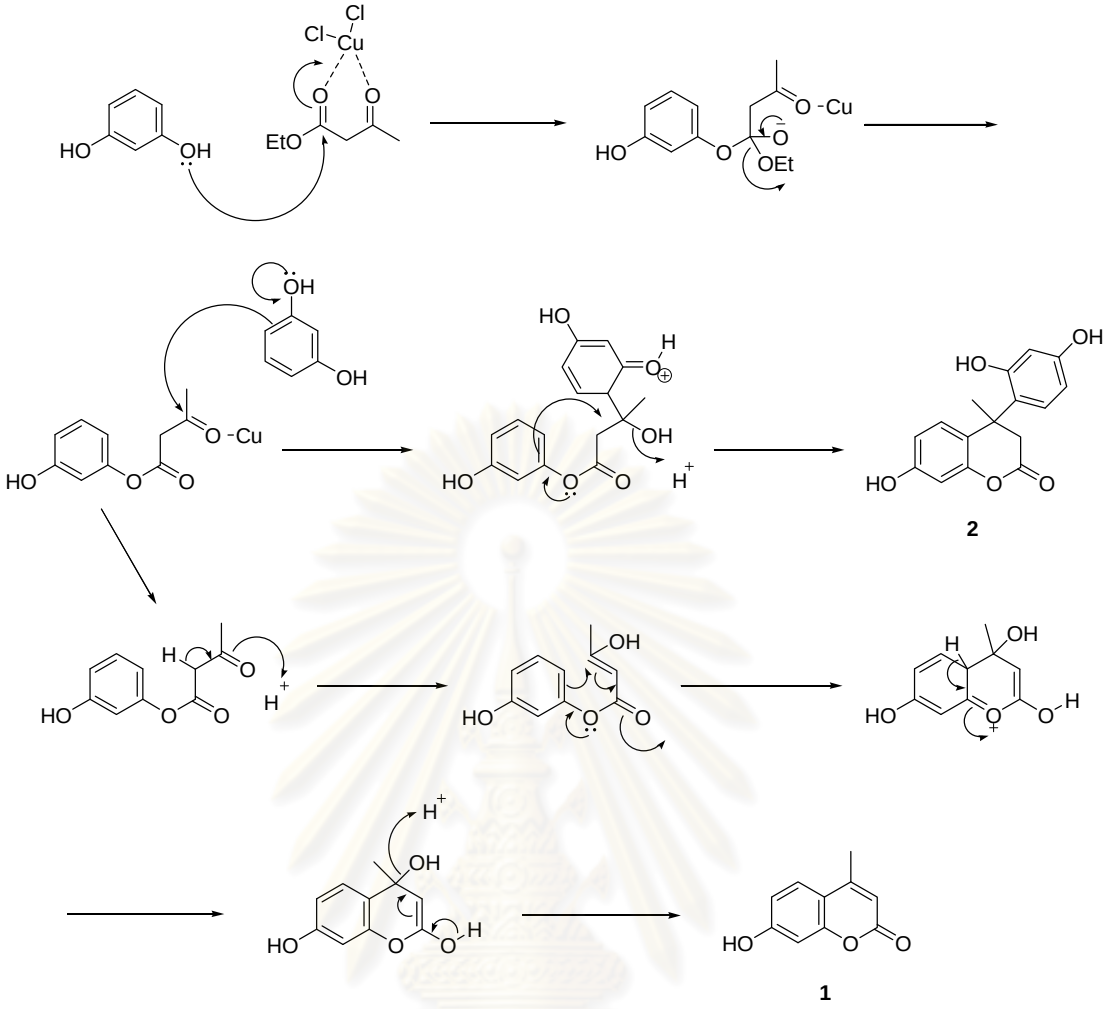


Figure 3.8 Kinetic study on the Pechmann condensation of resorcinol with ethyl acetoacetate catalyzed by $CuCl_2$

From Fig 3.8, the formation of **1** and **2** seemed to occur competitively from the same reaction intermediate. The maximum amount of **2** could be observed within 10 min. It could be pointed out that the formation of **1** would take place from the cyclization of the proposed intermediate. When the reaction time was prolonged, resorcinol mostly reacted with ethyl acetoacetate to furnish the proposed intermediate, therefore **2** was no longer generated. Nonetheless, **2** could not decompose to **1**. As while the formation of **1** increased continuously, the formation of **2** remained almost constant. The proposed mechanism for the formation of **1** and **2** is shown in Scheme 3.1.



Scheme 3.1 Proposed mechanism of the formation of Compound **1** and **2** catalyzed by $CuCl_2$

3.3 Effect of metal halide on Pechmann condensation of resorcinol with ethyl acetoacetate

To explore the feasibility of other metal halides catalyzed Pechmann condensation, the reaction of resorcinol and ethyl acetoacetate was carried out in the presence of 5 mol% metal halide catalyst. The results are presented in Table 3.3.

Table 3.3 Effect of metal halide on Pechmann condensation of resorcinol with ethyl acetoacetate (with no extra solvent)

Entry	Catalyst	% Isolated yield	
		1	**2**
1	-	0	0
2	$CrCl_3 \cdot 6H_2O$	99	trace
3	$CrBr_3 \cdot 6H_2O$	92	trace
4	$MnCl_2$	0	0
5	$CoCl_2$	0	0
6	$CuCl_2$	62	13
7	$SnCl_2 \cdot 2H_2O$	61	6
8	$NiCl_2$	0	0
9	$FeCl_3$	66	16
10	$InCl_3 \cdot H_2O$	46	19

Reaction conditions: resorcinol 5 mmol, ethyl acetoacetate 5 mmol, catalyst 5 mol% (0.25 mmol) at reflux temperature (neat) for 2 h.

The initial experiment focused on type of metal halides. It was observed that $CrCl_3 \cdot 6H_2O$ and $CrBr_3 \cdot 6H_2O$ could effectively catalyze the reaction at reflux temperature and gave the corresponding coumarins in excellent yield with high purity. Because Cr(III) is a hard Lewis acid catalyst according to the Hard-Soft Acid-Base theory, the hard acid Cr(III) was coordinated with the hard base oxygen of the carbonyl. The small size of Cr(III) atom could possibly make it proper for catalysis. However $CuCl_2$, $SnCl_2 \cdot 2H_2O$, $FeCl_3$ and $InCl_3 \cdot H_2O$ could also catalyze the reaction but giving two products of the corresponding coumarins in moderate to good yield. On the other hand, $MnCl_2$, $CoCl_2$ and $NiCl_2$ could not be used as a catalyst for this reaction.

The order of the efficient catalyst was $CrCl_3 \cdot 6H_2O > CrBr_3 \cdot 6H_2O > FeCl_3 \sim CuCl_2 \sim SnCl_2 \cdot 2H_2O > InCl_3 \cdot H_2O$. Based on these screening results, $CrCl_3 \cdot 6H_2O$ was selected for further study.

3.4 Effect of chromium(III) salts and complexes on Pechmann condensation of resorcinol with ethyl acetoacetate

Among various metal halides studied, chromium(III) salt was found to be the effective catalyst. Therefore, various chromium(III) salts and complexes such as $CrCl_3 \cdot 6H_2O$, $CrBr_3 \cdot 6H_2O$, $Cr(NO_3)_3 \cdot 9H_2O$, $Cr(acac)_3$ and $Cr(str)_3$ were examined. The results are exposed in Table 3.4.

Table 3.4 Effect of Cr(III) salts and complex on Pechmann condensation of resorcinol with ethyl acetoacetate (with no extra solvent)

Entry	Catalyst	Isolated yield (%)	
		1	**2**
1	$CrCl_3 \cdot 6H_2O$	99	trace
2	$CrBr_3 \cdot 6H_2O$	92	trace
3	$Cr(NO_3)_3 \cdot 9H_2O$	54	10
4	$Cr(acac)_3$	0	0
5	$Cr(str)_3$	0	0

Reaction conditions: resorcinol 5 mmol, ethyl acetoacetate 5 mmol, catalyst 5 mol% (0.25 mmol) at reflux temperature (neat) for 2 h.

Cr(III) salts, especially $CrCl_3 \cdot 6H_2O$ was the most effective catalyst for this reaction which provided **1** in excellent yield (99%, entry 1). A comparative study on the effect of $CrCl_3 \cdot 6H_2O$ and $CrBr_3 \cdot 6H_2O$ was conducted and found that $CrCl_3 \cdot 6H_2O$ exhibited its capability more effective than $CrBr_3 \cdot 6H_2O$. As chloride ligand is an electron withdrawing group with high electronegativity, it can thus improve the capability of metal for Pechmann condensation. $Cr(NO_3)_3 \cdot 9H_2O$ could also catalyze this reaction and gave two products of the corresponding coumarins in moderate yield while $Cr(acac)_3$ and $Cr(str)_3$ were not proper catalysts for this reaction possibly because of bulky structure of the ligands.

3.5 Effect of the amount of catalyst, temperature and reaction time

Another important factor for condition optimization on the Pechmann condensation is the effect of the amount of catalyst, temperature and reaction time. The results are demonstrated in Table 3.5.

Table 3.5 Effect of temperatures on Pechmann condensation of resorcinol with ethyl acetoacetate (with no extra solvent)

Entry	$CrCl_3 \cdot 6H_2O$ (mol%)	Temperature (°C)	Time (h)	Isolated yield (%)
1	5	RT	24	40
2	5	reflux	2	99
3	10	RT	24	68
4	10	reflux	2	94

Reaction conditions: resorcinol 5 mmol, ethyl acetoacetate 5 mmol.

It could be obviously seen that when the reaction was performed under reflux catalyzed by $CrCl_3 \cdot 6H_2O$ 5 mol% and 10 mol%, the yields of the desired product was satisfied within 2 h (99% entry 2 and 94% entry 4). Decreasing the reaction temperature to RT, this reaction gave the lower yield of product (40% entry 1 and 68% entry 3). The reaction nonetheless required quite long time to gain satisfactory yield compared with other previous systems cited such as the reaction carried out at 80 °C for 24 h catalyzed by $ZrOCl_2 \cdot 8H_2O$ 1 mol% [35].

3.6 Effect of solvent on Pechmann condensation

The study on the choice and amount of solvents was crucial for some instances that the starting materials are all solid or they could not mix homogeneously. Thus, various solvents including EtOH, THF, CH_2Cl_2, toluene, CH_3CN, isooctane, xylene and H_2O were investigated on their roles to affect the Pechmann condensation of resorcinol with ethyl acetoacetate. The results of the effect of solvent on this reaction are set out as shown in Table 3.6.

Table 3.6 Effect of solvent on Pechmann condensation of resorcinol with ethyl acetoacetate

Entry	Solvent	Time (h)	Isolated yield (%)
1	-	2	99
2	EtOH	2	16
3		6	29
4		6	70 [a]
5		10	56
6		24	82
7	THF	6	6
8		6	50 [a]
9	CH_2Cl_2	6	18
10	toluene	2	26
11		6	56
12		6	75 [a]
13		10	70
14		24	67
15	CH_3CN	6	18
16		6	81 [a]
17		24	21
18	isooctane	2	94
19		6	95 [a]
20	*p*-xylene	6	65
21		6	68 [a]
22	H_2O	6	18 [a]

Reaction conditions: resorcinol (5 mmol), ethyl acetoacetate (5 mmol), $CrCl_3 \cdot 6H_2O$ 5 mol% (0.25 mmol), solvent 3 mL at reflux temperature.

[a] solvent 1 mL.

From the above results concerning with the variation of solvent, isooctane provided the highest yield of product in 2 h (94%, entry 18). In contrast, THF, CH_2Cl_2 and CH_3CN should not be used as a solvent for this reaction. The catalyst maybe surround by these polar aprotic solvents, then the catalysis activity was obstructed. It

was therefore noticed that under this particular conditions, non-polar solvent was suitable for this reaction as the capability of the intermediate stabilization. EtOH was also an effective solvent for the long run within 24 h (82%, entry 6), while toluene was found to be good when the reaction was performed for some period of time (70%, entry 13). This present work clearly provided a simple condition for producing the desired product under solvent free condition (99%, entry 1).

It was revealed that when the amount of solvent used was reduced to 1 mL, the corresponding coumarin products were obtained in higher yield (entries 4, 8, 12, 16, 19 and 21). Isooctane was found to remain as the best solvent for this reaction (entry 19). In addition, when a small amount of water was employed as solvent (entry 22), the reaction provided the desired product in 18%. Because H_2O might attack carbonyl of β-ketoester, thus the corresponding products could not obtain in high yield.

3.7 Effect of the amount of catalyst

Effects of the amount of catalyst were explored to search for the appropriate amount of $CrCl_3 \cdot 6H_2O$ in this reaction. The results of this searching are tabulated in Table 3.7.

Table 3.7 Effect of the amount of catalyst on Pechmann condensation of resorcinol with ethyl acetoacetate (with no extra solvent)

Entry	$CrCl_3 \cdot 6H_2O$ (mol%)	Isolated yield (%)
1	0	0
2	1	50
3	5	99
4	10	94
5	20	87

Reaction conditions: resorcinol 5 mmol, ethyl acetoacetate 5 mmol at reflux temperature (neat) for 2 h.

It was lucidly seen that the amount of catalyst was directly influenced on the Pechmann condensation of resorcinol with ethyl acetoacetate. In the absence of $CrCl_3 \cdot 6H_2O$, the reaction did not proceed revealing the necessity of $CrCl_3 \cdot 6H_2O$ for the reaction. Increasing the amount of catalyst from 1 to 5 mol%, the substrate could

quantitatively transform to coumarin within 2 h. In the case of $CrCl_3 \cdot 6H_2O$ higher than 5 mol%, the yield of product was slightly decreased because of over amount of catalyst may obstruct the catalysis activity.

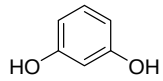
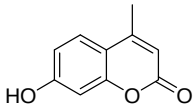
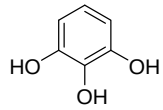
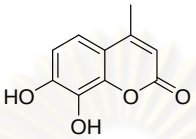
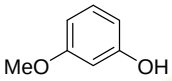
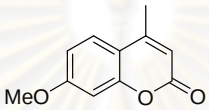
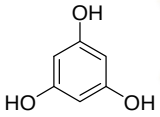
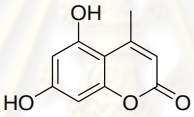
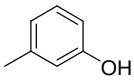
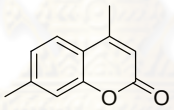
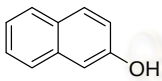
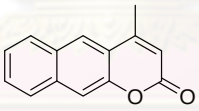
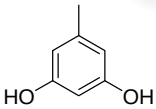
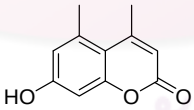
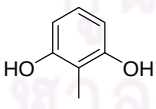
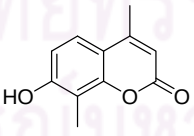
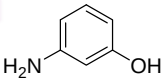
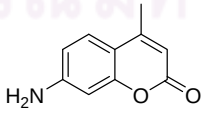
From the overall results observed, the type of metal halides, reaction temperature, reaction time, solvent system and amount of catalyst are affected the reaction. The optimized conditions for Pechmann condensation could be summarized as follows: the mixture of phenols (5 mmol), ethyl acetoacetate (5 mmol) and $CrCl_3 \cdot 6H_2O$ (5 mol%, 0.25 mmol) was carried out under solvent-free at reflux temperature for 2 h. This developed catalytic system was also utilized for other compounds, as discussed in the following topics.

3.8 The application of the developed system for synthesis of various coumarin derivatives

3.8.1 Various phenolic compounds

Various phenolic compounds were selected as the next chemical models to be examined. The goal of this examination was to study the effect of substituent on an aromatic ring on the Pechmann condensation. The Pechmann condensation of phenolic compounds including pyrogallol, 3-methoxyphenol, phloroglucinol, *m*-cresol, 2-naphthol, 2-methylresorcinol, orcinol and 3-aminophenol with ethyl acetoacetate was carried out using the protocol described in the general procedure catalyzed by $CrCl_3 \cdot 6H_2O$. The results are summarized in Table 3.8.

Table 3.8 Synthesis of coumarin derivatives *via* Pechmann condensation of phenols and ethyl acetoacetate

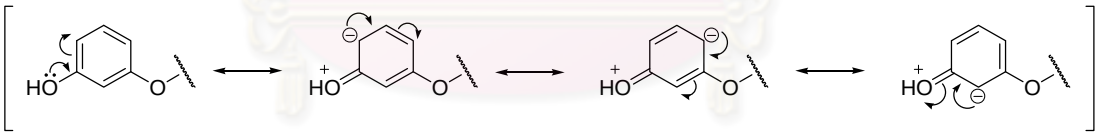
Entry	Phenol	Coumarins	time(h)	Yield(%)	Mp(°C)
1			2	99	184-185
2			2	78	241-243
			6	91	
3			2	14	160-162
			6	25	
4			2	100	283-285
5			2	no reaction	
6			2	no reaction	
7			2	23	258-259
8			2	71	137-138
9			2	8	225-227

Reaction conditions: phenol (5 mmol), ethyl acetoacetate (5 mmol), $CrCl_3 \cdot 6H_2O$ 5 mol% (0.25 mmol), no extra solvent at reflux temperature.

From Table 3.8, the effect of OH group at *para* position to the site of electrophilic substitution leading to the construction of the coumarin derivatives in high yield (entries 1, 2, 4 and 8). The Pechmann condensation of phloroglucinol with ethyl acetoacetate afforded the desired coumarin in quantitative yield under solvent-free condition (entry 4) as two OH groups of phloroglucinol at *ortho* and *para* position.

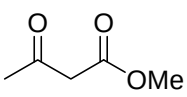
It was found that CH_3 at *ortho* position to the site of electrophilic substitution was steric therefore the coumarin product was acquired in lower yield (entry 7). However, the reaction requires the presence of a strong activating group in the ring. With low activation as alkyl group (entry 5) and aryl group (entry 6) the reaction does not proceed. Thus, the starting materials were quantitatively recovered.

The study of the effect of several substituents at *para* position to the site of electrophilic substitution provided some information clues (entries 1, 3, 5 and 9). The yield was increased in order of $CH_3 < NH_2 <$ OMe < OH. Thus, the more electron donating group on *para* position to the site of electrophilic substitution present, the higher yield was obtained. These substituents are clearly rendered electron to the benzene ring by resonance effect, resulting in the *para* position being electron rich and leading to the formation of the coumarin skeleton. The resonance effect is shown in the figure below.

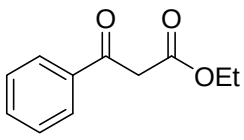


3.8.2 Various β-ketoesters

β-Ketoesters including methyl acetoacetate and ethyl benzoylacetate were investigated on their roles to affect the Pechmann condensation. The results of the effect of β-ketoester on this reaction are summarized in Table 3.9.

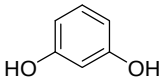
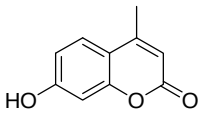
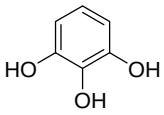
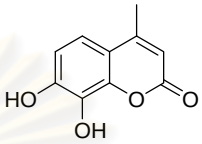
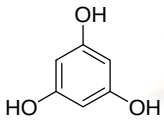
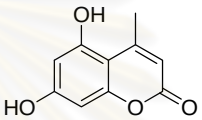
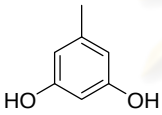
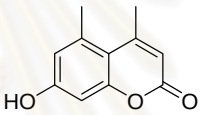
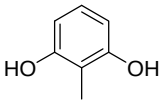
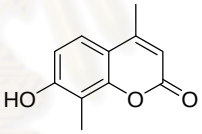
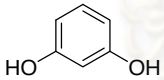
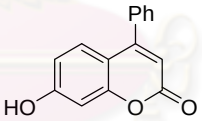
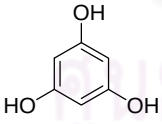
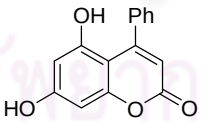
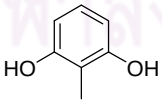
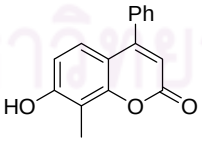
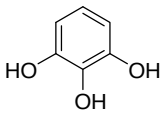
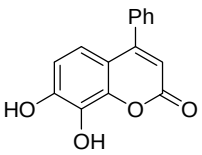


methyl acetoacetate



ethyl benzoylacetate

Table 3.9 Synthesis of coumarin derivatives *via* Pechmann condensation of phenols and β-ketoesters

Entry	Phenol	β-ketoester	Coumarin	Time(h)	Yield(%)
1		Methyl Acetoacetate		2	90
2		Methyl Acetoacetate		2	66
3		Methyl Acetoacetate		2	91
4		Methyl Acetoacetate		2	32
5		Methyl Acetoacetate		2	82
6		Ethyl Benzoylacetate		4	26
7		Ethyl Benzoylacetate		4	15
8		Ethyl Benzoylacetate		4	25
9		Ethyl Benzoylacetate		4	12

Reaction conditions: phenol (5 mmol), β-ketoester (5 mmol), $CrCl_3 \cdot 6H_2O$ 5 mol% (0.25 mmol), no extra solvent at reflux temperature.

From Table 3.9, ethyl benzoylacetate yielded the corresponding coumarin product in lower yield than that derived from ethyl acetoacetate. This was probably due to the fact that a phenyl group of β-ketoester was very bulky and may obstruct the formation of the coumarin skeleton. In addition, the phenyl group made a carbonyl carbon being less electrophilic (entries 6-9). On the other hand, a methyl group rendered the electrophilic property of the keto carbonyl site. Methyl acetoacetate yielded the corresponding coumarin in similar yield to that derived from ethyl acetoacetate (entries 1-5). It was observed that alkyl and aryl group of keto carbonyl could affect on the formation of the coumarin product.

The ^{1}H-NMR spectrum of 7-methoxy-4-methylcoumarin (**3**) (Fig 3.9) visualized the signal of methyl group at δ_H 2.40 (s, 3H). The proton signal of methoxy group on aromatic ring was attributed at δ_H 3.88 (s, 3H). The proton signal of aromatic ring connecting to a methoxy group was observed at δ_H 6.86 (dd, J = 2.5, 8.7 Hz, 1H). The following aromatic proton was discovered at δ_H 7.50 (d, J = 8.8 Hz, 1H). The proton signal of aromatic ring between O of the lactone ring and methoxy group discovered at δ_H 6.82 (s, 1H) and the olefinic proton adjacent to a carbonyl group could be assigned at δ_H 6.14 (s, 1H).

The ^{1}H-NMR spectrum of 5,7-dihydroxy-4-methylcoumarin (**4**) (Fig 3.10) visualized the signal of methyl group at δ_H 2.48 (s, 3H). The proton signal of aromatic ring between two hydroxyl groups was detected at δ_H 6.22 (s, 1H) The olefinic proton adjacent to a carbonyl group could be assigned at δ_H 6.14 (s, 1H) and the aromatic proton between hydroxyl group and O of the lactone ring was observed at δ_H 5.81 (s, 1H).

The ^{1}H-NMR spectrum of 7,8-dihydroxy-4-methylcoumarin (**5**) as shown in Fig 3.11 revealed the signal of methyl group detected at δ_H 2.33 (s, 3H). The two doublet signals of aromatic protons were positioned at δ_H 7.07 (J = 8.5 Hz, 1H) and 6.79 (J = 8.5 Hz, 1H) and the singlet signal of olefinic proton adjacent to a carbonyl group could be assigned at δ_H 6.10 (1H).

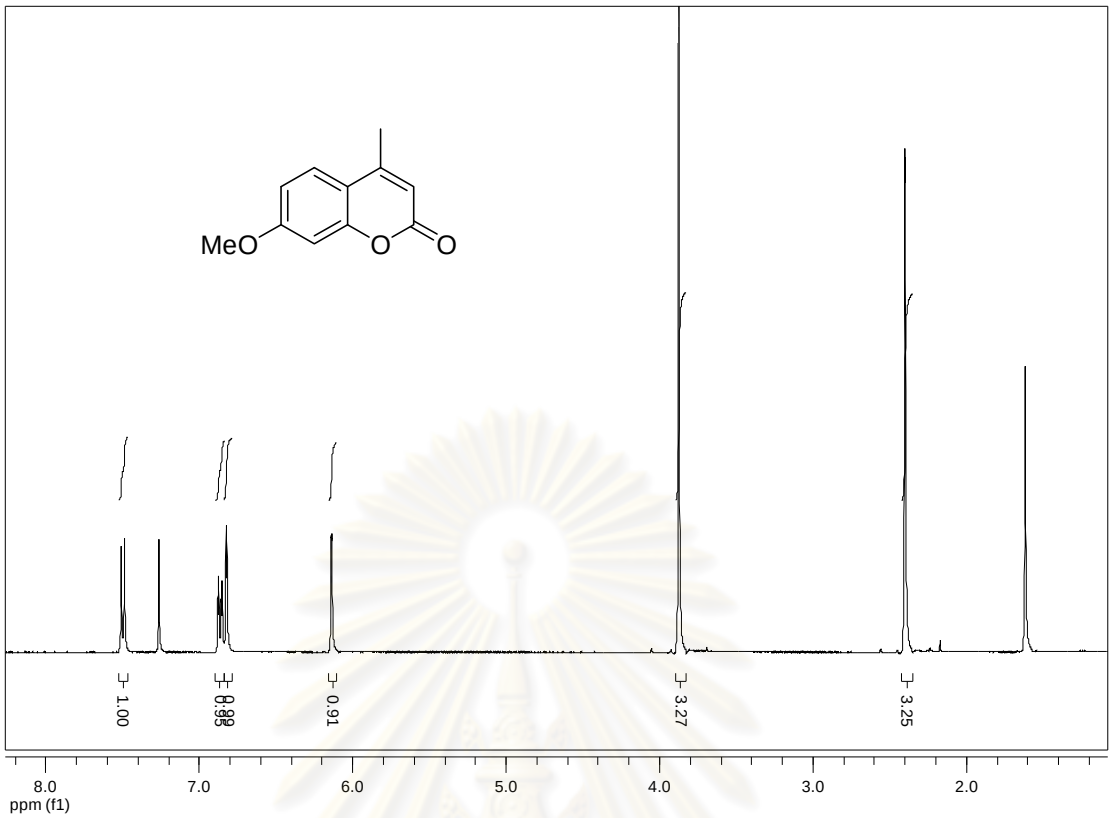


Figure 3.9 ^{1}H-NMR spectrum of 7-methoxy-4-methylcoumarin (**3**)

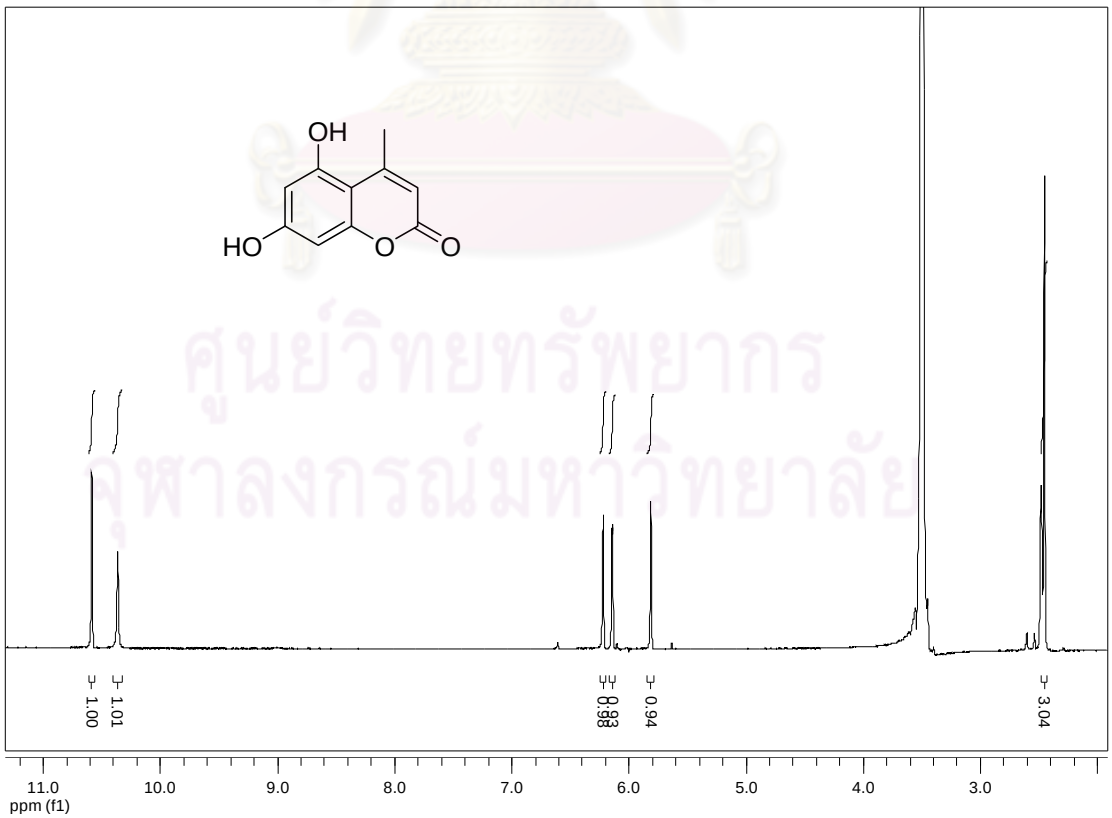


Figure 3.10 ^{1}H-NMR spectrum of 5,7-dihydroxy-4-methylcoumarin (**4**)

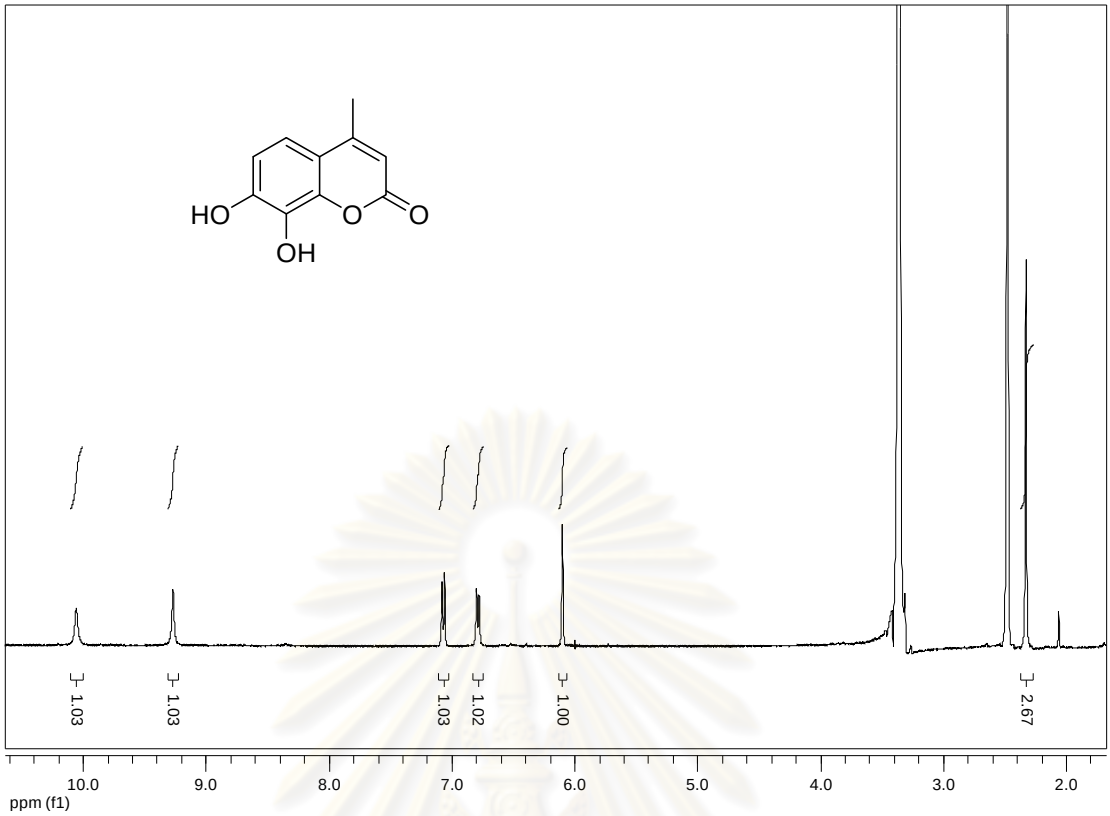


Figure 3.11 ^{1}H-NMR spectrum of 7,8-dihydroxy-4-methylcoumarin (**5**)

The ^{1}H-NMR spectrum of *7*-hydroxy-4,8-dimethylcoumarin (**6**) (Fig 3.12) exhibited he two signals of two methyl groups at δ_H 2.10 (s, 3H) and 2.30 (s, 3H). The two doublet signals of aromatic protons was attributed at δ_H 6.81 (J = 8.6 Hz, 1H) and 7.37 (J = 8.6 Hz, 1H). The singlet signal of olefinic proton adjacent to a carbonyl group could be assigned at δ_H 6.05 (s, 1H).

The ^{1}H-NMR spectrum of 7-hydroxy-4,5-dimethylcoumarin (**7**) (Fig 3.13) visualized two signals of two methyl groups at δ_H 2.24 (s, 3H) and 2.50 (s, 3H). The singlet signal of olefinic proton was detected at δ_H 6.00 (s, 1H) and aromatic protons signal could be assigned around δ_H 6.55 (d, J = 14.2 Hz, 2H).

The ^{1}H-NMR spectrum of 7-amino-4-methylcoumarin (**8**) as shown in Fig 3.14 displayed a significant singlet signal of the methyl group observed at δ_H 2.27 (3H). The singlet signal of olefinic proton adjacent to a carbonyl group could be assigned at δ_H 5.87 (1H). The signal of the amino group was visualized at δ_H 6.08 (s, 2H). The aromatic protons were observed at δ_H 7.37 (d, J = 8.6 Hz, 1H), 6.53 (dd, J = 2.0, 8.6 Hz, 1H) and 6.38 (d, J = 1.9 Hz, 1H).

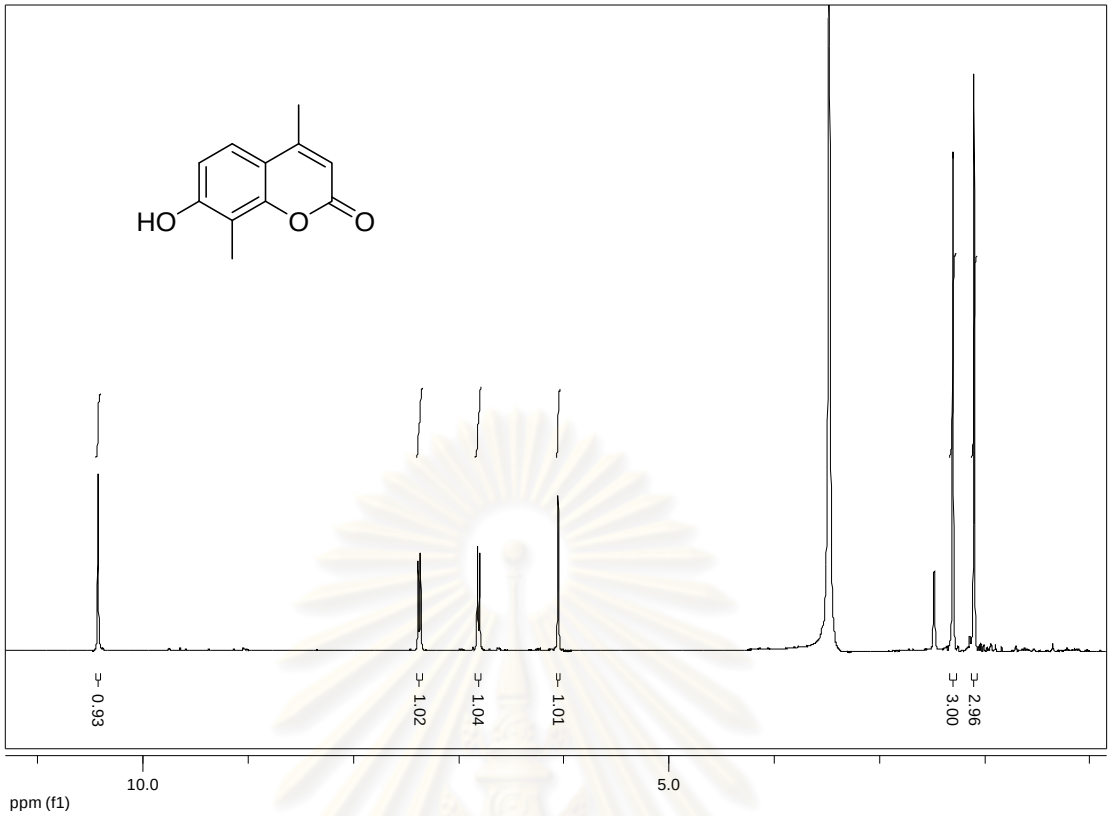


Figure 3.12 ^{1}H-NMR spectrum of *7*-hydroxy-4,8-dimethylcoumarin (**6**)

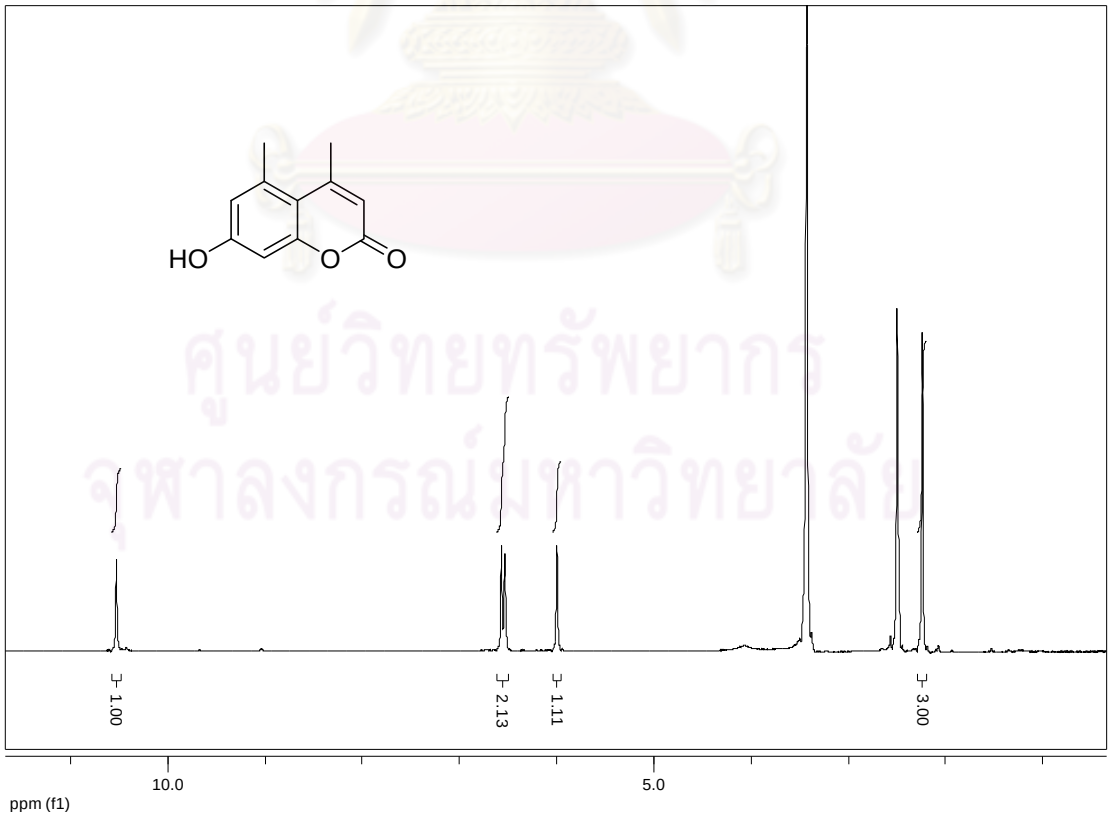


Figure 3.13 ^{1}H-NMR spectrum of 7-hydroxy-4,5-dimethylcoumarin (**7**)

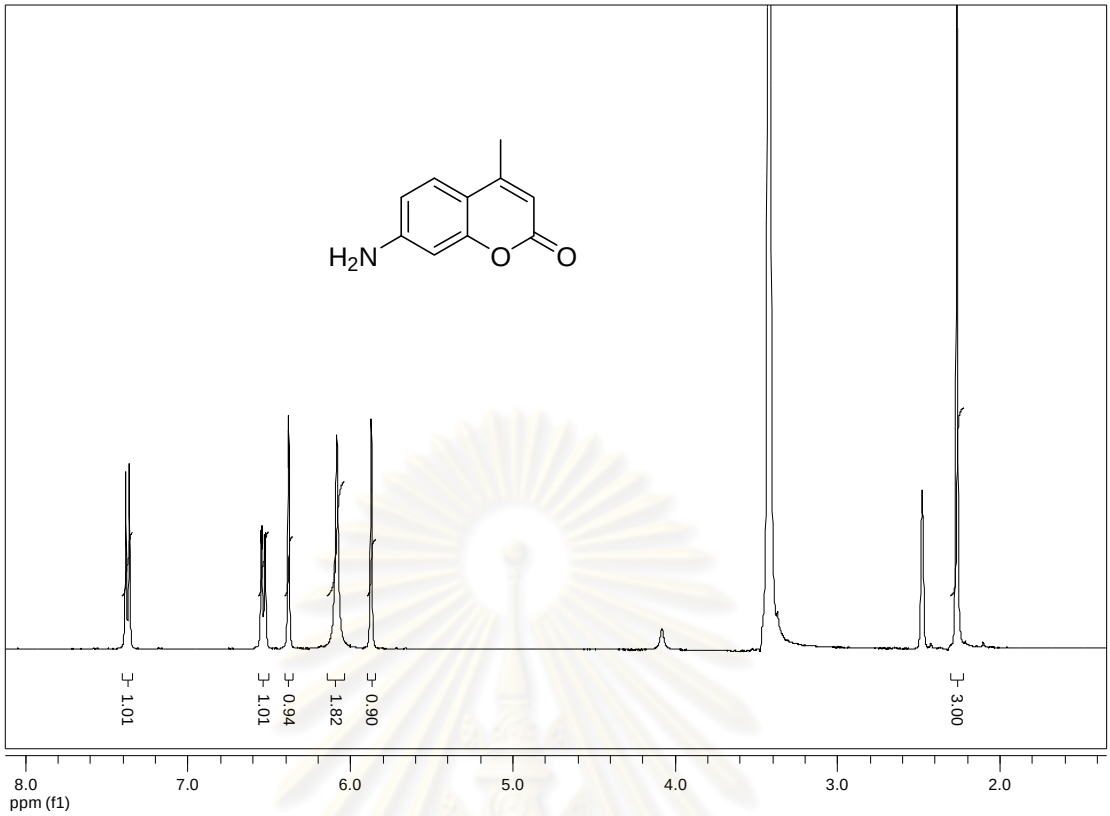


Figure 3.14 The ^{1}H-NMR spectrum of 7-amino-4-methylcoumarin (**8**)

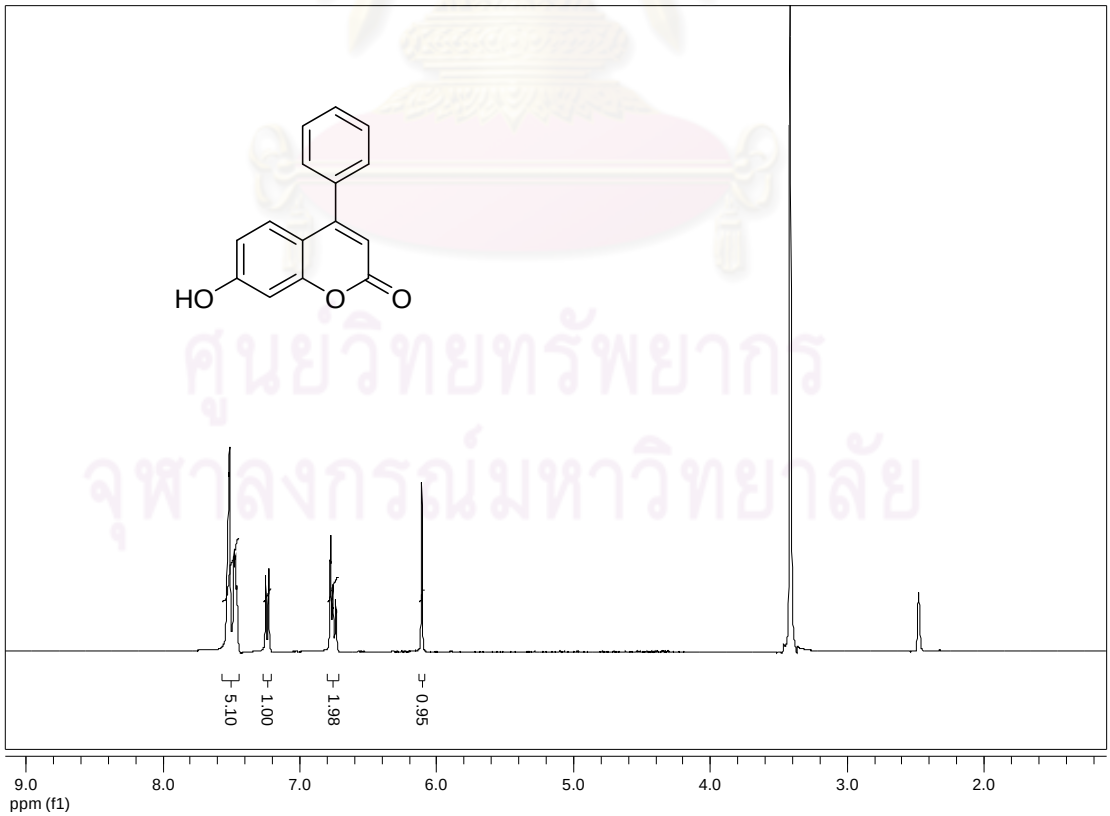


Figure 3.15 The ^{1}H-NMR spectrum of 7-hydroxy-4-phenylcoumarin (**9**)

The ^{1}H-NMR spectrum of 7-hydroxy-4-phenylcoumarin (**9**) as shown in Fig 3.15 revealed the signal of phenyl group detected around δ_H 7.46-7.52 (m, 5H). The signals of aromatic protons were positioned at δ_H 7.24 (d, J = 8.7 Hz, 1H) and 6.74-6.77 (m, 2H) and the singlet signal of olefinic proton adjacent to a carbonyl group could be assigned at δ_H 6.11 (1H).

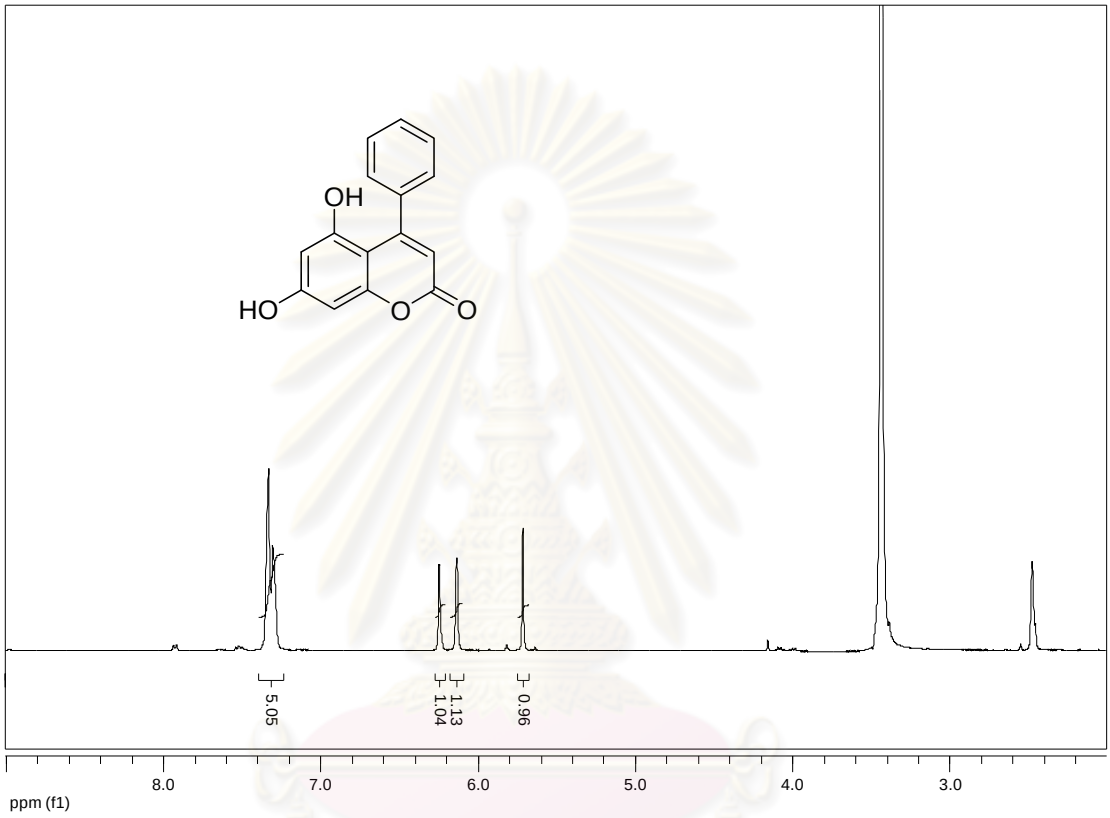


Figure 3.16 The ^{1}H-NMR spectrum of 5,7-dihydroxy-4-phenylcoumarin (**10**)

The ^{1}H-NMR spectrum of 5,7-dihydroxy-4-phenylcoumarin (**10**) (Fig 3.16) visualized multiplet signal of the phenyl group around δ_H 7.31-7.33 (5H). The signals of aromatic protons were positioned at δ_H 6.24 (s, 1H) and 6.14 (s, 1H). The singlet signal of olefinic proton adjacent to a carbonyl group could be assigned at δ_H 5.72 (1H).

The ^{1}H-NMR spectrum of 7-hydroxy-8-methyl-4-phenylcoumarin (**11**) (Fig 3.17) showed signal of the phenyl group around δ_H 7.46-7.52 (m, 5H). The signals of aromatic protons were positioned at δ_H 7.09 (d, J = 8.7 Hz, 1H) and 6.81 (d, J = 8.7 Hz, 1H). The singlet signal of olefinic proton adjacent to a carbonyl group could be assigned at δ_H 6.11 (1H) and the singlet signal methyl group revealed at δ_H 2.18 (3H).

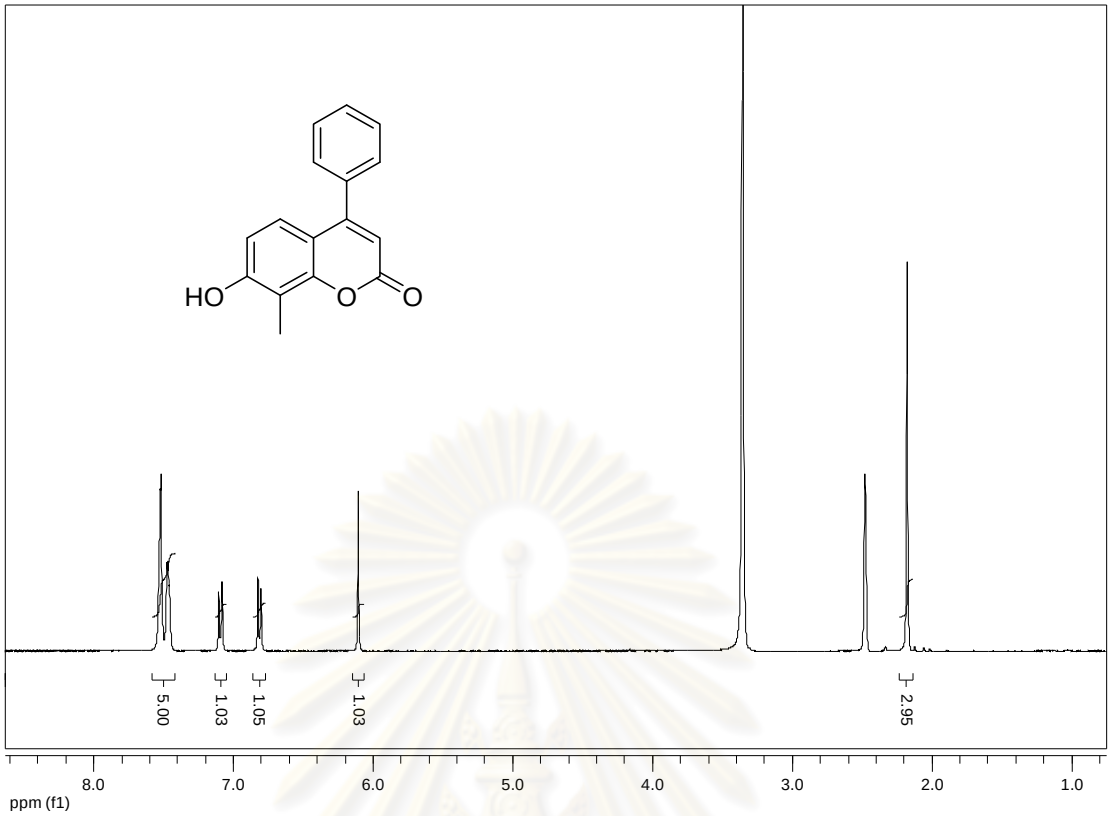


Figure 3.17 The ^{1}H-NMR spectrum of 7-hydroxy-8-methyl-4-phenylcoumarin (**11**)

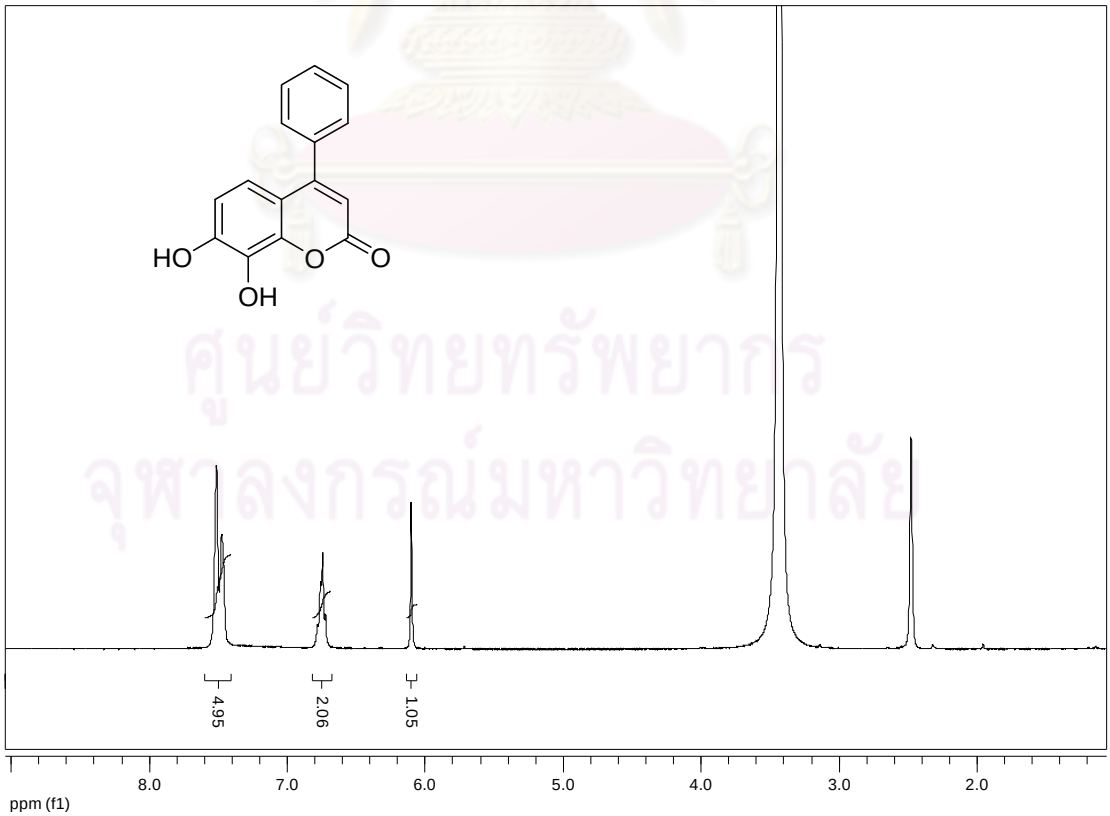
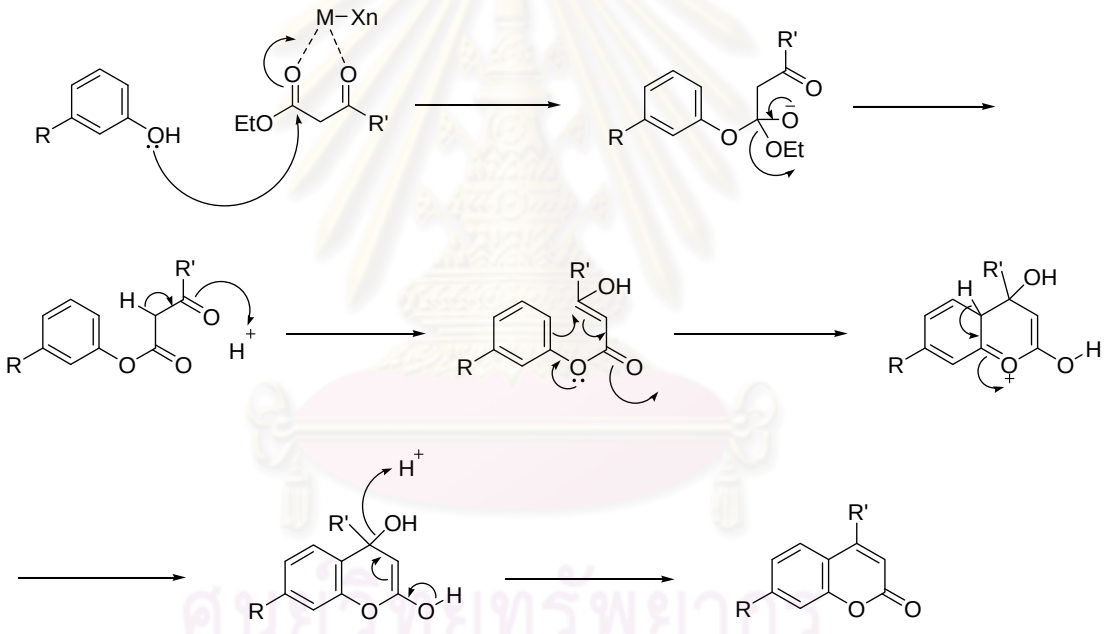


Figure 3.18 The ^{1}H-NMR spectrum of 7,8-dihydroxy-4-phenylcoumarin (**12**)

The ^{1}H-NMR spectrum of 7,8-dihydroxy-4-phenylcoumarin (**12**) (Fig 3.16) displayed signal of the phenyl group observed around δ_H 7.48-7.51 (m, 5H). The aromatic protons were visualized around δ_H 6.72-6.76 (m, 2H). The singlet signal of olefinic proton adjacent to a carbonyl group could be assigned at δ_H 6.10 (1H).

3.9 Proposed mechanism for Pechmann condensation catalyzed by metal halides

The mechanism of Pechmann condensation of phenols with β-ketoester employing metal halides as a catalyst was believed to proceed *via* the following pathway in the same fashion proposed in literature [36, 38]. The proposed mechanism is shown in Scheme 3.2.

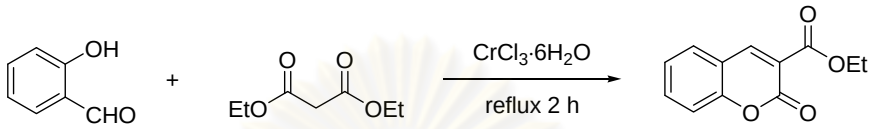


Scheme 3.2 Proposed mechanism for Pechmann condensation catalyzed by metal halides

The reaction is conducted with a strong Lewis acid. The acid catalyzes transesterification as well as keto-enol tautomerisation. The electrophilic attack on the benzene ring by protoned ketone carbonyl leads to the formation of the coumarin skeleton. This addition is followed by rearomatisation. Subsequent acid-induced elimination of water gives the product.

3.10 The application of the developed system for synthesis of coumarin *via* Knoevenagel condensation

Salicylaldehyde and diethyl malonate were selected as the next chemical models to be examined. This examination was to study the effectiveness of $CrCl_3 \cdot 6H_2O$ catalyst for Knoevenagel condensation. Salicylaldehyde and diethyl malonate were commercial available substrates.



13

Reaction conditions: salicylaldehyde 5 mmol (0.53 mL), diethyl malonate 5 mmol (0.76 mL), $CrCl_3 \cdot 6H_2O$ 5 mol% (0.25 mmol), no solvent at reflux temperature.

This reaction was performed in the presence of $CrCl_3 \cdot 6H_2O$ 5 mol% at reflux temperature for 2 hours. It was found that $CrCl_3 \cdot 6H_2O$ catalyst could catalyze Knoevenagel condensation to afford the 3-substituted coumarin. The corresponding coumarin, ethyl 3-coumarincarboxylate, was obtained in 14% isolated yield and identified by ^{1}H-NMR. Nevertheless, the improvement of $CrCl_3 \cdot 6H_2O$ catalyst systems for Knoevenagel condensation are imperative to investigate.

The ^{1}H-NMR spectrum of ethyl 3-coumarincarboxylate (**13**) as shown in Fig 3.19 displayed a significant triplet signal of the methyl group observed at δ_H 1.40 (J = 7.1 Hz, 3H). The quartet signal of methylene protons was detected at δ_H 4.41 (J = 7.1 Hz, 2H) while the aromatic protons of coumarin detected as multiplet signals at δ_H 7.31-7.36 (2H) and 7.60-7.66 (2H).The olefinic proton signal on the lactone ring was visualized at δ_H 8.52 (s, 1H).

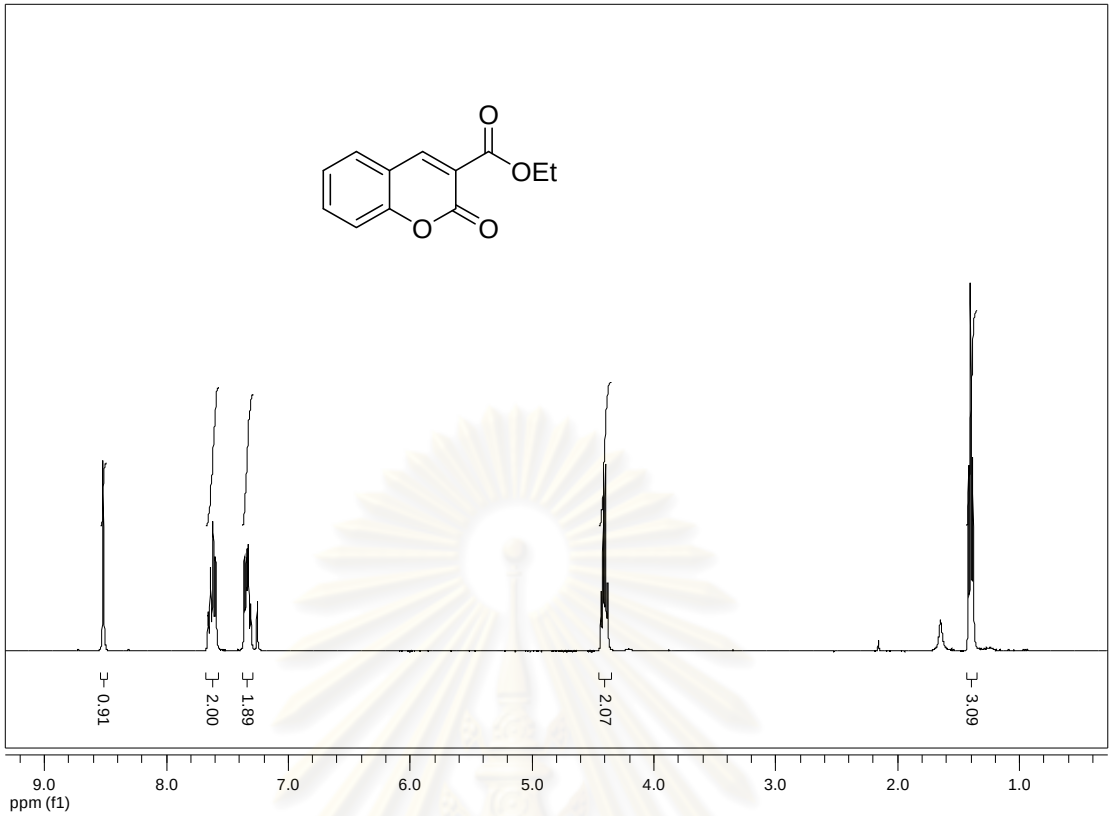
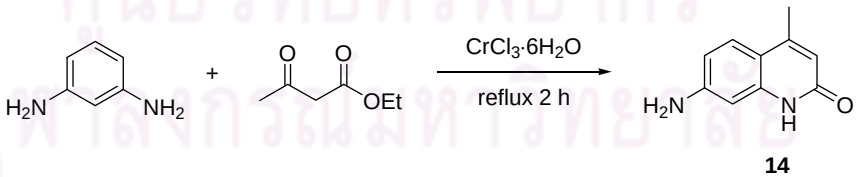


Figure 3.19 The ^{1}H-NMR spectrum of ethyl 3-coumarincarboxylate (**13**)

3.11 The application of the developed system for synthesis of quinolinone

m-Phenylenediamine and ethyl acetoacetate were selected as the chemical models to be examined. This examination was to study the effectiveness of $CrCl_3 \cdot 6H_2O$ catalyst for quinolinone synthesis. *m*-Phenylenediamine was a commercial available substrate.



14

Reaction conditions: *m*-phenylenediamine 5 mmol (0.54 g), ethyl acetoacetate 5 mmol (0.63 mL), $CrCl_3 \cdot 6H_2O$ 5 mol% (0.25 mmol), no solvent at reflux temperature.

This reaction was performed in neat in the presence of $CrCl_3 \cdot 6H_2O$ 5 mol% at reflux temperature for 2 hours. The $CrCl_3 \cdot 6H_2O$ could catalyze the reaction to afford the desired product. 7-Amino-4-methylquinolin-2-one was acquired in 22% isolated

yield and identified by ^{1}H-NMR. Notwithstanding, the improvement of $CrCl_3 \cdot 6H_2O$ catalyst systems for quinolinone synthesis are also interesting to investigate.

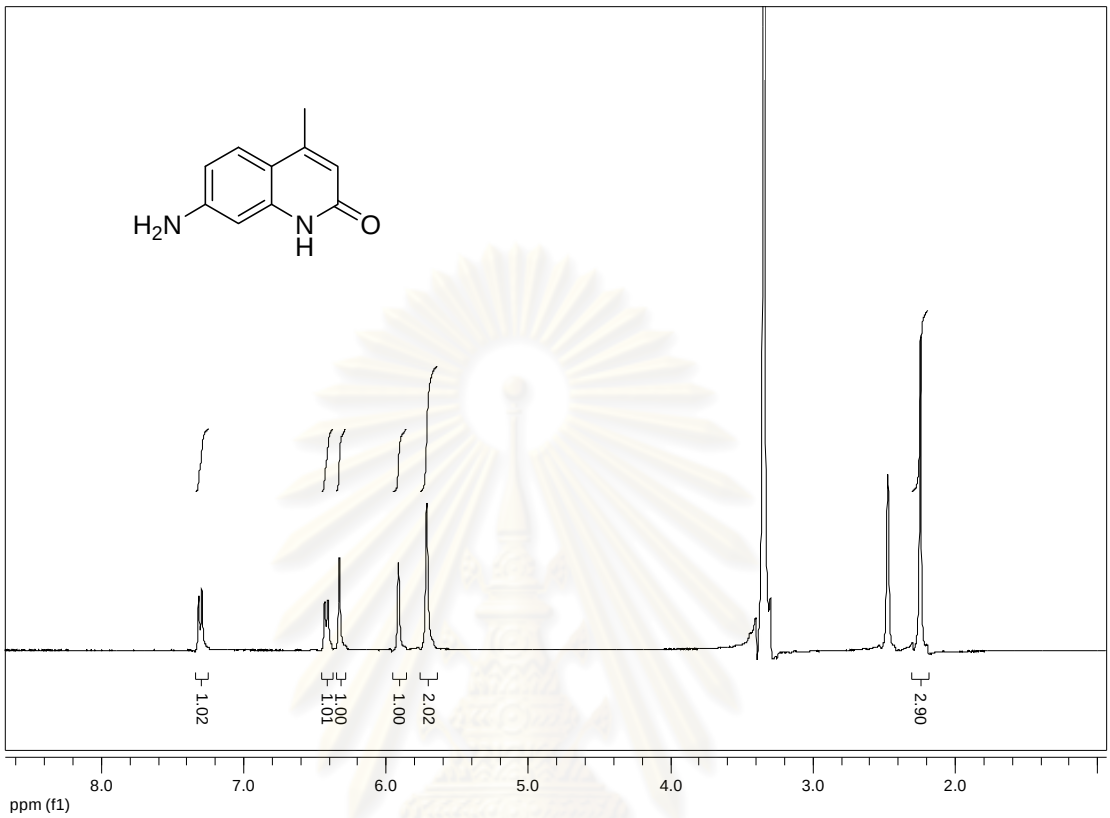


Figure 3.20 The ^{1}H-NMR spectrum of 7-amino-4-methylquinolin-2-one (**14**)

The ^{1}H-NMR spectrum of 7-amino-4-methylquinolin-2-one (**14**) as shown in Fig 3.20 displayed a significant singlet signal of the methyl group observed at δ_H 2.24 (3H). The singlet signal of olefinic proton adjacent to a carbonyl group could be assigned at δ_H 5.91 (1H). The signal of the amino group was visualized at δ_H 5.71 (s, 2H). The aromatic protons were observed at δ_H 7.30 (d, J = 8.6 Hz, 1H), 6.42 (d, J = 8.6 Hz, 1H) and 6.33 (s, 1H).

CHAPTER IV

CONCLUSION

During the course of this research, the development of the Pechmann condensation for the synthesis of coumarins was focused. It was disclosed that $CrCl_3 \cdot 6H_2O$ displayed as the best metal halide catalyst. Various factors: type of metal halides, reaction temperature, reaction time, solvent system and amount of catalyst have affected the yield of the coumarin products. The ligands with high electronegativities or containing electron withdrawing group and small structure can improve the capability of metal for Pechmann condensation of resorcinol and ethyl acetoacetate. The optimized conditions are summarized as follows: the mixture of phenols (1 equiv), ethyl acetoacetate (1 equiv) and catalyst (5 mol%) was carried out under solvent-free at reflux temperature for 2 h for utilization of $CrCl_3 \cdot 6H_2O$. These novel $CrCl_3 \cdot 6H_2O$ catalyst systems for the synthesis of coumarins were found that have not ever been reported. The applications of these systems for the synthesis of other coumarin derivatives were carried out. Various coumarin derivatives could be prepared in good yield. Especially, two natural product compounds, namely 7-hydroxy-4-methylcoumarin and 5,7-dihydroxy-4-methylcoumarin, were successfully prepared in satisfied yields.

Overture for the future work

This research concerned with the development for the synthesis of coumarin derivatives. The outcome opened many possibilities to deal with future exploration. The scale-up experiment utilizing of this reaction system should be performed since this reaction selectively provided only one coumarin product. The development of $CrCl_3 \cdot 6H_2O$ for other catalyst systems are imperative to investigate. From the academic view point, bioactive compounds, pharmaceutically active compounds and

certain chemicals containing heterocyclic nucleous are interesting to synthesize from coumarin product.

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