การเตรียมกรดแอลฟาคีโทและแอลฟาคีโทเอสเทอร์โดยใช้สารประกอบเชิงซ้อนโลหะแทรนซิชันคาร์บอกซิเลต

นายอดิศักดิ์ ชัยธานี

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์
คณะวิทยาศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2548

ISBN 974-14-3378-6

PREPARATION OF α-KETO ACIDS AND α-KETO ESTERS USING TRANSITION METAL CARBOXYLATE COMPLEXES

Mr. Adisak Chaitanee

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Petrochemistry and Polymer Science
Faculty of Science
Chulalongkorn University
Academic Year 2005

ISBN 974-14-3378-6

Thesis Title	Preparation of α-Keto Acids and α-Keto Esters using Transition Metal Carboxylate Complexes
By	Mr. Adisak Chaitanee
Field of Study	Petrochemistry and Polymer Science
Thesis Advisor	Assistant Professor Warinthorn Chavasiri, Ph.D.

Accepted by the Faculty of Science, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

T. Vitidsant
.....Deputy Dean for Administrative Affairs, Acting Dean, The Faculty of Science
(Associate Professor Tharapong Vitidsant, Ph.D.)

THESIS COMMITTEE

..... Chairman
(Associate Professor Supawan Tantayanon, Ph.D.)

Warinthorn Chavasiri
..... Thesis Advisor
(Assistant Professor Warinthorn Chavasiri, Ph.D.)

Padet Sidisuntorn
..... Member
(Professor Padet Sidisuntorn, Ph.D.)

W. Trakarnpruk
..... Member
(Associate Professor Wimonrat Trakarnpruk, Ph.D.)

T. Tuntulani
.....Member
(Associate Professor Thawatchai Tuntulani, Ph.D.)

อดิศักดิ์ ชัยธานี : การเตรียมกรดแอลฟาคีโทและแอลฟาคีโทเอสเทอร์โดยใช้สารประกอบเชิงซ้อนโลหะแทรนซิชันคาร์บอกซิเลต (PREPARATION OF α-KETO ACIDS AND α-KETO ESTERS USING TRANSITION CARBOXYLATE COMPLEXES) อ. ที่ปรึกษา: ผศ. ดร. วรินทร ชวศิริ, 70 หน้า. ISBN 974-14-3378-6.

จากการทดสอบเบื้องต้นของสารประกอบเชิงซ้อนนิกเกิลคาร์บอกซิเลต พบว่า นิกเกิลสเทียเรตสามารถเร่งปฏิกิริยาเปลี่ยนรูปเอทิลเฟนิลแอซิเทตได้เอทิลเบนโซอิลฟอร์เมตเป็นผลิตภัณฑ์หลักและเอทิลแมนดีเลตเป็นผลิตภัณฑ์รอง ในกรณีของสารประกอบเชิงซ้อนเหล็กคาร์บอกซิเลต พบว่าเหล็กไทรคลอโรแอซิเทตสามารถเร่งปฏิกิริยาการเปลี่ยนรูปเอทิลเฟนิลแอซิเทตไปเป็นเอทิลเบนโซอิลฟอร์เมตได้ในปริมาณที่สูง ได้ศึกษาภาวะที่เหมาะสมสำหรับปฏิกิริยาออกซิเดชันของเอทิลเฟนิลเอซิเทต ได้แก่ ชนิดและปริมาณของตัวเร่งปฏิกิริยา ชนิดและปริมาณของตัวออกซิแดนซ์ ตัวทำละลาย เวลาและอุณหภูมิ

ภายใต้ภาวะที่เหมาะสมสำหรับออกซิเดชันของเอทิลเฟนิลแอซิเทต สารอื่นที่เลือกมาศึกษา: เอทิลแมนดีเลต เอทิลไทโอฟีน-2-แอซิเทต เอทิล 4-คลอโรเฟนิลแอซิเทต เมทิล 4-เมทอกซีเฟนิลแอซิเทต เอทิล 4-เมทอกซีเฟนิลแอซิเทต บิวทิล 4-เมทอกซีเฟนิลแอซิเทตและเอทิล พาราโทลูอิลแอซิเทต สามารถเปลี่ยนรูปไปเป็นแอลฟาคีโทเอสเทอร์ที่สอดคล้องกันได้ในปริมาณที่ดีถึงดีมาก

สาขาวิชา.....ปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์.....ลายมือชื่อนิสิต.....

ปีการศึกษา.....2548.....ลายมือชื่ออาจารย์ที่ปรึกษา.....

4672482323 : MAJOR PETROCHEMISTRY AND POLYMER SCIENCE
KEY WORD: OXIDATION / CATALYST / α-KETO ACIDS / α-KETO ESTERS

ADISAK CHAITANEE: PREPARATION OF α-KETO ACIDS AND α-KETO ESTERS USING TRANSITION METAL CABOXYLATE COMPLEXES. THESIS ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., 70 pp. ISBN 974-14-3378-6.

Screening for nickel(II) carboxylate complexes disclosed that nickel(II) stearate coupled with THBP could catalyze the transformation of ethyl phenylacetate to ethyl benzoylformate as a major product and ethyl mandelate as a minor product. In the case of iron(III) carboxylate complexes, iron(III) trichloroacetate coupled with THBP could smoothly catalyze the transformation of ethyl phenylacetate to ethyl benzoylformate in high yield. The optimum conditions for the oxidation of ethyl phenylacetate including amount and type of catalyst, amount and type of oxidant, solvent, reaction time and reaction temperature were conducted.

Utilizing the developed optimum conditions for the oxidation of ethyl phenylacetate, other selected chemical models: ethyl mandelate, ethyl thiophene-2-acetate, ethyl (4-chlorophenyl)acetate, methyl (4-methoxyphenyl) acetate, ethyl (4-methoxyphenyl)acetate, butyl (4-methoxyphenyl)acetate and ethyl *p*-toluylacetate could be converted to corresponding α-keto esters in good to excellent yield.

Field of study Petrochemistry and Polymer Science Student's signature Adisak Chaitanee
Academic year ..... 2005 ..... Advisor's signature W. Chavasiri

ACKNOWLEDGEMENTS

The author wishes to express his highest appreciation to his advisor, Assistant Professor Dr. Warinthorn Chavasiri for his valuable instructions, very kind assistance, generous guidance and encouragement throughout the course of this research. Furthermore, sincere thanks are extended to Natural Products Research Unit, Department of Chemistry, Faculty of Science, Chulalongkorn University for the support of chemical and laboratory facilities.

The greatest thanks are also extent to Professor Dr. Padet Sidisuntorn, Associate Professor Dr. Supawan Tantayanon, Associate Professor Dr. Wimonrat Trakarnpruk and Associate Professor Dr. Thawatchai Tuntulani for their suggestions, comments, corrections and helps as thesis examiners. Moreover, thanks are extended to the Department of Chemistry and Program of Petrochemistry and Polymer Science, Faculty of Science, Chulalongkorn University for granting financial support to fulfill this study and provision of experimental facilities.

Further acknowledgement is extended to his friends for friendship and helps throughout the entire course of study. Especially, the author is very appreciate to his family members whose names are not mentioned for their love, assistance, understanding, encouragement and social support throughout his entire education. Without them, the author would never have been able to achieve this goal.

CONTENTS

Pages

Pages

Pages

LIST OF FIGURES

Figures **Pages**

LIST OF TABLES

Tables **Pages**

LIST OF SCHEMES

Schemes **Pages**

LIST OF ABBREVIATIONS

δ	chemical shift (NMR)
J	coupling constant (NMR)
cm^{-1}	wave number (IR)
ºC	degree Celsius
$CDCl_3$	deuterated chloroform
$Cr(TCA)_3$	chromium(III) trichloroacetate
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
d	doublet (NMR)
dd	doublets of doublet (NMR)
EtOAc	ethyl acetate
$Fe(TCA)_3$	iron(III) trichloroacetate
GC	gas chromatography
g	gram(s)
HCl	hydrochloric acid
Hz	hertz
LDA	lithium diisopropylamine
lit	literature
THF	tetrahydrofuran
^{1}H-NMR	proton nuclear magnetic resonance
H_2SO_4	sulfuric acid
equiv	equivalent(s)
h	hour(s)
IR	infrared
KBr	potassium bromide
$Mn(TCA)_2$	manganese(II) trichloroacetate
m	medium (IR)
m.p.	melting point
mL	milliliter(s)
mmol	millimole
m	multiplet (NMR)

$Ni(st)_2$	nickel(II) stearate
mol%	percent by mole
ppm	part per million
q	quartet (NMR)
quin	quintet (NMR)
R_f	retardation factor
s	singlet (NMR)
s	strong (IR)
sex	sextet (NMR)
TBHP	*tert*-butylhydroperoxide
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TEA	triethylamine
t	triplet (NMR)
w	watt
w	weak (IR)

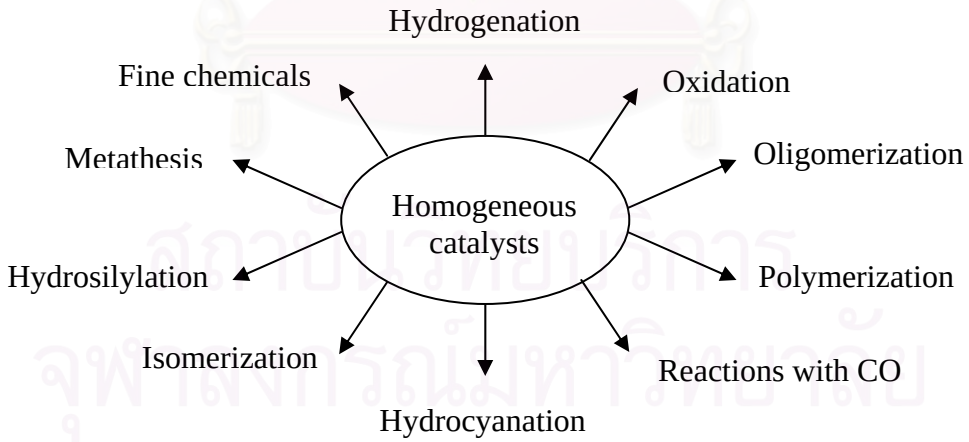
CHAPTER I

INTRODUCTION

1.1 Homogeneous catalysts in organic synthesis

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 catalyst (solid-state catalysts) and homogeneous catalysts. There are also intermediate forms such as homogeneous catalyst attached to solids (supported catalyst), also known as immobilized catalyst. The well-known biocatalysts (enzymes) also belong to this class.

In the last three decades homogeneous catalysis has undergone major growth. Many new processes with transition metal catalyst have been developed, and many new products have become available [1]. Homogeneous transition metal catalyzed reactions are now used in nearly all areas of chemical industry, as shown in Scheme 1.1.

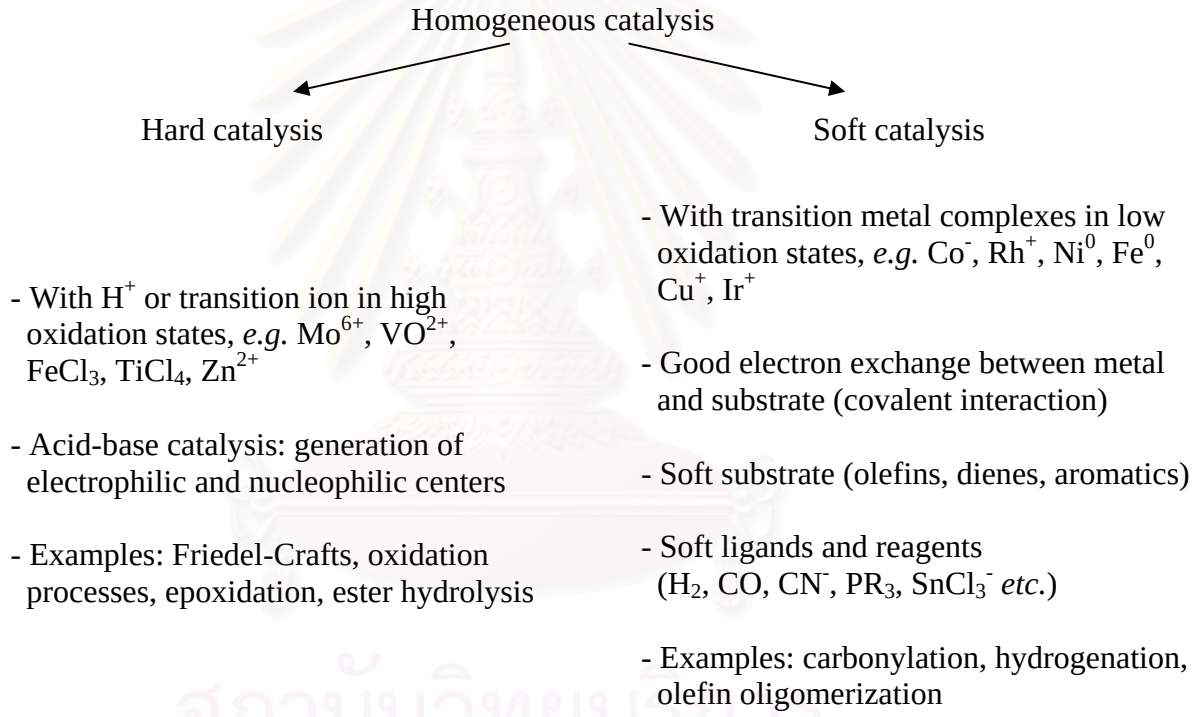


Scheme 1.1 Homogeneous transition metal reactions carried out industrially

The most important industrial application of homogeneous catalyst is the oxidation of hydrocarbon with oxygen or peroxides. Mechanistically, a distinction is made between:

- Homolytic processes: the transition metals react with formation of radicals, and the oxidant or reduction steps are one-electron processes.
- Heterolytic processes: normal two-electron of coordination chemistry.

Catalytic processes generally consist of complicated series of reactions, whereby the activation steps can place different demands on the catalyst. Previous reports have classified the homogeneous catalysis of organic reactions on the basis of HSAB concept [1]. 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" catalyst, providing a simple basis for understanding transition metal catalyzed processes as exhibited in Scheme 1.2.



Scheme 1.2 Hard and soft catalysis with transition metal compounds

Nowadays the broad spectrum of catalytic processes would be inconceivable without homogeneous transition metal catalysts, importance of which can 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 are fine chemicals?

It has not been known universally accepted definitions of bulk, fine and specialty chemicals, neither are these classifications based on any intrinsic properties. A substance that is currently viewed as a bulk chemical might well have been classified as a fine chemical as an earlier stage in its development. A useful working definition of a fine chemical is one with a price of higher than 10 US dollars kg^{-1} and a volume lower than 10,000 tons per annum on a worldwide basis [2]. It makes no distinction between fine chemicals, that are often intermediate, and specialty chemical such as pharmaceuticals, pesticides, flavors and fragrance. The type of technology used to manufacture these products is dictated more by volume than by product application.

From chemical viewpoint, fine chemicals are generally complex, multi-functional molecules and, consequently, are often of low volatility and limited thermal stability. This means that processes are generally performed in the liquid phase. Fine chemicals manufacture often involves multi-step syntheses and is generally performed in multipurpose equipment. This contrast with the manufacture of bulk chemicals usually involves continuous processing in dedicated plants. Hence, the emphasis in fine chemicals manufacture is on the development of processes that have broad scope and can be implemented in standard multipurpose equipment.

1.3 The importance of α-keto acids and α-keto esters

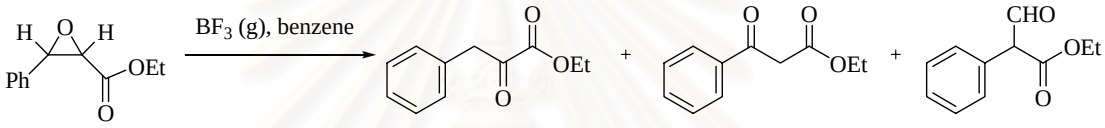
α-Keto acids and α-keto esters play an important role in food industry [3-5] and medical science [6,7]. Aryl α-keto esters have also been shown to be anti-sunburn compounds [8]. Interestingly, methyl and butyl (4-methoxybenzoyl)formates have recently been isolated from the hydrophilic extract of the ascidian *Polycarpa aurata* [9]. In addition, α-keto acids and α-keto esters have been described as some important key intermediates in synthesis of variety of heterocyclic compounds, such as acylhydroquinones [10], aziridine carboxylates [11], dihydropyrimidinones [12] and furan derivatives [13,14], in the synthesis of biologically active compounds [15-18], pharmaceutically active compounds [19], amino acids [20-22] and reduction to α-hydroxy acids/esters [23-28]. Due to the importance of these α-keto acids and α-keto esters, over the past decades, various methods have been reported for the synthesis of these compounds.

1.4 Methods for the syntheses of α-keto acids and α-keto esters

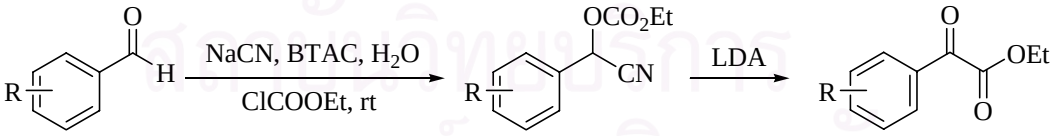
α-Keto acids and α-keto esters could be synthesized by many approaches such as Grignard reaction, hydrolysis, rearrangement, dehydration and oxidation reactions. Sometime these reactions could take place with many steps in well-known total synthesis.

1.4.1 By rearrangement reactions

The application of rearrangement reaction for transformation of ethyl β-phenylglycidate to ethyl phenylpyruvate was addressed by House and co-workers [29]. β-Phenylglycidate was performed in benzene in the presence of boron trifluoride gas as an acid-catalyzed reaction to yield ethyl phenylpyruvate, ethyl benzoylacetate and ethyl α-formylphenylacetate.

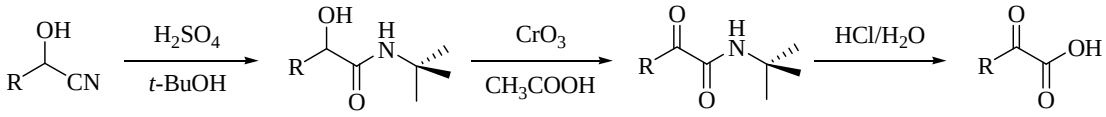


Thasana and co-workers addressed the conversion of benzaldehyde derivatives to the corresponding aryl α-keto ester derivatives [30]. The benzaldehyde derivatives were treated with NaCN and ethyl chloroformate in the presence of benzyltrimethylammonium chloride (BTAC) to furnish the corresponding aryl cyanohydrin carbonate ester derivatives. The rearrangement of aryl cyanohydrin carbonate ester derivatives with LDA in THF afforded the corresponding aryl α-keto ester derivatives.

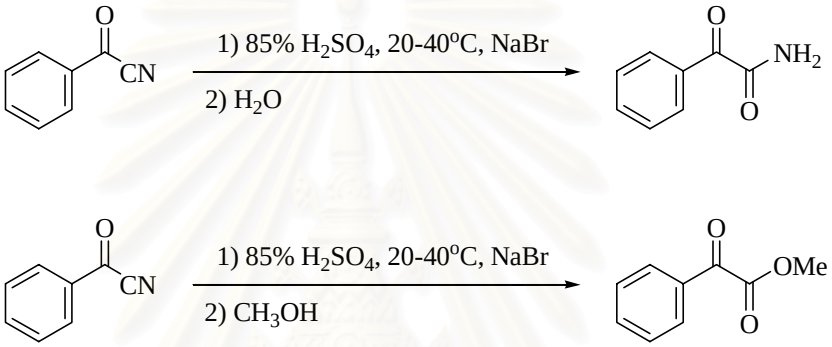


1.4.2 By hydrolysis reactions

Anotol and Medete reported the conversion of cyanohydrins to α-keto acids utilizing hydrolysis reaction [31]. The cyanohydrins were dissolved in *t*-butanol in the presence of H_2SO_4 as an acid catalyst. The mixture was stirred at 50°C to afford the corresponding α-hydroxyamides. α-Hydroxyamides were oxidized by CrO_3 in the presence of acetic acid to give α-keto amides. Then, α-keto amides were transformed to α-keto acids by hydrolysis reaction with aq HCl.

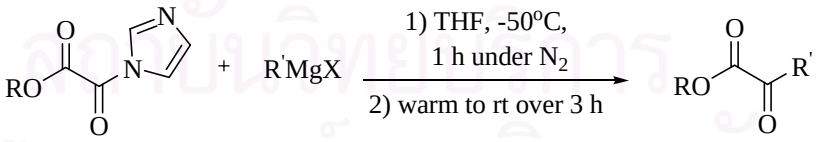


Photis published the hydrolysis of acylcyanide conversion to aryl α-keto esters [32]. The reaction was performed in a slurry 85% H_2SO_4 and NaBr. The acyl cyanide was added at room temperature afforded aryl α-keto amides. The mixture was heated at 70°C and then refluxed with methanol to give the corresponding aryl α-keto acid methyl esters.



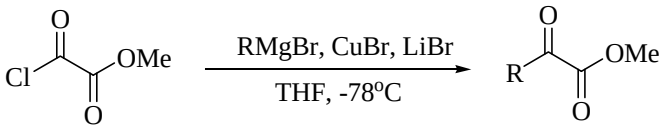
1.4.3 By Grignard reactions

Nimitz and Mosher applied the Grignard reaction for the synthesis of α-keto ester [33]. The reactions were performed by coupling ethyl or *t*-butyl α-oxo-1*H*-imidazole-acetate (1 equiv) and Grignard reagents (RMgX, 1 equiv) to yield the corresponding α-keto ester.

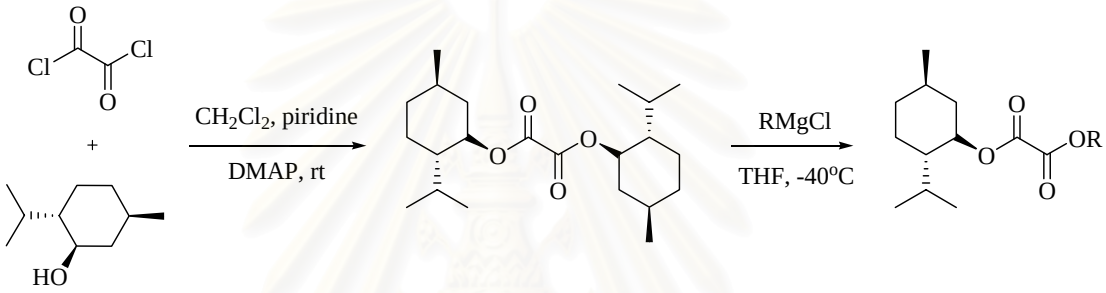


Remarkably, in the case of aromatic Grignard reagents, good yield of the desired products were gained while alkyl Grignard reagents gave low yield.

Babudri and co-workers reported the application of Grignard reactions for transformation of methyl oxalyl chloride to methyl α-keto ester [34]. The cross-coupling reactions of methyl oxalyl chloride with organocopper reagents derived from RMgBr, CuBr and LiBr (1.2, 1.2 and 2.4 equiv, respectively) afforded the corresponding methyl α-keto ester.

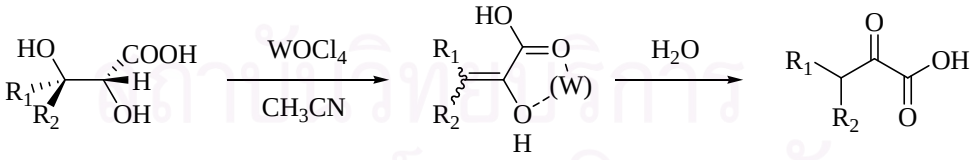


MaGee and co-workers published the transformation of oxalylchloride to the corresponding α-keto ester *via* Grignard reactions [35]. The oxalylchloride was treated with chiral alcohols in the presence of pyridine and DMAP to afford the corresponding oxalyldiesters. After that, Grignard reagent (*t*-butyl magnesium chloride, 1.5 equiv) was added to furnish the corresponding α-keto esters.

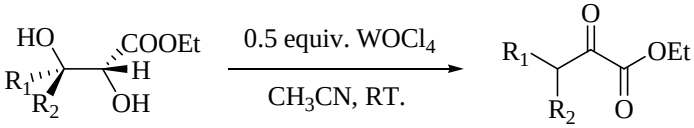


1.4.4 By dehydration reactions

Yu and Schwartz reported the transformation of 2,3-dihydroxycarboxylic acids to α-keto acids *via* dehydration reaction [36]. These carboxylic acids were performed in acetonitrile in the presence of $WOCl_4$ as a catalyst afforded the corresponding α-keto acids.

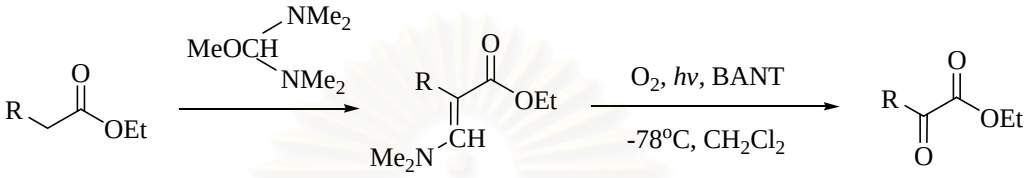


Under these conditions, the α-keto esters could be prepared from 2,3-dihydroxycarboxylate esters.

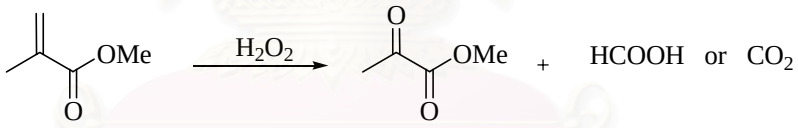


1.4.5 By oxidation reactions

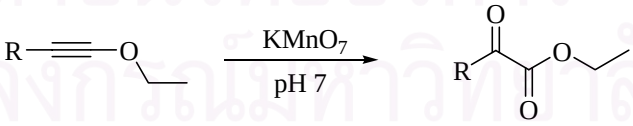
Wasserman and Ives reported the reaction of methyl phenylacetate derivatives with methoxybis(dimethylamino)methane to give the corresponding enamino esters [37]. Subsequently, photooxygenation of enamino in the presence of bisacenaphthalene-thiophene (BANT) as a sensitizer afforded the corresponding α-keto esters in high yield.



Inoue and co-workers reported the application of chromium salts as a catalyst for the oxidation of methyl methacrylate using aq H_2O_2 [38]. It was found that the oxidation with catalytic amount of chromium salts yielded methyl pyruvated as a major product accompanied with formic acid and carbon dioxide. Chromium salts also catalyzed the oxidation and activity decrease in the order of $Cr(OAc)_3$> $Cr(NO_3)_3$> $CrPO_4$> $CrCl_3$~ $Cr(SO_4)_3$.

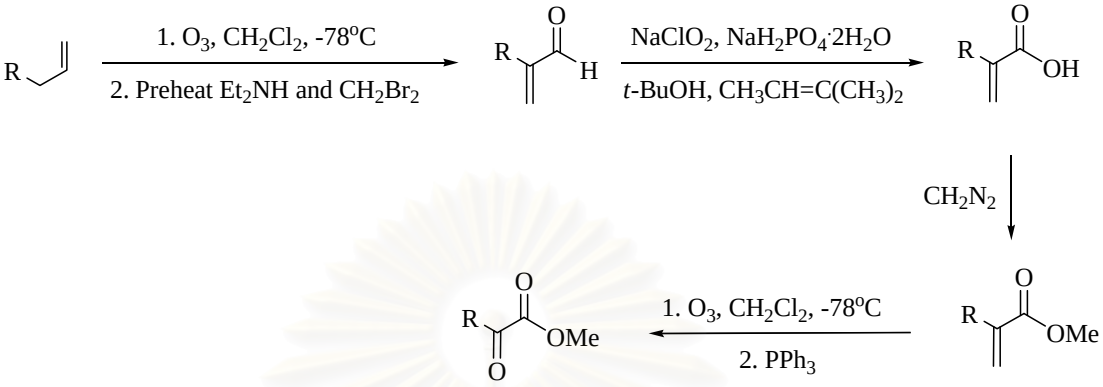


Tatlock reported the oxidation of alkynyl ether with potassium permanganate [39]. The reactions were carried out in buffer solution to give the corresponding α-keto esters in high yields.

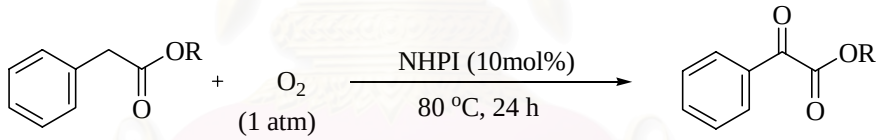


The total synthesis of α-keto esters were published by Hon and Lin [40]. The transformation of terminal alkene to α-keto esters could be accomplished by four steps. Firstly, the ozonolysis of alkenes with ozone in CH_2Cl_2 followed by the addition of a preheat mixture of CH_2Br_2 and diethylamine to afford the corresponding acroleins. Secondly, the acroleins were treated with $NaClO_2$ (2.3 equiv), $NaH_2PO_4 \cdot 2H_2O$ (2 equiv) and $CH_3CH=C(CH_3)_2$ (3 equiv) to give acrylic acids. Then,

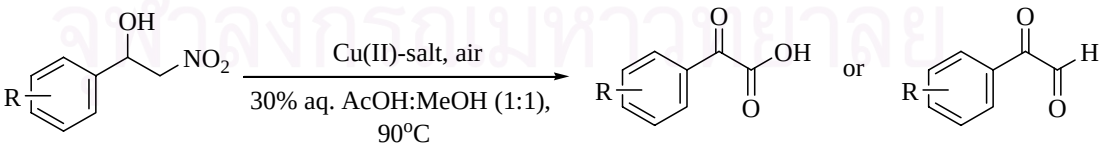
the acrylic acids were converted to methyl acrylate by addition of diazomethane (1 equiv). Finally, the ozonolysis of methyl acrylate with ozone in CH_2Cl_2 followed by reduction with PPh_3 (1 equiv) afforded the corresponding methyl α-keto esters.



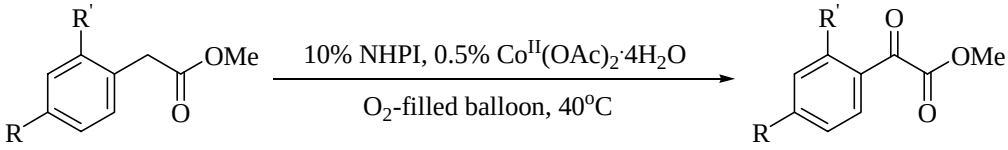
Matsunaka and co-workers reported the transformation of ethyl phenylacetate to ethyl benzoylformate [41]. The ethyl phenylacetate was treated with oxygen (1 atm) in the presence of 10 mol% of *N*-hydroxyphthalimide (NHPI) as a catalyst and tetra-*n*-butylamoniumbromide (TBAB) as an additive to yield ethyl benzoylformate in good yield.



Nikalje and co-workers published the oxidation of aryl nitroaldol catalyzed by $CuSO_4 \cdot 5H_2O$ to afford the corresponding aryl α-keto acids [42]. For aryl nitroaldol products bearing electron-withdrawing groups such as NO_2 and CN, the rate of reaction was slower than for substrates bearing electron-donating groups.

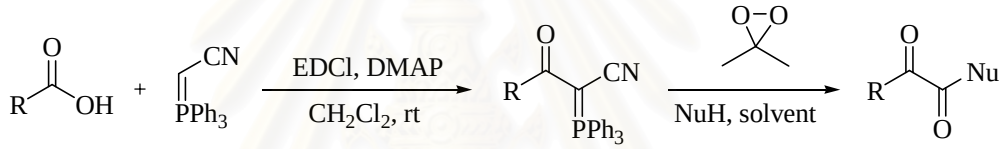


The application of *N*-hydroxyphthalimide (NHPI)/$Co(OAc)_2 \cdot 4H_2O$ as the catalytic systems for the oxidation of arylacetic esters was addressed by Wentzel and co-workers [43]. The oxidation of arylacetic esters were carried out in the presence of 10 mol% NHPI, 0.5 mol% $Co(OAc)_2 \cdot 4H_2O$ and O_2-filled balloon.

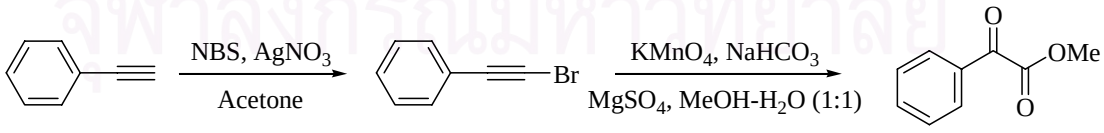


Remarkably, the conversion and selectivity towards glyoxylate exceed depending on kind and position of substituents on aromatic ring.

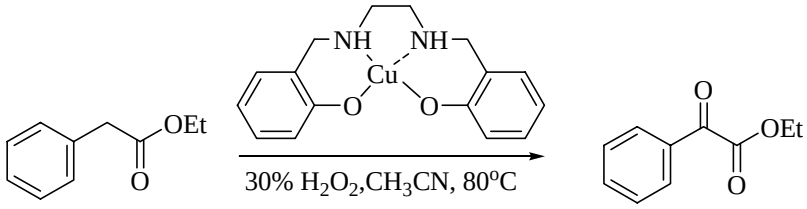
Wong and co-workers published the oxidative cleavage of cyanoketo-phosphoranes by using dimethyldioxirane [44]. The cyanoketophosphoranes were prepared by coupling of the corresponding carboxylic acids and (cyanomethylene) phosphorane in the presence of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCl) and 4-dimethylaminopyridine (DMAP). After that, the corresponding cyanoketophosphoranes were reacted with dimethyldioxirane and nucleophile performed the corresponding α-keto esters.



Li and Wu reported a two-step (bromination and permanganate oxidation) reaction which converted terminal alkynes to α-keto esters [45]. If the terminal alkynes contained the hydroxyl groups, the protection by reaction with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of amidazole was needed. After that, it was converted to the corresponding bromoalkynes by reaction with *N*-bromosuccinimide (NBS) (1.5 equiv) and $AgNO_3$ (0.4 equiv) in acetone. Then the bromoalkynes were treated with $KMnO_4$ (2 equiv), $NaHCO_3$ (0.5 equiv) and $MgSO_4$ (2 equiv) in mixture of methanol and H_2O (1:1) to afford methyl α-keto esters.

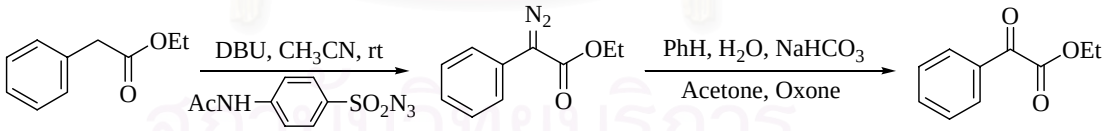


The application of metal Schiff-base (copper salen) complex in the oxidation of ethyl phenylacetate was published by Velusamy and Punniyamurthy [46]. Ethyl phenylacetate was treated with 30% H_2O_2 (10 equiv) in the presence of copper salen (0.1 mol%) to yield ethyl benzoylformate in high yield.



Lee and co-workers reported the application of [hydroxy(tosyloxy)iodo] benzene (HTIB, Koser's reagent) under solvent-free microwave irradiation (MWI) for oxidation of benzylic alcohols [47]. Methyl mandelate was treated with HTIB (1.2 equiv) under solvent-free MWI using a house hold microwave oven (700 W) for 40-1600 second to provide the methyl benzoylformate in high yield.

Ma and co-workers reported the transformation of methyl phenylacetate derivatives to the corresponding methyl benzoylformate in two steps [48]. First, ethyl phenylacetate derivatives were treated with *p*-acetamidobenzene-sulfonyl in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). After that, a mixture of oxone®, $NaHCO_3$, benzene, H_2O and acetone was added to the reaction mixture, to yield the corresponding methyl benzoylformate derivatives.



From the literature reviews, various methods could be successfully developed for the preparation of α-keto acids and α-keto esters. A few reports involving the preparative procedure of these compounds employing first row transition metal carboxylate complexes as catalyst have however been addressed. Nonetheless, the utilization of soluble metal carboxylate complexes as catalyst for the oxidation of organic substrate coupled with TBHP has not been addressed much in chemical literatures. Due to its inexpensiveness and ease of preparation, this research is therefore focused on the development of first row transition metal carboxylate

complexes for oxidation reaction to furnish α-keto acids and α-keto esters using ethyl phenylacetate as a chemical model.

1.5 The goal of this research

The destination of this research can be summarized as follows:

1. To synthesize and characterize transition metal carboxylate complexes.
2. To systematically study on the optimization conditions for the oxidation of ethyl phenylacetate by transition metal carboxylate complexes under mild reaction conditions.
3. To utilize the optimized conditions to oxidize a variety of substituted ethyl phenylacetates.

CHAPTER II

EXPERIMENTAL

2.1 Instruments and equipments

Spectrometers: Fouirer transform-infrared spectra (FT-IR) were performed on Nicolet Impact 410 FT-IR spectrometer. Solid samples were incorporated to potassium bromide (KBr) to form pellet. As a liquid sample, a drop of the liquid was squeezed between flat plates of sodium chloride cells. The ^{1}H-NMR spectra was obtained in deuterated chloroform ($CDCl_3$) or otherwise stated, with Fourier transform nuclear magnetic resonance spectrometer of Varian model Mercury+400 spectrometer.

Chromatography: Thin layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel (Merck's, Kieselgel 60 PF_{254}). Column chromatography was performed on silica gel (Merck's, Kieselgel 60G Art 7734 (70-230 mesh)) and aluminium oxide 90 (70-230 mesh ASTM). Gas chromatography analysis was carried out on Shimadzu gas chromatograph GC-14A instrument equipped with flame ionization detector (FID) using nitrogen as a carrier gas, the column used for chromatography was a capillary column type HP-5 (30m x 250mm) from Hewlett Packard company.

Melting points (m.p.) was measured on a Fisher-Johns melting point apparatus and are uncorrected.

2.2 Chemicals

All solvents used in this research were purified prior to use by standard methodology except for those which were reagent grades. The reagents utilized for synthesizing metal carboxylate complexes and all organic substrates were purchased from Fluka chemical company or otherwise stated were used without further purification.

2.3 Synthesis of metal carboxylate complexes

2.3.1 General procedure for synthesis of metal trichloroacetate complexes [49]

An excess of trichloroacetic acid (13 g, 79 mmol) was added to anhydrous metal chloride (6.15 mmol) in a round-bottomed flask under nitrogen atmosphere and the resulting mixture was stirred magnetically and refluxed for 48 h. The products were washed with *n*-hexane and filtered.

Fe(III) trichloroacetate$\cdot 1.5H_2O$: brown solid, 85% yield, m.p. 193-195°C, IR (KBr): 1661 (s), 1392 (s) and 851 (m) cm^{-1}.

Cr(III) trichloroacetate: green solid, 90%, m.p. >300°C, IR (KBr) : 1680 (s), 1408 (s) and 859 (m) cm^{-1}.

Ni(II) trichloroacetate: yellow solid, 80%, m.p. >300°C, IR (KBr) : 1630 (s), 1404 (w) and 680 (m) cm^{-1}.

Mn(II) trichloroacetate: light pink solid, 81%, m.p. >300°C, IR (KBr) : 1622 (s), 1400 (w) and 610 (m) cm^{-1}.

Cu(II) trichloroacetate: light blue solid, 84%, m.p. >300°C, IR (KBr) : 1626 (s), 1400 (w) and 598 (w) cm^{-1}.

2.3.2 Iron(III) trifluoroacetate complex [50]

This complex was prepared employing the similar method to that described for metal trichloroacetate complexes by using trifluoroacetic acid (5 mL, 44 mmol) and anhydrous iron(III) chloride (1 g, 6.15 mmol). The resulting red cake was collected and dried at 70°C for 3 h. Iron (III) trifluoroacetate was gained as red powder 2.39 g, 92% yield, m.p. 111-114°C (lit[52] 110°C).

IR (KBr): 1689 (s), 1211 (s), 1157 (s) and 725 (m) cm^{-1}.

2.3.3 Iron(III) carboxylate complexes [51]

Selected carboxylic acid 22 mmol was dissolved in dilute sodium hydroxide solution (0.88 g NaOH in 20 mL distilled water) at 80°C. After stirring the solution to homogeneity, iron (III) trichloride (1.18 g, 7.3 mmol) dissolved in 10 mL distilled water was added in one portion causing the precipitation which was then collected and dried *in vacuo*.

Fe(III) pivalate: red brown solid, 89% yield, m.p. >300°C, IR (KBr): 2864-2969 (w), 1525 (s), 1420 (m) and 1373 (w) cm^{-1}.

Fe(III) butyrate: red brown solid, 87% yield, m.p. >300°C, IR (KBr): 2961 (w), 1536 (s), 1424 (s) and 700 (m) cm^{-1}.

*Fe(III) benzoat*e: red brown solid, 80% yield, m.p. 247-250°C, IR (KBr): 1595 (w), 1527 (s), 1412 (s) and 715 (m) cm^{-1}.

Fe(III) 4-chlorobenzoate: red brown solid, 96% yield, m.p. 192-195°C, IR (KBr): 1688 (s), 1595 (s), 1416 (s) and 770 (m) cm^{-1}.

Fe(III) 4-nitrobenzoate: light brown solid, 87% yield, m.p. >300°C, IR(KBr): 1692 (m), 1579 (s), 1544 (s), 1416 (s), 1342 (s) and 731 (s) cm^{-1}.

Fe(III) 2,4-dinitrobenzoate: light brown solid, 83% yield, m.p. >300°C, IR(KBr): 1603 (s), 1536 (s), 1416 (s), 1345 (s), 856 (w) and 742 (w) cm^{-1}.

2.3.4 Synthesis of other metal carboxylate complexes

The preparation of various metal carboxylates could be accomplished by employing the general procedure for syntheses of iron carboxylate complexes.

VO(IV) stearate: army dark green solid, 95% yield, m.p. 90-95°C, IR (KBr): 2845-2920 (s), 1591 (m), 1465 (m) and 719 (w) cm^{-1}.

Cr(III) stearate: blue grey solid, 78% yield, m.p. 109-114°C, IR (KBr): 2844-2918 (s), 1536 (m), 1462 (m) and 723 (w) cm^{-1}.

Mn(II) stearate: white solid, 79% yield, m.p. 120-124°C, IR (KBr): 2846-2916 (s), 1563 (s), 1427 (m) and 718 (w) cm^{-1}.

Fe(III) stearate: light red solid, 85% yield, m.p. 108-114°C, IR (KBr): 2846-2916 (s), 1578 (m), 1464 (m) and 718 (w) cm^{-1}.

Co(II) stearate: violet solid, 77% yield, m.p. 223-226°C, IR (KBr): 2846-2916 (s), 1596 (m), 1467 (m) and 721 (w) cm^{-1}.

Ni(II) stearate: light green solid, 89% yield, m.p. >300°C, IR (KBr): 2844-2918 (s), 1564 (s), 1424 (s) and 719 (w) cm^{-1}.

Cu(II) stearate: sky-blue solid, 75% yield, m.p. 145-148°C, IR (KBr): 2846-2912 (s), 1557 (s), 1467 (m) and 718 (w) cm^{-1}.

Ni(II) caproate: light green solid, 72% yield, m.p. >300°C, IR (KBr): 2856-2957 (m), 1564 (s), 1424 (s) and 637 (m) cm^{-1}.

Ni(II) caprate: light green solid, 75% yield, m.p. >300°C, IR (KBr): 2848-2922 (s), 1556 (s), 1420 (m) and 626 (m) cm^{-1}.

Ni(II) myristate: light green solid, 94% yield, m.p. >300°C, IR (KBr): 2848-2922 (s), 1587 (s), 1416 (s) and 723 (w) cm^{-1}.

Ni(II) behenate: light green solid, 80% yield, m.p. 112-116°C, IR (KBr): 2844-2914 (s), 1564 (m), 1408 (m) and 715 (w) cm^{-1}.

Ni(II) p-toluate: green solid, 75% yield, m.p. >300°C, IR (KBr): 2856-2957 (w), 1610 (s), 1564 (s), 1392 (s) and 828 (s) cm^{-1}.

Ni(II) 2-naphthoate: green solid, 69% yield, m.p. >300°C, IR (KBr): 1599 (s), 1564 (s), 1400 (s), 824 (m) and 789 (m) cm^{-1}.

Ni(II) 4-chlorobenzoate: green solid, 90% yield, m.p. >300°C, IR (KBr): 1595 (s), 1548 (m), 1396 (s), 825 (m) and 774 (m) cm^{-1}.

Ni(II) picolinate: light blue solid, 79% yield, m.p. >300°C, IR (KBr): 1626 (s), 1591 (s), 1568 (s), 1387 (s) and 766 (m) cm^{-1}.

Ni(II) isonicotinate: green solid, 85% yield, m.p. >300°C, IR (KBr): 1595 (s), 1548 (s), 1381 (s), 828 (m) and 776 (m) cm^{-1}.

Ni(II) nicotinate: green solid, 80% yield, m.p. >300°C, IR (KBr): 1610 (s), 1568 (s), 1392 (s) and 758 (m) cm^{-1}.

2.4 Synthesis of starting esters

H_2SO_4 (3% by volume of alcohol) was added dropwise to catalyze the esterification between phenylacetic acid derivatives (1 equiv) and ethanol (3 equiv) [52]. The reaction mixture was refluxed until complete consumption of phenylacetic acid derivatives (TLC monitored). The reaction mixture was then cooled and ethanol was removed under reduced pressure. The concentrated mixture was added Et_2O and the extract was washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure.

Ethyl phenylacetate: colorless oil, 95% yield, ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.29 (t, *J* = 7.1 Hz, 3H), 3.66 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H) and 7.31-7.37 (m, 5H), IR (NaCl): 2902-3062 (s), 1731 (s), 1603 (w), 1252 (s) and 704 (s) cm^{-1}.

Ethyl (4-chlorophenyl)acetate: light yellow oil, 90% yield, ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.25 (t, *J* = 7.1 Hz, 3H), 3.57 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H) and 7.29 (d, *J* = 8.4 Hz, 2H), IR (NaCl): 2982 (m), 1736 (s), 1595 (w), 1250 (m) and 810 (m) cm^{-1}.

Ethyl (4-methoxyphenyl)acetate: light yellow oil, 87% yield, ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.24 (t, *J* = 7.2 Hz, 3H), 3.54 (s, 2H), 3.79 (s, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H) and 7.20 (d, *J* = 8.6 Hz, 2H), IR (NaCl): 2908-2985 (m), 1736 (s), 1612 (m), 1250 (s), 1034 (s) and 825 (m) cm^{-1}.

Ethyl p-toluylacetate: light yellow oil, 93% yield, ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.25 (t, *J* = 7.2 Hz, 3H), 2.33 (s, 3H), 3.57 (s, 2H), 4.10 (q, *J* = 7.1 Hz, 2H) and 7.12-7.19 (m, 4H), IR (NaCl): 2979 (m), 1735 (s), 1517 (m), 1494 (s) and 1254 (m) cm^{-1}.

Ethyl thiophene-2-acetate: dark brown oil, 83% yield, ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.28 (t, *J* = 7.2 Hz, 3H), 3.83 (s, 2H), 4.19 (q, *J* = 7.2 Hz, 2H) and 6.95-7.22 (m, 3H), IR (NaCl): 2976 (w), 1738 (s), 1439 (w), 1232 (m) and 696 (m) cm^{-1}.

Methyl (4-methoxyphenyl)acetate: light yellow oil, 95% yield, ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.57 (s, 2H), 3.68 (s, 3H), 3.79 (s, 3H), 6.86 (d, *J* = 8.7 Hz, 2H) and 7.20 (d, *J* = 8.6 Hz, 2H), IR (NaCl): 2955 (m), 1738 (s), 1611 (m), 1516 (s), 1248 (s) and 819 (m) cm^{-1}.

n-Butyl (4-methoxyphenyl)acetate: light brown oil, 90% yield, ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.91 (t, *J* = 7.3 Hz, 3H), 1.35 (sex, *J* = 7.3, 7.6 Hz, 2H), 1.60 (quin, *J* = 6.9, 7.7 Hz, 2H), 3.55 (s, 2H), 3.79 (s, 3H), 4.08 (t, *J* = 6.7 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H) and 7.20 (d, *J* = 8.5 Hz, 2H), IR (NaCl): 2958 (m), 1735 (s), 1614 (m), 1513 (s), 1248 (s) and 823 (m) cm^{-1}.

2.5 General procedure for the oxidation of ethyl phenylacetate

A solution of substrate (5 mmol) in solvent (5 mL) containing catalyst (0.2 mmol) in a round bottom flask and 70% TBHP (9 mmol) was added. The mixture was stirred at 70°C for 24 h. After the reaction was completed, 1 mL of the reaction mixture was taken and extracted with Et_2O. The combined extracts were washed with 25% H_2SO_4 and saturated solution of $NaHCO_3$, respectively. The organic layer was dried over anhydrous Na_2SO_4 and analyzed by GC with the addition of an exact amount of appropriate internal standard.

In addition, the study on the optimum conditions for oxidation of ethyl phenylacetate was divided into two parts: utilization of nickel(II) carboxylate complexes and utilization of iron(III) carboxylate complexes. Solvent and catalyst used in both parts are different. For the first part, isooctane and nickel(II) stearate were used as solvent and catalyst, respectively, while in the second part, the utilization of iron(III) carboxylate complexes, the reaction was carried out in pyridine in the presence of iron(III) trichloroacetate as a catalyst.

2.6 Study on the optimum conditions for oxidation of ethyl phenylacetate

Part I Utilization of nickel(II) carboxylate complexes

2.6.1 Effect of metal stearate complexes

The oxidation reaction was carried out in the same manner as previously described employing various metal stearates: VO(IV), Cr(III), Mn(II), Fe(III), Co(II), Ni(II) and Cu(II) stearate complexes as a catalyst.

2.6.2 Effect of nickel(II) carboxylate complexes

The oxidation reaction was carried out in the same manner aforementioned, switching from nickel(II) stearate to nickel(II) caproate, nickel(II) caprate, nickel(II) myrictate, nickel(II) behenate, nickel(II) 4-chlorobenzoate, nickel(II) *p*-toluate, nickel(II) pivalate, nickel(II) isonicotinate and nickel(II) nicotinate.

2.6.3 Effect of solvents

The oxidation reaction was carried out in the same manner as described above except for tetrahydrofuran (THF), pyridine, acetonitrile, DMF, TMEDA and TEA were used as a reaction medium

2.6.4 Effect of amount of oxidant

The oxidation reaction was carried out in the same manner as the former using TBHP as an oxidant. The amount of TBHP was also studied by variation for oxidation reaction: 0.0, 4.5, 9.0, 13.5, 18.0, 22.5 and 27.0 mmol.

2.6.5 Effect of amount of catalyst

The oxidation reaction was carried out as described in the general procedure, but the amount of the catalyst was varied: 0, 0.05, 0.10, 0.20, 0.30 and 0.40 mmol.

2.6.6 Effect of temperature

The oxidation reaction was performed according to the general procedure mentioned earlier using nickel(II) stearate as a catalyst, but different reaction temperature was varied: 30, 50, 70 and 90°C.

2.6.7 Kinetic study on the oxidation of ethyl phenylacetate catalyzed by nickel(II) stearate

The general procedure for the oxidation of ethyl phenylacetate using nickel(II) stearate as a catalyst was carried out at 70°C. At different reaction time proceeded: 1, 3, 6, 9, 18, 24, 36, 48 and 72 h, an aliquot from the reaction mixture was taken, worked up and analyzed by GC**.**

Part II Utilization of iron carboxylate complexes

2.6.8 Effect of metal trichloroacetate complexes

The oxidation reaction was carried out in the same manner as previously described employing various metal trichloroacetate: Cr(III), Mn(II), Fe(III), Ni(II) and Cu(II) trichloroacetates as a catalyst.

2.6.9 Effect of iron(III) carboxylate complexes

The oxidation reaction was carried out in the same manner aforementioned, switching from iron(III) trichloroacetate to iron(III) trifluoroacetate, iron(III) pivalate, iron(III) benzoate, iron(III) 4-nitrobenzoate, iron(III) 2,4-dinitrobenzoate and iron(III) butyrate.

2.6.10 Effect of the amount of catalyst

The oxidation reaction was carried out as described in the general procedure, but the amount of the catalyst was varied: 0, 0.05, 0.10, 0.15, 0.20, 0.30 and 0.40 mmol.

2.6.11 Effect of solvents

The oxidation reaction was carried out in the same manner as described above except for THF, CH_2Cl_2, $CHCl_3$, 1,4-dioxane, EtOH, DMF, TMEDA and acetonitrile was used as a reaction medium.

2.6.12 Effect of the amount of substrate

The oxidation reaction was carried out in the same manner as the former using iron(III) trichloroacetate as a catalyst with different amount of ethyl phenylacetate: 1, 3, 5, 10, 15 and 25 mmol

2.6.13 Effect of type and amount of oxidants

The oxidation reaction was carried out in the same manner as aforementioned, switching form TBHP to hydrogen peroxide (H_2O_2), 2-ethylbutylraldehyde/O_2, urea hydrogenperoxide and *m*-chloroperbenzoic acid (*m*-CPBA). The amount of TBHP was also studied by variation for oxidation reactions: 0.0, 4.5, 9.0, 13.5, 18.0, 22.5 and 27.0 mmol.

2.6.14 Effect of temperature

The oxidation reaction was performed according to the general procedure mentioned earlier using iron(III) trichloroacetate as a catalyst, but different reaction temperature was varied: 30, 50, 70 and 90°C.

2.6.15 Kinetic study on the oxidation of ethyl phenylacetate catalyzed by iron (III) trichloroacetate

The general procedure for the oxidation of ethyl phenylacetate using iron(III) trichloroacetate as a catalyst was carried out at 70°C. At different reaction time proceeded: 1, 3, 6, 9, 18, 24, 36, 48 and 72 h, an aliquot from the reaction mixture was taken, worked up and analyzed by GC.

2.7 Study on the oxidation of ethyl phenylacetate catalyzed by bicatalyst and tricatalyst of metal trichloroacetate complexes

2.7.1 Effect of bicatalyst

The oxidation reaction of ethyl phenylacetate catalyzed by bicatalyst was conducted. These reactions were carried out at 70°C, with different ratios of catalyst iron (III) trichloroacetate and other metal trichloroacetates: 1:1, 2:1, 3:1 and 4:1.

2.7.2 Effect of tricatalyst

Metal trichloroacetates were used in the oxidation reaction with the ratio of iron (III) trichloroacetate, chromium (III) trichloroacetate and manganese (II) trichloroacetate: 1:1:1, 2:1:1, 1:2:1, 1:1:2, 3:1:1, 1:3:1 and 1:1:3.

2.8 Synthesis of various α-keto esters

Selected ethyl aryl acetate derivatives, namely, ethyl mandelate, ethyl *p*-toluylacetate**,** ethyl thiophene-2-acetate, ethyl (4-chlorophenyl)acetate, methyl (4-methoxyphenyl)acetate, ethyl (4-methoxyphenyl)acetate and butyl (4-methoxy-phenyl)acetate were oxidized according to the general procedure as previously described. The aliquot (1 mL) of the reaction mixture was taken; worked up with 25% H_2SO_4, saturated $NaHCO_3$ and dried over anhydrous Na_2SO_4, analyzed by GC or ^{1}H-NMR spectroscopy.

General isolation procedure

After the reaction was finished, the oxidation product was separated as follows: the whole reaction mixture was extracted according to the general procedure and all the solvents were removed. The crude product was purified by silica gel column chromatography 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.

Ethyl mandelate: colorless oil, 11% yield, R_f 0.44 (hexane-EtOAc (7:1)), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.23 (t, *J* = 7.1 Hz, 3H), 4.15-4.29 (m, 2H), 5.15 (s, 1H) and 7.26-7.43 (m, 5H).

Ethyl benzoylformate: light yellow oil, 51% yield, R_f 0.25 (hexane-EtOAc (7:1)), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.45 (t, *J* = 7.3 Hz, 3H), 4.48 (q, *J* = 7.2, 2H) and 7.52-8.05 (m, 5H).

Ethyl (4-chlorobenzoyl)formate: light yellow oil, 38% yield, R_f 0.27 (hexane-EtOAc (7:1)), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.42 (t, *J* = 7.1 Hz, 3H), 4.45 (q, *J* = 7.1 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H) and 7.99 (d, *J* = 8.7 Hz, 2H).

Methyl (4-methoxybenzoyl)formate: light yellow oil, 50% yield, R_f 0.21 (hexane-EtOAc (7:1)), ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.90 (s, 3H), 3.96 (s, 3H), 6.97 (d, *J* = 9.0 Hz, 2H) and 8.01 (d, *J* = 9.0 Hz, 2H).

Ethyl (4-methoxybenzoyl)formate: light yellow oil, 72% yield, R_f 0.27 (hexane-EtOAc (7:1)), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.39 (t, *J* = 7.3 Hz, 3H), 3.85 (s, 3H), 4.41 (q, *J* = 7.4 Hz, 2H), 6.95 (d, *J* = 9.3 Hz, 2H) and 7.96 (d, *J* = 9.2 Hz, 2H).

n-Butyl (4-methoxybenzoyl)formate: light yellow oil, 59% yield, R_f 0.33 (hexane-EtOAc (7:1)), ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.96 (t, *J* = 7.4 Hz, 3H), 1.45 (sex, *J* = 7.4, 7.6 Hz, 2H), 1.76 (quin, *J* = 6.9, 7.7 Hz, 2H), 3.90 (s, 3H), 4.38 (t, *J* = 6.7 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H) and 7.99 (d, *J* = 8.8 Hz, 2H).

Ethyl p-toluyl-2-oxoacetate: light yellow oil, 42% yield, R_f 0.43 (hexane-EtOAc (7:1)), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.42 (t, *J* = 7.1 Hz, 3H), 2.44 (s, 3H), 4.44 (q, *J* = 7.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H) and 7.91 (d, *J* = 8.2 Hz, 2H).

Ethyl thiophene-2-oxoacetate: dark red brown oil, 32% yield, R_f 0.34 (hexane-EtOAc (7:1)), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.43 (t, *J* = 7.2 Hz, 3H), 4.44 (q, *J* = 7.2 Hz, 2H), 7.20 (dd, *J* = 4.0, 4.9 Hz, 1H), 7.82 (dd, *J* = 1.1, 4.9 Hz, 1H) and 8.14 (dd, *J* = 1.1, 3.9 Hz, 1H).

*Acetophenon*e: colorless liquid, quantitative yield, R_f 0.40 (hexane-EtOAc (7:1)), ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.61 (s, 3H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 2H) and 7.96 (d, *J* = 8.0 Hz, 2H).

Benzil: yellow crystal, quatitative yield, m.p. 95-98°C, R_f 0.44 (hexane-EtOAc (7:1)), ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.52 (t, *J* = 7.5 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 4H) and 7.98 (d, *J* = 7.3 Hz, 4H).

Acenaphthenequinone: light brown solid, 50% yield, m.p. 255-260°C, R_f = 0.38 (hexane-EtOAc (7:1)), ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.84 (t, *J* = 7.7 Hz, 2H), 8.33 (d, *J* = 8.1 Hz, 2H) and 8.64 (d, *J* = 7.3 Hz, 2H).

α-Tetralone: red brown solid, 74% yield, m.p. 126-130°C, R_f = 0.31 (hexane-EtOAc (7:1)), ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.14 (quin, *J* = 6.3 Hz, 2H), 2.66 (t, *J* = 6.3 Hz, 2H), 2.97 (t, *J* = 6.0 Hz, 2H), 7.24-7.33 (m, 2H), 7.47 (t, *J* = 6.3 Hz, 1H) and 8.04 (d, *J* = 7.8 Hz, 1H).

Xanthone: light brown solid, 95% yield, m.p. 170-174°C, R_f = 0.40 (hexane-EtOAc (7:1)), ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.39 (t, *J* = 6.8 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.73 (t, *J* = 8.8 Hz, 2H) and 8.35 (d, *J* = 8.0 Hz, 2H).

CHAPTER III

RESULTS AND DISCUSSION

Aryl α-keto esters have been recognized as important intermediates in the synthesis of a variety of oxygenated heterocycle, such as furan derivatives, and in the asymmetric synthesis of several biologically active compounds. In addition, it has also been possessed as anti-sunburn agent. This research mainly focuses on the synthesis of α-keto esters *via* the oxidation reaction. First row transition metal complexes including chromium(III), manganese(II), iron(III), nickel(II) and copper(II) carboxylate complexes were selected to screen for their catalytic capability. In this study, the reaction conditions were optimized using ethyl phenylacetate as a chemical model. Other substrates such as ethyl mandelate, ethyl (4-methoxyphenyl) acetate, ethyl (4-chlorophenyl)acetate, ethyl (3,4-methylenedioxyphenyl)acetate, ethyl *p*-toluylacetate, ethyl thiophene-2-acetate, methyl (4-methoxyphenyl)acetate and butyl (4-methoxyphenyl)acetate were selected for examining the scope of this developed oxidation system. In general, this system is composed of metal carboxylate complex as a catalyst, 70% TBHP as an oxidant in a reaction medium. Isooctane and pyridine were mostly used as a solvent. Other solvents such as acetonitrile, CH_2Cl_2, chloroform, *t*-butanol, TMEDA, 1,4-dioxane, DMF and other oxidizing agents including 30% H_2O_2, 2-ethylbutyraldehyde/O_2 and *m*-CPBA were employed in order to search for another alternatively appropriate oxidation system.

Part I: Utilization of nickel carboxylate complexes

The studied parameters for transformation of ethyl phenylacetate to ethyl benzoylformate were optimized by varying type of metal stearate complexes, carboxylate ligands, amount of oxidant, solvent, temperature and amount of catalyst. Then the optimized conditions were applied to the oxidation of other select compounds.

3.1 Synthesis and characterization of catalysts

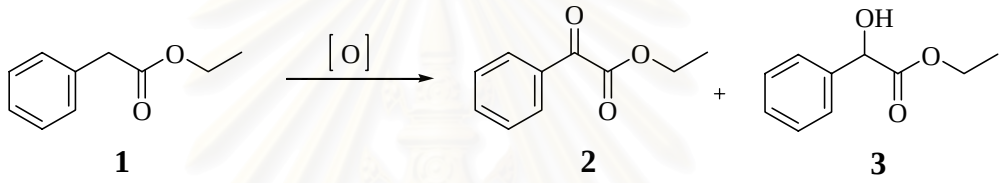
Metal stearate complexes were prepared by reacting metal chloride with stearic acid according to encyclopedia of chemical technology [51]. The complexes studied in this catalysis screening included vanadium(IV) oxide, chromium(III), manganese(II), iron(III), cobalt(II), nickel(II) and copper(II) stearate. Furthermore, nickel(II) carboxylates, for example, nickel(II) caproate, nickel(II) caprate, nickel(II) myristate, nickel(II) behenate, nickel(II) 4-chlorobenzoate, nickel(II) *p*-toluate, nickel(II) 2-naphthoate, nickel(II) pivalate, nickel(II) isonicotinate and nickel(II) nicotinate were prepared by reacting nickel(II) chloride with various carboxylic acids under basic conditions according to the previous protocol [51]. The identities of all synthesized complexes were confirmed by IR spectroscopy technique. Generally, the vibration band of free carboxylic acid displayed broad OH stretching peak at 2700-3400 cm^{-1}, at 1700-1725 cm^{-1} for asymmetric stretching of C=O and at 1395-1440 cm^{-1} for symmetric stretching of C-O bond [53]. In metal carboxylate complexes, the C=O and C-O stretching vibration band were shifted to 1520-1680 and 1380-1470 cm^{-1}, respectively. In addition, the absorption band of OH stretching was disappeared. The instance of IR spectrum of nickel(II) stearate is shown in Fig 3.1.

Figure 3.1 IR spectrum of $Ni(st)_2$

From Fig 3.1, the IR spectrum of nickel(II) stearate demonstrated asymmetric stretching of C=O at 1564 cm^{-1}, symmetric stretching of C-O at 1424 cm^{-1} and $-(CH_2)-$ rocking at 719 cm^{-1}.

3.2 Effect of metal stearates on the oxidation of ethyl phenylacetate (1)

1, a chemical model was prepared from the esterification of phenylacetic acid and ethanol catalyzed by H_2SO_4 [52]. Its identity was confirmed by ^{1}H-NMR spectrum (Fig 3.2). The ^{1}H-NMR spectrum of **1** visualized two signals of ethyl group at δ_H 1.29 (t, J = 7.1 Hz, 3H) and δ_H 4.19 (q, J = 7.1 Hz, 2H). The protons adjacent to aromatic ring could be observed as a singlet signal at δ_H 3.66 (2H), while the aromatic protons detected as multiplet signals around δ_H 7.31-7.37 (5H).



1 **2** **3**

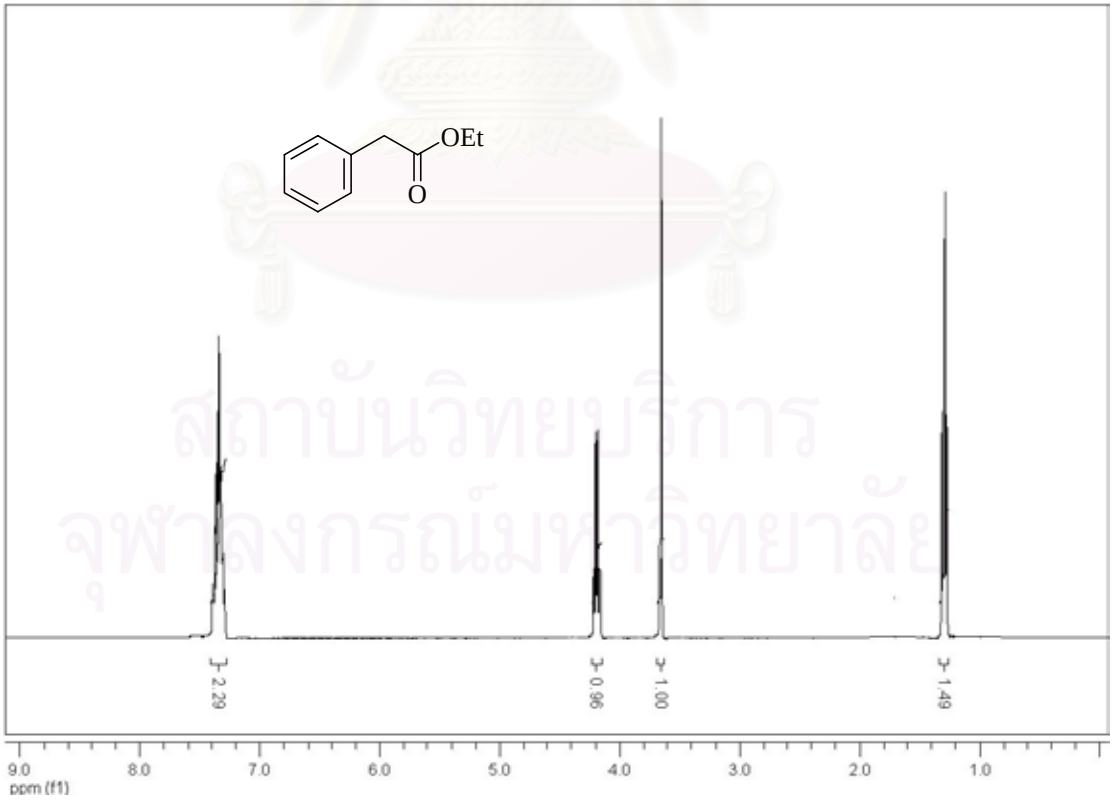


Figure 3.2 The ^{1}H-NMR spectrum of **1**

The oxidation of **1** by TBHP (1.8 equiv) catalyzed by $Ni(st)_2$ (0.04 equiv) afforded **2** and **3**. After the reaction was completed (monitored by TLC), the mixture was extracted and purified by column chromatography. These two products were identified by ^{1}H-NMR (Fig 3.3). The ^{1}H-NMR spectrum of **2** revealed two significant signals of ethyl group manifested at δ_H 1.45 (t, J = 7.3 Hz, 3H) and δ_H 4.48 (q, J = 7.2 Hz, 2H). The aromatic protons observed as mutiplet signal around δ_H 7.52-8.05 (5H). The structure of **3** was also clearly proved by ^{1}H-NMR (Fig 3.4). To illustrate this, two significant signals of ethyl group displayed at δ_H 1.23 (t, J = 7.1 Hz, 3H) and δ_H 4.15-4.29 (m, 2H). The proton neighboring to the aromatic ring detected singlet signal at δ_H 5.15 (1H). The aromatic protons observed as mutiplet signal around δ_H 7.30-7.48 (5H).

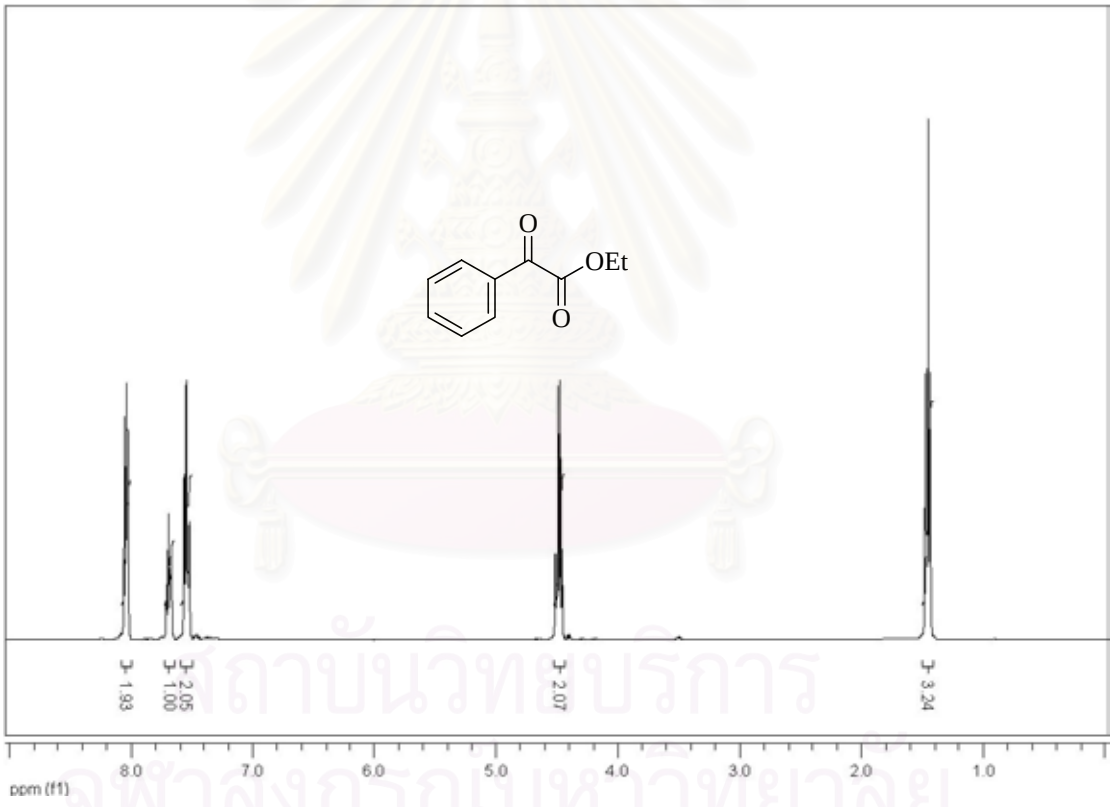


Figure 3.3 The ^{1}H-NMR spectrum of **2**

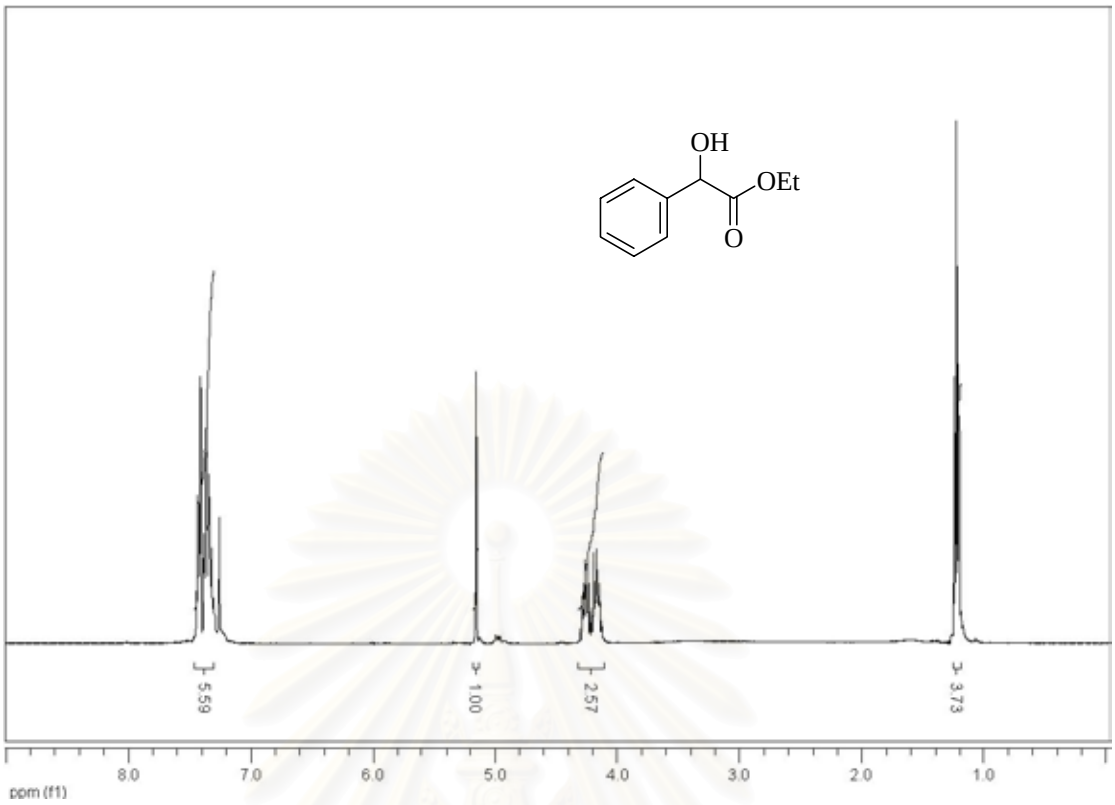


Figure 3.4 The ^{1}H-NMR spectrum of **3**

The effect of metal stearate on the oxidation of **1** was investigated. The results are presented in Table 3.1

Table 3.1 The effect of metal stearates on the oxidation of **1**

Entry	Metal stearate	% Yield		%Recovery of **1**	Mass balance
		2	**3**		
1	vanadium oxide(IV)	4	2	94	100
2	chromium(III)	13	13	70	96
3	manganese(II)	6	4	88	98
4	iron(III)	12	1	78	91
5	cobalt(II)	2	1	87	90
6	nickel(II)	22	11	62	95
7	copper(II)	13	0	86	99

Reaction conditions: **1** (5 mmol), metal stearate (0.2 mmol), TBHP (9 mmol) and isooctane (5 mL) at 70°C for 24 h.

From Table 3.1, in general, the oxidation of **1** yielded **2** as a main product while **3** being a minor one. Seven transition metal stearates in the first row of periodic table were selected to screen for potential catalyst revealed a wide range of oxidation catalytic capability. The order of the efficient catalyst was $Ni(st)_2 > Cr(st)_3 > Fe(st)_3 \sim Cu(st)_2 > VO(st)_2 \sim Mn(st)_2 \sim Co(st)_2$. Based on these screening results, $Ni(st)_2$ was selected for further study.

3.3 Effect of nickel(II) carboxylates on the oxidation of ethyl phenylacetate (1)

Carboxylic acids with different carbon atoms in the chain, including carproic acid (C_6), carpric acid (C_{10}), myristic acid (C_{14}), stearic acid (C_{18}), behenic acid (C_{22}) and aromatic carboxylic acids such as 4-chlorobenzoic acid, *p*-toluic acid, 2-naphthoic acid, pivalic acid, isonicotinic acid and nicotinic acid were chosen to react with Ni(II) chloride furnishing eleven Ni(II) carboxylate complexes. These Ni(II) carboxylates were utilized as a catalyst in the oxidation reaction of **1** to examine the effect of type of carboxylate ligands. The results are exposed in Table 3.2.

Table 3.2 The effect of nickel(II) carboxylates on the oxidation of **1**

Entry	Nickel caboxylate	% Yield		%Recovery of **1**	Mass balance
		2	**3**		
1	caproate (C_6)	25	5	61	91
2	carprate (C_{10})	24	4	63	91
3	myristate (C_{14})	24	9	62	95
4	stearate (C_{18})	22	11	62	95
5	behenate (C_{22})	12	4	76	92
6	4-chlorobenzoate	28	8	60	96
7	*p*-toluate	9	1	85	95
8	2-naphthoate	9	1	84	94
9	picolinate	7	1	90	98
10	isonicotinate	13	2	76	91
11	nicotinate	17	1	87	105

Reaction condition: **1** (5 mmol), Ni(II) carboxylate (0.2 mmol), TBHP (9 mmol) and isooctane (5 mL) at 70°C for 24 h.

Table 3.2 discloses that the yield of the desired products (**2**+**3**) was slightly increased when the carbon chain of carboxylate ligands were short (entries 1-5). The number of carbon atoms was on the other hand also affected the solubility in isooctane. To illustrate this, the complex with carboxylate ligands containing more carbon atoms gave poor solubility in isooctane of complexes. In the case of aromatic carboxylate ligands, the aromatic rings containing electron withdrawing group also gave good yield of the desired product (entry 6). In the case of pyridine carboxylate derivatives as a ligand (entries 9-11), the yield was differed possibly depending on the chelating effect of nitrogen atom. For α-pyridine carboxylate ligand, picolinate (entry 9), the nitrogen atom on a pyridine ring could be strongly chelated with nickel more than β- (isonicotinate, entry 10) and γ- (nicotinate, entry 11) pyridine carboxylate ligands; however the yield of **2** attained was increased, respectively. Because of fully chelated nickel-picolinate complex, there was a limitation of the unoccupied orbital of nickel atom to react with oxidant or substrate.

Thus, the nickel complex with the ligands bearing electron withdrawing group and short carbon chain provided the better yield of the desire product. This was an interesting point for further investigated in the future work.

3.4 Effect of solvents, amount of oxidant, amount of catalyst and temperature on the oxidation of ethyl phenylacetate (1)

3.4.1 Effect of solvents

Various solvents including acetronitrile, THF, pyridine, triethylamine (TEA), DMF, TMEDA and isooctane were investigated on their role to affect the oxidation of **1**. The results of the effect of solvent on this oxidation reaction are set out as shown in Table 3.3.

Table 3.3 The effect of solvents on the oxidation of **1**

Entry	Solvent	% Yield		%Recovery of **1**	Mass balance
		2	**3**		
1	DMF	0	0	99	99
2	acetonitrile	4	0	94	98
3	THF	0	1	103	104
4	ayridine	0	0	96	96
5	TEA	0	0	94	94
6	TMEDA	0	0	97	97
7	isooctane	22	11	62	95

Reaction condition: **1** (5 mmol), Ni(II) stearate (0.2 mmol), TBHP (9 mmol) and solvent (5 mL) at 70°C for 24 h.

Isooctane was found out to be the best solvent in the oxidation of **1** (entry 7) since it could well dissolve both **1** (organic substrate) and $Ni(st)_2$ (catalyst). In the case of employing polar solvent such as DMF, acetonittrile and THF (entries 1-3), the oxidation provided only a small amount of product. This mainly stemmed from their low capability to dissolve catalyst. When pyridine, TEA and TMEDA were used as solvent, the reaction did not take place.

From these results, isooctane was exhibited to be an appropriate solvent for the oxidation of **1** catalyzed by $Ni(st)_2$.

3.4.2 Effect of the amount of oxidant

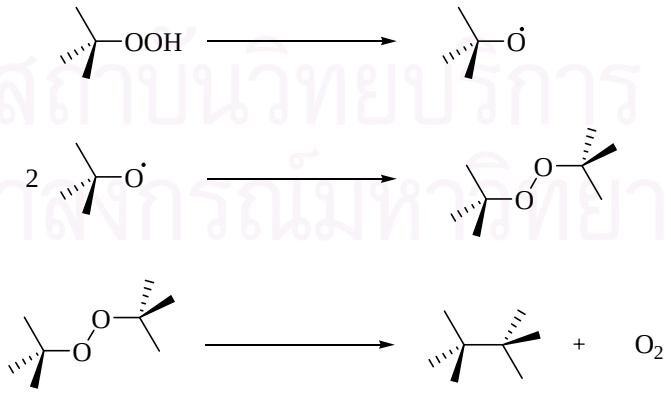
TBHP was selected as an oxidizing agent for the oxidation of **1**. The variation of yields may be affected by the amount of oxidizing agent used. The effect of the amount of TBHP on this reaction was examined and the results are exhibited in Table 3.4.

Table 3.4 The effect of amount of TBHP on the oxidation of **1**

Entry	TBHP (mmol)	% Yield		%Recovery of **1**	Mass balance
		2	**3**		
1	0	0	0	96	96
2	4.5	22	9	61	92
3	9.0	22	11	62	95
4	13.5	28	14	55	97
5	18.0	30	18	52	100
6	22.5	26	13	56	95
7	27.0	25	16	53	94

Reaction condition: **1** (5 mmol), Ni(II) stearate (0.2 mmol), TBHP (0-27 mmol) and isooctane (5 mL) at 70°C for 24 h.

From Table 3.4, the reactions with low amount of TBHP resulted in low conversion of **1**. TBHP in 3.6 equiv based on starting material were suited for proceeding the reaction with good yield. In the case of increasing amount of TBHP, the yields of both **2** and **3** decreased. This effect may be because the probability of collision between TBHP and itself was increased when the amount of TBHP was increased. According to previous literature, TBHP could possibly couple itself to furnish 2,2,3,3-tetramethylbutane. Therefore, TBHP present in an excess amount would quickly be destroyed because of self-coupling. The pathway of this evidence is shown in Scheme 3.1.



Scheme 3.1 The transformation of TBHP to 2,2,3,3-tetramethylbutane

3.4.3 Effect of the amount of catalyst

Effects of the amount of catalyst were explored to search for the appropriate amount of $Ni(st)_2$ in this reaction. The results of this searching are tabulated in Table 3.5.

Table 3.5 The effect of the amount of $Ni(st)_2$ on the oxidation of **1**

Entry	$Ni(st)_2$ (mmol)	% Yield		%Recovery of **1**	Mass Balance
		2	**3**		
1	0	5	1	90	96
2	0.05	16	6	80	92
3	0.10	19	7	68	94
4	0.20	22	11	62	95
5	0.30	20	10	61	91
6	0.40	12	4	76	92

Reaction condition: **1** (5 mmol), $Ni(st)_2$ (0-0.40 mmol), TBHP (9 mmol) and isooctane (5 mL) at 70°C for 24 h.

The highest yield was accomplished at 0.20 mmol of $Ni(st)_2$ as shown in Table 3.5 (entry 4). The products of these oxidation reaction were increased with increased amount of $Ni(st)_2$. In the case of $Ni(st)_2$ higher than 0.20 mmol, the products were slightly decreased. This may be because over amount of $Ni(st)_2$ congested the reaction between **1** and TBHP. In addition, increasing of the amount of $Ni(st)_2$ resulting in $Ni(st)_2$ could increasingly react with TBHP to generate oxo-$Ni(st)_2$. They could be transformed to inactive compounds such as bimetal compound. However, **1** could be oxidized to ethyl **2** and **3** efficiently when the amount of catalyst was lift up.

3.4.4 Effect of temperature

Another important factor for condition optimization on the oxidation reaction is the effect of temperature. The temperature in the reaction was varied from 30-90°C in order to search for the most felicitous temperature that accommodated the highest yields of **2** and **3**. The results are demonstrated in Table 3.6.

Table 3.6 The effect of temperature on the oxidation of **1**

Entry	Temperature (°C)	% Yields		%Recovery of **1**	Mass Balance
		2	**3**		
1	30	11	2	81	94
2	50	18	3	72	93
3	70	22	11	62	95
4	90	20	6	69	95

Reaction condition: **1** (5 mmol), $Ni(st)_2$ (0.2 mmol), TBHP (9 mmol) and isooctane (5 mL) at temperature between 30-90°C for 24 h.

The highest yield of **2** and **3** was accomplished at 70°C as displayed in Table 3.6 (entry 3). Consequently, the befitting temperature for this reaction is 70°C. According to the literature, Barton and coworkers reported that TBHP satisfied good yield of the desired product when it was used at 70°C [54]. At higher temperature, TBHP was quickly decomposed. Thus, the reaction was carried out at 90°C (entry 4) afforded a low yield. At lower temperature (entries 1 and 2), the conversion was provided in lower yields than that at 70°C. This was probably because TBHP was not homolytically dissociated to form radicals for initiating the oxidation reaction.

3.5 Kinetic study on the oxidation of ethyl phenylacetate (1) catalyzed by $Ni(st)_2$

The kinetic study on the oxidation of **1** was investigated to observe the optimum time for the progress of the reaction. The rate of the oxidation of **1** catalyzed by $Ni(st)_2$ utilizing TBHP in isooctane was explored. The kinetic analysis results of this reaction are exhibited in Fig 3.5.

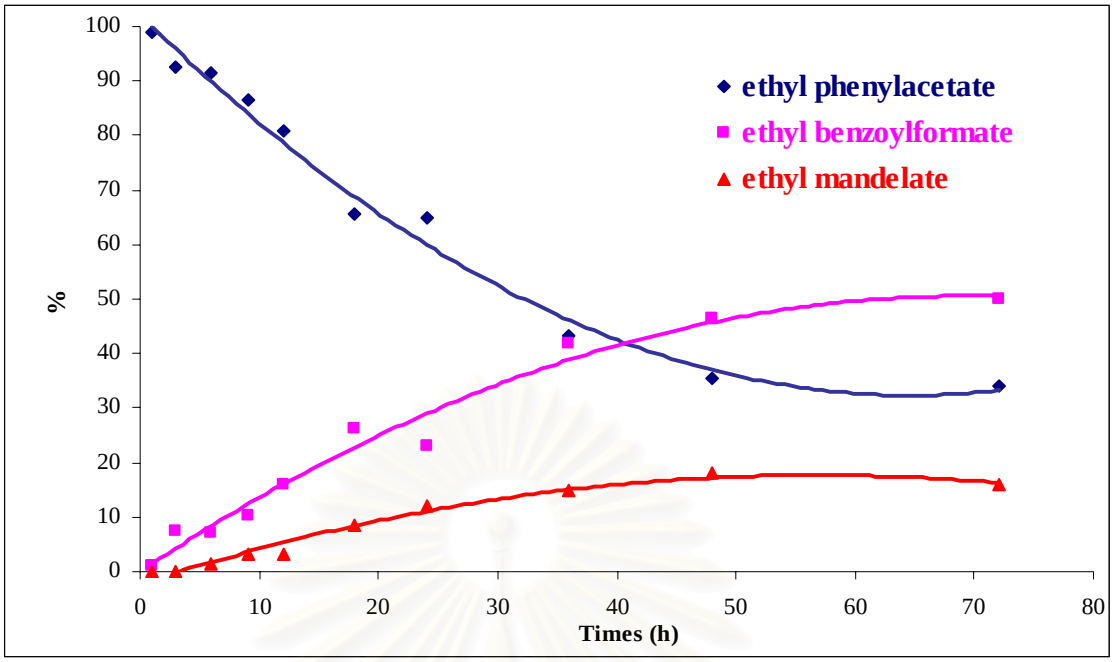


Figure 3.5 The kinetic study on the oxidation of **1** catalyzed by $Ni(st)_2$

Kinetic study on the oxidation of **1** is shown in Fig 3.5. For the variation of time, the most appropriate time for oxidation of **1** was disclosed to be around 48 h. The half life was resolved to be 20 h.

From the overall results observed, the type of carboxylate ligand, type of transition metal that coordinated with ligand, amount of oxidant, amount of catalyst, solvent system, reaction time and reaction temperature are affected the oxidation reaction. The optimized conditions for the oxidation of **1** could be summarized as follows: the mixture of **1** (5 mmol), TBHP (18 mmol) and $Ni(st)_2$ (4 mol%, 0.20 mmol) in isooctane (5 mL) at 70°C for 48 h. This ameliorated catalytic system was utilized for other compounds which will discuss in the following topics.

Part II: Utilization of iron carboxylate complexes

The previous results clearly revealed that ligands containing electron withdrawing group and short chain provided the higher yield of the desired product, whereas nickel(II) stearate and nickel(II) 4-chlorobenzoate were granted the moderate yield. Thus, trichloroacetic acid was chosen as a ligand of certain transition metals on the oxidation of **1** because it contained strong electron withdrawing group. Solvent "isoocatane" was switched to "pyridine" because the former could not dissolve metal trichloroacetate complexes.

3.6 Synthesis and characterization of metal carboxylates

Metal trichloroacetates were prepared by reacting anhydrous metal chloride with trichloroacetic acid according to previously reported protocol [49]. The complexes studied in this catalysis screening included chromium(III), manganese(II), iron(III), nickel(II) and copper(II) trichloroacetates. Furthermore, iron(III) carboxylates; for example, iron(III) pivalate, iron(III) butylate, iron(III) benzoate, iron(III) 4-chlorobenzoate, iron(III) 4-nitrobenzoate and iron(III) 2,4-dinitrobenzoate were prepared by reacting iron(III) chloride with various carboxylic acids under basic conditions according to encyclopedia of chemical technology [51]. In addition iron(III) trifluoroacetate was synthesized by reacting anh iron(III) chloride with trifluoroacetic acid according to that previously reported protocol [50]. The identities of all synthesized complexes were confirmed by IR spectroscopy technique. The generally vibration band of carboxylate ligands “asymmetric stretching of C=O, and symmetric stretching of C-O bond” were resembled to that of carboxylate ligands of nickel(II) carboxylate. The illustration of IR spectrum of $Fe(TCA)_3$ is exhibited in Fig 3.6.

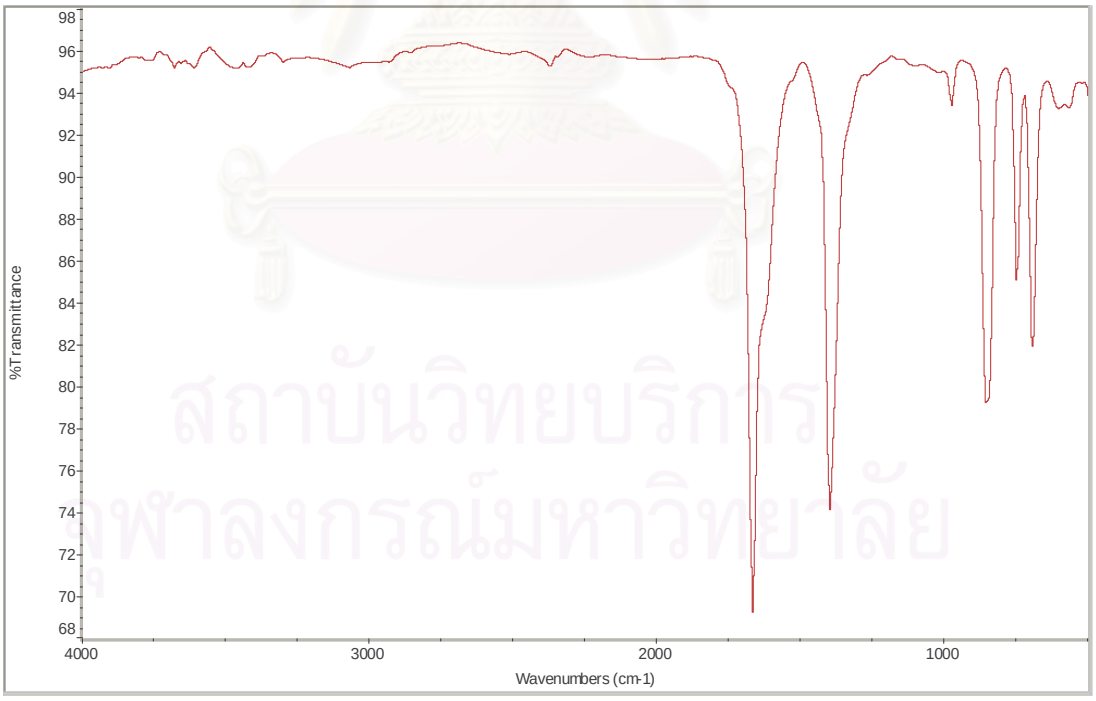


Figure 3.6 IR spectrum of $Fe(TCA)_3$

From Fig 3.6, the IR spectrum of $Fe(TCA)_3$ exhibited asymmetric stretching of C=O at 1661 cm^{-1} and symmetric stretching of C-O at 1392 cm^{-1}.

3.7 Effect of metal trichloroacetates on the oxidation of ethyl phenylacetate (1)

The aim of this study was screened for appropriate metal trichloroacetates that could transform **1** to **2** using TBHP and pyridine as oxidizing agent and solvent, respectively. The results are exhibited in Table 3.7.

Table 3.7 The effect of metal trichloroacetates on the oxidation of **1**

Entry	Metal trichloroacetate	% Yield of **2**	%Recovery of **1**	Mass balance
1	chromium(III)	33	57	90
2	manganese(II)	39	62	101
3	iron(III)	51	45	96
4	nickel(II)	20	83	103
5	copper(II)	10	83	93

Reaction condition: **1** (5 mmol), metal trichloroacetate (0.2 mmol), TBHP (9 mmol) and pyridine (5 mL) at 70°C for 24 h.

The oxidation of **1** was performed in pyridine in the presence of a variety of metal trichloroacetates. From Table 3.8, the oxidation system in the presence of $Fe(TCA)_3$ as a catalyst gave the best yield of **2** (51%, entry 3). In all cases, the only product detected was **2** while nonreacted **1** was recovered. None of **3** was observed. In the case of chromium(III) and manganese(II) trichloroacetates as a catalyst, the reactions could also be proceeded to give **2** in good yield (entries 1 and 2) whereas those trichloroacetates of nickel(II) and copper(II) did not behave as good oxidation catalysts since **2** was derived in low yield.

This examination manifestly revealed that $Fe(TCA)_3$ could be exposed as the best complex for this oxidation reaction in terms of yield of the desired product and selectivity of reaction. $Fe(TCA)_3$ would thus be selected as a catalyst for the oxidation of **1** on the future work.

3.8 Effect of iron(III) carboxylates on the oxidation of ethyl phenylacetate (1)

The objective of this study was to explore the effect of carbon chain length and aromatic carboxylate ligands on the oxidation of **1**. The carboxylic acids such as butyric acid, pivalic acid, trifluoroacetic acid, trichloroacetic acid, benzoic acid, 4-nitrobenzoic acid, 2,4-dinitrobenzoic acid and 4-chlorobenzoic acid were selected to react with iron(III) chloride to prepare a catalyst utilized in the oxidation reaction of **1**. The results are assembled in Table 3.8.

Table 3.8 The effect of iron(III) carboxylates on the oxidation of **1**

Entry	Iron(III) carboxylate	% Yield of **2**	%Recovery of **1**	Mass balance
1	butyrate	23	75	98
2	pivalate	25	71	96
3	trifluoroacetate	40	59	99
4	trichloroacetate	51	45	96
5	benzoate	21	71	92
6	4-nirobenzoate	19	73	92
7	2,4-dinitrobenzoate	23	72	95
8	4-chlorobenzoate	29	72	101

Reaction condition: **1** (5 mmol), iron(III) carboxylate (0.2 mmol), TBHP (9 mmol) and pyridine (5 mL) at 70°C for 24 h.

From Table 3.8, it was found that the carbon chain length of carboxylate ligands (entries 1-4) was affected on this oxidation reaction. The ligands containing electron withdrawing group (entries 3 and 4) could be performed oxidation reaction more efficient than those without activated group (entries 1 and 2). In the case of aromatic carboxylate ligands (entries 5-8), the oxidation reaction was accommodated with moderated yield. Considering the effect of electron withdrawing group (entries 6-8), the similar trend as discussed above was observed, *i.e.*, the higher yield was obtained with the ligands bearing electron withdrawing group.

The above results demonstrated the essence of being of the electron withdrawing group containing ligand that could improve the capability of the oxidation of **1**.

In addition, it should be noted that **1** under this particular conditions could be converted to **2** in good yield without by-product. The best condition for the production of **2** was visualized when $Fe(TCA)_3$ was used as a catalyst. Therefore, this complex would be utilized as a catalyst for further study on the condition optimization of **1**.

3.9 Effect of type of oxidants, amount of TBHP, amount of catalyst, solvents, temperature and amount of substrate

3.9.1 Effect of type of oxidants

A variety of oxidants have been reported. Common oxidants used were H_2O_2 and *m*-CPBA. Thus, type of oxidant was another parameter that needed to be evaluated for optimizing reaction conditions. The effects of the variation of oxidants coupled with $Fe(TCA)_3$ on the oxidation of **1** are tabulated as shown in Table 3.9.

Table 3.9 The effect of type of oxidants on the oxidation of **1**

Entry	Oxidants	% Yields		%Recovery of **1**	Mass balance
		2	**3**		
1	TBHP	51	0	45	96
2	30%H_2O_2	0	0	101	101
3	2-ethyl butyraldehyde/O_2	2	2	91	95
4	*m*-CPBA	0	0	93	93

Reaction condition: **1** (5 mmol), $Fe(TCA)_3$ (0.2 mmol), pyridine (5 mL) and oxidants (9 mmol) at 70°C for 24 h.

From Table 3.9, four types of oxidants were employed in the oxidation of **1**. It was observed that TBHP was the best oxidant chosen to utilize with $Fe(TCA)_3$ while H_2O_2, *m*-CPBA and 2-ethylbutyraldehyde/O_2 exhibited less capability as oxidant under this condition. That may be H_2O_2, *m*-CPBA and 2-ethylbutyraldehyde/O_2 could be rapidly decomposed at 70ºC.

3.9.2 Effect of the amount of TBHP

The effect of the amount of TBHP on the oxidation of **1** was investigated and the results are summarized in Table 3.10.

Table 3.10 The effect of the amount of TBHP on the oxidation of **1**

Entry	TBHP (mmol)	% Yield of **2**	%Recovery of **1**	Mass balance
1	0	0	99	99
2	4.5	27	76	103
3	9.0	51	45	96
4	13.5	61	36	97
5	18.0	39	57	96
6	22.5	38	55	93
7	27.0	37	57	94

Reaction condition: **1** (5 mmol), $Fe(TCA)_3$ (0.2 mmol), TBHP (0-27 mmol) and pyridine (5 mL) at 70°C for 24 h.

In the present study, employing 13.5 mmol of TBHP gave the highest yield of **2** without other product formation (entry 4). When TBHP was used less than 13.5 mmol (entries 1-3), the desired product was increased. In the case of utilizing TBHP more than 13.5 mmol (entries 5-7), the desired product was decreased. These results confirmed with those presented in Table 3.4 that the probability of collision of TBHP itself increased when the amount of TBHP was increased.

3.9.3 Effect of the amount of catalyst

The effect of amount of catalyst was inspected to competence on $Fe(TCA)_3$ catalyst complex on the oxidation of **1**. The variation of the amount of this complex and its effect on the oxidation reaction are illustrated in Table 3.11.

Table 3.11 The effect of the amount of $Fe(TCA)_3$ on the oxidation of **1**

Entry	$Fe(TCA)_3$ (mmol)	% Yield of **2**	%Recovery of **1**	Mass balance
1	0	0	105	105
2	0.05	38	54	92
3	0.10	49	44	93
4	0.15	57	46	103
5	0.20	51	45	96
6	0.30	54	44	96
7	0.40	59	47	106

Reaction condition: **1** (5 mmol), $Fe(TCA)_3$ (0-0.40 mmol), TBHP (9 mmol) and pyridine (5 mL) at 70°C for 24 h.

From Table 3.11, with the variation of the amount of catalyst, it was found that the optimum catalyst loading was 0.15 mmol (3 mol%, entry 4) because the reaction gave the best yield at lower catalyst loading. Thus, the amount of catalyst affected on the production of the desired product.

3.9.4 Effect of solvents

In this research, the homogeneous solvent was required. The effect of various solvents including pyridine, acetronitrile, THF, ethanol, *t*-butanol, 1,4-dioxane, DMF, TMEDA, CH_2Cl_2, $CHCl_3$, 3-picoline and 4-picoline were investigated on the oxidation of **1**. The results of the effect of solvent on this oxidation reaction are set out as shown in Table 3.12.

Table 3.12 The effect of solvents on the oxidation of **1**

Entry	Solvents	%Yield		%Recovery of **1**	Mass balance
		2	**3**		
1	pyridine	51	0	45	96
2	acetronitrile	12	15	65	92
3	CH_2Cl_2	7	36	58	101
4	$CHCl_3$	2	11	88	101
5	THF	0	0	91	91
6	TMEDA	0	0	97	97
7	DMF	4	0	85	89
8	1,4-dioxane	4	0	86	90
9	EtOH	1	trace	95	96
10	*t*-butanol	22	15	63	100
11	3-picoline	18	0	79	97
12	4-picoline	21	0	71	92

Reaction condition: **1** (5 mmol), $Fe(TCA)_3$ (0.2 mmol), TBHP (9 mmol) and solvents (5 mL) at 70°C for 24 h.

Among various solvents studied, pyridine was found to be an ideal solvent in this oxidation reaction. When pyridine was employed as the reaction medium (entry 1), the oxidation provided the highest amount of the desired product and free from byproduct. When acetronitrile and $CHCl_3$ were used (entries 2,4), the oxidation reaction expressed a small amount of **2** while **3** was detected as a main product. The same trend of the outcome was also observed when CH_2Cl_2 was used as solvent, the yield of **3** was significantly more than **2** about five fold (entry 3). Based on the results obtained, the direct synthesis of α-hydroxy esters carried out in CH_2Cl_2 was an intriguing point which should be continuously examined for the future work. In the case of DMF and 1,4-dioxane as a solvent (entries 7-8), low yield of **2** was detected. If THF and TMEDA were used as reaction medium, the oxidation reaction was not taken place.

From the above results, CH_2Cl_2 provided **3** more than **2** whereas pyridine afforded only **2**. It was interesting to observe the diverse effect of these two solvents. The amount of pyridine was thus experimented between 0-5 mL in the total volume of solvent 5 mL. The results are shown in Table 3.13.

Table 3.13 The effect of pyridine on the oxidation of **1**

Entry	pyridine (mL)	% Yield		Selectivity
		2	**3**	**2/3**
1	0	7	36	0.2
2	0.04	4	4	1
3	0.40	27	1	27
4	0.75	42	0	ND
5	1.25	45	0	ND
6	3.25	40	0	ND
7	5.00	51	0	ND

Reaction condition: **1** (5 mmol), $Fe(TCA)_3$ (0.2 mmol), TBHP (9 mmol) and pyridine + CH_2Cl_2 (5 mL) at 70°C for 24 h.

From Table 3.13, pyridine greatly revealed the influence on product distribution. The less of **3** was observed when pyridine was added. Interestingly, only 0.75 mL of pyridine was enough to alter the reaction pathway and exclusively produced **2** in good yield.

From these results, pyridine is the solvent of choice for performing oxidation of **1** under this particular condition to achieve solely **2**, while CH_2Cl_2 is also the proper solvent for manipulating α-hydroxy esters.

3.9.5 Effect of temperature

The study on the effect of temperature was reinvestigated using $Fe(TCA)_3$ as a catalyst for the oxidation of **1**. The results revealed the same trend as those observed previously using $Ni(st)_2$ as a catalyst**.** TBHP provided the best efficiency when it was used at 70°C. Therefore, the oxidation reaction of **1** was carried out at 70°C in the future experiments.

3.9.6 Effect of the amount of substrate

The effect of the amount of **1** between 1-25 mmol was the next parameter to examine. The results are accumulated in Table 3.14.

Table 3.14 The effect of the amount of substrate on the oxidation of **1**

Entry	**1** (mmol)	% Yield of **2**		%Recovery of **1**	Mass balance
		based on **1**	based on TBHP		
1	1	42	5	54	96
2	3	48	16	42	90
3	5	51	28	45	96
4	10	47	52	62	109
5	15	23	38	71	94
6	25	15	42	78	93

Reaction condition: **1** (1-25 mmol), $Fe(TCA)_3$ (0.2 mmol), TBHP (9 mmol) and pyridine (5 mL) at 70°C for 24 h.

From Table 3.14, it was observed that the amount of substrate affected the product yield. The yield of the desired product based on the oxidant was increased when the more substrate was used. That may provide higher opportunity to have collision between substrate and TBHP when the amount of substrate was increased. On the contrary, the lower yield of the desired product based on substrate was observed when the amount of substrate was increased. That was because the access amount of substrate could not converted to the desired product with the constant amount of TBHP.

3.10 Kinetic study on the oxidation of ethyl phenylacetate (1) catalyzed by $Fe(TCA)_3$

The kinetic study of the oxidation reaction of **1** catalyzed by $Fe(TCA)_3$ using TBHP as an oxidant and pyridine as an oxidation medium was examined. The results of kinetic analysis are exhibited in Fig 3.7.

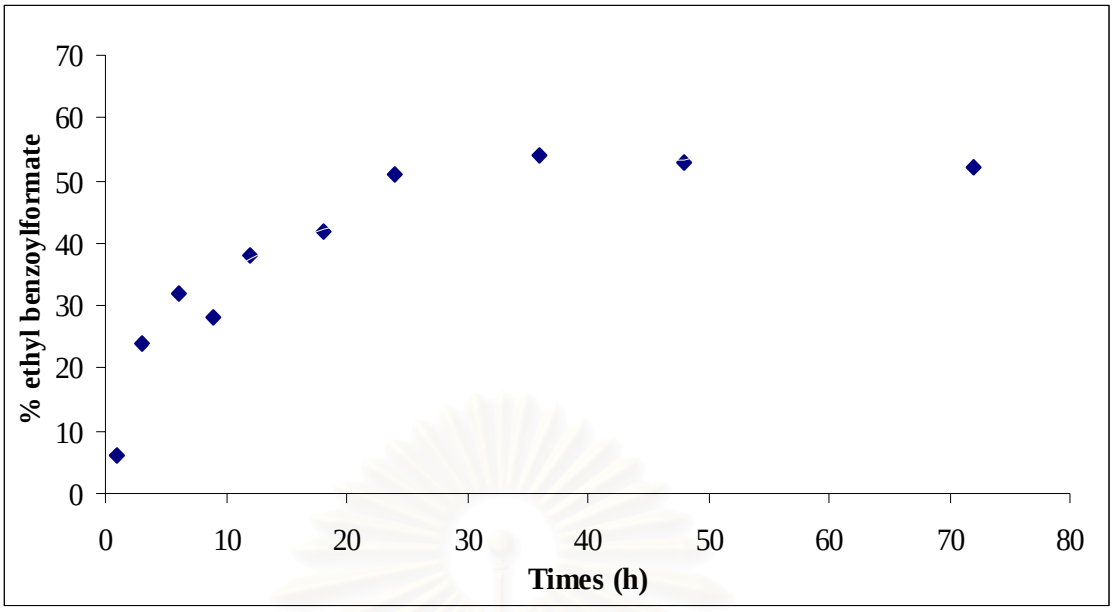


Figure 3.7 The kinetic study on the oxidation of **1** catalyzed by $Fe(TCA)_3$

From Fig 3.7, the highest yield of **2** was obtained when the reaction was carried out for 24 h. The half life of the developed reaction was determined to be 8 h. The haft life of the oxidation shorten than $Ni(st)_2$ was proceeded as a catalyst. It concluded that the developed oxidation reaction of **1** catalyzed by $Fe(TCA)_3$ revealed higher efficient than that of $Ni(st)_2$.

According to aforementioned results, it can be concluded that the optimized conditions for the oxidation of **1** are as follows: the mixture of **1** (5 mmol) as substrate, TBHP (13.5 mmol) as an oxidant, pyridine (5 mL) as the reaction medium and $Fe(TCA)_3$ (3 mol%, 0.15 mmol) as a catalyst was stirred at 70°C for 24 h.

3.11 Oxidation of ethyl phenylacetate (1) catalyzed by bicatalyst and tricatalyst of metal trichloroacetate complexes

From the results in previous sections, other metal trichloroacetates could also be employed for oxidation reaction, especially $Cr(TCA)_3$ and $Mn(TCA)_2$. In the endeavor to minimize the amount of $Fe(TCA)_3$ and to observe the aftermath of other metal trichloroacetates coupled with $Fe(TCA)_3$, a series of examination were carried out.

3.11.1 Effect of bicatalyst

From previous results, three metal trichloroacetates, namely $Fe(TCA)_3$, $Mn(TCA)_2$ and $Cr(TCA)_3$ provided the highest yield, respectively. Thus, $Mn(TCA)_2$

and $Cr(TCA)_3$ were chosen to coupled with $Fe(TCA)_3$ at four different ratios. The results are compared with that obtained from employing $Fe(TCA)_3$ alone and displayed in Table 3.15.

Table 3.15 The effect of bicatalyst on the oxidation of **1**

Entry	Catalyst	Fraction	% Yield of **2**	% Recovery of **1**	Mass balance
1	$Fe(TCA)_3$	-	51	45	96
2	$Mn(TCA)_2$	-	39	62	101
3	$Cr(TCA)_3$	-	33	57	90
4	$Fe(TCA)_3$ $Mn(TCA)_2$	1:1	63	40	103
5		2:1	46	42	88
6		3:1	45	42	87
7		4:1	47	41	88
8	$Fe(TCA)_3$ $Cr(TCA)_3$	1:1	29	62	91
9		2:1	23	68	91
10		3:1	26	65	91
11		4:1	29	61	90

Reaction condition: **1** (5 mmol), $Fe(TCA)_3$: another metal trichloroaceate (0.2 mmol), TBHP (9 mmol) and pyridine (5 mL) at 70°C for 24 h.

The results disclosed that the best combination of catalyst was $Fe(TCA)_3$ coupled with $Mn(TCA)_2$ in 1:1 ratio afforded 63% yield of the desired product. This was the highest yield observed and was even better than employing $Fe(TCA)_3$ alone. Other systems produced **2** in lower yield than the reaction system employing only $Fe(TCA)_3$.

3.11.2 Effect of tricatalyst

Additionally, tricatalyst systems were experimented for the oxidation of **1**. The different ratios of $Fe(TCA)_3$, $Mn(TCA)_2$ and $Cr(TCA)_3$ were paid attention in order to observed the effect of tricatalyst systems. The results are demonstrated in Table 3.16.

Table 3.16 The effect of tricatalyst on the oxidation of **1**

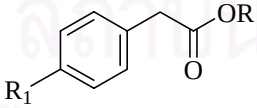
Catalyst	Fraction	% Yield of **2**	% Recovery of **1**	Mass balance
$Fe(TCA)_3 : Mn(TCA)_2 : Cr(TCA)_3$	1 : 1 : 1	31	63	94
	2: 1 : 1	34	60	94
	1 : 2 : 1	31	68	99
	1 : 1 : 2	30	57	87
	3 : 1 : 1	35	62	97
	1 : 3 : 1	30	63	93
	1 : 1 : 3	28	60	88

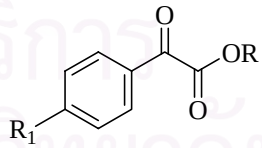
Reaction condition: **1** (5 mmol), $Fe(TCA)_3 : Mn(TCA)_2 : Cr(TCA)_3$ (0.2 mmol), TBHP (9 mmol) and pyridine (5 mL) at 70°C for 24 h.

In contrast to the outcome obtained from bicatalyst, tricatalyst did not expose spectacular results. The yield of the desired product was in fact slightly decreased when less $Fe(TCA)_3$ was used.

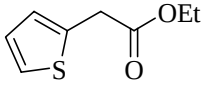
3.12 The application of the developed oxidation system for synthesis of various α-keto esters

Alkyl phenylacetate derivatives and ethyl thiophene-2-acetate were selected as the next chemical models to be examined. The goal of this examination was to study the effect of substituent group on aromatic ring on the oxidation reaction. Moreover, the effect of various alkyl esters was explored.

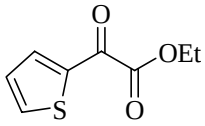




4 R = Et, R_1 = Cl
5 R = Et, R_1 = Cl
6 R = Et, R_1 = CH_3
7 R = Et, R_1 = CH_3
8 R = Me, R_1 = OMe
9 R = Me, R_1 = OMe
10 R = Et, R_1 = OMe
11 R = Et, R_1 = OMe
12 R = ^{n}Bu, R_1 = OMe
13 R = ^{n}Bu, R_1 = OMe



14



15

Alkyl phenylacetate derivatives and ethyl thiophene-2-acetate were mainly not commercial available substrates, thus needed to be prepared by esterification of its acid forms [52]. All compounds were identified by ^{1}H-NMR. ^{1}H-NMR spectrum of ethyl (4-chlorophenyl)acetate (**4**) (Fig 3.8) visualized two signals of ethyl group at δ_H 1.25 (t, *J* = 7.1 Hz, 3H) and δ_H 4.19 (q, *J* = 7.1, 2H). Benzylic protons could be detected at δ_H 3.66 (s, 2H) and aromatic protons were assigned around δ_H 7.31-7.37 (m, 5H).

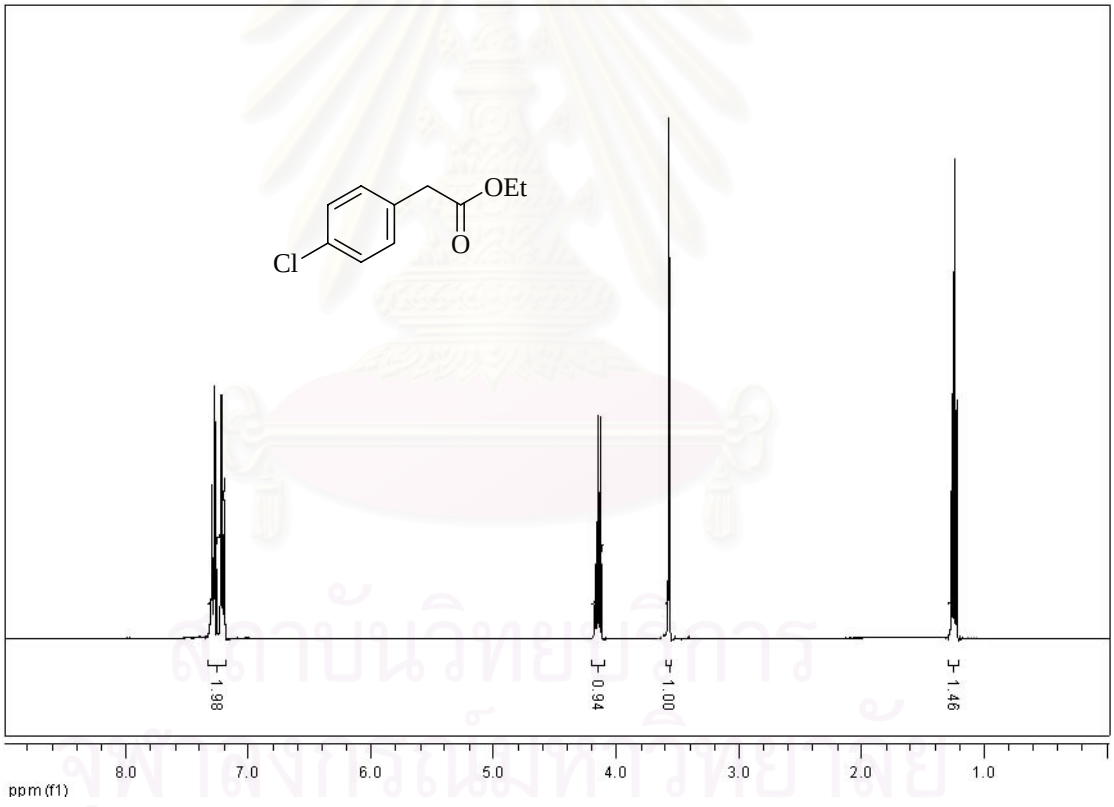


Figure 3.8 The ^{1}H-NMR spectrum of ethyl (4-chlorophenyl)acetate (**4**)

The ^{1}H-NMR spectrum of ethyl *p*-toluylacetate (**6**) (Fig 3.9) visualized two signals of ethyl group at δ_H 1.25 (t, *J* = 7.2 Hz, 3H) and δ_H 4.10 (q, *J* = 7.1 Hz, 2H). The signal of methyl group adjacent to aromatic ring was observed at δ_H 2.33 (s, 3H). The protons between aromatic ring and carbonyl group was detected at δ_H 3.57 (s, 2H) and aromatic proton signal could be assigned around δ_H 7.12-7.19 (m, 4H).

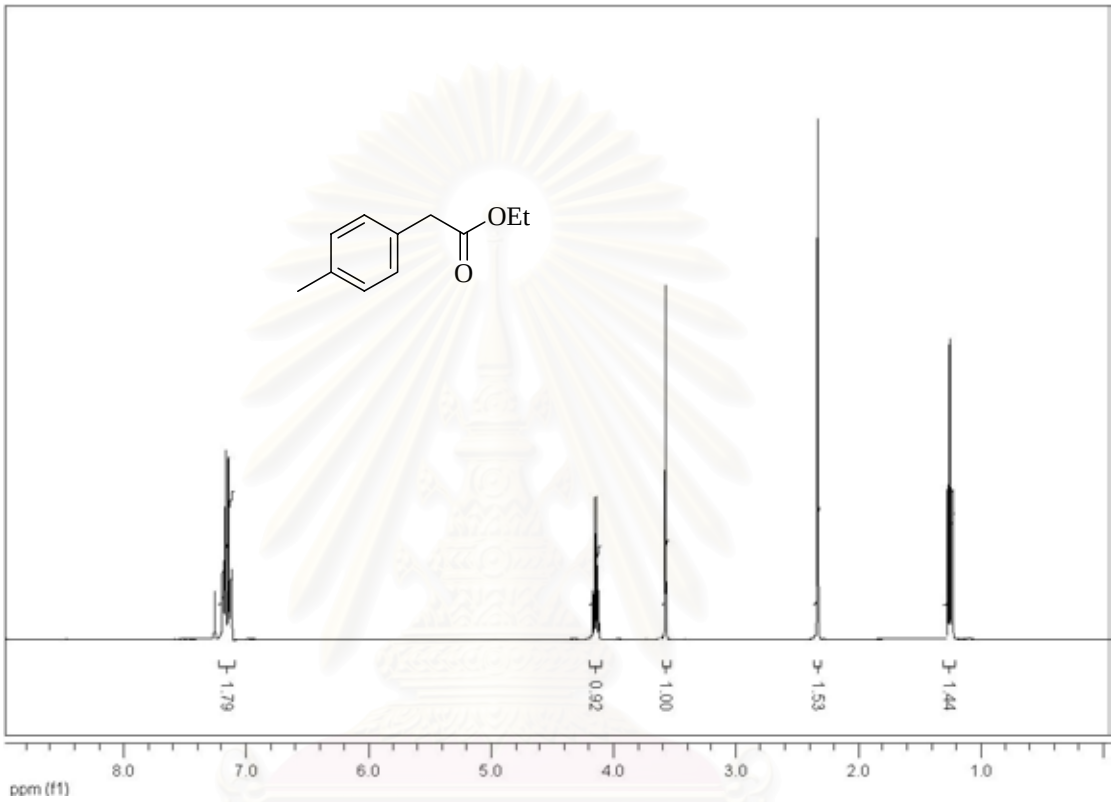


Figure 3.9 The ^{1}H-NMR spectrum of ethyl *p*-toluylacetate (**6**)

The ^{1}H-NMR spectrum of methyl (4-methoxyphenyl)acetate (**8**) (Fig 3.10) exhibited the benzylic proton signal at δ_H 3.57 (s, 2H). The signal of methyl group could be assigned at δ_H 3.68 (s, 3H). The methoxy proton on aromatic ring was detected at δ_H 3.79 (s, 3H). The signal of aromatic protons neighboring to a methoxy group was attributed at δ_H 6.86 (d, *J* = 8.7 Hz, 2H) and those of aromatic ring adjacent to a methylene group were discovered at δ_H 7.20 (d, *J* = 8.6 Hz, 2H).

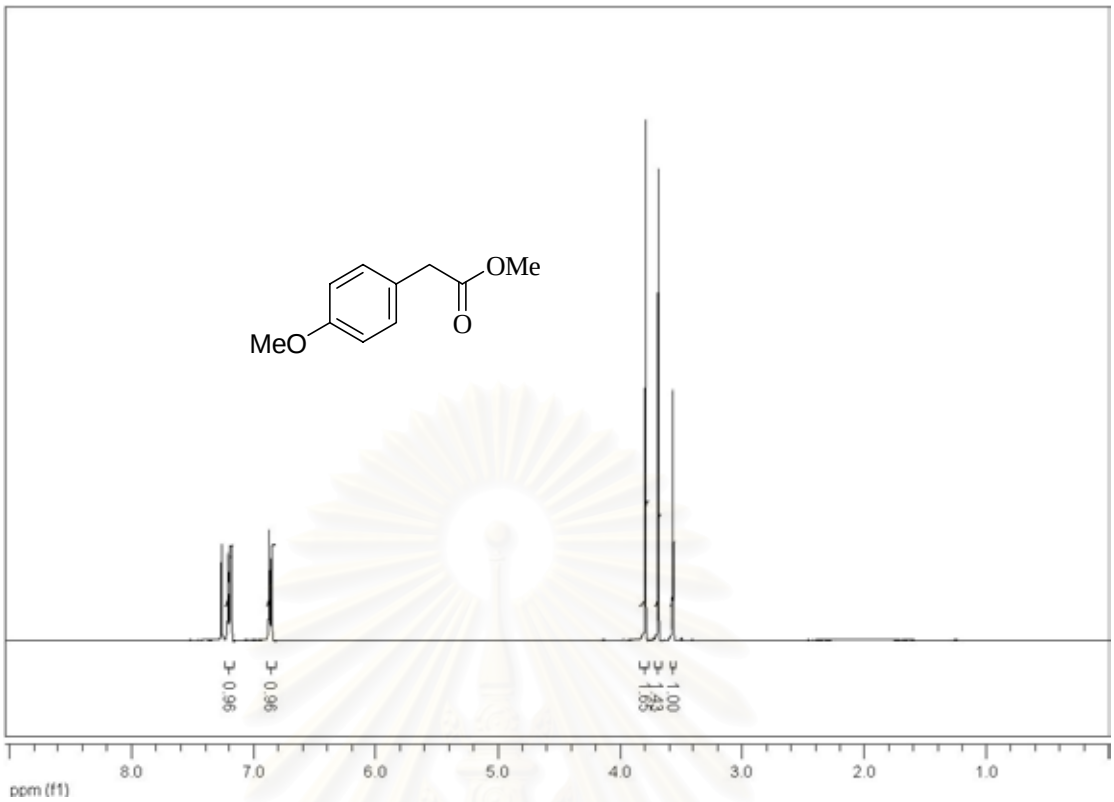


Figure 3.10 The ^{1}H-NMR spectrum of methyl (4-methoxyphenyl)acetate (**8**)

The ^{1}H-NMR spectrum of ethyl (4-methoxyphenyl)acetate (**10**) (Fig 3.11) visualized two signals of ethyl group at δ_H 1.24 (t, J = 7.2 Hz, 3H) and δ_H 4.14 (q, J = 7.2 Hz, 2H). The benzylic methylene protons were observed at δ_H 3.54 (s, 2H). The protons signal of methoxy group on aromatic ring was attributed at δ_H 3.79 (s, 3H). The signal of aromatic ring neighboring to a methoxy group was detected at δ_H 6.86 (d, J = 8.7 Hz, 2H) and those of aromatic ring next to methylene group was discovered at δ_H 7.20 (d, J = 8.6 Hz, 2H).

The ^{1}H-NMR spectrum of *n*-butyl (4-methoxyphenyl)acetate (**12**) (Fig 3.12) visualized four signals of butyl group at δ_H 0.91 (t, J = 7.4 Hz, 3H), δ_H 1.35 (sex, J = 7.3 Hz, 2H), δ_H 1.60 (quin, J = 6.7 Hz, 2H) and δ_H 4.08 (t, J = 6.7 Hz, 2H). The protons of benzylic methylene were assigned at δ_H 3.55 (s, 2H). The proton signal of methoxy group on aromatic ring was attributed at δ_H 3.79 (s, 3H). The protons signal of aromatic ring neighboring to a methoxy group wes observed at δ_H 6.86 (d, J = 8.6 Hz, 2H) and the protons signal of aromatic ring next to methylene group were discovered at δ_H 7.20 (d, J = 8.5 Hz, 2H).

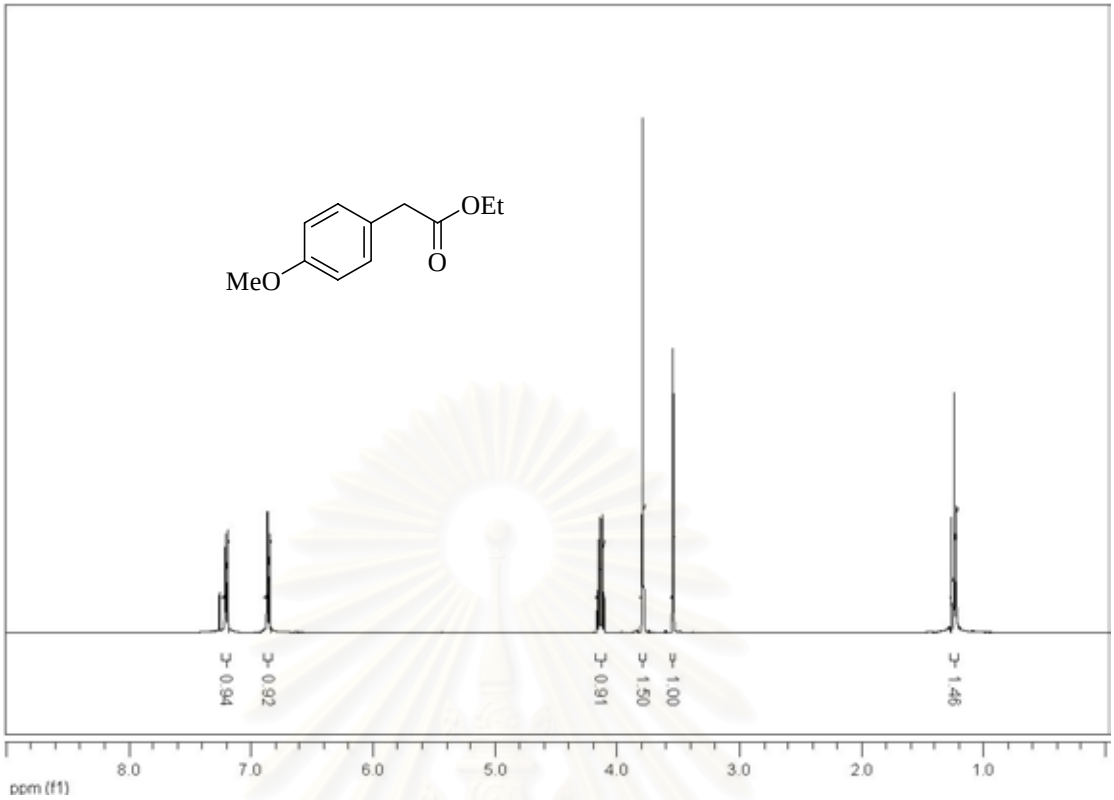


Figure 3.11 The ^{1}H-NMR spectrum of ethyl (4-methoxyphenyl)acetate (**10**)

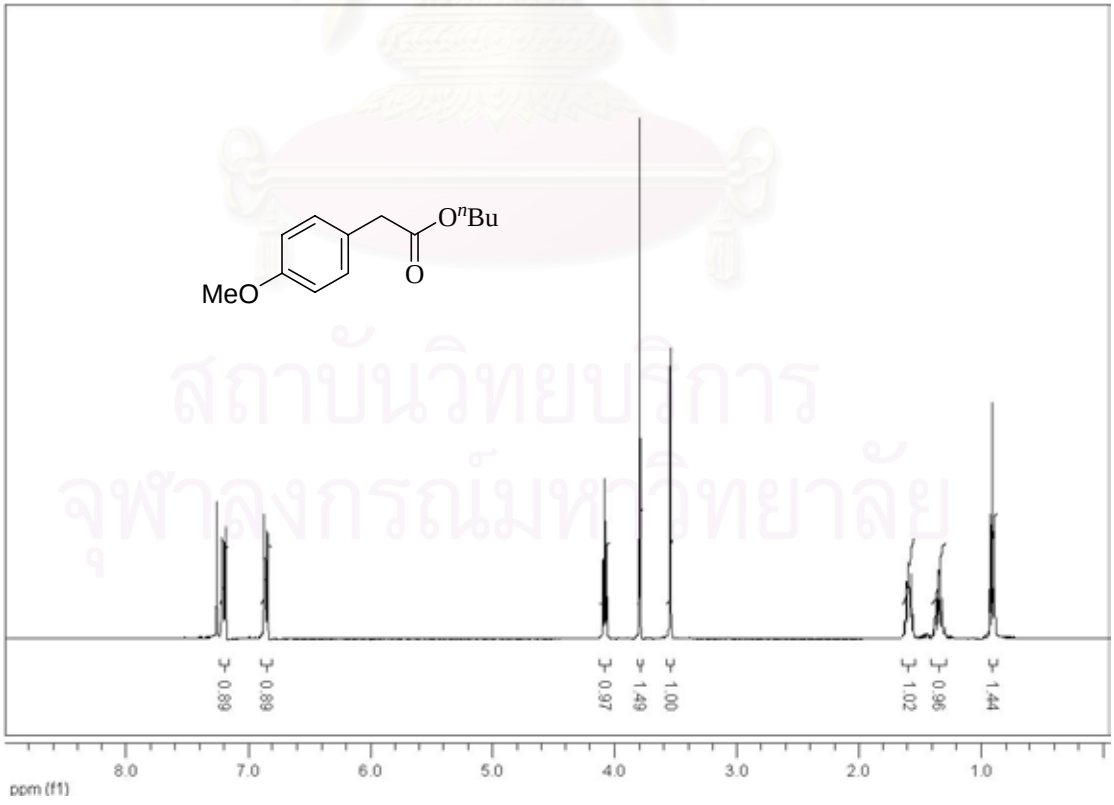


Figure 3.12 The ^{1}H-NMR spectrum of *n*-butyl (4-methoxyphenyl)acetate (**12**)

The ^{1}H-NMR spectrum of ethyl thiophene-2-acetate (**14**) as shown in Fig 3.13 revealed two signals of ethyl group detected at δ_H 1.28 (t, J = 7.2 Hz, 3H) and δ_H 4.19 (q, J = 7.2 Hz, 2H). The singlet signal of benzylic methylene protons was positioned at δ_H 3.83 (2H) and those of aromatic protons could be assigned around δ_H 6.95-7.22 (m, 3H).

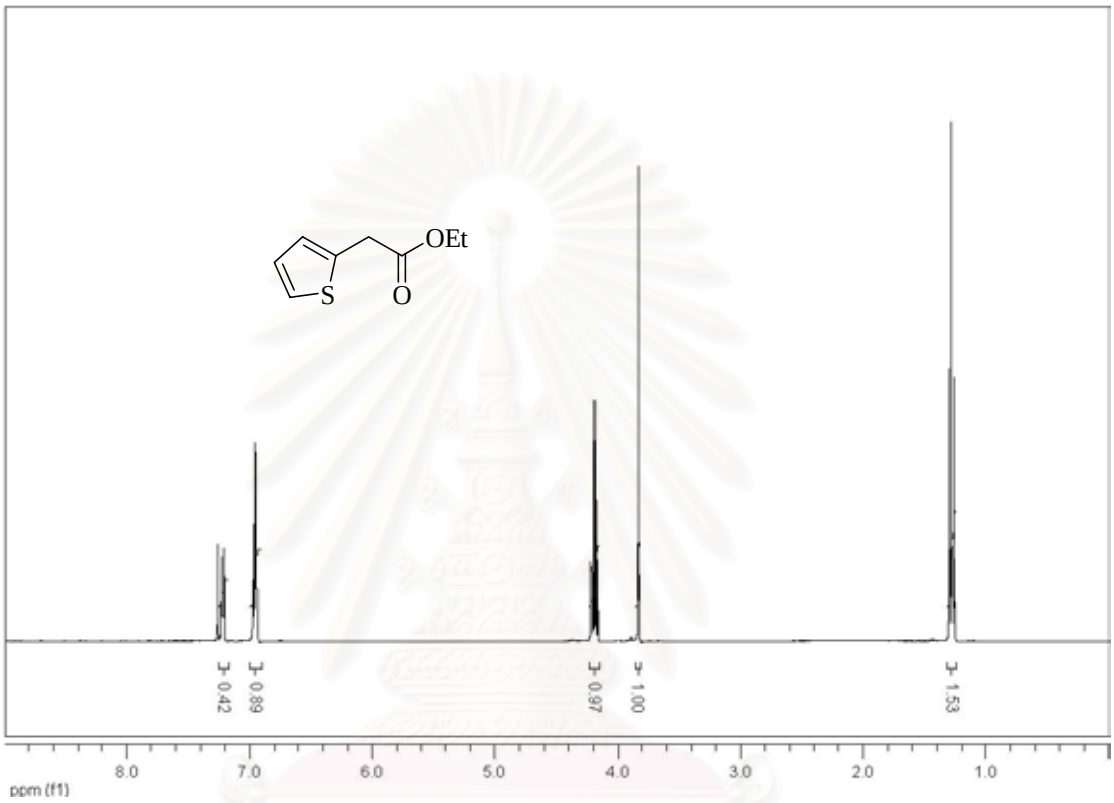


Figure 3.13 The ^{1}H-NMR spectrum of ethyl thiophene-2-acetate (**14**)

The oxidation of several alkyl phenylacetate including **3**, **4**, **6**, **8**, **10, 12** and **14** was carried out in the general procedure condition catalyzed by $Fe(TCA)_3$. The results are summarized in Table 3.17.

Table 3.17 The oxidation of selected esters catalyzed by $Fe(TCA)_3$

Entry	Substrate	Product	% Isolated yield
1	**3**	ethyl benzoylformate (**2**)	69, quant[a]
2	**4**	ethyl (4-chlorobenzoyl)formate (**5**)	38
3	**6**	ehyl *p*-toluyl-2-oxoacetate (**7**)	42
4	**8**	methyl (4-methoxybenzoyl)formate (**9**)	50
5	**10**	ethyl (4-methoxybenzoyl)formate (**11**)	72
6	**12**	*n*-butyl (4-methoxybenzoyl)formate (**13**)	59
7	**14**	ethyl thiophene-2-oxoacetate (**15**)	32

Reaction condition: substrate (5 mmol), $Fe(TCA)_3$ (0.2 mmol), TBHP (9 mmol) and pyridine (5 mL) at 70°C for 24 h.

[a]TBHP 6 mmol was used

From Table 3.15, the oxidation of α-hydroxy ester (**3**) afforded product **2** in 69% isolated yields under completely conversion of substrate when TBHP 9 mmol was used. The overoxidation of **2** may give benzoic acid. When TBHP 6 mmol was used, the oxidation of **3** impressively provided quantitative yield.

The study of the effect of several substituents at *para* position of aromatic ring provided some information clues (entries 2, 3 and 5). The yield was increased in order of $Cl < CH_3 < OMe$. Thus, the more electron donating group on aromatic ring present, the higher yield was obtained. This also implied that the active site of the catalyst used should be of electrophlilic in nature [55].

For the study on the effect of various alkyl esters (entries 4-6), ethyl ester afforded the best yield of α-keto esters. From electronic effect, the products should be increase in order of methyl, ethyl and butyl groups. In addition steric effect of alkyl esters should also have a marked effect, thus, the steric hindrance of butyl group affected the decreasing of the desired product.

In the case of the oxidation of ethyl thiophene-2-acetate (**14**), ethyl thiophene-2-oxoacetate (**15**) was achieved in moderate yield. The pure α-keto esters attained were purified by column chromatography and characterized by ^{1}H-NMR spectroscopy. The spectrum are discussed and shown below.

The oxidation of **4** afforded **5** in 38% isolated yield. This product was purified by silica gel column chromatography, the structure of **5** was confirmed by ^{1}H-NMR

spectrum (Fig 3.14). Two signals of ethyl group were detected at δ_H 1.42 (t, J = 7.1 Hz, 3H) and δ_H 4.45 (q, J = 7.1 Hz, 2H). The protons on aromatic ring adjacent to the carbon next to chlorine atom obtained at δ_H 7.49 (d, J = 8.8 Hz, 2H) and the protons on aromatic ring enfolded by carbonyl group shown at δ_H 7.99 (d, J = 8.7 Hz, 2H).

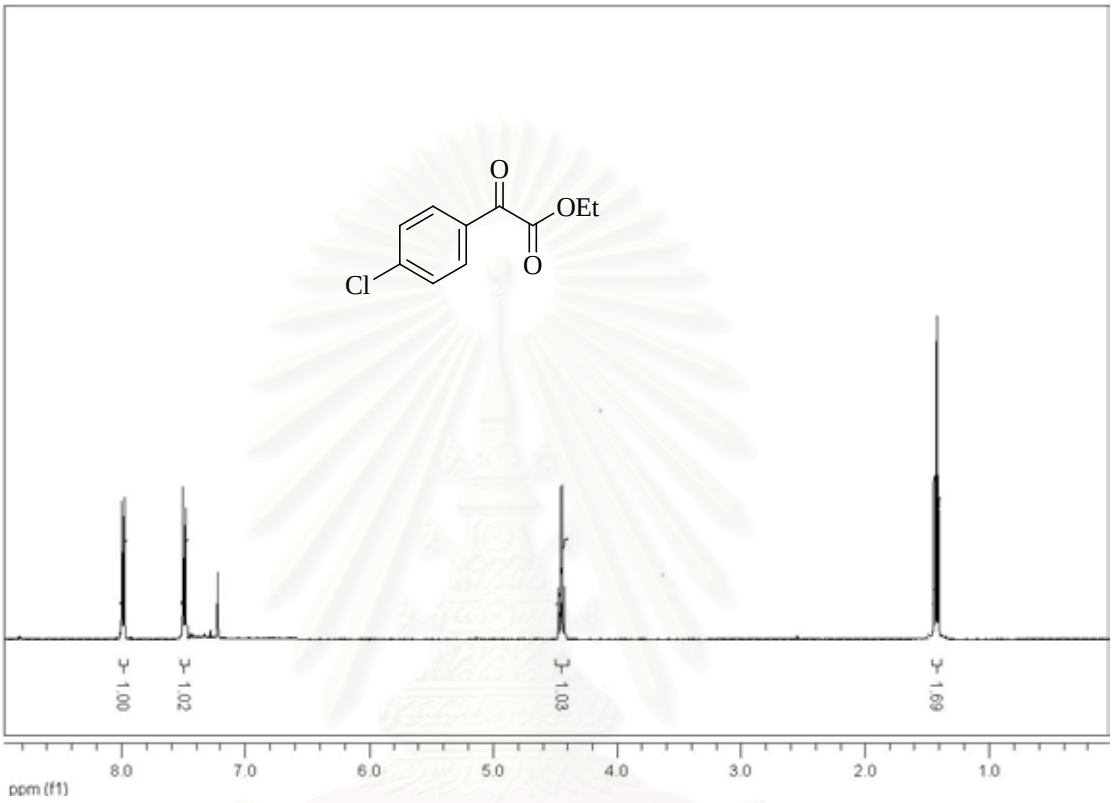


Figure 3.14 The ^{1}H-NMR spectrum of ethyl (4-chlorobenzoyl)formate (**5**)

The oxidation of **6** under the general procedure condition provided 42% isolated yield of **7**. The product **7** was purified by silica gel column chromatography, the structure of received product **7** was verified by ^{1}H-NMR spectrum (Fig 3.15). Two signals of ethyl group were detected at δ_H 1.42 (t, J = 7.1 Hz, 3H) and δ_H 4.44 (q, J = 7.2 Hz, 2H). The proton signal of methyl group on aromatic ring was observed at δ_H 2.44 (s, 3H). The aromatic protons neighboring to methyl group were discovered at δ_H 7.31 (d, J = 8.0 Hz, 2H) and the aromatic protons adjacent to a carbonyl group could be assigned at δ_H 7.91 (d, J = 8.2 Hz, 2H).

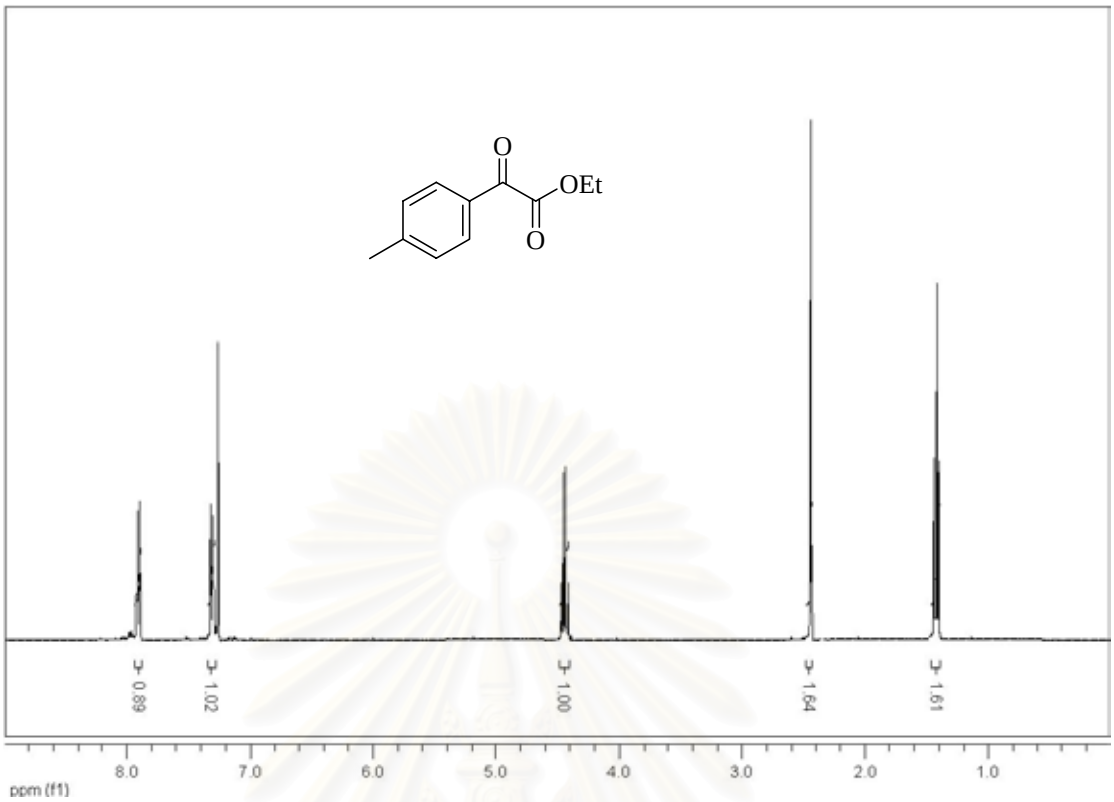


Figure 3.15 The ^{1}H-NMR spectrum of ethyl *p*-toluyl-2-oxoacetate (**7**)

Compound **9** was obtained by the oxidation of **8** under standard condition. The purification of **9** could be achieved by silica gel column chromatography in 50% isolated yield and the structure was characterized based upon a ^{1}H-NMR spectrum. The ^{1}H-NMR spectrum (Fig 3.16) displayed a significant singlet signal of the methyl group observed at δ_H 3.90 (3H). The singlet signal of the methoxy group on aromatic ring was detected at δ_H 3.96 (3H). The aromatic protons adjacent to the methoxy group could be assigned at δ_H 6.97 (d, J = 9.0 Hz, 2H) and aromatic protons neighboring to a carbonyl group were visualized at δ_H 8.01 (d, J = 9.0 Hz, 2H).

Under the general procedure condition, **10** could be transformed smoothly to give **11** in 72% yield. After purifying by silica gel column chromatography, the structure of the obtained product **11** was identified by ^{1}H-NMR spectrum. The ^{1}H-NMR spectrum (Fig 3.17) exhibited two signals of ethyl group at δ_H 1.39 (t, J = 7.3 Hz, 3H) and δ_H 4.41 (q, J = 7.4 Hz, 2H). The protons of methoxy group were detected at δ_H 3.85 (s, 3H). The protons on aromatic ring adjacent to methoxy group were visualized at δ_H 6.95 (d, J = 9.3 Hz, 2H) while the protons on aromatic ring enfolded by carbonyl group revealed at δ_H 7.96 (d, J = 9.2 Hz, 2H).

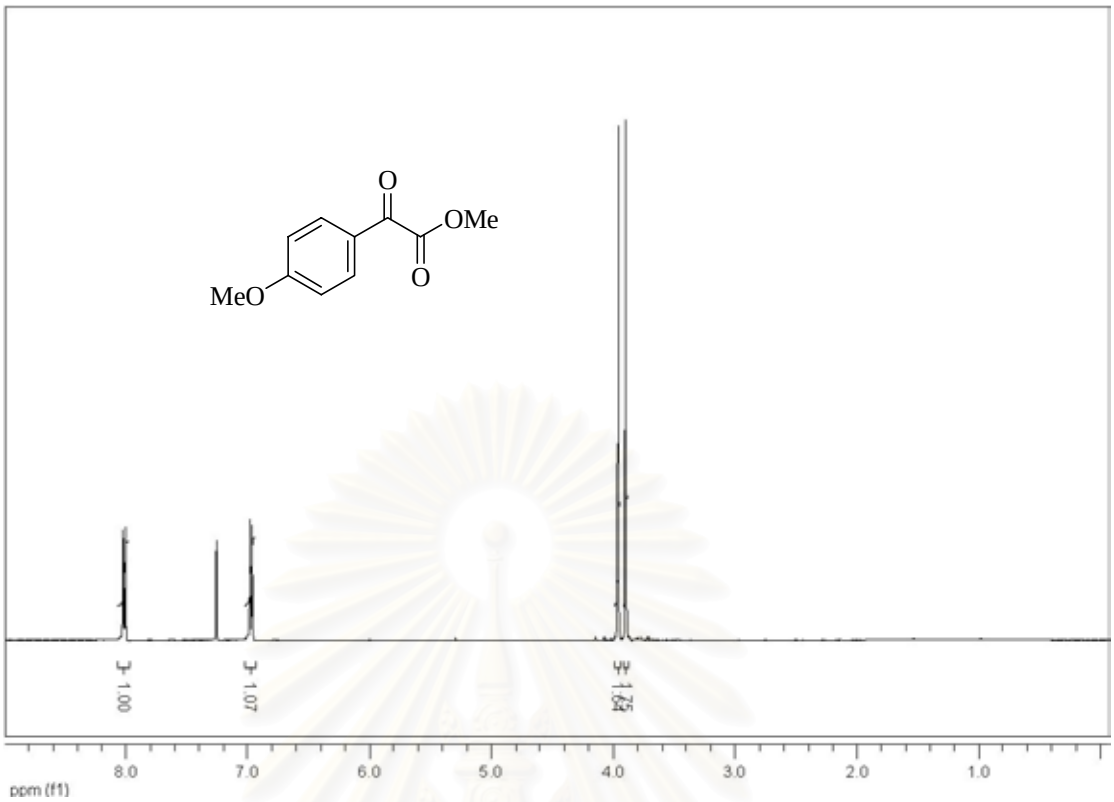


Figure 3.16 The ^{1}H-NMR spectrum of methyl (4-methoxylbenzoyl)formate (**9**)

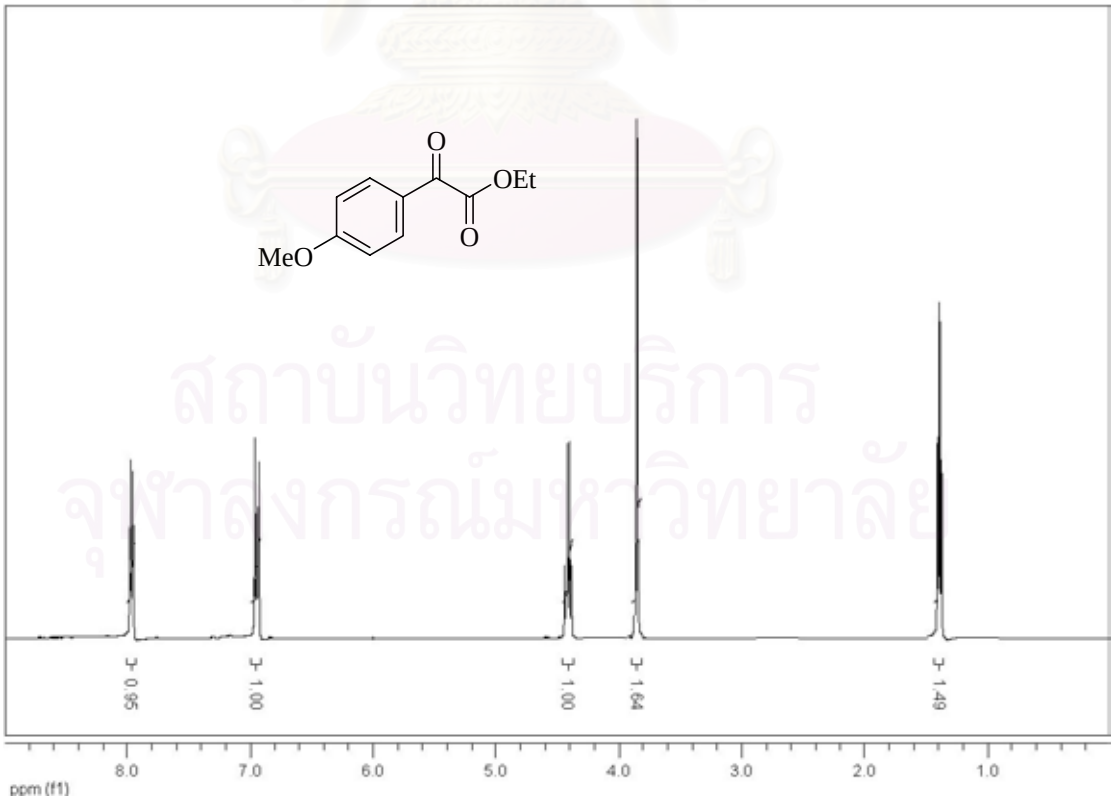


Figure 3.17 The ^{1}H-NMR spectrum of ethyl (4-methoxylbenzoyl)formate (**11**)

The oxidation **12** catalyzed by $Fe(TCA)_3$ under the general procedure afforded the product of **13** in 59% isolated yield. The product **13** was purified by silica gel column chromatography. The structure of **13** was characterized by ^{1}H-NMR spectrum (Fig 3.18). The ^{1}H-NMR spectrum of **13** visualized four signals of *n*-butyl group at δ_H 0.96 (t, J = 7.4 Hz, 3H), δ_H 1.45 (sex, J = 7.4 Hz, 2H), δ_H 1.76 (quin, J = 6.9 Hz, 2H) and δ_H 4.38 (t, J = 6.7 Hz, 2H). A singlet signal of the methoxy group on aromatic ring disclosed at δ_H 3.90 (3H). The protons on aromatic ring neighboring to the methoxy group could be assigned at δ_H 6.98 (d, J = 8.9 Hz, 2H) while the protons on aromatic ring adjacent to the carbonyl group were detected at δ_H 7.99 (d, J = 8.8 Hz, 2H).

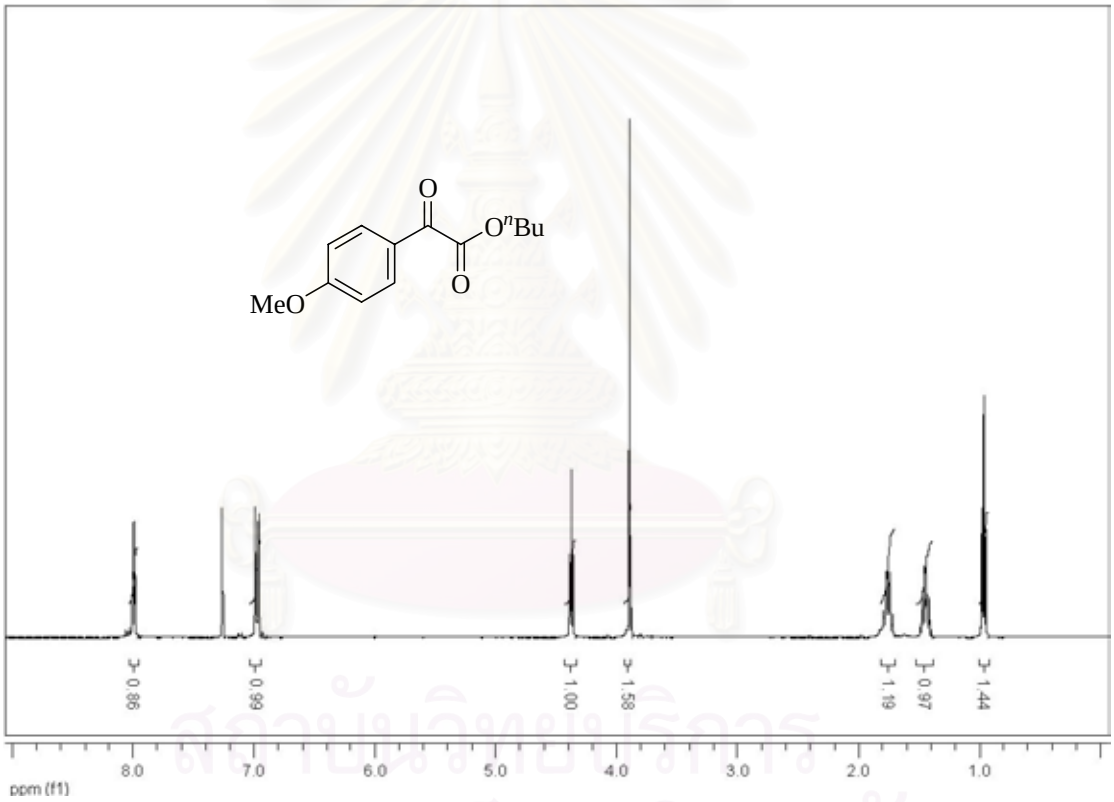


Figure 3.18 The ^{1}H-NMR spectrum of *n*-butyl (4-methoxylbenzoyl)formate (**13**)

Under the general condition, **14** was oxidized to give **15** in 32% isolated yield. The product **15** was purified by silica gel column chromatography. The structure of the obtained product **15** was identified by ^{1}H-NMR. The ^{1}H-NMR spectrum (Fig 3.19) showed two signals of ethyl group at δ_H 1.43 (t, J = 7.2 Hz, 3H) and δ_H 4.44 (q, J = 7.2 Hz, 2H). The aromatic protons could be assigned as follows: the center of three proton on aromatic ring was detected at δ_H 7.20 (dd, J = 4.0, 4.9 Hz, 1H) while the

proton on aromatic ring adjacent to carbonyl group was visualized at δ_H 7.82 (dd, *J* = 1.1, 4.9 Hz, 1H) and that on aromatic ring adjoined exhibited at δ_H 8.14 (dd, *J* = 1.1, 3.9 Hz, 1H).

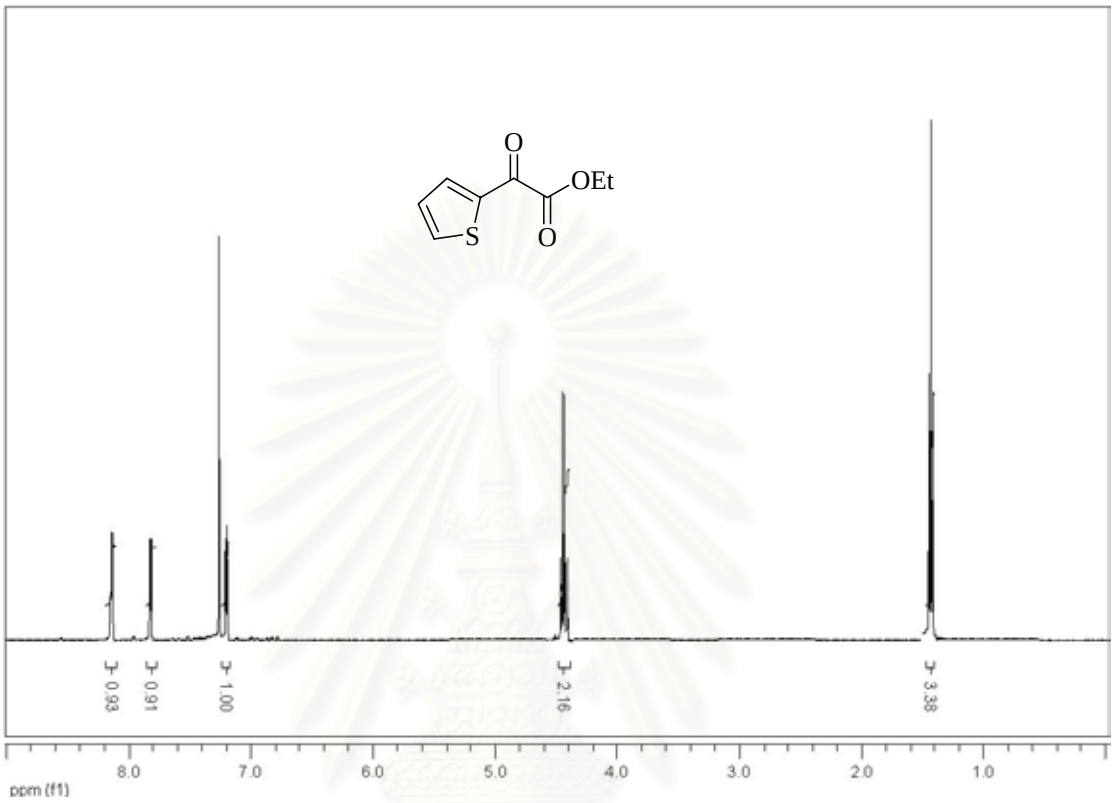
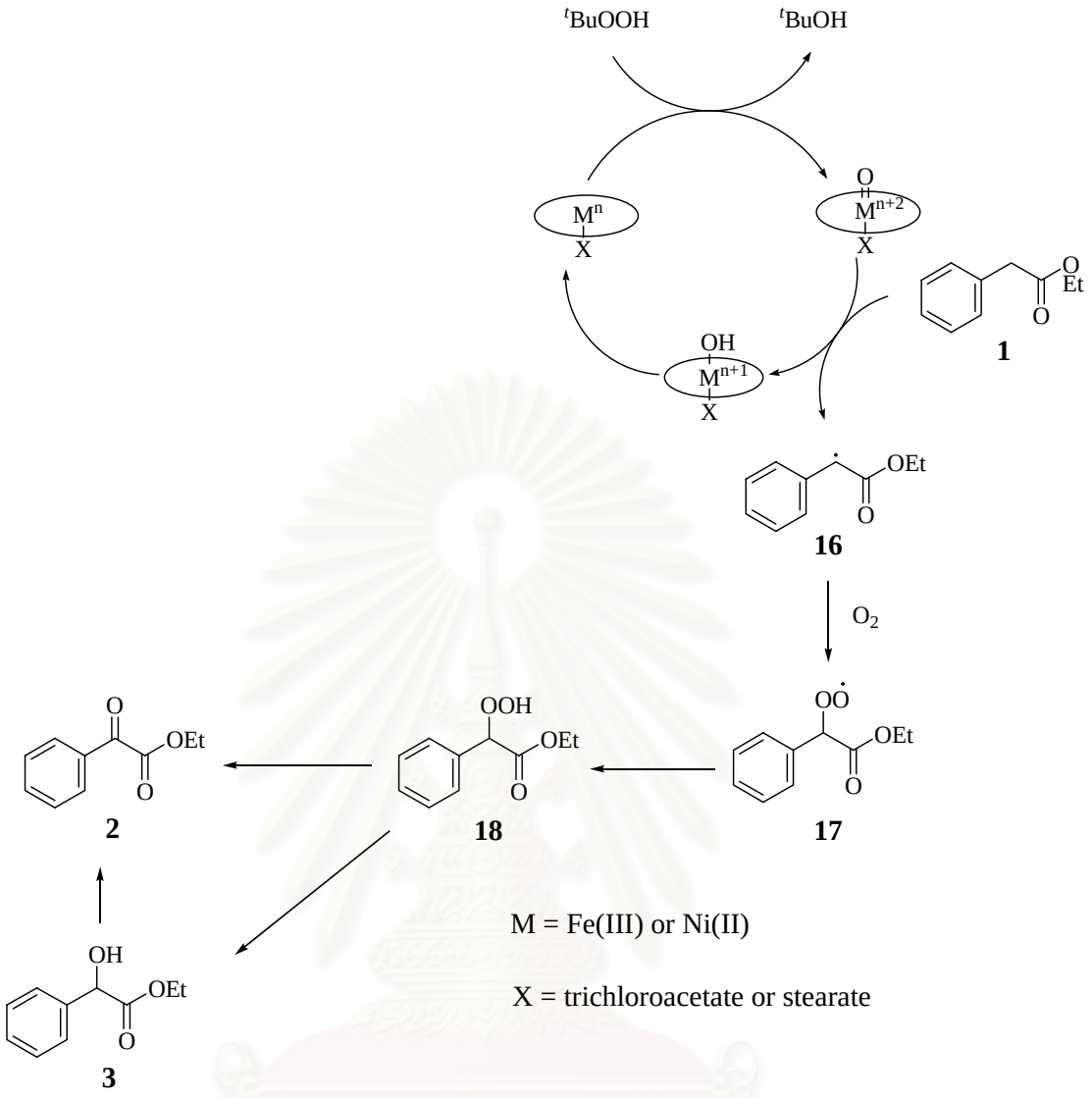


Figure 3.19 The ^{1}H-NMR spectrum of ethyl thiophene-2-oxoacetate (**15**)

3.13 Proposed mechanism for the oxidation of ethyl phenylacetate (1) catalyzed By $Fe(TCA)_3$ or $Ni(st)_2$

The mechanism of $Fe(TCA)_3$ or $Ni(st)_2$ oxidation of **1** employing TBHP as an oxidant was believed to proceed *via* free radical pathway in the same fashion proposed in literature [56]. Using **1** as a representive, the proposed mechanism is shown in Scheme 3.2.

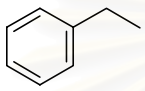


Scheme 3.2 Proposed mechanism for the oxidation of **1**

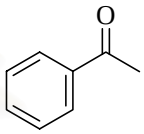
Firstly, $Ni(st)_2$ and $Fe(TCA)_3$ complexes were transformed to the corresponding high valent species (oxo compound). These species were then abstracted benzylic hydrogen of **1** to form the corresponding benzylic radical (**16**) and $M^{n+1}X(OH)$. The generated **16** was rapidly reacted with O_2 to give α-hydroperoxy radical intermediate (**17**), subsequently transform to relatively not stable α-hydroperoxide (**18**). The decomposition of **18** yielded **2** and **3.** Under these reaction conditions examined, **3** was further oxidized to **2**. In the case of utilization of $Fe(TCA)_3$ in the presence of pyridine, **3** was not generated. That may be because the process of pyridine abstracting the α-proton of **18** to generate **2** occurred vary fast.

3.14 The application of the developed system for the oxidation of benzylic methylene compounds

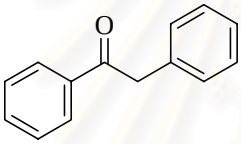
The aim of the present study was to extend the scope of the developed oxidation system for benzylic methylene compounds in the presence of $Fe(TCA)_3$. The chemical models including ethylbenzene (**19**), deoxybenzoin (**21**), acenaphthene (**23**), xanthene (**25**) and tetralin (**27**) were selected for study the efficiency of the oxidation system. The results of the oxidation of these substrates are summarized in Table 3.18.



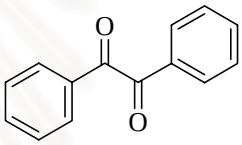
(**19**)



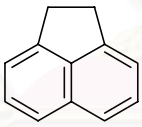
(**20**)



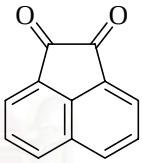
(**21**)



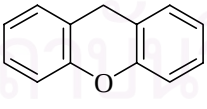
(**22**)



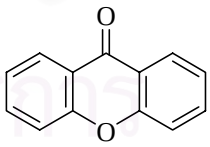
(**23**)



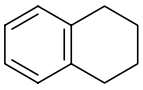
(**24**)



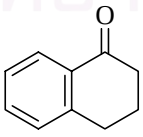
(**25**)



(**26**)



(**27**)



(**28**)

Table 3.18 The oxidation of benzylic methylene compounds catalyzed by $Fe(TCA)_3$

Entry	Substrate	Product	% Isolated yield
1	**19**	acetophenone (**20**)	quant
2	**21**	benzoin (**22**)	quant
3	**23**	acenaphthenequinone (**24**)	50
4	**25**	xanthone (**26**)	95
5	**27**	α-tetralone (**28**)	74

Reaction condition: substrate (5 mmol), $Fe(TCA)_3$ (0.2 mmol), TBHP (9 mmol) and pyridine (5 mL) at 70°C for 24 h.

Table 3.18 exhibits that **19** and **21** could be converted to **20** and **22** in quantitative yield (entries 1 and 2). For the oxidation of **23** provided **24** in moderate yield (entry 3). The oxidation of **27** afforded **28** in high yield (74% yield, entry 5). Comparing the result of the oxidation of **27** that reported recently, the use of $Cr(OAc)_3$ as catalyst with molecular oxygen also produced only low yield of **25** (33% yield). In the case of the oxidation of **25** gave excellent yield of **26** (entry 4).

From these results, $Fe(TCA)_3$ coupled with TBHP afforded the desired product in moderate to quantitative yield. Therefore, this developed system could be another alternative for oxidation of benzylic methylene compounds. The products were purified by column chromatography and confirmed their structures by ^{1}H-NMR . The ^{1}H-NMR spectra are discussed and displayed below.

The oxidation **19** catalyzed by $Fe(TCA)_3$ under the general procedure afforded **20** in quantitative yield. The product **20** was purified by silica gel column chromatography. The structure of **20** was characterized by ^{1}H-NMR. The ^{1}H-NMR spectrum of **20** (Fig 3.20) visualized singlet signals of methyl group at δ_H 2.61 (3H). The proton on aromatic ring at *meta* position of carbonyl group disclosed a triplet signal at δ_H 7.47 (J = 7.8 Hz, 1H). The protons on aromatic ring at *para* position of carbonyl group could be assigned at δ_H 7.57 (t, J = 7.4 Hz, 2H) while the protons on aromatic ring adjacent to carbonyl group were detected at δ_H 7.96 (d, J = 8.0 Hz, 2H).

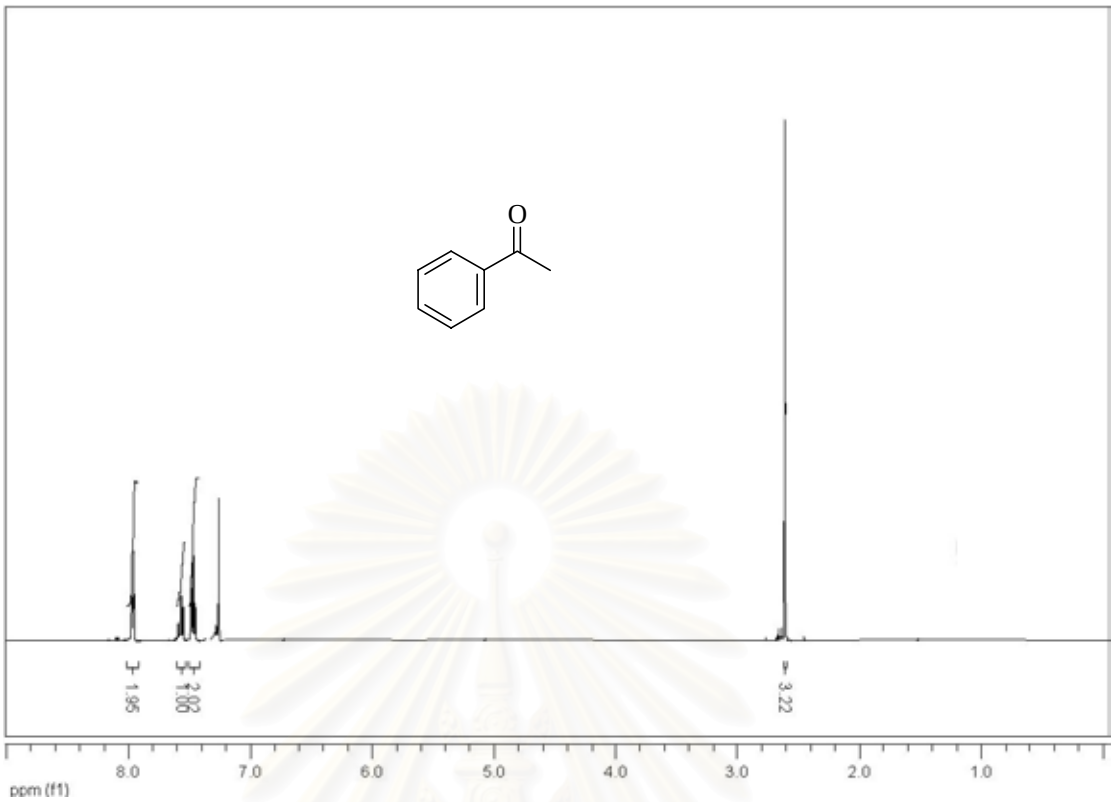


Figure 3.20 The ^{1}H-NMR spectrum of acetophenone (**20**)

The oxidation of **21** under the general procedure condition provided quantitative yield of **22**. The product **22** was purified by silica gel column chromatography, the structure of received product **22** was verified by ^{1}H-NMR spectrum (Fig 3.21). The proton on aromatic ring at *meta* position of carbonyl group was observed at δ_H 7.52 (t, J = 7.5 Hz, 2H). The proton on aromatic ring at *para* position of carbonyl group were discovered at δ_H 7.66 (t, J = 7.5 Hz, 4H) while the aromatic protons adjacent to a carbonyl group could be assigned at δ_H 7.98 (d, J = 7.3 Hz, 4H).

The oxidation of **23** afforded **24** in 50% isolated yield. This product was purified by silica gel column chromatography, the structure of the obtained product **24** was confirmed by ^{1}H-NMR spectrum. The ^{1}H-NMR spectrum (Fig 3.22) could be assigned for the triplet signal of the proton on aromatic ring at *meta* position of carbonyl group at δ_H 7.84 (J = 7.7 Hz, 2H). The protons on aromatic ring enfolded by carbonyl group showed at δ_H 8.33 (d, J = 8.1 Hz, 2H) and the protons on aromatic ring at *para* position of carbonyl group shown at δ_H 8.64 (d, J = 7.3 Hz, 2H).

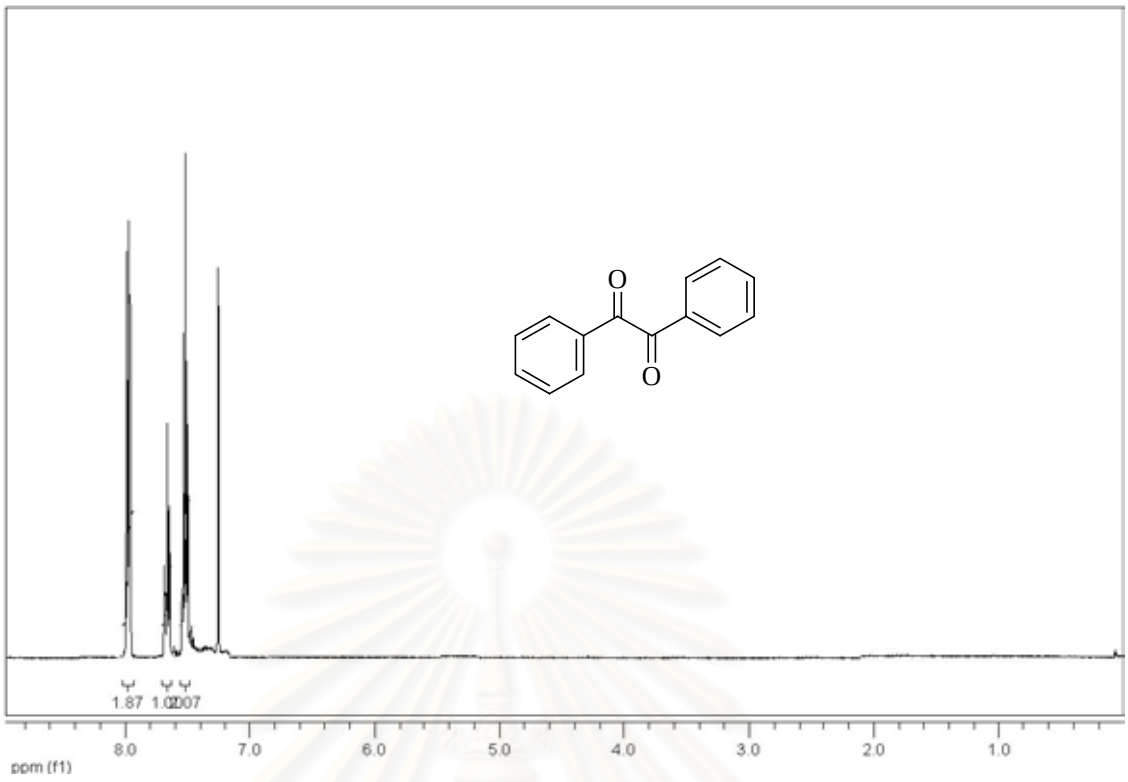


Figure 3.21 The ^{1}H-NMR spectrum of benzil (**22**)

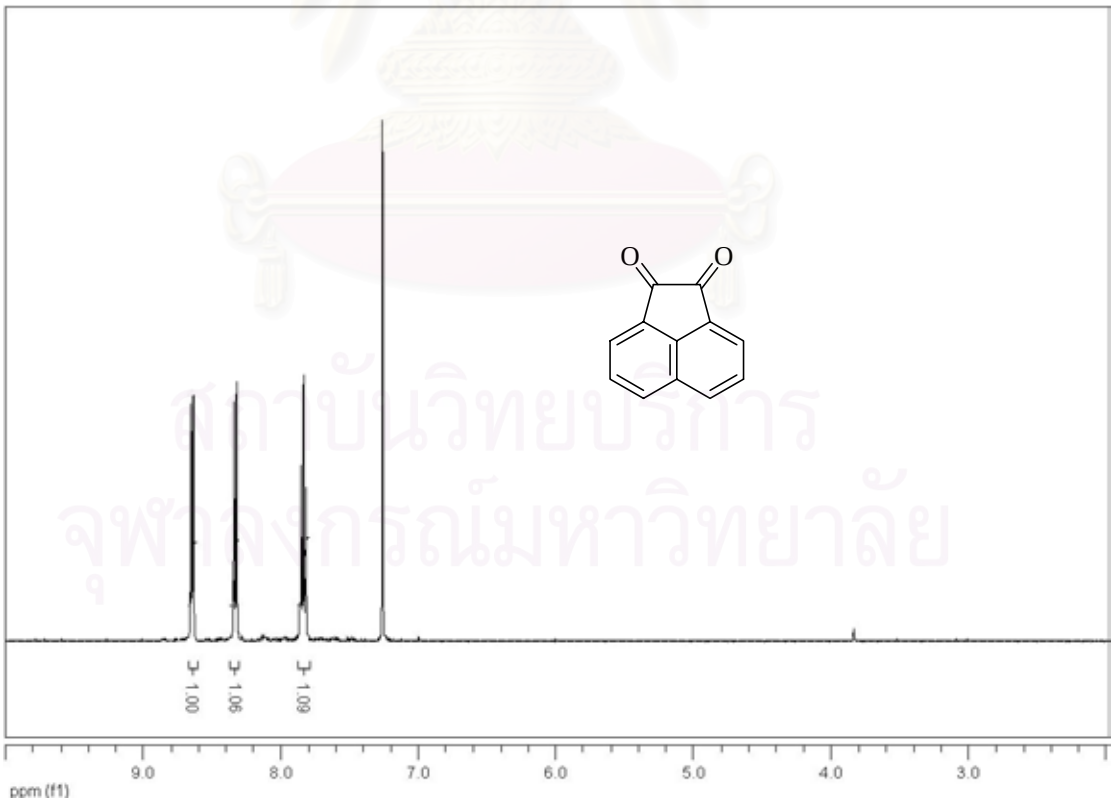


Figure 3.22 The ^{1}H-NMR spectrum of acenaphthenequinone (**24**)

Under the general procedure condition, **25** could be transformed smoothly to afford **26** in 95% isolated yield. After purifying by silica gel column chromatography, **26** was acheived. The ^{1}H-NMR spectrum (Fig 3.23) exhibited triplet signal of the protons at *meta* position of carbonyl group at δ_H 7.39 (J = 6.8 Hz, 2H). The protons adjacent to oxygen atom were detected at δ_H 7.50 (d, J = 8.4 Hz, 2H). The protons on aromatic at *para* position of carbonyl group were visualized at δ_H 7.73 (t, J = 8.8 Hz, 2H) while the protons on aromatic ring enfolded by carbonyl group revealed at δ_H 8.35 (d, J = 8.0 Hz, 2H).

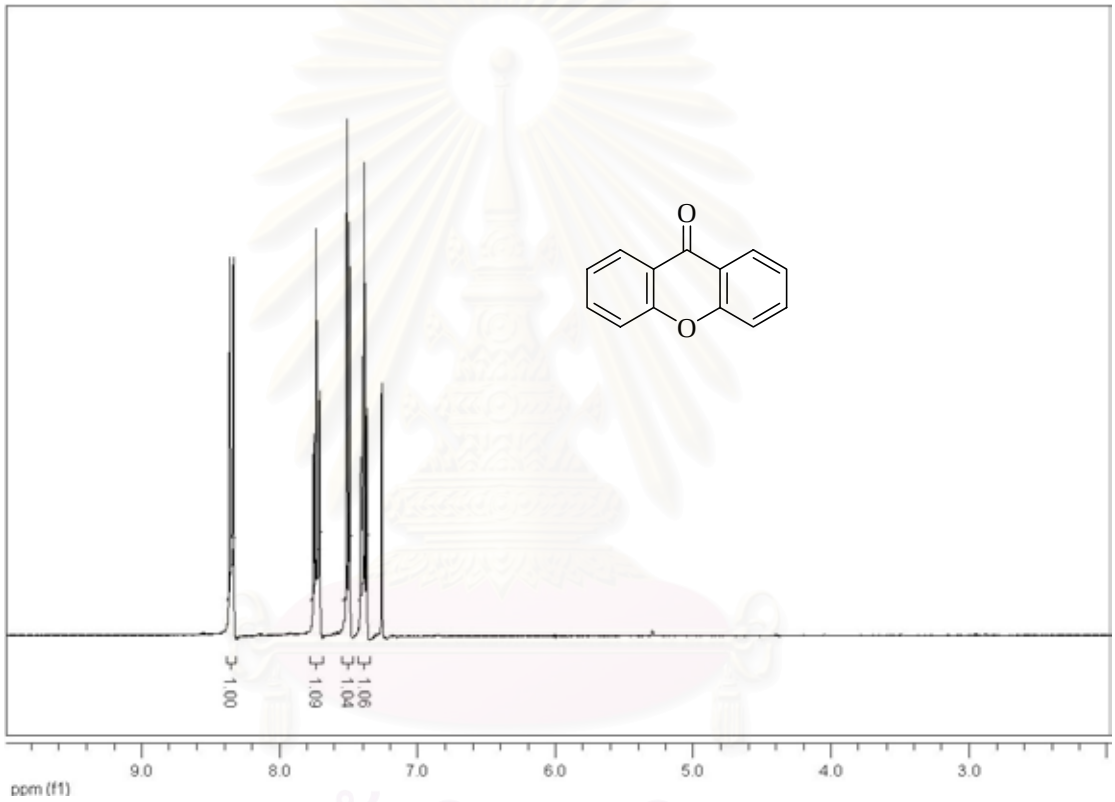


Figure 3.23 The ^{1}H-NMR spectrum of xanthone (**26**)

Compound **28** was obtained by the oxidation of **27** under standard condition. The compound **27** could be isolated by silica gel column chromatography in 74% isolated yield and the structure was characterized by ^{1}H-NMR spectrum. The ^{1}H-NMR spectrum (Fig 3.24) displayed a significant quintet signal of the protons at β-position of carbonyl group at δ_H 2.14 (J = 6.3 Hz, 2H). The triplet signal of γ-position was detected at δ_H 2.66 (J = 6.3 Hz, 2H). The α-protons adjacent to carbonyl group could be assigned at δ_H 2.97 (t, J = 6.0 Hz, 2H). The aromatic protons at *meta* position of carbonyl group were visualized around δ_H 7.24-7.33 (m, 2H). The *para* protons on

aromatic ring enfolded by carbonyl group revealed at δ_H 7.47 (t, *J* = 6.3 Hz, 1H) while the proton neighboring to a carbonyl group were visualized at δ_H 8.01 (d, *J* = 7.8 Hz, 1H).

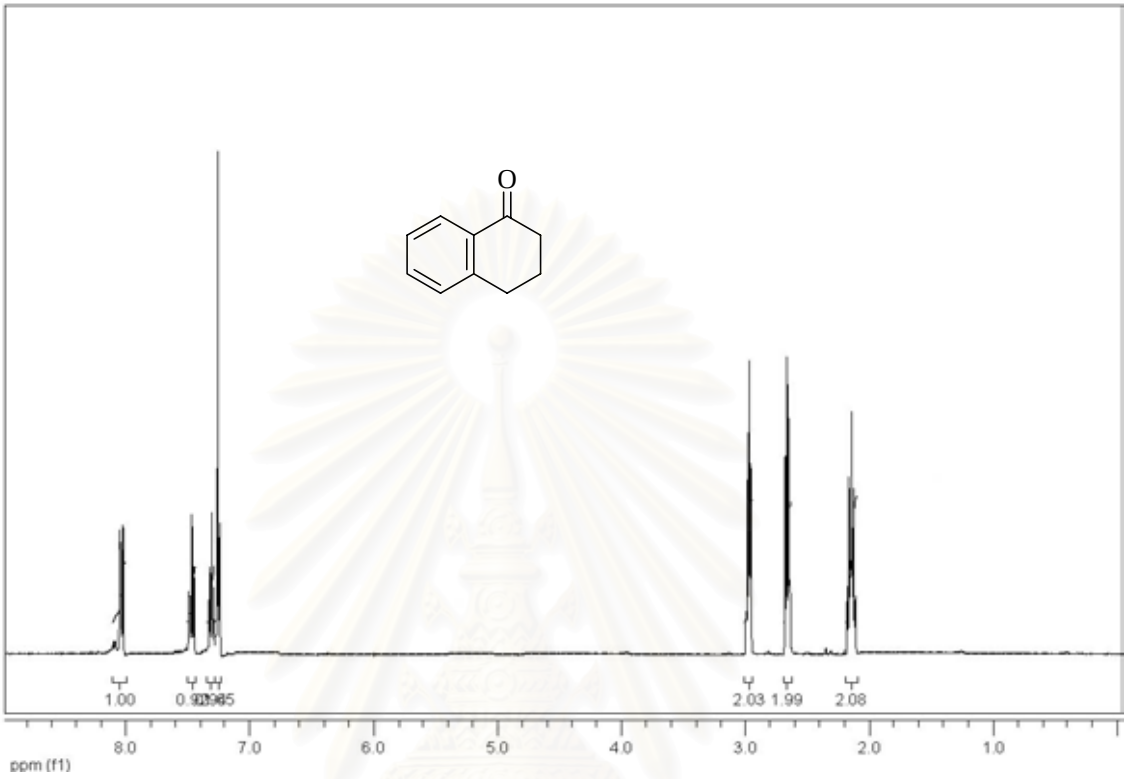


Figure 3.24 The ^{1}H-NMR spectrum of α-tetralone (**28**)

CHAPTER IV

CONCLUSION

During the course of this research, the development of the oxidation reaction for the synthesis of α-keto esters was focused. It was disclosed that $Ni(st)_2$ displayed as the best catalyst coupled with TBHP as an oxidant in isooctane as a reaction medium. The reaction could be also well proceeded using $Fe(TCA)_3$ and TBHP in pyridine. Various factors: type of ligands, oxidizing agent, solvent system, reaction time and reaction temperature have been affected to the yield of the oxidation product. The ligands containing electron withdrawing group and short carbon chain could improve the capability of metal for oxidation reaction of ethyl phenylacetate. The optimized conditions could be summarized as follows: the mixture of ethyl phenylacetate (5 mmol), TBHP (18 mmol) and catalyst (4 mol%, 0.20 mmol) was carried out in isooctane (5 mL) at 70°C for 48 h for utilization of $Ni(st)_2$ and the mixture of ethyl phenylacetate (5 mmol) as substrate, TBHP (13.5 mmol) as an oxidant, pyridine (5 mL) as the reaction medium and catalyst (3 mol%, 0.15 mmol) was stirred at 70°C for 24 h for utilization of $Fe(TCA)_3$. The application of these systems for the synthesis of other α-keto esters was carried out utilization $Fe(TCA)_3$. Various α-keto esters could be prepared in good yield. Especially, two natural products compounds, namely methyl (4-methoxybenzoyl)formate and butyl (4-methoxybenzoyl)formate were successfully prepared in satisfied yields.

Overture for the future work

This research concerned with the development for the synthesis of α-keto esters. The outcome opened many possibilities to deal with future exploration. The scale-up experiment utilizing of this oxidation system should be performed since this reaction selectively provided only α-keto esters product. The development of $Fe(TCA)_3$ for other catalyst systems are imperative to investigate. From the academic view point, bioactive compounds, pharmaceutically active compounds and certain chemicals containing chiral center are interesting to synthesize from α-keto esters.

REFERENCES

1. Hagen, J. *Industrial Catalysis*. Weinheim: Wiley-VCH GmbH, **1999**.
2. Sheldon, R. A.; Van Bekkum, H. *Fine Chemical through Heterogeneous Catalyst*. Weinheim: Wiley-VCH GmbH, **2001**.
3. Shakeel, Ur-R.; Patrick, F. F. Effect of Added α-Ketoglutaric acid, Pyruvic acid or Pyridoxal Phosphate on Proteolysis and Quality of Cheddar Cheese. *Food Chem*. **2002**, *76*, 21-26
4. Casey, M. G.; Bosset, J. O.; Bütikofer, U.; Fröhlich-Wyder, M-T. Effect of α-Keto Acids on the Development of Flavour in Swiss Gruyere-Type Cheese. *Lebensm.-Wiss. u.-Technol.* **2004**, *37*, 269-273.
5. Bart, A. S.; Wim, J. M. E.; Martin, A.; Gus, T. C. A. L.; Erwin, A. H. K.; Jan, T. M. W.; Gerrit, S. Chemicla Conversion of α-Keto Acids in Relation to Flavor Formation in Fermented Foods. *J. Agric. Food. Chem.* **2004**, *52*, 1263-1268.
6. Albert, H. O-Y.; James, L. B.; Mirza, B.; Robert, T. M.; Pyruvate-Enhanced Cardioprotection During Surgery with Cardiopulmomary Bypass. *J. Card. and Vas. Anes.* **2003**, *17*, 715-720.
7. Wada, N.; Matsuishi, T.; Nonaka, M.; Naito, E.; Yoshino, M. Pyruvate Dehydrogenase E1α Subunit Deficiency in a Female Patient: Evidence of Antenatal Origin of Brain Damage and Possible Etiology of Infantile Spasms. *Brain & Development* **2004**, *26*, 57-60.
8. Schulte, K.; Meinzinger, E. *Antisunburn Composition*. Ger. 949,521, 1956; *Chem. Abstr.* **1958**, *52*, 19024c.
9. Matthias, W.; Gabriele, M. K.; Anthony, D. W. New 4-Methoxybenzoyl Derivatives from the Ascidian *Polycaroa Aurata*. *J. Nat. Prod.* **2001**, *64*, 1556-1558.
10. George, A. K.; Alex, M. A Direct Route to Acylhydroquinone from α-Keto Acids and α-Carboxamido Acids. *Tetrahedron Lett.* **1998**, *39*, 3957-3960.
11. Marie-José, T.; Vincent, D.; Ivan, J.; Bernard, D. Reaction of Vinyl Triflates of α-Keto Esters with Primary Amines: Efficient Synthesis of Aziridine Carboxylates. *Tetrahedron* **2002**, *58*, 8425-8432.

12. Matthew, M. A.; Stephen, C. S.; Donald, R. J. Cyclic Ketones and Substituted α-Keto Acids as Alternative Substrates for Novel Biginelli-Like Scafold Syntheses. *Tetrahedron Lett.* **2003**, *44*, 4559-4562.
13. George, A. K.; Ning, Z. Hydrogen-Atom Abstraction/Cyclization in Synthesis. Direct Syntheses of Coumestan and Coumestrol. *J. Org. Chem.* **2000**, *65*, 5644-5646.
14. Bruno, T.; Brian, J. A Novel Approach to the Synthesis of 4-Aryl-furan-3-ols. *Tetrahedron Lett.* **2001**, *42*, 6429-6431.
15. Jeffrey, M. A.; Lori, K.; Hank, F. K.; Jeffrey, D. W. A Stereoselective Synthesis of *dl-threo*-Methylphenidate: Preparation and Biological Evaluation of Novel Analogues. *J. Org. Chem.* **1998**, *63*, 9628-9629.
16. Karsten, J.; Karl, A. J. Catalytic Asymmetric Direct α-Amination Reactions of 2-Keto Esters: A Simple Synthetic Approach to Optically Active *syn-β*-Amino-α-hydroxy Esters. *J. Am. Chem. Soc.* **2002**, *124*, 2420-2421.
17. Shizheng, Z.; Guifang, J.; Yong, X. A New Method for the Synthesis of *N*-Protected β-Amino-α-keto Esters from Fluoroalkanesulfonylazides and α-Keto Esters. *Tetrahedron* **2003**, *59*, 4389-4394.
18. Lee, J. M.; Lim, H. S.; Seo, K. C.; Chung, S. K. A Practical Diastereoselective Synthesis of β-Amino-α-hydroxy Carboxylates. *Tetrahedron Asymm.* **2003**, *14*, 3639-3641.
19. Senanayake, C. H.; Fang, K.; Grover, P.; Bakale, R. P.; Vandenbossche, C. P.; Wald, S. A. Rigid Aminoalcohol Backbone as a Highly Defined Chiral Template for the Preparation of Optically Active Tertiary α-Hydroxyl Acids. *Tetrahedron Lett.* **1999**, *40*, 819-822.
20. Berkowitz, B. B.; Schweizer, W. B. A New Retro-Aza-Ene Reaction: Formal Reductive Amination of an α-Keto Acid to an α-Amino Acid. *Tetrahedron* **1992**, *48*, 1715-1728.
21. Krix, G.; Bommarius, A. S.; Drauz, K.; Kottenhahn, M.; Schwarm, M.; Kula, M.-R. Enzymatric Reduction of α-Keto Acids Leading to L-Amino Acids, D- or L-Hydroxy Acids. *J. Biotech.* **1997**, **53**, 29-39.
22. Li, T.; Kootstra, A. B.; Fotheringham, I. G. Nonproteinogenic α-Amino Acid Preparation Using Equilibrium Shifted Transamination. *Organic Process Research & Development* **2002**, *6*, 533-538.

23. Guy, C.; Thomas, V. L.; Helen, L. Enantioselective Reduction of β,γ-Unsaturated α-Keto Acids Using *Bacillus Stearothermophilus* Lactase Dehydrogenase: A New Route to Functionalised Allylic Alcohols. *Tetrahedron Lett.* **1992**, *33*. 817-820.

24. Carpentier, J.-F.; Mortreux, A. Asymmetric Hydrogenation of α-Keto Acid Derivatives by Rhodium-{aminophosphine-phosphinite} Catalyst. *Tetrahedron Asymm.* **1997**, *8*, 1083-1099.

25. Xiaobin, Z.; Hanfan, L.; Manhong, L. Asymmetric Hydrogenation of α-Keto esters over Finely Dispersed Polymer-stabilized Platinum Clusters. *Tetrahedron Lett.* **1998**, *39*, 1941-1944.

26. Zhe, W.; Brittany, L.; Joseph, M. F. Enantioselective Synthesis of α-Hydroxy Carboxylic Acids: Direct Conversion of α-Oxocarboxylic acids to Enantiomerically Enriched α-Hydroxy Carboxylic Acids via Neighboring Group Control. *Tetrahedron Lett.* **1998**, *39*, 5501-5504.

27. LeBlond, C.; Wang, J.; Liu, J.; Andrews, A. T.; Sun, Y.-K. Highly Enantioselective Heterogeneously Catalyzed Hydrogenation of α-Keto esters under Mild Conditions. *J. Am. Chem. Soc.* **1999**, *121*, 4920-4921.

28. Fang, J.-M.; Chen, M.-Y.; Shiue, J.-S.; Lu, L.; Hsu, J.-L. Samarium Diiodide-mediated Asymmetric Reaction of 8-Phenylmethyl Esters. *Tetrahedron Lett.* **2000**, *41*, 4633-4636.

29. House, H. O.; Blaker, J. W.; Madden, D. A. The Rearrangement of Ethyl β-Phenylglycidate. *J. Am. Chem. Soc.* **1958**, *80*, 6386-6388.

30. Thasana, N.; Prochyawarakorn, V.; Tontoolarug, S.; Ruchirawat, S. Synthesis of Aryl α-Keto Esters via the Rearrangement of Aryl Cyanohydrin Carbonate Esters. *Tetrahedron Lett.* **2003**, *44*, 1019-1021.

31. Anatol, J.; Medete, A. Nouveau Precédé de Préparation des acides α-cétoniques. *Bull. Soc. Chem. Fr.* **1972**, 189-192.

32. James, M. P. Halide-Directed Nitrile Hydrolysis. *Tetrahedron Lett.*, **1980**, *21*, 3539-3540.

33. Jonathan, S. N.; Harry, S. M. A New Synthesis of α-Keto Esters and Acids. *J. Org. Chem.* **1981**, *46*, 211-213.

34. Francesco, B.; Vito, F.; Giuseppe, M.; Angela, P. A General and Straightforward Approach to α,ω-Ketoesters. *Tetrahedron* **1996**, *52*, 13513-13520.

35. David, I. M.; Tammy, C. M.; Marijanna, E. Asymmetric Synthesis of Chiral α-Keto Esters via Grignard Addition to Oxalates. *Tetrahedron Asymm.* **2003**, *14*, 3177-3181.

36. Bae Yu, H. K.; Schwartz, J. Tungsten Complex Induced Dehydration of 2,3-Dihydroxy-carboxylic Acids to α-Keto Acids. *Tetrahedron Lett.* **1992**, *33*, 6791-6794.

37. Wasserman, H. H.; Ives, J. L. Reaction of Singlet Oxygen with Enamino Carbonyl Systems. A General Method for the Synthesis of α-Keto Derivatives of Lactones, Esters, Amides, Lactams, and Ketones. *J. Org. Chem.* **1985**, *50*, 3573-3580.

38. Inoue, M.; Uragaki, T.; Kashiwagi, H.; Enomoto, S. The Oxidation of Methyl Acid Esters with H_2O_2 in the Presence of Chromium Catlysts. A Novel Route to pyruvic Acid Esters. *Chem. Lett.* **1989**, 99-100.

39. Tatlock, J. H. Oxidation of Alkynyl Ethers with Potassium Permanganate. A New Acyl Anion Equivalent for the Preparation of α-Keto Esters. *J. Org. Chem.* **1995**, *60*, 6221-6223.

40. Hon, Y.-S.; Lin, W.-C. An Efficient and Versatile Method for the Preparation of α-Keto Acid Derivatives from Terminal Alkenes. *Tetrahedron Lett.* **1995**, *36*, 7693-7696.

41. Matsunaka, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. A Remarkable Effect of Quaternary Bromide for the *N*-Hydroxyphthalimide-Catalyzed Aerobic Oxidation of Hydrocarbons. *Tetrahedron Lett.* **1999**, *40*,2165-2168.

42. Nikalje, M. D.; Ali, I. S.; Dewkar, G. K.; Sudalai, A. Synthesis of Aryl α-Keto-acids via the Cu-catalyzed Conversion of Aryl Nitroaldol Products. *Tetrahedron Lett.* **2000**, *41*, 959-961.

43. Wentzel, B. B.; Donners, M. P. J.; Alsters, P. L.; Feiters, M. C.; Nolte, R. J. M. *N*-Hydroxyphthalimide/Cobalt(II) Catalyzed Low Temperature Benzylic Oxidation Using Molecular Oxygen. *Tetrahedron* **2000**, *56*, 7797-7803.

44. Wong, M.-K.; Yu, C.-W.; Yuen, W.-H.; Yang, D. Synthesis of α-Keto Esters and Amindes via Oxidative Cleavage of Cyanoketophosphoranes by Dimethyldioxirane. *J. Org. Chem.* **2001**, *66*, 3606-3609.

45. Li, L.-S.; Wu, Y.-L. An Efficient Method for Synthesis of α-Keto Acid Esters from Terminal Alkynes. *Tetrahedron Lett.* **2002**, *43*, 2427-2430.

46. Velusamy, S.; Punniyamurthy, T. Copper(II)-catalyzed C-H Oxidation of Alkylbenzenes and Cyclohexane with Hydrogen Peroxide. *Tetrahedron Lett.* **2003**, *44*, *8955-8957*.

47. Lee, J. C.; Lee, J. Y.; Lee, S. J. Efficient Oxidation of Benzylic Alcohols with [Hydroxy(tosyloxy)iodo]benzene under Microwave Irradiation. *Tetrahedron Lett.* **2004**, *45*, 4939-4941.

48. Ma, M.; Li, C.; Peng, L.; Xie, F.; Zhang, X.; Wang, J. An Efficient Synthesis of Aryl α-Keto Esters. *Tetrahedron Lett.* **2005**, *46*, 3927-3929.

49. Jetipattaranat, W. *Epoxides Ring Opening Reaction Utilizing Transition Metal Catalysts.* Master's Thesis, Program of Petrochemistry and Polymer Science, Faculty of Science, Chulalongkorn University, **2003**.

50. Iranpoor, N.; Adibi, H. Iron(III) Trifluoroacetate as an Efficient Catalyst for Solvolytic and Nonsolvolytic Nucleophilic Ring Opening of Epoxides. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 675-680.

51. Kirk-Othmer *Encyclopedia of Chemical Technology*, 2nd ed., **1968**, 473.

52. Jarupinthusophon, S. *Catalitic Oxidation Cleavage of Terminal Olefins by Metal Stearate Complexes.* Master's Thesis, Program of Petrochemistry and Polymer Science, Faculty of Science, Chulalongkorn University, **2004**.

53. Silverstein, R. M. and Francis, X. *Spectrometric Identification of Organic Compounds*. 6th ed., Canada: John Wiley & Sons, **1998**, 71

54. Barton, D. H. R.; Beviere, S. D.; Hill, D. R. The Functionalization of Saturated Hydrocarbon Part XXIX. Application of *tert*-Butyl Hydroperoxide and Dioxygen using Soluble Fe(III) and Cu(II) Chelates. *Tetrahedron* **1994**, *50*, 2665.

55. Pine, S. H. *Organic chemistry*. 5th ed., Singapore: Mc Graw Hill, **1987**, 638.

56. Muzart, J. Chromium-catalyzed oxidation in organic synthesis. *Chem. Rev.* **1992,** *92*, 113-140.

VITA

Mr. Adisak Chaitanee was born on October 7, 1980 in Mahasarakham, Thailand. He graduated with Bachelor's Degree in Chemistry from Faculty of Science, Mahidol University in 2003. Since 2003, he has been a graduate student studying in the Program of Petrochemistry and Polymer Science, Faculty of Science, Chulalongkorn University. He was supported by research grant for this Master Degree's thesis from the Graduate School, Chulalongkorn University.

His present address is 111, Nhongsang, Wapeepathum, Mahasarakham, Thailand 44120.