แอลลิลิกออกซิเดชันของแอลคีนเร่งปฏิกิริยาด้วยสารประกอบเชิงซ้อนโลหะสเทียเรต

นางสาวภัทรพร อยู่ตรีรักษ์

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

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ลิขสิทธิ์ของจุฬาลงกรณ์มหาวิทยาลัย

ALLYLIC OXIDATION OF ALKENES CATALYZED BY METAL STEARATE COMPLEXES

Miss Pataraporn Eutrirak

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

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ภัทรพร อยู่ตรีรักษ์ : แอลลิลิกออกซิเดชันของแอลคีนเร่งปฏิกิริยาด้วยสารประกอบเชิงซ้อนโลหะสเทียเรต (ALLYLIC OXIDATION OF ALKENES CATALYZED BY METAL STEARATE COMPLEXES) อ. ที่ปรึกษา: ผศ. ดร.วรินทร ชวศิริ, 52 หน้า. ISBN 974-14-3354-9.

งานวิจัยนี้มุ่งเน้นที่จะพัฒนาระบบเร่งปฏิกิริยาโดยใช้โลหะสเทียเรตสำหรับแอลลิลิกออกซิเดชัน เมื่อใช้ไซโคลเฮกซีนเป็นสารต้นแบบ พบว่าทั้งตัวเร่งปฏิกิริยาและปริมาณ TBHP มีความจำเป็นต่อการเกิดปฏิกิริยา เมื่อใช้โครเมียมสเทียเรตร่วมกับสารออกซิแดนท์ TBHP ที่อุณหภูมิ 70°C เป็นเวลา 24 ชั่วโมง ให้สารประกอบคาร์บอนิลไม่อิ่มตัวที่ตำแหน่งแอลฟา-บีทาในปริมาณสูง และมีความเลือกจำเพาะที่ดี นอกจากนี้แอลลิลิกออกซิเดชันสามารถเกิดได้ดีในตัวทำละลายไม่มีขั้วแอโปรติก เช่น ไอโซออกเทน ทอลูอีน เบนซีน แอซีโทไนทริลและไพริดีน ภายใต้ภาวะที่เหมาะสม แอลคีนถูกออกซิไดซ์เป็นคีโทนไม่อิ่มตัวที่ตำแหน่งแอลฟา-บีทาในปริมาณที่ดีถึงดีเยี่ยมอย่างเลือกจำเพาะ นอกจากนี้แอลลิลิกออกซิเดชันของแอลฟา-ไพนีน 1-เมทิลไซโคลเฮกซีน แอลฟา-ไอโอโนน บีทา-ไอโอโนนและไอโซฟอโรนสามารถเกิดเป็นสารประกอบคาร์บอนิลไม่อิ่มตัวที่ตำแหน่งแอลฟา-บีทาอย่างเลือกจำเพาะในปริมาณปานกลางถึงสูง ระบบแอลลิลิกออกซิเดชันที่พัฒนาขึ้นเชื่อว่าเกิดผ่านกระบวนการฟรีแรดิคัล

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

สาขาวิชา…ปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์...ลายมือชื่อนิสิต.....
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PATARAPORN EUTRIRAK: ALLYLIC OXIDATION OF ALKENES CATALYZED BY METAL STEARATE COMPLEXES. THESIS ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., 52 pp. ISBN: 974-14-3354-9.

This research focuses on the development of a catalytic system using metal stearate for allylic oxidation. Cyclohexene was employed as a model substrate. Both types of catalyst and amount of TBHP are essential in promoting the reaction. With the use of TBHP as an oxidant in combination with chromium(III) stearate catalyst at 70°C for 24 hours afforded an α,β-unsaturated carbonyl compound in high yield with good selectivity. Moreover, the allylic oxidation worked well in non-polar aprotic solvent, such as isooctane, toluene, benzene, acetonitrile and pyridine. Under optimized conditions, alkenes were oxidized to the corresponding α,β-unsaturated ketone in good to excellent yield. Moreover, the allylic oxidation of α-pinene, 1-methylcyclohexene, α-ionone, β-ionone and isophorone could be fruitfully accomplished in moderate to high yield with excellent selectivity to the corresponding α,β-unsaturated carbonyl compounds. This developed allylic oxidation reaction was believed to undergo *via* a free radical process.

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จุฬาลงกรณ์มหาวิทยาลัย

Field of study Petrochemistry and Polymer Science Student's signature……..…….....…...
Academic year……..…2005…… Advisor's signature…...….....….....…

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LIST OF ABBREVIATIONS

b.p.	boiling point
b	broad (IR)
δ	chemical shift
$Cr(acac)_3$	chromium(III) acetylacetonate
J	coupling constant
°C	degree celsius
$CDCl_3$	deuterated chloroform
d	doublet (NMR)
dd	doublets of doublet (NMR)
EA	elemental analysis
GC	gas chromatography
g	gram (s)
Hz	hertz (NMR)
h	hour (s)
^{1}H-NMR	proton nuclear magnetic resonance
IR	infrared
MB	mass balance
m.p.	melting point
mL	milliliter (s)
mmol	millimole
m	multiplet (NMR)
ppm	part per million
%yield	percentage yield
%wt	percent by weight
Q	quartet (NMR)
R_f	retarding factor in chromatography
s	singlet (NMR)
s	strong (IR)

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LIST OF ABBREVIATIONS

TBHP	*tert*-butyl hydroperoxide
TLC	thin layer chromatography
t	triplet (NMR)
T.O.N.	turn over number
cm^{-1}	unit of wave number
w	weak (IR)

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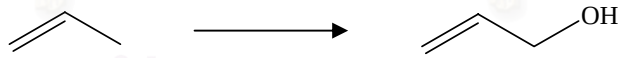
CHAPTER I

INTRODUCTION

The oxidation of alkenes and cycloalkenes may affect the double bonds, the rest of the molecule, or both in allylic positions. This also includes aromatic hydrocarbons containing double bonds in their side chains. Compounds containing double bonds and other functional groups, such as hydroxyl, carbonyl or carboxyl will be oxidized to give unsaturated alcohols, aldehydes, ketones, acids and esters [1].

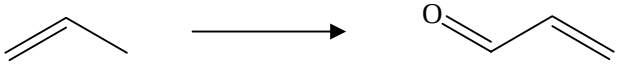
Allylic oxidation remains a reaction of considerable value in organic synthesis. This type of oxidation reaction can be divided into two types: reactions which produce allylic alcohols (eq 1.1) and those which directly produce α,β-unsaturated aldehydes or ketones (eq 1.2). Examples from the recent literature fall approximately equally into each type. Allylic oxidations can also take place with rearrangement (eqs 1.3 and 1.4). However, many reagents and reaction conditions can give either direct oxidation or oxidative rearrangement, and almost no allylic oxidation system exclusively gives one course of reaction in all cases. In many examples the course of oxidation depends mostly upon substrate structure.



(1.1)

(1.2)

(1.3)



(1.4)

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For most reagents, this pattern is multiplied in cases where several similar possible sites of oxidation exist around a particular double bond. While chemoselectivity and stereoselectivity are often good, poor regioselectivity is a weakness afflecting many allylic oxidation methods.

Among oxidations producing allylic alcohols or their derivatives, the modern variants of selenium dioxide oxidations are by far the most popular. Systems based on metal acetates, particularly palladium trifluoroacetate, can be very useful and are receiving increasing attention; however Kharasch-Sosnovsky reaction, once very common for allylic oxidation, is now rarely used. Sensitized photooxidation with singlet oxygen, a very well-known procedure, is still somewhat unpredictable and has perhaps received less consideration than it deserves.

Fewer methods exist for direct allylic/benzylic oxidation to give α,β-unsaturated carbonyl compounds. Some of these occur by initial oxidation to allylic alcohol, followed by a second oxidation or oxidative rearrangement step, and reagent systems often give mixtures of alcoholic and carbonyl products. The most valuable method for direct oxidation to enones involve chromium(VI), palladium or selenium reagents.

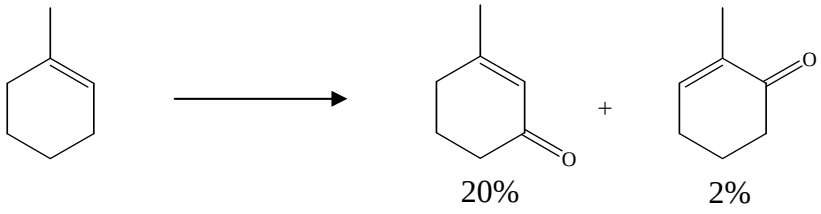
1.1 Allylic oxidation reactions producing α,β-unsaturated carbonyl compounds

Chromium(VI)-based Reagents

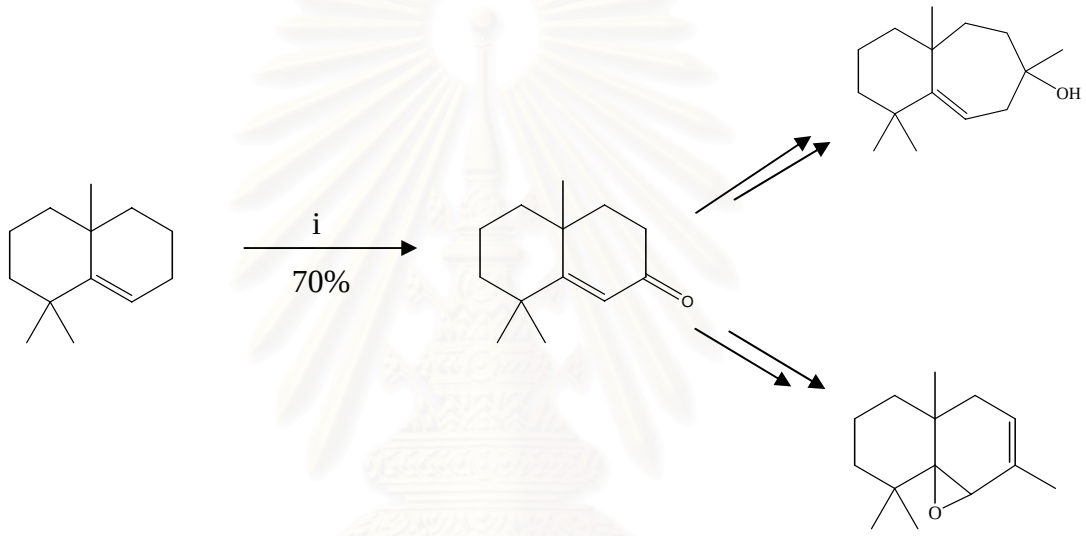
1.1.1 Chromic acid and simple chromate ester

Examples of the use of chromium(VI) reagents to promote the allylic oxidation of alkene to give α,β-unsaturated carbonyl compounds are common in literature [2,3]. The reaction was first reported by Teib and Schmidt [4] for the allylic oxidation of α-pinene to verbenone and verbenol, of dipentene to carvone and carveol, and of cyclohexene to cyclohexenol and cyclohexenone, using a solution of chromium trioxide in a mixture of acetic anhydride and carbon tetrachloride. However, yields were low and no synthetic use of this observation was made.

Chromic acid itself has been used in the oxidation of alkenes and in some cases allylic oxidation products were observed; for example, cyclohexene was converted to cyclohexenone in 37% yield and 1-methylcyclohexene was oxidized to a mixture of enones [5].

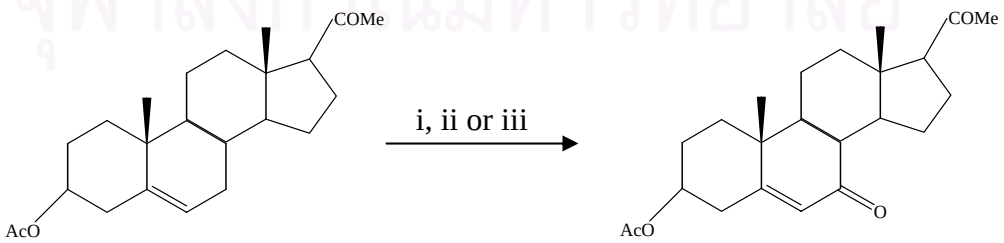


Extension of this type of reagent [6] was the use of sodium dichromate in acetic acid [7] to furnish the allylic oxidation of 4,4,10-trimethyl-Δ^5-octalin into 7-keto-4,4,10-trimethyl- Δ^5-octalin [8] in 65% yield. This reaction was employed in the total syntheses of (±)-widdrol and of (±)-thujopsene [9].



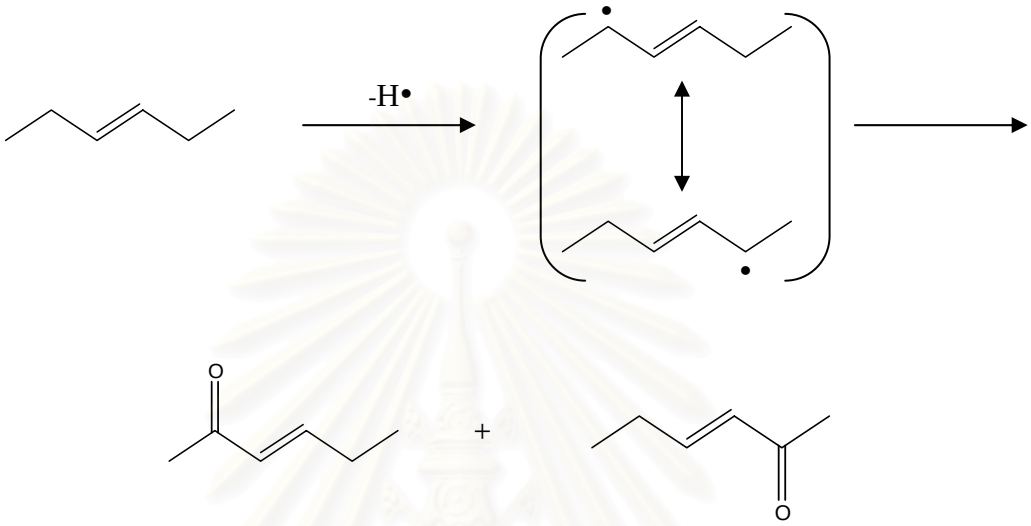
i, 1.4 equiv. $Na_2Cr_2O_7$, acetic acid, r.t./overnight, then 100ºC/2.5 h

Allylic oxidation of steroids, particularly at the 7–position, has evoked interest over many years. For example, chromium trioxide-acetic acid [10], sodium dichromate [11], and *t*-butyl chromate [12-15] have all been used in the oxidation of the 5-α-pregnane series.



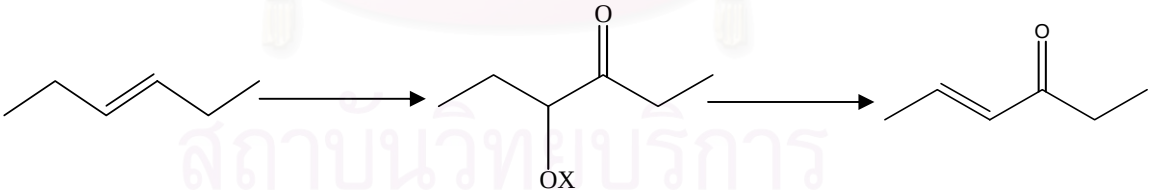
i, CrO_3,AcOH; 50%; ii, $Na_2Cr_2O_7$, AcOH, Ac_2O; 79%; iii, $(Bu^tO)_2CrO_2$; 62%

The overall mechanism of chromium(VI) allylic oxidation appears to consist of removal of a hydrogen atom or hydride ion from alkene, forming a resonance-stabilized allylic radical or carbocation, which is ultimately converted into the unsaturated ketone (Scheme 1.1) [16].



Scheme 1.1 The mechanism for allylic oxidation of alkene catalyzed by Cr(VI)

An alternative mechanism has also been proposed in which oxidation at the double bond leads to a ketol derivative, elimination of water from which then gives the unsaturated ketone (Scheme 1.2) [3].

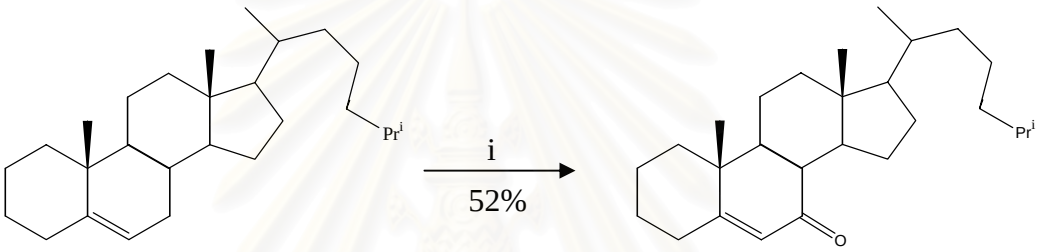


Scheme 1.2 The oxidation of alkene to ketol, elimination of water to unsaturated ketone by chromic acid [17]

The discovery of chromium trioxide-pyridine complex led to the accessibility of allylic oxidation under much less harsh conditions, typically room temperature reaction in dichloromethane solution [18,19] for a number of days, rather than high temperature conditions for extended periods. Dauben [20] proposed that the products of allylic oxidation using this reagent (according to Scheme 1.1) would be governed by a large number of factors, for example the steric accessibility of the allylic

hydrogen atom towards abstraction, the relative stabilities of possible allylic intermediate, and the stereoelectronic control of the oxygen transfer step at competing sites.

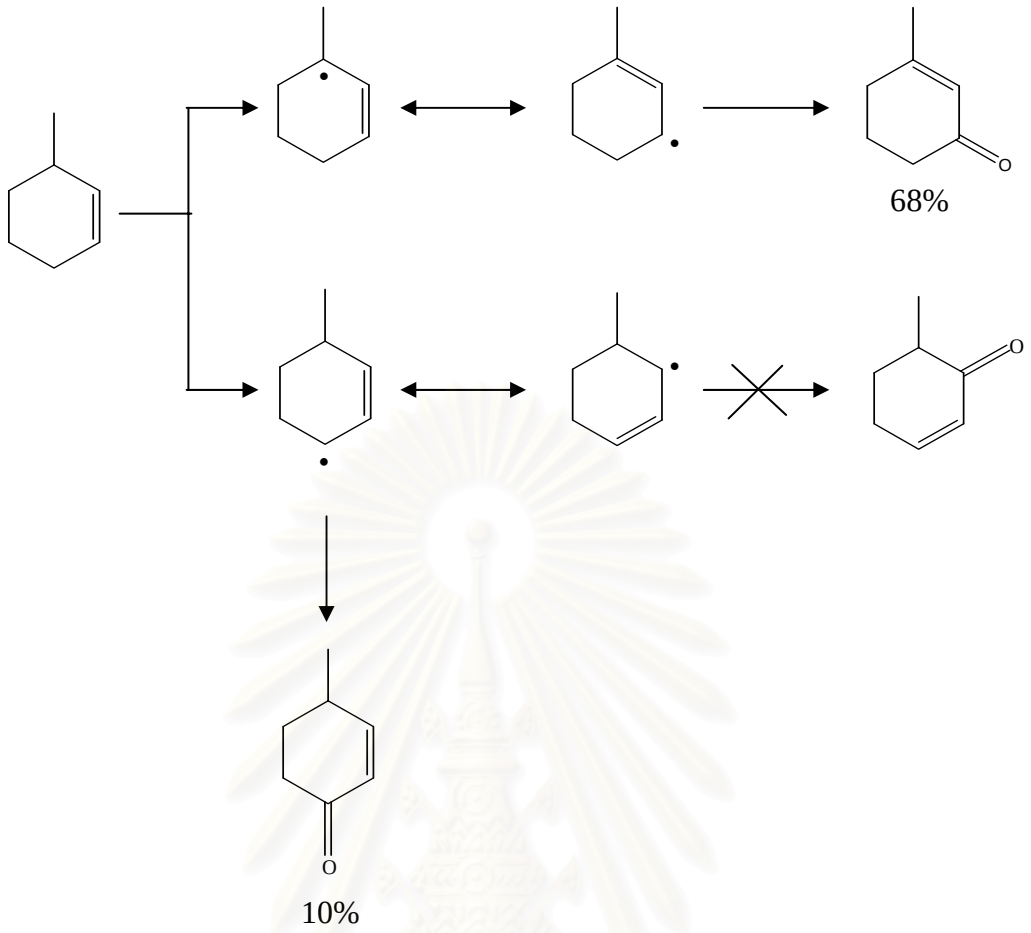
Allylic oxidation in steroid systems provides a good illustration of the factors controlling the reaction pathway. In the oxidation of cholest-5-ene, which has a rigid structure with two allylic hydrogen atoms at C-4 and C-7, assuming axial preference of hydrogen atoms for abstraction [21], an incoming chromium species should encounter steric hindrance from the methyl group above the plane and a less crowded approach from beneath. Indeed, allylic oxidation proceeds to yield only cholest-5-en-7-one in 52% yield.



i, 20 equiv. CrO_3•2Py, CH_2Cl_2, r.t./24 h

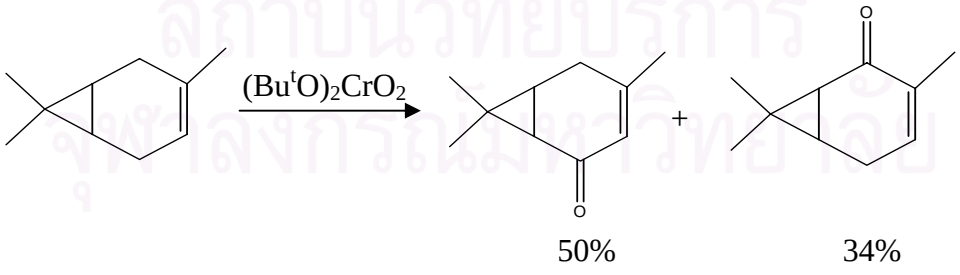
Dauben postulated that there was a preference for the abstraction of a tertiary allylic hydrogen atom which was stemmed from the relative stability of the intermediate radical (or ionic) species rather than relative C-H bond strengths (Scheme 1.3).

From an extensive survey of this reagent system, the following guidelines have been proposed: (i) allylic methyl groups are not readily oxidized; (ii) if more than one allylic methylene group is present in a conformationally flexible molecule, enones resuting from attacking at all positions are formed, while if the molecule is conformationally rigid, as in a steroid, selectivity is observed; and (iii) attack at an allylic methylene systems possessing steric hindrance towards hydrogen atom abstraction.

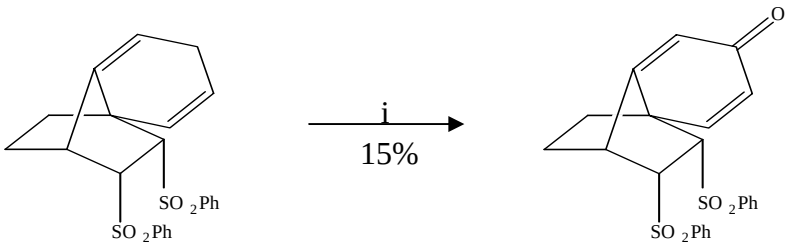


Scheme 1.3 The allylic oxidation of 3-methylcyclohexene

Allylic oxidation employing chromium(VI) reagents appears to be very much dependent upon the intrinsic nature of the substrate as to their regiochemical outcome. This is exemplified by the *t*-butyl chromate allylic oxidation of (+)-3-carene [21] where no great preference for either product exists.



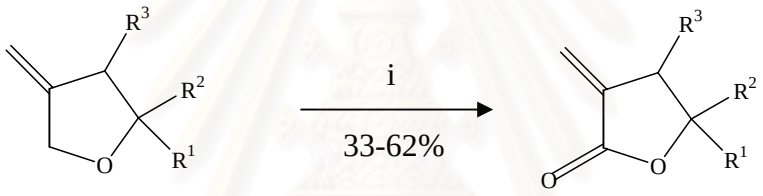
An attempted allylic oxidation of (**A**) was found by Paquette [22] to be difficult to achieve using a range of reagents due to problems with polymerization and rearrangement. The chromium trioxide-pyridine complex was the only reagent combination found to be successful, albeit in low yield.



(A)

i, 20 equiv. CrO_3•2Py, 25°C/24h

The chromium trioxide-pyridine complex was also found to be the reagent of choice in a synthesis of α–methylene-γ-butyrolactones (eq 1.5) [23]. This method was found to be superior to others tested, including selenium dioxide, chromium trioxide-acetic acid, and *t*-butyl chromate.



(1.5)

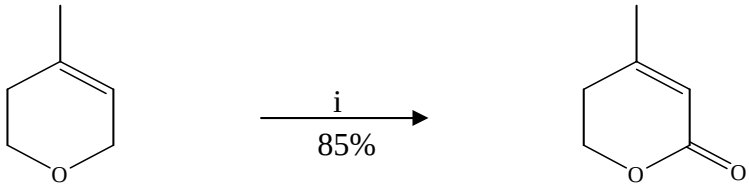
R^1, R^2 = H, Ph or alkyl
R^3 = H or alkyl

i, 20 equiv. CrO_3•2Py, CH_2Cl_2, reflux, 1 h

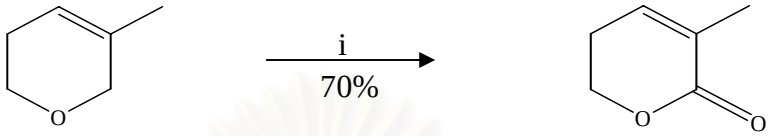
1.1.2 Pyridinium chlorochromate and dichromate

An alternative to chromium trioxide-pyridine complex is provided by pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC) [24]. These reagents, now ubiquitous for chromate-based oxidation of alcohols, overcome the hygroscopic nature of the chromium trioxide-pyridine complex [25] and are prepared by a less hazardous procedure [26]; both are commercially available as are several other derivative reagents.

PCC has been shown to be of particular value in the allylic oxidation of compounds containing an activated methylene group, such as 5,6-dihydropyrans [27].

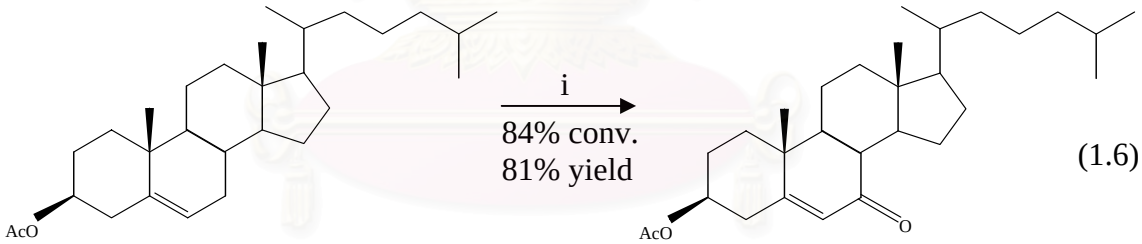


i, 1 equiv. PCC, 60-70°C/9 h



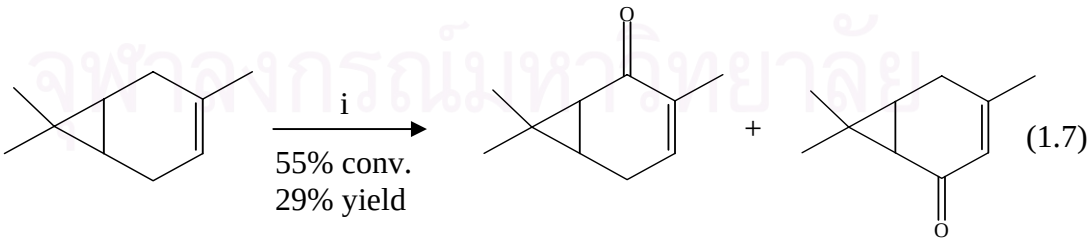
i, 1 equiv. PCC, 60-70°C/12 h

One drawback associated with this type of chromium species is the frequent requirement for a large excess of reagent. Recent attempts to combat this problem have involved the use of a PCC-celite mixture in benzene under reflux [28] and more successfully a TBHP-PDC mixture (eq 1.6) [29]. While this latter modification appears to be efficient and highly regioselective for steroidal substrates containing a rigid structure and provides a sterically crowded environment for the reacting double bond, the method can be rather poor in less hindered situations (*e.g.* eq 1.7) [29].



(1.6)

i, 4 equiv. PDC , Bu^{t}OOH, celite, anh. benzene, r.t.

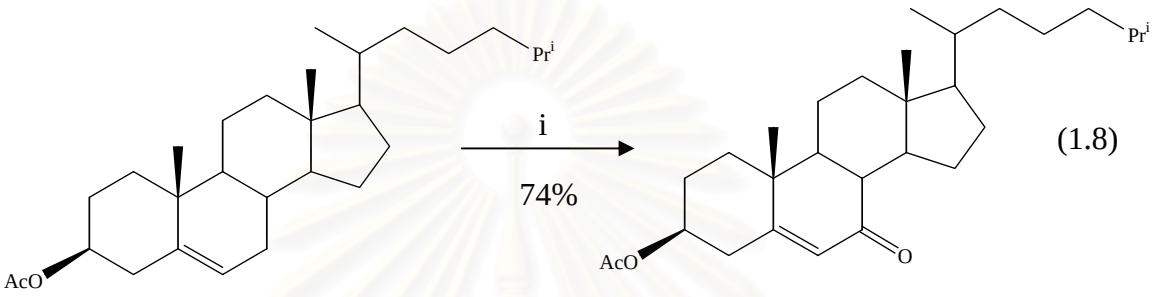


(1.7)

i, 2 equiv. PDC, Bu^{t}OOH, celite, anh. benzene, r.t.

1.1.3 Chromium trioxide-3,5-dimethylpyrazole

With the advent of the chromium trioxide-3,5-dimethylpyrazole complex as an oxidant [30,31], allylic oxidation has become far more valuable as a synthetic transformation. The reagent was applied by Salamond [17] to the allylic oxidation of cholesteryl benzoate to give the corresponding Δ^5-7-ketone (equation 1.8). However, a 20 molar excess of reagent was still required to affect the reaction in less than 30 min at room temperature.



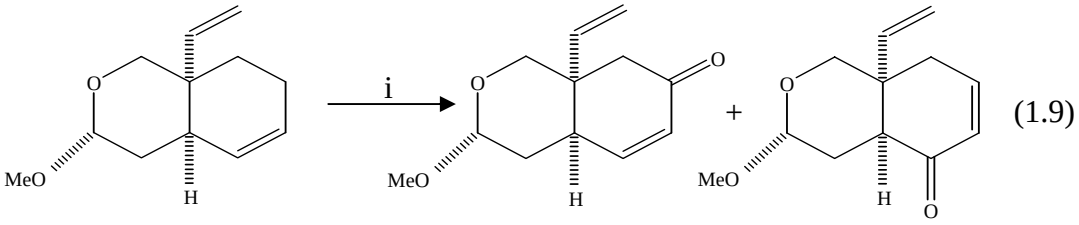
(1.8)

i, 12 equiv. CrO_3•3,5-DMP, CH_2Cl_2, -15°C, 4 h

The observed rate enhancement for this reagent over other chromium(VI) species has been rationalized as an effect of increased reagent solubility and by invoking the potential for acceleration by intramolecular participation by the pyrazole nucleus.

From a practical viewpoint, the reagent is simple to make and use. It is prepared *in situ* at low temperature (*ca*. 20-25 ˚C), requiring about 15 min to form prior to the addition of substrate. It is important to note that chromium trioxide should be thoroughly dried over phosphorus pentoxide before use.

Some fine examples of the synthetic use of this reagent are available in the literature [32]; for example in a total synthesis of vernolepin [33], intermediate (B), containing a fairly sensitive lactol ether unit, was selectively prepared by the use of chromium trioxide-dimethylpyrazole with formation of only 5% of the allylically rearranged product (eq 1.9).

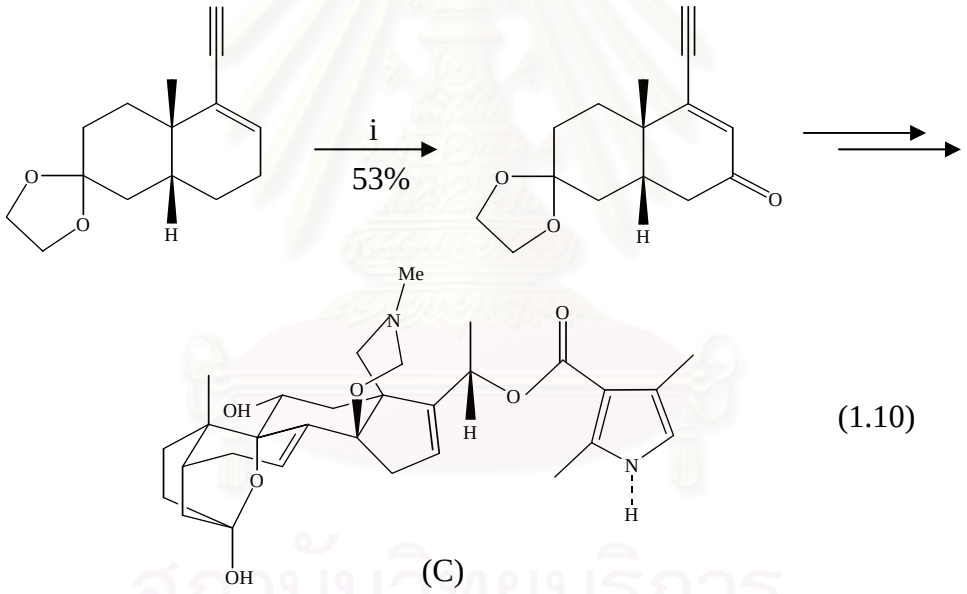


(1.9)

(B) 48% 5%

i, 20 equiv CrO_3•3,5-DMP, CH_2Cl_2, -20˚C/1 h then 0˚C/4 h

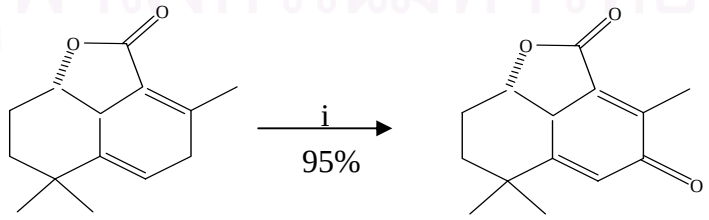
The reagent has been used by Magnus [34] in studies directed towards a synthesis of bachrachotoxin (C). A *cis*-decalin was oxidized selectively at the 7-position without the acetal or triple bond moieties present being affected (eq 1.10). The reagent has also found to use in an approach to forskolin [35]; cyclohexadienone (D) was prepared by exclusive oxidation at the 7-position of E (eq 1.11).



(1.10)

(C)

i, 30 equiv. CrO_3•3,5-DMP, CH_2Cl_2, r.t.

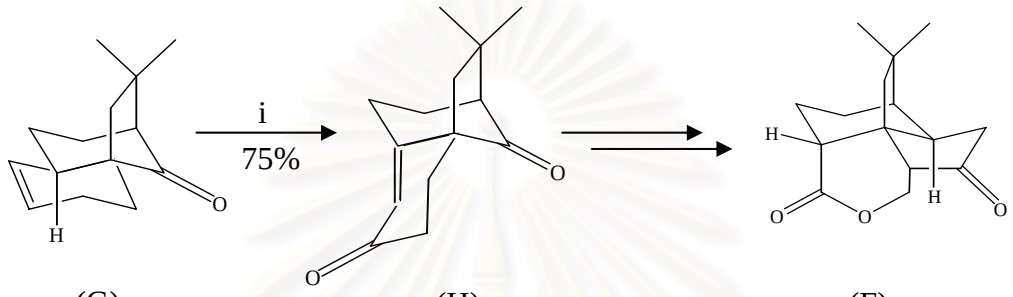


(1.11)

(E) (D)

i, 30 equiv. CrO_3•3,5-DMP, CH_2Cl_2, r.t.

An interesting example of the incorporation of this oxidation into a synthetic strategy can be seen in a route to quadrone (F) based on an intramolecular Diels-Alder reaction [36]. In this scheme highly selective allylic oxidative rearrangement of a *trans*-decalin (G) occurs to give a product (H) containing the double bond at a ring fusion position, allowing subsequent conversion to the desired *cis*-decalin system (Scheme 1.4). Neither of the other two possible ketonic oxidation products were observed.



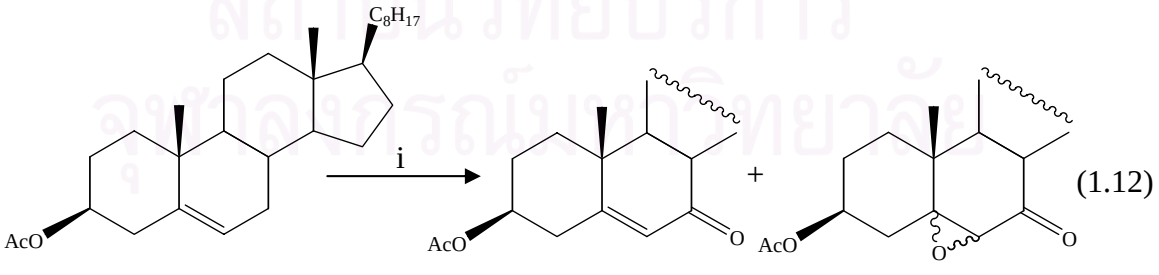
(G) (H) (F)

i, CrO_3•3,5-DMP, CH_2Cl_2

Scheme 1.4 Highly selective allylic oxidative rearrangement of a *trans*-decalin to the *cis*-decalin system

1.1.4 Other chromium-based reagents

A number of other chromium-based reagents have been developed for allylic oxidation; for example that of steroids by TBHP in the presence of a catalytic amount (0.05-0.50 mol equiv) of chromium trioxide [37] in dichloromethane at room temperature (eq 1.12). Yields vary from 32 to 69%. This modification is useful in terms of cost, operational simplicity and yields.

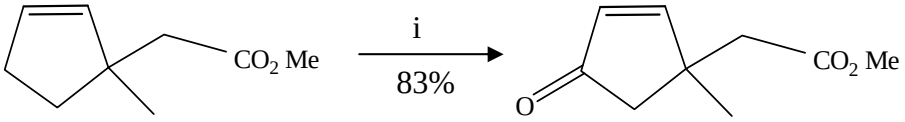


(1.12)

44% <2%

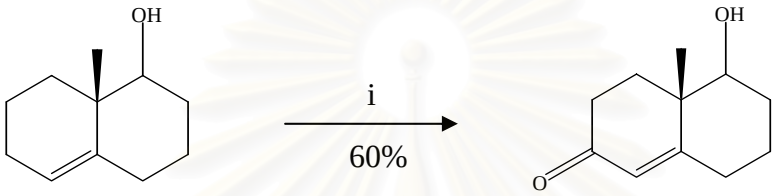
i, 0.4 equiv. CrO_3, TBHP, CH_2Cl_2, 5.5 h/r.t.

A chromium hexacarbonyl-TBHP system has also been developed with the remarkably chemoselective ability to affect allylic oxidation even in the presence of some secondary alcohols (eqs 1.13 and 1.14) [38-40].



(1.13)

i, 0.5 equiv. $Cr(CO)_6$, 1.2 equiv TBHP, MeCN, reflux/18 h



(1.14)

i, 0.25 equiv. $Cr(CO)_6$, 1.2 equiv. Bu^tOOH, MeCN, reflux/30 h

According to the literature review, the allylic oxidation of alkenes can lead to the formation of carbonyl compounds as ketone, aldehyde, alcohol, epoxide and carboxylic acid by using transition metal complex catalyst coupled with TBHP as an oxidant. However, there was no report involving the use of metal stearate complex catalyst. This present work focuses on the development of a catalytic system by using metal stearate complex catalysts which possess the adventage of being soluble in substrate or hydrocarbon solvent. Moreover, metal stearate complexes are inexpensive and easy to prepare. Catalytic efficiency of these complexes could be screened by using the allylic oxidation of cyclohexene as a model reaction.

1.2 The goal of this research

The aim of this research can be summarized as follows:

1. To synthesize transition metal sterate complexes
2. To study and develop the catalytic system for allylic oxdation of alkenes using metal stearate complex catalyst under optimized reaction conditions
3. To apply the optimized conditions for allylic oxidation of various selected alkenes

CHAPTER II

EXPERIMENTAL

2.1 General procedure

The reactants and products could be identified by different spectroscopic techniques. Melting points (m.p.) were determined with a Fisher-Johns melting point apparatus and are uncorrected. The FT-IR spectra were recorded on a Nicolet Impact 410 FT-IR spectrometer. Solid samples were incorporated with KBr to form pellet. As for liquid samples, a drop of the liquid was squeezed between flat plates of NaCl (transparent through the 625-4000 cm^{-1} region). Gas chromatographic analysis was carried out on a Shimadzu 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 of DB-WAX (30 m x 0.250 mm) from J & W Scientific company. 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)). The ^{1}H and ^{13}C-NMR spectra were obtained in deuterated chloroform ($CDCl_3$) or otherwise stated.

2.2 Chemical reagents

All solvents used in this research were purified prior to use by standard methodology except for those which were reagent grade. The reagents used for synthesizing metal stearate complexes and all organic substrates, *e.g.* cyclohexene, α-pinene, isophorone, methylcyclohexene *etc,* were purchased from Fluka chemical company and were used without further purification.

2.3 Syntheses of metal stearate complexes

General procedure for the syntheses of metal stearate complexes [41]

Stearic acid (22 mmol) was dissolved in 1 M NaOH solution at 80^{o}C. After the mixture was heated and transmuted homogeneously, a solution of metal chloride (7.3 mmol) dissolved in distilled water 10 mL was added dropwise. The mixture was continued heating at about 80 ^{o}C for about 30 min, the precipitate was collected and dried *in vacuo*.

Cr(III) stearate: blue gray solid (86%), m.p. 100-103°C. IR (KBr, cm^{-1}): 2856-2921 (w), 1720 (s), 1569 (s), 1461 (s) and 723 (s).

Mn(II) stearate: white solid (90%), m.p. 108-111 °C. IR (KBr, cm^{-1}): 2856(b), 1569-1720(w), 1461(s) and 718(0s).

Fe(III) stearate: orange solid (78%), m.p. 94-96 °C. IR (KBr, cm^{-1}): 2846-2912(w), 1705(s), 1583(s), 1461(s) and 723(s).

Co(II) stearate: pink solid (74%), m.p. 86-90 °C. IR (KBr, cm^{-1}): 2856-2912(w), 1630-1701(b), 1545(s) and 721(s).

Ni(II) stearate: light green solid (87%), m.p. 175-177 °C. IR (KBr, cm^{-1}): 2856-2903(w), 1564-1720(w), 1381(b) and 721(s).

Cu(II) stearate: light blue solid (92%), m.p. 138-139 °C. IR (KBr, cm^{-1}): 2903(s), 2846(s), 1592(s), 1404-1456(w) and 721(s).

Zn(II) stearate: white solid (81%), m.p. 115-120 °C. IR (KBr, cm^{-1}): 2908-2848(w), 1703(s), 1536(s), 1466(w) and 726(s).

VO(IV) stearate: army dark green solid (85%), m.p. 91-94 °C. IR (KBr, cm^{-1}): 2920-2845(s), 1590(m), 1466(m) and 720(w).

2.4 The general procedure for allylic oxidation of alkenes

For allylic oxidation of alkenes to a solution of substrate (50 mmol) with no extra organic solvent or substrate (5 mmol) in isooctane (5 mL) containing Cr(III) stearate (0.2 mmol) was added 70% TBHP (9 mmol). The mixture was stirred at 70°C for 24 hours. After the reaction finished, 1 mL of the reaction mixture was taken and extracted with diethyl ether. The combined extracts were washed with H_2O, dried over anhydrous Na_2SO_4 and analyzed by GC with the addition of an exact amount of appropriate internal standard.

2.5 Study on the optimum conditions for allylic oxidation of cyclohexene

2.5.1 Effect of metal stearate complexes

The allylic oxidation reaction was carried out as described in the general procedure employing seven transition metal stearate complexes: Ni(II), Co(II), Cu(II), Mn(II), Fe(III), Zn(II), VO(IV) stearates.

2.5.2 Effect of temperatures

The allylic oxidation reaction was carried out as described in the general procedure previously described using chromium(III) sterate as a catalyst, but the temperature was varied: 35, 50, 60 and 70°C.

2.5.3 Kinetic study on the oxidation of cyclohexene catalyzed by chromium(III) stearate

The allylic oxidation of cyclohexene catalyzed by chromium(III) stearate catalyst was carried out at 70°C. At different reaction times proceeded: 1, 3, 7.5, 12, 15, 18 and 24 hr, 1 mL of the reaction mixture was collected, worked up and dried over anhydrous Na_2SO_4, and finally analyzed by GC.

2.5.4 Effect of the amount of catalysts

The allylic oxidation reaction was carried out in the same manner as previously described by chromium(III) stearate as a catalyst, but the amount of catalyst was varied: 0, 0.02, 0.1, 0.2 and 0.3 mmol.

2.5.5 Effect of solvents

The allylic oxidation reaction was carried out in the same fashion as previously described but the solvent was changed to toluene, benzene, acetonitrile, THF, pyridine, pyridine:acetic acid (3:1), CCl_4, *n*-butanol, 1-methyl-2-pyrrolidone and 1,2-dichloroethane.

2.5.6 Effect of the amount of oxidants

The allylic oxidation reaction was carried out in the same manner as previously described using chromium(III) stearate as a catalyst with different amounts of the oxidant: 0, 9, 12, 15 and 18 mmol.

2.6 Syntheses of authentic samples

2-cyclohexenol

A solution of 2-cyclohexenone (15.0 g, 156 mmol) in 25 mL of ether was added to a stirred suspension of $LiAlH_4$ (1.6 g, 42.1 mmol) in 100 mL of anhydrous ether and the mixture was refluxed for 30 min. Water was slowly added to the cooled solution until H_2 gas was no longer evolved, followed by 10% H_2SO_4 until the precipitated aluminium hydroxide dissolved (pH~3). The phases were separated. The aqueous phase was saturated with NaCl and extracted twice with 100 mL of ether. The combined ether layers were washed with saturated $NaHCO_3$ and NaCl solutions and dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was distilled to give a colorless oil [42].

2-cyclohexenol: colorless oil, IR (KBr, cm^{-1}): 3320, 3020, 2910, 2850, 2815, 1655, 1445, 1430 and 1050; ^{1}H-NMR ($CDCl_3$) δ (ppm): 5.79 (m, 2H), 4.17 (m, 1H), 3.50 (s, 1H) and 2.2-1.2 (m, 6H).

verbenol

$NaBH_4$ (1 mmol) was added over a period of 5 min to a stirred solution of verbenone (2 mmol) in 1 mL of EtOH. Stirring was continued for 2 h at RT (followed by TLC: silica gel, ether). H_2O (1 mL) was added and the mixture was extracted three times with 25 mL of ether. The combined organic phases were washed with saturated NaCl solution and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was distilled *in vacuo* to give a colorless oil [42].

verbenol: colorless oil, IR (KBr, cm^{-1}): 3354, 2970, 2920, 2885, 2868, 1465 and 1373; ^{1}H-NMR ($CDCl_3$) δ (ppm): 5.37 (s, 1H), 3.68 (m, 1H), 2.62 (m, 1H), 2.05 (s, 1H), 1.92 (s, 2H), 1.71 (s, 3H) and 1.11 (s, 6H).

4,6-diethoxycarbonyl-3-methylcyclohexen-2-one

To a solution of ethyl acetoacetate (26.13 g), 3 g of powdered paraformaldehyde and 1.10 g of piperidine in 100 mL flask, the reaction was allowed to proceed at RT for 5 min. The reaction was chilled by cooling in iced water. When the vigorous reaction was over, the reaction mixture was homogenous. Dissolve the crude in 40 mL of dichloromethane in a separatory funnel and washed with 1M HCl, saturated $NaHCO_3$ and water, then dried over anhydrous Na_2SO_4 and evaporated to furnish 84% yield of 4,6-diethoxycarbonyl-3-methylcyclohex-2-none [43].

4,6-diethoxycarbonyl-3-methylcyclohexen-2-one: 84% yield, yellow liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.12 (m, 2H), 3.05 (t, *J* = 12.5 Hz , 1H), 1.98 - 2.22 (dd, *J* = 18.5, 18.6 Hz, 2H), 1.96 (m, 1H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 9.2 Hz, 3H)

3-methylcyclohexen-2-one

The crude product of 4,6-diethoxycarbonyl-3-methylcyclohexen-2-one obtained from previous preparation was dissolved in a mixture of 30 mL glacial acetic acid, 30 mL H_2SO_4 and 20 mL of water. The solution was then gently boiled under reflux for 6 h. The solution of 12.6 g NaOH in 35 mL of water was added and the mixture was extracted with three 15 mL portions of ether and dried over anhydrous Na_2SO_4. The residue was distilled under reduced pressure through a short fractionating column and the product was collected for the fraction with b.p. 95 ^{o}C /25 mmHg [43].

3-methylcyclohexen-2-one: 44% yield, brown liquid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 5.85 (m, H), 3.42 (t, *J* = 9.2 Hz, 2H), 2.35 (m, 2H), 2.05 (m, 2H) and 1.25 (m, 3H)

2.7 Study on the oxidation of various selected alkenes

Under optimum conditions, selected alkenes namely α-pinene, 1-methyl-cyclohexene, isophorone, α- and β-ionones were oxidized to the corresponding carbonyl compound employing the procedure previously described.

2.8 General isolation procedure

After the reaction was completed (followed by TLC), 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 an eluent. The equivalent fractions monitored by TLC were combined and the solvents were completely evaporated. The residue was recrystallized by an appropriate solvent or chromatographed over silica gel column to yield the desired carbonyl compound.

3-oxo-α-ionone: 32% yield, yellow oily liquid, R_f 0.30 (hexane:EtOAc 4:2); ^{1}H-NMR($CDCl_3$) δ (ppm): 6.70 (dd, *J* = 15.7, 9.5 Hz, 1H), 6.21 (d, *J* = 15.7 Hz, 1H), 6.00 (s, 1H), 2.7 (d, *J* = 9.5 Hz, 1H), 2.4 (d, *J* = 16.9 Hz, 1H), 2.30 (s, 3H), 2.14 (d, *J* = 16.9 Hz, 1H), 1.92 (s, 3H), 1.09 (s, 3H) and 1.02 (s, 3H); ^{13}C-NMR($CDCl_3$) δ

(ppm): 198.3 (1C, CO), 197.6 (1C, CO), 159.2 (1C), 143.6 (1C), 133.7 (1C), 126.8 (1C), 55.4 (1C), 47.3 (1C), 36.6 (1C), 27.8 (1C), 27.5 (1C), 27.3 (1C) and 23.5 (1C).

4-oxo-β-ionone: 16% yield, yellow oily liquid, R_f 0.23 (hexane:EtOAc 4:2); ^{1}H-NMR($CDCl_3$) δ (ppm): 7.25 (d, *J* = 16.5 Hz, 1H), 6.20 (d, *J* = 16.5 Hz, 1H), 2.53 (t, *J* = 6.7 Hz, 2H), 2.35 (s, 3H), 1.89 (t, *J* = 7.0 Hz, 2H), 1.79 (s, 3H), 1.24 (s, 3H) and 1.18 (s, 3H); ^{13}C-NMR($CDCl_3$) δ (ppm): 198.7 (1C, CO), 197.6 (1C, CO), 157.9 (1C), 140.4 (1C), 133.5 (1C), 131.3 (1C), 37.2 (1C), 35.5 (1C), 34.1 (1C), 29.7 (1C), 27.9 (1C), 27.2 (1C) and 13.4 (1C).

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CHAPTER III

RESULTS AND DISCUSSION

Allylic oxofunctionalization is defined, for the propose of this research, as the preparation of α,β-unsaturated ketones using TBHP as oxidant. Allylic oxidation and epoxidation are basically two competing processes for alkene functionalization both *in vivo* and *in vitro* [44]. Typically, allylic oxidation products are found when hydrogen abstraction is the dominant reaction. Electrophilic attack at the double bond of cyclic olefin leads to epoxidation or ring cleavage [45]. In contrast to epoxidation, allylic oxidation retains the olefinic functionality in the product allowing further useful transformations. Allylic oxidation is a process involving free radicals and is most likely to occur in the presence of low oxidation state transition metal species [44].

3.1 Syntheses and identification of metal stearate complexes.

In this study, several transition metal stearate complexes such as chromium(III), nickel(II), cobalt(II), copper(II), manganese(II), iron(III), zinc(II) and oxovanadium(IV) stearates were prepared. These catalysts were then used for allylic oxidation of alkenes. The metal stearate complexes were identified by comparison both physical properties (color and melting point) and IR spectroscopic data with those reported [46]. From the IR spectrum, stearic acid revealed a broad COOH peak at 2700-3400 cm^{-1}, 1703 cm^{-1} for asymmetric stretching of COO and 1471 cm^{-1} for symmetric stretching of COO. For asymmetric and symmetric stretching of COO of metal stearate complex catalysts, the IR spectra showed C=O bands at 1600-1700 $cm^{-1}$and 1400-1450 cm^{-1}, respectively. The COO peak shifts are indicative of complex formation. Both free acid and complexes showed a significant $(CH_2)_n$ skeletal vibration peak at 720 cm^{-1} [47]. The example of metal stearate complex, *i*.e. IR spectrum of chromium(III) stearate complex is shown in Fig 3.1.

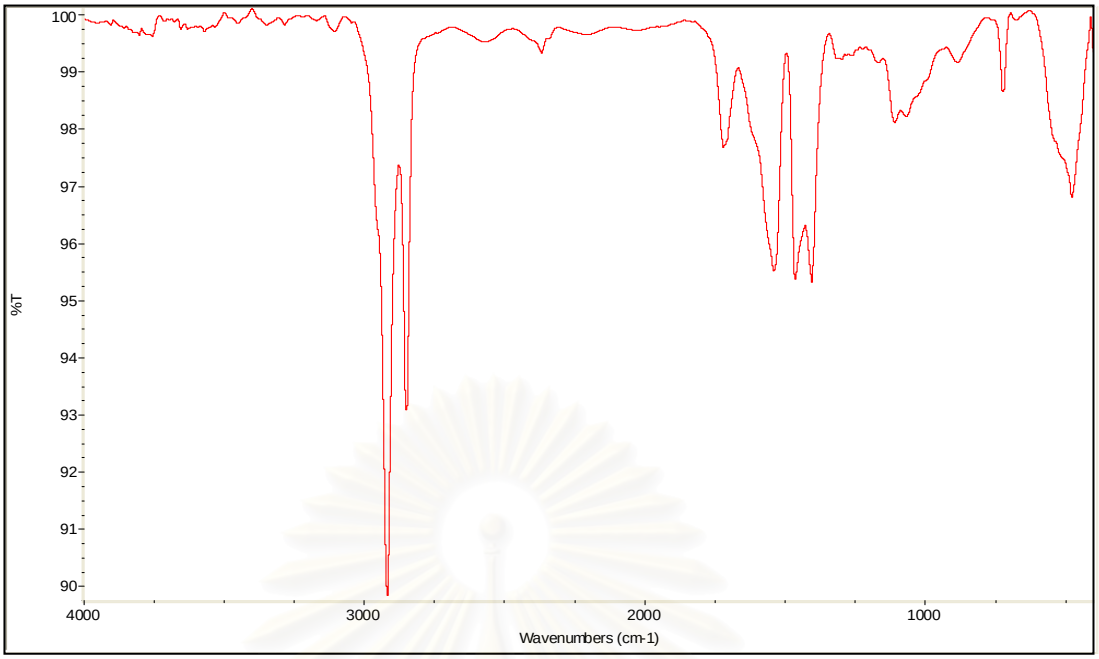

Figure 3.1 IR spectrum of chromium(III) stearate complex

From Fig 3.1, the IR spectrum of chromium(III) stearate complex exhibited C=O stretching at 1710 cm^{-1} and 1461-1541 cm^{-1} for asymmetric and symmetric stretching of COO, respectively together with $(CH_2)_n$ skeletal vibration peak at 723 cm^{-1}.

3.2 Study on the optimum conditions for allylic oxidation of cyclohexene.

Cyclohexene, one of the structurally simple cyclic olefins, provides the opportunity to study the effect of catalyst, temperature, kinetic, amount of catalyst, solvent and amount of oxidant that lead to preferably allylic oxidation.

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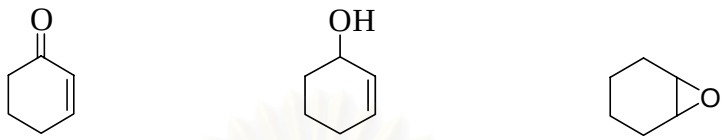
3.2.1 Effect of metal stearate complexes.

The experiments for determining the influence of metal stearate complexes on the catalytic activities and product selectivities of cyclohexene oxidation were performed at temperature of 70°C using 0.20 mmol of metal stearate catalysts and 50 mmol of cyclohexene. The results are shown in Table 3.1 and Fig 3.2.



1 **2** **3**

Table 3.1 Effect of metal stearate complexes on the oxidation of cyclohexene

Entry	Catalyst	Product (mmol)			Total yield (mmol)	Selectivity (one + ol / oxide)
		1	**2**	**3**		
1	$Cr(st)_3$	7.16	2.47	0.92	10.55	10.47
2	$Ni(st)_2$	5.53	3.23	0.81	9.57	10.81
3	$Co(st)_2$	2.85	1.76	0.34	4.95	13.56
4	$Cu(st)_2$	2.39	1.57	0.30	4.26	13.20
5	$Mn(st)_2$	2.26	1.45	0.28	3.99	13.25
6	$Fe(st)_3$	2.90	1.80	0.76	5.46	6.18
7	$Zn(st)_2$	1.00	1.31	0.33	2.64	7.00
8	$VO(st)_4$	4.00	2.29	0	6.29	-

Reaction conditions: cyclohexene (50 mmol), catalyst (0.20 mmol), TBHP (9 mmol) at 70°C for 24 h.

1 : cyclohexenone, **2** : cyclohexenol, **3** : cyclohexene oxide

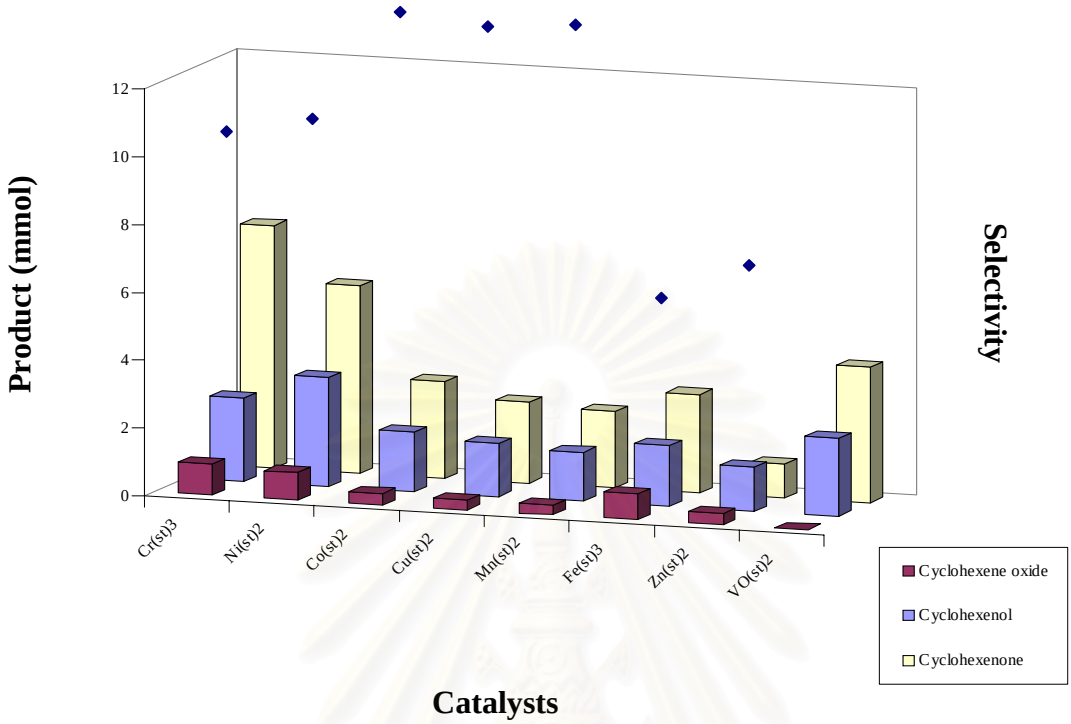


Figure 3.2 Effect of metal stearate catalysts on the oxidation of cyclohexene

The examination on the influence of metal stearate catalysts revealed that chromium(III) and nickel(II) stearates were appropriate catalysts for allylic oxidation of cyclohexene with good selectivity, (ketone+alcohol/epoxide, ~11) and high yield of product (ketone+alcohol ~10 mmol). Cobalt(II), manganese(II) and copper(II) stearate catalysts also provided high selectivity for allylic oxidation, ~13; however the quantity of product was low (~4 mmol).

From these present experimentals, it was found that chromium(III) stearate exhibited very intriguing catalytic activities, regarding the oxidation of cyclohexene being converted to cyclohexenone and cyclohexenol in high yields (7.16 and 2.47 mmol, respectively) and cyclohexene oxide (0.92 mmol) as by product. This study expressed that the conversion of cyclohexene over metal stearate catalysts investigated followed a sequence of $Cr(st)_3$>$Ni(st)_2$>$Co(st)_2$~$Cu(st)_2$>$Mn(st)_2$>$Fe(st)_3$. It could be the characteristic of metal dependence, which it affect to the activity and selectivity of the allylic oxidation products (cyclohexenone and cyclohexnol). These

preliminarily attractive results prompted for further investigation of this oxidation reaction.

3.2.2 Effect of temperatures.

To investigate the effect of temperature on the reactivity and product selectivity, the conversion of cyclohexene and the selectivities of the attained products from the allylic oxidation at temperatures ranging from 35°C to 70°C were observed. The results are shown in Table 3.2.

Table 3.2 Effect of temperature on cyclohexene oxidation catalyzed by chromium(III) stearate

Entry	Temperature (°C)	Product (mmol)			Total yield (mmol)	Selectivity (one+ol/ oxide)
		1	**2**	**3**		
1	35	2.36	0.22	0.55	3.13	4.69
2	50	2.80	0.58	0.57	3.95	5.93
3	60	3.79	1.11	0.71	5.61	6.90
4	70	7.16	2.47	0.92	10.55	10.47

Reaction conditions: cyclohexene (50 mmol), chromium(III) stearate (0.20 mmol), TBHP (9 mmol), temperature (35 – 70°C) for 24 h.

1 : cyclohexenone, **2** : cyclohexenol, **3** : cyclohexene oxide

The allylic oxidation was performed under atmospheric pressure in the absence of extra solvent. At temperature ranging from 35°C to 70°C, the reactivity and product selectivity of the complex were varied with the temperature. The selectivity of the products increased from 4.69 to 10.47 with temperature increasing from 35°C to 70°C. The main oxidation products were cyclohexenol and cyclohexenone, to which the best selectivities were up to 10.47, and the total yield was reached to 10.55 mmol at 70°C (entry 4). This might be suggested that TBHP could be homolytically cleavaged forming a radical to initiate the oxidation reaction, whereas the reaction carried out at lower temperature was not successful. This could be explained that TBHP did not probably expose well to form a radical to initiate the oxidation reaction (entries 1, 2 and 3). Therefore, the optimum temperature for this reaction is 70°C. According the literatures, both Barton and Chavez reported that

using TBHP would give good yield of the desired product when the reaction was performed at 70°C [48].

3.2.3 Kinetic study on the oxidation of cyclohexene catalyzed by chromium(III) stearate.

Kinetic investigations on the allylic oxidation of cyclohexene to cyclohexenone, cyclohexenol and cyclohexene oxide were conducted by varying the reaction time. The results are shown in Table 3.3.

Table 3.3 Kinetic study of cyclohexene oxidation catalyzed by chromium(III) stearate

Entry	Time (hr)	Product (mmol)			Total yield (mmol)	Selectivity (one + ol / oxide)
		1	**2**	**3**		
1	1	0.50	0.23	0.39	1.12	1.87
2	3	1.76	0.67	0.64	3.07	3.80
3	7.5	1.98	0.77	0.59	3.34	4.67
4	12	4.77	1.21	0.73	6.71	8.19
5	15	6.42	1.43	1.20	9.05	6.54
6	18	8.28	3.24	1.47	12.99	7.84
7	24	7.16	2.47	0.92	10.55	10.47

Reaction conditions: cyclohexene (50 mmol), chromium(III) stearate (0.20 mmol), TBHP (9 mmol) at 70°C for 1-24 h.

1 : cyclohexenone, **2** : cyclohexenol, **3** : cyclohexene oxide

As noticed from Table 3.3, it was clearly seen that the increasing of reaction time affected on the increment yield of the desired product. When the reaction time increased to 18 hrs, it was found that the yields of the product was decreased, the product might decompose to the unwanted desired product, while the selectivity was the highest. When the reaction time was increased, more allylic radicals were generated to produce more cyclohexenone and cyclohexenol.

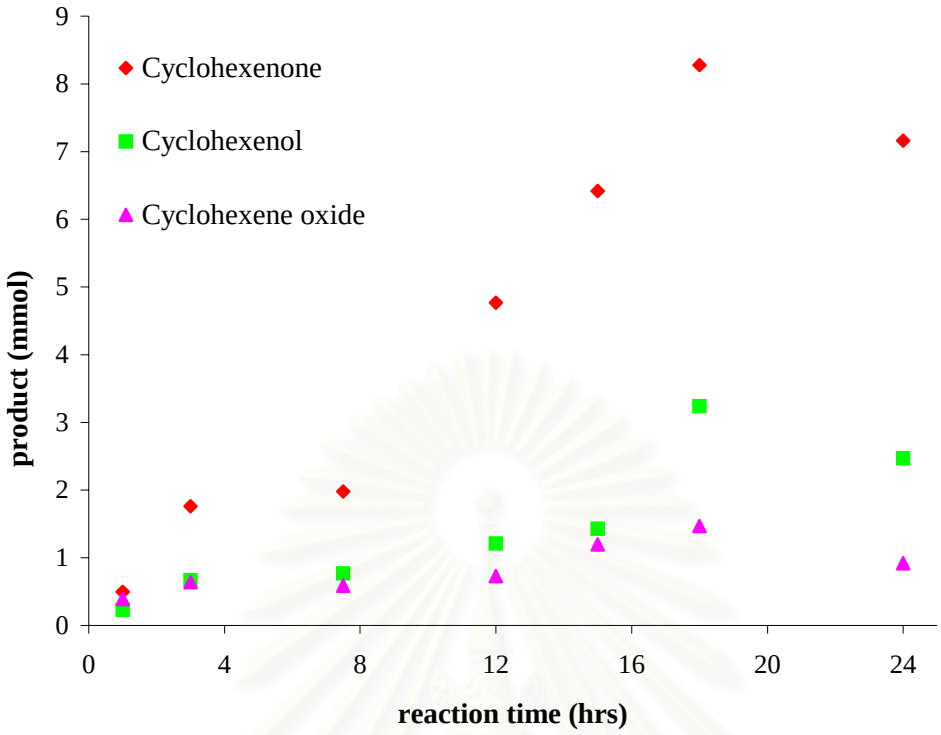


Figure 3.3 Kinetic study of cyclohexene oxidation catalyzed by chromium(III) stearate

Fig 3.3 reveals that the reaction time of 18 hrs was the most appropriate time for allylic oxidation of cyclohexene under optimum conditions. In terms of kinetic study, the results displayed that the half life of the reaction under this optimum conditions was approximately 9 hours.

3.2.4 Effect of the amount of catalysts.

The catalyst concentration varied from 0 to 0.3 mmol was examined for the allylic oxidation of cyclohexene. The results are presented in Table 3.4.

Table 3.4 Effect of the amount of catalyst on cyclohexene oxidation

Entry	Catalyst (mmol)	Product (mmol)			Total yield (mmol)	Selectivity (one + ol / oxide)	Turnover number*
		1	**2**	**3**			
1	0	1.11	0.56	0.18	1.85	9.28	-
2	0.02	3.42	1.09	0.36	4.87	12.53	243
3	0.10	4.62	1.60	0.56	6.78	11.11	73
4	0.20	7.16	2.47	0.92	10.55	10.47	53
5	0.30	4.17	1.88	0.64	6.69	9.47	22

Reaction conditions: cyclohexene (50 mmol), chromium(III) stearate (0-0.30 mmol), TBHP (9 mmol) at 70°C for 24 h.

1 : cyclohexenone, **2** : cyclohexenol, **3** : cyclohexene oxide

* turnover number (TON): moles of products produced per moles of chromium(III) stearate.

From Table 3.4, when Cr(III) stearate 0.20 mmol was used, the reaction gave the highest yield of cyclohexenone and cyclohexenol (~11 mmol). In addition, when the amount of catalyst was increased or decreased from 0.20 mmol, the yield was decreased. When 0.30 mmol of catalysts was used, the yield of the desired product was decreased. This might be explained by increasing agglomeration of catalyst when the amount of catalyst was increased as well as the rapid decomposition of TBHP and this might be occurred because the rapid interation of the reaction species taken place and may compete with the desired allylic oxidation route and gave unwanted side reaction products. Thus, it was clear that the catalyst at 0.2 mmol was the appropriate amount of catalysts for allylic oxidation of cyclohexene with good selectivity, (ketone+alcohol/epoxide, ~11) and high yield of product (ketone+alcohol ~11 mmol). Compared with selectivity of catalyst at 0.3 mmol, it gave the selectivity as similar to 0.2 mmol. Accounting on turnover number (TON), using the catalyst at 0.02 mmol provided the best turnover number of 243.

3.2.5 Effect of solvents.

The choice of solvent that could provide a homogeneous reaction had a crucial effect on the reactivity and product selectivity for the allylic oxidation reaction with TBHP. When the total volume of the reaction was less than 5 mL, an extra solvent was added to the reaction. The use of cyclohexene 5 mmol with extra diverse organic solvents was tried and the results are collected as shown in Table 3.5.

Table 3.5 Effect of solvents on the oxidation of cyclohexene catalyzed by chromium(III) stearate

Entry	Solvent	% Yield of product			∑	Selectivity (one + ol / oxide)
		1	**2**	**3**		
1	isooctane	23.04	12.44	0	35.48	-
2	toluene	28.37	0	6.00	34.37	4.73
3	benzene	28.01	0	4.40	32.41	6.37
4	acetonitrile	28.62	0.59	0	29.21	-
5	THF	4.67	5.42	0	10.09	-
6	pyridine	27.89	0	0	27.89	-
7	pyridine:acetic acid (3:1)	17.41	0	0	17.41	-
8	CCl_4	20.90	0	0	20.90	-
9	*n*-butanol	15.96	0	0	15.96	-
10	1-methyl-2-pyrrolidone	11.82	1.41	0	13.23	-
11	1,2-dichloroethane	0	0	0	0	-

Reaction conditions: cyclohexene (5 mmol), chromium(III) stearate (0.20 mmol), solvent (5 mL), TBHP (9 mmol) at 70°C for 24 h.

1 : cyclohexenone, **2** : cyclohexenol, **3** : cyclohexene oxide

The use of polar protic solvents such as *n*-butanol and 1-methyl-2-pyrrolidone resulted in low yield of the desired product. That may stem from the nonhomogenity of the substrate in these media. Interestingly, the use of non-polar aprotic solvents

such as isooctane, acetonitrile, pyridine, THF and CCl_4 resulted in high selectivity toward the allylic oxidation (cyclohexenone and cyclohexenol), which no epoxidation reaction (cyclohexene oxide product) took place. Other solvents such as toluene and benzene were also disclosed to be appropriate solvents in allylic oxidation of cyclohexene with good activity and selectivity of cyclohexenone in concomitance of the occurrence of trace epoxidation. It was thus clearly seen that 1,2-dichloroethane solvent did not occur allylic oxidation reaction because it was not soluble in catalyst and substrate.

These results clearly showed that isooctane was the solvent of choice because it was inexpensive, commercially available and could well dissolve both cyclohexene (organic substrate) and metal stearate complex (catalyst). Furthermore, it gave good selectivity to cyclohexenone (allylic oxidation product) under the reaction conditions explored.

3.2.6 Effect of the amount of oxidants.

The variation of the amount of oxidants was studied. TBHP was chosen as oxidant for allylic oxidation of cyclohexene. The results are presented in Table 3.6.

Table 3.6 Effect of the amount of TBHP on cyclohexene oxidation catalyzed by chromium(III) stearate

Entry	TBHP (mmol)	% Yield of product			∑
		1	**2**	**3**	
1	0	0.30	0.29	0.40	0.99
2	9	23.04	12.44	0	35.48
3	12	11.20	0	0	11.20
4	15	12.98	0	0	12.98
5	18	14.44	0	0	14.44

Reaction conditions: cyclohexene (5 mmol), chromium(III) stearate (0.20 mmol), isooctane (5 mL), TBHP (0-18 mmol) at 70°C for 24 h.

1 : cyclohexenone, **2** : cyclohexenol, **3** : cyclohexene oxide

The amount of TBHP in allylic oxidation was varied from 0-18 mmol. The attempt to find the most appropriate amount of TBHP that provided the desired product in high yield with excellent selectivity were performed. From Table 3.6, it

could be observed that when 9 mmol of TBHP was used, % yield of the desired product was high (~35%) with excellent selectivity of ketone+alcohol/epoxide. When the amount of TBHP was increased (18 mmol), the yield of product (cyclohexenone) was decreased. It might be explained that the reaction was obstructed by H_2O in TBHP. Nevertheless, the increasing of TBHP was not affected to yield of the product ; however, it gave cyclohexenone selectively.

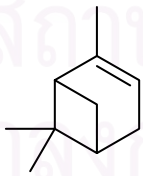
From the overall results obtained, metal stearate catalysts, temperature, reaction time, atmosphere, amount of catalysts, solvents, amount of oxidants affected the allylic oxidation reaction. The optimum conditions for allylic oxidation of cyclohexene were as follows: cyclohexene 5 mmol as substrate, chromium(III) stearate as catalyst at 70°C, isooctane 5 mL and TBHP 9 mmol as oxidant.

3.3 Allylic oxidation of selected alkenes.

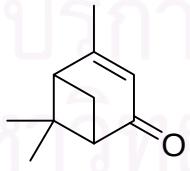
To illustrate the effects of metal stearate complexes, the amount of oxidants and solvents in allylic oxidation of structurally more complicated cyclic olefins, the allylic oxidation of the readily available α-pinene, 1-methylcyclohexene, α-ionone, β-ionone and isophorone was investigated.

3.3.1 The optimum conditions for the allylic oxidation of α-pinene (**4**).

The allylic oxidation of α-pinene has alluded the chemists. Verbenone (**5**), an important allylic oxidation product from α-pinene, is considered as a suitable precursor in the preparation of taxol, which has been introduced as a therapeutic agent [49].



(**4**)



(**5**)

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3.3.1.1 Effect of metal stearate.

The effects of metal stearate complexes in allylic oxidation of α-pinene (**4**) at 70°C for 24 h in isooctane were examined. The results are presented in Table 3.7.

Table 3.7 Effect of metal stearate complexes on the oxidation of α-pinene (**4**)

Entry	Catalyst	Percent		Mass balance
		4 (recovered)	**5**	
1	$Cr(st)_3$	41.85	53.19	95.04
2	$Cu(st)_2$	43.15	49.02	92.17
3	$Ni(st)_2$	48.65	43.44	92.09
4	$Co(st)_2$	70.97	18.57	89.54
5	$VO(st)_4$	85.11	6.35	91.46

Reaction conditions: α-pinene (**4**) (5 mmol), catalyst (0.20 mmol), isooctane (5 mL), TBHP (9 mmol) at 70°C for 24 h.

4 : α-pinene, **5** : verbenone

From Table 3.7, the oxidation of α-pinene (**4**) was directly led to the formation of the desired allylic oxidation product, verbenone (**5**). The influence of metal stearate catalysts revealed that chromium(III) and copper(II) stearates were appropriate catalysts providing excellent selectivity and high yield of product (ketone ~ 53% yield). Nickel(II) stearate catalyst gave moderate yield (~ 43 %) of verbenone (**5**), whereas cobalt (II) and oxovanadium(IV) stearates furnished the lowest yield of product (~ 19 % yield). From these present experimentals, chromium(III) stearate displayed attractive catalytic activities, regarding to the oxidation of α-pinene (**4**) being converted to verbenone (**5**) in high yield (~53%) with no epoxidation product detected. The role of Cr(III) complex was perhaps to accomplish the rapid of verbenyl hydroperoxide intermediate [50]. From the literatures reported by Allal and his co-workers, the use of $CuCl_2$ catalyst has been catalyzed oxidation of α-pinene using TBHP gave verbenone 71% yield with high selectivity [50]. These preliminarily attractive results prompted for further investigation of this oxidation reaction.

3.3.1.2 Effect of the amount of oxidants.

The amount of oxidants always play an important role to improve the allylic oxidation of α-pinene [51]. In this study, TBHP was chosen as an oxidant. The results of the variation of the amount of oxidant are shown in Table 3.8.

Table 3.8 Effect of the amount of TBHP on α-pinene (**4**) oxidation catalyzed by chromium(III) stearate

Entry	TBHP (mmol)	Percent		Mass balance
		4 (recovered)	**5**	
1	0	81.46	16.03	97.49
2	9	41.85	53.19	95.04
3	12	25.49	60.46	85.95
4	15	11.52	81.42	92.94
5	18	10.83	64.91	75.74

Reaction conditions: α-pinene (**4**) (5 mmol), chromium(III) stearate (0.20 mmol), isooctane (5 mL), TBHP (0-18 mmol) at 70°C for 24 h.

4 : α-pinene, **5** : verbenone

From Table 3.8, the amount of oxidant was varied from 0-18 mmol. α-Pinene 5 mmol, chromium(III) stearate catalyst and isooctane were added to the reaction for 24 h. When the amount of oxidant was increased from 0-18 mmol, % yield of the desired product (verbenone) was increased. Surprisingly, it was clear that when TBHP 15 mmol was used the highest yield of verbenone (**5**) was attained. Using 18 mmol of TBHP, it gave the lower yield of verbenone (**5**), this may be explained that when the amount of TBHP increased, the obtained products could be further oxidized to undesired products. This postulation could be supported by the mass balance of the reaction of 76 %. Compared with literature cited, Lajunen and co-worker reported that the oxidation of α-pinene catalyzed by [Co(II)Br_2-pyridine] complex at 50°C for 22 h, provided verbenone (**5**) 32 % yield**,** α-pinene oxide 14 % yield**,** *trans*-verbenol 14% yield and gave α-pinene (**4**) recovered 23% yield [52].

Verbenone (**5**) could be isolated from the reaction mixture and purified by silica gel column chromatography. The structure of verbenone (**5**) was characterized by IR spectroscopic data and confirmed by ^{1}H and ^{13}C-NMR. The IR spectrum of verbenone (**5**) is shown in Fig 3.4.

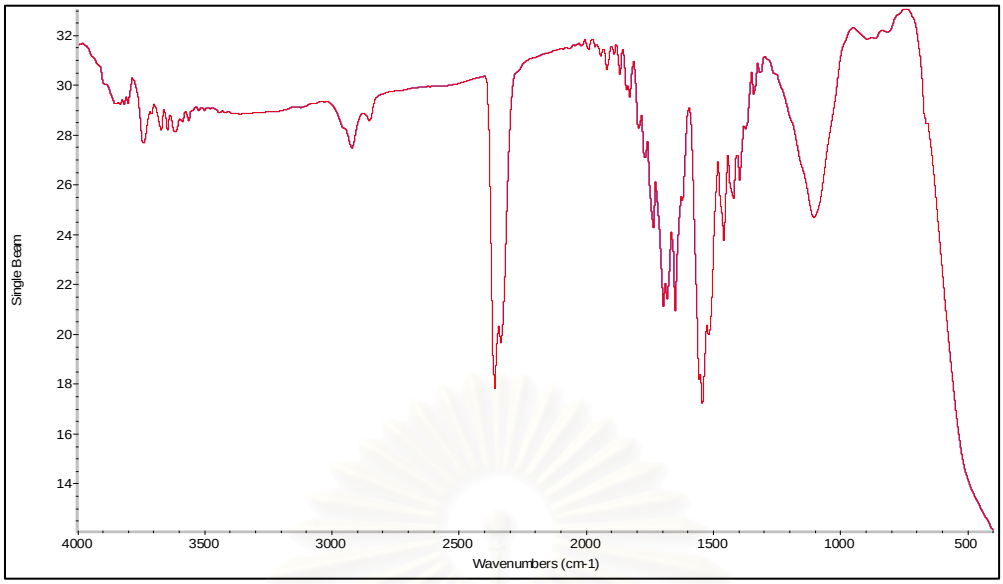


Figure 3.4 IR spectrum of verbenone (**5**)

From Fig 3.4, the IR spectrum of verbenone (**5**) exhibited C=O stretching at 1700 cm^{-1} and C=C stretching at 1580 cm^{-1}.

Moreover the structure of verbenone (**5**) was vertified by ^{1}H-NMR spectrum (Fig 3.5) and ^{13}C-NMR spectrum (Fig 3.6). The ^{1}H-NMR spectrum of verbenone (**5**) exhibited the characteristic of singlet proton peak at δ 5.45 (C=CH-C=O), at δ 1.74 of methyl protons, at δ 1.11 of methyl proton (CH_3-C-CH), at δ 2.80 and 2.62 (t, J = 6 Hz, H) showed the characteristic of triplet peaks of CH proton of cyclobutane and at δ 2.25 and 1.90 of CH_2 protons of cyclobutane. For the ^{13}C-NMR spectrum presented in Figure 3.6, the signal at δ 200.1 was belonged to a carbonyl carbon at δ 165.2 and 121.2 for ethylene carbons of C and CH respectively, at δ 57.6 for CH of cyclobutane, at δ 40.8 and 49.8 for CH and C of cyclobutane, respectively. At δ 26.6 for CH_2 of aliphatic carbon, at δ 20.7 and 24.5 for CH_3 groups.

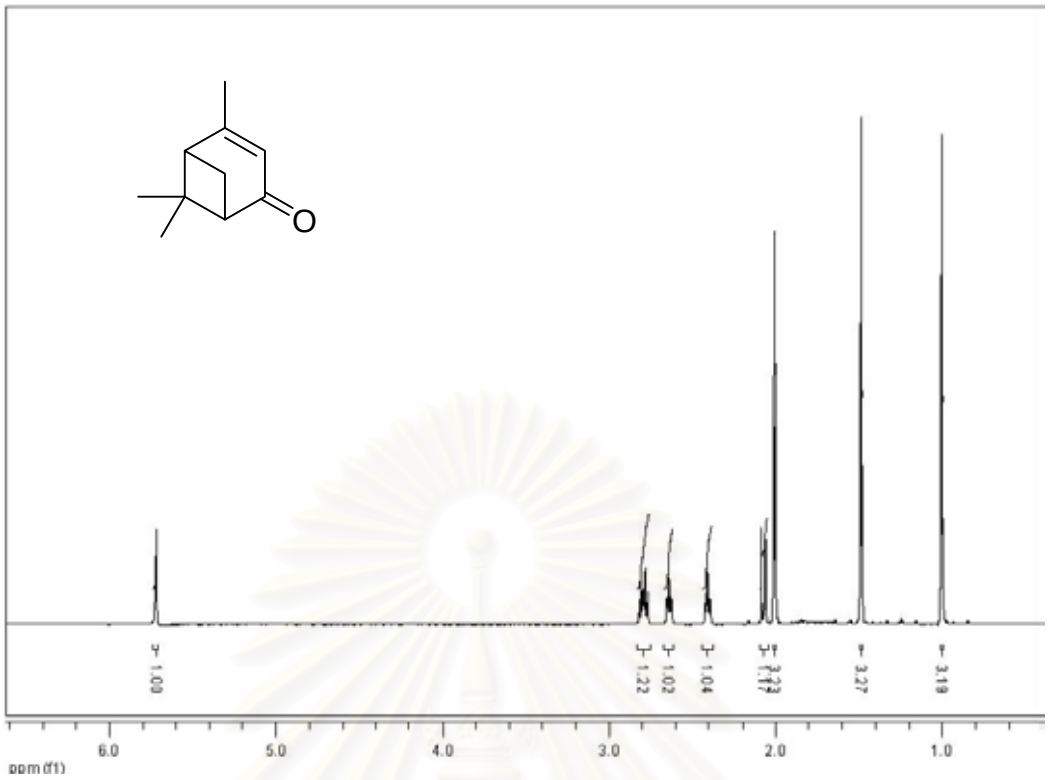


Figure 3.5 The ^{1}H-NMR spectrum of verbenone (**5**)

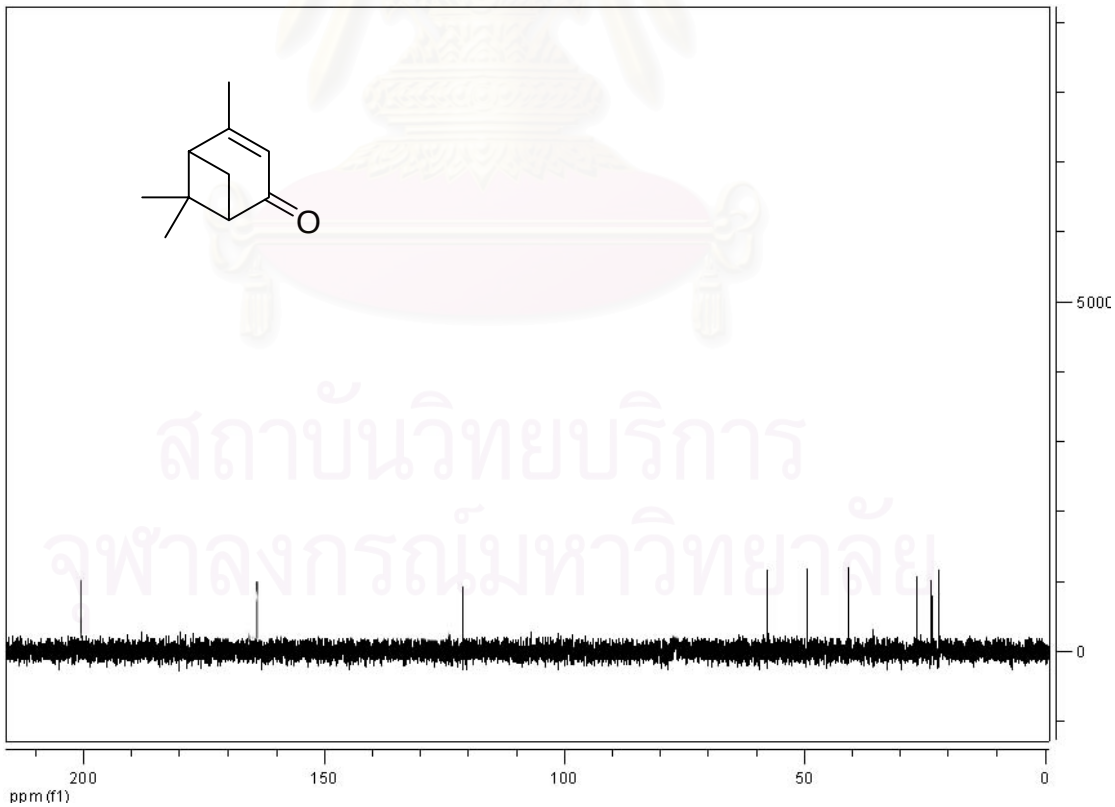
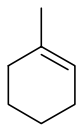


Figure 3.6 The ^{13}C-NMR spectrum of verbenone (**5**)

3.3.2 Optimum conditions for the allylic oxidation of 1-methylcyclohexene (**6**)

From previous results, chromium(III) stearate provided the excellent selectivity for allylic oxidation and yielded the desired product in good yield. The use of chromium(III) stearate was further explored for the allylic oxidation of 1-methylcyclohexene (**6**).



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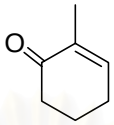

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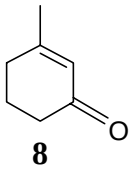

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From previous literature cited, Bellucci and co-workers reported that the oxidation of 1-methylcyclohexene (**6**) (20 mM) at 37°C for 30 minutes led to the formation of ketones **7** (1 nmol) and **8 (**13 nmol) which were believed to derive from the oxidation of initial allylic alcohols produced [53]. Another report was addressed by Kaneda and co-worker [54], under an oxygen atmosphere using an $VO(acac)_2$-AIBN catalyst system at 80°C for 1.5 h in 1,2-dichloroethane, an epoxy alcohol was obtained in 21 % yield with good selectivity [54].

Because of the potential significance of epoxy alcohols in general, it is important to examine the scope and limitation of their formation under this particular conditions examined.

3.3.2.1 Effect of solvent.

The effects of solvent are an important factor in allylic oxidation of 1-methylcyclohexene (**6**). In this study, four diverse types of solvents were examined and the results are shown in Table 3.9.

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Table 3.9 Effect of various solvents on the oxidation of 1-methylcyclohexene (**6**) catalyzed by chromium(III) stearate

Entry	Solvent	Product (mmol)		Selectivity
		7	**8**	**8**/**7**
1	isooctane	0.41	1.76	4.29
2	pyridine	0.18	0.58	3.22
3	benzene	0.10	0.54	5.40
4	toluene	0.14	0.60	4.29

Reaction conditions: 1-methylcyclohexene (**6**) (5 mmol), chromium(III) stearate (0.20 mmol), solvent (5 mL), TBHP (9 mmol) at 70°C for 24 h.

6: 1-methylcyclohexene, **7**: 2-methyl-2-cyclohexenone, **8**: 3-methyl-2-cyclohexenone

From Table 3.9, using benzene as solvent, the reaction yielded the desired allylic oxidation products **7** and **8**. These two products were purified by silica gel column chromatography and characterized their identities by ^{1}H-NMR. The selectivities of **8**/**7** were ~5. However, the quantity of product was quite low. Employing isooctane, the highest yield of the desired product (**7**+**8**) ~2 mmol with good selectivity **8**/**7** ~4 mmol was attained.

3.3.2.2 Effect of the amount of oxidants.

Effect of the amount of oxidant is another important factor in allylic oxidation of 1-methylcyclohexene (**6**). The reaction was achieved by chromium(III) stearate catalyst in isooctane at 70°C for 24 h. For further study, the amount of TBHP was utilized in the range of 0-18 mmol and the results are shown in Table 3.10.

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Table 3.10 Effect of the amount of TBHP on the oxidation of 1-methylcyclohexene (**6**) catalyzed by chromium(III) stearate

Entry	TBHP (mmol)	Product (mmol)		Selectivity (**8**/**7**)
		7	**8**	
1	0	0.25	0.40	1.60
2	9	0.41	1.76	4.29
3	12	0.28	1.44	5.14
4	15	0.24	1.39	5.79
5	18	0.19	1.38	7.26

Reaction conditions: 1-methylcyclohexene (**6**) (5 mmol), chromium(III) stearate (0.20 mmol), isooctane (5 mL), TBHP (0-18 mmol) at 70°C for 24 h.

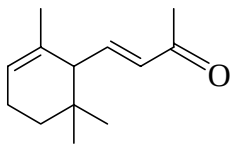
6: 1-methylcyclohexene**, 7**: 2-methyl-2-cyclohexenone, **8**: 3-methyl-2-cyclohexenone

From Table 3.10, when the amount of TBHP was increased, the better selectivity of **8**/**7** was lucidly observed. With 18 mmol of TBHP, the best selectivity of the desired products **8**/**7** ~7 and good yield of products (1.38 mmol) were gained. Compared with using 9 mmol of TBHP, the highest yield of the desired products (1.76 mmol) with good selectivity **8**/**7** ~4 was accomplished.

Furthermore, the site of allylic oxidation being taken place was believed to depend upon the stability and steric accessibility of the carbon radical center and the rate of recombination of the carbon radical with the methyl-bound oxygen.

3.3.3 Optimum conditions for the allylic oxidation of α-ionone (**9**)

Racemic (±)-α-ionone (**9**) and β-ionone (**11**) are important materials in the fragrance industry. In addition, the related materials of **9** include many compounds, which show bioactivity whereas **11** are important as a starting material for the synthesis of abscistic acid [55].



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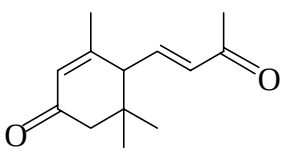

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3.3.3.1 Effect of the amount of oxidants.

The effect of the amount of oxidants on the allylic oxidation of α-ionone (**9**) under air atmosphere at 70°C for 24 h using isooctane as a solvent was investigated. The results are presented in Table 3.11.

Table 3.11 Effect of the amount of TBHP on α-ionone (**9**) oxidation catalyzed by chromium(III) stearate

Entry	TBHP (mmol)	Product (mmol)
		10
1	0	0.10
2	9	2.06
3	12	1.48
4	15	1.19
5	18	1.12

Reaction conditions: α-ionone (**9**) (5 mmol), chromium(III) stearate (0.20 mmol), isooctane (5 mL), TBHP (0-18 mmol) at 70°C for 24 h.

9: α-ionone, **10**: 3-oxo-α-ionone

From Table 3.11, it was observed that the amount of TBHP was the important factor to control the yield of the desired product. When TBHP 9 mmol was used, the reaction provided the highest yield of products (~41%) selectively. In addition, when the amount of TBHP was increased from 9 to 18 mmol, the yield of product was decreased. It might be explained that the reaction was oxidized to rearranged product, which could not detect by gas chromatography**.**

The identity of 3-oxo-α-ionone (**10**) was confirmed by ^{1}H and ^{13}C-NMR. The ^{1}H-NMR spectrum of 3-oxo-α-ionone (Fig 3.7) exhibited three olefin protons as double doublet, doublet and singlet signals at δ 6.70 (J = 15.7, 9.5 Hz), 6.21 (J = 15.7 Hz) and 6.00, respectively. The doublet signal of one proton at δ 2.70 (J = 9.5 Hz) was assigned as methine proton connecting two alkene groups. Two doublet signals of one methylene proton were visualized at δ 2.40 (J = 16.9 Hz) and 2.14 (J = 16.9 Hz). Four singlet signals of twelve protons at δ 2.30, 1.92, 1.09 and 1.02 were ascribed as four methyl groups. For ^{13}C-NMR spectrum as presented in Fig 3.8, the signal at δ 198.0 was belonged to a carbonyl carbon and at δ 130.0-160.0 for four signals of olefinic carbons.

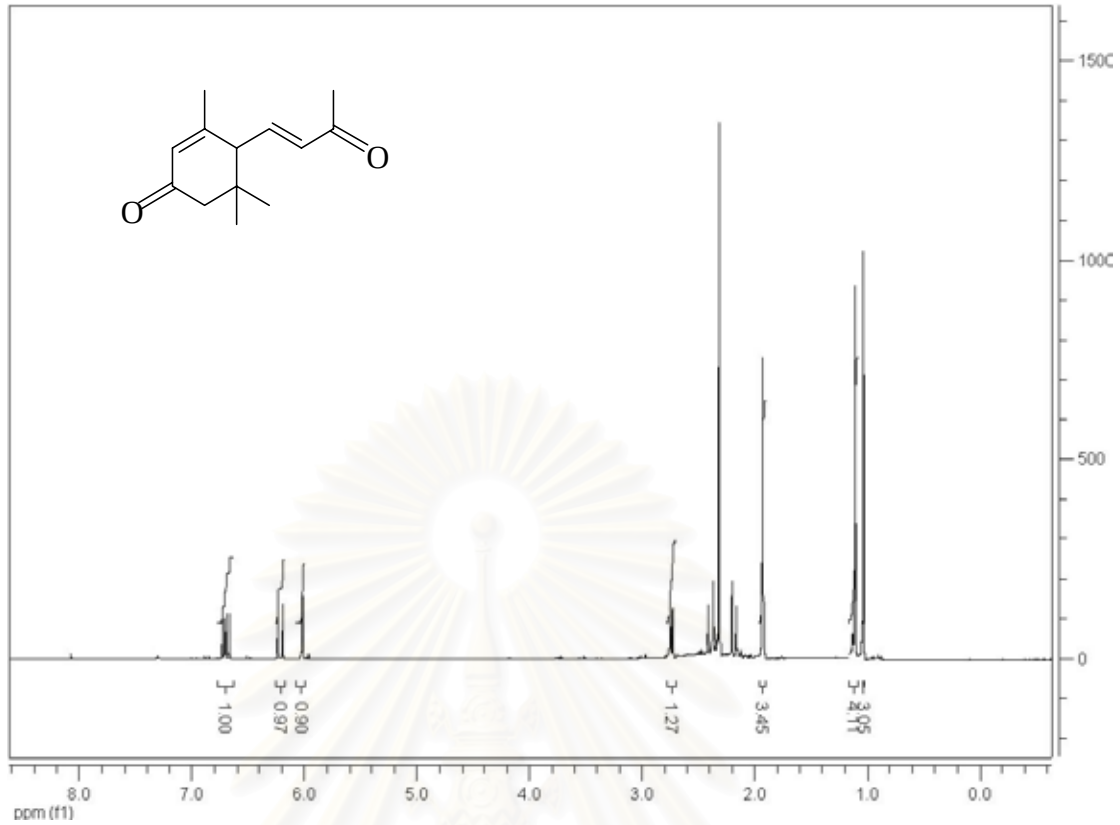

Figure 3.7 The ^{1}H-NMR spectrum of 3-oxo-α- ionone (**10**)

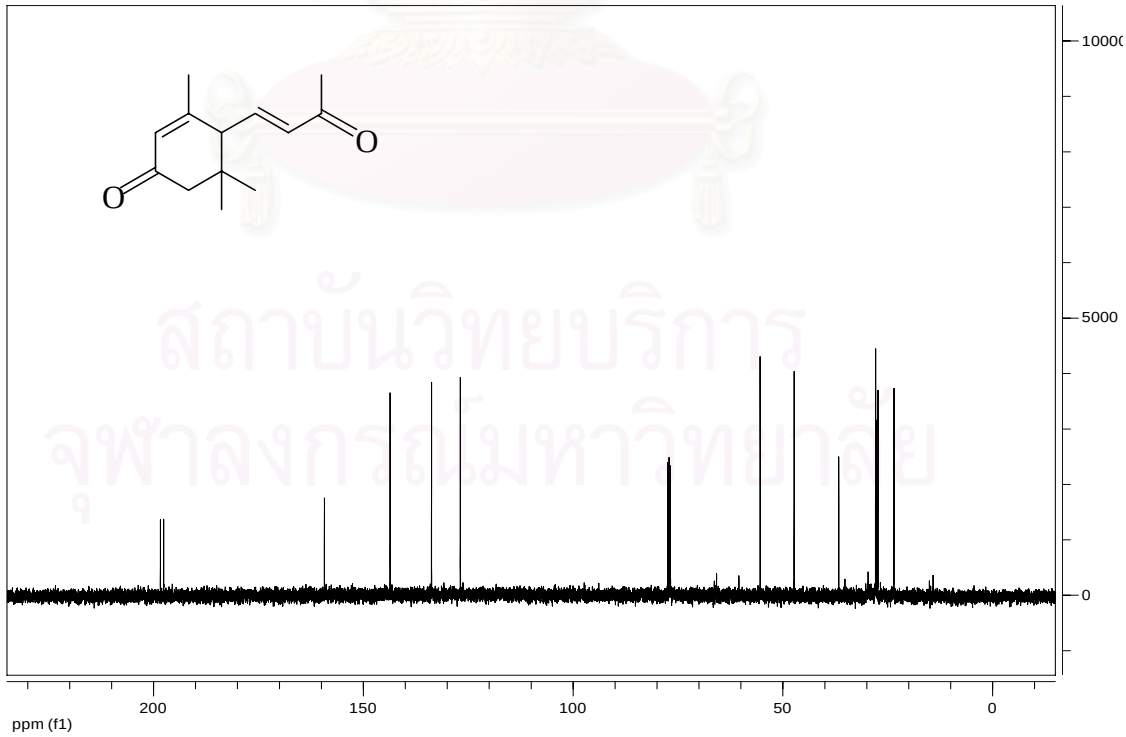

Figure 3.8 The ^{13}C-NMR spectrum of 3-oxo-α- ionone (**10**)

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3.3.4 Optimum conditions for the allylic oxidation of β-ionone (**11**)

3.3.4.1 Effect of the amount of oxidants.

From previous studies, the amount of TBHP had the crucial effect for allylic oxidation. The effect of the amount of TBHP on allylic oxidation of β-ionone (**11**) was investigated and the results are displayed in Table 3.12.

11 **12**

Table 3.12 Effect of the amount of TBHP on β-ionone (**11**) oxidation catalyzed by chromium(III) stearate

Entry	TBHP (mmol)	Product (mmol)
		12
1	0	0.04
2	9	0.81
3	12	0.65
4	15	0.55
5	18	0.46

Reaction conditions: β-ionone (**12**) (5 mmol), chromium(III) stearate (0.20 mmol), isooctane (5 mL), TBHP (0-18 mmol) at 70°C for 24 h.

11: β-ionone, **12:** 4-oxo-β-ionone

From Table 3.12, it was found that β-ionone was oxidized to ketone **12** selectively. Increasing the amount of TBHP from 9 to 15 mmol provided the lower yield of desired product. Surprisingly when TBHP 9 mmol was used, the highest yield of the desired product was attained. This implied that the reaction should carry out with 9 mmol of TBHP.

The structure of the desired product, 4-oxo-β-ionone (**12**) was identified by ^{1}H- and ^{13}C-NMR spectra. The ^{1}H-NMR spectrum of 4-oxo-β-ionone (Fig 3.9) displayed two doublet signals of one methylene proton were visualized at δ 7.25 (J = 16.5 Hz) and 6.20 (J = 16.5 Hz). Triplet signals of two protons at δ 2.53 (J = 6.7 Hz

were assigned as CH_2 as adjacent carbonyl group. A singlet signal of methyl proton was displayed at δ 2.35. At δ 1.89 (J = 7.0 Hz) exhibited triplet signals of methyl protons. Three singlet signals of nine protons at δ 1.79, 1.24 and 1.18 were ascribed as three methyl groups. Moreover, the ^{13}C-NMR spectrum of 4-oxo-β-ionone (Fig 3.10) exhibited the carbonyl carbon at δ 198.7 and δ ~130.0-160.0 for olefinic carbons.

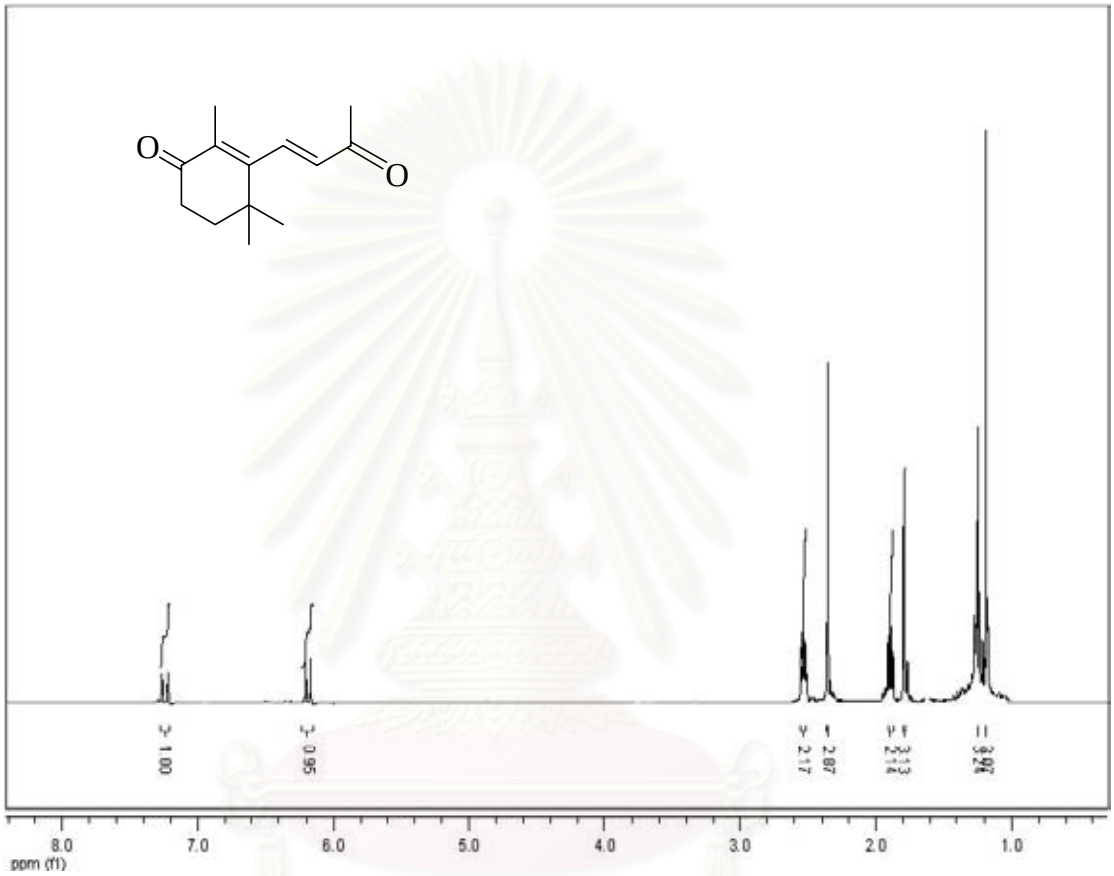

Figure 3.9 The ^{1}H-NMR spectrum of 4-oxo-β- ionone (**12**)

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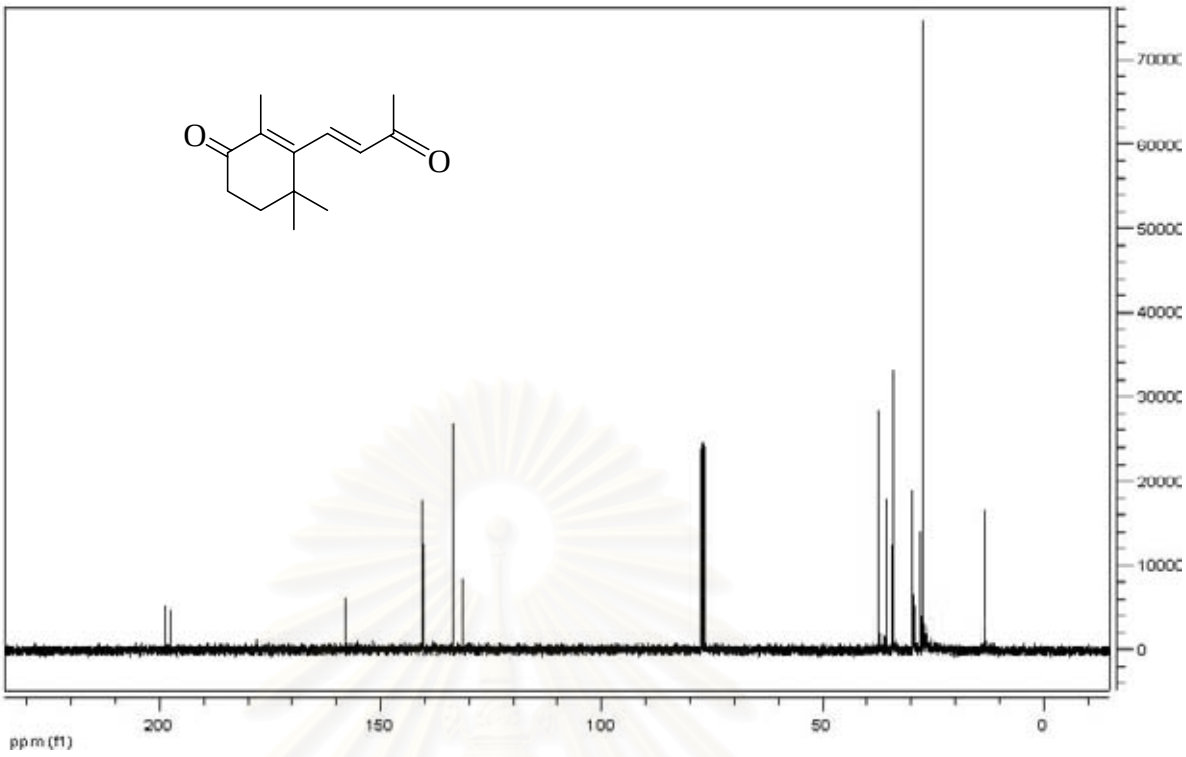
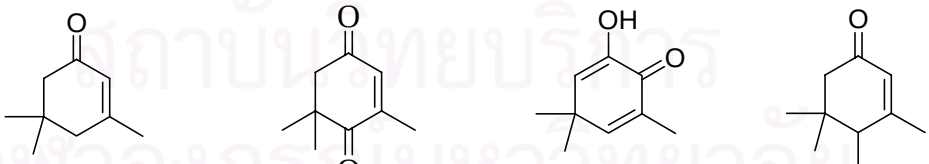


Figure 3.10 The ^{13}C-NMR spectrum of 4-oxo-β- ionone (**12**)

3.3.5 Optimum conditions for the allylic oxidation of isophorone (**13**)

Transition metal complexes have been found to be effective catalysts for the selective oxidation of cyclic olefins under mild conditions, such as the oxidation of α-isophorone (α-IP) (**13**) to ketoisophorone (KIP) (**14**), an important reaction for application in industries. Oxidation of α-IP (**13**) gave mainly KIP (**14**) as the major product along with small amount of side products **15** and **16** [56]**.**



13 **14** **15** **16**

15 = 4,4,6-Trimethyl-2-hydroxy-cyclohex-2,3-dien-1-one

16 = 3,5,5-Trimethyl-4-hydroxy-cyclohex-2-en-1-one

KIP(**14**) is used as a building block for the synthesis in terpene chemistry and for producing precursors of vitamin A, E series, carotenoids and as an intermediate

for the preparation of various flavoring and fragrance fine chemicals [56]. Many conventional oxidation routes have been described in literature to prepare **1**4 *via* the oxidation of **13** or β-isophorone. However, systematic studies involving kinetics of metal complexes catalyzed oxidation of β-isophorone to **14** under homogeneous conditions has not been reported in the literature. Compared with previous literature cited, Murphy and co-workers reported that the oxidation of α-isophorone (**13**) mediated by transition metal salts (Cr, Mn, Fe, Co, Cu) at more moderated temperatures in the presence of pyridine and H_2O_2 afforded moderated yields of KIP (**14**) [49]. Murphy and co-workers reported the allylic oxidation of **13** catalyzed by $Cr(acac)_3$ with DMSO/$KOBu^t$ at 115°C for 24 h, provided **14** 45.2 % yield [56].

These preliminarily attractive results prompted for further investigation of this oxidation reaction.

3.3.5.1 Effect of the amount of oxidants.

Utilizing the amount of oxidants is particularly attractive for allylic oxidation of isophorone (**13**). The amount of oxidants was varied from 0-18 mmol. The results are presented in Table 3.13.

Table 3.13 Effect of the amount of TBHP on isophorone (**13**) oxidation catalyzed by chromium(III) stearate

Entry	TBHP (mmol)	Product (mmol)
		14
1	0	0.01
2	9	0.98
3	12	1.00
4	15	1.04
5	18	1.48

Reaction conditions: isophorone (**13**) (5 mmol), chromium(III) stearate (0.20 mmol), isooctane (5 mL), TBHP (0-18 mmol) at 70°C for 24 h.

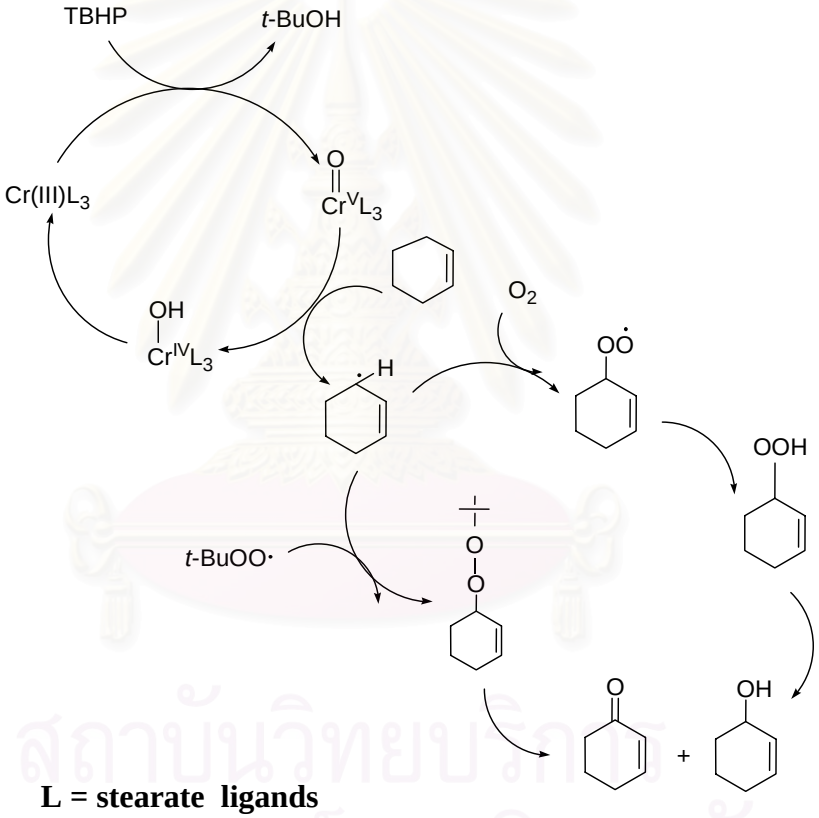
13: isophorone, **14**: ketoisophorone

From Table 3.13, KIP (**14**) was identified and quantified by GC, by comparison with authentic sample. The amount of the desired product increased, when the amount of TBHP was increased. When 18 mmol of TBHP was used, the

reaction furnished only ketoisophrone **(14)** and it gave the desired product in high yield (~30%) with the excellent selectivitiy.

3.4 Proposed mechanism for allylic oxidation of alkenes catalyzed by chromium(III) stearate using TBHP

The allylic oxidation of alkenes can furnish carbonyl compounds (ketone and/or alcohol). The reaction was believed to proceed *via* allylic proton abstraction by radical species from cleavage of TBHP catalyzed by chromium(III) complexes. The mechanism for allylic oxidation of cyclohexene catalyzed by chromium(III) stearate was proposed as shown in Scheme 3.1.



L = stearate ligands

Scheme 3.1 Proposed mechanism for allylic oxidation of cyclohexene catalyzed by chromium(III) stearate

From the proposed mechanism of allylic oxidation, cyclohexene was transformed to the desired products (cyclohexenone, cyclohexenol and cyclohexene oxide) *via* two pathways. The first one occurred from the addition of *t*-BuOO• to cyclohexene to give the intermediate and subsequently provided cyclohexene oxide as a major product. The second pathway involving the abstraction at allylic position to yield allylic radical which could react with *t*-BuOO• to give peroxide as an intermediate and finally it could decompose to cyclohexenone and cyclohexenol (Scheme 3.1). However, allylic radical could rapidly react with O_2 to give hydroperoxyl radical intermediate and subsequently transform to relatively not stable allylic hydroperoxide. The decomposition of allylic hydroperoxide (cyclohexenyl hydroperoxide) eventually yielded cyclohexenone and cyclohexenol.

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CHAPTER IV

CONCLUSION

One of the most important current topics of catalysis research is to find an efficient catalyst for allylic oxidation of alkenes to various organic molecules under mild condition. This research focuses on the use of transition metal complexes as homogeneous catalyst for allylic oxidation of alkenes.

The allylic oxidation of cyclohexene using TBHP as the oxidant with eight metal stearate catalysts, such as chromium(III), nickel(II), cobalt(II), copper(II), manganese(II), iron(III), zinc(II) and oxovanadium(IV) stearate was conducted. The most appropriate conditions were chromium(III) stearate 0.2 mmol, 70% TBHP 9.0 mmol and reaction time of 24 h at 70°C. Kinetic study, the half life of cyclohexene in oxidation reaction under optimized condition was approximately 9 h. The optimum conditions attained was further applied to various allylic alkenes including α-pinene, 1-methylcyclohexene, α-ionone, β-ionone and isophorone.

The allylic oxidation catalyzed by chromium(III) stearate catalysts for various alkenes for example α-pinene, 1-methylcyclohexene, α-ionone, β-ionone and isophorone provided verbenone, 3-methyl-2-cyclohexenone, 3-oxo-α-ionone, 4-oxo-β-ionone and ketoisophorone, respectively in moderate yield with excellent selectivities.

The mechanism for the allylic oxidation of alkenes catalyzed by chromium(III) stearate using TBHP was proposed. This involved the abstraction at allylic position to yield allylic radical which could react with *t*-BuOO• to give peroxide as an intermediate and finally decomposed to ketone and alcohol.

Suggestion for the future work

From the overall studies, the allylic oxidation of alkenes catalyzed by chromium(III) stearate could be applied in the large scale for chemical industry. The variety of alkenes, particularly those containing sensitive functional groups are still required for further investigation to observe the scope of this developed allylic oxidation reaction.

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