POTASSIUM PERMANGANATE/ CARBOXYLIC ACID/ ORGANIC SOLVENT: A POWERFUL REAGENT FOR C-C BOND FORMATION, ARYL COUPLING REACTIONS AND ENONE OXIDATION

IPSO-NITRATION OF ARYLBORONIC ACIDS WITH SILVER NITRITE/ TMSCl

A THESIS SUBMITTED TO
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HAMİDE FINDIK

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ABSTRACT

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IPSO-NITRATION OF ARYLBORONIC ACIDS WITH SILVER NITRITE/ TMSCl

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The first part of the thesis presents the $KMnO_4$/ carboxylic acid/ organic solvent which is a powerful reagent for C-C bond formation, aryl coupling reactions and enone oxidation. The α′-acetoxylation of enones and the α-acetoxylation of aromatic ketones were carried out with potassium permanganate and acetic acid, in which acetoxylation products were obtained in 74-96% yields. The same reaction was carried out with carboxylic acids other than acetic acid, which furnished corresponding acyloxy ketones with the same regioselectivity. For the first time, formyloxylation products were synthesized in a 61-85% yield by using formic acid. The potassium permanganate and acetic acid method was also used for aryl coupling reactions. The reaction of arylboronic acids and aryl hydrazines in benzene with potassium permanganate and acetic acid in turn furnished biaryls in a 85-96% yield.

We showed that potassium permanganate/carboxylic acid/organic solvent behaves as manganese(III) acetate.

In the second part of the thesis, ipso-nitration of arylboronic acids with $AgNO_2$/ TMSCl was performed. Nitration of aromatic compounds is one of the most extensively studied reactions, and nitroaryl moieties play key roles in the physical and chemical properties of many target molecules in organic synthesis. For electrophilic nitration of aromatic compounds, a wide variety of reagents are available to date. Most of them are very strong nitrating agents and often lead to further nitration and mixture of isomers. Since most nitrating agents are oxidants, oxidation of other functional groups can also occur, giving a mixture of products. Thus, a search for milder and selective nitrating agents is a good research goal. In this work, we aimed to apply $AgNO_2$/ TMSCl system to ipso nitration of arylboronic acids.

Keywords: Manganese (III) acetate, α'-acetoxylation, enones, biaryl compounds, dihydrofurane derivatives, arylboronic acids, ipso-nitration

ÖZ

POTASYUM PERMANGANAT/ KARBOKSİLİK ASİT/ ORGANİK ÇÖZÜCÜ: C-C BAĞ OLUŞUMU, BİARİL REAKSİYONLARI VE ENONLARIN OKSİDASYONU İÇİN GÜÇLÜ BİR REAKTİF

ARİLBORONİK ASİTLERİN GÜMÜŞ NİTRİT/ TMSCl İLE İPSO-NİTRASYONU

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Tez Yöneticisi: Prof. Dr. Ayhan S. Demir

Şubat 2009, 122 sayfa

Bu tezin birinci bölümü C-C bağ oluşumu, aril birleşme reaksiyonları ve enon oksitlenmelerinde güçlü bir reaktif olan $KMnO_4$/ karboksilik asit/ organik çözücü sistemiyle yapılan çalışmaları kapsamaktadır. Enonların α'- asetoksillenmeleri ve aromatik ketonların α-asetoksillenmeleri potasyum permanganat ve asetik asitle gerçekleştirilmiş ve asetoksilleme ürünleri %74-96 verimle elde edilmişlerdir. Aynı reaksiyon asetik asit yerine diğer karboksilik asitlerle de denenmiş ve ilgili asiloksi ketonlar aynı seçicilikle elde edilmişlerdir. Literatürde ilk kez, formik asit kullanılarak formilasyon ürünleri %61-85 verimlerle sentezlenmişlerdir. Potasyum permanganat ve asetik asit metodu biaril oluşma reaksiyonlarında da kullanılmıştır. Aril boronik asitler ve aril hidrazinler benzen içerisinde potasyum permanganat ve asetik asitle reaksiyona sokulduğunda biariller % 85-96 verimle elde edilmişlerdir. Çalışmalarımız potasyum permanganat/ karboksilik asit/ organik çözücü sisteminin Mangan(III) asetat eşdeğeri olarak davrandığını göstermiştir.

Tezin ikinci bölümünde, $AgNO_2$/TMSCl varlığında aril boronik asitlerin ipso nitrolanması gerçekleştirilmiştir. Aromatik bileşiklerin nitrolanması üzerinde çok çalışılan bir reaksiyondur ve nitroaril grubu organik sentezdeki birçok hedef molekülün fiziksel ve kimyasal özelliklerinde büyük rol oynamaktadır. Aromatik bileşiklerin elektrofilik nitrolanması için çok geniş çeşitlilikte reaktif bulunabilmektedir. Bunların birçoğu çok güçlü nitrolama ajanlarıdır ve daha ileri nitrolanmaya ve izomer karışımlarına sebebiyet vermektedirler. Çoğu nitrolama ajanları yükseltgeyici olduklarından, diğer fonksiyonel grupların oksidasyonları da gerçekleşebilmekte ve birden çok ürün oluşumuna sebep olmaktadır. Bu nedenle, daha ılımlı ve seçici nitrolama ajanlarının bulunması iyi bir araştırma konusudur. Bu çalışmada, $AgNO_2$/ TMSCl sistemi arilboronik asitlerin ipso-nitrolanmasında uygulanmış ve nitro bileşikleri yüksek verimlerle elde edilmişler. Böylece yeni alternatif bir nitrolama yöntemi geliştirilmiştir.

Anahtar kelimeler: Mangan (III) asetat, α'-asetoksilasyonu, enonlar, biaril bileşikler, dihidrofuran türevleri, aril boronik asitler, ipso-nitrolama.

To My Family,

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TABLE OF CONTENTS

LIST OF TABLES

TABLES

LIST OF FIGURES

FIGURES

CHAPTER 1

INTRODUCTION

1.1. Metal Oxidants in Organic Chemistry

In the past two decades, the elaboration of redox methods for the generation of radicals by the help of transition metal salts and their oxides has become a powerful impulse for the development of free-radical chemistry. The reactions, mediated by Mn^{3+}, Co^{3+}, Cu^{2+}, Fe^{3+}, Ag^{2+}, Pb^{4+}, Ce^{4+}, Mn^{4+}, V^{5+}, Ag^{+}, Cu^{+}, Fe^{2+}, and Cr^{2+} are the most widely explored[1-5]. In comparison with traditional methods of radical generation[3,5,6], redox initiators demonstrate remarkable regioselectivity, especially efficient with polyfunctional organic compounds. Furthermore, new types of radicals, unachievable by traditional approaches, may be successfully generated. The main difference is the dual role that the metal oxidants play in the reactions: first, one-electron oxidation of a carbonyl compound, producing an educt radical and, second, the oxidative interaction with the intermediate adduct radical, formed by addition of educt radical to the substrate. This is why the synthetic result of metalmediated reactions significantly differs from that of peroxide- or light-initiated processes. Correspondingly, the terminology used reflects the difference in the essence, i.e. “mediated” or “induced” for metal-participation reactions and “induced” for non-metal, traditional ones.

Manganese (III) acetate occupies a unique place among metal oxidants, the history of which, as an effective mediator for the interaction of unsaturated systems with carbonyl compounds, originates from the Bush and Finkbeiner and Heiba and Dessau

studies[7,8]. In the past three decades, multidimensional extension of this reaction has taken place, providing a number of novel accesses to different classes of organic compounds, as well as bringing an improved understanding of the nature of the process[9].

1.2 Reactions with Manganese (III) Acetate

1.2.1 General Knowledge on Manganese(III) Acetate

An extensive amount of work has been conducted using manganese(III) acetate as an oxidizing agent. Oxidations with manganese(III) acetate can be broadly divided into two classes:

1. Direct inner- or outer-sphere one-electron oxidation of the substrate after formation of an inner- or outer-sphere substrate-Mn(III) complex. Often subsequent oxidation of an intermediate radical is product determining. Numerous examples can be found in oxidations of alcohols, amino- and thiocompounds, carboxylic acids, and certain aromatics.

2. Indirect oxidation of the substrate after formation of an intermediate adduct free radical from interaction of manganese (III) acetate and an enolizable compound and subsequent addition or substitution of this radical to the substrate. Most examples here refer to aromatic substitution and oxidative addition of enolizable compounds to unsaturated systems.

The essential sequence of addition reactions of compounds, mostly bearing a hydrogen atom alpha to a carbonyl group, to olefinic and aromatic unsaturated systems in the presence of manganese (III) acetate is given in Figure 1.1.

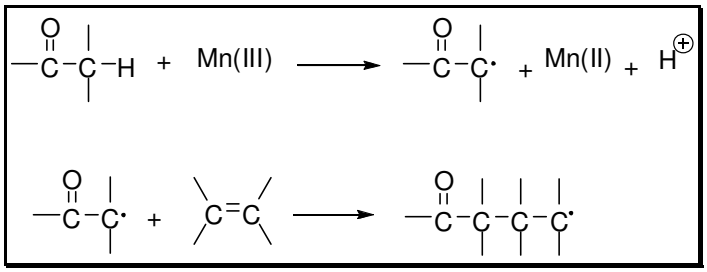


Figure 1.1. Addition reaction to olefinic systems in the presence of manganese (III) acetate

The fate of the primary adduct radical strongly depends on reaction conditions and the nature of the substrate. Substances that are less reactive to common oxidants are more interesting since here the unique properties of manganese (III) acetate as a free radical generator can be more fully exploited. Mn(III) bears many similarities with respect to a given substrate class with other one-electron oxidants like Co(III), Ce(IV), and some two-electron oxidants like Tl(III) and Pb(IV). It is often observed that owing to its lower reactivity, higher selectivities can be obtained with manganese (III) acetate as compared with other oxidizing agents. Many of these reactions proceed according to the simplified scheme shown below (Figure 1.2).

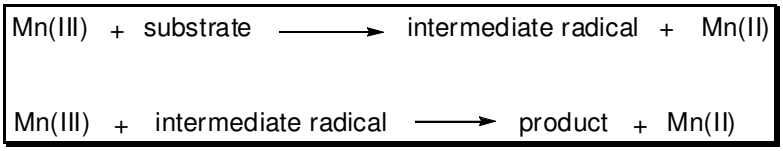


Figure 1.2. General reaction pattern for indirect oxidation mechanism of manganese (III) acetate

Complications may arise in the presence of water since water induces disproportionation of trivalent manganese into Mn(IV) and Mn(II) and alternative two-electron oxidations by Mn(IV) may take place[2].

1.2.2. Synthesis and Properties of Manganese (III) Acetate

Although a great amount of work has been done using manganese (III) acetate as an oxidizing agent, relatively little is known of the compound itself. Basically two forms are to be distinguished:

1. The hydrated form, which conforms with a molecular Formula $Mn(OAc)_3.2H_2O$, color cinnamon brown, easy to prepare reproducibly.
2. The anhydrous form, color dark brown, difficult to prepare reproducibly, molecular formula variable.

Since many oxidations with manganese (III) species are known to be influenced by small amounts of water, the latter form is preferred by many workers, especially for kinetic work. Moreover, small amounts of water cause disproportionation of Mn(III) acetate in glacial acetic acid. In acetic acid-water mixtures containing large amounts of water, manganese (III) acetate hydrolyzes slowly to mixtures $Mn(OH)_3$ and MnO_2. Both the hydrated and anhydrous forms have been made in various ways[10]. Many workers introduced special modifications, which certainly have affected the chemical composition and reactivity of the anhydrous form. In Table 1, the most important routes to manganese (III) acetate are given.

Table1. Routes to Manganese (III) Acetate

Reactants	**Oxidizing agent**	**Product**	**Reference**
$Mn(OAc)_2.4H_2O$, HOAc	$KMnO_4$	Dihydrate	11,12
$Mn(NO_3)_2.6H_2O$, Ac_2O	HNO_3	Anhydrous	13,14
$Mn(OAc)_2$, HOAc, Ac_2O	$KMnO_4$	Anhydrous	15-17
$Mn(OAc)_2$	O_3	Anhydrous	16
$Mn(OAc)_2.4\ H_2O$	Anodic oxidation	Dihydrate	18
$Mn(OAc)_2.4\ H_2O$	Cl_2	Dihydrate	19
$Mn(OAc)_2$, Et_3N, HOAc	O_2	Dihydrate	20
$Mn(OAc)_2$, ketone	O_2	Anhydrous	21

The solubility of manganese (III) acetate in acetic acid depends on the synthetic procedure used and the water content of the acetic acid. The compound should be dissolved by gentle heating. Table 2 gives some pertinent results.

Table 2. Solubility of Manganese (III) Acetate in Acetic Acid-Water Mixtures

Manganese (III) Acetate	HOAc	g/L dissolved (^{o}C)	Reference
Anhydrous	100%	10 (25)	15
Anhydrous	100%	3 (25)	16
Anhydrous	98%	150 (25)	16
Anhydrous	90%	Zero	16
Dihydrate	100%	160 (25)	16
Dihydrate	99%	Very low	16

Since the dihydrate dissolves poorly in water containing acetic acid, the anhydrous form is soluble in such systems only in a very limited range.

1.2.3. Anhydrous Manganese (III) Acetate

Synthesis and chemical constitution of Manganese (III) acetate is studied in detail by Hessel *et. al.*[16]. It was found that the chemical constitution of anhydrous manganese (III) acetate conforms to the experimental formula $Mn_3(CH_3COO)_8OH$ or $[Mn_3O(CH_3COO)_6.CH_3COO)^{-}$. When the compound is properly washed and recrystallized, this empirical formula is independent of the chemical route followed, viz., oxidation with $KMnO_4$, Pb(IV) acetate or O_3 of manganese (II) acetate or treating $Mn(NO_3)_2.6H_2O$ with acetic anhydride. In the literature treated by Hessel and also in later work, the anhydrous form is usually indicated as $Mn(OAc)_3$. This is certainly erroneous and mostly due to improper analytical procedures. A disadvantage of Hessel's purification method is that the anhydrous manganese (III) acetate is treated with water. The route developed by Vaerman[21], although claiming the production of $Mn(OAc)_3$, in fact produces acetic acid-formic acid mixed complexes of Mn(III) when acetone is used as a ketone. Formic acid formed by the

autooxidation from the ketone, is bound by both Mn(II) and Mn(III) acetate. These mixed acetate-formate complexes are less soluble in the medium used than manganese (III) acetate proper.

The crystal structure of anhydrous manganese (III) acetate was studied by Hessel and Romers[16-21]. These authors assume a linear polymer with empirical Formula $[Mn_3O(OAc)_6.AcOH.OAc]_n$. In the monomer unit, three manganese are connected by three pairs of acetate bridges and form an equilateral triangle with an oxygen atom in its center. Acetic acid molecules and acetate bridges between the monomer units complete the distorted octahedral coordination of the manganese atoms. In solution, a molecular weight of 640±75 is found[16] and as best representation the following structure is proposed:

$$[Mn_3O(OAc)_6.3AcOH]^+ [OAc]^-$$

Here the octahedral coordination of the manganese atoms in the trinuclear complex is completed by three acetic acid molecules. Anhydrous manganese (III) acetate dissolves slowly in most solvents at room temperature. It can be dissolved in many solvents without appreciable reduction by gentle warming. Examples are ethanol, pyridine, and to some extent benzene and chloroform. It reacts at relatively low temperatures (70^oC) with enolizable solvents such as acetone or methyl ethyl ketone, but is less reactive with simple esters like ethyl acetate. It is hardly soluble in acetonitrile and petroleum ether and decomposes in water. It exchanges acetate for carboxylic acid when dissolved in such acids[2].

1.2.4. Manganese (III) Acetate Dihydrate

The preparation of manganese (III) acetate dihydrate was first described by Christensen in 1883 and later elaborated in more detail[11,12]. It has been prepared by oxidation of manganese (II) acetate tetrahydrate by potassium permanganate[11,12,23], chlorine[19], and anodic oxidation[18].

The chemical constitution of the dihydrate comes close to $Mn(OAc)_3.2H_2O$. The solubility of the dihydrate in common solvents is similar to that of the anhydrous Form[16,23].

1.2.5. Oxidative Addition Reactions of Acids to Olefinic Unsaturated Systems

One of the more outstanding reactions initiated by manganese (III) acetate found by Bush and Finkbeiner[7] and Heiba and Dessau[8] is the oxidative addition of carboxylic acids to olefins leading to γ-butyrolactones. This reaction has been proven to be generally applicable, as exemplified by many workers, although lactones are not always major products.

Heating the one-electron oxidant $Mn(OAc)_3$ in acetic acid at reflux (115°C) generates the carboxymethyl radical **1**. This adds to alkenes **2** to give a radical **3**, which is oxidized by a second equivalent of $Mn(OAc)_3$ to give a γ-lactone **4** (Figure 1.3).

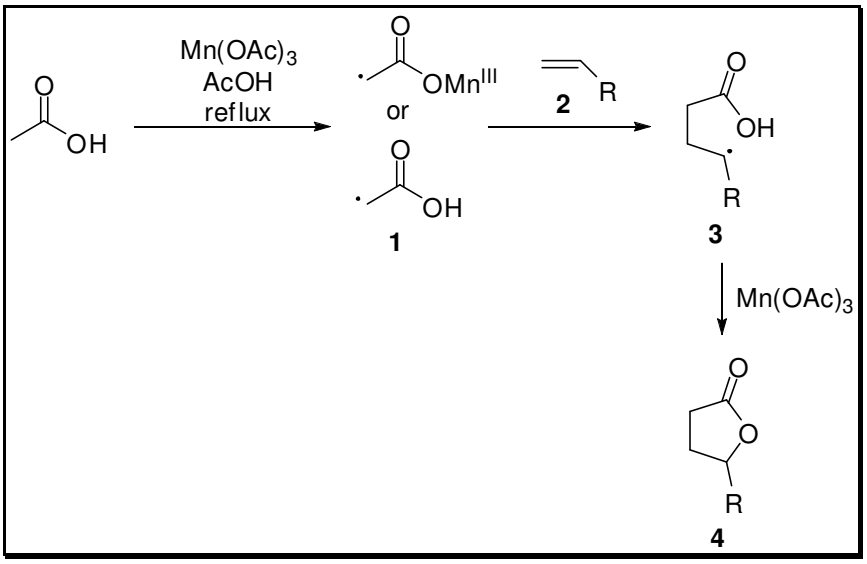


Figure 1.3. Formation of γ-lactones via $Mn(OAc)_3$ oxidation

This sequence of steps generates a radical oxidatively from acetic acid, efficiently forms a carbon-carbon bond, and produces a synthetically useful γ-lactone by oxidation of the carbon-centered radical. Unfortunately, Mn(III)-based oxidative cyclization of unsaturated acids is not possible, since the optimal solvent for this reaction, acetic acid, will be oxidized preferentially[24].

The course of the reaction and the formation of other major products depend largely on the nature of the substrate olefin, reacting acid, and on reaction conditions. There is now general agreement on the mechanism of this reaction together with its main side reactions. The major reactions involved in the Mn(III) acetate initiated addition of acetic acid to an α-olefin in acetic anhydride-acetic acid mixtures are given in figure 1.4 and 1.5[25].

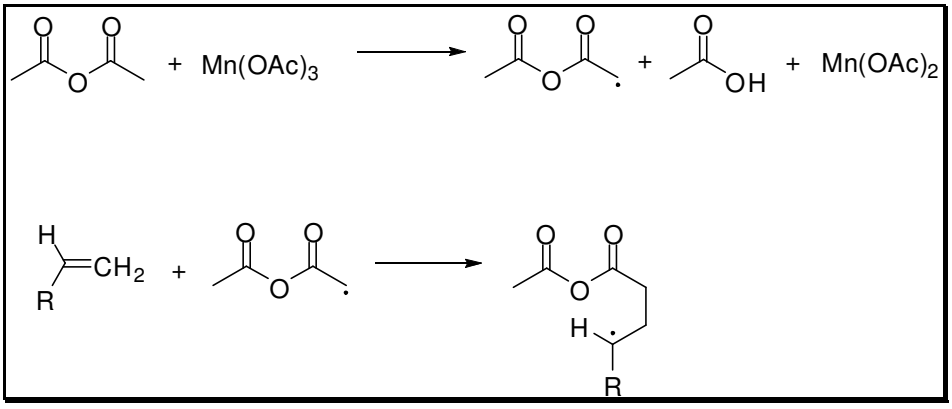


Figure 1.4. Mn(III) acetate initiated addition of acetic anhydride to olefines

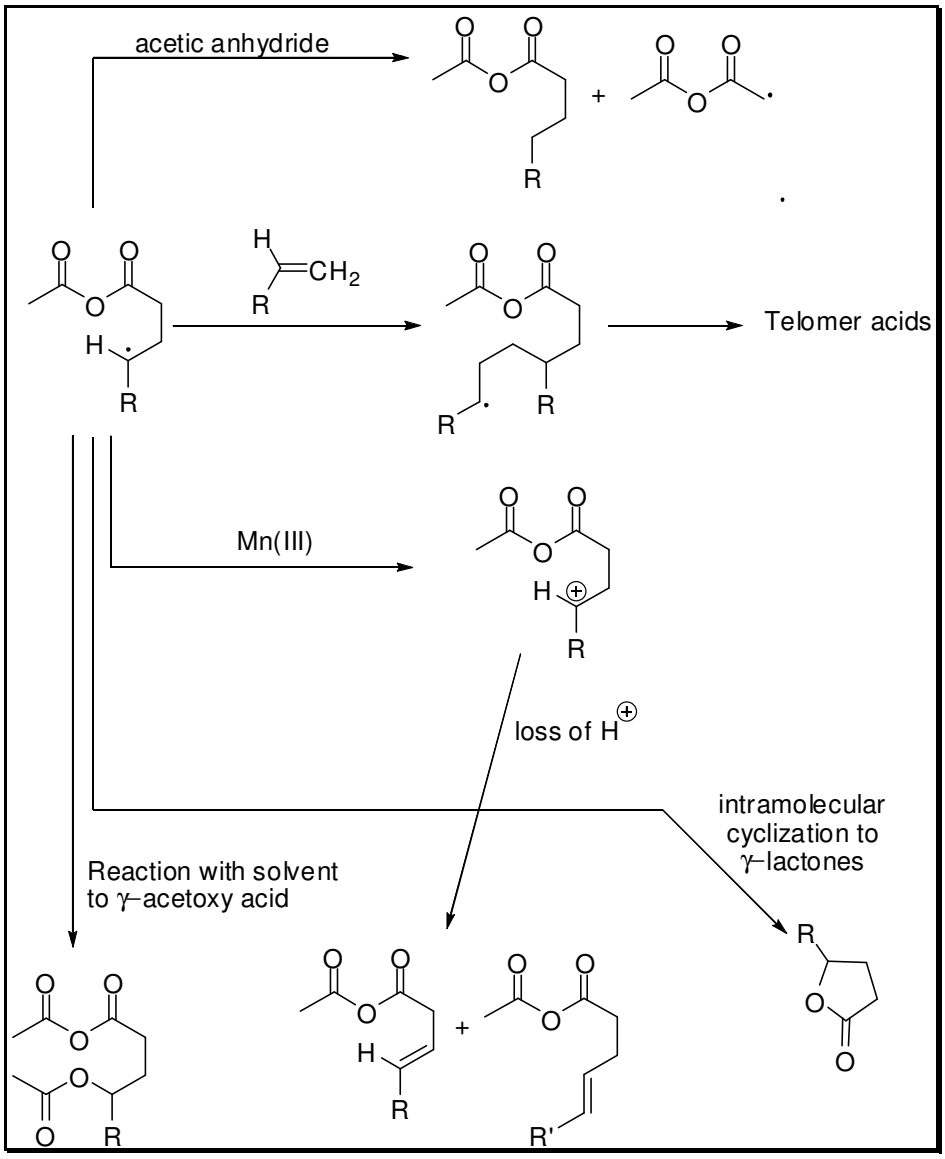


Figure 1.5. Mn(III) acetate initiated addition of acetic acid to an α-olefin in acetic anhydride-acetic acid mixtures

From this mechanistic view, the following basic requirements for oxidative addition can be drawn:

1. Direct generation of carboxyalkyl radicals. In the free acids this is largely limited to acetic, propionic and readily enolizable acids like cyanoacetic acid[26] the major competing reaction being formation of carboxyl radicals

$RCOO^{\cdot}$. In the presence of excess anhydride, carboxyalkyl radical formation is favored and a larger variety of acids can be used[25,27].

2. No oxidation of the primary formed carboxyalkyl radical. In the respect groups, increasing the electron density on carbon α to the carbonyl group increase the propensity of carboxyalkyl oxidation by Mn(III).

3. Rapid addition of the carboxyalkyl radical to the olefin. The reactivity of various olefins towards the carboxymethyl radical was studied by Heiba[26] and is found to be governed by the stability of the intermediate adduct radical and steric considerations. McQuillin and Wood[28] found evidence that some carboxyalkyl radicals may add reversibly to olefins. Slow addition may lead to competing reactions such as allylic hydrogen abstraction.

4. Rapid oxidation of the intermediate adduct radical to carbenium ion **5**. This is favored by a high Mn(III) concentration, high acid concentration, and high acetate concentration. The structure of the carbenium ion will determine whether lactonization or elimination of a proton to form a new unsaturated carboxylic acid will predominate. Moreover, with excess anhydride, formation of γ-acetoxyacid will compete strongly with ring-closure of the anhydride to a γ-lactone.

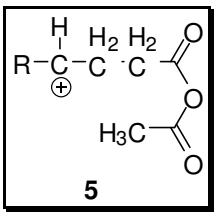


Figure 1.6. Carbenium ion

Also this step is sensitive to small amounts of Cu present, which leads to mixtures of γ- and δ-unsaturated carboxylic acids[29,30]. Low manganese (III)

concentrations may lead to a chain transfer reaction of the intermediate adduct radical with the solvent resulting in saturated carboxylic acids[25,31]. When under these conditions high olefin concentrations are applied, telomer and polymer products are formed[25].

Since so many parameters control effective lactone production, a large variety of reaction conditions is known in the literature. Three main media are put into practice: acetic acid-potassium acetate or sodium acetate mixtures[8]; acetic anhydride-acetic acid mixtures[7]; acetic anhydride-acetic acid-potassium acetate or sodium acetate mixtures[32]. Each may be used in its own right, depending largely on structural constraints of the substrate olefin. Oxidative addition of acetic acid **6** and other acids (notably propionic and cyanoacetic) **7** to simple olefins **8** is given in Figure 1.7 and 1.8 respectively.

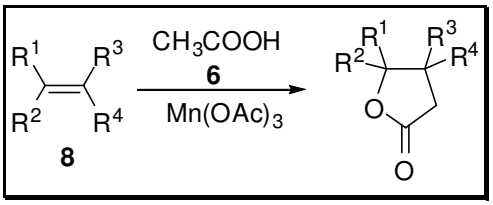


Figure 1.7 Oxidative addition of acetic acid to simple olefins

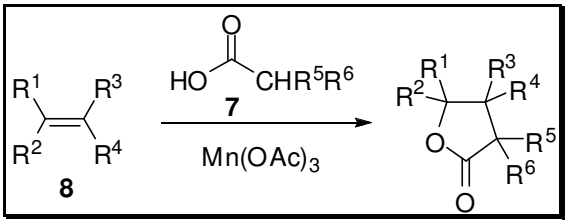
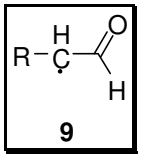


Figure 1.8. Oxidative addition of carboxylic acids to simple olefins

1.2.6. Mn(III) Acetate-Initiated Addition of Aldehydes to Olefinic Unsaturated Systems

Most free radical additions of aldehydes to olefins yield ketones as main products. Thus the peroxide, γ-radiation, and oxygen initiated addition of aldehydes to 1-alkenes provide a convenient method for the synthesis of ketones. The acyl radical R–Ç=O is believed to be formed as an intermediate in these systems. In the presence of manganese (III) acetate, a free radical addition of aldehydes to olefins is also observed. However, depending on reaction conditions, both the expected ketones and rather unexpected aldehydes can be formed. The primary intermediate from the interaction of manganese (III) acetate and the aldehyde is the formylalkyl radical **9** [33].



9

Figure 1.9. Formyloxy radical

Formation of acyl radicals R–Ç=O by chain transfer can be largely suppressed by working at high manganese (III) acetate concentrations and by addition of small amounts of Cu(II) acetate[34]. In the latter case, unsaturated aldehydes are formed. In the absence of polar solvents like acetic acid, manganese (III) acetate concentration is low and ketones are formed in high yields[35,36]. The most important reaction sequences are given in Figure 1.10. Since the formation of ketones is largely suppressed by addition of Cu(II) and at high Mn(III) concentrations, acyl radicals are most probably mainly formed via chain transfer of intermediate adduct radical (compound **10** in Figure 1.10) with aldehyde rather than chain transfer of formylalkyl radicals with aldehyde.

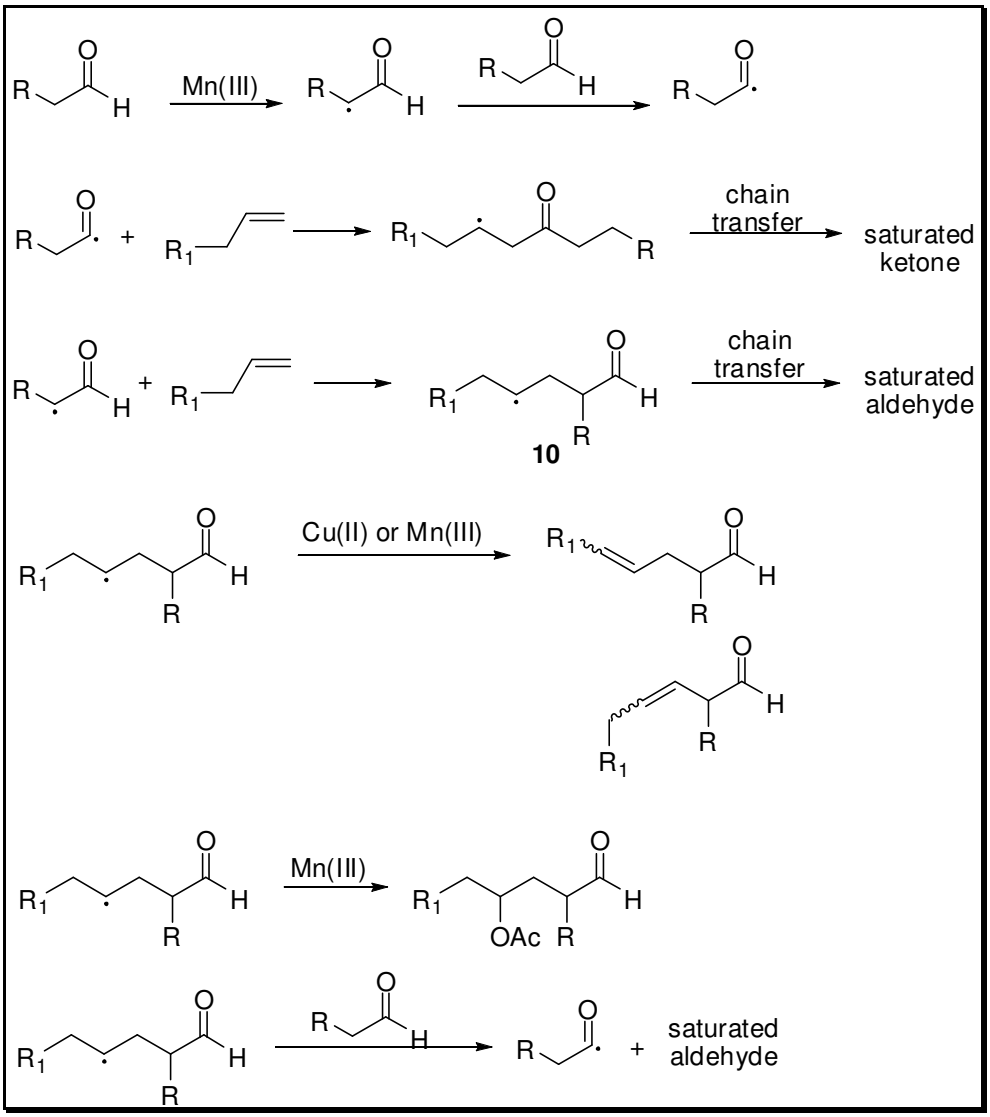


Figure 1.10. Reactions of acyl and formylalkyl radicals

1.2.7. Mn(III) Acetate-Initiated Addition of Ketones to Olefinic Unsaturated Systems

Organic peroxides and γ-radiation have been used to initiate the radical addition of ketones to olefins, although surprisingly little on such reactions is reported in the literature. The one-electron oxidation of enolizable ketones by manganese (III) acetate has offered a new and convenient method for the generation of α-oxo alkyl radicals[37,38] useful in a number of synthetic routes to saturated and unsaturated

ketones, substituted dihydrofurans, tetralones, and diketones. Although yields in most cases are only moderate, this reaction may still be the method of choice when the substrate olefins and ketones are readily available. Reactions have been performed with a great variety of ketones and olefins. The reactions are generally accelerated by addition of acetic acid, although product patterns may change. In the presence of Cu(II) acetate, unsaturated adducts are formed.

1.2.7.1. Formation of Higher Saturated, Unsaturated and Acetoxyketones

In the presence of manganese (III) acetate, simple ketones **11** like acetone, methylethylketone, cyclic ketones, α- and β-diketones like pyruvic ester, and acetylacetone can be added readily to a variety of olefins **12** like α-olefins, styrene, isobutylene, hydroxy-functional olefins, and 1-alkynes. In the absence of added acetic acid, the reaction is relatively slow and yields mainly saturated adducts **13**. When acetic acid is added in low amounts and the reaction is performed at higher temperatures, much of the manganese (III) acetate goes in solution and oxidizes the ketone-adduct radical. Thus under such conditions, large amounts of acetoxyketones **14** will be formed together with unsaturated ketones (Figure 1.11).

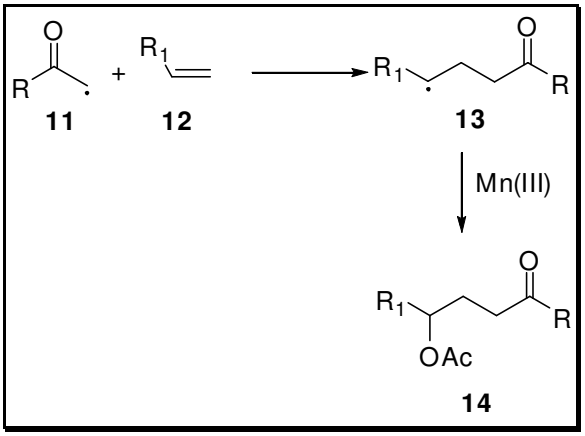


Figure 1.11. Addition of simple ketones to olefins in the presence of manganese (III) acetate

When saturated adducts are the products of choice and a fast reaction is wanted, such reactions can best be performed by slowly adding manganese (III) acetate, to obviate oxidation products, and olefin, to suppress telomerization to the ketone. The effect of the structure of α-oxo-alkyl-radical on rate of addition to unsaturated systems was clearly demonstrated by Vinogradov[39], primary radicals **15** adding more readily on alkenes and alkynes than secondary **16** and tertiary radicals **17**.

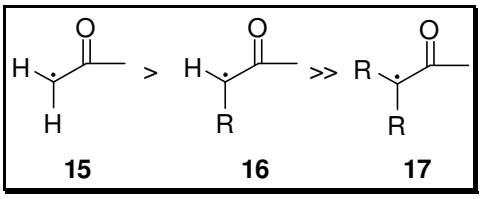


Figure 1.12. Primary, secondary and tertiary radicals

1.2.7.2. Formation of Dihydrofurans

Dihydrofurans may be formed from readily enolizable ketones **18** and olefins **19** in high yield in the presence of manganese (III) acetate. The reaction proceeds via addition of α-oxoalkyl radicals **20** to the olefin, oxidation of the intermediate adduct radical **21** to a carbenium ion **22**, and subsequent cyclization of this carbenium ion to the dihydrofuran **23** (Figure 1.13).

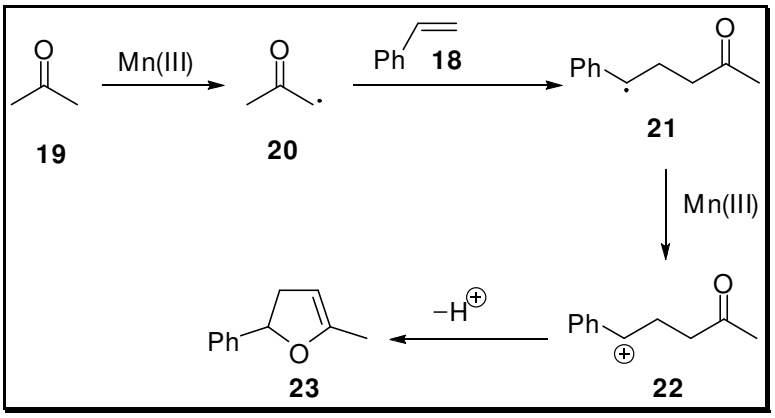


Figure 1.13. Formation of dihydrofurans from readily enolizable ketone **18** and olefin **19** in the presence of manganese (III) acetate

From this scheme, it can be rationalized that higher yields can be obtained with:

1. Readily oxidizable ketones like β-diketones.
2. Olefins with a vinylidene structure like α-methylstyrene and isobutylene.

Side products to be expected from this reaction are:

1. Saturated ketones, obtained by chain transfer from the intermediate adduct radical when this is less readily oxidized.
2. Unsaturated ketones and γ-acetoxy ketones, obtained from the intermediate carbenium ion when ring closure competes with H^+ elimination and acetoxylation by the solvent.

The reaction products with terminal olefins in all cases have consisted of only one isomer. The corresponding reactions of Tl(III) and Pb(IV) acetate have reportedly led to other isomers or mixtures of isomers and probably via ionic mechanisms.

Heiba and Dessau have reported in 1974 that β-keto esters and related dicarbonyl compounds are oxidized to radicals at 25-70°C in acetic acid[24]. The application of Mn(III) to oxidative free-radical cyclizations was investigated initially by Corey, Fristad, and Snider. Corey and Kang have reported the oxidative cyclization of unsaturated β-keto acids in 1984[40]. In 1985, Snider[41] has described the oxidative

cyclization of unsaturated β-keto esters[42] and Fristad has surveyed the cyclization of unsaturated malonic and cyanoacetic acids[43]. For instance, oxidation of ethyl acetoacetate **24** in the presence of styrene **25** affords a dihydrofuran **26** which was reported by Heiba *et.al.* (Figure 1.14)[24].

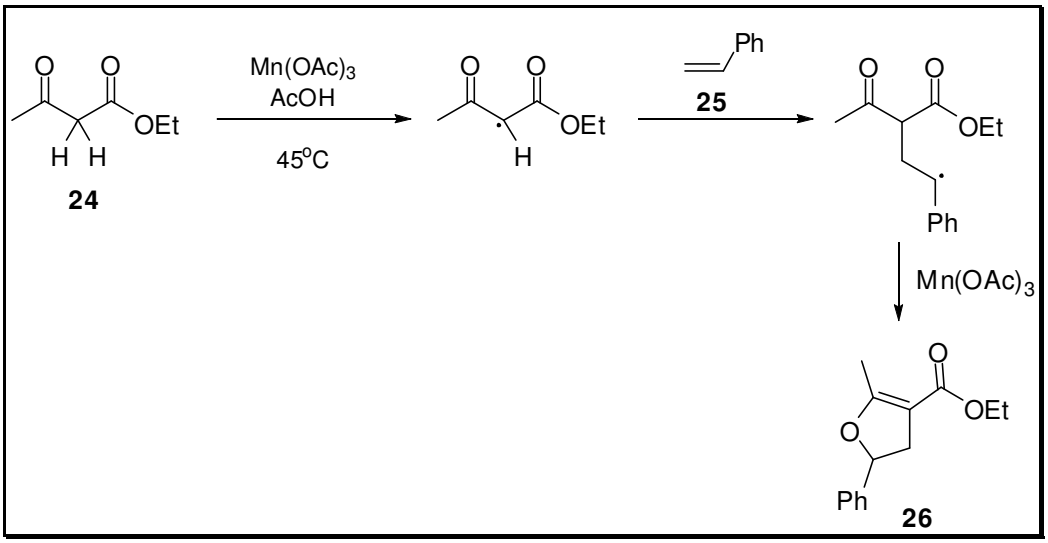


Figure 1.14. Oxidation of ethyl acetoacetate **24** in the presence of styrene **25.**

1.2.7.3. Formation of Tetralones

When an aromatic ketone such as acetophenone **27** is reacted with an olefin **10** in the presence of manganese (III) acetate, α-tetralones **28** can be formed according to Figure 1.15[44].

It follows from this reaction scheme that side products to be expected are:

1. Saturated linear ketones derived from chain transfer of the intermediate adduct radical; these can be suppressed by working at low acetophenone concentrations.
2. Unsaturated linear ketones and linear keto acetates from oxidation of the intermediate adduct radical.

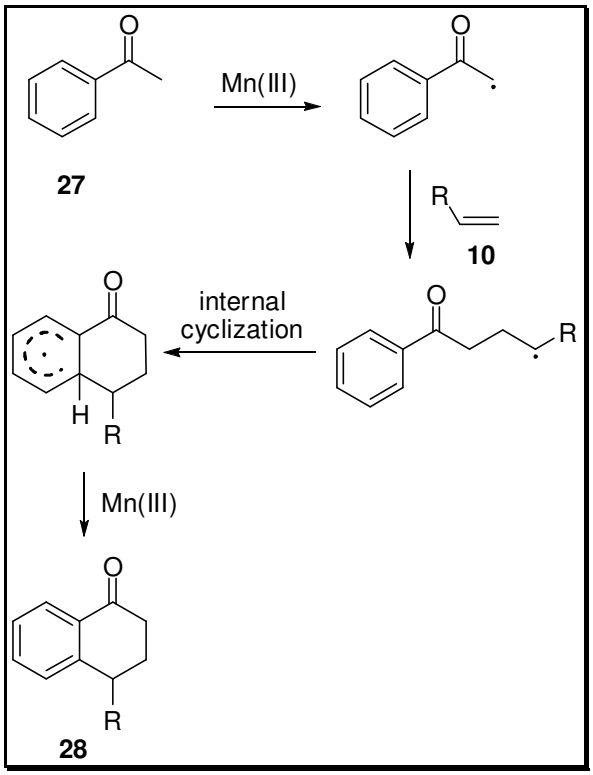


Figure 1.15. Synthesis of α-tetralones from acetophenone **27** and olefin **10** in the presence of manganese (III) acetate

1.2.7.4. Formation of 1,4-Diketones

Enol acetates as unsaturated substrates have been used in reactions with aliphatic[45] and terpenoic[46] ketones, resulting in access to 1,4-diketones, key intermediates in cyclopentenone synthesis.

When a ketone **29** is reacted with isopropenyl acetate **30** in the presence of manganese (III) acetate, the predominant nonpolymeric reaction product formed is a 1,4- diketone **31** according to Figure 1.16 [45].

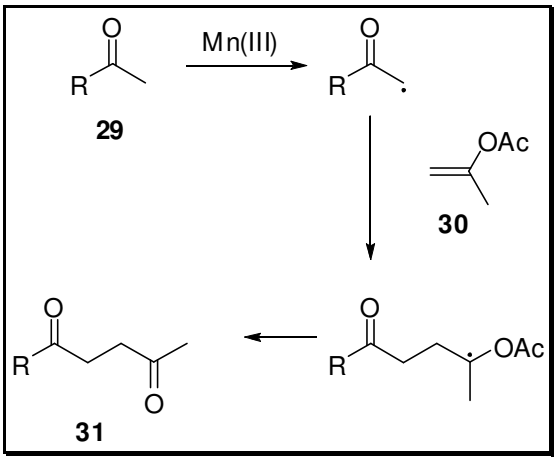


Figure 1.16. Formation of 1,4- diketone **31** via reaction of ketone **29** with isopropenyl acetate **30**

Although yields are only moderate, reportedly due to polymerization of isopropenylacetate, this route offers a single step preparation of 1,4-diketones from readily available reagents, and is much more selective than peroxide initiated reactions[46].

The addition of cyclohexanone **32** to isopropenyl acetate **30** results initially in adduct radical –an intermediate, formed by the addition of educt radical across the multiple bond of a substrate- **33**, which stabilizes by β-elimination of an acetyl group forming 1,4-diketone **34** (Figure 1.17)[9].

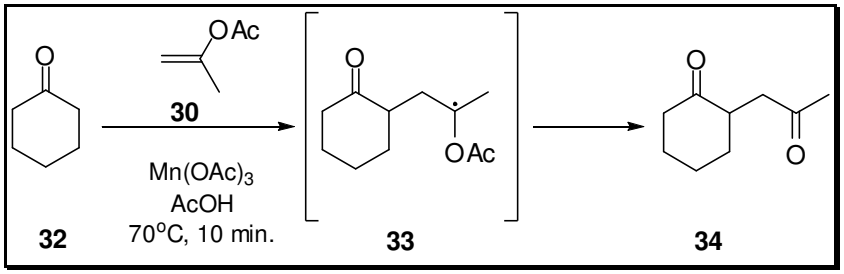


Figure 1.17. Addition of cyclohexanone to isopropenyl acetate

1.2.8. Aromatic Substitution Reactions

A number of methods have been reported for aromatic substitution reactions by radicals generated by manganese (III) acetate. Yields of these oxidative reactions largely depend on reaction conditions, structure of intermediate radicals, substrate, and the presence or absence of polar solvents like acetic acid. In many examples, yields of pure compounds are differently extracted from the original work. However, even when the yields are low, the products are obtained in one single step from simple compounds whereas alternative synthetic methods for many examples require multistep procedures.

The substitution reactions of this type require two equivalents of manganese (III) acetate as exemplified by the following reaction scheme for the substitution of acetone **16** to benzene **35** (Figure 1.18).

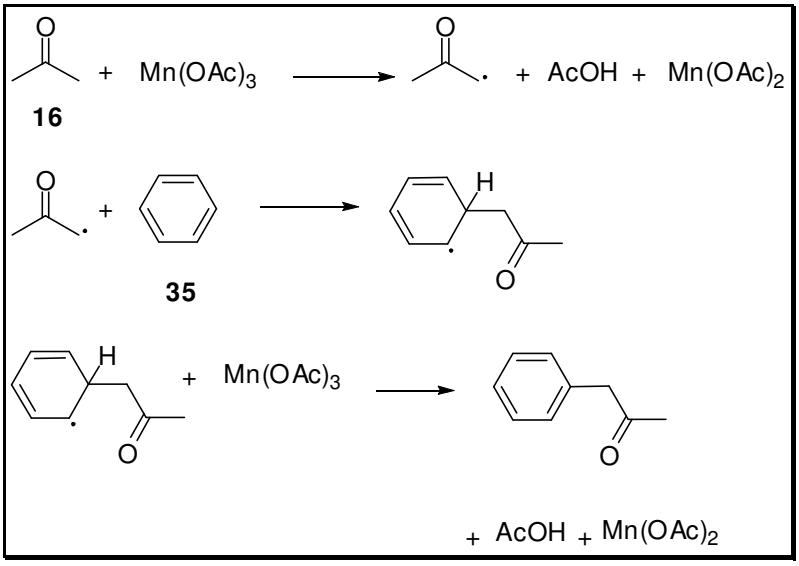


Figure 1.18. Aromatic substitution reactions by radicals generated by manganese (III) acetate.

1.2.9. $Mn(OAc)_3$ Mediated Biaryl Coupling Reactions

C-C bond-forming reactions leading to biaryls are very important because this approach is the key step in the synthesis of many natural and unnatural biaryls. There are various biaryl coupling methods, and the applications of these methods are reviewed comprehensively in the literature. A common method for the synthesis of simple unsymmetrical biaryls is the generation of aryl radicals in the presence of aromatic solvents. Although the product range of this approach is somewhat limited, it provides an easy access to a variety of unsymmetrical biaryls. Demir *et.al.* have recently shown that arylhydrazines **36** can be efficiently oxidized by manganese(III) acetate to produce aryl radicals that afford biaryls **37** in benzene with very good yields as shown in Figure 1.19 [47].

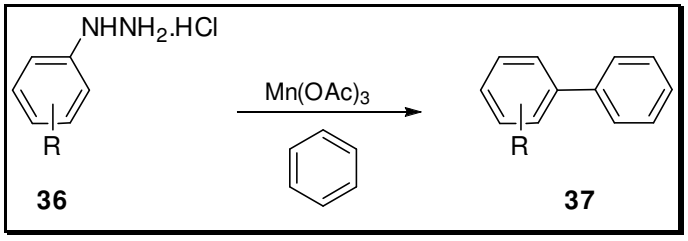


Figure 1.19. Reaction of arylhydrazine derivarives with benzene via manganese(III) acetate

Manganese(III) acetate bears many similarities, with respect to a given substrate class, with other one-electron oxidants like Co(III) and Ce(IV), and some two electron oxidants like Pb(IV). For comparison, phenylhydrazine was treated with cerium(IV) ammonium nitrate (CAN), Co(III) acetylacetonate and Pb(IV) acetate under similar conditions in Demir *et.al*'s study. Reaction of phenylhydrazine with Pb(IV) acetate gave two major products: biphenyl **37** and azobenzene **38** (5:1) and a trace amount of phenyl acetate **39**. The reaction of phenylhydrazine with Co(III) acetylacetonate gave two major products: biphenyl **37** and pyrazole derivative **40** (3:1 respectively). Treatment of phenylhydrazine with CAN (cerric ammonium

nitrate) furnished a mixture of products. The major fractions were identified as biphenyl **37** and azobenzene **38** (3:2 respectively). In addition to these compounds, complex mixtures of terphenyl isomers and azobenzene derivatives of biphenyls were detected by GC-MS. The isolated yields of products were very low and in all cases there were unidentifiable products.

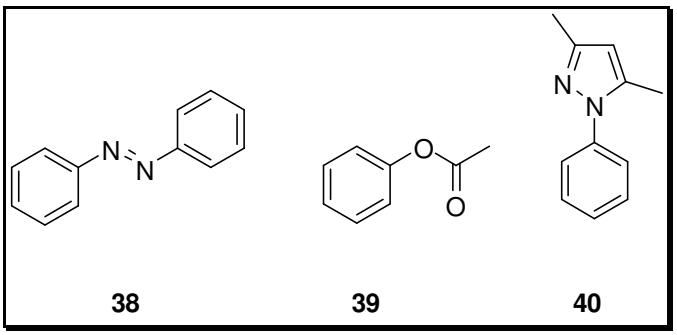


Figure 1.20. Azobenzene, phenyl acetate, pyrazole derivative

Mn(III) acetate is more selective and effective than Co(III), Ce(IV) and Pb(IV). Selectivities can be attributed to the slow formation of radicals with Mn(III) acetate. Co(III), Ce(IV) and Pb(IV) compounds are more powerful oxidants, and therefore less selective.

In the oxidation of monoarylhydrazines with several oxidizing agents, the observed products have been explained in terms of a generated phenyldiimide and its subsequent breakdown. A similar mechanism that is proposed for Pb(IV) acetate and Cu(II) is probably operating during the reaction, which is outlined in Figure 1.21 [41,48].

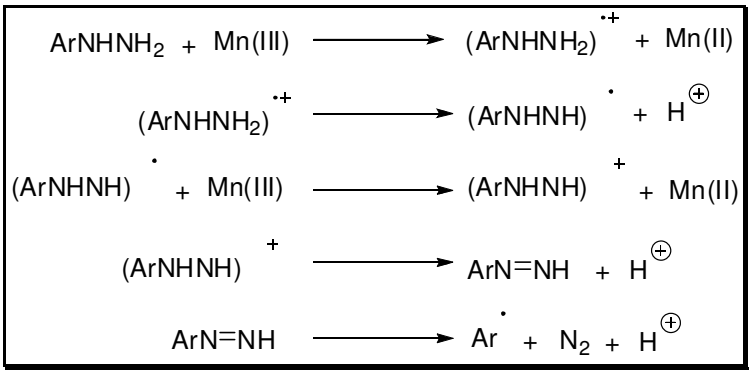


Figure 1.21. oxidation of monoarylhydrazines with Mn(III)

This study has shown that it is possible to oxidize arylhydrazines with Mn(III) acetate in benzene to form the corresponding phenyl-substituted benzene derivatives in good yield; access to biaryls works selectively, and coupling occurs where hydrazine departs. Using substituted benzenes as solvents furnishes isomeric mixtures of the corresponding biaryls.

Although the reaction is very efficient in benzene, Demir *et.al.* have also shown that it generally produces the corresponding heterobiaryls from arylhydrazines **36** in furan **41** and thiophene **42** with moderate to good yields (Figure 1.22) [49].

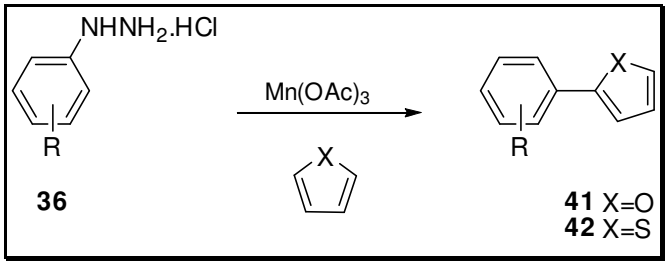


Figure 1.22. Synthesis of heterobiaryls from arylhydrazines with $Mn(OAc)_3$

This drawback of arylhydrazines prompted the same group to find a more suitable substrate as the source of aryl radicals. A suitable candidate for this reaction should

be much more reactive than arylhydrazinium salts under the reaction conditions yet stable enough to handle easily and not prone to side reactions. It is known that arylboronic acids decompose to aryl radicals in the presence of some oxidants[50]. Arylboronic acids are widely used as the organometallic counterpart in the Suzuki reaction. They are stable under atmospheric and aqueous conditions such that Suzuki coupling can be carried out with aqueous organic solvents. Therefore, Demir *et.al.* decided to investigate the oxidation of arylboronic acids with manganese(III) acetate in aromatic solvents and reported the synthesis of a variety of unsymmetrical biaryls **36** with in situ generated aryl radicals from arylboronic acids **43** with manganese (III) acetate as shown in Figure 1.23 [51].

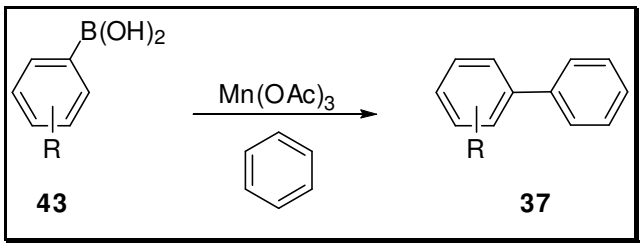


Figure 1.23. Synthesis of biaryls from arylboronic acids with $Mn(OAc)_3$

The yields were generally better than those from similar reactions reported previously. This had shown that arylboronic acids are suitable substrates for the generation of aryl radicals. This study has shown that a variety of radicals can be generated from the corresponding arylboronic acids. In the presence of organic solvents, these radicals afford the monosubstituted biaryls with yields generally higher than those from similar previously reported reactions. Reactions in benzene gave higher yields than those in furan **41** or thiophene **42**; the former was better in terms of yield (Figure 1.24).

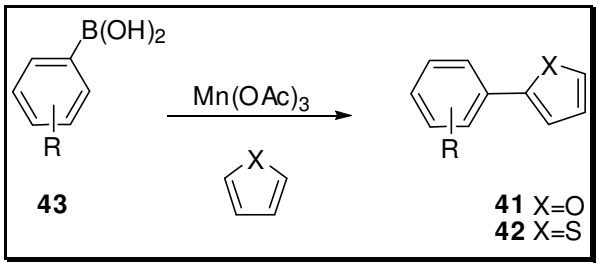


Figure 1.24. Synthesis of heterobiaryls from arylboronic acids with $Mn(OAc)_3$

1.2.10. Tandem Oxidative Cyclizations with Various Mn(III) Reagents and $Cu(OAc)_2$

The Mn(III)-based oxidative free-radical cyclization of **44a** and **44b** serves to introduce the factors that need to be understood to use these reactions in synthesis. Oxidative cyclization of β-keto ester **44a** with $Mn(OAc)_3$ affords a complex mixture of products. Primary and secondary radicals, such as **45a** and **45b**, are not oxidized by Mn(III). Heiba and Dessau have found that $Cu(OAc)_2$ oxidizes secondary radicals 350 times faster that $Mn(OAc)_3$ does and that the two reagents can be used together[38,44]. Oxidative cyclization of **44a** with 2 equiv of $Mn(OAc)_3$ and 0.1-1 equiv of $Cu(OAc)_2$ in acetic acid affords 71% of **46a**. $Cu(OAc)_2$ reacts with radical **45a** to give a Cu(III) intermediate that undergoes oxidative elimination to give **46a** [52,53]. A similar oxidative cyclization of **44b** affords 56% of **46b** as the major product (Figure 1.25).

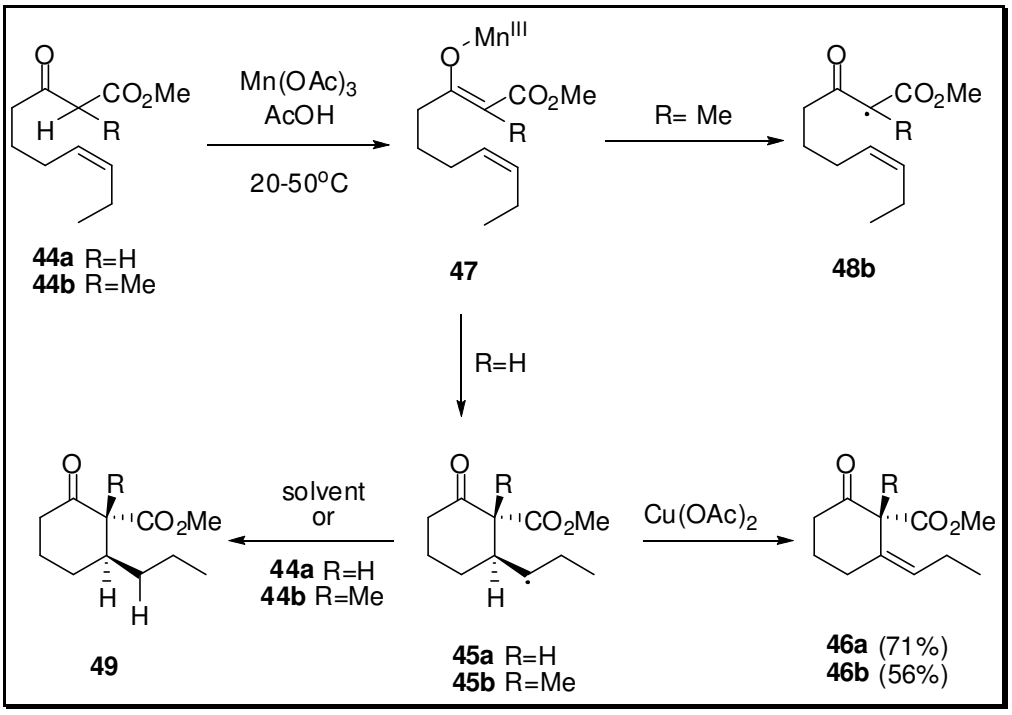


Figure 1.25. Tandem oxidative cyclizations with various Mn(III) reagents and $Cu(OAc)_2$

The first step in the reaction is the loss of a proton to give the Mn(III) enolate **47**. The next step of the reaction could involve cyclization of the unsaturated Mn(III) enolate **47** to give cyclic radical **45a**. This is the operative pathway for R=H. Alternatively, loss of Mn(II) could give the Mn-free free radical **48b**. This is the operative pathway for R=Me. Cyclization of **48b** from the conformation shown gives radical **45b** stereo- and regiospecifically. Finally, Cu(II) oxidation of **45a** and **45b** gives **46a** and **46b** regio- and stereospecifically.

Snider *et.al.* have examined the tandem oxidative cyclization of **50** with various Mn(III) reagents and $Cu(OAc)_2$[54]. Oxidative cyclization with $Mn(OAc)_3$ and $Cu(OAc)_2$ affords 86% of **51** and 0% of **52**, while use of $Mn(pic)_3$ (manganese(III)picolinate) and $Cu(OAc)_2$ leads to 0% of **51** and 15% of **52**. A series of control experiments established that the most likely explanation for this observation is that $Mn(pic)_3$, but not $Mn(OAc)_2$, reacts with the bicyclic radical **53** more rapidly than $Cu(OAc)_2$ does. This illustrates a general feature of oxidative

radical cyclizations. A one-electron oxidant, e.g., Mn(III), Cu(II), Ce(IV), etc., is needed for both the generation of the acyclic radical and oxidation of the cyclic radical. Furthermore, the lower valent metal salt produced in these oxidations must not react rapidly with any of the radical intermediates. $Mn(pic)_3$ does not meet these requirements, since $Mn(pic)_2$ reacts with the cyclic radical more rapidly than $Cu(OAc)_2$ does; the alkyl $Mn(pic)_2$ intermediate produced in this reaction apparently abstracts a hydrogen giving reduced products such as **52** (Figure 1.26).

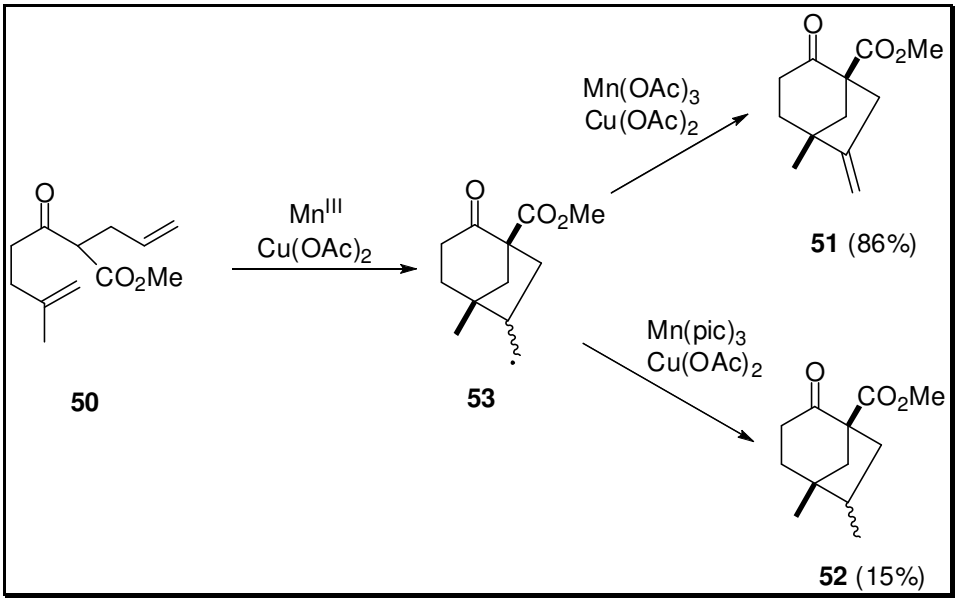


Figure 1.26. Tandem oxidative cyclization of **50** with various Mn(III) reagents and $Cu(OAc)_2$

Acetylacetonatomanganese (III) ($Mn(acac)_3$) and MnF_3 are other readily available Mn(III) reagents. $Mn(acac)_3$ has been extensively used for oxidative coupling of phenols [55]. While both are suitable for oxidative radical cyclizations, they appear to offer no advantages over $Mn(OAc)_3.2H_2O$ [54].

1.2.11. Mn(III) Acetate Mediated Oxidation of α,β-Unsaturated Ketones

The oxidation of α,β-unsaturated ketones **54** with manganese (III) acetate provided an efficient synthesis of α'-acetoxy-α,β-unsaturated ketones **55** (R'=CH_3), and the oxidation of **54** using manganese (III) acetate in the presence of an excess of a manganese (II) carboxylate or a carboxylic acid provided a general synthesis of α'-acyloxy- α,β-unsaturated ketones **55** (Figure 1.27).

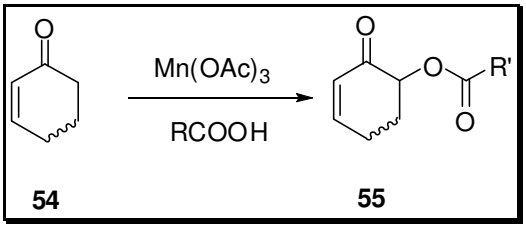


Figure 1.27. $Mn(OAc)_3$ mediated oxidation of α,β-unsaturated ketones

Demir *et.al.* [56-61] have comprehensively developed the α'-oxidation of enones to α'-acyloxyenones discovered by Hunter[62]. During the course of this work they have found that a wide variety of manganese (III) carboxylates could be prepared from $Mn(OAc)_3$ and the carboxylic acid *in situ* and used for α'-acyloxylation of enones and aryl alkyl ketones[56-61]. The utility of these manganese(III) carboxylates in oxidative free-radical cyclizations has not been examined.

Demir *et.al.* [57] have reported the extension of the oxidation process discovered by Hunter [62] to cyclic β-alkoxy- α,β-unsaturated ketones **56**, which exhibits the same regiochemical preference for oxidation at the α'-position to afford the α'-acyloxy- β-alkoxy-α,β-unsaturated ketones **57** in good yield (Figure 1.28). These α'-acyloxy- β-alkoxy- α,β-unsaturated ketones **57** are useful intermediates in the synthesis of natural products [63-71], and general procedures for the synthesis of **55** are either not available or involve multiple steps.

The conversion of cyclic β-diketones **58** to the β-alkoxy- α,β-unsaturated ketones **56** [72] and the oxidation of **56** using six equivalents of manganese (III) acetate[73] in combination with twelve equivalents of a carboxylic acid led to the α'-acyloxy- α,β-unsaturated ketones **57** in good yield. As in previous studies [56], the use of manganese (III) acetate as the sole oxidant was not successful, suggesting that an initial reaction between the manganese (III) acetate and the carboxylic acid led to an active "mixed" manganese (III) complex having both acetate and other carboxylate ligands. The interaction of the enol or enolate of **56** with this mixed manganese (III) complex presumably furnished the desired product **57**. Since the reduction and hydrolysis of α-acyloxy- β-alkoxy- α,β-unsaturated ketones provided access to γ- hydroxy- α,β-unsaturated ketones as exemplified in the case of (S)-6-Acetoxy-3-methoxy-2-methyl-2-cyclohexen-1-one **59** (Figure 1.28), this process extended the utility of the manganese (III) oxidation procedure to the oxidation of α,β-unsaturated ketones at either the α'-or γ-positions.

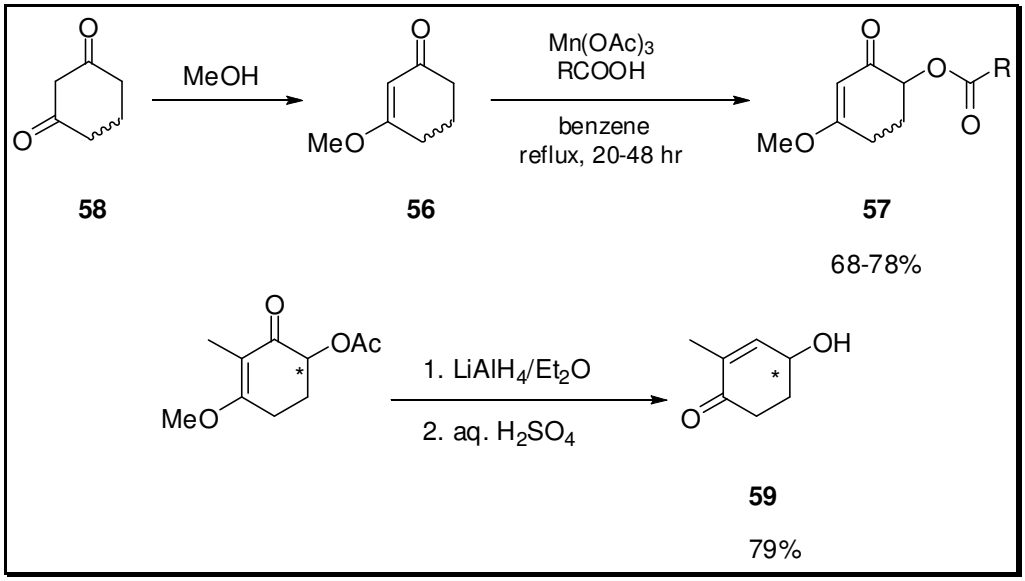


Figure 1.28. Synthesis, reduction and hydrolysis of α-acyloxy- β-alkoxy- α,β-unsaturated ketones

Demir *et.al.* [56] have demonstrated the synthesis of α'-acyloxy enones **55** either from enones **54** using manganese (III) acetate in combination with either manganese (II) carboxylates or carboxylic acids.

Initial efforts have focused on the application of manganese (III) chloroacetate, propionate, pivalate, and benzoate that were prepared according to the procedure of Vaerman and Bertrand[74]. In each case, the oxidation of an enone **54** with these manganese (III) compounds furnished only unchanged starting material, although the corresponding manganese (III) acetate prepared using this same procedure [74] or other procedures [75,76] was an effective oxidant for the α'-acetoxylation of enones.
The use, however, of 6 equiv of manganese (III) acetate *in combination with* 6 equiv of manganese (II) carboxylate led to the desired α'-acyloxy enones **55** in good yields (Figure 1.29).

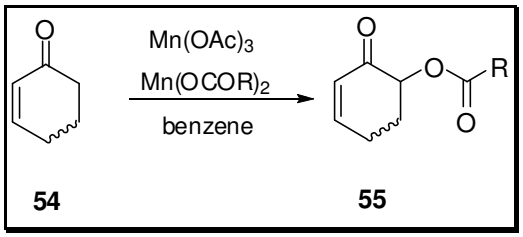


Figure 1.29. Acyloxilation of enones with manganese (III) acetate in combination with manganese (II) carboxylate

Oxidations conducted with 6 equiv of manganese (III) acetate in combination with 12 equiv of a carboxylic acid also proved to be particularly convenient procedure (Figure 1.30).

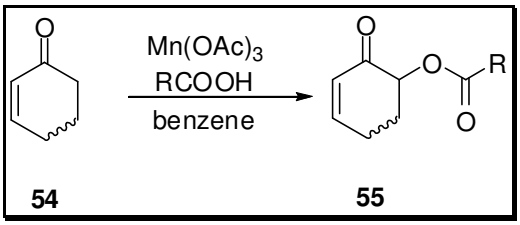


Figure 1.30. Acyloxylation of enones with manganese (III) acetate in combination with carboxylic acids

1.2.12. Mechanistic Considerations

The mechanism of oxidation of monocarbonyl substrates with $Mn(OAc)_3.2H_2O$ has been extensively studied. Fristad and Peterson have shown that the rate-determining step in the oxidation of acetic acid by $Mn(OAc)_3.2H_2O$, which is actually an oxocentered triangle of Mn(III) with bridging acetates [77], is the loss of a proton from a complexed acetate such as **60** to give **61** [78-82]. Rapid electron transfer to the oxocentered metal system gives radical **62**, which adds to the alkene to give **63** (Figure 1.31). The rate of the reaction is independent of alkene concentration, since the alkene is not involved in the rate-determining step.

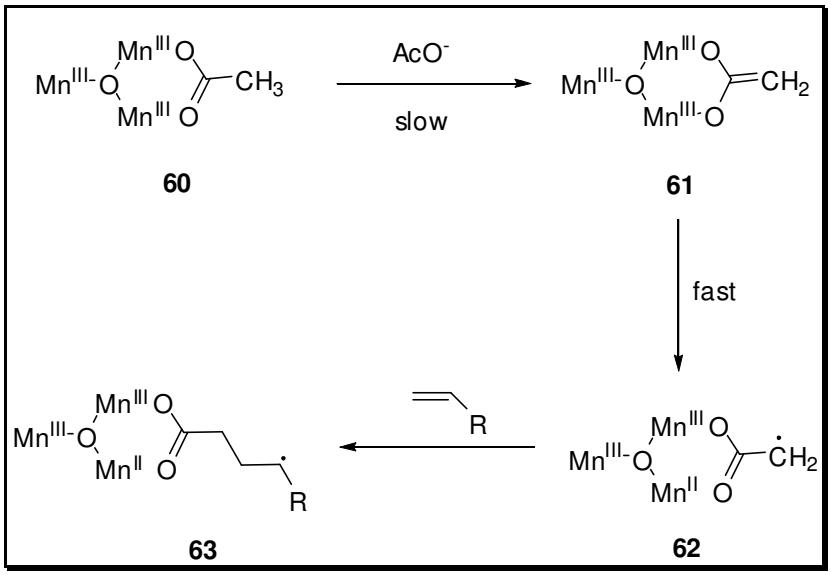


Figure 1.31. Mechanism of oxidation of monocarbonyl substrates with $Mn(OAc)_3.2H_2O$

Snider have found that a similar mechanism is operative in the oxidation of α-alkyl β-keto esters **64** (Figure 1.32) [83].

Enolization to give **65** is slow; electron transfer with loss of Mn(II) to give **66** is rapid which gives **67** with addition of alkene. The rate of the reaction is therefore independent of alkene concentration or the nature of the tether in cyclizations.

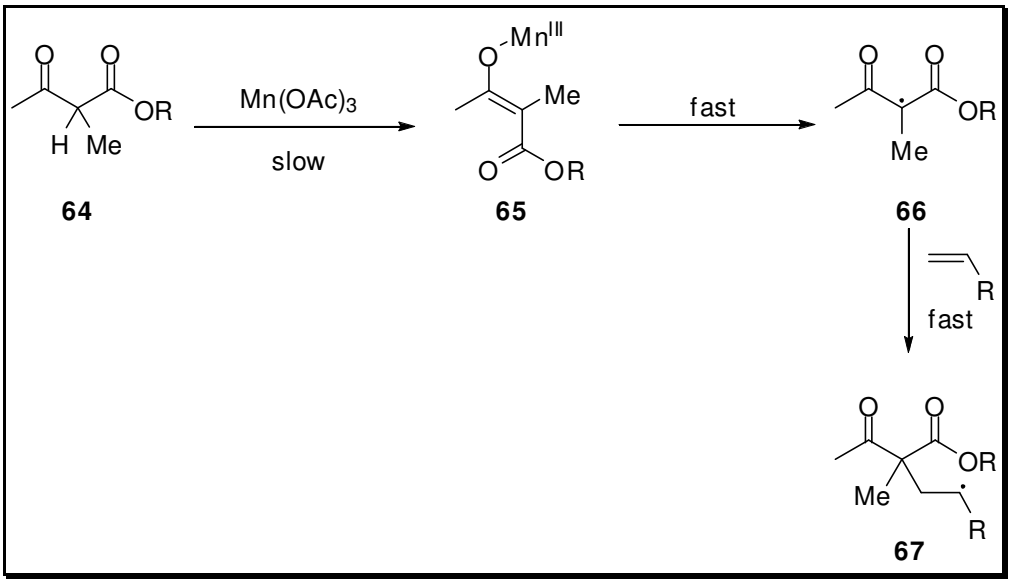


Figure 1.32. Mechanism of oxidation of α-alkyl β-keto esters

On the other hand, Snider have found that the enolization of α-unsubstituted β-keto esters **68** is fast and reversible, and electron transfer to give the radical is very slow (Figure 1.33) [83].

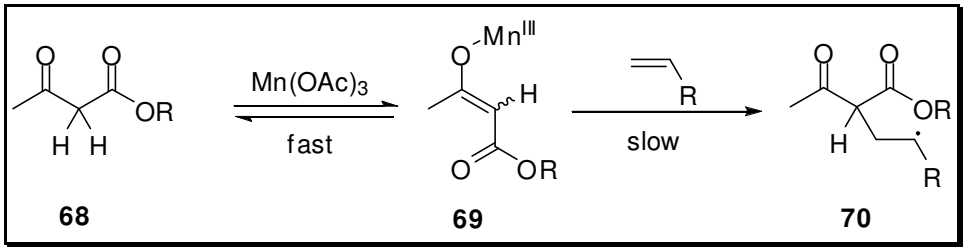


Figure 1.33. Rate-determining step in oxidation of α-alkyl β-keto esters

The rate-determining step depends on alkene concentration and is presumably the reaction of the Mn(III) enolate **69** with the alkene to give radical **70** with loss of Mn(II). β-Keto ester radicals analogous to **66** do not appear to be intermediates in these reactions. If addition of the alkene to the Mn(III) enolate is the rate determining

step, the length of the tether should, and does, affect the rate of oxidative cyclization of unsaturated β-keto esters. 6-*exo*-cyclization is more rapid than 5-*exo*cyclization [83]. The nature of the tether also affects the rate of oxidative cyclization of unsaturated β-keto acids [40].

A methyl group should slow down the formation of Mn(III) enolate **65**, since it is electron donating and decreases the acidity of the α-proton which is responsible for the change in the mechanism. On the other hand, the methyl group should facilitate the oxidation of **65** to **66** since it will stabilize the radical. Electrochemical data for the oxidation of enolates of β-dicarbonyl compounds to the radical in DMSO support this hypothesis. The nature of the reaction depends on two variables: the rate of formation of the Mn(III) enolate, which corresponds to the p*K*a, and the ease of oxidation of the enolate to give a free radical. For most compounds enolization is the rate-determining step. For very acidic compounds such as α-unsubstituted β-keto esters and β-diketones, enolization occurs readily and oxidation is slow.

Commercially available $Mn(OAc)_3.2H_2O$ has been used for the majority of oxidative cyclizations. Anhydrous $Mn(OAc)_3$ is slightly more reactive than the dihydrate. Reaction times with the anhydrous reagent are usually somewhat shorter but the yields of products are usually comparable. Both trifluoroacetic acid and potassium or sodium acetate have been used with $Mn(OAc)_3$. Use of trifluoroacetic acid as a cosolvent usually increases the rate of the reaction, but often decreases the yield of products. Acetate anion may accelerate enolization and act as a buffer. Acetic acid is the usual solvent for $Mn(OAc)_3.2H_2O$ reactions. DMSO, ethanol, methanol, dioxane, and acetonitrile can also be used, although higher reaction temperatures are required and lower yields of products are sometimes obtained. The use of ethanol can be advantageous in cyclizations to alkynes. Vinyl radicals formed by cyclization to alkynes are not readily oxidized by Mn(III) and will undergo undesired side reactions unless there is a good hydrogen donor available. Ethanol acts as a hydrogen donor, reducing the vinyl radical to an alkene and giving the α-hydroxyethyl radical, which is oxidized to acetaldehyde by Mn(III). Much higher yields of alkenes are obtained from cyclizations to alkynes in ethanol than in acetic acid [84].

$Mn(OAc)_3.2H_2O$ is not particularly expensive on a laboratory scale, but its use on an industrial scale may be problematic. Several groups have demonstrated that Mn(III) can be used in catalytic quantities and regenerated electrochemically *in situ* [85-89]. In some cases, good yields of products are obtained with only 0.2 equiv (10%) of Mn(III) or Mn(II). In other cases the electrochemically mediated reactions proceed in substantially lower yield or give different products. D'Annibale and Trogolo have reported that improved yields are obtained in some Mn(III) and Ce(IV) based oxidative cyclizations and additions if they are carried out with ultrasound irradiation [90-92].

Mn(III) will oxidize γ-carboxy radicals, e.g. **63**, to γ-lactones **71** regardless of whether the radical is secondary or tertiary [2,9]. Thus, the addition of acetic acid and substituted acetic acids to alkenes to give γ-lactones is a general reaction for all classes of alkenes. Mn(III) does not oxidize isolated primary or secondary radicals, so the oxidation of **63** may involve addition of the radical to the carboxylate to give **72**, which is readily oxidized to **71**, or the formation of **73** followed by reductive elimination of Mn(II) to yield **71** (Figure 1.34) [41].

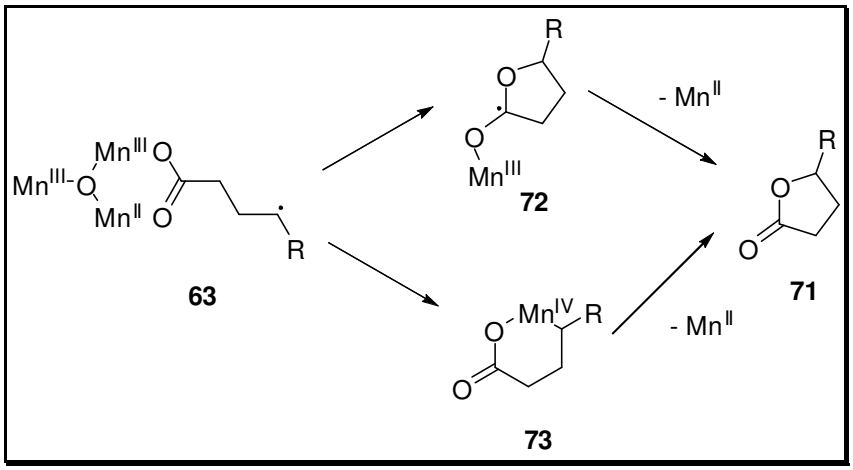


Figure 1.34. Oxidation of γ-carboxy radicals to γ-lactones

Addition of 1,3-dicarbonyl compounds to alkenes affords isolated radicals that do not contain a proximal manganese carboxylate, e.g., **46** and **53**. Mn(III) will oxidize tertiary radicals to cations that can lose a proton to give an alkene or react with solvent to give a tertiary acetate. Mn(III) will also oxidize allylic radicals to allylic acetates and cyclohexadienyl radicals, resulting from addition to aromatic rings, to the cation, which loses a proton to regenerate the aromatic system.

Mn(III) does not oxidize primary radicals such as **53** or secondary radicals such as **46**. If no cooxidant is used, hydrogen abstraction is the major pathway [41]. $Mn(OAc)_3$ is also involved in the termination step. It rapidly oxidizes tertiary radicals to cations that lose a proton to give an alkene or react with acetic acid to give acetate esters. $Mn(OAc)_3$ oxidizes allylic radicals to allylic acetates and oxidizes cyclohexadienyl radicals generated by additions to benzene rings to cations that lose a proton to regenerate the aromatic system. On the other hand, $Mn(OAc)_3$ oxidizes primary and secondary radicals slowly, so that hydrogen atom abstraction from solvent or starting material becomes the predominant process. Alkenes are formed efficiently from primary and secondary radicals by use of $Cu(OAc)_2$ as a cooxidant [41].

When 5,5-dimethylcyclohex-2-en-1-one **74** was treated with 4 mol equiv of manganese (III) acetate in glacial acetic acid, containing sodium acetate to raise the temperature of reflux, the only product was 6-acetoxy-5,5-dimethylcyclohex-2-en-1-one **75**. Clearly the ketone had not reacted at the double bond but α to the carbonyl to give the product α'-acetoxylation.

One can envisage several mechanisms for oxidation of the enones to the α'-acetoxyenones. For example, the formation of a metal enolate with acetate transfer (Figure 1.35) analogous to the lead tetraacetate oxidation of enones is possible.

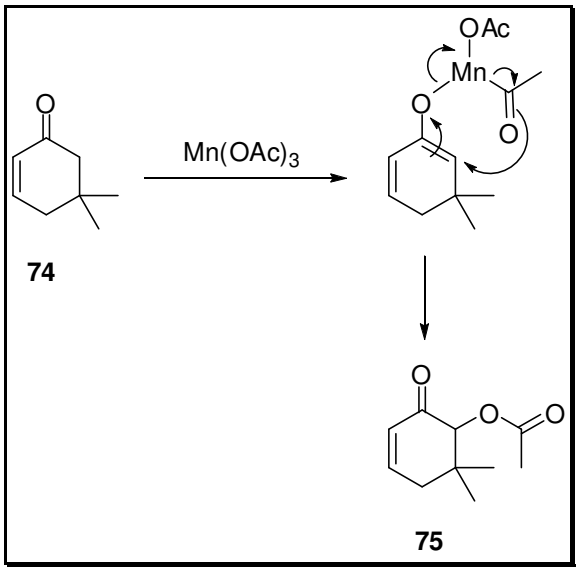


Figure 1.35. Suggested enolate mechanism for oxidation of enones to the α'-acetoxyenones with $Mn(OAc)_3$

However, since previous oxidations of carbonyl compounds with manganese (III) acetate have probably all involved the intermediacy of an α-keto radical resulting from the oxidation of an enol or enolate anion by Mn(III), it is possible that this α'-acetoxylation reaction also proceeds via α-keto radical **76** formation followed by ligand transfer oxidation to the product **75**. Oxidation of the α-keto radical to the carbocation by electron transfer is not favored due to the adjacent electronwithdrawing carbonyl group (Figure 1.36).

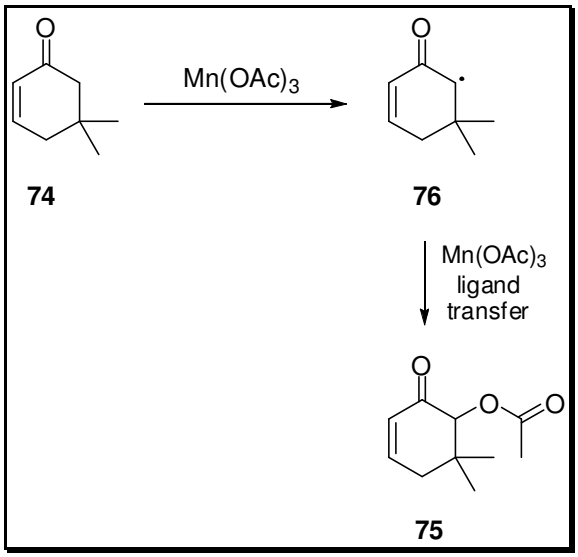


Figure 1.36. Suggested radicalic mechanism for oxidation of enones to the α'-acetoxyenones with $Mn(OAc)_3$

1.3 Reinvestigation of the synthetic and mechanistic aspects of $Mn(OAc)_3$

In $Mn(OAc)_3$ oxidation of enones, α'- acetoxylation of a great variety of substrates, there were some problems associated with the use of $Mn(OAc)_3$. A brief list of them is as follows:

(1) Excess $Mn(OAc)_3$ (4-6 eq.) is generally used for acceptable yields and reaction times;

(2) Many contradictory results can be seen when the literature reports are closely inspected [42].

These inconsistencies along with the use of an undesirable amount of $Mn(OAc)_3$ reduced the value of the method. Considering that there are not many simple methods for the direct acetoxylation of enones, optimization of $Mn(OAc)_3$ mediated α'-acetoxylation of enones, and reaching its maximum potential has great importance from a synthetic and economic point of view. Demir and co- workers reported their investigation of their understanding of the nature of this reaction, along with increasing its efficiency and reproducibility. They presented an improved procedure that was based on the use of acetic acid as a co-solvent. According to this procedure,

AcOH shortened the reaction time and increased the yields. The role of acetic acid could be related to an increased solubility of $Mn(OAc)_3$ in the reaction mixture. From a synthetic point of view, excellent results were obtained for a variety of structurally and synthetically important enones under optimized conditions. Although benzene was the most frequently used solvent it was also reported that cyclohexane and MeCN could also be used instead of benzene, and acetic anhydride could be used instead of acetic acid.

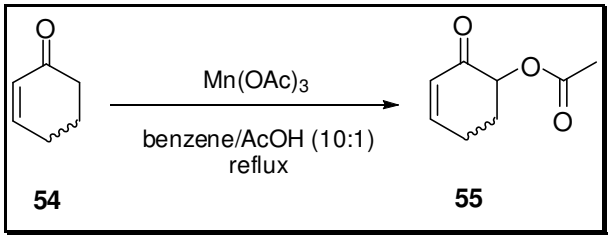


Figure 1.37. Improved procedure based on the use of acetic acid as a co-solvent

1.4. Ipso nitration with arylboronic acids

Although arylboronic acids[93] have been available for more than one hundred years, they have not been used much in organic synthesis until recently. Since they are comparatively stable compounds they have a wide range of applications in organic synthesis[44].

Aromatic substitution reactions have been investigated extensively [94-96]. When an electrophile attacks a substituted aromatic ring directly at the position bearing the substituent, the attack is termed *ipso*-attack [95,98,99].

Nitration of aromatic compounds is one of the most widely studied reactions and an immensely important industrial process. Nitroarenes play important roles as

precursors to industrial products, which has led to a very good understanding of the steps involved in the nitration reaction [100-103].

1.4.1. Nitration methods of arylboronic acids

Nitration of aromatic compounds is one of the most extensively studied reactions, and nitroaryl moieties play key roles in the physical and chemical properties of many target molecules in organic synthesis [54]. For electrophilic nitration of aromatic compounds, a wide variety of reagents are available to date [95,105]. Most of them are very strong nitrating agents and often lead to further nitration and mixture of isomers. Since most nitrating agents are oxidants, oxidation of other functional groups can also occur, giving a mixture of products. Thus, a search for milder and selective nitrating agents is a good research goal. In the last few decades, arylboronic acids [106] have been extensively used as versatile synthons in organic synthetic transformations involving various reactions such as Suzuki coupling[108] and multicomponent reactions for the synthesis of various amino acids and trifluoromethylated amines[109,110]. Fluorination of various derivatives of aryl/alkenylboronic acids has been reported [111].

For the nitration of arylboronic acids two important works are published. In earlier studies, Prakash et al. have shown regeoselective nitration of arylboronic acids with Crivello's reagent (ammonium nitrate/ trifluroacetic anhydride) (Figure 1.48) [112].

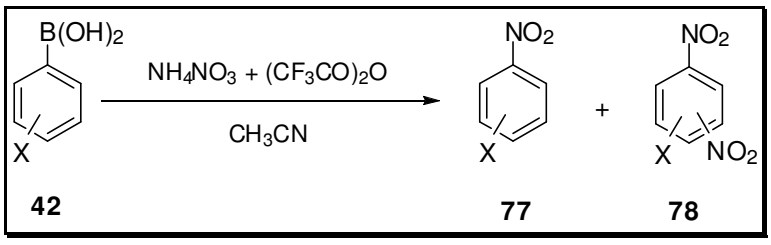


Figure 1.38. Nitration of arylboronic acids with Crivello's reagent.

However, during nitration with the relatively powerful Crivello's reagent, dinitration was also observed and the temperature had to be carefully regulated to avoid undesirable side reactions.

Recently same authors reported the *ipso*-nitration of arylboronic acids using inorganic nitrate salt and chlorotrimethylsilane and they found that the mixture of nitrate salt and chlorotrimethylsilane is found to be an efficient regioselective nitrating agent for the *ipso*-nitration of arylboronic acids to produce the corresponding nitroarenes in moderate to excellent yields with high selectivity (Figure 1.39).

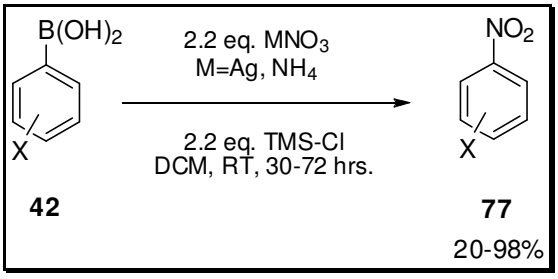


Figure 1.39. *Ipso*-nitration of arylboronic acids using inorganic nitrate salt and chlorotrimethylsilane

The suggested mechanism for the regioselective nitration of arylboronic acid carried out with $AgNO_3$/TMSCl was that TMS-Cl reacts with nitrate salts to generate the TMS-O-NO_2 species. The electronic interaction between the boronic acid group and the intermediate active nitrating agent TMS-O-NO_2 species through boron and the siloxy group due to the high oxophilicity of boron (Figure 1.40) helps the nitration to occur at the ipso position.

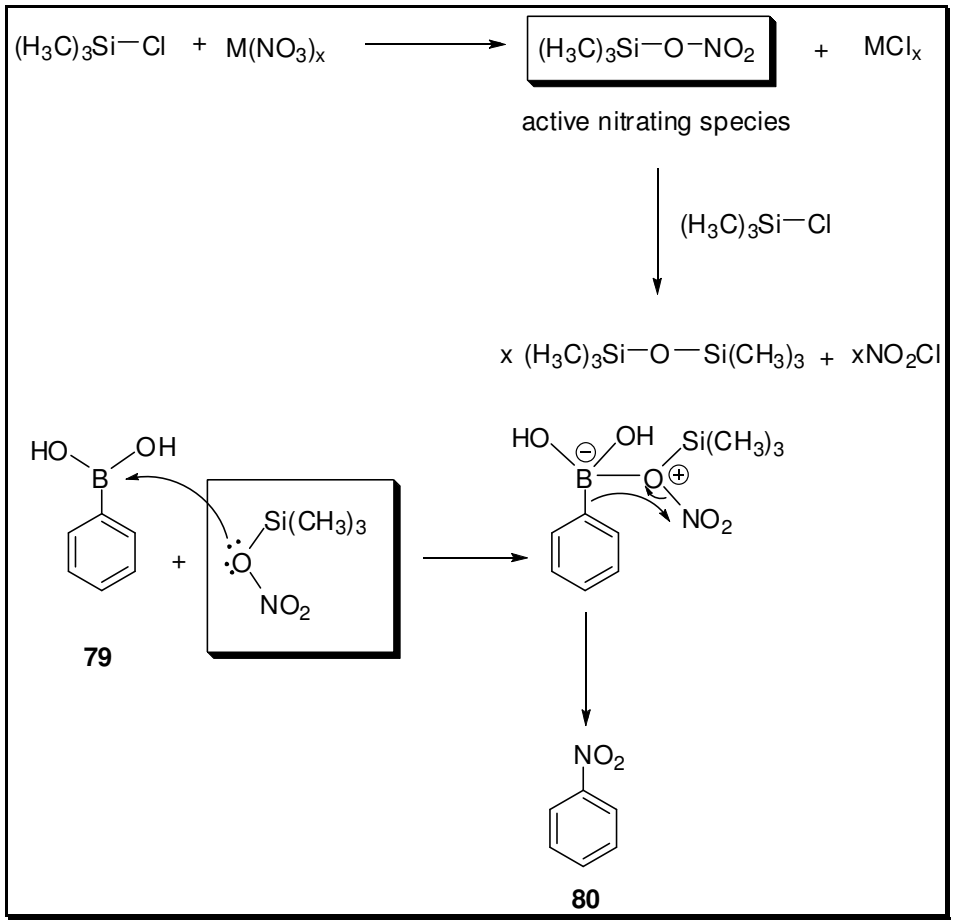


Figure 1.40. Suggested mechanism for the regioselective nitration of arylboronic acid

1.4.2. $AgNO_2$/TMSCl: General application

The 1,2,5-oxadazole-2-oxides (furoxans) have important pharmacological properties. They are found to exhibit potent anti HIV-1 activities [113] and they have the ability to increase the cytosolic levels of cCMP in C6 cells and vasodilatation. The NO-donor properties compared with other NO donors furoxans can exhibit a very desirable pharmacological profile: slow onset and long duration of action with no development of nitrate tolerance[114].

1,2,5-oxadiazole-2-oxides have been extensively investigated regarding their chemistry, their stability and their activity. The most frequently used synthetic

pathway for their preparations are: oxidation of dioximes, thermolysis of o-nitro-azides, dimerization of nitrile-N-oxides, oxidation of aromatic o-amino-nitro-derivatives and reaction of alkenes with N_2O_3 [115].

The reaction of dinitrogen trioxide, prepared either from concentrated sulphuric acid and sodium nitrite or from nitric oxide and air, with olefins affords 1,2-nitronitroso dimers, commonly referred to as pseudonitrosites. These adducts can be converted to the most soluble isomer, the corresponding 1,2-nitroximes [116].

According to the work done by Demir *et. al.*, the reaction of $AgNO_2$ with TMSCl affords N_2O_3 [117]. The addition of N_2O_3 to alkenes proceeds nitroso nitrate **82**, which are then converted into corresponding α-nitro ketones **83** and followed by cyclization into furoxans **84** in good yields. This work offers simple and effective method for the synthesis of furoxans (Figure 1.41).

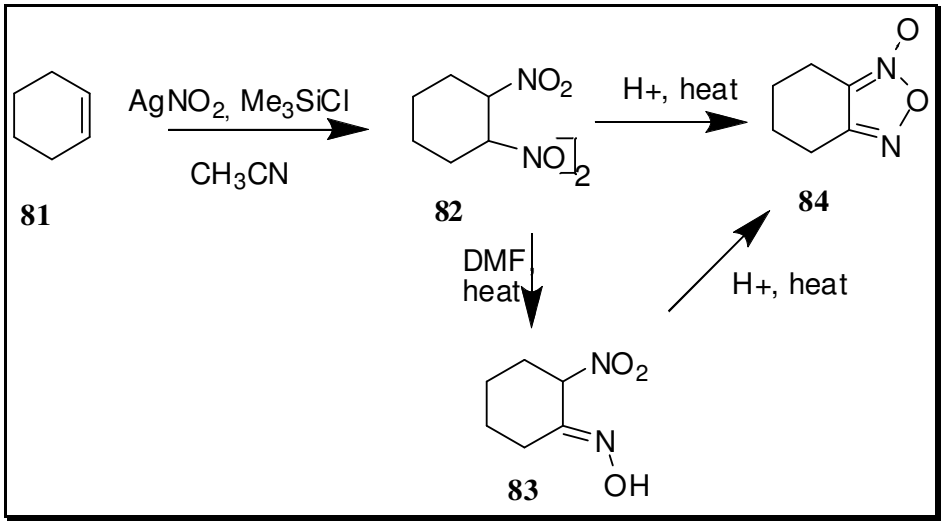


Figure 1.41. Synthesis of furoxanes via reaction of alkenes with $AgNO_2$/TMSCl

The aim of this work was first to prepare trimethylsilyl nitrite from $AgNO_2$ and TMSCl. Then addition of trimethylsilyl nitrite (as NO^+ and $^-OSiMe_3$ species) to alkenes to obtain the corresponding α-hydroxy oximes, it means direct conversion of

alkenes to α-hydroxy ketones, which are valuble intermediate in synthetic organic chemistry [115,116].

The structure of the products showed no evidence for the accepted products 1,2-hydroxyoxime *via* addition of trimethylsilylnitrite (NO^+ and $^-OSiMe_3$) to the double bounds.

In the literature similar products are obtained by the addition of N_2O_3 to the alkenes. For finding evidence for the possible formation of N_2O_3 and addition to double bond the TMSCl and silver nitrite are suspended in deuterated DMF at –5°C. The ^1H NMR spectrum showed the formation of hexamethyldisiloxane. With this result it's suggested that the reaction of $AgNO_2$ with TMSCl leads the formation of N_2O_3 and hexamethyldisiloxane. The formation and subsequent addition of N_2O_3 to alkene furnished nitroso nitrate as dimer. Heating of dimeric nitroso nitrate affords furoxan *via* formation of α-nitro oxime followed by elimination of water.

1.5. Aim of the work

Metal-promoted radical reactions have found widespread use in organic synthesis, in which one of the well-known examples of this application is the $Mn(OAc)_3$-mediated reaction. Manganese(III) acetate dihydrate ($Mn(OAc)_3$ $2H_2O$)-mediated free radical reactions have emerged as important synthetic methods for a new bond formation as well as bond breaking. The application of $Mn(OAc)_3$ promoted free-radical reactions in numerous regio-, chemo-, and stereoselective carbon-carbon, carbon-heteroatom bond formations have been developed in both inter- and intramolecular reactions. Several sources of $Mn(OAc)_3$ are described in the literature.

Although C-C-and C-O bond formation reactions of a great variety of substrates have been reported so far by us and others as successful, there are some problems associated with the use of $Mn(OAc)_3$. A brief list of them is as follows: (1) excess $Mn(OAc)_3$ (4–6 equiv.) is generally used for acceptable yields and reaction times; (2)

many contradictory results can be seen when the literature reports are closely inspected. These include the amount of $Mn(OAc)_3$ that was employed to carry out the desired conversion, in which irreproducible yields/reaction times were observed under the same set of conditions and in reaching its maximum potential shows great importance from a synthetic and economic point of view. In the first part of the thesis, we aimed to find and apply a new, simple and more convenient method which will replace $Mn(OAc)_3$.

Arylboronic acids have been extensively used as versatile synthons in organic synthesis involving various reactions. For the nitration of arylboronic acids two important works are published. In earlier studies, Prakash et al. have shown regeoselective nitration of arylboronic acids with Crivello's reagent (ammonium nitrate/trifluroacetic anhydride), However, during nitration with the relatively powerful Crivello's reagent, dinitration was also observed. Recently same authors reported the *ipso*-nitration of arylboronic acids using inorganic nitrate salt and chlorotrimethylsilane. In the second part of the thesis, we aimed to find a convenient and mild method for the nitration of arylboronic acids using silver nitrite and chlorotrimethylsilane.

CHAPTER 2

RESULTS AND DISCUSSION

2.1. Reactions with insitu generated manganese III acetate

There are two examples to the in situ generation of $Mn(OAc)_3$ in the literature. In the first example, Linker and coworkers performed the synthesis of manganese(III) acetate by the oxidation of $Mn(OAc)_2$ with potassium permanganate which is a well-known process [118]. Their approach was based on the in situ generation of $Mn(OAc)_3$ by $KMnO_4$ in the presence of the CH-acidic precursor **85** (Figure 2.1). Only catalytic amounts of manganese(III) are involved in this reaction cycle, which allows the generation of the radicals **86** under 'non-oxidative conditions'.

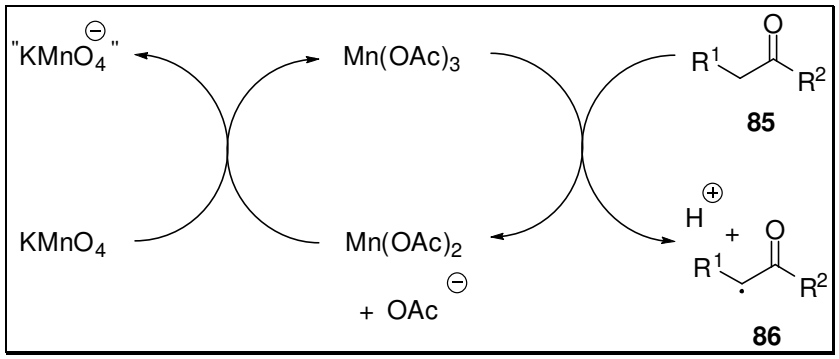


Figure 2.1: Generation of $Mn(OAc)_3$ by $KMnO_4$ in the presence of the CH-acidic precursor

The second example is the γ-lactone synthesis by the in situ generation of $Mn(OAc)_3$ with potassium permanganate and manganous acetate tetrahydrate or dihydrate (Figure 2.2)[119].

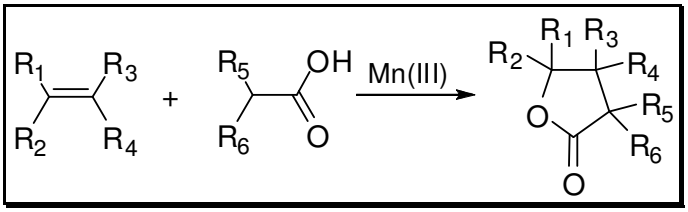


Figure 2.2. γ-Lactone synthesis by the in situ generation of $Mn(OAc)_3$

There are no examples to the application of in situ generation of $Mn(OAc)_3$ to the α'-acetoxylation of enones. Therefore we applied this system to this type of reactions. As the model substrate 1-indanone **87** was selected and its reaction with $Mn(OAc)_2$/ $KMnO_4$/acetic acid system is investigated. In an initial reaction $Mn(OAc)_2$ and $KMnO_4$ is dissolved in acetic acid and benzene (10:1). This solution is refluxed under Dean-Stark trap until the color of the solution turned brown. Then, 1-indanone was added to this solution and reflux was continued. The reaction is monitored by TLC, and then filtered and neutralized with $NaHCO_3$. After work-up, 2-acetoxyindanone **88** was isolated with 87% yield (Figure 2.3).

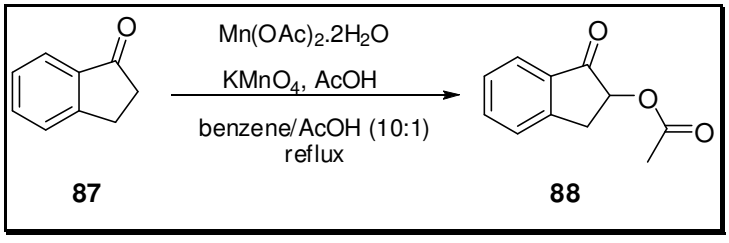


Figure 2.3. Application of in situ generation of $Mn(OAc)_3$ to the α'-acetoxylation of enones.

The same system is applied to other enone commercially available aromatic ketones and α'-acetoxy products are obtained with good to moderate yields which are summarized in Table 3.

Table 3. Examples to application of in situ generation of $Mn(OAc)_3$ to the α'-acetoxylation of enones.

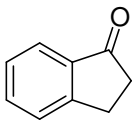
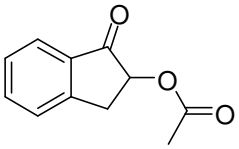
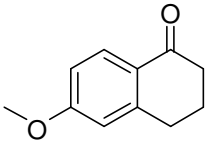
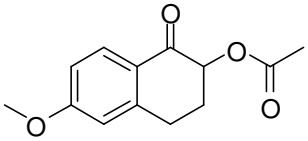
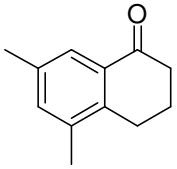
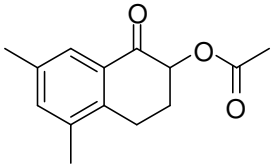
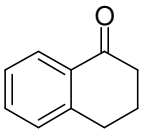
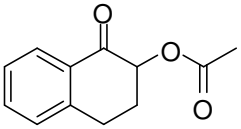
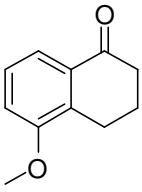
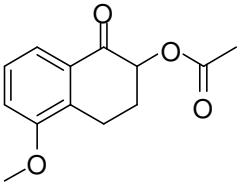
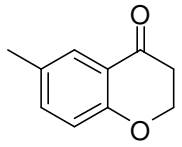
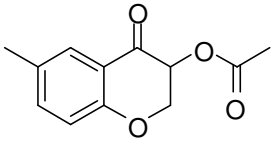
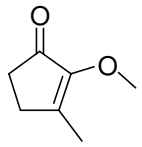
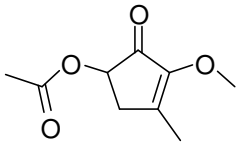
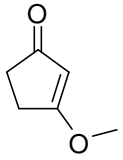
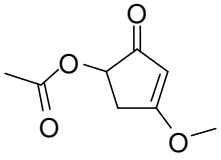
Starting Material	Product	Yield(%)
 **87**	 **88**	87
 **89**	 **90**	88
 **91**	 **92**	95
 **93**	 **94**	92
 **95**	 **96**	79

Table 3 cont'd

 **97**	 **98**	84
 **99**	 **100**	65
 **101**	 **102**	57

As shown in Table 3, substituted tetralone, chromanone and indanone systems can be converted into α-acetoxy derivatives selectively. No other position gives oxidation reactions. In addition to te aromatic ketones, protected cyclic 1,2-, 1,3-diketones are also given α'-acetoxy derivatives in moderate yields. They are interesting starting materials for prostaglandine synthesis. The protected 1,2-, 1,3-diketones are synthesized starting from 1,2-, 1,3- diketones according to the literature procedure.

The spectroscopic data (^{1}H-NMR, ^{13}C-NMR) are in aggrement with the structures. The typical peaks in the ^{1}H-NMR spectrum are the CH proton at 5-6 ppm and methyl group at around 2 ppm which belongs to the acetoxy group.

The mechanism of the reaction is the oxidation of Mn(II) to Mn(III) and the oxidation of enones which is performed by in situ generated Mn(III).

2.2. $KMnO_4$ / carboxylic acid/ organic solvent system

Although C–C and C–O bond formation reactions of a great variety of substrates have been reported so far by Demir *et. al*. and others as successful there are some problems associated with the use of $Mn(OAc)_3$ are described before[42]. A brief list of them is as follows: (1) excess $Mn(OAc)_3$ (4–6 equiv) is generally used for acceptable yields and reaction times; (2) many contradictory results can be seen when the literature reports are closely inspected. These include the amount of $Mn(OAc)_3$ and irreproducible yields/reaction times. After the investigation of the oxidation with in situ generated Mn(III)acetate from Mn(II)acetate, we investigated the possibility to generate Mn(III)acetate directly from $KMnO_4$ and acetic acid.

2.2.1 $KMnO_4$ / carboxylic acid/ organic solvent system for enone oxidations.

We selected 1-tetralone **93** as a model substrate and investigated its reaction with $KMnO_4$/acetic acid in benzene. In an initial reaction, $KMnO_4$ was dissolved in acetic acid and benzene. This solution was refluxed under a Dean–Stark trap until the color of the solution turned brown. Then, 1-tetralone **93** was added to this solution and reflux was continued. The reaction was monitored by TLC, and then filtered and neutralized with $NaHCO_3$. After work-up, 2-acetoxytetralone **94** was isolated in a 64% yield (Figure 2.4).

For optimization studies, several solvents are tried in the reaction such as benzene, acetonitrile, THF, DMF, cyclohexane and DCM. Best results are obtained with benzene. In order to determine the sufficient amount of the reactants, the reaction is performed with 1, 2, 3, and 4 equivalents of $KMnO_4$. 3 equivalent of $KMnO_4$ was the most efficient for the full conversion. With these optimized conditions, reaction furnished **94** in 89% yield.

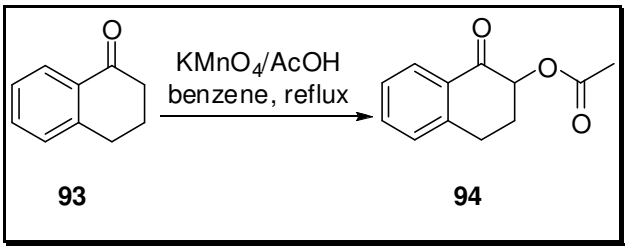


Figure 2.4. Oxidation of 1-tetralone **93** to 2-acetoxytetralone **94** via $KMnO_4$/acetic acid in benzene

Using this procedure, several enones and aromatic ketones were converted into their acetoxy derivatives as shown in Table 4. The reactions work with the same regioselectivity. The yields are comparable to the $Mn(OAc)_3$-mediated direct oxidation of ketones and tolerate many sensitive functional groups. Most of the starting materials are commercially available and the ketones **99**, **107**, **109**, **111** were synthesized according to the literature procedure[120].

Simple cyclic enones, protected 1,3-diketones and steroid structure containing enone systems in a ring gives the products in excellent yields. The compounds **91**, **97**, **103**, **105** gives no or trace amount of oxidation products. Only unreacted starting materials are isolated. Changing the solvent, reaction temperature etc. gives again no product.

Table 4. Oxidation of aromatic ketones and enones with $KMnO_4$/AcOH

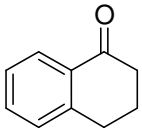
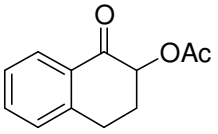
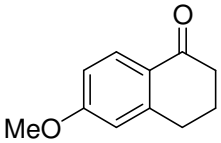
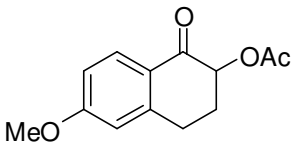
Starting material	Product	Yield(%)	Yield(%), Lit.
 **93**	 **94**	89	88[42]
 **89**	 **90**	85	97[42]

Table 4 cont'd

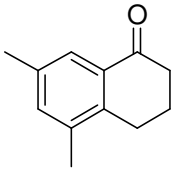
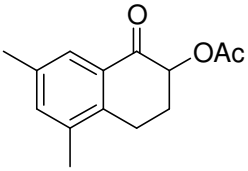
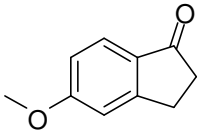
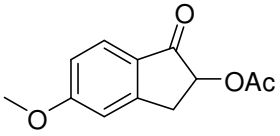
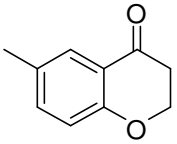
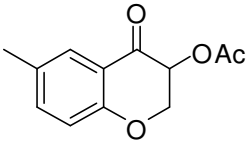
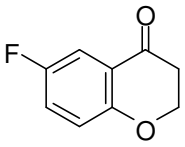
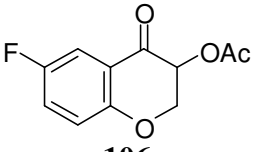
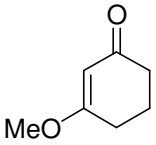
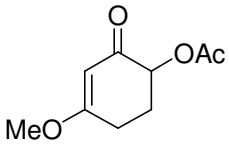
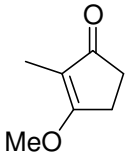
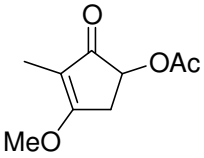
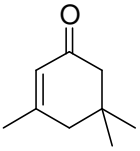
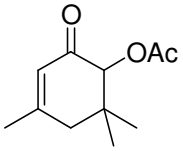
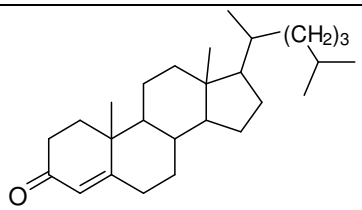
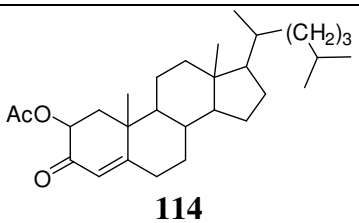
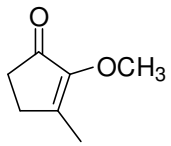
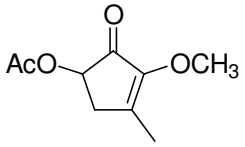
 **91**	 **92**	96	-
 **103**	 **104**	81	-
 **97**	 **98**	83	-
 **105**	 **106**	74	-
 **107**	 **108**	97	87[120]
 **109**	 **110**	75	88[56b]
 **111**	 **112**	86	99[42]
 **113**	 **114**	84	98[42]

Table 4 cont'd

 **99**	 **100**	88	88[121]

These results prompted us to try an oxidation reaction with carboxylic acid other than acetic acid, wherein we found that this method can in fact be applied for the acyloxylation of enones and aromatic ketones in high yields as shown in Table 5 (Figure 2.5).

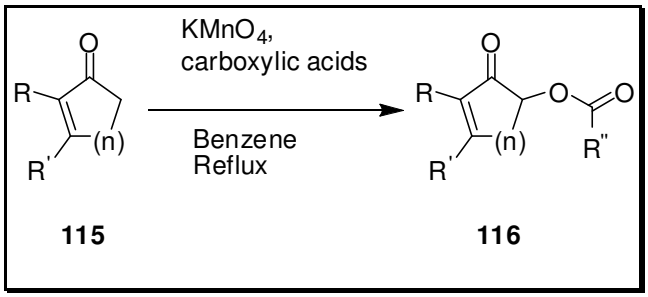


Figure 2.5. Acyloxylation of enones and aromatic ketones via $KMnO_4$/RCOOH

Table 5. Oxidation of aromatic ketones and enones with $KMnO_4$/RCOOH

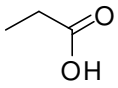
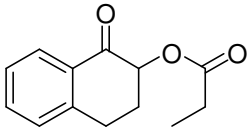
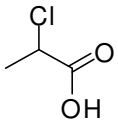
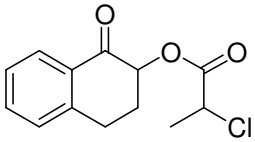
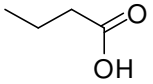
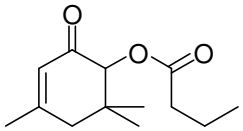
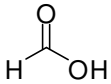
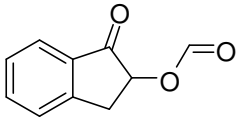
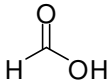
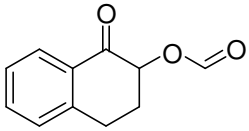
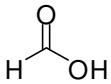
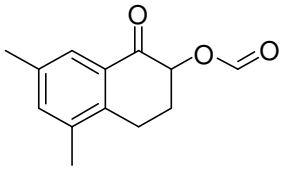
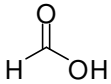
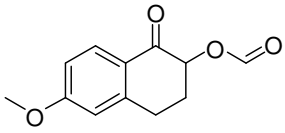
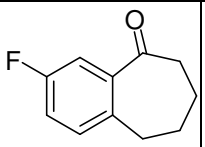
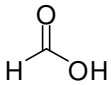
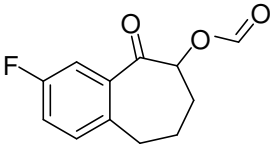
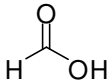
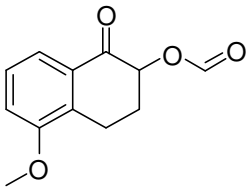
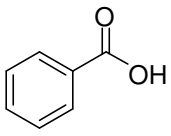
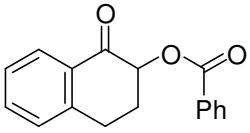
Starting material	Carboxylic acid	Product 3	Yield (%)	Yield (%) Lit.
93		 **117**	87	-
93		 **118**	91	67[122]

Table 5 cont'd

111		 **119**	82	-
87		 **120**	80	98[123]
93		 **121**	85	-
91		 **122**	75	-
89		 **123**	76	-
 **124**		 **125**	61	-
95		 **126**	70	-
93		 **127**	65	89[124]

The reaction tolerates several liquid carboxylic acids which have functional groups such as chloride. For the first time, formyloxylation was carried out with formic acid.

In the literature, rather few works have been presented about the direct formyloxylation of ketones (Lee *et al.* reported that an initial treatment of ketones with thallium(III) triflate, formed in situ by the reaction of thallium(III) acetate with trifluoromethanesulfonic acid, in DMF at 60 ^{o}C followed by the addition of small amounts of H_2O provided the formyloxy ketones)[123]. The spectroscopic data (^{1}H-NMR, ^{13}C-NMR) are in aggrement with the structures. The typical peaks in the ^{1}H-NMR spectrum are the CH proton at 5-6 ppm and H of the formyloxy group which is around 8 ppm. The products are obtained with excellent yields being independent of the ring size and functional groups of the enone systems. 5,6 and 7 membered ring systems gave the corresponding α-acetoxy products in good yields.

Problems occurred when using some solid carboxylic acids, these reactions were carried out without benzene, wherein only acetic acid was used as a solvent and the corresponding acyloxy derivatives were synthesized in good yield. By using benzoic acid, the product was isolated along with an acetoxy derivative as a minor product. It was possible then to separate the product by column chromatography. No product formation was observed by using chloroacetic acid, even when we used cyclohexane and DMF as a solvent.

4.2.2. $KMnO_4$/AcOH mediated aryl coupling reactions

Recently, Demir *et. al.* developed a general method for the synthesis of biaryls starting from arylhydrazines/aromatic solvents and arylboronic acids/aromatic solvents in the presence of $Mn(OAc)_3$. No isomerization of the formed radical was observed. Both the aryl coupling reactions, starting from arylhydrazines and arylboronic acids with benzene as a solvent, were carried out by using the $KMnO_4/CH_3COOH$ system. $KMnO_4$/acetic acid and benzene were refluxed under the Dean–Stark trap until the color of the solution turned brown. Then, arylboronic acid or arylhydrazine was added to this solution and reflux was continued. The reaction was controlled with TLC and the corresponding aryl coupling products were obtained in high yields with the same regioselectivity without isomerization.

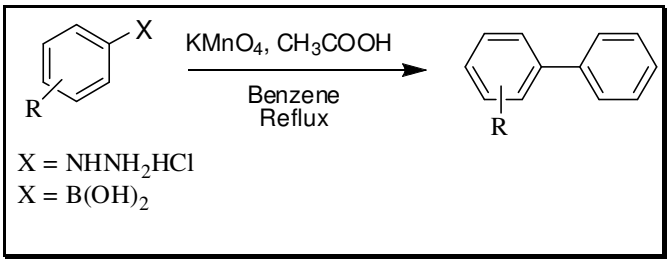


Figure 2.6. Synthesis of biaryls via $KMnO_4/CH_3COOH$ system

Arylboronic acids and arylhydrazines with the electron-withdrawing and electron-donating groups attached to the phenyl ring furnished comparable yields as shown in Tables 6 and 7 (Figure 2.6).

Table 6. Synthesis of biaryls from arylhydrazines via $KMnO_4/CH_3COOH$ system

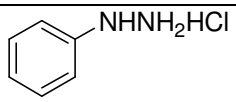
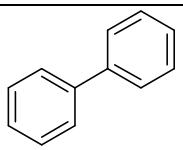
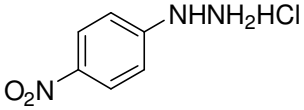
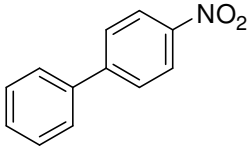
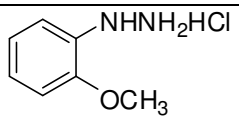
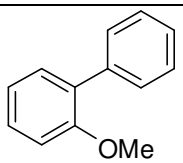
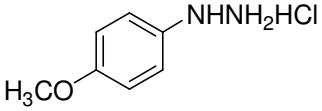
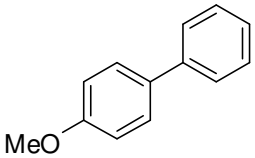
Arylhydrazine	**Biaryl**	**Yield (%)**	**Yield(%)$^{Lit.}$**
 **128**	 **129**	95	75[125]
 **130**	 **131**	95	93[125]
 **132**	 **133**	95	75[47]
 **134**	 **135**	90	83[47]

Table 6 cont'd

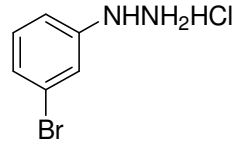
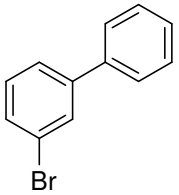
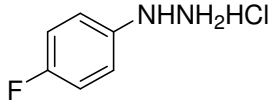
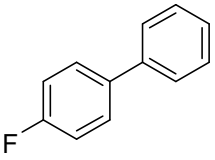
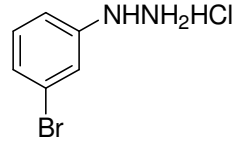
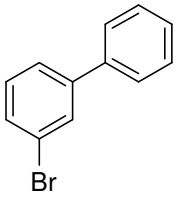
 **136**	 **137**	90	73[47]
 **138**	 **139**	85	92[126]
 **136**	 **137**	90	73[47]

Table 7. Synthesis of biaryls from arylboronic acids via $KMnO_4/CH_3COOH$ system

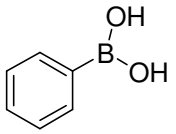
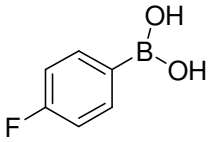
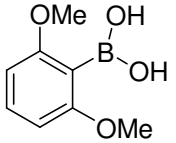
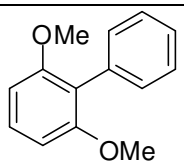
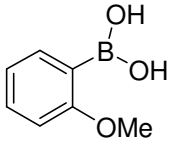
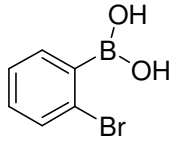
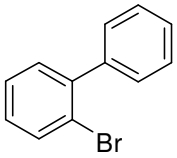
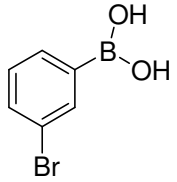
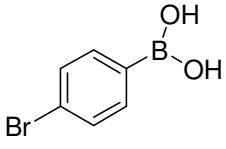
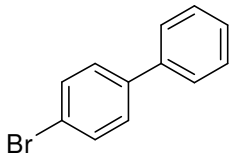
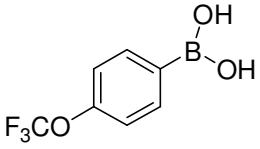
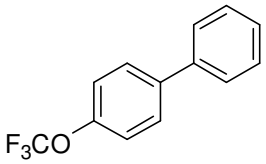
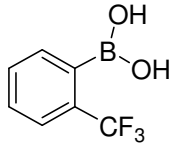
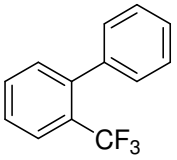
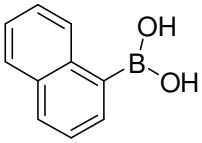
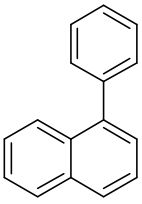
Arylboronic acid	Biaryl	Yield(%)	Yield(%)[Lit.]
 **79**	**129**	96	75[125]
 **140**	**139**	86	92[127]
 **141**	 **142**	90	89[128]
 **143**	**133**	90	89[128]

Table 7 cont'd

 **144**	 **145**	90	95[129]
 **146**	**137**	90	90[130]
 **147**	 **148**	88	92[131]
 **149**	 **150**	95	-
 **151**	 **152**	89	98[132]
 **153**	 **154**	87	94[126]

After all the reactions concluded, we found that the $KMnO_4/CH_3COOH$ system behaves as $Mn(OAc)_3$. Refluxing of $KMnO_4$/ CH_3COOH in organic solvent under the Dean–stark trap furnishes $Mn(OAc)_3$. In the case of the use of carboxylic acids other than acetic acid, the corresponding Mn(III) acyloxy derivative should be formed in order to obtain acyloxy ketones after the oxidation reaction. For the close inspection of the species for oxidation, after the reflux of the $KMnO_4$/RCOOH in benzene, the brown mixture was evaporated to dryness and cyclic voltammetric

studies were then carried out and compared with the commercially available Mn(III) acetate.

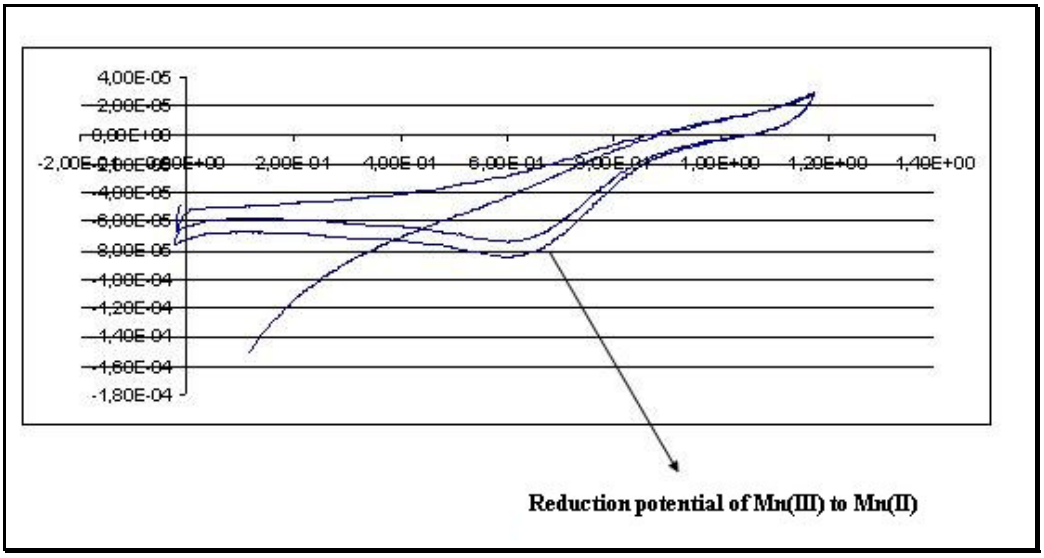


Figure 2.7. Cyclic voltammetry result for $KMnO_4$/acetic acid system

As a result, both reacted the same in cyclic voltammetry. The formation of Mn(III) species can be explained via the following equation:

$$4H^+(aq) + MnO_4^-(aq) \longrightarrow Mn^{3+}(aq) + O_2(g) + 2H_2O(l) \qquad (\Delta\Sigma^o = +\ 0.28\ V)$$

More work concerning the nature of oxidants is currently under investigation.

2.2.3. Formation of Dihydrofurans via $KMnO_4$/acetic acid/benzene system

Heiba and Dessau have reported in 1974 that β-keto esters and related dicarbonyl compounds are oxidized to radicals at 25-70°C in acetic acid[24]. The application of Mn(III) to oxidative free-radical cyclizations was investigated initially by Corey, Fristad, and Snider. Corey and Kang have reported the oxidative cyclization of

unsaturated β-keto acids in 1984[40]. In 1985, Snider[41] has described the oxidative cyclization of unsaturated β-keto esters[42] and Fristad has surveyed the cyclization of unsaturated malonic and cyanoacetic acids[43].

In the presence of $KMnO_4$/acetic acid/benzene system, dihydrofurans can also be formed in high yield from readily enolizable diketones and olefins. For example, the reaction of indene and ethyl acetoacetate furnishes the corresponding dihydrofuran derivative **157** in 65% yield (Figure 2.8). The reaction proceeds via addition of α-oxoalkyl radicals to the olefin, oxidation of the intermediate adduct radical to a carbenium ion, and subsequent cyclization of this carbenium ion to the dihydrofuran**.**

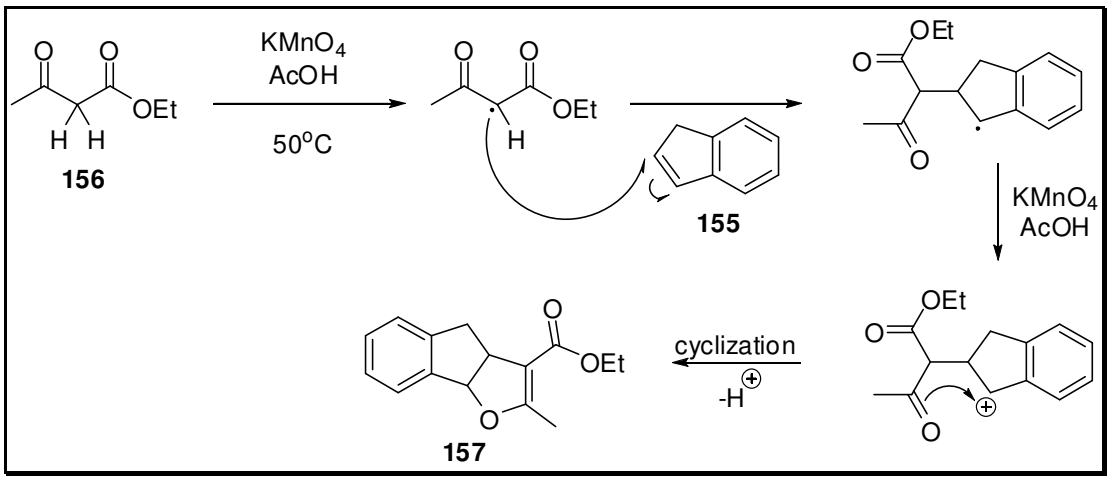


Figure 2.8. Reaction of indene and ethylacetoacetate in the presence of $KMnO_4$/acetic acid/benzene system

In the view of this result, same reaction is applied to other olefins and β-keto ester derivatives. Corresponding dihydrofurane derivatives are obtained with moderate to good yields (Table 8).

The spectroscopic data (^{1}H-NMR, ^{13}C-NMR) are in aggrement with the structures. The typical peak in the ^{1}H-NMR spectrum is the CH proton at around 6 ppm for **157**, **159**, **161** and **163** which belongs to the chiral center on the dihydrofurane ring. For

165, **166**, **168** and **169,** typical peak in ^{1}H-NMR is at around 3.2 ppm which belongs to the CH proton of the chiral center in dihydrofurane ring.

Table 8. Synthesis of dihydrofuran derivatives via $KMnO_4$/acetic acid/benzene system

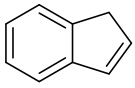
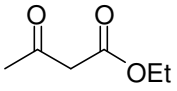
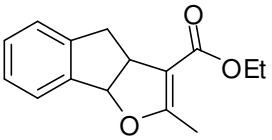
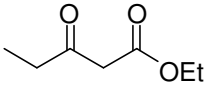
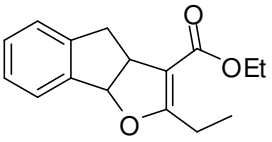
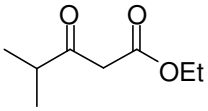
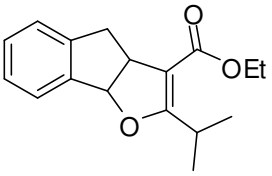
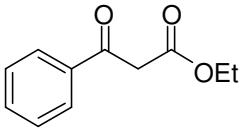
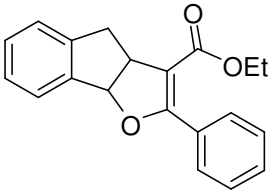
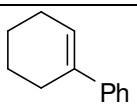
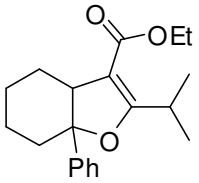
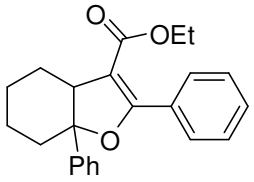
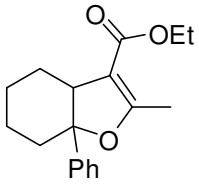
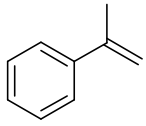
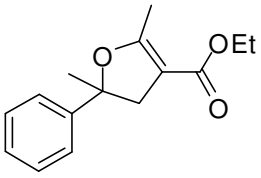
Alkene	β-keto ester	Product	Yield(%)
 **155**	 **156**	 **157**	66
155	 **158**	 **159**	72
155	 **160**	 **161**	67
155	 **162**	 **163**	70
 **164**	**160**	 **165**	70

Table 8 cont'd

164	**162**	 **166**	73
164	**158**	 **168**	68
 **167**	**156**	 **169**	65

As a result, we generated $Mn(OAc)_3$ reactions with $KMnO_4$/carboxylic acid/organic solvent system. This method gives cheaper, easier and improved yields than $Mn(OAc)_3$.

2.3. Microwave assisted reactions

It has long been known that molecules undergo excitation with electromagnetic radiation. This effect is utilized in household microwave ovens to heat up food. However, chemists have only been using microwaves as a reaction methodology for a few years. Some of the first examples gave amazing results, which led to a flood of interest in this novel technique.

Microwave radiation is converted into heat with high efficiency, so that "superheating" becomes possible at ambient pressure. Enormous accelerations in reaction time can be achieved, if superheating is performed in closed vessels under

high pressure; a reaction that takes several hours under conventional conditions can be completed over the course of minutes[133]. Thus, the advantages of using this method which is a green process include its environmental friendliness, simple manipulation, short reaction time, high regioselectivity, and good yields.

2.3.1. Microwave assisted oxidation and aryl coupling reactions with $Mn(OAc)_3$ and $KMnO_4$ / carboxylic acid/ organic solvent system

As a part of our ongoing research on the reactions of $Mn(OAc)_3$ and $KMnO_4$ / carboxylic acid/ organic solvent system, we decided to try enone oxidation and aryl coupling reactions under microwave conditions.

First, $Mn(OAc)_3$ reactions are performed by under microwave radiation. Silica gel and zeolite are tried as supporting surface. Beter results are obtained with zeolite. In order to distribute all of the substrates (which are solid in most cases) to the reaction medium several solvents such as benzene, acetonitrile, THF and cyclohexane are tried and benzene mixed with acetic acid is selected as the solvent to be used (Figure 2.9).

The reaction is also performed under different microwave conditions such as 200, 400, 600 and 800 watt and 800 watt was the best for conversions. Only drawback of this reaction is the hydrolysis of the acetoxy products to hydroxy derivatives in some cases.

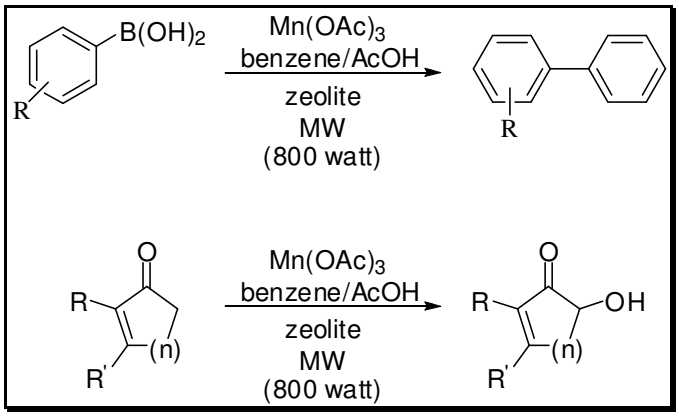


Figure 2.9. Synthesis of biaryls and enone oxidation reactions with $Mn(OAc)_3$ under MW radiation

In a typical reaction procedure, a mixture of $Mn(OAc)_3$, and enone which is dissolved in minimun amount of benzene-acetic acid mixture (10:1) and adsorbed on the zeolite surface was irradiated in a microwave oven for a period of time long enough to complete the reaction which is determined by TLC control. The reaction mixture was washed with a minimum amount of ether, and evaporation of the solvent furnished a crude product that was purified by column chromatography. Using this procedure, various enones were converted to their α-acetoxy or/and α-hydroxy derivatives through a one-step operation in 40–72% yield.

Same reaction is also performed with $KMnO_4$/AcOH/benzene system. First the $KMnO_4$/AcOH/benzene mixture is mixed with zeolite and irradiated under microwave radiation. After the conversion of the purple color of mixture into brown, enone is added and irradiation is continued. Products are obtained with similar yields with $Mn(OAc)_3$ case as summarized in Table 9 and 10.

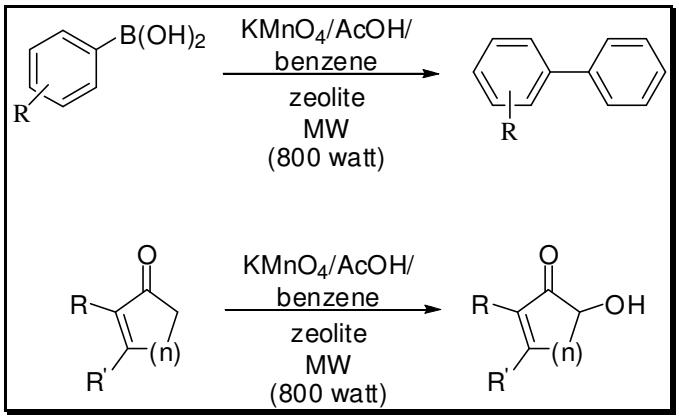


Figure 2.10. Synthesis of biaryls and enone oxidation reactions with $KMnO_4$/AcOH/benzene system under MW radiation

Table 9. Enone oxidation reactions with $Mn(OAc)_3$ and $KMnO_4$/AcOH/benzene system under MW radiation

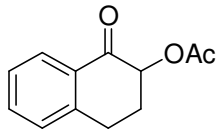
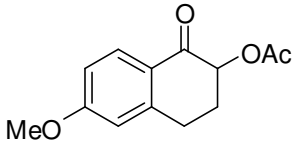
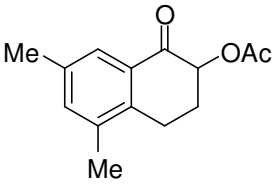
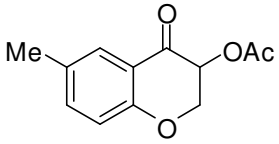
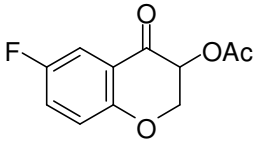
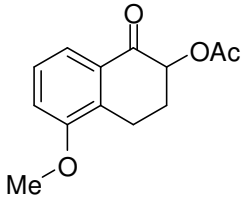
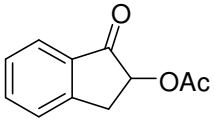
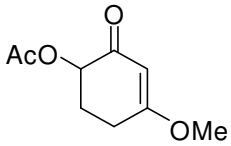
Product	Yield %	
	$Mn(OAc)_3$	**$KMnO_4$/AcOH/ Benzene System**
 **94**	50	52
 **90**	54	51
 **92**	61	58
 **98**	72	74

Table 9 cont'd

 **106**	65	62
 **96**	(40%)- acetoxy (40%)- hydroxy	Not tried
 **88**	60	62
 **108**	(50%)- hydroxy (50%)- acetoxy	(50%)- hydroxy (50%)- acetoxy

The α-acetoxy products are obtained with similar yields in both $Mn(OAc)_3$ and $KMnO_4$/AcOH system. In reactions of **96** and **108**, α-hydroxy products are also obtained with α-acetoxy products which may result from the hydrolysis of the acetoxylated products. Among these two reactions, $KMnO_4$/AcOH system gives higher yields and more easy work-up procedures which makes it more preferable.

Table 10. Aryl coupling reactions with $Mn(OAc)_3$ and $KMnO_4$/AcOH/benzene system under MW radiation.

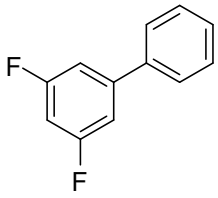
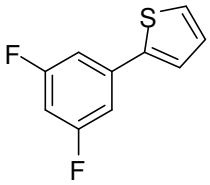
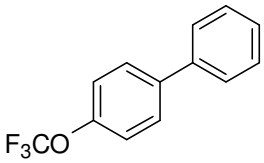
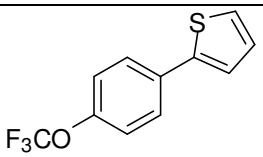
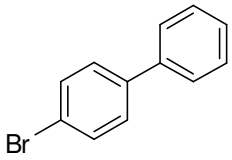
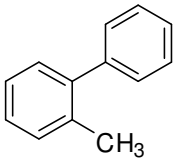
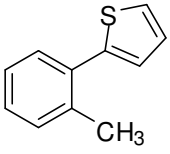
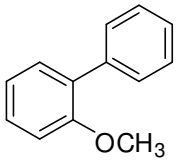
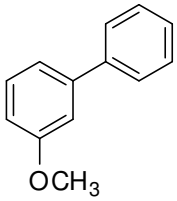
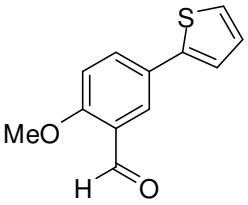
Product	Yield %	
	$Mn(OAc)_3$	**$KMnO_4$/AcOH/ Benzene system**
 **170**	85	90
 **171**	92	95
 **150**	78	84
 **172**	82	88
 **148**	84	87
 **173**	87	93
 **174**	91	95

Table 10 cont'd

 **133**	76	75
 **174**	92	98
 **176**	62	65

In synthesis of biaryls under microwave radiation besides benzene, heteroaromatic solvents are also tried such as furane and thiophene. Among these two aromatic solvents thiophene gave biaryls with high yields but in furane case lots of side products are formed and we couldn't get desired product in acceptable yields.

The reaction proceeds independent of the substituents of the arylboronic acid. Both arylboronic acids with electron withdrawing and electron releasing groups at ortho, para and meta positions gave corresponding biaryls in excellent yields.

2.4. Ipso-nitration reaction with arylboronic acis

Arylboronic acids have been extensively used as versatile synthons in organic synthesis involving various reactions. Nitration of aromatic compounds is one of the most extensively studied reactions, and nitroaryl moieties play key roles in the physical and chemical properties of many target molecules in organic synthesis [54]. Since most nitrating agents are oxidants, oxidation of other functional groups can

also occur, giving a mixture of products. Thus, a search for milder and selective nitrating agents is a good research goal.

Recently Demir *et. al.* has reported that the reaction of $AgNO_2$ with TMSCl furnished first N_2O_3 and hexamethylsiloxane. The reaction of $AgNO_2$/TMSCl with olefins affords nitrosonitrate, which are converted into α-nitroximes in good yield. Both nitrosonitrate and nitroximes are converted with acids into furoxane in high yield. The nitroso nitrates are obtained by addition of N_2O_3 to the olefines[117].

Using silver nitrite and chlorotrimethylsilane is a convenient and mild method for the nitration of arylboronic acids. This method furnishes the nitrated product in high yield (76-98% purity for the crude product itself) and is found to be selective and only ipso-nitration products are obtained. The reaction is easy to perform, and work-up avoids further purification in many cases. The effect of different solvents on the reaction system has also been investigated. Tetrahydrofurane (THF) was found to be the most suitable solvent. In other solvents such as 1,2-dichloroethane, the amount of chlorination increases.

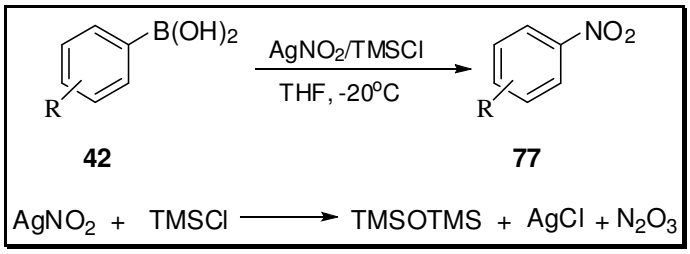


Figure 2.11. Ipso-nitration of aryl boronic acids via $AgNO_2$/TMSCl

In an initial reaction $AgNO_2$ and TMSCl was reacted in THF or in acetonitrile at –20 ^oC under argon and first white precipitate was formed. The mixture gave some gaseous products when the reaction temperature arises to room temperature. To the mixture of $AgNO_2$ and TMSCl at –20 ^oC was given phenylboronic acid **79** and the resulted mixture was stirred at this temperature for 3h under argon. After work up

only the product isolated was nitrobenzene (93% yield). Low yield formation was observed by using KNO_2 and $NaNO_2$ under similar conditions (25-36%). As shown in Table 11, representative arylboronic acids are converted into nitro derivatives in excellent yields. Monitoring of the reactions by GC-MS and analysis of the crude products by using NMR, IR spectroscopy showed that nitration of arylboronic acids with $AgNO_2$ and TMSCl takes place at the *ipso*-position of the aryl ring without ring nitration or sequential nitration. Also, the reaction proceeds independent of the nature and position of the substituents. Both arylboronic acids with e-withdrawing and e-releasing substituents gives corresponding nitro derivative in good yields.

Table 11. *Ipso*-nitration products and yields

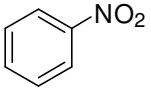
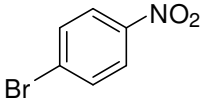
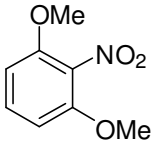
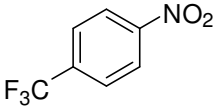
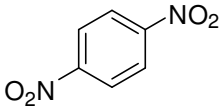
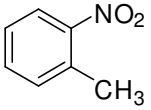
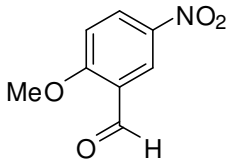
Product	Yield (%)
 **77a**	93
 **77b**	67
 **77c**	100
 **77d**	95
 **77e**	100
 **77f**	100

Table 11 cont'd

 **77g**	95

For finding evidence for the possible formation of N_2O_3 and addition to double bond the TMSCl and silver nitrite are suspended in deuterated DMF at –5°C. The ^{1}H NMR spectrum showed the formation of hexamethyldisiloxane. With this result we suggest that the reaction of $AgNO_2$ with TMSCl leads the formation of N_2O_3 and hexamethyldisiloxane. The formation and subsequent addition of N_2O_3 to alkene furnished nitroso nitrate as dimer. Heating of dimeric nitroso nitrate affords furoxan *via* formation of α-nitro oxime followed by elimination of water.

With aliphatic boronic acids, we were unable to obtain any nitrated product. This shows that the aromatic ring plays an important electronic role in the *ipso*-nitration. By the nitration reaction carried out with $AgNO_2$/TMSCl the interaction between the boronic acid group and the intermediate active nitrating agent N_2O_3 species through boron and the hexamethyldisiloxane due to the high oxophilicity of boron. This helps the nitration to occur at the ipso position.

CHAPTER 3

EXPERIMENTAL

3.1. Materials and Methods

In this study all compounds were identified by using Nuclear Magnetic Resonance Spectometer (NMR) (Bruker DPX 400 MHz) by using tetramethylsilane (TMS) as an internal Standard and deutereo chloroform as solvent. Chemical shifts were reported in ppm relative to $CHCl_3$ (^1H: d = 7.26) and $CDCl_3$ (^{13}C: d = 77.0) as an internal standard; coupling constants are reported in Hz.

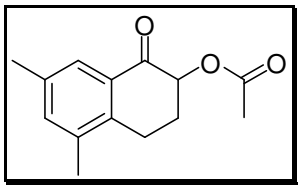
Flash column chromatography was done for purifying the products by using Merck Silica Gel 60 (partical size 40-63 μm). TLC was carried out on aluminum sheets precoated with silica gel 60F254 (Merck), and the spots were visualized with UV light (l = 254 nm). MS: ThermoQuest Finnigan multi Mass (EI, 70 eV). Melting points were measured on a capillary tube apparatus and are uncorrected. The microwave reactions were carried out in Milestone-Start microwave instrument.

3.2 Synthesis of acyloxy enones and biaryls via $KMnO_4$/ carboxylic acid/ organic solvent system

3.2.1 General procedure for α-acyloxylation of enones.

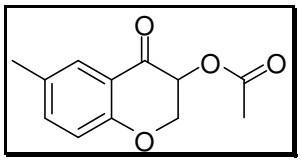
A solution of 3 mmol of $KMnO_4$ in 100 mL benzene–carboxylic acid (10:1) was stirred under reflux (Dean–Stark apparatus) until the purple color of $KMnO_4$ turned brown (15–30 min.). To this solution, 1 mmol of enone was added and reflux was continued. The reaction was monitored by TLC. After all the starting material was consumed, the reaction mixture was diluted with ether and neutralized with $NaHCO_3$. The resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum. If necessary, the crude products were purified by column chromatography using EtOAc–hexane as an eluent.

1,2,3,4-Tetrahydro-5,7-dimethyl-1-oxonaphthalen-2-yl acetate (92)



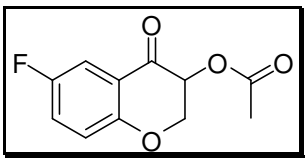
Yield 222 mg, 96%, yellow solid (mp 101–103 ^oC). IR ($CHCl_3$) ν_{max}: 763, 1608, 1693, 3447 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.09–2.20 (1H, m, CH), 2.15 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.27 (3H, s, CH_3), 2.20–2.45 (1H, m, CH_2), 2.80–3.00 (m, 2H, CH_2), 5.39 (1H, dd, *J*=5.0, 13.7 Hz, CH), 7.09 (1H, s, CH), 7.60 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 169.9, 138.2, 136.3, 136.2, 135.9, 131.7, 125.8, 74.2, 28.4, 25.0, 20.9, 19.3. Anal. Calcd for $C_{14}H_{16}O_3$ (232.28): C, 72.39; H, 6.94. Found: C, 72.61; H, 6.64.

3,4-Dihydro-6-methyl-4-oxo-2H-chromen-3-yl acetate (98)



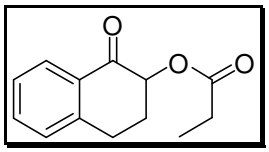
Yield 182 mg, 83%, yellow oil. IR (neat) ν_{max}: 762, 1060, 1609, 1693, 3443 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.12 (3H, s, CH_3), 2.25 (3H, s, $COCH_3$), 4.27 (1H, t, J=11.3 Hz, CH_2), 4.43 (1H, dd, J_1=5.4 Hz, J_2=11.0 Hz, CH_2), 5.52 (1H, dd, J_1=5.4 Hz, J_2=11.4 Hz, CH), 6.79 (1H, d, J=8.5 Hz, CH), 7.24 (1H, d, J=11.7 Hz, CH), 7.58 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.5, 68.3, 69.4, 117.5, 119.6, 127.2, 131.3, 137.2, 159.4, 169.0, 187.5. Anal. Calcd for $C_{12}H_{12}O_4$ (220.22): C, 65.45; H, 5.49. Found: C, 65.34; H, 5.67.

6-Fluoro-3,4-dihydro-4-oxo-2H-chromen-3-yl acetate (106)



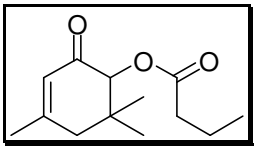
Yield 166 mg, 74%, yellow semisolid. IR ($CHCl_3$) ν_{max}: 762, 845, 1254,1612,1701, 3443 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.15 (3H, s, CH_3), 4.32 (1H, dd, J_1=5.4 Hz, J_2=11.3 Hz, CH_2), 4.48 (1H, dd, J_1=5.5 Hz, J_2=11.1 Hz, CH_2), 5.56 (1H, dd, J_1=5.5 Hz, J_2=11.4 Hz, CH), 6.91 (1H, dd, J_1=4.1 Hz, J_2=9.1 Hz, CH), 7.17–7.23 (1H, m, CH_3), 7.47 (1H, dd, J_1=5.5 Hz, J_2=11.1 Hz, CH, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 68.9, 69.6, 113.0 (d, $^2J_{CF}$=23.4 Hz), 119.8 (d, $^3J_{CF}$=7.2 Hz), 120.8 (d, $^3J_{CF}$=6.6 Hz), 124.2 (d, $^2J_{CF}$=24.6 Hz), 157.8, 158.0 (d, $^3J_{CF}$=241.9 Hz), 169.3, 187.1. Anal. Calcd for $C_{11}H_9FO_4$ (224.19): C, 58.93; H, 4.05. Found: C, 59.14; H, 4.27.

1,2,3,4-Tetrahydro-1-oxonaphthalen-2-yl propionate (117)



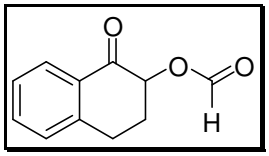
Yield 190 mg, 87%, brown viscous oil. IR ($CHCl_3$) ν_{max}: 762, 1060, 1615, 1710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, t, *J*=7.5 Hz, CH_3), 2.22 (1H, ddd, J_1=4.7 Hz, J_2=12.7 Hz, J_3=25.6 Hz, CH_3), 2.29– 2.53 (3H, m, CH_2, CH_2), 2.93–3.22 (2H, m, CH_2), 5.45 (1H, dd, J_1=5.2 Hz, J_2=13.2 Hz, CH), 7.18 (1H, t, *J*=4.8 Hz, CH), 7.25 (1H, t, *J*=7.5 Hz, CH), 7.41 (1H, t, *J*=7.0 Hz, CH), 7.95 (1H, d, *J*=7.8 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8, 9.2, 27.4, 28.0, 29.2, 74.2, 126.9, 127.9,128.5, 131.5,133.7,142.9,173.3,192.4. Anal. Calcd for $C_{13}H_{14}O_3$ (218.25): C, 71.54; H, 6.47. Found: C, 71.31; H, 6.29.

4,6,6-Trimethyl-2-oxocyclohex-3-enyl butyrate (119)



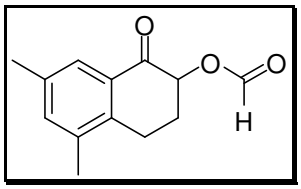
Yield 184 mg, 82%, yellow oil. IR (neat) ν_{max}: 1609, 1665, 1713, 3010 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.91–0.97 (9H, m, CH_3), 1.02 (3H, s, CH_3), 1.66 (2H, sextet, *J*=7.3 Hz, CH_2CH_3), 1.88 (3H, s, CH_3), 2.07–2.12 (1H, m, CH), 2.30–2.50 (3H, m, CH_2, CH_2), 5.12 (1H, s, CH), 5.81 (1H, s, CH); ^{13}C NMR (100 MHz, CDCl3) δ 13.7, 18.5, 20.0, 24.2, 27.3, 36.0, 37.6, 46.1, 80.0, 124.9, 158.0, 172.5, 192.4. Anal. Calcd for $C_{13}H_{20}O_3$ (224.3): C, 69.61; H, 8.99. Found: C, 69.42; H, 8.77.

1,2,3,4-Tetrahydro-1-oxonaphthalen-2-yl formate (121)



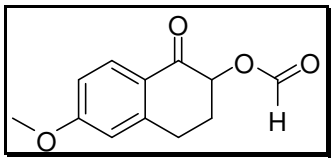
Yield 165 mg, 85%, yellow oil. IR (neat) ν_{max}: 740, 1612, 1690, 2933, 3435 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (1H, ddd, J_1=4.8 Hz, J_2=12.8 Hz, J_3=17.5 Hz, CH_2), 2.34–2.39 (1H, m, CH_2), 3.03 (1H, dt, J_1=4.5 Hz, J_2=17.0 Hz, CH_2), 3.12–3.20 (1H, m, CH_2), 5.54 (1H, dd, J_1=5.1 Hz, J_2=13.3 Hz, CH), 7.18 (1H, d, J=8.0 Hz, CH), 7.27 (1H, t, J=7.7 Hz, CH), 7.43 (1H, t, J=7.5 Hz, CH), 7.96 (1H, d, J=7.9 Hz, CH), 8.16 (1H, s, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 29.1, 73.9, 127.0, 128.1, 128.5, 131.5, 133.9, 42.7, 159.4, 191.3. Anal. Calcd for $C_{11}H_{10}O_3$ (190.2): C, 69.46; H, 5.30. Found: C, 69.33; H, 5.48.

1,2,3,4-Tetrahydro-5,7-dimethyl-1-oxonaphthalen-2-yl formate (122)



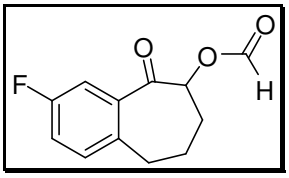
Yield 164 mg, 75%, brown oil. IR (neat) ν_{max}: 762, 1609, 1693, 2927, 3443 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.14–2.24 (1H, m, CH_2), 2.21 (3H, s, CH_3), 2.27 (3H, s, CH_3), 2.35–2.40 (1H, m, CH_2), 2.82–2.90 (1H, m, CH_2), 2.95–3.02 (1H, m), 5.51 (1H, dd, J_1=5.0 Hz, J_2=13.6 Hz, CH), 7.12 (1H, s, CH), 7.62 (1H, s, CH), 8.16 (1H, s, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 20.3, 24.3, 27.8, 73.2, 125.5, 131.1, 135.5, 135.8, 137.5, 159.0, 191.3. Anal. Calcd for $C_{13}H_{14}O_3$ (218.25): C, 71.54; H, 6.47. Found: C, 71.68; H, 6.55.

1,2,3,4-Tetrahydro-6-methoxy-1-oxonaphthalen-2-yl formate (123)



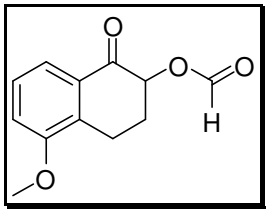
Yield 167 mg, 76%, yellow oil. IR (neat) ν_{max}: 1250, 1615, 1703, 2930, 3430 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.23 (1H, ddd, J_1=4.6 Hz, J_2=12.6 Hz, J_3=17.3 Hz, CH_2), 2.31–2.37 (1H, m, CH_2), 2.99 (1H, dt, J_1=3.6 Hz, J_2=16.9 Hz, CH_2), 3.07 - 3.15 (1H, m, CH_2), 3.79 (3H, s, OCH_3), 5.50 (1H, dd, J_1=5.4 Hz, J_2=12.9 Hz, CH), 6.56 (1H, s, CH), 6.77 (1H, dd, J_1=2.1 Hz, J_2=8.8 Hz, CH), 7.93 (1H, d, J=8.8 Hz, CH), 8.16 (1H, s, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 29.1, 55.3, 73.6, 112.5, 113.6, 125.0, 130.5, 145.2, 159.6, 164.0, 190.0. Anal. Calcd for $C_{12}H_{14}O_4$ (220.22): C, 65.45; H, 5.49. Found: C, 65.66; H, 5.27.

2-Fluoro-6,7,8,9-tetrahydro-9-oxo-5H-benzo[7]annulen-8-yl formate (125)



Yield 135 mg, 61%, colorless oil. IR (neat) ν_{max}: 762, 1605, 1692, 2926, 3440 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.73–1.84 (1H, m, CH_2), 2.00–2.23 (3H, m, CH_2, CH_2), 2.92–2.95 (1H, m, CH_2), 5.44 (1H, dd, J_1=6.9 Hz, J_2=12.6 Hz, CH), 7.04 (1H, td, J_1=2.7 Hz, J_2=10.7 Hz, CH), 7.11–7.16 (1H, m, CH), 7.38 (1H, dd, J_1=2.8 Hz, J_2=8.9 Hz, CH), 8.02 (1H, s, CHO); ^{13}C NMR ($CDCl_3$) δ 23.1, 28.6, 33.0, 76.9, 96.3,116.2 (d, J=27.8 Hz, CF), 119.3 (d, J=21.3 Hz, CF), 132.1 (d, J=7.2 Hz, CF), 137.5 (d, J=3.4 Hz, CF), 138.3 (d, J=6.4 Hz, CF), 159.8, 160.3, 163.6, 197.2. Anal. Calcd for $C_{12}H_{11}FO_3$ (222.21): C, 64.86; H, 4.99. Found: C, 64.73; H, 4.81.

1,2,3,4-Tetrahydro-5-methoxy-1-oxonaphthalen-2-yl formate (126)

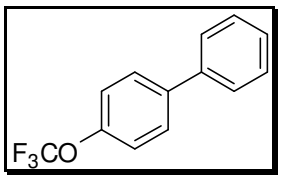


Yield 154 mg, 70%, brown oil. IR (neat) ν_{max}: 762, 1264, 1609, 1693, 2927, 3443 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.18 (1H, ddd, J_1=5.0 Hz, J_2=12.8 Hz, J_3=17.8 Hz, CH_2), 2.34–2.40 (1H, m, CH_2), 2.74–2.83 (1H, m, CH_2), 3.20 (1H, ddd, J_1=2.7 Hz, J_2=4.6 Hz, J_3=18.0 Hz, CH_2), 3.81 (3H, s, CH_3), 5.53 (1H, dd, J_1=5.0 Hz, J_2=13.6 Hz, CH), 6.95 (1H, d, J=8.0 Hz, CH), 7.22 (1H, t, J=8.0 Hz, CH), 7.55 (1H, d, J=7.9 Hz, CH), 8.17 (1H, s, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 28.2, 55.5, 114.5, 119.5, 127.6, 131.8, 132.6, 156.6, 159.5, 191.6. Anal. Calcd for $C_{12}H_{12}O_4$ (220.22): C, 65.45; H, 5.49. Found: C, 65.54; H, 5.71.

3.2.2 General procedure for the coupling of arylhydrazines or arylboronic acids via $KMnO_4$/ carboxylic acid/ organic solvent system

A solution of 3 mmol of $KMnO_4$ in 100 mL benzene–AcOH (10:1) was stirred under reflux (Dean–Stark apparatus) until the purple color of $KMnO_4$ turned brown (15–30 min.). To this solution 1 mmol of aryl hydrazine or arylboronic acid was added and reflux was continued. The reaction was monitored by TLC. After all the starting material was consumed, the reaction mixture was diluted with ether and neutralized with $NaHCO_3$. The resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum. If necessary, the crude products were purified by column chromatography using EtOAc–hexane as an eluent. In most cases, the direct filtering of the reaction mixture through a pad of silica provided pure products.

4-(Trifluoromethoxy)-1,10-biphenyl (142)



Yield 226 mg, 95%, white solid (mp 56–58 _C). IR (CHCl3) ν_{max}: 762, 832, 1245, 1625 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (2H, d, *J*=8.7 Hz, CH), 7.26 (1H, t, *J*=7.4 Hz, CH), 7.34 (2H, d, *J*=7.4 Hz, CH, CH), 7.44 (2H, t, *J*=7.4 Hz, CH, CH), 7.49 (2H, t, *J*=8.6 Hz, CH, CH); ^{13}C NMR (100 MHz $CDCl_3$) δ 121.2, 127.1, 127.6, 128.4, 128.8, 139.9, 140.1, 148.7. Anal. Calcd for $C_{13}H_9F_3$ (238.21): C, 65.55; H, 3.81. Found: C, 65.34; H, 3.77.

3.3. Synthesis of acyloxy enones and biaryls via $Mn(OAc)_3$, $KMnO_4$/ acetic acid system under microwave radiation

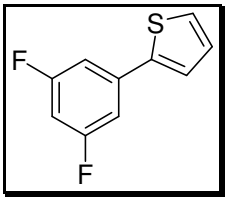
3.3.1 General procedure for α-acyloxylation of enones and biaryl synthesis via $Mn(OAc)_3$ under microwave radiation

To a solution of 0.3 mmol of $Mn(OAc)_3$ and 500 mg of zeolite in 5 mL benzene–AcOH (20:1) or thiophene- AcOH was added 0.1 mmol of aryl boronic acid or enone. This solution is stirred under 800 watt microwave radiation (30 min.-1 hour). The reaction is monitored by TLC. After all the starting material is consumed, the reaciton mixture was diluted with ether and neutralized with $NaHCO_3$. The resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum. If necessary, the crude products were purified by column chromatography using EtOAc–hexane as an eluent.

3.3.2 General procedure for a-acyloxylation of enones and biaryl synthesis via $KMnO_4$/ acetic acid system under microwave radiation

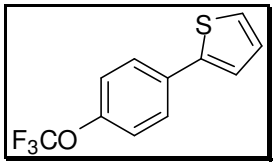
0.3 mmol of $KMnO_4$ and 500 mg of zeolite in 5 mL benzene–AcOH (20:1) or thiophene- AcOH was stirred under 800 watt microwave radiation until the color of the solution turns into brown.To this solution 0.1 mmol of aryl boronic acid or enone was added and stirred under 800 watt microwave radiation (30 min.-1 hour). The reaction is monitored by TLC. After all the starting material is consumed, the reaciton mixture was diluted with ether and neutralized with $NaHCO_3$. The resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum. If necessary, the crude products were purified by column chromatography using EtOAc–hexane as an eluent.

2-(3,5-difluorophenyl)thiophene (171)



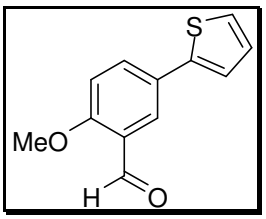
Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57-6.63 (1H, m, CH), 6-95-7.02 (3H, m, CH), 7.20 (2H, d, *J*=5.2 Hz, CH); ^{13}C-NMR (100MHz, $CDCl_3$) δ 102.5 (t, J_{CF}=24.7 Hz), 108.8 (dd, J_{CF1}=7.5, J_{CF2}=18.5 Hz), 121.7, 124.4, 126.0, 126.7, 128.1, 137.5 (t, J_{CF}=9.9 Hz), 141.9, 163.4 (dd, J_{CF1}=247, J_{CF2}=12.6 Hz).

2-(4-(trifluoromethoxy)phenyl) thiophene (172)



Brown solid, mp= 72.5-75.3 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (1H, t, *J*=4.2 Hz, CH), 7.13-7.32 (4H, m, CH), 7.52 (2H, d, *J*=8.6); ^{13}C-NMR (100MHz, $CDCl_3$) δ 121.3, 121.4, 123.6, 125.3, 126.1, 127.2, 127.7, 128.0, 133.3, 142.8, 148.5.

2-Methoxy-5-(thiophen-2-yl) benzaldehyde (176)

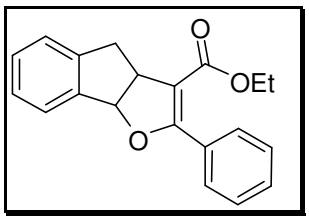


Green oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (3H, s, CH_3), 6.90-6.98 (2H, m, CH), 7.15-7.19 (2H, m, CH), 7.67 (1H, dd, J_1= 2.5, J_2= 8.7 Hz, CH), 7.96 (1H, d, *J*=2.5 Hz, CH), 10.39 (1H, s, CH); ^{13}C-NMR (100MHz, $CDCl_3$) δ 54.4, 110.9, 121.8, 123.5, 123.9, 124.6, 126.6, 126.9, 131.9, 141.7, 159.9, 187.6.

3.4 Synthesis of dihydrofurans from alkenes and 1,3 dicarbonyl copounds via $KMnO_4$/acetic acid/organic solvent system

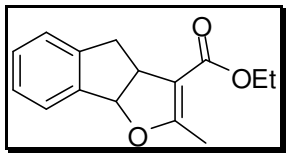
A solution of 3 mmol of $KMnO_4$ in 100 mL benzene–AcOH (10:1) was stirred under reflux (Dean–Stark apparatus) until the purple color of $KMnO_4$ turned brown (15–30 min.). To this solution 1 mmol of alkene and 1 mmol of 1,3 dicarbonyl compound was added and reflux was continued. The reaction was monitored by TLC. After all the starting materials were consumed, the reaction mixture was diluted with ether and neutralized with $NaHCO_3$. The resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum. If necessary, the crude products were purified by column chromatography using EtOAc–hexane as an eluent.

Ethyl 2-phenyl-4,8b-dihydro-3aH-indeno[1,2-b]furan-3-carboxylate (163)



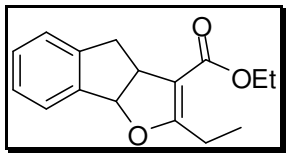
Yellow oil. ^{1}H-NMR($CDCl_3$) δ 1.20 (3H, t, *J*=7.0), 3.24 (1H, d, *J*=17.2), 3.42 (1H, dd, J_1=8.4, J_2= 17.2), 4.08-4.21 (2H, m), 4.28 (1H, dt, J_1=2.6, J_2= 9.0), 6.10 (1H, d, *J*=9.3), 7.22-7.35 (6H, m), 7.49 (1H, d, *J*=7.3 Hz), 7.64 (2H, d, *J*=7.7 Hz); ^{13}C-NMR($CDCl_3$) δ 14.6, 19.5, 19.7, 26.8, 39.0, 45.3, 59.1, 89.3, 104.0, 124.5, 125.3, 125.7, 126.9, 129.3, 133.9, 140.5, 142.8, 165.6, 175.4.

Ethyl 2-methyl-4,8b-dihydro-3aH-indeno[1,2-b]furan-3-carboxylate (157)



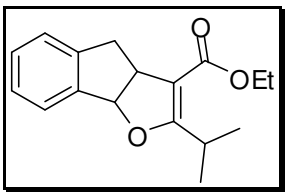
Colorless oil. ^{1}H-NMR($CDCl_3$) δ 1.27 (3H, t, *J*=7.1 Hz), 2.13 (3H, s), 3.13 (1H, d, *J*=17.1 Hz), 3.30 (1H, dd, J_1=6.2, J_2= 14.5 Hz), 4.03 (1H, t, *J*=8.5 Hz), 4.12-4.24 (2H, m), 5.95 (1H, d, *J*=9.2 Hz), 7.17-7.28 (3H, m), 7.41 (1H, d, *J*=7.8 Hz); ^{13}C-NMR($CDCl_3$) δ 14.4, 14.6, 39.1, 45.2, 59.2, 89.7, 106.3, 125.3, 125.7, 126.9, 129.4, 140.3, 143.1, 165.8, 167.5.

Ethyl 2-ethyl-4,8b-dihydro-3aH-indeno[1,2-b]furan-3-carboxylate (159)



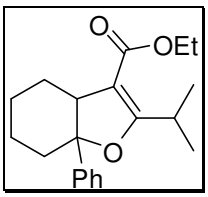
Yellow oil. ^{1}H-NMR($CDCl_3$) δ 0.98 (3H, t, *J*=7.6 Hz), 1.22 (3H, t, *J*=7.1 Hz), 2.45 (1H, m), 2.60 (1H, m), 3.05 (1H, dd, J_1=1.7, J_2= 17.1 Hz), 3.23 (1H, dd, J_1=8.3, J_2= 17.1 Hz), 3.96 (1H, t, *J*=8.3 Hz), 4.11 (2H, m), 5.88 (1H, d, *J*=9.1 Hz), 7.16 (3H, m), 7.34 (1H, d, *J*=4.4 Hz); ^{13}C-NMR($CDCl_3$) δ 11.1, 14.6, 21.5, 39.1, 45.3, 59.1, 89.5, 105.1, 125.3, 125.7, 126.9, 129.4, 140.4, 142.9, 165.5, 172.2.

Ethyl 2-isopropyl-4,8b-dihydro-3aH-indeno[1,2-b]furan-3-carboxylate (161)



Yellow oil. ^{1}H-NMR($CDCl_3$) δ 0.94 (2H, d, *J*=6.9 Hz), 1.13 (2H, d, *J*=6.9 Hz), 1.30 (3H, t, *J*=7.1 Hz), 3.12 (1H, dd, J_1=1.6, J_2= 17.0 Hz), 3.30 (1H, dd, J_1=8.2, J_2= 17.1 Hz), 3.54 (1H, septet, *J*=6.9 Hz), 4.02 (1H, dt, J_1=2.4, J_2= 8.8 Hz), 4.18 (2H, m), 5.95 (1H, d, *J*=9.1 Hz), 7.26 (3H, m), 7.42 (1H, d, *J*=7.4 Hz); ^{13}C-NMR($CDCl_3$) δ 14.6, 19.5, 19.7, 26.8, 39.0, 45.3, 59.1, 89.3, 104.0, 125.2, 125.6, 126.9, 129.3, 140.4, 142.8, 165.5, 175.3.

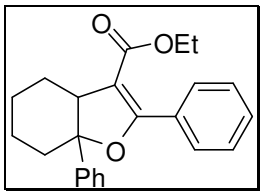
Ethyl 2-isopropyl-7a-phenyl-3a,4,5,6,7,7a-hexahydrobenzofuran-3-carboxylate (165)



Yellow oil. ^{1}H-NMR($CDCl_3$) δ 1.14-1.18 (6H, m), 1.34-1.65 (5H, m), 1.76-1.93 (3H, m), 3.27 (1H, t, *J*=5.3 Hz), 3.62 (1H, septet, *J*=6.9 Hz), 3.96-4.11 (2H, m), 7.15-7.18 (1H, m), 7.25 (2H, t, *J*=7.6 Hz), 7.32 (2H, t, *J*=7.2 Hz); ^{13}C-NMR($CDCl_3$) δ 14.5,

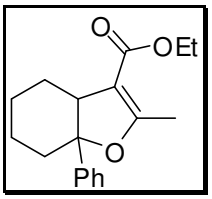
17.8, 18.4, 19.6, 19.9, 25.6, 27.1, 34.0, 46.9, 59.0, 89.4, 104.2, 124.1, 127.1, 128.7, 147.7, 165.5, 174.8.

Ethyl 2,7a-diphenyl-3a,4,5,6,7,7a-hexahydrobenzofuran-3-carboxylate (166)



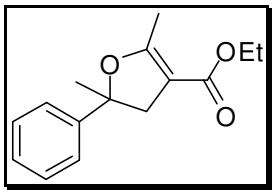
Yellow oil. ^{1}H-NMR($CDCl_3$) δ 1.08 (3H, t, *J*=7.1 Hz), 1.36-1.46 (1H, m), 1.55-1.69 (3H, m), 1.78-1.86 (1H, m), 2.06-2.12 (2H, m), 3.41 (1H, t, *J*=6.1 Hz), 3.93-4.03 (2H, m), 7.15 (1H, t, *J*=7.2 Hz), 7.24 (2H, t, *J*=7.6 Hz), 7.28-7.34 (3H, m), 7.38 (2H, d, *J*=7.6 Hz), 7.76-7.78 (2H, m) ; ^{13}C-NMR($CDCl_3$) δ 13.1, 18.3, 18.6, 26.2, 26.3, 33.7, 47.0, 58.3, 88.4, 107.3, 123.3, 124.3, 126.0, 126.5, 127.1, 128.3, 129.0, 129.5, 146.0, 163.1, 163.8.

Ethyl-2-methyl-7a-phenyl-3a,4,5,6,7,7a-hexahydrobenzofuran-3-carboxylate (168)



Yellow oil. ^{1}H-NMR($CDCl_3$) δ 1.13 (3H, t, *J*=7.1 Hz), 1.29-1.37 (1H, m), 1.45-1.59 (4H, m), 1.73-1.81 (1H, m), 1.90-1.96 (2H, m), 2.21 (3H, s), 3.20 (1H, t, *J*=5.6 Hz), 3.93-4.08 (2H, m), 7.11-7.15 (1H, m), 7.22 (2H, t, *J*=7.3 Hz), 7.27-7.31 (2H, m); ^{13}C-NMR($CDCl_3$) δ 14.4, 14.5, 18.8, 19.2, 26.4, 34.3, 46.9, 59.2, 90.2, 107.5, 124.3, 127.1, 128.2, 147.4, 166.1, 167.3.

Ethyl 2,5-dimethyl-5-phenyl-4,5-dihydrofuran-3-carboxylate(169)



Yellow oil. ^{1}H-NMR($CDCl_3$) δ 1.20 (3H, t, *J*=7.2 Hz), 1.60 (3H, s), 2.22 (3H, s), 3.00 (2H, dd, J_1=14.4 Hz, J_2=34.8 Hz), 4.07 (2H, q, *J*=7.2 Hz), 7.14-7.18 (1H,m), 7.23-7.28 (4H, m)

3.5. Ipso-nitration of arylboronic acids via $AgNO_2$/ TMSCl

To a solution of 0.1 mmol of $AgNO_2$ and 0.1 mmol TMSCl in THF at -20^{o}C was added 0.1 mmol of arylboronic acid under argon atmosphere. Reaction mixture is stirred for 3 hours at -20^{o}C. The solution is filtered and diluted with DCM and washed with NaCl solution. The resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum. If necessary, the crude products were purified by column chromatography using EtOAc–hexane as an eluent. In most cases, the direct filtering of the reaction mixture through a pad of silica provided pure products.

CHAPTER 4

CONCLUSION

In summary, in the first part of this thesis, the oxidation reactions of enones and aromatic ketones were carried out with potassium permanganate/carboxylic acid in an organic solvent and acyloxy enones were obtained in high yields. The potassium permanganate/carboxylic acid system in an organic solvent was applied to dihydrofuran synthesis and aryl coupling reactions with arylboronic acids and arylhydrazines, in which biaryl products were obtained in high yields. This method enables one to obtain Mn(III) acyloxy derivatives in situ. The reactions are simple, selective, and cheap compared to other methods. The results showed that the potassium permanganate/carboxylic acid system is a powerful substitute for manganese(III) acetate.

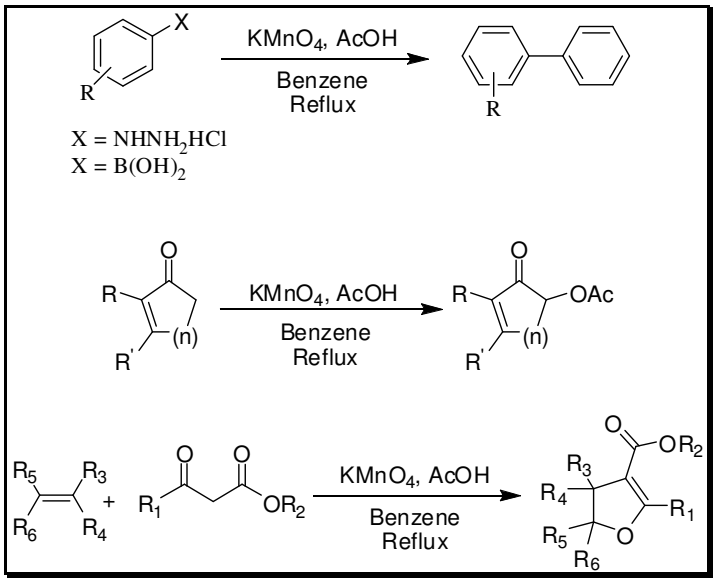


Figure 4.1. General reactions of $KMnO_4$/carboxylic acid/organic solvent system

In the second part of the thesis, a simple and convenient method for the *ipso*-nitration of arylboronic acids is developed. The method works well with a variety of functionalized arylboronic acids. Mild conditions and ease of workup are the salient features of this method.

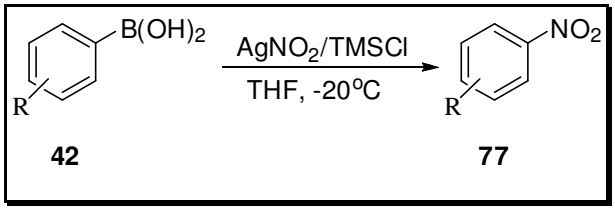


Figure 4.2. Ipso-nitration of arylboronic acids

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APPENDIX A

NMR DATA

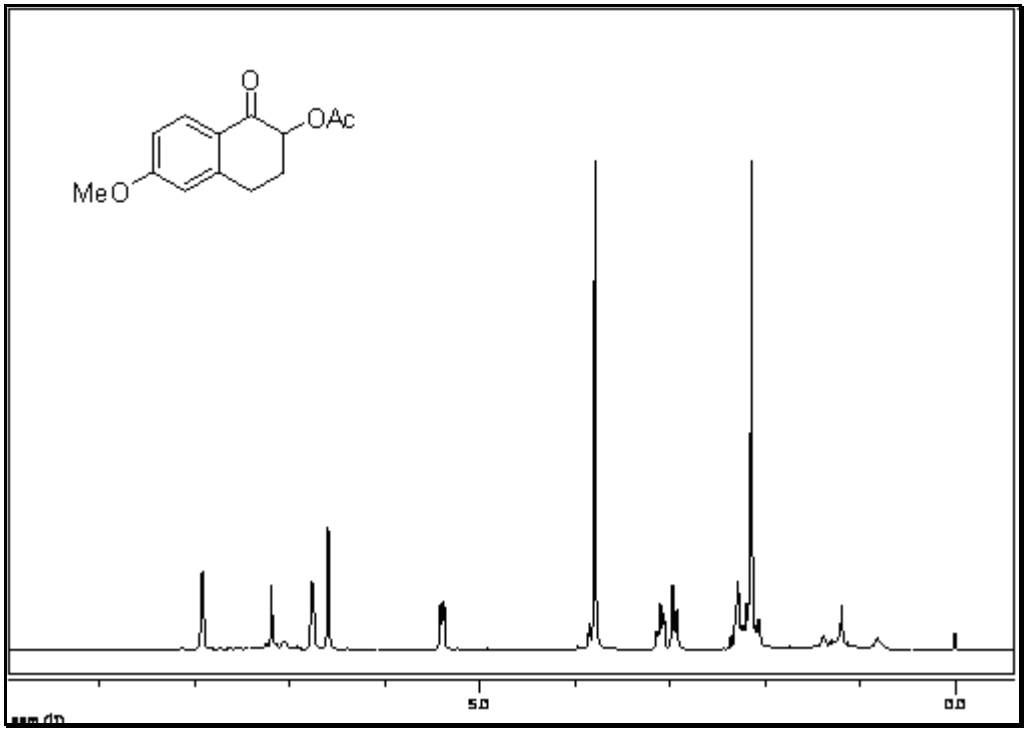

Figure 4.3 ^{1}H-NMR spectrum of 6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl acetate (**90**)

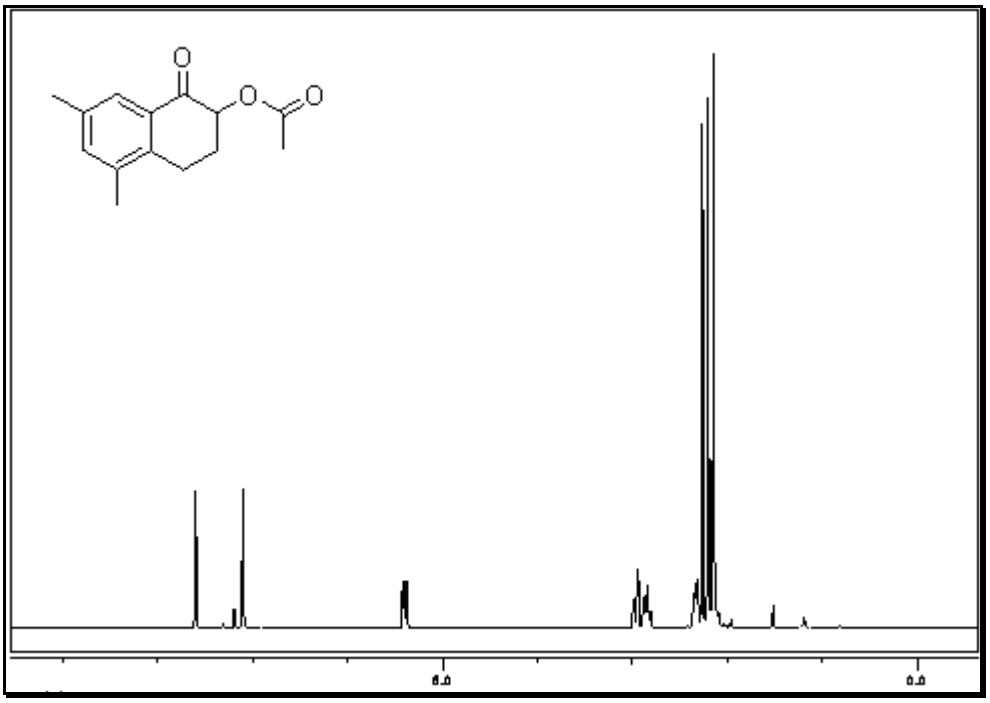

Figure 4.4 ^{1}H-NMR spectrum of 1,2,3,4-Tetrahydro-5,7-dimethyl-1-oxonaphthalen-2-yl acetate (**92**)

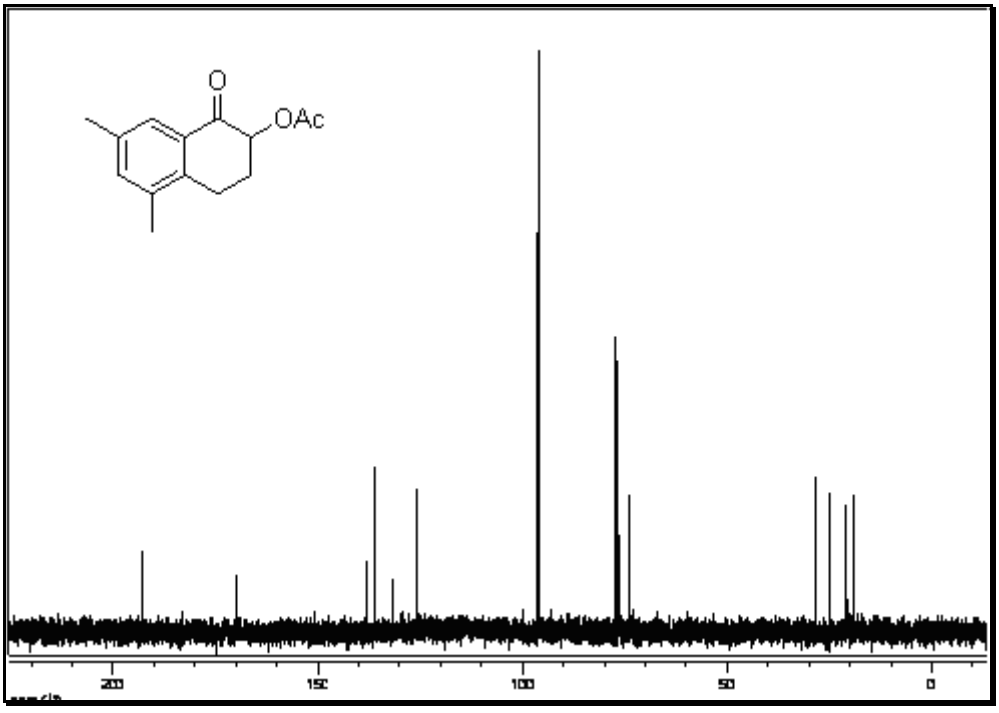

Figure 4.5 ^{13}C-NMR spectrum of 1,2,3,4-Tetrahydro-5,7-dimethyl-1-oxonaphthalen-2-yl acetate (**92**)

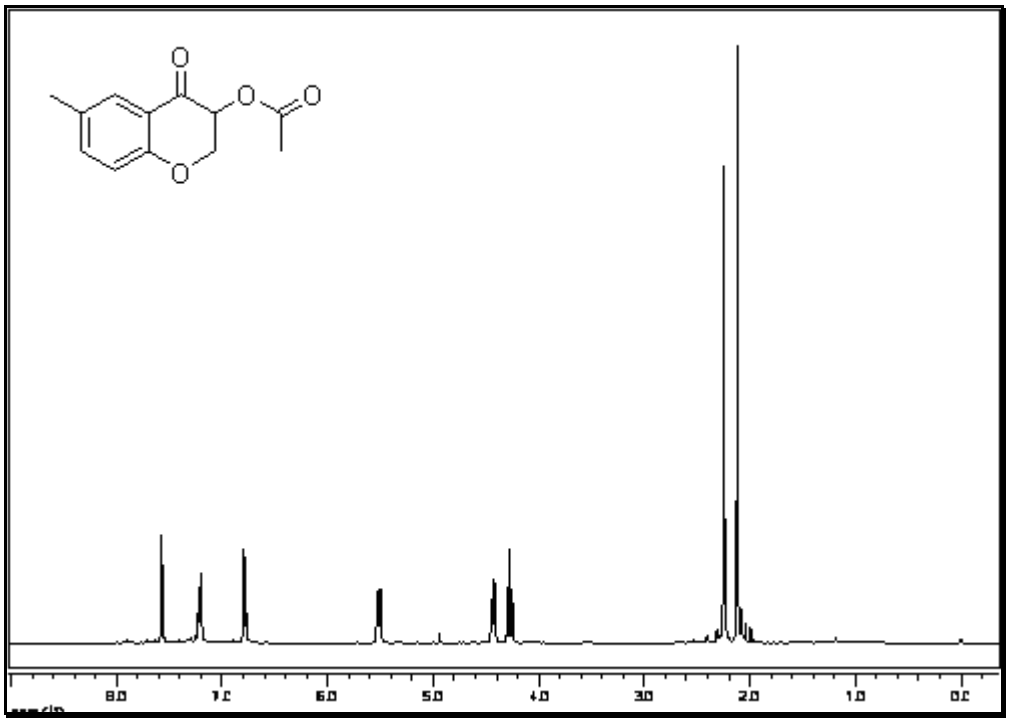

Figure 4.6 ^{1}H-NMR spectrum of 3,4-Dihydro-6-methyl-4-oxo-2H-chromen-3-yl acetate (**98**)

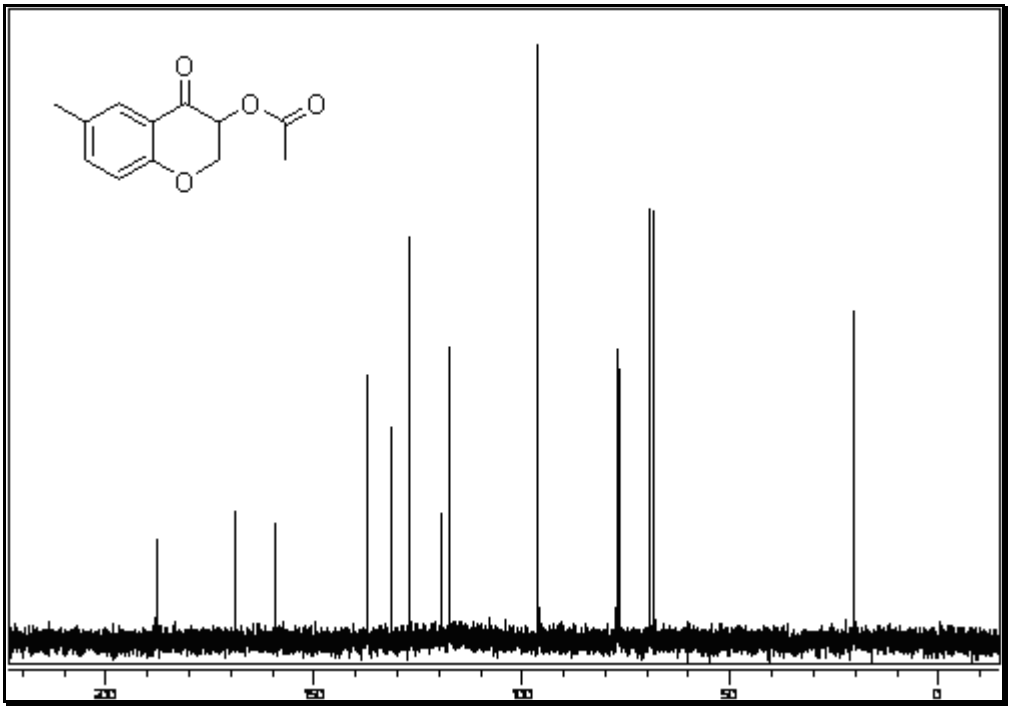

Figure 4.7 ^{13}C-NMR spectrum of 3,4-Dihydro-6-methyl-4-oxo-2H-chromen-3-yl acetate (**98**)

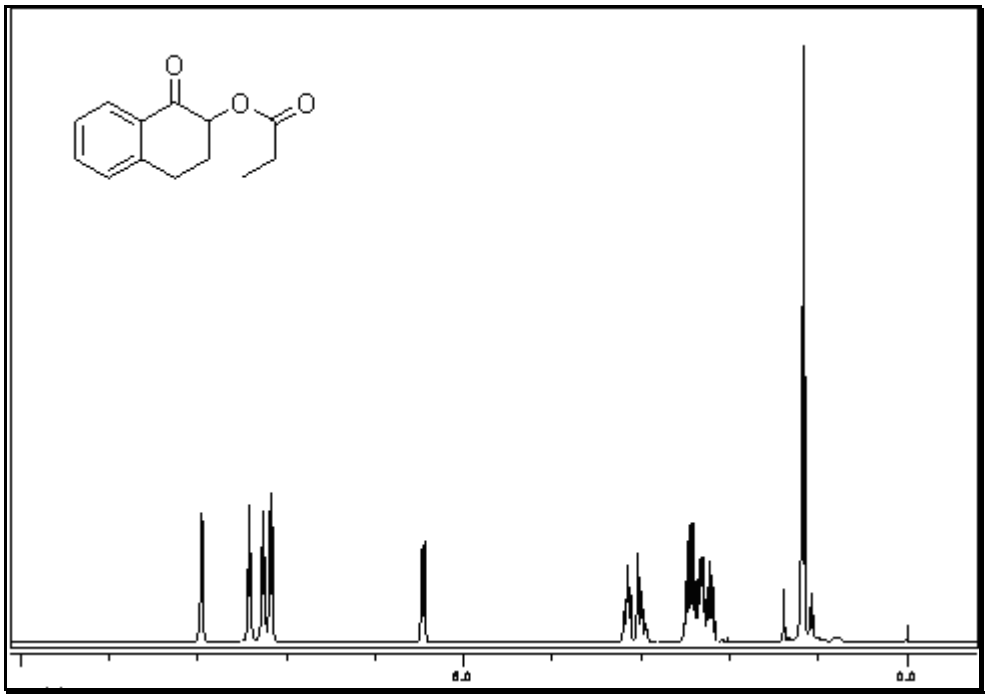

Figure 4.8 ^{1}H-NMR spectrum of 1,2,3,4-Tetrahydro-1-oxonaphthalen-2-yl propionate (**117**)

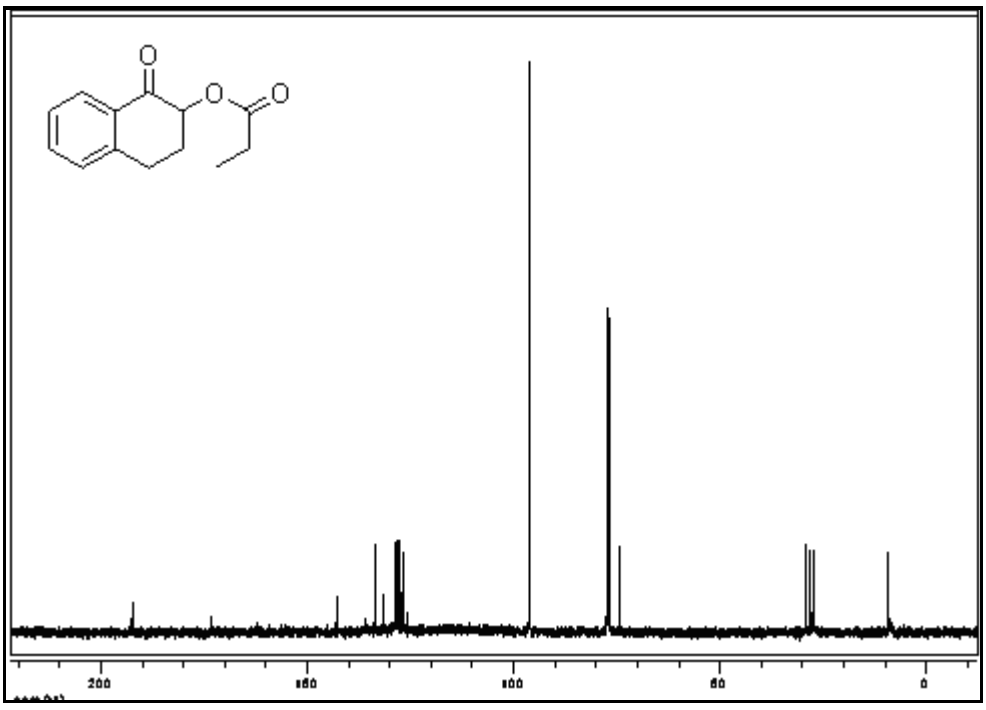

Figure 4.9 ^{13}C-NMR spectrum of 1,2,3,4-Tetrahydro-1-oxonaphthalen-2-yl propionate (**117**)

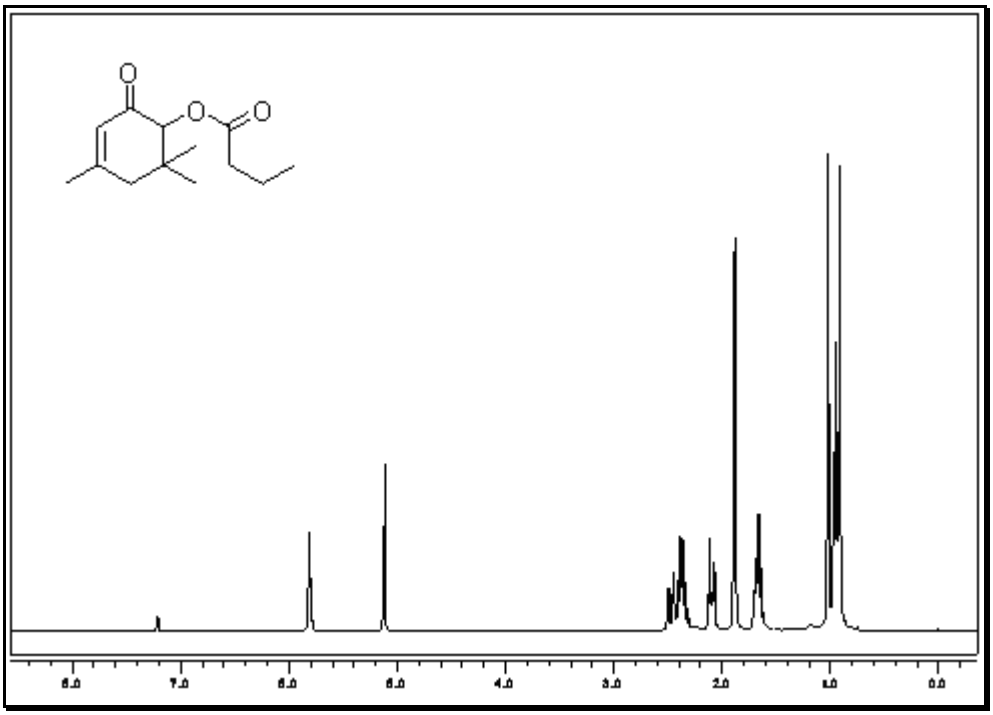

Figure 4.10 ^{1}H-NMR spectrum of 4,6,6-Trimethyl-2-oxocyclohex-3-enyl butyrate (**119**)

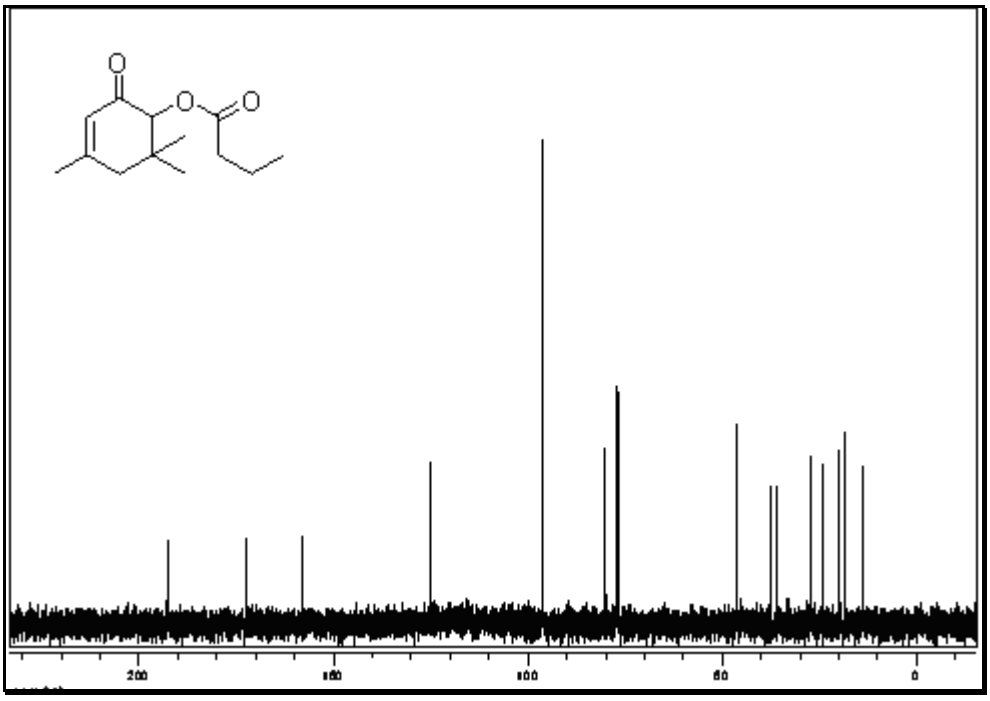

Figure 4.11 ^{13}C-NMR spectrum of 4,6,6-Trimethyl-2-oxocyclohex-3-enyl butyrate (**119**)

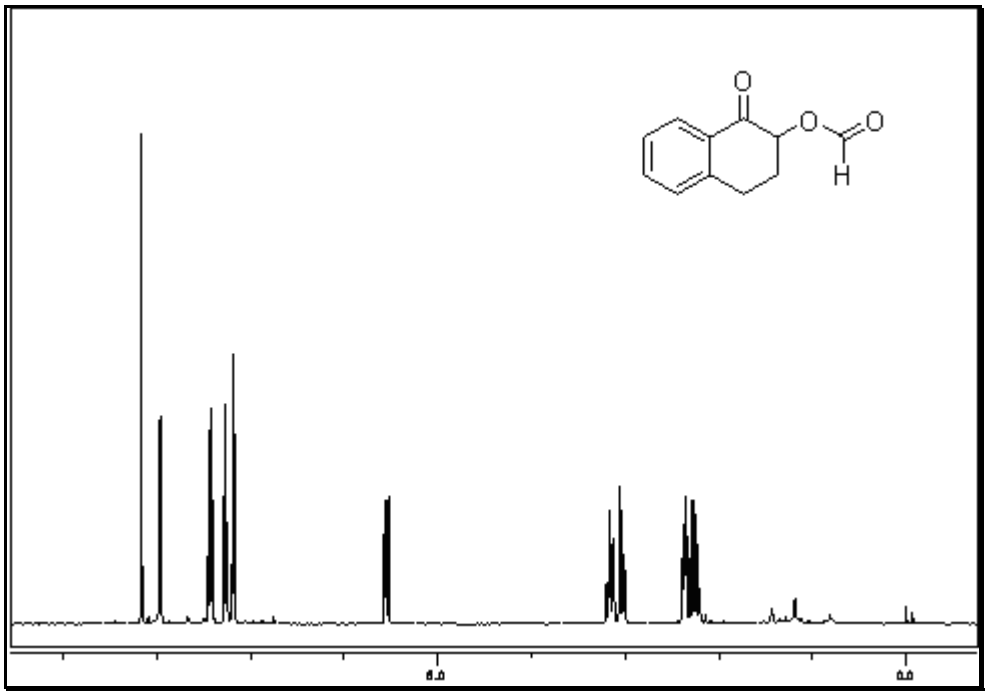

Figure 4.12 ^{1}H-NMR spectrum of 1,2,3,4-Tetrahydro-1-oxonaphthalen-2-yl formate (**121**)

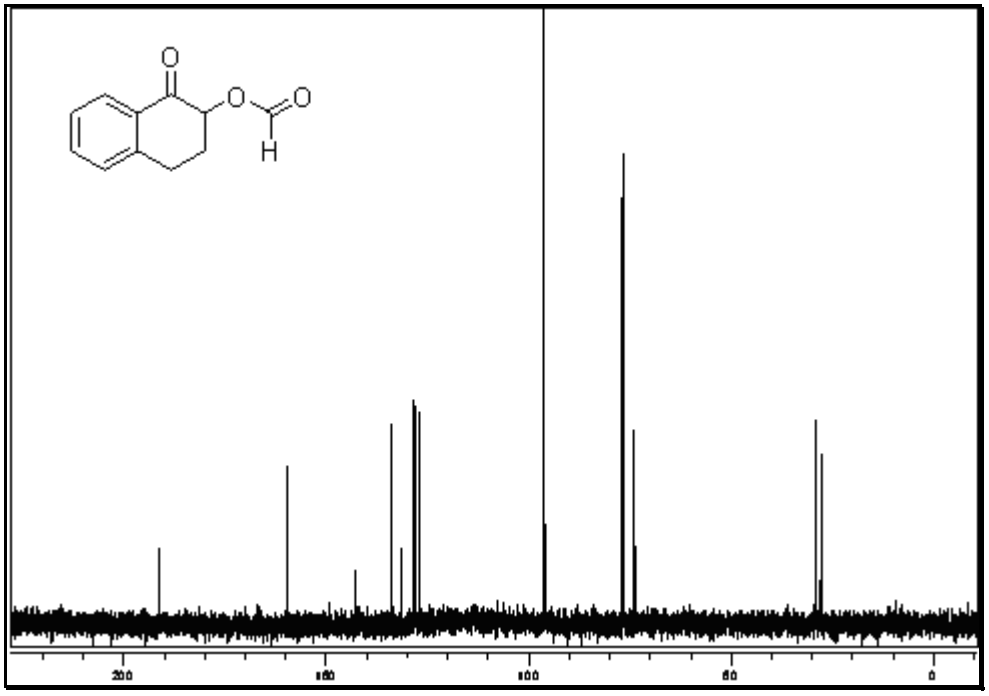

Figure 4.13 ^{13}C-NMR spectrum of 1,2,3,4-Tetrahydro-1-oxonaphthalen-2-yl formate (**121**)

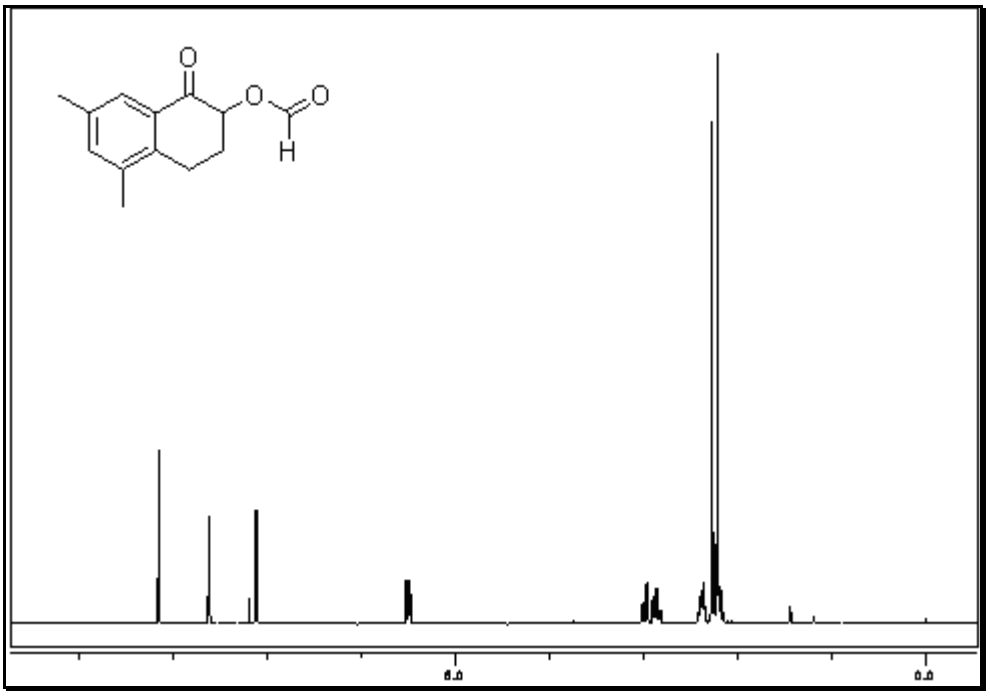

Figure 4.14 ^{1}H-NMR spectrum of 1,2,3,4-Tetrahydro-5,7-dimethyl-1-oxonaphthalen-2-yl formate (**122**)

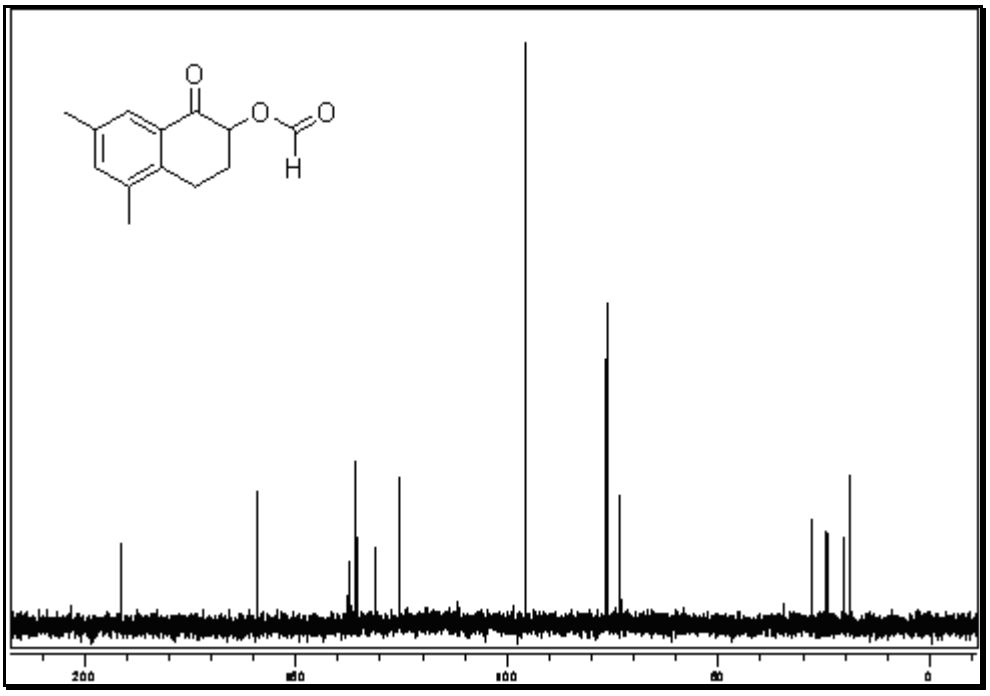

Figure 4.15 ^{13}C-NMR spectrum of 1,2,3,4-Tetrahydro-5,7-dimethyl-1-oxonaphthalen-2-yl formate (**122**)

Figure 4.16 ^{1}H-NMR spectrum of 1,2,3,4-Tetrahydro-6-methoxy-1-oxonaphthalen-2-yl formate (**123**)

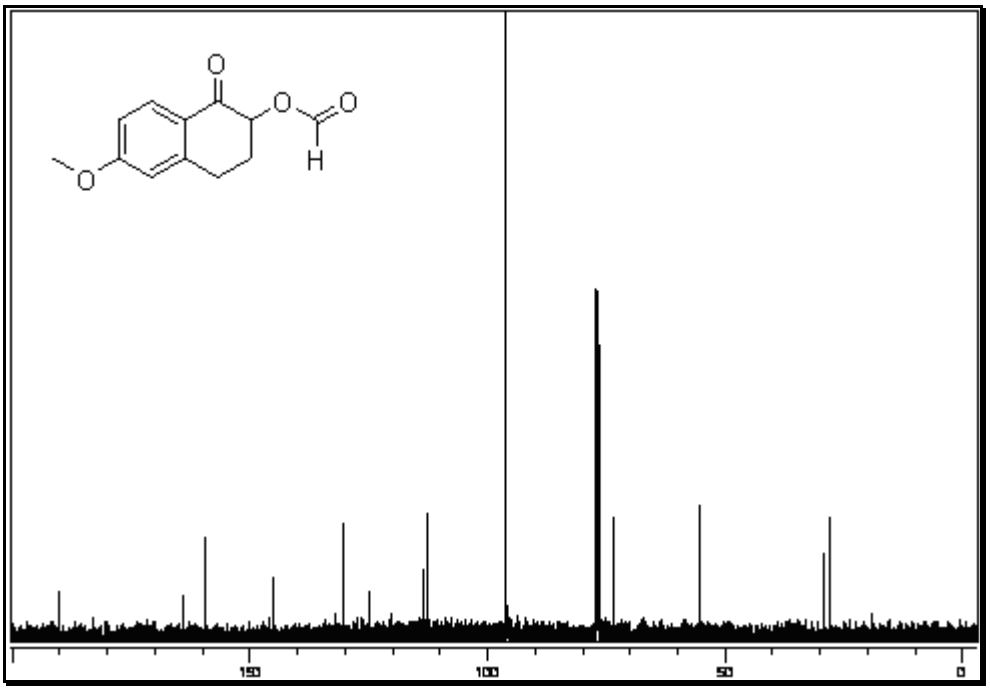

Figure 4.17 ^{13}C-NMR spectrum of 1,2,3,4-Tetrahydro-6-methoxy-1-oxonaphthalen-2-yl formate (**123**)

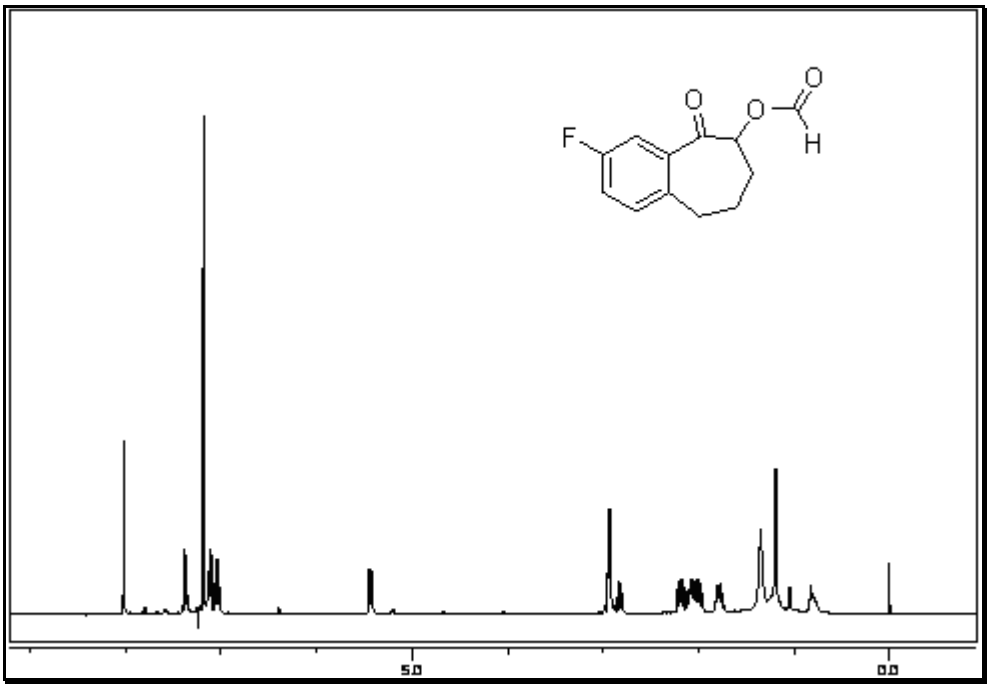

Figure 4.18 ^{1}H-NMR spectrum of 2-Fluoro-6,7,8,9-tetrahydro-9-oxo-5H-benzo[7]annulen-8-yl formate (**125**)

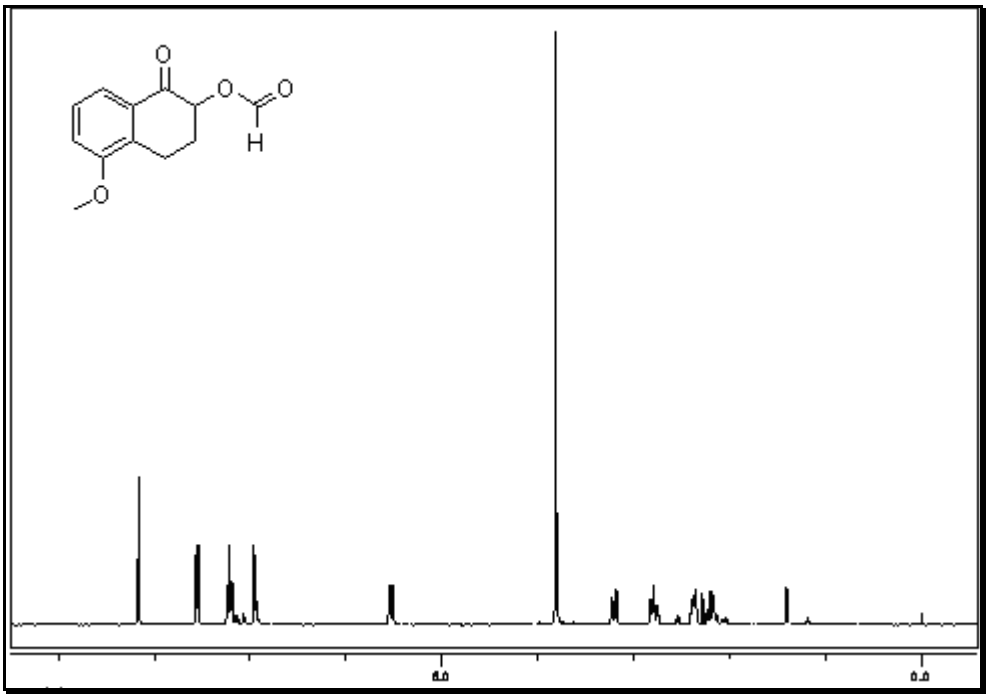

Figure 4.19 ^{1}H-NMR spectrum of 1,2,3,4-Tetrahydro-5-methoxy-1-oxonaphthalen-2-yl formate (**126**)

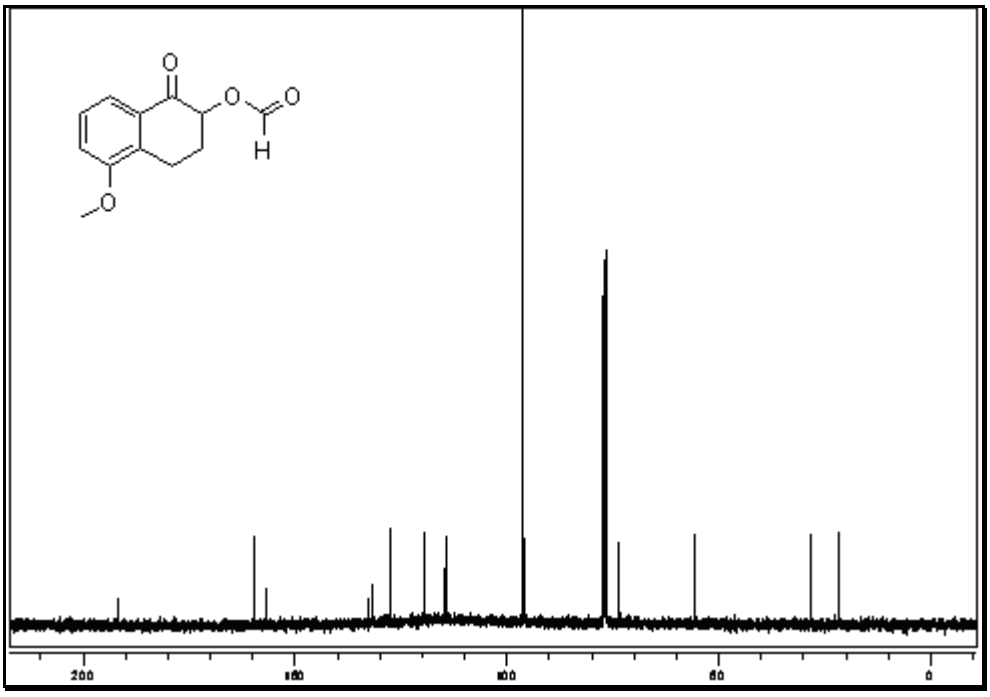

Figure 4.20 ^{13}C-NMR spectrum of 1,2,3,4-Tetrahydro-5-methoxy-1-oxonaphthalen-2-yl formate (**126**)

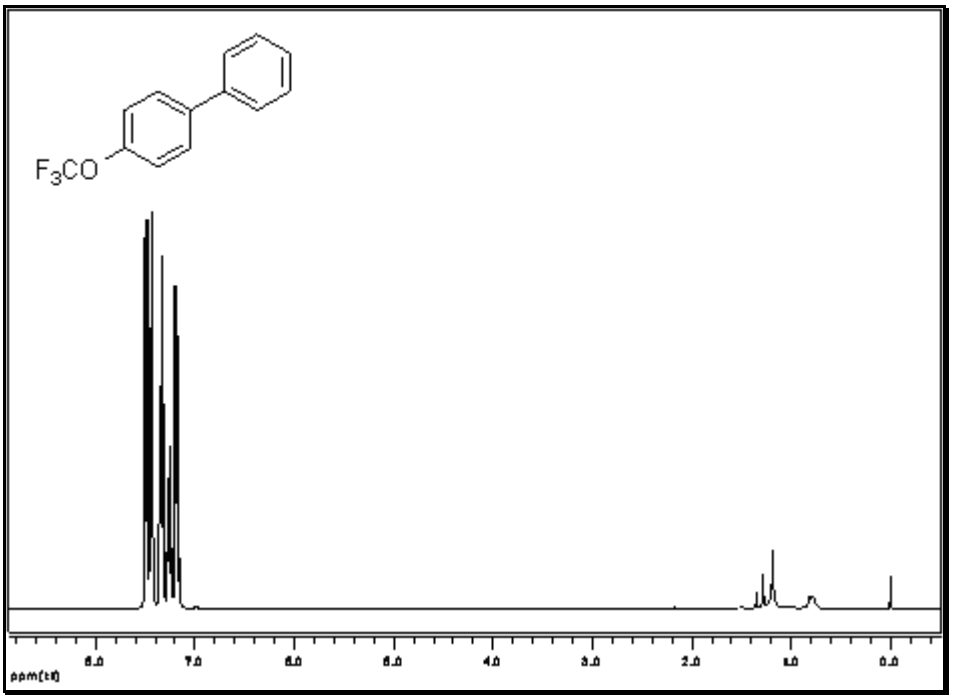

Figure 4.21 ^{1}H-NMR spectrum of 4-(Trifluoromethoxy)-1,10-biphenyl (**142**)

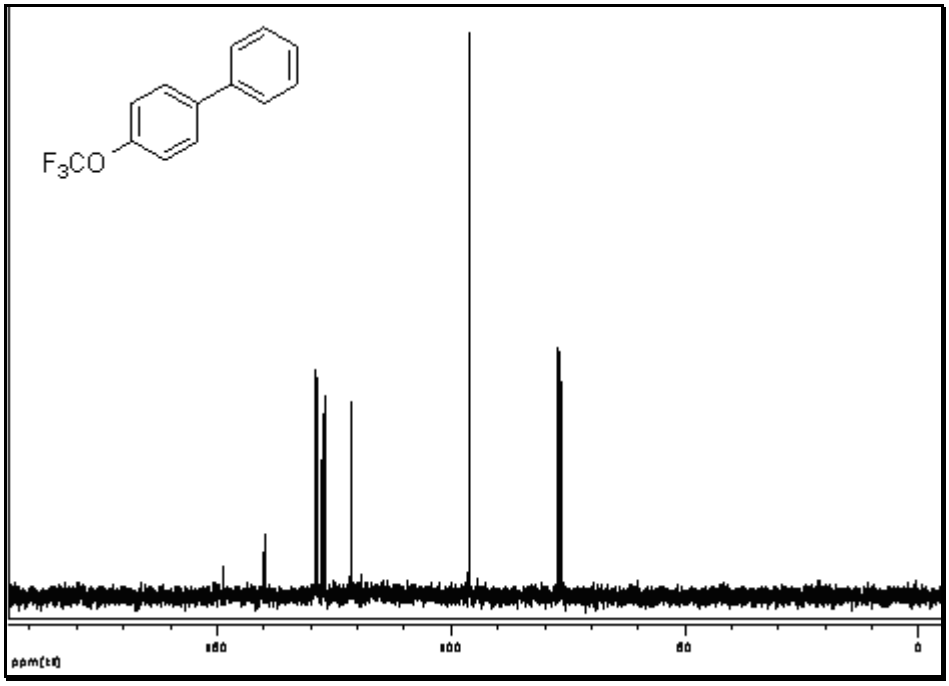

Figure 4.22 ^{13}C-NMR spectrum of 4-(Trifluoromethoxy)-1,10-biphenyl (**142**)

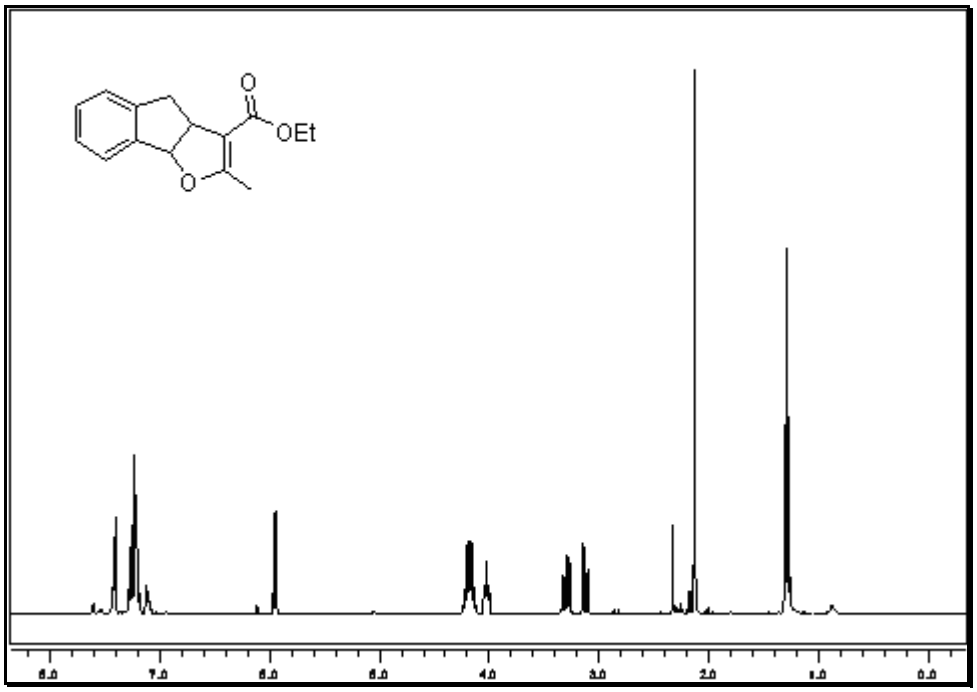

Figure 4.23 ^{1}H-NMR spectrum of Ethyl 2-methyl-4,8b-dihydro-3aH-indeno[1,2-b]furan-3-carboxylate (**157**)

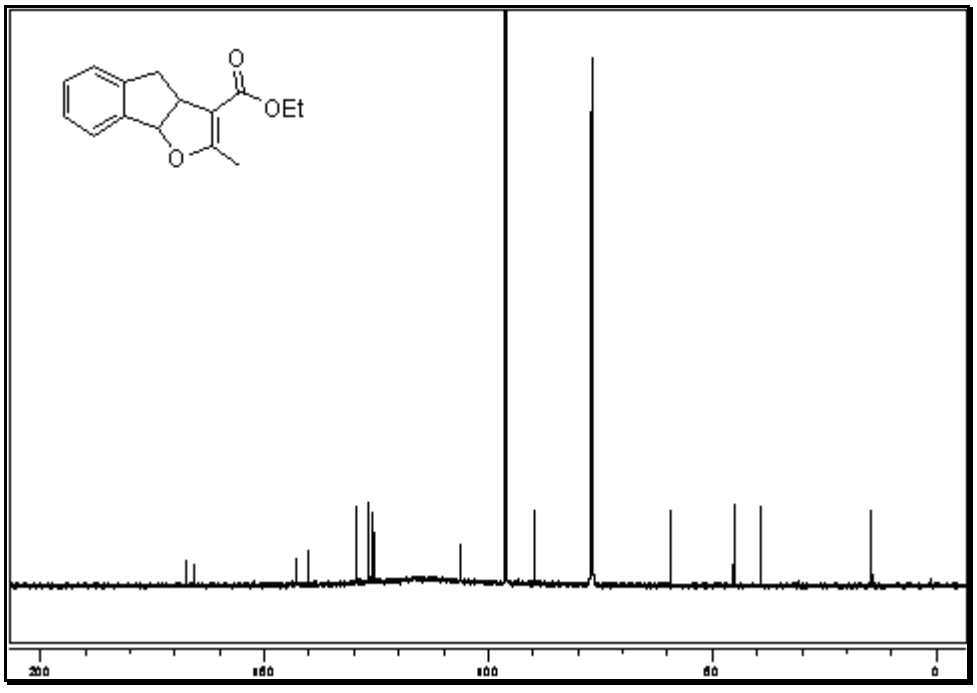

Figure 4.24 ^{13}C-NMR spectrum of Ethyl 2-methyl-4,8b-dihydro-3aH-indeno[1,2-b]furan-3-carboxylate (**157**)

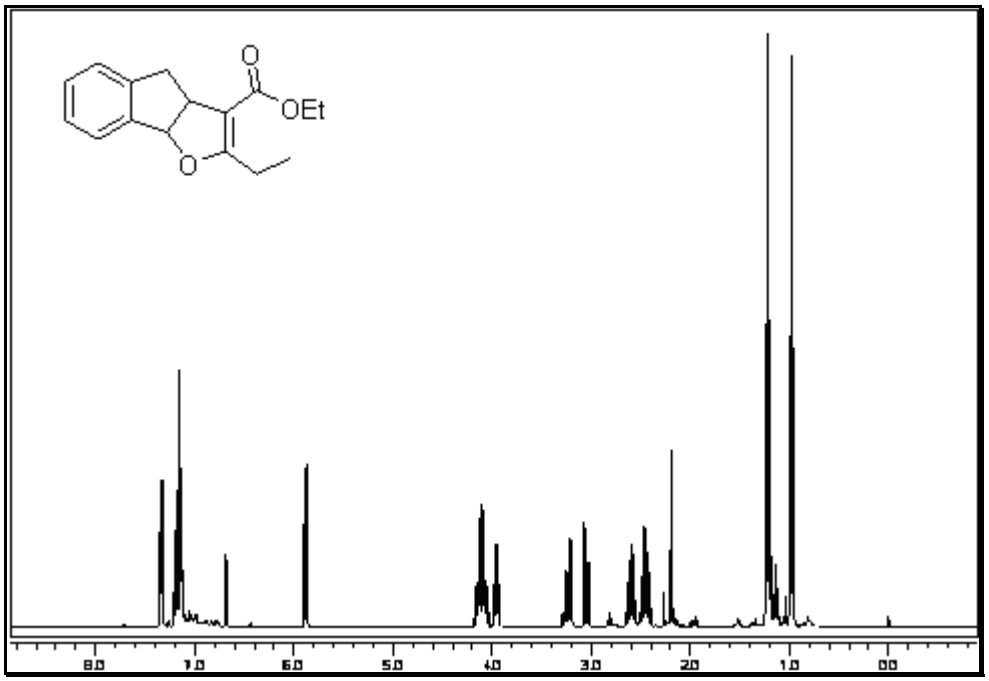

Figure 4.25 ^{1}H-NMR spectrum of Ethyl 2-ethyl-4,8b-dihydro-3aH-indeno[1,2-b]furan-3-carboxylate (**159**)

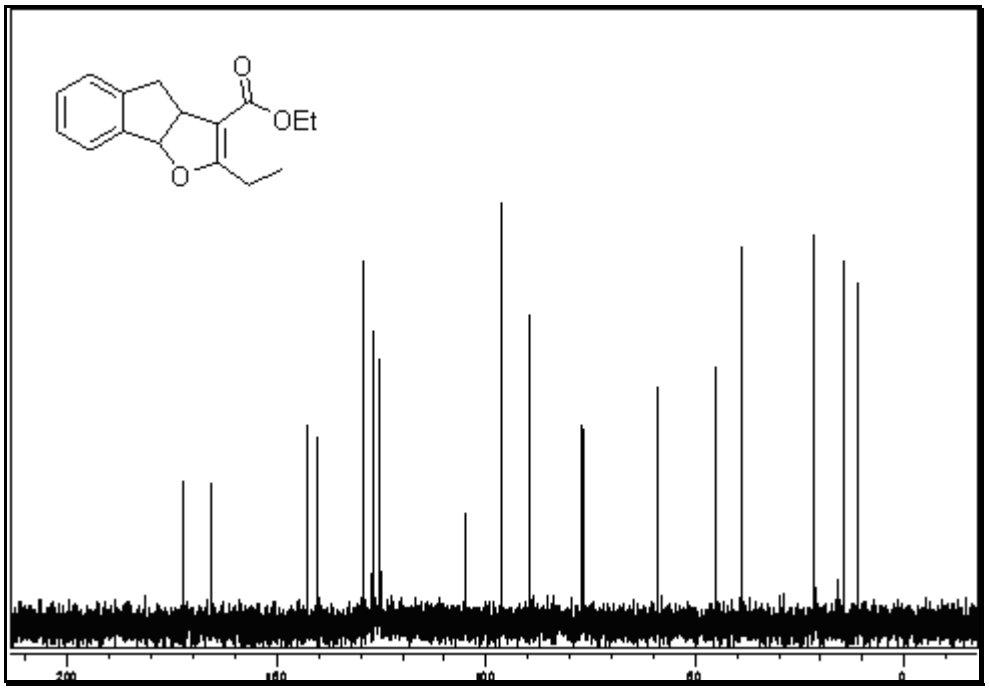

Figure 4.26 ^{13}C-NMR spectrum of Ethyl 2-ethyl-4,8b-dihydro-3aH-indeno[1,2-b]furan-3-carboxylate (**159**)

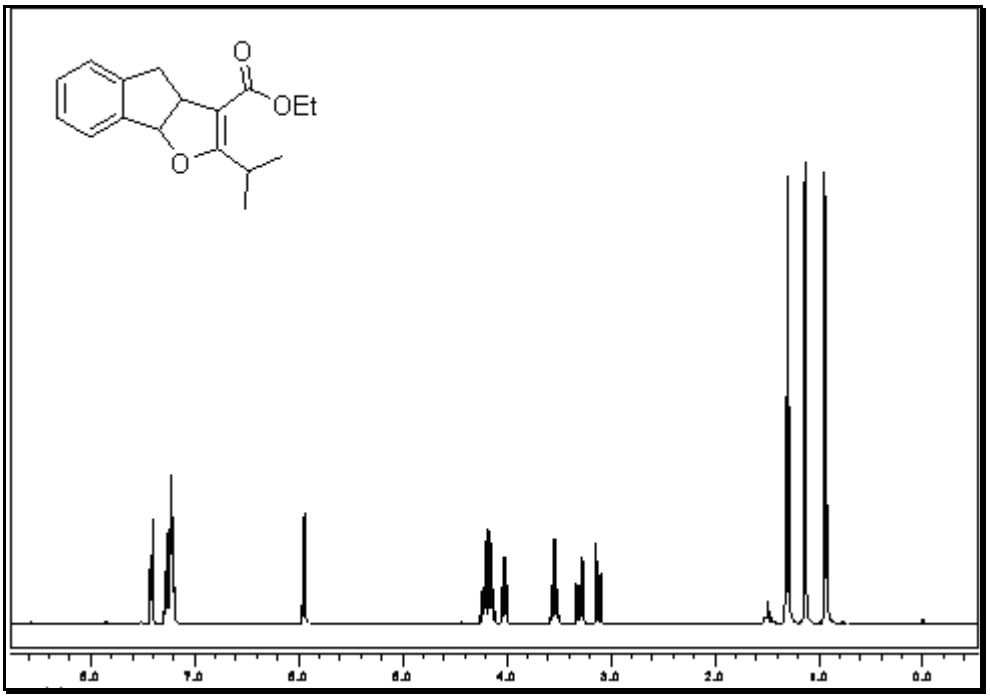

Figure 4.27 ^{1}H-NMR spectrum of Ethyl 2-isopropyl-4,8b-dihydro-3aH-indeno[1,2-b]furan-3-carboxylate (**161**)

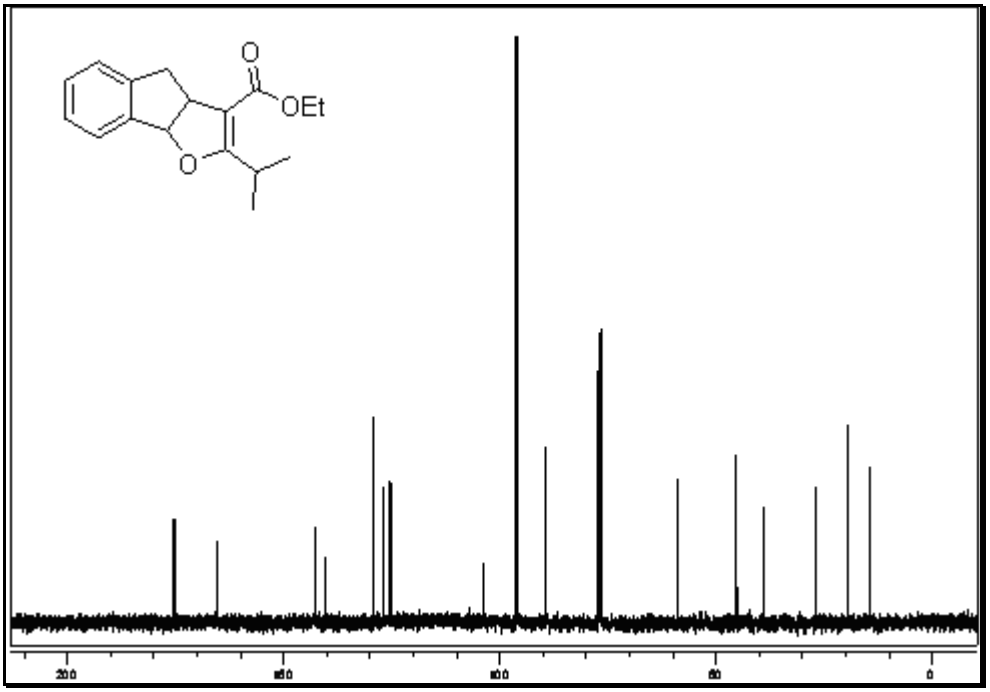

Figure 4.28 ^{13}C-NMR spectrum of Ethyl 2-isopropyl-4,8b-dihydro-3aH-indeno[1,2-b]furan-3-carboxylate (**161**)

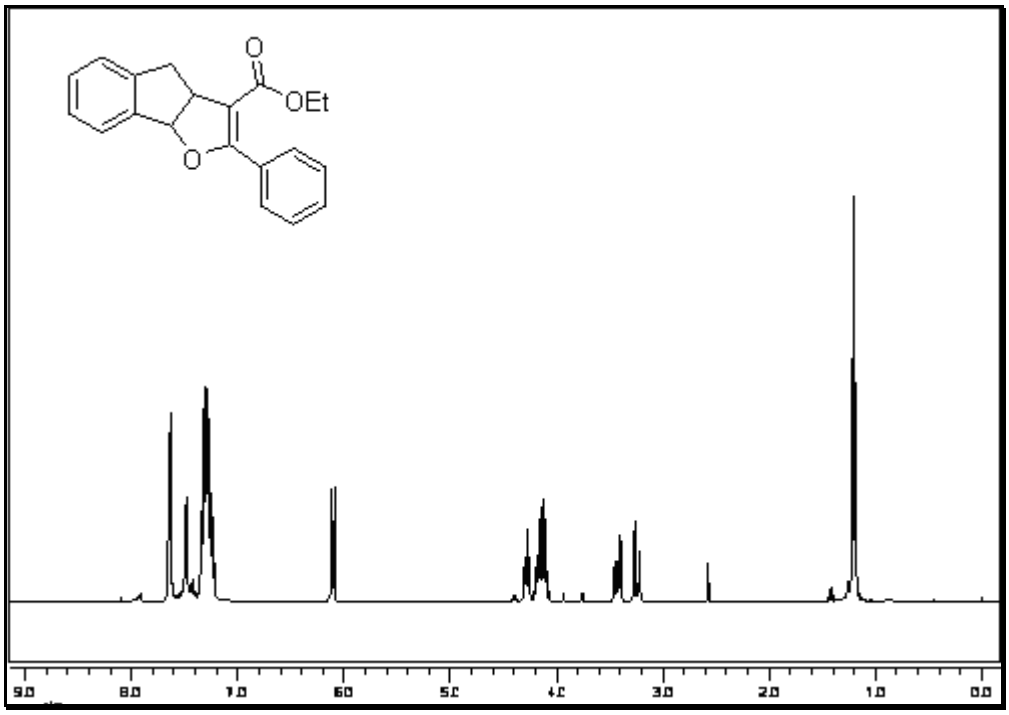

Figure 4.29 ^{1}H-NMR spectrum of Ethyl 2-phenyl-4,8b-dihydro-3aH-indeno[1,2-b]furan-3-carboxylate (**163**)

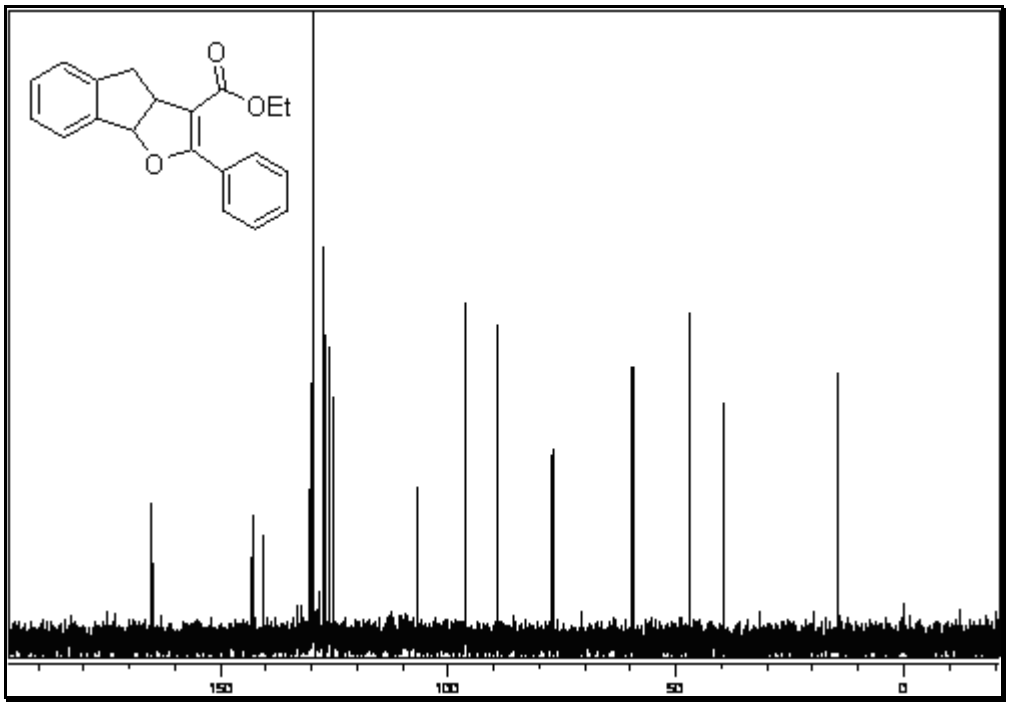

Figure 4.30 ^{13}C-NMR spectrum of Ethyl 2-phenyl-4,8b-dihydro-3aH-indeno[1,2-b]furan-3-carboxylate (**163**)

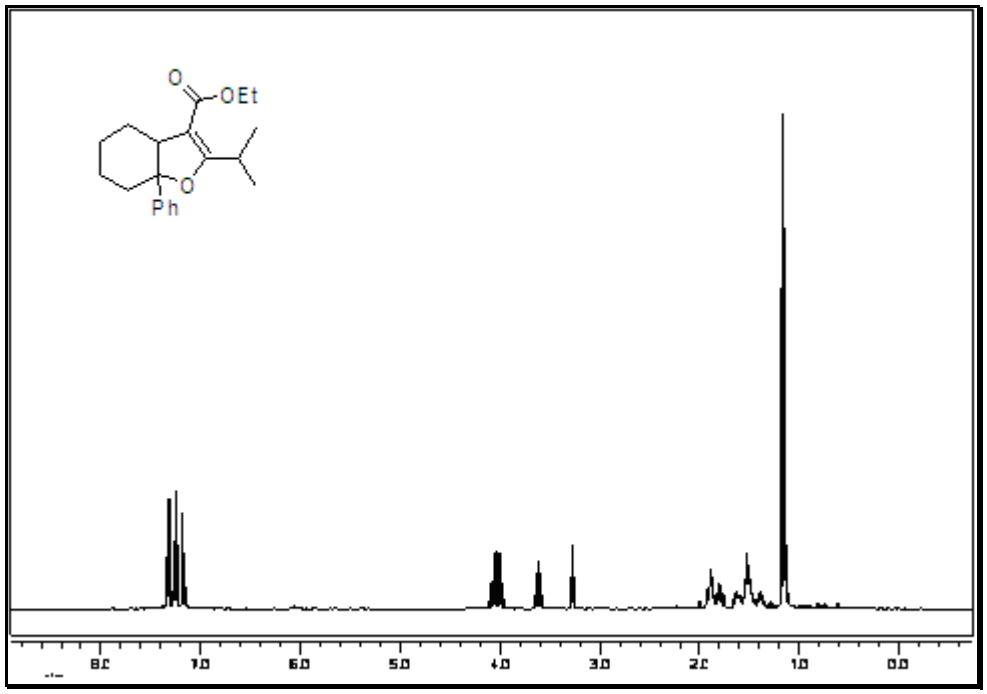

Figure 4.31 ^{1}H-NMR spectrum of ethyl 2-isopropyl-3a-phenyl-3a,4,5,6,7,7a-hexahydrobenzofuran-3-carboxylate (**165**)

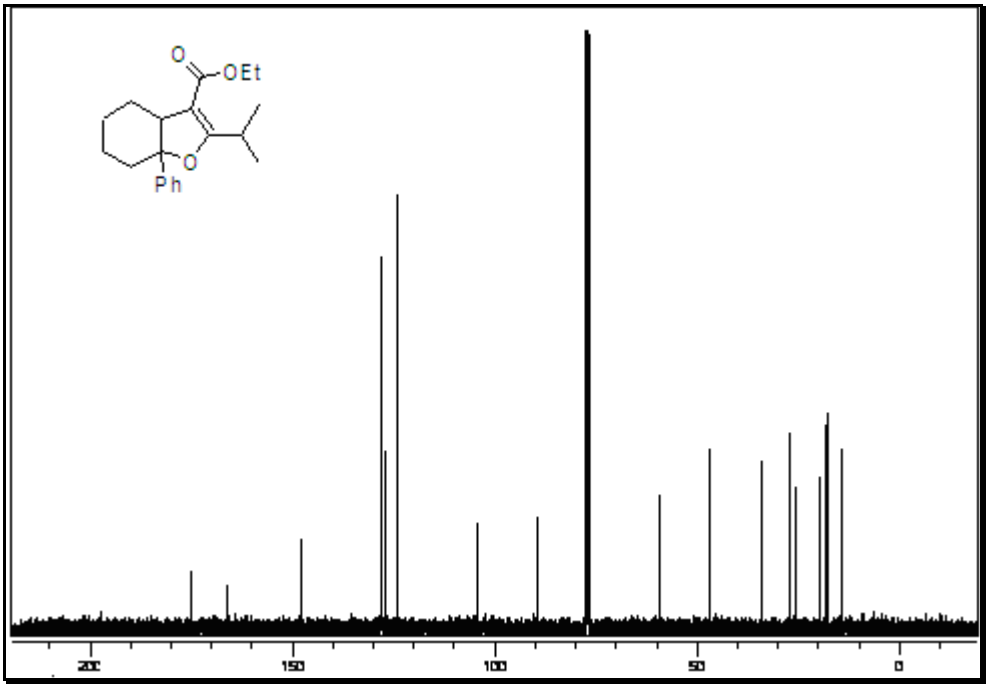

Figure 4.32 ^{13}C-NMR spectrum of ethyl 2-isopropyl-3a-phenyl-3a,4,5,6,7,7a-hexahydrobenzofuran-3-carboxylate (**165**)

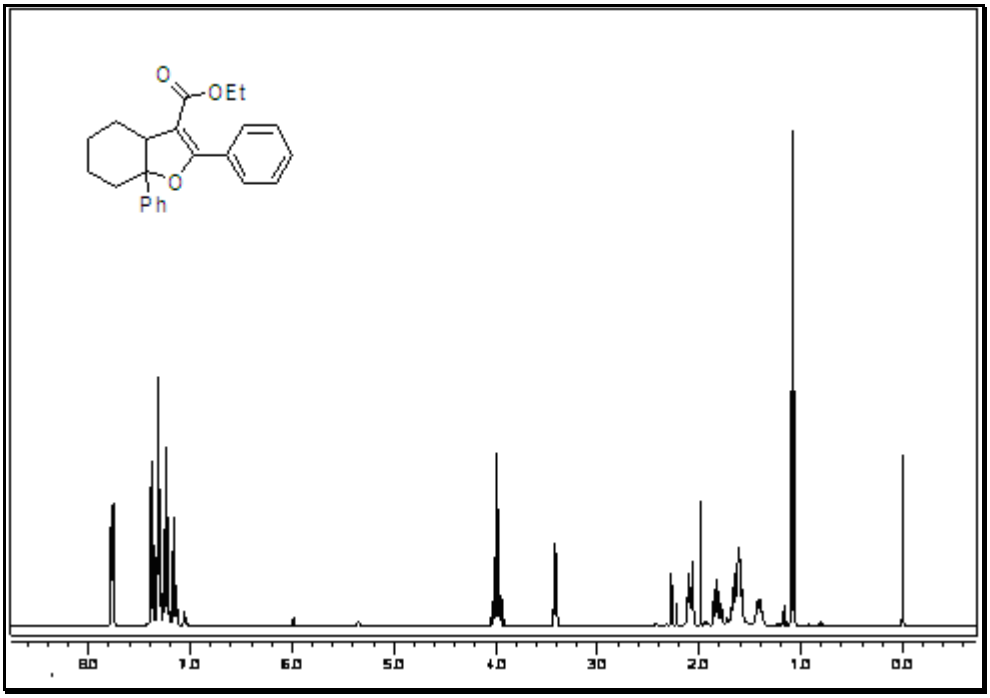

Figure 4.33 ^{1}H-NMR spectrum of ethyl 2,3a-diphenyl-3a,4,5,6,7,7a-hexahydrobenzofuran-3-carboxylate (**166**)

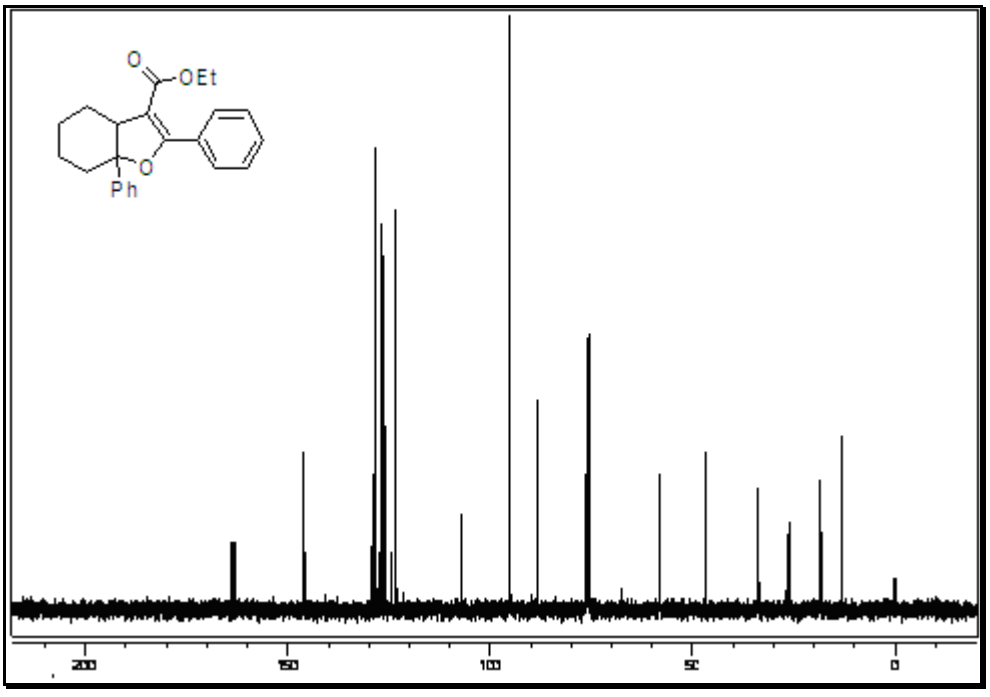

Figure 4.34 ^{13}C-NMR spectrum of ethyl 2,3a-diphenyl-3a,4,5,6,7,7a-hexahydrobenzofuran-3-carboxylate (**166**)

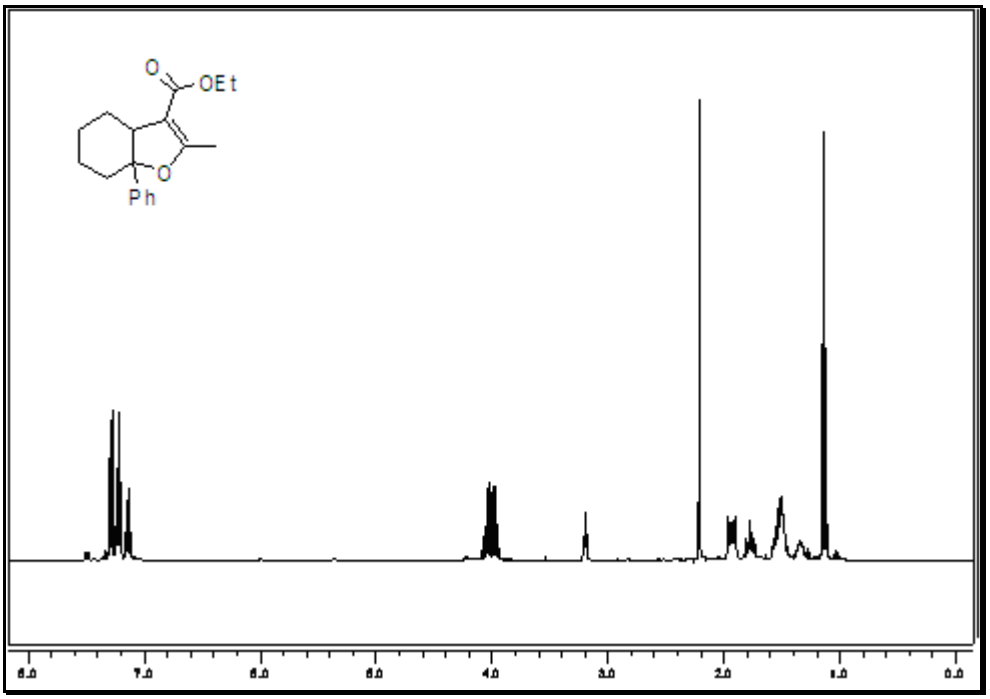

Figure 4.35 ^{1}H-NMR spectrum of ethyl 2-methyl-3a-phenyl-3a,4,5,6,7,7a-hexahydrobenzofuran-3-carboxylate (**168**)

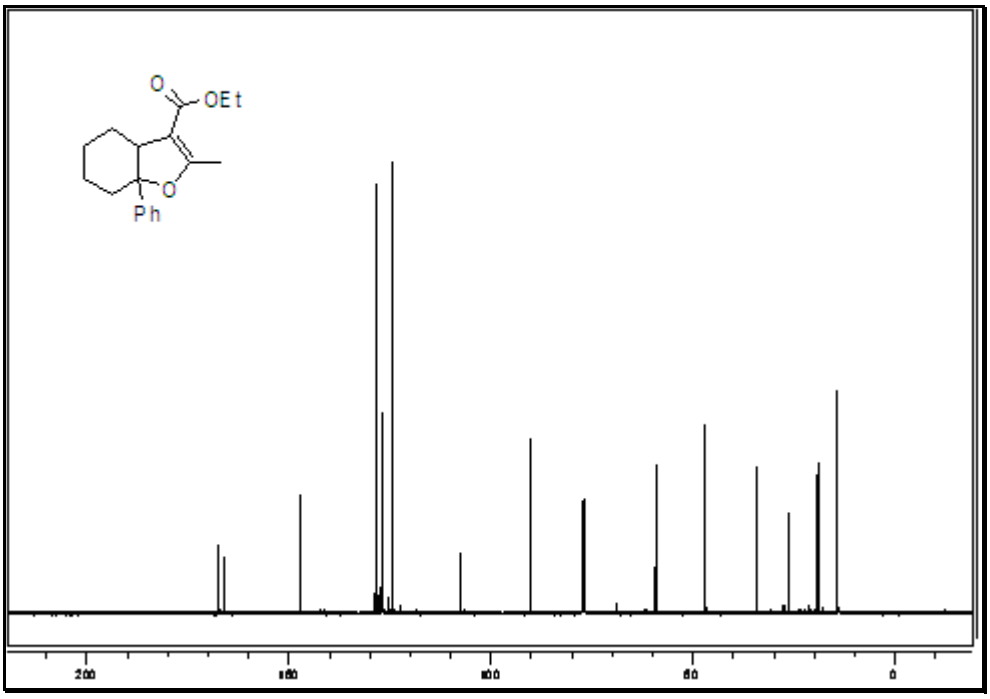

Figure 4.36 ^{13}C-NMR spectrum of ethyl 2-methyl-3a-phenyl-3a,4,5,6,7,7a-hexahydrobenzofuran-3-carboxylate (**168**)

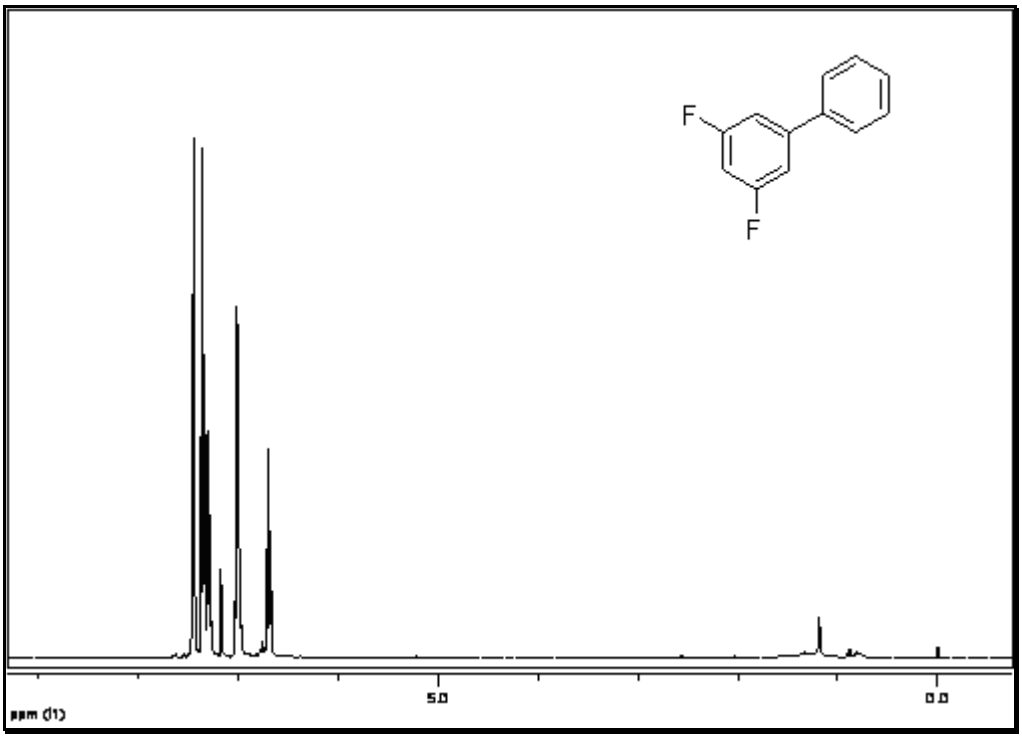

Figure 4.37 ^{1}H-NMR spectrum of 3,5-difluorobiphenyl (**169**)

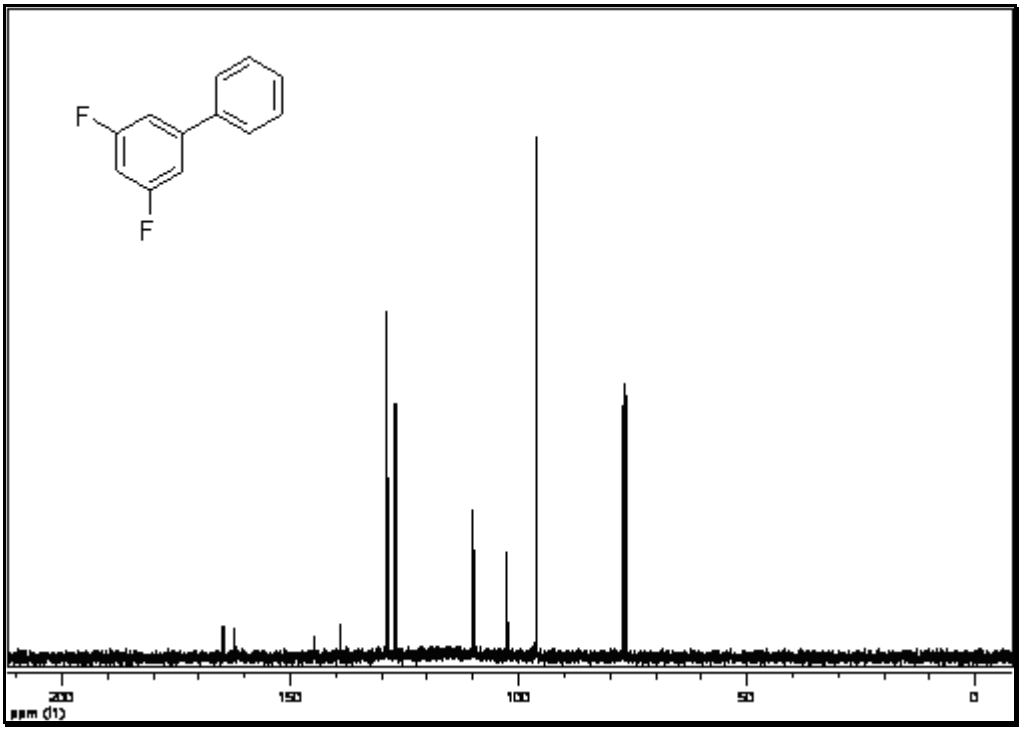

Figure 4.38 ^{13}C-NMR spectrum of 3,5-difluorobiphenyl (**169**)

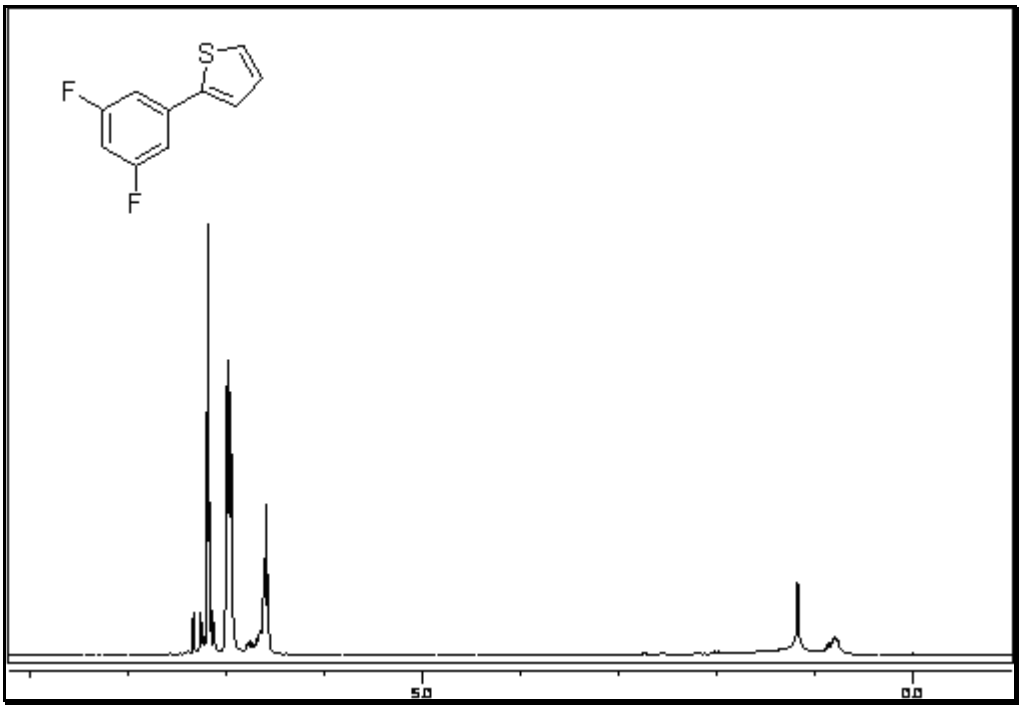

Figure 4.39 ^{1}H-NMR spectrum of 2-(3,5-difluorophenyl)thiophene (**170**)

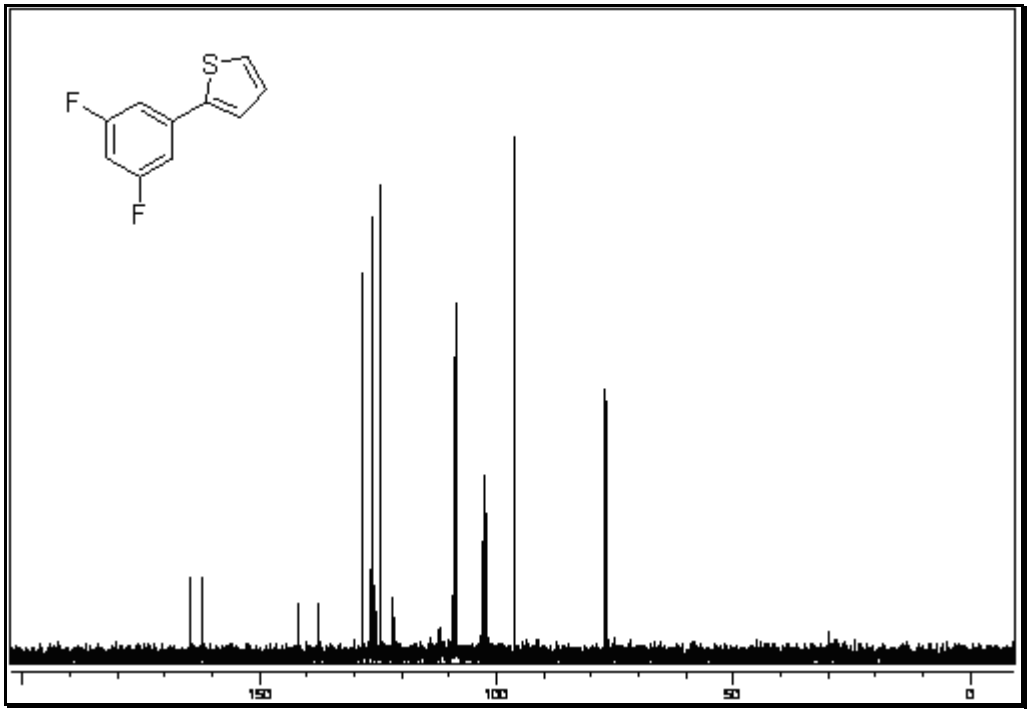

Figure 4.40 ^{13}C-NMR spectrum of 2-(3,5-difluorophenyl)thiophene (**170**)

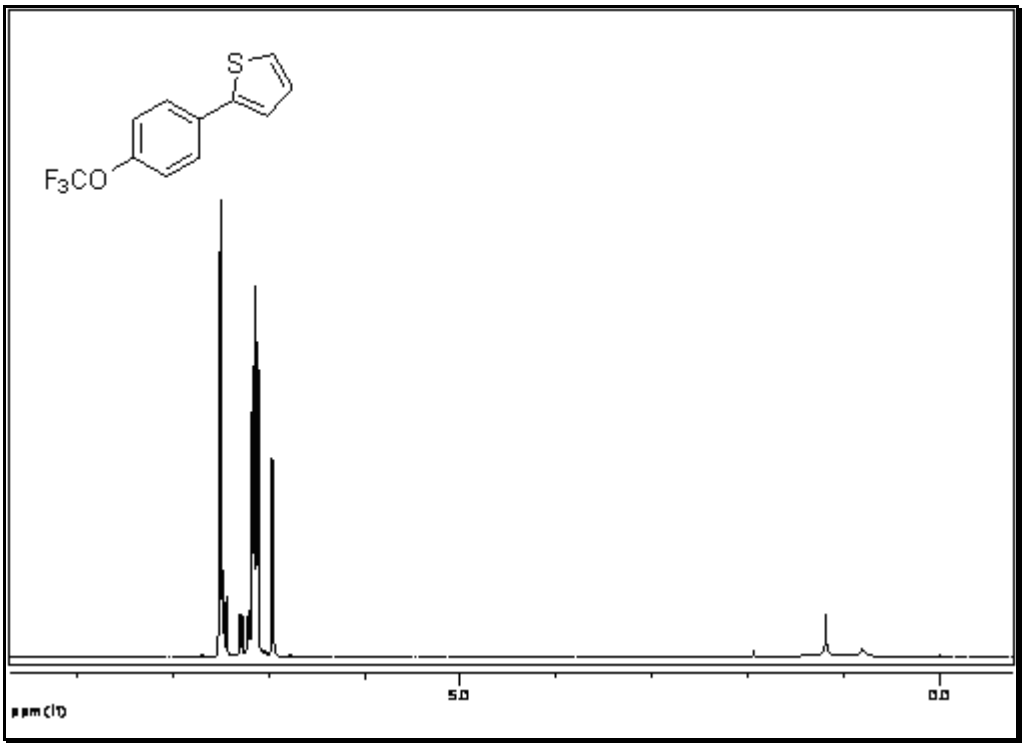

Figure 4.41 ^{1}H-NMR spectrum of 2-(4-(trifluoromethoxy)phenyl) thiophene (**171**)

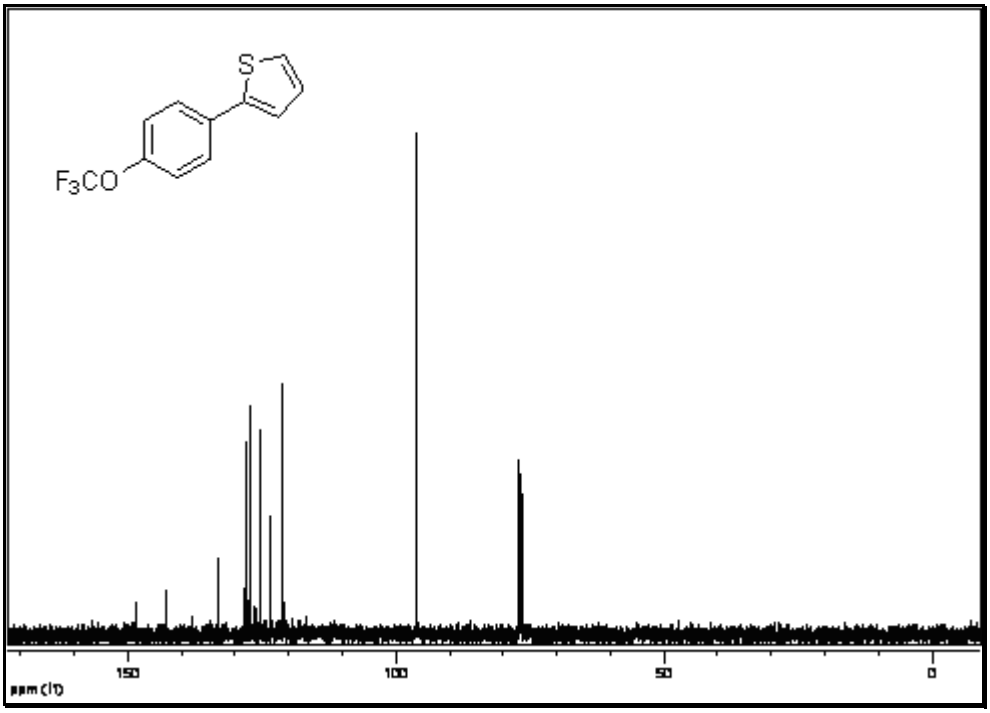

Figure 4.42 ^{13}C-NMR spectrum of 2-(4-(trifluoromethoxy)phenyl) thiophene (**171**)

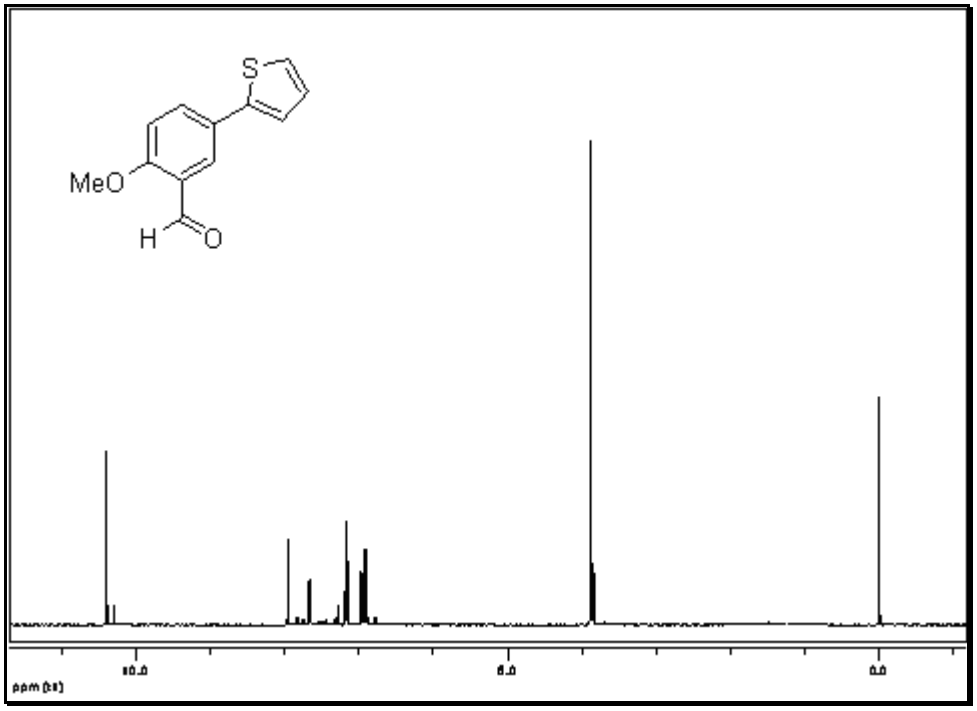

Figure 4.43 ^{1}H-NMR spectrum of 2-Methoxy-5-(thiophen-2-yl) benzaldehyde (**175**)

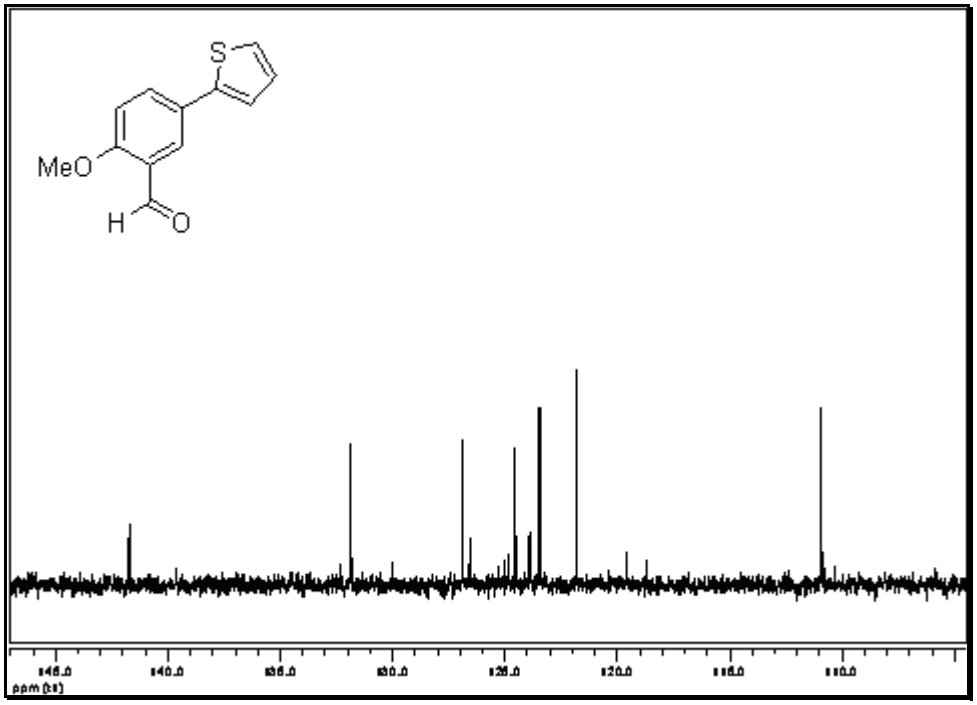

Figure 4.44 ^{13}C-NMR spectrum of 2-Methoxy-5-(thiophen-2-yl) benzaldehyde (**175**)

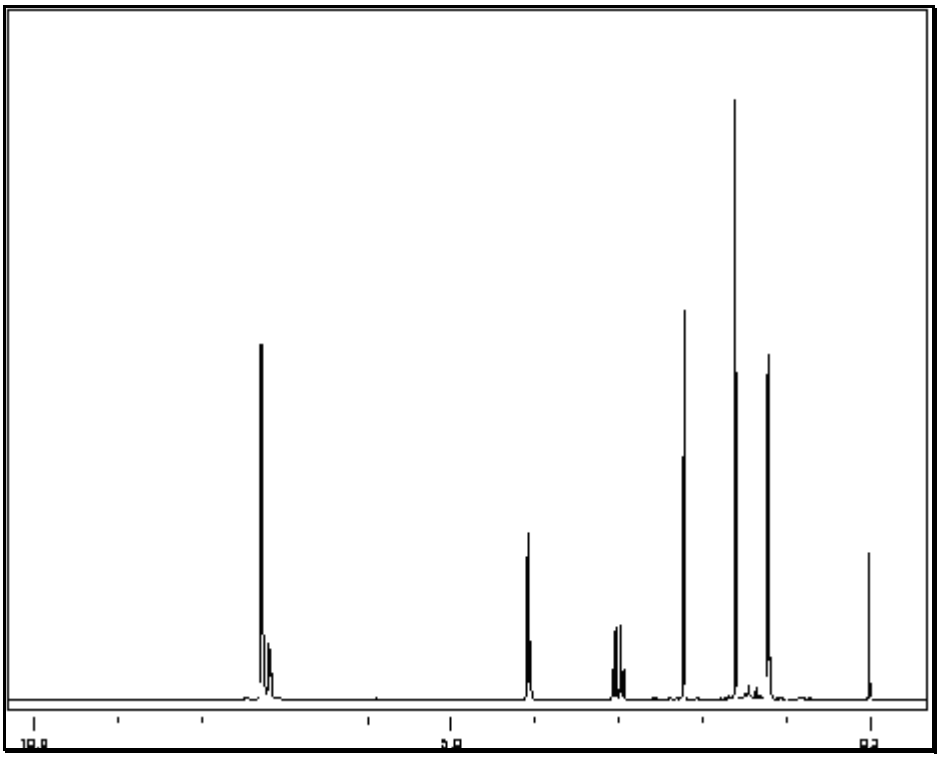

Figure 4.45 ^{1}H-NMR spectrum of ethyl 2,5-dimethyl-5-phenyl-4,5-dihydrofuran-3-carboxylate (**169**)

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PUBLICATIONS

1. Ayhan S. Demir, Hamide Findik, Elif Köse. A new and efficient chemoenzymatic route to both enantiomers of α'-acetoxy-α-methyl and γ-hydroxy-α-methyl cyclic enones. Tetrahedron: Asymmetry , 2004, 15, 777.

2. Demir, Ayhan S.; Findik, Hamide. "The reaction of alkenes with $AgNO_2$/TMSCl: The synthesis of 1,2,5-oxadiazole-2-oxides (furoxans) via nitroso nitrates." Letters in Organic Chemistry (2005), 2(7), 602-604.

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