ORGANOIRON IN THE SYNTHESIS OF ALKANOIC ACIDS AND HETEROCYCLIC PRECURSORS.

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in Partial Fulfillment of The Requirements
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in the
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by

Krystyna Lezynska

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ORGANOIRON IN THE SYNTHESIS OF ALKANOIC ACIDS AND HETEROCYCLIC PRECURSORS

BY

KRYSTYNA LEZYNSKA

A Thesis submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

ABSTRACT

The use of alkanoic acids and heterocycles such as azetinones or pyrimidines in medicinal chemistry is of great interest. The synthesis of these compounds is complicated by the toxicity of some of the reagents involved in the synthesis. Thus there is a growing need for the development of new routes in the preparation of alkanoic acids and some heterocycles. The methodological strategy proposed by our group involves the nucleophilic aromatic substitution (S_NAr) reactions of cyclopentadienyliron complexes of chloroarenes with ethyl 2-methylacetoacetate, ethyl 2-ethylacetoacetate, phenylsulphonylacetonitrile and ethyl cyanoacetate in the presence of potassium carbonate in DMF, followed by photolytic demetallation. Photolysis of the resulting S_NAr products, namely arylated ethyl cyanoacetates and ethylphenylsulphonylacetonitriles as well as complexed substituted alkanoic acid esters, led in our case to the liberation of the substituted arene ligands in high yields.

The synthetic strategy chosen for the synthesis of the compounds of interest has proven to be very applicable due to its ease, use of mild reaction conditions and versatility.

ACKNOWLEDGMENTS

I wish to thank my supervisor, Professor A.S. Abd-El-Aziz for his encouragement, support, patience and guidance during the course of my work and in the preparation of this thesis.

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1.0 INTRODUCTION

Since the discovery of bis(π-cyclopentadienyliron), widely known as ferrocene, in 1951, the synthesis of transition metal complexes and their effect on the course of chemical reactions has become a very important area of chemistry that is developing at an ever accelerating rate [1,2]. The interaction of an organic molecule with metallic species could lead to the formation of an intermediate organometallic compound. This intermediate could be stable or unstable. The reactivities of these compounds are of interest in synthetic chemistry. The complexed organic ligand could undergo different types of reactions compared to the uncomplexed molecule due to the interaction between the organic ligand and the metal [3].

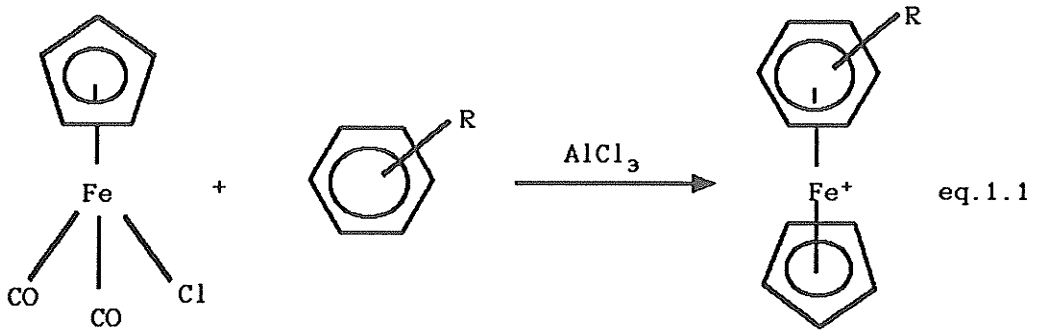
The use of organotransition metals such as chromium, manganese or iron in organic synthesis usually involves three stages; (i) the complexation of an organic compound to the transition metal; (ii) modification of the organic ligand, which is facilitated by the effects of the complexing metal; (iii) liberation of the modified organic ligand from the metallic moiety [4-6].

1.1 *Synthesis of Arene Complexes.*

There are a number of well known arene complexes, also recognized as sandwich compounds [7-11]. Examples of symmetrical sandwich complexes include bis(arene)chromium(0) and bis(arene)iron(II). Mixed sandwich compounds such as (η^6- arene)metaltricarbonyl and (η^6-arene)cyclopentadienylmetal complexes, where the metal could be Cr, Mo, W, Fe or Ru, also constitute a very important class due to the synthetic utility of these complexes in organic chemistry [12-13].

The low cost of the activating iron cyclopentadienyl moiety, the ease of complexation and decomplexation, the less- toxicity, as well as the possibility of using the temporary complexation for multiple activation steps make the iron-mediated reactions a powerful tool in synthetic organic chemistry.

The synthesis of η^6-arene-η^5-cyclopentadienyl iron complex cations was achieved for the first time through the reactions of cyclopentadienyldicarbonyliron halides with the corresponding aromatic hydrocarbons in the presence of anhydrous aluminum chloride, according to the equation 1.1.

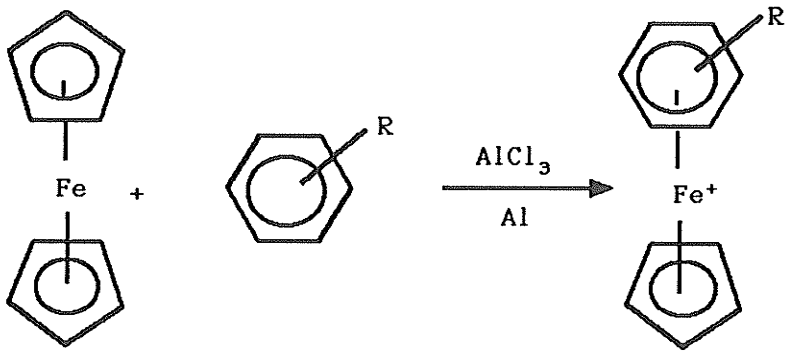


eq.1.1

After hydrolysis the complex cation was precipitated by the addition of appropriate anions such as iodide, or tribromide [14,15]. Cations prepared via this method include the benzene derivative $[(C_5H_5)Fe(C_6H_6)]^+$ and the mesitylene derivative $\{(C_5H_5)Fe[C_6H_3(CH_3)_3]\}^+$.

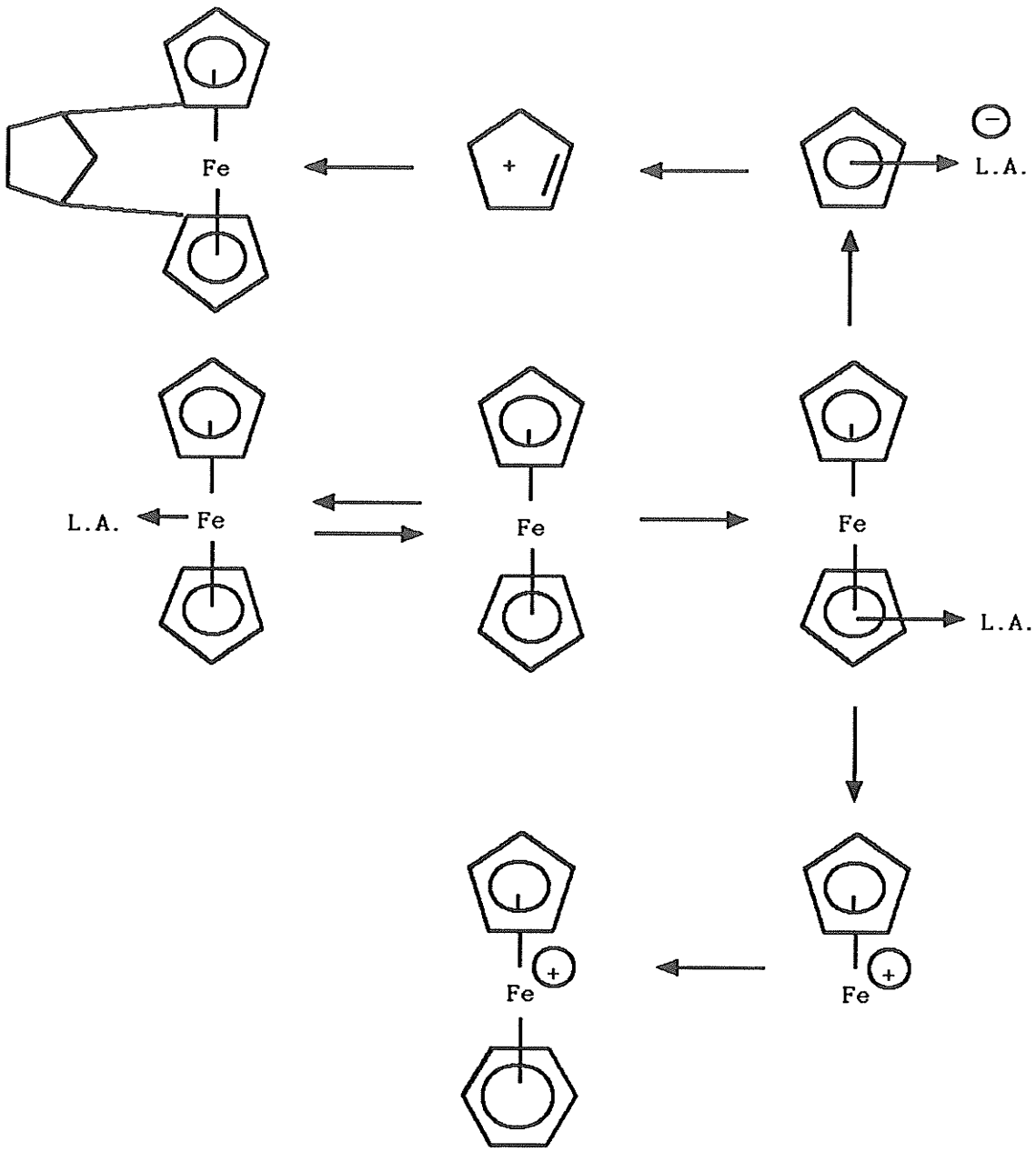
This route to the synthesis of $[(C_5H_5)Fe(arene)]^+$ cations was made obsolete through the subsequent discovery of the ligand exchange reaction by Nesmeyanov and co-workers [16,17]. They reported that the treatment of ferrocene with the aromatic hydrocarbon at 80-165°C in the presence of a two to four fold excess of aluminium chloride and a stoichiometric quantity of aluminum powder results in substitution of one of cyclopentadienyl (Cp) rings with the aromatic hydrocarbon to give the corresponding $[(arene)Fe(C_5H_5)]^+$ cation, isolated as its tetrafluoroborate or hexafluoro-phosphate salt. Various arene cyclopentadienyl complexes, including benzene, toluene, ethylbenzene,

xylene, chlorobenzene and biphenyl could easily be prepared using this methodology (eq. 1.2). In addition to the aromatic hydrocarbons, this group was also capable of preparing substituted toluenes, $X-C_6H_4-CH_3$, ($X=SCH_3$, CH_3CoNH, F) and acetoanilide.



eq.1.2

A mechanism for the ligand exchange reaction was first proposed by Nemeyanov et al. [18], and later on by Astruc et al. [19] (Scheme 1). According to this proposed mechanism, the complex formed between the aluminium chloride and the cyclopentadienyl ring allowed for weakening the cyclopentadienyliron bond which then could either break unimolecularly to form the cyclopentadienyliron cation unit, or could be trapped by the cyclopentadienyl anion or by the arene ring to give the η^6-arene-η^5-cyclopentadienyliron cation.



Scheme 1

A number of NMR studies have been reported for η^6-arene-η^5-cyclopentadienyliron cations [20-29]. The characteristic feature in the ^1H NMR spectrum of such complex cations is the shift in the cyclopentadienyl protons of about 1-2 ppm downfield from ferrocene. The arene protons are shifted upfield by about 1 ppm from those of the free arene. An extensive study of the ^1H NMR of three related classes of complexes, $[\eta^6\text{-}XC_6H_5\text{-}\eta^5\text{-}C_5H_5Fe]^+$, $[\eta^6\text{-}p\text{-}XC_6H_4(CH_3)\text{-}\ \eta^5\text{-}C_5H_5Fe]^+$ and $[\eta^6\text{-}C_6H_6\text{-}\eta^5\text{-}C_5H_4(X)Fe]^+$, were reported by Nesmeyanov and coworkers [26]. ^{13}C NMR of arene complexes also exhibit an upfield shift of about 40 ppm of the arene carbon compared to those of the uncomplexed arene. In the case of the cyclopentadienyl carbons of these complexes, a downfield shift of about 5-15 ppm from the ferrocene carbons was also reported. A detailed ^{13}C study by Steele et al. [21] confirmed the results of the earlier studies. In particular, the attempt was made to explain the fact that the chemical shifts of the complexed arenes were observed at fields higher than those for the corresponding free arenes. This effect was linked to a variety of possible causes: (i) metal-to-ligand π^*-back donation, (ii) ligand π-to-metal donation, (iii) ligand σ-to-metal donation and (iv) anisotropy of the neighboring metal atom.

According to an infrared (IR) study on CpFe complexed arenes conducted by Pavlik and Kriz [30], the cyclopentadienyl ring was characterized by bands at 780, 853, 1006, 1120, 1419 and 3095 cm^{-1} which lie in the characteristic range of the π-bonded cyclopentadienyl ring. An IR investigation of the series of a monosubstituted complexes has also been reported [31]. The characteristic bands for the complexed benzene ring are 3065, 2926,1445, 1011, 915, 824, and 737 cm^{-1}. The was no effect observed upon the introduction of a substituent into the benzene ring on the frequencies of the cyclopentadienyl ring and vice versa.

1.2 *Reactivity of Arene complexes.*

The coordination of an organic compound to a transition metal greatly alters the properties of the compound such that it could undergo completely different types of reactions from its uncomplexed molecule. In the frame of organometallic chemistry, two concepts illustrating the influence of transition-metal on the organic compounds are of special interest. The first is the activation of an organic molecule by π-coordinated, electron-withdrawing transition-metal groups [32]. For example, aromatic compounds usually

undergo electrophilic reactions but their complexation to metal moieties such as $Cr(CO)_3$, $FeCp^+$ or $Mn(CO)_3^+$, inhibits such reactivity and enhances the possibility of nucleophilic reactions. In a review by Astruc [33], arrangement of different metal activating moieties according to their electron withdrawing ability and the relative rates of their reactions with nucleophiles was reported. The results of this study are shown in Fig.1.

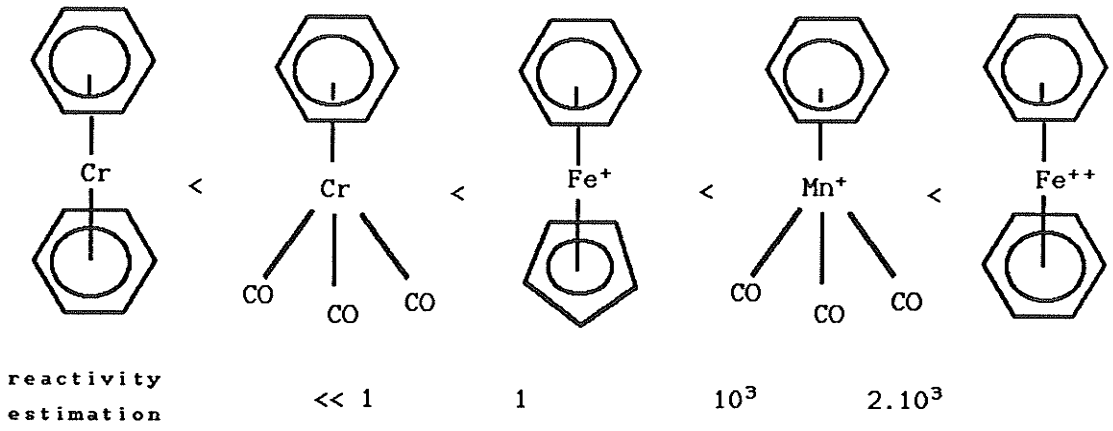


Fig. 1

The second concept is to switch the reactivity of the complex by addition or elimination of one or two electrons to or from the complex. This redox change could lead to an increase in the reaction rate by an order of 10^9 [34].

The emphasis of this thesis will focuse on the first concept , namely the effect of the transition-metal on the reactivity of the organic molecules, especially in the context of nucleophilic substitution reactions.

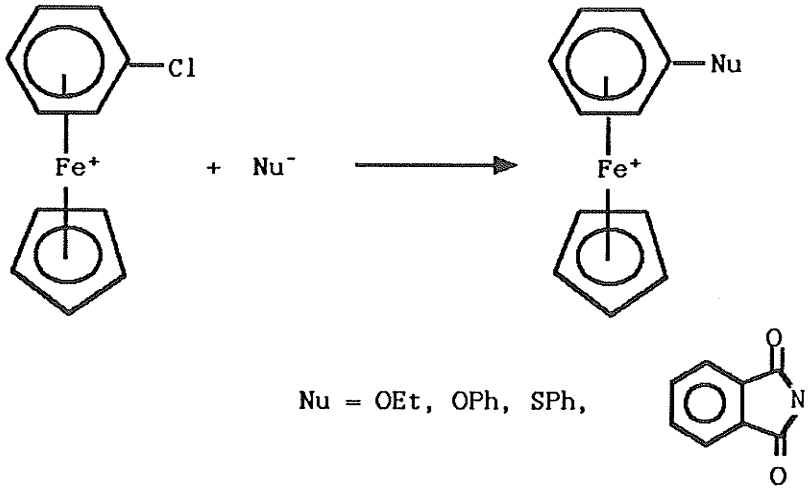
There are a number of examples of metal-coordinated complexes such as $CpFe^+$, $Mn(CO)_3^+$ and $Cr(CO)_3$, demonstrating the enhanced reactivity of these compounds. Reactions involving each part of the complex, i.e. the cyclopentadienyl ring (in the case of CpFe) and its substituents, the metal atom and the complexed arene ring and its substituents, have been reported [34-39].

1.2.1 *Nucleophilic Substitution Reactions of Iron Complexes.*

Chlorine substituents on either the six- or five-membered rings in $[\eta^6$-arene-η^5-cyclopentadienyliron$]^+$ derivatives are very reactive towards nucleophilic substitution [40-44]. The displacement of the chloro group could provide a very useful synthetic strategy based on the type and nature of the nucleophile. Also, the $FeCp^+$ complexes are unique due to their high reactivity and simple synthetic procedure compared to

these of $Cr(CO)_3$ [45] and various $Mn(CO)_3$ complexes [46]. It has been estimated that the chloro group in the chlorobenzene ligand is about 1000 times more reactive towards nucleophilic substitution than when it is located on the cyclopentadienyl ring. The $FeCp^+$ is a good withdrawing group and is equivalent to two nitro groups in terms of activation [36].

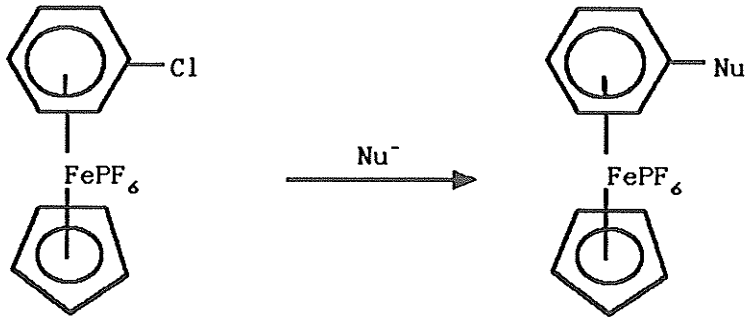
The first example of this type of reactions was demonstrated by Nesmeyanov and co-workers [47,48], where the chloro group on the arene ring was substituted by oxygen, sulfur and nitrogen containing nucleophiles (Scheme 2).



Scheme 2

Other interesting reaction leading to the formation of phenol and thiophenol complexes was developed by

Helling and Hendrickson [49]. In these reactions, the authors synthesized such complexes using the CpFe complex of chlorobenzene with hydroxide or hydrosulfide ions as shown in Scheme 3.



Nu = OH, SH

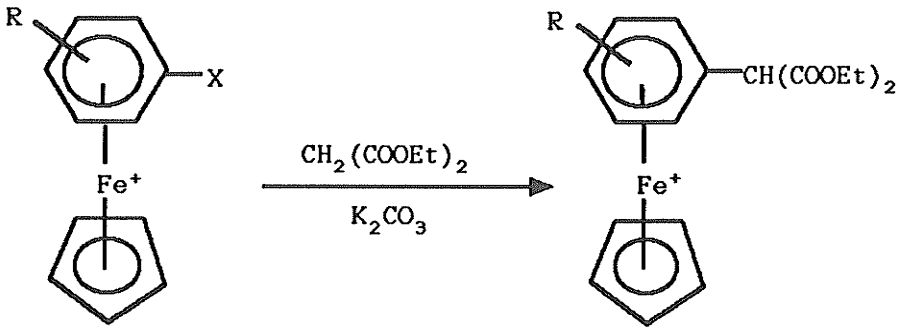
Scheme 3

Other types of O-, S- and N-containing nucleophiles have been utilized for the studies of the aromatic nucleophilic substitution reactions of cyclopentadienyl-iron complexes of mono- and dichlorobenzene [50,51]. Reactions of the dichlorobenzene complexes with anions of phenol, p-thiocresol, methanol or benzyl alcohol, as the source of nucleophile, resulted in the disubstitution of both chloro groups. Under conditions of high dilution monosubstitution of only one chloro group occurred. The nucleophilic aromatic substitution

reaction (S_NAr) of the nitro group in nitro-arene complexes worked almost as well as that of Cl^-. Such substitutions were achieved with O,S, and N nucleophilies [51]. The $[(C_5H_5)Fe(C_6H_5Cl)]$ $[BF_4]$ complex will also undergo nucleophilic substitution reaction with the sodium salt of a number of nucleophiles to give the corresponding $[(C_5H_5)Fe(C_6H_5X)]^+$ derivative [52,53].

Besides the use of O-, S- and nitrogen nucleophiles, carbon nucleophiles were also used to obtain a C-C bond. Lee et al. [50, 54], have used numerous carbon nucleophiles in the reactions with CpFe complexes of chloroarenes and nitroarenes. These nucleophiles include anions of acetylacetate, dibenzoylmethane and diethylmalonate. As an example, Scheme 4 [54] shows the reaction between chloroarene or nitroarene complexes and diethylmalonate. These reactions were carried out under very mild conditions resulting in the formation of C-C bonds. The yields were also quite high, thus offering a potentially useful synthetic route. Moriarty and co-workers [55,56] have also reported the nucleophilic substitution of Cl^- by stabilized carbanions, thus allowing the formation of C-C bond formation between the arene and an aliphatic or aromatic part. The carbanions used are stabilized in

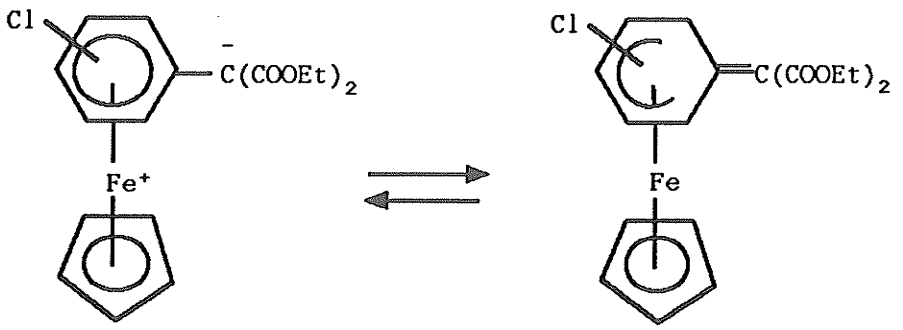
the benzylic positions by two carbonyl groups and generated by deprotonation of nucleophilies such as the anions of: diethylmalonate, 2,4-pentadione, benzylacetone, phenylsulphonylacetone, and (phenylsulphonyl)ethyl acetate.



R = H, CH_3
X = Cl, NO_2

Scheme 4

An attempt was also made to obtain disubstituted product [54]. It was observed however that deprotonation of a substitution product could give rise to a Zwitterion- cyclopentadienyl complex which would be more electron- rich than the starting dichlorobenzene complexes, and hence the second chloro group would not be displaced by the nucleophile as shown in eq.1.3 [54].



eq.1.3

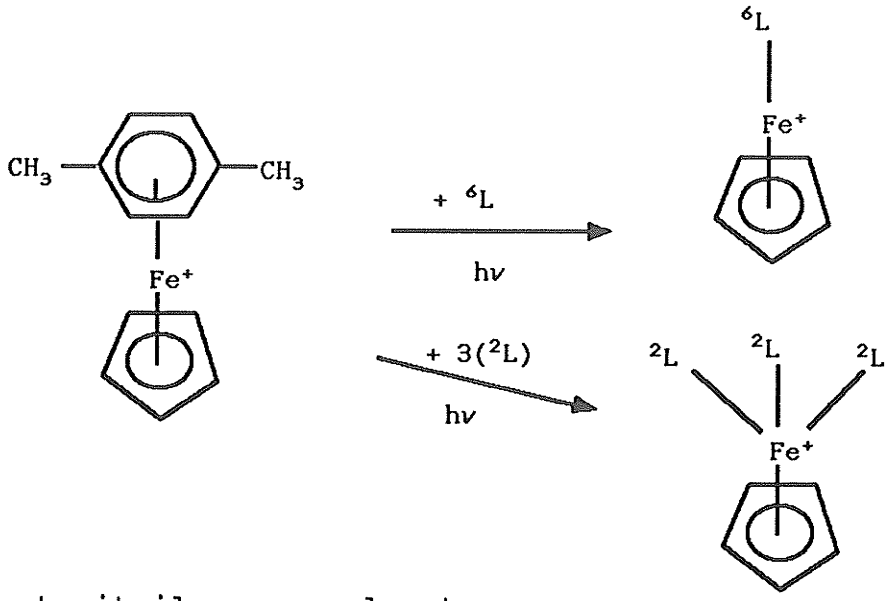
The disubstituted products were achieved when anions of diethyl ethylmalonate or diethyl methylmalonate were used as nucleophiles [57]. In this case, it was noticed that p- and m-dichlorobenzene complexes underwent S_NAr reactions to produce the disubstituted product while o-dichloro-benzene complex failed to give such a product due to some steric hindrance.

1.3 *Liberation of the Modified Arenes from their Metal Moieties.*

There are two general methods for decomplexation of η^6-arenes from their metal complexes [3]. These methods involve the displacement reactions of the arene ligands by other ligands and the removal of arenes using redox processes.

Oxidative methods include photolysis [58-60],Ce (IV), I_2 [61], $KMnO_4$, and MnO_2 [62]. Nesmeyanov et al., noted in 1963 that light accelerated the decomplexation of η^6-arene $-\eta^5$-cyclopentadienyliron cations in solution [63]. Later, Nesmeyanov investigated the effects of the irradiation of arene with light of wavelength 253-577 $m\mu$ [64]. A disproportionation reaction took place resulting in the free arene and the ferrocene. The study conducted by Gill and Mann [65-68] concentrated on the photochemically induced reactions using the cyclopentadienyliron complex of xylene. In the course of their study it was shown that the arene ligand can be replaced by one 6-electron ligand (for example, hexamethylbenzene, cycloheptatriene and cyclooctatetraene) or by three 2-electron ligands (such as trialkyl or triaryl phosphines, isocyanides, cyanides and CO) as described in eq.1.4.

Photolytic demetallation was also used by Abd-El-Aziz and de Denus [69,70] as part of a preparative organometallic approach in organic synthesis. Their studies have proven that photolytic liberation is a very effective method for the recovery of such organic compounds as some isomeric tolylcyanoacetates and arylated phenylsulphonylacetonitriles using dichloromethane/



eq.1.4

acetonitrile as a solvent.

Lee, Sutherland and their coworkers have utilized pyrolytic sublimation [71-73] as an alternative route for the liberation of arene ligands from their respective CpFe complexed cations. Both the pyrolytic sublimation and photolysis has proven to be successful in liberating the free arene ligand from the CpFe complexes.

Electrolysis has also been utilized in the removal of CpFe from arene ligands. Early electrochemical studies of arene cyclopentadienyliron compounds were carried out by Dessy et. al. [74], and have shown that the benzene and alkyl benzene complexes could add 1 electron to produce neutral complexes. Nesmeyanov et al. [75], observed that the arene complex exhibits two monoelectronic reduction waves for cyclopentadienyliron

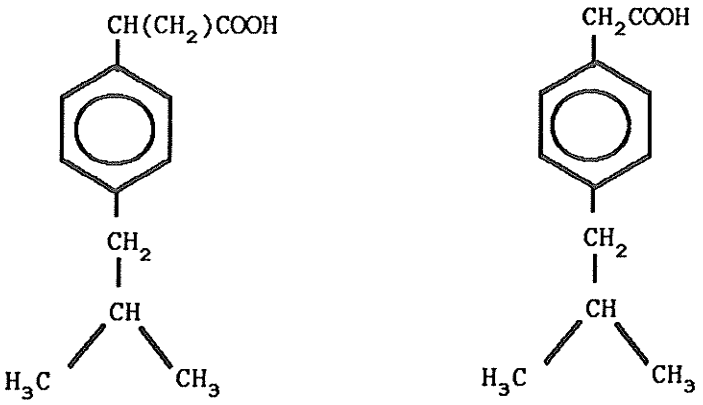
complexed arenes. Later it was shown by El Murr [76] that the first electron transfer step lead to the formation of an electroneutral 19 electron iron complex, while the transfer of the second electron gave a 20 electron anionic complex. Darchen [77,78] has also reported that the formation of an electroneutral iron complex would allow the exchange of the arene ligand for two molecules of the solvent (MeCN) with the formation of the 17-electron $(MeCN)_2CpFe^+$, or the exchange of the arene ligand for three $P(OMe)_3$ groups. Moinet et al. [79], have observed that the electroneutral complexes generated by the electrolysis of the corresponding arene complexes were unstable in water, water/alcohol or alcohol, and would undergo either decomposition, dimerization or catalytic reactions depending on the nature of the solvent and the arene. Moreover, Bowyer et al. [80], have also reported the decomposition of mono- and bis(iron)cyclophane complexes to give cyclophane, ferrocene and metallic iron. Others have successfully utilized the electrochemical method for the liberation of some functionalized arenes such as benzophenone and diethyl ethylphenylmalonate from their respective hexafluorophosphates [81,82].

1.4 *Traditional Synthetic Routes for the Target Compounds: Arylated Alkanoic Acids and Various Heterocyclic Precursors.*

1.4.1 Arylated Alkanoic Acids

Due to the therapeutic importance ,non-steroidal antiinflammatory agents (NSAI) constitute one of the largest class of drugs [83-85]. These compounds can be categorized, into three main classes, according to their chemical structure [86].

(1) Benzoic derivatives, in which aspirin is the most important representative.
(2) Aryl acetic acid compounds such as indomethacin, sulindac, diclofenac and ibufenac (Fig.2).
(3) α-Aryl propionic acids with ibuprofen as the highlight (Fig.2).



Ibuprofen Ibufenac

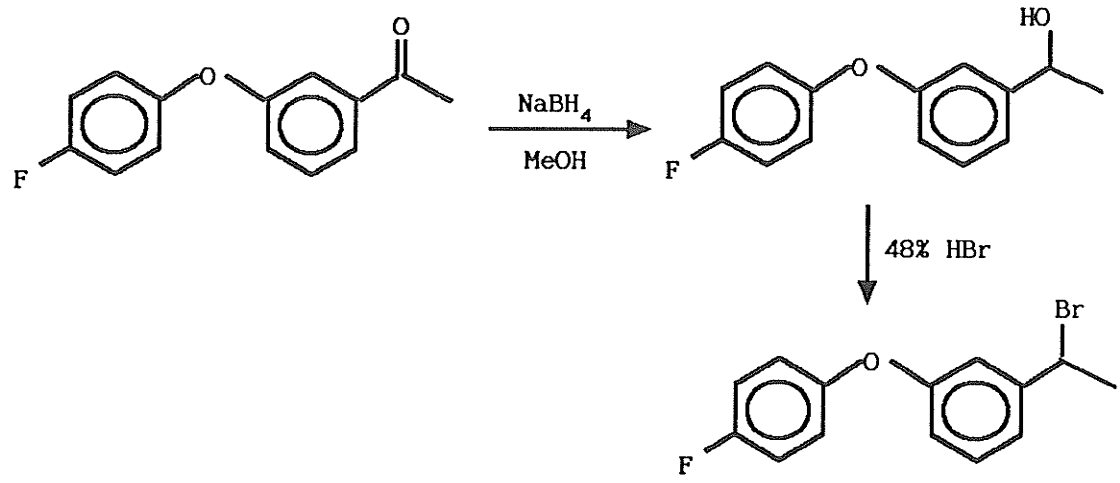
Figure 2

Among numerous mild anti-inflammatory, analgesic and antipyretic agents, aspirin has been the drug of choice for many decades. The side effects caused by the use of aspirin such as nausea, diarrhea, heartburn or leukopenia, gave rise to the search for NSAI agents with higher therapeutic activity and fewer side effects [87]. An interest in arylacetic acids, as one type of potentially useful NSAI agents, had developed in several laboratories. The initial studies, conducted at Boots and Merck, had utilized two plant growth regulators, indolylacetic acid and phenoxyacetic acid as basic structures for the preparation of arylacetic acids and subsequently NSAI agents [88,89]. Hydrophobic substitutions, effectively applied as activity-enhancing

groups in many pharmacological agents, in the form of aryl or alkyl substituents, readily converted these plant growth regulators into derivatives highly active in animal assays such as foot-edema, UV erythema, and adjuvant arthritis [85].

Further investigations in the field of arylacetic acids indicated that the methyl group introduction into the aliphatic side chain of substituted aryl acetic acids is very beneficial in enhancing anti-inflammatory activity of NSAI agents, such as ibuprofen, ketoprofen, naproxen and suprofen [90-95]. This success in the preparation of NSAI agents with higher therapeutic activity and milder side effects than aspirin, could explain in part the proliferation of the synthetic methods leading to these types of compounds. According to the building mode for the aliphatic side chain it was possible to differentiate several main synthetic routes for the preparation of substituted aryl acetic acids [86]. These include the introduction of the methyl radical to phenylacetic acid derivatives and terminal building of the carboxylic group through functionalization or by oxidation. In the frame of our work the second approach, namely carboxylic function introduction, is significant and shall be briefly reviewed.

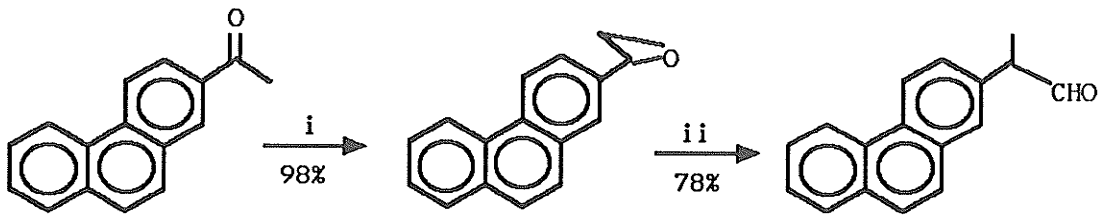
There are many ways to prepare 2-aryl propionic acids and their derivatives from the secondary α-aryl alkyl halide using classical organic methods. The synthesis of these halides was also derived from the standard procedures of reduction of acetophenones into the corresponding secondary alcohols followed by halogenation with hydrochloric acid as shown in Scheme 5 [96].



Scheme 5

Another way of preparing alkanoic acids is via epoxides. In this case, trimethylsulfonium iodide is added to acetophenones in a basic medium to give 3-aryl 1,2- epoxypropanes intermediates which then rearrange into hydratropaldehydes [97]. Through the subsequent oxidation of aldehydes the corresponding acids are

obtained (Scheme 6). This process is applied to the synthesis of ibuprofen as well as naproxen and ketoprofen in almost quantitative yield.

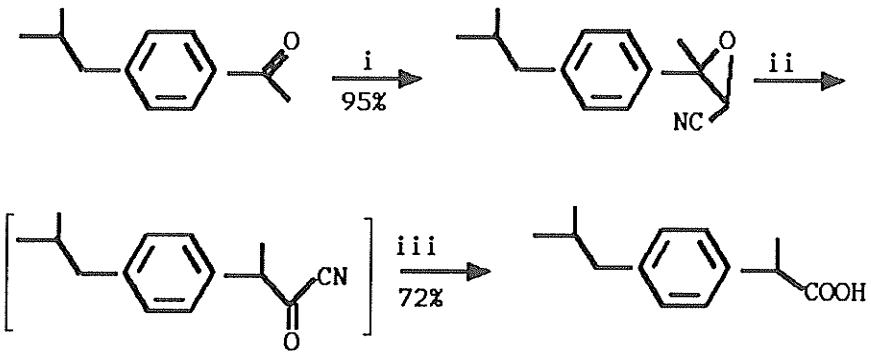


i) Me_3SI, NaH, DMSO/THF, 0°C, 0.25h then 25°C, 1.5h

ii) fluorisil PhH

Scheme 6

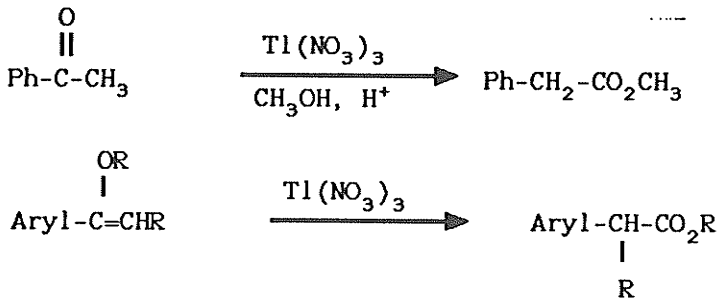
One of the most useful synthetic methods for the preparation of alkanoic acid esters is Darzens' reaction, which involves condensation of chloroacetonitrile with acetophenones as described in Scheme 7 [98].



i) chloroacetonitrile in t-AmONA/t-AMOH
ii) $LiCLO_4$, PhMe, reflux
iii) NaOH(aq)

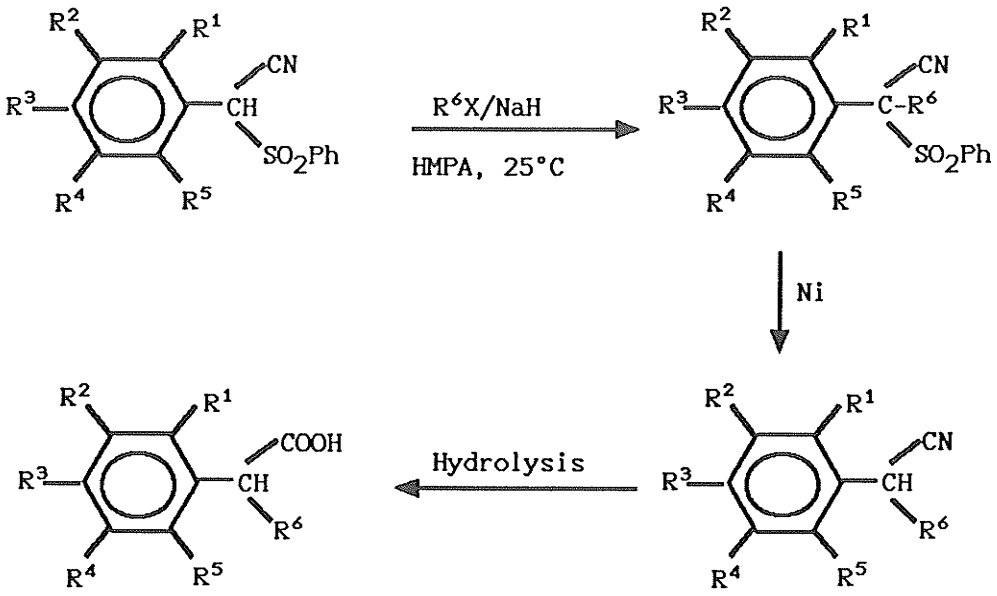
Scheme 7

McKillop et al. [99] have developed yet another method of synthesis for arylated alkanoic acids using thallium salt as shown in Scheme 8. Their synthesis involved a direct conversion of alkyl aryl ketones into esters of α-arylalkanoic acids by thallium(III)-promoted rearrangement.



Scheme 8

Arylated phenylsulphonylacetonitriles are very attractive starting materials for a variety of arylalkanoic acids and their derivatives of pharmaceutical interest [100, 101]. In the synthetic method reported by Suzuki et al. [101], arylated phenylsulphonylacetonitriles were prepared by the mode of nucleophilic substitution of aryl iodide and phenylsulphonylacetonitrile using sodium hydride as a base and copper(I) iodide as a catalyst. Subsequent alkylation, hydrogenation and hydrolysis produced the alkanoic acids (Scheme 9).



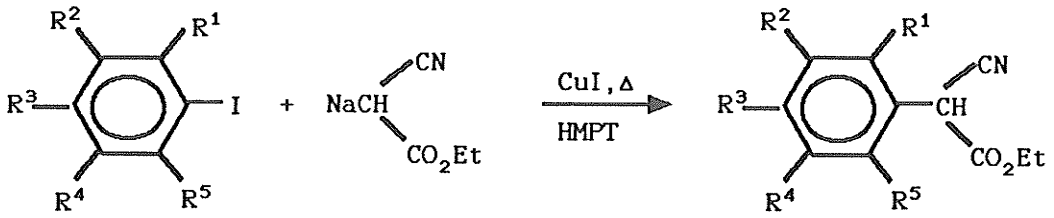
Scheme 9

Since the most complicated step in this synthesis was that of nucleophilic substitution, Sakamoto et al. [102] modified Suzuki's method and utilized palladium(0) as a catalyst. In spite of the drawbacks resulting from the reaction conditions, namely high temperatures and very toxic solvents, mono- and para-disubstituted compounds were obtained in fairly good yields. However, it has been reported that chlorobenzene fails to react under the condition outlined above. It was also observed that when substituents were placed at the ortho position on the aromatic ring the dramatic decrease in the alkanoic acid yield was observed.

1.4.2 Heterocyclic Precursors.

The ethyl arylcyanoacetates have been recognized as useful intermediates in the synthesis of various heterocyclic compounds such as azetinones, pyrimidines and oxazaphosphorinane derivatives [103-107]. There has been considerable interest in the development of more efficient synthetic routes leading to their preparation.

Although alkyl cyanoacetates are easily obtained from the direct nucleophilic substitution of ethyl cyanoacetate with alkyl halides, aryl halides do not react with the anions under the same conditions. In order to promote nucleophilic substitution reaction on the aromatic ring for the synthesis of ethyl arylcyanoacetates, numerous reagents and catalysts such as copper (I)iodide, aryllead triacetate or PdX_2L_2 have been applied [108,109]. Osuka et al. [109], reported a simple, one-step synthesis of arylated cyanoacetates via a copper(I) promoted arylation of cyanocetate with nonactivated aryl halide (Scheme 10). The arylation procceeded smoothly with aryl iodides, giving corresponding arylcyanoacetates in 70-73 % yields, however results were rather poor with aryl bromides. The reaction with aryl chlorides failed.



a) R = H
b) R = CH_3

a) 70 %
b) 73 %

Scheme 10

A very convenient method of synthesis of alkyl arylcyanoacetates via palladium-catalyzed aromatic substitution was reported in 1985 by Uno et al. [110]. Their study has indicated that in the presence of the palladium catalyst, namely dichlorobis [triphenylphosphine]palladium, aryl halides and metallated alkyl cyanoacetate in monoglyme reacted successfully to give ethyl α-cyano(phenyl)acetates in good yield (73-78%). Other iodoarenes such as iodotoluene, chloroiodobenzene, and iodonaphtalene reacted similarly with the anion, and the iodine atom on the aromatic ring was formally replaced by an ethoxycarbonyl(cyano)methyl group, giving the arylcyanoacetates in moderate yields (36-45%) [110].

1.5 *Nature and Scope of the Present Work.*

Nucleophilic substitution reactions of arenes complexed with cyclopentadienyliron(FeCp) could give rise to functionalization of the arene ring. This would, in turn provide a synthetically useful method for the preparation of organic compounds which potential use in medicinal chemistry.

The present work examines the utility of the nucleophilic substitution reactions of the FeCp complexes of chlorobenzenes and chlorotoluenes with carbon containing nucleophiles, such as ethyl 2-methyl-acetoacetate, ethyl 2-ethylacetoacetate, ethylphenyl-sulphonylacetonitrile and ethylcyanoacetate, followed by photolytic demetallation. This would provide an alternative route towards the synthesis of arylated alkanoic acid and heterocyclic precursors.

2.0 RESULTS AND DISCUSSION

2.1 *Synthesis of Chloroarene Complexes.*

The Lewis acid catalyzed ligand exchange reaction between ferrocene and a suitable arene was first explained and successfully conducted by Nesmeyanov and coworkers in 1963 [16,17]. In a typical ligand exchange reaction, the ratios of ferrocene : $AlCl_3$: Al : Arene used were 1:2:1:excess respectively. Arenes which exist as liquids require no solvent for reaction but those which occur in solid state are generally carried out in decalin or cyclohexane. The resulting cationic product is often isolated as its tetrafluoroborate or hexafluorophosphate salt. In general, the hexafluorophosphate anion is utilized due to the higher product yields and stability.

In this work, we have prepared chlorobenzene, isomeric chlorotoluenes and isomeric dichlorobenzenes. The detailed experimental procedures for the synthesis of these types of complexes are described in section 3.1. The results of characterization of these complexes, as well as their yields agree very well with literature data [15-23]. As an example, the ^{1}H and ^{13}C(APT: Attached Proton Test) NMR spectra of p-chlorotoluene are shown in Fig.3 and 4.

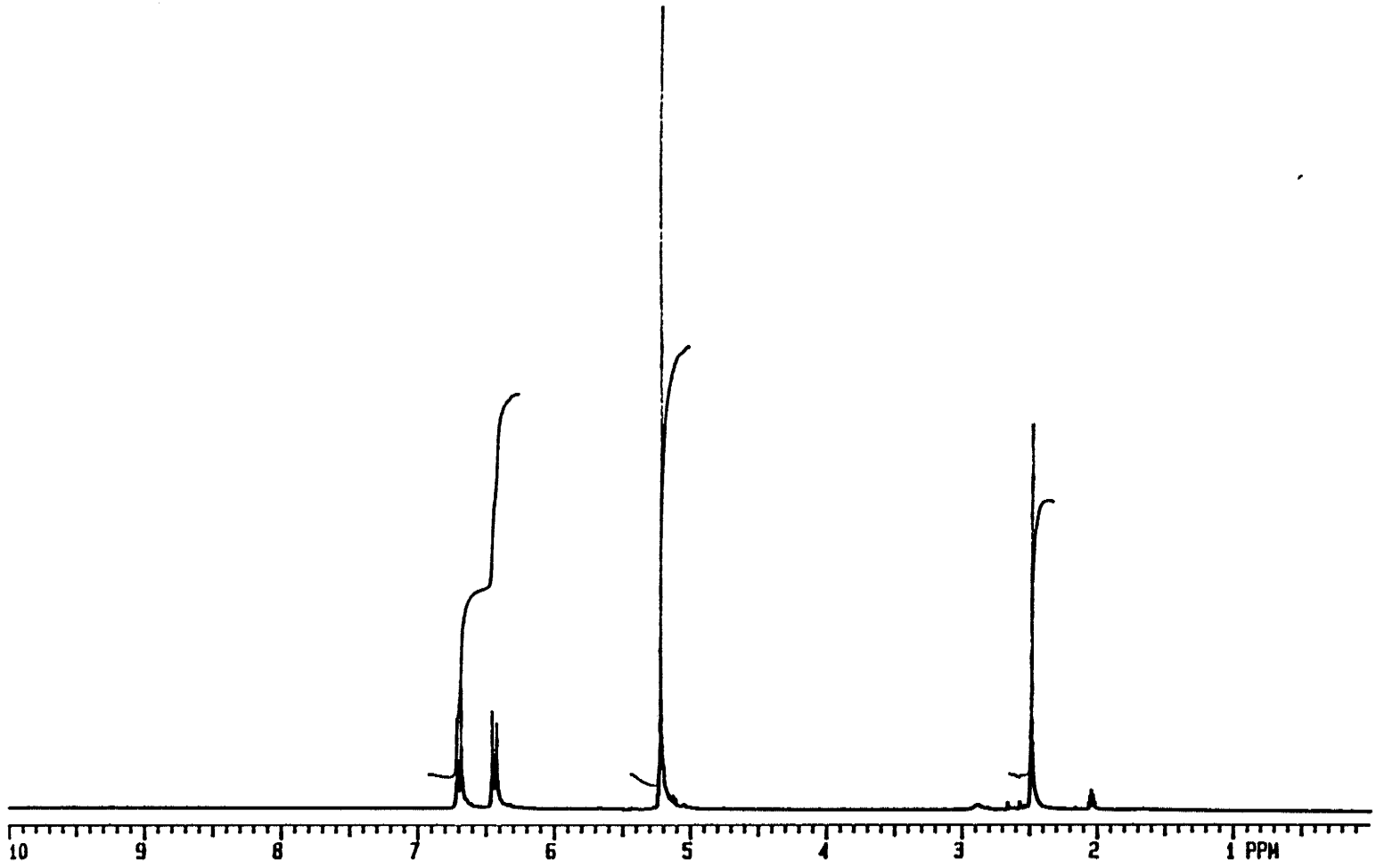


Fig.3 ^{1}H NMR spectrum of (η^{6}-p-chlorotoluene)-η^{5}-(cyclopentadienyl)hexafluorophosphate in CD_3COCD_3.

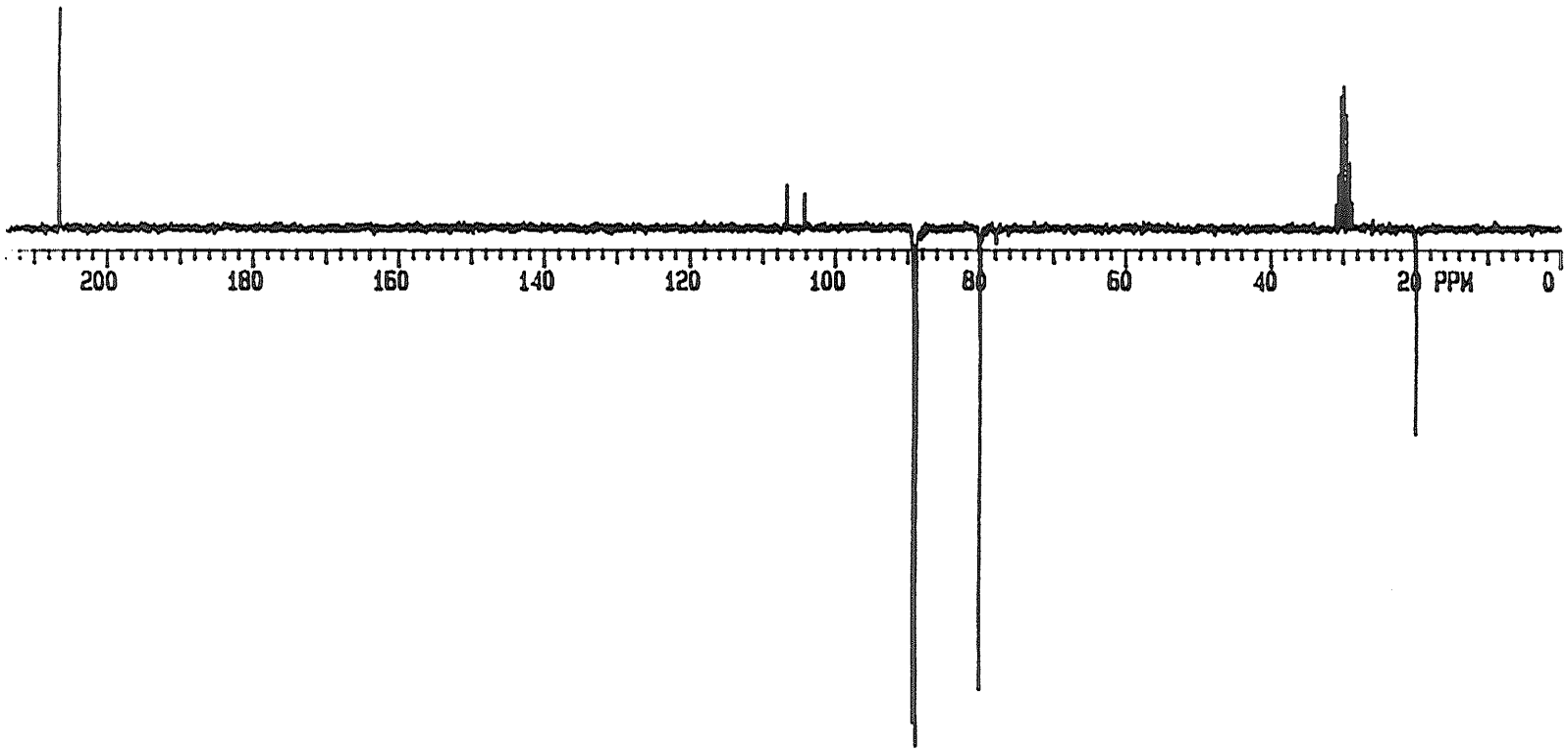


Fig.4 ^{13}C NMR(APT) spectrum of η^6-(p-chlorotoluene)-η^5-(cyclopentadienyl)hexafluorophosphate in CD_3COCD_3.

2.2 *Synthesis of Some Alkanoic Acid Esters.*

As stated in section 1.4.1, NSAI agents constitute one of the largest classes of drugs. Within this class of drugs the α-aryl propionic acids, as possible non-steroidal antiinflammatory agents, are of special interest to our research, since it could be prepared using cyclopentadienyliron moiety as an activating group.

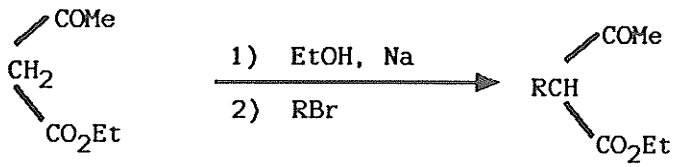
The number of methods proposed for the preparation of arylated alkanoic acids demonstrates the importance of these derivatives. The search for new synthetic methods has pointed out certain limitations of the initial methods. For example, the synthetic utility of the Willgerold- Kindler [85] reaction was limited by: (a) the reaction conditions, which involve high temperatures and sometimes high pressures; (b) the tedious and rather complicated isolation techniques; and (c) the yield of the products, which in many cases, is modest.

Some of the other methods for the synthesis of α-arylalkanoic acids, such as Danrzen's reaction, 1,2-Aryl Shift, are also limited by their required reaction conditions, yields, or the toxicity of some of the employed reagents [96-98].

Our interest in this field was directed towards the development of a new, economical, and less toxic synthetic route for the preparation of these types of compounds. Aromatic nucleophilic substitution reactions of η^6-arene-η^5-cyclopentadienyliiron complexes with various carbon nucleophilies, followed by photolysis, have proven to fulfill the requirements specified above.

2.2.1 *Synthesis of Ethyl 2-methylacetoacetate and Ethyl 2-ethylacetoacetate.*

Due to our interest in the formation of C-C bond, we have prepared ethyl methylacetoacetate and ethyl ethylacetoacetate according to the procedure outlined in Scheme 11 and described in the experimental section 3.2.2 [111]. The ^{1}H NMR and ^{13}C NMR spectra of ethyl methylacetoacetate are shown in Fig.5 and 6. These nucleophiles were then utilized in the aromatic nucleophilic substitution reactions.



I II RBr = MeBr
III RBr = EtBr

Scheme 11

2.2.2 *Arylation of Ethyl 2-Methylacetoacetate and Ethyl 2-Ethylacetoacetate.*

Aromatic nucleophilic substitution reactions (S_NAr) of arenes complexed to a metal moiety have been under investigation with various nucleophiles and different metallic species as possible routes for the synthesis of a wide range of organic compounds which could be useful in medicinal chemistry [50,51,54-57,69,70]. In the present work we have utilized this synthetic approach for the preparation of some complexed alkanoic acid esters.

The hexafluorophosphate salts of the complexed chlorobenzene (**4**) and isomeric chlorotoluenes (**5,6**) were utilized in this study (Scheme 12). The synthesis of these complexes are described in Section 3.1.1. Treatment of (**4,5,6,**) with ethyl methylacetoacetate or

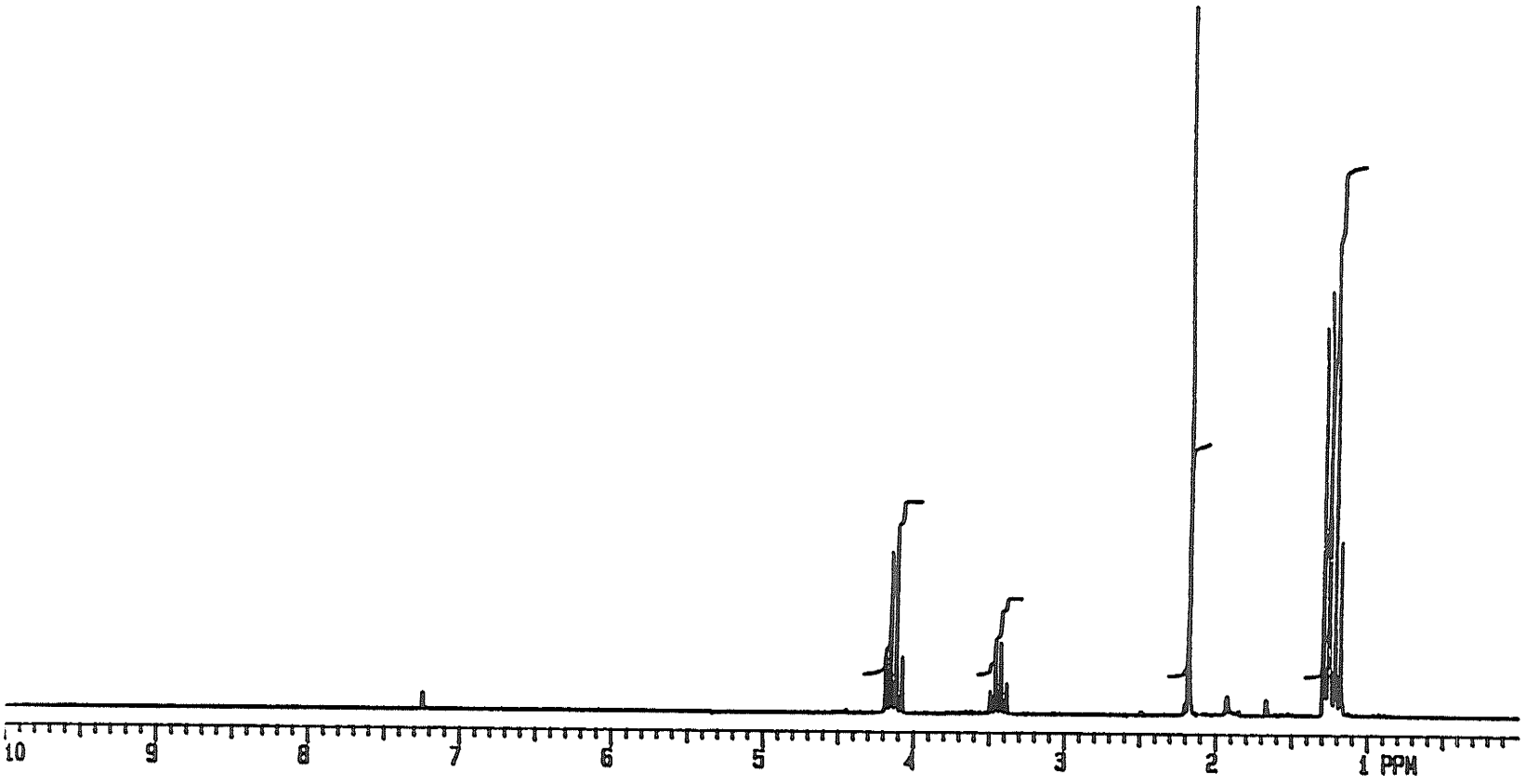


Fig.5 ^{1}H NMR spectrum of Ethyl 2-methylacetoacetate in $CDCl_3$.

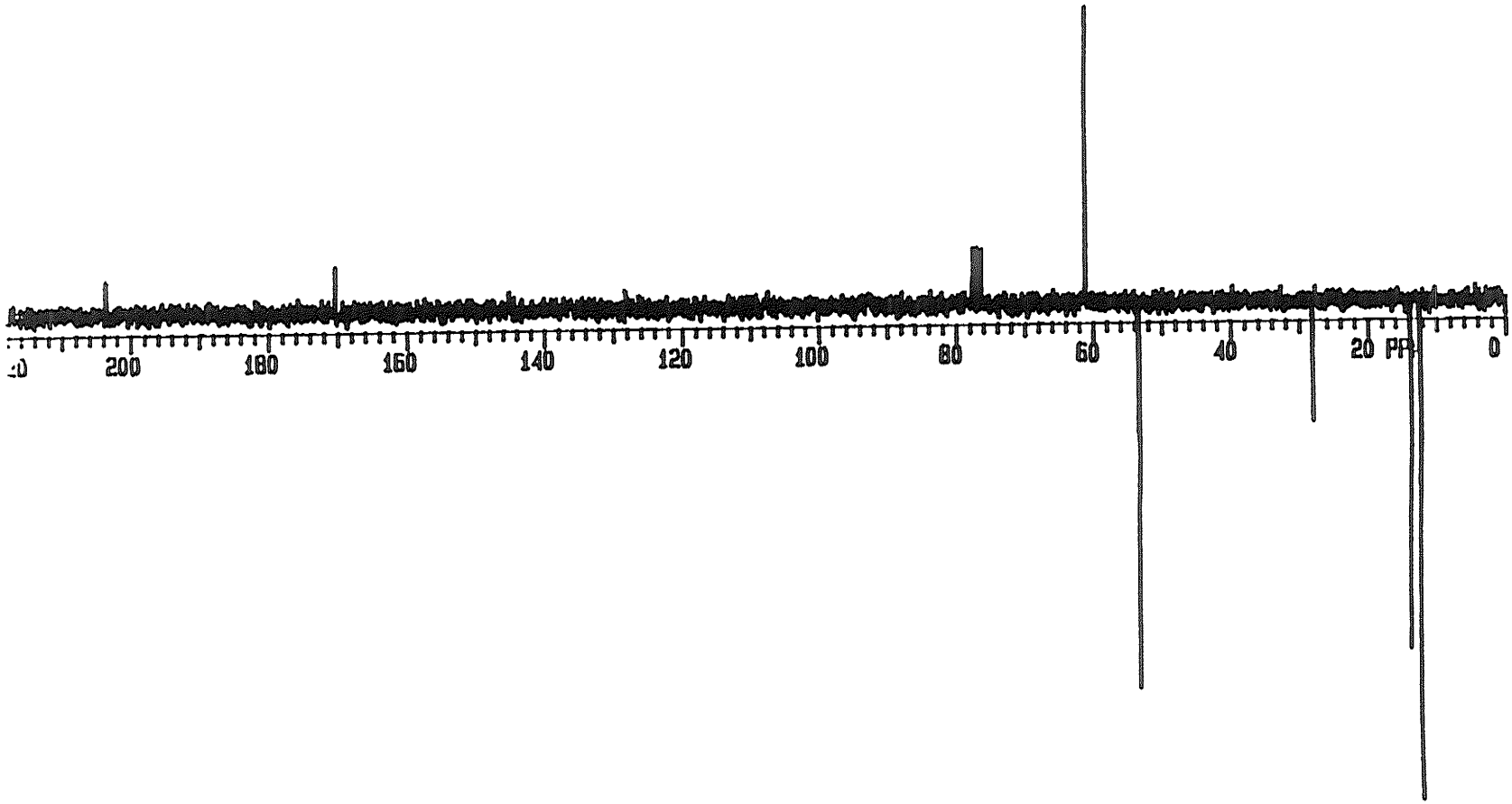
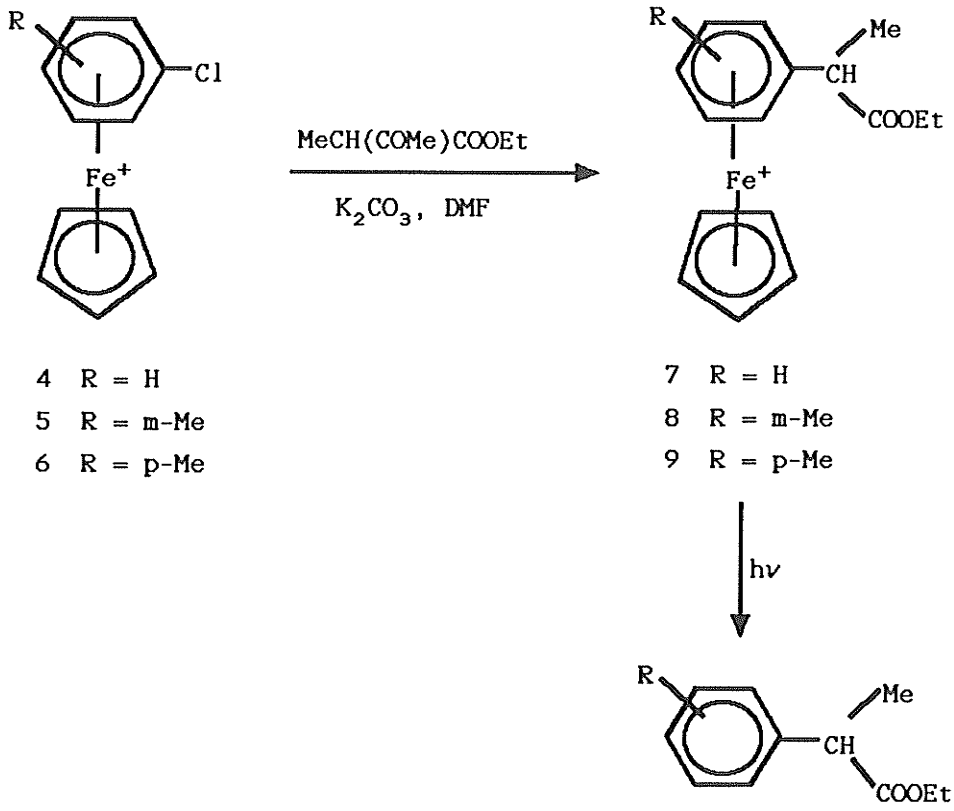


Fig.6 ^{13}C NMR(APT) spectrum of Ethyl 2-methylacetoacetate in $CDCl_3$.

ethyl ethyl- acetoacetate in the presence of potassium carbonate in DMF (N,N-dimethylformamide)gave the nucleophilic substitution products (**7-9** and **13-15**) with deacylation, as shown in Schemes 12 an 13. Moriarty and Gill [55,56] have observed the same phenomenon of deacylation when ethyl acetoacetate was used as a nucleophile. As illustrated in Schemes 12 and 13, the cyclopentadienyliron complexes of arylated ethyl propanoates and ethyl butanoates were easily prepared.



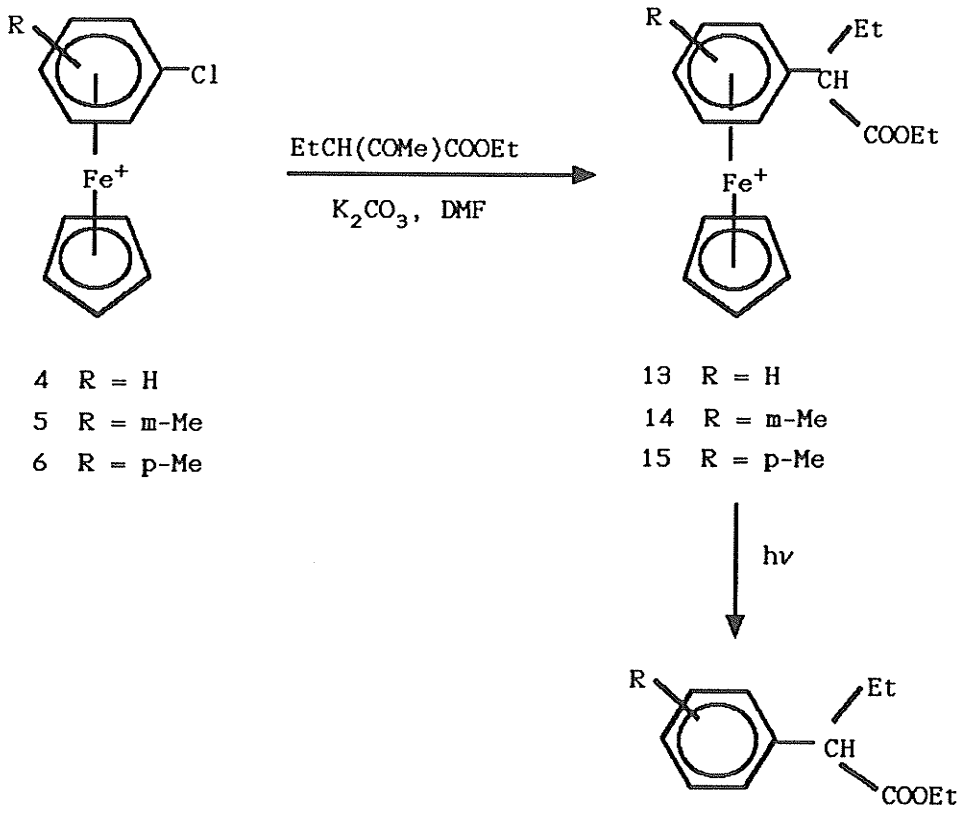
4 R = H
5 R = m-Me
6 R = p-Me

7 R = H
8 R = m-Me
9 R = p-Me

Scheme 12

10 R = H
11 R = m-Me
12 R = p-Me

These complexes were obtained in very good yields (71-89%). The structures of these new complexes were then determined using IR, ^{1}H and ^{13}C NMR. Chemical shifts and splitting patterns in both proton and carbon spectra indicate that deacylation occurred prior to the isolation of these complexes. The representative spectra of the complexes of interest are shown in Fig. 7-10.



4 R = H
5 R = m-Me
6 R = p-Me

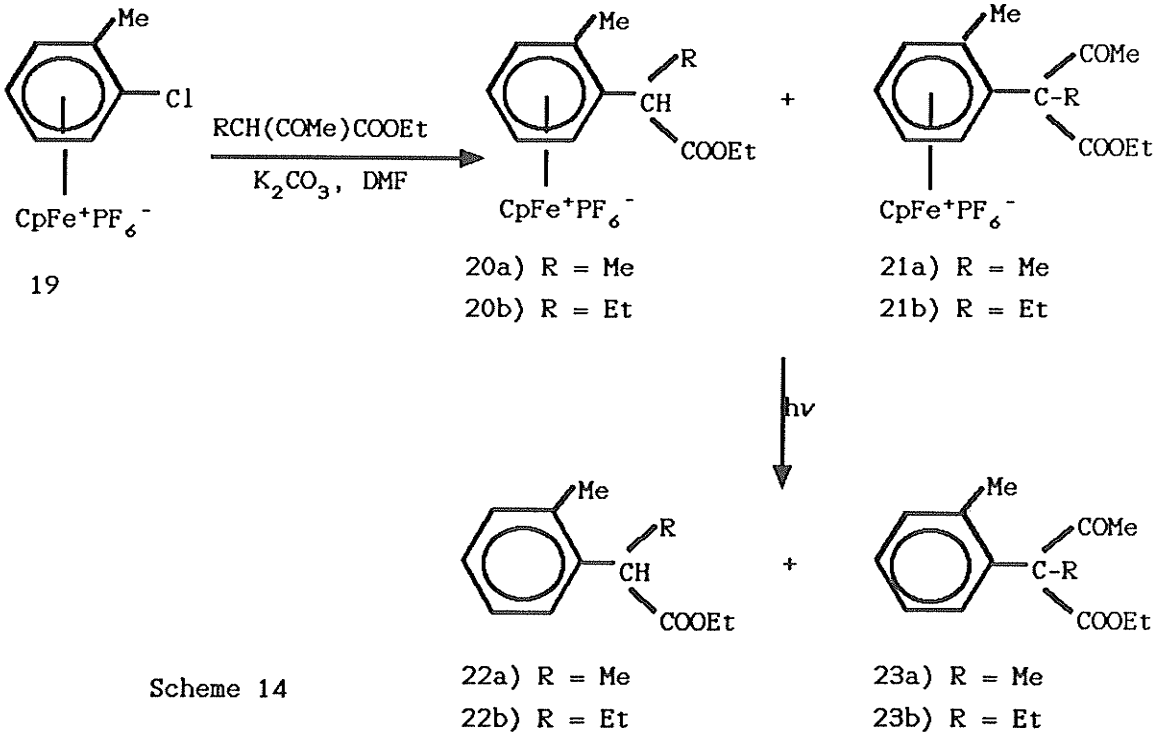
13 R = H
14 R = m-Me
15 R = p-Me

Scheme 13

16 R = H
17 R = m-Me
18 R = p-Me

This data, which are summarized in Tables 2.2.1, 2.2.2 2.2.3 and 2.2.4, are in full agreement with the expected values. The values for the stretching frequencies of the carbonyl groups, ranging from 1740 to 1735 cm^{-1}, provide further proof for the presence of the ester carbonyl group, and furthermore, for the structure of these complexes.

Besides the use of complexed m- and p-chlorotoluenes we have also used the o-chlorotoluene complex in this study. In these reactions, we always obtained a mixture of two products, the deacylated and the non-deacylated complexes (**20a,b** and **21a,b**) as shown in Scheme 14.



19

20a) R = Me
20b) R = Et

21a) R = Me
21b) R = Et

22a) R = Me
22b) R = Et

23a) R = Me
23b) R = Et

Scheme 14

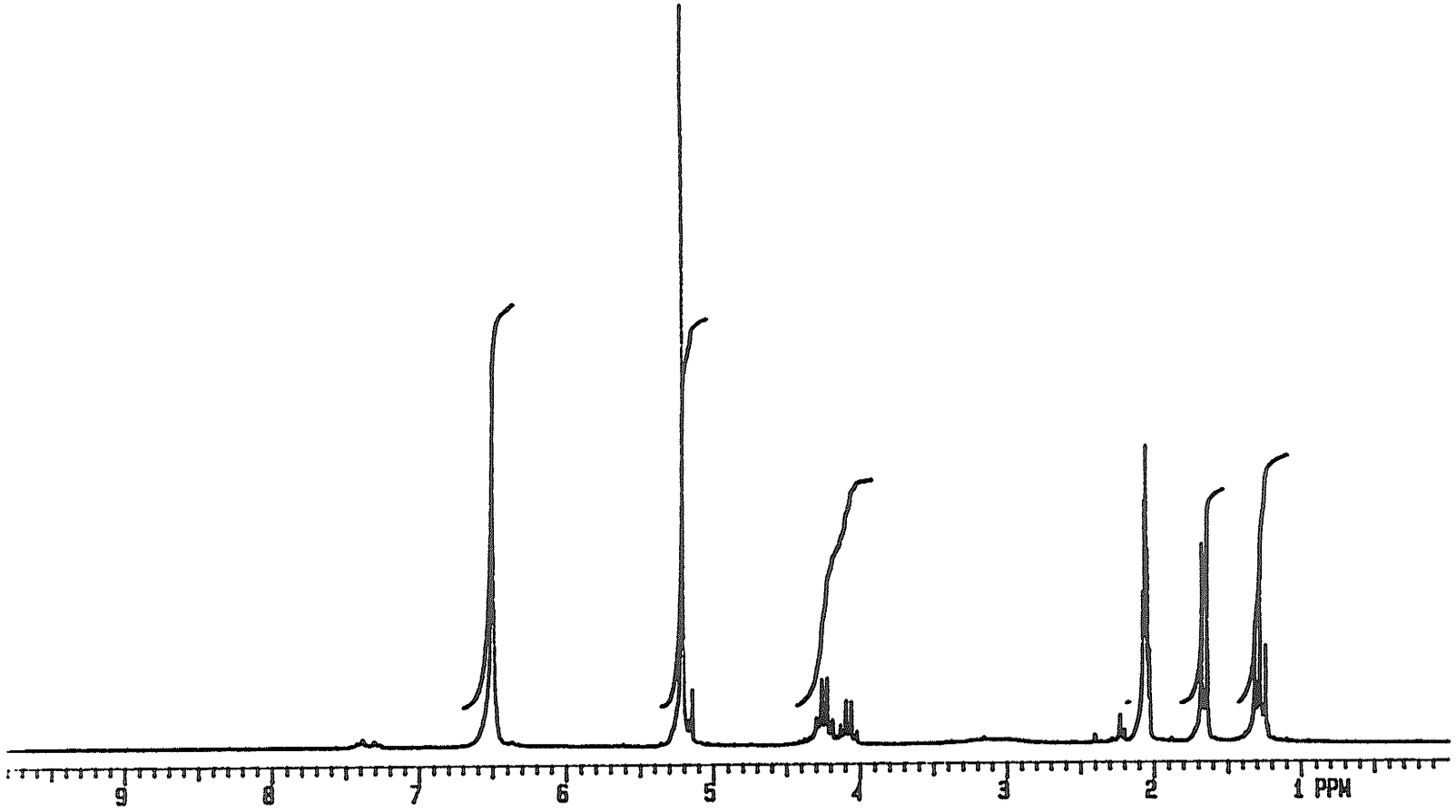


Fig.7 ^{1}H NMR spectrum of η^{6}-(ethyl 2-phenylpropanoate)-η^{5}-(cyclopentadienyl)hexafluorophosphate in CD_3COCD_3.

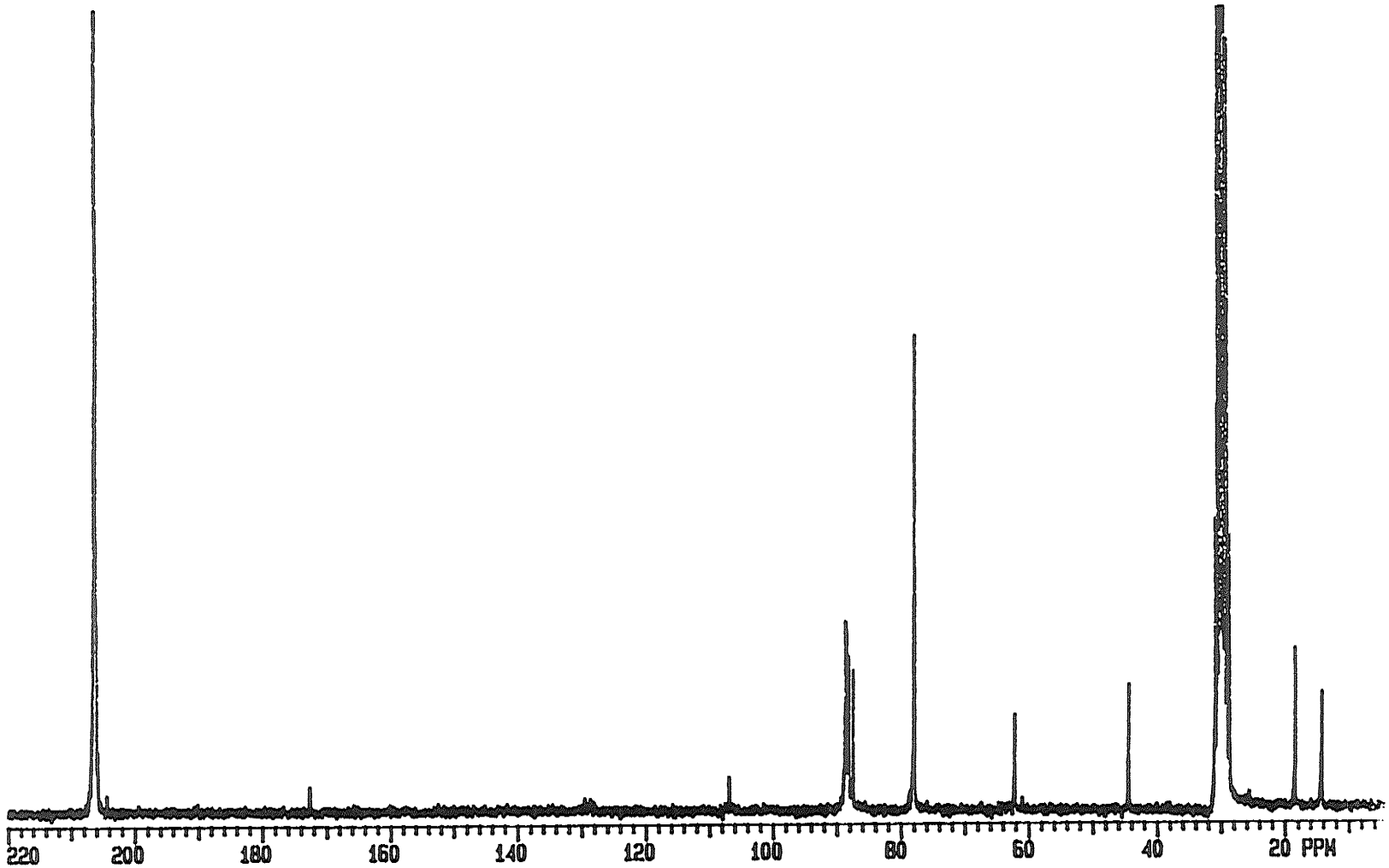


Fig.8 ^{13}C NMR spectrum of η^6-(ethyl 2-phenylpropanoate)-η^5-(cyclopentadienyl)hexafluorophosphate in CD_3COCD_3.

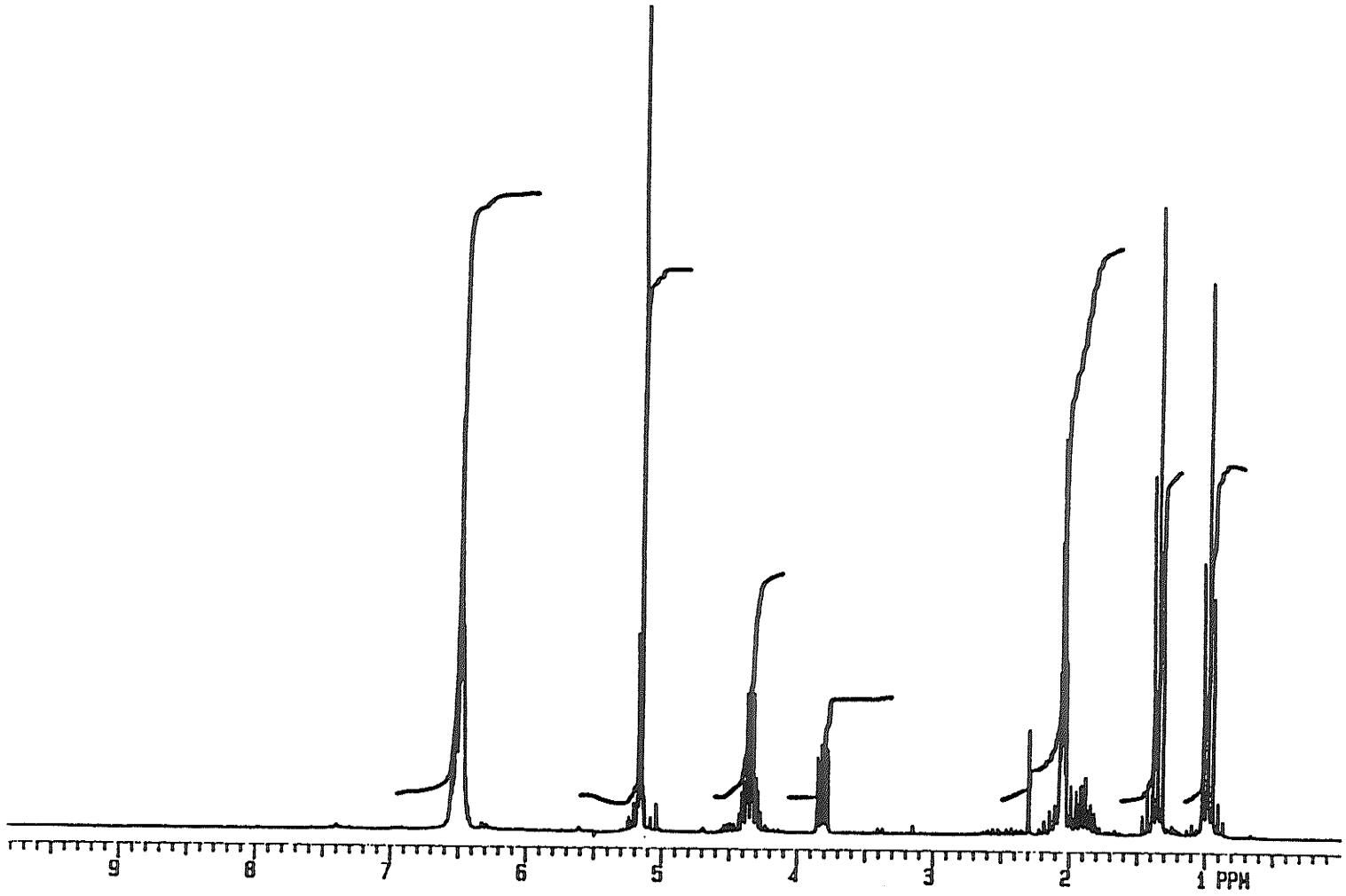


Fig.9 ^{1}H NMR spectrum of η^{6}-(ethyl 2-phenyl)butanoate)-η^{5}-(cyclopentadienyl)hexafluorophosphate in CD_3COCD_3.

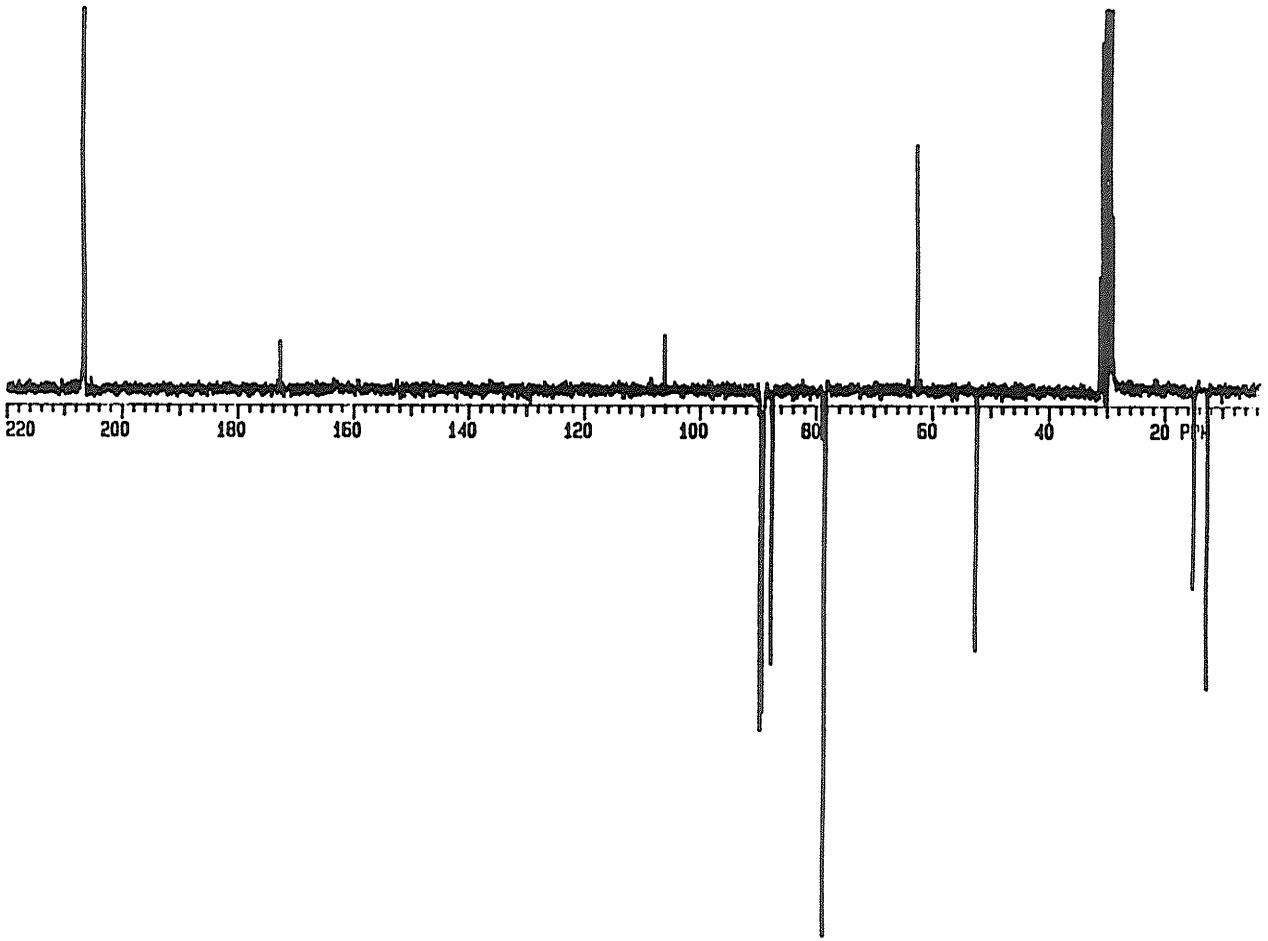


Fig.10 ^{13}C NMR(APT) spectrum of η^6-(ethyl 2-phenyl)-butanoate)-η^5-(cyclopentadienyl) hexafluorophosphate in CD_3COCD_3.

Table 2.2.1 ^{1}H NMR and yield data for complexes derived from nucleophilic substitution reactions of CpFe complexes of chloroarenes with ethyl 2-methylacetoacetate

		^{1}H NMR (δ, ppm), (CD_3COCD_3)		
Complex	% Yield	Aromatic	Cp	Others
7	71.6	6.50 (5H, br s,ArH)	5.20	4.26 (2H,q,*J* 7.0, CH_2)
				4.00 (1H,q,*J* 7.1,CH)
				1.67 (3H,d,*J* 7.2,CH*CH*$_3$)
				1.27 (3H,t,*J* 7.1,CH_2*CH*$_3$)
8	74.9	6.42 (4H,br s,ArH)	5.15	4.25 (2H,q,*J* 7.2,CH_2)
				4.05 (1H,q,*J* 7.1,CH)
				2.57 (3H,s,Ar*CH*$_3$)
				1.65 (3H,d,*J* 7.0,CH*CH*$_3$)
				1.28 (3H,t,*J* 7.0,CH_2*CH*$_3$)
9	84.0	6.38 (4H,br s,ArH)	5.13	4.22 (2H,q,*J* 7.1,CH_2)
				4.03 (1H,q,*J* 7.2,CH)
				2.54 (3H,s,Ar*CH*$_3$)
				1.62 (3H,d,*J* 7.1,CH*CH*$_3$)
				1.26 (3H,t,*J* 7.1,CH_2*CH*$_3$)

Table 2.2.2 ^{13}C NMR and IR data for complexes derived from nucleophilic substitution reactions of CpFe complexes of chloroarenes with ethyl 2-methylacetoacetate

Complex	i.r. (cm^{-1}) (neat)	^{13}C NMR (δ, ppm), (CD_3COCD_3) Aromatic	Others
7	1735 (CO)	107.33*,89.16, 89.08,88.94, 88.93,88.59	172.50(CO),78.39(Cp), 62.61(CH_2),44.86(CH), 18.81(CH*CH_3*),14.74(CH_2*CH_3*)
8	1740 (CO)	106.30*,104.11*, 88.80,88.15, 86.12,85.44	172.48(CO),78.19(Cp), 62.12(CH_2),44.29(CH), 20.54(Ar*CH_3*),18.49(CH*CH_3*), 14.32(CH_2*CH_3*)
9	1740 (CO)	105.08*,104.19*, 88.92,88.86, 87.43,86.66	172.91(CO),78.24(Cp), 62.11(CH_2),43.98(CH), 20.30(Ar*CH_3*),18.27(CH*CH_3*), 14.28(CH_2*CH_3*)

* denotes a quaternary carbon atom on the aromatic ring

Table 2.2.3 ^{1}H NMR and yield data for complexes derived from nucleophilic substitution reactions of CpFe complexes of chloroarenes with ethyl 2-ethylacetoacetate

		^{1}H NMR (δ, ppm), (CD_3COCD_3)		
Complex	% Yield	Aromatic	Cp	Others
13	72.5	6.53 (5H, br s,ArH)	5.16	4.36 (2H,q,*J* 7.0,COO*CH*$_2$CH$_3$)
				3.78 (1H,t,*J* 7.1,CH)
				1.91 (2H,m,*CH*$_2$CH$_3$)
				1.35 (3H,t,*J* 7.2,COOCH$_2$*CH*$_3$)
				0.98 (3H,t,*J* 7.3,CH$_2$*CH*$_3$)
14	71.4	6.42 (4H,br s,ArH)	5.12	4.35 (2H,q,*J* 7.1,COO*CH*$_2$CH$_3$)
				3.80 (1H,q,*J* 7.0,CH)
				2.58 (3H,s,Ar*CH*$_3$)
				1.92 (2H,m,*CH*$_2$CH$_3$)
				1.37 (3H,t,*J* 7.2,COOCH$_2$*CH*$_3$)
				0.98 (3H,t,*J* 7.3,CH$_2$*CH*$_3$)
15	76.1	6.40 (4H,br s,ArH)	5.10	4.12 (2H,q,*J* 7.2,COO*CH*$_2$CH$_3$)
				3.56 (1H,q,*J* 7.1,CH)
				2.55 (3H,s,Ar*CH*$_3$)
				1.12 (3H,t,*J* 7.2,COOCH$_2$*CH*$_3$)
				0.95 (3H,t,*J* 7.3,CH$_2$*CH*$_3$)

Table 2.2.4 ^{13}C NMR, and IR data for complexes derived from nucleophilic substitution reactions of CpFe complexes of chloroarenes with ethyl 2-ethylacetoacetate

Complex	i.r. (cm^{-1}) (neat)	^{13}C NMR (δ, ppm), (CD_3COCD_3) Aromatic	Others
13	1730 (CO)	106.13*,89.44, 89.36,89.07, 88.96,87.47	172.74(CO),78.39(Cp), 62.63(COO*CH*$_2$CH$_3$), 52.34(CH),29.63(*CH*$_2$CH$_3$), 14.87(COOCH$_2$*CH*$_3$), 12.59(CH$_2$*CH*$_3$)
14	1735 (CO)	105.10*,104.57*, 89.52,87.87, 86.86,84.99	172.27(CO),78.19(Cp), 62.11(COO*CH*$_2$CH$_3$), 51.83(CH),29.24(*CH*$_2$CH$_3$), 20.49(Ar*CH*$_3$), 14.41(COOCH$_2$*CH*$_3$), 12.14(CH$_2$*CH*$_3$)
15	1733 (CO)	104.13*,103.84*, 89.19,88.82, 88.07,86.23	172.22(CO),78.23(Cp), 62.09(COO*CH*$_2$CH$_3$), 51.41(CH),28.65(*CH*$_2$CH$_3$), 20.33(Ar*CH*$_3$), 14.39(COOCH$_2$*CH*$_3$), 12.09(CH$_2$*CH*$_3$)

*denotes a quaternary carbon atom on the aromatic ring

The proton NMR spectra of these mixtures were complicated, however the ratio of the two complexes were determined from the integrals of the cyclopentadienyl protons. This assignment was made on the basis of the distinctiveness of the two singlets of the cyclopentadienyl protons. The ratio varied from 1:1 to 2:1 in favour of the deacylated product.

2.2.3 *Photolysis of the CpFe Complexes of Alkanoic Acid Esters.*

Liberation of the alkanoic acid esters from their FeCp complexes is one the most important steps in this synthetic strategy. Since photoylsis is known to be an efficient route for the decomplexation of some (arene) cyclopentadienyliron complexes [69,70], we successfully applied this technique in the liberation of the desired products from their CpFe moieties. Complexes (**7-9**), and (**13-15**) were dissolved in a mixture of acetonitrile/ dichloromethane and were irradiated for 4 hours under a nitrogen atmosphere using a Xenon Lamp as the source of radiation. Purification of the products by column chromatography resulted in the isolation of the free esters (**10-12** and **16-18**) in yields ranging from 79-86%.

In the case of the complexed ortho substituents (**20 a,b,** and **21 a,b,**) the mixture was subjected to radiation as above. We were able to isolate the two uncomplexed products separately using column chromatography.

The photolysis of these mixtures resulted in an enrichment in the ratio of the deacylated to the non deacylated products, which indicated that deacylation also took place during photolysis. Fig.11 and 12 show the ^{1}H and ^{13}C NMR of the main product (deacetylated) after photolysis. The overall yields calculated on the basis of the chloroarene complexes of these deacylated products 22 a,b and 23 a,b are listed in Table 2.2.9. and Table 2.2.10.

The identities of all products were confirmed by ^{1}H and ^{13}C NMR, IR and MS and are listed in Tables 2.2.5., 2.2.6., 2.2.7., and 2.2.8, as well as 2.2.9., and 2.2.10. The major differences in the proton and carbon NMR of these compounds and the complexes were the absence of the cyclopentadienyl peak and the downfield shift of the arene peaks, as shown in Fig. 11, 12, 13 and 14.

Although some of these alkanoic acid esters have been prepared previously, our method offers an alternative route to the synthesis of the these compounds with high efficiency, high yield, accessibility and low cost of the starting materials.

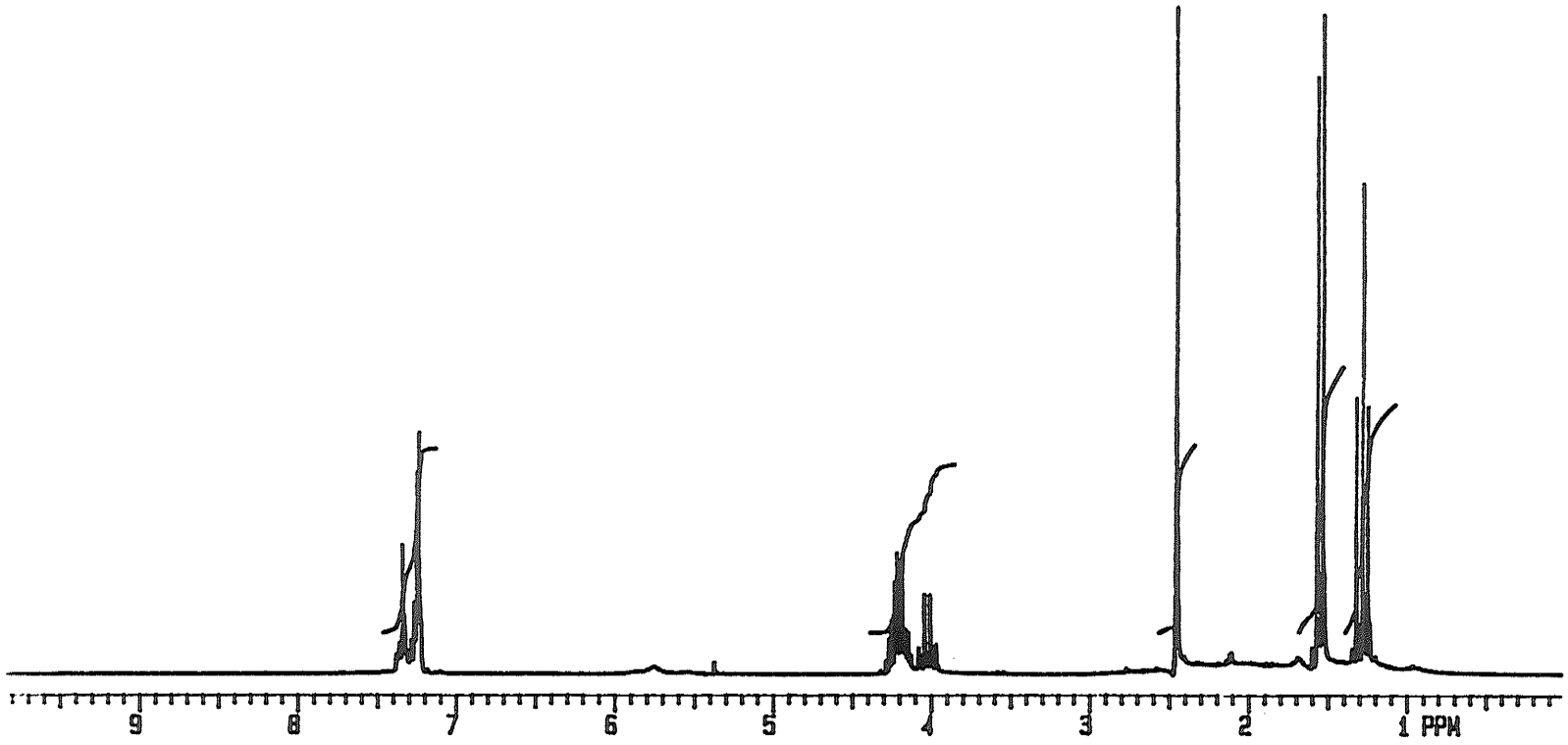


Fig.11 ^{1}H NMR spectrum of Ethyl 2-(o-tolyl)propanoate in $CDCl_3$.

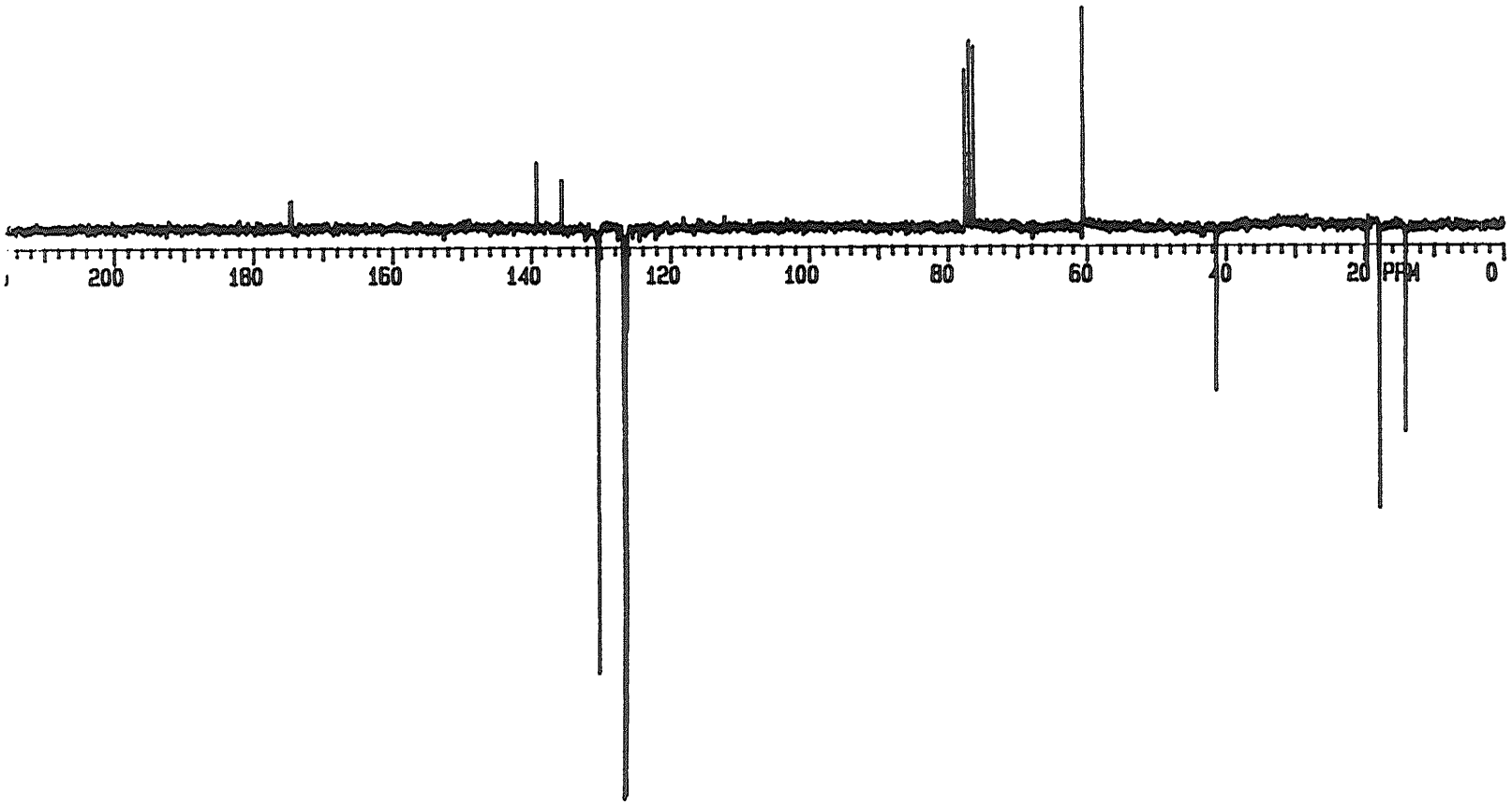


Fig.12 ^{13}C NMR(APT) spectrum of Ethyl 2-(o-tolyl)propanoate in $CDCl_3$.

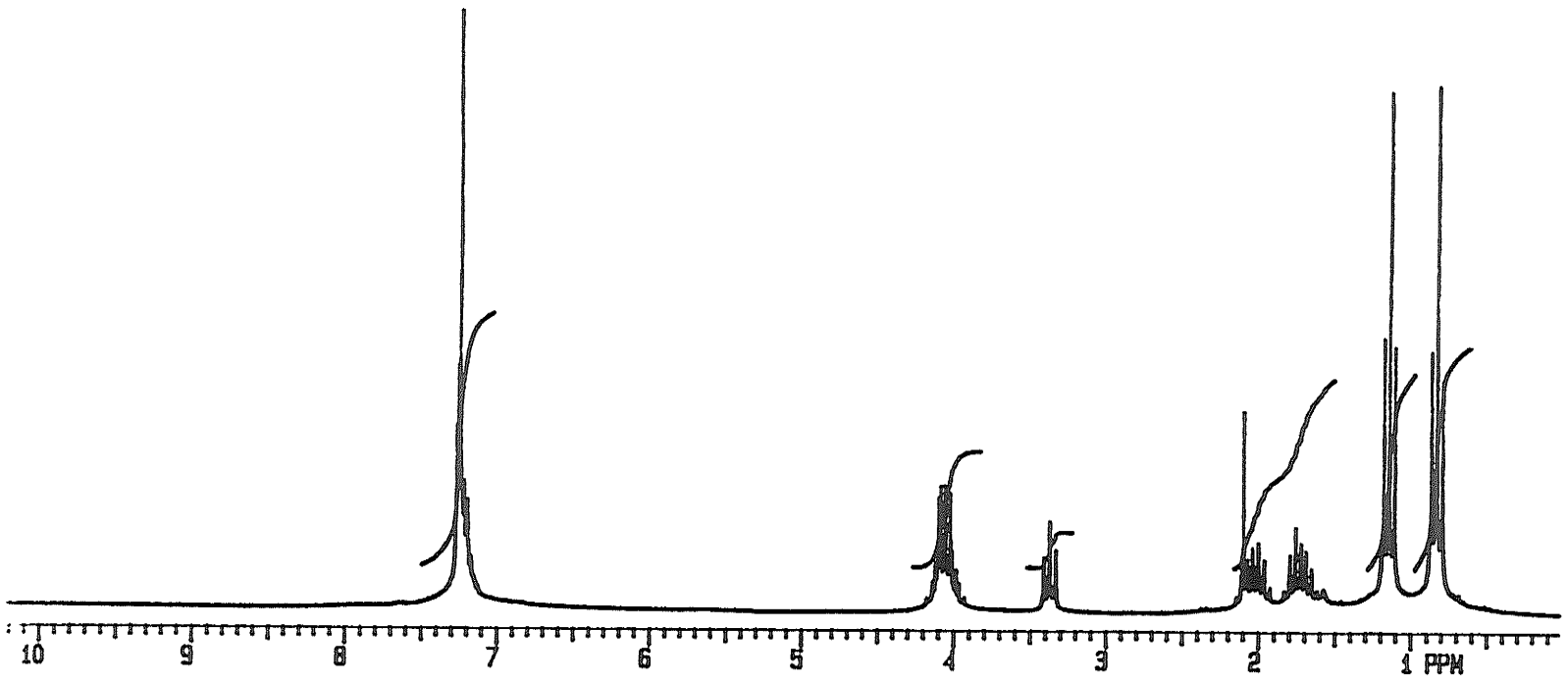


Fig.13 ^1H NMR spectrum of Ethyl 2-phenylbutanoate in $CDCl_3$.

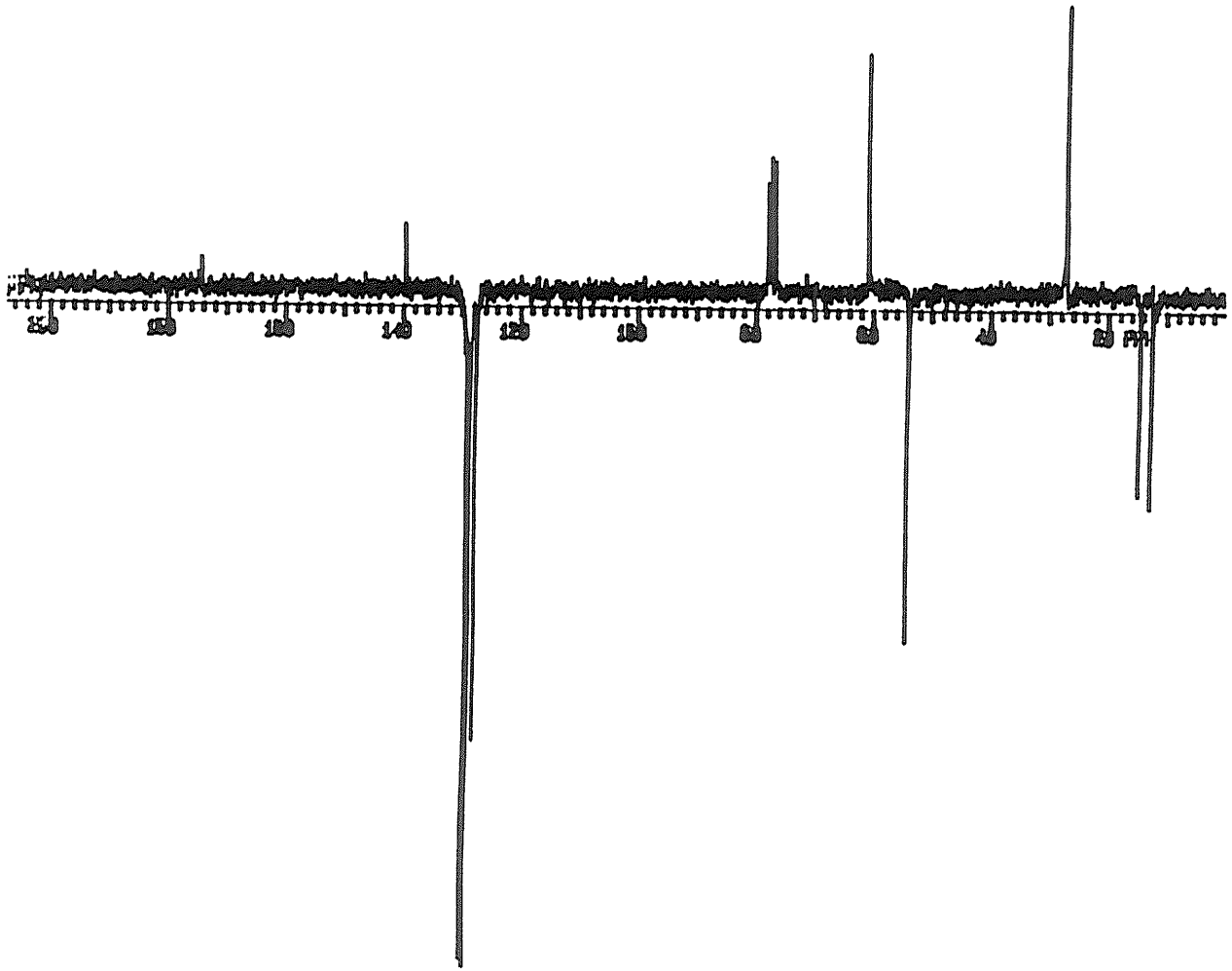


Fig.14 ^{13}C NMR(APT) spectrum of Ethyl 2-phenylbutanoate in $CDCl_3$.

Table 2.2.5 ^{1}H NMR and yield data for ethyl-(substituted phenyl or tolyl) propanoates

Compound	% Yield	^{1}H NMR (δ, ppm), ($CDCl_3$) Aromatic	Others
10	86.8	7.25 (5H, br s,ArH)	4.06 (2H,m,CH_2) 3.64 (1H,q,*J* 7.2,CH) 1.43 (3H,d,*J* 7.3,CH*CH*$_3$) 1.14 (3H,t,*J* 7.1,CH_2*CH*$_3$)
11	82.3	7.39-7.22 (4H,m,ArH)	4.26 (2H,m,CH_2) 3.80 (1H,q,*J* 7.1,CH) 2.48 (3H,s,Ar*CH*$_3$) 1.62 (3H,d,*J* 7.1,CH*CH*$_3$) 1.35 (3H,t,*J* 7.1,*CH*$_2$CH$_3$)
12	79.2	7.31-7.17 (4H,m,ArH)	4.20 (2H,m,CH_2) 3.72 (1H,q,*J* 7.1,CH) 2.39 (3H,s,Ar*CH*$_3$) 1.53 (3H,d,*J* 7.2,CH*CH*$_3$) 1.26 (3H,t,*J* 7.1,$COOCH_2$*CH*$_3$)

Table 2.2.6 ^{13}C NMR, IR, and MS data for ethyl-(substituted phenyl or tolyl) propanoates

Compound	i.r. (cm^{-1}) (neat)	m/z (M^+)	^{13}C NMR (δ, ppm), ($CDCl_3$) Aromatic	Others
10	1740(CO)	178	140.72*,128.54, 127.45,127.01	174.50(CO),60.67(CH_2), 45.59(CH),18.58(CH*CH3*), 14.11(CH_2*CH3*)
11	1730(CO)	192	140.65*,138.17*, 128.44,128.16, 127.78,124.46	174.60(CO),60.65(CH_2), 45.50(CH),21.40(Ar*CH3*), 18.63(CH*CH3*), 14.11(CH_2*CH3*)
12	1730(CO)	192	137.73*,136.59*, 129.22,127.29,	174.86(CO),60.59(CH_2), 45.14(CH),22.93(Ar*CH3*), 18.59(CH*CH3*), 14.08(CH_2*CH3*)

*denotes a quaternary carbon atom on the aromatic ring

Table 2.2.7 ^{1}H NMR and yield data for ethyl-(substituted phenyl or tolyl) butanoates

Compound	% Yield	^{1}H NMR (δ, ppm), ($CDCl_3$) Aromatic	Others
16	82.2	7.25 (5H, br s,ArH)	4.07(2H,m,COO*CH*$_2$CH$_3$)
			3.37 (1H,t,*J* 8.0,CH)
			1.72 (2H,m,*CH*$_2$CH$_3$)
			1.14 (3H,t,*J* 7.0,COOCH$_2$*CH*$_3$)
			0.83 (3H,t,*J* 7.3,CH$_2$*CH*$_3$)
17	82.5	7.37-7.20 (4H,m,ArH)	4.22 (2H,m, COO*CH*$_2$CH$_3$)
			3.45 (1H,t,*J* 7.7,CH)
			2.46 (3H,s,Ar*CH*$_3$)
			2.18 (1H,m,*CH*$_2$CH$_3$)
			1.90 (1H,m,*CH*$_2$CH$_3$)
			1.33 (3H,t,*J* 7.1,COOCH$_2$*CH*$_3$)
			1.02 (3H,t,*J* 7.2,CH$_2$*CH*$_3$)
18	80.1	7.21-7.10 (4H,m,ArH)	4.07 (2H,m,COO*CH*$_2$CH$_3$)
			3.43 (1H,t,*J* 7.5,CH)
			2.83 (3H,s,Ar*CH*$_3$)
			1.74 (2H,m,*CH*$_2$CH$_3$)
			1.15 (3H,t,*J* 7.2,COOCH$_2$*CH*$_3$)
			0.85 (3H,t,*J* 7.1,CH$_2$*CH*$_3$)

Table 2.2.8 ^{13}C NMR, IR, and MS data for ethyl-(substituted phenyl or tolyl) butanoates

Compound	i.r. (cm^{-1}) (neat)	m/z (M^+)	^{13}C NMR (δ, ppm), ($CDCl_3$) Aromatic	Others
16	1738(CO)	192	139.52*,128.73, 128.18,127.31	174.10(CO), 60.80(COO*CH*$_2$CH$_3$), 53.80(CH),27.04(CH$_2$*CH*$_3$) 14.38(COOCH$_2$*CH*$_3$), 12.38(CH$_2$*CH*$_3$)
17	1740(CO)	206	139.18*,138.02*, 128.58,128.32, 127.79,124.92	174.05(CO), 60.46(COO*CH*$_2$CH$_3$), 53.46(CH),26.78(CH$_2$*CH*$_3$) 21.35(ArCH$_3$), 14.17(COOCH$_2$*CH*$_3$), 12.13(CH$_2$*CH*$_3$)
18	1730(CO)	206	137.48*,137.25*, 129.88,128.56,	174.23(CO), 60.78(COO*CH*$_2$CH$_3$), 53.62(CH),27.56(CH$_2$*CH*$_3$) 20.96(ArCH$_3$), 14.47(COOCH$_2$*CH*$_3$), 12.32(CH$_2$*CH*$_3$)

*denotes a quaternary carbon atom on the aromatic ring

Table 2.2.9 ^{1}H NMR and yield data for ethyl 2-(o-tolyl)propanoate and ethyl 2-(o-tolyl)butanoate

Compound	% Yield	^{1}H NMR (δ, ppm), ($CDCl_3$) Aromatic	Others
22a	57.3	7.34-7.25 (4H,m,ArH)	4.21 (2H,m,CH_2) 4.02 (1H,q,*J* 7.2,CH) 2.46 (3H,s,Ar*CH*$_3$) 1.55 (3H,d,*J* 7.1,CH*CH*$_3$) 1.28 (3H,t,*J* 7.2,CH_2*CH*$_3$)
22b	55.8	7.29-7.12 (4H,m,ArH)	4.09 (2H,m,COO*CH*$_2$$CH_3$) 3.72 (1H,t,*J* 7.1,CH) 2.37 (3H,s,Ar*CH*$_3$) 2.08 (1H,m,*CH*$_2$$CH_3$) 1.75 (1H,m,*CH*$_2$$CH_3$) 1.16 (3H,t,*J* 7.2,$COOCH_2$*CH*$_3$) 0.90 (3H,t,*J* 7.2,$CH_2$*CH*$_3$)

Table 2.2.10 ^{13}C NMR, IR, and MS data for ethyl 2-(o-tolyl)propanoate and ethyl 2-(o-tolyl)butanoate

Compound	i.r. (cm^{-1}) (neat)	m/z (M^+)	^{13}C NMR (δ, ppm), ($CDCl_3$) Aromatic	Others
22a	1735(CO)	192	139.27*,135.66*, 130.43,126.83, 126.48,126.36	174.79(CO),60.64(CH_2), 41.41(CH),19.57(Ar*CH_3*), 17.88(CH*CH_3*), 14.12(CH_2*CH_3*)
22b	1728(CO)	206	137.78*,137.11*, 130.32,126.73, 126.25,126.11	172.60(CO), 60.47(COO*CH_2*CH_3), 48.74(CH),26.27(*CH_2*CH_3) 19.75 (Ar*CH_3*), 14.13(COOCH*CH_3*), 12.22(CH_2*CH_3*)

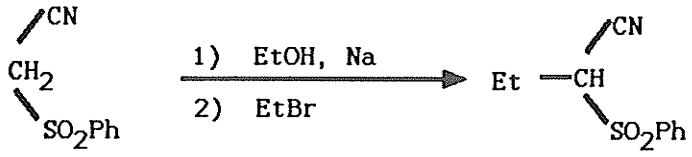
*denotes a quaternary carbon atom on the aromatic ring

2.3 *Reactions of Ethylphenylsulphonylacetonitriles.*

There has been considerable interest in the development of new and efficient routes to the synthesis of arylated phenylsulphonylacetonitriles [106-110]. They are of importance, as very attractive starting materials, in the synthesis of alkanoic acids. Since the synthesis of arylated phenylsulphonyl- acetonitriles cannot be achieved directly through nucleophilic substitution reactions of ethylphenyl-sulphonylacetonitrile anion with aryl halides, a number of synthetic strategies were developed to prepare arylated phenylsulphonylacetonitriles. These involve the application of certain organometallic reagents or catalysts to promote nucleophilic substitution on the aromatic ring [96]. In these types of reactions the most problematic step is the nucleophilic aromatic substitution. Recently, Abd-El-Aziz and de Denus have demonstrated that arylation of phenylsulphonylaceto-nitrile could be achieved using organoiron complexes [69]. Here we extended our investigation by preparing substituted phenylsulfonylacetonitriles and examining their reactivity towards CpFe arene complexes.

2.3.1 *Synthesis of Ethylphenylsulphonylacetonitrile.*

The synthetic route towards desired arylated ethyl phenylsulphonylacetonitriles began with the preparation of the source of a free nucleophile, namely ethyl phenylsulphonylacetonitrile. As illustrated in Scheme 15, the synthesis of targeted nucleophile involved two major steps. First is the deprotonation of the methylene group, and the second involved an alkylation reaction using ethyl bromide, which led to the desired compound. The detailed experimental procedure for the preparation and purification of ethylphenylsulphonylacetonitrile is described in section 3.3.1. The spectral data are listed in the experimental section and the ^{1}H and ^{13}C NMR are shown in Fig. 15 and 16.



Scheme 15

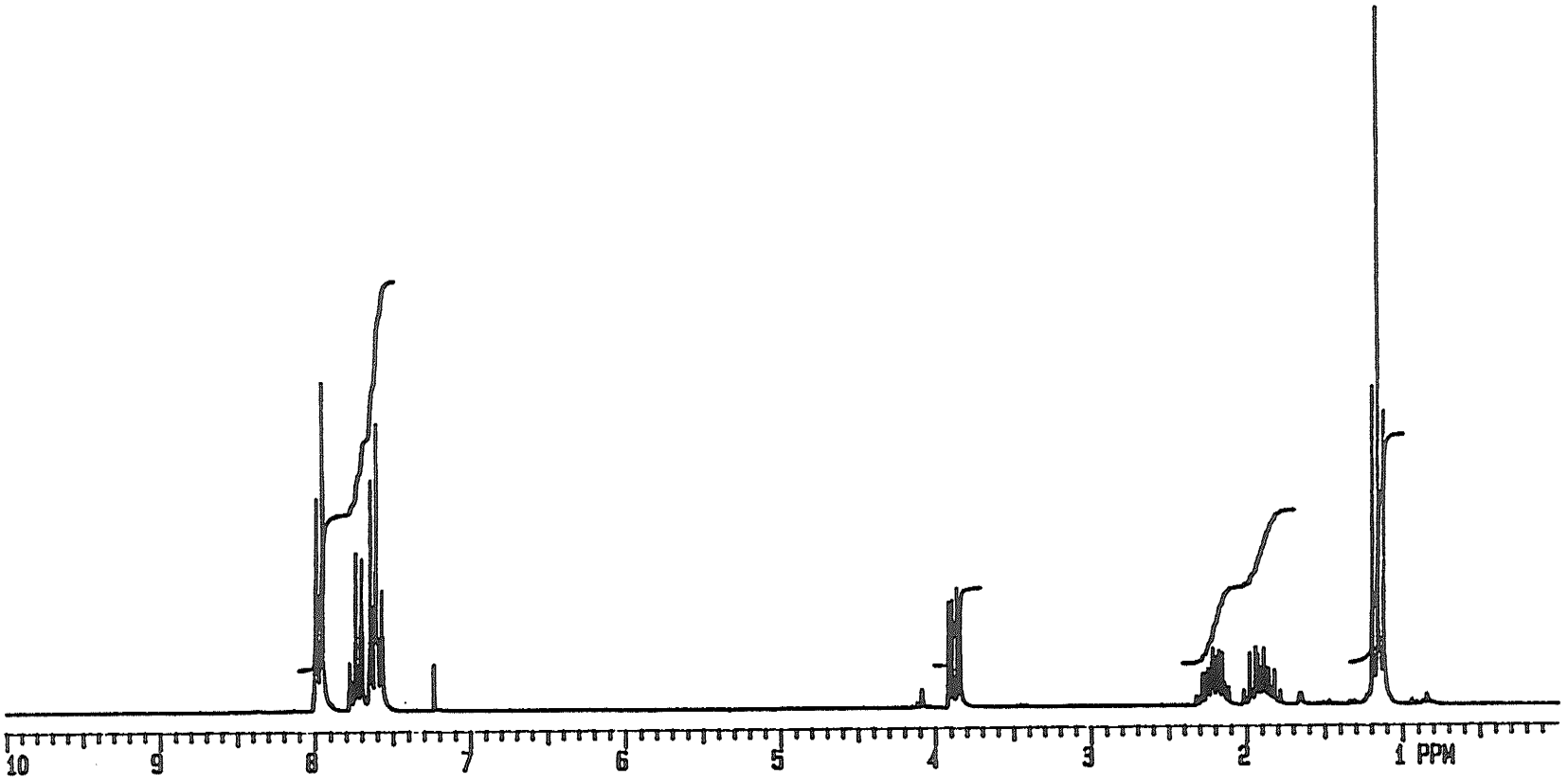


Fig.15 ^{1}H NMR spectrum of Ethylphenylsulphonylacetonitrile in $CDCl_3$.

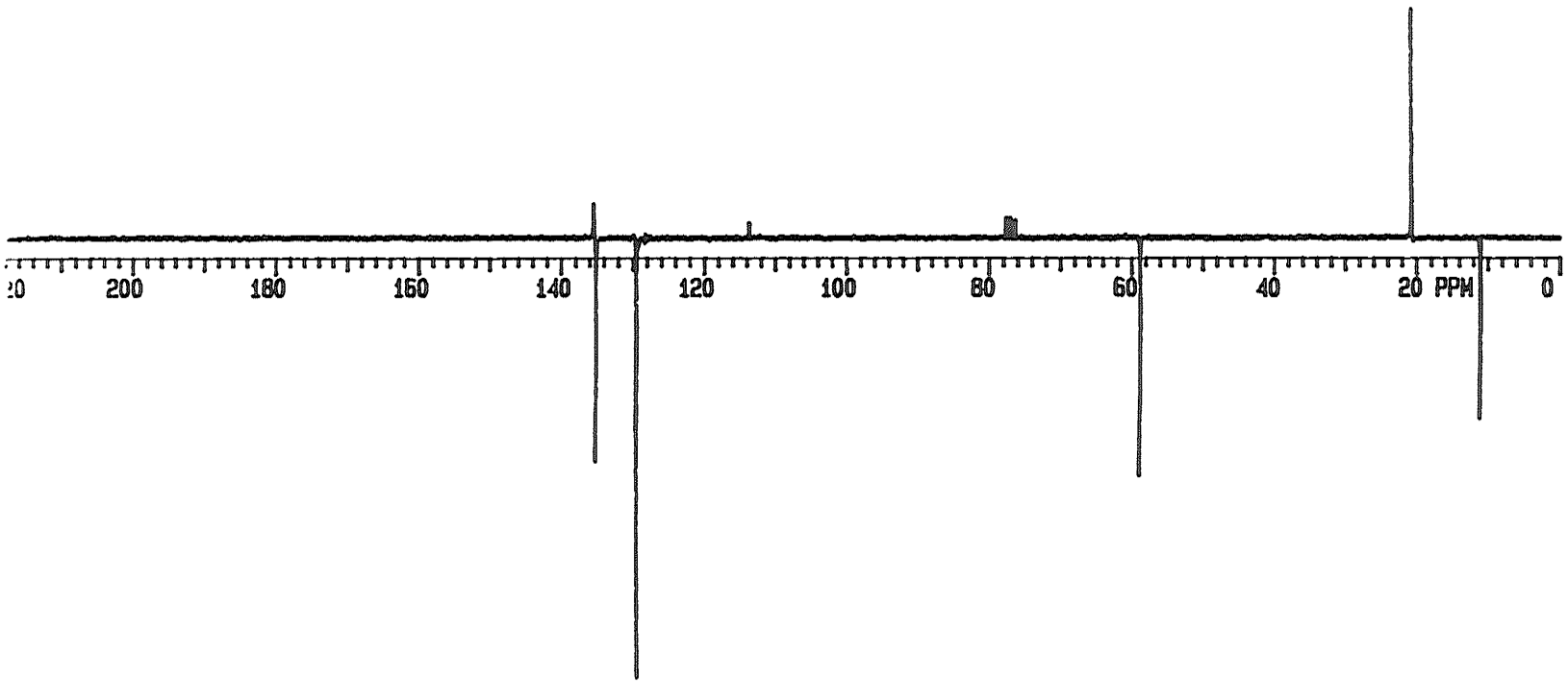


Fig.16 ^{13}C NMR spectrum of Ethylphenylsulphonylacetonitrile in $CDCl_3$.

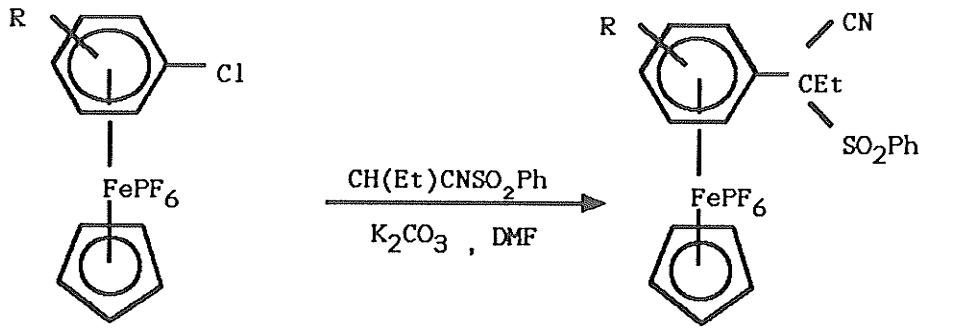
2.3.2 *Arylation of Ethylphenylsulphonylacetonitrile.*

After our success in the synthesis of the nucleophile, we examined the reactivity of this nucleophile with arene complexes.

The reaction between ethylphenylsulphonylacetonitrile and the iron complexes (**4-6**) in the presence of potassium carbonate in N,N-dimethylformamide, led to the formation of complexed arylated ethylphenylsulphonyl-acetonitriles (**26-28**) as shown in Scheme 16.

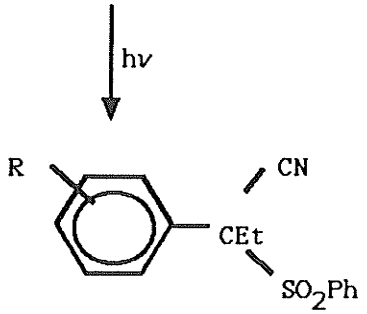
These complexes were isolated as yellow-brown solids in very good yields (79-85%). ^{1}H and ^{13}C NMR as well as IR were utilized for the characterization of the prepared complexes. The representative NMR spectra for an example of complexed arylated ethylphenylsulphonyl-acetonitrile is shown in Fig. 17 and 18. In the ^{1}H NMR spectra of these complexes, a very distinctive singlet appeared around δ 5.30-5.36. This is characteristic of the cyclopentadienyl(Cp) ring. For the complexes (**26-28**) the phenylsulphonyl protons appeared as multiplets in the regions between δ 7.61-7.64 (4H) and δ 7.67-7.89 (1H). The aromatic protons for the complexes specified above showed resonance in the region between 6.72-6.24, depending on the substitution pattern. The ^{13}C NMR(APT) was also in agreement with expectations, as shown in Tables 2.3.1., and 2.3.2. The characteristic peak of Cp moiety appeared for desired complexes at 79.07 (**26**),

79.39 (**27**) and at 79.35 (**28**)respectively.



4 R = H
5 R = m-Me
6 R = p-Me

26 R = H
27 R = m-Me
28 R = p-Me



Scheme 16

29 R = H
30 R = m-Me
31 R = p-Me

The aromatic carbons resonated in the regions between 106.84 to 98.49, with the quaternary carbon on the aromatic ring at 98.49 for monosubstituted product, at 105.16 and 99.00 for p-CH_3 substituted complex, and at 106.84 and 96.42 for m-CH_3 substituted complex. The IR analysis confirmed the presence of CN and SO_2 groups, since the characteristic stretches for these groups appeared at 2340 and 1335, 1160 cm^{-1}, respectively.

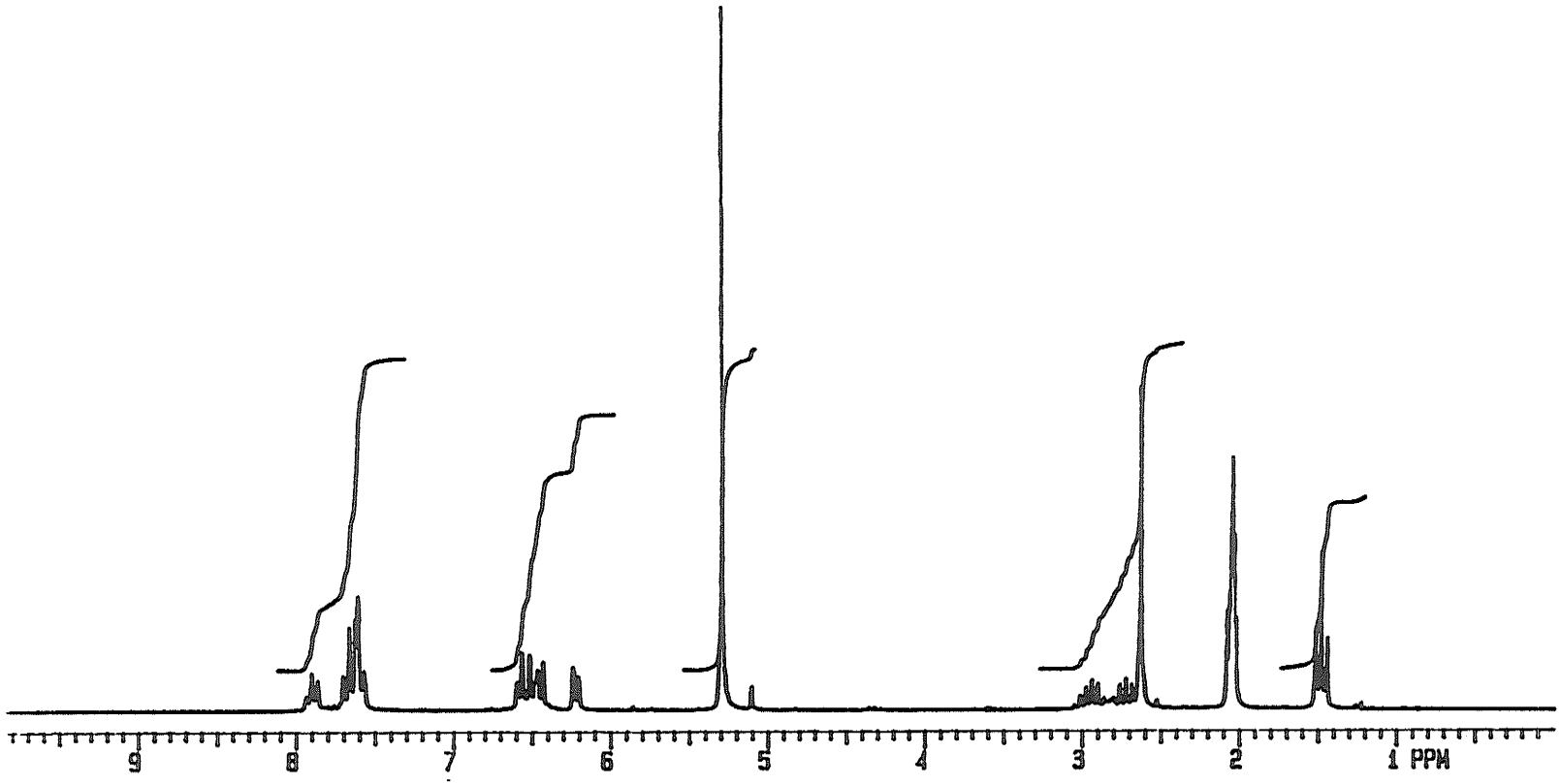


Fig.17 ^{1}H NMR spectrum of η^{6}-[(p-tolyl)ethylphenylsulphonyl-acetonitrile]-η^{5}-(cyclopentadienyl) hexafluoro-phosphate in CD_3COCD_3.

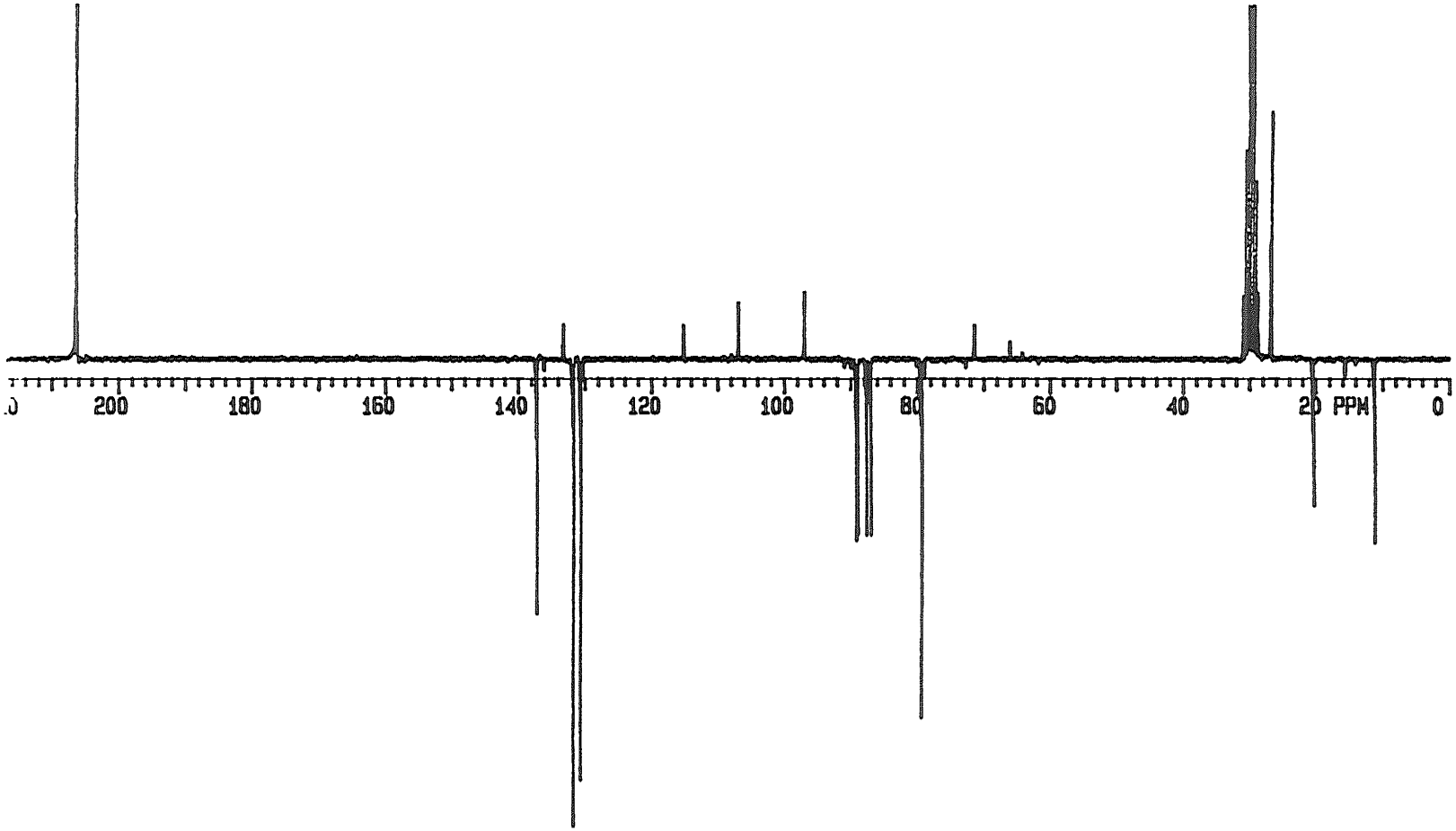


Fig.18 ^{13}C NMR(APT) spectrum of η^6-[(p-tolyl)ethylphenyl-sulphonylacetonitrile]-η^5-(cyclopentadienyl) hexafluorophosphate in CD_3COCD_3.

Table 2.3.1 ^{1}H NMR and yield data for complexes derived from nucleophilic substitution reactions of CpFe complexes of chloroarenes with ethylphenylsulphonylacetonitrile

		^{1}H NMR (δ, ppm), (CD_3COCD_3)		
Complex	% Yield	Aromatic	Cp	Others
26	79.0	6.72 (2H, m, ArH)	5.36	7.89 (1H, m, SO_2Ph)
		6.57 (1H, m, ArH)		7.64 (4H, m, SO_2Ph)
		6.29 (2H, d, *J* 6.4, ArH)		2.97 (1H, m,CH_2)
				2.76 (1H, m,CH_2)
				1.10 (3H,t,*J* 7.0,CH_3)
27	85.0	6.63 (2H, m, ArH)	5.30	7.68 (1H, m,SO_2Ph)
		6.53 (2H, m, ArH)		7.61 (4H, m,SO_2Ph)
				2.99 (1H, m, CH_2)
				2.76 (1H, m, CH_2)
				2.47 (3H,s,$ArCH_3$)
				1.49 (3H,t,*J* 7.4,CH_3)
28	78.5	6.53 (3H, m, ArH)	5.31	7.67 (1H, m,SO_2Ph)
		6.24 (1H, m, ArH)		7.62 (4H, m,SO_2Ph)
				2.95 (1H, m,CH_2)
				2.72 (1H, m, CH_2)
				2.64 (3H, s, $ArCH_3$)
				1.06 (3H, t, *J* 7.0,CH_3)

Table 2.3.2 ^{13}C NMR and IR data for complexes derived form nucleophilic substitution reactions of CpFe complexes of chloroarenes with ethylphenylsulphonylacetonitrile

Complex	i.r. (cm^{-1}) (neat)	^{13}C NMR (δ, ppm), (CD_3COCD_3) Aromatic	Others
26	2340 (CN) 1335 (SO_2) 1158 (SO_2)	98.49*,90.51, 88.92,88.80, 88.76,88.15	137.65(SO_2Ph),133.13*(SO_2Ph), 131.65(SO_2Ph),130.61(SO_2Ph), 115.04(CN),79.07(Cp), 26.71(CH_2), 11.20(CH_3)
27	2240 (CN) 1335 (SO_2) 1160 (SO_2)	105.16*,99.00*, 90.93,88.34, 87.97,86.55	137.26(SO_2Ph),134.80*(SO_2Ph), 131.83(SO_2Ph),130.61(SO_2Ph), 115.40(CN),79.39(Cp), 26.58(CH_2),20.19($ArCH_3$), 11.25(CH_3)
28	2240 (CN) 1335 (SO_2) 1160 (SO_2)	106.84*,96.92*, 89.18,88.95, 87.51,86.99	137.23(SO_2Ph),133.19*(SO_2Ph), 131.75(SO_2Ph),130.65(SO_2Ph), 115.14(CN),79.35(Cp), 26.74(CH_2),20.40($ArCH_3$), 11.21(CH_3)

* denotes a quaternary carbon atom on the aromatic ring

2.3.3 *Photolysis of the Complexed Ethylphenylsulphonylacetonitriles.*

Liberation of the arylated ethylphenylsulphonylacetonitriles from their iron complexes was achieved via photolytic demetallation, giving the free organic ligands, in yields ranging from 80-85%.

The identities of the photolyzed products were confirmed by ^{1}H and ^{13}C NMR, IR, and MS. The major differences in the ^{1}H and ^{13}C NMR of these compounds from the complexes are the absence of the cyclopentadienyl peak and the shift of the arene peak downfield in the latter. IR, and MS data have also confirmed the structural features of the organic compounds of interest (Fig. 19 and 20). The CN stretch for the compounds (**29-31**) appeared at 2240, 2305 and 2300, respectively. The SO_2 bands showed in the range between 1330 and 1325, as well as 1158-1160. MS has clearly shown the molecular ion peaks of these compounds. The results of spectroscopic analysis are listed in Tables 2.3.3., and 2.3.4.

2.4 *Reactions of Ethylcyanoacetates.*

Ethyl cyanoacetates are well known, versatile synthetic intermediates in the synthesis of various heterocyclic compounds, which have important uses in medicinal chemistry [86].

Reactions of ethylcyanoacetates with isomeric chlorotoluene complexes, which led to the arylation of the ethylcyanoacetates, were conducted by Abd-El-Aziz et al. [69]. It is our goal in this study to continue with the use of isomeric dichlorobenzenes as starting materials.

2.4.1 *Arylation of Ethyl Cyanoacetates.*

Isomeric dichlorobenzene complexes (**32-34**) were prepared in the same fashion as the previously reported chloroarene complexes [23].

Reactions of the product complexes (**32-34**) with ethyl cyanoacetates in the presence of potassium carbonate in N,N-dimethylformamide, led to the formation of complexed arylated ethyl cyanoacetates (**35-37**) as shown in Scheme 17.

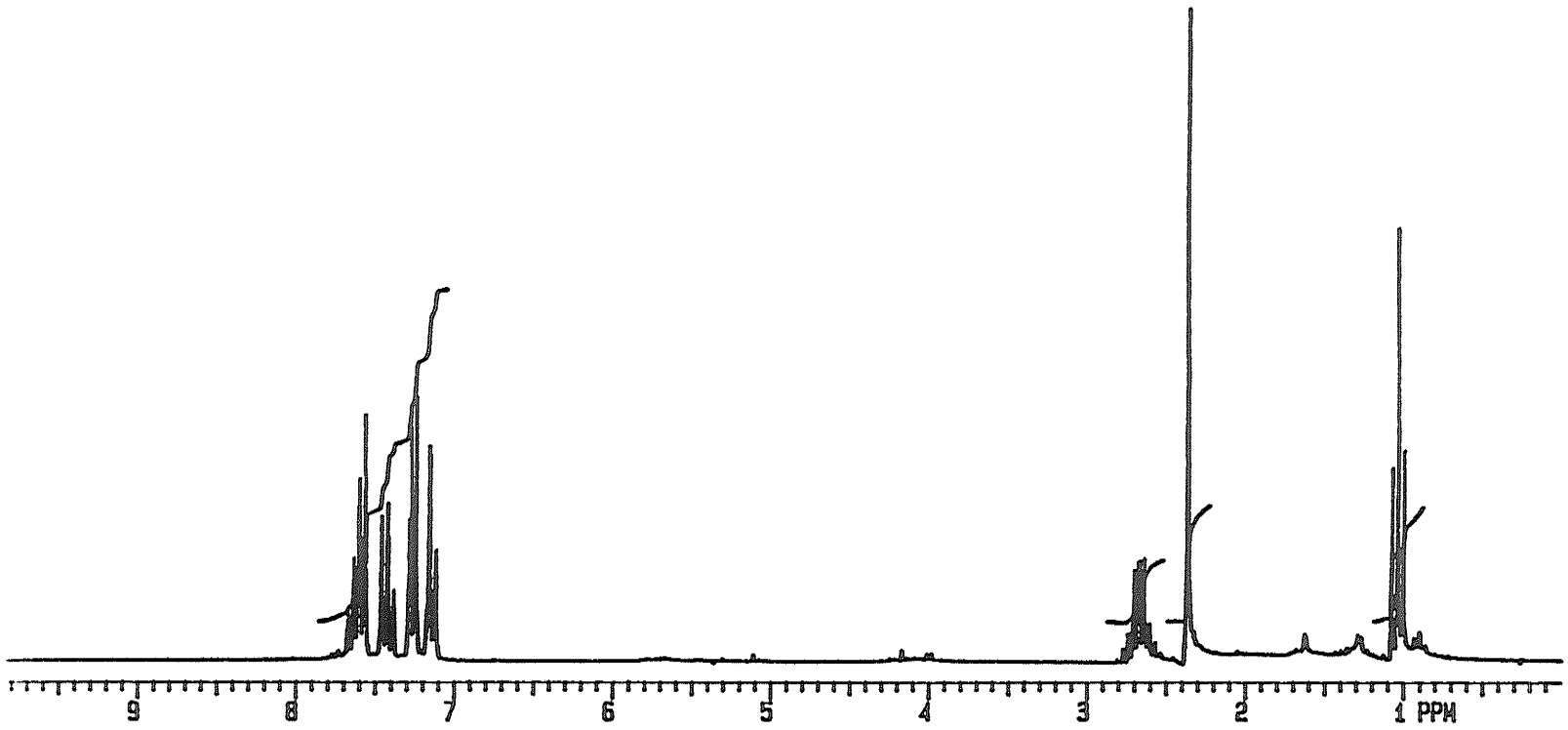


Fig.19 ^{1}H NMR spectrum of p-Tolyl(ethylphenylsulphonyl-acetonitrile) in $CDCl_3$.

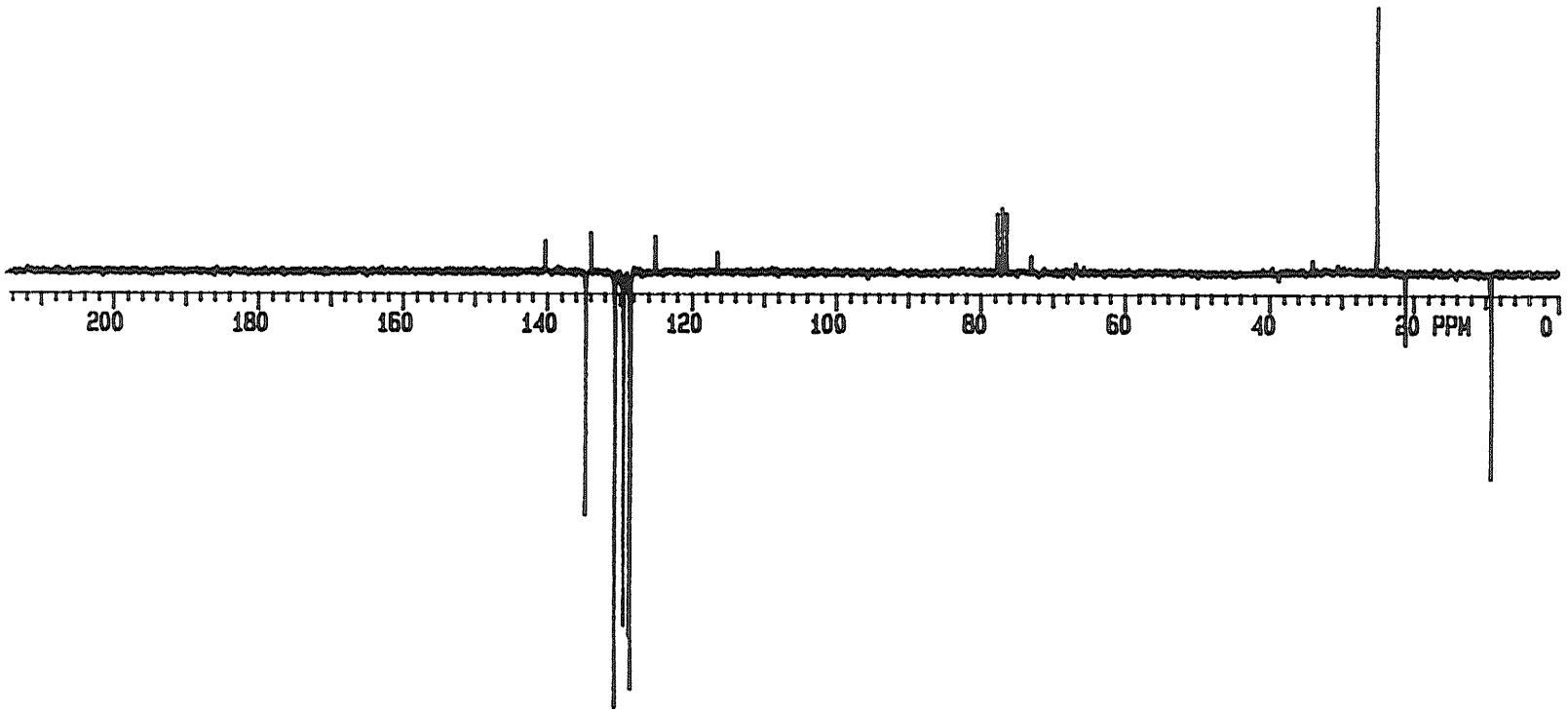


Fig.20 ^{13}C NMR spectrum of p-Tolyl(phenylsulphonylaceto-nitrile) in $CDCl_3$.

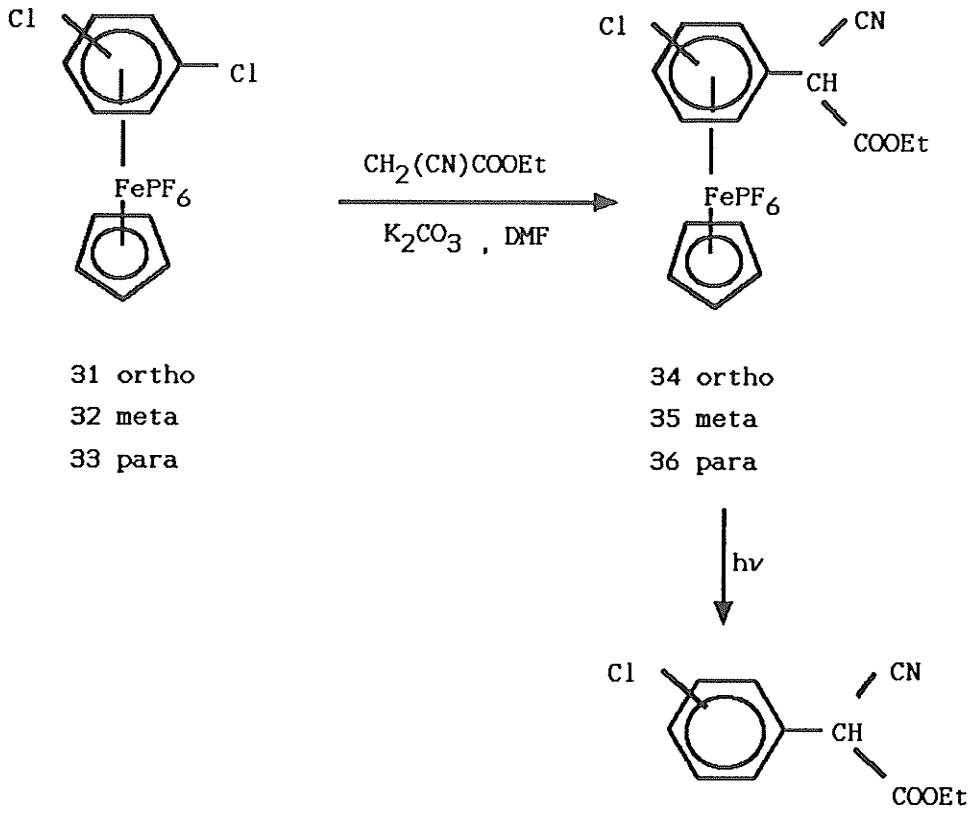
Table 2.3.3: ^1H NMR and yield data for phenyl ethylphenylsulphonylacetonitrile, m-tolyl-(ethylphenylsulphonylacetonitrile) and p-tolyl-(ethylphenylsulphonylacetonitrile)

Compound	% Yield	^1H NMR (δ, ppm), ($CDCl_3$) Aromatic	Others
29	80.0	7.63 (4H, m,ArH & SO_2Ph)	2.63 (2H,m,CH_2)
		7.34 (6H, m,ArH & SO_2Ph)	1.02 (3H,t,*J* 7.3,CH_3)
30	85.1	7.20 (4H, m,ArH)	7.57 (3H,m,SO_2Ph)
			7.44 (2H, m,SO_2Ph)
			2.68 (2H,m,CH_2)
			2.28 (3H,s,$ArCH_3$)
			1.05 (3H,t,*J* 7.4,CH_3)
31	80.0	7.26 (2H, d,*J* 6.3,ArH)	7.60 (3H,m,SO_2Ph)
		7.14 (2H,d,*J* 6.4,ArH)	7.42 (2H, m,SO_2Ph)
			2.67 (2H,m,CH_2)
			2.37 (3H,s,$ArCH_3$)
			1.04 (3H,t,*J* 7.4,CH_3)

Table 2.3.4 ^{13}C NMR, IR, and MS data for phenyethylphenylsulphonylaceto-nitrile, m-tolyl-(ethylphenylsulphonylacetonitrile), and p-tolyl-(ethylphenylsulphonylacetonitrile)

Compound	i.r. (cm^{-1}) (neat)	m/z (M^+)	^{13}C NMR (δ, ppm), ($CDCl_3$) Aromatic	Others
29	2340(CN) 1340(SO_2) 1158(SO_2)	285	128.73,128.65, 128.53,128.52, 128.49,128.21*	134.69(SO_2Ph), 133.81*(SO_2Ph), 130.50(SO_2Ph), 129.98(SO_2Ph), 116.31(CN), 25.02(CH_2), 9.21(CH_3)
30	2300(CN) 1330(SO_2) 1158(SO_2)	299	138.62*,129.23, 128.57,127.99*, 125.54	134.68(SO_2Ph), 133.85*(SO_2Ph), 130.72(SO_2Ph), 130.59(SO_2Ph), 116.43(CN),24.91(CH_2), 21.29($ArCH_3$),9.23(CH_3)
31	2305(CN) 1330(SO_2) 1160(SO_2)	299	140.29*,128.65, 128.47,125.05*	134.66(SO_2Ph), 133.66*(SO_2Ph), 130.62(SO_2Ph), 129.47(SO_2Ph), 116.48(CN),25.05(CH_2), 21.13($ArCH_3$),9.21(CH_3)

*denotes a quaternary carbon atom on the aromatic ring



31 ortho
32 meta
33 para

34 ortho
35 meta
36 para

Scheme 17

37 ortho
38 meta
39 para

These complexes were isolated as yellow solids in very good yields ranging from (71-81%). ^{1}H and ^{13}C NMR as well as IR were used to characterized the prepared complexes (Fig. 21 and 22). In the ^{1}H NMR spectra of these complexes a very distinctive singlet appeared in the region between δ 5.46-5.47. This is characteristic of the complexation with the FeCp moiety. The remaining peaks were assigned based on the structures of the

products, as well as on the integration for each peak. The results obtained for both ^{1}H and ^{13}C NMR were in agreement with expected values. The peaks of interest in the IR were the CN, and CO stretches. They have appeared in the region between 2310-2200 and 1755-1760 cm^{-1} respectively. The summary of the results for the spectroscopic analysis are listed in Tables 2.4.1. and 2.4.2.

2.4.2 *Photolysis of the Complexed Ethyl Cyanoacetates.*

The free aromatic ligands of ethylcyanoacetates were obtained by using photolysis as a means of decomplexation, as illustrated in Scheme 17. In doing so the FeCp moiety cleaves from the complex leaving the free aromatic ligands which are easily isolated by column chromatography. The pure products were obtained as yellow oils. The desired compounds were isolated in yields ranging from 79-84%.

The identities of all photolyzed products were confirmed by ^{1}H and ^{13}C NMR, IR, and MS. The results of those analysis are listed in Tables 2.4.3. and 2.4.4. The major differences in the spectral analysis between the complexed and uncomplexed products are as follows. In the case of ^{1}H and ^{13}C NMR, due to the loss of the FeCp moiety, there is an absence of the Cp signal.

There is also an evident shift in the position of the aromatic signals to the lower field. For example, in the ^1H NMR of an ortho substituted complex **35**, the Cp signal occurs at δ 5.47 and the aromatic protons appear in the range between δ 7.05 and 6.71. After the decomplexation, the spectrum of the free ligand does not show the peak due to the iron moiety, as well the aromatic protons exhibit the shift in their position to the region between δ 7.38-7.46. The representative spectra of the compounds of interest are shown in Fig. 23 and 24.

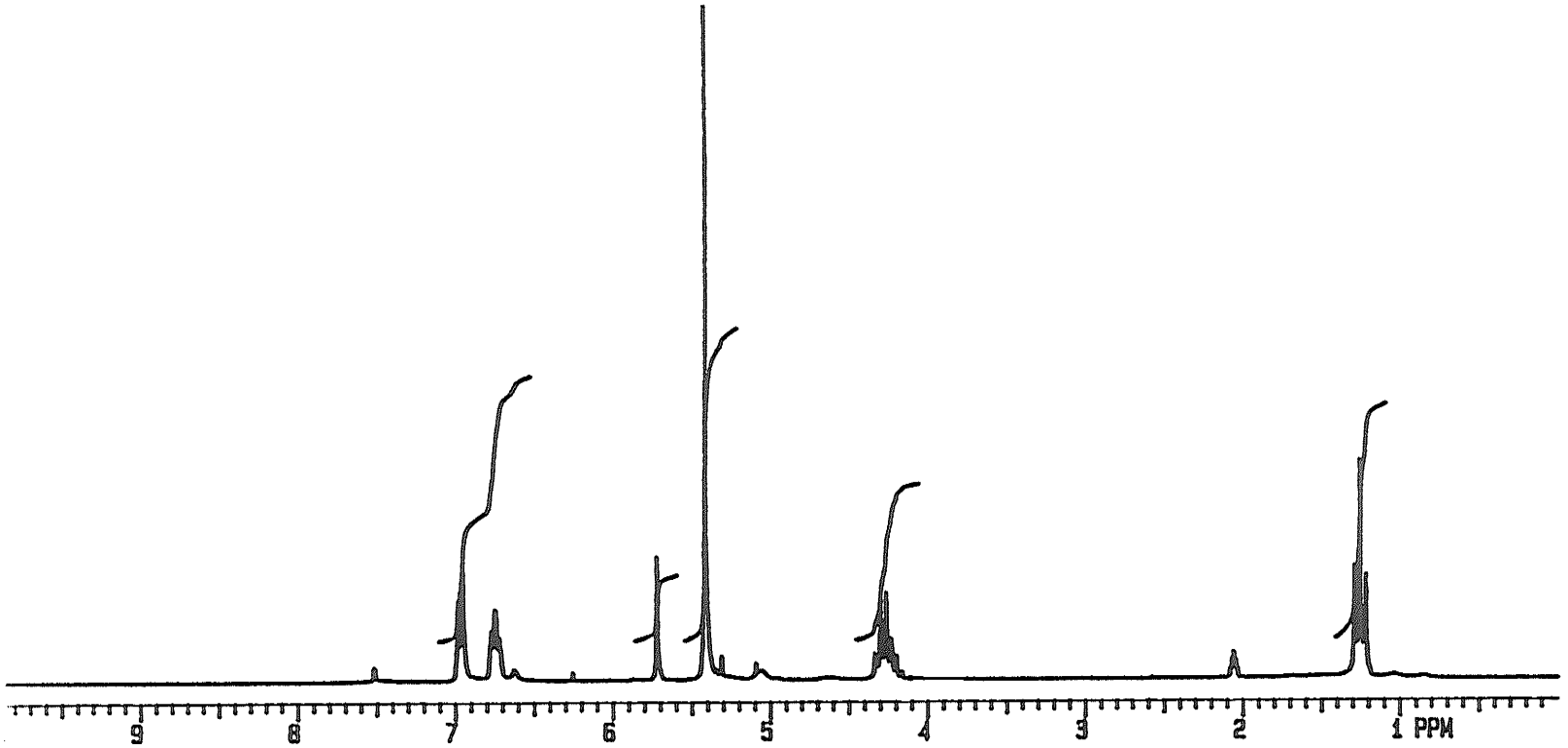


Fig.21 ^{1}H NMR(APT) spectrum of η^{6}-[ethyl(p-chloro)phenyl (cyanoacetate]-η^{5}-(cyclopentadienyl) hexafluoro-phosphate in CD_3COCD_3.

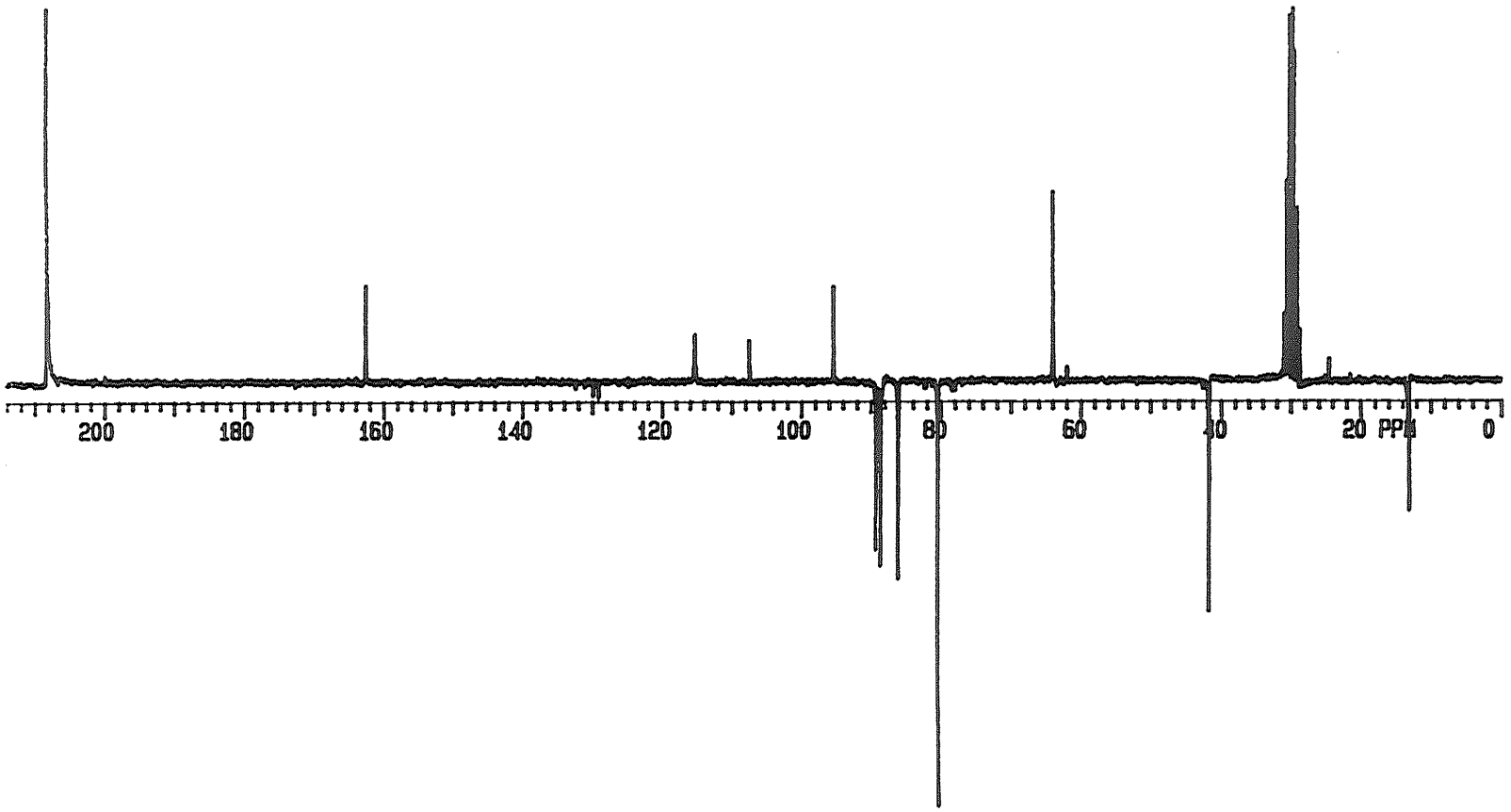


Fig.22 ^{13}C NMR(APT) spectrum of η^6-[ethyl(p-chloro)phenyl-(cyano)acetate]-η^5-(cyclopentadienyl) hexafluorophosphate in CD_3COCD_3.

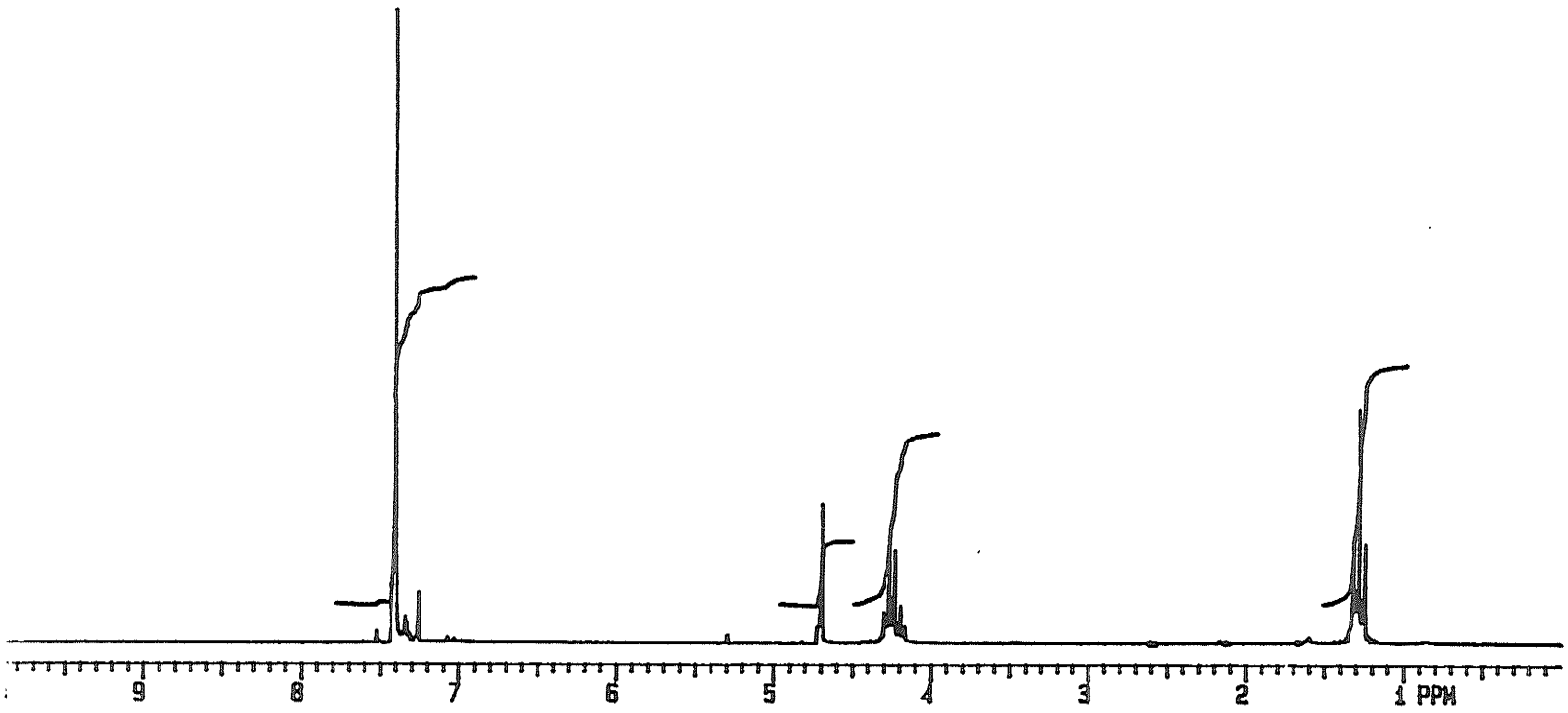


Fig.23 ^{1}H NMR spectrum of Ethyl (p-chloro)phenyl (cyano)acetate in $CDCl_3$.

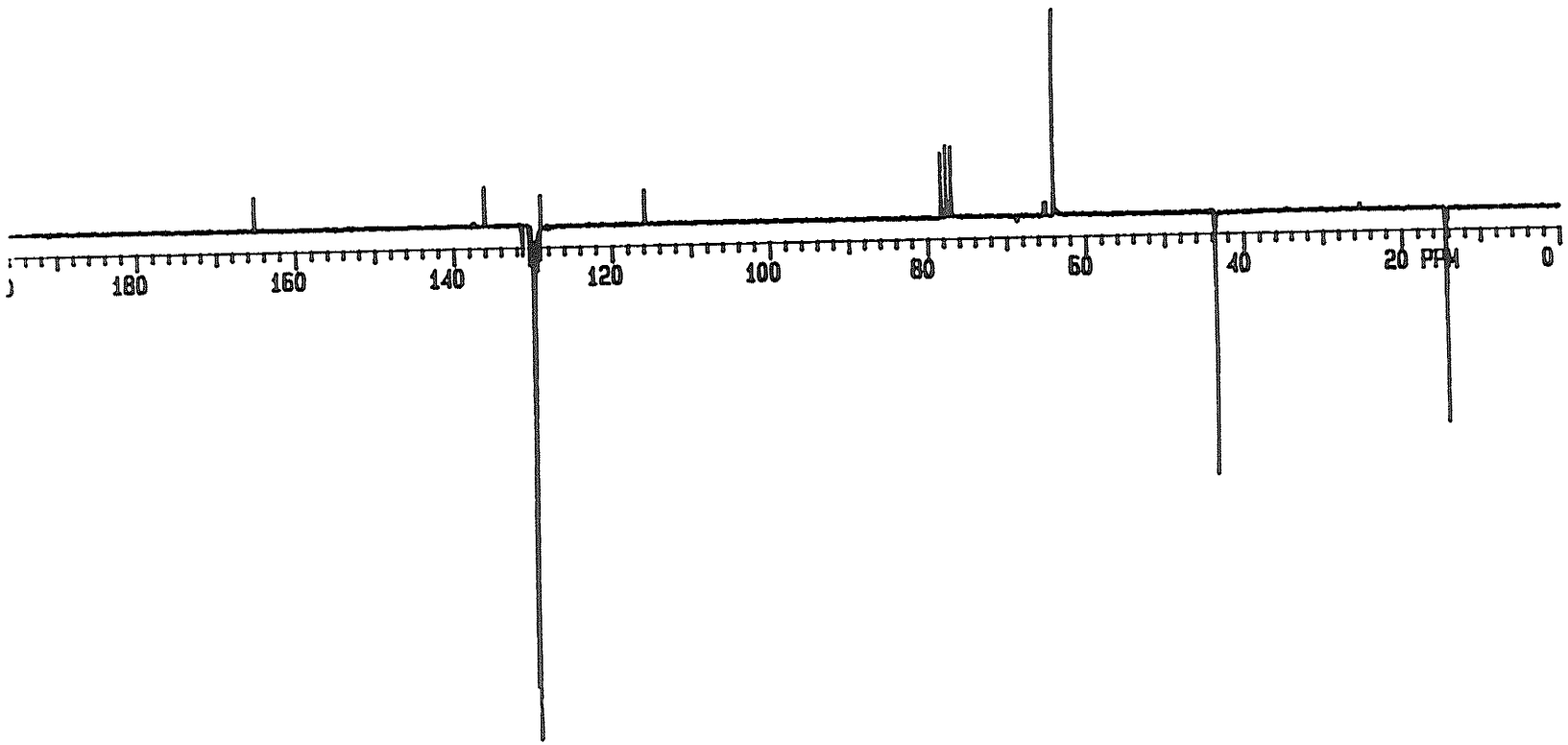


Fig.24 ^{13}C NMR(APT) spectrum of Ethyl (p-chloro)phenyl (cyano)acetate in $CDCl_3$.

Table 2.4.1 ^{1}H NMR and yield data for complexes derived from nucleophilic substitution reactions of CpFe complexes of dichloroarenes with ethyl cyanoacetate

		^{1}H NMR (δ, ppm), (CD_3COCD_3)		
Complex	% Yield	Aromatic	Cp	Others
35	71.0	7.05 (1H,d,*J* 7.3,ArH) 6.85 (2H,m,ArH) 6.71 (1H,t,*J* 6.1,ArH)	5.47	6.26 (1H,s,CH) 4.30 (2H,q,*J* 6.8,CH_2) 1.25 (3H,t,*J* 7.2,CH_3)
36	74.0	7.05-6.65 (4H,t,*J* 6.1,ArH)	5.46	5.83 (1H,s,CH) 4.31 (2H,q,*J* 7.1,CH_2) 1.26 (3H,t,*J* 7.1,CH_3)
37	81.0	6.97 (2H,d,*J* 6.5,ArH) 6.74 (2H,d,*J* 6.5,ArH)	5.46	5.72 (1H,s,CH) 4.25 (2H,q,*J* 7.1,CH_2) 1.25 (3H,t,*J* 7.0,CH_3)

Table 2.4.2 ^{13}C NMR, and IR data for complexes derived from nucleophilic substitution reactions of CpFe complexes of dichloroarenes with ethyl cyanoacetate

Complex	i.r. (cm^{-1}) (neat)	^{13}C NMR (δ, ppm), (CD_3COCD_3) Aromatic	Others
35	2305(CN) 1755(CO)	108.56*,95.30*, 89.90,89.71, 88.53,87.12	162.48(CO),114.85(CN), 80.87(Cp),64.67(CH_2), 41.56(CH),13.76(CH_3)
36	2200(CN) 1760(CO)	107.08*,96.04*, 89.82,88.96, 87.98,86.41	162.45(CO),115.26(CN), 80.28(Cp),63.93(CH_2), 41.74(CH),13.02(CH_3)
37	2310(CN) 1760(CO)	107.48*,95.34*, 88.64,88.55, 88.52,86.11	162.54(CO),115.30(CN), 80.41(Cp),63.91(CH_2), 41.67(CH),13.07(CH_3)

*denotes a quaternary carbon atom on the aromatic ring

Table 2.4.3 ^{1}H NMR and yield data for ethyl chlorophenyl(cyano)acetate

Compound	% Yield	^{1}H NMR (δ, ppm), ($CDCl_3$) Aromatic	Others
38	82.0	7.38-7.46 (4H, br s,ArH)	4.70 (1H,s,CH) 4.23 (2H,q,*J* 7.2,CH_2) 1.26 (3H,t,*J* 7.1,CH_3)
39	84.0	7.35 (4H, br s,ArH)	4.67 (1H,s,CH) 4.25 (2H,q,*J* 7.1,CH_2) 1.27 (3H,t,*J* 7.0,CH_3)
40	79.0	7.39 (4H, br s,ArH)	4.68 (1H,s,CH) 4.23 (2H,q,*J* 7.1,CH_2) 1.26 (3H,t,*J* 7.1,CH_3)

Table 2.4.4 ^{13}C NMR, IR, and MS data for ethyl chlorophenyl(cyano)acetate

Compound	i.r. (cm^{-1}) (neat)	m/z (M^+)	^{13}C NMR (δ, ppm), ($CDCl_3$) Aromatic	Others
38	2220(CN) 1750(CO)	223	129.32,129.20, 127.89,123.05*	164.50(CO),115.60(CN), 63.29(CH_2),43.76(CH), 13.87(CH_3)
39	2260(CN) 1755(CO)	223	135.15*,131.59*, 130.51,129.48, 128.09,126.08	164.34(CO),115.23(CN), 63.56(CH_2),43.20(CH), 13.82(CH_3)
40	2300(CN) 1750(CO)	223	135.40*,129.49, 129.25,128.37*,	164.52(CO),115.22(CN), 63.49(CH_2),43.05(CH), 13.82(CH_3)

*denotes a quaternary carbon atom on the aromatic ring

3.0 EXPERIMENTAL

All chemicals used, such as ferrocene, aluminum trichloride anhydrous, aluminum powder, decalin, and the chloroarenes, are commercially available and were used without further purification. Other commercially available chemicals which were an asset in the nucleophilic substitution reactions and demetallation reactions include ethyl acetoacetate, methyl acetoacetate, potassium carbonate, magnesium sulphate, phenyl sulphonylacetonitrile, ammonium hexafluoro-phosphate, silica gel (60-100 mesh), and potassium t-butoxide. Solvents such as tetrahydrofuran (THF), N,N-dimethyl-formamide (DMF), diethyl ether, hexane acetonitrile, chloroform, acetone, deuteroacetone, deuterochloroform were also commercially available and all but THF were used without further purification. THF was freshly distilled, according to standard procedure [111].

^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded on a Gemini 200 NMR spectrometer; with chemical shifts being calculated from the solvent signals. MS spectra were separated on a HP 5970 Series Mass Selective Detector in m/z units. IR were recorded using a Perkin-Elmer 781 spectrophotometer.

3.1 *Synthesis of Chloroarene Complexes.*

Starting complexes (**4-6**), (**19**) and (**32-34**) were prepared through ligand exchange reactions. The general procedure used for complexes of interest is described in the following section.

3.1.1 *Synthesis of η^6-arene-η^5-cyclopentadienyliron hexafluorophosphate complexes.*

In a 500 mL 3-necked round bottom flask were placed 100 mmol ferrocene ($FeCp_2$), 200 mmol aluminum trichloride ($AlCl_3$), 100 mmol aluminum powder, and 250 mmol of the substituted arene (chlorobenzene,o-, m-,p-dichloro- benzene, and o- m-,or p-chlorotoluene). Decalin (60 mL) was used as a solvent if necessary. The mixture was then heated at 130-145°C, under nitrogen atmosphere for 5 hours. The mixture was then cooled to 50°C and poured into 400 mL of ice water and stirred for 10 minutes. The greenish-orange solution was then suction filtered through sand. The filtrate was washed with 4 x 75 mL of ether (3 times with petroleum ether, once with diethyl ether) in a separatory funnel to remove the organic layer. After washing, 60 mmol of

ammonium hexafluorophosphate (NH_4PF_6) was added and the solution turned a greenish-yellow as it was stirred for 10 minutes. The crude precipitate was collected by filtration and redissolved in dichloromethane. This was subsequently dried over anhydrous magnesium sulfate for 10 minutes. The solution was filtered into a 1000 mL round bottom flask and the dichloromethane was concentrated to a volume of 80-100 mL using a rotary evaporator. Addition of diethyl ether to the concentrated solution (dark green) resulted in the precipitation of the pure products (**4-6**, **19**, **32-34**). This was collected by suction filtration and the product was dried under vacuum for 1 hour. The final products were characterized by ^1H and ^{13}C NMR (APT). The results obtained through such an analysis agreed very well with the spectroscopic data reported previously.

3.2 *Synthesis of Some Alkanoic Acid Esters Precursors.*

3.2.1 *Preparation of Ethyl 2-methylacetoacetate and Ethyl 2-ethylacetoacetate.*

In a flame dried 500 mL 3-necked flask equipped with a condenser and $CaCl_2$ drying tube, was placed 150 mL of 95% ethanol. Metallic sodium (0.326 mol) was then added. After all of the sodium had dissolved, 0.300 mol

of ethyl acetoacetate was added to the warm solution of sodium ethoxide. Followed immediately, was added 0.3 mol of methyl or ethyl bromide . The reaction mixture was then heated for 3 hours and allowed to sit for 4.5 days. Next the mixture was filtered (the reaction flask was washed with ethanol) and the ethanol was removed by the use of the rotary evaporator to a volume of 65 mL. Next, 250 mL of H_2O and 3 mL of concentrated HCl were added. The mixture was transferred to a separatory funnel and the aqueous layer was drawn off. The mixture was then washed with approximately 50 ml of H_2O, and then dried over $MgSO_4$. The mixture was then filtered into a 100 ml round bottomed flask for vacuum distillation. Following distillation, the pure products were then characterized using IR , ^1H and ^{13}C NMR. The results of the above are as follow:

Ethyl 2-methylacetoacetate

^1H NMR (δ, ppm, $CDCl_3$) shows 4.12 (2H,q, J 7.2, CH_2), 3.43 (1H, q, J 7.1, CH), 2.17 (3H, s, $-COCH_3$), 1.25 (3H, t, J 7.2, CH_2CH_3), 1.24 (3H, d, J 7.3, $CHCH_3$); ^{13}C NMR (δ, ppm, $CDCl_3$) shows 203.15 ($CO CH_3$), 170.43 ($CO_2CH_2CH_3$), 61.21 (CH_2), 53.53 (CH), 28.25 ($COCH_3$), 13.95 (CH_2CH_3), 12.58 ($CHCH_3$); IR (cm^{-1}, neat) shows stretches at 1738 and 1720 for the carbonyl groups.

Ethyl 2-ethylacetoacetate

^{1}H NMR (δ, ppm, $CDCl_3$) shows 4.22 (2H,q, J 7.2, CH_2), 3.32 (1H, t, J 7.3, CH), 2.21 (3H, s, $-COCH_3$), 1.87 (2H, m, CH_2CH_3), 1.26 (3H, t, J 7.2, $CO_2CH_2CH_3$), 1.2 (3H, t, J 7.4 CH_2CH_3); ^{13}C NMR (δ, ppm, $CDCl_3$) shows 203.02 ($COCH_3$), 169.61 ($CO_2CH_2CH_3$), 61.18 (CO_2CHCH_3), 61.01 (CH), 28.56 ($COCH_3$), 21.38 (CH_2CH_3), 13.88 ($CO_2CH_2CH_3$); IR (cm^{-1}) shows stretches at 1740, 1720 for the carbonyl groups.

3.2.2 *Synthesis of η^6-(ethyl 2-aryl)propanoates (or butanoates)-η^5-cyclopentadienyliron(II) hexafluorophosphate complexes.*

A mixture of 2.0 mmol of the chloroarene cyclopentadienyliron hexafluorophosphate, 2.2 mmol of ethyl methylacetoacetate or ethyl ethylacetoacetate and 5.0 mmol of potassium carbonate in 10 mL DMF was stirred under nitrogen with heating at 50°C for 8 hours. The red reaction mixture was filtered rapidly into 15 mL of 10% HCl, the reaction flask was then washed with ethanol and the washings also filtered into the HCl. The ethanol was then removed using a rotary evaporator. To the remaining DMF solution, two mmol of ammonium hexafluoro- phosphate in 20 mL of H_2O was added. The

product was then recovered by extraction with dichloromethane, washed several times with water (7 x 25 mL) and dried over magnesium sulfate. The solvent was evaporated and the residual material was then washed with diethyl ether (3 x 25 mL) to yield the final products **(7-9),(13-15)** and **(20a,b; 21a,b)**.

3.2.3 *Photolysis η^6-(ethyl 2-aryl)propanoates (or butanoates)-η^5-cyclopentadienyliron(II) hexafluorophosphate.*

One mmol of the substituted arene cyclopentadienyl-iron complexes was dissolved in 40 mL of 3/1 dichloromethane/acetonitrile mixture in a pyrex tube. The solution was deoxygenated by bubbling nitrogen through it for 0.5 hours prior to the photolysis. The photolytic apparatus was equipped with a Xenon lamp and the sample was irradiated at room temperature for 4 hours. The solvent was concentrated to a volume of 2-3 mL using the rotary evaporator. The residue was purified by passage through a short column (5 cm) of packed silica gel (60-100 mesh). The target product was eluted with $CHCl_3$, while byproducts of the photolysis (for example ferrocene and some iron salts), were recoverd with hexane fraction. Removal of the solvent

from the eluate gave the expected liberated arenes. The resulting products(**10-12**), (**16-18**) as well as **22a,b**,and **23 a,b** were then subjected to the standard spectroscopic tests(^{1}H and ^{13}C NMR, as well as IR and MS).

3.3 *Reactions of Ethylphenylsulphonylacetonitriles.*

3.3.1 *Synthesis of Ethylphenysulphonylacetonitrile.*

In a very dry 250 mL 3-necked flask equipped with a stir bar, condenser and a calcium chloride drying tube, was placed 80 mL of absolute ethanol (as shown in the scheme 5). Three and a half grams of metallic sodium was added (in small pieces) to the ethanol very slowly. After all of the sodium was dissolved, 27.2 g of phenylsulphonyl acetonitrile was added slowly to the warm solution of sodium ethoxide. Without delay, 16 mL of ethyl bromide was added slowly to the solution, upon which it turned slightly yellow color. The mixture was then filtered, the reaction flask washed with ethanol, and the ethanol was also filtered. The ethanol was then concentrated from the filtrate to a volume of 75 mL. This was added to 125 mL of ice water and 1.5 mL of concentrated hydrochloric acid. The mixture was transferred to a separatory funnel and the aqueous sodium bromide layer was drawn off. At this point there

existed a yellowish oil which stuck to the walls of the separatory funnel. This was the product which was subsequently dissolved in ethanol, and dried over anhydrous magnesium sulphate.

The mixture was then filtered into a round bottom flask and was placed on the rotary evaporator to remove all of the ethanol. From this resulted a yellowish oil with some white precipitate. Analysis using proton NMR indicated the mixture of unreacted phenylsulphonyl-acetonitrile, ethylphenylsulphonylacetonitrile (the major product) and ethyl ethylphenylsulphonyl aceto-nitrile. It was thus necessary to separate the three products by column chromatography. The target product, ethyl phenylsulphonylacetonitrile, was eluted with the mixture of diethyl ether/hexane (1:3). It was then characterized by IR, ^{1}H and ^{13}C NMR. The results of these analysis are:

^{1}H NMR (δ,ppm),($CDCl_3$) shows peaks at 8.00 (1H,m,SO_2Ph), 7.96 (4H,m,SO_2Ph), 2.00 (2H,m,CH_2), 1.10 (3H,t, J 7.0, CH_3); ^{13}C NMR (δ,ppm),($CDCl_3$) shows 135.50 (SO_2Ph), 135.14 (SO_2Ph), 129.50 (SO_2Ph), 113.76 (CN), 20.68 (CH_3), 11.06 (CH_3); IR(cm^{-1}) shows stretches at 2340 (CN), 1340 (SO_2) and 1158 (SO_2).

3.3.2 *Synthesis of(η^6-arylethylphenylsulphonyl-acetonitrile)(η^5-cyclopentadienyl)iron(II) hexafluorophosphate Complexes.*

A mixture of 1 mmol of FeCp of chloroarene complex, 2.5 mmol of potassium carbonate, 1.05 mmol of ethylphenylsulphonylacetonitrile, and 10 mL of N,N-dimethyl formamide was stirred at room temperature for 7 hours. The resulting red reaction mixture was rapidly filtered into 10 mL of 10% hydrochloric acid. The reaction flask was washed with ethanol and added to the filtrate. The ethanol was removed under reduced pressure at 25°C using the rotary evaporator. A concentrate solution of NH_4PF_6 was added and the mixture was then stirred for 10 minutes and the resulting yellow product was collected by filtration.

The final products (**26-28**) were analyzed using IR, ^1H and ^{13}C NMR. The results obtained are listed in Tables 2.3.1 and 2.3.2.

3.3.3 *Photolysis of (η^6-arylethylphenylsulphonyl-acetonitrile)(η^5-cyclopentadienyl)iron(II) hexafluorophosphate Complexes.*

Iron complexes (**26-28**) were subjected to photolysis

in the photolytic apparatus equipped with a Xenon lamp. One mmol of complexes (**26-28**) was dissolved in the mixture of CH_2Cl_2/CH_3CN (30 mL: 10 mL) in a pyrex tube. The solution was deoxygenated by bubbling nitrogen through it. The reaction vessel was then irradiated at room temperature for the period of 2 hours. Following the standard procedure, the solvent was concentrated to a volume of 1-2 mL using the rotary evaporator and the concentrate was introduced to a column of silica gel, prepared in hexane. The residue was washed with hexane and the product eluted with chloroform, by passage through the short column. Removal of the solvent from the elute gave the expected liberated arenes (**29-31**). Their spectral data, and respective yields will be reported in Tables 2.3.3 and 2.3.4.

3.4 *Reactions with Ethyl cyanoacetates.*

3.4.1 *Synthesis of (η^6-ethyl-(chlorophenyl) cyanoacetate)(η^5-cyclopentadienyl)iron(II) hexafluorophosphate complexes.*

A mixture of the starting cation (1 mmol), potassium carbonate (2.5 mmol), and ethyl cyanoacetate (1.05 mmol)

in DMF (10 mL) was stirred at room temperature under a nitrogen atmosphere for 7 hours. The resulting dark red reaction mixture was filtered into 10% aqueous hydrochloric acid (10 mL). Concentrated aqueous ammonium hexafluorophosphate was added to the reaction mixture and the product was extracted with dichloromethane (3 X 50 mL). The combined extract was washed with water (4 X 40 mL), dried ($MgSO_4$) and evaporated under reduced pressure at 25°C. The residual yellow oil was washed with diethyl ether (3 X 20 mL) and was dissolved in CH_2Cl_2 and precipitated by diethyl ether.

The final products were subjected to spectroscopic analysis via IR, ^1H and ^{13}C NMR. The results of these analyses are tabulated in Table 2.4.1 and 2.4.2.

3.4.2 *Photolysis of (η^6-ethyl-(chlorophenyl) cyanoacetate)(η^5-cyclopentadienyl)iron(II) hexafluorophosphate Complexes.*

General procedure for photolysis was used. Each of the complexes, **35-37** was separately dissolved in the mixture of CH_2Cl_2/CH_3CN (30 mL/10 mL) in a pyrex tube. The resulting solution was deoxygenated, after which it was placed in the photochemical apparatus

described previously, and irradiated at room temperature for 2 hours. The solvent was concentrated to a volume of 1-2 mL using a rotary evaporator. The residue was applied to a silica gel column and eluted with chloroform. Removal of the solvent from the elute gave the expected free arene. The spectral data (IR, ^{1}H and ^{13}C NMR, MS) and percent yields are reported in Tables 2.4.3 and 2.4.4.

4.0 CONCLUSION

Aromatic nucleophilic substitution reactions (S_NAr) of arene complexed to an iron moiety with various carbon nucleophiles, followed by photolysis, have been under our investigation as a possible novel route to the compounds of interest. This methodology has proven successful with ethyl 2-methylacetoacetate, 2-ethylacetoacetate, phenylsulphonylacetonitrile and ethyl cyanoacetate as nucleophiles, and various chloroarene cyclopentadienyliron (CpFe) complexes as substrate.

Specifically, treatment of chlorobenzene and

isomeric chlorotoluenes (m- and p-) with ethyl methylacetoacetate or ethyl ethylacetoacetate in the presence of potassium carbonate in DMF produce the nucleophilic substitution products (7-9 and 13-15) with deacylation in high yields (71-89%). Besides the use of complexed m- and p-chlorotoluene, we have also applied the above methodology to the o-chlorotoluene complex. In these reactions we always obtained a mixture of deacylated and non-deacylated complexes. Photolysis was chosen as a method of demetallation of our S_NAr products. In the case of p- and m- complexes, photolysis resulted in the generation of the uncomplexed alkanoic acid esters, **10-12** and **16-18**. The photolysis of o- complex mixtures resulted in the enrichment of the deacylated and non-deacylated alkanoic acid esters. The overall yield for these compounds ranged between 55 to 57%.

To further explore the versatility of this synthetic strategy, we carried out nucleophilic substitution reactions of chloroarene complex (**4-6** ,**19** and **34-36**) with ethylphenylsulphonylacetonitrile and ethyl cyanoacetate. These reactions led to the formation of the desired products, namely complexed arylated ethyl- phenylsulphonylacetonitriles and ethyl cyanoacetates, in good yields ranging form 71-94%.
Photolysis of these complexes have proven once again

appropriate for the liberation of the free aromatic ligands **30-33**,and **40-42** in very good yield.

In conclusion, we would like to point out that in the synthesis of much desired alkanoic acid precursors and heterocyclic precursors, our method of nucleophilic substitution followed by photolysis have proven to be superior to the other approaches previously reported, due to its ease and use of mild reagents. As well it is worth stressing that the methodology chosen by our group demonstrates its versatility by facilitating the introduction of various functional groups to the ethyl ethylcyanoacetates, phenylsulphonylacetonitriles as well as the ethyl cyanoacetates.

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