CARBON MONOXIDE AS REAGENT IN THE FORMYLATION OF AROMATIC COMPOUNDS

by

Johannes Alexander Willemse

Dissertation in fulfillment of the requirements for the degree

Magister Scientiae

in

Chemistry

in the

Faculty of Science

at the

Rand Afrikaans University

Supervisor: Prof. C.W. Holzapfel

Co-supervisor: Dr B.C.B. Bezuidenhoudt

September 2003

Acknowledgements

My sincere gratitude is extended to the following people:

- Prof. C.W. Holzapfel for his tremendous enthusiasm and support
- Dr. B.C.B Bezuidenhoudt for his proficient tutelage and forbearance during this study
- Sasol for financial support
- Ms A. Ranwell and M. Ajam for supplying most of the ionic liquids
- Dr. J. Coetzee and Ms M. Kirk for NMR data recording and interpretation
- Mr. A. Tolmay for Mass Spectrometry data recording
- My colleagues drr. P. van Heerden, J. Dixon and C. Grove for their support
- This study is dedicated to my wife Marietjie; my daughter Luchelle and son Wynand and with special recognition to my parents for their sacrifices and devotion

Phillipians 4:13: “I can do all things through Christ, who strengthens me”

TABLE OF CONTENTS

Abbreviations

NMR	nuclear magnetic resonance
MO	molecular orbital
M.p.	melting point
B.p.	boiling point
FID	flame ionisation detector
PHBAld.	*para*-hydroxy-benzaldehyde
p-Tolualdd.	*para*-tolualdehyde
PAA	*para*-anisaldehyde
OAA	*ortho*-anisaldehyde
BCD	*beta*-cyclodextrin
THF	tetrahydrofuran
TMS	tetramethylsilane
[bmim]	1-butyl-3-methylimidazolium
[hexmim]	1-hexyl-3-methyl-imidazolium
[omim]	1-octyl-3-methyl-imidazolium
[bmim]BTA	1-butyl-3-methylimidazolium trifluoromethane sulfonimide
h	hour
eq	equivalents
psi	pounds per square inch
atm	atmospheric
min	minutes
Press.	pressure
Conv.	conversion
Sec. Prod.	secondary products

SYNOPSIS

Sasol endeavors to expand its current business through the beneficiation of commodity feedstreams having marginal value into high-value chemicals via cost-effective processes. In this regard Merisol, a division of Sasol has access to phenolic and cresylic feedstreams, which have the potential to be converted to fine chemicals.

Targeted products include *para*-anisaldehyde, *ortho*- and *para*-hydroxybenzaldehyde which are important intermediates for the manufacture of chemicals used in the flavor and fragrance market and various other chemicals. The use of CO technology (HF/BF_3) to produce these aldehydes in a two-step process from phenol as reagent is economically attractive due to the relative low cost and other benefits associated with syngas as reagent. The aim of the study was to evaluate and understand this relatively unexplored approach to the formylation of aromatic compounds.

The reactivity of both phenol and anisole proved to be much lower than that of toluene. The main aldehyde isomer (*para*) produced in these $HF/BF_3/CO$ formylations as well as of other *ortho-para* directing mono-substituted benzenes tested in our laboratories were in accordance with published results. Efforts to increase substrate conversion resulted in substantial secondary product formation and mechanistic investigations showed this to be a consequence of the inherent high acidity of the reaction environment.

The effect of different substituents on the relative formylation rates of benzene derivatives was investigated. These results showed that methyl groups are activating while halogens are deactivating relative to benzene as substrate. The decrease in reactivity from fluorobenzene> chlorobenzene> bromobenzene is in accordance with formylation trends observed in other acidic systems.

Deuterium labeling experiments were applied to gain additional information on the formylation reaction mechanism. This study provided interesting but inconclusive results in support of the so-called intra-complex mechanism.

All reported studies as well as our own work suggested that HF and BF_3 in (at least) stoichiometric amounts are required for effective formylation with CO. Under these conditions this methodology for effecting aromatic formylation is not economically viable. Industrial application of formylation using CO will require the development of new catalysts or methodology to allow the use of HF/BF_3 in a catalytic way. In this regard ionic liquids as a new and ecological-friendly field was explored. Chloro-aluminate ionic liquids promote the carbonylation of alkylated aromatic compounds, but fails in the case of oxygenated aromatics. Aldehyde yields of formylation in the acidified neutral ionic liquids were generally similar compared to reactions conducted in HF as solvent/catalyst. Formylation of anisole and toluene, but not of phenol in the neutral ionic liquids resulted in increased secondary product formation in comparison with hydrogen fluoride used as solvent/catalyst. This difference in behavior is not understood at present, but suggests that phenol is a good substrate for formylation in this medium, particularly with the development of a system catalytic with respect to HF/BF_3 in mind.

OPSOMMING

Ten einde sy huidige omset te verhoog, streef Sasol daarna om kommoditeits voerstrome met marginale waarde deur ekonomies lewensvatbare prosesse na hoëwaarde chemikalieë om te skakel. In hierdie verband beskik Merisol, ‘n divisie van Sasol, oor fenoliese- en kresielsuur strome wat potensiëel na fyn chemikalieë omgeskakel kan word. Produkte soos *para*-anysaldehied, en *orto*- en *para*-hidroksiebensaldehied, wat belangrike intermediêre in hoofsaaklik die reuk- en smaakmiddel mark is, is as moontlike teiken verbindings hiervoor ge identifiseer.

Aangesien CO tegnologie (met HF/BF_3 as katalisator) nuttig aangewend kan word om genoemde aldehiede ekonomies in ‘n twee-stap proses vanaf fenol te vervaardig en as gevolg van die lae koste en ander voordele wat met sintesegas binne Sasol geassosieer kan word, is hierdie studie rakende die relatief onbekende veld van aromatiese formilering mbv CO onderneem.

In teenstelling met die algemeen aanvaarde orde van reaktiwiteit, is tydens hierdie studie gevind dat die reaktiwiteit van beide fenol en anisole in HF/BF_3/CO formilerings, veel laer as die van tolueen is. Wat selektiwiteite betref is in ooreenstemming met literatuur resultate gevind dat by alle substrate met *orto-para* rigtende substituente, die *para*-isomeer as hoofproduk gevorm word. Pogings gerig op die verbetering van fenol omsetting was onsuksesvol en het tot substansiële sekondêre produkvorming gelei. Meganistiese studies het getoon dat die hoë suurgehalte van die reaksiemedium waarskynlik hiervoor verantwoordelik is.

Die effek van subtituente op die relatiewe formileringsreaktiwiteit van verskillende benseen derivate het getoon dat metielgroepe aktiverend en halogene deaktiverend tov benseen optree. Die waargenome afname in die reaktiwiteit van fluoor- > chloor- > broombenseen is ook in ooreenstemming met formileringsneigings wat by ander suursisteme waargeneem is.

Ten einde meer insig mbt die meganisme van die HF/BF_3/CO formilerings reaksie te verkry, is deuterium verrykkingseksperimente uitgevoer. Hoewel interessante resultate aanduidend van die sogenaamde intra-kompleks meganisme verkry is, was dit nie eenduidig nie en kon geen finale gevolgtrekking ivm die meganisme van die reaksie dus hieruit gemaak word nie.

In ooreenstemming met literatuur bevindinge, is ook tydens hierdie ondersoek bevind dat beide HF en BF_3 in stoichiometriese hoeveelhede benodig word vir effektiewe formilering van fenoliese substrate met CO. Die hoe koste van HF en BF_3 sou die toepassing hiervan op industriele skaal egter onekonomies maak, met die gevolg dat enige industriele formilering van fenole met CO dus die ontwikkeling van nuwe katalisatore of metodologie vir die katalitiese benutting van HF en BF_3 noodsaak. Aangesien die gebruik van ioniese vloeistowwe ‘n moontlike oplossing vir hierdie probleem kon bied, is die effek van hierdie ekologies vriendelike verbindings op die formileringsreaksie van fenole met CO vervolgens bestudeer.

Weens die feit dat formilering van alkielbensene mbv chloro-aluminaat ioniese vloeistowwe bekend is, is die effek van hierdie reagense op die reaksie van geoksigeneerde aromate aanvanklik ondersoek. Aangesien slegs demetilering van anisool met hierdie reagens waargeneem kon word, is die fokus van die ondersoek vervolgens na die benutting van aangesuurde neutrale ioniese vloeistowwe verskuif en is bevind dat aldehied opbrengste in ooreenstemming is met die opbrengste van reaksies waar HF as oplosmiddel/katalisator gebruik is. In teenstelling met die reaksies van fenol, het die formilering van anisool en tolueen onder hierdie kondisies tot verhoogde sekondêre produk vorming in vergelyking met reaksies van HF as oplosmiddel/katalisator, gelei. Hoewel onverklaarbaar, suggereer hierdie bevinding dat fenol ‘n goeie substraat vir formilering in hierdie medium is; veral indien die omtwikkeling van ‘n nuwe katalitiese sisteem met betrekking tot HF/BF_3 in gedagte gehou word.

CHAPTER 1

AROMATIC ALDEHYDE SYNTHESES

1. INTRODUCTION

The synthetic routes to aromatic aldehydes are as numerous as they are diverse, indicating not only the intrinsic value of aldehydes as synthetic intermediates, but also the scarcity of truly general routes towards aldehydes themselves. This resulted in the realization of a number of relatively specific syntheses that often relies on partial oxidation and reduction where the danger of over-reaction is always present. Although carbonylation chemistry offers a limited number of general synthetic routes to aldehydes that are both selective and high yielding, these routes often use readily available starting materials. The two most generally useful substrates for carbonylative aldehyde synthesis are halo-carbons and alkenes.[1] This study will however focus primarily on the synthesis of aldehydes from arenes.

1.1 Comparison of Ketone and Aldehyde Syntheses

Acylation of both aromatic and aliphatic compounds can be carried out with relative ease using acyl halides, acid anhydrides, ketenes, nitriles, amides, acids and esters in the presence of Friedel-Craft catalysts to give ketones.[2] Similar substitution reactions with formic acid derivatives are therefore expected to yield the appropriate aldehydes. However, since the anhydride and acyl halides of formic acid, with the exception of formyl fluoride,[3] are either not known or are not sufficiently stable to be used in Friedel-Crafts type acylation reactions, this objective cannot be fully realized. Table 1.1 compares the main ketone syntheses (based on acylating reagents) with the corresponding aldehyde syntheses (based on formylating reagents).

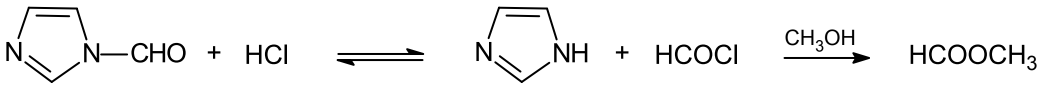
Table 1.1: Comparison of aldehyde and ketone synthesis.

KETONE SYNTHESIS	Acyl halides	Acid Anhydrides	Ketenes	Nitriles	Amides	Acids	Esters
ALDEHYDE SYNTHESIS	CO + HCl (Gattermann-Koch) Formyl fluoride Dichloro *ortho*-formates	Acetic-formic anhydride	CO	HCN (Gattermann) BrCN (Karrer)	Formamides (Vilsmeier)	Formic acid	Ortho-formates

2. FORMYLATING AGENTS

2.1 Formic acid and Derivatives

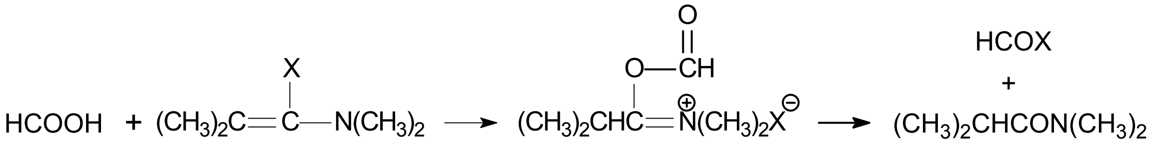
With the exception of formyl fluoride, which is the only known stable halide of formic acid and used as an electrophilic aromatic formylating agent in the presence of mainly boron trifluoride, no other formyl halides have been isolated.[4] Although the preparation of formyl chloride by high-temperature photo-chlorination of formaldehyde was reported,[5] isolation of the compound could not be substantiated.[6,4] Staab *et al.*,[7] however, generated the elusive formyl chloride by passing HCl into a solution of 1-formimidazole in CH_3Cl at –60°C (Eq 1.1).



(1.1)

No physical data of the unstable compound were given as it was immediately trapped by methanol to give methyl formate at -60°C.

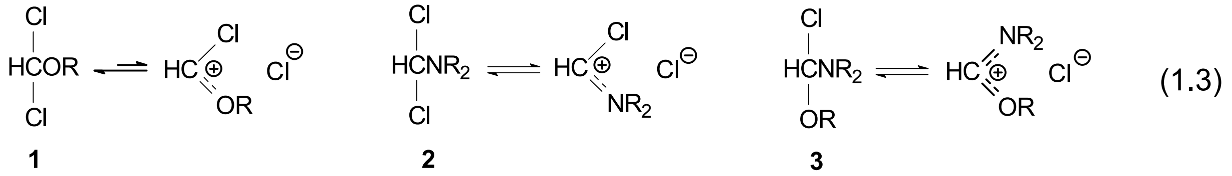
An improved *in situ* preparation of formyl chloride as well as of formyl fluoride and even the bromide and iodide from formic acid and tetramethyl-α-halogeno enamines at or below room temperature in high yield under neutral conditions was reported by Ghosez *et al.*[8] (Eq 1.2).



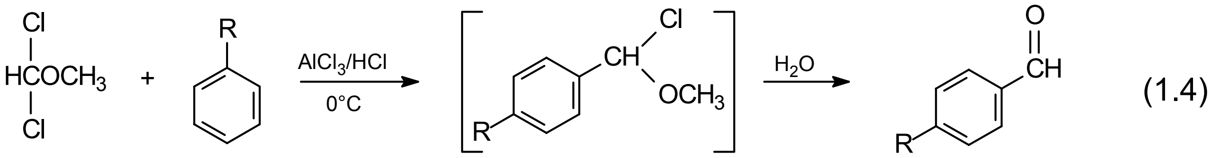
$$HCOOH + (CH_3)_2C{=}\overset{X}{\overset{|}{C}}{-}N(CH_3)_2 \longrightarrow (CH_3)_2CH\overset{O-\overset{\overset{O}{\|}}{C}H}{\overset{|}{C}}{=}\overset{\oplus}{N}(CH_3)_2X^{\ominus} \longrightarrow \begin{matrix}HCOX\\+\\(CH_3)_2CHCON(CH_3)_2\end{matrix} \quad (1.2)$$

Again, the formyl chloride was detected only by its conversion into methyl formate while the other formyl halides were converted into formanilide.

Dichloromethyl ethers and dichloromethyl amines are able to act as formyl chloride equivalents in the formylation of aromatics and olefins. The reactivity of the formylating agent is determined by the nature of the substituent, which determines the electrophilicity of the formyl carbon. Thus, the reactivity for electrophilic formylation decreases in the order 1>2>3 (Eq 1.3).



α,α-Dichlorodimethyl ether is capable of formylating benzene or a slightly activated arene such as toluene in the presence of a Friedel-Crafts catalyst to yield benzaldehyde and tolualdehyde in yields of 37% and 80%, respectively (Eq 1.4).[9]



Nesmejanow *et al.*[10] were the first to prepare formyl fluoride in a yield of 16% from anhydrous formic acid, potassium fluoride and benzoyl chloride (Eq 1.5).

$$HCOOH + KF + PhCOCl \longrightarrow HCOF + PhCOOH + KCl \qquad (1.5)$$

Mashentsev[11] prepared it from benzoyl fluoride and formic acid in a 36% yield. Olah *et al.*[12] used KHF_2 as alternative reagent to produce formyl fluoride from formic acid and benzoyl chloride. In two improved preparation methods Olah *et al.*[13] prepared formyl fluoride by fluorinating formic acid with cyanuric fluoride in pyridine or by reacting benzoyl fluoride with sodium formate. According to Olah it is possible to achieve a successful formylation reaction by dissolving the generated formyl fluoride in a solution containing the aromatic, followed by the introduction of BF_3 as catalyst. A number of aromatic aldehydes were prepared using this method in yields varying from 56 to 78% (Table 1.2).

Table 1.2: Formylation of aromatic using formyl fluoride.[a]

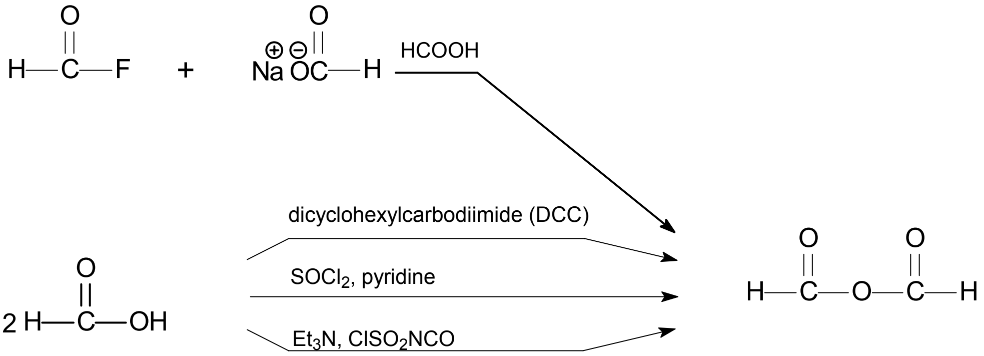
Substrate	Product	Yield (%)
Benzene	Benzaldehyde	56
Toluene	Tolualdehyde	75
Xylene	Dimethylbenzaldehyde	78
2,4,6-trimethyl benzene	2,4,6-trimethylbenzaldehyde	70
2,3,4,6-tetramethyl benzene	2,3,4,6-tetramethyl benzaldehyde	72
Naphthalene	Naphtaldehyde	20, α-isomer and 67, β-isomer

[a] 0.5mol of the substrate was dissolved in 150ml CS_2 followed by the passing through of a 1:1 formyl fluoride boron trifluoride mixture with stirring while maintaining the reaction temperature between 0 and 10°C for 3hours.

Formyl fluoride reacts with alcohols and phenols in the presence of triethylamine to form the corresponding formates in yields of 73-92% for primary and secondary aliphatic alcohols, while benzyl alcohol and phenol gave the corresponding esters in 69% and 75% yields, respectively (Eq 1.6).

$$\mathrm{ROH} + \mathrm{HCOF} + \mathrm{Et_3N} \longrightarrow \mathrm{ROC(=O)H} + \mathrm{Et_3NHF} \qquad (1.6)$$

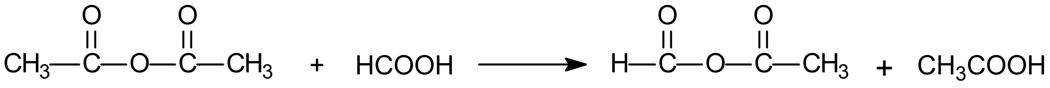
Olah[14] prepared the elusive formic anhydride in a reaction of formyl fluoride with sodium formate at -78°C and he extended the preparation of this reagent by three condensation reactions (Eq 1.7).



(1.7)

Conversion of *p*-nitrophenol into *p*-nitrophenyl formate in good yield by reaction with this *in situ* generated reagent confirmed that it can act as a formylating agent. However, attempts to formylate aromatics failed due to the instability of the anhydride above -40°C. Also, the presence of acid catalysts leads to the decomposition of the formic anhydride even at low temperatures.

Mixed anhydrides of formic acid with higher homologous acids anhydride are well known and stable. Béhal[15,16] prepared acetic-formic anhydride from acetic anhydride and formic acid, yielding a suitable formylating agent for the formylation of *N*-formyl derivatives from the corresponding amines (Eq 1.8).



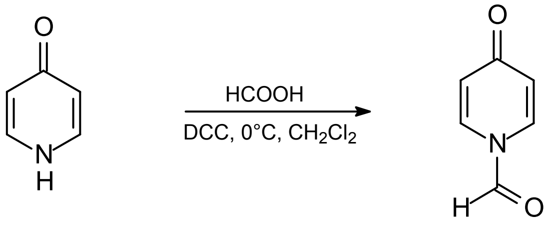
$$\mathrm{CH_3C(=O)OC(=O)CH_3} + \mathrm{HCOOH} \longrightarrow \mathrm{HC(=O)OC(=O)CH_3} + \mathrm{CH_3COOH} \qquad (1.8)$$

Graves[17] and Roe *et al.*[18] synthesized acetic-formic anhydride by reaction of ketene with anhydrous formic acid (Eq 1.9).

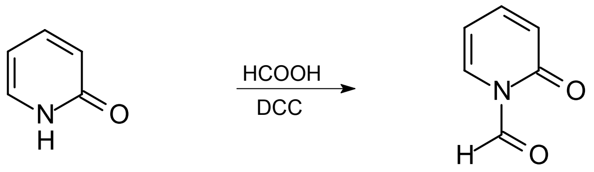
$$CH_2{=}C{=}O + HCOOH \longrightarrow H-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-CH_3 \qquad (1.9)$$

Olah *et al.*[19] attempted to use the acetic formic anhydride as a Friedel-Crafts formylating agent. However, exclusive acetylation of the aromatics was always accompanied by carbon monoxide evolution.

Formic acid in conjunction with appropriate dehydrating agents is also used as formylating agents. Thus, *N*-formylation of pyridones is achieved with relative ease using formic acid and dicyclohexylcarbodiimide (DCC) at 0°C (Eq 1.10 and 1.11).[20]

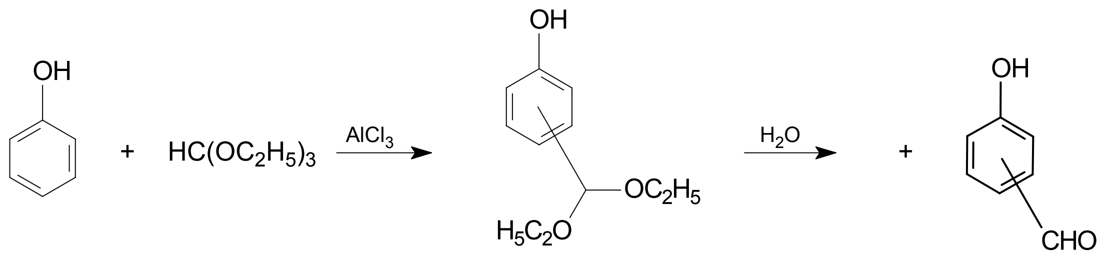


(1.10)



(1.11)

Gross and co-workers[21] reported an interesting direct aldehyde synthesis using alkyl ortho-formates that is particularly suitable for phenols, as alkylformates are unable to act as formylating agents under Friedel-Crafts conditions. Aldehydes of phenol are obtained in good yields when phenols react with orthoformates in the presence of aluminum chloride (Eq 1.12).



(1.12)

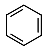
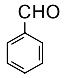
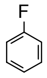
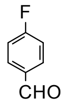
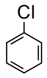
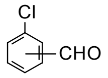
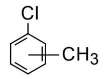
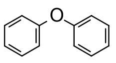
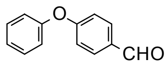
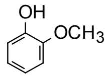
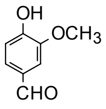
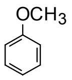
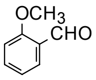
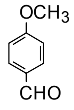
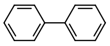
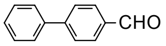
Results obtained by formylation of phenolic compounds with orthoformates are summarized in Table 1.3.

Table 1.3: Formylation of phenols by alkyl orthoformates.

Substrate	Product	Yield (%)
m-cresol	Formyl-*m*-cresols	66
2,5-dimethylphenol	4-Hydroxy-2,5-dimethylbenzaldehyde	41
3,5-dimethylphenol	Formyl-3,5-dimethylphenols	51
3,4-dimethylphenol	2-Hydroxy-4,5-dimethylbenzaldehyde	44
Thymol	Formyl-thymols	59
α-naphthol	Formyl-α-naphthols	97
β-naphthol	1-Formyl-2-hydroxynaphthalene	41
Pyrocatechin	3,4-Dihydroxybenzaldehyde	45
Resorcinol	2,4-Dihydroxybenzaldehyde	64
Orcinol	2,4-Dihydroxy-6-methylbenzaldehyde	66
Pyrogallol	2,3,4-Trihydroxybenzaldehyde	92
Hydroxyhydroquinone	2,4,5-Trihydroxybenzaldehyde	89
Phloroglucinol	2,4,6-Trihydroxybenzaldehyde	96

Formylation of various aromatic substrates can be achieved with fair to good results using methylformate in the presence of HF-BF_3 (Table 1.4).[22,23]

Table 1.4: Formylation of aromatics with $HCOOCH_3$/HF/BF_3

Run	Substrate[a]	HF (eq.)	BF_3 pressure at 0°C (bar)	Temp (°C)	Time (h)	Conv. (%)	Major Products	Yield (%)
1		40	10	50	6	90		72
2		40	10 2.5	60 40	6 4	95 55		81 51
3		40	10	60	6	15	 	- -
4		40	5 10 10	50 50 30	5 5 5	80 85 20		50 53 13
5		40	5	50	5	90		40
6		40	10	50	4	25	 	15 11
7		40	2.5	40	4	69		49

[a] 1,3 eq $HCOOCH_3$ in every case.

Table 1.4 shows that benzene is formylated rather easily while fluorobenzene yields the corresponding aldehyde with total selectivity for the *para* isomer. Chlorobenzenes show poor reactivity while the formation of chloro-toluene, in a competing reaction, indicates the alkylation potential of methyl formate under the reaction conditions.

2.2 Gattermann-Koch Reaction

Gattermann and Koch[24] were not able to prepare formyl chloride but instead discovered that CO and HCl in the presence of $AlCl_3$ and cuprous chloride behave like the hypothetical formyl chloride and react with toluene in a manner similar to other acid chlorides (Eq 1.13).

$$CH_3C_6H_5 + CO + HCl \xrightarrow[Cu_2Cl_2]{AlCl_3} CH_3C_6H_4CHO \qquad (1.13)$$

The Gattermann-Koch reaction was the first direct aldehyde synthesis reported and found many industrial applications for the preparation of aldehydes from simple aromatic hydrocarbons such as benzene, alkylbenzenes, naphthalenes etc. In their paper they reported passing a 2CO:1HCl (volume) mixture through toluene containing aluminum chloride and cuprous chloride.[25] *p*-Tolualdehyde was obtained in a 50% yield at 20-25°C. The synthesis failed for benzene but when aluminum bromide was used a 90% yield of benzaldehyde was obtained.22[,26] The aluminum chloride-benzaldehyde complex was identified as a suitable catalyst for benzaldehyde synthesis[27] and has been used by Holloway *et al.*[28] to reduce the induction period in the high-pressure synthesis of benzaldehyde with aluminum chloride. Hardy[29] found the optimum temperature to be 35°C for the high-pressure synthesis of benzaldehyde with aluminum chloride. He reported that the aluminum chloride complexes with either benzaldehyde or ethyl ether and function as accelerators. Calculations by Eley and Campbell[30] have shown that the synthesis of benzaldehyde is only rendered thermodynamically favorable by the formation of the benzaldehyde aluminum chloride complex as a stable end-product. This result explained the failure to find a true contact synthesis of benzaldehyde when working at 1atm pressure.[31]

The Gattermann-Koch reaction can be carried out under two major types of conditions *i.e.* at atmospheric pressure where Cu_2Cl_2 is necessary as a promoter or complexing agent and secondly at high-pressure where the presence of Cu_2Cl_2 is not necessary. The Gattermann-Koch aldehyde synthesis is a suitable method for the preparation of simple aromatic aldehydes such as benzaldehyde and tolualdehyde. Formylation of *ortho* and *para*-directing mono-substituted benzenes yield the *para*-isomer as main product. Examples of mono-substituted benzenes converted to the *para*-substituted benzaldehydes include toluene, ethylbenzene, isopropylbenzene, *t*-butylbenzene, *t*-amylbenzene, cyclohexylbenzene, 3-methylcyclohexylbenzene, di-phenyl, fluoro-benzene and chlorobenzene.[32]

In the di-substituted benzene series *o*- and *m*-xylene give the expected products. However, *p*-xylene undergoes isomerisation to furnish 2,4-dimethylbenzaldehyde.[28] The tri-substituted benzene series *i.e.* mesitylene and pseudo-cumene yield normal formylation products.[28,33] Tetralin and di-isopropyltetralin in the naphthalene series are reported to undergo Gattermann-Koch formylation whereas naphthalene itself is formylated in the modified reaction using HF and BF_3 as catalyst.

Carbonylation of halogenated- and alkyl-substituted benzenes in good yield, involving the use of catalytic amounts of aqueous hydrochloric acid, has recently been reported (Table 1.5).[34,35,36]

Table 1.5: Formylation of aromatics using $AlCl_3$, CO and catalytic amounts of aqueous HCl (0.01mol/mol $AlCl_3$)

Entry	Substrate (mmol)	$AlCl_3$ (mmol)	Solvent	CO Press. (psi)	Temp (°C)	Time (h)	Aldehyde	Yield (%)
1	*o*-Xylene (625)	750	Chlorotoluene	110	5	18	3,4-dimethyl-benzaldehyde	88.7
2	Tetralin (640)	770	Chlorotoluene	200	-4 to 0	14	Tetralin-aldehyde	89.4
3	2-fluoro-toluene (4540)	1719.7	4-Me-anisole	550	30	66	4-fluoro-3-me-benzaldehyde	86.7
4	3-fluoro-toluene (4572)	756.6	None	200	60	17	4-fluoro-2-me-benzaldehyde (88.4%) 2-fluoro-4-me-benzaldaldehyde (11.6%)	76.2
5	2-fluoro-*m*-xylene (386)	468	1,2-dichloro-benzene	200	50	16	4-fluoro-3,5-dimethyl-benzaldehyde (73.8%) 3-fluoro-2,4-dimethyl benzaldehyde (26.2%)	68.6
6	3-fluoro-*o*-xylene (789)	468	1,2-dichloro-benzene	200	50	28	4-fluoro-2,3-dimethyl-benzaldehyde (89.1%) 2-fluoro-3,4-dimethyl-benzaldehyde (10.9%)	79.1
7	Fluorobenzene (5203)	1654.9	4-Me-anisole	550	30	89	4-fluorobenzaldehyde	64.3

Few examples of the reaction in the heterocyclic series have been reported. Thiophene yields only traces of thiophene aldehyde, probably as a result of substrate decomposition and polymerization during the reaction. Formylation of dibenzo-*p*-dioxane gives 2-

formyldibenzo-*p*-dioxane, whereas dialkylaminobenzenes cannot be formylated this way as the resultant dialkylaminobenzaldehydes undergo subsequent condensation reactions. Similarly, deactivated aromatics with *meta*-directing substituents can generally not be formylated using the Gattermann-Koch reaction.

Gresham *et al.*[37] effected an interesting modification to the original Gattermann-Koch reaction and by replacing $AlCl_3$ and HCl with anhydrous HF and BF_3. Using a mole ratio of HF:BF_3 equal to 1:1, a CO pressure of 50bar and a reaction temperature of around 0°C, naphthalene, benzene, toluene, *p*-xylene and diphenyl were formylated to the corresponding aldehydes (Table 1.6).

Table 1.6: CO formylation of aromatics using HF and BF_3 as catalyst.

Entry	Substrate	Mols of substrate	Mols of $HF \cdot BF_3$	Temp. (°C)	Time (min)	Press. (bar)	Product	Conv. (%)
1	Toluene	0.75	0.75	-32 to -12	24	14 to 37	*p*-Tolualdehyde	40.6
2	Benzene	0.5	1	-21 to -7	13	8 to 50	Benzaldehyde	19
3	*m*-Xylene	0.5	1	-38 to -14	13	8 to 50	2,4-Dimethyl-benzaldehyde	80
4	*p*-Xylene	0.5	1	-10 to 6	22	8 to 50	2,5-Dimethyl-benzaldehyde	70
5[a]	Naphthalene	0.5	1	-30 to 20	10	8 to 50	α-Naphthaldehyde	74

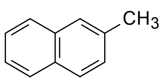
[a] Cyclopentane as solvent

Takezaki *et al.*[38,39,40,41] carried out kinetic studies on the formylation of aromatics, including toluene, *m*-xylene, anisole and phenol with CO in a HF/BF_3 medium under pressurized conditions. Kudo *et al.*[42] investigated the formylation of naphthalene compounds, including 1- and 2-methyl-naphthalene, 1,2,3,4-tetrahydro-2-methyl-naphthalene and 5,6,7,8-tetrahydro-2-methyl-naphthalene with pressurized CO in a HF-BF_3 medium at ambient temperature (Table 1.7).

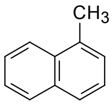
Table 1.7: CO formylation of methyl-naphthalene compounds.[a]

Run	Substrate	Temp. (°C)	Conv. (%)	Total Yield (%)	Aldehyde isomer distribution (%)								
					2	3	4	5	6	7	8	9	10
1	1a	25	93	72	33	17	11	25	14				
2	1b	25	100	70					96	4			
3	1c	25	100	98							49	51	
4	1d	0	100	84									100

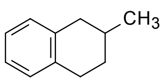
[a] Conditions: Substrate (16mmol), HF(2mol), BF_3(6atm), CO(50atm), 2h.



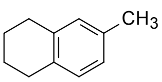
1a



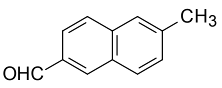
1b



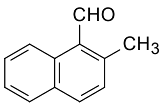
1c



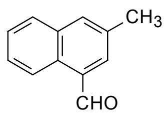
1d



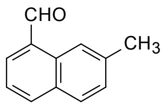
2



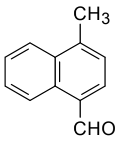
3



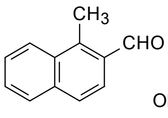
4



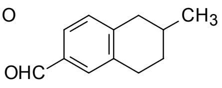
5



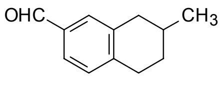
6



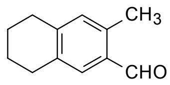
7



8



9



10

In contrast to 1a the reaction of 1b proceeded with high positional selectivity affording the 4-formylated product 6 (96%) together with a small amount of by-product 2-formyl-1-methyl-naphthalene 7 (4%) (Table 6 Run 2). The formylation of 1d under similar conditions produced the 3-formylated compound 10 exclusively in high yield (Table 1.6 Run 4).

Fujiyama *et al.*[43,44] invented a continuous process for producing alkylbenzaldehydes through alkylbenzene-HF-BF_3 complexation and formylation with CO in the same reactor.

An improved process for the formylation of phenol and phenol derivatives using the HF/BF_3/CO system is described by Weisse *et al.*[45] in a patent to Hoechst Aktiengesellschaft (Table 1.8).

Table 1.8: Formylation of hydroxy aromatic compounds using the HF/BF_3/CO system.[a]

Run	Substrate (mmol)	BF_3 (mmol)	Temp. (°C)	Time (h)	Press. (bar)	Aldehyde isomer	Yield (%)
1	Phenol (100)	206	40	1	50	p-hydroxybenzaldehyde	80
						o-hydroxybenzaldehyde	0.1
2	*o*-Cresol (100)	203	40	14	100	4-hydroxy-3-methyl-benzaldehyde	95
3	*o*-Cresol (100)	206	40	22	100	4-hydroxy-3-methyl-benzaldehyde	82
						2-hydroxy-3-methylbenzaldehyde	17
4	2,6-dimethylphenol (100)	213	22	1	110	4-hydroxy-3,5-dimethylbenzaldehyde	98
5	3,4-dimethylphenol (100)	208	40	22	110	2-hydroxy-4,5-dimethylbenzaldehyde	98
6	3,4-dimethylphenol (100)	206	40	22	100	2-hydroxy-4,5-dimethylbenzaldehyde	85
						5,6-dimethyl-2-hydroxybenzaldehyde	4.5
7	5,6,7,8-tetrahydro-2-naphtol (33.7)	73 HF 2.5	40	18	150	3-hydroxy-5,6,7,8-tetrahydro-2-naphthaldehyde	95
8	2-ethylphenol (100)	202	40	1	50	4-hydroxy-3-ethylbenzaldehyde	95

[a] Anhydrous hydrofluoric acid (5mol) except Run 7 used 2.5mol HF.

Other catalysts such as HF-SbF_5,[46,47,48,49,50,51,52], CF_3SO_3H-SbF_5[47,48,53,54] and HSO_3F-SbF_5[55,56,57] have also been used in the formylation of alkyl benzenes with carbon monoxide. Mono and di-formylation of aromatic compounds were studied by Tanaka *et al.*[47,48] in a HF-SbF_5 system in a one-pot reaction (Table 1.9).

Table 1.9: Formylation of aromatics using the HF/SbF_5/CO system.[a]

Run	Substrate	SbF_5:substrate Molar ratio	Time (h)	Yields (%) for Mono-Aldehyde[b]	Yields (%) for Di-aldehyde[c]	Regioselectivity (%) for *ortho*	Regioselectivity (%) for *meta*	Regioselectivity (%) for *para*
1	Toluene	0.5	1	34	-	2.9	0.3	96.8
2	Toluene	20	1	96	-	22.2	0.5	77.3
3	Diphenyl	1	2	97 (0:0:100)	0	0	0	100
4	Diphenyl	2.5	2	18 (0:0:100)	77 (6:8:86)	9	0	91
5	Diphenylmethane	1	2	15 (2:0:98)	2 (0:0:100)	2	0	98
6	Dibenzyl	1	2	38 (48:2:50)	26 (15:9:76)	32	1	67
7	1,3-Diphenylpropane	1	2	50 (2:2:96)	24 (3:6:91)	4	1	95

[a] Conditions: HF (500mmol), SbF_5 (10mmol), substrate (10mmol), under 20atm CO pressure at 0°C unless otherwise stated. [b] isomer ratio of *o-:m-:p-*formyldibenzyl. [c] Isomer ratio of *o,o'-:o,p'-:p,p'*-diformyldibenzyl.

Dibenzyl formylation was carried out by Tanaka *et al.*[48] Various Lewis acids in HF were used to investigate the influence of acidity on regioselectivity. The order of acidity[58] are SbF_5>TaF_5>BF_3>NbF_5 and the results displayed in Table 1.10 indicate that both the *ortho* regioselectivity and aldehyde yield decreased with a decrease in Lewis acidity.

Table 1.10: Influence of Lewis acidity on formylation regioselectivity.[a]

Run	Lewis acid	Yields (%) for Mono-aldehyde[b]	Yields (%) for Di-aldehyde[c]	Regioselectivity (%) for *ortho*	Regioselectivity (%) for *meta*	Regioselectivity (%) for *para*
1	SbF_5	38 (48:2:50)	26 (15:9:76)	32	1	67
2	TaF_5	45 (48:1:51)	26 (12:6:82)	30	1	69
3	BF_3	34 (41:1:58)	18 (9:6:85)	26	1	73
4	NbF_5	28 (23:2:75)	7 (6:6:88)	18	1	81

[a] Conditions: HF (500mmol), Lewis acid (10mmol), dibenzyl (10mmol) under 20atm CO pressure at 0°C for 2h. Regioselectivity% presents the total mono- and dialdehyde regioselectivity. [b] isomer ratio of *o-:m-:p-*formyldibenzyl. [c] Isomer ratio of *o,o'-:o,p'-:p,p'*-diformyldibenzyl.

In an interesting patent of Exxon Chemicals, formylation of alkyl aromatic compounds using Lewis acids ($GaBr_3$, $GaCl_3$, TaF_5, NbF_5 and $NbBr_5$) and CO in the absence of added HF is claimed.[59] Toluene (17% conversion) is formylated to the aldehydes (89% *para*-, 10% *ortho*-, 1% *meta*-tolualdehyde) using a $GaCl_3$:toluene molar ratio of 0.16 and a CO pressure of 74bar at room temperature for 7 hours.

Formylation of aromatic compounds such as benzene, toluene, xylenes, mesitylene, indan, tetralin, fluoro-, chloro- and bromobenzene in HSO_3F-SbF_5 under atmospheric CO pressure at 0°C was achieved in high yields (Substrate:HSO_3F:SbF_5 mol ratio of 20:174:138).[56] Under reduced molar ratios of SbF_5:HSO_3F both formylation and sulfonation take place.

Regioselective formylation of toluene, *m*- and *p*-xylene and mesitylene has been achieved using trifluoromethanesulfonic acid and CO as reagents.[60,61,54] The formation rate of *p*-tolualdehyde increases with increasing amounts of acid to such an extend that a 99.1% yield is obtained with a acid:substrate ratio of 20mol/mol at 25°C and 138bar CO pressure for 30 minutes.[62]

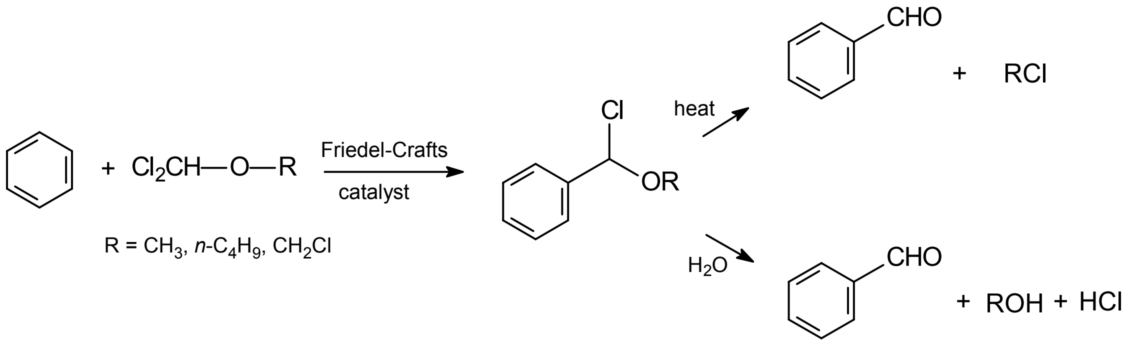
In one of a few examples of aromatic formylation using a solid acid catalyst, toluene was carbonylated to *p*-tolualdehyde in low yield (1.7%) using a calcined mixture of $Zr(OH)_4$, $Cr(NO_3)_3$ and $(NH_4)SO_4$ at 50°C.[63,64]

2.3 Chloromethylene Dibenzoate and Dichloro Alkyl Ethers

Wenzel[65] reported the formation of mesitylaldehyde on the addition of chloromethylene dibenzoate and anhydrous aluminum chloride to a benzene solution of mesitylene followed by a hydrolytic work-up (Eq 1.14). Anisole reacts in a similar manner with chloromethylene dibenzoate to give anisaldehyde (80% yield) while reaction with benzene produces only diphenylcarbinol benzoate

$$(C_6H_5COO)_2CHCl + C_6H_5OR \xrightarrow{AlCl_3} (C_6H_5COO)_2CHC_6H_4OR \xrightarrow{H_2O} ROC_6H_4CHO + 2C_6H_5COOH \quad (1.14)$$

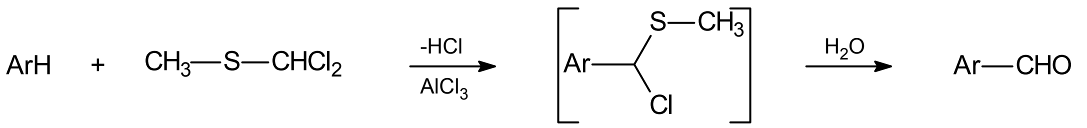
Rieche, Gross and Höft[66] found that dichloromethyl alkyl ethers interact with aromatics and some heterocyclic compounds in the presence of Friedel-Crafts catalysts to give aldehydes in good yields. The intermediates in these reactions are relatively unstable α-alkoxybenzyl chlorides that decompose thermally or on the addition of water to yield aldehydes (Eq 1.15).[67]



(1.15)

The dichloromethyl alkyl ether is generally added to a solution or suspension of the aromatic substrate and the catalyst ($TiCl_4$, $SnCl_4$, $SnBr_4$, $FeCl_3$ or $AlCl_3$) in methylene chloride, *n*-hexane or carbon disulfide.[68,69] Gross, Rieche and Matthey[70] prepared phenolic aldehydes in good yields using this method.

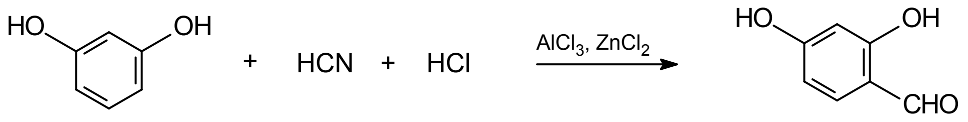
Gross and Mirsch[71] found that reaction of aromatics with dichloro methyl methyl sulfide and aluminum chloride yield aromatic aldehydes. However, the yields were lower compared to using dichloromethyl ethers as formylating agent. Cumene aldehyde was obtained in a 41%, mesityl aldehyde in 49% and 2-naphthyl aldehyde in 52% yield (Eq 1.16).



(1.16)

2.4 Gattermann Synthesis72

As the Gattermann-Koch reaction fails to produce aldehydes from phenol and phenolic ethers, Gattermann and co-workers[73,74] developed an alternative method that produces aldehydes from phenols, phenol ethers and heterocyclic compounds successfully.[75] The method involves the addition of HCN and HCl to the aromatic substrate, with or without the presence of an acidic halide catalyst (Eq 1.17)



(1.17)

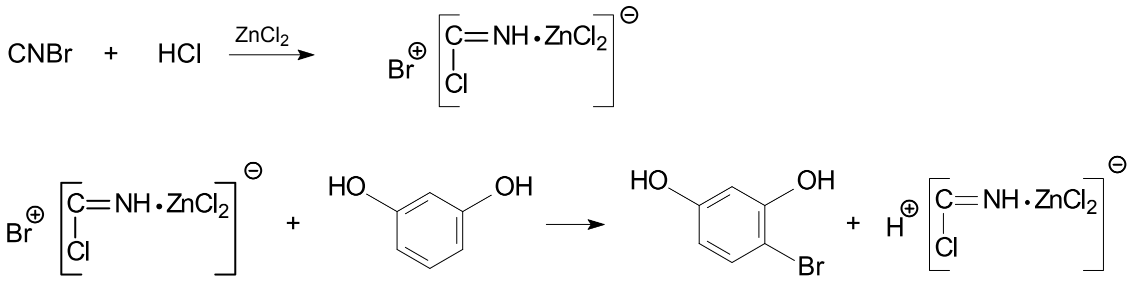
Benzene can be used as solvent as it is un-reactive under the reaction conditions.

Gattermann's reaction was successfully applied by Hinkel *et al.*[76,77,78]to include the formylation of benzene, toluene, acenaphthene, anthracene, diphenyl, naphthalene and hydrindene.

Limitations of the reaction include de-halogenation and halogen exchange in substituted pyrroles,[79] while condensation products are obtained from the formylation of aniline, dimethylaniline and diphenylamine.[80]

Adams[81,82] introduced the relatively safer $Zn(CN)_2$ to replace anhydrous hydrogen cyanide as catalyst in 1923. By passing HCl through a mixture of aromatic substrate and $Zn(CN)_2$ the required HCN was produced *in situ* with $ZnCl_2$ as catalyst. Zinc cyanide is prepared conveniently by mixing an aqueous solution of sodium cyanide and an alcoholic solution of zinc chloride. Niedzielsky *et al.*[83] replaced HCN with the inexpensive and easy to handle NaCN and KCN in most cases where the corresponding HCN + HCl + $AlCl_3$ system is effective.

Karrer[84] introduced cyanogen bromide in place of HCN in the Gattermann reaction in 1919 and prepared resorcinol- and phloroglucinaldehyde in unspecified yields. The excess aromatic substrate acts as a bromine acceptor in the reaction (Eq 1.18).[85]

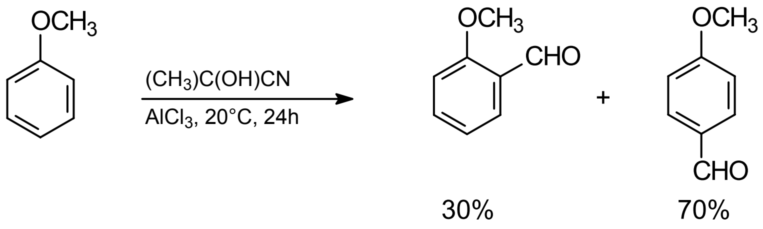


1

(1.18)

The intermediate complex (1) reacts with another aromatic molecule to give the aldehyde upon hydrolysis. Apart from the higher boiling point of BrCN compared to HCN allowing easier handling, the advantage of this method over the conventional Gattermann or Adams technique has not been proved conclusively.

Rahm *et al.*[86] describes the formylation of anisole (50% isolated yield) and alkylated benzenes in fair yield using acetone cyanohydrin (Eq 1.19). Similar to the Gattermann reaction no formylation is obtained with pyrrole and only traces of aldehydes were observed with phenol and furane as substrates.



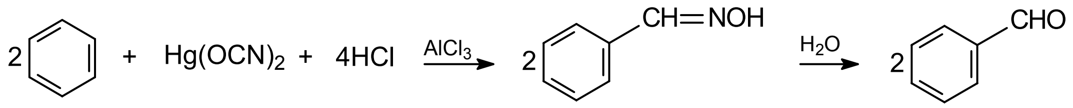
(1.19)

2.5 Formyl Chloride Oxime and Ethoxalyl Chloride

Scholl and co-workers[87] reported that mercury cyanate (fulminate) and HCl reacts with benzene in the presence of $AlCl_3$ to give benzaldoxime and benzonitrile, whereas the aldoxime of resorcinol and by-product dioxybenzonitrile is produced from the same reagents but in the absence of $AlCl_3$ (Eq 1.20).

Scholl discovered that if sublimed aluminum chloride is used as catalyst substituted benzonitriles are the main product, but by using a mixture of sublimed aluminum chloride, crystallized aluminum chloride hexahydrate and dried aluminum hydroxide yields of 65-70% oxime is obtained.

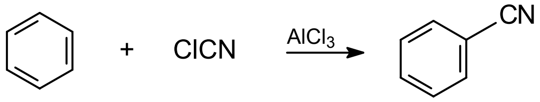
$$Hg(ONC)_2 + 4HCl \longrightarrow 2ClCH{=}NOH + HgCl_2$$



(1.20)

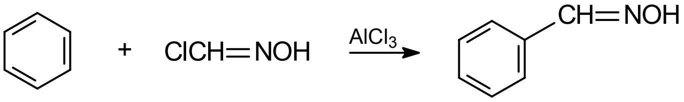
According to Böeseken[88], Nef's oxime is formed as intermediate in the condensation between mercury fulminate and benzene. The oxime is easily dehydrated by $AlCl_3$ to produce cyanogen chloride, which would then react with benzene to form benzonitrile, the by-product in Scholl's reaction (Eq 1.21).

$$\underset{\text{Nef's oxime}}{ClCH{=}NOH} + AlCl_3 \xrightarrow{-H_2O} ClCN$$



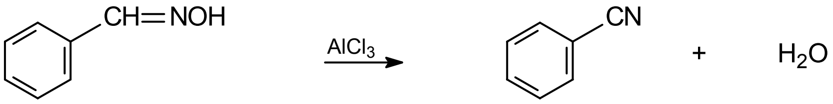
(1.21)

Should the catalyst not be active enough or present in sufficient amounts to effect dehydration of the primarily formed oxime the reaction would proceed to yield the aldoximes obtained by Scholl (Eq 1.22).



(1.22)

Olah69 supports this theory but points out that the formation of benzonitrile could also be possible via benzaldoxime dehydration by $AlCl_3$ (Eq 1.23).



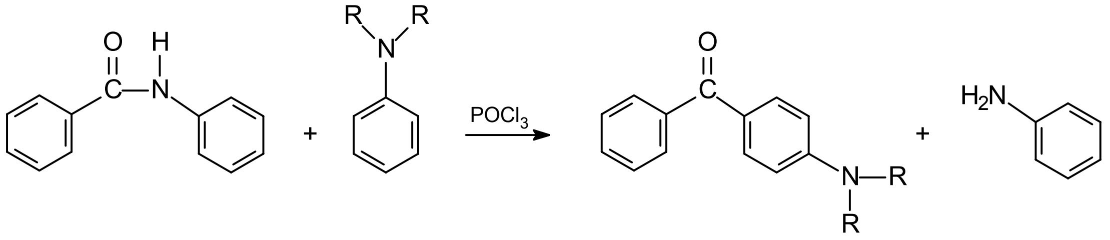
(1.23)

Bouveault[89] found that ethoxalyl chloride condenses with benzene and alkylbenzenes in the presence of anhydrous aluminum chloride to give esters of phenylglyoxalic acids in yields generally in excess of 70%. These could be hydrolyzed and de-carboxylated to the corresponding aldehydes (Eq 1.24).

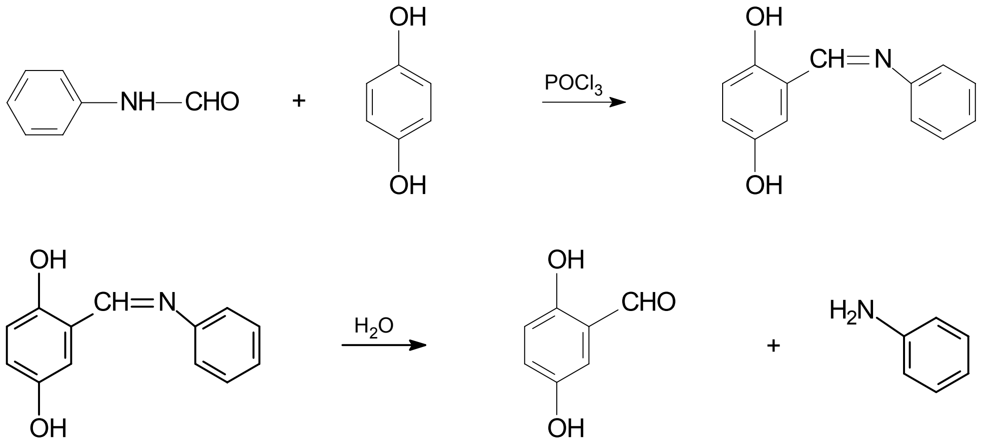
$$C_6H_6 + ClCOCOOC_2H_5 \xrightarrow{AlCl_3} C_6H_5COCOOC_2H_5 \xrightarrow[-CO_2]{H_2O} C_6H_5CHO \qquad (1.24)$$

2.6 Vilsmeier-Haack reaction

The Vilsmeier-Haack synthesis involves the preparation of aldehydes from formamides, (*N*-methylformanilide, dimethylformamide, etc.) as formylating agents in the presence of phosphorus oxytrichloride ($POCl_3$). It is a special application of the acylation reaction that uses carboxylic acid amides and $POCl_3$ for the preparation of ketones.[90] The first acylation of aromatic compounds using carboxylic acid amides and $POCl_3$ was carried out in 1887 in a reaction of benzanilide with *N,N*-dialkylanilines to give the corresponding ketones (Eq 1.25).[91]



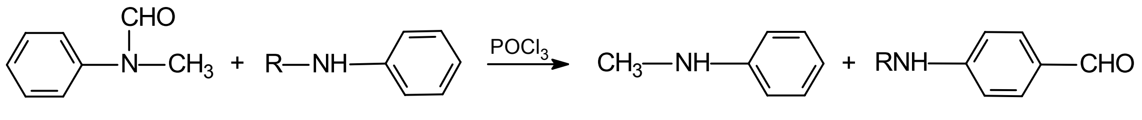
(1.25)



(1.26)

Dimroth and Zoepritz[92] attempted to extend the acylation reaction to aldehyde preparation using formanilide to replace other acid amides in 1902. However, the formylation reaction failed for *N,N*-dialkylanilines, but good yields were obtained in the case of poly-hydroxy aromatics (Eq 1.26).

Vilsmeier and Haack[93] found that *N*-methylformanilide reacts with alkylanilines in the presence of $POCl_3$ to give the corresponding alkyl-aminobenzaldehydes (Eq 1.27).

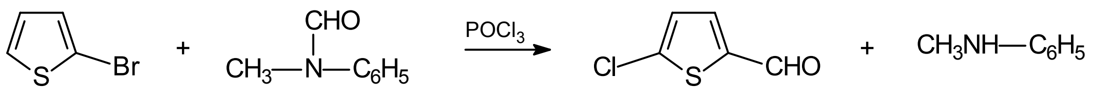


(1.27)

The Vilsmeier and related reactions are amongst the most widely used reactions in organic chemistry. Although the first application of the reaction was for the preparation of poly-oxybenzaldehydes, it was not only extended later to *N*-alkyl- and *N,N*-dialkylaminobenzaldehydes, but also to aldehydes of alkyl- and di-alkylanilines, phenols, naphthols, phenol ethers, naphthol ethers, anthracene, alkylanthracenes, benzanthracene, acenaphthene, azulene and derivatives, pyrene, pyrrole and derivatives, thiophene and derivatives, indole and derivatives and many other compounds.

New formamide derivatives have also been introduced into the reaction and as such dimethylformamide became one of the most frequently used formylating agents of this type. Lambooy[94] found similar activity of dimethylformamide and methylformanilide in the Vilsmeier reaction ($POCl_3$ catalyst).

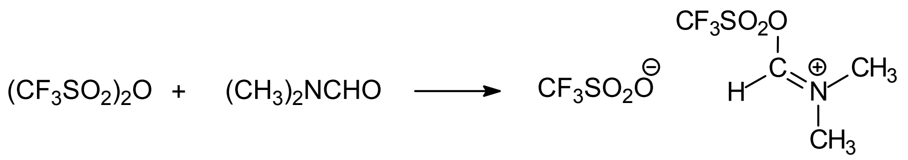
In some special cases the usual method involving the use of $POCl_3$ has to be modified, as halogen exchange takes place in some instances, for example 2-bromothiophene is converted into 5-chloro-thiophene-aldehyde under the standard reaction conditions (Eq 1.28).[95]



(1.28)

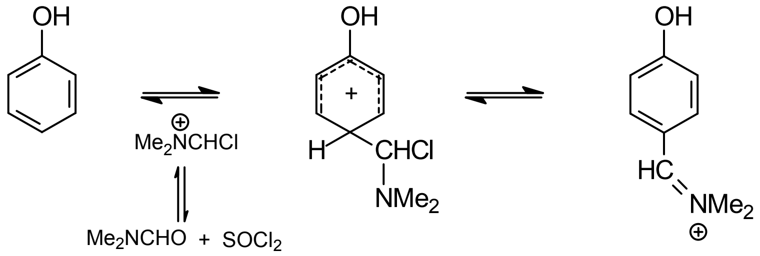
King and Nord[96] found that bromothiophene aldehyde can be obtained in good yield if $POCl_3$ is replaced by $POBr_3$.

Generally, the Vilsmeier reaction fails for benzene, alkylbenzenes and naphthalene.[97] The reaction gives low yields in the case of phenol ethers if the *para*-position is already occupied and fails for highly substituted benzofurans,[98] indicating that the presence of a sufficiently reactive (labile) hydrogen atom on the aromatic ring is necessary for successful application. However, Martinez *et al.*[99] reported the formylation of 1,3,5-trimethylbenzene, naphthalene, acenaphthene, anthracene and phenanthrene in fair yield using the trifluoromethanesulphonic anhydride/dimethylformamide complex (Eq 1.29).



$$(CF_3SO_2)_2O + (CH_3)_2NCHO \longrightarrow CF_3SO_2\overset{\ominus}{O} \quad H{-}\overset{\overset{CF_3SO_2O}{|}}{C}{=}\underset{\underset{CH_3}{|}}{\overset{\oplus}{N}}{-}CH_3 \qquad (1.29)$$

It was established that other reactive halides such as thionyl chloride ($SOCl_2$) and phosgene ($COCl_2$) also react with formamide derivatives and it has been shown that the active formylating species (chloroiminium salts) is similar in each case.[100] The chloroiminium salts react with electron rich aromatics (e.g. hydroxy- and alkoxybenzenes) to afford both *ortho* and *para* aldehydes on hydrolysis (Eq 1.30).[101]



(1.30)

2.7 Formylation of Organometallic Compounds

Aryl- and heteroaryl halides can be converted to organolithium reagents which on reaction with iron pentacarbonyl to give adducts $[ArCOFe(CO)_4]^-$. These generate aldehydes in moderate yields on acidification of the reaction mixture (Eq 1.31).[102]

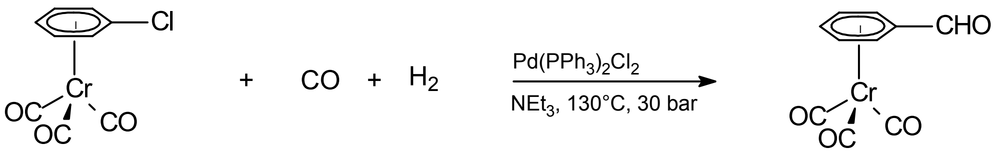
$$ArX \xrightarrow{Li} ArLi \xrightarrow{Fe(CO)_5} \overset{\oplus}{Li}\,[ArCOFe(CO)_4]^{\ominus} \xrightarrow{\overset{\oplus}{H}} ArCHO \qquad (1.31)$$

In the presence of palladium-phosphine complexes such as $Pd(PPh_3)_2X_2$ (X=Cl, Br or I), aryl, heteroaryl and vinylic halides are catalytically converted to aldehydes on treatment with synthesis gas (CO/H_2). Although a stoichiometric amount of tertiary amine is necessary to remove the hydrogen halide formed in the reaction, the yields are generally good, given the somewhat forced conditions (50-100bar at 100-150°C) (Eq 1.32).[103]

$$ArX + R'_3N + CO + H_2 \longrightarrow R'_3NHX + ArCHO \qquad (1.32)$$

Interestingly the formylation of *o*-dibromobenzene yields only benzaldehyde due to reductive removal of the second bromine group. The reactivity of the iodides and bromides are comparable.

With iodo compounds yields are particularly high as they carbonylate more rapidly compared to the chloride and bromide derivatives. This can be ascribed to the greater ease of oxidative addition of the C−I bond to the zero-valent palladium complex. Activation to oxidative addition of the C−Cl bond in chloroarene may be achieved by the formation of the corresponding arenetricarbonyl derivative, after which palladium-catalyzed formylation of the complex proceeds in fair yield at 30 bar CO/H_2 pressure at 130°C (Eq 1.33).[104]



(1.33)

The results obtained for various chloroarenes show that coordination of the tricarbonylchromium group to the chloroarenes enables their carbonylation even in the presence of moderately electron donating groups. The reaction fails in the absence of the tricarbonylchromium group.

Another communication[105] indicates that palladium catalysis can allow low-pressure carbonylation of free chloroarenes to the aldehydes in the presence of the bulky chelating ligand 1,3-*bis*(di-isopropylphosphino)propane (dippp). Very high yields of aromatic aldehydes can be obtained from the corresponding chloroarenes under relatively mild conditions (6bar, 150°C) by using formate ion as the hydrogen source and $Pd(dippp)_2$ as catalyst (Eq (1.34). The Pd(0) complex can be conveniently generated *in situ* under reducing reaction conditions by the use of $Pd(OAc)_2$ and dippp.

$$\mathrm{ArCl} + \mathrm{CO} + \mathrm{HCO_2Na} \xrightarrow[6\ \mathrm{bar},\ 150°\mathrm{C}]{\mathrm{Pd(dippp)_2}} \mathrm{ArCHO} + \mathrm{CO_2} + \mathrm{NaCl} \qquad (1.34)$$

Results of the aryl chloride formylation experiments show that the formylation reaction is specific to the dippp ligand. It is interesting to note that complexes of smaller or larger chelate sizes catalyze de-halogenation rather than formylation and that *ortho* substituents significantly reduce the reaction rate.

Poly(methylhydrosiloxane) (PMHS) as hydrogen donor in the presence of $Pd(PPh_3)_4$ have been successfully employed to formylate aryl and benzyl halides at low carbon monoxide pressure (Eq 1.35).[106]

$$\mathrm{ArI} + \mathrm{CO} + \mathrm{PMHS} \xrightarrow{\mathrm{Pd(PPh_3)_4}} \mathrm{ArCHO} \qquad (1.35)$$

A similar type of reaction uses tributyltin hydride as hydrogen donor in the formylation of a wide variety of substrates including aryl and vinyl iodides, benzylic halides, vinyl triflates and allylic halides under mild reaction conditions (1-3bar CO pressure at 50°C for 2.5-3.5hours) (Eq 1.36).[107,108]

$$\mathrm{RI} + \mathrm{CO} + \mathrm{Bu_3SnH} \xrightarrow{\mathrm{Pd(PPh_3)_4}} \mathrm{RCHO} \qquad (1.36)$$

Arenediazonium tetrafluoroborates (ArN_2BF_4 where Ar=X-C_6H_4; X=H, 2-Me, 3-Me, 4-Me, 4-MeO, 4-MeCO, 2-Ph, 2-Cl, 3-Cl, 4-Cl, 4-Br, 4-I, 3-NO_2 and 4-NO_2), like iodoarenes are converted into aldehydes in good yield by palladium-catalyzed carbonylation in the presence of poly-methylhydrosiloxane (PMHS) at room temperature. The rather slow reaction rate is remarkably enhanced by replacing the polymeric silane with Et_3SiH (Eq 1.37).[109]

$$ArN_2BF_4 + CO + Et_3SiH \xrightarrow{Pd(OAc)_2} ArCHO \qquad (1.37)$$

The formylation of various ArN_2BF_4 compounds were carried out with Et_3SiH or PMHS as reducing agents. Good yields of ArCHO were obtained for all the substituted benzenes, except the 2-NO_2. Reactions with PMHS were slow at room temperature and required 4 to 12 hours for completion.

Halo-naphthalenes, and more particularly 1,6-dibromo-2-methoxynaphthalene (10mmol) are converted into 2-formyl-6-methoxynaphthalene in good yield (80%) with Ph_3P (0.5mmol), $Pd(OAc)_2$ (0.1mmol) and Et_3N (22mmol) in toluene with a 1:1 CO/H_2 molar ratio at 150°C and 40bar pressure.[110]

A recent Japanese patent[111] reported the formylation of 3,5-bis(trifluoromethyl)iodobenzene in DMF with CO:H_2 (1:1) at 1.5MPa in the presence of palladium acetate, tri-*o*-tolylphosphine and triethylamine to furnish 3,5-bis(trifluoromethyl)benzaldehyde in 42% isolated yield.

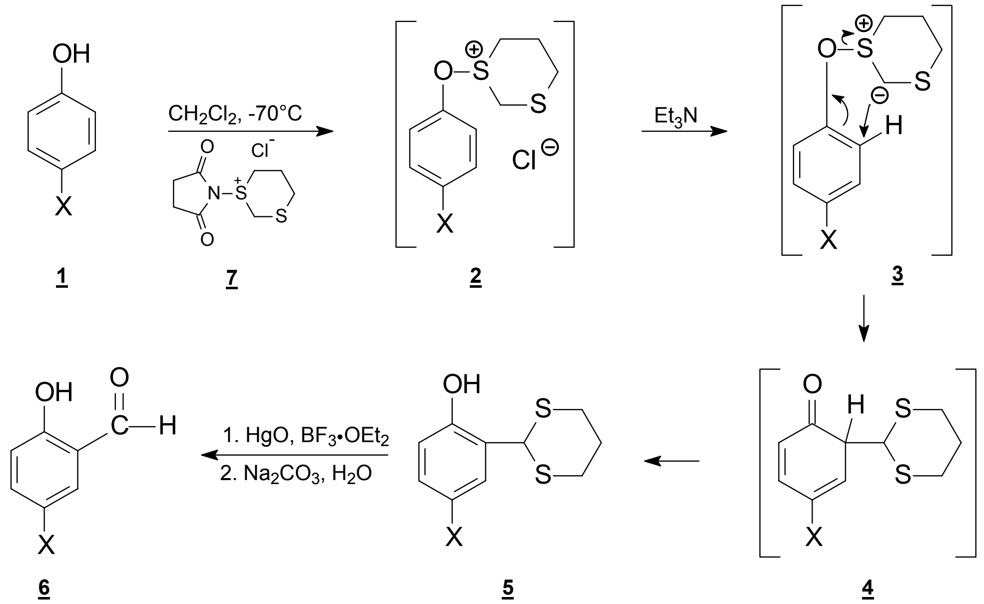
2.8 Selective *ortho* formylation of phenols

Gassman and Amick[112] introduced two methods, both similar to 2,4-rearrangement to effect *ortho* formylation of phenols.[113] Although products were obtained in only moderate (20-45%) yields, the reactions are attractive in effecting exclusive *ortho* substitution (Eq 1.38).

Table 1.11: Formylation of phenolic substrates.[a]

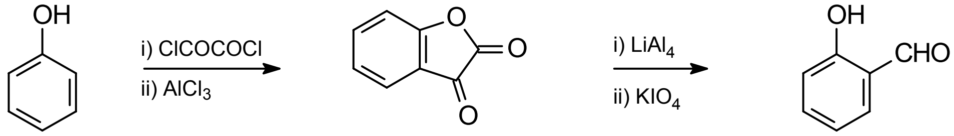
Entry	Substrate with X	% yield of 5[b]	%yield of 6 from 5	Overall %yield of 6 from 1
1	Cl	42	79	33
2	H	30	67	20
3	CH_3	46	76	35
4	OCH_3	39	78	30

[a] 1.7eq of substrate was reacted with 1eq of reagent (7) for 15 min at -70°C followed by the addition of Et_3N. This was followed by a water wash, organic phase separation and drying. [b] %yield of 5 was based on un-recovered phenol. The % conversion ranged from 64-74%.



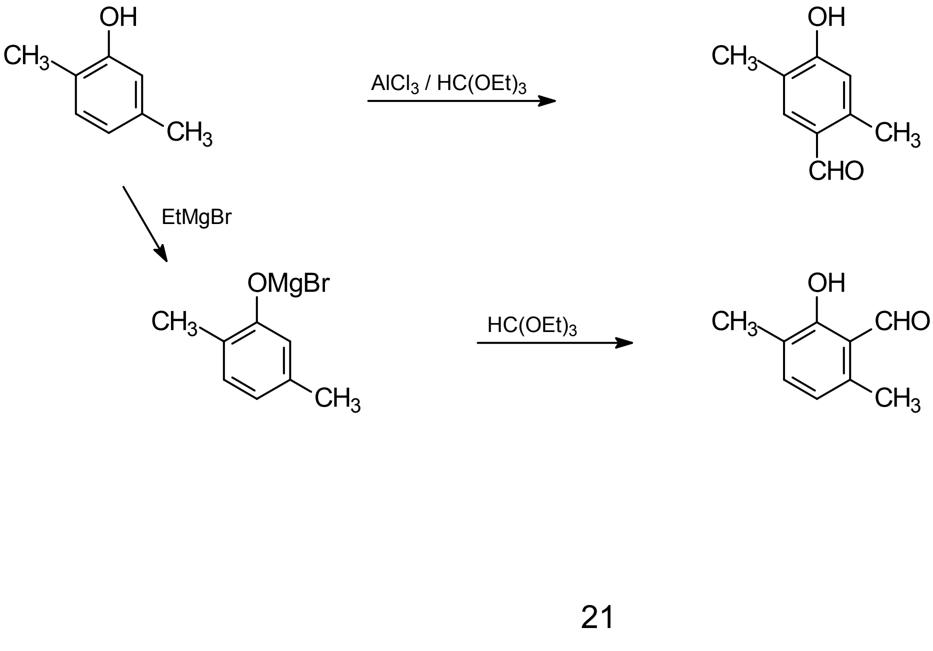
(1.38)

Another *ortho* formylation method that is useful since it is also applicable to phenols containing bulky substituents, involves three stages and furnish products in yields as high as 65%, even with di-*tert*-butyl-phenols (Eq 1.40).[114]



(1.39)

Reaction of phenoxy-magnesium halides with orthoformates is an older method for regioselective *ortho* formylation and gives moderate yields (30-55%) with simple alkyl phenols, however yields are very low when bulky groups, halo, nitro or carboxy substituents are present (Eq 1.40).[115] Contrary to this the formylation of free phenol with aluminum chloride-triethylorthoformate yields the *para*-isomer (Eq 1.40).[116]

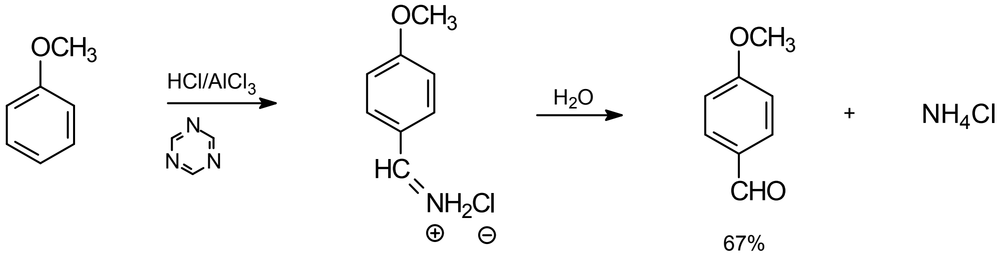


(1.40)

2.9 Duff Reaction

The Duff reaction[117,118] is a formylation method normally used for electron-rich aromatics such as phenols and aromatic amines with the formylating agent being hexamethylenetetramine in the presence of glycerol or acetic acid. Conditions are rigorous and the yields are generally low, but the main value is the occurrence of mainly *ortho* substitution.[119]

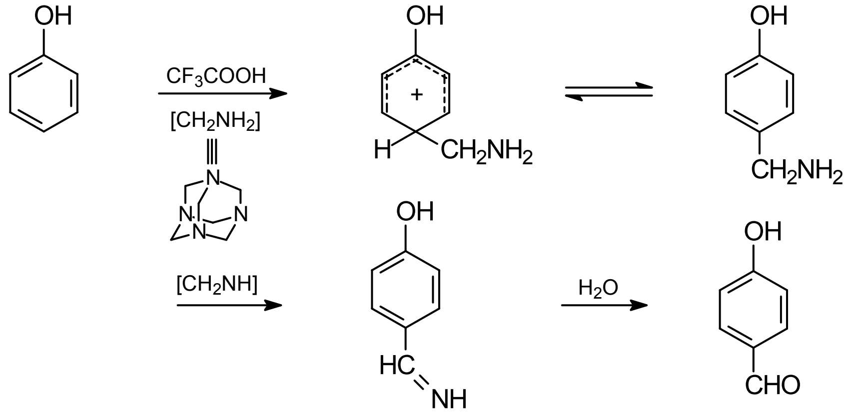
Kreutzberger *et al.*[120,121] used the HCl/$AlCl_3$ system to produce aldehydes in good yield from alkylbenzenes, phenols and phenol ethers (Eq 1.41).



(1.41)

Using this method for substituting aluminum trichloride with hydrofluoric acid, trifluoromethoxy benzene ($C_6H_5OCF_3$) is formylated in excellent yield and *para*-selectivity at 80°C for 5hours.[122]

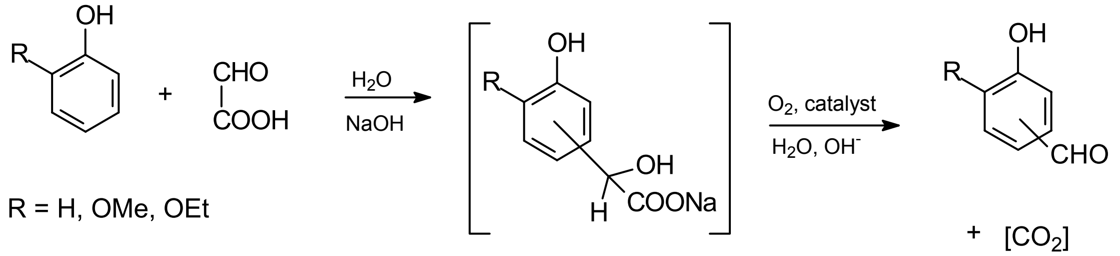
A modern adaptation uses trifluoroacetic acid as catalyst. That allows for formylation of aromatics such as toluene and xylene and even electron deficient phenols such as 2,4-difluorophenol under mild conditions in good yields.[123] A high order of *para* regioselectivity is exhibited even for phenols.[124] The mechanism involves fast aminomethylation followed by a rate-determining dehydrogenation step to the imine similar to that observed in the Sommelet reaction; hydrolysis then gives the aldehyde (Eq 1.42).[125]



(1.42)

2.10 Glyoxylic Acid

Condensation of phenols with glyoxylic acid in basic media to furnish substituted mandelic acids, which yield the corresponding aldehyde on homogeneous catalytic oxidative de-carbonylation. Information regarding the process is mostly confined to patent literature (Eq 1.43).[126,127,128] The conversion of phenol to *p*-hydroxybenzaldehyde was achieved in an overall yield of 66%.

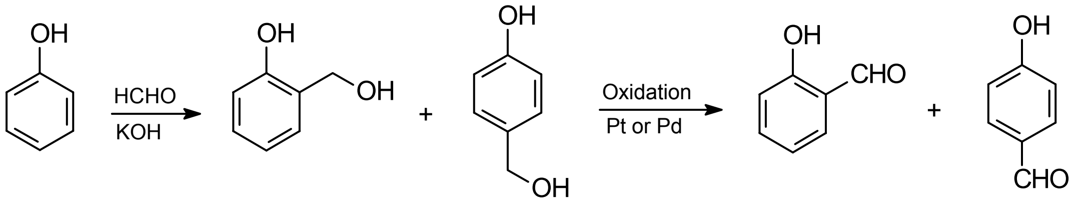


(1.43)

A negative aspect of this reaction is the formation of unwanted di-mandelic acid side-products due to the higher reactivity of the 2- and 4-hydroxymandelic acid compared to phenol. Formation of these side-products is minimized by the addition of excess phenol, generally two or more equivalents.

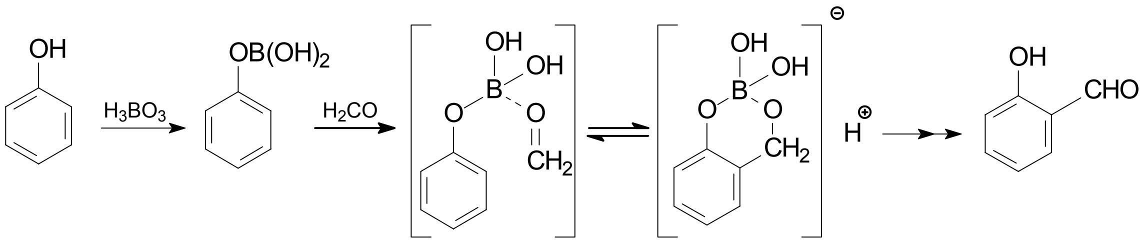
2.11 Saligenin Reaction

A widely used industrial process for the production of salicylaldehyde is the Saligenin process that produces hydroxybenzyl alcohols (o- and *p*-isomers) from the base-catalyzed reaction of formaldehyde with phenol, followed by oxidation using a palladium or platinum catalyst to produce the hydroxybenzaldehyde (Eq 1.44).[129,130,131]



(1.44)

In a refinement of the process the reaction of phenyl metaborate with formaldehyde followed by catalytic oxidation under atmospheric pressure has been reported to give salicylaldehyde directly from phenol without isolation of any intermediary products with aldehyde yields as high as 93% (Eq 1.45).[132]


(1.45)

Casiraghi *et al.*[133] reported that the reaction of paraformaldehyde and magnesium phenoxides, produced from phenol and ethylmagnesium bromide in benzene as solvent in the presence of stoichiometric amounts of hexamethylphosphoric triamide (HMPTA) resulted in formylation exclusively at the *ortho* position. In an improved method by Skattebøll *et al.*[134], phenolic derivatives are formylated selectively *ortho* to the hydroxy group by paraformaldehyde with magnesium dichloride-triethylamine as base in the absence of HMPTA, which is being regarded as a potent carcinogen.

Sartori *et al.*[135] recently synthesised substituted salicylic aldehydes in good yields and excellent selectivities from alkyl substituted phenols with formaldehyde and montmorillonite KSF-Et_3N as heterogeneous catalyst (Eq 1.46 and Table 1.12). Unfortunately recycling of the montmorillonite was problematic, as only one additional cycle yielding 36% of product was possible.

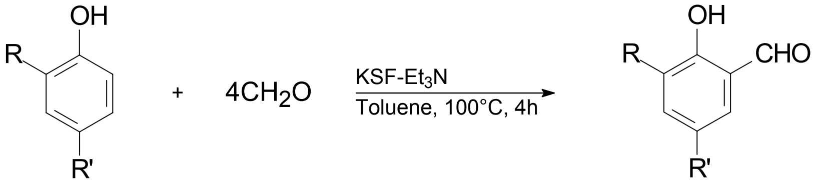
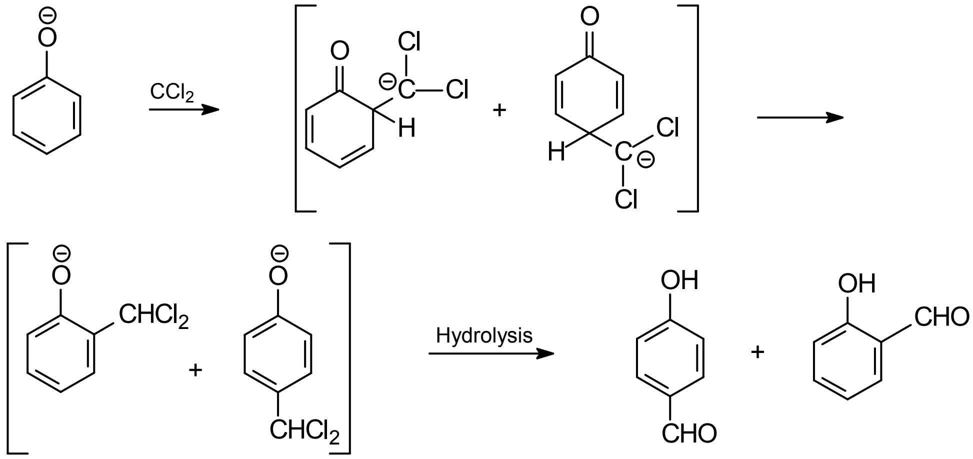

(1.46)

Table 1.12: Synthesis of various salicylic aldehydes.

Run	R	R'	Yield (%)	Conversion (%)	Selectivity (%)
1	$(CH_3)_3C$	CH_3	67	74	90
2	$(CH_3)_3C$	$(CH_3)_3C$	70	79	89
3	CH_3	H	60	65	92
4	$(CH_3)_3C$	H	63	70	90
5	CH_3	$C_{10}H_{21}$	65	71	91

2.12 Reimer Tiemann Reaction

Formylation of phenol with chloroform in a basic medium was first proposed in 1876 by Reimer and Tiemann.[136] Treatment of phenol with aqueous chloroform and aqueous sodium hydroxide results in the formation of benzal chlorides that are rapidly hydrolyzed by the alkaline medium to produce the *ortho* aldehyde predominantly (Eq 1.47).[137,138,139,140]



(1.47)

Several attempts were made to shift the regioselectivity towards the *para*-product. Phenols irradiated in chloroform are converted in the corresponding 2- and 4-substituted benzaldehydes by a mechanism involving attack by the dichloromethyl radical to produce the *para* and *ortho*-aldehyde in 46% and 19% yield respectively.[141,142]

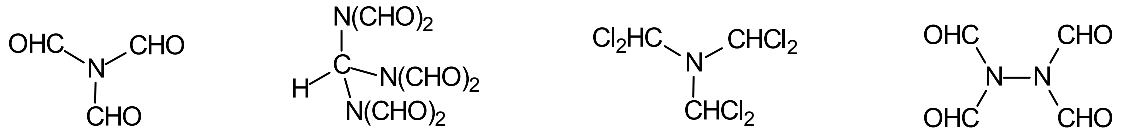
Increased *para* selectivity has been reported by using potassium, cesium and ammonium hydroxide as bases instead of sodium hydroxide.[143] The addition of *B*-cyclodextrin (BCD) afforded 100% *para* selectivity due to formation of a preferentially *para* ternary molecular complex between the phenolate ion, BCD and the dichlorocarbene intermediate.[144,145,146,147] Although the presence of BCD does not enhance the total aldehyde production, it reduces the proportion of other isomeric aldehydes formed in favour of the *para*-product. Recently Zhang *et. al.*[148] reported the synthesis of *p*-hydroxybenzaldehyde from phenol and chloroform in NaOH solution using BCD as catalyst in excellent yield and selectivity (98.6% and 100% respectively).

A modified Reimer-Tiemann reaction was performed using tertiary amines to give the *para*-aldehyde as main product. A total phenol conversion of 74% together with 66% and 7% *para*-and *ortho*-aldehyde yield respectively, were obtained.[149] Similarly, reaction of phenol and $CHCl_3$ in an aqueous alkali solution in the presence of polyethylene glycol (PEG) gave after acid hydrolysis the *para*- and *ortho*-aldehyde in 75% and 16% yield respectively.[150]

2.13 Alternative Reactions

Periasamy[151] *et al.* obtained aldehydes in good yield from poly-cyclic aromatic hydrocarbon radical anions prepared by the addition of sodium to the aromatic hydrocarbon in THF, followed by formylation with carboxylic acid esters or *N,N*-dialkyformamides. Reactions of sodium naphthalenide, -anthracenide and -phenanthrenide with ethyl formate yielded the corresponding aldehydes. Substituted naphthalenes *e.g*. acenaphthene and 2-methylnaphthalene are also formylated using *N,N*-dialkylformamides, but in low yields (20% and 26% respectively).

Kantlehner *et al.*[152] reported the formylation of (hetero)aromatic compounds including unsubstituted and alkyl-substituted aromatics, aromatic ethers, tertiary aromatic amines, fused aromatic rings and thiophenes using new formylating agents (Scheme 1.1) based on formamide derivatives in the presence of Lewis acids.



Triformamide

Tris(diformylamino)-methane

Tris(dichloromethyl)-amine

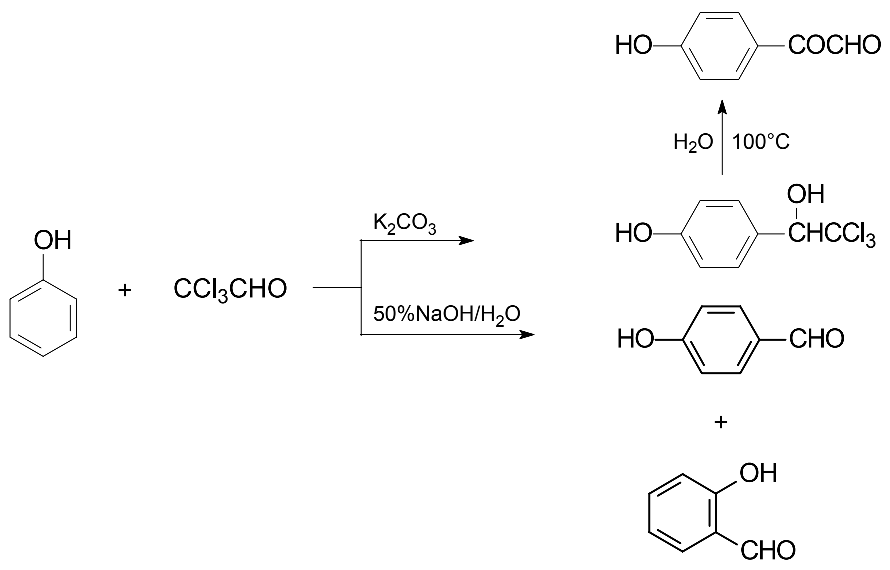
N,N,N',N'-tetraformyl-hydrazine

Scheme 1.1: New formylating agents based on formamide derivatives

Anisaldehyde (96% *p*-isomer, 4% *o*-isomer) was prepared in good yield (62%) from anisole (187mmol) using $ZnCl_2$ (31.6mmol) and tris(dichloromethyl)amine (15.8mmol) under mild conditions (3hours at 60°C). Although excellent selectivities for the *para*-aldehyde were achieved, stoichiometric amounts of the formamide derivative and two equivalents of Lewis acid per formyl group transferred are required, resulting in an *E*-factor (kg of waste per kg product) ranging from 4 to 11.

Methoxy- and methyl substituted naphthalenes are rapidly formylated in moderate yield in the presence of malonic acid and manganese(III) acetate at 70°C.[153] Using the same oxidation conditions, anisole, 1,3-dimethoxybenzene and 1,2,3-trimethoxybenzene were inactive and afforded only small amounts of benzaldehydes and benzoic acids.

The reaction of trichloro-acetaldehyde (chloral) with phenols under base catalysis leads to *p*-hydroxyaryltrichloroethanols together with some *o*-isomer. The corresponding aromatic hydroxy aldehydes are produced after reaction with aqueous alkali or boiling in water (Eq 1.48).[154]


OH
+
CCl3CHO
K2CO3
50%NaOH/H2O
HO
COCHO
H2O
100°C
OH
CHCCl3
CHO
+
OH
CHO

(1.48)

2.14 REFERENCES

[1] Colquhoun H.M., Thompson D.J., Twigg M.V., *“Carbonylation: Direct Synthesis of Carbonyl Compounds”*, Plenum Press, New York and London, **1991**.

[2] Olah G.A., *Friedel-Crafts and Related Reactions*, Vol.3, John Wiley & Sons New York, **1964**.

[3] Nyesmejanov A. N., Kahn E.I., *Ber.*, 67,**1934**, *370*.

[4] Olah G.A., Kuhn S.J., *J. Am. Chem. Soc.*, 82, **1960**, *2380*.

[5] Krauskopf K.B., Rolefson C.K., *J. Am. Chem. Soc.*, 56, **1934**, *2542-2548*.

[6] Olah G., Kuhn S., *Acta Chim. Acad. Sci. Hung.*, 10, **1956**, *233*.

[7] Staab H.A., Datta A.P., *Angew. Chem.*, *Int. Ed. Engl.*, 3, **1964**, *132*.

[8] Devos A., Remion J., Frisque-Hesbain A.M., Colens A., Ghosez L., *J. Chem. Soc. Chem. Commun.*, **1979**, *1180*.

[9] de Haan F.P., *et al.*, *J. Org. Chem.*, 49, **1984**, *3963-3966*.

[10] Nesmejanow A.N., Kahn E.J., *Ber.*, 67, **1934**, *370-373*.

[11] Mashentsev A.I., *J. Gen. Chem.* USSR, 16, **1946**, *203*.

[12] Olah G., Kuhn S., *J. Am. Chem. Soc.*, 82, **1960**, *2380*.

[13] Olah G., Nojima M., Kerekes I., *Synthesis*, **1973**, *487-488*.

[14] Olah G.A., Vankar Y.D., Arvanaghi M., Sommer J., *Angew. Chem. Int. Ed. Engl.*, 18, **1979**, *614*.

[15] Béhal A., *Compt. Rend.*, 128, **1899**, *1460*.

[16] Huffman C.W., *J. Org. Chem.*, 23, **1958**, *727-729*.

[17] Graves G.W., *US. Patent 2135709*, **1938**.

[18] Hurd C.D., Roe A.S., *J. Am. Chem. Soc.*, 61, **1939**, *3355-3359*.

[19] Olah G., Kuhn S., *J. Am. Chem. Soc.*, 82, **1960**, *2380*.

[20] Effenberger F., Mück A.O., Bessey E., *Chem. Ber.*, 113, **1980**, *2086-2099*.

[21] Gross H., Rieche A., Matthey G., *Ber.*, 96, **1963**, *308*.

[22] Saint-Jalmes L., Rochin C., Janin R., Morel M., *Ind. Chem. Libr.*, 8(Roots of Organic Development), Elsevier, **1996**, *325-335*.

[23] Rochin C., Crochemore M., Ratton S., *EP 300861* to Rhône-Poulenc Chimie, **1988**.

[24] Gattermann L., *Ann.*, 347, **1906**, *347-386*.

[25] Gattermann L., Koch J.A., *Ber.*, 30, **1897**, *1622-1624*.

[26] Reformatsky S.N., *J. Russ. Phys. Chem. Soc.*, 33, **1901**, *154*.

---

[27] Demann E., Krebs W., Borchers H., *C.A.*, 33, **1939**, *6257*.

[28] Holloway J.H., Krase N.W., *Ind. Eng. Chem.*, 25, **1933**, *497-502*.

[29] Hardy D.V.N., *J. Soc. Chem. Ind.*, 67, **1948**, *150-155*.

[30] Campbell N., Eley D.D., *Nature*, 154, **1944**, *85*.

[31] Eley D.D., Ph.D. Thesis, Cambridge, England, **1940**.

[32] Blank H.U., Wolters E., Neuner O., *EP 64690* to Bayer A.G., **1982**.

[33] Renner C.A., *US 4195040* to du Pont de Nemours, E.I., **1980**.

[34] Scrivens W.A., Lever J.G., *US 6080892* to Milliken & Company, **2000**.

[35] Anderson J.D.O., Scrivens W.A., *US 6297405* to Milliken & Company, **2001**.

[36] Anderson J.D.O., Scrivens W.A., *US 6300525* to Milliken & Company, **2001**.

[37] Gresham W.F., Tabet G.E., *U.S. Patent 2485237* to E.I. du Pont de Nemours, **1949**.

[38] Takezaki Y, Sugita N., Kudo K., Kubo H., Yasutomi T., Yuasa S., *J. Jpn. Petrol. Inst.*, 7, **1964**, *564-573*.

[39] Takezaki Y, Sugita N., Teranishi H., Kudo K., Inoue A., *Bull. Jpn. Petrol. Inst.*, 9, **1967**, *45-52*.

[40] Takezaki Y, Sugita N., Kudo K., Teranishi H., *Sekign Gakkaishi*, 11, **1968**, *690-695*.

[41] Takezaki Y, Sugita N., *Kogyo Kagaku Zasshi.*, 69, **1966**, *907-912*.

[42] Doko Y., Kudo K., Minami Y., Mori S., Sugita N., *Sekiyu Gakkaishi*, 40, (2), **1997**,*115- 123.*

[43] Fujiyama S., Matsumoto S., *US 4460794* to Mitsubishi Gas Chemical Co, **1984**.

[44] Fujiyama S., Kasahara T., *Hydrocarbon Process*, 57, **1978**, *147-149*.

[45] Weisse L., Neunteufel R., Strutz H., *US 5395978* to Hoechst Aktiengesellschaft, **1995**.

[46] Oelderik J.M., Kwantes A., *GB 1128966* to Shell, **1968**.

[47] Tanaka M., Fujiwara M., Xu Q., Souma Y., Ando H., Laali K.K., *J. Am. Chem. Soc.*, 119, **1997**, *5100-5105*.

[48] Tanaka M., Fujiwara M., Xu Q., Ando H., Raeker T., *J. Org. Chem.*, 63, **1998**, *4408-4412*.

[49] Tanaka M., Fujiwara M., Ando H., Souma Y., *Chem. Commun.*, 2, **1996**, *159-160*.

[50] Tanaka M., Fujiwara M., Ando H., Souma Y., *J. Org. Chem.*, 58, **1993**, *3213-3215*.

[51] Tanaka M., Souma Y., *J. Chem. Soc.*, *Chem. Commun.*, **1991**, *1551-1553*.

[52] Olah G.A., Pelizza F., Kobayashi S., Olah J.A., *J. Am. Chem. Soc.*, 98, **1976**, *296*.

[53] Tanaka M., Fujiwara M., Ando H., *J. Org. Chem.*, 60, **1995**, *2106-2111*.

---

[54] Olah G.A., Laali K., Farooq O., *J. Org. Chem.*, 50, **1985**, *1483-1486*.

[55] Tanaka M., Fujiwara M., Ando H., *J. Org. Chem.*, 60, **1995**, *3846-3850*.

[56] Tanaka M., Iyoda J., Souma J., *J. Org. Chem.*, 57, **1992**, *2677-2680*.

[57] Souma Y., Tanaka M., *Stud. Surf. Sci. Catal.*, 90(Acid-Base Catalysis II), **1994**, *93-96*.

[58] Gillespie R.J., Liang J., *J. Am. Chem. Soc.*, 110, **1988**, *6053*; Olah G.A., Prakash G.K.S., Sommer J., *Superacids*, Wiley-Interscience, New York, **1985**; Kramer G.M., *J. Org. Chem.*, 40, **1975**, *302*.

[59] Saleh R.Y., Becker C., Michaelson R.C., Schlosberg M.C., *WO 00/15593* to Exxon Chemical Patents Inc, **2000**.

[60] Booth B.L., El-Fekky T.A., Noori G.F.M., *Jounal of Chemical Soc. Perkin I*, **1980**, *181- 185*.

[61] Schiraldi D.A., Kenvin J.C., *US 5910613* to HNA Holdings, **1999**.

[62] Sood D.S., Sherman S.C., Iretskii A.V., Kenvin J.C., Schiraldi D.A., White M.G., *Journal of Catalysis*, 199, **2001**, *149-153*.

[63] Bruce D.A., Occelli M.L., Schiraldi D.A., Sood D.S., Sullivan C.E., White M.G., *US 5679867* to Hoechst Celanese Corp., **1997**.

[64] Hamilton L.A., Landis P, Landis P.S., *US 3369048* to Mobil Oil Corp., **1968**.

[65] Wenzel F., Bellak L., *Monatsh.*, 35, **1914**, *965-967*.

[66] Rieche A., Gross H., Höft E., *Ber.,* 93, **1960**, *88-94*.

[67] Straus F., Weber H.J., *Ann.*, 498, **1932**, *101-128*.

[68] Frank W.C., Veazey R.L., Mahurter J.J., Jenkins M.J., Fairfax N.R., *US 5457239* to Union Camp Corp., **1995**.

[69] Lang J.F., *US 5138099* to Mallinckrodt Specialty Chemicals Co., **1997**.

[70] Gross H., Rieche A., Matthey G., *Ber.*, 96, **1963**, *308*.

[71] Olah G.A., Kuhn S.J., *Friedel-Crafts and Related Reactions*, Vol. 3, Interscience Publishers, New York-London-Sydney, **1964**.

[72] Truce W.E., *Org. React.*, 9, **1957**, *37-72*.

[73] Gattermann L., *Ber.*, 31, **1898**, *1149-1152*.

[74] Gattermann L., Beschelmann W., *Ber.*, 31, **1898**, *1765-1769*.

[75] March J., *Advanced Organic Chemistry 3rd Ed.*, John Wiley & Sons, New York, **1985**, *488*.

[76] Hinkel L.E., Ayling E.E., Beynon J.H., *J. Chem. Soc.*, **1936**, *339-346*.

[77] Hinkel L.E., Ayling E.E., Morgan W.M., *J. Chem. Soc.*, **1932**, *2793-2798*.

---

[78] Hinkel L.E., Dunn R.T, *J. Chem. Soc.*, **1931**, *3343-3349*.

[79] Corwin A.H., Kleinspahn G.G., *J. Am. Chem. Soc.*, 75, **1953**, *2089-2095*.

[80] Hinkel L.E., Ayling E.E., Beynon J.H., *J. Chem. Soc.*, **1937**, *778-780*.

[81] Adams R., Levine I., *J. Am. Chem. Soc.*, 45, **1923**, *2373-2377*.

[82] Adams R., Montgomery E., *J. Am. Chem. Soc.*, 46, **1924**, *1518-1521*.

[83] Niedzielsky E.L., Nord F.F., *J. Am. Chem. Soc.*, 63, **1941**, *1462*; *J. Org. Chem.*, 8, **1943**, *147-152*.

[84] Karrer P., *Helv. Chim. Acta*, 2, **1919**, *89-94*.

[85] Houben J., Weyl T., *Methoden der Organischen Chemie*, Vol VII, **1954**.

[86] Rahm A., Guilhemat R., Pereyre M., *Synth. Commun.*, 12(6), **1982**, *485-487*.

[87] Nef J.U., *Ann.*, 280, **1894**, *3017*.

[88] Böeseken J., *Rec. Trav. Chim.*, 24, **1905**, *6-18*.

[89] Bouveault L., *Bull. Soc. Chim. France*, (3), 15, **1896**, *1014-1021*; 17, **1897**, *363*, *940*, *943*, *947*.

[90] Jutz C., *Adv. Org. Chem.*, 9, **1976**, *225-253*.

[91] Farbwerke Hoechst, *German Pat. 44077*, **1887**; *Frdl.*, 2, **1887**, *23*.

[92] Dimroth O., Zoepritz R., *Ber.*, 35, **1902**, *993-997*.

[93] Vilsmeier A., Haack A., *Ber.*, 60, **1927**, *119-122*.

[94] Lambooy J.P., *J. Am. Chem. Soc.*, 78, **1956**, *771-774*.

[95] King W.J., Nord F.F., *J. Org. Chem.*, 13, **1948**, *635-640.*

[96] King W.J., Nord F.F., *J. Org. Chem.*, 14, **1949**, *405-410, 638-642.*

[97] Buu-Hoï N. P., Xuong N.D., Sy M., Lejeune G., Tien B., *Bull. Soc. Chim. France*, **1955**, *1594*.

[98] Naik R. M., Thakor V.M., *J. Org. Chem.*, 22, **1957**, *1630-1633*.

[99] Martinez A.G., Alvarez R.M., Barcina J.O., Cerero S.de la M., Vilar E.T., Fraile A.G., Hanack M., Subramanian L.R., *J. Chem. Soc., Chem. Commun.*, **1990**, *1571-1572*.

[100] Martin G.J., Poignant S., *J.C.S. Perkin II*, **1974**, *642-646*.

[101] Buu-Hoï N.P. et al., Bull. Soc. Chim. France, **1955**, 1594.

[102] Ryang M., Rhee I., Tsutsumi S., *Bull. Chem. Soc. Jpn.*, 37, **1964**, *341-343*.

[103] Schoenberg A., Heck R.F., *J. Am. Chem. Soc.*, 96, **1974**, *7761*.

[104] Mutin R., Lucas C., Thivolle-Cazat J., Dufaud V., Dany F., Basset J.M., *J. Chem. Soc., Chem. Commun.*, **1988**, *896*.

---

[105] Y. Ben-David, M. Portnoy, D. Milstein, *J. Chem. Soc., Chem. Commun.*, **1989**, *1816*.

[106] Pri-Bar, O. Buchman, *J. Org. Chem.*, 49, **1984**, *4009*.

[107] Baillargeon V.P., Stille J.K., *J. Am. Chem. Soc.*, 108, **1986**, *452-461*.

[108] Baillargeon V.P., Stille J.K., *J. Am. Chem. Soc.*, 105, **1983**, *7175*.

[109] Kikukawa K., Totoki T., Wada F., Matsuda T., *J. Organomet. Chem.*,**1984**, *270*, *283*.

[110] Pardigon O., Metz F., *WO 9847848* to Rhodia Chimie, **1998**.

[111] Komata T., Jpn. Kokai Tokkyo Koho JP 2002 12572, **2002**.

[112] Gassman P.G., Amick D.R., *Tetrahedron Letters*, 11, 38, **1974**, *889-892*, *3463-3466*.

[113] Pine S.H., *Org. Reactions*, 18, **1971**, *403-464*.

[114] Zwanenberg D.J., Reynen W.A.P., *Synthesis*, **1979**, *624.*

[115] Casnati G., Crisafulli, Ricca A., *Tetrahedron Letters,* **1965**, *243*.

[116] Gross H., Rieche A., Matthey G., *Chem. Ber.*, 96, **1963**, *308*.

[117] Duff J.C., *J. Chem. Soc.*, **1941**, *547*.

[118] Duff J.C., Furness V.I., *J. Chem. Soc*, **1952.**, *1159*.

[119] Allen C.F.H., Leubner G.W., *Org. Synth. Coll. Vol. 4*, **1963**, *866-869*.

[120] Kreutzberger A., *Arch. Pharm.*, 304, **1971**, *362*.

[121] Kreutzberger A., *Arch. Pharm.*, 302, **1969**, *828*.

[122] Kysela E., Klauke E., *DE 3304202* to Bayer A.G., **1984**.

[123] Weidner-Wells M.A., Fraga-Spano S.A., *Synth. Commun.*, 26(14), **1996**, *2775-2781*.

[124] Smith W.E., *J. Org. Chem.*, 37, **1972**, *3972*.

[125] Ogata Y. *et al.*, *Tetrahedron*, 24, **1968**, *5001*.

[126] Maggioni P., Minisci F., *BE 85993* to Brichima S.P.A., **1979**.

[127] *JP 81 158733* to Mitsui Toatsu Chemicals, **1981**.

[128] Scouteeten A., Christidis Y., *German Offen. 2-944 295*, **1980**.

[129] Eapen K.C., Yeddanapalli L.M., *Makromol. Chem.*, 119, **1968**, *4-19*.

[130] Le Ludec J., *DE 2612844* to Rhône-Poulenc, **1976**.

[131] Marchand P.A.R., Grenet J.B., *US 3321526* to Rhône-Poulenc, **1967**.

[132] Cerveny L. *et al., Chem. Techn.*, 28, **1976**, *557*.

---

[133] (a) Casiraghi G., Casnati G., Cornia M., Pochini A., Puglia G., Sartori G., Ingaro R., *J. Chem. Soc., Perkin Trans. I*, **1978**, *318*; (b) Casiraghi G., Casnati G., Puglia G., Sartori G., Terenghi G., *J. Chem. Soc., Perkin Trans. I*, **1980**, *1862.*

[134] Hofsløkken N.U., Skattebøll L., *Acta Chemica Scandinavica*, 53, **1999**, *258-262*.

[135] Bigi F., Conforti M.L., Maggi R., Sartori G., *Tetrahedron*, 56, **2000**, *2709-2712*.

[136] Reimer K., Tiemann F., *Ber*., 9, **1876**, *824-828*.

[137] Wynberg H., *Chem. Rev*., 60, **1960**, *169-184*.

[138] Thoer A., Denis G., Delmas M., Gaset A., *Synthetic Commun*., 18, **1988**, *2095-2101*.

[139] Annick T. *et al*., *WO 8700167* to Institut National Polytechnique de Toulouse, Fr., **1987**.

[140] Fumio T., *JP 05271141* to Mitsui Toatsu Chemicals, **1993**.

[141] Kemp D.S., *J. Org. Chem*. 36, **1971**, *202*.

[142] Al-Rawi J.M.A., Bloxsidge J.P., O'Brien C., Caddy D.E., Elvidge J.A., Jones J.R., *J.C.S. Perkin II*, **1974**, *1635-1638*.

[143] Brady O.L., Jakobovits J., *J. Chem. Soc*., **1950**, *767-777.*

[144] Komiyana M., Hirai H., *J. Am. Chem. Soc*., 105, **1983**, *2018*.

[145] Divakar S. *et al*., *Indian Journal of Chemistry*, Section B-Organic Chemistry Including Medicinal Chemistry, 31, 543, **1992**.

[146] Ravichandran R., *Journal of Molecular Catalysis A: Chemical*, 130, **1998,** L205-L207.

[147] Ishii H., Takahashi R., Mimura Y., Inoue Y., *Tokyo Kogyo Koto Senmon Gakko Kenkyu Hokokusho*, 22, **1990**, *95-97*.

[148] Ding G., Zhang G., *Guilin Gongxueyuan Xuebao*, 21(4), **2001**, *392-393*.

[149] Xinteng D. *et al*., *Kexue Tongbao*, 32, 860, **1987**.

[150] Yongita Y. et al., Hunan Shifan Daxue Ziran Kexue Xuebao, 12, 318, **1989**.

[151] Periasamy M., Reddy M.R., Bharathi P., *Synth. Commun*. 29(4), **1999**, *677-683*.

[152] Bagno A., Kantlehner W., Scherr O., Vetter J., Ziegler G., *Eur. J. Org. Chem*., 15, **2001**, *2947-2954*.

[153] Nishino H., Tsunoda K., Kurosawa K., *Bull. Chem. Soc. Jpn*, 62, **1989**, *545-550*.

[154] Luknitskii F.I., *Chemical Reviews*, Vol. 75, No. 3, **1975**, *259-289*.

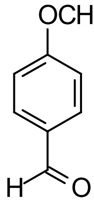
CHAPTER 2

CO as reagent in the formylation of aromatic compounds

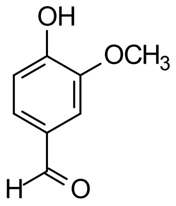
1. INTRODUCTION

Sasol, through its various divisions endeavours to expand its current business in a number of ways. One such strategy concentrates on the beneficiation of current commodity feedstreams having marginal value into high-value chemicals via cost-effective processes.

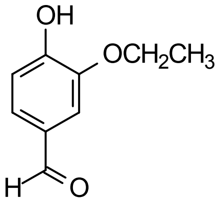
Hydroxy- and alkoxy aldehydes are important products that are primarily used in the flavour and fragrance market and as intermediates in the manufacturing of agrochemicals, pharmaceuticals, cosmetics and the electroplating industry.[155] *Para*-anisaldehyde or PAA (1), *ortho*- and *para*-hydroxybenzaldehyde, vanillin (2), ethyl vanillin (3), protocatechuic aldehyde (4), veratraldehyde (5) and piperonal (6) are the most important products. Merisol, a division of Sasol having excess to phenolic and cresylic feedstreams, expressed interest in the possible production of PAA as a high-value fine chemical. However, as a new aldehyde producer, market penetration could be extremely difficult and a competitive advantage is required over the rest of the producers. This can be realised in a number of ways, one of which includes a reduced product price. However, this will necessitate amongst others, cheaper feedstock and reagent costs as well as an economically feasible process compared to the competitor's.



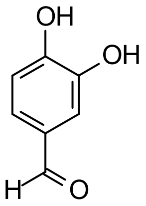
1



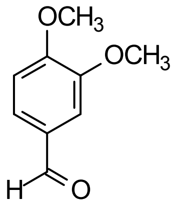
2



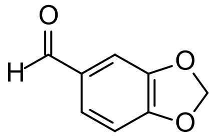
3



4

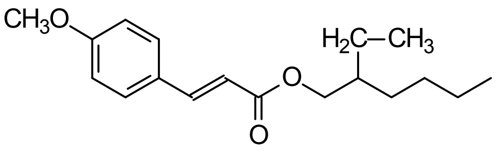


5



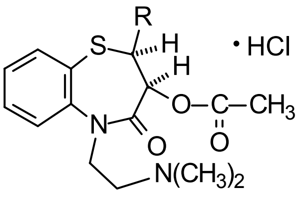
6

PAA is an important precursor in the manufacture of OMC [2-ethylhexyl-p-methoxy-cinnamate (7), a UV adsorber in sunscreens] as well as of various pharmaceuticals, e.g., the coronary therapeutic Diltiazem (8) and chemotherapeutics like trimethoprim (9).[156]

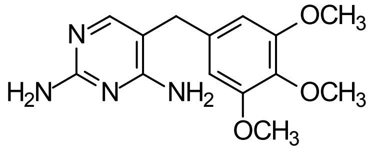


R = $C_6H_5OCH_3$

7

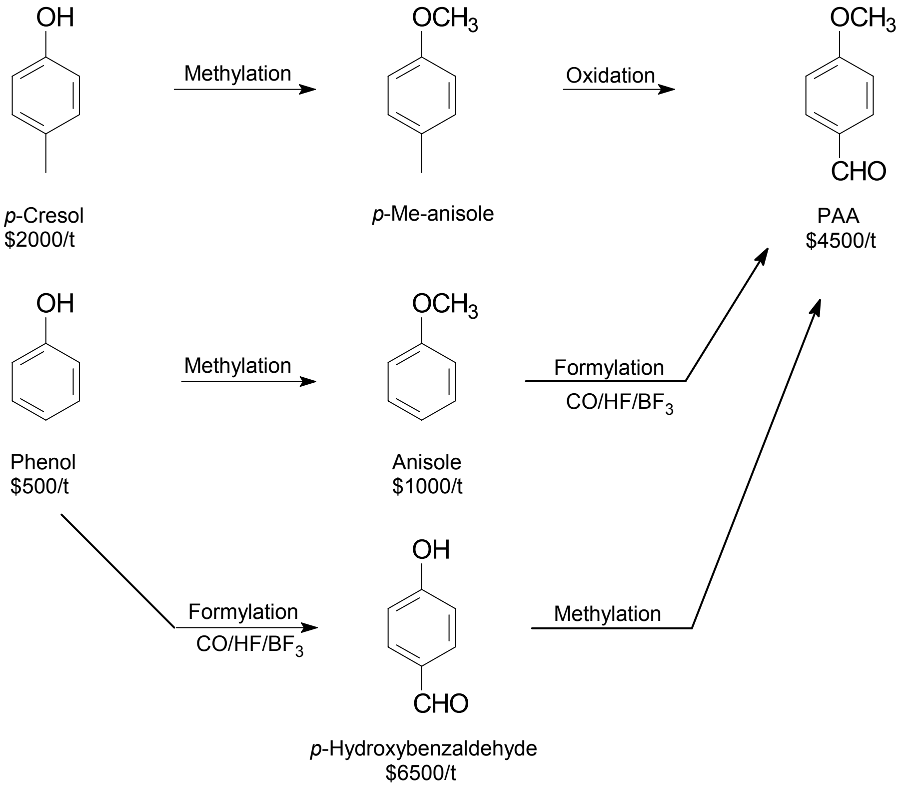


8



9

PAA is mainly produced in a two-step process involving *O*-methylation of *p*-cresol to *p*-methylanisole followed by benzylic oxidation to the corresponding aldehyde using manganese dioxide and sulphuric acid (Scheme 2.1).[157] Other industrial processes employ liquid-phase oxidation in the presence of cobalt catalysts[158] and electrochemical oxidation in the presence of lower aliphatic alcohols *via* the corresponding anisaldehyde dialkyl acetal.[159] These processes suffer from the drawback of either producing a large amount of salt effluent that needs to be disposed of and/or making use of expensive feedstock as starting material. In a patent by Hoechst Aktiengesellschaft, phenol was claimed to be converted to *p*-hydroxybenzaldehyde in high yield (80%) by formylation using anhydrous hydrofluoric acid, boron trifluoride and carbon monoxide under mild temperature.[160] Although this process employs reagents, especially hydrogen fluoride and boron trifluoride in stoichiometric amounts that are considered harmful to human health and the environment, the one-step nature and relatively cheap feedstock utilised in the process appears to be economically beneficial.



Scheme 2.1: Comparison of the current industrial PAA process from *p*-cresol against possible cheaper alternative processes from phenol or anisole.

If this technology could be applied to the production of PAA from anisole, having a selling price of almost half that of *p*-cresol, in a catalytic way, this would give Merisol the competitive advantage required to enter into the market (Scheme 2.1).

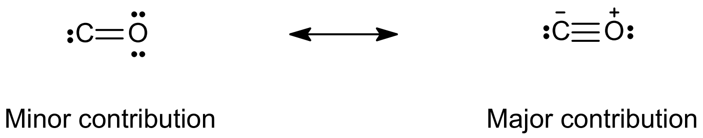
Furthermore, carbon monoxide is produced in abundance as side-product in Sasol's Fischer-Tropsch water-gas shift reaction, making it a cheap and subsequently attractive formylating agent. Thus, using CO as reagent in the formylation process will result in further reduced production costs.

2. FORMYLATION UTILIZING HF/BF$_3$ AS CATALYST

Although many processes using a variety of reagents other than CO exist for formylation of aromatic compounds, hydrogen fluoride and boron trifluoride are the only catalyst system claimed to produce hydroxy aldehydes effectively from phenol derivatives in conjunction with CO as formylating agent. In spite of the fact that HF and BF$_3$ are regarded as environmentally unfriendly gasses, their catalytic usage could be beneficial with minimal effect on the environment.

2.1 The Carbon Monoxide Molecule

The carbon monoxide molecule can be described in conventional valence bond terms as having two canonical forms; one having the carbene-like structure in which divalent carbon is linked to oxygen by a double bond and the other a dinitrogen-like form, in which both atoms carry a lone pair and are linked by a triple bond [Eq (2.1)].



$$:C{=}\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}} \longleftrightarrow :\overset{-}{C}{\equiv}\overset{+}{O}: \qquad (2.1)$$

The chemistry of carbon monoxide is, however, more often rationalised on a qualitative molecular orbital (MO) basis rather than in terms of its valence bond description. Figure 2.1 depicts the energy level MO diagram for carbon monoxide with occupied orbital energies determined by photoelectron spectroscopy. An approximate correlation can be made between valence bond and MO descriptions through assignment of the filled orbitals 4σ and 5σ^* to lone pairs on oxygen and carbon respectively and orbitals 3σ and 1π to the triple bond.[161]

Thus, carbon monoxide is a metastable molecule that is almost inert under mild conditions, but becomes very reactive when subjected to high pressure or elevated temperature and can be easily activated by catalysts.

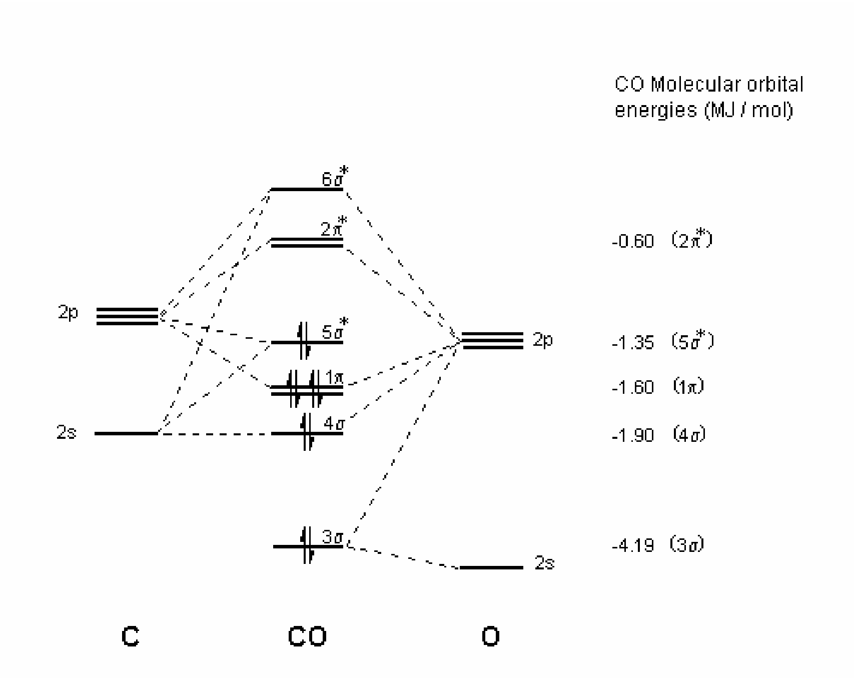


Figure 2.1: Molecular orbital description of carbon monoxide

2.2 Properties of hydrogen fluoride

The unique physical properties of hydrogen fluoride allow it to be an excellent solvent for a variety of organic and inorganic solutes. Being a liquid at convenient temperature and pressure (bp 19.5°C at 1atm) allows for greater ease of handling compared to other gasses *e.g.*, hydrogen chloride. It has a lower vapour pressure (363.8 mmHg at 0°C), longer liquid range (102.9 atm°C) and a higher dielectric constant (175 at –73°C and 84 at 0°C) that is characteristic of hydrogen-bonded liquids when compared to the other hydrogen halides.[162] Although a monomeric structure is formed above 80°C, equilibrium between HF and its hexamer, $(HF)_6$, with a puckered ring structure is obtained at lower temperatures. The crystal structure consists of planar zigzag chain polymers with an F−H−F distance of 2.55Å and an H−F−H angle of 120° (Figure 2.2).[163]

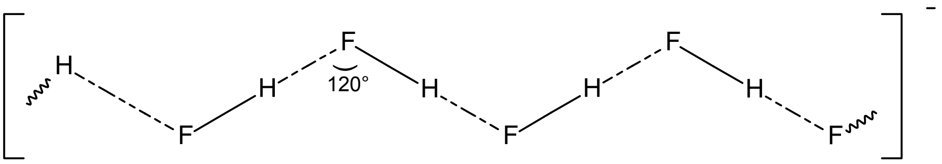


Figure 2.2: Structure of crystalline hydrogen fluoride.

The self-ionisation equilibria or auto-protolysis of liquid HF are demonstrated in Eq (2.2). The high Hammett acidity function[164] of the anhydrous acid ($-H_0=11$)[165] compared to HCl can be partly attributed to the formation of stable hydrogen-bonded anions *e.g.*, HF_2^-, $H_2F_3^-$ etc.

$$2HF \rightleftharpoons H_2F^{\oplus} + F^{\ominus} \qquad K \sim 10^{-10}$$

$$F^{\ominus} + HF \rightleftharpoons HF_2^{\ominus} \overset{HF}{\rightleftharpoons} H_2F_3^{\ominus} \text{ etc.} \qquad (2.2)$$

The acidity of anhydrous hydrofluoric acid can be adjusted conveniently over a wide range: On addition of alkali metal fluorides the acidity is reduced; while the inverse effect is obtained on addition of BF_3. In the latter case acidity is enhanced by removal of fluoride ions [Eq (2.3)]:[166]

$$BF_3 + F^{\ominus} \longrightarrow BF_4^{\ominus} \qquad (2.3)$$

Hydrogen fluoride is not only known to be a pollutant harmful to plants having the strongest phytotoxic action of all gases, but also for causing bony fluorosis, a human disease associated with extended periods of exposure. Finally, it is incompatible with glass with which it reacts to form the highly stable SiF_4.[167]

2.3 Properties of boron trifluoride

Boron trifluoride (bp –99°C) is one of the most powerful acceptor molecules known and has a strong tendency to combine with atoms having unshared electron pairs to increase its six outer shell electrons to a stable electronic configuration of eight, thus forming a coordinate covalent bond.[168] It is a gas at room temperature and has trigonal symmetry with X−B−X angles of 120°. Mootz *et al.*[169] reported a crystal structure for the meta-stable phase of BF_3 at –131°C in which the boron atoms are trigonal prismatic with $B-X_{eq}$ bond lengths of 126 - 131Å and $B-X_{ax}$ bond lengths of 268 - 271Å.

The chemistry of trivalent boron halides is dominated by the unfilled boron p_z-orbital allowing the ready forming of adducts with a variety of electron donors, thus functioning as Lewis acids. The relative strengths of boron halides as Lewis acids are in the order $BBr_3 > BCl_3 \geq BF_3$, which is opposite to that expected on either steric grounds or on the basis of electronegativity. This can partially be explained in terms of boron-halogen π-bonding. Overlap of the un-filled boron p_z-orbital with the non-bonding filled orbitals on the halides reduces the electron acceptor ability of the molecule, but increases the strength of the B−X bonds. The boron-halide p_z overlap decreases with increasing size of the halide resulting in the B−F bond in BF_3 being one of the strongest single bonds known. Boron trifluoride chemistry is dominated by Lewis acid-base reactions whereas halide displacement reactions predominate in BBr_3 and BI_3 adducts, which is the cause of this relative instability.[170,171,172]

The formation of coordination compounds between boron trifluoride and organic oxy-compounds are well known and a rule announced by Landolph[166] states that boron trifluoride combines in a definite mole to mole ratio with aldehydes and ketones.

2.4 Properties of the active HF/BF_3 catalyst

Solutions of BF_3 in hydrogen fluoride are commonly known as superacids as their acidity are higher compared to conventional strong acids such as sulphuric acid.[173,174] Industrial applications of this system include hydro depolymerisation of coal to liquid hydrocarbons,[175] the preparation of carbon fibre[176] and isomerisation[177] of saturated straight chain hydrocarbons to highly branched hydrocarbons which can be added to fuel to increase the octane number. HF/BF_3 is also frequently used in Friedel-Crafts alkylation reactions[178]. The main advantages of the system being the high stability of HF and BF_3 as well as the easy recovery of both gasses due to their gaseous nature at room temperature.[179]

Studies on the interaction between hydrogen fluoride and boron trifluoride have been documented. According to Sharp[180], reaction to produce HBF_4 is unlikely unless an electron donor is present to solvate the proton. McCaulay *et al.*[181,182] investigated the HF/BF_3 system and did not find any sign of interaction in the absence of a base. Vapour pressure measurements involving individual xylene isomers indicated all the isomers react rapidly and reversibly with HF/BF_3 to form a complex in which the mol ratio of boron trifluoride to hydrocarbon is one. They postulated that the reaction of complex formation is the sum of two reaction steps [Eq (2.4)].

$$\begin{array}{lcl} \mathrm{Ar} + \mathrm{HF} & \rightleftharpoons & \mathrm{ArH^+} + \mathrm{F^-} \\ \mathrm{F^-} + \mathrm{BF_3} & \rightleftharpoons & \mathrm{BF_4^-} \\ \hline \mathrm{Ar} + \mathrm{HF} + \mathrm{BF_3} & \longrightarrow & \mathrm{ArH^+BF_4^-} \end{array} \qquad (2.4)$$

Hughes *et al.*[183] investigated the solubility of boron trifluoride (bp –99°C) in hydrogen fluoride over a wide temperature range (Table 2.1). The rapid increase in solubility with decreasing temperature below the critical temperature (between 4.4 and –26°C) suggests possible HF/BF_3 coordination.

Table 2.1: Solubility of gaseous boron trifluoride in liquid hydrogen fluoride

Temp (°C)	Partial Pressure BF_3 (psi)	Mole % BF_3 in solution
-81	14.7	8.76
-74	14.7	7.46

Temp (°C)	Partial Pressure BF_3 (psi)	Mole % BF_3 in solution
-73	14.7	4.96
-26	14.7	3.29
4.4	14.7	0.64
20.5	14.7	0.51
43.3	14.7	0.34

Kilpatrick *et al.*[184] postulated the equilibrium reaction (Eq 2.5) from the addition of BF_3 to HF.

$$BF_3 + 2HF \rightleftharpoons BF_4^- + H_2F^+ \qquad (2.5)$$

This follows from the auto-protolysis reaction equilibrium of hydrofluoric acid [(Eq2.6)], which is displaced to the right by boron trifluoride by the reaction (Eq 2.7).

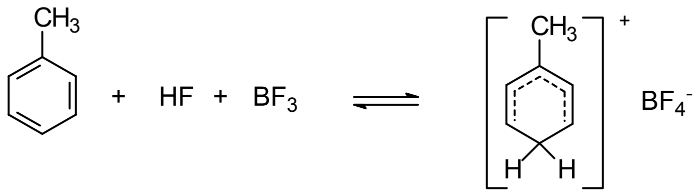
$$2HF \rightleftharpoons H_2F^+ + F^- \qquad (2.6)$$

$$BF_3 + F^- \rightleftharpoons BF_4^- \qquad (2.7)$$

According to Olah *et al.*,[185] boron trifluoride ionises in anhydrous HF and the stoichiometric compound exists only in excess HF or in the presence of suitable proton acceptors *e.g.* NaF [Eq (2.8)].

$$BF_3 + 2HF \rightleftharpoons BF_4^- + H_2F^+ \qquad (2.8)$$

Olah *et al.*[186,187] was successful also in isolating the boron trifluoride-hydrogen fluoride complexes of the methylbenzenes: toluene, *m*-xylene, mesitylene and *iso*durene and determined their respective melting points and specific conductivities [Eq (2.9)].



(2.9)

Kim *et al.*[188] studied $BF_3 + (HF)_{1\text{-}7}$ clusters using density functional theory calculations to elucidate the superacidity associated with HF/BF_3 systems. They found that $BF_3 + (HF)_{1\text{-}3}$ are essentially weakly bound Van der Waals complexes due to long intermolecular B-F bond distances. In $BF_3 + (HF)_4$ and $BF_3 + (HF)_5$ the B-F bond distance is significantly shortened so that ring structures are adopted that are stabilised by multiple hydrogen bonding between hydrogen and fluorine. The B-F bond distance is further shortened when two additional HF molecules are bound to BF_3 through hydrogen bonding, indicating both increased stability and acidity of the system through the addition of excess HF. Although gas phase interaction between BF_3 and HF is weak, the fluorine atom transfer reaction can occur in a BF_3/HF solution to produce the solvated BF_4^- ion and an H_2F^+ ion, provided that a sufficient number of HF ligands are available.

Acidity measurements of a 7mol% BF_3 solution in hydrogen fluoride using electro-chemical determinations indicated a Hammett acidity ($-H_o$) of 16.6, classifying it as a super acid (Fig 2.3).[189]

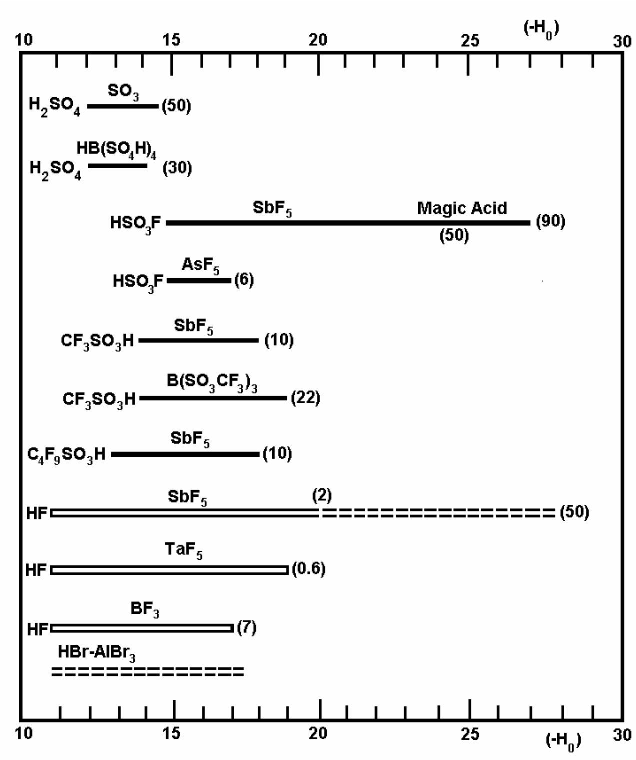


Figure 2.3: Acidity ranges for the most common superacids. The solid and open bars have been measured using indicators, while the broken bars are estimated by kinetic measurements.

The highest acidity level measured according to the H_o acidity scale is around -27 for 90% SbF_5 in HSO_3F. However, based on rate measurements in superacidic reactions the fluoroantimonic acid system is predicted to be even stronger [Fig 2.3]. Similar to BF_3 in HF, SbF_5 also ionises in dilute solutions to produce the H_2F^+ cation. The lower Hammett acidity of the HF/BF_3 system compared to SbF_5 and TaF_5, can be attributed to the lower concentration of the H_2F^+ cation produced in the HF/BF_3 system. The HF/BF_3

system is however strong enough to protonate many weak bases and is an efficient and widely used catalyst.[190,191]

Although tetrafluoroboric acid (HBF_4) is believed to be the superacid responsible for CO formylation, it has never been isolated.[192] Gay-Lussac *et al.*[193] prepared it by passing an excess of boron trifluoride into cold water with crystallisation of boric acid upon cooling [Eq (2.10)].

$$4BF_3 + 3H_2O \longrightarrow 3HBF_4 + H_3BO_3 \qquad (2.10)$$

Fischer *et al.*[194] prepared HBF_4 from boric acid and a 50% aqueous solution of hydrofluoric acid, while Berzelius[166] used concentrated hydrofluoric acid. Wamser[195] has shown that the reaction proceeds in at least two steps, the first being the rapid formation of the hydroxy moiety [Eq (2.11)], followed by the slow formation of HBF_4 [Eq (2.12)].

$$H_3BO_3 + 4HF \longrightarrow HBF_3OH + HF + 2H_2O \qquad (2.11)$$

$$HBF_3OH + HF \rightleftharpoons HBF_4 + H_2O \qquad (2.12)$$

Concentrated aqueous- and diethyl ether solutions of HBF_4 are well known and commercially available. Our attempts to isolate the superacid from these solutions *via* reduced pressure distillation were not successful and is indicative of the strong complex formation between the acid and the oxygen moiety of ether and water.

3. SUBSTRATE AND CATALYST EVALUATION

3.1 Phenol and Anisole

Although a plethora of reagents does exist for the formylation of aromatic hydrocarbons with CO as reagent, this reaction generally fails with phenolic substrates. However, only a single patent[196] by Hoechst Aktiengesellschaft and two papers by Takezaki,[197,198] which utilise HF/BF_3 as catalyst, describe the formation of phenolic aldehydes by formylation with CO. In order to compare this HF/BF_3 promoted formylation of phenolics to that of aromatic hydrocarbons, a study was initiated with phenol and anisole as substrates (Table 2.2). A reaction temperature of 45°C was used and is in accordance with that reported in literature.[199] The progress of the reactions was followed by GC analysis of samples taken at regular intervals.

Table 2.2: CO formylation of various aromatic substrates using anhydrous HF (50eq) and BF_3 (2eq) as catalysts.

Run	Substrate	Temp (°C)	Time (h)	Products (mass%)			Conv. (%)
				p-Aldehyde	*o*-Aldehyde	Secondary Products*	
1	Toluene	45	1	91	5	3	>99
2	Phenol	45	1	43	1	5	49
3	Phenol	45	4.5	80	6	13	99
4	Anisole	45	1	38	6	7	51
5	Anisole	45	4.5	50	13	27	90
6	Anisole	45	4.5	13	5	5	23

* See figure 2.4

With toluene as substrate formylation proceeded in a high yield (99%) with respect to aldehyde formation and with good *para*-selectivity (90%) in a reaction time of only 1 hour. The reaction was carried out on phenol under the same reaction conditions. Surprisingly, the reactivity of phenol proved to be much lower than that of toluene and a reaction time of more than 4 hours was required to obtain acceptable yields, *albeit* with reduced *para*-selectivity. When the reaction was extended to anisole, only small differences compared to phenol were observed within the first hour of the reaction, but at extended reaction times phenol proved to give better conversions. The results indicate that the reaction is sustained for a longer time with phenol than with anisole.

Although unreacted substrate can be separated from the reaction mixture and recycled back to the reactor, this adds to the capital costs since reactor size needs to be increased for a given supply market demand. Thus, maximising product yield is one of the factors imperative to minimisation of production costs.

In an attempt to increase product yields through increased mass transfer, a modified gas-entrainment stirrer was tested, using anisole as substrate. This resulted in decreased yields and conversions (Table 2.2 Run 6), indicating that mass transfer of CO is not a limiting factor in the reaction.

Aldehydes of 4-nonylphenol are used as precursors for foaming agents in the mining chemical industry, thus presenting an opportunity to utilise the HF/BF_3/CO technology. However, the formylation of 4-nonylphenol at 45°C furnished mainly dealkylated secondary products including phenol together with its formylation product, *p*-hydroxybenzaldehyde.

The main aldehyde isomer produced in the HF/BF_3/CO formylations of all of the *ortho-para* directing mono-substituted benzenes tested in our laboratories is in accordance with published results.[200,201,202,203] We also found that extending the reaction times from 1 hour to 4.5 hours lead towards a decrease in the *para-ortho* ratio in the case of both phenol and anisole. This may suggest gradual change from a product of kinetic control to a product of thermodynamic control indicative of the reversibility of the formylation process.

The high acidity level in the reaction mixture provides ample opportunity for side reactions to occur. The amounts of side product generated by these acidic conditions were generally on the low side (<10%). However, these amounts increased dramatically with increased reaction times. On increasing the reaction time of anisole from 1 to 4.5-hours the side product amount increased four-fold while the aldehyde product increased by only half during the same period. Although anisole de-alkylation may occur under the reaction conditions, only low amounts of phenol (<1%) were detected.

The MS fragmentation patterns of by-products detected by GC indicated that majority of secondary products (10 - 14) most probably arose from acid catalysed reactions between the substrate and the corresponding formylation products.

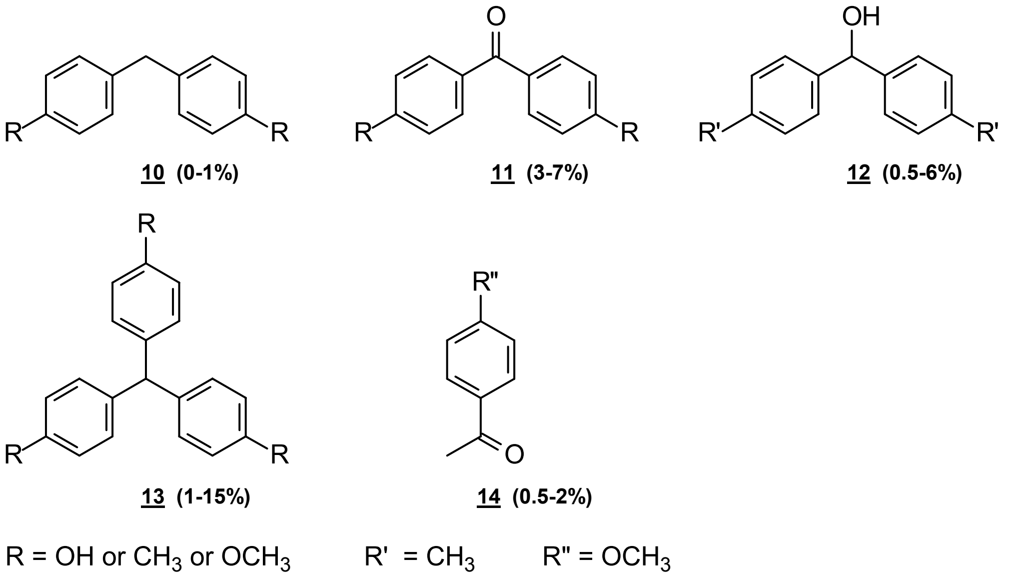


Figure 2.4: Secondary products obtained during CO formylation reactions of toluene, anisole and phenol using HF/BF_3 as catalyst. (Yield ranges in brackets)

3.2 Evaluation of Other Catalyst/Reaction Systems

In an effort to obtain augmented yields and selectivities in the CO formylation of phenol, anisole and toluene, a few reactions were initiated during which the type and amount of Lewis- and Brønsted acid were varied.

Although literature states that phenolic compounds are not responsive to CO formylation in the presence of $AlCl_3$ and hydrogen chloride, the possibility of some aldehyde formation using excess aluminum trichloride was investigated.

Attempted phenol formylation with excess aluminum trichloride did not yield any aldehyde products, even at elevated CO pressures and extended reaction times (Table 2.3 Run 1 and 2). Superacid $H^+AlCl_4^-$ may be on the lower end of the acidity scale compared to $H^+BF_4^-$ resulting in reduced protonation ability which may be an essential requirement for the formylation reaction.

Nitrobenzene was used as solvent in an investigation as it is frequently used in Friedel-Crafts reactions and facilitates the solubility of aluminum chloride. However, nitrobenzene may inhibit the formylation reaction as the polar NO_2 group competes with CO in the protonation reaction (CHO^+), resulting in low or no reactivity.[204] Another possible reason for the apparent unreactivity of phenol under these conditions was proposed by Olah[202] and involves the formation of phenyl formate (*O*-formylation of phenol). These compounds decarbonylate easily, instead of undergoing acid catalysed Fries rearrangement to the aldehyde [Eq (2.13)].

$$C_6H_5OH \quad + \quad CO \quad \xrightleftharpoons[AlCl_3]{H^+} \quad C_6H_5OOCH \qquad (2.13)$$

Table 2.3: CO formylation of aromatic compounds using various Lewis- and Brønsted acids as catalysts

Run	Substrate (mmol)	Reactants (mmol)	Temp (°C)	Time (h)	Conv. (%)	Product
1 [a]	Phenol (106)	$AlCl_3$ (212) CO 50bar	33-55	12	-	-
2[b]	Phenol (19)	$AlCl_3$ (64) CO 72bar	28-50	60	-	-
3[a]	Anisole (93)	$AlCl_3$ (196) CO 50bar	33	12	>95	Only phenol and tarry material
4	Anisole (50)	$AlCl_3$ (100) HF (2500) CO 50bar	5-30	22	3	Phenol 1% PAA 1% Secondary Products 1%
5	Toluene (25)	HF (1250) CO 50bar	45	1	21	*p*-Tolualdehyde 12%
6	Toluene (185)	BF_3 (80) CO 50bar	45	1	-	-
7	Anisole (100)	HF (1400) BF_3 (217)	40	4.5	92	PAA 20% OAA 11%

Run	Substrate (mmol)	Reactants (mmol)	Temp (°C)	Time (h)	Conv. (%)	Product
		CO 50bar				Secondary Products 61%
8	Anisole (50)	HF (2390) BF_3 (7) CO 50bar	40	1	8	PAA 3% OAA <1% Secondary Products 4% Phenol 1%
9 [c]	Toluene (22)	H_2O (2340) CO 60bar	275	3	-	-
10	Anisole (50)	HF (2560) BF_3 (118) CO_2 42bar	45	1.5	-	-

[a] 25ml nitrobenzene as solvent [b] 50ml nitrobenzene as solvent [c] Super-critical water as solvent

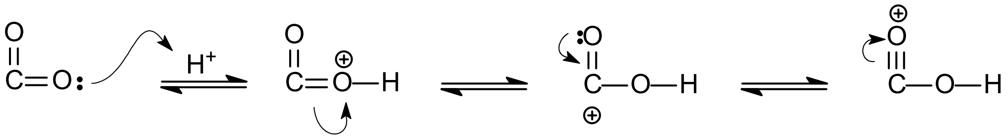
Extending this reaction to anisole as substrate, no aldehyde product was observed, while extensive de-alkylation of anisole to phenol occurred (Run 3). The important role of an added Brønsted acid (hydrogen fluoride) was confirmed as some aldehyde product was obtained from anisole in the presence of aluminium trichloride together with HF (Run 4).

In order to gain a better understanding of their individual roles, hydrogen fluoride and boron trifluoride were used separately as catalysts in the formylation of toluene. The fact that no aldehyde products were obtained from BF_3 as catalyst and only a minor amount from HF, accentuates the effect of their combined potential. This effect is evident when results of Run 5 and 6 in Table 2.3 are compared with Run 1 in Table 2.2.

Minimising reagent volumes from an industrial perspective makes economic sense, hence the effect of less hydrogen fluoride and boron trifluoride respectively with regard to the anisole reaction was investigated. However, decreasing the hydrogen fluoride from 50 to 14 equivalents not only reduces the yield and selectivity towards the *p*-aldehyde, but a substantial increase in secondary product formation was observed. (Table 2.3 Run 7 *vs* Table 2.2 Run 5) The dramatic effect of less boron trifluoride (0.14 eq) is evident from the drop in the *p*-aldehyde yield to 3%. This result confirmed the important facilitating role of the Lewis acid. (Table 2.3 Run 8 *vs* Table 2.2 Run 4)

Since near-supercritical water may act as an acid[205], it offers an environmentally benevolent alternative for the replacement of undesirable solvents and catalysts and may potentially assist in the formylation of aromatic aldehydes using carbon monoxide. As toluene is the most likely to formylate under these conditions, it was the obvious choice of substrate. However, no reaction occurred at 275°C under CO pressure of 60bar in near-supercritical water, which may be ascribed to the non-superacidity of the solvent (Table 2.3 Run 9).

Carbon dioxide in its liquid or supercritical state has prodigious potential as an environmentally benign reaction medium or reactant for sustainable chemical synthesis. The possibility of using carbon dioxide as carboxylation agent of anisole in the presence of hydrogen fluoride and boron trifluoride to *p*-anisic acid, followed by reduction to the corresponding aldehyde was briefly investigated. Carbon dioxide should technically be easier to protonate than carbon monoxide. [*cf* the four resonance structures (Eq 2.14) of protonated carbon dioxide that increases the stability of the cation to a much higher degree when compared to only two resonance structures of CO (paragraph 2.1).] However HF/BF_3 promoted carboxylation of anisole in supercritical CO_2 was not observed (Table 2.3, Run 10).


(2.14)

The possible interaction of HF and BF_3 to obtain HBF_4 as active catalyst in CO formylation reactions was noted in literature[206,207] and raised the expectation of HBF_4 in diethyl ether being an appropriate acid catalyst. The use of HBF_4OEt_2 from an industrial and environment perspective is advantageous as it enables easy handling and excludes the need for mixing HF and BF_3 gasses that are harmful to the environment and infrastructure.

HBF_4OEt_2 was subsequently used in an attempt to formylate both phenol and toluene in the presence of CO (Table 2.4). However, no reaction was observed probably due to the stability of the complex between HBF_4 and diethyl ether.

Table 2.4: Attempted CO formylation of aromatics using 54% HBF_4 in diethyl ether.

Run	Substrate	Reagents	Temp (°C)	Time (h)	Product
1	Phenol (32mmol)	$HBF_4 \cdot OEt_2$(160mmol); CO 83bar	25	14	-
2	Toluene (13mmol)	$HBF_4 \cdot OEt_2$(156mmol); CO 83bar	30	24	-

The successful utilisation of strong solid acids and superacids in Friedel-Crafts acylation described in the literature[208] suggests its application in the CO formylation of aromatic substrates. Advantages regarding the replacement of homogeneous liquid acids by heterogeneous solid acids as catalysts in the chemical industry would not only bring about ease of separation from the reaction mixture allowing continuous operation, regeneration and re-utilisation of the catalyst, but also include corrosion-free operation and less impact on the environment.

The acidity values reported for sulphated metal oxides is highest in the case of sulphated zirconia (SO_4^{2-}/ZrO_2) and is comparable to that of HF/BF_3.[209,210] Another attractive feature of this catalyst is its dual Lewis- and Brønsted acidity that might be beneficial to our specific application.[211,212]

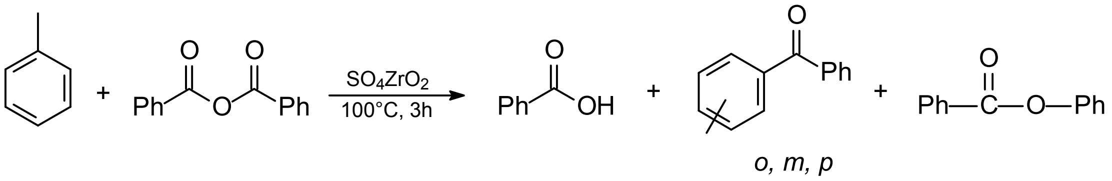
Toluene, due to its high reactivity in $HF/BF_3/CO$ formylation reactions was initially used as formylation substrate with un-activated sulphated zirconiumoxide as acid catalyst. No reaction occurred even after extended reaction times and increased temperatures (Table 2.5, Run 1 and 2).

Table 2.5: Attempted CO formylation and acylation of aromatics using sulphated zirconiumoxide as catalyst.

Run	Substrate (mmol)	SO_4ZrO_2 (g)	CO (bar)	Acylating Agent (mmol)	BF_3 (mmol)	Temp (°C)	Time (h)	Product
1	Toluene (386)	31[a]	80		-	60	2.5	-
2	Toluene (336)	20[a]	80		-	100	15	-
3	Toluene (333)	20[b]	80		-	100	20	-
4	Toluene (292)	2[a]	-	Acetic-anhydride (25)	-	100	3	-
5	Toluene (141)	1[c]	-	Benzoic-anhydride (4)	-	100	3	-
6	Toluene (141)	1[c]	-	Benzoic-anhydride (4)	-	100	3	*o-, m-*, *p*-Me-benzophenone, benzoic acid
7	Toluene (271)	3[c]	50		-	45	12	-
8	Anisole (231)	5[c]	50		-	45	12	-
9	Toluene (271)	5[c]	50		44	45	12	*p*-Toluald. 0.1%
10	Anisole (231)	5[c]	50		263	45	12	Phenol, no ald.
11	Phenol (266)	5[c]	50		208	45	12	*p*-Hydroxybenz-ald. 0.1%

[a] un-activated, [b] activated at 150°C for 2h in argon, [c] calcined at 500°C for 50h in air

In an effort to reduce the Brønsted acidity and increase the Lewis acidity, water was removed from the catalyst at 150°C. This catalyst also did not promote formylation (Run 3). These results raised the question whether the material used showed any catalytic activity. A literature procedure[213] for acylation using benzoic acid anhydride failed (Run 5), which suggests that it may still contain small amounts of moisture, not removed during the activation step. Since good acylation yields with calcined sulphated zirconiumoxide were reported the same activating conditions were applied to the catalyst. With this catalyst 2-, 3-, and 4-methyl-benzophenone, benzoic acid and phenyl benzoate were obtained identified by GC-MS analysis as acylation products using benzoic acid anhydride (Run 6) [Eq (2.15)].



(2.15)

The formation of phenyl benzoate was both unexpected and inexplicable. GC-MS fragmentation patterns of pure benzoic acid anhydride dissolved in dried toluene indicated the presence of phenyl benzoate. It is possible that due to the high split-inlet temperature (250°) in the gas chromatograph, the anhydride decomposes to the ester with the loss of CO.

Freshly calcined catalyst was then utilised in CO formylation reactions using toluene and anisole as substrates respectively. However, no aldehyde products were observed (Runs 7 and 8).

BF_3 is known to form complexes with aldehydes and according to calculations done by Eley *et.al.*[214], synthesis of benzaldehyde is rendered thermodynamically more favourable by the formation of the benzaldehyde-aluminum-chloride-complex as a stable product. Thus, the addition of BF_3 to the reaction mixture using calcined sulphated zirconium oxide could possibly facilitate aldehyde formation.

On addition of BF_3, *para*-aldehyde isomers were obtained *albeit* in very low yield (0.1%) from toluene and phenol as substrates using the same conditions whereas only de-alkylation occurred in the case of anisole (Runs 9,10,11). The formation of aldehyde product is at least in line with the predicted enhancing effect of boron trifluoride on the reaction thermodynamics.

In a final effort to establish CO formylation with heterogeneous catalysts, fluoridised silica-alumina (used effectively as an hydrofluoric acid alternative in the liquid phase alkylation of benzene[215]), was activated and investigated for catalytic anisole formylation (Table 2.6). As in the case of the other heterogeneous catalysts, no formylation was observed.

Table 2.6: Attempted CO formylation of anisole using fluoridised silica-alumina[a] as acid catalyst

Run	Substrate (mmol)	Engelhard 483-11 (g)	CO (bar)	BF_3 (mmol)	Temp (°C)	Time (h)	Product
1	Anisole (231)	5	50	264	45	14	-

[a] Activated at 350°C for 2hours under argon

Although the super acidity of sulphated zirconium oxide is widely accepted, Fărcaşiu[216] indicated that traditional acidity measurements, *i.e*. Hammett type, can not be applied to solid acids. He showed that the exceptional catalytic activity of sulphated zirconia and other sulphated metal oxides (SMO) is not justified by their acid strength and that they are in fact not superacidic at all. He argues that sulphated zirconium exhibits a bi-functional character in which oxidation in the initiation step is combined with acid catalysed reaction of the intermediates formed. Oxidation is normally achieved through the reduction of the sulphate or added redox promotors, which increases the catalytic activity but not the acid strength.

3.3 Mechanism Studies

3.3.1 Formylation Mechanisms

Understanding the $CO/HF/BF_3$ formylation mechanism would be beneficial to the extend that it would facilitate reaction optimisation, minimisation of side-product formation and provide an indication of whether the reaction can be performed under catalytic conditions. As little is known in the literature of the reaction mechanism in the case of anisole, efforts were focused on this aspect.

The mechanism of the conventional electrophilic aromatic substitution reaction is expected to consist of four steps: (i) formation of an electrophile (E^+) by activation with a Lewis- or Brønsted acid (A), (ii) attack of the electrophile on the aromatic compound (ArH) resulting in a π-complex (iii) conversion of the π-complex into a σ-complex, (iv) followed by the loss of a proton from the σ-complex to give the product (Eq 2.16). The formation and attack of the electrophile are separate steps *i.e*. the electrophile is formed and dispersed in the reaction medium before attack on the aromatic compound takes place.

$$P + A \longrightarrow E^+ \overset{ArH}{\rightleftharpoons} \underset{\pi\text{-complex}}{[ArH\cdot E^+]} \longrightarrow \underset{\sigma\text{-complex}}{[ArHE^+]} \longrightarrow ArE + H^+ \qquad (2.16)$$

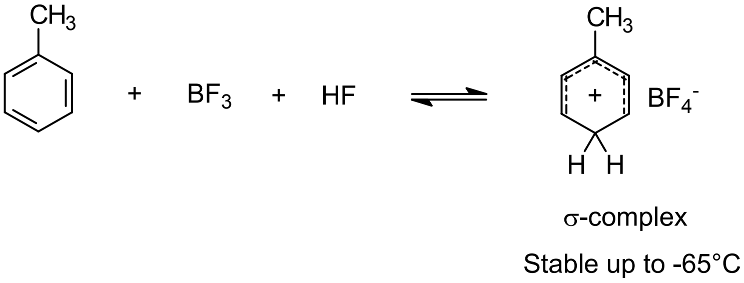
P = pro-electrophile A = Lewis- or Brønsted acid

The active acid involved in the initiation of the formylation reaction following HF and BF_3 addition to the substrate, is believed to be the super acidic HBF_4, since excess amounts of hydrofluoric acid are used (Eq 2.17). Although the active acid is indicated as being HBF_4, it must be taken into account that the existence of this super acid has only been demonstrated in the presence of nucleophilic/basic reagents (*cf* paragraph 2.4). The probability of the active electrophile being a species similar to that indicated in eq 2.18 can therefore not be excluded.

$$BF_3 + HF \rightleftharpoons HBF_4 \qquad (2.17)$$

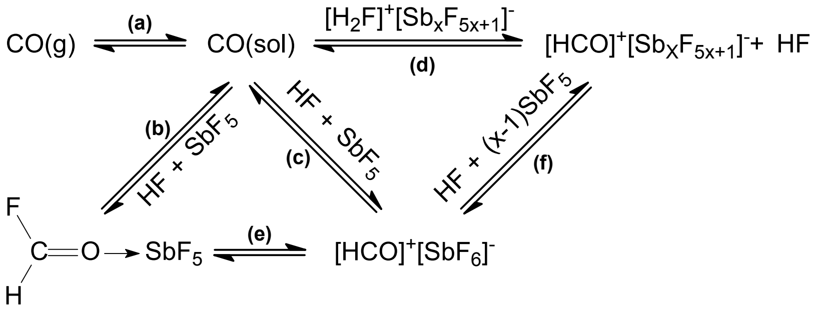
$$BF_3 + HF + CO \rightleftharpoons HCO^+BF_3^- \qquad (2.18)$$

Since both CO and toluene (or anisole or phenol) are nucleophilic/basic compounds and the reaction is performed in a super acidic medium (with excess acid), the formation of the initial electrophile and corresponding nucleophile are by no means trivial and needs careful consideration. Furthermore, the protonation of toluene by the HF/BF_3 system has been reported by Olah *et al.*[217] (Eq 2.19), while the existence of an HCO^+ containing ion pair has recently been demonstrated by Gladysz *et al.*[218]



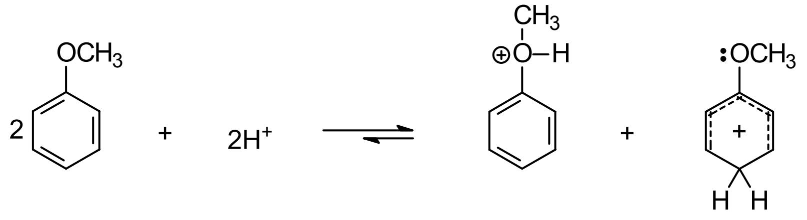
(2.19)

During their investigation on the behaviour of CO in the super acid system, HF-SbF_5 (1:1), by high pressure NMR, the existence of equilibria as indicated in Scheme 2.2 could also be identified by the Gladysz group.

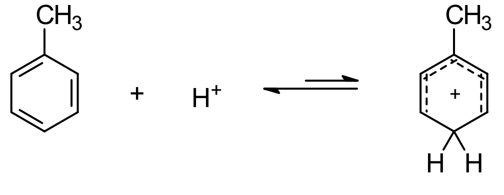


Scheme 2.2: Proposed equilibria in the superacid HF-SbF_5 under CO pressure

For the reaction to proceed *via* the conventional electrophilic aromatic substitution mechanism, CO must be protonated, while the aromatic substrate acts as nucleophile. On the other hand, if the aromatic substrate is assumed to be the more basic, the reaction should proceed by a nucleophilic aromatic substitution pathway, with CO being the nucleophile. Since no products originating from nucleophilic displacement of the halogen could be detected during the reaction of halogenated benzenes with CO under the same conditions (*cf* paragraph 3.4), it must be assumed that CO acts as the more basic reagent during the reaction between CO and toluene and is being protonated to form the active electrophile (E^+ in Eq 2.16). If however, the basicity of both reagents is assumed to fall in close proximity of each other and excess acid is used, the protonation of both CO and the aromatic substrate is a definite probability and the reaction should be governed by the presence and position of protonation equilibria. In this instance where CO is the more basic component it should be protonated to a higher degree than the aromatic substrate, with the protonation equilibrium of the aromatic reactant more to the left (Eq 2.20 or 2.21), *i.e.* some un-protonated molecules are available to act as nucleophiles and thus allowing the reaction to proceed. The higher reactivity of toluene *vs* phenol and anisole could therefore be attributed to the latter substrates being protonated to a higher degree than toluene (due to higher basicity) thus leading to lower concentrations of unprotonated and, therefore, reactive substrate (Eq 2.20).



(2.20)



(2.21)

Although the conventional mechanism, as indicated above (Eq 2.16), might prevail during these reactions, it only holds true if it is assumed that CO is the more basic of all reactants employed. In order to validate this assumption it was decided to perform some reactions with only one equivalent of super acid (relative to toluene) on mixtures (1:1) of toluene and phenol or anisole respectively. If CO is the more basic reagent, the presence of the other aromatic compound would have limited effect on the toluene formylation reaction rate. The presence of phenol or anisole during the reaction of toluene, however, had a profound inhibiting effect on the formylation of the toluene (Table 2.7), while very little formylation of the added phenol or anisole took place under these conditions. A plausible explanation for these results could be that these compounds are more basic than toluene while their susceptibility to protonation under the prevailing conditions is better or at least comparable to that of CO. Indirect evidence that anisole and phenol are more basic than toluene is provided by the relative stability of the cations of toluene and anisole. In this regard Takezaki *et al.*[219] reported a melting point (with some decomposition[217]) of -65°C for the 1:1:1 complex of toluene, HF and BF_3 while -60°C was reported for the anisole-HF-BF_3 complex, both at atmospheric pressure.

Table 2.7: CO formylation of various substrates using BF_3 (1eq to toluene) and hydrogen fluoride (50eq) at 40°C and 50bar CO pressure

Substrate	Time (min)	Toluene (%)	*p*-Toluald. (%)	*o*-Toluald. (%)	Phenol (%)	PHBAld. (%)	Anisole (%)	PAA (%)	Sec. Prod. (%)
Toluene	15	4	81	4	-	-	-	-	11
	30	2	80	4	-	-	-	-	14
	60	<0.1	83	5	-	-	-	-	12
1:1Toluene-Phenol									
	15	44	6	-	46	3	-	-	1
	30	40	10	-	44	5	-	-	1
	60	36	14	-	43	6	-	-	2
1:1 Toluene-Anisole									
	15	45	4	-	-	-	48	1	2
	30	44	5	-	-	-	46	3	2
	60	43	5	-	-	-	44	5	3

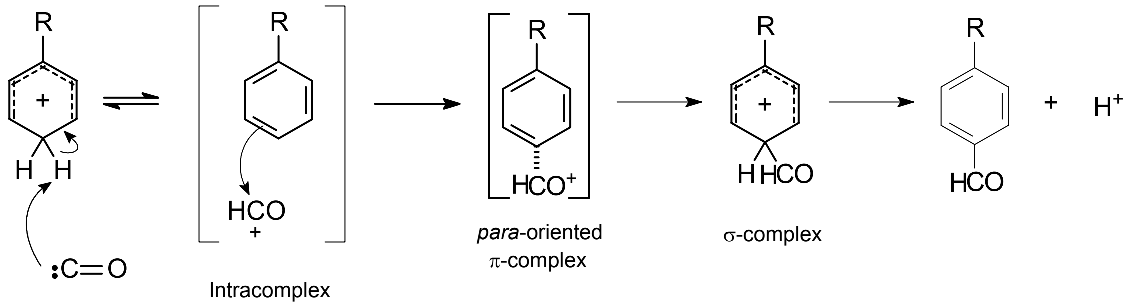
Although the formation of the aldehydes from toluene, phenol and anisole could be explained by the conventional mechanism, as discussed above, this mechanism is based on the assumption that the protonation of CO is at least as feasible as that of the aromatic substrates. According to Gladysz *et al.*[218] the protonated species of CO (at room temperature under 28bar CO pressure) could only be detected while employing HF-SbF_5, the strongest super acid known, and not even with HSO_3F-SbF_5 (a weaker acid by a factor 1000), the second member in the series of super acids (*cf* paragraph 2.4).

Therefore, it is justifiable to assume that the protonation of CO is extremely difficult compared to that of the aromatic substrates involved in the formylation reactions (*vide supra*) and that the equilibria involved should rather be to the left for equation 2.18[*] and right for equation 2.20. This would render the concentration of reacting species in the proposed electrophilic aromatic substitution extremely low and be expected to result in almost no reaction; a result in direct contrast to experimental observations.

Cacace[220] and Tanaka[221], however, proposed an alternative mechanism for the formation of products and the difference in reactivity observed for the different substrates in this study. In the Cacace-Tanaka mechanism (Eq 2.22) it is proposed that the protonated aromatic compound act as an acid to protonate the pro-electrophile (CO in this case) with the formation of a so-called intracomplex. The formation of the intracomplex is followed by attack of the liberated aromatic nucleophile on the newly formed electrophile leading to a π-complex, which is then transformed into a σ-complex before releasing a hydrogen ion and formation of the final product (Eq 2.23).

$$P + ArH_2^+ \longrightarrow [ArH_2^+ \cdot P] \rightleftharpoons \underset{\pi\text{-complex}}{[ArH \cdot E^+]} \longrightarrow \underset{\sigma\text{-complex}}{[ArHE^+]} \longrightarrow ArE + H^+ \qquad (2.22)$$

P = pro-electrophile



(2.23)

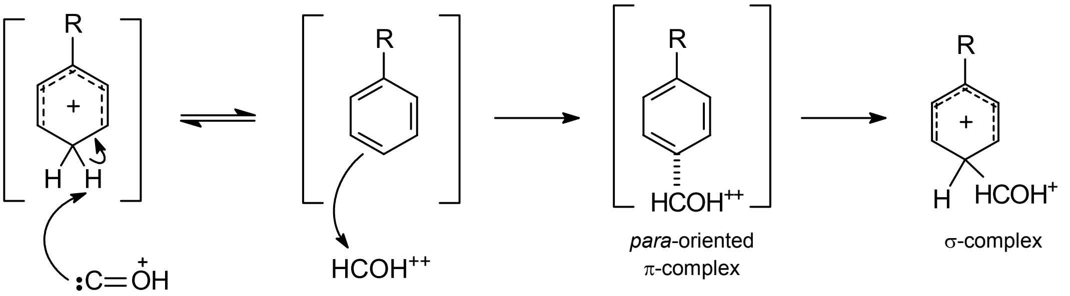
The increased reactivity of toluene compared to anisole (and phenol) could probably be explained in terms of the former reacting at least partially through the conventional mechanism, while for the more basic anisole and phenol the reaction would proceed through the intracomplex mechanism. In this instance the aromatic substrate can be protonated to a large extent and still allow the reaction to proceed by an electrophilic aromatic substitution pathway. Only limited quantities of unprotonated CO would also be

---

[*] Low conversion of CO into HCO^+ was also indicated by Tanaka *et al.* (*Trends Org. Chem.*, 7, **1998**, *45*)

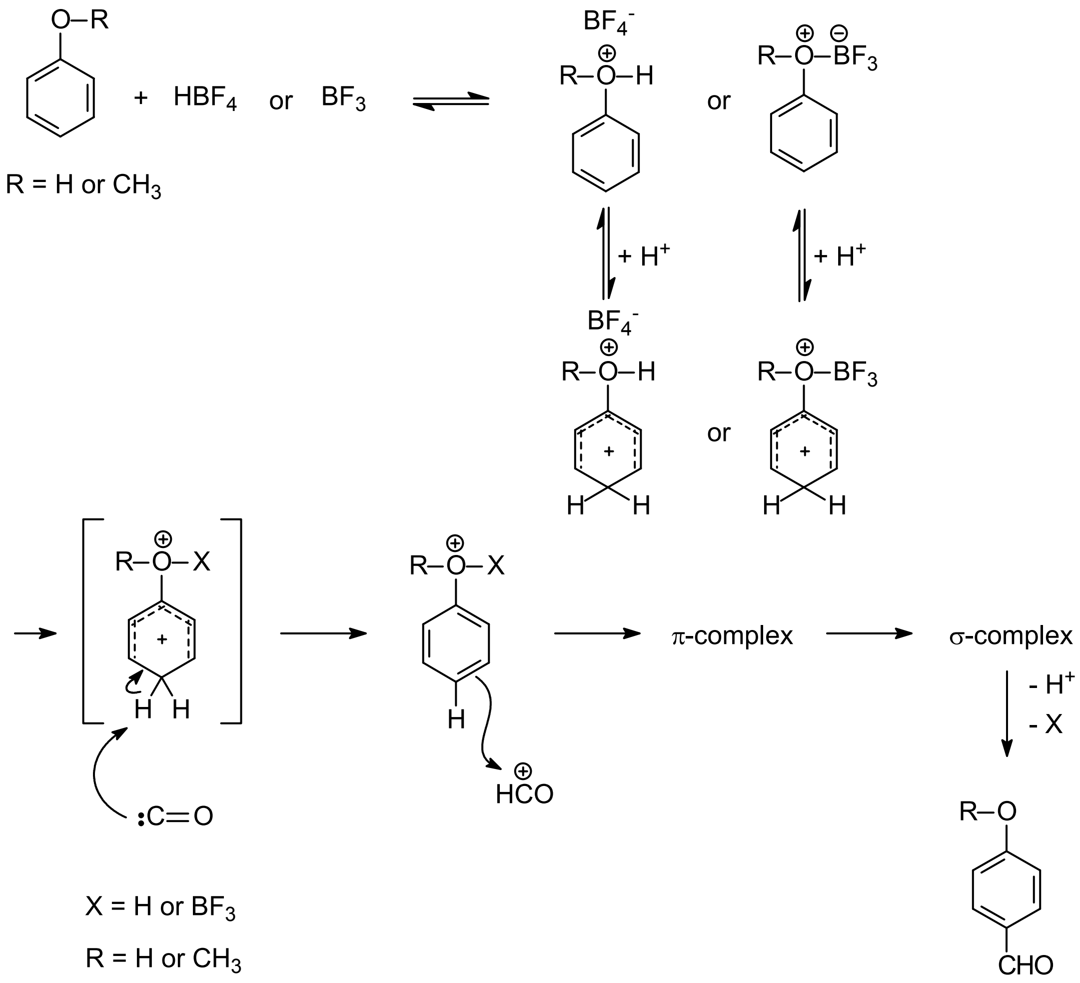
required to act as pro-electrophile during the reaction. The higher reactivity of phenol *vs* anisole is probably explicable in terms of the fact that phenol is less basic than anisole and would therefore be more prone to protonate CO after formation of the intracomplex.

Although it has been reported in a Molecular Modelling study that the formation of a formyl dication ($HCOH^{++}$) by the action of HF/SbF_5 on CO is associated with extremely high activation energy[222], this species has been proposed by several authors[223] as the active electrophile in formylation reactions utilising CO and HF/SbF_5. The formation of a formyl dication could, therefore, also be invoked as plausible explanation for electrophilic aromatic substitution reactions in case of full protonation of both CO and the aromatic substrate by the HF/BF_3 super acid (Eq 2.24).



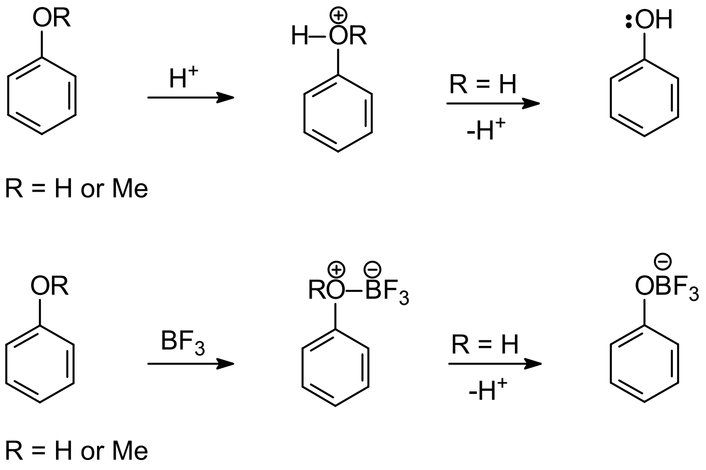
(2.24)

The dication concept can also be extended to the formation of the anisole- and phenol dication as reported by Takezaki[224] who isolated an anisole/HF/BF_3 complex containing a 1:1:2 ratio of reactants (Scheme 2.3). Protonation of the pro-electrophile CO *via* the intracomplex mechanism is followed by electrophilic aromatic substitution with formation of the π- and σ -complex respectively followed by aldehyde formation through the loss of a proton and X. The corresponding rate of formylation is expected to be slower than in the case of toluene due to the lower nucleophilicity of the protonated anisole.



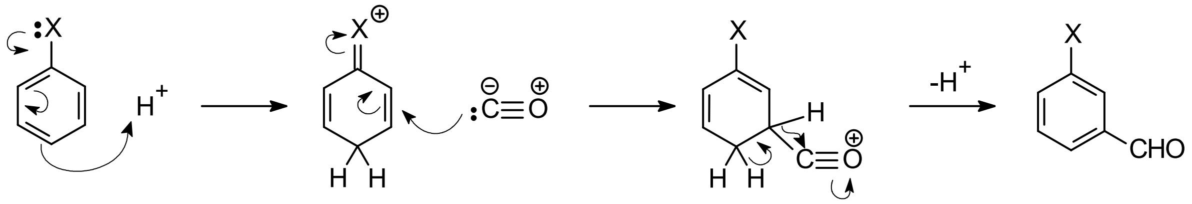
Scheme 2.3: Dication formation with resulting intracomplex formylation to the aldehyde.

A third possible explanation for the reduced reactivity of anisole and phenol compared to that of toluene could be that the former two substrates are deactivated towards electrophilic aromatic substitution by reaction of the alcohol or ether moiety with either the Lewis (BF_3) - or Brønsted ('HBF_4') acid. In this instance the first equivalent of acid would be consumed by reaction with the oxygen (Scheme 2.4), and the second equivalent effecting protonation of CO. Inductive deactivation of the aromatic ring by the cationic oxygen will result in reduced reactivity of the aromatic system. Since the positive charge resulting from complexation of phenol with BF_3 on the phenolic entity could be neutralised by proton loss to the reaction medium, phenol is expected to be more reactive than anisole under the reaction conditions (Scheme 2.4). Additional support for this explanation is provided by the reported isolation of an anisole/HF/BF_3 complex containing a 1:1:2 ratio of reactants.[226]



Scheme 2.4: Protonated anisole/phenol.

Yet another possible formylation mechanism that needs to be considered, involve direct nucleophilic attack of CO on the protonated aromatic system. However, this mechanism (Scheme 2.5) can be discounted since it will result in *meta*-substituted aldehydes in the case of toluene, phenol and anisole as substrates.



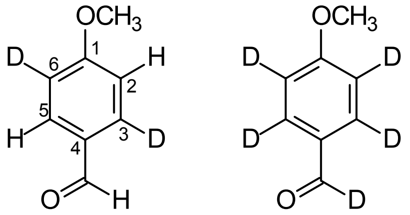
Scheme 2.5: *Meta*-aldehyde formation through nucleophilic aromatic substitution of groups that contain an unshared pair of electrons on the atom connected to the ring.

The different substrates studied showed big differences in reactivity but little variation in product selectivity. While *meta*-substitution is not expected in the reactions of activated aromatic substrates, *i.e.* toluene, phenol, and anisole, the virtual absence of *ortho* substituted products can only be explained in terms of the mechanistic pathway of the reactions. Since early intermediates could be associated with the π-complex and thus low regioselectivity, it must be concluded that the important intermediates in these reactions have a σ-complex nature resulting in high *para*-selectivity[225]. According to Tanaka *et al.*[226] the intracomplex mechanism could be associated with high *para* regioselectivity in the formylation of methylnaphthalene when the Lewis acid to substrate molar ratio was less than 1. In contrast, lower regioselectivity, indicative of the conventional mechanism, was observed when the molar ratio exceeded 1. Even-though the Lewis acid to substrate molar ratio exceeded 1 during the present study, relatively high *para* selectivity was still observed for all substrates. No conclusive deductions as to the prevailing mechanism, *i.e.* intracomplex or conventional, could therefore be made from the regio-isomer distribution of products either.

3.3.2 Deuterium Labelling Experiments

The uncertainty about the mechanism(s) of the formylation reaction of anisole and phenol, on the one hand, and toluene on the other, presented a challenging investigative opportunity. Deuterium labelling as a tool to probe reaction mechanisms is widely used and in this regard the use of deuterium fluoride could indicate whether protonation in the initial stages of the reaction occurs preferentially on the aromatic ring or on the carbon monoxide molecule.

Deuterium fluoride (50eq), prepared from sodium fluoride and concentrated deuterated sulphuric acid, was used in the formylation of anisole (1eq) with BF_3 (2eq) for 2 hours at 45°C. The ^{1}H-NMR spectrum of the *p*-aldehyde product (Plate 17, experimental section) indicated singlets in both the aldehyde and methyl regions as well as two singlets in the aromatic region. Integrals of 1 for the formyl group (inert to exchange with DF) and both sets of aromatic protons respectively and 14 for the methyl protons could be explained in terms of the presence of at least two deuterated *p*-anisaldehyde isomers (Fig 2.5).



<u>**15**</u> <u>**16**</u>

Figure 2.5: Deuterated *p*-anisaldehyde isomers obtained from $DF/BF_3/CO$ formylation.

The position of the *ortho*-proton in <u>15</u> was identified using NOESY (Plates 19 and 20) experiments. The ^{13}C-NMR spectrum also supported the conclusion. The isomers are present in a 1:3 ratio. Although H-D exchange occurred freely, the appearance of the proton in the aldehyde moiety of (<u>15</u>), points strongly to the presence of the intracomplex reaction mechanism where the hydrogen or deuterium originates from the aromatic ring as opposed to from CDO^+. The existence of the D-atom on the aldehyde moiety of (<u>16</u>) may result from H-D exchange prior to formylation or CO protonation. The extensive exchange of other aromatic hydrogen atoms may be a consequence of the long reaction times.

In an effort to minimise H-D exchange, the reaction time with toluene was reduced to 20 minutes. ^{1}H-NMR (Plate 21) analysis, after isolation and purification of the aldehyde product, indicated singlets in both the aldehyde and methyl regions in addition to two singlets in the aromatic region. Integrals in the ^{1}H-NMR spectrum varied from 1 for the aldehyde- to two for the aromatic- and 15 for the methyl protons and only partial structures could be allocated (Fig 2.6). The excess in methyl protons compared to aldehyde and aromatic protons are indicative of the existence of partial structure <u>17</u>, while the two 2H singlets suggests the existence of <u>18</u> or both <u>19</u> and <u>20</u>. ^{1}H-NMR integral calculations indicated the deuterated aldehyde moiety to be present in 80% with the remainder being CHO. ^{13}C-NMR integrals show at least two isomers containing the CHO and CDO moieties in 37% and 67% respectively (Plate 22). As in the previous case, the appearance of the proton in the aldehyde moiety points strongly to the presence of the intracomplex mechanism where the hydrogen originates from the aromatic ring as opposed to CDO$^+$. Again, the deuterated aldehyde moiety may originate from CDO or D-transfer after exchange.

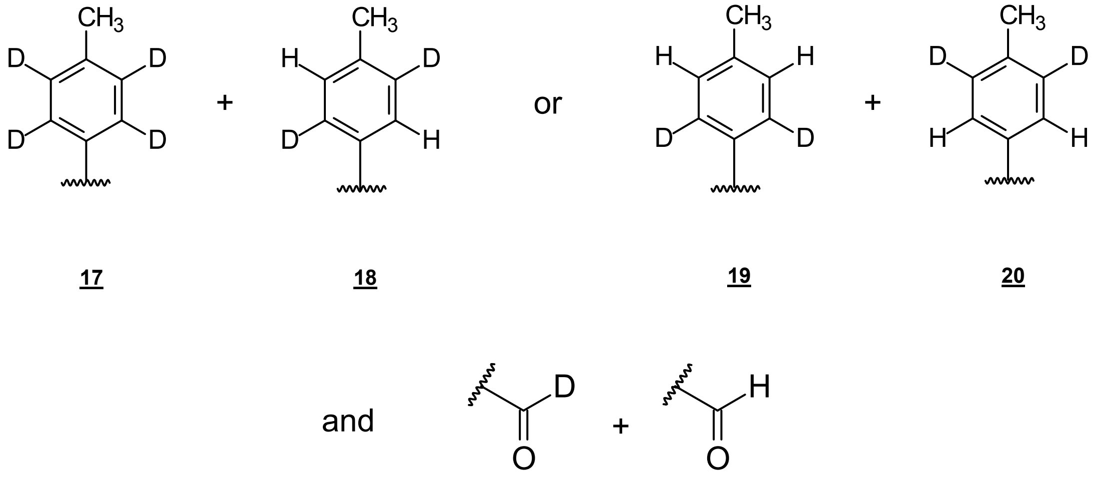
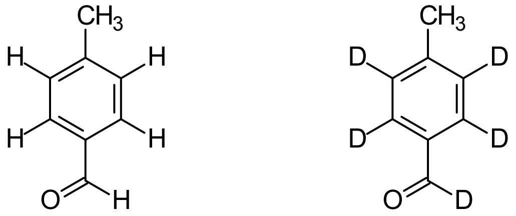


Figure 2.6: Deuterated *p*-tolualdehyde isomers obtained from DF/BF$_3$/CO formylation.

Since the isotope effect would render D-transfer less facile compared to H-transfer, an attempt was made to show that protonation do not occur preferentially on the carbon monoxide molecule in the case of toluene. The hydrogen containing substrate was replaced with d$_5$-toluene and formylated under similar conditions using hydrogen fluoride while the reaction time was reduced even further to 10 minutes to minimise H-D exchange.

The ^{1}H-NMR of the aldehyde product displayed an AA'BB'-system (J=8.75) in addition to singlets corresponding to CHO (Plate 23). Integrals ranged from one for CHO- to two for aromatic-H and four for the methyl protons. The spectrum is indicative of two isomers <u>21</u> and <u>22</u> in a ratio of 4:1 (Fig 2.7). This interpretation was in line with the ^{13}C-NMR spectrum that indicated a CHO to CDO ratio of 10:1 (Plates 24 and 25). The occurrence of deuterium in the aldehyde moiety (<u>22</u>) again strongly supports the intracomplex reaction where the deuterium originates from the aromatic ring as opposed to CHO^+.



<u>**21**</u> <u>**22**</u>

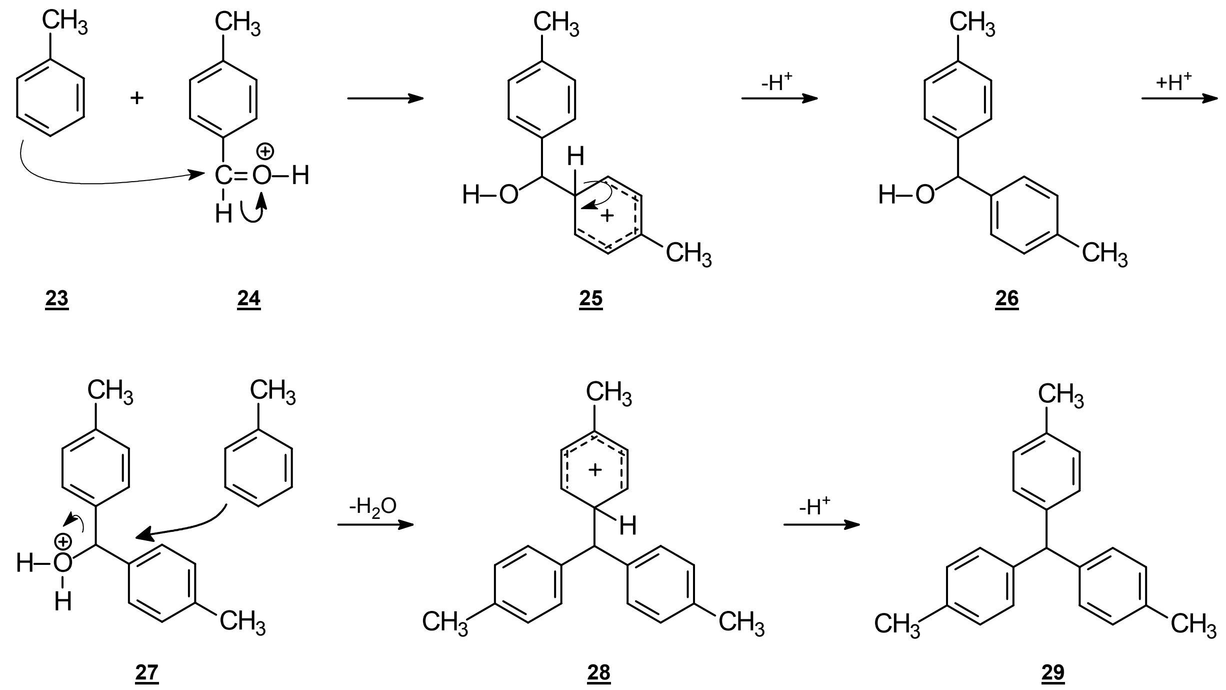
Figure 2.7: Deuterated *p*-tolualdehyde isomers obtained from HF/BF_3/CO formylation.

In all of the deuterium labelling experiments proton and deuterium exchange occurred freely on the aromatic ring, which complicated structure elucidation and therefore mechanistic conclusions tremendously. Despite this, compounds that could have originated only from the intracomplex mechanism were obtained in all reactions.

3.3.3 Mechanism of Secondary Product Formation

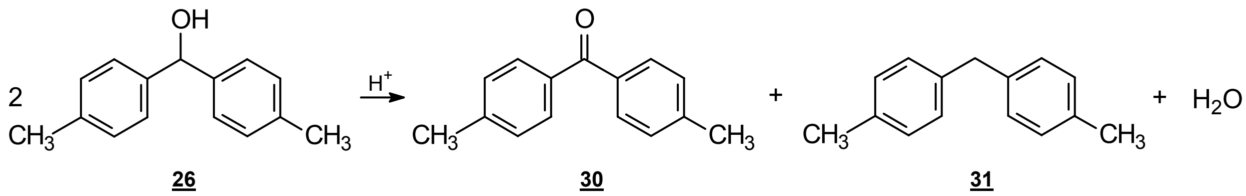
GC-MS-fragmentation patterns indicated the following secondary products isomers resulting from the formylation of toluene: dimethylbenzophenone (<u>30</u>), di(methylphenyl)-methane (<u>31</u>), tri(methylphenyl)methane (<u>29</u>) and di(methylphenyl)-methanol (<u>26</u>). The formation of the various side-products is explicable in terms of a two-step mechanism.

In the first step acid catalysed addition of toluene to the aldehyde product leads to the key-intermediate in the reaction, the alcohol (<u>26</u>) (Scheme 2.6). If this reaction is followed by an acid catalysed substitution of the OH by another toluene molecule the "trimer" (<u>29</u>) is formed.



Scheme 2.6: Nucleophilic addition of toluene to *p*-tolualdehyde.

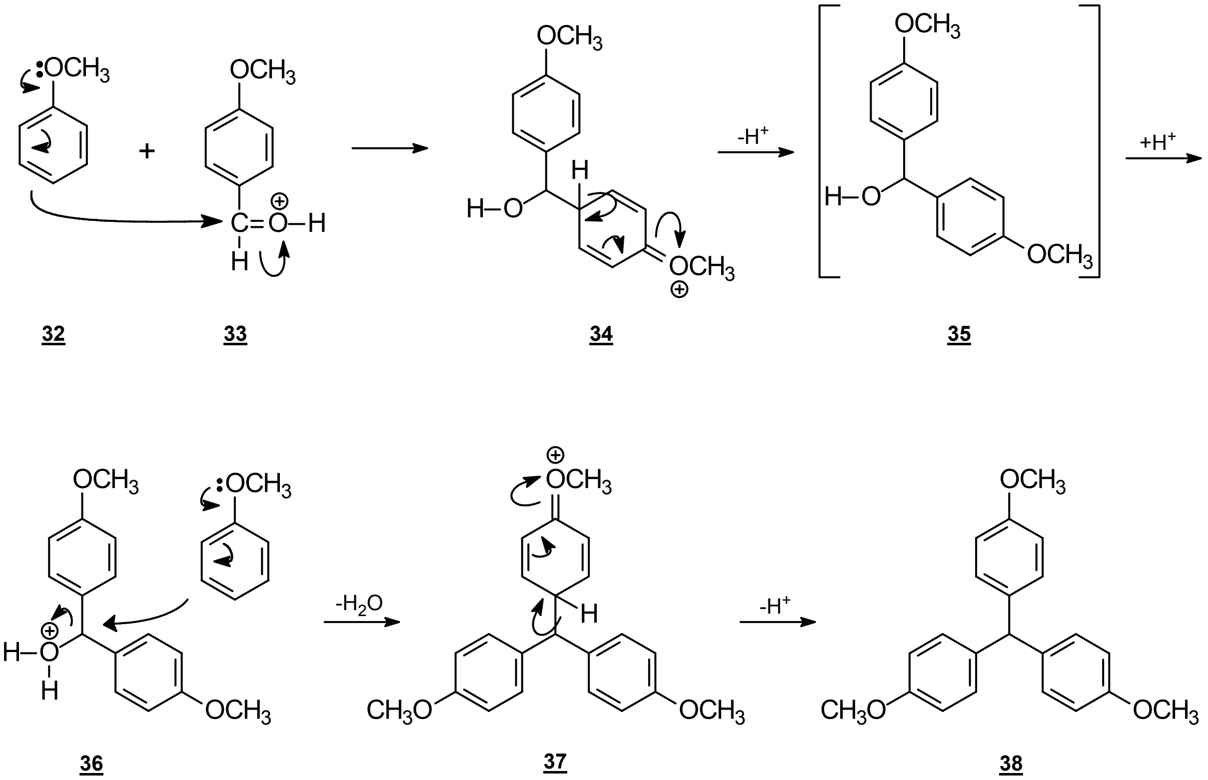
An acid catalyzed oxidation/reduction process could be suggested for the formation of 4,4'-dimethylbenzophenone (30) and di(4-methylphenyl)methane (31) (Scheme 2.7).



Scheme 2.7: Proposed redox disproportionation reaction

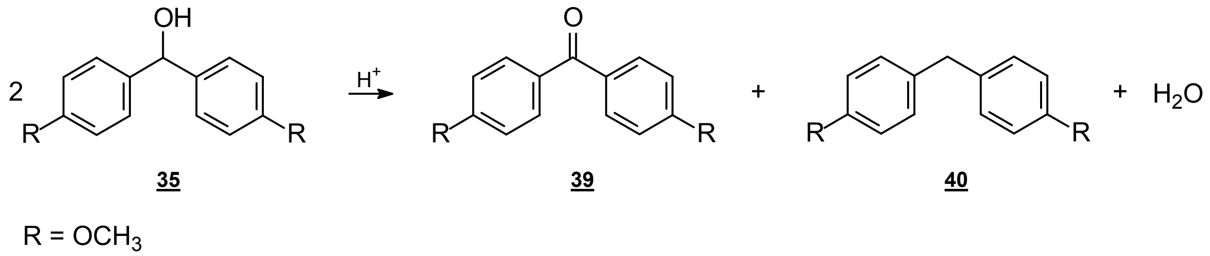
Formation of (29) and (31) in the CO formylation of toluene in HF/BF_3[227] as well as in trifluorosulphonic acid[228] were reported in the literature.

Secondary products of the anisole reaction were similar to those obtained for the toluene reaction with the exception that di(4-methoxyphenyl)methanol was not found. The absence of this alcohol can probably be ascribed to its higher reactivity leading to further reactions more readily than in the case of the toluene equivalent (Scheme 2.8).



Scheme 2.8: Nucleophilic addition of anisole to PAA

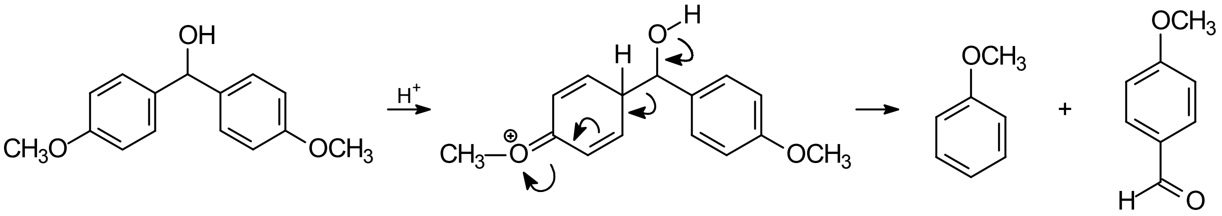
In an effort to confirm the proposed mechanism for by-product formation in the anisole reaction, anisole and PAA was added to hydrogen fluoride and BF_3 in the absence of carbon monoxide under typical reaction conditions (Table 2.8, Run 1). Isomers of the products (38), (39) and (40) were obtained in a 7:1:1 ratio and again none of the alcohol (35) was detected. The remaining question, *i.e.* whether (39) and (40) are formed from the proposed intermediate (35) was addressed by subjecting the separately prepared alcohol (35) to the reaction conditions in the absence of a nucleophile (Scheme 2.9).



Scheme 2.9: Proposed redox disproportionation reaction

Although care should be taken in the handling of the highly reactive alcohol (35), it could easily be prepared in almost quantitative yield by $NaBH_4$ reduction of the ketone (39). Normal neutralisation of the excess $NaBH_4$ and decomposition of the resultant alcohol borate complex with hydrochloric acid however could not be applied and the alcohol was isolated through an acetone/water work-up. The pure white di(4-methoxyphenyl)-

methanol crystals were subsequently added to HF/BF_3 under typical reaction conditions (Table 2.8, Run 2). This resulted in the formation of benzophenone, diphenylmethane as well as the "trimer". These products were however accompanied by smaller amounts of anisole and *p*-methoxyacetophenone. Anisole probably arises by an acid catalysed decomposition reaction (Scheme 2.10).

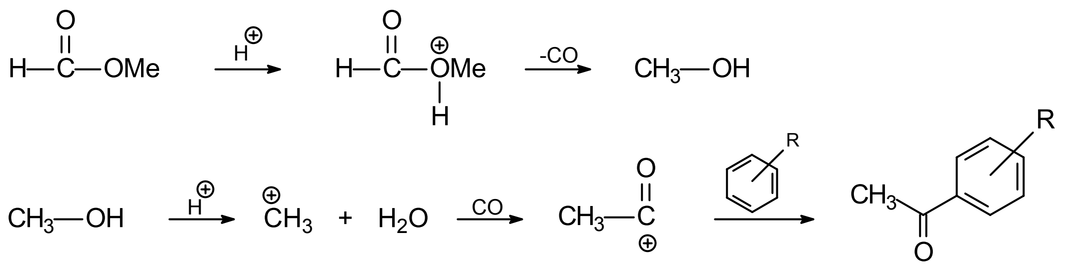


Scheme 2.10: Formation of anisole via acid catalysed decomposition

Table 2.8: Reactions in HF/BF_3 in the absence of CO

Run	Substrate	Reagents	Temp (°C)	Time (h)	Result
1	Anisole (25mmol)	PAA (25mmol) HF (2500mmol) BF_3 (111mmol)	45	3.5	Di(4-methoxyphenyl)methane (2%) 4,4'-dimethoxybenzophenone (2%) Tri(4-methoxyphenyl)methane (14%)
2	Di(4-methoxyphenyl)methanol (20mmol)	HF (1025mmol) BF_3 (41mmol)	45	3.5	Anisole (10%) *p*-methoxyacetophenone (2%) Di(4-methoxyphenyl)methane (22%) 4,4'-dimethoxybenzophenone (30%) Tri(4-methoxyphenyl)methane (23%)

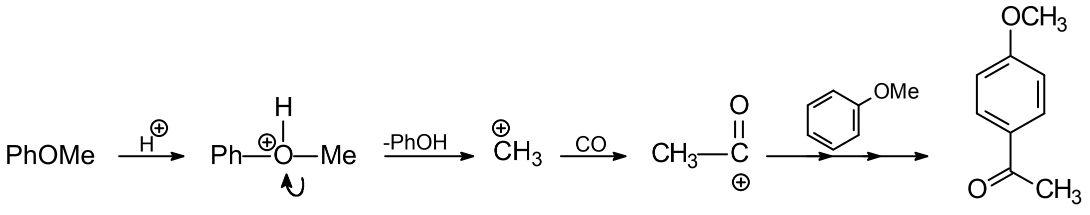
The occurrence of *p*-methoxyacetophenone (46) as secondary product in both of the mechanistic studies as well as with anisole formylation reaction was rather surprising. The same product was however reported by Saint-Jalmes *et al.*[20] during the $HCO_2Me/HF/BF_3$ formylation of anisole. These workers postulated the acid catalysed decomposition of methyl formate into methanol and CO as first step in the reaction. This is followed by dehydration of the liberated methanol with the formation of the methyl cation (43), which is then carbonylated to produce the acylium ion (44). Subsequent nucleophilic attack of anisole on 44 then produces the observed acetophenone (45) (Scheme 2.11).



43 44 45

Scheme 2.11: Acetophenone formation during $HCO_2Me/HF/BF_3$ formylation of anisole

In a similar way, anisole (32) may be dealkylated to phenol and the methyl cation, which in turn is converted into the acylium ion, which reacts with anisole to produce 46 (Scheme 2.12).



32 43 44 46

Scheme 2.12: Acetophenone formation during $CO/HF/BF_3$ formylation of anisole

The investigations into the secondary product mechanisms lead to some insight regarding the overall picture. The formation of addition- and other secondary products resulting from reaction between the substrate and the aldehyde product has a profound impact on a number of important issues. Firstly, secondary products are produced right from the start of the reaction *i.e.* as soon as the first molecule of aldehyde is produced. Thus, extended reaction times to increase the *p*-aldehyde yield will exacerbate secondary product formation and decrease expensive feed capacity. Although shorter reaction times should minimise this problem, it will result in additional production- and capital costs, as larger amounts of feed will have to be recycled. Furthermore, increased reactor size will be necessary due to the lower product yield.

3.4 Formylation of other substrates

A better understanding of the formylation reaction is important and warranted the evaluation of the effect of other ring substituents on the reaction. Chlorobenzene was used to provide information on the influence of deactivating groups on the aromatic ring, while the effect of steric hindrance and increased activation was assessed using diphenyl ether and *p*-methyl anisole as substrate respectively. Although not important from a mechanistic point of view, the aldehyde from 4-nonylphenol has industrial applications and was therefore included in the study. The results are summarised in table 2.9.

Table 2.9: CO formylation of various aromatic substrates using anhydrous HF (50eq) and BF_3 (2eq) as catalysts.

Run	Substrate	Temp (°C)	Time (h)	Products (mass%)			Conver-sion (%)
				p-Aldehyde	o-Aldehyde	Secondary Products	
1	Nonylphenol	45	0.5	-	-	>99	>99
2	Chlorobenzene	45	4.5	31	1	<1	32
3	Diphenyl ether	45	1	85	0	12	97
4	4-Me-anisole	45	2	-	85	14	>99
5	Toluene	45	1	91	5	3	>99
6	Phenol	45	1	43	1	5	49
7	Anisole	45	1	38	6	7	51

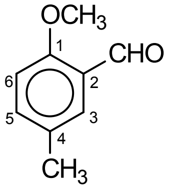
The formylation of nonylphenol yielded a myriad of products of which only phenol and *p*-hydroxybenzaldehyde could be identified unambiguously. Since no 4-nonyl-salicylaldehyde was found, it is clear that de-alkylation of the substrate prevailed under the super acidic conditions of the reaction. (Table 2.9).

As expected, the reactivity of chlorobenzene turned out to be low with only 32% conversion even after extended reaction times of 4.5hours. The activated substrates, diphenyl ether and 4-methylanisole, on the other hand, showed reactivities comparable to that of toluene (97 and 99% conversions respectively under the same conditions), *albeit* with a higher degree of secondary product formation (12 and 14% respectively *vs* 3% for toluene). Although the high reactivity of 4-methylanisole was expected in the presence of two activating groups, that of DPE was somewhat surprising and can probably be ascribed to the sterically hindered oxygen being less available for complexation with BF_3. Booth *et al.*[166] also reported a lack of evidence for the formation of coordination complexes between DPE and BF_3.

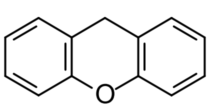
The relative bulky substituents on the benzene rings of chlorobenzene and diphenyl ether probably inhibited *ortho* substitution (≤1%) contributing to an observed extremely high *para*-selectivity. Another contributing factor to the apparent high *para*-selectivity in the use of DPE is that the ortho-aldehyde rapidly converts into components (<u>48</u>) and (<u>49</u>) by a known reaction mechanism demonstrated earlier (*cf* paragraph 3.3.3).

In the case of 4-methylanisole, the question arose as to which of the *ortho* positions would be preferred in the substitution process. A strong NOE between the methyl groups and hydrogens 3 and 5 confirms the assigned structure (47) of the product.

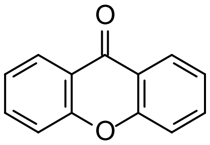
The aldehyde product in the DPE reaction was accompanied by two major secondary products, *i.e*. 9H-xanthene (48) and the xanthone (49), probably originating in a way similar to that of the benzophenone (39) and diphenyl methane (40) during the anisole reaction (*cf* paragraph 3.3.3) (Scheme 2.13).



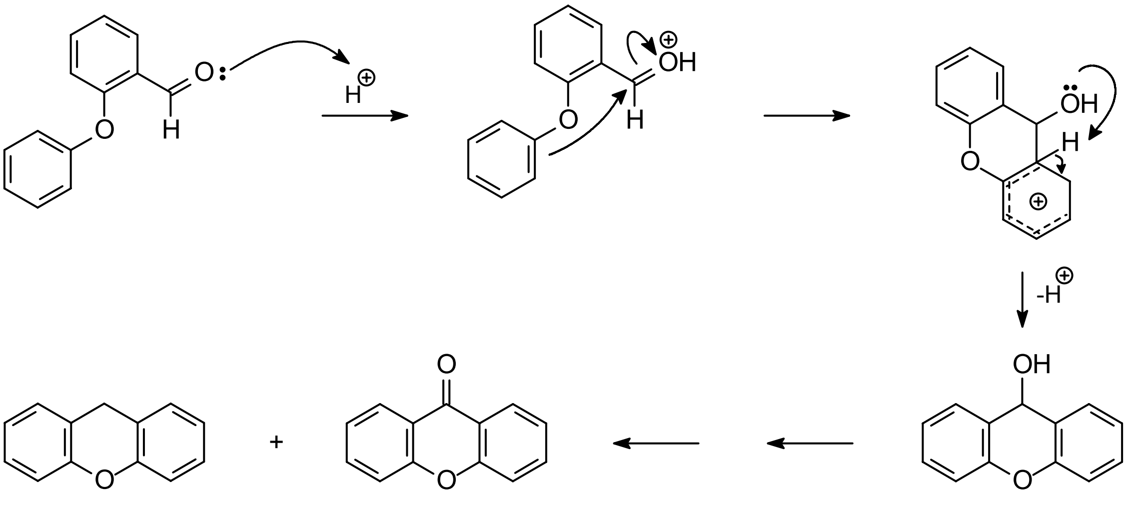
47



48



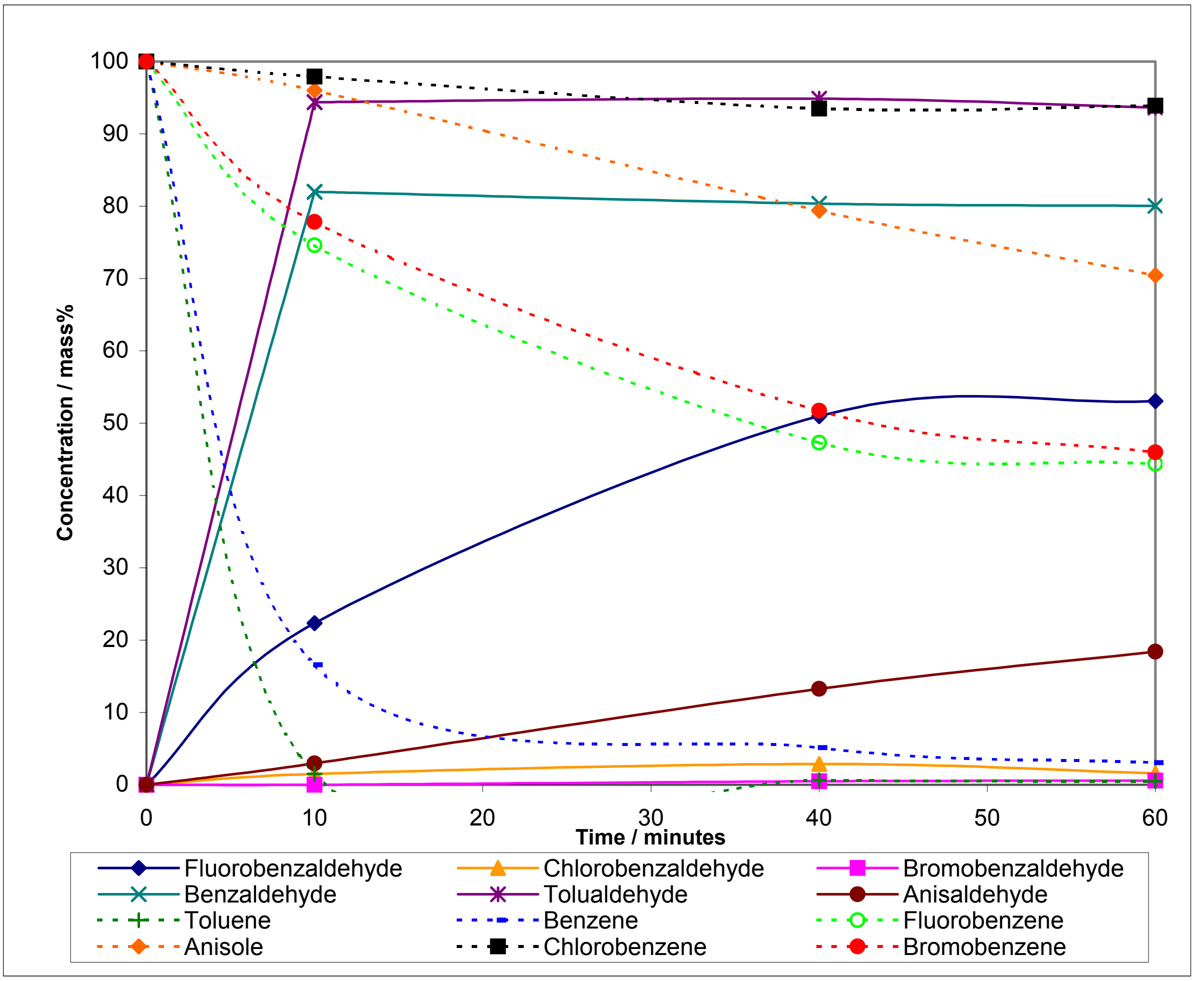
49



48 **49**

Scheme 2.13: Mechanism of 9H-xanthene and xanthone formation

In order to establish relative rates between different substrates, the effect of different substituent groups on *p*-aldehyde formation was compared over time. All reactions (2eq BF_3 and 50eq HF) were conducted in the presence of *n*-decane as internal standard (20 mass% with respect to the substrate) under 50bar CO pressure. From the results represented in Graph 2.1 it is clear that the formylation rate of toluene and benzene are significantly higher compared to the other substrates and maximum aldehyde yield was achieved after only ten minutes. Thereafter a gradual drop in aldehyde yield was observed, indicating that the rate of secondary product formation now becomes faster than aldehyde formation. Of the non-alkyl substituted benzenes, fluorobenzene shows the fastest rate of formylation with little evidence of further reaction of the resulting aldehyde. The formylation of chlorobenzene is extremely slow and it appears that the rate of aldehyde formation is soon overtaken by further reactions of the aldehyde. It is clear that anisole has not reached maximum aldehyde yield after one hour and that extended reaction time is necessary to determine the point of maximum aldehyde yield. Although the reactivity of bromobenzene appears to be high under the reaction conditions, debromonation mainly occurred under the conditions resulting in the production of mainly benzaldehyde with little bromobenzaldehyde (<1%). It is further evident that the concentration of aldehyde product from toluene, anisole and chlorobenzene at one hour is somewhat less compared to previous results (*cf*. Table 2.9). This may be due to the effect of dilution resulting from the addition of the internal standard and the reduced solubility of carbon monoxide in *n*-decane. The reaction rates decreases from toluene> benzene> fluorobenzene> anisole> chlorobenzene emphasising the fact that for electrophilic aromatic substitution reactions, methyl groups are activating while halogens are deactivating relative to benzene as substrate. The decrease in reactivity from fluorobenzene> chlorobenzene> bromobenzene is in accordance with formylation trends observed in HSO_3F-SbF_5[229] and HCO_2CH_3-HF-BF_3 [20] catalyst systems. The higher reactivity of fluorobenzene compared to chlorobenzene is probably explicable in terms of the intracomplex reaction mechanism. Protonation of chlorobenzene should be accomplished easier (stronger base) compared to fluorobenzene due to the lower electronegativity of the chlorine. Protonated chlorobenzene, however will be a weaker acid compared to protonated fluorobenzene and as a result would not be able to activate the pro-electrophile to the same extend as the latter, effecting lower formylation reactivity. The increased reactivity of toluene over benzene originates in the better nucleophilicity associated with toluene and suggests that both toluene and benzene are formylated *via* the conventional mechanism.



Graph 2.1: Aromatic *p*-aldehyde product and substrate distributions over time during the CO formylation of aromatic hydrocarbons in HF/BF_3 at 45°C

Different substituents in the vicinity of a reaction centre may influence a given system (*e.g*. benzene ring) to react in different ways. Studying the effects of substituents on reaction rates of polar reactions in particular may provide valuable mechanistic information.[230]

Polar reactions involve interactions between a nucleophile and electrophile and factors that will facilitate the process are supply of electrons to the nucleophilic centre and withdrawal of electrons from the electrophilic centre. Common substituents used to bring about these electronic perturbations are OH, Me, Cl, F, NO_2, CN.

Hammett showed that a plot of log K_A for benzoic acid ionization against a plot of log k for ester hydrolysis over many substituents is reasonably linear. All the *meta*- or *para*-substituents are exerting a similar effect in each of these quite dissimilar reactions.

Hammett made the first attempt to describe the effects of substituents on such reaction rates in a numerical way. For *m*- and *p*-XC_6H_4Y, he set up the equation

$$\log \frac{k}{k_0} = \sigma\rho$$

where k_0 is the rate- or equilibrium constant for X = H, k is the constant for the group X, ρ is the constant for a given reaction under a given set of conditions and σ is a constant characteristic of the group X. The σ values are numbers that sum up the resonance plus field effects of a group X attached to a benzene ring, but fails for groups in the *ortho*-position due to additional steric effect.

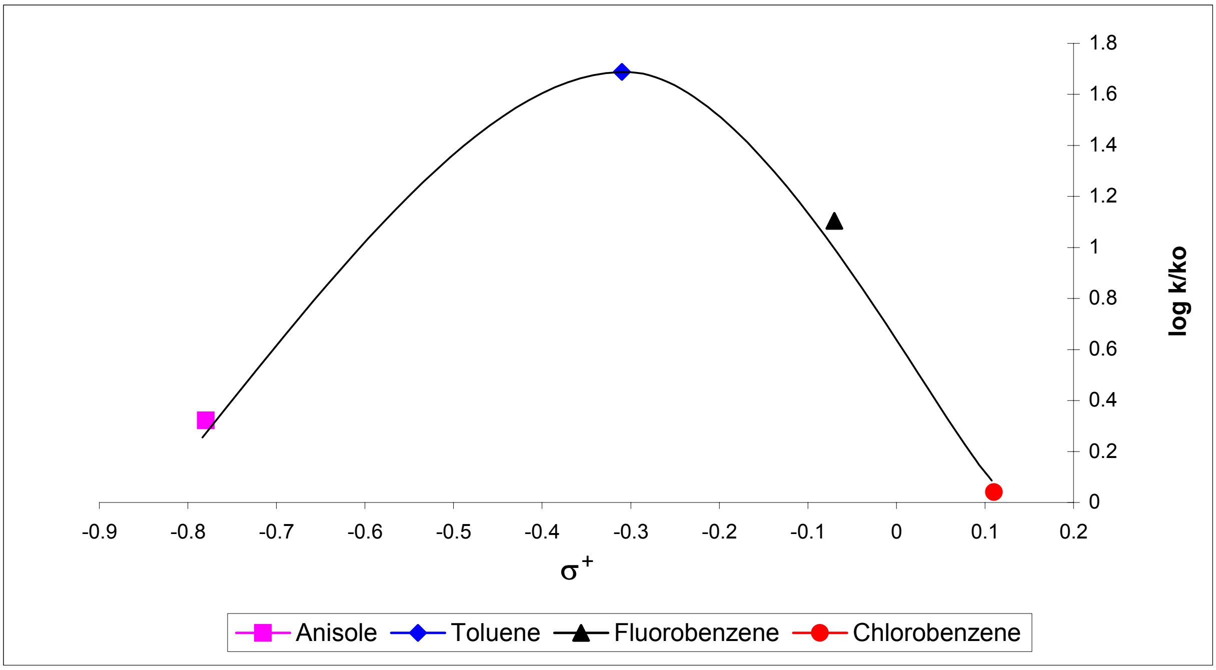
With the ρ values calculated from an experimental set of reactions and the known σ values for other groups, rates may be predicted for reactions that have not been run.

Some reactions do not fit the treatment and for those, two new sets of σ values have been devised: σ^+ values for cases in which an electron donating group interacts with a developing positive charge in the transition state (including electrophilic aromatic substitutions) and σ^- values for where electron withdrawing groups interact with developing negative charge.

As in all linear free-energy relationships, the Hammett equation expresses the similarity of behaviour among two or more sets of reactions. Various types of non-linear behaviour between rates and σ-values may be encountered and include: random deviations due to experimental error, mechanistic change, enhanced resonance and variable resonance interactions.

Sporadic change in the energetically-preferred mechanism may take place after altering a substituent due to the availability of two pathways of similar energy with very different electronic demands. This will result in a sudden change in the slope of the Hammett plot. Changes in the rate-determining step of a multi-step reaction or a unique reaction pathway will also result in discontinuity.

In graph 2.2, the relative reactivities compared to benzene of toluene, fluoro-, chlorobenzene and anisole are plotted as a function of their respective σ^+-values. A linear plot starting from chlorobenzene through fluorobenzene and toluene down to anisole is expected in line with decreasing σ^+-values. The slope of the plot however deviates drastically with anisole, indicative of a different reaction pathway or intermediate involved in this case e.g. competitive protonation on the methoxy substituent.



Graph 2.2: Hammett plot* for CO/HF/BF_3 formylation reactions

* rates were equated with conversion at a given reaction time

3.5 Conclusion

From this study it seems that oxygenated aromatic compounds are less reactive towards acidic CO formylation in comparison to alkylated ones and this effect can be explained by the relative acid-base properties of the substrate and carbon monoxide. More than stoichiometric amounts of acid are required for acceptable rates and yields. Various acids apart from the HF/BF_3 system were investigated without success in an attempt to facilitate formylation of anisole. Deuterium labelling experiments as a tool to probe the possible reaction mechanism provided interesting but inconclusive results in support of the intra-complex mechanism. Secondary product formation was shown to result mainly from acid catalysed reactions between the substrate and the aldehyde product. Preliminary economic evaluations indicated boron trifluoride to be the major cost driver in these reactions, necessitating its quantitative recovery. A successful HF/BF_3 retrieval process is described by Fujiyama *et al.*[231,232] and involves the decomposition of the *p*-tolualdehyde complex in the presence of fluorine substituted aromatic compounds with recovery of the aldehyde, HF and BF_3 in excess of 99%. Such a process could be applicable to PAA production. However, it may require prior removal of the unreacted substrate in order to prevent secondary product formation. A typical approach would be to remove anisole selectively from the product stream without the application of heat *e.g.* liquid-liquid extraction followed by the acid recovery process.

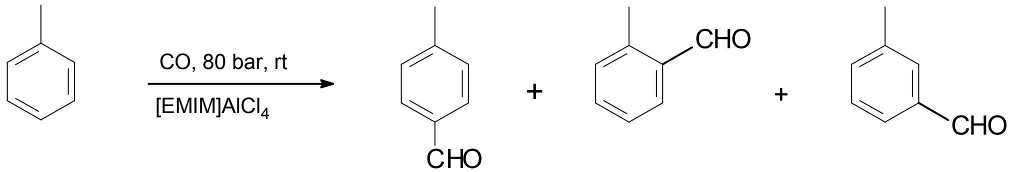
In the light of the difficult economic application of formylation with CO, the development of new catalysts or methodology will be required to allow the use of HF/BF_3 in a catalytic way. One such an alternative may be found in the exploration of a new and ecological-friendly field, *i.e.* ionic liquids.

4. IONIC LIQUIDS AS SOLVENT FOR HF/BF_3 CATALYSED REACTIONS

4.1 Introduction

Ionic liquids are non-volatile liquid salts at room temperature with physical and chemical properties that can be tailored to facilitate not only the reactivity of specific reactions, but also the regioselectivity.

The first CO formylation reaction of aromatic compounds using an ionic liquid was described by Kniften *et al.*[233] who carbonylated toluene in *N*-butylpyridinium-aluminum-tetrachloride under drastic conditions (100°C, 4h, 207bar CO pressure) to obtain the *para*-aldehyde in low yield of 6.6%. Excellent yields and selectivities were however obtained by Exxon Mobil Chemical Co.[234] when an ionic liquid consisting of alkyl imidazolium- and $AlCl_4^-$ ions were used (Eq 2.25). Recovery of the temperature labile aldehyde was conveniently achieved by using a wiped film evaporator separating the ionic liquid from the aldehyde. Since literature precedent for formylation of aromatic compounds exist, it was therefore decided to investigate this possibility as method for the production of PAA using HF/BF_3 in a catalytic way.



89% *p*- + 10% *o*- +1% *m*-
conversion = 24 - 66%

(2.25)

4.2 General definitions and characteristics of ionic liquids

Although the discovery of ionic liquids can be dated back to 1914 when Walden[235] reported the formation of ethyl ammonium nitrate (m.p. 12°C) from the reaction of ethylamine with concentrated nitric acid, no interest in these compounds was shown at the time. Over the last few years however, ionic liquids are emerging as an attractive "green" alternative technology in organic and organometallic chemistry. This "green" technology involves the reduction of waste from industrial processes. Sheldon[236] defines the *E*-factor, environmental efficiency, of a process as the weight ratio of by-products to that of the desired product(s) (Table 2.10).

Table 2.10: Sheldon *E*-factor for different industries

Industry	Production (tons pa)	E-factor
Oil Refining	10^6-10^8	0.1
Bulk Chemicals	10^4-10^6	1-5
Fine Chemicals	10^2-10^4	5-50
Pharmaceuticals	10^1-10^3	25-100

The exact definition of an ionic liquid pertaining to the melting point is not clear-cut as some variations are found in literature. Wasserscheid *et al.*[237] defines an ionic liquid as a liquid consisting of mainly ions having a liquid range below 100°C. Gordon[238] describes ionic liquids as a liquid which is composed entirely of ions with melting points of below 100−150°C, while Hagiwara *et al.*[239] exclude ionic species having a melting point higher than 25°C.

Ionic liquids exhibit interesting physical properties that could lead to the substitution of volatile organic solvents[240] by these compounds. These properties can be summarised as follows:

No measurable vapour pressure.

Good solubility properties over a wide range of both organic and inorganic materials.

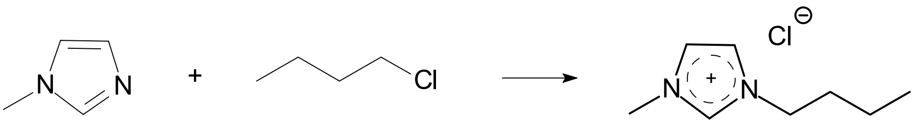
The potential to be highly polar yet non-coordinating solvents.

Provide a non-aqueous, polar alternative for two-phase systems.

4.3 Synthesis of ionic liquids

Ionic liquids typically consist of a bulky hetero-carbon cation *e.g.* alkyl imidazolium or –pyridinium in combination with an anion *e.g*. BF_4^- or PF_6^-.

The first step in ionic liquid synthesis involves quaternization or alkylation of 1-methylimidazole using chlorobutane for example to obtain the cation (Eq 2.26).[241,242,243]



(2.26)

Some of the most important cations are shown in Scheme 2.14:

Imidazolium ion Pyridinium ion Ammonium ion Phosphonium ion

Scheme 2.14: Important types of cations in ionic liquids

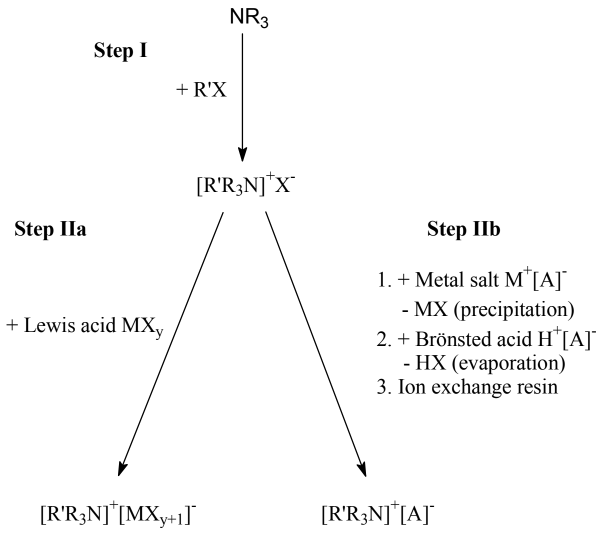
Salts having melting points of less than 100°C with altered anions are obtained by quaternization reactions with different alkylation reagents (Table 2.11)

Table 2.11: Examples of ionic liquids that can be formed by direct quaternization

Ionic Liquid	Alkylation Reagent	M.p. (°C)	Ref.
$[EMIM]CF_3SO_3$ [a]	Methyl triflate	-9	244
$[BMIM]CF_3SO_3$ [b]	Methyl triflate	16	249
$[Ph_3POc]OTs$ [c]	OcOTs	70-71	245
$[Bu_3NMe]OTs$	MeOTs	62	246
[BMIM]Cl	Chlorobutane	65-69	247

[a] EMIM = 1-ethyl-3methylimidazolium; CF_3SO_3 = triflate anion [b] BMIM = 1-*n*-butyl-3-methylimidazolium [c] Oc = octyl; Ts = $H_3CC_6H_4SO_2$ (tosyl)

When it is not possible to produce the desired anion directly from the quaternization reaction (Step I), two other different routes are possible (Scheme 2.15). An ammonium halide $[R'R_3N]^+X^-$ can for example be treated with a Lewis acid MX_y to give the ionic liquid $[R'R_3N]^+$ $[MX_{y+1}]^-$(Step IIa). The halide ion X^- can alternatively, (Step IIb) be exchanged with the desired anion by either addition of a metal salt $M^+[A]^-$ over an ion exchanger, or removal of the halide ion using a strong acid $H^+[A]^-$ (Scheme 2.15).



Scheme 2.15: Example of the synthesis paths for the preparation of ionic liquid from an ammonium salt[248]

When excess Lewis acid MX is added to the ammonium salt, additional anionic species are formed from further acid-base reactions by the already present anion. This is observed with chloroaluminate melts, *e.g.* Eq 2.27 and 2.28.[249]

$$\overset{\oplus}{[R'R_3N]}\,\overset{\ominus}{AlCl_4} + AlCl_3 \rightleftharpoons \overset{\oplus}{[R'R_3N]}\,\overset{\ominus}{Al_2Cl_7} \qquad (2.27)$$

$$\overset{\oplus}{[R'R_3N]}\,\overset{\ominus}{Al_2Cl_7} + AlCl_3 \rightleftharpoons \overset{\oplus}{[R'R_3N]}\,\overset{\ominus}{Al_3Cl_{10}} \qquad (2.28)$$

The formation of different anions is dependent on the chloride/$AlCl_3$ ratio. The addition of aluminum trichloride to the chloride initially results in the formation of the $AlCl_4^-$ ion and this is essentially the only anion present at an aluminum trichloride mole-fraction of exactly 0.5. At $x(AlCl_3)>0.5$, multi-nuclear chloroaluminate anions are formed which are in equilibrium with one another, the $AlCl_4^-$ ion and at very high $AlCl_3$ mole fractions with dimeric aluminum trichloride (Eq 2.27 and 2.28). Chloroaluminates are well known, however other ionic liquids may also be prepared from a halide and Lewis acid (Table 2.12).

Table 2.12: Examples of ionic liquids that can be generated by the reaction of a halide with a Lewis acid

Ionic Liquid [a]	Established anion	Ref
[cation]Cl/$AlCl_3$	Cl^-, $AlCl_4^-$, $Al_2Cl_7^-$, $Al_3Cl_{10}^-$	[250,251]
[cation]Cl/$AlEtCl_2$	$AlEtCl_3^-$, $Al_2Et_2Cl_5^-$	[252]
[cation]Cl/BCl_3	Cl^-, BCl_4^-	[253]
[cation]Cl/CuCl	$CuCl_2^-$, $Cu_2Cl_3^-$, $Cu_3Cl_4^-$	[254]
[cation]Cl/$SnCl_2$	$SnCl_3^-$, $Sn_2Cl_5^-$	[255]

[a] cation = pyridinium or imidazolium ion.

Ionic liquids of the type $[\text{cation}]^+[\text{A}]^-$ are formed using Step IIb, (Scheme 2.10) and contain only one anion species once the exchange reaction reaches completion (Table 2.13).

Table 2.13: Examples of ionic liquids prepared by anion exchange

Ionic Liquid [a]	Ref
$[\text{cation}]BF_4$	256,257
$[\text{cation}]PF_6$	258
$[\text{cation}]SbF_6$	259
$[\text{cation}]NO_3$	260
$[\text{cation}]CH_3CO_2$	261
$[\text{cation}]HSO_4$	262
$[\text{cation}]B(Et_3Hex)$	263

[a] cation = pyridinium, imidazolium, ammonium ion.

The above-mentioned methods can also be used to prepare previously unknown combinations of cations and anions that may result in low-melting salts with the possibility to obtain ionic liquids with new properties.[264]

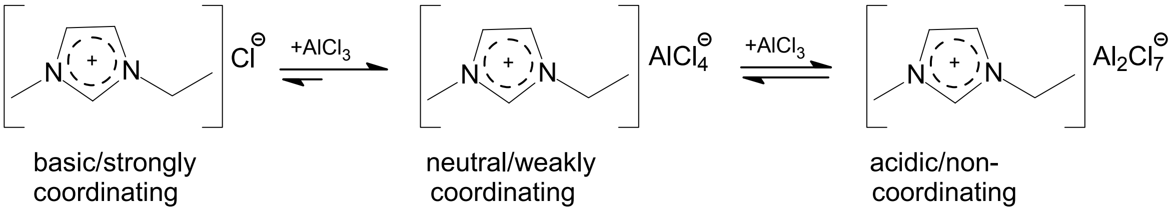
4.4 Acidity and coordination ability of ionic liquids

The acidity and coordination properties of an ionic liquid are dependant on the nature of its anion. Different anions realise many intermediate levels between "strongly basic/strongly coordinating" and "strongly acidic/practically non-coordinating" (Table 2.14).[265]

Table 2.14: Coordinative characteristics of various anions

Basic/strongly coordinating	Acidity/coordination	Acidic/non-coordinating
	Neutral/weakly coordinating	
Cl^-	$AlCl_4^-$	$Al_2Cl_7^-$
Ac^-	$CuCl_2^-$	$Al_3Cl_{10}^-$
NO_3^-	SbF_6^-	
SO_4^{2-}	BF_4^-	$Cu_2Cl_3^-$
	PF_6^-	$Cu_3Cl_4^-$

Scheme 2.16 illustrates the ionic liquids that produce a neutral anion (*e.g.* $AlCl_4^-$) or an acidic anion (*e.g.* $Al_2Cl_7^-$) from a basic anion (*e.g.* Cl^-) by addition of a Lewis acid (*e.g.* $AlCl_3$).



Scheme 2.16: Acidity control of ionic liquids by the ratio of halide to Lewis acid exemplified for 1-ethyl-3-methylimidazolium (EMIM) chloroaluminate melt

Chloroaluminate melts qualify as basic when the molar ratio of $AlCl_3$ is smaller than 0.5. A neutral melt has an $AlCl_3$ ratio of exactly 0.5, and essentially only the anion $AlCl_4^-$ is present.[266] Finally, an acidic chloroaluminate melt is one in which the $AlCl_3$ ratio is larger than 0.5 and consists of the anions $Al_2Cl_7^-$ and $Al_3Cl_{10}^-$ which act as very strong Lewis acids.[267,268]

"Latent acidity" and "super acidity" are two interesting phenomena in the field of acid base chemistry in ionic liquids.

Latent acidity of ionic liquid arises when weak bases are added to buffered neutral chloroaluminate ionic liquid. These neutral ionic liquids are formed when excess alkali metal chloride (MCl) is added to an acidic chloroaluminate ionic liquid (Equation 2.28).[269,270] The alkali metal chloride (MCl) reacts with the acidic chloroaluminate dimers until the ionic liquid becomes neutral.

$$Al_2Cl_7^{\ominus} + MCl \rightleftharpoons 2AlCl_4^{\ominus} + M^{\oplus} \qquad (2.28)$$

A buffered ionic liquid is one in which the neutrality is maintained by reaction of excess alkali metal chloride when acid $AlCl_3$ is added. The latent acidity of this neutral system becomes observable when a weak base (B) such as *N,N*-dimethylaniline, pyrrole, or acetylferrocene is added.[271,272] Reaction between the added base and the $AlCl_3$ results in adduct formation with precipitation of the alkali chloride MCl (Eq 2.29).

$$B + AlCl_4^{\ominus} + M \rightleftharpoons B\text{-}AlCl_3 + MCl_{(s)} \qquad (2.29)$$

The reaction is not detected in the absence of excess alkali metal cations. The latent acidity of different ionic liquids have been quantitatively measured by Osteryoung *et al.*[273]

Superacidity have been observed when strong mineral acids were dissolved in acidic chloroaluminate ionic liquids.[274,275] Smith[276] and co-workers investigated the acidity of ionic liquids by the protonation of aryl compounds with a solution of HCl gas in acidic [EMIM]Cl/AlCl$_3$ ionic liquids and the acidity were measured quantitatively by UV spectroscopy. Acid strength was obtained as a function of the ionic liquid's acidity, which was clearly above that of 100% sulphuric acid (Fig 2.8).[277]

The superacidity of chloroaluminate ionic liquids is explained by the reaction of the dissolved hydrogen chloride and the acidic species in the melt, which releases protons with extremely low solvation and thus very high reactivity (Eq 2.30).

$$HCl + Al_2Cl_7^- \rightleftharpoons [H]^+_{nonsolvated} + 2AlCl_4^- \qquad (2.30)$$

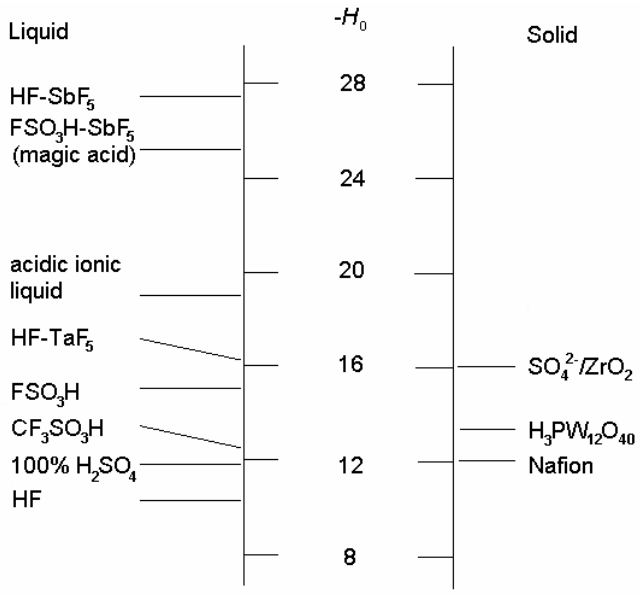


Figure 2.8: Acid strength of super acid ionic liquids compared to conventional super acids

Superacidic ionic liquids are much safer and easier to handle compared to normal super acid systems and could therefore represent promising alternatives to the conventional super acids.[278]

The cation of an ionic liquid can also influence the acidity of a system and a weak Lewis acidity is attributed by the imidazolium ion itself. The catalytic effect of imidazolium bromide melts in Diels-Alder reactions is reported to be related to this weak acidity of the imidazolium ion.[279] Moreover, the H atom in the α-position of an imidazolium ion possesses significant Brønsted acidity which could be beneficial for reactions involving transition metal complexes as *in situ* carbene complexes can be formed in the presence of base.[280]

4.5 Ionic Liquids as Solvents for Transition Metal Catalyzed Reactions

Ionic liquids are being researched extensively in the fields of hydrogenation,[281] oxidation,[282] oligomerization,[283] hydroformylation,[284] Heck and Suzuki reactions,[285] Trost-Tsuji couplings,[286] Friedel-Crafts reactions,[287] Diels-Alder reactions,[288] electrophilic nitrations,[289] and palladium catalysed carbonylation of aryl halides.[290]

4.6 Formylation Reactions in Ionic Liquids

The unique properties of ionic liquids in general, allow these compounds to be versatile reagents and solvent for many reactions. The enhanced reactivity and isomer selectivity brought about by ionic liquids in many reactions may also be applicable to phenolic derivatives used in CO formylation, hence the interest to explore these possibilities.

The superacidity of chloro-aluminate melts, (*cf* paragraph 4.4) allows them to be ideal candidates for CO formylations. In order to compare the formylation of phenolics to that of aromatic hydrocarbons in ionic liquids, a study of formylation using CO in an ionic liquid was started with toluene as substrate and acidic chloro-aluminate melts (Table 2.15). A 1:1 mol ratio of toluene to ionic liquid with mol fraction $AlCl_3$ = 0.67 gave moderate yields of the aldehyde derivative at mild temperature (Runs 1 and 2). When the ethyl-derivative of the melt was used, a slight increase in the conversion was observed which may be attributed to the higher solubility of CO in this specific melt.

Table 2.15: Formylation of aromatic substrates in chloro-aluminate ionic liquids at 83bar CO pressure*

Run	Substrate (mmol)	Ionic Liquid (mmol)	Conditions	Products (%)	Conversion (%)
1	Toluene (41)	$BmimAlCl_4$ (44)	rt 1h	*p*-Tolualdehyde (22) *o*-Tolualdehyde (2.7)	25
2	Toluene (42)	$EmimAlCl_4$ (50)	rt 1h	*p*-Tolualdehyde (37) *o*-Tolualdehyde (1)	38
3	Anisole (37)	$BmimAlCl_4$ (37)	rt 1h	-	-
4	Anisole (39)	$BmimAlCl_4$ (38)	rt 1h $AlCl_3$ complexation followed by substrate addition	-	-
5	Anisole (14)	$BmimAlCl_4$ (129)	70°C 1.5h	-	-
6	Phenol (42)	$EmimAlCl_4$ (108)	60°C 4.5h	-	-
7	Phenol (42)	$BmimAlCl_4$ (128) Cu_2O 0.03g	45°C 0.5h	-	-

*All reactions molfraction(x) $AlCl_3$ in alkylmimCl = 0.67 except run 7 x($AlCl_3$) = 0.75

Subjecting anisole to similar reaction conditions however, led to no detectable formylation. Since Al-complexation to anisole could have effected a reduction in the acidity of the ionic liquid, it was decided to minimise this possibility by CO-Al pre-complexation. The ionic liquid was therefor pressurised with CO for a short period at room temperature before anisole addition at atmospheric pressure (Run 4). Apart from de-alkylation to phenol (<1%) together with alkylation of anisole to methoxy-2-methyl benzene, the bulk of the substrate remained unchanged. The lack of any formylation activity could arise from inadequate amounts of uncomplexed Al-ions, thus leading to lower acidity. The substrate was therefore treated with excess chloro-aluminate melt (3:1) and the substrate was introduced at 83bar CO pressure (Run 5). Although a slight increase in anisole dealkylation (compared to the previous run) was observed, the bulk of substrate remained unchanged. Addition of toluene to the reaction mixture and subsequent formation of tolualdehyde confirmed reaction conditions conducive to formylation.

Although it is known, that phenol cannot be formylated under ordinary Gattermann-Koch conditions,[291] it was decided to evaluate acidic ionic liquids in this regard. Phenol was subjected to a chloro-aluminate ionic liquid containing (mol fraction $AlCl_3$ 0.67 *vs.* 0.75) an excess of $AlCl_3$. The substrate however remained unchanged with no detectable aldehyde generation. Since it is also known that Gattermann-Koch formylations should either be performed at elevated pressures (100-250bar) or with addition of CuCl[292] or Cu_2O[293] to enhance CO solubility through formation of $Cu(CO)_4^+$ species, the reaction was repeated in the presence of Cu_2O. Again no aldehyde product could be detected. Although this result points towards the inadequate acidity of chloro-aluminate ionic liquids with regard to CO formylation of phenols, the solubility of CO and the unknown effect of the addition of the copper salts to IL's on the solubility of CO in the IL's may be a contributing factor. From these results, it is clear that chloro-aluminate ionic liquids are able to formylate methyl activated benzene derivatives, but not oxygen-containing aromatics.

The potential super acid capability of excess aqueous HBF_4 and HPF_6 in ionic liquid may facilitate formylation reactions of aromatics and were subsequently investigated. Toluene, being highly susceptible to CO formylation under acidic conditions, was therefor subjected to treatment with excess HPF_6 and HBF_4 in $BmimPF_6$ and $BmimBF_4$ respectively (Table 2.16, Runs 1 and 2). No formylation products were obtained which may be explained in terms of the HBF_4- and HPF_6-water complexes being exceptionally stable and thus not acidic enough to facilitate the formylation reaction.

Table 2.16: Formylation of aromatic substrates in acidified neutral ionic liquids at 50bar CO pressure

Run	Substrate (mmol)	Ionic Liquid (mmol)	Reagents (mmol)	Conditions	Products (%)	Conv. (%)
1	Toluene (37)	$BmimPF_6$ (18g)	$aqHPF_6$ (88)	rt 1h	-	-
2	Toluene (40)	$BmimBF_4$ (17g)	$aqHBF_4$ (111)	rt 1h	-	-
3	Phenol (21)	$BmimBF_4$ (14g)	CF_3SO_3H (106)	rt 1h	-	-
4	Anisole (11)	OmimBTA (20g)	CF_3SO_3H (154) BF_3 (82)	45°C 4.5h	PAA (0.6) OAA (0) Phenol (5)	10

Triflic acid is known as one of the strongest monoprotic organic acids ($-H_o = 14$) and it is used in processes for production of aldehydes from alkyl benzenes have been described.[294] It was decided to investigate whether this acid in IL's can promote anisole formylation, despite the fact that this acid was not successfully used in this way even at high CO pressure.[295] Anisole dissolved in $omimBF_4$ containing excess (5-14eq) triflic acid under CO was reacted at 45°C or at room temperature. Phenol in $bmimBF_4$ was treated in the same way. No formylation products were however obtained. Since BF_3 is known to form stable complexes with aldehydes thus rendering the reaction thermodynamically more favourable,[296] subsequent reactions with triflic acid were carried out in the presence of excess BF_3 (8eq). PAA was obtained in only minute quantities while some de-alkylation of the substrate occurred (Run 4). Although triflic acid is in the range of low super acidity, it must therefore be concluded that its acidity is insufficient for formylation of oxygen containing aromatics.

It was now decided to revert to the use of HF/BF_3 and evaluate its efficacy in ionic liquids. If this super acid could be used in catalytic quantities and remain in the ionic liquid during separation of the product, it could form the basis of a viable industrial process. Toluene, anisole and phenol were successfully formylated in $bmimBF_4$ following HF/BF_3 acidification (Table 2.17, Runs 1, 2 and 3). The total aldehyde yield of phenol (32%) was significantly higher compared to both toluene (5%) and anisole (7%) under similar conditions. Although a reaction time of 12hours was allowed, the total aldehyde yield of all three substrates remained inferior to earlier results obtained (Table 2.2). The difference between conversion and aldehyde product obtained in the case of toluene and anisole are mainly attributed to the formation of the same secondary products observed in the HF/BF_3 system (*cf* Figure 2.4).

Although these formylations gave some aldehyde product, yields remained poor and had to be improved if the process were to be any way near commercially applicable. While it is known that the physical properties of ionic liquids can be changed by utilizing different cationic- and anionic species, it has also been described that the solubility of gasses such as CO, O_2 and H_2 are influenced by the constituents of a particular ionic liquid. In general, it has been found that imidazolium cations with increased chain lenth favours high CO solubility while it is also enhanced by anions such as BF_4^- and BTA^-.[297] With this in mind the alkyl chain-length of the cations were changed from 4 to 8 and the anions from BF_4^- to PF_6^- to BTA^-. Changing the ionic liquid cation from Bmim to Omim resulted in a dramatic increase in aldehyde yield for phenol (31 to 91%), but only a moderate improvement (7 to 26%) was reached in the case of anisole. Substituting the BF_4^- counter anion for PF_6^- afforded slightly lower aldehyde yields for anisole (Runs 7 and 8). When the PF_6^- counter anion was replaced with trifluoromethanesulfonimide (BTA) however, significantly higher aldehyde yields (45%) were obtained for anisole (Run 9). The increase in alkyl chain-length resulted in further improvement (Runs 9 and 10). The lower yields of PAA can be attributed to the formation of secondary products. The presence of even small amounts of moisture in the ionic liquid was detrimental to the formylation reaction (Run 12 compared to run 10).

Anisole was subjected to formylation with reduced amounts of HF (2eq) and BF_3 (0.5eq) under otherwise similar reaction conditions (Run 11). Although high conversion of anisole to phenol and alkylated phenol were observed, no aldehyde products were produced. It is thus clear that this particular type of ionic liquid is unable to facilitate the catalytic use of HF/BF_3 in formylation reactions.

Table 2.17: Formylation of aromatic substrates in acidified neutral ionic liquids at 50bar CO pressure

Run	Substrate (mmol)	Ionic Liquid (mmol)	Reagents (mmol)	Conditions	Products (%)	Conv. (%)
1	Toluene (11)	$BmimBF_4$ (46g)	HF (555) BF_3 (25)	45°C 12h	*p*-Tolualdehyde (5)	44
2	Anisole (11)	$BmimBF_4$ (45g)	HF (555) BF_3 (21)	45°C 12h	PAA (7) OAA (0.2) Phenol (21)	40
3	Phenol (11)	$BmimBF_4$ (41g)	HF (550) BF_3 (44)	45°C 12h	PHBAldehyde (31) OHBAldehyde (1)	35
4	Phenol (11)	$OmimBF_4$ (20g)	HF (550)	rt 12h	PHBAldehyde (83)	97

Run	Substrate (mmol)	Ionic Liquid (mmol)	Reagents (mmol)	Conditions	Products (%)	Conv. (%)
			BF_3 (69)	45°C 6h	OHBAldehyde (8)	
5	Anisole (11)	$OmimBF_4$ (20g)	HF (550) BF_3 (59)	45°C 12h	PAA (26) OAA (2)	99
6	Anisole (11)	$OmimBF_4$ (20g)	HF (550) BF_3 (81)	45°C 4.5h	PAA (26) OAA (2)	83
7	Anisole (11)	$OmimPF_6$ (20g)	HF (550) BF_3 (47)	45°C 4.5h	PAA (20) OAA (1)	84
8	Anisole (11)	$HexmimPF_6$ (20g)	HF (550) BF_3 (61)	45°C 4.5h	PAA (15) OAA (1)	67
9	Anisole (11)	OmimBTA (20g)	HF (550) BF_3 (69)	45°C 4.5h	PAA (45) OAA (2)	90
10	Anisole (11)	BmimBTA (20g)	HF (550) BF_3 (63)	45°C 1h	PAA (8) OAA (1) Phenol (2)	30
11	Anisole (300)	OmimBTA (20g)	HF (600) BF_3 (150)	45°C 4.5h	Phenol and alkylated anisole	76
12	Anisole (11)	BmimBTA (20g) 0.3% H_2O	HF (550) BF_3 (35)	45°C 4.5h	No reaction	-

4.7 Conclusions

Chloro-aluminate ionic liquids promote the carbonylation of alkylated aromatic compounds, but fails in the case of oxygenated aromatics. Aldehyde yields of formylation in the acidified neutral ionic liquids were generally similar compared to reactions conducted in HF as solvent/catalyst (*cf* Table 2.2). The increase in aldehyde yields with the use of extended alkyl chain lengths of the cationic part of the melt, may be due to improved CO solubility. HF/BF_3-acidified neutral ionic liquids showed both increases in *para*-selectivity compared to HF as solvent and catalyst. Formylation of anisole and toluene, but not of phenol in the neutral ionic liquids resulted in increased secondary product formation in comparison with hydrogen fluoride used as solvent/catalyst. This difference in behaviour is not understood at present, but suggests that phenol is a good substrate for formylation in this medium, particularly with the development of a system catalytic with respect to HF/BF_3 in mind.

4.8 REFERENCES

[155] Maliverney C., Mulhauser M., *Kirk-Othmer Encyclopedia of Chemical Technology,* 4th ed., Vol 13 (Ed. Howe-Grant M.), John Wiley, New York, **1994**, 1030-1042.

[156] Fiege H., *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed., **2002** Electronic Release, Wiley-VCH, Weinheim, Germany.

[157] Bauer K., Garbe D., Surburg H., *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed., **2002** Electronic Release, Wiley-VCH, Weinheim, Germany.

[158] Imamura J., *Yuko Gosei Kagaku Kyokaishi*, 37, **1979**, 667; *Chem. Abstr. 92*, **1980**, 6158d.

[159] Degner D., Barl M., Siegel H., *DE 2848397* to BASF, **1978**.

[160] Weisse L., Neunteufel R., Strutz H., *US 5395978* to Hoechst Aktiengesellschaft, **1995**.

[161] Colquhoun H.M., Thompson D.J., Twigg M.V., *"Carbonylation: Direct Synthesis of Carbonyl Compounds"*, Plenum Press, New York and London, **1991**, *9*.

[162] Greenwood N.N., Earnshaw A., *Chemistry of the Elements*, Pergamon Press New York, **1986**, *949*.

[163] Cotton F.A., Wilkinson G., *Advanced Inorganic Chemistry 5th ed.*, **1988**, *94*.

[164] Hammet L.P., Deyrup A.J., *J. Am. Chem. Soc.*, 54, **1932**, *2721-2739*.

[165] Gillespie R.J., Peel T.E., *Adv. Phys. Org. Chem.*, 9, **1972**, *1-24*.

[166] Mackor E.L., Hofstra A., van der Waals J.H., *Trans. Faraday Soc.*, 54, **1958**, *66-83*.

[167] Aigueperse, J., Surburg H., *Ullmann's Encyclopedia of Industrial Chemistry, 6th ed.*, **2002** Electronic Release, Wiley-VCH, Weinheim, Germany.

[168] Booth H.S., Martin D.R., *Boron Trifluoride and its Derivatives*, John Wiley and Sons New York, **1949**, *1-291*.

[169] D. Mootz, M. Steffen, *Angew. Chem.* 92, **1980**, *481*; *Angew. Chem. Int. Ed. Engl.*, 19, **1980**, *483*.

[170] R.J. Brotherton, C.J. Weber, C.R. Guibert, J.L. Little, *Ullmann's Encyclopedia of Industrial Chemistry 6th ed.*, **2000**, Electronic Release.

[171] F.A. Cotton, G. Wilkinson, *Advanced Inorganic Chemistry 5th ed.*, **1988**, *174*.

[172] D.B. Beach, W.L. Jolly, *J. Phys. Chem.*, 88, **1984**, *4647*.

[173] Olah G.A., Prakash G.K.S., Sommer J., *Superacids*, John Wiley & Sons New York, **1985**.

---

[174] O'Donnel T.A., Superacids and Acidic Melts as Inorganic Reaction Media, VCH, New York, **1993**.

[175] Olah G.A., Brude M.R., Husain E.H., *Fuel*, 63, **1984**, *1130*.

[176] Korai Y., Nakamura M., Mochida I., *Carbon*, 29, **1991**, *561*.

[177] Olah G.A., Lucas J., *J. Am. Chem. Soc*., 89, **1967**, *4739-4744*.

[178] Olah G.A., *Friedel-Crafts Chemistry*, John Wiley & Sons, New York, **1973**.

[179] Olah G.A., *Friedel-Crafts and Related Reactions, Vol.1*, John Wiley & Sons New York, **1993**.

[180] Sharp D.W.A., *Advan. Fluorine Chem*., 1, **1960**, *68-128*.

[181] McCaulay D.A., Lien A.P., Shoemaker B.H., *Ind. Eng. Chem*., 42, **1950**, *2103-2107*.

[182] McCaulay D.A., Lien A.P., *F. Amer. Chem. Soc*., 73, **1951**, *2013-2017*.

[183] Hughes E.C., Darling S.M., *Ind. Eng. Chem*., 43, **1951**, *746-750*.

[184] Kilpatrick M., Luborsky F.E., *J. Am. Chem. Soc*., 76, **1954**, *5865-5868*.

[185] Olah G.A., Prakash G.K.S., Sommer J., *Superacids*, John Wiley & Sons New York, **1985**, *51-52*.

[186] Olah G.A., Kuhn S.J., *Nature* (London), 178, **1956**, *693-694*.

[187] Olah G.A., Kuhn S.J., *J. Am. Chem. Soc*., 80, **1958**, *6535-6539*.

[188] Kim D., Klein M.L., *Chem. Phys. Lett*., 308, **1999**, *235-241*.

[189] Olah G.A., Prakash G.K.S., Sommer J., *Superacids*, John Wiley & Sons New York, **1985**, *9*.

[190] MacLean C., MacKor E.L., *Disc. Farad. Soc*., 34, **1962**, *165-176*.

[191] Brouwer P.M., MacKor E.L., MacLean C., *Recl. Trav. Chim. Pays-Bas*., 84, **1965**, *1564*.

[192] Brotherton R.J., Weber C.J., Guibert C.R., Little J.L., *Ullmann's Encyclopedia of Industrial Chemistry, 6th ed*., **2002** Electronic Release, Wiley-VCH, Weinheim, Germany.

[193] Thenard L.J., Gay-Lussac J.L., *Ann. Chim*., 69, **1809**, *204-220*.

[194] Fischer F., Thiele K., *Anorg. Allgem. Chem*., 67, **1910**, *302-316*.

[195] Wamser C.A., *J. Am. Chem. Soc*., 70, **1948**, *1209-1215*.

[196] Weisse L., Neunteufel R., Strutz H., *US 5395978* to Hoechst Aktiengesellschaft, **1995**.

[197] Takezaki Y, Sugita N., Kudo K., Teranishi H., *Sekign Gakkaishi*, 11, **1968**, *690-695*.

[198] Takezaki Y, Sugita N., Teranishi H., Kudo K., Inoue A., *Bull. Jpn. Petrol. Inst*., 9, **1967**, *45-52*.

---

[199] Weisse L., Neunteufel R., Strutz H., *US 5395978* to Hoechst Aktiengesellschaft, **1995**; Colquhoun H.M., Thompson D.J., Twigg M.V., *“Carbonylation: Direct Synthesis of Carbonyl Compounds”*, Plenum Press, New York and London, **1991**.

[200] Doko Y., Kudo K., Minami Y., Mori S., Sugita N., *Sekiyu Gakkaishi*, 40(2), **1997**, *115-123*.

[201] Olah G.A., Pelizza F., Kobayashi S., Olah J.A., *J. Am. Chem. Soc*., 98, **1976**, *296-297*.

[202] Olah G.A., Ohannesian I., Arvanaghi M., *Chem. Rev*., 98, **1987**, *296*.

[203] Tanaka M., Iyoda J., Souma Y.J., *Org. Chem*., 57, **1992**, *2677*.

[204] Olah G.A., *Friedel-Crafts and Related Reactions*, Vol.3, John Wiley & Sons New York, **1964**, *1153-1256*.

[205] Eckert C.A., Liotta C.L., Brown J.S., *Chemistry & Industry*, Febr, **2000**, *94-97*.

[206] Olah G.A., Prakash G.K.S., Sommer J., *Superacids*, John Wiley & Sons New York, **1985**, *51-5*.

[207] Kilpatrick M., Luborsky F.E., *J. Am. Chem. Soc*., 76, **1954**, *5865-5868*.

[208] Arata K., *Advances in Catalysis*, 37, **1990**, *165-211*; Arata K., *Appl Catal*., 143, **1996**, *3*; Arata K., Nakamura H., Shouji M., *Applied Catal., A*, 197(2), **2000**, *213-219*; Clark J.H., Monks G.L., Nightingale D.J., Price P.M., White J.F., *J. Catal*., 193, **2000**, *348-350* and *Catalysis of Organic Reactions*, Ford (Ed), **2001**, *135-143*; Yadav G.D., Pujari A.A., *Green Chem*., 1(2), **1999**, *69-74*.

[209] Hino M., Arata K., *J. Chem. Soc., Chem. Commun*., **1980**, *815*.

[210] Olah G.A., Prakash G.K.S., Sommer J., *Superacids*, John Wiley & Sons New York, **1985**, *9*.

[211] Morterra C., Cerrato G., Bolis V., Di Cero S., Signoretto M., *J. Chem. Soc., Faraday Trans*., 93, **1997**, *1179*.

[212] Quaschning V., Deutsch J., Druska P., Niclas H.J., Kemnitz E., *J. Catal*., 177, **1998**, *164*.

[213] Arata K., Nakamura H., Shouji M., *Applied Catal., A*, 197(2), **2000**, *213-219*.

[214] Campbell N., Eley D.D., *Nature*, 154, **1944**, *85*.

[215] Kocal J.A., *US 5196574* to UOP, **1993**.

[216] Fărcaşiu D, *Catal. Lett*., 71(1-2), **2001**, *95-104*.

[217] Olah G. A., Kuhn S. J., *J. Am. Chem. Soc*., 80, **1958**, *6535*.

[218] De Rege, P.J.F., Gladysz J.A., Horvath I.T., *Science*, 276, **1997**, *776*.

---

[219] Takezaki Y, Sugita N., Teranishi H., Kudo K., Inoue A., *Bull. Jpn. Petrol. Inst.*, 9, **1967**, *45-52*.

[220] Aschi M., Attina M., Cacace F., *J. Am. Chem. Soc.*, 117, **1995**, *12832-12839*; Aschi M., Attina M., Cacace F., *Res. Chem. Intermed.*, 22, **1996**, *645-658*; Aschi M., Attina M., Cacace F., D'Arcangelo G, *J. Am. Chem. Soc.*, 120, **1998**, *3982-3987*.

[221] Tanaka M., *Trends Org. Chem.*, 7, **1998**, *45-61*; Tanaka M., Fujiwara M., Ando H., Xu Q., Raeker T.J., *J. Org. Chem.*, 63, **1998**, *4408-4412*; Tanaka M., Fujiwara M., Ando H., *J. Org. Chem.*, 60, **1995**, *3846-3850*; Tanaka M., Fujiwara M., Ando H., Laali K.K., *J. Am. Chem. Soc.*, 119, **1997**, *5100-5105*; Tanaka M., Fujiwara M., Ando H., Souma Y., *Chem. Commun.*, 2, **1996**, *159-160*.

[222] Raugei S., Klein M.L., *J. Phys. Chem., B*, 105, **2001**, *8212-8219*.

[223] De Rege, P.J.F., Gladysz J.A., Horvath I.T., *Science*, 276, **1997**, *776*; Olah G.A., *Angew. Chem., Int. Ed. Engl.*, 32, **1993**, *767*; Sato Y., Yato M., Ohwada T., Saito S., Shudo K., *J. Am. Chem. Soc.*, 117, **1995**, *3037*.

[224] Takezaki Y, Sugita N., Teranishi H., Kudo K., *Inoue A., Bull. Jpn. Petrol. Inst.*, 9, **1967**, *45-52*.

[225] Olah G.A., Kobayashi S.J., *J. Am. Chem. Soc.*, 93, **1971**, *6964*; Olah G.A., Kobayashi S.J., Tashiro M., *J. Am. Chem. Soc.*, 94, **1972**, *7448*.

[226] Tanaka M., *Trends Org. Chem.*, 7, **1998**, *45-61*.

[227] Olah G.A., Laali K., Farooq O., *J. Org. Chem.*, 50(9), **1985**, *1483-1486*.

[228] Roberts R.M., El-Khawaga, Sweeney K.M., El-Zohry M.F., *J. Org. Chem.*, 52(8), **1987**, *1591-1599*.

[229] Tanaka M., Iyoda J., Souma Y., *J. Org. Chem.*, 57, **1992**, *2677-2680*.

[230] Isaacs N.S., *Physical Organic Chemistry*, Longman Group UK Limited, **1987**, *129-170.*

[231] Fujiyama S., Takahashi T., Takagawa M., Ozao S*., US 3988424*, **1976**.

[232] Fujiyama S., Kasahara T., *Hydrocarbon Process*, 57, **1978**, *147-149*.

[233] Knifton J.F., *US 4554383* to Texaco Inc, **1985**.

[234] Saleh R.Y., *US 6320083*, **2000**.

[235] Walden P., *Bull. Acad. Imper. Sci*. (St. Petersburg), **1914**, 1800.

[236] Sheldon R.A., *J. Chemical Tech. Biotech*., 68, **1997**, 381-388.

[237] Wasserscheid P., Keim W., *Angew. Chem., Int. Ed*., 39, **2000**, *3772-3789*.

[238] Gordon C.M., *Applied Catalysis A: General*, 222, **2001**, 101-117.

[239] Hagiwara R., Ito Y., *Journal of Fluorine Chemistry*, 105, **2000**, *221-227*.

---

[240] Holbrey J.D., Seddon K.R., *Clean Prod. Processes*, 1, **1999**, *223-236*.

[241] Wilkes J.S., Levisky J.A., Wilson R.A., Hussey C.L., *Inorg. Chem.*,21, **1982**, *1263-1264*.

[242] Carlin R.T., Wilkes J.S. in *Chemistry of Nonaqueous Solutions*, VCH, Weinheim, **1994**, *277-306*.

[243] Hussey C.L., *Pure Appl. Chem*., 60, **1988**, *1763-1772*.

[244] Bonhôte P., Dias A.P., Papageorgiou N., Kalyanasundaram K., Grätzel M., *Inorg. Chem*., 35, **1996**, *1168-1178*.

[245] Karodia N., Guise S., Newlands C., Anderson J.A., *Chem. Commun*., **1998**, *2341-2342*.

[246] Waffenschmidt H., *Dissertation*, RWTH Aachen, Germany, **2000**.

[247] Wilkes J.S., Levisky J.A., Wilson R.A., Hussey C.L., *Inorg. Chem*., 21, **1982**, *1263-1264*.

[248] Wasserscheid P., Keim W., *Angew. Chem., Int. Ed*., 39, **2000**, *3772*.

[249] Oye H.A., Jagtoyen M., Oksefjell T., Wilkes J.S., *Mater. Sci. Forum*, 73-75, **1999**, *183-189*.

[250] Karpinski Z.J., Osteryoung R.A*., Inorg. Chem*., 23, **1984**, *1491-1494*.

[251] Abdul-Sada A.A.K., Greenway A.M., Seddon K.R., Welton T., *Org. Mass Spectrom*, 28, **1993**, *759-765*.

[252] Chauvin Y., Einloft S., Olivier H., *Ind. Eng. Chem. Res*., 34, **1995**, *1149-1155*.

[253] Williams S.D., Schoebrechts J.P., Selkirk J.C., Mamantov G., *J. Am. Chem. Soc*., 109, **1987**, *2218-2219*.

[254] Chauvin Y., Olivier-Bourbigou H., *Chemtech*, 25, **1995**, *26-30*.

[255] Parshall G.W., *J. Am. Chem. Soc*., 94, **1972**, *8716-8719*.

[256] Wilkes J.S., Zaworotko M.J., *J. Chem. Soc. Chem. Commun*., **1992**, *965-967*.

[257] Suarez P.A.Z., Dullius J.E.L., Einloft S., De Souza R.F., Dupont J., *Polyhedron*, 15, **1996**, *1217-1219*.

[258] Fuller J., Carlin R.T., de Long H.C., Haworth D., *J. Chem. Soc. Chem. Commun*., **1994**, *299-300*.

[259] Chauvin Y., Olivier-Bourbigou H., *Chemtech*, 25, **1995**, *26-30*.

[260] Wilkes J.S., Zaworotko M.J., *J. Chem. Soc. Chem. Commun*., **1992**, *965-967*.

[261] Wilkes J.S., Zaworotko M.J., *J. Chem. Soc. Chem. Commun*., **1992**, *965-967*.

[262] Keim W., Korth W., Wasserscheid P., *WO 2000016902*, **2000** [Chem. Abstr. 132 (**2000**) P238691.

---

[263] Ford W.T., Hauri R.J., Hart D.J., *J. Org. Chem.*, 38, **1973**, *3916-3918*.

[264] Zingg S.P., Dworkin A.S., Sorlie M., Chapman D.M., Buchanan A.C., Smith G.P., *J. Electrochem. Soc.*, 131, **1984**, *1602-1608*.

[265] Chauvin Y., Olivier-Bourbigou H., *Chemtech*, 25, **1995**, *26-30*.

[266] Carlin R.T., Wilkes J.S. in *Chemistry of Nonaqueous Solutions*, VCH, Weinheim, **1994**, *277-306*.

[267] Karpinski Z.J., Osteryoung R.A., *Inorg. Chem.*, 23, **1984**, *1491-1494*.

[268] Abdul-Sada A.A.K., Greenway A.M., Seddon K.R., Welton T., *Org. Mass Spectrom.*, 28, **1993**, *759-765*.

[269] Melton T.J., Joyce J., Meloy J.T., Boon J.A., Wilkes J.S., *J. Electrochem. Soc.*, 137, **1990**, *3865-3869*.

[270] Scordilis-Kelley C., Fuller J., Carlin R.T., Wilkes J.S., *J. Electrochem. Soc.*, 139, **1992**, *694-699*.

[271] Quarmby I.C., Mantz R.A., Goldenberg L.M., Osteryoung R.A., *Anal. Chem.*, 66, **1994**, *3558-3561*.

[272] Quarmby I.C., Osteryoung R.A., *J. Am. Chem. Soc.*, 116, **1994**, *2649-2650*.

[273] Koronaios P., King D., Osteryoung R.A., *Inorg. Chem.*, 37, **1998**, *2028-2032*.

[274] Smith G.P., Dworkin A.S., Pagni R.M., Zingg S.P., *J. Am. Chem. Soc.*, 111, **1989**, *525-530*.

[275] Ma M., Johnson K.E., *J. Am. Chem. Soc.*, 117, **1995**, *1508-1513*.

[276] Smith G.P., Dworkin A.S., Pagni R.M., Zingg S.P., *J. Am. Chem. Soc.*, 111, **1989**, *525-530*.

[277] Hussey C.L., *Adv. Molten Salt Chem.*, 5, **1983**, *185-230*.

[278] Smith G.P., Dworkin A.S., Pagni R.M., Zingg S.P., *J. Am. Chem. Soc.*, 111, **1989**, *525-530*.

[279] Howarth J., Hanlon K., Fayne D., McCormack P., *Tetrahedron Lett.*, 38, **1997**, *3097-3100.*

[280] Arduengo A.J., Harlow R.I., Kline M., *J. Am. Chem. Soc.* 113, **1991**, *361-363*; Arduengo A.J., Dias H.V.R., Harlow R.L., Kline M., *J. Am. Chem. Soc.*, 114, **1992**, *5530-5534;* Cheek G.T., Spencer J.A. in *9th Int. Symp. on Molten salts* (Eds.: Hussey C.L., Newman D.S., Mamantov G.,. Ito Y.), The Electrochem. Soc., New York, **1994**, *426-432*; Xu L., Chen W., Xiao J., *Organometallics*, 19, **2000**, *1123-1127*.

---

[281] Suarez P.A.Z., Dullius J.E.L., Einloft S., de Souza R.F., Dupont J., *Polyhedron*, 15, **1996**, *1217-1219*; Chauvin Y., Muβmann L., Olivier H., *Angew. Chem. Int. Ed. Engl.*, 34, **1995**, *2698-2700*; Suarez P.A.Z., Dullius J.E.L., Einloft S., de Souza R.F., J. Dupont, *Inorg. Chem. Acta*, 255, **1997**, *207-209*; Dyson P.J., Ellis D.J., Parker D.G., Welton T., *Chem. Commun.*, **1999**, *25-26*; Müller L.A., Dupont J., de Souza R.F., *Makromol. Chem. Rapid Commun.*, 19, **1998**, *409-411*; Steines S., Drieβen-Hölscher B., Wasserscheid P., *J. Prakt. Chem.*, 342, **2000**, *348-354*; Drieβen-Hölscher B., Heinen J., *J. Organomet. Chem.* 570, **1998**, *141-146*; Heinen J., Tupayachi M.S., Drieβen-Hölscher B., *Catalysis Today,* 48, **1999**, *273-278*; Chauvin Y., Muβmann L., Olivier H., *Angew. Chem.* 107, **1995**, *2941-2943*; Monteiro A.L., Zinn F.K., de Souza R.F., J. Dupont, *Tetrahedron: Asymmetry*, 2, **1997**, *177-179*.

[282] Song C.E., Roh E.J., *Chem. Commun.*, **2000**, *837-838*; Song C.E., Roh C.R., Roh E.J., Choo D.J., *Chem. Commun.*, **2000**, *1743*; Howarth J., *Tetrahedron Lett.*, 41, **2000**, *6627.*

[283] Pardy R.B.A., Tkatschenko I., *J. Chem. Soc. Chem. Commun.*, **1981**, *49-50*; Ascenso J.R., Carrando M.A.A.F. De C.T., Dias A.R., Gomez P.T., Piadade M.F.M., Romao C.C., Revillon A., Tkatschenko I., *Polyhedron*, 8, **1989**, *2449-2457*; Grenouillet P., Neibecker D., Tkatschenko I., *J. Organomet. Chem.*, 243, **1983**, *213-222*; Gehrke J.P., Taube R., Balbolov E., Kurtev K., *J. Organomet. Chem.* 304, **1986**, C4-C6; Silva S.M., Suarez P.A.Z., de Souza R.F., Dupont J., *Polymer Bull.*, 40, **1998**, *401-405*; Chauvin Y., Gilbert B., Guibard I., *J. Chem. Soc. Chem. Commun.*, **1990**, *1715-1716*; Chauvin Y., Olivier H., Wyrvalski C.N., Simon L.C., de Souza R.F., *J. Catal.*, 165, **1997**, *275-278*, Simon L.C., Dupont J., de Souza R.F., *J. Mol. Catal.* 175, **1998**, *215-220*.

[284] Waffenschmidt H., Wasserscheid P., *J. Mol. Catal.*, 164, **2000**, *61-67*; Knifton J.F., *J. Mol. Catal.*, 43, **1987**, *65-78*, Chauvin Y., Muβmann L., Olivier H., *Angew. Chem.* 107, **1995**, *2941-2943*; Chauvin Y., Muβmann L., Olivier H., *Angew. Chem. Int. Ed. Engl.*, 34, **1995**, *2698-2700*; Chauvin Y., Muβmann L., Olivier H., *FR 95/14,147*, **1995** [*Chem. Abstr.* **1997**, 127, P3 41298k].

[285] Kaufmann D. E., Nouroozian M., Henze H., *Synlett*, **1996**, *1091-1092*; Herrmann W.A., Böhm V.P.W., *J. Organomet. Chem.*, 572, **1999**, *141-145*; Böhm V.P.W., Herrmann W.A., *Chem. Eur. J.*, 6, **2000**, *1017-1025*; Xu L., Chen W., Xiao J.,

---

Organometallics, 19, **2000**, *1123-1127*; Xu L.J., Chen W.P., Ross J., Xiao J.L., *Org. Lett*., 3, **2001**, 295; Mathews C.J., Smith P.J., Welton T., *Chem. Commun*., **2000**, *1249*.

[286] Chen W., Xu L., Chatterton C., Xiao J., *Chem. Commun*., **1999**, *1247-1248*; de Bellefon C., Pollet E., Grenouillet P., *J. Mol. Catal*. 145**, 1999**, *121-126*.

[287] Boon J.A., Levisky J.A., Pflug J.L., Wilkes J.S., *J. Org. Chem*., 51, **1986**, *480*, Dowdy D.D., Gore P.H., Waters D.N., *J. Chem. Soc., Perk. Trans*., 2, **1991**, *1149*; Olah G.A., *Friedel-Crafts Chemistry*, Wiley-Interscience, New York, **1973**; Brown H.C., Marino G., Stock L.M., *J. Am. Chem. Soc*., 81, **1959**, *3310*; Baranger P.M., *Bull. Soc. Chim. Fr*., **1931**,*1213-1222*; Judefind W.L., Reid E.E., *J. Am. Chem. Soc*., 42, **1920**, *4993*; Green L., Hemeon I., Singer R.D., *Tetrahedron Lett*., 41, **2000**, *1343*.

[288] Fisher T., Sethi A., Welton T., Woolf J., *Tetrahedron. Lett*., 40, **1999**, *793*; Howarth J., Hanlon K., Fayne D., McCormack P., *Tetrahedron Lett*., 38, **1997**, *3097*; Song C.E., Shim W.H., Roh E.J., Lee S., Choi J.H., *Chem. Commun*., **2001**, *1122*.

[289] Zhao D., Wu M., Kou Y., Min E., *Catalysis Today*, 2654, **2002**, *24*; Laali K.K., Gettwert V.J., *J. Org. Chem*. 66, **2001**, *35*.

[290] Mizushima E., Hayashi T., Tanaka M., *Green Chem*., 3, **2001**, *76*.

[291] March J., *Advanced Organic Chemistry 3rd Ed*., John Wiley & Sons, New York, **1985**, *488*.

[292] March J., Advanced Organic Chemistry 3rd Ed., John Wiley & Sons, New York, **1985**, *488*.

[293] Kramer G.M., Weissman W., Brown H.C., *US Patent 4518798* to Exxon R&E Co, **1985**.

[294] Howell R.D., McCown J.D., *Chem. Rev*., 77, **1977**, 69; Schiraldi D.A., Kenvin J.C., *US Patent 5910613* to HNA Holdings Inc., **1999**; Booth B.L., El-Fekky T.A., *J. Chem. Soc., Perkin Trans.,* 1, **1979**, *2441-2446*; Sood D.S., Sherman S.C., Iretskii, A.V., Kenvin J.C., Schiraldi D.A., White M.G., *J. Catal*., 199(1), **2001**, *149-153*.

[295] Schiraldi D.A., Kenvin J.C., *US Patent 5910613* to HNA Holdings Inc., **1999**

[296] Campbell N., Eley D.D., *Nature*, 154, **1944**, *85*.

[297] Sasol Technology R&D, Unpublished Results, **2001**.

CHAPTER 3

EXPERIMENTAL

1 INTRODUCTION

The synthesis of aromatic aldehydes comprised the use of high pressures and extremely toxic reagents that also required the exclusion of moisture, not only to benefit reaction yields, but also to minimize corrosion of experimental apparatus. Naturally, the safety aspects surrounding the laboratory set-up were of paramount importance and should receive attention prior to commencement of experimental work.

1.1 Personal Protective Equipment

The use of personal protective equipment was essential, as hydrogen fluoride is notorious for inducing bony fluorosis, a condition that weakens the human skeletal structure through continuous inhalation of vapors and skin contact. This safety equipment consisted of special hydrogen fluoride resistant gloves, a long-sleeve suit and a face shield due to the high CO pressures employed.

1.2 Reactor

A 100ml Parr reactor constructed from Hasteloy-C and equipped with a gas entrainment stirrer with variable speed was used during all formylation reactions. Special PTFE seals were used as the normal acid resistant seals were incompatible with the HF/BF_3 combination.

1.3 Reagents

The high toxicity of reagents CO, HF and BF_3 necessitated all reactions to be conducted in a fume-hood.

2 GENERAL EXPERIMENTAL PROCEDURE

2.1 HF Formylation Reactions

Pre-cooled (4°C) substrate (10-300mmol, dried as described in 3.2.7) was added to the reactor positioned in an ice-bath under an inert gas flow (N_2). This was followed by careful addition of hydrogen fluoride (0.6-2.5mol, 99.95%, Pelchem, 4°C) from a 1litre cylinder.

The reactor lid was sealed and the reactor pressurized with boron trifluoride (20-300mmol, 99.98%, Messer Griesheim) until the required mass was obtained whilst stirring. The required CO pressure (50-80bar, 99.99%) was applied and the resulting exotherm (3-10°C) aided in heating the mixture to the required temperature. On completion of the reaction (10min-24h), the reactor was cooled in ice water and the CO pressure released as reaction mixture reached temperature of 5°C. The reaction mixture was quenched in 500ml ice followed diethyl ether extraction (4x20ml). Neutralization of the acid using aqueous K_2CO_3 to pH=7 was followed by drying with Na_2SO_4. The course of the reaction was followed by GC analysis. The ^{1}H, ^{13}C and mass spectra of compounds formed in the formylation reaction are included as an addendum to the experimental section. Compounds formed in the formylation reaction were initially identified by analysis of the MS fragmentation patterns followed by direct comparison with authentic materials.

2.2 HF Formylation Reactions in Ionic Liquid

The same protocol as described in 3.2.1 was used for reactions conducted in ionic liquid which was added prior to the substrate. No extraction of the ionic liquid was done. Diethyl ether was added to reduce the viscosity of the reaction mixture followed by GC analysis.

2.3 Deuterium Fluoride Preparation and DF Formylation Reactions

A 600ml Parr reactor, used to produce the deuterium fluoride, was coupled *via* a ¼" stainless steel tubing to the 100ml Parr formylation reactor to enable transfer of the produced DF. To NaF (dried at 120°C for 3 days, 120g), D_2SO_4 (150g) was added drop-wise, whilst maintaining the 100ml reactor at –50°C using a CO_2/ acetonitrile/ chloroform mixture. The NaF/D_2SO_4 mixture temperature was increased to 170°C and maintained for 2hours to distill the yielding 29gram of deuterium fluoride. Keeping the formylation reactor at –50°C, pre-cooled formylation substrate (29mmol) was added using a syringe followed by BF_3 (58mmol) addition. The remaining formylation procedure is similar to that described in 3.2.1.

2.4 Preparation of di-(4-methoxyphenyl)methanol

In a round bottom flask 10gram 4,4'-dimethoxybenzophenone (41.3mmol) was dissolved in ethanol (200ml) and THF (200ml). To the solution 1.6gram $NaBH_4$ (42.3mmol) was added whilst stirring at rt. An additional 2gram of $NaBH_4$ (52.9mmol) was added with continued stirring overnight. The reaction mixture was quenched with 200ml of acetone and distilled at 35°C and 300mBar (Repeated 3x). The resultant borate salt was dissolved in water (100ml) and the alcohol extracted with diethyl ether (50ml). Vacuum distillation of the diethyl ether solution (40°C at 120mbar) furnished the white alcohol crystals in quantitative yield. Water from the crystals was removed azeotropically with benzene.

2.5 Ionic Liquid Preparation

The ^{1}H-NMR spectra of ionic liquids prepared and used in the reactions are collected in an addendum to the experimental section.

2.5.1 1-Butyl-3-methylimidazolium chloride [bmim]Cl, 1-hexyl-3-methyl-imidazolium chloride [hexmim]Cl and 1-octyl-3-methyl-imidazolium-chloride [omim]Cl

1-methylimidazole (99%) was freshly distilled from CaH_2 and stored under argon and 4Å molecular sieves. A stirred mixture of distilled 1-methylimidazole (246g, 3mol), alkylhalide (1.6-3.6mol, 99.5% anhydrous) was refluxed for 48hours under argon. Subsequent formation of two layers was followed by separation and the excess chloro-alkane was removed *in vacuo* at 120°C overnight. Quantities of alkylhalides: chlorobutane (3.6mol), chlorohexane (1.6mol), chloro-octane (1.6mol)

2.5.2 1-Butyl-3-methylimidazolium trifluoromethane sulfonimide [bmim]-[$N(SO_2CF_3)_2$] or [bmim]BTA

To an aqueous solution of *N*-lithiotrifluoromethanesulfonyl amide (LiBTA) (24.69g, 0.086mol in 30ml) was added an aqueous solution of [bmim]Cl (15.02g, 0.086mol in 30ml) and the mixture was stirred for 2h at rt. The [bmim]BTA produced was separated from the aqueous layer and washed with distilled water (5x100ml) to remove residual LiCl salt. The ionic liquid was subsequently heated at 120°C under vacuum overnight to remove traces of water.

2.5.3 1-Octyl-3-methylimidazolium trifluoromethane sulfonimide [omim]-[N(SO_2CF_3)$_2$] or [omim]BTA

To an aqueous solution of *N*-lithiotrifluoromethanesulfonyl amide (LiBTA) (24.69g, 0.086mol in 30ml) was added an aqueous solution of [omim]Cl (19.85g, 0.086mol in 30ml) and the mixture was stirred for 2h at rt. The [omim]BTA produced was separated from the aqueous layer and washed with distilled water (5x100ml) to remove residual LiCl salt. The ionic liquid was subsequently heated at 120°C under vacuum overnight to remove traces of water.

2.5.4 1-Butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4

Fluoroboric acid (89.36g of 48% aqueous solution, 0.44mol) was added to an aqueous solution of [bmim]Cl (77.31g, 0.44mol in 140ml) at 0°C. Addition of the acid was gradually done with continuous stirring. After addition of the fluoroboric acid was completed, the temperature of the reaction medium was increased to 20°C and the mixture left overnight. Portions of dichloromethane (5x80ml) were used to extract the ionic liquid preceded the removal of traces of un-reacted fluoroboric acid with distilled water (10x100ml). Removal of the remaining dichloromethane and water occurred *in vacuo* at 120°C overnight.

2.5.5 1-Octyl-3-methylimidazolium tetrafluoroborate [omim]BF_4

In a similar procedure to 2.5.4, [omim]Cl (101.54g, 0.44mol in 140ml) was used.

2.5.6 1-Butyl-3-methylimidazolium hexafluorophosphate [bmim]PF_6

To an aqueous stirred solution of [bmim]Cl (118.19g, 0.6773mol in 150ml) at 0°C was added aqueous 50% excess hexafluorophosphoric acid (200ml of 60% solution). The resulting bi-phasic system was stirred for 4hours followed by dichloromethane extraction (5x80ml) to remove the ionic liquid. A water wash (10x100ml) using distilled water was used to remove un-reacted acid prior to the removal of dichloromethane and water *in vacuo* overnight at 120°C.

2.5.7 1-Hexyl-3-methylimidazolium hexafluorophosphate [hexmim]PF_6

To a stirring solution of [hexmim]Cl (137.31g, 0.6773mol) and water (150ml) at 0°C, 50% excess hexafluorophosphoric acid (200ml of 60% aqueous solution) was slowly added. The resulting bi-phasic system was stirred for 4hours followed by dichloromethane extraction (5x80ml) to remove the ionic liquid. A water wash (10x100ml) using distilled water remove un-reacted acid. The dichloromethane and water were removed *in vacuo* overnight at 120°C.

2.5.8 1-Octyl-3-methylimidazolium hexafluorophosphate [omim]PF_6

Using the same procedure as described in 3.2.4.6, aqueous stirred solution of [omim]Cl (156.30g, 0.6773mol) at 0°C was added to aqueous 50% excess hexafluorophosphoric acid (200ml of 60% solution).

2.5.9 1-Butyl-3-methylimidazolium tetrachloroaluminate [bmim]$AlCl_4$ x($AlCl_3$) = 0.67

Freshly sublimed aluminum trichloride (99.9%, 89.34g, 0.67mol) was carefully added to [bmim]Cl (57.64g, 0.33mol) whilst stirring under an argon atmosphere. The resulting ionic liquid was stored under argon.

2.5.10 1-Butyl-3-methylimidazolium tetrachloroaluminate [bmim]$AlCl_4$ x($AlCl_3$) = 0.75

Freshly sublimed aluminum trichloride (99.9%, 100.0g, 0.75mol) was carefully added to [bmim]Cl (43.67g, 0.25mol) whilst stirring under an argon atmosphere. The resulting ionic liquid was stored under argon.

2.5.11 1-Ethyl-3-methylimidazolium tetrachloroaluminate [emim]$AlCl_4$ x($AlCl_3$) = 0.67

Freshly sublimed aluminum trichloride (99.9%, 89.34g, 0.67mol) was carefully added to [emim]Cl (48.38g, 0.33mol) whilst stirring under an argon atmosphere. The resulting ionic liquid was stored under argon.

2.6 Chromatography

2.6.1 Flash Column Chromatography

A glass column (15x350mm) was filled with silica gel (70-230mesh, 60Å, 100gram for each 1gram of product) mixed with the chosen mobile phase. Slight N_2 pressure (50kPa) was applied to force air bubbles out and a thin layer (5mm) of acid washed sand was added onto the gel. The product was carefully applied on top of the sand and the pure components obtained through the chosen mobile phase in 10ml fractions.

2.6.2 Gas Chromatography

A Hewlett-Packard 4890 Series II equipped with a capillary, non-polar PONA column (50m x 0.25mm id x 0.25μm) and a glass liner split injector was used for quantifying purposes. Plate 26 indicates a typical gas chromatogram obtained of the reaction product after formylation. The following set points were used:

Oven Temp	100°C
Initial Time	10min
Rate	5°C/min
Final Temp	300°C
Detector	FID
Column Flow	1ml/min
Split Flow	150ml/min
Carrier Gas	Helium

Where possible the response factors of the different compounds with regard to the detector were determined using standard samples with known concentrations. Internal standards were used to quantify compounds in reaction mixtures. Retention times (minutes) of important constituents of products of formylation include the following:

Compound	Retension Time (min.)
Anisole	4.70
OAA	7.06
PAA	7.18
p-Methoxyacetophenone	8.13
Di(4-methoxydiphenylmethane isomer	14.55
Dimethoxybenzophenone isomer	17.70
Trimethoxy-phenylmethane isomers	25.37 and 29.03
Toluene	4.41
o-tolualdehyde	6.42
p-tolualdehyde	6.59
Di-(methylphenyl)methane isomers	15.96 and 16.34
Di-(methylphenol)methanol isomer	20.16
Dimethylbenzophenone isomers	20.42 and 20.99
Tri-(methylphenyl)methane isomers	27.90 and 28.69

Compound	Retension Time (min.)
Phenol	4.33
o-Hydroxybenzaldehyde	4.93
p-Hydroxybenzaldehyde	7.29
Di-(hydroxyphenyl)methane isomer	14.6
Dihydroxybenzophenone isomer	18.16
Tri-(hydroxyphenyl)methane isomer	32.47

2.7 Drying of Reagents

Drying of substrates were conducted in a still under inert (Ar) conditions using sodium metal lumps as drying agent and benzophenone as indicator.

2.8 Spectrometric and Spectroscopic Methods

2.8.1 Nuclear Magnetic Resonance (NMR)

NMR spectroscopy was conducted on both a Bruker Avance 500 and a Varian Inova 400 instrument. Chemical shift as parts-per-million (ppm) on the δ-scale and coupling constants (J) in Hz were used throughout. Unless stated otherwise, all NMR-spectra were recorded in $CDCl_3$ at 30°C with TMS as internal standard. The following abbreviations were used:

s = singulet
br = broad
d = doublet
t = triplet
q = quartet
i = impurity
m = multiplet

2.8.2 Mass Spectrometry (MS)

A Hewlett-Packard HP5973 mass spectrometer equipped with a photon multiplier was used for determination of accurate mass and recording of mass spectra. Unless stated otherwise, the molecular ion was generated *via* Electron Impact (EI). The following abbreviation was used:

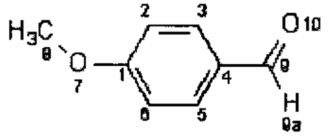
M^+ = molecular ion

M.W. = molar weight

Addendum: NMR-, MS- and GC spectra of key compounds

Plate 1: ^1H NMR spectrum of *p*-Anisaldehyde

Solvent: $CDCl_3$



Proton	PPM	Multiplicity	Coupling Constant, (J)
3,5	7.87	d	8.5
2,6	7.04	d	8.5
9a	9.92	s	-
8	3.92	s	-

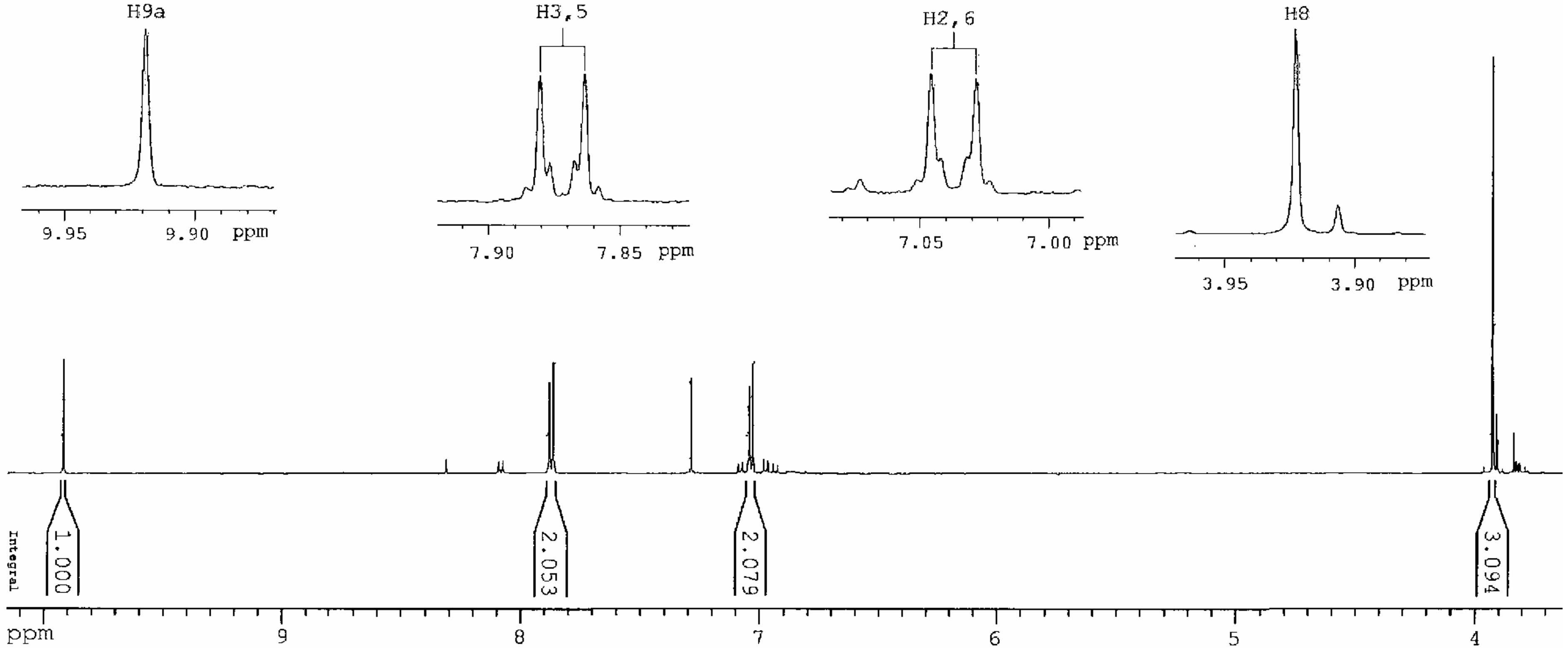
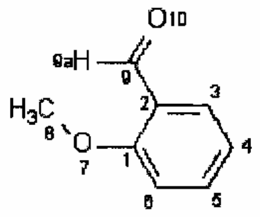


Plate 2: ^{1}H NMR spectrum of *o*-Anisaldehyde

Solvent: $CDCl_3$



Proton	PPM	Multiplicity	Coupling Constant, (J)
4,6	7.00-6.93	m	-
9a	10.43	s	-
3	7.78	dd	1.9, 7.5
5	7.51	ddd	1.9, 7.3, 8
8	3.88	s	-

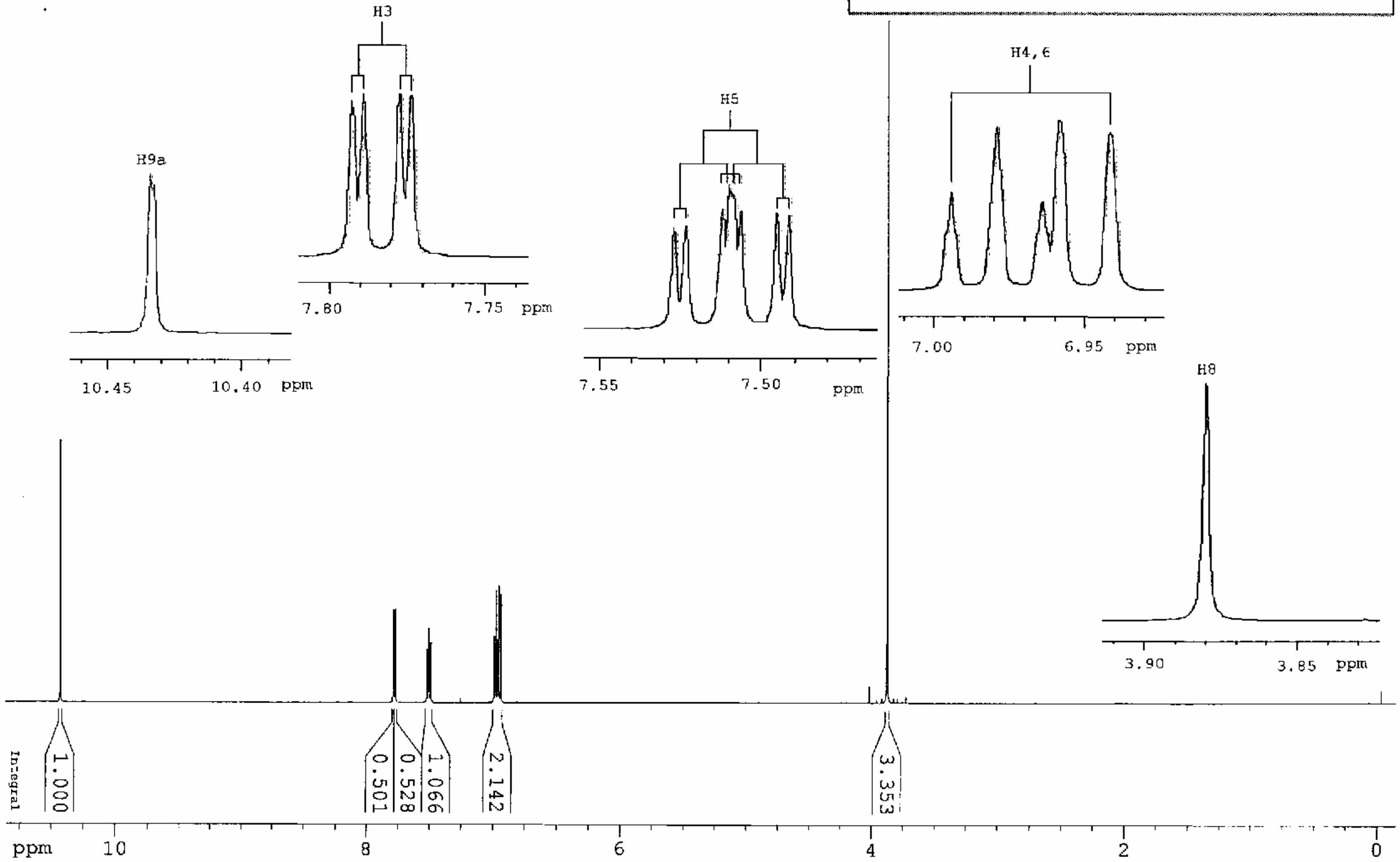
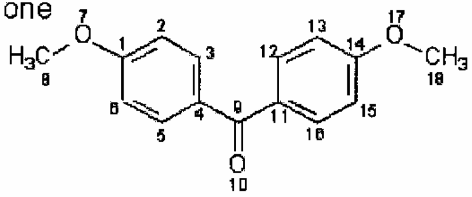


Plate 3: ^{1}H NMR spectrum of 4,4'-dimetoxybenzophenone

Solvent: $CDCl_3$



Proton	PPM	Multiplicity	Coupling Constant, (J)
3,5,12,16	7.82	d	8.5
2,6,13,15	6.99	d	8.5
8,18	3.92	s	-

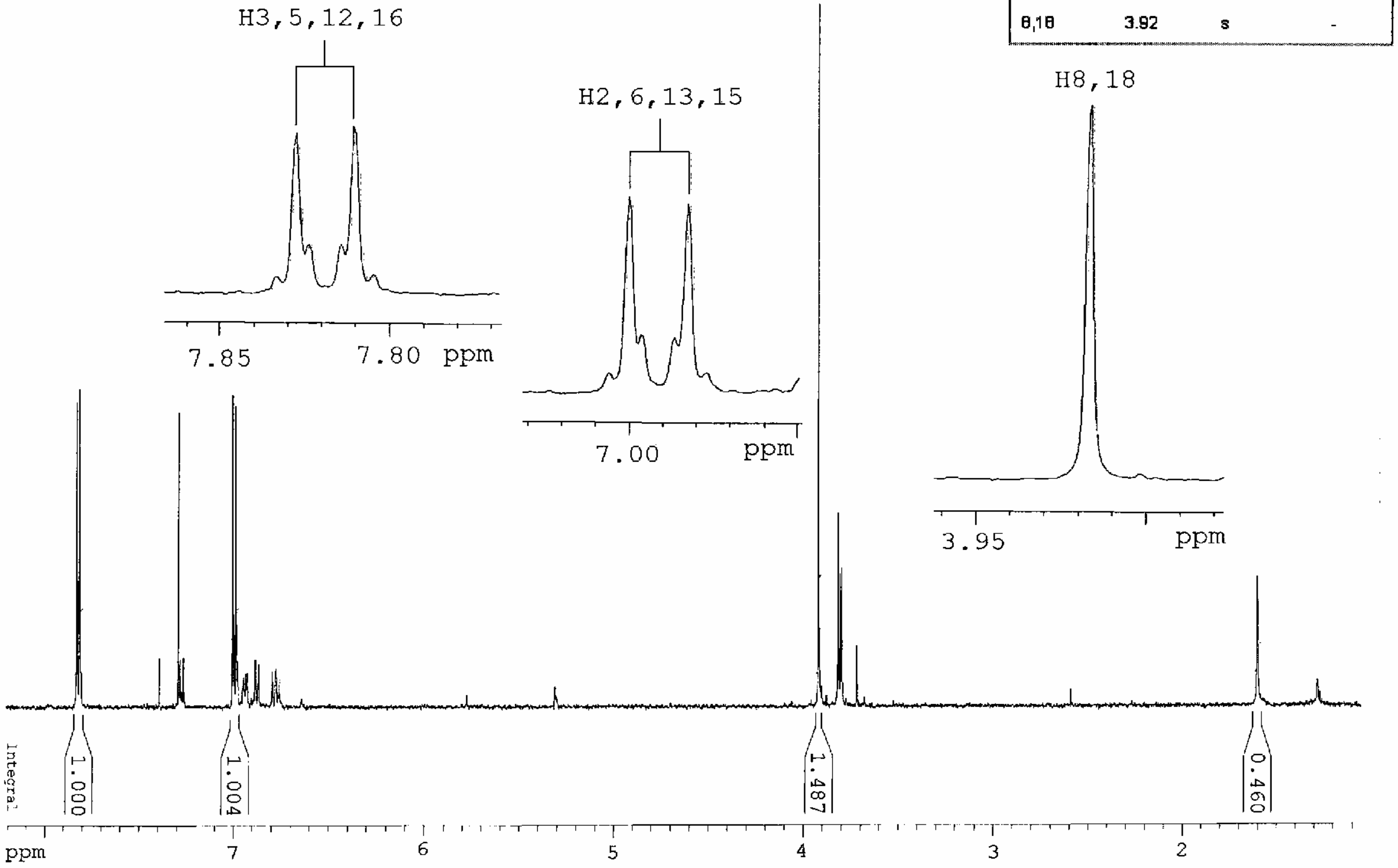
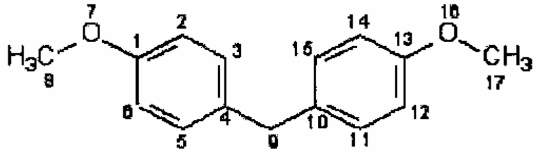


Plate 4: ^1H NMR spectrum of Di-(4-metoxyphenyl)methane

Solvent: $CDCl_3$



Proton	PPM	Multiplicity	Coupling Constant, (J)
3,5,11,15	7.12	d	8.5
2,6,12,14	6.86	d	8.5
9	3.90	br.s	-
8,17	3.81	s	-

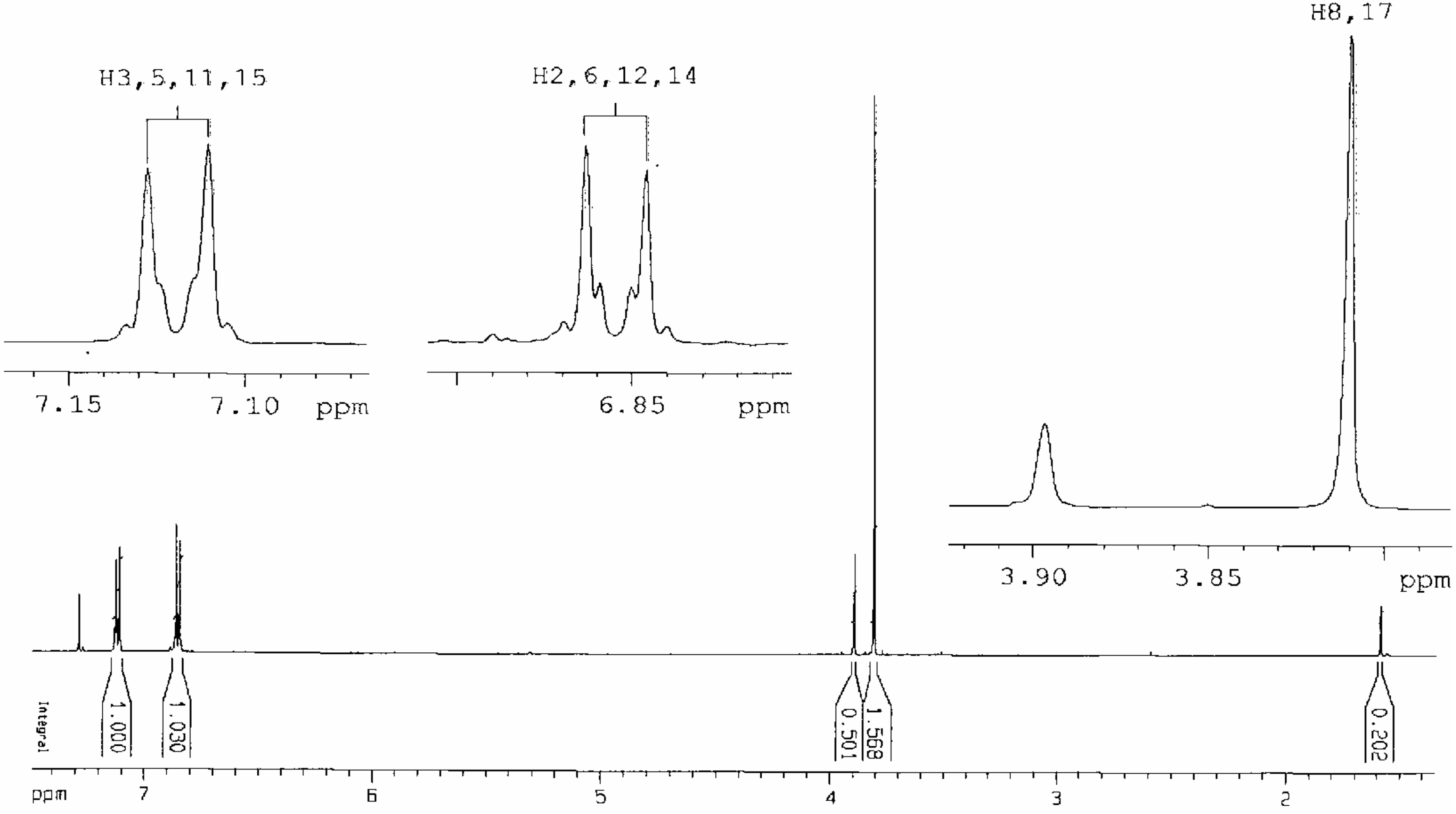
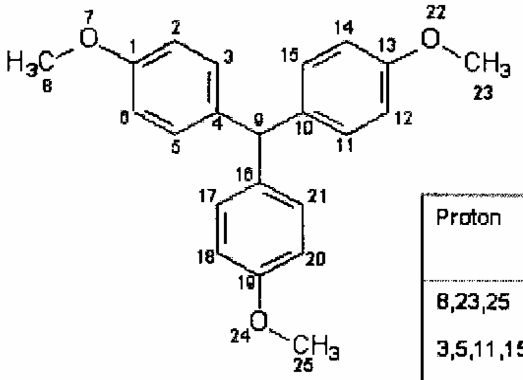


Plate 5: ^{1}H NMR spectrum of Tri(4-metoxyphenyl)methane

Solvent: $CDCl_3$



Proton	PPM	Multiplicity	Coupling Constant, (J)
8,23,25	3.81	s	-
3,5,11,15,17,21	7.05	d	8.5
2,6,12,14,18,20	6.85	d	8.5
9	5.44	br.s	

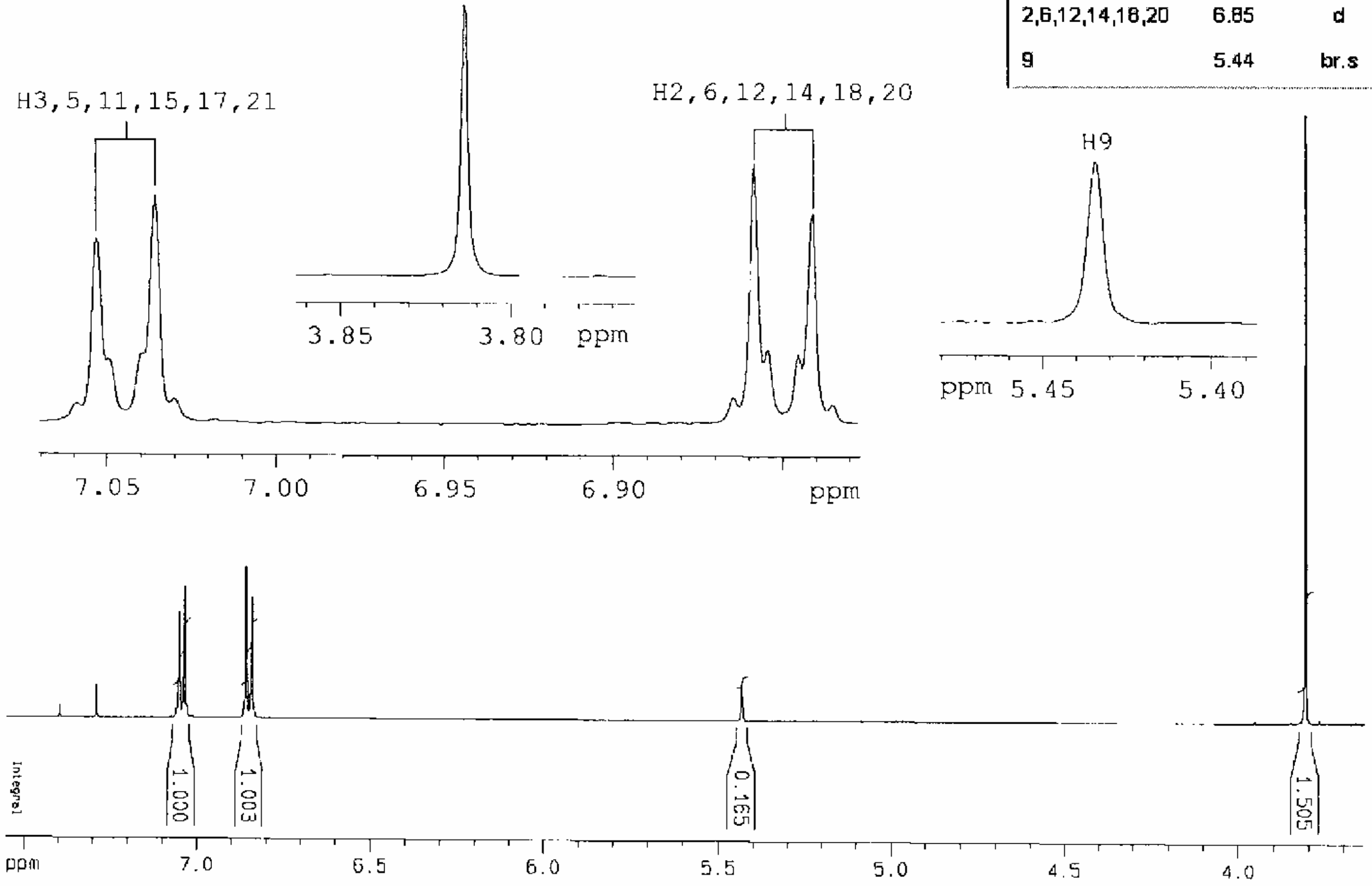
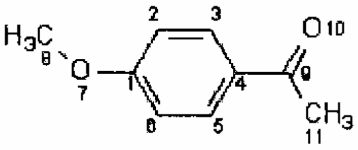


Plate 6: ^1H NMR spectrum of *p*-Methoxyacetophenone

Solvent: $CDCl_3$



Proton	PPM	Multiplicity	Coupling Constant, (J)
3,5	7.97	d	8.5
2,6	6.96	d	8.5
8	3.90	s	-
11	2.59	s	-

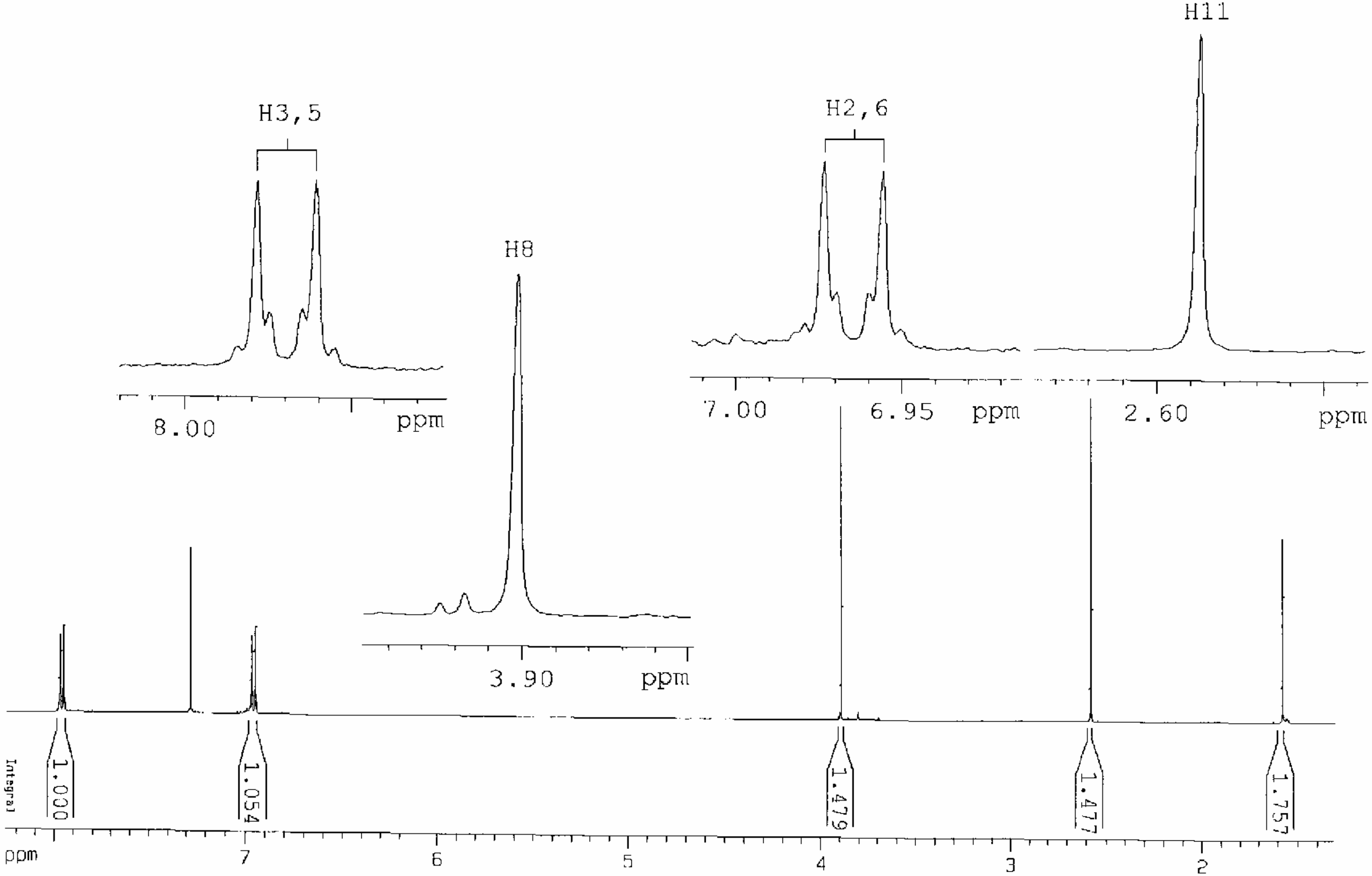
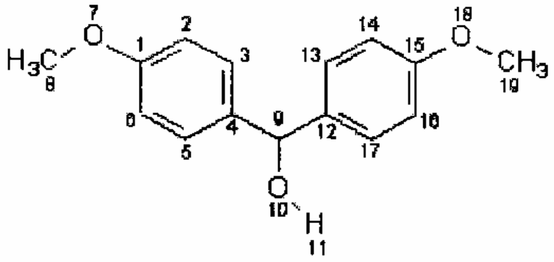


Plate 7: ^1H NMR spectrum of Di(4-metoxyphenyl)methanol

Solvent: $CDCl_3$



Proton	PPM	Multiplicity	Coupling Constant, (J)
2,6,14,16	6.89	d	8.5
3,5,13,17	7.30	d	8.5
9	2.20	s	-
8,19	3.82	s	-
11	5.79	s	-

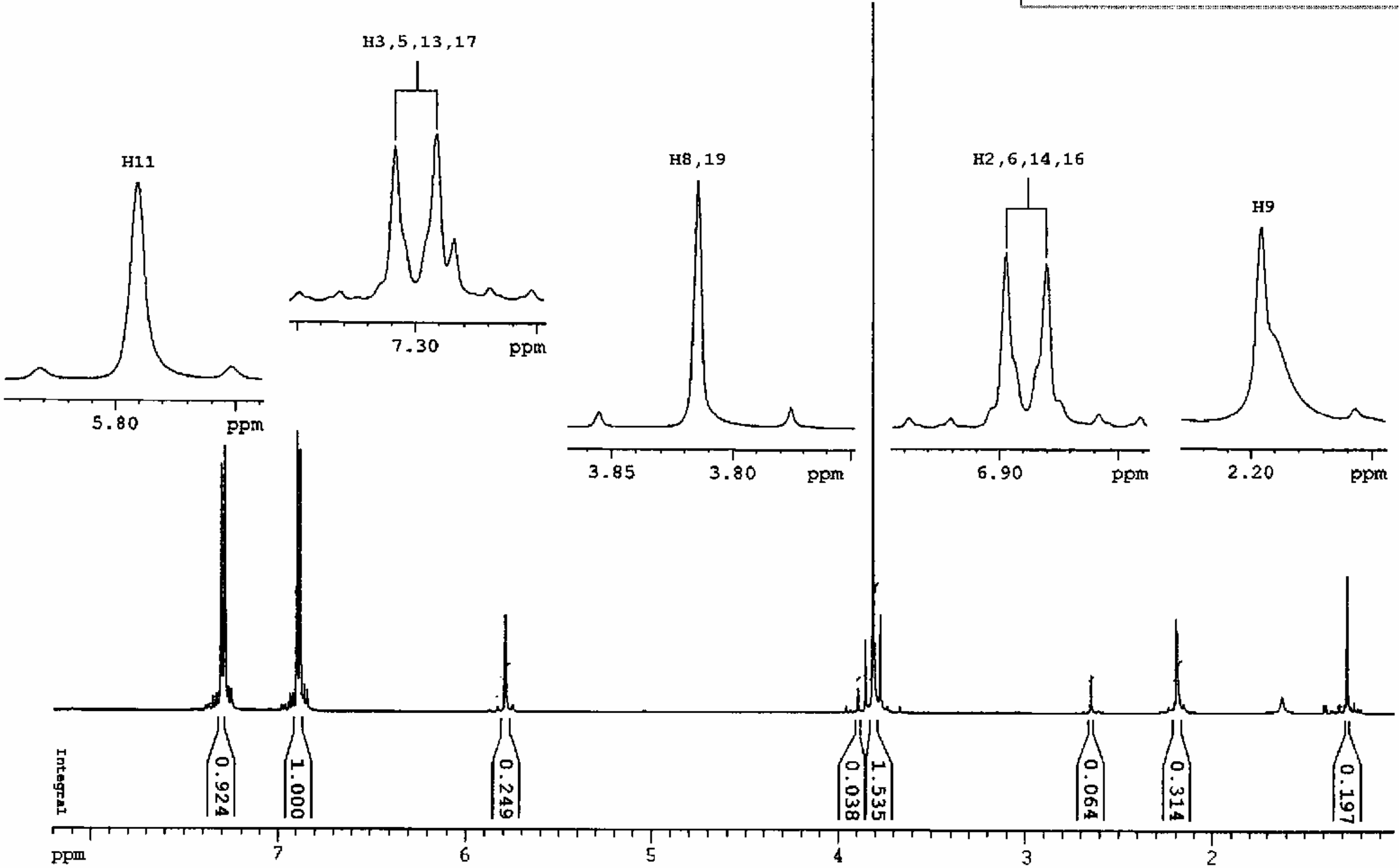


Plate 8: ^{1}H NMR spectrum of 1-Butyl-3-methylimidazolium tetrachloroaluminate [bmim]$AlCl_4$

Solvent: $CDCl_3$

Proton	PPM	Multiplicity	Coupling Constant, (J)
1	3.78	s	-
2	4.03	t	3.0
3	1.78-1.68	m	-
4	1.26-1.16	m	-
5	0.76	t	4.2
8	8.24	s	-
9	7.23	s	-
10	7.19	s	-

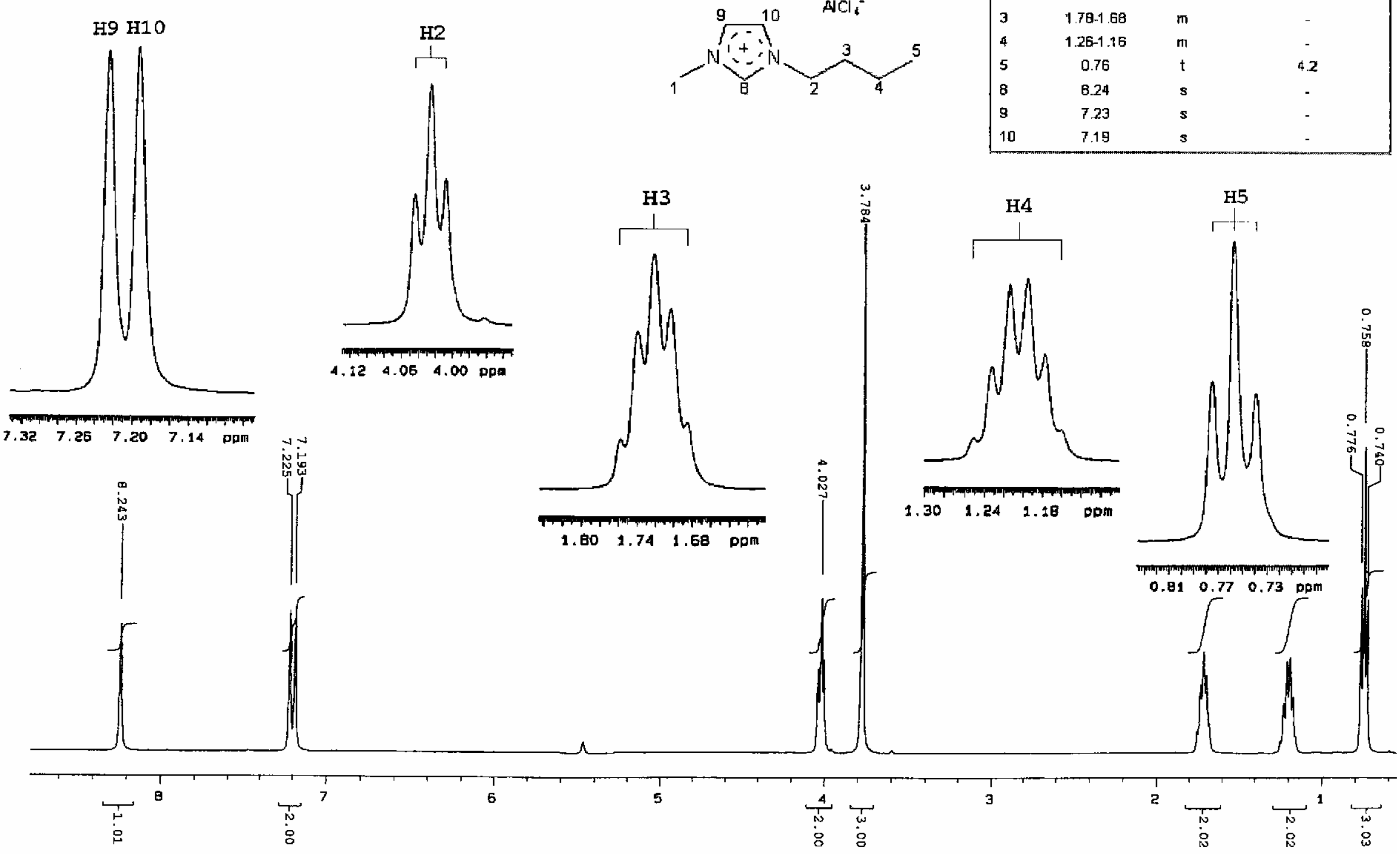
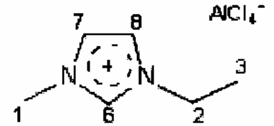


Plate 9: ^{1}H NMR spectrum of 1-Ethyl-3-methylimidazolium tetrachloroaluminate [emim]$AlCl_4$

Solvent: $CDCl_3$

Proton	PPM	Multiplicity	Coupling Constant, (J)
1	3.71	s	-
2	4.05-3.95	m	-
3	1.20	t	7.9
6	9.10	s	-
7	7.47	s	-
8	7.41	s	-



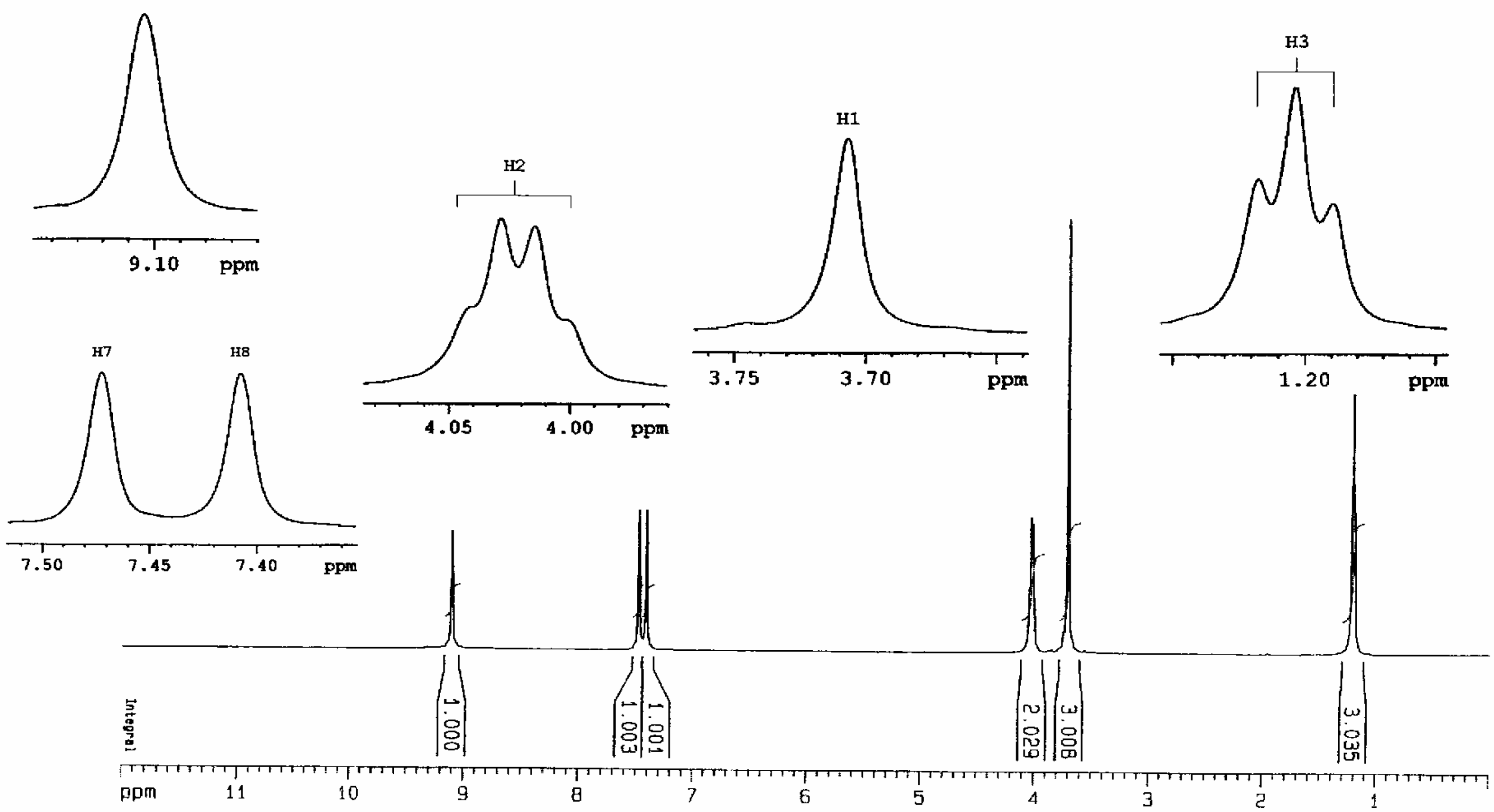


Plate 10: ^1H NMR spectrum of 1-Butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4

Solvent: $CDCl_3$

Proton	PPM	Multiplicity	Coupling Constant, (J)
1	3.99	s	-
2	4.21	t	7.5
3	1.93-1.86	m	-
4	1.44-1.36	m	-
5	0.99	t	7.5
8	8.86	br s	-
9	7.35	br s	-
10	7.30	br s	-

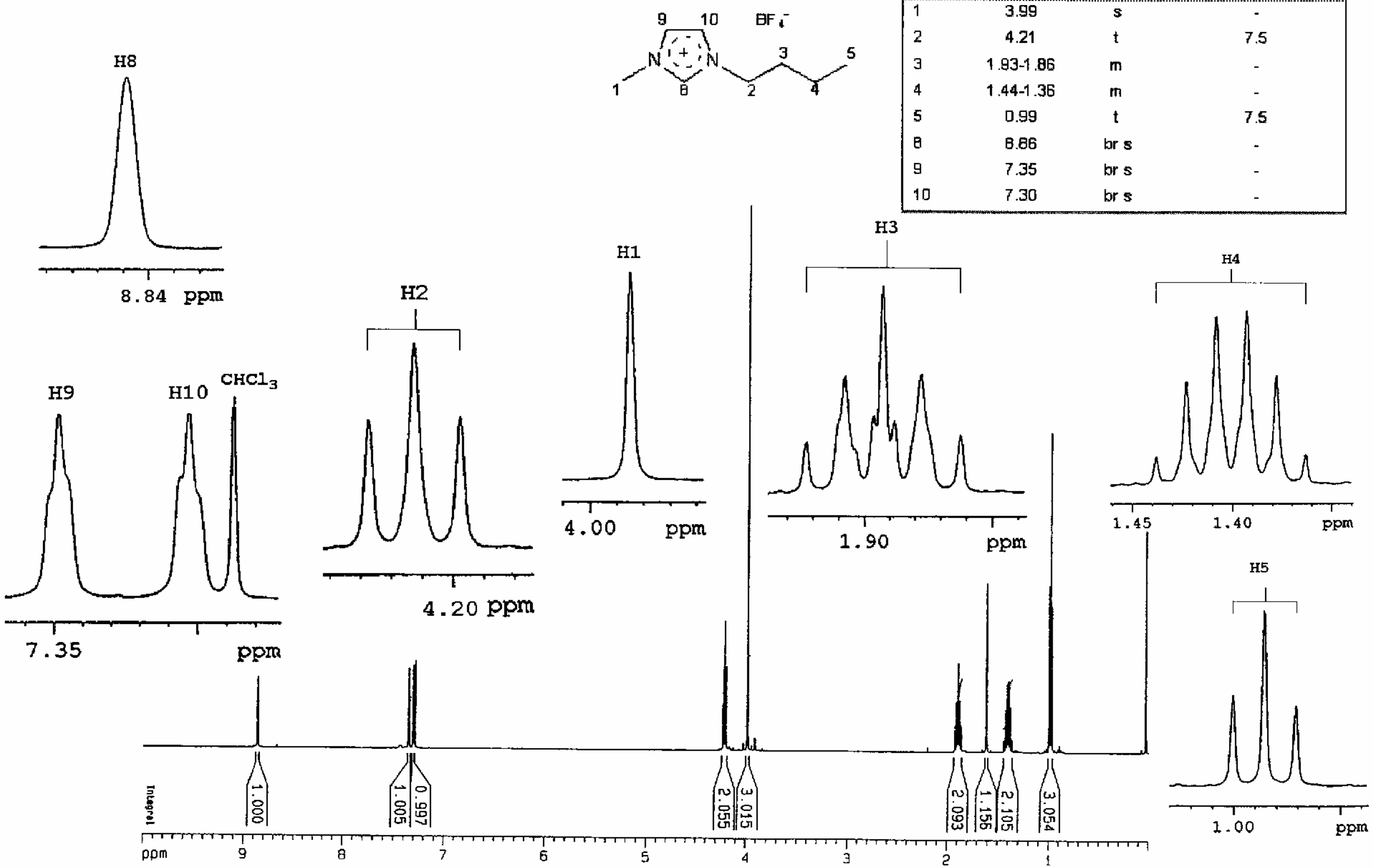
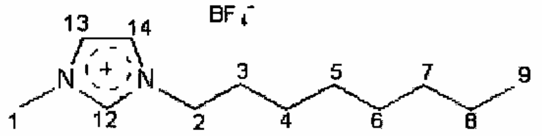


Plate 11: ^{1}H NMR spectrum of 1-Octyl-3-methylimidazolium tetrafluoroborate[omim]BF_4

Solvent: $CDCl_3$

Proton	PPM	Multiplicity	Coupling Constant, (J)
1	3.96	s	-
2	4.18	t	4.5
3	1.89	t	2.0
4-8	1.40-1.20	m	-
9	0.88	t	2.0
12	8.78	s	-
13	7.42	s	-
14	7.35	s	-



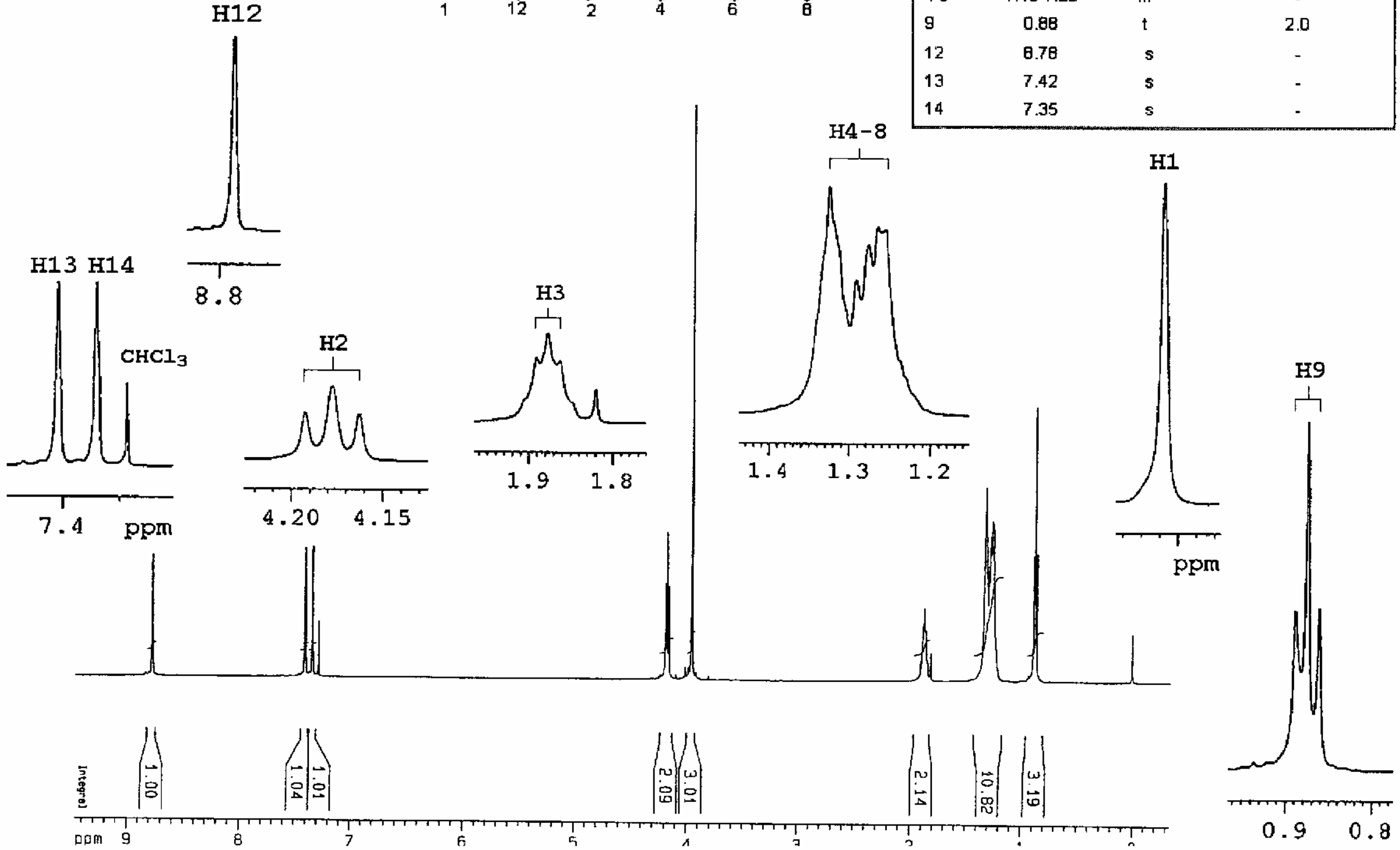
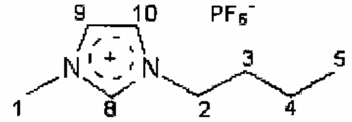


Plate 12: ^1H NMR spectrum of 1-Butyl-3-methylimidazolium hexafluorophosphate [bmim]PF_6

Solvent: $CDCl_3$



Proton	PPM	Multiplicity	Coupling Constant, (J)
1	3.86	s	-
2	4.12	t	7.0
3	1.86-1.77	m	-
4	1.35-1.25	m	-
5	0.88	t	7.0
8	8.37	br s	-
9	7.34	br s	-
10	7.30	br s	-

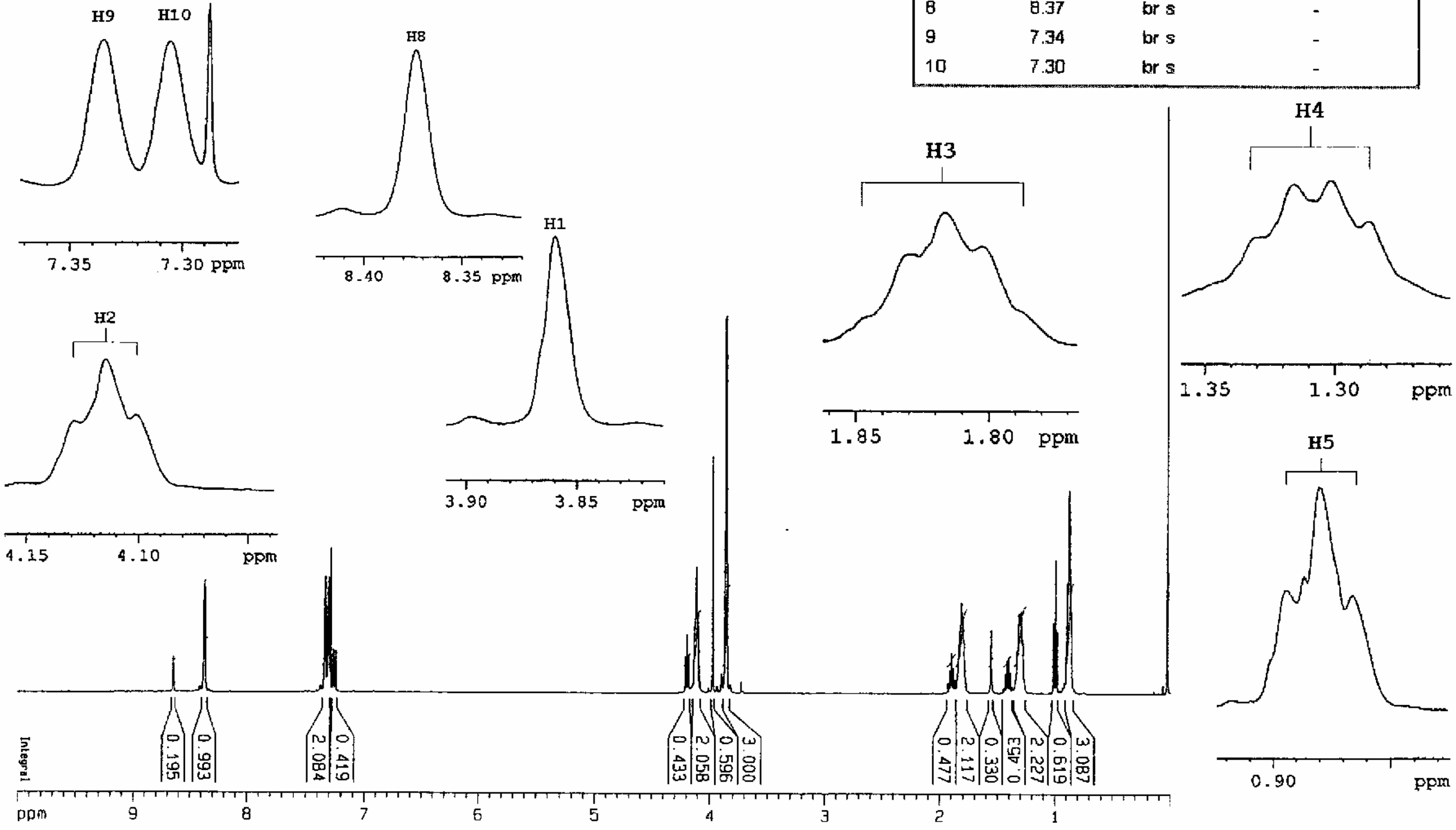


Plate 13: ^1H NMR spectrum of 1-Hexyl-3-methylimidazolium hexafluorophosphate $[hexmim]PF_6$

Solvent: $CDCl_3$

Proton	PPM	Multiplicity	Coupling Constant, (J)
1	3.94	s	-
2	4.16	t	6.0
3	1.93-1.85	m	-
4-6	1.40-1.27	m	-
7	0.90	t	6.0
8	8.55	s	-
9	7.31	s	-
10	7.27	s	-

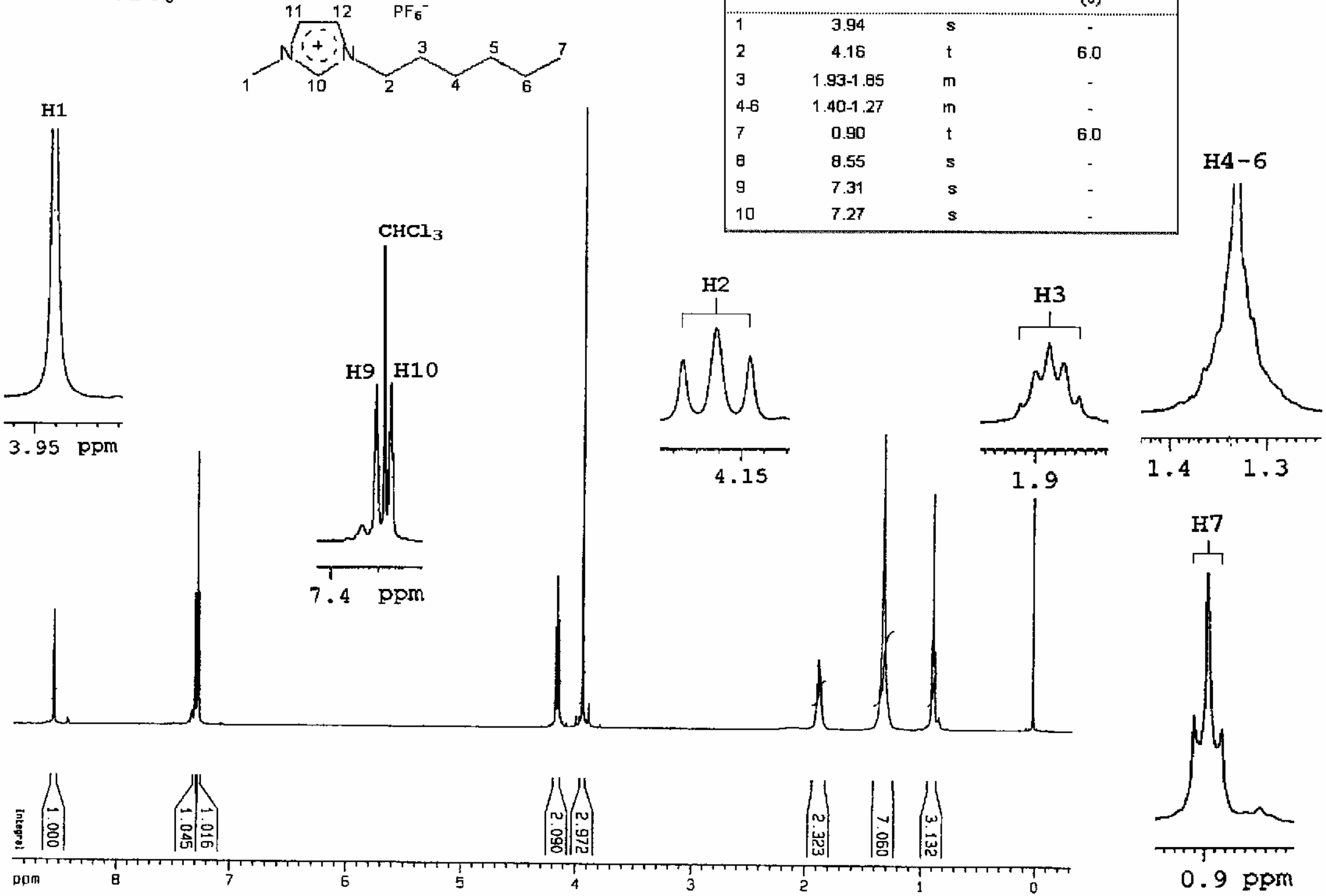


Plate 14: ^{1}H NMR spectrum of 1-Octyl-3-methylimidazolium hexafluorophosphate [omim]PF_6

Solvent: $CDCl_3$

Proton	PPM	Multiplicity	Coupling Constant, (J)
1	3.91	s	-
2	4.14	t	7.0
3	1.90-1.83	m	-
4-8	1.35-1.23	m	-
9	0.87	t	7.0
10	8.46	br s	-
11	7.33	br s	-
12	7.30	br s	-

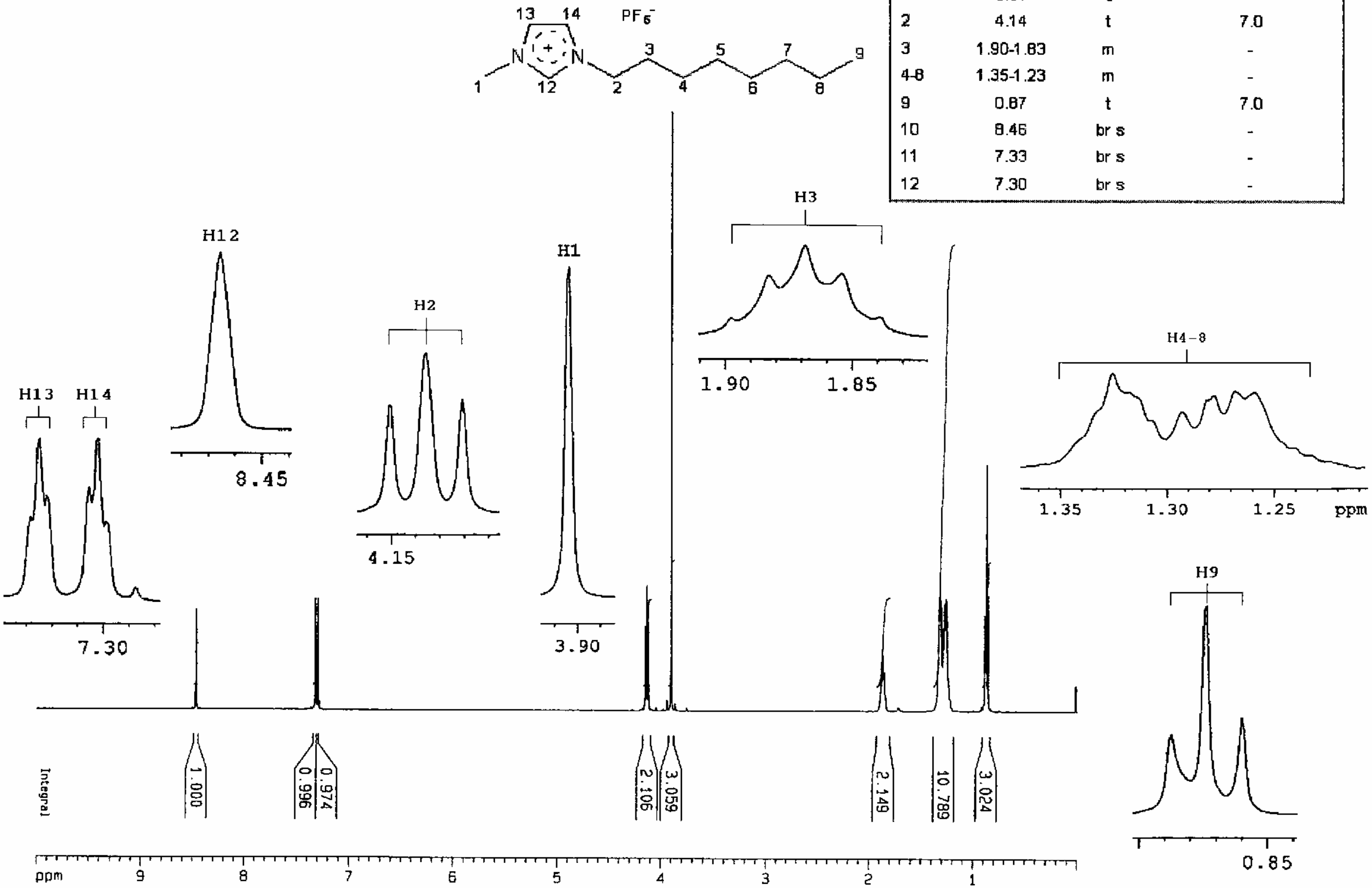
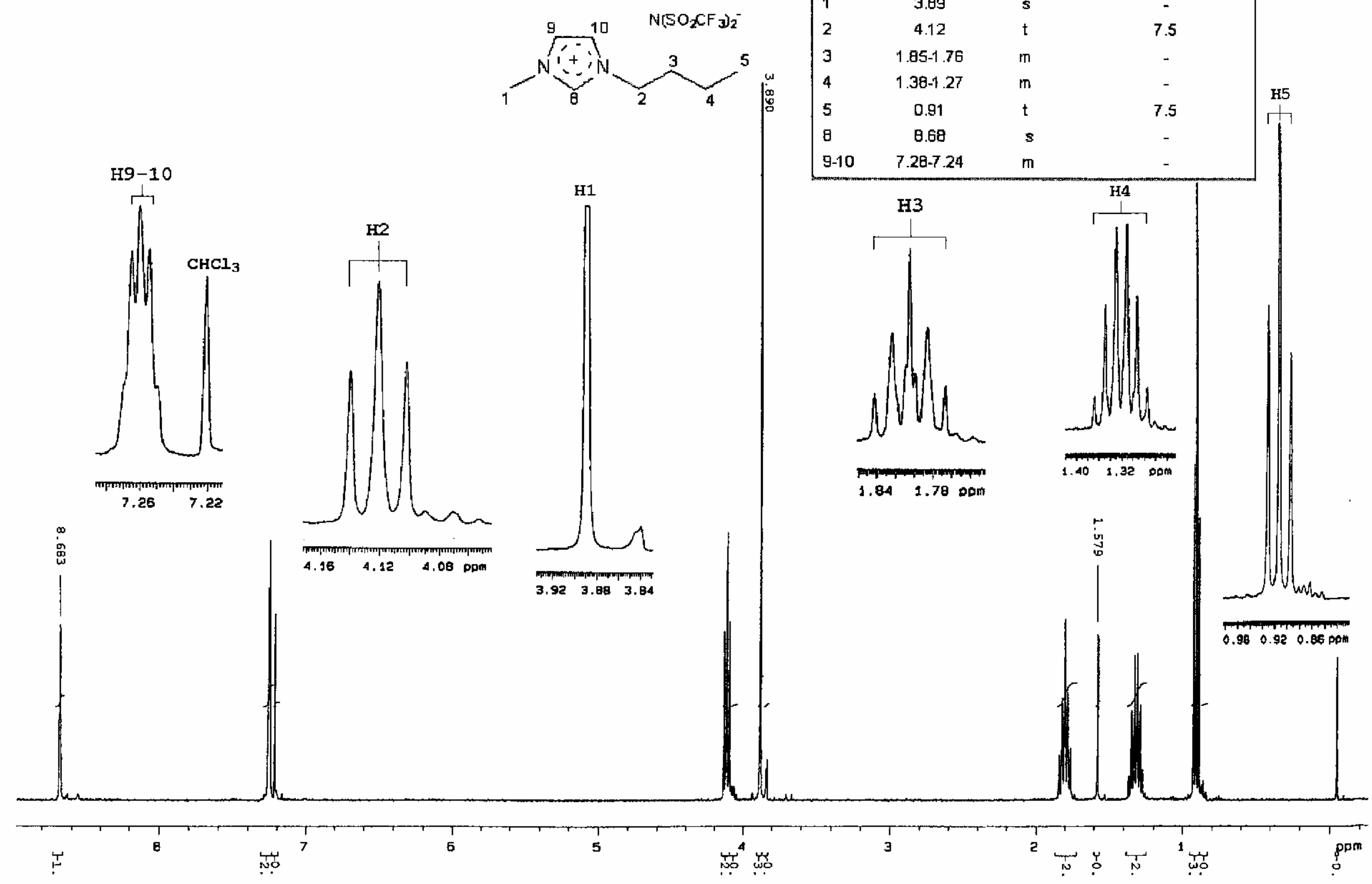


Plate 15: ^{1}H NMR spectrum of 1-Butyl-3-methylimidazolium trifluoromethane sulfonimide [bmim]BTA

Solvent: $CDCl_3$

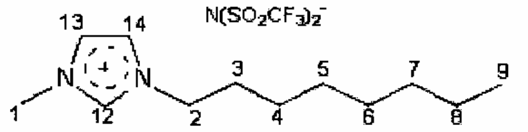


Proton	PPM	Multiplicity	Coupling Constant, (J)
1	3.89	s	-
2	4.12	t	7.5
3	1.85-1.76	m	-
4	1.38-1.27	m	-
5	0.91	t	7.5
8	8.68	s	-
9-10	7.28-7.24	m	-

Plate 16: ^{1}H NMR spectrum of 1-Octyl-3-methylimidazolium trifluoromethane sulfonimide [omim]BTA

Solvent: $CDCl_3$

Proton	PPM	Multiplicity	Coupling Constant, (J)
1	3.16	s	-
2	3.50	t	7.5
3	1.40-1.30	m	-
4-8	1.15-0.90	m	-
9	0.75-0.70	m	-
12	7.82	s	-
13-14	6.60	dd	1.3;37.9



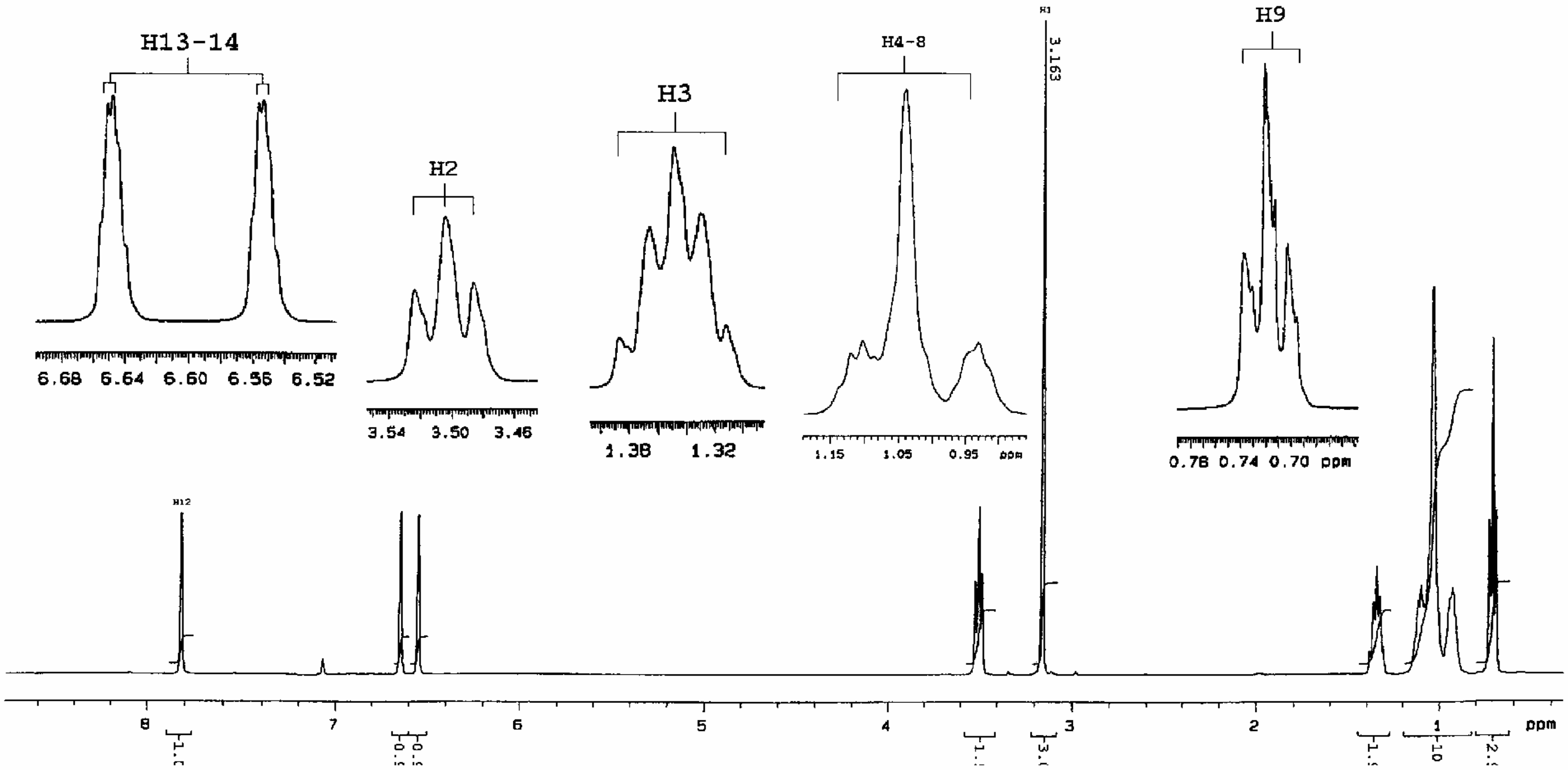


Plate 17: ^{1}H NMR spectrum of anisole after treatment with DF/BF$_3$/CO

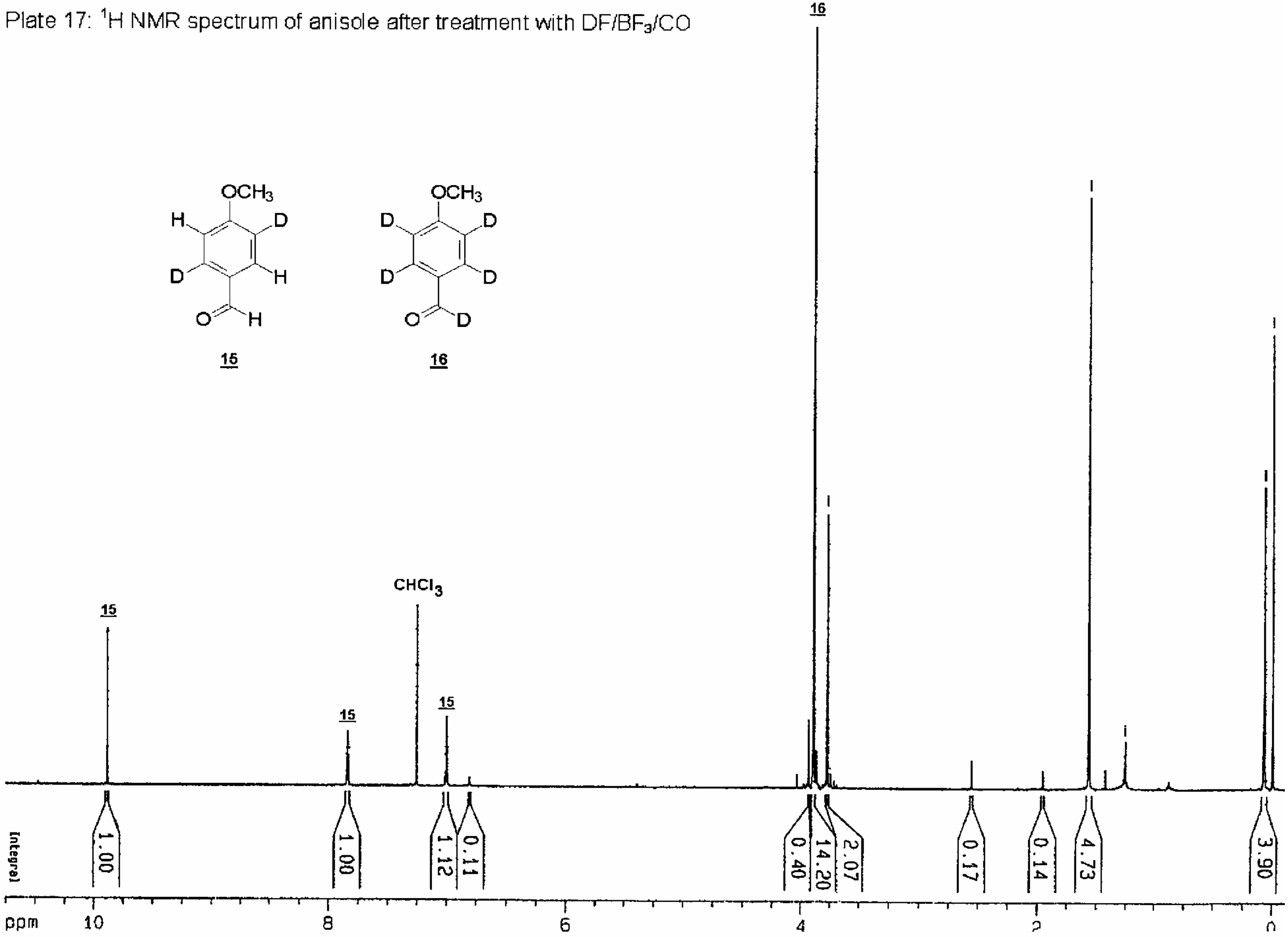


Plate 18: ^{13}C NMR spectrum of anisole after treatment with $DF/BF_3/CO$

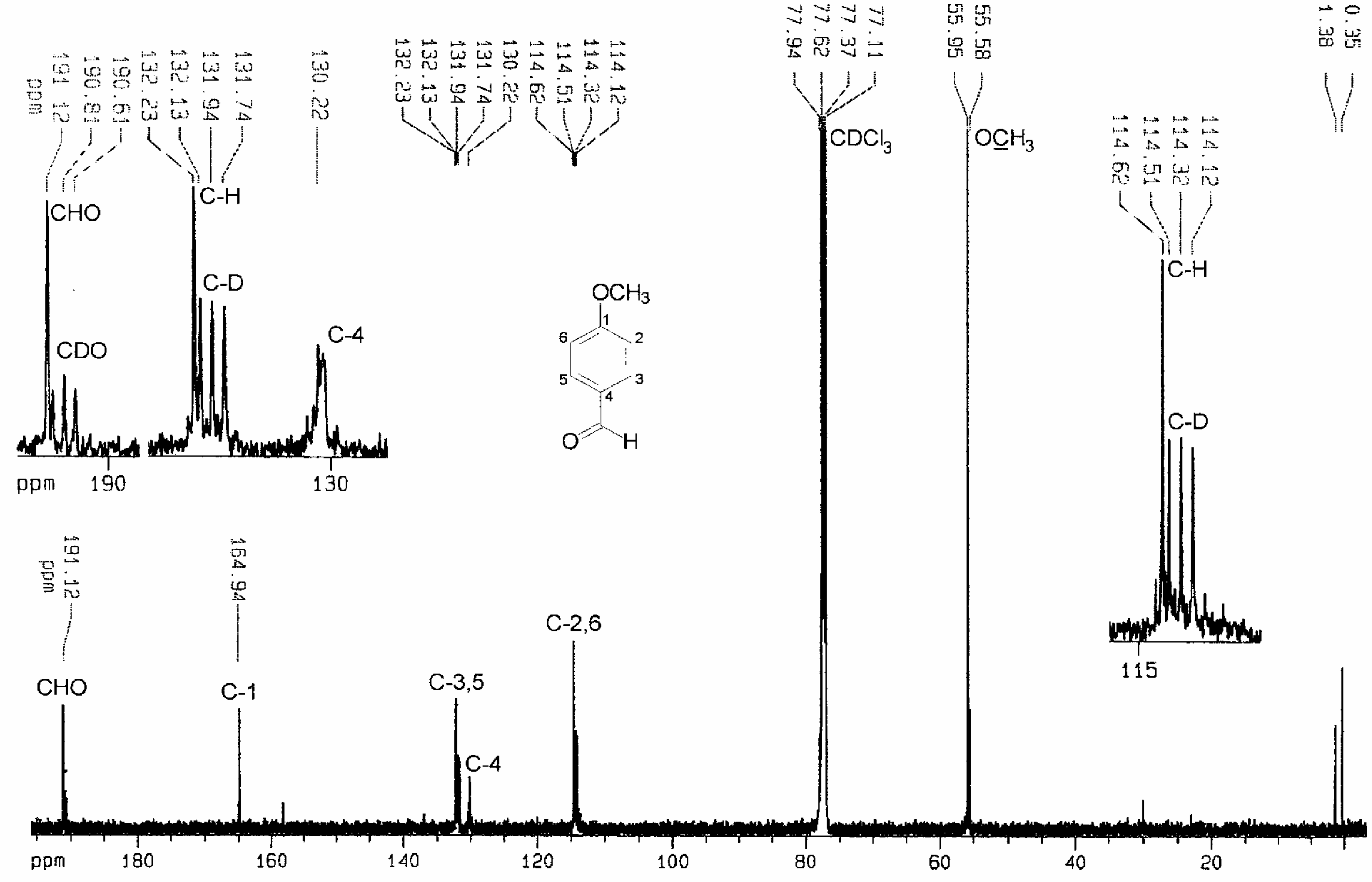


Plate 19: NOESY of anisole after treatment with DF/BF$_3$/CO

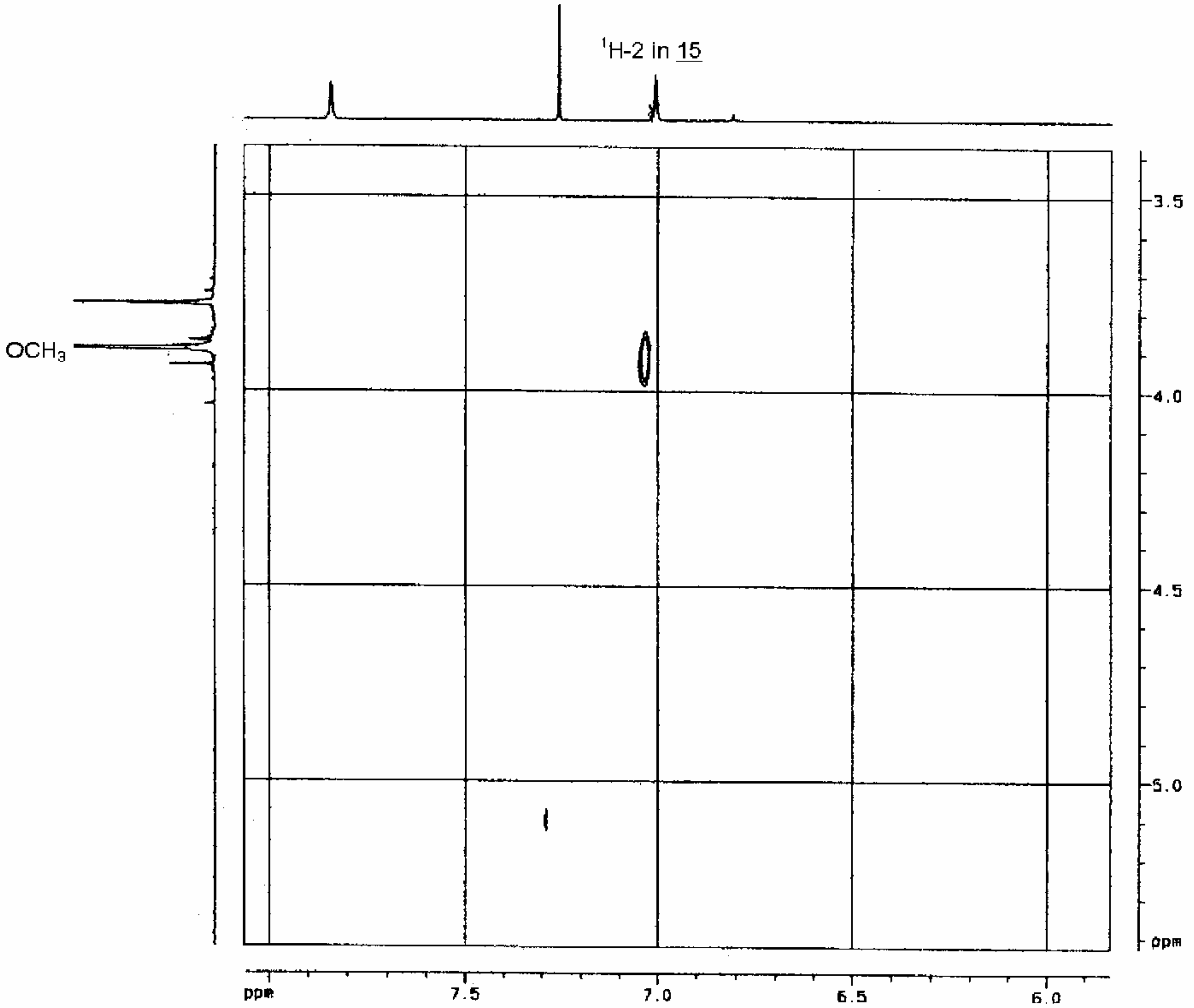


Plate 20: NOESY of anisole after treatment with DF/BF$_3$/CO

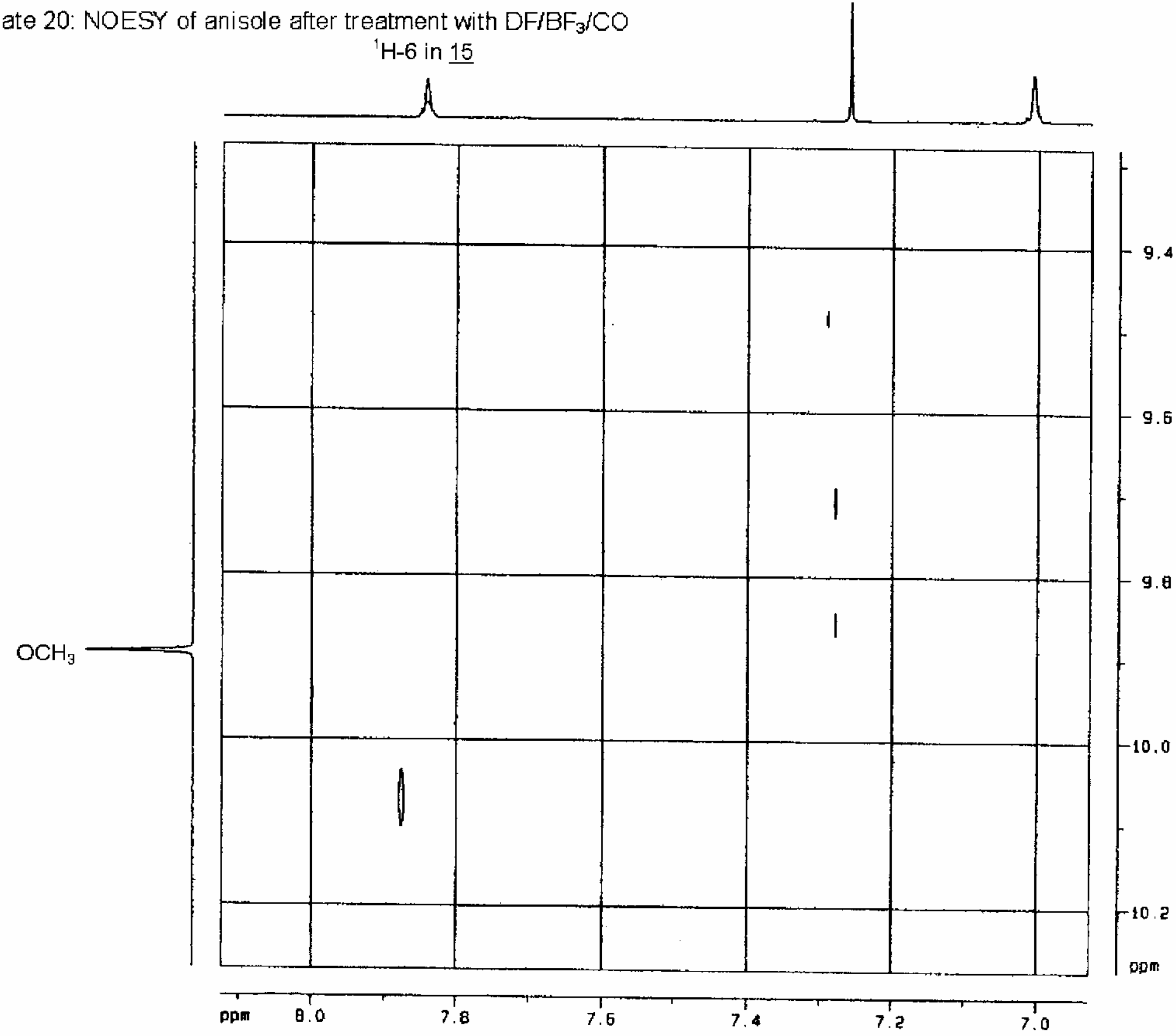


Plate 21: ^{1}H NMR spectrum of toluene after treatment with DF/BF$_3$/CO

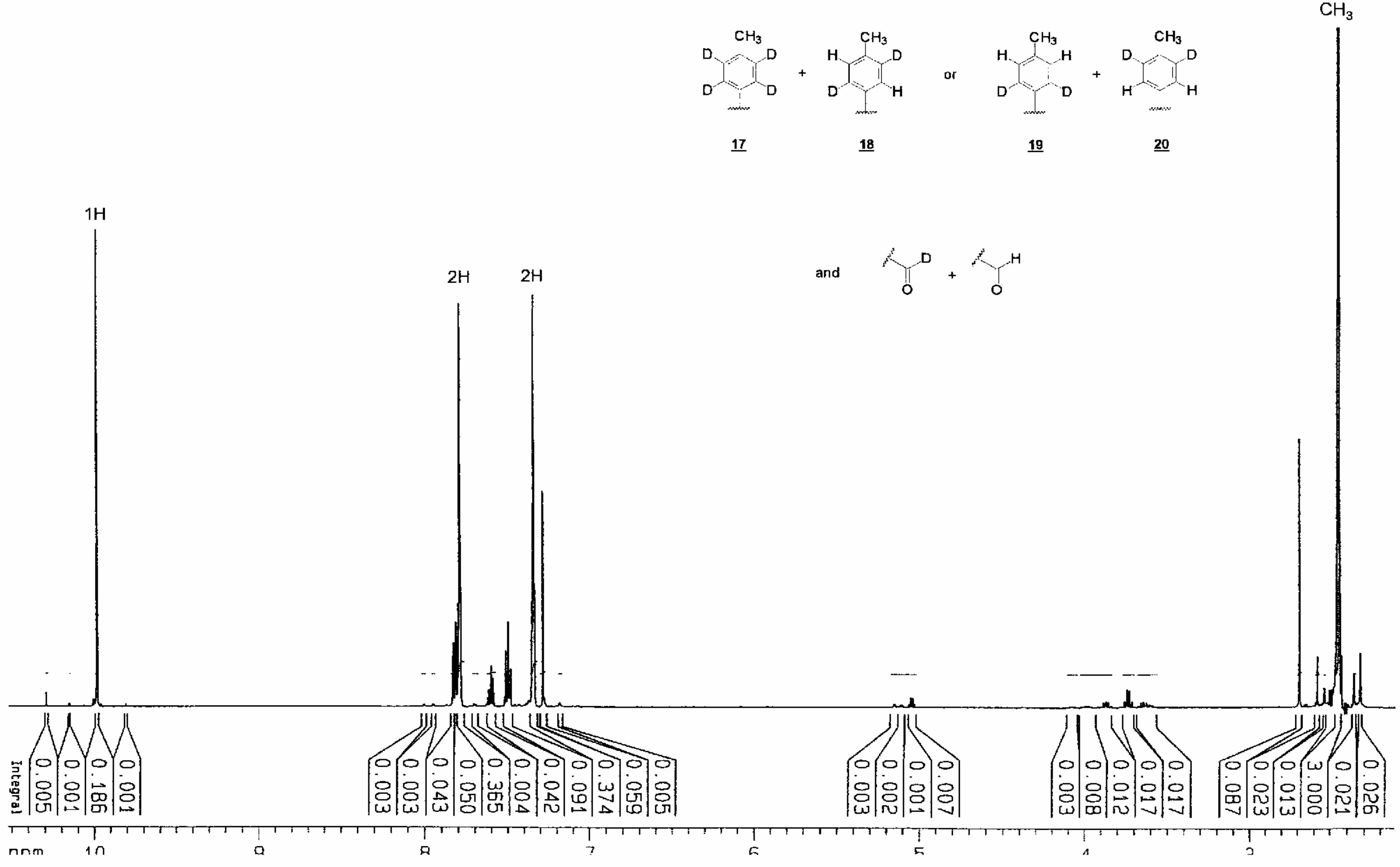


Plate 22: ^{13}C NMR spectrum of toluene after treatment with $DF/BF_3/CO$

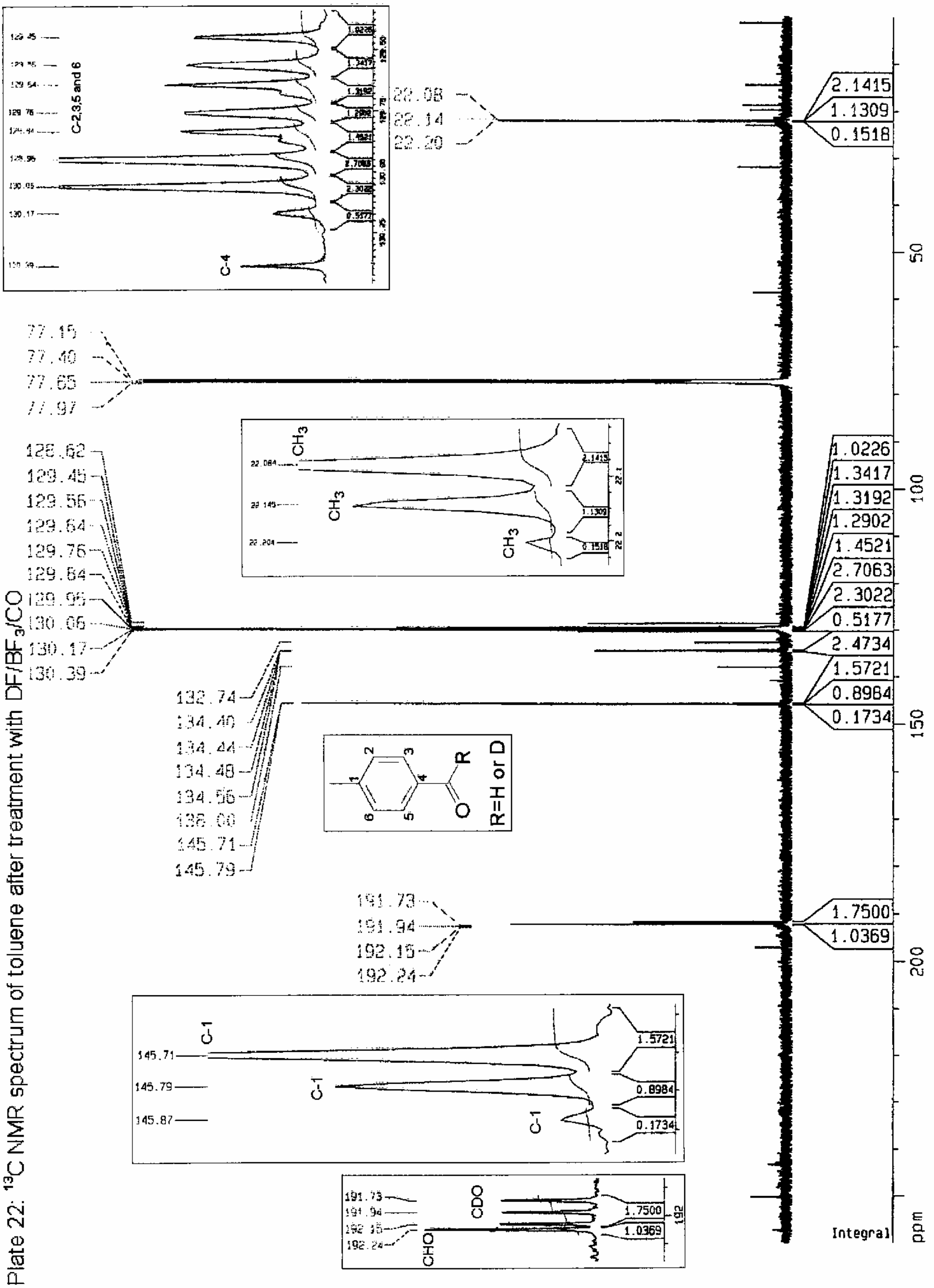


Plate 23: ^{1}H NMR spectrum of toluene-d_5 after treatment with HF/BF$_3$/CO

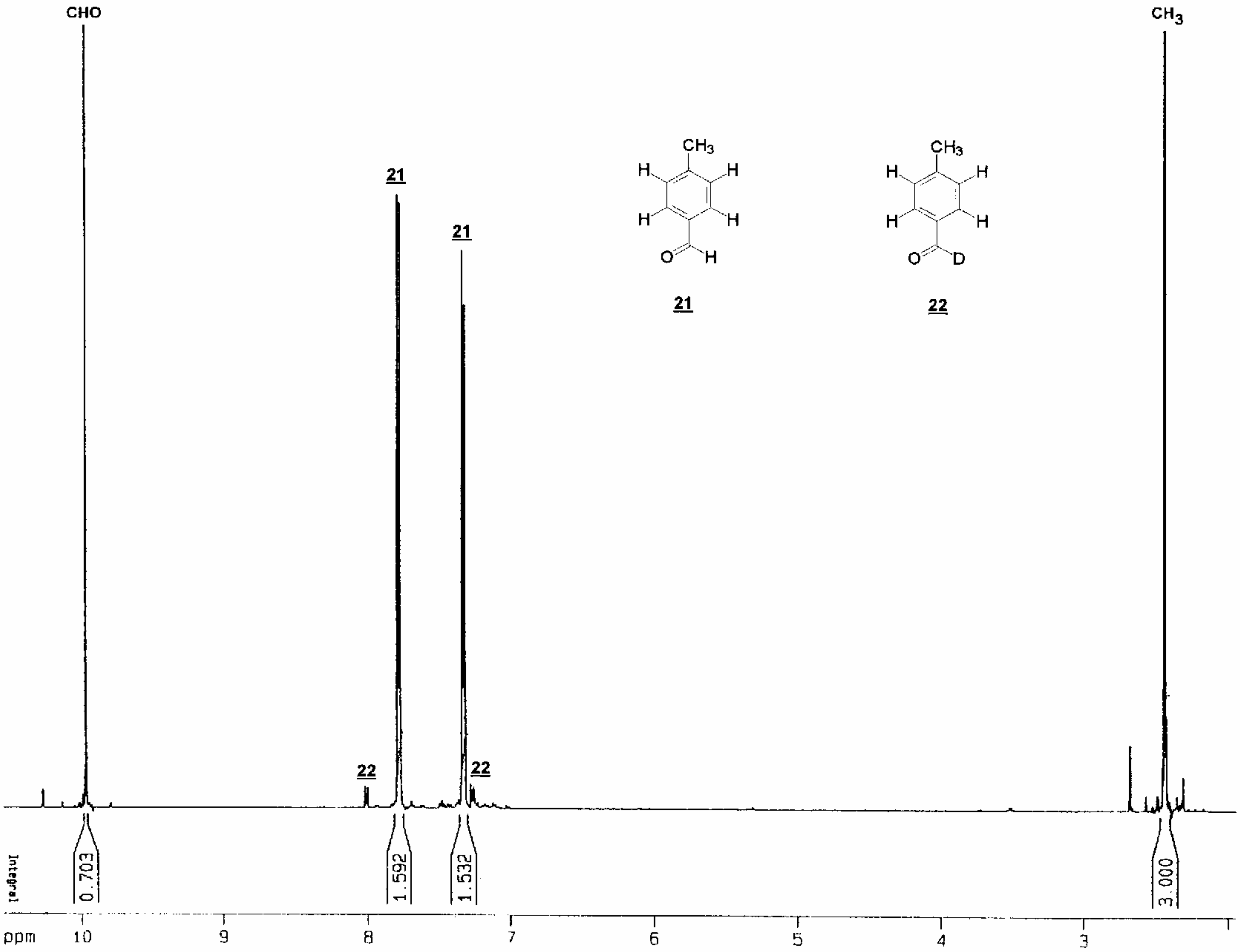


Plate 24: ^{13}C NMR spectrum of toluene-d_5 after treatment with $HF/BF_3/CO$

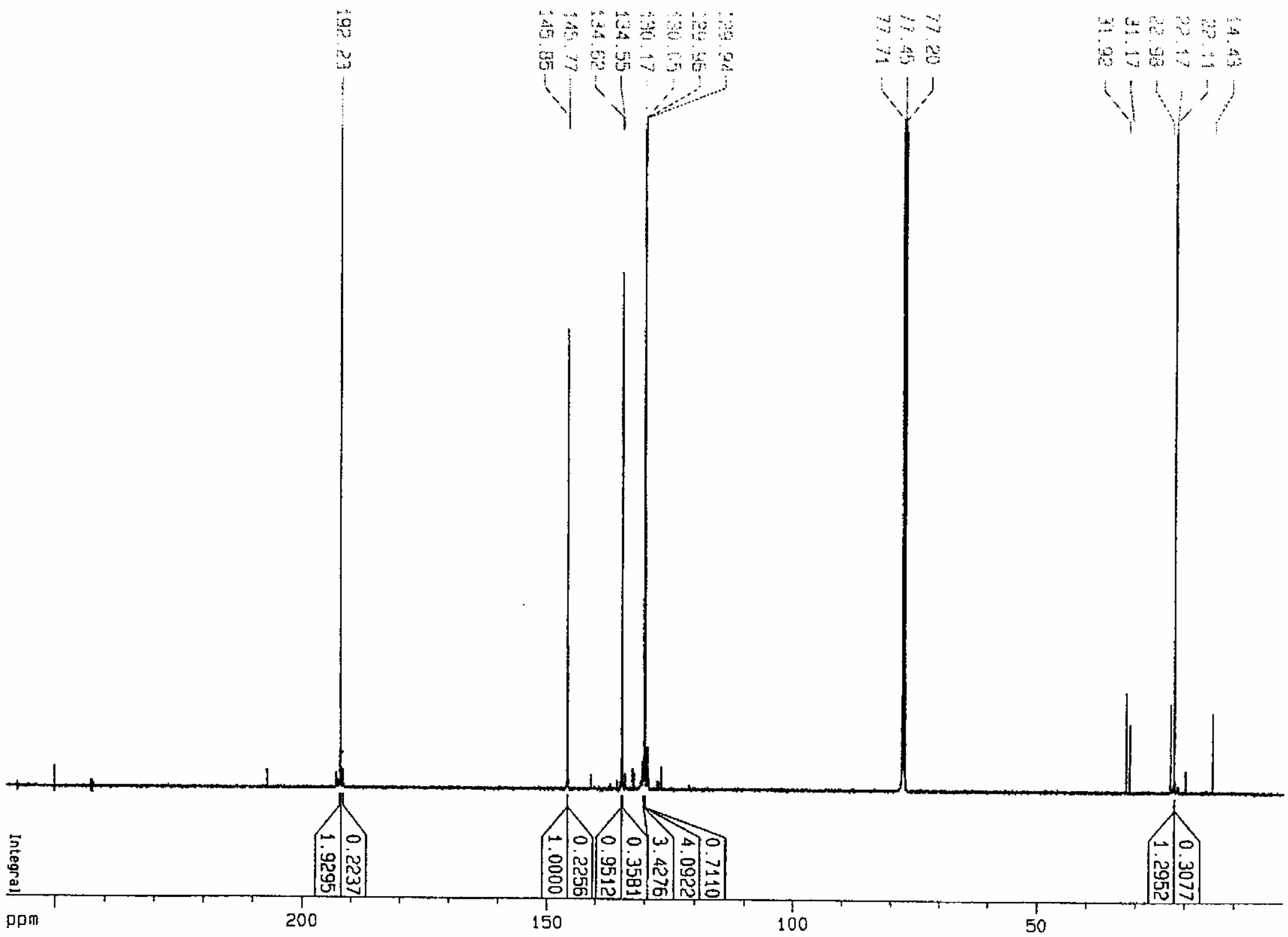


Plate 25: Extension of ^{13}C NMR spectrum of toluene-d_5 after treatment with HF/BF$_3$/CO

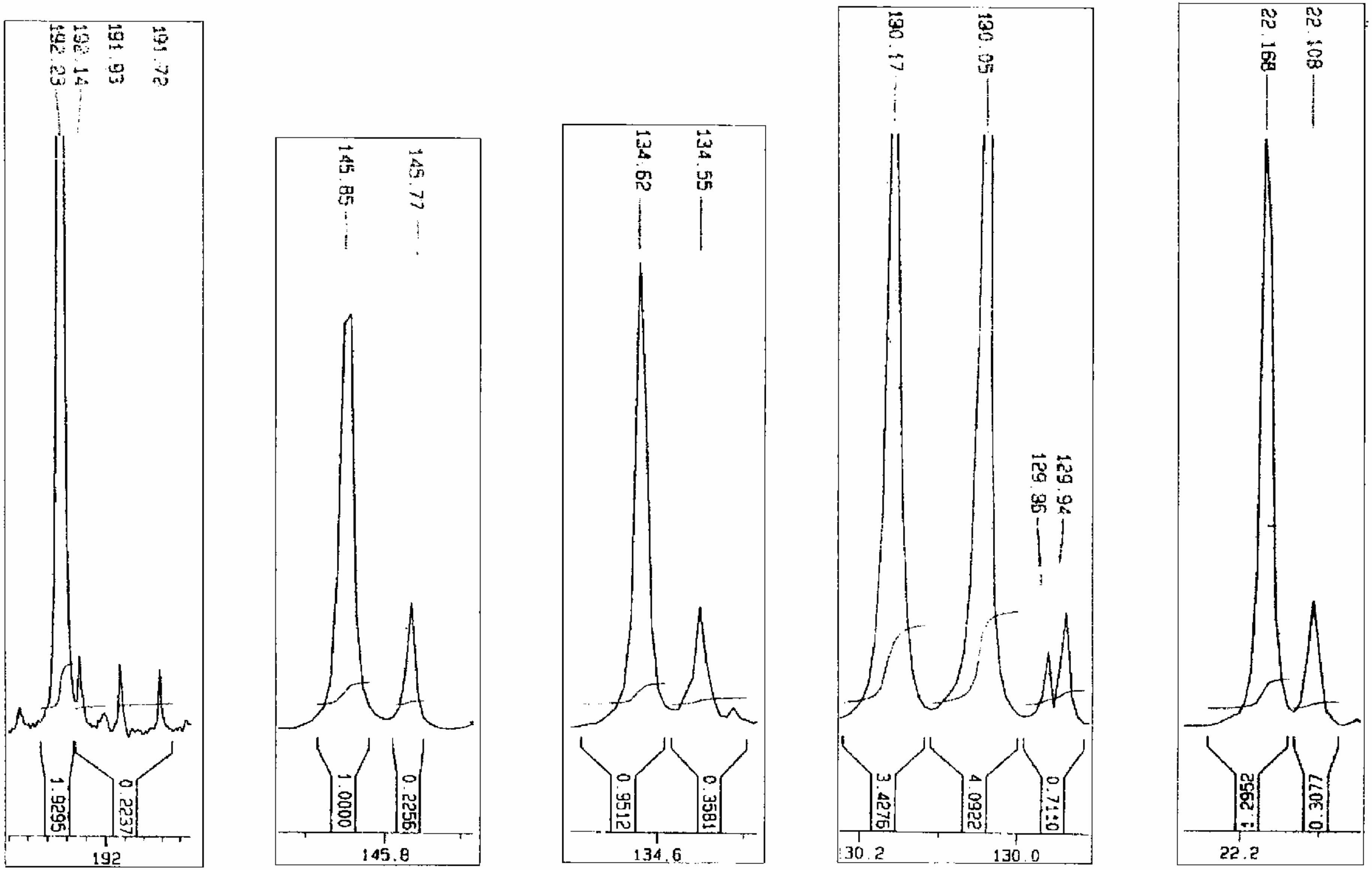


Plate 26: Example of a GC chromatogram on the formylation of anisole

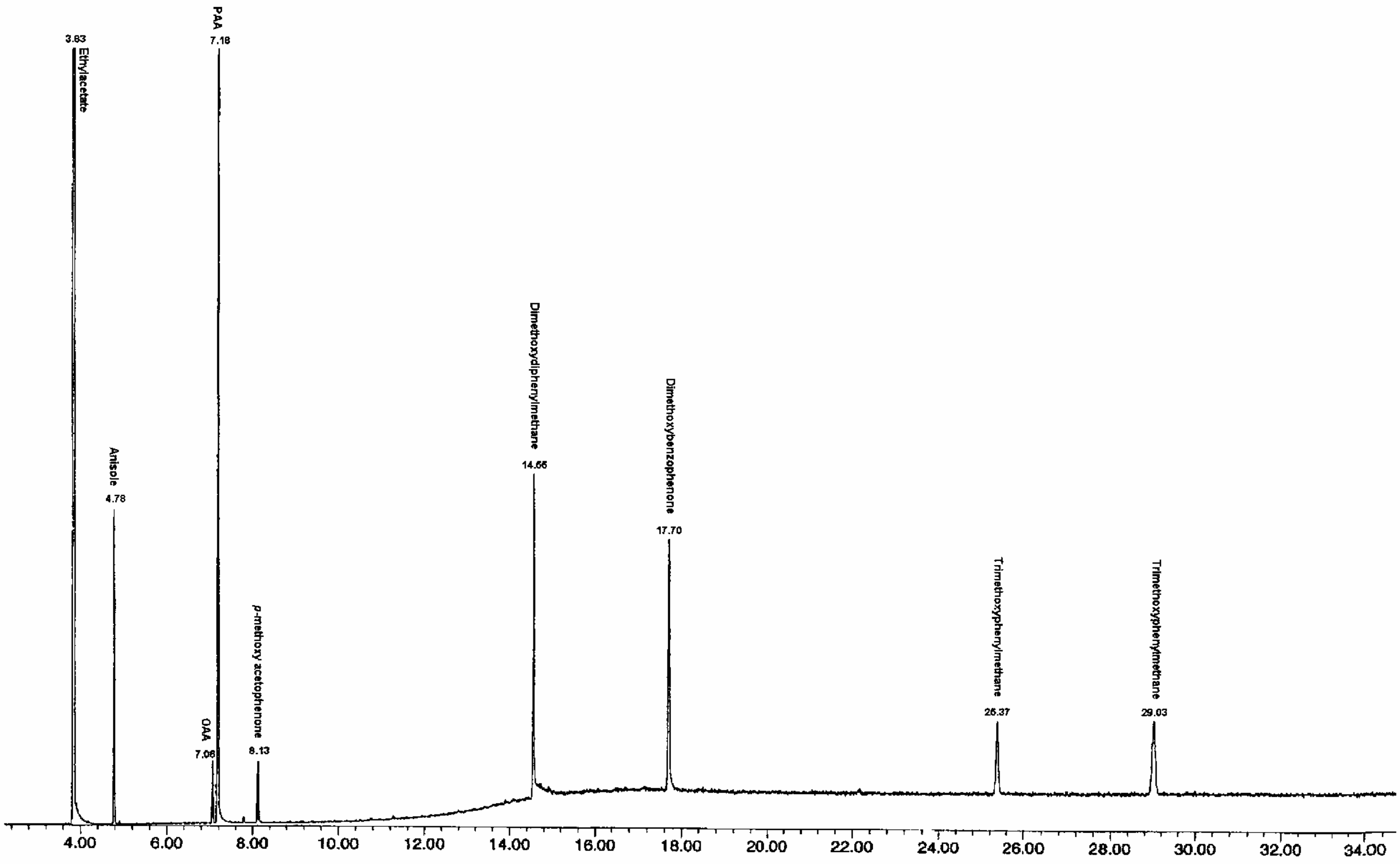


Plate 27: Mass spectrum of Methoxyacetophenone

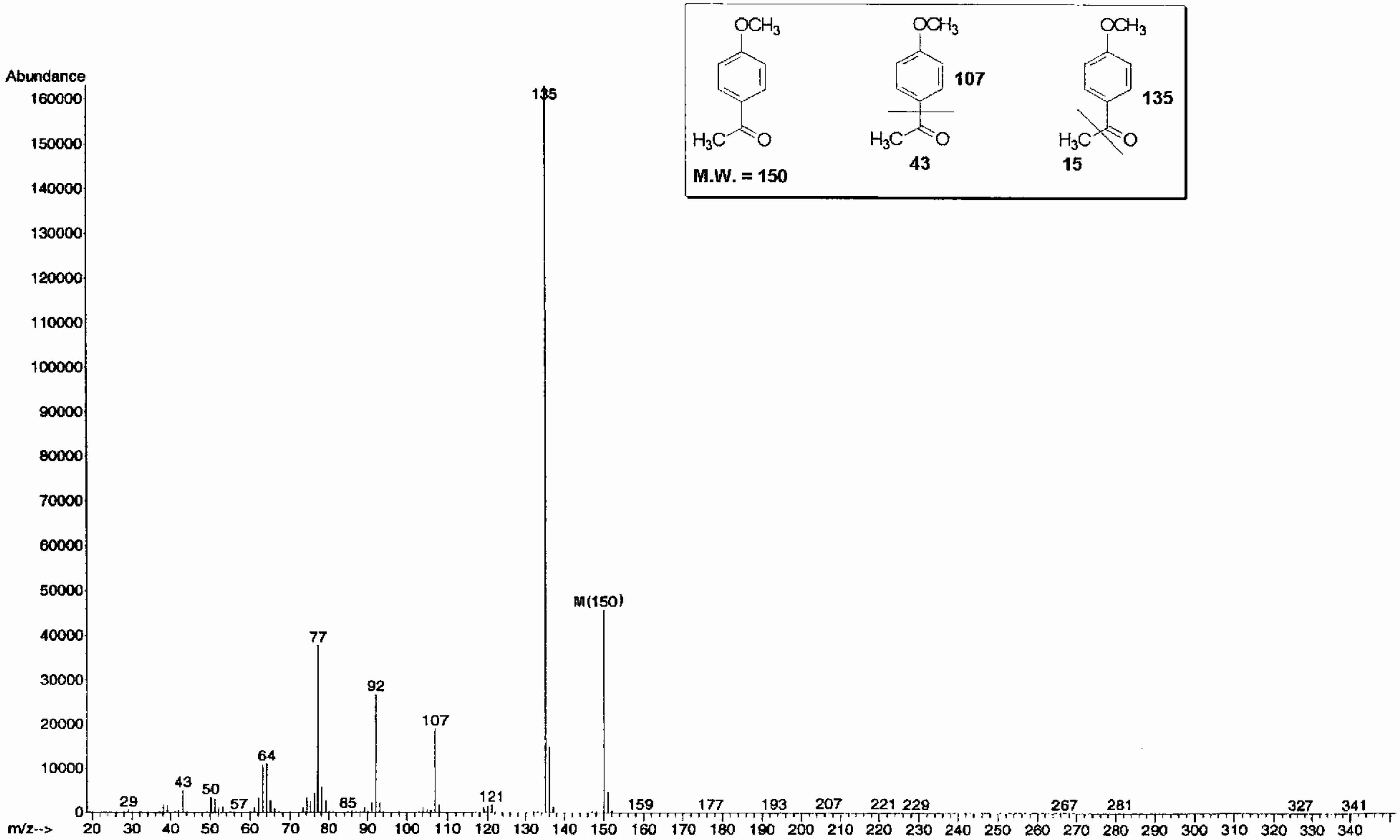


Plate 28: Mass spectrum of Methoxybenzaldehyde

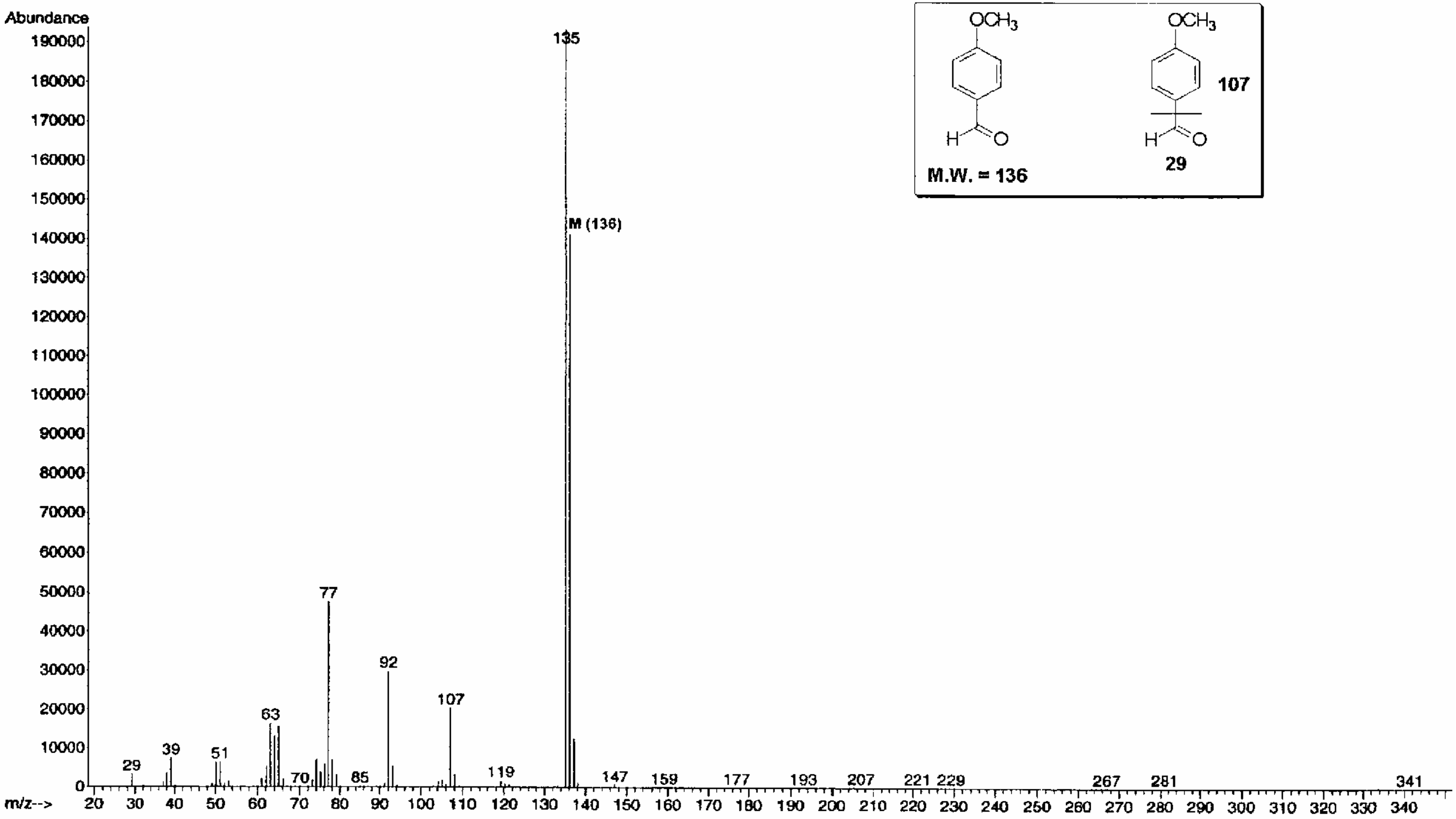


Plate 29: Mass spectrum of Di-(methoxyphenyl)methane

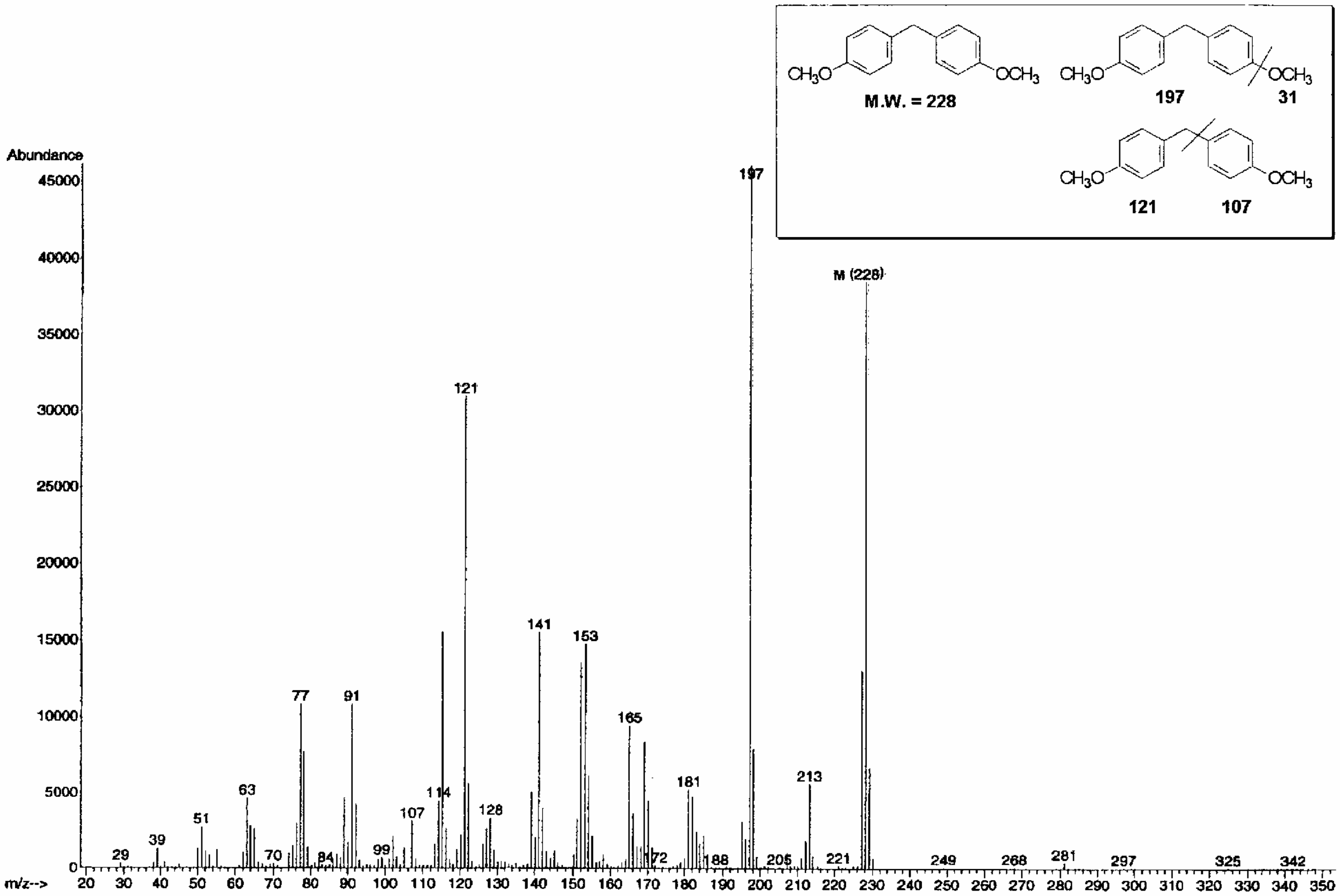


Plate 30: Mass spectrum of Dimethoxybenzophenone