Elemental fluorine as a valid synthetic reagent

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A Thesis Entitled

Elemental Fluorine as a Valid Synthetic Reagent

Submitted by

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For Valerie, Andrew and Alan.

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Memorandum

The work described in this thesis was carried out in the University of Durham between the 1st October 1991 and 30th September 1994. This thesis is the work of the author, except were acknowledged by reference, and has not been submitted for any other degree.

The work has been presented, in part, at:

1. *Direct Fluorination Revisted*, R. D. Chambers, J. Hutchinson, C. J. Skinner and J. Thomson, Presented at the 14th International Symposium on Fluorine Chemistry, Yokohama, Japan, July 1994.

2. *Halogenation Using Elemental Fluorine*, R.D. Chambers, C.J. Skinner, J. Moilliet and M. J. Atherton, Presented at the 14th International Symposium on Fluorine Chemistry, Yokohama, Japan, July 1994.

3. *Direct Fluorination of Substituted Aromatic Compounds*, R. D. Chambers, J. Thomson, J. Hutchinson, C. J. Skinner and M.J. Atherton, Presented at the 14th International Symposium on Fluorine Chemistry, Yokohama, Japan, July 1994.

And in paper or patent form in:

4. *Process for the Preparation of 3- or 5-Fluoroaromatic Compounds.*, R. D. Chambers, C. J. Skinner, M. J. Atherton and J. S. Moilliet, Eur. Pat. Appl. EP 566,268 (Cl. C07B39 / 00) 20 Oct 1993; GB Appl. 92 / 8,123 13th April. 1992.

5. *Process for the Polyfluorination of Aromatic Compounds*, R. D. Chambers, C. J. Skinner, J. Hutchinson, J. T. Thomson, M. J. Atherton and J. S. Moilliet, U.K Appl 9325757.4 16th December 1993.

6. *Halogenation of Aromatics Using Elemental Fluorine*, R. D. Chambers, C. J. Skinner, M. J. Atherton and J. S. Moilliet , U.K Appl 9414972.1 26th July 1994.

7. *Functionlisation of Heterocyclic Compounds Using Elemental Fluorine*, R. D. Chambers, G. Sandford, C. J. Skinner and M. J. Atherton, U.K Appl 9414973.9 26th July 1994.

8. *Nitrofluorination of Aromatic compounds Using Elemental Fluorine*, R. D. Chambers, C. J. Skinner, M. J. Atherton and J. S. Moilliet, Submitted to Patent Office.

9. *Process for the Fluorination of Heterocycles Using Elemental Fluorine*, R. D. Chambers, C. J. Skinner, G. Sandford and M. J. Atherton, In preparation.

10. *Electrophilic Fluorination Using Elemental Fluorine* , R.D. Chambers, C. J. Skinner, J. Thomson, J. Hutchinson, Accepted for publication in *J. Chem. Soc., Chem. Commun.* (November 1994).

11. *Elemental Fluorine as an 'Enabler' for the Generation of Powerful Electrophiles from other Halogens,* R. D. Chambers, C. J. Skinner, M. J. Atherton and J. S. Moilliet , Accepted for publication in *J. Chem. Soc, Chem. Commun* (November 1994).

Abstract

Elemental Fluorine as a Valid Synthetic Reagent

C. J. Skinner, Univ. of Durham, 1994.

Chapter I

Chapter I reviews the uses of elemental fluorine in selective organic synthesis and its use in the generation of selective electrophilic fluorinating agents.

Chapter II

Chapter II describes a systematic investigation into suitable solvents for the direct fluorination of deactivated aromatic systems. After highlighting 98% formic acid and 98 % sulphuric acid as excellent media for fluorinations, a number of other protonic acids were investigated. The work confirms the power of the resulting *in situ* fluorinating species is dependent on the pKa of the protonic acid.

Chapter III

Chapter III describes the use of elemental fluorine, in combination with strong acids, for the generation of powerful electrophilic halogenating agents derived for iodine, bromine and some interhalogens. The use of iodoaromatics in the incorporation of perfluoroalkyl groups into aromatics is also detailed.

Chapter IV

Chapter IV describes the use of elemental fluorine, in combination with iodine, for the direct fluorination of pyridines and quinoline in the 2- position. The use of elemental fluorine and an alcohol in the 2-alkoxylation of pyridine is also described. Investigation into a number of other potential nucleophiles for the 2- functionalisation of pyridines is also detailed.

Chapter V-VII

Experimental details relating to Chapters II-IV.

Appendix One-Three

Relevant ^{1}H nmr, ^{13}C nmr, ^{19}Fnmr, FT / IR data and mass spectra data.

Elemental Fluorine as a Valid Synthetic Reagent

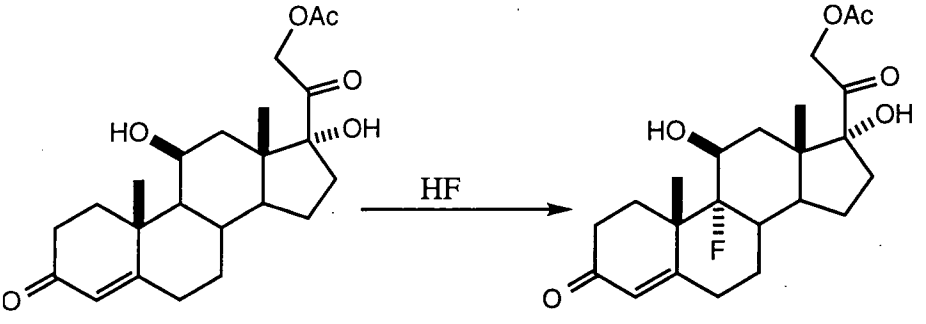
Contents

Chapter I. Elemental Fluorine in Organic Synthesis

I.1. Fluorine in Organic Chemistry

The chemistry of fluorine and its compounds is a comparitively young science. Hydrogen fluoride was first dicovered by Scheele in 1771 and elemental fluorine first prepared by Moissan in 1886[1]. The systematic investigation of the chemistry of organofluorine compounds did not start before 1900 with the work of Swarts[2] but it was the pioneering work of Midgley and Henne[3] in the 1930's demonstrating fluoromethanes as effective refrigerants that initiated a wave of research into organofluorine chemistry. Tetrafluoroethene was first obtained by Ruff and Bretschneider in 1933, who decomposed CF_4 in an electric arc[4] while Locke *et al* developed a synthesis which involved the zinc dehalogenation of CF_2ClCF_2Cl[5]. The formation of PTFE was discovered around 1940 and in the same period chlorotrifluoroethylene was found to polymerise to give a stable product (Kel-F*). In 1937 Simons prepared and isolated the first range of perfluorocarbons and identified their extreme stability which made them ideal for the Manhattan project of World War II.

While the halofluorocarbons represented the largest area of fluorine chemistry, it was the pioneering work by Fried in the preparation and demonstration of the biological activity (10.7 times greater than the parent compound) of 9α-fluorohydrocortisone acetate **[E-1]** that generated interest in the incorporation of fluorine into a wide variety of biologically active molecules[6]. The attractiveness and utility of fluorine as a substituent in biologically active molecules stemed from the pronounced electronic effects that may result on fluorination as well as on the fact that fluorine is not a sterically demanding substituent[7].



[E-1]

Because the introduction of fluorine can have a profound affect of the properties of organofluorine compounds be they pesticides, anaesthetics[8,9], pharmaceuticals[10], perfluorinated liquids[11], polymers[12], refrigerants[13] or dyes[14] fluorine containing

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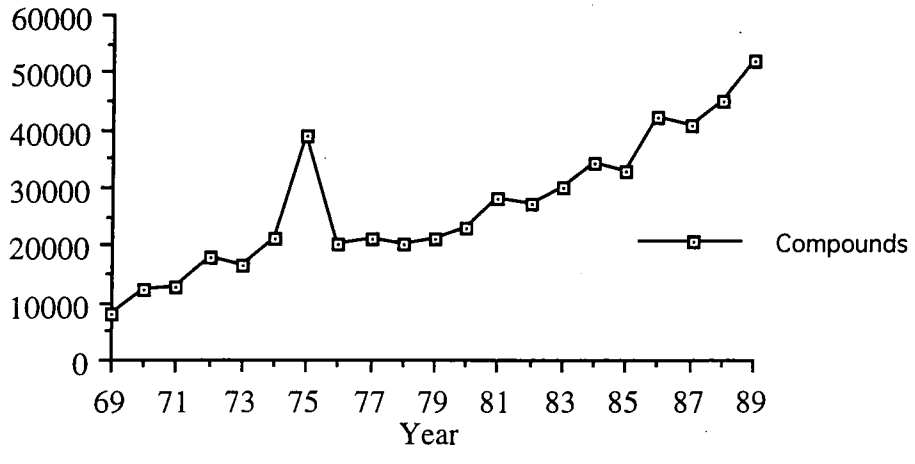
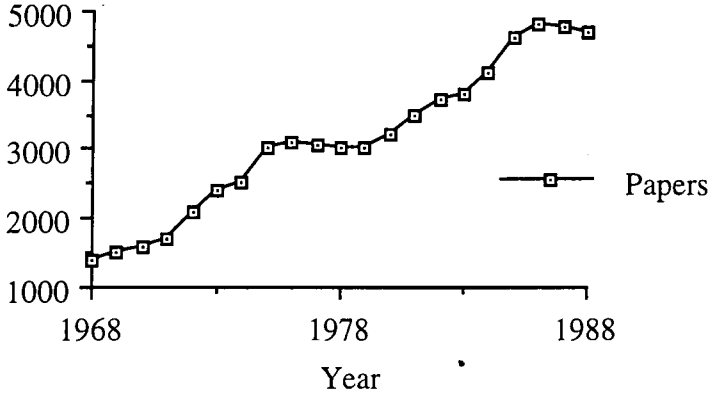
* Trade name of Minnesota Mining and Manufacturing Co., U.S.A.

compounds are now appropriate to every area of organic chemistry, the following graphs illustrating this dramatic growth since the late 1960's (Graph 1, Graph 2).

Graph 1: Number of New Fluorinated Compounds Described Each Year



Graph 2: Number of Organofluorine Papers Published Each Year



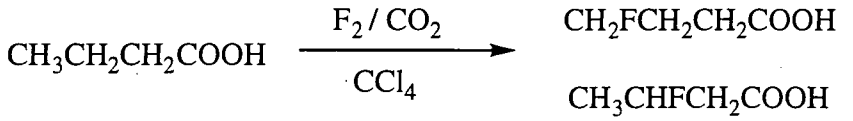
A conservative estimate is that $50,000,000 can now be associated with fluorine in organic chemistry every year[15]. With such large scale interest one would imagine there to be a spectrum of reagents available for the introduction of fluorine into organic compounds. This however is not the case, and until the late 1960's the primary source of fluorine, elemental fluorine, had been considered too reactive and dangerous to be practical for the fluorination of organic molecules[16].

I.2. Historical Development of Direct Fluorination

Molecular fluorine was first prepared in 1886 by Moissan[1], consequently he was also the first to attempt to react the element with organic compounds. His attempts to fluorinate CH_4, $CHCl_3$ and CCl_4 resulted in 'burning' of the organic compound with frequent explosions taking place[17]. In 1890 he claimed to have isolated carbon tetrafluoride from the reaction of carbon with fluorine[18], but his results were later to be

found in error by the Belgium chemist Swarts[2]. Emphasis on 'taming' the reactions of elemental fluorine continued with Ruff *el al* who demonstrated the first controlled vapour phase fluorination of CCl_4 to produce CF_4[19]. Other workers in the field included Calfee and Bigelow who achieved further success by dilution of the elemental fluorine with nitrogen prior to the reaction[20]. Further advances in the field of vapour phase reactions were made by Musgrave *et al* who used a variety of packed reactors to bring further over the fluorination reaction[21] but eventually vapour phase fluorination was superseded by cobalt trifluoride process.

Bockemüller *et al* was the first to demonstrate selective liquid phase fluorination by dissolving an organic compound in an 'inert' solvent and then bubbling a mixture of fluorine and an 'inert' gas through the solution. Using this method he selectively fluorinated *n*-butyric and *iso*-butyric acid **[E-2]**[22].



n-Butyric acid β- γ Fluorobutyric acid

[E-2]

In 1937 Simons and Block found mercury promoted the reaction between carbon and fluorine enabling them to isolate and characterise CF_4, C_2F_6, C_3F_8, C_4F_{10}, cyclo-C_6F_{12} and C_6F_{14}[23,24]. These compounds were also found to be extremely thermally stable and this led to the suggestion by Simons that they might be resistant to UF_6 making them appropriate to the Manhattan Project of World War II and begining a wider interest into organofluorine chemistry.

I.3. Properties of Elemental Fluorine

I.3.a. Physical Properties

Fluorine, is a pale green gas and its salts are more abundant in the earth's crust (0.065%) than those of chlorine (0.055%) forming concentrated deposits in minerals such as fluorite (or fluorospar CaF_2), cryolite Na_3AlF_6 and fluoroapatite $3Ca_3(PO_4)2Ca(F,Cl)_2$. Only one isotope is found in nature, but ^{18}F with a half life of 109.7min is available and can be used as a tracer. Most of the physical properties of the halogens are summarised in the Table 1.

Table 1: The Physical Properties of the Halogens.

Property	Fluorine	Chlorine	Bromine	Iodine
Density of solid g/cm^3	1.3	1.9	3.4	4.9
Melting point ^oC	-223	-102	-7.3	114
Boiling Point ^oC	-187	-34.7	58.8	183
Critical Temp.^oC	-129	144	311	553
Critical Pressure atm	55	76.1	102	-
Heat of Vapourisation kj / mol	6.9	18.6	31.2	43.6
Heat of dissociation kj / mol	158.3	239.0	189.8	148.7
Covalent Radius Å	0.72	0.99	1.14	1.33
Ionisation Potential ev	17.42	13.01	11.84	10.44
Electron affinity ev	4.13	3.75	3.53	3.2
Electronegativity	4.0	3.0	2.8	2.5

I.3.b. Chemical Properties

Fluorine is chemically the most reactive of all elements and combines directly at ordinary or elevated temperatures with all other elements except nitrogen and the lighter noble gases. It will also attack many other compounds, particularly organic compounds, the driving force being the extremely favourable formation of a X-F bond (see Table 2) coupled with the extremely low dissociation energy of elemental fluorine.

Table 2: Variation in X-F Bond Strenghts.

Bond	Bond Energy KJ / mol
CF_4	487
$-CF_3$	478
$-CF_2$	458
-CF	449
H-F	562
-NF	272
-PF	490

I.4. Production of Elemental Fluorine

I.4.a. Electrochemical

Although fluorine was first isolated by Moissan in 1886 as a product of the electrolysis of anhydrous hydrogen fluoride containing potassium hydrogen fluoride (KHF_2), modern developments into the production of elemental fluorine may be traced back to the introduction of the fused potassium fluoride / AHF as the electrolyte[25].

Developments in the small scale preparation of fluorine were quickly applied to its large scale commercial production[26] which can be accomplised under three different sets of conditions.

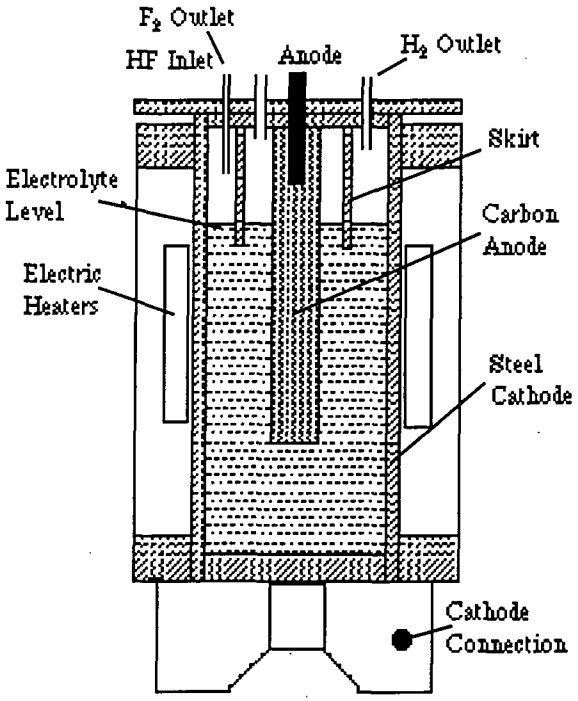
i) Low Temperatures (*ca.*-33°C), using HF containing less than 20% of potassium fluoride by weight.

ii) Medium Temperatures (*ca.* 100°C), using molten KF.2HF (m.p. 71.7°C).

iii) High Temperatures (*ca.* 250°C), using molten KF.HF (m.p. 239°C).

During electrolysis, contamination of the product is difficult to avoid due to the volatility of the hydrogen fluoride. The use of fused potassium fluorides, even at higher operating temperatures, reduces this problem because the vapour pressure of HF is significantly reduced. Corrosion problems are reduced by the use of such metals as nickel, copper, or Monel®, all of which are soon covered with a protective fluoride coating. The literature contains some detailed descriptions of some commercial cells[26], which can be schematically represented described thus:

Figure 1:Schematic Representation of a Fluorine Cell.



I.4.b. Chemical Synthesis

A purely chemical, as opposed to elctrochemical, synthesis of F_2 is extremely difficult because decomposition of fluorine compounds to liberate F_2 is thermodynamically very unfavourable. The first chemical synthesis of fluorine **[E-3]** was detailed by Steel *et al* in 1959[27].

$$IF_7{\cdot}AsF_5 + 2KF \xrightarrow{>200^{\circ}C} KIF_6 + KAsF_6 + F_2$$

[E-3]

The first practiable chemical synthesis of F_2 **[E-4]** was recently been demonstrated by Edwards[28].

$$K_2MnF_6 + SbF_5 \longrightarrow 2KSbF_6 + MnF_3 + 0.5F_2$$

[E-4]

The underlying principle is that the stronger Lewis Acid (SbF_5) can displace the weaker Lewis Acid (MnF_4) from its salt which then, being an unstable compound, decomposes once liberated.

I.5. Energetics of Fluorination

I.5.a. Bond Strength

For a long time the enthalpy of dissociation of elemental fluorine was believed to be in the range of 250-290 KJ / mol. These values were determined by a number of experimentalists between 1920 and 1950 and were purely based on extrapolation of the values for iodine, bromine and chlorine. There was considerable surprise when around 1950 the value was found to be around 159 KJ / mol. Mulliken[29] observed that single N-N bonds in hydrazines, O-O bonds in peroxides and the F-F bond were all weaker and longer (relative to the appropriate atomic radii) than the corresponding single P-P, S-S and Cl-Cl linkages. He rationlised this by postualting the partial *pd* hybridisation imparts pronounced multiple bond character to the P-P, S-S and Cl-Cl single bonds, which is not possible in the single bonds of F-F, N-N and O-O. Caldow and Coulson rationlised the low dissociation energy of F-F bond purely on the relatively large electron-electron repulsions between the constituent atoms[30].

I.5.b. Initiation Processes

Direct reactions between most organic molecules and elemental fluorine are extremely exothermic because of the high heats of formation of C-F and H-F (see Table 2). The extremely exothermic nature of the reaction coupled with very low dissociation energy of elemental fluorine means that the most likely process for fluorination is a radical chain reaction (**Scheme 1**).

$$F_2 \longrightarrow 2F\bullet$$

$$RH + F\bullet \longrightarrow R\bullet + HF$$

$$R\bullet + F_2 \longrightarrow RF + F\bullet$$

Scheme 1

Radical chain processes are normally initiated by the dissociation of a molecule with a weak bond, which is normally brought about thermally or photochemically. However, quite high temperatures are required before fluorine is appeciably dissociated ($K \approx 10^{-20}$ atm. at room temperature[31]) which has led to debate over the initiation process for free radical fluorination. It is generally accepted that the low activation energy of the hydrogen abstraction reaction would mean that even this very low level of dissociation could be sufficient to start the chain process but Miller suggested an alternative initiation mechanism in which fluorine reacts with a hydrocarbon molecule to yield a radical (**Scheme 2**)[32-34].

$$RH + X_2 \longrightarrow R\bullet + HX + X\bullet$$

X=F	$\Delta H \approx 17$ kj mol^{-1}
X=Cl	$\Delta H \approx 226$ kj mol^{-1}
X=Br	$\Delta H \approx 283$ kj mol^{-1}

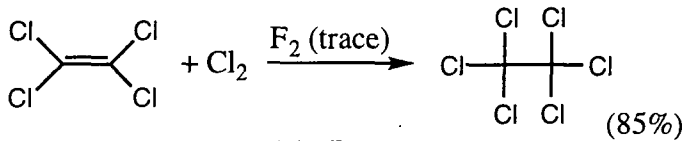
Scheme 2

Experimental evidence for the above initiation process is extremely difficult to obtain, but for reactions with alkenes the thermodynamics make Miller's process far more likely **[E-5]**[31].

$\Delta H \approx -4.8$kj mol^{-1}

[E-5]

The reaction of tetrachloroethene with chlorine was cited as supporting experimental evidence. It was shown that a mixture of tetrachloroethene and chlorine did not react until a trace of fluorine was introduced whereupon chlorination of the tetrachloroethene took place**[E-6]**[33].



[E-6]

Later, when the insolubility of fluorine gas in many organic solvents, including those used by Miller[31] became apparent, the validity of Miller's experimental results were questioned . It was likely that the reaction was occuring at the gas / liquid interface or even in the gas phase of bubbles where the temperature is unknown and uncontrolled making the degree of dissociation difficult to predict ($K \approx 3.8 \times 10^{-5}$ at 277°C and $K \approx 2.1 \times 10^{-3}$ at 520°C[35]).

I.5.c. Directive Effects

Initially it was expected that fluorination reactions should be completely unselective[17]. Generally it is true that with unsubstituted hydrocarbons, fluorinations show considerably less selectivity than other processes. The first evidence that fluorination could be selective was provided by Bockemüller, who selectively fluorinated n-butyric and iso-butyric acids[22]. It was later demonstrated that his results are similar to those obtained for chlorination. Later the first attempt to make a quantitative study of the monofluorination of aliphatic compounds was made by Anson *et al*[36], using a technique developed earlier by Tedder[37]. The relative rates of substitution by fluorine of the primary, secondary and tertiary hydrogens in *n*-butane and *iso*-butane were compared with chlorination (see Table 3).

Table 3: The Relative Rates of Substitution of Hydrocarbons by Fluorine.

	—CH_3	$\diagdown CH_2 \diagup$	—CH
F•	1	1.3	2.5
Cl•	1	4.6	10.3

The results showed that fluorination was, as expected, considerably less selective than chlorination. Variation in temperature demonstrated that the selectivity of chlorination decreased with an increase in temperature, the fluorinations appeared unaffected. Again the problem of the low solubility of fluorine was encountered, but subsequently strong evidence for the high temperatures in the gas phase of the bubbles was obtained[38]. Further studies were continued, but in the gas phase in which temperature was well controlled[39]. The following results were obtained(see Table 4):

Table 4: The Selectivity of Different Radicals X• for Primary, Secondary and Tertiary Hydrogen Atoms in the Alkanes[40].

$$X\bullet + RH \longrightarrow R\bullet + HX$$

	Relative Selectivies at 300°K			*Differences in Activation Energy KJ / mol*		
	$-CH_3$	$>CH_2$	$-\overset{\vert}{C}H-$	E_p-E_s	E_p-E_t	E_p
X=F	1	1.2	1.4	0.4		1.2
X=Cl	1	3.9	5.1	2.0	2.3	4.2
$X=CD_3$	1	35		8.8	-	46.2
$X=CH_3$	1			9.7	12.2	47.9
X=Br	1	82	1600			58.8

Tedder *et al* found the lack of selectivity difficult to reconcile with Bockemüller's results with butyric acids. Later, following the work of Henne who demonstrated the importance of electron-withdrawing groups in the chlorination of 1,1,1-trifluorobutane and 1,1,1-trifluoropropane[41,42], it was found that fluorination is relatively more affected by substitution, or polar effects, than chlorination or bromination .

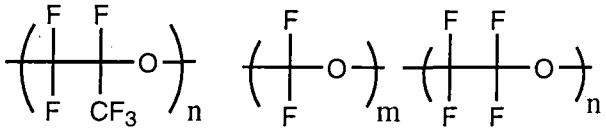
I.6. Fluorine as a Reagent in Organic Chemistry

I.6.a. Fluorination of Carbon

In 1937 Simons *et al* claimed to have isolated C_3F_8, C_4F_{10}, C_5F_{12}, C_6F_{14} from the direct reaction of carbon and fluorine[23,24]. Earlier workers had investigated the reaction[43-45] but had found that frequent and violent explosions resulted. Simons *et al* overcame the technical difficulties by fluorinating the carbon in a packed copper gauze reactor[20,46] in the presence of a mercury catalyst at high temperatures to produce perfluorinated products. Using four electrochemical cells[47] to provide a large quantity of fluorine, a significant amount of perfluorinated material was produced allowing the molecular weight of the material to be determined. The isolation also allowed Simons to investigate the chemical properties. He concluded " The fluorocarbons approach the inert gases in properties more closely than any other compounds."

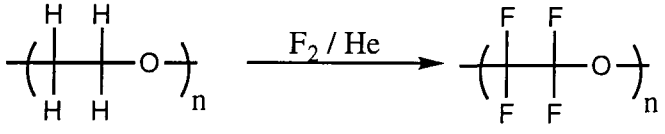
I.6.b. Perfluorination

Perfluorinated liquids were initially developed in the 1940's for the Manhattan Project; their extreme stability and chemically resistant nature makes them ideal for handling elemental fluorine and UF_6. Recently it was demonstrated that perfluoropolyethers are extremely high performance lubricants[48,49] which are now used as the lubricants of choice for almost all civilian and military space activities[11]. Initially only two forms of perfluoropolyethers were known, one prepared from a polymerisation of hexafluoropropene oxide (**1**), Krytox[50], and the other prepared from the photochemical polymerisation of oxygen and tetrafluoroethene, Fomlin Z (**2**)[51].



(1) **(2)**

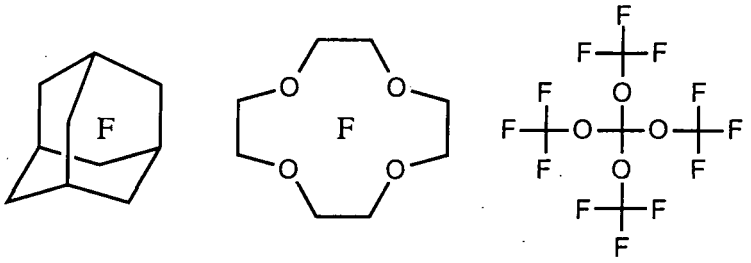
Recently the work of Lagow has allowed the direct synthesis of perfluorinated compounds via the direct fluorination of the hydrocarbon systems using elemental fluorine which has revolutionised this area of research. His first published example was the conversion of a polyethene oxide into a perfluoropolythene oxide[**E-7**][48,49]. Perfluoropolythene-oxide is not available through existing polymerisation technology due to the very high heat of polymerisation leading to problems of explosion.



[E-7]

Lagow is able to control the fluorination process by variation in temperature and dilution which, when used in conjunction with a variety of solvents, prevents the potential problem of the polymers cross-linking. He exploited the high solubility of fluorine in fluorocarbons, in the same manner as oxygen (upto 30% by volume[52]), to overcome the other major problem, the removing the last few hydrogen atoms. Thus with proper activation, usually heat, the last protons are easily removed from a liquid that acts as an extremely good solvent for fluorine. In the case of a solid fluorocarbon it was found that simply pressurising with fluorine would remove the residual hydrogens producing fluorocarbons where the hydrogen content is as low as three parts per billion[11].

In 14 years the Lagow process for perfluorination has been extended to produce many new classes of organic compounds including perfluoroadamantanes (**3**)[53,54], perfluorocrown ethers (**4**)[55,56] and perfluoro orthocarbonates (**5**)[57].



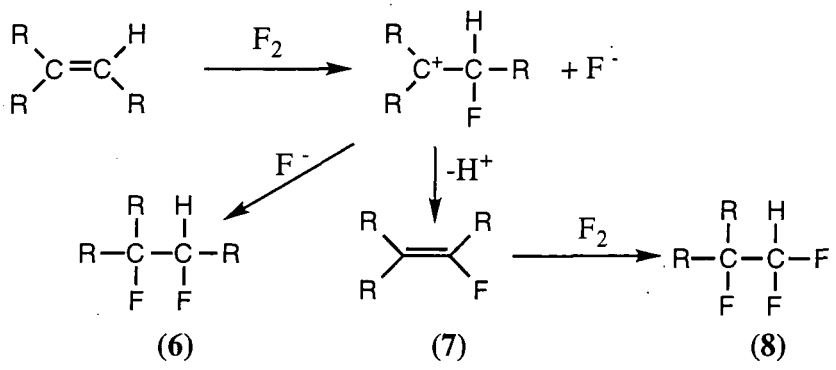
(3) (4) (5)

I.6.c. Fluorine as an Electrophile

I.6.c.i. Fluorination of Alkenes

Merritt recognized the electrophilic nature of F_2 during his investigation of the addition of elemental fluorine to alkenes[58,59]. Fluorination of cis-stilbene with an equivalent of undiluted F_2 at low pressure and temperature in fluorocarbon solvents in the presence of molecular sieve resulted in products which showed the syn mode of addition predominated. Merritt ruled out a free radical pathway due to the observed selectivity and the reaction conditions, in favour of a concerted pathway.

However, a mechanism (**Scheme 3**) such as the one proposed by Barton and Hesse[60] for the reaction of CF_3OF with alkenes is more reasonable. The postulated α-fluorocarbocation gives rise to the vinyl fluoride (**7**) by loss of a proton or adds fluoride to give the difluoride (**6**). The vinyl fluoride (**7**) can then be converted to the trifluoride (**8**) which is one of the observed products.

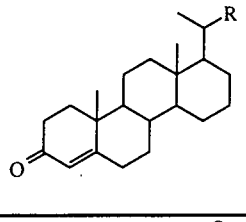
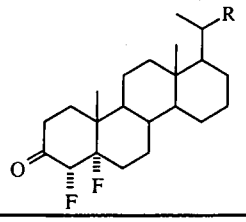
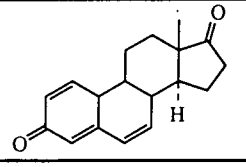
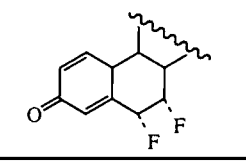
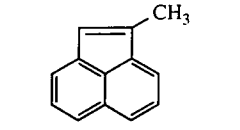
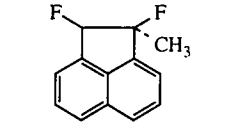


(6) (7) (8)

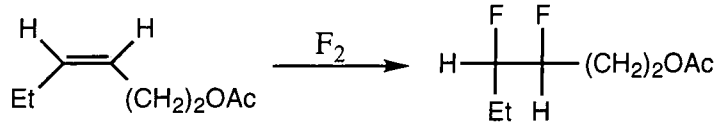
Scheme 3

Direct addition of fluorine to a variety olefins were also investigated by Merritt *et al* under the same conditions of temperature and solvent (see Table 5).

Table 5: The Fluorination of a Variety of Alkenes.

Substrate	Product	Yield(%)	Ref.
		60-70	61
		10	62
		20	58

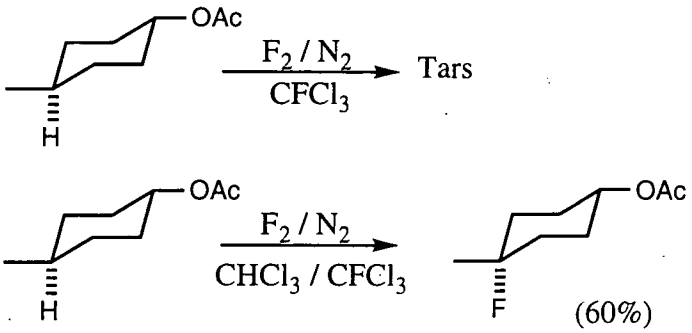
Later, the electrophilic addition of fluorine to alkenes was investigated by Rozen *et al* who encouraged the electrophilic process using a polar solvent, low temperature and low fluorine concentration[63]. Using an alcohol to produce more polarisation in the fluorine molecule he successfully fluorinated a range of alkenes **[E-8]**.



[E-8]

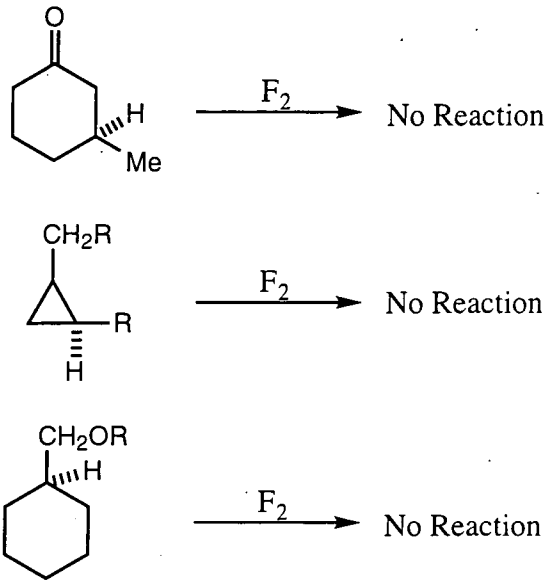
I.6.c.ii. Selective Fluorination of Tertiary C-H Bonds

Electrophilic substitutions on a saturated carbon site are very rare, but of theoretical interest. Much of the work in this area has been covered in a review by Olah[64]. Most reactions are impractical and are characterised by low yields, since the electrophiles used do not provide an adequate driving force. It was postulated by Rozen *et al* that fluorine, if behaving as an electrophile, should be one of the strongest, even capable of reacting with a saturated CH site. Simple low temperature fluorination in a mixture of $CFCl_3$:$CHCl_3$ produced a high yielding electrophilic reaction **[E-9]**[65]. The high yield was accompanied by full retention of configuration, which Rozen claimed ruled out any radical mechanism, since a tertiary radical if formed, should have resulted in a mixture of isomers.



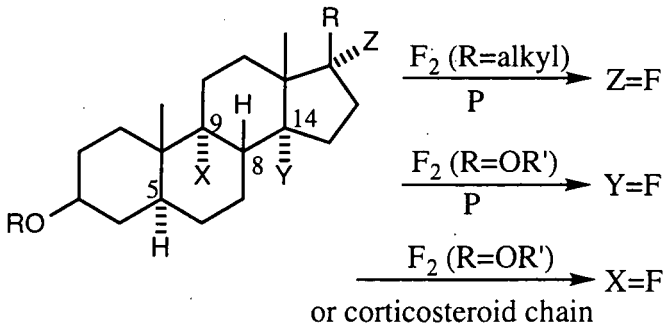
[E-9]

A mechanism was suggested based on the earlier work of Olah[64], involving a non-classical three centre two electron carbocation. Since the electrophile will attack the electrons of the C-H bond, the attack should be from the same face, thus resulting in a retention of configuration as observed in Rozen's process. If the tertiary hydrogen is too close to an electron-withdrawing group or has a low *p* orbital contribution, as in the cyclopropane ring[66], no electrophilic reactions are observed **[E-10]**.



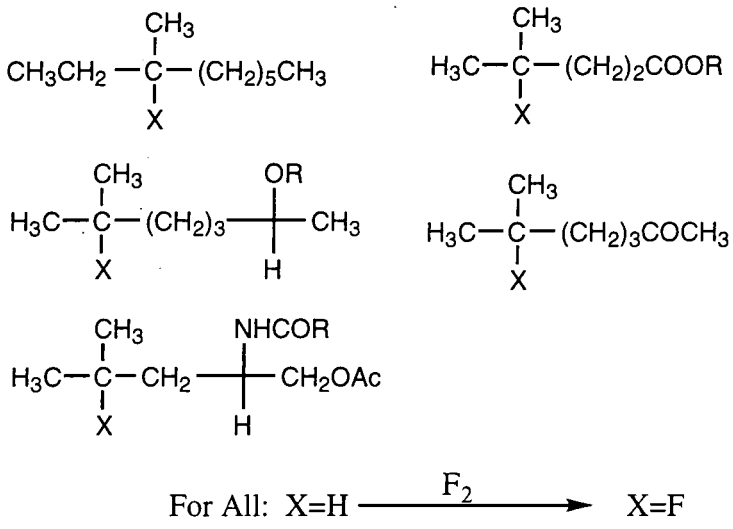
[E-10]

Rozen *et al* demonstrated that by using electron withdrawing substitutents in various places, fluorination of any tertiary hydrogens in a steroid skeleton was possible (**Scheme 4**). This method, coupled with a dehydrogenation process, can produce double bonds thus serving as an entry point into biologically important steroids[67].



Scheme 4

Rozen *et al* demonstrated that provided the functional group is removed from the tertiary site, electrophilic substitution can be carried out in a variety of substrates **(Scheme 5)**[68].

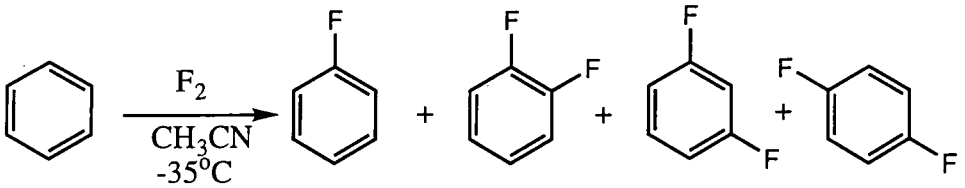


Scheme 5

I.6.c.iii. Fluorination of Aromatic Compounds

I.6.c.iii.1) Benzene

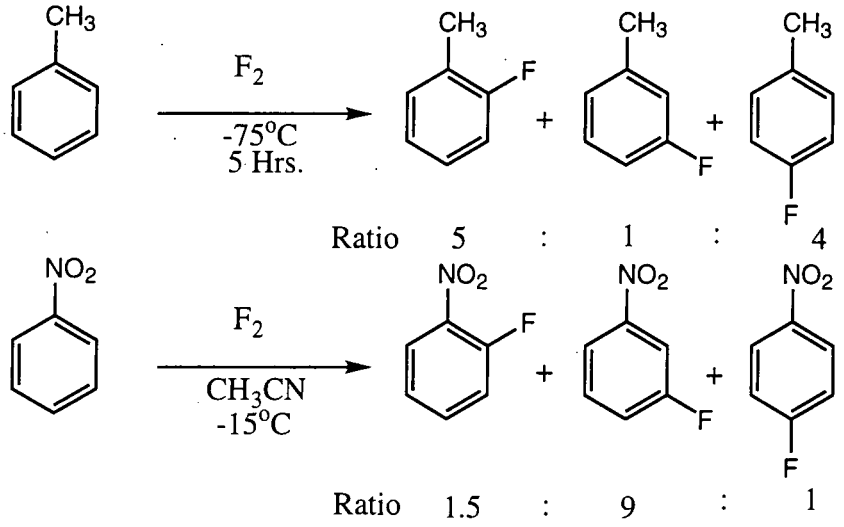
Grakauskas fluorinated of a 6% solution of benzene in acetonitrile at -35°c at a 0.7:1 molar ratio of fluorine to produce the following results **[E-11]**[69].



Ratio 60 : 4 : 1 : 5

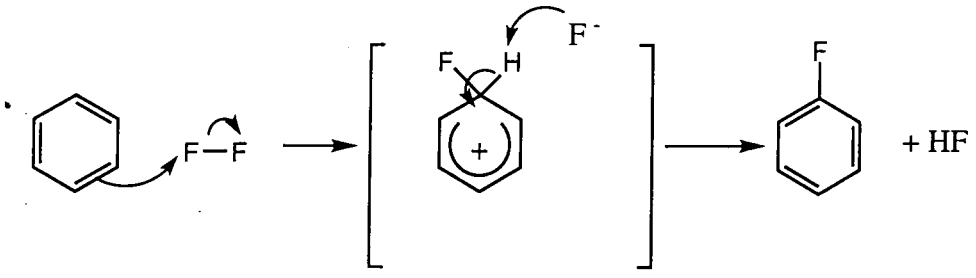
[E-11]

From the ratio of the *ortho- / para-* products to the *meta-* product he concluded fluorination proceeds via electrophilic substitution analogous to the ionic halogenations of other aromatic compounds. The fluorination of toluene and nitrobenzene **[E-12]**, performed under near identical conditions, further supported this mechanism.



[E-12]

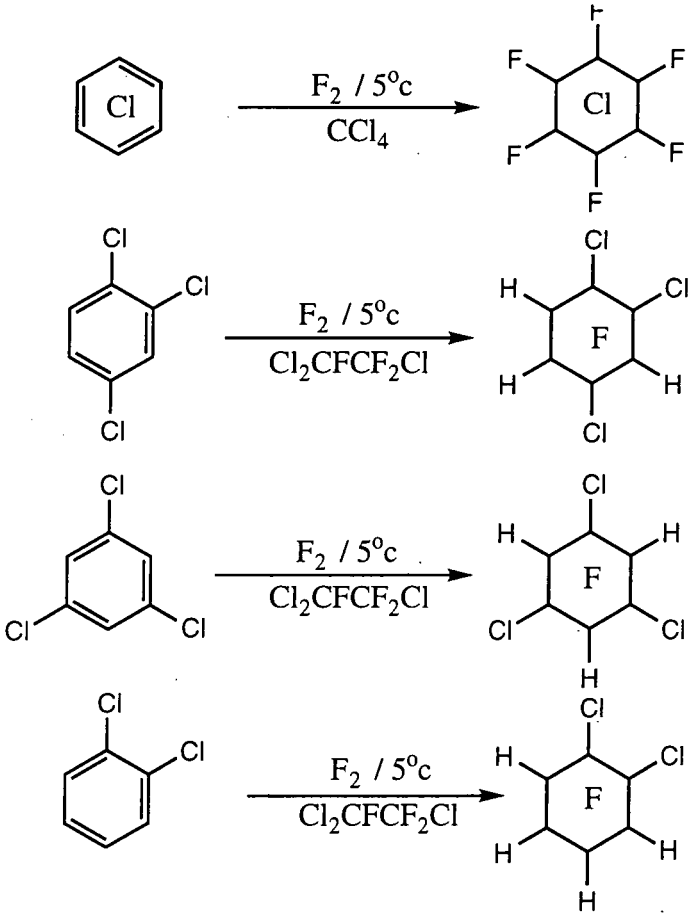
Toluene underwent electrophilic substitution predominantly in the ortho / para position and nitrobenzene in the meta position as shown by the above experimental data. Grakauskas proposed mechanism can be summarised as follows (**Scheme 6**).



Scheme 6

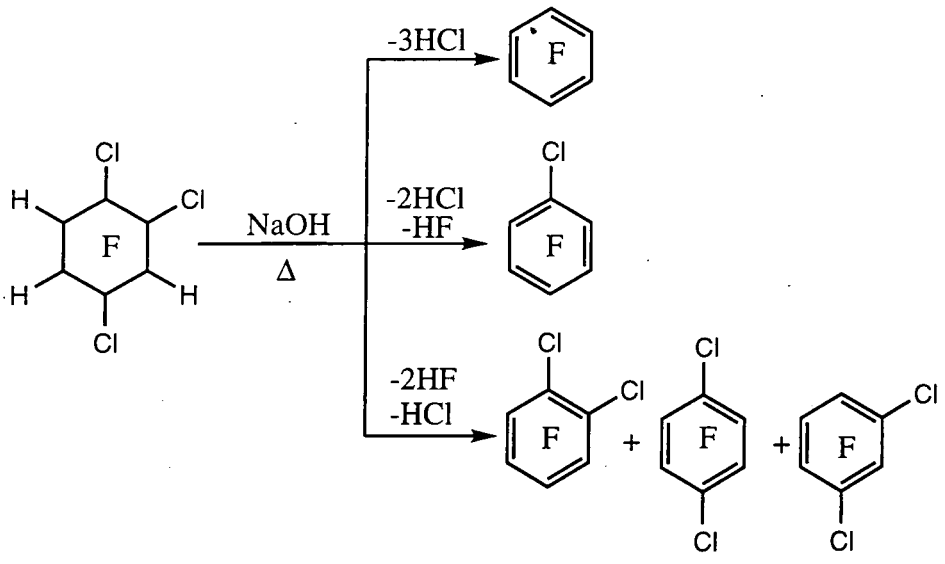
I.6.c.iii.2) Haloaromatics

Grakauskas repeated the earlier work of Chambers *et al* except using fluorine as a fluorinating agent instead of chlorine trifluoride[70]. He described the fluorination of a range of chloroaromatics, even at high flowrates, as smooth reactions **[E-13]**[71].



[E-13]

Following the isolation of the fluorinated products, dehydrohalogenation with strong base produced a range of aromatic products **[E-14].**



[E-14]

I.6.c.iii.3) Fluorobenzene on Molecular Sieve

Following work by Baker and Eng concerning the use of molecular sieve beds in chlorination of hydrocarbons[72], Sams *et al* made use of molecular sieves for the fluorination of organic molecules (see Table 6)[73]. The molecular sieves enabled the localisation of the substrate, preventing the combination of substrate radicals, thus leading to a large reduction in the amount of polymeric material formed during the reactions. The molecular sieve maintained at low temperature also acted as an effective heat dissipator (see Figure 2.).

Figure 2: Apparatus Used for Fluorinating Substrates on a Molecular Sieve Bed.

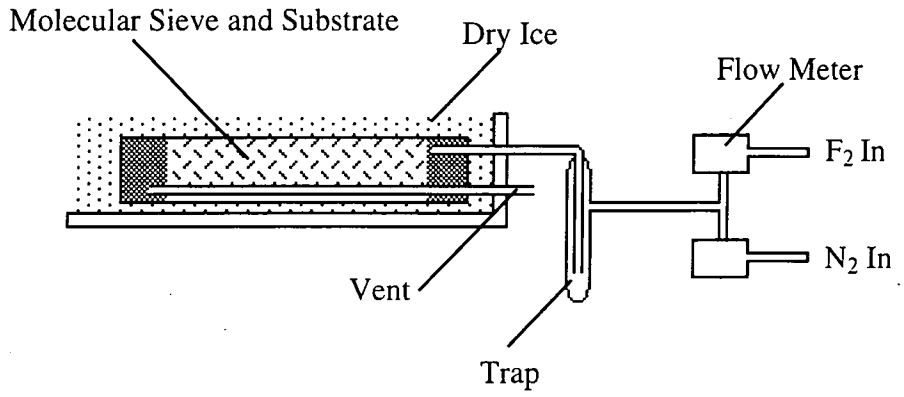
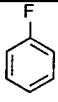
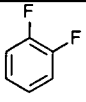
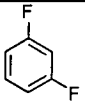
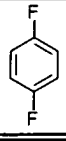


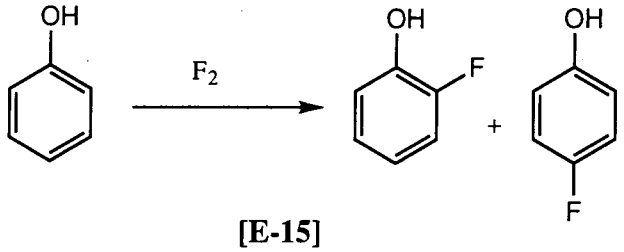
Table 6: Fluorination of Fluorobenzene on Molecular Sieve.

	Difluorobenzene, % Yield			
F_2/ 				Total
0.5	1.09	0.66	2.62	4.4
0.75	1.33	0.807	3.73	5.9
1.00	1.63	1.16	3.76	6.5
2.00	3.89	0.196	5.38	9.5
3.00	8.12	0	11.61	19.7
4.00	3.05	0	6.10	9.1

A major problem with this technique proved to be hydrofluoric acid. This, when produced by the fluorination reaction, then proceeded to react with the silicates present in the molecular sieves reducing the possible sites for reaction and could only be overcome by replacing the sieve for each reaction. No further investigation has been made into this area.

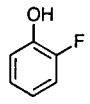
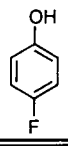
I.6.c.iii.4) Aryl Oxygen Compounds

Misaki studied the fluorination of phenol under a variety of solvents and temperatures **[E-15]**[74]. When a 10% solution of phenol in acetonitrile, tetraglyme, methanol and chloroform were fluorinated at -20°C over a period of 90 minutes a range of conversions were obtained with yields as high as 85% being recorded (see Table 7).



[E-15]

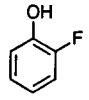
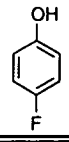
Table 7 : The Fluorination of Phenol in a Variety of Solvents.

Temp.	Solvent	Conversion	% Yield 		Isomer Ratio
-20°C	CH_3CN	56.0%	38.9	10.7	3.64
-20°C	TG*	53.9%	54.7	21.9	2.50
20°C	CH_3OH	53.5%	47.7	13.3	3.59
5°C	H_2O	52.9%	7.0	2.6	2.69
5°C	CF_3COOH	52.0%	56.1	17.0	3.30
-20°C	$CHCl_3$	51.4%	54.5	30.2	1.80

A relatively large amount of phenol was converted to products other than the *o*- and *p*-fluorophenols when water was used as a solvent. It was demonstrated that increasing the polarity of the reaction mixture, by addition of a Lewis Acid such as BF_3 , increased the conversion during the fluorination of phenol to 64% but no greater yield of monofluorophenols was found (see Table 8).

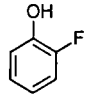
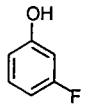
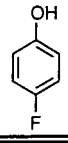
* TG - Tetraglyme [$CH_3(OCH_2CH_2)_4OCH_3$].

Table 8: Fluorination of Phenol in the Presence of Lewis Acids.

Reaction Conditions				% Yield		Isomer
Temp.	Solv.	Catalyst	Conv.			Ratio
-20	CH_3CN	-	56.1%	38.9	10.7	3.64
-20	CH_3CN	BF_3	64.2%	34.4	12.3	2.80
-20	CH_3CN	$FeCl_3$	50.7%	42.0	13.6	3.09

Further investigation into the fluorination of phenol was made using HF as a solvent and comparing it to CH_3CN (see Table 9). Previous work using HF as a solvent for fluorinations had shown it to be extremely useful and resistant to the effects of fluorine.

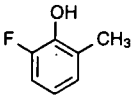
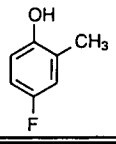
Table 9: Fluorination of Phenol in HF.

Temp.	Solvent	Conversion	Yield% 			Ortho / Para
-10°C	CH_3CN	90.8 %	44.4	23.0	10.1	1.93
-10°C	HF	94.8 %	14.6	15.1	5.4	0.97
-10°C	65 % HF	100 %	25.8	25.0	19.5	1.03

Anhydrous HF proved to be a poor solvent for the production of monofluorophenols from phenol itself. The conversion of 94.8% was accompanied by a yield of 35% compared to the yield of 77% from the acetonitrile fluorination. The yield in 65% HF proved to be substantially better.

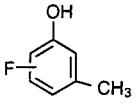
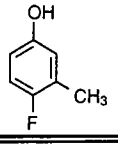
The fluorination of *o*-cresol gave approximately a range *o:p* ratio in the region of 1:1 as expected (see Table 10).

Table 10: Fluorination of *o*-Cresol in a Variety of Solvents.

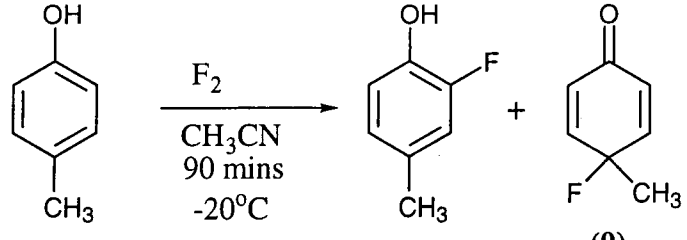
Temp.	Solvent	Conv.	% Yield 		Ratio
0°C	CH_3CH	65.0%	23.1	26.5	0.87
-20°C	CH3CN	70.8%	22.5	27.5	0.82
0°C	TG*	58.0%	28.4	39.7	0.72
-20°C	TG*	65.0%	29.2	43.1	0.68
-20°C	$CHCl_3$	74.7%	25.3	26.2	0.97

The fluorination of *m*-cresol produced a mixture of *o*-substituted products that could not be separated, the major products being the 2-fluoro derivatives (see Table 11).

Table 11: Fluorination of *m*-Cresol in a Variety of Solvents.

Temp.	Solv.	Conv.	% Yield 		Ratio
0°C	CH_3CH	68.0%	46.2	18.4	2.51
-20°C	CH3CN	67.7%	46.4	20.7	2.24
0°C	TG*	61.7%	43.6	23.7	1.84
-20°C	TG*	65.7%	40.9	14.6	2.80
-20°C	$CHCl_3$	68.0%	32.7	14.6	2.24

Fluorination of *p*-cresol **[E-16]** gave the expected *o*-derivative but also produced a non aromatic compound **(9)**[75].



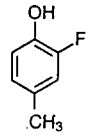
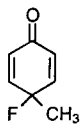
(9)

[E-16]

* TG- Tetraglyme.

For the fluorination of *p*-cresol, the choice of solvent had a marked influence on the relative amounts of the two observed products, the product due to substitution and the product of addition. Conversions were high with all solvents, but the ratio of substitution to addition products changed from 6.27:1 with CF_3COOH to 1.07:1 in tetraglyme (see Table 12).

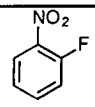
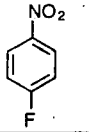
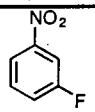
Table 12: Fluorination of *p*-Cresol in a Variety of Solvents.

Temp.	Solv.	Conv.	% Yield 		Ratio
-20°C	CH_3OH	70.0%	35.0	23.9	1.46
-20°C	$CHCl_3$	70.9%	37.4	8.5	4.40
5°C	CF_3COOH	68.3%	41.4	6.6	6.27
-20°C	CH_3CN	78.0%	38.4	23.1	1.67
-20°C	TG*	69.5%	45.3	42.1	1.07

I.6.c.iii.5) Mechanism

In 1970 Knunyants *et al* fluorinated nitrobenzene, α,α,α-trifluorotoluene, benzene and toluene in a variety of solvents at 5°C using elemental fluorine diluted with nitrogen[76]. They observed the formation of all possible isomers in ratios that were consistent with an electrophilic mechanism (see Table 13).

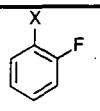
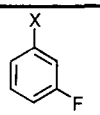
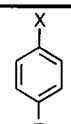
Table 13: The Fluorination of Nitrobenzene in a Variety of Solvents.

	HF	CH_3COOH	CF_3COOH	CH_3COOH + BF_3	CF_2ClCCl_2F
Conversion	55.5%	28.8%	52.8%	71.2%	51.2%
	3.9%	3.8%	9.9%	5.1%	1.5%
	2.0%	2.2%	9.4%	9.1%	1.2%
	9.6%	13.6%	36.6%	28.1%	5.2%
Yield	15.5%	19.6%	55.9%	42.3%	7.9%
Unknowns	0.02%	-	0.08%	0.13%	2%(tar)

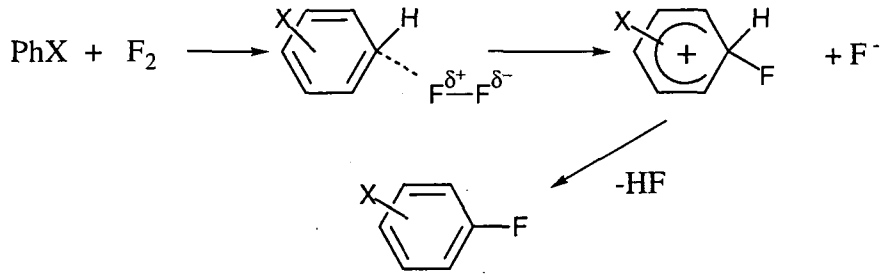
Following the work of Charles[77] and Dannley[78,79] who observed isomer ratios indicative of electrophilic substitutions during the action of electrophilic radicals such as benzoyl peroxides on alkylbenzenes, benzotrihalides and a number of substituted benzenes Knunyants *et al* further investigated the mechanism of fluorination. They compared the fluorination of nitrobenzene with a uv initiated radical chlorination of nitrobenzene. The reaction produced isomer ratios that were of the same order for both processes (*ortho, meta, para* fluorination [0.4 : 4.3: 1] chlorination [0.2: 3 : 1]) leading Knunyants *et al* to postulate that fluorination takes place by a radical mechanism when the ease of dissociation of fluorine fluorine bond is considered (≈140 KJ / mol[80]).

In 1978 Cacace *et al* published data on substrate selectivity and orientation for direct fluorination[81]. In a later investigation into the mechanism of the liquid phase fluorination Cacace *et al* used a much broader range of substrates[82]. Because of the poor solubility of fluorine in most organic solvents, which often results in a heterogeneous reaction[31], all reactions were performed at high dilution, at low temperatures, in the absence of light and in an inert solvent (CCl_3F, C_6F_6, C_7H_8 and CH_2F_2). At very low conversions (<0.1%) the following results were obtained for the reactivity of various substrates when fluorinated with elemental fluorine in CCl_3F at -78°C relative to benzene (see Table 14).

Table 14: The Rate of Fluorination for Variety of Aromatics Compared to Benzene

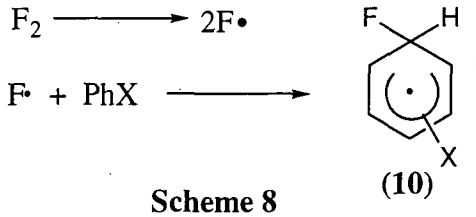
Substituent (X)	*k* C_6H_5X:*k* C_6H_6			
CH_3	4.7	60	11	29
CN	0.022	27	62	13
NO_2	0.017	9	80	11
CF_3	0.030	16	64	20
OCH_3	54	76	0.5	23.5
Br	0.12	23	17	60
Cl	0.16	40	16	46
F	0.40	22	13	65

A plot of the partial rate factors *vs* σ^+ gave a smooth linear dependence and a value for ρ^+ of -2.45 (chlorination -10.0; bromination 12.1), equivalent to -1.60 at 25°C. This characterised fluorine as one of the most reactive and least selective of all electrophiles[83] and fluorination as a polar process, proceeding via the formation of an arenium ion and fluoride ion **(Scheme 7)**.



Scheme 7

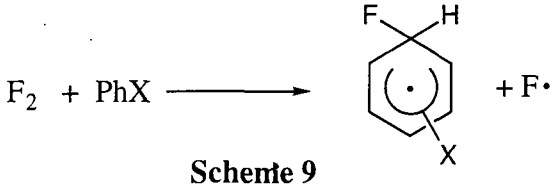
The possibility of the fluorination proceeding via a radical mechanism was also addressed by Cacace *et al.* A radical mechanism would involve the formation of a fluorocyclohexadienyl intermediate (**10**) via addition of fluorine atoms or direct attack of elemental fluorine (**Scheme 8**).



(**10**)

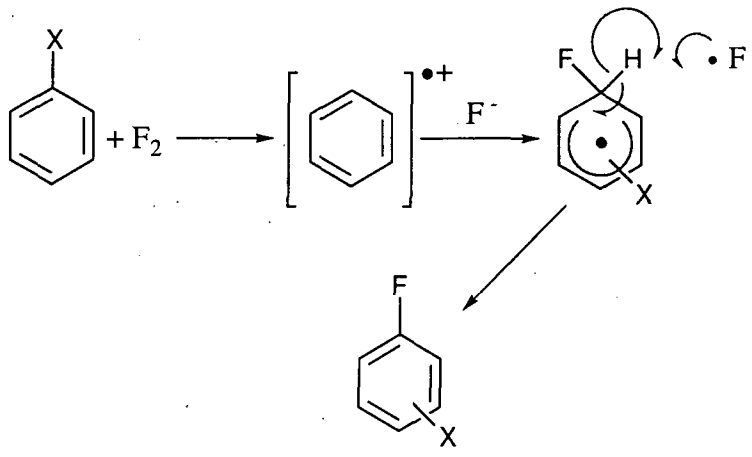
Scheme 8

The same authors argued that a process, analagous to that described by Miller[32-34] for alkyl systems, could also produce a cyclohexadienyl radical (**Scheme 9**).



Scheme 9

However, electron withdrawing groups such as NO_2 or CN would direct radical substitution ortho / para, whereas electrophilic aromatic substitution directs meta[84-86]. Earlier work on the radical substitution of nitrobenzene had confirmed only 10% of the obtained products were *meta* substituted nitrobenzenes[87], dramatically contrasting with the results obtained by Cacace *et al* , enabling them to rule out the possiblity of fluorination proceeding via a radical pathway involving a cyclohexadienyl radical. A radical mechanism (**Scheme 10**) based upon an intermediate radical cation was also discounted.

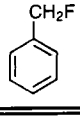


Scheme 10

It has been established that F^- fails to undergo nucleophilic attack on an aromatic cation[88, 89].

The fluorination of toluene gave benzyl fluoride in addition to fluorotoluenes, the yield of benzyl fluoride was dependant on the temperature and rate of fluorination (see Table 15).

Table 15: The Yield of Benzyl Fluoride during the Fluorination of Toluene.

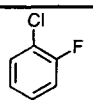
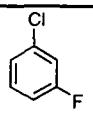
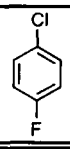
Solvent	Temperature	% Yield 
CCl_3F	-97°C	10%
CCl_3F	-78°C	20%
CCl_3F	0°C	50%

The substitution of the alkyl group during the fluorination of toluene is consistant with a radical mechanism, indicating that both electrophiles and electrophilic radicals could be particpating in the fluorination process.

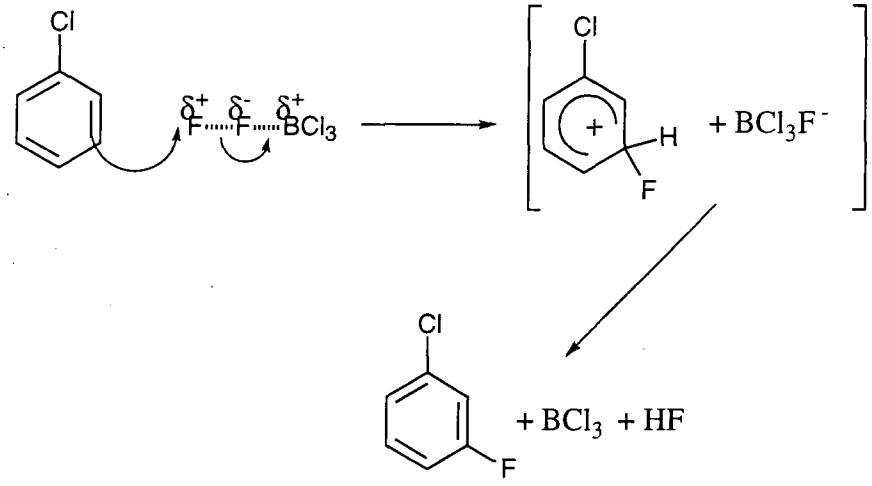
I.6.c.iii.6) Lewis Acid Mediated Fluorinations

Purrington investigated the effect of Lewis acids on fluorination reactions in nonpolar solvent[90]. All the reactions were performed at low temperature, using a 5% F_2 / N_2 mixture (see Table 16).

Table 16: Fluorination of a Variety of Aromatics in the Presence on a Lewis Acid.

Lewis Acid	L. A./ PhCl	$FCCl_3$:CH_2Cl_2	% Conv.			
- None	-	0.0	10.5	4.7	1.2	4.6
- None	-	0.0	9.5	3.7	0.9	4.9
BCl_3	0.11	1.0	27.2	7.1	2.2	18.0
BCl_3	0.56	5.0	62.2	13.0	3.1	45.9
BCl_3	0.90	8.0	95.2	15.2	6.7	73.3
$AlCl_3$	0.17	0.2	15.2	8.2	2.4	4.6
$AlCl_3$	0.56	0.5	21.2	11.2	4.0	5.9
$AlCl_3$	1.01	0.9	39.2	20.7	8.0	11.2

As the results show, the addition of the Lewis acids to an aromatic substrate in a nonpolar solvent affects not only the conversion but also the regioselectivity. Purrington suggested that the increased electrophilicity of the agent is responsible for the general decrease in the amount of meta isomer in all reactions. The following mechanism was suggested for the fluorination with BCl_3 (**Scheme 11**) concurring with the electrophilic mechanism suggested by Grakauskas[69].



Scheme 11

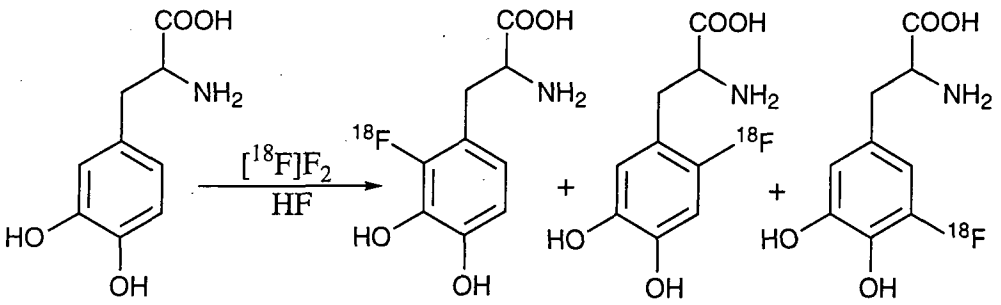
She concluded that the above reactions show that selective fluorination is possible with elemental fluorine.

I.6.c.iii.7) Radio Labelling with Elemental Fluorine

In 1973 ^{18}F labelled aromatic amino acids found interest as radiotracers for use in positron emission tomography (PET). This was due to the small structural changes caused by the fluorine atom and the favourable nuclear properties of ^{18}F ($t_{1/2}$=110 mins

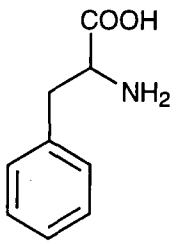
; 97% β^+; E_{max}=0.635MeV). The physiological motivation was to find a pancreas imaging agent [91,92]. As the PET technology developed other potential uses in biochemistry became clear because amino acids play an important role as precursors to proteins, neurotransmitters and hormones[93,94].

Direct radiofluorination with ^{18}F was successfully applied to the labelling of some radiopharmaceuticals with only a few electrophilic centres[95-98]. Not only was direct fluorination easy to perform but the main advantage is the possibility of using the underivatised compound in contrast to the use of functionlised analogues required for the classical Balz Schieman reaction. The most prominent example being 6-[^{18}F]fluorodopa **[E-16]** labelled with [^{18}F]F_2[99],which has been used in the study of dopamine uptake in the brain of patients suffering from Parkinson's disease[100]. The fluorination gives the desired 6-fluorodopa in a 5.8% chemical yield and a 3.0% radiochemical yield with 2- and 5-fluorodopa in 1.2% and 1.7% yield as the major by-products In the synthesis, liquid HF was used to minimize the oxidation of the *L*-dopa, which is initiated by the deprotonation of the hydroxyl group.



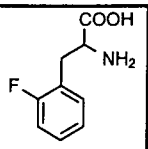
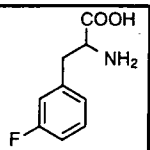
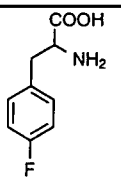
[E-16]

6-[^{18}F]Fluorodopa has also been labelled in an esterified form[101]. More recently the 2-,3- and 4-[^{18}F]fluorophenylalanines were labelled with dilute [^{18}F]F_2.Coenen *et al* conducted a systematic study on the regiospecifity of direct radiofluorination on phenylalanine **(11)** demonstrating that solvents with high acceptor values, especially trifluoroacetic acid, are particularly well suited to direct radio fluorination (see Table 17)[102].



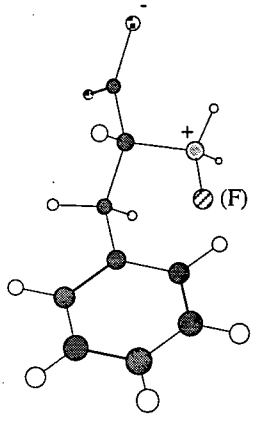
(11)

Table 17: The Radiofluorination of Phenylalanine in a Variety of Solvents.

Substrate	Solvent	Radiochemical yield(%)	*Isomers* 		
Phenylalanine	TFA	28	72.5	13.9	13.6
Phenylalanine	TFA/BF_3	30	78.9	11.6	9.5
Phenylalanine	H_2O	22	58.1	18.0	23.9

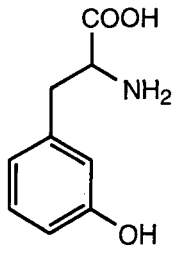
The high level of *ortho* substitution is unusual when compared to the direct fluorination of most ortho / para activating groups. Coenen *et al* suggested a chelating effect as found in electrophilic thallation[103], but upon consideration, an intra-molecular fluorination by the in-situ formation of an N-F or an O-F bond is the most likely explanation (see Fig. 3).

Fig. 3: A Potential N-F Reagent Derived form an Amino Acid.



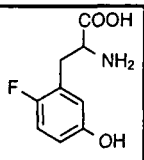
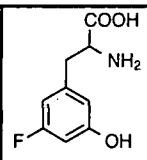
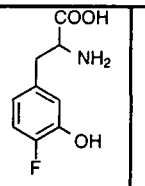
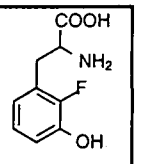
Direct fluorination of phenylalanine over a temperature range of -15°C to 25°C did not change the isomer distribution of the resulting products. Coenen *et al* also found that variation of the substrate concentration by a factor of upto 10 did not change the overall yield from the fluorination reaction, which contrasted with similar work concerning dopa[99] where increasing the molar ratio of dopa to fluorine resulted in a three fold increase in yield. This was attributed higher concentration of dopa forcing electrophilic substitution as opposed to oxidation to which dopa is more susceptible.

Following their success in synthesising [^{18}F] fluorinated catechols Chirakal *et al* investigated the synthesis of [^{18}F]fluoro-*m*-tyrosine **(12)** over a range of temperatures in a variety of solvents (see Table 17)[104].



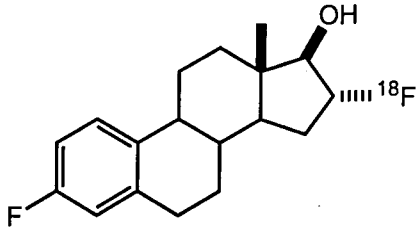
(12)

Table 17: The Radiofluorination of *m*-Tyrosine in a Variety of Solvents.

				Isomers			
Solvent	Temp	Recov(%)	Radio. Yield%				
CH_3CN / BF_3	-35°C	53	20	23	28	2	35
CF_3COOH	+4°C	55	15	35	9	5	49
HF/ CsF	-70°C	55	44	36	8	3	50
HF	-70°C	60	43	35	4	-	60
HF/ BF_3	-70°C	14	5	14	-	-	86

Again in a similar manner to the work of Coenen *et al*, the expected products from an electrophilic substitution were only observed during fluorination in CH_3CN / BF_3, in other solvents the major product was 6-fluoro-m-tyrosine. They found that as the acidity of the reaction is increased less 4-fluorotyrosine was formed.

Recent developments in PET has allowed it to be further extended to the detection of cancer in a variety of applications such as diagnosing breast tumours using a ^{18}F labelled estrogen **(13)** as the marker[105,106].



16α-[^{18}F]-17β-Fluoroestradiol

(13)

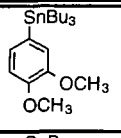
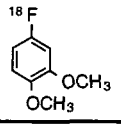
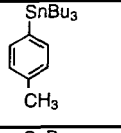
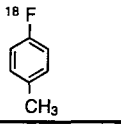
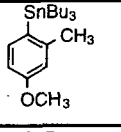
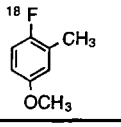
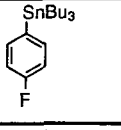
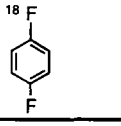
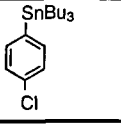
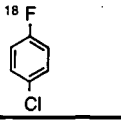
I.6.c.iii.8) Site Specific Fluorination

The group IVb organometallics (Si, Ge, Sn, Pb) have been employed successfully in halogenating aromatic compounds with chlorine and iodine[107]. These demetallation reactions have enabled the site specific substitution of a metal moiety, acting as a good leaving group, by lower halogens in high yield. Prior to 1980 the major synthetic application for this process has been the introduction of radio-labelled bromine and iodine into aromatic systems. The success of the halodemetallation reactions for the introduction of radio nuclei prompted an investigation into the feasibility of the process for the introduction of a short lived fluorine species.

In 1980 Adam *et al* [108] demonstrated that elemental fluorine ($^{18}F_2$) could be used to form fluoroaromatic compounds from Group IVb metalloarenes by fluorodemetallation. The fluorodemetallation of tributylphenyltin with elemental fluorine ($^{18}F_2$) at -78°C in $CFCl_3$ produced fluorobenzene in a 70% yield (38% radiochemical yield). Fluorodemetallation of other Group IVb metalloarenes gave disappointing yields of the desired fluorinated aromatic systems.

The high yield of fluorobenzene in the tributylphenyltin reaction initiated a large amount of research into the feasibility of fluorodemetallation of aryl-tin compounds, not only as a route to short lived radio labelled aromatic compounds[108-111], but also as a general synthetic route to fluoroaromatics (see Table 18)[112-115].

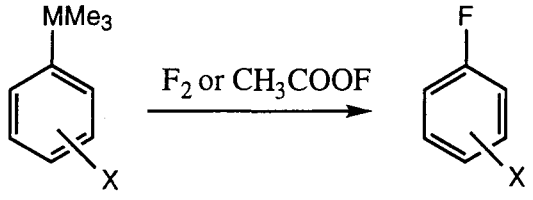
Table 18: Radiofluorination of a Range of Organotin Compounds.

Substrate	Products	Radiochemical yield %
		56
		82
		52
		>95
		>95

Chambers *et al* investigated the fluorodemetallation of a series of aryl-tin compounds with elemental fluorine, caesium fluoroxysulfate and trifluoroacetyl hypofluorite[113-115]. The highest yields in the fluorodemetallations were obtained with

cesium fluoroxysulfate. An investigation into fluorodemetallation of aryl-mercury compounds was also made with good results[114,115].

A number of aryl trimethylsilanes have been successfully substituted at the ipso position with both radioactive elemental fluorine and acetyl hypofluorite (CH_3COOF^{18})[116]. Reaction yields were low and gave various F for H substitutions. In a publication by Coenen and Moerlein[112], the reactivity of a series of aryl-trimethylmetal systems (M=Sn, Ge, Si) with elemental fluorine and acetyl hypofluorite **[E-17]** were compared[see Table 19 (Elemental Fluorine), Table 20 (Acetyl Hypofluorite)].



[E-17]

Table 19: The Fluorination of Aryltrimethylmetal Systems Using Elemental Fluorine.

	% Chemical Yield		
MMe_3-Ar-X	Sn	Ge	Si
X= OCH_3	70.4	3.5	19.8
CH_3	78.4	40.6	22.4
F	73.8	55.9	30.4
H	64.4	40.4	23.0
Br	34.2	24.8	10.2
CF_3	35.0	10.4	2.4

Table 20: The Fluorination of Aryltrimethylmetal Systems Using Acetyl Hypofluorite.

	% Chemical Yield		
MMe_3-Ar-X	Sn	Ge	Si
OCH_3	66.0	-	-
CH_3	16.4	9.1	-
H	68.2	8.5	3.5
CF_3	36.3	-	-

It was found that for a given substituent all fluorodemetallation yields decrease in the order Sn > Ge > Si corresponding to the increase of carbon-metal bond energies (Sn-C 257KJ / mol; Ge-C 308KJ / mol; Si-C 352KJ / mol) and the decrease in carbon

metal bond lengths (Sn-C 1.54Å; Ge-C 1.36Å; Si-C 1.31Å), factors which disfavour aromatic demetallation.

It was also found that the fluorination yields for a given trimethyl metal substituent are dependent on the nature of the second subsitituent on the aromatic ring. The reactivity of the trimethyl metal compounds increased as the electron withdrawing substituents (NO_2, CF_3, Br) are replaced by H and F. When electron donating substituents (CH_3, OCH_3) are present, however, no further increase in yield is observed.

I.6.d. Electrophilic Reagents Derived from Fluorine

I.6.d.i. Introduction

Mild and selective introduction of fluorine into organic compounds is of increasing interest because of the attractive effects of fluorine on the physical, chemical or biochemical processes[117]. In the past reactive, explosive or toxic reagents such as elemental fluorine, perchloryl fluoride[118] or fluorooxy compounds[119-123] have been deliberately ignored as a source of electrophilic fluorine by most workers due to their potentially hazardous nature. This has prompted enormous efforts into the development of a range of reagents which are designed to provide 'F^+' in an easily available form for the laboratory chemist.

I.6.d.ii. *N*-Fluoro-*N*-Alkylsulfonamides

In 1984 Barnette reported the synthesis of a range *N*-fluoro-*N*-alkylsulfonamides (see Table 21)[124]. The fluorosulfonamides were generally stable, crystalline compounds and in many cases easily prepared from readily available *N*-alkylsulfonamides by direct fluorination using fluorine diluted with nitrogen **[E-18]**.

$$RSO_2NHR' \xrightarrow{F_2 / N_2} RSO_2NFR'$$

[E-18]

Table 21: Preparation of *N*-Fluoro-*N*-alkylsulfonamides , RSO_2NFR'.

Compound	R	R'	Yield%
1	*p*-tolyl	methyl	59
2	*p*-tolyl	*t*-butyl	14
3	*p*-tolyl	exo-2-norbornyl	47
4	*p*-tolyl	endo-2-norbornyl	71
5	*p*-tolyl	cyclohexyl	11
6	*p*-tolyl	neopentyl	57
7	*n*-butyl	neopentyl	50

Treatment of a range of anions, which had previously been generated using base, with the sulfonamides demonstrated them as effective reagents for the incorporation of fluorine into malonates, ketones, organometallics. Functionalisation of some aromatics was also possible (see Table 22).

Table 22: Treatment of a Range of Nucleophiles with *N*-Fluorosulfonamides.

Compound	Product	Base	Solvent	Reagent*	Yield
PhMgBr	PhF	-	Et_2O	2	50%
1-Naphthol	2-F-1-naphthol	KH	THF	2	60%
Anisole	3-Fluoroanisole	n-BuLi	$PhCH_3$/THF	3	24%
$PhCH(COOEt)_2$	$PhCF(COOEt)_2$	NaH	$PhCH_3$/THF	6	53%
$CH_3(CH_2)_{13}MgBr$	$CH_3(CH_2)_{13}F$	KH	$PhCH_3/Et_2O$	3	15%
$Ph_2CHCOOH$	$Ph_2CFCOOCH_3$	n-BuLi	$PhCH_3$/THF	3	69%

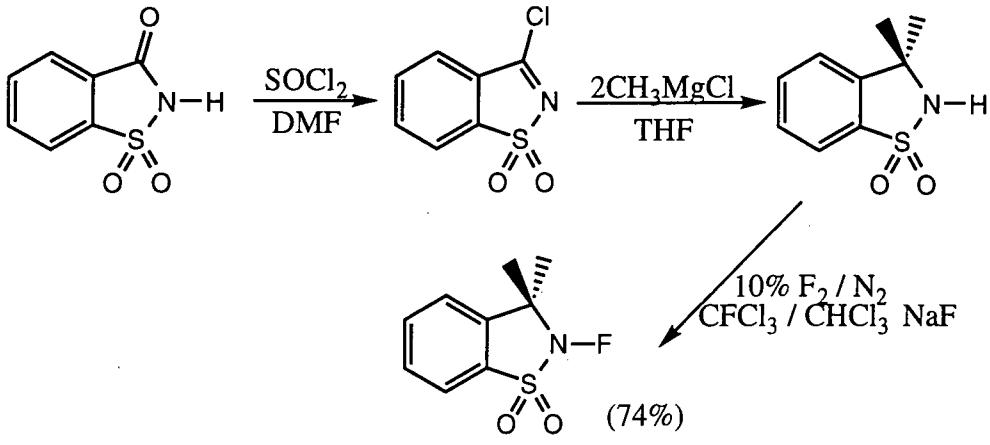
Generally the reactions were favoured in non-polar solvents like benzene, toluene or hexane. For strongly basic anions such as organometallics, β-elimination of HF from the reagents becomes a major side reaction. In these cases use of a nonpolar or solvent mixture was found to suppress elimination.

I.6.d.iii. Saccharin derived *N*-Fluorosultams

The commercial availability of a range of *N*-fluorosulfonamides quickly demonstrated that all these reagents underwent competing HF elimination as an unwanted side reaction during the fluorination process. The preparation of the active *N*-fluorosultams, derived from saccharin, produced active reagents **(Scheme 12)**

* See above table for reagent.

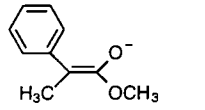
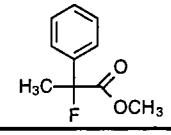
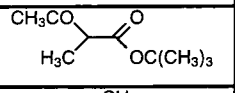
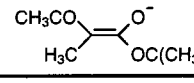
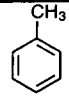
specifically designed not to undergo the competing β-elimination reaction associated with the *N*-fluoro-*N*-alkylsulfonamides[125].



Scheme 12

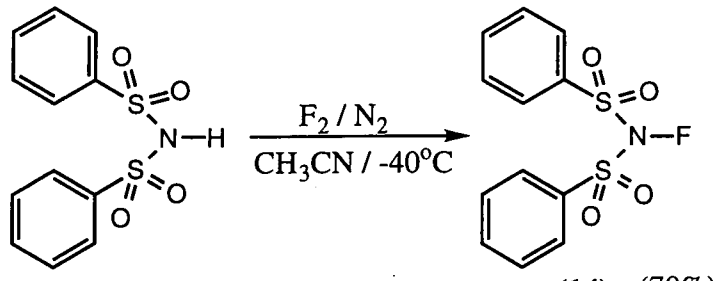
An investigation of the reactivity of these systems demonstrated that the reagents themselves were relatively activate but were not reactive enough to functionalise aromatic systems (see Table 23).

Table 23: Functionlisation of Nucleophiles with *N*-Fluorosultams.

Enolate	Product	Yield	HF Elimination Product %
		78%	-
		70%	-
	-	-	-

I.6.d.iv. *N*-Fluorobenzenesulfonimide

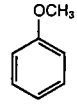
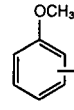
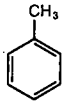
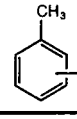
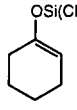
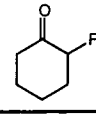
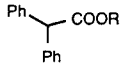
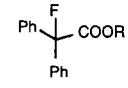
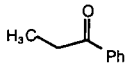
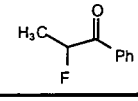
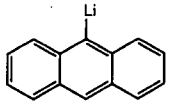
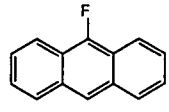
Later Differding *et al* synthesised the *N*-fluorobenzenesulfonimides. These reagents were synthesised in high yield from commercially available materials using elemental fluorine **[E-19]**[126].



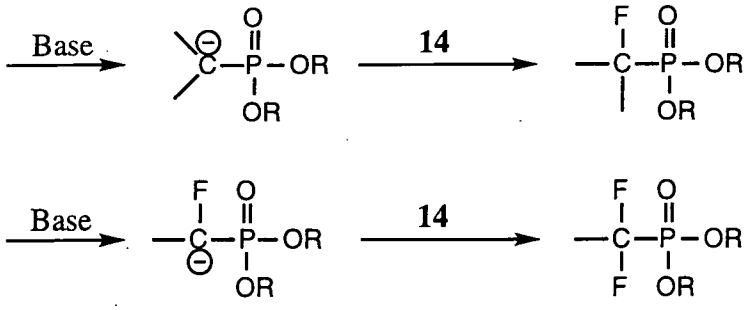
[E-19] **(14)** (70%)

The reactions of *N*-fluorobenzenesulfonimide with a range of nucleophiles were investigated (see Table 24). These reagents proved to be significantly more activated that the *N*-fluorosultams, allowing them to be used for the functionalistion of a range of aromatic compounds.

Table 24: Functionlisation of a Variety of Nucleophiles with *N*-Fluorobenzenesulfonimide.

Precursor	Conditions	Product	Yield
	22eqiv, 150°C, 5h		100% o / m / p 58:5:37
	50eqiv, reflux, 9d		19% o / m / p 65:7:28
	1equiv, RT, 24h		46%
	KHMDS, 1.2 equiv, -78°C-RT		82%
	LDA, 1.2equiv, -78°C-RT		85%
	1.2equiv, -78°C-RT		76%

N-Fluorobenzenesulfonimides were also employed in the synthesis of fluoro and difluorophosphates. Classically fluorophosphates have been prepared via Wittig reactions[127], palladium catalysed reactions of iododifluoromethylphosphonate to alkenes[128] or using DAST to substitute fluorine for hydroxyl groups[129]. Differding *et al* demonstrated that *N*-fluorobenzenesulfonimides could be used to effectively fluorinate alkyl phosphate anions, inserting up to 2 fluorine atoms (**Scheme 12**)[130].

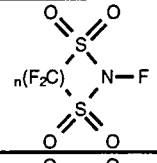
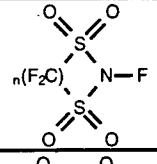
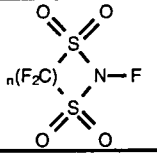


Scheme 12

I.6.d.v. *N*-Fluoroperfluoroalkylsulfonimide

In 1987 DesMarteau *et al* synthesised the first *N*-fluoroperfluoroalkylsulfonimides. They were prepared via direct fluorination of the corresponding perfluoroalkylsulfonimide (see Table 24)[131].

Table 24: The Synthesis of *N*-Fluoroperfluoroalkylsulfonimides.

Compound	Yield
$(CF_3SO_2)_2NF$	95%
$CF_3SO_2N(F)SO_2C_4F_9$	96%
$CF_3SO_2N(F)SO_2C_6F_{13}$	93%
$C_4F_9SO_2N(F)SO_2C_6F_{13}$	88%
 n=2	77%
 n=3	61%
 n=4	86%
$CF_3SO_2N(F)CH_3$	11%

The *N*-fluoroderivatives were all stable for long periods when stored in fluoropolymer plastic containers. Prolonged storage in pyrex resulted in slow etching of the glass. Investigation of the reactivity of these reagents demonstrated that they could be used for the functionalistion of a range of aromatic compounds (see Table 25).

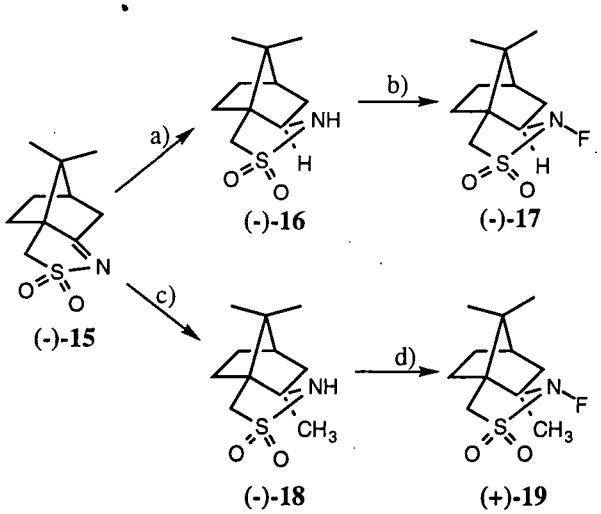
Table 25: Reaction of a Range of Aromatics with *N*-Fluoroperfluoroalkylsulfonimides.

Compound	Conditions	Products	Yield
Nitrobenzene	neat, 12hrs	No reaction	0%
Toluene	neat, 10hrs	2-fluorotoluene	74%
		3-fluorotoluene	4%
		4-fluorotoluene	22%
Anisole	neat, 2hrs	2-fluoroanisole	69%
		3-fluoroanisole	24%
		4-fluoroanisole	7%
Benzene	neat, 18hrs	monofluorobenzene	50%

Further investigation into the reactivity of these systems was also conducted by DesMarteau *et al.* They demonstrated that the perfluoroalkylsulfonylimides were effective reagents for the functionalistion of carbonyl compounds[132], olefins[133], dicarbonyls[134, 135] and steroids[136].

I.6.d.vi. Enantioselective Fluorinations

Enormous effort was made in the area of selective fluorinating agents which are effective in fluorinating metal enolates, transforming them into α-fluoro carbonyl compounds with control of regiochemistry. However, they do not provid control over sterochemistry. By synthesising two camphor derived *N*-fluorosultams **(17)** and **(19)** Differding *et al* produced the first enantioselective fluorinating reagent **(Scheme 13)**[137].



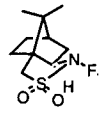
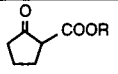
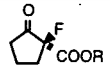
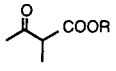
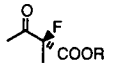
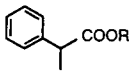
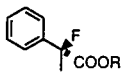
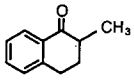
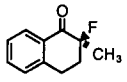
Scheme 13

a) LAH; THF b) 10% F_2 / N_2 $CHCl_3$ / $CFCl_3$

c)CH_3MgI / CuCl d) 10% F_2/N_2CHCl_3 / $CFCl_3$

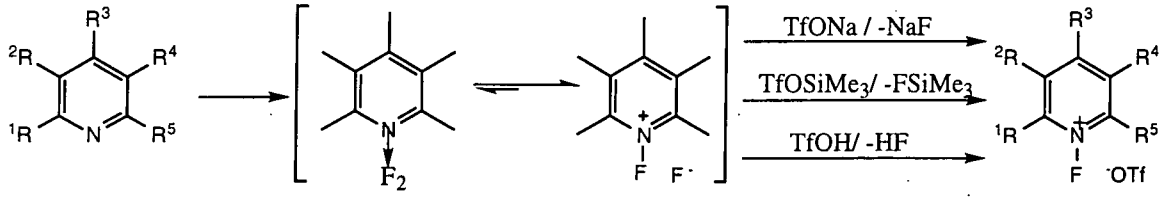
Preliminary reactions with a range of metal enolates generated under standard conditions demonstrated the enantioselective action of the fluorinating reagent (**17**) (see Table 26). The *N*-fluorosultam (**19**) designed to minimise the competing HF elimination proved to be too deactivated because of steric hindrance.

Table 26: Fluorination of a Range of Anions with Camphor Derived *N*-Fluorosultams.

Reagent	Starting Material	Product	Conditions	ee*	Yield
 (-)-14			NaH, Et_2O, 1.5equiv (-)-14	70%	63%
			LiH, Et_2O, 1.3equiv (-)-14	<10%	31%
			LDA, Et_2O, 1.2equiv (-)-14	35%	27%
			LDA, Et_2O, 1.3equiv (-)-14	35%	35%

I.6.d.vii. *N*-Fluoropyridinium Salts

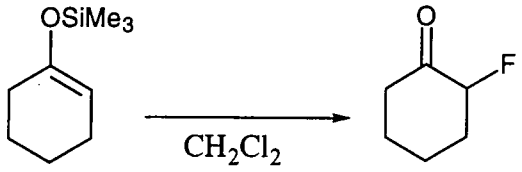
Following the work of Simons[138] and Meinert[139,140] concerning the fluorination of pyridine Umemoto *et al* succeeded in preparing *N*-fluoropyridine triflate and a large number of its analogues (**Scheme 14**)[141,142].



Scheme 14

* Enantiomeric excess (ee) determined by ^{1}H-NMR shift experiments using TAE.

Using a standard reaction **[E-20]** it was found that *N*-fluoropyridinium triflates had a higher reactivity compared to pyridinium salts with other counter-anions such such as BF_4^-, SbF_6^- and ClO_4^- (see Table 28).

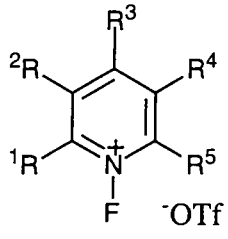


[E-20]

Table 28: Fluorination Using a Variety of *N*-Fluoropyridinium Salts.

Salt	Temp.	Time	Yield
$^-$OTf	R.t.	7h	87
BF_4^-	R.t.	72h	Trace
BF_4^-	Reflux	6h	41
SbF_6^-	Reflux	8h	23
ClO_4^-	Reflux	19h	0

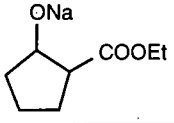
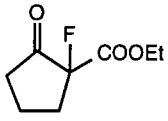
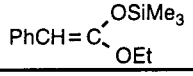
Furthermore, examination showed that the fluorinating ability could be tailored by the introduction of electron-withdrawing or electron-donating substitutents. It was clear that the fluorinating potential was directly related to the electron density of the positive nitrogen site, or of the whole π system. In general, Umemoto *et al* found that less activated triflates were better for fluorinating reactive substrates, while reactive triflates were better for less active substrates (see Table 29)[143].



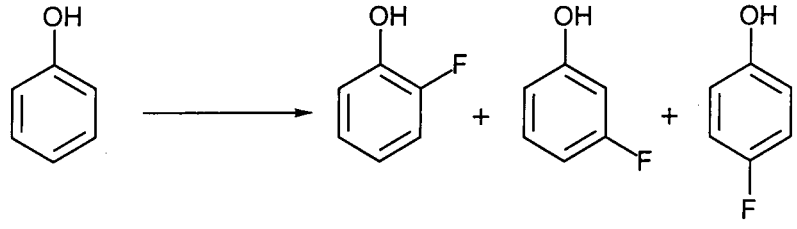
1 R^{1-5} =H
2 $R^{1,3,5}$ =Me, $R^{2,4}$ =H
3 $R^{1,3,5}$ =H, $R^{2,4}$ =Cl
4 $R^{1,5}$ =COOMe, $R^{2,3,4}$ =H

Scheme 15

Table 29: Fluorination of a Variety of Nucleophiles with a Variety of *N*-Fluoropyridinium Triflates.

Salt	Substrate	Product	Solvent	Temp	Time	Yield
4	Benzene	PhF	Benzene	Reflux	24h	56%
4	Anisole	*o*-F-Anisole *p*-F-Anisole	CH_2Cl_2	Reflux	24h	44% 48%
4	n-$C_{12}H_{25}MgCl$	n-$C_{12}H_{25}F$	Et_2O	0°C	0.5hr	75%
2	CH_3C^- $(COOEt)_2Na^+$	$CH_3CF(COOEt)_2$	THF	0°C	0.17hr	78%
2	PhMgCl	PhF	THF	0°C	0.17hr	58%
2			THF	O0C	0.17hr	78%
1		PhCHFCOOEt	CH_2Cl_2	Reflux	2hrs	65%

Fluorination of phenol **[E-21]** with a series of *N*-fluoropyridinium triflates (**Scheme 15**) over a range of reaction times demonstrated the variation in reactivity that may be achieved by substitution of the pyridine ring (see Table 25).



(20) **(21)** **(22)**

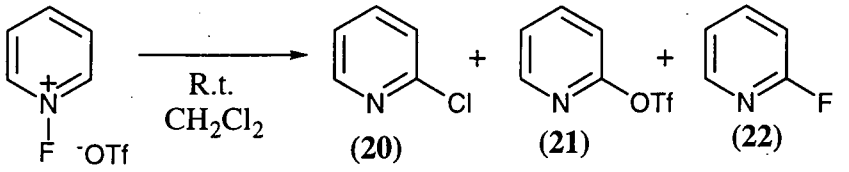
[E-21]

Table 25: Fluorination Using *N*-Fluoropyridinium Triflates in a Range of Solvents.

Salt	Solvent	Temp.	Time	Conversion	**20**	**21**	**22**
1		100	24h	75%	51%	18%	6%
2		100	24h	75%	47%	31%	3%
3	DCM	Reflux	5h	73%	60%	18%	7%
4	DCM	R.t	18h	78%	30%	24%	3%

The reaction of pyridine and 2-fluoropyridine with elemental fluorine was first noted to by Simons to result in the formation of 2-fluoropyridine and 2,6-difluoropyridine respectively[138]. During the synthesis and investigation of a range of *N*-

fluoropyridinium triflates Umemoto *et al* noted that an interesting base initiated decomposition occurred, which produced the 2-fluoropyridine**[E-22]**[144,145].



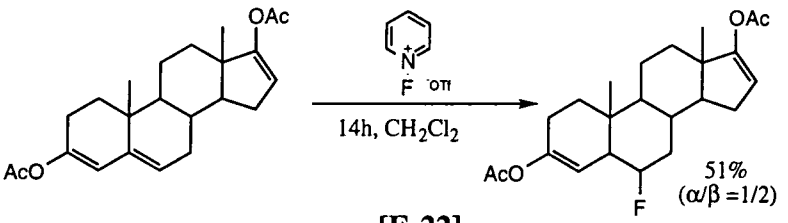
[E-22]

Table 30: The Decompositon of *N*-Fluoropyridinium Triflates in a Variety of Bases.

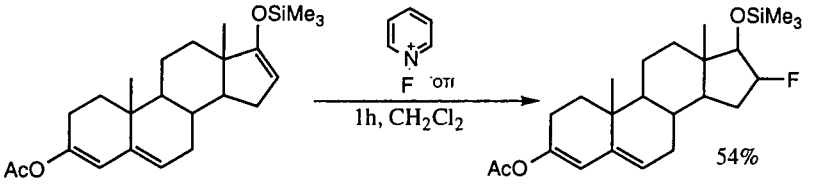
Base	Time	**20**	**21**	**22**
Et_3N	5mins	62%	21%	5%
Et_2NH	5mins	63%	22%	6%
NaOMe	10mins	25%	7%	5%
t-BuOK	10mins	35%	5%	7%

It was evident that this was an extremely effective method for the direct preparation of 2-fluoropyridines from pyridines. The well known Balz-Schiemann reaction[146] or Finger reaction[147], the alternative methods from preparation of fluoropyridines, require either 2-aminopyridines or 2-chloropyridines which are also difficult to prepare. Also, the harsh conditions required for both these preparations makes them of limited application to the preparation of 2-fluoropyridines having electron-withdrawing substituents.

Fluorination of a variety of steroids demonstrated that the pyridinium triflates did display a high selectivity. In a steroid with two reaction sites of conjugated and non-conjugated vinyl acetate moiety, pyridinium triflate reacted at the conjugated site only **[E-22]**. In a steroid with a silyl enol ether and a conjugated acetate, the only product resulted form substitution at the former site only **[E-23]**[142].

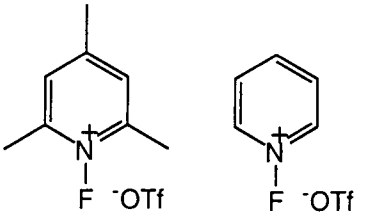


[E-22]



[E-23]

The α-fluorination of sulfides is of increasing importance since sulfides are important biologically active compounds such as in the β-lactam functionality of antibiotics[148] or amino acids[149]. There are a number of reported methods for the preparation of α-fluorosulfides, the direct fluorination with xenon difluoride[150], the conversion of sulfoxides to α-fluorosulfides with diethylaminosulfur trifluoride (DAST)[151] or replacement α-chloro sulfides with dry KF and 18-Crown-6[152]. Umemoto *et al* found that the reaction of sulfides, possessing α-hydrogens, with a range of pyridinium salts (**23,24**) resulted in the easy formation of α-fluorosulfides (see Table 31)[153].



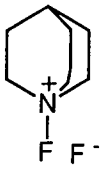
(23) **(24)**

Table 31: The Fluorination of Sulfides Using *N*-Fluoropyridinium Triflates.

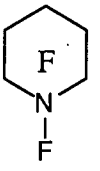
Salt	Substrate	Product	Solvent	Temp	Time	Yield
23	$PhSCH_3$	$PhSCH_2F$	CH_2Cl_2	R.t.	4hr	85%
24	$PHSCH_3$	$PHSCH_2F$	CH_2Cl_2	R.t.	6hr	56%
23	*p*-Cl-Ph-SCH_3	*p*-Cl-Ph-SCH_2F	CH_2Cl_2	R.t.	8hr	87%
23	*n*-$C_{12}H_{25}SCH_3$	*n*-$C_{12}H_{25}SCH_2F$	CH_2Cl_2	R.t.	17.5hr	44%
23	*n*-$C_{12}H_{25}SCH_3$	*n*-$C_{12}H_{25}SCH_2F$	CH_3CN	R.t.	18hr	-
23	$PhCH_2SCH_3$	$PhCH_2SCH_2F$	CH_2Cl_2	R.t.	0.5hr	77%
23	CH_3SCH_2COOEt	$CH_3SCHFCOOEt$	CH_2Cl_2	R.t.	8hr	46%

I.6.d.viii. *N*-Fluoroquinuclidium Salts

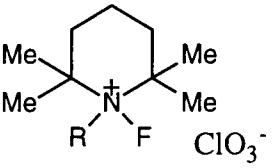
Whilst considering how to overcome the problems associated with the use of perfluoro-*N*-fluoropiperidine (**26**)[154] as a fluorinating agent, Banks *et al* discovered *N*-fluoroquinculidium fluoride (**25**) and its piperidinium analogues (**27**)[155,156]. All these compounds were attractive because they are synthesised via high yielding direct fluorination and function as reasonably reactive fluorinating agents.



(25)



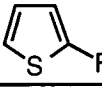
(26)



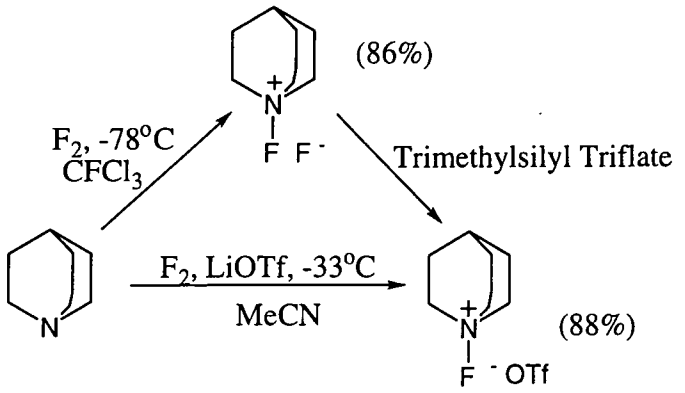
(27)

The reactivity of *N*-fluoroquinclidium fluoride was investigated using a series of nucleophiles. The following results were published (see Table 32).

Table 32: The Fluorination of a Range of Nucleophiles Using *N*-Fluoroquinuclidium Salts.

Starting Material	Product	Yield	Conditions
$PhSiCl_3$	PhF	22%	THF / -50°C
$PhC^-(CO_2Et)_2\ Na^+$	$PhCF(CO_2Et)_2$	56%	THF / -10°C
$Me_2C^-NO_2\ Li^+$	Me_2CFNO_2	47%	MeOH / 0°C
		10%	Et_2O / 0°C
PhMgX	PhF	26%	Et_2O / RT

Unfortunately, particularly from the viewpoint of using *N*-fluoroquinuclidium fluoride to effect site-selective fluorination via alkali metal derivatives or Grignard reagents, it is extremely hygroscopic. Banks *et al* investigated a range of possible counter anions, and found that conversion to the triflate analogue proved to be the most straightforward and solved the hygroscopicity problems (**Scheme 16**)[157,158].



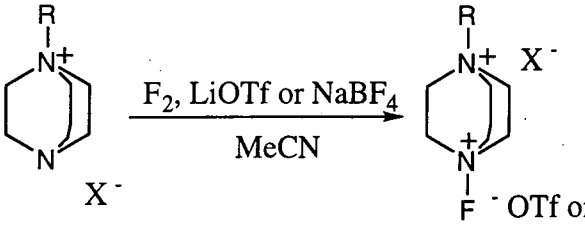
Scheme 16 **(28)**

Investigating the reactivity of *N*-fluoroquinuclidium with various counter ions confirmed the triflate as the most active fluorinating agent (see Table 33)[158].

Table 33: Fluorination Using *N*-Fluoroquinuclidium Triflates.

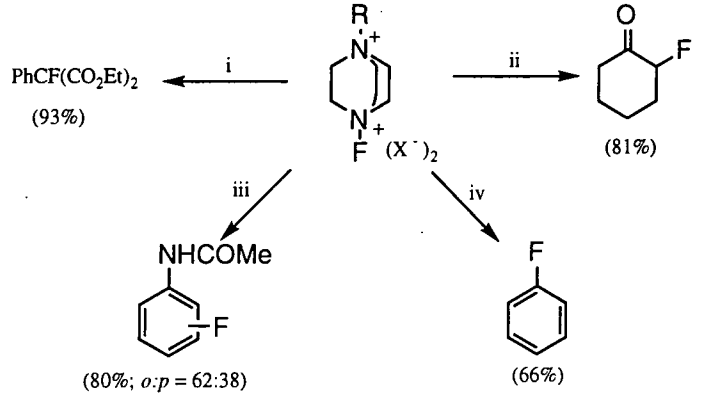
		Salt Used and Yield			
Starting Material	Product	F^-	$CF_3SO_3^-$	$CF_3CO_2^-$	BF_4^-
PhMgBr	PhF	26	26	-	-
$PhC^-(CO_2Et)_2\ Na^+$	$PhCF(CO_2Et)_2$	56	52	-	-
$Me_2C^-NO_2\ Li^+$	Me_2CFNO_2	47	72	56	50
$PhSO_2Na$	$PhSO_2F$	-	94	-	-
PhOH	2-F-PhOH 3-F-PhOH 4-F-PhOH	-	100	-	-

More recently Banks *et al* investigated the fluorination of 1,4-diazobicyclo[2.2.2]octane and its monoquaternary salts **[E-24]**[159]. The objective was to produce an electrophilic fluorinating reagent which was more reactive than the *N*-fluoroquinuclidinium salts[155,156].

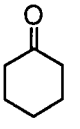


R=Me, CH_2Cl, CF_3CH_2 **[E-24]** (87-95%)
X= TfO^-, BF_4^-

The strategy of incorporating a second quaternized bridgehead nitrogen into the ring system produced a more reactive system and also allowed the fluorinating 'power' of the system to be tuned through the variation in electronegativity of the quaternizing group. Reaction of the 1-alkyl-4-fluoro-1,4-diazobicyclo[2.2.2]octane* with a variety of substrates (**Scheme 17**) demonstrated that selective fluorination was possible with this reagent[159,160].



i) $PhC^{-}(CO_2Et)_2\ Na^{+}$, THF:DMF (2:1), 25°C, 30mins

ii)  , CH_2Cl_2, 20°C

iii) PhNHCOMe, MeCN, reflux, 15min

iv) PhMgBr, Et_2O, 25°C, 2hr

Scheme 17

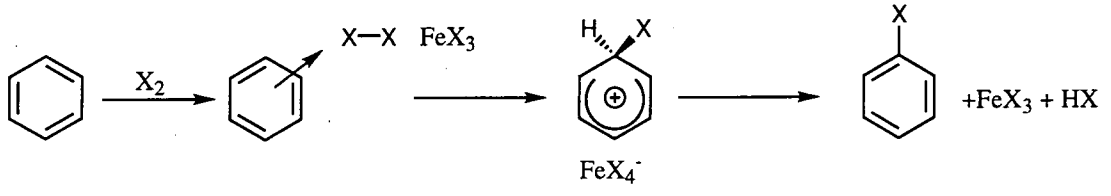
* Now more commonly known as the Selectfluor ™ Reagent of Air Products and Chemicals.

Chapter II The Direct Fluorination of Deactivated Aromatic Compounds

II.1. Introduction

Early attempts to incorporate fluorine into organic molecules demonstrated the extreme reactivity of elemental fluorine, many workers finding that their attempts resulted in explosions due to exothermic nature of the reaction[1,31,43,161]. These early experiments involving direct fluorination did not attract many researchers, and consequently elemental fluorine has been neglected as a synthetic reagent until relatively recently. The use of elemental fluorine in selective synthesis has been reviewed in Chapter 1.

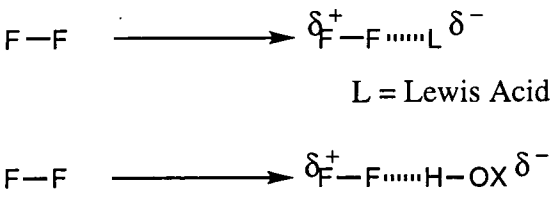
Direct halogenation of aromatics usually requires the presence of a Lewis Acid catalyst to assist in polarising the attacking halogen molecule, so as to provide it with an electrophilic end **(Scheme 18)**.



X= Halogen

Scheme 18

From consideration of this mechanism we concluded that effective polarisation of the fluorine molecule was important for direct fluorination and could be a crucial factor in forcing an entirely electrophilic fluorination process whilst inhibiting the radical reactions commonly associated with the direct fluorination of aromatics. Clearly a Lewis Acid could be used to achieve this polarisation but we also believed the same effect could be achieved using a protonic acid **(Scheme 19)**.



Scheme 19

Additional parameters that obviously needed consideration were the following, some of which have been explored by other workers.

i) Dilution of the F_2 gas with an inert gas such as N_2 or Ar[22,162].

ii) The use of solvents to reduce the relative local heat of reaction[82].

iii) Rapid and effective mixing to reduce the possibility of the formation of local 'hot spots'.

iv) Cooling the fluorination reaction to reduce the contribution of radical processes to the formation of products.

v) The use of deactivated aromatic substrates (the use of aromatics containing two deactivating groups could help to moderate and bring more orientational control to the reaction).

II.2. Initial Reactions

II.2.a. Reactor Design

Our initial fluorinations were performed in glass vessels (see Fig. 3)[163]. Prior to fluorination a 10% mixture of fluorine in nitrogen in a 800ml passivated stainless steel cylinder was prepared. This mixture was then introduced into the glass vessel via a $12/100^{th}$ (I.D.) PTFE capillary inlet tube at *ca.* 4ml min^{-1} while the solution was continuously stirred using a magnetic PTFE stirrer and cooled in a cryostat .

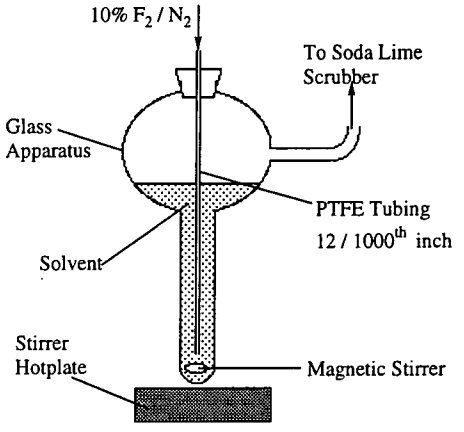
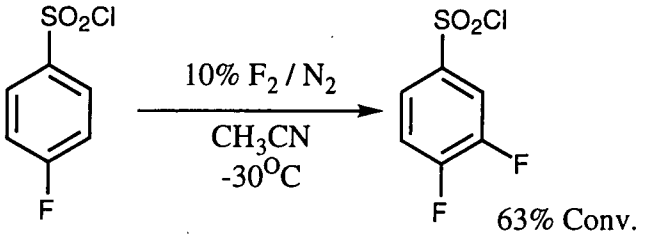


Figure 3: Fluorination Reactor(I).

II.2.b. Fluorination of 4-Fluorobenzenesulphonyl Chloride

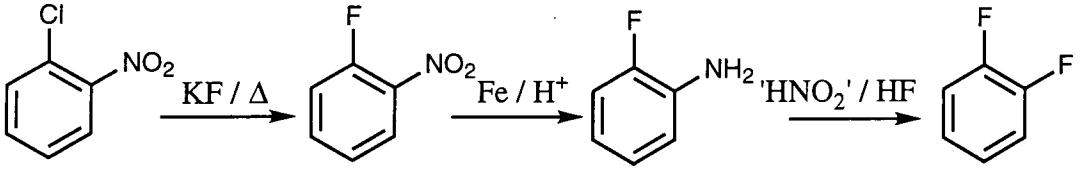
Initially we investigated the fluorination of 4-fluorobenzenesulphonyl chloride under the same conditions used by Rock who had demonstrated that the direct fluorination of a deactivated aromatic showed a significant amount electrophilic reaction[163]. The substrate was dissolved in CH_3CN, cooled to -30° and then fluorinated using dilute elemental fluorine (a 10% mixture of F_2 in N_2) **[E-25]**. Following work up the product 3,4-difluorobenzenesulphonyl chloride was identified against an authentic sample by ^{19}F nmr and g.c. / m.s..



[E-25]

The production of 3,4-difluorobenzenesulphonyl chloride can be rationalised by consideration of the directing effects of the substituents. The SO_2Cl group is meta directing (deactivating) and F is ortho / para directing (deactivating) towards electrophilic attack, confirming fluorine is acting as an electrophile under these reaction conditions. The formation of the product was also accompanied by the formation of large quantities of polymeric material suggesting that the fluorination reaction still possessed a considerable radical nature at temperatures as low as -30°C.

The production of 3,4-difluorobenzenesulphonyl chloride in high conversion is of industrial relevance because desulphonation leads to 1,2-difluorobenzene[164,165]. On the industrial scale, 1,2-difluorobenzenes are prepared by multistep synthesis, an example of which follows (**Scheme 20**)[166].

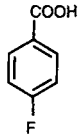
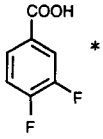
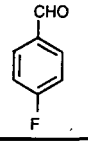
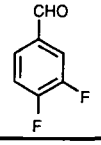
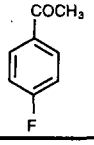
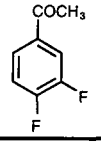


Scheme 20

II.2.c. Fluorination of Substituted 4-Fluoro Compounds

A series of fluorinations of deactivated aromatics were performed under the same conditions as the initial fluorination of 4-fluorobenzenesulphonyl chloride (see Table 34). Products were identified by ^{19}F nmr and g.c. / m.s. against authentic samples obtained from commercial sources[167].

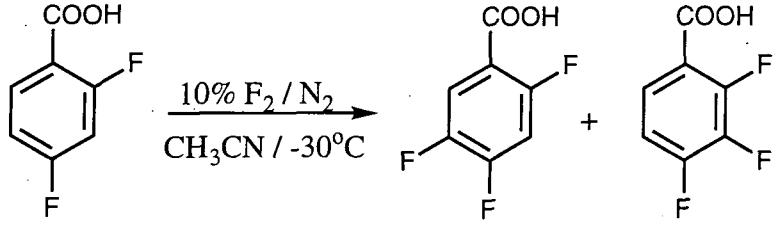
Table 34: The Fluorination of 4-Fluoro Substituted Aromatics.

Starting Material	Major Product	Conditions	Conversion+
	 *	-30°C, CH_3CN, 2.0eq F_2	76%
		-30°C, CH_3CN, 2.0eq F_2	47%
		-30°C, CH_3CN, 2.0eq F_2	48%

In each case the formation of the 3,4-difluorinated product, indicative of electrophilic substitution, was accompanied by the formation of considerable quantities of unidentifiable polymeric material confirming that both radical and electrophilic process were ocurring under these reactions conditions.

II.2.d. 2,4-Difluorobenzoic Acid

The fluorination of 2,4-difluorobenzoic acid was also performed under the same conditions **[E-26]**.



Composition 40% 13%

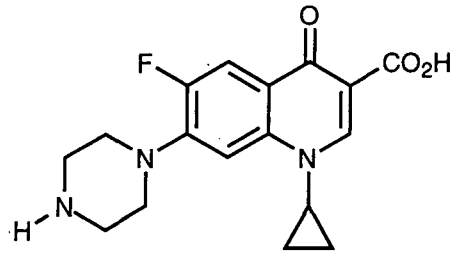
Conversion 53%

[E-26]

The two major products were identified by ^{19}F against authentic samples as 2,4,5-trifluorobenzoic acid and 2,3,4-trifluorobenzoic acid, two industrially important compounds often used in the synthesis of fluoroquinolone antibacterials[168-173] such as Ciprofloxacin® **(29)**.

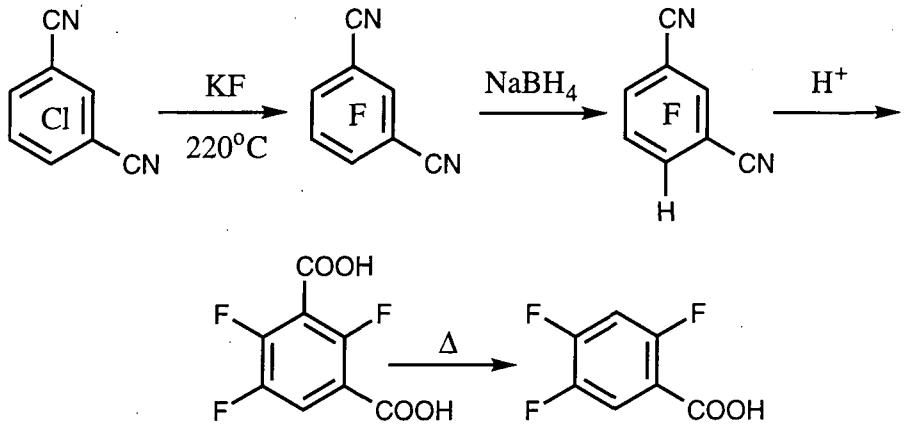
+ Conversion calculated by ^{19}F nmr.

* Product characterised by ^{19}F nmr and m.s.



(29)

Previously these trifluorinated aromatic compounds have only been available through multistep syntheses, an example of which follows (**Scheme 21**)[174].



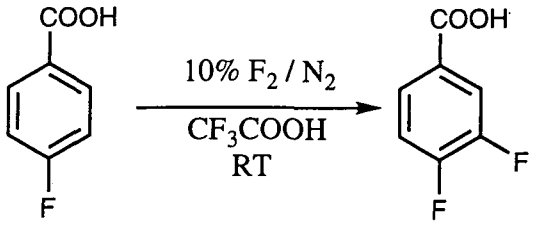
Scheme 21

II.2.e. Fluorination in Trifluoroacetic Acid(TFA)

These early reactions demonstrated that electrophilic fluorination was possible, but was accompanied by the formation of polymeric material. Examination of the reaction mixtures by ^{19}F nmr confirmed that acetonitrile was also being fluorinated under the reaction conditions to produce 1-fluoroacetonitrile, 1,1-difluoroacetonitrile and 1,1,1-trifluoroacetonitrile and maybe other unidentified materials. To reduce these side reactions we believed that further polarisation of the fluorine molecule was required so fluorination using trifluoroacetic acid, a protonic acid, as the solvent was investigated.

II.2.e.i. 4-Fluorobenzoic Acid

Fluorination of 4-fluorobenzoic acid in trifluoroacetic acid (TFA) at room temperature produced the following reaction **[E-27]**.



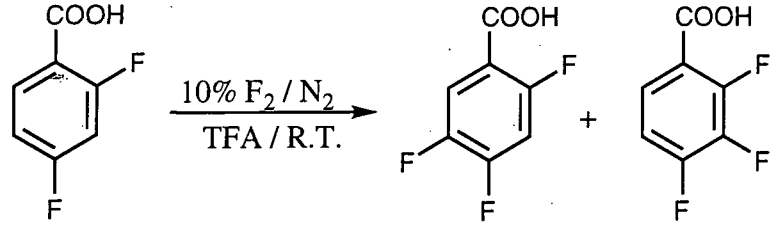
72% Conversion

[E-27]

Fluorination in TFA at room temperature resulted in a conversion that was remarkably similar to that observed for fluorination in CH_3CN. Following workup, it was possible to isolate and fully characterise the product, 3,4-difluorobenzoic acid, thus confirming a definite improvement in the quality (i.e. electrophilic nature) of the fluorination reaction.

II.2.e.ii. 2,4-Difluorobenzoic Acid

The fluorination of 2,4-difluorobenzoic acid again using TFA as a solvent at room temperature produced the following reaction **[E-28]**.



Composition 35% 19%

Conversion 54%

[E-28]

The use of TFA as a solvent again produced a similar reaction with 2,4-difluorobenzoic acid to those using acetonitrile as a solvent at -30°C. The approximate 45°C difference in temperature between the reactions further indicates that solvent can have an effect on the fluorination reaction.

II.2.f. Conclusions

i) These early fluorinations proved to be extremely crude, suffering from polymer formation in significant quantities. We concluded that to improve later reactions better mixing of the fluorinations was essential to prevent localised heating and consequent polymer formation.

ii) It appeared that using protonic acids as solvents in the fluorination reaction had an effect that required investigation. Using trifluoroacetic had led to an improvement in

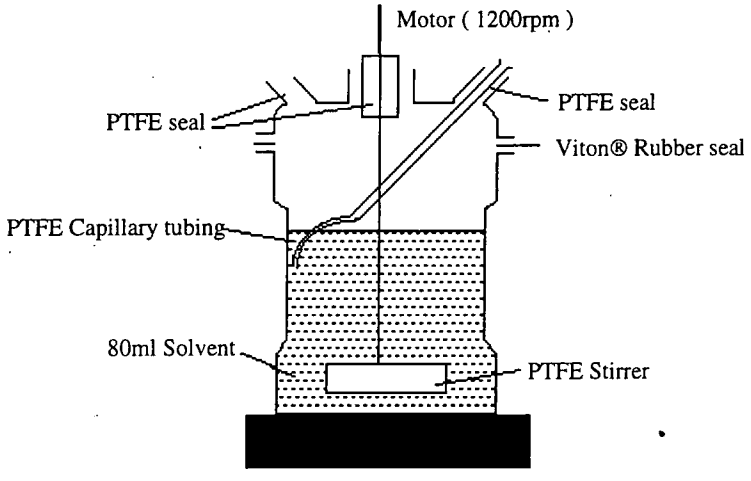
the fluorination reaction, but it was not an ideal solvent due to its toxicity, cost and the difficulty in its removal from the aromatic substrates

II.3. Effect of Solvent on Fluorination

II.3.a. Fluorination in a Variety of Solvents

A new fluorination reactor (Fig. 4) was designed to improve mixing during reactions. The all glass vessel had baffles cut into its side to aid dispersal of the dilute fluorine gas and was stirred via a PTFE bar driven by a *'Citenco'* motor at approximately 600rpm. The dilute fluorine was introduced at *ca.* 8-12ml min^{-1} via capillary PTFE tubing fed through a molded FEP tube. The major seal between the two halves of the reactor was cut from Viton® sheet and all other seals were made from PTFE. The exhaust gases were fed via 1/4" FEP* tubing through a tube packed with 150g soda lime. The reactor could also be cooled via a cryostat.

Figure 4: Fluorination Reactor (II).



Using 4-fluorobenzoic acid the effect of solvent on the fluorination reaction was investigated by running an identical series of fluorination reactions in a number of commonly available solvents.

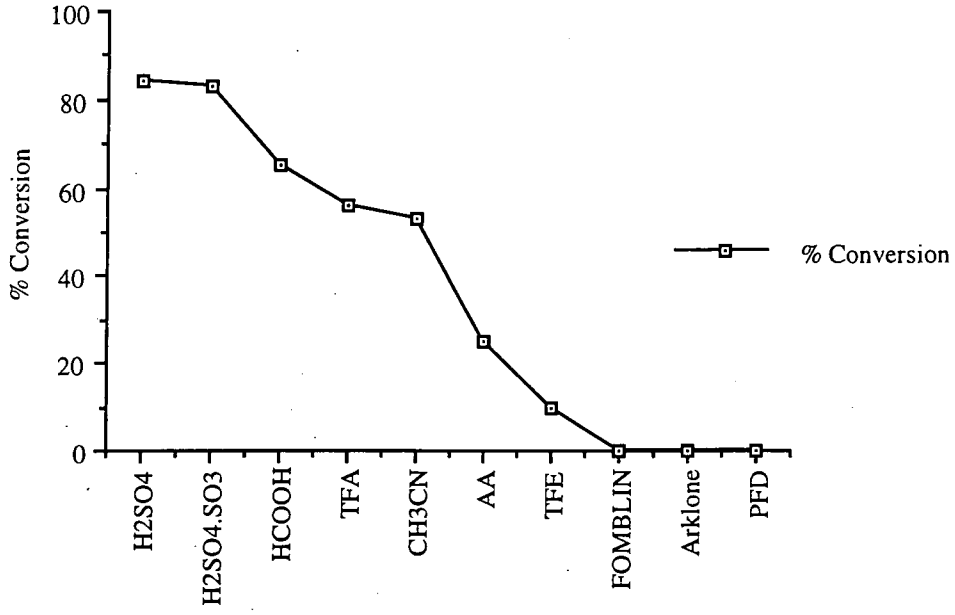
* FEP: A co-polymer of hexafluoropropene and tetrafluoroethene.

Table 35: The Fluorination of 4-Fluorobenzoic Acid in a Variety of Solvents.

Solvent*	Temp.	Conversion+
98% H_2SO_4	r.t.	84%
30% $H_2SO_4.SO_3$	r.t.	83%
HCOOH	r.t.	65%
TFA	r.t.	56%
CH_3CN	r.t.	53%
AA	r.t.	25%
TFE	r.t.	10%
FOMBLIN	r.t.	0%
ARKLONE	r.t.	0%
PFD	r.t.	0%

Graph 3. shows that conversion to the product, 3,4-difluorobenzoic acid, increased as the dielectric constant[175,176] and / or acidity[175] of the solvent increased (see Graph 4, 5).

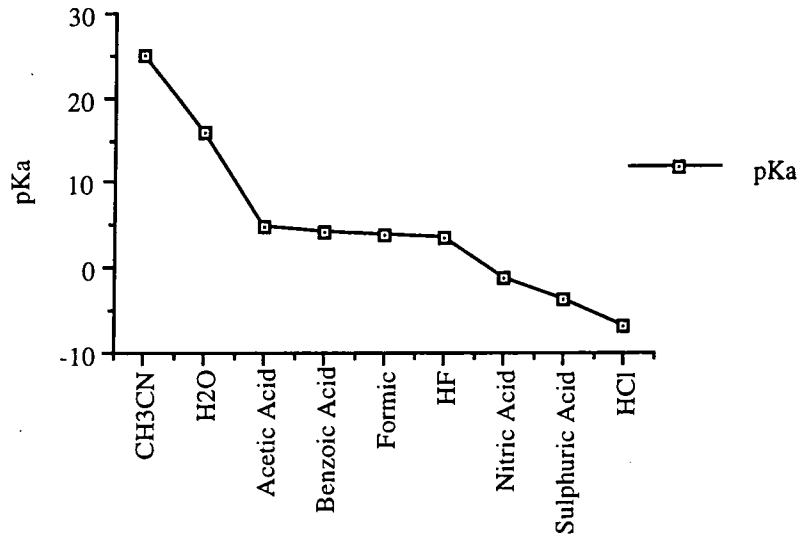
Graph 3: Fluorination of 4FBA in a Variety of Solvents



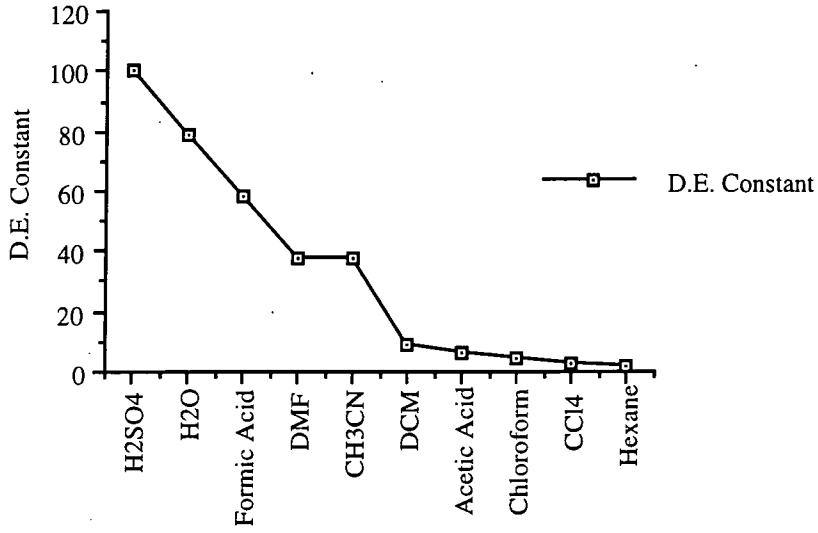
* *TFA- CF_3COOH; AA- CH_3COOH; TFE- CF_3CH_2OH; Arklone-CCl_2FCClF_2; PFD-$C_{10}F_{18}$.*

\+ Conversion Calculated by ^{19}F nmr.

Graph 4: The pKa values of a Range of Solvents

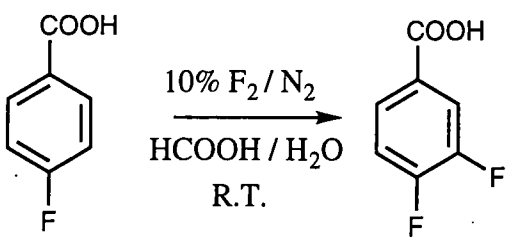


Graph 5: Dielectric Constant of Some Common Solvents



II.3.b. Dielectric Constant vs. Acidity

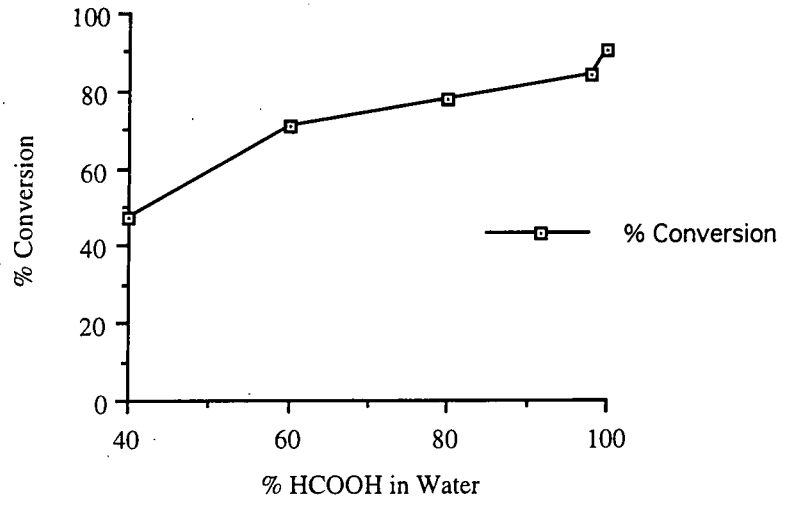
Fluorination in a variety of solvents had indicated that dielectric constant and / or acidity played a crucial role in the fluorination process. To investigate which factor was crucial a number of identical fluorinations **[E-29]** were conducted in a range of formic acid / water mixtures.



[E-29]

The results (see Graph 6) indicated that as dilution of the formic acid decreased the conversion to 3,4-difluorobenzoic acid increased. When the relative dielectric constants of water and formic acid are considered, [H_2O ε 78.5 (25.0°C); HCOOH ε 58.5 (10°C)][176] the dilution of the formic acid should have increased the dielectric constant of the resulting solution but decreased its acidity and this result demonstrated that acidity is the most important factor in the fluorination reaction.

Graph 6: Fluorination of 4-Fluorobenzoic Acid in Formic Acid / Water Mixtures



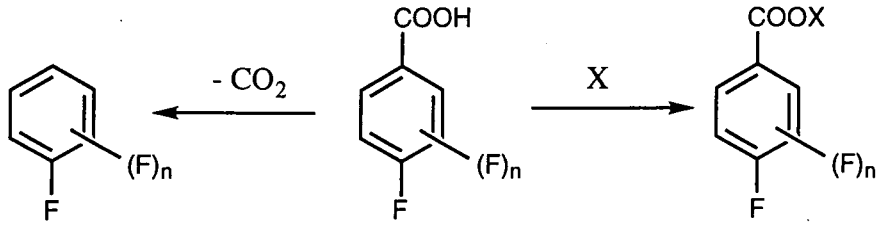
II.4. Large Scale Fluorinations

II.4.a. Introduction

The reactor design (see Fig. 4) enabled easier isolation of products but with a relatively low level of recovery which was attributed to the large excess of solvent in which the fluorinations were being conducted (11.3mmol in 80ml of solvent). To further improve the fluorination reaction and confirm it as a synthetically useful technique, later fluorinations were conducted on a larger scale which involved designing a new reactor.

II.4.b. Analysis of Product Mixtures

The earlier examples of fluorination in acidic media, such as H_2SO_4, had demonstrated that multiple substitution could result. Before pursuing reactions on the larger scale it was decided to investigate the possibility of producing a simple method of further characterising the mixtures of fluorinated benzoic acids that were likely to be produced. Two approaches were considered (**Scheme 22**). Functionlisation of the resulting polyfluorobenzoic acids to produce ester products allowing analysis by g.c. / m.s., or decarboxylation of polyfluorobenzoic acids to the volatile polyfluorobenzenes also allowing analysis by g.c. / m.s.

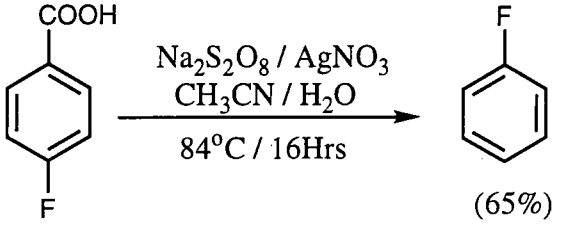


Scheme 22

For each of the following reactions its applicability to quantitative analysis, via calibration of the mass spectrometer, was also considered which required a quantitative conversion to polyfluorobenzene or esters.

II.4.b.i. Sodium Persulphate

The oxidation of the 4-fluorobenzoic acid, using sodium persulphate **[E-30]**, to produce fluorobenzene was investigated[177].



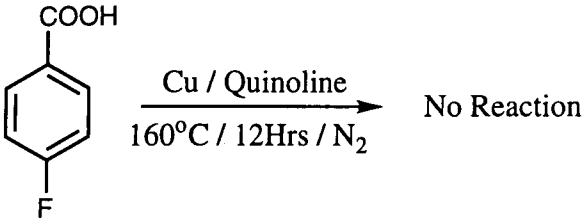
[E-30]

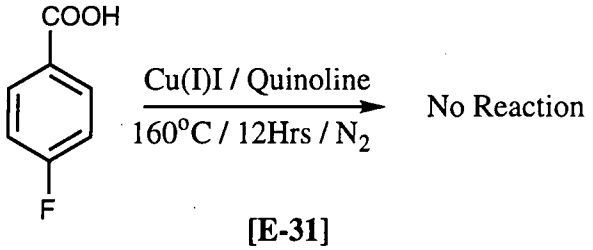
A maximum conversion of 65% to fluorobenzene was achieved but the resulting mixture of volatiles coupled with the low conversion made the reaction unsuitable for quantitative analysis.

II.4.b.ii. Copper / Quinoline

II.4.b.ii.1) 4-Fluorobenzoic Acid

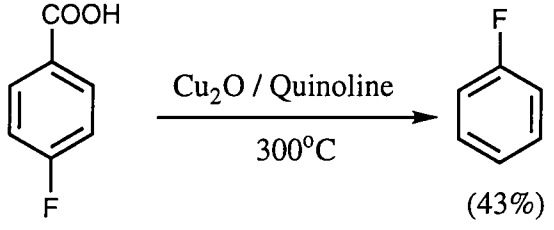
Caincross *et al* decarboxylated aromatic acids by heating with a mixture of Cu powder and quinoline under an inert atmosphere[178]. The attempted decarboxylation of 4-fluorobenzoic acid **[E-31]** under these conditions produced no fluorobenzenes.





[E-31]

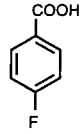
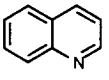
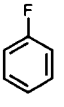
Recently Toussaint *et al* decarboxyated a range of aromatic compounds by heating the acid in the presence of Cu_2O and quinoline at high temperatures[179]. Using these conditions decarboxylation of 4-fluorobenzoic acid to fluorobenzene was achieved **[E-32]**.



[E-32]

Decarboxylations over a range of temperatures produced the following results (see Table 36).

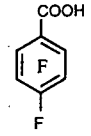
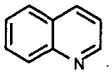
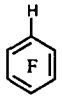
Table 36: The Decarboxylation of 4-Fluorobenzoic Acid at a Range of Temperatures

	Temp °C	Cu_2O		 Yield. (%)
0.5g	300	0.6g	0.9g	43
0.5g	200	0.6g	0.9g	32
0.5g	150	0.6g	0.9g	0
0.8g	100	0.9g	1.4g	0

II.4.b.ii.2) Perfluorobenzoic Acid

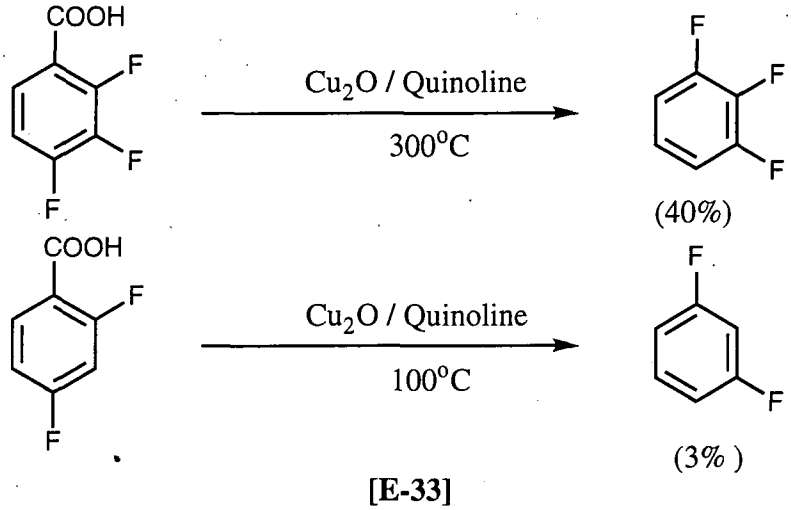
Decarboxylation of pentafluorobenzoic acid over a range of temperatures produced the following results (see Table 37).

Table 37: The Decarboxylation of 4-Fluorobenzoic Acid at a Range of Temperatures

	Temp °C	Cu_2O		 Yield. (%)
0.7g	300	0.6g	0.9g	94
0.7g	200	0.6g	0.9g	87
0.7g	150	0.6g	0.9g	76
1.03g	100	0.9g	1.4g	74

II.4.b.ii.3) Polyfluorobenzoic Acids

The decarboxylation of 2,3,4-trifluorobenzoic acid and 2,4-difluorobenzoic acid using copper(I) oxide and quinoline produced the following results **[E-33]**.



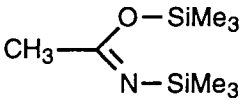
[E-33]

II.4.b.ii.4) Conclusion

Decarboxylation is an ideal method of separation of polyfluorobenzoic acids on a large scale. Gradual increase in temperature during a decarboxylation of a polyfluorobenzoic acid mixture should result in selective decarboxylation, followed by the polyfluorobenzene distilling out of the reaction mixture. Unfortunately, the conversion to fluorobenzenes in our sealed system did not allow its use as an analytical method.

II.4.b.iii. Silylation

Two possible routes to esters were considered; functionalisation to produce an alkyl ester[180] or functionalisation to produce a silyl ester[181,182]. Using bis(trimethylsilyl)acetamide (BSA) **(30)**[183] the silyl esters of all the polyfluorobenzoic acids were prepared enabling easy identification of the trimethylsilylated fluorination products. All reactions with BSA were found to be quantitative.



(30)

Initially g.c./ m.s. using a fused silicone column failed to produce an adequate separation of all eight polyfluorobenzoic acids. However, using a DB-624¥ capillary gas chromatography column, separation was achieved allowing g.c. / m.s. analysis of the large scale fluorinations of 4-fluorobenzoic and 2,4-difluorobenzoic acid.

II.4.c. Design of a Large Scale Reactor

The new reactor design (see Fig. 5) was based on the earlier glass fluorination reactor with a shaped bottom section and baffles cut into the side of the reactor. The PTFE stirrer bar was replaced with a stainless steel entraining stirrer which caused the gas inside the reactor to recirculate but also required the fitting of a locating cup in the bottom of the reactor. To further aid dispersion a passivated HPLC* filter was added to the end of the fluorine inlet, resulting in a large reduction of the volume of fluorine bubbles introduced into the stirred solution. Because of the rigid nature of the stirrer bar it was possible to replace the *'Citenco'* stirrer with a IKAMAG brushless motor, capable of stirring at between 0-2000rpm with minimal vibration. The combination of the shaped section and increased speed of mixing resulted in the gas bubbles being 'trapped' in the bottom of the reactor for a much longer period improving the efficiency of the fluorinations. The increased scale required the reactor to be fed from a passivated 3.7litre stainless steel cylinder at a flow rate of *ca.* 40ml min^{-1}. Due to the increased scale of the reactor the exhaust was connected, via 1/4" FEP tubing, to a much larger tube containing between 200g-400g of soda lime. The reactor could also be cooled via an external loop from a HAAKE cryostat.

¥ Donated by Zeneca PTD, Huddersfield Works.

* Hastealloy HPLC Prefilter [Alltech 1/16" (1.5mm) fitting, pore size 10μ].

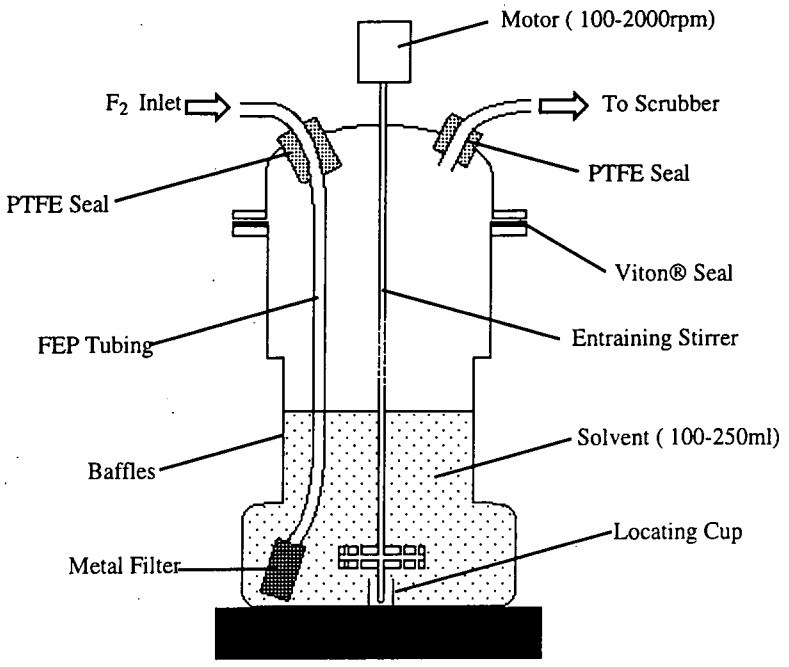


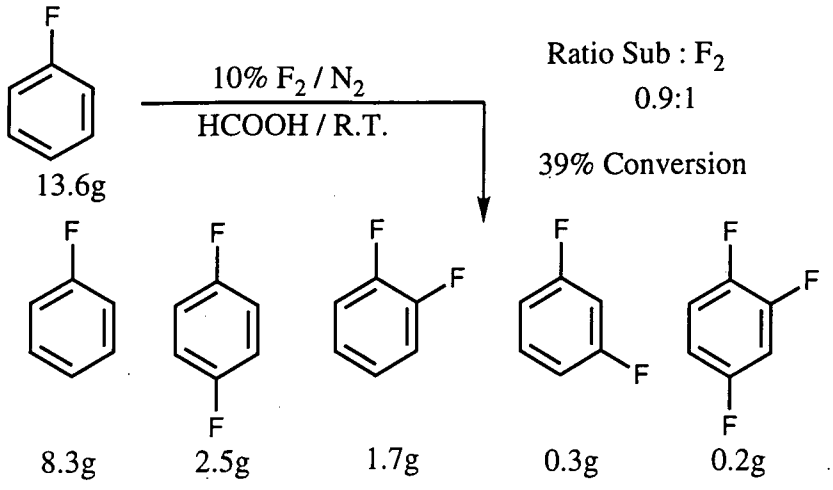
Figure 5: Fluorination Reactor(III).

II.4.d. Fluorination in Formic Acid

II.4.d.i. Fluorobenzene

Fluorobenzene was fluorinated (fluorine to substrate ratio of 0.9:1) in 98% formic acid at room temperure to test the combination of the new reactor and protonic solvents on the fluorination procedure. Analysis, by a combination of ^{19}F nmr and g.c / m.s. against the commercially available materials, confirmed that the new fluorination reactor had dramatically improved the procedure **[E-34]***. The combination of effective mixing and protonic solvent had virtually eliminated the polymeric material obtained in many of the earlier fluorination reactions. The ratios of isomers also confirmed the process as electrophilic with 1,4-difluorobenzene being formed preferentially.

* Mass of material determined by ^{19}F nmr against a standard of α,α,α-trifluoromethyltoluene.



[E-34]

II.4.d.ii. 4-Fluorobenzoic Acid

A series of fluorinations in 98% formic acid were run over a range of substrate to fluorine ratios and the products were identified by ^{19}F nmr against the authentic materials. Further identification was achieved by conversion to the trimethylsilyl esters using BSA (**30**) and comparison against the authentic materials by g.c. / m.s. (see Table 38). Graphical representation of the results (see Figure 6) demonstrated conversion increased with an increase in the fluorine substrate ratio and the unknown material remained reasonably constant at 1%-5%. Recovery in the reactions was not 100%, but we feel the material recovered shows an accurate representation of the composition of the reaction mixture following fluorination.

Figure 6: Fluorination of 4-Fluorobenzoic Acid in Formic Acid

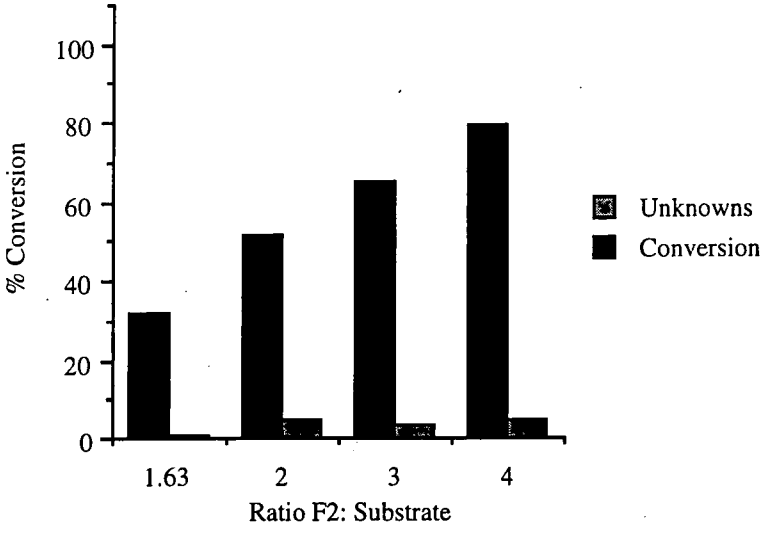
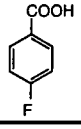
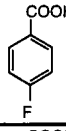
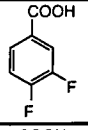
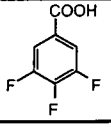
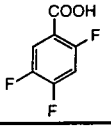


Table 38: Fluorination of 4-Fluorobenzoic Acid in Formic Acid at a Number of Fluorine to Substrate Ratios*.

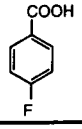
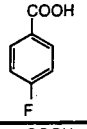
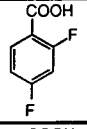
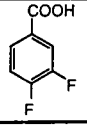
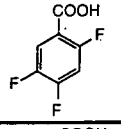
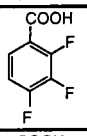
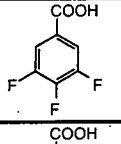
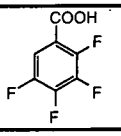
Substrate : F_2 Ratio	1:1.6	1:2	1:3	1:4
	11.5g	11.6g	4.0g	6.0g
Isolated Material	10.5g	8.8g	3.1g	5.3g
Conversion	32%	51%	65%	79%
	7.8g	5.6g	1.4g	1.8g
	2.7g	2.8g	1.6g	3.5g
	-	-	-	0.2g
	-	-	-	0.2g
Unknowns	0.1g	0.4g	0.1g	0.3g

II.4.e. Fluorinations in Sulphuric Acid

II.4.e.i. 4-Fluorobenzoic Acid

Earlier work on the effect of solvents and the fluorination process had demonstrated that sulphuric acid, a very strong protonic acid, was the best solvent for the electrophilic fluorination of 4-fluorobenzoic acid. To further investigate this result a series of fluorinations of 4-fluorobenzoic acid in 98% sulphuric acid were conducted over a range of substrate to fluorine ratios. Following workup the products were identified by ^{19}F nmr against the authentic materials. Further identification was achieved by conversion to the trimethylsilyl esters, using BSA (**30**), and comparison against the authentic materials by g.c. / m.s (See Table 39)

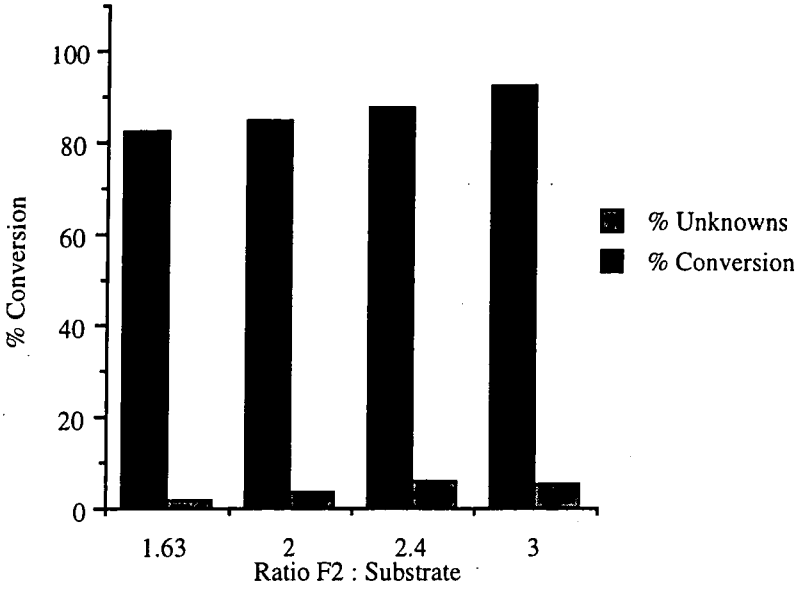
Table 39: Fluorination of 4-Fluorobenzoic Acid in Sulphuric Acid at a Number of Fluorine to Substrate Ratios*.

Substrate : F_2 Ratio	1:1.6	1:2	1:2.4	1:3
	14.4g	11.5g	7.1g	7.7g
Isolated Material	11.6g	10.6g	5.2g	5.9g
Conversion	82.6%	84.8%	87.9%	92.3%
	2.5g	1.8g	0.8g	0.6g
	-	-	0.1g	0.1g
	6.8g	6.2g	2.7g	3.4g
	1.2g	0.8g	0.4g	0.6g
	0.6g	0.4g	0.1g	0.2g
	0.2g	0.4g	0.2g	0.5g
	-	0.7g	0.5g	0.3g
Unknowns	0.2g	0.4g	0.4g	0.3g

Graphical representation (see Figure 7) again clearly shows that conversion increases with an increase in fluorine to substrate ratio. Using sulphuric acid as a solvent resulted in multiple fluorine substitution and produced up to tetafluorobenzoic acid at room temperature indicating that the combination of fluorine and sulphuric acid produces an extremely powerful electrophilic fluorinating species. Complete recovery of the products from the strong acid was difficult but we feel these results give a good representation of the composition of the whole reaction mixture. If further investigation had been made into the fluorination of the polyfluorobenzoic acids continuous extraction should have enabled higher recovery of the fluorinated products.

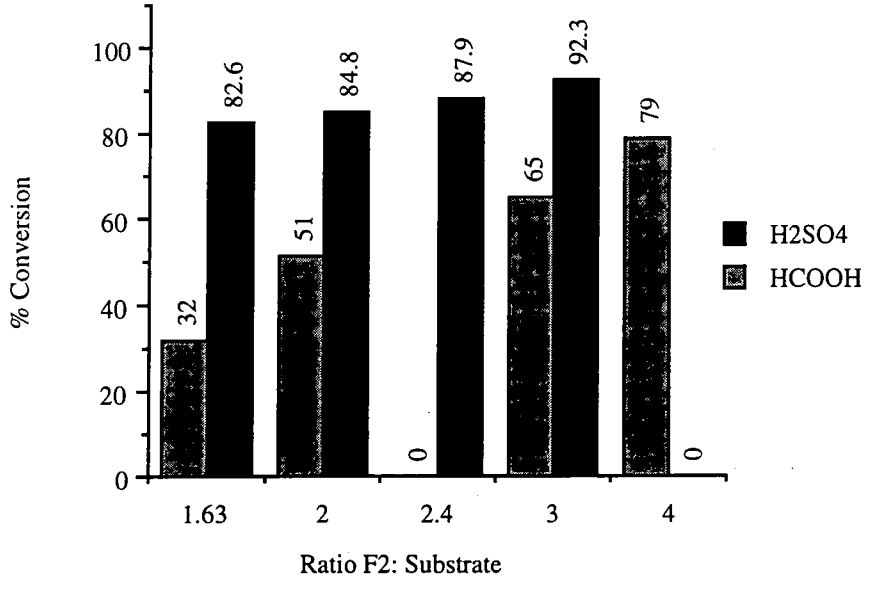
* Mass of material determined by ^{19}F nmr against a standard of α,α,α-trifluoromethyltoluene.

Figure 7: The Fluorination of 4FBA in Sulphuric Acid



Combination of the data from both sets of reactions can also be used to show the relative effect of the increasing acidity on the fluorination of 4-fluorobenzoic acid under identical conditions (see Figure 8).

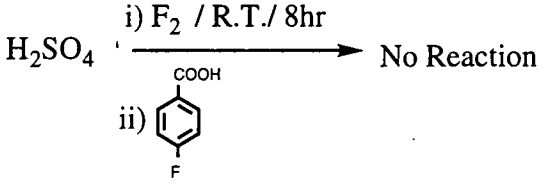
Figure 8: The Fluorination of 4-Fluorobenzoic Acid in H2SO4 and HCOOH



II.4.e.ii. Two Stage Fluorination of 4-Fluorobenzoic Acid

The reaction of 4-fluorobenzoic acid, sulphuric acid and fluorine in a two stage process was investigated. Following consideration of the work detailed by Soloman claiming that the passage of oxygen difluoride through either SO_3 or H_2SO_4 resulted in the formation of FSO_2OF[184] this reaction was undertaken with the utmost care. Fluorosulphuryl hypofluorite (FSO_2OF) is classified in the same highly dangerous and

unpredictable class as nitryl hypofluorite (O_2NOF)[185] and perchloryl hypofluorite (O_3ClOF)[186]* which according to Schreeve are "the three bad guys of inorganic hypofluorites"[187], their reactions with organic substrates being characterised by extreme reactivity and explosions[188]. The fluorination of sulphuric acid over a period of eight hours followed by addition of 4-fluorobenzoic acid gave no conversion to any fluorinated products suggesting that the powerful electrophilic fluorinating agent formed during the earlier reactions was unstable under our reaction conditions **[E-35]**.



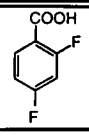
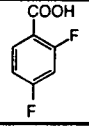
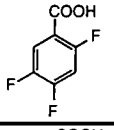
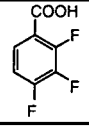
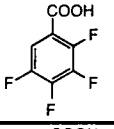
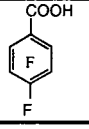
[E-35]

II.4.e.iii. 2,4-Difluorobenzoic Acid

The fluorination of 2,4-difluorobenzoic acid in 98% sulphuric acid further confirmed that an extremely powerful electrophilic fluorinating species is formed by the passage of fluorine through sulphuric acid with the formation of pentafluorobenzoic acid at room temperature (see Table 40). Following workup the products were identified by ^{19}F nmr against the authentic materials. Further identification was achieved by conversion to the trimethylsilyl esters using BSA (**30**) and comparison against the authentic materials by g.c. / m.s.

* It is likely that this compound was first prepared by Fr. Ficter and E. Brünner *Helv. chim. Acta.*, 1929, **12**, 305 but was incorrectly identified.

Table 40: Fluorination of 2,4-Difluorobenzoic Acid in Sulphuric Acid.

Substrate : F_2 Ratio	1:2
	13.0g
Isolated Material	9.4g
Conversion	89.2%
	1.4g
	3.7g
	1.4g
	1.1g
	0.3g
Unknowns	1.4g

II.4.f. Conclusions

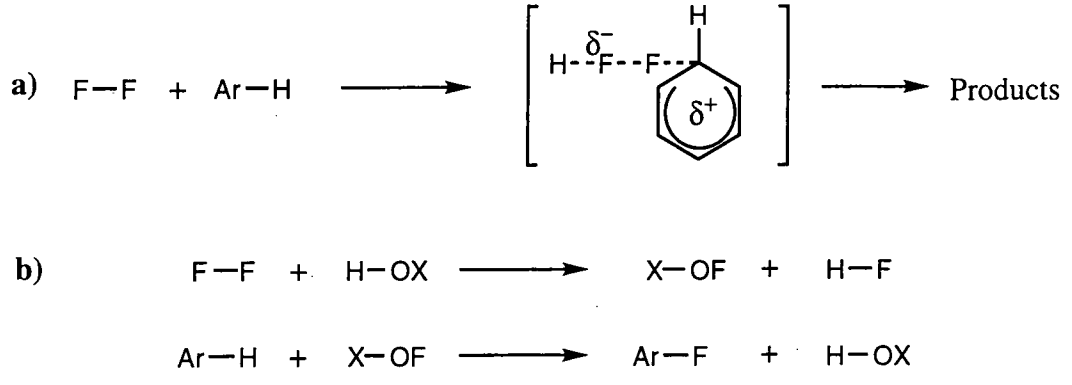
i) The use of formic and sulphuric acids as solvents for the fluorination of deactivated aromatics provides a dramatic improvement on any previously reported conditions for the fluorination of deactivated aromatics. Formic acid produces monosubstitution at all but high fluorine to substrate ratios. It has further advantages in that it is cheap and relatively non-toxic. Sulphuric acid clearly produces a dramatic rise in the reactivity of the resulting electrophile allowing multiple fluorine atoms to be inserted at room temperature. Surprisingly, no examples of fluorination of aromatics in these two common organic solvents can be found in the literature.

ii) The above data demonstrate the improvement in the fluorination reaction as a result of using the new reactor. In contrast to the earlier examples, both conversion and recovery have improved as a result of running reactions at higher concentrations. In each reaction the level of unknowns produced has remained at a small percentage of the total isolated material. Cooling could also be used to further enhance the selectivity of the fluorinations, again reducing the likelihood of radical process. When formic acid is

used as the solvent the minimum temperature is limited to 4°C[167] and with 98% sulphuric acid to 3°C[189].

iii) The orientations of substitution observed during the fluorination of the aromatic substrates are consistent with an electrophilic process.

iv) The remaining question is how far the HF formation proceeds before the C-F bond formation begins. There are effectively two extremes (**Scheme 23**). In mechanism **a)** the protonic acid is involved in the polarisation of the fluorine molecule in the reaction mixture. In mechanism **b)**, the passage of fluorine through the protonic acid results in the formation of a fluoroxy compound which then fluorinates the substrate.



Scheme 23

Because of the generally unstable nature of most fluoroxycompounds at room temperature there is no other obvious way to distinguish between the two mechanisms detailed in (**Scheme 23**). It is also probable that the mechanism of fluorination is dependent on the substrate and for most substrates, except the extremely activated or deactivated, will be partway between the two.

II.4.g. Fluorination in Other Acids

Following the series of fluorinations in sulphuric and formic acid, fluorination of 4-fluorobenzoic acid in a range of other acids was investigated to determine the scope of fluorination in acidic solvents.

II.4.g.i. Orthophosphoric Acid(85%)

Fluorination of 4-fluorobenzoic acid was attempted in orthophosphoric acid (H_3PO_4). No reaction was observed by ^{19}F nmr and only starting material was recovered after workup.

II.4.g.ii. Hydrochloric Acid(42%)

Fluorination of 4-fluorobenzoic acid was also attempted in hydrochloric acid. No reaction was observed by ^{19}F nmr and only starting material was recovered after workup.

II.4.g.iii. Hydrobromic Acid(48%)

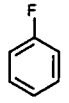
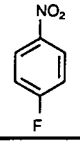
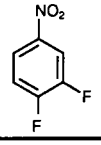
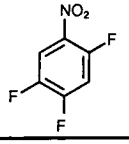
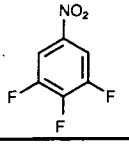
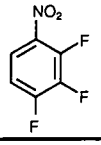
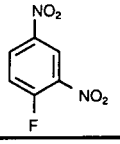
Fluorination of 4-fluorobenzoic acid using the same conditions as those used for fluorination in hydrochloric also failed to produce any fluorination reaction.

II.4.g.iv. Nitric Acid(90%)

II.4.g.iv.1) Fluorobenzene

The fluorination of fluorobenzene in 90% nitric acid was investigated. Following reaction and workup the products were characterised by a combination of ^{19}F nmr and g.c. / m.s. against the commercially available authentic materials (see Table 41). The 'blank' reaction performed without fluorine also showed a 100% conversion to nitrated products.

Table 41: Fluorination of Fluorobenzene in 90% Nitric Acid.

Substrate : F_2 Ratio	1:0	1:2
	6.8g	15.0g
Isolated Material	6.2g	15.5g
Conversion	100%	100%
	4.3g	5.6g
	-	6.0g
	-	0.7g
	-	0.8g
	-	0.2g
	-	0.6
Other Products	1.9g*	0.0g
Unknowns	-	1.6g

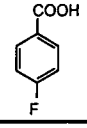
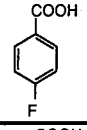
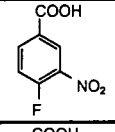
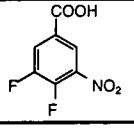
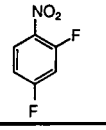
II.4.g.iv.2) 4-Fluorobenzoic Acid

The fluorination of 4-fluorobenzoic acid was also attempted in 90% nitric acid and the resulting products were characterised by ^{19}F nmr against the commercially available authentic materials. Further characterisation was achieved by converting the product mixture to a trimethylsilylated ester using BSA **(30)** and comparing the components by g.c. / m.s. to the previously prepared trimethylsilyl esters of the commercially available authentic materials. The 'blank' reaction performed without fluorine showed a 5% conversion to a nitrated product 4-fluoro-3-nitrobenzoic acid. Surprisingly, after workup and characterisation of the fluorination reaction all products

* 2-fluoronitrobenzene.

were found to be nitrated (see Table 42) indicating that fluorine had activated the nitration reaction.

Table 42: Fluorination of 4-Fluorobenzoic Acid in 90% Nitric at a Number of Fluorine to Substrate Ratios*.

Substrate : F_2 Ratio	Control+	1:2
	3.0g	11.5g
Isolated Material	2.9g	9.9g
Conversion	5%	100%
	2.8g	0.0g
	0.2g	2.2g
	-	4.7g
	-	0.8g
Unknowns	-	2.2g

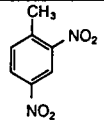
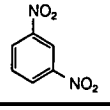
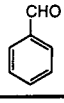
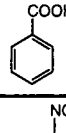
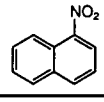
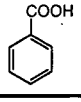
II.4.g.iv.3) Mechanism of Fluoronitration

Strong nitric acid, such as the 90% nitric acid used in the above reactions, contains dissolved NO_2 in excess of the amount that can be hydrated to $HNO_3 + NO$[190]. The fluorination of NO_2 with elemental fluorine is known and produces nitryl fluoride (NO_2F) a powerful nitrating agent[189,191,192]. Nitration with nitryl fluoride is presumed to go via the NO_2^+ ion, and hence products are similar in nature to those prepared with 'nitrating acid' i.e. mixed sulphuric and nitric acid. Hetherington and Robinson made a comprehensive study of the action of nitryl fluoride on organic compounds and these are summarised in Table 43[193].

*Mass of material determined by ^{19}F nmr against a standard of α,α,α-trifluoromethyltoluene.

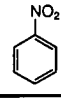
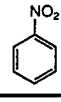
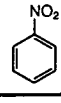
+ Reaction under identical conditions without the addition of elemental fluorine.

Table 43: The Nitration of Organic Compounds Using NO_2F.

Aromatic	Solvent	Product	Yield%
	-		65%*
	-		55%
	-		60%
	-		Trace
	-		Trace
	CS_2		35%
	CS_2	No Reaction	-

Reactions of *m*-Cresol, anisole, diphenyl ether, aniline, furan and quinoline with nitryl fluoride all gave tars. The work of Price and Shears allowed comparison between nitration using nitryl fluoride and nitryl chloride (See Table 44)[194].

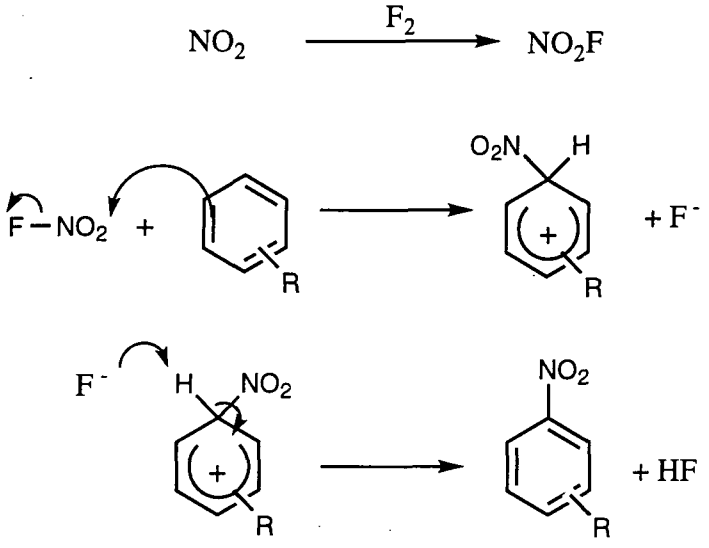
Table 44: The Nitration of Nitrobenzene With NO_2F and NO_2Cl.

Nitrating Agent	Aromatic	Solvent	Product	Yield%
NO_2Cl		-		27-35%
NO_2Cl		HF		70%
NO_2F		-		65%*

Nitryl fluoride is clearly a stronger nitrating agent, but interestingly reactions of nitryl chloride in HF show a large increase in reactivity. This is possibly due to the *in situ* formation of nitryl fluoride or a result of conducting the reactions in a extremely polar solvent such as HF. It therefore seems reasonable that the fluorination reactions in 90%

* Also *m*-dinitrobenzene <5%.

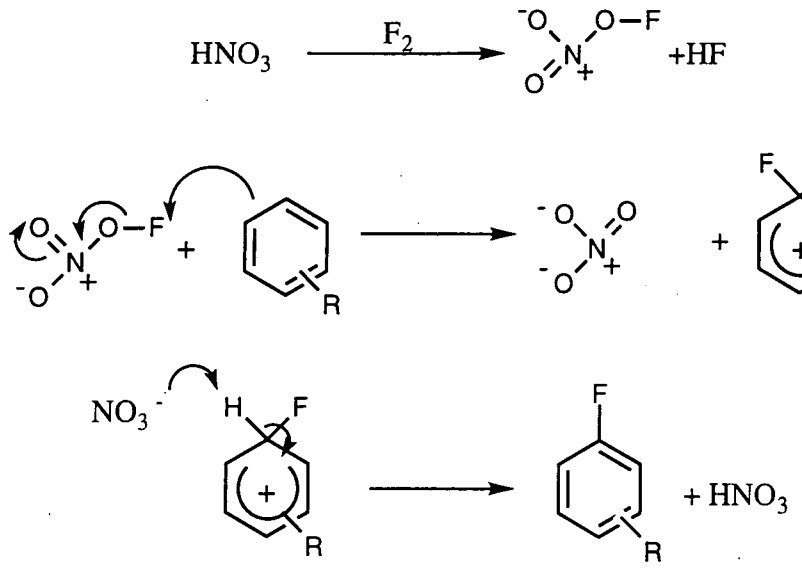
nitric acid could result in the formation of nitryl fluoride, which would then be responsible for the nitration of fluorobenzene and 4-fluorobenzoic acid via a mechanism as described below (**Scheme 24**).



Scheme 24

The mechanism of fluorination in nitric acid is as equally uncertain as the mechanism for fluorination in other strong acids, the question again being how far the formation of H-F proceeds before the formation C-F is completed (**Scheme 23**). However, in contrast to the fluorination of sulphuric acid, the fluorination of nitric acid with elemental fluorine is known and produces fluoronitrate ($FONO_2$)[192].

Fluoronitrate was isolated and characterised through the courageous work of Cady[195,196]. He prepared this explosive compound by bubbling dilute fluorine through nitric acid (concentrations upto 6N). The work was punctuated by explosions and the unpleasant physiological properties of the product. Many organic compounds such as ethanol and aniline were found to explode when contacted with fluoronitrate however, its *in situ* formation in very low concentrations relative to that of the substrate seems to have resulted in the moderation of its reactivity if formed during our fluorinations. A possible mechanism for fluorination involving fluoronitrate is described below (**Scheme 25**).

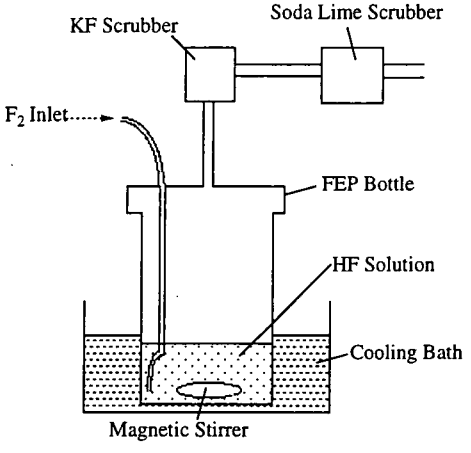


Scheme 25

II.4.g.v. Hydrogen Fluoride

Fluorination of 4-fluorobenzoic acid was attempted in various concentrations of HF. Due to the extremely corrosive nature of HF all the reactions were performed using an all FEP / PTFE apparatus (see Figure 9).

Figure 9: Apparatus for Fluorination in HF Solutions



II.4.g.v.1) 40%HF

Fluorination of 4-fluorobenzoic acid in 40% HF was unsuccessful. This was attributed to the low solubility of the aromatic substrate in the aqueous acid.

II.4.g.v.2). 62%HF

Fluorination of 4-fluorobenzoic acid in 62% HF was also unsuccessful. Again there was the problem of the low solubility of the aromatic substrate in the aqueous acid.

II.4.g.v.3). 100%HF

Fluorination of 4-fluorobenzoic acid in anhydrous HF was successful. Examination of the product by ^{19}F nmr showed a very extensive reaction had occurred producing a range of polyfluorobenzoic acids, including pentafluorobenzoic acid. The reaction also produced large amount of polymeric material making isolation impossible

II.4.g.vi. Fluorosulphuric Acid(100%)

The fluorination of 4-fluorobenzoic acid was then attempted in another strong acid, fluorosulphuric acid (HSO_3F). Again following workup, ^{19}F nmr confirmed a reaction similar to fluorination in anhydrous HF. Production of all the polyfluorobenzoic acids had clearly occurred but was again accompanied by a large amount of unknown material.

II.4.g.vii. Trifluoromethanesulphonic Acid(Triflic Acid)

Fluorination of 4-fluorobenzoic acid in triflic acid (CF_3SO_3H) under the same conditions used for the fluorination in fluorosulphuric acid resulted in an extensive reaction. Analysis by ^{19}F nmr confirmed that all possible polyfluorobenzoic acids were observed, but their formation was also accompanied by the production of a large amount of unidentifiable material which made further characterisation impossible.

II.4.g.viii. 'Super Acids'[175]

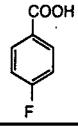
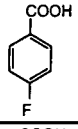
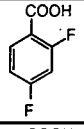
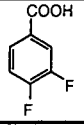
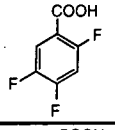
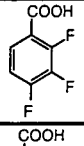
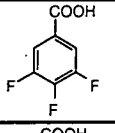
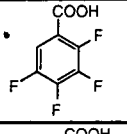
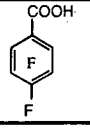
II.4.g.viii.1) Fluorination With a Solid Super Acid (Nafion)

A heterogenous fluorination of 4-fluoronitrobenzene with Nafion®, a solid superacid in the form of coated glass beads was also attempted[197] using dichloromethane as a solvent for the reaction but following work up, ^{19}F nmr confirmed that no fluorination reaction had occurred.

II.4.g.viii.2) Fluorination in Antimony Pentafluoride / HF

The fluorination of 4-fluorobenzoic acid was also attempted in both antimony pentafluoride and HF / antimony pentafluoride(1:1), two extremely strong acids[198]. Due to the corrosive nature of both of these liquids all reactions were performed in the PTFE / FEP apparatus (see Figure 9). The following results were obtained after work up (see Table 45).

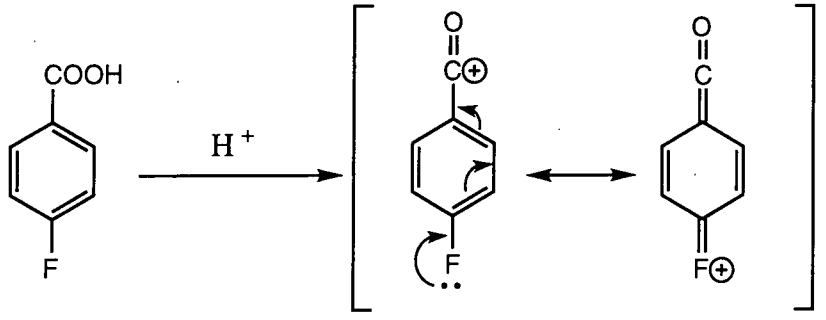
Table 45: Composition of Product after Fluorination of 4-Fluorobenzoic Acid* in Antimony Pentafluoride and HF / Antimony Pentafluoride(1:1) .

Solvent	SbF_5	HF/ SbF_5
	1.63g	1.63g
Isolated Material	1.6g	1.4g
Conversion	60%	69%
	40%	31%
	1.8%	0.1%
	24.8%	30.5%
	3.3%	0.7%
	4.5%	10.1%
	4.2%	5.9%
	4.2%	5.6%
	1.5%	0.8%
Unknowns	12.1%	15.3%

In contrast to the fluorinations of 4-fluorobenzoic acid in the three very strong acids (HSO_3F[199], HF[198] and CF_3SO_3F[200]), fluorination in antimony pentafluoride and HF / SbF_5 did not produce the high levels of unidentifiable material. Examination of the ratios of the polyfluorobenzoic acids indicated that the formation of 2,3,4-trifluorobenzoic and 3,4,5-trifluorobenzoic acids was favoured confirming that either the carboxylic acid group has been converted to a strongly deactivating and meta directing group and / or fluorine has been converted to a more strongly deactivating and

* Fluorine to substrate ratio of 2:1.

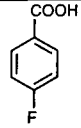
ortho directing group. Similar effects have been observed during the bromination of phenols in HF / SbF_5[201] and in the above case it seems likely that the formation of the 3,4,5-trifluorobenzoic acid is the result of conversion by the super acid solution of the -COOH group into the -COH^+OH group which is then lost to give the acylium ion (**Scheme 26**). This protonation would not only result in substitution predominantly meta to the protonated carboxylic acid group, but would also significantly deactivate the aromatic substrate, explaining the lower conversion and reduced formation of unidentifiable materials when compared to fluorination in other very strong acids such as triflic acid or AHF.



Scheme 26

Investigation by ^{13}C nmr into the effect of these 'super acids' on the substrate was also conducted (see Table 46). The data demonstrate that dissolving 4-fluorobenzoic acid in HF / SbF_5 results in large shifts in some of resonances, particularly the carbon of the carbonyl group. These shifts are consistent with protonation of the carbonyl group when attached to an aromatic ring and observed via ^{13}C nmr, as described by Olah *et al* [202].

Table 46: ^{13}C nmr Data for 4-Fluorobenzoic Acid in D_6-DMSO and HF/SbF_5.

	$\delta_C(D_6\text{-DMSO})$	$\delta_C(HF/SbF_5)$
3C	114.8	120.4
1C	126.7	81.6
2C	131.4	144.3
4C	164.3	176.6
C=O	165.8	153.5

II.5. Conclusions

i) The selective fluorination of deactivated systems has been demonstrated as readily achievable using elemental fluorine.

ii) Our work has demonstrated that the acidity of the solvent has a dramatic effect on the reaction with strong acids producing multiple fluorine substitution on even a deactivated aromatic substrate. The exception seems to be when the acid is of sufficient strength to protonate any substituent attached to the aromatic ring subsequently deactivating the aromatic substrate towards electrophilic attack.

iii) These results suggest that for most fluorinations it should be possible to correlate the strength of the electrophilic fluorinating species produced between an acid and elemental fluorine to the requirements for selectively fluorinating an aromatic species thus making selective fluorination of activated and deactivated aromatics possible.

iv) It has become clear from the work concerning fluorination in 90% nitric acid that fluorine can also have an activating effect on other electrophiles. Further work must be undertaken to determine if this activation can be extended to other electrophiles such iodine, bromine, chlorine, SO_3 or carbon electrophiles.

Chapter III. The Synthesis of Haloaromatic Compounds

III.1. Iodoaromatics

III.1.a. Introduction

Iodoaromatics have been used in organic synthesis for about 100 years. The incorporation of an iodine atom into an aromatic substrate usually allows substitution reactions to occur under relatively mild conditions, resulting in high yielding reactions which are often used in the formation of C-C or C-Heteroatom bonds. A number of these reactions are listed in Table 47.

Table 47: Use of Iodoaromatic Compounds in Organic Synthesis.

Reagent	Product	Reference
Δ/ Cu	Ar-Ar	203
Ar^2Cu	Ar^1-Ar^2	204
CF_3CO_2Na/ CuI	Ar-CF_3	205
CuCN	Ar-CN	206
PhSNa/ CuI	Ar^1-S-Ph	207
CF_3SCu	Ar^1-S-CF_3	208
CuSCN	Ar^1-S-S-Ar^1	209
Cl_2	Ar^1-ICl_2	210
XeF_2	Ar^1-IF_2	210
hv / PhH	Ar^1-Ph	209
"Ni"	Ar^1-Ar^1	211
"Pd"/ Ar^2MgBr	Ar^1-Ar^2	212
$Bu_4N^+Br^-$/ "Ni"	Ar^1-Br	213

More recently, iodoaromatic compounds have gained considerable importance in metabolism and radiolabelling studies. Thyroid hormones, amphetamines and corticosteroids have been investigated by using radio-iodine derivatives[214] making a simple method which inserts an iodine isotope highly desirable.

However, iodine is an extremely difficult halogen to incorporate and because of its low electrophilicity direct iodination is only effective with activated aromatic systems. Generally for iodination to occur an oxidising agent must normally be present to oxidise I_2 to a more powerful electrophile*. This inability to perform direct

* It is often stated that the function of the oxidising agent is to oxidise the liberated HI that would otherwise reduce the aryl iodide. However this statement is incorrect. See A. R. Butler, *J. Chem. Educ.*, 1971 **48**, 508.

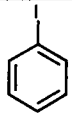
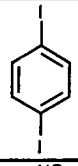
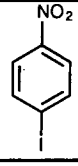
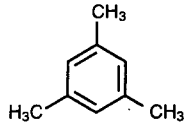
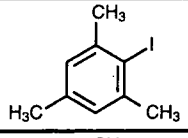
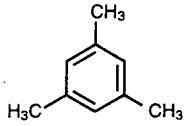
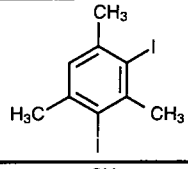
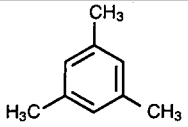
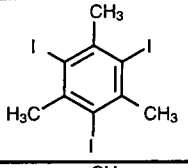
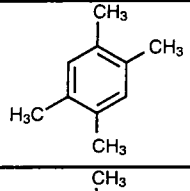
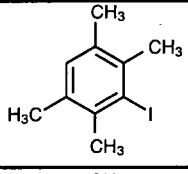
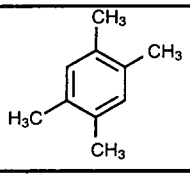
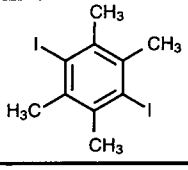
iodination in a fashion similar to fluorination, chlorination or bromination has prompted development of a large range of alternative methods of introducing iodine into organic molecules which have recently been the subject of a review by Merkuskev[215]. Some of the more recent or commonly used techniques are summarised below.

III.1.b. Common Syntheses of Iodoaromatics

III.1.b.i. Direct Iodination

Classically a mixture of concentrated nitric acid and concentrated sulphuric acid has proved to be a very useful oxidant in the iodination of aromatic compounds [Trokov-Novikov method]. Using this method alkylbenzenes, halobenzenes and oxygen containing aromatic compounds have all been successfully iodinated (see Table 48)[216]. Generally, iodinations in this system are carried out between 40°C and 100°C, with the oxidising solution added dropwise with vigorous stirring. Reactions at elevated temperatures also require the addition of a small volume of low boiling solvent such chloroform which washes sublimed iodine from the walls of the reactor back into the reaction mixture.

Table 48: Direct Iodination of Aromatic Compounds using I_2 / HNO_3 / H_2SO_4.

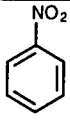
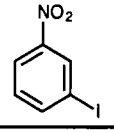
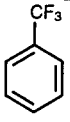
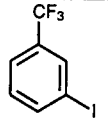
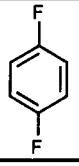
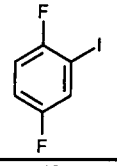
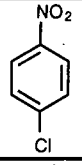
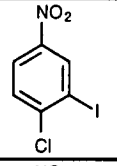
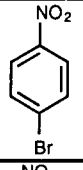
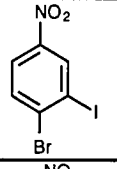
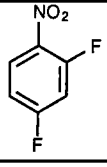
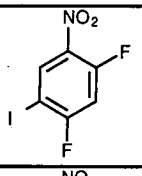
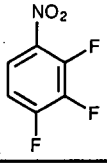
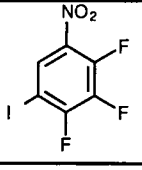
Arene	Aryl Iodide	Time(h)	Temp.(°C)	Yield (%)	Ref
		1	45	80	217
		1	110	45	218
		1.7	110	46	219
		2	r.t.	88	220
		3	70	80	220
		5	70	63	220
		1.5	r.t.	100	220
		3	70	88	220

At elevated temperatures, the presence of a relatively high ratio of nitric acid / sulphuric acid to aromatic compound also results in a significant amount of competing nitration, providing a possible one-step route to iodonitroaromatics. The simplicity of this iodination method coupled with the availability of the oxidising agents has insured that direct iodination is often the method of choice in both laboratory and industry[215].

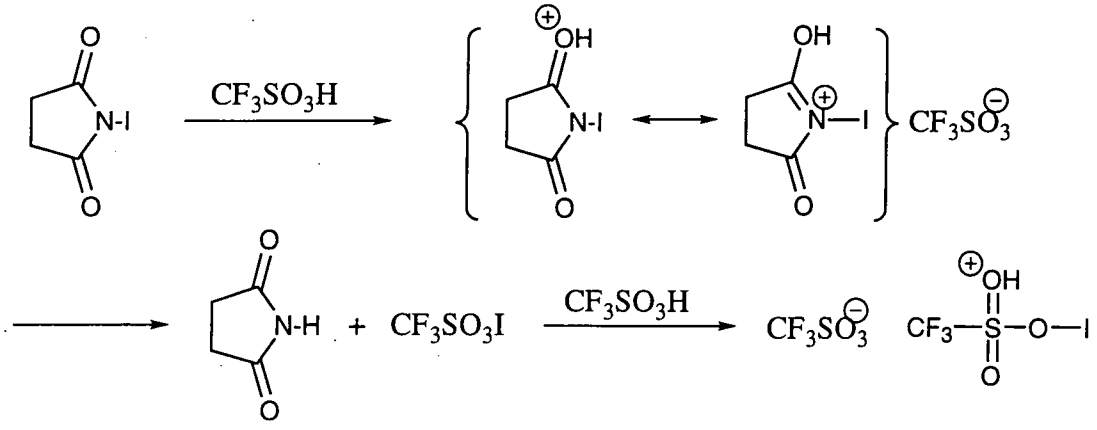
III.1.b.ii. Iodination Using *N*-Iodosuccinimide

Recently Olah *et al* demonstrated that deactivated aromatics could be iodinated using *N*-iodosuccinimide in the presence of trifluoromethanesulfonic acid (triflic acid) to give iodoarenes in good yields (see Table 49)[221].

Table 49: Iodination of aromatics using NIS / Triflic Acid.

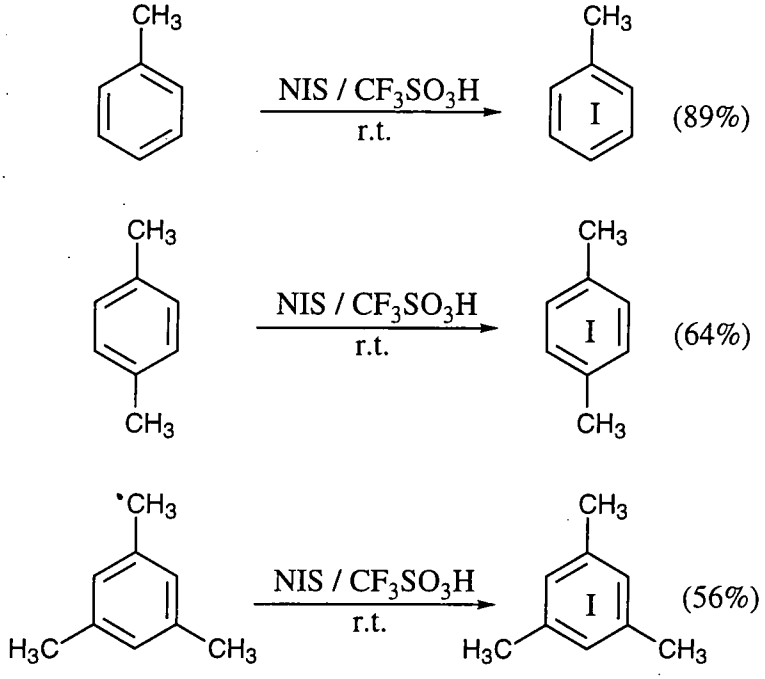
Arene	Aryl Iodide	Yield(%)
		85
		80
		83
		84
		80
		75
		60

A two molar equivalent of triflic acid was used to achieve nearly quantitative iodination of moderately deactivated arenes whereas a five fold excess of triflic acid was generally necessary to achieve satisfactory iodination of more severely deactivated arenes such as halo or polyhalonitrobenzenes. Olah *et al* suggested the iodination involved the *in situ* generation of protosolvated iodine (1) trifluoro-methanesulfonate **(Scheme 27)**.



Scheme 27

The NIS / triflic acid system is also an efficient method for the preparation of periodo-aromatics **[E-36]**[222].

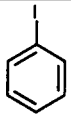
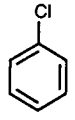
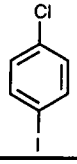
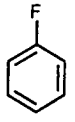
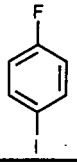
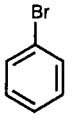
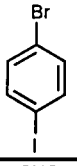
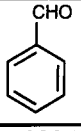
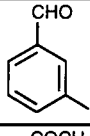
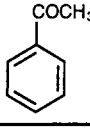
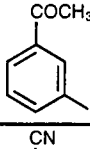
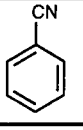
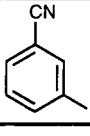


[E-36]

III.1.b.iii. Aromatic Iodination Using Iodine Fluoride

Recently Rozen *et al* described a method for the incorporation of iodine into organic molecules using iodine monofluoride (IF), preformed via the reaction of iodine and 10% fluorine in $CFCl_3$ at -78°C[223]. In a later publication, Rozen *et al* iodinated a range of aromatic compounds and demonstrated that, depending on reaction temperature and time, iodination of aromatic molecules was possible without the presence of Friedel-Crafts catalysts (see Table 50)[224].

Table 50: The Iodination of Aromatics Using a Preformed IF Solution.

Arene	Aryl Iodide	Temp.	Yield(%)
		-78	95+
		-20	98
		-20	85
		-20	90
		25	85
		25	35
		25	90

Sensitive groups, such as aromatic aldehydes remained intact, possibly due to IF being a weak oxidiser. However, nitrobenzene a more deactivated molecule was recovered unchanged after 24 hrs at room temperature and strongly activated rings, such as phenol or anisole, suffered destruction when added to the IF solution at temperatures as low as -78°C.

III.1.c. Iodination of Aromatics Using Elemental Fluorine

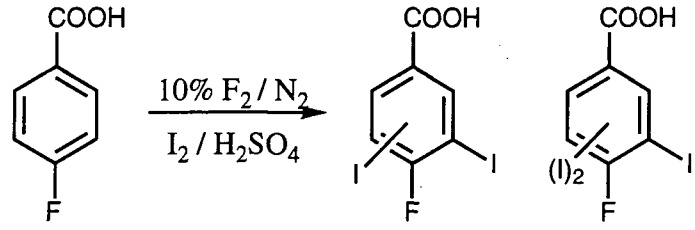
III.1.c.i. Initial Reactions

Earlier work concerning the direct fluorination of aromatics had demonstrated that the passage of fluorine through a strong acid such as H_2SO_4 had produced an extremely powerful electrophilic fluorinating agent. In a similar fashion, the passage of fluorine through 90% nitric acid had also produced a powerful nitrating agent in addition to a fluorinating agent. We then investigated the effect of a combination of

+ 30% conversion to product.

sulphuric acid and fluorine on the halogenation of an aromatic species using another elemental halogen to assess if a similar activation could be achieved.

The initial reaction was performed using 4-fluorobenzoic acid and an excess of iodine in 98% sulphuric acid **[E-38]**. Following the passage of fluorine through the mixture, work up and analysis by a combination of ^{19}F nmr g.c. / m.s. and m.s. confirmed that upto three iodine atoms had been inserted into 4-fluorobenzoic acid.



Conversion 100%

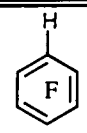
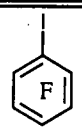
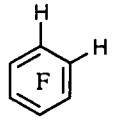
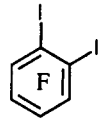
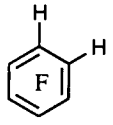
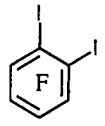
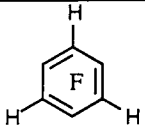
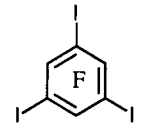
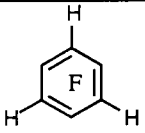
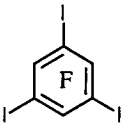
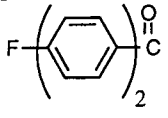
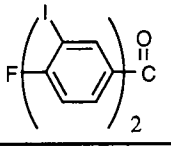
[E-38]

This high level of iodine substitution into a deactivated aromatic system confirmed that fluorine could be used to activate aromatic iodination. Further investigation was then focused on adapting the conditions to allow selective iodination or polyiodination of an aromatic substrate.

III.1.c.ii. Iodination of Polyfluorobenzenes

The iodination reaction was further examined using polyfluorobenzenes as substrates. The reactions were performed at room temperature with a slight excess of I_2 (see Table 51). Following reaction, workup was achieved by pouring into an ice / metabisulphite ($Na_2S_2O_5$) solution followed by extraction with dichloromethane. Recrystallisation or distillation produced the pure iodoaromatic. All iodination reactions went to complete conversion.

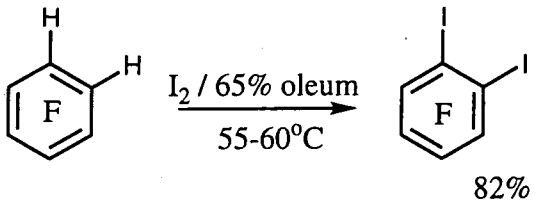
Table 51: The Iodination of a Number of Polyfluorobenzenes.

S.M.	Product	Conditions	Yield
		r.t., H_2SO_4, 1.2eq F_2 1.2eq I_2	55%
		r.t., H_2SO_4, 2.2eq F_2 2.2eq I_2	66%
		r.t., H_2SO_4, 113*, 2.2eq F_2 2.2eq I_2	76%
		r.t., H_2SO_4, 113*, 2.2eq F_2 2.2eq I_2	86%
		r.t., H_2SO_4, 3.2eq F_2 3.2eq I_2	39%
		r.t., H_2SO_4, 113*, 2.2eq F_2 3.2eq I_2	63%
		r.t., H_2SO_4, 2.2eq F_2 3.2eq I_2	38%

The results demonstrated that the production of fluoroiodoaromatics, which are difficult to obtain via other routes (eg. 1,2,3,4-tetrafluoro-5,6-diiodobenzene **[E-39]**[225]), is relatively simple using this methodology. It is also clear that the reduction of the volume of sulphuric acid in the reaction mixture by the use of a co-solvent such as CF_2ClCCl_2F[+] resulted in an improvement in yield relative to the reactions performed in neat 98% sulphuric acid.

* Reaction mixture contained 120ml H_2SO_4 and 30ml CCl_2FCF_2Cl.

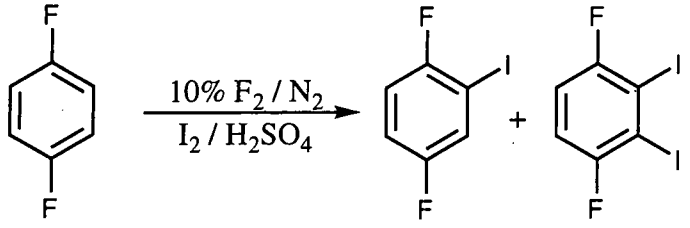
+ Note: 113 (CF_2ClCCl_2F) is immiscible with H_2SO_4.



82%

[E-39]

However the extremely electrophilic source of iodine produced by the passage of fluorine through 98% sulphuric acid and iodine proved too activated for the selective iodination of some less deactivated substrates **[E-40]**.



Composition 59% 41%

Conversion 100%

[E-40]

Attempted distillation of this mixture resulted in extensive decomposition of the products making separation impossible and highlighting the need to produce one iodinated product.

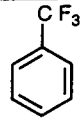
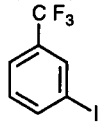
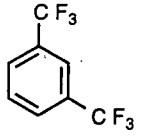
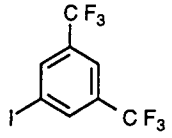
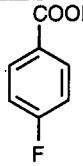
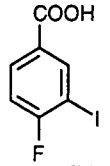
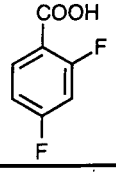
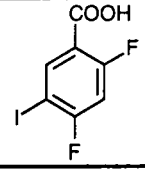
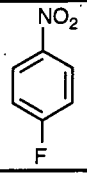
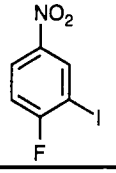
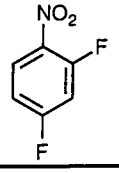
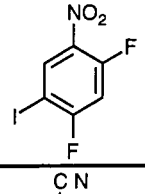
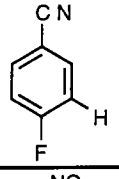
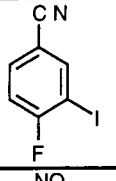
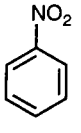
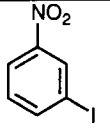
III.1.c.iii. Iodination of a Range of Aromatics

Further investigation was made into the iodination process using a larger range of aromatics to assess the suitability of other functional groups. In all reactions the conversion to the monoiodinated product was 100% (see Table 52). Following reaction, workup was achieved by pouring into an ice / metabisulphite ($Na_2S_2O_5$) solution and running off the CF_2ClCCl_2F* followed by extraction with dichloromethane. The products were then isolated by distillation or recrystallisation. In all the following reactions the quantity of iodine used was halved relative to the reactions of the polyfluorobenzenes.

---

* The CF_2ClCCl_2F contained some iodinated product. Simple rotary evaporation allowed recovery of the CF_2ClCCl_2F and isolation of the crude product which was combined with the crude product obtained by extraction with dichloromethane.

Table 52: The Iodination of a Range of Aromatics

S.M.	Product	Conditions	Yield(%)
		r.t., H_2SO_4, 113*, 1.2eq F_2 0.6eq I_2	83%
		r.t., H_2SO_4, 113*, 1.2eq F_2 0.6eq I_2	83%
		r.t., H_2SO_4, 113*, 1.2eq F_2 0.6eq I_2	59%
		r.t., H_2SO_4, 113*, 1.2eq F_2 0.6eq I_2	77%
		r.t., H_2SO_4, 113*, 1.2eq F_2 0.6eq I_2	70%
		r.t., H_2SO_4, 113*, 1.2eq F_2 0.6eq I_2	84%
		r.t., H_2SO_4, 113*, 1.2eq F_2 0.6eq I_2	84%
		r.t., H_2SO_4, 1.2eq F_2 0.6eq I_2	51%

The results demonstrated that this method is extremely effective in the production iodoaromatics that are difficult to prepare via other methodologies. Of particular interest are the iodinations of 2,4-difluorobenzoic acid and 2,4-difluoronitrobenzene which resulted in the formation of only one of the two possible isomers. This was in contrast to fluorination of the same substrates which produced both isomers in a 3:1 ratio of 5-isomer to 3-isomer (see Chapter II). The addition of CF_2ClCCl_2F to the reaction mixture as a co-solvent again improved the yields. We

* Reaction mixture contained 120ml H_2SO_4 and 30ml CCl_2FCF_2Cl.

believe this is simply because decreasing the volume of concentrated H_2SO_4 makes extraction into an organic solvent easier during the workup.

III.1.c.iv. Effect of Solvent on the Iodination Process

III.1.c.iv.1) The Use of Co-Solvents

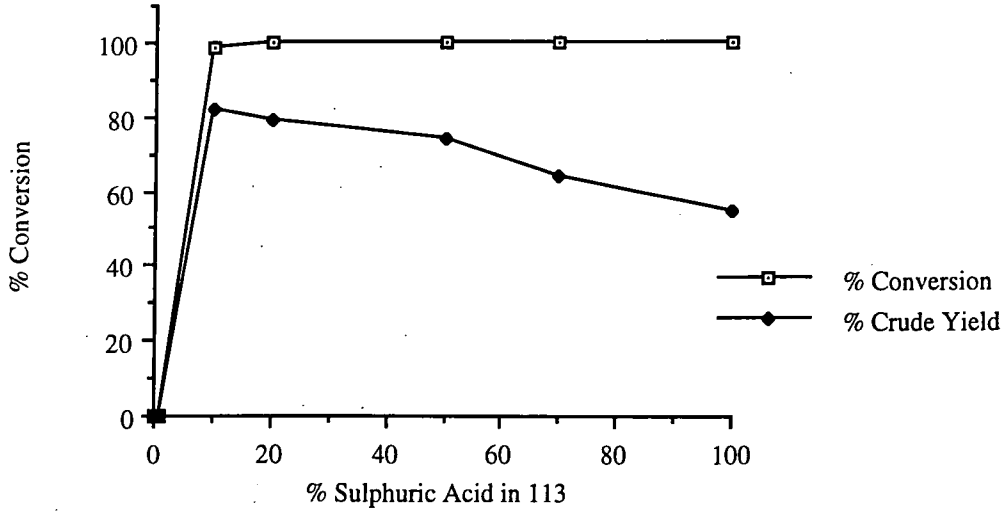
Following the earlier work which had demonstrated that the addition of CF_2ClCCl_2F had a beneficial effect on the iodination reaction, a series of iodination reactions were undertaken to determine the optimum volume of CF_2ClCCl_2F. This was done by performing a series of iodinations of nitrobenzene at a range of ratios of CF_2ClCCl_2F : H_2SO_4 and comparing the conversion and crude yield for each separate iodination reaction (see Table 53).

Table 53: The Iodination of Nitrobenzene using CF_2ClCCl_2F as a Co-solvent.

% CF_2ClCCl_2F v/v	% H_2SO_4 v/v	Conversion (%)	Crude Yield (%)
100	0	0	0
99	1	0	0
90	10	98.4	82
80	20	100	79
50	50	100	74
30	70	100	64
0	100	100	55

Graphical representation of these results shows that approximately 10% H_2SO_4 by volume produced the highest conversion and yield in the iodination reactions (see Graph 7).

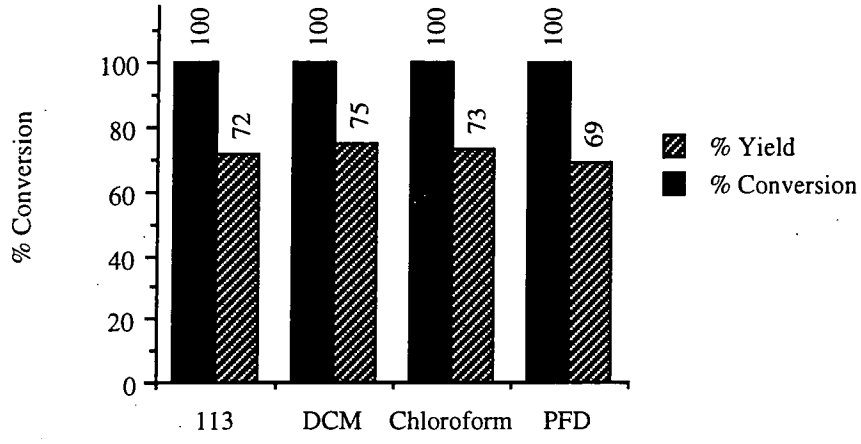
Graph 7: The Iodination of Nitrobenzene Using 113 as a Co-Solvent



This low level of sulphuric acid relative to the overall volume of the reaction mixture makes this methodology even more applicable to large scale production of iodoaromatics. Relative to other routes, the low level of waste and by-products resulting from an iodination run in 10% v / v sulphuric acid coupled with the low cost of elemental fluorine and elemental iodine should make this one of the better routes to iodoaromatics.

The use of other co-solvents in the iodination process was also investigated. This was again done by running an identical series of iodinations of nitrobenzene with a 1:1 mixture of co-solvent* and H_2SO_4 (see Figure 10).

Figure 10: The Use of Co-Solvents in the Iodination of Nitrobenzene



The results confirmed that all the investigated solvents produced near identical reactions, differing little from the reactions using CF_2ClCCl_2F as a co-solvent. Perfluorodecalin¥ (PFD) is prefered as a co-solvent because of its easy recovery from the reaction mixture, but more importantly because its use after 1995 is not banned by the Copenhagen Agreement.

III.1.c.iv.2) Effect of Acid Strength on the Iodination Process.

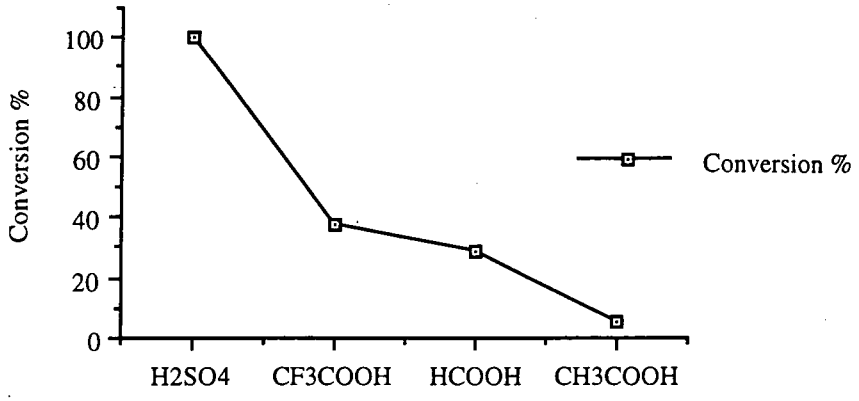
An investigation was made into the role of acid in the iodination process. The work concerning co-solvents had already demonstrated acid was necessary but we determined to find what strength of acid was required to produce the activating effect on the iodination process. This was investigated by performing a series of iodinations of α,α,α-trifluorotoluene under the standard conditions, in a number of mineral and organic acids (see Graph 8).

---

* 113- CF_2ClCCl_2F; DCM- CH_2Cl_2; PFD- $C_{10}F_{16}$.

¥ When the reaction mixture was added to the ice/metabisulphite solution pure PFD separated out allowing its easy recovery from the reaction mixture.

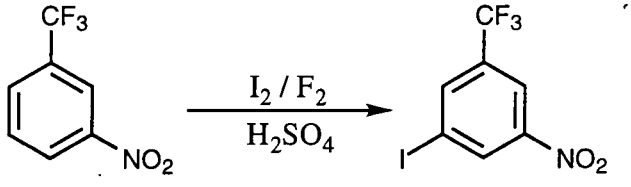
Graph 8: The Iodination of Trifluorotoluene in a Range Of Acids



The results clearly show the acidity of the system is extremely important and the ability to iodinate is clearly linked to the pk_a value (see Graph 4). This suggests that for the iodination of more activated systems eg. 1,4-difluorobenzene simple tailoring of the acid strength could result in the selective iodination making this methodology applicable to both activated and deactivated systems.

III.1.c.v. Limitations of the Iodination Methodology

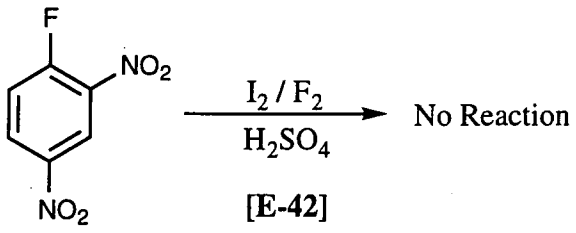
Earlier work had demonstrated that this iodination methodology using 98% sulphuric acid was limited towards the iodination of activated aromatics. The iodination of a range of very deactivated aromatics were also attempted to find the limitations of the iodination methodology towards deactivated aromatics. The iodination of 3-trifluoromethylnitrobenzene under the standard conditions showed only a 14% conversion to the iodinated product, 3-nitro-5-trifluoromethyliodobenzene **[E-41]**.



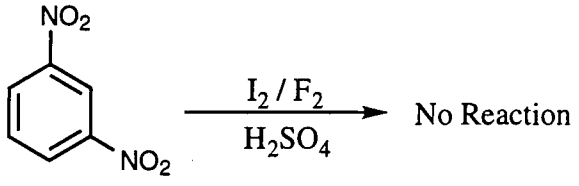
14% Conversion

[E-41]

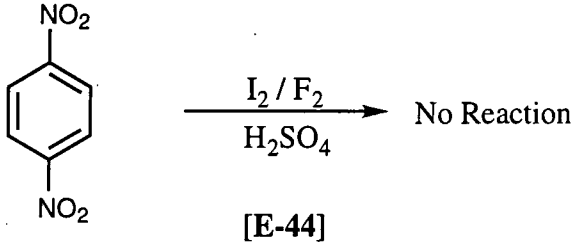
The attempted iodination of Sanger's Reagent (2,4-dinitrofluorobenzene) **[E-42]**, 1,3-dinitrobenzene **[E-43]** and 1,4-dinitrobenzene **[E-44]** produced no iodinated products.



[E-42]



[E-43]



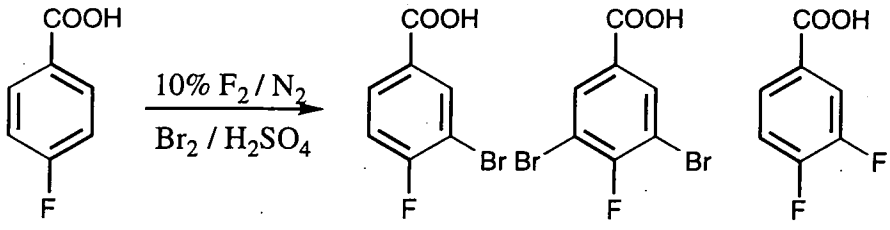
[E-44]

Further investigation could be made into the effect of a stronger acids such as fluorosulphuric or triflic acid. It seems likely that increasing the strength of the acid would result in the formation of a more powerful *in situ* iodinating species, as observed with fluorination in acids stronger than sulphuric acid (see Chapter II), making iodination of extremely deactivated aromatics possible and further extending the utility of the the iodination methodology.

III.2. Bromination of Using Elemental Fluorine

III.2.a. Initial Reaction

In a similar fashion to the initial iodination reaction, 4-fluorobenzoic acid was used for an investigation into the effect of elemental fluorine on direct bromination. Following the passage of fluorine through a mixture of 4-fluorobenzoic acid, bromine and sulphuric acid **[E-45]** analysis confirmed that substitution of upto 2 bromine atoms had occurred. This indicated that elemental fluorine could also be used to activate aromatic bromination.



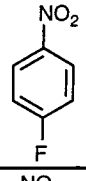
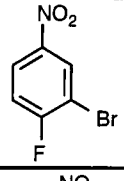
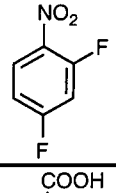
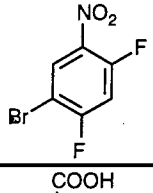
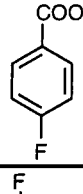
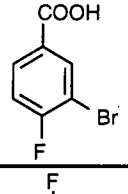
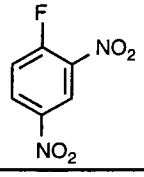
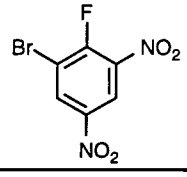
Conversion 77%

[E-45]

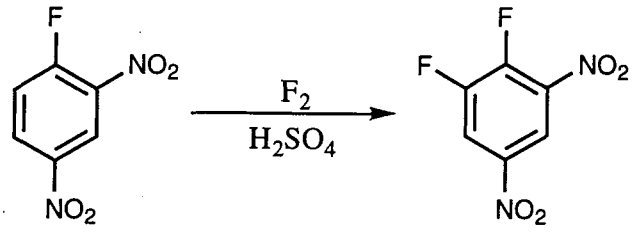
III.2.b. Bromination of a Range of Aromatics

A number of bromination reactions were performed under identical conditions to those used for the iodination reactions. The brominations were also worked up under an identical procedure to the iodination reactions and purification was achieved by distillation or recrystallisation. Complete conversion of the aromatics to bromoaromatics was observed in all the reactions (see Table 54).

Table 54: Bromination of a Range of Aromatics.

S.M.	Product	Conditions	Yield(%)
		r.t., H_2SO_4, 0.6eq Br_2 1.2eq F_2	59
		r.t., H_2SO_4, 0.6eq Br_2 1.2eq F_2	65
		r.t., H_2SO_4, 0.6eq Br_2 1.2eq F_2	65
		r.t., H_2SO_4, 0.6eq Br_2 1.2eq F_2	60

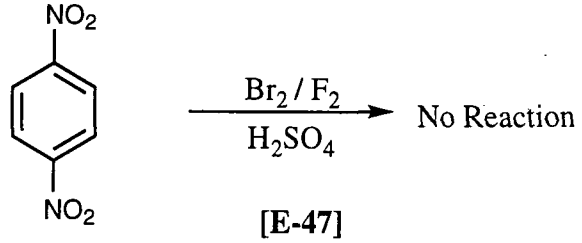
The species produced by the passage of fluorine through bromine and sulphuric acid proved to be extremely powerful. The fluorination of Sanger's Reagent (2,4-dinitrofluorobenzene)**[E-46]** under identical conditions used for the bromination produced a conversion of only 9% compared to a conversion of 100% for the bromination reaction. The earlier iodination of Sanger's Reagent under similar conditions failed to produce any reaction **[E-42]**.



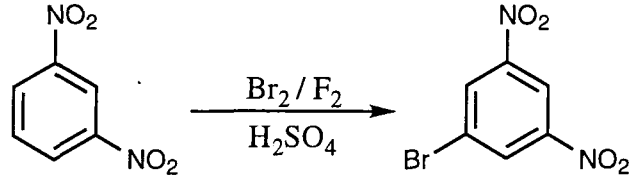
[E-46] 9% Conversion

III.2.c. Limitations of the Bromination Methodology

In a similar fashion to the investigation of the iodination system, the limitation of the bromination system using sulphuric acid was also investigated. The attempted bromination of 1,4-dinitrobenzene **[E-47]** produced no brominated product. Bromination of 1,3-dinitrobenzene **[E-48]** produced a 48% conversion to the brominated product, 1,3-dinitro-5-bromobenzene.



[E-47]



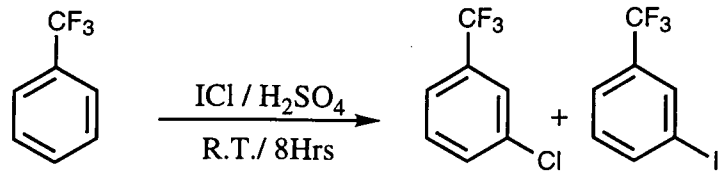
48% Conversion

[E-48]

III.3. Reactions of Interhalogen Compounds

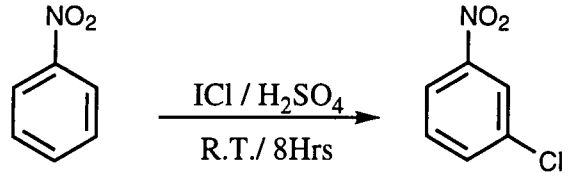
III.3.a. Iodine Monochloride

The effect of fluorination on halogenation with an interhalogen, iodine monochloride, was also investigated. A series of reactions were performed producing the following results **[E-49]**

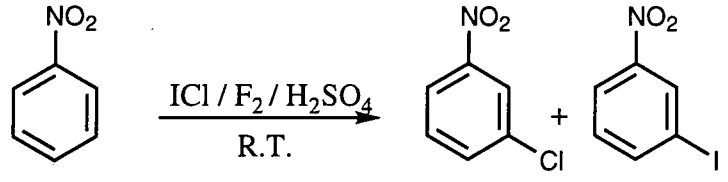


Composition 60 : 24

Conversion 83%



Conversion 9%



Composition 44 % : 45 %

Conversion 100%

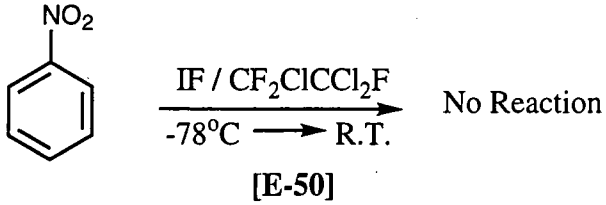
[E-49]

In the above fluorination of nitrobenzene using iodine monochloride and sulphuric acid activation of the electrophilic substitution has again been observed. Interestingly, when an interhalogen is used as the halogen source we observed incorporation of both halogens. Theoretically the activation of direct chlorination would be possible but would provide a number of practical difficulties, it is therefore possible that an interhalogen could be used to effect chlorination using the our methodology.

III.4. Mechanism of Halogention Using Elemental Fluorine

III.4.a. Reaction of Preformed IF without Acid

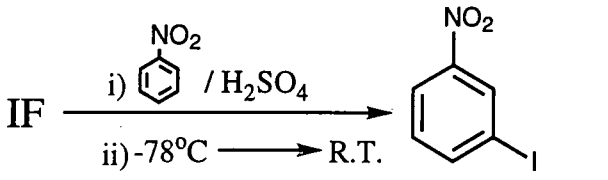
Previously Rozen *et al* had demonstrated that preformed IF did not react with deactivated aromatics such as nitrobenzene[224]. Repeating this attempted iodination of nitrobenzene **[E-50]** confirmed that preformed IF does not react with nitrobenzene even when warmed to room temperature.



[E-50]

III.4.b. Reaction of Preformed IF with Acid

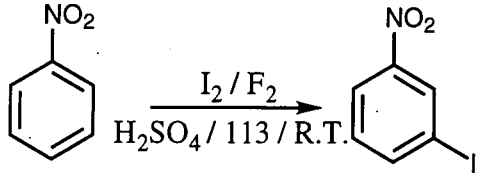
When preformed IF was reacted with with nitrobenzene dissolved in sulphuric acid **[E-51]** a low level of conversion to 3-iodonitrobenzene was observed.



12% Conversion

[E-51]

In contrast to the above two reactions, the iodination of nitrobenzene using our described methodology **[E-52]** produces 3-iodonitrobenzene in high conversion and high yield.

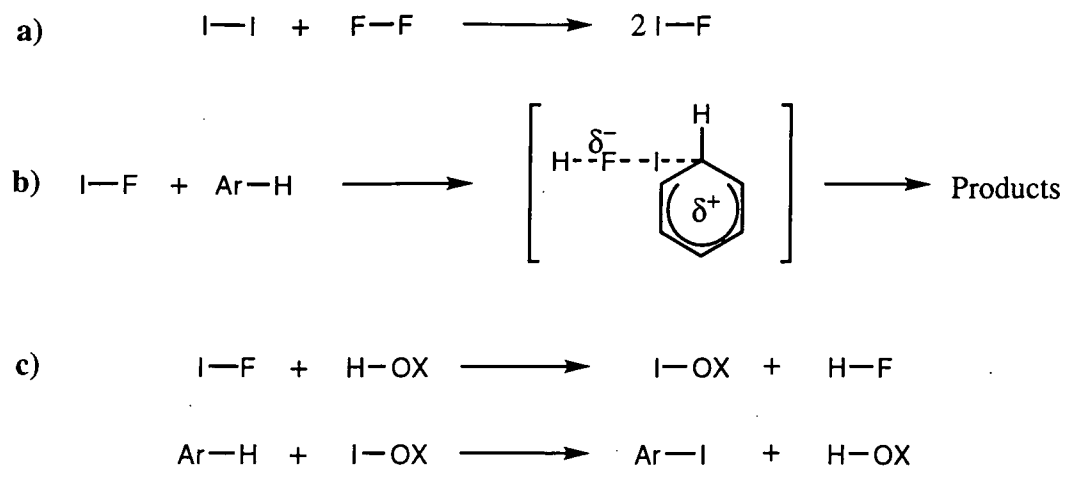


74% Yield

[E-52]

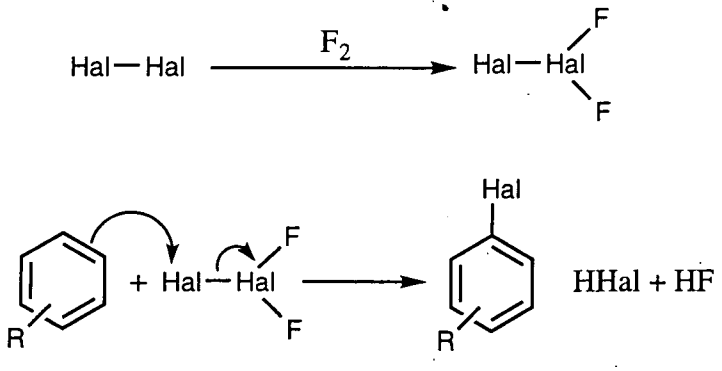
III.4.c. Conclusion

The described reactions between nitrobenzene and preformed iodine monofluoride confirms that preformed iodine monofluoride does not react with nitrobenzene in an aprotic solvent. However, the reactions between nitrobenzene and preformed iodine monofluoride do not exclude the acid catalysed reaction of iodine monofluoride with the aromatic substrate. In this type of mechanism there is the remaining question of how far the HF formation would proceed before the formation of the carbon-halogen bond. In a similar fashion to the mechanism postulated for fluorination (**Scheme 23**) one could envisage there being two extremes (**Scheme 28**). Following formation of the iodine monofluoride **a**), in mechanism **b**) the protonic acid is involved in the further polarisation of the halogen monofluoride in the reaction mixture. In mechanism **c**), the reaction of iodine monofluoride and protonic acid produces an *in situ* haloxy compound which then halogenates the substrate.



Scheme 28

It is also necessary to consider that the passage of fluorine through the elemental halogen and sulphuric acid could also result in the formation of a hypervalent halogen species. In this system, if formed, $HalF_2^-$ could act as a better leaving group than Hal^- thus producing a more powerful electrophile (**Scheme 29**). However, when the stoichiometry, conversions and yields of the iodination and bromination reactions are considered it is clear that all the available halogen atoms are substituted onto the aromatic during the reactions, making the formation of large quantities of a hydrogen halide impossible. Also, the reactions involving iodine monochloride confirmed that both chlorine and iodine atoms are substituted onto the aromatic during the reactions making a mechanism involving a hypervalent species seem quite unlikely.



Scheme 29

III.5. Fluorination of Iodoaromatics

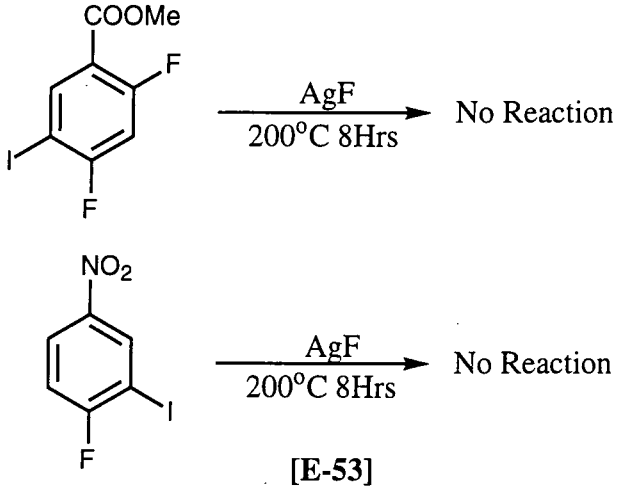
III.5.a. Introduction

Much of the earlier work concerning fluorination had been direct towards the synthesis of 2,4,5 and 2,3,4 trifluorinated substituted aromatics. Investigation had demonstrated that their synthesis was possible by fluorination, but resulted in a mixture

of both possible isomers along with a range of other fluorinated aromatics (See Chapter II). The iodination of substrates such as 2,4-difluorobenzoic acid and 2,4-difluoronitrobenzene had been shown to be selective in the production of 2,4-difluoro-5-iodo compounds in high conversion and equally high yield. We undertook to determine if these iodoaromatics could be fluorinated to produce the trifluorinated derivatives providing a more effective route to these industrially important substrates[174].

III.5.b. Fluorination with Silver Fluoride

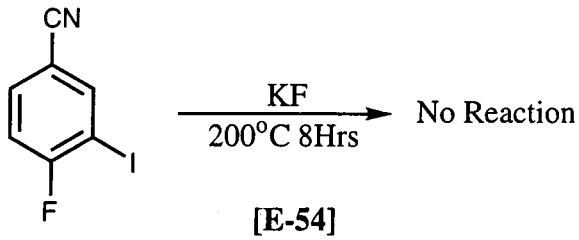
Classically AgF is used in organic chemistry to replace halogens with fluorine in a variety of substrates[226]. These reactions can be carried out under relatively mild conditions so even sensitive compounds such as halogenoesters can be fluorinated, halogen exchange with silver fluoride has also been described with some aromatic derivatives[227]. A number of attempted fluorinations with AgF confirmed that it could not be used to fluorinate our deactivated iodoaromatics **[E-53]**.



[E-53]

III.5.c. Fluorination with Potassium Fluoride

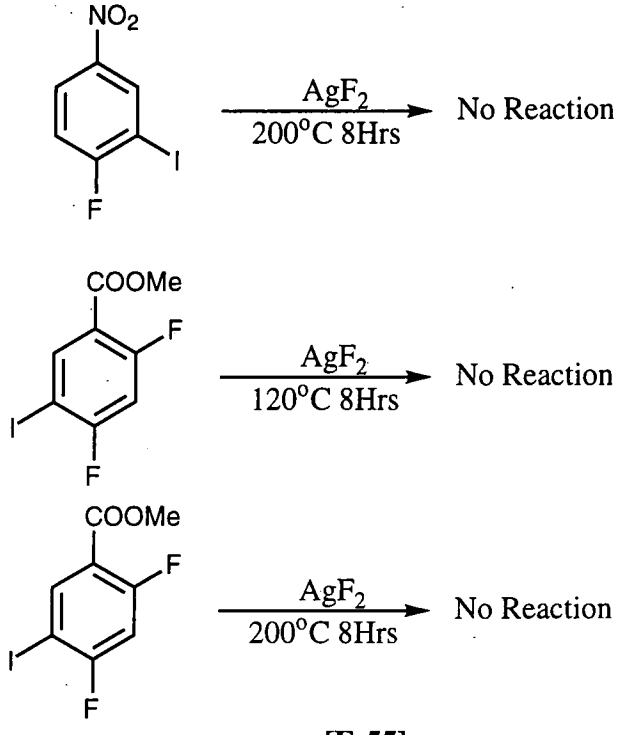
The fluorination of 4-fluoro-3-iodobenzonitrile was attempted to determine if the iodine atom could simply be replaced by heating with KF. Following reaction and workup it was clear that replacement was not possible with KF **[E-54]**.



[E-54]

III.5.d. Fluorination with Silver Difluoride

In contrast to AgF, high valency metal fluorides such as AgF_2 are powerful fluorinating agents capable of replacing even very unreactive halogens by fluorine though they are rarely used for this purpose[226,228]. A number of fluorinations were attempted with AgF_2 **[E-55]**.



[E-55]

In all the above reactions no fluorination was observed. However during the fluorination of 4-fluoro-3-iodobenzonitrile trace amounts of difluorobenzene were detected by g.c. / m. s. suggesting that a small amount of fluorination and elimination of the nitrile functionality had occurred **[E-56]**.

[E-56]

III.6. Perfluoroalkylation Reactions

III.6.a. Introduction

In recent years, a great deal of interest has been directed towards compounds containing perfluoroalkyl groups[229]. Generally, these compounds have high thermal and

chemical stability while the perfluoroalkyl group also increases lipophilicity, making it a particularly attractive substituent for pharmaceutical and agrochemical products. The perfluoroalkyl substituent, and in particular the trifluoromethyl group, is physically very small since both carbon and fluorine are small first row elements, producing little steric requirement compared to a trichloromethyl group. A perfluoroalkyl group also has a high electronegativity, similar to that of oxygen[230], and is very hydrophobic. Finally,the strength of the C-F bond confers an extra stability on the molecule.

The first known trifluoromethylated compound, α,α,α-trifluorotoluene, was reported by Swarts in 1898. Over the following sixty years few new methods were developed for the production of perfluoroalkylated compounds, with most progress being made in the last thirty years. However, when compared to other synthetic methodologies the means of incorporating perfluoroalkyl substituents are relatively limited. Generally these methods of preparation may be divided into four groups.

i) The conversion of a trisubstituted methyl group (CX_3) into a trifluoromethylated group[231,232].
ii) The use of trifluoromethylcopper[233].
iii) Reactions involving trifluoromethyl radicals[226].
iv) Other methods (eg. trifluorometylcations[234,235] and reactions of trifluoromethyl trialkylsilanes[236]).

III.6.b. Trifluoromethylation Using Sodium Trifluoroacetate

Recently an effective method for the perfluoroalkylation of iodoaromatic compounds has been described which involves the decarboxylation of sodium trifluoroacetate in a copper assisted process (**Scheme 30**)[237-239].

$$ArI + CF_3CO_2Na + CuI \xrightarrow{i} ArCF_3$$

i, *N*-methylpyrrolidin-2-one, N_2, 160°C, 4 h

Scheme 30

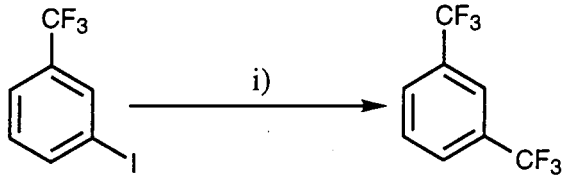
Until now, this procedure has been limited by the availability of iodoaromatic substrates but its combination with our iodination methodolgy should provide an excellent route to perfluoroalkylated aromatics.

III.6.b.i Aromatics Containing No Fluorine Atoms

The substrates were heated at 160°C with vacuum dried copper(I) iodide and sodium trifluoroacetate in NMP (*N*-methylpyrrolidin-2-one) for upto 5 hours under a nitrogen atmosphere. The reactions were followed by g.c./ m.s. which was also used to confirmed the identity of the products via its library searching facility.

III.6.b.i.1) 3-Iodotrifluorotoluene

The trifluoromethylation of 3-iodotrifluoromethylbenzene was successful producing bis-1,3-trifluoromethylbenzene **[E-57]**.

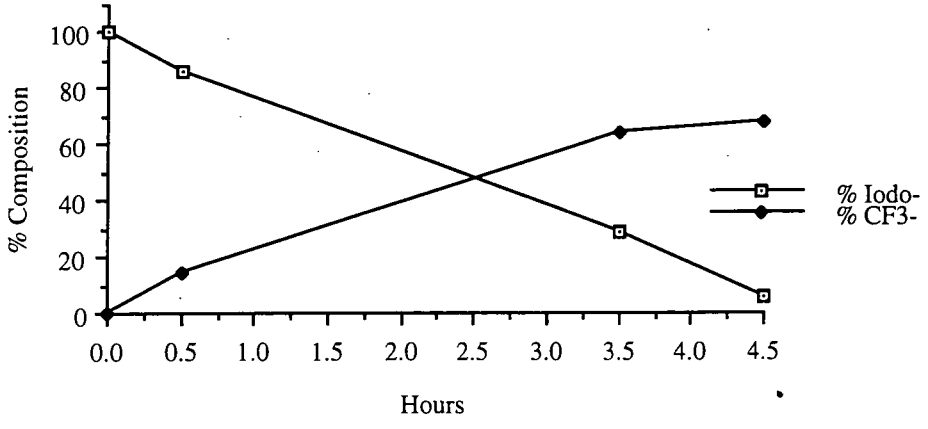


i) CF_3COONa / CuI / NMP / 160°C / N_2

[E-57]

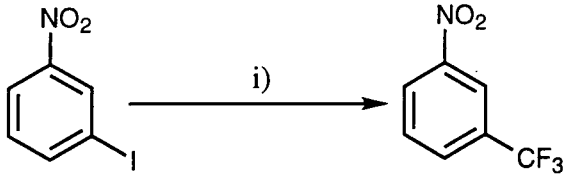
During the trifluoromethylation of 3-iodotrifluoromethylbenzene no products indicative of Ullman Coupling were observed. Trifluoromethylbenzene, indicative of reductive dehalogenation was however observed (See Graph 9).

Graph 9: The Trifluoromethylation of 3-Iodotrifluoromethylbenzene



III.6.b.i.2) 3-Iodonitrobenzene

Trifluoromethylation of 3-iodonitrobenzene **[E-58]** was also successful under the standard conditions.



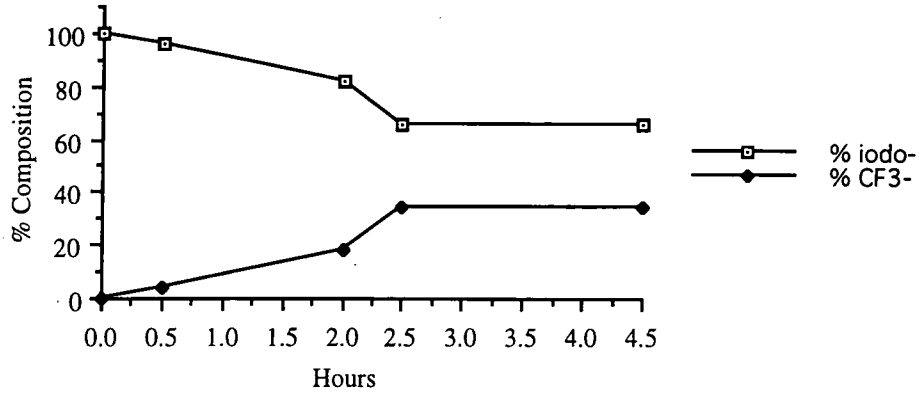
i) CF_3COONa / CuI / NMP / 160°C / N_2

[E-58]

The low overall conversion was unexpected when considering the suggested nucleophilic character of the trifluoromethyl species[239] and suggests that some form of

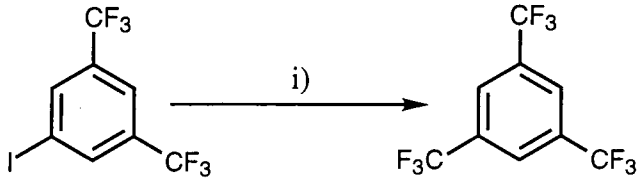
complexation is occuring between a copper species and the 3-iodonitrobenzene which inhibits reactivity (See Graph 10).

Graph 10: The Trifluoromethylation of 3-Iodonitrobenzene



III.6.b.i.3) 1,3-Bistrifluoromethyl-5-iodobenzene

Trifluoromethylation of 1,3-bistrifluoromethyl-5-iodobenzene was successful **[E-59]**. However the product *tris* -1,3,5-trifluoromethylbenzene proved to be too volatile to allow the reaction to be followed by g.c./ m.s.



i) CF_3COONa / CuI / NMP / 160°C / N_2

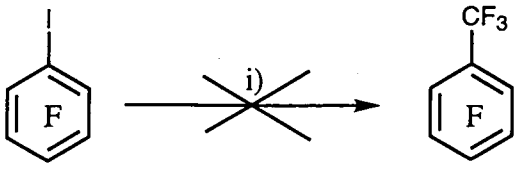
[E-59]

III.6.b.ii. Fluoroaromatics

Carr *et al* observed that when fluoroaromatics were used as substrates in the perfluoroalkylation reaction the substrates were not perfluoroalkylated but underwent Ullmann coupling and reductive dehalogenation[238]. A number of polyfluoropolyiodobenzenes were investigated as substrates to determine if perfluoroalkylation was possible.

III.6.b.ii.1) Iodopentafluorobenzene

In contrast to the work described by Carr *et al* prolonged heating of 6-iodo-1,2,3,4,5-pentafluorobenzene under the conditions described in the original paper **[E-60]** resulted in the formation of no perfluoroalkylated products or coupled products[238].

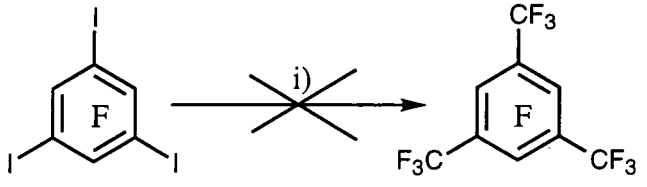


i) CF_3COONa / CuI / NMP / 160°C / N_2

[E-60]

III.6.b.ii.2) 1,3,5-Trifluoro-2,4,6-triiodobenzene

Attempted perfluoroalkylation of 1,3,5-trifluoro-2,4,6-triiodobenzene under the conditions described in the original paper resulted in the formation of no perfluoroalkylated products. However a large number of coupled products were observed **[E-61]**.

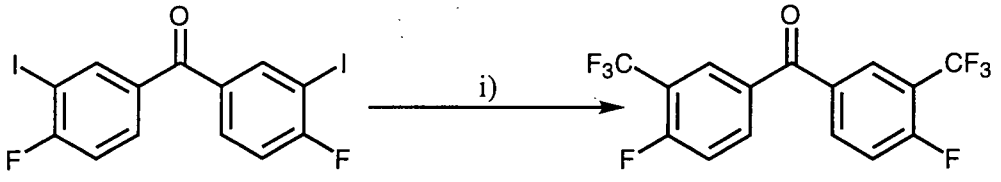


i) CF_3COONa / CuI / NMP / 160°C / N_2

[E-61]

III.6.b.ii.3) 4,4'-Difluorobenzophenone

Perfluoroalkylation of 4,4'-difluoro-3,3'-diiodobenzophenone under the standard conditions was successful **[E-62]**. The non-volatile product and monoperfluoroalkylated intermediate allowed the reaction to be followed by g.c. / m.s.

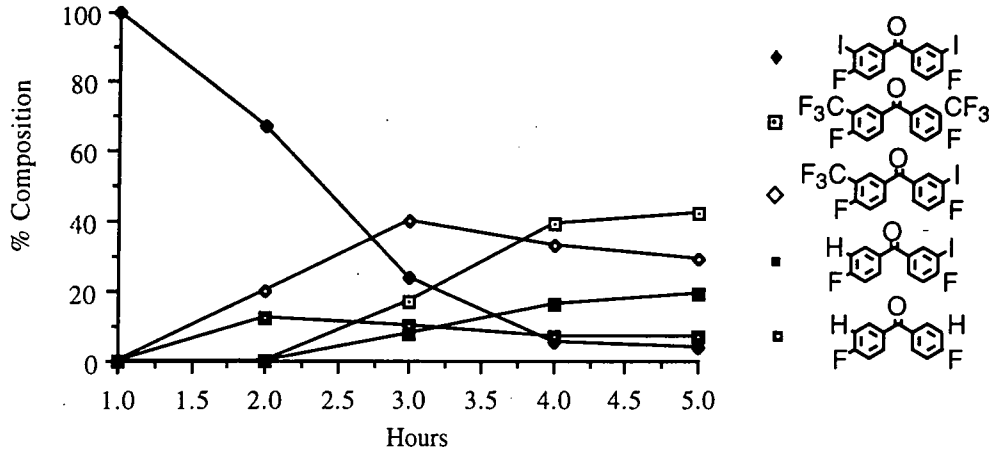


i) CF_3COONa / CuI / NMP / 160°C / N_2

[E-62]

In contrast to most other perfluoroalkylation reactions, a significant amount of reductive dehalogenation was observed (See Graph 11).

Graph 11: The Trifluoromethylation of 4,4'-Difluoro-3,3'-diiodobenzophenone



III.7. Conclusions

i) It has been demonstrated that elemental fluorine has a activating effect on halogenation reactions when performed in acidic media and that, by simple control of the initial stoichiometry of the reaction mixture multiple halogen substitution is also possible. Because the fluorine gas is in a very low concentration throughout the halogenation reaction the substrate is always in a large excess resulting in production of usually only one product.

ii) In the case of bromination, the resulting *in situ* species is extremely reactive and possibly more reactive than elemental fluorine. It is able to electrophilically substitute compounds that classically expected to undergo nucleophilic attack.

iii) Using interhalogen compounds such as ICl, it is also possible to effect both chlorination and iodination thus providing a route to chloroaromatics. Activation of elemental chlorination should also be possible but practically very difficult.

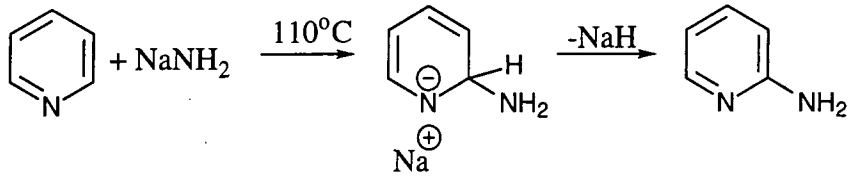
iv) The use of co-solvents such as CF_2ClCCl_2F and PFD allows the volume of the acid in the reaction to be reduced. This is very significant if the process is to be operated on a larger scale as it will significantly reduce waste emissions, making the process more environmentally acceptable than most routes to iodoaromatics.

v) Combination of the halogenation procedure with existing perfluoroalkylation reactions could allow the synthesis of a number perfluoroalkylated aromatics that are unavailable through other routes.

Chapter IV The Synthesis of 2-Substituted Heterocycles via Direct Fluorination

IV.1. Introduction

In contrast to the chemistry of benzene, which is dominated by electrophilic substitution, the electrophilic substitution of pyridine is difficult with attack occurring mainly at the 3- and 5- positions in the pyridine ring system. Consequently, the most widely used synthetic approach in producing substituted pyridines involves nucleophilic attack by strong nucleophiles such as alkoxides, hydrazines, thiolates and stabilised carbanions on a 2-halopyridine[240]. One of the few examples of nucleophilic displacement of hydride at the 2- and / or 6- position is the well known Chichibabin reaction[241]. This amination is carried out by heating pyridine with powdered sodamide in an inert solvent such as *N,N*-dimethylaniline at temperatures upto 140°C (**Scheme 31**).



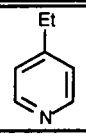
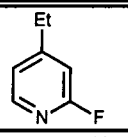
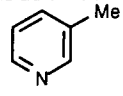
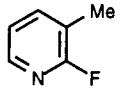
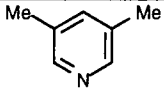
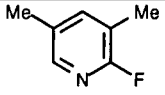
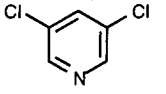
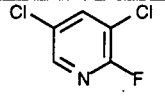
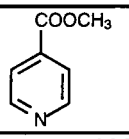
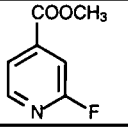
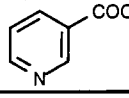
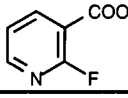
Scheme 31

A similar reaction is known in which 2-pyridone is prepared in low yield by passing pyridine vapour over molten potassium hydroxide at 300°C[241]. Analogous reactions concerning quinoline and isoquinoline are however preparatively useful. Recently, a number of workers have described methodology involving elemental fluorine which ultimately results in functionalisation of a pyridine or quinoline, a summary of which follows.

IV.1.a. The Direct Fluorination of Pyridine Derivatives

The direct fluorination of pyridine was first reported by Simons in 1948[138]. Although 2-fluoropyridine was a product of the fluorination, Simons claimed that pyridine or 2-fluoropyridine could be used as an inert solvent for direct fluorination. Later Van Der Puy demonstrated this as incorrect, fluorinations of aromatics conducted in pyridine giving 2-fluoropyridine as the major product. He demonstrated that fluorination of pyridine or substituted pyridines in the 2-position was possible with elemental fluorine (See Table 55)[242,243].

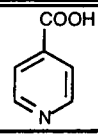
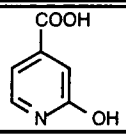
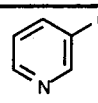
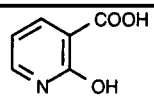
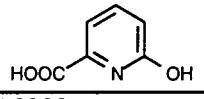
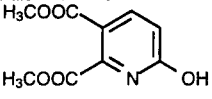
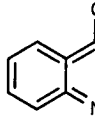
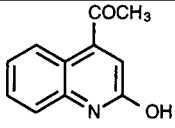
Table 55: Fluorination of Substituted Pyridines Using Elemental Fluorine.

Pyridine	Product	Temperature	Yield(%)*
		-25°C	32
		-25°C	43
		0°C	37
		25°C	46
		0°C	61
		0°C	36

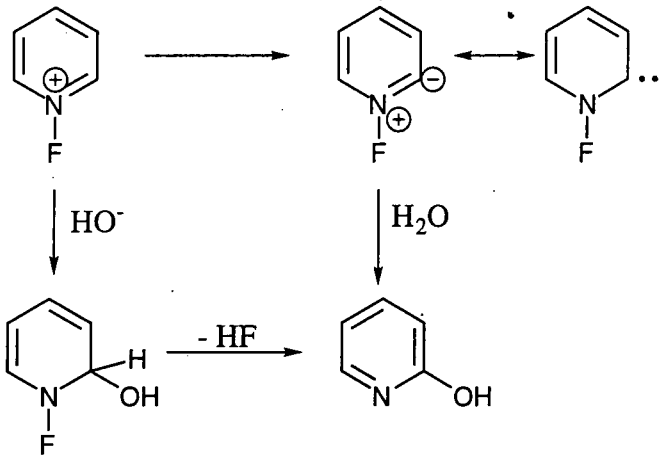
Van Der Puy also described methodology for the preparation of 2-pyridones via the direct fluorination of pyridine carboxylic acids or the esters of pyridine carboxylic acids in aqueous media[244]. The esters of pyridine and quinoline carboxylic acids were fluorinated at 0-25°C in water / acetonitrile mixtures; pyridine carboxylic acids were fluorinated in the form of their potassium salts (See Table 56). No 2-fluoropyridine derivatives were detected at any time during the reaction and were later shown to be resistant to the reaction conditions, confirming that the 2-pyridones were not formed by hydrolysis of the corresponding 2-fluoropyridines[244].

* Crude isolated yields based on amount of F_2 added.

Table 56: Formation of Pyridones Using Elemental Fluorine in Aqueous Solutions.

Pyridine	Product	Conditions	Yield(%)
		H_2O, 0°C, 2eq KOH, 2eq F_2	62
		H_2O, 0°C, 2eq KOH, 2eq F_2	73*
		H_2O, 0°C, 2eq KOH, 2eqF_2	51
		2:1 CH_3CN / H_2O, 0°C, 0.5eq F_2	56
		2:1 CH_3CN / H_2O, 25°C, 0.5eq F_2	75

He postulated that following formation of a *N*-fluoropyridinium cation two possibilities could be considered for its conversion into the observed products. Direct attack of water or hydroxide on the *N*-fluoropyridinium cation produced the 2-hydroxyl derivative or alternatively deprotonation of the *N*-fluoropyridinium cation gave a carbene which then reacted with water to produce the product (**Scheme 32**). However, deprotonation under these conditions seems unlikely suggesting simple attack by hydroxide on the *N*-fluoropyridinium fluoride as the most likely route to the pyridone products.

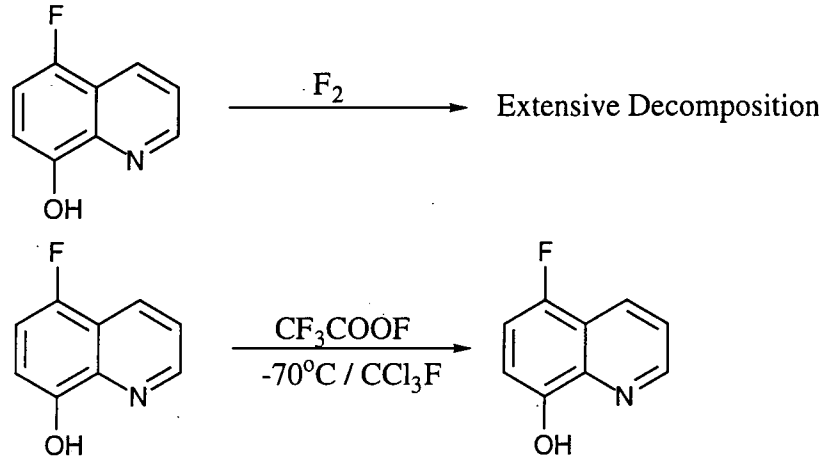


Scheme 32

* Combined yield of 2-OH-3-COOH and 2-OH-5-COOH.

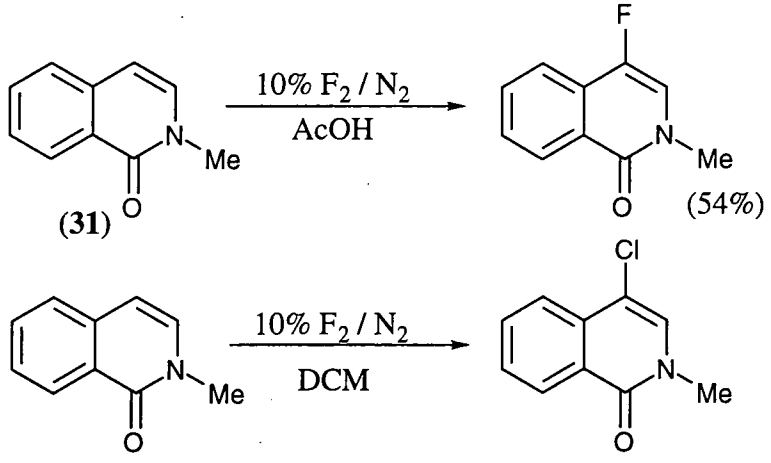
IV.1.b. Direct Fluorination of Quinoline and Isoquinoline

The direct fluorination of quinoline was accompanied by extensive fragmentation of the hetero-ring, but fluorination with trifluoromethyl hypofluorite in trichlorofluoromethane at -70°C converted 5-fluoro-8-hydroxyquinoline into the 5,7-difluoro-8-hydroxyquinoline **[E-63]**[245].



[E-63]

The fluorination of isoquinolines using elemental fluorine has been achieved by conversion into the 2-methylisocarbostyril **(31)** followed by fluorination with a 10% mixture of fluorine in argon using acetic acid as the solvent. When dichloromethane was used as the solvent for the fluorination of isoquinoline only the 4-chloroanalogue was formed **[E-64]**[246].

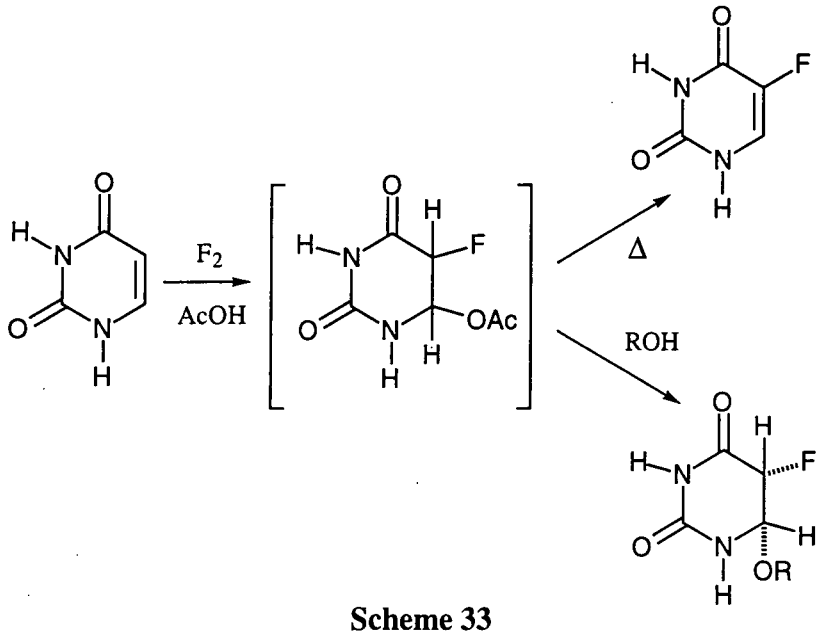


[E-64]

IV.1.c. Direct Fluorination of Uracil

Cech employed direct liquid phase fluorination in the production of 5-fluorouracil, the poor solubility of uracil in most organic solvents prompting the use of acetic acid as a solvent[247]. He claimed the fluorination caused a syn addition across the

double bond, followed by the formation of an unstable acetoxy intermediate which could then be thermally decomposed to give 5-fluorouracil (**Scheme 33**).



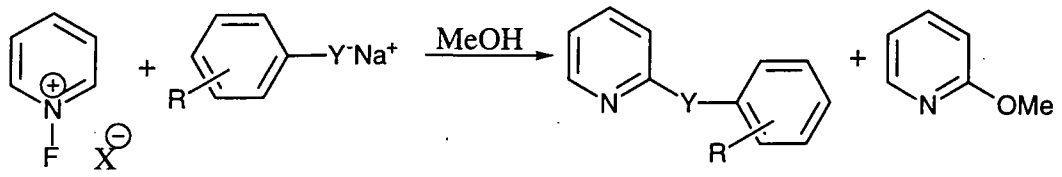
Scheme 33

Many other nucleosides of uracil have also been fluorinated under similar conditions in high conversions and yields[247-252].

IV.1.d. Reactions of *N*-Fluoropyridinum Salts

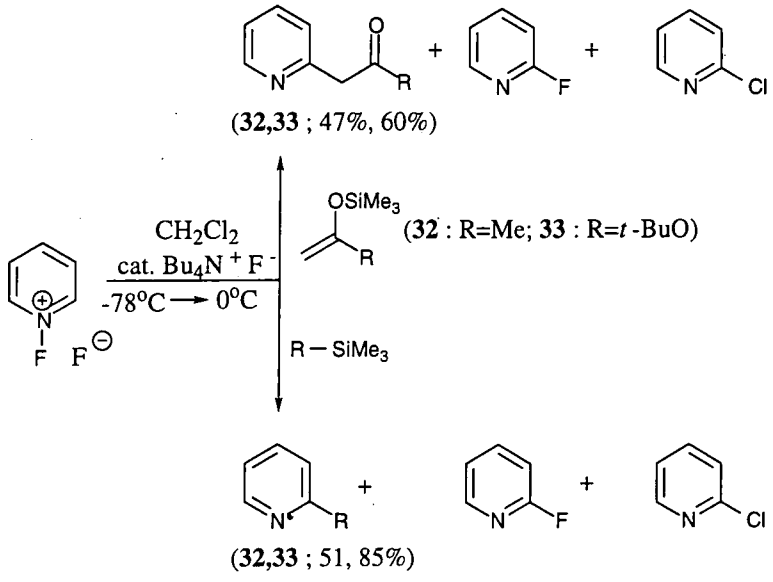
Umemoto *et al* reported the first stable 1:1 salts of *N*-fluoropyridinium* and a counterion via the direct fluorination of pyridine derivatives with elemental fluorine[141]. More recently *N*-fluoropyridinium salts have been used in the synthesis of 2-fluoro-[253], 2-chloropyridines[254,255], 2-bromopyridines[254,255] and also for the introduction of amido[144], posphonio[256] and arsino[256] functionalities at the 2 position of pyridine. Kiselyov *et al* further extended the utility of *N*-fluoropyridinium salts reporting the synthesis of 2-(arylthio)pyridines, 2-(aryloxy)pyridines and 2-(heteroaryl)pyridines by reactions of *N*-fluoropyridinium triflate or tetrafluoroborate with the corresponding *S*-, *O*- and *N*- centred nucleophiles. The reaction products also included 2-methoxypyridine and other minor products (**Scheme 34**)[257].

* The reaction of quinoline under similar conditions generates unstable *N*-fluoroquinolinium fluoride that decomposes at <-50°C. See H. Meinert, *Z. Chem.*,1965, **5**, 64.



Scheme 34

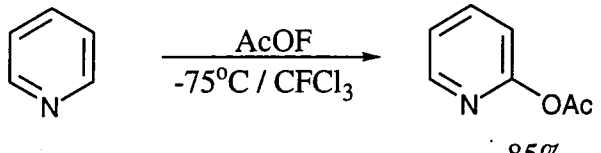
Later, Kiselyov *et al* described a methodology for synthesis of 2-substituted pyridines based on a reaction with *N*-fluoropyridinium fluoride. The salt, generated by bubbling elemental fluorine diluted with argon through a solution of pyridine in DCM at -78°C, was allowed to react with a silicon reagent to give the 2-substituted pyridine[258]. Its formation was accompanied by the formation of 2-fluoropyridine and 2-chloropyridine, which was itself derived from reaction of the *N*-fluoropyridinium fluoride with dichloromethane (**Scheme 35**).



Scheme 35

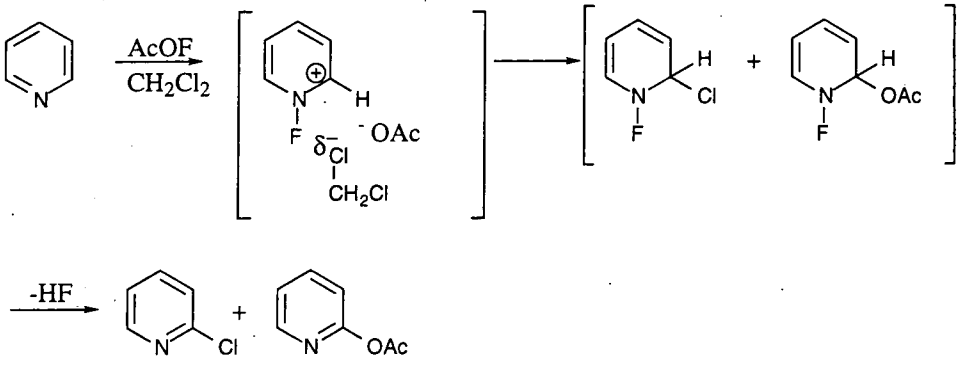
IV.1.e. Reaction of Pyridine with Acetyl Hypofluorite

Rozen *et al* described the reaction of pyridine with preformed acetyl hypofluorite which produced 2-acetoxypyridine in high yield **[E-65]**. A similar reaction was observed with quinoline[254].



[E-65]

Later, Rozen *et al* sfound that conducting the reactions in a range of solvents such as CH_2Cl_2, CH_2Br_2 and primary alcohols led to the formation of 2-chloropyridines, 2-bromopyridines and 2-alkoxypyridines in addition to the formation of the expected 2-acetoxypyridine. In contrast to reactions conducted in alkyl chlorides or alkyl bromides, treatment of pyridine with acetyl hypofluorite in the presence of an alkyl iodide solvent, such as methyl iodide or diiodomethane, resulted in oxidation of the alkyl iodide. Quinoline was found only to undergo acetoxylation and alkoxylation under similar conditions[255]. This was attributed to the *N*-fluoroquinolinium salt being less electrophilic, due to the delocalisation of the positive charge over the rings thus making abstraction of chloride from dichloromethane unlikely (**Scheme 36**).



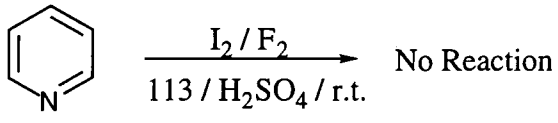
Scheme 36

IV.2. Direct Fluorinations of Pyridine and Substituted Pyridines

IV.2.a. Iodination / Fluorination of Pyridine

The direct iodination of pyridine is extremely difficult, and even when conducted in oleum gives only 18% of 3-iodopyridine[259]. Consequently, iodination of pyridine is usually achieved via metallation and quenching with iodine[260], Sandmeyer reactions[261] or halogen exchange reactions[262].

Following the success of the electrophilic iodination of substituted benzenes (see Chapter III) we attempted the direct iodination of pyridine under similar conditions used for the iodination of aromatics. Following workup, analysis by a combination of ^1H, ^{13}C and g.c. / m.s. confirmed that no reaction had occurred **[E-66]**.

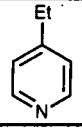
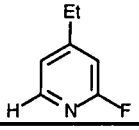
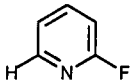
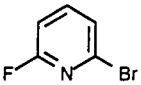


[E-66]

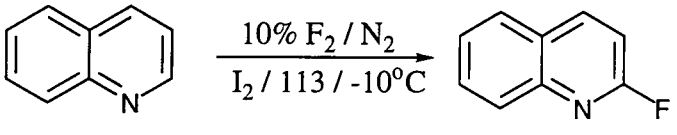
We believe this failure to produce any iodinated product can be explained in terms of protonation dramatically reducing the reactivity of the pyridine towards the electrophilic iodinating agent . The fluorination of a 1:1 mixture of pyridine and iodine

in CF_2ClCCl_2F at -10°C* in the absence of sulphuric acid produced a high conversion to 2-fluoropyridine. Two other substituted pyridines were fluorinated under these conditions (see Table 57) and the identities of the products confirmed by a combination of ^{19}F, ^{13}C nmr and g.c. / m.s. against literature data[242,243].

Table 57: The Fluorination of Pyridine Using Iodine and Fluorine.

Pyridine	Product	Conditions	% Conversion	% Yield
		113, -10°C, 0.6eq I_2, 1.2eq F_2	90%	53% Yield
		113, -10°C, 0.6eq I_2, 1.2eq F_2	58%	-
		113, -10°C, 0.6eq I_2, 1.2eq F_2	41%	-

It appears that the addition of iodine produces a moderation of the fluorination reaction and, in the case of 4-ethylpyridine, the conversion and yield compares favourably with the work of Van Der Puy[242,243]. To further demonstrate the utility of this methodology the fluorination of quinoline was attempted. Gershon had demonstrated that the direct fluorination of quinoline was impossible[245] but using our system, fluorination to produce 2-fluoroquinoline was shown to be readily achievable **[E-67]**.



Conversion 100%
Yield 50%

[E-67]

It is clear from the isolated yields that the optimum conditions for extraction need further investigation to enable development of this methodology.

The site of substitution in the above fluorinations makes an electrophilic process unlikely, the usual sites for electrophilic substitution being the 3- and 5- positions which have the greatest π-electron density; the initial fluorination may therefore be at the nitrogen as observed by other workers[141]. Nucleophilic displacement, by an addition-elimination mechanism would then produce the fluoropyridine or fluoroquinoline.

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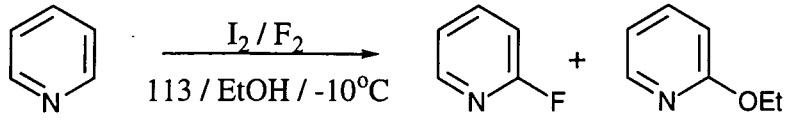
* In contrast to the earlier work on iodination of aromatics which used a mixed solvent system, these reactions were cooled to prevent loss of the CF_2ClCCl_2F solvent.

Fluorination of pyridine using iodine and a 10% mixture of fluorine in nitrogen at -10°C in a mixture of CF_2ClCCl_2F and ethanol resulted in the formation of significant quantities of 2-ethoxypyridine **[E-68]**.

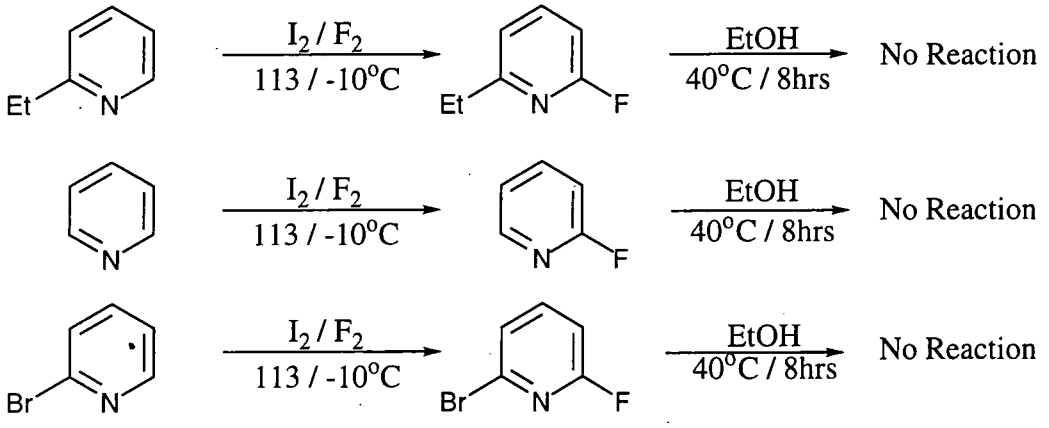


Composition 14% 48%

Conversion 62%

[E-68]

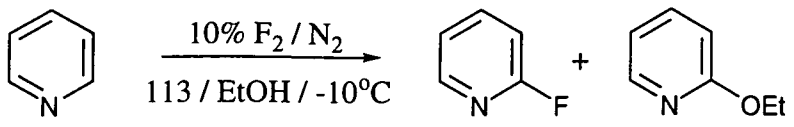
A series of reactions were then conducted to determine if the 2-fluoropyridines were stable under these conditions. Fluorination of three pyridine derivatives with iodine and fluorine in CF_2ClCCl_2F produced the expected fluoro derivatives*. Addition of ethanol, followed by stirring for 8hrs at 40°C gave no ethoxylated pyridines confirming that the 2-ethoxypyridines were not formed by ethoxylation of the corresponding 2-fluoropyridines **[E-69]**.



[E-69]

An investigation was also then made to determine if iodine was crucial in the ethoxylation of pyridine. The fluorination of a mixture of pyridine, ethanol and CF_2ClCCl_2F at -10°C in the absence of iodine produced a similar reaction confirming iodine as unnecessary in the alkoxylation reaction **[E-70]**.

* Confirmed by ^{19}F nmr and g.c. / m.s.



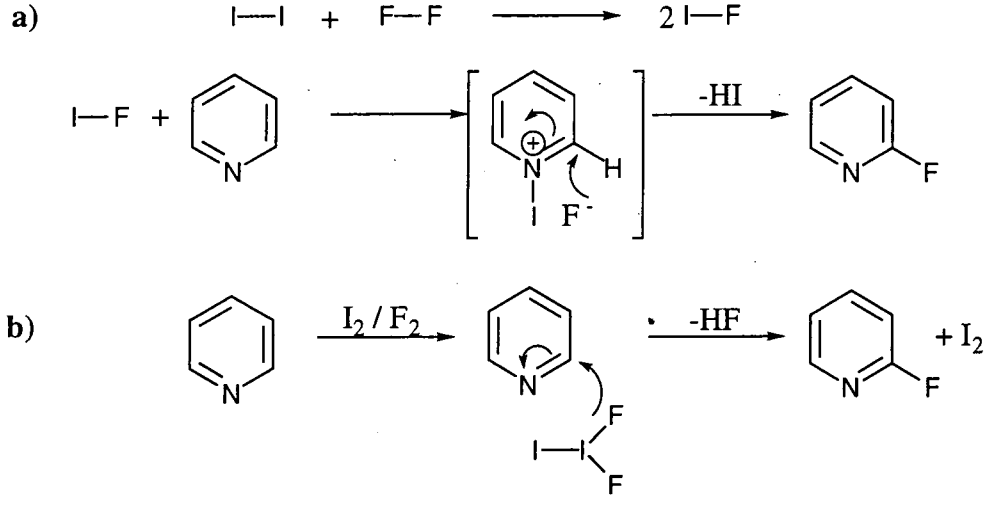
Composition 14% 47%

Conversion 61%

[E-70]

IV.2.b. Mechanism of Fluorination With Iodine and Fluorine

The direct fluorination of quinoline does not occur confirming iodine as important in the fluorination process. Its role is unclear, but two possibilities may be considered (**Scheme 36**). The first **a)** involves the *in situ* formation of iodine monofluoride. This would react with pyridine, producing a *N*-iodopyridinium cation and simple nucleophilic attack of F^- and elimination of HI results in formation of the fluorinated heterocycle. In mechanism **b)**, the passage of fluorine through the solution results in the formation a hypervalent iodine species, itself co-ordinated to the nitrogen atom of the pyridine system. Nucleophilic attack by F^- and the subsequent elimination of HF results in formation of the fluorinated heterocycle.



Scheme 36

IV.3. Functionlisation of Pyridines

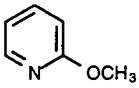
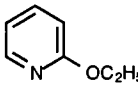
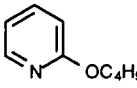
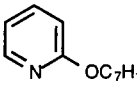
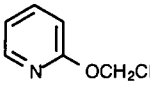
IV.3.a. The Use of Oxygen as a Nucleophile

IV.3.a.i. Pyridine

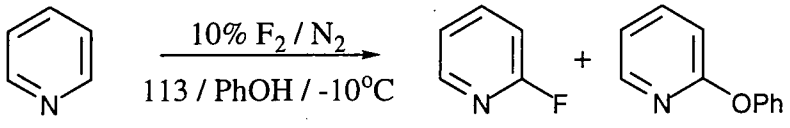
Conditions for the functionalisation of pyridine with an alcohol, in the absence of iodine, using elemental fluorine were then optimised. We found that four equivalents of alcohol produced high conversions to the 2-alkoxypyridines while significantly reducing the conversion to 2-fluoropyridine. Use of four equivalents of alcohol also made removal of the excess alcohol reasonably easy. Following fluorination, the reaction mixture was poured into water and the solution then made basic. Continuous

extraction overnight with dichloromethane followed by rotary evaporation and distillation produced the pure 2-alkoxypyridines (See Table 58).

Table 58: The Functionlisation of Pyridine Using Elemental Fluorine and an Alcohol.

Pyridine	Product	Conditions	Conversion	Yield
		113, -10°C, 4eq MeOH, 1.2eqF_2	67%	54%
		113, -10°C, 4eq EtOH, 1.2eqF_2	61%	50%
		113, -10°C, 4eq BuOH, 1.2eqF_2	86%	58%
		113, -10°C, 4eq $C_7H_{15}OH$, 1.2eqF_2	70%	43%*
		113, -10°C, 4eq CF_3CH_2OH, 1.2eqF_2	63%	60%

Functionalisation of pyridine using phenol was also attempted under similar conditions to those used above **[E-71]**. Following workup, g.c. / m.s. analysis showed that in addition to 2-phenoxypyridine and 2-fluoropyridine significant amounts of fluorophenol (*o*-, *m*- and *p*- isomers) was formed.



Composition 24% 8%

Conversion 32%

[E-71]

Reactions involving phenols could possibly be improved by the use of a less activated phenols thus encouraging prefential attack at the pyridine molecule and leading to more of the 2-substituted pyridine.

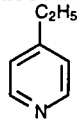
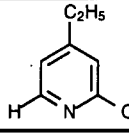
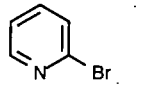
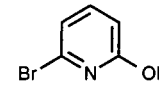
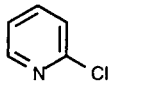
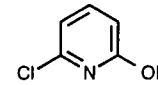
IV.3.a.ii. Substituted Pyridines

The alkoxylation of a number of substituted pyridines was investigated under the reaction conditions. Following the standard workup, the identity of the products was

* Decomposed slightly upon distillation.

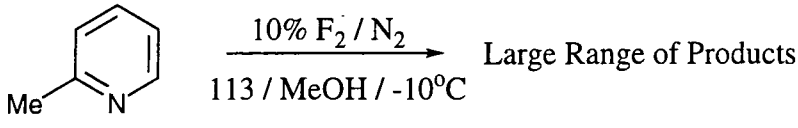
confirmed by a combination of ^{13}C nmr and g.c. / m.s compared to data given in the literature (See Table 59)[263].

Table 59: The Alkoxylation of Substituted Pyridines Using Elemental Fluorine.

Pyridine	Product	Conditions	% Conversion	% Yield
		113, -10°C, 4eq MeOH, 1.2eqF_2	92%	37%
		113, -10°C, 4eq EtOH, 1.2eqF_2	45%	-
		113, -10°C, 4eq EtOH, 1.2eqF_2	37%	-

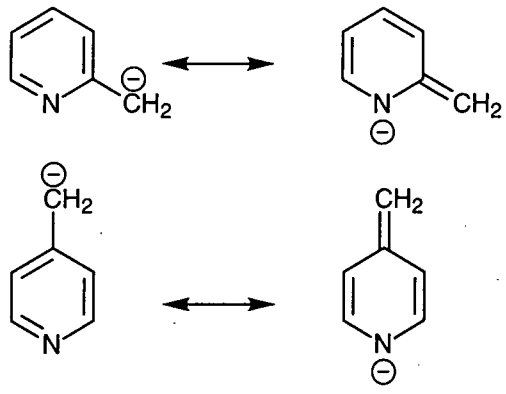
The effect on conversion of electron withdrawing substituents in the 2- position demonstrates that the degree of reaction is dependant on the electron density at the nitrogen atom. The isolated yields further confirms that investigation should be made into the conditions for isolation of these products.

Functionlisation of 2-methylpyridine was also attempted using elemental fluorine. After work up a combination of ^{1}H, ^{13}C, ^{19}F nmr and g.c. / m.s. confirmed the formation of a large range of products, indicative of both methoxylation and fluorination at a number of positions in the molecule **[E-72]**.



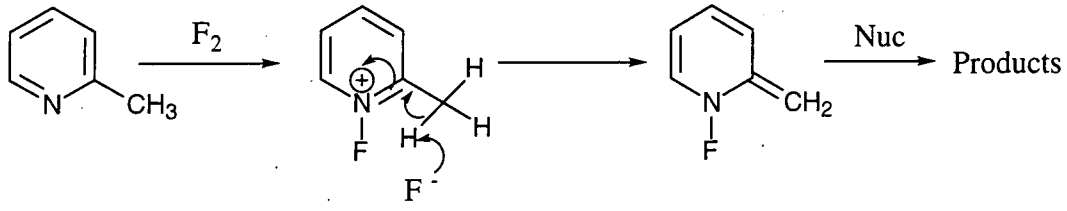
[E-72]

Alkyl groups in the 2- and 4-positions in pyridine and pyridinium cations are activated by the ring nitrogen making them more acidic than toluene[264]. This can be explained in terms of the mesomeric stabilisation available to the anions (**Scheme 37**).



Scheme 37

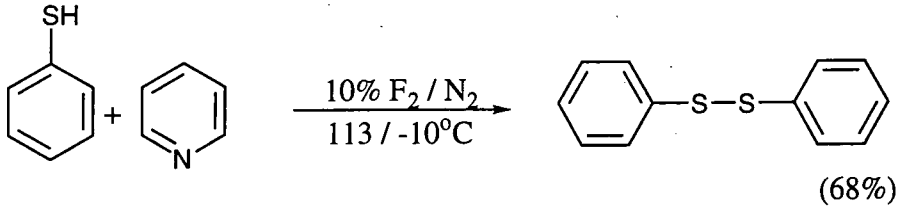
The acidity of these substituent hydrogens therefore makes nucleophilic attack at the alkyl group more likely than nucleophilic attack at the C2 of the pyridine molecule. This type of attack would produce a very reactive intermediate, which can then be further attacked producing the large range of products observed in the reaction (**Scheme 38**).



Scheme 38

IV.3.b. Use of Sulphur as a Nucleophile

The functionalisation of pyridine using a thiol as the nucleophile was also investigated. The initial reaction was conducted using thiophenol because of the problems of containment associated with the continuous passage of large volumes of nitrogen and fluorine through the more volatile aliphatic thiols. The mixture of pyridine and thiophenol was fluorinated at -10°C and following workup a large amount of solid was isolated, analysis identifying it as diphenyldisulphide. No substituted pyridines or fluorinated disulphides were observed **[E-73]**.



(68%)

[E-73]

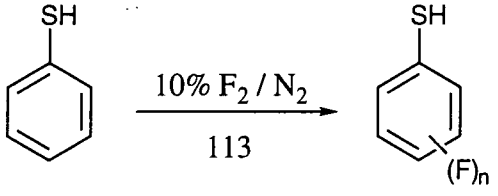
Oxidation of thiols to disulphides is easily achieved, hydrogen peroxide being the most commonly used reagent, but the transformation can also be accomplished with thallium

(II) acetate, Br_2, NO or NO_2. The reaction is also reversible, simple treatment with zinc and acid producing the thiol **[E-74]**[175].

$$R{-}SH \underset{Zn\,/\,H^+}{\overset{Br_2}{\rightleftharpoons}} R{-}S{-}S{-}R + 2HBr$$

[E-74]

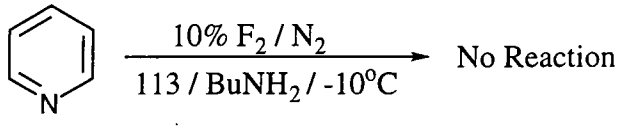
Fluorination of thiophenol in the absence of pyridine produced only fluorinated thiophenols thus confirming the formation of a mild *in situ* oxidising agent between pyridine and elemental fluorine **[E-75]**.



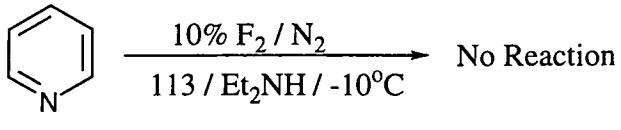
[E-75]

IV.3.c. The Use of Nitrogen as a Nucleophile

In an attempt to mimic the Chichibabin reaction using elemental fluorine, the fluorination of pyridine with a number of amines was investigated. The fluorinations were carried out in the usual fashion, the mixture of pyridine, amine and CF_2ClCCl_2F was cooled to -10°C and then fluorinated using a 10% mixture of fluorine in nitrogen. Following reaction the mixture was poured into water and then extracted with DCM. In the reactions **[E-76]**, **[E-77]** no products indicative of the *ortho* substitution of pyridine were observed. In all reactions, evidence of a number of minor reactions consistent with oxidation of the amines were observed by g.c. / m.s.

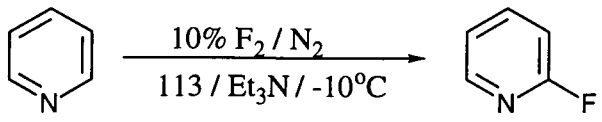


[E-76]



[E-77]

Following the fluorination of a mixture of triethylamine, pyridine and CF_2ClCl_2F no 2-aminated product was observed. However, a 20% conversion to 2-fluoropyridine was observed by g.c. and g.c. / m.s.. The product was not isolated **[E-78]**.

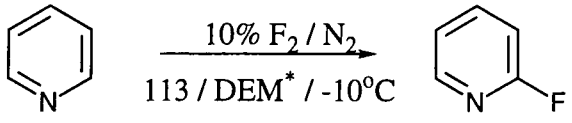


20% Conversion

[E-78]

IV.3.d. The Use of a Potential Carbon Nucleophile

Fluorination of pyridine in the presence of a potential carbon nucleophile, diethyl malonate (DEM), using a 10% mixture of fluorine in nitrogen at -10°C and CF_2ClCCl_2F gave no carbon-carbon bond formation. A conversion of 40% to 2-fluoropyridine was observed by g.c. and g.c. / m.s. but the product, 2-fluoropyridine, was not isolated. The diethylmalonate was however recovered unchanged **[E-79]**.

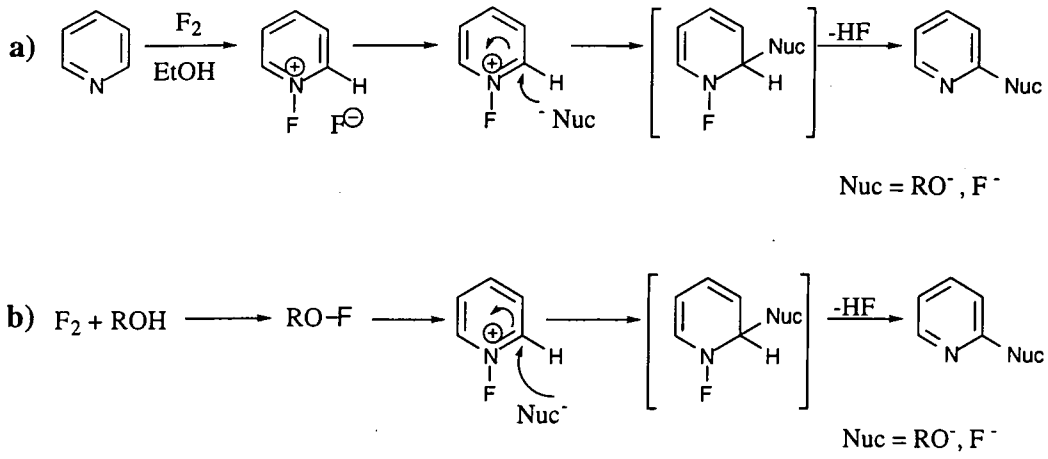


Conversion 40%

[E-79]

IV.3.e. Mechanism of Reaction

It is likely that the functionalisation of pyridine using fluorine and an alcohol proceeds via one of two possible mechanisms (**Scheme 40**). In **a**) the passage of fluorine through the solution results in the formation of *N*-fluoropyridinium fluoride and then nucleophilic attack by either fluoride ion or alkoxide ion followed by elimination of HF produces either 2-fluoropyridine or the 2-alkoxypyridine. In **b**), the passage of fluorine results in the formation of an *in situ* fluoroxy system, derived from the alcohol, which then attacks the pyridine producing an *N*-fluoropyridinium cation. Nucleophilic attack by alkoxide produces the 2-alkoxypyridine but this is again in competition with attack by fluoride ion. Elimination of HF then results in formation of the 2-substituted derivatives.



Scheme 40

IV.4. Conclusions

a) The direct fluorination of pyridines and quinolines has been demonstrated as readily achievable using a combination of iodine and fluorine in a non-polar solvent. Further investigation is required to determine the optimum conditions, stoichiometry and work-up for the reaction. This is the only methodology available that allows the selective fluorination of quinoline and is therefore of considerable interest[265].

b) The alkoxylation of pyridine has been demonstrated as relatively simple using elemental fluorine and an alcohol in contrast to many examples where *N*-fluoropyridinium fluoride has been preformed at low temperature, converted to the triflate and then treated with an alcohol. Development of the functionalisation with a phenol could provide a new route to a range of important agrochemicals[266].

c) The combination of pyridine and fluorine could be useful as a relatively mild and easily controlled *in situ* oxidising agent. The formation of low quantities of an oxidising species during the fluorination enables easy control of a reaction, thus leading to usually one major product.

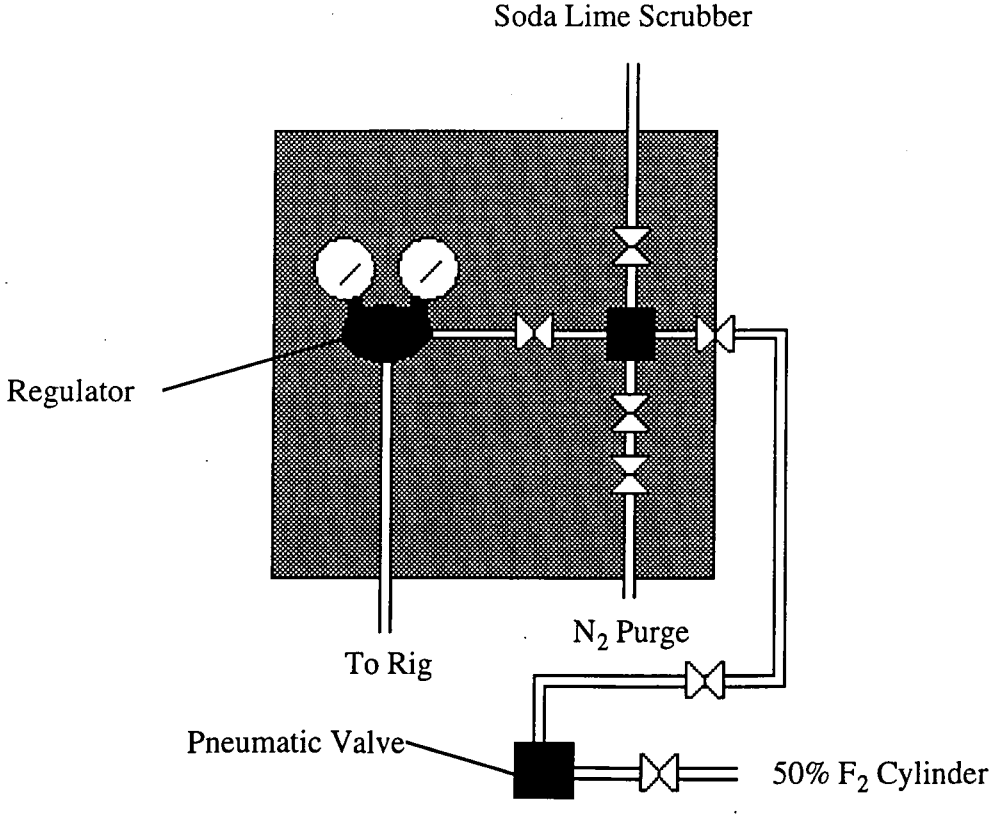
Experimental Section

The Use of Pressurised Fluorine in the Laboratory

Gaseous Fluorine reacts violently even at room temperature with most organic and inorganic materials including asbestos and water[226]. Utmost care is therefore necessary when working with it, since leakage of the apparatus may cause explosions or fires. The inhalation of fluorine is also extremely dangerous* and the effect resembles the effect of chlorine and ozone. Therefore equipment containing elemental fluorine must be housed in a well ventilated area and when operating such equipment one should wear both nitrile rubber gloves and a face shield because fluorine burns the skin like hydrogen fluoride. The treatment of fluorine burns is the same as that of hydrogen fluoride[226].

The collaboration between BNFL Fluorochemicals and Prof. R. D. Chambers has enabled further development of techniques for the safe handling of elemental fluorine. The fluorine is supplied in a cylinder as a 50% mixture in nitrogen and housed in its own extracted cabinet. In addition to the cylinder valve, further controlled is achieved by the addition of a pneumatic value which can be remotely used to halt the flow of fluorine in case of emergency. The pressure of the fluorine is also regulated by a fluorine resistant regulator to a maximum pressure of 3atm (see Fig.10).

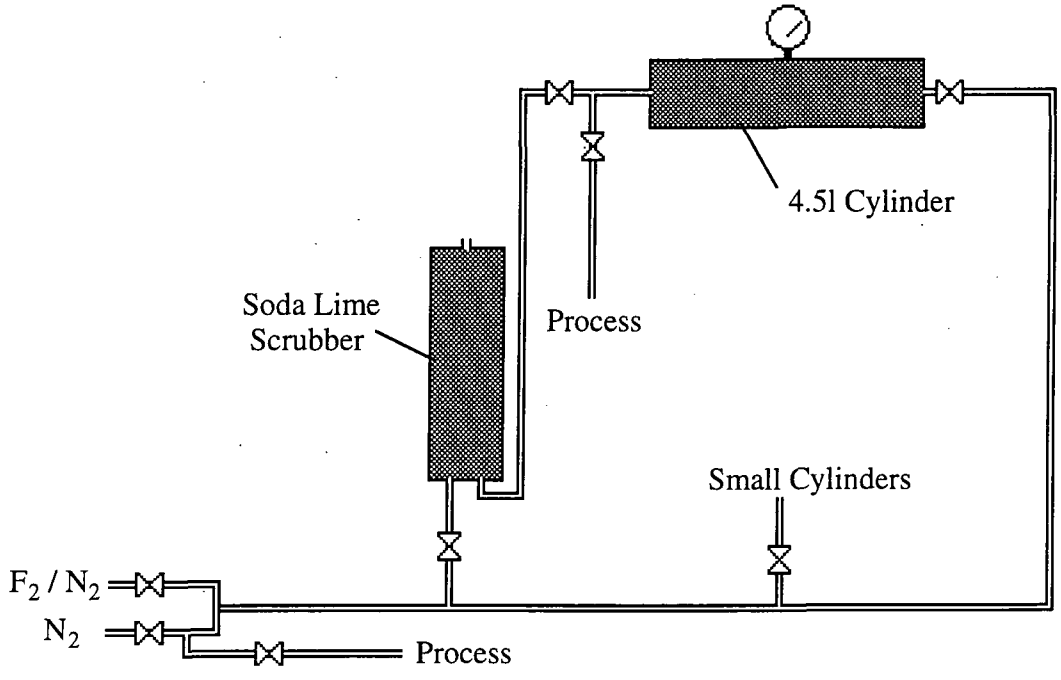
Figure 10: Schematic Representation of Valving Inside the Cabinet Containing the Fluorine Cylinder.



* Short Term O.E.S. 1.p.p.m; LC_{50} (Rat) $\leq 0.5 mg\ l^{-1}$.

The fluorine is supplied from the ventilated cabinet containing the fluorine cylinder via passivated 1/4" stainless steel pipe to a rig fitted with passivated 1/4" stainless steel pipe and passivated Monel® valves (see Fig. 11). This rig can be used to fill small cylinders (800-3700ml) which are then transferred to other fumecupboards[¥] for small scale fluorination reactions. The large rig is also fitted with a 4500ml cylinder which can filled with the 50% fluorine / nitrogen mixture allowing large scale fluorination reactions to be run. The rig is also fitted with a fluorine resistant control valve and fluorine resistant flow meter enabling very accurate control over gas flow during the large scale fluorinations.

Figure 11: Schematic Representation of the Stainless Steel Rig For Filling of Cylinders or Conducting Large Scale Fluorination Reactions



N.B. Fluorination Reactions Must Never Be Run Directly From The Large 50% Fluorine / Nitrogen Cylinder

[¥] All fluorinations are performed in a seperate fluorine laboratory equipped with stainless steel fume hoods, HF / F_2 burn treatments, eye baths and full body shower. All operations requiring elemental fluorine are performed in the presence of at least two trained operators.

Instrumentation and Reagents

Gas Liquid Chromatographic Analysis

Analyses were carried out using a Hewlett Packard 5890A gas liquid chromatograph equipped with a 25 m cross-linked methyl silicone capillary column or DB-624 capillary column.

Elemental Analysis

Carbon, hydrogen, and nitrogen elemental analyses were obtained using a Perkin-Elmer 240 Elemental Analyser or a Carlo Erba Strumentazione 1106 Elemental Analyser. Analysis for halogens was performed as described in the literature

NMR Spectra

^{1}H, ^{19}F, ^{13}C nmr. spectra were recorded on a Varian VXR200 (200MHz), Bruker AC250 (250 MHz), a Varian VXR400S (400MHz) and a Bruker AC500 (500MHz) nmr spectrometer

FT / IR Spectra

Infrared spectra were recorded on a Perkin-Elmer 1600 FT/IR spectrometer using KBr discs (solid samples) or thin films between two KBr plates (liquid samples).

Mass Spectra

Mass spectra of solid samples were recorded on a VG 7070E spectrometer. G.c. / m.s. were recorded on a Fisons Trio 1000(Mass range 0-1000) linked to the Hewlett Packard 5790A gas chromatograph fitted with a 25 m cross-linked methyl silicone capillary column or DB-624 capillary column.

Distillation

Fractional distillation of product mixtures was carried out using a Fischer Spahltroh MMS255 small concentric tube apparatus. Boiling points were recorded during the distillation.

Melting Points

Melting points were carried out at atmospheric pressure and are uncorrected.

Reagents and Solvent

Unless otherwise stated, chemicals were used as received from suppliers (Aldrich, Fluorochem, Fluka, Jansen, BDH). Solvents were dried by standard methods and stored over a molecular sieve (type 4A).

Chapter V. Experimental to Chapter II.

V.1. Small Scale Fluorinations in Acetonitrile

Prior to all fluorinations an 800ml cylinder was charged with 2atm of 50% F_2 in N_2. This was then diluted to 9atm with N_2 to produce a 10% mixture of F_2 in N_2 which was then used for all the fluorination reactions.

General Procedure

A solution containing an aromatic compound (15mmol) in CH_3CN(30ml) was placed in a fluorination apparatus with attached soda lime filled drying tube and cooled in a cryostat to -30°C under a flow of nitrogen. Elemental fluorine(35mmol) was passed through the stirred solution using narrow bore PTFE tubing. Once the addition of fluorine was complete the solution was warmed to room temperature under a flow of nitrogen. The identity of the products was comfirmed by comparison against the commercially available materials by a combination of g.c., g.c. / m.s. and ^{19}F nmr.

V.1.a. 4-Fluorobenzenesulphonyl Chloride

The solvent was then removed under vacuum leaving a brown oil (1.1g). Analysis by ^{19}F nmr (235MHz; $CDCl_3$; $CFCl_3$) showed the oil contained two major products 4-fluorobenzenesulphonyl chloride -101.4 (1F, m) and 3,4-difluorobenzenesulphonyl chloride -126.0 (1F, m), -133.7 (1F, m) in a ratio of 37:63. ^{19}F nmr also confirmed that the oil also contained a large number of other products. The volatiles were then removed by vacuum transfer to leave a polymeric residue(0.6g) and yield a low melting point solid(0.4g). Analysis by g.c. / m.s. confirmed that the mixture contained 4-fluorobenzenesulphonyl chloride *m/z*, (EI^+) 194 (M^+, 2.2%) and 3,4-difluorobenzenesulphonyl chloride *m/z*, (EI^+) 212 (M^+, 3.6%) and a range of unidentifiable materials..

V.1.b. 4-Fluorobenzoic Acid

The mixture was poured into an excess of water and extracted with diethyl ether(3x25ml) and dried($MgSO_4$) . The solvent was removed under reduced pressure to leave a brown solid(1.7g). Analysis by ^{19}F nmr (235MHz; $CDCl_3$; $CFCl_3$) and mass spectrometry showed the solid contained 4-fluorobenzoic acid -104.4 (1F, m); *m/z* , (EI^+), 140 (M^+, 58.5%) and 3,4-difluorobenzoic acid -128.2 (1F, m) and -136.5 (1F, m); *m/z* , (EI^+), 158 (M^+, 14.1%) in a ratio of 24:76. Analysis by ^{19}F nmr confirmed that the solid also contained a number of other unidentifiable products.

V.1.c. 4-Fluoroacetophenone

The volatiles were removed by vacuum transfer leaving a brown polymeric residue(1.2g). The volatiles were then added to an excess of water(100ml) followed by

extraction with diethylether(3x25ml). After washing ($NaHCO_3$ x1,water x2) and drying ($MgSO_4$), diethylether was removed by rotary evaporation leaving a colourless oil (0.7g). Analysis by ^{19}F nmr (235MHz; $CDCl_3$; $CFCl_3$) and g.c./ m.s. showed the oil contained two major products 4-fluoroacetophenone -107.2 (1F, m); *m/z* , (EI^+), 138 (M^+, 19.1%) and 3,4-difluoroacetophenone -132.4 (1F, m) and -140.6 (1F, m); *m/z* , (EI^+), 156 (M^+, 23.7%) in a ratio of 52:48. ^{19}F nmr also confirmed that the oil contained a small number of other unidentifiable products.

V.1.d. 4-Fluorobenzaldehyde

The volatiles were removed by vacuum transfer leaving a brown polymeric residue(1.0g). The volatiles were then added to an excess of water(100ml) followed by extraction with diethylether(3x25ml). After washing ($NaHCO_3$ x1,water x2) and drying ($MgSO_4$), diethylether was removed by rotary evaporation leaving a colourless oil (0.6g). Analysis by ^{19}F nmr (235MHz; $CDCl_3$; $CFCl_3$) and g.c./ m.s. showed the oil contained two major products 4-fluorobenzaldehyde -104.4 (1F, m); *m/z* , (EI^+), 124 (M^+, 56.4%) and 3,4-difluorobenzaldehyde -129.2 (1F, m) and -137.4 (1F, m); *m/z* , (EI^+), 142 (M^+, 72.8%) in a ratio of 53:47. ^{19}F nmr also confirmed that the oil contained a small number of other unidentifiable products.

V.1.e. 2,4-Difluorobenzoic acid

The mixture was poured into an excess of water and extracted with diethyl ether(3x25ml) and dried($MgSO_4$) . The solvent was removed under reduced pressure to leave a brown solid(1.4g). Analysis by ^{19}F nmr (235MHz; $CDCl_3$; $CFCl_3$) and mass spectrometry showed the solid contained three major components 2,4-difluorobenzoic acid -100.1 (1F, m) and -102.4 (1F, m); 2,4,5-trifluorobenzoic acid -108.3 (1F, m), -123.3 (1F, m), and -141.2 (1F, m); 2,3,4-trifluorobenzoic acid 124.4 (1F, m), -128.8 (1F, m) and -158.6 (1F, m) in a ratio of 47:40:13. Analysis by ^{19}F nmr confirmed that the solid also contained a small number of other unidentifiable products.

V.2. Fluorinations in Trifluoroacetic Acid

General Procedure

A solution containing an aromatic carboxylic acid(15mmol) in CF_3COOH(30ml) was placed in a fluorination apparatus with attached soda lime filled drying tube. Elemental fluorine(35mmol) was passed through the stirred solution using narrow bore PTFE tubing. Following the passage of fluorine the mixture was added to an excess of water and extracted with diethyl ether(3x25ml). After drying ($MgS0_4$) the diethyl ether was removed by rotary evaporation.

V.2.a. 4-Fluorobenzoic Acid

4-Fluorobenzoic acid produced an off-white solid(1.2g). Analysis of the solid by ^{19}F nmr (235MHz; $CDCl_3$; $CFCl_3$) showed it to contain two major products 4-fluorobenzoic acid and 3,4-difluorobenzoic acid in a ratio of 28:72. ^{19}F nmr also confirmed the solid contained a number of other minor products. Vacuum sublimation of the residue produced a single product 3,4-difluorobenzoic acid, a white crystalline solid (0.2g, 13.2%); m.p. 119-121°C (lit.[167], 122-124°C); (Found: C, 53.58 H, 2.2 ; Calc. for $C_7H_4F_2O_2$ C , 53.2 H, 2.5%); δ_F(235MHz; $CDCl_3$; $CFCl_3$) -128.8(1F, m) and-136.4 (1F, m); *m/z* (EI^+) 158 (M^+, 88.03%).

V.2.b. 2,4-Difluorobenzoic Acid

The mixture was poured into an excess of water and extracted with diethyl ether(3x25ml) and dried($MgSO_4$) . The solvent was removed under reduced pressure to leave an off white solid(1.6g). Analysis by ^{19}F nmr (235MHz; $CDCl_3$; $CFCl_3$) and mass spectrometry showed the solid contained three major components 2,4-difluorobenzoic acid -100.5 (1F, m) and -103.1 (1F, m); 2,4,5-trifluorobenzoic acid -108.7 (1F, m), -123.9 (1F, m) and -141.4 (1F, m); 2,3,4-trifluorobenzoic acid -124.9 (1F, m), -129.0 (1F, m), and -158.9 (1F, m) in a ratio of 46:35:19. Analysis by ^{19}F nmr confirmed that the solid also contained a small number of other unidentifiable products.

V.4. Fluorination in a Variety of Solvents

V.4.a. General Method

A solution containing 4-fluorobenzoic acid(2.1g, 15mmol) in the solvent(30ml) was placed in a fluorination apparatus with attached soda lime filled drying tube. Elemental fluorine(35mmol) was passed through the stirred solution using narrow bore PTFE tubing. If the reaction was to be conducted at lower temperature the fluorination apparatus containing the mixture was cooled in a HAAKE cryostat to the required temperature prior to fluorination. The conversion was calculated from the ^{19}F nmr spectra against a standard of α,α,α-trifluorotoluene.

V.4.b. Fluorination in Formic Acid(100%-40%)

V.4.b.i. Preparation of Anhydrous Formic Acid[267]

Formic acid(96%) was stirred with boric anhydride for 12hrs. Boric anhydride was prepared by melting boric acid in an oven at high temperature, cooling in a desiccator, and powdering.The anhydrous formic acid was then collected by distillation under nitrogen at 100.7°c.

V.4.b.ii. Fluorination in Formic Acid(100%-40%)

General Procedure

A solution containing 4-fluorobenzoic acid(1.63g, 11.6mmol) in 100-40% HCOOH (80ml) was placed in a fluorination apparatus with attached soda lime filled drying tube. Elemental fluorine(35mmol) was passed through the stirred solution using narrow bore PTFE tubing. The resulting mixture was analysed by ^{19}F nmr against a standard of α,α,α-trifluorotoluene to calculate the conversion to 3,4-difluorobenzoic acid.

Volume Formic Acid	Volume H_2O	% Formic Acid
Drying Boric Anhydride	-	100%
No dilution necessary	-	98%
100ml	20ml	80%
100ml	60ml	60%
100ml	140ml	40%

V.5. Decarboxylation of Fluorobenzoic Acids

V.5.a. Oxidation with Sodium Persulphate

A mixture of 4-fluorobenzoic acid(5g, 35mmol), silver(I) nitrate(0.5g, 2.9mmol), sodium persulphate (26g, 125mmol), water(25ml) and acetonitrile(70ml) were refluxed for 16hrs. The reaction mixture was then distilled. Extraction of the residue with dichloromethane(2x25ml), followed by rotary evaporation gave 4-fluorobenzoic acid(1.7g) indicating a conversion to products of 65%. Analysis of the distillate by ^{19}F nmr against an external standard of α,α,α-trifluorotoluene(1.5g, 10.3mmol) confirmed the product as fluorobenzene(2.0g, 88%).

V.5.b. Decarboxylation with Copper Powder

A mixture of 4-fluorobenzoic acid(3.0g, 21mmol), copper powder(3.0g, 46.9mmol) and quinoline(30g, 232mmol) was heated at 160°C under an atmosphere of N_2 for 12hrs. After the mixture had cooled, it was extracted with diethylether (3x25ml). Analysis by g.c. / m.s. showed no reaction had occurred.

V.5.c. Decarboxylation with Copper(I) Iodide

A mixture of 4-fluorobenzoic acid(3.0g, 21mmol), copper(I) iodide(4.0g, 20.9mmol) and quinoline(10g, 77.5mmol) was heated at 160°C under an atmosphere of N_2 for 12hrs. After the mixture had cooled, it was extracted with diethylether (3x25ml). Analysis by g.c. / m.s.. showed no reaction had occurred.

V.5.d. Decarboxylation with Copper(I) Oxide

General Procedure

A Carius tube was charged with polyfluorobenzoic acid, copper(I) oxide(0.6g, 4.2mmol) and quinoline(0.9g, 7.0mmol). The tube was sealed and heated to the required temperature. After 8hrs the tube was opened and volatile material removed under vacuum. Analysis of the liquid by g.c. / m.s. confirmed it as the appropriate polyfluorobenzene.

V.5.d.i. 4-Fluorobenzoic Acid

Temperature	Acid (g,mmol)	Product (g)	Yield of Fluorobenzene*
100°C	0.8g,5.7mmol	-	-
150°C	0.5g,5.7mmol	-	-
200°C	0.5g,3.6mmol	0.1g	32%
300°C	0.5g,3.6mmol	0.2g	43%

V.5.d.ii. Pentafluorobenzoic Acid

Temperature	Acid (g,mmol)	Product (g)	Yield of Pentafluorobenzene¥
100°c	1.0g,4.7mmol	0.6g	74%
150°C	0.7g,4.7mmol	0.6g	76%
200°C	0.7g,4.7mmol	0.7g	87%
300°c	0.7g,3.3mmol	0.5g	90%

V.5.d.iii. 2,3,4-Trifluorobenzoic Acid

2,3,4-Trifluorobenzoic acid (0.6g, 3.4mmol) , copper(I) oxide(0.6g, 4.2mmol) and quinoline(0.9g, 7.0mmol) gave 1,2,3-trifluorobenzene(0.18g, 40%) n.m.r spectrum 11; i.r. spectrum 3; mass spectrum 3.

V.5.d.iv. 2,4-Difluorobenzoic Acid

2,4-Difluorobenzoic acid (0.9g, 5.7mmol) , copper(I) oxide(0.9g, 4.2mmol) and quinoline(1.4g, 7.0mmol) gave 1,3-difluorobenzene(0.02g, 3%) n.m.r spectrum 12; i.r. spectrum 4; mass spectrum 4.

V.6. Preparation of Trimethylsilyl Esters Using BSA

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* n.m.r spectrum 9; i.r. spectrum 1; mass spectrum 1.

¥ n.m.r spectrum 10; i.r. spectrum 2; mass spectrum 2.

V.6.a. 4-Fluorobenzoic Acid

4-Fluorobenzoic acid(1.88g, 8.9mmol) was dissolved in anhydrous acetonitrile(15ml). Bistrimethylacetamide(2.0g,9.9mmol) was added to the solution under a flow of nitrogen. Analysis by a combination of g.c./ m.s and ^{19}F nmr confirmed a 100% conversion to trimethylsilyl-4-fluorobenzoate; n.m.r spectrum 13; mass spectrum 5.

V.6.b. 2,4-Difluorobenzoic Acid

2,4-Difluorobenzoic acid(1.0g, 6.3mmol) was dissolved in anhydrous acetonitrile(15ml). Bistrimethylacetamide(1.9g, 9.9mmol) was added to the solution under a flow of nitrogen. Analysis by a combination of g.c./ m.s and ^{19}F nmr confirmed a 100% conversion to trimethylsilyl-2,4-difluorobenzoate; n.m.r spectrum 14; mass spectrum 6.

V.6.c. 3,4-Difluorobenzoic Acid

3,4-Difluorobenzoic acid(0.5g, 3.2mmol) was dissolved in anhydrous acetonitrile(15ml). Bistrimethylacetamide(0.9g, 5.0mmol) was added to the solution under a flow of nitrogen. Analysis by a combination of g.c./ m.s and and ^{19}F nmr confirmed a 100% conversion to trimethylsilyl-3,4-difluorobenzoate; n.m.r spectrum 15; mass spectrum 7.

V.6.d. 2,4,5-Trifluorobenzoic Acid

2,4,5-Trifluorobenzoic acid(0.1g, 0.6mmol) was dissolved in anhydrous acetonitrile(2ml). Bistrimethylacetamide(0.4g, 2.2mmol) was added to the solution under a flow of nitrogen. Analysis by a combination of g.c./ m.s and and ^{19}F nmr confirmed a 100% conversion to trimethylsilyl-2,4,5-trifluorobenzoate; n.m.r spectrum 16; mass spectrum 8.

V.6.e. 2,3,4-Trifluorobenzoic Acid

2,3,4-Trifluorobenzoic acid(0.1g, 0.6mmol) was dissolved in anhydrous acetonitrile(2ml). Bistrimethylacetamide(0.4g, 2.2mmol) was added to the solution under a flow of nitrogen. Analysis by a combination of g.c./ m.s and and ^{19}F nmr confirmed a 100% conversion to trimethylsilyl-2,3,4-trifluorobenzoate; n.m.r spectrum 17; mass spectrum 9.

V.6.f. 3,4,5-Trifluorobenzoic Acid

3,4,5-Trifluorobenzoic acid(0.1g, 0.6mmol) was dissolved in anhydrous acetonitrile(2ml). Bistrimethylacetamide(0.4g, 2.2mmol) was added to the solution under a flow of nitrogen. Analysis by a combination of g.c./ m.s and and ^{19}F nmr confirmed a 100% conversion to trimethylsilyl-3,4,5-trifluorobenzoate; n.m.r spectrum 18; mass spectrum 10.

V.6.g. 2,3,4,5-Tetrafluorobenzoic Acid

2,3,4,5-Tetrafluorobenzoic acid(0.15g, 0.8mmol) was dissolved in anhydrous acetonitrile(2ml). Bistrimethylacetamide(0.4g, 2.2mmol) was added to the solution under a flow of nitrogen. Analysis by a combination of g.c./ m.s and and ^{19}F nmr confirmed a 100% conversion to trimethylsilyl-2,3,4,5-tetrafluorobenzoate; n.m.r spectrum 19; mass spectrum 11.

V.6.g. 2,3,4,5,6-Pentafluorobenzoic Acid

2,3,4,5-Pentafluorobenzoic acid(0.15g, 0.8mmol) was dissolved in anhydrous acetonitrile(2ml). Bistrimethylacetamide(0.4g, 2.2mmol) was added to the solution under a flow of nitrogen. Analysis by a combination of g.c./ m.s and and ^{19}F nmr confirmed a 100% conversion to trimethylsilyl-2,3,4,5,6-pentafluorobenzoate; n.m.r spectrum 20; mass spectrum 12.

V.7. Large Scale Fluorinations

Prior to all fluorinations, a 3700ml cylinder was charged with 2atm of 50% F_2 in N_2. This was then diluted to 9atm with N_2 to produce a 10% mixture of F_2 in N_2 which was then used for all the fluorination reactions.

V.7.a. Fluorination of Fluorobenzene in Formic Acid

A solution containing fluorobenzene(13.6g, 142mmol) in 98% formic acid (200ml) was placed in a fluorination apparatus with attached soda lime filled drying tube. Fluorine gas (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using narrow bore PTFE tubing at *ca.* 40ml min^{-1}. The mixture was added to an excess of water (1000ml) and extracted with dichloromethane (3x50ml) and dried ($MgSO_4$). Analysis of the resulting mixture by ^{19}F nmr against an external standard of α,α,α-trifluorotoluene(3.3g, 22.5mmol) showed a conversion of 42% from fluorobenzene. The mixture contained fluorobenzene(8.3g), δ_F -116.0 (1F, m); *m/z* , (EI^+), 96 (M^+, 100%), 197; 1,2-difluorobenzene(1.7g), δ_F -143.6 (2F, m); *m/z*, (EI^+), 114 (M^+, 100%); 1,3-difluorobenzene(0.3g), δ_F -143.6 (2F, m); *m/z*, (EI^+), 114 (M^+, 100%); 1,4-difluorobenzene(2.46g), δ_F -124.5 (2F, m); *m/z* , (EI^+), 114 (M^+, 100%) and 1,2,4-trifluorobenzene(0.2g), δ_F -117.3 (1F, m), -135.3(1F, m) and -145.3 (1F, m); *m/z*, (EI^+), 132 (M^+, 100%).

V.7.b. 4-Fluorobenzoic Acid

In each of the following examples the mixtures of fluoro & polyfluorobenzoic acids were analysed first, by comparison of the ^{19}F nmr spectra of the mixtures, with the spectra of authentic samples. More accurate quantitative analysis of the components in these mixtures was obtained by conversion of the carboxylic acids to their more

volatile silyl esters, by treatment with bis(trimethylsilyl) acetamide (BSA) and then analysis by g.c. / mass spec.. Therefore the following mass-spectrometry data refers to the corresponding silyl esters.

V.7.b.i. Fluorination in Formic Acid

General Procedure

A solution containing 4-fluorobenzoic acid in 98% formic acid (200ml) was placed in a fluorination apparatus with attached soda lime filled drying tube. Fluorine gas (165mmol*) as a 10% mixture in nitrogen was then passed through the stirred solution using narrow bore PTFE tubing at *ca.* 40ml min^{-1}. The mixture was added to an excess of water (1000ml) and the resulting solid product was filtered off under vacuum. The filtrate was then extracted with dichloromethane (3x50ml). After drying ($MgSO_4$), the dichloromethane was removed under vacuum to leave an off-white solid.

V.7.b.ii. 1:1.63 Substrate : Fluorine Ratio

4-Fluorobenzoic acid (11.3g, 82.1mmol) produced a white solid(10.5g). Analysis of the solid by ^{19}F nmr against an external standard of fluorobenzene (7.3g, 50.1mmol) showed a conversion of 32% from 4-fluorobenzoic acid. The product contained 4-fluorobenzoic acid(7.8g); n.m.r spectrum 1; *m/z*, (EI^+) 212 (M^+, 3.2%), 197 (-CH_3, 100%); 3,4-difluorobenzoic acid(2.7g); n.m.r spectrum 3; *m/z*, (EI^+) 230 (M^+, 2.4%), 215 (-CH_3, 100%) and unidentifiable material(0.1g).

V.7.b.iii. 1:2 Substrate : Fluorine Ratio

4-Fluorobenzoic acid (11.3g, 82.1mmol) produced a white solid(10.5g). Analysis of the resulting solid by ^{19}F nmr against an external standard of fluorobenzene(4.98g, 34.11mmol) showed a conversion of 51.5% from 4-fluorobenzoic acid. The product contained 4-fluorobenzoic acid(5.6g), n.m.r spectrum 1, *m/z*, (EI^+) 212 (M^+, 3.8%), 197 (-CH_3, 100%); 3,4-difluorobenzoic acid(2.8g), n.m.r spectrum 3, *m/z*, (EI^+) 230 (M^+, 2.8%), 215 (-CH_3, 100%) and unidentifiable material(0.3g).

V.7.b.iv. 1:3 Substrate : Fluorine Ratio

4-Fluorobenzoic acid (4.0g, 28.2mmol) produced a white solid(3.1g). Analysis of the resulting solid by ^{19}F nmr against an external standard of α,α,α-trifluorotoluene(1.7g, 11.6mmol) showed a conversion of 65.3% from 4-fluorobenzoic acid. The product contained 4-fluorobenzoic acid(1.4g), n.m.r spectrum 1, *m/z*, (EI^+) 212 (M^+, 3.2%), 197 (-CH_3, 100%); 3,4-difluorobenzoic acid(1.6g), n.m.r spectrum 3, *m/z*, (EI^+) 230 (M^+, 2.4%), 215 (-CH_3, 100%) and unidentifiable material(0.2g).

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* Except for 1:1.63 substrate: fluorine where 133mmol F_2 was used.

V.7.b.v. 1:4 Substrate : Fluorine Ratio

4-Fluorobenzoic acid (6.0g, 42.9mmol) produced a white solid(5.3g). Analysis of the resulting solid by ^{19}F nmr against an external standard of α,α,α-trifluorotoluene(5.7g, 38.9mmol) showed a conversion of 79.2% from 4-fluorobenzoic acid. The product contained 4-fluorobenzoic acid(1.2g), n.m.r spectrum 1, *m/z*, (EI^+) 212 (M^+, 3.2%), 197 (-CH_3, 100%); 3,4-difluorobenzoic acid(3.5g), n.m.r spectrum 3, *m/z*, (EI^+) 230 (M^+, 2.4%), 215 (-CH_3, 100%); 2,4,5-trifluorobenzoic acid(0.2g), n.m.r spectrum 4, *m/z*, (EI^+) 248 (M^+, 1.2%), 233 (-CH_3, 100%); 2,3,4-trifluorobenzoic (0.1g), n.m.r spectrum 5, *m/z*, (EI^+) 233 (-CH_3, 5.1%); 3,4,5-trifluorobenozoic acid(0.2g), n.m.r spectrum 6, *m/z*, (EI^+) 248 (M^+, 1.5%), 233 (-CH_3, 94.6%) and unidentifiable material(0.3g).

V.7.c. Fluorination in Sulphuric Acid

General Procedure

A solution containing 4-fluorobenzoic acid in 98% sulphuric acid(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube. Elemental fluorine(165mmol)* as a 10% mixture in nitrogen was then passed through the stirred solution using narrow bore PTFE tubing at *ca.* 40ml min^{-1}. The resulting mixture was worked up by adding the mixture to an excess of water(1000ml) and the resulting solid product was filtered off under vacuum. The filtrate was then extracted with dichloromethane (3x50ml). After drying ($MgSO_4$), the dichloromethane was removed under vacuum and a white solid resulted.

V.7.c.i. 1:1.63 Substrate : Fluorine Ratio

4-Fluorobenzoic acid(14.4g, 102.9mmol) produced a white solid(11.6g). Analysis of the resulting solid by ^{19}F nmr against an external standard of α,α,α-trifluorotoluene(2.7g, 18.8mmol) showed a conversion of 82.6% from 4-fluorobenzoic acid . The product contained 4-fluorobenzoic acid(2.5g), n.m.r spectrum 1, *m/z*, (EI^+) 212 (M^+, 3.28%), 197 (-CH_3, 100%); 3,4-difluorobenzoic acid(6.8g), n.m.r spectrum 3, *m/z*, (EI^+) 230 (M^+, 2.76%), 215 (-CH_3, 100%); 2,4,5-trifluorobenzoic acid(1.2g), δ_F n.m.r spectrum 4, *m/z*, (EI^+) 248 (M^+, 1.09%), 233 (-CH_3, 100%); 2,3,4-trifluorobenzoic (0.6g), n.m.r spectrum 5, *m/z*, (EI^+) 248 (M^+, 2.29%), 233 (-CH_3, 93.90%); 3,4,5-trifluorobenzoic acid(0.2g), n.m.r spectrum 6, *m/z*, (EI^+) 248 (M^+, 1.31%), 233 (-CH_3, 100%) and unidentifiable material(0.2g).

* Except in the case of 1:2.4 substrate : Fluorine where 82.5mmol of F_2 was used.

V.7.c.ii. 1:2 Substrate : Fluorine Ratio

4-Fluorobenzoic acid(11.5g, 82.5mmol) produced a white solid(10.6g). Analysis of the resulting solid by ^{19}F nmr against an external standard of α,α,α-trifluorotoluene(3.2g, 21.8mmol) showed a conversion of 84.8% from 4-fluorobenzoic acid . The product contained 4-fluorobenzoic acid(1.8g), n.m.r spectrum 1, *m/z*, (EI^+) 212 (M^+, 3.3%), 197 (-CH_3, 100%); 3,4-difluorobenzoic acid(6.2g), n.m.r spectrum 3, *m/z*, (EI^+) 230 (M^+, 2.8%), 215 (-CH_3, 100%); 2,4,5-trifluorobenzoic acid(0.8g), n.m.r spectrum 4, *m/z*, (EI^+) 248 (M^+, 1.1%), 233 (-CH_3, 100%); 2,3,4-trifluorobenzoic (0.4g), n.m.r spectrum 5, *m/z*, (EI^+) 248 (M^+, 2.3%), 233 (-CH_3, 93.9%); 3,4,5-trifluorobenozoic acid(0.4g), n.m.r spectrum 6, *m/z*, (EI^+) 248 (M^+, 1.3%), 233 (-CH_3, 100%); 2,3,4,5-tetrafluorobenozoic acid(0.7g), n.m.r spectrum 7, *m/z*, (EI^+) 266 (M^+, 0.5%), 251 (-CH_3, 60.3%) and unidentifiable material(0.4g).

V.7.c.iii. 1:2.4 Substrate : Fluorine Ratio

4-Fluorobenzoic acid(7.1g, 55.0mmol) produced a white solid(5.2g). Analysis of the resulting solid by ^{19}F nmr against an external standard of α,α,α-trifluorotoluene(3.6g, 24.9mmol) showed a conversion of 87.9% from 4-fluorobenzoic acid . The product contained 4-fluorobenzoic acid(0.8g), n.m.r spectrum 1, *m/z*, (EI^+) 212 (M^+, 3.28%), 197 (-CH_3, 100%); 2,4-difluorobenzoic acid (0.1g), n.m.r spectrum 2, *m/z*, (EI^+) 230 (M^+, 2.6%), 215 (-CH_3, 100%); 3,4-difluorobenzoic acid(2.7g), n.m.r spectrum 3, *m/z*, (EI^+) 230 (M^+, 2.8%), 215 (-CH_3, 100%); 2,4,5-trifluorobenzoic acid(0.4g), n.m.r spectrum 4, *m/z*, (EI^+) 248 (M^+, 1.1%), 233 (-CH_3, 100%); 2,3,4-trifluorobenzoic (0.1g), n.m.r spectrum 5, *m/z*, (EI^+) 248 (M^+, 2.3%), 233 (-CH_3, 93.9%); 3,4,5-trifluorobenzoic acid(0.2g), n.m.r spectrum 6, *m/z*, (EI^+) 248 (M^+, 1.3%), 233 (-CH_3, 100%); 2,3,4,5-tetrafluorobenozoic acid(0.5g), n.m.r spectrum 7, *m/z*, (EI^+) 266 (M^+, 0.5%), 251 (-CH_3, 60.3%) and unidentifiable material(0.4g).

V.7.c.iv. 1:3 Substrate :Fluorine Ratio

4-Fluorobenzoic acid(7.7g, 55.0mmol) produced a white solid(5.9g). Analysis of the resulting solid by ^{19}F nmr against an external standard of α,α,α-trifluorotoluene(3.6g, 24.9mmol) showed a conversion of 92.3% from 4-fluorobenzoic acid . The product contained 4-fluorobenzoic acid(0.6g), n.m.r spectrum 1, *m/z*, (EI^+) 212 (M^+, 3.28%), 197 (-CH_3, 100%); 2,4-difluorobenzoic acid (0.1g), n.m.r spectrum 2, *m/z*, (EI^+) 230 (M^+, 2.4%), 215 (-CH_3, 100%); 3,4-difluorobenzoic acid(3.4g), n.m.r spectrum 3, *m/z*, (EI^+) 230 (M^+, 2.8%), 215 (-CH_3, 100%); 2,4,5-trifluorobenzoic acid(0.6g), n.m.r spectrum 4, *m/z*, (EI^+) 248 (M^+, 1.1%), 233 (-CH_3, 100%); 2,3,4-trifluorobenzoic (0.2g), n.m.r spectrum 5, *m/z*, (EI^+) 248 (M^+, 2.3%), 233 (-CH_3, 93.9%); 3,4,5-trifluorobenozoic acid(0.5g), n.m.r spectrum 6, *m/z*, (EI^+) 248 (M^+, 1.3%), 233 (-CH_3, 100%); 2,3,4,5-tetrafluorobenozoic acid(0.3g), n.m.r spectrum 7, *m/z*, (EI^+) 266 (M^+, 0.5%), 251 (-CH_3, 60.3%) and unidentifiable material(0.3g).

V.7.d. Fluorination of 2,4-Difluorobenzoic Acid

In the following example the mixtures of fluoro & polyfluorobenzoic acids were analysed first, by comparison of the ^{19}F nmr spectra of the mixtures, with the spectra of authentic samples. More accurate quantitative analysis of the components in these mixtures was obtained by conversion of the carboxylic acids to their more volatile silyl esters, by treatment with bis(trimethylsilyl) acetamide (BSA) and then analysis by g.c. / m. s.. Therefore the quoted mass-spectrometry data refers to the corresponding silyl esters.

V.7.d.i. Sulphuric Acid(1:2 Sub:Fluorine)

2,4-Difluorobenzoic acid(13.0g, 82.3mmol) produced a white solid (9.6g). Analysis of the solid by ^{19}F nmr against an external standard of α,α,α-trifluorotoluene(4.1g, 28.1mmol) showed a conversion of 88.9% from 2,4-difluorobenzoic acid . The product contained 2,4-difluorobenzoic acid(1.4g), n.m.r spectrum 2; 2,4,5-trifluorobenzoic acid(3.7g), n.m.r spectrum 4, *m/z*, (EI^+) 248 (M^+, 1.1%), 233 (-CH_3, 100%); 2,3,4-trifluorobenzoic (1.4g), n.m.r spectrum 5, *m/z*, (EI^+) 248 (M^+, 2.3%), 233 (-CH_3, 93.9%); 2,3,4,5-tetrafluorobenozoic acid(1.1g), n.m.r spectrum 7, *m/z*, (EI^+) 266 (M^+, 0.5%), 251 (-CH_3, 60.3%); 2,3,4,5,6-pentafluorobenzoic acid (0.3g), n.m.r spectrum 8, *m/z*, (EI^+) 269 (-CH_3, 60.2) and unidentifiable material(1.1g).

V.8. Fluorination in a Range of Acids

General Procedure

A solution containing an aromatic substrate in the acid(80ml) was placed in a fluorination apparatus fitted with a tube filled with soda lime. Elemental fluorine(35mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using narrow bore PTFE tubing at *ca.* 4.0ml min^{-1}.The resulting mixture was worked up by adding the mixture to an excess of water(500ml) followed by extraction with dichloromethane(3x25ml). After drying ($MgSO_4$), dichloromethane was removed under vacuum to leave a solid.

V.8.a. Orthophosphoric Acid

4-Fluorobenzoic acid(1.6g,11.3mmol) gave a white solid (1.6g). Analysis of the solid by ^{19}F nmr confirmed it as starting material.

V.8.b. Hydrochloric Acid(40%)

4-Fluorobenzoic acid(1.6g,11.3mmol) gave a white solid (1.6g). Analysis of the solid by ^{19}F nmr confirmed it as starting material.

V.8.c. Hydrobromic Acid(48%)

4-Fluorobenzoic acid(1.6g,11.3mmol) gave a white solid (1.5g). Analysis of the solid by ^{19}F nmr confirmed it as starting material.

V.8.c. Fluorination in Nitric Acid

V.8.c.i. Fluorination of Fluorobenzene (1:1 Sub:Fluorine)

Fluorobenzene(15.0g, 156mmol) was slowly added to cooled 90% nitric acid(150ml) and placed in a fluorination apparatus with attached soda lime filled drying tube. Fluorine gas (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using narrow bore PTFE tubing at *ca.* 40ml min^{-1}. The mixture was added to an excess of water (1000ml),extracted with dichloromethane (3x50ml).and dried ($MgSO_4$). The dichloromethane was removed under rotary evaporation to leave a yellow oil(15.5g). Analysis of the resulting mixture by ^{19}F nmr against an external standard of α,α,α-trifluorotoluene(g, mmol) showed a conversion of 100% from fluorobenzene. The product contained 4-fluoronitrobenzene(5.6g), δ_F -108.9 (1F, m); *m/z* , (EI^+), 141 (M^+, 71.4%); 3,4-difluoronitrobenzene(6.0g), δ_F -128.3 (1F, m), -131.5 (1F, m); *m/z* , (EI^+), 159 (M^+, 92.9%); 2,4,5-trifluoronitrobenzene(0.7g), δ_F -118.6 (1F, m), -123.3 (1F, s),-138.9 (1F, m); *m/z* , (EI^+), 177 (M^+, 92.9%); 2,3,4-trifluoronitrobenzene(0.2g), δ_F -123.9 (1F, m), -128.9 (1F, m),-159.6 (1F, m); *m/z,* (EI^+), 177 (M^+, 92.9%) ; 3,4,5-trifluoronitrobenzene(0.8g), δ_F -131.5 (2F, m), -151.1 (1F, m); *m/z* , (EI^+), 177 (M^+, 92.9%) and 2,4-dinitrofluorobenzene(0.6g), δ_F -104.0 (1F, m); *m/z,* (EI^+), 186 (M^+,100%) and unidentifiable material (1.6g).

V.8.c.ii. Fluorination of 4-fluorobenzoic Acid(1:2 Sub:Fluorine)

4-Fluorobenzoic acid(11.5g, 82.1mmol) was slowly added to cooled 90% nitric acid(150ml) in a fluorination apparatus with attached soda lime filled drying tube. Fluorine gas (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using narrow bore PTFE tubing at *ca.* 40ml min^{-1}. The mixture was added to an excess of water (1000ml), extracted with dichloromethane (3x50ml).and dried ($MgSO_4$). The dichloromethane was removed under rotary evaporation to leave a yellow solid(9.9g). Analysis of the resulting mixture by ^{19}F nmr against an external standard of α,α,α-trifluorotoluene(2.4g, 16.6mmol) showed a conversion of 100% from 4-fluorobenzoic acid. The product contained 3-nitro-4-fluorobenzoic acid(2.2g), δ_F -110.9 (1F, m), *m/z* , $CI^+(CH_4)$, 258 (M^+, 100%); 3-nitro-4,5-difluorobenzoic acid(4.7g), δ_F -131.9 (1F, m), -135.0 (1F, m), *m/z,* $CI^+(CH_4)$, 276 (M^+, 100%); 2,4-difluoronitrobenzene (0.8g) δ_F -107.8 (2F, m), *m/z,* (EI^+) 186 (M^+, 100%) and a range of unidentifiable materials(1.6g).

V.8.d. Fluorination in HF Solutions

V.8.d.i. Fluorination of 4-Fluorobenzoic acid in 40% HF

4-Fluorobenzoic acid(1.63g, 11.3mmol) was placed in a FEP fluorination apparatus with attached soda lime filled drying tube and KF scrubbing unit. Aqueous HF(40ml) was then poured into the container. Elemental fluorine(35mmol) was passed through the stirred solution using narrow bore PTFE tubing. After the passage of fluorine the mixture was poured into a large excess of ice-water. Extraction with DCM (3x25ml), drying($MgSO_4$) and rotary evaporation of the solvent produced a yellow solid (1.5g). Analysis by ^{19}F nmr confirmed it as starting material.

V.8.d.ii. Fluorination of 4-Fluorobenzoic acid in 62% HF

4-Fluorobenzoic acid(1.63g, 11.3mmol) was placed in a FEP fluorination apparatus with attached soda lime filled drying tube and KF scrubbing unit. Aqueous HF(40ml) was then poured into the container. Elemental fluorine(35mmol) was passed through the stirred solution using narrow bore PTFE tubing. After the passage of fluorine the mixture was poured into a large excess of ice-water. Extraction with DCM (3x25ml), drying(MgSO4) and rotary evaporation of the solvent produced a yellow solid (1.4g). Analysis by ^{19}F nmr confirmed it as starting material.

V.8.d.iii. Fluorination of 4-Fluorobenzoic acid in Anhydrous HF

4-Fluorobenzoic acid(1.63g, 11.3mmol) was placed in a FEP fluorination apparatus with attached soda lime filled drying tube and KF scrubbing unit. Anhydrous HF(40ml) was then poured into the container. The fluorination apparatus containing the mixture was cooled by an external coil from a HAAKE cryostat to 0^oC Elemental fluorine(35mmol) was passed through the stirred solution using narrow bore PTFE tubing. After the passage of fluorine the mixture was poured into a large excess of ice-water. Extraction with DCM (3x25ml), drying($MgSO_4$) and rotary evaporation of the solvent produced a brown oil (0.8g). Analysis by ^{19}F nmr showed an extensive reaction had taken place.

V.8.e. Fluorosulphuric Acid

4-Fluorobenzoic acid(1.6g,11.3mmol) produced a brown oil (2.0g). Analysis by ^{19}F nmr confirmed an extensive reaction had occurred producing a range of polyfluorobenzoic acids and a large amount of unidentifiable material.

V.8.f. Fluorination of 4-Fluorobenzoic Acid in Triflic Acid

4-Fluorobenzoic acid(1.6g,11.3mmol) produced a brown oil (1.8g). Analysis by ^{19}F nmr confirmed an extensive reaction had occurred producing a range of polyfluorobenzoic acids and a large amount of unidentifiable material.

V.8.f. Fluorination in 'Super Acids'

V.8.f.i. Fluorination of 4-fluorobenzoic acid with Nafion® Beads

A solution containing 4-fluoronitrobenzene(19.4g, 137.5mmol) and Nafion® beads(25g) in dichloromethane(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube. Elemental fluorine(165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using narrow bore PTFE tubing at *ca.* 40ml min^{-1}. The resulting mixture was filtered to remove the Nafion® beads then poured into an excess of water(1000ml) and extracted with dichloromethane (3x50ml). After drying ($MgSO_4$), the dichloromethane was removed under vacuum and a yellow oil resulted(17.4g). Analysis of the resulting oil by ^{19}F nmr and g.c./ m.s. confirmed it as starting material, 4-fluoronitrobenzene.

V.8.f.ii. Antimony Pentafluoride

4-Fluorobenzoic acid(1.63g, 11.3mmol) was placed in the FEP fluorination apparatus fitted with soda lime filled drying tube and KF scrubbing unit. The fluorination apparatus was then cooled by an external coil from a HAAKE cryostat to 0°C Freshly distiled SbF_5 (20g,92.3mmol) was then slowly poured into the container under a flow of nitrogen. Elemental fluorine(35mmol) was passed through the stirred solution using narrow bore PTFE tubing. After the passage of fluorine the mixture was poured into a large excess of ice-water. Extraction with DCM (3x25ml), drying($MgSO_4$) and rotary evaporation of the solvent produced an off white solid (1.6g). Analysis of the resulting solid by ^{19}F nmr showed the product contained 4-fluorobenzoic acid n.m.r spectrum 1;; 2,4-difluorobenzoic acid n.m.r. spectrum 2; 3,4-difluorobenzoic acid n.m.r spectrum 3; 2,4,5-trifluorobenzoic acid n.m.r spectrum 4; 2,3,4-trifluorobenzoic n.m.r spectrum 5; 3,4,5-trifluorobenozoic acid n.m.r spectrum 6; 2,3,4,5-tetrafluorobenozoic acid n.m.r spectrum 7; 2,3,4,5,6-pentafluorobenzoic acid n.m.r spectrum 8 and unidentifiable material in a ratio of 40:1.8:24.8:3.3:4.5:4.2:4.2:1.5:15.3.

V.8.f.iii. HF / SbF_5 (1:1)

V.8.f.iii.1) Preparation of HF / SbF_5 (1:1)

Antimony pentafluoride (153.2g, mmol) was cooled in an FEP bottle under a stream of nitrogen to 0°C. Anhydrous HF (15g, 750mmol) was added slowly with vigourous stirring. The resulting brown solution was stored in the sealed FEP container at low temperature until it was required.

V.8.f.iii.2) Fluorination of 4-fluorobenzoic Acid in HF/ SbF_5(1:1)

4-Fluorobenzoic acid(1.63g, 11.3mmol) was placed in the FEP fluorination apparatus fitted with soda lime filled drying tube and KF scrubbing unit. The fluorination apparatus was then cooled by an external coil from a HAAKE cryostat to 0°C The 1:1 mixture of HF / SbF_5 (80ml) was then slowly poured into the container under a flow of nitrogen. Elemental fluorine(35mmol) was passed through the stirred solution using narrow bore PTFE tubing. After the passage of fluorine the mixture was poured into a large excess of ice-water. Extraction with DCM (3x25ml), drying($MgSO_4$) and rotary evaporation of the solvent produced a yellow solid(1.44g). Analysis of the resulting solid by ^{19}F nmr showed the product contained 4-fluorobenzoic acid n.m.r spectrum 1; 2,4-difluorobenzoic acid n.m.r. spectrum 2; 3,4-difluorobenzoic acid n.m.r spectrum 3; 2,4,5-trifluorobenzoic acid n.m.r spectrum 4; 2,3,4-trifluorobenzoic n.m.r spectrum 5; 3,4,5-trifluorobenozoic acid n.m.r spectrum 6; 2,3,4,5-tetrafluorobenozoi acid n.m.r spectrum 7; 2,3,4,5,6-pentafluorobenzoic acid n.m.r spectrum 8 and unidentifiable material in a ratio of 31:0.1:30.5:0.7:10.1:5.9:5.6:0.8:12.1

Chapter VI. Experimental To Chapter III

Prior to all reactions, a 3700ml cylinder was charged with 2atm of 50% F_2 in N_2. This was then diluted to 9atm with N_2 to produce a 10% mixture of F_2 in N_2 which was then used for all the fluorination reactions.

VI.1. Iodination

VI.1.a. Initial Reaction

A solution containing 4-fluorobenzoic acid(11.5g, 82.1mmol) and iodine(41.9g, 165mmol) in 98% sulphuric acid(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml) and extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). ^{19}F nmr. showed a conversion of 100% from 4-fluorobenzoic acid. The mixture contained two components 3,5-diiodo-4-fluorobenzoic acid -66.4 (1F, m); *m/z* * , (EI^+) 464 (M^+, 23.1%) 449 (-CH_3, 100%) and 2,3,5-triiodo-4-fluorobenzoic acid -52.1 (1F, m); *m/z*, (EI^+) 518 (M^+, 13.7%) 391 (-I, 100%). No further attempts at isolation were undertaken because of the extreme insolubility of the products.

VI.1.b. Polyfluorobenzenes

General Procedure

A solution containing the polyfluorobenzene and iodine in 98% sulphuric acid(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml) and extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). Dichloromethane was removed under vacuum to leave an oil or solid which was then purified by distillation or recrystalisation from ethanol to afford a single product.

VI.1.b.i. 1,2,3,4,5-Pentafluorobenzene

1,2,3,4,5-pentafluorobenzene(23.1g, 137.5mmol) and iodine(41.9g, 165mmol) gave 6-iodo-1,2,3,4,5-pentafluorobenzene(22.1g, 55%); b.p. 61.4°C / 15mm (lit.[268], 162-163°C); (Found: C, 24.7%: Calc. for C_6F_5I C , 24.5%); n.m.r spectrum 21; i.r. spectrum 5; mass spectrum 13.

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* As trimethylsilyl ester

VI.1.b.ii. 1,2,3,4-Tetrafluorobenzene

1,2,3,4-tetrafluorobenzene(11.3g, 75mmol) and iodine(41.9g, 165mmol) gave 5,6-diiodo-1,2,3,4-tetrafluorobenzene(20g, 66%); m.p. 48-50°C (lit.[269] , 50.5-51.8°C) ; b.p. 100°C / 2mm; (Found: C, 18.12: Calc. for $C_6F_4I_2$ C , 17.93%); n.m.r spectrum 22; i.r. spectrum 6; mass spectrum 14.

VI.1.b.iii. 1,2,4,5-Tetrafluorobenzene

A solution containing 1,2,4,5-tetrafluorobenzene(11.3g, 75mmol) and iodine(21.9g, 165mmol) in 98% sulphuric acid(120ml) and Arklone®(30ml)* was placed in a fluorination apparatus with attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml), extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). G.c. / m.s. showed a conversion of 100% from 1,2,4,5-tetrafluorobenzene. Dichloromethane was removed under vacuum to leave a white solid (23.0g, 76.3%) which was recrystallised from EtOH to afford a single product, 3,6-diiodo-1,2,4,5-tetrafluorobenzene(20.5g, 68%) m.p.109-111°C (lit.[270], 109-111°C); (Found: C, 17.59: Calc. for $C_6F_4I_2$ C , 17.93 %); n.m.r spectrum 23; i.r. spectrum 7; mass spectrum 15.

VI.1.b.iv. 1,3,5-Trifluorobenzene

1,3,5-trifluorobenzene(6.8g, 51.5mmol) and iodine(41.9g, 165mmol) gave 1,3,5-trifluoro-2,4,6-triiodobenzene(10.2g, 39%); m.p.143-145°C (lit.[271] , no m.p. given); (Found: C, 13.98: Calc. for $C_6F_3I_3$ C , 14.14 %); n.m.r spectrum 24; i.r. spectrum 8; mass spectrum 16.

VI.1.b.v. 1,3,5-Trifluorobenzene

A solution containing 1,3,5-trifluorobenzene(6.9g, 52.3mmol) and iodine(21.9g, 165mmol) in in 98% sulphuric acid(120ml) and Arklone®(30ml) was placed in a fluorination apparatus with attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml), extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). G.c. / m.s. showed a conversion of 100% from 1,3,5-trifluorobenzene. Dichloromethane was removed under vacuum to leave an off-white solid (18.6g, 69.7%) which was recrystallised from EtOH to afford a single product,1,3,5-trifluoro-2,4,6-triiodobenzene(16.6g, 63%); m.p. 143-

* ICI Trade name for CF_2ClCCl_2F.

145°C (lit.[271] , no m.p. given); (Found: C, 14.00: Calc. for $C_6F_3I_3$ C , 14.14 %); n.m.r spectrum 24; i.r. spectrum 8; mass spectrum 16.

VI.1.b.vi. 4,4'-Difluorobenzophenone

4,4'-difluorobenzophenone(16.4g, 75.2mmol) and iodine(41.9g, 165mmol) gave 4,4'-difluoro-3,3'-diiodobenzophenone(13.5g, 38.3%); m.p. 129-131°C; (Found: C, 33.00 ; H , 1.22: Calc. for $C_{13}H_6F_2I_2O$ C, 33.22 ; H, 1.29 %); n.m.r spectrum 25; i.r. spectrum 9; mass spectrum 17.

VI.1.b.vii. 1,4-Difluorobenzene

A solution containing 1,4-difluorobenzene(25.0g, 219mmol) and iodine(21.9g, 86mmol) in 98% sulphuric acid(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml) and extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). G.c. / m.s. showed a conversion of 100% from 1,4-difluorobenzene and confimed the two major products as 1,4-difluoro-2-iodobenzene(59%) and 1,4-difluoro-2,3-diiodobenzene(41%). Attempted distillation resulted in decomposition of the products.

VI.1.c. Iodination of a Range of Aromatics

General Procedure

A solution containing an aromatic and iodine in in 98% sulphuric acid(120ml) and Arklone®(30ml) was placed in a fluorination apparatus with attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml), extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). Dichloromethane was removed under rotary evaporation to leave either an oil or solid which was purified either by distillation or recrystallisation from ethanol to afford a single product.

VI.1.c.i. Nitrobenzene

Nitrobenzene(16.9g, 137.5mmol) and iodine(21.0g, 82.7mmol) gave 3-iodonitrobenzene(17.4g, 51%) b.p. 116°C / 1.5mm (lit.[167] , 280°C); (Found: C, 28.82 ; H , 1.54; N , 5.54: Calc. for $C_6H_4INO_2$ C , 28.94 ; H , 1.62 ; N , 5.63 %); n.m.r spectrum 26; i.r. spectrum 10; mass spectrum 18.

VI.1.c.ii. α,α,α-Trifluorotoluene

α,α,α-Trifluorotoluene (21.1g, 144.5mmol) and iodine (21.9g, 86.2mmol) gave 3-iodo-α,α,α-trifluorotoluene(32.6g, 82.9%) b.p. 116°C / 1.5mm (lit.[167] , 82-82.5°C / 25mm); (Found: C, 30.75;H , 1.40: Calc. for $C_7H_4F_3I$ C , 30.88 ; H , 1.47 %); n.m.r spectrum 27; i.r. spectrum 11; mass spectrum 19.

VI.1.c.iii. 1,3-Bistrifluoromethylbenzene

1,3-Bistrifluoromethylbenzene (29.4g, 137.5mmol) and iodine (21.9g, 86.2mmol) gave 1,3-bis(trifluoromethyl)-5-iodobenzene (27.5g, 83%) b.p. 58°C / 26mm; (Found: C, 28.00; H , 0.86: Calc. for $C_8H_3F_6I$ C , 28.24 ; H , 0.88 %); n.m.r spectrum 28; i.r. spectrum 12; mass spectrum 20.

VI.1.c.iv. 4-Fluorobenzoic Acid

4-Fluorobenzoic acid (19.3g, 137.5mmol) and iodine (21.2g, 83.5mmol) gave 4-fluoro-3-iodo-benzoic acid (21.4g, 58.5%); m.p. 174-176°C (lit.[272], 175-176°C); (Found: C, 31.52 ; H , 1.42: Calc. for $C_7H_4FIO_2$ C , 31.58; H , 1.50 %); n.m.r spectrum 29; i.r. spectrum 13; mass spectrum 21.

VI.1.c.v. 2,4-Difluorobenzoic Acid

2,4-Difluorobenzoic acid (21.8g, 137.5mmol) and iodine (21.9g, 86.2mmol) gave 2,4-difluoro-5-iodobenzoic acid (29.9g, 76.6%); m.p.151-152°C; (Found: C, 29.61 ;H , 1.12: Calc. for $C_7H_3F_2IO_2$ C , 29.58 ; H , 1.06 %); n.m.r spectrum 30; i.r. spectrum 14; mass spectrum 22.

VI.1.c.vi. 2,4-Difluoronitrobenzene

2,4-Difluoronitrobenzene(21.1g, 144.5mmol) and iodine (21.9g, 86.2mmol) gave 2,4-difluoro-5-iodonitrobenzene (32.8g, 83.6%); (Found: C, 25.10 ;H , 0.70: N , 4.91: Calc. for $C_6H_2F_2INO_2$ C , 25.3 ; H , 0.70 ; N , 4.91 %); n.m.r spectrum 32; i.r. spectrum 16; mass spectrum 24.

VI.1.c.vii. 4-Fluorobenzonitrile

4-Fluorobenzonitrile (16.6g, 137.5mmol) and iodine (21.9g, 86.2mmol) gave 4-fluoro-3-iodobenzonitrile(28.5g, 84%) m.p. 57-59°C ; (Found: C, 34.29; H , 1.18: N ,

5.64: Calc. for C_7H_3FIN C , 34.01 ; H , 1.21 ; N , 5.67 %); n.m.r spectrum 33; i.r. spectrum 17; mass spectrum 25.

VI.1.c.viii. 4-Fluoronitrobenzene

4-Fluoronitrobenzene (21.1g, 144.5mmol) and iodine (21.9g, 86.2mmol) gave 4-fluoro-3-iodonitrobenzene(25.7g, 70%); (Found: C, 26.94 ;H ,1.09: N , 5.24: Calc. for $C_6H_3FINO_2$ C , 26.97 ; H , 1.12 ; N , 5.24 %); n.m.r spectrum 34; i.r. spectrum 18; mass spectrum 26.

VI.1.d. Effect of Solvent on Iodination

VI.1.d.i. Volume Of Co-Solvent

General Procedure:

A solution containing nitrobenzene (16.9g, 137.5mmol) and iodine (21.9g, 86.2mmol) in the required volume of 98% sulphuric acid and Arklone® was placed in a fluorination apparatus with an attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml) , extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). G.c. / m.s. was used to determine the conversion. The dichloromethane was removed under vacuum to leave the crude product thus enabling determination of the crude yield.

VI.1.d.ii. Different Co-Solvents

General Procedure:

A solution containing nitrobenzene (16.9g, 137.5mmol) and iodine (21.9g, 86.2mmol) in 98% sulphuric acid(75ml) and the co-solvent(75ml) was placed in a fluorination apparatus with an attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml) , extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). G.c. / m.s. was used to determine the conversion. The dichloromethane was removed under vacuum to leave the crude product thus enabling determination of the crude yield.

VI.1.d.iii. Use of Different Acids

General Procedure:

A solution containing trifluoromethylbenzene (20.1g, 137.5mmol) and iodine (21.9g, 86.2mmol) in the acid(150ml) was placed in a fluorination apparatus with an attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE

tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml) , extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). G.c. / m.s. was used to determine the conversion.

VI.1.e. Limitation of Iodination

VI.1.e.i. Iodination of 3-Nitrotrifluoromethylbenzene

A solution containing 3-nitrotrifluoromethylbenzene(26.3g, 137.5mmol) and iodine (21.9g, 86.2mmol) in in 98% sulphuric acid(120ml) was placed in a fluorination apparatus with an attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml), extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). G.c. / m.s. showed a conversion of 14% from 3-nitrotrifluoromethylbenzene to 5-iodo-3-nitrotrifluoromethylbenzene δ_C(100.6MHz; $CDCl_3$; TMS) 93.9 (s, 5-C), 120.4 (m, 6-C), 128.2 (m, CF_3) 135.8 (s, 4-C), 140.3 (m, 2-C), 142.7 (m, 4-C); δ_H(200.6MHz; $CDCl_3$; TMS) 7.9 (m, 4-H), 8.3 (m, 6-H), 8.8 (m, 2-H); *m/z* , (EI^+) 317 (M^+, 65.6%) 271 ($-NO_2$, 23.6%)

VI.1.e.ii. Iodination of Sanger's Reagent

A solution containing 2,4-dinitrofluorobenzene(25.4g, 137.5mmol) and iodine (21.9g, 86.2mmol) in in 98% sulphuric acid(120ml) was placed in a fluorination apparatus with an attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml), extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). G.c. / m.s. showed no conversion to iodinated product.

VI.1.e.iii. Iodination of 1,3-Dinitrobenzene

A solution containing 1,3-dinitrobenzene(23.1g, 137.5mmol) and iodine (21.9g, 86.2mmol) in in 98% sulphuric acid(120ml) was placed in a fluorination apparatus with an attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml), extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). G.c. / m.s. showed no conversion to iodinated product.

VI.1.e.iv. Iodination of 1,4-Dinitrobenzene

A solution containing 1,4-dinitrobenzene(23.1g, 137.5mmol) and iodine (21.9g, 86.2mmol) in in 98% sulphuric acid(120ml) was placed in a fluorination apparatus with an attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml), extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). G.c. / m.s. showed no conversion to iodinated product.

VI.2. Bromination

VI.2.a. Initial Reaction

A solution containing 4-fluorobenzoic acid(11.5g, 82.1mmol) and bromine(26.4g, 165mmol) in 98% sulphuric acid (200ml) was placed in a fluorination apparatus with attached soda lime filled drying tube. Fluorine gas (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml), extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). Analysis of the resulting solution by ^{19}F nmr against an external standard of α,α,α-trifluorotoluene(3.1g, 21.2mmol) showed a conversion of 92% from 4-fluorobenzoic acid. The solution contained 4-fluorobenzoic acid(0.9g); δ_F -107.0 (1F, m); *m/z* *, (EI^+) 212 (M^+, 3.4%), 197 (-CH_3, 100%); 3,4-difluorobenzoic acid(0.6g); δ_F -132.1 (1F, m) and -137.9 (1F, m); *m/z* *, (EI^+) 230 (M^+, 2.6%), 215 (-CH_3, 100%); 3-bromo-4-fluorobenzoic acid(7.9g); δ_F -101.5 (1F, m); *m/z* *, (EI^+) 292 (M^+, 6.5%), 277 (-CH_3, 100%); 3,5-dibromo-4-fluorobenzoic acid(1.4g) δ_F -93.9 (1F, m)+ and unidentifable material (1.4g).

VI.2.b. A Range of Aromatics

General Procedure

A solution containing an aromatic and bromine in 98% sulphuric acid (150ml) was placed in a fluorination apparatus with an attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml), extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). The dichloromethane was removed under vacuum leaving a solid or an

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* As the trimethylsilyl ester

+ By ^{19}F nmr only.

oil which was then purified by recrystallisation from ethanol or distillation to afford a single product.

V1.2.b.i. 4-Fluoronitrobenzene

4-Fluoronitrobenzene (19.4g, 137.5mmol) and bromine (21.2g, 83.5mmol) gave 3-bromo-4-fluoronitrobenzene (21.4g, 58.5%); m.p. 57-59°C (lit.[273], 58-59°C); (Found: C, 32.6 H , 1.31 ; N , 6.14: Calc. for $C_6H_3BrFNO_2$ C , 32.9 ; H , 1.37 ; N , 6.39 %); n.m.r spectrum 35; i.r. spectrum 19; mass spectrum 27.

V.2.b.ii. 2,4-Difluoronitrobenzene

2,4-Difluoronitrobenzene (21.9g, 137.5mmol) and bromine (26.0g, 83.5mmol) gave 5-bromo-2,4-diflluoronitrobenzene(21.2g, 65.4%) b.p. 98 °C / 8mm (lit.[274], 97°C); (Found: C, 30.43 ;H , 0.83: N ,.5.92: Calc. for $C_6H_2BrF_2NO_2$ C , 30.38 ; H , 0.84 ; N , 5.91 %); n.m.r spectrum 36; i.r. spectrum 20; mass spectrum 28.

VI.2.b.iii. 4-Fluorobenzoic Acid

4-Fluorobenzoic acid (19.3g, 137.5mmol) and bromine (21.2g, 83.5mmol) gave 3-bromo-4-fluorobenzoic acid (16.8g, 65%); m.p. 137-139°C (lit.[167], 138-140°C); (Found: C, 38.46 ;H , 1.64: Calc. for $C_7H_4BrFO_2$ C , 38.53 ; H , 1.8 %); n.m.r spectrum 37; i.r. spectrum 21; mass spectrum 29.

VI.2.b.iv. 2,4-Dinitrofluorobenzene

2,4-Dinitrofluorobenzene (25.4g, 137.5mmol) and bromine (26.0g, 83.5mmol) gave 2-bromo-4,6-dinitro-fluorobenzene(21.8g, 60.0%); (Found: C, 27.34 ; H , 0.68 ; N , 10.41: Calc. for $C_6H_2BrFN_2O_4$ C , 27.3 ; H , 0.76 ; N , 10.6 %); n.m.r spectrum 38; i.r. spectrum 22; mass spectrum 30.

VI.2.c. Limitation of Bromination

VI.2.c.i. Bromination of 1,3-Dinitrobenzene

A solution containing 1,3-dinitrobenzene(23.1g, 137.5mmol) and bromine (26.1g, 165mmol) in in 98% sulphuric acid(120ml) was placed in a fluorination apparatus with an attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml) , extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). G.c. / m.s. showed a conversion of 48% from 1,3-dinitrobenzene to 3,5-dinitrobromobenzene *m/z*., (EI^+) 248 (M^+, 26.0%) 202 (-NO_2, 5.6%)

VI.2.c.ii. Bromination of 1,4-Dinitrobenzene

A solution containing 1,4-dinitrobenzene(23.1g, 137.5mmol) and bromine (26.1g, 165mmol) in in 98% sulphuric acid(120ml) was placed in a fluorination apparatus with an attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml), extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). G.c. / m.s. showed no conversion to brominated products.

VI.3. Reactions of Interhalogens

VI.3.a. Reactions of Iodine Monochloride

VI.3.a.i. Trifluoromethylbenzene

A solution of trifluoromethylbenzene(4.8g, 32.5mmol), iodine monochloride (6.3g, 39.1mmol) and sulphuric acid(20ml) was stirred overnight. The solution was then poured into a 5% solution of sodium metabisulfite(500ml), extracted with dichloromethane (3x10ml) and then dried($MgSO_4$). Analysis by g.c. / m.s showed a 84% conversion from α,α,α-trifluoromethylbenzene to two products 3-chlorotrifluoromethylbenzene(60%) *m/z* (EI^+) 159 (M^+, 20.0%), 157 (M^+, 61.2%) and 3-iodotrifluoromethylbenzene (24%) *m/z* (EI^+) 272 (M^+, 51.6%)

VI.3.a.ii. Nitrobenzene without Fluorination

A solution of nitrobenzene(4.0g, 32.5mmol), iodine monochloride (6.3g, 39.1mmol) and sulphuric acid(20ml) was stirred overnight. The solution was then poured into a 5% solution of sodium metabisulfite(500ml), extracted with dichloromethane (3x10ml) and then dried($MgSO_4$). Analysis by g.c. / m.s showed a 9% conversion from nitrobenzene to 3-chloronitrobenzene(44%) *m/z* (EI^+) 159 (M^+, 20.0%), 157 (M^+, 61.2%).

VI.3.a.iii. Nitrobenzene with Fluorination

A solution of nitrobenzene(16.9g, 137.5mmol), iodine monochloride (26.8g, 82.5mmol) and sulphuric acid(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tube at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite(1500ml), extracted with dichloromethane (3x100ml) and then dried($MgSO_4$). The dichloromethane was removed under vacuum to leave a red liquid(22g). Analysis by g.c. / m.s showed a 100% conversion from nitrobenzene to two major products and confirmed them as 3-chloronitrobenzene(44%) *m/z* (EI^+) 159 (M^+, 20.0%), 157 (M^+, 61.2%) and 3-iodonitrobenzene(45%) *m/z* (EI^+) 249 (M^+, 100%), 203 ($M^+ - NO_2$).

VI.4. Investigation into Mechanism

VI.4.a. Preformed IF Without Acid

A solution of iodine(43.8g, 137.5mmol) in CF_2ClCl_2F(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube and cooled to -78°C using a solid CO_2 / acetone slush bath. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tube at *ca.* 40ml min^{-1}. After the fluorine had been added to the solution an aliquot was removed by syringe and ^{19}F nmr confirmed the formation of IF [δ_F(235MHz) -160.0ppm (1F,s)]. A previously cooled solution of nitrobenzene(16.9g, 137.5mmol) dissolved in CF_2ClCCl_2F(75ml) was then added to the bulk solution and allowed to warm to room temperature with stirring. The solution was then poured into a 5% solution of sodium metabisulfite(1500ml) and the organic layer run off. The aqueous layer was then extracted with dichloromethane (3x100ml) and the organics combined and then dried($MgSO_4$). The CF_2ClCCl_2F was removed under vacuum to leave a yellow liquid. Analysis by g.c. / m.s showed no conversion to 3-iodonitrobenzene.

VI.4.b. Preformed IF With Acid

A solution of iodine(43.8g, 137.5mmol) in CF_2ClCl_2F(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube and cooled to -78°C using a solid CO_2 / Acetone slush bath. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tube at *ca.* 40ml min^{-1}. After the fluorine had been added to the solution an aliquot was removed by syringe and ^{19}F nmr confirmed the formation of IF [δ_F(235MHz) -160.0ppm (1F,s)]. A previously cooled solution of nitrobenzene(16.9g, 137.5mmol) dissolved in sulphuric acid(75ml) was then added to the bulk solution and allowed to warm to room temperature with stirring. The solution was then poured into a 5% solution of sodium metabisulfite(1500ml) and the organic layer run off. The aqueous layer was then extracted with dichloromethane (3x100ml) and the organics combined and then dried($MgSO_4$). The dichloromethane and CF_2ClCCl_2F were removed under vacuum to leave a light pink liquid. Analysis by g.c./ m.s showed a 12% conversion from nitrobenzene to 3-iodonitrobenzene.

VI.5. Fluorination of Iodoaromatics

VI.5.a. Preparation Methyl-2,4-difluoro-5-iodobenzoate

Diazomethane was prepared according to standard laboratory procedures[275] and slowly added to a cooled solution of 2,4-difluorobenzoic acid(3.0g, 19mmol) in dry diethylether(20ml) until the colour persisted and the evolution of gas ceased. The solvent was then removed by rotary evaporation to leave a clear solid (2.9g, 89%) which was purified by vacuum transfer to afford a single product methyl 2,4-difluoro-5-

iodobenzoate (2.6g, 80%); m.p. 32-34°C; n.m.r spectrum 31; i.r. spectrum 15; mass spectrum 23.

VI.5.b. Silver Fluoride

VI.5.b.i. 4-Fluoro-3-iodonitrobenzene

A Carius tube was charged with 4-fluoro-3-iodonitrobenzene(0.9g, 3.4mmol) and silver fluoride(0.9g, 6.8mmol). The tube was sealed and heated to the required temperature. After 8hrs the tube was opened extracted with dichloromethane (2x10ml), filtered and then dried($MgSO_4$) . Analysis by g.c. / m.s. confimed no fluorination had taken place.

VI.5.b.ii. Methyl-2,4-difluoro-5-iodobenzoate

A Carius tube was charged with methyl-2,4-difluoro-5-iodobenzoate(1.0g, 3.4mmol) and silver fluoride(0.9g, 6.8mmol). The tube was sealed and heated to the required temperature. After 8hrs the tube was opened extracted with dichloromethane (2x10ml), filtered and then dried($MgSO_4$). Analysis by g.c. / m.s. showed no fluorination had taken place.

VI.5.c. Potassium Fluoride

VI.5.c.i. 4-Fluoro-3-iodobenzonitrile

A Carius tube was charged with 4-fluoro-3-iodobenzonitrile(0.8g, 3.4mmol) and dry potassium fluoride(0.4g, 6.8mmol). The tube was sealed and heated to the required temperature. After 8hrs the tube was opened extracted with dichloromethane (2x10ml), filtered and then dried($MgSO_4$) . Analysis by g.c. / m.s. showed no fluorination had taken place.

VI.5.d. Silver Difluoride

VI.5.d.i. 4-Fluoro-3-iodonitrobenzene

A Carius tube was charged with 4-fluoro-3-iodonitrobenzene(0.9g, 3.4mmol) and silver difluoride(1.0g, 6.8mmol). The tube was sealed and heated to the required temperature. After 8hrs the tube was opened extracted with dichloromethane (2x10ml), filtered and then dried($MgSO_4$) . Analysis by g.c. / m.s. confimed no fluorination had taken place.

VI.5.d.ii. Methyl-2,4-difluoro-5-iodobenzoate

A Carius tube was charged with methyl-2,4-difluoro-5-iodobenzoate(1.0g, 3.4mmol) and silver fluoride(1.0g, 6.8mmol). The tube was sealed and heated to the required temperature. After 8hrs the tube was opened extracted with dichloromethane (2x10ml), filtered and then dried($MgSO_4$). Analysis by g.c. / m.s. confimed no fluorination had taken place.

VI.5.c.iii. 4-Fluoro-3-iodobenzonitrile

A Carius tube was charged with 4-fluoro-3-iodobenzonitrile(0.8g, 3.4mmol) and silver fluoride(1.0g, 6.8mmol). The tube was sealed and heated to the required temperature. After 8hrs the tube was opened extracted with dichloromethane (2x10ml), filtered and then dried($MgSO_4$) . Analysis by g.c. / m.s. confimed a trace amount of 1,2-difluorobenzene *m/z* (EI^+) 114 (M^+, 100%).

VI.6. Perfluoroalkylation Reactions

General Procedure:

A mixture of copper(I) iodide (2.0g, 10.5mmol) and sodium trifluoroacetate (0.8g, 5.9mmol) were stirred in a three necked flask fitted with suba-seals and a condensor under vacuum for 8hrs or until completely dry. The substrate (3.9mmol) was then added to the flask either by syringe if it was a liquid or in a glove bag under the flow of dry nitrogen if it was a solid. NMP (*N* -methylpyrrolidin-2-one) (20ml) was then syringed into the flask. The mixture was stirred under nitrogen at 160°C for upto five hours. Every half hour a small sample was removed using a syringe, filtered and then analysed using g.c./ m.s. The trifluoromethylated products were identified either by the molecular ion peak, fragmentation pattern or more usually by the library searching facility present on the g.c. / m.s. Further integration of the g.c. / m.s. chromatogram allowed the composition of the perfluoroalkylation reaction to be identified at each of the relevant time points.

Chapter VII. Experimental To Chapter IV

Prior to all reactions, a 3700ml cylinder was charged with 2atm of 50% F_2 in N_2. This was then diluted to 9atm with N_2 to produce a 10% mixture of F_2 in N_2 which was then used for all the fluorination reactions.

VII.1. Attempted Iodination of Pyridine

A solution containing pyridine(10.9g, 137.5mmol) and iodine(41.9g, 165mmol) in 98% sulphuric acid(20ml) and Arklone(130ml) was placed in a fluorination apparatus with attached soda lime filled drying tube and allowed to cool to -10°C under a flow of dry nitrogen. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was allowed to reach room temperature then poured into an iced 5% solution of sodium metabisulfite(1500ml) and neutralised with sodium bicarbonate. It was then continously extracted with dichloromethane(200ml) over a period of 8hrs. The organic phase was then dried($MgSO_4$) and the solvent removed by rotary evaporation to leave a brown oil(6.9g). Analysis by g.c. / m.s. and ^1H nmr showed the oil to contain pyridine (100%) *m/z* , (EI^+), 79 (M^+, 100%).

VII.2. Fluorination Using Iodine and Fluorine

General Procedure

A solution containing the pyridine and iodine(10.9g, 42.9mmol) in Arklone(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube and allowed to cool to -10°C under a flow of dry nitrogen. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was allowed to reach room temperature and then poured into a metabisulphite solution(1500ml) and then neutralised with sodium bicarbonate. It was then continously extracted with dichloromethane(200ml) over a period of 8hrs. The organic phase was then dried($MgSO_4$) and the solvent removed by rotary evaporation to leave an oil.

VII.2.a. 4-Ethylpyridine

4-Ethylpyridine(14.7g, 137.4mmol) gave a brown oil(10.2g). Vacuum transfer followed by analysis by g.c. / m.s. showed a conversion of 90% from 4-ethylpyridine to 2-fluoro-4-ethylpyridine. Addition of 1N HCl(2ml) followed by vacuum transfer produced pure colourless oil 2-fluoro-4-ethylpyridine(8.2g, 53%); nmr spectrum 39; i.r. spectrum 23; mass spectrum 31.

VII.2.b. Pyridine

Pyridine(10.9g, 137.5mmol) gave a brown oil (9.5g). Vacuum transfer followed by analysis by g.c. / m.s. showed a conversion of 59% from pyridine. The oil contained 2-fluoropyridine δ_H (199.975MHz, $CDCl_3$, TMS) 6.7 (1H, m), 6.9 (1H, m) 7.2 (1H, m) 8.2 (1H, m); δ_C (50.289MHz; $CDCl_3$; TMS) 109.4 (d, $^2J_{C-F}$ 37.1, 3-C), 121.3 (d, $^4J_{C-F}$ 4.2, 5-C), 141.2 (d, $^3J_{C-F}$ 7.7, 4-C), 147.5 (d, $^2J_{C-F}$ 14.5, 6-C), 163.5 (d, $^1J_{C-F}$ 237.4, 2-C); δ_F (235.342MHz; $CDCl_3$; $CFCl_3$) -67.7 (1F, s, 4-F); *m/z* (EI^+) 177 (M^+, 45.7%) 175 (M^+, 45.4%); pyridine *m/z* (EI^+) 79 (M^+, 100%) and 2,6-difluoropyridine *m/z* (EI^+) 115 (M^+, 100%) in a ratio of 56%:41%:3%.

VII.2.c. 2-Bromopyridine

2-Bromopyridine(21.6g, 137.5mmol) gave a brown oil (23.0g). Vacuum transfer followed by analysis by g.c. / m.s. showed a conversion of 43% from 2-bromopyridine. The oil contained 2-bromo-6-fluoropyridine δ_H (199.975MHz, $CDCl_3$, TMS) 7.0 (1H, m), 7.9 (2H, m) ; δ_C (50.289MHz; $CDCl_3$; TMS) 108.5 (d, $^2J_{C-F}$ 34.9, 3-C), 125.8 (d, $^4J_{C-F}$ 4.9, 5-C), 142.1 (s, 1-C), 143.5 (d, $^3J_{C-F}$ 7.5, x-C), 162.0 (d, $^1J_{C-F}$ 242.4, 2-C); δ_F (235.3MHz; $CDCl_3$; $CFCl_3$) -65.7 (1F, s, 4-F); *m/z* (EI^+) 177 (M^+, 45.7%) 175 (M^+, 45.4%); 2-bromopyridine *m/z* (EI^+) 157 (M^+, 58.1%) 159 (M^+, 452.3%); 2-fluoropyridine *m/z* (EI^+) 97 (M^+, 100%) and unidentified material in a ratio of 33%:57%:8%:2%.

VII.2.d. Quinoline

A solution containing the quinoline(10.6g, 82.5mmol) and iodine(21.0g, 82.5mmol) in Arklone(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube and allowed to cool to -10°C under a flow of dry nitrogen. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was allowed to reach room temperature and then poured into a metabisulphite solution(1500ml) and then neutralised with sodium bicarbonate. It was then extracted with dichloromethane(3x100ml) and then dried($MgSO_4$). The solvent was removed by rotary evaporation to leave an oil (7.2g). Distillation .afforded a yellow oil which was confirmed as 2-fluoroquinoline (6.5g, 54%); b.p. 134-136 (lit.[276], 109°C / 5mm); n.m.r spectrum 46; i.r. spectrum 30; mass spectrum 38.

VII.3. Initial Ethoxylation Reactions

VII.3.a. Reaction of Pyridine, Iodine, Ethanol and Fluorine

A solution containing the pyridine(10.9g, 137.5mmol), iodine(21.9g, 86mmol) and ethanol(12g, 281mmol) in Arklone(100ml) was placed in a fluorination apparatus with attached soda lime filled drying tube and allowed to cool to -10°C under a flow of dry nitrogen. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then

passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was allowed to reach room temperature and then poured into a metabisulphite solution(1500ml) and neutralised with sodium bicarbonate. It was then continously extracted with dichloromethane(200ml) over a period of 8hrs. The organic phase was then dried($MgSO_4$) and the solvent removed by rotary evaporation to leave an oil(6.9g). Analysis by g.c./ m.s. confirmed the oil contained 3 components pyridine *m/z* (EI^+) 79 (M^+, 93%); 2-fluoropyridine *m/z* (EI^+) 97 (M^+, 100%) and 2-ethoxypyridine *m/z* (EI^+) 123 (M^+, 28.4%) in a ratio of 38:14:48.

VII.3.b. Two Stage Reactions

General Procedure

A solution containing the pyridine(137.5mmol) and iodine(21.9g, 86.2mmol) in Arklone(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube and allowed to cool to -10°C under a flow of dry nitrogen. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was allowed to reach room temperature. Ethanol(12g, 260mmol) was then added to the mixture which was left to stir for 8hrs at around 40°C. The mixture was then poured into an excess of water(1500ml) and neutralised with sodium bicarbonate. It was then continously extracted with dichloromethane(200ml) again over a period of 8hrs. The organic phase was then dried ($MgSO_4$) and the solvent removed by rotary evaporation to leave an oil which was analysed by a combination of ^1H nmr ^{19}F nmr and g.c. / m.s.

VII.3.c. Reaction of Pyridine, Ethanol and Fluorine

A solution containing the pyridine(10.9g, 137.5mmol) and ethanol(15g, 326mmol) and Arklone(100ml) was placed in a fluorination apparatus with attached soda lime filled drying tube and allowed to cool to -10°C under a flow of dry nitrogen. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was allowed to reach room temperature and then poured into an excess of water(1500ml) and neutralised with sodium bicarbonate. It was then continously extracted with dichloromethane(200ml) over a period of 8hrs. The organic phase was then dried($MgSO_4$) and the solvent removed by rotary evaporation to leave an oil(7.2g). Analysis by g.c./ m.s. confirmed the oil contained 3 components pyridine *m/z* (EI^+) 79 (M^+, 94%); 2-fluoropyridine *m/z* (EI^+) 97 (M^+, 100%) and 2-ethoxypyridine *m/z* (EI^+) 123 (M^+, 28.9%) in a ratio of 39:14:47.

VII.3. Alkoxylation of Pyridine

General Procedure

A solution containing the pyridine and the alcohol in Arklone(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube and allowed to cool to -10°C under a flow of dry nitrogen. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at ca. 40ml min^{-1}. After the fluorine had been added the solution was allowed to reach room temperature and then poured into an excess of water(1500ml) and neutralised with sodium bicarbonate. It was then continously extracted with dichloromethane(200ml) over a period of 8hrs. The organic phase was then dried($MgSO_4$) and the solvent removed by rotary evaporation to leave an oil which was then distilled under vacuum to produce pure 2-alkoxypyridine.

VII.3.a. Methanol

Pyridine(10.9g, 137.5mmol) and methanol(15.8g, 494mmol) gave a colourless oil, 2-methoxypyridine(4.1g, 54%); b.p. 140-142°C (lit.[167], 142°C); n.m.r spectrum 40; i.r. spectrum 24; mass spectrum 32.

VII.3.b. Ethanol

Pyridine(10.9g, 137.5mmol) and ethanol(20.0g, 434mmol) gave a colourless oil, 2-ethoxypyridine(4.0g, 50%); b.p. 36.1°C / 4mm (lit.[277], 157-160°C); n.m.r spectrum 41; i.r. spectrum 25; mass spectrum 33.

VII.3.c. 1-Butanol

Pyridine(10.9g, 137.5mmol) and 1-butanol(32g, 432mmol) gave a colourless oil, 2-butoxypyridine(6.4g, 58%); b.p. 47°C / 1mm (lit.[167], 200°C); n.m.r spectrum 42; i.r. spectrum 26; mass spectrum 34.

VII.3.d. 2,2,2-Trifluoroethanol

Pyridine(10.9g, 137.5mmol) and 2,2,2-trifluoroethanol(49.5g, 432mmol) gave a colourless oil, 2-(2,2,2-trifluoroethoxy)pyridine(3.8g, 60%); b.p. 41°C / 4mm (lit.[278], no b.p. given); n.m.r spectrum 43; i.r. spectrum 27; mass spectrum 35.

VII.3.d. 1-Heptanol

Pyridine(10.9g, 137.5mmol) and 1-heptanol(49.9g, 432mmol) gave a colourless oil, 2-heptoxypyridine(8.9g, 43%); b.p. 102°C / 1mm; n.m.r spectrum 44; i.r. spectrum 28; mass spectrum 36.

VII.4. Alkoxylation of Substituted Pyridines

General Procedure

A solution containing the pyridine and the alcohol in Arklone(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube and allowed to cool to -10°C under a flow of dry nitrogen. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at *ca.* 40ml min^{-1}. After the fluorine had been added the solution was allowed to reach room temperature and then poured into an excess of water(1500ml) and neutralised with sodium bicarbonate. It was then continously extracted with dichloromethane(200ml) over a period of 8hrs. The organic phase was then dried($MgSO_4$) and the solvent removed by rotary evaporation to leave an oil.

VII.4.a. 4-Ethylpyridine

4-Ethylpyridine(14.7g, 137.5mmol) and methanol(15.8g, 494mmol) gave a brown oil(10.5g). This was then distilled to give a colourless oil, 4-ethyl-2-methoxypyridine(4.1g, 38%); b.p. 137-139°C; n.m.r spectrum 45; i.r. spectrum 29; mass spectrum 37.

VII.4.b. 2-Bromopyridine

2-Bromopyridine(21.9g, 137.5mmol) and ethanol(22.7g, 494mmol) gave a brown oil (14.2g). Vacuum transfer followed by analysis by g.c. / m.s. showed a conversion of 46.1% from 2-bromopyridine. The oil contained 2-ethoxypyridine *m/z* (EI^+) 123 (M^+, 22.54%); 2-bromo-6-fluoropyridine *m/z* (EI^+) 177 (M^+, 100%) 175 (M^+, 100%) and 2-bromopyridine *m/z* (EI^+) 159 (M^+, 15.81%) 157 (M^+, 15.81%); 2-bromo-6-ethoxypyridine *m/z* (EI^+) 203 (M^+, 30.5%) 201 (M^+, 31.2%) 188 (M^+-CH_3, 90.1%) 186 (M^+-CH_3, 94.0%) in a ratio of 10.9%:5.6%:54%:30%.

VII.4.c. 2-Chloropyridine

2-Chloropyridine(15.6g, 137.5mmol) and ethanol(22.7g, 494mmol) gave a brown oil (10.1g). Vacuum transfer followed by analysis by g.c. / m.s. showed a conversion of 37% from 2-chloropyridine. The oil contained 2-chloropyridine *m/z* (EI^+) 115 (M^+, 26.0%) 113 (M^+, 77.4%); 2-ethoxypyridine *m/z* (EI^+) 123 (M^+, 28.1%) and 2-chloro-6-ethoxypyridine *m/z* (EI^+) 159 (M^+, 15.5%) 157 (M^+, 46.6%) 142 (M^+-CH_3, 100%) in a ratio of 70%:6%:24.0%.

VII.4.d. 2-Methylpyridine

2-Methylpyridine(12.9g, 138.7mmol) and methanol(15.8g, 493mmol) gave a brown oil (8.2g). Vacuum transfer followed by analysis by g.c. / m.s. showed a conversion to an extremely large range of products that did not allow analysis of the mixture.

VII.5. Reactions of Pyridine with Other Potential Nucleophiles

VII.5.a. Thiophenol

A solution containing the pyridine(10.9g, 137.5mmol) and thiophenol(27g, 245.5mmol) in Arklone(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube and allowed to cool to -10°C under a flow of dry nitrogen. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at ca. 40ml min^{-1}. After the fluorine had been added the suspension was allowed to reach room temperature and then poured into an excess of water(1500ml) and neutralised with sodium bicarbonate. The solid was removed by vacuum filtration, washed with water and Arklone.and then dried under vacuum to yield a pink solid(18.3g). Analysis by m.s. and ^{1}H, ^{13}C and ^{19}F nmr confirmed it as phenyl disulphide(68%) m.p. 56-58°C (lit.[167], 58-60°C); δ_C (50.289MHz; $CDCl_3$; TMS) 127.1 (s, 4-C, 4'-C), 127.5 (s, 3-C, 3'-C, 5-C, 5'-C), 129.0 (s, 2-C, 2'-C, 6-C, 6'-C), 137.0 (s, 1-C, 1'-C); δ_H (199.975M; $CDCl_3$; TMS) 7.2 (1H, m, 4-H, 4'-H), 7.3 (1H, m, 3-H, 3'-H, 5-H, 5'-H), 7.5 (m , 2-H, 2'-H, 6-H, 6'-H); *m/z* (EI^+) 218 (M^+, 32.71%) 110 (M^+-C_6H_5S, 100%).

VII.5.b. Amines

General Procedure

A solution containing the pyridine and the amine in Arklone(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube and allowed to cool to -10°C under a flow of dry nitrogen. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at ca. 40ml min^{-1}. After the fluorine had been added the solution was allowed to reach room temperature and then poured into an excess of water(1500ml) and neutralised with sodium bicarbonate. It was then continously extracted with dichloromethane(200ml) over a period of 8hrs. The organic phase was then dried($MgSO_4$) and the solvent removed by rotary evaporation to leave an oil.

VII.5.b.i. Butylamine

Pyridine(10.9g, 137.5mmol) and butylamine(36g, 493mmol) gave a brown oil (4.8g). Vacuum transfer followed by analysis by g.c. / m.s. confimed the oil contained an number of unidentifiable components none of which were functionlised pyridines.

VII.5.b.ii. Diethylamine

Pyridine(10.9g, 137.5mmol) and diethylamine(36g, 493mmol) gave a brown oil (5.2g). Vacuum transfer followed by analysis by g.c. / m.s confirmed the oil contained only unreacted pyridine *m/z* (EI^+) 79 (M^+, 100%).

VII.5.b.iii. Triethylamine

Pyridine(10.9g, 137.5mmol) and triethylamine(33.0g, 326.7mmol) gave a brown oil (6.8g). Vacuum transfer followed by analysis by g.c. / m.s. confimed the oil contained two components pyridine *m/z* (EI^+) 79 (M^+, 92%); 2-fluoropyridine *m/z* (EI^+) 97 (M^+, 100%) in a ratio of 80:20.

VII.5.c. Diethylmalonate

A solution containing the pyridine(10.9g, 137.5mmol) and diethylmalonate(39.6g, mmol) in Arklone(150ml) was placed in a fluorination apparatus with attached soda lime filled drying tube and allowed to cool to -10°C under a flow of dry nitrogen. Elemental fluorine (165mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using a narrow bore PTFE tubing at ca. 40ml min^{-1}. After the fluorine had been added the solution was allowed to reach room temperature and then poured into an excess of water(1500ml) and neutralised with sodium bicarbonate. It was then continously extracted with dichloromethane(200ml) over a period of 8hrs. The organic phase was then dried($MgSO_4$) and the solvent removed by rotary evaporation to leave a brown oil(40g). Analysis by g.c. / m.s. confimed that the reaction mixture contained 3 components pyridine *m/z* (EI^+) 79 (M^+, 90%); 2-fluoropyridine *m/z* (EI^+) 97 (M^+, 100%) in a ratio of 60:40 and unreacted diethylmalonate *m/z* (EI^+) 133 (M^+, 38.5%).

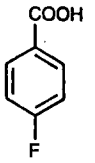
Appendices

Appendix One Nuclear Magentic Resonance Spectra

No.1	4-Fluorobenzoic Acid
No. 2	2,4-Difluorobenzoic Acid
No. 3	3,4-Difluorobenzoic Acid
No. 4	2,4,5-Trifluorobenzoic Acid
No. 5	2,3,4-Trifluorobenzoic Acid
No. 6	3,4,5-Trifluorobenzoic Acid
No. 7	2,3,4,5-Tetrafluorobenzoic Acid
No. 8	2,3,4,5,6-Pentafluorobenzoic Acid
No. 9	Fluorobenzene
No. 10	1,2,3,4,5-Pentafluorobenzene
No. 11	1,2,3-Trifluorobenzene
No. 12	1,3-Difluorobenzene
No. 13	Trimethylsilyl-4-fluorobenzoate
No. 14	Trimethylsilyl-2,4-difluorobenzoate
No. 15	Trimethylsilyl-3,4-difluorobenzoate
No. 16	Trimethylsilyl-2,4,5-trifluorobenzoate
No. 17	Trimethylsilyl-2,3,4-trifluorobenzoate
No. 18	Trimethylsilyl-3,4,5-trifluorobenzoate
No. 19	Trimethylsilyl-2,3,4,5-tetrafluorobenzoate
No. 20	Trimethylsilyl-2,3,4,5,6-pentafluorobenzoate
No. 21	6-Iodo-1,2,3,4,5-pentafluorobenzene
No. 22	5,6-Diiodo-1,2,3,4-tetrafluorobenzene
No. 23	3,6-Diiodo-1,2,4,5-tetrafluorobenzene
No. 24	1,3,5,4-Trifluoro-2,4,6-triiodobenzene
No. 25	4,4'-difluoro-3,3'-diiodobenzophenone
No. 26	3-Iodonitrobenzene
No. 27	3-Iodo-α,α,α-trifluorotoluene
No. 28	1,3-Bistrifluoromethyl-5-iodobenzene
No. 29	4-Fluoro-3-iodobenzoic Acid
No. 30	2,4-Difluoro-5-iodobenzoic Acid
No. 31	Methyl-2,4-Difluoro-5-iodobenzoate
No. 32	2,4-Difluoro-5-iodonitrobenzene
No. 33	4-Fluoro-3-iodobenzonitrile
No. 34	4-Fluoro-3-iodonitrobenzene
No. 35	3-Bromo-4-fluoronitrobenzene
No. 36	5-Bromo-2,4-difluoronitrobenzene
No. 37	3-Bromo-4-fluorobenzoic Acid
No. 38	2-Bromo-4,6-dinitrofluorobenzene

No. 39	4-Ethyl-2-fluoropyridine
No. 40	2-Methoxypyridine
No. 41	2-Ethoxypyridine
No. 42	2-Butoxypyridine
No. 43	2-(2,2,2-trifluoroethoxy)pyridine
No. 44	2-Heptoxypyridine
No. 45	4-Ethyl-2-methoxypyridine
No. 46	2-Fluoroquinoline

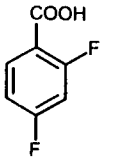
No. 1 **4-Fluorobenzoic Acid**



(400MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.15	m	2	3H, 5H
	8.14	m	2	2H, 6H
^{19}F	-104.2	tt $^3J_{F-H}$ 8.3, $^4J_{F-H}$ 5.6		4F
^{13}C	115.7	d $^2J_{C-F}$ 21.0		3C, 5C
	125.6	d $^4J_{C-F}$ 3.0		1C
	132.9	d $^3J_{C-F}$ 10.0		2C, 6C
	166.3	d $^1J_{C-F}$ 255.0		4C
	170.8	s		C=O

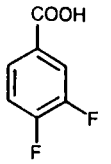
No. 2 **2,4-Difluorobenzoic Acid**



(250MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	6.93	m	1	5H
	7.0	m	1	6H
	8.08	ddd $^3J_{H-F}$ 8.8, $^3J_{H-F}$ 8.8, $^4J_{F-H}$ 6.8	1	3H
^{19}F	-99.8	s	1	4F
	-103.3	s	1	2F

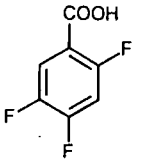
No. 3 **3,4-Difluorobenzoic Acid**



(400MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.29	m	1	5H
	7.93	m	1	2H
	7.95	m	1	6H
^{19}F	-128.2	dddd $^3J_{F-F}$ 21.1, $^3J_{F-H}$ 9.4, $^4J_{F-H}$ 7.5, $^4J_{F-H}$ 4.1	1	4F
	-135.9	dddd $^3J_{F-F}$ 18.8, $^3J_{F-H}$ 12.8, $^4J_{F-H}$ 9.0, $^5J_{F-H}$ 1.1	1	3F
^{13}C	117.6	d $^2J_{C-F}$ 18		5C
	119.6	d $^2J_{C-F}$ 20.0		2C
	126.2	dd $^3J_{C-F}$ 5, $^4J_{C-F}$ 3		6C
	127.4	dd $^3J_{C-F}$ 7, $^4J_{C-F}$ 4		1C
	150.2	dd $^1J_{C-F}$ 251, $^2J_{C-F}$ 13		3C
	154.3	dd $^1J_{C-F}$ 257, $^2J_{C-F}$ 12		4C
	170.4	d $^4J_{C-F}$ 1		C=O

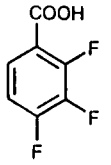
No. 4 **2,4,5-Trifluorobenzoic Acid**



(400MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.06	td $^3J_{H-F}$ 9.6, $^4J_{H-F}$ 6.4	1	3H
	7.89	ddd $^3J_{H-F}$ 10.0, $^4J_{H-F}$ 8.8, $^4J_{H-F}$ 6.8	1	6H
^{19}F	-107.6	dtd J_{F-F} 15.8, J_{F-H} 9.8, J_{F-H} 6.8	1	2F
	-122.8	ddd J_{F-H} 21.4, J_{F-H} 19.2, J_{F-H} 9.8	1	4F
	-140.7	dtd J_{F-F} 27.5, J_{F-H} 10.6, J_{F-H} 6.0	1	5F
^{13}C	107.4	dd $^2J_{C-F}$ 28, $^2J_{C-F}$ 21		3C
	113.9	dd $^2J_{C-F}$ 11, $^3J_{C-F}$ 4		6C
	120.6	d $^2J_{C-F}$ 21		1C
	146.5	ddd $^1J_{C-F}$ 248.0, $^2J_{C-F}$ 13, $^4J_{C-F}$ 4		5C
	154.1	dt $^1J_{C-F}$ 259, $^2J_{C-F}$ 14		4C
	158.7	dd $^1J_{C-F}$ 261, $^3J_{C-F}$ 10		2C
	167.9	s		C=O

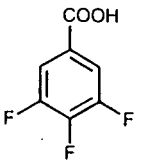
No. 5 **2,3,4-Trifluorobenzoic Acid**



(400MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.09	tdd $^3J_{H-F}$ 9.2, $^3J_{H-H}$ 9.2, $^4J_{H-F}$ 6.8, $^5J_{H-F}$ 2.0	1	5H
	7.84	m	1	6H
^{19}F	-123.8	m	1	4F
	-128.1	m	1	2F
	-158.1	m	1	3F
^{13}C	112.3	dd $^2J_{C-F}$ 18, $^3J_{C-F}$ 4		5C
	115.2	s		1C
	127.0	dd $^3J_{C-F}$ 9, $^3J_{C-F}$ 4		6C
	140.6	dt $^1J_{C-F}$ 253.0, $^2J_{C-F}$ 15		3C
	152.5	dd $^1J_{C-F}$ 269, $^2J_{C-F}$ 14		2C
	154.8	dd $^1J_{C-F}$ 269, $^2J_{C-F}$ 7		4C
	168.0	s		C=O

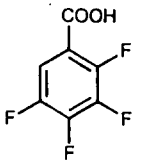
No. 6 **3,4,5-Trifluorobenzoic Acid**



(250MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	7.76	m	2	2H, 6H
^{19}F	-132.0	m	2	3F, 5F
	-150.5	m	1	4F
^{13}C	114.9	m		2C, 6C
	125.0	td $^3J_{C-F}$ 7.4, $^4J_{C-F}$ 4.5		1C
	143.9	dt $^1J_{C-F}$ 261.2, $^2J_{C-F}$ 15.3		4C
	151.1	ddd $^1J_{C-F}$ 252.5, $^2J_{C-F}$ 10.4, $^3J_{C-F}$ 3.4		3C, 5C
	169.8	m		C=O

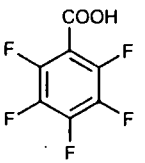
No. 7 2,3,4,5-Tetrafluorobenzoic Acid



(400MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	7.703	dt d $^3J_{H-F}$ 12.4, $^4J_{H-F}$ 6.0, $^5J_{H-F}$ 2.4		6H
^{19}F	-133.560	dddd $^3J_{F-F}$ 20.3, $^3J_{F-H}$ 13.5, $^4J_{F-F}$ 10.5, $^5J_{F-F}$ 6.0	1	5F
	-137.224	dddd $^3J_{F-F}$ 21, $^4J_{F-F}$ 13.5, $^4J_{F-H}$ 10.2, $^5J_{F-F}$ 3.0	1	2F
	-144.882	m	1	4F
	-152.753	tt $^3J_{F-F}$ 19.9, $^4J_{F-F}$ 2.6	1	3F
^{13}C	167.508	s		C=O
	148.920	d $^1J_{C-F}$ 223.8		2C
	146.369	d $^1J_{C-F}$ 206.6		5C
	144.362	d $^1J_{C-F}$ 263.2		4C
	141.457	d $^1J_{C-F}$ 256.6		3C
	113.687	d $^2J_{C-F}$ 21.0		6C

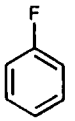
No. 8 2,3,4,5,6-Pentafluorobenzoic Acid



(400MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^{19}F	-136.9	ddd $^3J_{F-F}$ 25.6, $^4J_{F-F}$ 12.0, $^4J_{F-F}$ 6.0	2	2F, 6F
	-147.1	tt $^3J_{F-F}$ 21.1, $^4J_{F-F}$ 5.6	1	4F
	-160.4	m	2	3F, 5F
^{13}C	107.1	m $^2J_{C-F}$ 14.5		1C
	137.8	m $^1J_{C-F}$ 256.3		3C, 5C
	143.8	m $^1J_{C-F}$ 261.0		4C
	146.0	m $^1J_{C-F}$ 260.6		2C, 6C
	163.3	s		C=O

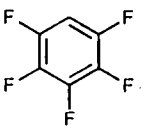
No. 9 Fluorobenzene



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	7.01	m	2	2H, 6H
	7.23	m	1	4H
	7.27	m	2	3H, 5H
^{19}F	-133.6	s	1	1F
^{13}C	115.4	d $^2J_{C-F}$ 21.0		2C, 6C
	124.1	d $^4J_{C-F}$ 3.2		4C
	130.0	d $^3J_{C-F}$ 7.9		3C, 5C
	163.0	d $^1J_{C-F}$ 245.3		1C

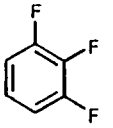
No. 10 1,2,3,4,5-Pentafluorobenzene



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	6.94	m	1	6H
^{19}F	-141.0	s	2	1F, 6F
	-151.7	s	1	3F
	-163.1	s	2	2F, 4F
^{13}C	100.9	td $^2J_{C-F}$ 23.1 , $^3J_{C-F}$ 3.2		6C
	137.6	m $^1J_{C-F}$ 210.7		2C, 5C
	142.7	m $^1J_{C-F}$ 215.0		3C
	146.7	m $^1J_{C-F}$ 249.1		1C, 5C

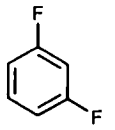
No. 11 1,2,3-Trifluorobenzene



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	6.9-7.1	b	3	4H, 5H, 6H
^{19}F	-135.9	s	2	1F, 3F
	-162.3	s	1	2F
^{13}C	113.4	m		4C, 6C
	124.7	m		5C
	140.5	dt		
		$^1J_{C-F}$ 249.2, $^3J_{C-F}$ 15.2		
	152.0	ddd		1C, 2C
		$^1J_{C-F}$ 249.2, $^3J_{C-F}$ 9.8, $^4J_{C-F}$ 3.5		

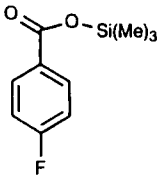
No. 12 1,3-Difluorobenzene



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	6.77	m	1	2H
	6.81	m	2	4H, 6H
	7.25	m	1	5H
^{19}F	-111.4	s		1F, 3F
^{13}C	104.1	t		2C
		$^2J_{C-F}$ 25.0		
	111.4	dd		4C, 6C
		$^2J_{C-F}$ 15.5, $^4J_{C-F}$ 9.0		
	130.8	t		5C
		$^3J_{C-F}$ 9.7		
	163.5	dd		1C, 3C
		$^1J_{C-F}$ 248.3, $^3J_{C-F}$ 12.1		

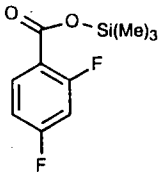
No. 13 **Trimethylsilyl-4-fluorobenzoate**



(250MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.97	m	2	2H,6H
	7.01	m	2	3H,5H
	0.33	s	9	Me
^{19}F	-105.1	s	1	4F

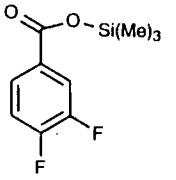
No. 14 **Trimethylsilyl-2,4-difluorobenzoate**



(250MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.91	m	1	6H,5H
	6.82	m	2	3H
	0.33	s	9	Me
^{19}F	-102.32	s	1	2F
	-103.81	s	1	4F

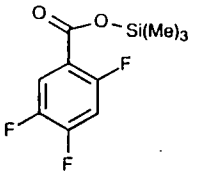
No. 15 **Trimethylsilyl-3,4-difluorobenzoate**



(250MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.76	m	2	2H,6H
	7.15	m	1	5H
	0.34	s	9	Me
^{19}F	-131.14	s	1	3F
	-137.47	s	1	4F

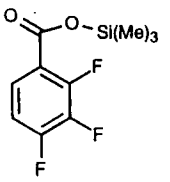
No. 16 **Trimethylsilyl-2,4,5-trifluorobenzoate**



(250MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.66	m	2	6H
	6.86	m	2	3H
	0.25	s	9	Me
^{19}F	-109.12	s	1	2F
	-126.14	s	1	5F
	-142.20	s	1	4F

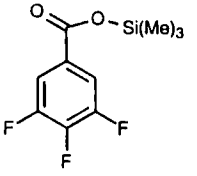
No. 17 **Trimethylsilyl-2,3,4-trifluorobenzoate**



(250MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.63	m	2	6H
	6.90	m	2	5H
	0.30	s	9	Me
^{19}F	-127.13	s	1	2F
	-130.75	s	1	4F
	-160.08	s	1	3F

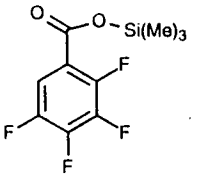
No. 18 **Trimethylsilyl-3,4,5-trifluorobenzoate**



(250MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.66	m	2	2H,6H
	0.41	s	9	Me
^{19}F	-133.52	s	2	3F,5F
	-153.66	s	1	4F

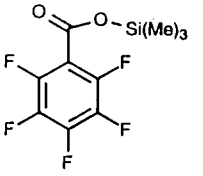
No. 19 **Trimethylsilyl-2,3,4,5-tetrafluorobenzoate**



(250MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.52	m	1	6H
	0.35	s	9	Me
^{19}F	-135.35	s	1	5F
	-138.95	s	1	2F
	-148.23	s	1	4F
	-154.43	s	1	3F

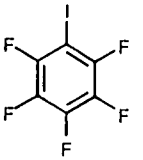
No. 20 **Trimethylsilyl-2,3,4,5,6-pentafluorobenzoate**



(250MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	0.35	s	-	Me
^{19}F	-140.01	s	1	2F,6F
	-150.95	s	1	4F
	-162.29	s	1	3F,5F

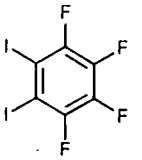
No. 21 **6-Iodo-1,2,3,4,5-pentafluorobenzene**



(400MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^{19}F	-120.0	ddd $^3J_{F\text{-}F}$ 18.1	2	1F, 5F
	-153.3	tt $^3J_{F\text{-}F}$ 19.9	1	3F
	-159.6	dd $^3J_{F\text{-}F}$ 15.8 , $^4J_{F\text{-}F}$ 2.6	2	2F, 4F
^{13}C	66.4	t $^2J_{C\text{-}F}$ 28.3		6C
	137.9	m $^1J_{C\text{-}F}$ 256.8		1C, 5C
	142.5	dtt $^1J_{C\text{-}F}$ 255.3 , $^2J_{C\text{-}F}$ 13.7 , $^3J_{C\text{-}F}$ 4.6		3C
	148.0	m $^1J_{C\text{-}F}$ 245.5		2C, 4C

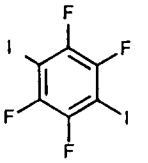
No. 22 **5,6-Diiodo-1,2,3,4-tetrafluorobenzene**



(400MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^{19}F	-102.4	AA'XX' J_{AX} 22.5 $J_{AX'}$ -4.4 , $J_{AA'}$ 19.2 $J_{XX'}$ 9.3	2	2F, 3F
	-151.2	AA'XX' J_{AX} 22.5 , $J_{AX'}$ -4.4 , $J_{AA'}$ 19.2 $J_{XX'}$ 9.3	1	1F, 4F
^{13}C	90.6	m $^2J_{C\text{-}F}$ 24.4		5C, 6C
	134.0	m $^1J_{C\text{-}F}$ 260.0		1C, 4C
	147.8	m $^1J_{C\text{-}F}$ 247.0		2C, 3C

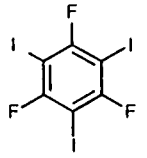
No. 23 1,2,4,5-Tetrafluoro-3,6-diiodobenzene



(400MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^{19}F	-118.0	s	4	1F, 2F, 4F, 5F
^{13}C	72.9	t $^{2}J_{C-F}$ 27.9		3C, 6C
	146.6	m $^{1}J_{C-F}$ 250.4		1C, 2C, 4C, 5C

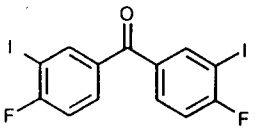
No. 24 1,3,5-Trifluoro-2,4,6-triiodobenzene



(400MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^{19}F	-69.0	s	3	1F, 3F, 5F
^{13}C	63.8	td $^{2}J_{C-F}$ 34.5 , $^{4}J_{C-F}$ 3.8		2C, 4C, 6C
	162.2	dt $^{1}J_{C-F}$ 243.8 , $^{3}J_{C-F}$ 7.6		1C, 3C, 5C

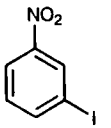
No. 25 4,4'-difluoro-3,3'-diiodobenzophenone



(400MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^{1}H	7.18	dd $^{3}J_{H-F}$ 8.4 , $^{3}J_{H-H}$ 7.6	2	5H, 5'H
	7.74	ddd $^{3}J_{H-H}$ 8.5 , $^{4}J_{H-F}$ 4.8, $^{4}J_{H-H}$ 2.0	2	6H, 6'H
	8.20	dd $^{4}J_{H-F}$ 6.0 , $^{4}J_{H-H}$ 2.0	2	2H, 2'H
^{19}F	-86.0	ddd $^{3}J_{F-F}$ 7.2, $^{4}J_{F-F}$ 4.9	2	4F, 4'F
^{13}C	81.8	d $^{2}J_{C-F}$ 26.7		3C, 3'C
	115.7	d $^{2}J_{C-F}$ 24.4		5C, 5'C
	132.1	d $^{3}J_{C-F}$ 8.8		6C, 6'C
	141.2	d $^{4}J_{C-F}$ 2.6		2C, 2'C
	141.4	d $^{3}J_{C-F}$ 3.1		1C, 1'C
	164.4	d $^{1}J_{C-F}$ 253.7		4C, 4'C
	191.0	s		C=O

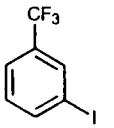
No. 26 3-Iodonitrobenzene



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.34	dd $^3J_{H-H}$ 4.0	1	5H
	8.0	ddd $^3J_{H-H}$ 7.8 , $^4J_{H-H}$ 1.6, $^4J_{H-H}$ 1.0	1	4H
	8.17	ddd $^3J_{H-H}$ 8.1 , $^4J_{H-H}$ 2.2 , $^4J_{H-H}$ 1.1	1	6H
	8.45	t $^4J_{H-H}$ 2.0	1	2H
^{13}C	94.3	s		3C
	123.3	s		6C
	131.4	s		5C
	132.6	s		2C
	144.0	s		4C
	144.1	s		1C

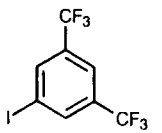
No. 27 3-Iodo-α,α,α-trifluorotoluene



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	7.1	t $^3J_{H-H}$ 7.9	1	5H
	7.5	d $^3J_{H-H}$ 7.8	1	4H
	7.7	d $^3J_{H-H}$ 7.9	1	6H
	7.9	s	1	2H
^{19}F	-69.2	s		CF_3
^{13}C	94.5	s		3C
	123.5	q $^1J_{C-F}$ 272.9		CF_3
	124.9	q $^3J_{C-F}$ 3.6		6C
	130.8	s		5C
	132.8	q $^2J_{C-F}$ 32.7		1C
	134.7	q $^3J_{C-F}$ 3.8		2C
	141.0	s		4C

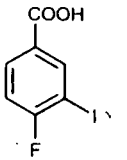
No. 28 **1,3-Bistrifluoromethyl-5-iodobenzene**



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	7.9	s	1	2H
	8.1	s	2	4H, 6H
^{19}F	-63.7	s	6	CF_3
^{13}C	94.2	s		5C
	122.2	m		2C
	122.6	q $^3J_{C-F}$ 3.7		CF_3
	133.5	q $^1J_{C-F}$ 273.1		1C, 3C
	138.1	d $^2J_{C-F}$ 33.8		4C, 6C
		$^3J_{C-F}$ 3.4		

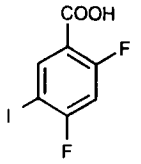
No. 29 **4-Fluoro-3-iodobenzoic Acid**



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	7.1	dd $^3J_{H-H}$ 7.5 , $^3J_{H-F}$ 8.6	1	5H
	8.0	ddd $^3J_{H-H}$ 8.6 , $^4J_{H-F}$ 4.9, $^4J_{H-H}$ 2.1	1	6H
	8.5	dd $^4JH_{-H}$ 2.2 , $^4J_{H-F}$ 6.1	1	2H
^{19}F	-88.8	s	1	4F
^{13}C	81.3	d $^2J_{C-F}$ 26.6		3C
	115.8	d $^2J_{C-F}$ 24.8		5C
	127.0	d $^4J_{C-F}$ 3.3		1C
	132.6	d $^3J_{C-F}$ 8.9		6C
	142.0	d $^3J_{C-F}$ 3.3		2C
	165.2	d $^1J_{C-F}$ 254.3		4C
	169.8	s		C=O

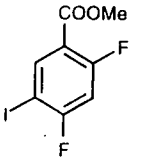
No. 30 **2,4-Difluoro-5-iodobenzoic Acid**



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	6.9	m $^3J_{H-F}$ 7.6	1	3H
	8.5	m $^4J_{H-F}$ 6.7	1	6H
^{19}F	-80.5	s	1	2F
	-103.0	s	1	4F
^{13}C	75.4	d $^2J_{C-F}$ 26.6		5C
	105.8	d $^2J_{C-F}$ 24.8		3C
	142.8	d $^4J_{C-F}$ 3.3		6C
	143.1	d $^3J_{C-F}$ 8.9		1C
	163.1	d $^3J_{C-F}$ 3.3		2C
	165.7	d $^1J_{C-F}$ 254.3		4C
	167.1	s		C=O

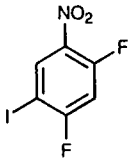
No. 31 **Methyl-2,4-Difluoro-5-iodobenzoate**



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	4.0	m $^3J_{H-F}$ 7.6	3	Me
	6.92	dd $^3J_{H-F}$ 10.3, $^4J_{H-F}$ 7.7		3H
	8.33	t $^4J_{H-F}$ 7.5	1	6H
^{19}F	-81.8	s	1	2F
	-103.9	s	1	4F
^{13}C	53.1	s		Me
	75.2	dd $^2J_{C-F}$ 26.4, $^4J_{C-F}$ 4.2		5C
	106.0	t $^2J_{C-F}$ 27.4		3C
	117.1	d $^2J_{C-F}$ 4.0		1C
	142.8	dd $^3J_{C-F}$ 1.8, $^3J_{C-F}$ 3.9		6C
	162.9	d $^3J_{C-F}$ 4.1		C=O
	163.2	dd $^1J_{C-F}$ 264.6, $^3J_{C-F}$ 11.5		4C
	164.9	dd $^1J_{C-F}$ 254.6, $^3J_{C-F}$ 12.1		2C

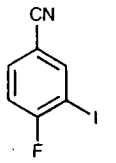
No. 32 **2,4-Difluoro-5-iodonitrobenzene**



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.24	dd $^3J_{H-F}$ 10.3 , $^3J_{H-F}$ 7.8	1	3H
	8.54	t $^4J_{H-F}$ 7.2	1	6H
^{19}F	-78.8	s	1	2F
	-112.0	s	1	4F
^{13}C	73.4	dd $^2J_{C-F}$ 26.6 , $^4J_{C-F}$ 4.6		5C
	105.0	dd $^2J_{C-F}$ 29.5 , $^2J_{C-F}$ 25.2		3C
	132.7	s		1C
	134.8	s		6C
	154.9	dd $^1J_{C-F}$ 268.4 , $^3J_{C-F}$ 12.3		2C
	163.2	dd $^1J_{C-F}$ 257.3 , $^3J_{C-F}$ 11.4		4C

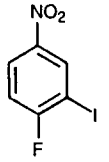
No. 33 **4-Fluoro-3-iodobenzonitrile**



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	7.2	m	1	5H
	7.7	m	1	6H
	8.1	m	1	2H
^{19}F	-83.8	s	1	4F
^{13}C	82.1	d $^2J_{C-F}$ 27.5		3C
	110.3	d $^4J_{C-F}$ 4.0		1C
	116.5	s		CN
	116.6	d $^2J_{C-F}$ 25.4		5C
	134.3	d $^3J_{C-F}$ 8.8		6C
	143.3	d $^4J_{C-F}$ 3.2		2C
	164.3	d $^1J_{C-F}$ 255.0		4C

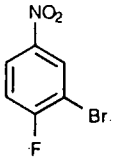
No. 34 4-Fluoro-3-iodonitrobenzene



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.2	dd $^3J_{H-H}$ 6.9 , $^3J_{H-F}$ 9.0	1	5H
	8.3	ddd $^3J_{H-H}$ 9.1 , $^4J_{H-H}$ 2.8 , $^3J_{H-F}$ 4.3	1	6H
	8.7	dd $^4J_{H-H}$ 2.8 , $^4J_{H-F}$ 5.3	1	2H
^{19}F	-83.6	s	1	4F
^{13}C	81.3	d $^2J_{C-F}$ 28.6		3C
	116.0	d $^2J_{C-F}$ 26.6		5C
	125.9	d $^3J_{C-F}$ 9.3		6C
	135.2	d $^3J_{C-F}$ 3.7		2C
	144.6	d $^4J_{C-F}$ 1.8		1C
	165.5	d $^1J_{C-F}$ 265.2		4C

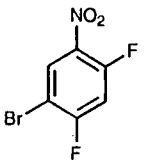
No. 35 3-Bromo-4-fluoronitrobenzene



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	7.32	dd $^3J_{H-H}$ 7.4 , $^3J_{H-F}$ 9.1	1	5H
	8.24	ddd $^3J_{H-H}$ 9.0 , $^4J_{H-H}$ 2.8 , $^4J_{H-F}$ 4.1	1	6H
	8.50	dd $^4J_{H-H}$ 2.7 , $^4J_{H-F}$ 5.8	1	2H
^{19}F	-96.0	ddd $^3J_{F-H}$ 7.3 , $^4J_{F-H}$ 5.9 , $^4J_{F-H}$ 4.1	1	4F
^{13}C	110.1	d $^2J_{C-F}$ 23.5		3C
	117.1	d $^2J_{C-F}$ 24.6		5C
	124.9	d $^3J_{C-F}$ 9.1		6C
	128.3	s		1C
	129.6	d $^3J_{C-F}$ 2.2		2C
	162.9	d $^1J_{C-F}$ 258.3		4C

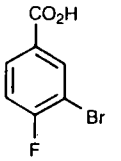
No. 36 5-Bromo-2,4-difluoronitrobenzene



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	7.20	dd $^4J_{H-H}$ 7.8 , $^4J_{H-F}$ 10.3	1	3H
	8.40	dd $^3J_{H-F}$ 7.4 , $^3J_{H-F}$ 7.4	1	6H
^{19}F	-91.2	ddd $^3J_{F-H}$ 14.3 , $^4J_{F-H}$ 7.9, $^4J_{F-H}$ 7.1	1	2F
	-112.2	ddd $^3J_{F-H}$ 14.3 , $^4J_{F-H}$ 10.2, $^4J_{F-H}$ 7.9	1	4F
^{13}C	104.7	dd $^2J_{C-F}$ 23.5 , $^4J_{C-F}$ 4.5		5C
	107.6	t $^2J_{C-F}$ 27.4		3C
	129.1	s		1C
	131.0	t $^3J_{C-F}$ 2.5		6C
	155.7	dd $^1J_{C-F}$ 268.7 , $^3J_{C-F}$ 11.8		2C
	162.4	dd $^1J_{C-F}$ 260.3 , $^3J_{C-F}$ 11.1		4C

No. 37 3-Bromo-4-fluorobenzoic Acid



(200MHz, $CDCl_3$, $CFCl_3$)

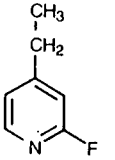
	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	7.22	dd $^4J_{H-H}$ 8.4 , $^4J_{H-F}$ 8.4	1	5H
	8.07	ddd $^3J_{H-H}$ 4.7 , $^4J_{H-F}$ 4.3 , $^4J_{H-H}$ 2.1	1	6H
	8.35	dd $^3J_{H-F}$ 6.6 , $^4J_{H-H}$ 2.1	1	2H
^{19}F	-98.0	ddd $^3J_{F-H}$ 8.3 , $^3J_{F-H}$ 6.8, $^4J_{F-H}$ 4.9	1	4F
^{13}C	110.1	d $^2J_{C-F}$ 21.6		3C
	117.2	d $^2J_{C-F}$ 23.1		2C
	127.2	s		1C
	132.0	d $^3J_{C-F}$ 8.8		6C
	136.6	d $^3J_{C-F}$ 1.9		2C
	163.2	d $^1J_{C-F}$ 256.3		4C
	170.8	s		C=O

No. 38 2-Bromo-4,6-dinitrofluorobenzene

(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants ()	Relative Intensity	Assigment
^1H	9.0	m	2	3H, 5H
^{19}F	-99.8	s	1	1F
^{13}C	113.7	d $^2J_{C-F}$ 22.9		2C
	121.7	s		5C
	134.2	s		3C
	137.9	d $^3J_{C-F}$ 10.3		6C
	143.7	d $^4J_{C-F}$ 4.6		4C
	156.6	d $^1J_{C-F}$ 273.0		1C

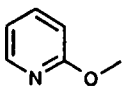
No. 39 4-Ethyl-2-fluoropyridine



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	1.1	t	3	CH_3
	2.5	q J_{H-H} 9.2, J_{H-H} 8.4	2	CH_2
	6.6	s	1	5H
	6.8	m	1	6H
	7.9	d J_{H-F} 5.1	1	3H
^{19}F	-69.9	s		2F
^{13}C	13.9	s		CH_3
	27.9	s		CH_2
	108.4	d $^2J_{C-F}$ 37.0		3C
	121.4	d $^4J_{C-F}$ 5.7		5C
	147.2	d $^3J_{C-F}$ 15.5		4C
	159.4	s		6C
	164.2	d $^1J_{C-F}$ 236.5		2C

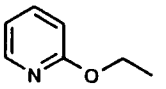
No. 40 **2-Methoxypyridine**



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	3.91	s	3	CH_3O
	6.71	dd $^3J_{H-H}$ 8.4, $^4J_{H-H}$ 0.9	1	3H
	6.80	td $^3J_{H-H}$ 6.1, $^4J_{H-H}$ 0.8	1	5H
	7.49	td $^3J_{H-H}$ 6.7, $^4J_{H-H}$ 2.0	1	4H
	8.15	d $^3J_{H-H}$ 4.0	1	6H
^{13}C	53.5	s		CH_3O
	111.3	s		3C
	116.9	s		5C
	138.7	s		4C
	147.2	s		6C
	164.5	s		2C

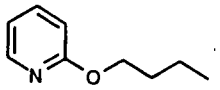
No. 41 **2-Ethoxypyridine**



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	1.1	m		CH_3
	4.2	m		OCH_2
	6.5	m		3H
	6.6	m		5H
	7.3	m		4H
	7.9	m		6H
^{13}C	14.6	s		CH_3
	61.4	s		CH_2O
	111.1	s		3C
	116.4	s		5C
	138.4	s		4C
	146.9	s		6C
	164.0	s		2C

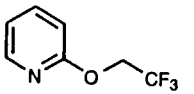
No. 42 **2-Butoxypyridine**



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	0.96	t $^3J_{H-H}$ 7.24	3	CH_3^4
	1.47	q $^3J_{H-H}$ 8.1	2	CH_2^3
	1.74	q $^3J_{H-H}$ 7.0	2	CH_2^2
	4.29	t $^3J_{H-H}$ 6.5	2	CH_2O
	6.71	dd $^3J_{H-H}$ 4.3 , $^4J_{H-H}$ 0.7	1	3H
	6.81	td $^3J_{H-H}$ 6.5 , $^4J_{H-H}$ 1.1	1	5H
	7.52	td	1	4H
	8.14	m	1	6H
^{13}C	13.9	s		CH_3^4
	19.4	s		CH_2^3
	31.3	s		CH_2^2
	65.7	s		CH_2O
	111.1	s		3C
	116.6	s		5C
	138.5	s		4C
	146.9	s		6C
	164.1	s		2C

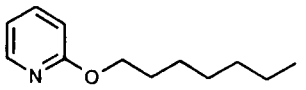
No. 43 **2-(2,2,2-trifluoroethoxy)-pyridine**



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	4.76	q $^3J_{H-F}$ 8.6	2	CH_2O
	6.83	m $^3J_{H-H}$ 8.4	1	3H
	6.94	td $^3J_{H-H}$ 6.1, $^3J_{H-H}$ 0.9	1	5H
	7.62	td $^3J_{H-H}$ 8.7, $^4J_{H-H}$ 1.9	1	4H
	8.13	dd $^3J_{H-H}$ 4.9, $^4J_{H-H}$ 1.1	1	6H
^{13}C	62.2	q $^2J_{C-F}$ 35.0		CH_2O
	111.3	s		3C
	118.4	s		5C
	124.1	q $^1J_{C-F}$ 275.0		CF_3
	139.4	s		4C
	146.8	s		6C
	162.0	s		2C

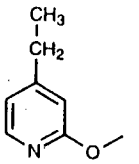
No. 44 2-Heptoxypyridine



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	0.89	t $^3J_{H-H}$ 5.2	3	CH_3^7
	1.31	b	8	CH_2^{3-6}
	1.80	m	2	CH_2^2
	4.23	t $^3J_{H-H}$ 6.7	2	CH_2O
	6.72	dd $^3J_{H-H}$ 8.4, $^4J_{H-H}$ 0.9	1	3H
	6.82	td $^3J_{H-H}$ 5.1, $^4J_{H-H}$ 1.6	1	5H
	7.53	td $^3J_{H-H}$ 8.4 , $^3J_{H-H}$ 1.3	1	4H
	8.13	dd $^3J_{H-H}$ 4.7, $^4J_{H-H}$ 1.2	1	6H
^{13}C	14.1	s		CH_3^7
	22.7	s		CH_2^6
	26.1	s		CH_2^5
	29.2	s		CH_2^4
	31.9	s		CH_2^3
	32.9	s		CH_2^2
	66.1	s		CH_2O
	111.2	s		3C
	116.5	s		5C
	138.5	s		4C
	146.8	s		6C
	164.1	s		2C

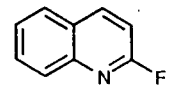
No. 45 4-Ethyl-2-methoxypyridine



(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	1.21	t $^3J_{H-H}$ 7.6	3	CH_3
	2.58	q $^3J_{H-H}$ 7.8	2	CH_2
	3.91	s	3	OCH_3
	6.57	m	1	3H
	6.71	m	1	5H
	8.04	d $^3J_{H-H}$ 5.3	1	6H
^{13}C	14.3	s		CH_3
	28.1	s		CH_2
	53.3	s		OCH_3
	109.7	s		3C
	117.1	s		5C
	146.6	s		6C
	155.9	s		4C
	164.6	s		2C

No. 46 **2-Fluoroquinoline**



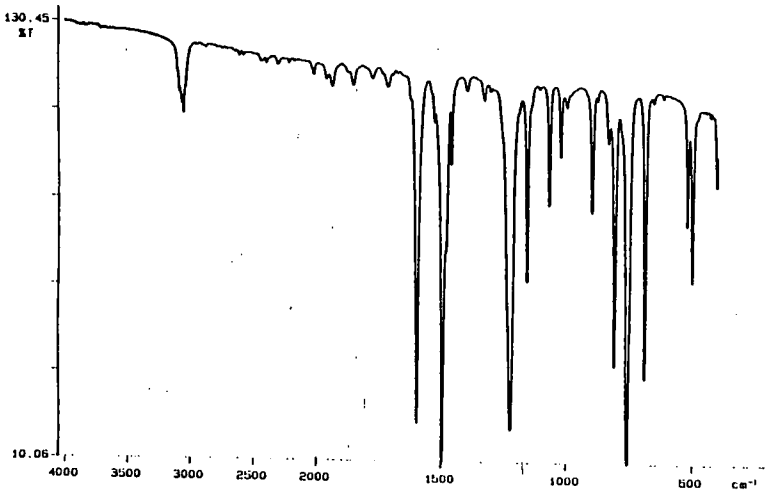
(200MHz, $CDCl_3$, $CFCl_3$)

	Chemical Shifts(ppm)	Multiplicity Coupling Constants (Hz)	Relative Intensity	Assigment
^1H	7.01	dd $^3J_{H-F}$ 8.7, $^4J_{H-H}$ 2.8	1	3H
	7.46	t $^3J_{H-H}$ 7.2, $^3J_{H-H}$ 7.2	1	6H
	7.66	t $^3J_{H-H}$ 7.8, $^3J_{H-H}$ 7.8	1	7H
	7.77	d $^3J_{H-H}$ 8.2	1	8H
	7.87	d $^3J_{H-H}$ 8.4	1	5H
	8.18	t $^3J_{H-H}$ 8.4, $^4J_{H-F}$ 8.4	1	4H
^{19}F	-62.4	s		2F
^{13}C	110.4	d $^2J_{C-F}$ 42.4		2C
	126.6	d $^4J_{C-F}$ 2.5		4C
	127.3	s		9C
	126.0	s		5C
	128.4	s		6C, 7C
	131.0	s		8C
	142.5	d $^3J_{C-F}$ 9.9		3C
	148.0	d $^1J_{C-F}$161.0		1C

Appendix Two Infra Red Spectra

No. 1	Fluorobenzene
No. 2	1,2,3,4,5-Pentafluorobenzene
No. 3	1,2,3-Trifluorobenzene
No. 4	1,3-Difluorobenzene
No. 5	6-Iodo-1,2,3,4,5-pentafluorobenzene
No. 6	5,6-Diiodo-1,2,3,4-tetrafluorobenzene
No. 7	3,6-Diiodo-1,2,4,5-tetrafluorobenzene
No. 8	1,3,5-Trifluoro-2,4,6-triiodobenzene
No. 9	4,4'-difluoro-3,3'-diiodobenzophenone
No. 10	3-Iodonitrobenzene
No. 11	3-Iodo-α,α,α-trifluorotoluene
No. 12	1,3-Bistrifluoromethyl-5-iodobenzene
No. 13	4-Fluoro-3-iodobenzoic Acid
No. 14	2,4-Difluoro-5-iodobenzoic Acid
No. 15	Methyl-2,4-Difluoro-5-iodobenzoate
No. 16	2,4-Difluoro-5-iodonitrobenzene
No. 17	4-Fluoro-3-iodobenzonitrile
No. 18	4-Fluoro-3-iodonitrobenzene
No. 19	3-Bromo-4-fluoronitrobenzene
No. 20	5-Bromo-2,4-difluoronitrobenzene
No. 21	3-Bromo-4-fluorobenzoic Acid
No. 22	2-Bromo-4,6-dinitrofluorobenzene
No. 23	4-Ethyl-2-fluoropyridine
No. 24	2-Methoxypyridine
No. 25	2-Ethoxypyridine
No. 26	2-Butoxypyridine
No. 27	2-(2,2,2-trifluoroethoxy)pyridine
No. 28	2-Heptoxypyridine
No. 29	4-Ethyl-2-methoxypyridine
No. 30	2-Fluoroquinoline

No. 1 Fluorobenzene

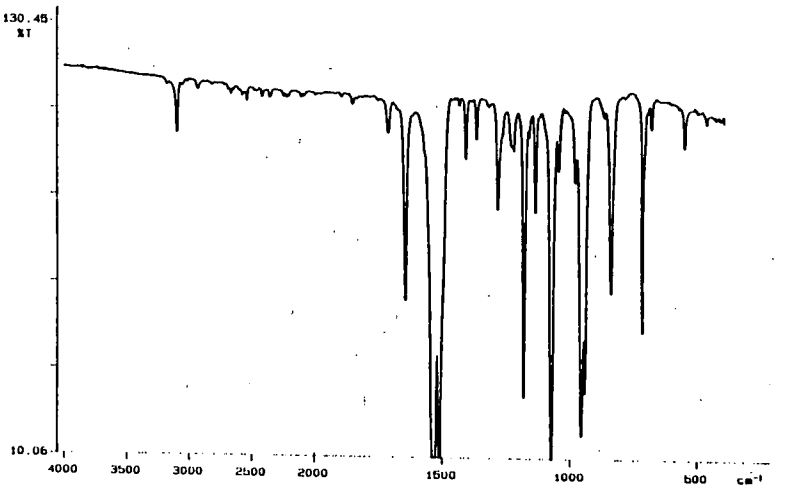


PEAK X 4000.0 400.0
threshold 1.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3062.5	108.40	3049.3	105.77	2398.1	119.90	2310.4	119.55
2019.9	117.04	1936.5	113.77	1852.6	114.21	1774.7	116.09
1713.1	113.87	1595.4	20.95	1525.6	104.24	1494.4	10.34
1457.6	92.52	1394.0	113.20	1324.6	110.64	1219.0	19.35
1154.6	60.25	1065.5	81.51	1020.0	95.32	995.1	108.91
895.6	80.04	830.0	99.26	805.4	37.17	752.9	10.06
685.0	34.01	518.4	76.30	498.5	60.85	404.1	87.32

28 peaks found

No. 2 1,2,3,4,5-Pentafluorobenzene

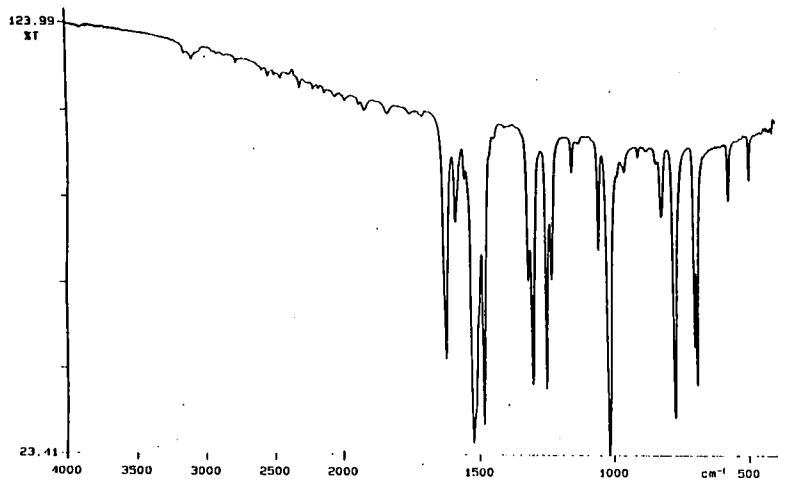


PEAK Z 4000.0 400.0
threshold 1.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3098.2	99.97	2931.5	112.18	2665.5	110.95	2541.4	109.10
2418.0	110.19	2357.1	110.14	2222.4	110.14	1854.1	108.55
1714.2	100.65	1645.6	53.52	1532.3	2.46	1510.7	8.42
1436.0	108.58	1409.8	93.75	1367.8	99.31	1283.8	79.48
1222.1	96.13	1180.2	26.57	1162.3	99.91	1136.9	78.67
1072.0	9.52	1045.5	90.67	981.6	87.50	955.4	16.58
941.4	28.40	869.0	105.76	839.8	56.59	718.1	45.94
685.7	102.61	555.6	97.61	470.0	104.20		

31 peaks found

No. 3 1,2,3-Trifluorobenzene

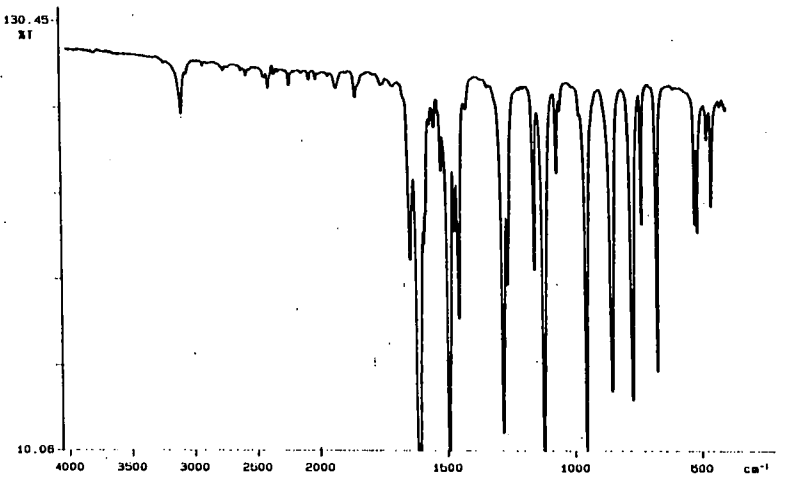


PEAK Z 4000.0 400.0
threshold 1.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3088.4	115.57	2537.7	111.81	2448.2	111.49	2311.4	109.29
1918.2	104.20	1834.6	103.51	1621.3	45.75	1587.8	78.09
1554.9	88.17	1521.9	26.02	1482.3	30.22	1317.5	64.48
1300.3	39.99	1249.6	39.04	1230.0	64.81	1153.8	90.01
1056.0	71.79	1016.5	23.41	960.2	90.15	909.1	93.66
823.0	79.67	773.0	32.09	700.9	48.43	690.8	39.90
574.6	83.31	498.5	88.22				

26 peaks found

No. 4 1,3-Difluorobenzene

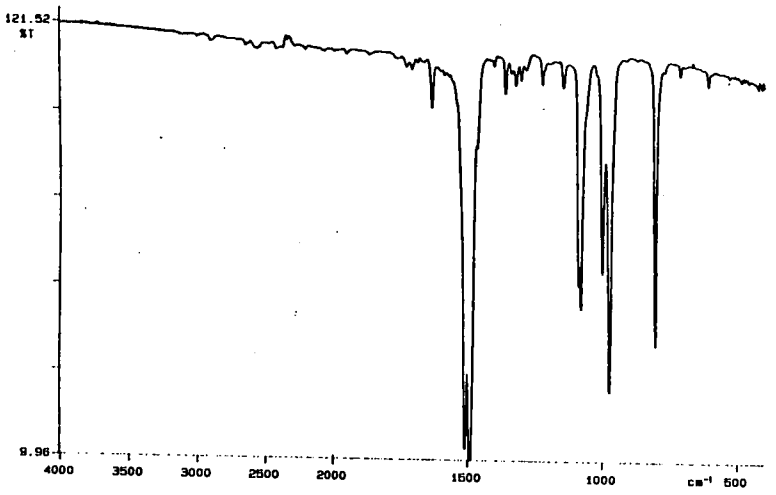


PEAK Z 4000.0 400.0
threshold 1.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3085.1	104.75	2747.8	116.83	2567.7	115.57	2391.0	111.95
2345.1	115.88	2224.7	112.72	2068.1	114.38	2012.0	114.43
1926.9	112.04	1851.3	109.62	1751.7	112.95	1641.7	63.60
1611.9	7.91	1604.4	7.55	1587.7	68.15	1562.5	101.88
1544.9	101.23	1518.2	89.02	1491.3	5.41	1467.0	71.71
1450.7	47.60	1421.1	106.35	1277.7	15.18	1261.0	56.59
1155.9	60.02	1118.4	5.66	1067.5	88.46	1053.2	105.97
951.4	10.42	850.8	27.07	770.6	24.81	734.0	72.90
673.5	32.80	522.5	74.04	511.6	71.33	475.9	97.83
455.9	79.14	426.3	107.37	403.2	106.33		

39 peaks found

No. 5 6-Iodo-1,2,3,4,5-pentafluorobenzene

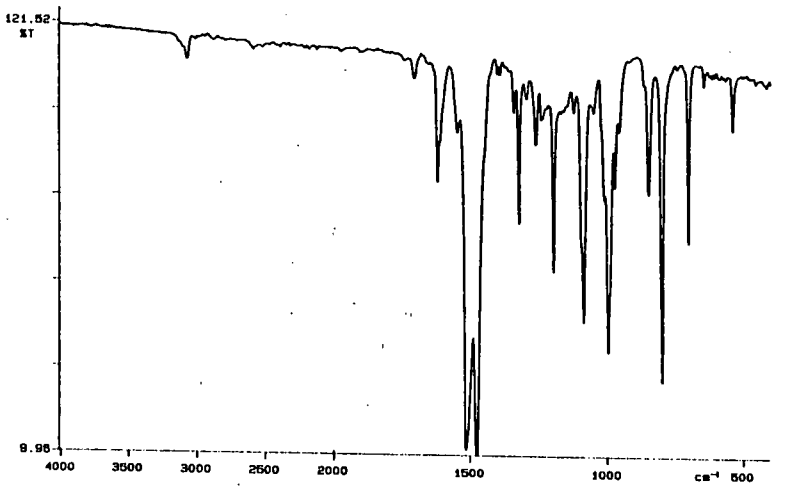


PEAK X 4000.0 405.5
threshold 1.00%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
2911.8	117.14	2655.2	116.12	2569.3	115.40	2427.5	115.35
1952.5	114.51	1729.5	111.54	1710.1	111.04	1635.2	101.05
1511.3	12.85	1492.8	9.96	1406.1	112.08	1363.8	105.14
1325.0	107.22	1305.2	108.51	1285.7	111.26	1226.0	107.60
1147.7	106.93	1089.8	55.56	1081.2	49.44	1002.0	58.48
975.8	27.83	806.0	40.27	713.9	110.35	610.3	107.83
490.1	108.90	428.6	107.31	414.9	107.30	407.8	107.68

28 peaks found

No. 6 5,6-Diiodo-1,2,3,4-tetrafluorobenzene

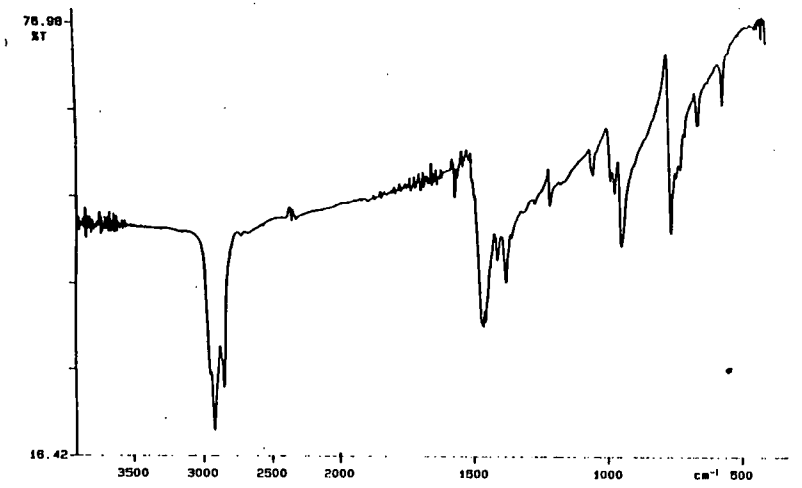


PEAK Y 4000.0 405.5
threshold 1.00%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3077.2	112.29	2592.6	115.01	2395.9	115.64	1706.4	108.13
1620.9	81.20	1548.5	94.24	1515.8	11.52	1476.9	10.15
1403.9	109.53	1394.2	109.22	1343.3	99.64	1324.5	70.25
1296.5	103.14	1263.2	91.29	1243.0	97.82	1198.8	58.10
1125.3	99.95	1089.5	45.04	1054.1	99.83	1014.0	76.92
1000.5	37.06	976.1	80.00	961.0	94.90	852.8	78.59
803.8	29.77	751.9	111.31	706.2	65.18	651.3	107.21
622.2	109.26	571.7	108.73	543.3	95.40	460.6	107.88
420.5	107.02						

33 peaks found

No. 7 3,6-Diiodo-1,2,4,5-tetrafluorobenzene

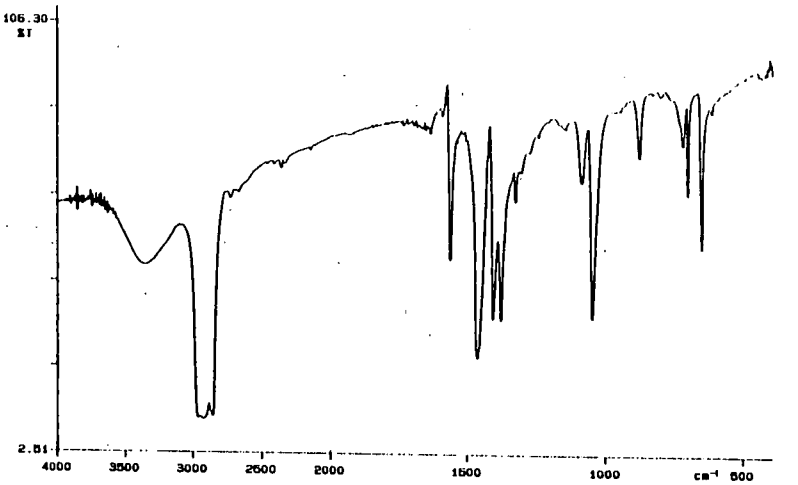


PEAK X 3915.1 400.0
threshold 2.00%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3849.1	47.12	3812.1	47.69	3740.9	47.58	3708.3	48.05
3684.8	47.83	3665.9	47.67	3644.0	47.87	2921.4	20.18
2852.1	26.03	2350.3	49.36	1692.9	53.82	1650.0	54.44
1632.1	54.84	1584.9	52.83	1462.3	34.74	1408.2	44.11
1376.9	41.03	1212.7	51.76	1050.9	56.12	988.6	53.58
947.1	46.03	780.8	47.90	667.6	63.08	553.5	65.87
416.1	75.20						

26 peaks found

No. 8 1,3,5-Trifluoro-2,4,6-Triiodobenzene

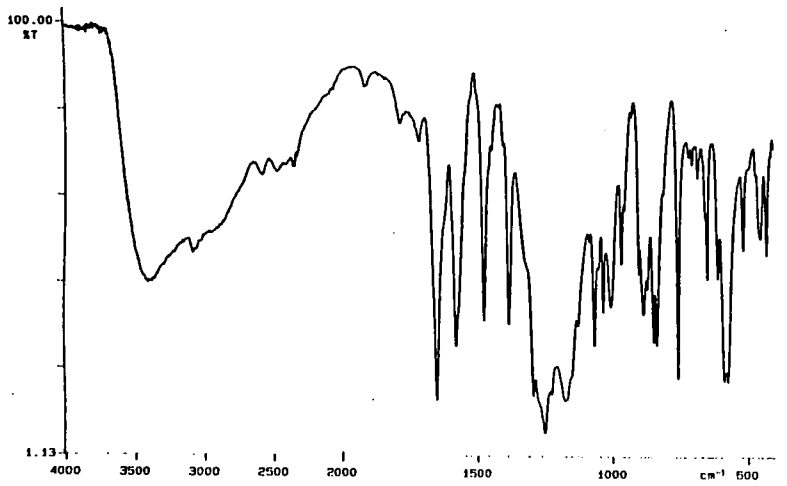


PEAK X 4000.0 400.0
threshold 2.00%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3896.2	62.27	3849.1	60.90	3812.0	61.99	3740.5	61.85
3729.6	62.37	3708.5	62.48	3684.8	61.89	3665.8	61.47
3644.0	60.67	3349.5	47.98	2918.8	10.77	2854.3	11.63
1632.7	60.48	1589.8	64.62	1563.6	49.72	1462.2	28.22
1407.1	35.79	1377.2	35.44	1328.3	64.14	1148.0	61.76
1089.2	68.81	1048.9	36.14	880.2	76.14	722.1	78.14
704.6	66.01	653.8	63.12				

26 peaks found

No. 9 4,4'-Difluoro-3,3'-diiodobenzophenone

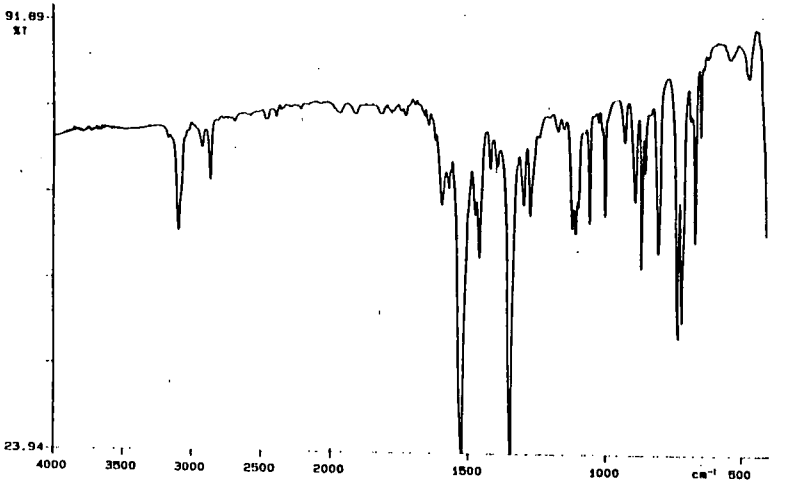


PEAK Y 4000.0 405.5
threshold 1.00%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3901.6	97.83	3883.0	98.09	3851.8	97.20	3819.4	98.43
3799.9	98.37	3749.2	97.25	3742.0	97.72	3733.1	97.41
3708.7	97.27	3687.7	94.95	3409.1	40.62	3086.3	47.53
2592.0	65.36	2484.0	66.14	2362.5	67.34	2342.2	69.65
1917.8	85.89	1789.7	77.45	1717.8	73.32	1653.9	14.01
1583.6	26.35	1478.9	32.24	1387.4	31.33	1295.6	15.09
1252.2	6.56	1177.1	14.02	1128.6	31.16	1087.6	50.52
1068.6	26.62	1036.0	33.98	1008.1	35.66	969.0	45.43
956.2	57.89	928.1	79.16	904.0	42.98	887.3	33.84
872.7	39.68	849.4	27.35	838.0	26.86	759.6	18.50
718.0	70.10	705.9	68.41	685.8	65.30	658.0	56.01
651.6	41.99	613.3	42.14	590.0	18.73	576.2	18.47
518.5	48.66	455.7	51.39	432.2	47.29		

51 peaks found

No. 10 3-Iodonitrobenzene

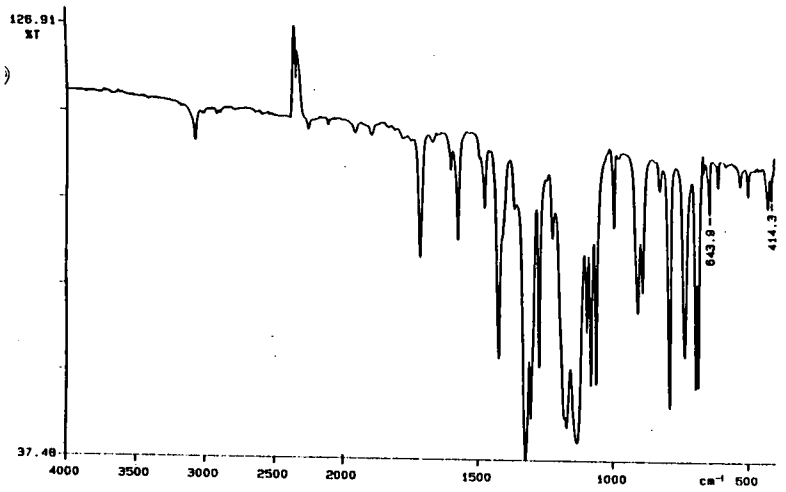


PEAK X 4000.0 400.0
threshold 2.00%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3089.4	68.84	2916.5	72.01	2857.6	66.84	1724.2	77.50
1598.4	63.43	1570.8	68.00	1523.3	24.15	1476.9	61.68
1459.9	65.05	1418.7	69.31	1392.7	69.68	1345.2	23.94
1295.8	63.65	1272.1	61.82	1118.0	59.71	1104.8	59.05
1054.4	60.86	997.7	61.81	924.7	73.79	887.2	64.30
863.4	63.66	850.1	68.74	800.5	65.98	728.6	42.61
713.2	45.00	662.7	57.73	642.1	74.66	534.9	87.05
465.1	84.04						

29 peaks found

No. 11 3-Iodo-α,α,α-trifluorotoluene

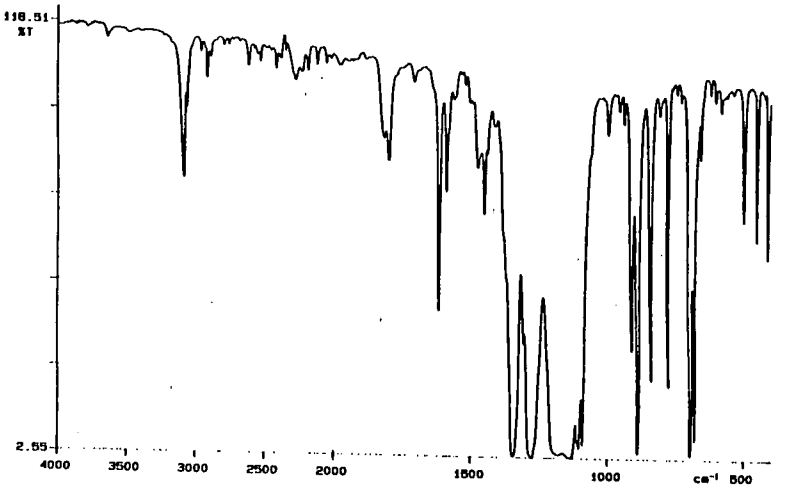


PEAK Y 4000.0 400.0
threshold 0.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3756.0	112.71	3667.2	112.49	3068.4	103.32	2914.3	108.61
2387.7	108.18	2348.2	116.11	2252.7	105.90	2108.7	106.81
1954.5	105.31	1893.1	104.86	1778.3	104.24	1713.5	79.55
1666.4	103.64	1600.1	97.77	1573.8	83.16	1474.2	90.03
1422.1	58.78	1363.1	89.95	1320.1	37.48	1302.6	46.14
1270.5	56.66	1220.6	83.90	1168.9	44.47	1130.7	41.32
1094.4	64.05	1080.0	52.98	1060.6	53.63	996.1	86.02
978.6	100.79	908.5	68.70	890.7	72.90	827.2	94.18
790.5	48.62	735.1	59.47	694.2	52.88	684.3	52.22
664.3	97.92	643.9	89.17	611.8	94.92	581.7	99.49
529.8	95.25	500.2	93.17	462.0	98.54	427.2	90.68
414.3	92.46						

45 peaks found

No. 12 1,3-Bis(trifluoromethyl)-5-iodobenzene

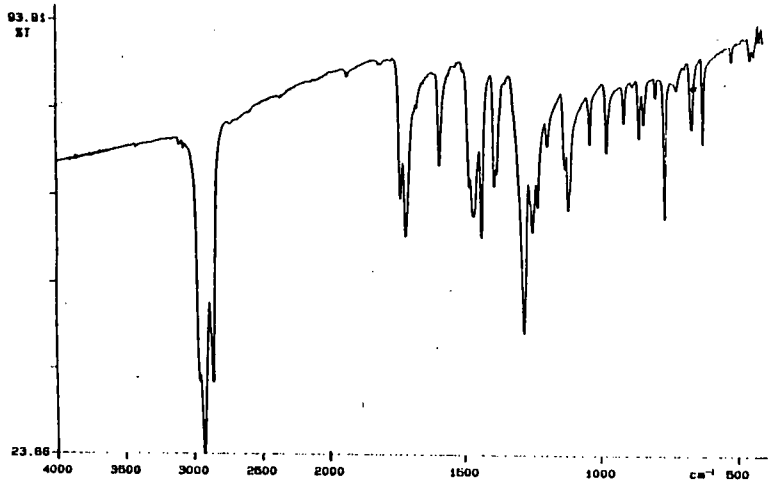


PEAK X 4000.0 400.0
threshold 0.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3861.4	117.68	3781.8	117.09	3638.6	114.47	3478.1	115.84
3085.8	77.40	3061.1	96.16	2959.6	111.30	2915.9	104.20
2889.3	109.83	2794.8	113.03	2759.4	113.19	2680.9	114.14
2615.6	107.75	2574.6	112.20	2549.9	110.72	2528.1	108.83
2453.1	111.84	2414.0	107.18	2382.1	109.73	2348.2	111.72
2274.6	104.11	2230.9	106.29	2186.0	106.68	2121.5	108.34
2055.0	108.87	2022.8	110.03	1978.4	108.26	1946.1	109.25
1882.4	110.14	1819.0	89.05	1801.2	83.15	1709.8	104.22
1617.9	41.89	1591.1	74.75	1563.3	99.69	1536.1	106.35
1522.9	103.73	1505.4	98.92	1477.4	81.36	1453.6	68.60
1442.2	85.31	1415.3	92.65	1344.4	3.13	1309.1	33.82
1276.7	2.59	1136.1	2.97	1104.6	5.73	1091.5	6.49
999.4	91.08	958.4	97.35	941.8	93.86	911.3	32.22
888.5	4.40	841.9	24.27	810.4	96.43	778.7	21.71
762.8	103.56	746.7	102.23	730.8	100.19	696.6	3.91
681.3	8.01	657.8	84.78	622.3	102.40	604.3	100.24
583.6	97.62	538.3	102.53	497.5	67.38	449.9	62.29
424.0	101.49	409.2	57.53				

70 peaks found

No. 13 4-Fluoro-3-iodobenzoic Acid

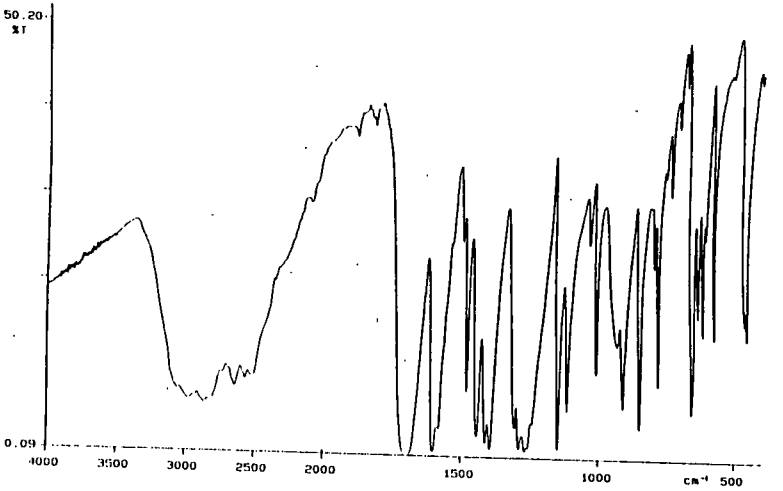


PEAK X 4000.0 400.0
threshold 0.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3846.4	71.82	3410.3	73.77	3096.0	74.22	3065.4	73.66
2952.0	35.84	2922.6	24.09	2852.7	35.70	1930.9	85.32
1813.7	87.30	1733.9	65.71	1713.6	59.70	1588.7	71.21
1477.2	67.64	1461.9	62.95	1432.1	59.55	1386.1	67.75
1377.9	69.85	1276.8	44.23	1243.7	60.52	1223.9	64.50
1190.0	74.44	1122.9	70.79	1113.0	64.04	1034.0	74.59
973.8	73.31	910.2	78.18	880.0	84.09	856.1	75.84
839.1	77.97	797.1	82.35	763.5	62.48	722.0	83.58
692.1	86.97	664.7	77.35	624.1	74.79	518.3	88.23
449.9	88.52	436.8	89.10	415.9	91.29		

39 peaks found

No. 14 2,4-Difluoro-5-iodobenzoic Acid

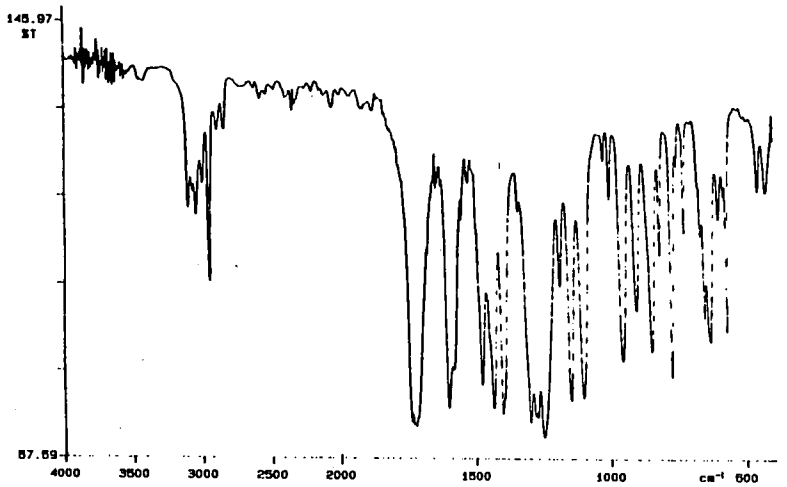


PEAK X 4000.0 400.0
threshold 1.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
2855.0	5.86	2636.6	7.93	1817.8	38.75	1695.5	0.09
1599.8	0.66	1495.5	25.37	1477.6	7.79	1440.6	2.57
1409.5	1.81	1391.8	1.10	1302.3	3.63	1287.3	1.12
1265.7	0.85	1145.8	1.14	1112.1	5.68	1031.7	25.31
1006.9	10.09	930.4	13.62	910.2	6.15	849.7	3.61
794.3	22.76	781.1	8.73	734.1	31.18	706.9	39.35
681.7	44.11	657.2	5.59	634.6	17.05	616.7	14.87
604.8	26.13	576.0	14.58	465.6	16.17	456.8	14.52

32 peaks found

No. 15 Methyl-2,4-difluoro-5-iodobenzoate

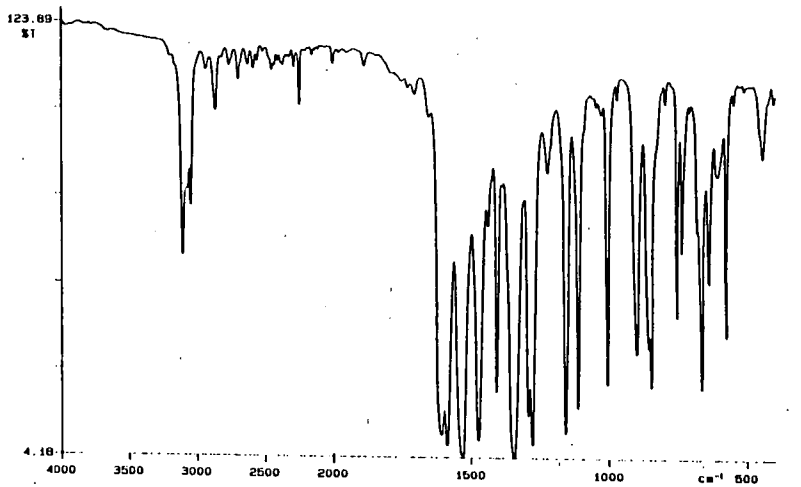


PEAK X 4000.0 400.0
threshold 0.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3966.1	138.21	3939.0	138.18	3928.0	138.04	3913.6	137.38
3896.4	136.36	3888.2	138.13	3880.0	138.75	3877.5	137.58
3866.2	137.72	3860.0	137.16	3849.4	133.17	3833.8	136.19
3816.0	138.60	3812.2	135.68	3804.0	138.34	3797.8	136.20
3775.6	137.18	3764.1	137.68	3756.1	138.01	3747.7	136.99
3740.9	134.23	3729.9	135.26	3718.2	137.11	3707.0	135.63
3697.7	136.66	3685.0	134.00	3670.0	136.56	3666.0	133.35
3653.9	136.30	3644.9	133.05	3625.2	133.46	3615.8	135.79
3604.9	135.51	3592.1	136.43	3583.7	134.87	3563.2	134.54
3542.0	135.28	3427.4	134.08	3103.0	108.51	3074.3	111.54
3046.3	107.01	3002.3	113.42	2953.2	93.66	2898.6	124.26
2845.8	124.41	2715.8	133.07	2627.8	132.77	2583.6	130.67
2545.2	131.54	2484.3	132.53	2401.4	130.88	2352.1	128.32
2335.4	129.57	2210.2	132.26	2152.9	132.39	2122.0	131.40
2061.1	129.03	2013.5	131.52	1964.8	131.30	1921.8	128.79
1882.0	128.42	1865.7	130.61	1737.9	65.04	1722.2	64.22
1682.1	99.24	1650.1	112.64	1643.8	113.59	1632.5	113.30
1603.0	68.06	1584.8	75.88	1556.2	106.17	1537.5	114.32
1530.5	113.76	1479.7	72.77	1436.3	68.09	1403.3	66.86
1345.9	108.09	1299.8	65.19	1280.5	66.46	1271.1	66.11
1247.9	62.18	1190.2	93.03	1147.1	69.64	1102.3	70.31
1028.0	118.49	1006.4	110.88	959.4	77.88	909.9	88.21
852.4	79.85	823.5	99.42	778.3	74.62	760.5	117.57
734.0	103.56	709.9	126.12	673.1	103.40	658.2	86.63
636.6	82.01	606.5	106.81	587.6	111.35	575.6	83.39
532.0	128.96	498.1	126.88	460.3	112.60	431.7	112.16

104 peaks found

No. 16 2,4-Difluoro-5-iodonitrobenzene

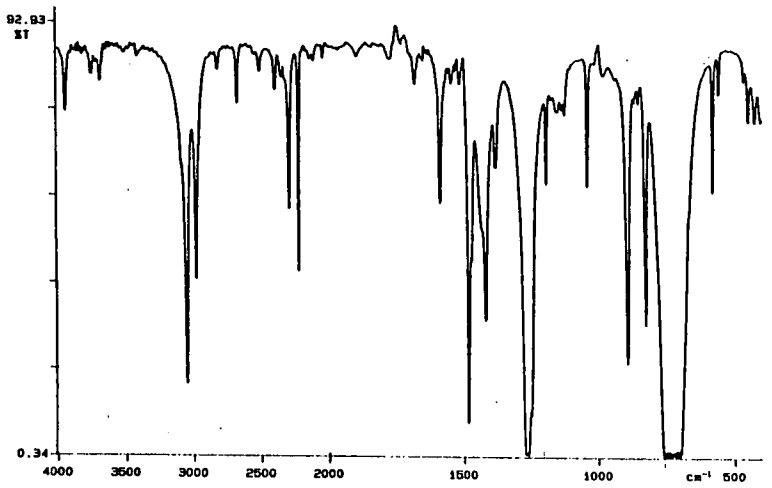


PEAK X 4000.0 400.0
threshold 0.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3971.5	122.51	3106.6	59.98	3046.1	73.35	2939.8	111.05
2866.7	99.85	2764.8	112.25	2698.6	108.42	2628.2	112.60
2587.3	111.46	2560.1	113.60	2517.3	116.15	2452.2	111.07
2434.4	112.39	2410.1	113.67	2371.9	112.47	2341.4	114.78
2323.0	114.66	2291.3	112.09	2252.3	101.12	2161.0	115.46
2117.0	117.00	2009.9	113.09	1982.1	116.23	1955.2	116.23
1892.1	112.53	1755.1	108.45	1733.1	106.53	1708.7	104.80
1657.6	98.53	1607.2	10.56	1587.6	7.59	1531.1	4.62
1472.7	9.10	1441.9	68.46	1407.8	22.62	1344.5	4.37
1293.0	15.99	1277.8	7.98	1224.3	83.39	1157.4	11.22
1111.8	18.26	1048.5	101.84	1030.3	99.56	1004.8	24.75
974.1	103.85	899.7	33.51	856.1	35.06	846.5	24.15
800.4	102.94	754.0	42.42	735.5	61.64	712.3	100.81
664.5	23.79	636.7	53.22	607.6	82.69	575.6	37.31
552.6	103.00	533.2	107.95	515.5	106.68	444.8	88.07
408.1	103.36						

61 peaks found

No. 17 4-Fluoro-3-iodobenzonitrile

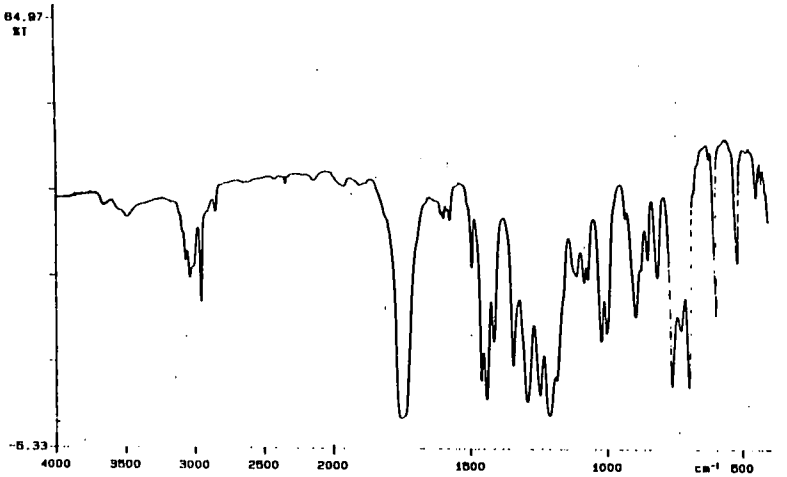


PEAK Z 4000.0 405.5
threshold 1.00%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3943.1	77.78	3873.1	88.94	3853.8	88.50	3821.0	88.66
3752.2	84.61	3690.1	82.95	3649.7	88.98	3619.2	89.39
3053.6	22.66	2986.1	44.45	2829.8	86.51	2684.8	79.47
2520.6	86.68	2410.3	81.49	2360.8	81.84	2305.1	59.18
2144.1	87.78	2053.9	88.29	1792.3	90.39	1734.4	93.84
1685.1	90.51	1663.3	90.79	1635.9	88.90	1593.4	85.97
1567.4	42.41	1551.9	82.14	1518.0	91.41	1421.3	37.10
1409.4	9.64	1331.9	73.95	1260.3	1.77	1153.8	80.61
1052.5	51.20	981.9	86.34	895.8	33.91	754.1	0.87
750.0	1.85	736.2	2.16	720.4	2.31	716.0	0.57
708.2	2.61	702.3	2.16	658.2	35.30	451.3	83.83

44 peaks found

No. 18 4-Fluoro-3-iodonitrobenzene

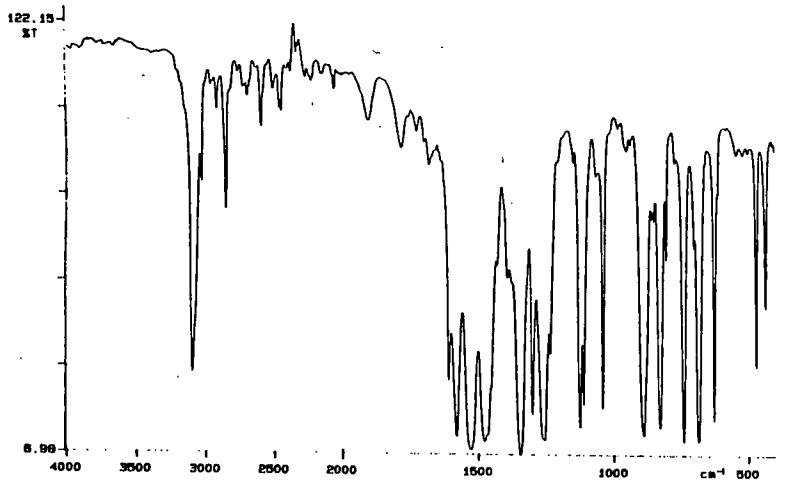


PEAK X 4000.0 400.0
threshold 0.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3850.7	47.57	3645.8	45.75	3483.6	43.24	3065.4	34.18
3035.1	30.65	2953.8	25.40	2846.5	44.56	2412.3	51.52
2337.1	50.49	2136.0	51.35	1959.7	50.10	1900.9	50.36
1750.2	1.20	1607.1	44.12	1597.0	43.37	1574.5	43.01
1495.9	33.00	1459.5	9.06	1439.7	5.26	1415.9	17.34
1344.7	12.36	1292.4	4.68	1245.1	6.14	1210.1	1.81
1184.2	9.18	1112.1	31.29	1083.6	30.04	1069.7	30.61
1021.7	17.48	1001.9	19.17	930.0	43.41	895.7	22.71
850.3	34.89	815.8	31.11	760.8	8.14	728.2	19.87
696.9	7.94	618.1	56.30	599.9	22.98	552.0	59.96
517.6	34.15	480.0	57.75	444.0	48.14	440.1	48.89
436.1	50.88	432.0	51.54	426.0	54.01	424.0	51.00
420.0	52.31						

49 peaks found

No. 19 3-Bromo-4-fluoronitrobenzene

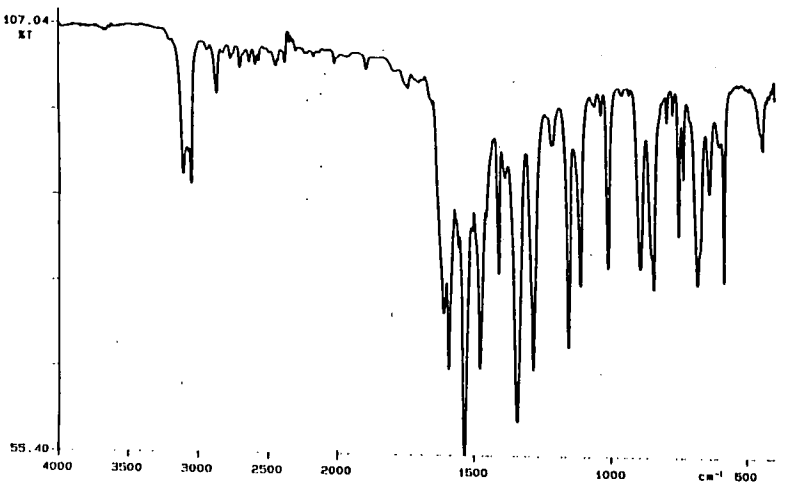


PEAK Y 4000.0 405.5
threshold 2.00%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3106.6	28.61	3042.1	79.55	2929.7	99.22	2866.8	72.39
2707.6	102.85	2608.4	94.34	2519.9	104.80	2473.6	99.56
2458.9	98.89	2391.9	109.42	2348.1	114.33	2281.2	107.98
2238.3	106.88	2152.8	108.92	2066.8	104.93	1908.0	96.56
1786.9	89.29	1730.4	93.83	1684.6	84.68	1611.8	26.91
1583.0	11.94	1530.9	8.31	1479.9	10.60	1397.5	54.64
1347.2	6.98	1303.3	17.90	1258.5	11.08	1237.1	34.05
1151.6	85.44	1127.1	14.36	1113.9	20.35	1043.5	19.69
955.7	89.07	891.0	12.37	864.0	70.25	855.9	69.75
830.7	14.53	809.5	59.54	742.6	10.87	705.7	62.77
688.3	10.88	630.8	16.18	548.2	88.08	474.6	30.41
440.1	46.78						

45 peaks found

No. 20 5-Bromo-2,4-difluoronitrobenzene

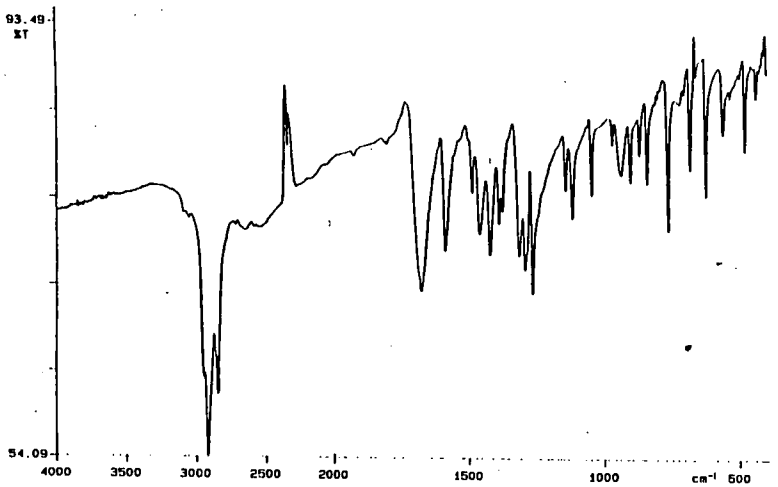


PEAK X 4000.0 400.0
threshold 1.00%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3114.5	89.05	3056.9	87.88	2870.0	98.91	2771.3	103.07
2704.3	102.00	2636.1	102.71	2592.1	102.44	2443.1	102.29
2379.4	102.70	2019.7	102.70	1894.0	102.05	1743.9	99.85
1615.6	72.60	1595.1	65.87	1559.9	80.45	1535.2	55.40
1480.8	65.97	1413.9	77.57	1388.2	89.18	1342.6	59.59
1286.3	65.93	1219.2	93.23	1158.7	68.71	1115.6	76.12
1064.7	98.00	1041.9	96.93	1015.4	78.31	897.6	78.31
848.3	75.73	800.1	96.08	778.0	97.11	754.5	82.30
736.4	89.08	685.0	76.43	640.8	87.56	586.3	76.49
445.6	92.86						

37 peaks found

No. 21 3-Bromo-4-fluorobenzoic Acid

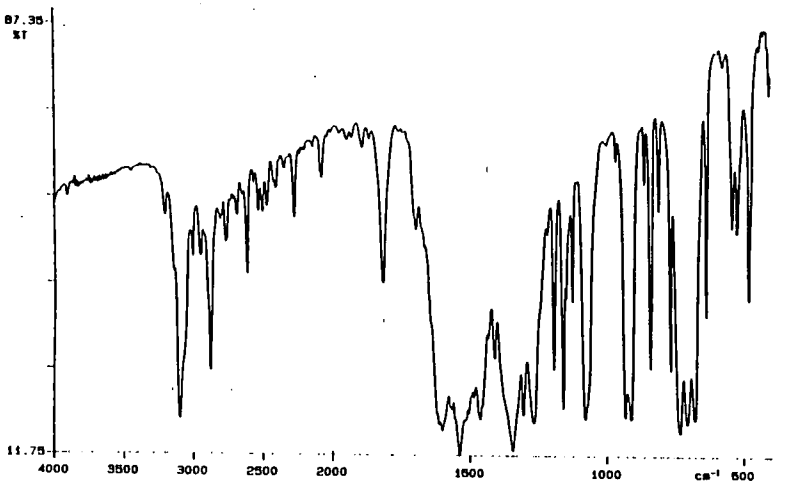


PEAK X 4000.0 400.0
threshold 1.00%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
2922.2	54.14	2852.7	59.75	2348.4	82.42	2282.8	78.77
1679.7	69.40	1591.0	73.05	1490.8	78.32	1462.6	74.62
1424.6	72.76	1391.4	75.53	1377.7	76.66	1315.3	72.64
1292.8	71.39	1264.4	69.19	1142.2	78.64	1117.9	75.98
1047.4	78.17	970.0	82.80	938.9	80.11	904.0	79.33
870.4	81.87	842.9	79.27	765.9	74.80	684.3	80.49
663.6	89.03	626.6	78.10	561.9	83.81	481.8	82.27
440.1	87.12						

29 peaks found

No. 22 2-Bromo-4,6-dinitrofluorobenzene

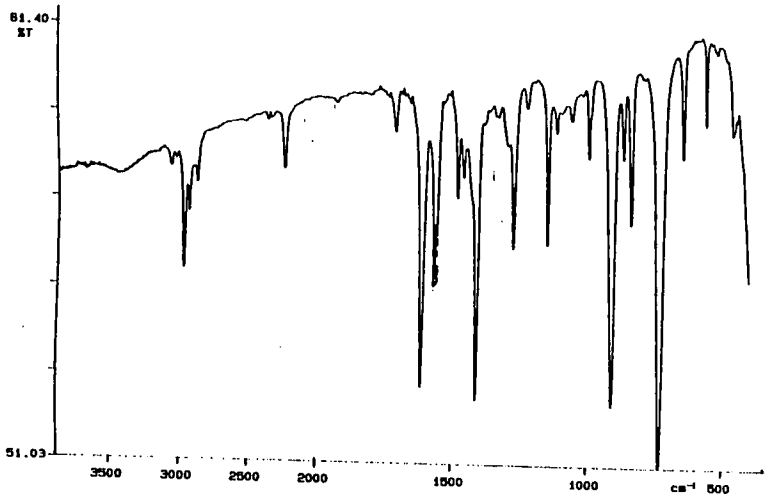


PEAK X 4000.0 400.0
threshold 0.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3907.6	57.14	3849.6	58.66	3828.8	58.56	3812.1	58.79
3740.9	59.18	3729.8	59.27	3706.8	59.70	3685.1	59.47
3665.9	59.70	3644.6	59.85	3625.3	59.95	3583.9	60.72
3448.2	61.51	3201.9	53.85	3095.1	18.25	3005.7	46.71
2946.6	46.84	2876.1	26.56	2806.5	53.20	2767.6	49.34
2711.9	56.77	2684.7	53.98	2647.0	57.53	2613.4	43.66
2566.0	59.62	2532.2	54.86	2501.3	54.58	2471.7	55.60
2407.3	58.80	2346.2	62.37	2274.1	53.69	2236.6	64.84
2218.0	65.47	2201.6	65.57	2142.5	66.14	2078.5	60.77
2012.8	68.66	1973.8	68.58	1947.5	67.43	1930.5	67.79
1892.2	66.10	1866.1	67.57	1817.6	42.35	1760.0	68.97
1697.7	51.64	1601.5	16.27	1567.3	19.98	1537.7	11.75
1504.2	19.31	1486.0	22.22	1462.9	18.38	1434.0	32.71
1409.9	29.05	1343.7	12.73	1304.8	19.08	1266.8	17.72
1217.1	50.96	1193.1	27.28	1158.6	20.29	1148.1	39.72
1124.4	39.24	1078.8	18.51	1001.4	66.94	967.4	64.02
933.5	18.82	912.5	18.44	864.0	59.63	841.8	27.40
810.1	55.34	766.0	26.74	732.7	16.01	707.1	17.61
679.2	18.31	634.3	36.68	575.4	80.79	540.3	52.26
521.4	51.21	476.4	39.43	443.8	83.49	431.7	86.23
405.0	75.81						

81 peaks found

No. 23 4-Ethyl-2-fluoropyridine

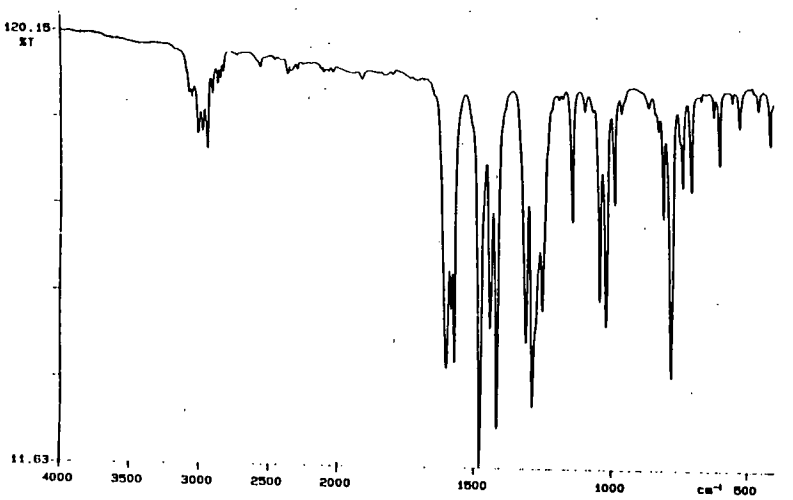


PEAK Y 3876.4 400.0
threshold 0.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3676.4	71.09	3449.1	70.86	3064.5	71.55	2973.4	64.46
2937.2	68.40	2878.6	70.40	2239.8	71.51	1710.5	74.29
1614.2	56.42	1568.2	64.04	1558.5	67.00	1481.9	69.70
1459.3	71.13	1412.5	55.62	1331.1	75.46	1277.2	66.22
1223.9	76.15	1148.8	66.55	1115.9	74.45	1059.5	75.31
997.5	72.67	911.5	55.34	868.8	72.69	840.0	68.04
732.6	51.03	647.4	72.79	563.3	75.07	522.1	80.22
461.9	74.51						

29 peaks found

No. 24 2-Methoxypyridine

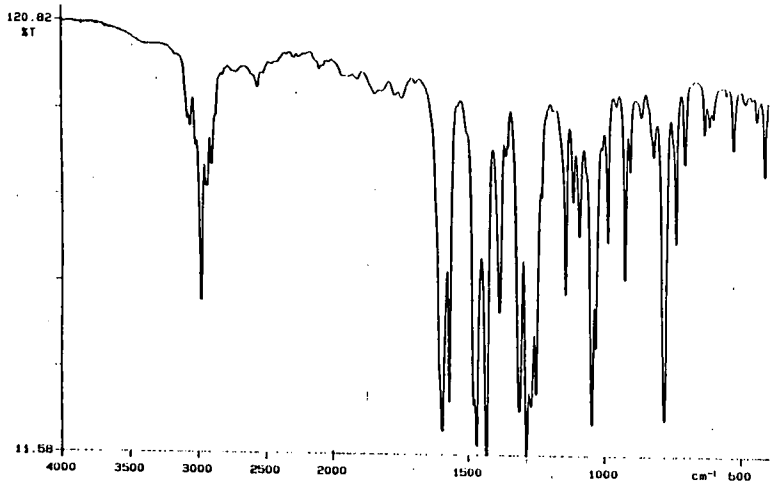


PEAK X 4000.0 400.0
threshold 0.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3076.8	104.87	3056.2	103.82	3012.9	94.64	2979.7	95.23
2944.2	90.78	2908.0	104.84	2869.9	107.42	2848.8	108.63
2827.9	110.26	2730.0	114.56	2561.3	111.65	2359.8	110.08
2341.4	110.78	2289.8	111.32	2098.6	110.68	2062.9	110.89
2030.4	110.70	1910.0	109.17	1827.9	110.27	1797.8	110.47
1706.7	109.12	1602.0	36.86	1584.2	51.54	1571.9	37.81
1480.2	11.63	1442.5	47.04	1418.1	21.22	1312.0	43.52
1289.6	27.17	1252.6	51.64	1191.5	104.79	1178.3	105.06
1142.4	73.95	1096.9	101.99	1067.7	101.90	1043.8	54.08
1020.4	47.86	987.1	78.31	962.2	101.65	863.5	103.36
826.6	97.30	810.3	75.08	780.7	35.16	737.9	83.16
705.3	82.01	668.2	105.17	621.2	101.20	601.4	88.77
553.8	104.78	526.8	98.34	457.5	102.89	414.1	94.11

52 peaks found

No. 25 2-Ethoxypyridine

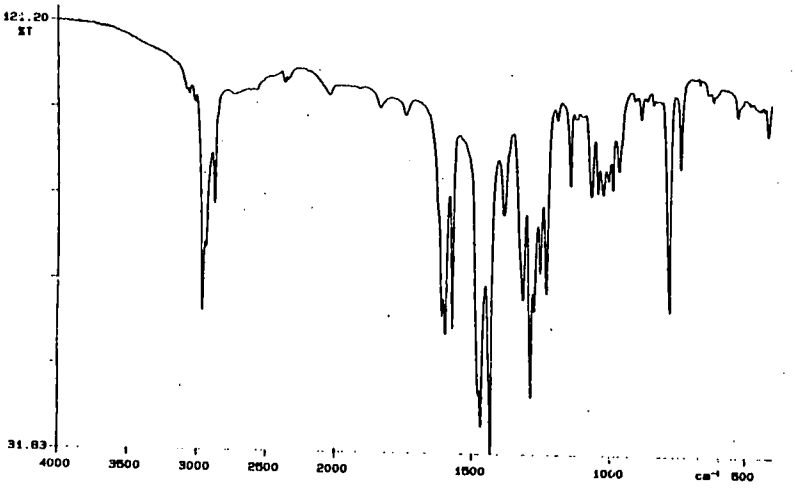


PEAK X 4000.0 400.0
threshold 0.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3853.7	119.86	3837.8	120.13	3751.1	119.96	3075.8	96.52
3056.8	94.79	3015.5	89.71	2980.0	50.31	2942.2	79.43
2900.3	84.95	2719.6	108.28	2561.7	104.63	2288.1	112.18
2254.2	112.30	2101.7	109.49	1910.3	107.05	1844.6	103.36
1771.8	103.10	1745.2	102.42	1696.2	106.16	1596.6	17.73
1570.7	24.88	1479.9	24.40	1469.9	13.97	1434.0	11.58
1387.1	48.32	1364.5	88.13	1313.6	22.96	1288.5	12.06
1271.0	24.29	1251.7	27.35	1232.2	77.65	1189.9	99.57
1142.6	52.84	1116.1	76.52	1092.5	67.81	1046.9	19.64
1032.5	39.37	987.8	66.10	956.5	101.12	924.1	56.39
905.0	84.43	863.9	98.35	818.3	88.43	780.4	20.89
737.6	65.91	704.2	86.34	633.5	94.15	615.9	96.17
602.5	98.20	553.7	104.15	527.3	90.13	485.4	102.03
461.8	102.95	442.4	97.65	413.9	83.33		

55 peaks found

No. 26 2-Butoxypyridine

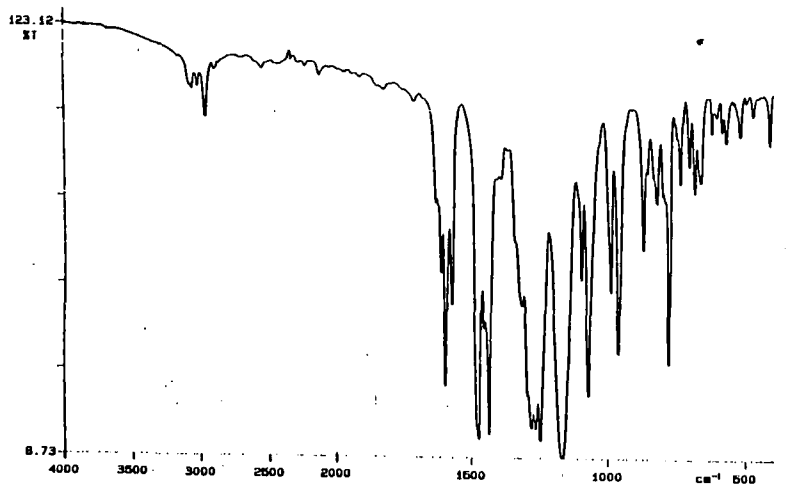


PEAK Y 4000.0 400.0
threshold 1.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3056.7	106.46	2959.2	61.17	2873.0	83.54	2360.3	109.05
2037.8	106.77	1832.6	104.25	1741.0	102.78	1608.1	60.66
1595.7	57.07	1570.0	58.37	1468.5	37.77	1433.3	31.91
1383.3	82.19	1313.1	64.39	1287.6	43.97	1273.4	62.02
1251.7	70.14	1228.6	65.86	1190.0	102.37	1142.3	88.66
1065.8	86.49	1042.4	87.09	1023.2	86.89	1004.2	89.65
988.0	87.68	965.7	91.93	884.4	102.88	780.0	62.15
736.6	92.47	616.6	106.83	526.7	103.68	413.0	99.69

32 peaks found

No. 27 2-(2,2,2-Trifluoroethoxy)pyridine

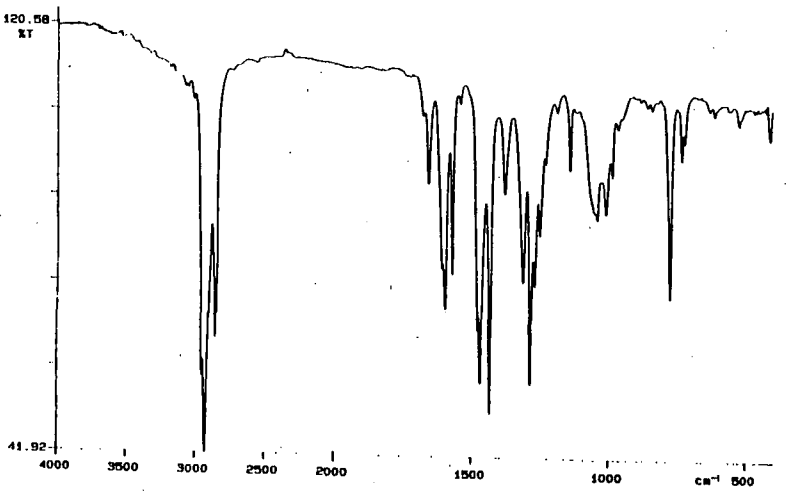


PEAK X 4000.0 400.0
threshold 1.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3065.7	106.32	3024.1	106.84	2966.3	98.89	2902.2	111.35
2559.4	111.82	2134.1	110.16	1828.8	106.57	1715.5	103.68
1617.3	58.12	1600.2	27.55	1576.2	49.64	1475.4	13.85
1455.4	43.33	1437.1	14.95	1315.6	49.38	1280.9	16.80
1265.3	16.62	1247.7	13.54	1168.2	8.73	1099.6	56.49
1072.9	25.55	992.3	53.20	964.1	36.94	874.3	64.55
824.8	77.16	780.1	33.96	737.0	82.49	704.1	86.99
685.6	79.92	663.6	82.79	621.8	95.86	585.2	96.24
570.3	93.59	520.1	95.19	497.7	104.12	473.3	100.70
412.3	92.76						

37 peaks found

No. 28 2-Heptoxypyridine

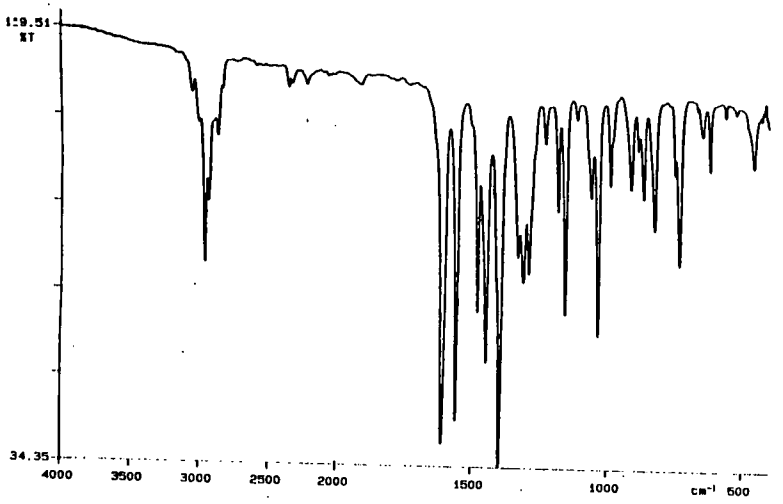


PEAK Y 4000.0 400.0
threshold 1.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3369.2	103.58	2954.5	56.20	2928.2	41.92	2856.6	63.30
1656.2	92.44	1595.8	69.43	1570.2	75.79	1542.7	107.22
1477.7	65.51	1467.7	55.66	1433.1	50.11	1378.7	90.76
1312.6	74.48	1287.1	55.41	1271.3	73.75	1252.1	83.09
1190.3	105.98	1142.0	95.30	1042.6	86.18	1011.3	87.40
988.3	94.18	846.2	106.75	779.6	71.93	736.2	97.52
725.3	100.68	615.9	105.80	525.4	104.13	408.7	101.44

28 peaks found

No. 29 4-Ethyl-2-methoxypyridine

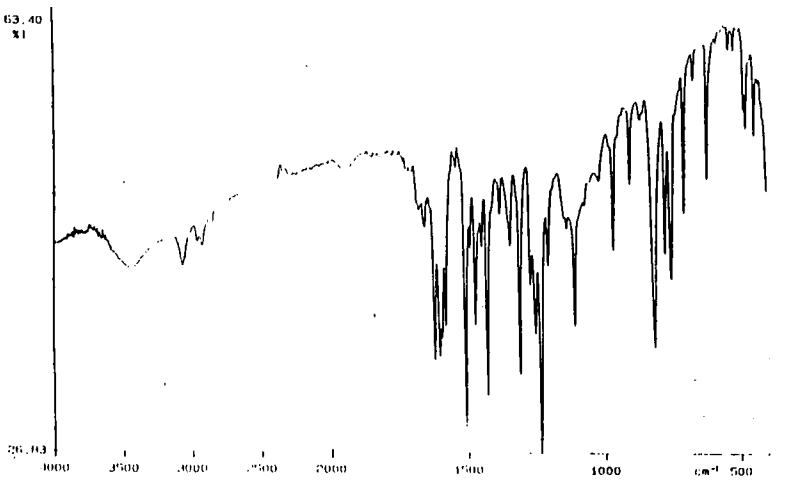


PEAK X 4000.0 400.0
threshold 1.50%; band

cm-1	%	cm-1	%	cm-1	%	cm-1	%
3056.0	107.32	2970.2	74.07	2945.4	85.98	2875.0	98.92
2358.2	108.63	2222.4	109.27	1912.9	109.50	1613.0	39.07
1560.4	43.67	1481.6	65.26	1449.5	55.27	1398.0	34.35
1331.1	76.15	1312.0	71.36	1291.3	73.04	1227.7	98.58
1183.4	85.34	1157.6	65.06	1112.0	103.54	1060.9	88.17
1035.9	60.93	989.8	90.54	912.9	90.10	885.8	97.55
866.4	88.06	825.8	81.97	750.4	92.87	733.6	75.09
646.7	100.63	620.2	93.79	562.6	104.48	457.1	94.66

32 peaks found

No. 30 2-Fluoroquinoline



PEAK X 4000.0 400.0
threshold 1.50%; band

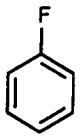
cm-1	%	cm-1	%	cm-1	%	cm-1	%
3447.9	42.53	3066.6	42.73	2923.8	44.40	1656.9	46.15
1621.1	34.57	1603.0	34.90	1580.4	37.49	1508.6	28.85
1491.6	44.16	1473.0	37.66	1450.0	44.40	1429.9	31.35
1383.8	47.23	1345.7	44.51	1310.5	33.33	1271.7	41.14
1253.0	36.94	1232.9	26.83	1206.1	42.90	1108.9	37.59
968.3	44.17	907.9	49.75	870.0	55.35	819.1	35.77
778.8	43.85	755.4	41.72	707.6	47.30	672.6	58.70
621.8	50.09	543.7	61.23	524.0	61.13	477.9	54.66
447.0	53.91						

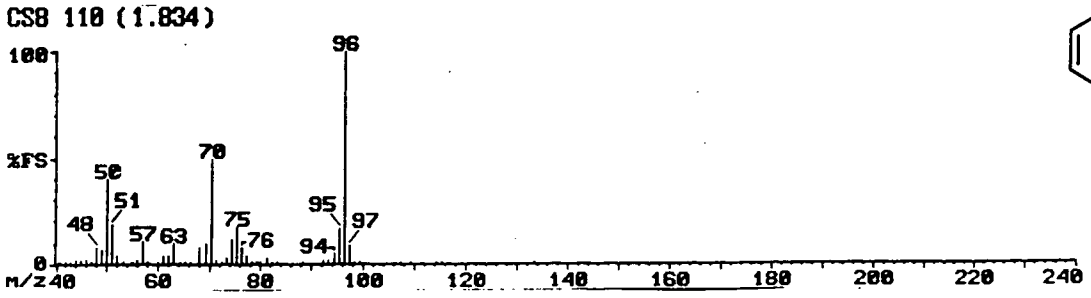
33 peaks found

Appendix Three Mass Spectra

No. 1	Fluorobenzene
No. 2	1,2,3,4,5-Pentafluorobenzene
No. 3	1,2,3-Trifluorobenzene
No. 4	1,3-Difluorobenzene
No. 5	Trimethylsilyl-4-fluorobenzoate
No. 6	Trimethylsilyl-2,4-difluorobenzoate
No. 7	Trimethylsilyl-3,4-difluorobenzoate
No. 8	Trimethylsilyl-2,4,5-trifluorobenzoate
No. 9	Trimethylsilyl-2,3,4-trifluorobenzoate
No. 10	Trimethylsilyl-3,4,5-trifluorobenzoate
No. 11	Trimethylsilyl-2,3,4,5-tetrafluorobenzoate
No. 12	Trimethylsilyl-2,3,4,5,6-pentafluorobenzoate
No. 13	6-Iodo-1,2,3,4,5-pentafluorobenzene
No. 14	5,6-Diiodo-1,2,3,4-tetrafluorobenzene
No. 15	3,6-Diiodo-1,2,4,5-tetrafluorobenzene
No. 16	1,3,5-Trifluoro-2,4,6-triiodobenzene
No. 17	4,4'-difluoro-3,3'-diiodobenzophenone
No. 18	3-Iodonitrobenzene
No. 19	3-Iodo-α,α,α-trifluorotoluene
No. 20	1,3-Bistrifluoromethyl-5-iodobenzene
No. 21	4-Fluoro-3-iodobenzoic Acid
No. 22	2,4-Difluoro-5-iodobenzoic Acid
No. 23	Methyl-2,4-Difluoro-5-iodobenzoate
No. 24	2,4-Difluoro-5-iodonitrobenzene
No. 25	4-Fluoro-3-iodobenzonitrile
No. 26	4-Fluoro-3-iodonitrobenzene
No. 27	3-Bromo-4-fluoronitrobenzene
No. 28	5-Bromo-2,4-difluoronitrobenzene
No. 29	3-Bromo-4-fluorobenzoic Acid
No. 30	2-Bromo-4,6-dinitrofluorobenzene
No. 31	4-Ethyl-2-fluoropyridine
No. 32	2-Methoxypyridine
No. 33	2-Ethoxypyridine
No. 34	2-Butoxypyridine
No. 35	2-(2,2,2-trifluoroethoxy)pyridine
No. 36	2-Heptoxypyridine
No. 37	4-Ethyl-2-methoxypyridine
No. 38	2-Fluoroquinoline

No. 1 M.Wt. 96 EI+

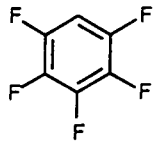


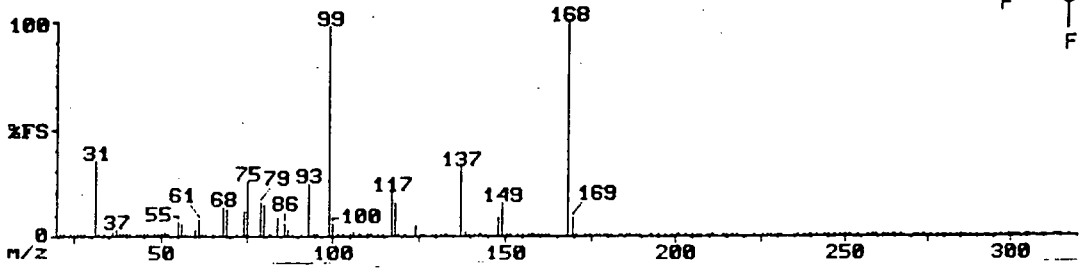


CS8 110 (1.834) 3194880

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
40	0.48	55	0.32	71	2.08	92	1.63
41	0.02	56	1.82	72	0.38	93	1.47
42	0.01	57	10.38	73	3.24	94	5.26
43	0.08	58	0.36	74	11.67	95	16.67
44	2.08	60	0.79	75	17.05	96	100.00
45	1.88	61	3.94	76	7.50	97	8.59
46	1.68	62	3.69	77	3.88	98	0.25
47	0.74	63	9.74	78	0.24	99	0.03
48	7.31	64	0.62	79	0.09	107	0.01
49	6.99	65	0.25	80	0.17	109	0.01
50	39.49	66	0.02	81	2.82	114	0.07
51	18.08	68	7.92	82	0.16	115	0.01
52	3.72	69	9.49	83	0.02	133	0.01
53	0.15	70	49.23	88	0.01		

No. 2 M.Wt. 168 EI+

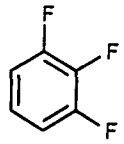


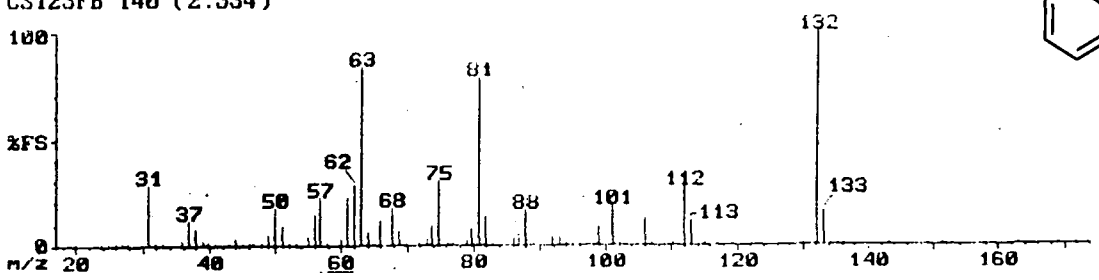


CS5 97 (1.617) 4128768

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.04	94	0.63	169	8.43	248	0.00
22	0.00	95	0.02	170	0.27	250	0.01
24	0.30	99	98.02	173	0.01	251	0.00
25	0.23	100	5.46	174	0.01	254	0.00
26	0.02	101	0.13	176	0.00	257	0.00
27	0.01	103	0.00	177	0.00	258	0.00
28	0.11	105	1.12	179	0.01	259	0.00
31	34.92	106	2.33	180	0.00	262	0.00
32	0.60	107	0.09	181	0.00	262	0.00
34	0.00	108	0.01	183	0.00	263	0.00
36	1.69	110	1.30	184	0.00	264	0.00
37	3.37	111	0.38	185	0.01	265	0.00
38	0.12	113	0.48	186	0.00	267	0.02
39	0.01	114	0.02	189	0.00	271	0.00
40	0.01	117	20.54	189	0.00	272	0.00
41	0.02	118	15.58	192	0.01	273	0.00
43	0.47	119	0.82	193	0.00	274	0.00
44	0.92	120	0.03	195	0.00	276	0.00
45	0.02	121	0.01	197	0.00	278	0.00
46	0.00	124	4.81	199	0.19	279	0.00
48	0.82	125	0.19	200	0.01	280	0.00
49	1.09	126	0.01	201	0.00	282	0.00
50	0.58	129	0.55	203	0.00	284	0.00
51	1.98	130	1.29	205	0.02	285	0.00
52	0.02	131	0.12	206	0.00	285	0.00
55	6.35	132	0.03	207	0.01	287	0.01
56	6.08	133	0.04	209	0.01	288	0.00
57	0.16	137	32.14	210	0.00	290	0.01
60	2.58	138	1.56	211	0.00	292	0.00
61	8.13	140	0.06	214	0.00	293	0.01
62	1.36	141	0.01	215	0.00	296	0.00
63	0.16	142	0.00	216	0.01	297	0.01
65	0.16	143	0.00	218	0.00	300	0.00
68	13.49	145	0.00	223	0.02	301	0.00
69	12.30	148	8.73	225	0.00	301	0.00
72	0.38	149	15.67	227	0.00	302	0.00
74	11.81	150	1.03	228	0.00	303	0.00
75	25.30	151	0.04	229	0.02	305	0.00
79	15.48	153	0.01	230	0.00	305	0.00
80	14.48	155	0.01	231	0.00	307	0.00
81	0.55	156	0.00	236	0.00	310	0.00
82	0.12	157	0.00	238	0.00	310	0.00
84	8.43	158	0.00	240	0.00	313	0.00
86	5.41	159	0.00	240	0.00	314	0.00
87	3.27	160	0.01	241	0.00	315	0.00
88	0.11	161	0.01	244	0.00	317	0.00
91	0.33	162	0.01	245	0.00		
93	24.31	168	100.00	247	0.03		

No. 3 M.Wt. 132 EI+

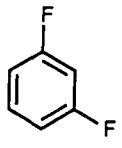


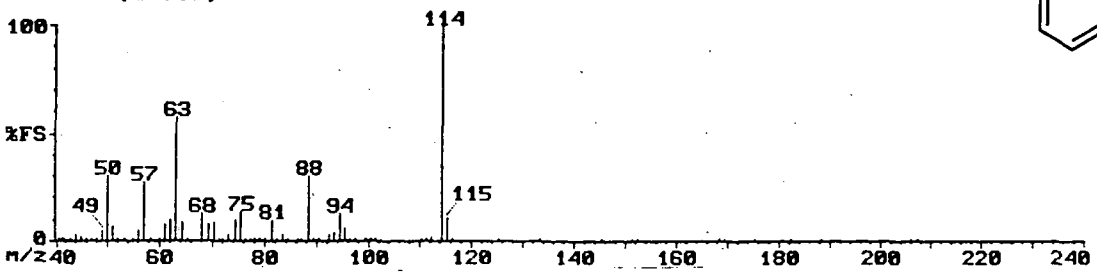


CS123FB 140 (2.334) 4177920

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.05	36	2.11	46	0.10	56	14.71	68	17.25	79	3.36	92	5.32	107	0.50	132	100.00
24	0.25	37	11.57	47	0.06	57	22.53	69	6.37	80	7.35	93	5.29	110	0.62	133	15.49
25	0.64	38	7.65	48	1.10	58	0.72	78	1.05	81	78.43	94	1.44	112	27.86	134	0.51
26	1.87	39	1.69	49	4.51	60	2.84	72	0.63	82	13.92	95	0.17	113	11.86	143	0.08
27	0.24	40	0.08	50	17.86	61	21.86	73	3.01	83	0.55	96	0.02	114	0.77	149	0.02
28	0.49	41	0.06	51	8.53	62	28.63	74	9.51	86	3.19	99	0.33	115	0.03	151	0.02
31	28.24	43	0.30	52	0.20	63	83.92	75	38.20	87	4.51	101	10.43	117	0.17	163	0.13
32	1.12	44	2.52	53	0.02	64	6.23	76	0.89	88	16.96	102	0.91	119	0.06	169	0.08
33	0.40	45	1.04	55	3.77	66	11.27	77	0.05	89	0.66	106	12.75	130	1.15		

No. 4 M.Wt. 114 EI+

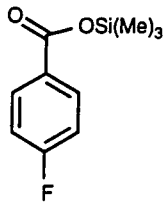


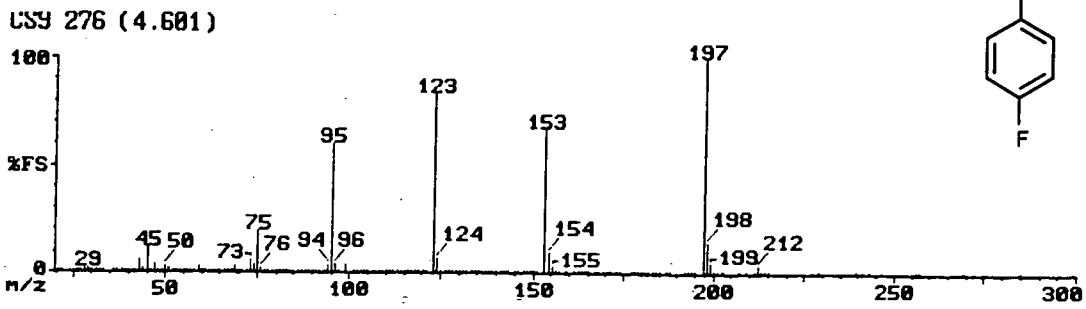


CS8 103 (1.717) 3915776

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
40	0.17	61	8.05	82	0.68	112	1.58
41	0.02	62	9.83	83	2.51	114	100.00
42	0.01	63	57.74	84	0.14	115	10.67
43	0.16	64	8.58	86	0.57	116	0.32
44	2.48	65	0.31	87	1.43	125	0.02
45	1.61	68	12.45	88	29.71	133	0.01
46	0.30	69	7.74	89	1.31	145	0.03
47	0.67	70	8.58	90	0.03	151	0.04
48	0.97	71	0.38	92	2.80	152	0.01
49	5.28	72	0.34	93	3.82	168	0.02
50	29.71	73	2.67	94	12.45	169	0.02
51	7.22	74	9.31	95	5.49	175	0.03
52	0.32	75	13.49	96	0.34	182	0.01
53	0.02	76	0.83	97	0.02	188	0.01
55	1.02	77	0.08	99	0.99	206	0.02
56	5.05	78	0.05	100	0.06	207	0.01
57	27.20	79	0.54	101	0.02		
58	0.42	80	0.95	110	0.12		
60	1.28	81	9.31	111	0.26		

No. 5 M.Wt. 212 EI+

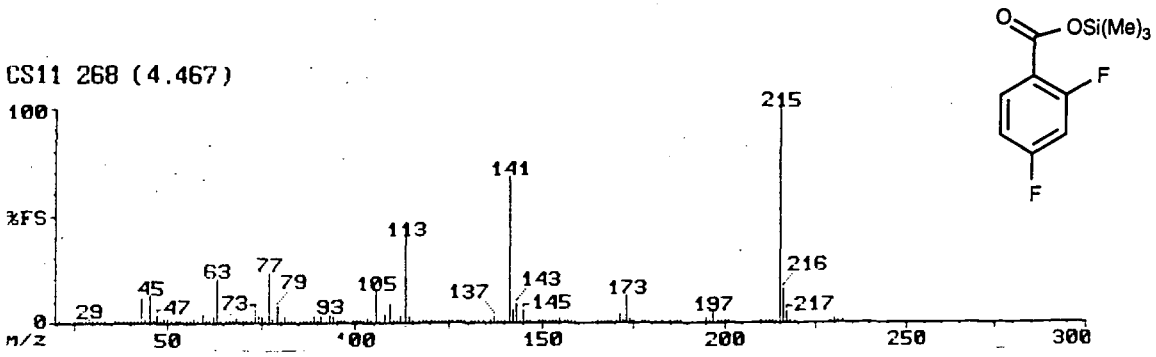




CS9 276 (4.601) 1998848

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.03	69	2.78	116	0.05	167	0.86
22	0.01	70	0.50	117	0.45	168	0.19
24	0.01	71	0.38	118	0.06	169	0.08
25	0.03	72	1.17	119	0.10	170	0.02
26	0.28	73	5.58	120	0.06	171	0.04
27	1.08	74	3.69	121	0.23	173	0.02
28	1.83	75	19.47	123	83.61	174	0.01
29	2.04	76	2.13	124	6.45	177	0.03
30	0.26	77	1.43	125	0.60	178	0.08
31	0.85	78	0.17	126	0.07	179	0.05
32	0.26	79	0.43	127	0.04	180	0.03
33	0.05	80	0.08	128	0.02	181	0.45
36	0.03	81	0.31	129	0.22	182	0.36
37	0.17	82	0.17	130	0.04	183	0.09
38	0.36	83	0.54	131	0.08	184	0.02
39	0.93	84	0.18	132	0.18	185	0.04
40	0.09	85	0.19	133	0.08	187	0.02
41	0.69	86	0.07	134	0.06	188	0.01
42	0.99	87	0.25	135	0.12	192	0.02
43	5.84	88	0.05	136	0.11	193	0.09
44	2.09	89	0.54	137	0.68	194	0.03
45	11.42	90	0.40	138	0.20	195	0.04
46	0.83	91	0.88	139	1.31	197	100.00
47	3.89	92	0.40	140	0.28	198	14.14
48	0.23	93	0.91	141	0.09	199	4.46
49	0.58	94	4.20	142	0.02	200	0.42
50	2.95	95	59.84	143	0.04	201	0.07
51	1.87	96	4.30	145	0.15	202	0.01
52	0.14	97	0.34	146	0.03	207	0.01
53	0.74	99	3.64	147	0.05	209	0.01
54	0.20	101	0.17	148	0.02	211	0.59
55	0.96	102	0.05	149	0.14	212	4.30
56	0.37	103	0.24	150	0.05	213	0.71
57	1.28	104	0.28	151	0.11	214	0.21
58	0.91	105	0.26	153	67.21	215	0.03
59	2.51	106	0.04	154	9.27	227	0.02
60	0.63	107	0.26	155	2.87	229	0.02
61	0.75	108	0.12	156	0.24	239	0.02
62	0.51	109	0.49	157	0.04	241	0.02
63	0.99	110	0.12	159	0.03	243	0.01
64	0.15	111	0.17	161	0.01	256	0.02
65	0.20	112	0.05	162	0.01	257	0.02
66	0.11	113	0.10	163	0.03	269	0.02
67	0.21	114	0.03	164	0.01	285	0.04
68	1.34	115	0.05	165	0.07	299	0.04

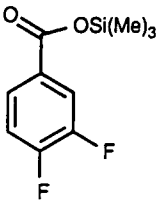
No. 6 **M.Wt. 230** **EI+**

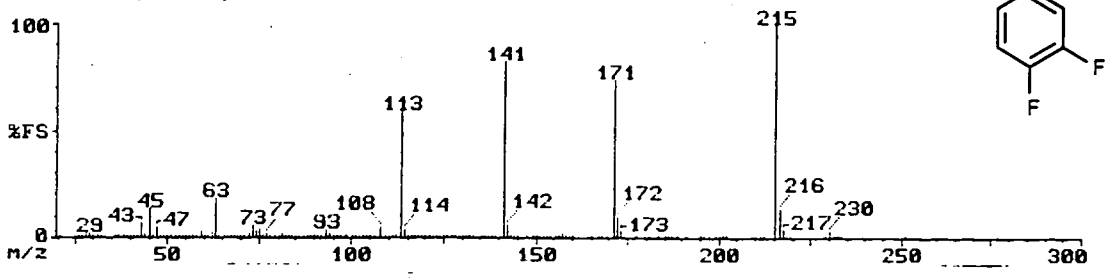


CS11 268 (4.467) — 413696

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.02	69	1.01	114	2.89	166	0.10
25	0.04	70	0.32	115	0.23	167	0.58
26	0.37	71	0.40	117	0.80	168	0.12
27	1.39	72	1.07	118	0.11	169	0.89
28	2.00	73	5.51	119	0.92	170	0.18
29	2.41	74	3.36	120	0.12	171	3.91
30	0.33	75	3.34	121	0.41	172	0.64
31	1.33	76	0.90	122	0.72	173	12.19
32	0.36	77	23.02	123	1.05	174	1.55
33	0.06	78	1.92	124	0.12	175	0.56
36	0.04	79	7.61	125	0.62	177	0.88
37	0.32	80	0.64	126	0.13	178	0.15
38	0.29	81	2.83	127	0.16	179	0.09
39	0.82	82	0.50	128	0.10	181	0.29
40	0.10	83	0.69	129	0.11	183	0.16
41	0.38	84	0.09	131	0.26	185	1.02
42	1.14	85	0.07	132	0.06	186	0.19
43	11.63	86	0.21	133	0.22	187	0.34
44	2.09	87	0.72	134	0.07	188	0.03
45	12.81	88	0.19	136	2.27	195	1.53
46	1.01	89	2.95	137	3.23	196	0.25
47	3.88	90	1.14	138	0.40	197	4.70
48	0.25	91	3.08	139	0.60	198	0.71
49	2.32	92	0.87	140	0.51	199	0.49
50	1.47	93	3.40	141	68.32	200	0.22
51	0.62	94	2.66	142	5.38	201	0.12
52	0.10	95	0.70	143	8.66	210	0.41
53	0.82	96	0.13	144	1.01	211	0.29
54	0.18	97	0.09	145	5.45	212	0.07
55	0.79	99	0.14	146	0.64	213	0.13
56	0.50	100	0.11	147	0.33	214	0.47
57	1.64	101	0.26	149	0.86	215	100.00
58	1.07	102	0.10	150	0.15	216	15.10
59	3.70	103	2.18	151	0.70	217	4.76
60	0.56	104	0.30	152	0.13	218	0.45
61	1.16	105	14.67	153	0.42	219	0.05
62	2.74	106	1.39	154	0.17	229	0.16
63	20.54	108	4.21	155	1.86	230	1.55
64	1.30	109	8.54	156	0.34	231	0.27
65	0.63	110	0.98	157	0.61	232	0.09
66	0.13	111	0.42	158	0.19		
67	0.23	112	2.85	159	0.13		
68	1.56	113	40.10	165	0.15		

No. 7 **M.Wt. 230** **EI+**

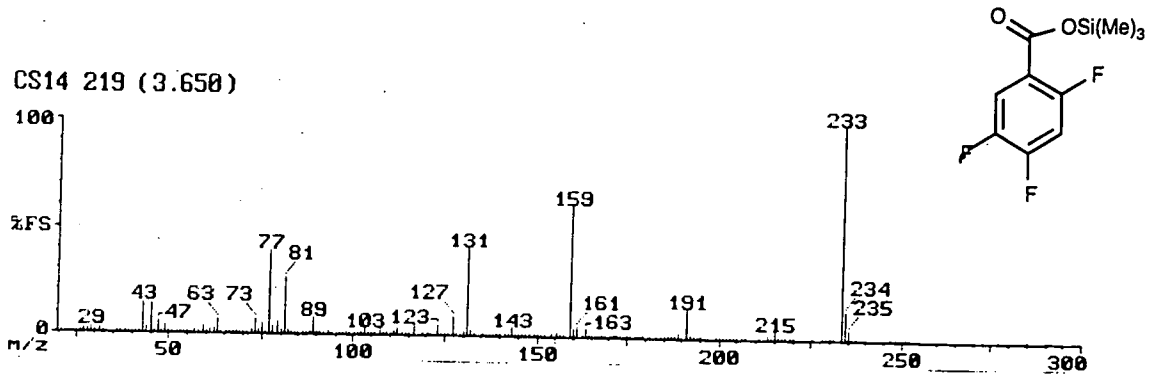




CS16 232 (3.867) 8888884

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
30	0.02	68	1.32	111	0.26	157	1.59
35	0.03	69	0.77	112	2.37	158	0.27
36	0.29	70	0.30	113	59.56	159	0.11
37	1.07	71	0.29	114	3.95	160	0.01
38	1.60	72	1.65	115	0.18	165	0.04
39	2.38	73	5.79	116	0.02	167	0.11
30	0.31	74	2.93	117	0.08	168	0.04
31	1.44	75	3.95	118	0.03	169	0.13
32	0.18	76	0.41	119	0.13	171	73.53
33	0.05	77	2.22	120	0.03	172	9.74
36	0.02	78	0.36	121	0.29	173	2.58
37	0.39	79	0.77	122	0.50	174	0.23
38	0.32	80	0.21	123	0.17	177	0.02
39	0.84	81	1.79	124	0.03	181	0.03
40	0.06	82	0.26	125	0.24	183	0.05
41	0.27	83	0.24	126	0.11	185	0.84
42	1.13	84	0.04	127	0.27	186	0.14
43	6.85	85	0.06	128	0.08	187	0.06
44	2.13	86	0.17	129	0.06	188	0.01
45	13.60	87	0.75	130	0.03	189	0.02
46	0.99	88	0.18	131	0.07	191	0.00
47	4.41	89	0.61	132	0.02	195	0.07
48	0.23	90	0.15	133	0.03	196	0.25
49	0.85	91	0.44	135	0.03	197	0.18
50	1.41	92	0.66	136	0.04	199	0.54
51	0.59	93	3.58	137	0.11	200	0.30
52	0.09	94	2.26	138	0.09	201	0.08
53	0.82	95	0.35	139	0.15	202	0.02
54	0.16	96	0.06	141	82.35	211	0.08
55	0.76	97	0.06	142	6.20	212	0.02
56	0.46	98	0.02	143	0.73	215	100.00
57	1.46	99	0.14	144	0.07	216	13.24
58	1.11	100	0.11	145	0.06	217	4.18
59	2.94	101	0.32	147	0.03	218	0.36
60	0.60	102	0.06	149	0.08	219	0.04
61	1.28	103	0.51	150	0.02	229	0.26
62	2.69	104	0.09	151	0.05	230	2.91
63	18.38	105	1.09	152	0.11	231	0.45
64	1.10	106	0.11	153	0.13	232	0.14
65	0.26	108	5.06	154	0.08	233	0.06
66	0.10	109	0.57	155	0.70	251	0.02
67	0.11	110	0.15	156	0.18		

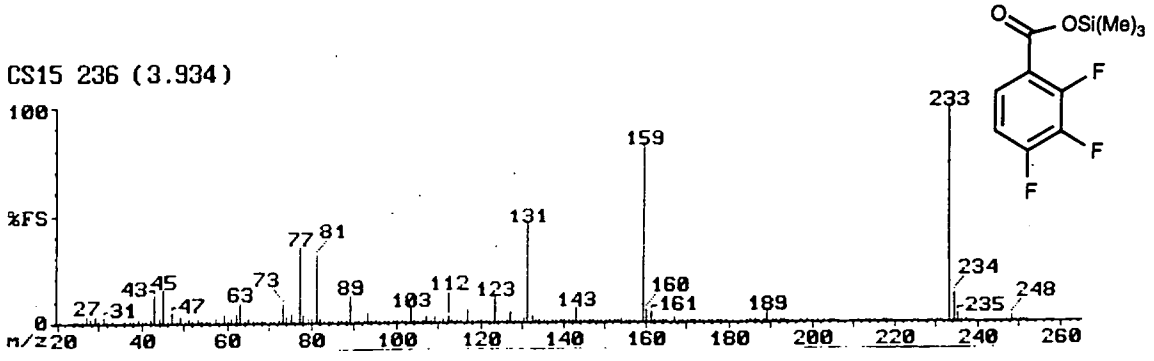
No.8 **M.Wt. 248** **EI+**



CS14 219 (3.650) 1622016

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
30	0.03	76	1.36	129	0.20	185	0.49
34	0.01	77	38.64	130	1.67	186	0.11
35	0.03	78	3.60	131	40.91	187	0.67
36	0.34	79	5.43	132	2.90	188	0.14
37	2.38	80	1.94	133	0.18	189	2.68
38	2.04	81	25.76	135	0.95	190	0.38
39	2.87	82	1.47	136	0.12	191	13.89
30	0.36	83	0.58	137	0.84	192	1.72
31	2.16	84	0.07	138	0.10	193	0.62
32	0.26	85	0.25	139	0.56	194	0.05
33	0.05	86	0.42	140	0.80	195	0.92
36	0.03	87	0.59	141	1.34	196	0.14
37	0.37	88	0.12	142	0.09	197	0.07
38	0.15	89	7.51	143	3.68	199	0.25
39	1.14	90	0.65	144	0.45	200	0.04
40	0.10	91	0.94	145	0.28	201	0.11
41	0.60	92	0.78	146	0.09	202	0.03
42	1.42	93	1.67	147	0.18	203	0.61
43	14.90	94	0.28	148	0.04	204	0.13
44	2.68	95	0.41	149	0.75	205	0.26
45	13.89	96	0.20	150	0.10	206	0.04
46	1.04	97	0.34	151	0.19	207	0.03
47	5.43	98	0.10	152	0.06	211	0.03
48	0.33	99	1.14	154	1.91	213	1.67
49	3.58	100	0.42	155	2.02	214	0.37
50	0.77	101	0.84	156	0.32	215	4.23
51	1.15	102	0.53	157	0.29	216	0.56
52	0.11	103	3.39	159	61.62	217	0.52
53	1.28	104	0.76	160	4.61	218	0.18
54	0.22	105	0.38	161	5.30	219	0.11
55	1.10	106	0.10	162	0.60	220	0.02
56	0.64	107	2.94	163	4.29	225	0.02
57	1.74	108	1.18	164	0.50	228	0.26
58	1.25	109	1.85	165	0.26	229	0.18
59	3.74	110	0.26	166	0.03	230	0.05
60	0.61	111	2.18	167	0.99	231	0.05
61	2.34	112	3.09	168	0.15	233	100.00
62	3.20	113	0.65	169	0.38	234	13.76
63	7.01	114	0.09	170	0.07	235	4.48
64	0.47	115	0.14	171	0.27	236	0.40
65	0.75	117	4.67	172	0.13	237	0.05
66	0.26	119	0.15	173	1.74	247	0.09
67	0.18	120	0.06	174	0.32	248	1.34
68	0.87	121	0.35	175	0.59	249	0.22
69	0.32	122	0.08	176	0.14	250	0.06
70	0.30	123	4.99	177	0.18	251	0.16
71	0.40	124	0.45	178	0.02	252	0.02
72	1.89	125	0.60	179	0.02	285	0.02
73	7.13	126	1.34	181	0.01		
74	2.04	127	8.59	183	0.14		
75	4.48	128	0.93	184	0.07		

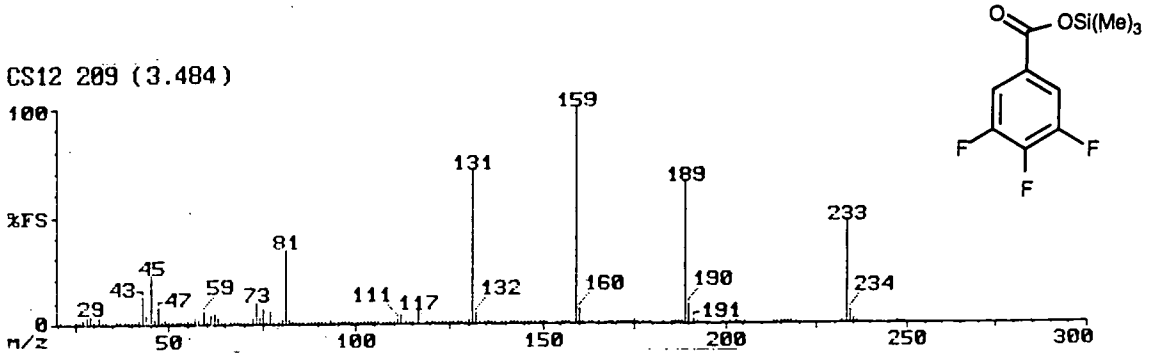
No. 9 M.Wt. 248 EI+



CS15 236 (3.934) 1884160

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.03	74	8.57	124	1.03	175	0.44
24	0.01	75	4.08	125	0.48	176	0.12
25	0.03	76	1.20	126	1.07	177	0.10
26	0.37	77	35.22	127	4.46	178	0.01
27	3.64	78	3.86	128	0.57	179	0.01
28	2.09	79	2.34	129	0.24	181	0.02
29	3.33	80	1.92	130	1.90	183	0.06
30	0.40	81	31.52	131	45.22	184	0.04
31	2.50	82	1.83	132	3.15	185	0.20
32	0.25	83	0.92	133	0.19	186	0.06
33	0.06	84	0.09	134	0.05	187	0.68
36	0.03	85	0.47	135	1.48	188	0.11
37	0.36	86	0.46	136	0.22	189	5.33
38	0.23	87	0.59	137	0.77	190	0.95
39	2.09	88	0.17	138	0.08	191	0.26
40	0.16	89	12.23	139	0.32	192	0.04
41	0.90	90	1.14	140	0.54	193	0.03
42	1.59	91	1.36	141	1.48	194	0.01
43	12.66	92	0.94	142	0.10	195	0.02
44	2.88	93	5.22	143	6.36	197	0.06
45	15.22	94	0.50	144	0.76	199	0.26
46	1.13	95	0.44	145	0.39	200	0.04
47	4.95	96	0.47	146	0.11	201	0.04
48	0.30	97	0.61	147	0.35	203	0.39
49	3.11	98	0.12	148	0.07	204	0.06
50	0.79	99	1.25	149	1.25	205	0.06
51	1.97	100	0.34	150	0.17	211	0.02
52	0.20	101	0.75	151	0.09	213	0.07
53	2.00	102	1.05	152	0.04	214	0.20
54	0.26	103	6.85	153	0.05	215	0.06
55	1.29	104	1.30	154	2.11	217	0.22
56	0.65	105	0.66	155	1.14	218	0.07
57	2.31	106	0.13	156	0.26	219	0.05
58	1.40	107	2.50	157	0.22	228	0.43
59	4.18	108	0.96	159	81.74	229	0.59
60	0.62	109	2.68	160	6.20	230	0.11
61	2.31	110	0.36	161	5.27	231	0.04
62	3.70	111	2.09	162	0.63	233	100.00
63	9.40	112	3.22	163	0.28	234	13.80
64	0.66	113	0.70	164	0.03	235	4.24
65	1.48	114	0.08	165	0.10	236	0.39
66	0.50	115	0.16	167	1.60	237	0.05
67	0.24	117	5.38	168	0.22	247	0.08
68	1.06	118	0.21	169	0.40	248	3.00
69	0.44	119	0.16	170	0.07	249	0.45
70	0.35	120	0.06	171	0.17	250	0.14
71	0.42	121	0.84	172	0.06	251	0.11
72	2.16	122	0.20	173	1.11	252	0.02
73	8.37	123	11.85	174	0.24		

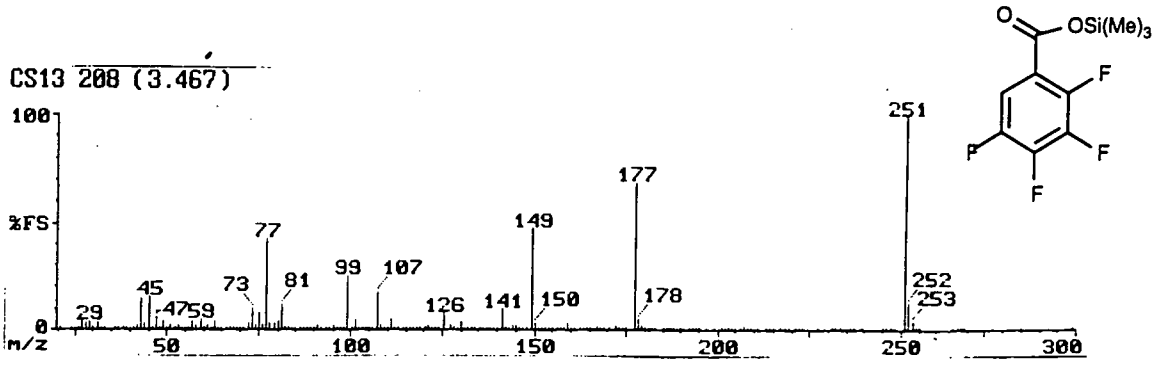
No. 10 **M.Wt. 248** **EI+**



CS12 209 (3.484) 1007616

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.05	70	0.45	114	0.06	165	0.05
25	0.05	71	0.50	115	0.13	167	0.18
26	0.50	72	3.33	117	5.72	168	0.04
27	2.24	73	9.25	119	0.19	169	0.07
28	3.13	74	2.95	120	0.07	170	0.24
29	4.32	75	7.22	121	0.32	171	0.12
30	0.55	76	0.76	122	0.09	172	0.13
31	3.18	77	6.28	123	0.82	173	0.86
32	0.41	78	0.65	124	0.10	174	0.23
33	0.08	79	1.14	125	0.36	175	1.91
36	0.05	80	2.41	126	0.19	176	0.30
37	0.44	81	33.74	127	1.26	177	0.09
38	0.28	82	1.91	128	0.26	179	0.02
39	1.00	83	0.45	129	0.27	183	0.03
40	0.11	84	0.10	130	1.83	185	0.08
41	0.77	85	0.21	131	71.14	186	0.03
42	2.16	86	0.47	132	4.93	187	0.10
43	12.50	87	0.65	133	0.21	188	0.12
44	3.84	88	0.16	134	0.05	189	64.63
45	22.46	89	0.98	135	0.15	190	8.43
46	1.62	90	0.19	136	0.05	191	2.41
47	7.42	91	0.36	137	0.20	192	0.19
48	0.40	92	1.02	139	0.45	199	0.04
49	1.75	93	1.91	140	0.93	201	0.04
50	0.86	94	0.26	141	0.16	203	0.62
51	1.03	95	0.37	142	0.03	204	0.08
52	0.17	96	0.32	143	0.60	205	0.07
53	1.42	97	0.21	144	0.21	213	0.05
54	0.32	98	0.12	145	0.33	214	0.39
55	1.63	99	1.39	146	0.14	215	0.08
56	0.86	100	0.33	147	0.15	216	0.02
57	2.95	101	0.38	148	0.03	217	0.34
58	2.03	102	0.26	149	0.11	218	0.13
59	5.41	103	0.76	150	0.03	219	0.06
60	1.14	104	0.14	151	0.05	232	0.17
61	3.86	105	0.41	154	0.05	233	46.34
62	4.45	106	0.13	155	0.19	234	6.15
63	2.62	107	0.82	156	0.13	235	1.85
64	0.20	108	0.25	157	0.09	236	0.16
65	0.32	109	1.04	159	100.00	247	0.04
66	0.17	110	0.25	160	7.22	248	0.43
67	0.24	111	2.16	161	0.94	249	0.07
68	1.30	112	3.68	162	0.10		
69	0.58	113	0.37	163	0.06		

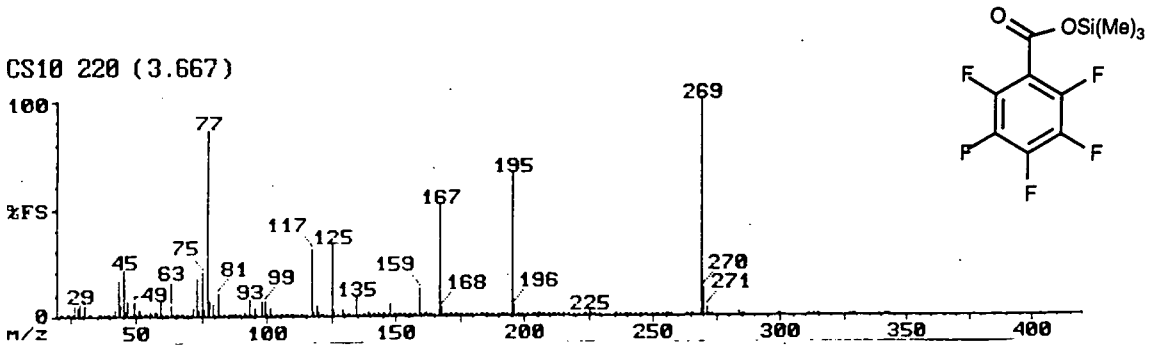
No. 11 **M.Wt. 266** **EI+**



CS13 208 (3.467) :785856

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
30	0.04	79	3.05	134	0.05	191	0.95
34	0.01	80	3.84	135	0.34	192	0.13
35	0.04	81	12.10	136	0.21	193	0.30
36	0.41	82	0.77	137	0.25	194	0.22
37	3.45	83	0.97	138	0.07	195	0.04
38	2.45	84	0.28	139	0.77	197	0.02
39	3.90	85	0.48	140	0.17	199	0.03
30	0.46	86	0.54	141	9.63	201	0.06
31	2.94	87	0.62	142	0.83	202	0.03
32	0.28	88	0.25	143	0.40	203	0.12
33	0.09	89	0.30	144	1.94	204	0.05
36	0.04	90	0.05	145	2.09	205	0.59
37	0.23	91	1.68	146	0.48	206	0.09
38	0.10	92	0.74	147	0.30	207	1.73
39	0.76	93	1.32	148	0.88	208	0.28
40	0.08	94	0.22	149	47.71	209	0.09
41	0.66	95	1.72	150	3.18	211	0.03
42	1.85	96	0.97	151	0.17	213	0.03
43	14.11	97	0.32	152	0.03	214	0.01
44	3.07	98	0.80	153	0.45	215	0.05
45	15.83	99	25.69	154	0.11	217	0.23
46	1.16	100	1.51	155	0.25	218	0.04
47	5.91	101	5.28	156	0.04	219	0.02
48	0.35	102	1.32	157	0.38	221	0.24
49	3.67	103	0.30	158	0.59	222	0.04
50	0.48	104	0.07	159	2.59	223	0.03
51	1.48	105	0.42	160	0.20	227	0.01
52	0.12	106	0.11	161	1.33	229	0.02
53	1.58	107	17.43	162	0.20	231	0.07
54	0.28	108	1.56	163	0.12	232	0.48
55	1.38	109	0.29	164	0.05	233	1.86
56	0.65	110	0.30	165	0.17	234	0.27
57	3.73	111	4.47	166	0.04	235	0.31
58	1.53	112	0.44	167	1.82	236	0.07
59	4.53	113	0.21	168	0.23	237	0.06
60	0.71	114	0.39	169	0.11	239	0.01
61	2.24	115	0.69	170	0.05	245	0.02
62	0.80	116	0.09	172	1.58	246	0.24
63	3.57	117	1.06	173	0.84	247	0.24
64	0.27	118	0.45	174	0.32	248	0.08
65	0.25	119	0.46	175	0.17	251	100.00
66	0.23	120	0.42	177	68.81	252	12.96
67	0.26	121	1.69	178	4.99	253	4.13
68	0.68	122	0.59	179	1.63	254	0.36
69	0.48	123	0.41	180	0.20	255	0.05
70	0.38	124	0.08	181	0.14	265	0.06
71	0.73	126	7.86	182	0.02	266	0.80
72	2.74	127	1.76	183	0.04	267	0.13
73	9.35	128	0.16	185	0.78	268	0.04
74	1.98	129	1.03	186	0.18	269	0.02
75	8.08	130	3.84	187	0.30	285	0.03
76	1.69	131	1.16	188	0.05	299	0.03
77	42.89	132	0.26	189	0.88		
78	3.25	133	0.11	190	0.15		

No. 12 **M.Wt. 284** **EI+**



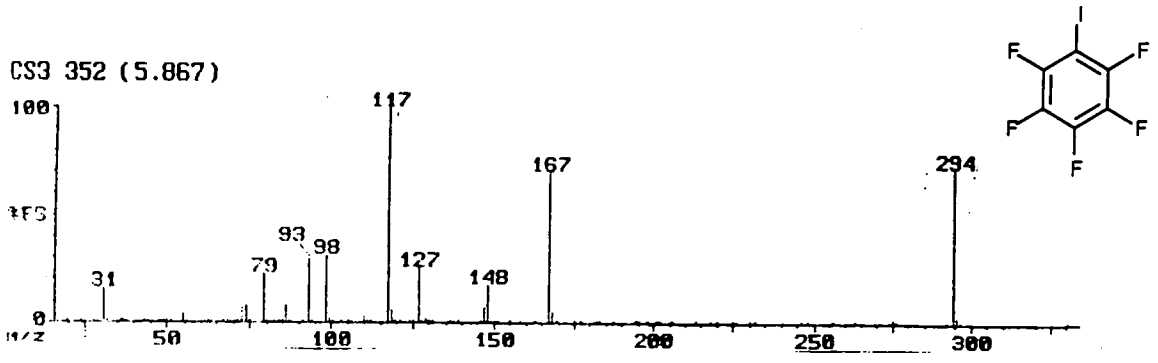
CS10 220 (3.667) 1654784

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.05	78	6.44	137	0.63	195	66.34
22	0.01	79	6.19	138	0.67	196	4.70
24	0.02	80	0.75	139	1.98	197	0.55
25	0.04	81	11.01	140	0.98	198	0.08
26	0.56	82	0.78	141	0.44	199	0.11
27	4.89	83	0.63	142	0.08	201	0.05
28	3.42	84	0.28	143	1.53	203	0.36
29	6.00	85	0.74	144	0.39	204	0.14
30	0.73	86	0.91	145	2.12	205	0.34
31	4.76	87	0.39	146	0.33	206	0.06
32	0.36	88	0.17	147	0.26	207	0.13
33	0.12	89	0.80	148	6.06	208	0.08
36	0.05	90	0.10	149	0.91	209	0.55
37	0.10	91	2.31	150	0.09	210	0.11
38	0.12	92	0.34	151	0.06	211	0.05
39	0.82	93	7.74	152	0.06	212	0.11
40	0.11	94	0.55	153	0.07	213	0.04
41	1.35	95	4.33	154	0.34	215	0.02
42	2.89	96	0.49	155	0.29	217	0.02
43	16.58	98	6.50	156	0.08	219	0.03
44	4.76	99	6.87	157	0.99	221	0.09
45	21.04	100	0.53	158	0.34	223	0.38
46	1.55	101	3.57	159	12.81	224	0.10
47	6.68	102	0.43	160	1.07	225	2.15
48	0.45	103	0.23	161	0.44	226	0.29
49	6.93	104	0.10	162	1.67	227	0.11
50	0.58	105	1.05	163	0.40	229	0.03
51	2.60	106	0.27	164	0.69	235	0.50
52	0.13	107	0.38	165	0.23	236	0.08
53	1.38	108	0.14	167	51.49	237	0.05
54	0.40	109	1.19	168	4.27	239	0.18
55	2.26	110	0.94	169	0.22	240	0.04
56	0.68	111	1.16	170	0.04	241	0.03
57	1.87	112	0.41	171	0.23	243	0.01
58	2.06	113	0.72	172	0.18	245	0.03
59	6.31	114	1.01	173	0.29	247	0.02
60	0.67	115	0.36	174	0.06	250	0.97
61	0.91	117	30.69	175	0.18	251	0.15
62	0.68	118	1.86	176	0.45	252	0.05
63	4.64	119	4.46	177	1.45	254	0.03
64	0.35	120	1.83	178	0.12	255	0.04
65	0.79	121	0.43	179	0.29	256	0.02
66	0.16	122	0.07	180	0.06	257	0.04
67	0.45	123	0.36	181	0.07	263	0.28
68	0.35	125	32.67	183	0.22	264	0.15
69	0.83	126	2.72	184	0.05	265	0.45
70	0.50	127	0.28	185	1.19	266	0.07
71	1.07	129	2.95	186	0.17	269	100.00
72	3.62	130	0.36	187	0.12	270	12.93
73	17.08	131	0.25	188	0.05	271	4.15
74	3.26	132	1.02	190	1.19	272	0.36
75	20.05	133	0.78	191	0.74	273	0.05
76	3.39	135	8.48	192	0.44	284	1.90
77	86.14	136	0.77	193	0.17	285	0.32

CS10 220 (3.667) 1654784

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
286	0.11	313	0.35	328	0.05	342	0.03
299	0.07	314	0.09	329	0.01		
300	0.02	315	0.01	339	0.08		
311	0.05	327	0.07	341	0.11		

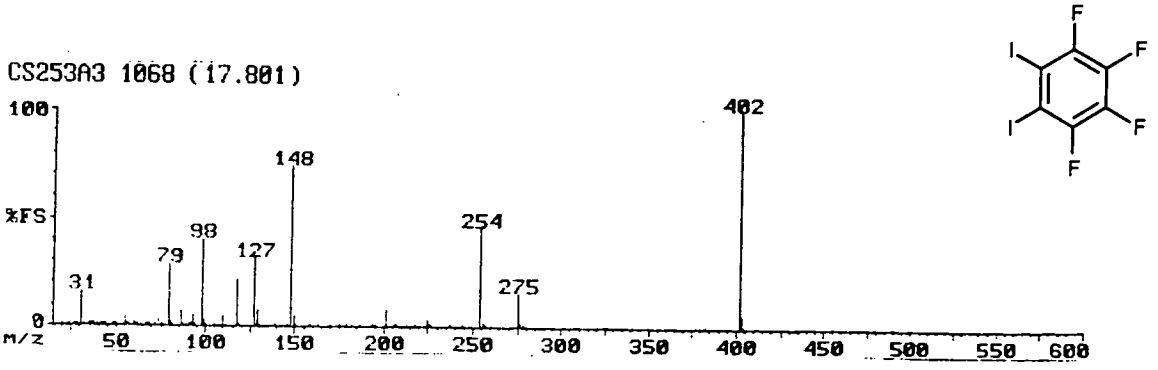
No. 13 M.Wt. 294 EI+



CS3 352 (5.867) 1720329

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.03	50	0.16	71	0.05	91	0.68	117	100.00	137	0.25	160	5.06	202	0.03	253	0.42
24	0.11	51	0.02	72	0.30	93	29.29	118	5.77	139	0.35	169	0.18	206	0.26	275	2.29
28	0.11	55	3.74	74	7.68	94	0.97	119	0.17	146	0.21	170	0.48	213	0.03	276	0.16
31	15.24	56	0.15	75	0.33	98	38.95	121	0.04	147	7.02	175	0.08	218	0.05	292	0.05
32	0.24	60	1.15	79	21.90	99	2.05	124	0.21	148	17.62	177	0.04	220	0.03	294	71.43
36	0.07	61	0.08	80	1.25	100	0.08	125	0.02	149	1.13	182	0.49	225	0.62	295	2.96
37	0.05	62	0.41	81	0.07	103	0.01	127	25.48	150	0.05	183	0.04	226	0.03	296	0.11
38	0.01	63	0.03	82	0.02	105	1.21	128	0.18	151	0.16	187	0.11	230	0.04	330	0.05
43	0.25	67	1.28	84	0.05	106	0.07	129	2.13	155	0.04	194	0.51	232	0.02		
44	0.04	68	0.10	85	0.04	110	3.23	130	0.15	158	0.24	195	0.03	246	0.02		
48	0.47	69	1.13	86	7.74	111	0.21	131	0.03	163	0.25	198	0.13	248	0.03		
49	0.03	70	0.02	87	0.35	112	0.05	136	1.24	167	69.52	201	0.07	256	0.04		

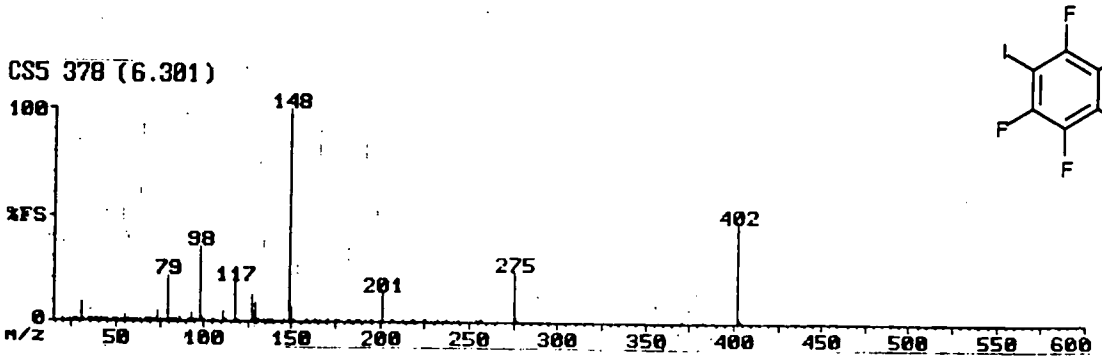
No. 14 **M.Wt. 402** **EI+**



CS253A3 1068 (17.801) 638784

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.03	38	0.05	56	0.17	74	3.81	94	0.15	128	0.54	163	0.54	207	0.09	257	0.14
24	0.09	39	0.04	57	0.04	75	0.20	98	39.61	129	7.51	170	0.34	213	0.05	275	15.75
27	0.04	41	0.08	60	1.56	79	28.57	99	2.60	130	0.50	175	0.15	218	0.21	276	1.53
28	0.24	42	0.04	61	0.14	80	1.63	100	0.10	139	0.40	179	0.05	225	2.00	278	0.07
29	0.05	43	0.32	62	0.39	81	0.09	105	0.15	146	0.11	182	1.11	226	0.15	383	0.39
31	15.26	44	0.13	63	0.10	86	6.74	110	4.59	148	74.03	187	0.25	227	0.05	402	100.00
32	0.28	48	0.62	67	1.43	87	0.31	111	0.32	149	4.91	194	1.30	237	0.12	403	5.76
35	0.03	49	0.05	68	0.11	91	0.95	117	21.27	150	0.19	195	0.05	244	0.11	404	0.19
36	1.22	50	0.16	69	0.21	92	0.07	118	1.13	151	0.25	201	7.47	254	45.45		
37	0.08	55	3.98	72	0.41	93	4.55	127	38.84	158	0.19	206	1.24	256	2.05		

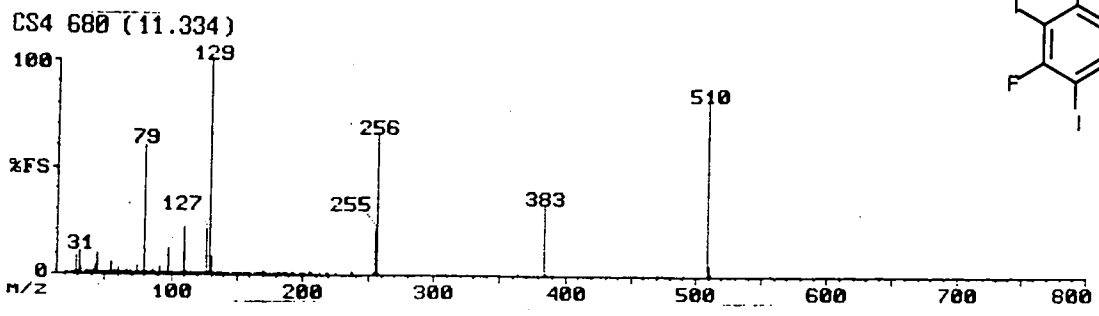
No. 15 M.Wt. 402 EI+

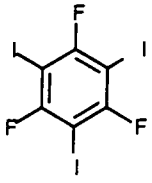


CS5 378 (6.301) 1359872

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.05	41	0.06	60	0.96	79	21.08	98	34.64	130	0.58	166	0.02	201	13.33	275	23.49
24	0.06	42	0.03	61	0.00	80	1.24	99	2.32	131	0.03	170	0.76	206	0.72	276	2.01
26	0.02	43	0.17	62	0.10	81	0.08	100	0.09	134	0.07	171	0.02	207	0.05	277	0.09
27	0.03	44	0.25	63	0.06	82	0.02	105	0.22	135	0.02	175	0.12	213	0.02	371	0.04
28	0.70	45	0.02	67	0.75	83	0.02	106	0.02	138	0.05	177	0.03	218	0.15	383	0.09
29	0.04	48	0.25	68	0.07	84	0.02	110	4.50	139	0.34	182	0.60	219	0.01	402	46.69
31	0.51	49	0.03	69	0.16	86	2.33	111	0.30	146	0.15	183	0.02	225	1.28	403	2.28
32	0.39	50	0.07	70	0.02	87	0.12	112	0.02	148	100.00	187	0.19	226	0.07	404	0.07
35	0.02	51	0.01	71	0.03	91	0.58	117	18.00	149	6.70	188	0.01	232	0.01		
36	0.64	53	0.01	72	0.30	92	0.07	118	1.00	150	0.30	189	0.02	237	0.07		
37	0.04	55	2.82	73	0.04	93	3.58	119	0.04	151	0.18	191	0.02	244	0.07		
38	0.04	56	0.13	74	5.27	94	0.13	127	12.73	158	0.23	194	0.44	254	0.24		
39	0.03	57	0.05	75	0.23	95	0.02	128	0.56	163	0.28	195	0.02	256	1.39		
40	0.04	58	0.01	77	0.02	96	0.01	129	8.43	164	0.02	199	0.02	257	0.09		

No. 16 **M.Wt. 510** **EI+**

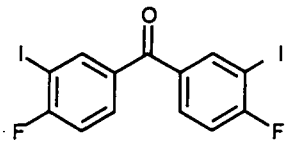


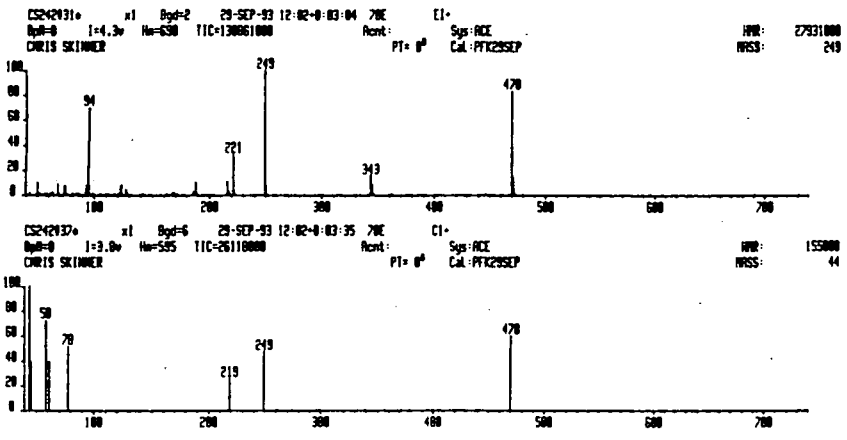


CS4 680 (11.334)

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
10	0.44	44	0.90	64	0.28	84	0.57	105	0.28	125	0.20	149	0.81	175	0.25	254	0.36
12	0.86	45	0.32	65	0.16	85	0.83	106	0.12	127	21.86	150	0.15	177	0.86	255	11.54
14	0.11	46	0.19	66	0.11	86	2.07	107	0.21	128	1.40	151	0.47	179	0.07	256	15.00
15	0.86	47	0.10	67	1.59	87	0.47	108	0.15	129	100.00	152	0.13	182	1.20	257	4.76
16	0.27	48	0.43	68	0.52	88	0.10	109	0.30	130	0.37	153	0.12	183	0.09	258	0.58
27	0.82	49	0.86	69	1.73	89	0.09	110	22.31	131	0.47	154	0.86	185	0.22	309	0.11
28	0.13	50	0.21	70	0.73	91	1.68	111	2.07	132	0.14	155	0.14	187	1.00	364	0.43
29	1.53	51	0.18	71	1.24	92	0.41	112	0.48	133	0.18	157	0.11	188	0.10	383	31.92
30	1.28	52	0.11	72	1.01	93	0.89	113	0.33	134	0.10	158	0.46	192	0.16	384	3.49
31	18.67	53	0.30	73	1.33	94	0.23	114	0.15	135	0.20	159	0.10	194	0.90	385	0.23
32	0.17	54	0.33	74	0.58	95	0.58	115	0.29	136	0.13	161	0.09	199	0.20	491	0.86
35	0.11	55	5.38	75	0.28	96	0.44	116	0.14	137	0.20	163	0.85	201	0.64	510	30.77
36	1.53	56	1.88	76	0.88	97	0.86	117	0.26	139	0.82	164	0.10	206	1.78	511	4.78
37	0.17	57	2.09	77	0.42	98	13.08	118	0.10	140	0.10	165	0.14	207	0.29	512	0.18
38	0.30	58	0.46	78	0.12	99	1.26	119	0.10	141	0.15	166	0.34	213	0.19		
39	0.67	59	0.27	79	50.00	100	0.19	120	0.10	142	0.08	167	0.23	218	1.12		
40	0.44	60	2.79	80	3.99	101	0.23	121	0.23	143	0.12	168	0.07	219	0.13		
41	2.19	61	0.55	81	0.90	102	0.14	122	0.17	146	0.31	170	2.19	225	1.03		
42	0.86	62	0.12	82	0.52	103	0.12	123	0.29	147	0.15	171	0.22	237	1.59		
43	1.70	63	0.08	83	1.01	104	0.15	124	0.13	148	0.10	173	0.07	238	0.17		

No. 17 M.Wt. 470 EI+ / CI+





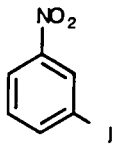
CS242#31* x1 Bgd=2 29-SEP-93 12:02+0:03:04 70E EI+ 2.1
BpM=0 I=4.3v Hm=690 TIC=130861000 Acnt: Sys:ACE
CHRIS SKINNER PT= 0 Cal:PFK29SEP

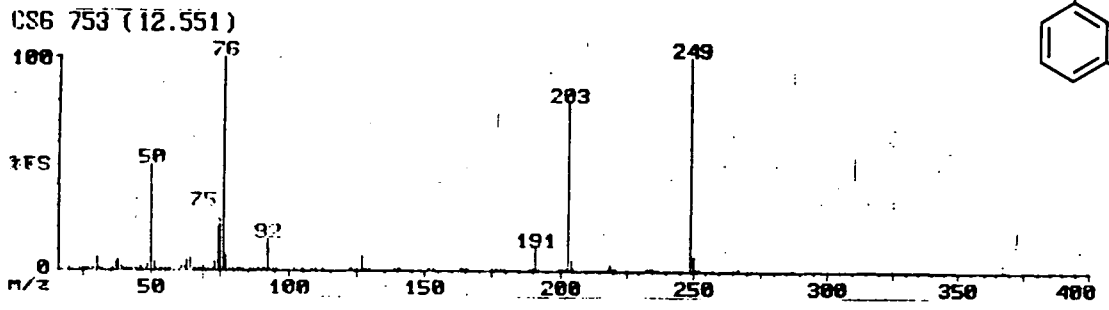
Mass	% Base	Mass	% Base
43.03	1.68	127.95	2.14
49.02	0.40	141.06	0.88
50.03	9.83	162.08	0.61
51.04	1.04	167.09	0.97
53.02	0.56	168.10	2.21
56.03	0.41	169.10	0.60
57.03	1.05	171.52	0.77
57.09	0.34	186.09	1.84
58.06	0.39	187.10	2.81
61.03	1.10	188.11	9.53
62.04	1.56	189.11	1.20
63.05	2.02	216.11	10.27
68.03	8.52	217.12	2.31
69.04	1.15	218.12	0.45
73.03	1.03	221.01	31.73
74.04	7.25	222.01	2.86
75.05	6.37	249.00	100.00
76.05	0.47	250.00	7.62
81.04	1.03	251.01	0.44
84.05	0.38	314.04	0.32
85.04	0.39	342.01	0.81
86.04	0.62	343.00	14.50
87.05	0.54	344.01	7.62
92.04	1.91	345.00	1.01
93.04	7.26	362.01	0.59
93.55	0.32	374.96	0.29
94.05	69.85	446.25	0.64
95.05	7.92	469.92	83.29 F
96.06	0.49	470.95	13.47 F
98.04	0.79	471.96	1.10
99.05	0.50	595.89	0.45
105.05	0.65		
110.05	0.36		
111.07	0.62		
117.05	0.40		
118.06	0.32		
121.05	0.38		
122.05	5.98		
123.06	7.71		
124.07	0.66		
126.94	3.72		

CS242#37* x1 Bgd=6 29-SEP-93 12:02+0:03:35 70E CI+ 3.1
BpM=0 I=3.8v Hm=595 TIC=26118000 Acnt: Sys:ACE
CHRIS SKINNER PT= 0 Cal:PFK29SEP

Mass	% Base
44.03	0.62
58.05	0.45
78.04	0.31
469.61	0.37

No. 18 M.Wt. 249 EI+



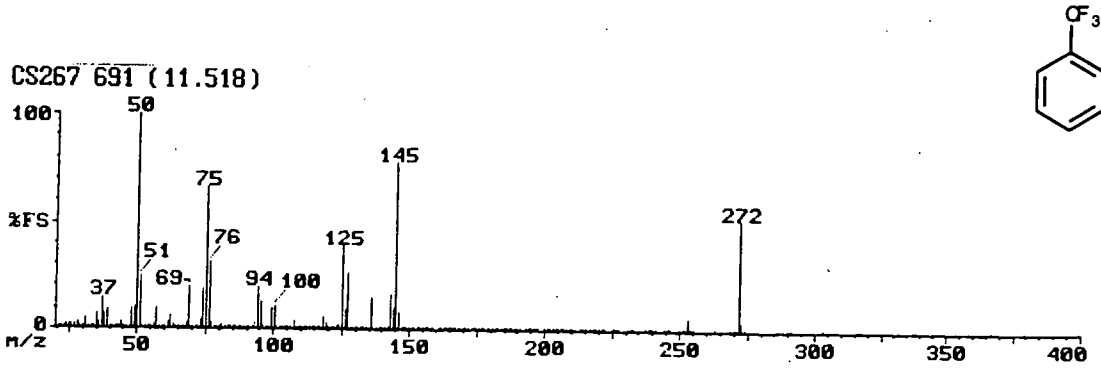


CS6 753 (12.551)

BEAE56

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.02	39	2.07	52	0.46	67	0.07	82	0.04	104	0.03	141	0.06	189	0.04	221	0.04
24	0.24	40	0.23	53	0.31	68	0.05	83	0.03	105	0.03	151	0.07	190	0.03	233	0.30
25	0.17	41	0.13	54	0.07	69	0.06	86	0.14	108	0.03	152	0.67	191	10.31	234	0.07
26	0.64	42	0.09	55	0.09	70	0.02	87	0.24	110	0.11	153	0.41	192	0.58	235	0.07
27	0.37	43	0.10	56	0.05	72	0.26	88	0.13	112	0.03	163	0.08	200	0.08	237	0.03
28	1.13	44	0.65	57	0.05	73	4.00	89	0.06	122	0.31	164	0.25	201	0.27	249	100.00
29	0.18	45	0.06	60	0.36	74	20.50	90	0.47	123	0.10	165	0.50	202	0.28	250	6.50
30	6.01	46	1.75	61	1.73	75	21.33	91	0.30	125	0.08	166	0.03	203	78.67	251	0.62
31	0.07	47	0.03	62	2.01	76	99.53	92	14.22	127	0.46	175	0.05	204	5.18	252	0.06
32	0.25	48	0.25	63	5.24	77	7.14	93	1.05	128	0.52	176	0.74	205	0.17	267	0.06
36	0.40	49	2.87	64	6.31	78	0.33	94	0.22	129	0.03	177	0.01	218	0.08		
37	3.76	50	49.76	65	0.08	79	0.07	95	0.04	139	0.14	178	0.05	219	2.99		
38	4.53	51	3.88	66	0.23	81	0.04	102	0.16	140	0.06	179	0.02	220	0.23		

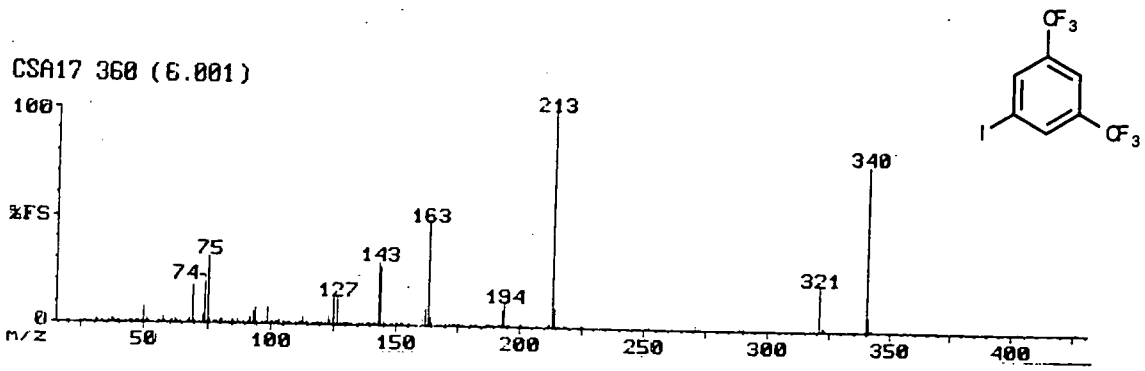
No. 19 M.Wt. 272 EI+



CS267 691 (11.518) 2064384

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.48	74	18.25	128	1.04	185	0.02
21	0.02	75	65.87	129	0.07	186	0.01
22	0.01	76	31.35	130	0.07	187	0.01
23	0.01	77	2.80	131	0.06	188	0.06
24	1.70	78	0.21	132	0.07	189	0.07
25	2.18	79	0.62	133	0.06	190	0.02
26	2.39	80	1.38	134	0.02	191	0.02
27	1.92	81	1.84	136	14.88	193	0.04
28	3.27	82	0.41	138	0.04	194	0.05
29	0.79	83	0.16	139	0.08	195	0.12
30	0.15	84	0.08	140	0.05	196	0.21
31	4.96	85	0.28	141	0.04	197	0.02
32	0.66	86	0.27	142	0.27	200	0.09
33	0.14	87	0.82	143	16.27	201	0.57
34	0.03	88	1.18	144	10.02	202	0.17
35	7.24	89	0.12	145	77.78	203	0.33
36	3.10	90	0.02	146	7.79	204	0.04
37	14.48	91	0.13	147	0.38	205	0.01
38	7.19	92	0.50	148	0.04	206	0.05
39	8.78	93	2.60	149	0.07	207	0.21
40	0.56	94	19.25	150	0.09	208	0.03
41	0.99	95	12.90	151	0.07	209	0.02
42	0.57	96	1.40	152	0.95	210	0.01
43	0.99	97	0.13	153	0.41	211	0.02
44	2.65	98	0.23	154	0.02	213	0.03
45	1.09	99	9.38	155	0.05	214	0.18
46	0.14	100	10.71	156	0.03	215	0.03
47	0.39	101	0.98	157	0.03	217	0.03
48	9.23	102	0.08	158	0.01	218	0.08
49	9.42	103	0.10	159	0.04	219	0.09
50	100.00	104	0.20	161	0.02	220	0.18
51	24.21	105	0.72	162	0.05	221	0.03
52	1.30	106	1.22	163	0.12	222	0.06
53	0.32	107	4.37	164	0.40	225	0.12
54	0.16	108	0.38	165	0.62	226	0.02
55	1.08	109	0.06	166	0.03	227	0.01
56	2.10	110	0.05	167	0.04	231	0.01
57	9.33	111	0.19	168	0.03	232	0.02
58	0.41	112	0.21	169	0.05	233	0.01
59	0.09	113	0.14	170	0.10	237	0.01
60	0.24	114	0.25	171	0.05	238	0.02
61	2.50	115	0.09	172	0.04	239	0.01
62	5.61	116	0.03	173	0.05	240	0.14
63	2.36	117	0.28	174	0.03	241	0.03
64	0.38	118	5.51	175	0.06	244	0.01
65	0.15	119	2.62	176	1.19	245	0.03
66	0.10	120	0.18	177	0.68	246	0.01
67	0.23	121	0.04	178	0.04	250	0.01
68	2.50	122	0.08	179	0.03	251	0.05
69	19.25	123	1.66	180	0.02	252	0.07
70	1.24	124	1.66	181	0.02	253	5.46
71	0.12	125	39.09	182	0.41	254	0.42
72	0.91	126	8.68	183	0.49	255	0.01
73	3.57	127	25.79	184	0.08	263	0.02

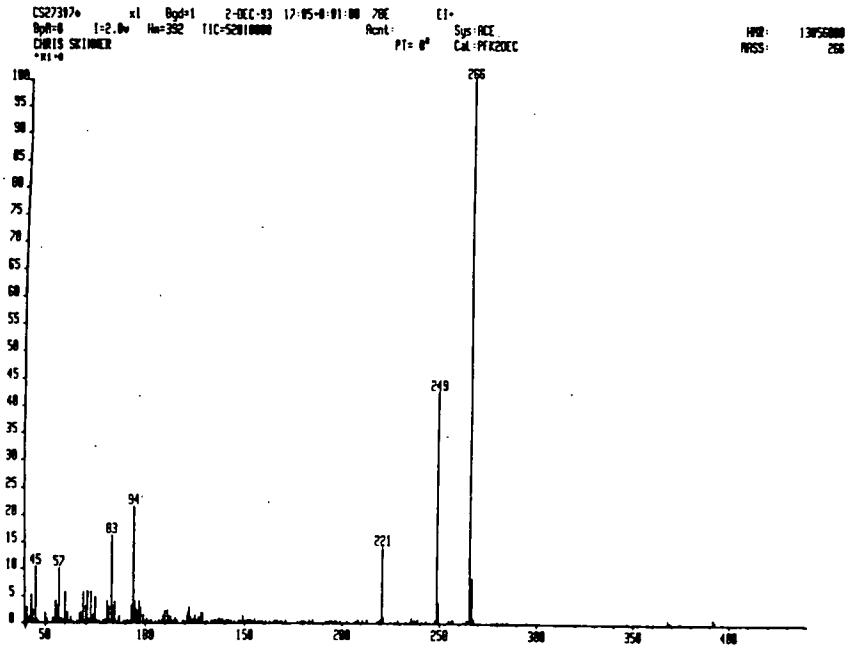
No. 20 **M.Wt. 340** **EI+**

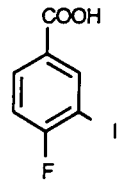


CSA17 360 (6.001) 1867776

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.02	77	0.15	123	5.26	176	0.42
25	0.02	78	0.02	124	1.77	177	0.10
26	0.05	79	0.92	125	12.34	181	0.18
27	0.04	80	1.95	127	12.50	182	0.07
28	0.13	81	1.99	128	0.65	183	0.13
31	2.04	82	0.18	129	0.04	187	0.08
32	0.08	84	0.34	130	0.17	188	0.03
33	0.03	85	1.64	131	0.06	189	0.02
36	0.15	86	1.12	132	0.17	192	0.36
37	1.77	87	1.88	136	0.18	193	7.57
38	2.25	88	0.95	137	0.73	194	11.02
39	0.42	89	0.05	138	0.05	195	0.92
40	0.02	91	0.13	139	0.09	196	0.05
43	0.02	92	2.44	140	0.03	200	0.19
44	0.10	93	5.70	141	0.22	201	0.16
45	0.03	94	7.57	142	0.36	207	0.04
47	0.03	95	0.92	143	29.39	211	0.07
48	0.13	97	0.60	144	26.75	212	2.43
49	1.43	98	0.33	145	2.04	213	100.00
50	7.68	99	8.17	146	0.10	214	8.50
51	2.43	100	0.95	148	0.09	215	0.35
52	0.06	101	1.15	149	0.08	218	0.04
55	0.19	102	0.06	150	0.10	225	0.09
56	0.97	103	0.86	151	0.19	249	0.03
57	2.70	104	1.48	152	0.34	251	0.04
58	0.10	105	1.54	153	0.04	252	0.02
60	0.18	106	0.88	155	0.29	271	1.51
61	1.64	107	0.26	156	0.17	272	0.11
62	1.59	108	0.02	161	3.23	289	0.02
63	1.26	110	0.07	162	7.46	290	0.12
64	0.11	111	0.31	163	47.15	321	20.83
67	0.09	112	1.41	164	3.43	322	1.55
68	2.08	113	4.06	165	0.19	323	0.07
69	17.11	114	0.25	167	0.12	340	76.32
70	0.27	115	0.01	168	0.09	341	6.80
72	0.33	117	1.08	170	1.40	342	0.26
73	3.73	118	1.43	172	0.02	426	0.02
74	19.08	119	0.89	173	0.39		
75	30.70	120	0.06	174	1.06		
76	1.56	122	0.22	175	0.42		

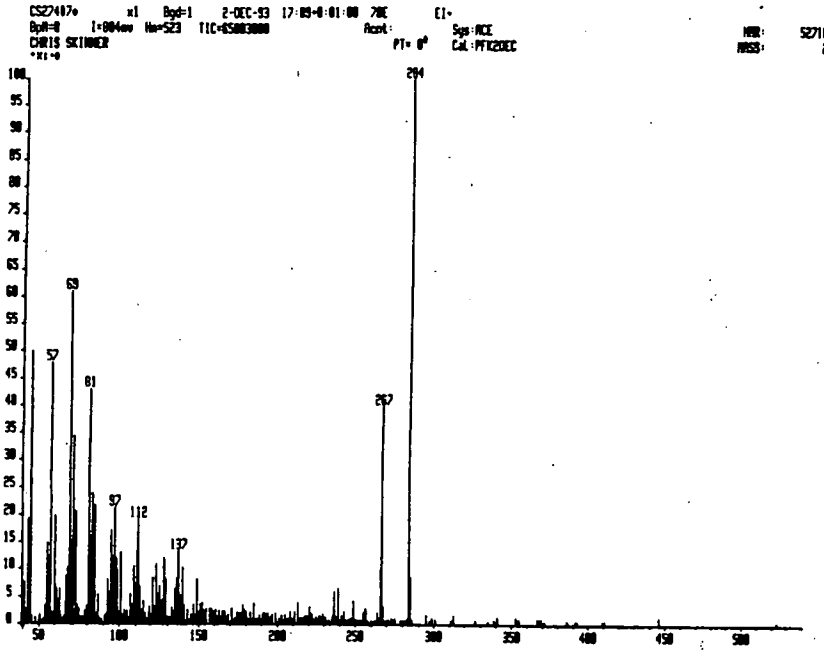
No. 21 **M.Wt. 266** **EI+**

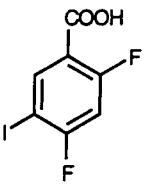




Mass	% Base		Mass	% Base
41.02	2.78		119.00	0.38
42.01	1.19		120.96	1.62
43.02	5.10		121.96	2.93
43.99	2.34		123.01	1.05
45.01	10.35		124.04	0.76
45.99	0.54		125.05	1.39
49.99	1.78		126.04	0.44
51.00	0.70		126.83	0.97
54.02	0.91		127.04	0.80
55.02	3.92		127.85	1.95
56.03	3.11		129.01	1.76
57.02	10.14		130.98	0.33
58.02	0.93		133.01	0.37
59.01	0.46		135.03	0.63
59.99	5.51		136.03	0.42
61.00	1.84		137.04	0.91
62.99	1.09		138.03	0.61
67.02	1.80		139.00	0.67
68.00	1.95		140.01	0.35
69.02	5.68		141.04	0.62
70.03	3.09		141.84	0.51
71.04	5.88		143.02	0.39
72.02	0.60		145.01	0.33
72.99	5.76		147.01	0.42
73.99	1.52		148.96	1.31
74.98	4.68		151.04	0.49
75.99	0.44		152.04	0.65
79.00	0.41		153.04	0.47
80.01	0.57		155.02	0.68
81.02	3.92		157.01	0.36
82.01	2.96		166.06	0.35
82.99	16.21		167.01	0.42
84.01	3.08		171.03	0.38
85.04	3.92		183.08	0.37
86.02	0.33		185.04	0.53
87.00	1.16		208.07	0.31
90.99	0.47		208.80	0.51
91.98	0.34		211.08	0.41
92.98	3.24		213.04	0.56
93.97	21.46		219.79	0.61
94.97	3.92 F		220.09	0.38
95.05	2.60 F		220.80	14.04
96.02	2.18		221.87	1.00
97.04	3.92		229.07	0.37
98.02	2.73		236.07	0.83
99.04	1.44		237.07	0.37
100.99	0.72		237.80	0.36
102.00	0.33		239.10	0.62
102.99	0.51		247.78	0.47
105.00	0.31		248.77	42.52
107.02	0.50		249.79	3.64
108.03	0.40		255.06	0.46
109.03	1.34		256.08	0.38
109.99	2.21		257.09	0.54
111.02	2.35		264.09	0.41
112.04	1.11		265.77	100.00
113.03	1.15		266.78	8.18
114.00	0.40		267.77	0.66
115.00	0.86		368.14	0.78
116.01	0.41		369.07	0.31

No. 22 M.Wt. 284 EI+

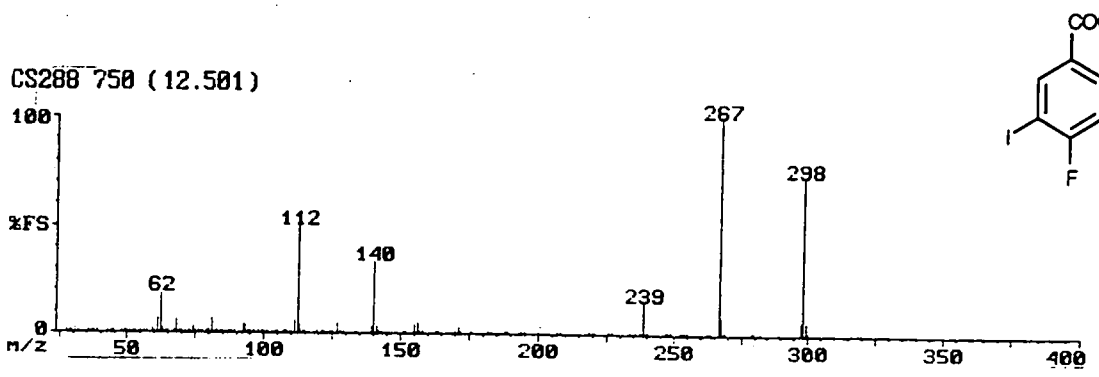




CS27487e x1 Bgd=1 2-DEC-93 17:09+0:01:00 70E EI+ 1.1
Bpk=0 I=804mv Hm=523 TIC=65003000 Acnt: Sys:ACE
CHRIS SKINNER PT= 0 Cal:PFK2DEC

Mass	% Base
41.02	7.42
42.01	2.52
43.02	19.12
43.99	4.69
45.01	49.76
46.00	1.37
47.94	1.02
49.99	0.47
50.98	1.67
53.00	0.70
54.02	3.19
55.02	14.82
56.03	11.91
57.04	47.68
58.03	2.64
59.01	1.84
59.99	19.77
60.99	6.26
61.98	4.17
62.99	6.34
63.92	1.99
63.99	0.49
65.00	0.66
66.01	1.35
67.02	8.56
68.02	10.24
69.03	60.94
70.03	15.18
71.04	34.26
72.03	1.99
72.99	20.45
73.99	3.36
74.97	2.68
75.98	1.06
76.99	1.18
77.99	0.99
79.00	2.28
80.01	3.28
81.01	42.90
82.02	15.84
83.03	23.81
84.02	14.55
85.03	21.55
86.03	1.69
86.98	5.24
87.99	0.99
89.00	0.68
90.99	1.38
91.98	1.83
92.99	7.99
94.00	5.71
95.03	17.09
96.02	12.22
97.03	21.13
98.02	11.99
99.04	9.73
99.98	2.24
100.95	12.96
101.99	1.61
102.87	2.41
102.98	0.76
104.99	2.33
106.01	1.06
107.02	5.35
108.02	3.41
109.03	10.36
110.02	7.19
111.02	13.26
111.94	19.18 F
112.04	6.87 F
113.00	6.72
114.00	2.49
115.00	4.08
116.00	1.86
116.99	0.93
117.99	0.66
119.00	3.05
120.01	1.59
121.02	8.39
122.02	3.13
123.03	10.79
124.04	5.35
125.04	6.92
126.04	3.05
126.95	4.23
127.86	12.03
129.00	8.18
129.99	1.18
130.97	1.20
131.97	0.46
133.01	2.92
134.02	2.22
135.03	6.26
136.04	8.18
137.04	13.24
138.04	5.07
139.00	3.87
139.94	10.24
141.00	3.38
142.04	0.42
143.01	2.54
144.01	0.59
145.01	1.57
146.01	0.82
147.00	3.49
148.02	1.57
148.97	8.08
150.00	2.05
150.93	3.49
152.03	3.81
152.81	2.28
153.03	2.90
154.03	1.52
155.02	2.68
156.96	2.79
157.93	2.68
158.93	2.24
160.00	0.85
161.01	2.41
162.02	1.10
163.03	2.37
164.03	1.16
165.02	2.26
166.05	2.14
166.99	2.09
168.03	1.23
169.00	1.65
171.02	2.79
172.03	0.61
173.02	1.01
175.03	2.03
175.95	1.75
177.03	1.94
177.99	3.41
179.01	2.45
180.02	2.14
181.04	1.16
182.07	0.76
183.07	2.11
183.99	0.78
185.02	3.62
186.04	0.65
187.02	0.82
189.04	1.44
190.05	0.72
191.05	1.90
192.05	1.88
193.05	1.56
194.07	1.94
195.06	1.06
196.08	1.16
197.08	1.54
199.03	1.94
201.04	0.82
202.80	1.67
203.04	1.44
204.05	0.65
205.05	1.57
206.06	0.74
207.00	0.87
208.06	2.16
209.06	1.08
210.08	0.57
211.08	2.18
213.04	3.76
214.05	0.82
215.05	1.06
217.06	0.97
218.07	1.44
218.79	0.44
219.06	1.28
220.08	0.82
220.83	3.07
222.05	1.69
223.03	0.95
224.09	0.81
225.08	1.18
226.79	0.78
227.05	1.44
228.05	1.08
229.06	1.82
231.06	1.23
232.06	0.36
233.08	0.65
235.06	1.08
235.77	1.59
236.07	5.77
237.07	2.33
237.76	1.10
238.08	0.80
238.86	6.43
239.78	0.55
240.07	0.63
241.05	1.46
242.07	1.10
243.07	2.12
244.06	0.76
245.07	0.59
246.08	0.70
247.08	0.97
248.78	4.02
250.08	0.91
251.05	0.74
252.09	0.61
253.11	0.76
254.10	0.44
255.05	2.01
255.77	0.47
256.07	2.77
257.08	2.41
258.08	0.47
260.07	0.63
262.08	0.57
263.78	1.65
264.08	2.09
264.76	0.78
265.08	1.06
266.78	10.04
266.75	39.80
267.75	3.09
269.10	0.65
270.06	0.34
271.07	0.70
273.07	0.99
275.09	0.91
278.99	0.53
280.05	0.55
280.86	0.65
282.75	0.51
283.04	0.93
283.73	100.00
284.78	8.40
285.74	0.80
294.93	1.61
297.02	0.44
299.08	1.02
301.11	0.68
311.07	0.57
313.09	1.42
327.11	0.53

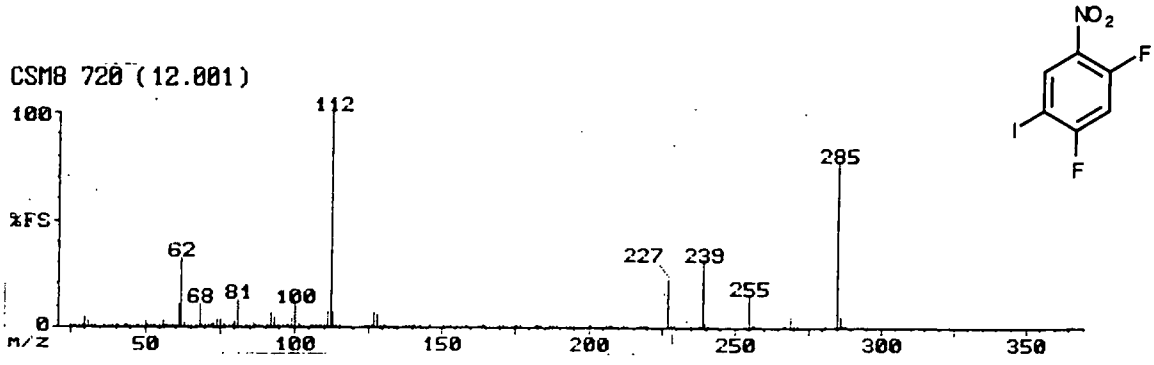
No. 23 M.Wt. 298 EI+



CS288 750 (12.501) 479232

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
28	0.84	73	1.10	114	0.40	195	0.04
29	1.28	74	3.18	115	0.21	200	0.06
30	0.58	75	1.03	119	0.08	207	0.10
31	1.84	76	0.09	121	0.30	208	0.08
32	0.32	77	0.21	122	0.05	219	0.10
36	0.15	79	0.68	123	0.12	220	0.25
37	0.91	80	1.60	124	0.05	221	0.09
38	0.31	81	6.41	125	0.28	226	0.09
39	0.13	82	0.40	127	4.75	227	0.16
43	0.11	83	0.05	128	0.95	234	0.06
44	0.59	84	0.07	129	0.07	236	0.09
45	0.15	85	0.09	134	1.27	238	0.14
48	0.09	86	0.89	139	2.44	239	14.96
49	0.42	87	0.18	140	32.69	240	1.14
50	1.23	88	0.08	141	3.34	247	0.06
51	0.34	89	0.06	142	0.37	248	0.09
52	0.04	91	0.34	143	0.09	249	0.12
53	0.19	92	4.11	151	0.31	253	0.26
55	0.28	93	3.90	152	0.19	254	0.18
56	1.23	94	0.52	155	3.63	255	0.08
57	0.67	95	0.91	156	4.81	263	0.07
59	2.42	96	0.13	157	0.39	264	0.09
60	0.31	98	0.05	158	0.09	267	100.00
61	6.62	99	0.79	163	0.08	268	7.91
62	18.59	100	0.78	164	0.12	269	0.59
63	2.00	101	0.41	170	0.16	279	0.30
64	0.11	104	0.06	171	2.90	280	0.07
65	0.06	105	0.08	172	0.38	282	0.24
67	0.32	107	0.20	176	0.13	297	5.66
68	6.20	108	0.07	182	0.06	298	72.65
69	0.49	110	0.53	183	0.24	299	6.20
70	0.05	111	5.77	188	0.08	300	0.56
71	0.45	112	49.15	189	0.09		
72	0.18	113	4.11	194	0.31		

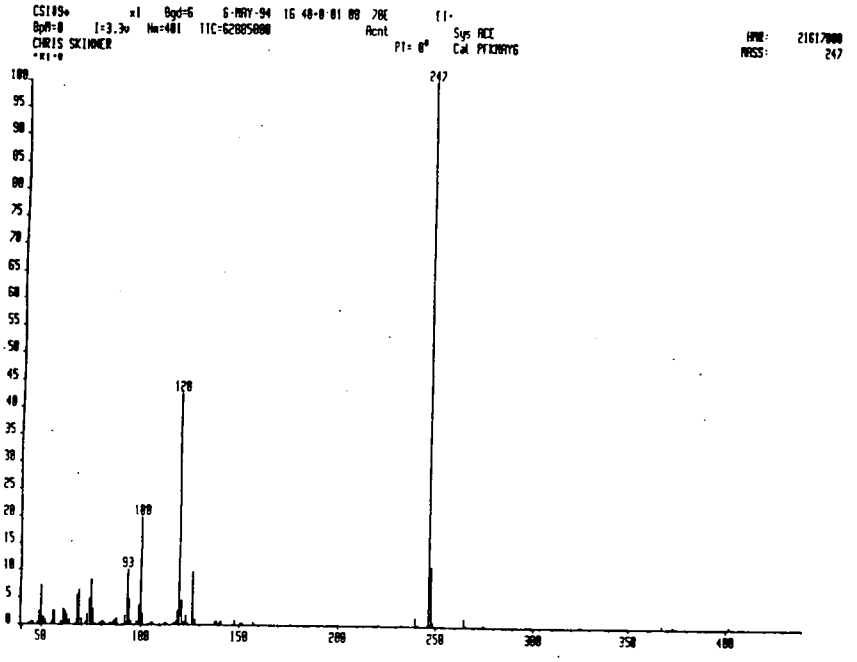
No. 24 M.Wt. 285 EI+

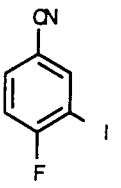


CSM8 720 (12.001) 1179648

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
25	0.02	68	10.50	108	0.37	184	0.03
26	0.02	69	0.78	109	0.12	187	0.07
27	0.02	70	0.19	110	0.76	188	0.14
28	0.23	71	0.09	111	8.85	189	0.20
29	0.03	72	0.30	112	100.00	194	0.60
30	5.25	73	1.65	113	7.12	195	0.08
31	2.63	74	4.93	114	0.31	200	0.10
32	0.13	75	3.67	115	0.04	201	0.10
33	0.02	76	1.69	124	0.08	206	0.03
36	0.23	77	0.13	125	0.04	207	0.21
37	1.25	78	0.07	126	0.76	208	0.04
38	0.38	79	1.43	127	7.12	212	0.03
39	0.06	80	2.93	128	5.99	213	0.02
40	0.02	81	12.50	129	0.44	218	0.04
41	0.03	82	1.09	130	0.37	219	0.20
43	0.05	83	0.11	131	0.04	220	0.16
44	0.41	84	0.04	138	0.20	227	22.57
45	0.07	85	0.04	139	0.15	228	1.22
46	1.06	86	1.74	140	0.03	229	0.04
47	0.05	87	0.52	141	0.11	235	0.03
48	0.17	88	0.14	143	0.17	238	1.10
49	0.76	89	0.03	146	0.03	239	30.56
50	2.97	91	0.56	151	0.06	240	2.06
51	0.63	92	6.60	152	0.25	241	0.04
52	0.17	93	5.25	153	0.02	254	0.07
53	0.07	94	0.66	157	0.04	255	14.41
55	0.72	95	0.13	158	1.37	256	0.92
56	2.69	96	0.03	159	0.16	257	0.04
57	0.86	97	0.04	163	0.14	267	0.04
58	0.09	98	0.12	164	0.21	269	4.54
59	0.02	99	3.65	165	0.05	270	0.31
60	0.66	100	10.33	170	0.26	271	0.07
61	10.50	101	1.67	171	0.04	281	0.03
62	31.60	102	0.21	175	0.05	285	77.08
63	2.11	103	0.02	176	0.32	286	4.97
64	1.00	105	0.12	177	0.36	287	0.49
65	0.07	106	0.31	182	0.16	288	0.04
67	0.44	107	0.10	183	0.60	366	0.02

No. 25 **M.Wt. 247** **EI+**

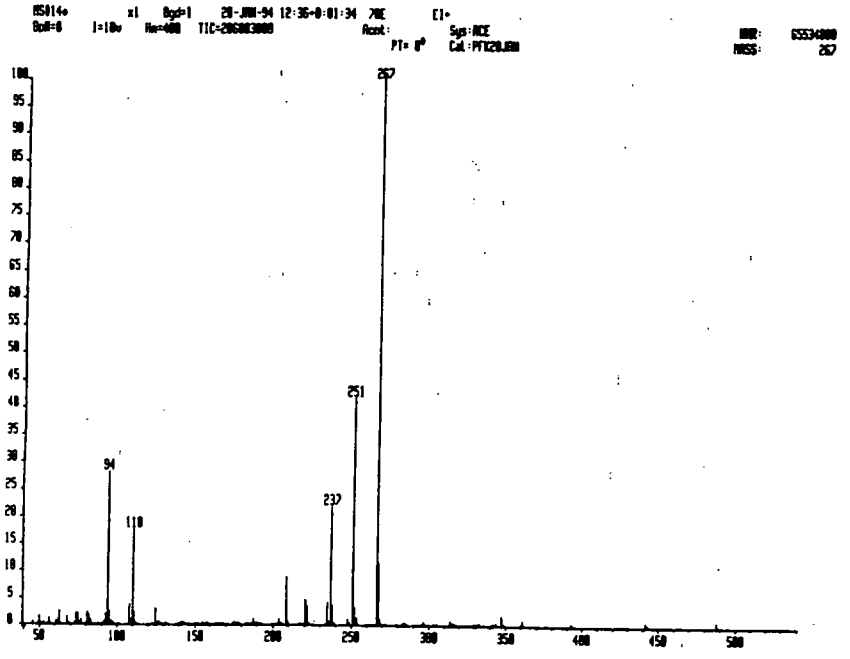


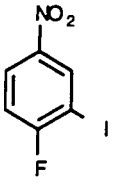


CS1#9* x1 Bgd=6 6-MAY-94 16:40+0:01:08 70E EI+ 1.3
BpM=0 I=3.3v Hm=401 TIC=62885000 Acnt: Sys:ACE
CHRIS SKINNER PT= 0 Cal:PFKMAY6

Mass	% Base
45.00	0.50
46.00	0.43
49.00	2.37
50.00	7.12
51.01	1.31
52.01	0.79
54.99	0.31
55.99	2.48
57.00	2.37
59.99	0.42
60.99	2.82
62.00	2.37
63.00	1.80
64.00	0.93
67.99	5.37
68.99	6.29
69.99	0.98
71.99	0.34
72.99	1.86
73.99	4.74
74.99	8.18
76.00	2.76
78.98	0.35
79.99	0.48
80.99	0.60
84.99	0.34
85.98	0.53
86.99	0.94
87.99	1.24
91.98	1.61
92.99	10.02
93.99	4.74
95.00	0.61
97.97	0.59
98.98	3.57
99.99	19.73
100.99	1.91
105.99	0.31
112.99	0.35
116.97	0.36
117.98	0.61
118.98	2.47
119.99	42.52
120.99	4.33
122.99	0.50
123.43	1.54
126.88	9.60
127.88	0.85
137.97	0.41
138.98	0.63
139.99	0.31
140.97	0.57
147.95	0.74
150.98	0.31
156.99	0.47
240.00	1.39
246.87	100.00
247.88	10.93
248.88	0.66
264.87	1.42

No. 26 M.Wt. 267 EI+

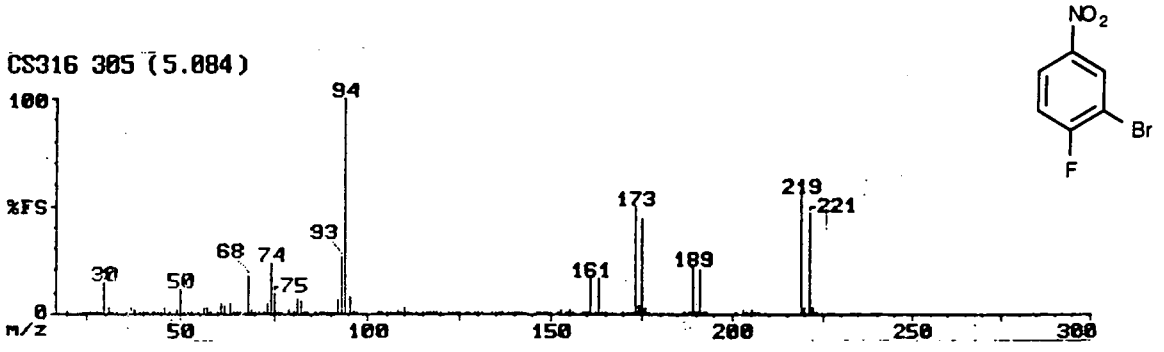




MS#14* x1 Bgd=1 20-JAN-94 12:36+0:01:34 70E EI+ 1.1
BpM=0 I=10v Hm=488 TIC=206083000 Acnt: Sys:ACE
PT= 0 Cal:PFK20JAN

Mass	% Base		
45.96	0.47		
49.98	1.45	187.92	1.00
52.97	0.36	203.91	0.99
56.98	1.01	208.79	8.83
60.97	0.48	209.79	0.51
61.98	0.78	220.78	4.51
62.98	2.41	221.79	3.42
67.96	1.37	234.77	4.11
72.96	0.31	235.77	0.61
73.96	1.99	236.76	21.80
74.97	1.97	237.77	3.55
76.95	0.89	247.77	0.96
80.95	2.16	250.75	41.81
81.96	1.77	251.76	3.28
82.97	0.81	253.64	1.25
91.94	0.55	266.73	100.00 FO
92.95	1.96	267.76	11.44 F
93.96	28.08	268.76	1.06
94.96	2.32	296.74	0.62
95.97	0.78	313.75	0.79
96.95	0.45	347.62	1.64
107.95	3.72	360.72	0.87
108.95	0.91	392.58	0.44
109.94	17.57	441.58	0.78
110.95	2.35	487.54	0.94
111.96	0.61		
124.94	2.98		
125.94	0.35		
126.82	0.53		
141.94	0.45		
175.90	0.34		

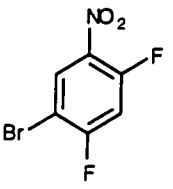
No. 27 M.Wt. 221 EI+

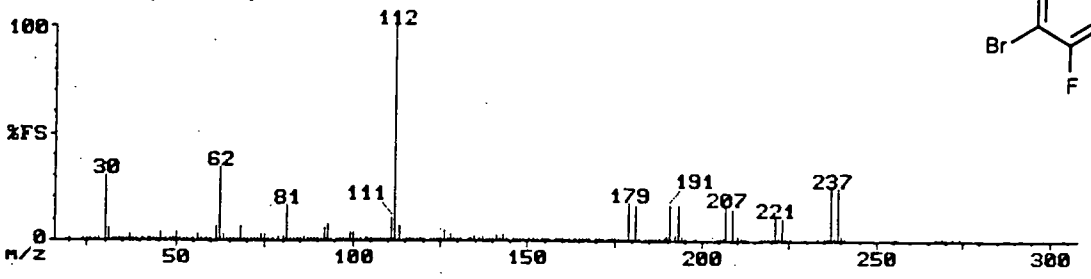


CS316 305 (5.084) 892988

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.01	65	0.07	109	0.34	154	0.30
24	0.05	66	0.04	110	3.38	155	2.21
25	0.18	67	0.25	111	1.38	156	0.21
26	0.39	68	17.78	112	0.11	159	0.04
27	0.11	69	1.73	113	1.10	160	0.07
28	0.34	70	0.19	115	0.11	161	16.51
29	0.10	71	0.09	116	0.26	162	0.87
30	14.45	72	0.45	117	0.52	163	16.06
31	2.84	73	4.93	118	0.28	164	0.52
32	0.23	74	23.17	119	0.40	165	0.02
33	0.18	75	9.63	120	0.04	170	0.04
36	0.45	76	1.20	122	0.18	171	0.11
37	2.61	77	0.20	123	0.12	172	0.70
38	1.68	78	1.55	124	0.16	173	49.54
39	0.47	80	0.84	125	0.11	174	3.56
40	0.07	81	6.34	127	0.03	175	43.58
41	0.04	82	6.19	128	0.77	176	2.78
43	0.05	83	1.21	129	0.34	177	0.11
44	0.35	84	0.15	130	0.78	187	0.09
45	0.16	86	0.30	131	0.32	188	0.06
46	2.75	87	0.43	134	0.09	189	21.79
47	0.28	88	0.29	135	1.35	190	1.40
48	0.26	89	0.08	136	0.14	191	20.64
49	1.58	90	0.24	137	1.30	192	1.30
50	11.93	91	0.41	138	0.05	193	0.09
51	1.25	92	7.05	139	0.06	201	0.03
52	0.31	93	26.15	140	0.15	203	2.18
53	0.12	94	100.00	141	0.21	204	0.15
55	0.59	95	7.34	142	0.12	205	2.12
56	2.58	96	0.32	143	0.16	206	0.15
57	2.72	97	0.06	146	0.16	207	0.05
58	0.23	103	0.04	147	0.38	219	55.05
60	0.65	104	0.22	148	0.18	220	3.27
61	4.90	105	0.20	149	0.39	221	46.79
62	4.33	106	0.45	150	0.03	222	3.04
63	4.62	107	0.21	152	0.11	223	0.30
64	0.52	108	1.51	153	2.26		

No. 28 M.Wt. 239 EI+

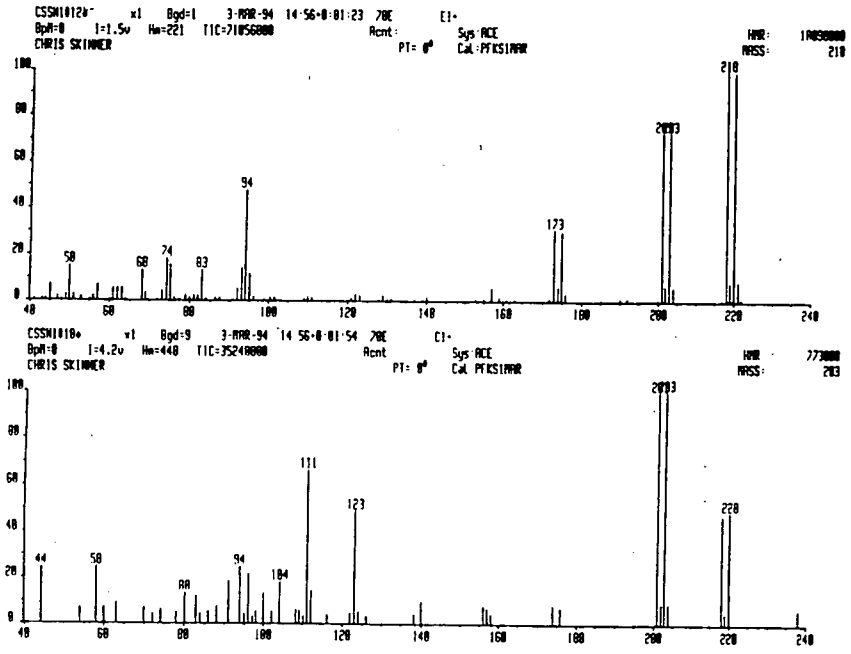


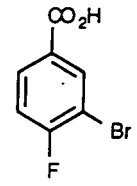


CS308 620 (10.334) 1409024

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.05	74	3.78	126	4.65	181	16.86
24	0.14	75	3.40	127	0.65	182	0.82
25	0.32	76	1.13	128	2.45	184	0.02
26	0.24	77	0.67	129	1.34	185	0.03
27	0.19	79	3.16	130	0.49	186	0.05
28	1.82	80	3.23	131	1.13	187	0.07
30	30.23	81	16.21	133	0.03	188	0.04
31	5.81	82	1.31	134	0.14	189	0.06
32	0.28	83	0.22	135	1.65	190	1.69
33	0.07	84	0.06	136	0.17	191	16.42
34	0.01	85	0.06	137	1.62	192	2.83
35	0.62	86	1.47	138	0.16	193	16.28
36	1.04	87	0.64	139	0.06	194	1.49
37	3.03	88	0.18	140	0.12	195	0.10
38	0.94	89	0.05	141	2.60	198	0.02
39	0.22	90	0.04	142	0.47	204	0.03
40	0.03	91	0.52	143	2.60	205	0.24
41	0.11	92	5.96	144	0.15	206	0.23
42	0.04	93	7.41	146	0.58	207	15.55
43	0.18	94	0.84	147	0.35	208	1.76
44	0.92	95	0.22	148	0.58	209	14.61
45	0.09	96	0.10	149	0.37	210	1.82
46	3.63	97	0.08	150	0.04	211	0.16
47	0.15	98	0.14	152	0.11	212	0.03
48	0.58	99	3.98	153	0.36	217	0.05
49	1.36	100	4.05	154	0.13	218	0.08
50	4.14	101	1.38	155	0.35	219	0.09
51	1.20	102	0.27	156	0.03	220	0.15
52	0.37	104	0.29	158	0.72	221	10.97
53	0.34	104	0.18	159	0.61	222	0.58
54	0.02	105	0.18	160	0.09	223	10.47
55	0.64	106	0.42	161	0.58	224	0.71
56	2.71	107	0.17	162	0.24	225	0.08
57	1.20	108	0.44	163	0.03	233	0.03
58	0.06	109	0.15	164	0.02	235	0.05
59	0.05	110	0.63	165	0.13	236	0.07
60	0.60	111	10.90	166	0.02	237	24.13
61	6.61	112	100.00	167	0.16	238	1.45
62	34.30	113	6.90	168	0.05	239	23.84
63	2.54	114	0.40	170	0.04	240	1.73
64	0.63	115	0.12	171	0.53	241	0.18
65	0.10	116	0.22	172	0.60	255	0.04
66	0.04	117	0.20	173	0.69	256	0.02
67	0.25	118	0.18	174	0.60	267	0.03
68	7.27	119	0.13	175	0.10	269	0.02
69	0.78	120	0.02	176	0.04	270	0.05
70	0.23	122	0.11	177	0.05	272	0.04
71	0.12	123	0.06	178	0.19	274	0.03
72	0.23	124	0.21	179	17.15	304	0.02
73	0.93	125	0.14	180	0.83		

No. 29 **M.Wt. 220** **EI+ / CI+**



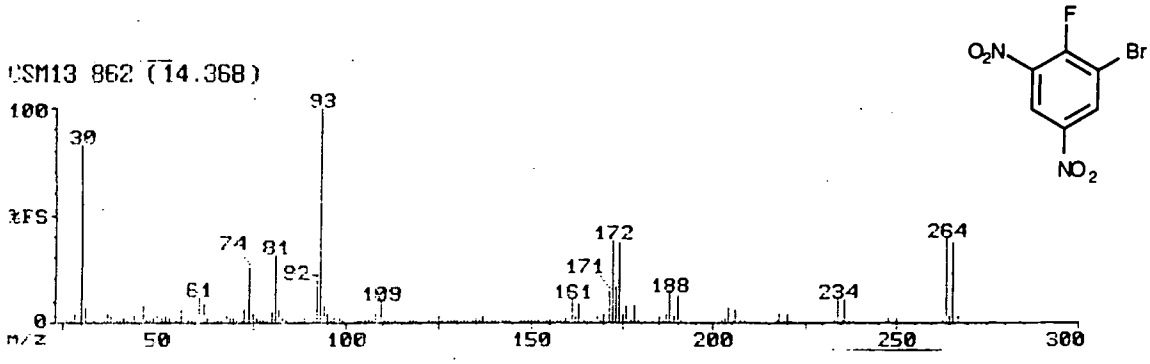


CSSN1#12* x1 Bgd=1 3-MAR-94 14:56+0:01:23 70E EI+ 1.1
BpM=0 I=1.5v Hm=221 TIC=71056000 Acnt: Sys:ACE
CHRIS SKINNER PT= 0 Cal:PFKS1MAR

Mass	% Base
41.03	0.39
43.05	0.51
43.99	0.57
44.99	7.01
47.01	1.82
49.00	2.40
50.01	14.80
51.02	2.40
53.00	1.34
55.00	0.43
56.00	1.92
57.01	6.49
57.07	0.90
60.00	0.50
61.00	5.21
62.01	5.17
63.02	5.13
64.03	0.45
68.00	12.84
69.01	3.16
69.51	0.35
71.99	0.36
73.00	4.09
74.01	17.75
75.02	15.00
76.02	0.92
78.91	1.93
79.92	0.99
80.91	1.67
81.01	1.91
81.91	0.86
82.01	1.92
83.02	13.11
84.02	0.77
86.46	0.94
87.46	0.91
92.00	5.07
93.00	13.86
94.01	47.77
95.02	11.34
96.01	1.22
98.95	0.32
100.46	1.08
101.46	1.02
108.98	0.51
110.01	1.30
111.03	1.02
121.00	1.06

Mass	% Base
122.00	2.39
123.01	2.20
127.91	0.46
128.98	1.97
129.92	0.33
130.97	0.71
139.00	0.34
140.01	1.32
152.92	0.66
154.92	0.76
156.97	5.07
158.97	1.50
160.93	0.50
162.92	0.35
171.92	1.01
172.92	30.46
173.95	5.73
174.92	29.52
175.94	2.74
189.93	1.18
191.92	1.11
199.91	0.50
200.91	72.98
201.92	6.30
202.91	73.02
203.92	5.38
217.91	100.00
218.92	8.03
219.20	0.34
219.91	99.45
220.20	0.38
220.92	8.19
221.92	0.64

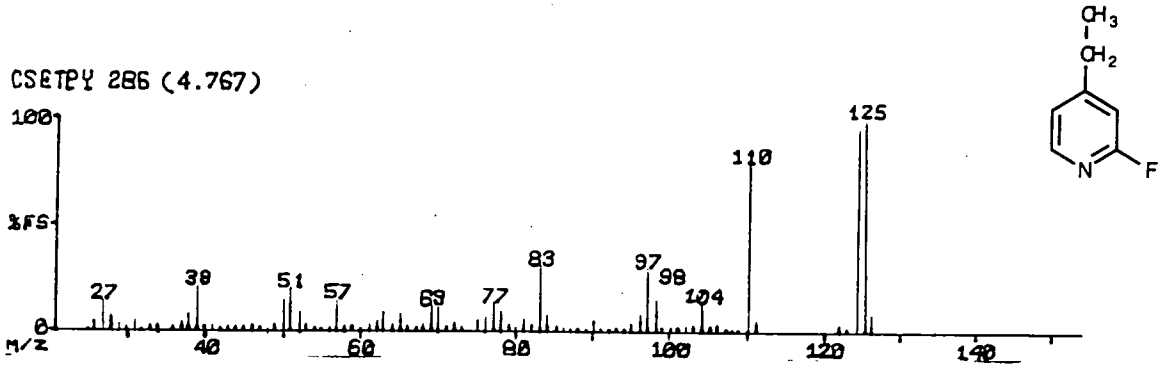
No. 30 **M.Wt. 266** **EI+**



CSM13 862 (14.368) 75776

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
26	0.29	73	6.00	125	2.81	172	38.18
27	0.40	74	25.34	126	0.53	173	16.98
28	3.72	75	3.40	127	1.26	174	37.16
30	82.43	76	2.11	128	0.74	175	3.46
31	7.01	77	0.82	129	0.25	176	8.02
32	1.73	78	0.73	130	0.70	177	0.78
33	0.20	79	1.92	131	1.29	178	7.60
36	0.51	80	4.69	132	0.27	179	0.60
37	3.97	81	31.08	133	1.22	183	0.63
38	2.68	82	6.08	134	0.38	185	3.04
39	0.94	83	1.52	135	2.41	186	0.98
40	0.84	84	0.41	136	0.79	187	4.18
41	1.48	86	0.80	137	2.49	188	13.60
42	0.37	87	1.03	138	0.82	189	2.81
43	0.52	88	0.87	139	0.87	190	12.92
44	2.62	89	1.60	140	0.25	191	1.20
46	8.02	90	0.36	141	0.94	202	0.96
47	0.43	91	0.41	142	0.71	203	2.03
48	0.59	92	19.34	143	0.88	204	6.33
49	1.73	93	100.00	144	0.45	205	0.54
50	3.06	94	8.19	147	0.70	206	5.41
51	1.69	95	3.42	148	0.88	207	0.75
52	2.81	96	1.39	149	0.99	208	0.45
53	1.94	97	1.92	150	0.73	217	0.28
55	0.88	98	1.54	151	0.65	218	3.99
56	5.57	99	0.34	152	0.39	219	0.93
57	2.05	103	0.29	153	0.25	220	3.80
58	0.53	104	0.41	154	1.30	221	0.40
59	0.59	105	0.71	155	1.82	233	0.27
60	1.39	106	1.67	156	1.18	234	10.64
61	11.99	107	1.35	157	1.15	235	0.54
62	9.04	108	4.33	158	0.41	236	10.56
63	2.34	109	9.63	159	2.26	237	0.93
64	0.76	110	1.11	160	2.22	238	1.19
65	0.66	111	1.16	161	10.98	248	1.54
66	0.44	113	0.80	162	2.49	250	1.67
67	0.41	117	0.51	163	8.95	263	0.62
68	3.32	118	0.31	164	0.77	264	38.51
69	1.98	119	0.45	168	3.29	265	2.91
70	1.67	122	1.21	169	0.42	266	36.82
71	0.77	123	0.41	170	3.46	267	2.60
72	0.33	124	0.39	171	14.95		

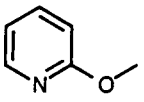
No. 31 **M.Wt. 125** **EI+**

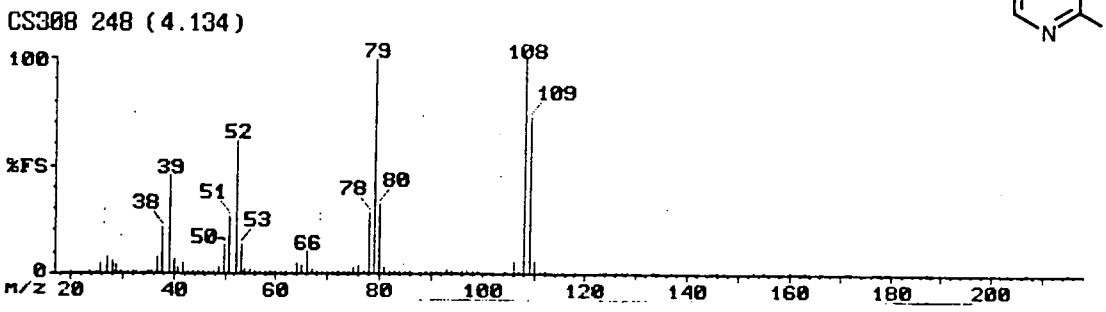


CSETPY 286(4.767)

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
24	0.04	51	19.84	77	12.45	103	0.42
25	0.25	52	8.60	78	8.60	104	13.36
26	3.82	53	3.16	79	2.68	105	1.58
27	13.66	54	1.41	80	1.40	106	3.16
28	6.98	55	0.29	81	4.38	107	1.44
29	2.58	56	1.75	82	3.24	108	0.51
30	0.11	57	14.47	83	29.96	109	1.09
31	4.78	58	1.49	84	6.68	110	78.54
33	0.33	59	2.13	85	1.54	111	4.88
34	1.90	60	0.64	86	0.41	112	0.17
36	0.03	61	3.19	87	0.16	120	0.09
37	0.18	62	3.57	88	0.19	121	0.18
38	6.45	63	8.30	89	0.55	122	2.94
39	20.75	64	3.37	90	4.73	123	0.94
40	1.92	65	8.10	91	0.63	124	97.57
41	2.71	66	1.02	92	1.05	125	100.00
42	0.94	67	0.28	93	0.63	126	7.79
43	0.10	68	3.29	94	1.40	127	0.36
44	2.38	69	11.34	95	3.29	128	0.35
45	2.20	70	10.93	96	6.88	138	0.08
46	2.88	71	2.15	97	29.15	139	0.09
47	0.63	72	3.54	98	14.47	142	0.15
48	0.77	73	0.70	99	1.11	143	0.27
49	2.43	74	1.92	100	0.20	144	0.03
50	14.78	75	5.29	101	0.08		

No. 32 **M.Wt. 109** **EI+**

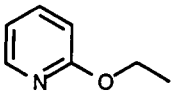


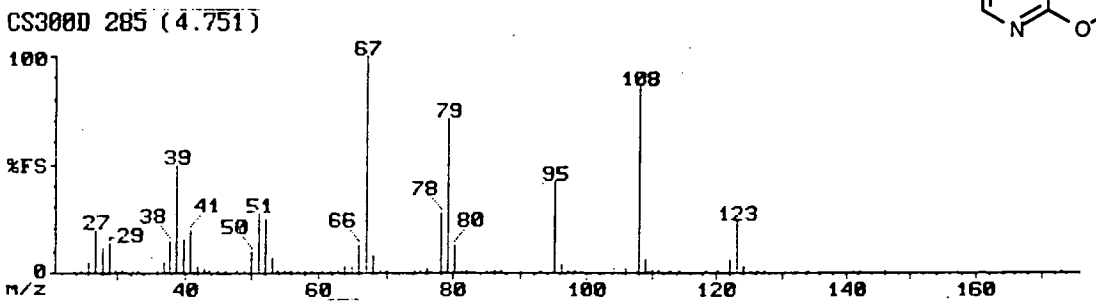


CS308 248 (4.134) 1490944

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
30	0.02	48	0.33	72	0.05	98	1.32
34	0.10	49	8.63	73	0.04	99	0.15
35	0.60	50	13.12	74	0.27	104	0.01
36	4.81	51	26.65	75	2.81	106	5.98
37	7.35	52	62.09	76	3.74	107	0.42
38	5.63	53	13.26	77	1.13	108	100.00
39	3.61	54	2.09	78	28.57	109	72.53
40	0.81	55	2.18	79	100.00	110	6.16
41	0.91	56	0.73	80	32.14	111	0.46
42	0.32	57	0.53	81	3.00	112	0.05
43	0.39	58	0.39	82	0.24	124	0.15
35	0.01	59	0.05	83	0.10	126	1.41
36	0.66	60	0.07	84	0.34	127	1.34
37	7.30	61	0.08	85	0.08	128	0.09
38	21.70	62	0.41	86	0.12	133	0.03
39	45.60	63	1.41	89	0.02	137	0.02
40	7.07	64	5.15	90	0.04	146	0.02
41	3.18	65	3.98	91	0.29	153	0.03
42	5.22	66	10.30	92	0.05	155	0.02
43	0.50	67	1.65	93	2.32	160	0.03
44	0.20	68	0.67	94	0.89	163	0.07
45	0.14	69	0.30	95	0.08	187	0.02
46	0.14	70	1.00	96	0.56	207	0.07
47	0.13	71	0.13	97	1.96	215	0.03

No. 33 M.Wt. 123 EI+

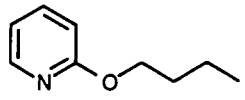


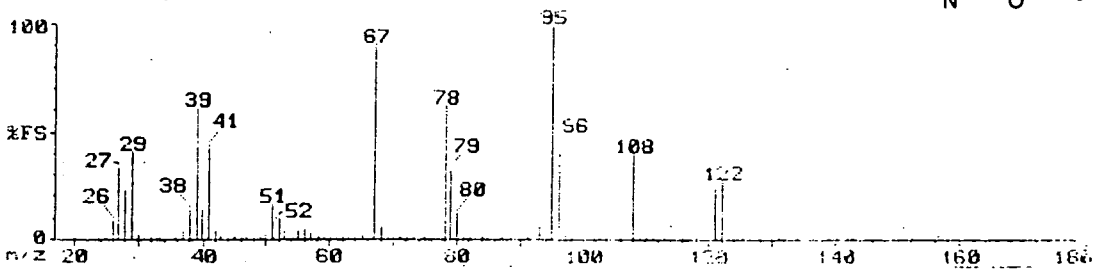


CS300D 285 (4.751) 2228224

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
24	0.05	46	0.24	68	7.40	106	1.87
25	0.38	48	0.12	69	0.48	108	85.29
26	4.92	49	1.25	70	0.12	109	5.61
27	19.30	50	9.24	74	0.03	110	0.36
28	11.17	51	27.39	75	0.99	111	0.04
29	13.24	52	24.26	76	1.72	113	0.39
30	0.57	53	6.43	78	27.02	114	0.04
31	0.19	54	1.07	79	70.59	118	0.01
32	0.14	55	0.49	80	12.50	120	0.23
33	0.03	56	0.30	81	0.65	122	5.47
36	0.25	57	0.24	82	0.06	123	23.16
37	4.83	58	0.22	85	1.19	124	3.22
38	14.52	59	0.03	86	0.11	125	0.25
39	49.26	61	0.22	87	0.01	126	0.37
40	15.63	62	0.26	93	1.00	127	0.03
41	18.93	63	0.88	95	42.10	134	0.02
42	3.31	64	2.80	96	3.86	141	0.27
43	2.27	65	2.59	97	0.42	142	0.03
44	0.26	66	12.87	98	0.07	146	0.03
45	0.43	67	100.00	104	1.52	173	0.11

No. 34 **M.Wt. 151** **EI+**

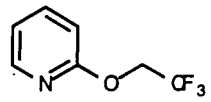


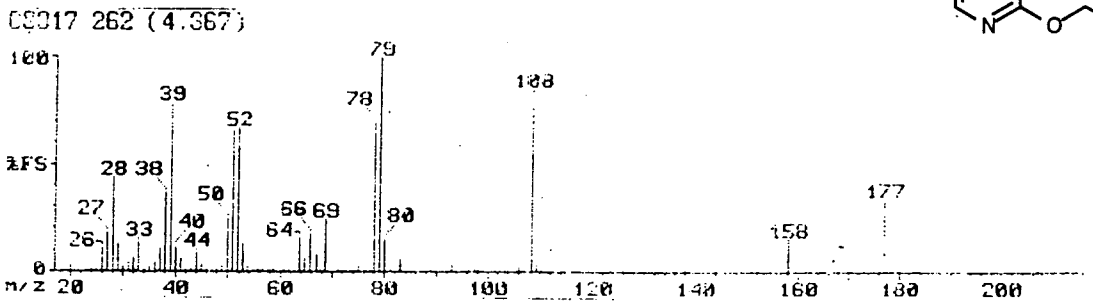


CS311F 531 (8.851) 4177920

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.02	51	16.57	81	1.62	131	33.63
24	0.35	52	9.41	82	0.12	132	37.06
25	1.27	53	4.09	83	0.06	133	1.50
26	9.12	54	0.52	84	0.05	134	0.25
27	32.55	55	3.95	85	0.30	135	0.02
28	22.75	56	4.93	86	0.05	138	0.03
29	41.18	57	2.72	87	0.02	131	0.08
30	1.53	58	0.10	89	0.05	132	0.10
31	0.58	59	0.03	90	0.06	134	0.52
32	0.12	60	0.05	91	0.26	136	1.03
33	0.03	61	0.07	93	5.37	139	0.02
33	0.15	62	0.14	95	100.00	140	0.01
36	0.62	63	0.43	96	41.96	142	0.02
37	5.05	64	1.29	97	1.74	143	0.01
38	13.73	65	1.96	98	0.14	146	0.06
39	61.18	67	90.59	102	0.05	148	0.26
40	13.33	68	5.44	104	2.25	151	7.75
41	43.52	69	0.31	106	4.71	152	4.73
42	3.80	70	0.07	108	39.61	153	0.38
43	3.21	71	0.04	109	3.70	154	0.03
44	0.58	72	0.12	110	0.25	155	0.02
45	0.13	73	0.03	111	0.04	156	0.01
46	0.10	75	0.72	113	0.22	161	0.03
47	0.09	76	1.43	114	0.05	170	0.01
48	0.18	78	68.35	116	0.06	173	0.33
49	0.93	79	31.76	117	0.24	174	0.02
50	5.22	80	11.47	119	0.23		

No. 35 **M.Wt. 177** **EI+**

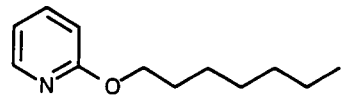


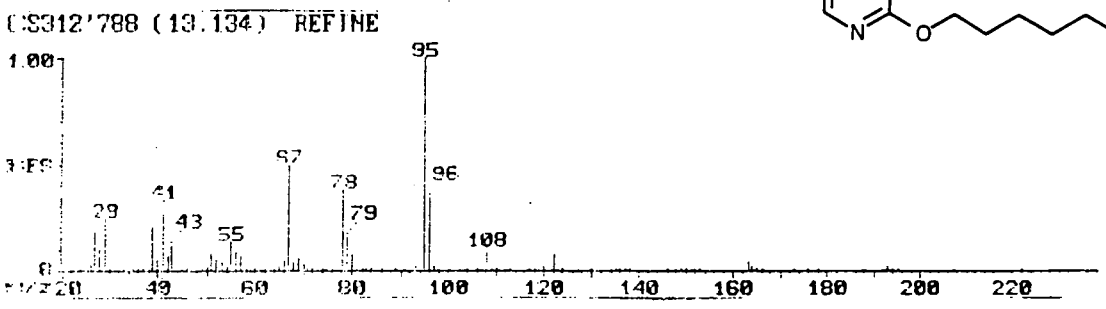


CS317 262(4.367)

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.50	38	36.45	55	0.07	86	0.54
21	0.02	39	72.75	56	0.75	87	0.43
22	0.12	40	15.92	57	0.89	92	1.30
23	0.07	41	2.71	58	0.65	93	0.56
24	0.08	42	0.94	64	3.37	97	0.45
25	0.25	44	10.20	64	13.37	100	0.34
26	10.82	46	0.08	65	9.10	104	2.45
27	20.66	47	0.10	66	21.02	106	2.87
28	46.70	48	0.08	67	10.28	108	90.23
29	15.20	49	0.98	68	13.29	109	6.42
30	0.11	50	14.78	69	22.34	110	0.46
31	1.78	51	68.12	78	78.60	158	28.34
33	15.33	52	70.01	79	100.00	159	2.00
34	1.90	53	10.16	80	11.40	177	40.32
36	0.03	54	2.02	83	5.96	178	2.87
37	0.18						

No. 36 **M.Wt. 193** **EI+**

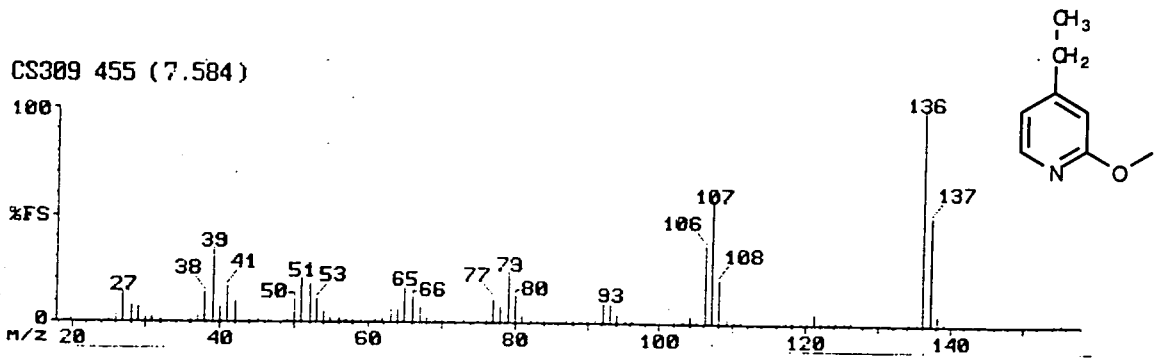




CS312'788 (13.134) REFINE 2621440

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
24	0.19	52	4.65	80	7.54	134	0.37
25	0.64	53	4.22	81	0.64	135	0.67
26	4.18	54	1.72	82	0.15	136	0.87
27	18.28	55	14.06	83	0.45	137	0.74
28	9.77	56	8.36	84	0.07	138	0.08
29	24.69	57	6.68	86	0.04	146	0.08
30	0.79	58	0.31	89	0.03	148	0.88
31	0.23	60	0.03	91	0.15	149	0.48
32	0.04	61	0.06	93	2.14	150	1.10
33	0.03	62	0.13	95	100.00	151	0.34
35	0.02	63	0.34	96	33.59	152	0.04
36	0.16	64	0.69	97	1.93	153	0.02
37	1.22	65	1.82	98	0.28	163	3.79
38	3.52	66	4.80	104	0.63	164	1.81
39	20.78	67	49.38	106	2.12	165	0.20
40	4.77	68	3.67	108	10.94	166	0.02
41	33.13	69	6.25	109	1.36	173	0.06
42	6.48	70	3.05	110	0.09	176	0.23
43	11.88	71	0.23	113	0.50	178	0.19
44	0.60	72	0.04	117	0.13	192	0.41
45	0.08	73	0.20	118	0.15	193	2.35
46	0.03	74	0.09	120	2.23	194	1.08
48	0.07	75	0.42	122	7.58	195	0.13
49	0.29	76	0.96	123	0.64	207	0.03
50	2.23	78	37.66	124	0.07	222	0.01
51	7.85	79	15.63	130	0.03		

No. 37 M.Wt. 137 EI+

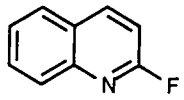


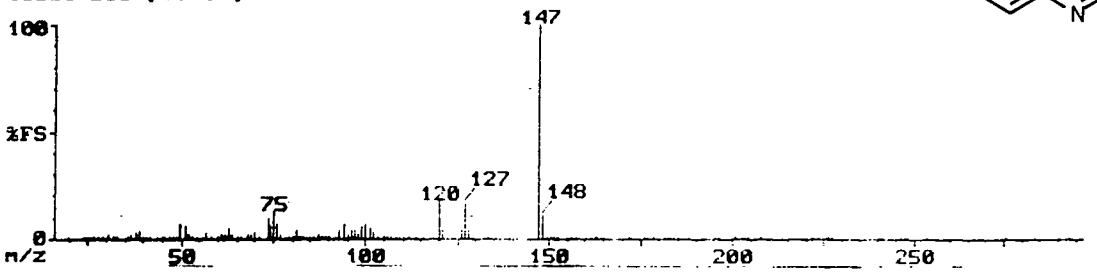
CS309 455 (7.584)

184320

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.06	52	17.64	78	8.06	107	56.11
25	0.15	53	10.83	79	23.06	108	20.42
26	3.13	54	4.69	80	12.36	109	2.16
27	13.89	55	2.16	81	2.57	110	0.64
28	7.95	56	1.49	82	0.76	111	0.13
29	6.77	57	0.52	83	0.14	117	0.15
30	1.66	58	0.69	84	0.23	118	0.29
31	1.56	59	0.09	85	0.13	119	0.23
32	0.69	61	1.40	87	0.12	120	0.78
36	0.14	62	2.20	88	0.17	121	4.38
37	3.30	63	5.97	89	0.28	122	1.31
38	13.19	64	5.56	90	0.57	123	0.12
39	34.44	65	16.25	91	2.22	124	0.13
40	7.15	66	11.25	92	8.65	125	0.10
41	16.25	67	6.49	93	9.72	126	0.10
42	9.58	68	1.49	94	4.24	134	0.88
43	1.07	69	0.28	95	0.80	135	0.08
44	0.38	70	0.22	96	0.26	136	100.00
45	0.17	73	0.13	102	0.31	137	50.56
47	0.49	74	0.56	103	0.17	138	4.41
49	1.07	75	1.35	104	3.30	139	0.32
50	10.28	76	2.14	105	1.21	154	0.11
51	20.69	77	11.11	106	35.56	155	0.13

No. 38 M.Wt. 147 EI+





CS501 268 (4.467) 4177920

Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int	Mass	Rel Int
20	0.05	45	0.36	65	0.23	85	0.78	105	0.72	128	4.09	150	0.03	180	0.01	240	0.02
24	0.11	46	0.38	66	0.05	86	1.19	106	0.42	129	0.35	159	0.02	195	0.01	241	0.01
25	0.33	47	0.05	68	1.48	87	2.16	107	0.61	132	0.06	160	0.02	196	0.02	246	0.01
26	1.37	48	0.21	69	1.74	88	1.19	108	0.36	133	0.10	161	0.00	200	0.01	247	0.02
27	1.21	49	0.97	70	2.58	89	1.37	109	0.09	134	0.04	162	0.02	201	0.03	248	0.02
28	0.74	50	5.86	71	0.27	90	0.30	110	0.05	135	0.01	163	0.07	202	0.02	253	0.01
29	0.03	51	5.42	73	9.30	92	1.00	111	0.03	138	0.02	164	0.05	203	0.01	273	0.04
31	2.40	52	1.72	74	5.49	93	3.58	112	0.14	139	0.02	165	0.09	204	0.01	274	0.01
32	0.14	53	0.16	75	12.84	94	7.86	114	0.29	141	0.02	172	0.02	207	0.01	275	0.01
33	0.31	54	0.02	76	5.86	95	2.28	116	0.59	142	0.02	176	0.01	208	0.04	293	0.01
36	0.42	56	0.64	77	1.96	96	3.53	118	0.58	147	100.00	177	0.01	209	0.01		
37	2.33	57	2.50	78	0.48	97	3.55	120	17.55	148	10.59	178	0.02	219	0.01		
38	2.79	58	0.21	79	0.15	98	1.81	121	5.00	149	0.44	181	0.02	220	0.02		
39	4.00	60	1.19	80	0.51	99	5.98	122	0.38	150	0.04	182	0.07	221	0.01		
40	2.25	61	1.53	81	3.49	100	7.94	123	0.18	151	0.03	183	0.32	222	0.02		
41	0.11	62	2.40	82	0.22	101	5.32	124	0.17	152	0.02	184	0.07	223	0.01		
42	0.03	63	5.02	83	0.46	102	3.19	126	7.16	156	0.06	185	0.03	225	0.02		
44	0.52	64	1.74	84	0.21	103	0.79	127	15.57	157	0.02	186	0.00	227	0.01		

Appendix Four: *Requirements for the Board of Studies*

The Board of Studies in Chemistry requires that each postgraduate research thesis contains an appendix listing:-

(1) all research colloquia, seminars and lectures arranged by the Department of Chemistry during the period of the author's residence as a postgraduate student;

(2) lectures organised by Durham University Chemical Society;

(3) details of the postgraduate induction course;

(4) all research conferences attended and papers presented by the author during the period when research for the thesis was carried out.

1991 - 1994

1991

October 17 Dr. J. A. Salthouse, University of Manchester*
Son et Lumiere - a demonstration lecture.

October 31 Dr. R. Keely, Metropolitan Police Forensic Science
Modern Forensic Science.

November 6 Prof. B. F. G. Johnson†, University of Edinburgh
Cluster-Surface Analogies.

November 7 Dr. A. R. Butler, St. Andrews University
Traditional Chinese Herbal Drugs.

November 13 Prof. D. Gani†, St. Andrews University*
The Chemistry of PLP Dependant Enzymes.

November 20 Dr. R. More O'Ferrall†, Dublin*
Some Acid-Catalysed Rearrangements in Organic Chemistry.

November 28 Prof. I. M. Ward, Leeds University
The Science & Technology of Orientated Polymers.

December 4 Prof. R. Grigg†, Leeds University
Palladium Catalysed Cyclisation and Ion Capture Processes.

December 5 Prof. A. L. Smith, ex Unilever
Soap Detergents and Black Puddings.

December 11 Dr. W. A. Cooper†, Shell Research
Colloid Science, Theory, and Practice.

1992

January 16 Dr. N. J. Long, University of Exeter
Metallocenophanes-Chemical sugar-tongs.

January 22 Dr. K. D. M. Harris†, University of St. Andrews*
Understanding the Prperties of Solid Inclusion Compounds.

January 29 Dr. A. Holmes†, University of Cambridge*
Cycloaddition Reactions in the Service of the Synthesis of Piperidine and ndolizidine Natural Products.

January 30 Dr. M. Anderson, Sittingbourne Research Centre, Shell Research
Recent Advances in the Safe and Selective Chemical Control of Insect Pests.

February 12 Dr. D. E. Fenton†, University of Sheffield*
Polynuclear Complexes of Molecular Clefts as Models for Copper Biosites.

February 13 Dr. J. Saunders, Glaxo Group Research Limited
Molecular Modelling in Drug Discovery.

February 19 Prof. E. J. Thomas†, University of Manchester
Application of Organo-Stannanes to Organic Synthesis.

February 20 Prof. E. Vogel, University of Cologne*
The Musgrave Lecture: Porrphyrins, Molecules of Interdisciplinary Interest.

February 25 Prof. J. F. Nixon, University of Sussex
Phosphoalkylenes, New Building Blocks in Inorganic and Organometallic Chemistry.

February 26 Prof. M. L. Hitchman†, University of Stratheclyde
Chemical Vapour Deposition.

March 5 Dr. N. C. Billingham, University of Sussex
Degradable Plastics - Myth or Magic ?

March 11 Dr. S. E. Thomas†, Imperial College London*
Recent Advances in Organoiron Chemistry.

March 12 Dr. R. A. Hann, ICI Image Data
Electronic Photography - An Image of the Future

March 18 Dr H. Maskill†, University of Newcastle
Concerted or stepwise fragmentation in a deamination-type reaction.

April 7 Prof. D. M. Knight, Philosophy Department, University of Durham
Interpreting experiments: the begining of electrochemistry.

May 13 Dr. J-C. Gehret, Ciba Geigy, Basel*
Some aspects of Industrial Agrochemical Research.

October 15 Dr M. Glazer & Dr. S. Tarling, Oxford University & Birbeck College, London
It Pays to be British! - The Chemist's Role as an Expert Witness in Patent Litigation.

October 20 Dr. H. E. Bryndza, Du Pont Central Research
Synthesis, Reactions and Thermochemistry of Metal (Alkyl) Cyanide Complexes and Their Impact on Olefin Hydrocyanation Catalysis.

October 22 Prof. A. Davies, University College London
The Ingold-Albert Lecture The Behaviour of Hydrogen as a Pseudometal.

October 28 Dr. J. K . Cockcroft, University of Durham
Recent Developments in Powder Diffraction.

October 29 Dr. J. Emsley, Imperial College, London
The Shocking History of Phosphorus.

November 4 Dr. T. P. Kee, University of Leeds
Synthesis and Co-ordination Chemistry of Silylated Phosphites.

November 5 Dr. C. J. Ludman, University of Durham*
Explosions, A Demonstration Lecture.

November 11 Prof. D. Robins†, Glasgow University*
Pyrrolizidine Alkaloids : Biological Activity, Biosynthesis and Benefits.

November 12 Prof. M. R. Truter, University College, London
Luck and Logic in Host - Guest Chemistry.

November 18 Dr. R. Nix†, Queen Mary College, London
Characterisation of Heterogeneous Catalysts.

November 25 Prof. Y. Vallee. University of Caen
Reactive Thiocarbonyl Compounds.

November 25 Prof. L. D. Quin†, University of Massachusetts, Amherst
Fragmentation of Phosphorous Heterocycles as a Route to Phosphoryl Species with Uncommon Bonding.

November 26 Dr. D. Humber, Glaxo, Greenford
AIDS - The Development of a Novel Series of Inhibitors of HIV.

December 2 Prof. A. F. Hegarty, University College, Dublin
Highly Reactive Enols Stabilised by Steric Protection.

December 2 Dr. R. A. Aitken†, University of St. Andrews
The Versatile Cycloaddition Chemistry of $Bu_3P.CS_2$.

December 3 Prof. P. Edwards, Birmingham University
The SCI Lecture - What is Metal?

December 9 Dr. A. N. Burgess†, ICI Runcorn*
The Structure of Perfluorinated Ionomer Membranes.

1993

January 20 Dr. D. C. Clary†, University of Cambridge
Energy Flow in Chemical Reactions.

January 21 Prof. L. Hall, Cambridge*
NMR - Window to the Human Body.

January 27 Dr. W. Kerr, University of Strathclyde*
Development of the Pauson-Khand Annulation Reaction : Organocobalt Mediated Synthesis of Natural and Unnatural Products.

January 28 Prof. J. Mann, University of Reading
Murder, Magic and Medicine.

February 3 Prof. S. M. Roberts, University of Exeter
Enzymes in Organic Synthesis.

February 10 Dr. D. Gillies†, University of Surrey
NMR and Molecular Motion in Solution.

February 11 Prof. S. Knox, Bristol University
The Tilden Lecture: Organic Chemistry at Polynuclear Metal Centres.

February 17 Dr. R. W. Kemmitt†, University of Leicester
Oxatrimethylenemethane Metal Complexes.

February 18 Dr. I. Fraser, ICI Wilton
Reactive Processing of Composite Materials.

February 22 Prof. D. M. Grant, University of Utah
Single Crystals, Molecular Structure, and Chemical-Shift Anisotropy.

February 24 Prof. C. J. M. Stirling†, University of Sheffield*
Chemistry on the Flat-Reactivity of Ordered Systems.

March 10 Dr. P. K. Baker, University College of North Wales, Bangor
'Chemistry of Highly Versatile 7-Coordinate Complexes'.

March 11 Dr. R. A. Y. Jones, University of East Anglia
The Chemistry of Wine Making.

March 17 Dr. R. J. K. Taylor†, University of East Anglia*
Adventures in Natural Product Synthesis.

March 24 Prof. I. O. Sutherland†, University of Liverpool
Chromogenic Reagents for Cations.

May 13 Prof. J. A. Pople, Carnegie-Mellon University, Pittsburgh, USA*
The Boys-Rahman Lecture: Applications of Molecular Orbital Theory

May 21 Prof. L. Weber, University of Bielefeld
Metallo-phospha Alkenes as Synthons in Organometallic Chemistry

June 1 Prof. J. P. Konopelski, University of California, Santa Cruz*
Synthetic Adventures with Enantiomerically Pure Acetals

June 2 Prof. F. Ciardelli, University of Pisa
Chiral Discrimination in the Stereospecific Polymerisation of Alpha Olefins

June 7 Prof. R. S. Stein, University of Massachusetts
Scattering Studies of Crystalline and Liquid Crystalline Polymers

June 16 Prof. A. K. Covington, University of Newcastle
Use of Ion Selective Electrodes as Detectors in Ion Chromatography.

June 17 Prof. O. F. Nielsen, H. C. Arsted Institute, University of Copenhagen
Low-Frequency IR - and Raman Studies of Hydrogen Bonded Liquids.

September 13 Prof. Dr. A. D. Schlüter, Freie Universität Berlin, Germany
Synthesis and Characterisation of Molecular Rods and Ribbons.

September 13 Prof. K. J. Wynne, Office of Naval Research, Washington, U.S.A.
Polymer Surface Design for Minimal Adhesion

September 14 Prof. J. M. DeSimone, University of North Carolina, Chapel Hill, U.S.A.
Homogeneous and Heterogeneous Polymerisations in Enviromentally Responsible Carbon Dioxide.

September 28 Prof. H. Ila., North Eastern University, India
Synthetic Strategies for Cyclopentanoids via OxoKetene Dithiacetals.

October 4 Prof. F. J. Feher†, University of California at Irvine
Bridging the Gap between Surfaces and Solution with Sessilquioxanes.

October 14 Dr. P. Hubberstey, University of Nottingham
Alkali Metals: Alchemist's Nightmare, Biochemist's Puzzle and Technologist's Dream.

October 20 Dr. P. Quayle†, Unversity of Manchester
Aspects of Aqueous Romp Chemistry.

October 23 Prof. R. Adams†, University of S. Carolina
The Chemistry of Metal Carbonyl Cluster Complexes Containing Platinum and Iron, Ruthenium or Osmium and the Development of a Cluster Based Alkyne Hydrogenating Catalyst.

October 27 Dr. R. A. L. Jones†, Cavendish Laboratory*
'Perambulating Polymers'.

November 10 Prof. M. N. R. Ashfold†, University of Bristol
High-Resolution Photofragment Translational Spectroscopy: A New Way to Watch Photodissociation.

November 17 Dr. A. Parker†, Laser Support Facility
Applications of Time Resolved Resonance Raman Spectroscopy to Chemical and Biochemical Problems.

November 24 Dr. P. G. Bruce†, University of St. Andrews
Synthesis and Applications of Inorganic Materials.

December 1 Prof. M. A. McKervey†, Queens University, Belfast*
Functionlised Calixerenes.

December 8 Prof. O. Meth-Cohen, Sunderland University*
Friedel's Folly Revisited.

December 16 Prof. R. F. Hudson, University of Kent
Close Encounters of the Second Kind.

January 26 Prof. J. Evans†, University of Southhampton
Shining Light on Catalysts.

February 2 Dr. A. Masters†, University of Manchester*
Modelling Water Without Using Pair Potentials.

February 9	Prof. D. Young†, University of Sussex *Chemical and Biological Studies on the Coenzyme Tetrahydrofolic Acid.*
February 16	Prof. K. H. Theopold, University of Delaware, U.S.A *Paramagnetic Chromium Alkyls: Synthesis and Reactivity.*
February 23	Prof. P. M. Maitlis†, University of Sheffield *Why Rodium in Homogenous Catalysis.*
March 2	Dr. C. Hunter†, University of Sheffield* *Non Covalent Interactions between Aromatic Molecules.*
March 9	Prof. F. Wilkinson, Loughborough University of Technology *Nanosecond and Picosecond Laser Flash Photolysis.*
March 10	Prof. S.V. Ley, University of Cambridge* *New Methods for Organic Synthesis.*
March 25	Dr. J. Dilworth, University of Essex *Technetium and Rhenium Compounds with Applications as Imaging Agents.*
April 28	Prof. R. J. Gillespie, McMaster University, Canada* *The Moleculr Structure of some Metal Fluorides and OxoFluorides: Apparent Exceptions to the VSEPR Model.*
May 12	Prof. D. A. Humphreys, McMaster University, Canada *Bringing Knowledge to Life*

† Invited specially for the graduate training programme.

First Year Induction Course

This course consists of a series of one hour lectures on the services available in the department.

Departmental Organisation -	Dr. E.J.F. Ross
Safety Matters -	Dr. G.M. Brooke
Electrical Appliances -	Mr. B.T. Barker
Chromatography and Microanalysis -	Mr. T.F. Holmes
Atomic Absorptiometry and Inorganic Analysis -	Mr. R. Coult
Library Facilities -	Mr. R.B. Woodward
Mass Spectroscopy -	Dr. M. Jones
Nuclear Magnetic Resonance Spectroscopy -	Dr. R.S. Matthews
Glass-blowing Techniques -	Mr. R. Hart / Mr. G. Haswell

Research Conferences Attended

December 1991	Modern Aspects of Sterochemistry, Sheffield University.
April 1992	Northeast Graduate Symposium, Durham.
December 1992	ICI Case Mechanism Meeting, Manchester.
July 1993	2nd Anglo-Russian-Ukranian Symposium on Fluorine Chemistry, Durham.
July 1994	14th International Symposium on Fluorine Chemistry,Yokohama, Japan.

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