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NUCLEOPHILIC SUBSTITUTION AND CYCLISATION REACTIONS OF SOME POLYFLUORO-HETEROAROMATIC AND POLYFLUOROAROMATIC COMPOUNDS

by

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University of Durham

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March 1994.

Statement of Copyright

Declaration

The work described in this thesis was carried out in the Department of Chemistry at the University of Durham between October 1990 and September 1993. All the work is my own, unless stated to the contrary, and it has not been submitted previously for a degree at this or any other University.

To Mum and Dad.

Acknowledgements.

I would like to thank the following people for there assistance over the past three and a bit years. Firstly, I thank my supervisor Dr. Gerald M. Brooke for his continual support during the course of this work. Secondly, I thank all of the staff in the department for the high level of services provided, particularly those involved with nmr, mass spectroscopy, micro analysis and glass blowing. I also thank all the inhabitants both past and present, of lab 27 for all the good times, my housemates past and present for putting up with me, and all of my friends, in particular Matt, Ian and Don's Family. Finally I thank my Parents for all their help both financial and otherwise and to Liz for her understanding.

Abstract

Nucleophilic Substitution and Cyclisation Reactions of some Polyfluoro-Heteroaromatic and Polyfluoroaromatic Compounds.

This thesis describes the reactions of some highly fluorinated aromatic and heteroaromatic compounds, in particular derivatives of naphthalene, quinoline and isoquinoline.

Chapter 1 provides a general introduction to the preparation, reactions and applications of fluorine containing organic materials.

Chapter 2 describes the reactions of some quinoline- and isoquinoline-thiolates with dimethyl acetylenedicarboxylate in an attempt to form six membered heterocycles.

Chapter 3 describes nucleophilic substitution reactions of heptafluoro-quinoline and -isoquinoline with sulphur and oxygen nucleophiles. The sulphur nucleophiles are found to attack the 6- site in the isoquinoline and the 4- site in the quinoline. The oxygen nucleophiles attack the 1- site in the isoquinoline and 2- and 4- sites in the quinoline.

Chapter 4 describes competition experiments of heptafluoro-quinoline and -isoquinoline with nucleophiles. Relative rates of attack at the 1- position and 6- position in the isoquinoline are determined for a variety of nucleophiles. The relative rates of two nucleophiles are determined for 4- attack in the quinoline. The relative reactivities of the two heterocycles are determined for two different nucleophiles.

Chapter 5 describes the pyrolysis of heptafluoro-2-naphthyl propynoate which yield two difluoro-butenone derivatives. These decarbonylate under further pyrolysis to yield a 1,1-difluorocyclopropene. All the products were identified by X-ray crystallography.

Chapter 6 gives experimental details for Chapter 2 to Chapter 5.

Christopher Drury (March 1994)

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Chapter 1

Introduction to Organo-Fluorine Chemistry.

Chapter 1.

Introduction to Organo-Fluorine Chemistry.

1.1 Why is Fluorine so Interesting?

Fluorine is the most electronegative element in the periodic table[1]. It can replace hydrogen in a wide variety of organic systems without major distortion of the geometry due to the similar sizes of fluorine and hydrogen. Since fluorine is electronically very different from hydrogen, the chemical properties of the fluorine analogue will differ greatly from those of the hydrocarbon system, especially if all or most of the hydrogen atoms are replaced with fluorine. The preference of fluorine as a leaving group is as a negatively charged species (F^-) unlike hydrogen which prefers to leave as a positively charged species (H^+). The electronegativity of fluorine (4.0 Pauling scale) is nearly twice that of hydrogen (2.1); consequently fluorine forms stronger bonds to carbon than does hydrogen. Fluorine has three lone pairs of electrons crowded into a small space whereas hydrogen has none so that electron repulsion effects arise[2].

1.1.1 Physical Properties of Organofluorine compounds

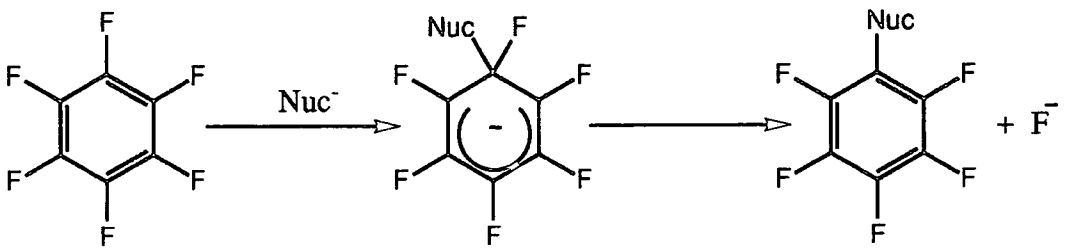
Fluorocarbon compounds generally have high thermal stability. Their boiling points and freezing points are very similar to those of their hydrocarbon counterparts, which at first may seem to be surprising considering the increased mass of the fluorocarbon; however the increase in mass is offset by a reduction in intermolecular forces in the fluorocarbon.[2] The compressibilities of fluorocarbon liquids are higher than most other liquids and fluorocarbons have high dielectric strengths, high resistivities and low dielectric losses making them excellent electrical insulators.[3]

Fluorine like hydrogen has a nucleur spin of one half, enabling fluorocarbons to be examined by ^{19}F nmr spectroscopy in an analogous fashion to the use of proton nmr in hydrocarbon systems. Indeed fluorine nmr is a very powerful tool aided by the high receptivity of the ^{19}F nucleus (0.83 relative to ^1H) and 100% natural abundance.[4]

1.1.2 Chemical Properties

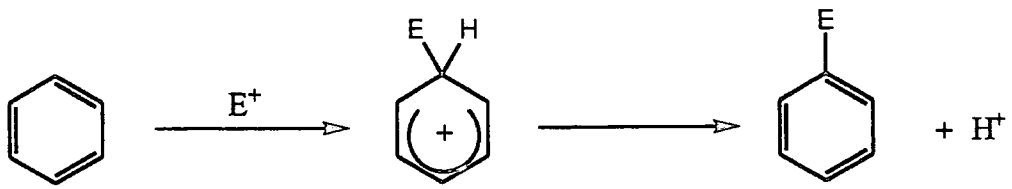
Saturated fluorocarbons are generally highly inert. They are unaffected by boiling acids and alkalis or reducing and oxidising agents under normal conditions. They do however react at high temperature with some metals capable of stripping fluorine from them, a process which can be used to prepare polyfluorinated aromatic compounds[3]. (See later).

Polyfluorinated alkenes and aromatic compounds undergo nucleophilic attack as opposed to the conventional electrophilic attack found in hydrocarbon systems (Scheme 1.1). Thus the chemistry is of a 'complementary' or 'mirror image' nature[2].



$$CF_2{=}CF\text{-}R_F \xrightarrow{Nuc^-} Nuc\text{-}CF_2\text{-}\bar{C}F\text{-}R_F \longrightarrow \text{Products}$$

whereas



$$CH_2{=}CH\text{-}R \xrightarrow{E^+} E\text{-}CH_2\text{-}\overset{+}{C}H\text{-}R \longrightarrow \text{Products}$$

Scheme 1.1

1.1.3 Industrial Applications of Organofluorine Compounds

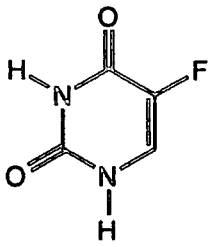
Dichlorodifluoromethane was introduced in 1930 as a direct replacement of the toxic and odorous refrigerant gas ammonia. It was non toxic, relatively inexpensive and at the time thought to be unreactive. A number of other saturated fluorocarbons followed shortly.

With the outbreak of World War II, interest arose in atomic weaponry. Fissionable ^{235}U needed to be separated from the more abundant ^{238}U and it was found that gas diffusion of UF_6 could achieve this reasonably satisfactorily. In addition chemically inert compounds capable of withstanding the highly reactive UF_6 were required for use in the gas diffusion process particularly as coolants, lubricants and for polymers that could be fabricated into gaskets[5]. Fluorocarbons fitted this role well.

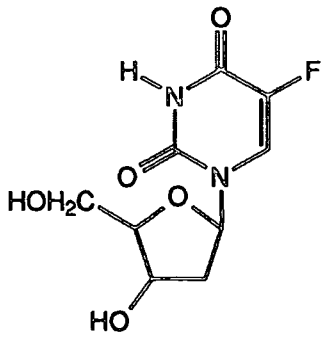
Polytetrafluoroethylene (PTFE) was first prepared by accident in 1938. This highly stable waxy solid with a low co-efficient of friction has found a wide range of applications including gaskets, insulators, non-stick surfaces and artificial body part replacements. Glass coated with PTFE can withstands the elements, is translucent and flame resistant, while expanded PTFE (Goretex®) is used in weather-proof clothing and footwear. The Goretex® membrane is porous to water vapour since its holes are 700 times larger than a water molecule, but being thousands of times smaller than a water droplet the membrane is waterproof. In addition the pores are all so small and sufficiently malaligned that the membrane is also windproof. Organofluorine compounds have also found uses in dyes, paints, stain repellants for the textiles industry, plastics and elastomers.[3]

Many organofluorine compounds are used in medicine[6], there being several factors that can cause an increase in the effectiveness of a drug by substituting hydrogen for fluorine. Fluorine's small size allows it to mimic the steric requirements of hydrogen at an enzyme receptor site while the strong inductive effect of fluorine can influence neighbouring sites in terms of reactivity and stability. Lipid solubility is also increased by replacement of hydrogen by fluorine, enhancing rates of absorption of the drug which can often be the single largest influence in increasing pharmacological activity. The presence of fluorine can also block an essential biochemical reaction.

Fluorine is found in some anti-cancer and anti-viral drugs. 5-Fluorouracil and the less toxic 5-fluoro-deoxy-β-uridine have found use in cancer chemotherapy.

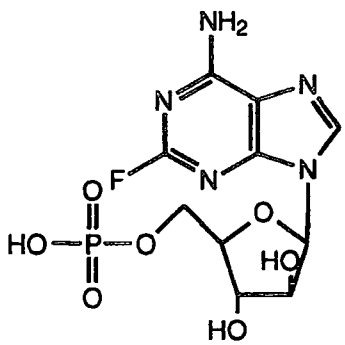


5-Fluorouracil

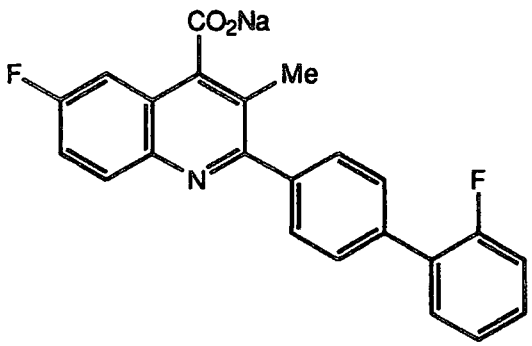


5-Fluoro-2'-deoxy-β-uridine

Both materials once anabolised are competitive inhibitors of the production of thymidylic acid, a required component of DNA. This inhibits tumour growth since the 5-fluorouracil accumulates in the rapidly growing cancerous cells. Other anticancer drugs include Fludarabine and 4-quinolinecarboxylic acid DuP-785.



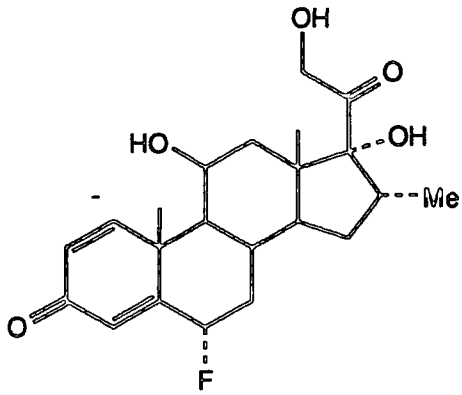
Fludarabine



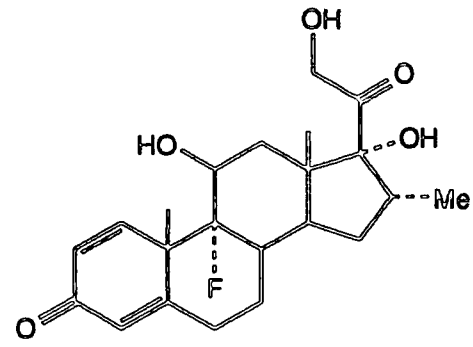
DuP-785

Inhalation anaesthetics containing fluorine are important materials; Halothane ($CF_3CHClBr$) is an exceedingly effective general anaesthetic. Others include Fluoromar ($CF_3CH_2OCH=CH_2$), enflurane (CHF_2OCF_2CHFCl) and isoflurane ($CHF_2OCHClCF_3$).

Anti-inflammatory drugs containing fluorine, both steroidal and non-steroidal are in use. Steroidal drugs are especially effective in the treatment of rheumatoid arthritis, paramethasone and dexamethasone being important examples.

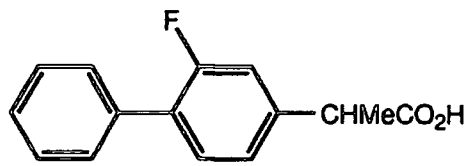


Paramethasone

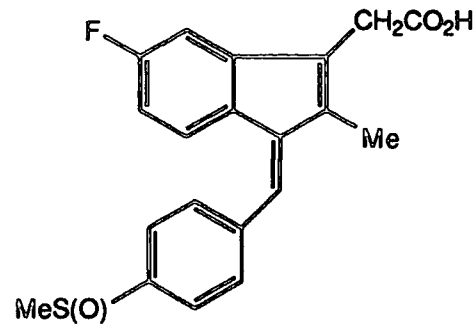


Dexamethasone

Steroidal drugs are very powerful but often have undesirable side effects. Non steroidal drugs have been developed to overcome this and include Flurbiprofen and Sulindac.



Flurbiprofen (Froben®)



Sulindac (Clinoril®)

Other medicinal applications of fluorine containing organic compounds include antibiotics, anxiolytics, antidepressants, sedative hypnotics, muscle relaxants and anorectics.

Fluorochemicals have been tried as blood substitutes and successfully tested on human volunteers in Japan. Fluosol DA[7] is water-based with perfluorodecalin (14%) as the major ingredient. Since Fluosol only contains a low concentration of perfluorodecalin, it is really a blood extender rather than a true substitute. The surfactant in Flurosol has been found to have side effects in some patients but the use of mixed fluorocarbon/hydrocarbon surfactants.(e.g. $C_8F_{17}CH{=}CHC_8H_{17}$) has improved the mixing of the fluorocarbon and water. HemaGen have developed a series of perfluorocarbon compounds stabilised by lecithin and triglycerides which can be sterilised at 121°C. Clinical trials have begun on a 40% perfluorocarbon emulsion which

has a shelf life of 6-12 months, but a half life of only 7-10 days in the body. Other promising oxygen transporting blood substitutes[8] are perfluoro-N-methyldecahydroisoquinoline (FMIQ) and in particular, perfluorooctylbromide. FMIQ demonstrates improved emulsion stability over Fluosol while still retaining a reasonable organ retention time of 11 days. FMIQ's drawback is that its preparation and purification is difficult and expensive. Perfluorooctyl bromide (PFOB) shows great promise as a blood substitute and it can be prepared at a far higher purity (99.9%) than perfluorodecalin (98% purity), which is obviously an important consideration if it is to be administered to a patient. PFOB has a high gas solubility (50ml O_2 per 100ml PFOB cf. 43ml O_2 per 100ml of perfluorodecalin) and a exceedingly short half life in the body of 4 days (7 days for perfluorodecalin). The PFOB emulsion is stable for over a year at room temperature wheras the perfluorodeclin emulsion has to be kept frozen. PFOB emulsion has the added advantage of being a contrast agent for magnetic resonance imaging and x-ray studies of the gastro intestinal tract.

A controversial use of organofluorine compounds is chlorofluorocarbons as aerosol propellants, refrigerants, solvents, foam blowing agents and fire extinguishers.[3] Concerns over ozone depletion has lead to a withdrawal of these materials resulting in the chemical challenge of finding suitable alternatives.

1.2 Preparation of Organofluorine compounds

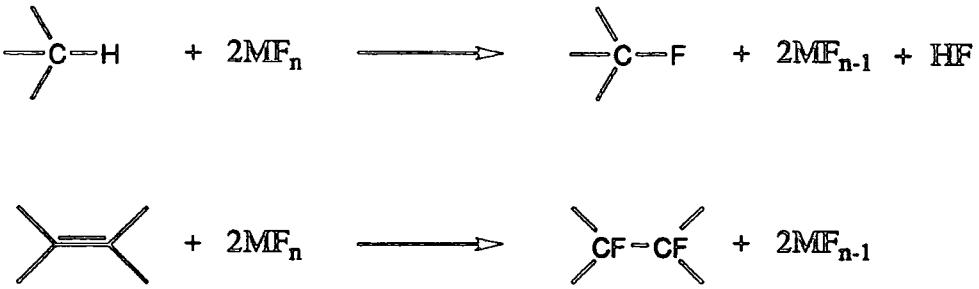
The first ever synthesis of a C-F bond was by Dumas and Peligot and took place over 150 years ago[9] (Scheme 1.2). Since that historical occasion, many processes for incorporating fluorine into organic molecules have been devised.

$$(CH_3O)_2SO_2 + 2KF \longrightarrow 2CH_3F + K_2SO_4$$

Scheme 1.2. *The first ever synthesis of a C-F bond.*

1.2.1 High Valency Metal Fluorides

Exhaustive fluorination to yield fluorocarbon products can be achieved by some high valency metal fluorides. The high valency metal fluoride is reduced to a lower valency fluoride as the reaction proceeds (Scheme 1.3)[10].

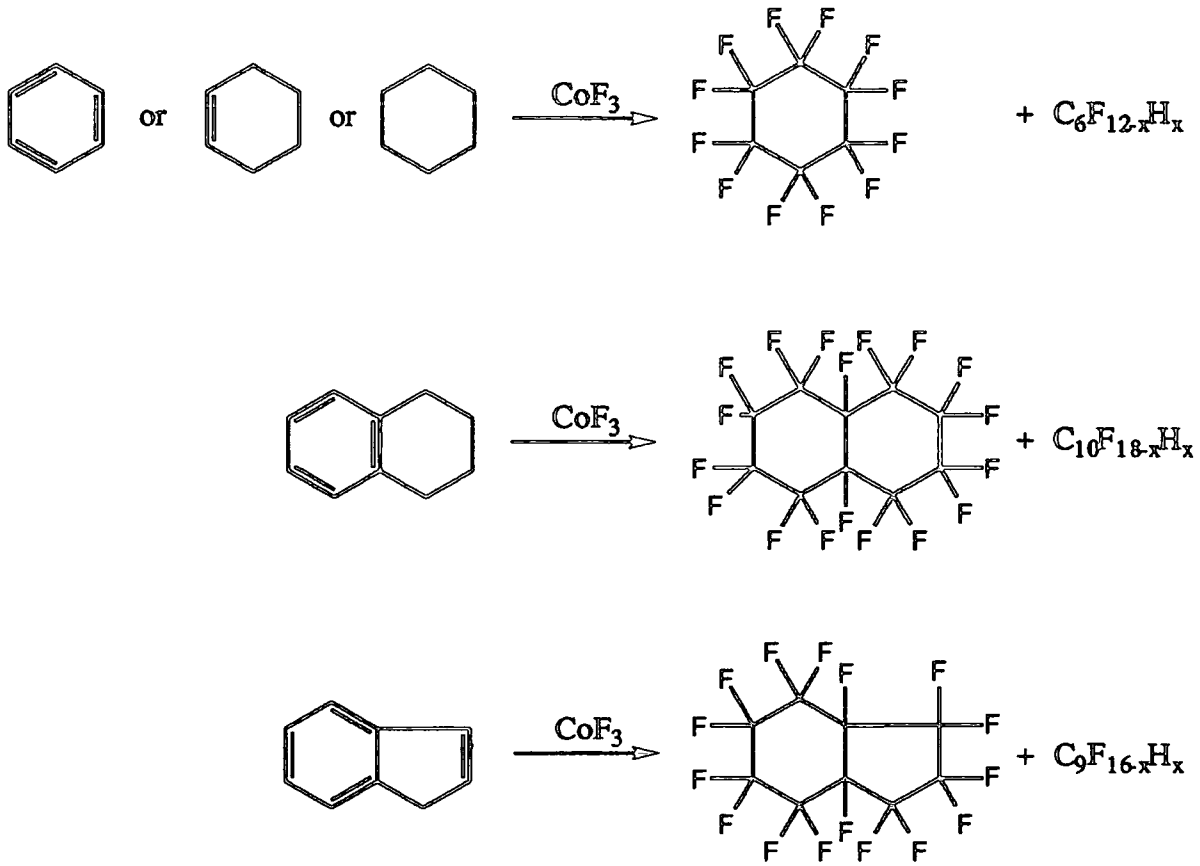


Scheme 1.3. *The course of fluorination by a high valency metal fluoride.*

The most important high valency fluorinating agent is cobalt trifluoride; however others have been used to some extent and include silver difluoride, manganese trifluoride, cerium tetrafluoride and lead tetrafluoride. The metal fluoride is prepared from a lower valency metal fluoride or chloride by the action of elemental fluorine.

Cobalt trifluoride fluorination can be operated in a two stage process. The organic material to be fluorinated is passed over the heated (150-400°C) cobalt trifluoride and the product collected in traps. The yields are increased if the the metal fluoride is agitated during the reaction. Once complete, the apparatus is purged with nitrogen and then the cobalt difluoride reconverted back to the trifluoride by passage of fluorine over the difluoride heated to 250°C

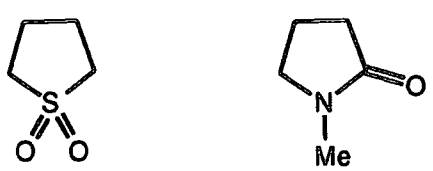
The use of high valency metal fluorides produces less fragmentation than direct fluorination by elemental fluorine, probably because the heat of the overall reaction is split between the two stages i.e. generation of the trifluoride and the reaction of the trifluoride with the organic material[11]. Some examples are shown in scheme 1.4



Scheme 1.4. *Some examples of fluorination by cobalt trifluoride.*

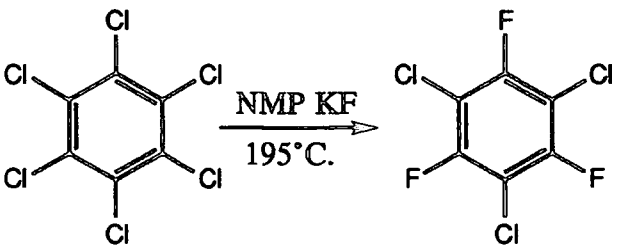
1.2.2 Halogen Exchange (Halex) By Alkali Metal Fluorides

Halogen exchange[12] by alkali metal fluorides provides a convenient method for substituting fluorine into an organic compound. The reaction can either be performed in solution or without solvent, in which case the reaction is performed in the melt or in an autoclave. The solution technique requires a solvent capable of dissolving the alkali metal fluoride, the most effective solvents being those containing the first row heteroatoms oxygen and nitrogen, which can donate electrons to the alkali metal cation. Examples of these solvents are sulpholan, dimethyl sulphone and N-methyl-2-pyrrolidone



Sulpholan N-methyl-2-pyrrolidone

Systems not using solvents allow the use of higher temperatures either in the melt or in an autoclave. Halogen exchange works best with haloaromatic compounds containing other electronegative substituents, providing a practical laboratory route to many polyfluoroaromatics. Hexachlorobenzene reacts with potassium fluoride in N-methylpyrrolidone (NMP) (195°C) to give a trichlorotrifluorobenzene, dichlorotetrafluorobenzenes and chloropentafluorobenzene. In the higher boiling sulpholan (230-240°C) a trace of hexafluorobenzene is produced while at 450-500°C in an autoclave without solvent, reasonable yields of C_6F_6 are produced. All these reactions are shown in Scheme 1.5).



Sulpholan KF, 230-240°C. C_6F_6 + C_6F_5Cl + $C_6F_4Cl_2$ + 1,3,5-$C_6F_3Cl_3$

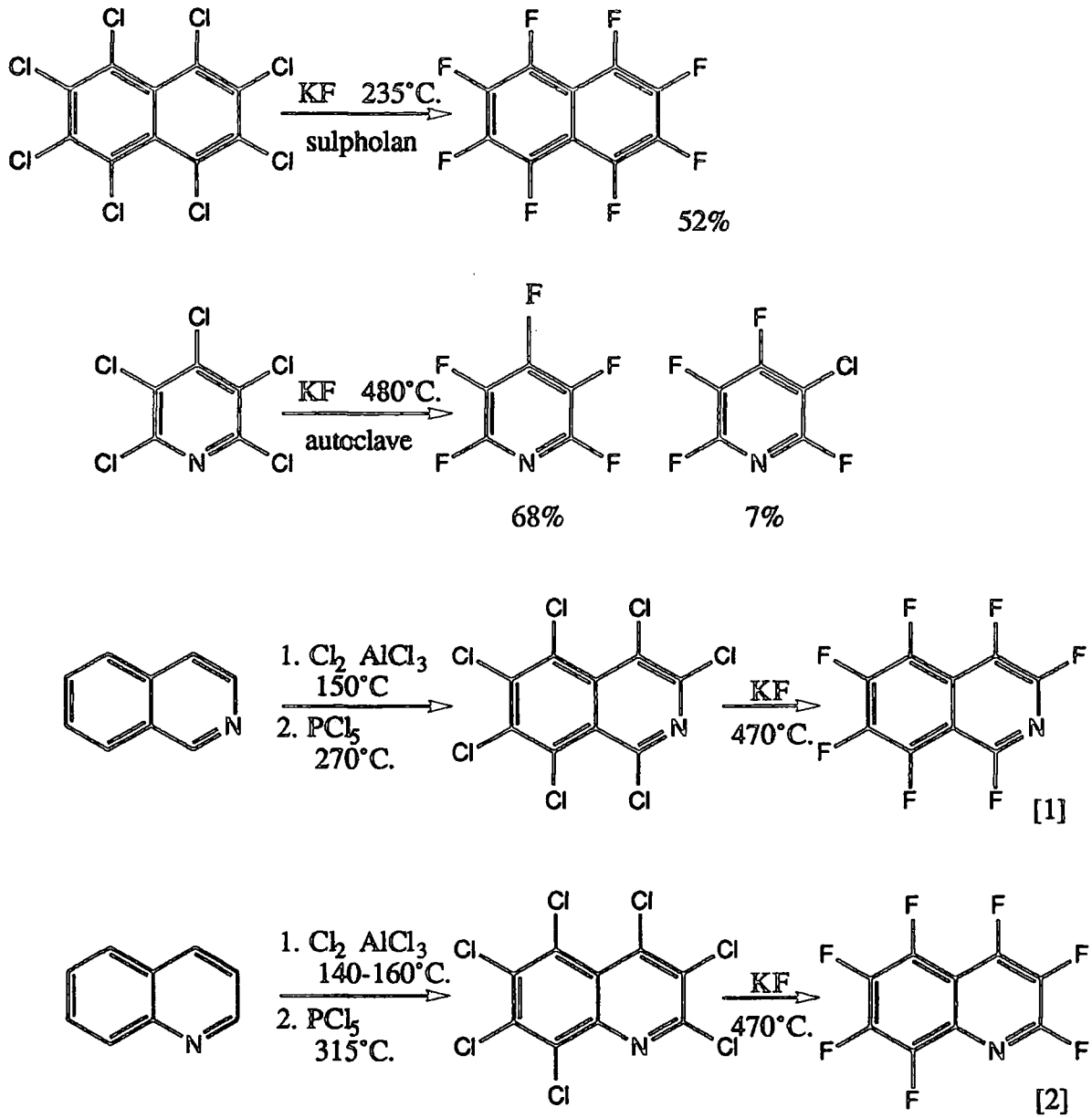
0.4% 25% 24% 30%

Autoclave KF, 450-500°C. C_6F_6 + C_6F_5Cl + $C_6F_4Cl_2$ + 1,3,5-$C_6F_3Cl_3$

21% 20% 14% 12%

Scheme 1.5. *Some reactions of hexachlorobenzene with potassium fluoride.*

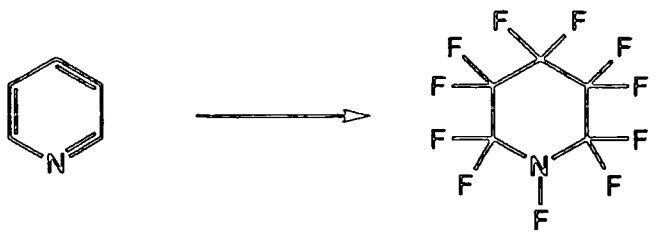
The method can generally be used to prepare perfluoroaromatic and perfluoroheteroaromatic compounds; examples (shown in Scheme 1.6) include octafluoronapthalene, pentafluoropyridine and the subjects of much investigation in this thesis, heptafluoroquinoline [1] and heptafluoroisoquinoline [2][13].



Scheme 1.6. *The preparation of some polyfluoroaromatics by the HALEX procedure.*

1.2.3 Electrochemical Fluorination

Electrochemical Fluorination was discovered by Simons. The organic compound is dissolved in anhydrous hydrogen fluoride and a direct current of 5-6V passed between the two nickel electrodes. Hydrogen is evolved at the cathode and the material is fluorinated at the anode. A low voltage is maintained preventing elemental fluorine from being generated. Electrochemical fluorination allows the retention of certain functional groups or related reactive centres, some examples are shown in Scheme 1.7[3,11].



$(C_2H_5)_3N \longrightarrow (C_2F_5)_3N$

$CH_3COF \longrightarrow CF_3COF \xrightarrow{Hydrolysis} CF_3COOH$

$CH_3SO_2F \longrightarrow CF_3SO_2F$

$C_6H_5NH_2 \longrightarrow C_6F_5NF_2$

Scheme 1.7. *Some examples of electrochemical fluorination.*

1.2.4 Direct Fluorination.

Direct fluorination of a hydrocarbon is proposed to proceed via a radical chain mechanism, the overall change being:-

$$F_2 + RH \longrightarrow RF + HF \quad \Delta G = -435\ KJmol^{-1}$$

and the reaction steps of initiation, propagation and termination are shown in Scheme 1.9.[3]

Initiation

$$F_2 \longrightarrow 2\dot{F}$$

$$F_2 + RH \longrightarrow \dot{R} + HF + \dot{F}$$

Propagation

$$RH + \dot{F} \longrightarrow \dot{R} + HF$$

$$\dot{R} + F_2 \longrightarrow RF + \dot{F}$$

Termination

$$\dot{R} + \dot{F} \longrightarrow RF$$

$$\dot{R} + \dot{R} \longrightarrow R_2$$

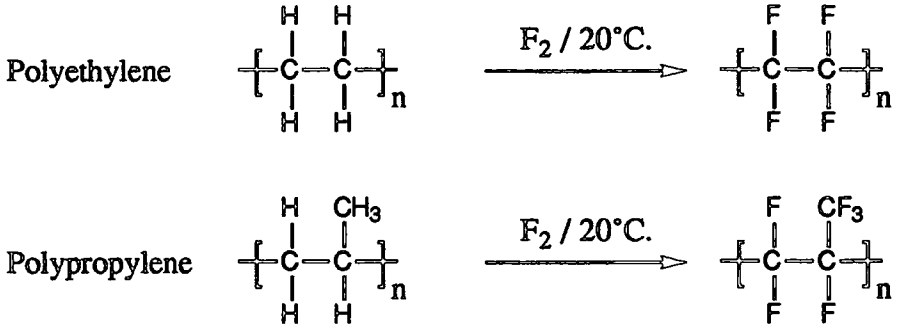
Scheme 1.8. *The reaction pathway of direct fluorination.*

Direct fluorination has to be carefully controlled[14], the large negative free energy can lead to large amounts of generated heat causing scission of carbon to carbon bonds, but more dangerous is the possibility of explosion. For successful direct fluorination, the reaction must be controlled and reaction at adjacent carbon centres avoided on a short timescale to reduce the amount of fragmentation of the carbon backbone. Several methods have been developed for the control of direct fluorination.

1.2.4.1 La-Mar Fluorination

This technique is named after its inventors Lagow and Margrave. The hydrocarbon to be fluorinated is injected into the front compartment of a multizone, tubular cryogenically cooled reactor. The reactor is packed with copper turnings which act as a heatsink and also ensure a thin film of solidified organic material is exposed to the fluorine. The fluorine heavily diluted with nitrogen is passed over the organic material. As time goes on the temperature and the concentration of fluorine are slowly increased. The material becomes more volatile as the reaction proceeds and moves through the reactor[3]. The process has been used with success on several polymers

including polyethylene, polypropylene, polystyrene and polyacrylonitrile, some examples of which are shown in Scheme 1.9.[14]



Scheme 1.9 *Examples of direct fluorination of some polymers.*

1.2.4.2 Porous Tube Fluorination

Successful direct fluorination has been achieved on a laboratory scale in a vapour phase reactor. The reactor comprises of a porous metal tube, closed at one end and mounted inside a stainless steel jacket. Pressurised fluorine usually diluted with SF_6, helium or nitrogen is fed into the porous tube from where it diffuses into the outer tube which contains a flow of vaporised organic material also diluted with carrier gas as required. Hexafluoroacetone has been prepared in this fashion from ordinary hydrocarbon acetone[3].

1.2.4.3 Surface Fluorination of polymers

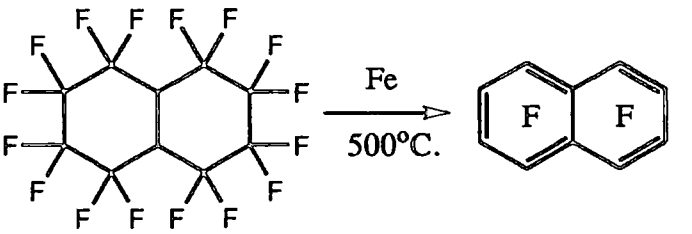
The La-Mar procedure described above allowed hydrocarbon polymers to be converted into their perfluoroderivatives by reaction with elemental fluorine diluted with helium of nitrogen. This however only works for finely ground polymer, since if the polymer is not finely ground the hydrocarbon core is retained. This can however be an advantage for surface treatment of polymers. Thus polyethylene bottles can be surface treated by blowing the bottle with a fluorine/nitrogen mixture (1% fluorine) during the manufacturing process. The plastic bottles are then suitable for holding solvents, cosmetics, paints etc. The same technique can also be used for making plastic fuel tanks for cars, and plastic shipping containers suitable for the transportation of solvents and glues[3].

1.3 Reactions of Organofluoro Compounds.

1.3.1 Perfluoroalkanes

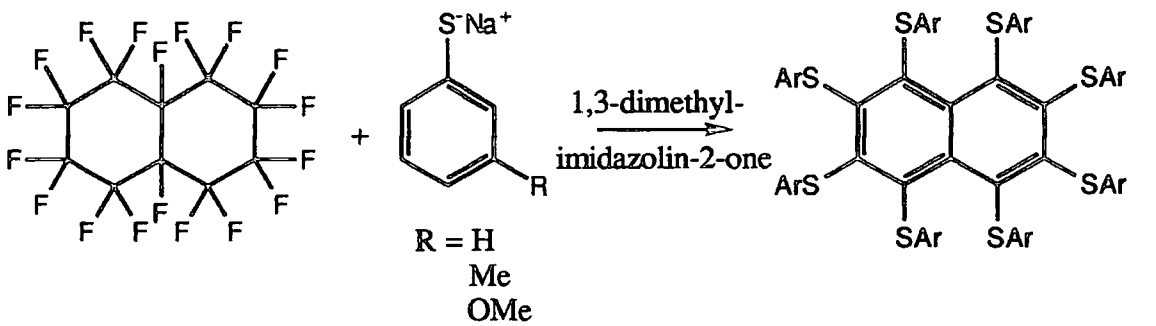
Perfluoroalkanes are generally very unreactive. The carbon framework of a perfluoralkane is shielded by the electron lone pairs of the fluorines and it is thus insulated from attack. The chemistry of perfluoroalkanes is generally limited to relatively high temperature reactions.

Perfluorocycloalkanes can be defluorinated by hot iron or nickel to give the corresponding perfluoroaromatic compound (Scheme 1.10)[15].



Scheme 1.10. *Defluorination of perfluorodecalin to form octafluoronaphthalene*[16].

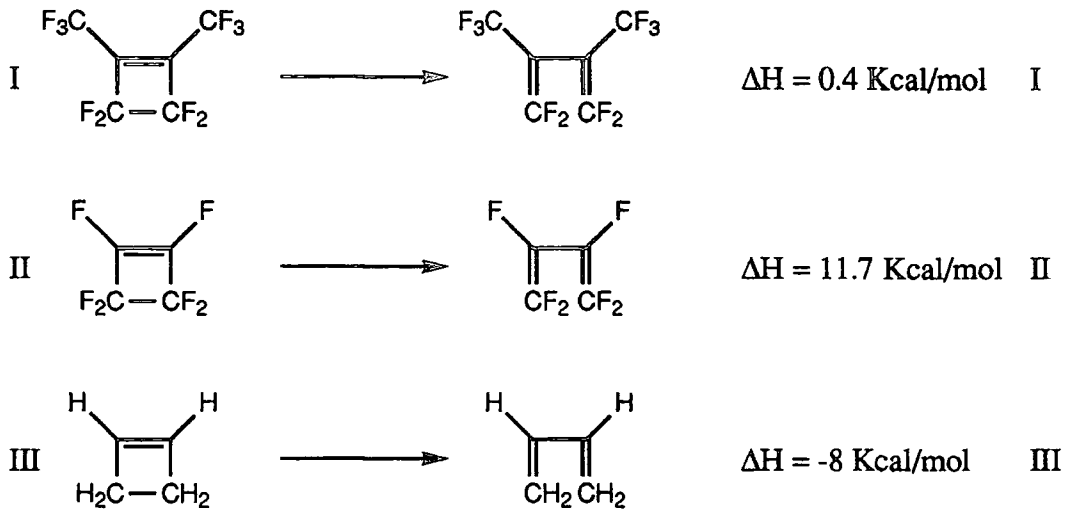
An exception[17] to the high reaction temperatures is the room temperature reaction of some sodium thiophenates with perfluorodecalin (Scheme 1.11) producing octakisphenylthionaphalenes materials of interest as hosts in clathrates[18].



Scheme 1.11. *The reaction of perfluorodecalin with some thiophenates at room temperature*

1.3.2 Polyfluoroalkenes

Fluorine attached to a carbon centre prefers that centre to be saturated (alkanic) as opposed to unsaturated (alkenic). This is reflected when considering the ring opening reactions of 3 cyclobutene derivatives shown in Scheme 1.12.[15]



Scheme 1.12. *The enthalpy of ring opening for three cyclobutene derivatives.*

Reactions II and III in Scheme 1.12 clearly show that the perfluorinated derivative has lower energy when cyclised, but the opposite is true for the hydrocarbon system. In considering I and II, the only difference is that perfluoroalkyl groups are attached to the unsaturated carbon in I, whereas in II fluorine is attached to the unsaturated carbon. This gives a direct indication of the effect of fluorine attached to unsaturated carbon. Quite clearly the fluorine attached to the unsaturated carbon is destabilising. This destabilising effect, known as I_π repulsion, is a consequence of the interaction of the π system with the fluorine lone pairs as shown in Figure 1.1.[15]

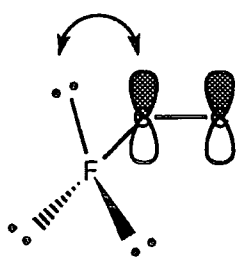
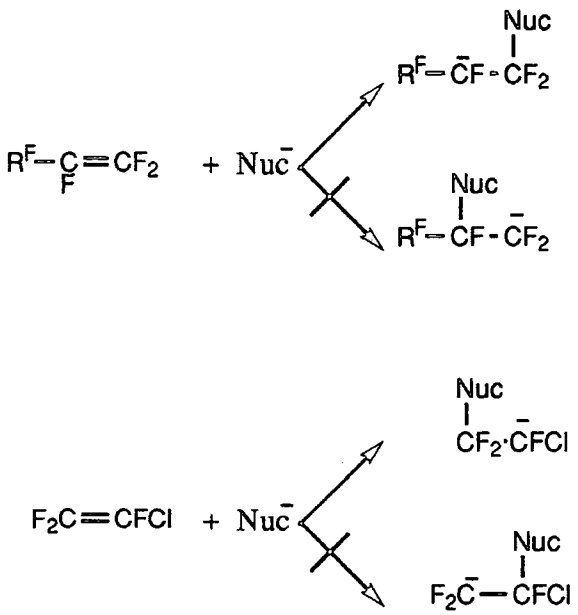


Figure 1.1. *I_π repulsion of fluorine lone pairs and π system.*

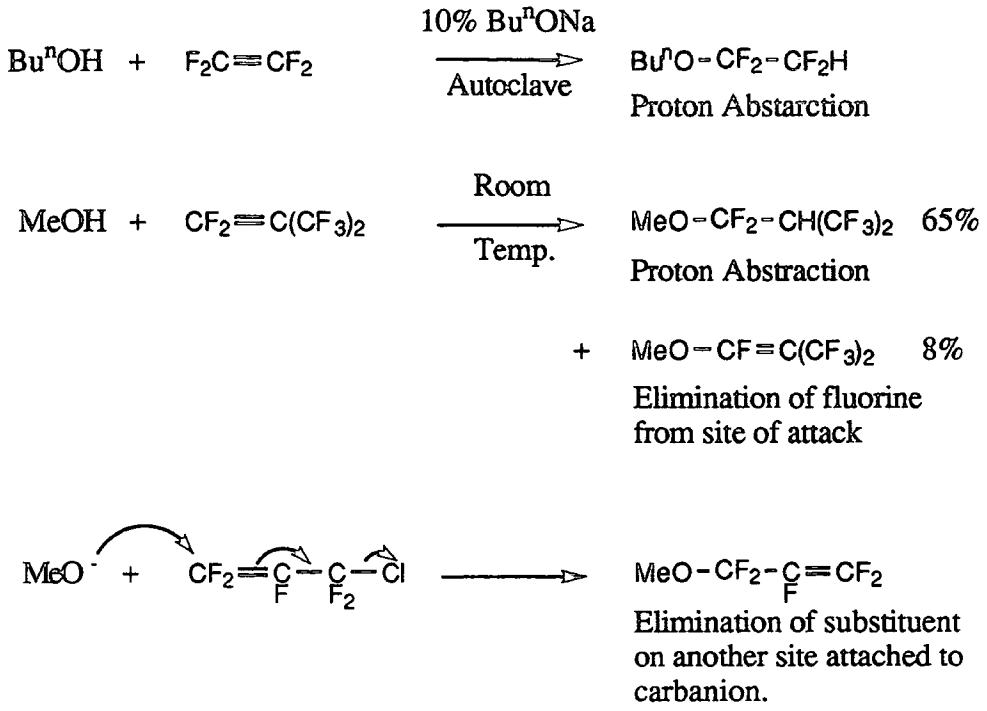
1.3.2.1 Nucleophilic attack on Fluorinated Alkenes.

Fluorinated alkenes are generally susceptible to attack by nucleophiles, attack occuring at the site that will lead to the most stabilised carbanion (Scheme 1.13). i.e the carbanion which has the least number of attached fluorines and the largest number of perfluoroalkyl groups. Chlorine attached to the carbanion unlike fluorine is however stabilising.



Scheme 1.13. *The reaction of some polyfluoroalkenes with nucleophiles.*

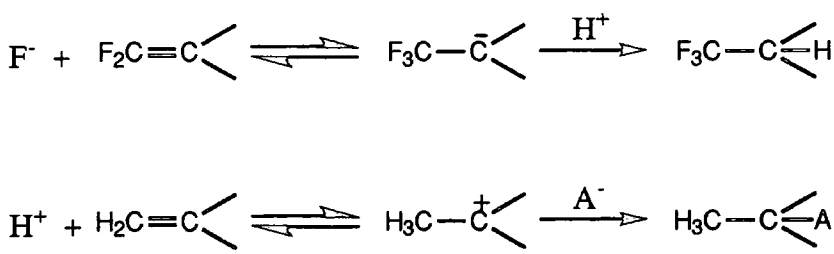
The resultant carbanion can then react to give several products as shown in Scheme 1.14. The carbanion could abstract a proton from the solvent, or a substituent could be ejected from an adjacent site, either from the same carbon as that at which attack occured, or at another carbon attached to the carbanion to give a rearrangement[15].



Scheme 1.14. *Possible courses of reaction of a carbanion in a fluorinated system.*

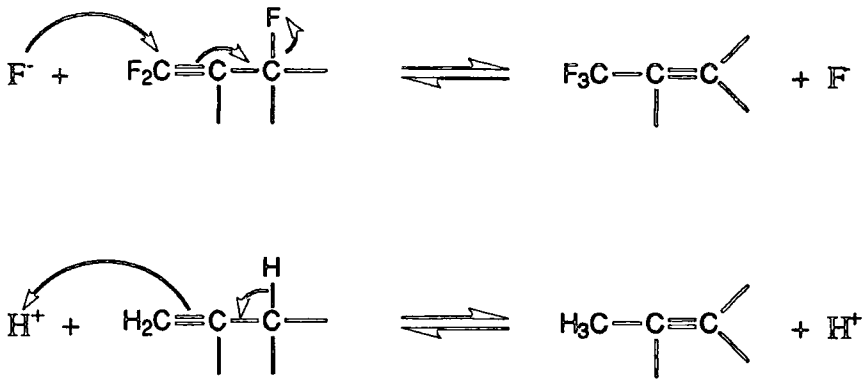
1.3.2.2 Fluoride Ion Induced Reactions

A carbanion can be generated by the nucleophilic action of a fluoride ion on the alkene. This is the organofluorine equivalent to the action of a proton on unsaturated hydrocarbon (Scheme 1.15).



Scheme 1.15. *Addition of fluoride ion and proton to respective alkenic systems.*

Analogous rearrangements can similarly occur as shown in Scheme 1.16.



Scheme 1.16. *Analogous fluoride ion and proton rearrangements in respective systems.*

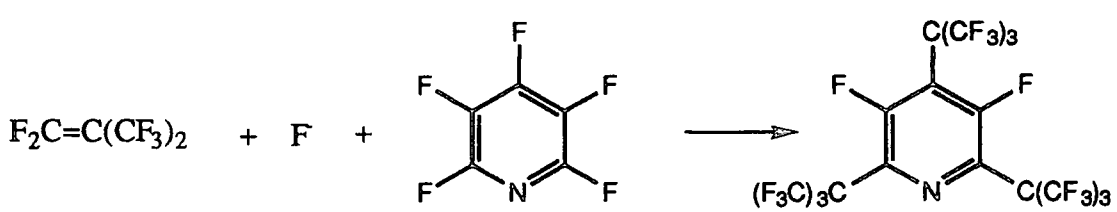
Fluoride ion exchange has been investigated with isotopically labelled fluoride ion, which becomes incorporated into the fluoro-alkene by the carbanion mechanism taking place. i.e $^{18}F^-$ adds to the alkene to form the carbanion and then a fluoride ion either $^{18}F^-$ or $^{19}F^-$ is eliminated to revert to the alkene. The overall reaction with a large excess of RbF^{18} is shown in Scheme 1.17[15].

$$F_2C{=}CFCF_3 \;+\; Rb^{18}F \rightleftharpoons C_3{}^{18}F_6 \;+\; RbF$$

Scheme 1.17. *Incorporation of ^{18}F into a perfluoroalkene.*

Alternatively the resultant carbanion from fluoride ion attack can be trapped by means of another reagent as shown in Scheme 1.18.

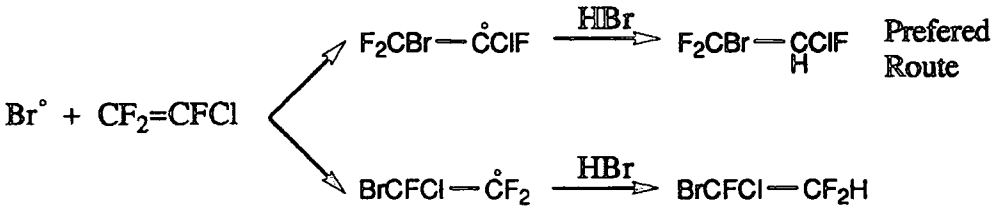
$$F_2C{=}CFCF_3 \;+\; F^- \underset{\text{acetonitrile}}{\rightleftharpoons} (CF_3)_2\bar{C}F \xrightarrow{I_2} (CF_3)_2CFI$$



Scheme 1.18. *The trapping of a carbanion by means of another reagent.*

1.3.2.3 Free Radical reactions of Polyfluorinated Alkenes.

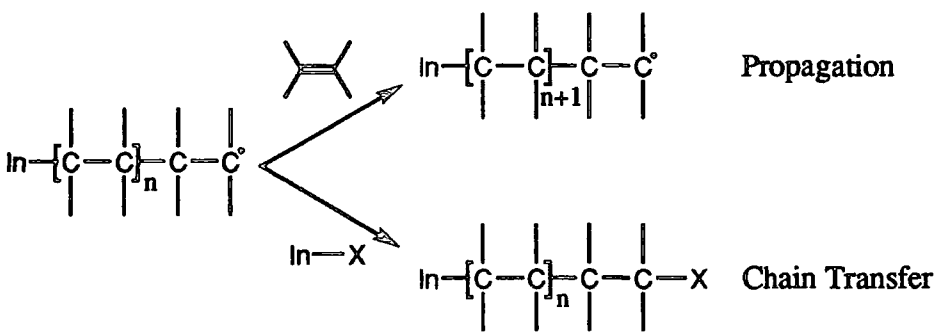
Free radical attack can occur with fluoro-alkenes[15]. The single unpaired electron generally sites itself on the carbon with the most substituents, in order of preference: chlorine, fluorine and hydrogen. Thus in the reaction of HBr with CF_2CFCl shown in Scheme 1.19 the single unpaired electron sites itself on the CFCl group as opposed to the CF_2 group.



Scheme 1.19. *The two possible routes of radical attack on chlorotrifluoroethene.*

Polymerisation and Telomerisation.

Polymers and telomers can form if propagation is allowed to ensue and chain transfer is minimised (Scheme 1.20)[15].



Scheme 1.20. *Propagation and Chain Transfer steps during the process of polymerisation.*

Propagation to give telomers occurs if the bond in the chain transfer agent is strong, thus reducing chain transfer, or if a higher concentration of alkene to chain transfer agent is used; (see Figure 1.2).

Figure 1.2. *Effect on composition of Telomer with a) Strong bond in chain transfer agent. b) Weaker bond in chain transfer agent and c) higher ratio of monomer to chain transfer agent.*

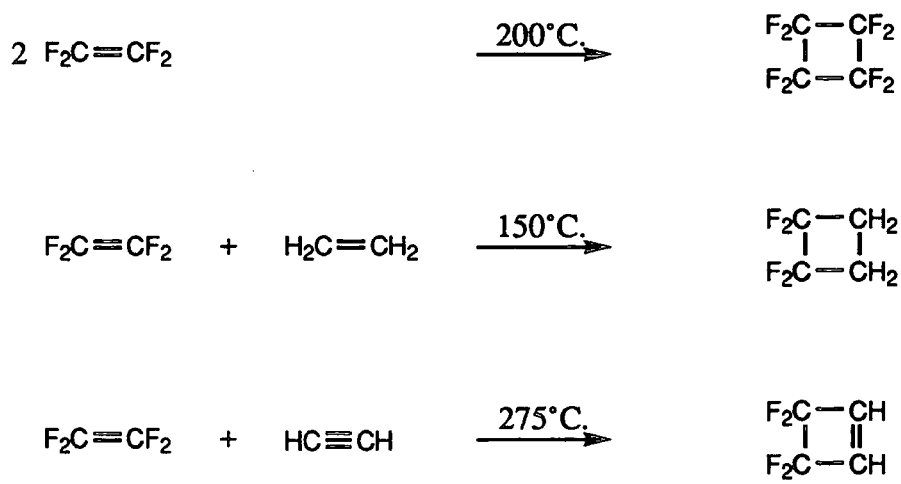
		Composition of $R_f(CH_2CF_2)_nI$					
		n = 1,	2,	3,	4,	5,	6,
	$CF_3I : CH_2CF_2$						
a)	1:1	46	33	14	5	1	
	$(CF_3)_2CFI : CH_2CF_2$						
b)	1:1	87	13	trace			
c)	1:4	2	21	29	26	18	4

Polymerisation as well as telomerisation can also occur to give useful products. Suitable monomers are C_2F_4, CF_2CFH, CF_2CH_2, CF_2CFCl and CF_2CFBr but more forcing conditions are required for $CF_2{=}CFCF_3$.

1.3.2.4 Cycloaddition Reactions of perfluoro alkenes.

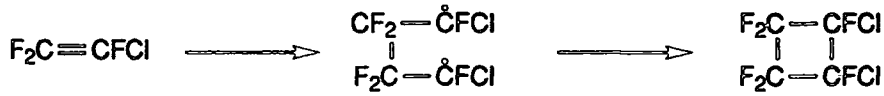
a) $2\pi + 2\pi$

Tetrafluoroethene dimerises to form octafluorocyclobutane, a reaction which does not occur with hydrocarbon ethene. Fluoro-alkenes readily form four membered rings not only by co-dimerisation but also by reaction with other alkenes and unsaturated hydrocarbons. Some examples are shown in Scheme 1.21.



Scheme 1.21. *Examples of $2\pi + 2\pi$ cycloaddition reactions.*

A stepwise radical mechanism as shown in Scheme 1.22 is proposed as opposed to a concerted process which is symmetry forbidden for thermal processes[15].

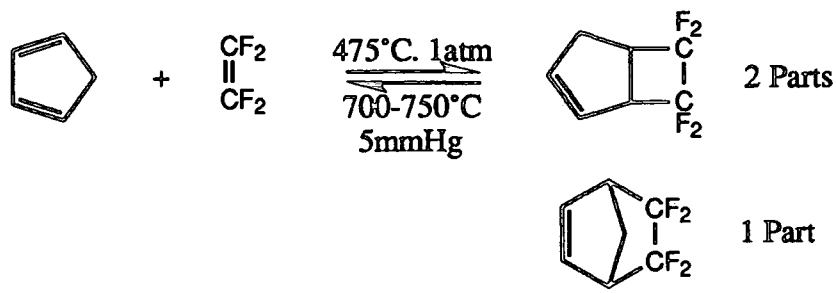


Most stable di-radical

Scheme 1.22. *Stepwise radical dimerisation of chlorotrifluoroethene.*

b) 4π + 2π (Diels Alder)

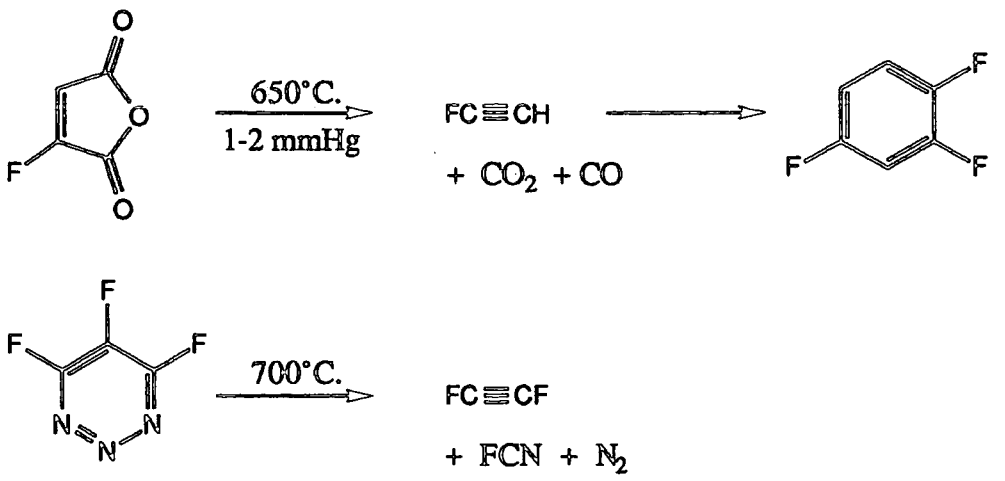
When a diene is used as one component two cycloaddition reactions are possible, 2π + 2π and 4π + 2π. In many cases the 2π + 2π cycloaddition occurs; however sometimes a significant proportion of the product is from the 4π + 2π reaction. An example of where 2π + 2π and 4π + 2π compete is shown in Scheme 1.23[15].



Scheme 1.23. *Competing 4π + 2π and 2π + 2π mechanisms.*

1.3.3 Fluoroalkynes

The pyrolysis of monofluoromaleic anhydride yields monofluoroacetylene[15], a material which is dangerously explosive. Difluoroacetylene[19] has been recently prepared free from impurities from perfluoro-1,2,3-triazine. Both preparations are shown in Scheme 1.24.



Scheme 1.24. *Preparation on monofluoro- and difluoro-acetylene.*

Fluoroacetylenes are high in energy due to the repulsive interaction of the two sets of π electrons with the electron pairs on fluorine as shown in Figure 1.3.

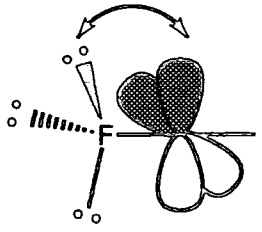
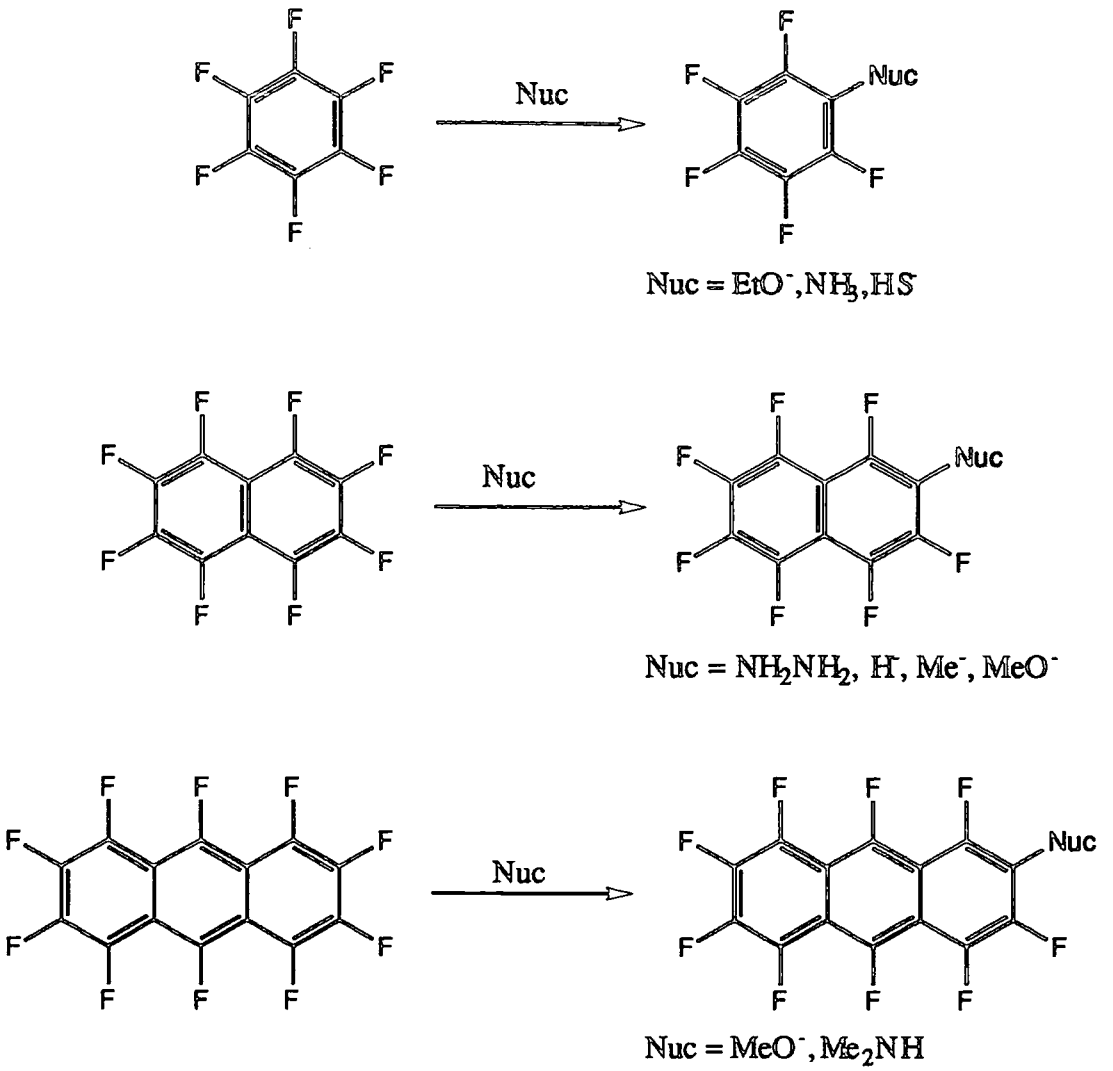


Figure 1.3. *Electron pair replusion of fluorine lone pairs with the two π systems.*

1.3.4 Polyfluoroaromatic Compounds.

1.3.4.1 Nucleophilic Aromatic Substitution in Polyfluoroaromatics.

Polyfluoroaromatic systems readily undergo nucleophilic substitution, examples of many substrates with a wide variety of nucleophiles exist[12]. Some examples are shown here in Scheme 1.25 and the rationalisation of the site of attack in polyfluoroaromatics will be discussed later in detail.

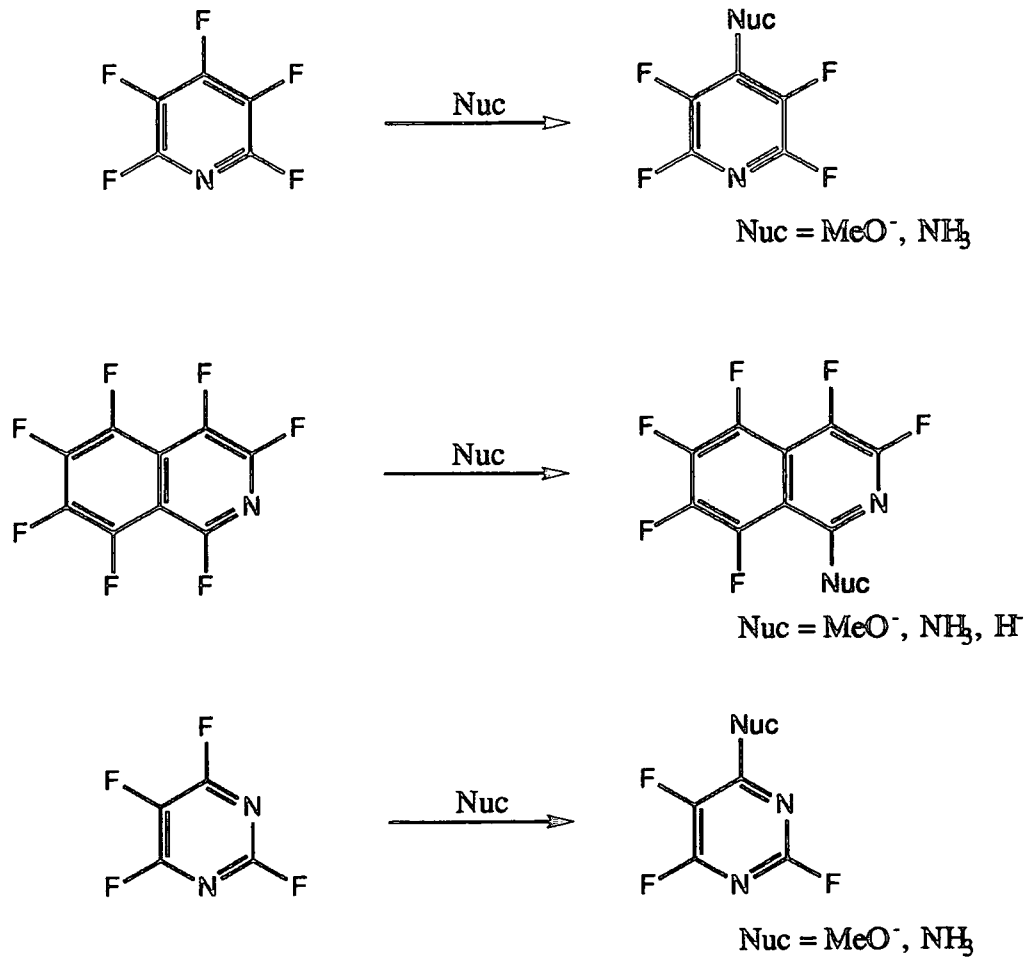


Scheme 1.25. *The reaction of some polyfluoroaromatic compounds with nucleophiles*[35-39].

1.3.4.2 Nucleophilic Aromatic Substitution in Nitrogen containing polyfluoro-heteroaromatics.

Nitrogen containing heterocyclic fluoroaromatics undergo substitution much more readily than their fluorocarbon analogues. For example, pentafluoropyridine undergoes nucleophilic substitution far more readily than hexafluorobenzene. Substitution usually occurs at the carbon para to the nitrogen if this bears fluorine or if not, attack occurs ortho to the ring nitrogen[12]. Some examples of nucleophilic substitution in fluorinated aza aromatics are shown in Scheme 1.26; It should be noted that in the second example there is no fluorine on the position para to ring nitrogen and the nucleophile attacks the ortho

site. The rationalisation of the site of attack in polyfluoro-aza-aromatics will be discussed in detail later.



Scheme 1.26. *Nucleophilic Substitution in some polyfluoro-aza-aromatics*[25-27].

Chapter 2

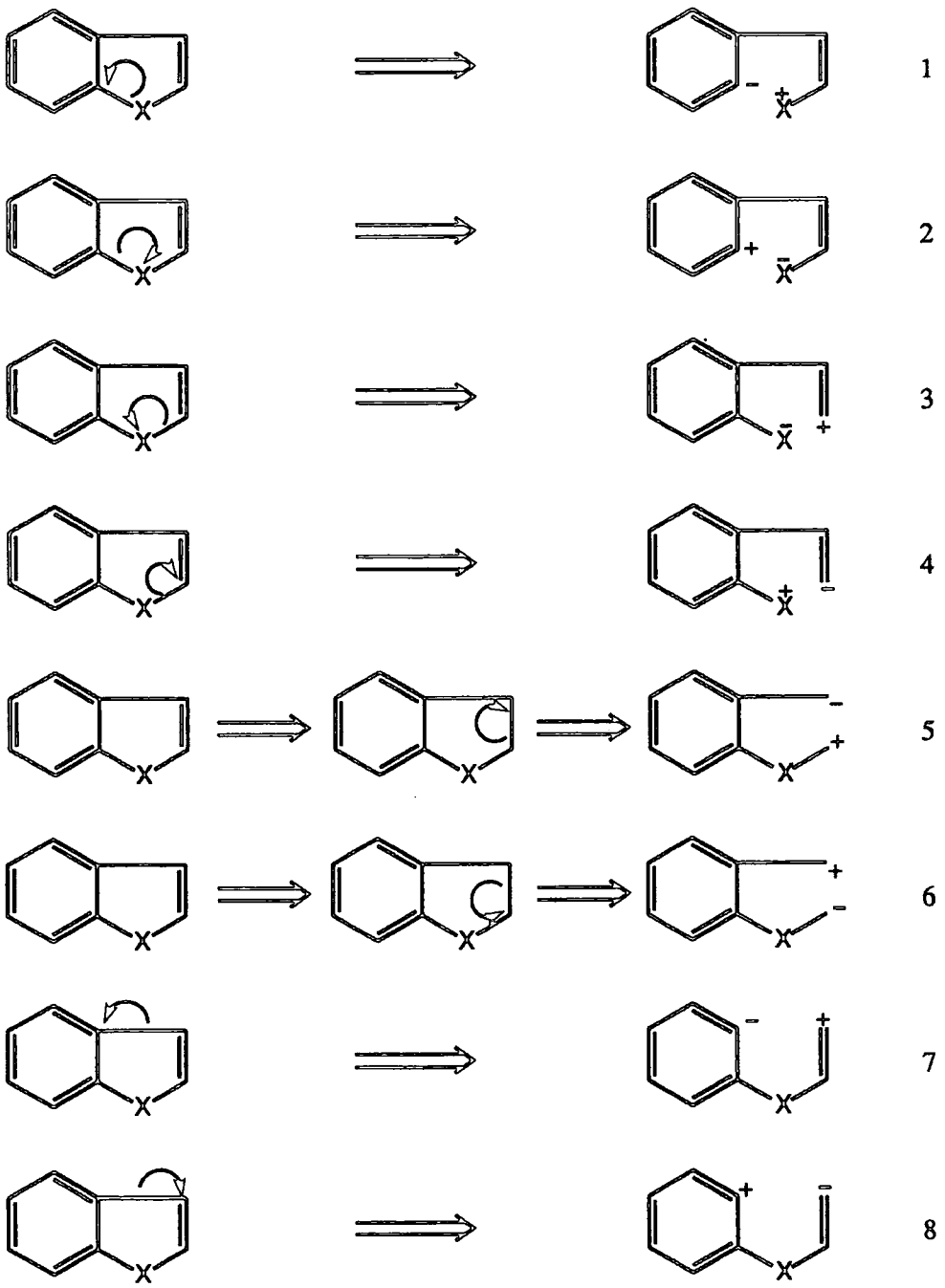
The Reactions of Polyfluoro- Isoquinoline and Quinoline-Thiolates with Dimethyl Acetylenedicarboxylate.

Chapter 2

The Reactions of Polyfluoro- Isoquinoline and Quinoline -Thiolates with Dimethyl Acetylenedicarboxylate.

2.1 Background

The synthesis of fused five memebered heterocyclic rings attached to a fluorinated aromatic framework are of interest as counterparts to their hydrocarbon analogues. Disconnection of benzo[b]thiophene reveals the possibilities for synthesis of these materials (Scheme 2.1. [X=S]).

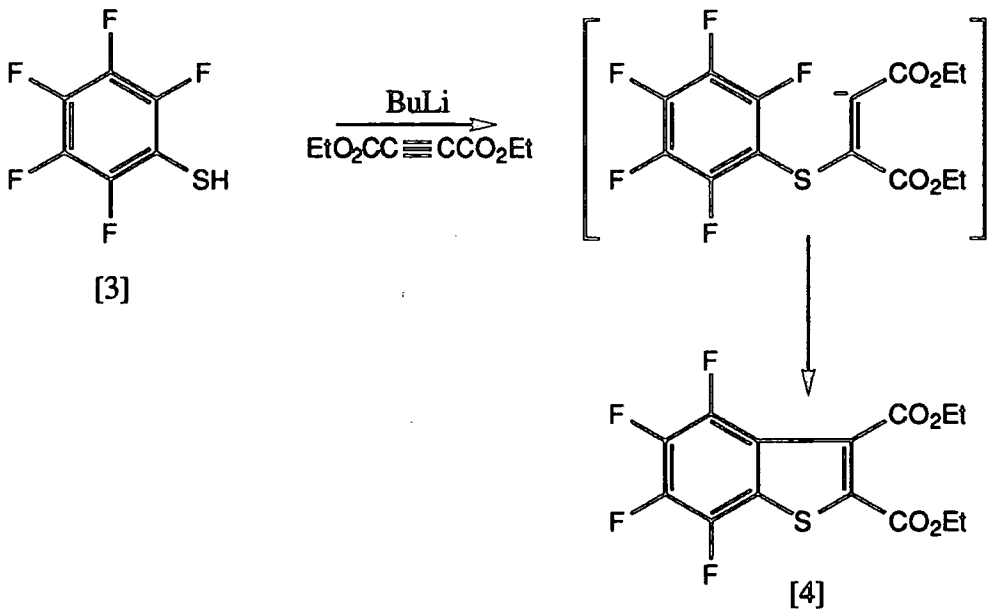


Scheme 2.1. *Disconnection analysis on a five membered heterocyclic system.*

Routes 2 and 8 in Scheme 2.1 require nucleophilic attack of the aromatic ring to form the cyclised product. These cyclisations can only take place with substrates where nucleophilic attack can occur, e.g fluoroaromatic compounds.

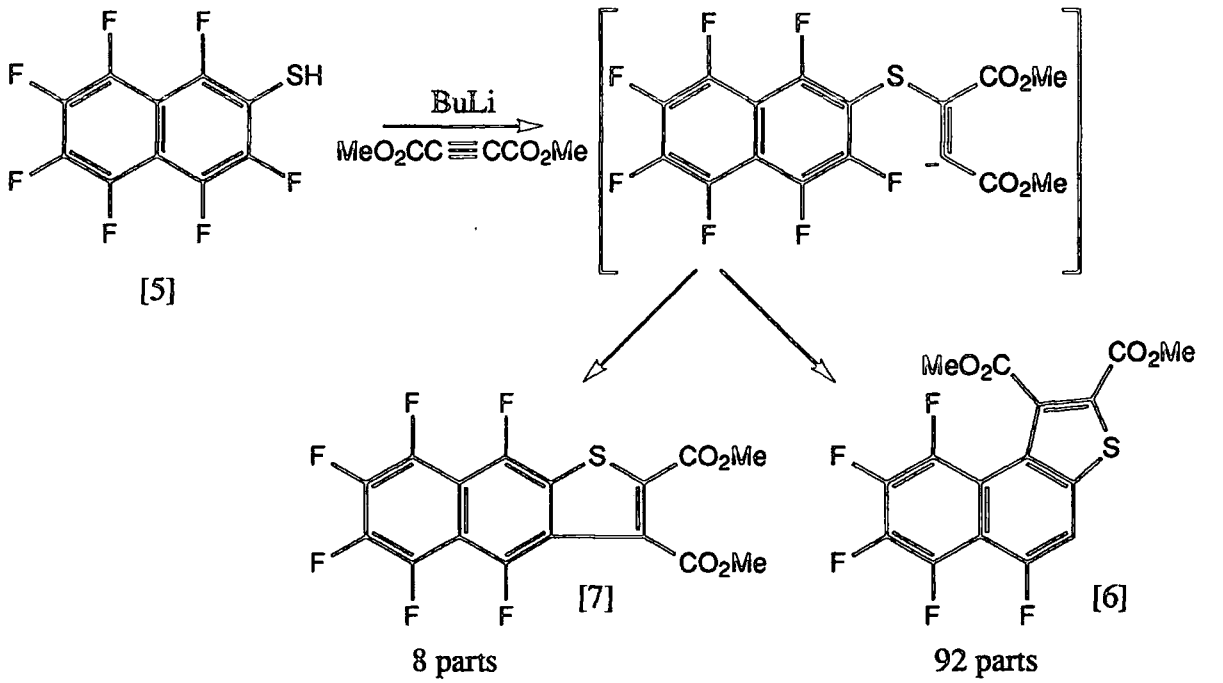
2.1.1 Cyclisation Reactions leading to Thiophenes

The first example of Type 8 cyclisation was performed when pentafluorothiophenol [3] was treated with butyllithium and diethyl acetylenedicarboxylate (DEAD)[28]. The overall reaction is shown in Scheme 2.2. The product was the 4,5,6,7-tetrafluoro-benzo[b]thiophene derivative [4].



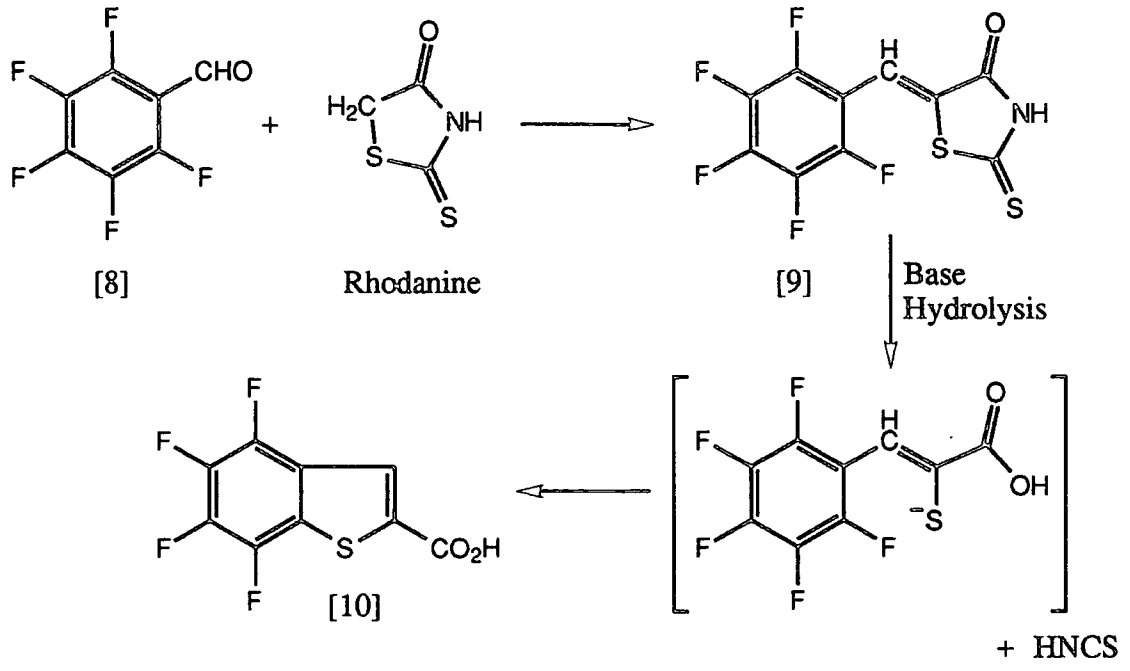
Scheme 2.2. *The first synthesis of a 4,5,6,7-tetrafluorobenzo[b]thiophene.*

The reaction was later extended to the 2-naphthalenethiol [5][29], where an interesting orientation problem arises since cyclisation of the lithium salt of [5] with dimethyl acetylenedicarboxylate can take place in two directions, with replacement of either the 1-F or the 3-F to form compounds [6] and [7] respectively as shown in Scheme 2.3. The 1-F was replaced preferentially (92 parts) over the 3-F (8 parts) indicating that attack at the 1- position had the lower localisation energy.



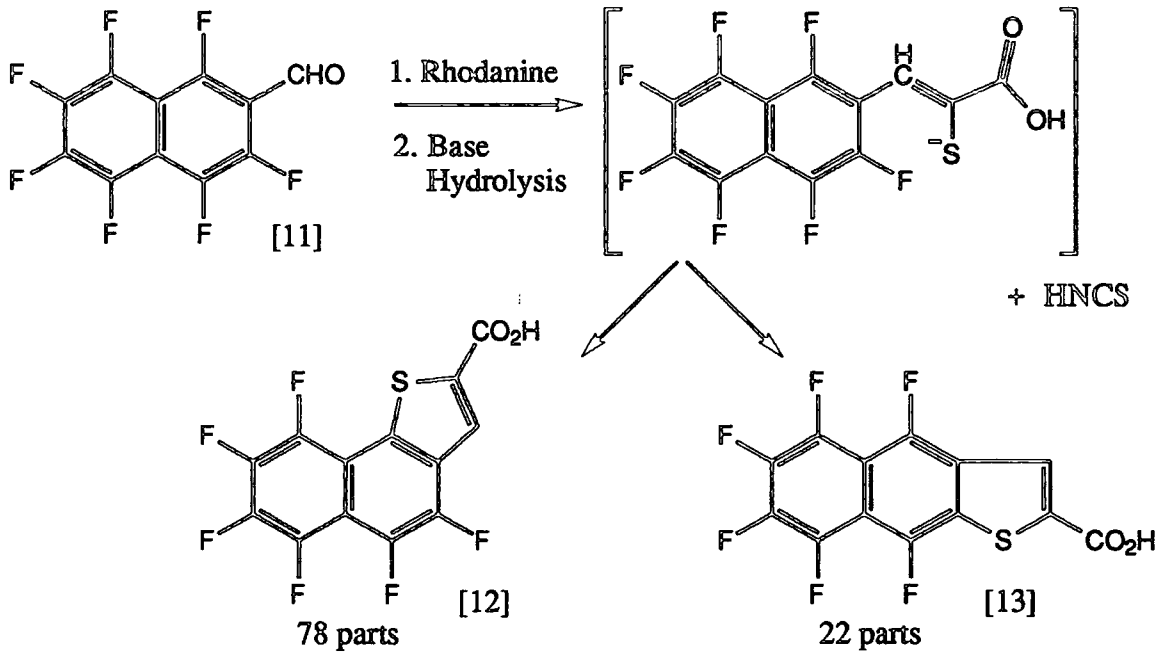
Scheme 2.3. *Extension of the original benzo[b]thiophene synthesis to include the naphthalene system.*

Shortly after the publication of the original work on the diethyl acetylenedicarboxylate cyclisation, came a second process from workers at Birmingham[30] which also yielded a benzo[b]thiophene. This process also proceeded via intramolecular nucleophilic attack to complete cyclisation, but differed from the DEAD cyclisation since it was the heteroatom which performed the nucleophilic attack, (Type 2 reaction in Scheme 2.1). Rhodanine was condensed with pentafluorobenzaldehyde [8], forming a benzylidine derivative [9], which upon base hydrolysis underwent nucleophilic intramolecular cyclisation to form the 4,5,6,7-tetrafluorobenzo[b]thiophene derivative [10]. The whole synthetic route is shown in Scheme 2.4.



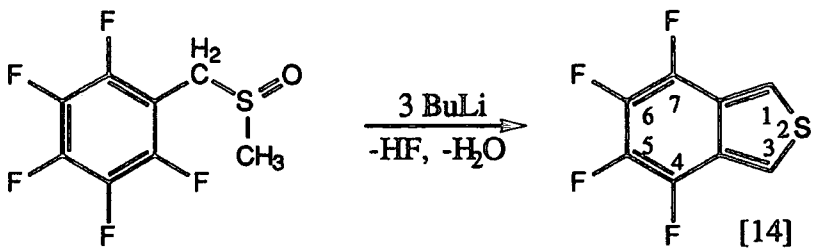
Scheme 2.4. *A second synthesis of a 4,5,6,7-benzo[b]thiophene derivative.*

This reaction was also extended by Brooke[31] to the naphthalene system, since again an interesting orientation problem arises, (see Scheme 2.5). When 1,3,4,5,6,7,8-heptafluoronaphthalene-2-carbaldehyde [11] was reacted with rhodanine and then with base, the products formed were the angular thiophene [12] (78 parts) and the linear thiophene [13] (22 parts) which were formed by displacement of the 1-F and the 3-F respectively.



Scheme 2.5. *The 'Birmingham Rhodanine' benzo[b]thiophene synthesis applied to the naphthalene system.*

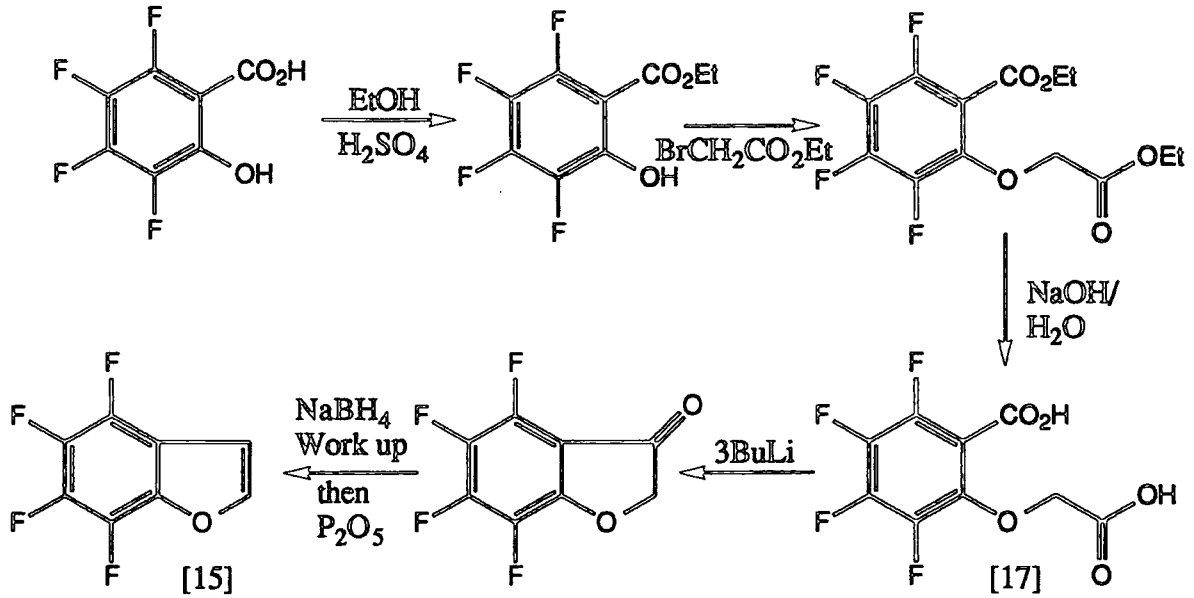
More recent work, shown in Scheme 2.6, has provided a convenient route to 4,5,6,7-tetrafluoro-benzo[c]thiophene [14][32]. This route also utilises intramolecular nucleophilic substitution of Type 8; to form a fused heterocycle, however it should be noted that the heteroatom is at position 2 rather than position 1.



Scheme 2.6. *The synthesis of 4,5,6,7-tetrafluorobenzo[c]thiophene [14].*

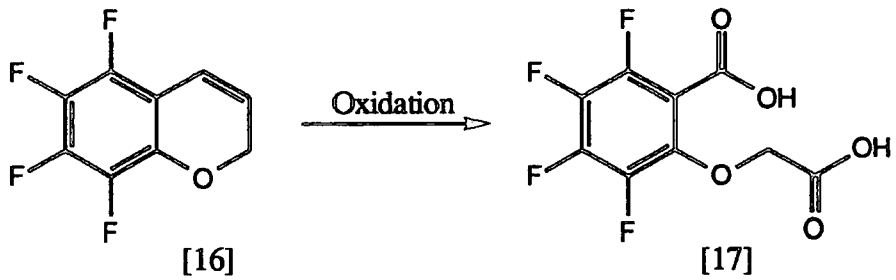
2.1.2 Cyclisation Reactions leading to Furans.

The formation of polyfluorinated compounds containing cyclised furans have also been studied. A conventional cyclisation of Type 6 in Scheme 2.1, as shown in Scheme 2.7, ultimately yielded 4,5,6,7-tetrafluorobenzo[b]furan [15][33].



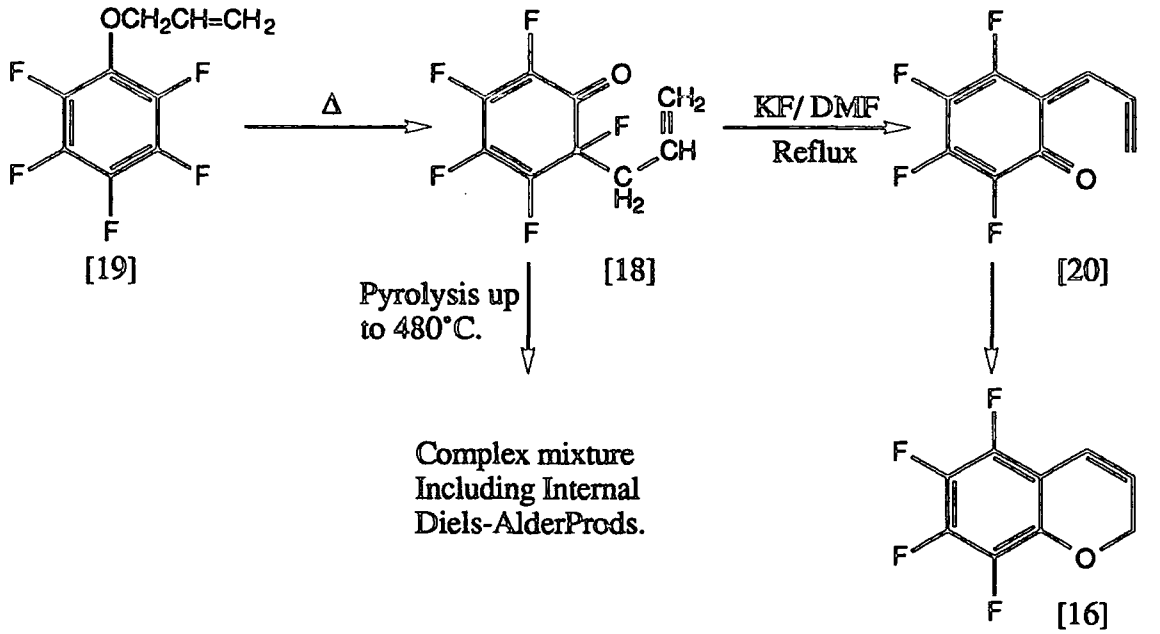
Scheme 2.7. *Conventional route to 4,5,6,7-tetrafluorobenzo[b]furan [15].*

A simpler route to the precursor to 4,5,6,7-tetrafluorobenzo[b]furan was envisaged[34] by oxidation of 5,6,7,8-tetrafluorochromen [16] to the di-carboxylic acid [17] (Scheme 2.8). The di-carboxylic acid [17] could then be taken through to the benzo[b]furan [15] as shown in the last two steps of Scheme 2.7.



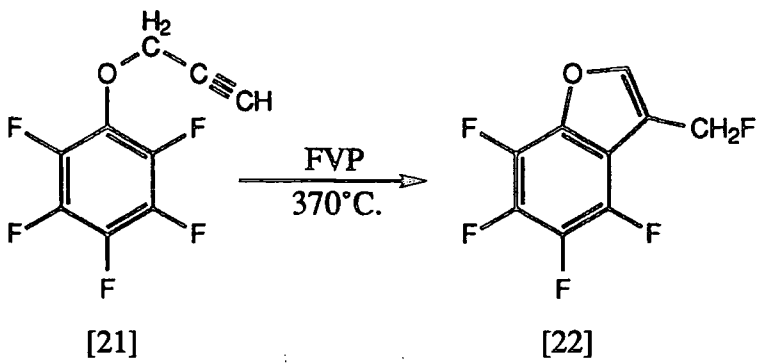
Scheme 2.8. *Proposed oxidation of the tetrafluorochromen [16] to the di-acid [17].*

The pyrolytic defluorination of the Claisen rearrangement product [18] readily prepared from pentafluorophenyl prop-2-enyl ether [19] was a potential route to the diene [20], which upon electrocyclic rearrangement would form the chromen [16] (Scheme 2.9). However, pyrolysis of [18] failed to eliminate HF even at 480°C, but later work did produce the chromen [16] when the pentafluorophenyl prop-2-enyl ether [19] was treated with potassium fluoride in dimethylformamide at reflux temperature (Scheme 2.9).



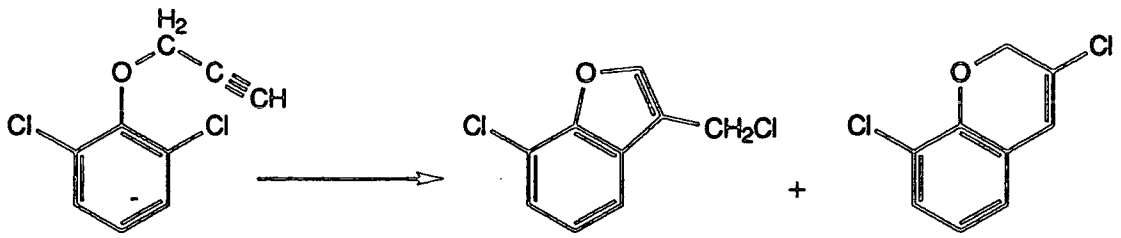
Scheme 2.9.

As an extension to the above work, the polyfluoroaryl prop-2-ynyl ethers were investigated[35]. Pyrolysis of the pentafluorophenyl compound [21] at 370°C through a silica tube containing quartz wool gave a tarry product which contained, as the major component, 2-fluoromethyl-4,5,6,7-tetrafluorobenzo[b]furan [22] (Scheme 2.10).



Scheme 2.10. *Flash Vacuum Pyrolysis (FVP) of pentafluorophenyl prop-2-ynyl ether [21].*

Previously Schmid et al[36]. had carried out the reaction with 2,6-dichlorophenyl prop-2-ynyl ether [23], (see Scheme 2.11), and obtained as the main products, 7-chloro-2-chloromethylbenzo[b]furan [24] and 3,8-dichloro-2H-1-benzopyran [25].

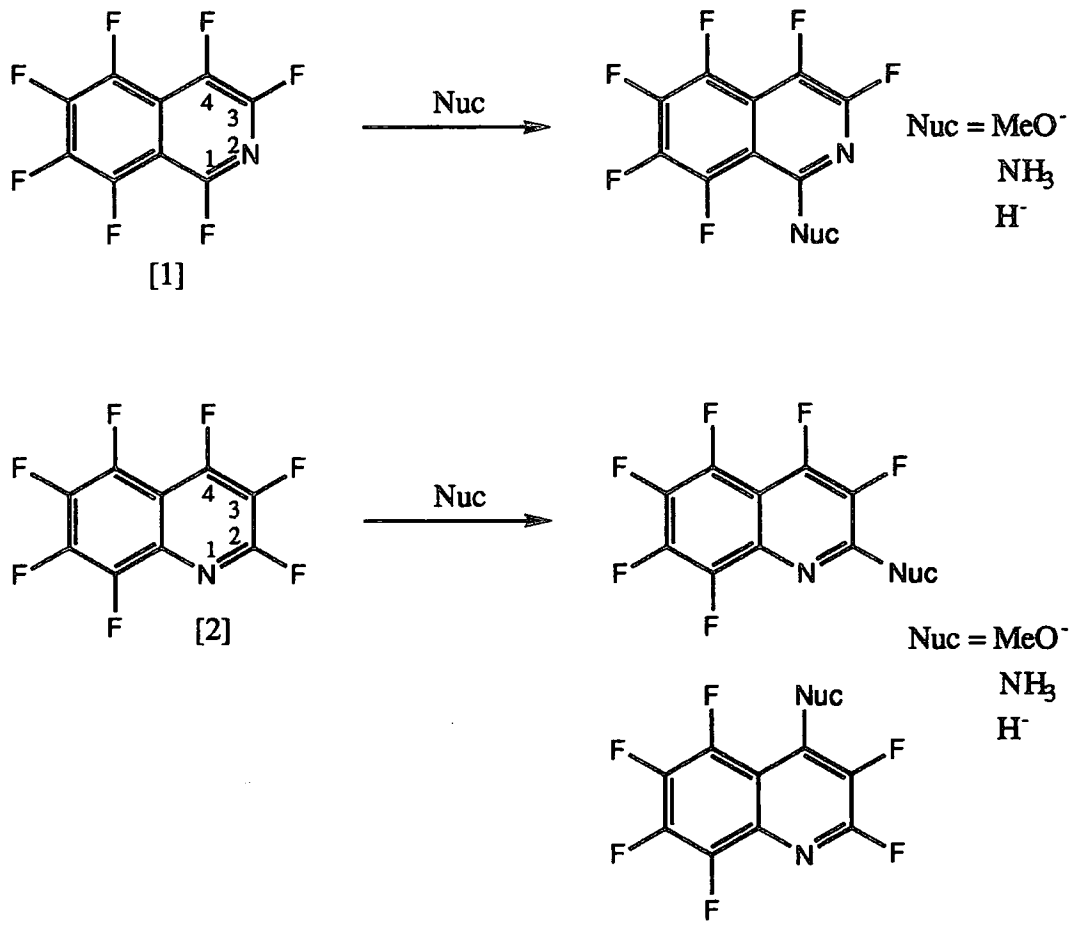


[23] [24] [25]

Scheme 2.11.

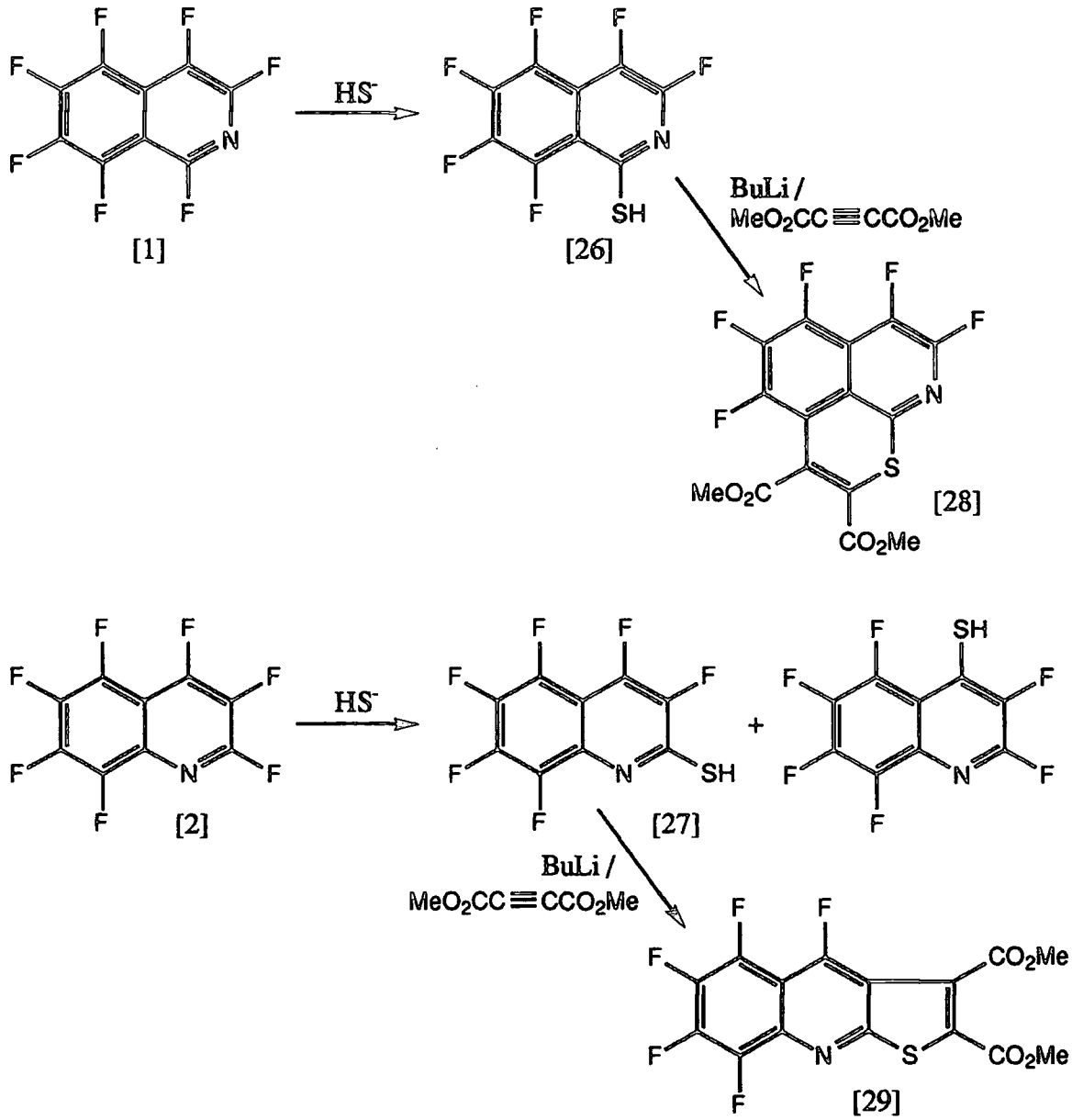
2.2 Recent Work

It was of interest to try and synthesise a six membered fused heterocycle and a linear fused heterocycle unambiguosly. Nucleophilic substitution reactions with heptafluoroisoquinoline [1] had shown mono-substitution to take place at the 1-position[26]. Similar reactions with heptafluoroquinoline [2] gave substitution at the 2- and 4- positions (scheme 2.12)[26].



Scheme 2.12. *Nucleophilic substitution reactions of heptafluoro-isoquinoline [1] and -quinoline [2].*

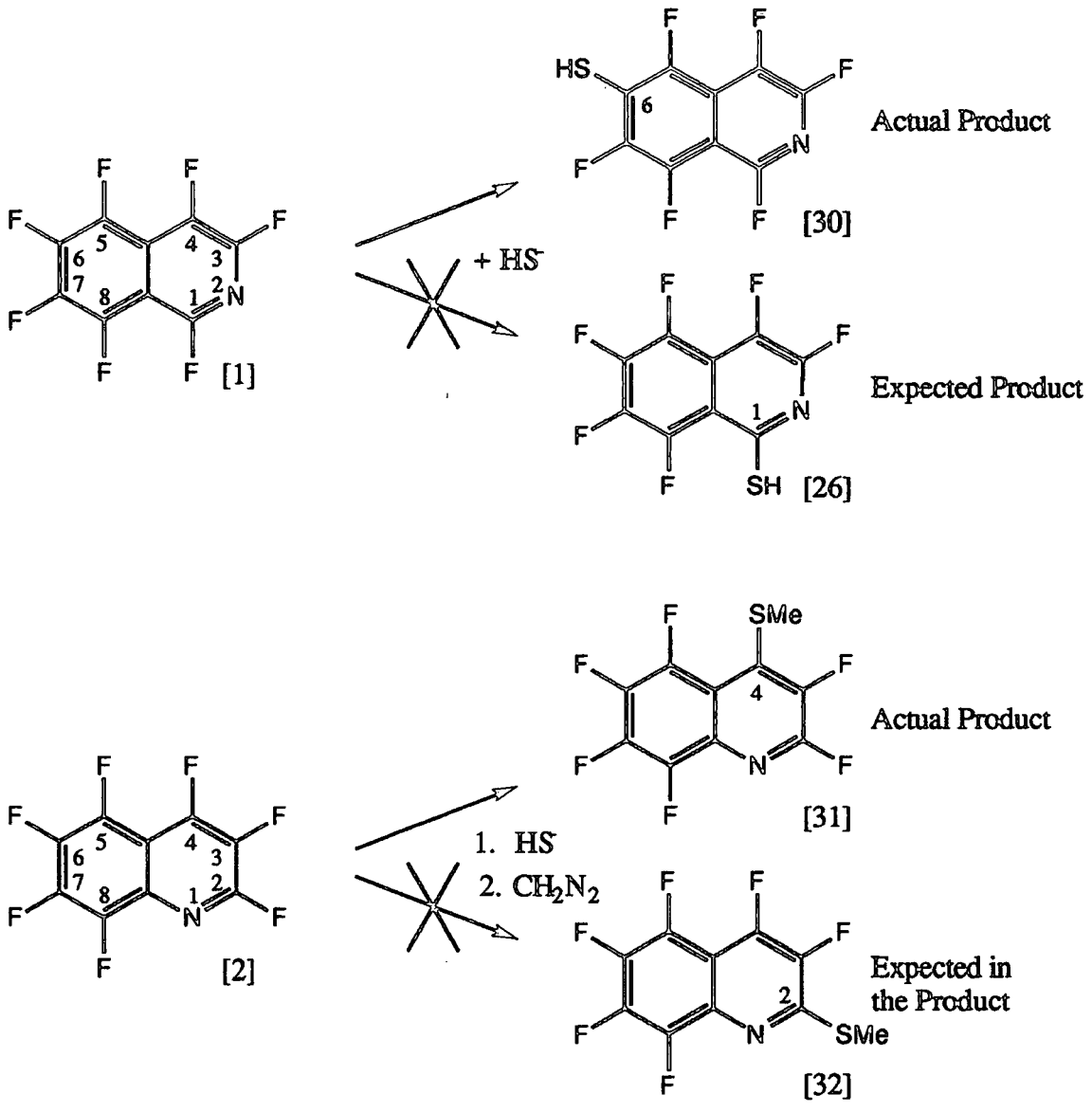
The thiol derivatives of two of these substrates [26] and [27] were considered to be the ideal candidates for trying to make a six membered heterocycle [28], and a five membered linear heterocycle [29] since the respective cyclisations, shown in Scheme 2.13, could only take place in one direction.



Scheme 2.13. *Proposed synthesis of a six membered sulphur heterocycle and an unambiguous linear five membered sulphur heterocycle.*

When heptafluoroisoquinoline [1] reacted with sodium hydrosulphide the 6-thiol [30] was surprisingly, the exclusive product. The equivalent reaction with heptafluoroquinoline [2] followed by methylation with diazomethane, (the unmethylated thiol was initially found to be unstable in the work up procedure), suprisingly gave the 4-

methylthioquinoline [31][37]. Quite clearly from the preceeding work the 1-isoquinolinethiol [26] and the 2-methylthioquinoline [32] had been expected. Both reactions are shown in Scheme 2.14

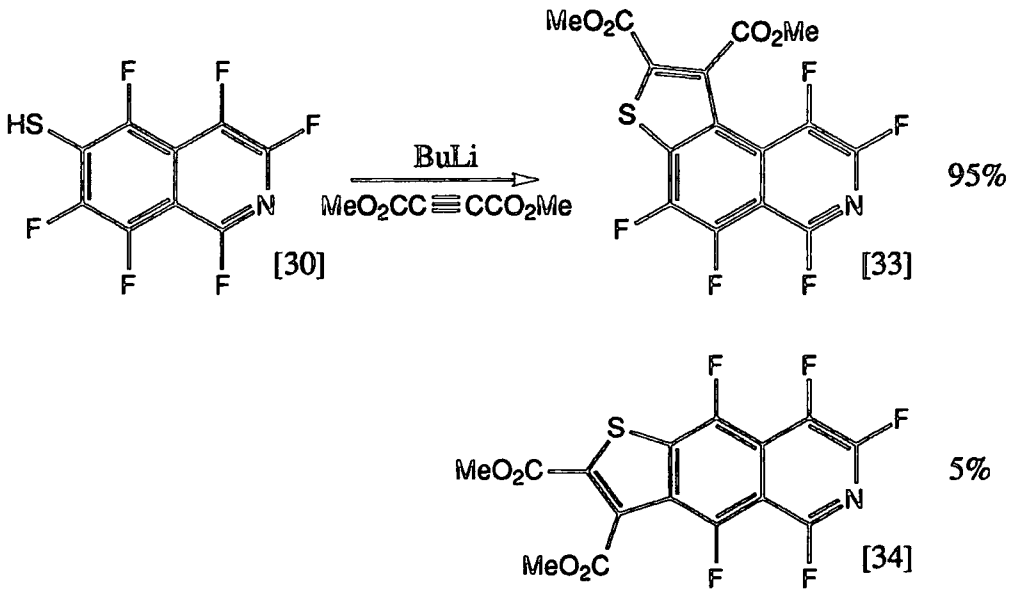


Scheme 2.14. *The reaction of [1] and [2] with sodium hydrosulphide.*

Clearly further investigation of the reactions of heptafluoro-isoquinoline [1] and -quinoline [2] was required and this matter is taken up in Chapter 3.

The cyclisation reaction of the sodium salt of the 6-isoquinolinethiol [30] with dimethyl acetylenedicarboxylate (DMAD) was performed[38] and is shown in Scheme 2.15. In this reaction, as with the napthalene system described earlier, cyclisation can take place in two directions, with, in this case, dispacement of either the 5-F or the 7-F.

The 5-F is displaced preferentially, giving predominantly the angular thiophene derivative [33] (95%) accompanied by some of the linear thiophene derivative [34] (5%).

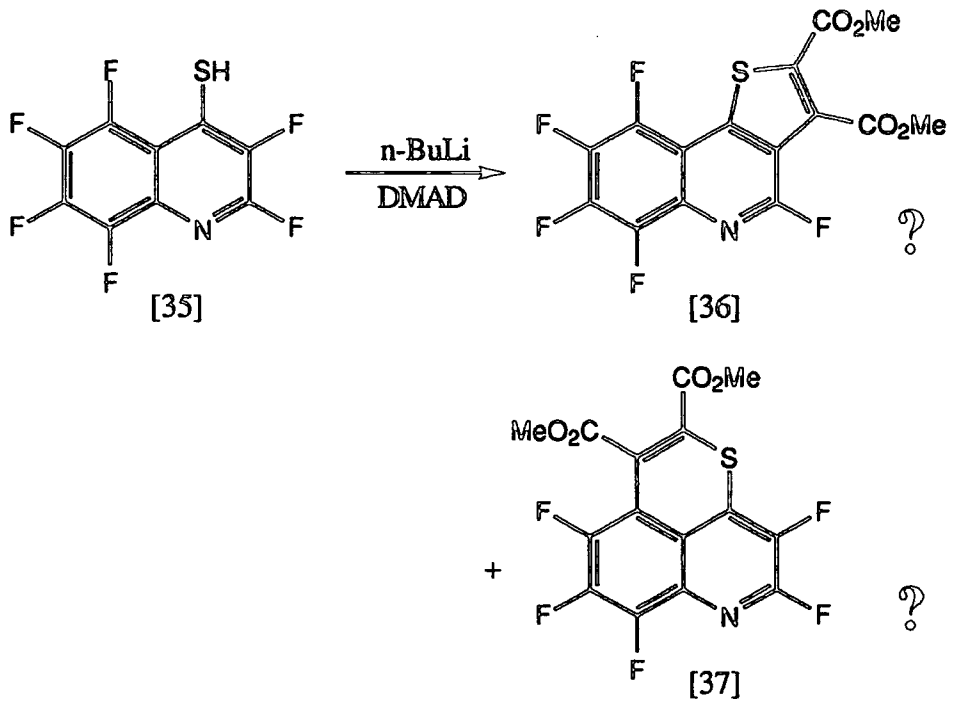


Scheme 2.15.

2.3 New Work

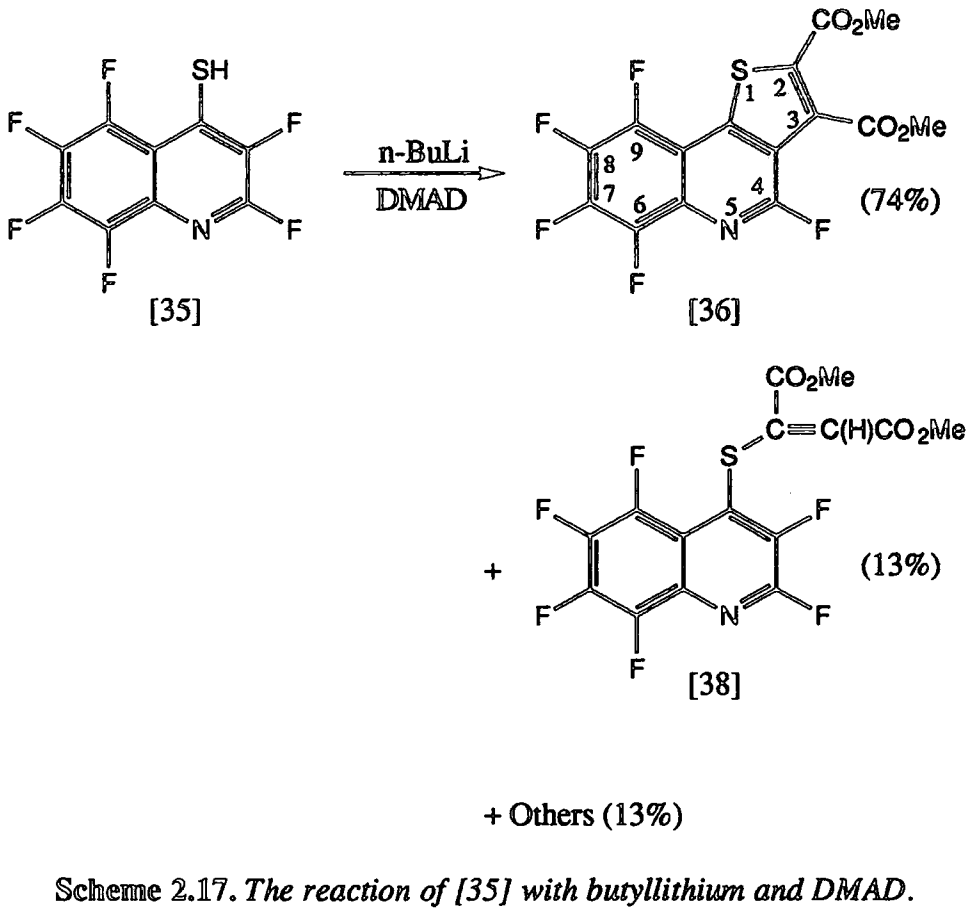
2.3.1 Reaction of Hexafluoro-4-quinolinethiol with butyllithium and subsequent reaction with Dimethyl Acetylenedicarboxylate (DMAD)

The lithium salt of the 4-quinolinethiol [35] could potentially react with DMAD to give a cyclised product by dispacement of the 3 fluorine, (yielding a five membered heterocycle [36]), or by displacement of the 5 fluorine, (giving a six membered heterocycle [37]), by a new cyclisation reaction as shown in Scheme 2.16.



Scheme 2.16. *Potential cyclisation reactions of the lithium salt of [35] with DMAD.*

The 4-quinolinethiol [35] was prepared by reacting sodium hydrosulphide with heptafluoroquinoline [2] in ethylene glycol and dry dimethylformamide (DMF) at ca. -6°C. A cold work up procedure (0°C.) enabled the 4-thiol [35] to be isolated as a stable compound. The 4-quinolinethiol was then treated in THF at -63°C with one equivalent of n-butyllithium, followed by DMAD. The mixture was warmed to room temperature and the crude product, examined by ^{19}F nmr spectroscopy, revealed a major product [36] (74%), a minor product [38] (13%) and unidentified products (13%) of which there were at least four (Scheme 2.17).

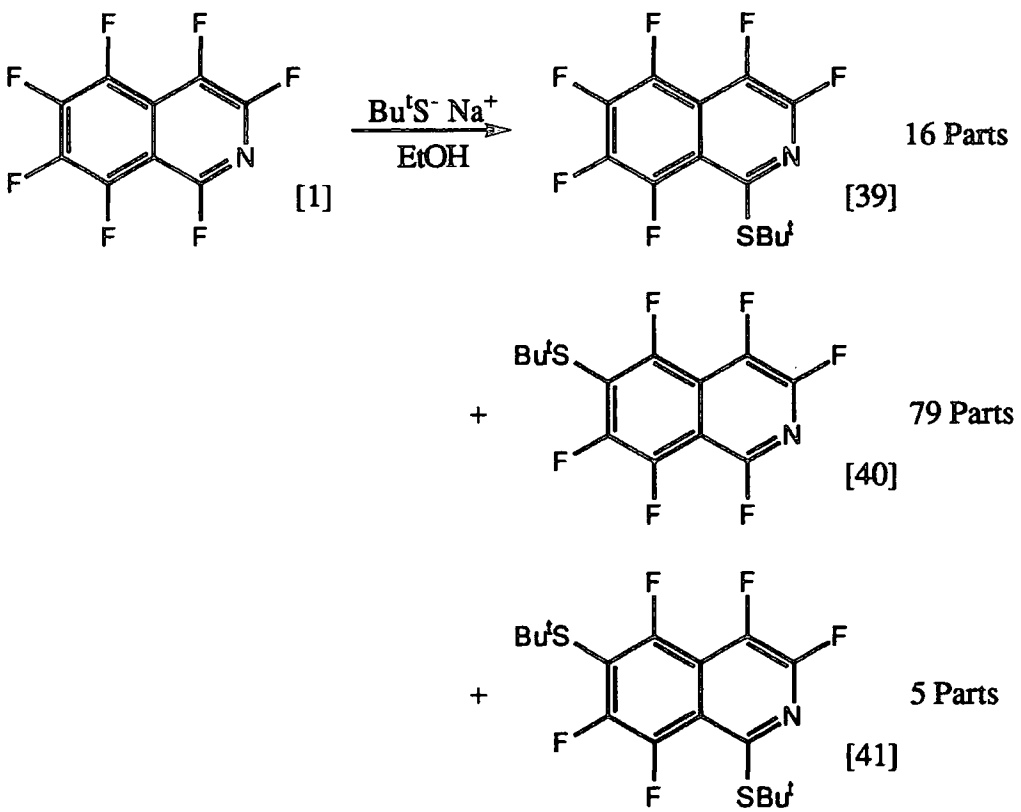


Scheme 2.17. *The reaction of [35] with butyllithium and DMAD.*

The major [36] and minor [38] components were separated and isolated in a separate experiment by chromatography. The major product [36] was the fused heterocycle formed from displacement of the 3 fluorine in the parent 4-quinolinethiol [35], and was identified from its ^{19}F nmr spectrum which showed only five absorptions (i.e one fluorine had been replaced during the reaction). The lowest absorption at -59.8ppm due to the fluorine at position 4 in the new heteocycle had been deshielded by 18.3ppm [-59.8 - (-78.1)] and its multiplicity reduced to a singlet from a doublet in the parent. This demonstrates clearly that cyclisation had in fact taken place with displacement of the 3 fluorine from the parent species. The minor product [38] was the the addition product of the thiol to the alkyne triple bond in DMAD, and was also, identified by nmr spectroscopy, the ^{19}F nmr revealing six absorptions (hence no fluorine had been replaced) and the ^{1}H nmr spectra showed a singlet resonance at 7.00 ppm due to the alkenic hydrogen as well as the two methyl ester singlets at 3.87 and 3.63 ppm. The stereochemistry of the alkene was not established.

2.3.2 Dealkylation of the 1-(t-butylthio)isoquinoline [39]: Unstable 3,4,5,6,7,8-Hexafluoro-1-Isoquinolinethiol [26]

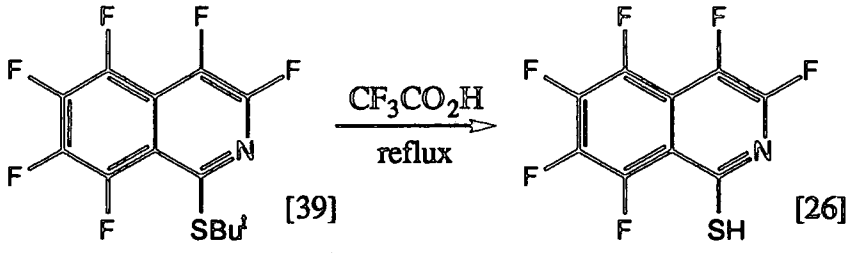
The dealkylation of the 1-(t-buytlthio)isoquinoline [39] was investigated as a possible route to the the 1-isoquinolinethiol [26], a material of primary interest since it could potentially undergo a cyclisation reaction with DMAD to form a six membered sulphur containing heterocycle as described earlier. Heptafluoroisoquinoline [1] reacts with sodium t-butylthiolate, (see Chapter 3), to give the 1-t-butylthio-isoquinoline [39] (16 parts) along with the major product the 6-t-butylthio-isoquinoline [40] (79 parts), and a small proportion of the 1,6-di(t-butylthio)isoquinoline [41] (5 parts) (Scheme 2.18).



Scheme 2.18. *The reaction of heptafluoroisoquinoline [1] with tert-butylthiolate.*

The 1-t-buylthioisoquinoline [39] isolated pure from [40], [41] and unreacted [1] by column chromatography (carbon tetrachloride and silica) and re-crystallisation, underwent dealkylation when refluxed with trifluoroacetic acid (Scheme 2.19). However, the resultant 1-isoquinolinethiol was found to decompose rapidly particularly

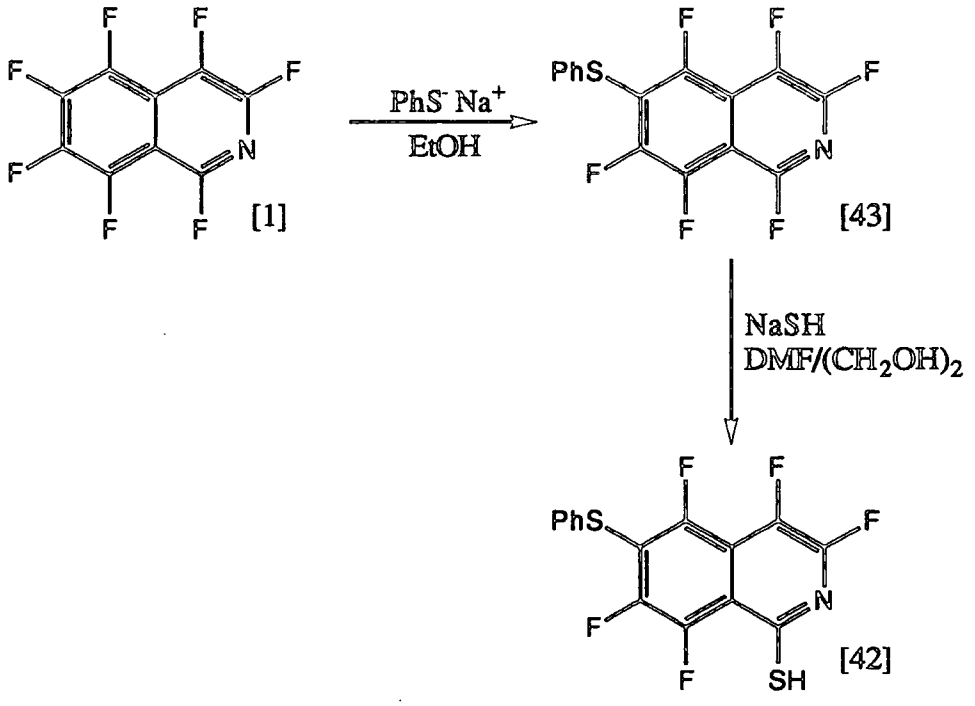
in solution, which is probably due to intermolecular reactions of the 1-thiol with the reactive 6 position. The 1-thiol [26] was identified by correct mass by mass spectroscopy, and by six absorptions in the ^{19}F nmr spectrum, none of which were in the region where the 1-F would be expected, (i.e. -60 to -70 ppm.).



Scheme 2.19. *Dealkylation of the 1-tert-butylisoquinoline [39].*

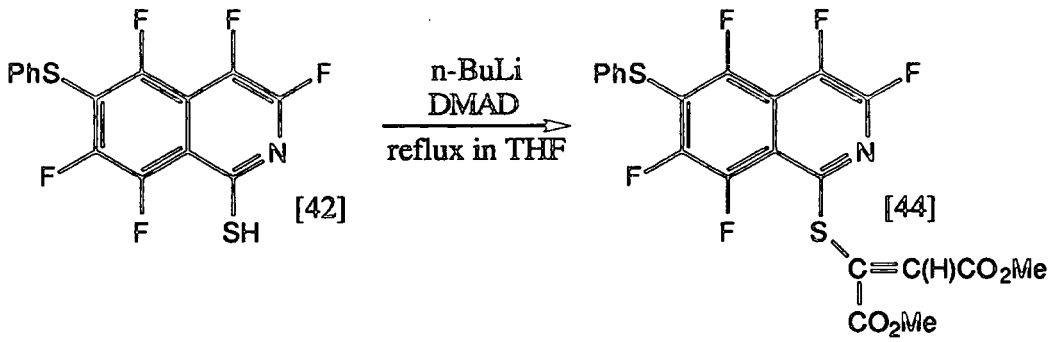
2.3.3 Synthesis of the 6-phenylthio-1-isoquinolinethiol [42], and its reaction with n-butyllithium and DMAD.

Since the 1-isoquinolinethiol [26] was found to be unstable, the 6-phenylthio-1-thiol [42] derivative was prepared. The introduction of the phenylthio group at the 6 position provided a convienient synthesis of a 1-isoquinolinethiol, (see Scheme 2.20), since the 6-phenylthio-isoquinoline [43] is easily prepared from the isoquinoline [1], in an almost quantitative yield, (see Chapter 3) and this is readily converted into the 6-phenylthio-1-isoquinolinethiol [42] by the action of sodium hydrosulphide in ethylene glycol and dry dimethylformamide (DMF) at <10°C. The 6-phenylthio group also blocked the reactive 6- position from potential intermolecular attack by the 1-thiol.



Scheme 2.20. *Preparation of the 6-phenylthioisoquinoline-1-thiol [42].*

The 6-phenylthio-1-isoquinolinethiol [42] was identified by ^{19}F nmr spectroscopy. The low field fluorine of the 1-position in the 6-phenylthio derivative at ca. -63ppm was absent, indicating that substitution had taken place at the 1- position. In addition there was only one large peri coupling constant present (60Hz) due to fluorines at positions 4 and 5. The 6-phenylthio-1-isoquinolinethiol [42] could not be isolated pure; its rate of decomposition was however significantly less than that of [26]. The 6-phenylthio-1-isoquinolinethiol [42] in THF was cooled to -63°C and treated with n-butyllithium, followed by DMAD. The resultant mixture was warmed to room temperature and then refluxed for 10 days. The crude product examined by ^{19}F nmr spectroscopy showed a complex mixture of products. Chromatographic separation of the mixture gave only one identifiable product [44] (10%), which was the result of addition of the thiolate to the alkyne triple bond in DMAD (Scheme 2.21).



Scheme 2.21. *The reaction of [42] with butyllithium and DMAD.*

The adduct was identified by elemental analysis, correct molecular mass by mass spectrometry, and by nmr spectroscopy. The ^{19}F nmr showed five absorptions, (i.e no fluorines had been replaced), all of which had undergone only small shifts (<4ppm) due to the functionalisation of the sulphur at position 1. The ^{1}H nmr showed singlets at 7.11ppm for the alkenic hydrogen and at 3.82 and 3.79ppm due to the methyl esters, while multiplets for the phenylthio substituent were seen at 7.43 and 7.32ppm. The stereochemisty of the alkene in [44] was unresolved.

2.3.4 Discussion

Cyclisation of the lithium salt of the 4-quinolinethiol [35] with DMAD took place by displacement of the fluorine at position 3, the formation of a six membered ring through dispacement of the fluorine at position 5 in the parent thiol [35] could not be detected. It could however have been present among the many minor components in the reaction and so cannot be totally ruled out.

No cyclised product could be detected from the potentially unambiguous six membered heterocyclic ring-forming reaction of the lithium salt of 6-phenylthio-1-isoquinoline [42] with DMAD. The conclusion must be that cyclisation to give a six membered ring is unfavourable, even to the extent that if no five membered ring forming reaction is available then no cyclisation takes place. The addition to form a carbanion must take place, but no subsequent cyclisation occurs.

Chapter 3

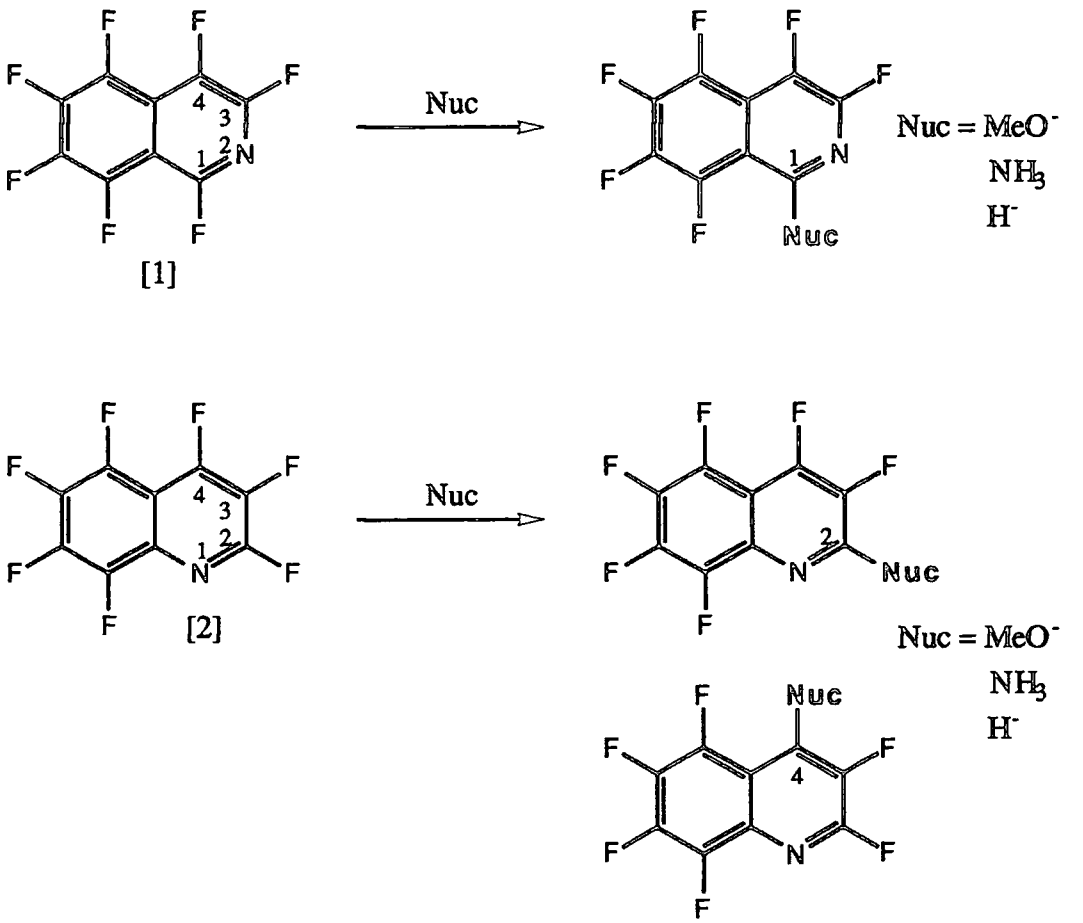
Nucleophilic Substitution Reactions of Heptafluoro-Isoquinoline [1] and -Quinoline [2]

Chapter 3

Nucleophilic Substitution Reactions of Heptafluoro-Isoquinoline [1] and Quinoline [2].

3.1 Background

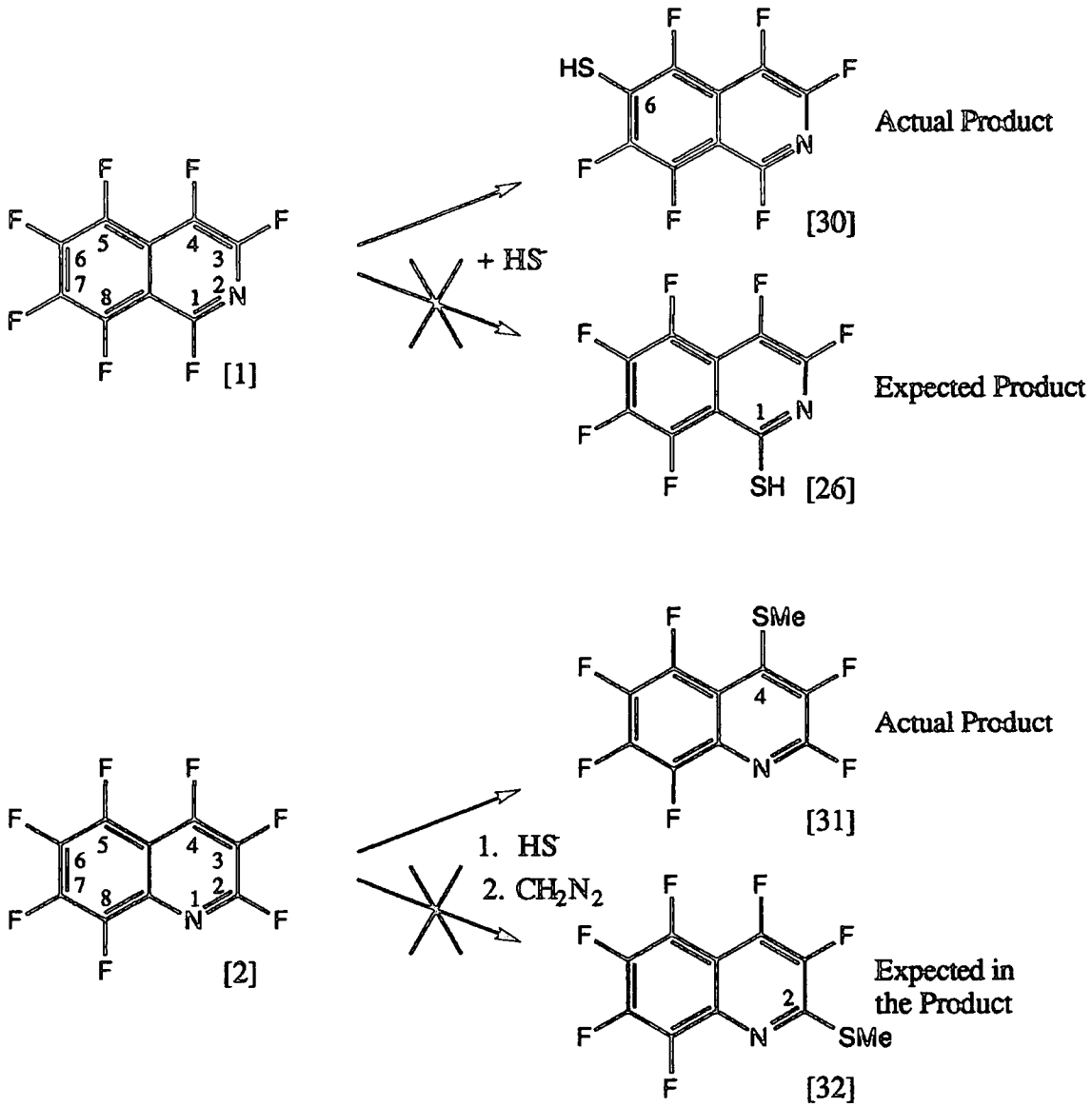
In 1966 the preparation and reactions of heptafluoro-isoquinoline [1] and quinoline [2] were first described[13]. Heptafluoroisoquinoline [1] was shown to react with a variety of nucleophiles (e.g ammonia, ethoxide and hydride) to give exclusive 1-substitution, while heptafluoroquinoline [2] reacted with the same variety of nucleophiles to give 2- and 4- substitution (Scheme 3.1.)[26].



Scheme 3.1. *The reaction of [1] and [2] with nucleophiles.*

In the Background to the previous chapter, the nucleophilic substitution reactions of sodium hydrosulphide with heptafluoroisoquinoline [1] and heptafluoroquinoline [2] were described. In these reactions (Scheme 3.2) substitution, remarkably, took place at the 6- position for the isoquinoline [1] and at the 4- position

with the quinoline [2]. The position of nucleophilic displacement of fluorine from polyfluoroaromatics is usually nucleophile independent.



Scheme 3.2. *Reaction of [1] and [2] with sodium hydrosulphide.*

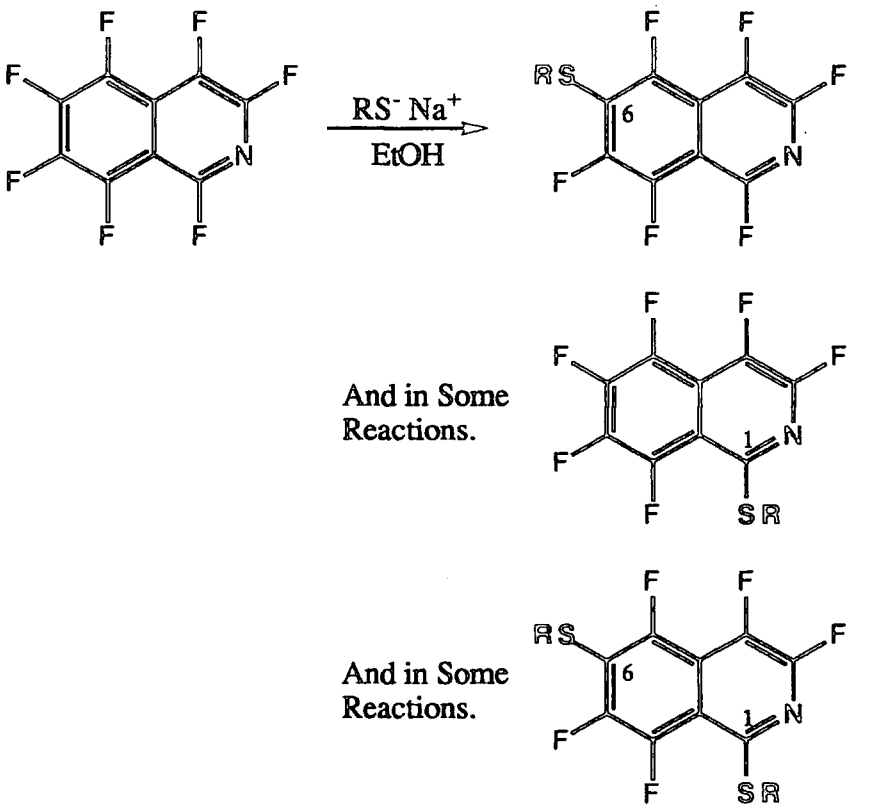
It was quite clear that a further investigation of this profound change in orientation, for nucleophilic displacement of fluorine from [1] and [2] was required

3.2 Results

Reactions with the isoquinoline [1].

The isoquinoline [1] was reacted with sulphur nucleophiles of increasing steric complexity. Those chosen were methylthiolate, isopropylthiolate[39] and tert-butylthiolate. The isoquinoline [1] was also reacted with a variety of sulphur

nucleophiles of varying electronic requirements. These were all para substituted phenylthiolates and the substituents in order of increasing elecron demand were N,N-dimethylamino, methoxy, hydro (i.e. the parent phenylthiolate) and nitro. All of the thiolates were prepared by reacting the corresponding thiol with sodium ethoxide in ethanol. The thiolate was then added to the isoquinoline [1], also in ethanol, cooled to <-80°C.



Scheme 3.3. *The reaction of [1] with some thiolates.*

In each case substitution took place in the 6- position, with in some cases some 1-substitution and/or 1,6-disubstitution products also being formed (Scheme 3.3). The identities of all the products are shown in Table 3.1a. The proportions of the products from the reaction were determined by ^{19}F nmr spectroscopy and the results are shown in Table 3.1b which includes some results with oxygen nucleophiles which will be refered to later.

Table 3.1a.

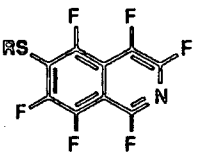
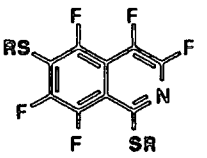
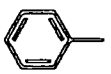
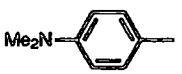
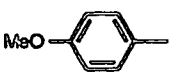
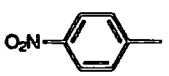
R=			
H	[26]	[30]	
Bu^t	[39]	[40]	[41]
		[43]	[45]
Me	[46]	[47]	[48]
Pr^i	[49]	[50]	[51]
	[52]	[53]	[54]
	[55]	[56]	[57]
		[58]	

Table 3.1b. *Reactions of Heptafluoroisoquinoline [1] with Nucleophiles.*

		Product Ratio[a]		
Nucleophile	Solvent	1-isomer (%)	6-isomer (%)	1,6-disubstituted product (%)
HS^-	DMF/EG		100 [30][b]	
HS^-	MeOH	8 [26]	92 [30][b]	
MeS^-	EtOH	22 [46]	73 [47]	5 [48]
Pr^iS^-	EtOH	24 [49][39]	71 [50][39]	5 [51][39]
Bu^tS^-	EtOH	16 [39]	79 [40]	5 [41][b]
$C_6H_5S^-$	EtOH		99 [43]	1 [45]
$4\text{-}Me_2NC_6H_4S^-$	EtOH	0.5 [52]	97.5 [53]	2 [54]
$4\text{-}MeOC_6H_4S^-$	EtOH	0.5 [55]	97.5 [56]	2 [57]
$4\text{-}NO_2C_6H_4S^-$	EtOH		100 [58]	
EtO^-	EtOH	94 [60]	6 [61]	0 [62]
MeO^-	MeOH	97 [63]	3 [64]	
$C_6H_5O^-$	EtOH	93 [65]	7 [66]	
$4\text{-}NO_2C_6H_4O^-$	EtOH	100 [67]		

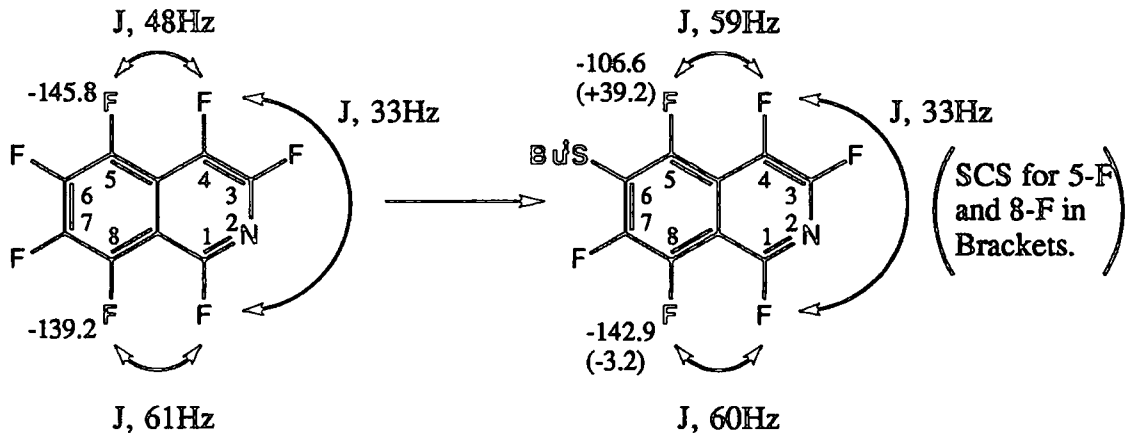
a) Calculated on the basis of starting material converted (compound numbers in brackets).

b) With a 10-fold excess of Bu^tSH present.

The products were separated in the majority of cases by column chromatography and/or vacuum sublimation. They were identified by ^{19}F nmr in conjunction with information about the parent isoquinoline [1], particularly the two low field absorptions at -62.1 and -96.7 ppm due the 1-F and 3-F respectively, and the large coupling constants $J_{1\text{-}F,4\text{-}F}$ 33Hz, $J_{1\text{-}F,8\text{-}F}$ 61Hz and $J_{4\text{-}F,5\text{-}F}$ 48Hz. The 1- sulphides were identified easily by the absence of a low field peak at ca. -62 ppm and the presence of only one large peri coupling constant due to fluorines at positions 4 and 5. The 6- sulphides (see Fig. 3.1) were also identified by ^{19}F nmr spectroscopy; for example with the 6-tert-

butylthioisoquinoline [40], the 1-F resonated at -62.5ppm and the 3-F resonated at -97.3ppm. The large coupling constants of the 1-F ($J_{1\text{-}F,8\text{-}F}$ 60Hz and $J_{1\text{-}F,4\text{-}F}$ 33Hz) revealed fluorines at position 8 (-142.9) and position 4 (-153.0) respectively. The large peri coupling ($J_{4\text{-}F,5\text{-}F}$ 59Hz) of position 4, revealed the fluorine at position 5. The substituent could therefore only be at position 6 or 7.

Fig. 3.1. *Determination that substituent is at position 6 in [40] by examining the SCS of fluorines 5 and 8.*



The distinction between the substituent being at position 6 or 7 in [40] was made by examining the substituent chemical shift (SCS) of the 5-F and the 8-F, since a sulphur substituent deshields fluorines ortho to it by 20 to 40ppm[29]. The 5-F was deshielded by 39.2ppm [-106.6 -(-145.8)] from its position in the parent [1], but the 8-F was shielded by 3.2ppm [-142.9 -(-139.7)] from its position in the parent [1]. The substituent is clearly at position 6, the fluorine at position 7 being deshielded by 28.6ppm [-153.1 -(-124.5)].

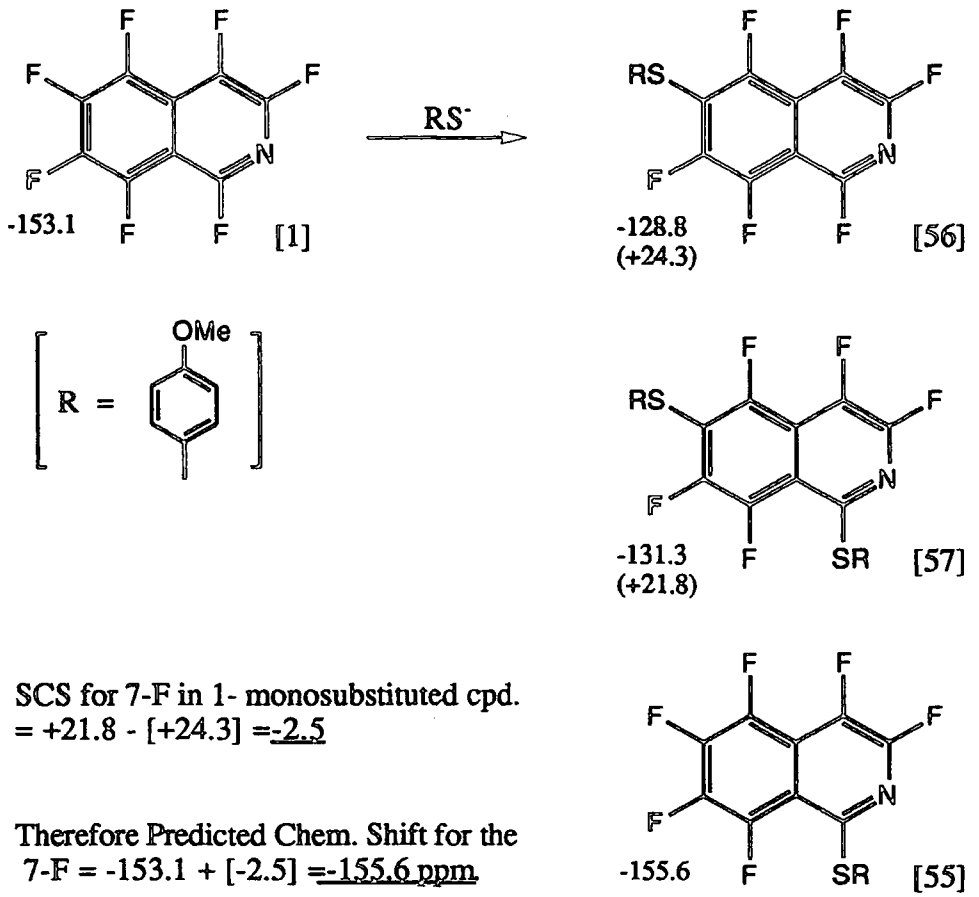
The 1,6-disubstituted compounds were identified in a similar fashion to the 1- and 6- monosubstitued compounds. For example the 1,6-di(tert-butylthio)isoquinoline [41] was identified by the presence of only five fluorines of which only one was at low field (the 3-F at -97.7ppm). The low field peak present in the parent [1] at ca. -62ppm was absent indicating one substituent was at position 1. The single large peri coupling constant ($J_{4\text{-}F,5\text{-}F}$ 65Hz) revealed fluorines at positions 4 and 5 at -159.1 and -106.9ppm respectively. Once again the 5-F had been deshielded significantly (38.9ppm) [-145.8

-(-106.9)] indicating the second substituent was at position 6. Fluorines at position 7 (a doublet) and at position 8 (a triplet) resonated at -128.3 and -140.1 ppm respectively.

In some cases the 1- compound was present in only a very low proportion and isolation of the material would have required large amounts of the isoquinoline [1] to be consumed. Hence the 1- compound was identified using substituent chemical shift approach based on ^{19}F nmr data for the 6- monosubstituted and the 1,6-disubstituted compounds, the 1,6-disubstituted compound being easily prepared from the 6-monosubstituted compound by action of one more equivalent of the relevent nucleophile.

Substituent chemical shifts (SCS) are calculated relative to chemical shifts in the parent compound, in this case heptafluoroisoquinoline [1]. SCS's are additive, (i.e.the SCS of a particular fluorine in a disubstitued compound is the sum of the SCS's of the same fluorine in the two monosubstituted compounds). Similarly the SCS of a particular fluorine in a monosubstituted compound can be calculated from the SCS's of the disubstituted compound and the other monosubstituted compound by difference. Fig 3.2 shows such a calculation of the chemical shift for the 7-F in the 1-(4-methoxyphenylthio)isoquinoline using data for the 6-(4-methoxyphenylthio)isoquinoline and the 1,6-di(4-methoxyphenylthio)isoquinoline. Table 3.2 shows all the predicted chemical shifts and the actual chemical shifts for all the positions, (except the 6-F, where insufficient data is available) in the 1-(4-methoxyphenylthio)isoquinoline [55]; the differences between the predicted and experimental chemical shifts are less than one ppm.

Fig 3.2. *Calculation of the chemical shift for the 7 fluorine on [55] using data for [1], [56] and [57].*



SCS for 7-F in 1- monosubstituted cpd.
= +21.8 - [+24.3] =-2.5

Therefore Predicted Chem. Shift for the
7-F = -153.1 + [-2.5] =-155.6 ppm

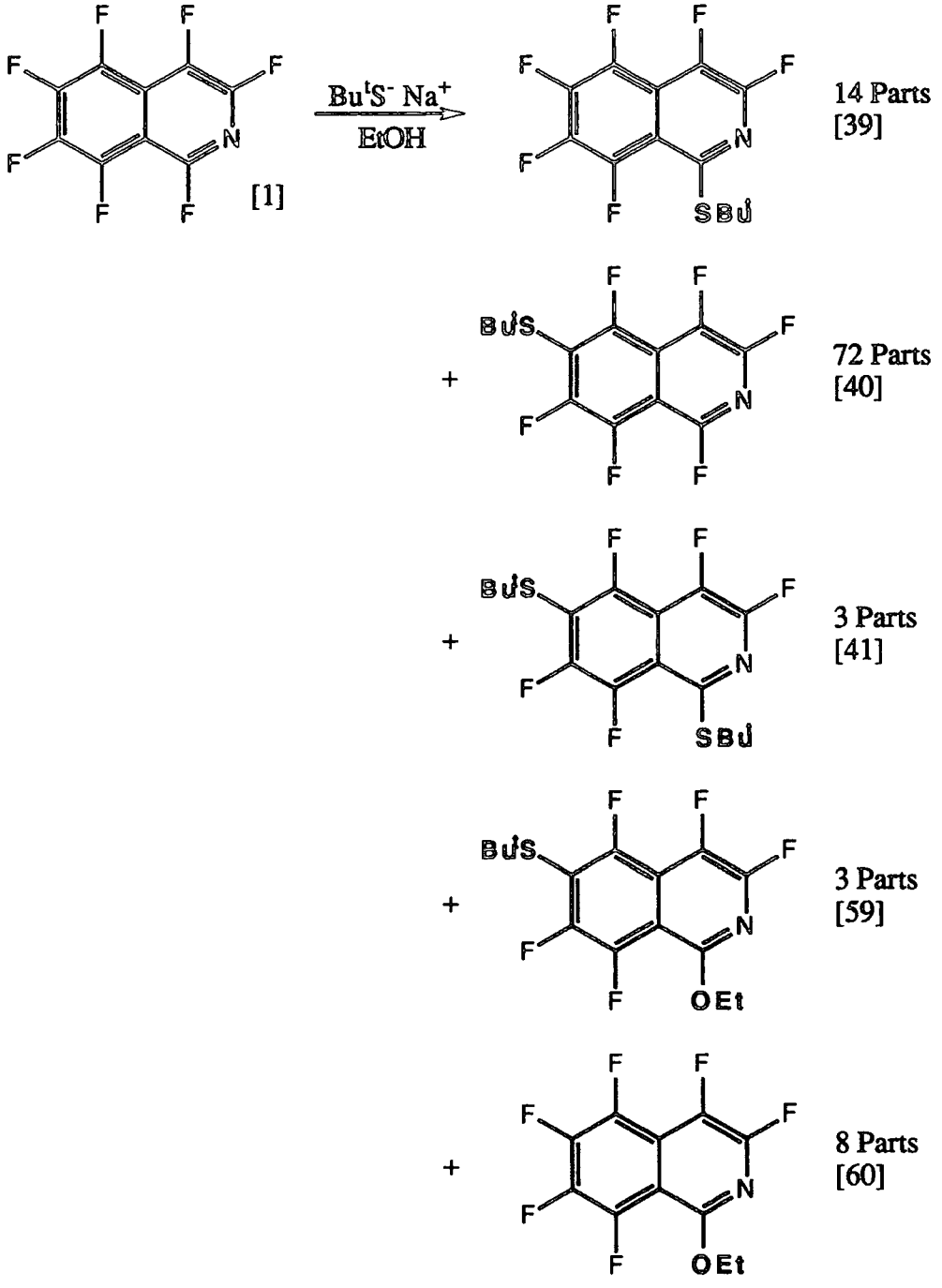
Experimental Value for the 7-F = -155.8

Table 3.2. *Calculated and Experimental shifts for [55].*

Position	Predicted Chem Shift	Experimental Chem Shift
3-F	-95.4	-95.6
4-F	-159.9	-160.0
5-F	-145.3	-146.0
7-F	-155.6	-155.8
8-F	-133.4	-133.8

The reaction of the tert-butylthiolate with [1] produced a product which was complicated by the formation of some ethoxy products (Scheme 3.4). The tert-butylthio

compounds [39],[40] and [41] were accompanied by the 1-ethoxy-6-tert-butyl-isoquinoline [59] and the 1-ethoxyisoquinoline [60] in the ratio 14 : 72 : 3 : 3 : 8 respectively. The formation of ethoxy products [59] and [60] was suppressed when a ten fold excess of the thiol was present.

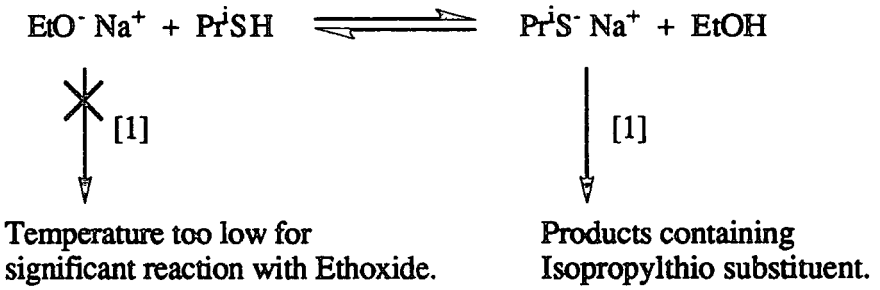


Scheme 3.4. *Reaction of [1] with tert-butylthiolate with no excess of tert-butanethiol present. Formation of ethoxy substituted products [59] and [60].*

It is clear that the thiol and the ethoxide are in equilibrium:-

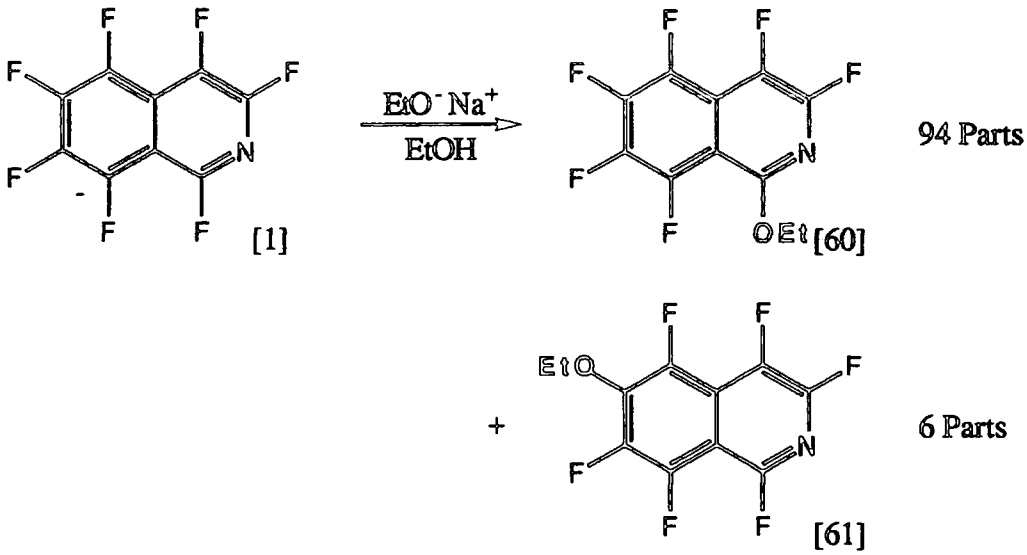
$$EtO^- Na^+ + Bu^tSH \rightleftharpoons Bu^tS^- Na^+ + EtOH$$

and since the acidities of tert-butanethiol is higher than that of the ethoxide (pKa's 11.05 and 16.00 respectively)[40], the equilibrium lies over to the right hand side. The acidity of the tert-butylthiol and isopropylthiol are virtually the same (pKa's 11.05 and 10.86 respectively)[40] and hence it would be surprising if the differing position in equilibrium was responsible for the formation of ethoxy products with the tert-butylthiolate. What is more likely is that t-butylthiolate is less reactive than isopropylthiolate due to the increase in steric size of the tert-butylthiolate. The lower reactivity of the tert-butylthiolate means that a higher temperature would be required for significant reaction and if the reaction temperature was high enough, then the residual ethoxide could compete effectively for the isoquinoline [1]. This situation would not arise with the isopropylthiolate as reaction of the thiolate takes place at a much lower temperature. As the thiolate is used up, (see Scheme 3.5.), the ethoxide/thiolate equilibrium is restored until no more nucleophile is present, hence no visible ethoxide products are formed with isopropylthiolate despite the presence of some ethoxide in the reaction mixture.



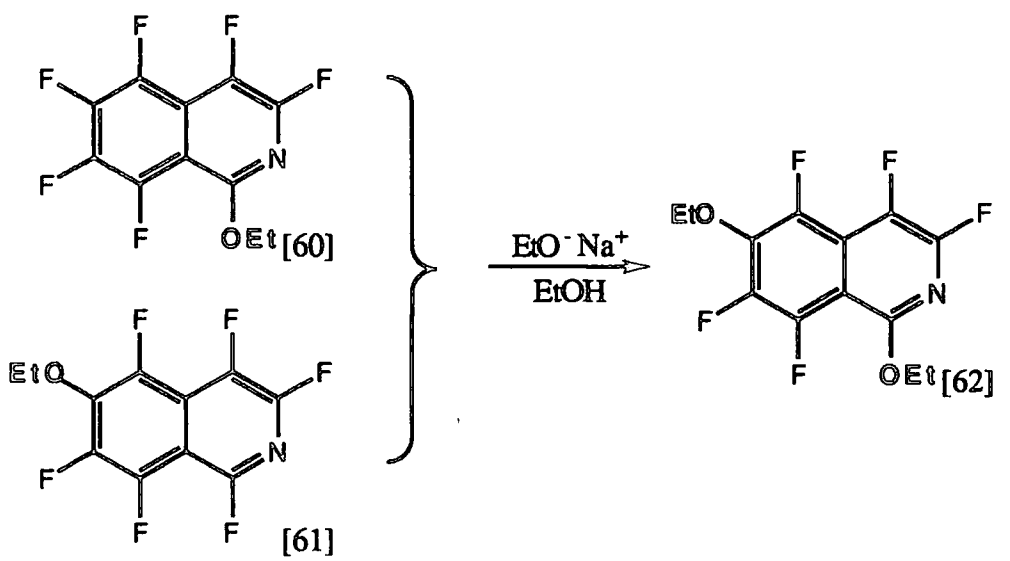
Scheme 3.5. *Equilibrium reaction of sodium ethoxide and iso-propylthiolate.*

The 1-ethoxy-isoquinoline [60] formed in the reaction of [1] with tert-butylthiolate, was identified by its synthesis in a separate experiment. The isoquinoline [1] reacted with sodium ethoxide in ethanol to give the 1- [60] and the 6- [61] isomers in the ratio 94 : 6 respectively as shown in Scheme 3.6.



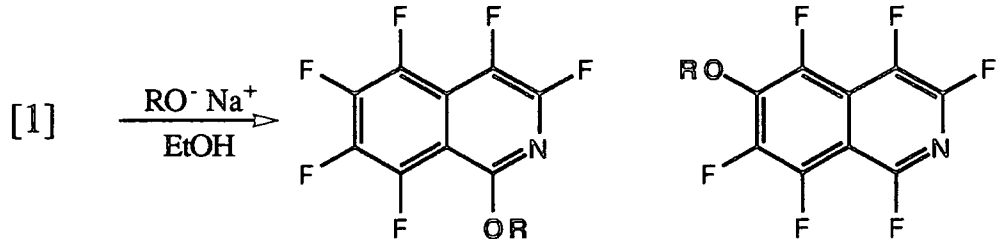
Scheme 3.6. *Reaction of [1] with sodium ethoxide.*

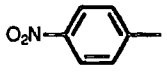
The 1-ethoxy-isoquinoline [60] was identified by the absence of a low field peak at ca -62ppm, and the presence of only one large peri coupling constant due to fluorines at positions 4 and 5. The 6-ethoxy-isoquinoline [61] was identified by ^{19}F nmr and calculated nmr shifts based on SCS calculations using information about the 1-ethoxy-isoquinoline [60] and the 1,6-di(ethoxy)isoquinoline [61], the latter being prepared by reacting the monoethoxy isoquinolines [60] and [61] with one further equivalent of ethoxide (see Scheme 3.7.).



Scheme 3.7. *Reaction of [60] and [61] with further ethoxide. Synthesis of [62].*

The reaction of sodium methoxide with the isoquinoline [1], a reaction first reported in 1966 to give exclusive 1- substitution, was repeated in view of the formation of some 6- product in the reaction of ethoxide and [1]. The 1- [63] and the 6- [64] methoxyisoquinolines were formed in the ratio 97 : 3 respectively. The isoquinoline [1] was reacted with two further oxygen nucleophiles; sodium phenoxide and sodium 4-nitrophenoxide. The results of all the experiments are shown in Table 3.1b. for comparison with the sulphur nucleophiles, and the identities of the products are given in Scheme 3.8.



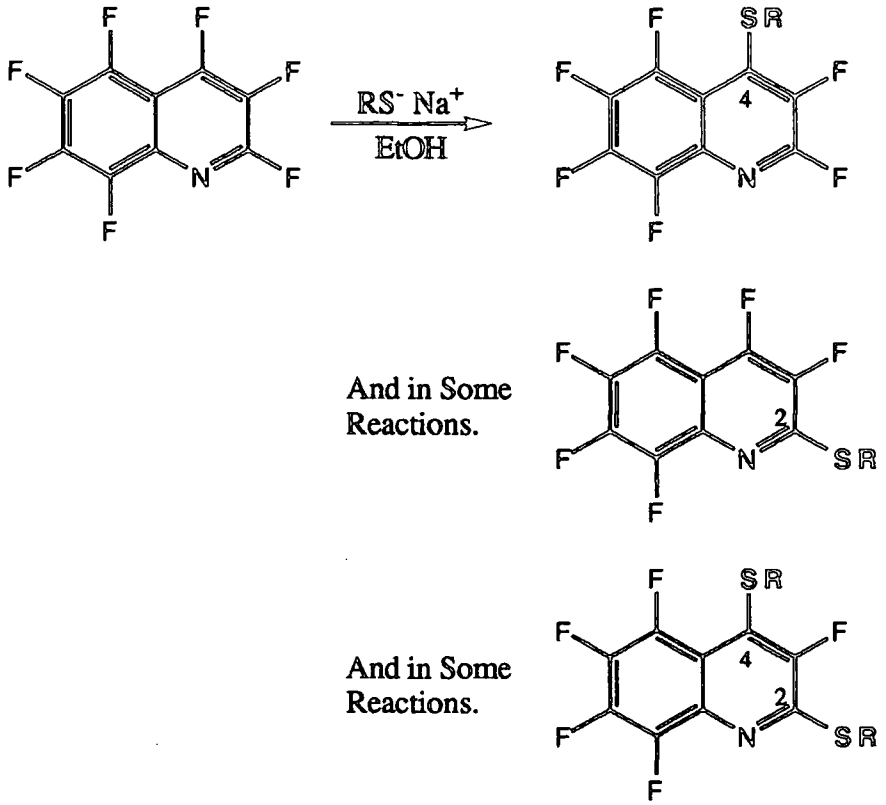
R = Me	97 [63]	3 [64]
R = Et	94 [60]	6 [61]
	93 [65]	7 [66]
	100 [67]	

Scheme 3.8. *Reaction of [1] with some oxygen nucleophiles. The product ratios (%) based on converted [1] are given along with the compound numbers in brackets.*

Reactions of the Quinoline [2].

Heptafluoroquinoline [2] in ethanol cooled to <-85°C, was treated with a variety of sulphur nucleophiles in ethanol; sodium hydrosulphide and the sodium salts of methanethiol, isopropylthiol, tert-butanethiol, and thiophenol. In all cases except with hydrosulphide and thiophenol, 2- and 4- monosubstituted products were formed as well as the 2,4-disubstituted product (see Scheme 3.9). The identities of all the products are

shown in Table 3.3a. The proportions of the products are all shown in Table 3.3b., which also includes some results with oxygen nucleophiles and ammonia which will be referred to later.



Scheme 3.9. *The reaction of [2] with a various sodium thiolates.*

Table 3.3a.

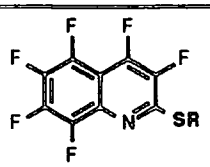
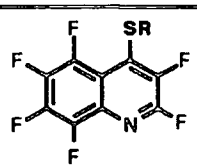
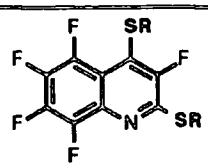
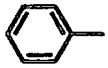
R=			
Me	[32]	[31]	[68]
H		[35]	
Pr^i	[69]	[70]	[71]
Bu^t	[72]	[73]	[74]
		[75]	

Table 3.3b. *Reactions of Heptafluoroquinoline [2] with Nucleophiles.*

		Product Ratio[a]		
Nucleophile	Solvent	2-isomer (%)	4-isomer (%)	2,4-disubstituted product (%)
HS^-	DMF/EG		>95 [35][39]	
MeS^-	EtOH	4 [32]	95 [31]	1 [68]
Pr^iS^-	EtOH	5[69][39]	91 [70][39]	4 [71][39]
Bu^tS^-	EtOH	5[72]	93 [73]	2 [74][b]
$C_6H_5S^-$	EtOH		>97 [75]	
EtO^-	EtOH	76[77]	24 [78]	
$C_6H_5O^-$	EtOH	37 [79]	63 [80]	
$4\text{-}NO_2C_6H_4O^-$	EtOH	16 [81]	84 [82]	
NH_3	Acetone	43 [83]	57 [84]	

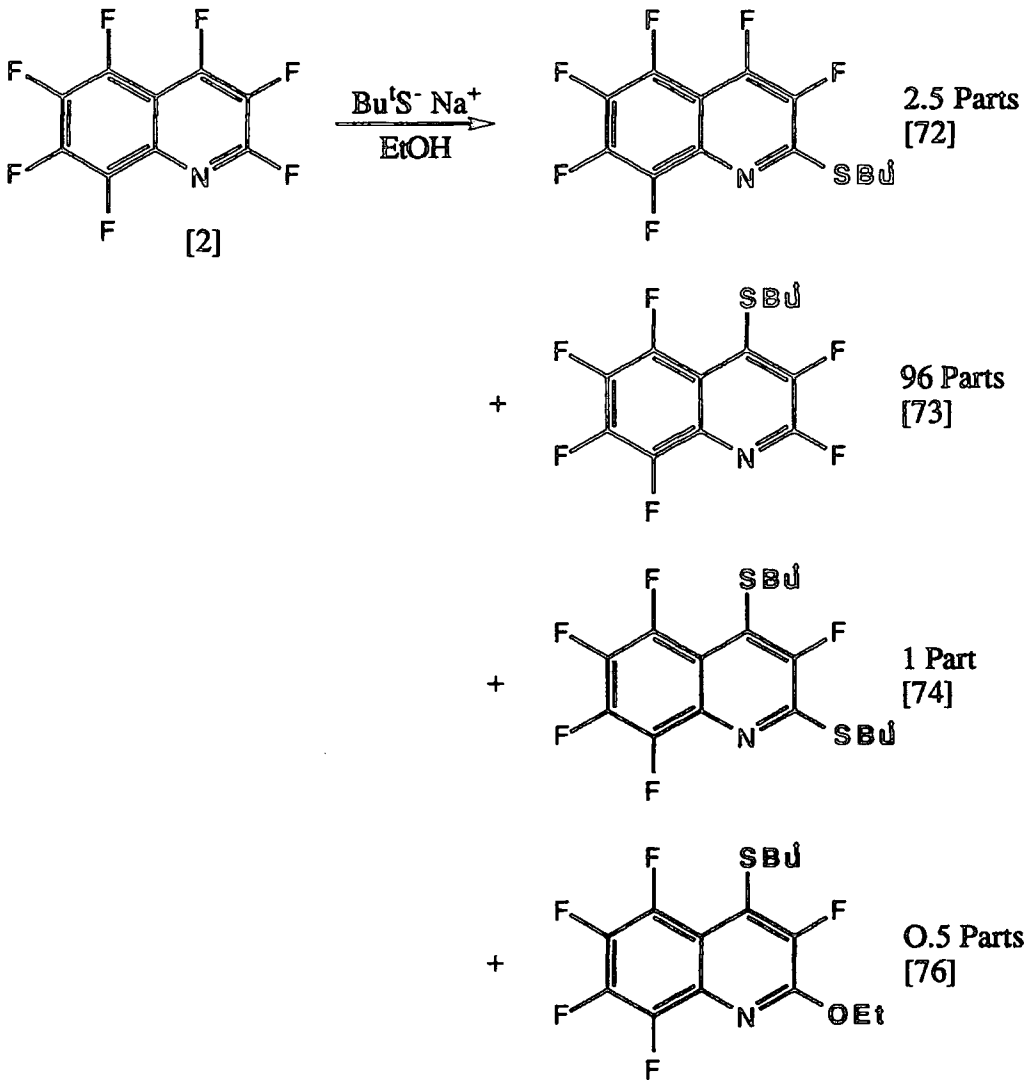
a) Calculated on the basis of starting material converted (compound numbers in brackets)

b) With a 10-fold excess of Bu^tSH present.

In most cases the products were separated by various combinations of column chromatography, sublimation, and recrystallisation and then identified by ^{19}F nmr spectroscopy in conjunction with information available for the parent [2], in particular the low field resonance at -72.4 due to the 2-F which in turn revealed the 3-F at -160.8 ppm ($J_{2\text{-}F,3\text{-}F}$ 26Hz). The 3-F revealed the 4-F at -124.1ppm ($J_{3\text{-}F,4\text{-}F}$ 26Hz), the large peri coupling constant (46Hz) of which revealed the fluorine at position 5 (-146.1 ppm.). The 2- substituted sulphides were identified clearly by the absence of the low field peak at ca -72 ppm which can be attributable to the 2-F in [2]. In addition the fluorine at position 3- was deshielded by 12 to 15ppm from its position in the parent [2], the magnitude being dependent on the bulk of the sulphide at position 2-. The 4- sulphides were identified by the absence of the large peri coupling constant observed in [2] due to fluorines at

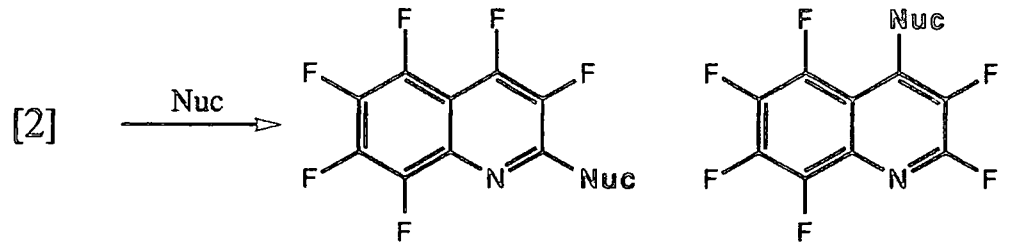
positions 4 and 5, and by the large substituent chemical shift of the 3-F, typically 24 to 39 ppm, the magnitude varying with the size of the neighbouring sulphide. The 2,4-disulphides were identified by the absence of the fluorine at position 2- and the absence of the large peri coupling constant due to fluorines at positions 4- and 5- in conjunction with the singlet character of the fluorine at position 3-, which was deshielded by 42 to 55ppm from its position in [2] by the two sulphide substiuents situated ortho to it.

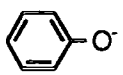
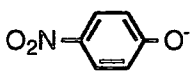
The quinoline [2] like the isoquinoline [1], reacted with the sodium salt of tert-butanethiol in ethanol to produce some product incorporating the ethoxy group as shown in Scheme 3.10. The 2- [72] and 4- [73] sulphides and the 2,4-disulphide [74] were accompanied by the 2-ethoxy-4-tert-butyl-quinoline [76] in the ratio 2.5 : 96 : 1 : 0.5 respectively. Again a ten fold excess of tert-butanethiol in the reaction mixture suppressed the formation of ethoxy substituted product.



Scheme 3.10. *The reaction of [2] with tert-butanethiolate in ethanol. Formation of [76].*

Heptafluoroquinoline [2] in ethanol was also reacted with a variety of oxygen nucleophiles with increasing electron demand; sodium salts of ethoxide, phenoxide and 4-nitro-phenoxide. In all cases 2- and 4- ethers were formed in the product and were identified by ^{19}F nmr; the 2- ethers being identified by the absence of a low field peak at ca.-70 ppm and the 4- ethers being identified by the absence of the large peri coupling constant, the signal for the 5-F in the parent being the one retained in the 4- ether. The results are shown in Scheme 3.11 and Table 3.2 for comparison with the sulphur nucleophiles. In addition, the result of the reaction of [2] with ammonia, a reaction first performed in 1966 is also given.

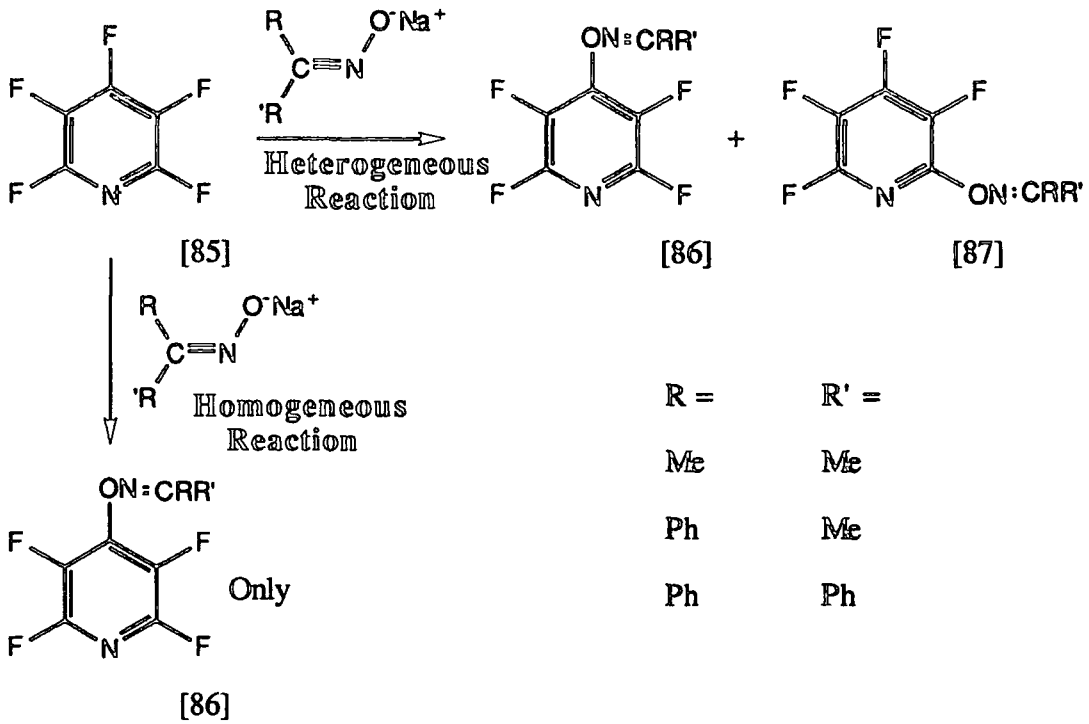


Nuc =	EtO^-	76 [77]	24 [78]
		37 [79]	63 [80]
		16 [81]	84 [82]
	NH_3	43 [83]	57 [84]

Scheme 3.11. *Reaction of [2] with some oxygen nucleophiles and ammonia. The product ratios (%) based on converted [2] are given along with the compound numbers in brackets.*

3.3 Discussion

It is quite clear that a remarkable change of orientation is taking place when the nucleophile is changed from an oxygen centre to a sulphur centre. The only previously reported system where a significant change in orientation has occured with respect to nucleophilic substitution in a polyfluoroaromatic compound, was with some sodium oximates and pentafluoropyridine [85]. When the reaction was performed as a homogeneous mixture (using solvents such as ethanol), then only 4- product [86] was formed as expected. If however a heterogeneous reaction was performed (using solvents such as diethyl ether), then significant amounts of 2- substitution product [87] were formed. An interaction between the lone pair on nitrogen and the sodium cation was regarded as being responsible for the formation of 2- product[41].



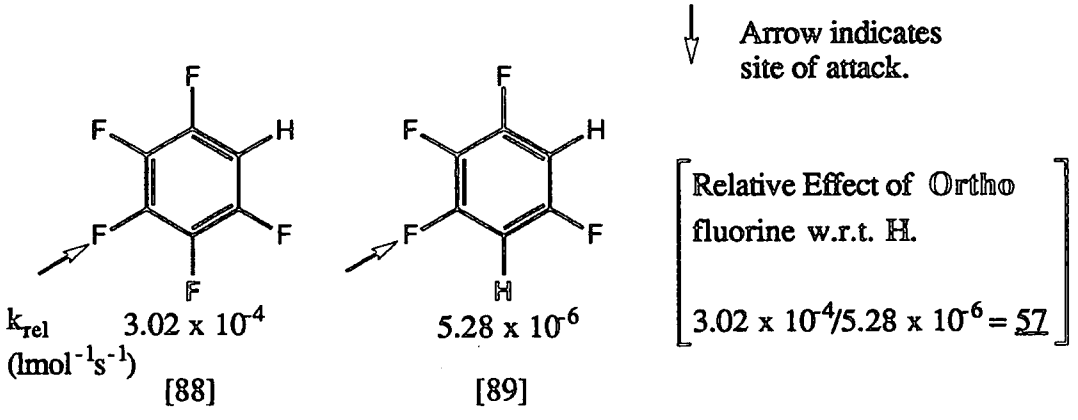
Scheme 3.12. *Reaction of Pentafluoropyridine [85] with some sodium oximates.*

The possibility of a single electron transfer mechanism taking place was examined since the difference in orientation of a sulphur and oxygen nucleophile could be based on a change of mechanism. It would be more likely that the single electron transfer mechanism occuring would take place for the sulphur nucleophiles rather than oxygen nucleophiles. The possibility of this mechanism for the sulphur nucleophiles was ruled out by performing one reaction of a sulphur nucleophile and the isoquinoline [1] in the dark and with the presence of a radical inhibitor. Sodium phenylthiolate in ethanol was added to a cooled (<-80°C) mixture of heptafluoroisoquinoline [1], m-dinitrobenzene and ethanol with the exclusion of light. The mixture was warmed up to -30°C, before being re-cooled to -50°C and the reaction quenched with trifluoroacetic acid. After work up the crude reaction product contained unreacted isoquinoline [1] (45%) and the 6-phenylthio-isoquinoline [43] (55%). It is clearly very unlikely that substitution in the 6- position in the isoquinoline [1] takes place via a single electron transfer mechanism, since the crude product was exactly the same as when the reaction was performed under illuminated conditions with no radical inhibitor present.

A quantitative approach by Chambers[42,43] has enabled the activation of fluorine towards nucleophilic substitution at various positions to be determined, relative

to hydrogen at the same position. The effect of ring nitrogen on various positions has also been determined. The basics of how these activating effects were determined are outlined below.

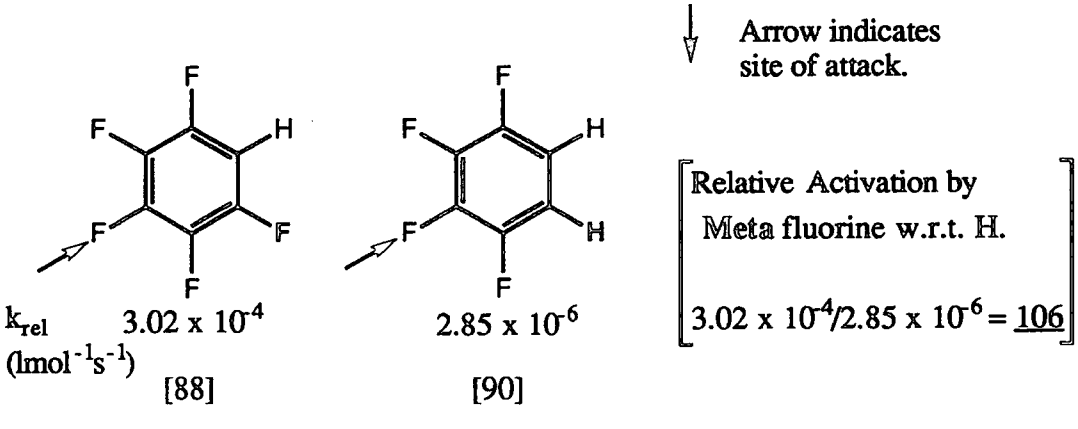
Rate constants for nucleophilic substitution of pentafluorobenzene [88] and 1,3,4,5-tetrafluorobenzene [89] by sodium methoxide were compared to give a measure the effect of fluorine ortho to the reaction site with respect to hydrogen at the same position (Scheme 3.13).



Scheme 3.13. *Measure of the effect of fluorine ortho to the reaction site.*

Fluorine ortho to the site of nucleophilic attack is activating with respect to hydrogen at the same position by a factor of 57.

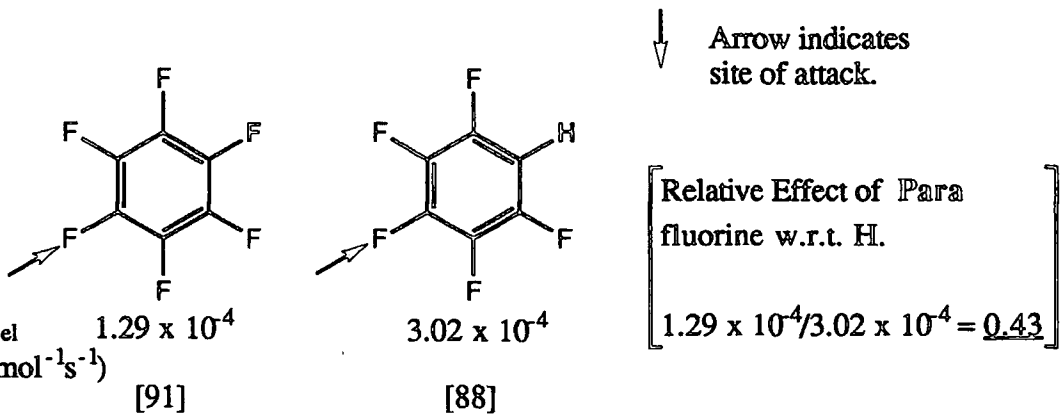
A comparison of the rate constants for nucleophilic substitution of pentafluorobenzene [88] and 1,2,3,4-tetrafluorobenzene [90] provides a measure of the effect of fluorine meta to the reaction site with respect to hydrogen at the same position (Scheme 3.14).



Scheme 3.14. *Measure of the effect of fluorine meta to the reaction site.*

Fluorine meta to the site of nucleophilic attack is activating with respect to hydrogen at the same position by a factor of 106.

Similarly comparison of the rate constants for nucleophilic substitution of hexafluorobenzene [91] and pentafluorobenzene [88] gave a measure of the activity of fluorine para to the site of reaction (Scheme 3.15).



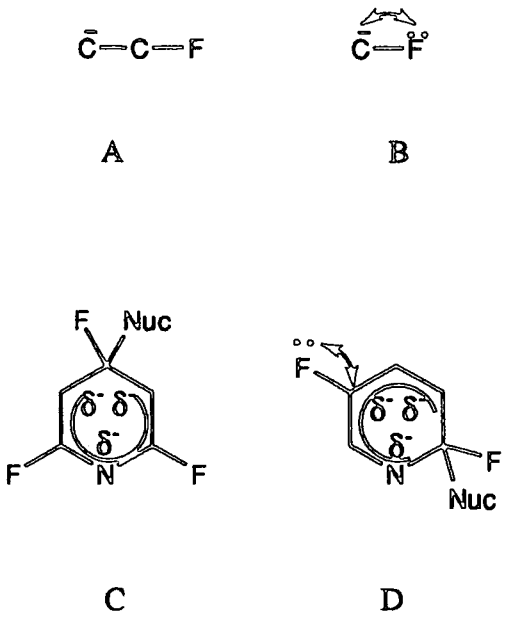
Scheme 3.15. *Measure of the effect of fluorine para to the reaction site.*

Fluorine para to the site of nucleophilic attack is slightly deactivating with respect to hydrogen at the same position by a factor of 0.43. The result for the para fluorine can be compared with Russian work by Sokolenko et al. who found the relative rates of attack of C_6F_6 and C_6F_5H by methoxide at 60°C. to be 0.65 : 1[44].

From these results, it is clear that fluorine ortho and meta to the site of attack are strongly activating wheras fluorine para to the site of attack is slightly deactivating with repect to hydrogen at the same position.

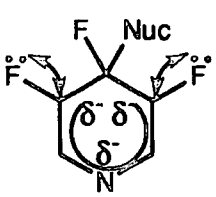
A similar study with some polyfluoropyridines[43,45] in dioxan/water with ammonia as the nucleophile found the relative activation of fluorine ortho, meta and para to the site of attack to be 31 : 23 : 0.26 relative to hydrogen at the same position. The effects of fluorine ortho, meta and para to the site of attack are remarkably similar to those found with the polyfluorobenzenes and methoxide described above, i.e 57 : 106 : 0.43 for fluorine ortho, meta and para to the site of attack respectively.

The effect of fluorine meta and para to the site of attack is easily explained[45] by examining the possible structures of the transition states shown in Scheme 3.16.



Scheme 3.16.

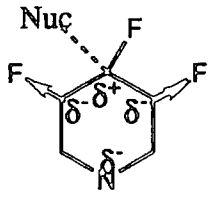
The fluorine in situation A has been found to be carbanion stabilising through inductive effects; therefore fluorine meta to the site of attack as in situation C is able to stabilise the transition state, and hence is activating with respect to nucleophilic attack. Fluorine in situation B however is slightly destabilising due to electron pair repulsion, and this explains why fluorine para to the site of attack is slightly destabilising, since the para fluorine is attached to a centre of localised negative charge, as in situation D. The effect of fluorine ortho to the reaction site is not quite so easily rationalised since like the fluorine para to the reaction site, it too, (see Scheme 3.17), is adjacent to a centre of localised negative charge and therefore ought to be destabilising.



Scheme 3.17.

However this is clearly not the case experimentally. There must therefore be some activating effect which offsets the conjugative deactivating effect to give an overall net activating effect. This has been described as an initial state effect where the ortho

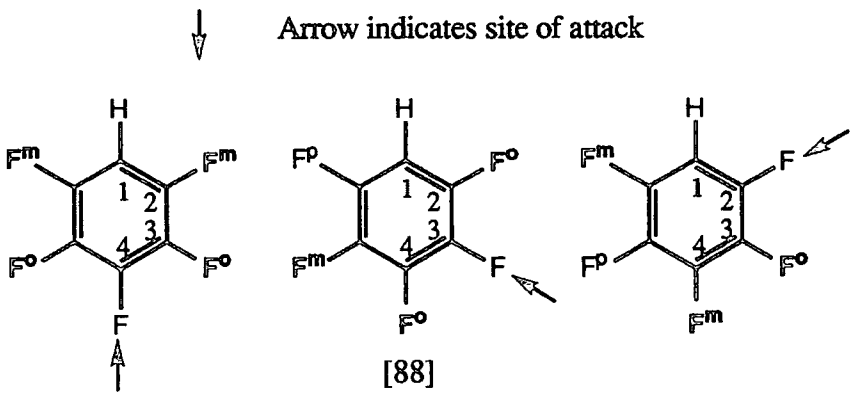
fluorines polarize the site of attack, thus making the centre more susceptable to nucleophilic attack as shown in Scheme 3.18.



Scheme 3.18. *Polarisation of the site of attack by ortho fluorines.*

The orientation of substitution in polyfluoroaromatics is determined by a necessity to maximise the number of activating fluorines (and minimise the number of deactivating fluorines) around the centre of attack.

Nucleophilic substitution reactions of pentafluorobenzene [88][46] have been found to take place by predominant displacement of the fluorine para (4-F) to the hydrogen atom; (i.e the site with the largest number of activating fluorines and least number of deactivating fluorines as shown in Scheme.3.19.).

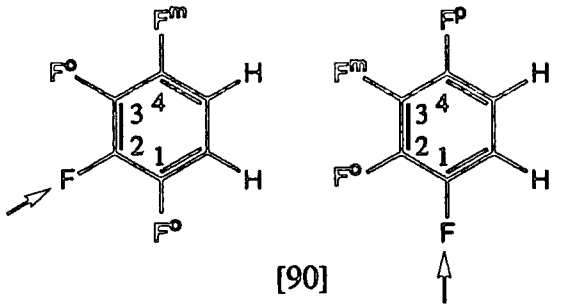


[88]

4 Activating F	3 Activating F	3 Activating F
(2 ortho + 2 meta)	*(2 ortho + 1 meta)*	*(1 ortho + 2 meta)*

Scheme 3.19. *The three possible sites of substitution of fluorine in [88].*

In 1,2,3,4-tetrafluorobenzene [90][47] the 2- fluorine is displaced in preference to the 1- fluorine since the 2- fluorine has 3 activating fluorines, whereas the 1- fluorine has only 2 activating fluorines (Scheme 3.20).



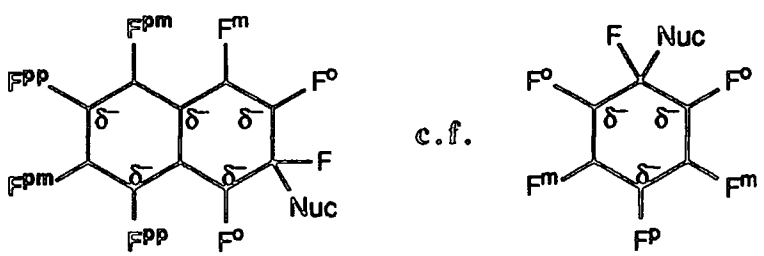
[90]

3 Activating F *(2 ortho + 1 meta)*

2 Activating F *(1 ortho + 1 meta)*

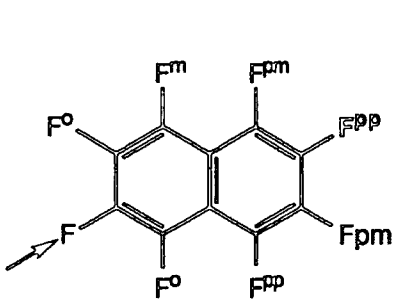
Scheme 3.20. *The two possible sites of displacement of fluorine in [90].*

The effect of fluorines in polycyclic sytems which are attached to a ring, remote from the reaction centre, have also been determined[48]. The fluorines in the remote ring were defined as 'pseudo meta' (pm) if attached to a carbon adjacent to a centre of localised negative charge [similar to a normal meta fluorine (m)], and 'pseudo para' (pp) if attached to a carbon bearing localised negative charge [similar to a normal para fluorine (p)] (Scheme 3.21.) Polyfluoronaphthalene derivatives were used as the model compounds and kinetic studies were performed at 25°C with methoxide in methanol as the nucleophile. Statistical corrections were applied where necessary.

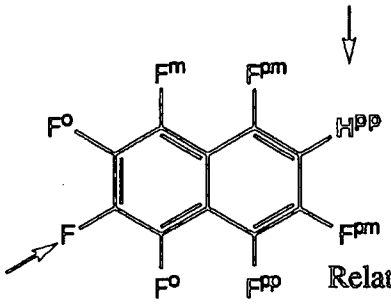


Scheme 3.21. *Comparison of pseudo meta fluorine with meta fluorine and pseudo para fluorine with para fluorine.*

The reaction rates of octafluoronaphthalene [92] and 2-hydro-perfluoronaphthalene [93] were compared (Scheme 3.22) to determine the effect of pseudo para fluorine compared with hydrogen at the same position.



[92]



[93]

Arrow indicates site of attack.

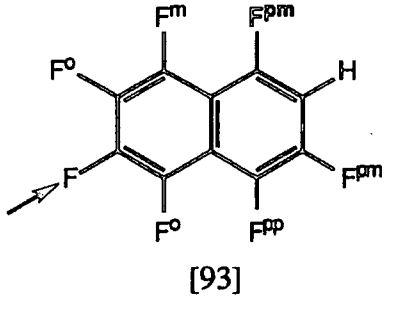
Relative Effect of Pseudo Para fluorine w.r.t. H.

k_{rel} ($lmol^{-1}s^{-1}$)	1.12×10^{-3}	1.38×10^{-3}	$1.12 \times 10^{-3}/1.38 \times 10^{3} = \underline{0.81}$

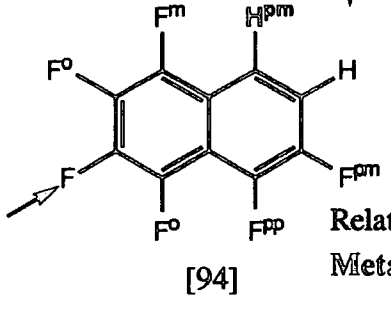
Scheme 3.22. *Measure of the effect of fluorine pseudo para to the reaction site.*

Fluorine 'pseudo para' to the site of nucleophilic attack is slightly deactivating by a factor of 0.81 and hence has an effect similar to normal para fluorine.

Reaction rates for 2-hydro-perfluoronapthalene [93] and 1,2-dihydro-perfluoronapthalene [94] were compared (Scheme 3.23), to determine the effect of pseudo meta fluorine compared with hydrogen at the same position.



[93]



[94]

Arrow indicates site of attack.

Relative Effect of Pseudo Meta fluorine w.r.t. H.

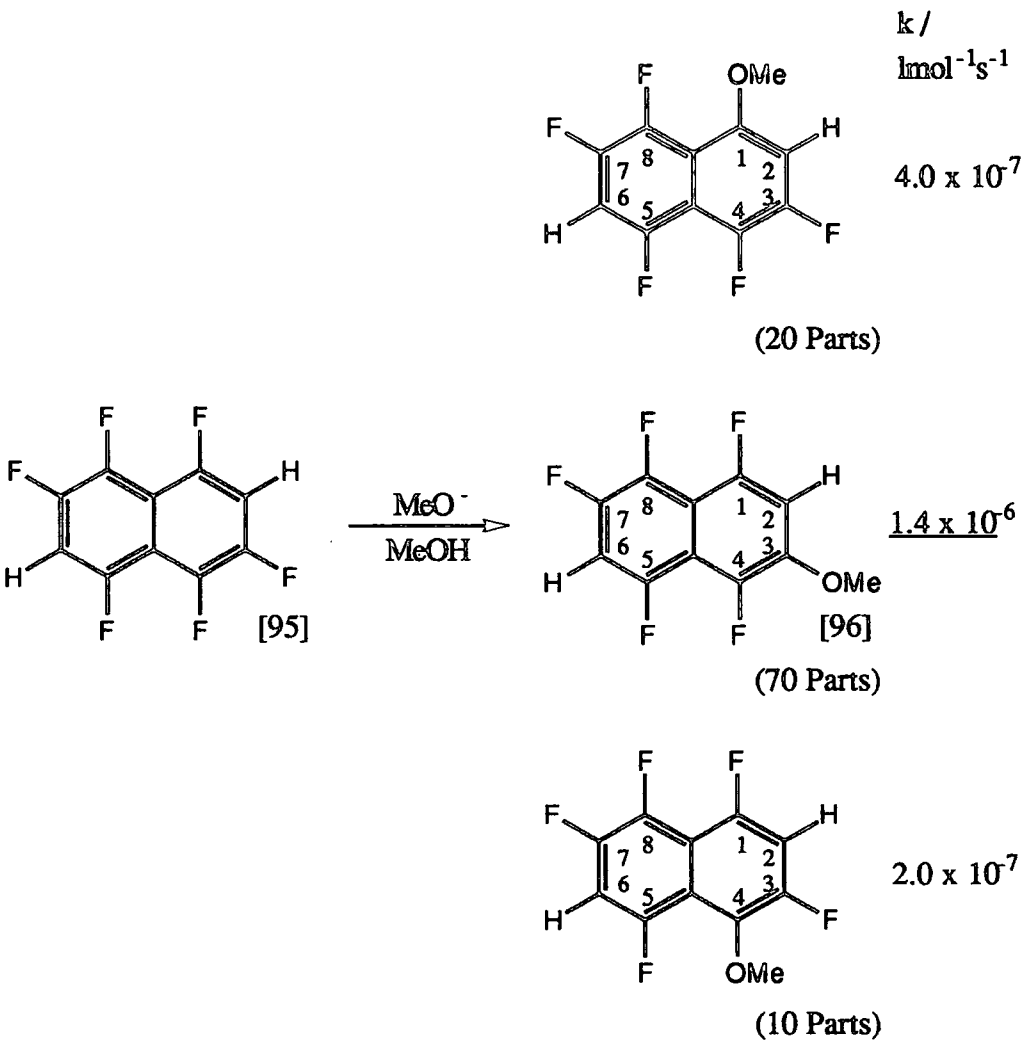
k_{rel} ($lmol^{-1}s^{-1}$)	1.38×10^{-3}	4.55×10^{-5}	$4.55 \times 10^{-5}/1.38 \times 10^{-3} = \underline{30}$

Scheme 3.23. *Measure of the effect of fluorine pseudo meta to the reaction site.*

Fluorine 'pseudo meta' to the site of nucleophilic attack is strongly activating by a factor of 30 and therefore has a similar effect to normal meta fluorine.

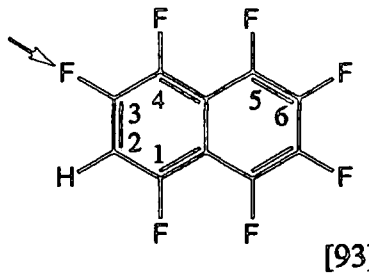
The activation by ortho fluorine in a polycyclic system was estimated as follows. The rate constant for 3- attack of 2,6-dihydro-perfluoronaphthalene [95] was

calculated from the overall rate constant and integrations from ^{19}F nmr spectroscopy, since 2,6-dihydro-perfluoronaphthalene is monosubstituted by methoxide at the 1-, 3- and 4- positions in the proportions 20 : 70 : 10 respectively, as shown in Scheme 3.24.



Scheme 3.24. *Monosubstitution of [95] at the 1-, 3- and 4- positions.*

An estimation for the hypothetical calculated rate of attack at position 3- in 2-hydro-perfluoronaphthalene [93] can then be made by taking the rate constant for 3-attack in 2,6-dihydro-perfluoronaphthalene [95], yielding [96] and applying correction for replacing the 6 hydrogen with pseudo meta fluorine (Scheme 3.25).

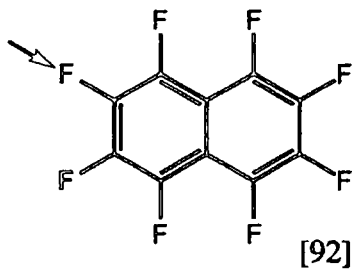


[93]

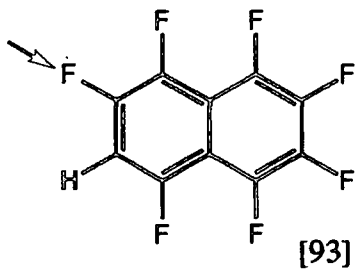
$k_{theoretical} = 1.4 \times 10^{-6} \times 30$
$lmol^{-1}s^{-1} = 4.6 \times 10^{-5}$

Scheme 3.25. *Calculation of the theoretical rate constant for 3- attack in 2-hydro-perfluoronaphthalene [93].*

A measure of the effect of ortho fluorine can then be calculated by comparing the above rate constant for 3- attack in [93] with the rate constant for 2- attack in octafluoronaphthalene [92] (Scheme 3.26).



[92]



[93]

Relative Effect of Ortho Fluorine w.r.t Hydrogen.

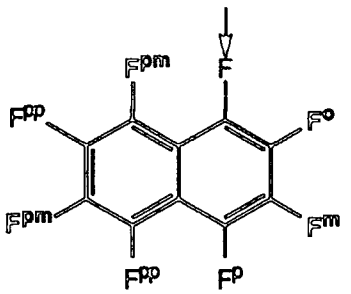
$= 1.12 \times 10^{-3} / 4.6 \times 10^{-5}$
$=$ ca. 25.

k_{rel} 1.12×10^{-3} 4.6×10^{-5}

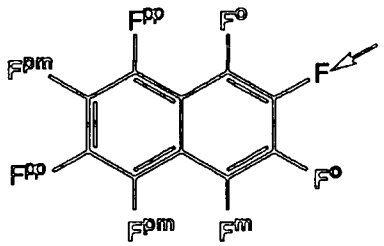
Scheme 3.26. *Measure of the effect of fluorine ortho to the reaction site.*

Fluorine situated ortho to the site of substitution in a polycyclic polyfluoroaromatic is activating by a factor of 25 with respect to hydrogen at the same position. This is similar to the effect of ortho fluorine in a simple polyfluoroaromatic.

The experimentally established data shows that nucleophilic attack occurs at the 2- position[23] in octafluoronaphthalene[92], with small amounts of 1- substitution (<9%) observed with some poorer nucleophiles[49]. Nucleophilic substitution in decafluoroanthracene [97] occurs at the 2- position[24]. In both substrates the 2- position is the site which posesses the greatest number of activating fluorines (and the least number of deactivating fluorines), (see Scheme 3.27).

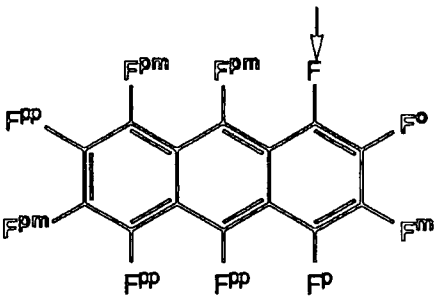


[92]

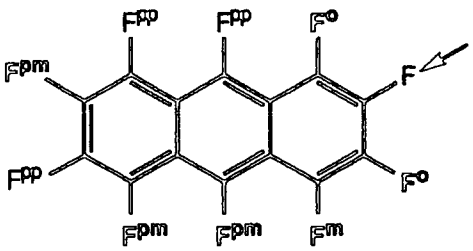


4 Activating Fluorines
1o + 1m + 2pm

5 Activating Fluorines
2o + 1m + 2pm

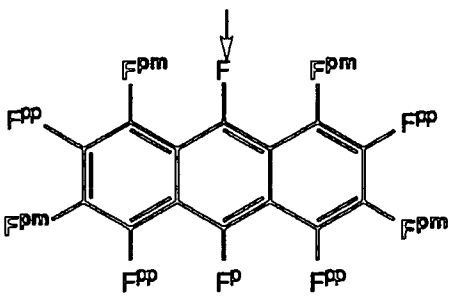


[97]



5 Activating Fluorines
1o + 1m + 3pm

6 Activating Fluorines
2o + 1m + 3pm



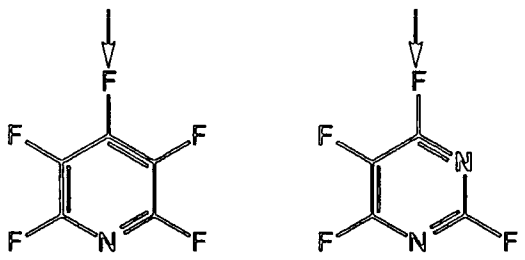
4 Activating Fluorines
4pm

Scheme 3.27. *The possible sites of displacement of fluorine in [92] and [97].*

The effect of introducing ring nitrogen into benzenoid aromatics have been determined[50]. The rate constants for nucleophilic attack on some polyfluorinated pyridines and diazines with ammonia in dioxan/water 60:40 v/v have been measured. Comparison of the relevant heterocycles has allowed the activation effect of ring nitrogen ortho, meta and para to the site of nucleophilic attack to be determined relative to a C-F, and using the data above, C-H at the same position.

The comparison of rate constants for nucleophilic substitution in pentafluoropyridine [85] and tetrafluoropyrimidine [98], gives a measure of the relative

activating effect of ring nitrogen ortho to the site of attack relative to C-F (Scheme 3.28.).



[85] [98]

k 6.80×10^{-4} 1.35
($lmol^{-1}s^{-1}$)

↓ Arrow indicates site of attack.

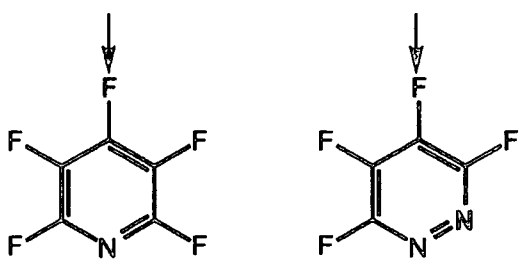
Effect on Reaction Rate of Ring Nitrogen Ortho to Reaction Site w.r.t . C-F.

$= 1.35 / 6.80 \times 10^{-4}$
$= \underline{2.0 \times 10^{3}}$

Scheme 3.28. *Determination of the effect of ring nitrogen ortho to the site of attack.*

Ring nitrogen situated ortho to the site of nucleophilic attack is activating by a factor of 2000 relative to C-F, and since fluorine ortho to the site of attack is activating by a factor of 31 relative to hydrogen, then the effect of ring nitrogen ortho to the site of attack relative to C-H is activating by a factor of 2000 x 31 = 62000.

A similar approach to that described above, but with pentafluoropyridine [85] and tetrafluoropyridazine [99] provides a measure of the activating effect of ring nitrogen meta to the site of attack (Scheme 3.29).



[85] [99]

k 6.80×10^{-4} 2.52×10^{-2}
($lmol^{-1}s^{-1}$)

↓ Arrow indicates site of attack.

Effect on Reaction Rate of Ring Nitrogen Meta to Reaction Site w.r.t . C-F.

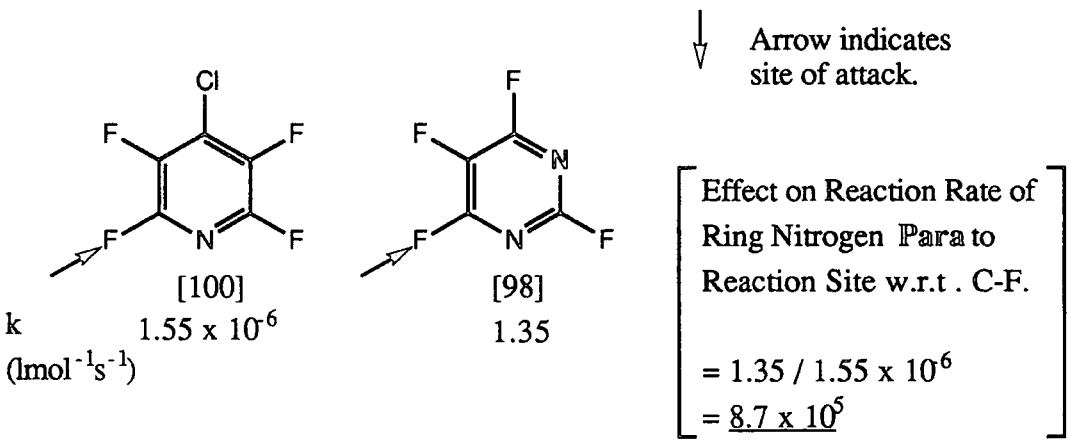
$= 2.52 \times 10^{-2} / 6.80 \times 10^{-4}$
$= \underline{37}$

Scheme 3.29. *Determination of the effect of ring nitrogen meta to the site of attack.*

Ring nitrogen which is situated meta to the site of nucleophilic attack is activating by a factor of 37 relative to C-F at the same position. The effect of fluorine meta to the site of

attack is activating with respect to hydrogen at the same position by a factor of 23, hence the effect of ring nitrogen on the meta position relative to C-H at the same position is activation by 37 x 23 = 850.

The effect of nitrogen para to the site of attack is estimated by the comparison of the rate of displacement of fluorine from 4-chloro-tetrafluoropyridine [100] and tetrafluoropyrimadine [98] (Scheme 3.30). It should be noted that the 4-chloro substituent in the tetrafluoropyridine has to be present since fluorine at the 4-position would be displaced preferentially to the 2- fluorine in [100]. The effect however, of chlorine and fluorine meta to the site of attack (as in this case) are virtually identical, being activating in both cases by a factor of 24 and 23 respectively.[51]



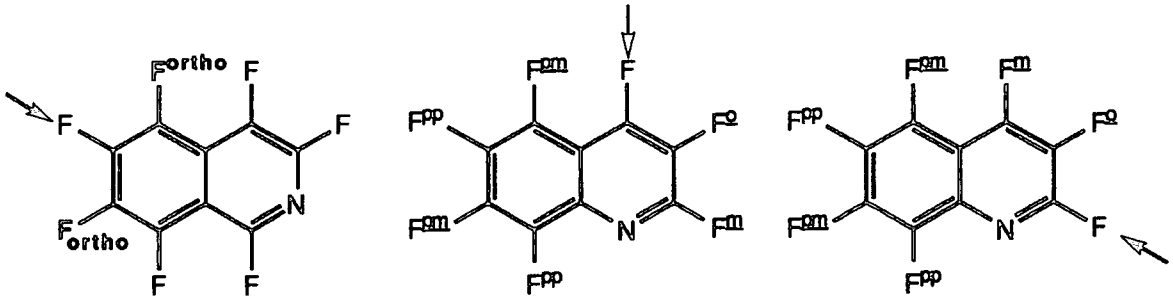
Scheme 3.30. *Determination of the effect of ring nitrogen para to the site of attack.*

Ring nitrogen situated para to the site of nucleophilic attack is strongly activating relative to C-F at the same position. The effect of fluorine para to the site of attack relative to hydrogen at the same position is slightly deactivating by a factor of 0.26, hence the effect of ring nitrogen para to the site of attack relative to C-H at the same position is activation by a factor of $8.7 \times 10^5 \times 0.26 = 230000$.

Ring nitrogen significantly activates all positions in the monocyclic heterocycles relative to both C-F and C-H at the same positions, with the para position being the most activated, followed by ortho. If this theory is applied to the isoquinoline [1], attack at the 1- position could be rationalised using the fact that the 1-F is ortho to the ring nitrogen, (the most activated position by ring nitrogen, since there is no position

para to ring nitrogen). It is unclear, therefore, why with sulphur nucleophiles the 6 fluorine is displaced preferentially from [1], although no measure of the effect of ring nitrogen located in a remote ring was available and this could be significant. Substitution in the quinoline [2] could be rationalised using the fact that the fluorines displaced are ortho and para to the ring nitrogen, however, it is not clear why the fluorine para to the ring nitrogen is not always displaced preferentially since this is the most activated by ring nitrogen.

Initial thoughts were directed towards the idea that, since the sulphur nucleophiles were more reactive than the oxygen nucleophiles, then the system as a whole would be more reactive with the sulphur nucleophiles. Attention had been drawn to the fact that the effect of fluorine ortho to the site of attack increases relative to fluorine meta to the site of attack, with the reactivity of the system[48]. Substitution at the 6-position in the isoquinoline [1] with sulphur nucleophiles could be due to an increase in activation of the two fluorines ortho to the 6- site. This theory could not however be transfered to the quinoline [2] since attack at the 2- and 4- positions have the same number of activating fluorines, and more importantly the number of fluorines ortho to the site of attack is the same for both 2- and 4- attack (i.e. one) (Scheme 3.31).



Scheme 3.31.

It was therefore necessary to perform some kinetic work to try and establish whether there was a connection between orientation and reactivity in heptafluoro-isoquinoline [1] and -quinoline [2].

Chapter 4

Competition Experiments of Heptafluoro-Isoquinoline [1] and -Quinoline [2] towards Nucleophiles

Chapter 4

Competition Experiments of Heptafluoro-Isoquinoline [1] and -Quinoline [2] towards Nucleophiles.

4.1 Results.

Competition experiments where two or three nucleophiles compete for the same substrate were performed. An equimolar amount of the nucleophiles was added to a small proportion of the substrate [1] or [2]. The conditions ensure a gross excess of each nucleophile is always present and hence that the reactions are parallel pseudo first order; a system which ensures the ratio of the products is the ratio of the rate constants (see Appendix 2).

All the reactions were performed at low temperature (<-85°C) with subsequent warm up (<-35°C), followed by quenching with trifluoroacetic acid to prevent further substitution of the products. Competition experiments with [1] were performed with various combinations of ethoxide, isopropylthiolate and various para substituted benzenethiolates [para group being N,N-dimethylamino, methoxy, hydro (i.e. the parent benzenethiol) and nitro]. The results are all shown in Table 4.1 and a worked example of how the results were produced is also given.

Table 4.1 *Relative Reactivities of [1] and [2] towards Nucleophiles*

	$4\text{-}Me_2N\text{-}C_6H_4S^-$	$4\text{-}MeO\text{-}C_6H_4S^-$	Pr^iS^-	$C_6H_5S^-$	EtO^-	$4\text{-}NO_2\text{-}C_6H_4S^-$
Reaction with the Isoquinoline [1] :						
At position 6	12,000	3000	400	300	1	0.25
At position 1			10		1	
Reaction with the Quinoline [2] :						
At position 4				1000	1	

Phenylthiolate, isopropylthiolate and ethoxide were all competing for a small quantity (ca. 4mol% rel. to each nucleophile) of isoquinoline [1] (See 6.4.1.iii). The sodium salts of the nucleophiles in ethanol were added to a cooled (<-85°C) ethanolic solution of the isoquinoline [1]. The mixture was allowed to warm to -70°C and then the reaction was quenched with trifluoroacetic acid. The crude product after work up was shown by ^{19}F nmr to contain unreacted starting material [1] (45%) and the products (55%): the 6-phenylthioisoquinoline [43] , the 1-isopropylthioisoquinoline [49], the 6-isopropylthioisoquinoline [50], the 1,6-di(isopropylthio)isoquinoline [51] and the 1-ethoxyisoquinoline [60] in the ratio 36 : 12 : 47 : 2 : 2 respectively, see Fig 4.1. and Scheme 4.1.

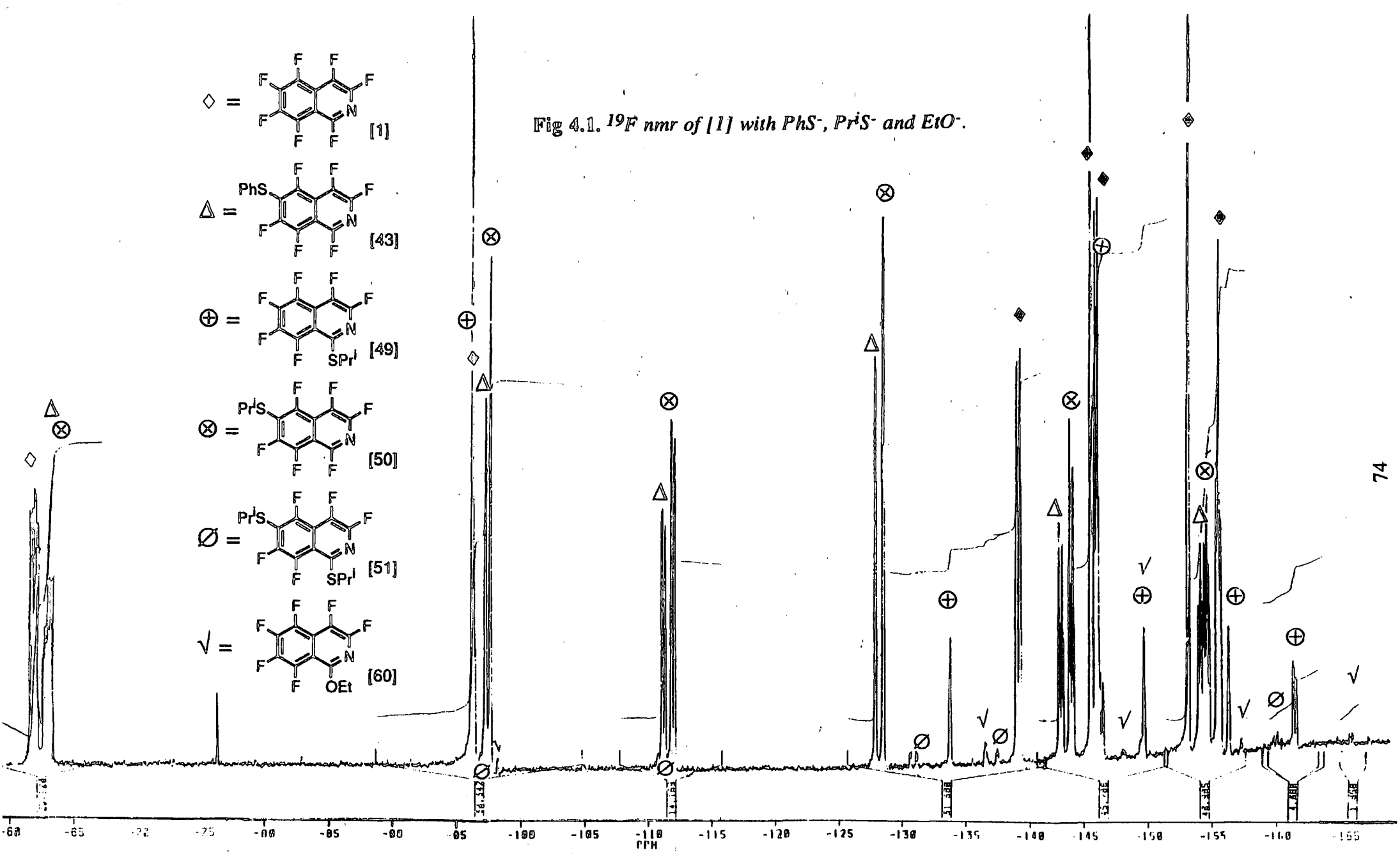
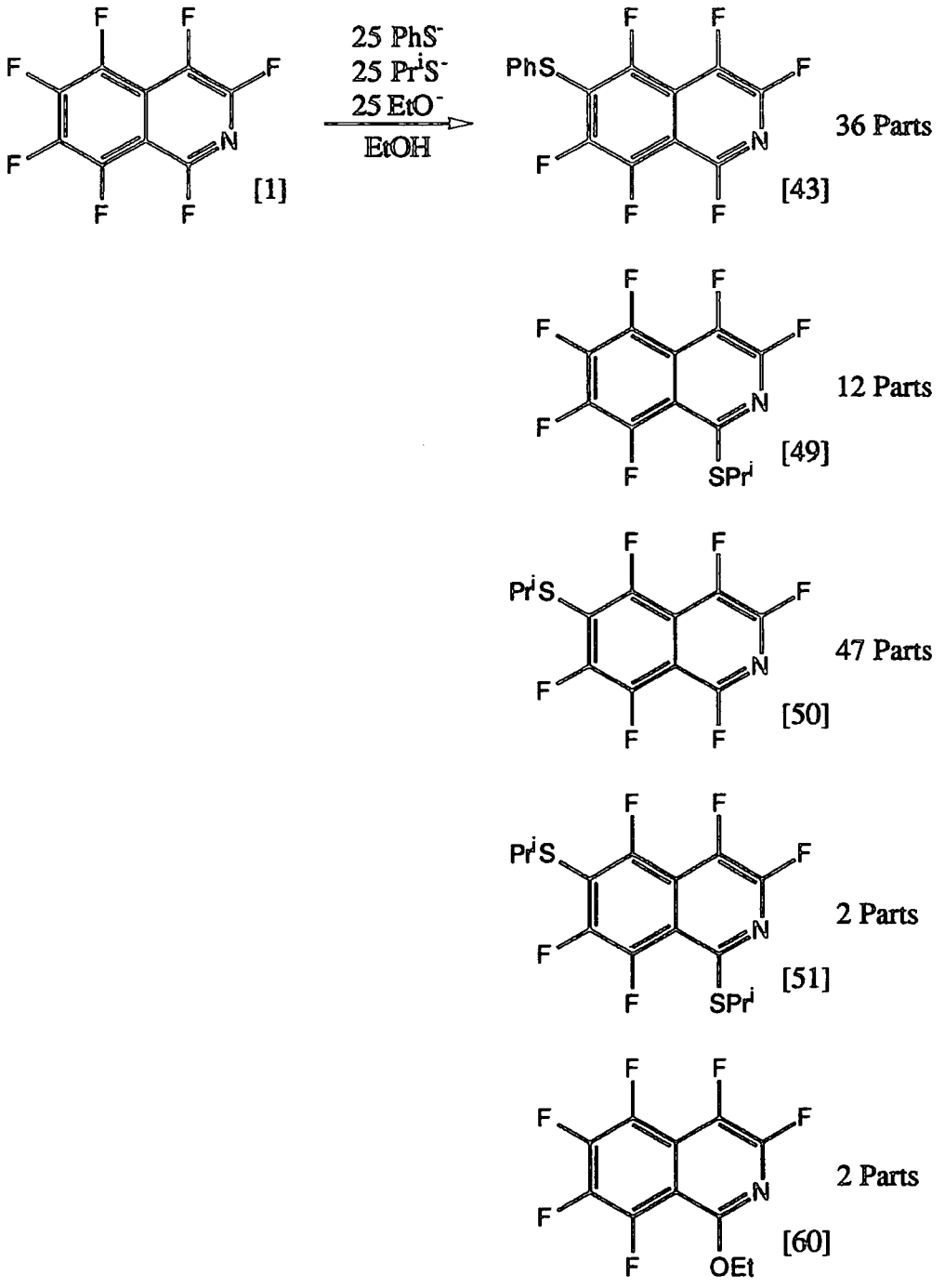


Fig 4.1. *^{19}F nmr of [1] with PhS^-, Pr^iS^- and EtO^-.*

The 1,6-di(isopropylthio)isoquinoline [51] could come from either of the mono substituted derivatives [49] and [50] by action of more isopropylthiolate; however, the proportion of [51] is at a significantly low enough level to not make a large difference to the results (see below).



Scheme 4.1. *Competition reaction of [1] with three nucleophiles.*

Since the 1-ethoxy-isoquinoline [60] must be accompanied by the 6-ethoxy-isoquinoline [61] in the ratio 94 : 6, when ethoxide alone is reacted with the isoquinoline

[1] (see Chapter 3), the mixture from the competition experiment must contain 6 / 94 x 2 parts of the 6-ethoxy-isoquinoline [61] (0.13 parts and 0.06% of total crude product), a level which is below the detection limit of nmr instrument, typically 0.5%.

At the 6- position

Reactivity of the thiolates with respect to ethoxide.

For phenylthiolate

Reactivity of PhS^- : EtO^-

36 : 6/94 x 2 ca. 300 : 1

Assuming the 1,6-diisopropylthioisoquinoline [51] comes from the 6-sulphide [50].

For isopropylthiolate

Reactivity of Pr^iS^- : EtO^-

49 : 6/94 x 2 ca. 400 : 1

Assuming the 1,6-diisopropylthioisoquinoline [51] comes from the 1-sulphide [49].

Reactivity of Pr^iS^- : EtO^-

47 : 6/94 x 2 ca. 400 : 1

At the 1- position

Assuming the 1,6-diisopropylthioisoquinoline [51] comes from the 6-sulphide [50].

Reactivity of Pr^iS^- : EtO^-

12 : 2 6 :1

or assuming the 1,6-diisopropylthioisoquinoline [51] comes from the 1-sulphide [49].

14 : 2 7 : 1

These results compare well with the separate two nucleophile experiments of phenylthiolate / ethoxide and isopropylthiolate / ethoxide where reactivity at the 6-position in [1] was found to be 300 : 1 and 600 : 1 respectively; the reactivity at the 1-position in the isopropylthiolate / ethoxide competition experiment was 10 : 1.

No comparison for phenylthiolate at the 1- position was possible since no detectable level of the 1-phenylthio-isoquinoline is formed in the reaction of [1] with phenylthiolate (see Chapter 3).

The competition experiments with the most reactive nucleophiles (4-substituted -N,N-dimethylamino and -methoxy benzenethiolates) were repeated under different conditions since it was of concern that at the initial point of addition of the nucleophile to substrate there would be a momentary excess of substrate. The isoquinoline [1] in ethanol was precooled to -90°C and added to the nucleophiles dissolved in ethanol, also cooled to -90°C The reaction was then quenched with trifluoroacetic acid in ethanol, also precooled to -90°C The product ratio was exactly the same as before.

To ensure that the trifluoroacetic acid added as the reaction quenching agent was not taking part in any reaction of [1] with the residual thiols, thiophenol, trifluoroacetic acid and [1] were stirred for one hour and then shown by ^{19}F nmr spectroscopy to contain only [1]. Heating the mixture at 70°C for 2.5 hours also gave only unreacted [1]. It had been shown previously that reaction of the quinoline [2] in concentrated sulphuric acid with methanol at 0°C gave selective substitution of the 2-position[13].

Phenylthiolate and ethoxide were allowed to compete for a small quantity of quinoline [2]. The estimation of the relative reactivities of the two nucleophiles could only be performed at the 4- position since the phenylthiolate does not give any detectable product for 2- substitution. The results are given in Table 4.1.

The relative reactivities of the two heterocycles [1] and [2] were determined both for attack by ethoxide, and phenylthiolate. In each experiment a small amount of the sodium salt of the nucleophile in ethanol was added to a cooled (<-80°C) ethanolic solution of the two heterocycles. The mixture was allowed to warm up to room temperature and the crude product examined by ^{19}F nmr. The experiment with ethoxide as nucleophile gave a product containing starting materials [1] and [2] (97.75% total) and three products (2.25%): the 1-ethoxyisoquinoline [60], the 2-ethoxyquinoline [77] and

the 4-ethoxyquinoline [78] in the ratio 12 : 68 : 20 respectively. The ratio of the 2-ethoxy-quinoline [77] to 4-ethoxy-quinoline [78] was 3.4 : 1; precisely the same ratio as when [2] alone is reacted with ethoxide (see Chapter 3).

The relative reactivity of the isoquinoline [1] and the quinoline [2] towards ethoxide:

Isoquinoline [1] : Quinoline [2]

1- ethoxy [60] : 2- and 4- ethoxy [77] + [78]

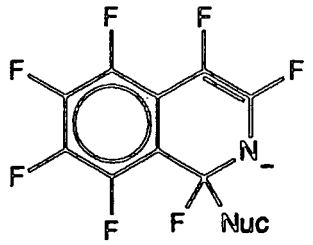
12 : 88 ca. 1 : 7

The quinoline [2] is more reactive than the isoquinoline towards ethoxide by a factor of ca. 7. A similar experiment with phenylthiolate as the nucleophile found the quinoline [2] to be ca. 30 times more reactive than the isoquinoline [1] towards nucleophilic attack.

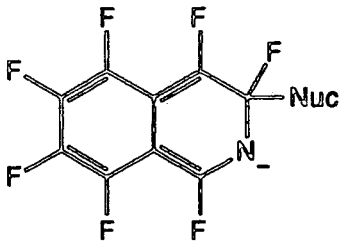
4.2 Discussion

The competition experiments showed that there is no correlation between the reactivity of the system and the site of substitution. In fact, 6- attack occurs in the isoquinoline [1], for both benzenethiolate and 4-nitro-benzenethiolate, despite the former being more reactive than ethoxide at the 6- position and the latter less reactive than ethoxide at the 6- position; the ethoxide prefers 1- attack in [1].

The effects of fluorine ortho, meta, para, pseudo meta and pseudo para to the site of attack and effect of ring nitrogen were examined. With the isoquinoline [1] there is no position para to ring nitrogen bearing a fluorine (the position para to ring nitrogen is the most activated to nucleophilic substitution), thus attack may be expected ortho to ring nitrogen since the effect of ring nitrogen in polyfluoroheteroaromatics is usually the dominating factor with regard to the site of substitution; i.e at the 1- position and the 3-position. Attack at the 3- position is ruled out on the basis that for localisation of the negative charge on ring nitrogen, a total loss of aromaticity would be required, whereas for 1- attack aromaticity can be partially retained (Scheme 4.2).



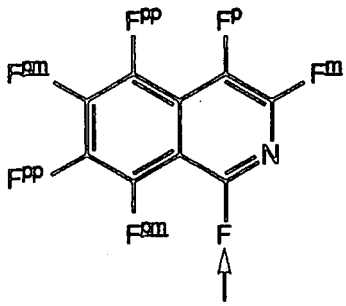
1- Attack



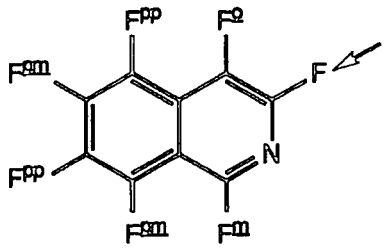
3- Attack

Scheme 4.2. *Attack at the 1- and 3- positions in [1] with localisation of the negative charge on ring nitrogen.*

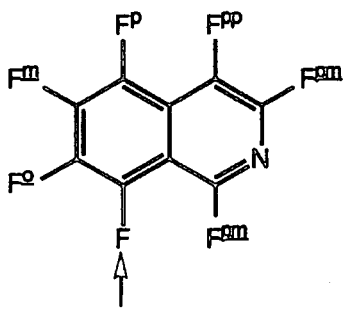
There has been no attempt made to measure the influence of ring nitrogen on positions remote from the heterocyclic ring, and this may be significant. A count of the number of activating fluorines for attack at all positions where the negative charge can be localised on ring nitrogen, reveals the 6- position to have the most activating fluorines and the 1- position to have the least number of activating fluorines (scheme 4.3).



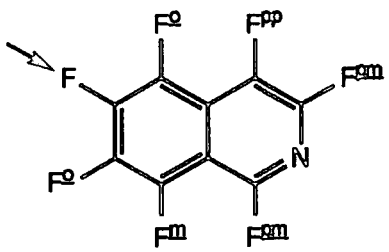
3 Activating Fluorines
3 Deactivating Fluorines



4 Activating Fluorines
2 Deactivating Fluorines



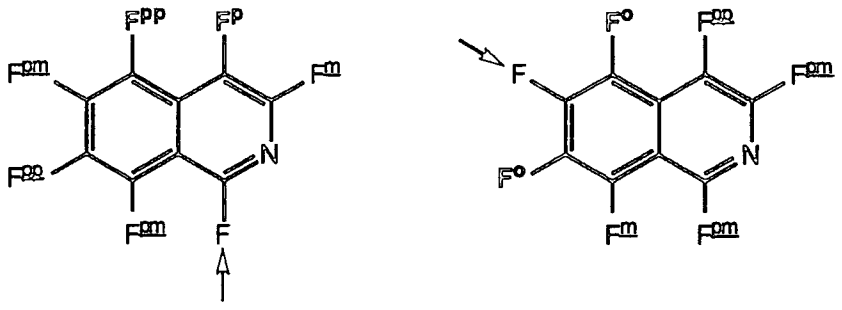
4 Activating Fluorines
2 Deactivating Fluorines



5 Activating Fluorines
1 Deactivating Fluorines

Scheme 4.3.

The difference in terms of 'types' of fluorine between attack at position 6- and position 1- in [1], is that the 6- position has <u>two activating</u> ortho fluorines whereas the 1- position has <u>one deactivating</u> para fluorine and <u>one deactiavting</u> pseudo para fluorine, (see Scheme 4.4).



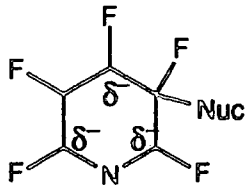
Fluorine Types common to 1- and 6- attack:- F^{m}, $F^{pp} + 2F^{pm}$.

Activation of the 6- position by fluorine relative to the 1- position =
$(F^{o} \times F^{o}) / (F^{p} \times F^{p}) = (25 \times 25) / (0.26 \times 0.81) =$ ca. 3000

F^{x} = activation of fluorine
at position x relative to
hydrogen at same position.

Scheme 4.4. *Activation of the 6- position by Fluorine relative to the less activated 1- position.*

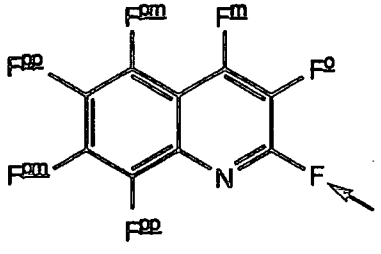
The 6- position is more activated than the 1- position by the fluorines by a factor of 3000. Thus, since ring nitrogen activates the 1- position ortho to it by a factor of 62000 relative to C-H, then ring nitrogen pseudo para to the 6- position would only need to activate the system by a factor of 21 (62000 / 3000) relative to C-H at the same position to make the 6- position the preferred site of attack. Ring nitrogen activates all sites in monocyclic aza-benzenes, including the meta position by a factor of 850 relative to C-H, a position which doesn't permit localisation of the negative charge in the Wheland type intermediate (Scheme 4.5).



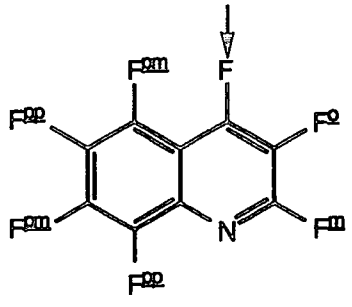
Scheme 4.5. *Hypothetical nucleophilic attack meta to ring nitrogen in pentafluoropyridine.*

Attack at the 6- position in [1] would allow localisation of the negative charge on ring nitrogen, albeit with loss of aromaticity of the whole system, and therefore ought to considerably activate the system to nucleophilic attack. Since ring nitrogen activates the meta position by 850 relative to C-H at the same position, the 6- position in [1] ought to be activated considerably more than a factor of 21. It would therefore be reasonable to say that the 6- position would be the normal site of substitution in [1] with respect to nucleophilic substitution, with attack at the 1- position being the oddity.

The activating and deactivating fluorines for 2- and 4- attack in the quinoline [2] in terms of 'type',however, are identical, i.e. one ortho, one meta, two pseudo meta and two pseudo para (Scheme 4.6).



4 Activating Fluorines
2 Deactivating Fluorines



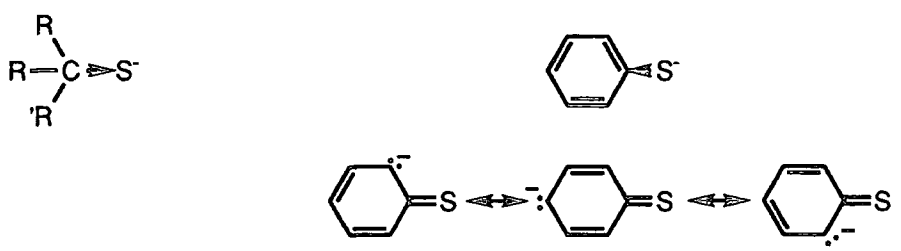
4 Activating Fluorines
2 Deactivating Fluorines

Scheme 4.6.

It has been found in previously reported work[50], that ring nitrogen directs attack most strongly toward the para position; therefore it would be reasonable to expect attack in the quinoline [2] to occur at the 4- position and not the 2- position.

The difference in hardness or softness of the incoming nucleophile is the only remaining obvious explaination for the change of orientation by oxygen and sulphur nucleophiles. The original nucleophilic substitution experiments of the isoquinoline [1] and the quinoline [2] performed in 1966, used nucleophiles which are classified as 'hard'. The ring nitrogen causes the position ortho to itself to be harder than the other positions in the heterocycle by a polarisation effect, and hence attack by hard nucleophiles occurs at the 1- position in the isoquinoline [1] and the 2- position in the quinoline [2]. An initial coulombic interaction is held responsible for the hard nucleophile preferring the position ortho to ring nitrogen[52]. Increasingly 'softer' oxygen nucleophiles (ethoxide, phenoxide and 4-nitro-phenoxide) studied in the present work have shown an increasing favour for the 4- position in the quinoline [2]. However no change of orientation with the isoquinoline [1] and the 'softer' aryl oxygen nucleophiles was seen. The balance of power must therefore be finer for the quinoline [2] than it is for the isoquinoline [1].

The hardest sulphur nucleophiles would be the alkanethiolates, since the alkyl group will push additional charge onto the sulphur, (Scheme 4.7), and these do indeed show some affinity for the 1- position in [1] and the 2- position in [2], whereas the softer aryl thiolates which allow delocalisation of the negative charge into the aromatic ring show no or virtually no affinity for the 1- position in [1] and the 2- position in [2].



Increased charge on S
⇨Harder Nucleophile

Decreased charge on S
⇨ Softer Nucleophile

Scheme 4.7. *Effect on hardness/softness of sulphur centre by alkyl/aryl group.*

Finally, since it has been predicted that ring nitrogen pseudo para to the reaction site has a significant activation effect, it seems reasonable to try and estimate its value, although a somewhat crude approach is applied where certain assumptions have to be made. Firstly it is assumed that the effects of fluorine and ring nitrogen determined in other work are the same for the bicyclic heteroaromatic isoquinoline [1]. Secondly, data for attack on [1] by the nucleophiles 4-methoxyphenylthiolate and 4-N,N-dimethylaminophenylthiolate are used since proportions of both 1- and 6- products are formed (necessary for the calculation), the former being assumed not to come about from an initial coulombic interaction between the 1- position and the nucleophile, despite this being highly likely since [1] with phenylthiolate gives no 1- mono-substituted product; the calculation will therefore give a minimum value for the effect of ring nitrogen pseudo para to the site of attack, with the real value possibly being somewhat higher.

Heptafluoroisoquinoline reacts with the 4-methoxyphenylthiolate (and also with 4,N,N-dimethylaminophenylthiolate) to give the 1- sulphide, the 6- sulphide and the 1,6-disulphide in the ratio 0.5 : 97.5 : 2 respectively. Fluorines attached to the heterocycle activate the 6- position over the 1- position by a factor of 3000 and ring nitrogen activates the position ortho to it by a factor of 62000 compared to C-H at the same position.

The effect of ring nitrogen pseudo para (Ring Npp) to the reaction site can be calculated from the increase in activation of the 6- site over the 1- site by fluorine (Inc Act by F at 6- posn), the effect of ring nitrogen ortho to the site of attack and the proportions of 6- product and 1- product formed in the reaction of [1] with 4-N,N-dimethylaminothiophenate.

Thus:-

(Effect Ring Npp) x (Inc Act by F at 6- posn) / (6- Prod) = (Effect Ring Northo) / (1-Prod)

Then if the 1,6-disulphide comes from the 1- sulphide, the ratio of 6- Prod : 1- prod will be 97.5 : (2.0 + 0.5)

Effect Ring Npp = (97.5 / 2.5) * 62000 / 3000

= ~800

or if the 1,6-disulphide comes from the 6- sulphide, the ratio of 6- Prod : 1- prod will be (97.5+ 2.0) : 0.5

Effect Ring Npp = (99.5 / 0.5) * 62000 / 3000

= ~4000

Ring Nitrogen situated pseudo para to the site of reaction is therefore activating by a factor at least 800 to 4000 relative to C-H at the same position, and probably activates considerably more than this since when the isoquinoline [1] is reacted with phenylthiolate no 1- sulphide is detectable. Ring nitrogen pseudo para to the reaction site activates the position to attack by an effect at least as strong as that of ring nitrogen meta to the site of attack.

Chapter 5

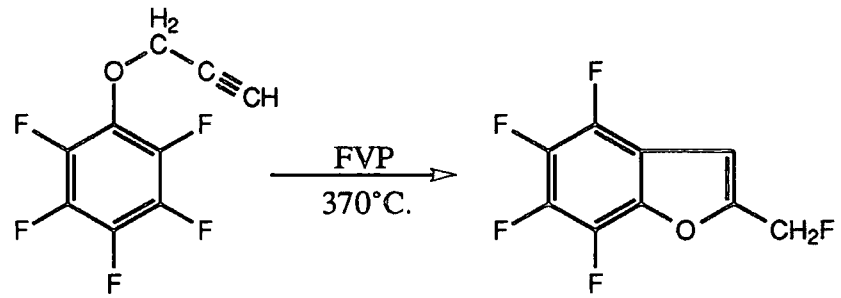
The Pyrolysis of some Highly Fluorinated Naphthalene Derivatives.

Chapter 5.

The Pyrolysis of some Highly Fluorinated Naphthalene Derivatives.

5.1 Background

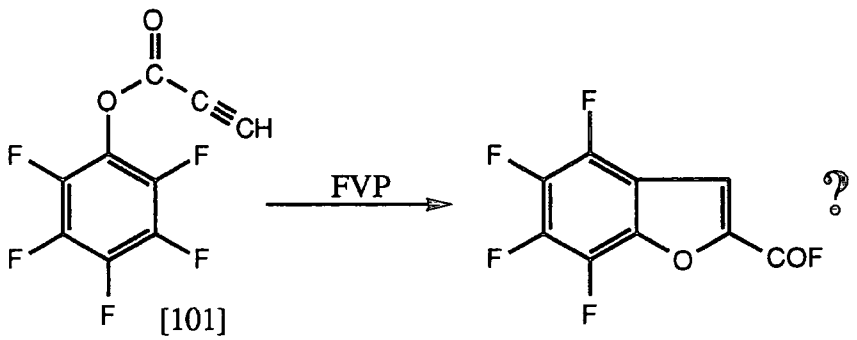
In Chapter 2, it was noted that flash vacuum pyrolysis (FVP) of pentafluorophenyl prop-2-ynyl ether [21] produced a tetrafluorobenzo[b]furan derivative [22] (Scheme 5.1)[35].



[21] [22]

Scheme 5.1. *FVP of pentafluorophenyl prop-2-ynyl ether [21].*

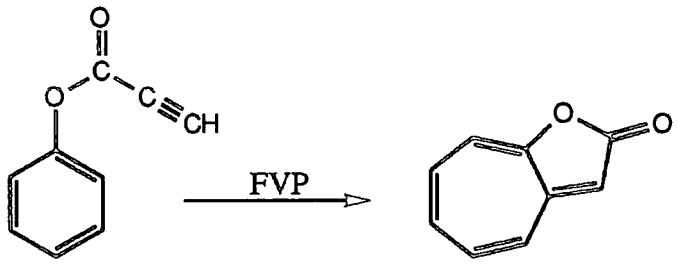
The possibility of extending this reaction to the pentafluorophenyl propynoate [101], shown in Scheme 5.2, was of interest, the only difference between the materials being that the CH_2 in the ether is replaced with a carbonyl functionality making an ester.



[101]

Scheme 5.2. *Possible course of reaction: FVP of [101].*

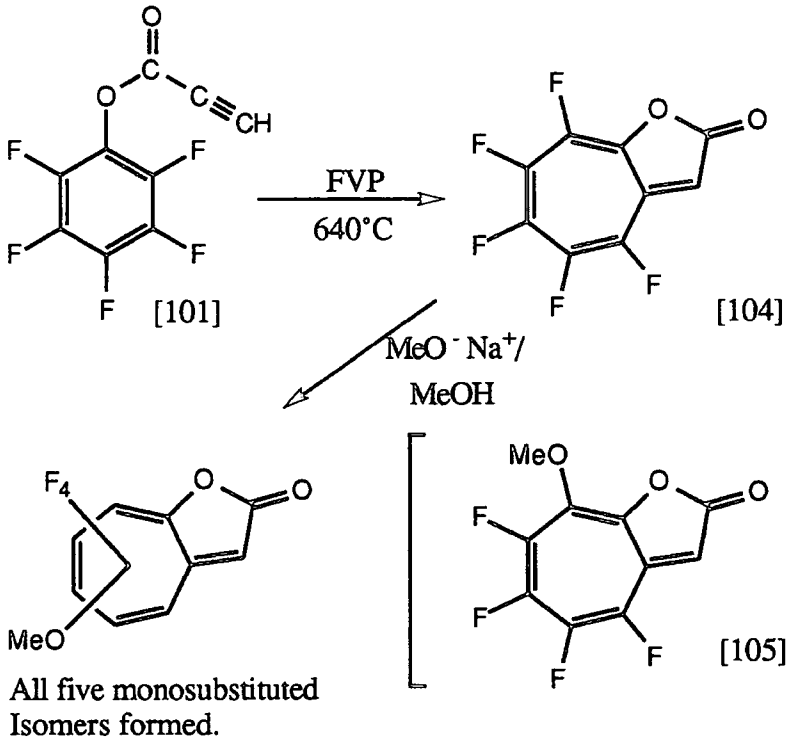
Trahanovsky had already investigated the FVP of the hydrocarbon analogue of [101], phenyl propynoate [102], and found it to undergo ring expansion to form 2H-cyclohepta[b]furan-2-one [103] (Scheme 5.3)[53].



[102] [103]

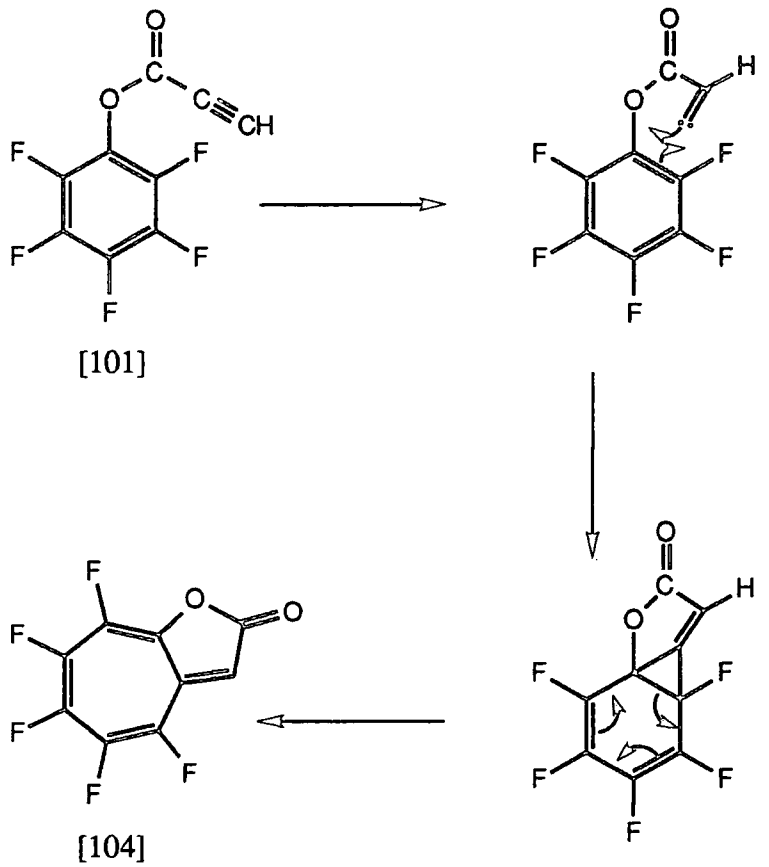
Scheme 5.3. *FVP of [102] to form [103].*

It was clearly of interest to see what course the pentafluorophenyl analogue [101] would take on pyrolysis. Flash vacuum pyrolysis of [101] at 640°C gave a very dark product yielding a golden yellow solid. This was positively identified as [104] by nmr spectroscopy and by X-ray crystallographic analysis of the monomethoxy derivative [105], one of the five formed by the reaction of [104] with sodium methoxide in methanol (Scheme 5.4)[54].



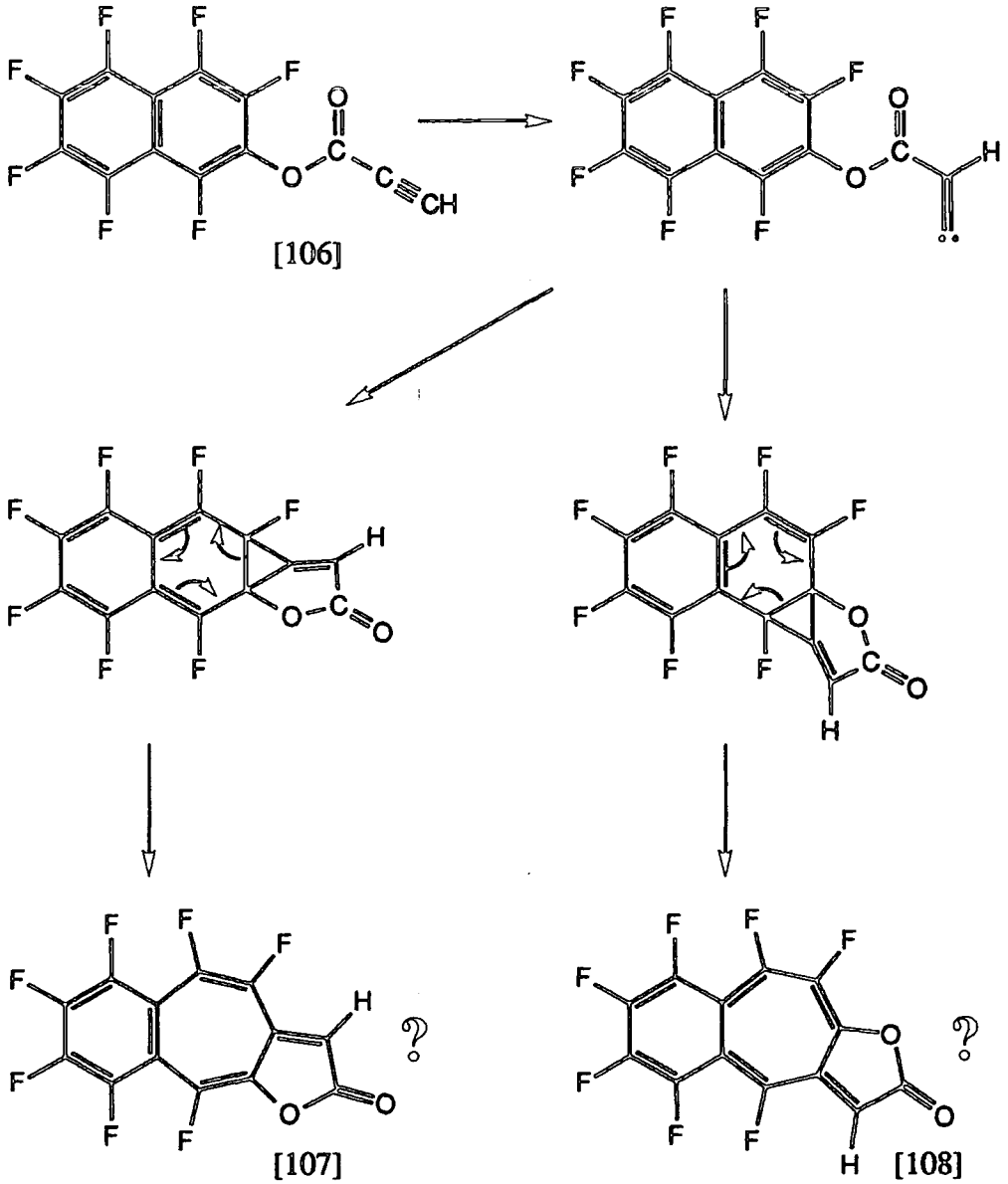
Scheme 5.4. *FVP of [101] to form [104]. Reaction of [104] with methoxide.*

The mechanism of the reaction was proposed to proceed via an acetylene-methylene carbon rearrangement followed by insertion of the carbene into the benzene ring via a three membered intermediate (Scheme 5.5.).



Scheme 5.5. *Mechanism of formation of [104].*

Cyclisation reactions of highly fluorinated aromatics where closure can take place in two different directions have been investigated[29,31]. The possibility of extending the seven membered ring-forming reaction to the naphthalene system [106] was therefore clearly of interest, since carbene insertion could take place in two different directions giving the possible products [107] and [108] (Scheme 5.6).

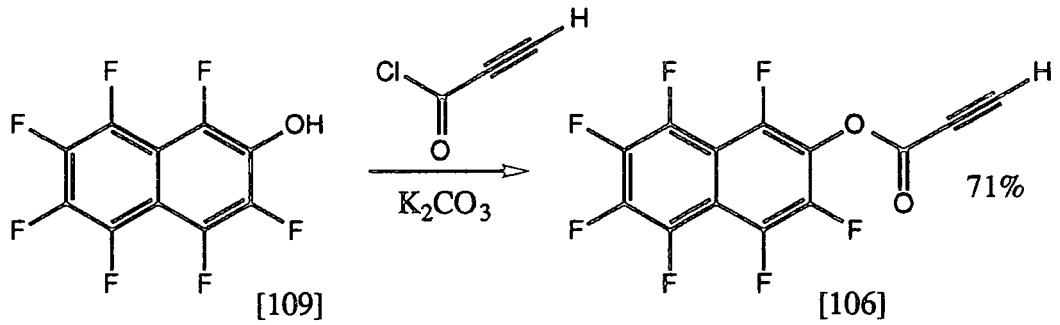


Scheme 5.6. *Proposed Products [107] and [108] from FVP of [106] via carbene insertion mechanism.*

5.2 Results.

5.2.1 Preparation and Flash Vacuum Pyrolysis of 1,3,4,5,6,7,8-Heptafluoro-2-naphthyl propynoate [106]

Heptafluoro-2-naphthyl propynoate [106] was prepared in 71% overall yield by treating an aqueous solution of 1,3,4,5,6,7,8-heptafluoro-2-naphthol[23] [109] and excess potassium carbonate with propynoyl chloride[55] in light petroleum (Scheme 5.7).



Scheme 5.7. Preparation of [106]

The ester [106] was identified by nmr and infra-red spectroscopy in conjunction with elemental analysis and correct molecular mass by mass spectrometry. Seven absorptions were retained in the ^{19}F nmr of which four were peri fluorines. The ^{1}H nmr contained only one signal due to the alkynic hydrogen, a singlet at 3.30ppm. Infra red spectroscopy showed strong absorptions for the terminal alkyne and the ester functionality.

Flash vacuum pyrolysis (FVP) of the ester [106] through a silica tube (50cm x 2cm) packed with silica tubing (5mm x 5mm) at 550°C/0.01mmHg (see Fig. 5.1) yielded a black oily product. No golden yellow material could be seen. The ^{19}F nmr of the crude reaction product showed 2 main products accompanied by indeterminable number of other products with resonances particularly in the region 130 to 160 ppm (Fig 5.2).

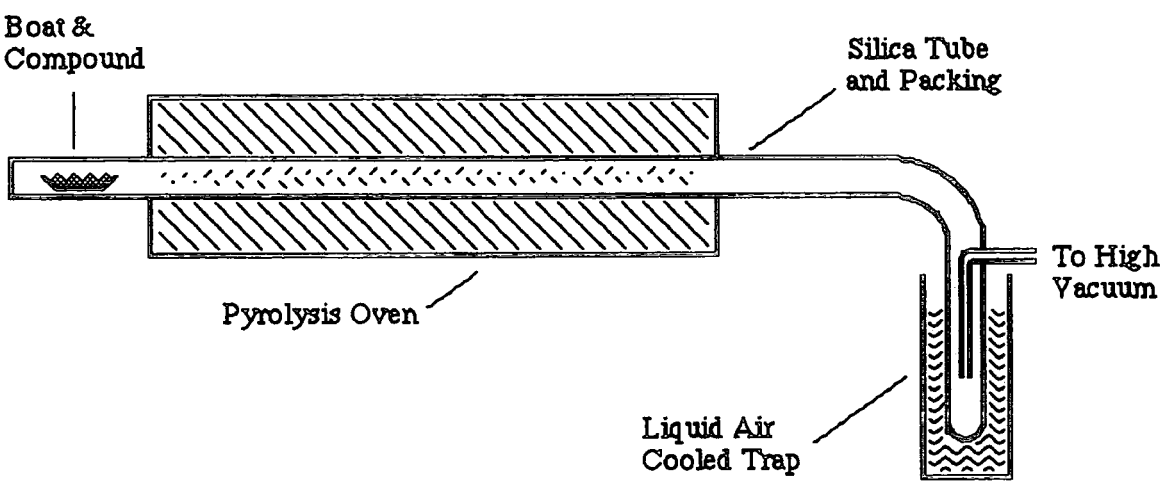
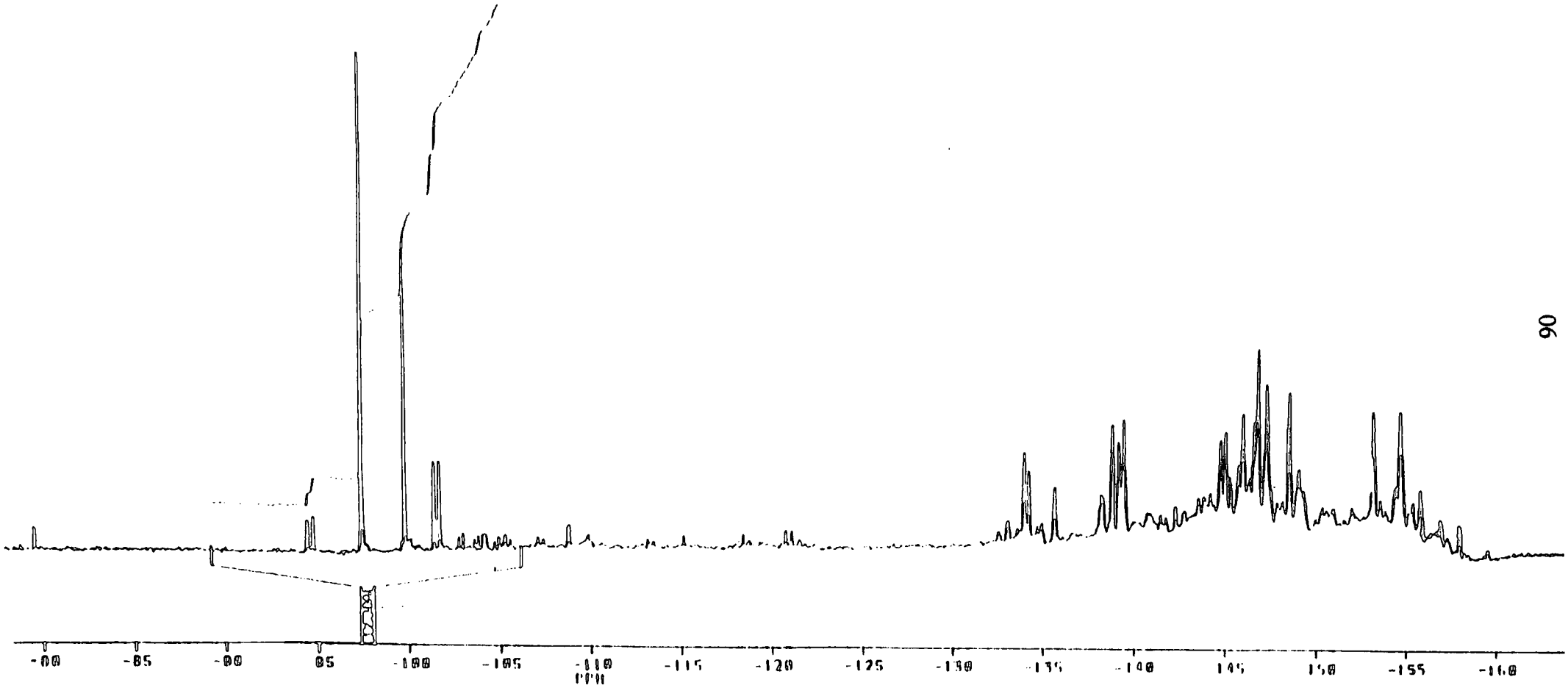
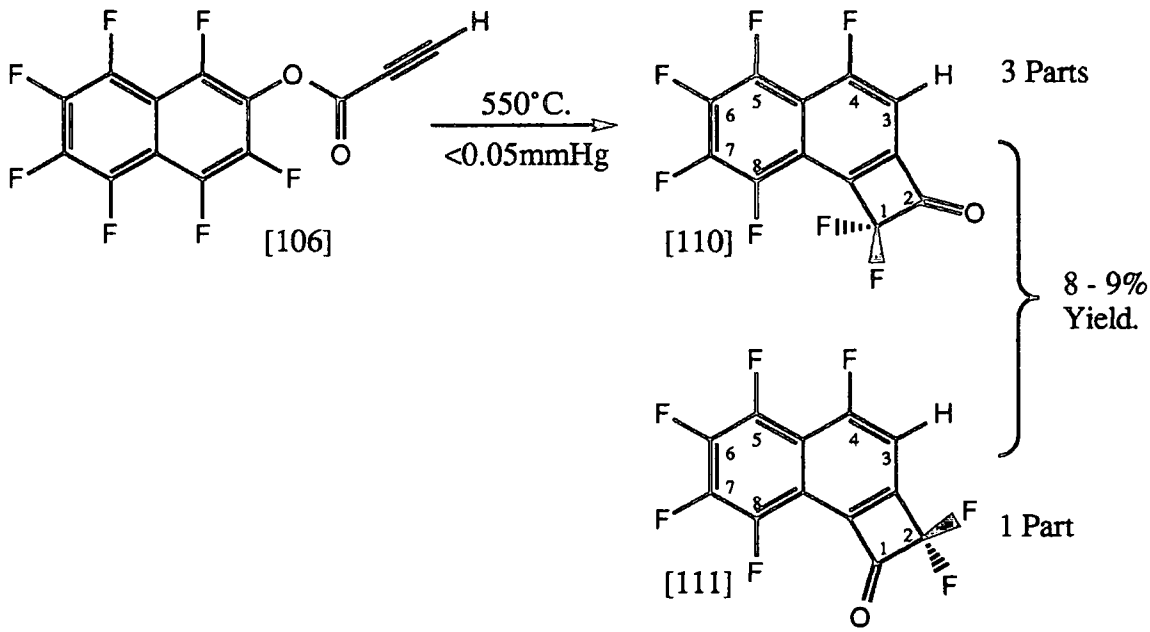


Fig 5.1. *Pyrolysis apparatus as used in FVP of [106].*

Fig 5.2. *Crude Pyrolysis of [106].*



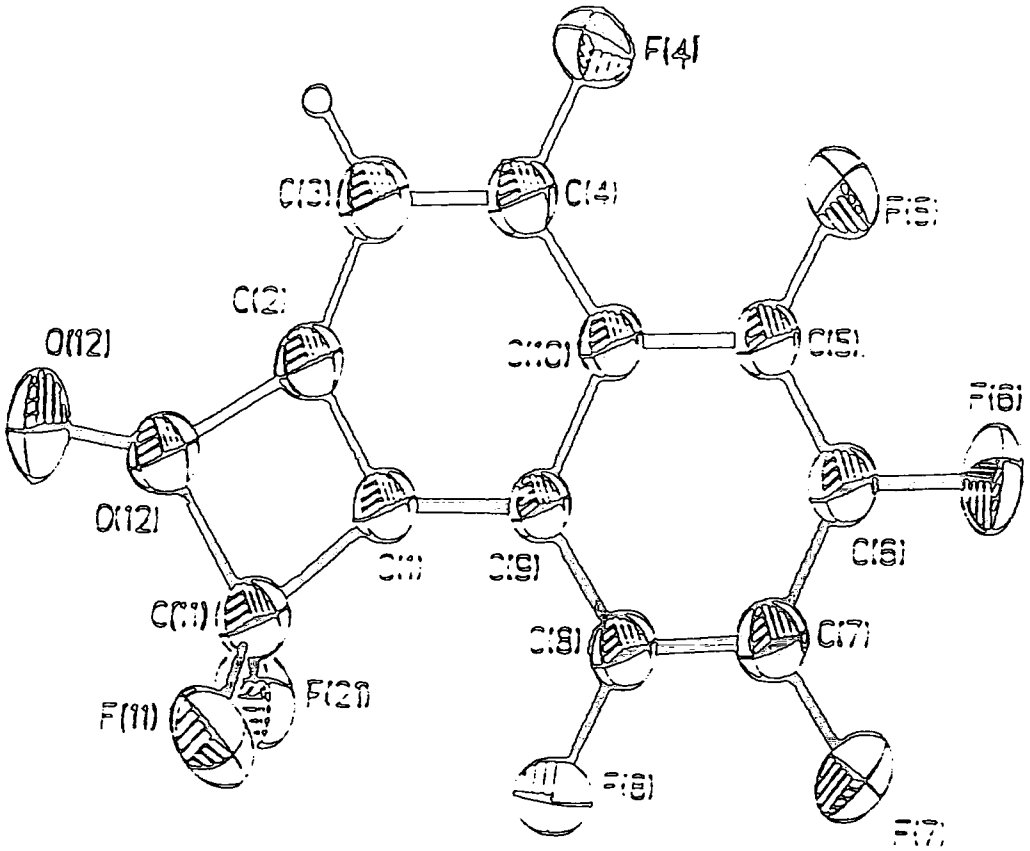
The two main products, isomers, formed in 8-9% total overall yield were 1,2-dihydro-1,1,4,5,6,7,8-heptafluoro-cyclobuta[a]napthalene-2-one [110] and 1,2-dihydro-2,2,4,5,6,7,8-heptafluoro-cyclobuta[a]napthalene-1-one [111] present in a 3 : 1 ratio respectively (Scheme 5.8). The isomers [110] and [111] were separated from the crude tar and then from one another by extensive chromatography, sublimation and recrystallisation.



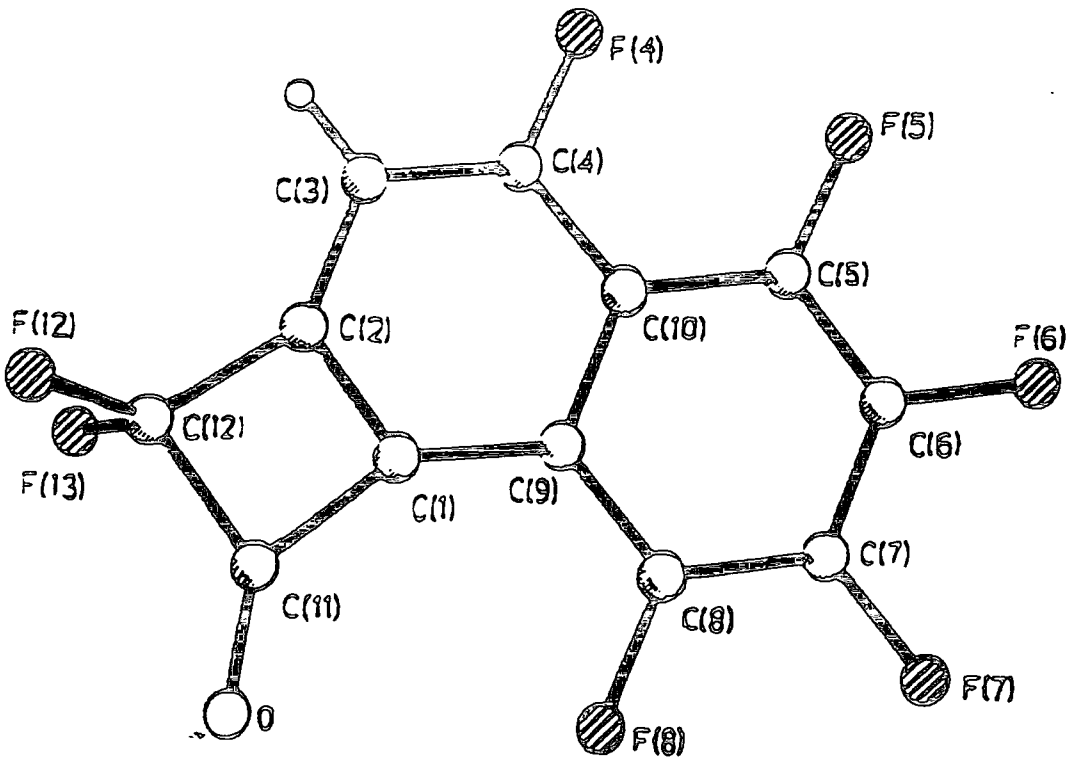
Scheme 5.8. *FVP of [106] to form compounds [110] and [111] in 8 to 9% overall yield.*

The structures of both [110] and [111] were determined by X-ray crystallographic analysis (Fig. 5.3), and then the ^{19}F nmr spectra of both isomers were assigned. Compound [110] showed six resonances (Fig. 5.4) of which two were relatively low field absorptions: firstly a singlet at -97.0 ppm of twice the intensity of the other peaks which could be clearly assigned to the two fluorines attached to position 1; and secondly a peri fluorine absorption, a simple doublet at -101.3 ppm, which was assigned to the fluorine at position 4. The second peri fluorine a doublet of triplets, resonated at -138.9 ppm and was due to the 5 fluorine while fluorines at positions 6,7 and 8, all triplets, resonated in the region -138 to -149 ppm.

Fig 5.3. *X-ray Crystal Structures of [110] and [111].*



[110]



[111]

Fig 5.4. ^{19}F *nmr of [110].*

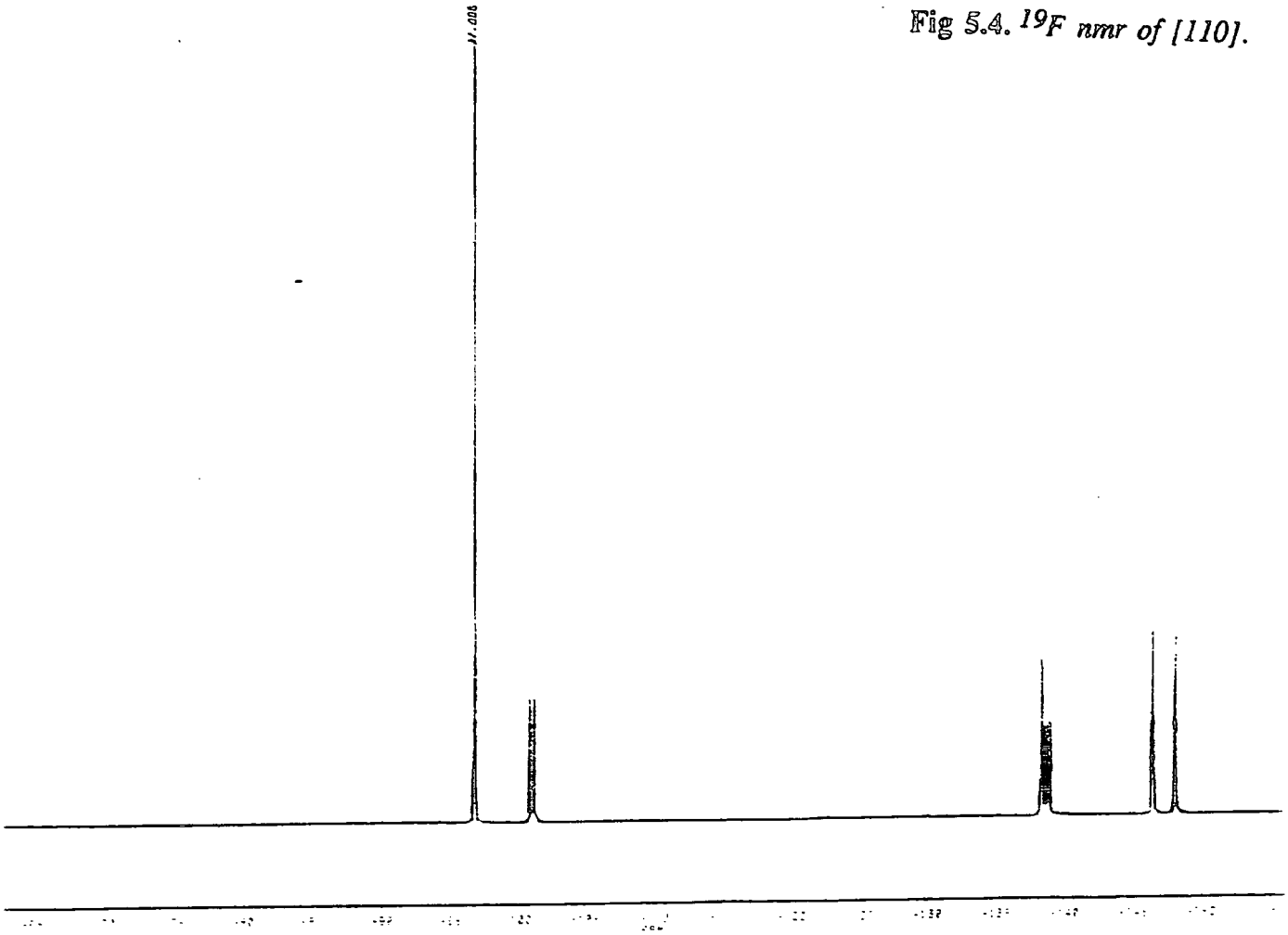
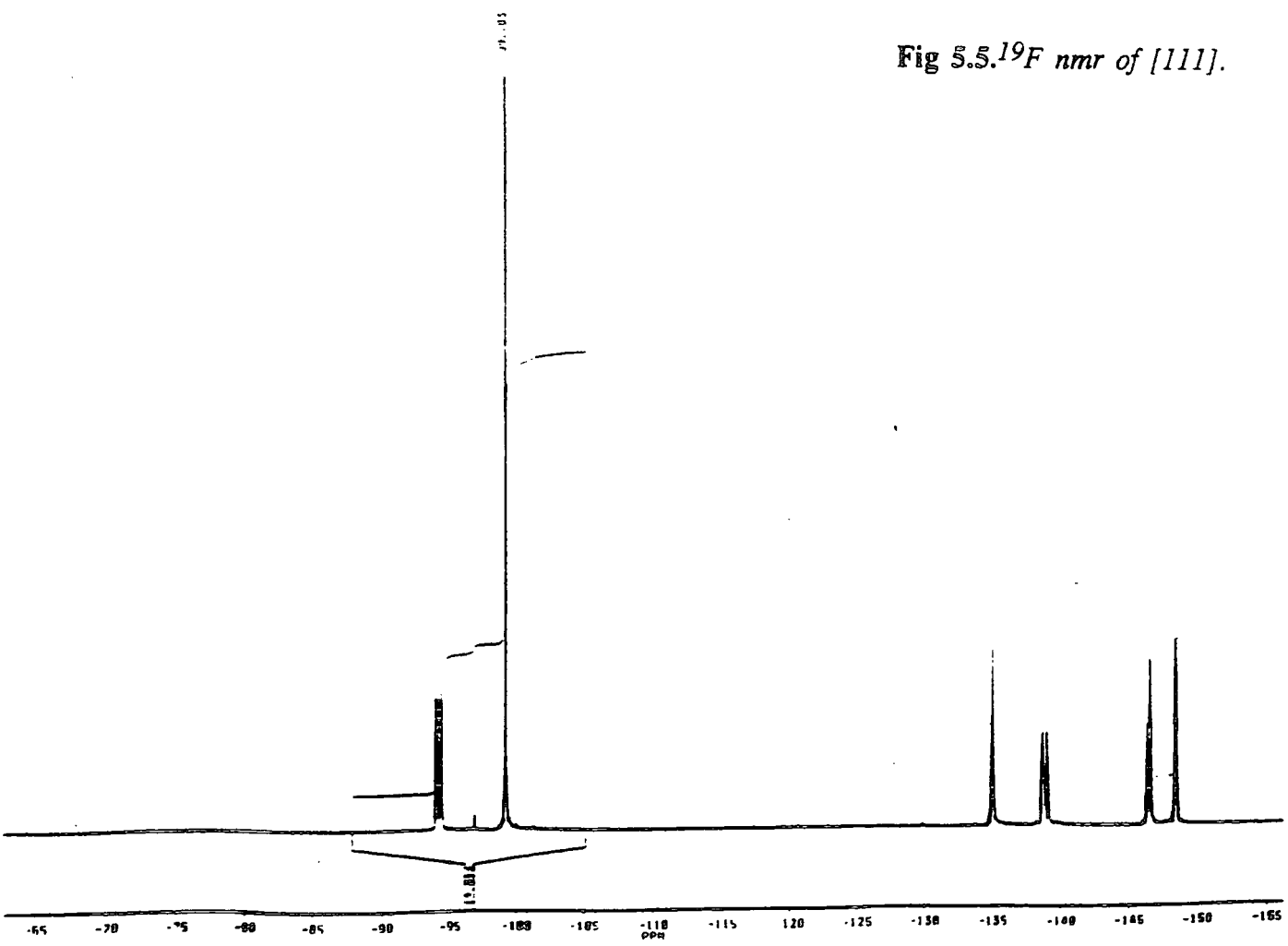


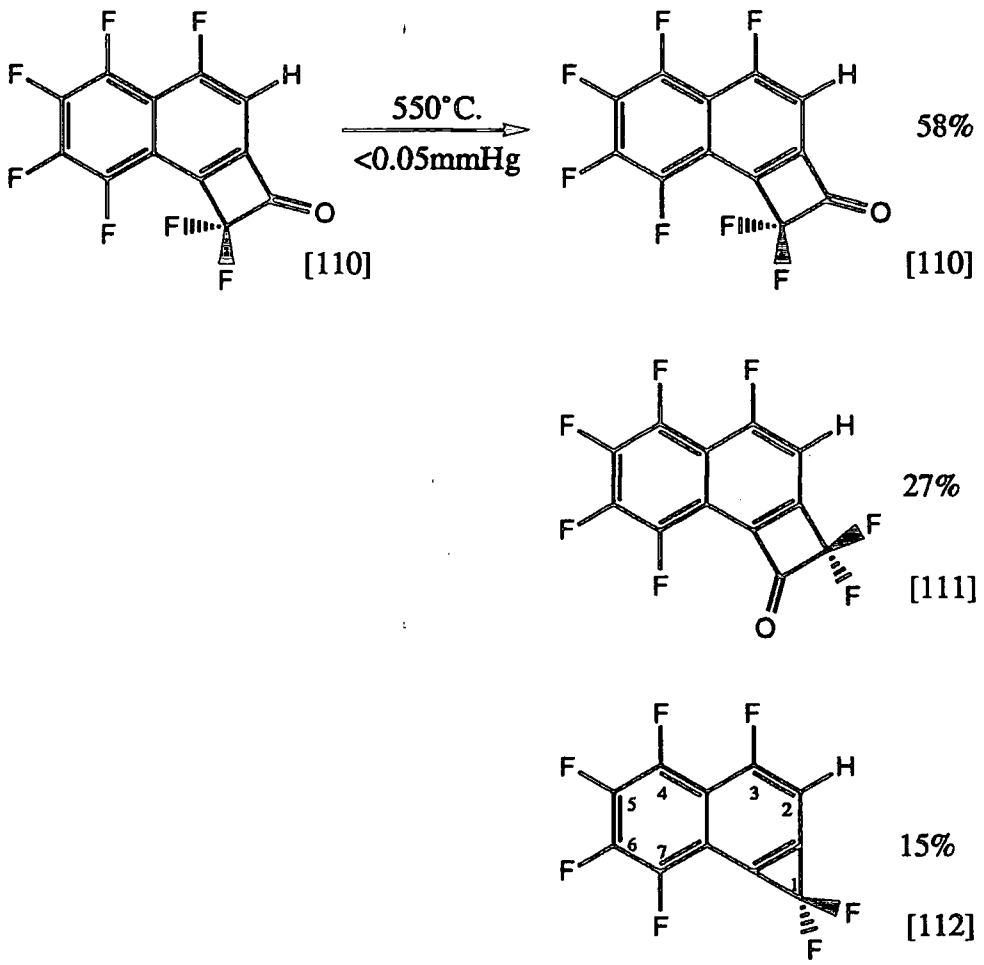
Fig 5.5. ^{19}F *nmr of [111].*



Compound [111], structurally very similar to [110], not surprisingly has a very similar ^{19}F nmr spectrum to [110] (Figs. 5.4 and 5.5). It too shows six resonances: two at low field due to the CF_2 group (-99.2 ppm) and the peri fluorine at position 4 (-94.2 ppm); the peri 5 fluorine at -139.8 ppm and the fluorines at positions 6,7 and 8, all triplets, in the region -135 to -149 ppm. The single aromatic proton not suprisingly resonated at ca. 7.5 ppm for both [110] and [111].

5.2.2 Isomerisation and further reaction of 1,2-dihydro-1,1,4,5,6,7,8-heptafluoro-buta[a]napthalene-2-one [110]

FVP of analytically pure [110] (Scheme 5.9) under exactly the same conditions as before gave a mixture, shown by ^{19}F nmr (Fig 5.6) to contain: recovered [110] (58%), its isomer [111] (15%) and a new compound [112] (27%), later identified in a separate experiment as 1,1,4,5,6,7,8-heptafluoro-1H-cycloprop[a]naphthalene.



Scheme 5.9. *Pyrolysis of [110]. Formation of the compound [112].*

Additional quantities of [112] were obtained from the pyrolysis of a mixture of [110] and [111]. Compounds [110] and [111] were not separated prior to pyrolysis as their structural similarities made separation difficult and wasteful of material.

FVP of the mixture of [110] and [111] in a 3 : 1 ratio respectively under the same conditions as before, (i.e 550°C/0.05mmHg), gave product accumulation in two places. The majority of the product (77%) solidified in the pyrolysis tube near the exit from the oven. This material was found, by ^{19}F nmr, to be primarily a mixture of the isomers [110] and [111] (Fig. 5.7). The remainder of the product (23%) collected in a liquid nitrogen cooled trap, connected between the exit of the pyrolysis tube and the vacuum line. This material by ^{19}F nmr was primarily [112] (Fig. 5.8), but also contained small quantities of [110] and [111] (20% total). Vacuum sublimation allowed [112] to be isolated free from [110] and [112] by virtue of its greater volatility. The structure of [112] was positively identified by X-ray crystallographic analysis (Fig. 5.9). The low field absorption in the ^{19}F nmr (Fig. 5.10) was due to the CF_2 group in the cyclopropene ring, while the remainder of the ^{19}F nmr absorptions were in similar places to those in [110] and [111]. Interestingly the single aromatic hydrogen absorption in the proton nmr spectrum was a doublet of triplets. Heteronucleur decoupling nmr experiments confirmed that the doublet character of the hydrogen resonance was due to coupling to the peri fluorine ortho to it at position 3 ($J_{2\text{-}H,3\text{-}F}$, 7Hz) and that the triplet character was due to coupling of the hydrogen to the two fluorines at position 1, i.e. the CF_2 group in the cyclopropene ring system ($J_{2\text{-}H,1\text{-}F}$, 3.6Hz).

5.3 Discussion

It is clear from this work that the products from the pyrolysis of 1,3,4,5,6,7,8-heptafluoronaphthyl propynoate are entirely different from those found with the FVP of 2,3,4,5,6-pentafluorophenyl propynoate [101] and phenyl propynoate [102]. A mechanism proceeding via an internal Diels-Alder reaction, with subsequent $2\pi + 2\pi$ cycloaddition, loss of carbon monoxide and fluoride ion shifts is now proposed (Scheme 5.10).

Fig 5.6. *Crude Pyrolysis of 11101.*

Fig 5.7. Crude Pyrolysis of [110] and [111]: Product Collected in Pyrolysis Tube

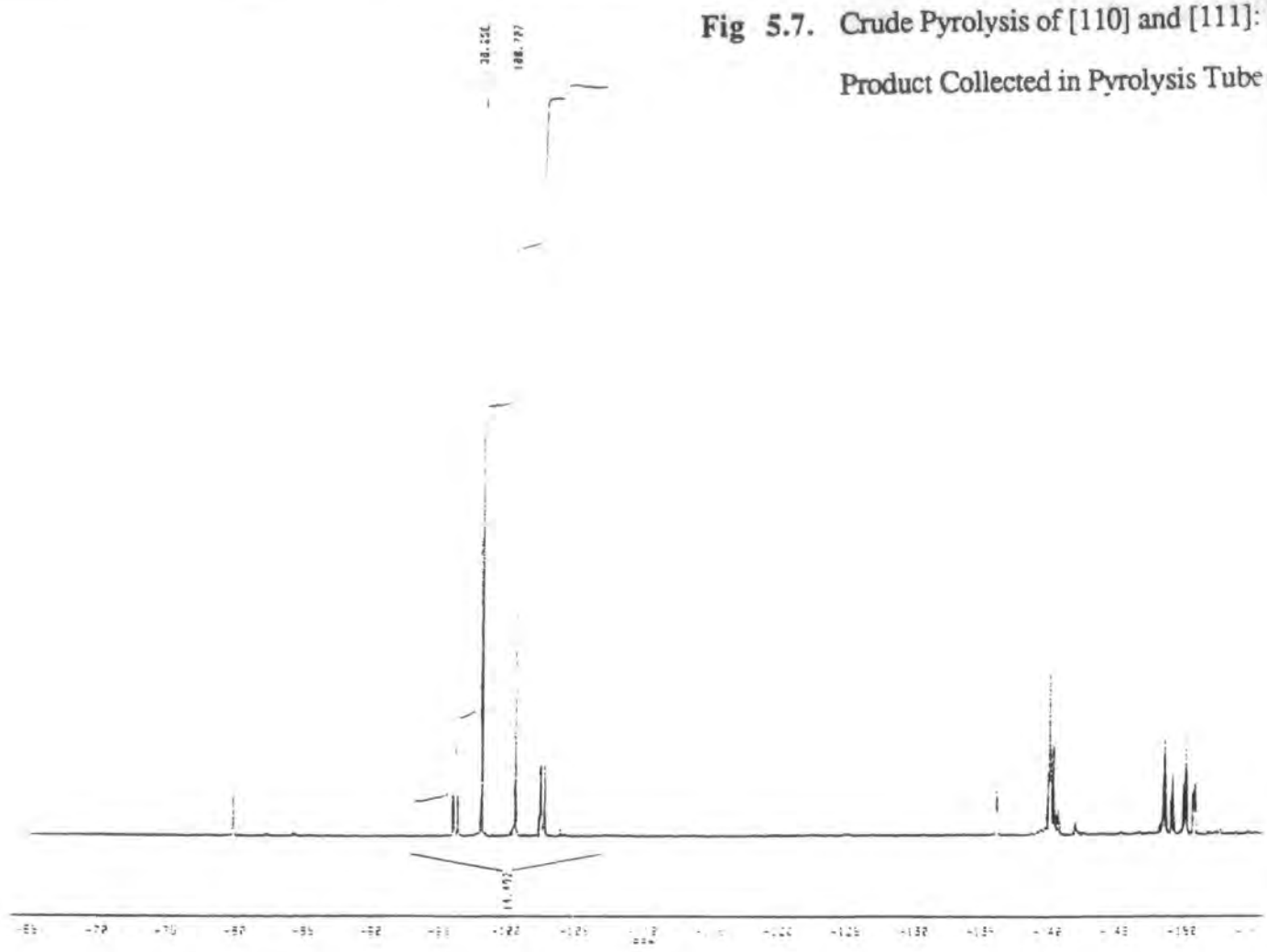
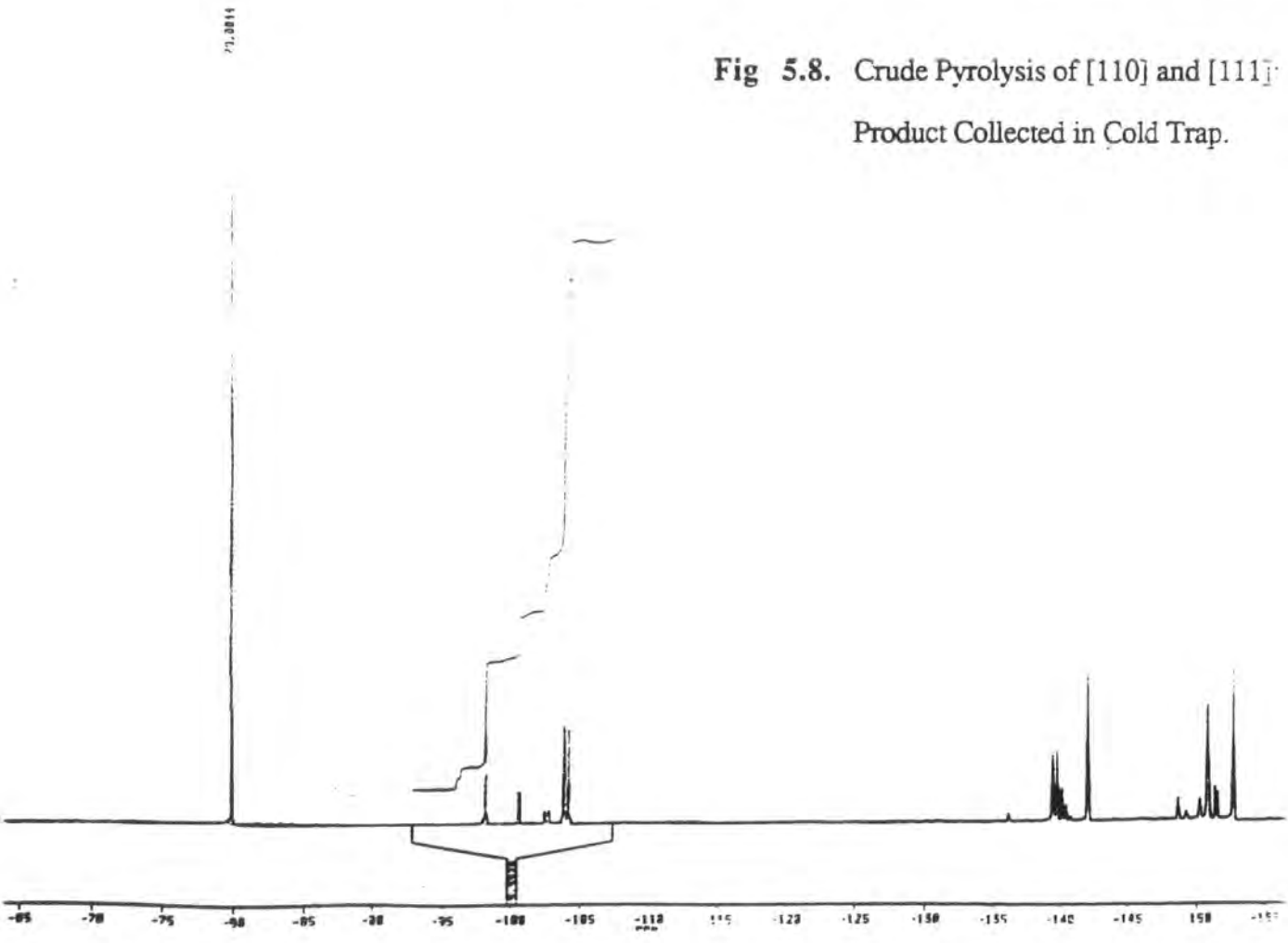


Fig 5.8. Crude Pyrolysis of [110] and [111]: Product Collected in Cold Trap.



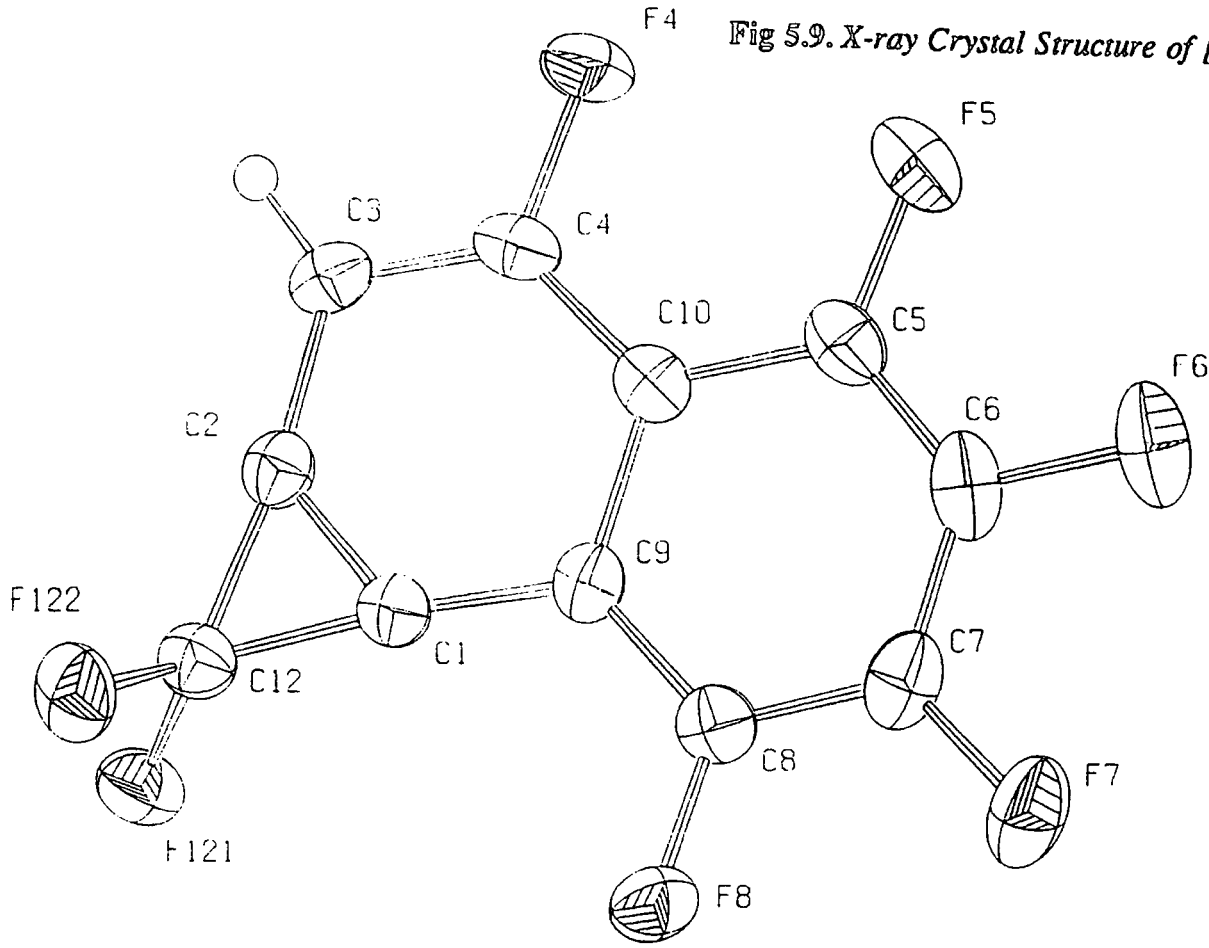
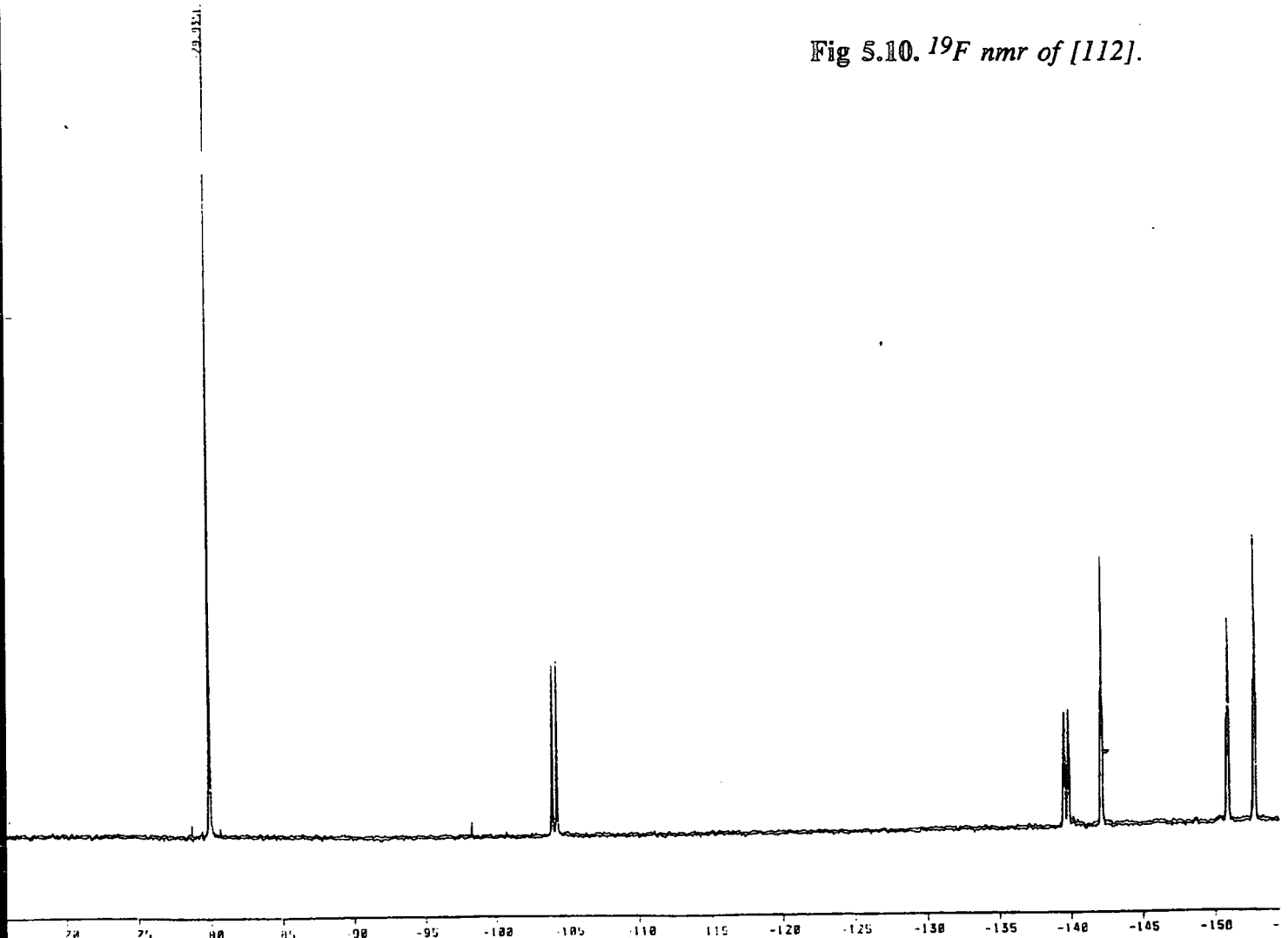
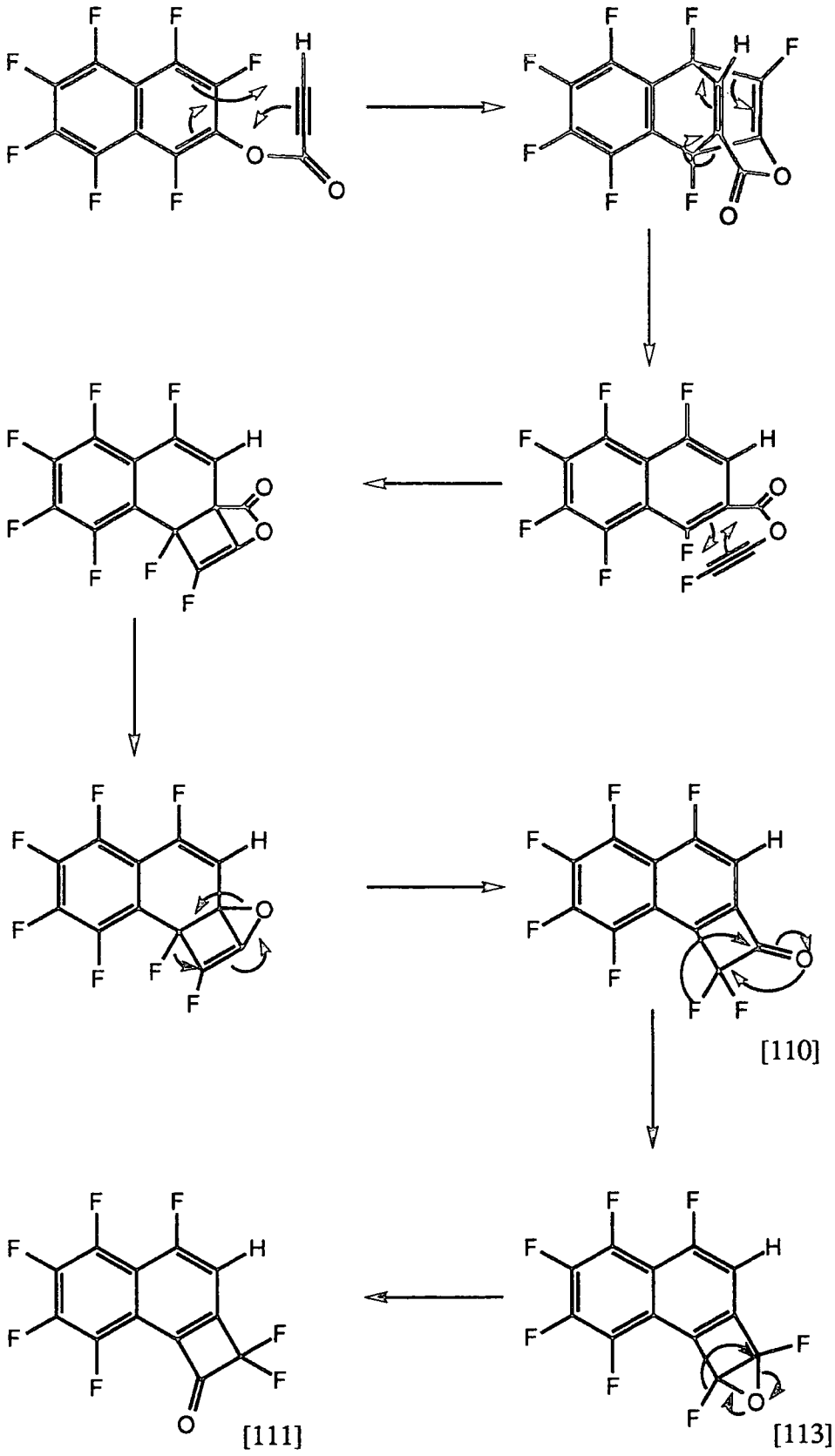


Fig 5.9. *X-ray Crystal Structure of [112].*

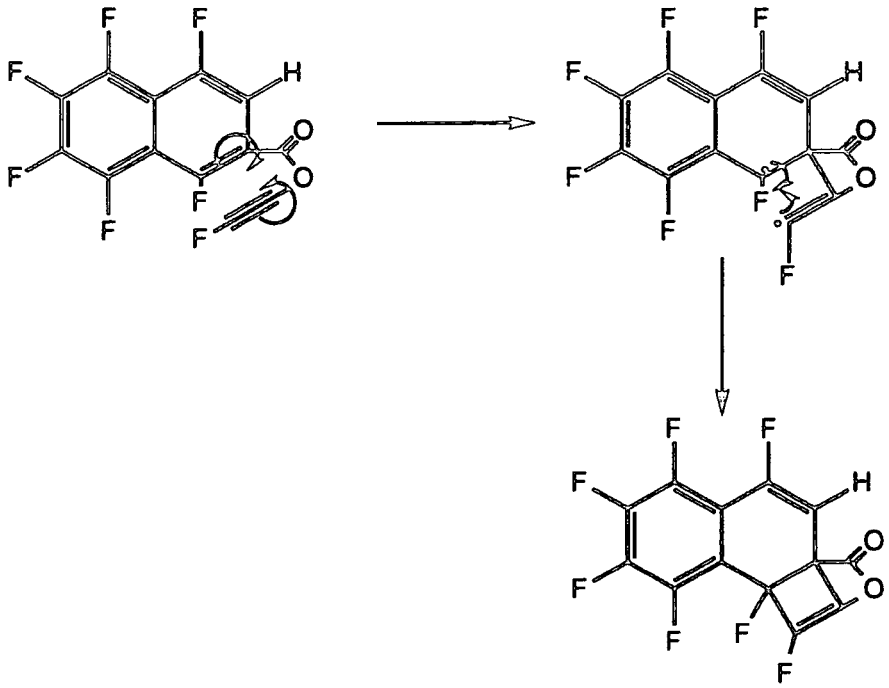
Fig 5.10. *^{19}F nmr of [112].*





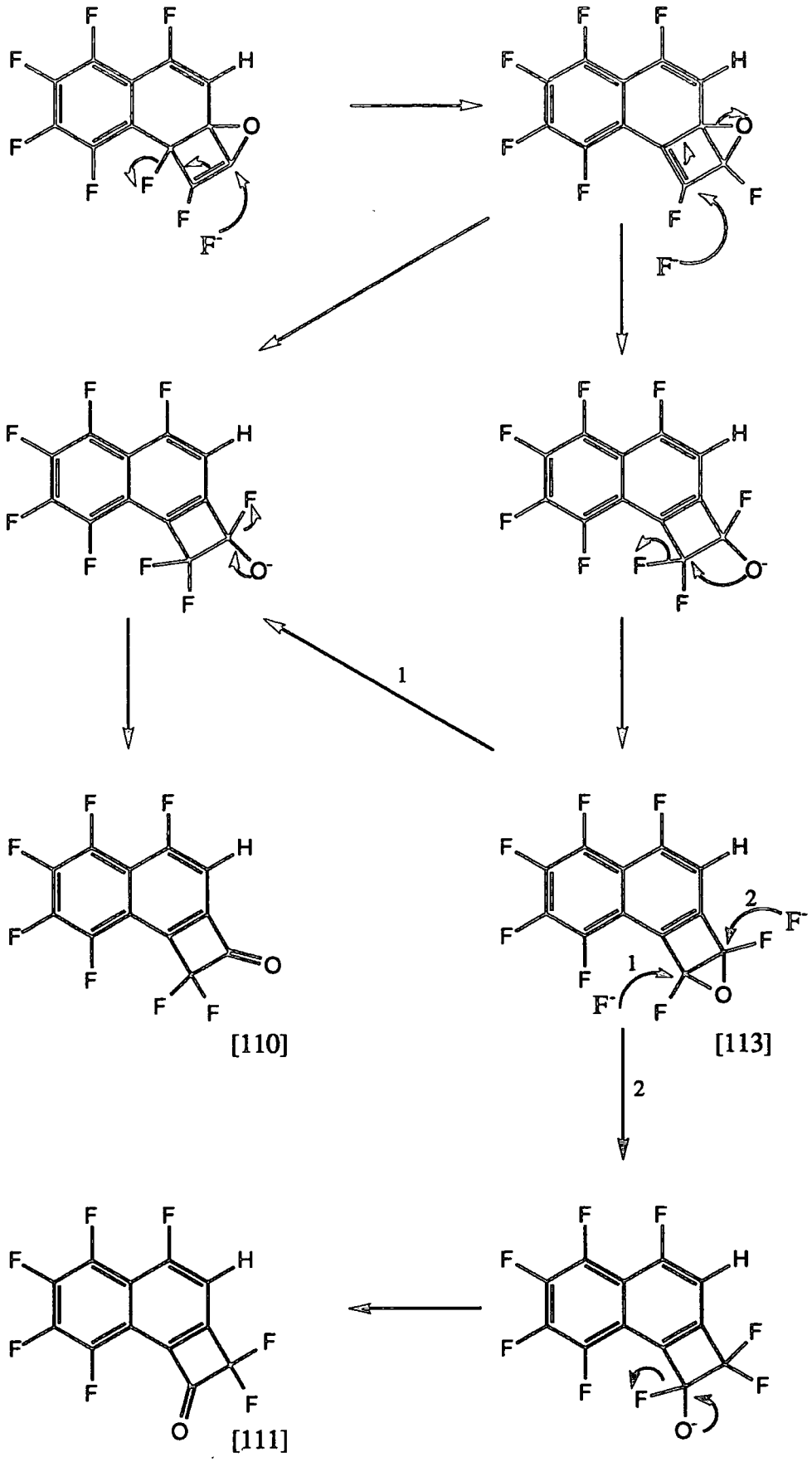
Scheme 5.10. *Mechanism of formation of [110] and [111].*

The intervention of a radical mechanism, as shown in Scheme 5.11, for the $2\pi + 2\pi$ cycloaddition is a strong possibility since cyclisations of this type are symmetry forbidden for a thermal concerted process[56].



Scheme 5.11. *$2\pi + 2\pi$ cycloaddition reaction via radical mechanism.*

There is also a possibility of the fluoride ion shifts being induced by fluoride ions from the pyrolysis tube (Scheme 5.12). It is worth noting that during the course of the work the pyrolysis tube was broken, and its replacement, (made from new silica glass but fitted with the original packing) gave significantly reduced yields of [110] and [111] in the first few pyrolysis experiments for which it was used. This strongly suggests the intervention of fluoride ions from the tube. Interestingly pyrolysis experiments on [110] and [111] with the new tube gave virtually no [112]. However, once the tube had become etched then [112] was produced in reasonable yield.

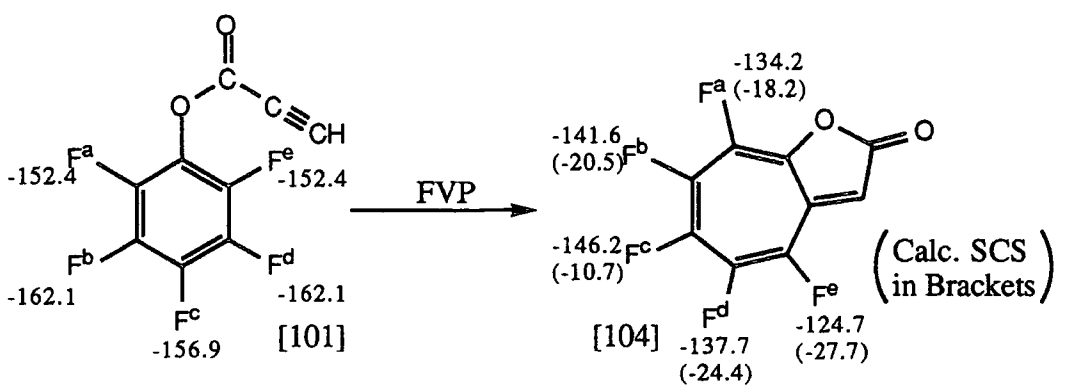


Scheme 5.12. *Proposed fluoride ion induced fluoride ion shifts in the mechanism of formation of [110] and [111].*

The quantity of cyclopropa[a]naphthalene [112] formed during the pyrolysis of the propynoate ester [106] is exceedingly small (see low field singlet at ca -79ppm in Fig. 5.2). This could be viewed as surprising since pyrolysis of the buteneone [110] under exactly the same conditions, leads to the formation of [112] in reasonable yield (27%). This suggests that the final step or steps proceed in a cooler part of the pyrolysis tube, since contact of [110] with a hotter part of the pyrolysis tube would lead to significant formation of the propene product [112].

The pyrolysis of [110] gave the isomeric product [111] in addition to the cyclopropene [112]. This suggests that isomerisation of [110] to [111] takes place via the common intermediate [113] (schemes 5.10 and 5.12).

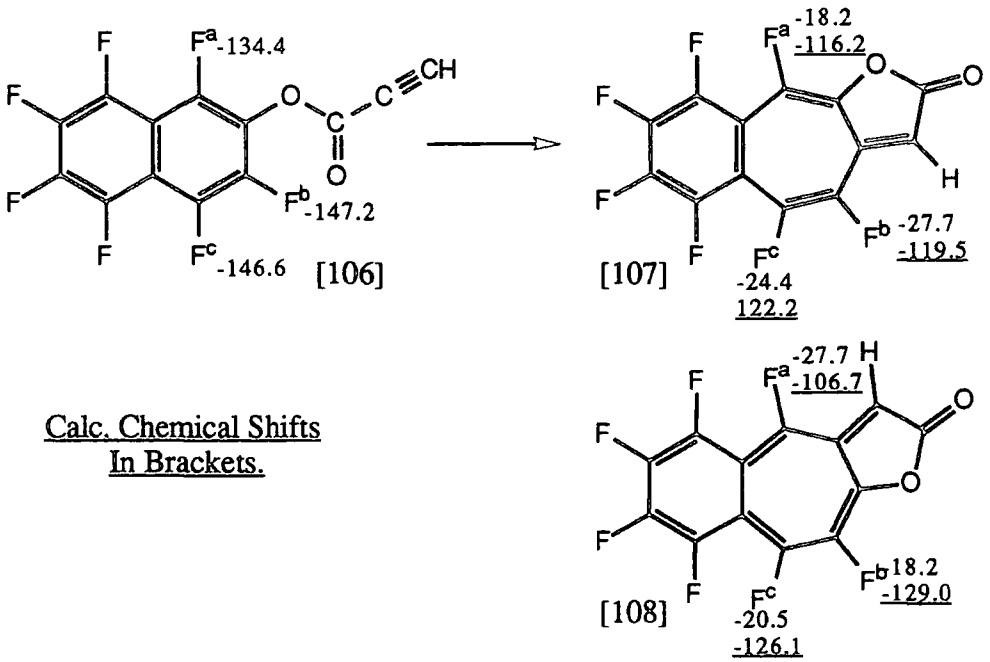
A substituent chemical shift approach can be applied to try and predict some of the fluorine absorptions in the ^{19}F nmr spectrum for the naphthalene equivalents [107] and [108] of the pentafluoro-2H-cyclohepta[b]furan-2-one [104]. Changes in the chemical shifts are calculated for the fluorines in the propynoate ester [101] going to the furan-2-one [104] and these are shown in Scheme 5.13. These data are then applied crudely to the naphthalene system to predict some of the fluorine chemical shifts in the proposed furan-2-ones [107] and [108] (Scheme 5.14).



Scheme 5.13.

During the ring expansion, fluorine (a) has moved -18.2 ppm [-152.4 -(-134.2)]. The same calculation can be performed for fluorines (b) to (e) and all these chemical shifts can then be applied to the **two** proposed products [107] and [108],

formed as a result of heptafluoro-2-naphthyl propynoate [106] reacting by the same mechanism as the phenyl analogue [101].

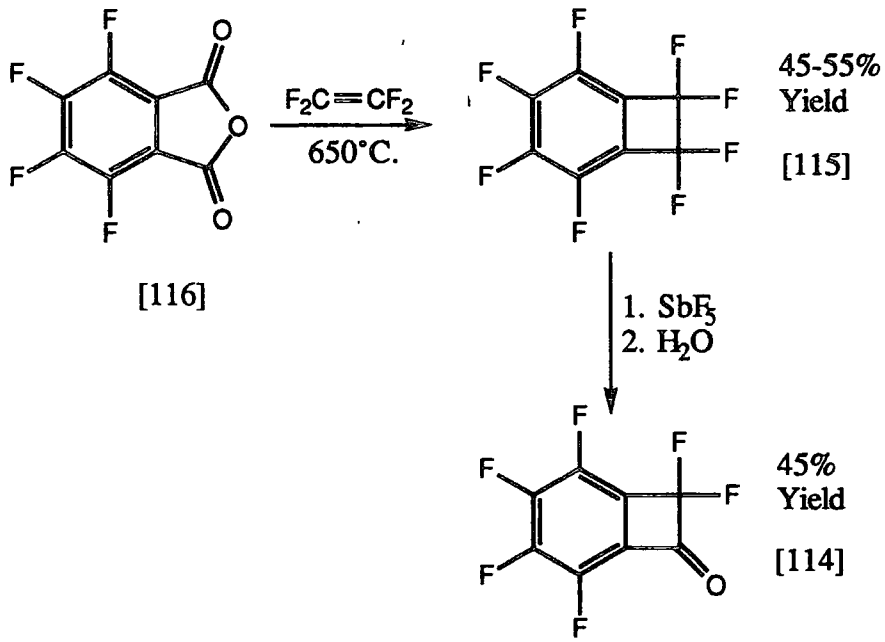


Scheme 5.14. *Proposed Chemical Shifts for proposed furan-2-ones [107] and [108].*

In Scheme 5.14, the fluorine at position (a) in structure [107] is in a similar position to that of fluorine (a) in [104], hence fluorine (a) in [107] will be shifted -18.2 ppm from its position in the parent ester [106] and would be predicted to resonate at -116.2ppm [-134.4 - (-18.2)]. Likewise fluorine (b) in [107] is in a similar position to fluorine (e) in [104], and since fluorine (e) in [104] is shifted -27.7ppm from its position in the ester [101], then fluorine (b) in [107] would resonate at -119.5 ppm [-147.2 -(-27.7)]. Similar calculations for fluorine (c) in [107] and fluorines (a) to (c) in [108] give three predicted absorptions for both [107] and [108]. Compound [107] would consequently have absorptions at ca. -116.2, -119.5 and -122.2 ppm in the ^{19}F nmr spectrum, and compound [108] would have absorptions at ca.-106.7, -129.0 and -126.1 ppm. No significant absorptions (Fig. 5.2) can be seen in the region -122 to -131ppm, essentially ruling out any formation of [108]. Absorptions in the range -113 to -122ppm are seen, but are exceedingly small, and if they could be attributable to [107], [107] would represent only a very small quantity of the product. The failure to produce any

bright yellow colour during the pyrolysis also suggests that [107] and [108] are not formed.

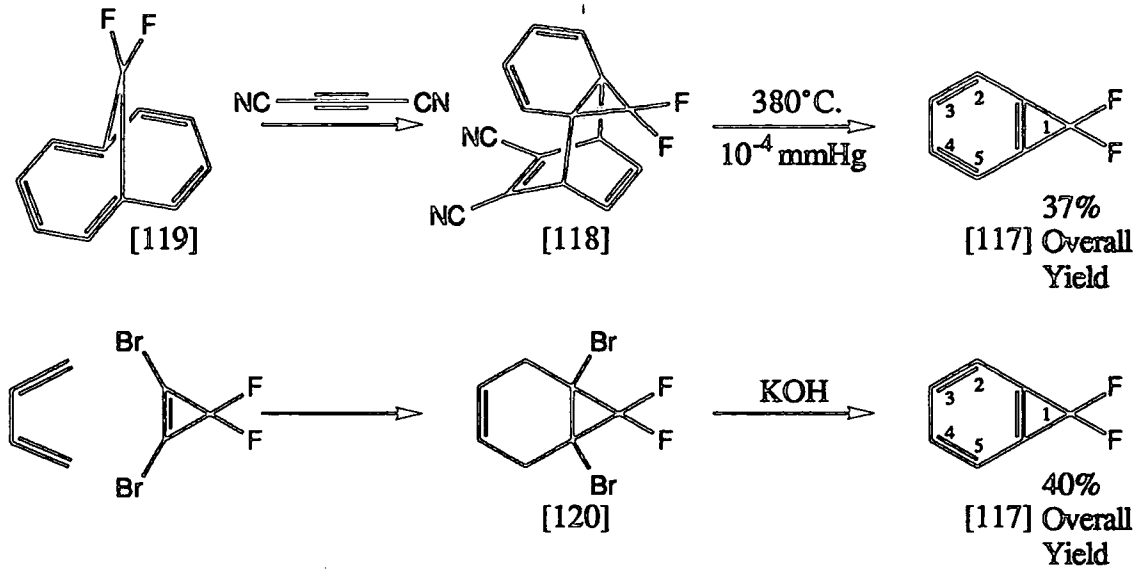
Perfluorobenzocyclobutenone [114] has been prepared by treatment of perfluorobenzocyclobutene [115] with SbF_5, followed by water[57]. The perfluorobenzocyclobutene [115] was prepared by co-pyrolysis of tetrafluorophthalic anhydride [116] with tetrafluoroethylene at 650°C (Scheme 5.15). Perfluorobenzocyclobutenone [114] is obviously very similar in structure to [110] and [111], essentially being only one fused benzene different. The ^{19}F nmr absorption for the CF_2 fluorines in [114] is at -95.5ppm. The corresponding signals for [110] and [111] are at -101.3 and -99.2 ppm respectively; i.e they are very similar. The carbonyl in [114] absorbs in the infra red at 1820cm^{-1}. The corresponding absorptions in [110] and [111] both occur at 1800cm^{-1}; again an excellent agreement [a second smaller absorption is seen in the i.r. spectrum of [110] at 1830cm^{-1} (see Appendix 4)].



Scheme 5.15. *Preparation of perfluorocyclobutenone [114].*

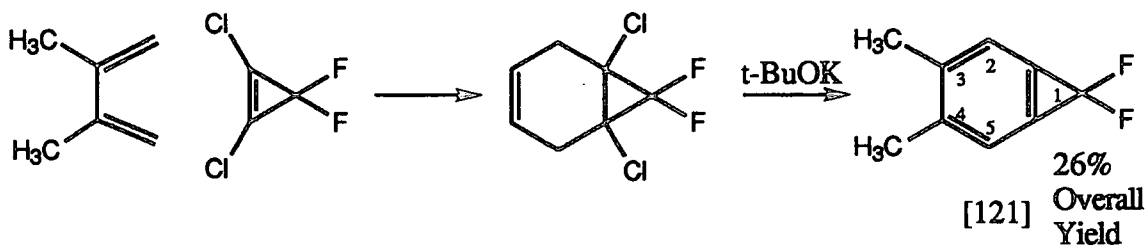
1,1-Difluorobenzocyclopropenes have been prepared previously[58,59]. The 1,1-difluorobenzocyclopropene[58] [117] was prepared by pyrolytic cleavage of a 1,6-methano-[10]annulene-dicyanoacetylene adduct [118], which had been prepared from dicyanoacetylene and 11,11-difluoro-1,6-methano-[10]annulene [119]. An alternative synthesis of 1,1-difluorobenzocyclopropene [117] is the action of potassium hydroxide

on 1,6-dibromo-7,7-difluorobicyclo[4.1.0]hept-3-ene [120], which is prepared by the Diels Alder reaction of 1,3-butadiene and 1,2-dibromo-3,3-difluorocyclopropene (Scheme 5.16).



Scheme 5.16. *Preparation of 1,1-difluorobenzocyclopropene [117].*

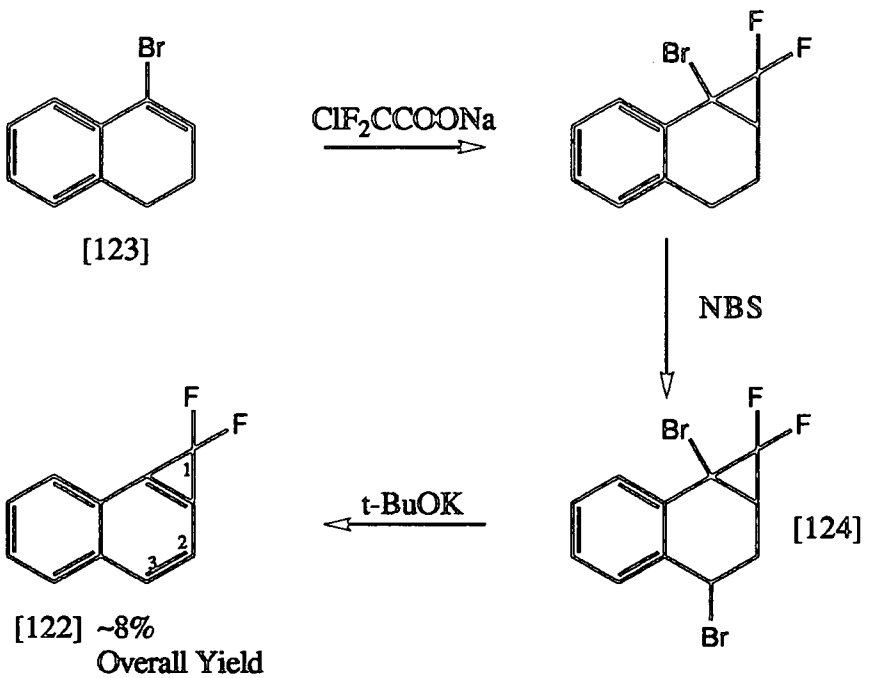
The ^{19}F nmr of the 1,1-difluorobenzocyclopropene [117] had a triplet absorption at -80.4ppm, the splitting being due to coupling of the fluorines to the equivalent hydrogens at C-2 and C-5 ($J_{2\text{-}H,1\text{-}F}$ 3.4Hz). The 3,4-dimethyl derivative[59] of [117], [121], was prepared using a procedure similar to the second synthesis of [117] (Scheme 5.17). Nmr spectroscopy showed that the fluorines here too coupled to the hydrogens at C-2 and C-5 ($J_{2\text{-}H,1\text{-}F}$ 4.5Hz). The hydrogens at C-2 and C-5 resonated at ca. 7.3 ppm.



Scheme 5.17. *Preparation of [121].*

1,1-Difluoronapthocyclopropene [122] has been synthesised[60], as shown in Scheme 5.17, from 4-bromo-1,2-dihydronaphthalene [123] via the addition of difluorocarbene, followed by the introduction of a benzylic bromine substituent by action of N-bromo-succinimide (NBS), to give the cyclopropane derivative [124]. Compound

[124] was then dehydrobrominated with t-BuOK at -78°C to give 1,1-Difluoronapthocyclopropene [119] which was observed by both ^{1}H and ^{19}F nmr at -30°C, the material being unstable above this temperature. The CF_2 fluorines resonated at -76ppm and coupled to the hydrogen at position 2 with a coupling constant of $J_{2\text{-}H,1\text{-}F}$ 3.9Hz



Scheme 5.18. *Preparation of [122].*

The nmr shifts and coupling constants for the 1,1-difluoropropenes described above are in excellent agreement with the results reported here for [112], where the CF_2 fluorines resonated at -79.0ppm in the ^{19}F nmr with a coupling to the single hydrogen of $J_{1\text{-}F,2\text{-}H}$ 3.6Hz which itself resonated at 7.36ppm in the ^{1}H nmr spectrum.

A structural search using the Cambridge Crystallographic database[61] revealed that no crystal structure containing the 1,1-difluorocyclopropene unit has been reported previously. The cyclopropene derivative [112], described in this thesis is therefore a first in terms of a positive structure determination by X-ray crystallography, and supports the previously reported aromatic type 1,1-difluorocyclopropenes in terms of the chemical shift of fluorines in the difluoro unit (-79.0 ppm.) and the $J_{2\text{-}H,1\text{-}F}$ coupling of the adjacent proton and fluorines of 3.6Hz.

Chapter 6

Experimental.

Chapter 6.

Experimental.

6.1 GENERAL.

6.1.1 Instrumentation.

NMR spectra were recorded on the following instruments and at the frequencies listed: Bruker AC250 ^{1}H (250.133MHz), ^{19}F (235.360MHz); Varian 400MHz ^{1}H (399.952MHz), ^{19}F (376.33MHz). Absorption multiplicities have been abbreviated as follows: s(singlet), d(doublet), t(triplet), q(quartet), m(multiplet) and b(broad). Chemical shifts are quoted as δ in ppm with respect to the following references: ^{19}F (upfield from external $CFCl_3$), ^{1}H (downfield from internal TMS).
Mass spectra were recorded on a VG 7070E mass spectrometer. Molecular ions M^+ are quoted for electron ionisation unless otherwise stated.
Elemental analyses were performed on a Carlo ERBA C,H,N Elemental Analyser 1106.
Infra red spectra were recorded on Perkin Elmer 577 and 457 grating or Perkin Elmer 1615 FTIR spectrometers using KBr discs with nujol mulls or neat liquids.

6.1.2 Techniques

Volatile materials were handled in a conventional glass vacuum system in conjunction with an Edwards E2M2 two stage high vacuum pump. The silica gel used for chromatography was Merck Kieselgel 60 (230-400 mesh).

Commercial compounds were used as received from the supplier. Chromatography solvents were redistilled and reaction solvents were dried prior to use according to standard procedures.

6.2 EXPERIMENTAL FOR CHAPTER TWO.

6.2.1 REACTIONS OF HEPTAFLUOROQUINOLINE [2] WITH SODIUM HYDROSULPHIDE AND SUBSEQUENT REACTION WITH DIMETHYL ACETYLENEDICARBOXYLATE (DMAD).

i. In Ethylene glycol and Dimethylformamide.

The quinoline [2] (0.249g, 0.98mmol) in a mixture of anhydrous dimethylformamide (DMF) (5ml) and ethylene glycol (EG) (2.5ml), was treated at -10 to -6°C over 2 minutes with sodium hydrosulphide (0.102g, 1.82mmol) in a mixture of DMF (5ml) and EG (2.5ml). The mixture was warmed to 15°C, then cooled to -15°C, and DMAD (150µl, 0.174g, 1.22 mmol) added. The mixture was warmed to room temperature and left to stir for 12 hours. The mixture was then diluted with water, acidified (H_2SO_4, 2M) and the product extracted into ether. The ether extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The product (0.381g) was shown by ^{19}F nmr to contain the non-cyclised DMAD adduct [38], an unidentified F_5 compound and the cyclised DMAD product [36] (see later) in the ratio 77 : 21 : 2 respectively. The ^{19}F nmr in addition showed 36 small unassigned peaks. Flash chromatography of the product on silica using dichloromethane as elutant, gave enrichment of the major component as the fastest moving component (0.142g). This was combined with enriched major component from a similar experiment and was recrystallised to give the dimethyl 1-(2,3,5,6,7,8-hexafluoro-4-quinolylthio)ethene-1,2-dicarboxylate [38] m.p. 109.0-109.5°C [from light petroleum (b.p. 60-80°C)] (Found: C, 43.50; H, 1.62; N, 3.29%; M^+, 411. $C_{15}H_7F_6NO_4S$ requires C, 43.81; H, 1.72; N, 3.41%; M, 411); δ_F ($CDCl_3$) -77.0 (d, 2-F), -128.5 (d, 3-F), -140.6 (t, 5-F), -147.9 (t), -152.2 (t), -154.3 (t) (all unassigned); $J_{2\text{-}F,3\text{-}F}$ 31Hz; δ_H ($CDCl_3$) 3.87 (s, CH_3), 3.63 (s, CH_3), 7.00 (s, alkenic C-H).

ii. In THF.

The quinoline [2] (0.256g, 1.01mmol) in anhydrous THF (10ml), was treated at -10°C with a solution of sodium hydrosulphide in THF (10ml) at -10°C The

mixture was maintained at -2°C for 70 minutes after which it was cooled to -20°C and DMAD (160µl, 0.184g, 1.30mmol) was added. The mixture was warmed to room temperature and the crude product diluted with water, acidified (H_2SO_4, 2M) and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated, and the crude product (0.377g) shown by ^{19}F nmr to contain starting material [2] (35%) and two major products (65%): the cyclised product [36] (see later) and the non cyclised adduct [38] in the ratio 33 : 67 respectively. The nmr showed 18 other small unassigned peaks.

iii. With NaSH in Dimethylformamide and Ethylene Glycol, and Reaction of the Crude Thiol with Butyllithium Followed by DMAD in THF.

The quinoline [2] (0.240g, 0.94mmol) in a mixture of dimethylformamide (DMF) (5ml) and ethylene glycol (EG) (2.5ml) was treated at -6 to -4°C over 2 minutes with sodium hydrosulphide (0.090g, 1.60mmol) in a mixture of DMF (5ml) and EG (2.5ml). The mixture was maintained at -2°C for 70 minutes, then rapidly worked up by diluting with precooled ether (-10°C) and iced water, and acidifying with precooled acid (H_2SO_4, 2M) (0°C). The cold extracts were dried ($MgSO_4$), filtered and the solvent evaporated under high vacuum at room temperature. The residue was dissolved in THF (10ml) and cooled to -60°C, butyllithium (370µl, 0.59mmol) was added and the mixture maintained at -60°C for 15 minutes before DMAD (115µl, 0.133g, 0.94mmol) in THF (5ml) was added at -65°C The mixture was warmed to room temperature and left to stir for 12 hours. The mixture was then diluted with cold water and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered, the solvent evaporated and the crude product (0.265g) shown by ^{19}F nmr to contain the cyclised product [36] and the non cyclised adduct [38] in the ratio 59 : 41 respectively. The ^{19}F nmr showed 28 other small peaks (all unassigned except for five which were due to the same unidentified F_5 compound as in 6.2.1.i). Flash chromatography of the crude product on silica using dichloromethane as elutant gave as the faster moving component, enriched non-cyclised product [38] (0.058g) and as the slower moving component the dimethyl 4,5,6,7,9-pentafluoro-thieno[3,2-c]quinoline-2,3-dicarboxylate [36] (0.014g) m.p. 117.0-117.5°C

[from light petroleum (b.p. 60-80°C)] (Found: C, 45.79; H, 1.47; N, 3.48%; M^+, 391. $C_{15}H_6F_5NO_4S$ requires C, 46.05; H, 1.55; N, 3.58%; M, 391); δ_F ($CDCl_3$) -59.8 (s, 4-F), -140.2 (td, 9-F), -146.5 (td), -151.4 (t), -155.7 (td) (all unassigned); δ_H ($CDCl_3$) 4.10 (s, CH_3), 4.02 (s, CH_3).

6.2.2 Reaction of the 4-Quinolinethiol [35] with Butyllithium and DMAD.

The quinolinethiol [35] (0.097g, 0.36mmol) (see 6.3.2.1.i) in anhydrous THF (15ml), was treated at -63°C with butyllithium (0.25ml, 1.6M, 0.40mmol), followed by DMAD (60µl, 0.069g, 0.48mmol) in THF (5ml), at -63°C over 1 minute. The mixture was warmed to 10°C, diluted with cold water, acidified (H_2SO_4, 2M) and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (0.164g) was shown by ^{19}F nmr to contain cyclised product [36] and the non cyclised adduct [38] in the ratio 85 : 15 respectively.

6.2.3 ATTEMPTED PREPARATION AND SUBSEQUENT CYCLISATION OF THE 1-ISOQUINOLINETHIOL [26] AND DERIVATIVES WITH DMAD.

i. Dealkylation of the 1-(t-butylthio)isoquinoline [39]: Unstable 3,4,5,6,7,8-Hexafluoro-1-Isoquinolinethiol [26].

The 1-(t-butylthio)isoquinoline [39] (0.047g, 0.14mmol) (see 6.3.1.1.ii) was refluxed in trifluoroacetic acid (2.5ml) for 10 hours, after which time the mixture was cooled to room temperature, and then the acid evaporated in vacuo (0.01mmHg) at room temperature. Sublimation of the crude product (room temp, 0.01mmHg) gave as the sublimate (0.017g) a mixture of the 1-(t-butylthio)isoquinoline [39] (11%) and the 3,4,5,6,7,8-hexafluoro-1-isoquinolinethiol [26] (89%) (by ^{19}F nmr); the 1-isoquinolinethiol [26] in the mixture showed δ_F ($CDCl_3$) -95.7 (d, 3-F), -136.9 (broad s, 8-F), -145.1 (dt, 5-F), -147.5 (broad s, 6-F), -154.7 (t, 7-F), -158.2 (dd,4-F); $J_{4\text{-}F,5\text{-}F}$ 51.8Hz; M^+, 269; C_9HF_6NS requires M, 269. This material decomposed rapidly in solution, but column chromatography on silica using CH_2Cl_2/ light petroleum (b.p. 60-

80°C) as elutant enabled the more slowly eluting thiol to be obtained as a very short lived material free from starting material.

ii. The Synthesis of the 6-Phenylthio-1-isoquinolinethiol [42], followed by Reaction with n-BuLi and DMAD.

The 6-phenylthioisoquinoline [43] (0.537g, 1.55mmol) (see 6.3.1.2.i) in ethylene glycol (2.5ml) (EG) and dry dimethylformamide (DMF) (5ml) at <-10°C was treated with sodium hydrosulphide (0.462g, 8.2mmol) in EG (2.5ml) and DMF (5ml) at <-10°C The mixture was left to stir for ten minutes, poured into iced water, acidified (H_2SO_4, 2M), and the product extracted into ether. The ether extracts were washed with base (NaOH, 2M), the separated aqueous layer was then acidified (H_2SO_4, 2M) and the product extracted into ether. These ether extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude product (0.418) was shown by ^{19}F nmr to be slightly impure (ca. 95% purity) 3,4,5,7,8-pentafluoro-6-phenylthio-1-isoquinolinethiol [42] δ_F ($CDCl_3$) -96.2 (d, 3-F), -110.3 (dd, 5-F), -129.9 (d, 7-F), -140.2 (broad s, 8-F), -156.6 (dd 4-F); $J_{4\text{-}F,5\text{-}F}$ 60Hz; $J_{3\text{-}F,4\text{-}F}$ 19Hz; δ_H ($CDCl_3$) 7.42 (m, HC_{arom}), 7.31 (m, HC_{arom}), 4.63 (broad s, -SH); M^+, 359, $C_{15}H_6F_5NS_2$ requires M, 359. The 6-phenylthio-1-isoquinolinethiol [42] (0.418g, 1.16mmol) in anhydrous THF (250ml) cooled to -63°C was treated with butyllithium (0.65ml, 1.6M, 1.0mmol), and after 15 minutes DMAD (0.13ml, 1.0mmol) in anhydrous THF was added. The mixture was warmed to room temperature and then refluxed for 10 days. After cooling, the product was diluted with water and the product extracted into ether. The ether extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue was then separated by chromatography on silica with $CHCl_3$/light petroleum (b.p. 40-60°C) (1 : 1 v/v). Three fractions were collected and fraction 3 (0.255g) contained the noncyclised DMAD, adduct material [44] and other impurities. Fraction 3 was re-chromatographed as before and 6 fractions were collected. Fraction 5 contained dimethyl 1-(3,4,5,7,8-pentafluoro-6-phenylthio-1-isoquinolylthio)ethene-1,2-dicarboxlate [44].(0.056g) m.p.116.0 -116.5°C [from light petroleum (b.p. 60-80°C)] (Found C, 50.69; H,2.43; N, 2.73; M^+, 502 [Cl]. $C_{21}H_{12}F_5NO_4S_2$ requires C, 50.30; H, 2.41; N,2.79%; M, 501); δ_F ($CDCl_3$) -97.3 (d,

3-F), -110.3 (dd, 5-F), -129.1 (d, 7-F), -136.9 (t, 8-F), -155.2 (dd 4-F); $J_{4\text{-}F,5\text{-}F}$ 61Hz; $J_{3\text{-}F,4\text{-}F}$ 18Hz; δ_H ($CDCl_3$) 7.43 (m, HC_{arom}), 7.32 (m, HC_{arom}), 7.11 (s, C=CH), 3.82 (s, CH_3), 3.79 (s, CH_3). The ^1H integrals were 2 : 3 : 1 : 3 : 3 respectively.

6.3 EXPERIMENTAL FOR CHAPTER THREE.

6.3.1 REACTIONS OF HEPTAFLUOROISOQUINOLINE [1] WITH NUCLEOPHILES.

6.3.1.1 The Isoquinoline with Alkylthiolates.

i. With sodium methylthiolate.

The solution made by passing excess methanethiol gas[62] through sodium ethoxide in ethanol (0.369M, 2.4ml, 0.88mmol) was added to a solution of the isoquinoline [1] (0.248g, 0.97mmol) in anhydrous ethanol (40ml) at -85 to -90°C, over 2 minutes. The mixture was warmed to room temperature, acidified (H_2SO_4, 2M) and the product extracted into ether. The combined ether extracts were dried ($MgSO_4$), filtered, the solvent evaporated, and the crude product (0.226g) shown by ^{19}F nmr spectroscopy to contain unreacted starting material [1] (12%) and three products (88%): the 1-(methylthio)isoquinoline [46], the 6-(methylthio)isoquinoline [47] and the 1,6-di(methylthio)isoquinoline [48] in the ratio 22 : 73 : 5 respectively. Flash chromatography of the crude product on silica using carbon tetrachloride as elutant gave enrichment of the two faster moving components while crystallisation of the mixture of the two slowest eluting components [one of which was unreacted isoquinoline (1)] gave 1,3,4,5,7,8-hexafluoro-6-(methylthio)isoquinoline [47] m.p. 47.5-48.0°C [from light petroleum (b.p. 60-80°C)] (Found: C, 42.46; H, 1.14; N, 4.78%; M^+, 283. $C_{10}H_3F_6NS$ requires C, 42.41; H, 1.07; N, 4.95%; M, 283); δ_F ($CDCl_3$) -63.1 (ddd, 1-F), -97.5 (s, 3-F), -114.7 (dd, 5-F), -130.3 (d, 7-F), -143.8 (dt, 8-F), -154.9 (ddd, 4-F); $J_{1\text{-}F,4\text{-}F}$ 35Hz; $J_{1\text{-}F,8\text{-}F}$ 57Hz; $J_{4\text{-}F,5\text{-}F}$ 54Hz; $J_{5\text{-}F,8\text{-}F}$ 19.3Hz; δ_H ($CDCl_3$) 2.72 (narrow triplet, CH_3, J 1.1Hz [ref. 63]). Further flash chromatography of the enriched faster moving components on silica using light petroleum (b.p. 60-80°C) as elutant gave as the faster moving component 3,4,5,6,7,8-hexafluoro-1-(methylthio)isoquinoline [46]

m.p. 65.0-65.5°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 42.12; H, 1.08; N, 4.78%; M^+, 283. $C_{10}H_3F_6NS$ requires C, 42.41; H, 1.07; N, 4.95%; M, 283); δ_F ($CDCl_3$) -96.6 (d, 3-F), -134.5 (t, 8-F), -145.7 (dt, 5-F), -149.0 (t, 6-F), -155.7 (t, 7-F), -161.4 (dd, 4-F); $J_{3\text{-}F,4\text{-}F}$ 18Hz; $J_{4\text{-}F,5\text{-}F}$ 51Hz; δ_H ($CDCl_3$) 2.63 [s, CH_3)]. A larger amount of the minor, slower eluting disubstituted compound was prepared from the 6-sulphide [47]. The solution made by passing excess methanethiol gas through a solution of sodium ethoxide solution, prepared by reacting sodium (0.0105g, 0.46 mmol) with anhydrous ethanol (2.5ml), was added to a solution of the 6-methylthioisoquinoline [47] (0.124g, 0.44mmol) in anhydrous ethanol (30ml) at -85 to -90°C over 2 minutes. The mixture was warmed to room temperature, acidified (H_2SO_4, 2M) and the product extracted into ether. The ether extracts were dried ($MgSO_4$), filtered, the solvent evaporated and the crude product (0.116g) was shown by TLC to contain starting material and one other component. The product was sublimed under high vacuum, initially at 100°C, and the sublimate exhaustively re-sublimed at 40°C to remove the starting material [47]. The residue was recrystallised to give 3,4,5,7,8-pentafluoro-1,6-di(methylthio)isoquinoline [48] m.p. 106.0-106.5°C [from light petroleum (b.p. 60-80°C)] (Found: C, 42.41; H, 2.13; N, 4.08%; M^+, 311. $C_{11}H_6F_5NS$ requires C, 42.44; H, 1.94; N, 4.50%; M, 311); δ_F ($CDCl_3$) -97.7 (d, 3-F), -114.0 (dd, 5-F), -132.9, (d, 7-F), -138.5 (t, 8-F), -160.7 (dd, 4-F); $J_{3\text{-}F,4\text{-}F}$ 19Hz; $J_{4\text{-}F,5\text{-}F}$ 61Hz; $J_{5\text{-}F,8\text{-}F}$ 19Hz; δ_H ($CDCl_3$) 2.62 (s, CH_3) at C-1, 2.66 ($d^{ref.\ 63}$, CH_3) at C-6.

ii. With sodium t-butylthiolate.

The solution made by reacting sodium (0.196g, 8.5mmol) with anhydrous ethanol (10ml) followed by addition of a slight excess of t-butanethiol (1.00ml, 8.9mmol), was added to a solution of the isoquinoline [1] (2.35g, 9.2mmol) in anhydrous ethanol (280ml) at -91°C, over a period of 20 minutes. The mixture was warmed to room temperature and left to stir for 12 hours. The solvent was evaporated, water added and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered, the solvent evaporated and the crude residue (2.87g) shown by ^{19}F nmr

($CDCl_3$) to contain unreacted starting material [1] (12%) and five other products (88%): 1-(t-butylthio)isoquinoline [39], the 6-(t-butylthio)isoquinoline [40], the 1,6-di(t-butylthio)isoquinoline [41], the 1-ethoxyisoquinoline [60] and the 1-ethoxy-6-(t-butylthio)isoquinoline [59] in the ratio 14 : 72 : 3.5 : 7 : 3.5 respectively. Flash chromatography of the crude product on silica using carbon tetrachloride as elutant gave as the faster moving components, enriched minor products, while recrystallisation of the slowest moving component gave 1,3,4,5,7,8-hexafluoro-6-(t-butylthio)isoquinoline [40] m.p. 127.0-127.5°C [from light petroleum (b.p. 60-80°C)] (Found: C, 47.74; H, 2.85; N, 4.16%; M^+, 325. $C_{13}H_9F_6NS$ requires C, 48.00; H, 2.79; N, 4.31%; M, 325); δ_F ($CDCl_3$) -62.5 (ddd, 1-F), -97.3 (3-F), -106.6 (dd, 5-F), -124.5 (d, 7-F), -142.9 (dt, 8-F), and -153.0 (ddd, 4-F); $J_{1\text{-}F,4\text{-}F}$ 33Hz; $J_{1\text{-}F,8\text{-}F}$ 60Hz; $J_{4\text{-}F,5\text{-}F}$ 59Hz; $J_{5\text{-}F,8\text{-}F}$ 21Hz; δ_H ($CDCl_3$) 1.42 [s, $(CH_3)_3C$]. Re-chromatography of the enriched faster moving components on silica using light petroleum (b.p. 40-60°C) as elutant gave as the fastest moving component 3,4,5,6,7,8-hexafluoro-1-(t-butylthio)isoquinoline [39] m.p. 71.5-72.0°C [from light petroleum (b.p. 60-80°C)] (Found: C, 48.30; H, 2.79; N, 4.09%; M^+, 325. $C_{13}H_9F_6NS$ requires C, 48.00; H, 2.79; N, 4.31%; M, 325); δ_F ($CDCl_3$) -96.7 (d, 3-F), -132.3 (t, 8-F), -145.9 (dt, 5-F), -149.5 (t, 6-F), -156.0 (ddd, 7-F), -161.3 (dd, 4-F); $J_{3\text{-}F,4\text{-}F}$ 21.5Hz; $J_{4\text{-}F,5\text{-}F}$ 54.4Hz; δ_H ($CDCl_3$) 1.68 [s, $(CH_3)_3C$]. The combined later fractions contained the two disubstituted compounds [41] and [59] (identified by ^{19}F nmr), present in only a low proportion. Consequently they were synthesised separately from the 6-sulphide [40]. The solution made by reacting sodium (0.077g, 3.4mmol) with anhydrous ethanol (10ml) followed by addition of a slight excess of t-butanethiol (0.42ml, 3.7mmol), was added to a solution of 6-(t-butylthio)isoquinoline [40] (1.000g, 3.07mmol) in anhydrous ethanol (130ml) at -95 to -105°C over a period of 15 minutes. The mixture was warmed to room temperature. The solvent was evaporated, water added and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered, the solvent evaporated and the residue (1.09g) shown by ^{19}F nmr ($CDCl_3$) to contain two products: the 1,6-di(t-butylthio) compound [41] (50%) and the 1-ethoxy-6-(t-butylthio) compound [59] (50%). Flash chromatography of the product on silica using carbon tetrachloride as elutant gave as the faster moving

component 3,4,5,7,8-pentafluoro-1,6-di(t-butylthio)isoquinoline [41], an oil. (Found: C, 51.84; H, 4.44; N, 3.20%; M^+, 395. $C_{17}H_{18}F_5NS_2$ requires C, 51.63; H, 4.59; N, 3.54%; M, 395); δ_F ($CDCl_3$) -97.7 (d, 3-F), -106.9 (dd, 5-F), -127.8 (d, 7-F), -135.5 (t, 8-F), -159.1 (dd, 4-F); $J_{3\text{-}F,4\text{-}F}$ 20.5Hz; $J_{4\text{-}F,5\text{-}F}$ 65Hz; $J_{5\text{-}F,8\text{-}F}$ 20Hz; δ_H ($CDCl_3$) 1.39 [s, $(CH_3)_3C$] at C-1, 1.69 [s, $(CH_3)_3C$] at C-6. The slower moving component was 3,4,5,7,8-pentafluoro-1-ethoxy-6-(t-butylthio)isoquinoline [59] m.p. 99.5-100.0°C [from light petroleum (b.p. 60-80°C)].(Found: C, 51.28; H, 3.81; N, 3.77%; M^+, 351. $C_{15}H_{14}F_5NOS$ requires C, 51.28; H, 4.02; N, 3.99%; M, 351); δ_F ($CDCl_3$) -99.5 (d, 3-F), -109.0 (dd, 5-F), -128.3 (d, 7-F), -140.1 (t, 8-F), -163.8 (dd, 4-F); $J_{3\text{-}F,4\text{-}F}$ 18Hz; $J_{4\text{-}F,5\text{-}F}$ 60.6Hz; $J_{5\text{-}F,8\text{-}F}$ 20.9Hz; δ_H ($CDCl_3$) 1.39 [s, $(CH_3)_3C$], 1.50 [t, CH_3] and 4.54 [quart, CH_2]. The synthesis and characterisation of the sixth component (revealed by ^{19}F nmr of the crude reaction product as the 1-ethoxy-isoquinoline [60]) is described later (see 6.3.1.3.ii).

iii. With sodium t-butylthiolate with an excess of t-butanethiol present.

The solution made by reacting sodium (0.021g, 0.9mmol) with anhydrous ethanol (10ml) followed by an approximately 10 fold excess of t-butanethiol (1.16ml, 10mmol), was added to a solution of isoquinoline [1] (0.263g, 1.0mmol) in anhydrous ethanol (50ml) at -90°C over 10 minutes. The mixture was warmed to room temperature, the solvent was evaporated in vacuo, water added to the residue and the product extracted into ether. The extracts were dried ($MgSO_4$), the solvent evaporated and the residue (0.284g) shown by ^{19}F nmr ($CDCl_3$) to contain unreacted starting material [1] (2%) and three products (98%) (all characterised previously): the 1-(t-butylthio) compound [39], the 6-(t-butylthio) compound [40] and the 1,6-di(t-butylthio) compound [41] in the ratio 16 : 79 : 5 respectively.

6.3.1.2 The Isoquinoline with Arylthiolates.

i. With sodium thiophenate.

The solution made by reacting sodium (0.0212g, 0.92mmol) with anhydrous ethanol (10ml) followed by slight excess of thiophenol (0.105ml, 1.02mmol), was

added to a solution of the isoquinoline [1] (0.261g, 1.02mmol) in anhydrous ethanol (30ml), at -80 to -90°Cover a period of 2 minutes. The mixture was warmed to room temperature, acidified (H_2SO_4) and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered, the solvent evaporated and the crude residue (0.348g) shown by ^{19}F nmr to contain residual starting material (3%) and two other components (97%): the 6-(phenylthio)isoquinoline [43] and the 1,6-di(phenylthio)isoquinoline [45] in the ratio 99 : 1.respectively. Recrystallisation of the crude product gave 1,3,4,5,7,8-hexafluoro-6-(phenylthio)isoquinoline [43] m.p. 120.5-121.0°C [from light petroleum (b.p. 60-80°C)] (Found: C, 52.30; H, 1.40; N, 4.02%; M^+, 345. $C_{15}H_5F_6NS$ requires C, 52.18; H, 1.46; N, 4.06%; M, 345; δ_F ($CDCl_3$) -62.7 (ddd, 1-F), -97.2 (s, 3-F), -111.3 (dd, 5-F), -127.9 (d, 7-F), -142.6 (dt, 8-F), -153.9 (ddd, 4-F); $J_{1\text{-}F,4\text{-}F}$ 34Hz; $J_{1\text{-}F,8\text{-}F}$ 60.2Hz; $J_{4\text{-}F,5\text{-}F}$ 55Hz; $J_{5\text{-}F,8\text{-}F}$ 19.5 Hz; δ_H ($CDCl_3$) 7.36 (m, HC_{arom}), 7.48 (m, HC_{arom}). The minor component [45] was prepared in a separate experiment. The solution made by reacting sodium (0.022g, 0.96mmol) with anhydrous ethanol (5ml) followed by excess of thiophenol (0.10ml, 0.97mmol), was added to a solution of the isoquinoline [1] (0.126g, 0.49mmol), in anhydrous ethanol (30ml), at -70 to -76°C, over a period of 1 minute. The mixture was warmed to room temperature, acidified (H_2SO_4, 2M), the product extracted into ether, dried ($MgSO_4$), filtered and the solvent evaporated. Exhaustive sublimation (100°C/0.05mmHg) to remove any mono-substituted product followed by sublimation of the residue (140°C/ 0.05mmHg), gave as sublimate 1,6-di(phenylthio)-3,4,5,7,8-pentafluoroisoquinoline [45] m.p. 141.5-142.0°C [from light petroleum (b.p. 100-120°C)] (Found: C, 58.30; H, 2.31; N, 3.15%; M^+, 435. $C_{21}H_{10}F_5NS_2$ requires C, 57.93; H, 2.31; N, 3.22%; M, 435); δ_F ($CDCl_3$) -95.9 (d, 3-F), -110.7 (dd, 5-F), -130.3 (d, 7-F), -136.6 (t, 8-F) and -157.8 (d, 4-F); $J_{4\text{-}F,5\text{-}F}$ 61Hz; δ_H ($CDCl_3$) 7.58, 7.48, 7.34 (all m, HC_{arom})

ii. With sodium 4-methoxythiophenate.

The solution made by reacting sodium (0.0074g, 0.32mmol) with anhydrous ethanol (5ml) followed by addition of excess 4-methoxythiophenol (0.20ml, 1.6mmol), was added to a solution of the isoquinoline [1] (0.104g, 0.41mmol) in anhydrous

ethanol (30ml) at -85 to -80°C, over a period of 2 minutes. The mixture was warmed to room temperature, diluted with water and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered, the solvent evaporated and the crude residue (containing excess 4-methoxythiophenol) shown by ^{19}F nmr to contain the 1-(4-methoxyphenylthio)-isoquinoline [55], the 6-(4-methoxyphenylthio)-isoquinoline [56] and the 1,6-di(4-methoxyphenylthio)-isoquinoline [57] in the ratio 0.5 : 97.5 : 2 respectively. The minor mono-substituted component 3,4,5,6,7,8-hexafluoro-1-(4-methoxyphenylthio)isoquinoline [55] was identified from its ^{19}F nmr spectrum [δ_F ($CDCl_3$) -95.6 (d, 3-F), -133.8 (t, 8-F), -146.0 (dt, 5-F), -149.2 (bt, 6-F), -155.8 (t, 7-F) and -160.0 (dd, 4-F)] in conjunction with substituent chemical shift data (SCS) from the 6-(4-methoxyphenylthio)isoquinoline [56] and 1,6-di(4-methoxyphenylthio)isoquinoline [57] which were both prepared separately as follows.

Sodium 4-methoxythiophenate in ethanol was prepared by reacting sodium metal (0.200g, 8.68mmol) with anhydrous ethanol (10ml) followed by the addition of excess 4-methoxythiophenol (1.1ml, 8.9mmol). The volume was then made up to 25ml with further anhydrous ethanol. A portion of the sodium 4-methoxythiophenate solution (3.9ml, 1.35mmol) was added to a solution of the isoquinoline [1] (0.366g, 1.43mmol) in anhydrous ethanol (30ml), at -80°C, over a period of one minute. The mixture was warmed to room temperature and then 17ml of the resultant solution withdrawn for later use to make the di-substituted product [57]. The remainder was diluted with water and the product extracted into ether. The combined ether layers were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (0.220g) was sublimed (140°C, 0.1mmHg) and the sublimate recrystallised to give 1,3,4,5,7,8-hexafluoro-6-(4-methoxyphenylthio)-isoquinoline [56] m.p. 90.5-91.0°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 51.31; H, 1.85; N, 3.65%; M^+, 375. $C_{16}H_7F_6NOS$ requires C, 51.21; H, 1.88; N, 3.73%; M, 375; δ_F ($CDCl_3$) -62.9 (ddd, 1-F), -97.5 (s, 3-F), -112.6 (ddd, 5-F), -128.8 (d, 7-F), -143.1 (dt, 8-F), -154.2 (ddd, 4-F); $J_{1\text{-}F,4\text{-}F}$ 33Hz; $J_{1\text{-}F,8\text{-}F}$ 59.5Hz; $J_{4\text{-}F,5\text{-}F}$ 56Hz; δ_H ($CDCl_3$) 7.44 (d, HC_{arom}), 6.79 (d, HC_{arom}), 3.74 (s, CH_3). The 17ml of crude reaction mixture withdrawn earlier was re-cooled to -58 to -62°C, and a further portion of the sodium 4-methoxythiophenate solution (2.0ml,

0.69mmol) was added over a period of one minute. The mixture was warmed to room temperature and worked up as before. The crude residue (0.302g) was sublimed (140°C, 0.1mmHg) and the sublimate recrystallised to give the 3,4,5,7,8-pentafluoro-1,6-di(4-methoxyphenylthio)-isoquinoline [57] m.p. 145.5-155.0°C [from light petroleum (b.p. 100-120°C)]. (Found: C, 56.09 H, 2.84; N, 2.71%; M^+, 495. $C_{23}H_{14}F_5NO_2S_2$ requires C, 55.75; H, 2.85; N, 2.83%; M, 495; δ_F ($CDCl_3$) -96.2 (d, 3-F), -112.1 (dd, 5-F), -131.3 (d, 7-F), -136.8 (t, 8-F), -158.4 (dd, 4-F); $J_{4\text{-}F,5\text{-}F}$ 61Hz; δ_H ($CDCl_3$) 7.51 (d, HC_{arom}), 7.46 (d, HC_{arom}), 7.00 (d, HC_{arom}), 6.87 (d, HC_{arom}), 3.88 (s,CH_3), 3.82 (s, CH_3).

iii. With sodium 4-(N,N-dimethylamino)thiophenate.

The solution made by reacting sodium (0.0076g, 0.33mmol) with anhydrous ethanol (5ml) followed by addition of 4-(N,N-dimethylamino)thiophenol[64] (0.18g, 1.2mmol), was added to a solution of the isoquinoline [1] (0.116g, 0.45mmol) in anhydrous ethanol (30ml) at -85 to -80°C, over a period of 2 minutes. The mixture was warmed to room temperature, diluted with water and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered, the solvent evaporated and the crude residue (containing excess 4-(N,N-dimethylamino)thiophenol) shown by ^{19}F nmr to contain unreacted starting material (0.5%) and the products (99.5%): 1-(4-(N,N-dimethylamino)phenylthio)isoquinoline [52], 6-(4-(N,N-dimethylamino)phenylthio)isoquinoline [53] and 1,6-di(4-(N,N-dimethylamino)phenylthio)isoquinoline [54] in the ratio 0.5 : 97.5 : 2 respectively. The crude residue was sublimed (140°C, 0.1mmHg) and the sublimate recrystallised to give 1,3,4,5,7,8-hexafluoro-6-(4-(N,N-dimethylamino)phenylthio)isoquinoline [53] m.p. 155.0-155.5°C [from light petroleum (b.p. 100-120°C)]. (Found: C, 52.33; H, 2.52; N, 7.01%; M^+, 388. $C_{17}H_{10}F_6N_2S$ requires C, 52.58; H, 2.60; N, 7.21%; M, 388; δ_F ($CDCl_3$) -63.1 (ddd, 1-F), -98.0 (s, 3-F), -113.6 (dd, 5-F), -129.2 (d, 7-F), -143.5 (dt, 8-F), -154.5 (dt, 4-F); $J_{1\text{-}F,4\text{-}F}$ 33Hz; $J_{1\text{-}F,8\text{-}F}$ 59.5Hz; $J_{4\text{-}F,5\text{-}F}$ 55.5Hz; δ_H ($CDCl_3$) 7.47 (d, HC_{arom}), 6.62 (d, HC_{arom}), 2.97 (s, CH_3). The minor component 3,4,5,6,7,8-hexafluoro-1-(4-N,N-dimethylaminophenylthio)isoquinoline [52] was identified by its

^{19}F nmr spectrum [δ_F ($CDCl_3$) -94.7 (3-F), -132.8 (8-F), -144.8 (5-F), -149.2 (6-F), -156.0 (7-F) and -160.5 (4-F)] in conjunction with SCS data from the 6-(4-(N,N-dimethylamino)phenylthio)isoquinoline [53] (see above) and the 1,6-di(4-(N,N-dimethylamino)phenylthio)isoquinoline [54] which was prepared and characterised in a separate experiment as follows.

The solution made by reacting sodium (0.020g, 0.88mmol) with anhydrous ethanol (5ml) followed by addition of 4-(N,N-dimethylamino)thiophenol, was added to a solution of the isoquinoline [1] (0.099g, 0.38mmol) in anhydrous ethanol (30ml) at -85°C over one minute. The mixture was warmed to room temperature and stirred for one hour. The crude mixture was diluted with water and the product extracted into ether. The combined extracts were washed with a small amount of water and then dried ($MgSO_4$), filtered and the solvent evaporated. The crude product (0.043g) was heated at 140°C in vacuo at 0.1mmHg to remove any 6- monosubstituted compound [53] and the residue recrystallised to give 3,4,5,7,8-pentafluoro-1,6-di(4-(N,N-dimethylamino)phenylthio)isoquinoline [54] m.p. 195.5-196.0°C [from light petroleum (b.p. 100-120°C)]. (Found: C, 57.58 H, 3.88; N, 7.84%; M^+, 522. $C_{25}H_{20}F_5N_3S_2$ requires C, 57.57; H, 3.86; N, 8.06%; M, 522; δ_F ($CDCl_3$) -96.3 (d, 3-F), -113.1 (dd, 5-F), -131.8 (d, 7-F), -136.7 (t, 8-F), -159.3 (dd, 4-F); $J_{4\text{-}F,5\text{-}F}$ 61Hz; δ_H ($CDCl_3$) 7.46 (d, HC_{arom}), 7.36 (d, HC_{arom}), 6.74 (d, HC_{arom}), 6.62 (d, HC_{arom}), 3.02 (s, CH_3), 2.97 (s, CH_3).

iv. With sodium 4-nitrothiophenate.

The solution made by reacting sodium (4.6mg, 0.20mmol) with anhydrous ethanol (5ml) followed by addition of 4-nitrothiophenol (0.0511g) in anhydrous ethanol (1ml), was added to a solution of the isoquinoline [1] (0.102g, 0.40mmol) in anhydrous ethanol (30ml), at -90 to -80°C over 2 minutes. The mixture was warmed to room temperature, diluted with water and the product extracted into ether. The ether extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (containing excess 4-nitrothiophenol) was shown by ^{19}F nmr to contain unreacted starting material [1] (11%) and the 6-(4-nitrophenylthio)-isoquinoline [58] (89%) only. The crude residue

was sublimed (140°C, 0.1mmHg) and the sublimate recrystallised to give the 1,3,4,5,7,8-hexafluoro-6-(4-nitrophenylthio)-isoquinoline [58] m.p. 112.0-112.5°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 46.15 H, 1.03; N, 7.05%; M^+, 390. $C_{15}H_4F_6N_2O_2S$ requires C, 46.16; H, 1.03; N, 7.18%; M, 390; δ_F ($CDCl_3$) -61.7 (ddd, 1-F), -95.7 (s, 3-F), -109.1 (dd, 5-F), -127.6 (d, 7-F), -141.1 (dt, 8-F), -153.0 (ddd, 4-F); $J_{1\text{-}F,8\text{-}F}$ 60.3Hz, $J_{1\text{-}F,4\text{-}F}$ 34Hz, $J_{4\text{-}F,5\text{-}F}$ 55.5Hz; δ_H ($CDCl_3$) 8.19 (d, HC_{arom}), 7.46 (d, HC_{arom}).

6.3.1.3 The Isoquinoline with Alkoxides.

i. With sodium methoxide.

The solution made by reacting sodium (0.0093g, 0.40mmol) with anhydrous methanol (5ml), was added to a solution of the isoquinoline [1] (0.121g, 0.47mmol) in anhydrous methanol (30ml) at -82 to -84°C over 2 minutes. The mixture was allowed to warm to room temperature, acidified (H_2SO_4, 2M) and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (0.140g) was shown by ^{19}F nmr. to contain residual starting material [1] (26%) and two products (74%): the 1-methoxy-isoquinoline [63] and the 6-methoxy-isoquinoline [64], in the ratio 97 : 3 respectively The mono-methoxyethers had been characterised previously.[26]

ii. With sodium ethoxide.

The solution made by reacting sodium (0.0062g, 0.27mmol) with anhydrous ethanol (5ml), was added to a solution of the isoquinoline [1] (0.093g, 0.36mmol) in anhydrous ethanol (30ml) at -88 to -92°C over 2 minutes. The mixture was warmed to room temperature, acidified (H_2SO_4, 2M) and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (0.085g) was shown by ^{19}F nmr to contain residual starting material [1] (17%) and two products (83%): 1-ethoxy-isoquinoline [60] and the 6-ethoxy-isoquinoline [61], present in the ratio 94 : 6 respectively. A previous larger scale experiment (500mg starting material) similar to that described above gave upon recrystallisation the 1-ethoxy-

3,4,5,6,7,8-hexafluoroisoquinoline [60] m.p. 52.0-52.5°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 47.10; H, 1.78; N, 4.77%; M^+, 281. $C_{11}H_5F_6NO$ requires C, 46.99; H, 1.79; N, 4.98%; M, 281); δ_F ($CDCl_3$) -98.2 (d, 3-F), -136.8 (d, 8-F), -147.6 (dt, 5-F), -148.9 (t, 6-F), -156.9 (t, 7-F), -165.8 (dd, 4-F); $J_{4\text{-}F,5\text{-}F}$ 49Hz; $J_{5\text{-}F,8\text{-}F}$ 17.8Hz;.δ_H ($CDCl_3$) 4.45 [q, CH_2], 1.43 [t, CH_3].

The reaction of isoquinoline [1] and ethoxide as above, but with a slight excess of ethoxide present, gave as the product (by ^{19}F nmr) 1-ethoxyisoquinoline [60] and 1,6-di(ethoxy)isoquinoline [62] only, in the ratio 84 : 16 respectively. No residual starting material [1] or 6-ethoxyisoquinoline [61] were detectable, i.e. the 6-ethoxyisoquinoline [61] had reacted further preferentially. The 1,6-di(ethoxy)isoqunoline [62] was prepared as follows: the solution made by reacting sodium (0.010g, 0.43mmol) with anhydrous ethanol (5ml) was added to a solution of the 1-ethoxy-isoquinoline [60] (0.121g, 0.43mmol) in anhydrous ethanol (30ml) at -92 to -95°C over a period of 2 minutes. The mixture was allowed to warm up to room temperature, acidified (H_2SO_4, 2M) and the product extracted into ether. The ether extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The residual oil (0.126g) was distilled to give a yellow oil, 1,6-di(ethoxy)-3,4,5,7,8-pentafluoroisoquinoline [62]. (Found: C, 51.26; H, 3.45; N, 4.47%; M^+, 307. $C_{13}H_{10}F_5NO_2$ requires C, 50.82; H, 3.28; N, 4.56%; M, 307); δ_F ($CDCl_3$) -100.4 (d, 3-F), -139.8 (t, 8-F), -142.7 (dd, 5-F), -151.9 (d, 7-F), -166.5 (dd, 4-F); $J_{4\text{-}F,5\text{-}F}$ 54.8Hz; $J_{3\text{-}F,4\text{-}F}$ 18Hz; δ_H ($CDCl_3$) 1.47 (t, CH_3), 4.47 (overlapping q, CH_2).

6.3.1.4 The Isoquinoline with Aryloxides.

i. With sodium phenoxide.

Sodium phenoxide in ethanol was prepared by reacting sodium metal (0.022g, 0.96mmol) with anhydrous ethanol (10ml) and adding excess phenol (0.85g, 9.0mmol). A portion of the above solution (2.5ml, 0.24mmol of nucleophile) was added a solution of the isoquinoline [1] (0.080g, 0.31mmol) in anhydrous ethanol (30ml) at -90°C , over a period of one minute. The mixture was warmed to room temperature

before being diluted with water and the product extracted into ether. The combined ether layers were washed with a small amount of water, dried ($MgSO_4$), filtered and the solvent evaporated. The excess phenol was removed by passing the crude material down a short (2.5" x 1" outside diameter) silica column with CCl_4 as elutant, (the phenol is left at the top of the column). The solvent was evaporated and the crude material (0.082g) was shown by ^{19}F nmr spectroscopy to contain residual starting material (25%) and the products (75%) : 1- [65] and 6- [66] phenoxy substituted isoquinolines (8 parts) in the ratio 93 : 7 respectively; and 1- and 6- ethoxy substituted isoquinolines (2 parts) in the ratio 92 : 8 respectively. Exhaustive sublimation of the product (45°C/0.1mmHg) and recrystallisation of the residue gave 3,4,5,6,7,8-hexafluoro-1-phenoxy-isoquinoline [65] m.p. 126.5-127.0°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 55.09; H, 1.45; N, 3.98%; M^+, 329. $C_{15}H_5F_6NO$ requires C, 54.73; H, 1.53; N, 4.25%; M, 329); δ_F ($CDCl_3$) -96.8 (d, 3-F), -136.4 (t, 8-F), -147.0 (dt, 5-F), -147.7 (t, 6-F), -155.6 (t, 7-F), -162.2 (dd, 4-F); $J_{4\text{-}F,5\text{-}F}$ 49Hz; $J_{5\text{-}F,8\text{-}F}$ 17Hz; δ_H ($CDCl_3$) 7.39 [m, HC_{arom}], 7.20 [m, HC_{arom}]. The presence of the 6-phenoxy isomer [66] was inferred from two separate absorptions in the ^{19}F nmr spectra of the crude reaction product δ_F ($CDCl_3$) -62.9 (ddd, 1-F) and -141.0 (dt, 8-F).

ii. With sodium 4-nitrophenoxide.

Sodium 4-nitrophenoxide in ethanol was prepared by reacting sodium metal (0.018g, 0.80mmol) with anhydrous ethanol (10ml) and adding excess 4-nitrophenol (0.61g, 4.3mmol). A portion of this solution (2.0ml, 0.16mmol of nucleophile) was added to a solution of the isoquinoline [1] (0.052g, 0.20mmol) in anhydrous ethanol (30ml), at -90°C over a period of thirty seconds. The mixture was warmed to room temperature before being diluted with water and the product extracted into ether. The combined ether layers were washed with a small amount of water, dried ($MgSO_4$), filtered and the solvent was evaporated. The crude residue (0.065g) was shown by ^{19}F nmr spectroscopy to contain only residual starting material [1] (99%) and the product (1%) 1-(4-nitrophenoxy)-isoquinoline [67]. The experiment was repeated at reflux temperature for two hours and gave as crude product (by ^{19}F nmr analysis), residual

starting material (13%) and the products (87%): the 1-(4-nitro-phenoxy)-isoquinoline [67] and 1-ethoxy-isoquinoline [60] in the ratio 93:7 respectively. Exhaustive sublimation (50°C, 0.1mmHg) of the crude product and chromatography of the residue on silica with $CCl_4/CHCl_3$ 1 : 3 v/v to remove excess 4-nitrophenol gave 3,4,5,6,7,8-hexafluoro-1-(4-nitrophenoxy)-isoquinoline [67] m.p. 145.0-145.5°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 48.01; H, 0.93; N, 7.35%; M^+, 374. $C_{15}H_4F_6N_2O_3$ requires C, 48.15; H, 1.08; N, 7.49%; M, 374); δ_F ($CDCl_3$) -96.9 (d, 3-F), -136.7 (t, 8-F), -146.0, -146.2 (overlapping multiplets 5-F, 6-F), -154.0 (t, 7-F), -159.6 (dd, 4-F); $J_{4\text{-}F,5\text{-}F}$ 49Hz; $J_{5\text{-}F,8\text{-}F}$ 18Hz; δ_H ($CDCl_3$) 8.36 [d, HC_{arom}], 7.42 [d, HC_{arom}].

6.3.2 REACTIONS OF HEPTAFLUOROQUINOLINE [2] WITH NUCLEOPHILES.

6.3.2.1 The Quinoline with Thiolates

i. With sodium hydrosulphide

The quinoline [2] (0.261g, 1.02mmol) in a mixture of anhydrous dimethylformamide (DMF) (5ml) and ethylene glycol (EG) (2.5ml), was treated at -6 to -4°C over 2 minutes with sodium hydrosulphide (0.0977g, 1.74mmol) in a mixture of DMF (5ml) and EG (2.5ml). The mixture was maintained at -2°C for 30 minutes and then rapidly worked up by diluting with precooled ether (-10°C) and iced water, and acidifying with precooled acid (H_2SO_4, 2M) (0°C). The organic layers were dried ($MgSO_4$), filtered and the solvent evaporated under high vacuum. The crude product (0.284g) was sublimed (60°C, 0.5mmHg) to give the sublimate (0.195g, 71%), the ^{19}F nmr of which showed it to be the 4-thiol accompanied by two minor components (neither of which gave an absorption slightly upfield of -124.1ppm where the 4-F would be expected in the 2-thiol from SCS calculations), present in the ratio 95 : 5 respectively. Recrystallisation of the sublimate gave 2,3,5,6,7,8-hexafluoro-4-quinolinethiol [35] m.p. 106.5-107.0°C [from light petroleum (b.p. 60-80°C)] (Found: C, 40.13; H, 0.31; N, 5.12%; M^+, 269. C_9HF_6NS requires C, 40.16; H, 0.37; N, 5.20%; M, 269); δ_F

($CDCl_3$) -78.1 (d, 2-F), -136.1 (dt, 3-F), -143.3 (m, 5-F), -148.1 (td), -152.3 (td), -156.2 (td) (all unassigned). δ_H ($CDCl_3$) 4.66 (dd, S-H); $J_{H,3\text{-}F}$ 9.3Hz; $J_{H,5\text{-}F}$ 27.3Hz.

ii. With sodium methylthiolate.

The solution made by passing excess methanethiol gas[62] through sodium ethoxide in ethanol (0.369M, 2.4ml, 0.88mmol) was added to a solution of the quinoline [2] (0.250g, 0.98mmol) in anhydrous ethanol (40ml) at -85 to -90°C over 2 minutes. The mixture was warmed to room temperature, acidified (H_2SO_4, 2M) and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered, the solvent evaporated and the residue (0.264g) was shown by ^{19}F nmr to contain residual starting material [2] (2.5%) and three other components (97.5%): the 2- (methylthio)quinoline [32], the 4-(methylthio)quinoline [31] and the 2,4-di(methylthio) quinoline [68] in the ratio 4 : 95 :1 respectively. Compounds [32], [31] and [68] had been prepared previously and characterised by G.M. Brooke.[37]

iii. With sodium t-butylthiolate.

The solution made by reacting sodium (0.435g, 0.0189mol) with anhydrous ethanol (20ml) followed by slight excess of t-butanethiol (2.4ml, 0.0213mol), was added to a solution of the quinoline [2] (5.25g, 0.0207mol) in anhydrous ethanol (400ml) at -95 to -105°C over a period of 5 minutes. The mixture was warmed to room temperature, the solvent was evaporated, water added and the product extracted into ether. The extracts were washed with water, dried ($MgSO_4$), the solvent evaporated and the residue (6.95g) shown by ^{19}F nmr spectroscopy ($CDCl_3$) to contain unreacted starting material [2] (10%) and the products (90%): the 2-(t-butylthio)quinoline [72], the 4-(t-butylthio)quinoline [73], the 2,4-di(t-butylthio)quinoline [74] and the 2-ethoxy-4-(t-butylthio)quinoline [76] in the ratios 2.5 : 96 : 1 : 0.5 respectively. The major component [73] was was recrystallised from the crude reaction product to give 2,3,5,6,7,8-hexafluoro-4-(t-butylthio)-quinoline [73] m.p. 115.0-115.5°C [from light petroleum (b.p. 60-80°C)] (Found: C, 47.91; H, 2.44; N, 3.96%; M^+, 325. $C_{13}H_9F_6NS$ requires C, 48.00; H, 2.79; N, 4.31%; M, 325); δ_F ($CDCl_3$) -76.4 (d, 2-F), -122.1 (d, 3-F),

-140.6 (dd, 5-F) and -148.3 (t), -152.9 (s), -154.3 (t), (all unassigned); $J_{2\text{-}F,3\text{-}F}$ 33Hz; δ_H ($CDCl_3$) 1.40 [s, $(CH_3)_3C$].

Flash chromatography of the mother liquors from the recrystallisation, on silica with carbon tetrachloride as elutant gave in the first fractions a mixture enriched in minor components. Re-chromatography of the enriched minor components on silica, with carbon tetrachloride again as elutant gave further enrichment of the faster moving minor components, which in turn were separated on silica using light petroleum (b.p. 60-80°C) as elutant to give as the fastest moving component 3,4,5,6,7,8-hexafluoro-2-(t-butylthio)quinoline [72] m.p. 48.5-49.0°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 47.89; H, 2.70; N, 4.11%; M^+, 325. $C_{13}H_9F_6NS$ requires C, 48.00; H, 2.79; N, 4.31%; M, 325); δ_F ($CDCl_3$) -136.3 (dd, 4-F), -146.4 (d, 3-F), -147.2 (m, 5-F), and -150.9 (t), -154.2 (t), -157.8 (dt) (all unassigned); $J_{3\text{-}F,4\text{-}F}$ 16Hz; $J_{4\text{-}F,5\text{-}F}$ 44Hz; δ_H ($CDCl_3$) 1.74 [s, $(CH_3)_3C$]. The combined later fractions contained the two disubstituted compounds [74] and [76] (identified by ^{19}F nmr spectroscopy) present in only a small proportion. These were obtained separately in another experiment as follows.

The solution made by reacting sodium (0.079g, 3.4mmol) with anhydrous ethanol (10ml) followed by addition of a slight excess of t-butanethiol (0.5ml, 4.4mmol), was added to a solution of 2,3,5,6,7,8-hexafluoro-4-(t-butylthio)quinoline [73] (1.03g, 3.2mmol) in anhydrous ethanol (140ml) at -90 to -93°C over a period of 5 minutes. The mixture was warmed to room temperature, the solvent was evaporated, water added and the product extracted into ether. The extracts were dried ($MgSO_4$), the solvent evaporated and the residue (1.218g) shown by ^{19}F nmr to contain two major products: the 2,4-di(t-butylthio) compound [74] (59%) and the 2-ethoxy-4-(t-butylthio) compound [76] (41%). Flash chromatography of the product on silica with carbon tetrachloride as elutant gave as the faster moving component 3,5,6,7,8-pentafluoro-2,4-di(t-butylthio)quinoline [74] m.p. 104.5-105.0°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 51.92; H, 4.75; N, 3.46%; M^+, 395. $C_{17}H_{18}F_5NS_2$ requires C, 51.63; H, 4.59; N, 3.54%; M, 395); δ_F ($CDCl_3$) -106.2 (s, 3-F), -141.9 (m, 5-F), and -151.3, -156.4, -157.8 (all t, all unassigned); δ_H ($CDCl_3$) 1.75 [s, 2-$(CH_3)_3C$], 1.37 [s,

4-(CH_3)$_3$C]; and as the slower moving component 3,5,6,7,8-pentafluoro-2-ethoxy-4-(t-butylthio)quinoline [76] m.p. 106.0-106.5°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 51.51%; H, 4.08; N, 3.81%; M^+, 351. $C_{15}H_{14}F_5NOS$ requires C, 51.28; H, 4.02; N, 3.99%; M, 351); δ_F ($CDCl_3$) -120.1 (s, 3-F), -142.3 (m, 5-F), and -151.6 (t), -156.4 (dt), -159.8 (dt) (all unassigned); δ_H ($CDCl_3$) 1.38 [s, 4-(CH_3)$_3$C], 1.53 [t, CH_3), 4.82 [q, CH_2].

iv. With sodium t-butylthiolate with an excess of t-butanethiol.

The solution made by reacting sodium (0.0178g, 0.77mmol) with anhydrous ethanol (10ml), followed by an approximately ten fold excess of t-butanethiol (1.02ml, 9.05mmol), was added to a solution of the quinoline [2] (0.232g, 0.91mmol) in anhydrous ethanol (50ml) at -85 to -90°C over 2 minutes. The mixture was warmed to room temperature, acidified (H_2SO_4, 2M) and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (0.259g) was shown by ^{19}F nmr to contain unreacted starting material [2] (14%) and the products (86%): the 2-(t-butylthio)quinoline [72] , the 4-(t-butylthio)quinoline [73] and the 2,4-di(t-butylthio)quinoline [74] in the ratio 5 : 93 : 2 respectively.

v. With sodium thiophenate.

The solution made by reacting sodium (0.0196g, 0.85mmol) with anhydrous ethanol (10ml) followed by slight excess of thiophenol (120µl, 1.17mmol), was added to a solution of the quinoline [2] (0.249g, 0.98mmol) in anhydrous ethanol (30ml) at -80 to -90°C over a period of 2 minutes. The mixture was warmed to room temperature, diluted with water, acidified (H_2SO_4, 2M) and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude product (0.329g) was shown by ^{19}F nmr to contain residual starting material (<2%) and the 2,3,5,6,7,8-hexafluoro-(4-phenylthio)quinoline [75] (>97%). Recrystallisation of the crude product gave 2,3,5,6,7,8-hexafluoro-(4-phenylthio)quinoline [75] m.p. 121.5-122.0°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 51.88; H, 1.40; N, 3.85%: M^+, 345. $C_{15}H_5F_6NS$ requires C, 52.18; H, 1.46; N, 4.06%; M, 345); δ_F ($CDCl_3$)

-77.2 (d, 2-F), -127.5 (d, 3-F), -139.7 (d, 5-F), -148.1, -152.7, -154.9 (all t, unassigned); $J_{2\text{-}F,3\text{-}F}$ 28Hz; δ_H ($CDCl_3$) 7.35 (m, C_{arom}), 7.45 (m, C_{arom}).

6.3.2.2 The Quinoline with Ammonia.

Aqueous ammonia (0.110ml, d 0.88, 1.88 mmol) was added to a stirred solution of the quinoline [2] (0.086g, 0.34mmol) in acetone (3ml), and the mixture stirred for a further 45 minutes after which the product was poured onto ice and extracted into ether. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (0.074g) was shown by ^{19}F nmr to contain the 4-amino-2,3,5,6,7,8-hexafluoroquinoline [84] and the 2-amino-3,4,5,6,7,8-hexafluoroquinoline in the ratio 57 : 43 respectively[26].

6.3.2.3 The Quinoline with Alkoxides and Aryloxides.

i. With sodium ethoxide in ethanol.

Sodium ethoxide (1ml, 0.348M, 0.35mmol) was added to a solution of the quinoline [2] (0.096g, 0.38mmol)in ethanol (30ml) at -70 to -85°C over a period of 2 minutes. The mixture was warmed to room temperature, acidified (H_2SO_4, 2M) and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude product (0.099g) was shown by ^{19}F nmr to contain residual starting material (5%) and the products (95%):- the 2-ethoxy-quinoline [77] and the 4-ethoxy-quinoline [78] in the ratio 76 : 24 respectively. In a further experiment, the two products were separated by chromatography on silica with CCl_4 as elutant to give as faster component the 4-ethoxy-2,3,5,6,7,8-hexafluoroquinoline [78] m.p 35.5-36.0°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 47.13; H, 1.78; N, 4.86%; M^+, 281. $C_{11}H_5F_6NO$ requires C, 46.99; H, 1.79; N, 4.98%; M, 281); δ_F ($CDCl_3$) -76.3 (d, 2-F), -143.9 (t, 5-F), -150.1 (t), -153.2 (t), -157.7 (t) (all unassigned) -160.6 (d, 3-F); $J_{2\text{-}F,3\text{-}F}$ 27.5Hz. δ_H ($CDCl_3$) 1.53 (t, CH_3), 4.66 (q, CH_2). The slower moving component was the 2-ethoxy-3,4,5,6,7,8-hexafluoroquinoline [77] m.p. 41.5-42.0°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 46.75; H, 1.83; N, 4.75%; M^+, 281. $C_{11}H_5F_6NO$ requires C, 46.99; H, 1.79; N, 4.98%; M, 281); δ_F ($CDCl_3$) -133.0 (dd,

4-F), -147.8 (dt, 5-F), -151.2 (t), -154.3 (t), -159.8 (t) (all unassigned) -161.0 (broad s, 3-F); $J_{4\text{-}F,5\text{-}F}$ 45.8Hz. δ_H ($CDCl_3$) 1.51 (t, CH_3), 4.65 (q, CH_2).

ii. With sodium phenoxide.

Sodium phenoxide in ethanol was prepared by reacting sodium metal (0.137g, 5.95mmol) with anhydrous ethanol (10ml) and adding excess phenol (2.95g, 31.3mmol). The volume was made up to 25ml with further anhydrous ethanol. A portion of the sodium phenoxide solution (6.3ml, 1.49mmol) was added to a solution of the quinoline [2] (0.476g, 1.86mmol) in anhydrous ethanol (100ml), at -90°C, over a period of one minute. The mixture was warmed to room temperature, diluted with water and the product extracted into ether. The combined ether layers were washed with a small portion of water, dried ($MgSO_4$), filtered and the solvent evaporated. The crude material (0.852g) was shown by ^{19}F nmr spectroscopy to contain residual starting material (16%) and the products (84%) :- 2- [79] and 4-phenoxy substitued quinolines [80] (9.3 parts) in the ratio 37 : 63 respectively and 2- [77] and 4- [78] ethoxy substituted quinolines (0.7 parts) in the ratio 71 : 29 respectively. Exhaustive sublimation of the product (40°C, 0.1mmHg) removed excess phenol along with [2], [77] and [78]. Chromatography of the residue on silica with CCl_4 as elutant gave as faster moving component 3,4,5,6,7,8-hexafluoro-2-phenoxy-quinoline [79] m.p. 76.5-77.0°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 55.01; H, 1.39; N, 4.13%; M^+, 329 $C_{15}H_5F_6NO$ requires C, 54.73; H, 1.53; N, 4.25%; M, 329); δ_F ($CDCl_3$) -130.5 (dd, 4-F), -147.6 (dt, 5-F), -149.8 (t), -153.4 (t), -158.1 (t) (all unassigned), -159.7 (broad s, 3-F); $J_{4\text{-}F,5\text{-}F}$ 45.5Hz; δ_H ($CDCl_3$) 7.45 [m, HC_{arom}], 7.32 [m, HC_{arom}]. The slower moving component was 2,3,5,6,7,8-hexafluoro-4-phenoxy-quinoline [80] m.p. 109.5-110.0°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 54.72; H, 1.34; N, 4.03%; M^+, 329 $C_{15}H_5F_6NO$ requires C, 54.73; H, 1.53; N, 4.25%; M, 329); δ_F ($CDCl_3$) -74.5 (d, 2-F), -145.5 (t, 5-F), -148.9 (t), -151.8 (overlaping multiplets [2 signals]) (one 3-F and one unassigned), -155.4 (td , unassigned); δ_H ($CDCl_3$) 7.38 [m, HC_{arom}], 7.20 [m, HC_{arom}], 7.00 [m, HC_{arom}].

iii. With sodium 4-nitrophenoxide.

Sodium 4-nitrophenoxide in ethanol was prepared by reacting sodium metal (0.195g, 8.4mmol) with anhydrous ethanol (10ml) and adding excess 4-nitrophenol (5.63g, 40mmol). The volume was then made up to 25ml with further anhydrous ethanol. A portion of the sodium 4-nitrophenoxide solution (6.0ml, 2mmol) was added to a solution of the quinoline [2] (0.691g, 2.7mmol) in anhydrous ethanol (100ml), cooled to -86°C, over a period of one minute. The mixture was then warmed to room temperature, diluted with water and the product extracted into ether. The combined ether layers were washed with a small portion of water, dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (2.18g) was shown by ^{19}F nmr spectroscopy to contain residual starting material (61%) and the products (39%) : two 4-nitrophenoxy isomers (9.5 parts), the 2-(4-nitrophenoxy)quinoline [81] and 4-(4-nitrophenoxy)quinoline [82], in the ratio 16 : 84 respectively and two ethoxy isomers (0.5 parts), the 2-ethoxyquinoline [77] and 4-ethoxyquinoline [78], in the ratio 80 : 20 respectively. The excess 4-nitrophenol was removed from the product by column chromatography on silica using CCl_4 as elutant, and rechromatography using light petroleum (b.p. 60-80°C) as elutant removed [2], [77] and [78]. The two remaining compounds were washed off the column with chloroform and distilled (120°C/0.1mmHg) to give an inseparable mixture of 3,4,5,6,7,8-hexafluoro-2-(4-nitrophenoxy)quinoline [81] and 2,3,5,6,7,8-hexafluoro-4-(4-nitrophenoxy)quinoline [82] [ratios 17 : 83 respectively by ^{19}F nmr]. (Found: C, 48.04; H, 0.88; N, 7.12%; M^+, 374 $C_{15}H_4F_6N_2O_3$ requires C, 48.15; H, 1.08; N, 7.49%; M, 374). Nmr data for 3,4,5,6,7,8-hexafluoro-2-(4-nitrophenoxy)quinoline [81]; δ_F ($CDCl_3$) -128.5 (dd, 4-F), -146.8 (dt, 5-F), -149.4 (t), -152.1 (t), -156.5 (t) (all unassigned), -159.3 (bs , 3-F); $J_{4\text{-}F,5\text{-}F}$ 45.5Hz; δ_H ($CDCl_3$) 8.36 [d, HC_{arom}], 7.56 [d, HC_{arom}]. Nmr data for 2,3,5,6,7,8-hexafluoro-4-(4-nitrophenoxy)quinoline [82]; δ_F ($CDCl_3$) -73.1 (d, 2-F), -146.3 (broad t, 5-F), -147.4 (broad t, unassigned), -150.3 (t, 2 signals; one 3-F and one unassigned), -153.6 (t, unassigned); $J_{2\text{-}F,3\text{-}F}$ 25Hz; δ_H ($CDCl_3$) 8.29 [d, HC_{arom}], 7.09 [d, HC_{arom}]

6.4 EXPERIMENTAL FOR CHAPTER FOUR.

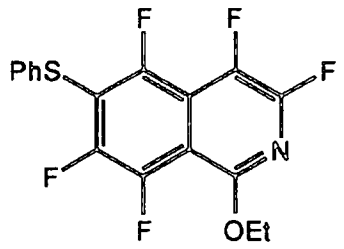
6.4.1 COMPETITION EXPERIMENTS OF HEPTAFLUORO-ISOQUINOLINE [1] WITH NUCLEOPHILES.

i. Phenylthiolate versus Ethoxide attacking the Isoquinoline [1]

The solution made by reacting sodium (0.152g, 6.62mmol) with anhydrous ethanol (17ml) followed by addition of thiophenol (0.364g, 3.31mmol) (i.e. equimolar proportion of phenylthiolate and ethoxide), was added to a solution of the isoquinoline [1] (0.0343g, 0.134mmol) in anhydrous ethanol (40ml) at -85 to -90°C over 5 minutes. The mixture was allowed to warm to -60°C, quenched with trifluoroacetic acid (1ml) and then warmed to room temperature. The product was extracted into dichloromethane and the organic layer washed three times with water. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude product (0.0364g) was shown by ^{19}F nmr to contain unreacted starting material [1] (18%) and the products (82%): the 6-phenylthioisoquinoline [43], the 1-ethoxy-6-phenylthioisoquinoline [125] and the 1-ethoxy-isoquinoline [60] in the ratio 95 : 1.5 : 3.5 respectively. All the products had been characterised previously except the 1-ethoxy-6-phenylthioisoquinoline [125] which was prepared as follows:

The solution made by reacting sodium (0.0101g, 0.44mmol) with anhydrous ethanol (5ml), followed by addition of thiophenol (80µl, 0.78mmol) was added to a solution of the 1-ethoxy-isoquinoline [60] (0.105g, 0.37mmol) in anhydrous ethanol (30ml) at room temperature. The mixture was left to stir overnight, acidified (H_2SO_4, 2M) and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue which contained thiophenol was purified by column chromatography on silica with dichloromethane as elutant. The faster moving component was recrystallised to give 1-ethoxy-3,4,5,7,8-pentafluoro-6-phenylthioisoquinoline [125] m.p. 144.5-145.0°C [from light petroleum (b.p. 60-80°C)]. (Found: C, 55.08; H, 2.92; N, 3.66%; M^+, 371. $C_{17}H_{10}F_5NOS$ requires C,

54.99; H, 2.71; N, 3.77%; M, 371); δ_F ($CDCl_3$) -99.2 (d, 3-F), -112.9 (dd, 5-F), -131.4 (d, 7-F), -139.7 (t, 8-F), -164.4 (dd, 4-F); $J_{4\text{-}F,5\text{-}F}$ 57.8Hz; $J_{5\text{-}F,8\text{-}F}$ 19Hz; δ_H ($CDCl_3$) 1.47 (t, CH_3), 4.51 (q, CH_2), 7.29 (m, C_{arom}), 7.42 (m, C_{arom}).



[125]

ii. Isopropylthiolate versus Ethoxide attacking the Isoquinoline [1]

A standard solution containing an equimolar amount of ethoxide and isopropylthiolate was prepared by reacting sodium (0.224g, 9.73mmol) in anhydrous ethanol (15ml) followed by addition of isopropylthiol (0.369g, 4.84mmol) in a 25ml standard flask. The volume was made up to 25ml with further anhydrous ethanol. A portion of this solution (13ml, 0.194M in thiolate and ethoxide, 2.5mmol of each nucleophile) was added to a solution of the isoquinoline (0.0255g, 0.10mmol) in anhydrous ethanol (40ml) at -88 to -95°C over 10 minutes. The mixture was warmed to -70°C and then cooled to -90°C before being quenched with trifluoroacetic acid. The mixture was warmed to room temperature, water added and the product extracted into dichloromethane. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (0.057g) was shown by ^{19}F nmr to contain residual starting material [1] (67%) and four products (33%): the 1-isopropylthioisoquinoline [49], the 6-isopropylthioisoquinoline [50], the 1,6-di(isopropylthio)isoquinoline [51] and the 1-ethoxyisoquinoline [60] in the ratio 20 : 78 : <0.5 : 2 respectively. The isopropylthioethers had all been characterised previously.[39]

iii. Isopropylthiolate versus Phenylthiolate versus Ethoxide attacking the Isoquinoline[1].

A standard solution containing an equimolar amount of all three nucleophiles was prepared by reacting sodium (0.270g, 0.012mol) with anhydrous ethanol (15ml) in

a 25ml standard flask, followed by addition of thiophenol (0.430g, 3.9mmol), isopropylthiol (0.297g, 3.9mmol) and further ethanol to make up 25ml. A portion of this solution (16ml, 0.156M in each nucleophile, 2.5mmol in each nucleophile) was added to a solution of the isoquinoline (0.0257g, 0.10mmol) in anhydrous ethanol (40ml) at -88 to -95°C over 10 minutes. The mixture was warmed to -70°C then cooled to -90°C and quenched with trifluoroacetic acid. The mixture was then warmed to room temperature, water added and the product extracted into dichloromethane. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (a liquid due to the thiols) was shown by ^{19}F nmr to contain residual starting material [1] (45%) and five products (55%): the 6-phenylthioisoquinoline [43], the 1-isopropylthioisoquinoline [49], the 6-isopropylthioisoquinoline [50], the 1,6-di(isopropylthio)isoquinoline [51] and the 1-ethoxyisoquinoline [60] in the ratio 36 : 12 : 47 : 2 : 2 respectively.

iv. 4-Methoxyphenylthiolate versus Phenylthiolate attacking the Isoquinoline[1].

A standard solution containing an equimolar amount of 4-methoxyphenylthiolate and phenylthiolate was prepared by reacting sodium (0.241g, 0.0105mol) with anhydrous ethanol (10ml) followed by addition of thiophenol (0.577g, 5.23mmol) and 4-methoxythiophenol (0.738g, 5.26mmol). The volume was then made up to 25ml with further anhydrous ethanol. A portion of this solution (12.5ml, 2.6mmol of each thiolate) was added to a solution of the isoquinoline [1] (0.027g, 0.11mmol) in anhydrous ethanol (40ml), cooled to -86 to -80°C, over a period of four minutes. The mixture was warmed to -70°C before being re-cooled to -90°C, quenched with trifluoroacetic acid (1ml) and warmed to room temperature. The mixture was diluted with water and the product extracted into ether. The combined ether extracts were washed with a small portion of water, dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (containing excess thiols) was shown by ^{19}F nmr to contain residual starting material (8%) and the products (92%): the 6-(4-methoxyphenyl)isoquinoline [56] and the 6-phenylthioisoquinoline [43] in the ratio 91 : 9 respectively. A reverse addition experiment, [i.e. adding cooled ethanolic isoquinoline [1] solution (-90°C) to a

equimolar mixture of the cooled nucleophiles in ethanol (-90°C)], followed by quenching with cooled trifluoroacetic acid in ethanol (-90°C) gave precisely the same result as when adding the nucleophiles to the substrate.

v) 4-Methoxyphenylthiolate versus 4-N,N-Dimethylaminophenylthiolate attacking the Isoquinoline[1].

A standard solution containing an equimolar amount of 4-methoxyphenylthiolate and 4-N,N-dimethylaminophenylthiolate[64] was prepared by reacting sodium (0.223g, 9.7mmol) with anhydrous ethanol (10ml) followed by addition of 4-methoxythiophenol (0.682g, 4.86mmol) and 4-N,N-dimethylaminothiophenol (0.751g, 4.90mmol). The volume was then made up to 25ml with further anhydrous ethanol. A portion of this solution (10ml, 1.9mmol of each thiolate) was added to a solution of the isoquinoline [1] (0.020g, 0.078mmol) in anhydrous ethanol (40ml), cooled to -87 to -90°C, over a period of two minutes. The mixture was then quenched with pre-cooled (-90°C) trifluoroacetic acid (1ml) in ethanol (5ml) and then warmed to room temperature. The mixture was diluted with water and then neutralised (H_2SO_4, 2M) to pH 6.0 before the product was extracted into ether. The combined ether extracts were washed with a small amount of water, dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (containing excess thiols) was shown by ^{19}F nmr to contain two products only: the 6-(4-N,N-dimethylaminophenylthio)isoquinoline [53] and the 6-(4-methoxyphenyl)isoquinoline [56] in the ratio 78 : 22 respectively. A reverse addition experiment, [i.e. adding cooled ethanolic isoquinoline [1] (-90°C) to a equimolar mixture of the cooled nucleophiles in ethanol (-90°C)], followed by quenching with cooled trifluoroacetic acid in ethanol (-90°C) gave precisely the same result as when adding the nucleophiles to the substrate.

vi. 4-Nitrophenylthiolate versus Ethoxide attacking the Isoquinoline[1].

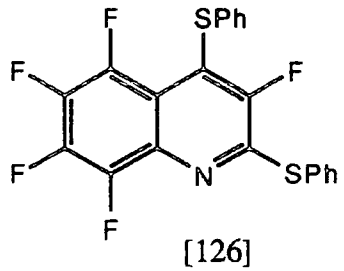
A standard solution containing an equimolar amount of 4-nitrophenylthiolate and ethoxide was prepared by reacting sodium (0.223g, 9.7mmol) with anhydrous ethanol (10ml) followed by addition of 4-nitrothiophenol (0.823g, 4.8mmol, 91% pure). The volume was then made up to 25ml with further anhydrous ethanol. A portion of this

solution (12.5ml, 2.4mmol of each nucleophile) was added to a solution of the isoquinoline [1] (0.025g, 0.098mmol) in anhydrous ethanol (40ml), cooled to -75 to -85°C, over a period of five minutes. The mixture was then warmed to -35°C over a period of five minutes and re-cooled to -80°C before being quenched with trifluoroacetic acid (1ml). The mixture was then warmed to room temperature, diluted with water and the product extracted into ether. The combined ether extracts were washed with a small portion of water, dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (containing excess thiol) was shown to contain starting material (1%) and the products (99%): the 1-ethoxyisoquinoline [60], the 6-ethoxyisoquinoline [61] and the 6-(4-nitrophenylthio)-isoquinoline [58] in the ratio 95 : 4 : 1 respectively.

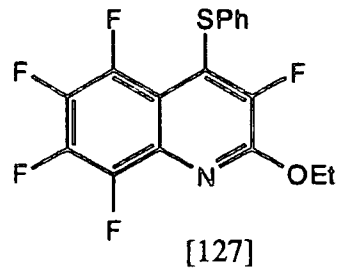
6.4.2 COMPETITION EXPERIMENTS OF HEPTAFLUORO-QUINOLINE [2] WITH NUCLEOPHILES.

i. Phenylthiolate versus Ethoxide attacking the Quinoline [2].

The solution made by dissolving sodium (0.131g, 5.7mmol) in anhydrous ethanol (14ml) followed by addition of thiophenol (0.315g, 2.9mmol) was added to a solution of the quinoline [2] (0.028g, 0.11mmol) in anhydrous ethanol (40ml) at -95 to -85°C over 5 minutes. The mixture was then quenched at -85°C with trifluoroacetic acid (1ml) and the mixture warmed to room temperature. The mixture was diluted with water, the product extracted into dichloromethane and the organic layer washed three times with water. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude product (0.0361g) was shown by ^{19}F nmr to contain three products: the 4-phenylthioquinoline [75], the 2,4-di(phenylthio)quinoline [126] and the 2-ethoxy-4-phenylthioquinoline [127] in the ratio 92 : 4.5 : 3.5 respectively. Closer examination by overnight ^{19}F nmr (~30,000 scans) showed the 2-ethoxy-quinoline [77] to be present in 1 part per 300 parts 4-phenylthioquinoline [75]. The di-substituted quinolines [126] and [127] were prepared and characterised as follows:



[126]



[127]

a) The solution made by reacting sodium (0.0072g, 0.31mmol) with anhydrous ethanol (10ml), followed by a slight excess of the thiophenol (40µl, 0.39mmol), was added to a solution of the 4-phenylthioquinoline [75] (0.084g, 0.24mmol) in anhydrous ethanol (30ml) at -85 to -90°C over a period of 3 minutes. The mixture was warmed to room temperature and the crude mixture diluted with water, acidified (H_2SO_4, 2M) and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude product was sublimed (100°C, 0.2mmHg) to give as sublimate (0.045g) 3,5,6,7,8-pentafluoro-2,4-di(phenylthio)quinoline [126] m.p. 113.0-113.5°C [from light petroleum (b.p. 60-80°C)] (Found: C, 58.26; H, 2.35; N, 3.09%; M^+, 435. $C_{21}H_{10}F_5NS_2$ requires C, 57.93; H, 2.31; N, 3.22%; M, 435); δ_F ($CDCl_3$) -111.5 (s, 3-F), -142.0 (m, 5-F), -149.9, -155.4, -156.9 (all t, unassigned); δ_H ($CDCl_3$) 7.31 (m, HC_{arom}), 7.46 (m, HC_{arom}), 7.48 (m, HC_{arom}).

b) The solution made by reacting sodium (0.0108g, 0.47mmol) with anhydrous ethanol (5ml) followed by a slight excess of thiophenol (60µl, 0.58mmol) was added to a solution of the quinoline [2] (0.141g, 0.55mmol) in anhydrous ethanol (50ml) at -85 to -90°C over a period of 2 minutes. The mixture was warmed to room temperature and then diluted with water, acidified (H_2SO_4, 2M) and the product extracted into ether. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (0.200g) was heated at 50°C under vacuo to remove excess starting material by sublimation. The residue in anhydrous ethanol (50ml), cooled to -88 to -92°C was treated over one minute with the solution made by reacting sodium (0.018g, 0.76mmol) with anhydrous ethanol (5ml). The mixture was warmed to room temperature and then worked up as before. The crude residue (0.193g) was sublimed at 100°C under vacuo (0.01mmHg) to give as sublimate 2-ethoxy-3,5,6,7,8-pentafluoro-4-phenylthioquinoline [127] m.p. 95.5-96.0°C [from light petroleum (b.p. 60-80°C)] (Found: C, 54.72; H,

2.56; N, 3.72%; M^+, 371. $C_{17}H_{10}F_5NOS$ requires C, 54.99; H, 2.71; N, 3.77%; M, 371); δ_F ($CDCl_3$) -124.2 (s, 3-F), -142.7 (m, 5-F), -151.3, -155.9, -159.9 (all t, unassigned); δ_H ($CDCl_3$) 1.49 (t, CH_3), 4.61 (q, CH_2), 7.31 (m, HC_{arom}), 7.33 (m, HC_{arom}).

6.4.3 COMPETITION EXPERIMENTS OF HEPTAFLUORO-QUINOLINE [2] and -ISOQUINOLINE [1]: Relative Reactivity of the Heterocycles.

i. The Isoquinoline [1] versus The Quinoline [2] attacked by Ethoxide

To a solution of the quinoline [2] (0.049g, 0.19mmol) and isoquinoline [1] (0.050g, 0.20mmol) in anhydrous ethanol (30ml) was added sodium ethoxide in ethanol (0.55ml, 0.0141M, 7.8mmol) at -82 to -85°C over 2 minutes. The mixture was warmed to room temperature, acidified (H_2SO_4, 2M) and the product extracted into ether. The ether extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (0.062g) was shown by ^{19}F nmr to contain residual isoquinoline [1] (48.25%), residual quinoline [2] (49.50%) and three products (2.25%): the 1-ethoxyisoquinoline [60], the 2-ethoxyquinoline [77] and the 4-ethoxyquinoline [78] in the ratio 12 : 68 : 20 respectively.

ii. The Isoquinoline [1] versus The Quinoline [2] with phenylthiolate

A standard solution of sodium phenylthiolate in ethanol was prepared by reacting sodium (0.227g, 9.87mmol) with anhydrous ethanol (15ml) and thiophenol (1.5ml, 0.015mol). The volume was then made up to 25ml with further anhydrous ethanol. To the isoquinoline [1] (0.050g, 0.19mmol) and quinoline [2] (0.050g, 0.19mmol) in anhydrous ethanol (6ml) was added at -85°C small portions of the standard solution (40µl, 16µmol for the first run and then 80µl, 32µmol for the subsequent runs). After each addition the mixture was warmed to room temperature and the mixture examined by ^{19}F nmr. The mixture was then recooled to -85°C and the process repeated until all of one substrate (the quinoline [2]) had been used up. ^{19}F nmr of the first run showed only 4-phenylthioquinoline [75] and starting materials [1] and [2]

to be detectable. ^{19}F nmr of runs 2 to 4 show the relative proportions of 4-phenylthioquinoline [75] to 6-phenylthioisoquinoline [43] to be 27 : 1 respectively.

6.5 EXPERIMENTAL FOR CHAPTER FIVE.

6.5.1 Reaction of Propynoyl Chloride with the Potassium Salt of 1,3,4,5,6,7,8-Heptafluoro-2-naphthol [109].

Propiolic acid (4.1g, 0.059 moles) was added dropwise to phosphorus pentachloride (20.6g, 0.099moles), cooled externally by an ice bath, over two minutes. The product was then immedietely distilled at room temperature (0.05mmHg) into a trap cooled by liquid air. The distillate was worked up rapidly by dissolving it in pre-cooled petroleum ether (b.p. 40-60°C) (-30°C), and shaking it with iced water (15ml) to hydrolyse and remove $POCl_3$. The washing process was repeated twice, with the petroleum ether layer being re-cooled to -30°C between each washing. The organic layer was added to a solution of 1,3,4,5,6,7,8-heptafluoro-2-naphthol[23] [109] (5.27g, 0.020moles) and excess potassium carbonate (12.1g, 0.088moles) in water (50ml), cooled externally by an ice bath. The two phase solution temperature was maintained at 2°Cfor 30 minutes and then the organic layer was separated, dried ($MgSO_4$), filtered and the solvent evaporated to give the crude ester (4.53g, 72% based on the 2-naphthol) which was virtually pure by ^{19}F nmr spectroscopy (>95%). Recrystallisation gave heptafluoro-2-naphthyl propynoate [106] [from light petroleum (b.p. 60-80°C)] m.p 93.5-94.0°C (Found C, 48.75; H, 0.26%; M^+ 322. $C_{13}HF_7O_2$ requires C, 48.47; H, 0.31%; M, 322. $\delta_F(CDCl_3)$ -134.0 (dd, 1-F), -144.8 (dt, 8-F), -145.7, -146.6 (both dt, 4-F/5-F unnasigned), -147.2 (bs, 3-F), -153.1 (t, 6-F), -154.6 (bs, 7-F); $J_{1\text{-}F,8\text{-}F}$ 62.4Hz; $J_{4\text{-}F,5\text{-}F}$ 58.6Hz; δ_H ($CDCl_3$) 3.30 (s, alkynic CH). Unreacted heptafluoro-2-naphthol [109] was recovered by acidification of the aqueous phase (H_2SO_4, 2M) and subsequent extraction with ether. The ether extracts were dried ($MgSO_4$), filtered and the solvent evaporated to give recovered heptafluoro-2-naphthol [109] (0.54g).

6.5.2 Flash Vacuum Pyrolysis of 1,3,4,5,6,7,8-Heptafluoro-2-Naphthyl Propynoate [106].

Flash Vacuum Pyrolysis (FVP) of heptafluoro-2-napthenyl propynoate [106] (4.13g) in separate experiments (approx 500mg each) at 550°C/0.05mmHg through a silica tube (50cm x 2cm) packed with silica tubing (5mm x 5mm), yielded a black oily product (3.48g total), which by ^{19}F nmr contained only two products present in significant proportion (8-9% total); compounds [110] and [111] present in a 3 : 1 ratio respectively . The two products were separated from the tar by column chromatography on silica (7" x 2.5") with a mixture of CCl_4 and $CHCl_3$ as elutant (3 : 1 v/v). Twelve fractions were collected each of 2cm, except the first which was 10cm. Fraction four (0.93g) contained essentially the two compounds [110] and [111], which by ^{19}F nmr contained seven fluorines each, none of the other fractions contained any identifiable material. Fraction four was further separated by chromatography on silica (6.5" x 1.5") with light petroleum (b.p. 40-60°C) and diethyl ether (80 : 20 v/v) as elutant. Twelve fractions were collected each of $2cm^3$, except the first which was $10cm^3$. Fraction five (0.18g) was enriched [111] and fractions six to nine (0.29g) were mainly [110]. In a similar previous chromatography experiment, crystals of mainly [111] (also containing ca. 10% [110]) were obtained upon partial evaporation of the solvent from the faster moving component. These crystals were identified by x-ray crystallographic analysis[65] (see Appendix 3) and then compound [111] isolated pure by a combination of preparative TLC with light petroleum (b.p. 40-60°C) and diethyl ether (80 : 20 v/v) as elutant, followed by recrystallisation to analytical purity to give 1,2-dihydro-2,2,4,5,6,7,8-heptafluoro-cyclobuta[a]naphthalene-1-one [111] (1% based upon [106]), [from light petroleum (b.p 60-80°C) and diethyl ether {80 : 20 v/v}] m.p. 102.0-102.5°C (Found C, 49.24; H, 0.37%; M^+, 294. $C_{12}HF_7O$ requires C, 49.00; H, 0.34%; M, 294) δ_F ($CDCl_3$) -94.2 (dd, 4-F); -99.2 (s, CF_2) [Int 2]; -139.8 (dt, 5-F); -135.0; -146.5; -148.4 (all t, all unnasigned); $J_{4\text{-}F,5\text{-}F}$ 71Hz. δ_H ($CDCl_3$) 7.60 (d, $J_{H\text{-}4F}$, 8.5Hz). $\nu_{C=O}$ 1800cm^{-1}. Sublimation (60°C, 0.05mmHg) of fractions six to nine (0.29g), followed by recrystallisation of the sublimate, gave [identified by x-ray

crystallography[65] (see Appendix 3)] 1,2-dihydro-1,1,4,5,6,7,8-heptafluoro-cyclobuta[a]naphthalene-2-one [110] (0.187g, 5% based on [106]), [from light petroleum (b.p 60-80°C) and diethyl ether {80 : 20 v/v}] .m.p. 99.5-100.0°C (Found C, 49.07; H, 0.35%; M^+, 294. $C_{12}HF_7O$ requires C, 49.00; H, 0.34%; M, 294) δ_F ($CDCl_3$) -97.0 (s, CF_2) [Int 2]; -101.3 (d, 4-F); -138.9 (dt, 5-F); -138.5; -146.5; -148.2 (all t, all unnasigned); $J_{4\text{-}F,5\text{-}F}$ 69Hz. δ_H ($CDCl_3$) 7.39 (d, $J_{H\text{-}4F}$, 9Hz). $\nu_{C=O}$ 1800 cm^{-1}, a second smaller absorption is seen at 1830cm^{-1}, (see Appendix 4, spectra no. 36).

6.5.3 Further Pyrolysis of 1,2-dihydro-1,1,4,5,6,7,8-Heptafluoro-cyclobuta[a]naphthalene-2-one [110].

FVP of [110] (26mg) at 550°C (0.01mmHg), through the same pyrolysis tube described above, gave recovered starting material [110] (58%), accompanied by the isomer [111] (15%) and a new compound [112] (27%). The new compound was later identified in a separate experiment described below as 1,1,4,5,6,7,8-heptafluoro-1H-cyclopropa[a]naphthalene [112]. Further quantities of [112] for isolation and characterisation were prepared by FVP of a 3 : 1 mixture of [110] and [111], which had been prepared as described previously, but without the second (petrol / ether) chromatographic experiment. FVP of [111] and [110] (72mg) as before (550°C/0.05mmHg) gave solid product deposited in two separate places: most of the product (52mg), predominantly [111] [33%] and [110] [64%], but also some [112] [4%] was deposited in the pyrolysis tube near to the tube's exit from the oven, the remainder (16mg), predominantely [112] [82%], but also some [111] [4%] and [110] [14%], was caught in a liquid nitrogen cooled trap between the exit of the pyrolysis tube and the vacuum line. Compound [112] caught in the nitrogen cooled trap was separated from [111] and [110] by sublimation (0°C,0.05mmHg). The sublimate was identified by x-ray crystallography[66] (see Appendix 3) as 1,1,4,5,6,7,8-heptafluoro-1H-cyclopropa[a]naphthalene [112] [9.5 mg, 15% based on [111] and [110]] m.p. 53.5-54.0°C (Found M^+, 266. $C_{11}HF_7$ requires M, 266). δ_F ($CDCl_3$) -79.0 (s, 1-F) [Int 2]; -103.0 (d,3-F); -138.8 (dt, 4-F); -140.1 (t, 7-F); -148.9 and -150.9 (both t, unassigned

5-F,6-F); $J_{3\text{-}F,4\text{-}F}$ 73Hz. δ_H ($CDCl_3$) 7.36 (overlapping dt); $J_{2\text{-}H,1\text{-}F}$ 3.6Hz; $J_{2\text{-}H,\ 3\text{-}F}$ 7Hz.

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Appendices

APPENDIX 1.

First Year Induction Course: October 1990.

The following one hour lectures given by the department were attended.

1. Safety.
2. Electrical appliances and infrared spectroscopy.
3. Chromatography.
4. High Pressure Techniques.
5. Atomic Absorbance and Microanalysis.
6. Mass spectroscopy.
7. Nuclear magnetic resonance
8. Information Retrieval.
9. Glass blowing.
10. Computing.

Colloquia, Lectures and Seminars from Invited Speakers.

* = attended by the author.

During the period: 1990 to 1991.

1990.

October 11 Dr. W.A. Macdonald*, ICI, Wilton.
Materials for the Space Age.

October 24 Dr. M. Bochman, University of East Anglia.
Synthesis, Reactions and Catalytic Activity of Cationic Titanium Alkyls.

October 26 Prof. R. Soulen*, South Western University, Texas.
Preparation and Reactions of Bicycloalkenes.

October 31 Dr. R. Jackson*, Newcastle University.
New Synthetic Methods: α-Amino Acids and Small Rings.

November 1 Dr. N. Logan*, Nottingham University.

Rocket Propellants.

November 6 Dr. P. Kocovsky, Uppsala University.

Stereo-Controlled Reactions Mediated by Transition and Non-Transition Metals.

November 7 Dr. D. Gerrard, British Petroleum.

Raman Spectroscopy for Industrial Analysis.

November 8 Dr. S.K. Scott*, Leeds University.

Clocks, Oscillators and Chaos.

November 14 Prof. T. Bell*, SUNY, Stoney Brook, USA.

Functional Molecular Architecture and Molecular Recognition.

November 21 Prof. J. Pritchard, Queen Mary and Westfield College, London University.

Copper Surfaces and Catalysts.

November 28 Dr. B.J. Whitaker, Leeds University.

Two-Dimensional Velocity Imaging of State-Selected Reaction Products.

November 29 Prof. D. Crout, Warwick University.

Enzymes in Organic Synthesis.

December 5 Dr. P.G. Pringle*, Bristol University.

Metal complexes with Functionalised Phosphines.

December 13 Prof. A.H. Cowley, University of Texas.

New Organometallic Routes to Electronic Materials.

1991.

January 15 Dr. B.J. Alder, Lawrence Livermore Labs., California.
Hydrogen in all its Glory.

January 17 Dr. P. Sarre, Nottingham University.
Comet Chemistry.

January 24 Dr. P.J. Saddler, Birkbeck College, London.
Design of Inorganic Drugs: Precious Metals, Hypertension + HIV.

January 30 Prof. E. Sinn*, Hull University.
Coupling of Little Electrons in Big Molecules. Implications for the Active Sites of (Metalloproteins and other) Macromolecules.

January 31 Dr. D. Lacey*, Hull University.
Liquid Crystals.

Febrary 6 Dr. R. Bushby*, Leeds University.
Biradicals and Organic Magnets.

February 14 Dr. M.C. Petty*, Durham University.
Molecular Electronics.

February 20 Prof. B.L. Shaw, Leeds University.
Synthesis with Coordinated, Unsaturated Phosphine Ligands.

February 28 Dr. J. Brown*, Oxford University.
Can Chemistry Provide Catalysts Superior to Enzymes?

March 6 Dr. C. M. Dobson, Oxford University.
NMR Studies of Dynamics in Molecular Crystals.

March 7 Dr. A. Markam*, ICI Pharmaceuticals.
DNA Fingerprinting.

April 24. Prof. R.R. Schrock, Massachusetts Institute of Technology.
Metal-ligand Multiple Bonds and Metathesis Initiators.

April 25 Prof. T. Hudlicky*, Virginia Polytechnic Institute.
Biocatalysis and Symmetry Based Approaches to the Efficient Synthesis of Complex Natural Products.

June 20 Prof. M.S. Brookhart, University of N. Carolina.
Olefin Polymerisations, Oligomerizations and Dimerisations using Electrophilic Late Transition Metal Catalysts.

July 29 Dr. M.A. Brimble, Massey University, New Zealand.
Synthetic Studies Towards the Antibiotic Griseusin-A.

During the period: 1990 to 1991.

1991.

October 17 Dr. J.A. Salthouse*, University of Manchester.
Son et Luminiere - a demonstration lecture.

October 31 Dr. R. Keeley*, Metropolitan Police Forensic Science.
Modern forensic science.

November 6 Prof. B.F.G. Johnson, Edinburgh University.
Cluster-surface analogies.

November 7 Dr. A.R. Butler*, St Andrews University.
Traditional Chinese herbal drugs: a different way of treating disease.

November 13 Prof. D. Gani*, St Andrews University.
The Chemistry of PLP-dependent enzymes.

November 20 Dr. R. More O'Farrall*, University College, Dublin.
Some acid-catalysed rearrangements in organic chemistry.

November 28 Prof. I.M. Ward, IRC in Polymer Science, University of Leeds.

The SCI Lecture: the science and 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.D. Cooper, Shell Research.

Colloid Science: theory and practice.

1992.

January 22 Dr. K.D.M. Harris, St. Andrews University.

Understanding the properties of solid inclusion compounds.

January 29 Dr. A. Holmes*, Cambridge University.

Cycloaddition reactions in the service of the synthesis of piperidine and indolizidine 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 Prof. D.E. Fenton, Sheffield University.

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*, Manchester University.

Applications of organostannanes to organic synthesis.

February 20 Prof. E. Vogel, University of Cologne.

The Musgrave Lecture Porphyrins: Molecules of Interdisciplinary Interest.

February 25 Prof. J.F. Nixon, University of Sussex.

The Tilden Lecture Phosphaalkynes: new building blocks in inorganic and organometallic chemistry.

February 26 Prof. M.L. Hichman, Strathclyde University.

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.

Recent advances in organoiron chemistry.

March 12 Dr. R.A. Hann*, ICI Imagedata.

Electronic Photography - An Image of the Future.

March 18 Dr. H. Maskill, Newcastle University.

Concerted or stepwise fragmentation in a deamination-type reaction.

April 7 Prof. D.M. Knight, Philosophy Department, University of Durham.

Interpreting experiments: the beginning of electrochemistry.

May 13 Dr. J-C Gehret, Ciba Geigy, Basel.

Some aspects of industrial agrochemical research.

During the period: 1992 to 1993.

1992.

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. Ørsted Institute, University of Copenhagen

Low-Frequency IR - and Raman Studies of Hydrogen Bonded Liquids

APPENDIX 2.

Proof of ratio of products equals ratio of relative rates for parallel pseudo first order mechanism[67].

$$A + N \xrightarrow{k_1} P_1$$

$$B + N \xrightarrow{k_2} P_2$$

If $[A_o]$ and $[B_o] >> [N]$ then:-

$$\frac{d[P_1]}{dt} = k_1[N][A_o]; \qquad [P_1] = k_1[A_o] \int [N]dt$$

$$\frac{d[P_2]}{dt} = k_1[N][B_o]; \qquad [P_2] = k_2[B_o] \int [N]dt$$

$$\therefore \quad \frac{[P_1]}{[P_2]} = \frac{k_1[A_o]}{k_2[B_o]}$$

and if $[A_o] = [B_o]$ then:- $\frac{[P_1]}{[P_2]} = \frac{k_1}{k_2}$

APPENDIX 3.

X-Ray crystallographic study of [111], [110] and [112].[68]

X-ray single crystal diffraction measurements were performed using Rigaku AFFC6S four-circle diffractometer (graphite monochromated Mo-K_α radiation, $2\theta/\omega$ scan mode). For [110], [111] and [112] the cell dimensions were measured at room and low temperature, and the intensity data were collected at low temperature, using and Oxford Cryosystems liquid nitrogen cooled system. For [110], a room temperature data set has also been collected, but the crystal was slowly decomposing during the exposure (as indicated by an decrease of intensities of three check reflections in 15 hours), thus affecting the quality of the data. No absorption correction was applied in each case except for [112] where it made no difference.

All three structures were solved by direct methods and refined by full matrix least squares (non-hydrogen atoms with anisotropic thermal parameters, H atoms refined with isotropic ones using SHELXTLPLUS or SHELX93 programs. For [111], difference fourier map revealed significant residual peaks of electron density on bond distances from C(11) and C(12). Therefore we supposed the crystal to be solid solution of [111] with a small amount of [110], with the positions of all but O and two F atoms coinciding. The extra peaks were refined as atoms O(12), F(11) and F(21) in isotropic approximation. The refinement of occupancies yielded 90.2(5)% for [111] and 9.8(5)% for [110]. This assumption was later confirmed by chromatographic isolation and X-ray characterisation of the minor component [110] from the crystals of [111].

Crystal data and other experimental details for [110] and [111] are presented in Table A3.1, atomic coordinates in Table A3.2, bond distances and (relevant) angles in Table A3.3. The same information for [112] is presented in Tables A3.4 to A3.6. The additional material, deposited at the Cambridge Crystallographic Data Centre, comprises thermal parameters, and all the results of room temperature study of [110], which exhibit no systematic differences from the low temperature results, apart from the higher thermal librations.

Table A3.1. Crystal data and experimental details for [111] and [110].

Compound	[111]		[110]	
Crystal size, mm	0.11 x 0.40 x 0.40		0.02x0.25 x0.30	0.05x0.27 x0.60
System, space group	monoclinic C2/c		monoclinic $P2_1/c$	
Temperature, K	290	125	290	155
a, Å	15.766(5)	15.578(5)	7.322(2)	7.282(2)
b, Å	13.027(3)	13.008(3)	12.377(2)	12.221(2)
c, Å	11.008(3)	10.788(3)	11.823(3)	11.709(2)
ß, °	114.66(2)	114.34(3)	106.80(2)	106.76(3)
V, $Å^3$	2054.6 (1.1)	1991.5 (1.0)	1025.7(3)	997.7(2)
$\mu(\mu_o\text{-}K_\alpha)$, cm^{-1}		2.1	2.1	2.1
D_o, gcm^{-3}		1.96	1.905	1.96
Z		8	4	4
F(000)		1152	576	576
Max 2θ, °		60	50	55
No. of Independent data		2837	1793	2337
Observed data $\|F\| > 4\sigma(F)$		2084	795	1681
No. of variables		197	121[a]	185
R		0.045	0.044	0.039
wR=R'		0.056	0.048	0.050
Goodness of fit		1.86	1.64	1.64
Max residual peak, $eÅ^{-3}$		0.41	0.27	0.38
Max hole, $eÅ^{-3}$		-0.24	-0.22	-0.24

Table A3.2. Atomic coordinates ($x10^4$) in [111] and [110]

	[111]			[110]		
	x	y	z	x	y	z
F(4)	154(1)	9521(1)	-1130(1)	4570(2)	2136(1)	1279(1)
F(5)	1485(1)	10428(1)	-1525(1)	1868(2)	2847(1)	-493(1)
F(6)	3319(1)	10594(1)	-915(1)	-1830(2)	2815(1)	-1727(1)
F(7)	4595(1)	9352(1)	928(1)	-4384(2)	1579(1)	-1067(1)
F(8)	4024(1)	7918(1)	2293(1)	-3198(2)	267(1)	915(1)
F(11)	2897(18)	7224(18)	4247(21)	-687(2)	-1502(1)	2647(1)
F(21)	2780(16)	6024(15)	2957(21)	-1099(2)	-139(1)	3720(1)
F(12)	1040(1)	7111(1)	3593(1)			
F(22)	897(1)	5919(1)	2113(1)			
O(11)	3061(1)	6525(1)	3681(2)			
O(12)	885(35)	6323(23)	3085(37)	3232(3)	-1034(2)	4695(2)
C(1)	2094(1)	7738(1)	1798(2)	701(3)	243(2)	2296(2)
C(2)	1144(1)	7659(2)	1497(2)	2613(3)	232(2)	2927(2)
C(3)	442(2)	8239(2)	486(2)	4010(3)	855(2)	2617(2)
C(4)	777(1)	8927(2)	-166(2)	3334(3)	1495(2)	1625(2)
C(5)	2080(2)	9793(2)	-581(2)	689(3)	2197(2)	-110(2)
C(6)	3018(2)	9886(2)	-283(2)	-1215(3)	2196(2)	-747(2)
C(7)	3688(1)	9253(2)	690(2)	-2552(3)	1547(2)	-411(2)
C(8)	3398(1)	8540(1)	1365(2)	-1951(3)	905(2)	581(2)
C(9)	2443(1)	8435(1)	1108(2)	-22(3)	883(2)	1262(2)
C(10)	1753(1)	9068(1)	95(2)	1363(3)	1535(2)	911(2)
C(11)	2364(1)	6947(2)	2892(2)	94(3)	-534(2)	3121(2)
C(12)	1283(1)	6855(2)	2565(2)	2304(4)	-561(2)	3832(2)
H(3)	-277(19)	8178(18)	199(25)	5235(40)	828(22)	3115(23)

Table A3.3. Bond lengths (Å) and angles (°) for [111] and [110].

	[111]	[110]		[111]	[110]
F(4)-C(4)	1.338(2)	1.342(3)	F(5)-C(5)	1.341(2)	1.338(3)
F(6)-C(6)	1.340(3)	1.340(3)	F(7)-C(7)	1.334(3)	1.334(2)
F(8)-C(8)	1.342(2)	1.338(3)	C(1)-C(2)	1.381(3)	1.376(3)
C(1)-C(9)	1.416(3)	1.410(3)	C(1)-C(11)	1.491(3)	1.508(4)
C(2)-C(3)	1.405(3)	1.400(4)	C(2)-C(12)	1.505(3)	1.499(3)
C(3)-C(4)	1.367(3)	1.368(3)	C(3)-H(3)	1.03(3)	0.92(3)
C(4)-C(10)	1.440(3)	1.439(3)	C(5)-C(6)	1.366(3)	1.372(3)
C(5)-C(10)	1.410(3)	1.409(3)	C(6)-C(7)	1.403(3)	1.397(4)
C(7)-C(8)	1.366(3)	1.366(3)	C(8)-C(9)	1.403(3)	1.401(3)
C(9)-C(10)	1.436(2)	1.435(3)	O(11)-C(11)	1.201(2)	
C(11)-C(12)	1.576(3)	1.584(3)	C(11)-F(11)	1.40(2)	1.359(3)
C(11)-F(21)	1.35(2)	1.354(3)	C(12)-O(12)	1.21(5)	1.192(3)
C(12)-F(12)	1.353(3)		C(12)-F(22)	1.357(2)	
C(2)-C(1)-C(9)	122.1(2)	122.4(2)	C(2)-C(1)-C(11)	93.4(2)	95.0(2)
C(9)-C(1)-C(11)	144.5(2)	142.5(2)	C(1)-C(2)-C(3)	124.0(2)	123.6(2)
C(1)-C(2)-C(12)	94.0(1)	92.9(2)	C(3)-C(2)-C(12)	142.0(2)	143.5(2)
C(2)-C(3)-C(4)	114.2(2)	114.9(2)	C(2)-C(3)-H(3)	126(1)	118(2)
C(4)-C(3)-H(3)	120(1)	127(2)	F(4)-C(4)-C(3)	118.0(2)	118.8(2)
F(4)-C(4)-C(10)	116.6(2)	116.6(2)	C(3)-C(4)-C(10)	125.4(2)	124.6(2)
F(5)-C(5)-C(6)	117.5(2)	117.7(2)	F(5)-C(5)-C(10)	121.4(2)	121.7(2)
C(6)-C(5)-C(10)	121.1(2)	120.7(2)	F(6)-C(6)-C(5)	120.4(2)	120.0(2)
F(6)-C(6)-C(7)	118.4(2)	118.3(2)	C(5)-C(6)-C(7)	121.2(2)	121.7(2)
F(7)-C(7)-C(6)	119.4(2)	119.0(2)	F(7)-C(7)-C(8)	121.3(2)	121.9(2)
C(6)-C(7)-C(8)	119.3(2)	119.2(2)	F(8)-C(8)-C(7)	120.5(2)	120.4(2)
F(8)-C(8)-C(9)	118.3(2)	118.4(2)	C(7)-C(8)-C(9)	121.1(2)	121.2(2)
C(1)-C(9)-C(8)	124.4(2)	124.3(2)	C(1)-C(9)-C(10)	115.9(2)	115.8(2)
C(8)-C(9)-C(10)	119.7(2)	119.9(2)	C(4)-C(10)-C(5)	124.2(2)	123.9(2)
C(4)-C(10)-C(9)	118.4(2)	118.7(2)	C(5)-C(10)-C(9)	117.4(2)	117.4(2)
O(11)-C(11)-C(1)	139.0(2)		C(1)-C(11)-F(11)	120(1)	116.9(2)
C(1)-C(11)-F(21)	129(1)	117.2(2)	F(11)-C(11)-F(21)	96(1)	105.4(2)
O(11)-C(11)-C(12)	134.0(2)		C(1)-C(11)-C(12)	87.0(1)	84.8(2)
F(11)-C(11)-C(12)	112(1)	116.0(2)	F(21)-C(11)-C(12)	113(1)	116.2(2)
F(12)-C(12)-F(22)	106.4(2)		F(12)-C(12)-C(2)	117.2(2)	
F(22)-C(12)-C(2)	116.5(2)		F(12)-C(12)-C(11)	115.6(1)	
F(22)-(C12)-C(11)	115.0(2)		C(2)-C(12)-C(11)	85.5(2)	87.3(2)
C(2)-C(12)-O(12)	144(2)	138.5(2)	C(11)-C(12)-O(12)	130(2)	134.2(2)

Table A3.4. Crystal data and structure refinement for [112]

Compound	[112]
Crystal size, mm	0.5 x 0.5 x 0.2
System, space group	monoclinic P2(1)/n
Temperature, K	293(2)
a, Å	8.702(2)
b, Å	11.364(2)
c, Å	9.372(2)
α, °	90
ß, °	100.62(3)
γ, °	90
V, Å^3	910.9(3)
wavelength Å	0.71073
D_o, gcm^{-3}	1.940
Z	4
Absorption co-efficient, mm^{-1}	0.214
F(000)	520
θ range, °	2.85 to 25.00
Index ranges	0<=h<=10
	0<=k<=13
	-11<=l<=10
Reflections Collected	1719
No. of Independent data	1610 [R(int) = 0.0150]
No. of variables	167
Final R Indices [I>2σ(I)	R1 = 0.0312,
	wR2 = 0.0838
R indices (all data)	R1 = 0.0547,
	wR2 = 0.0936
Goodness of fit on F^2	1.075
Max diff peak, eÅ^{-3}	0.212
Max hole, eÅ^{-3}	-0.229

Table A3.5. Atomic Co-ordinates ($x10^4$) and equivalent isotropic displacements parameters ($A^2 \times 10^3$) for [112].

	x	y	z	U(eq)
F(5)	1479(1)	9453(1)	1454(1)	43(1)
F(121)	6101(1)	12136(1)	7577(1)	36(1)
F(7)	5299(2)	11981(1)	281(1)	49(1)
F(4)	1149(1)	9264(1)	4109(1)	42(1)
F(8)	6045(1)	12745(1)	3093(1)	38(1)
F(6)	3056(2)	10361(1)	-473(1)	49(1)
F(122)	4220(2)	13390(1)	7006(1)	41(1)
C(10)	2956(2)	10594(2)	3396(2)	27(1)
C(9)	4135(2)	11482(2)	3755(2)	26(1)
C(7)	4561(3)	11560(2)	1303(2)	35(1)
C(8)	4914(2)	11937(2)	2704(2)	30(1)
C(3)	2480(2)	10452(2)	5941(2)	30(1)
C(6)	3390(3)	10718(2)	918(2)	36(1)
C(4)	2213(2)	10121(2)	4517(2)	29(1)
C(5)	2598(2)	10246(2)	1916(2)	32(1)
C(1)	4371(2)	11817(2)	5232(2)	26(1)
C(2)	3614(2)	11346(2)	6214(2)	28(1)
C(12)	4699(2)	12298(2)	6674(2)	29(1)
H(3)	1939(25)	10117(20)	6607(26)	38(6)

Table A3.6. Bond Lengths [Å] and angles [°] for [112].

F(5)-C(5)	1.339(2)	F(121)-C(12)	1.364(2)
F(7)-C(7)	1.336(2)	F(4)-C(4)	1.349(2)
F(8)-C(8)	1.346(2)	F(6)-C(6)	1.344(2)
F(122)-C(12)	1.363(2)	C(10)-C(5)	1.420(3)
C(10)-C(9)	1.434(3)	C(10)-C(4)	1.437(3)
C(9)-C(8)	1.394(3)	C(9)-C(1)	1.414(3)
C(7)-C(8)	1.362(3)	C(7)-C(6)	1.396(3)
C(3)-C(4)	1.364(3)	C(3)-C(2)	1.406(3)
C(3)-H(3)	0.93(2)	C(6)-C(5)	1.370(3)
C(1)-C(2)	1.338(3)	C(1)-C(12)	1.437(3)
C(2)-C(12)	1.449(3)		
C(5)-C(10)-C(9)	116.4(2)	C(5)-C(10)-C(4)	124.2(2)
C(9)-C(10)-C(4)	119.4(2)	C(8)-C(9)-C(1)	126.2(2)
C(8)-C(9)-C(10)	121.0(2)	C(1)-C(9)-C(10)	112.8(2)
F(7)-C(7)-C(8)	121.7(2)	F(7)-C(7)-C(6)	119.0(2)
C(8)-C(7)-C(6)	119.3(2)	F(8)-C(8)-C(7)	119.9(2)
F(8)-C(8)-C(9)	119.2(2)	C(7)-C(8)-C(9)	120.8(2)
C(4)-C(3)-C(2)	111.4(2)	C(4)-C(3)-H(3)	121.8(14)
C(2)-C(3)-H(3)	126.8(14)	F(6)-C(6)-C(5)	119.8(2)
F(6)-C(6)-C(7)	118.3(2)	C(5)-C(6)-C(7)	121.8(2)
F(4)-C(4)-C(3)	117.5(2)	F(4)-C(4)-C(10)	116.1(2)
C(3)-C(4)-C(10)	126.4(2)	F(5)-C(5)-C(6)	118.0(2)
F(5)-C(5)-C(10)	121.3(2)	C(6)-C(5)-C(10)	120.7(2)
C(2)-C(1)-C(9)	124.4(2)	C(2)-C(1)-C(12)	62.84(14)
C(9)-C(1)-C(12)	172.4(2)	C(1)-C(2)-C(3)	125.6(2)
C(1)-C(2)-C(12)	61.93(14)	C(3)-C(2)-C(12)	172.2(2)
F(122)-C(12)-F(121)	105.0(2)	F(122)-C(12)-C(1)	123.0(2)
F(121)-C(12)-C(1)	122.1(2)	F(122)-C(12)-C(2)	122.6(2)
F(121)-C(12)-C(2)	122.9(2)	C(1)-C(12)-C(2)	55.24(13)

APPENDIX 4.

Infra Red Spectra

All samples run as nujol mulls unless stated otherwise.

1. 3,4,5,6,7,8-hexafluoro-1-isoquinolinethiol [26]
2. 2,3,5,6,7,8-hexafluoro-4-quinolinethiol [35]
3. dimethyl 4,5,6,7,9-pentafluoro-thieno[3,2-c]quinoline-1,2-dicarboxylate [36]
4. dimethyl 1-(2,3,5,6,7,8-hexafluoro-4-quinolylthio)ethene-1,2-dicarboxylate [38]
5. 3,4,5,6,7,8-hexafluoro-1-(t-butylthio)isoquinoline [39]
6. 1,3,4,5,7,8-hexafluoro-6-(t-butylthio)isoquinoline [40]
7. 3,4,5,7,8-pentafluoro-1,6-di(t-butylthio)isoquinoline [41]
8. 3,4,5,7,8-pentafluoro-6-phenylthio-1-isoquinolinethiol [42]
9. 1,3,4,5,7,8-hexafluoro-6-(phenylthio)isoquinoline [43]
10. dimethyl 1-(3,4,5,7,8-pentafluoro-6-phenylthio-1-isoquinolylthio)ethene-1,2-dicarboxlate [44]
11. 1,6-di(phenylthio)-3,4,5,7,8-pentafluoroisoquinoline [45]
12. 3,4,5,6,7,8-hexafluoro-1-(methylthio)isoquinoline [46]
13. 1,3,4,5,7,8-hexafluoro-6-(methylthio)isoquinoline [47]
14. 3,4,5,7,8-pentafluoro-1,6-di(methylthio)isoquinoline [48]
15. 1,3,4,5,7,8-hexafluoro-6-(4-(N,N-dimethylamino)phenylthio)isoquinoline [53]
16. 3,4,5,7,8-pentafluoro-1,6-di(4-(N,N-dimethylamino)phenylthio)isoquinoline [54]
17. 1,3,4,5,7,8-hexafluoro-6-(4-methoxyphenylthio)-isoquinoline [56]
18. 3,4,5,7,8-pentafluoro-1,6-di(4-methoxyphenylthio)-isoquinoline [57]
19. 1,3,4,5,7,8-hexafluoro-6-(4-nitrophenylthio)-isoquinoline [58]
20. 3,4,5,7,8-pentafluoro-1-ethoxy-6-(t-butylthio)isoquinoline [59]
21. 1-ethoxy-3,4,5,6,7,8-hexafluoroisoquinoline [60]
22. 1,6-di(ethoxy)-3,4,5,7,8-pentafluoroisoquinoline [62] (neat liq.).
23. 3,4,5,6,7,8-hexafluoro-1-phenoxy-isoquinoline [65]
24. 3,4,5,6,7,8-hexafluoro-1-(4-nitrophenoxy)-isoquinoline [67]

25. 3,4,5,6,7,8-hexafluoro-2-(t-butylthio)quinoline [72]

26. 2,3,5,6,7,8-hexafluoro-4-(t-butylthio)-quinoline [73]

27. 3,5,6,7,8-pentafluoro-2,4-di(t-butylthio)quinoline [74]

28. 2,3,5,6,7,8-hexafluoro-(4-phenylthio)quinoline [75]

29. 3,5,6,7,8-pentafluoro-2-ethoxy-4-(t-butylthio)quinoline [76]

30. 2-ethoxy-3,4,5,6,7,8-hexafluoroquinoline [77]

31. 4-ethoxy-2,3,5,6,7,8-hexafluoroquinoline [78]

32. 3,4,5,6,7,8-hexafluoro-2-phenoxy-quinoline [79]

33. 2,3,5,6,7,8-hexafluoro-4-phenoxy-quinoline [80]

34. 3,4,5,6,7,8-hexafluoro-2-(4-nitrophenoxy)quinoline [81] and 2,3,5,6,7,8-hexafluoro-4-(4-nitrophenoxy)quinoline [82] (ratios 17 : 83 respectively by ^{19}F nmr) (neat liquid).

35. heptafluoro-2-naphthyl propynoate [106]

36. 1,2-dihydro-1,1,4,5,6,7,8-heptafluoro-cyclobuta[a]naphthalene-2-one [110]

37. 1,2-dihydro-2,2,4,5,6,7,8-heptafluoro-cyclobuta[a]naphthalene-1-one [111]

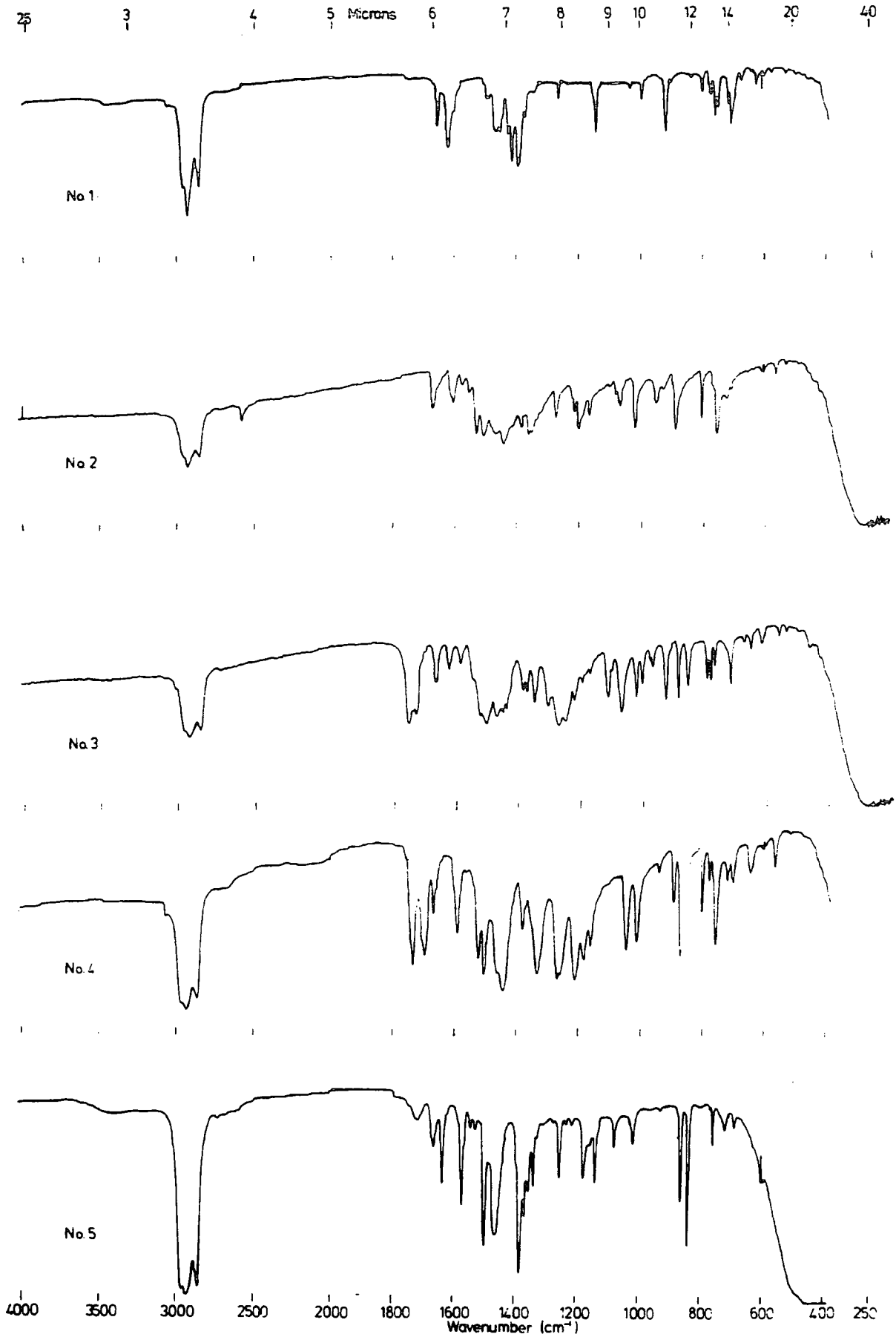
38. 1-ethoxy-3,4,5,7,8-pentafluoro-6-phenylthioisoquinoline [125]

39. 3,5,6,7,8-pentafluoro-2,4-di(phenylthio)quinoline [126]

40. 2-ethoxy-3,5,6,7,8-pentafluoro-4-phenylthioquinoline [127]

FTIR spectra

41. 1,1,4,5,6,7,8-heptafluoro-1H-cyclopropa[a]naphthalene [112]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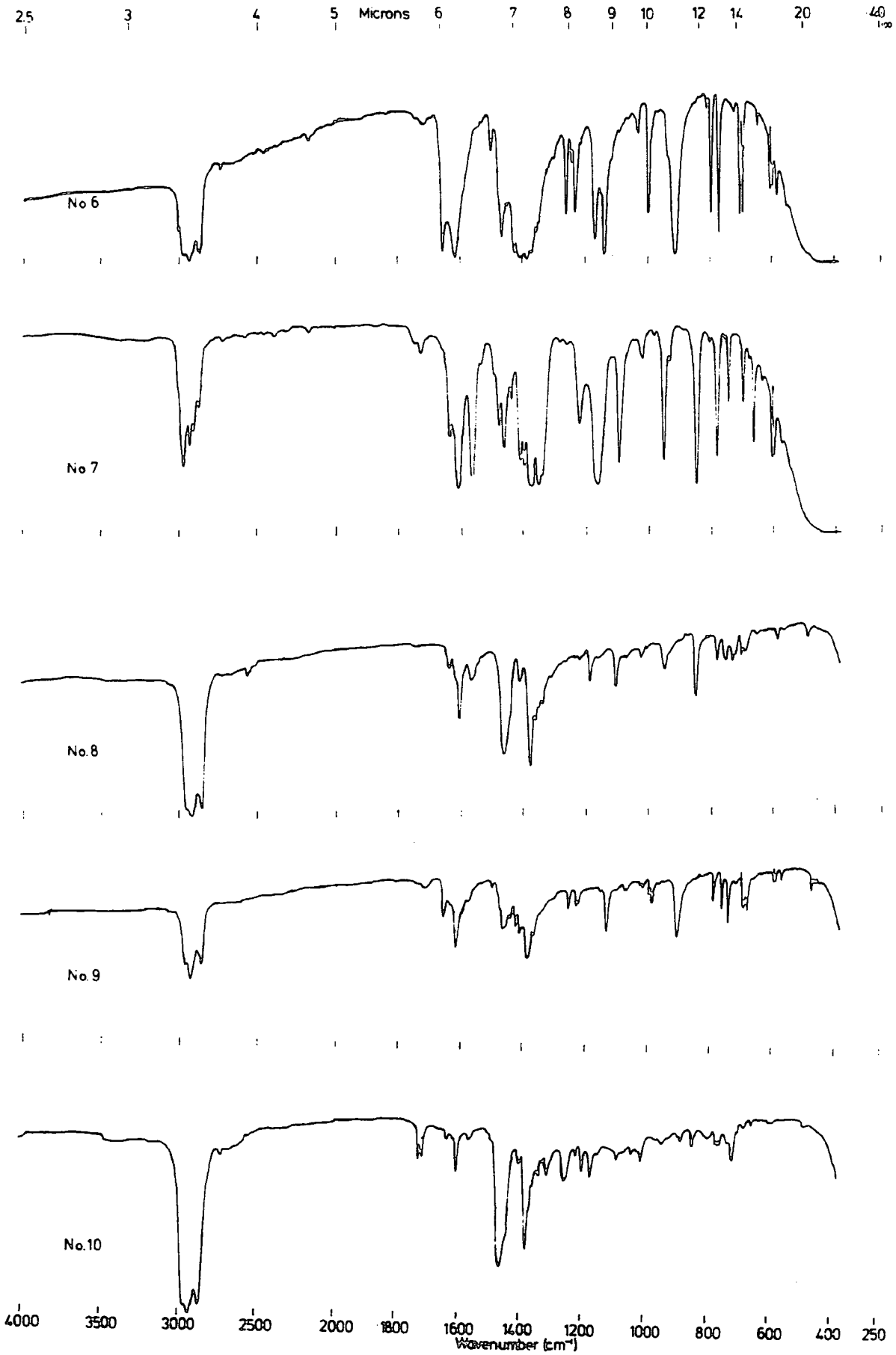
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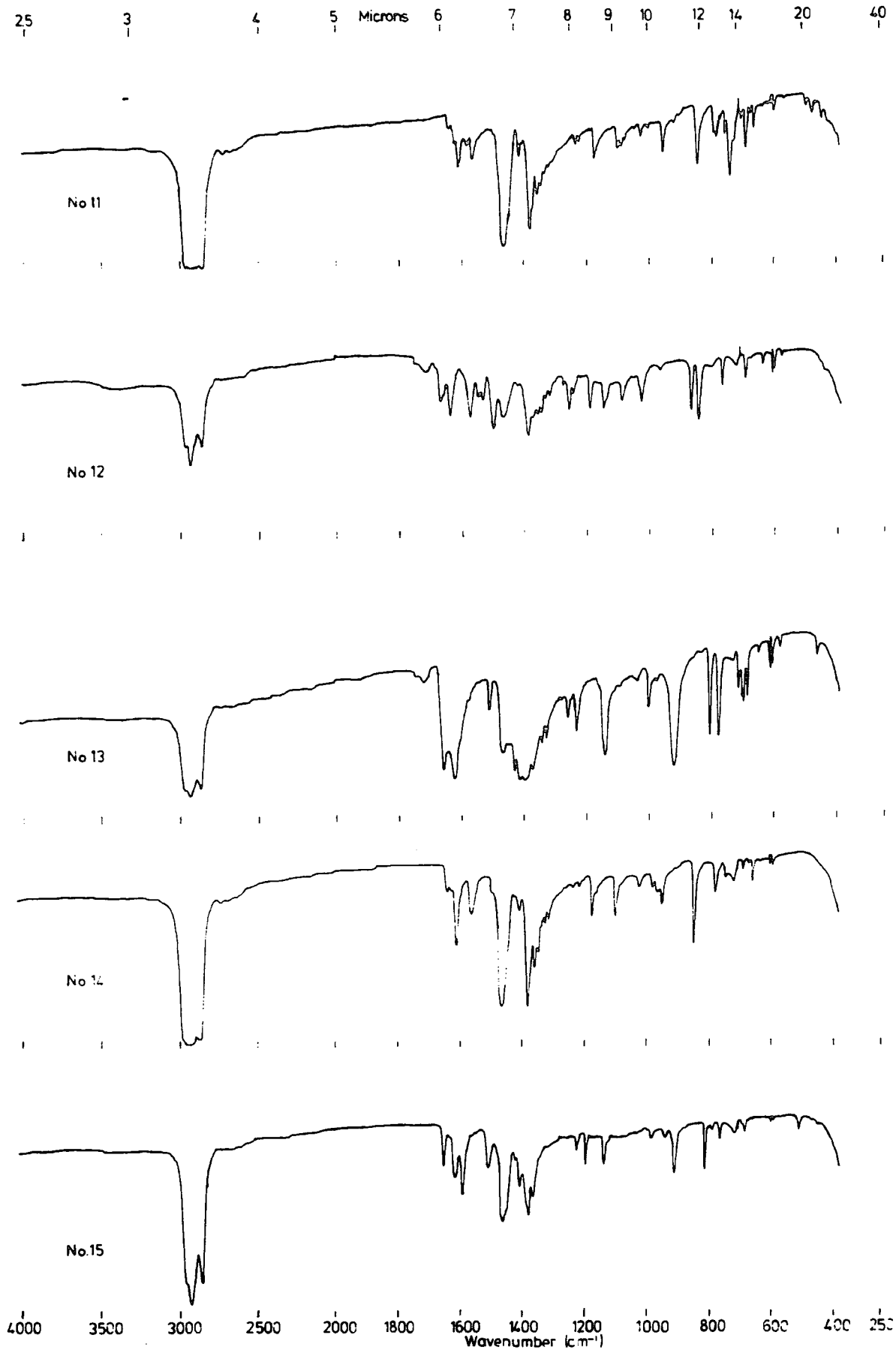
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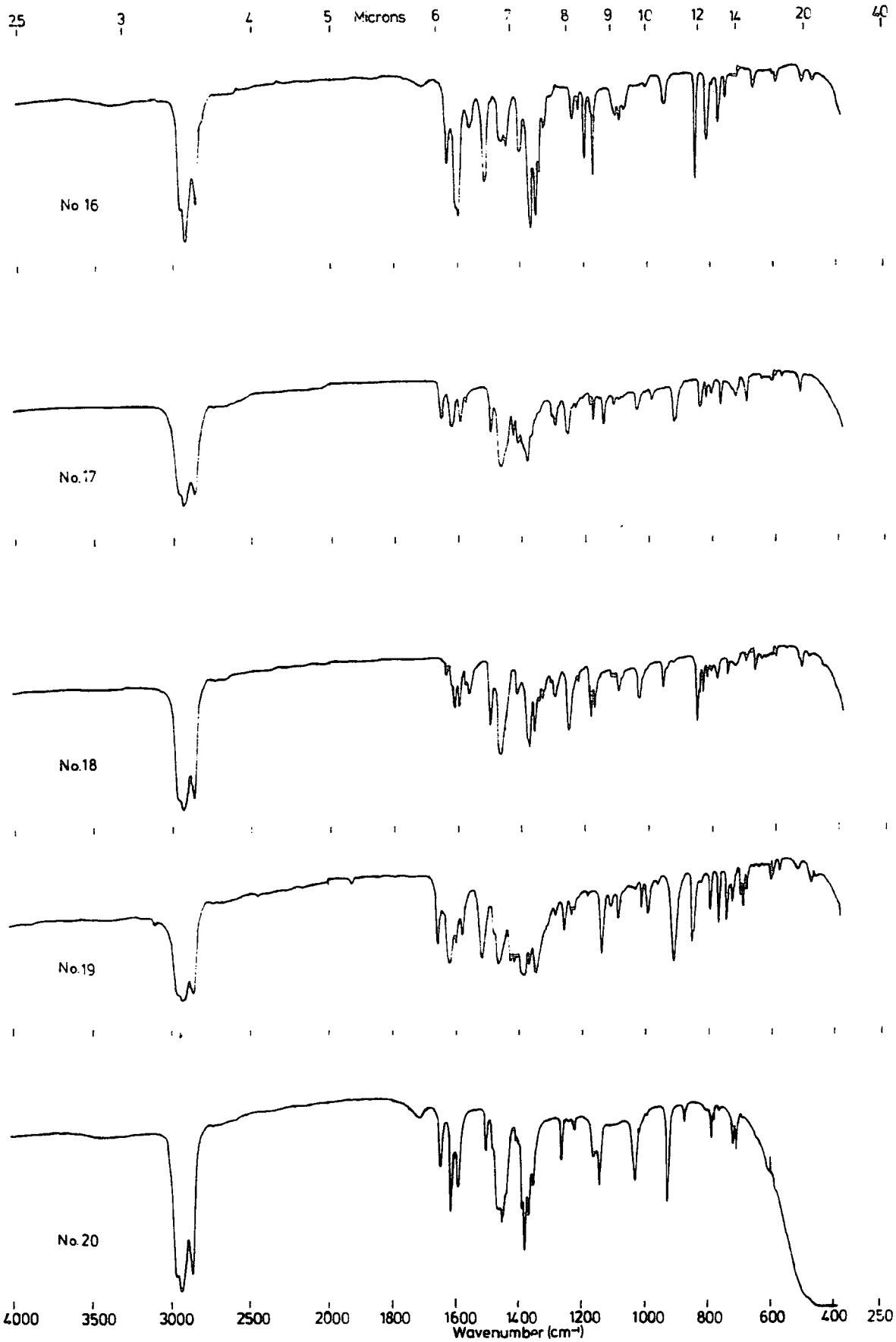
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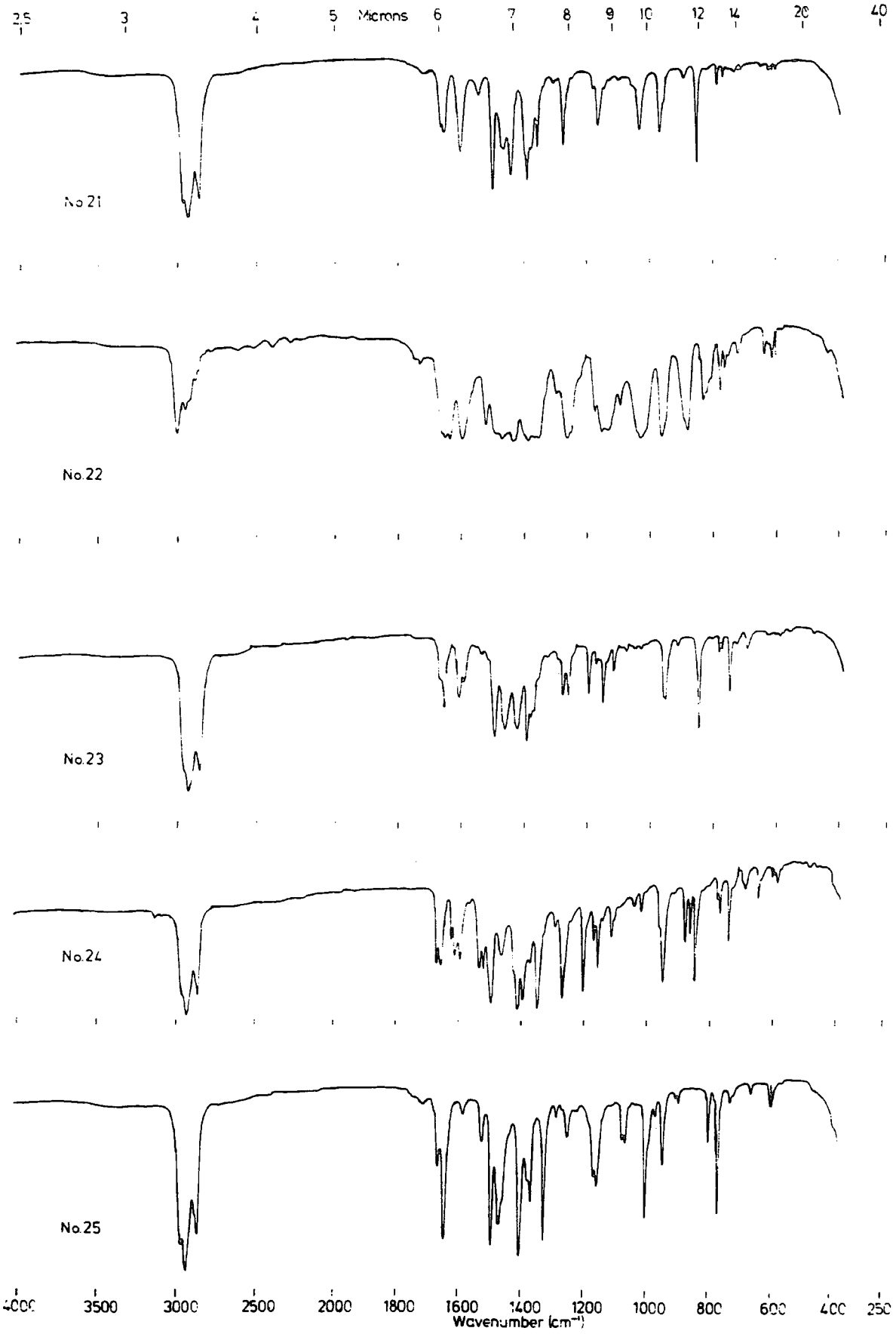
Wavenumber (cm⁻¹)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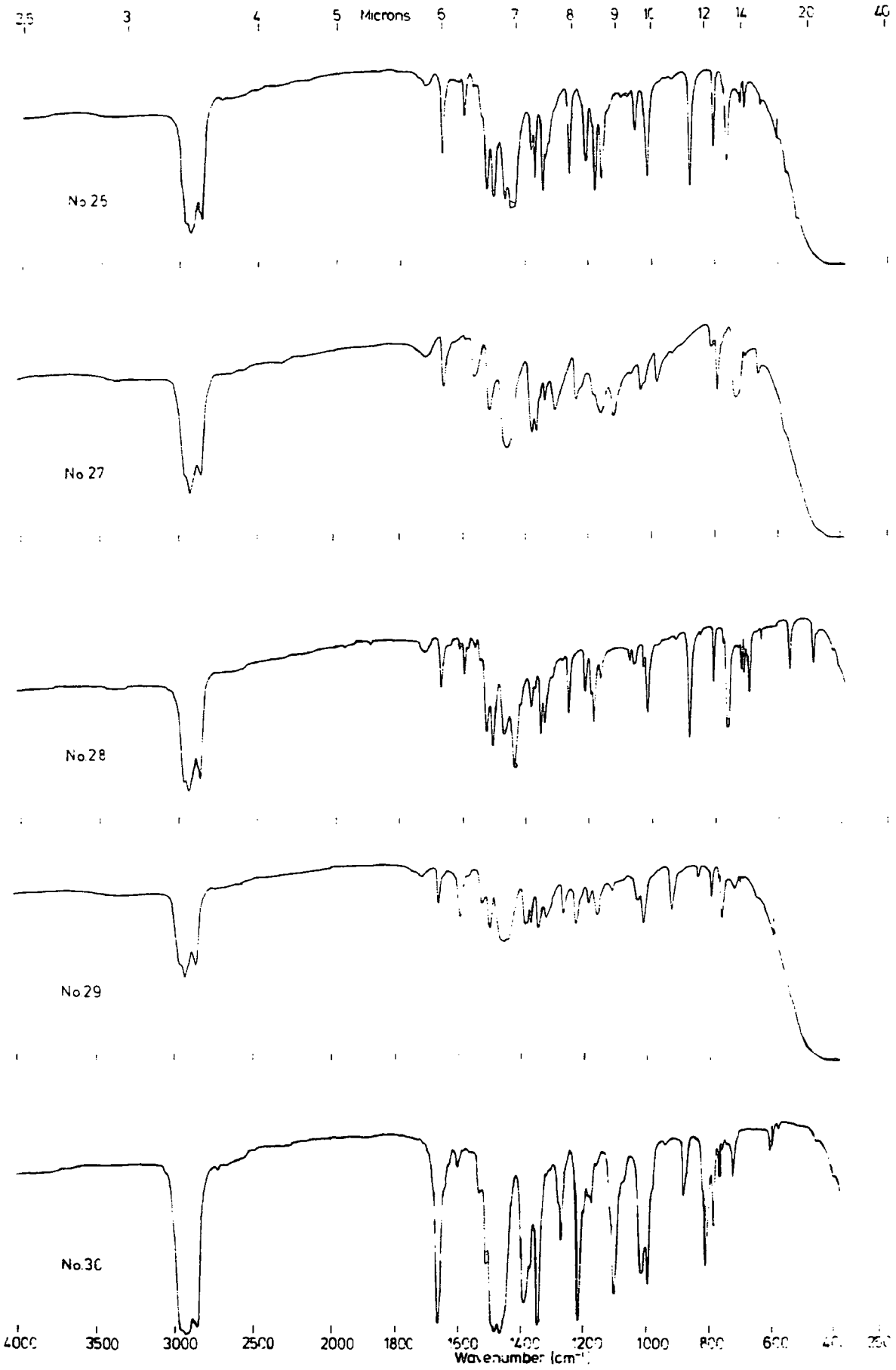
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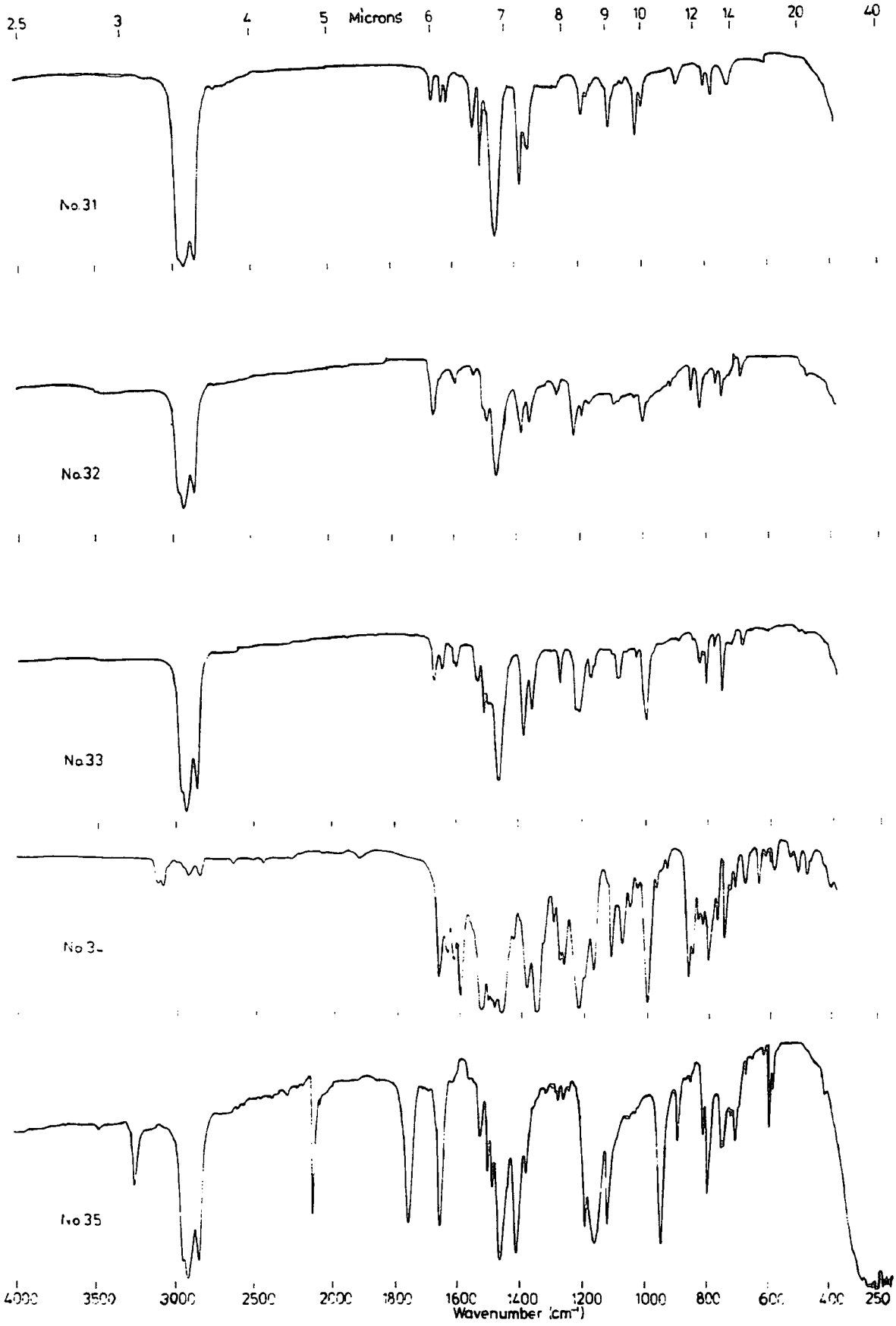
Wavenumber (cm⁻¹)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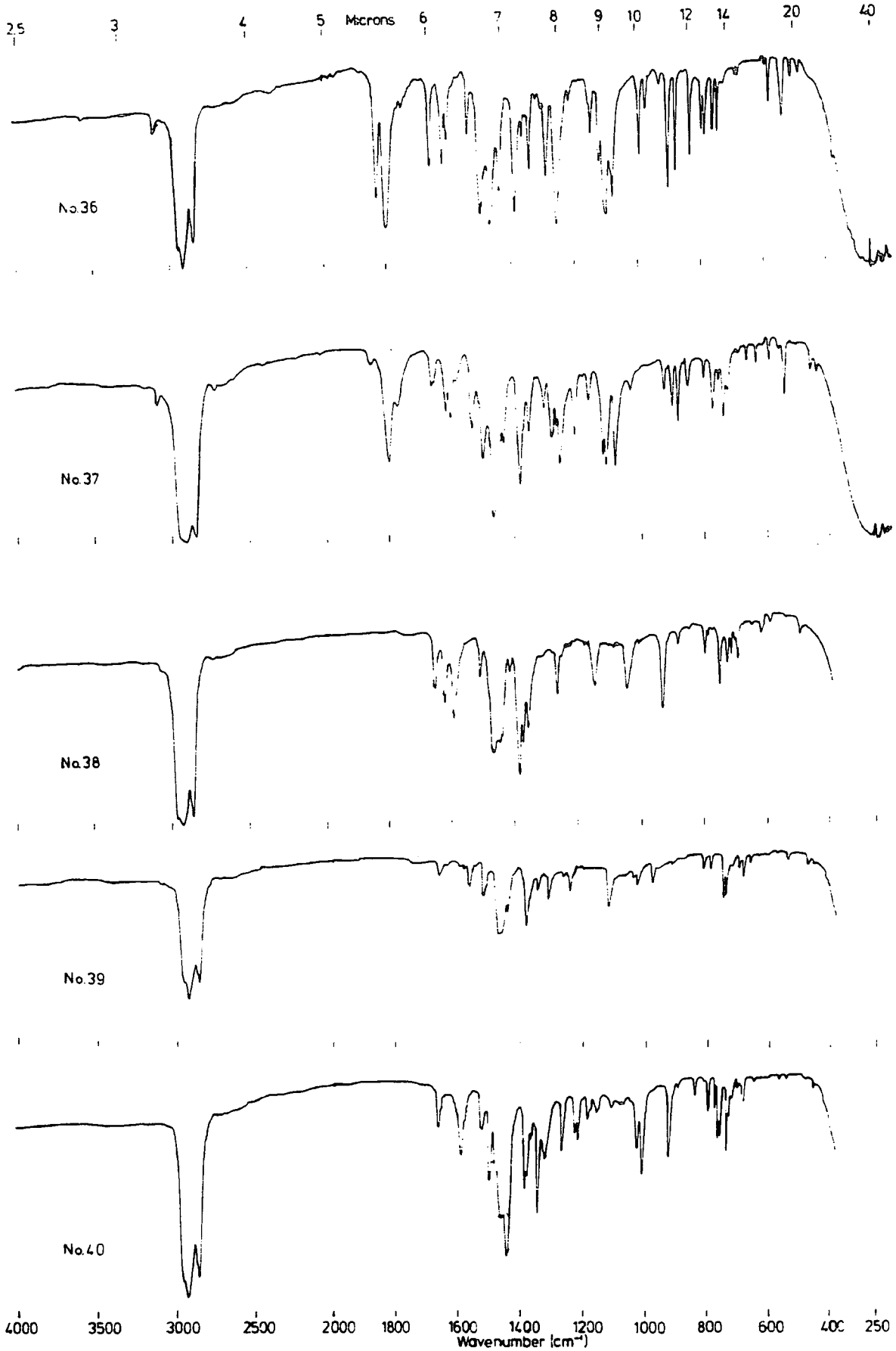
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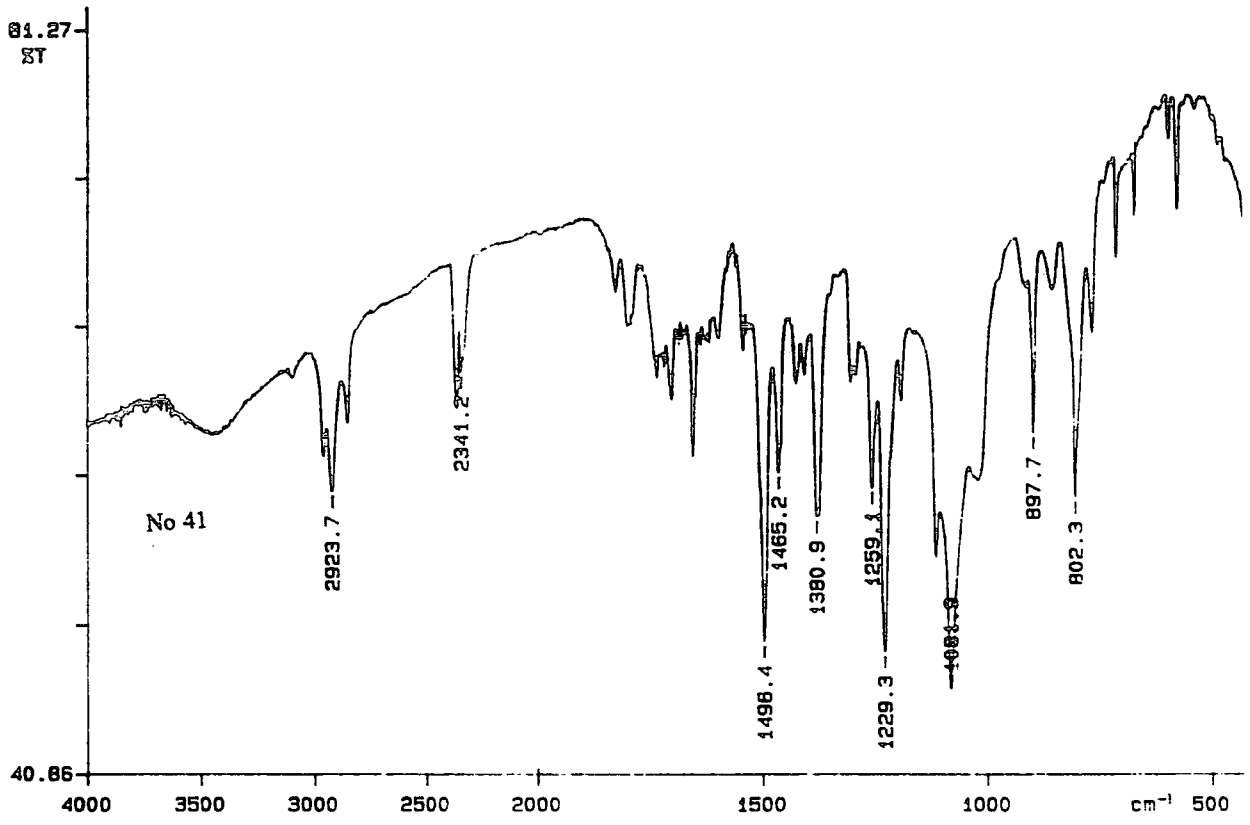
Wavenumber (cm⁻¹)



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