perfluoroalkylaromatic compounds

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UNIVERSITY OF DURHAM

A THESIS

entitled

PERFLUOROALKYLAROMATIC COMPOUNDS

Submitted by

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(GRADUATE SOCIETY)

A candidate for the degree of Doctor of Philosophy

Department of Chemistry

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for

my family

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MEMORANDUM

The work described in this thesis was carried out in the University of Durham between October 1982 and September 1985. This thesis is the work of the author, except where acknowledged by reference, and has not been submitted for any other degree.

ABSTRACT

Trifluoromethyl-substituted compounds find applications as both pharmaceutical and plant protection products. As these compounds have to undergo rigorous tests before being placed on the market, improved methods are required for the introduction of the trifluoromethyl group which could be applied to the production of ^{14}C-labelled molecules for use in metabolic studies.

Two sources of the trifluoromethyl group mentioned only briefly in the literature, bis(trifluoromethyl)mercury and sodium trifluoroacetate, were both developed as reagents for the synthesis of substituted trifluoromethylbenzenes. Trifluoromethylation with sodium trifluoroacetate was extended to the preparation of alkyl, alkenyl, and heterocyclic trifluoromethyl compounds, and up to three groups were introduced into an aromatic nucleus. The mechanism of this interesting copper-promoted reaction was investigated and an intermediate of the form $[CF_3CuI]^-$ is proposed.

Introduction of higher perfluoroalkyl groups from their respective sodium perfluoroalkanecarboxylic acids was attempted and the mechanistic features compared with those of the trifluoromethylation reaction.

A poly-substituted trifluoromethyl aromatic compound, 1,3,5-tris(trifluoromethyl)benzene, was produced by fluorination of trimesic acid with sulphur tetrafluoride and its chemistry investigated. It is fairly unreactive but readily forms a sterically hindered lithium derivative which undergoes many reactions typical of an organolithium compound. Mercury and copper derivatives were also prepared and used in coupling reactions with iodobenzene.

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INTRODUCTION

General Introduction

Elemental fluorine was first isolated by Moissan nearly one hundred years ago but, despite pioneering work by Swarts, it is only in the forty years since the Manhattan Project that the potential of fluorine chemistry has been realised.

The introduction of dichlorodifluoromethane as a refrigerant marked the beginning of the commercial application of fluorocarbons and since then the usage has increased dramatically. Highly fluorinated compounds with their chemical inertness and unique properties find a wide range of uses from fire extinguishers and aerosols to anaesthetics and blood substitutes. One of the best known is the polymer, polytetrafluoroethylene, the non-stick properties of which are applied in the coating of cooking utensils. The complete replacement of hydrogen by fluorine in these compounds results in total lack of biological activity. Pronounced biological activity is found in compounds with low fluorine content and, with the development of methods for the selective introduction of small amounts of fluorine, the use of fluorine-containing pharmaceuticals and pesticides is becoming increasingly common.

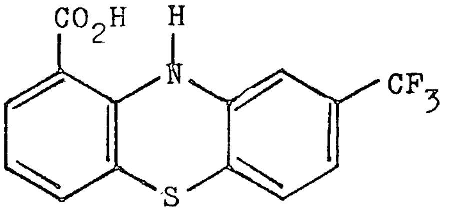
In tandem with the discovery of new compounds with unique and commercially useful properties has grown the new chemistry that arises from replacing hydrogen in many systems with fluorine, the most electronegative of the elements. In contrast to the chemistry of hydrocarbon olefins and aromatic compounds, which is based on electrophilic reagents and carbocations, that of fluoro-olefins and polyfluoroaromatic compounds involves nucleophilic reagents and carbanions. From the analogy which can be drawn between the negative fluoride ion in fluorocarbon chemistry and the positive hydrogen ion in hydrocarbon chemistry has grown the idea of mirror-image chemistry.

Chapter 1

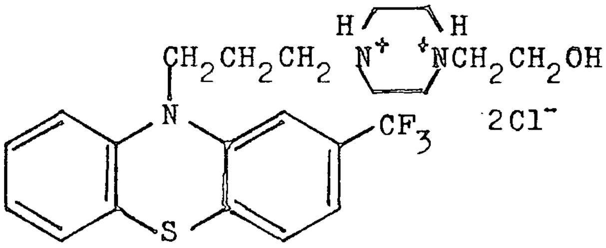
Perfluoroalkylaromatic Compounds

1.A. Some Commercial Applications of Trifluoromethylaromatic Compounds

The development of techniques for the selective introduction of fluorine into organic molecules has resulted in a vast increase in the number of fluorine-containing drugs such as the anti-inflammatory drug fluhazin (1) and fluphenazine.HCl (2) which is the most potent of the phenothiazine tranquillisers.



(1)



(2)

There are four main reasons for incorporating fluorine into pharmaceuticals;

(i) fluorine most closely resembles hydrogen in its steric requirements at receptor sites,

(ii) fluorine with its high electronegativity frequently alters electronic effects and reactivity,

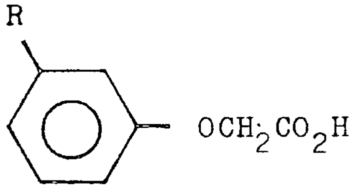
(iii) the strength of the carbon-fluorine bond is greater than that of the carbon-hydrogen bond and so imparts increased oxidative and thermal stability,

(iv) fluorine may increase lipid solubility and enhance rates of absorption and transport of drugs in vivo.

Tho trifluoromethyl group is among the most lipophilic of all substituents and this may be the most important factor in its improvement of pharmacological activity. A measure of its lipophilicity may be gained from the hydrophobic parameters (π) shown in Table (1.A.1). The values are relative to that for the hydrogen substituent and an increasing value indicates greater lipophilicity.

Table (1.A.1) Hydrophobic Parameters [1]

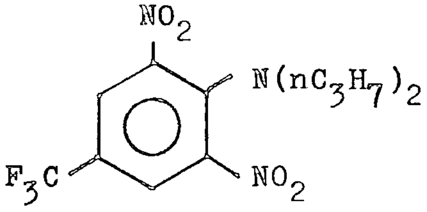
R	π
SCF_3	+1·58
SF_5	+1·50
OCF_3	+1·21
CF_3	+1·07
SO_2CF_3	+0·93
Cl	+0·76
CH_3	+0·51
F	+0·13
NO_2	+0·11
H	0
CO_2H	-0·15
OH	-0·49



$$\pi = \log P_X - \log P_H$$

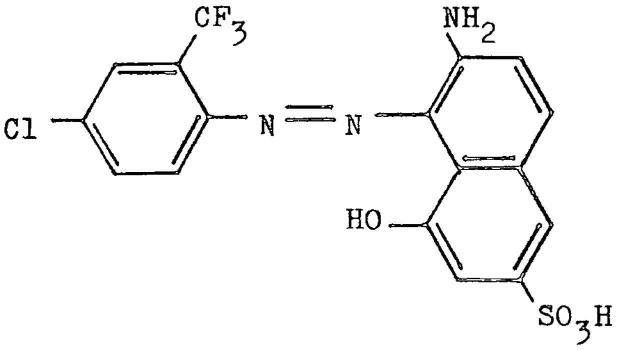
P_X is the octan-1-ol/water partition coefficient of the derivative and P_H that of the parent.

The trifluoromethyl derivatives are the largest subgroup of the listed fluorine-containing pesticides. The function of the trifluoromethyl group is again to act as a lipophile and assist take-up by the system of the toxic group. Trifluralin (3), produced by Eli Lilly, is one of the most commercially successful herbicides of past decades.



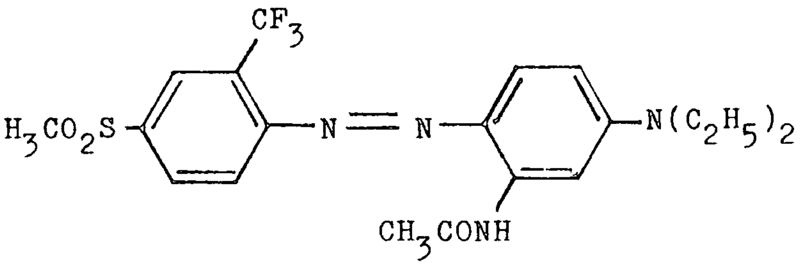
(3)

Trifluoromethyl derivatives are also important in the dyestuffs industry. The light and wash fastness of monoazo dyes, such as CI acid red 266 (4), is increased by substituting a trifluoromethyl group ortho to the azo bridge.



(4)

The inclusion of the trifluoromethyl group reduces the sublimation fastness of the dye CI disperse red 210 (5) compared to that of its chlorosubstituted analogue but this has been turned to advantage in the modern dye transfer processes.



(5)

Rigorous tests must be carried out before pesticides and pharmaceuticals can be put onto the market. Consequently new methods of introducing the trifluoromethyl group into specific sites in aromatic molecules are needed, since the known methods are frequently not suited to the production of the carbon-14 labelled trifluoromethyl compounds required for use in metabolic studies.

1.B. Introduction of the Perfluoroalkyl Group into Aromatic Compounds

Before proceeding to describe any new methods for introducing perfluoroalkyl groups into aromatic compounds it seems appropriate to review those presently in use. The reactions have been grouped under six main headings. The first two sections deal with transformations of functional groups already present in the molecule and the remaining four are concerned with direct methods for introducing the perfluoroalkyl group into the arene.

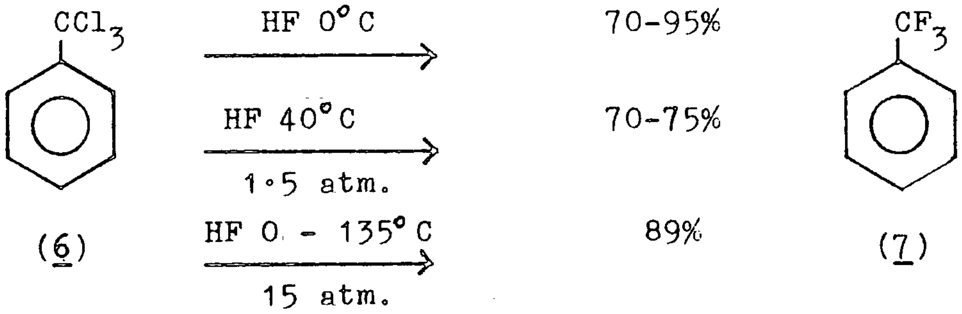
1.B.i. Halogen Substitution Reactions

Halogen exchange is by far the most widely explored method for introduction of fluorine into organic molecules and as it is the industrially preferred process a large volume of chemical and patent literature has been devoted to it. Reactions using hydrogen fluoride and mixed antimony fluorides are described briefly here and more extensive coverage can be found in references 2 and 3. Some additional examples to those in the text are given in Table (1.B.1).

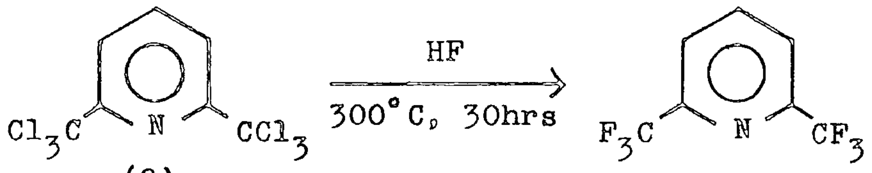
1.B.i.a. Anhydrous Hydrogen Fluoride.

Anhydrous hydrogen fluoride is a cheap and readily available reagent for halogen exchange and can be used either alone or in conjunction with antimony pentahalides as catalysts. It is formed by treatment of calcium fluoride with conc. sulphuric acid, and is a colourless liquid which boils at 19·5°C and fumes in air. The liquid and its vapour cause serious burning and so it is essential that suitable protection is used.

When used alone hydrogen fluoride will substitute only the most reactive of halides in which the neighbouring groups are able to stabilise a carbocationic centre. Trichloromethylbenzene (6) can be converted to trifluoromethylbenzene (7) over a range of temperatures and conditions.[4,5,6]



Single halogens attached to an aromatic ring are inert towards hydrogen fluoride in the presence of the most powerful of catalysts and nitro, ether, carboxyl, and sulphonyl groups can also be tolerated.[7] Pyridines can also be trifluoromethylated in this way but in the case of 2,6-bis(trichloromethyl)pyridine (8) longer reaction times are necessary as catalysts have proved ineffective.[8]



(8)

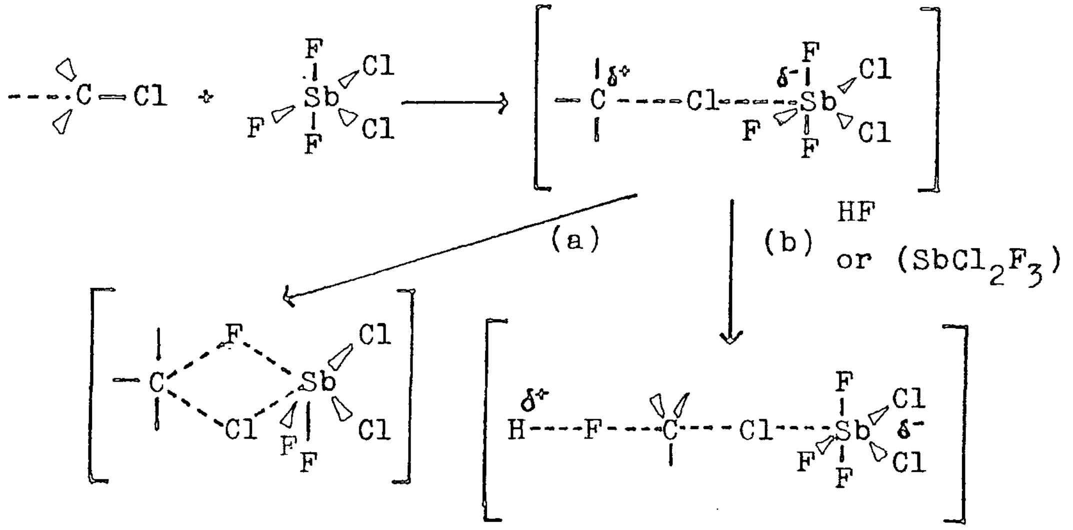
Antimony catalysts, usually antimony pentachloride or antimony trichloride with bromine or chlorine, enhance halogen exchange and allow the reaction to be carried out under milder conditions. The HF/Sb(V) system is the industrially used method of fluorination and can be run as a continuous process in which partially fluorinated material is recycled along with unused hydrogen fluoride. The reaction course is complicated but involves halogen exchange between the trichloromethylaromatic compound and pentavalent antimony chlorofluorides formed in situ. A simplified scheme is shown:-

$$SbCl_5 + 3HF \longrightarrow SbF_3Cl_2 + 3HCl$$

$$ArCCl_3 + SbF_3Cl_2 \longrightarrow ArCF_3 + SbCl_5$$

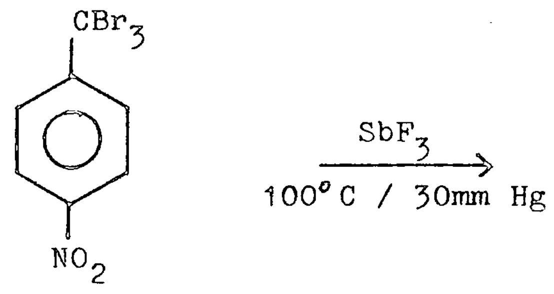
The reaction is basically stepwise nucleophilic displacement of chlorine in which the antimony halide acts as a Lewis acid in assisting removal of the chlorine. The efficiency of the process may arise from the greater strength of the chlorine-antimony bond compared to fluorine-antimony, and the ability of antimony to form high stability hexacoordinate complexes. These are suggested intermediates in the mechanism shown in Scheme (1.1).[7] The transition state collapses by fluorine transfer either intramolecularly (a) or from a second molecule of hydrogen fluoride or catalyst (b), the exact method is unknown.

Scheme (1.1) Catalysis of Halogen Exchange by Antimony Pentahalides



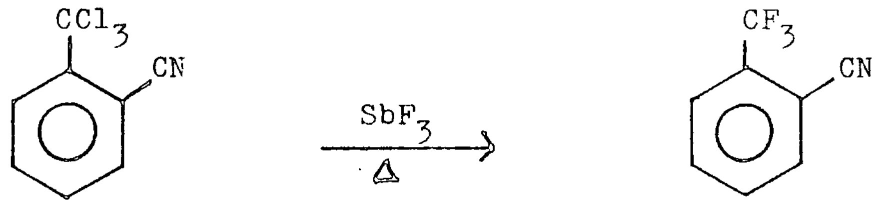
1.B.i.b. Antimony Fluorides (Swarts' Reactions)

Halogen exchange reactions using antimony fluorides as the source of fluorine were pioneered by Swarts and still bear his name. Antimony trifluoride has a similar reactivity to hydrogen fluoride and is preferred for laboratory use as it is a solid and is more easily handled. Fluorination of trichloromethylbenzene using antimony trifluoride was reported to be accompanied by tar formation resulting in low yields of trifluoromethylbenzene[2] but improved yields of up to 85% have been obtained by adding excess antimony trifluoride portionwise to the refluxing trichloromethylbenzene and distilling off the product as it is formed.[9] Cyano (9)[10] and nitro (10)[11] substituted trifluoromethyl benzenes have also been formed.



90%

(10)



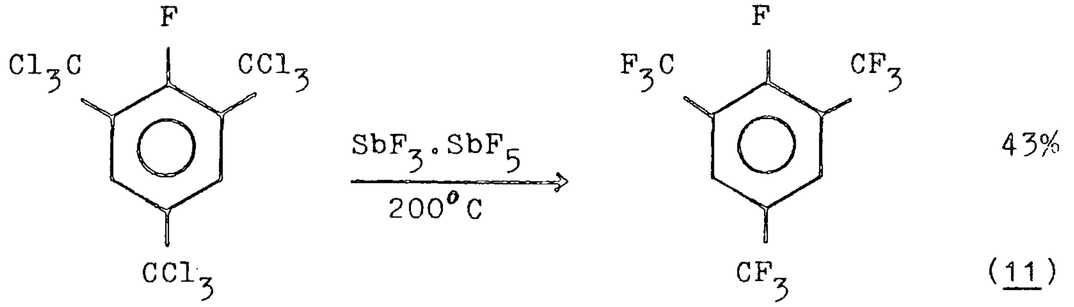
77%

(9)

Single halogens in aromatic compounds are usually unreactive but 2-iodothiophene[12] and trichlorotriazine[13] can both be fluorinated by antimony halides.

Fluorinating activity can be increased dramatically by addition of chlorine or bromine to transform the trivalent antimony either partly or wholly to the pentavalent state. The fluorinating power of the mixed reagent is directly related to the proportion of pentavalent antimony present, antimony pentafluoride itself is sufficiently powerful to saturate an aromatic ring.[2] The mixed reagent will substitute fluorine for chlorine in all the compounds which are fluorinated by antimony trifluoride but under less vigorous conditions.

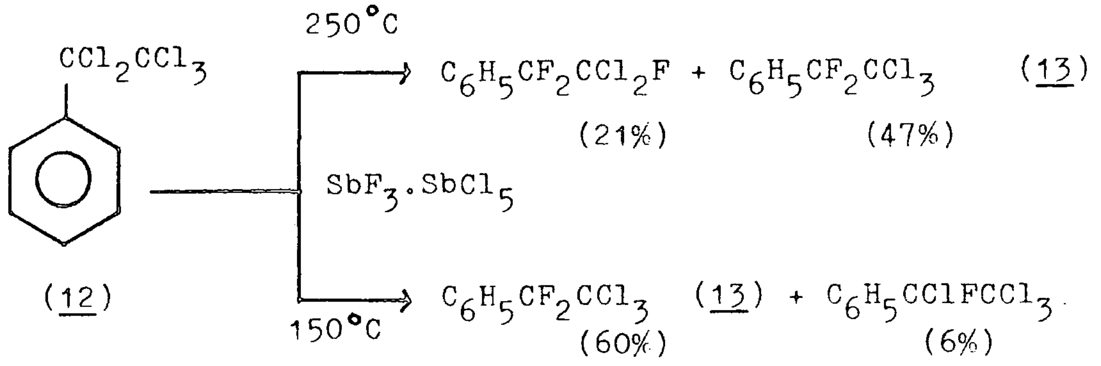
Polytrifluoromethylbenzenes such as 1-fluoro-2,4,6-tris(trifluoromethyl)benzene (<u>11</u>) can also be formed.[14]



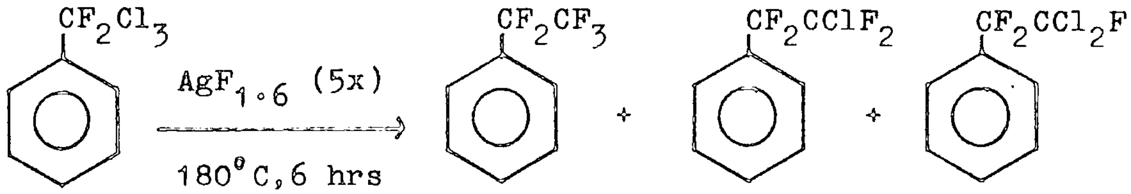
(<u>11</u>)

The HF.Sb(V) and Sb(III).Sb(V) systems behave similarly and the same reaction intermediates are envisaged.

Halogen substitution of pentachloroethylbenzene (<u>12</u>) is much more difficult than that of trichloromethylbenzene and even using antimony trifluoride / antimony pentachloride only the dichloromethylene group can be substituted.[15]



The trichlorodifluoroethylbenzene (<u>13</u>) formed was treated with the powerful fluorinating agent silver (I) fluoride but after five reactions only a small amount of the fully fluorinated product was formed.[16]



(13) 1% 20% 47%

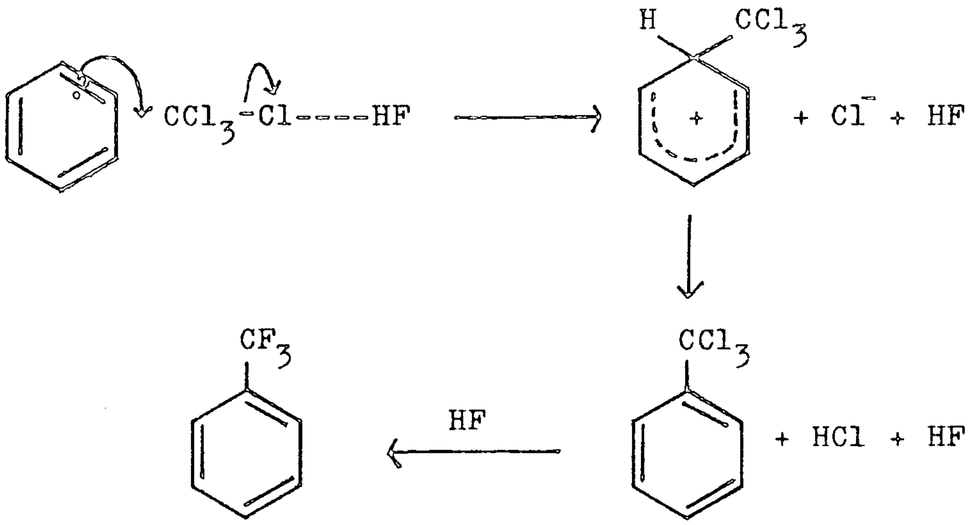
1.B.i.c. Hydrogen Fluoride / Tetrachloromethane[17]

The reaction is similar to those previously described in that halogen exchange takes place but the trifluoromethyl group is derived from tetrachloromethane rather than being present in the aromatic compound.

$$ArH \xrightarrow[HF]{CCl_4} ArCF_3 + HCl$$

The method is based on the ability of hydrogen fluoride to fluorinate trichloromethyl groups and catalyse electrophilic substitutions of the Friedel Crafts type, enabling carbon-carbon and carbon-fluorine bonds to be formed in the same reaction. A likely mechanism for the formation of trifluoromethylbenzene is shown in Scheme (1.2)

Scheme (1.2) Trifluoromethylation of Benzene with Hydrogen Fluoride and Tetrachloromethane

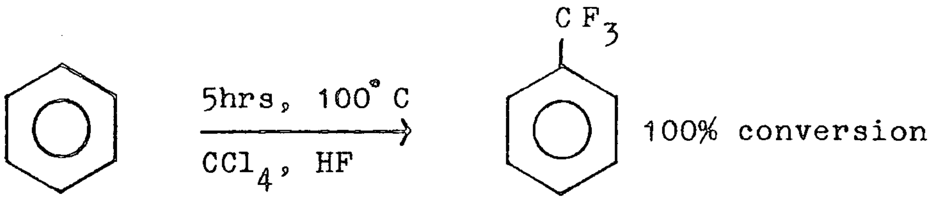


Two other possible reaction products, trichlorofluoromethane (<u>14</u>) and triphenylfluoromethane (<u>15</u>), are observed to differing extents.

$$\begin{aligned} \mathrm{ArH} + \mathrm{CCl_4} + (\mathrm{HF})_n &\longrightarrow \mathrm{ArCF_3} + 4\mathrm{HCl} \\ &\longrightarrow \mathrm{ArH} + \underset{(\underline{14})}{\mathrm{CFCl_3}} + \mathrm{HCl} \\ &\longrightarrow \mathrm{Ar_2CF_2} + \mathrm{HCl} \xrightarrow{\mathrm{ArH}} \underset{(\underline{15})}{\mathrm{Ar_3CF}} + \mathrm{HCl} \end{aligned}$$

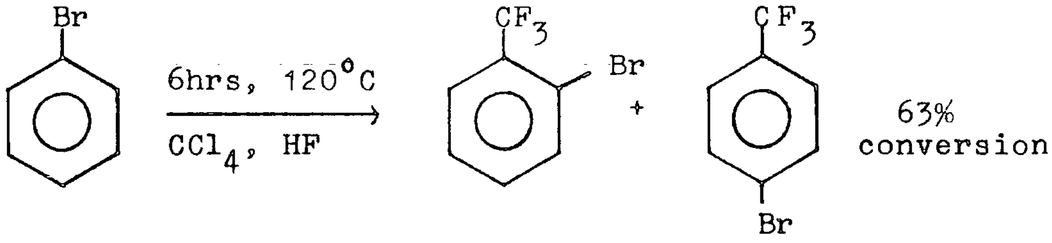
Trichlorofluoromethane is formed in some quantity in all reactions but becomes the major product in the case of very electrophilic aromatics such as nitrobenzene and trifluoromethylbenzene. This explains why disubstitution is not observed. The multiple arylation only becomes important if unsuitable experimental conditions are used and so can be avoided.

The arene, hydrogen fluoride and tetrachloromethane are heated together in an autoclave under pressurised nitrogen. In order to achieve complete conversion the latter two reagents are added in excess. Trifluoromethylbenzene (7) is obtained from benzene by reaction at 100°C for five hours.



(7)

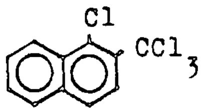
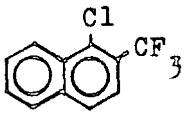
In substituted benzenes the isomer distribution follows the rules of electrophilic substitution and cannot be altered by varying the reaction conditions. Trifluoromethylation of bromobenzene (16) yields the ortho- and para-isomers in the expected 2:1 ratio.



(16) 2 : 1

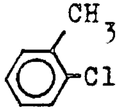
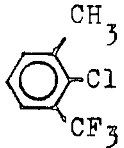
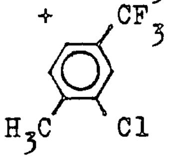
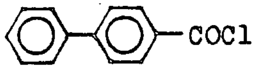
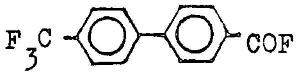
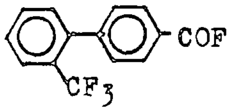
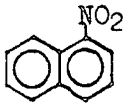
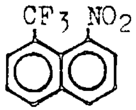
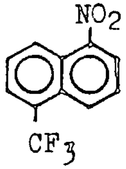
The reaction of toluene (17) though is remarkably unselective and a high proportion of the meta-isomer is formed.

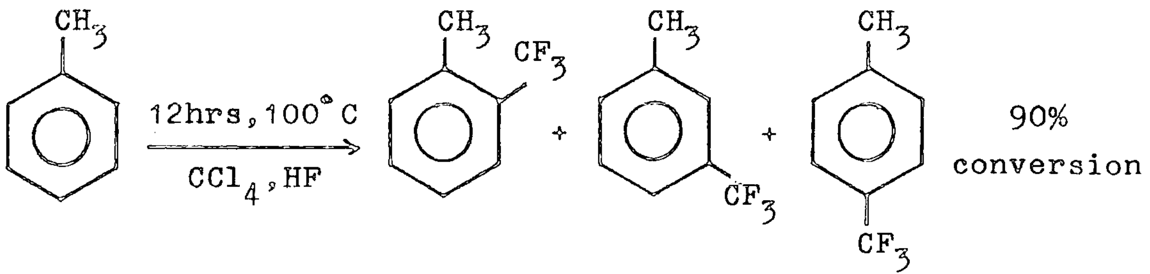
Table (1.B.1) Halogen Substitution Reactions

Starting Material	Fluorinating Agent	Conditions	Product	Yield %	Ref.
$1,3,5\text{-}C_6H_3(CCl_3)_3$	HF	200°C, 20hr, 133atm	$1,3,5\text{-}C_6H_3(CF_3)_3$	49	14
$4\text{-}Cl\cdot C_6H_4\cdot CCl_3$	HF	110°C, 1-2hr, 10-14atm	$4\text{-}Cl\cdot C_6H_4\cdot CF_3$	-	18
$2,4\text{-}(CCl_3)_2\cdot C_5H_3N$	HF	204°C	$2,4\text{-}(CF_3)_2\cdot C_5H_3N$	45	8
$2,4\text{-}(CCl_3)_2\cdot C_6H_3Cl$	$SbCl_5/HF$	20°C	$2,4\text{-}(CF_3)_2\cdot C_6H_3Cl$	91	19
$1,3,5\text{-}(CCl_3)_3\cdot C_3N_3$	$SbF_3/SbCl_5$	reflux distillation	$1,3,5\text{-}(CF_3)_3\cdot C_3N_3$	90	21
	SbF_3	C_6H_5Cl, reflux, 9hr		90	20
$C_6H_5OCF_3$	CCl_4/HF	100°C, 5hr, N_2(3-5bar)	$CF_3\cdot C_6H_4\cdot OCF_3$ (o:p = 1:3)	56	17

continued

Table (1.B.1) continued

Starting Material	Fluorinating Agent	Conditions	Product	Yield %	Ref.
	CCl_4/HF	100°C, 6hr, N_2(3-5bar)	 + (1:2) 	86	17
	CCl_4/HF	110°C, 6hr, N_2(3-5bar)	 + (9:1) 	90	17
	CCl_4/HF	110°C, 6hr, N_2(3-5bar)	 + (1:1) 	22	17



(17) 13 : 42 : 45

Further examples of the reaction are listed in Table (1.B.1)

1.B.ii. Reaction of Carboxyl Groups with Sulphur Tetrafluoride and its Derivatives

Sulphur tetrafluoride, which was first isolated in 1954,[22] is a specific and unique fluorinating agent for the conversion of the carbonyl group to difluoromethylene. Reaction of sulphur tetrafluoride with carboxylic acids and their derivatives provides a direct and general method for the introduction of the trifluoromethyl group.

Several preparations of sulphur tetrafluoride have been noted[22] and of these the most practical is described by Tullock.[23]

$$3SCl_2 + 4NaF \xrightarrow[50-70^\circ C]{CH_3CN} SF_4 + S_2Cl_2 + 4NaCl$$

A newer preparation involves heating sulphur dichloride in pyridinium poly(hydrogen fluoride) and collecting the sulphur tetrafluoride formed in a cold trap.[24]

$$3SCl_2 \xrightarrow[45^\circ C]{pyridine/(HF)_x} SF_4 + S_2Cl_2$$

Despite its toxicity, comparable to that of phosgene, and ready hydrolysis to hydrogen fluoride the gaseous sulphur tetrafluoride can easily be handled in dry glass apparatus. Trifluoromethylation reactions are usually carried out in stainless steel autoclaves in the presence of a halogenated solvent to improve solubility of the organic reagent and moderate the vigour of the reaction.

The reaction of a carboxyl group with sulphur tetrafluoride is a two stage process.[22]

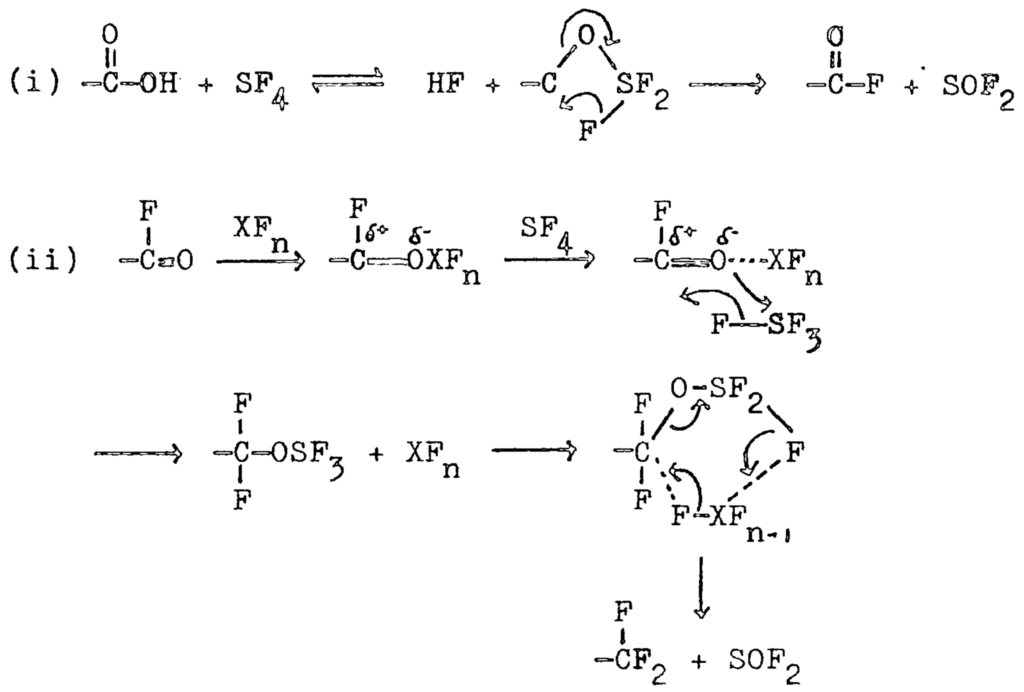
(1) $C_6H_5COOH + SF_4 \longrightarrow C_6H_5COF + HF + SOF_2$

(2) $C_6H_5COF + SF_4 \longrightarrow C_6H_5CF_3 + SOF_2$

The first step, in which the hydroxyl group is replaced by fluorine, occurs at or below room temperature and the acyl fluoride formed may be isolated. The second step, involving replacement of the carbonyl oxygen requires elevated temperatures although in the presence of a Lewis acid catalyst less vigorous conditions are necessary.

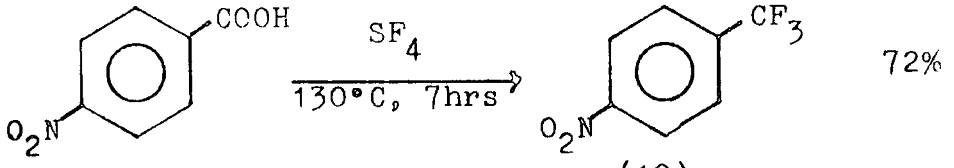
The suggested mechanism, shown in scheme (1.3) is discussed in detail in reference 25. At higher temperatures SF_4 can play the role of XF_n but the efficacy of hydrogen fluoride, produced in the formation of the acyl fluoride, as a catalyst in the second stage was first realised when carboxylic acids were found to react more readily with sulphur tetrafluoride than their anhydrides. The fluorides BF_3, AsF_3, PF_5, and TiF_4 are more potent catalysts and catalytic ability has been related to increased Lewis acidity.[22]

Scheme (1.3) Fluorination of the Carboxyl Group with Sulphur Tetrafluoride



XF_n = Lewis acid catalyst

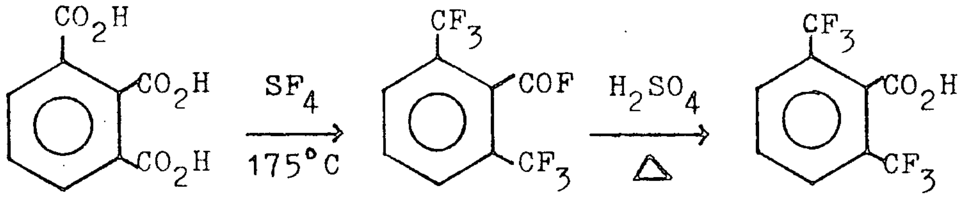
General conditions for the conversion of aryl carboxylic acids with sulphur tetrafluoride involve heating at 120-180°C for 3-24 hours,[25] formation of p-nitrotrifluoromethylbenzene (10) is given as an example.



(10)

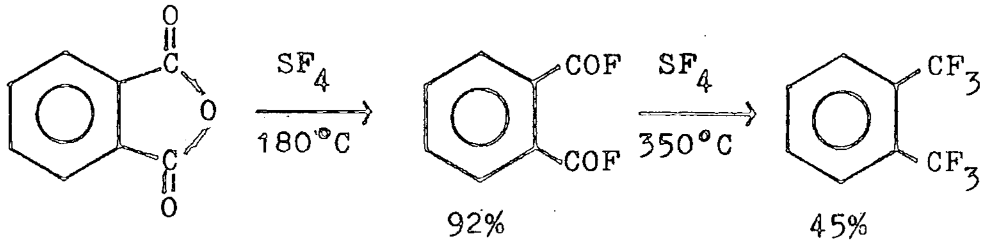
Substituents including F, Cl, Br and NO_2 can be tolerated although fluorine - chlorine exchange has been noted in pyrimidines.[26] As esters are less reactive towards sulphur tetrafluoride they can be used to protect hydroxyl and carboxyl groups. The method applies equally well to benzenoid[27] and heterocyclic systems, thiazoles[28] and even sensitive furans[29,30] have been trifluoromethylated in this way. Examples of these reactions are given in Table (1.B.2).

In reactions with polysubstituted carboxylic acids the degree of fluorination can be controlled by varying the amount of sulphur tetrafluoride. Steric hindrance has been shown to lead to selective reaction at less hindered groups,[31] for example even at the elevated temperature of 340°C a third trifluoromethyl group cannot be introduced into hemimetallic acid (18).



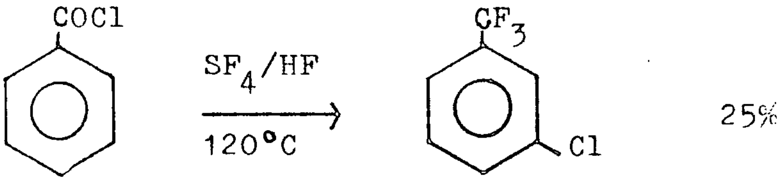
(18)

Acid anhydrides and sodium salts have to be treated much more vigorously than the corresponding acids as the formation of the acyl fluoride produces no hydrogen fluoride to catalyse the second stage of the reaction. At lower temperatures reaction stops after the first stage unless a catalyst is added.[27] Phthalic anhydride (19) must be heated to 350°C to produce 1,2-bis(trifluoromethyl) benzene (20) although the acid fluoride can be formed at 180°C.



(19) (20)

The reaction of benzoyl chloride (21) produces an unexpected product, initial exchange of chlorine by fluorine is followed by further fluorination and also chlorination of the ring forming m-chlorotrifluoromethylbenzene (22).[27] The nature of the chlorinating agent is unknown.

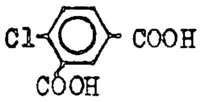
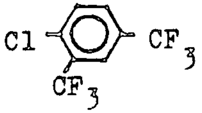
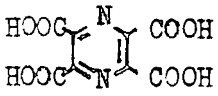


(21) (22)

Esters must be heated at temperatures above 300°C to induce reaction with sulphur tetrafluoride alone, hence their role as protecting groups, but reaction will occur at temperatures as low as 170°C in the presence of hydrogen fluoride and still lower if boron trifluoride is used.[25] Amides are rather more reactive and cleave the carbonyl-nitrogen bond to form acyl fluorides prior to further reaction, although if there is no N-H bond α,α-difluoroamines may be formed.

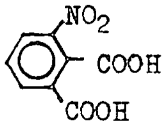
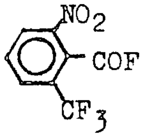
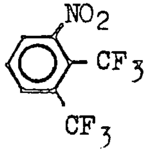
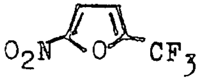
Phenylsulphur trifluoride [32] will also fluorinate

Table (1.B.2) Reaction of Carboxyl Groups with Sulphur Tetrafluoride and its Derivatives

Starting Material	Fluorinating Agent	Conditions	Product	Yield %	Ref.
C_6H_5COOH	SF_4	120°C, 6hr	C_6H_5COF + $C_6H_5CF_3$	41 22	27
$1,2,4,6\text{-}C_6H_2(COOH)_4$	SF_4	150°C, 6hr	$1,2,4,6\text{-}C_6H_2(CF_3)_4$	77	27
$C_6H_5COOCH_3$	SF_4	300°C, 6hr	$C_6H_5CF_3$	55	27
$C_6H_5CONH_2$	SF_4	150°C, 8hr	$C_6H_5CF_3$	13	27
$C_6H_5COCF_3$	SF_4	100°C, 8hr	$C_6H_5CF_2CF_3$	65	27
	SF_4	150°C, 8hr		62	27
	SF_4	150°C, 6hr		20	27

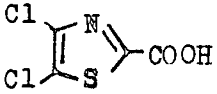
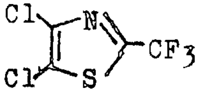
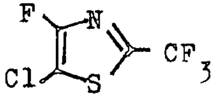
continued

Table (1.B.2) continued

Starting Material	Fluorinating Agent	Conditions	Product	Yield %	Ref.
	SF_4	100-140° C, 8hr		85	31
			+ 	7	
	SF_4	120°C, 7hr		57	33
$1,4\text{-}C_6F_4(COOH)_2$	SF_4	200°C, 24hr	$1,4\text{-}C_6F_4(CF_3)_2$	54	34
$4\text{-}C_5H_4NCOOH$	SF_4/HF	120°C, 8hr	$4\text{-}C_5H_4NCF_3$	57	35

continued

Table (1.3.2) continued

Starting Material	Fluorinating Agent	Conditions	Product	Yield %	Ref.
	SF_4/HF	100°C, 15hr	 + 91 : 9 	-	36
$C_6H_5C(=O)Cl$	$C_6H_5SF_3$	100-115°C, 5hr	$C_6H_5CF_3$	11	32

carboxyl derivatives forming trifluoromethylated compounds and has the advantage of being a liquid which can be used for small scale reactions at atmospheric pressure. It is prepared in high yield in a reaction between phenyl disulphide and silver difluoride.

$$(C_6H_5S)_2 \quad + \quad 6AgF_2 \xrightarrow[CClF_2CCl_2F]{} \underset{66\%}{2C_6H_5SF_3} \quad + \quad 6AgF$$

Although less toxic than sulphur tetrafluoride it still liberates hydrogen fluoride and so suitably inert reaction vessels must be used. Reactions with carboxylic acids are carried out at 120-150°C, if necessary a non-volatile catalyst such as titanium tetrafluoride can be added.

1.B.iii. Perfluoroalkylphenyliodonium Trifluoromethylsulphonates and Related Reagents

Perfluoroalkylphenyliodonium trifluoromethylsulphonates (FITS reagents) can be used for the introduction of perfluoroalkyl groups into aromatic compounds under very mild conditions.[37] As shown in Scheme (1.4) they are prepared by reaction of perfluoroalkyl iodides with trifluoroacetic anhydride and hydrogen peroxide to form bis(trifluoroacetoxy)iodoperfluoroalkanes, which on further reaction with triflic acid form the FITS reagent.[38] The nature of the perfluoroalkyl group is shown by a number suffixed to the name FITS, hence pentafluoroethylphenyliodonium trifluoromethylsulphonate is referred to as FITS-2 as the ethyl group contains two carbon atoms.

Scheme (1.4) <u>Preparation of FITS reagents</u>

$$R_fI \xrightarrow[0^{\circ}C-r.t., 1-24hrs]{30\%H_2O_2, (CF_3CO)_2O} R_fI(OCOCF_3)_2 \qquad 84-98\%$$

$$R_fI(OCOCF_3)_2 \xrightarrow[0^{\circ}C(3hrs), r.t.(12hrs)]{CF_3SO_3H, benzene, CF_3CO_2H} R_fI(Ph)OSO_2CF_3$$

67-85%

FITS-m

$R_f = C_mF_{2m=1}$

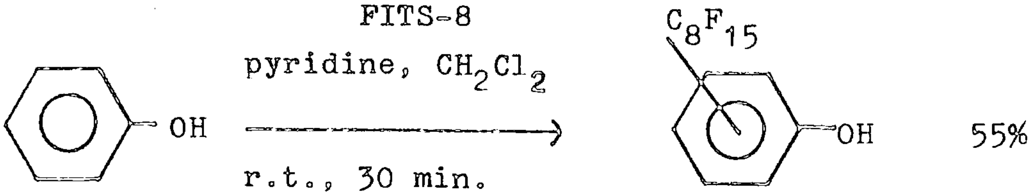
$Ph = C_6H_5$

In the presence of pyridine as a weak base and a solvent such as acetonitrile or dichloromethane FITS reagents react with aromatic compounds substituting a hydrogen with a perfluoroalkyl group. The temperature necessary depends on the electron density of the π system. Phenol, furan, thiophene, and pyrrole with a high π electron density react smoothly at 0°C to room temperature whereas π electron deficient compounds react in refluxing solvent. Yields are usually high and benzene (<u>23</u>) can be converted almost quantitively.

$$C_6H_6 \xrightarrow[reflux, 60 min]{FITS-6, pyridine} C_6H_5C_6F_{13} \qquad 97\%$$

(<u>23</u>)

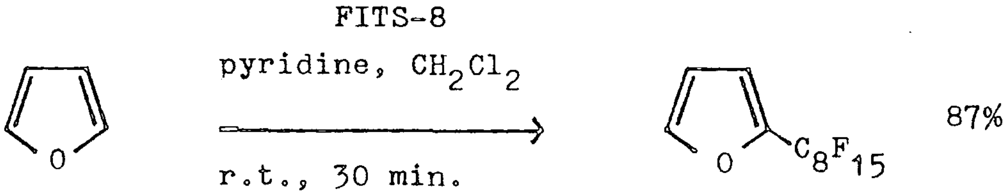
Perfluoroalkylation of most substituted benzenes results in a mixture of isomers. Phenol (<u>24</u>) reacts at room temperature with FITS-8 yielding a mixture of ortho-, para-, and meta-isomers.



(24)

o:m:p = 4·1:1:4·6

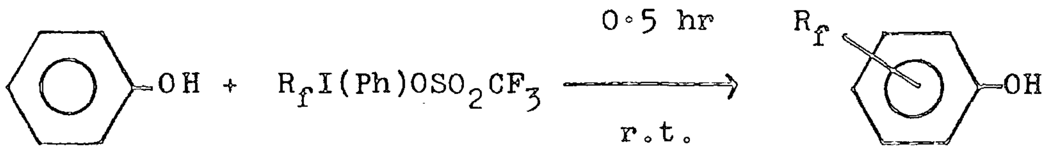
Furan (25) is perfluoroalkylated only in the 2-position as are thiophene and pyrrole.



(25)

Further examples are given in Table (1.B.3).

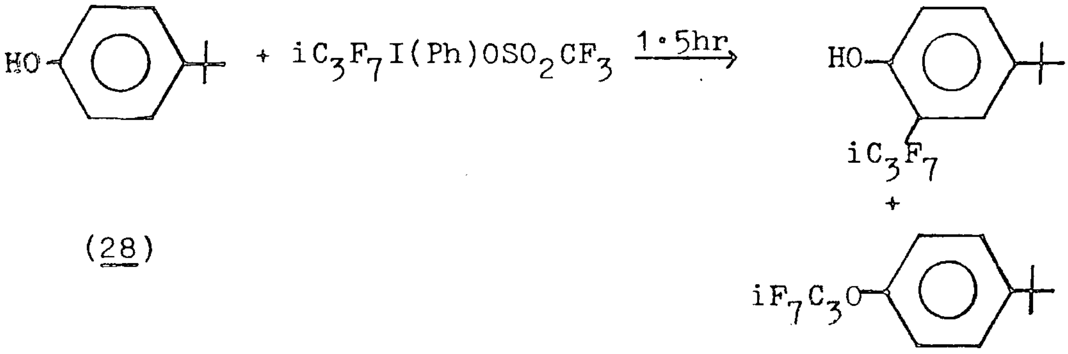
The isomer distribution in phenol can be affected by the bulkiness of the FITS reagent and it is possible to force perfluorolkylation onto the oxygen rather than carbon[39]. The effect of steric repulsion between the hydroxyl group and FITS can be shown by comparing the o/p ratio in reaction between FITS-2 (26) and FITS-3i (27).



$R_f = C_2F_5$ (26) o/p = 1

$R_f = iC_3F_7$ (27) o/p = 0·67

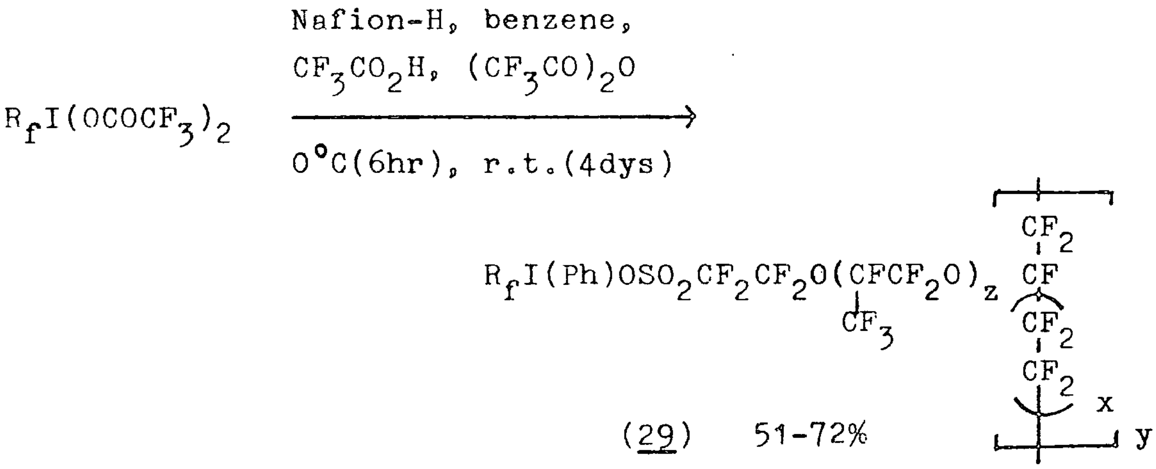
The proportion of ortho-isomer formed decreases when the more bulky perfluoroisopropyl group is introduced. If the para position is blocked as in 4-t-butylphenol (28) the perfluoroisopropyl group can be forced to substitute the phenolic hydrogen.



(28)

The phenol substituted product is the major component at room temperature and predominates in a high temperature reaction. The irrelevance of solvent polarity combined with the very small amount of phenolic substitution when FITS-3 is used in the same reaction confirm that this is a steric effect.

Despite the high yields and mild conditions the use of FITS for perfluoroalkylation of aromatic compounds had two practical disadvantages. The isolation of the FITS reagent after preparation required many recrystallisations, and the separation of products and recovery of the expensive triflic acid after the perfluoroalkylation reaction was difficult. These difficulties have been overcome with the introduction of polymer supported FITS,[40] in which the FITS reagent is immobilised on a perfluorosulphonic acid resin Nafion-H. The Nafion is treated with a bis(trifluoroacetoxy)iodoperfluoroalkane and benzene in trifluoroacetic acid / anhydride and the FITS-Nafion resin (29) is filtered off.



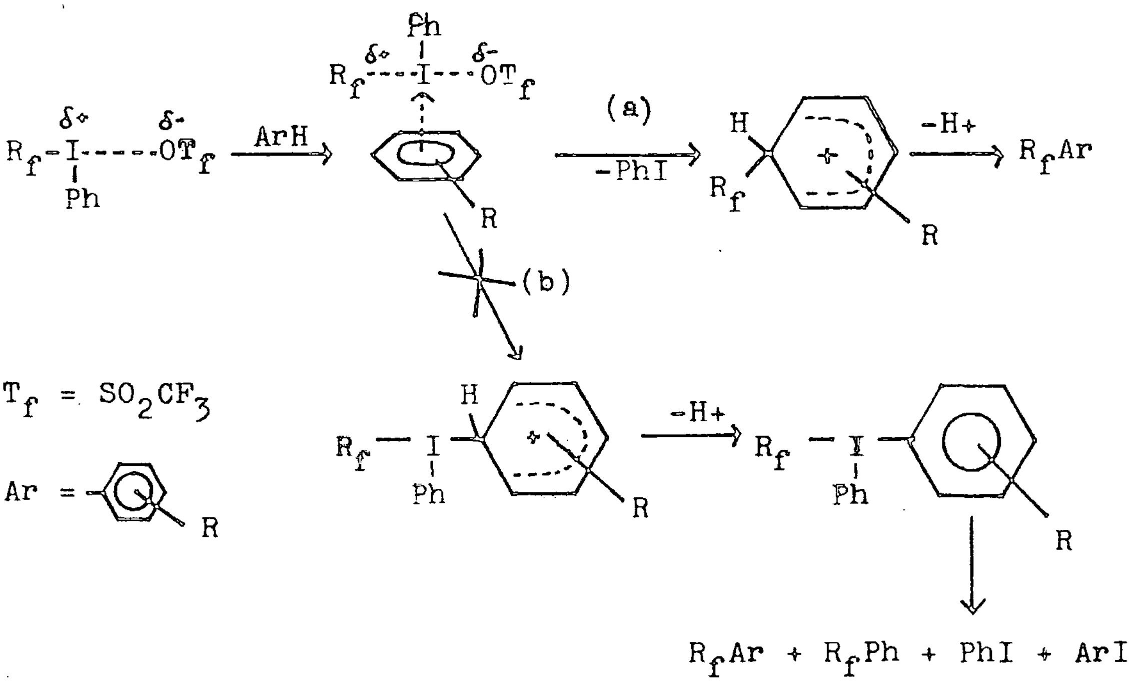
$$R_fI(OCOCF_3)_2 \xrightarrow[0^\circ C(6hr),\ r.t.(4dys)]{Nafion\text{-}H,\ benzene,\ CF_3CO_2H,\ (CF_3CO)_2O} R_fI(Ph)OSO_2CF_2CF_2O(\underset{CF_3}{CF}CF_2O)_z\,CF\!-\!\left[(CF_2CF_2)_x\right]_y$$

(29) 51-72%

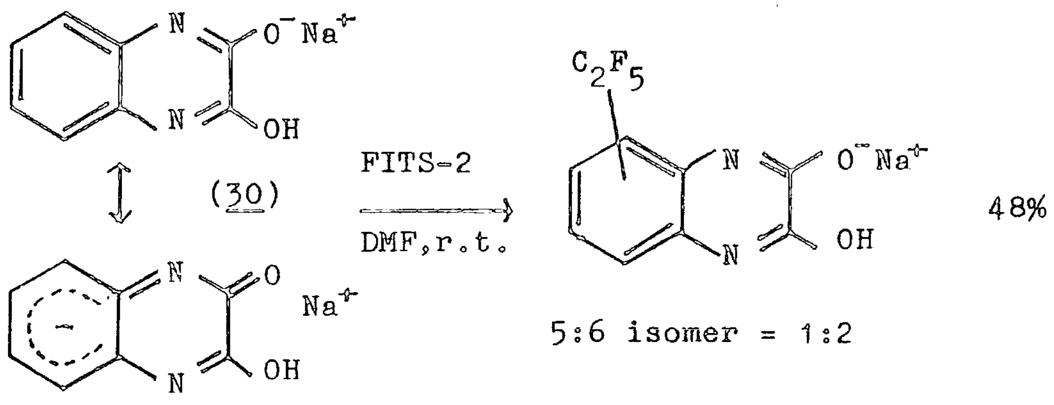
The perfluoroalkylation proceeds exactly as with the unbound FITS, the perfluorosulphonic acid resin taking the place of the triflate group. The product is easily separable by filtration from the insoluble resin which is recovered as the pyridinium salt and regenerated by treatment with acid.

The proposed mechanism [37] for perfluoroalkylation with FITS is shown in Scheme (1.5). The first step is assumed to be formation of a π complex between the FITS and aromatic compound, of the two possible reactions of the complex (b) is discarded as R_f-Ph and ArI are not observed as reaction products. The high proportion of ortho- and para-isomers formed from π electron rich aromatic compounds supports route (a).

Scheme (1·5) <u>Mechanism for the perfluoroalkylation of aromatics with FITS</u>



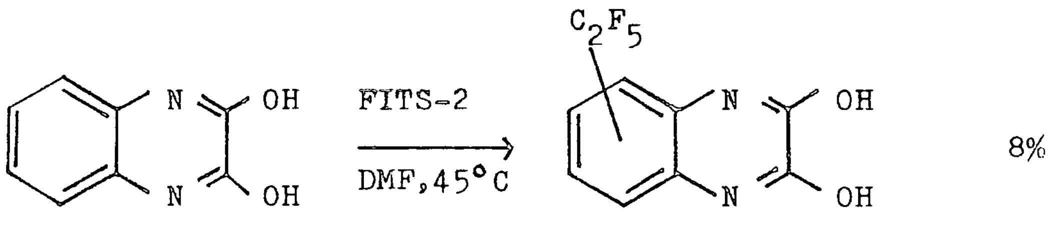
The imtermediate π complex can explain the ready reactivity of the sodium salt of quinoxalinedione (<u>30</u>) compared with quinoxalinedione (<u>31</u>) itself.[37]



(30)

5:6 isomer = 1:2

48%



(31)

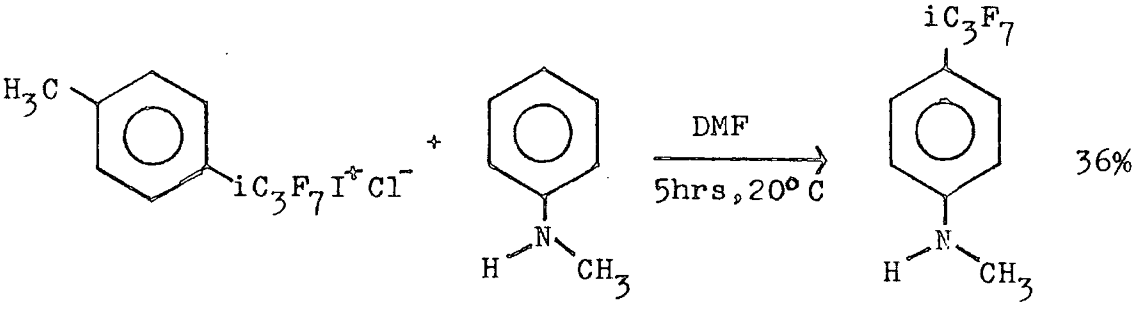
5:6 isomer = 1:2

8%

In the sodium salt (30) there is an increase of π electron density on the benzene ring which promotes complex formation. Significant formation of ortho- and para-isomers in the reaction of methylbenzoate suggests that the reaction of π electron deficient aromatic compounds is accompanied by free radical attack of R_f° generated by homogeneous cleavage of the R_f-I bond in FITS.

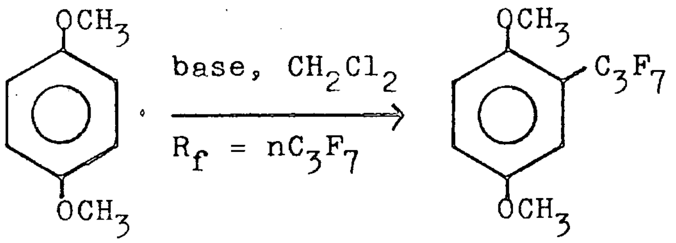
Compounds related to FITS have been used in similar reactions. Perfluoroalkylphenyliodonium sulphates (FIS) react similarly to FITS but yields are generally lower.^{37} This is attributed to the facts that sulphate is a poorer leaving group than triflate and FIS is generally less soluble in organic solvents than FITS.

Perfluoroisopropyl-p-tolyliodonium chloride has been used to introduce the perfluoroisopropyl group into methylaminobenzene (32).[41] The yield is however poor and no attempt was made to extend the process to other aromatic compounds.



(32)

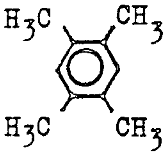
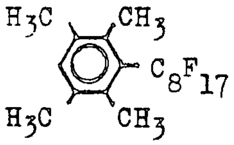
The relative reactivity of the three perfluoroalkylating agents was demonstrated by the reaction with 1,4-dimethoxybenzene (33). The yields show FIS and FITS to be far superior to perfluoroalkyl-p-tolyliodonium chloride.[37]



(33)

	% yield	temp.	time (min.)
FITS-3	58	r.t.	15
FIS-3	63	reflux	20
R_fI(p-tolyl)Cl	6	reflux	30

Table (1.B.3) Perfluoroalkylphenyliodonium Trifluoromethyltoluenesulphonates and Related Reagents

Starting Material		Conditions	Product	Isomer Ratio o : m : p	Yield* %	Ref.
C_6H_5	FITS-6	pyridine, reflux, 60min	$C_6F_{13}.C_6H_5$		97(81)	37
$C_6H_5.OH$	FITS-8	pyridine, CH_2Cl_2, r.t., 10min	$C_8F_{17}.C_6H_4.OH$	4.1 : 4 : 4.6	55(26)	37
$C_6H_5.N(CH_3)_2$	FITS-8	CH_3CN, reflux, 60min	$C_8F_{17}.C_6H_4.N(CH_3)_2$	1 : 0 : 2.7	-(37)	37
$C_6H_5.COOCH_3$	FITS-8	pyridine, CH_3CN, r.t., 60min	$C_8F_{17}.C_6H_4.COOCH_3$	1 : 1 : 1.3	54(35)	37
C_4H_4S	FITS-8	pyridine, CH_2Cl_2, r.t., 15min	$2\text{-}C_8F_{17}.C_4H_3S$		73(40)	37
	FITS-8	pyridine, CH_3CN, 60°C, 7min			32	37
C_6H_6	FIS-6	pyridine, C_6H_6, reflux, 90min	$C_6F_{13}.C_6H_5$		70	37
C_4H_4S	FIS-8	pyridine, CH_2Cl_2, 20min	$2\text{-}C_8F_{17}.C_4H_3S$		60	37
C_6H_6	FITS-8 Nafion	pyridine, 80°C, 120min	$C_8F_{17}.C_6H_5$		89	40
C_4H_4S	FITS-8 Nafion	pyridine, 80°C, 120min	$2\text{-}C_8F_{17}.C_4H_3S$		95	40

* g.l.c. yield (isolated yield)

1.B.iv. Sources of Perfluoroalkyl Radicals

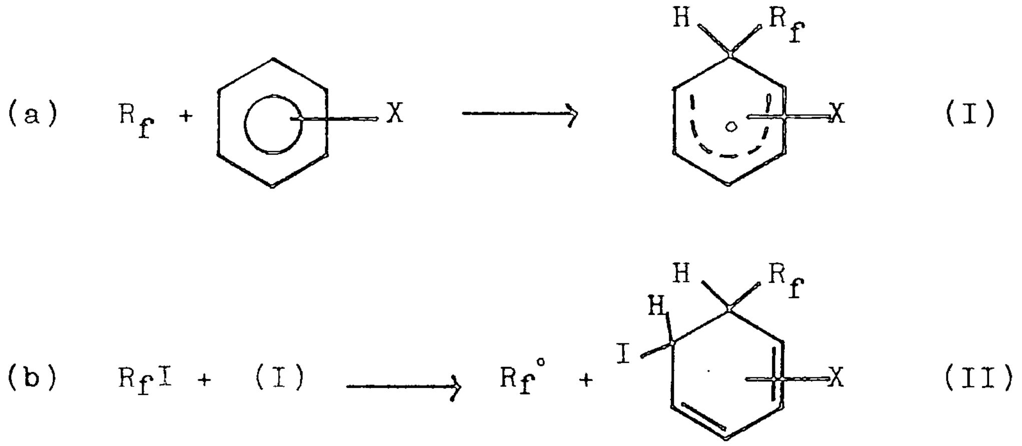
The most common method of generating perfluoroalkyl radicals for synthetic purposes is by homolytic cleavage of the perfluoroalkyl iodide carbon-iodine bond.[42,43] Radicals produced by photolysis of perfluoroalkylsulphinyl chlorides have also been used to produce perfluoroalkyl-aromatic compounds.[44] Perfluoroketones and fluoroazoalkanes yield perfluoroalkyl radicals on pyrolysis but radicals from these sources have been used mainly for mechanistic studies rather than synthesis. The results of these investigations into the structure and properties of perfluoroalkyl radicals are discussed in reference 7. Other methods for the production of perfluoroalkyl radicals which will be discussed further are electrochemical processes,[45] plasma generation,[46] and the reaction between perfluoroacyl chlorides and nickel carbonyl.[47]

1.B.iv.a. Perfluoroalkyl Iodides

Perfluoroalkyl radicals are produced from perfluoroalkyl iodides by homolytic cleavage of the carbon-iodine bond. The necessary energy can be produced either thermally[42] or photochemically.[43] The radical initiator benzoyl peroxide will not induce a reaction between trifluoromethyl iodide and bromobenzene[42] but bis-t-butyl peroxide has been used to initiate the perfluoroalkylation of a range of aromatic compounds.[48]

It is generally agreed [43,49] that the first step in the perfluoroalkylation reaction is the formation of a sigma complex between the arene and perfluoroalkyl radical but the rest of the mechanism outlined in Scheme (1.6) is less certain.

Scheme (1.6) <u>The Radical Perfluoroalkylation of Aromatic Compounds</u> [43]



(c) $\text{(II)} \longrightarrow XC_6H_4R_f + HI$

(d) $HI + R_fI \longrightarrow I_2 + R_fH$

(e) $\text{(I)} + R_fI \longrightarrow XC_6H_4R_f + R_f^\circ + HI$

(f) $\text{(I)} + R_f^\circ \longrightarrow XC_6H_4R_f + R_fH$

(g) $\text{(I)} + I^\circ \longrightarrow XC_6H_4R_f + HI$

(h) $HI \xrightarrow[h\nu]{} H^\circ + I^\circ \xrightarrow[Hg]{} HgI$

A chain mechanism propagated by steps (b) - (d) is favoured for the thermally induced process [49] although (e) is an alternative to steps (c) and (b). Fluoroform is formed in appreciable yields in both thermal reactions and photochemical reactions in which mercury is not used. As the complex radical (I) and a perfluoroalkyl radical are unlikely to meet in the liquid phase or at other than low pressures in the gaseous phase the fluoroform is more likely to arise from step (d) rather than (f). Photochemical reactions with mercury give rise to very little fluoroform and it is suggested that in this case the reaction proceeds via steps (c), (e) and/or (g).[43] The hydrogen iodide produced is photochemically decomposed (h) and as the iodine radicals are consumed by the mercury there is no possibility of recombination and fluoroform formation. The hydrogen radical is assumed to be absorbed by the small amounts of by-products which form the high boiling residues.

The use of perfluoroalkyl radicals generated by thermal cleavage of perfluoroalkyl iodides in the direct perfluoroalkylation of aromatic compounds was first described by Tiers in 1960.[42]

$$\mathrm{ArH} + 2\mathrm{R_fI} \xrightarrow{250^\circ\mathrm{C}} \mathrm{R_fAr} + \mathrm{R_fH} + \mathrm{I_2}$$

The method involves heating the aromatic compound and perfluoroalkyl iodide in a sealed system at 250°C and its scope is limited only by the stability of the arene under such vigorous conditions. The yield of the perfluoroalkyl aromatic compound is usually around 60-65%. Disubstitution also occurs to a varying extent dependent on the ratios of reactants, when there is no excess of aromatic compound the yield of the disubstituted product can be as high as 25%. A 2:1 mixture of perfluoroheptyl iodide and benzene gives rise to a mixture of mono (34) and bis (35) perfluoroheptyl benzenes on thermolysis at 250°C.

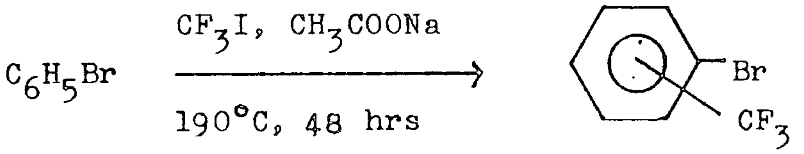
$$C_6H_6 \xrightarrow[C_7F_{15}I]{250^{\circ}C, 15hrs} \underset{(\underline{34})}{\underset{62\%}{C_6H_5C_7F_{15}}} + \underset{(\underline{35})}{\underset{26\%}{C_6H_4(C_7F_{15})_2}} + C_7F_{15}H$$

Recently a comprehensive study of the reaction[50] has shown that the perfluoroalkylation of benzene with perfluorodecyl iodide can take place at temperatures as low as 190°C yielding perfluorodecylbenzene (36) and 1-H-perfluorodecane (37) as the main products, although traces of other products were formed along with an insoluble black tar composed mainly of iodine and decomposition products.

$$C_6H_6 + C_{10}F_{21}I \xrightarrow[190^{\circ}C, 6hrs]{CH_3COONa} \underset{(\underline{36})}{\underset{70\%}{C_6H_5C_{10}F_{21}}} + \underset{(\underline{37})}{\underset{5\%}{C_{10}F_{21}H}}$$

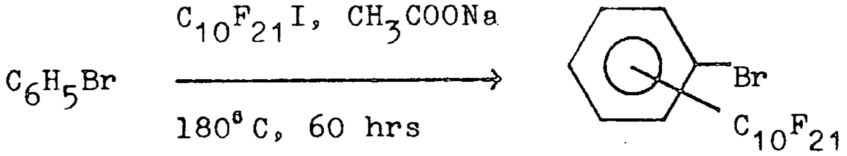
The yield of perfluoroalkylated product is higher at this temperature and the amounts of 1-H-perfluoroalkane and the bis-perfluoroalkylated product are reduced. The addition of sodium acetate, which increases the yield of perfluoroalkylated product at 190°C, has no effect on the yield at higher temperatures.

Benzenes with substituents including halogen, perfluoroalkyl, and nitrile have also been perfluoroalkylated in this way[42] but give rise to isomeric mixtures of perfluoroalkyl arenes. The isomer distribution in the perfluoroalkylation of bromobenzene has been studied and a marked difference noted between the isomer ratios in the case of bromotrifluoromethylbenzenes (38) and bromoperfluorodecylbenzenes (39).[50]



(38)

o 48% m 30% p 22% (61%)

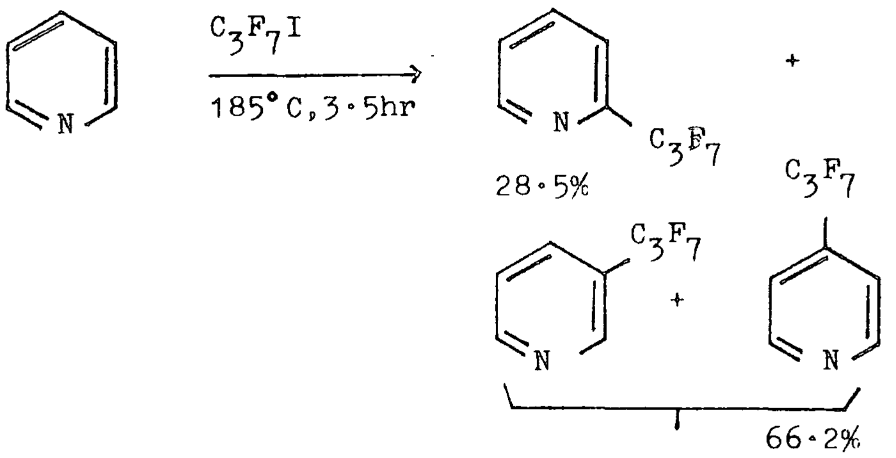


(39)

o 10% m 49% p 41% (65%)

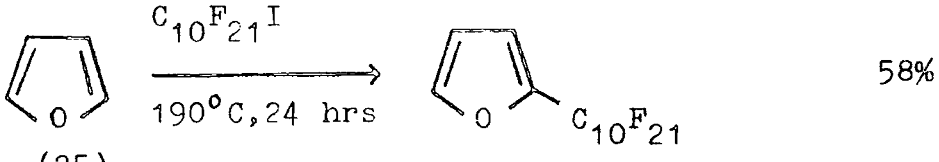
Steric hindrance could explain the reduced amount of ortho product obtained in reaction with perfluorodecyl iodide but as there is very little difference in the distributions from fluoro- and iodobenzenes it is unlikely to be the whole explanation.

Interest in the application of this method to the perfluoroalkylation of nitrogen heterocycles has arisen from their usage as dyestuffs. Pyridine can be perfluoroalkylated under relatively mild conditions if excess base is used to neutralise the hydrogen iodide formed. The mixture of heptafluoropyridines (<u>40 a-c</u>) formed from the reaction between pyridine and heptafluoropropyl iodide at 185°C can be partially separated on the basis of their bascities[51].

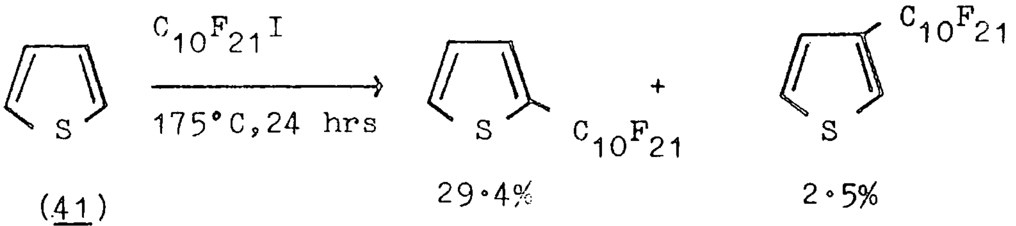


(<u>40a-c</u>)

Picolines[52] and thiazolines[53] have also been reacted with heptafluoropropyl iodide under similar conditions. Pyrrole, indole, and imidazole yield no perfluoroalkylated products but as large quantities of black tar are formed it is suggested that these heterocycles are readily polymerised under the reaction conditions.[50] It has proved possible however to perfluoroalkylate N-methyl pyrroles in moderate yields.[54] Furan (25) is perfluoroalkylated entirely, and thiophene (41) predominantly, in the 2-position. In both cases the yields are low compared to benzene and insoluble black tars are formed.



(25)



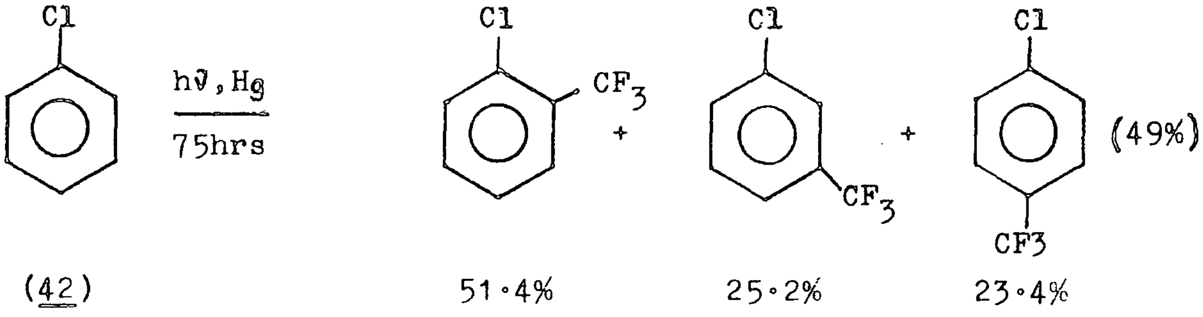
(41)

Further examples of thermally promoted reactions between aromatic compounds and perfluoroalkyl iodides are listed in Table (1.B.4).

The initial attempts to induce a reaction between halobenzenes and trifluoromethyl iodide using ultraviolet irradiation failed to produce any halotrifluoromethylbenzenes.[49] The photochemical process was found to be proceeding at a very slow rate presumably because recombination of the iodine atoms and trifluoromethyl radicals was occuring preferentially to further reaction. Mercury was added to remove the iodine atoms and provide a greater supply of trifluoromethyl radicals.[43]

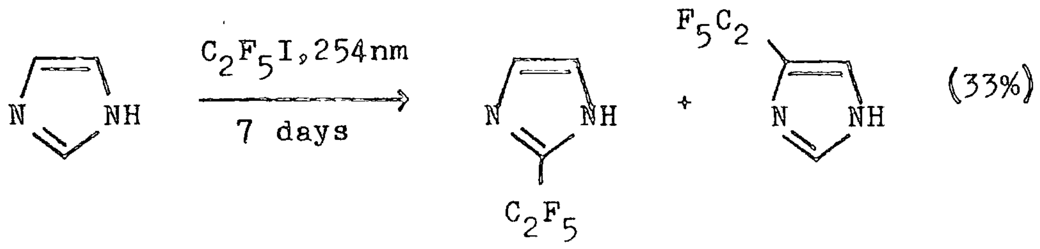
$$CF_3I \rightleftharpoons CF_3^{\circ} + I^{\circ} \xrightarrow{Hg} HgI \longrightarrow HgI_2$$

The yields were further improved by using a five fold excess of halobenzene and a pyrex vessel, as when silica was used a greater amount of products arising from the breakdown of the aromatic carbon-halogen bond were observed. Irradiation of chlorobenzene (42) under these conditions gave a mixture of isomers in 49% yield and trace amounts of other products.



(42)

Pyridine,[55] pyrrole[55] and various imidazoles[56] have been trifluoromethylated without the addition of mercury. Photochemical reactions are especially useful in the preparation of perfluoroalkyl substituted imidazoles as the more complicated precursors cannot survive the high temperatures at which the thermally initiated reactions are carried out. The perfluoroalkyl iodide and a fivefold excess of the imidazole in methanolic solution are irradiated for a week resulting in an isomeric mixture of perfluoroalkylated products in upto 80% yield. The 4-(or 5-) isomer always predominates over the 2-isomer and this preference is more marked for the C_2-C_{10} radicals than with the less electrophilic trifluoromethyl radical. The reaction has been carried out with a range of perfluoroalkyl iodides and substituted imidazoles. The pentafluoroethylation of imidazole (43) is shown here and more examples can be found in Table (1.B.4)

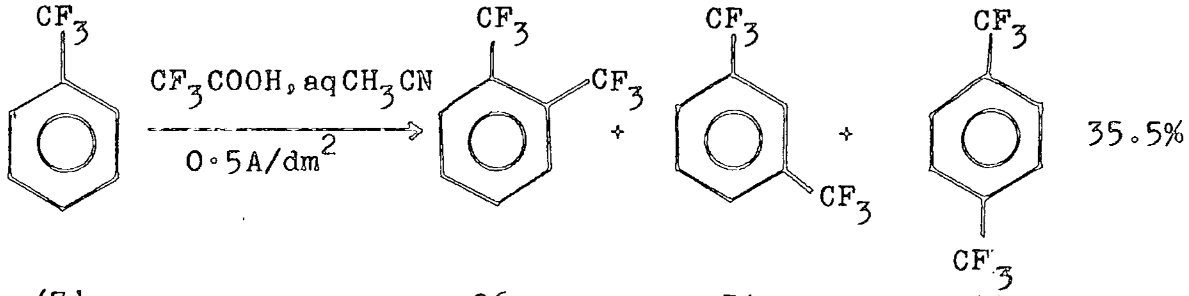


(43) 25% 46%

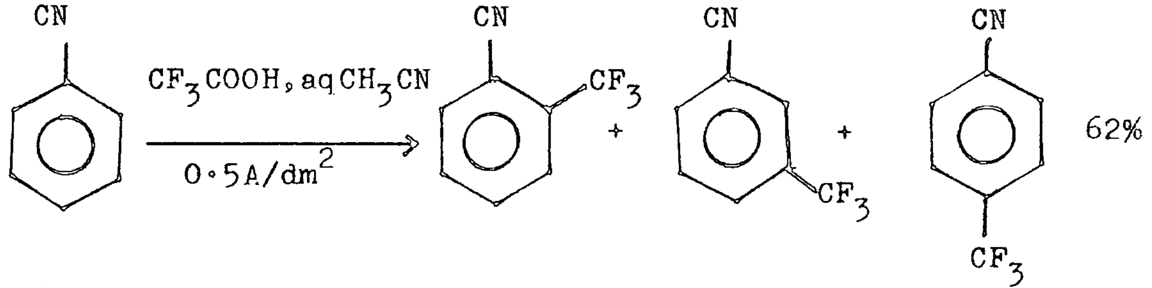
Gamma ray initiation of radical formation has proved useful in this reaction but is less easy[56] to use and resulted in hydrogen formation and a consequent pressure build-up.

1.B.iv.b. Electrochemical process

The electrolysis of trifluoroacetic acid and substituted benzenes in aqueous acetonitrile results in the formation of trifluoromethylated products.[45] Benzene itself is trifluoromethylated in very low yield and a marked amount of tarring occurs but when electron withdrawing substituents are present the yields are quite high, although conversion is low because of the difficulty of attacking the compounds with electrophilic radicals. Trifluoromethylbenzene (7) and benzonitrile (44) are trifluoromethylated in 35.5% and 65% yields respectively producing isomeric mixtures.

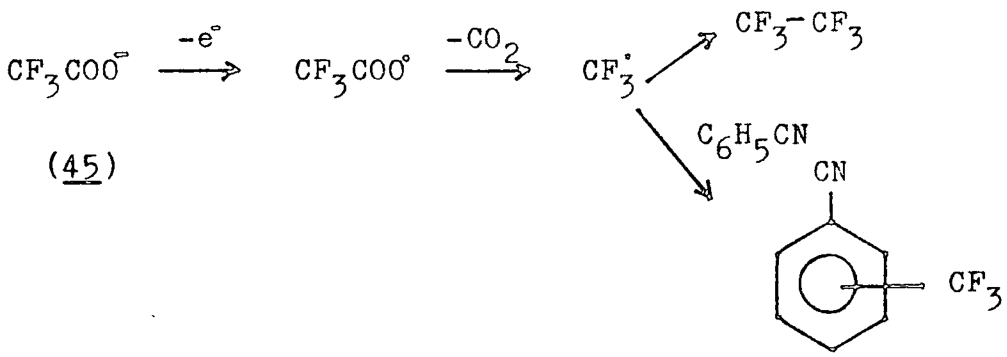


(7) 26 : 34 : 40



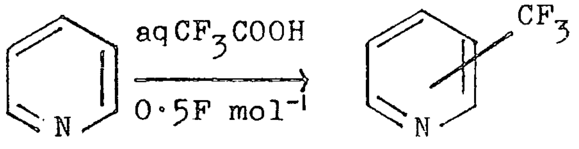
(44) 44 : 16 : 40

The isomeric ratios and parallel formation of carbon dioxide and hexafluoroethane suggest that the trifluoroacetate ion (45) is oxidised at the anode forming a radical which then decarboxylates leaving the trifluoromethyl radical which can either dimerise or attack the arene.



(45)

Direct proof of this has been gained by a study of polarisation curves for the system. Pyridine (46) has also been trifluoromethylated electrochemically.[57] The efficiency of the substitution and isomeric ratios are dependent upon the amount of trifluoroacetic acid used but the highest yield obtained was 7%.



α 27% β 38% γ 35%

(<u>46</u>) (7%)

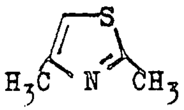
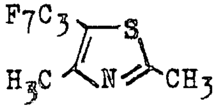
1.B.iv.c. Plasma Generated Radicals

Extremely reactive trifluoromethyl radicals can be generated by cleavage of hexafluoroethane in a low temperature radio frequency discharge.[58] This process has the advantage of producing highly reactive radicals at or near room temperature so that decomposition of the substrate molecule and products formed by reaction with the trifluoromethyl radical is less likely to be a problem. This method, previously used to produce organometallic compounds, has been applied to the formation of trifluoromethylbenzene from bromobenzene (<u>16</u>).[46]

$$CF_3^{\circ} + \underset{(\underline{16})}{C_6H_5Br} \longrightarrow \underset{15\%}{C_6H_5CF_3} + \underset{60\%}{C_6H_5F}$$

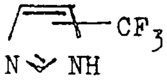
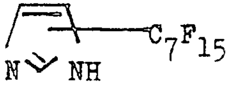
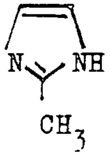
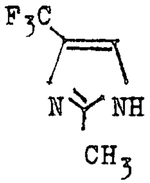
The origin of the fluorobenzene is uncertain but it is suggested that its formation might result from

Table (1.B.4) Radicals as a Source of the Perfluoroalkyl Group

Arene	Rf° Source	Conditions	Product		Isomer		Yield	Ref.
				2 (o)	3 (m)	4 (p)	%	
C_6H_6	$C_8F_{17}SOCl$	120°C,21.5hr,uν	$C_6H_5.C_8F_{17}$				25	44
C_6H_6	C_4F_9I	,10hr,$((CH_3)_3CO)_2$	$C_6H_5.C_4F_9$				16	48
$Cl.C_6H_5$	$C_{10}F_{21}I$	210°C,72hr, H_3COONa	$Cl.C_6H_4.C_{10}F_{21}$	(18)	(44)	(37)	79	50
$I.C_6H_5$	$C_{10}F_{21}I$	210°C,24hr, H_3COONa	$I.C_6H_4.C_{10}F_{21}$	(13)	(49)	(38)	50	50
C_5H_5N	$C_{10}F_{21}I$	200°C,24hr	$C_5H_4N.C_{10}F_{21}$	51	40	9	65	50
$4\text{-}CH_3.C_5H_4N$	C_3F_7I	175°C,3.5hr	$4\text{-}CH_3.C_5H_3N.C_3F_7$	74	26		63	52
$N\text{-}CH_3.C_4H_4N$	C_2F_5I	190°C, 3hr	$N\text{-}CH_3.C_4H_3N.C_2F_5$	100			30	54
	C_3F_7I	200°C					50	53
C_5H_5N	CF_3I	hν ,72hr	$C_5H_4N.CF_3$	47	33	20	81	55

continued

Table (1.B.4) continued

Arene	Rf° Source	Conditions	Product	Isomer 2 (o)	 3 (m)	 4 (p)	Yield %	Ref.
C_4H_4NH	CF_3I	hν ,48hr	$C_4H_3NH.CF_3$	100			33	55
C_6H_6	CF_3I	hν ,100hr	$C_6H_5.CF_3$				65	43
	CF_3I	hν ,168hr		32%		47%	-	56
	$C_7F_{15}I$	hν ,168hr		14%		34%	-	56
	CF_3I	hν ,168hr					95	56
$CF_3.C_6H_5$	C_3F_7COCl	150°C,8hr,$Ni(CO)_4$	$CF_3.C_6H_4.C_3F_7$	mixture not separated			30	47
$CH_3.C_6H_5$	C_3F_7COCl	150°C,12hr,$Ni(CO)_4$	$CH_3.C_6H_4.C_3F_7$	mixture not separated			70	47

elimination of difluorocarbene from a vibrationally excited trifluoromethyl compound.

1.B.iv.d. Perfluoroacyl Chlorides and Nickel Carbonyl

Perfluoroacyl chlorides and nickel carbonyl form fluorinated products derived from perfluoroacyl or perfluoroalkyl radicals and polyfluorocarbenes. The nature of the product depends upon the conditions and reactant.[47] In reaction with substituted benzenes at 150°C perfluoroalkyl aromatic compounds are formed in yields ranging from 30-80%.

$$ArH + R_fCOCl + Ni(CO)_4 \longrightarrow ArR_f + R_fH + NiCl_2 + CO$$

Heptafluoropropylbenzene (47) can be formed in 70-80% yield when the ratio of benzene to perfluorobutyryl chloride is about ten. A reduction in this ratio leads to formation of the bis substituted product and a reduced yield of the monosubstituted compound.

$$C_6H_6 + C_3F_7COCl \xrightarrow[150^\circ C, 6hrs]{Ni(CO)_4} \underset{(47)}{C_6H_5C_3F_7} \quad 70\text{-}80\%$$

The perfluoroalkylation of the substituted benzenes led to the production of isomeric mixtures which were not separated. Examples of these reactions can be found in Table (1.B.4.)

1.B.v. Organometallic Compounds as a Source of the Perfluoroalkyl Group

Whilst organometallic compounds generally have many applications in organic synthesis the use of perfluoroalkyl metallic reagents has been much more limited.

Perfluoroalkyl lithiums and Grignard reagents are too unstable to be used, except in special circumstances when they are generated in the presence of a reactant, as decomposition occurs readily by elimination of metal fluoride.[59] Trifluoromethyl lithium (<u>48</u>) may have only a fleeting existence and readily loses lithium fluoride forming difluorocarbene. Higher homologs (<u>49</u>) decompose forming fluoroalkenes.

$$\underset{(\underline{48})}{CF_3Li} \xrightarrow{-LiF} (:CF_2) \longrightarrow CF_2{=}CF_2$$

$$\underset{(\underline{49})}{CF_3(CF_2)_nCF_2CF_2Li} \xrightarrow{-LiF} CF_3(CF_2)_nCF{=}CF_2$$

Conversely other perfluoroalkyl metallic reagents have been considered to be too stable. Perfluoroalkyl mercurials, the first reported fluoroorganometallics, have proved disappointing synthetically but bis-(trifluoromethyl) cadmium-base has been used as a source of difluorocarbene and a ligand exchange reagent.[60] Perfluoroalkyl copper and zinc compounds have both been used in perfluoroalkylation of arenes and will be described in more detail. As interest in trifluoromethyl compounds has increased there has been a recent revival in the preparation of trifluoromethylmetallic compounds as potential sources of the trifluoromethyl group.[61]

1.B.v.a. Organocopper Compounds

Perfluoroalkyl copper compounds can be used to replace either halogen, usually iodine, or hydrogen in aromatic compounds with the perfluoroalkyl group and these two reactions will be discussed separately.

McLoughlin and Thrower developed a method for introduction of a perfluoroalkyl group into a specific site in an arene by a copper promoted reaction between a perfluoroalkyl iodide and iodoaromatic compound.[62] Substitution was found to take place exclusively at the site occupied by iodine.

$$R_fI + ArI \xrightarrow{Cu} R_fAr + CuI. \quad R_f = C_mF_{2m-1} \quad m \geqslant 3.$$

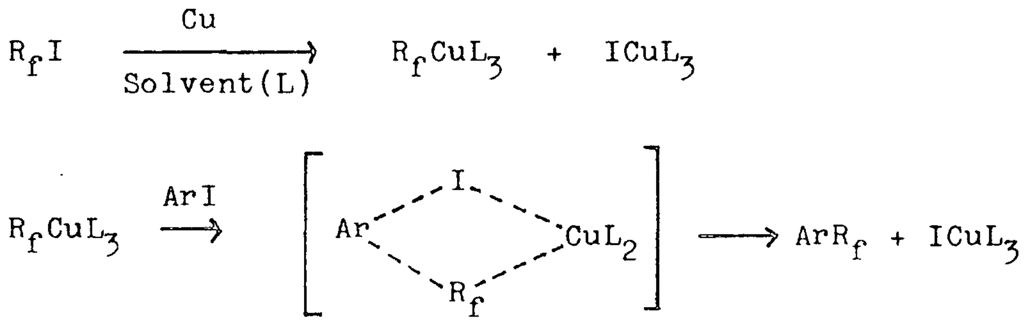
It became apparent that organocopper intermediates were involved when it was shown that the reaction could be carried out in two stages. The first stage involves stirring the copper and perfluoroalkyl iodide in dimethylsulphoxide at 120°C forming a homogeneous perfluoroalkyl copper solution. Subsequent treatment with iodobenzene gives the perfluoroalkylbenzene in 60-70% yield.

1. $$Cu + R_fI \xrightarrow[120^\circ C]{DMSO/N_2} R_fCu$$

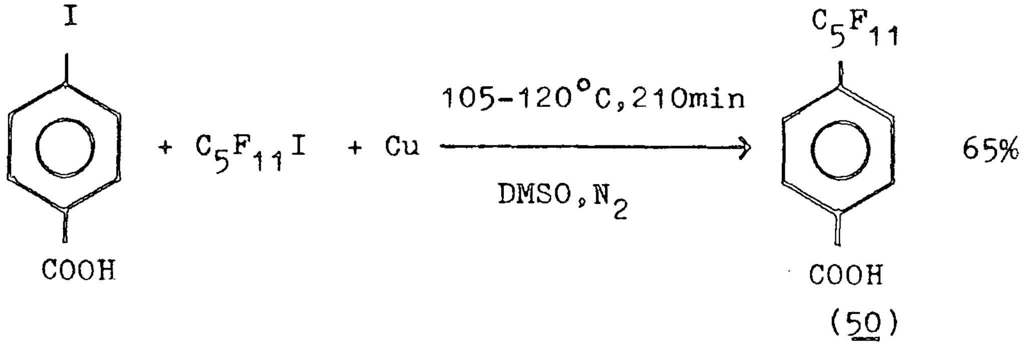
2. $$R_fCu + ArI \xrightarrow[120^\circ C]{DMSO/N_2} CuI + R_fAr$$

The suggested mechanism is shown in Scheme (1.7) and involves a four centre transition state between the perfluoroalkyl copper and aromatic iodide in which ligand exchange occurs. A co-ordinating solvent is necessary although a small amount in an inert solvent such as hexafluorobenzene will promote the reaction in high yield. The solvent must be a good ligand in order to stabilise the perfluoroalkyl copper and dissolve copper (I) iodide keeping the copper surface clean, however too strong a ligand will not easily exchange with the aryl iodide allowing formation of the four centre transition state. To some extent the two stages of the reaction have differing solvent requirements and of the aprotic solvents used dimethylsulphoxide best meets those of the whole reaction. The mechanism is supported by the observed ease of halogen displacement from the aromatic halide I>Br>>Cl and the fact that no ionic decomposition products are observed which rules out the possibility of free carbanions.

Scheme (1.7) <u>Mechanism for the Exchange of Iodine for the Perfluoroalkyl Group using Perfluoroalkyl Copper Reagents</u>



Synthetic reactions are usually carried out in one stage without preformation of the perfluoroalkyl copper. The copper, perfluoroalkyl iodide, and aromatic iodide are stirred with dimethylsulphoxide under an inert atmosphere at 110-130°C, as in the example given in which p-perfluoropentylbenzoic acid (50) is formed.



(50)

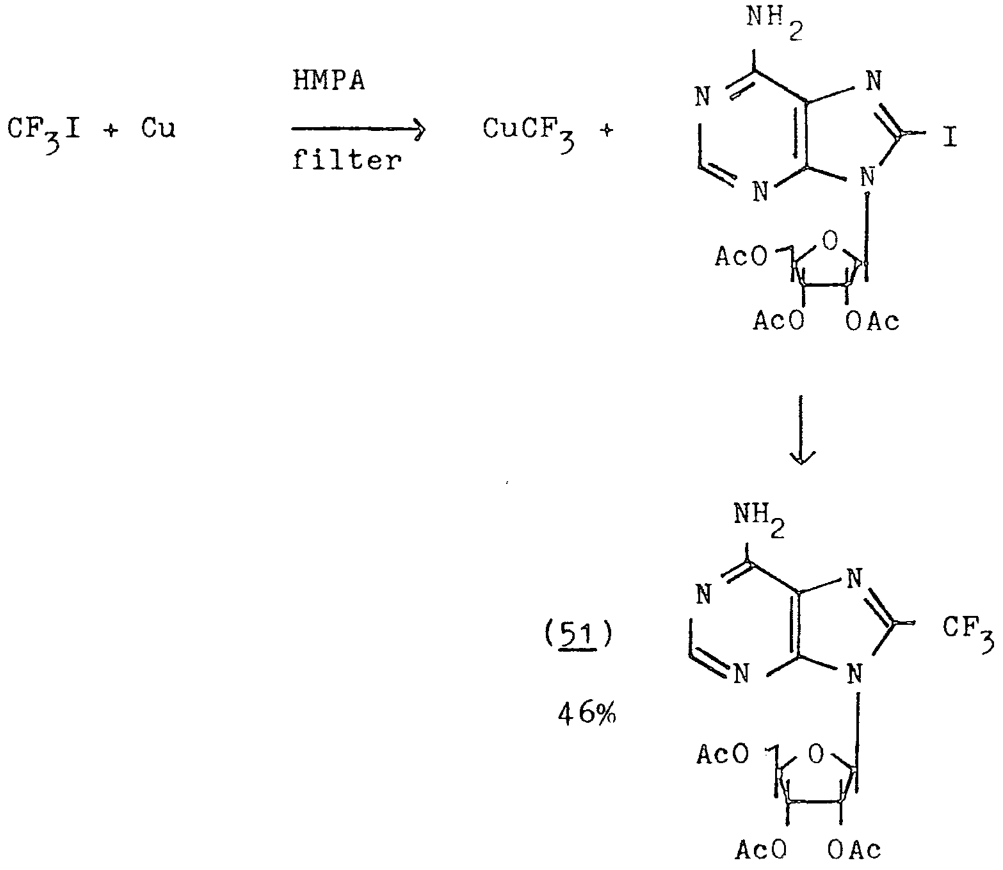
Yields are usually increased if an excess of copper and aromatic iodide are used, although with dimethylsulphoxide as a solvent stoichiometric amounts can be used. Large amounts of other solvents are needed to act as a heat sink and in preparation of large quantities of material it is preferable to add the perfluoroalkyl iodide to the other reagents at reaction temperature. It is a clean reaction in which the most common by-products are the fluoroalkane and those formed by reductive dehalogenation of the iodoaromatic compound, only when Ullman coupling occurs does separation of the products become difficult. The reaction is applicable to benzenoid and heterocyclic aromatic compounds and a wide range of substituents can be tolerated including alkyl, alkoxy, nitro, carboxyl, amino and hydroxyl groups. Further examples are given in Table (1.B.5). Fluorine and chlorine remain unaffected during the reaction but bromine can be substituted. In reactions of p-bromoiodobenzene and iodofluoroalkanes the yields of products formed by replacement of bromine were 10-15% compared to 50-60% yields from iodine replacement.

The method was extended to include introduction of the trifluoromethyl group by Kobayashi.[63,64] As trifluoromethyl iodide is a gas the reaction has to be carried out in a sealed vessel with mechanical shaking. Using a fifteenfold excess of trifluoromethyl iodide a reaction time of 24 hours is needed to obtain trifluoromethylbenzene (7) in 74% yield.

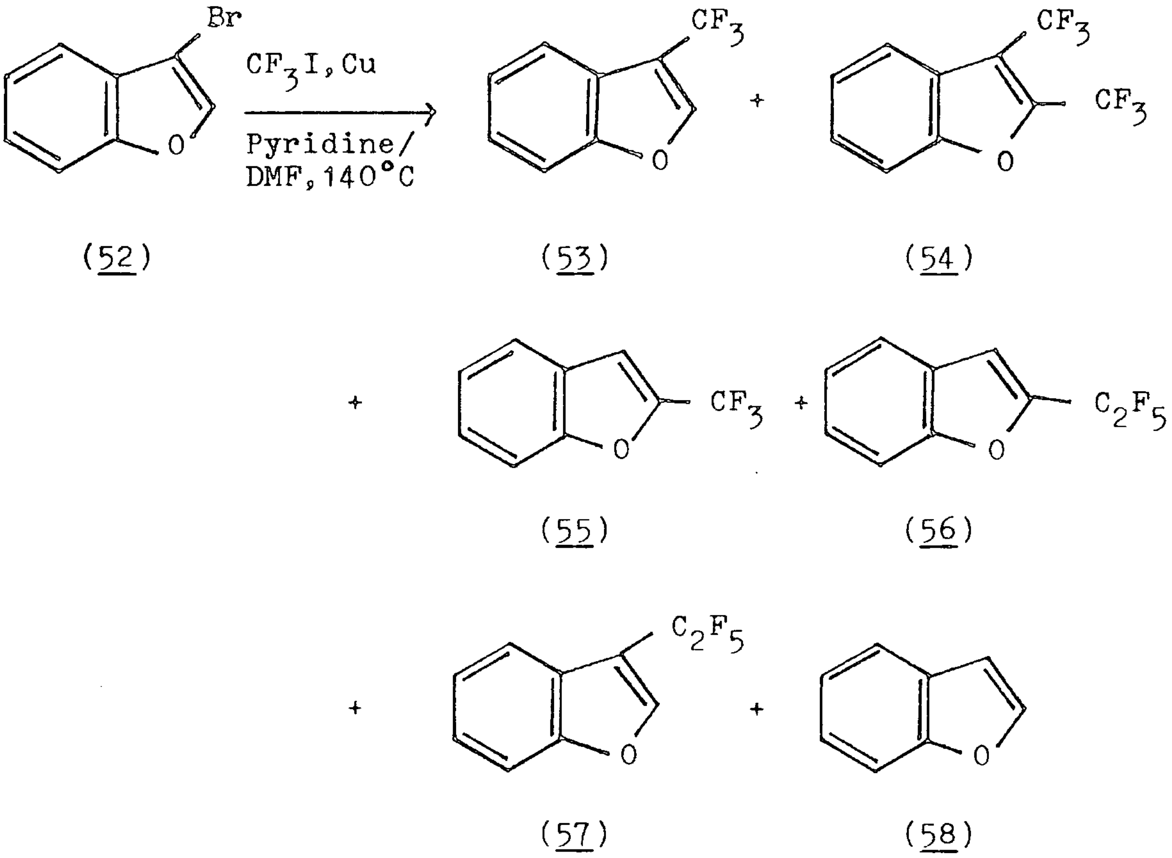
$$C_6H_5I + CF_3I \xrightarrow[130\text{-}140^\circ C, 24hrs]{Cu, DMF} \underset{(\underline{7})}{C_6H_5CF_3} \qquad 74\%$$

Dimethylformamide is the best solvent, although bromobenzene which is not trifluoromethylated in these conditions gives a small amount of trifluoromethylbenzene if hexamethylphosphoramide is used instead. Copper produced by precipitation from copper sulphate solution when reacted with zinc has been shown to be preferable to commercially available material.

A further development has allowed the trifluoromethylation of purine and pyrimidine nucleosides to be carried out.[65] The perfluoroalkyl copper solution in hexamethylphosphoramide is first filtered to remove excess copper, which promotes reductive dehalogenation, and then added to the aromatic iodide. This method also has the advantage that a lower temperature can be employed for the second stage allowing thermally unstable compounds to be trifluoromethylated. By this method 2'3'5'-tri-O-acetyl-8-trifluoromethyladenosine (51) has been produced in 46% yield. Care must be taken as HMPA is reported to be highly carcinogenic.



In two cases reported recently unusual products have been observed in perfluoroalkylation reactions.[66, 67] Whilst at 110°C in dimethylformamide the trifluoromethylation of bromobenzofuran (52) proceeds smoothly, unusual products are obtained if the temperature is increased or pyridine used as the solvent.[66]



(52) (53) (54) (55) (56) (57) (58)

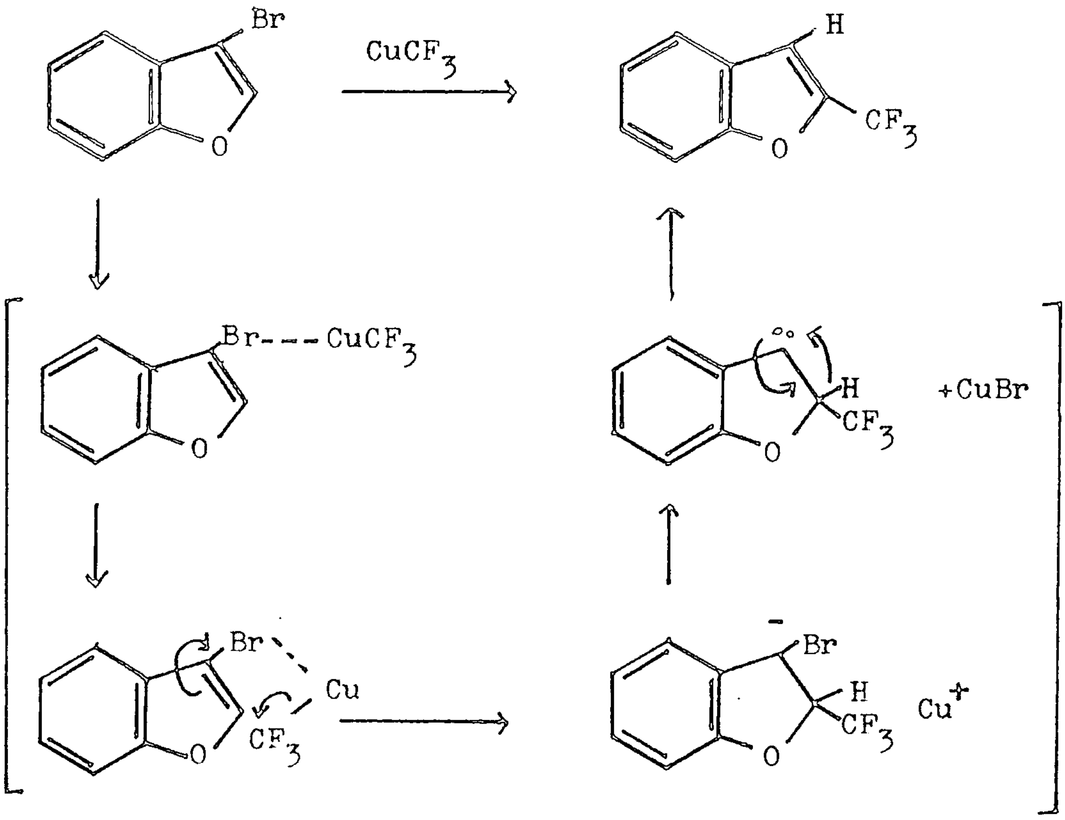
The abnormal products arise from cine-substitution (54), (55), (56), formation of the bis-trifluoromethylated product (54), reductive dehalogenation (55), (56), (58), and pentafluoroethylation (56), (57). As bromobenzene formed approximately equivalent amounts of the trifluoromethyl, pentafluoroethyl and hydrogen substituted products on reaction with trifluoromethyl iodide and copper in pyridine solution it is suggested that pentafluoroethylation is due to the low reactivity of the bromoaromatic compounds. If the aromatic halide is not particularly reactive the trifluoromethyl copper decomposes giving difluorocarbene which can insert into a trifluoromethyl-copper bond giving pentafluoroethyl copper. (59)

$$CF_3Cu \longrightarrow :CF_2 + CuF \xrightarrow{CF_3Cu} CF_3CF_2Cu$$

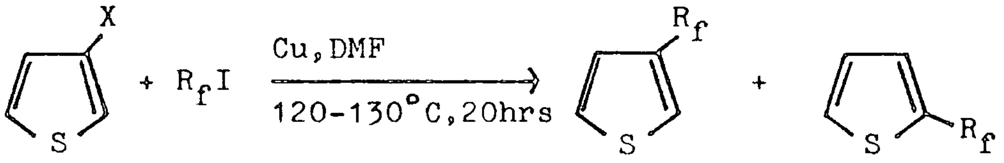
(59)

As cine-substitution would pass unobserved in bromobenzene, p-bromoanisole, which is electron rich like benzofuran, was trifluoromethylated. No cine-substitution was observed in this case and so it must be due to the specific nature of the benzofuran system. A suggested mechanism involving addition of the trifluoromethyl group to the localised bond between the 2- and 3-positions of the furan ring followed by hydride ion migration and bromide elimination is shown in Scheme (1.8). Attack at an electron rich double bond by a nucleophilic species does seem unlikely and the possibility of a benzyne intermediate ought not to be dismissed.

Scheme (1.8) Formation of Rearrangement Products in the Trifluoromethylation of 3-Bromobenzofuran



A similar rearrangement has been observed in the perfluoroalkylation of 3-iodo- and bromo-substituted thiophenes (60).[67]



(60) 82-100% 4-18%

X = I, Br

$R_f = CF_3, C_4F_9, C_8F_{17}$

Trifluoromethylation of 3-iodothiophene gives only the 3-substituted product and 3-bromothiophene does not react. However with the higher perfluoroalkyl iodides 2-substitution occurs and the ratio of 2:3 isomer is determined by the halogen. Iodine is the better leaving group and so less rearrangement occurs in the perfluoroalkylation of 3-iodothiopene. The same mechanism is assumed to operate as in the case of 3-bromobenzofuran.

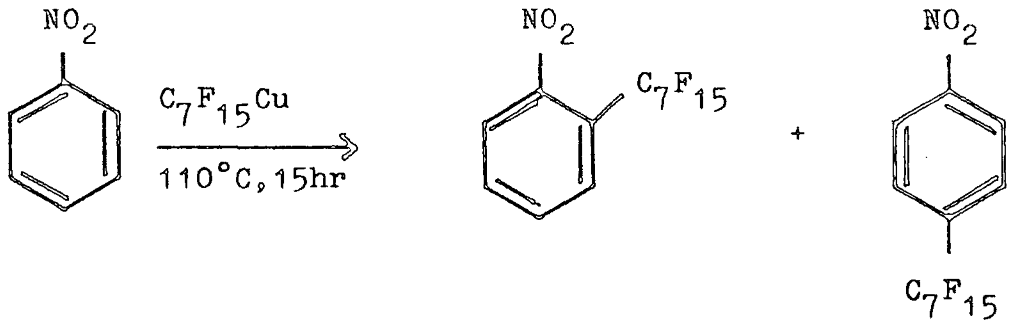
Perfluoroalkyl copper compounds can also be used to substitute a perfluoroalkyl group for hydrogen in an aromatic compound, although isomeric mixtures will be formed if a substituted benzene is used. The method of Coe and Milner[68] involves preformation of the organocopper reagent in solution before addition of the aromatic compound.

$$C_7F_{15}I + Cu \xrightarrow[110^\circ C, 45min]{DMSO} C_7F_{15}Cu \xrightarrow[110^\circ C, 15hr]{benzene}$$

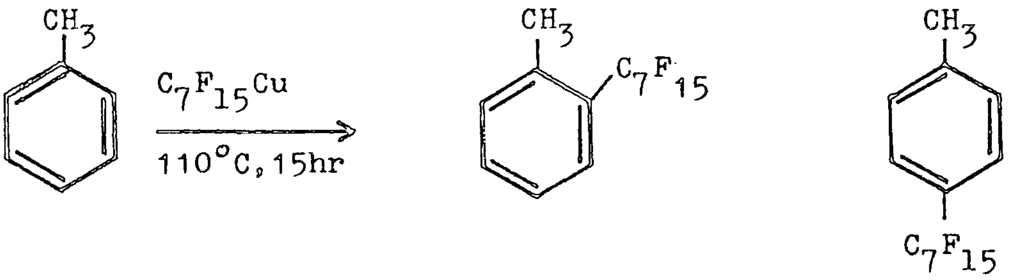
$$C_7F_{15}C_6H_5 + C_7F_{15}H + Cu$$

The intermediacy of perfluoroalkyl copper compounds has been proved by the facts that no reaction occurs when copper is omitted from the reaction mixture, ruling out thermal decomposition of the perfluoroalkyl iodide, and very little perfluoroalkylation is observed without preformation of the organocopper reagent. As metallic copper and 1-H-perfluoroalkane are produced a free radical mechanism has been proposed and is shown in Scheme (1.9a).

The products from reaction of nitrobenzene (61) and toluene (17) with perfluoroheptyl copper do not show the expected isomer distribution for radical attack, but perfluoroalkyl radicals are known to be electrophilic and capable of some orientation.



(61) 1 : 1



(17) 1 : 2

Scheme (1.9) Radical Mechanisms for Reaction between Perfluoroalkyliodides and Arenes in the Presence of Copper

(a)[68]

$R_fCu \longrightarrow R_f^\circ + Cu$

$R_f^\circ + ArH \longrightarrow R_fArH^\circ$

$R_fArH^\circ \longrightarrow R_fAr + H^\circ$

$R_f^\circ + RH \longrightarrow R_fH + R^\circ$

$2R^\circ \longrightarrow R_2$

$2H^\circ \longrightarrow H_2$

$R_f = C_nF_{2n+1}$
RH = Solvent

(b)[69]

$$\begin{aligned}
2R_fX + 2Cu + ArH &\longrightarrow R_fAr + R_fH + 2CuX \\
2R_fX + 2Cu &\longrightarrow 2R_f^{\circ} + 2CuX \\
R_f^{\circ} + ArH &\longrightarrow R_fArH^{\circ} \\
R_fArH^{\circ} &\longrightarrow R_fAr + H^{\circ} \\
R_f^{\circ} + H^{\circ} &\longrightarrow R_fH
\end{aligned}$$

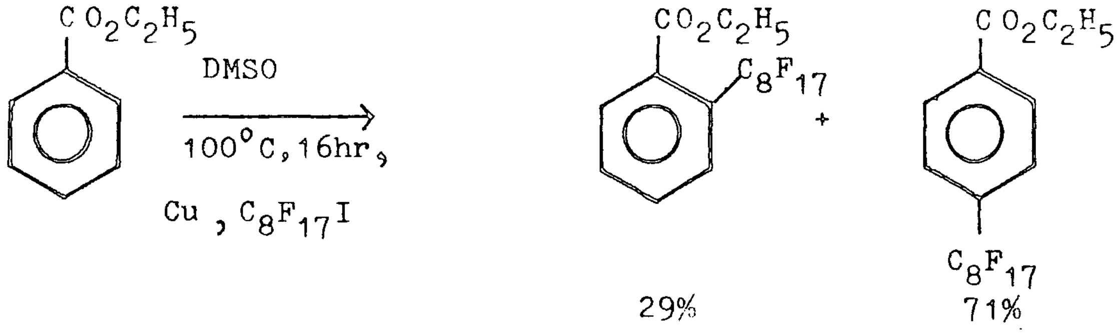
$$(2H^{\circ} \longrightarrow H_2)$$

This method has the disadvantages that a large excess of the aromatic compound is necessary and the yields are low (5-36%). A one step synthesis of perfluorooctylated benzenes from perfluorooctyl iodide, benzene and copper has since been developed in which stoichiometric amounts of arene are used and the yields for a range of substituted arenes are between 38 and 57%.[69]

$$2\ C_8F_{17}I + ArH + 2Cu \xrightarrow{DMSO} 2\ C_8F_{17}Ar + C_8F_{17}H + 2CuI$$

These results are inconsistent with those of Coe and Milner who found that reaction between benzene, perfluoroheptyl iodide, and copper gave only a small yield of perfluoroheptylbenzene unless the organocopper reagent was prepared before addition of the benzene.[68] It is suggested that in this case an undefined active species other than an organocopper compound is involved.[69] A radical mechanism consistent with the stoichiometry of the reaction is shown in Scheme (1.9b). This reaction scheme does however limit the yield of perfluoroalkylated benzene to 50%, based upon the perfluoroalkyl iodide used, and as yields greater than this have been obtained the generation of molecular hydrogen must be considered as a termination step. Removal of hydrogen radicals from the system in this way frees more perfluoroalkyl radicals to combine with the arene.

In practice perfluoroalkyl iodide (1.0mmol), benzene (2mmol), and copper (2mmol) are heated in dimethylsulphoxide at 100°C for 16 hours. Reaction of ethylbenzoate (62) with perfluorooctyl iodide gave a mixture of o- and p-product in 37% yield.[69]



(62) 37% yield

A range of functional groups including hydroxy, amino, halogen, carbamoyl, and alkoxy groups can be tolerated and more examples are given in Table (1.B.5). The para-isomer was the major product in every case and no meta-isomer was observed except in the reaction of methylphenoxyacetate. The use of dimethylsulphoxide as a solvent is extremely important, other aprotic solvents gave large quantities of the 1-H-perfluoroalkane and very little perfluoroalkylated product. Only one trifluoromethylation reaction has been carried out, that of p-chloroaniline and the yield of trifluoromethylated product was very small.

1.B.v.b. Ultrasound Promoted Perfluoroalkylation of Aromatic Compounds.

Ultrasound irradiation is a relatively new means of promoting chemical reactions and an outline of its history can be found in ref.70. Perfluoroalkyl aromatic compounds can be prepared in an ultrasound promoted reaction between an aryl halide and perfluoroalkylzinc iodide which is formed in situ from zinc and a perfluoroalkyl iodide.[71] The reaction is carried out in tetrahydrofuran using a palladium catalyst and the whole apparatus is immersed in the waterbath of an ultrasound laboratory cleaner.

$$R_fI + ArI \xrightarrow[\substack{Pd(Ph_3P)_2Cl_2 \\ \text{Ultrasound}}]{Zn,\ THF} R_fAr$$

As the perfluoroalkyl group substitutes the iodine in the aromatic compound the site of reaction can be predicted and no isomers are formed. Trifluoromethylbenzene (7) is formed in 82% yield and further examples are given in Table (1.B.5).

$$C_6H_5I + CF_3I \xrightarrow[\text{Zn, THF}]{PdCl_2(PPh_3)_2} C_6H_5CF_3 \quad 82\%$$

Ultrasound, ½hr (7)

Palladium black can also be used to promote the reaction and it is suggested that the actual catalyst is Pd(0) which takes place in the catalytic oxidation-reduction cycle shown in Scheme (1.10).

Scheme (1.10) A Mechanism for Ultrasound Promoted Perfluoroalkylation

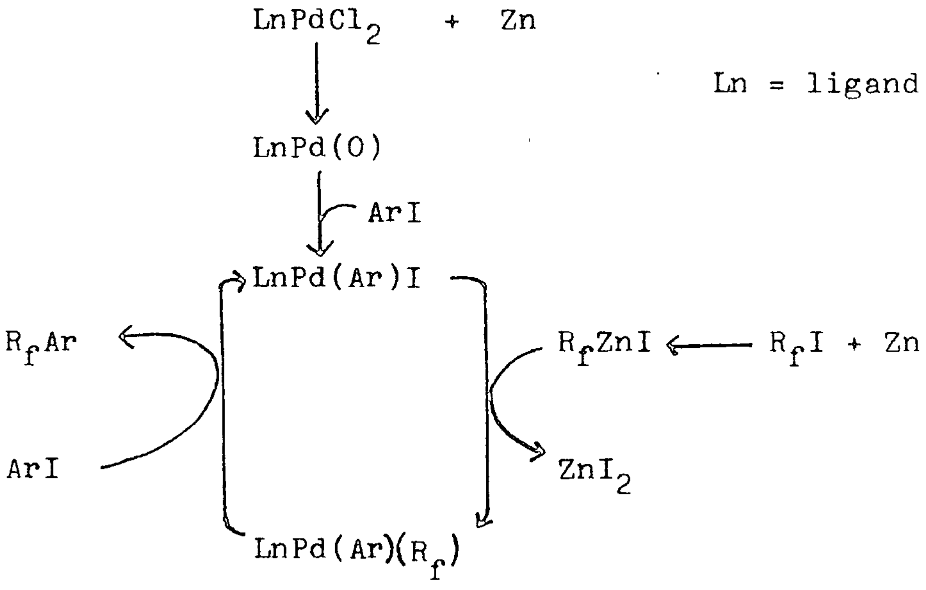
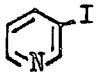
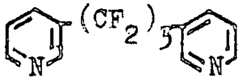


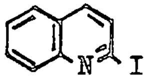
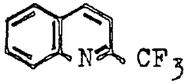
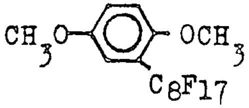
Table (1.B.5) Organometallic Compounds as a Source of the Perfluoroalkyl Group

Arene	Alkyliodide	Metal	Solvent	Conditions	Product	Yield %	Ref.
m-I.C_6H_4.NH_2	$C_9F_{19}I$	Cu	DMSO	210min,105-120°C	m-C_9F_{19}.C_6H_4.NH_2	45	62
	$C_3F_6I_2$	Cu	DMF	90min,126°C		52	62
m-I.C_6H_4.OC(=O)CH_3	C_3F_7I	Cu	DMF	* i 60min,135°C ii 50min,125-135°C	m-C_3F_7.C_6H_4.OC(=O)CH_3	65	62
p-Br.C_6H_4.CH(CH_3)OH	$C_7F_{15}I$	Cu	DMSO	* i 30min,125°C ii 720min,125°C	p-C_7F_{15}.C_6H_4.CH(CH_3)OH	65	62
C_6H_5I	$C_7F_{15}I$	Cu	DMSO	* i 60min,110-120°C ii 120min,110°C	C_6H_5.C_7F_{15}	70	62
o-CH_3.C_6H_4I	CF_3I	Cu	DMF	11hr,130-140°C	o-CH_3.C_6H_4.CF_3	28	64
o-$C_6H_4I_2$	CF_3I	Cu	DMF	24hr,140°C	o-$C_6H_4(CF_3)_2$	32	64
p-CH_3O.C_6H_4.I	CF_3I	Cu	DMF	20hr,130-140°C	p-CH_3O.C_6H_4.CF_3	86	64

* R_fI added to other reactants at reaction temperature

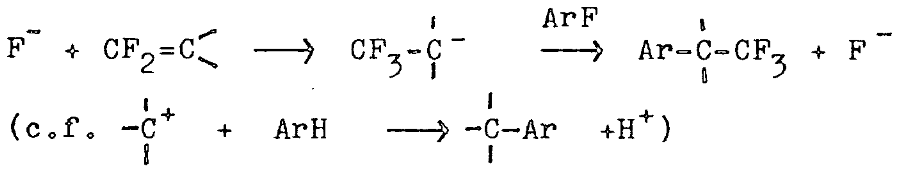
continued

Table (1.B.5) continued

Arene	Alkyliodide	Metal	Solvent	Conditions	Product	Yield %	Ref.
p-$NO_2 \cdot C_6H_4 \cdot I$	CF_3I	Cu	DMF	30hr, 135° C	p-$NO_2 \cdot C_6H_4CF_3$	51	64
	CF_3I	Cu	DMF	20hr, 135° C		60	64
	$C_8F_{17}I$	Cu	DMSO	16hr, 100°C		57	69
$NH_2 \cdot C_6H_5$	$C_8F_{17}I$	Cu	DMSO	16hr, 100°C	$NH_2 \cdot C_6H_4 \cdot C_8F_{17}$ o12% m16% p72%	58	69
$OH \cdot C_6H_5$	$C_8F_{17}I$	Cu	DMSO	16hr, 100° C	$OH \cdot C_6H_4 \cdot C_8F_{17}$ o48% p52%	38	69
$C_2H_5O_2C \cdot C_6H_5$	$C_8F_{17}I$	Cu	DMSO	16hr, 100°C	$C_2H_5O_2C \cdot C_6H_4 \cdot C_8F_{17}$ o29% p71%	37	69
C_6H_5I	C_3F_7I	Zn	THF	30min, $PdCl_2(PPh_3)_2$, ultrasound	$C_6H_5 \cdot C_3F_7$	78	71
p-$CH_3 \cdot C_6H_4 \cdot I$	iC_3F_7I	Zn	THF	30min, $PdCl_2(PPh_3)_2$, ultrasound	p-$CH_3 \cdot C_6H_4 \cdot$ iC_3F_7	81	71

1.B.vi Nucleophilic Friedel Crafts Reactions

Perfluoroalkylcarbanions, generated by reaction between fluoride ion and fluoroolefins, are trapped by polyfluoroaromatic compounds in a process similar to the cationic Friedel Crafts reaction. Nucleophilic Friedel Crafts reactions, as they have come to be known, provide a useful method of introducing the perfluoroalkyl group into a highly fluorinated aromatic system.[72,59]

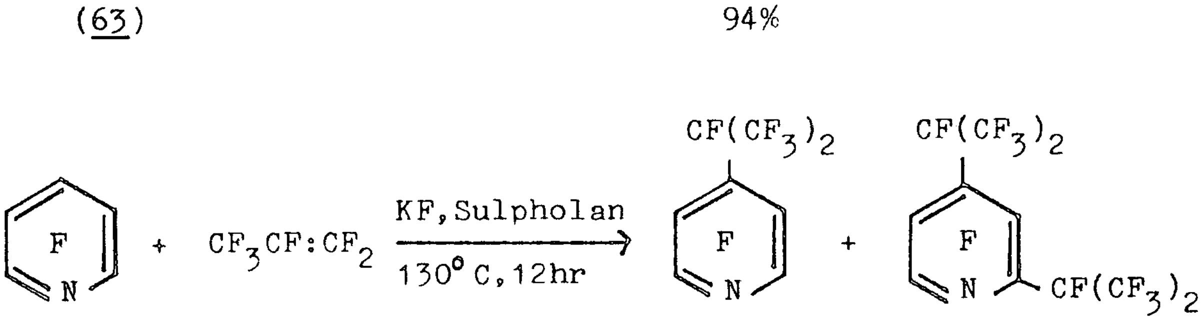


$$F^- + CF_2{=}C\Big< \longrightarrow CF_3{-}\overset{|}{\underset{|}{C}}{}^- \xrightarrow{ArF} Ar{-}\overset{|}{\underset{|}{C}}{-}CF_3 + F^-$$

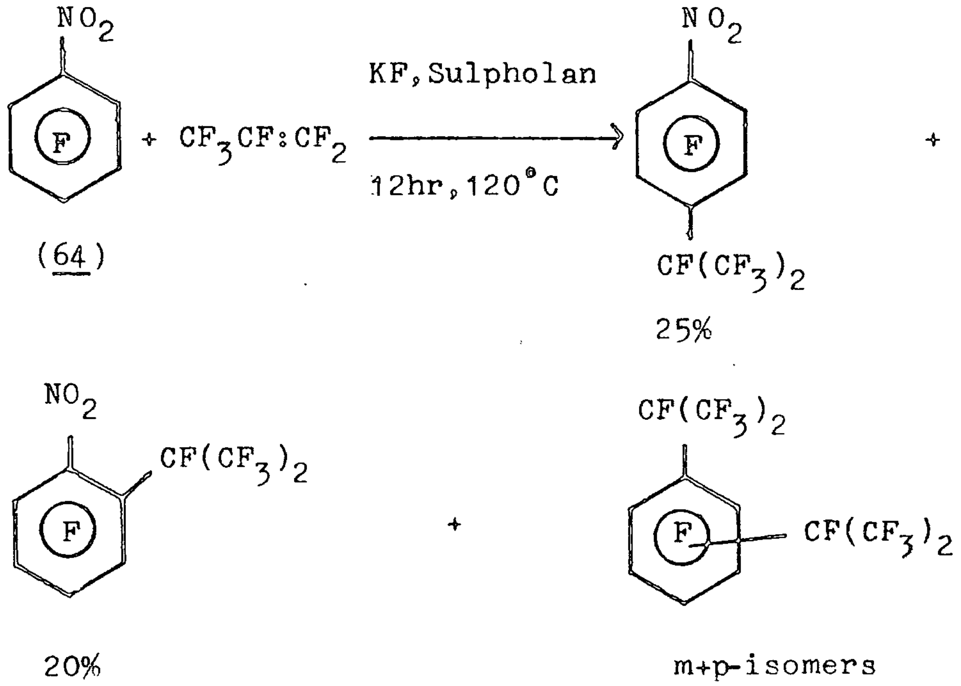
$$(\text{c.f. } {-}\overset{|}{\underset{|}{C}}{}^+ + ArH \longrightarrow {-}\overset{|}{\underset{|}{C}}{-}Ar \;\; + H^+)$$

Pentafluoropyridine (63) is particularly reactive towards nucleophilic reagents and when heated in sulpholan with hexafluoropropene and potassium fluoride forms perfluoro-4-isopropylpyridine in high yield.[75]

(63)



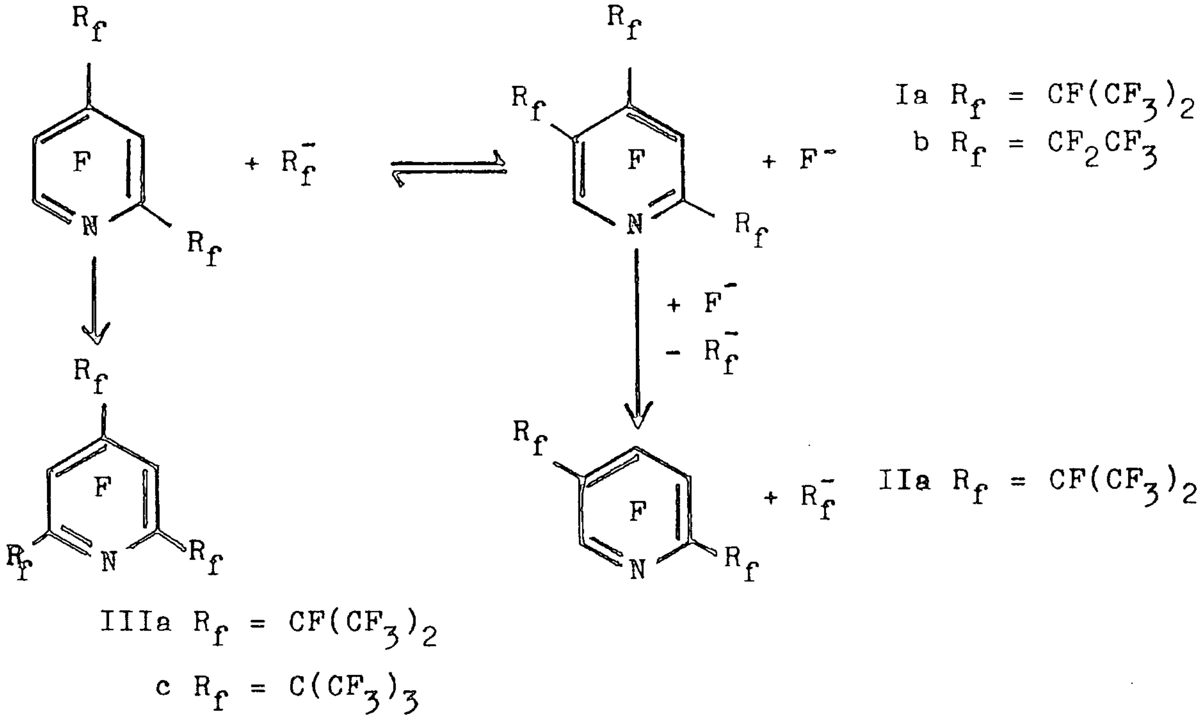
Other perfluorinated compounds which may be perfluoroalkylated in this way include octafluorotoluene,[73] methylpentafluorobenzoate,[73] pyridazines,[74] pyrimidines,[75] and triazines.[76] Examples of these reactions can be found in Table (1.B.6). Attempts to perfluoroalkylate hexafluorobenzene and 1.3.5-trichlorotrifluorobenzene proved unsuccessful.[73] The reaction of pentafluoronitrobenzene (64), which shows similar reactivity to pentafluoropyridine, is interesting in that at lower temperatures perfluoro(isopropyl)benzene becomes the main product.[73]



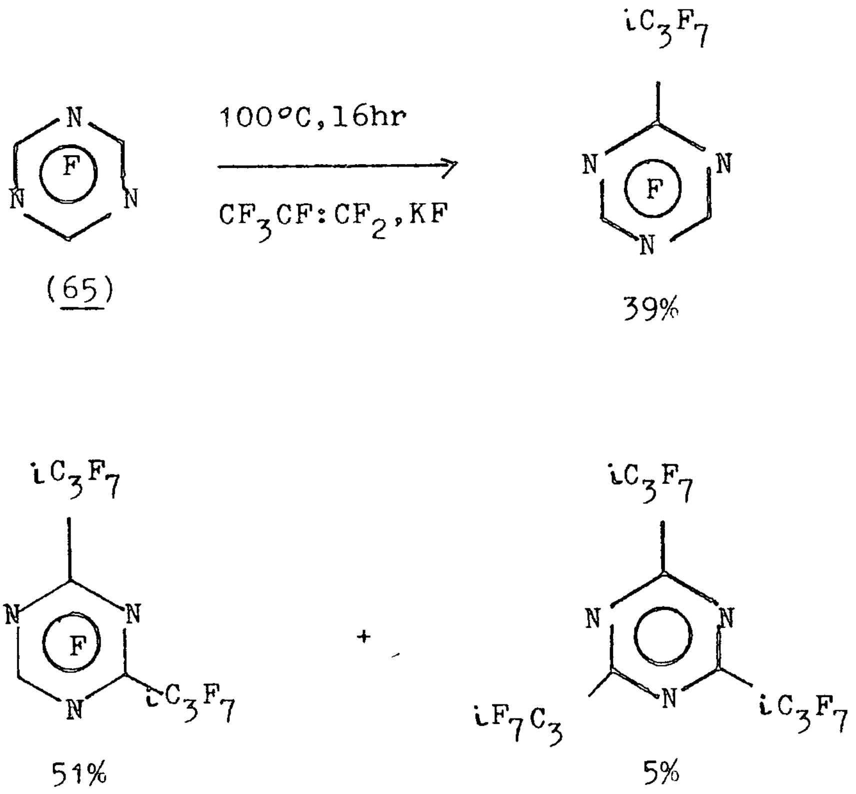
A limiting feature in all of these reactions is the tendency of the olefins to form dimers and trimers in the presence of metal fluorides.

The formation of polysubstituted perfluoroalkylaromatics involves three considerations; (a) after two perfluoroalkyl groups are present these may control the site of further attack, (b) some reactions are reversible and (c) substitution at the site most activated to attack sometimes results in crowding and leads to competition between kinetic and thermodynamic control of the products. Possible products in the perfluoroalkylation of pentafluoropyridine are shown in Scheme (1.11). In the addition of a third perfluoroalkyl anion the groups already present control the substitution and so the preferred position for attack is C-5. The 2,4,5-trimer formed by addition of the isopropyl group in this position (Ia) is sterically crowded and so, at higher temperatures and in the present of fluoride ion, rearrangement occurs to the thermodynamically preferred isomer (IIIa). Another disubstituted isomer (IIa) is also formed.

Scheme (1.11) Polyperfluoroalkylation of Pentafluoropyridine.



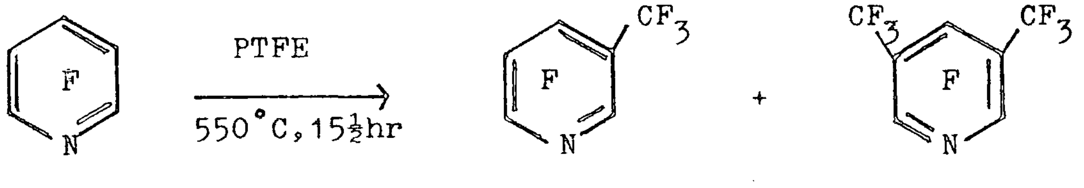
Trisubstitution of pentafluoropyridine with hexafluoropropene thus results in a mixture of kinetic and thermodynamic isomers.[78] Substitution by a very bulky group such as the perfluorotertiarybutyl anion results solely in formation of the thermodynamically preferred isomer (IIIc)[79] whilst the only trisubstituted perfluoroethyl derivative is the kinetically preferred 2,4,5-isomer (Ib).[80] The variation in the orientation of the trisubstitution products obtained with any olefin depends upon the reversibility of the process and crowding in the 2,4,5-isomer. Carbanion stabilities, reversibility of the reaction, and crowding decrease in the same sequence $(CF_3)_3C > (CF_3)_2CF > CF_3CF_2$. Only 1,3,5-trifluorotriazine (65) has been completely perfluoroalkylated.[76]



Trifluoromethyl anions for use in this procedure can be produced from difluorocarbene.

$$F^- + \left[:CF_2\right] \rightleftharpoons \bar{C}F_3 \xrightarrow{Ar_fF} Ar_fCF_3 + F^-$$

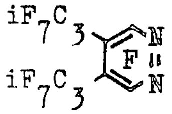
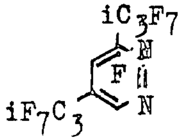
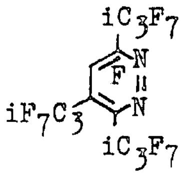
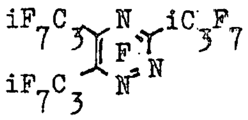
Attempts to promote trifluoromethylation using sodium chlorodifluoroacetate and hexafluoropropene epoxide as the sources of difluorocarbene have proved unsuccessful but the reaction of pentafluoropyridine (63) with polytetrafluoroethylene has resulted in the formation of perfluoromethyl compounds.[81]



(63) 6% 60%

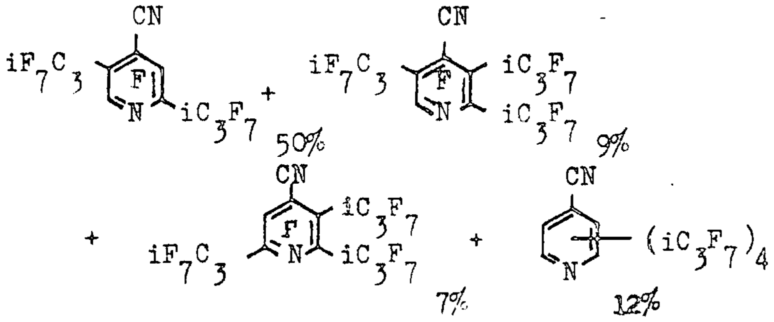
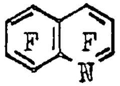
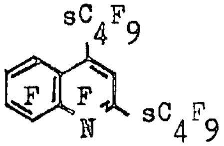
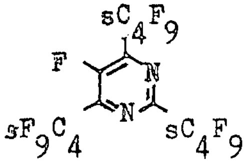
Difluorocarbene is expected to be the intermediate, since on pyrolysis PTFE gives tetrafluoroethylene which probably forms difluorocarbene at these temperatures as it does on photolysis. The carbene could either insert into the pyridine carbon-fluorine bond or, as is thought more likely, add across the double bond forming an intermediate tropylidene (66) which rearranges to give the perfluoromethylpyridine.

Table (1.B.6) Nucleophilic Friedel Crafts Reactions

Arene	Alkene	Conditions	Product	Yield %	Ref.
$CF_3{\cdot}C_6F_5$	$CF_3CF{:}CF_2$	40°C,13hr,CsF,Tetraglyme	$4\text{-}CF_3{\cdot}C_6F_4{\cdot}iC_3F_7$	59	73
$CN{\cdot}C_6F_5$	$CF_3CF{:}CF_2$	125°C,15hr,KF,Sulpholan	$CN{\cdot}C_6F_4{\cdot}iC_3F_7$	30	73
	$CF_3CF{:}CF_2$	80°C,20hr,KF,Sulpholan		80	74
	$CF_3CF{:}CF_2$	150°C,17hr,KF,Sulpholan	 46% +  20%		74
	$CF_3CF{:}CF_2$	100°C,2hr,CsF,no solvent		52	84

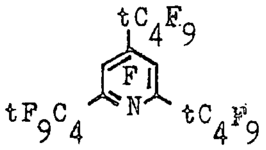
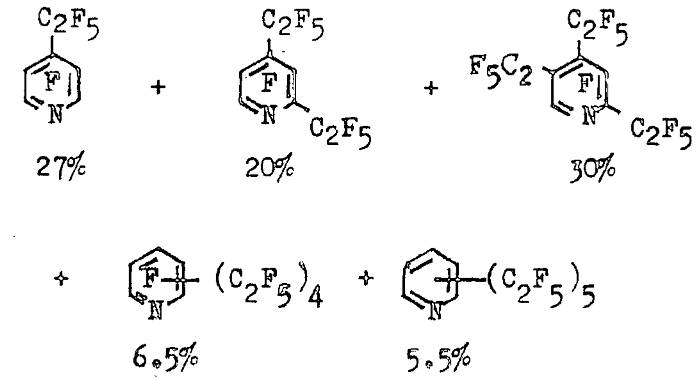
continued

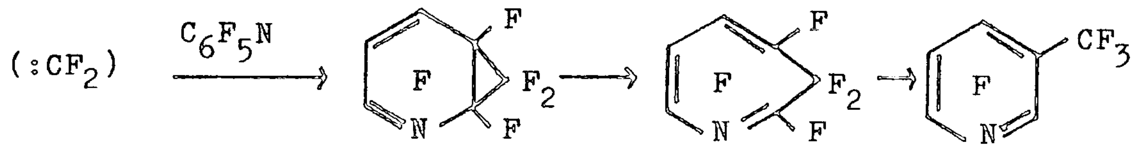
Table (1.B.6) continued

Arene	Alkene	Conditions	Products	Yield %	Ref
	$CF_3CF{:}CF_2$	70°C,20hr,CsF.CH_3CN			82
$CF_3.C_6F_5$	$CF_3CF{:}CFCF_3$	85°C,96hr,CsF,Tetraglyme	4-$CF_3C_6F_4.sC_4F_9$	60	83
	$CF_3CF{:}CFCF_3$	100°C,12hr,CsF,Sulpholan		28	83
	$CF_3CF{:}CFCF_3$	135°C,84hr,CsF,Tetraglyme		51	83

continued

Table (1.B.6) continued

Arene	Alkene	Conditions	Product	Yield %	Ref.
	$(CF_3)_2C{:}CF_2$	80°C, 7hr, CsF, Tetrahydrothiophen-dioxide		85	79
	$CF_2{:}CF_2$	80°C, 8hr, CsF, Tetrahydrothiophen-dioxide			80



(66)

This suggested route is backed by the isolation of a tropylidene in an analogous reaction between hexafluorobenzene and bis(trifluoromethyl)carbene.

1.B.vii Miscellaneous Reactions

The methods of producing perfluoroalkylaromatic compounds gathered under this heading are those which, whilst worthy of mention, do not warrant separate discussion or fit neatly into previous sections.

A new trifluoromethylating agent, N-trifluoromethyl N-nitrosobenzene sulphonamide, (67), has been developed from trifluoronitrosomethane.[85]

$$CF_3NO \xrightarrow[-75°C]{NH_2OH} \underset{(67)}{\left[CF_3-N=N-OH\right]} \xrightarrow[tBuOK]{PhSO_2Cl} CF_3N(NO)SO_2Ph \qquad 57\%$$

The trifluoromethylation reaction is very similar to that using trifluoromethyl iodide (1.B.iv), but gives better yields in a shorter period of time and avoids the use of gaseous reagents. A mixture of the sulphonamide, benzene and a biacetyl sensitiser are irradiated in acetonitrile solution using a 400w high pressure mercury lamp and trifluoromethyl benzene (7) is produced in 24% yield.

$$C_6H_6 \xrightarrow[CH_3CN,\ 5hr,\ u\nu]{CF_3N(NO)SO_2Ph} \underset{(\underline{7})}{C_6H_5CF_3} \qquad 24\%$$

A small range of substituted benzenes and pyrrole have been trifluoromethylated, the benzenes giving rise to isomeric mixtures of trifluoromethyl products.

Perfluorinated alkylbenzenes can be produced by exhaustive fluorination of the corresponding alkyl benzene forming a perfluorocyclohexane which is then partially defluorinated by passage over iron gauze at 450-500°C. Perfluoroethylbenzene (<u>68</u>)[86] and perfluoro-p-xylene (<u>69</u>)[87] are formed in this way.

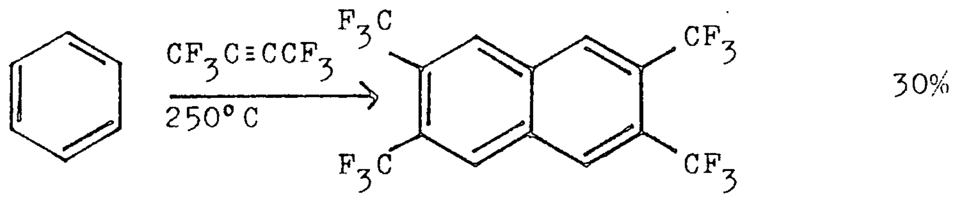
$$C_6H_5C_2H_5 \xrightarrow[300\text{-}350^\circ C]{CoF_3} C_6F_{11}C_2F_5 \xrightarrow[490^\circ C]{Fe} C_6F_5C_2F_5 \qquad (\underline{68})$$

$$p\text{-}C_6H_4(CH_3)_2 \xrightarrow[300\text{-}350^\circ C]{CoF_3} C_6F_8(CF_3)_2 \xrightarrow[450\text{-}500^\circ C]{Fe} \underset{(\underline{69})}{p\text{-}C_6F_4(CF_3)_2}$$

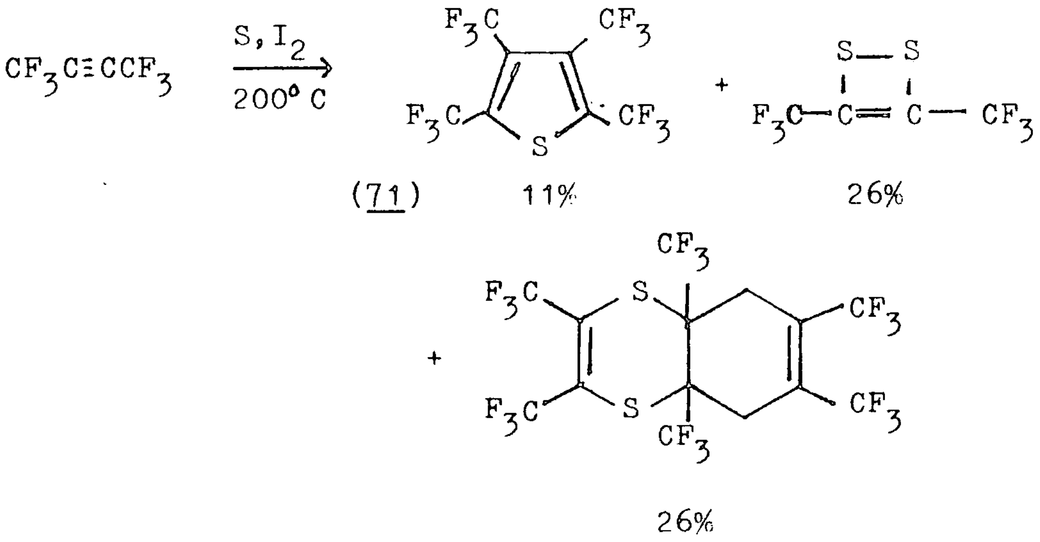
40-45%

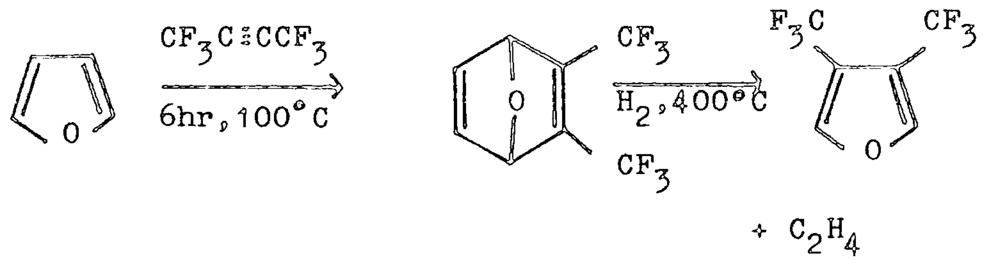
Perfluoroalkyl heterocyclic compounds are often synthesised from smaller molecules in which the perfluoroalkyl group is already present rather than adding the group to a complete heterocyclic structure. Examples include the cycloaddition of nitrile oxides to perfluoroalkylethynes forming isoxazoles[88] and the preparation of benzoxazoles from hexafluoro-1,2-epoxypropane and o-aminophenols.[89] These reactions fall out of the scope of this review and will not be discussed further but more examples can be found in ref. 90.

A few perfluoroalkylaromatic compounds have been produced in cycloaddition reactions of acetylenes and nitriles and will be mentioned briefly although these too come into the class of total synthesis rather than introduction of the perfluoroalkyl group.
Perfluorobut-2-yne has been used in the preparation of 2,3,6,7-tetrakis(trifluoromethyl)naphthalene (70)[91], 2,3,4,5-tetrakis(trifluoromethyl)thiophene (71)[92], 3,4-bis(trifluoromethyl)furan (72)[93], and hexakis-(trifluoromethyl)benzene (73).[94,95]



(70)





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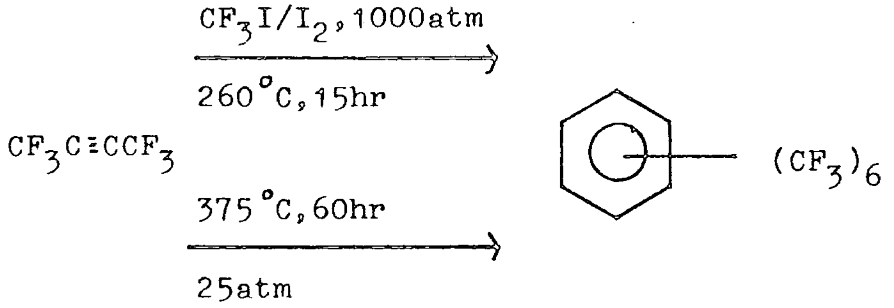
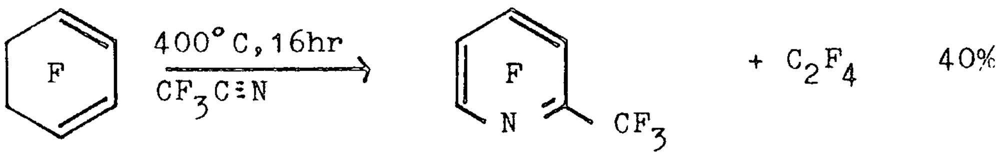


(73)

Perfluoroacetonitrile can be used to prepare perfluoro-2-methylpyridine (74)[96] which is unobtainable by nucleophilic attack on perfluoropyridine (1.B.vi) and perfluoroalkynitriles generally can be trimerised to produce 2,4,6-perfluoroalkyltriazines (75).[97]



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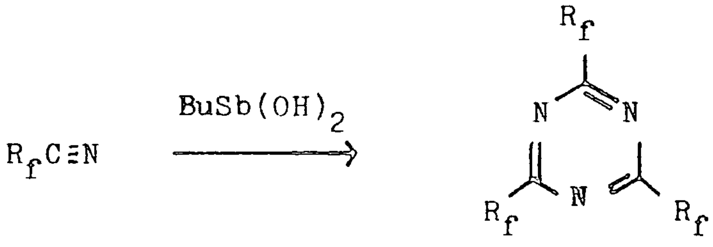

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DISCUSSION

Chapter 2

Bis(trifluoromethyl)mercury as a Source of Trifluoromethyl Group.

2.A. Introduction

The main methods for introducing the trifluoromethyl group discussed in the previous chapter have their attendant drawbacks. Hydrogen fluoride and sulphur tetrafluoride can be used only to modify a group, trichloromethyl or carboxyl, already present in the molecule and their use presents handling difficulties. Trifluoromethyl iodide, which can be used as a source of the trifluoromethyl group in either a radical or copper promoted reaction, is an expensive gaseous reagent and necessitates the use of sealed tubes or autoclaves. The radical reaction also produces a mixture of isomers rather than substitution into a specific site.

A new synthesis of trifluoromethylated aromatic compounds, from bis(trifluoromethyl)mercury and aromatic halides in the presence of copper, has been described briefly.[98] In principle this reaction has the advantages that no gaseous reagents are involved so glass apparatus can be used at atmospheric pressure and the trifluoromethyl group is specifically incorporated in place of the halogen. Bis(trifluoromethyl)mercury is easily prepared[99] from the readily available materials mercury(II) oxide and trifluoroacetic acid, which can be prepared in the ^{14}C-labelled form[100] to provide radiolabelled trifluoromethyl aromatic compounds. This chapter is devoted to an investigation of the method and the interesting reaction mechanisms involved.

2.B. Preparation of Bis(trifluoromethyl)mercury.

An easy route to bis(trifluoromethyl)mercury (76) has been published which involves copyrolysis of potassium carbonate and mercury(II) trifluoroacetate (77), produced by reaction between trifluoroacetic acid and mercury(II) oxide.[99]

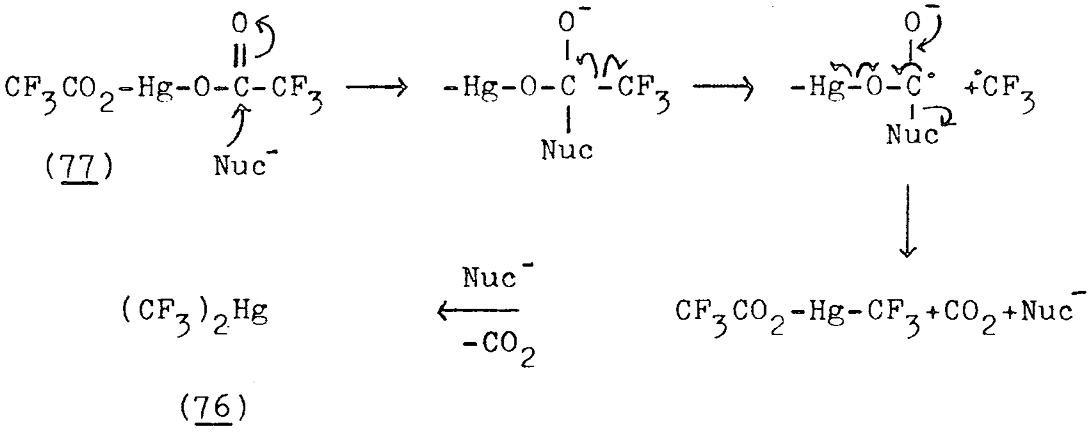
$$\mathrm{HgO} + \mathrm{CF_3COOH} \xrightarrow{50^\circ\mathrm{C},\ 10\mathrm{min.}} \underset{(77)}{(\mathrm{CF_3COO})_2\mathrm{Hg}}$$

$$(\mathrm{CF_3COO})_2\mathrm{Hg} \xrightarrow[180\text{-}200^\circ\mathrm{C},\ 40\mathrm{min.}]{\mathrm{K_2CO_3},\ 20\mathrm{mmHg}} \underset{(76)}{(\mathrm{CF_3})_2\mathrm{Hg}} + 2\mathrm{CO_2}$$

Mercury(II) trifluoroacetate was formed in over ninety percent yield by stirring a mixture of trifluoroacetic acid and mercury(II) oxide overnight, but preliminary problems were encountered in the preparation of bis(trifluoromethyl)-mercury (76).[101] The pyrolysis was carried out following the brief experimental details given and the yield was, at 33%, much lower than that quoted. Using the method outlined in greater detail in another paper[102] a 74% yield of (76) was obtained. In the latter case the trifluoroacetate was easier to dry as it was produced in anhydrous trifluoroacetic acid rather than in aqueous solution as in the previous work.[101] This is probably the explanation for the increased yield as the main difference between the two methods was a change in the design of the apparatus which is unlikely to have caused such an increase.

The yield of mercurial (<u>76</u>) was slightly increased to 87% when the carbonate was replaced by potassium fluoride in the pyrolysis reaction. As fluoride ion, a strong nucleophile, will also promote the decarboxylation it is suggested that the carbonate anion is acting as a weak nucleophile in a process such as that outlined in Scheme (2.1)

Scheme (2.1) <u>Decarboxylation of Mercury(II) Trifluoroacetate.</u>



$Nuc^- = F^-$ or CO_3^{2-}

2.C. Trifluoromethylation using Bis(trifluoromethyl)mercury.

2.C.i. Synthesis.

The trifluoromethylation reaction is envisaged in the original paper as being a two stage process.[98] In the first stage the mercurial (76) and copper powder are heated in N-methylpyrrolidone (NMP) or dimethylacetamide (DMAC) under dry nitrogen to form a trifluoromethyl copper solution (78). The haloaromatic compound is added to this solution in the second stage of the process and the mixture is heated at 150°C for three hours.

$$\underset{(\underline{76})}{(CF_3)_2Hg} \quad + \quad 2\ Cu \quad \xrightarrow[\text{2hr,140°C}]{\text{NMP/DMAC,}N_2} \quad \underset{(78)}{2CuCF_3+Hg}$$

$$CuCF_3 \quad + \quad ArI \quad \xrightarrow[\text{3hr,150°C}]{\text{NMP/DMAC,}N_2} \quad ArCF_3+CuI$$

Two practical routes were suggested; A in which the two stages are carried out consecutively, and B in which the excess copper is filtered off under nitrogen before addition of the haloaromatic compound. The yields were claimed to be 10-20% higher when Method B was used.

The trifluoromethylation of iodobenzene using Method A resulted in an 85% yield of trifluoromethylbenzene which compares very favourably with that quoted by the original workers (65%)[98] and p-nitrotrifluoromethylbenzene was produced in 55% yield from p-iodonitrobenzene. (The yields in all these reactions were calculated from the g.l.c. traces of the reaction mixtures using an internal standard.) However, using Method B which should result in a higher yield, no trifluoromethylation of either iodobenzene or p-iodonitrobenzene was observed and the iodoarenes were recovered unchanged. Using stoichiometric amounts of reagents instead of the fourfold excess of (78) originally quoted[98] a 7.5% yield of trifluoromethylbenzene was obtained from Method B. At first it was felt that this apparent discrepancy between the present and original[98] results could have arisen as a result of air getting into the system during the filtration process allowing oxidation of (78) to occur. Later results, however, cast doubt upon whether (78) was actually formed in the first stage of the reaction. The integration of the ^{19}F nmr signal of the mercurial solution was unchanged after the initial reaction to form (78)[101] and analysis of the filtrate showed that very little copper take-up or deposition of mercury had occurred. This copper was precipitated from copper(II) sulphate solution by metallic zinc but that from a commercial sample gave similiar results.

As these results suggest that (78) is not formed in the first stage there seems little point in "preparing" it and so a single stage reaction was developed in which all the reactants were heated at 140°C for three hours. The yield of trifluoromethylbenzene (7) was 83%, comparable to that obtained by the two stage Method A, and so all further reactions have been carried out using this "one-pot" method.

$$(CF_3)_2Hg + Cu + C_6H_5I \xrightarrow[\text{3hrs, 140°C}]{\text{NMP, } N_2} \underset{(7)}{C_6H_5CF_3} \qquad 83\%$$

The trifluoromethylation of bromobenzene (16) under these conditions gave very little (7) but the yield increased to 38% when the reaction temperature was raised to 165°C. There was no noticeable substitution of chlorine in chlorobenzene even at the elevated temperature.

$$(CF_3)_2Hg + Cu + \underset{(16)}{C_6H_5Br} \xrightarrow[\text{3hrs, 165°C}]{\text{NMP, } N_2} \underset{(7)}{C_6H_5CF_3} \qquad 38\%$$

A range of substituted iodo- and bromobenzenes have been trifluoromethylated using these procedures and the results are shown in Table (2.1). A heterocyclic compound, 3-iodopyridine, has been trifluoromethylated and it has also proved possible to substitute both of the iodine atoms in 1,4-di-iodobenzene with trifluoromethyl groups. The products are all known compounds, the identities of which were confirmed from mass spectra and ^{19}F nmr data. The yields were calculated from the g.l.c. traces of the reaction mixtures using an internal standard. Only three of the products were isolated, p-nitrotrifluoromethylbenzene by ether extraction and 3-trifluoromethylpyridine and trifluoromethylbenzene by vacuum transference.

Table (2.1) Trifluoromethylation of Haloaromatic Compounds with Bis(trifluoromethyl)mercury

	Product	Yield %
iodobenzene	trifluoromethylbenzene	83
3-iodopyridine	3-trifluoromethylpyridine	79
p-iodonitrobenzene	p-nitrotrifluoromethylbenzene	82
1,4-diiodobenzene	1,4-bis(trifluoromethyl)benzene	73
bromobenzene	trifluoromethylbenzene	38
p-bromotrifluoromethylbenzene	1,4-bis(trifluoromethyl)benzene	62
o-bromotoluene	o-trifluoromethyltoluene	49

The trifluoromethylation of pentafluoroiodobenzene (79) gave two other products besides the expected octafluorotoluene (80), these were decafluorobiphenyl (81) and pentafluorobenzene (82).

$$\begin{array}{ccccccccc} (CF_3)_2Hg + & C_6F_5I & + Cu & \xrightarrow[\text{3hrs, }140^\circ C]{NMP, N_2,} & C_6F_5CF_3 & + & (C_6F_5)_2 & + & C_6F_5H \\ & & & & 25\% & & 7\% & & 28\% \\ & (79) & & & (80) & & (81) & & (82) \end{array}$$

This is the only reaction in which reductive dehalogenation (82) and Ullman coupling (81) have been observed. As copper(I) iodide, unlike metallic copper, is not known to promote Ullman coupling or reduction[103] it has been used in place of copper in an attempt to avoid these side reactions. No formation of the biphenyl occurred but the yield of (82) increased considerably.

$$\begin{array}{ccc} (CF_3)_2Hg + C_6F_5I + CuI \xrightarrow[3hrs,\,140^{\circ}C]{NMP,\,N_2,} & C_6H_5CF_3 + & C_6F_5H \\ & 19\% & 81\% \\ (\underline{79}) & (\underline{80}) & (\underline{82}) \end{array}$$

2.C.ii Mechanism

The results outlined in the previous section cast doubt upon the original suggestion that trifluoromethyl copper (78) is an intermediate in the reaction. However, as no trifluoromethylbenzene is obtained on heating a mixture of iodobenzene and bis(trifluoromethyl)mercury (76) under reaction conditions and no decomposition of (76) is observed, the copper obviously plays an essential part in the reaction. An excess of copper is used in the reaction and if the quantity added is reduced eightfold, such that it becomes the limiting reagent, the yield of (7) is reduced from 83% to 32% which discounts the suggestion that copper plays a catalytic role.

$$\begin{array}{ccc} (CF_3)_2Hg + C_6H_5I \xrightarrow[140^{\circ}C,3hrs]{NMP,\,Cu\ (x^1/_8),} & C_6H_5CF_3 & 32\% \\ (\underline{76}) & (\underline{7}) & \end{array}$$

The solid residue obtained from the trifluoromethylation of iodobenzene contained 83% of the mercury and 87% of the copper originally added to the mixture. The mercury was present as metallic mercury but it could not be ascertained whether the copper was in the form of copper(0) or copper(I) iodide.

Following the success of the "one-pot" trifluoromethylation reactions and the observations that no reaction occurs between the mercurial (76) and iodobenzene [101] or copper and (76) it appears that both the aromatic halide and copper are involved in the first step of the reaction and two intermediates have been suggested. The copper could insert into the aryl carbon-halogen bond forming an organocopper compound (83). Direct reaction between (76) and (83) is unlikely, however, since both the aryl and trifluoromethyl groups carry a formal negative charge.

$$\mathrm{Cu} + \mathrm{Ar{-}I} \longrightarrow \underset{(\underline{83})}{\mathrm{Ar{-}Cu{-}I}} \xrightarrow{\mathrm{Hg(CF_3)_2}\ (\underline{76})} \mathrm{ArCF_3} + \mathrm{CuI}$$

Alternatively copper(I) halide, formed in situ from reaction between copper and halogen produced by the decomposition of a small amount of arylhalide, could combine with the trifluoromethyl group forming an intermediate (84) which then attacks the aryl halide.

$$\mathrm{CuI} + \underset{(\underline{76})}{\mathrm{(CF_3)_2Hg}} \longrightarrow \underset{(\underline{84})}{\mathrm{CuCF_3I}} \xrightarrow{\mathrm{ArI}} \mathrm{ArCF_3} + \mathrm{CuI}$$

If this was the reaction pathway the addition of a small amount of iodine might be expected to increase the yield of trifluoromethylbenzene but only a small increase from 83% to 88% occurred which is not conclusive. Although copper(I) iodide will promote the reaction if used instead of copper the yield of (7) is somewhat decreased. However, copper(I) iodide added to the reaction mixture could well be less reactive than that produced in situ.

$$(CF_3)_2Hg + C_6H_5I \xrightarrow[140^{\circ}C, 3hrs]{CuI, NMP, N_2} \underset{(7)}{C_6H_5CF_3} \qquad 53\%$$

The substituents on the benzene ring have very little effect on the yields of trifluoromethylated products, but iodobenzenes are more reactive than the bromobenzenes. This could reflect the greater strength of the carbon-bromine bond compared to that of carbon-iodine, or the greater polarisability of iodine compared to bromine. The latter would be important in a concerted process where copper is pulling the halogen away as the trifluoromethyl group attacks the aromatic ring. The differing reactivity of iodo- and bromobenzenes also suggests that the cleavage of the carbon-halogen bond is part of the rate determining step.

2.D. Conclusion

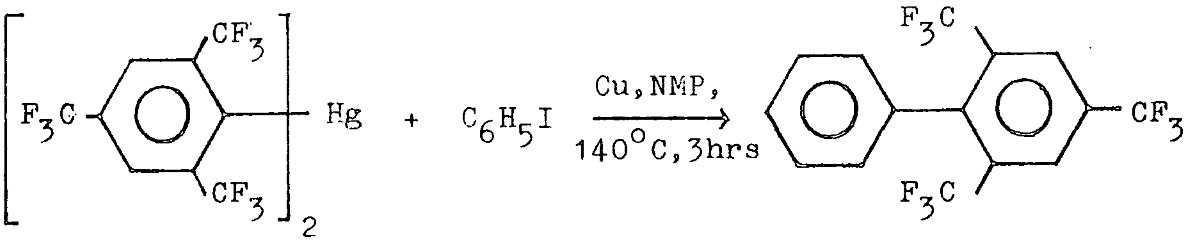
It has been demonstrated that the reaction between an aromatic iodide or bromide and bis(trifluoromethyl)mercury in the presence of copper is an effective method for the introduction, in high yield, of the trifluoromethyl group into a specific site within an aromatic system. The mechanisms of copper promoted substitution reactions are not in general well understood and conflicting experimental results, which cannot be encompassed by one mechanism, have been obtained. In this case it has been shown that trifluoromethylcopper is not, as first suggested, an intermediate and some alternatives have been given.

The reaction could be extended to allow the introduction of higher perfluoroalkyl groups to be carried out. A route to bis(perfluoroalkyl)mercurials has been developed which involves reaction between a perfluoroalkyl anion, generated from fluoride ion and a perfluoroalkene, and mercury(II) fluoride or chloride.[104]

$$R_fCF{=}CF_2 \xrightarrow{F^-} R_f\overset{-}{C}FCF_3 \xrightarrow{HgCl_2} (R_fCFCF_3)_2Hg$$

If these mercurials react in a similar way to bis(trifluoromethyl)mercury with haloaromatic compounds, a novel and simple route from alkenes to perfluoroalkyl benzenes would be available.

Bis(2,4,6-tris(trifluoromethyl)phenyl)mercury (85) has been used to prepare 2,4,6-tris(trifluoromethyl)biphenyl (86), a reaction which is described in Chapter 6.



(85) (86)

Chapter 3

Sodium Trifluoroacetate as a Source of the Trifluoromethyl Group. (I) Synthesis.

3.A. Introduction

A route to trifluoromethylsubstituted aromatic compounds using sodium trifluoroacetate as a source of the trifluoromethyl group has recently been outlined by some Japanese workers.[105] The reaction, carried out in the presence of copper(I)iodide, results in the substitution of bromine or iodine in an aromatic halide with the trifluoromethyl group.

$$\mathrm{ArI} \xrightarrow[\text{n-methylpyrrolidone}]{\mathrm{CF_3COO^-Na^+/CuI}} \mathrm{ArCF_3}$$

The reaction has been carried out for the substituted benzenes and pyridine, as shown in Table (3.1), the resulting trifluoromethyl compounds being produced in high yield. A similar reaction has been used to trifluoromethylate iodopentamethylbenzene in hexamethylphosphoramide solution[106] but in this case a considerable amount of the parent hydrocarbon was also formed along with a small amount of the decamethyldiphenylether.

Table (3.1) Trifluoromethylation of Aromatic Halides with Sodium Trifluoroacetate[105]

Aromatic Compound	Product	Yield✲ %	
m-iodotoluene	m-trifluoromethyltoluene	88	
p-iodonitrobenzene	p-nitrotrifluoromethylbenzene	47	(39)‡
p-chloroiodobenzene	p-chlorotrifluoromethylbenzene	68	
p-iodomethoxybenzene	p-methoxytrifluoromethylbenzene	59	(42)‡
1-iodonaphthalene	1-trifluoromethylnaphthalene	82	(78)‡
m-bromotoluene	m-trifluoromethyltoluene	58	
2-bromopyridine	2-trifluoromethylpyridine	41	

✲ yields determined by g.l.c.

‡ yields isolated by column chromatography

This method has several advantages over that using bis(trifluoromethyl)mercury outlined in the previous chapter in that the starting material is easily prepared, the whole process can be carried out at atmospheric pressure, and the use of toxic mercurials is avoided.

3.B. Trifluoromethylation using Sodium Trifluoroacetate.

3.B.i. The Nature of the Halogen.

Iodobenzene when heated at 160°C with copper(I) iodide and sodium trifluoroacetate (87) in n-methylpyrrolidone (NMP) for four hours under a nitrogen atmosphere, as described in the original paper,[105] is converted into trifluoromethylbenzene (7) in 87% yield.

$$C_6H_5I \quad + \quad \underset{(87)}{CF_3COONa} \quad + \quad CuI \quad \xrightarrow[160^\circ C, 4hrs]{NMP, N_2} \quad \underset{(7)}{C_6H_5CF_3} \qquad 87\%$$

Bromobenzene, when treated similarly, gave a slightly lower yield (68%) of (7). Chlorobenzene could not be trifluoromethylated under these conditions and was unchanged. This trend in reactivity, $C_6H_5I > C_6H_5Br \gg C_6H_5Cl$, is similar to that shown in the trifluoromethylation reactions with bis(trifluoromethyl)mercury but the difference in reactivity between bromo- and iodobenzene is much less marked.

Although substitution of chlorine in chlorobenzene was not achieved, some chloroaromatic systems which are activated toward nucleophilic attack have been trifluoromethylated. This was first observed in the trifluoromethylation of 2-chloro-5-iodo-pyridine when a small amount (7%) of 2,5-bis(trifluoromethyl)pyridine (88) was formed. Trifluoromethylation of 2-chloro-5-trifluoromethylpyridine gave 27% of (88).

3.B.ii. Yields of Trifluoromethylated Products.

The scope of the reaction in the original work was confined to introducing one trifluoromethyl group into a substituted halobenzene or pyridine.[105] This method has now been extended to include a wider range of benzenoid and heterocyclic compounds and also some non-aromatic halogen compounds. It has also proved possible to introduce more than one trifluoromethyl group into a molecule. The yields quoted in the tables in this section are all calculated from the g.l.c. traces of the reaction mixtures using an internal standard because they are a reproducible measure of the extent of reaction whereas isolated yields are dependent upon the efficiency of the separation techniques used.

3.B.ii.a. Benzenoid Aromatic Compounds.

The yields of a range of substituted trifluoromethylbenzenes produced by this method are shown in Table (3.2). Substituents on the benzene ring, whether electron donating or withdrawing, have little effect upon the yield of trifluoromethylated product. The only exception to this

Table (3.2) Formation of Trifluoromethyl Derivatives of Benzenoid Aromatic Compounds

Halocompound	Equivalents of CF_3COONa	Product	Yield %
iodobenzene	1	trifluoromethylbenzene	84
p-iodonitrobenzene	1	p-nitrotrifluoromethylbenzene	64
1,4-diiodobenzene	2	1,4-bis(trifluoromethyl)benzene	93
	1	1,4-bis(trifluoromethyl)benzene	24
		p-iodotrifluoromethylbenzene	24
p-iodotrifluoromethylbenzene	1	1,4-bis(trifluoromethyl)benzene	73
p-chloroiodobenzene	1	p-chlorotrifluoromethylbenzene	98
o-chloroiodobenzene	1	o-chlorotrifluoromethylbenzene	87
iodopentamethylbenzene	1	pentamethyltrifluoromethylbenzene	60 ✲
pentafluoroiodobenzene	1	decafluorobiphenyl	44
		pentafluorobenzene	46
bromobenzene	1	trifluoromethylbenzene	68
m-bromotoluene	1	m-trifluoromethyltoluene	78
p-bromotrifluoromethylbenzene	1	1,4-bis(trifluoromethyl)benzene	62
1,3,5-tribromobenzene	3	1,3,5-tris(trifluoromethyl)benzene	48

✲ Calculated from ^{19}F nmr spectrum of the reaction mixture with an internal standard.

is pentafluoroiodobenzene, the most electron deficient iodobenzene derivative used, which is not trifluoromethylated but converted into the Ullmann coupled and reductively dehalogenated products in approximately equivalent yields. When bis(trifluoromethyl)mercury was used to trifluoromethylate pentafluoroiodobenzene these compounds were formed in addition to the expected product octafluorotoluene.

3.B.ii.b. Heterocyclic Aromatic Compounds.

The yields of trifluoromethylated products from heterocyclic compounds shown in Table (3.3) are generally lower than those from benzene deriatives. This reduction in yield is thought to result from formation of co-ordination complexes between the heterocycle and copper(I) ions. The copper is prevented from assisting the decarboxylation of the trifluoroacetate ions and this is reflected in the large amounts of sodium trifluoroacetate shown by ^{19}F nmr to be present after the reaction. The effects of co-ordinating agents upon the reaction will be considered in more detail in (4.B.ii.c.).

It was expected that the trifluoromethylation of 2-amino-5-iodopyridine would prove difficult because of the possibility of co-ordination between the amino group and copper(I) iodide and so the acetylated form (89) was prepared. In neither case was any trifluoromethylation observed and a bright red tar was obtained from (89) suggestive of complex formation. Only half of the

Table (3.3) Formation of Trifluoromethyl Derivatives of Heterocyclic Compounds.

Halocompound	Product	Yield %
2-amino-5-iodopyridine	-	-
2-amino-5-iodopyridine acetyl derivative	-	-
2-chloro-5-iodopyridine	2chloro-5-trifluoromethylpyridine	85
	2,5-bis(trifluoromethyl)pyridine	7
2-chloro-5-trifluoromethylpyridine	2,5-bis(trifluoromethyl)pyridine	27
2-iodothiophene	2-trifluoromethylthiophene	46
2-bromopyrimidine	2-trifluoromethylpyrimidine	34
2-iodo-n-methylimidazole	-	-

2-iodothiophene used in the reaction could be accounted for as either the trifluoromethylated product or recovered thiophene and as the copper(I) iodide remained in the solution after the reaction it is assumed that a complex was formed. Imidazoles, which could not be trifluoromethylated, are known to form copper-complexes.[56]

3.B.ii.c. Non-Aromatic Compounds.

In order to investigate the possibility of using this method to substitute a halogen not directly attached to an aromatic ring, the trifluoromethylation of an alkyl, alkenyl, and alkynyl halide was attempted. The halides used were chosen because they were readily available, or could be easily prepared, and both they and the potential trifluoromethylated compound were sufficiently involatile so as not to present any practical difficulties. The results are summarised in Table (3.4).

Table (3.4) Formation of Trifluoromethyl Derivatives of Non-Aromatic Compounds

halocompound	product	yield %
(2-bromoethenyl)benzene	3,3,3-trifluoroprop-1-enylbenzene	53
(2-bromo-2-fluoroethenyl)benzene	3,3,3,2-tetrafluoroprop-1-enylbenzene	59
phenylbromoacetylene	1,4-diphenyl-1,3-butadiyne	72
n-iodopentane	1,1,1-trifluorohexane	40

The reaction mixture after the attempted trifluoromethylation of the alkynyl halide, phenylbromoacetylene, contained no volatile products and no fluorine. Extraction of the mixture with diethyl ether gave a crystalline solid which proved to be 1,4-diphenyl-1,3-butadiyne in 72% yield. It appears that in this case Ullman-type coupling takes place in preference to trifluoromethylation. The reaction was unusual in that on mixing the reactants the copper(I) iodide dissolved immediately forming a turquoise solution, possibly a copper acetylide had been formed. The same product has also been produced by reaction between copper(I) iodide and the acetylene alone, although in a smaller yield.

The alkyl halide, n-iodopentane, has been trifluoromethylated forming 1,1,1-trifluorohexane, a volatile liquid which was separated from most of the solvent by vacuum transference. A small amount of pentane was also formed. The mass spectrum showed clearly the breakdown pattern for a C_5 alkyl chain and the trifluoromethyl group at 69 a.m.u., however no molecular ion was observed. The presence of the trifluoromethyl group was confirmed by the ^{19}F nmr spectrum.

3.B.iii. Isolation of the Products.

Various techniques have been used to isolate the trifluoromethylated products including steam distillation and extraction, both continuously and in a separating funnel, of the aqueous solution of the reaction mixture with a solvent such as pentane or methylene chloride. As a result of these experiments two methods have proved to be particularly satisfactory and the decision as to which is used depends upon the volatility of the product. Volatile materials, such as 1,3,5-tris(trifluoromethyl)-benzene, have been isolated by a variation on the flash distillation process in which the reaction mixture is dropped onto heated glass wool and the volatile products are swept by a constant nitrogen flow into a trap cooled in liquid air. The product can be taken up in ether and washed with water to remove any solvent which may have been carried across. Initially the process was carried out under vacuum but larger quantities of solvent were carried into the trap. Less volatile products can be isolated by adding the reaction mixture to two or three times its own volume of water and extracting the solution with pentane. The pentane can be mostly removed by distillation through a vigreux column and analytically pure samples were obtained by preparative g.l.c. This process was used to isolate ^{14}C-labelled p-chloropentafluoroethylbenzene which, because of its radioactive label, could be followed throughout the extraction using a Geiger counter. The aqueous reaction mixture was washed with pentane until the activity remained constant. Of the product formed in the reaction 80% was extracted into pentane solution along with some recovered iodo-compound.

Attempts were made to remove some of the problems encountered in isolating the products by reducing the volume of NMP used or changing the solvent. However most of the changes made had an adverse effect on the yield of trifluoromethylated product and were consequently abandoned. In decreasing the solvent to a half and a quarter of the original volume the yields of trifluoromethylbenzene, produced from iodobenzene, decreased dramatically from 81% to 42% and 30% respectively. The boiling point of NMP is not sufficiently different from those of the trifluoromethylated products to allow complete separation by vacuum transference or flash distillation in every case. If the high boiling point solvents, sulpholane and diphenylsulphone (m.p.150°C) proved to be good solvents for the trifluoromethylation reaction it would be possible to distil the volatile products from the reaction mixture. However, in both cases, iodobenzene was recovered after attempted trifluoromethylation. Dimethylformamide, in which iodobenzene was converted to trifluoromethylbenzene in 70% yield, has proved to be nearly as good a solvent as NMP.

3.B.iv. Reductive Dehalogenation.

A study of the trifluoromethylation of bromobenzene has been carried out using a mixture of 'cold' bromobenzene and ^{14}C-labelled material allowing the reaction to be followed by g.l.c. Surprising results were obtained because, instead of an expected 70% yield of trifluoromethylbenzene, only 57% of the trifluoromethylated product was formed and 16% of the bromobenzene had been reductively dehalogenated forming benzene.

The original paper[105] claims that the intrusion of moisture causes hydrogen substitution of the halogen to occur, but as the materials had all been dried and stored under nitrogen it seemed unlikely that this was the explanation. Furthermore, when the reaction was carried out with added water neither trifluoromethylbenzene nor benzene were formed and an orange solid was precipitated which appeared from analysis to be copper mixed with a small amount of copper(I) iodide.

The reaction mixture was analysed by radio-g.l.c. which has an advantage over the gas density balance in that the peak areas are independent of temperature. As a result of this the chromatogram was run with a temperature ramp from 80°C - 180°C and the improved resolution may have resulted in the separation of the benzene and trifluoromethylbenzene peaks which had coalesced in previous chromatograms run at a constant high temperature. In order to ensure that this had not occurred a reaction mixture from the trifluoromethylation of 'cold' bromobenzene was analysed by g.l.c. using several different temperatures and column packings but no evidence of benzene formation was observed.

As a consequence of the fact that benzene formation has only been observed in the reaction of labelled bromobenzene it has been suggested that the radioactivity has caused a change in the reaction path. However, no benzene was formed in the trifluoromethylation of ^{14}C-iodobenzene and although radiolabelled materials have been observed to take different, and often free radical, paths to that taken when 'cold' materials are used, the activity is usually much higher than in this case.[107]

The formation of reductively dehalogenated products has also been observed in the trifluoromethylation of pentafluoroiodobenzene and 1,3,5-tribromobenzene. It could be that this side reaction occurs to some very small extent in all reactions but only becomes noticeable in a few cases for a reason yet to be recognised.

3.C. Halogen Exchange.

Halogen exchange was first noticed in the trifluoromethylation of ^{14}C-labelled bromobenzene. A small peak, containing 4% of the activity present in the solution, was seen in the radio-chromatogram of the reaction mixture and was shown by comparison of retention times to be iodobenzene. This was confirmed by m.s.g.l.c. analysis of the reaction mixture for a similar reaction using unlabelled bromobenzene. When the initial amount of sodium trifluoroacetate was reduced this side reaction occurred in preference to trifluoromethylation and iodobenzene was formed in 37% yield. Halogen exchange will also occur when copper(I) iodide and bromobenzene are heated together. The 23% yield of iodobenzene obtained after heating this mixture overnight, in order to be sure that equilibrium had been reached, can be increased to 37% by heating for a further two hours after the addition of a small amount of sodium trifluoroacetate. Unlike the trifluoromethylation reaction, halogen exchange is not affected by moisture.

Halogen exchange between copper(I) halides and halobenzenes is a well known reaction but this example is unusual since it is not favoured by the observed ease of halogen displacement in either the aryl halide (ArI>ArBr>ArCl) or copper(I) halide (CuCl>CuBr>CuI).[108] Previous work has shown that whilst conversion of 1-iodonaphthalene (<u>90</u>) to 1-bromonaphthalene with copper(I) bromide can be achieved quantitively, the reverse reaction gives (<u>90</u>) in only 30% yield even after prolonged heating with a tenfold excess of copper(I) iodide.[109]

$$\begin{array}{ccccccc} C_{10}H_7I & + & CuBr & \xrightarrow[\text{24hr, 115°C}]{\text{pyridine}} & CuI & + & C_{10}H_7Br \\ 0{\cdot}08\text{mol} & & 0{\cdot}8\text{mol} & & & & 100\% \\ (\underline{90}) & & & & & & \end{array}$$

$$\begin{array}{ccccccc} C_{10}H_7Br & + & CuI & \xrightarrow[\text{24hr, 115°C}]{\text{pyridine}} & CuBr & + & C_{10}H_7I \\ 0{\cdot}08\text{mol} & & 0{\cdot}8\text{mol} & & & & 30\% \\ & & & & & & (\underline{90}) \end{array}$$

This exchange of bromine for iodine has been noted in aromatic dye compounds and maximised by addition of sodium iodide to the reaction mixture.[103] Halogen exchange between iodobenzenes and sodium iodide – 131 catalysed by copper and copper(I) salts has been used as a method of preparing radiolabelled iodoarenes.[110] Various combinations of copper and sodium iodide were used in an attempt to maximise the yield in the bromobenzene/copper(I) iodide system, the results of which are shown in Table (3.5). The reaction mixtures were analysed after various time intervals by g.l.c. and the ratio of bromo- and iodobenzenes calculated from the peak areas. Equilibrium was obtained within the first hour of reaction in all cases. The results show that while addition of sodium iodide in a quantity equal to or less than the amount of copper(I) iodide increases the amount of halogen exchange slightly, addition of any greater quantity causes the yield of iodobenzene to fall considerably.

Table (3.5) Maximisation of Halogen Exchange by Addition of Sodium Iodide.

C_6H_5Br (mmol)	CuI (mmol)	NaI (mmol)	C_6H_5I/C_6H_5Br
5	10	-	0·31
5	20	-	0·14
5	10	10	0·40
5	20	10	0·39
5	10	20	V.small

The increase in the yield of iodobenzene when a stoichiometric amount of sodium iodide is added can be explained by the formation of the soluble complex ion $[CuI_2]^-$. Reaction would be expected to be easier in a homogeneous solution. This idea can also be extended to explain the beneficial effect of a small amount of sodium trifluoroacetate since it is possible that $[Cu(CF_3COO)I]^-$ is formed. When larger amounts of sodium iodide are added the position of equilibrium for complex formation will be driven towards co-ordinatively saturated species which inhibit the reaction. Halogen exchange is an example of copper assisted nucleophilic substitution, a class of reaction which is subject to spectacular solvent effects and inhibitions by ligands.[111]

Chapter 4

Trifluoromethylation Reactions using Sodium Trifluoroacetate as a Source of the Trifluoromethyl Group (II) Mechanism

4.A. Introduction

In the previous chapter sodium trifluoroacetate was shown to be a readily available source of the trifluoromethyl group which, in the presence of copper(I) iodide, can be introduced into a range of iodo-or bromo-substituted benzenoid and heterocyclic aromatic compounds. Having proved the synthetic utility of the method, the work described in this chapter set out to investigate the reaction mechanism. Experimental results have led to the conclusion that the reaction is an example of copper assisted nucleophilic attack and so, before discussing the trifluoromethylation reaction, the chemistry of copper and its role in promoting nucleophilic attack will be discussed briefly.

4.A.i. Copper Chemistry

4.A.i.a. Oxidation States[108,112]

Copper is the twenty-ninth element in the periodic table and has the electronic structure $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^6\ 3d^{10}\ 4s^1$. The first three ionisation potentials are 7·72, 20·29 and 36·83 eV and it is the relatively high first ionisation potential which contributes to the 'noble' character of the metal. Copper has two principle oxidation states +1 and +2, although in a few complexes it is found in the +3 state.

The relative stabilities of the 0, I, and II oxidation states are very sensitive to changes in the environment and the equilibrium (1) can easily be displaced in either direction.

$$(1) \quad 2\ Cu(I) \rightleftharpoons Cu(0) + Cu(II)$$

Although in the gas phase the equilibrium is strongly in favour of Cu(I) in aqueous solution the large heat of hydration of Cu(II) compared with that of Cu(I) compensates for the higher second ionisation potential making hydrated Cu(II) the more stable state. All simple copper(I) salts disproportionate in water, with the equilibrium constant $K \approx 10^6$. This constant varies greatly in the presence of ligands for which Cu(I) and Cu(II) have different affinities, copper(I) is stabilised by ammonia as the ion $[Cu(NH_3)_2]^+$ ($K = 2x10^{-2}$) whereas the chelating ligand, 1,2-diaminoethane, coordinates preferentially with Cu(II)($K = 10^5$). It is normally found that the Cu(I) state becomes more stable as the covalent nature of the Cu-X bond increases with polarising ligands. This is illustrated in the increasing stability of copper(I) halides on descending the group from fluorine to iodine. The electrode potentials suggest that no copper(I) iodide would be formed in reaction (2) if it were a completely ionic substance whereas in fact the reaction goes to completion, partially assisted by the low solubility of the iodide.

$$(2) \quad Cu^{2+} + 2I^- \longrightarrow CuI + \tfrac{1}{2}I_2.$$

4.A.i.b. Complex Formation

Copper(I) forms thermodynamically stable compounds with polarisable or π accepting ligands such as alkenes, alkynes and aromatic nuclei[108]. The bonding between the ligand and metal in the latter case is synergic, with σ-donation from the ligand to the metal ion and π-donation from the metal d-orbitals into empty π^* orbitals of the ligand. The stability of copper(I) halide complexes in aqueous solution increases in the order $Cl < Br < I$. Synergic bonding with the halogen d-orbitals and polarisation of the halogen by the copper(I) ion have both been suggested to occur in these complexes. When associated with polarisable or π-bonding ligands copper(I) usually has the co-ordination number four and tetrahedral stereochemistry but with other ligands such as ammonia the co-ordination number is two and two linear bonds are formed.

Copper(II) forms complexes with numerous ligands[113] and exhibits the co-ordination number either six or four. The stereochemistry of these complexes is either distorted octahedral or square planar.

Complex formation occurs as a stepwise process involving a series of equilibria for each of which there is an equilibrium constant.

$$M + L \overset{K_1}{\rightleftharpoons} ML$$

$$ML + L \overset{K_2}{\rightleftharpoons} ML_2$$

$$ML_2 + L \overset{K_3}{\rightleftharpoons} ML_3 \quad \text{etc.}$$

Typically the equilibrium constants decrease $K_1 > K_2 > K_3$ because as each successive ligand adds there are less available sites and an increased possibility of steric hindrance from the ligands already attached. If the ligands are charged electrostatic effects also hinder further addition. There are however some exceptions to this general trend.

Both copper(I) and copper(II) are suited to catalyse numerous organic reactions because of their ability to form complexes with a wide variety of ligands and because formation and dissociation of these complexes can occur very rapidly. The small energy difference between the oxidation states can also be important since after conversion of the metal or its salts to another oxidation state during a catalysed reaction, an oxidising or reducing agent within the system can promote reversion to the original state so regenerating the active species.

4.A.ii. Copper Assisted Nucleophilic Aromatic Substitution.

The ipso substitution of aryl halide promoted by copper compounds was first described by Ullmann in 1901 and since then has become a widely used reaction.[111] Two kinds of copper promoted reactions, both of which are formally nucleophilic aromatic substitutions, are shown in Scheme (4.1.) These are ligand exchange reactions (A) and copper catalysed reactions of an aryl halide with a nucleophile, in which the copper is present as the metal, oxide or a salt (B). It has been proposed that copper(I) species are intermediates in the catalytic reaction and so both processes may share the same mechanism.[114]

Scheme (4.1.) Copper Promoted Nucleophilic Attack upon Aromatic Halides.

(A) $\text{ArHal} + \text{CuNuc} \longrightarrow \text{ArNuc} + \text{CuHal}$

(B) $\text{ArHal} + \text{Nuc}^- \ (\text{NucH}) \xrightarrow{\text{Cu}^+} \text{ArNuc} + \text{Hal}^- \ (\text{HHal})$

Hal = I, Br, Cl NucH = ArNH_2, ArOH

Nuc^- = I^-, Br^-, Cl^-, CN^-, OH, C:CAr, ArO, ArS etc.

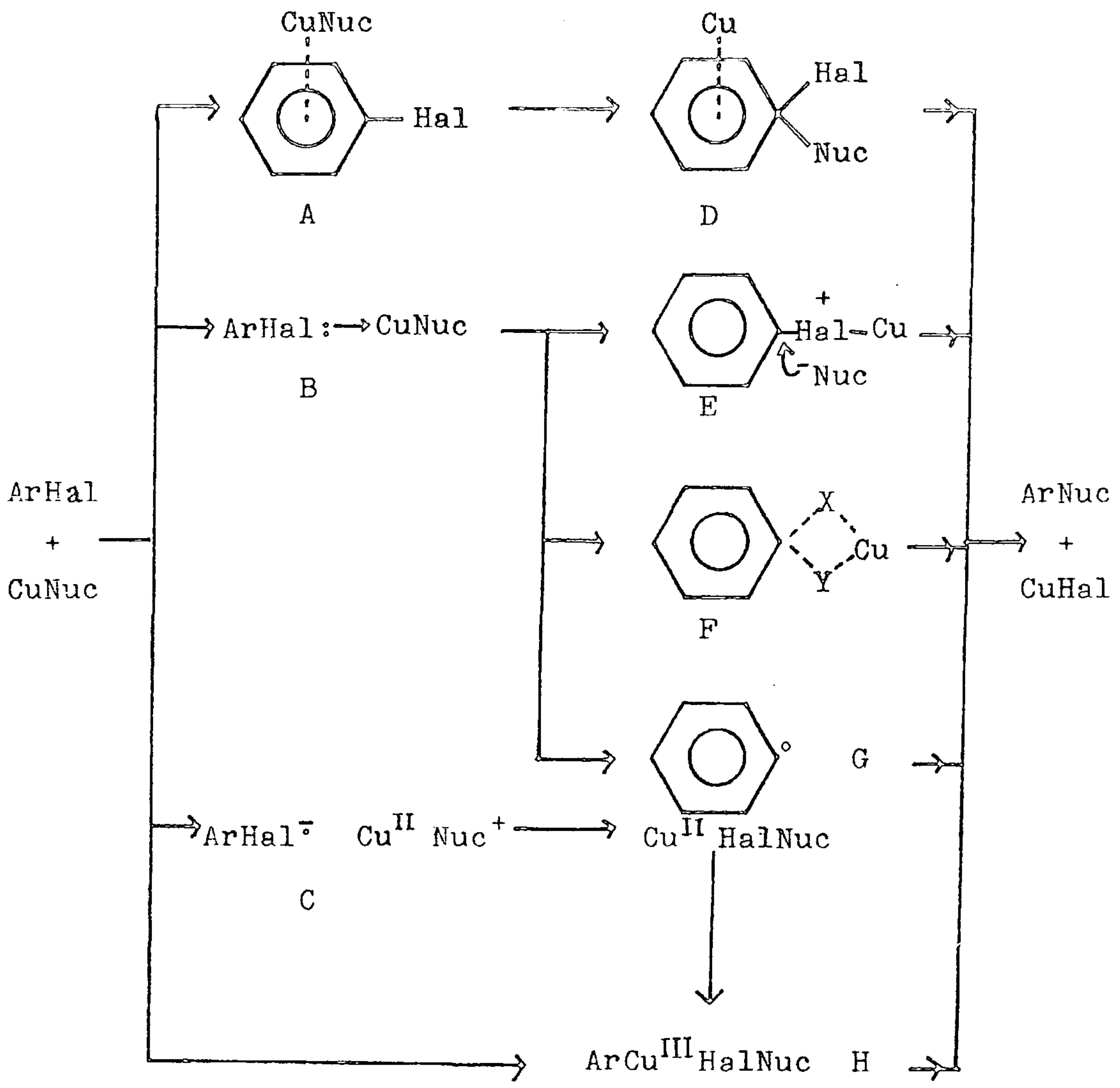
These reactions have been the subject of reviews[108,111,115] and recently a kinetic study of the ligand exchange process was carried out.[114]

Any mechanism for these nucleophilic reactions must be able to explain the observed order of halogen reactivity, which is opposite to that of uncatalysed reactions, the slight effect of meta-or para-substituents compared with the marked activating effect of chelating ligands in the ortho-position, and the specific attack at halogen.

The susceptibility of these reactions to solvent effects and inhibitions by ligands suggests that formation of a co-ordination complex between the aryl halide and copper is an important feature of the reaction. If this assumption is true the mechanistic problems involve the structure of the intermediate and its decomposition into products, possible routes for this are shown in Scheme (4.2.)[111]

There have been several reports of the derivation of Hammett Plots for these reactions[111] all of which have given σ values in the range 0·1 - 1·1 which, while suggesting nucleophilic character, are low compared with those for nucleophilic aromatic substitutions in the absence of copper. Low σ values have been reported to be characteristic of reactions which involve a bridge weakly transmitting the electron withdrawing effect of the substituent between the aromatic ring and reaction centre,[111] arguments which have been used to support the initial formation of the complex B. The ease of formation of this complex should follow the polarisability of the halogen, explaining the observed order of exchange I $>$ Br $>$ Cl, and be assisted by a chelating ortho-substituent. The proposed intermediacy of the π-complex (A) cannot explain either of these observations. After the formation of B, ligand exchange can occur through three possible intermediates, all of which have been considered in the mechanism of copper promoted halogen exchange.[108] These are intermediate ionisation (E), formation of a radical with the copper alternating between oxidation states I and II (G), and a four-centre concerted process (F). The ionic mechanism (E) was found attractive since a positive charge upon the halogen would increase its lability to nucleophilic attack.[115] An objection to the formation of an intermediate radical is that formation of a bivalent iodine-containing

Scheme (4.2) Possible Intermediates in the Copper Assisted Nucleophilic Substitution of Aromatic Halides[111]



species is unlikely.[108] However G has since been suggested as an intermediate resulting from the radical ion C in an electron-transfer mechanism,[114] and has the advantage that loss of the phenyl radical from the solvent cage would result in the reductive dehalogenation often seen as a side reaction. It has also been suggested that a trivalent copper species formed from G[111,114] or directly by insertion of copper into the aryl carbon-halogen bond[111] could be a possible intermediate.

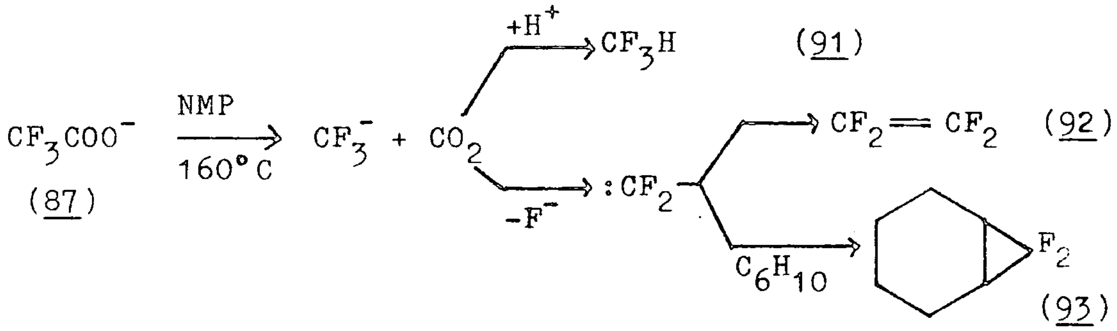
This brief discussion lends weight to the point made earlier in Chapter 2 that copper promoted reactions are, in general, not well understood and many experimental results have been reported which cannot be encompassed by a single mechanism.

4.B. Investigation of the Reaction Mechanism.

4.B.i. The Role of Sodium Trifluoroacetate.

On prolonged heating of a mixture of bromobenzene, copper(I) iodide, and sodium trifluoroacetate (87) the yield of trifluoromethylbenzene reached a maximum of 57% despite the fact that some bromobenzene remained. Further bromobenzene was added to displace the equilibrium which might have been achieved, but neither this nor the addition of copper(I) iodide had any effect on the yield of trifluoromethylbenzene, although more iodobenzene was formed by halogen exchange. The addition of a further amount of sodium trifluoroacetate was necessary to cause trifluoromethylation of the remaining bromobenzene, which was surprising since (87) was originally present in a fourfold excess.

Trifluoromethylation of iodobenzene with the concentration of (87) reduced eightfold, such that it became the limiting reagent, showed that only 22% of the trifluoroacetate was converted into the trifluoromethyl group and the ^{19}F nmr spectrum of the reaction mixture indicated that trifluoromethylbenzene was the only fluorine-containing compound present. Fluorine must be lost from the system and the most likely explanation is that decarboxylation of the trifluoroacetate (87) occurs at reaction temperature and fluoroform (91) is lost from the system. Tetrafluoroethylene (92) is another possible product of decarboxylation but its formation, by difluorocarbene coupling, would result in fluoride ion remaining in solution.



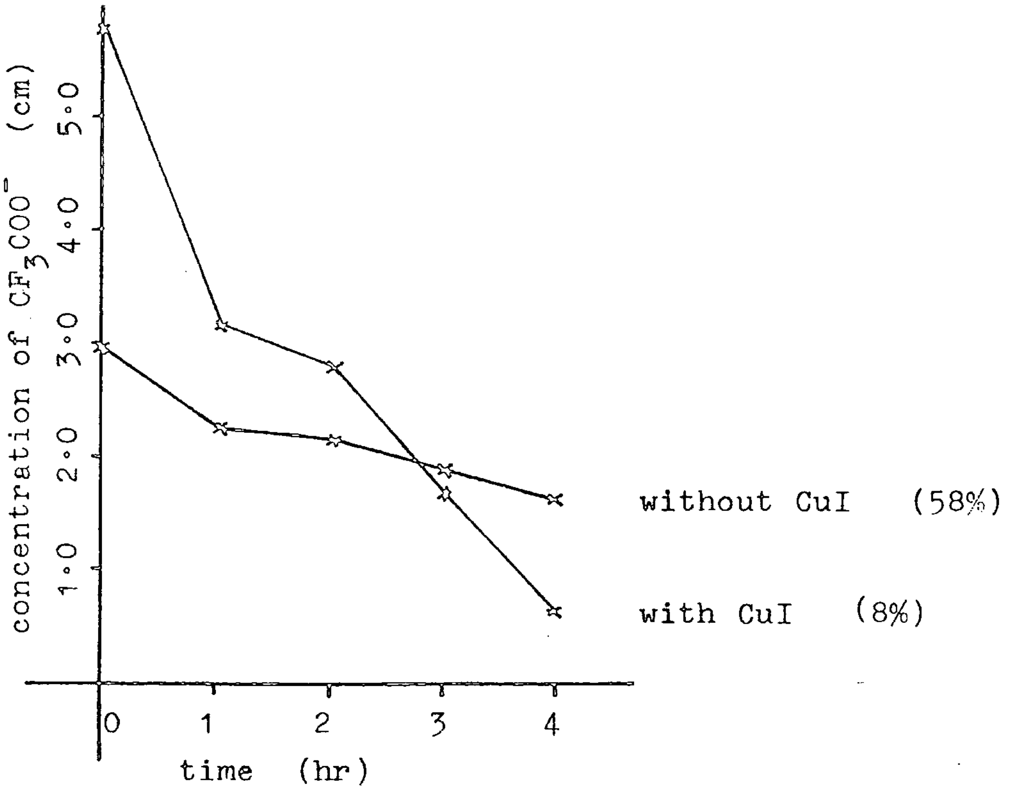
Formation of fluoroform was demonstrated by heating a solution of (87) and cyclohexene in NMP and using a cold trap to collect the gas given off. Any difluorocarbene produced would have been trapped by the cyclohexene but no difluoronorcarane (93) was observed in the g.l.c. trace of the mixture. The reaction was also repeated in the presence of benzene and pentafluoropyridine, acting as radical and anion traps respectively, to determine whether decarboxylation proceeded via anion or radical intermediates. In neither case were products from trapping observed. It was found that tetrafluoropyrimidine, an excellent anion trapping agent, decomposed on heating in NMP.

4.B.i.a. Copper Promoted Decarboxylation.

Decarboxylation of (<u>87</u>) has been carried out both alone and in the presence of copper(I) iodide, the reaction being followed by integrating the ^{19}F nmr peak areas of samples taken at regular intervals. This process was more difficult for solutions containing copper(I) iodide since low concentrations of paramagnetic copper(II) ions caused peak broadening to occur. The results are shown in Diagram (4.1.) and indicate that decarboxylation occurs in both cases but that copper(I) iodide assists the process almost doubling the rate of reaction.

Special apparatus was designed in order to collect and measure the quantities of gases produced in the decarboxylation process. A sealed vessel which could be opened directly into a vacuum line via a glass-metal seal was used for the reaction and gaseous products were condensed through a tube filled with carbosorb, to remove carbon dioxide, into a gas bulb of known volume. The gas collected was shown by i.r. spectroscopy to be fluoroform and the quantity produced was calculated from the pressure exerted by the known volume. Carbon dioxide produced was measured by weighing the carbosorb tube before and after

Diagram (4.1) Decarboxylation of Sodium Trifluoroacetate



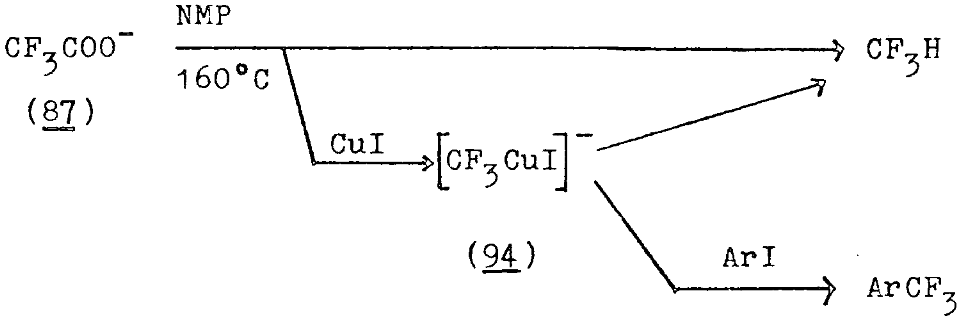
absorption. Decarboxylation of sodium trifluoroacetate alone gave rise to a 50% yield of fluoroform and in the presence of copper(I) iodide between 50-75% of (87) decarboxylated.

These results explain the necessity for a large initial excess of trifluoroacetate since decarboxylation occurs freely at the reaction temperature in both copper promoted and uncatalysed processes and only a small amount of the trifluoroacetate is involved in further reaction to form the trifluoromethylated product. The ^{19}F nmr signal at 80·4 p.p.m. observed in most reaction mixtures can be assigned to fluoroform entrained in the solution.

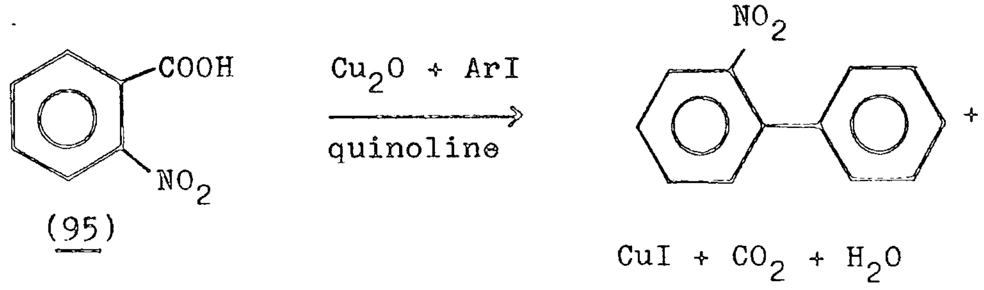
In the copper promoted reaction the mass spectrum of the gaseous products showed a trace amount of trifluoromethyl iodide is formed.

4.B.i.b. Formation of the Proposed Intermediate by Other Methods.

It is suggested that the trifluoroacetate ion decarboxylates in a process assisted by copper(I) iodide forming an intermediate $[CF_3CuI]^-$ (94), which either decomposes producing fluoroform or takes part in further reaction with the aromatic halide forming a trifluoromethyl-substituted product.



Copper salts are known to promote decarboxylation of carboxylic acids and their salts[112] and the formation of organocompounds results from the decarboxylation of some aromatic copper carboxylates. Pentafluorophenyl copper has been isolated from the decarboxylation of copper(I) pentafluorobenzoate in quinoline and the decarboxylation of o-nitrobenzoic acid (95), in the presence of copper(I) oxide and an aryl iodide, leads to the formation of a biphenyl presumably via an organocopper intermediate.[117]


(95)

However, excepting fluorene-9-carboxylic acid, alkanoic acids and their copper salts had not been decarboxylated under the same conditions as vinylic or aromatic acids.[118]

The formation of an intermediate of this type has been investigated by using two other methods to prepare perfluoroalkyl anions which might subsequently be trapped by copper(I) iodide forming $[R_fCuI]^-$.

A method has been developed for the production of trichloromethyl anions from trichloroacetic acid under conditions in which it is possible to trap the anions before their conversion to chloroform or dichlorocarbene.[119] The solvating properties of dimethylsulphoxide (DMSO) are such that the acid protons are strongly solvated and so unreactive, whilst the poorly solvated and unstable trichloroacetate ions readily decarboxylate. It was hoped that if a similar solution of trifluoromethyl anions could be produced they would be free to react with copper(I) iodide, forming $[CF_3CuI]^-$ (<u>94</u>), without the complication of fluoroform formation.

$$CF_3COOH \xrightarrow[-CO_2]{DMSO} CF_3^- \xrightarrow{CuI} \underset{(\underline{94})}{[CF_3CuI]^-} \overset{ArI}{\nrightarrow}$$

In practice, although at 160°C the trifluoroacetate decarboxylated, no reaction with iodobenzene occurred but as later results have shown the great effect that solvent as a bulk ligand can have on the process it is probable that the copper(I) ions were well solvated and not available for reaction. However, the results have confirmed that copper(I) iodide is necessary to promote the trifluoromethylation reaction.

Perfluoroalkyl anions can also be formed by reaction between fluoride ion and a perfluoroalkene. Two alkenes, perfluoropropene (<u>96</u>) and perfluorocyclohexene, have been heated with fluoride ion, copper(I) iodide and iodobenzene.

$$\underset{(96)}{CF_3CF{:}CF_2} \xrightarrow{F^-} (CF_3)_2CF^- \xrightarrow{CuI} [(CF_3)_2CFCuI]^- \overset{ArI}{\nrightarrow}$$

Perfluoropropene was found to form oligomers at the reaction temperature of 160°C and perfluorocyclohexene, which has less tendency to oligomerise, was recovered from the reaction mixture with most of the iodobenzene. No evidence of any perfluoroalkylation of the iodobenzene was observed. It is possible that the perfluoroalkyl anion has to be formed within the co-ordination sphere of the copper(I) ion, as would occur in decarboxylation of the complex ion $[CuICF_3COO]^-$.

4.B.i.c. Phenyl Trifluoroacetate as a Possible Intermediate.

Another feasible reaction path is the copper assisted nucleophilic attack of the trifluoroacetate ion upon the aryl halide producing phenyl trifluoroacetate (97) which then loses carbon dioxide, maybe in a copper assisted reaction, to yield trifluoromethylbenzene.

$$C_6H_5I + CF_3COO^- \xrightarrow{CuI} \underset{(97)}{C_6H_5OCOCF_3} \xrightarrow[\Delta]{(CuI?)} C_6H_5CF_3 + CO_2$$

However the ester (97) was recovered after heating with copper(I) iodide under reaction conditions and the copper(I) iodide did not appear to go into solution as it usually does at the reaction temperature. If phenyl trifluoroacetates are intermediates in the production of trifluoromethylbenzenes it seems probable that they would have been observed in the reaction mixtures if only in trace quantities.

4.B.i.d. A Hammett Plot for the Trifluoromethylation Reaction.

If the trifluoromethylation reaction is carried out for a range of para-substituted iodobenzenes then, from the Hammett Equation (A), a plot of the σ value of the substituent against the log of the rate constant for the substituted benzene divided by that of iodobenzene itself should yield a value for the gradient ρ. This value is a measure of the extent to which the reaction is dependent on the electron withdrawing or donating power of the substituents and is related to the electronic character of the transition state.[120]

$$\text{(A)}\quad \lg \frac{k_X}{k_H} = \sigma\rho$$

k_X = rate constant for a substituted iodobenzene

k_H = rate constant for iodobenzene itself.

The reaction is not first order but a pseudo first order rate constant can be calculated (B) if the trifluoroacetate is present in a large excess and the rate is measured over the shortest time-span compatible with a yield of trifluoromethylated product large enough to measure accurately.

$$\text{(B)}\quad -\frac{d[\mathrm{ArI}]}{dt} = k[\mathrm{ArI}][\mathrm{CF_3}] = k'[\mathrm{ArI}]$$

$$\ln \frac{[\mathrm{ArI}]_o}{[\mathrm{ArI}]_t} = k't$$

k' = pseudo first order rate constant

Rate constants were measured for eight substituted iodobenzenes and the resulting Hammett Plot is shown in

Diagram (4.2.) A Hammett Plot for the Trifluoromethylation Reaction.

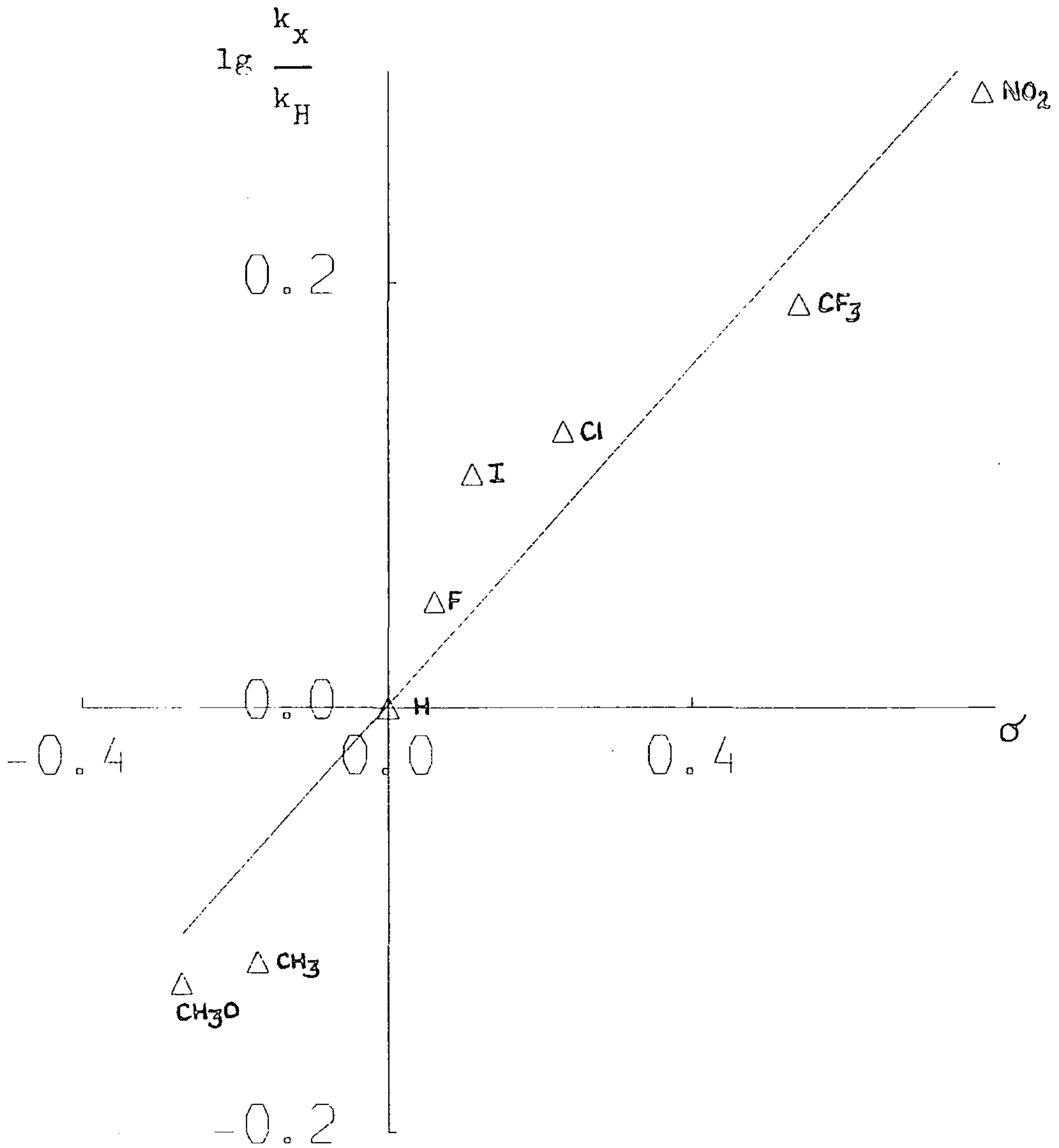


Diagram (4.2). The ρ value calculated from the best straight line is + 0·46 which, while showing the reaction is to some extent facilitated by electron withdrawing groups, fits in with the observation that substituents on the benzene ring have little effect on the yield of trifluoromethylated products. A value of + 0·46 is consistent with other ρ values observed for copper assisted nucleophilic attack which lie within the range + 0·1 - 1·1.[111]

These results have also provided further evidence against a free radical reaction which was previously thought unlikely because of the specific nature of the attack. Calculation of relative rate constants for the addition of electrophilic trifluoromethyl radicals to various substituted benzenes has shown that electron donating rather than withdrawing groups enhance the reaction.[121]

4.B.ii. The Role of Copper(I) Iodide

The reactions described in the previous chapter were all carried out using copper(I) iodide. When copper(I) bromide was used in the trifluoromethylation of iodobenzene a decreased yield (46%) of trifluoromethylbenzene was produced and the remainder of the iodobenzene was converted to bromobenzene. The yield of trifluoromethylated product from bromobenzene fell from 70% to 13% when copper(I) iodide was replaced by the bromide. Both from the possibility of halogen exchange with iodo-compounds and reduced yields of trifluoromethylated products, copper(I) bromide appears to be inferior to copper(I) iodide in promoting the trifluoromethylation reaction.

4.B.ii.a. Quantity Required.

Although copper(I) iodide remains unchanged throughout the reaction it must be present in a stoichiometric amount in order to achieve high yields of the trifluoromethylated products. A tenfold reduction in the amount of iodide present caused the yield of trifluoromethylbenzene produced from bromobenzene to drop from 70% to 12%. However when the copper(I) iodide was restored to its usual level the yield rose to 47% on heating for a further two hours. The decarboxylation process must have been hindered by the reduction in copper(I) iodide since the trifluoroacetate would normally have been completely converted to fluoroform or trifluoromethylbenzene during the initial four hour reaction period.

4.B.ii.b. Use of Copper in Oxidation States 0,I and II.

An investigation of the trifluoromethylation of iodobenzene using copper in oxidation states 0, I and II showed that reaction takes place in all three cases. However metallic copper and copper(II) chloride were considerably less successful in promoting the formation of trifluoromethylbenzene, with 10% and 12% yields respectively, than was copper(I) iodide which promoted a 68% yield of trifluoromethylated product. The reaction involving copper(II) chloride was complicated by the formation of chlorobenzene (21%) in a halogen exchange process.

An early review[115] suggested that copper(I) ions are probably the real catalysts in copper assisted nucleophilic reactions although if copper(II) ions are present they might also have a catalytic effect. More recently it has been suggested that copper(I) species are the effective catalysts[111] and that the halogen exchange reaction between copper(II) bromide (9) and iodobenzene involves an equilibrium between copper(I) and (II) bromides where only copper(I) is active in the ligand exchange process.[114]

$$\underset{(\underline{9})}{CuBr_2} \rightleftharpoons CuBr + \tfrac{1}{2}Br_2$$

4.B.ii.c. Effect of Added Co-ordinating Agents

Copper promoted reactions are known to be susceptible to spectacular solvent and ligand effects. The initial formation of a complex between the aryl halide and copper species appears to be important and requires that the copper compound is co-ordinatively unsaturated or can easily be made so.[111] This assumption explains why reactions can be variable in rate or even completely inhibited depending upon the solvent molecules, reagents, or added complexing agents competing as ligands for the metal.

In investigating the scope of the trifluoromethylation reaction the reduced reactivity of the heterocyclic compounds compared to that of the benzenoid species was suggested to result from co-ordination. Copper(I) iodide was often seen to dissolve immediately on addition to a reaction mixture containing a heterocyclic halogen compound. Further investigation of the effect of co-ordinating agents upon the reaction was carried out by the addition of excess quantities of quinoline and sodium iodide to the trifluoromethylation of iodobenzene. Both of these compounds are good ligands for copper(I) and should drive the equilibria for complex formation towards the co-ordinatively saturated species $[CuL_4]^+$ when present in excess. In both cases the copper(I) iodide dissolved immediately on addition to the mixture showing soluble complexes were formed. Addition of quinoline reduced the yield of trifluoromethylbenzene from 83% to 39% whilst sodium iodide completely halted the reaction. The large quantity of sodium trifluoroacetate remaining in the sodium iodide reaction can be explained by the assumption that decarboxylation takes place in a copper-carboxylate complex which cannot be formed if the copper(I) is bound up in a stable $[CuI_4]^{3-}$ complex. These results show clearly that the co-ordinating ability of copper(I) is important in the trifluoromethylation reaction.

It has been observed that the addition of a stoichiometric amount of a co-ordinating agent can have a beneficial effect upon the yields of products in copper-

promoted reactions. Whilst the presence of four molar equivalents of pyridine will inhibit the halogen exchange between aryl bromides and copper(I) chloride, the addition of one equivalent enhances the rate of exchange.[111]
It was hoped that the addition of a stoichiometric amount of quinoline or iodide ions would assist the trifluoromethylation reaction by taking copper(I) iodide into solution as a complex yet still leave co-ordination sites vacant. This did not occur. Addition of quinoline had little effect on the yield of trifluoromethylbenzene which fell from 83% to 78% but sodium iodide again completely halted the reaction.

4.B.ii.d. Replacement of Copper(I) Iodide by Silver(I) Iodide.

When copper(I) iodide was replaced by silver(I) iodide no formation of trifluoromethylbenzene was observed after the usual reaction period. However the ^{19}F nmr spectrum of the reaction mixture showed that very little sodium trifluoroacetate remained in solution. It appears that silver(I) iodide will catalyse the decarboxylation of the trifluoroacetate but the trifluoromethyl group is not introduced into the aromatic halide.

Silver prefers to form two co-linear bonds in its complexes and because of this the first two equilibrium constants, K_1 and K_2, are high whilst K_3 and K_4 are much smaller.[112] Although $[AgL_2]^+$ is the preferred complex

$[AgL_3]^+$ and $[AgL_4]^+$ are known. This preference for bis-co-ordination could explain the lack of trifluoromethylated product since silver(I), already having one co-ordinated iodide ion, would be less likely to be able to accommodate both the trifluoromethyl group and aryl iodide as ligands so that exchange of the trifluoromethyl group for iodide could occur.

4.B.iii. Effect of Ortho-Substituents on the Aryl Halide.

4.B.iii.a. Steric Effects.

In a competition reaction between o- and p-chloroiodobenzenes the o-isomer was found to be trifluoromethylated slightly less readily than the p-isomer. Initially the p:o ratio of the chloroiodobenzene mixture was 1:1·1 but at the end of the reaction it had risen to 1:1·2. The reduced reactivity of the o-isomer can be explained by steric hindrance, as the bulky chlorine atom next to the reaction site in the o-isomer is more likely to interfere with the attack by the trifluoromethyl group than the smaller hydrogen atom present in the p-isomer. This result also implies that attack of the trifluoromethyl group assisted by the copper(I) iodide is involved in the rate determining step.

Iodopentamethylbenzene, which has two methyl groups in ortho positions has been trifluoromethylated in 60% yield.

4.B.iii.b. Chelating Effects.

Although substituents in the meta and para positions of aryl halides have previously been noted to have very little effect in copper assisted reactions, the presence of a potential chelating substituent, such as the nitro or carboxyl group, in the ortho position has an activating effect.[111]

The trifluoromethylation of o-iodonitrobenzene gave only a 20% yield of the o-trifluoromethyl compound, compared with a 65% yield of p-nitrotrifluoromethylbenzene, and some nitrobenzene was also formed. When a mixture of the para- and ortho-isomers was trifluoromethylated in a direct competition reaction only p-nitrotrifluoromethylbenzene was formed and the yield (42%) was lower than usual. In both cases the copper(I) iodide dissolved immediately forming a bright green solution on addition of the o-isomer. A green homogeneous solution was also formed when the trifluoromethylation of o-iodobenzoic acid was attempted. One explanation for these observations would seem to be the formation of a very stable complex. However, a mixture of o-iodonitrobenzene and copper(I) iodide in NMP does not become homogeneous when stirred under nitrogen without the addition of sodium trifluoroacetate.

Chapter 5

Introduction of Other Fluoroalkyl Groups

As the introduction of the trifluoromethyl group from sodium trifluoroacetate proved so successful the method was extended to the sodium salts of other perhaloalkane carboxylic acids. This chapter describes the attempted formation of some pentafluoroethyl-, heptafluoropropyl-, and trichloromethyl- derivatives and compares the mechanism of these reactions with that proposed for the trifluoromethylation reaction.

5.A. Synthesis

5.A.i. Pentafluoroethyl Group

Introduction of the pentafluoroethyl group into iodobenzene under the same conditions as were used for the trifluoromethylation reaction resulted in a fall in the iodobenzene concentration to 16% of its initial value, and the formation of one product, pentafluoroethylbenzene. Unlike the trifluoromethylation process some sodium salt remained in solution and so a range of reactions was carried out with increased quantities of copper(I) iodide and iodobenzene to maximise the yield. The results are shown in Table (5.1), and indicate that the highest yield of pentafluoroethylbenzene is obtained when sodium pentafluoropropanoate (10 mmol), iodobenzene (7·5 mmol) and copper(I) iodide (10 mmol) are heated in NMP (20 ml) at 170°C.

Table (5.1) Optimisation of the Yield of Pentafluoroethylbenzene *

C_6H_5I	CuI	% C_6H_5I		% $C_2F_5C_6H_5$	
mmol	mmol	1 hr	2 hr	1 hr	2 hr
2·5	5·0	0	–	–	–
5·0	5·0	39	35	–	–
5·0	7·5	0	–	–	80
7·5	10·0	26	13	74	87

* reaction temperature 170°C, C_2F_5COONa 10 mmol / 20 ml solvent, yield calculated by g.l.c. analysis after addition of an internal standard.

These conditions were used to introduce the pentafluoroethyl group into both benzenoid and heterocyclic aromatic and non-aromatic molecules; in all of these reactions the heating was continued for three hours so as to be sure of obtaining the maximum yield of product.

5.A.i.a. Benzenoid Aromatic Compounds

Sodium pentafluoropropanoate (<u>98</u>) was used to produce a range of substituted pentafluoroethylbenzenes.

$$\underset{(\underline{98})}{CF_3CF_2COONa} + ArX + CuI \xrightarrow[3hr, 170^\circ C]{N_2, NMP} ArCF_2CF_3$$

Both iodo- and bromoarenes were used and up to three pentafluoroethyl groups were introduced into one aromatic nucleus. The compounds which were produced are listed in Table (5.2) with the g.l.c. yields. As the concentrations of products were greater than in the trifluoromethylation

Table (5.2) <u>Pentafluoroethyl Derivatives of Benzenoid Aromatic Compounds</u>

Halocompound	Product	% Yield	
		g.l.c.	isolated
iodobenzene	pentafluoroethylbenzene	86	-
p-diiodobenzene	1,4-bis(pentafluoroethyl)benzene	83	-
p-bromotrifluoromethylbenzene	p-pentafluoroethyltrifluoromethylbenzene	71	19
1,3,5-tribromobenzene	1,3,5-tris(pentafluoroethyl)benzene	-	31
p-iodonitrobenzene	p-nitropentafluoroethylbenzene	51	-
p-chloroiodobenzene	p-chloropentafluoroethylbenzene	75	54
o-chloroiodobenzene	o-chloropentafluoroethylbenzene	62	14

reactions, isolation of the material has proved simpler and so these yields are also tabulated where appropriate. Most of the products were sufficiently volatile to enable separation from the reaction mixture either by vacuum transference or, preferably, by the flash separation technique described previously.

5.A.i.b. Heterocyclic Aromatic Compounds

Two heterocyclic halogen compounds were used in this reaction and the results are shown in Table (5.3). As in the trifluoromethylation reactions the yields of pentafluoroethyl-substituted heterocycles are lower than those of benzenoid aromatic compounds and substantial amounts of the sodium salt remain in solution after the reaction. Trace amounts of the reductively dehalogenated product were observed in the reaction of 2-chloro-5-iodopyridine and this was the source of the major product in the pentafluoroethylation of 2-iodothiophene. The formation of a trace quantity of the disubstituted product, 2,5-bis(pentafluoroethyl)pyridine, showed that chlorine can be substituted in a sufficiently activated system.

5.A.i.c. Non-Aromatic Compounds

The results of the pentafluoroethylation of an alkyl, alkenyl, and alkynyl halide are given in Table (5.4).

On analysis by g.l.c. the 1-iodopentane reaction mixture showed one volatile component which was isolated as a colourless liquid and identified as 1,1,1,2,2-pentafluoroheptane. The mass spectrum showed the characteristic pattern for

Table (5.3) Pentafluoroethyl Derivatives of Heterocyclic Aromatic Compounds

Halocompound	Product	% Yield g.l.c.
2-chloro-5-iodopyridine	2-chloro-5-pentafluoroethylpyridine	30
	2,5-bis(pentafluoroethyl)pyridine	trace
2-iodothiophene	2-pentafluoroethylthiophene	28
	thiophene	35

Table (5.4) Pentafluoroethyl Derivatives of Non-Aromatic Compounds

Halocompound	Product	% Yield g.l.c.	 isolated
1-iodopentane	1,1,1,2,2-pentafluoroheptane	-	22
(2-bromoethenyl)benzene	(4,4,4,3,3-pentafluoro-1-butenyl)benzene	53	-
bromophenylacetylene	-	-	-

breakdown of a C_5 alkyl chain and a pentafluoroethyl group (119 a.m.u.) although no molecular ion peak was observed. The low isolated yield, together with the absence of pentane or iodopentane, suggests that some material has escaped from the system and it would have been preferable to carry out the reaction in a sealed tube.

No pentafluoroethyl-substituted product was obtained from bromophenylacetylene and the ^{19}F nmr indicated that no fluorine-containing compounds remained in the reaction mixture. It appears that the phenylacetylene coupled forming a buta-1,3-diyne, as previously observed in the attempted trifluoromethylation of this compound.

5.A.i.d. Reductive Dehalogenation

Thiophene was the main product from the pentafluoroethylation of 2-iodothiophene and trace amounts of hydrogen-substituted compounds were also observed in the reactions of 2-chloro-5-iodopyridine and the chloroiodobenzenes. The intrusion of moisture has been suggested as a cause of this side reaction[105] but addition of water in the pentafluoroethylation of p-chloroiodobenzene completely halted the process and the starting material was recovered. As in the trifluoromethylation reaction copper was precipitated and the usual discoloration of the solvent did not occur, (see Chapter 3.B.iv.). Darkening of the solvent would appear to result from decomposition caused by the abstraction of hydrogen to produce fluoroform.

5.A.ii. Heptafluoropropyl Group

As the introduction of the pentafluoroethyl group was so easily accomplished it was expected that introduction of the heptafluoropropyl group using sodium heptafluorobutanoate would be equally successful, but this has not proved to be so.

A reaction between sodium heptafluorobutanoate, copper(I) iodide and iodobenzene was attempted at a range of temperatures from 100°C to 170°C. The mixture bubbled vigorously indicating rapid decarboxylation when heated at 170°C, whilst at 100°C a large amount of heptafluorobutanoate remained in solution after a prolonged reaction time. At both of the intermediate temperatures, 132°C and 150°C, about a third of the iodobenzene was converted to heptafluoropropylbenzene and heptafluoropropane was also produced.

It is surprising that the addition of one difluoromethylene unit to a perfluoroalkyl chain should have such an effect on the reactions of a carboxylic anion. A possible reason for this will be discussed in section (5.B.i.).

5.A.iii. Trichloromethyl Group

A paper[106] describing the use of sodium trifluoroacetate and copper(I) iodide in hexamethylphosphoramide solution as a trifluoromethylating agent for polymethyliodobenzenes stated that the process could be extended to include the formation of trichloromethyl derivatives. However, trichloromethylation in NMP solution has not proved to be successful. Even at room temperature the reaction mixture discoloured and bubbled slightly and on heating the decarboxylation became vigorous. After stirring the mixture at room temperature for an hour g.l.c. analysis showed that the iodobenzene concentration remained constant although two volatile products were formed, one of which appeared to be chloroform from its mass spectrum.

5.B. Mechanism

5.B.i. Decarboxylation

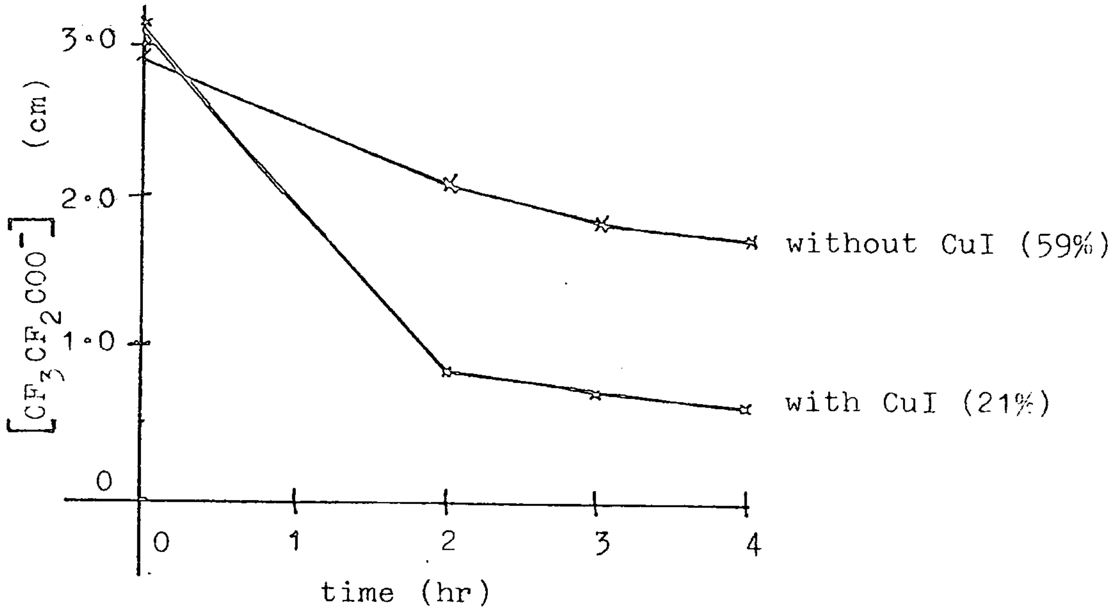
Before the reactions of sodium pentafluoropropanoate and heptafluorobutanoate with iodobenzene were attempted, the temperatures at which decarboxylation occurred were found by stirring a solution of the sodium salt in NMP under a partial vacuum and noting the pressure changes as the temperature was slowly increased. A steady fall in the vacuum was taken to be indicative of decarboxylation, and the temperatures at which this occurred are shown in Table (5.5).

Table (5.5) Determination of Decarboxylation Temperatures

Salt	Decarboxylation Temperature (°C) without CuI	with CuI
sodium pentafluoropropanoate	160	140
sodium heptafluorobutanoate	145	145

Decarboxylation of the pentafluoropropanoate anion begins at a much lower temperature when copper(I) iodide is present, and its function in assisting decarboxylation at the reaction temperature has been demonstrated by sampling solutions of the salt heated at 170°C, both with and without copper(I) iodide, and integrating the areas under the ^{19}F nmr peaks. The concentrations shown in Diagram (5.1) are an average of those obtained from integration of both the CF_3 and CF_2 signals in each case.

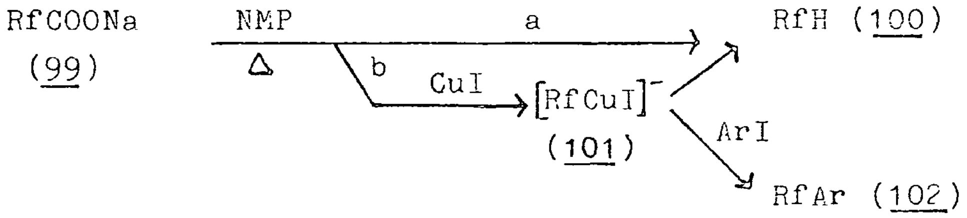
Diagram (5.1) Decarboxylation of Sodium Pentafluoropropanoate



Over a four hour period the concentration of sodium pentafluoropropanoate fell to 59% of its original concentration when heated alone, compared with a drop of 21% when copper(I) iodide was present. Most of the decarboxylation took place within the two hours, which is in agreement with the observation that the major proportion of the pentafluoroethyl-substituted product is formed within this time.

Samples taken after the solution had cooled were shown to contain entrained pentafluoroethane. No pentafluoroethyl iodide was observed in the ^{19}F nmr spectrum but m.s.g.l.c. of some reaction mixtures has shown trace amounts to be present.

In contrast to sodium pentafluoropropanoate, the temperature at which sodium heptafluorobutanoate decarboxylated was found to be independent of added copper(I) iodide and this observation could explain the great differences in the yields of perfluoroalkylbenzenes formed. In the previous chapter a scheme for the decarboxylation of sodium trifluoroacetate was suggested which can be applied to sodium perfluoroalkane carboxylates (<u>99</u>) generally.



Decarboxylation can occur in either an unassisted (a) or assisted (b) process and the amount of the perfluoroalkylbenzene (<u>102</u>) formed depends on the relative rates of the two reactions. In the case of trifluoroacetate or pentafluoropropanoate anions, which decarboxylate more readily in the presence of copper(I) iodide, the assisted process is favoured and the intermediate (<u>101</u>) goes on to react with the aryl iodide forming (<u>102</u>). The decarboxylation of heptafluorobutanoate occurs at 140°C whether or not copper(I) iodide is present, and mostly proceeds via the unassisted process forming a 1-H-perfluoroalkane (100). However, assisted decarboxylation still continues to a small extent since some heptafluoropropylbenzene is produced. Decarboxylation of sodium trichloroacetate occurred at room temperature, and in this case the lack of trichloromethyl-substituted products suggests the unassisted process occurs so rapidly that all of the anion decarboxylates by this route and no (101) is formed.

5.B.ii. Common Features in the Introduction of Trifluoromethyl and Pentafluoroethyl Groups

Several common features have been noted in the introduction of the trifluoromethyl and pentafluoroethyl groups and these will be discussed in turn.

5.B.ii.a. Use of Copper in Oxidation States 0, I, and II.

Yields of the trifluoromethylated product obtained from iodobenzene were shown to be greatest when copper(I) iodide was used, although metallic copper and copper(II) chloride promoted the reaction to a smaller extent. The same trend was observed in the formation of pentafluoroethylbenzene, the yields of which are shown in Table (5.6).

Halogen exchange was again observed when copper(II) chloride was used and in this case chlorobenzene was obtained in a much greater yield, presumably because the pentafluoroethylation reactions were carried out at 170°C instead of 160°C.

Table (5.6) Use of Copper in Oxidation States 0, I, and II *

Copper Compound	$C_6H_5CF_2CF_3$ %	C_6H_5I %	C_6H_5Cl %
copper(0)	18 (10)	85 (88)	-
copper(I) iodide	67 (68)	27 (34)	-
copper(II) chloride	10 (12)	28 (60)	52 (21)

* (%) are the yields for the same reactions using trifluoroacetate

In order to achieve the maximum yield of pentafluoroethyl-substituted product the copper(I) iodide must be present in a greater molar quantity than the iodo-compound. This is demonstrated in the results obtained for the optimisation reactions (Table (5.1)), and compares with the decreased yields of trifluoromethylbenzene produced when the initial copper(I) iodide concentration was decreased tenfold.

5.B.ii.b. Effect of Co-ordinating Agents

The importance of the co-ordinating ability of copper(I) in the trifluoromethylation mechanism was demonstrated by the reduction in the yield of trifluoromethylbenzene when excess amounts of the co-ordinating agents quinoline and iodide ions were added to the reaction mixture. Complex formation obviously plays an equally important part in introduction of the pentafluoroethyl group since addition of excess quinoline reduces the yield of pentafluoroethylbenzene from 62% to 43%, and the presence of an excess quantity of sodium iodide completely halts the reaction.

In both cases sodium pentafluoropropanoate remained in solution showing that the formation of complex ions $[CuL_4]^+$ with iodide or quinoline ligands had hindered copper assisted decarboxylation.

Addition of stoichiometric amounts of copper(I) iodide and a potential ligand would result in the formation of a soluble complex ion without blocking all four co-ordination sites, and in homogenous solution the yield of perfluoroalkylbenzene might be increased. The addition of quinoline did result in an increased yield of pentafluoroethylbenzene but the yield fell to 17% in the presence of iodide ions.

5.B.ii.c. Effect of Ortho-substituents on the Aryl Halide

A competition reaction between p- and o-chloroiodobenzenes showed that there is a slight preference for pentafluoroethylation of the p-substituted isomer. Initially the o- and p-isomers were in the ratio 1·08 : 1 whereas after reaction the ratio of the remaining chloroiodobenzenes was 1·4 : 1. The same preferential reaction was observed to a lesser extent in the trifluoromethylation of these isomers and the more marked effect in this case gives weight to its initial explanation as a steric effect.

5.B.ii.d. Conclusion

Two differences have been observed in the introduction of trifluoromethyl and pentafluoroethyl groups; the pentafluoropropanoate ion is used far more efficiently as

75% is converted into pentafluoroethylbenzene compared with only 25% of the trifluoroacetate ion forming trifluoromethylbenzene, and some copper is precipitated in the pentafluoroethylation reaction. However, the similarities previously discussed outweigh these differences suggesting that the same intermediate, $[R_fCuI]^-$, is involved in both reactions. The success of the pentafluoroethylation process has provided evidence against a reaction mechanism involving a free perfluoroalkyl anion since the pentafluoroethyl anion (9) would be expected to lose fluoride ion readily forming tetrafluoroethylene.

$$\underset{(\underline{9})}{CF_3CF_2^-} \xrightarrow{-F^-} CF_2{=}CF_2$$

In co-ordination with copper as a complex ion $[CF_3CF_2CuI]^-$ the pentafluoroethyl group could be more stable to fluoride loss allowing it to react further without decomposition.

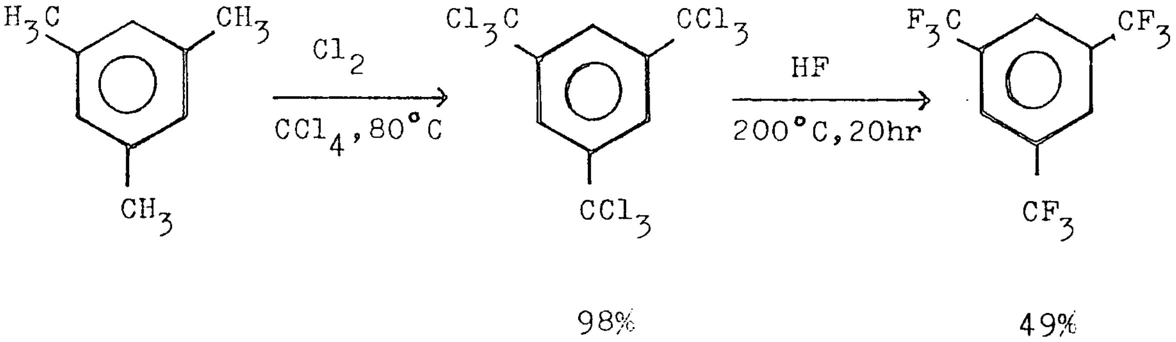
Chapter 6

Reactions of 1,3,5-Tris(trifluoromethyl)benzene and its Derivatives.

6.A. Introduction

Although the chemical and physical properties of trifluoromethyl aromatic compounds have been reviewed[90], the chemistry of systems with several trifluoromethyl groups attached to the ring remains largely undeveloped. These compounds are potentially interesting since they should be susceptible to nucleophilic attack and the high acidity of the hydrogen atoms will allow formation of sterically hindered lithium derivatives.

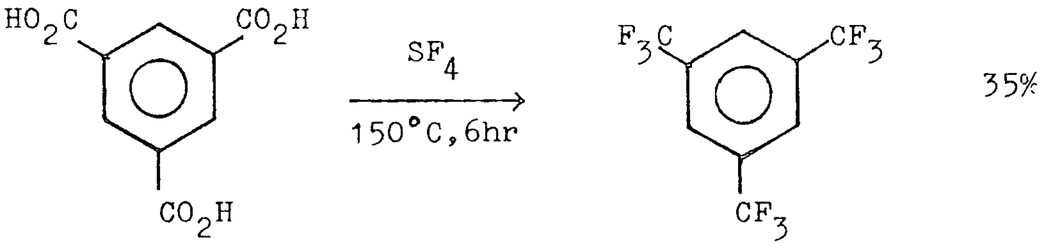
The compound chosen for investigation was 1,3,5-tris-(trifluoromethyl)benzene (103), which has previously been prepared by chlorination of mesitylene and subsequent reaction with hydrogen fluoride.[14]



(103)

It was noted that (103) was stable to many reagents including a mixture of chromic oxide in acetic acid with which it was refluxed for ten days.[14] Since this initial work the only recorded reactions of (103) have been fluorination with lead tetrafluoride[122] or fluorine/nitrogen[123], reaction with bromine trifluoride forming an unidentified mixed halogen compound[124], and replacement of the fluorine atoms with chlorine by heating with a mixture of sodium chloride, hydrochloric acid and aluminium trichloride.[125] The nmr spectra[126, 127] and ionisation potentials[128] have also been investigated.

Formation of the trifluoromethyl compound (103) in a reaction between sodium trifluoroacetate and 1,3,5-tribromobenzene was described in Chapter 3, but the larger quantities needed for the present work were produced by the fluorination of trimesic acid (104) with sulphur tetrafluoride.



(104) (103)

6.B. Reactions of 1,3,5-Tris(trifluoromethyl)benzene

The direct incorporation of a number of functional groups into the trifluoromethyl compound (103) has been attempted and the results are summarised in Diagram (6.1).

6.B.i. Halogenation

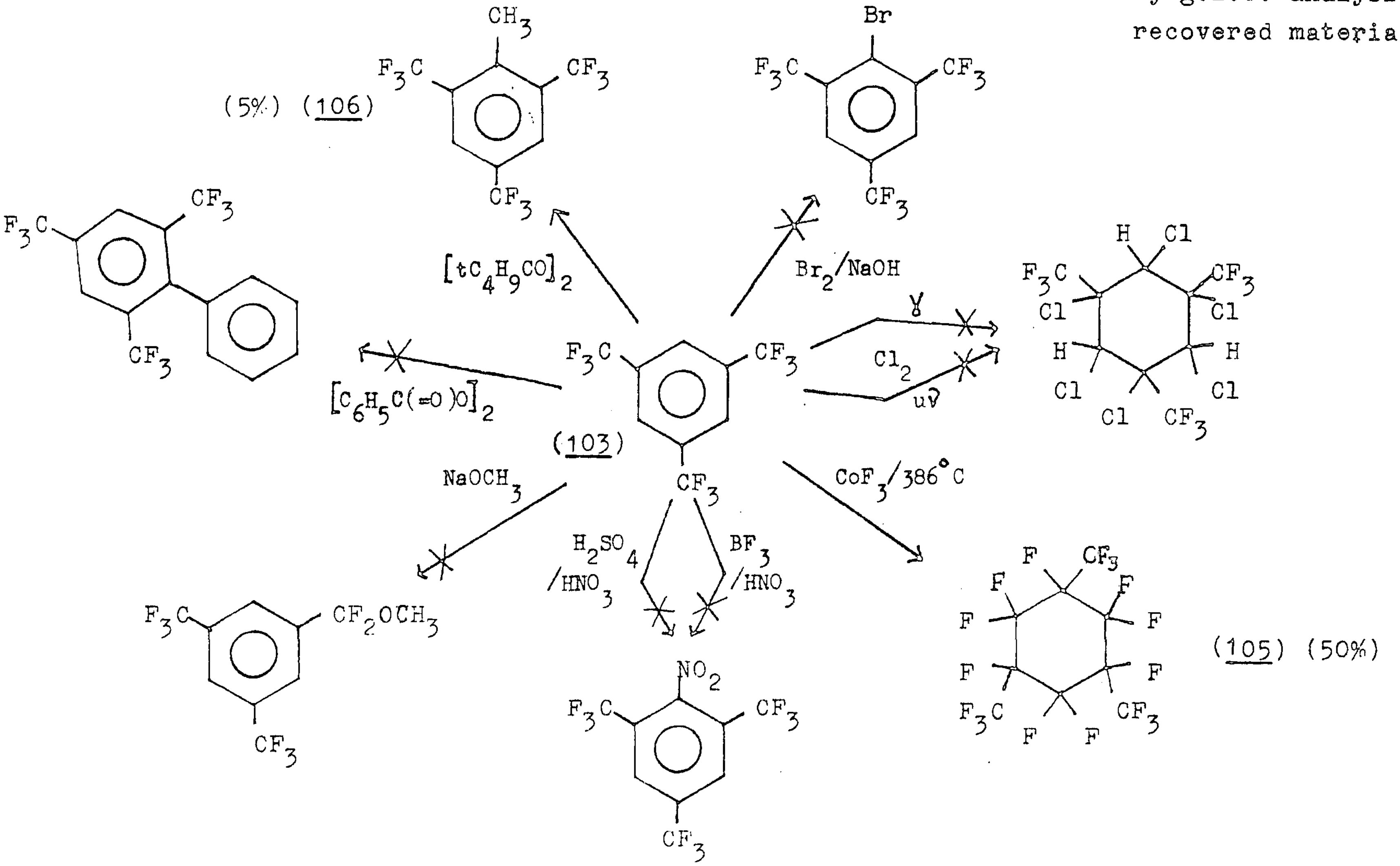
Fluorination of (103) was carried out by passing the material through a cobalt trifluoride bed[59] at a range of temperatures from 140°C - 386°C. At the lowest temperature no fluorination took place but by raising the temperature of the bed the proportion of (103) recovered decreased, although even at 386°C some remained. This temperature was necessary in order to obtain a simple mixture from which isolation of the components was practicable. Two main products were formed and the major component was isolated by preparative scale g.l.c. and shown to be the fully fluorinated product, perfluoro-1,3,5-trimethylcyclohexane (105).

The production of a saturated system by addition of chlorine to (103) was attempted in a radical process initiated by either gamma irradiation from a cobalt-60 source or ultra-violet irradiation. In both cases chlorine and tris(trifluoromethyl)benzene (103) were recovered.

Replacement of hydrogen in (103) with bromine also proved unsuccessful. It was hoped that the acidity of the hydrogen atoms might be sufficiently great as to allow bromination with a mixture of sodium hydroxide solution and

Diagram (6.1) <u>Reactions of 1,3,5-Tris(trifluoromethyl)benzene</u>

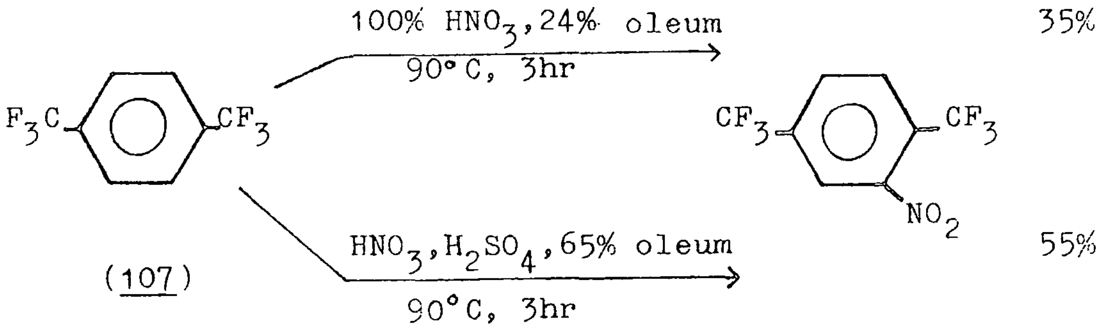
(% yields were obtained by g.l.c. analysis of recovered materials)



bromine. An acidic proton would be plucked off by the hydroxide ion leaving an anion to react further with the bromine. However despite vigorous shaking to ensure mixing of the fluorocarbon and aqueous layers no reaction was observed and (<u>103</u>) was recovered.

6.B.ii. <u>Nitration</u>.

Nitration of the tris(trifluoromethyl) compound (<u>103</u>) might be expected to be difficult since it involves the attack of an electrophilic species on a benzene ring with three strongly electron withdrawing groups. It has been reported that 1,4-bis(trifluoromethyl)benzene (<u>107</u>) is resistant to nitration and vigorous conditions are necessary to achieve reaction.[3]



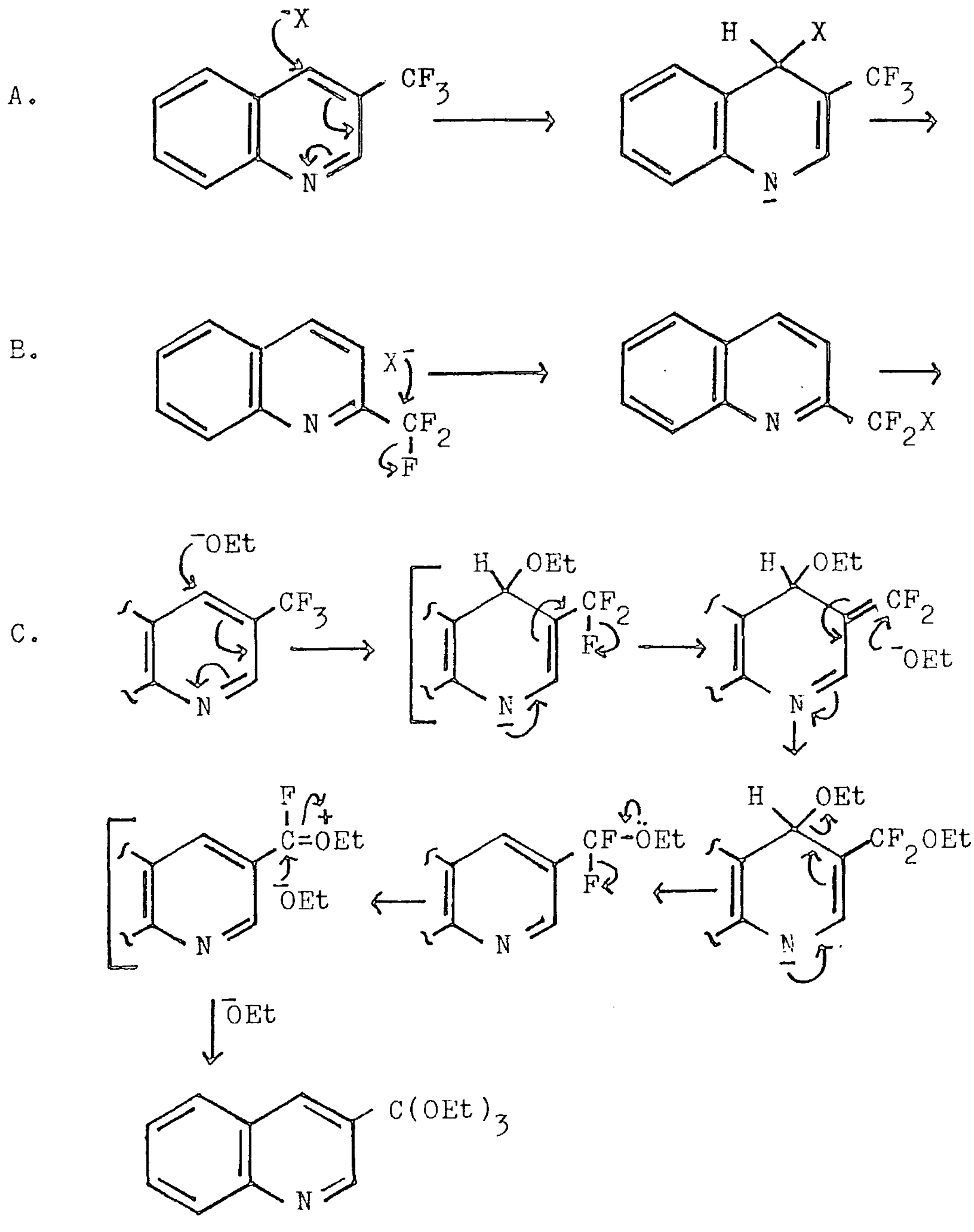
(<u>107</u>)

Not only has (<u>103</u>) an extra trifluoromethyl group but this group is meta-directing and there are no available meta positions in the 1,3,5-tris(trifluoromethyl) compound. The nitration of (103) has been attempted with both a nitric/sulphuric acid mixture[129] and boron trifluoride in fuming nitric acid[130], a powerful nitrating agent which is claimed to give 80-90% yields for difficult nitrations, but in both cases the original material was recovered.

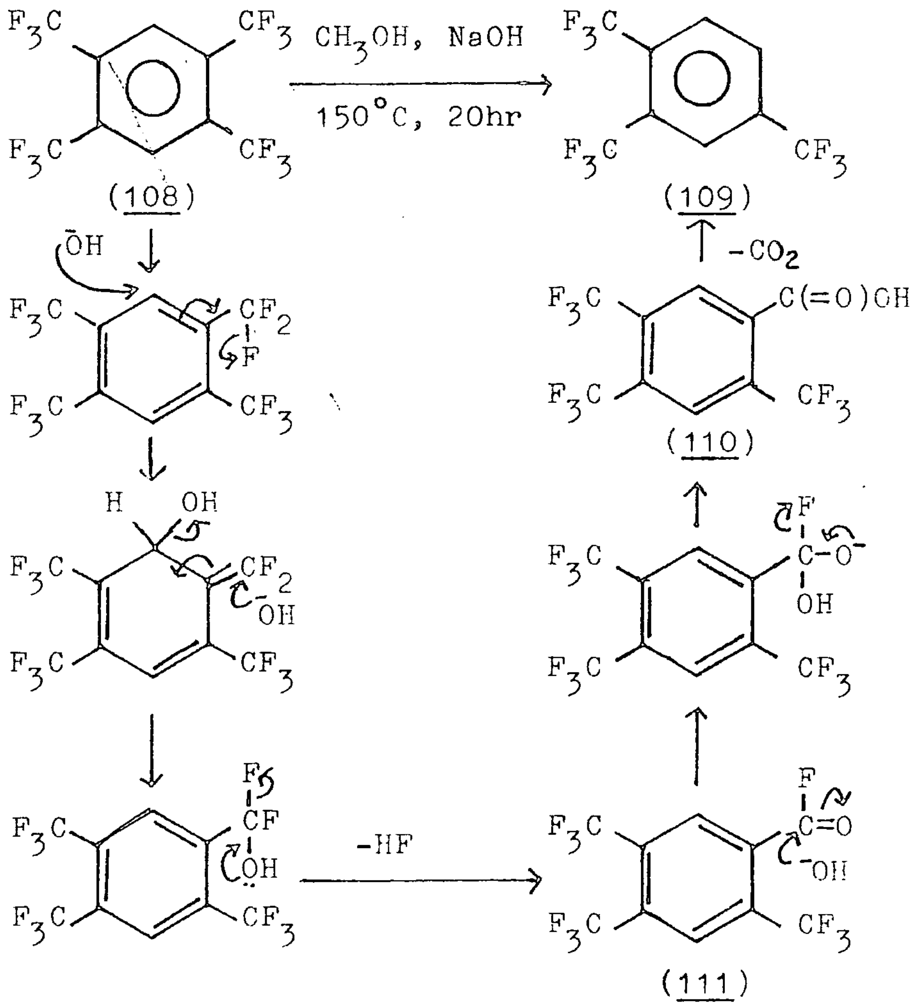
6.B.iii. Reaction with Methoxide Ions.

Kobayashi has shown that the trifluoromethyl group on an aromatic ring, which was previously thought to be very stable, can be converted to a carboxylic acid or ester in a nucleophilic substitution.[131,132] As the aromatic nucleus involved was the electron deficient quinoline, it was thought the reactions might be equally applicable to (103). Two possible modes of attack were proposed and are shown in Scheme (6.1). As the 4-position of the ring is susceptible to nucleophilic attack, type A attack was expected for 3-trifluoromethylquinoline whilst the 2-, and 4-isomers were expected to react in the S_N2 reaction B. Only the 3-isomer reacted with ethoxide ions, producing 3-(triethoxymethyl)quinoline which was readily hydrolysed to the ester, and since all three isomers should be equally susceptible to the S_N2 process, it seemed that type A attack must have occurred. The proposed mechanism, shown in Section C of Scheme (6.1), involves this initial attack followed by stepwise attack of successive ethoxide ions on the side chain. All three isomers reacted with hydroxide ions at elevated temperature producing the corresponding carboxylic acids. As trifluoromethylbenzene was recovered unchanged it was assumed that the electron withdrawing character of the quinoline ring favoured the S_N2 attack (B).

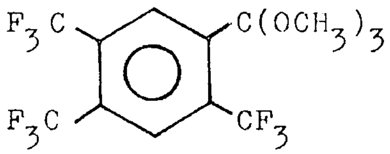
Scheme (6.1) Nucleophilic Attack upon Trifluoromethylquinolines.



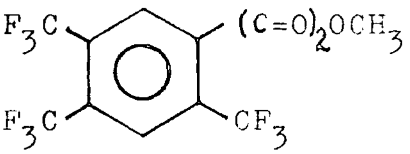
When (103) was heated with methoxide ions in refluxing methanol no reaction occurred, nor were any products observed at elevated temperatures. However 1,2,4,5-tetrakis-(trifluoromethyl)benzene (108) was found to undergo reaction. The reaction was carried out twice producing differing products as in the first case the methanol appears to have been damp and so the reaction was with hydroxide rather than methoxide ions. The main product in the first reaction was identified as 1,2,4-tris(trifluoromethyl)benzene (109), which was assumed to have been formed by attack of hydroxide ions forming a carboxylic acid (110) which then decarboxylated under reaction conditions.



A suggested mechanism for the reaction is shown although the acid fluoride (111) could also have been formed by initial S_N2 attack upon the trifluoromethyl group as proposed by Kobayashi.[132] The acyl fluoride (111) was a minor product in the reaction along with two other compounds which were the major products in the second reaction. The lesser of these compounds, 12% of the recovered material, was identified as methyl-2,4,5-tris-(trifluoromethyl)benzoate which can be produced from methoxide attack on (109) by an analogous route to that proposed for hydroxide attack. The major product, 34% of the recovered material, is still unidentified since the information gained from spectroscopy cannot be reconciled with a feasible reaction product. By analogy with the reaction of 3-trifluoromethylquinoline[132] the product should be the trimethoxymethyl compound (112), loss of a methoxy group from which would give the base peak (355 a.m.u.) in the mass spectrum. However (112) would not survive the hydrolysis involved in the work up.



(112)



(113)

The data available shows the compound contains a carbonyl group (i.r.), a methoxide group and two aromatic protons (^{1}H nmr), and three trifluoromethyl groups (^{19}F nmr) which combined with the highest mass (368 a.m.u.) and a strong $CH_3O(C=O)$ fragment in the mass spectrum suggests the keto-ester. However the base peak doesnot fit in with a logical breakdown of (113) and a feasible mechanism for its formation has not been devised.

It is possible that the base peak is a fragment in the breakdown of a compound of larger molecular mass than (113) and since the rest of the molecule remains intact then further substitution must be in the side chain. The reaction is obviously more complicated than it first appeared and requires further investigation.

6.B.iv. Reactions with Radical Sources.

Two compounds, benzoyl peroxide and di-t-butyl peroxide, were heated with the trifluoromethyl compound (103) in order to investigate its reactivity towards radicals.

Benzoyl peroxide (114) undergoes thermal decomposition in two stages, first forming the benzoyloxy radical by cleavage of the oxygen-oxygen bond followed by decarboxylation to produce the phenyl radical.

$$(C_6H_5C(=O)O)_2 \longrightarrow 2C_6H_5C(=O)O^{\circ} \longrightarrow 2C_6H_5^{\circ} + 2CO_2$$

(114)

The amount of phenyl radical produced depends on the relative rates of decarboxylation and reaction of the benzoyloxy radical with other available molecules.[133] Benzoyl peroxide was refluxed with (103) for two days producing a yellow liquid, found to be mainly recovered (103), and a white solid which appeared from the mass spectrum to be a mixture of benzoic and phenylbenzoic acids. The formation of these products, which would be expected to arise from the thermal decomposition of benzoyl peroxide in the absence of any other material,[133] coupled with the recovery of (103) suggest that it is inert to the phenyl and benzoyloxy radicals produced.

Di-t-butyl peroxide (115) also cleaves in a two stage process in which initial formation of the t-butoxy radical is followed by its decomposition into methyl radicals and acetone.[133]

$$((CH_3)_3C\text{-}O)_2 \longrightarrow 2(CH_3)_3C\text{-}O^{\circ} \longrightarrow 2(CH_3)_2C{=}O + 2CH_3^{\circ}$$

(115)

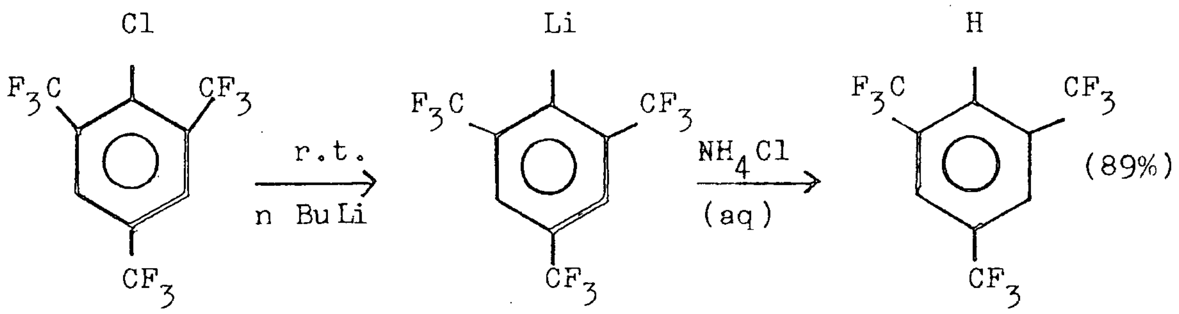
In similarity to the benzoyl peroxide decomposition, the further breakdown of the t-butoxy radical competes with attack on other available molecules. On heating a mixture of di-t-butylperoxide and (103) in a carius tube there was no reaction with the t-butoxy radicals which instead decomposed further forming methyl radicals. A small amount of (113) was attacked by these radicals forming 1-methyl-2,4,6-tris(trifluoromethyl)benzene (106) and the remainder was recovered with some acetone. Ethane, formed by coupling of the methyl radicals, is a probable product and when the reaction was initially carried out in a steel tube a slight pressure was released suggesting some was produced. The carius tube was coated with a brown insoluble film.

The fact that of the four radicals produced (benzoyloxy, phenyl, 5-butoxy, and methyl) only the smallest methyl radical undergoes reaction with (103) suggests that steric factors maybe important in determining the reaction course.

6.C. Preparation and Reactions of 2,4,6-Tris-(trifluoromethy)phenyl Lithium.

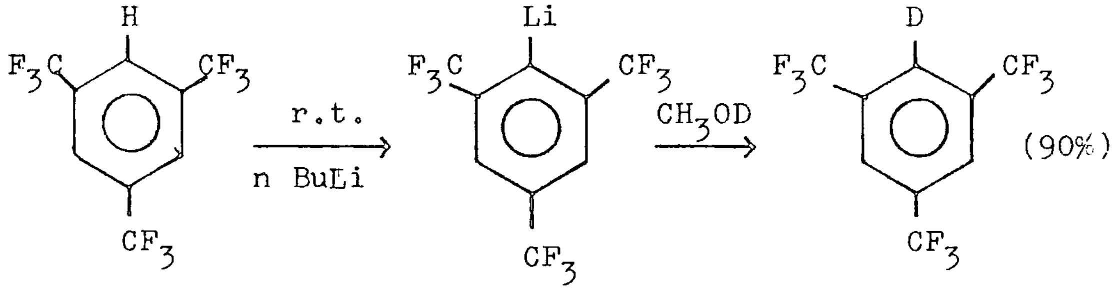
6.C.i. Preparation.

There is one recorded preparation of 2,4,6-tris-(trifluoromethyl)phenyl lithium (116) in the literature,[134] which was achieved by reaction between 1-chloro-2,4,6-tris-(trifluoromethyl)benzene (117) and butyl lithium. The percentage conversion of (117) - (116) was found by hydrolysis of the lithium derivative with ammonium chloride.



(117) (116)

In the present work the lithium derivative (116) was prepared by reaction between the tris(trifluoromethyl)-benzene (103) and butyl lithium at both room temperature and 0°C. The yields of deuterium substituted (103) produced by hydrolysis with methanol-OD showed that the % conversions of (103) - (116) achieved were 90 and 66 respectively.



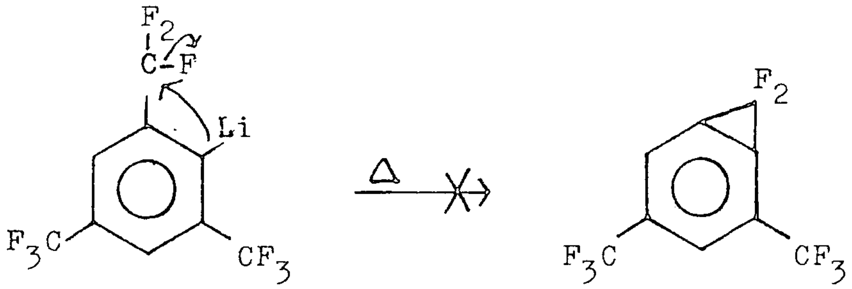
(103) (116)

At room temperature the conversion of (103) to the lithium derivative compares well with that of the chlorine substituted compound (117) and all subsequent reactions have been carried out at this temperature. Formation of a di-lithium derivative was attempted but even after reflux only 11% of the bis-deuterium substituted product was formed on hydrolysis.

6.C.ii. Stability

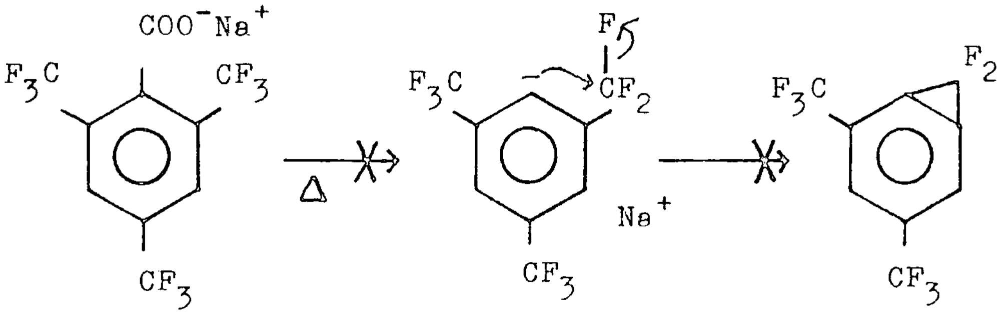
The lithium derivative (116) is stable in ether and on storage in a sealed nmr tube showed little sign of decomposition after a month. This is in marked contrast to pentafluorophenyl lithium which readily loses lithium fluoride, a decomposition mode which is common in compounds containing fluorine and lithium in a vicinal position. Pentafluorophenyl lithium is usually prepared at -78°C since even at -10°C 25% decomposition occurs within forty minutes.[3]

It was hoped that on heating (116) might be forced to split out lithium fluoride forming a cyclopropane derivative (118). However, after heating an ethereal solution of (116) at 90°C in a sealed tube, recovered (103) was the main product on hydrolysis.



(116) (118)

The same compound is also a possible product in the decarboxylation of sodium 2,4,6-tris(trifluoromethyl) benzoate (119).



(119) (118)

Thermogravimetric analysis showed that (119) decomposed at around 300°C. The products of this decomposition were a tarry residue and a multicomponent mixture. No evidence of the formation of (118) was obtained.

These results suggest that the trifluoromethyl group fluorine atoms are not liable to nucleophilic attack, a fact which was also demonstrated by the lack of reaction with methoxide ion (6.B.iii).

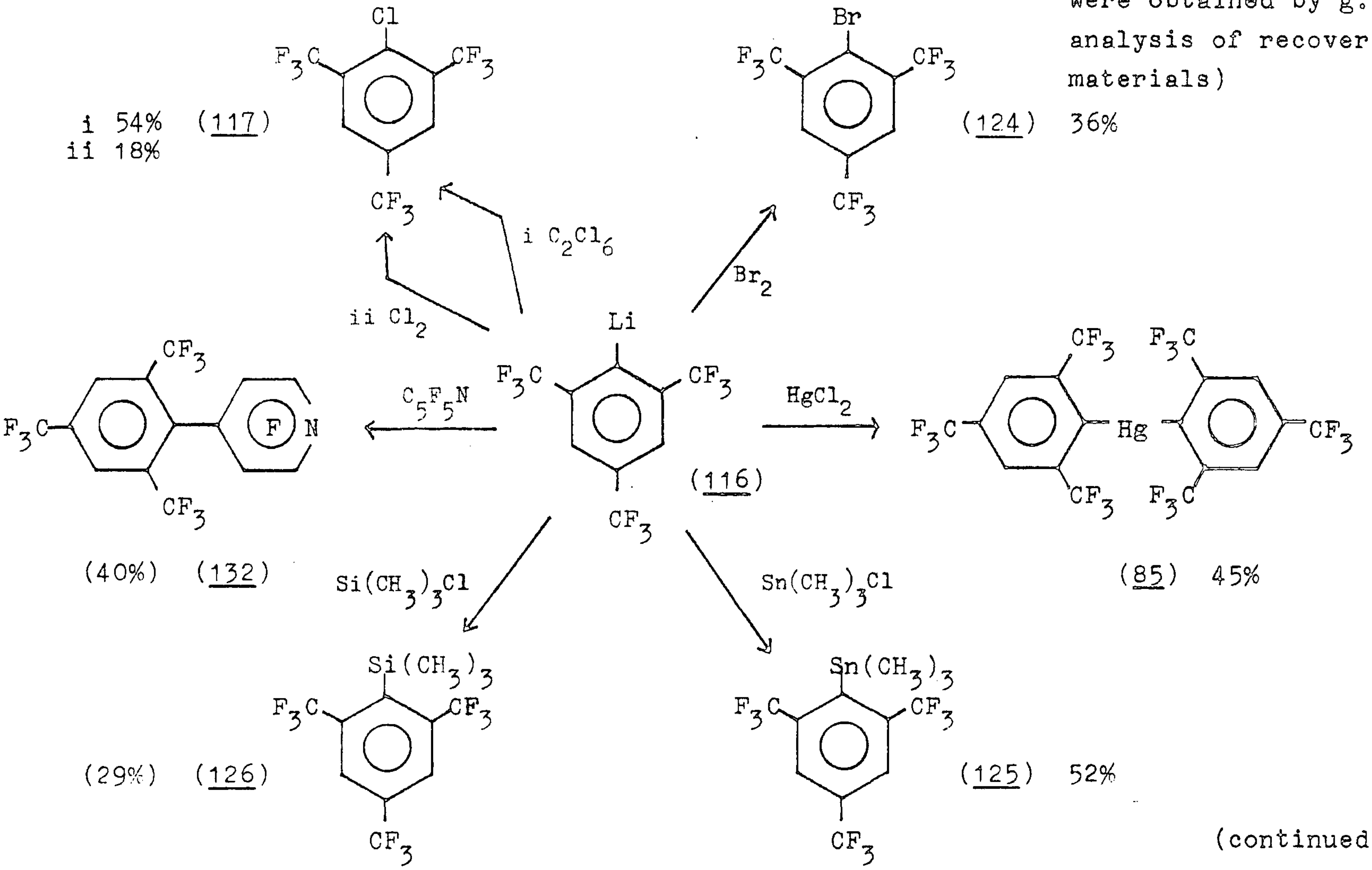
As (116) was so stable its isolation was attempted, but proved unsuccessful because, although a crystalline solid was formed on removal of the solvents, it became intractable on handling. As all the manipulations were carried out under nitrogen, (116) must be very sensitive to trace amounts of moisture which would cause partial hydrolysis and produce the tacky solid observed.

6.C.iii Reactions.

Many of the usual reactions of organolithium compounds[135] have been successfully applied to 2,4,6-tris(trifluoromethyl)phenyl lithium (116) and synthesis via this intermediate lithium compound has proved to be the most successful method of introducing functional groups into (103). The products of these reactions are shown in Diagrams (6.2a & b) and only the reaction with acetyl chloride will be discussed in detail. Given that the formation of the lithium derivative (116) is almost quantitative some of the yields were quite low and it appears the limiting factor

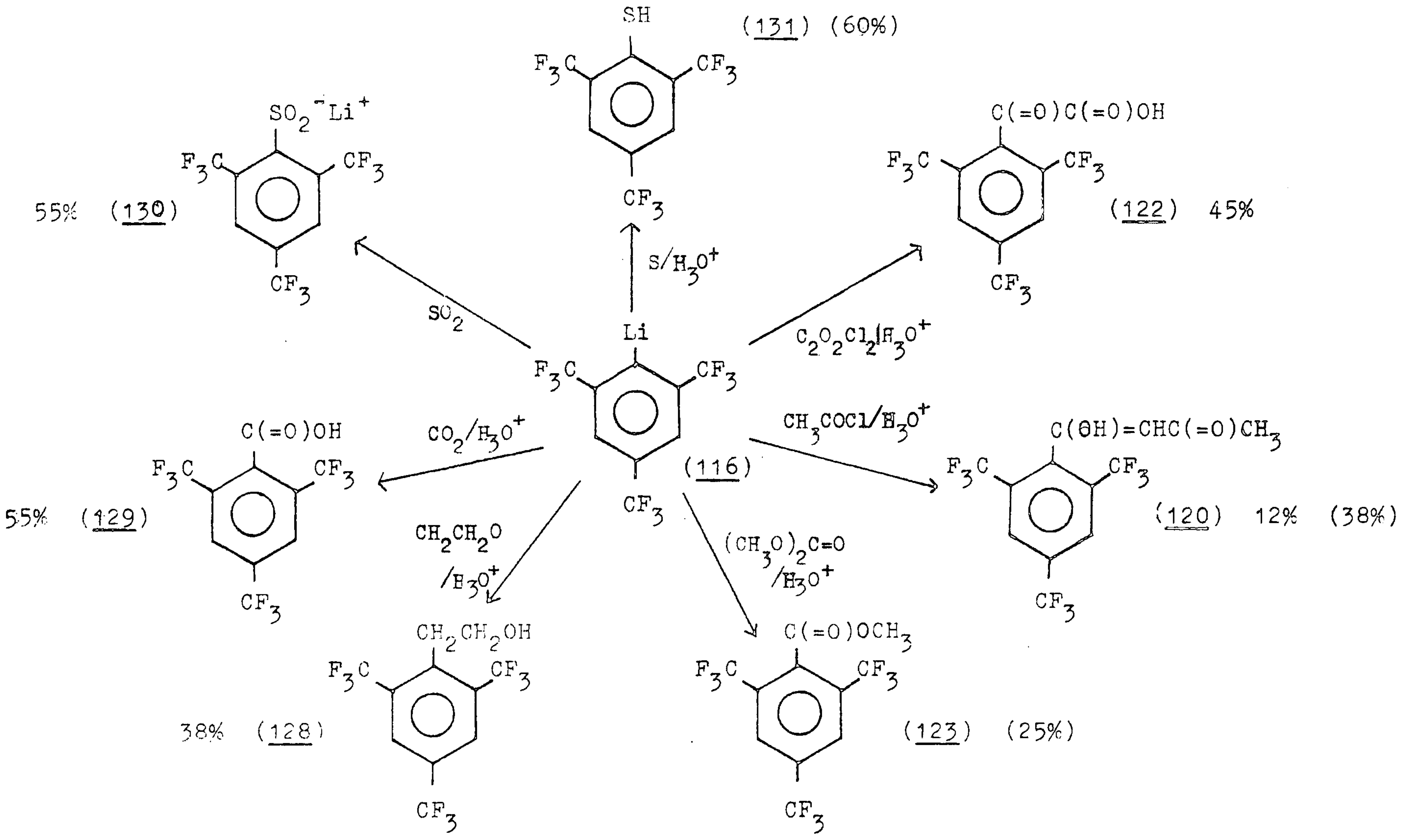
Diagram (6.2a) Reactions of 2,4,6-Tris(trifluoromethyl)phenyl Lithium

(isolated yields are given in most cases, (%) values were obtained by g.l.c. analysis of recovered materials)



(continued)

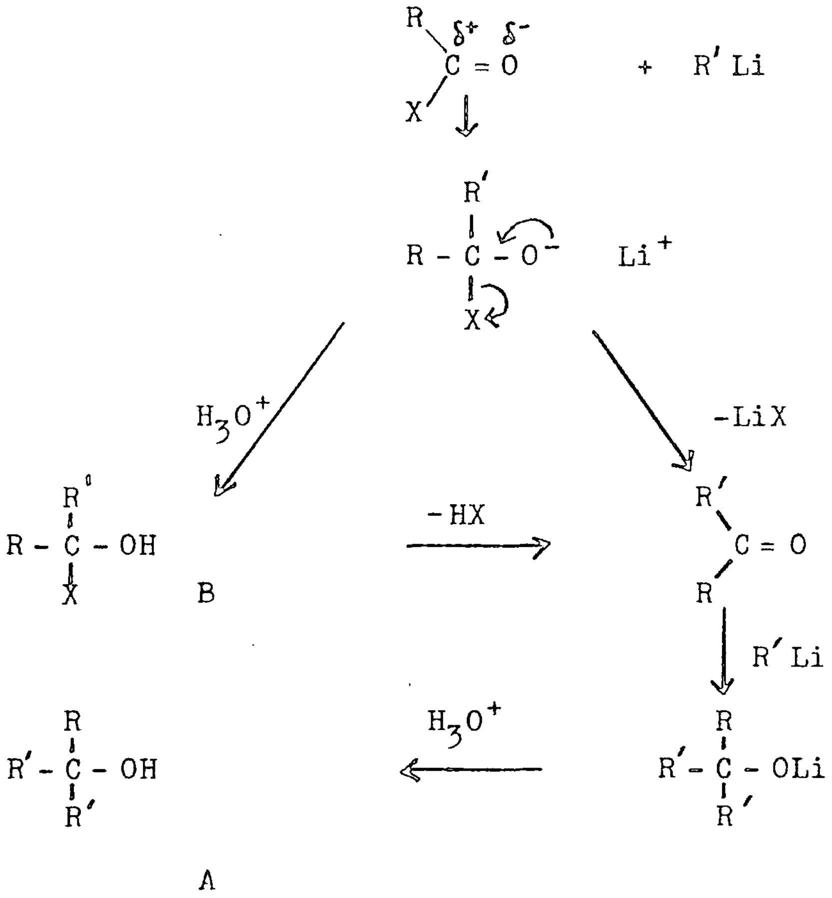
Diagram (6.2b) **Reactions of 2,4,6-Tris(trifluoromethyl)phenyl Lithium** (continued)



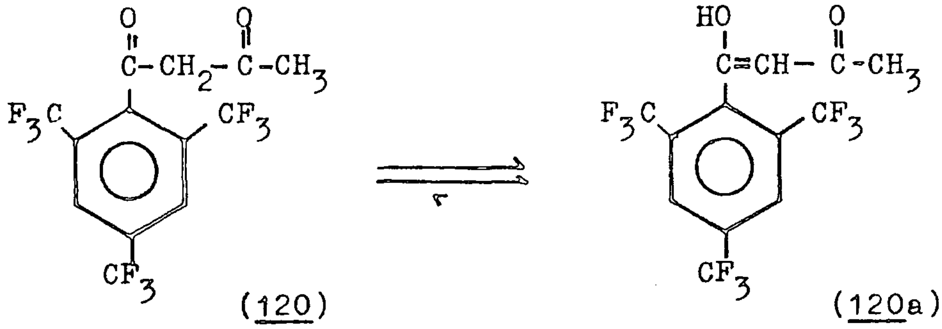
in the reaction is the reactivity of the substrate. In a crowded system the bulk of the attacking group is also likely to be an important consideration.

The reaction between an organolithium compound and an acyl derivative can proceed in several stages, as shown in Scheme (6.2), and the products formed depend upon the efficiency of the leaving group. With aldehydes or ketones the leaving group is poor and so the reaction does not proceed beyond the first stage, giving the alcohol B on hydrolysis. Halide ions are exceptionally good leaving groups and so the final product is the tertiary alcohol A. Ketones are observed as the product if the reaction is slowed by steric hinderance, as might be expected to be the case in the reaction between (<u>116</u>) and acetyl chloride. However the major product was neither the expected methyl ketone, a small amount of which was observed by m.s.g.l.c. of the reaction mixture, or a tertiary alcohol but was identified from its mass spectrum and elemental analysis as a diketone, 1-[2,4,6-tris(trifluoromethyl)phenyl)]-1,3-butanedione (<u>120</u>).

Scheme (6.2) Reaction between an Organolithium Compound and an Acyl Derivative[135]



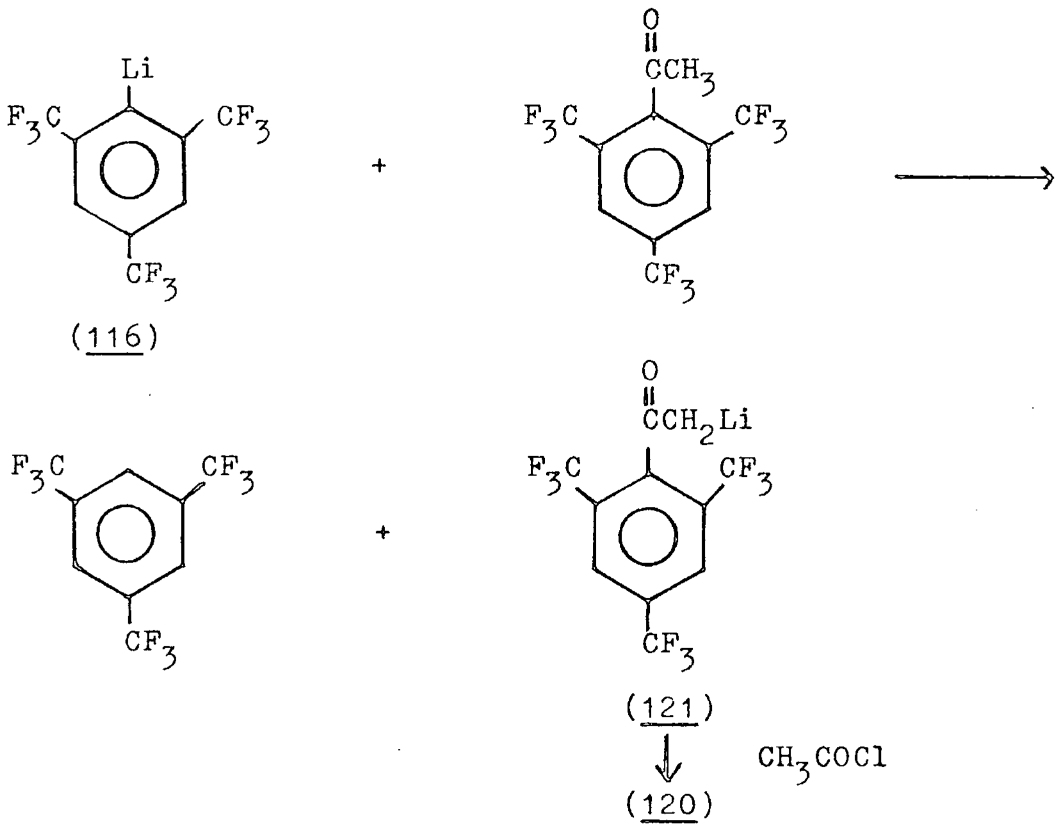
The ^1H and ^{13}C nmr spectra suggest that it is wholly in the enol form (120a).



(120) (120a)

There appears to be no hydrogen bonding between the carbonyl oxygen and enolic proton since in the ^{1}H nmr the proton resonance occurs at 4·85 ppm suggesting weak hydrogen bonding, and a strong ketone absorption appears in the i.r. spectrum rather than the lower frequency enol absorption resulting from resonance-stabilised hydrogen bonding.[136] The enolic proton may instead be loosely bonded to the fluorines of the trifluoromethyl group.

The formation of this diketone (120) has been explained by assuming that the reaction between (116) and acetyl chloride to form the methyl ketone is slow and proton exchange between the ketone and (116) is occurring resulting in the formation of another lithium derivative (121) which reacts more quickly with the acetyl chloride.



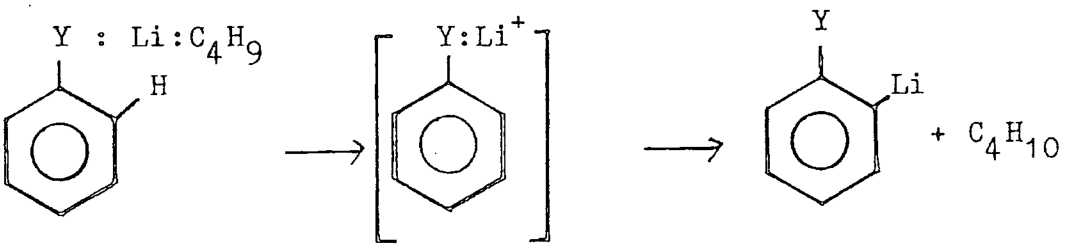
6.C.iv. Comparison of the Acidity of Protons in (103) and Pentafluorobenzene.

A comparison of the acidity of the protons in (103) and pentafluorobenzene was carried out by competitive lithiation of a mixture of the two compounds.

$$\begin{array}{ccccccccc} C_6F_5H & + & (CF_3)_3C_6H_3 & \xrightarrow[-65^\circ C]{\text{i BuLi ii MeOD}} & C_6F_5D & + & C_6F_5H & + & (CF_3)_3C_6H_3 \\ 75\% & & 25\% & & 66\% & & 9\% & & 25\% \\ & & (\underline{103}) & & & & & & \end{array}$$

The reaction was performed at a sufficiently low temperature so as to prevent decomposition of pentafluorophenyl lithium and on hydrolysis with methanol-OD deuteropentafluorobenzene was the only deuterium substituted product observed. As the mixture had been stirred for a prolonged period in order to obtain the thermodynamically, rather than kinetically, favoured product, the hydrogen atom in pentafluorobenzene must be markedly more acidic than those in the tris(trifluoromethyl)benzene (103). This is in agreement with quoted pKa values for the two compounds, 25 and 31 respectively, which were determined by isotope exchange using lithium or caesium cyclohexylamide.

The greater acidity of pentafluorobenzene can be explained by the larger inductive effect of fluorine compared to the trifluoromethyl group, an argument which was previously used to explain the order of ease of metallation ($-F > -OCH_3 > -CF_3 > -H$) observed for substituted benzenes.[137] This relationship would be expected if the inductive effect of the substituent group determined the ease of reaction by with-drawing electrons from the carbon-hydrogen bond and so increasing the acidity of the hydrogen. Lithiation was formulated as the removal of a proton in a nucleophilic attack by the butyl anion. Predominantly ortho-substitution was observed in the metallation of fluorobenzene and trifluoromethylbenzene which was explained by assuming there is initial co-ordination of the lithium to the electron pairs of the substituent. This co-ordination would further enhance the inductive effect.[137]

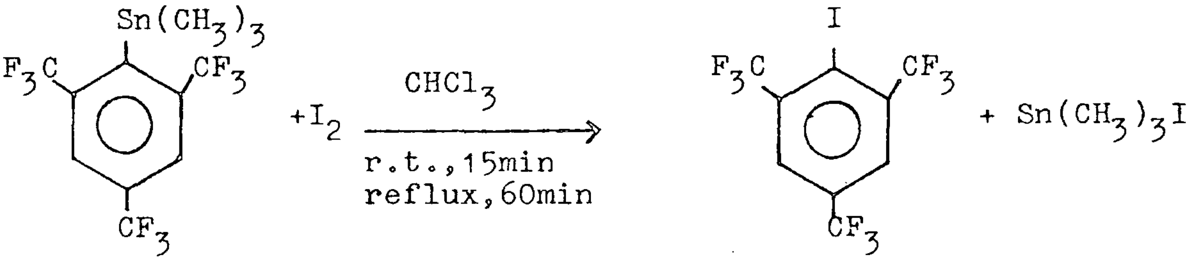


Y = F, CF_3

6.D. Reactions of 1,3,5-Tris(trifluoromethyl)benzene Derivatives.

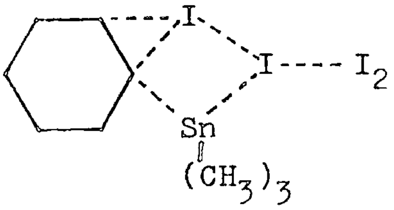
6.D.i. Trimethyl-[2,4,6-tris(trifluoromethyl)phenyl]-tin (125)

The cleavage by halogens of the tin-carbon bond in an aryl tin compound is a well known reaction which has been applied to (125) in an attempt to produce 1-iodo-2,4,6-tris(trifluoromethyl)benzene (127).[169]



(125) (127)

However, even after reflux, neither dissipation of the iodine colouration nor formation of (127) was observed and (125) was recovered from the reaction mixture. The stability of the carbon-tin bond in this case was thought to be enhanced by the three trifluoromethyl groups, as the reaction is an example of electrophilic aromatic substitution which is hindered by electron withdrawing substituents and the cyclic transition state (133) proposed would be difficult to achieve in the presence of two bulky ortho-substituents.[138]

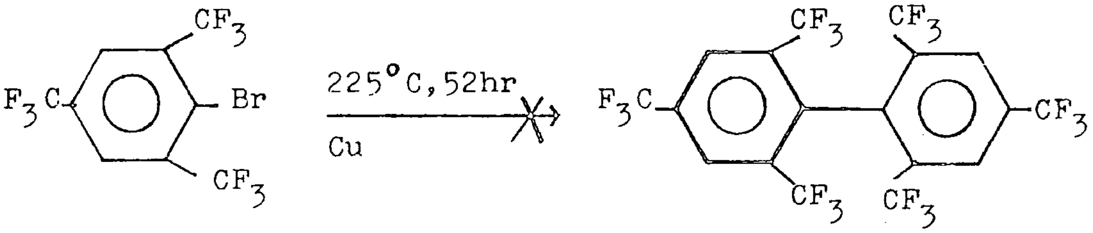


(The aromatic electrons are omitted for simplicity)[138]

(133)

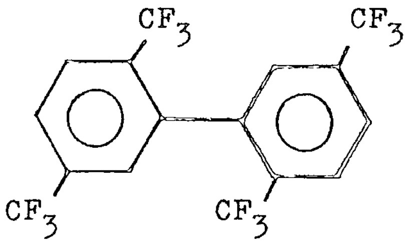
6.D.ii. 1-Bromo-2,4,6-tris(trifluoromethyl)benzene (124)

The possibility of performing an Ullmann coupling reaction with the bromine substituted derivative (124) was interesting since the resultant biphenyl (134) with four ortho-trifluoromethyl groups would be very crowded.

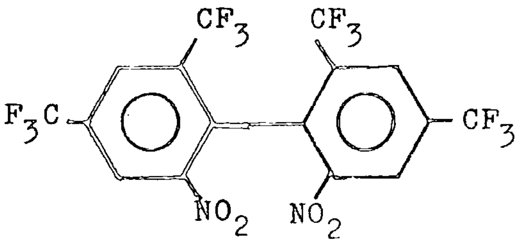


(124) (134)

The presence of two ortho trifluoromethyl groups in 2,'2, 5,'5-tetrakis(trifluoromethyl)biphenyl (135) has been reported to prevent coplanarity and inhibit resonance between the two rings[139] and, despite the fact that a small amount of 2,2'-dinitro-4,4,'6,6'-tetrakis(trifluoromethyl)-biphenyl (136) with four bulky ortho substituents has been formed[140], no coupling was observed in the present reaction.



(135)



(136)

Formation of the symmetrical biphenyl (134) by photolysis of the lithium derivative (116), a method which has produced high yields of biphenyl from phenyl lithium[141], was also unsuccessful.

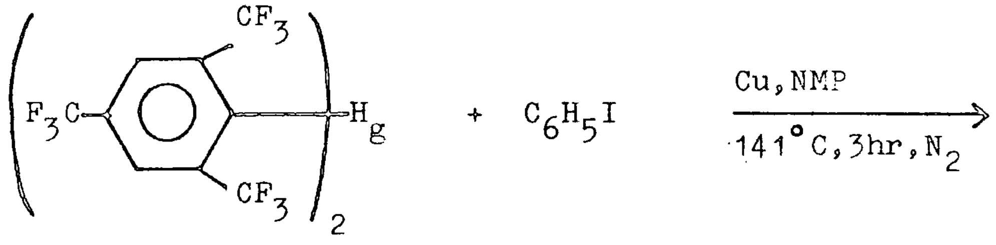
The bromo-derivative (124) will undergo Ullmann coupling with iodobenzene forming the unsymmetrical biphenyl 2,4,6-tris(trifluoromethyl)biphenyl (86).

$$\underset{(124)}{(CF_3)_3C_6H_2Br} + C_6H_5I \xrightarrow[225°C,40hr]{Cu} \underset{(86)}{(CF_3)_3C_6H_2\cdot C_6H_5} + C_6H_5\cdot C_6H_5$$

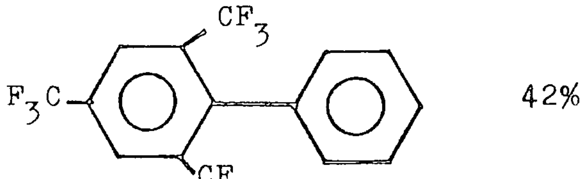
Even in this case (124) is not particularly reactive since it accounted for half of the material recovered whilst the substituted biphenyl (86) was only 11% of the product mixture. The major product was biphenyl (27%) itself formed by coupling between iodobenzene molecules. Halogen exchange had also occurred between the remaining iodobenzene and copper(I) bromide produced in the Ullman reaction, resulting in bromobenzene formation.

6.D.iii. Di[2,4,6-tris(trifluoromethyl)phenyl]mercury (85)

The trifluoromethylation reaction of bis(trifluoromethyl)mercury with iodobenzene in the presence of metallic copper has been extended to include the introduction of the 2,4,6-tris(trifluoromethyl)phenyl group produced in the cleavage of (85). Using the same reaction conditions described in Chapter 2 the biphenyl (86) has been formed from iodobenzene and (85).



(85)



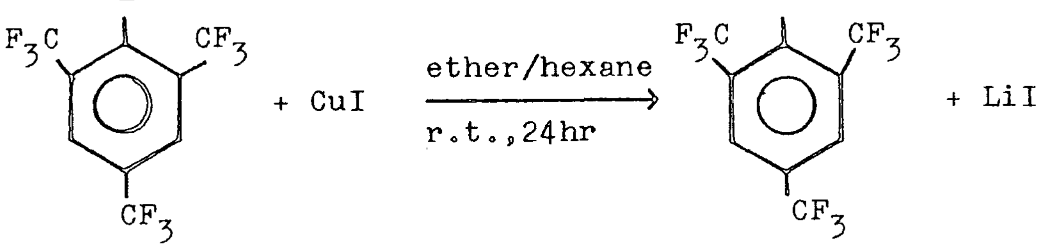
(86)

Analysis of the mercury content of the solid residue showed that at least 85% of the mercurial had decomposed. The remaining 58% of the 2,4,6-tris(trifluoromethyl)phenyl group was accounted for as tris(trifluoromethyl)benzene (<u>103</u>) presumably having picked up a proton from the solvent. This reaction, like the trifluoromethylation procedure, could probably be applied to substituted halobenzenes as well as iodobenzene.

6.C.iv. "<u>2,4,6-Tris(trifluoromethyl)phenyl Copper</u>" (<u>137</u>)

The preparation and reactions of pentafluorophenyl copper have been well studied[142,143] and the methods described have been employed to produce 2,4,6-tris(trifluoromethyl)phenyl copper (<u>137</u>), and investigate some of its reactions.

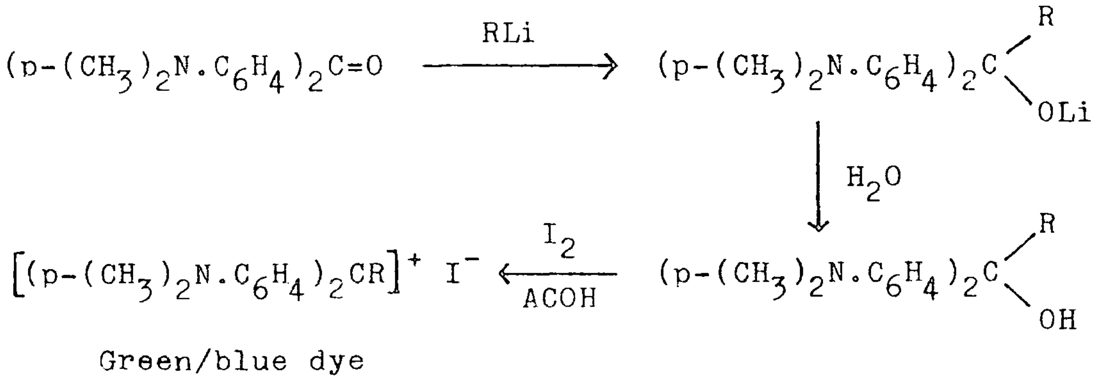
The organocopper compound (<u>137</u>) was prepared in ethereal solution by reaction between copper(I) iodide and the lithium derivative (<u>116</u>)[144]. The reaction was assumed to be complete when the Gilman colour test (the chemistry of which is shown in Scheme (6.3)) proved negative.



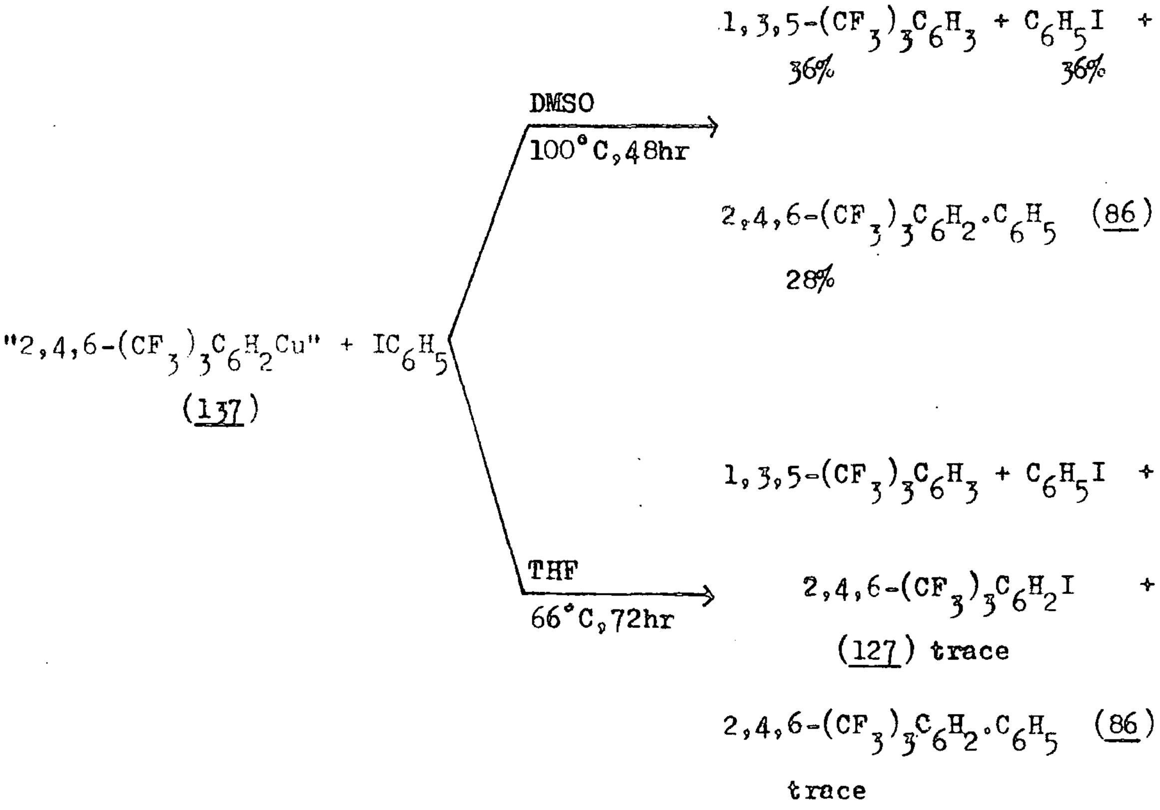
(<u>116</u>) (<u>137</u>)

The representation of (137) in the equation is not meant to imply any particular structure for the organocopper compound as the solution also contains lithium iodide and solvent molecules and several complexes of phenyl copper have been observed, the nature of which depends on the reagents, solvents and stoichiometry of the preparative reaction.[145] The rate and product distributions in reactions of pentafluorophenyl copper, prepared from bromopentafluorobenzene and a Grignard reagent, have been shown to vary with magnesium halide concentration suggesting different reactive organocopper species.[142] Isolation of (137) as a dioxan complex[143] was attempted but proved difficult as the precipitated complex was very fine and awkward to filter. The greyish white solid produced was analysed and found to contain both iodine and lithium as well as the expected elements. Its i.r. spectrum (nujol mull) compared fairly well with a composite spectrum of nujol, dioxan and 1,3,5-tris(trifluoromethyl)-benzene.

Scheme (6.3) <u>The Gilman Colour Test</u>[135]



In order to prove the existence of (137) some reactions characteristic of organocopper compounds needed to be performed but the two simplest, hydrolysis to an arene and coupling on oxidation[142], were not appropriate in this case since (137) was formed from an arene and coupling to form the symmetrical biphenyl has not been achieved. The Ullman coupling of 1-bromo-2,4,6-tris(trifluoromethyl)benzene and iodobenzene was successful and so coupling of the organocopper compound (137) with iodobenzene was chosen as a suitable reaction. The two processes are very similar and organocopper compounds have been suggested as intermediates in the Ullmann Reaction.



Two solvents, tetrahydrofuran and dimethylsulphoxide, were used and the products and yields differed in the two cases. In DMSO 2,4,6-tris(trifluoromethyl)biphenyl (86) produced in the coupling reaction accounted for 36% of the recovered material, whilst in THF the iodobenzene and (103) were the major components and only trace amounts of biphenyl (86) and the halogen exchanged product (127) were obtained. This issimilar to the reaction between pentafluorophenyl copper and iodobenzene which was reported to be very slow in refluxing THF[142] although it occurred readily enough in DMSO.[143] Since the conversion of the tris(trifluoromethyl)benzene (103) to its lithium derivative is almost quantitive and the Gilman colour test showed this was all consumed, (103) present after the reaction must have been produced by hydrolysis of uncoupled copper compound.

EXPERIMENTAL

Instrumentation

A. Preparative Work

Nmr Spectra Fluorine and proton spectra were recorded on a Varian EM360L spectrometer operating at 56·4 and 60 MHz respectively or a Bruker HK90 spectrometer with FT facility operating at 84·68 MHz for the fluorine nucleus. Chemical shifts are quoted in ppm relative to external chlorotrifluoromethane and TMS. Carbon-13 spectra were recorded on a Bruker WH-360 spectrometer operating at 90·6 MHz. The chemical shifts are quoted in ppm relative to TMS.

Ultra Violet Spectra U.V. spectra were recorded on a Pye Unicam S18-100 Ultraviolet spectrophotometer using diethyl ether as the solvent.

Infra-red Spectra I.R. spectra were recorded on a Perkin Elmer 457 grating i.r. spectrophotometer using KBr discs or plates. Gaseous samples were condensed into a cylindrical cell with KBr windows.

Elemental Analysis Carbon, hydrogen and nitrogen analyses were obtained using a Perkin Elmer 240 Elemental Analyser. Analysis for halogens was performed as described in the Literature.[146] Copper and mercury analyses were obtained using a Perkin Elmer Atomic Absorption Spectrometer.

Mass Spectra Mass spectra of solutions were run on a VG Micromass 12B Spectrometer fitted with a Pye 104 Gas Chromatograph or a VG 7070E Spectrometer with a Capillary Column Gas Chromotograph (25 m fused silica column with O_{v1} coating). The mass spectra of solid or one component liquid samples were run on a VG 7070E Spectrometer with electron impact, chemical ionisation, and negative ionisation modes.

Gas Liquid Chromatographic Analysis   This procedure was carried out using a Varian Aerograph Model 920 (Gas density balance detector) or Pye 104 Gas Chromatograph (flame ionisation detector) with packed columns. The column packings are as follows;

Col 1	5% polyethylene glycol 20 m
Col 2	10% polyethylene glycol 20 m
Col O	5% or 10% silicone gum rubber
Col O_{v101}	5% or 10% O_{v101}
Col K	20% Krytox
Col DNP	10% dinonylphthalate

A Hewlett Packard 5890A Gas Chromatograph fitted with a fused silica column with O_{v1} Coating was also used. Preparative g.l.c. was performed on a Varian Aerograph Model 920 with a packed column as described in the experimental details.

Fractional Distillation   Fractional distillation of product mixtures was carried out using a Fischer Spaltrohr MMM 202 system unless stated otherwise.

Melting and Boiling Points   These were determined at atmospheric pressure and are uncorrected.

B. Calculation of Yields

For the reasons explained in the discussion chapters the yields of products in many of the perfluoroalkylation reactions were calculated from g.l.c. analysis of the reaction mixture. A gas density balance was used to produce the chromatogram since the response of this detector is directly proportional to the mass of a component in the reaction mixture,[147] as shown in equation 1.

$$1. \qquad \text{Weight of a component} = \frac{X.A.M_S}{(M_S-M_{cg})}$$

M_S = Molecular mass of solute

M_{cg} = Molecular mass of carrier gas (nitrogen)

A = peak area X = machine constant

As a result of this relationship, quantative analysis can be carried out without the necessity of calibration.

The mass of product expected to be present in a 250 μl sample of the reaction mixture was calculated, assuming 100% reaction, and an equivalent mass of a suitable standard was weighed accurately into a small sample tube to which 250 μl of the reaction mixture was added. The standard was chosen so as to have a retention time similar to that of the product, but such that all the peaks of interest could be completely resolved, and approximately the same molecular mass. After shaking the mixture well to ensure that the standard was evenly distributed, a chromatogram was obtained and the peaks of interest cut out and weighed to five decimal place accuracy. Since the molecular masses of the compound and standard were the same, the peak area of the compound would be equivalent to that of the standard if a 100% yield had been achieved and so the actual yield can be calculated from the ratio of the peak areas.

In some cases a suitable standard of equivalent molecular weight could not be found and so the method had to be altered. A known weight of p-bromotrifluoromethylbenzene was added to a 250μl sample of the reaction mixture and the peak areas of this standard and the product obtained as before. The peak area of the standard was substituted into equation 1 to calculate the machine constant X, which could then be used to calculate the weight of product in 250μl of solution and from this the percentage yield.

Radiochemical Experiments

Some of the trifluoromethylation reactions described were carried out using ^{14}C-labelled benzene derivatives provided by the Physics and Radioisotopes Service Section of I.C.I., within whose laboratories the work was done.

The ^{14}C-labelled compounds were supplied in ether and the activity of the solution had to be calculated.

Calculation of the Total Activity of the Bromobenzene/Ether Solution.

Bromobenzene solution (5 μl) was dissolved in a known mass of methanol and the total mass measured. A weighed amount of methanolic solution was added to scintillator solution and counted by liquid scintillation. The latter part of this process was repeated and the results used to calculate the activity of the original ether solution.

Methanol (g)	19·7270	19·7580
Methanol+C_6H_5Br (g)	19·7324	19·7634
Mass added to scintillator solution	0·4983	0·4893
Disintegrations per minute	275862	264879
d.p.m./5μl	10923980	10700959
μCi/5μl	4·97	4·86
mCi/ml	0·99	0·97

Average value 0·985 mCi/ml

The activities of the other solutions were;

p-chloroiodobenzene 0·16mCi/ml, o-chloroiodobenzene 0·10mCi/ml, and iodobenzene 0·12 m Ci/ml.

The trifluoromethylation reactions were carried out using inactive halobenzene mixed with a small quantity of ^{14}C-labelled compound so that the reaction mixtures could be analysed by radio-g.l.c. This technique has the advantage that the area of the peaks is related to the number of disintegrations per minute and, unlike those from a gas density balance, independent of temperature. As a result of this, calculation of yields is still possible when the chromotograph is run with a temperature ramp, which allows better separation of the more volatile peaks and a reduced retention time for higher boiling materials. The proportion of ^{14}C-labelled material was chosen such that the expected yield of trifluoromethylated product would give a full scale deflection on the chromatogram, working on the assumption that the detector is 20% efficient and so only twenty out of every hundred disintegrations result in a count being registered.

Calculation of the Proportion of ^{14}C-labelled Iodobenzene Necessary.

A full scale deflection in the $CF_3C_6H_5$ peak = 3000 c.p.m.

Detector is 20% efficient so 3000 c.p.m. = $\frac{3000 \times 100}{20}$ =

$1{\cdot}5 \times 10^4$ d.p.m. = $6{\cdot}8 \times 10^{-3} \mu$Ci

1 l injection into radio-g.l.c. must contain $6{\cdot}8 \times 10^{-3} \mu$Ci

Activity per ml of reaction solution = $\underline{\underline{6{\cdot}8\ \mu\text{Ci}}}$

Preferred level of activity is 10 - 50 μCi per reaction so 4 ml reaction volume is used requiring 27·2 μCi.

Assuming 100% conversion of C_6H_5I to $C_6H_5CF_3$ the activity provided by the ^{14}C-iodobenzene must be $\underline{\underline{27\cdot2\ \mu Ci}}$.

Activity of the iodobenzene/ether solution is 0·12 m Ci/ml

$$\text{so } \frac{27\cdot2}{0\cdot12 \times 10^3} = \underline{\underline{226\mu l}} \text{ are required per reaction}$$

Specific activity of the iodobenzene = 1·5 m Ci/mmol.

$$\text{so } \frac{27\cdot2}{1\cdot5 \times 10^3} = \underline{\underline{0\cdot018 \text{ mmol}}} \text{ of } ^{14}C\text{-iodobenzene has an activity of } 27\cdot2\ \mu Ci.$$

In a 4 ml reaction volume 0·5 mmol of iodobenzene are required, the remaining 0·482 mmol is inactive material.

The peak areas of the radio-chromatogram were integrated electronically and from these were calculated the percentages of the total activity in any peak. Provided that no activity has been lost from the solution these values are equivalent to the yield of the compound. In order to ascertain whether any loss of activity had occurred an activity balance was carried out for each reaction, an example of which is given below.

Calculation of the Activity Balance for the Trifluoromethylation of ^{14}C-bromobenzene.

The mass of NMP and bromobenzene in the reaction mixture was calculated. Before and after the reaction samples of the reaction solution (2–3µl) were weighed into phials of scintillator solution and counted using liquid scintillation. Since the rubber seal was found to have absorbed activity it was washed in scintillator solution and counted. From these results the activity present in the solution at the beginning and end of the reaction period was calculated.

mass of NMP and bromobenzene 4·2097 g

		Sample Activity		Total Activity
	sample g	d.p.m.	µCi	µCi
Initial Solution	0·0038	64308	$2{\cdot}9\text{x}10^{-2}$	30·8
	0·0040	61004	$2{\cdot}7\text{x}10^{-2}$	30·7
		30·75 µCi		
Final Activity	0·0032	42795	$1{\cdot}9\text{x}10^{-2}$	26·6
	0·0041	57016	$2{\cdot}6\text{x}10^{-2}$	26·6
		26·06 µCi		
+ activity absorbed in septum		4·03		
		30·13 µCi		

98% activity accounted for

Chapter 7

Experimental for Chapter 2

7.A. Reagents and Solvents

N-Methylpyrrolidone was distilled under reduced pressure (87°C, 10 mmHg) onto molecular sieve (4A) and stored under dry nitrogen.

Mercury(II) Trifluoroacetate (77) Mercury(II) oxide (23·76 g, 0·11 mol) was slowly added to trifluoroacetic acid (50·16 g, 0·44 mol) and the mixture stirred until the reaction was completed. The water and excess acid were removed under reduced pressure before drying under vacuum of the white crystalline product (77) (43 g, 92%).

Bis(trifluoromethyl)mercury (76)[102] Oven dried potassium carbonate (38·64 g, 0·28 mol) and (77) (57·78 g, 0·14 mol) were ground together forming an intimate mixture and placed in a 500 ml pyrolysis vessel equipped with a 30 mm diameter side arm. The mixture was heated to 200°C under a vacuum of 20 mmHg and the product, a white crystalline solid, sublimed coating the side arm and was identified from literature data (35 g, 74%); $\delta_F(CDCl_3)$ 38·5 (S, J $^{198}Hg-C-C-^{19}F$ 1289 Hz, CF_3) (Lit.,[172] 38·5, J 1251 Hz).

Activated Copper Powder. Hydrated copper(II) sulphate (100 g, 0·4 mol) was dissolved in hot water (350 ml), and zinc dust (35 g, 0·54 mol) was added gradually with stirring until the blue colour of the solution faded. The precipitated copper powder was washed in water and hydrochloric acid (2M) before filtration, it was then washed with ethanol and ether and dried under vacuum.

The iodo and bromobenzenes used were either commercial samples or supplied by I.C.I.

7.B. Trifluoromethylation Reactions using Bis(trifluoromethyl)mercury (76)

N.B. CARE MUST BE TAKEN IN HANDLING THE TOXIC MERCURIAL (76)

Residues from the trifluoromethylation reaction were dissolved in conc. nitric acid and all glassware was immersed in nitric acid before washing. The nitric acid/ mercury salt solution was neutralised with base and hydrogen sulphide bubbled through until precipitation of black mercuric sulphide ceased. The precipitate was filtered and sealed in a plastic container for disposal by burial.

7.B.i. Method A

7.B.i.a. Iodobenzene

A mixture of (76) (3·38 g, 10 mmol), copper powder (2·54 g, 40 mmol), and NMP (20 ml) was stirred under nitrogen for two hours at 140°C. A solution of iodobenzene (4·08 g, 20 mmol) in NMP (5 ml) was added and the heating continued for two hours. Comparison of the g.l.c. trace (Col 1,150°C) of the reaction mixture with that of a standard solution showed trifluoromethylbenzene had been formed in 85% yield. The reaction mixture was cooled in liquid nitrogen and the volatile material separated by vacuum transference, warming the mixture gently until the solvent began to boil. The colourless liquid obtained was washed with water to remove any traces of NMP and shown, by comparison of the mass spectrum with that of the authentic material, to be trifluoromethylbenzene, m/z 146(M^+).

7.B.i.b. p-Iodonitrobenzene.

A mixture of (<u>76</u>) (3·38 g, 10 mmol), copper powder (2·54 g, 40 mmol), and NMP (20 ml) was stirred under nitrogen for two hours at 140°C. A solution of p-iodonitrobenzene (4·98 g, 20 mmol) in NMP (5 ml) was added and the heating continued for a further three hours. From the g.l.c. (Col 1,170°C) of the reaction mixture with an internal standard the yield of product was calculated to be 65%. The mixture was added to water and extracted with diethyl ether. The extracts were dried over magnesium sulphate and the ether removed leaving a waxy orange solid, p-nitrotrifluoromethylbenzene (2·27 g, 59%), m.p. 36°C; ν_{max} (KBr disc) 1540, 1455(N-O), 860 (C-N)cm^{-1}; m/z 191 (M^+).

7.B.ii. <u>Method B</u>

7.B.ii.a. p-Iodonitrobenzene

A mixture of (<u>76</u>) (3·38 g, 10 mmol), copper powder (2·54 g, 40 mmol), and NMP (20 ml) was stirred under nitrogen for two hours at 140°C. The excess copper was filtered off under nitrogen using a glass scinter, before addition of a solution of p-iodonitrobenzene (1·25 g, 5 mmol) in NMP (10 ml). The mixture was stirred at 150°C for a further three hours. The steam-volatile components were removed by steam distillation and extracted from the resulting aqueous solution with diethyl ether. Removal of the ether left a white crystalline solid shown by comparison of the i.r. spectrum with that of the authentic material to be p-iodonitrobenzene.

This preparation was repeated with iodobenzene, but no trifluoromethylation was observed to have taken place.

7.B.ii.b. Iodobenzene

A mixture of (76) (3·38 g, 10 mmol), copper powder (2.54 g, 40 mmol), and NMP (20 ml) was stirred under nitrogen for two hours at 140°C. The excess copper was filtered off under nitrogen through a glass scinter, before addition of a solution of iodobenzene (4·08 g, 20 mmol) in NMP (10 ml). The mixture was heated at 150°C for a further three hours. The volatile material was separated by vacuum transference and found to be the colourless liquid trifluoromethylbenzene (0·22 g, 7·5%) identified by comparison with the authentic material.

7.B.iii 'One Pot' Reactions

7.B.iii.a. Substituted Iodobenzenes (General procedure)

A mixture of (76) (3·38 g, 20 mmol), copper powder (2·54 g, 40 mmol), iodobenzene (15 mmol), and NMP (25 ml) was stirred under nitrogen at 140°C for three hours. The resulting mixture was analysed by m.s.g.l.c. (Col 1, 150°C) and ^{19}F nmr, and the yield calculated by g.l.c.

Table (7.B.1) **Trifluoromethylation of Substituted Iodobenzenes using Bis(trifluoromethyl)mercury**

substituted iodobenzene	product	yield %	δ_F p.p.m.[‡]	m/z (M^+)
iodobenzene	trifluoromethylbenzene	83	63·5	146[†]
p-iodonitrobenzene	p-nitrotrifluoromethylbenzene	82	63·2	191
1,4-diiodobenzene	1,4-bis(trifluoromethyl)benzene	73	63·7	214
3-iodopyridine	3-trifluoromethylpyridine	79[*]		

[*] isolated by vacuum transferance and identified by comparison of i.r. with the authentic material.

[†] identified by comparison of spectra with those of the authentic material.

[‡] comparison of literature values see Ref. 154

after addition of an internal standard. The compounds were identified from the molecular ion peak, fragmentation pattern of the mass spectra and, where possible, by comparison of spectra with those of the authentic material. The results are shown in Table (7.B.1).

7.B.iii.b. Bromobenzene

A mixture of (76) (3·38 g, 10 mmol), copper powder (2·54 g, 40 mmol), bromobenzene (2·36 g, 15 mmol), and NMP (25 ml) was stirred under nitrogen at 140°C for three hours. The resulting mixture was analysed by m.s.g.l.c. (Col 1, 150°C) and found to contain NMP, bromobenzene (86%) and trifluoromethylbenzene (5%).

7.B.iii.c. Substituted Bromobenzenes (General Procedure)

A mixture of (76) (3·38 g, 10 mmol), copper powder (2·54 g, 40 mmol), bromobenzene (15 mmol) and NMP (25 ml) was stirred under nitrogen at 165°C for three hours. The resulting mixture was analysed by m.s.g.l.c. (Col 1, 150°C) and ^{19}F nmr and the yield of product was calculated by g.l.c. after addition of an internal standard. The compounds were identified from the molecular ion peak, fragmentation pattern of the mass spectrum and, where possible, by comparison of the spectra with those of the authentic materials. The results are shown in Table (7.B.2).

Table (7.B.2) Trifluoromethylation of Substituted Bromobenzenes using (76)

substituted bromobenzene	product	yield %	δ_F p.p.m.‡	m/z (M^+)
bromobenzene	trifluoromethylbenzene	38	63·5	146 *
	+ bromobenzene	57		*
p-bromotrifluoromethylbenzene	1.4-bis(trifluoromethyl)benzene	62	63·7	214 *
	+ p-bromotrifluoromethylbenzene	40	62·7	
o-bromotoluene	o-trifluoromethyltoluene	49	63·1	160
	+ o-bromotoluene	40		*

* identified by comparison of the spectra with those of the authentic material

‡ for a comparison with literature values see Ref. 154

7.B.iii.d. Chlorobenzene

A mixture of (<u>76</u>) (3·38 g, 10 mmol), copper powder (2·54 g, 40 mmol), chlorobenzene (1·69 g, 15 mmol), and NMP (25 ml) was stirred under nitrogen at 140°C for three hours. The mixture was analysed by m.s.g.l.c. (Col 1, 150°C) and found to contain NMP and chlorobenzene (94%). Further heating at 165°C for three hours did not result in any further reaction.

7.B.iii.e. Pentafluoroiodobenzene-1

A mixture of (<u>76</u>) (3·38 g, 10 mmol), copper powder (2·54 g, 40 mmol), pentafluoroiodobenzene (4·41 g, 15 mmol) and NMP (25 ml) was stirred under nitrogen at 140°C for three hours. The mixture was analysed by m.s.g.l.c. (Col 1, 100°C) and ^{19}F nmr and, on comparison of the spectra with those of authentic materials, found to be a mixture of four components; NMP, octafluorotoluene (25%), pentafluorobenzene (21%), decafluorobiphenyl (7%).

7.B.iii.f. Pentafluoroiodobenzene-2

A mixture of (<u>76</u>) (3·38 g, 10 mmol), copper(I) iodide (7·6 g, 40 mmol), pentafluoroiodobenzene (4·41 g, 15 mmol), and NMP (25 ml) was stirred under nitrogen at 140°C for three hours. The mixture was analysed by m.s.g.l.c. (Col 1, 100°C) and ^{19}F nmr and, on comparison of the spectra with those of authentic materials, was found to contain three components; NMP, octafluorotoluene (19%), pentafluorobenzene (81%).

7.C. Mechanistic Studies

7.C.i.a. Trifluoromethylation with a Reduced Amount of Copper.

A mixture of (76) (3·38 g, 10 mmol), copper powder (0·28 g, 5 mmol), iodobenzene (3·06 g, 15 mmol), and NMP (20 ml) was stirred under nitrogen at 140°C for three hours. The g.l.c. (Col 1, 150°C) of the reaction mixture was compared with those of standard solutions to calculate the amount of remaining iodobenzene (65%) and yield of trifluoromethylbenzene (37%).

7.C.i.b. Trifluoromethylation with Copper replaced by Copper(I) iodide.

A mixture of (76) (3·38 g, 10 mmol), copper(I)iodide (7·6 g, 40 mmol), iodobenzene (3·06 g, 15 mmol), and NMP (25 ml) was stirred under nitrogen at 140°C for three hours. The g.l.c. (Col 1, 150°C) of the reaction mixture was compared to those of standard solutions to calculate the yield of trifluoromethylbenzene (53%) and amount of remaining iodobenzene (39%).

7.C.i.c. Treatment of Copper Filtrates.

Ether was poured through the scinter to wash the filtrate and remove organic material before it was dried under suction. The dry filtrate was dissolved in aqua regia (40 ml) and the volume made upto 1000 ml with water. A small amount of the solution was analysed by atomic absorbtion spectroscopy for copper and mercury content.

7.C.ii.a. Trifluoromethylation with Added Iodine.

A mixture of (76) (3·38 g, 10 mmol), copper powder (2·54 g, 40 mmol), iodobenzene (3·06 g, 15 mmol), a few crystals of iodine, and NMP (25 ml) was stirred under nitrogen at 140°C for three hours. The g.l.c. (Col 1, 135°C) of the mixture was compared with that of a standard solution to calculate the yield of trifluoromethylbenzene (88%) and amount of remaining iodobenzene (11%).

Chapter 8

Experimental for Chapter 3.

8.A. Reagents and Solvents.

N-Methylpyrrolidone - as described in Chapter 7.

Dimethylsulphoxide and N,N-dimethylformamide were both distilled under reduced pressure. The middle fractions were collected over a molecular sieve (4A) and stored under nitrogen.

Sodium trifluoroacetate (87) Sodium hydroxide pellets (4 g, 0·1 mol) were added slowly to a mixture of trifluoroacetic acid (11·4 g, 0·1 mol) and water (10 ml) which was stirred until the pellets dissolved. The water was removed under reduced pressure and the white crystalline product was dried under vacuum at 60°C before storage under nitrogen.

2-Amino-5-iodopyridine A solution of 2-aminopyridine (13·5 g, 0·14 mol) in 1,2-dichloroethane (45 ml) was cooled in an ice bath. Potassium carbonate (450 g, 0·31 mol) and iodine (40·2 g, 0·16 mol) were added to the stirred solution and the stirring was continued at ice bath temperature for one hour and at room temperature overnight. The mixture was cooled to 5°C and the precipitate filtered and washed with cooled solvent. Recrystallisation from benzene gave the white crystalline solid 2-amino-5-iodopyridine (10·6 g, 32%), m.p. 126°C (Lit.,[149] 128·5°C); (Found: C, 27·5; H, 2·9; N, 13·0. Calc for $C_5H_5N_2I$: C, 27·27; H, 3·18; N, 12·72%).

2-Amino-5-iodopyridine (acetylated form) A mixture of 2-amino-5-iodopyridine (4·5 g, 20 mmol), acetic acid (9 ml) and a few drops of conc. sulphuric acid was boiled for two minutes. Water (2 ml) was added dropwise and the mixture allowed to stand for fifteen minutes. The precipitate was filtered and recrystallised from 50% aqueous alcohol yielding the white crystalline solid N-acetyl-2-amino-5-iodopyridine (4·25 g, 81%), (Found: C, 32·2; H, 2·5; N, 10·3. Calc for $C_7H_7IN_2O$: C, 32·06; H, 2·67; N, 10·68%).

p-Iodotrifluoromethylbenzene A mixture of p-aminotrifluoromethylbenzene (8·4 g, 51 mmol), conc. sulphuric acid (3 ml) and water (45 ml) was stirred for 1hr. The mixture was cooled to 0-5°C in an ice bath and diazotised by addition of a solution of sodium nitrite (3·6 g, 52 mmol) in water (12 ml). A solution of potassium iodide (15 g, 90 mmol) in water (15 ml) was added dropwise so as to maintain the temperature below 5°C. After addition was completed the mixture was stirred for an hour whilst warming to room temperature. The dark solution was decolourised by the addition of sodium bisulphite and the product, a yellow oil, was isolated by steam distillation. The oil was dissolved in ether and dried over magnesium sulphate. Fractional distillation under reduced pressure produced a colourless liquid which was shown by g.l.c. (10% Col 0,100°C) to be a single product, p-iodotrifluoromethylbenzene, b.p. 59·5°C, 5mmHg: lit.[153] 185-186°C); δ_F 63; m/z 272 (M^+).

Phenylbromacetylene[148] and 2-chloro-5-iodopyridine[149] were prepared by methods described in the literature. Other iodo and bromo compounds were obtained from commercial sources.

8.B. Trifluoromethylation Reactions using Sodium Trifluoroacetate (87).

8.B.i.a. Trifluoromethylation of Benzenoid Aromatic Compounds

General Procedure

A mixture of (87) (2·72 g, 20 mmol), copper(I) iodide (1·91 g, 10 mmol), halobenzene (1·7-5·0 mmol), and NMP (40 ml) was stirred under nitrogen at 160°C for four hours. The mixture was analysed by m.s.g.l.c. (Col 2) and the yield of product calculated from the g.l.c. of the reaction mixture incorporating an internal standard. The trifluoromethylated products were identified from the molecular ion peak, fragmentation pattern of the mass spectrum and, where possible, by comparison with the spectra of authentic materials. The results are shown in Table (8.1).

Table (8.1) Trifluoromethylation of Benzenoid Aromatic Compounds.

Arene	mmol	Product	Yield %	M/Z (M^{+})	^{19}F nmr p.p.m.‡
iodobenzene	5	trifluoromethylbenzene	87	146	63·5 *
bromobenzene	5	trifluoromethylbenzene	68	146	63·3 *
chlorobenzene	5	-	-	-	-
p-iodonitrobenzene	5	p-nitrotrifluoromethylbenzene	64	191	62·7
1,4-diiodobenzene	2·5	1,4-bis(trifluoromethyl)benzene	93	214	63·3
1,4-diiodobenzene	5	1,4-bis(trifluoromethyl)benzene	24	214	64·0
		p-iodotrifluoromethylbenzene	24	272	63·7 *
p-iodotrifluoromethylbenzene	5	1,4-bis(trifluoromethyl)benzene	73	214	63·0
p-chloroiodobenzene	5	p-chlorotrifluoromethylbenzene	98	180/182	63·4
o-chloroiodobenzene	5	o-chlorotrifluoromethylbenzene	87	180/182	63·0
iodopentamethylbenzene	5	pentamethyltrifluoromethylbenzene	60		50·7
pentafluoroiodobenzene	5	decafluorobiphenyl	44	334	*
		pentafluorobenzene	46	168	
m-bromotoluene	5	m-trifluoromethyltoluene	78	160	61·3
p-bromotrifluoromethylbenzene	5	1,4-bis(trifluoromethyl)benzene	62	214	63·2
1,3,5-tribromobenzene	1·7	1,3,5-tris(trifluoromethyl)benzene	48	282	63·0 *
		1,3-bis(trifluoromethyl)benzene	41	214	

* These compounds were identified by comparison of the spectra with those of the authentic material.
‡ For a comparison of literature values see Ref. 154

8.B.ii.a. Trifluoromethylation of Heterocyclic Aromatic Compounds.

General Procedure

A mixture of (87) (2·72 g, 20 mmol), copper(I) iodide (1·91 g, 10 mmol), halogenated heterocycle (5 mmol) and NMP (40 ml) was stirred under nitrogen at 160°C for four hours. The mixture was analysed by m.s.g.l.c. (Col 2) and the yield of product was calculated from the g.l.c. of the reaction mixture incorporating an internal standard. The trifluoromethylated products were identified by the molecular ion peak and fragmentation pattern of the mass spectra. The results are shown in Table (8.2).

8.B.iii.a. Trifluoromethylation of (2-bromoethenyl)benzene.

General Procedure

A mixture of (87) (2·72 g, 20 mmol), copper(I) iodide (1·91 g, 10 mmol), (2-bromoethenyl)benzene (0·92 g, 5 mmol) and NMP (40 ml) was stirred under nitrogen at 160°C for four hours. The mixture was analysed by m.s.g.l.c. (Col 2) and ^{19}F nmr, and the product yield calculated from the g.l.c. after addition of an internal standard. From the molecular ion peak and fragmentation pattern of the mass spectrum and the ^{19}F nmr spectrum the product was identified as 3,3,3-trifluoro-1-propenylbenzene (53·5%),[157] δ_F 63·4; m/z 172 (M^+).

Table (8.2) Trifluoromethylation of Heterocyclic Aromatic Compounds.

Heterocyclic compound	Product	Yield %	M/Z (M)	^{19}Fnmr p.p.m
2-amino-5-iodopyridine	-			
N-acetyl-2-amino-5-iodopyridine	-			
2-chloro-5-iodopyridine	2-chloro-5-trifluoromethylpyridine[155]	85	181/183	
	2,5-bis(trifluoromethyl)pyridine	7	215	
2-chloro-5-trifluoromethylpyridine	2,5-bis(trifluoromethyl)pyridine	27	215	
2-iodothiophene	2-trifluoromethylthiophene[156]	46	152	54·7
2-bromopyrimidine	2-trifluoromethylpyrimidine	34	148	70·7
2-iodo-N-methylimidazole	-			

8.B.iii.b. Trifluoromethylation of (2-bromo-2-fluoroethenyl)benzene.

(This sample was kindly provided by -
Prof.H.Koch, Ithaca College, U.S.A.)

A mixture of (87) (0·66 g, 5 mmol), copper(I) iodide (0·48 g, 2·5 mmol), (2-bromo-2-fluoroethenyl)benzene (6:1, E/Z somer) (0·25 g, 1·25 mmol), and NMP (10 ml) was stirred under nitrogen at 160°C for four hours. The mixture was analysed by m.s.g.l.c. (Col 2, 130°C) and ^{19}F nmr, and the yield of product calculated by g.l.c. after addition of an internal standard. The product was identified from the molecular ion peak and fragmentation pattern of the mass spectrum, as 3,3,3,2-tetrafluoro-1-propenylbenzene (59%), δ_F 71 (d,CF_3) 135·4 (d of m, F); m/z 190(M^+).[158]

8.B.iii.c. Attempted Trifluoromethylation of Phenylbromoacetylene.

A mixture of (87) (1·32 g, 10 mmol), copper(I) iodide (0·96 g, 5 mmol), phenylbromoacetylene (0·45 g, 2·5 mmol), and NMP (20 ml) was stirred under nitrogen at 160°C for four hours. The reaction mixture was added to water and extracted with diethyl ether. The ethereal solution was washed with water and dried over $MgSO_4$ before removal of ether leaving a brown solid. This was sublimed at 60°C, onto a cold finger. The yellow crystals collected were shown to be impure 1,4-diphenylbuta-1,3-diyne (0·18 g, 72%), m.p. 78-82°C (lit.,[151] 87-88°C); ν_{max} (KBr disc)

915, 755, 680, 520 cm; λ_{max} (diethylether) 248, 258, 288, 305, 326 nm, (lit.,[151] (ethanol) 227, 247, 257, 287, 306, 307 nm): δ_H (CCl_4) 7·2; m/z 202 (M^+).

This reaction was repeated and after recrystallisation from ethanol-water (1:1) gave white crystals of 1,4-diphenylbuta-1,3-diyne, m.p. 82-84°C (lit.,[152] 87°C). Best elemental analysis found: C, 93·50, H, 5.6. Calc. for $C_{16}H_{10}$: C, 95·01; H, 4·95%).

8.B.iii.d. Coupling of Phenylbromoacetylene using Copper(I) Iodide.

A mixture of copper(I) iodide (0·96 g, 5 mmol), phenylbromoacetylene (0·45 g, 2·5 mmol), and NMP (20 ml) was stirred under nitrogen at 160°C for four hours. The mixture was then added to water and extracted with diethyl ether. The ethereal solution was washed with water and dried over $MgSO_4$. The ether was removed and yellow crystals sublimed from the residue onto a cold finger. Recrystallisation from ethanol-water (1:1) gave white crystals of 1,4 diphenyl-1, 3-butadiyne (0·8 g, 33%).

8.B.iii.e. Trifluoromethylation of 1-Iodopentane.

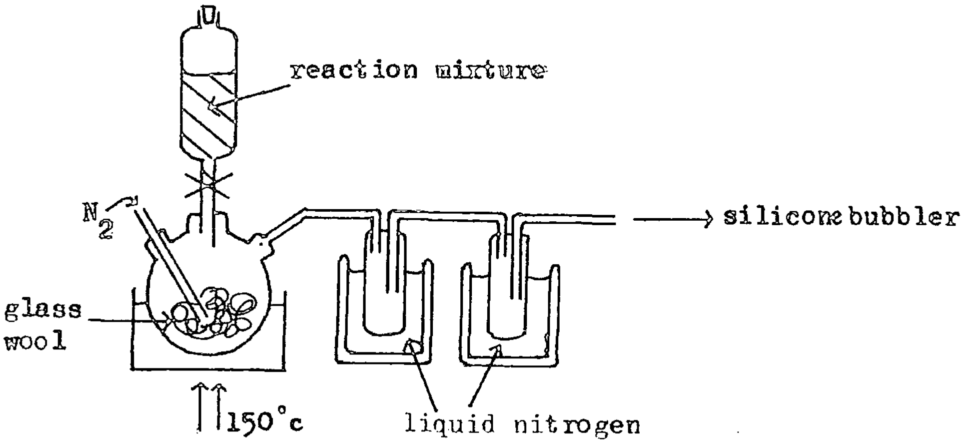
A mixture of (87) (2·72 g, 2 mmol), copper(I) iodide (1·91 g, 10 mmol), 1-iodopentane (0·99 g, 5 mmol), and NMP (20 ml) was stirred under nitrogen at 160°C for four hours. The volatile components were separated by vacuum transference, analysed by capillary m.s.g.l.c. and ^{19}F nmr, and shown to contain NMP, pentane m/z 71 (M^+-1), and one other component which was 1,1,1-trifluorohexane, m/z 71 (C_5H_{11}), 70 (C_5H_{10}), 55 (C_4H_7), 43 (C_3H_7), 42 (C_3H_6), and 69 (CF_3); δ_F 76 (CF_3).[160]

8.B.iv. Isolation of the Products.

8.B.iv.a. Isolation of 1,3,5-tris(trifluoromethyl)benzene.

A mixture of (87)(1·36 g, 10 mmol), copper(I) iodide (0·96 g, 5 mmol), 1,3,5-tribromobenzene (0·25 g, 0·8 mmol) and NMP (20 ml) was stirred under nitrogen at 160°C for four hours. The reaction mixture with an added internal standard was analysed by m.s.g.l.c. (10% P.E.G.20m, 150°C) and, from the molecular ion peak and fragmentation pattern of the mass spectrum, was shown to contain 1,3,5-tris-(trifluoromethyl)benzene (48%), m/z 282 (M^+) and 1,3-bis(trifluoromethyl)benzene (41%), m/z 214 (M^+). The products were isolated by dropping the reaction mixture onto heated glass wool and carrying the volatile material with a stream of nitrogen, into a trap immersed in liquid air. The apparatus is illustrated in Diagram (8.B.1). A small quantity of colourless liquid was obtained and shown by g.l.c. (10% P.E.G.20m, 130°C) to contain NMP (1·7g), 1,3,5-tris(trifluoromethyl)benzene (0·09 g, 82% recovery) and 1,3-bis(trifluoromethyl)benzene (0·07 g, 100% recovery).

Diagram (8.B.1). Isolation of Volatile Products.



8.B.iv.b. Isolation of p-Chloropentafluoroethylbenzene.

A mixture of sodium pentafluoropropanoate (0·37 g, 2 mmol), copper(I) iodide (0·38 g, 2 mmol), p-chloroiodobenzene (0·32 g, 1·34 mmol), ^{14}C-chloroiodobenzene (0·04 g, 0·16 mmol , 250 μCi), and NMP (4 ml) was stirred under nitrogen at 170°C for three hours. The mixture was analysed by radio-g.l.c. (Col 2) and found to contain p-chloroiodobenzene (24%) and p-chloropentafluoroethylbenzene (62%), by comparison of retention times. The mixture was thrown into water and the organic products extracted with aliquots of pentane (5 ml) until the activity, as measured by Geiger counter, was no longer reduced on extraction. The pentane solution was washed with water to remove any NMP and dried over $MgSO_4$. The activity was measured by scintillation counting and the solution found to contain 168 μCi(69%) of active material which was shown by comparison of g.l.c. retention times to be distributed as p-chloropentafluoroethylbenzene (71%) and p-chloroiodobenzene (24%).

8.B.iv.c. Use of Dimethylformamide (DMF) as a Solvent.

A mixture of (87) (0·66 g, 5 mmol), copper(I) iodide (0·48 g, 2·5 mmol), iodobenzene (0·25 g, 1·25 mmol), and DMF (10 ml) was stirred under nitrogen at 150°C for four hours. The mixture was analysed by m.s.g.l.c. (10% Col O, 150°C), and the product identified as trifluoromethylbenzene by comparison with spectra of the authentic material. After addition of an internal standard the yield was calculated from ^{19}F nmr peak areas to be 70%.

8.B.iv.d. Use of Diphenylsulphone as a Solvent.

A mixture of (87) (0·66 g, 5 mmol), copper(I) iodide (0·48 g, 2·5 mmol), iodobenzene (0·25 g, 1·25 mmol), and diphenylsulphone (10 g) was stirred at 160°C for four hours under nitrogen. The volatile materials were separated under vacuum transference, the reaction mixture being heated to 150°C to keep the solvent molten, and analysed by g.l.c. (Col 2, 140°C). Comparison with the authentic material showed that the liquid was iodobenzene (0·14 g, 56% recovery).

8.B.iv.e. Use of Sulpholane as a Solvent.

A mixture of (87) (0·66 g, 5 mmol), copper(I) iodide (0·48 g, 2·5 mmol), iodobenzene (0·25 g, 1·25 mmol), and sulpholane (10 ml) was stirred under nitrogen at 155°C for four hours. The reaction mixture was then warmed at 50°C and the volatile materials removed under vacuum transference. The liquid collected was analysed by g.l.c. (Col 2,140°C) and by comparison with the authentic material shown to be iodobenzene (0·13 g, 52% recovery).

8.B.iv.f. The Effect of a Decreased Solvent Volume.

Three mixtures were made up containing (87) (1·32 g, 10 mmol), copper(I) iodide (0·96 g, 5 mmol) iodobenzene (0·52 g, 2·5 mmol), and varying amounts of NMP (5,10,20 ml). The solutions were stirred under nitrogen at 160°C for four hours, in the same oilbath. After the reaction the mixtures were analysed by g.l.c. (Col 2,140°C) and the yields of trifluoromethylbenzene were calculated after incorporation of an internal standard. The results are shown in Table (8.3).

Table (8.3) The Effect of a Decreased Solvent Volume.

Solvent Volume ml.	Yield of Trifluoromethylbenzene %
20	81
10	42
5	30

8.B.v. Reductive Dehalogenation.

8.B.V.a. Trifluoromethylation of ^{14}C-Bromobenzene.

A mixture of (87) (0·28 g, 2 mmol), copper(I) iodide (0·19 g, 1 mmol), bromobenzene (11 μl active + 40 μl inactive, 0·5 mmol), and NMP (4 ml) were stirred under nitrogen at 155°C for five hours. The mixture was analysed by radio-g.l.c. (Col 2,80–180°C) and found, by comparison of retention times to contain; benzene (16·3%) bromobenzene (19·3%), iodobenzene (4%), and trifluoromethylbenzene (56·8%). Activity balance: Initial Activity 35·2 μCi, final activity 34·4 μCi, retention of activity 97%.

8.B.v.b. Trifluoromethylation of Bromobenzene with Added Water.

A mixture of (<u>87</u>) (1·32 g, 10 mmol), copper(I) iodide (0.96 g, 5 mmol), bromobenzene (0·39 g, 2·5 mmol), NMP (19 ml), and water (1 ml) was stirred under nitrogen at 155°C for four hours. The mixture was analysed by g.l.c. (Col 1) and found by comparison with standard solutions to contain bromobenzene (47%) and iodobenzene (31·5%). The orange precipitate was filtered and washed with ether before analysis which showed it to be copper-based, (Found: Cu, 77; C, 0; H, 0; N,0%).

8.C. Halogen Exchange.

8.C.i.a. Halogen Exchange in the Trifluoromethylation of Bromobenzene.

A mixture of (<u>87</u>) (1·36 g, 10 mmol), copper(I) iodide (1·91 g, 10 mmol), bromobenzene (0·78 g, 5 mmol), and NMP (20 ml) was stirred under nitrogen at 160°C for four hours. The reaction mixture was analysed by m.s.g.l.c. (Col 1, 150°C) and was shown to contain, by comparison with the mass spectra of authentic materials, NMP, trifluoromethylbenzene, bromobenzene, and iodobenzene.

8.C.i.b. Trifluoromethylation of ^{14}C-Bromobenzene with the Sodium Trifluoroacetate Concentration Halved.

A mixture of (87) (0·14 g, 1 mmol, copper(I) iodide (0·20 g, 1 mmol), bromobenzene (11·5 μl inactive + 40 μl active, 0·5 mmol) and NMP (4 ml) was stirred under nitrogen at 155°C for four hours. The mixture was analysed by radio-g.l.c. (Col 2, 80-180°C) and found to contain iodobenzene (37%) which was identified by comparison of the retention time of an authentic sample. Activity balance: Initial activity 31·5 μCi, final activity 27·6 μCi, retention of activity 88%.

8.C.i.c. Reaction between Copper(I) Iodide and ^{14}C-Bromobenzene.

A mixture of copper(I) iodide (0·19 g, 1 mmol), bromobenzene (11·5 μl active + 40 μl inactive, 0·5 mmol), and NMP (4 ml) was stirred under nitrogen at 154°C overnight. The mixture was analysed by radio-g.l.c. (Col 2, 80-180°C) and shown to contain bromobenzene (77%) and iodobenzene (23%) which were identified by comparison of the retention times of authentic materials. After addition of a small amount of (87) and further heating for two hours the yield of iodobenzene rose to 37%. Activity balance: Initial activity 30·8 μCi, final activity 30·13 μCi, retention of activity 98%.

8.C.i.d. Maximisation of Halogen Exchange by Addition of Sodium Iodide.

Mixtures of bromobenzene (0·79 g, 5 mmol), copper(I) iodide (10–20 mmol), sodium iodide (10–20 mmol), and NMP (20 ml) were stirred under nitrogen at 160°C for four hours. Samples were removed at intervals and analysed by g.l.c. (10% P.E.G.20m, 150°C). The results are shown in Table (8.C.1).

Table (8.C.1) Maximisation of Halogen Exchange.

CuI mmol	NaI mmol	C_6H_5I/C_6H_5Br 1hr	2hr	4hr
10	-	0·30	-	0·27
20	-	0·14	0·14	0·13
10	10	-	0·38	0·41
20	10	-	0.39	-
10	20		v.small	

Chapter 9

Experimental to Chapter 4

9.A. Reagents and Solvents

The basic reagents and solvents are as described in Chapter 8.

Phenyl trifluoroacetate was prepared from trifluoroacetic anhydride and phenol as described in the literature.[3]

9.B. Reactions

9.B.i. The Role of Sodium Trifluoroacetate (87)

9.B.i.a. Trifluoromethylation of ^{14}C-Labelled Bromobenzene over a Prolonged Timespan.

A mixture of (87) (0·28 g, 2 mmol), copper(I) iodide (0·19 g, 1 mmol), bromobenzene (11·5 μl inactive + 40 μl active, 0·5 mmol), and NMP (4 ml) were stirred under nitrogen at 155°C overnight. The mixture was analysed by radio-g.l.c. (Col 2, 80-180°C) and found by comparison of retention times to contain bromobenzene (19%), trifluoromethylbenzene (57%), benzene (16%), and iodobenzene (4%). On addition of further copper(I) iodide (0·19 g, 1 mmol) and bromobenzene (11·5 μl inactive + 40 μl active, 0·5 mmol) and heating for two hours, the amount of iodobenzene increased to 23%.

This reaction was repeated and after heating overnight (87) (0·14 g, 1 mmol) was added and the mixture heated for a further two hours. Analysis by radio-g.l.c. (Col 2, 80-150°C) showed the yield of trifluoromethylbenzene was increased from 57% to 68%.

Activity balance: Initial activity 30·8 μCi, final activity 30·13 μCi, retention of activity 98%.

9.B.i.b. Trifluoromethylation with a Limiting Quantity of (87)

A mixture of (87) (0·68 g, 5 mmol), copper(I) iodide (1·91 g, 10 mmol), iodobenzene (2·04 g, 10 mmol), and NMP (40 ml) was stirred under nitrogen for four hours at 160°C. The mixture was analysed by g.l.c. (Col 1, 150°C) and, by comparison with standard solutions, found to contain iodobenzene (65%) and trifluoromethylbenzene (22%).

9.B.i.c. Decarboxylation of (87)

A mixture of (87) (2·72 g, 20 mmol), cyclohexene (1·64 g, 20 mmol) and NMP (40 ml) was stirred under nitrogen at 160°C for four hours. The gaseous products were collected in a trap cooled to liquid nitrogen temperature and shown from the i.r. spectrum to contain fluoroform, ν_{max} 1370, 1150 cm^{-1} (lit.,[161] 3035 s, 1352 s, 1209 m, 1152 s and 509 cm^{-1}).

The reaction mixture was analysed by m.s.g.l.c. (Col 1, 120°C) and ^{19}F nmr and shown by comparison with the spectra of the authentic materials to contain (87) and cyclohexene.

9.B.i.d. Trapping of Possible Intermediates.

A mixture of (87) (2.72 g, 20 mmol), benzene (10 ml), and NMP (20 ml) was sealed in a carius tube and heated in a rocking autoclave for four hours at 160°C. The mixture was analysed by m.s.g.l.c. (Col 1, 140°C) and ^{19}F nmr and shown, by comparison of the spectra with those of authentic materials, to contain sodium trifluoroacetate, benzene and NMP.

The reaction was repeated replacing benzene with pentafluoropyridine. Neither m.s.g.l.c. or ^{19}F nmr showed any evidence of CF_3^- capture by the pyridine.

9.B.i.e. Monitoring of the Decarboxylation Reaction with ^{19}F nmr.

Two mixtures of (87) (2·72 g, 10 mmol) and NMP (40 ml) were made and copper(I) iodide (1·91 g, 10 mmol) was added to one. Both solutions were stirred under nitrogen at 160°C for four hours in the same oilbath. Samples were removed through a rubber septum, by syringe, at hourly intervals and the concentration of (87) was measured by integrating the ^{19}F peak area. The results are shown in Table (9·1).

Table (9·1) Monitoring of the Decarboxylation Reaction by ^{19}F nmr.

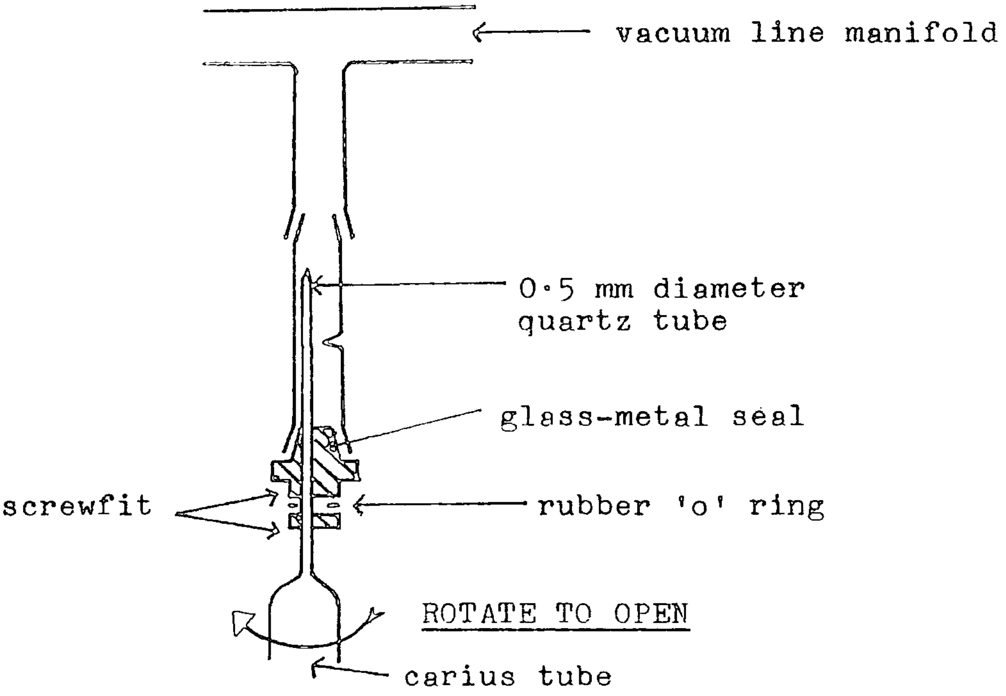
Time (hr)	Trifluoroacetate Ion Concentration with CuI (cm)	without CuI (cm)
0	5·80	3·00
1	3·10	2·25
2	2·80	2·15
3	1·70	1·90
4	0·50	1·70

9.B.i.f. Analysis of the Gaseous Products from Decarboxylation.

A solution of (87) (2·66 g, 19 mmol) in NMP (20 ml) was sealed in a carius tube with a 150mm x 5mm diameter neck and heated at 150°C in a rocking autoclave for four hours. The tube was attached to a vacuum line via a glass metal seal and special adaptor with a constriction (see Diagram 9.1) so that the tube could be opened under vacuum and the gaseous products trapped. The gas was condensed into a gas bulb of known volume through a tube containing carbosorb and magnesium perchlorate to absorb the carbon dioxide. The gas was warmed to room temperature and the pressure exerted measured to calculate the yield. Analysis by m.s. and i.r. showed the gas was fluoroform (50%), ν_{max} 3040, 2280, 1370 and 1150 cm^{-1} (lit.,[161] 3035, 1352 vs, 1209, 1152 vs, and 509 cm^{-1}); m/z 70 (M^+), 69 (M^+-H).

The reaction was repeated with the addition of copper(I) iodide and the yield of fluoroform was found to be 75% contaminated with a trace amount of trifluoromethyl iodide, m/z 196 (M^+) and 127 (I). The carbosorb/$Mg(ClO_4)_2$ was weighed before and after the absorption of carbon dioxide which was shown to be produced in 55% yield. The actual value for the percentage of material decarboxylated must be between 55 and 75%. Some of the carbon dioxide produced had passed through the carbosorb trap into the gas bulb and increased the apparent yield of fluoroform.

Diagram (9.1)



9.B.i.g. Decarboxylation of Trifluoroacetic Acid in DMSO.

A mixture of trifluoroacetic acid (5 ml) and DMSO (20 ml) was heated in a sealed tube in a rocking autoclave for two hours at 160°C. The gaseous products were collected and shown from the mass spectrum to contain; carbon dioxide, m/z 44; dimethyl sulphide, m/z 62 (M^+), 61 (M^+-1) and 47 (M^+-CH_3); and 1,1,1-trifluorodimethyl sulphide m/z 116 (M^+), 97 (M^+-F) and 69 (CF_3).

9.B.i.h. Attempted Trifluoromethylation in DMSO.

A mixture of trifluoroacetic acid (0·76 g, 10 mmol), copper(I) iodide (0·96 g, 5 mmol), iodobenzene (0·51 g, 2·5 mmol), and DMSO (20 ml) was stirred under nitrogen at 160°C for three hours. The mixture was analysed by m.s.g.l.c. (Col 1, 140° C) and ^{19}F nmr, and shown to contain iodobenzene, m/z 204 and dimethyl sulphide m/z 62 (M^+), and 47 (M^+-CH_3, 100%).

9.B.i.j. Perfluoroalkenes as a Source of the Perfluoroalkyl Group.

A mixture of perfluoropropene (3 g, 20 mmol), potassium fluoride (1·16 g, 20 mmol), copper(I) iodide (1·91 g, 10 mmol), iodobenzene (1·02 g, 5 mmol) and NMP (20 ml) was sealed in a metal tube and heated at 150°C for four hours in a rocking autoclave. The tube was then vented in a fume cupboard and the reaction mixture was analysed by m.s.g.l.c. (Col 1, 120°C). On comparison with authentic samples it was found to contain NMP, iodobenzene, and a mixture of perfluoropropene oligomers.

This reaction was repeated replacing perfluoropropene with perfluorocyclohexene and sealing the mixture in a carius tube. Analysis by m.s.g.l.c. (Col 2, 140°C) and comparison with the spectra of the authentic material showed the reaction mixture to contain perfluorocyclohexene, iodobenzene (74%) and benzene.

9.B.i.k. Attempted Decarboxylation of Phenyl Trifluoroacetate.

A mixture of phenyl trifluoroacetate (0·95 g, 5 mmol), copper(I) iodide (1·91 g, 10 mmol), and NMP (40 ml) was stirred under nitrogen at 140°C for four hours. The mixture was analysed by g.l.c. (Col 1, 140°C) and ^{19}F nmr. Comparison with the authentic material showed the mixture contained phenyl trifluoroacetate and NMP.

9.B.i.m. A Hammett Plot for the Trifluoromethylation Reaction.

Copper(I) iodide (0·4761 g, 2.5 mmol) and (<u>87</u>) (1·72 g, 12·5 mmol) were added to each of two solutions, one containing iodobenzene (1·25 mmol) and the other a substituted iodobenzene (1·25 mmol) in NMP (10 ml). The mixtures were immersed in an oilbath at 150°C and stirred under nitrogen for one hour before cooling in an ice/salt bath. The concentration of iodobenzene remaining was then calculated from the g.l.c. (Col 2) after addition of an internal standard.

This procedure was repeated for a range of p-substituted iodobenzenes and from the results was calculated a pseudo-first order rate constant which was used to produce a Hammett Plot. The results are shown in Table (9·2).

Table (9.2) **A Hammett Plot for the Trifluoromethylation Reaction**

p-substituent	H	Cl	NO_2	H	CH_3	H	CH_3O
σ value	0.00	+0.23	+0.78	0.00	-0.17	0.00	-0.27
ArI (g)	0.2506	0.2981	0.3122	0.2506	0.2709	0.2507	0.2982
$[ArI]_o$ (mmol/10ml)	1.247	1.250	1.254	1.247	1.248	1.247	1.249
$[ArI]_t$ (mmol/10ml)	0.944	0.856	0.720	0.609	0.720	0.992	1.052
$[ArI]_o$ / $[ArI]_t$	1.321	1.460	1.742	2.048	1.733	1.257	1.187
kt	0.28	0.38	0.55	0.73	0.55	0.23	0.17
kt_X / kt_H	1.00	1.36	1.98	1.00	0.75	1.00	0.74
$\lg(kt_X / kt_H)$	0.00	0.13	0.29	0.00	-0.12	0.00	-0.13

p-substituent	H	I	H	F	H	CF_3
σ value	0.00	+0.18	0.00	+0.06	0.00	+0.54
ArI (g)	0.2556	0.4188	0.2506	0.2773	0.1279	0.1692
$[ArI]_o$ (mmol/10ml)	1.253	1.248	1.247	1.249	0.627	0.622
$[ArI]_t$ (mmol/10ml)	1.029	0.894	0.736	0.687	0.448	0.430
$[ArI]_o$ / $[ArI]_t$	1.218	1.396	1.694	1.819	1.270	1.450
kt	0.20	0.33	0.53	0.60	0.24	0.37
kt_X / kt_H	1.00	1.65	1.00	1.13	1.00	1.54
$\lg(kt_X / kt_H)$	0.00	0.22	0.00	0.05	0.00	0.19

9.B.ii. The Role of Copper(I) Iodide.

9.B.ii.a. Use of Copper(I) Bromide.

A mixture of (87) (1·32 g, 10 mmol), copper(I) bromide (0·72 g, 5 mmol), iodobenzene (0·51 g, 2·5 mmol), and NMP (20 ml) was stirred under nitrogen at 160°C for four hours. The mixture was analysed by g.l.c. (Col 1, 140°C) and by comparison with standard solutions shown to contain trifluoromethylbenzene (45%) and bromobenzene (48%).

This reaction was repeated replacing iodobenzene with bromobenzene and the mixture shown to contain trifluoromethylbenzene (13%) and bromobenzene (82%).

9.B.ii.b. Reduced Amount of Copper(I) Iodide.

A mixture of (87) (0·27 g, 2 mmol), copper(I) iodide (0·02 g, 0·1 mmol), bromobenzene (11·5 µl inactive + 40 µl active, 0·5 mmol), and NMP (4 ml) was stirred under nitrogen at 155°C for four hours. The mixture was analysed by radio-g.l.c. (Col 2, 80-180°C) and by comparison of retention times, found to contain trifluoromethylbenzene (12%), bromobenzene (78%), and iodobenzene (9%).

A further amount of copper(I) iodide (0·19 g, 1 mmol) was added and the mixture heated for two hours after which it was shown by radio-g.l.c. to contain trifluoromethylbenzene (47%), bromobenzene (34%), benzene (10%), and iodobenzene (9%). Activity balance. Initial activity 32·07 µCi, final activity 31·1 µCi, Retention of Activity 97%.

9.B.ii.c. Use of Copper in Oxidation States 0, I, and II.

Three mixtures containing (87) (0·66 g, 5 mmol), iodobenzene (0·25 g, 1·25 mmol), copper (2·5 mmol) in oxidation state 0, I or II, and NMP (10 ml) were stirred under nitrogen at 160°C for four hours. The mixtures were analysed by g.l.c. (Col 2, 140°C) and the yields calculated after incorporation of an internal standard. Chlorobenzene was identified by comparison of its mass spectrum with that of the authentic material. The results are shown in Table (9.3).

Table (9.3) Use of Copper in Oxidation States 0, I, and II.

Copper Compound	mass (g)	$C_6H_5CF_3$ %	C_6H_5I %	C_6H_5Cl %
copper(0)	0·16	10	88	-
copper(I) iodide	0·48	68	34	-
copper(II) chloride	0·34	12	60	21

9.B.ii.d. Effect of Co-ordinating Agents upon the Reaction.

Three mixtures of (87) (0·66 g, 5 mmol), iodobenzene (0·25 g, 1·25 mmol), copper(I) iodide (0·48 g, 2·5 mmol), and NMP (10 ml) were made up. Quinoline (see table) was

was added to two of the mixtures before all three were stirred under nitrogen at 155°C for four hours. The mixture was then analysed by g.l.c. (Col 2, 140°C) and the yields of trifluoromethylbenzene and iodobenzene were calculated after addition of an internal standard.

This experiment was repeated exchanging quinoline for sodium iodide and analysed in the same way. The amount of sodium trifluoroacetate remaining in solution was estimated by integrating the area under the ^{19}F nmr peak at 76 ppm.

The results are shown in Table (9·4).

Table (9·4) Effect of Co-ordinating Agents upon the Reaction.

Co-ordinating agent	mmol	$C_6H_5CF_3$ %	C_6H_5I %	CF_3COO^- %
quinoline	2·5	78		
	10	39		
	none	83		
sodium iodide	2·5	-	90	72
	12	-	93	60
	none	96	-	none

9.B.iii. Effect of Ortho-Substituents on the Aryl Halide

9.B.iii.a. A Competition Trifluoromethylation of p- and o-Chloroiodobenzene.

A mixture of (87) (0·27 g, 2 mmol), copper(I) iodide (0·19 g, 1 mmol), o-chloroiodobenzene (180 µl active and 44 µl inactive, 0·38 mmol), p-chloroiodobenzene (113 µl active and 0·087 g inactive, 0·38 mmol), and NMP (4 ml) was stirred under nitrogen at 160°C for four hours. The mixture was analysed before and after reaction by radio-g.l.c. and the ratio of the p- and o-isomer peaks measured. The activity in these two peaks, as a percentage of the total activity, is a measure of the extent of the reaction. The results are shown in Table (9.5).

Activity balance. Initial activity 40·3 µCi, final activity 34·8 µCi, Retention of activity 86%.

Table (9.5) A Competition Trifluoromethylation of p- and o-Chloroiodobenzenes.

Ratio of Peak Areas p:o	Activity (% of total)	Time (hr)
1 : 1·1	100	0
1 : 1·2	18	4

9.B.iii.b. Trifluoromethylation of o-Iodonitrobenzene.

A mixture of (87) (1·36 g, 10 mmol), copper(I) iodide (0·96 g, 5 mmol), o-iodonitrobenzene (0·62 g, 2·5 mmol), and NMP (20 mmol) was stirred under nitrogen at 160°C for four hours. The yield was calculated from the nmr spectrum after addition of p-bromotrifluoromethylbenzene as a standard, as the g.l.c. retention time of the product was coincident with the solvent. The reaction produced o-nitrotrifluoromethylbenzene (20%), δ_F 60·5.

The reaction mixture was added to water (30 ml) and extracted with pentane. After washing the pentane solution with water, to remove any traces of NMP, and drying over $MgSO_4$, the larger part of the pentane was removed under vacuum and the residue analysed by m.s.g.l.c. (Col 2, 190°C). It was shown to contain, from the molecular ion peak and fragmentation pattern of the mass spectrum, o-nitrotrifluoromethylbenzene and nitrobenzene.

9.B.iii.c. A Competition Trifluoromethylation of o- and p-Iodonitrobenzenes.

A mixture of (87) (0·68 g, 5 mmol), copper(I) iodide (0·48 g, 2·5 mmol), o-iodonitrobenzene (0·15 g, 0·62 mmol), p-iodonitrobenzene (0·15 g, 0·62 mmol) and NMP (10 ml) was stirred under nitrogen at 160°C for four hours. The mixture was analysed by ^{19}F nmr which showed only the p-isomer had been trifluoromethylated. The yield of product was calculated from the g.l.c. (Col 2, 150°C) after addition of an internal standard to the reaction mixture. A 42% yield of p-nitrotrifluoromethylbenzene had been produced.

Chapter 10

Experimental for Chapter 5

10.A. Reagents and Solvents

Sodium pentafluoropropanoate (98). Pentafluoropropanoic acid (15·6 g, 0·1 mol) was added dropwise to a stirred solution of sodium hydroxide (3·8 g, 0·095 mol) in water (10 ml). The water was removed under reduced pressure and the white crystalline product dried under vacuum before storage under nitrogen.

Sodium heptafluorobutanoate was prepared by the same method using heptafluorobutanoic acid (21·4 g, 0·1m).

Sodium trichloroacetate was a commercial sample dried under vacuum and stored under nitrogen.

10.B. Synthesis

10.B.i. Pentafluoroethyl Group

10.B.i.a. Determination of Optimum Conditions

A mixture of iodobenzene (2·5 - 7·5 mmol), copper(I) iodide (5-10 mmol), (98) 7·32 g, 10 mmol) and NMP (20 ml) was stirred under nitrogen at 160 (170)°C for four hours and samples were taken at intervals for analysis by ^{19}F nmr and m.s.g.l.c. (Col 2). Two volatile products were formed and identified, from ^{19}F nmr and the molecular ion peak and fragmentation pattern of the mass spectrum, as pentafluoroethane, m/z 119 (M^+), and pentafluoroethylbenzene, δ_F 85·7 ($\underline{CF_3}CF_2$), 115·5 ($CF_3\underline{CF_2}$); m/z 196(M^+), 127(M^+-CF_3), 77(C_6H_5).

The quantities of reagents and yields of product, calculated by g.l.c. analysis after addition of an internal standard, are given in Table(10.1).

Table (10·1) Determination of the Optimum Conditions for the Pentafluoroethylation Reaction.

Temperature °C	C_6H_5I mmol	CuI mmol	$\%C_6H_5I$ 1hr	2hr	4hr	$\%CF_3CF_2C_6H_5$
160	2·5	5·0	43	31	16	84
170	2·5	5·0	0	-	-	-
170	5·0	5·0	39	35	-	-
170	5·0	7·5	0	-	-	80
170	7·5	1·0	0	-	-	87

10.B.i.b. Pentafluoroethylation of ^{14}C-labelled Iodobenzene.

A mixture of (98) (0·37 g, 2 mmol), copper(I) iodide (0·38 g, 2 mmol), iodobenzene (226 μl active + 160 μl inactive, 1·5 mmol), and NMP (4 ml) was stirred under nitrogen at 170°C for 3 hours. The mixture was analysed at intervals by radio-g.l.c. and the results are shown in Table (10.2). The components of the mixture were identified by comparison of the retention times with authentic materials.

Table (10.2) Pentafluoroethylation of ^{14}C-Labelled Iodobenzene

Reaction Time hr	$CF_3CF_2C_6H_5$ %	C_6H_5I %
0·5	6	94
1·0	77	23
1·5	88	12
3·0	86	14

10.B.i.c. Pentafluoroethylation of Substituted Halobenzenes

General Procedure

A mixture of (98) (1·86 g, 10 mmol), copper(I) iodide (1·96 g, 10 mmol), substituted halobenzene (2·5 - 7·5 mmol), and NMP (20 ml) was stirred at 170°C under nitrogen for three hours. The reaction mixture was analysed by m.s.g.l.c. (Col 2) and ^{19}F nmr, and the products identified from the molecular ion peak and fragmentation pattern of the mass spectra. The yields were calculated by g.l.c. analysis after addition of an internal standard, and are shown in Table (10.3).

Products from some of the reactions were isolated as described below;

Iodobenzene. The reaction mixture was added to water (50 ml) and extracted with pentane. The pentane solution was washed with water to remove any traces of NMP, dried over $MgSO_4$, and the pentane removed by distillation. G.l.c. analysis (Col 10% O) showed the residue (0·7 g) to be composed of pentane (47%) and pentafluoroethylbenzene[155] (53%), δ_F 86 (3F, $\underline{CF_3}CF_2$-), 114 (2F, $CF_3\underline{CF_2}$-); m/z 196 (M^+, 19·7%), 127 (100), 77 (19·5).

<u>p-Bromotrifluoromethylbenzene</u>. The volatile material was removed from the reaction mixture by vacuum transference and added to its own volume of water. The mixture was shaken so as to dissolve the NMP in the water, which was removed with a syringe and $MgSO_4$ added to the remaining liquid. The liquid was isolated by vacuum transference and g.l.c. (Col 2) showed one component, identified as p-pentafluoroethyltrifluoromethylbenzene[155] (0·37 g, 19%), (Found: C, 40·6; H, 1·9; F, 57·2. Calculated for $C_9H_4F_8$: C, 40·91; H, 1·52; F, 57·58%); δ_F 64 (3F, CF_3-), 85·8 (3F, $\underline{CF_3}CF_2$-), 115·7 (2F, $CF_3\underline{CF_2}$-); ν_{max} 1410, 1320, 1285, 1210, and 1000 cm^{-1}; m/z 264 (M^+), 195 (100%).

<u>1,3,5-Tribromobenzene</u>. The volatile material was isolated by vacuum transference, as described previously, yielding a colourless liquid identified as <u>1,3,5-tris(pentafluoroethyl)-benzene</u> (0·27 g, 20%), (Found: C; 33·6; H, 0·8; F, 65·5. $C_{12}H_3F_{15}$ requires C, 33·30; H, 0·69; F, 65·97%); I.R. No 1; δ_F 85 (3F, $\underline{CF_3}CF_2$-), 115 (2F, $CF_3\underline{CF_2}$-); M.S. No 1.

Extraction by flash distillation resulted in a 31% yield of product with the same analysis.

Table (10.3) Pentafluoroethylation of Substituted Halobenzenes.

Halobenzene	mmol	Products	Yield %	m/z (M^+)	^{19}F nmr ppm CF_3	^{19}F nmr ppm CF_2
iodobenzene	7.5	pentafluoroethylbenzene[155]	86	196	85.7	115.0
p-diiodobenzene	3.8	1,4-bis(pentafluoroethyl)benzene [155]	83	314	86.0	115.8
p-bromotrifluoromethylbenzene	7.5	p-pentafluoroethyltrifluoromethylbenzene [155]	71	264	85.8	115.7
		p-iodotrifluoromethylbenzene	5	272	-	-
1,3,5-tribromobenzene	2.5	1,3,5-tris(pentafluoroethyl)benzene	-	432	87.0	117.0
p-iodonitrobenzene	7.5	p-nitropentafluoroethylbenzene [66]	51	241	85.7	115.5
p-chloroiodobenzene	7.5	p-chloropentafluoroethylbenzene	75	230/232	86.0	115.3
o-chloroiodobenzene	7.5	o-chloropentafluoroethylbenzene	62	230/232	84.7	111.5

p-Chloroiodobenzene. The product was isolated from the bulk of the reaction mixture by the flash distillation technique described in Chapter 7. The liquid obtained was washed with a small amount of water and dried over $MgSO_4$ from which it was removed by vacuum transference yielding a colourless liquid identified as p-chloropentafluoroethylbenzene (1·09 g, 54%), Found: C, 41·9; H, 1·7. $C_8H_4F_5Cl$ requires C, 41·6; H, 1·7%); I.R. No 13; δ_F 85·5 (3F, $C\underline{F}_3CF_2$), 115·3 (2F, $CF_3C\underline{F}_2$-); M.S. No 21.

o-Chloroiodobenzene. The product was isolated by flash distillation as described previously and an analytically pure sample was obtained by preparative scale g.l.c. The product was a colourless liquid, o-chloropentafluoroethylbenzene (0·24 g, 14%), (Found: C, 41·8; H, 2·08. $C_8H_4F_5Cl$ requires C, 41·6; H, 1·7%); I.R. No 14; δ_F 83·8 (3F, $C\underline{F}_3CF_2$-), 111·3 (2F, $CF_3C\underline{F}_2$-); M.S. No 22.

10.B.i.d. Pentafluoroethylation of 2-chloro-5-Iodopyridine.

A mixture of (98) (1·86 g, 10 mmol), copper(I) iodide (1·91 g, 10 mmol), 2-chloro-5-iodopyridine (1·79 g, 7·5 mmol), and NMP (20 ml) was stirred under nitrogen at 170°C for two hours. The mixture was analysed by m.s.g.l.c. (Col 2, 140°C) and shown to contain 2-chloro-5-pentafluoroethylpyridine (30%), δ_F 86 ($C\underline{F}_3CF_2$-); 116 ($CF_3C\underline{F}_2$-); m/z 231/233 (M^+) and trace amounts of 2-chloropyridine m/z 113/115, and 2,5-bis (pentafluoroethyl)pyridine m/z 315. The products were identified from the molecular ion peak and fragmentation patterns in the mass spectra and the yields calculated after addition of an internal standard.

10.B.i.e. Pentafluoroethylation of 2-Iodothiophene.

A mixture of (98) (0·46 g, 2·5 mmol), copper(I) iodide (0·48 g, 2·5 mmol), 2-iodothiophene (0·40 g, 7·5 mmol), and NMP (5 ml) was stirred at 170°C for three hours. The reaction mixture was analysed ^{19}F nmr and m.s.g.l.c. (Col 2) and the yields calculated by g.l.c. after addition of an internal standard. From the molecular ion peaks and fragmentation patterns in the mass spectra the products were identified as thiophene (35%), M/Z 84 and 2-pentafluoroethylthiophene (28%), δ_F 86 (3F, $C\underline{F}_3CF_2$-), 105 (2F, $CF_3C\underline{F}_2$-); m/z 202 (M^+).

10.B.i.f. Pentafluoroethylation of (2-bromoethenyl)-benzene.

A mixture of (98) (0·46 g, 2·5 mmol), copper(I) iodide (0·48 g, 2·5 mmol), (2-bromoethenyl)benzene (0·35 g, 1·8 mmol), and NMP (5 ml) was stirred under nitrogen at 170°C for three hours. The mixture was analysed by ^{19}F nmr and m.s.g.l.c. (Col 2) and the yields calculated after addition of an internal standard. From molecular ion peak and fragmentation patterns in the mass spectrum the product was identified as (4,4,4,3,3,-pentafluoro-1-butenyl)benzene[157] (53%), m/z 222.

10.B.i.g. Pentafluoroethylation of 1-Iodopentane.

A mixture of (98) (0·46 g, 2·5 mmol), copper(I) iodide (0·48 g, 2·5 mmol), 1-iodopentane (0·38 g, 1·9 mmol), and NMP (5 ml) was stirred under nitrogen at 170°C for three hours. The volatile material was isolated by vacuum transference and shown by g.l.c. (Col 2, 100°C) to contain one major component which by comparison of retention times was neither pentane nor 1-iodopentane. A small analytical sample was obtained from preparative scale g.l.c. (Col 10% O) and identified from ^{19}F nmr and the mass spectrum as 1,1,1,2,2-pentafluoroheptane (0·08 g, 22%), δ_F 83·7 (3F, $C\underline{F}_3CF_2$-), 122·6 (2F, $CF_3C\underline{F}_2$-); m/z 119 (C_2F_5), 69 (CF_3), 71 (C_5H_{11}), 43 (C_3H_7).

10.B.i.h. Addition of Water to the Reaction Mixture.

A mixture of (98) (0·37 g, 2·0 mmol), copper(I) iodide (0·38 g, 2·0 ml), p-chloroiodobenzene (0·36 g, 1·5 mmol), and NMP (4 ml) was stirred under nitrogen at 170°C for three hours. The mixture was analysed by g.l.c. (Col 2, 130°C) and, on comparison with a standard solution, shown to contain only p-chloroiodobenzene. An orange/red precipitate was formed during the reaction.

10.B.ii. Heptafluoropropyl Group.

10.B.ii.a. Formation of Heptafluoropropylbenzene.

A mixture of sodium heptafluorobutanoate (2·36 g, 10 mmol), copper(I) iodide (0·96 g, 5 mmol), iodobenzene

(0·51 g, 2·5 mmol), and NMP (20 ml) was stirred under nitrogen at 132°C for three hours. Samples were taken at intervals and the amounts of iodobenzene remaining were calculated by comparison ofthe g.l.c. (Col 1) with that of a standard solution. During the first hour the concentration of iodobenzene fell to 70% of the original value and thereafter remained constant. After three hours the reaction mixture was analysed by ^{19}F nmr and m.s.g.l.c. (Col 1) and shown to contain two products identified, from the molecular ion peaks and fragmentation patterns in the mass spectra, as heptafluoropropane, δ_F 76 ($C\underline{F}_3CF_2CF_2H$), 114 ($CF_3C\underline{F}_2CF_2H$), and 124 ($CF_3CF_2C\underline{F}_2H$); m/z 151 ($H^+-19$); and heptafluoropropylbenzene,[155] δ_F 81 ($C\underline{F}_3CF_2CF_2-$), 112 ($CF_3C\underline{F}_2CF_2-$) and 127 ($CF_3CF_2C\underline{F}_2-$); m/z 246 ($M^+$).

This was the highest conversion achieved in several reactions carried out at various temperatures from 100°C, at which a large amount of sodium heptafluorobutanoate remained in solution, to 170°C where decarboxylation could be seen to take place immediately from the vigorous bubbling of the mixture on being immersed in the oil bath.

10.B.iii. Trichloromethyl Group.

10.B.iii.a. Attempted Formation of Trichloromethylbenzene.

A mixture of sodium trichloroacetate (1·84 g, 10 mmol), copper(I) iodide (0·96 g, 5 mmol), iodobenzene

(0·51 g, 2·5 mmol), and NMP (20 ml) was stirred under nitrogen at room temperature. After an hour the mixture was analysed by m.s.g.l.c. (Col 1) and two volatile components were found, one of which appeared from the mass spectrum to have the correct fragmentation for chloroform although the peak intensities were not identical to those of an authentic sample. The absence of a C_6H_5 (m/z 77) fragment suggested that no trichloromethylbenzene had been formed and this was confirmed when comparison of the g.l.c. with that of a standard solution showed the concentration of iodobenzene remained constant.

10.C. Mechanism.

10.C.i. Decarboxylation.

10.C.i.a. Investigation of the Decarboxylation Temperatures.

Sodium pentafluoropropanoate (98) (0·89 g, 5 mmol) was placed in a side arm of a flask containing NMP (20 ml). The flask was attached to a vacuum line through a reflux condenser and evacuated. After the solvent had degassed the system was let down to ½ atm. pressure of nitrogen and the flask tipped to add (98). The solution was stirred whilst the temperature was slowly increased until a steady pressure increase, due to decarboxylation, was noted on the manometer.

This experiment was repeated with sodium heptafluorobutanoate and then with both sodium salts in the presence of copper(I) iodide (0·48 g, 2.5 mmol) which was dissolved in the NMP before degassing. The results are shown in Table (5.5).

10.c.i.b. Monitoring of the Decarboxylation of (98) with ^{19}F nmr.

Two mixtures of (98) (0·46 g, 2.5 mmol) and NMP (5 ml) were made and copper(I) iodide ()·48 g, 2·5 mmol) was added to one. Both solutions were stirred under nitrogen at 170°C for four hours in the same oil bath. Samples were removed through a rubber septum, by syringe, at hourly intervals and the concentration of (98) was measured by integrating the ^{19}F peak area. The results are shown in Table (10.5). Two values are given for each reaction since both the CF_3 and CF_2 peaks were integrated and gave slightly different results.

Table (10.5) Monitoring of the Decarboxylation Reactions of (98) with ^{19}F nmr.

Time	Pentafluoropropanoate Concentration (cm)			
hr	Without CuI		With CuI	
	CF_2	CF_3	CF_2	CF_3
0	25	34	25	38
2	16	25	6	10
3	15	22	5·5	9
4	14	21	5	8

The last samples obtained were found to contain entrained pentafluoroethane, δ_F 86·7 (CF_3), 142·7 (d, J_{H-F} 56·4 Hz, CF_2) Lit.[3], J 52·6).

10.C.ii. Common Features in the Introduction of the Trifluoromethyl and Pentafluoroethyl Groups.

10.C.ii.a. Use of Copper in Oxidation States 0, I and II.

Three mixtures containing (98) (0·93 g, 5 mmol), copper (5 mmol) in oxidation state 0, I, II, iodobenzene (0·76 g, 3·8 mmol), and NMP (10 ml) were stirred under nitrogen at 170°C for three hours. The mixtures were analysed by g.l.c. (Col 2, 130°C) and the yields calculated after incorporation of an internal standard. Chlorobenzene was identified by comparison of its mass spectrum with that of the authentic material. The results are shown in Table (10.6).

Table (10.6) Use of Copper in Oxidation States 0, I and II.

Copper compound	mass g	$C_6H_5CF_2CF_3$ %	C_6H_5I %	C_6H_5Cl %
copper(0)	0·32	18	85	
copper(I) iodide	0·96	67	27	
copper(II) chloride	0·67	10	28	52

10.C.ii.b. Effect of Co-ordinating Agents upon the Reaction.

Three mixtures of (98) (0·46 g, 2·5 mmol), copper(I) iodide (0·48 g, 2·5 mmol), iodobenzene (0·38 g, 1·8 mmol), and NMP (5 ml) were made up. Quinoline (0-10 mmol) was added to two of the mixtures before all three were stirred under nitrogen at 170°C for two hours. The mixture was then analysed by g.l.c. (Col 2, 130° C) and the yields of pentafluoroethylbenzene and iodobenzene calculated after addition of an internal standard. The amount of sodium pentafluoropropanoate remaining in solution was calculated by integrating the area of the ^{19}F nmr peaks at 84 and 120 ppm both before and after the reaction.

This experiment was repeated with sodium iodide in place of quinoline. The results of both reactions are shown in Table (10.7).

Table (10.7) Effect of Co-ordinating Agents upon the Reaction.

Coordinating Agent	mmol	$CF_3CF_2C_6H_5$ %	IC_6H_5 %	$CF_3CF_2COO^-$ %
sodium iodide	2·5	17	78	33
	8·25	0	94	59
	0	74	25	11
quinoline	2.5	83	23	10
	10·0	43	50	40
	0	62	30	15

10.B.ii.c. A Competition Pentafluoroethylation of p- and o-Chloroiodobenzenes.

A mixture of (<u>98</u>) (0·37 g, 2 mmol), copper(I) iodide (0·38 g, 2 mmol), o-chloroiodobenzene (180 μl active + 120 μl inactive, 1 mmol), p-chloroiodobenzene (113 μl active + 0·24 g inactive, 1 mmol), and NMP (4 ml) was stirred under nitrogen for three hours at 170°C. Samples were taken at intervals for analysis by radio-g.l.c. and the ratio of the p- and o-isomer peaks measured. The activity in these two peaks, as a percentage of the total activity, is a measure of the extent of the reaction. The results are shown in Table (10·8).

Activity Balance: Initial activity 36.5 μCi, Final activity 37·9 μCi, Retention of activity 103%.

Table (10.8) A Competition Pentafluoroethylation of p- and o-Chloroiodobenzenes.

Ratio of Peak Areas p:o	Activity % of total	Time hr
1 : 1·08	100	0
1 : 1·20	54	1
1 : 1·40	33	3

Chapter 11

Experimental to Chapter 6

11.A. Reagents and Solvents

1,3,5-Tris(trifluoromethyl)benzene (103) Trimesic acid (150 g, 0·7 mol) was placed in a 1 litre capacity autoclave which was then cooled in liquid nitrogen before the addition of sulphur tetrafluoride (500 g, 4·6 mol). The autoclave was sealed, allowed to warm to room temperature and then heated at 150°C for six hours. After venting to release unused sulphur tetrafluoride and gaseous products the liquid contents were poured onto crushed ice to remove unreacted acid and hydrogen fluoride. The lower layer was separated, washed with sodium hydroxide (2 M) and dried over $MgSO_4$. Fractional distillation to remove partially fluorinated material yielded a colourless liquid 1,3,5-tris(trifluoromethyl)benzene (64 g, 33%), b.p. 118-120°C (lit.[14], 119·6°C 750 mm Hg); δ_F 65·3 (lit.[162], 64·3); δ_H 8·1 (lit.[162], 8·1); m/z 282 (M^+), 263 (-F), 213 ($-CF_3$).

When this reaction was repeated with double the quantities of reagents in the same autoclave the yield fell to (27 g, 14%) and the major products were incompletely fluorinated materials.

Copper powder was prepared from copper sulphate solution as described in Chapter 7.

n-Butyl lithium was a commercial sample dispersed as a 1·6 M solution in hexane.

Tetrahydrofuran was supplied dry by the Departmental Technical Services (distillation from lithium aluminium hydride and then potassium metal).

1,4-Dioxane was refluxed over sodium metal until the reaction ceased and the sodium surface remained clean. It was then distilled from the sodium and stored under nitrogen.

Diethyl ether was dried over sodium wire.

11.B. Reactions of 1,3,5-tris(trifluoromethyl)benzene: (103)

11.B.i. Halogenation.

11.B.i.a. Fluorination using Cobalt Trifluoride.

The cobalt trifluoride bed was heated to 386°C and (103) (5 g, 18 mmol) was passed over the bed in a stream of nitrogen (50 ml min^{-1}). A colourless liquid (7 g) was collected and on analysis by g.l.c. (Col DNP, 60°C) was shown to consist of two main components and some unchanged material. The major component (50%) was isolated by preparative scale g.l.c. (Col DNP, 60°C) and identified as perfluoro-1,3,5-trimethylcyclohexane,[163] (Found: C, 24·1; C_9F_{18} requires: C, 24·0%); I.R. No 2; m/z 4·31 (M^+- 19).

This process was repeated at a range of temperatures from 140°C to 386°C. Very little fluorination occurred at 140°C and at the intermediate temperatures, 175°C and 290°C, complex mixtures were obtained.

11.B.i.b. Attempted Promotion of Chlorination with γ-irradiation.

Chlorine (650 cm^3, 29 mmol) and (<u>103</u>) (1·9 g, 6·7 mmol) were sealed in a nickel tube and irradiated with γ-rays, produced by a ^{60}Co source, for seven days. The tube was then vented to release unused chlorine and the liquid analysed by g.l.c. (Col 5% O, 80°C). Comparison of the retention time with that of the authentic material showed it to be recovered (<u>103</u>).

11.B.i.c. Attempted Promotion of Chlorination with Ultraviolet Light.

Chlorine (650 cm^3, 29 mmol) and (<u>103</u>) (2·82 g, 10 mmol) were sealed in a quartz tube and irradiated by uv light (254 nm) for two days. Analysis of the liquid by g.l.c. (Col 5% O, 80°C) and comparison of the retention time with that of the authentic material showed it to be recovered (<u>103</u>), (2·82 g, 100%).

11.B.i.d. Attempted Bromination with Bromine and Sodium Hydroxide.

A mixture of sodium hydroxide (0·4 g, 10 mmol), (<u>103</u>) (2·82 g, 10 mmol), bromine (0·8 g, 5 mmol) and water (25 ml) was formed in an ice cooled autoclave, which was sealed and rocked (to ensure mixing) for twenty four hours at 100°C. On opening the autoclave the contents were seen to be a red-brown solid and solution. The solid was filtered off, and the solution washed with ether to extract the organic components. The ether layer was dried with $MgSO_4$ and the solvent removed by distillation. The residue was shown, by g.l.c. (Col 5% O, 80–170°C) analysis and comparison of the retention time with that of the authentic material, to be recovered (103), (2·1 g, 74%).

11.B.ii. Nitration.

11.B.ii.a. Attempted Nitration with a Nitric/Sulphuric Acid Mixture.[129]

A mixture of (103) (2·79 g, 10 mmol) and conc. sulphuric acid (2 ml) was cooled to 16°C in a cold water bath. To this was added, with vigorous stirring to mix the two layers, a mixture of conc. sulphuric (0·63 ml) and conc. nitric (0·75 ml) acids. After an hour the temperature was raised to 80°C for a further two hours. The mixture was then poured onto ice and the lower layer was extracted into ether, dried with $MgSO_4$ and the ether distilled off. The residue was identified by comparison of g.l.c. (Col 5% O) retention times as recovered (103) (2·5 g, 90%).

11.B.ii.b. Attempted Nitration with Boron Trifluoride and Fuming Nitric Acid.[130]

Boron trifluoride was bubbled through a mixture of sulpholane (3.5 ml) and fuming nitric acid (0·8 ml) at 0°C until a saturated solution was formed. To this was added (103) (2·82 g, 10 mmol) and the mixture was stirred at 70°C for two hours, before being poured onto crushed ice. The lower layer was ether extracted, dried with $MgSO_4$ and the solvent removed by distillation leaving a residue which was shown by comparison of g.l.c. (Col 5% O) retention times to be recovered (<u>103</u>) (2·7 g, 96%).

11.B.iii. <u>Reaction with Methoxide Ions.</u>

11.B.iii.a. 1,3,5-tris(trifluoromethyl)benzene.

Sodium (0·23 g, 10 mmol) was dissolved under nitrogen in methanol (20 ml) to form a sodium methoxide solution. After addition of (<u>103</u>) to this solution it was refluxed for twenty four hours and then poured onto water to remove the methanol and sodium methoxide. The fluorocarbon layer was extracted into ether and dried over $MgSO_4$ before removal of the excess solvent by distillation. The residue was analysed by g.l.c. (Col 5% O, 80°C) and shown by comparison of retention times to be recovered (<u>103</u>), (2·08 g, 74%). The absence of any other fluorine containing components in the reaction mixture was confirmed by ^{19}F nmr.

This reaction was repeated at the higher temperatures of 115°C and 150°C, the mixture being heated in a rocking autoclave, and in both cases only (<u>103</u>) was recovered. However some decomposition had occurred since a brown tar was formed and the quantities of (<u>103</u>) recovered were smaller than in the previous reaction.

11.B.iiib. 1,2,4,5-Tetrakis(trifluoromethyl)-benzene (108)

A solution of sodium methoxide in methanol (15 ml) was prepared by dissolving sodium (0·5 g, 10 mmol) in the solvent under an inert atmosphere. This solution and (108) (3·5 g, 10 mmol) was sealed in a nickel tube and rocked at 150°C for 20 hours. The mixture was poured into water and the organic material ether extracted. After drying over $MgSO_4$ the solvent was removed leaving an orange liquid (2·31 g) which was analysed by m.s.g.l.c. (Col 5% O, 150°C) and found to contain five components; recovered (108) (20%), acid fluoride (111) (12%), m/z 282 (46%), m/z 340 (11%) and m/z 355 (12%). The major component was isolated by preparative scale g.l.c. (Col 10% O) and found to be a colourless liquid, 1,2,4-tris(trifluoromethyl)benzene (109), (Found: C, 38·5, H; 0·7, $C_9H_2F_9$ requires C; 38·30, H; 1·06%); δ_F 61·3 (2, CF_3), 65·3 (1, CF_3) (lit.[162], 60·84, 60·86, 64·66); δ_H 8·1 (2), 7·9 (1) (lit.[162], 8·1, 7·9); m/z 282 (M^+), 263 (M^+ - 19), 262 (M^+ - 50), 213 (M^+ - 69).

This experiment was repeated using methanol which had previously been distilled onto molecular sieve (4A). The product mixture (1·7 g) was analysed by m.s.g.l.c. (Col 5% O, 150°C) and found to contain 4 components; recovered (108) (32%), acid fluoride (111) (14%), methyl-2,3,5-tris(trifluoromethyl)benzoate (12%), m/z 340 (M^+), 309 (M^+ - 31), 281 (M^+ - 59), and m/z 355 (34%).

The major product was isolated by preparative scale g.l.c. (Col 10% O) and was a colourless liquid which remains unidentified, δ_F 61·3 (1, CF_3), 62 (2, CF_3); δ_H 8·2 (2), 3·9 (3, CH_3O); ν_{max} 3080 (CH aromatic), 2960 (CH aliphatic), 1740 (C = O), 1100 - 1350 (C-F) cm^{-1}; m/z 368 (0.75), 355 (100·00), 309 (46·78), 281 (9·47), 59 (18·45).

11.B.iv. Reaction with Radical Sources.

11.B.iv.a. Benzoyl Peroxide.

A mixture of benzoyl peroxide (2·42 g, 15 mmol) and (<u>103</u>) (2·82 g, 10 mmol) was stirred under nitrogen at 80°C for two days. A yellow solution was formed which became turbid when stirring ceased and was separated into a yellow liquid and a creamy solid soluble in ether. Analysis of the yellow liquid by g.l.c. (Col 10% O) and comparison of the retention times with the authentic material showed it to be mainly recovered (<u>103</u>). The solid was recrystallised from absolute ethanol and shown, by g.l.c. analysis of its ether solution and comparison with the retention time of the authentic material, not to be biphenyl. The mass spectrum suggested that it was a mixture of benzoic acid; m/z 122 (M^+), 105 (M^+ - COOH) and phenylbenzoic acids; m/z 198 (M^+), 181 (M^+ - OH), 153 (M^+ - COOH).

11.B.iv.b. Di-t-butyl Peroxide.

A mixture of di-t-butyl peroxide (0·73 g, 5 mmol) and

(103) (2·82 g, 10 mmol) was sealed in a Carius tube and shaken in a rocking autoclave for 24 hours at 115°C. The tube was found to be lined with a brown film which was only slightly soluble in ether. A brown liquid (3·00 g) was recovered and analysed m.s.g.l.c. (Col 10% O) and ^{19}F nmr. Comparison with the authentic materials showed the mixture was mainly composed of (103) with some acetone. About 5% of (103) had been converted into a product identified, from the fragmentation pattern of the mass spectrum and ^{19}F nmr of the reaction mixture, as 1-methyl-2,4,6-tris(trifluoromethyl)benzene, δ_F 63 and 62·7, m/z 296 (M$^+$), 277 (M$^+$F), 276 (M$^+$-HF), 227 (M$^+$-69).

11.C. Preparation and Reactions of 2,4,6-Tris(trifluoromethyl)phenyl Lithium (116)

11.C.i. Preparation.

11.C.i.a. Preparation and Reaction with Methanol-OD to Establish the Yield.

A solution of (103) (2·82 g, 10 mmol) in diethyl ether (7 ml) was stirred at room temperature under nitrogen and butyl lithium in hexane solution (7 ml, 10 mmol) was added dropwise so as to prevent vigorous boiling of the ether. The mixture was stirred for an hour before addition of methanol-OD (0·5 ml) and filtration of the precipitated lithium methoxide. Excess solvent was removed by distillation and the residue was analysed by m.s.g.l.c.

(Col 10% O). Comparison of the 282 (MH^+) and 283 (MD^+) a.m.u. peak heights showed that 90% of (103) had been converted into the deuterium substituted compound.

This reaction was repeated at 0°C and a 66% conversion was obtained.

11.C.i.b. Formation of the Di-lithium Compound.

A solution of (103) (1·41 g, 5 mmol) in diethyl ether (10 ml) was stirred at room temperature under nitrogen and butyl lithium (7 ml, 10 mmol) was added dropwise. The mixture was refluxed for an hour before addition of methanol-OD (0·5 ml) and treatment of the mixture as in the previous experiment. Comparison of the 282 (MH^+), 283 (MD^+), and 284 (MD_2^+) a.m.u. peak heights showed that, although only 4% of (103) remained, the major product was the mono-deuterium substituted compound (85%) and only a small amount of the bis-deuterium substituted product (11%) had been formed.

11.C.ii. Stability.

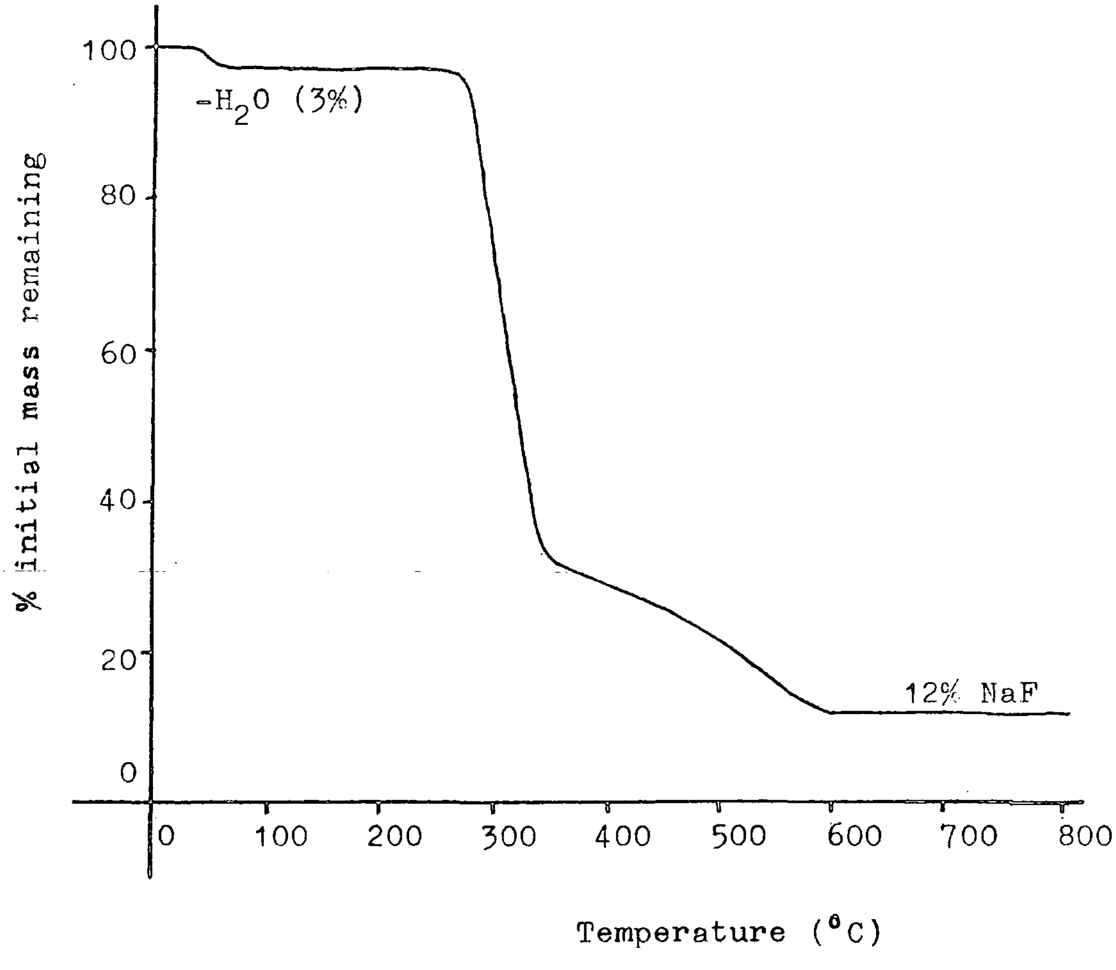
11.C.ii.a. Formation of Sodium 2,4,6-Tris(trifluoromethyl)benzoate (119)

A mixture of 2,4,6-tris(trifluoromethyl)benzoic acid (1·49 g, 4·6 mmol) in water (10 ml) was prepared and to this was added with stirring sodium hydroxide (0·18 g, 4·6 mmol). The water was removed under reduced pressure and the white solid, sodium 2,4,6-tris(trifluoromethyl)benzoate, dried under vacuum before storage under nitrogen.

11.C.ii.b. Thermogravimetric Analysis of Sodium 2,4,6 Tris(trifluoromethyl)benzoate (119)

A small sample of (119) (7·45 mg) was heated from 20 - 860°C at a rate of 20°C/min and the percentage weight loss was recorded. The results are shown in Diagram (11.1).

Diagram (11·1)



11.C.ii.c. Attempted Decarboxylation.

A flask equipped with a cold finger and a side arm containing (115) (0·5 g) was connected to a vacuum pump through two traps cooled in liquid air. The apparatus was evacuated (≤1 mmHg) and the flask heated to 300°C in a Woods metal bath. When this temperature was attained the side arm was tipped so that the contents fell into the flask. Immediately the solid turned black and bubbled leaving a small amount of tar. No product had sublimed onto the cold finger but a small amount of colourless liquid was collected in the traps. On analysis by m.s.g.l.c. (capillary, 80 - 250°C) it was found to be a complicated multicomponent mixture.

11.C.iii. Reactions.

All of the reactions were carried out under a nitrogen atmosphere.

11.C.iii.a. Chlorine.

A solution of (116) (~15 mmol) in hexane (10 ml) and ether (10 ml) was prepared as described previously. The flask was attached to a gas bulb, which had been filled with chlorine (300 ml, 13 mmol), the solution cooled in liquid nitrogen and the system evacuated before the connecting tap was opened allowing the chlorine to condense onto the ether solution. The mixture was allowed to warm to room temperature, with stirring, and a white precipitate of lithium chloride formed which was dissolved by addition of water. The organic layer was collected and dried over

$MgSO_4$ before removal of the solvents and recovered (103) by fractional distillation. A small amount of product (0·51 g, 12%) was collected by distillation leaving a dark residue which was run through a silica packed column with petroleum ether. Removal of the ether left a colourless liquid also identified as 1-chloro-2,4,6-tris(trifluoromethyl)benzene[14] (117) (2·23 g, 54%), ^{19}F nmr Table (A.1), ^{13}C nmr Table (A.3); I.R. No 4; M.S. No 2.

This experiment was originally carried out by bubbling chlorine through the ethereal solution of (116) for two hours. However a complicated mixture of products was obtained since chlorination of the ether had occurred.

11.C.iii.b. Hexachloroethane.[164]

A solution of (116) (~ 15 mmol) in ether (10 ml) and hexane (10 ml) was prepared as described previously. To this was added a solution of hexachloroethane (3·5 g, 15 mmol) in ether (12 ml) and the mixture was stirred at room temperature for thirty minutes, before addition of water. The organic layer was separated and dried over $MgSO_4$. Analysis of the mixture, after removal of most of the solvent, by m.s.g.l.c. (Col 10% O_{v101}, 100°C) showed the presence of recovered (103), tetrachloroethene, hexachloroethane and the chlorinated product. A small amount of colourless liquid was recovered by fractional distillation and identified as 1-chloro-2,4,6-tris(trifluoromethyl)benzene 117 (0·85 g, 18%), b.p. 151°C (Lit.[14], 152·4°C, 750 mmHg).

11.C.iii.c. Bromine.

A solution of (<u>116</u>) (~10 mmol) in hexane (7 ml) and ether (7 ml) was prepared as described previously. To this was added dropwise a solution of bromine (1·6 g, 10 mmol) in ether (7 ml) and lithium bromide was precipitated. Water was added and the organic layer was separated and dried over $MgSO_4$. The product mixture was separated by fractional distillation and after removal of the solvents two fractions were obtained, recovered (<u>103</u>) and a colourless liquid (41-43°C, 6 mmHg) identified as 1-bromo-2,4,6-tris(trifluoromethyl)benzene (<u>124</u>) (0·45 g, 12%), δ_F 65 (2, s, CF_3), 66 (1, s, CF_3) (lit.[162], 63·91 (2), 64·47 (1)); I.R. No 5; M.S. No 3.

The brown residue from the distillation was run down a silica packed column with petroleum ether. After removal of the ether a colouless liquid identified as the brominated product was obtained (0·88 g, 24%).

11.C.iii.d. Trimethyltin Chloride.

A solution of (<u>116</u>) (~15 mmol) in hexane (10 ml) and ether (10 ml) was prepared as described previously. To this was added dropwise a solution of trimethyltin chloride (2·98 g, 15 mmol) in ether (10 ml). The mixture was stirred overnight before addition of water. The organic layer was separated, dried under nitrogen and the solvents and recovered (103) removed under vacuum leaving a yellow liquid (3·48 g, 52%). This was distilled collecting a colourless liquid identified as trimethyl-[2,4,6-tris-(trifluoromethyl)phenyl]-tin, (125) (Found: C, 32·4; H, 2·7, Calculated for $C_{12}H_{11}F_9Sn$: C, 32·43; H, 2·47; ^{19}F nmr Table (A.1); ^{1}H nmr, Table (A.2); δ ^{119}Sn ($CDCl_3$, $Sn(CH_3)_4$, 6·98; I.R. No 11; m.s. No 11 (C.I.), 12 (E.I.).

(Comparative ^{119}Sn shifts; See Ref. 165.)

11.C.iii.e. Trimethylsilyl Chloride.

A solution of (116) (~15 mmol) in hexane (10 ml) and ether (10 ml) was prepared as described previously. To this was added trimethylsilyl chloride (1·88 ml, 15 mmol) and the mixture was stirred overnight. The precipitation of lithium chloride was not as dense as usual and on addition of water the formation of lithium hydroxide was obvious. After extraction of the organic layer with ether and drying over $MgSO_4$, the solvent and recovered trimethylsilyl chloride was removed by distillation leaving an orange liquid (2·39 g) which was analysed by m.s.g.l.c. (Capillary, 100-180°C). The mixture was shown to contain three main components, identified from the molecular ion peaks and fragmentation patterns as: (103), m/z 282 (M^+); hexamethyl disiloxane[166], m/z 147 (M^+-CH_3), 73 ($Si(CH_3)_3$); and trimethyl-[2,4,6-tris(trifluoromethyl)phenyl]-silane

(126), m/z 339 ($M^{+}-CH_3$), 262 ($C_9H_2F_8^{+}$), 73 ($Si(CH_3)_3^{+}$). From comparison of the g.l.c. (Col O_{v101}, 180°C) peak areas the yield of silane was estimated to be 29%.

11.C.iii.f. Mercury(II) Chloride.

A solution of (116) (~15 mmol) in hexane (10 ml) and ether (10 ml) was prepared as described previously. To this was added mercury(II) chloride (2·03 g, 7·5 mmol) followed by ether (20 ml) to ensure a homogeneous solution and the mixture was stirred at room temperature for three days. The solution was then poured onto ice and the yellow-white crystalline solid was filtered off and dried under suction. The solid was sublimed (60°C, <1 mmHg) producing a white crystalline solid which was recrystallised from chloroform/ethanol yielding bis-[2,4,6-tris(trifluoromethyl)phenyl]mercury (85) (2·59 g, 45%), m.p. 78-80°C; (Found: C, 27·9; H, 0·2 Calculated for $C_{18}H_4HgF_{18}$: C, 28·35; H, 0·52%); ^{19}F nmr Table (A.1); ^{1}H nmr Table (A.2); ^{13}C nmr Table (A.3); M.S. No 14 (C.I.), 15 (N.I.), 16 (E.I.).

11.C.iii.g. Acetyl Chloride.

The acetyl chloride was distilled prior to use and the fraction boiling at 51-52°C was collected.

A solution of (116) (15 mmol) in hexane (10 ml) and ether (10 ml) was prepared as described previously. To this was added acetyl chloride (1·07 ml, 15 mmol) and the mixture was stirred for 30 minutes, during which time a white precipitate of lithium chloride formed. Water was added to hydrolyse any acetyl chloride and dissolve the lithium chloride and the organic layer was separated by ether extraction. After drying over $MgSO_4$ the solvent was removed by distillation and the residue (3·09 g) analysed by g.l.c. (Col 10% O_{v101}, 100°C) which showed it to be composed of recovered (103) (60%) and two unidentified components (38% and 2%). The major unknown component was isolated by preparative scale g.l.c. (Col 10% O) and identified as the colourless liquid 1-[2,4,6-tris(trifluoromethyl)phenyl]-1,3-butanedione (120) (0·35 g, 12%); (Found: C, 42·3; H, 1·5 Calculated for $C_{13}H_7F_9O_2$: C, 42·62; H, 1·91%); ^{19}F nmr Table (A.2); ^{13}C nmr: Table (A.3); I.R. No 6; M.S. No 4.

11.C.iii.h. Oxalyl Dichloride.

A solution of (116) (~15 mmol) in hexane (10 ml) and ether (10 ml) was prepared as described previously. To this was added oxalyl dichloride (0·64 ml, 7·5 mmol) causing an immediate exothermic reaction and precipitation of lithium chloride. After stirring for 30 minutes the mixture was poured into water, acidified and the organic layer separated by ether extraction. The ether solution was shaken with an aqueous solution of sodium bicarbonate to extract any acidic material as its sodium salt. The aqueous layer was separated and acidified before extraction of the organic layer with ether. The resulting two ether solutions were dried over $MgSO_4$.

The ether was removed from the acidic material under suction leaving a white solid which was sublimed onto a cold finger yielding the white crystalline solid 2-[2,4,6-tris(trifluoromethyl)phenyl]-2-oxoethanoic acid (122). (1·19 g, 45%), m.p. 113°C; (Found: C, 37·1; H, 0·5. Calculated for $C_{11}H_3F_9O_3$; C, 37·28; H, 0·85); ^{19}F nmr Table (A.1); ^{1}H nmr Table (A.2); I.R. No 9; M.S. No 7 (E.I.), 8 (C.I.), 9 (N.I.).

Removal of the solvent from the neutral ethereal solution left an intractable orange solution which was shown by m.s.g.l.c. (Col 10% 'O', 200°C) to contain recovered (103).

11.C.iii.j. Dimethyl Carbonate.

The dimethyl carbonate was distilled before use collecting the fraction which boiled at 90-91°C.

A solution of (113) (~15 mmol) in hexane (10 ml) and ether (10 ml) was prepared as described previously. To this was added dimethyl carbonate (1·35 ml, 15 mmol) and the mixture was stirred for thirty minutes before addition of dilute sulphuric acid. The organic material was extracted into ether, dried over $MgSO_4$ and the solvent removed by distillation. Analysis of the residue by g.l.c. (Col 10% O, 125-150°C) showed it to consist of two components, one of which was recovered (103). The mixture was fractionally distilled yielding (103) and a white crystalline solid identified as methyl-2,4,6-tris-(trifluoromethyl)benzoate (123) (0·2 g, 4%), ^{19}F nmr Table (A.1); ^{1}H nmr Table (A.2); M.S. No.18.

The product appeared to decompose on standing becoming orange preventing further analysis. From the g.l.c. trace the yield of product was calculated to be 25%.

11.C.ii.k. Ethylene Oxide.

A solution of (116) (~15 mmol) in hexane (10 ml) and ether (10 ml) was prepared as described previously. The flask was attached to a gas bulb, which had been filled with ethylene oxide (600 ml, 26 mmol), the solution cooled in liquid nitrogen and the system evacuated before the connecting tap was opened allowing the ethylene oxide to condense onto the ether solution. The mixture was stirred for an hour before addition of dilute hydrochloric acid and ether extraction of the organic material. Removal of the solvent under reduced pressure yielded a pale yellow powder from which was sublimed, at 90°C, a white solid. Recrystallisation from petroleum ether (60-80) gave a white crystalline solid identified as 2-[2,4,6-tris(trifluoromethyl)phenyl]-ethanol (128). (1·7 g, 35%) m.p. 74-75°C; (Found: C, 40·6; H, 2·2. Calculated for $C_{11}H_7F_9O$: C, 40·49; H, 2·15%); ^{19}F nmr Table (A.1); ^{1}H nmr Table (A.2); I.R. No 7; M.S. No 19 (E.I), 20 (C.I.).

11.C.iii.l. Carbon Dioxide.

A solution of (116) (~10 mmol) in hexane (7 ml) and ether (7 ml) was prepared as described previously. To this was added excess solid CO_2 and the mixture stirred until it attained room temperature. Water was added and the ether layer was separated and dried over $MgSO_4$. After removal of the solvent under reduced pressure the residue (0·43 g) was analysed by g.l.c. (Col 10% O) and shown by comparison of retention times to be recovered (103). The aqueous layer was acidified with dilute hydrochloric acid and ether extracted. The solvent was removed under reduced pressure leaving a white crystalline solid which was dried under vacuum and recrystallised from 50:50 benzene/petroleum ether (40/60) before identification as 2,4,6-tris(trifluoromethyl)benzoic acid (129)[167] (1·49 g, 46%). m.p. 185-186°C; equivalent weight 324; (Found: C, 37·1; H, 0·6, F, 52·1; $C_{10}H_3F_9O_2$ requires, C, 36·81; H, 0·92; F, 52·45%); ^{19}F nmr Table (A·1); I.R. No 8; M.S. No 6.

11.C.iii.m. Sulphur Dioxide[168]

A solution of (116) (15 mmol) in hexane (10 ml) and ether (10 ml) was prepared as described previously. The flask was attached to a gas bulb, which had been filled with sulphur dioxide (600 ml, 26 mmol), the solution cooled in liquid nitrogen, and the system evacuated before the connecting tap was opened allowing the sulphur dioxide to condense onto the ethereal solution. The mixture was stirred and allowed to warm to room temperature before filtration of the dense precipitate. After washing with ether and air-drying the cream powder was identified as lithium 2,4,6-tris(trifluoromethyl)phenyl sulphinate (130) (2·92 g, 55%); ^{19}F nmr Table (A.1); miz 329 ($C_9H_2F_9SO^+$), 262 (100%, $C_9F_8H_2$).

This compound gave a positive Smiles' Test.[150]

11.C.iii.n. Sulphur.

A solution of (116) (~15 mmol) in hexane (10 ml) and ether (10 ml) was prepared as described previously. To this was added sulphur (0·48 g, 15 mmol) and the mixture was stirred for an hour before addition of dilute sulphuric acid. The organic material was extracted into ether solution and dried over $MgSO_4$. After removal of the solvent by distillation and filtration of the fine precipitate of sulphur, which formed on reducing the volume, the mixture was analysed by g.l.c. (Col 10% O, 150°C) and shown to contain one product in 60% yield. A pungent smelling colourless liquid was isolated by preparative scale g.l.c. (Col 10% O) and identified as 2,4,6-tris-(trifluoromethyl)benzene-thiol (131), (Found: C, 34·7; H, 0·8 Calculated for $C_9H_3F_9S$: C, 34·39; H, 0·96%); ^{19}F nmr Table (A.1); ^{1}H nmr Table (A.2); I.R. No 10; M.S. No 10.

11.C.iii.p. Pentafluoropyridine.

A solution of (116) (~15 mmol) in hexane (10 ml) and ether (10 ml) was prepared as described previously. To this was added pentafluoropyridine (2·54 g, 15 mmol) and the solution was stirred for an hour at room temperature and refluxed for a further hour. Water was then added and the organic material was extracted into ethereal solution and dried over $MgSO_4$. After removal of the solvents by distillation, the residue was analysed by g.l.c. (Col 10% O, 145°C) and one product was observed in 40% yield. A white crystalline solid was separated by preparative scale g.l.c. (Col 10% O) and identified as 2,3,5,6-tetrafluoro-4-[2,4,6-tris(trifluoromethyl)phenyl]-pyridine (132), (Found: C, 39·0; H, 0·6; N, 3·0: Calculated for $C_{14}H_2F_{13}N$: C, 38·99; H, 0·46; N, 3·25%); ^{19}F nmr Table (A.1); I.R. No 12; M.S. No 13.

11.C.iv. Measurement of the Relative Acidities of 1,3,5-Tris(trifluoromethyl)benzene and Pentafluorobenzene.

11.C.iv.a. A Competitive Lithiation Reaction.

A solution of 1,3,5-tris(trifluoromethyl)benzene (0·94 g, 3·3 mmol) and pentafluorobenzene (1·68 g, 10 mmol) in ether (7 ml) was cooled in an acetone / CO_2 slush bath. The solution was stirred whilst butyl lithium (8 mmol) in hexane (5 ml) was added dropwise maintaining the temperature below -65°C. After stirring for five hours methanol-OD (1·5ml) was added and the mixture allowed to warm to room temperature. The ether solution was dried over $MgSO_4$ and the solvents removed by distillation before analysis by m.s.g.l.c. (Col K, 70°C). Comparison of the

M^+ and $(M + 1)^+$ peak heights of each component showed that, whilst 1,3,5-tris(trifluoromethyl)benzene remained unchanged, 88% of the pentafluorobenzene had undergone deutenium exchange via the organolithium intermediate.

11.D. Reactions of Some 1,3,5-Tris(trifluoromethyl)benzene Derivatives.

11.D.i.a. Cleavage of Trimethyl -[2,4,6-tris(trifluoromethyl)phenyl]-tin (125)[169].

A mixture of (125) (3.3 g, 7·5 mmol), iodine (1·9 g, 7·5 mmol), and trichloromethane (37 ml) was stirred at room temperature for fifteen minutes. As the iodine colour did not disappear the mixture was then refluxed for an hour. The unreacted iodine was removed by reaction with sodium thiosulphate and the mixture fractionally distilled yielding solvent and recovered (125).

11.D.ii. 1-Bromo-2,4,6-tris(trifluoromethyl)benzene (124) - Ullmann Coupling.

11.D.ii.a. Attempted Formation of a Symmetrical Biphenyl.[170]

A mixture of (124) (0·9 g, 2·5 mmol) and copper powder (0·32 g, 5 mmol) was sealed in a carius tube and heated at 196°C in a rocking autoclave for four hours. As no reaction appeared to have occurred during this period the temperature was raised to 225°C and the heating continued for fifty-two hours. The mixture was then washed from the tube with ether and the copper removed by filtration. After removal of the solvent the liquid was analysed by g.l.c. (Col 10% o, 100–175°C) and shown by comparison of retention times to be recovered (<u>124</u>).

11.D.ii.b. With Iodobenzene.

A mixture of (<u>124</u>) (0·9 g, 2.5 mmol), iodobenzene (0·5 g, 2·5 mmol), and copper powder (0·64 g, 10 mmol) was sealed in a carius tube and heated at 225°C in a rocking autoclave for forty-eight hours. The mixture was washed from the tube with ether and the sediment removed by filtration. After removal of the solvent the residue was analysed by m.s.g.l.c. (Col 10% O, 178°C) and the components were identified, from molecular ion peaks and comparison of retention time with authentic materials where possible, as 1,3,5-tris(trifluoromethyl)benzene (<u>103</u>), recovered (<u>124</u>), (48%); bromobenzene (10%); 2,4,6-tris-(trifluoromethyl)biphenyl (<u>86</u>), (11%), M.S. No 17; and biphenyl (27%).

11.D.iii. <u>Di[2,4,6-tris(trifluoromethyl)phenyl]-mercury</u> (<u>85</u>).

11.D.iii.a. Formation of 2,4,6-Tris(trifluoromethyl)-biphenyl.

A mixture of (<u>85</u>) (2·07 g, 2·7 mmol), copper powder (0·89 g, 14 mmol), iodobenzene (1·07 g, 5.25 mmol), and NMP (9 ml) was stirred at 141°C, under nitrogen for three hours. The reaction mixture was analysed by m.s.g.l.c. (Col 2, 150°C) and ^{19}F nmr. The components were identified, by comparison of the retention times of the authentic materials and from the molecular ion peaks, as; 1,3,5-tris(trifluoromethyl)benzene, iodobenzene, and 2,4,6-tris(trifluoromethyl)biphenyl, δ_F 58·7 (2,CF_3), 64 (1,CF_3), m/z 358 (100%, M^+). The yield of biphenyl was calculated as 42% from the g.l.c. after addition of an internal standard.

The solid residue was separated by filtration through a glass scinter, washed with ether and air dried before being dissolved in aqua regia (35 ml). The solution was made up to 1000 ml with water and analysed by atomic absorbtion spectrometry. It was found to contain 0·46 g of mercury as metallic mercury and 0·61 g of copper as copper(I) iodide. Both of these values are probably low since the precipitate was so fine that some solid passed through the scinter.

11.D.iv. "<u>2,4,6-Tris(trifluoromethyl)phenyl Copper.</u>"

11.D.iv.a. Formation and Attempted Isolation[143,144]

A solution of the organolithium derivative (<u>116</u>) was prepared by adding butyl lithium (10 mmol) in hexane (7 ml) dropwise to a solution of 1,3,5-tris(trifluoromethyl)benzene (2·82 g, 10 mmol) in ether (10 ml) whilst stirring under nitrogen. The solution was stirred for an hour and a small amount was removed for a Gilman colour test.[171] After addition of this sulphate to remove excess iodine formation of a green coloration showed that the lithium derivative (<u>116</u>) was present, butyl lithium gave a blue solution.

Copper(I) iodide (1·91 g, 10 mmol) was added and the solution was stirred for twenty-four hours, after which the colour test wasnegative suggesting that "2,4,6-tris-(trifluoromethyl)phenyl copper" had been produced.

Dioxane (10 ml) was added to the mixture and the solid was filtered under nitrogen on a fine glass scinter. The solid was washed with ether and the last traces of solvent were blown off with nitrogen. After this the solid was washed out with ether into a flask and dried under vacuum before analysis, (Found: C, 22·7; H, 3·6; Cu, 7·0; Li, 2·7; I, 28·5%). The i.r. spectrum (nujol) compared well with the combined spectra of dioxan, 1,3,5-tris(trifluoromethyl)benzene and nujol.

11.D.iv.b. Coupling with Iodobenzene.

The copper derivative was prepared in ether/hexane solution from 1,3,5 tris(trifluoromethyl)benzene (<u>103</u>) (0·98 g, 3·5 mmol) as described previously. Iodobenzene (0·72 g, 3·5 mmol) and dioxane (5 ml) were added to the mixture and the ether was removed by distillation under nitrogen. The residue was heated under nitrogen at 100°C for forty-eight hours. Ammonium chloride and ammonia solution were added to the mixture to dissolve the copper salts and the organic material was extracted into ether solution. After drying over $MgSO_4$ the ether was removed by distillation and the residue analysed by m.s.g.l.c. (Col 10% O, 140°C) and ^{19}F nmr. Comparison of retention times with authentic materials and the molecular ion peaks were used to identify the components as; (103) (28%); iodobenzene (36%); and 2,4,6-tris(trifluoromethyl)biphenyl, (36%), m/z 358; (M^+); δ_F 59·5 $(2,CF_3)$, 64·7 $(1,CF_3)$.

When this reaction was repeated using THF as the solvent the recovered material was mainly composed of (103) and iodobenzene with trace amounts of 2,4,6-tris(trifluoromethyl)biphenyl and 1-iodo-2,4,6-tris(trifluoromethyl)-benzene, m/z 408 (M^+).

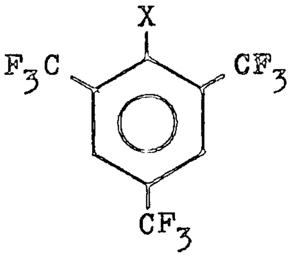
APPENDICES

APPENDIX 1

NMR SPECTRA

Table (A.1)	fluorine-19
Table (A.2)	proton
Table (A.3)	carbon-13

Table (A.1.) Derivatives of 1,3,5-Tris(trifluoromethyl) benzene - ^{19}F nmr spectra.✻



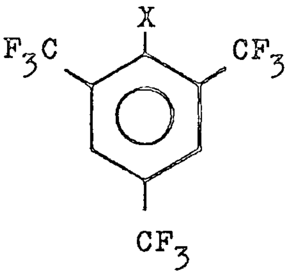
	X	o-CF_3	p-CF_3	other
(103)	H	65·3	65·3	
(116)	Li^+	64·3	64·5	
(117)	Cl	65·0	65·4	
(124)	Br	65·0	66·0	
(125)	$Sn(CH_3)_3$	58·7	64·7	
(85)	$HgC_6H_2(CF_3)_3$†	61·0	63·6	
(120)	$C(OH)=CHC(=O)CH_3$	60·3	65·4	
(122)	$C(=O)C(=O)OH$†	58·0	63·4	
(123)	$C(=O)OCH_3$†	62·3	65·6	
(128)	CH_2CH_2OH †	59·3	63·6	
(129)	$C(=O)OH$ ‡	61·4	65·0	
(130)	$SO_2^-Li^+$‡	55·7	64·2	
(131)	SH	64·7	65·7	
(132)	C_5F_4N†	61·0	63·4	89·4(M,2,5C-F) 140·0(M,3,4C-F)

✻ quoted in p.p.m. relative to $CFCl_3$

† $CDCl_3$ solvent

‡ $(CD_3)_2CO$ solvent

Table (A.2.) Derivatives of 1,3,5-Tris(trifluoromethyl)-benzene - ^{1}H nmr spectra.[*]



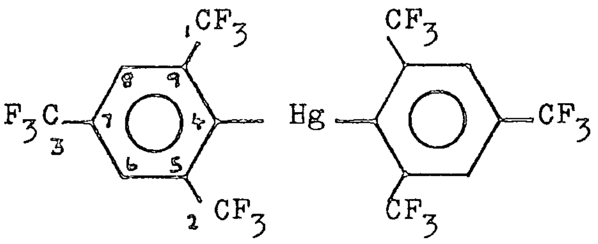
	X	m-H	other
(103)	H	8·1	
(125)	$Sn(CH_3)_3$	8·1	0·8 ($C\underline{H}_3$)
(85)	$HgC_6H_2(CF_3)_3$[‡]	8·1	
(120)	$C(OH){=}CHC({=}O)CH_3$	8·3	5·6(C=C$\underline{H}$),4·8(C-O$\underline{H}$),2·0(C$\underline{H}_3$)
(122)	$C({=}O)C({=}O)CH$[‡]	7·7	8·4 (O$\underline{H}$)
(123)	$C({=}O)OCH_3$[‡]	8·2	4·0 (C$\underline{H}_3$)
(128)	CH_2CH_2OH[‡]	8·1	4·9 (O$\underline{H}$), 2·8, 2·2 (C$\underline{H}_2$)
(131)	SH	8·0	4·3 (S$\underline{H}$)

[*] Quoted in p.p.m. relative to TMS

[‡] $CDCl_3$ solvent

Table (A.3.) Derivatives of 1,3,5-Tris(trifluoromethyl)-benzene - ^{13}C nmr.

1.

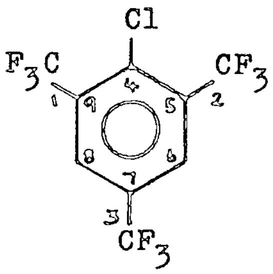


(85)

CDl_3 solvent

p.p.m.	multiplicity	J (Hz)	assignment
123·76	q	268·5	$\underline{C}F_3$ (1+2)
122·76	q	277·1	$\underline{C}F_3$ (3)
139·67	q	32·2	$\underline{C}(CF_3)$ (5+9)
131·86	q	33·5	$\underline{C}(CF_3)$ (7)
125·55	s		$\underline{C}$-H (6+8)
163·30	s		$\underline{C}$-Hg (4)

2.

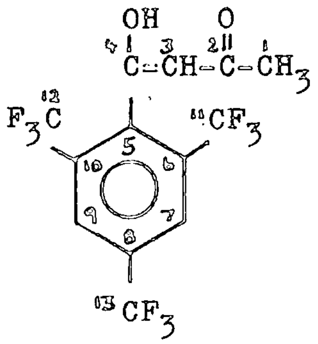


(117)

$CDCl_3$ solvent

p.p.m.	multiplicity	J (Hz)	assignment
129·51	q	32·1	$\underline{C}(CF_3)$ (5+9)
127·36	q	34·6	$\underline{C}(CF_3)$ (7)
118·88	q	273·6	$\underline{C}F_3$ (1+2)
119·26	q	271·1	$\underline{C}F_3$ (3)
124·82	s		$\underline{C}$-H (6+8)
132·90	s		$\underline{C}$-Cl (4)

3.



(120)

$CDCl_3$ solvent

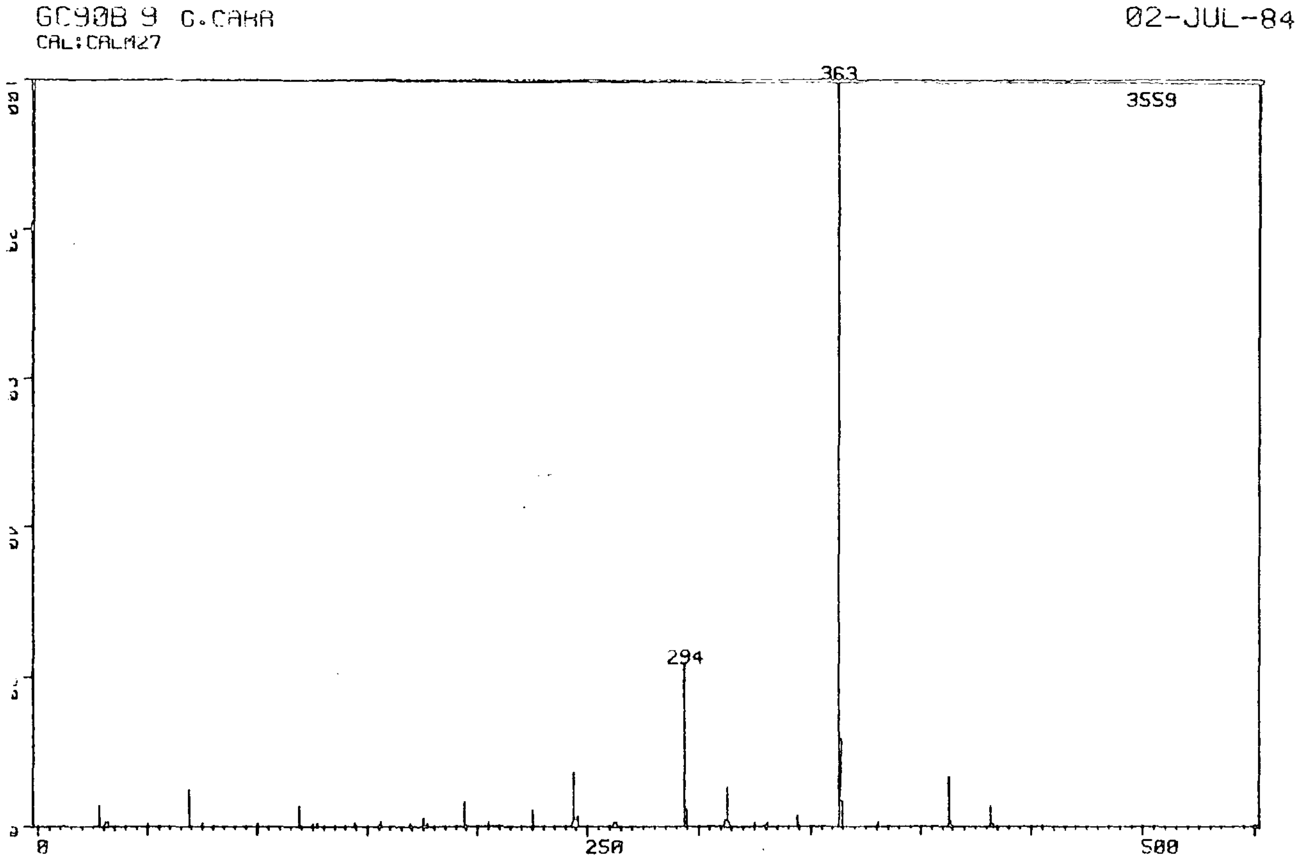
p.p.m.	multiplicity	J (Hz)	assignment
122·36	q	271·7	$\underline{C}F_3$ (11+12+13)
132·49	q	31·6	$\underline{C}$ (CF_3) (6+10)
131·88	q	34·4	$\underline{C}$ (CF_3) (8)
126·74	s		$\underline{C}$-H (7+9)
107·19	s		C=$\underline{C}$ -H (3)
21·22	s		$\underline{C}H_3$ (1)
166·88	s		$\underline{C}$=O (2)
143·60	s		C=$\underline{C}$-OH (4)
137·05	s		C-C-OH (5)

(Comparative ^{13}C shifts and coupling constants can be found in Ref. 162.)

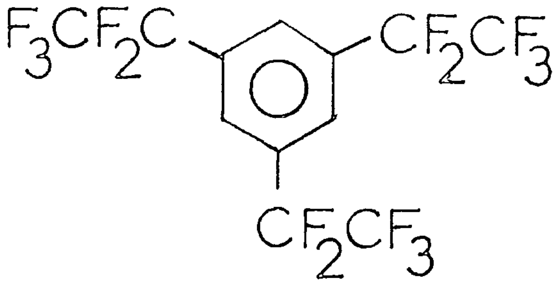
APPENDIX 2

MASS SPECTRA

1. 1,3,5-tris(pentafluoroethyl)benzene
2. 1-chloro-2,4,6-tris(trifluoromethyl)benzene (117)
3. 1-bromo-2,4,6-tris(trifluoromethyl)benzene (124)
4. 1-[2,4,6-tris(trifluoromethyl)phenyl]-1,3-butanedione (120)
5. 2,4,6-tris(trifluoromethyl)benzoic acid (129) (CI)
6. 2,4,6-tris(trifluoromethyl)benzoic acid (129)
7. 2-[2,4,6-tris(trifluoromethyl)phenyl]-2-oxo-ethanoic acid (122)
8. 2-[2,4,6-tris(trifluoromethyl)phenyl]-2-oxo-ethanoic acid (122) (CI)
9. 2-[2,4,6-tris(trifluoromethyl)phenyl]-2-oxo-ethanoic acid (122) (NI)
10. 2,4,6-tris(trifluoromethyl)benzene-thiol (131)
11. trimethyl-[2,4,6-tris(trifluoromethyl)-phenyl]-tin (125) (CI)
12. trimethyl-[2,4,6-tris(trifluoromethyl)-phenyl]-tin (125)
13. 2,3,5,6-tetrafluoro-4-[2,4,6-tris(trifluoromethyl)-phenyl]-pyridine (132)
14. di[2,4,6-tris(trifluoromethyl)phenyl]mercury (85) (CI)
15. di[2,4,6-tris(trifluoromethyl)phenyl]mercury (85) (NI)
16. di[2,4,6-tris(trifluoromethyl)phenyl]mercury (85)
17. 2,4,6-tris(trifluoromethyl)biphenyl (86)
18. methyl-2,4,6-tris(trifluoromethyl)benzoate (123)
19. 2-[2,4,6-tris(trifluoromethyl)phenyl]-ethanol (128)
20. 2-[2,4,6-tris(trifluoromethyl)phenyl]-ethanol (128) (CI)
21. p-chloropentafluoroethylbenzene
22. o-chloropentafluoroethylbenzene

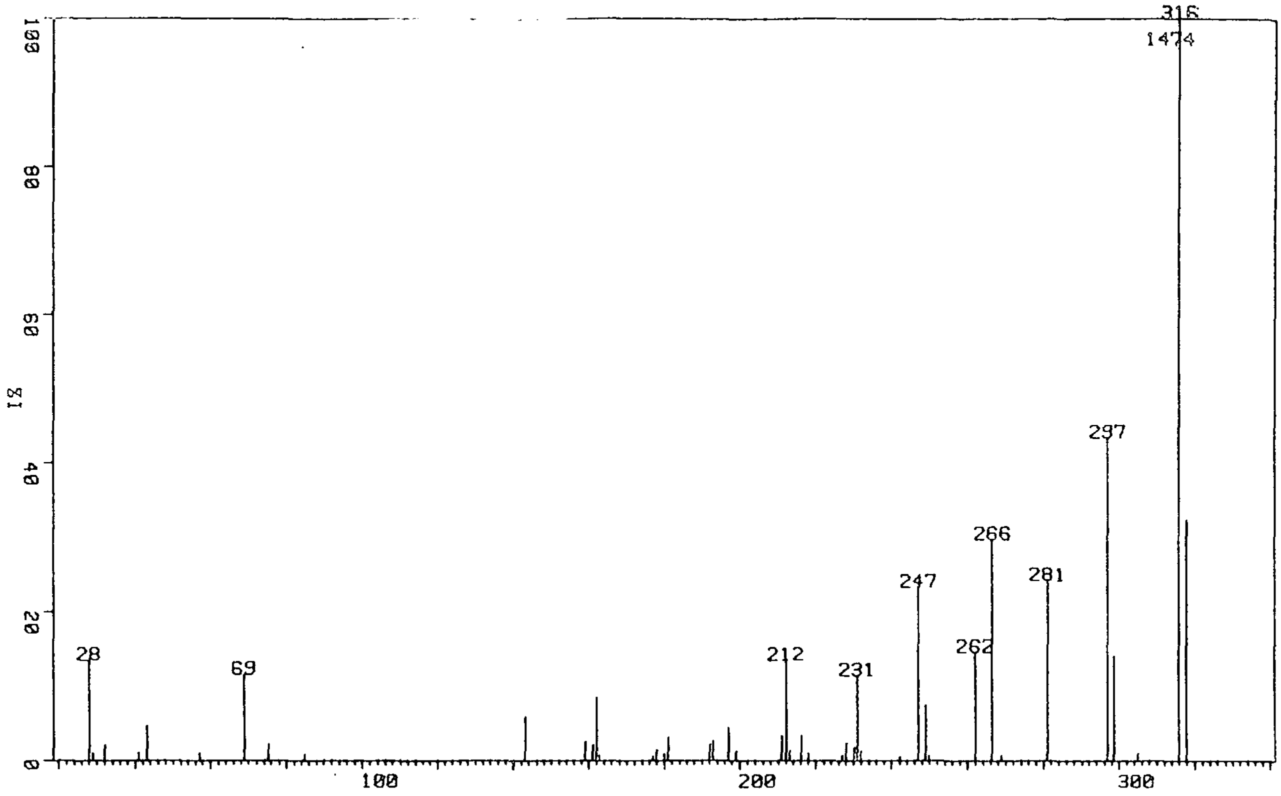


PEAK NO.	MASS	%HT. BASE
1	28.06	2.87
2	30.84	0.51
3	31.95	0.56
4	49.87	0.37
5	68.96	4.95
6	75.07	0.42
7	99.92	0.42
8	118.95	2.78
9	125.04	0.34
10	126.91	0.39
11	144.01	0.48
12	155.99	0.59
13	168.91	0.42
14	174.95	1.15
15	176.87	0.42
16	193.95	3.26
17	194.93	0.28
18	204.95	0.56
19	224.92	2.22
20	242.89	0.42
21	243.88	7.16
22	244.95	0.93
23	245.81	1.40
24	261.91	0.48
25	262.94	0.59
26	293.89	21.89
27	294.96	2.33
28	311.90	0.96
29	312.91	5.25
30	313.91	0.70
31	324.94	0.45
32	330.89	0.42
33	343.92	1.49
34	362.78	100.00
35	363.88	11.77
36	364.64	3.46
37	380.89	0.65
38	412.94	6.72
39	413.89	0.84
40	431.95	2.84
41	433.01	0.34

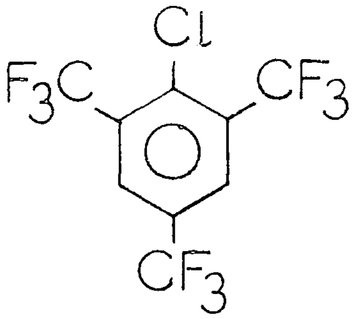


(1)

GC125X 74   G.CARR   12-APR-85
CAL:CALM21   STA: 12:8



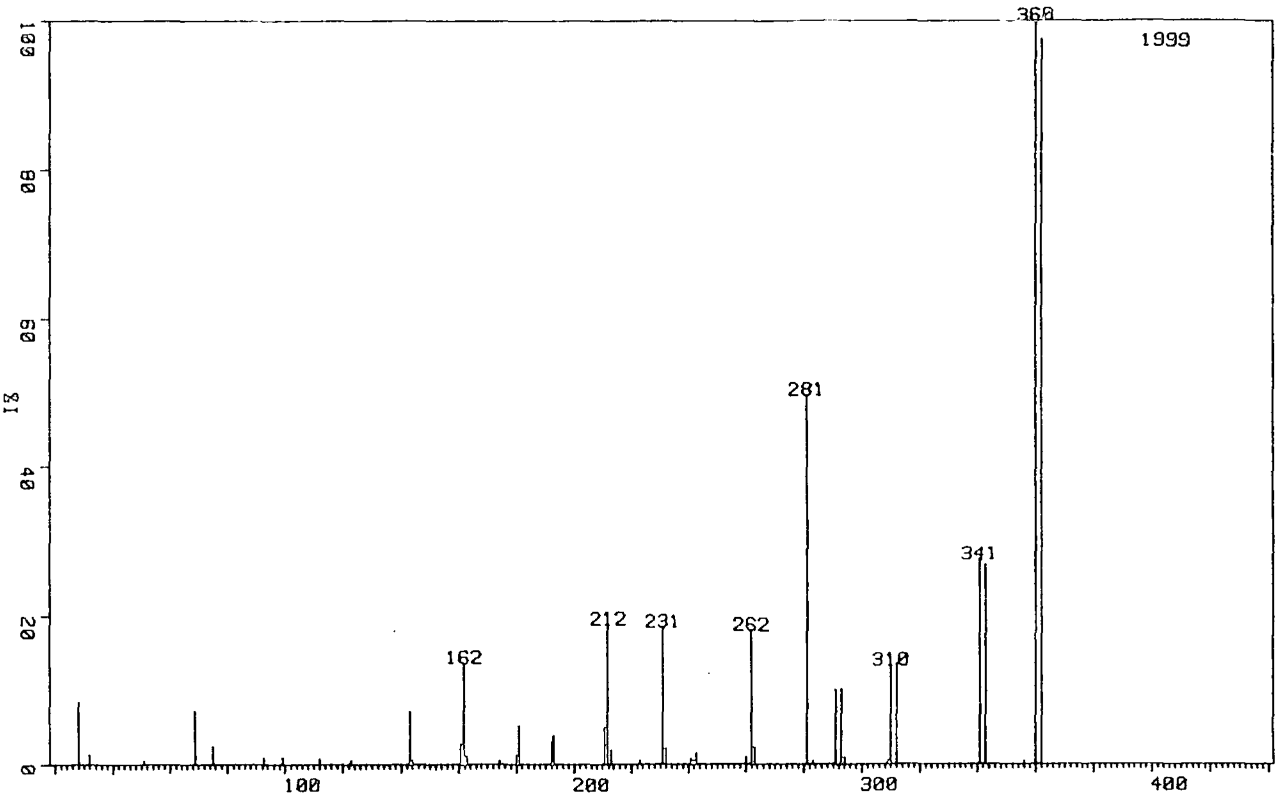
MASS	%HT. BASE
28.13	13.50
29.02	1.02
32.01	2.10
40.98	1.09
43.15	4.68
57.14	1.02
68.96	11.60
75.07	2.24
85.00	0.88
142.98	5.97
158.96	2.58
160.94	2.17
161.95	8.55
162.95	0.75
176.96	0.61
177.96	1.49
179.91	0.95
180.93	3.19
191.93	2.24
192.98	2.71
196.92	4.41
198.88	1.29
210.94	3.39
211.96	13.57
212.97	1.42
215.99	3.39
217.99	1.09
227.00	0.75
227.98	2.37
229.95	1.90
230.98	11.47
231.96	1.29
242.00	0.54
246.98	23.34
248.88	7.46
249.89	0.75
261.96	14.59
266.42	29.78
268.92	0.75
280.99	24.22
296.82	43.42
298.55	14.04
304.95	1.02
315.84	100.00
317.74	32.50



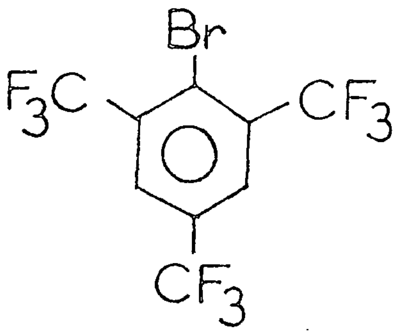
(2)

G118RX 78 G.CARR
CAL:CALM7 STA:

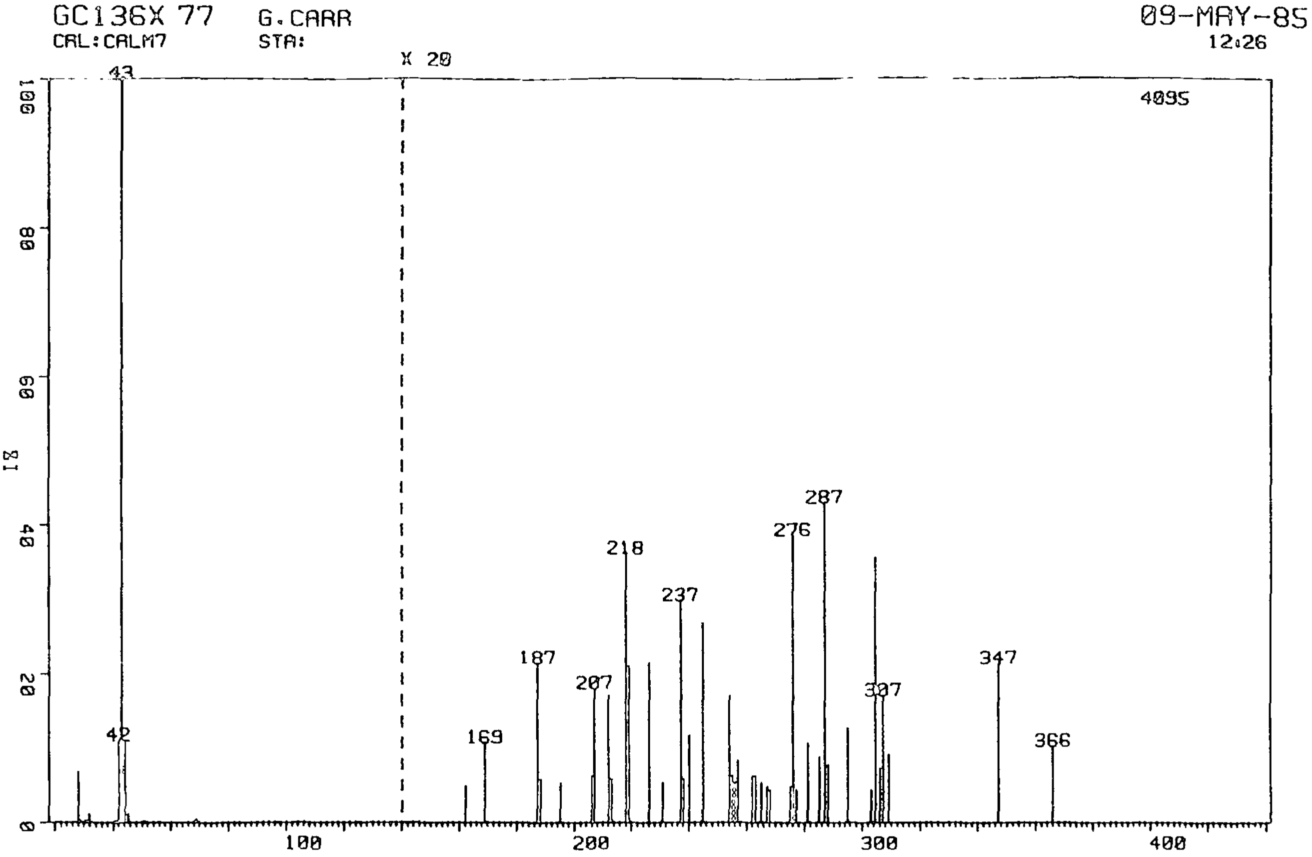
09-MAY-85
12:33



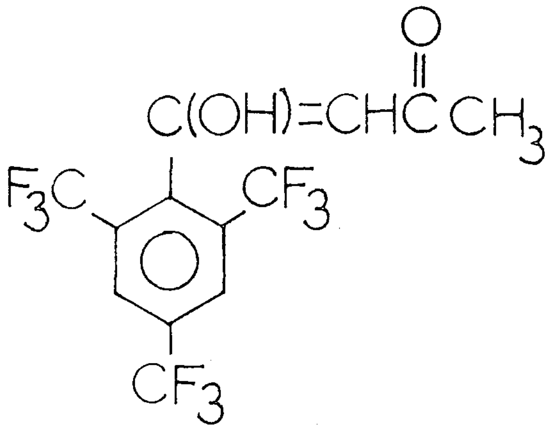
	%HT. BASE
68.97	7.25
75.09	2.45
93.04	1.00
98.98	1.00
112.01	0.80
122.99	0.65
143.04	7.15
144.04	0.55
160.97	2.85
161.98	13.66
163.01	1.15
174.04	0.55
179.94	1.35
180.97	5.25
191.97	3.10
192.99	3.95
210.91	5.10
211.96	18.91
212.94	1.95
223.00	0.50
230.83	18.51
232.02	2.15
240.95	0.85
241.98	0.55
242.98	1.45
259.96	1.00
261.83	18.06
263.03	2.30
281.09	49.57
283.05	0.45
290.97	10.11
292.86	10.26
294.03	0.95
309.04	0.50
310.02	13.36
311.97	13.56
340.87	27.56
342.85	26.91
356.18	0.45
360.01	100.00
362.12	97.55



(3)



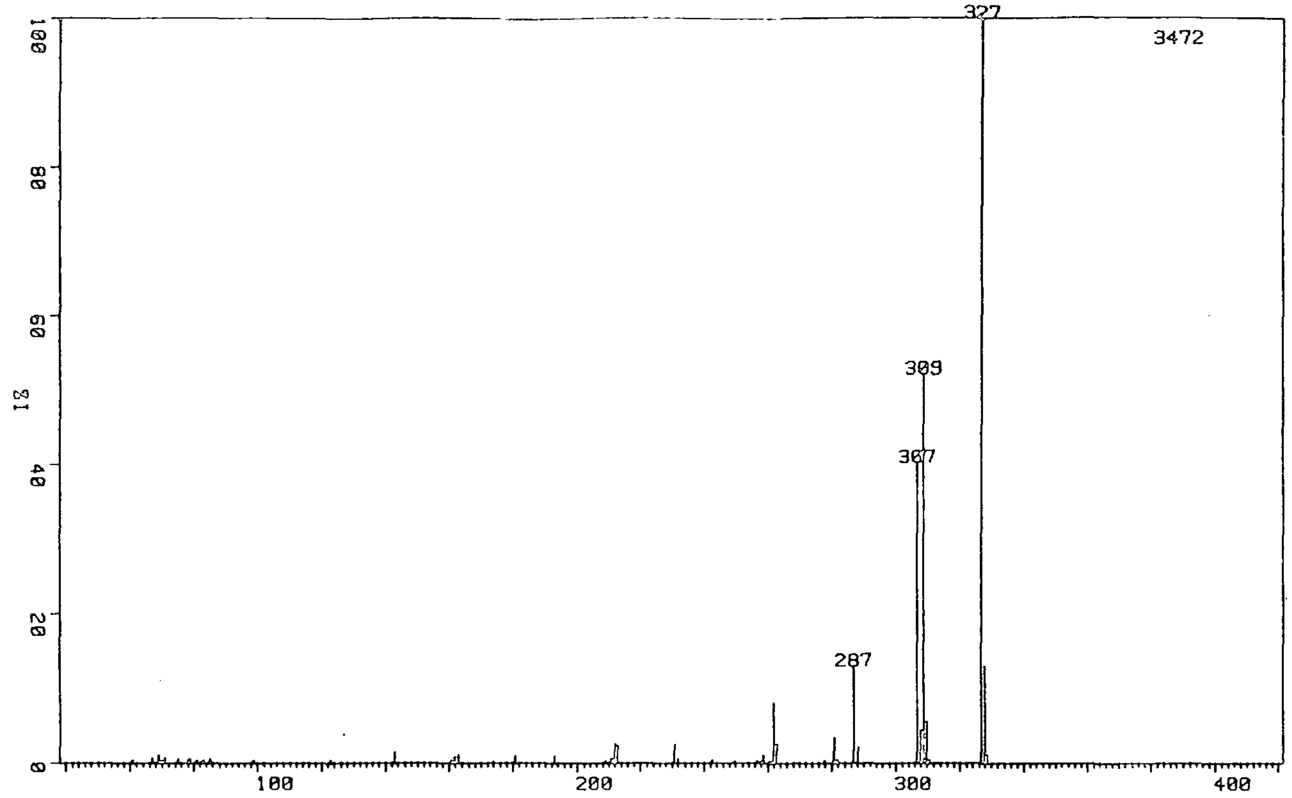
MASS	%HT. BASE
28.06	6.84
28.94	0.27
30.86	0.22
31.94	1.12
40.92	0.27
40.96	0.24
42.02	11.01
42.19	0.22
42.23	0.27
42.27	0.27
43.09	100.00
43.97	0.20
44.12	10.74
45.14	1.15
50.92	0.22
68.98	0.37
162.00	0.24
169.02	0.54
187.03	1.07
188.03	0.29
195.03	0.27
206.07	0.32
207.03	0.90
211.96	0.85
213.05	0.29
218.00	1.81
219.02	1.05
226.08	1.07
230.99	0.27
237.03	1.49
238.02	0.29
239.96	0.59
245.04	1.34
254.03	0.85
255.02	0.32
256.05	0.27
257.04	0.42
261.96	0.32
263.03	0.32
265.00	0.27
267.01	0.24
267.94	0.22
275.04	0.24
276.06	1.93
277.04	0.22
281.05	0.54
285.07	0.44
287.03	2.15
288.09	0.39
295.05	0.63
303.02	0.22
304.46	1.78
306.05	0.37
307.08	0.85
309.02	0.46
347.01	1.07
366.08	0.51



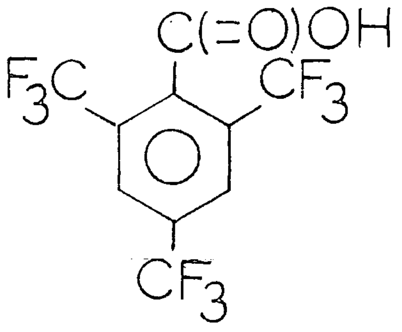
(4)

GC134X 5 G.CARR I-BU CI
CAL:CALT20 STA:

03-OCT-85
0:52

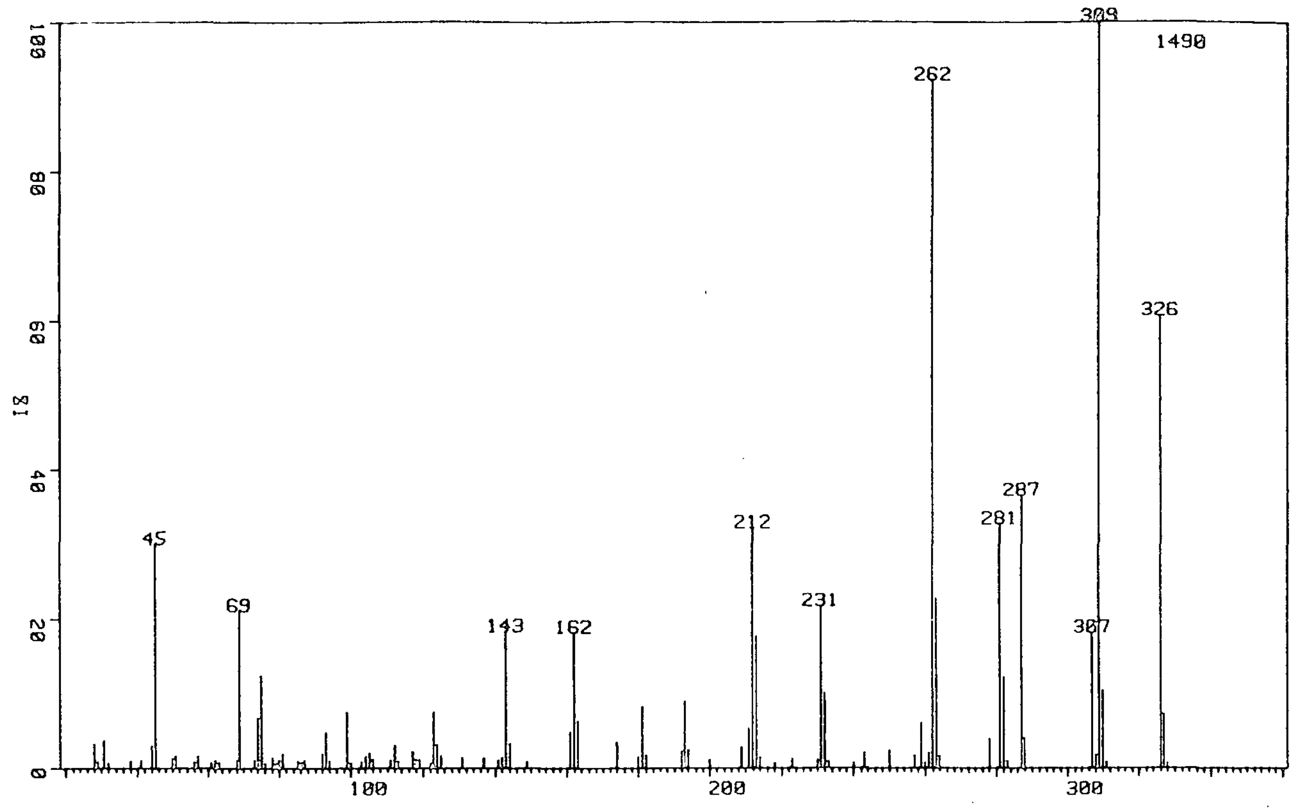


MASS	%HT. BASE		
60.89	0.43	256.74	0.29
67.01	0.66	258.72	1.04
68.94	1.09	260.71	0.35
69.88	0.32	261.73	8.09
70.93	0.72	262.77	2.59
74.95	0.43	277.74	0.32
77.94	0.46	280.71	3.49
78.90	0.58	281.74	0.40
80.92	0.40	286.72	13.02
83.01	0.40	288.01	2.16
85.05	0.58	306.68	40.32
98.84	0.40	307.67	4.49
122.83	0.43	308.66	52.10
142.79	1.56	309.65	5.62
160.76	0.43	310.66	0.43
161.80	0.86	326.63	99.97
162.85	1.18	327.65	13.05
173.87	0.35	328.65	1.18
180.81	1.01		
192.86	1.04		
208.80	0.32		
210.77	0.60		
211.79	2.59		
212.82	2.36		
230.73	2.53		
231.80	0.60		
242.77	0.43		
249.72	0.32		

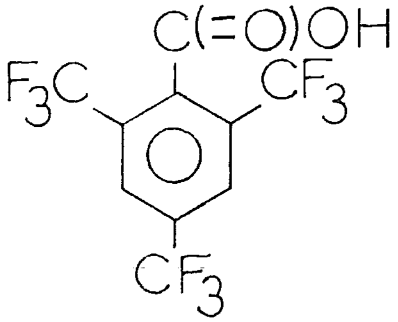


(5)

GC134X 8 G.CARR EI 03-OCT-85
CAL:CALT20 STA: 1:23



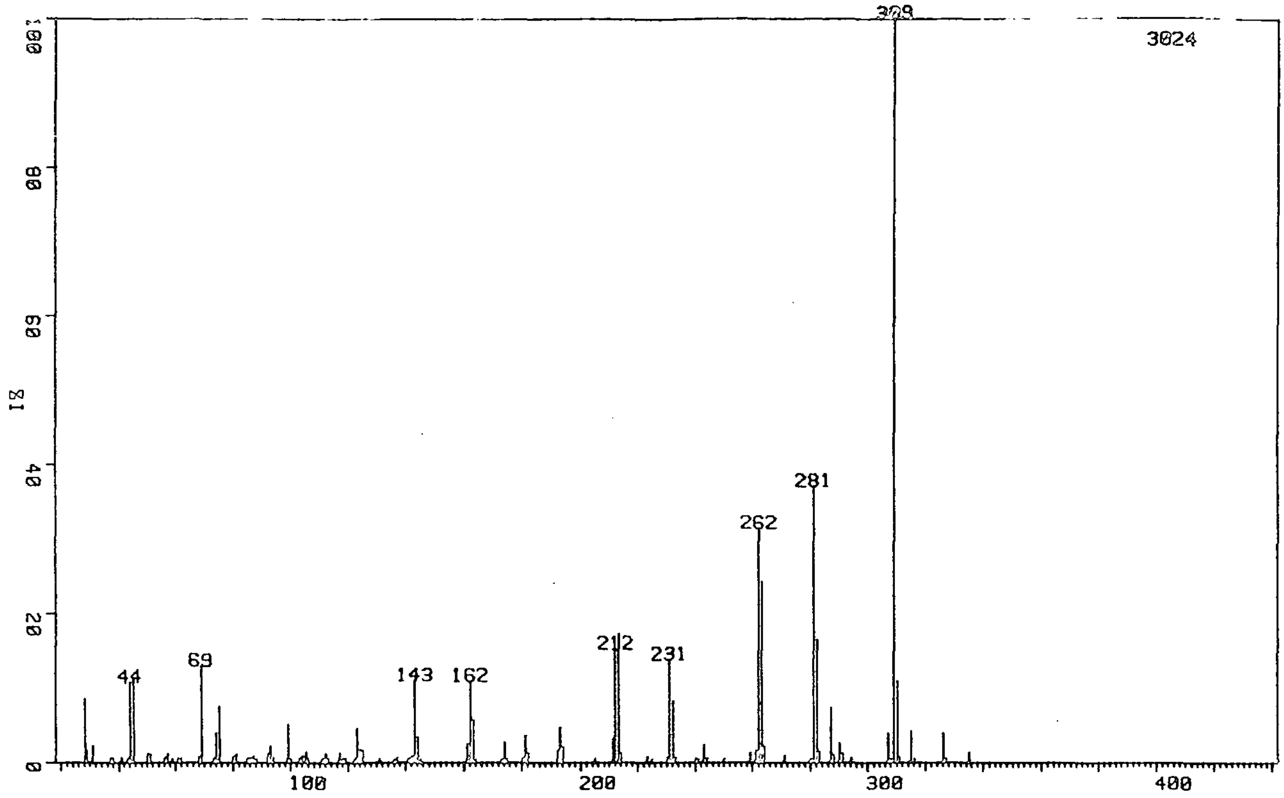
MASS	%HT. BASE
28.11	3.22
44.06	3.09
45.08	30.07
68.93	21.14
73.00	1.07
74.03	6.85
75.03	12.48
92.99	4.90
98.93	7.52
122.95	7.52
123.97	3.15
142.98	18.32
144.00	3.22
160.90	4.90
161.94	18.19
162.96	6.38
173.93	3.56
179.85	1.54
180.91	8.26
181.94	1.74
191.91	2.35
192.92	8.99
193.95	2.48
199.88	1.14
208.91	2.75
210.90	5.37
211.94	32.15
212.95	17.58
230.91	21.74
231.95	10.07
258.89	6.11
259.92	0.74
260.92	2.08
261.94	92.28
262.95	22.82
263.97	1.68
277.92	3.96
280.89	32.75
281.95	12.28
282.96	1.01
286.94	36.51
287.92	4.09
306.91	18.19
307.90	1.81
308.89	100.00
309.88	10.40
310.92	0.87
325.94	60.67
326.93	7.32
327.93	0.74



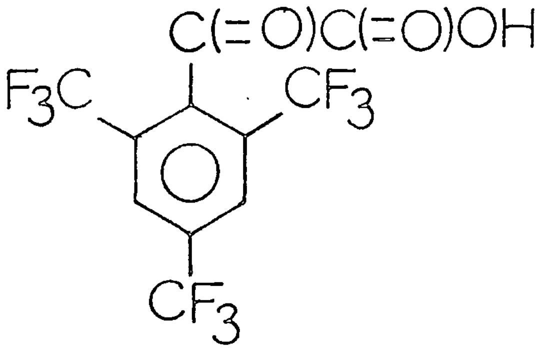
(6)

GC150X 5 G.CARR EI
CAL:CALT1 STA:

273
29-AUG-85
0:51

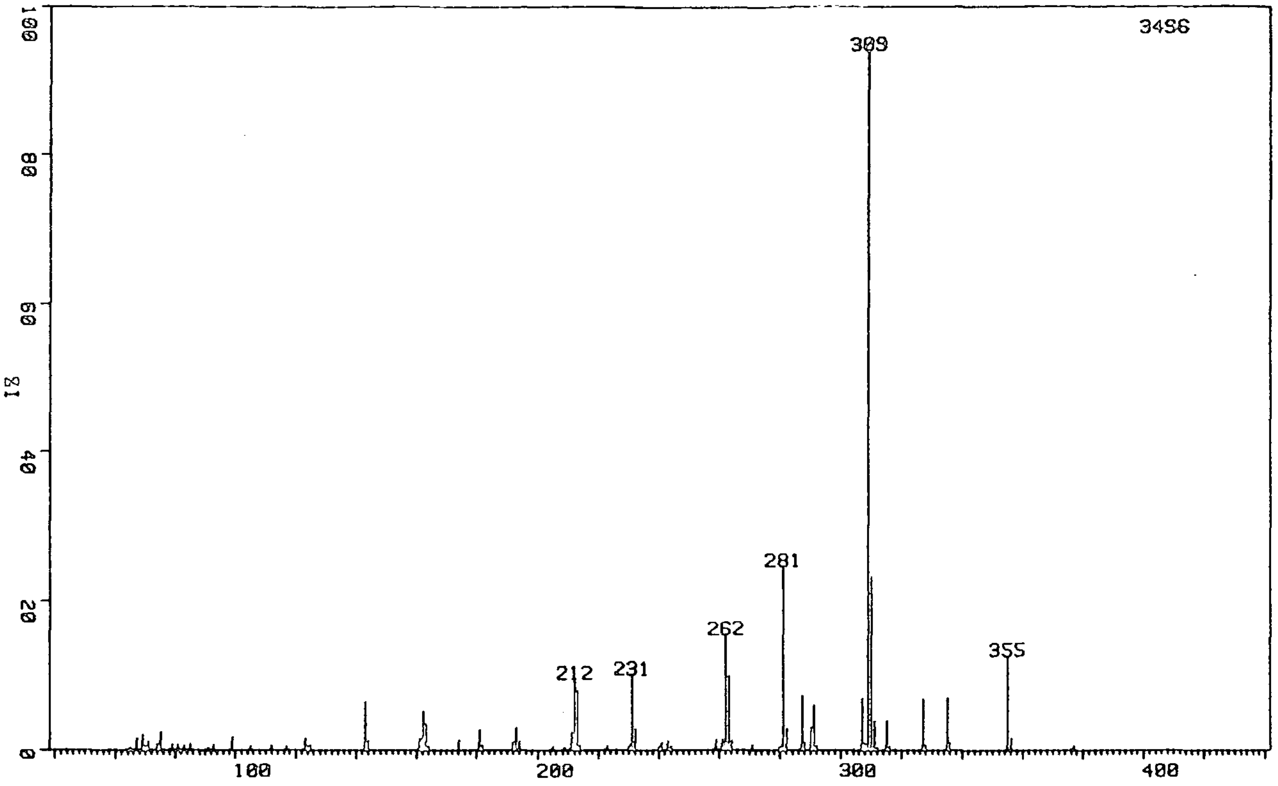


MASS	%RI. BASE
44.12	10.85
45.13	11.08
68.98	12.75
143.02	11.04
144.03	3.47
145.03	0.36
160.98	2.58
162.01	10.95
163.03	5.75
164.03	0.40
173.00	0.40
174.01	2.74
175.02	0.43
179.94	0.60
180.97	3.70
181.99	1.42
191.98	1.79
193.01	4.79
194.02	2.15
205.01	0.46
210.97	3.31
211.96	15.31
213.01	17.43
214.00	1.42
222.98	0.86
224.97	0.43
229.93	0.83
230.97	13.89
231.98	8.37
258.97	1.45
260.96	1.75
261.98	31.48
262.99	24.34
264.01	2.28
270.95	0.99
279.92	0.43
280.96	37.04
281.97	16.57
282.98	1.52
286.97	7.37
287.95	1.09
289.92	2.68
290.96	1.36
293.96	0.69
306.94	4.07
307.93	0.56
308.92	100.00
309.92	11.04
310.91	0.83
314.96	4.33
315.96	0.56
325.94	4.00
326.93	0.53
334.94	1.46

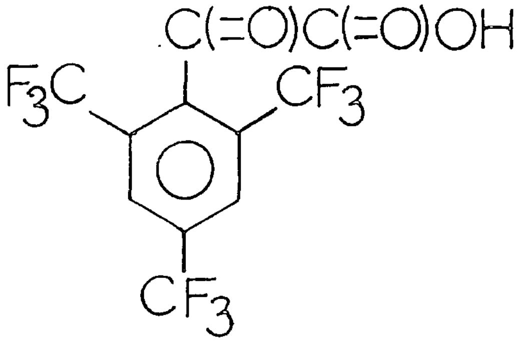


(7)

GC150X 8 G.CARR CI I.BU 29-AUG-85
CAL:CALT1 STA: 1:16

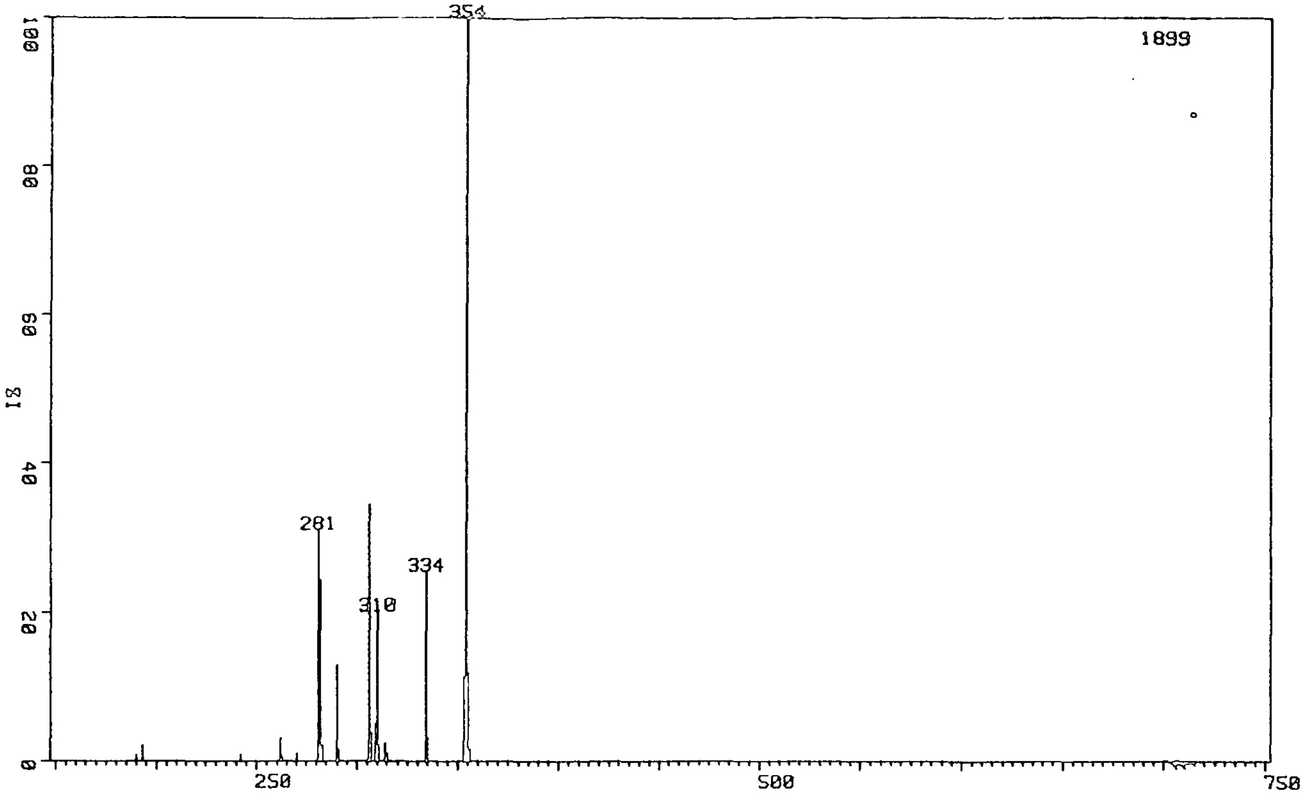


MASS	%HT. BASE		
		270.88	0.74
142.89	6.46	279.88	0.40
143.94	1.34	280.90	24.71
160.84	1.57	281.91	2.92
161.91	5.26	284.91	7.32
162.93	3.60	287.90	1.03
210.87	2.46	289.92	3.12
211.92	9.58	290.89	6.09
212.93	8.04	291.96	0.60
213.94	0.72	306.91	6.95
222.90	0.51	307.90	0.97
229.85	0.54	308.89	94.28
230.89	10.15	309.91	23.34
231.95	2.92	310.92	3.98
239.90	0.40	311.95	0.34
240.91	1.06	314.94	4.00
242.94	1.29	315.93	0.49
243.95	0.54	326.92	6.89
258.91	1.43	327.92	0.77
260.89	1.43	334.89	7.01
261.93	15.56	335.91	1.00
262.95	9.90	354.87	12.64
263.93	1.34	355.92	1.66

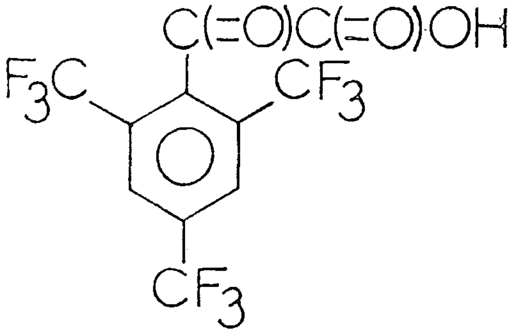


(8)

GC150X 11 G.CARR NEG I.BU 29-AUG-85
CAL:CALN1 STA: 1:51

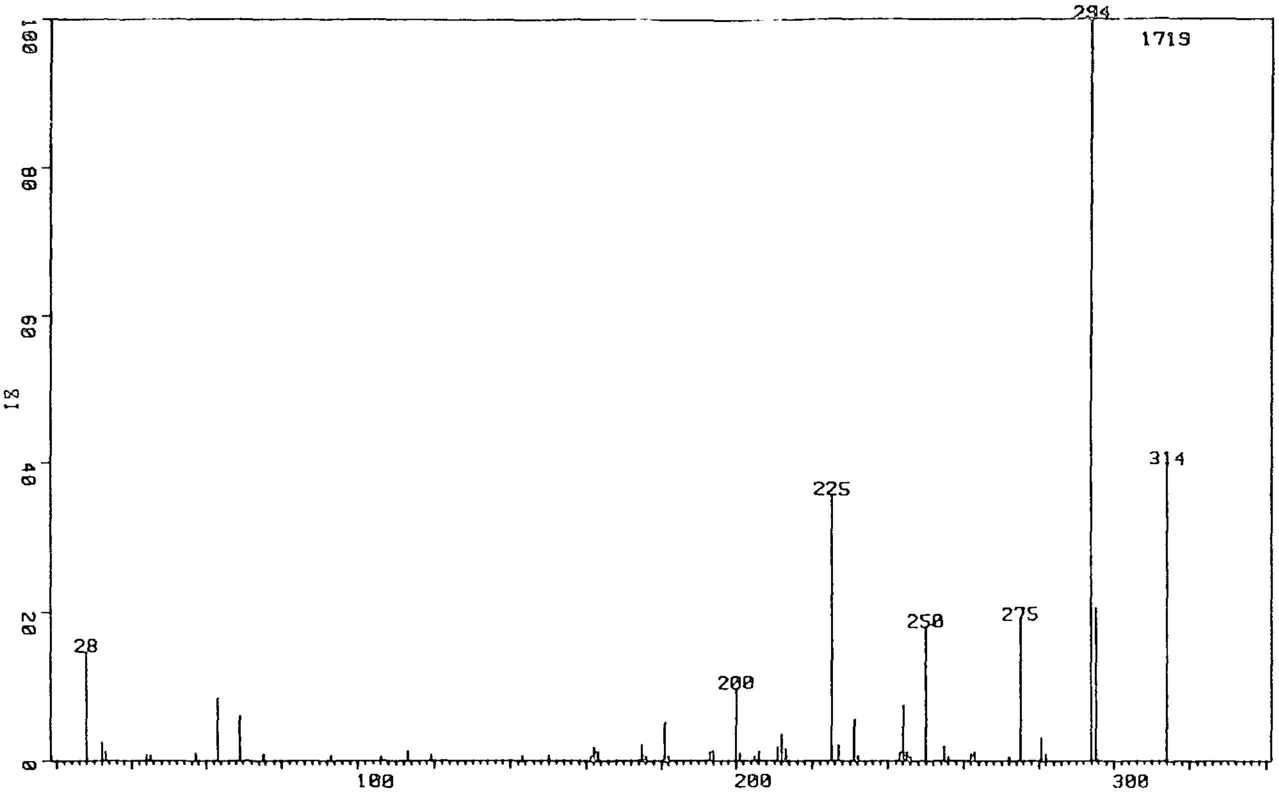


MASS	%HT. BASE
281.02	31.17
282.03	24.38
283.05	2.21
290.03	12.95
291.02	1.47
306.04	34.49
307.04	3.74
309.03	5.11
310.00	20.17
311.03	2.16
314.03	2.47
315.03	1.00
334.05	25.59
335.05	3.16
353.04	11.37
354.06	100.00
355.08	11.95
356.07	1.58

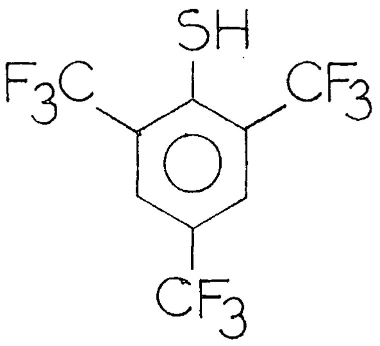


(9)

GC156X 21 G.CARR 24-SEP-85
CAL:CALM1S STA: 3:12

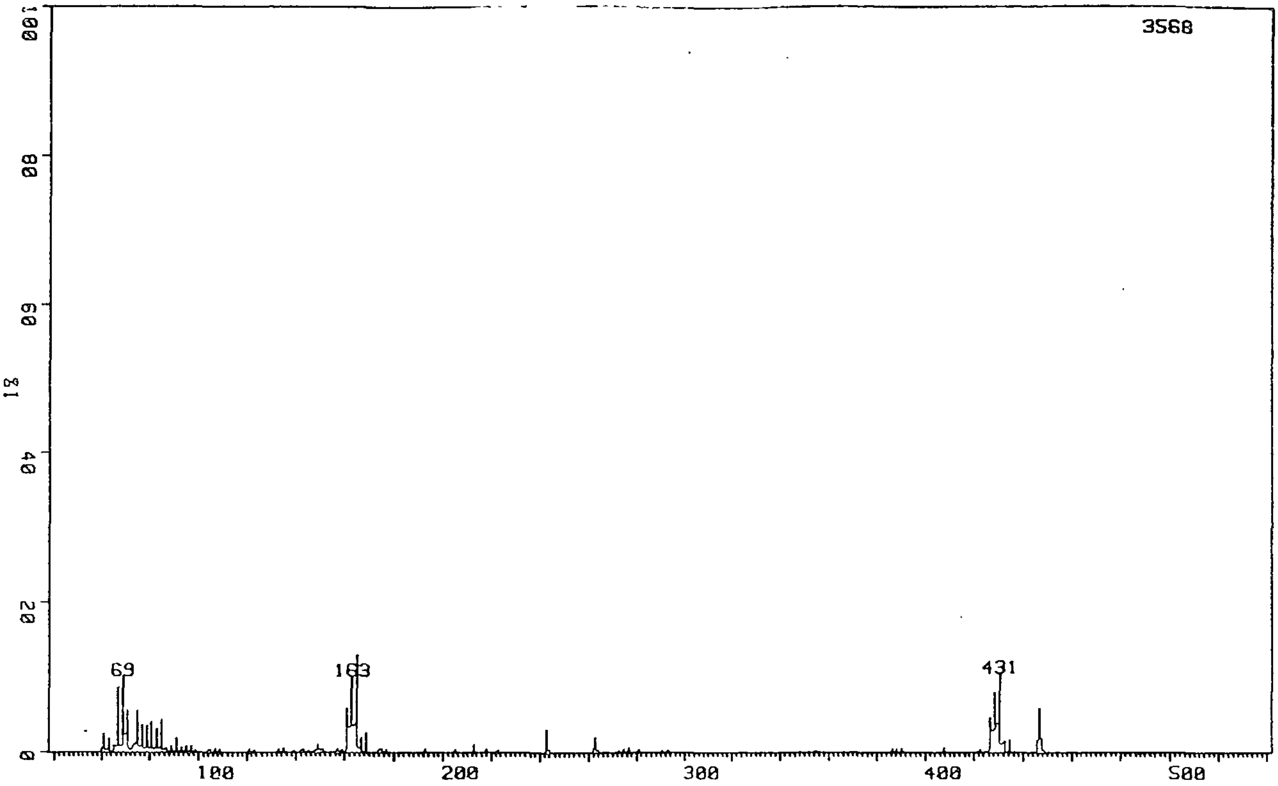


MASS	%HT. BASE
28.07	14.72
31.96	2.62
33.03	1.34
44.12	0.99
45.12	0.81
57.19	1.11
63.09	8.55
69.05	6.11
75.18	0.99
93.11	0.81
106.12	0.64
113.07	1.40
119.07	0.81
143.18	0.76
150.06	0.76
161.17	0.52
162.14	1.86
163.12	1.22
175.06	2.15
176.04	0.64
181.07	5.29
182.11	0.70
193.11	1.28
194.08	1.34
200.04	9.71
201.09	1.11
205.07	0.64
206.09	1.28
211.08	1.98
212.10	3.66
213.05	1.69
225.15	35.72
227.04	2.15
231.10	5.70
232.18	0.76
243.11	1.16
244.08	7.45
245.08	1.16
246.12	0.52
250.03	18.09
255.05	2.09
256.17	0.64
262.07	0.99
263.06	1.28
272.10	0.58
275.20	19.02
280.92	3.08
281.99	0.99
293.98	100.00
295.28	20.71
314.07	39.97

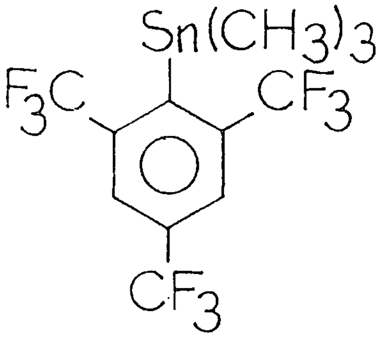


(10)

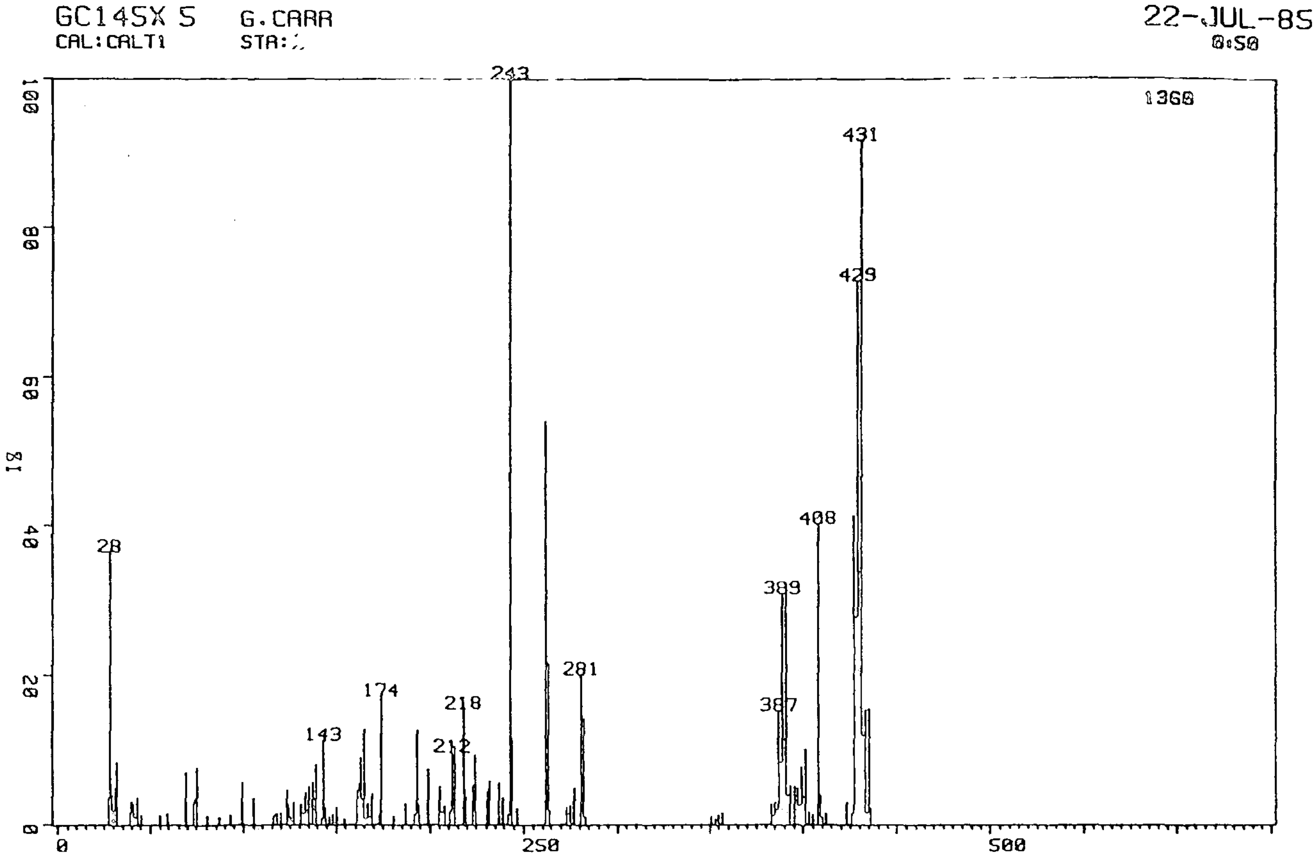
GC145X S G.CARR CI I.BU 22-JUL-85
CAL:CALT1 STA:4 0:51



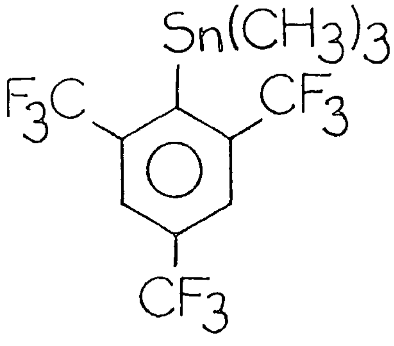
MASS	%HT. BASE
68.97	10.12
160.82	5.91
161.88	3.34
162.91	10.09
163.09	0.56
163.93	3.78
164.94	12.98
165.92	0.53
166.91	1.93
168.88	2.66
422.54	0.31
426.53	4.68
427.50	2.94
428.52	8.04
429.49	3.92
430.51	10.54
431.51	1.26
432.50	1.54
434.50	1.63
445.69	1.65
446.66	5.94
447.68	1.93
448.69	0.34



(11)

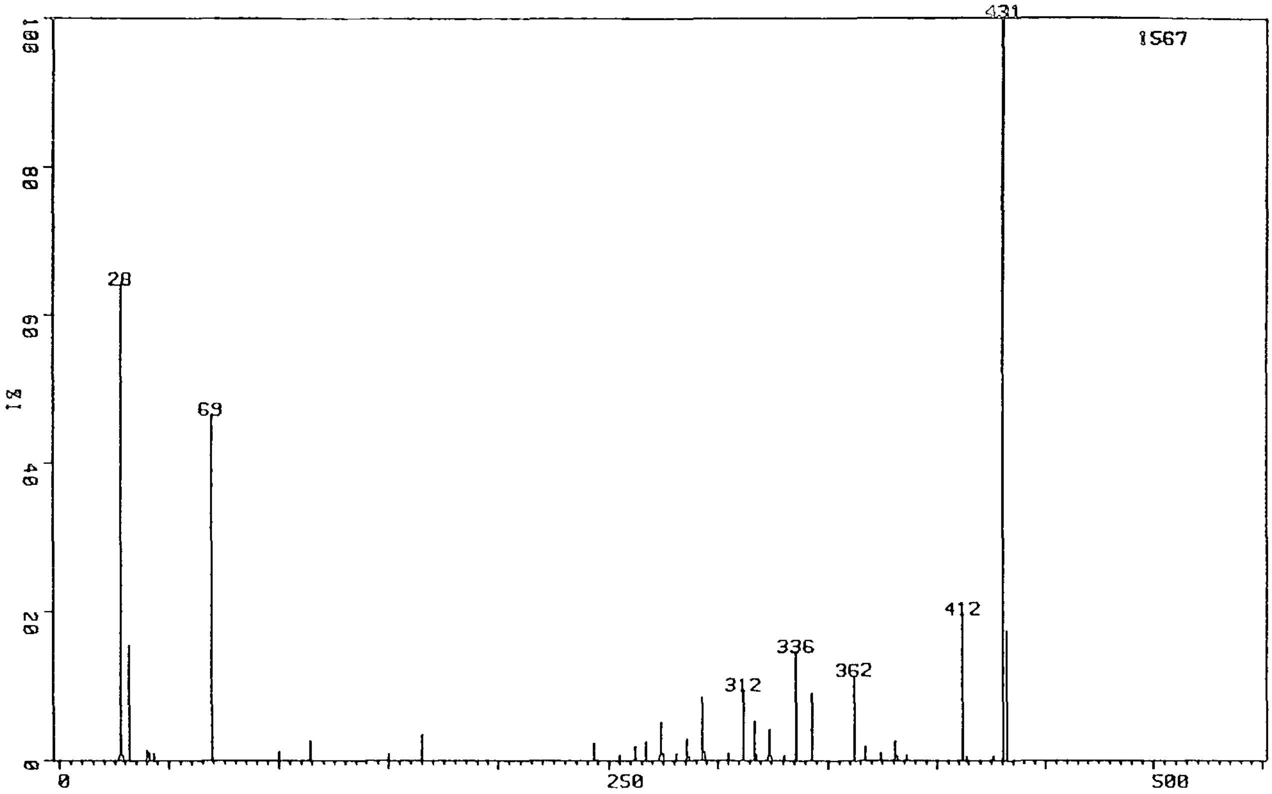


MASS	%HT. BASE
143.07	11.32
165.01	12.79
174.04	17.28
193.01	12.65
211.99	9.78
213.00	10.59
217.98	15.59
242.96	100.00
243.97	11.76
281.04	20.15
282.05	14.34
382.92	2.87
383.95	1.25
384.94	3.16
385.94	1.91
386.93	15.29
387.92	8.46
388.87	30.96
389.94	11.54
390.91	32.28
391.93	4.04
392.94	5.29
394.95	5.29
396.91	5.00
397.89	2.65
398.94	7.79
399.92	3.75
400.91	10.15
402.93	1.84
404.94	1.47
407.93	40.22
408.94	4.04
409.98	1.10
411.99	1.54
422.97	3.09
425.98	1.69
426.96	41.40
427.97	27.87
428.95	72.87
429.97	33.90
430.95	91.76
431.95	12.13
432.95	15.44
433.98	1.69
434.98	15.59
435.98	2.35

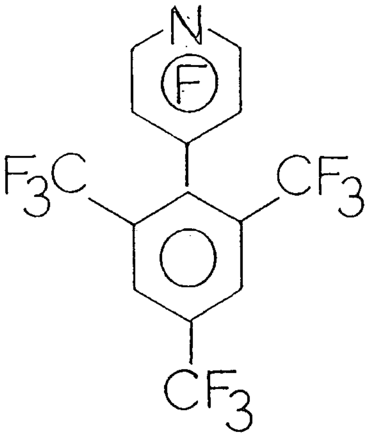


(12)

GC154X 29　G.CARR　07-AUG-85
CAL:CALM31　STA:　4:51

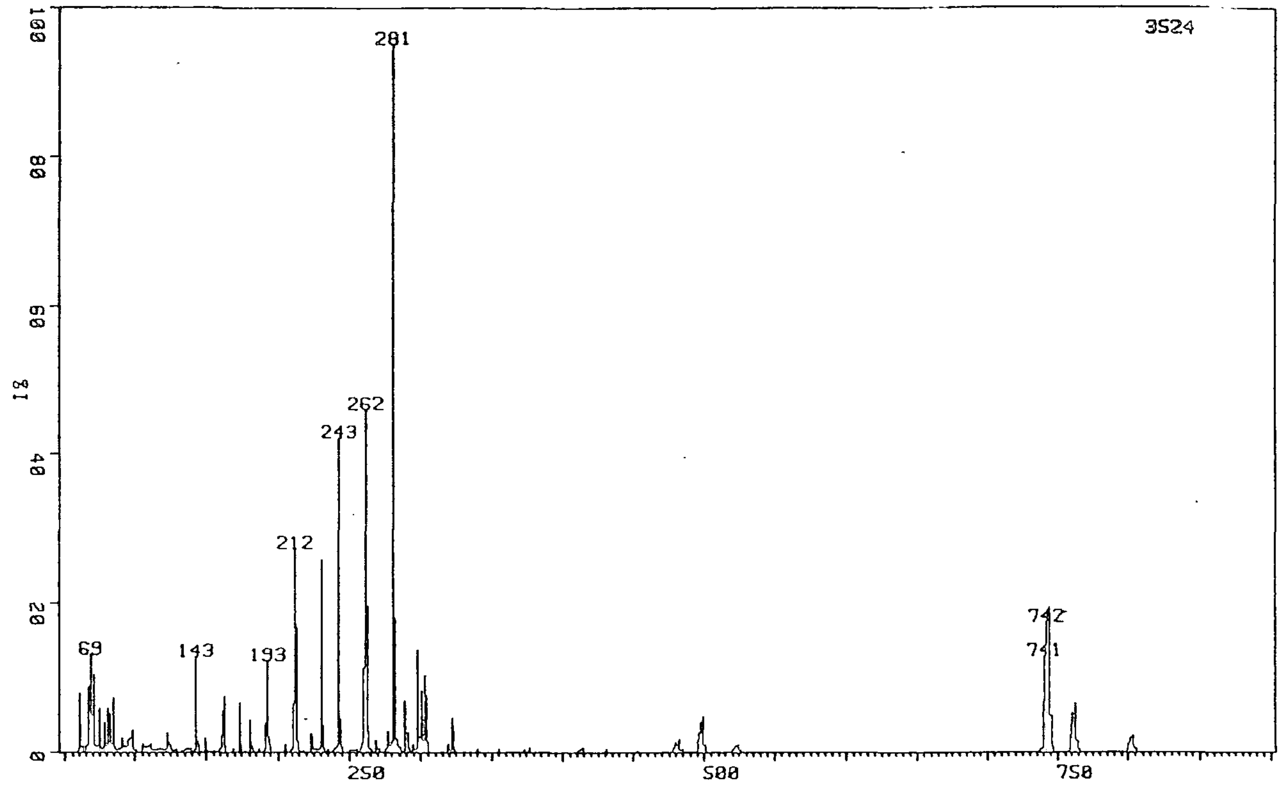


MASS	%HT. BASE		
27.05	0.70		
27.96	64.01		
28.87	0.77		
31.91	15.51		
39.84	1.47		
41.01	1.08		
43.18	1.02	317.02	5.42
69.01	46.39	318.02	0.83
100.03	1.28	323.21	0.57
114.12	2.74	323.98	4.28
150.06	0.96	325.00	0.64
165.19	3.51	331.03	0.77
243.19	2.43	336.09	14.61
255.21	0.83	342.91	9.19
262.14	1.98	362.06	11.36
267.05	2.62	366.98	1.98
273.12	0.64	374.06	1.08
274.00	5.23	381.05	2.68
275.08	1.02	382.14	0.64
281.10	1.02	386.11	0.83
286.01	3.06	412.01	19.66
287.08	0.64	414.04	0.64
292.83	8.62	426.17	0.64
294.03	1.21	430.70	100.00
304.99	1.08	432.27	17.55
312.02	9.38		

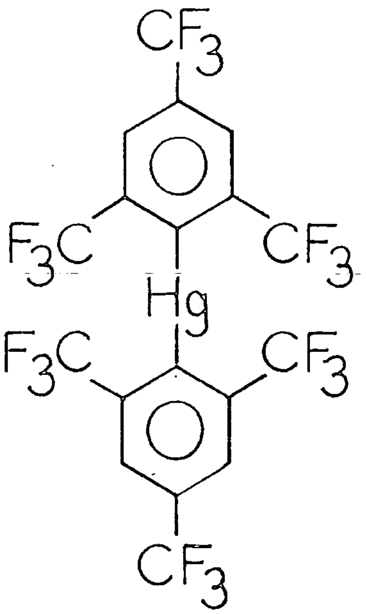


(13)

GC156X 4 G.CARR CI I.BU 23-JUL-85
CAL:CALT1 STA: 0:42

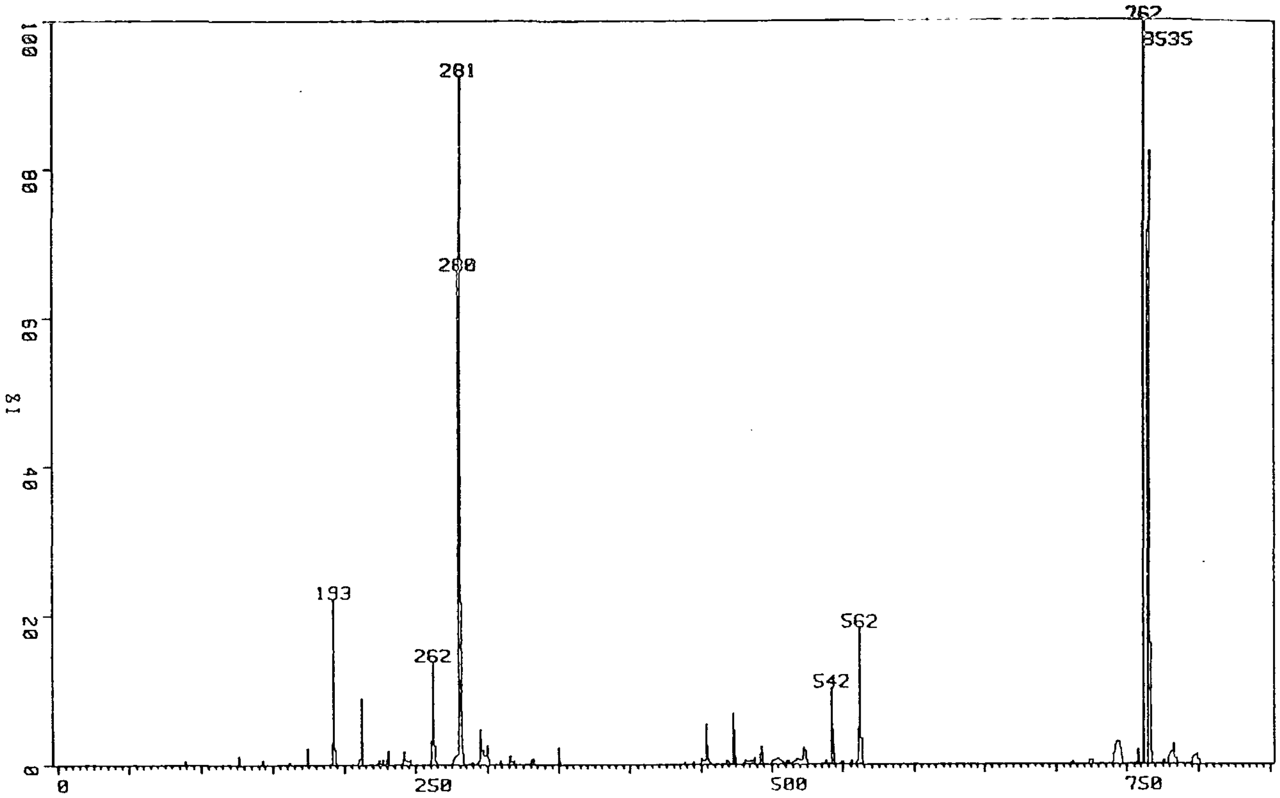


MASS	%HT. BASE				
68.97	12.98				
69.93	4.35				
70.98	10.32				
142.88	12.67				
191.88	3.92				
192.93	12.20	499.38	4.85		
193.94	2.16	500.42	0.59		
194.97	1.15	501.37	1.07		
210.86	6.48	520.31	0.48		
211.91	27.00	521.31	0.62		
212.92	16.54	522.36	1.04		
213.93	1.51	523.35	0.64		
230.90	25.57	524.36	1.09		
231.94	3.59	526.36	0.34		
242.92	41.69	737.76	0.39		
243.93	4.49	738.74	0.42		
259.91	11.13	739.72	6.62		
260.86	11.27	740.77	12.73		
261.91	45.42	741.82	17.27		
262.92	19.34	742.86	11.66		
280.88	93.94	743.89	19.26		
281.92	17.77	744.84	4.01		
478.45	0.59	745.81	4.91		
479.38	1.12	746.88	0.87		
480.33	1.37	758.83	2.24		
481.39	0.93	759.78	3.73	799.66	0.81
482.36	1.77	760.80	5.16	800.64	1.32
484.44	0.45	761.82	3.84	801.63	1.93
495.42	1.65	762.85	6.50	802.71	1.21
496.40	2.66	763.86	1.60	803.66	2.24
497.40	3.95	764.85	1.49	804.74	0.50
498.39	2.66	765.84	0.36	805.77	0.53

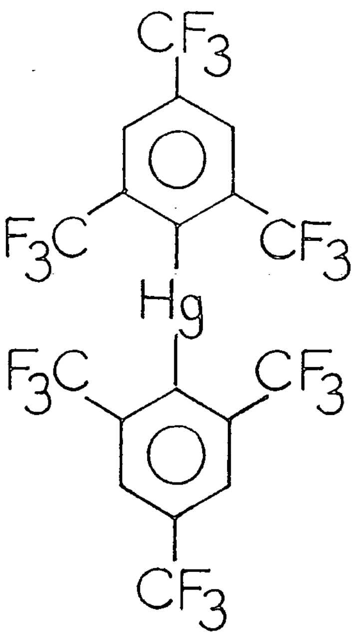


(14)

GC156X 0 G.CARR NEG. I.BU 23-JUL-85
CAL:CALN1 STA: 5 0:6



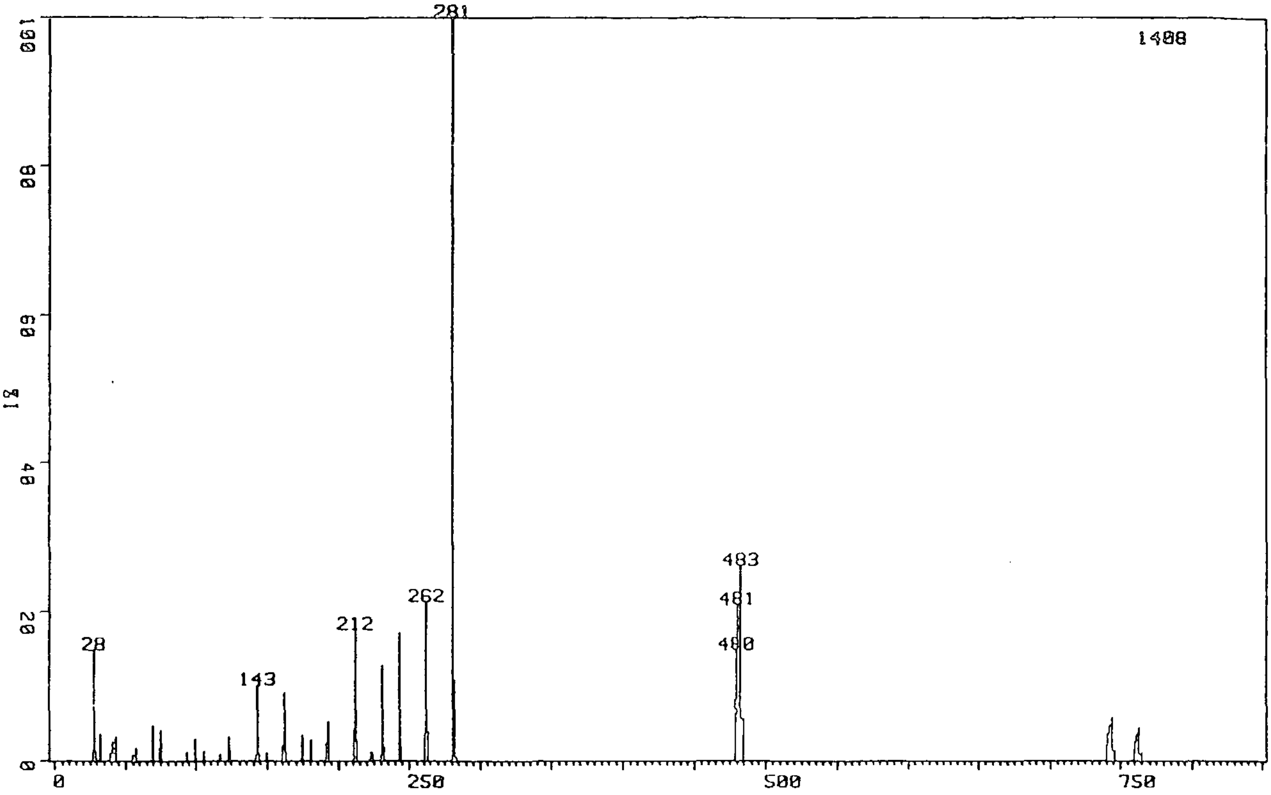
MASS	%HT. BASE
193.02	22.26
194.02	2.12
212.04	7.00
261.02	3.22
262.04	13.80
263.06	2.57
280.00	66.31
281.02	92.56
282.03	21.73
444.14	0.40
450.13	0.88
452.14	0.42
453.10	0.57
454.10	5.49
455.10	2.55
456.10	0.85
457.10	0.28
468.09	0.62
469.12	0.34
470.15	0.40
473.10	6.90
474.08	4.61
475.08	1.05
481.10	0.34
482.08	0.68
484.08	0.42
486.08	0.51
488.13	0.93
492.09	1.44
493.08	2.46
494.08	1.56
500.05	0.51
501.07	0.37
502.03	0.71
503.05	0.48
504.06	0.08
505.08	0.88
506.09	0.71
507.06	0.54
508.07	0.34
511.09	0.42
512.08	0.54
515.03	0.31
516.02	0.31
517.05	0.45
518.04	0.82
520.06	0.68
522.07	1.22
523.07	2.35
524.08	1.90
525.09	0.71
538.07	0.51
542.06	10.24
543.05	4.55
544.10	1.50
549.07	0.31
550.07	0.31
556.10	0.54
560.02	0.31
561.05	4.84
562.03	18.32
563.06	3.56
564.09	0.57
712.10	0.31
724.07	0.62
726.16	0.59
741.01	1.47
742.01	2.63
743.01	3.11
744.01	2.46
745.01	3.03
746.01	2.12
747.01	0.91
758.00	2.07
762.15	100.00
764.98	71.51
766.01	82.35
767.04	16.15
768.07	1.56
776.05	0.54
779.02	0.91
780.04	1.33
781.03	1.67
782.00	1.50
783.04	2.72
784.01	0.65
784.98	0.79
796.01	0.93
797.01	1.24
798.00	1.22
798.99	1.44
800.06	0.62
800.99	0.45



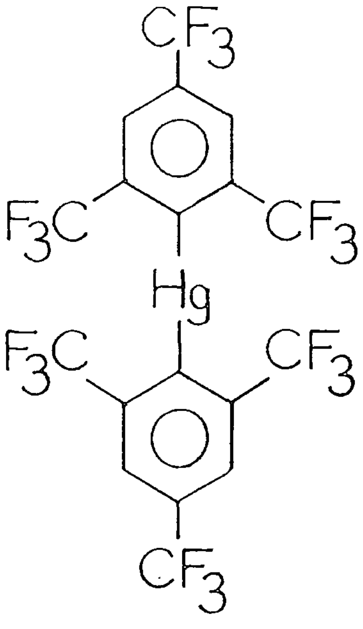
(15)

GC156X 4　G.CARR
CAL:CALT1　STA:.

23-JUL-85
0:42

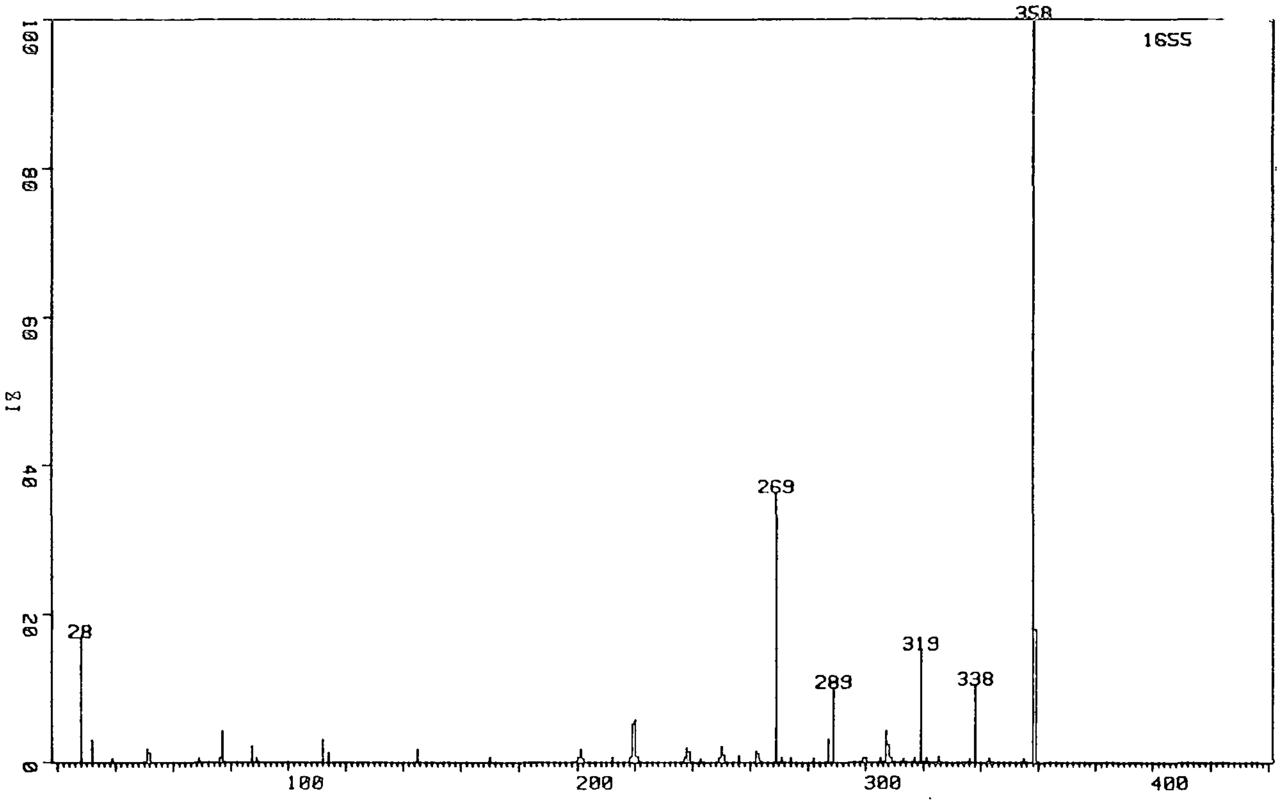


MASS	%HT. BASE				
27.30	1.49	210.85	4.33		
28.17	14.91	211.92	17.38		
29.05	1.28	212.93	2.77		
32.03	3.62	222.89	1.28		
38.99	0.99	223.94	0.92		
39.82	1.21	229.87	0.05		
40.97	2.63	230.92	12.86		
42.06	0.85	231.94	1.92		
43.13	3.34	242.93	17.26		
55.13	0.92	243.94	1.92		
57.12	1.78	260.89	3.69		
68.94	4.76	261.94	21.38		
74.05	1.78	262.95	3.98		
75.05	4.19	280.89	100.00		
93.01	1.35	281.93	10.87		
98.95	3.05	282.94	0.64		
105.02	1.42	478.54	8.24		
116.94	0.92	479.53	14.91		
122.93	3.27	480.53	20.95		
123.96	1.49	481.55	12.93		
141.91	0.85	482.53	26.21		
142.93	10.16	483.54	2.56		
143.93	0.99	484.56	3.75		
148.90	1.21	740.07	2.06		
160.86	2.13	741.06	3.76		
161.93	9.16	742.05	4.83	760.04	2.56
162.95	1.28	743.12	3.27	761.05	3.62
173.97	3.55	744.01	5.97	761.97	2.63
180.87	2.91	745.07	1.35	763.01	4.55
191.91	2.41	746.07	1.49	763.95	0.78
192.92	5.40	759.03	1.56	765.04	1.21

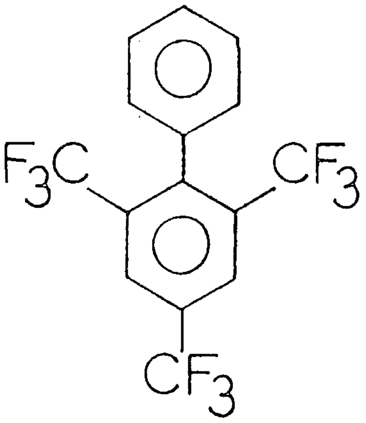


(16)

GC160X 15 G.CARR 24-SEP-85
CAL:CALM23 STA: 2:20



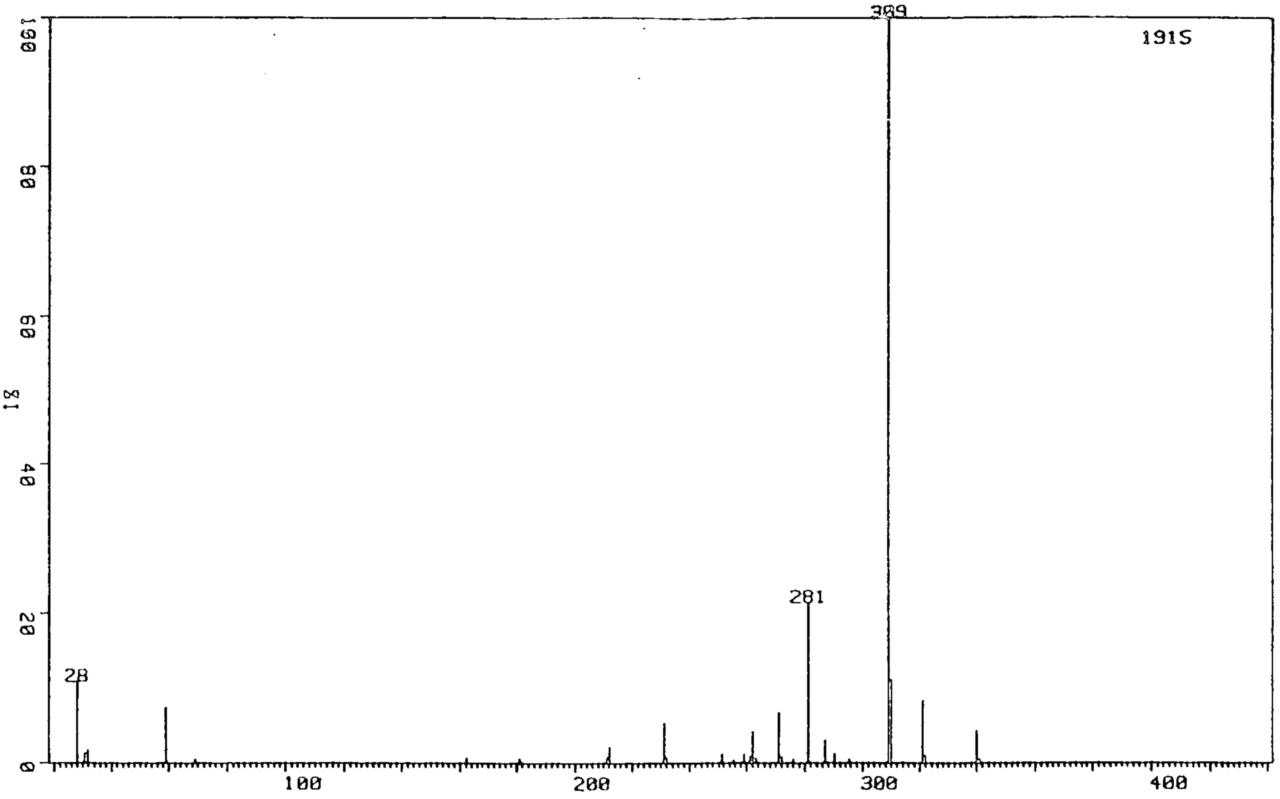
MASS	%HT. BASE
28.08	16.86
31.96	3.08
38.97	0.54
50.98	1.87
52.07	1.33
68.99	0.60
76.10	0.66
77.10	4.35
87.47	2.24
89.06	0.60
112.01	3.20
114.06	1.39
145.12	1.81
170.06	0.73
200.07	0.73
201.09	1.81
202.13	0.54
212.02	0.73
218.07	0.79
219.02	5.32
220.01	5.86
221.05	0.91
237.09	0.66
238.05	2.05
239.05	1.57
242.99	0.48
249.10	0.66
250.06	2.24
251.07	1.09
256.15	1.03
262.09	1.63
263.07	1.27
269.09	36.31
281.94	0.66
286.98	3.26
288.88	10.09
307.09	4.41
308.07	2.48
319.05	15.29
321.06	0.73
325.10	0.85
336.17	0.54
338.05	10.57
343.08	0.66
354.86	0.60
357.99	100.00
359.12	18.01



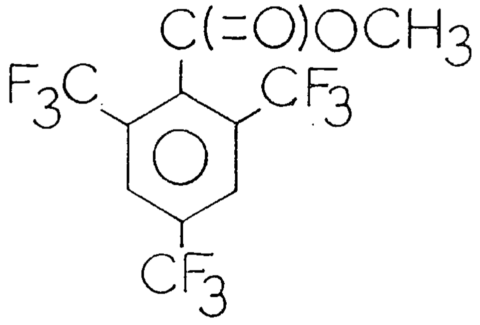
(17)

GC149X 23 G.CARR
CAL:CALM1S STA:

24-SEP-85
3:29



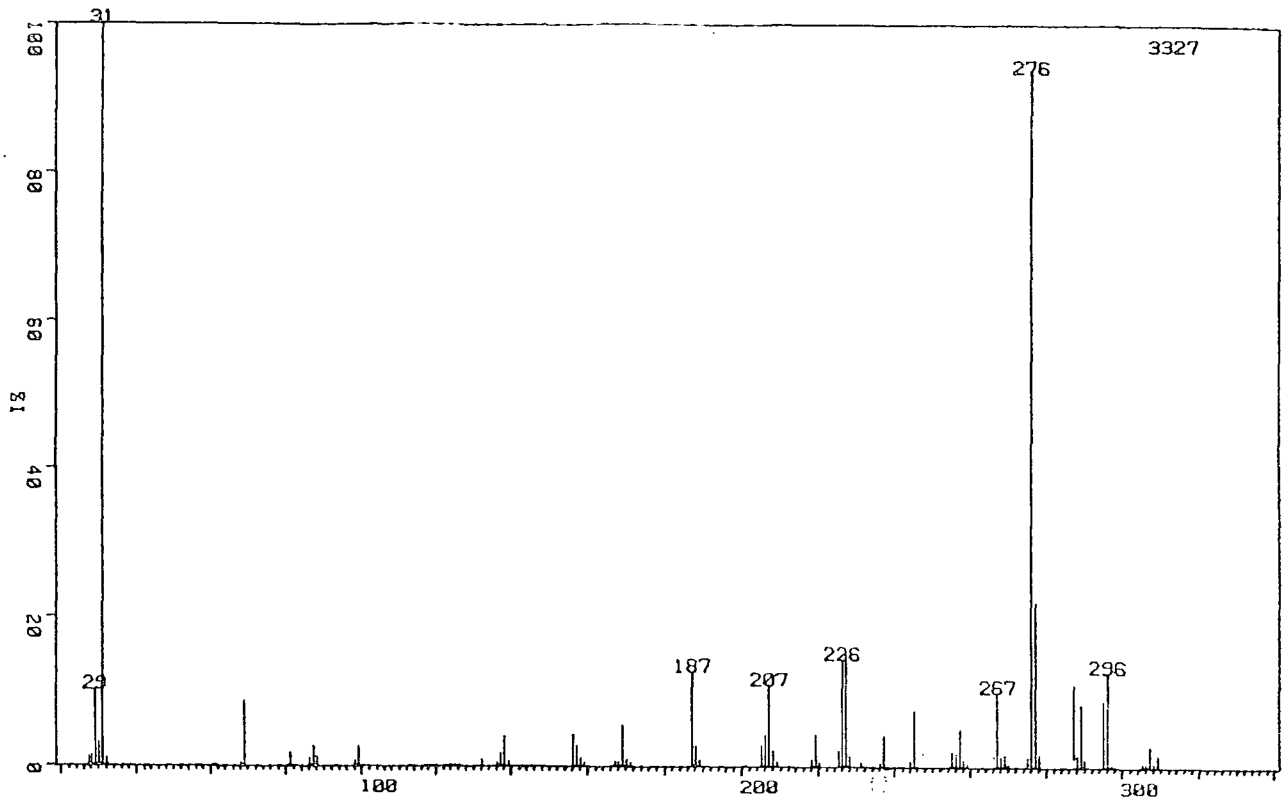
MASS	%HT. BASE
28.07	10.91
30.86	1.41
31.96	1.78
59.01	7.47
69.04	0.57
162.22	0.68
181.14	0.68
211.11	0.84
212.11	2.19
231.06	5.38
232.14	0.73
251.12	1.25
255.37	0.42
259.05	1.15
261.10	0.89
262.04	4.23
263.12	0.68
271.05	6.84
272.07	0.84
276.05	0.52
281.09	21.46
287.03	3.13
290.06	1.31
295.14	0.57
309.00	100.00
309.99	11.17
321.04	8.41
322.03	0.99
339.96	4.33
341.01	0.57



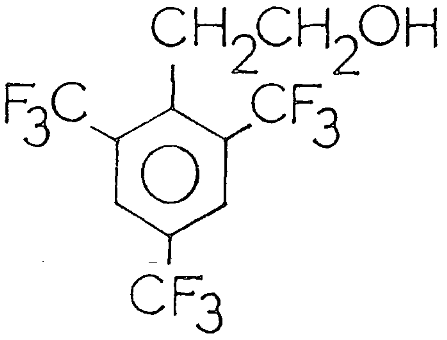
(18)

GC111X 0 G.CARR EI
CAL:CALT31 STA:

20-JAN-85
1.0

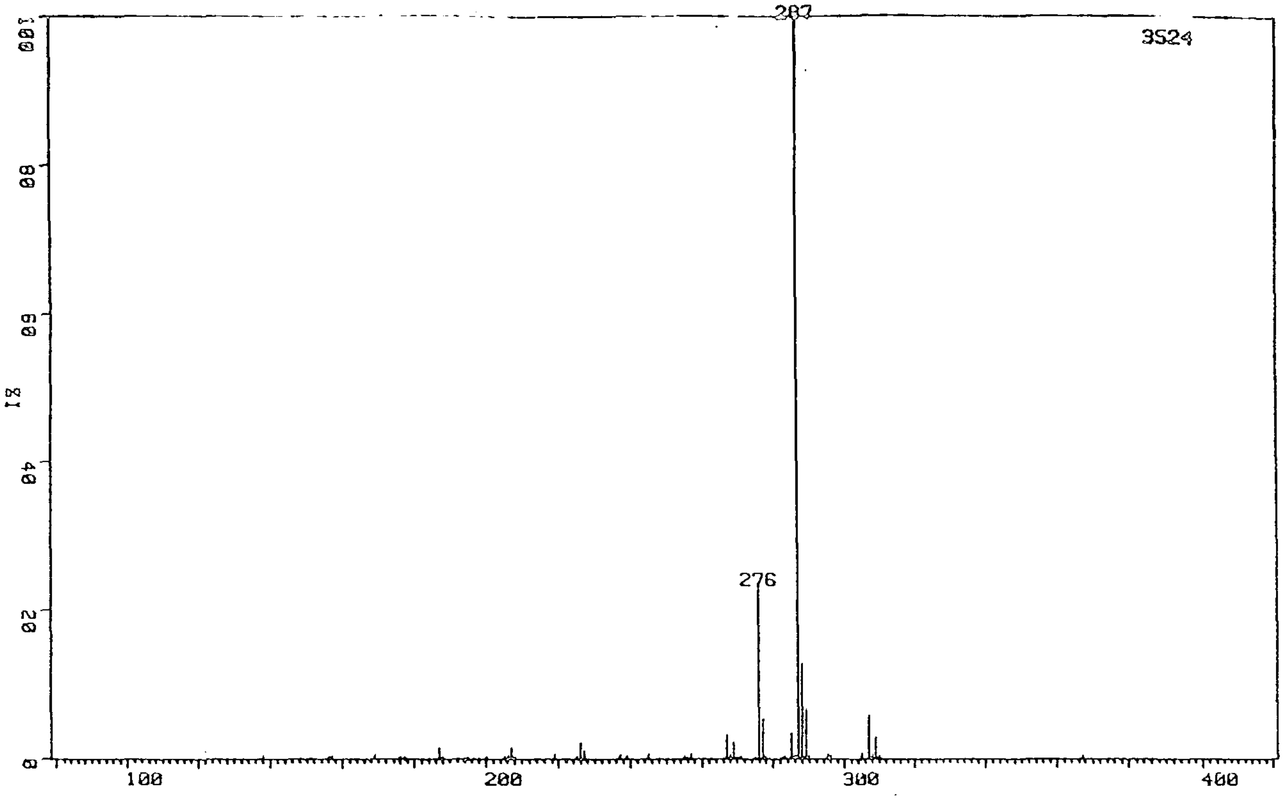


MASS	%HT. BASE	MASS	%HT. BASE
27.24	1.41		
28.11	1.56		
28.98	10.22		
29.81	3.22		
30.90	100.00	225.07	2.19
68.98	8.87	226.08	14.40
137.06	1.89	227.07	15.21
138.05	4.06	228.07	1.56
151.04	1.65	237.07	4.33
156.07	4.48	238.06	1.89
157.07	2.80	239.05	2.34
158.06	1.17	245.07	7.69
162.03	1.26	255.05	7.07
163.05	1.35	256.05	2.01
169.04	5.53	257.06	5.20
170.01	1.05	258.06	1.14
175.07	1.20	263.07	1.14
176.07	3.31	266.06	1.50
177.06	3.10	268.07	1.62
187.06	12.74	269.03	1.77
188.04	2.83	275.05	1.41
194.05	1.17	276.05	93.57
195.07	2.28	277.05	22.21
200.01	1.41	278.05	1.77
205.06	2.89	287.08	11.15
206.06	4.45	288.06	1.65
207.05	10.94	289.04	8.57
208.05	2.34	290.06	1.08
212.04	1.92	295.09	8.99
213.05	1.35	296.08	12.77
218.06	1.11	297.09	1.41
219.04	4.49	309.07	1.71

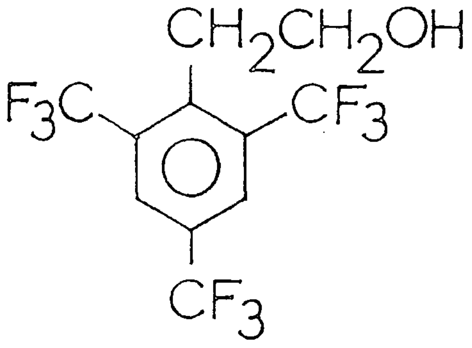


(19)

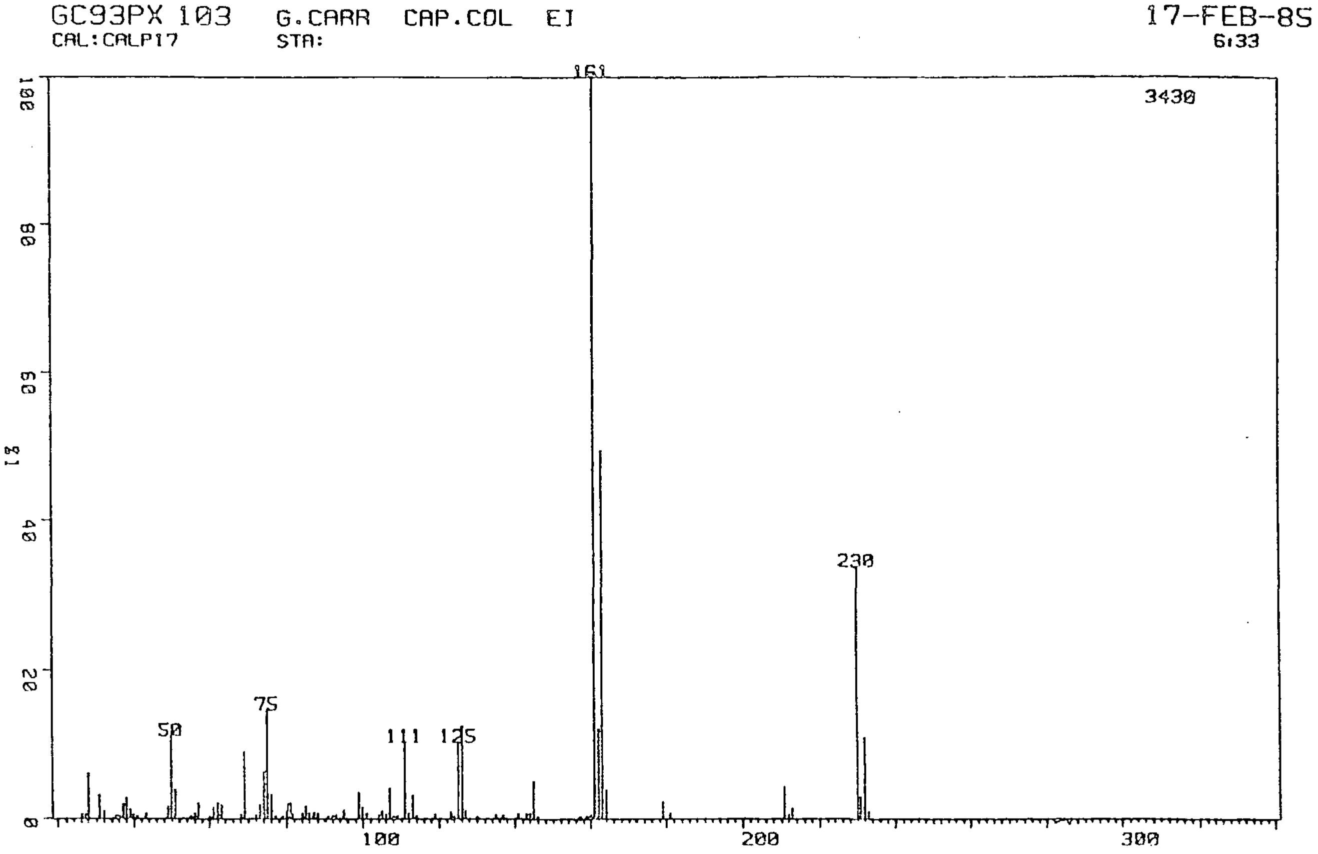
GC111X 0 G.CARR CI I-BU 20-JAN-85
CAL:CALT31 STA: 1:34



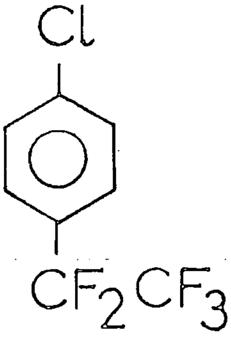
MASS	%HT. BASE
139.05	0.45
151.03	0.23
156.04	0.43
157.07	0.37
169.03	0.54
174.05	0.40
177.07	0.34
187.04	1.50
188.02	0.34
195.05	0.26
199.96	0.26
205.03	0.43
206.04	0.60
207.02	1.56
208.03	0.37
219.00	0.74
225.03	0.37
226.05	2.27
227.04	1.33
237.00	0.65
238.98	0.37
245.02	0.79
255.00	0.43
256.00	0.28
257.01	0.82
267.00	3.26
267.99	0.74
268.98	2.24
269.97	0.34
271.00	0.43
274.97	0.26
276.00	23.30
277.00	5.48
278.00	0.43
284.01	0.43
285.00	3.46
286.01	0.57
286.99	99.74
288.01	12.85
288.99	6.38
289.97	0.79
295.03	0.51
296.02	0.60
305.03	0.91
307.05	5.93
308.04	0.74
309.00	3.04
310.05	0.37
367.10	0.45



(20)

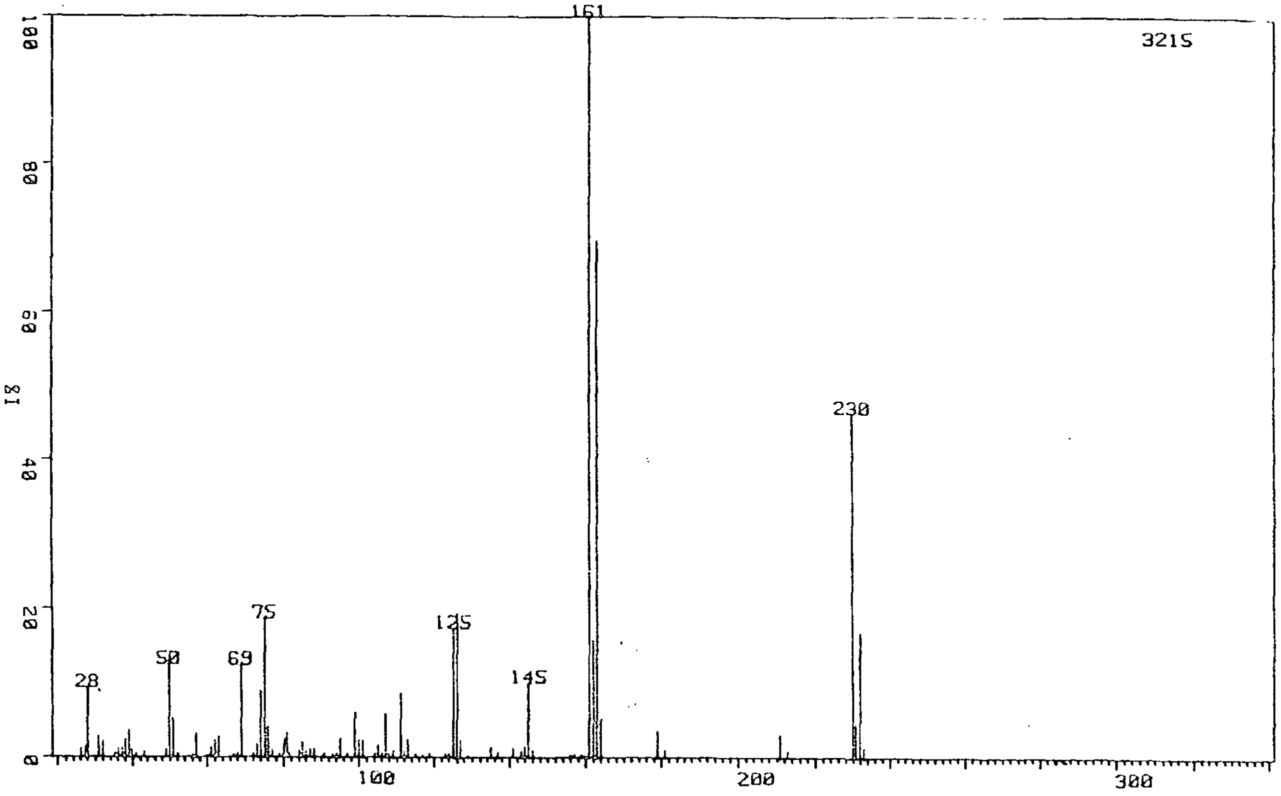


MASS	%HT. BASE
35.10	0.47
36.10	0.44
37.09	2.01
49.86	11.20
50.92	3.99
55.06	0.29
56.06	0.90
57.04	2.27
59.84	0.32
60.91	1.57
61.97	2.27
62.49	0.38
63.02	1.95
67.98	0.67
68.91	9.04
71.93	0.55
72.98	1.95
74.01	6.41
75.02	14.66
76.03	3.35
77.01	0.41
78.90	0.32
79.85	1.14
80.39	2.01
80.93	2.19
81.44	0.73
83.99	0.79
85.00	1.72
86.01	0.85
86.99	0.96
87.97	0.85
90.87	0.32
91.95	0.38
92.97	0.50
95.02	1.20
98.91	3.62
99.87	1.60
100.95	0.85
104.00	0.44
105.00	1.17
106.00	0.70
107.00	4.20
110.89	10.38
111.96	0.90
112.97	3.18
124.99	10.41
125.98	12.59
126.97	1.17
144.98	5.13
160.83	100.00
161.90	12.13
162.93	49.45
163.95	3.97
178.88	2.30
180.89	0.85
210.84	4.34
211.90	0.44
212.89	1.49
229.83	33.82
230.84	3.03
231.87	10.96
232.88	1.02

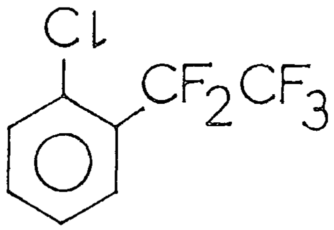


(21)

GC930X 113   G.CARR   CAP.COL   EI   17-FEB-85
CAL:CALP17   STA: 7:11



MASS	%HT. BASE		
35.10	0.59	95.05	2.52
36.10	1.21	96.99	0.47
37.10	1.46	98.95	6.10
49.86	12.57	99.91	2.49
50.93	5.26	100.95	2.27
52.01	0.44	105.01	1.65
56.06	0.44	106.01	0.96
57.05	3.23	107.01	5.97
59.84	0.28	108.00	0.47
60.91	1.40	108.89	1.06
61.98	2.33	110.93	8.65
62.50	0.56	111.97	1.00
63.02	2.74	112.98	2.55
66.99	0.40	124.98	17.42
67.98	0.75	125.99	19.41
68.92	12.47	126.99	2.46
71.93	0.53	134.92	1.43
72.98	1.93	136.92	0.72
74.02	8.96	140.85	1.24
75.03	18.76	142.95	1.03
76.04	4.07	143.96	1.52
77.01	1.03	144.99	10.11
78.91	0.44	160.85	100.00
79.86	1.84	161.91	15.93
80.39	2.58	162.93	69.64
80.93	3.33	163.94	5.35
81.44	0.68	178.87	3.58
83.99	1.06	180.88	1.12
85.00	2.02	210.83	3.20
86.02	0.87	229.85	46.44
86.99	1.21	230.85	4.63
87.98	1.12	231.86	16.92
90.87	0.45	232.87	1.59

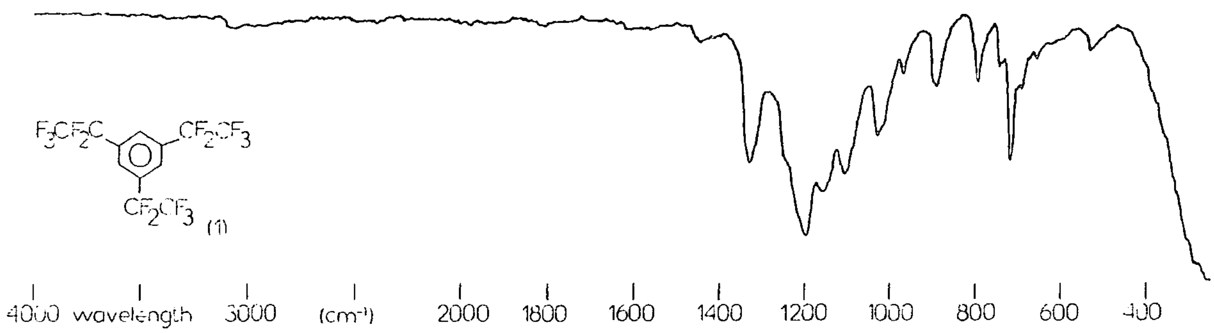


(22)

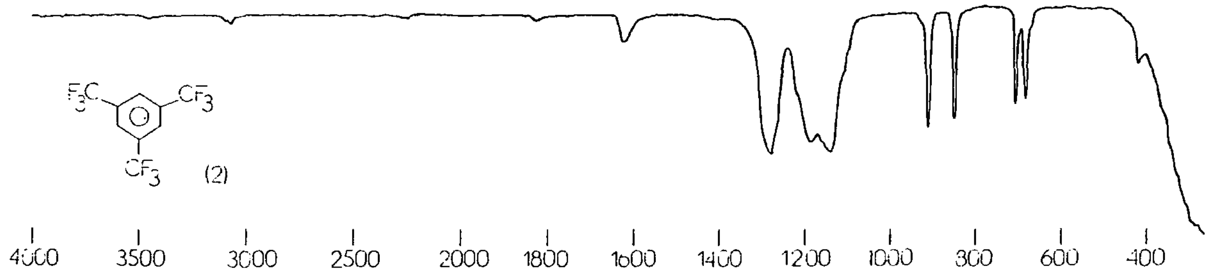
APPENDIX 3

INFRA-RED SPECTRA

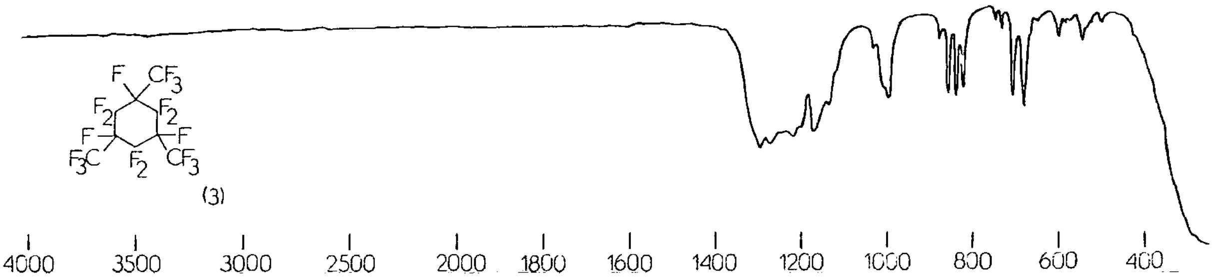
1. 1,3,5-tris(pentafluoroethyl)benzene
2. 1,3,5-tris(trifluoromethyl)benzene (103)
3. perfluoro-1,3,5-trimethylcyclohexane (105)
4. 1-chloro-2,4,6-tris(trifluoromethyl)benzene (117)
5. 1-bromo-2,4,6-tris(trifluoromethyl)benzene (124)
6. 1-[2,4,6-tris(trifluoromethyl)phenyl]-1,3-butanedione (120)
7. 2-[2,4,6-tris(trifluoromethyl)phenyl]-ethanol
8. 2,4,6-tris(trifluoromethyl)benzoic acid (129)
9. 2-[2,4,6-tris(trifluoromethyl)phenyl]-2-oxo-ethanoic acid (122)
10. 2,4,6-tris(trifluoromethyl)benzene-thiol (131)
11. trimethyl-[2,4,6-tris(trifluoromethyl)phenyl]-tin (125)
12. 2,3,5,6-tetrafluoro-4-[2,4,6-tris(trifluoromethyl)-phenyl]-pyridine (132)
13. p-chloropentafluoroethylbenzene
14. o-chloropentafluoroethylbenzene


F3CF2C
CF2CF3
CF2CF3
4000
wavelength
3000
(cm-1)
2000
1800
1600
1400
1200
1000
800
600
400

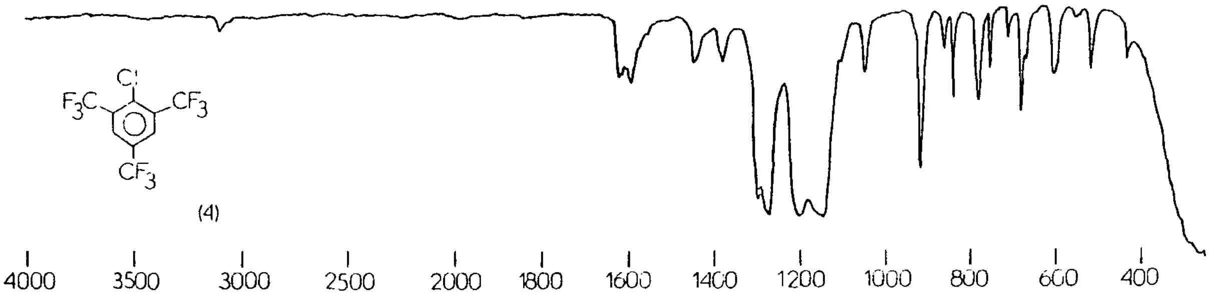
(1)


F3C
CF3
CF3
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
300
600
400

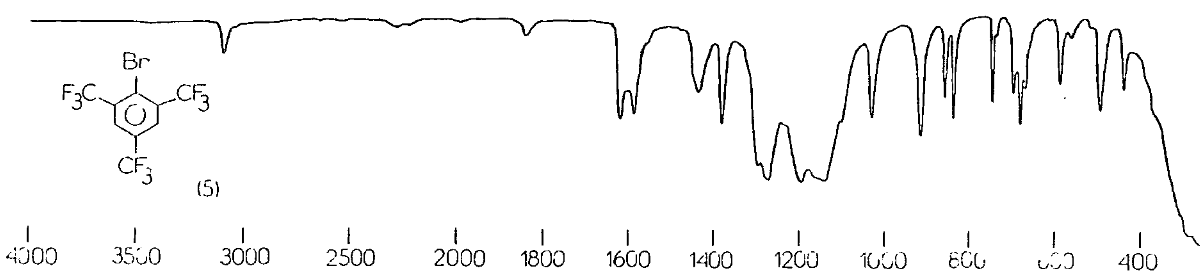
(2)


F
CF3
F2
F2
F
F
F3C
F2
CF3
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400

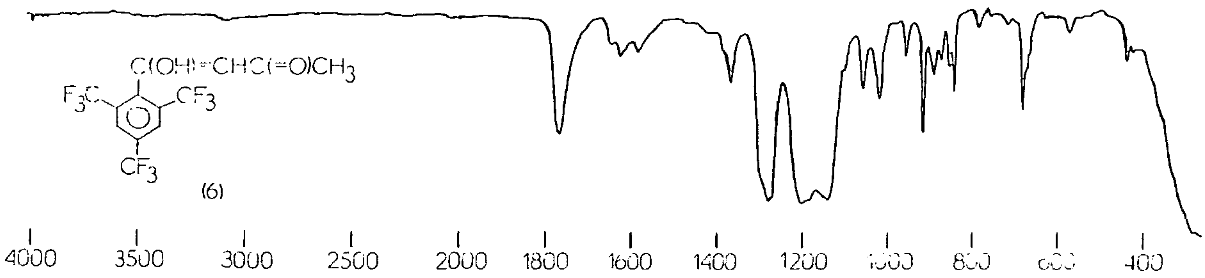
(3)


Cl
F3C
CF3
CF3
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400

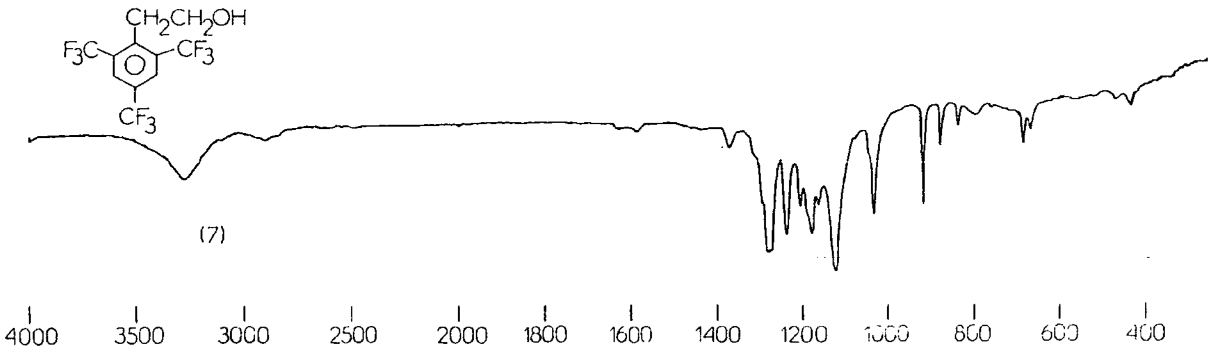
(4)


Br
F3C
CF3
CF3
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400

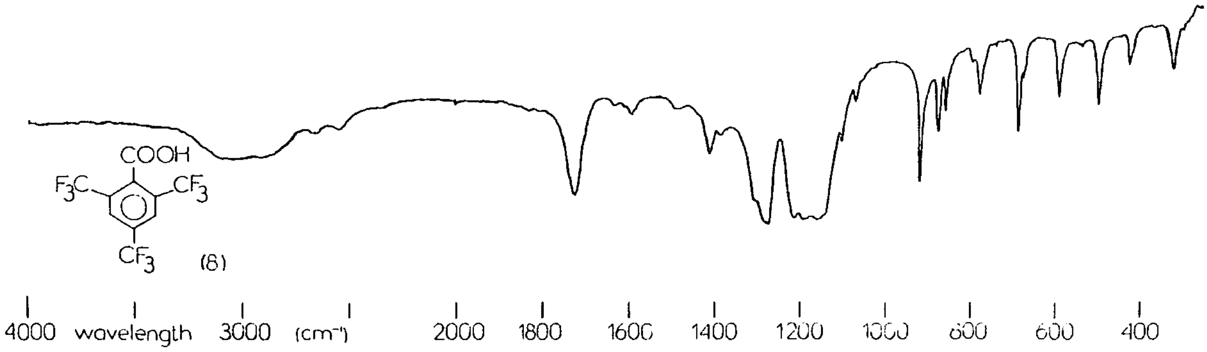
(5)


C(OH)=CHC(=O)CH3
F3C
CF3
CF3
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400

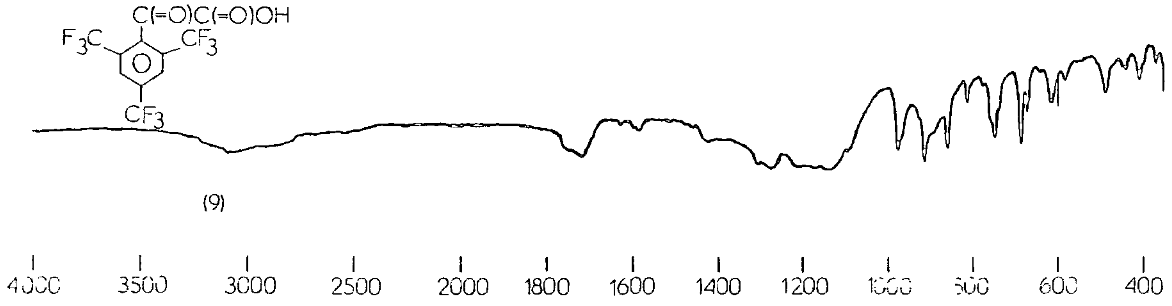
(6)


CH2CH2OH
F3C
CF3
CF3
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400

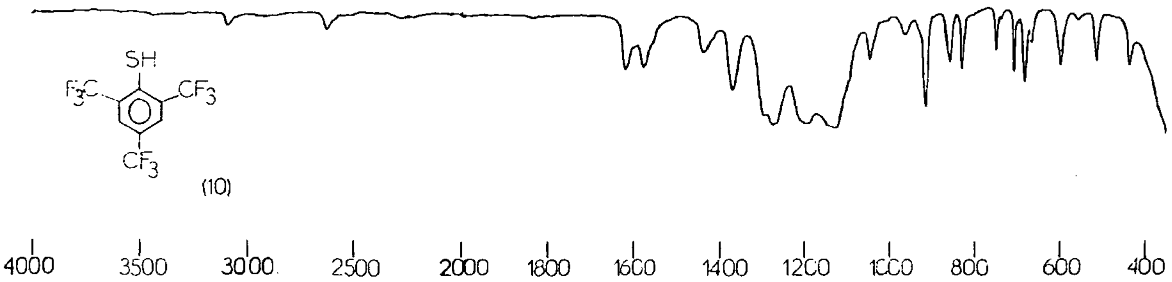
(7)


COOH
F3C
CF3
CF3
4000
wavelength
3000
(cm⁻¹)
2000
1800
1600
1400
1200
1000
800
600
400

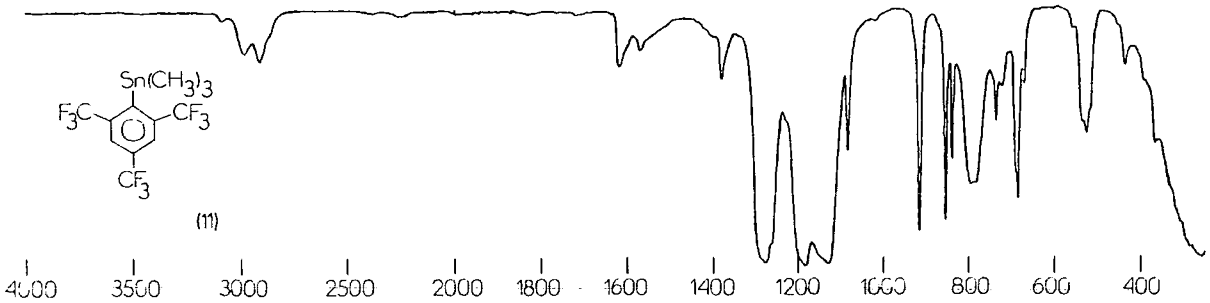
(8)


C(=O)C(=O)OH
F3C
CF3
CF3
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400

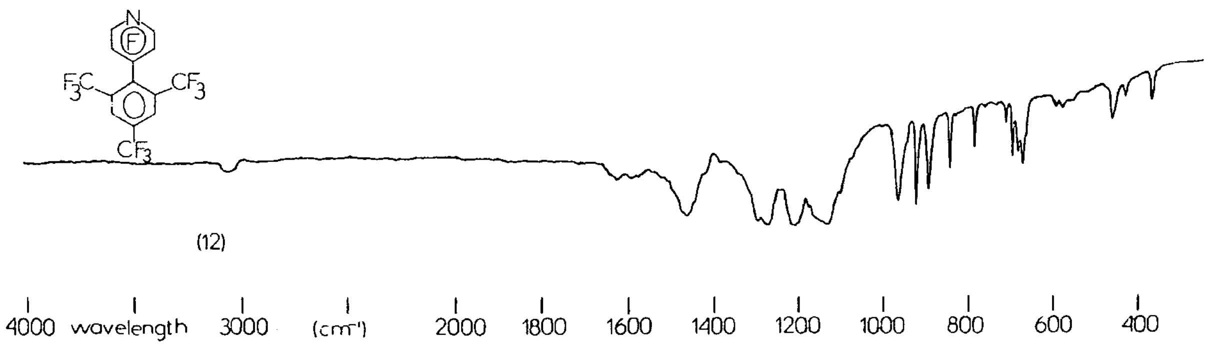
(9)


SH
F3C
CF3
CF3
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400

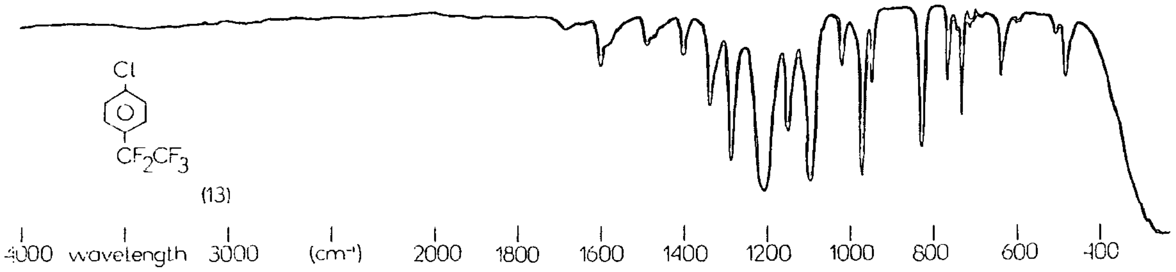
(10)


Sn(CH3)3
F3C
CF3
CF3
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400

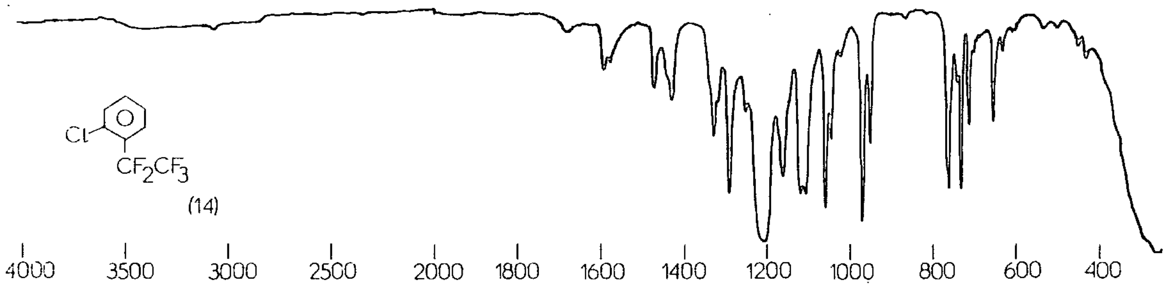
(11)


N
F
F3C
CF3
CF3
4000
wavelength
3000
(cm-1)
2000
1800
1600
1400
1200
1000
800
600
400

(12)


Cl
CF2CF3
4000
wavelength
3000
(cm⁻¹)
2000
1800
1600
1400
1200
1000
800
600
400

(13)


Cl
CF2CF3
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400

(14)

APPENDIX 4

The Board of Studies in Chemistry requires that each postgraduate thesis contains an appendix listing;

a) all research colloquia, seminars and lectures arranged by the Department of Chemistry during the period of the author's residence as a postgraduate student,

b) all research conferences attended and papers presented by the author during the period in which the research for the thesis was carried out,

c) details of the postgraduate induction course.

a) Research Colloquia, Seminars and Lectures.

1982

13 October	Dr W.J.Feast (University of Durham), "Approaches to the synthesis of conjugated polymers".
14 October	Prof. H.Suhr (University of Tubingen,F.R.G.), "Preparative Chemistry in non-equilibrium plasmas".
14 October	Mr F.Shenton (County Analyst, Durham), "There is death in the pot".
27 October	Dr C.E.Housecroft (Oxford High School/Notre Dame University), "Bonding capabilities of butterfly-shaped Fe_4 units, implications for C-H bond activation in Hydrocarbon complexes.
28 October	Prof. M.F.Lappert, F.R.S. (University of Sussex), "Approaches to asymmetric synthesis and catalyses using electron olefins and some of their metal complexes". "The chemistry of some unusual subvalent compounds of the main group 1V and V elements".
4 November	Dr D.H.Williams (University of Cambridge), "Studies on the structures and modes of action of antibiotics".

11 November	Dr J.Cramp (I.C.I. p.l.c.), "Lasers in Industry".
15 November	Dr G.Bertrand (University of Toulouse, France), "Curtius rearrangement in organometallic series. A route for hybrid species".
24 November	Prof. G.G.Roberts (Applied Physics, University of Durham), "Langmuir Blodgett films: Solid state polymerisation of diacetylenes".
25 November	Dr D.H.Richards (P.E.R.M.E., Ministry of Defence), "Terminally functional polymers, their syntheses and uses".
2 December	Dr G.M.Brooke (University of Durham), "The fate of the ortho-fluorine in 3,3-sigmatropic reactions involving polyfluoroaryl and heteroaryl systems".
8 December	Dr G.Wooley (Trent Polytechnic), "Bonds in transition metal-cluster compounds".

<u>1983</u>

12 January	Dr D.C.Sherrington (University of Strathclyde), "Polymer-supported phase transfer catalysts".
27 January	Prof. D.W.A.Sharp (University of Glasgow), "Some redox reactions in fluorine chemistry".
9 February	Dr P.Moore (University of Warwick), "Mechanistic studies in solution by stopped flow F.T. nmr and high pressure nmr line broadening".
10 February	Sir Geoffery Allen F.R.S. (Unilever Ltd), "UK Research Ltd".
17 February	R.S.C. Centenary Lecture. Prof. A.G. McDiarmid, (University of Pennsylvania), "Metallic Covalent Polymers: $(SN)_x$ and $(CN)_x$ and their derivatives".

21 February	Dr R.Lynder Bell (University of Cambridge), "Molecular Motion in the cubic phase of NaCN".
2 March	Dr D.Bloor (Queen Mary College, University of London), "The solid-state chemistry of diacetylene moromers and polymers".
3 March	Prof. A.C.T.North (University of Leeds), "The use of a computer display system in studying molecular structure and interactions".
8 March	Prof. D.C.Bradley F.R.S. (Queen Mary College, University of London), "Recent developments in organo-imido-transition metal chemistry".
9 March	Dr D.M.J.Lilley (University of Dundee), "DNA, Sequence, symmetry and supercooling".
11 March	Prof. H.G.Viehe, (University of Louvain, Belgium), The W.K.R. Musgrave Lecture. "Oxidations on sulphur", "Fluorine substitutions in radicals".
16 March	Dr I.Gosney (University of Edinburgh), "New extrusion reactions; Organic synthesis in a hot tube".
25 March	Prof. F.G.Baglin (University of Nevada, U.S.A.) "Interaction induced Raman spectroscopy in supra-critical ethane".
21 April	Prof. J.Passmore (University of New Brunswick, U.S.A.) "Novel selenium-iodine cations".
4 May	Prof. P.H.Plesh (University of Keele), "Binary ionisation equilibria between two ions and two molecules. What Ostwald never thought of".
10 May	Prof. K.Burger (Technical University of Munich, F.R.G.), "New reaction pathways from trifluoromethyl- substituted heterodienes to partially fluorinated heterocyclic compounds".

11 May	Dr N.Isaacs (University of Reading), "The application of high pressures to the theory and practice of organic chemistry".
13 May	Dr R.de Koch (Calorin College, Grand Rapids, Michigan/Free University, Amsterdam), "Electronic structural calculations in organometallic cobalt cluster molecules. Implications for metal surfaces".
16 May	Prof. R.J.Lagow (University of Texas, U.S.A.), "The chemistry of polylithium organic compounds. An unusual class of matter".
18 May	Dr D.M.Adams (University of Leicester), "Spectroscopy at very high pressures".
25 May	Dr J.M.Vernon (University of York), "New heterocyclic chemistry involving lead tetra acetate".
15 June	Dr A.Pietrzykowski (Technical University of Warsaw/University of Strathclyde), "Synthesis structure and properties of aluminoxanes".
22 June	Dr D.W.H.Rankin (University of Edinburgh), "Floppy molecules - the influence of phase on structure".
5 July	Prof. J.Miller (University of Camfirias, Brazil), "Reactivity in nucleophilic substitution reactions".
5 October	Prof. J.P.Maier (University of Basel, Switzerland), "Recent approaches to spectroscopic characterisation of cations".
12 October	Dr C.W.McLeland (University of Port Elizabeth, Australia), "Cyclisation of aryl alcohols through the intermediacy of alkoxy radicals and aryl radical cations".
19 October	Dr N.W. Alcock (University of Warwick), "Aryl Tellurium (lV) compounds, patterns of primary and secondary bonding".

20 October	Prof. R.B.Cundall (University of Salford), "Explosives".
26 October	Dr R.H.Friend (Cavendish Laboratory, University of Cambridge), "Electronic properties of conjugated polymers".
3 November	Dr G.Richards (University of Oxford), "Quantum pharmacology".
10 November	Dr G.Taylor (Sterling Organic), "Applied chemistry and the Pharmaceutical industry".
24 November	Prof. D.A.King (University of Liverpool), "Chemistry in two dimensions".
30 November	Prof. I.Cowie (University of Stirling), "Molecular interpretation of non-relaxation processes in polymer glasses".
1 December	Dr J.D.Coyle (The Open University), "The problem with sunshine".
14 December	Prof. R.J.Donovan (University of Edinburgh), "Chemical and physical processes involving the ion pair states of the halogen molecules".

<u>1984</u>

10 January	Prof R.Hester (University of York), "Nano second laser spectroscopy of reaction intermediates".
18 January	Prof. R.K.Harris (University of East Anglia), "Multi-nuclear solid state magnetic resonance".
26 January	Prof. T.L.Blundell (Birkbeck College, London), "Biological recognition: Interactions of macro molecular surfaces".
2 February	Prof. N.B.H.Jonathon (University of Southampton), "Photoelectron spectroscopy - a radical approach".
8 February	Dr B.T.Heaton (University of Kent), "Multinuclear n.m.r. studies".
15 February	Dr R.M.Paton (University of Edinburgh), "Heterocyclic synthesis using nitrile sulphides".

16 February	Prof. D.Phillips (The Royal Institution), "Luminescence and photochemistry - a light entertainment".
23 February	Prof. F.G.A.Stone, F.R.S. (University of Bristol), "The use of carbene and carbyne groups to synthesise metal clusters". The Waddington Memorial Lecture.
1 March	Prof. A.J.Leadbetter (Rutherford Appleton Laboratories), "Liquid Crystals".
7 March	Dr R.T.Walker (University of Birmingham), "Synthesis and biological properties of some 5-substituted uracil derivatives; yet another example of serendipity in antiviral chemistry".
8 March	Prof. D.Chapman (Royal Free Hospital School of Medicine, University of London), "Phospholipids and biomembranes: basic structure and future techniques".
21 March	Dr P.Sherwood (University of Newcastle), "X-ray photoelectron spectroscopic studies of electrode and other surfaces".
23 March	Dr A.Ceulemans (Catholic University of Leuven), "The development of field type models of bonding in molecular clusters".
28 March	R.S.C. Centenary Lecture. Prof. H.Schmidbaur (Technical University of Munich F.R.G.), "Ylides in co-ordination sphere of metals; synthetic, structural and theoretical aspects".
2 April	Prof. K.O'Driscoll (University of Waterloo), "Chainending reactions in free radical polymerisation".
3 April	Prof. C.H.Rochester (University of Dundee), "Infrared studies of adsorption at the solid-liquid interface".
25 April	Dr R.M.Acheson (Department of Biochemistry, University of Oxford), "Some heterocyclic detective stories".

27 April	Dr T.Albright (University of Houston), "Sigmatropic rearrangements in organometallic chemistry".
14 May	Prof. W.R.Dolbier Jr (University of Florida), "Cycloaddition reactions of fluorinated allenes".
16 May	Dr P.J.Garrett (University College, London), "Syntheses with dilithiated vicinal diesters and carboximides".
31 May	Dr A.Haaland (University of Oslo), "Electron diffraction studies of some organometallic compounds".
11 June	Dr G.B.Street (I.B.M. San Jose), "Conducting polymers derived from pyrroles".
19 September	Dr C.Brown (I.B.M. San Jose), "New Superbase reactions - organic compounds".
21 September	Dr H.W.Gibson (Signal UOP Research Centre, Des Plaines, Illinois), "Isomerisation of polyacetylene".
18 October	Dr N.Logan (University of Nottingham), "N_2O_4 and rocket fuels".
19 October	Dr A.Germain (Universite du Languedoc, Montpelier), "Anodic oxidation of perfluoro organic compounds in perfluoroalkane sulphonic acids".
24 October	Prof. R.K.Harris (University of Durham), "N.m.r. of solid polymers".
1 November	Prof. B.J.Aylett (Queen Mary College, University of London), "Silicon-dead common or refined".
7 November	Prof. W.W.Porterfield (Hampden Sidney College, U.S.A.), "There is no borane chemistry (only geometry)".
7 November	Dr H.S.Munro (University of Durham), "New information from E.S.C.A. data".
15 November	Prof. B.T.Golding (University of Newcastle-upon-Tyne), "The vitamin B_{12} mystery".

21 November	Dr W.J.Feast (University of Durham), "A plain man's guide to polymeric organic materials".
22 November	Prof. D.T.Clark (I.C.I. New Science Group), "Structure, bonding, reactivity and synthesis as revealed by E.S.C.A."
28 November	Dr T.A.Stephenson (University of Edinburgh), "Some recent studies in platinum metal chemistry".
29 November	Prof. C.J.M.Stirling (University College of North Wales), "Molecules taking the strain".
6 December	Prof. R.D.Chambers (University of Durham), "The unusual world of fluorine chemistry".

1985

24 January	Dr A.K.Covington (University of Newcastle-upon-Tyne), "Chemistry with chips".
31 January	Dr M.L.H.Green (University of Oxford), "Naked atoms and negligee ligands".
7 February	Prof. A.Ledwith (Pilkington Bros.), "Glass as a high technology material".
13 February	Dr G.W.J.Fleet (University of Oxford), "Synthesis of some alkaloids from carbohydrates".
14 February	Dr J.A.Salthouse (University of Manchester), "Son et Lumiere, (a chemical energy show)".
19 February	Dr D.J.Mincher (University of Durham), "Stereoselective syntheses of some novel anthracyclinones related to the anti-cancer drug adriamycin and to the steffimycin antibiotics".
21 February	Prof. P.M.Maitlis F.R.S. (University of Sheffield), "What use is Rhodium".
27 February	Dr R.E.Mulvey (University of Durham), "Some unusual lithium complexes".
7 March	Dr P.J.Rodgers (I.C.I. plc Agricultural Division, Billingham), "Industrial polymers from bacteria".

7 March	Dr P.W.Atkins (University of Oxford), "Magnetic reactions".
12 March	Prof. K.J.Packer (BP Research Centre), "Nmr investigations of the structure of solid polymers".
14 March	Prof. A.R.Katritzky FRS (University of Florida), "Some adventures in heterocyclic chemistry".
21 March	Dr M.Poliakoff (University of Nottingham), "New methods for detecting organometallic intermediates in solution".
28 March	Prof. H.Ringsdorf (Organic Chemistry Institute, University of Mainz), "Polymeric liposomes as models for biomembranes and cells".
24 April	Dr M.C.Grossel (Bedford College, University of London), "Hydroxypyridone dyes - bleachable one dimensional metals?".
1 May	Dr D.Parker (I.C.I. plc Petrochemicals and Plastics Division, Wilton), "Applications of radioisotopes in industrial research".
7 May	Prof. G.E.Coates (formerly of University of Wyoming, U.S.A.) "Chemical education in Britain and America: Successes and deficiencies".
8 May	Prof. D.Tuck (University of Windsor, Ontario), "Lower oxidation state chemistry of indium".
8 May	Prof. G.Williams (University College of Wales, Aberystwyth), "Liquid crystalline polymers".
9 May	Prof. R.K.Harris (University of Durham), "Chemistry in a spin: Nuclear magnetic resonance".
14 May	Prof. J.Passmore (University of New Brunswick), "The synthesis and characterisation of some novel selenium - iodine cations, aided by ^{77}Se nmr spectroscopy".

15 May	Dr J.E.Packer (University of Auckland, New Zealand), "Studies of free radical reactions in aqueous solution using ionising radiation".
17 May	Prof. I.D.Brown (Institute for Materials Research, McMaster University, Canada), "Bond valence as a model for inorganic chemistry".
21 May	Dr D.L.H.Williams (University of Durham), "Chemistry in Colour".
22 May	Dr R.Grimmett (University of Otago, Dunedin, New Zealand), "Some aspects of nucleophilic substitution in imidozoles".
22 May	Dr M.Hudlicky (Virginia State University, Blacksburg), "Preferential elimination of hydrogen fluoride from vicinal bromofluorocarbons".
13 June	Dr D.Woollins (Imperial College, University of London), "Metal-sulphur-nitrogen complexes".
14 June	Prof. Z.Rappoport (The Hebrew University, Jerusalem), "The rich mechanistic world of nucleophilic vinylic substitution."
19 June	Dr T.N.Mitchell (University of Dortmund), "Some synthetic and nmr-spectroscopic studies of organotin compounds".
26 June	Prof. G.Shaw (University of Bradford), "Some synthetic studies in imidazole nucleosides and the antitiotic coformycin".
12 July	Dr K.Laali (Hydrocarbon Research Institute, University of Southern California), "Recent developments in superacid chemistry and mechanistic considerations in electrophilic aromatic substitutions; a progress report."

b) Research Conferences Attended.

Graduate Symposium, Durham, April 1983.

17th Sheffield Symposium on "Modern Aspects of Sterochemistry", Sheffield, 21st December, 1983.

Graduate Symposium, Durham, April, 1984.

International Symposium on "Chemistry of Carbanions", Durham, 16-20 July, 1984.

Graduate Symposium, Durham, April, 1985.

c) Postgraduate Induction Course.

In each part of the course, the uses and limitations of the various services available were explained.

Departmental Organisation - Dr E.J.F.Ross

Safety Matters - Dr M.R.Crampton

Electrical Appliances and Infra-red Spectroscopy - Mr R.N.Brown

Chromotography and Micro Analysis - Mr T.F.Holmes

Atomic Absorption Spectrometry and Inorganic Analysis - Mr R.Coult

Library Facilities - Mr R.B.Woodward

Mass Spectrometry - Dr M.Jones

Nuclear Magnetic Resonance Spectroscopy - Dr R.S.Matthews

Glassblowing Techniques - Mr R.Hart and Mr G.Haswell

REFERENCES

1. R.E.Banks, 'Organofluorine Chemicals and their Industrial Applications', Ellis Horwood, New York, 1979.
2. A.K.Barbour, L.J.Belf, and M.W.Buxton, Adv. Fluorine Chem, 1963, 3, 181.
3. M.Hudlicky, 'Chemistry of Organic Fluorine Compounds', Ellis Horwood, New York, 2nd Edn.
4. F.Smith, M.Stacey, J.C.Tatlow, J.K.Dawson, and B.R.J. Thomas, J. Appl. Chem., 1952, 2, 97.
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