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Trifluoromethylations and Related Reactions in Organic Chemistry

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1. Introduction

Trifluoromethylated compounds have found a large number of industrial uses from dyes and polymers, to pharmaceuticals and agrochemicals. The influence of the trifluoromethyl group in biologically active molecules is often associated with the increased lipophilicity that this substituent imparts. In addition, its electronegativity and relatively small size (only two and a half times the volume of a methyl group) are also contributing factors.[1,2] The dye industry has often found that trifluoromethylation of chromophores results in increased light fastness as well as a shift in colour (both bathochromic and hypsochromic) compared to their non-fluorinated counterparts.[3,4] Improved chemical and thermal stability, in addition to increased solubility and diverse mechanical and electrical properties of trifluoromethylated polymers are quoted as the reasons for the interest in trifluoromethyl containing molecules as sources of new materials.[5]

Although a number of reviews have recently been published regarding the preparation of fluorinated compounds[2] and trifluoromethylketones[6] there appears to be none dealing specifically with the many methods available to trifluoromethylate organic compounds.* This review concerns itself not only with such methods, but also the preparation of trifluoromethylated compounds by fluorination of suitably substituted methyl moieties in addition to the synthesis of the related 1,1,1-trifluoroethyl, trifluoromethoxy and trifluoromethylthio compounds.

2. Physical Properties of the Trifluoromethyl Group

The Van der Waals radius of 2.7 Å for a trifluoromethyl group compares to 2.0 Å for $-CH_3$ and 3.5 Å for $-CCl_3$, whilst its Van der Waals volume (hemisphere) of 42.5 $Å^3$ compares to that of 16.8 $Å^3$ for the methyl group.[7] The effect of replacing a methyl by a trifluoromethyl moiety on bond length is dependent upon the electronegativity of the atom

* D.J. Burton and Z.-Y. Yang have just published a Tetrahedron Report [228] on perfluoroalkyl metal reagents which does cover some of the methods available for preparing trifluoromethylated compounds.

to which the C_1 substituent is attached (see Table 2.1).[8] However, it is suggested that there should be little or no effect on bond lengths when a trifluoromethyl group replaces a methyl attached to a carbon atom. Thus replacement of a methyl by a trifluoromethyl should result in minimal disruption to an enzyme-substrate complex.[1,7]

Compound $Y(CX_3)_n$	Electronegativity of Y[1]	C-Y bond length X=H	X=F	$\Delta r = rCF_3 - rCH_3$
P-$(CX_3)_3$	2.06	1.844	1.904	+0.060
H-CX_3	2.20	1.099	1.102	+0.003
I - CX_3	2.21	2.139	2.138	-0.001
S-$(CX_3)_2$	2.44	1.805	1.819	+0.014
Se-$(CX_3)_2$	2.48	1.945	1.980	+0.035
Br - CX_3	2.74	1.939	1.923	-0.016
Cl - CX_3	2.83	1.781	1.752	-0.029
N-$(CX_3)_3$	3.07	1.458	1.426	-0.032
O-$(CX_3)_2$	3.50	1.416	1.369	-0.047
F - CX_3	4.10	1.385	1.319	-0.066

Table 2.1 Effect of Substituting a Trifluoromethyl Group for Methyl on Bond Lengths.

[1] Allred-Rochow Electronegativities

Other properties of the trifluoromethyl group include an electronegativity similar to that of oxygen[9] and a large hydrophobic parameter[10] (Table 2.2). The latter parameter is often used as a measure of lipophilicity, showing that trifluoromethylated molecules should be more able to traverse lipid membranes than their non-fluorinated analogues,[1] though a recent paper suggests that lipophilicity is very dependant upon the position of the moiety within the molecule.[10b] Finally, the strong C-F bond in trifluoromethylated compounds confers extra stability upon a molecule.[1]

Overall the trifluoromethyl group imparts a variety of physical properties upon a molecule unlike any other substituent.

Atom/Group	Electronegativity[1]	Hydrophobicity[2]
H	2.1	0.00
C	2.5	-
CH_3	2.3	0.51
^tBu	2.3	1.68
OCH_3	2.7	0.12
CF_3CH_2	2.9	-
Cl	3.0	0.76
O	3.5	-
CF_3	3.5	1.07
OCF_3	3.7	1.21
F	4.0	1.22
NO_2	-	0.11
SCF_3	-	1.58
SO_2CF_3	-	0.93
Ph	-	1.89

Table 2.2: Electronegativities and Hydrophobic Parameters for Various Substituents.

1. Pauling Scale.
2. As measured by the relative partition coefficients of meta substituted 3-phenoxyacetic acids between octan-1-ol and water.[10]

3. Chemical Reactions Involving The Trifluoromethyl Group

Although the trifluoromethyl group is often considered to be chemically inert, it is known to undergo a variety of reactions. The one most commonly encountered is hydrolysis, though the hydrolytic behaviour of a trifluoromethyl group is very dependent upon its position in a molecule. Hence, there are many examples in which the trifluoromethyl group withstands quite vigorous conditions, as illustrated in Figure 3.1.[11,12]

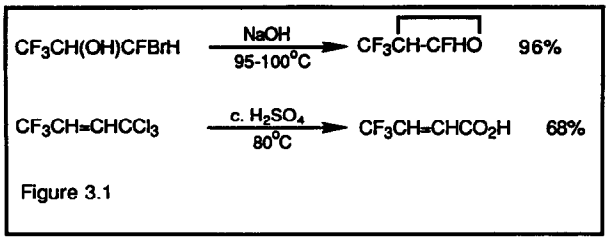


Figure 3.1

However, trifluoromethylated aromatics will undergo hydrolysis, but only in acidic media (Figure 3.2).[13]

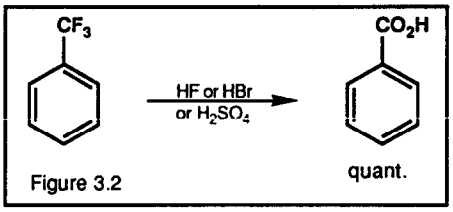


Figure 3.2

Conversely, trifluoromethyl groups α to carboxylic acids (or their functional derivatives) are susceptible to hydrolysis only in basic media. The mechanism of hydrolysis involves the elimination of hydrogen fluoride followed by attack of water to yield the difluorohydroxymethyl moiety, which undergoes further elimination of hydrogen fluoride and attack of water to give finally the acid (see Figure 3.3).[14] This reaction has proved useful for the preparation of trifluoromethyl containing building blocks from α,β-bis(trifluoromethyl) carboxylic acid derivatives, which in turn can be prepared

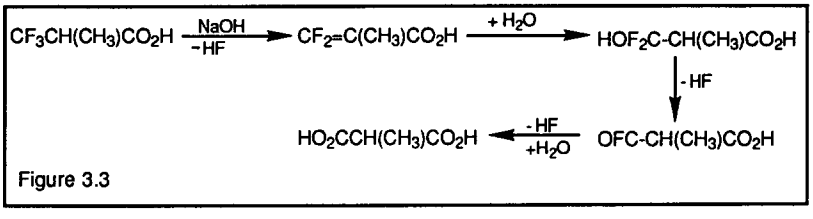


Figure 3.3

electrochemically from the corresponding α,β-unsaturated molecule (see Section 5.4 and Figure 3.4).[15, 16]

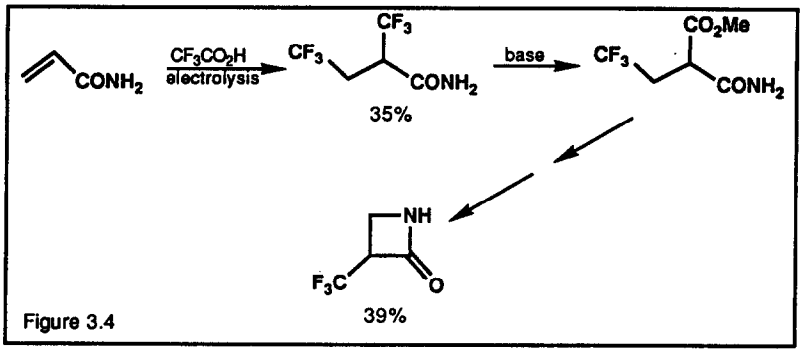


Figure 3.4

2-Trifluoromethylimidazoles also undergo facile base induced hydrolysis to yield the carboxylic acid. Additionally, they react with ammonia in a similar fashion to give cyano compounds (Figure 3.5).[17]

The ability of certain trifluoromethyl groups to lose fluoride ions has been exploited in the preparation of α-trifluoromethyl carboxylic acid esters.[18] The initial attack of an organometallic nucleophile on methyl 2-trifluoromethylpropenoate yields a difluoroalkene, which can be converted back to the trifluoromethyl group by addition of tetrabutylammonium fluoride (Figure 3.6).

The ability to lose fluoride ions has also been exploited in the preparation of quinolines by the action of a strong base on ketimines derived from 2-(trifluoromethyl)-aniline. The proposed mechanism involves the sequential loss of a fluoride ion and attack by the base to yield a molecule which can then undergo electrocyclisation to the quinoline (see Figure 3.7).[19]

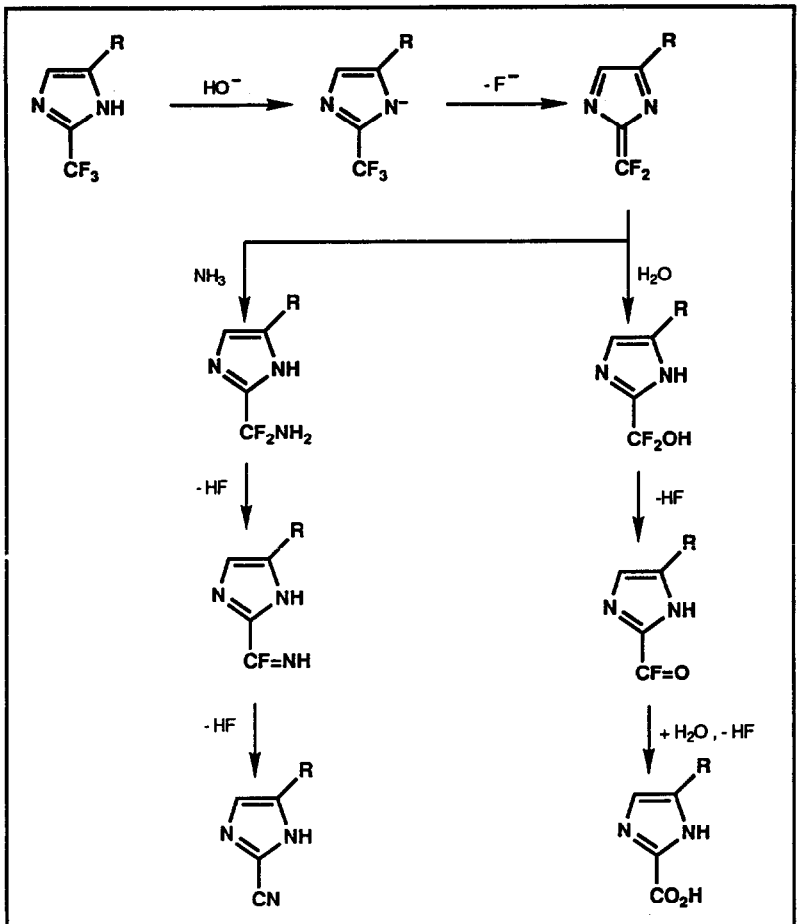


Figure 3.5

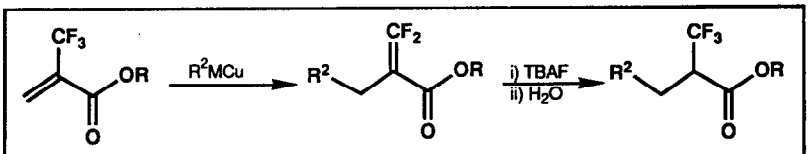


Figure 3.6

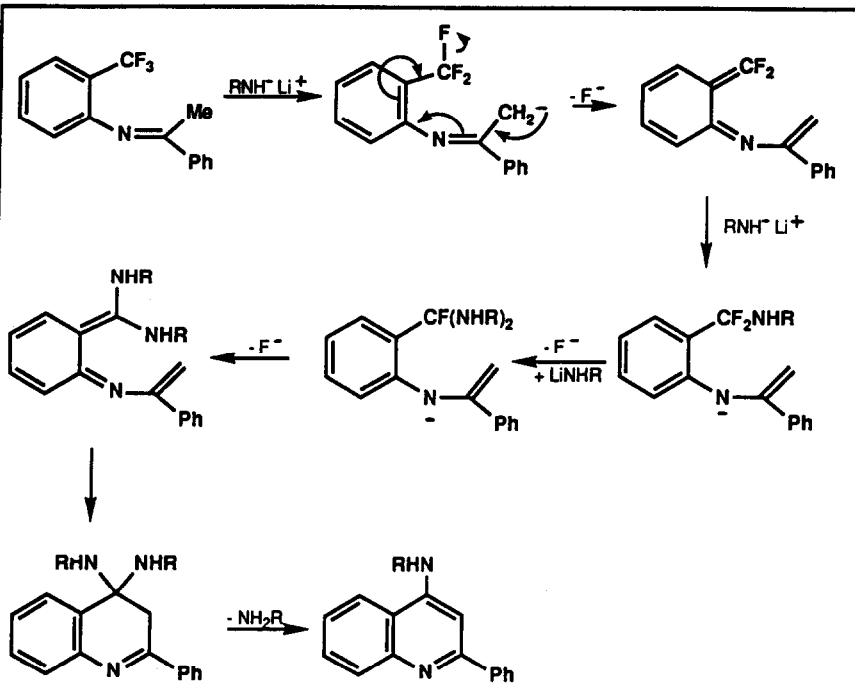


Figure 3.7

The biological degradation of a trifluoromethyl group has been reported as a cause of enzyme inhibition.[20] Two examples of such inhibition are illustrated in Figure 3.8 and involve attack by the enzyme on the trifluoromethylated molecule, resulting in the loss of fluoride and the formation of a covalent bond between the enzyme and the inhibitor. The resulting difluoromethylene moiety is then hydrolysed to a carbonyl function.

In addition to the hydrolysis of a trifluoromethyl group, chlorination and reduction reactions have been reported . Chlorination of benzotrifluorides is readily achieved using aluminium trichloride, thus making this Lewis acid unsuitable for use as a catalyst in aromatic reactions (see Figure 3.9).[21] The reduction of the trifluoromethyl group is carried out using Raney nickel and cobalt alloy in alkaline medium (Figure 3.10).[24]

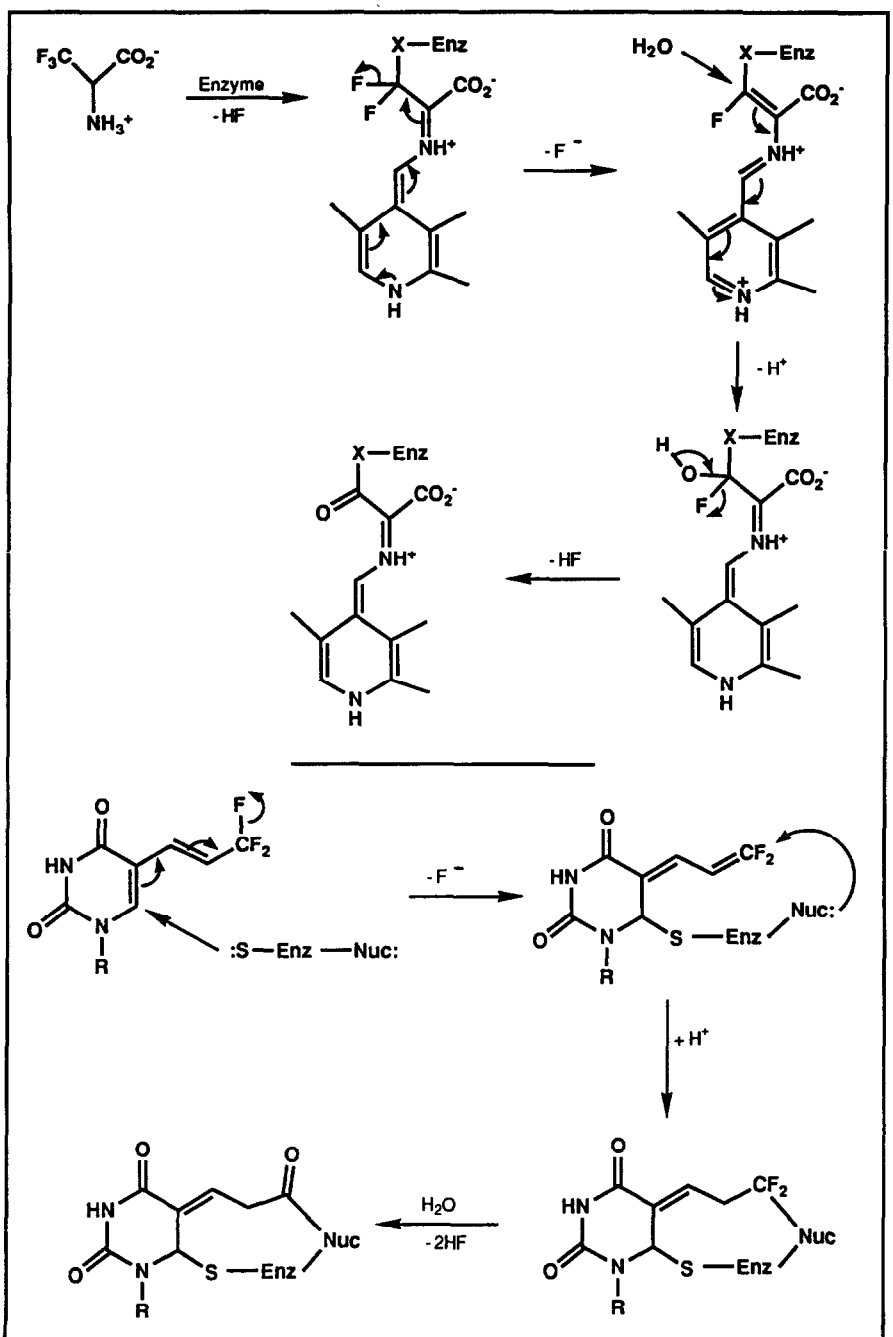


Figure 3.8 : Degradation of Trifluoromethyl Groups by Biological Systems.

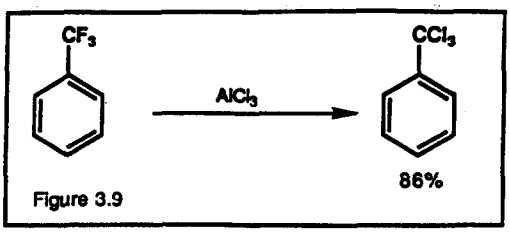


Figure 3.9

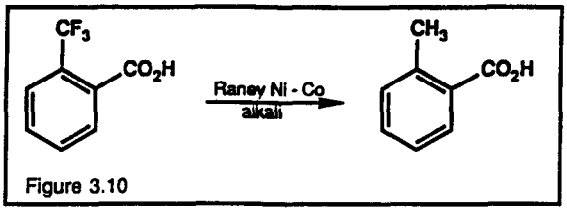


Figure 3.10

The reactivity of a trifluoromethyl group adjacent to an imine has been exploited in the preparation of oxazoles, thiazoles and imidazoles. When bis(trifluoromethyl) substituted heterodienes are reacted with tin(II) chloride, five membered rings result, as illustrated in Figure 3.11.[23]

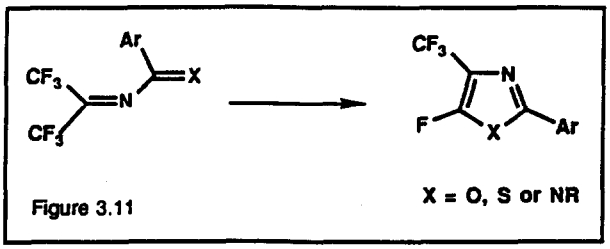


Figure 3.11

Finally, trifluoromethyl ketones are known to undergo elimination of fluoroform in alkaline conditions to yield the carboxylic acid (Figure 3.12).[12, 25]

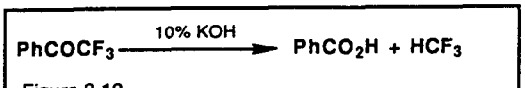


Figure 3.12

The incorporation of a trifluoromethyl group naturally effects the chemistry of neighbouring functional groups. Simple illustrations of this include the increased acidity of trifluoroethanol over ethanol (pka's of 12,4 and 16 respectively),[7] the increased

electrophilicity of trifluoromethyl carbonyl functions as compared to their hydrocarbon analogues,[6] and the decreased basicity of trifluoromethyl substituted amines.[26]

The presence of fluorine in a molecule increases its oxidative and thermal stability as a result of the strong C-F bond. This can be illustrated in the oxidation of trifluoromethylnaphthalenes, where the only product observed results from the oxidation of the ring not containing the trifluoromethyl moiety (Figure 3.13).[27]

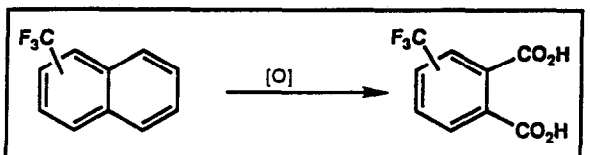


Figure 3.13

4. Preparation of Trifluoromethylated Aromatics and Trifluoromethylated Heteroaromatics

In 1898 F. Swarts prepared the first trifluoromethyl containing molecule, benzotrifluoride.[28] Over the next 60 years few variations or new methods were reported, with the real explosion occurring in the last 30 years.

The methods which have been developed for the preparation of trifluoromethylaromatics and trifluoromethylated heteroaromatics can be divided into four main categories: the conversion of a substituted methyl group to a trifluoromethyl group, the use of trifluoromethylcopper, the use of trifluoromethyl radicals and finally methods which do not fit into the above categories.

4.1 Conversion of $-CX_3$ to $-CF_3$

At the end of the last century, F. Swarts discovered that the mildest fluorinating reagent he had developed, antimony trifluoride, could be used to convert benzotrichloride into benzotrifluoride (Figure 4.1).[12,28]

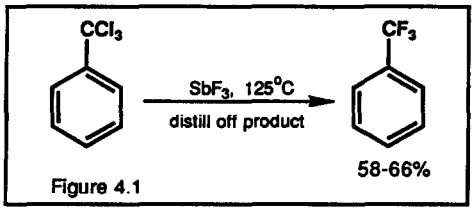


Figure 4.1

Later it was found that hydrogen fluoride could also fluorinate benzotrichloride to yield the trifluoride.[29] These methods are still used today, one example being the industrial preparation of 3-aminobenzotrifluoride from toluene (Figure 4.2).[30]

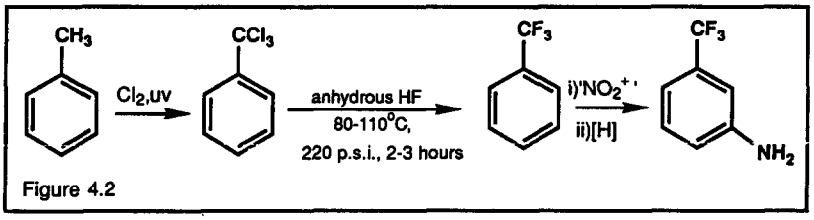


Figure 4.2

The use of hydrogen fluoride or antimony trifluoride has a number of disadvantages relating to the harsh conditions they impose and their toxicity. These facts have lead to the development of milder alternative reagents such as aluminium trichloride/fluorotrichloromethane[21] and silver tetrafluoroborate.[22] The yields when silver tetrafluoroborate is used are moderate, but certain benzotrichlorides have been found to be quantitatively converted to their trifluoride derivative when aluminium trichloride and fluorotrichloromethane are used. The conditions for this latter fluorinating system are relatively mild (room temperature in a pressure vessel), but so far only polychlorobenzotrichlorides have been reported to react. However, if a polychlorobenzene (other than hexachlorobenzene) is exposed to the aluminium trichloride-

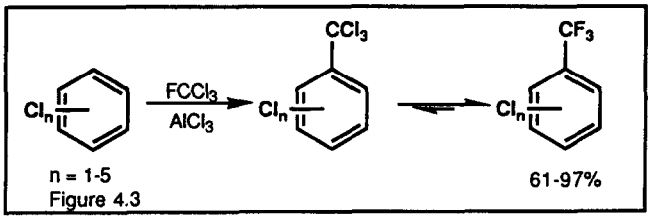


Figure 4.3

fluorotrichloromethane system, then a polychlorobenzotrifluoride is produced (Figure 4.3).

The incorporation of a trifluoromethyl group using variations on the antimony trifluoride or hydrogen fluoride systems has also been claimed in a number of patents (Figure 4.4).[31] In general, a tetrahalomethane is reacted with an aromatic substrate in the presence of the fluorinating reagent and a catalyst to yield mixtures of benzotrifluorides.

In addition to benzotrichlorides, aromatic orthothioesters, prepared from their corresponding acids[32], have been used as precursors to benzotrifluorides. The conversion is carried out in two steps by the sequential addition of N-bromosuccinimide (or equivalent) followed by hydrogen fluoride in pyridine (Figure 4.5). The reaction is carried out at low temperature and the yields vary from moderate to good (34-67%) depending upon substrate.

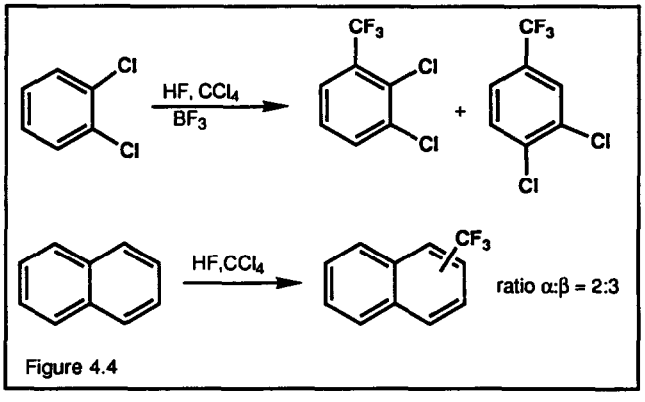


Figure 4.4

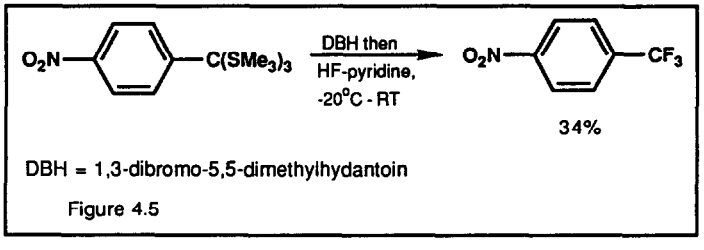


Figure 4.5

A limited number of aromatic dithiocarboxylic acids have also been employed in the preparation of benzotrifluorides.[33] The dithiocarboxylic acid can be prepared by the reaction of an aromatic Grignard reagent with carbon disulphide[34], and reacts with xenon

difluoride to give the desired product in 40 to 77% yield (Figure 4.6). However, the cost of xenon difluoride makes the reaction less attractive.

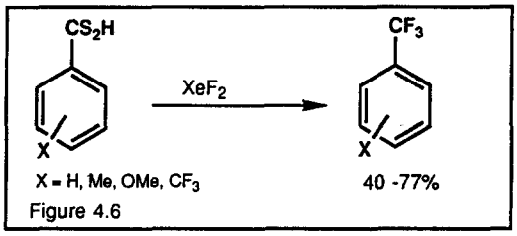


Figure 4.6

Finally, sulphur tetrafluoride can be used to convert benzoic acids containing a wide range of substituents to benzotrifluorides (Figure 4.7). It has been shown that electron withdrawing groups on the aromatic ring reduce the yield of benzotrifluoride when sulphur tetrafluoride is used alone. However, the addition of excess hydrogen fluoride to

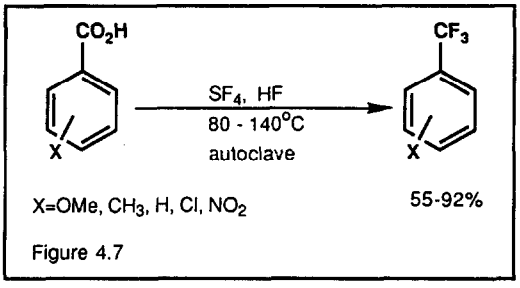


Figure 4.7

the reaction mixture not only improves the yields, but also allows milder reaction conditions to be employed. Further, methyl esters of aromatic carboxylic acids have been shown to produce benzotrifluorides in good yield when the sulphur tetrafluoride and hydrogen fluoride system is employed. The toxicity of the reagents coupled with the relatively high cost of the sulphur tetrafluoride and the use of pressure vessels do make this route less attractive.

Diethylaminosulphur trifluoride (DAST), a more easily handled derivative of sulphur tetrafluoride, has only been reported to convert benzoic acid into benzotrifluoride in the presence of sodium fluoride (Figure 4.8). The reactions of both sulphur tetrafluoride and DAST have been extensively covered in two reviews by Wang and Hudlicky.[35]

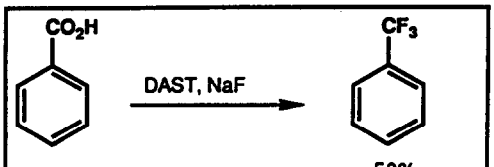


Figure 4.8

4.2 Use of Trifluoromethylcopper and Related Reactions

Perfluoroalkyl iodides were first reported to couple with aromatic iodides in the presence of copper to yield perfluoroalkylaromatics in 1968.[36] Shortly thereafter, two papers were published in which iodoaromatics were trifluoromethylated using iodotrifluoromethane and copper metal.[37] The reactive species in these systems was thought to be '$CuCF_3$', but it was not until 1986 that any spectroscopic evidence for this intermediate was given.[38] It was shown by ^{19}F N.M.R. that trifluoromethylcopper, in this case generated by the metathesis of trifluoromethyl cadmium with copper (I) salts (Figure 4.9) contains three distinct, but not fully identified forms (hereafter denoted A, B and C).

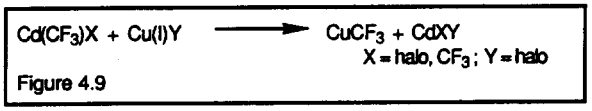


Figure 4.9

The initial product of the metathetical reaction is species A and is the most reactive with respect to the trifluoromethylation of iodoaromatics. When no substrate is present, species A is converted to B and C, where C is the least reactive species. Over time, all three species are converted to perfluoroethylcopper. More recent work has shown that two of these species are CF_3CuL (L = metal halide) and $CdI^+[(CF_3)_2Cu^-)]$.[38b] The latter compound is easily oxidised by oxygen to form $CdI^+[(CF_3)_4Cu]^-$, a Cu^{III} species. If, instead of oxygen, thiuramdisulphide is used as the oxidant, a stable copper (III) complex is formed (Figure 4.10), whose structure has been determined by X-ray analysis. This complex begins to decompose at temperatures over 100 °C, yet it is at this temperature that

trifluoromethylation occurs. More details regarding the exact nature of the trifluoromethylcopper species have yet to be determined.

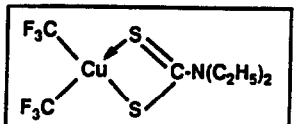


Figure 4.10

In as much that the term 'trifluoromethylcopper' obviously refers to more than one species, it will be used to denote all such species in this Report.

4.2.1 Preparation of Trifluoromethylcopper

There are a large number of ways in which trifluoromethylcopper can be prepared. Several of these methods involve preforming trifluoromethylcopper solutions while others allow the species to form 'in situ'. Certain advantages have been found in preforming trifluoromethylcopper from iodotrifluoromethane and copper metal and removing the excess copper metal.[39] These include the ability to monitor the reaction with time (reactions using iodotrifluoromethane at high temperatures are normally carried out in an autoclave), the use of much milder reaction conditions (e.g. lower temperatures) and the reduction in side products generated due to the reaction of copper metal with the aromatic substrate.

Trifluoromethylcopper solutions may also be prepared by the reaction of copper metal with bis(trifluoromethyl) mercury[40] (which is prepared by the thermal decomposition of mercury trifluoroacetate[41]), though the toxicity of the mercury reagent makes this system less attractive.

More recently, N-trifluoromethyl-N-nitrosotrifluoromethane sulphonamide (TNS-Tf) has been reacted with copper metal in acetonitrile to yield a brown solution of trifluoromethylcopper (Figure 4.11). TNS-Tf is synthesized from trifluoronitrosomethane, hydroxylamine and trifluoromethanesulphonyl chloride.[42]

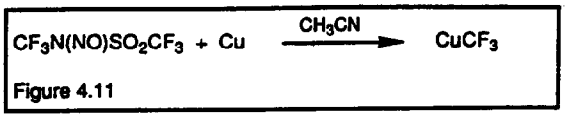


Figure 4.11

An electrochemical method of preparing trifluoromethylcopper solutions utilises the cheap and readily available bromotrifluoromethane.[222] The reactions is carried out by electrolysing a solution of a supporting electrolyte and a complexing agent in dimethylformamide using a copper anode, while gaseous bromotrifluoromethane is bubbled through the cell. The presence of the complexing agent prevents precipitation of copper bromide and it takes about six hours to reduce 30 mmols of bromotrifluoromethane.

Finally, as described previously , copper (I) salts undergo methathetical reactions with both trifluoromethyl cadmiums ($Cd(CF_3)_2$ or $Cd(CF_3)X$, X = halide) and trifluoromethyl zincs ($Zn(CF_3)_2$ or $Zn(CF_3)X$)to yield solutions of trifluoromethylcopper.[38]

The remaining reports concerning the trifluoromethylation by trifluoromethylcopper are 'one pot' systems in which '$CuCF_3$' is presumed to be the trifluoromethylating agent. Both iodotrifluoromethane and bromotrifluoromethane have been exploited as trifluoromethyl sources in these systems. Although bromotrifluoromethane is less expensive than iodotrifluoromethane, the reported yields are lower. Trifluoromethyl-sulphonyl chloride also reacts with copper metal in the presence of an iodoaromatic to yield trifluoromethylated products, but as yet little information is available.[66]

Metal trifluoroacetates have been used to trifluoromethylate aromatics, although only when copper iodide is present.[43-46] There is evidence to suggest that the reaction mechanism involves the 'in situ' formation of $[CuCF_3I]^-$ via the decarboxylation of the trifluoroacetate.[43]

More recently, trifluoromethyltriethylsilane has been used in the trifluoro-methylation of aromatic iodides. The reaction takes place in the presence of an equivalent of a copper (I) salt and a fluoride ion source.[47]

A number of reports have described the use of compounds containing a difluoromethylene moiety as precursors to trifluoromethylcopper. The first of these

employs difluorodihalomethanes, which react with copper metal in the presence of a dialkylamide solvent to ultimately yield '$CuCF_3$'.[48] The mechanism for this transformation is laid out in Figure 4.12[49] and involves the formation of a difluorocarbenoid species. This species reacts with both the solvent, to yield difluoromethyldimethylamine ($CF_2HN(CH_3)_2$, a FAR - like reagent[50]), and the fluoride ion generated by the difluoromethyldimethylamine. If the '$CuCF_3$' reagent generated in this way does not immediately react with a substrate, further reaction will occur with the difluorocarbenoid species to yield perfluoroethyl copper and from this, higher perfluoroalkyl species.

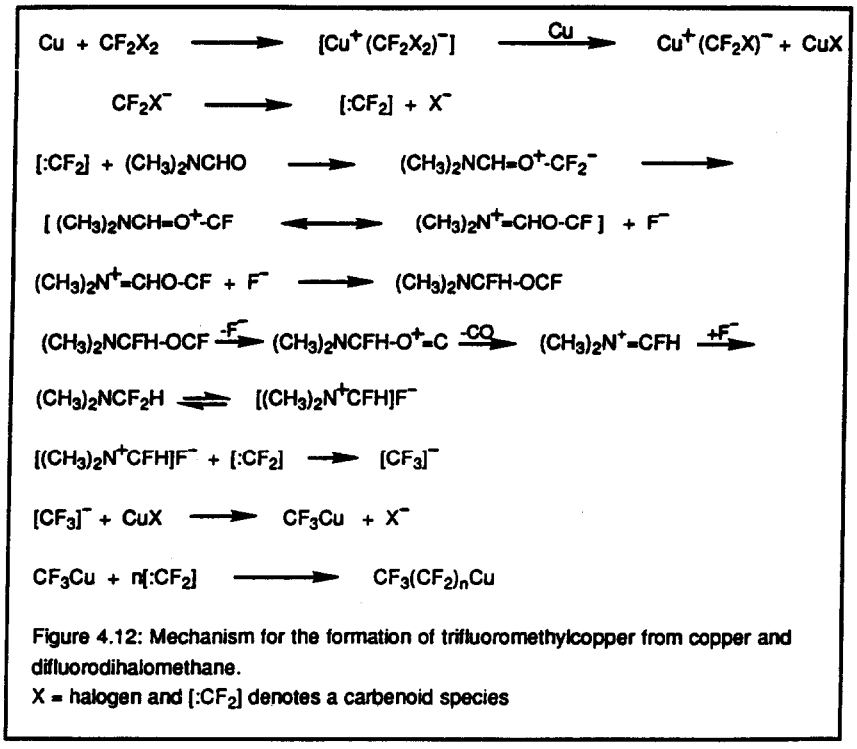


Figure 4.12: Mechanism for the formation of trifluoromethylcopper from copper and difluorodihalomethane.
X = halogen and [:CF_2] denotes a carbenoid species

Sulphonyl fluorides containing a difluoromethylene moiety have also been used in the preparation of trifluoromethylcopper. Methyl fluorosulphonyldifluoroacetate ($MeO_2CCF_2SO_2F$) reacts with copper iodide to yield initially difluorocarbene and fluoride

ion, which go on to form trifluoromethylcopper.[51] Similarly fluorosulphonyldifluoromethyl iodide yields difluorocarbene and fluoride ions upon reaction with copper metal, which go on to form trifluoromethylcopper (Figure 4.13).[52]

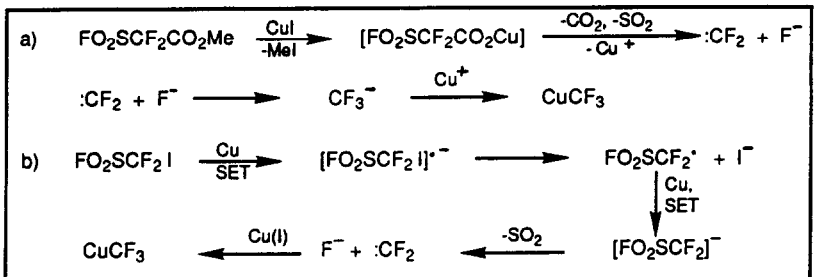


Figure 4.13: Reactions of sulphonyl fluoride in the preparation of trifluoromethylcopper

The most recently reported method of generating trifluoromethylcopper from a difluoromethylene precursor utilises the readily available methyl chlorodifluoroacetate.[221] The reaction is thought to proceed in a similar fashion to methyl fluorosulphonyldifluoroacetate. The initial step involves the elimination of methyl iodide and the formation of chlorodifluorocopper acetate upon reaction of the acetate with copper iodide. The copper chlorodifluoroacetate then decomposes yielding copper chloride, carbon dioxide and difluorocarbene. This latter species is sequentially trapped by fluoride ion (potassium fluoride is added to the reaction mixture) and copper (I) to utimately yield trifluoromethylcopper.

A summary of the methods in which trifluoromethylcopper can be generated is given in Figure 4.14.

4.2.2 Reactions of Trifluoromethylcopper

The first reaction of trifluoromethylcopper to be considered is its decomposition. Solutions of trifluoromethylcopper are sensitive to air and must be handled under inert atmospheres.[39] It is also known that trifluoromethylcopper slowly converts to pentafluoroethylcopper.[38] The result of this decomposition has been noted in a number of

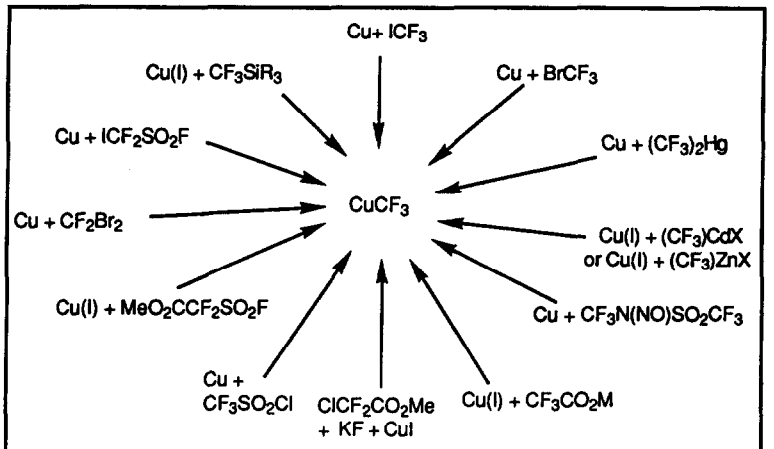


Figure 4.14: Methods of preparing trifluoromethylcopper

trifluoromethylation reactions where, in addition to trifluoromethyl products, pentafluoroethyl aromatics are observed (Figure 4.15). This is always the situation when the substrate does not readily react well with trifluoromethylcopper (eg. unactivated bromo and chloro aromatics).[53]

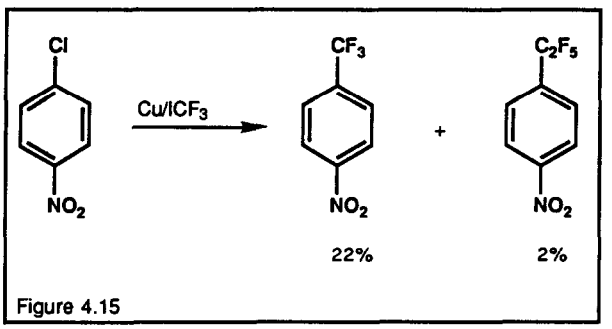


Figure 4.15

Since the mechanism of formation of pentafluoroethylcopper from trifluoromethylcopper is thought to involve difluorocarbenoid species, it is of little surprise that perfluoroalkyl copper species are readily formed in the copper/difluorodihalomethane/ amide system.[49] Only very reactive substrates remove the trifluoromethylcopper fast enough to prevent the formation of perfluoroalkyl coppers. The chain extension reaction

can be suppressed by the addition of fluoride ions, resulting, however, in lower yields of trifluoromethylated products.[48]

Given this inhibition of the chain extension process by fluoride ions, it is interesting to note that perfluoroethyl side products are observed in the fluoride ion catalysed trifluoromethylation of iodoaromatics using trifluoromethyltriethylsilane and copper iodide[47] This suggests that free trifluoromethyl anions are present, since these are known to be very unstable, decomposing to difluorocarbene and fluoride ions even at very low temperatures.[57]

Further, it is worth mentioning that no perfluoroalkyl side products are found when the methyl fluorosulphonyldifluoroacetate/copper iodide and fluorosulphonyl-difluoromethyl iodide/copper trifluoromethylating systems are employed, even though the trifluoromethylcopper is generated from difluorocarbene.

When considering the reactions of trifluoromethylcopper with haloaromatics, it is best to deal with iodo-, bromo- and chloro- substrates separately. However, the mechanism in operation for all of these substrates is thought to be the same; copper assisted nucleophilic substitution, as illustrated in Figure 4.16. Since iodoaromatics have been the most widely employed, these will be considered first and will be used to compare the various trifluoromethylating systems.

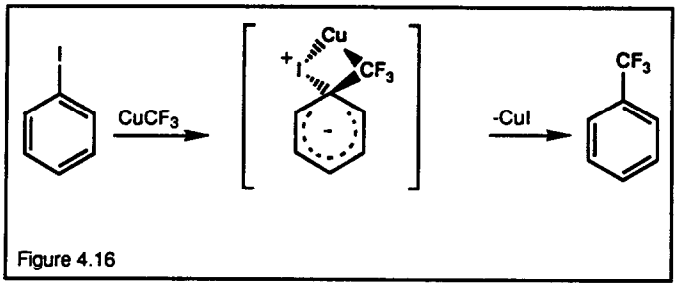


Figure 4.16

The nucleophilic nature of the reaction is confirmed by the ρ value of +0.46 obtained from a crude Hammett plot of the reaction of para-substituted iodoaromatics with the sodium trifluoroacetate/copper iodide trifluoromethylation system.[43] Therefore, the

presence of an electron withdrawing substituent is expected to enhance the reaction, whilst electron donating substituents will inhibit it.

A wide range of substituents can be present in the aromatic ring during the trifluormethylation reaction, with the only obvious exceptions being the strongly electron donating substituents -OH and -NH_2 (the protic nature of the former substituent may also account for the lack of reaction of substrates containing it).

A comparison of the relative abilities of the different system to difluoromethylate iodobenzene, p-iodonitrobenzene and p-chloroiodobenzene is given in Table 4.1. The lowest yields reported employed bromotrifluoromethane as the source of the trifluoromethyl group.[55] However, a recent patent claimed high yields for the preparation of trifluoromethyluridines using bromotrifluoromethane and copper (Figure 4.17).[58]

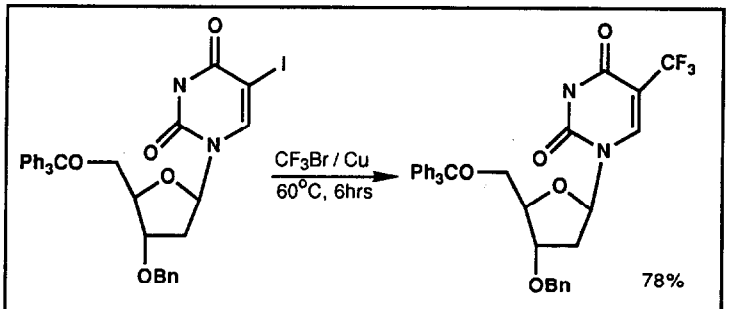


Figure 4.17

The other trifluoromethylating systems are relatively similar in their ability to convert iodobenzenes to benzotrifluorides. Each system has advantages and disadvantages (eg cost, toxicity of reagents, availability of reagents, reaction conditions) and the choice of one over another will depend on the individual case being examined.

It is also clear from Table 4.1 that the solvents employed are invariably dipolar and aprotic, though it has been shown that in the case of the difluorodihalomethane/copper/ N,N-dialkylamide system only a stoichiometric quantity of dialkylamide is required and that the reaction can be run in chlorobenzene.[59] It is difficult to judge which solvent, if

'CuCF$_3$' Source	Time	Temperature	Solvent	PRODUCT/% YIELD $C_6H_5CF_3$	p-$NO_2C_6H_9CF_3$	p-$ClC_6H_5CF_3$	ref
Cu/ICF$_3$	6 hrs	150 °C	DMF[1]	45%	-	-	37b
	14-30 hrs	130-140 °C	DMF[1]	74%	51%	-	54
Cu/BrCF$_3$	20 hrs	130 °C	HMPA[1]	11%	-	-	55
Cu/$(CF_3)_2$Hg	3 hrs	150 °C	NMP	65%	88%	-	40
Cu/TNS-Tf	18-19 hrs	100 °C	HMPA/CH_3CN (5:3) or NMP/CH_3CN	-	[68%]	[74%]	42
CuI/$CdCF_3X$	-	-	DMF	80%	-	-	56
CuI/CF_3CO_2M	4 hrs	160 °C	NMP	(72%)	(39%)	(68%)	46
	4 hrs	160 °C	NMP	(87%)	(64%)	-	43
CuI/CF_3SiEt_3/F	24 hrs	80 °C	NMP/DMF[1] 1:1	-	(99%)[3]	35%	47
Cu/CF_2X_2	-	70°C	DMF	[100%]	75%	-	38
CuI/$MeO_2CCF_2SO_2F$	2.5-4.5 hrs	65-70 °C	DMF	84%[2]	80[2]%	90%	51
Cu / ICF_2SO_2F	6-7 hrs	80 °C	DMF	80%[2]	83[2]%	84%	52
$ClCF_2CO_2Me$/CuI/KF	8 hrs	100-120°C	DMF	88%	89%	81%	221

Table 4.1: Reaction of Iodoaromatics with Various Trifluoromethylating Reagents.
[1]. Reaction carried out in a sealed tube, [2]. Yield based on trifluoromethylating reagent used, [3]. perfluoroethylaromatics observed.
[ ] denotes ^{19}F NMR yields and ( ) denotes g.l.c.yields.

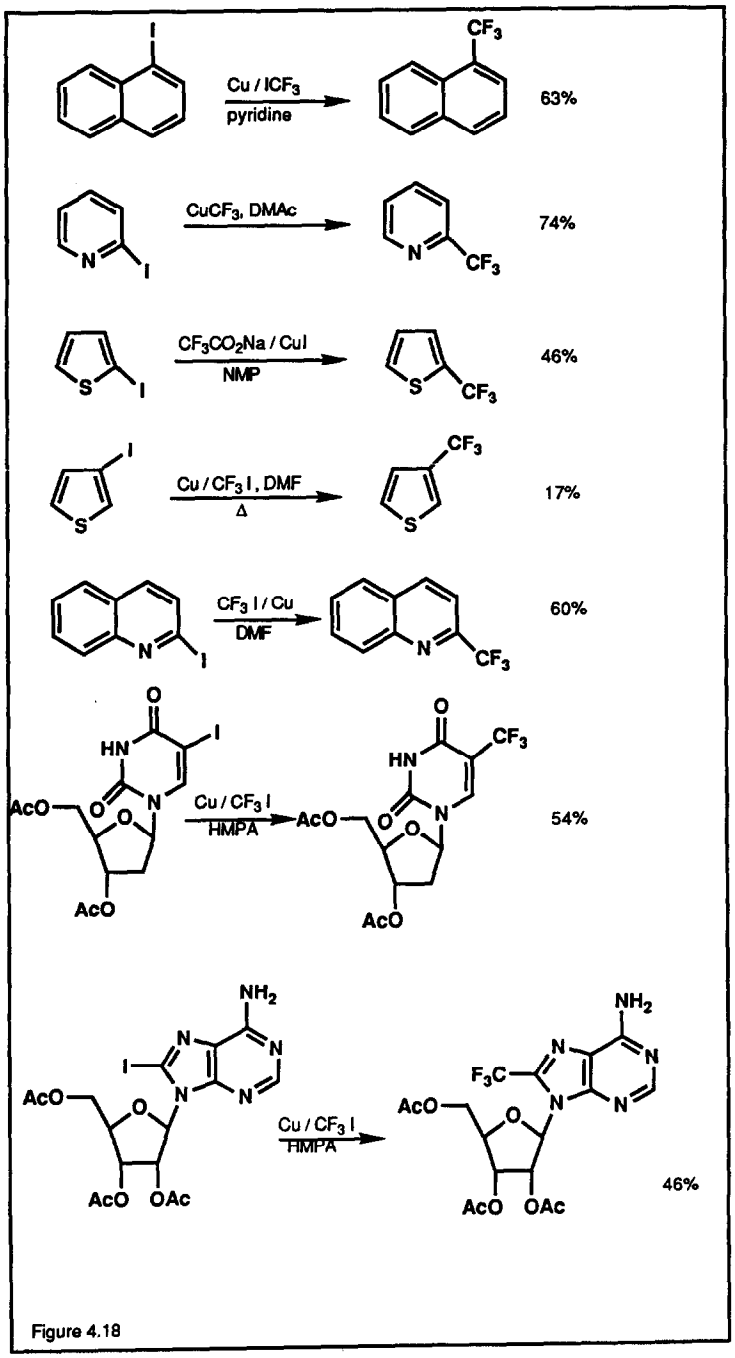

Cu / ICF3
pyridine
63%
CuCF3, DMAc
74%
CF3CO2Na / CuI
NMP
46%
Cu / CF3I, DMF
Δ
17%
CF3I / Cu
DMF
60%
Cu / CF3I
HMPA
54%
Cu / CF3I
HMPA
46%

Figure 4.18

any, is best since solvents are often quoted as interchangeable and in most cases only one or two solvents have been investigated. However, for certain systems it is possible to be more exact. The iodotrifluoromethane/copper system appears to give better yields in the order pyridine > hexamethylphosphoramide (HMPA) >> N,N-dimethylformamide (DMF) > acetonitrile.[54] Indeed, chlorobenzene itself is quoted as reacting with iodotrifluoromethane/copper in pyridine, albeit in low yield, whereas in other solvent systems it is found to be inert. In the case of the sodium trifluoroacatate/copper iodide system, N-methyl-2-pyrrolidinone (NMP), hexamethylphosphoramide and N,N-dimethylformamide

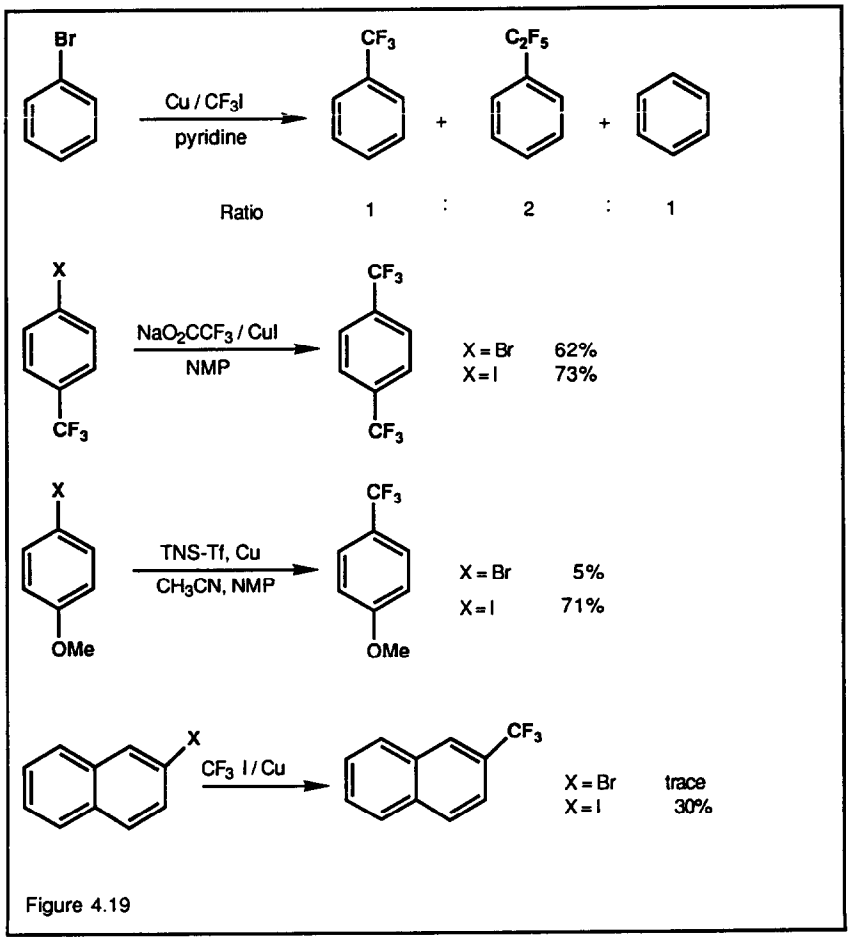


Figure 4.19

have all been used to good effect,[43, 44, 46] though it is reported that with sulpholane and diphenylsulphone no trifluoromethylation was observed.[43]

In addition to iodobenzenes, a wide range of other iodoaromatics and hereroaromatics have undergone successful trifluoromethylation reactions. Examples include iodonaphthalenes,[47, 60, 221, 222] iodopyridines,[40, 43] iodoquinolines,[54] iodonucleosides[58, 61, 38c] and iodothiophenes[62, 43] (Figure 4.18). It is worth noting that the free -NH_2 group in the purine example does not inhibit the reaction,[61] as is the case for iodoanilines and aminoiodopyridines.[43]

When bromoaromatics or bromoheteraromatics are used instead of their iodo-analogues lower yield are recorded.[42, 43, 46, 51, 52, 54, 60a, 221, 222] In addition, reactions are sometimes complicated by the formation of perfluoroethyl and dehalogenated aromatics[53] (Figure 4.19). Nevertheless, the fact that a number of patents have claimed the preparation of trifluoromethylated compounds from bromoaromatics shows that these compounds can be exploited successfully[45, 63] (Figure 4.20).

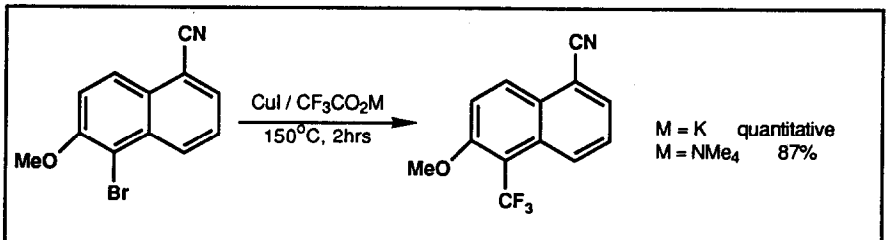


Figure 4.20

Further, trifluoromethyl nucleosides have been prepared from the corresponding bromonucleosides in reasonable yield (Figure 4.21).[61, 64]

The least investigated of the halo- substrates are chloroaromatics. The few early reports quoted low yields and perfluoroethyl side products when any reaction was observed (Figure 4.22).[53, 54] However, it has been shown recently that certain chloroaromatics react specifically and give reasonable yields of trifluoromethylated products.[59, 65] In order for the chloroaromatics to react specifically it should possess a

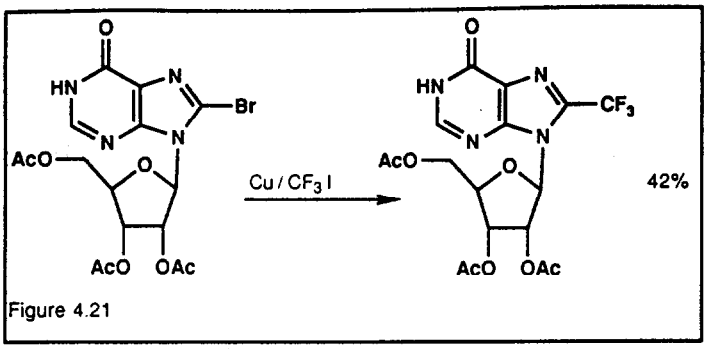


Figure 4.21

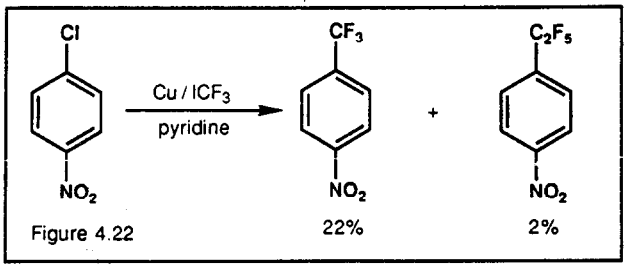


Figure 4.22

suitable ortho group (NO_2, CHO, CO_2Me, COR) and be electron deficient. The ortho-group is essential for smooth replacement of the chlorine (Figure 4.23) and the reaction is thought to proceed via the transition state shown in Figure 4.24.

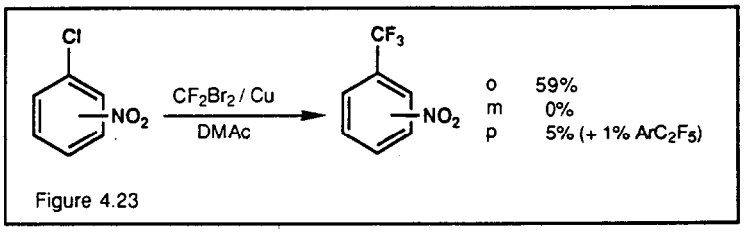


Figure 4.23

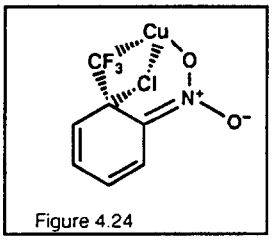


Figure 4.24

If the chlorine is not sufficiently activated by electron withdrawing groups, then side products are observed (Figure 4.25). The perfluroalkyl side products result from the reaction of trifluoromethylcopper with difluorocarbene generated by the reaction of copper with dibromodifluoromethane (see Section 2.1). When the substrate is sufficiently reactive, it removes all the trifluoromethylcopper before it can undergo chain elongation reactions.

The use of a trifluoromethylating system which does not involve 'difluorocarbene' in the formation of trifluoromethylcopper would be expected to reduce the problem of perfluoroalkylation. This is observed when either trifluoromethanesulphonyl chloride/ copper and the bromotrifluoromethane/copper anode systems are employed.[66, 222]

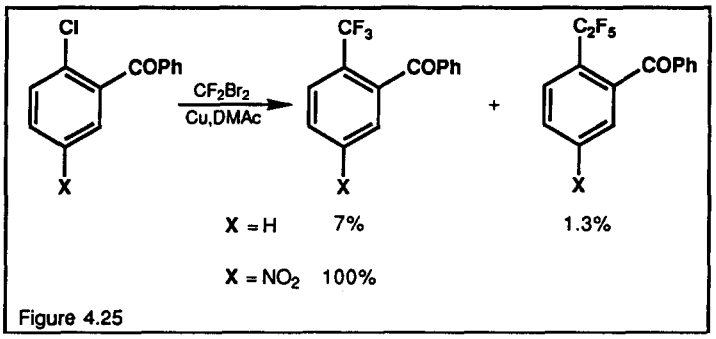


Figure 4.25

Chloroheteroaromatics have also been found to trifluoromethylate in reasonable yield (Figure 4.26).[43, 54, 65]

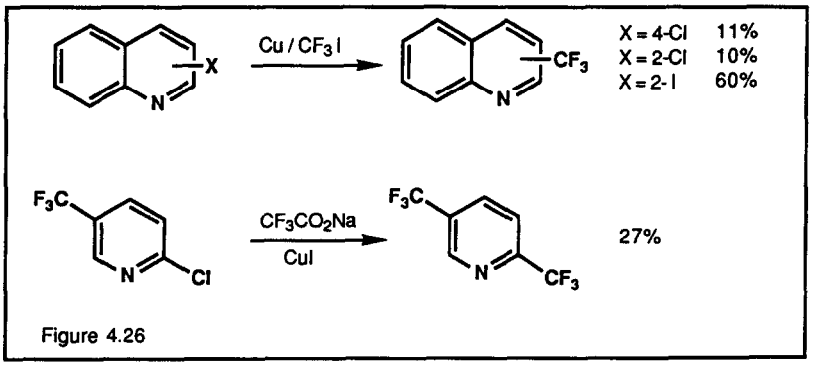


Figure 4.26

As with chloroaromatics, when the dibromodifluoro-methane/copper system was employed perfluoroalkylated products were observed unless the chlorine atom was further activated by an appropriate ortho electron withdrawing group.[59, 65] (Figure 4.27).

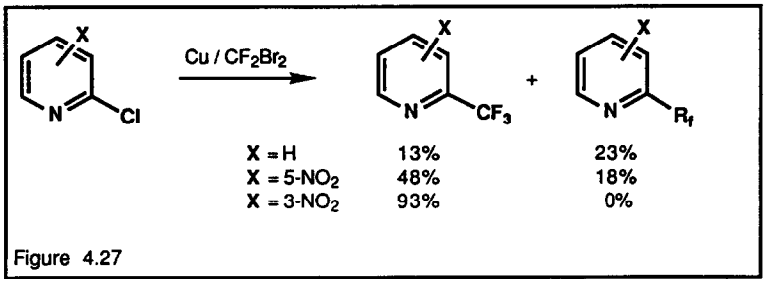


Figure 4.27

Trifluoromethyl nucleosides have also been prepared using their chloro- adducts[61] (Figure 4.28).

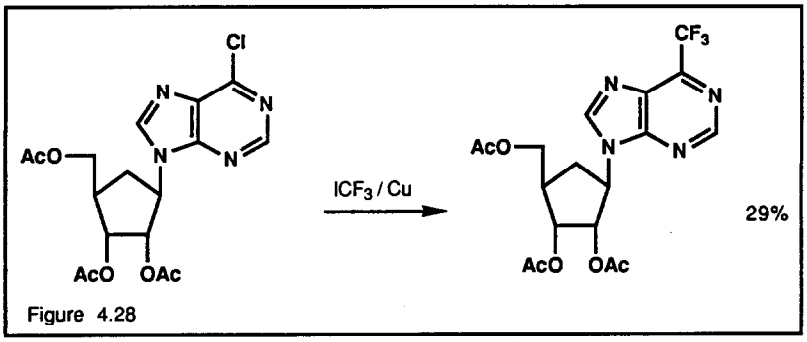


Figure 4.28

Not all haloaromatic substrates yield the ipso substituted product in reactions with trifluoromethylcopper and there is even an example where trifluoromethylcopper reacts with a non-halogenated compound (pyridine).[53] These reactions are illustrated in Figure 4.29.

Finally, in a report concerning the use of the dihalodifluoromethane/copper showed that the addition of certain high surface area solids (eg charcoal) increased the rate of the trifluoromethylation reaction Figure 4.30. However, when charcoal was added to the reaction of substrates which had previously been shown to give perfluoroalkylated

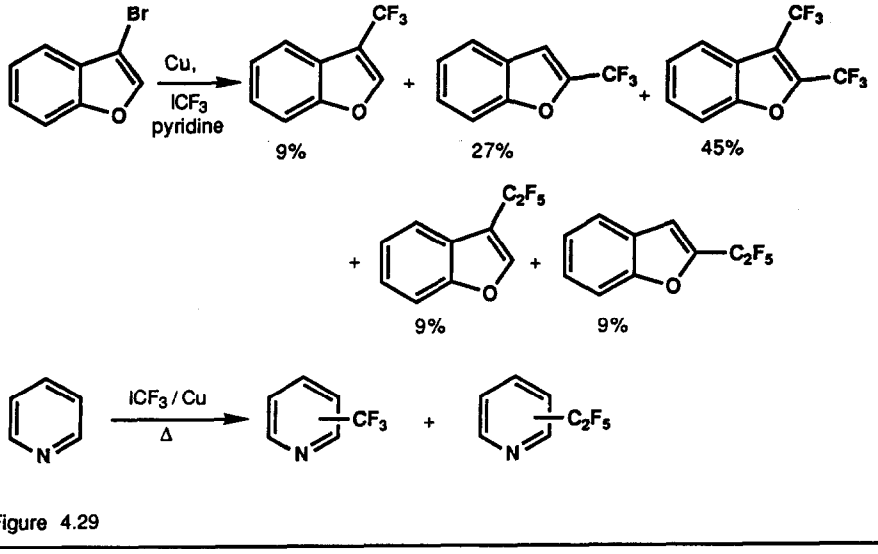


Figure 4.29

products, the quantity of these products increased substantially. The increase in the rate of reaction is thought to be a result of reducing the "dimensionality" of the system thereby making it more likely for reactive species to come into contact.[65b]

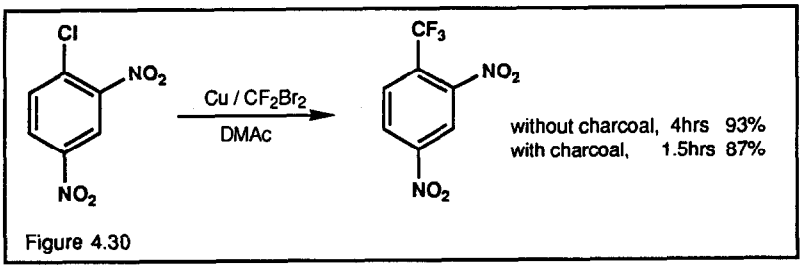


Figure 4.30

4.2.3 Other Reactions

Two reports exist where trifluoromethylation apparently goes via a trifluoromethyl anion type species, but does not involve copper (I). Both potassium[67] and silver[68] trifluoroacetate have been used in this respect. In the example of potassium trifluoroacetate, 1,3,5-trinitrobenzene was trifluoromethylated to produce initially a stable

Meisenheimer intermediate, which could be decomposed to the aromatic compound using *tert*-butyl hypochlorite (Figure 4.31).

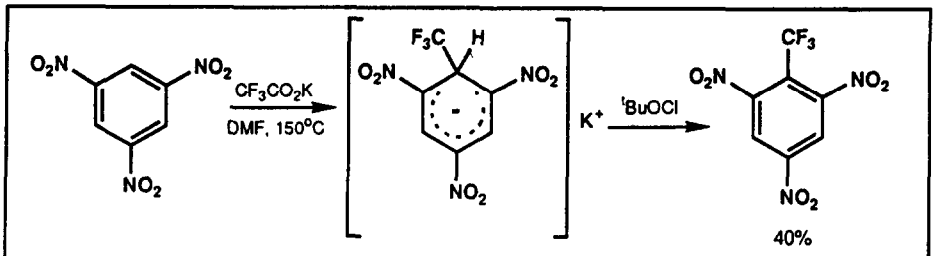


Figure 4.31

4.3 The Use of Trifluoromethyl Radicals

4.3.1 Generation of Trifluoromethyl Radicals

Trifluoromethyl radicals were first reported to trifluoromethylate aromatics in 1948.[69] The radical is electrophilic in nature[70c], and may be generated by photochemical, electrochemical, thermal or chemical reactions.

A large number of molecules have been used as precursors to trifluoromethyl radicals in photochemical reactions. The best known is probably iodotrifluoromethane,[71, 72, 73, 74] though bromotrifluoromethane,[75,76] *bis*(trifluoromethyl)mercury,[77] diazotrifluoromethane,[70] *bis*(trifluoromethyl)tellenium,[78, 79] N-trifluoromethyl-N-nitrososulphonamides[42,80] and *tris*(trifluoromethyl) antimony[78,79] have all been exploited. When iodotrifluoromethane was used, the addition of mercury was found to improve yields dramatically.[71] The mercury effectively removes iodine radicals, thus leaving the trifluoromethyl ones to react with the substrate. Similarly, N-trifluoromethyl-N-nitrososulphonamides ($CF_3N(NO)SO_2R$) require the presence of biacetyl in order for reaction to occur.

In a paper which investigated the relative abilities of a number of trifluoromethyl radical sources including iodotrifluoromethane, *bis*(trifluoromethyl)mercury,

bis(trifluoromethyl)cadmium, *bis*(trifluoromethyl)tellurium and *tris*(trifluoromethyl) antimony it was found that *bis*(trifluoromethyl)tellurium was the most suitable trifluoromethylating reagent in photochemical reactions (Figure 4.32).[78]

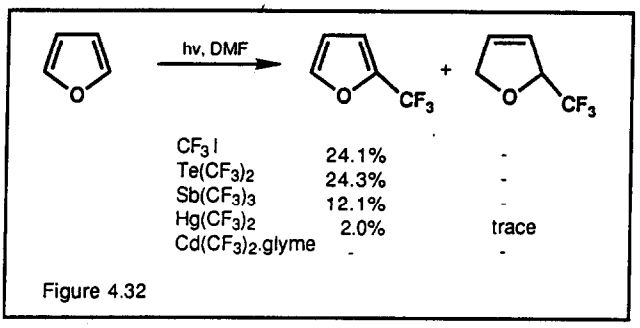


Figure 4.32

Bis(trifluoromethyl)tellurium has also been used to thermally generate trifluoromethyl radicals,[79] as has iodotrifluoromethane,[81, 82, 83] bromotrifluoromethane,[84] hexafluoroacetone,[92] N-trifluoromethyl-N-nitrosotrifluoromethylsulphonamide[42] and trifluoromethylazo-sulphonylbenzene.[86]

Electrochemical generation of trifluoromethyl radicals invariably used solutions of partially neutralised trifluoroacetic acid,[87, 88] or bromotrifluoromethane[138] whilst the chemical methods are more varied. Thus, trifluoromethyl radicals can be generated by the reaction of trifluoromethyl bromide with zinc/sulphur dioxide or sodium dithionite[93], xenon difluoride with trifluoroacetic acid,[89] *bis*(trifluoroacetyl)peroxide with suitable substrates[90,91] or sodium trifluoromethanesulphinate with t-butyl hydroperoxide.[93b]

The mechanism for generation of trifluoromethyl radicals from bromotrifluoromethane is laid out in Figure 4.33 and involves electron transfer from the radical anion of sulphur dioxide to bromotrifluoromethane.[93]

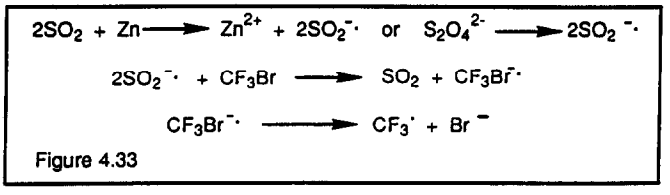


Figure 4.33

When xenon difluoride and trifluoroacetic acid are mixed, trifluoromethyl radicals are generated by the decomposition of xenon trifluoroacetates. However, fluorination by xenon difluoride also may occur as was the case when anisole and toluene were used as substrates.[89] The generation of trifluoromethyl radicals from *bis*(trifluoroacetyl)peroxide requires the substrate to act as an electron donor (see Figure 4.34), placing limits on the

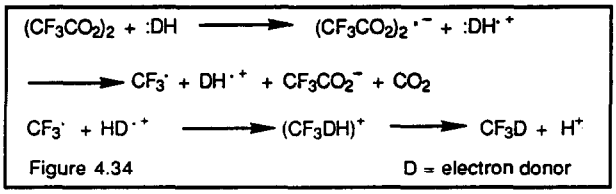


Figure 4.34

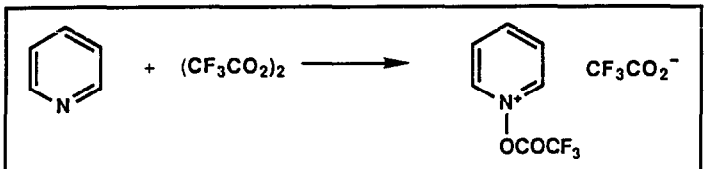


Figure 4.35

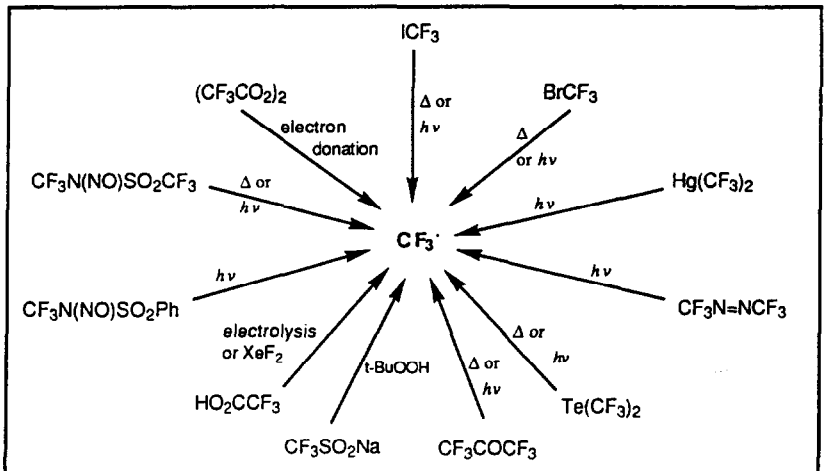


Figure 4.36: The methods available to prepare trifluoromethyl radicals

type of molecule which may be trifluoromethylated.[90, 91] So, for example, pyridine cannot be trifluoromethylated since it reacts with *bis*(trifluoroacetyl) peroxide as a nucleophile rather than an electron donor (see Figure 4.35). However electron rich benzenes, furans, thiophenes, pyrroles, indoles and non nucleophile pyridines (such as 2,6-*bis*(t-butyl)-pyridine) will react to form the desired products.

The methods of generating trifluoromethyl radicals are summarised in Figure 4.36.

4.3.2 Reaction of Trifluoromethyl Radicals with Aromatics

The electrophilic trifluoromethyl radicals react with electron rich aromatics including benzene,[73, 78, 81] naphthalene,[75, 76] haloaromatics,[70, 71, 82, 91, 92] xylenes,[91] toluenes,[91] anilines,[93, 96] acetanilides[42], phenols[82, 93] and anisoles[42, 80, 91, 93b] (see Figure 4.37). The different methods of generating trifluoromethyl radicals are compared in Table 4.2. The Table is incomplete since no one substrate has been employed in every system. However, by far the best yields recorded for the trifluoromethylation of benzene used iodotrifluoromethane and mercury.[71]

As is exemplified by the reaction of naphthalene, trifluoromethyl radicals are not highly specific. However they do show a marked preference for sites of high electron density in the HOMO,[75] supporting the mechanism laid out in Figure 4.38.

Heteroaromatics react with various degrees of regioselectivity. Pyrroles and N-alkylpyrroles,[73, 74, 90] 2-substituted imidazoles,[72] thiophene,[91] furan,[91] uracil,[77, 80, 88] uridine[42] and 2'-deoxyuridine[89] all react to give just one product. Various trifluoromethylating systems are compared with these substrates in Figure 4.39. It is worth noting that in the reactions of *bis*(trifluoroacetyl) peroxide, N-methylpyrrole does not react, whilst pyrrole itself gives moderately good yields of the trifluoromethylated product. This compares to the iodotrifluoromethane/*hv* system which led to similar quantities of both trifluoromethylpyrrole and N-methyltrifluoromethylpyrrole. It is

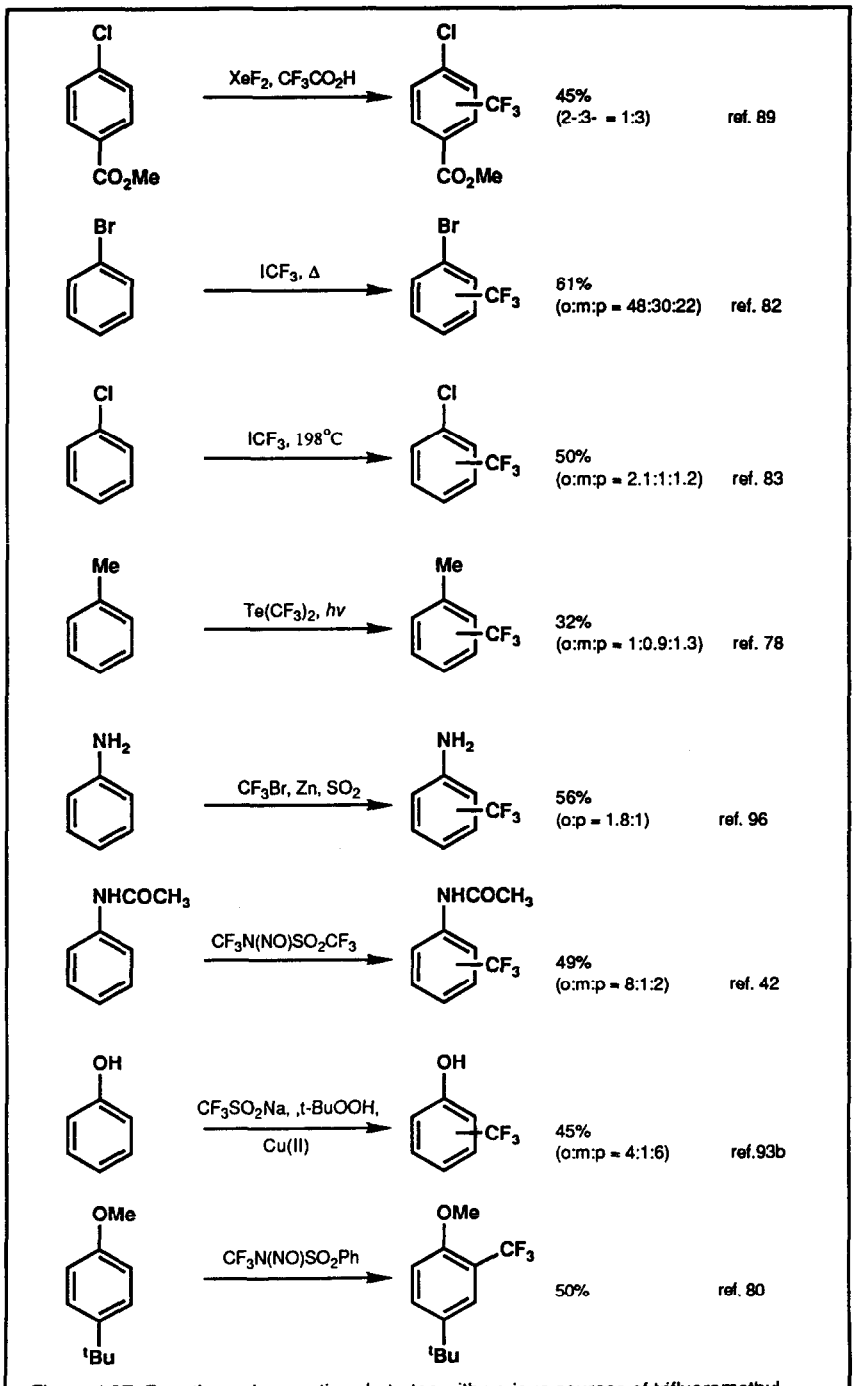


Figure 4.37: Reactions of aromatic substrates with various sources of trifluoromethyl radicals

CF_3-Source	Conditions	Products/Yields			Ref.
		$PhCF_3$	CF_3-naphthalene	(Ratio α:β)	
ICF_3	*hν*/Hg	65%	-		71
ICF_3	*hν*	14%	-		73
$BrCF_3$	*hν*	-	13%	(3.5:1)	75
$BrCF_3$	NaS_2O_4	(17%)			93
$CF_3N(NO)SO_2CF_3$	*hν*/biacetyl	[49%][1]	14%	(8.1:1)	42
$CF_3N(NO)SO_2Ph$	*hν*/biacetyl	[24%][1]	[39%]	(6.3:1)	80
CF_3CO_2H	XeF_2	[33%][1]	-		89
$(CF_3)_2Hg$	*hν*	(4%)	-		78
$(CF_3)_2Hg$	Δ (150 °C)	(51%)	-		78
$(CF_3)_2Te$	*hν*	(20%)[2]	-		78
$(CF_3)_2Te$	Δ (150 °C)	(31%)[3]	-		78
$(CF_3CO_2)_2$	Δ(70 °C)	(54%)	-		91

Table 4.2: Reaction of Trifluoromethyl Radicals with Benzene and Naphthalene.

[1] Yield based on quantity of trifluoromethyl radical source used, [2] 5-Trifluoromethyl cyclohexadiene also produced (4%), [3] *Bis*(trifluoromethyl)benzene (20%), 5-trifluoromethylcyclohexadiene (8%) and 5,6-*bis*(trifluoromethyl)cyclohexadiene (16%) also produced, [ ] denotes ^{19}F NMR yields, ( ) denotes glc yields

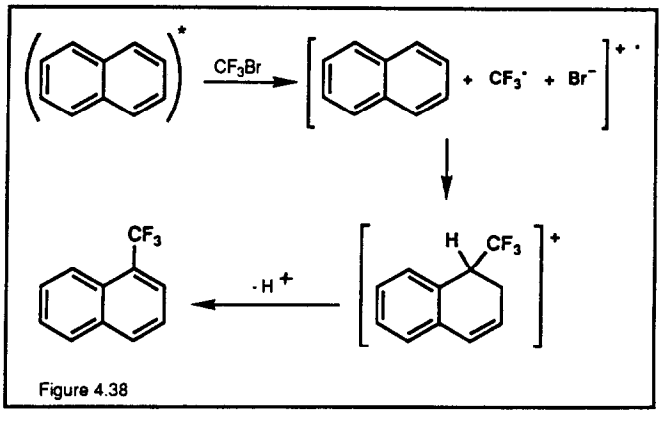
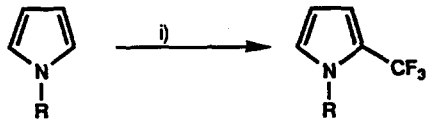
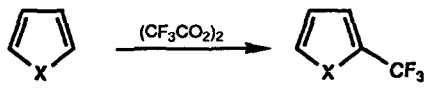


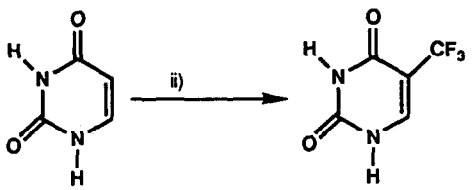
Figure 4.38



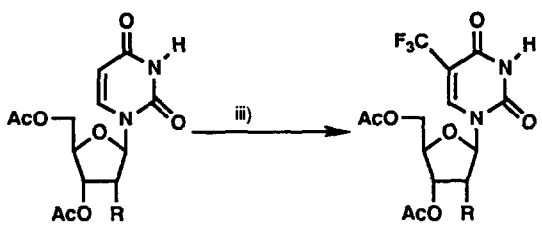
R = Me	i) = CF_3Br, *hv*	6.5%	ref. 75
	CF_3I, *hv*	35%	ref. 73
	$(CF_3CO_2)_2$	trace	ref. 90
	CF_3Br, Zn, SO_2	52%	ref. 93
R = Bn	i) = CF_3I, *hv*	60%	ref. 74
R = H	i) = CF_3I, *hv*	33%	ref. 73
	$(CF_3CO_2)_2$	56%	ref. 90



X = S	(72%)	ref. 91
X = O	(53%)	ref. 91



ii) = $Hg(CF_3)_2$	>60%	ref. 77
CF_3CO_2H, electrolysis	60%	ref. 88
CF_3Br, *hv*	11%	ref. 75



R = OAc,	iii) = $CF_3N(NO)SO_2CF_3$	30%	ref. 42
R = H	iii) = CF_3CO_2H, XeF_2	33%	ref. 89

Figures in ( ) refer to g.l.c. yields.

Figure 4.39

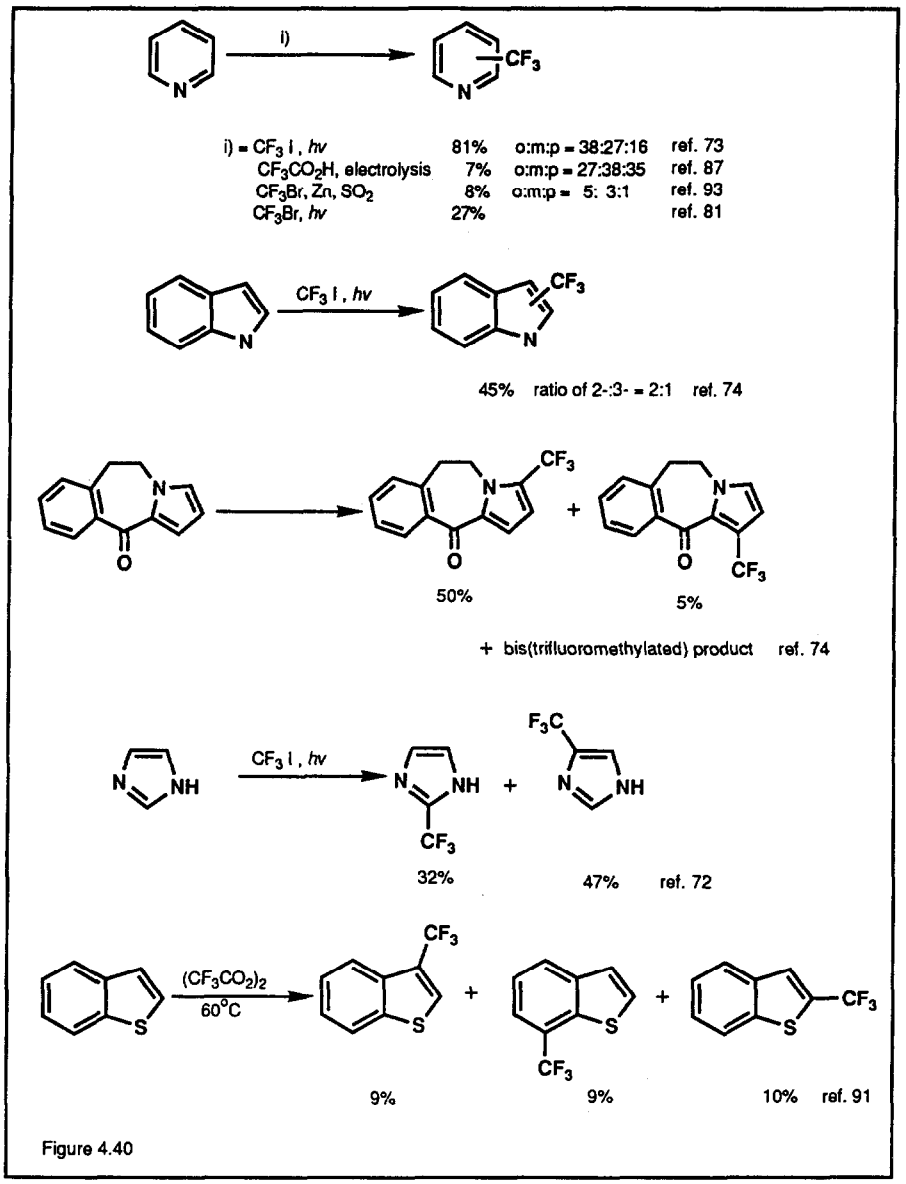

i)
i) = CF3 I , hv 81% o:m:p = 38:27:16 ref. 73
CF3CO2H, electrolysis 7% o:m:p = 27:38:35 ref. 87
CF3Br, Zn, SO2 8% o:m:p = 5: 3:1 ref. 93
CF3Br, hv 27% ref. 81
CF3 I , hv
45% ratio of 2-:3- = 2:1 ref. 74
50%
5%
+ bis(trifluoromethylated) product ref. 74
CF3 I , hv
32%
47% ref. 72
(CF3CO2)2
60°C
9%
9%
10% ref. 91

Figure 4.40

suggested that the lack of reactivity of *bis*(trifluoroacetyl)peroxide with N-methylpyrrole is a result of nucleophilic attack by the pyrrole rather than the required electron transfer (see Figure 4.39).

A number of other heteroaromatics showing less regioselectivity have been used as substrates in radical trifluoromethylation. These include pyridines,[73, 81, 84, 87, 93] imidazoles,[72] benzothiophene[91] and dihydropyrrolobenzazepinones.[74] Figure 4.40 gives representative examples of the reactions of these substrates.

Finally, it has been found that the imidazole ring in a peptide chain can be photochemically trifluoromethylated to give two products isolable by HPLC.[94] The fact that imidazole residues trifluoromethylate more readily than either benzenes or indoles may lead to greater application of this technique to prepare modified peptides. (Figure 4.41)

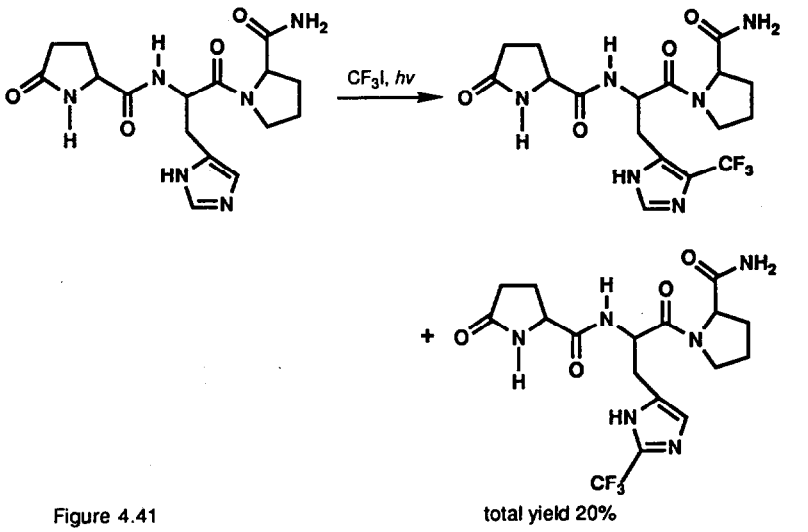


Figure 4.41 total yield 20%

4.4 Other Methods

(Trifluoromethyl)dibenzothiophenium salts and their seleno analogues have been prepared (see Figure 4.42) and used to trifluoromethylate anilines.[95] Although no mechanism is given for this reaction, it is probably based on trifluoromethyl radicals, since the type of substrates employed (electron rich aromatics, disulphides, enamines) are known to undergo reaction via radical addition. Further, when the thiophenium salt reacts with

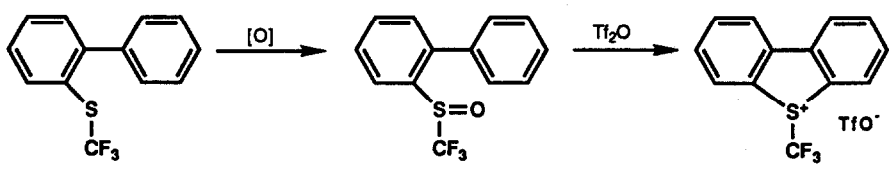
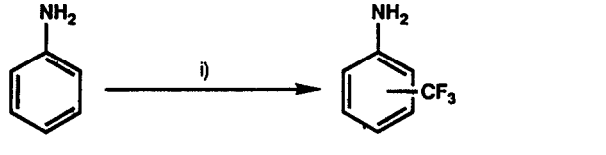


Figure 4.42: Preparation of (trifluoromethyl)dibenzothiophenium triflate

aniline, the ratio of isomers produced is similar to that observed with trifluoromethyl radicals.[96] (see Figure 4.43).



i) = (trifluoromethyl)dibenzophenium triflate 83% o:p = 2.2:1 ref. 95
= CF_3Br, Zn, SO_2 56% o:p = 1.8:1 ref. 96

Figure 4.43

Trifluoromethylaromatics have been produced by flash thermolysis of the corresponding trifluoroacetate (see Figure 4.44). The yields are low and the products include the trifluoromethoxy compound. The reaction is not thought to be radical in nature since only the ipso substituted isomer is observed.[97]

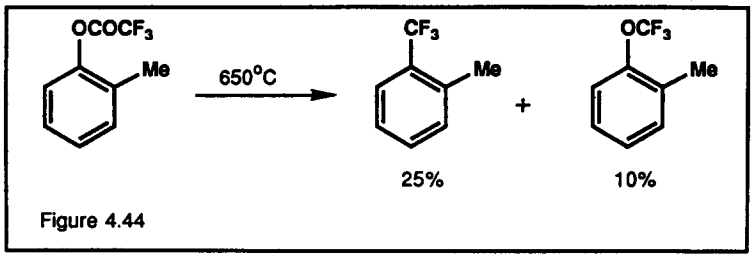


Figure 4.44

Trifluoromethyl cations, generated in the gas phase by ^{60}Co γ irradiation of tetrafluoromethane, react with pyrrole, furan and thiopene to give trifluoromethylated products. The reaction however is not regioselective and results in the formation of both α and β-trifluoromethylated products.[98]

Finally, although not strictly within the scope of this section, trifluoromethylated phenols and anilines have been produced in two steps from benzoquinones. In the first step, a trifluoromethyltrialkylsilane is added to benzoquinone to yield the siloxy derivative of the trifluoromethylcarbinol. The protected carbinol is subsequently reduced to 4-trifluoromethylphenol (Figure 4.45) or reductively aminated to 4-trifluoromethylaniline.[99]

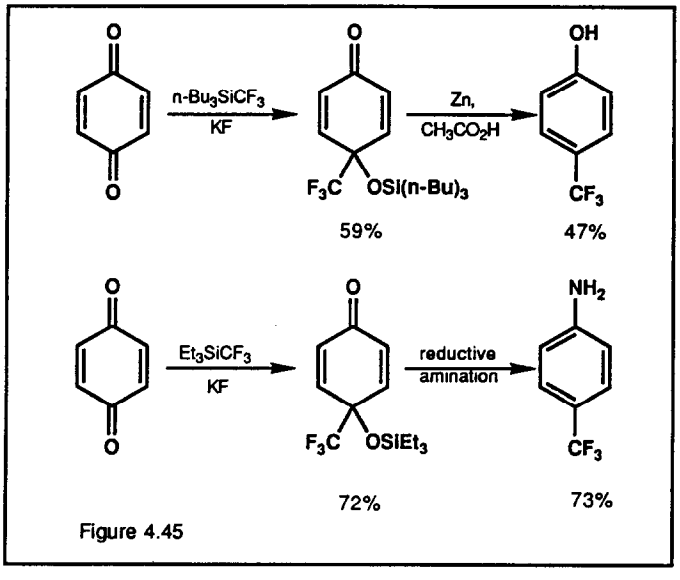


Figure 4.45

5. Preparation of Trifluoromethylated Alkanes, Alkenes and Alkynes

This section describes the preparation of non-aromatic compounds in which the trifluoromethyl group is isolated from carbonyl derivatives and from carboxylic acid derivatives. The methods available for the preparation of these latter compounds will be discussed in the following section, while those employed in the synthesis of the former will be divided into the same broad categories used to describe the preparation of trifluoromethylated aromatics.

5.1 Conversion of $-CX_3$ to $-CF_3$

Trichloroaliphatics are normally much less reactive that benzotrichlorides with respect to their reaction with antimony fluorides. This is illustrated by the fact that hexachloroethane yields a trifluoromethylated compound only after all other possible chlorines have been replaced upon reaction with SbF_3Cl_2 (Figure 5.1.).[100]

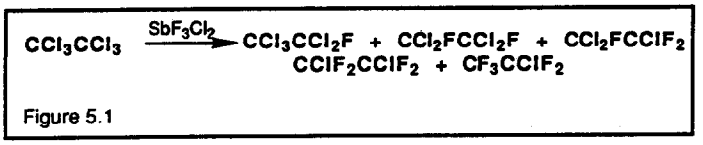


Figure 5.1

Methods have been devised to convert aliphatic trichlorides and tribromides to their their trifluoride analogues as shown below in the preparation of fluoroform,[101] 1,1,1-trifluoroethane,[101] 1,1,1-trifuoropropane[102] and 1,1,1-trifluorobutane (Figure 5.2).[102]

Some aliphatic and alkenic substrates have been found to react more readily (Figure 5.3).[103] These substrates contain other substituents (C=C, CH_2CF_3 etc.) close to the trichloromethyl moiety to modify its behaviour. Thus 1,1,1-trichloro-3,3,3-fluoropropane can be converted to the hexafluoro compound in good yield using mercury difluoride[103a] while 1,1,1,2-tetrachloroethane can be converted to 2-chloro-1,1,1-trifluoroethane using hydrogen fluoride/antimony dichlorotrifluoride.[103c] Certain 1,1,1-trichloroprop-2-enes can be converted to their trifluoro analogues using the same relatively mild conditions that enable benzotrichloride to be fluorinated, though 1,1,1-trichloropropene itself showed no signs of reactivity.[103b] However, 1,1,1-trifluoropropene has been prepared by the

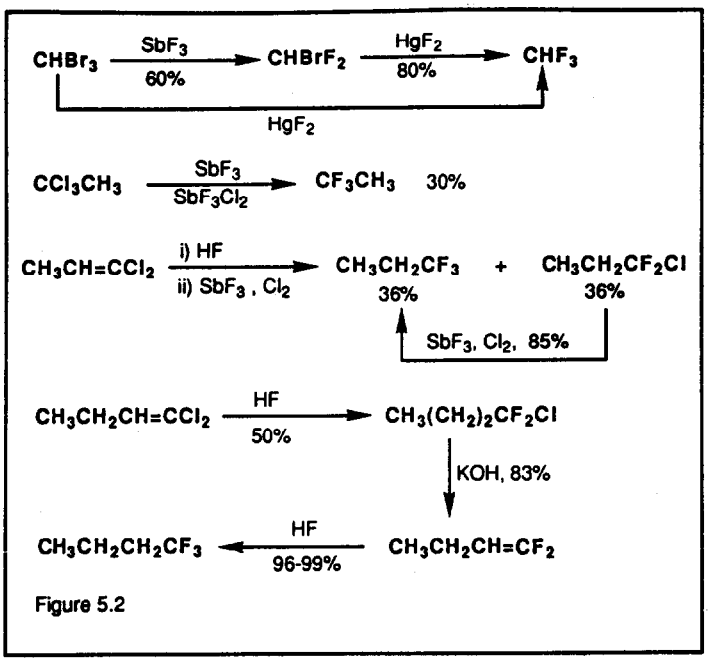


Figure 5.2

addition of hydrogen fluoride to difluoroethane in the presence of formaldehyde and methanol.[104] These examples are all illustrated in Figure 5.3.

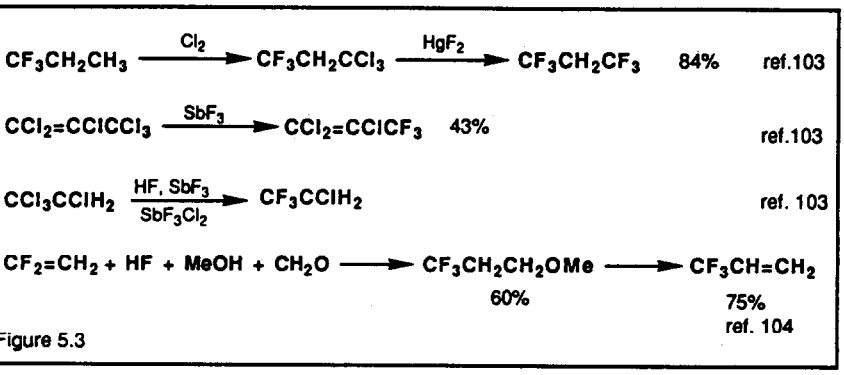


Figure 5.3

The use of hydrogen fluoride and antimony pentachloride as a fluorinating reagent has recently been reinvestigated with the conclusion that the active species is antimony tetrachlorofluoride ($SbCl_4F$).[105] The reaction of this reagent with chloroform yields

difluorochloromethane as the major product since replacement of the last chlorine is very slow.

In addition to the use of antimony fluorides for the conversion of trichloro- to trifluoromethyl groups, a report exists which utilises the cheaper and more easily handled potassium fluoride (Figure 5.4).[106a] Industrially, hexafluoroacetone is prepared from hexachloroacetone using hydrogen fluoride in the presence of chromium(III) salts.[106b] The product resulting from the fluorination of octachloropropane was used in the preparation of *bis*(trifluoromethyl) alkenes via a Wittig reaction.[106c]

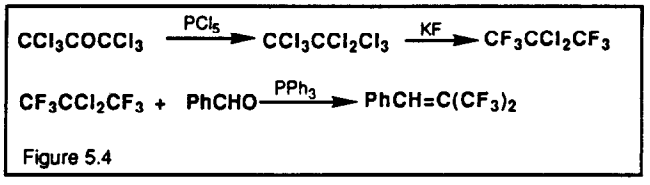


Figure 5.4

In the same fashion that benzotrifluorides can be prepared from benzoic acid using sulphur tetrafluoride, trifluoromethyl aliphatics and alkenes may also be synthesised. In addition to the desired trifluoromethylated materials, *bis*(difluoroalkyl)ethers are also observed. The quantity of ether produced depends greatly on its stability, since it can undergo decomposition in the presence of hydrogen fluoride to the acid fluoride and the trifluoromethylated compound (Figure 5.5).

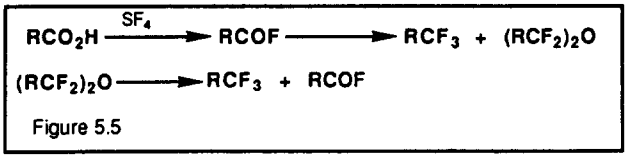


Figure 5.5

In addition to the free acid, carboxylic acid derivatives also undergo reaction to yield the trifluoride. The subject has been extensively reviewed with a few examples given in Figure 5.6.[35] In one example, sulphur tetrafluoride has been used in conjunction with formic acid and hydrogen fluoride to trifluoromethylate adamantane (Figure 5.7).[107]

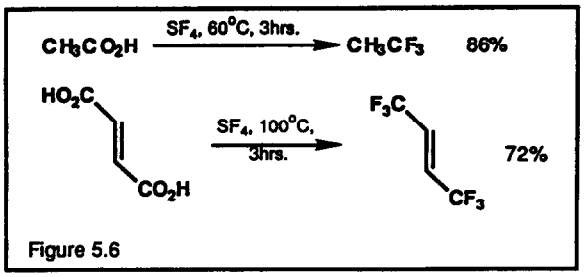


Figure 5.6

Figure 5.7

Finally, diethylaminosulphur trifluoride (DAST) has been used to prepare 1,1,1-trifluoroalk-2-enes by reaction with 1,1-difluoro-3-hydroxyalk-2-enes. These latter compounds can be readily prepared by the reaction of either 1,1-difluoroethenyl lithium[223] or 1,1-dichloro-2,2,2-trifluoroethyl zinc halides and aluminium trichloride[225] with ketones and aldehydes (Figure 5.8).

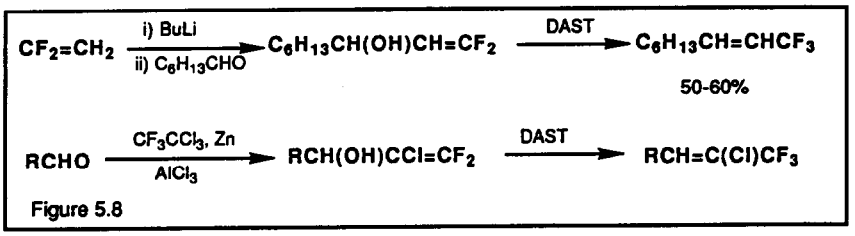


Figure 5.8

5.2 The Use of Trifluoromethylcopper and Related Reactions

In addition to preparing trifluoromethyl aromatics and heteroaromatics, trifluoromethyl copper has been employed in the preparation of a wide variety of aliphatic and alkenic trifluoromethylated compounds. The methods employed to prepare trifluoromethyl copper are identical to those described in Section 4.2. Substrates which have been found to react include aliphatic iodides, bromides and chlorides, vinyl bromides

and iodides as well as some alcohols. The results obtained from various substrates and trifluoromethylating conditions are laid out in Table 5.1. Yields are dependent upon both trifluoromethylating conditions and substrates employed, and as can be seen these methods provide a useful way into trifluoromethylated materials.

Although alcohols give poor yields of trifluoromethylated products with the copper/dibromodifluoromethane system, no perfluoroalkylated products are observed. This is in contrast to the reactions of aliphatic halides with the same system where perfluoroalkylated products are always produced. However, fluorides and formates were also produced from the alcohols helping to account for the low yield. Furthermore, only primary allyl alcohols and benzyl alcohols yielded trifluoromethylated products when heated with copper, dibromodifluoromethane and dimethylformamide.[108]

Finally, alkynes can be hydrotrifluoromethylated using trifluoromethylcuprates, which are formed 'in situ' from iodotrifluoromethane, zinc and a copper salt under ultrasonic irradiation (Figure 5.9).[111]

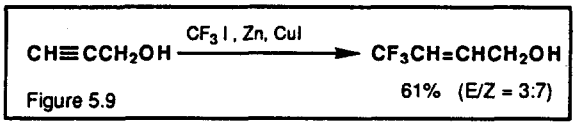


Figure 5.9

5.3 The Use of Trifluoromethyl Radicals and Related Reactions

Trifluoromethyl radicals react with alkenes and alkynes to yield trifluoromethyl alkanes and alkenes respectively (Figure 5.10). The trifluoromethyl radical attacks predominantly at the least substituted carbon,[112, 113, 114] though attack at the more substituted one is sometimes observed, as is the formation of oligomeric products. In the reaction of iodotrifluoromethane with alkynes, a different isomer is produced depending upon the substrate. For example, when acetylene is employed, the product is the E isomer,[115] whereas propyne and but-2-yne yield predominantly the Z-isomer.

Substrate	Conditions	Product	Yield	ref
$C_{10}H_{21}Br$	$CuCF_3$/HMPA[1]	$C_{10}H_{21}CF_3$	(13%)[2]	39
$C_{10}H_{21}I$	$CuCF_3$/HMPA[1]	$C_{10}H_{21}CF_3$	(48%)[2]	39
$C_5H_{11}I$	CuI/NaO_2CCF_3	$C_5H_{11}CF_3$[3]	40%	43
$PhCH = CHCH_2Br$	$CuCF_3$/HMPA[1]	$PhCH = CHCH_2CF_3$	37%	39
$PhCH = CHCH_2Cl$	Cu/CF_2Br_2/DMF	$PhCH = CHCH_2CF_3$	(62%)[4]	108
$PhCH= CHCH_2OH$	Cu/CF_2Br_2/DMF	$PhCH = CHCH_2CF_3$	29%[5]	108
$PhCH_2Br$	$CuCF_3$/HMPA[1]	$PhCH_2CF_3$	65%	39
" "	$FO_2SCF_2CO_2Me/CuI$	" "	61%	51
" "	$R_3SiCF_3/F^-/CuI$	" "	73%	47
" "	$ClCF_2CO_2Me/F^-/CuI$	" "	84%	221
$pNO_2C_6H_4CH_2Br$	$CuCF_3$[6]	$pNO_2C_6H_4CH_2CF_3$	88%	40
" "	FO_2SCF_2I/Cu	" "	90.4%	52
PhCH = CHBr	$R_3SiCF_3/F^-/CuI$	$PhCH = CHCF_3$	51%	47
" "	$CuCF_3$/HMPA[1]	" "	65%	39
" "	CF_3CO_2Na/CuI	" "	(54%)	43
" "	$FO_2SCF_2CO_2Me/CuI$	" "	62%	51
" "	FO_2SCF_2I/Cu	" "	79%	52
" "	$ClCF_2CO_2Me/F^-/CuI$	" "	81%	221
$HC\equiv CCH_2Br$	CF_3CdBr, CuI	$CF_3CH=C=CH_2$	43%	109
$HC\equiv CCH_2OTs$	CF_3Cu	" "	68%	110

Table 5.1 Reaction of Various Trifluoromethylating Systems with Aliphatic Halides.

( ) denotes g.l.c. yields, [ ] denotes ^{19}F NMR yields

[1] from CF_3I and Cu in HMPA, [2] n-decyl fluoride also observed as a product (32% for X =Br, 6% for X = I), [3] product now stated to be $C_5H_{11}O_2CCF_3$,[109] [4] perfluoroalkyl products also observed, [5] cinnamyl fluoride and cinnamyl formate also produced, [6] from $Hg(CF_3)_2$ and copper metal.

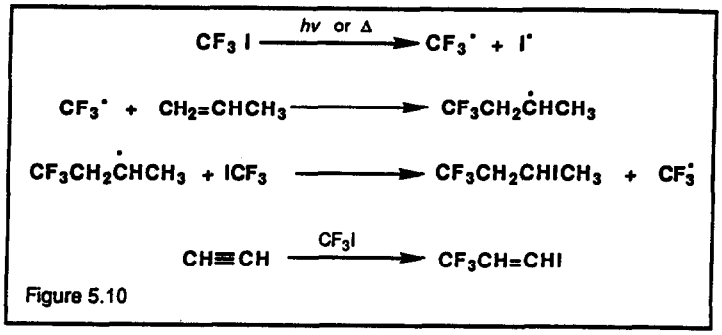


Figure 5.10

The 1-trifluoromethyl-2-iodo adducts obtained from the addition of iodotrifluoromethane to alkenes and alkynes can be converted to trifluoromethylalkenes and trifluoromethylalkynes respectively by elimination of hydrogen iodide using potassium hydroxide (Figure 5.11).[113, 114] With dienes and enynes, 1,4-addition is observed in both the liquid and gas phases when iodotrifluoromethane is used .[116]

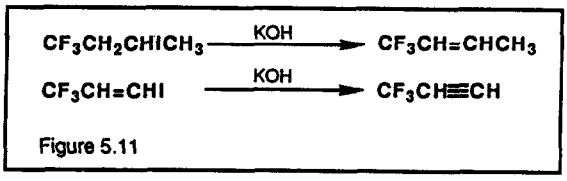


Figure 5.11

Trifluoromethyl radicals, produced using *bis*(trifluoromethyl)mercury and *bis*(trifluoromethyl)tellurium, have been used to trifluoromethylate alkenes yielding the 1,2-*bis*(trifluoromethylated) product.[78] The tellurium compound was found to give better yields of trifluoromethylated materials than either iodotrifluoromethane or *bis*(trifluoromethyl)mercury (Figure 5.12).[78]

The xenon difluoride/trifluoroacetic acid system does not yield purely trifluoromethylated compounds with alkenes and alkynes. Products from the reaction of styrene include 1,1,1,2-tetrafluoro- and 1,2-difluoro-3-phenylpropane in addition to a number of trifluoroacetates.[89b]

More recently, a number of catalysts have been found to promote the addition of CF_3X across double bonds. These catalysts include $Ru_3(CO)_{12}$[117] and triethylborane[118] for iodotrifluoromethane and $RuCl_2(PPh_3)_2$ for trifluoromethanesulphonyl chloride[119]

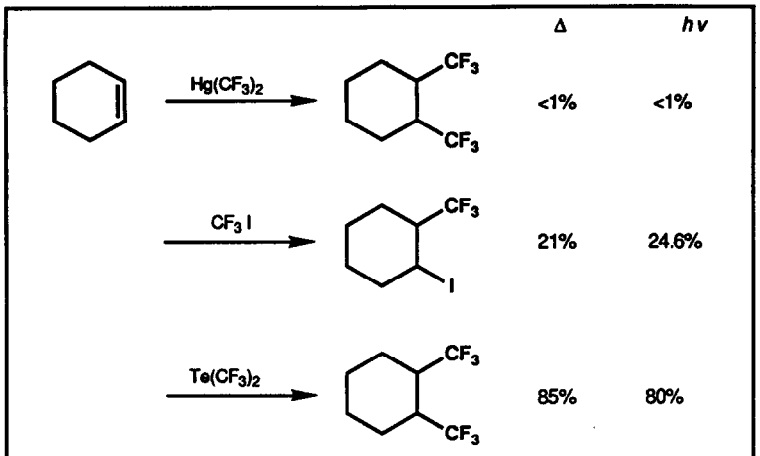


Figure 5.12

(Figure 5.13). In the latter example, CF_3 and Cl are added across the double bond when temperatures greater than 120 °C are employed, whilst below this temperature a mixture of both CF_3SO_2 and Cl, and CF_3 and Cl addition is observed.[119]

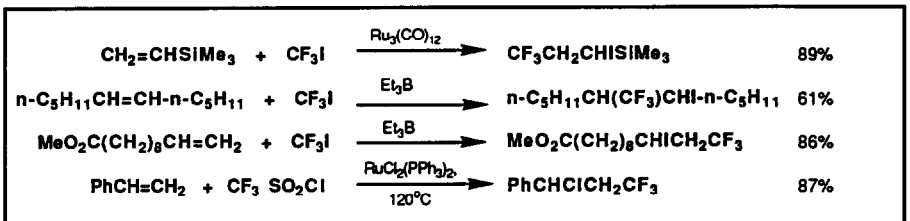


Figure 5.13

Triethylborane has also been used to catalyse the addition of iodotrifluoromethane to both terminal and internal alkynes (Figure 5.14). The products were found to have the iodine and trifluoromethyl group in a *trans* relationship.[118]

The cheaper bromotrifluoromethane can also be used in the preparation of trifluoromethylalkanes by addition to double bonds. The reaction is achieved either in the

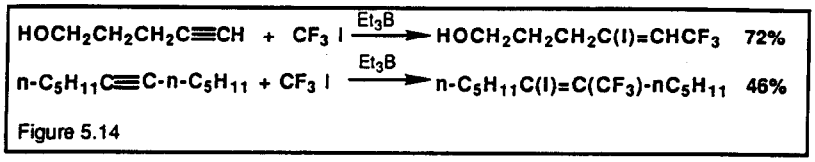


Figure 5.14

presence of sodium phenylselenide, sodium phenyltellurolate[120] or zinc metal in acetic acid.[121] Phenylselenide reacts with bromotrifluoromethane by electron transfer from the selenide to yield trifluoromethyl radicals, which can then react with the alkene to give the 1-trifluoromethyl-2-phenylselenide adduct, as illustrated in Figure 5.15. In addition to the desired product, trifluoromethylselenobenzene and diphenyldiselenide are observed.[120] Sodium tellurolate reacts in a similar fashion, though lower reaction temperature can be used (-80°C to -100°C).

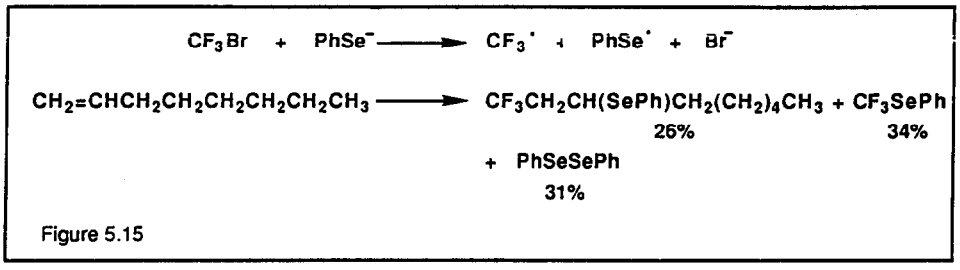


Figure 5.15

Zinc metal in acetic acid has been employed to facilitate the hydrotrifluoromethylation of undecanoic acid using bromotrifluoromethane. The presence of dimeric species in addition to the desired 12,12,12-trifluorododecanoic acid suggests a radical mechanism (Figure 5.16).

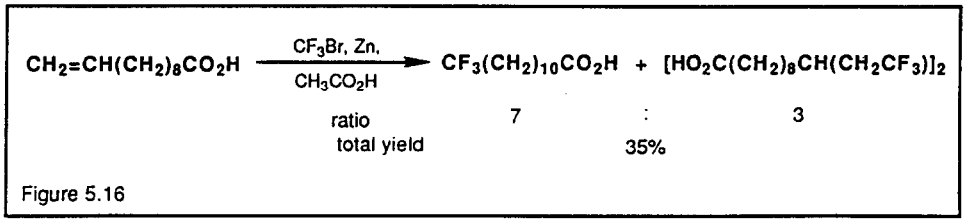


Figure 5.16

Finally, the recombination of radicals produced by photolysis of trifluoromethylazo compounds has been used to prepare trifluoromethylalkanes (Figure 5.17).[122] The starting materials for the preparation of the azo compounds are trifluoronitrosomethane and an amine, with *bis*(trifluoromethylated) compounds obtainable from diamines. In order to obtain good yields viscous solvents are required to encourage the caged radical recombination process.

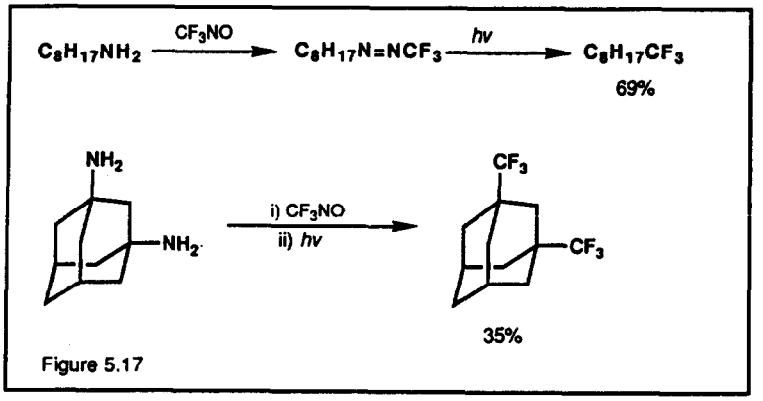


Figure 5.17

5.4 Electrochemical Methods

Trifluoromethyl radicals can be generated from solutions of partially neutralised trifluoroacetic acid. Since trifluoroacetic acid is relatively cheap, the reactions of trifluoromethyl radicals generated in this manner have been extensively investigated. These reactions can be categorized into two broad sections, radical recombination and addition to alkenes.

1,1,1-Trideuterio-2,2,2-trifluoroethane has been produced by the cross Kolbe reaction between trifluoroacetic acid and d_3-acetic acid. In order to obtain good yields, it is necessary to slowly add the trifluoroacetic acid to a solution of deuteroacetic acid which is being electrolysed.[123a] This radical recombination method has also been used to prepare ethyl 3,3,3-trifluoropropanoate from malonic acid mono ethyl ester (Figure 5.18) though 2-alkyl malonic acid mono ethyl esters gave much more complex reaction mixtures.[124]

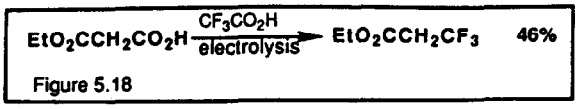


Figure 5.18

When propanoic acid was electrolysed with trifluoroacetic acid, the products observed were not a result of radical recombination, but of addition of trifluoromethyl radicals to ethene. The ethene having been produced by hydrogen atom loss from the ethyl radical, which is generated by decarboxylation of the acid.[123]

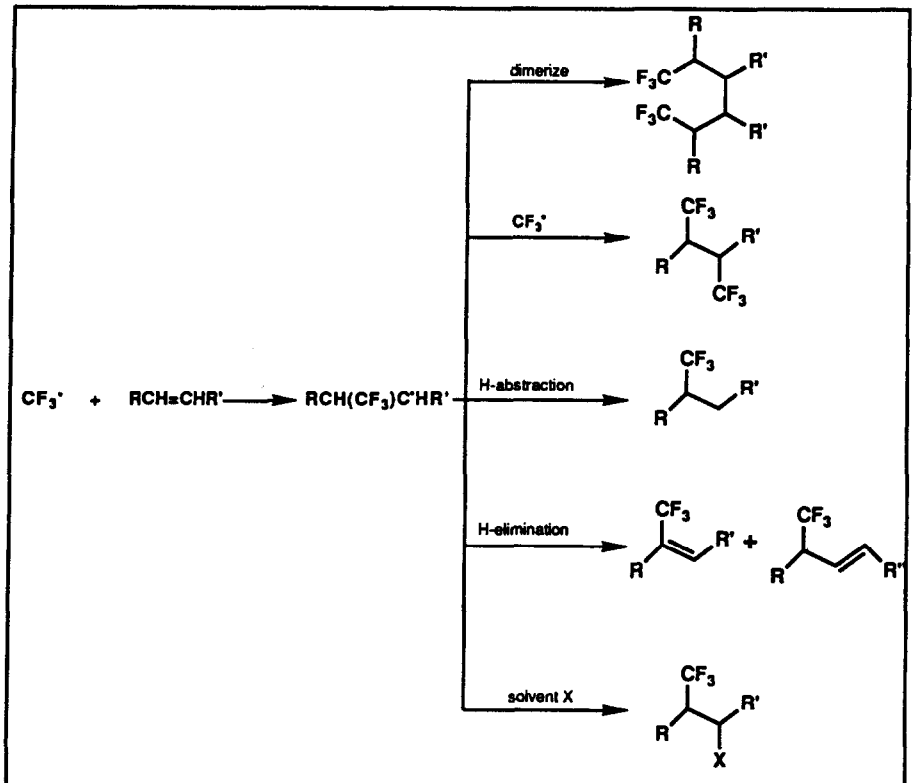


Figure 5.19: Reactions of electrochemically generated trifluoromethyl radicals with alkenes

The addition of electrochemically generated trifluoromethyl radicals to alkenes yields a number of products resulting from the reaction of an intermediate alkyl radical ($RCHCF_3$-C·HR') with other radicals or the solvent (Figure 5.19). The relative

distribution of these products depends upon the nature of the substituents on the double bond, in addition to the current density and temperature. Naturally, in order for any trifluoromethylated products to be observed, trifluoroacetic acid must be oxidised in preference to the olefin. Thus, electron rich olefins such as methyl 2-phenylpropenoate do not yield trifluoromethylated products.[125, 126]

For compounds containing isolated double bonds the dimerized product is usually the major one, though hydrogen abstraction and elimination products are also observed (Figure 5.20).[127, 128] The generation of the latter products has allowed trifluorododecanoic acid to be produced in 12% overall yield from undecanoic acid by electrochemical trifluoromethylation followed by hydrogenation of the resultant products.[129]

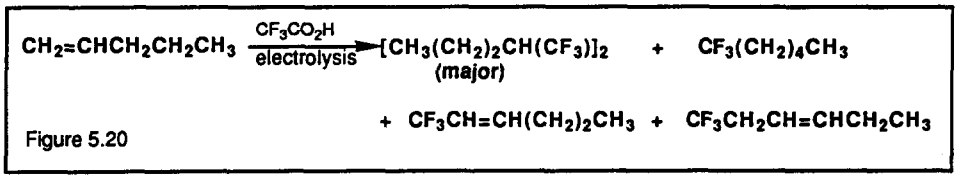


Figure 5.20

Monomeric trifluoromethylated products have been observed when isopropenyl acetate, allyl alcohol and 3-methylbut-3-enonitrile are present during the electrolysis of trifluoroacetic acid (Figure 5.21).[130, 131]

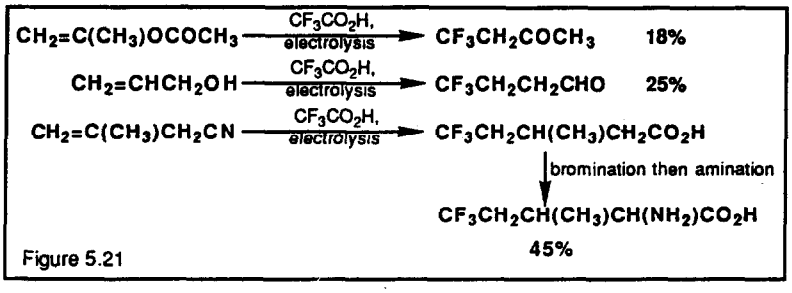


Figure 5.21

Further, when a molecule contains two isolated double bonds, such as diallylamine, it is possible to form a cyclic product (Figure 5.22).[131c]

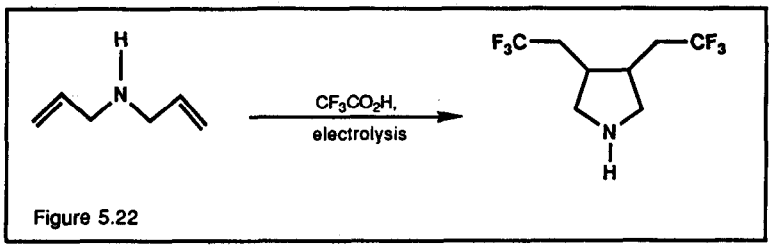


Figure 5.22

When α,β-unsaturated carboxylic acids (and their functional derivatives) are present during the electrolysis of trifluoroacetic acid, the products observed are different to those normally found when compounds containing isolated double bonds are employed. In the majority of examples the *bis*(trifluoromethyl) monomeric compound is the major product (see Figure 5.23).[15, 124, 132, 133]

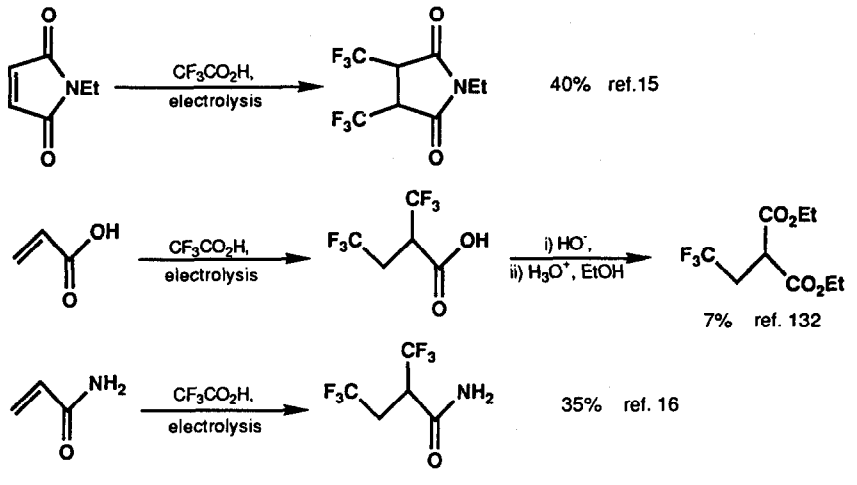


Figure 5.23

However, there are a number of examples where this is not the case (Figure 5.24). For example, methyl acrylate gives predominantly the dimeric product upon reaction with electrochemically generated trifluoromethyl radicals,[134] while methyl 2-methacrylate yields a mixture of products[125] and fumaronitrile produces the monotrifluoromethylated

material.[135] In this latter case, the mechanism of trifluoromethylation has changed, the fumaronitrile is reduced at the cathode to give, after hydrogen abstraction, a radical which reacts with trifluoromethyl radical (formed at the anode, see Figure 5.25).[135]

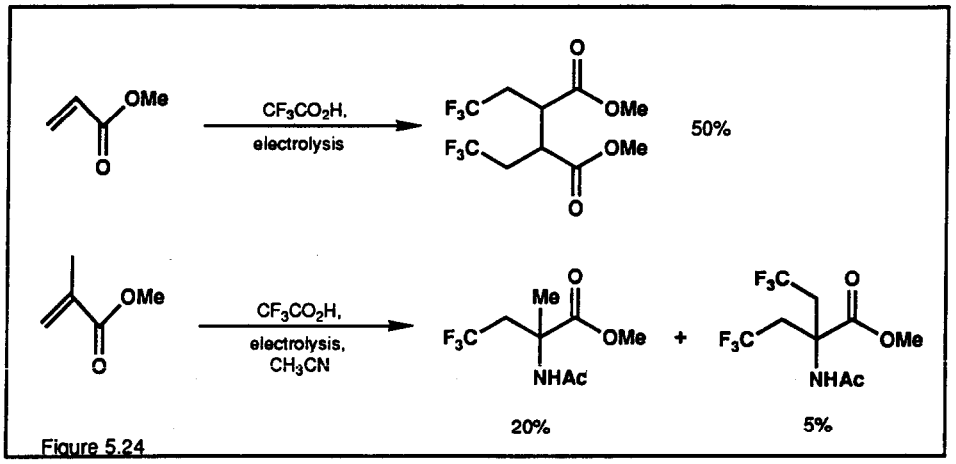


Figure 5.24

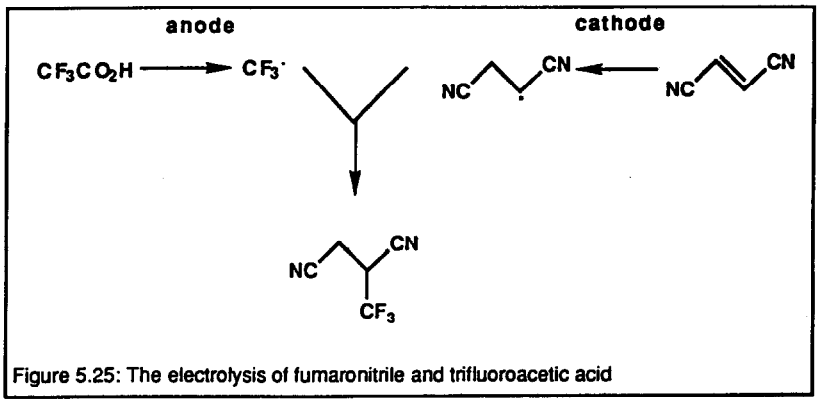


Figure 5.25: The electrolysis of fumaronitrile and trifluoroacetic acid

When β-keto esters are present during the electrolysis, the products are found to be very temperature dependent.[136] For example, when octyl 3-oxobutanoate is used as the substrate, at high temperatures (60 °C) octyl 2-trifluoromethyl-3-oxobutanoate (31%) is formed exclusively. At low temperatures (-40 °C) octyl 3,3,3-trifluoropropanoate (47%) is the sole product, whilst at intermediate temperatures both of these compounds are observed (eg 0 °C, 15% butanoate and 43% propanoate, see Figure 5.26).

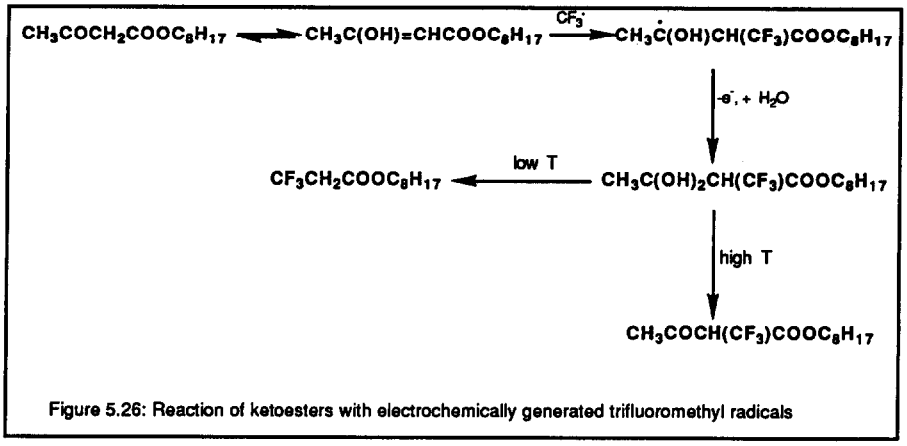


Figure 5.26: Reaction of ketoesters with electrochemically generated trifluoromethyl radicals

The reaction mechanism is thought to involve the addition of trifluoromethyl radicals to the enol form of the molecule, followed by oxidation and hydrolysis to yield a geminal dihydroxy intermediate. At low temperature, the intermediate decomposes with breakage of the carbon-carbon bond, whilst at high temperature the carbon-oxygen bond breaks. By employing enol acetates, only the trifluoromethylketoester is observed, as is illustrated in Figure 5.27.

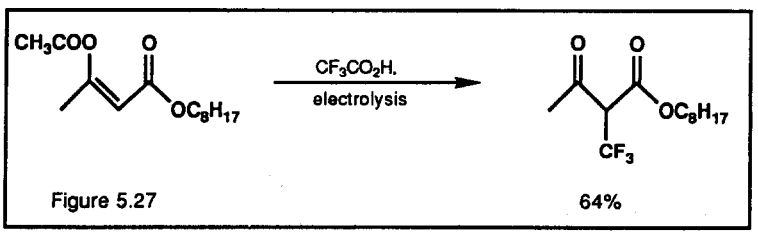


Figure 5.27 64%

In addition to trifluoroacetic acid, trifluoromethyl bromide has been employed in electrolysis experiments. The generation of trifluoromethyl radicals from bromotrifluoromethane has been closely studied.[137] When an electron transfer catalyst (ETC) such as terephthalonitrile is used, electron rich olefins such as styrene, can be trifluoromethylated.[138] However, the electron transfer catalyst can also become involved

in the chemistry of the reaction, as was observed when butyl vinyl ether was the substrate. (see Figure 5.28)[138]

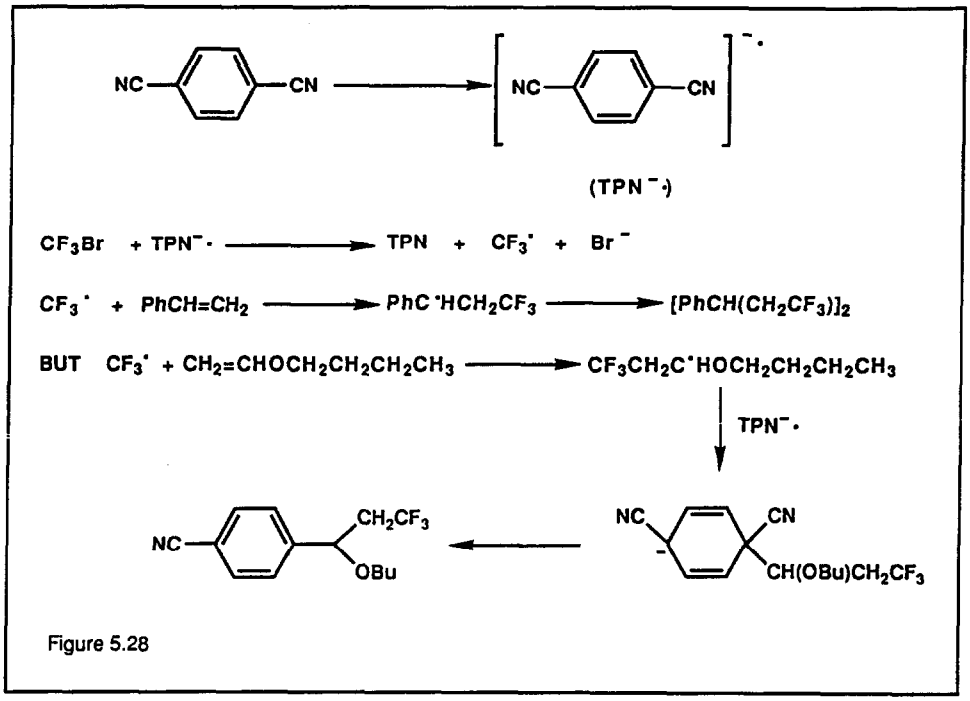


Figure 5.28

Overall, although the yields of the electrochemical trifluoromethylation are often low, the starting trifluoromethyl containing materials are relatively cheap and the electrochemical methods provide useful ways of generating trifluoromethyl building blocks.

5.5 Other Methods.

The enzymes catalase and urease, in the presence of a suitable cofactor, have been employed in the trifluoromethylation of alkynes.[139] Both internal and terminal alkynes can be trifluoromethylated, albeit in low yield (Figure 5.29). This remarkable reaction appears

to be the first enzymatic trifluoromethylation reaction and, like most enzymatic reactions, it was found to be stereospecific, producing the E alkene.

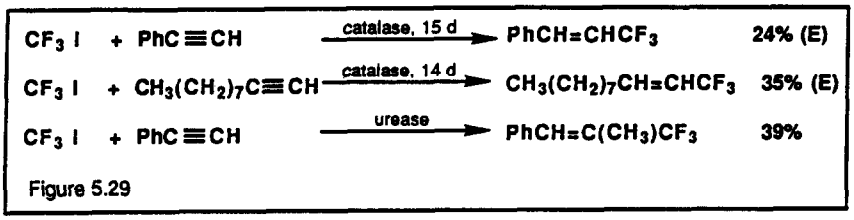


Figure 5.29

(Trifluoromethyl)dibenzothiophenium triflate and its seleneo analogue have been used to trifluoromethylate lithium salts of alkynes (Figure 5.30) as well as anilines (see Section 4.4) and sulphides (see Section 7). The seleno analogue was found to give better yields with alkynides, in contrast to all the other reactions reported where the sulphonium salts always gave better yields.[95] This appears to be the only report of a trifluoromethyl group being directly incorporated onto an sp hybridised carbon. It should be noted that alkyl Grignard and alkyllithiums did not trifluoromethylate under the same conditions.

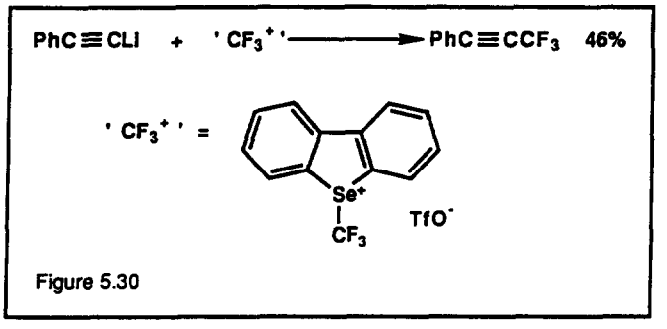


Figure 5.30

Highly electrophilic perfluoroalkanes have been trifluoromethylated using hexaethylphosphorous triamide and bromotrifluoromethane (Figure 5.31).[140] This trifluoromethylating system has been used previously to prepare trifluoromethyl silicon and phosphorous derivatives.[141] Indeed, hexaethylphosphorous triamide and bromotrifluoromethane are used to prepare the trifluoromethylating reagents CF_3SiR_3 (see Sections 4.4 and 6.1).[142]

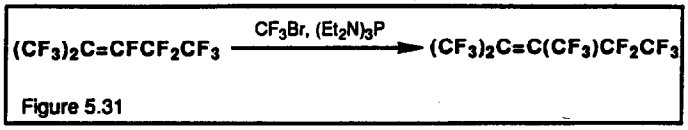


Figure 5.31

Finally, methyl groups on pyridines have been trifluoromethylated using triflic anhydride though the desired products are contaminated with triflates (see Figure 5.32).[143]

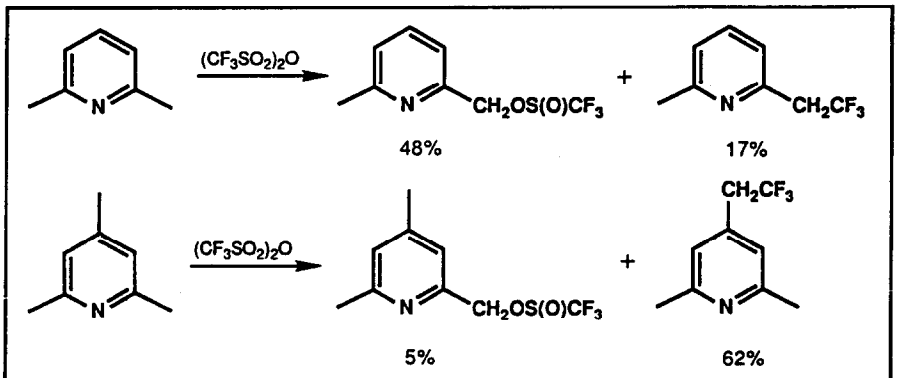


Figure 5.32

6. Preparation of Trifluoromethylketones, Trifluoromethylcarbinols and α-Trifluoromethylketones and carboxylic acids

This section looks specifically at the methods of incorporating a trifluoromethyl group on or adjacent to a carbon containing an oxygen substitutent (alcohol, carbonyl, carboxylic acid and derivatives). In a recent review,[6] the preparation of trifluoromethyl ketones has been considered. However, trifluoromethylation reactions which generate ketones are included in this section for completeness. The preparation of these compounds can be divided into the broad categories of trifluoromethyl metal reagents and radical based processes.

It should be remembered that trifluoromethyl groups adjacent to carboxylic acids (and their functional derivatives) are readily hydrolysed by base (see Section 3) and that trifluoromethylketones can also be prepared by oxidation of trifluoromethyl carbinols.[6]

6.1 Trifluoromethyl Metal Reagents and Related Reactions

Trifluoromethyl magnesium iodide, though difficult to prepare and unstable, will react with acyl chlorides, carbon dioxide and nitriles to yield trifluoromethyl carbonyls and carboxylic acids (see Figure 6.1).[144]

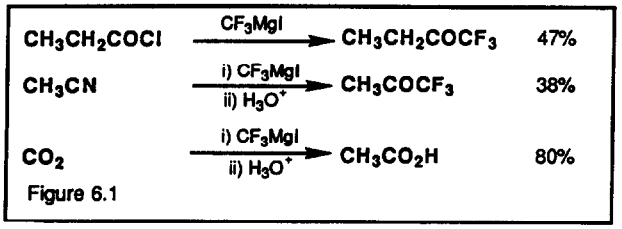


Figure 6.1

It also reacts with ethylene oxide to yield 3,3,3-trifluoropropan-1-ol,[144] but only one report has appeared concerning the reaction of the Grignard reagent with carbonyl compounds[144b] even though corresponding reactions with perfluoroalkyl magnesium halides have been well documented.[145]

Perfluoroalkyllithiums have been prepared[57, 146], but the trifluoromethyl compound is unstable even at -100 °C and attempts to react it 'in situ' with carbonyl compounds resulted in the formation of tetrafluoroethylene.[57]

Greater success has been obtained using zinc and halotrifluoromethanes in the trifluoromethylations of aldehydes, ketones, activated carboxylic acids, anhydrides, esters, enamines and some imminium salts (see Figure 6.2).

Further, dimethylformamide will react with trifluoromethylzinc in the presence of chlorodimethyl(2,3-dimethylbutan-2-yl)silane to yield a stable hemiaminal, which can be hydrolysed to give trifluoroacetaldehyde.[224] The reaction of acid chlorides has not been reported since these compounds preferentially react with zinc[147,148] A number of techniques have been employed including ultrasonic irradiation,[149, 159] the use of an electron transfer catalyst (see Figure 6.3),[151] transition metal catalysis,[150] the Barbier procedure[147, 148, 152] and the use of a sacrificial zinc electrodes.[85, 153]

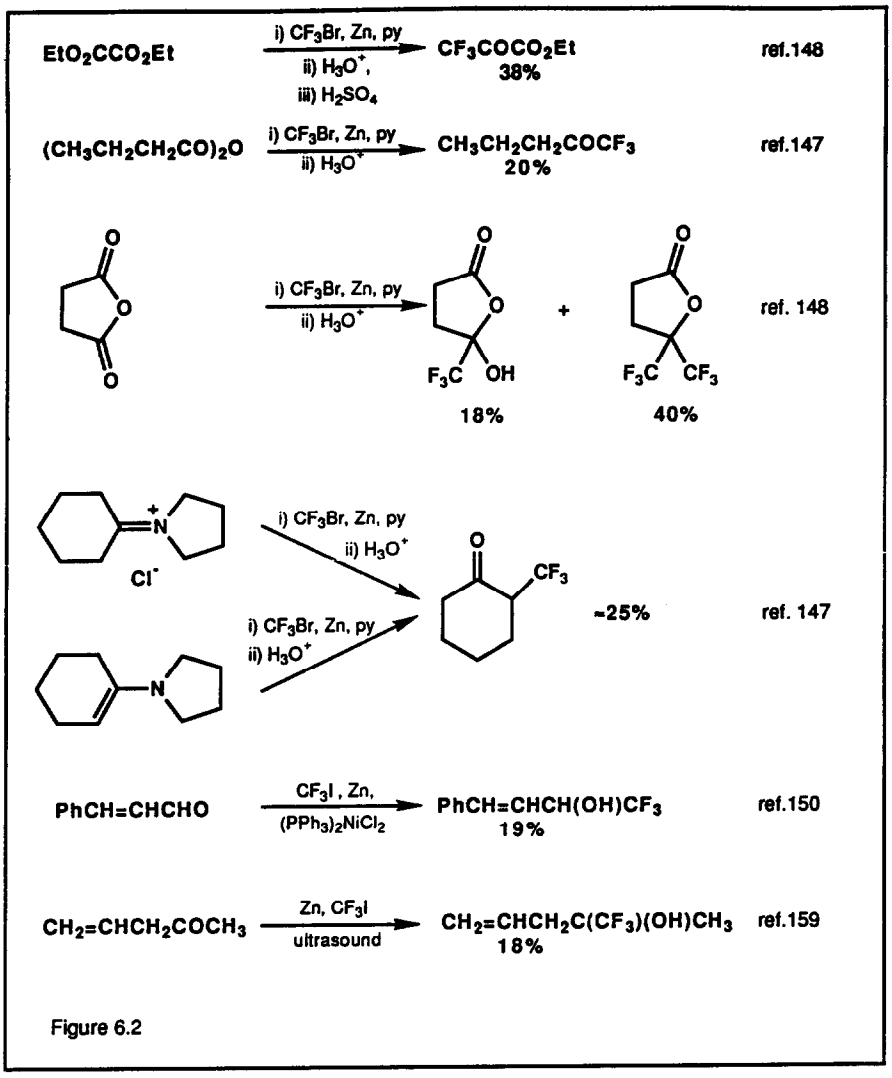


Figure 6.2

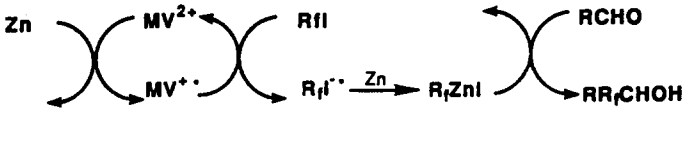


Figure 6.3: the mechanism proposed for the use of the electron transfer catalyst methyl viologen (MV^{2+}) for the trifluoromethylation of carbonyl compounds.

It appears that the reaction involving zinc occurs near the metal surface[147] and not in solution, since solvated perfluoroalkylzinc species have been found to be fairly unreactive.[148, 154] Indeed, the formation of solvated organozinc species was found to be a competing reaction in the electroreduction of bromotrifluoromethane using a sacrificial zinc electrode (Figure 6.4).[85] These various procedures are compared with respect to their ability to trifluoromethylate benzaldehyde and acetophenone in Table 6.1.

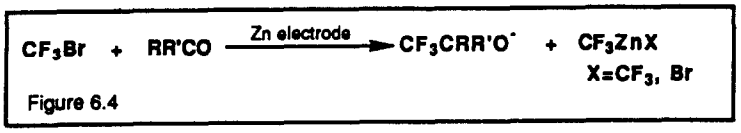


Figure 6.4

In general ketones are less reactive than aldehydes and it is often necessary to add other reagents to the trifluoromethylating system in order to further improve the yield. So for example, when a sacrificed zinc electrode was employed, it was found necessary to add tetramethylethylenediamine (TMEDA) and zinc bromide (see Figure 6.5) in order to increase the yield of trifluoromethylated products from ketones,[85, 153], whilst in the ultrasonically promoted reactions dichlorobis(cyclopentadienyl)titanium(II) was added.

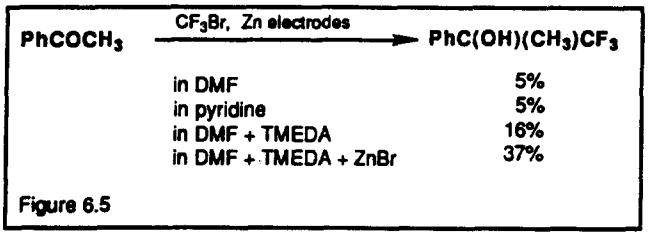


Figure 6.5

Of the zinc based systems, the use of the sacrifical zinc electrodes gives the best yields. However, two non-zinc based systems not only give comparable yields of trifluoromethylated products from aldehydes, but also give much higher yields from ketones. The first of these uses trialkyltrifluoromethylsilanes and requires the presence of fluoride or alkoxide ions in order to produce, after acid work up, the trifluoromethylated carbinol.[155]

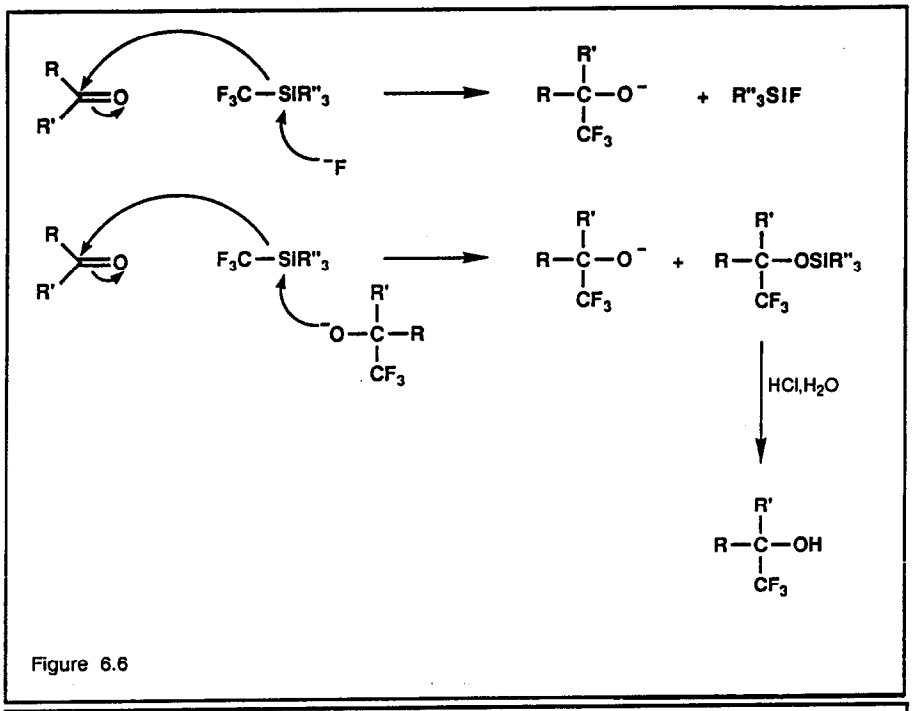


Figure 6.6

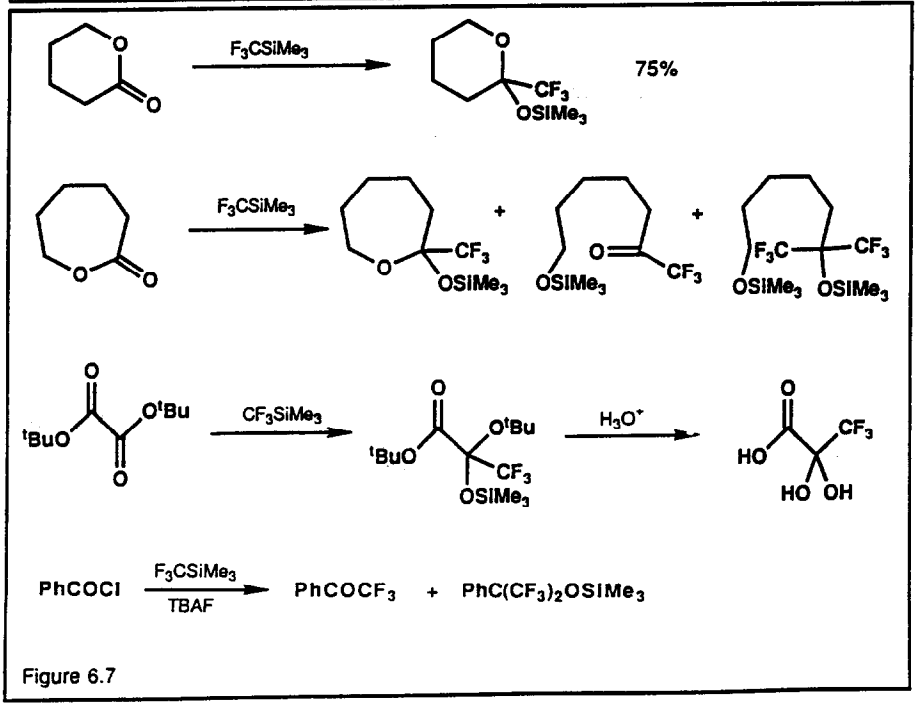


Figure 6.7

The mechanism for this transformation is laid out in Figure 6.6 and involves an anion chain process. In addition to their ability to trifluoromethylate aldehydes and ketones, trialkyltrifluoromethylsilanes react with lactones, activated esters and even acid halides (see Figure 6.7).[142, 156] In the short time since these reagents were first reported, they have already been utilised to prepare trifluoromethylated steriods,[155] sugars (Figure 6.8),[157] indenes,[158] phenols and anilines,[99] suggesting that they are convenient and versatile reagents to use.

The second non-zinc based system employs an electrochemically generated base to deprotonate trifluoromethane in the presence of a carbonyl compound, leading to the trifluoromethylated product.[160] Although aldehydes react readily with the 'trifluoromethyl anion', ketones require the presence of hexamethyldisilazane (HMDS). The base employed in this system can be generated chemically, but yields are higher if the electrochemical procedure is employed and long chain tetraalkylammonium salts added. The mechanism

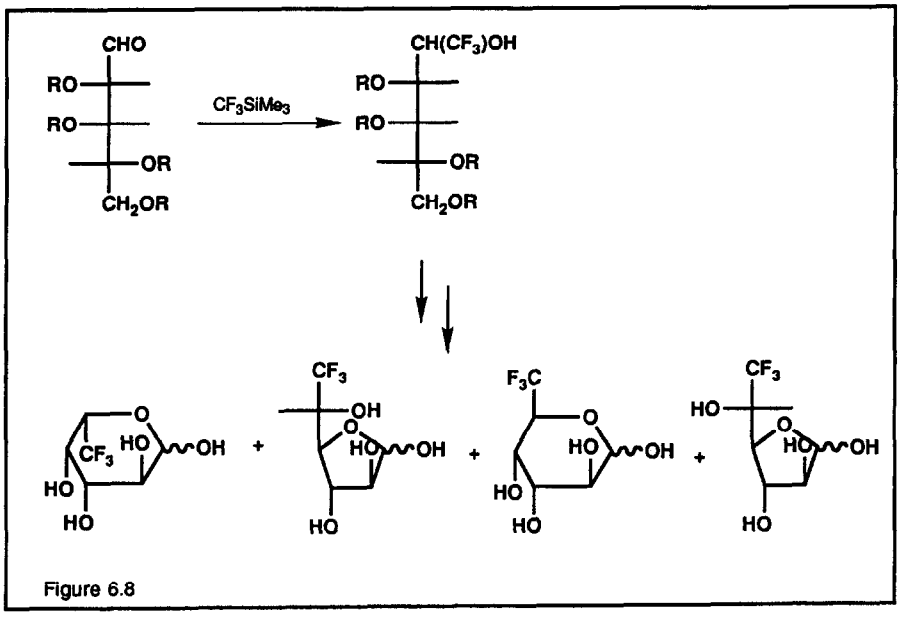


Figure 6.8

CF_3· Source	Reaction Conditions	Solvent	Temp.	Time	Product/%Yield		Ref.
					$PhCH(OH)CF_3$	$PhC(OH)(CH_3)CF_3$	
CF_3I	Zn, ultrasound	DMF	RT	1/2-1.5 hrs	72%	36%	149, 159
CF_3Br	Zn, ultrasound	DMF	RT	3 hrs	56%	33%	159
CF_3I	Zn, MV^{2+}	CH_3CN	RT	15 hrs	52%	-	151
CF_3I	Zn,$(Ph_3P)_2NiCl_2$	DMF	RT	3-4 hrs	44%	-	150
CF_3Br	Zn electrode	DMF	-10 °C	4-5 hrs	95%	37%[3]	85, 153
CF_3Br	Zn, +ve pressure	py	20 °C	4 hrs	52%	20%	147, 152
CF_3H	base[4]	DMF	-	-	80%	60%[5]	160
R_3SiCF_3	TBAF	THF	0-RT	1 hr	85%	74%	142

Table 6.1: Trifluoromethylation of Benzaldehyde and Acetophenone by Various Trifluoromethylating Systems.

[1] Cp_2TiCl_2 also added.

[2] MV^{2+} = methyl viologen.

[3] TMEDA amd $ZnBr_2$ also added.

[4] base = anion of 2-pyrrolidinone; tetralkylammonium salt also added.

[5] hexamethyldisilazane also added.

proposed for the trifluoromethylation of carbonyls using this system is laid out in Figure 6.9 and as can be seen from Table 6.1 the yields reported from both aldehydes and ketones are high.

Another method of trifluoromethylating carbonyl compounds using a trifluoromethyl anion equivalent utilises trifluoronitrosomethane, but the lack of examples reported prevent comparison to the procedures mentioned above. The trifluoronitrosomethane is reacted with *bis*(trimethylsilyl)amide in the presence of a

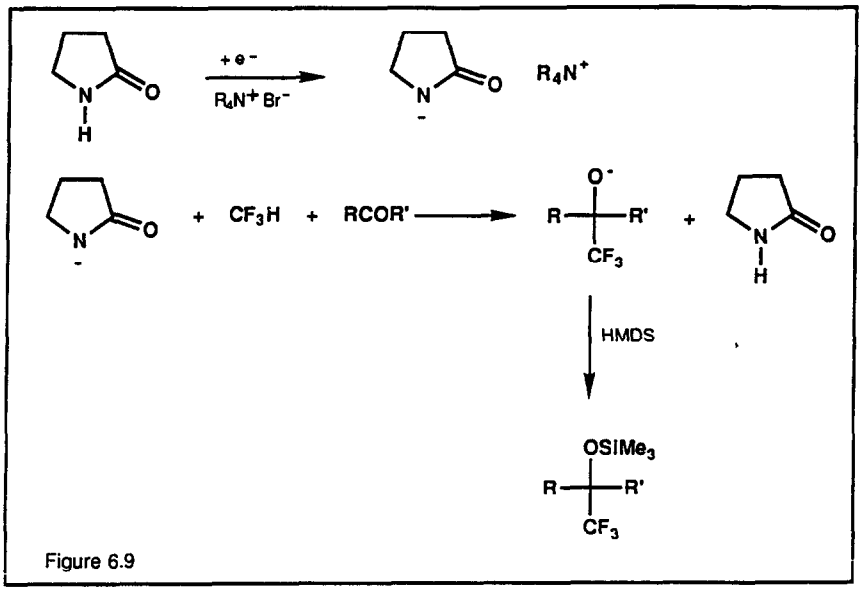


Figure 6.9

carbonyl compound at low temperatures (-100 °C), initially forming trimethylsilyl-(trifluoromethyl)diazene, which reacts with the carbonyl compound to yield the trifluoromethyl carbinol in low yield (Figure 6.10).[161]

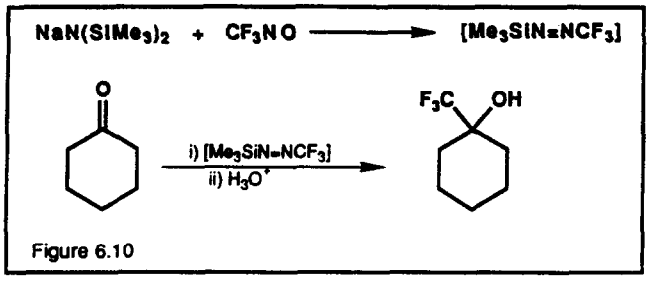


Figure 6.10

Finally, trifluoromethyl copper does react with acid bromides to yield trifluoromethyl ketones[39] and with α-bromoacetamides to yield α-trifluoromethyl-acetamide[51] (Figure 6.11).

6.2 Use of Trifluoromethyl Radicals and Related Reactions

The reaction of electrochemically generated trifluoromethyl radicals with

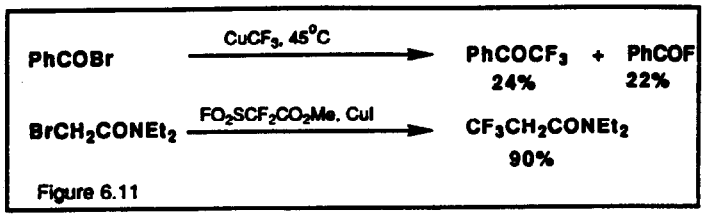


Figure 6.11

α,β-unsaturated carboxylic acids (and their functional derivatives) has already been described in Section 5.4. The reactions of trifluoromethyl radicals generated by other methods with α,β-unsaturated ketones, enamines, silyl enol ethers, and ketene silyl acetates have been used to prepare α-trifluoromethylketones and α-trifluoromethyl-carboxylic acids (and their functional derivatives). For example, steroids containing dienone systems have been trifluoromethylated photochemically using iodotrifluoromethane. The trifluoromethyl radical attacked predominantly adjacent to the ketone as illustrated in Figure 6.12.[162]

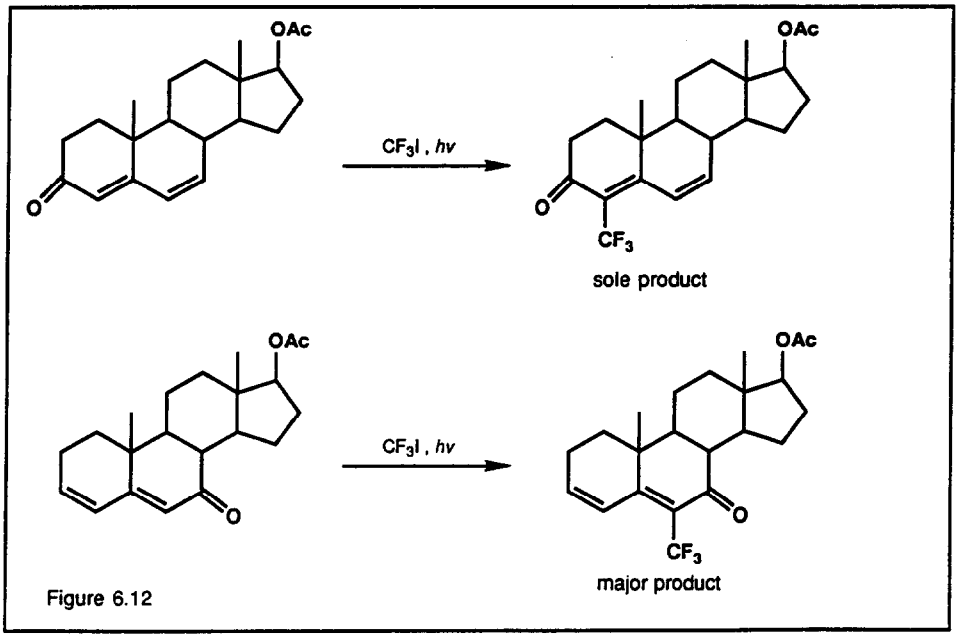


Figure 6.12

When the substrates are enamines, it is not always necessary for UV light to be used in order for trifluoromethylation with iodotrifluoromethane to occur.[163] Only in cases where the double bond of the enamine is not sufficiently electron rich or where the lone pair on the nitrogen is not available for electron transfer, is irradiation by ultraviolet light required. The mechanism for the unassisted trifluoromethylation of enamines involves the formation of a charge-transfer complex, as a result of electron donation by the nitrogen atom, followed by the addition of trifluoromethyl radicals to the double bond (see Figure 6.13). In order for the chain process to proceed, it is necessary for the material used to be completely free of oxygen.

Difluorodihalomethanes have been found to react in a similar fashion to iodotrifluoromethane with enamines,[164] yielding instead α-difluorohaloketones after

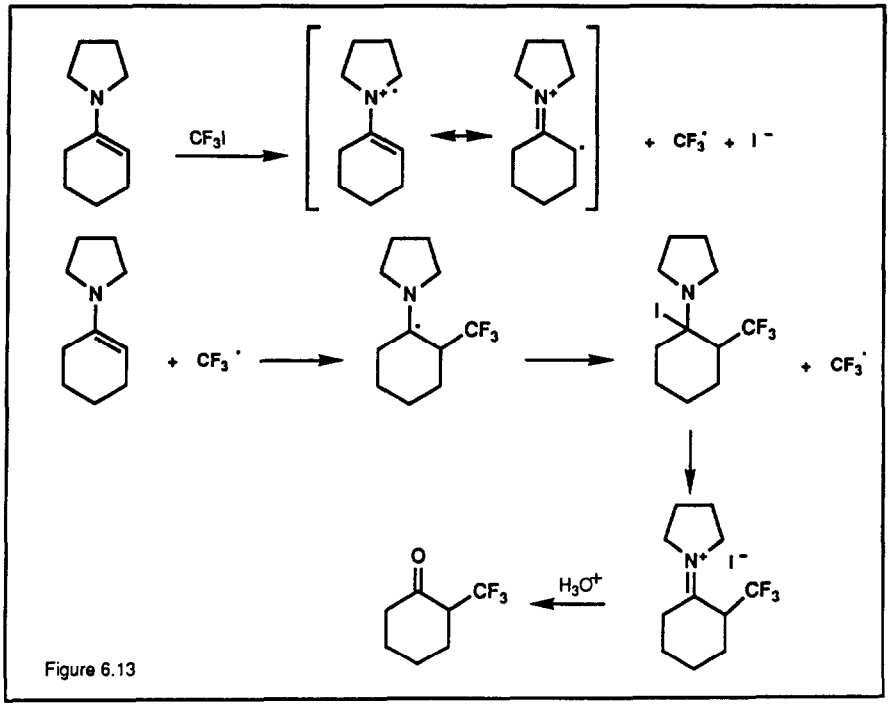


Figure 6.13

hydrolysis. These difluorohalomethyl compounds are unstable, but can be converted to α-trifluoromethyl analogues by reaction with tetrabutylammonium fluoride trihydrate ($TBAF.3H_2O$, see Figure 6.14).

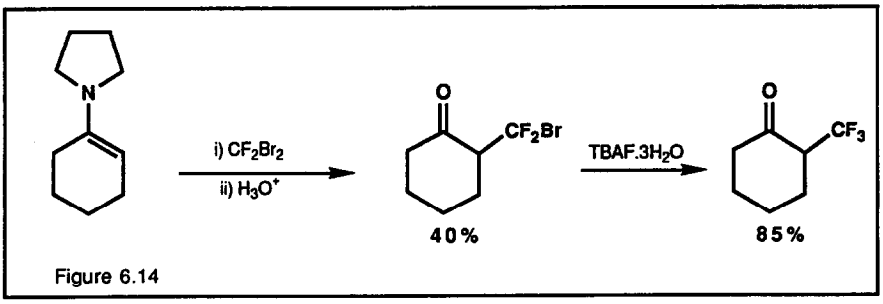


Figure 6.14

Better yields of α-trifluoromethylcyclohexanone were obtained using the electrophilic trifluoromethylation agent (trifluoromethyl)dibenzothiophenium triflate and 1-pyrrolidinocyclohexane (Figure 6.15), though the product was contaminated with

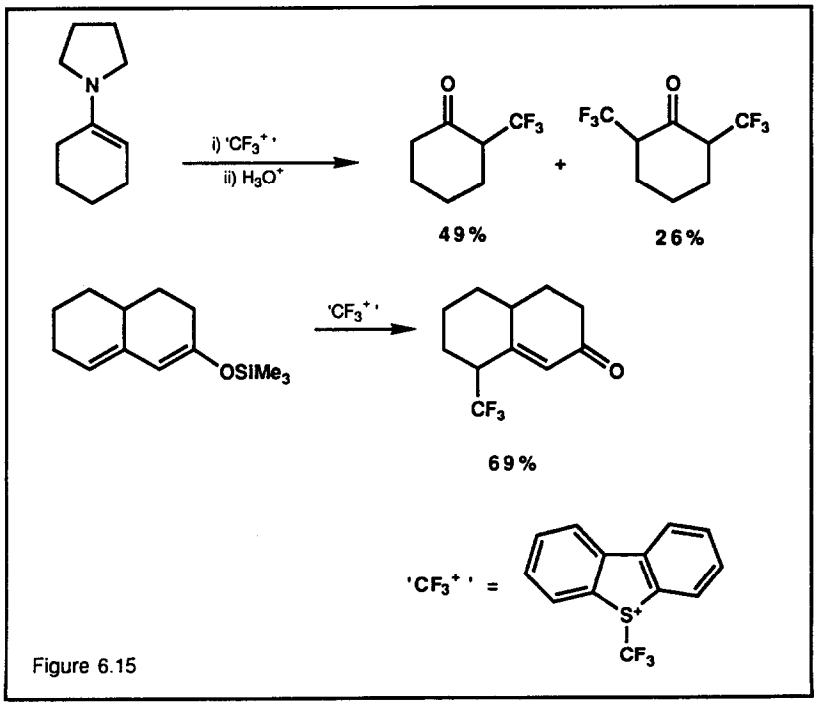


Figure 6.15

2,6-*bis*(trifluoromethyl) cyclohexanone.[95] When the silyl enol ethers of cyclohexanone was used instead of an enamine, the reaction was more specific, yielding only the mono-trifluoromethylated product (65%). Silyl enol ether of α,β-unsaturated ketones also reacted with the thiophenium salt, but yielded the γ-trifluoromethylated material (see Figure 6.15).

Finally, silyl enol ethers have also been trifluoromethylated using iodotrifluoromethane in the presence of triethylborane and a suitable base (eg 2,6-dimethylpyridine). Internal and terminal silyl enol ethers can be employed yielding, after hydrolysis, α-trifluoromethyl ketones (Figure 6.16), while ketene silyl acetals can be used to synthesise α-trifluoromethyl carboxylates (Figure 6.16).[165]

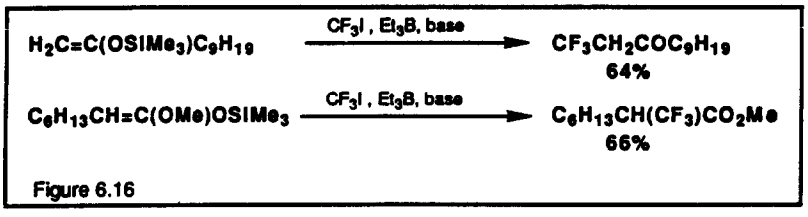


Figure 6.16

7. Trifluoroethylation and Related Reactions

With the success of trifluoromethylated compounds in a variety of industrial applications, interest has developed in the properties of 2,2,2-trifluoroethylated materials, especially where the trifluoroethyl group is attached to an aromatic ring.

The methods applicable for the conversion of C_1 moieties to a trifluoromethyl group have been investigated with respect to the formation of a trifluoromethyl substituent. The halogen exchange reaction using antimony trifluoride required the presence of antimony pentachloride and still gave poor yields and mixtures of products (Figure 7.1) typical of aliphatic trichlorides (see Section 5.1).[166]

More success has been found using sulphur tetrafluoride and arylacetic acids, though the difficulty in using sulphur tetrafluoride limits its usefulness.[167, 35b]

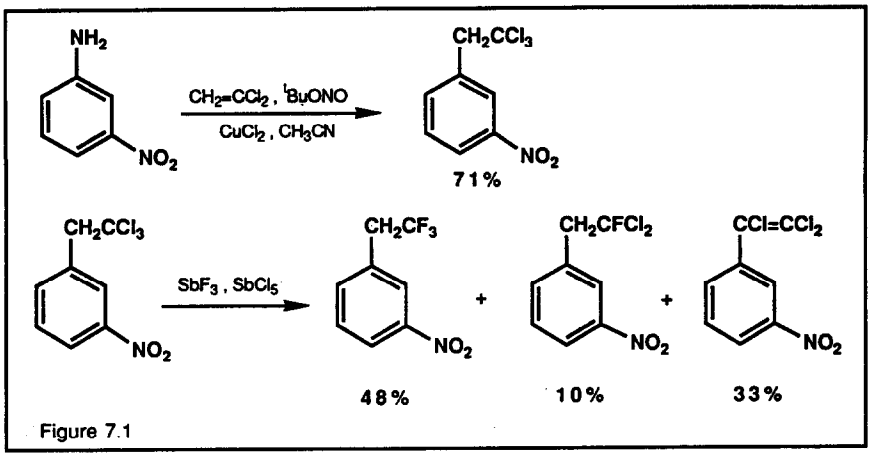


Figure 7.1

The direct incorporation of a trifluoroethyl group has been attempted using 1-iodo-2,2,2,-trifluoroethane, copper and iodobenzene, but the yield was low (Figure 7.2).[37b] However, benzyl halides do react with trifluoromethyl copper to give the same product in better yield (see Section 5.2).

Other methods all involve the reduction of more readily available trifluoroethylated materials (α,α,α-trifluoroacetophenone or 1-aryl-2,2,2-trifluoroethanol). Although the Clemmensen reduction of trifluoroacetophenones did not yield the desired product (see

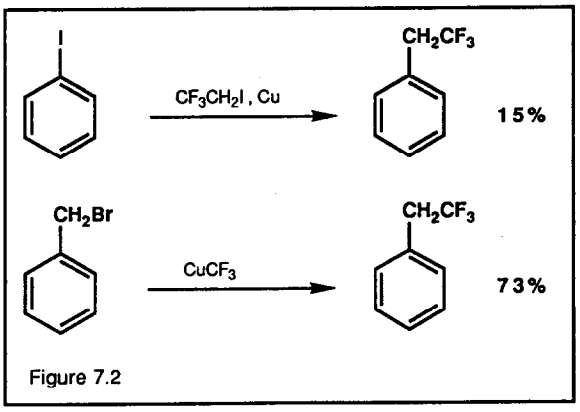


Figure 7.2

Figure 7.3)[168], a more convoluted method of reduction did prove successful (Figure 7.4).[169]

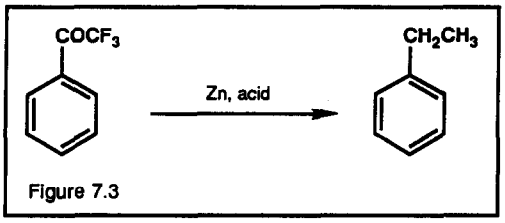


Figure 7.3

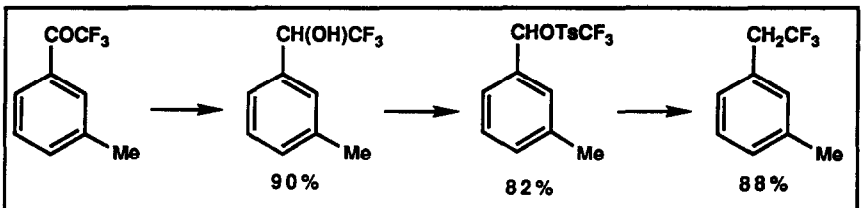


Figure 7.4

Both the α,α,α-trifluoroacetophenone and the 1-aryl-2,2,2-trifluoroethanol are easily prepared. The methods available for the synthesis of the acetophenone have recently been reviewed,[6] while the alcohol can either be prepared by the trifluoromethylation of benzaldehydes (see Section 6.1) or by the direct incorporation of the $CF_3CH(OH)$ moiety (Figure 7.5).[170]

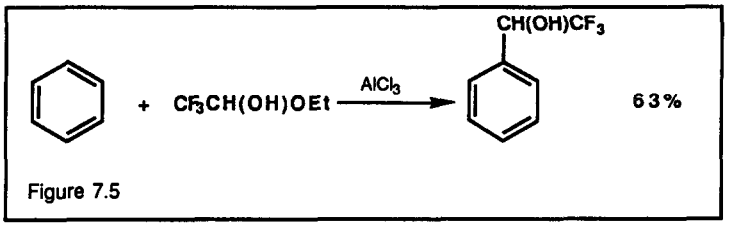


Figure 7.5

More recently, attention has focused on the use of 2,2,2-trifluoro-1-(phenylthio)-ethane since it is readily alkylated and the phenylthio group can then be removed using a tin hydride to yield the desired product (see Figure 7.6).[171, 172]

Finally, some aliphatic substrates have to be trifluoroethylated directly using iodotrifluoroethane or indirectly by trifluorodichloroethylation, followed by removal of the

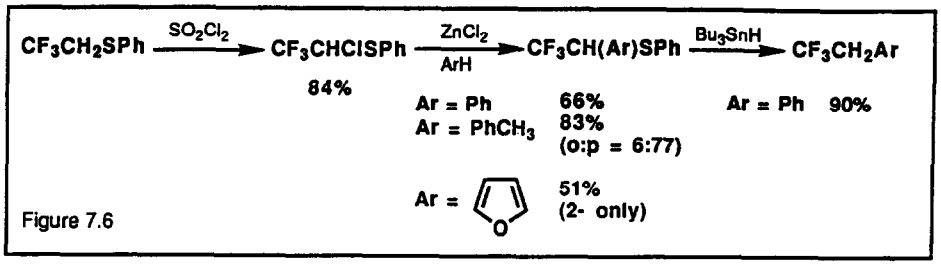


Figure 7.6

chlorines. The examples of direct trifluoroethylation involves the addition of 1-iodo-2,2,2-trifluoroethane to silyl enol ethers[165] or across triple bonds,[118] using triethylborane as catalyst (Figure 7.7).

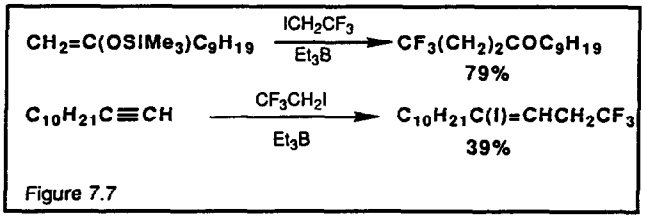


Figure 7.7

Although 2,2,2-trifluoro-1,1-dichloroethylation of carbonyl compounds has been reported in a number of papers,[173] the dechlorination of the product to yield the trifluoroethylated product has only recently been reported.[174] This report also describes the preparation of chiral trifluorodichloroethylated alcohols (see Figure 7.8).

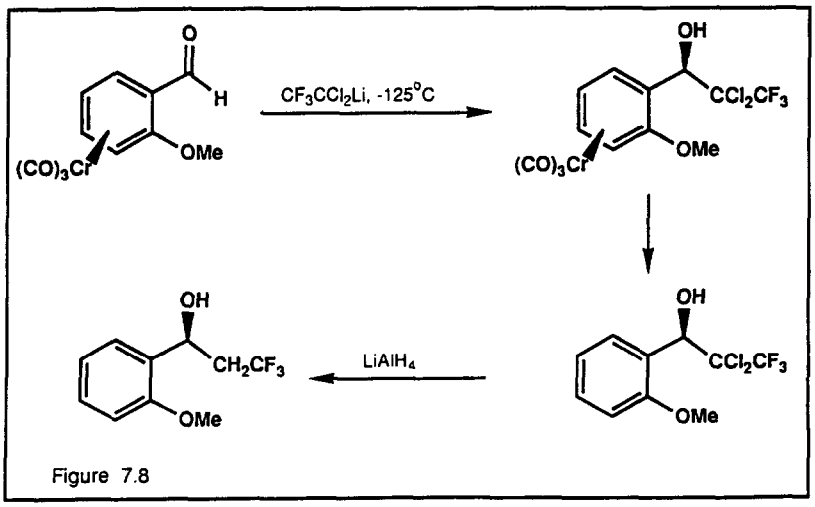


Figure 7.8

8. Preparation of Trifluoromethoxy Compounds

The advantage of incorporating a trifluoromethoxy group into a molecule may be described in terms of its properties. The trifluoromethoxy group is both more electron withdrawing and lipophilic than its methoxy analogue.[175] It is also thermally and chemically resistant to attack by acids, bases, organometallic reagents and oxidising/reducing agents.[176, 177] When substituted on an aromatic ring, the trifluoromethoxy group exhibits similar electron withdrawing behaviour to the alkoxy group but also acts to deactivate the aromatic system.[178] Finally, selectivity during aromatic substitution is also introduced by the directing effect of this substituent (o,p director).[176]

8.1 Conversion of -OCX_3 to -OCF_3

A method for incorporating a trifluoromethoxy group was discovered inadvertently during a study of the phenyl ester of chlorothiocarbonic acid. The trifluoromethoxy derivative may be formed by introducing a halothiocarbonyl group into a molecule followed by chlorination to the trihalomethyl form. This step is then followed by fluorination using antimony trifluoride and a catalytic amount of antimony pentachloride (Figure 8.1).[179]

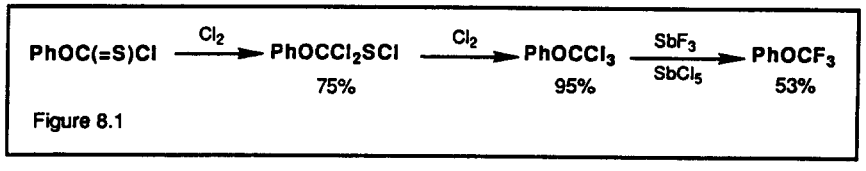


Figure 8.1

Previously, the standard precursor was a methoxy group with chlorination and subsequent fluorination of the trichloromethoxy group yielding the desired product (Figure 8.2).[180]

Aryl trifluoromethyl ethers may also be prepared by reacting phenols containing a wide variety of substituents with hydrogen fluoride in excess carbon tetrachloride using a closed pressure vessel under autogeneous pressure (Figure 8.3).[181]

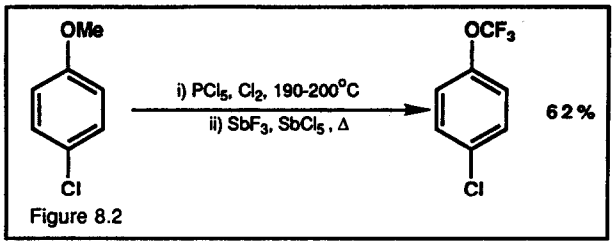


Figure 8.2

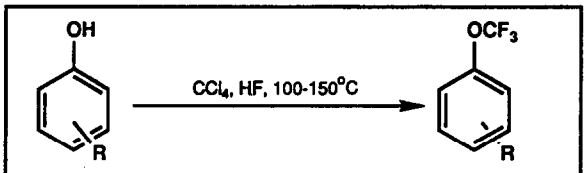


Figure 8.3

However, substrates containing ortho substituents capable of hydrogen bonding to the hydroxy group have not produced trifluoromethoxy compounds by this method. It should also be mentioned that use of a molar equivalent of tetrachloromethane lowered product yield, while milder reaction conditions produced chlorodifluoromethoxy derivatives.[182] Furthermore, a catalytic amount of boron trifluoride increased the yield of the 1-nitro-4-trifluoromethoxybenzene from 4-nitrophenol.[181]

The highest yields in the synthesis of aryl trifluoromethyl ethers from phenols are afforded when the phenol is substituted with electron withdrawing groups, surmised to protect the aromatic ring from attack by intermediates. The only exception to this rule is the cyano group which undergoes side reactions leading to low yields of the desired product.[181]

The synthesis of 3-trifluoromethoxy aniline via nitration-reduction of trifluoromethoxy benzene is often difficult due to reaction conditions (toxic reagents, low yields, etc) and unavailability of starting materials. An alternative method involves the selective amination of 2-chloro(trifluoromethoxy)benzene prepared from 2-chlorophenol (Figure 8.4).[183] 4-Chloro-3-(trifluoromethoxy)aniline is prepared from 2,6-dichlorophenol in a similar manner with yields slightly higher than the mono chloro

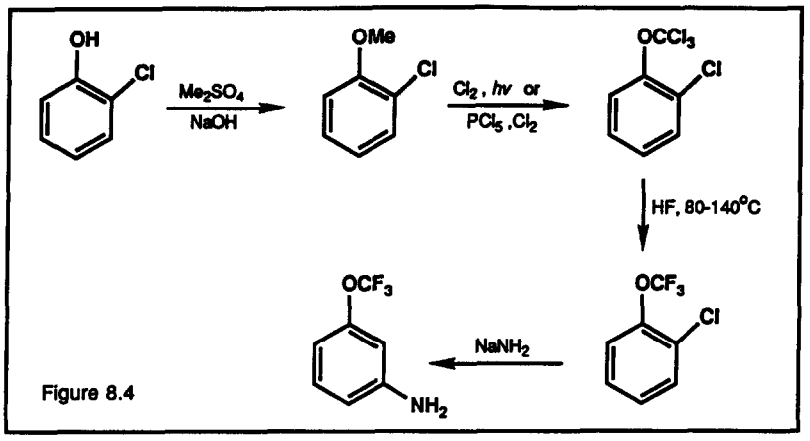


Figure 8.4

precursor. The reaction remains regiospecific with only one chlorine substituted by an amino group.[183]

An alternative synthesis of aryl trifluoromethyl ethers from phenols involves reaction with carbonyl fluoride,[184] followed by sulphur tetrafluoride (Figure 8.5).[176] Use of sulphur tetrafluoride requires a temperature of between 150-175 °C for complete reaction of the carbonyl group and decreased tar formation. In contrast to the reaction described in Figure 8.3, compounds containing ortho substituents capable of H-bonding may be successfully trifluoromethylated if sodium fluoride is present.[176]

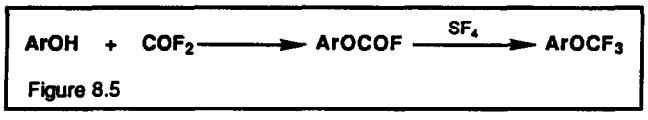


Figure 8.5

In the synthesis of trifluoromethoxy ethers using carbonyl fluoride, the fluoroformate shown in Figure 8.5 was rarely isolated. One exception is the low temperature reaction of ethylene glycol with excess carbonyl fluoride in the presence of sodium fluoride. In addition to *bis*(trifluoromethoxy) ethane, two by products included β–trifluoromethoxyethyl fluoroformate ($CF_3OCH_2CH_2O_2CF$) and 2-fluoro-1-(trifluoromethoxy) ethane ($CF_3OCH_2CH_2F$). Finally, alkyl alcohols require the presence of an electron withdrawing substituent on the β-carbon in order for reaction to be observed.

In a similar fashion, trifluoromethoxy benzene can be synthesized from phenols by esterification of the hydroxy group with trifluoroacetic acid, followed by pyrolysis to give the desired product, albeit in low yield and contaminated with benzotrifluoride (Figure 8.6).[97]

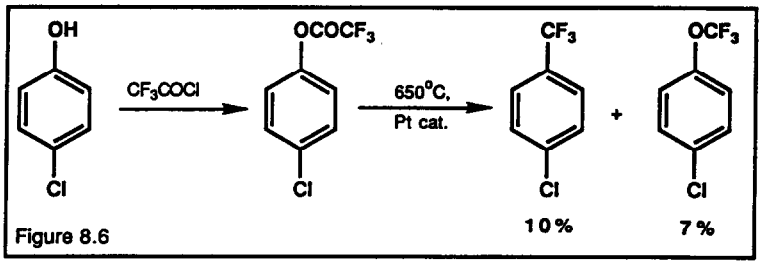


Figure 8.6

8.2 Direct Incorporation of the Trifluoromethoxy Group

Trifluoromethyl hypofluorite, first synthesized in 1948, was examined in the late 1950's with the purpose of introducing the trifluoromethoxy group directly into organic molecules. Initially, the compound was reacted with methane, chloroform and carbon tetrachloride and under mild conditions acted solely as a fluorinating agent.[185]

When unsaturated compounds are reacted with trifluoromethyl hypofluorite under vigorous conditions, identical results to those observed using the previously mentioned saturated compounds are obtained. In contrast, under milder reaction conditions, the addition of a trifluoromethoxy group was detected (Figure 8.7), though the limited number of examples makes the utility of the method difficult to assess.

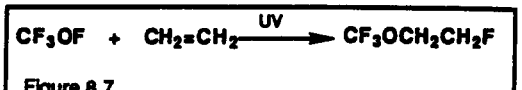


Figure 8.7

The introduction of the trifluoromethoxy substituent into carbohydrates may be achieved under mild conditions using *tris*(dimethylamino)sulfonium trifluoromethoxide ($[(CH_3)_2N]_3S^+ CF_3O^-$, $TAS^+ CF_3O^-$) as a reagent.[175] This compound is prepared by

reacting carbonyl fluoride with *tris*(dimethylamino)sulfonium difluorotrimethylsiliconate in anhydrous THF at -75 °C.[186]

Although the trifluoromethoxide anion is a relatively poor nucleophile, when reacted with primary triflate esters of carbohydrates, the anion displaces the triflate ester under generally mild conditions. The more sterically hindered secondary triflates require harsher reaction conditions and in addition to the desired product, the fluorinated compound is also produced (Figure 8.8).[175]

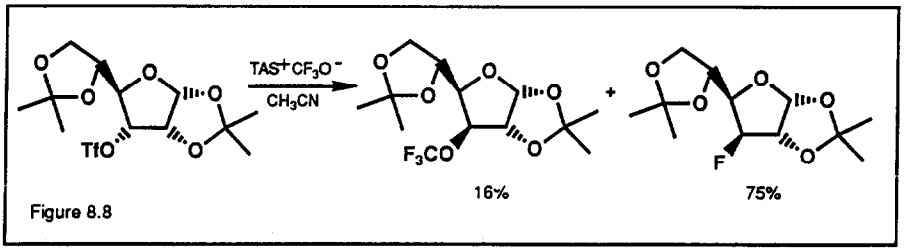


Figure 8.8

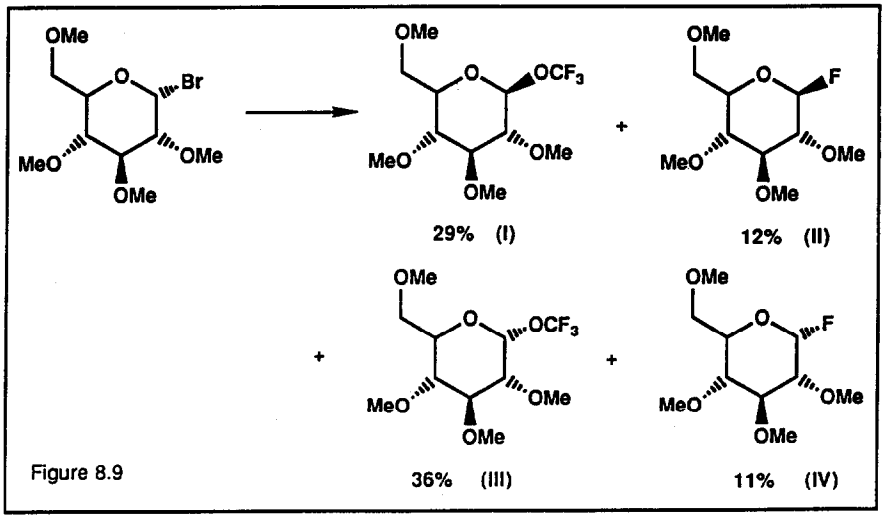


Figure 8.9

Glycosyl halides react with $TAS^+ CF_3O^-$ to yield a mixture of β-trifluoromethoxy-glucoside (I), α-glycosyl fluoride (IV), α-trifluoromethoxyglucoside (III) and β-glucosyl fluoride (II) (Figure 8.9) the last two being inseparable by chromatography or distillation.

In an attempt to prepare the free trifluoromethoxy-β-D glucopyranoside, an acetobromoglucose was reacted successfuly with $TAS^+ CF_3O^-$. However, deacetylation of the product with the trifluoromethoxy group remaining intact could not be afforded.[175]

9. Preparation of Trifluoromethyl Sulphides

The high lipophilicity of the trifluoromethylthiol group has rendered it useful in the pharmaceutical and agrochemical fields.[187] When examining the trifluoromethylthiol unit, one must take into account that although this group is similar in behaviour to the trifluoromethoxy functionality, sulphur is larger and more polarizable than oxygen. However, the presence of the electronegative trifluoromethyl group results in a contraction of the d orbitals on sulphur thereby increasing the overlap between the trifluoromethylthio moiety and the adjacent π system.[178]

9.1 Conversion of $-SCX_3$ to $-SCF_3$

Trifluoromethyl aromatics may be synthesized in relatively good yield by photoinitiated chlorination of phenyl methyl sulphide followed by fluorination using antimony trifluoride (Figure 9.1).[188]

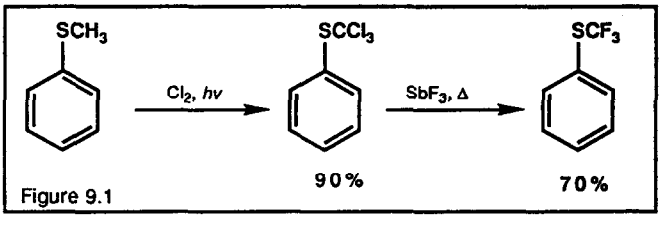


Figure 9.1

The aromatic ring in these examples may contain chloro- or nitro- substituents. However, more severe conditions and the use of catalytic quantities of boron trifluoride are required in the fluorination step if electron withdrawing substituents are present.[197] Additionally, the reaction is not always applicable to substrates containing ortho substituents.

An example of pharmaceutically useful compounds are the trifluoromethylated phenothiazine derivatives.[189] 3-Trifluoromethylmercaptodiphenylamine is prepared from the reaction of acetanilide and 3-bromophenyltrifluoromethyl sulphide, which in turn is prepared by the fluorination of the trichloro- derivative using antimony trifluoride (Figure 9.2).[190]

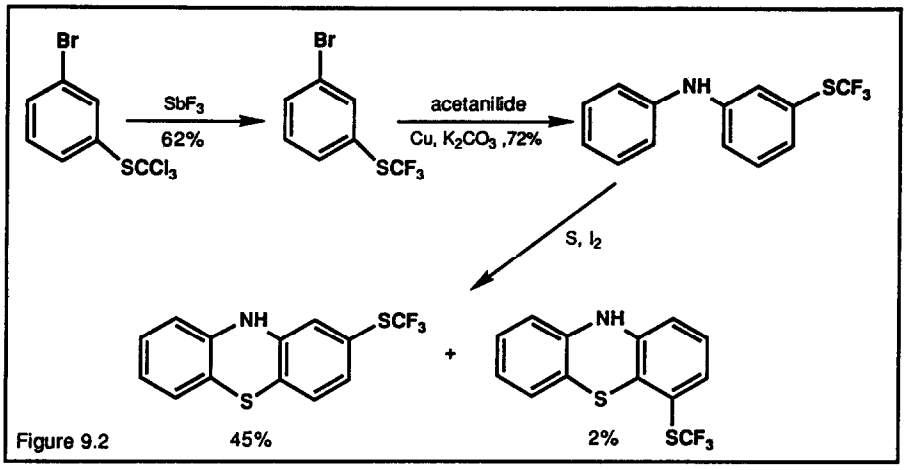


Figure 9.2

9.2 Direct Incorporation of the Trifluoromethylthio Group

Direct incorporation of trifluoromethyl thiol units into a molecule may be achieved by several methods. These methods are generally divided into two main categories: nucleophilic substitution using metal trifluoromethylthiols, or radical reactions using trifluoromethanesulphenyl chloride or trifluoromethane thiol.

Among the nucleophilic trifluoromethylthiol metal compounds is *bis*(trifluoromethylthiol)mercury which may be prepared by reaction of *bis*(trifluoromethyl) -disulphide[191] with mercury (Figure 9.3a)[192] or by passing carbon disulphide over mercury(II) fluoride (Figure 9.3b).[193]

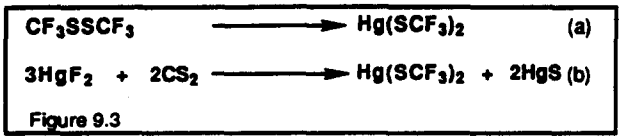


Figure 9.3

The complex is soluble in a wide range of solvents and will easily coordinate to donor solvents.[193] Stoichiometric amounts of *bis*(trifluoromethylthio)mercury will substitute halogen atoms in a series of alkyl halides (Figure 9.4),[193,194] though the toxicity of mercury makes this route unattractive.

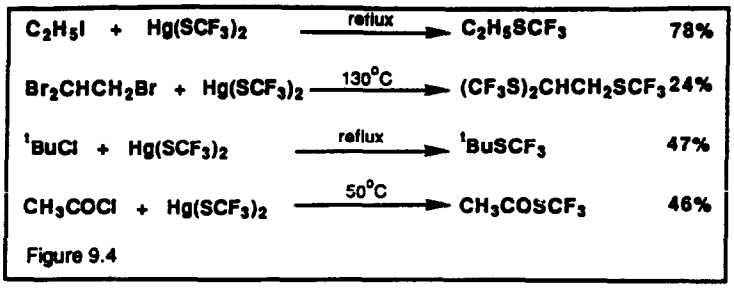


Figure 9.4

Trifluoromethylthiosilver was first prepared in 1959 by reaction of aqueous silver nitrate and bis(trifluoromethylthio)mercury.[193] Following this, in 1961 the compound was directly prepared from silver(I) fluoride and carbon disulphide.[195] An example of trifluoromethylthiolation using trifluoromethylthiosilver is the reaction with tropylium bromide to give 7-trifluoromethylthiocycloheptatriene (Figure 9.5).[196] Upon oxidation of this compound, the tropylium trifluoromethylsulphonate was formed rather than the desired sulphone.

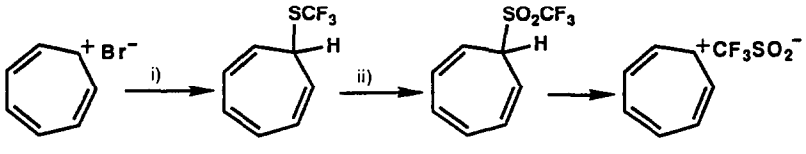


Figure 9.5: i) $AgSCF_3$, ii) p-$O_2NC_6H_4CO_3H$

The reaction of trifluoromethylthiocopper with aryl bromides and iodides can be used to prepare aryl trifluoromethyl sulphides containing a wide variety of substituents

(Figure 9.6), in contrast to the limitations of the chlorination-fluorination method discussed previously.

Other advantages of this method include increased yield and selectivity,[198] though lower yields are recorded for compounds containing electron donating substituents.[197] In addition to aryl halides, trifluoromethylthiocopper reacts metathetically with haloheteroaromatics to give the desired product (Figure 9.7).[197]

Trifluoromethylthiocopper can be conveniently prepared from *bis*(trifluoromethyl)-disulphide with copper powder in DMF or a similar solvent.[199] Alternatively,

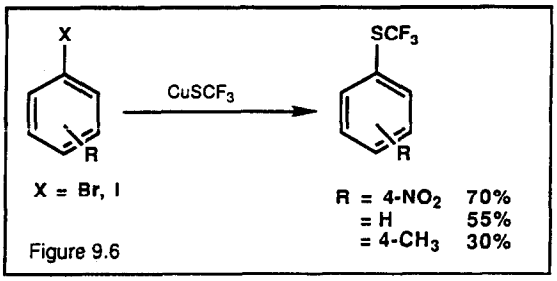


Figure 9.6

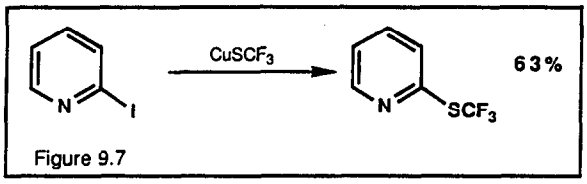


Figure 9.7

trifluoromethylthiocopper is prepared from *bis*(trifluoromethylthio)mercury and copper powder or trifluoromethylthiosilver and copper(I) bromide.[198,200]

In order to improve yields and the purification of products, supported reagent versions of the copper salt were examined. Experimental results showed that using alumina as a support resulted in higher yields than those obtained using charcoal or silica, though the reagent had to be used soon after its preparation as it does decompose with time.[200] The reactions with the supported reagent version of trifluoromethylthiocopper proved much cleaner than those which employed the unsupported salt.

A final source of the trifluoromethanethiolate anion (SCF_3^-) is not obtained from a metal complex but is generated 'in situ' by the reaction of thiocarbonyl fluoride[192] and calcium or potassium fluoride. Although thiocarbonyl fluoride produces the best yield, it is often more convenient to use the liquid trimer *bis*(trifluoromethyl)trithiocarbonate ($(CF_3)_2C=S$)as a source for trifluoromethanthiolate ion (Figure 9.8)[201]

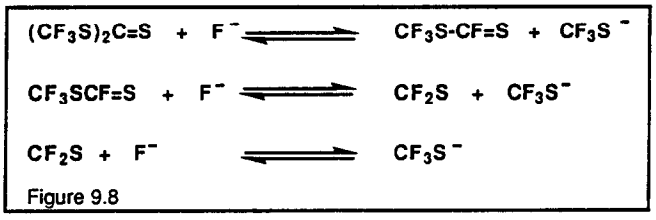


Figure 9.8

When reacted with pentafluoropyridine, the resulting product is 4-(trifluoromethylthio)tetrafluoropyridine.[202] Further reaction with trifluoromethanthiolate led to the isolation of *bis*- and *tris*(trifluoromethylthio)fluoropyridines (Figure 9.9).[201]

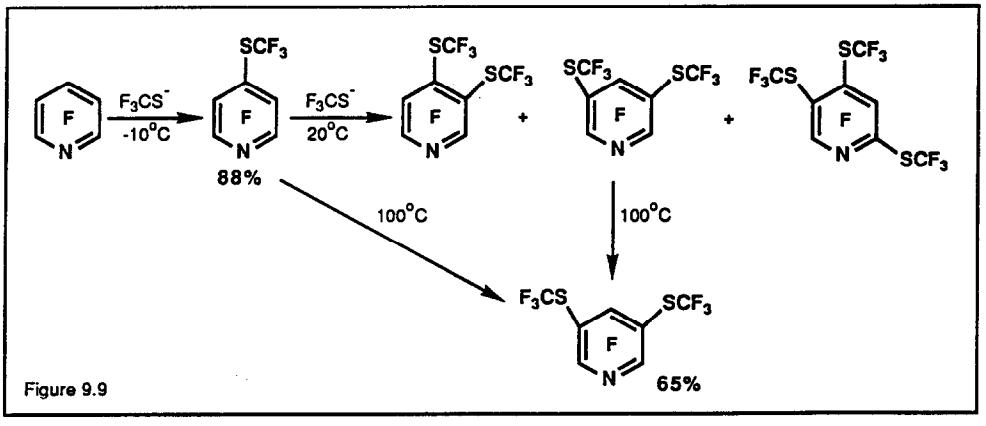


Figure 9.9

In the trifluoromethylthiolation of tetrafluoropyrazine, the extent of substitution may be selectively controlled by the number of equivalents of thiolating reagent used in the reaction (Figure 9.10).[203]

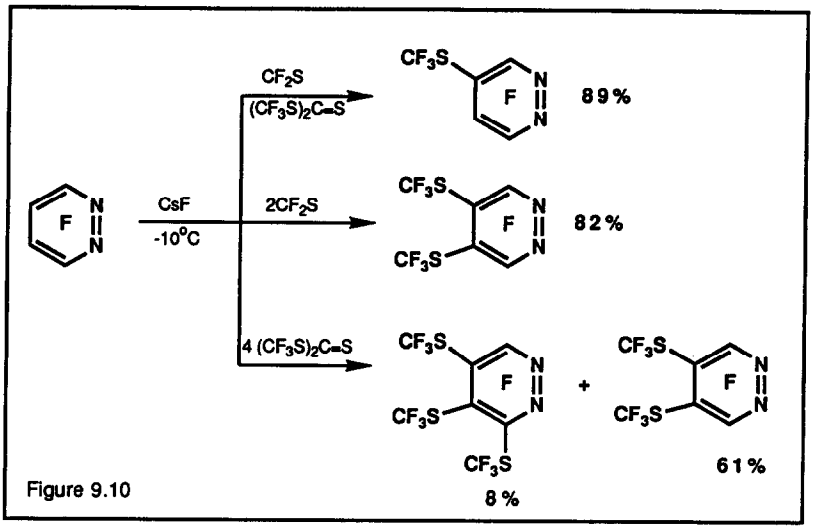


Figure 9.10

However, no tetrasubstituted product was isolated when an excess of trifluoromethanthiolate is used. In contrast, the reaction of tetrafluoropyrimidine with a molar equivalent of thiocarbonyl fluoride yields mono, di-, and tri-substituted products (Figure 9.11) whereas *bis*(trifluoromethyl)trithiocarbonate produces only compounds the mono- and 4,5-*bis*(trifluoromethylthio) compounds.[203]

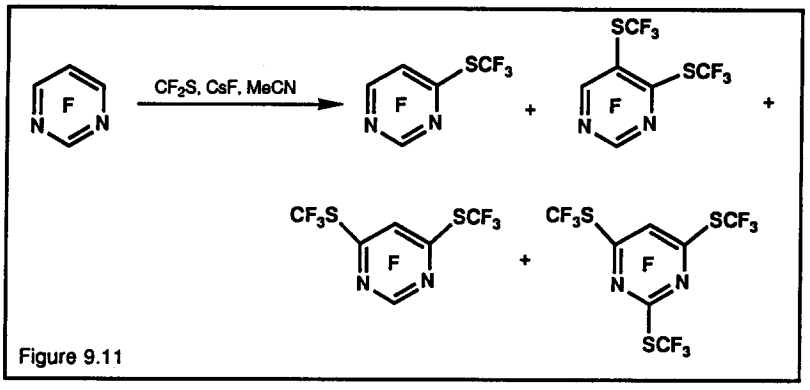


Figure 9.11

Trifluoromethanesulphenyl chloride, prepared from trichloromethanesulphonyl chloride and sodium fluoride,[204] provides a useful, radical based method for introducing trifluoromethylthio groups into haloolefins, saturated hydrocarbons, and a variety of

aromatic substrates. However, it should be mentioned that this method is often unsuccessful when the substrate is electron deficient.[201]

Trifluoromethylthiolation of haloolefins occurs by free radical addition of trifluoromethanesulphenyl chloride initiated by UV radiation, X-rays or azonitrile catalyst. These reactions are summarized in Table 9.1.[205]

The free radical mechanism involving initial addition of a trifluoromethylthio radical does not, however, account for the formation of both isomers. Furthermore, as will be described later, the orientation is generally opposite to that observed by the addition of trifluoromethanethiol. It must therefore be assumed that not only trifluoromethylthio radicals but chloro radicals are attacking species. This would not only account for the mixed products, but would retain the consistency that the radical always attacks to produce

Olefin	Trifluoromethylthio products	% yield
$CFH = CF_2$	CF_3SCF_2CFHCl	50
	$CF_3SCFHCF_2Cl$	11
$CF_2 = CFCF_3$	$CH_3SCF_2CFClCF_3$	63
	$CF_3SCF\ (CF_3)\ CF_2Cl$	37
	$CF_3SCF_2CF\ (SCF_3)\ CF_3$	10
$ClCF = CF_2$	$CF_3SCF\ ClCF_2Cl$	42
	$CF_3SCF_2CFCl_2$	12
$CH_3OCF = CF_2$	$CH_3OCF\ (SCF_3)\ CF_2SCF_3$	11
	$CH_3OCF\ (SCF_3)\ CF_2Cl$	16
	$Ch_3OCF\ (Cl)\ CF_2SCF_3$	26
$CH_2 = CHCl$	$CF_3SCHCl\ CH_2Cl$	73
	$CF_3SCH_2CHCl_2$	4
$CF_2 = CH_2$	$CF_3SCF_2\ CH_2Cl$	40
	$CF_3SCH_2CF_2Cl$	11

Table 9.1: Reaction of Trifluoromethanesulphenyl Chloride with Various Olefins.

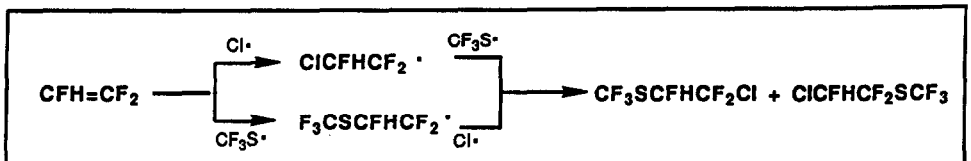


Figure 9.12

the most stable alkyl radical (see Figure 9.12).[205]

The free radical chain reactions of trifluoromethanesulphenyl chloride with saturated hydrocarbons yields both trifluoromethyl alkyl sulphides and chloroalkanes.[206] The product ratio varies depending upon the alkane precursor. For example sulphenyl chloride produces trifluoromethylthiocyclohexane and 1-chlorocyclohexane in 45% and 28% yield respectively. A very different reaction occurs using n-butane (Figure 9.13)[206] with only 1% chlorobutane resulting. Yet a similar reaction with isobutane produced a number of products as described in Figure 9.13.

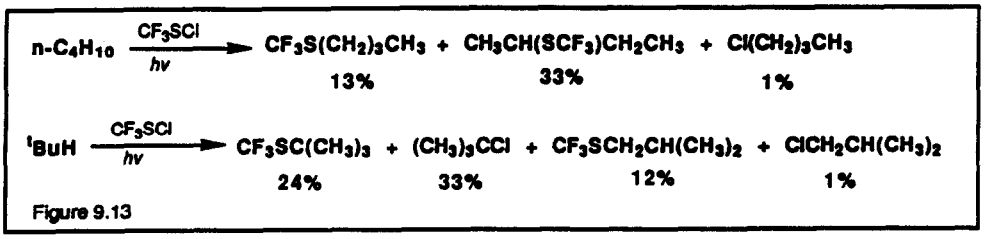


Figure 9.13

Trifluoromethylthiolation of heteroaromatics using trifluoromethanesulphenyl chloride also occurs by free radical chain mechanisms (Figure 9.14).[207]

Methyl, dimethyl, carboxy and acetyl pyrroles may be mono- or disubstituted (depending upon their reactivity) with trifluoromethanesulphenyl chloride.[207] In contrast, pyridine does not react directly with trifluoromethanesulphenyl chloride but will react as *tetrakis*(1,2,-dihydro-1-pyridyl)aluminate to yield 3-[(trifluoromethylthio]pyridine (Figure 9.15).[208]

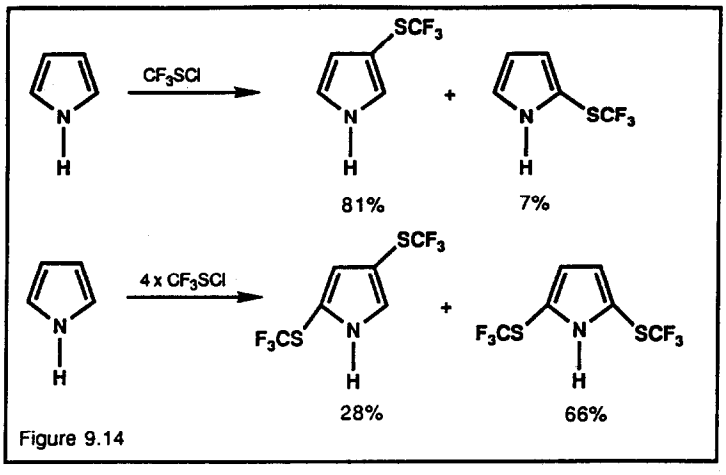


Figure 9.14

Aryl trifluoromethyl sulphides may be synthesized by reacting aryl Grignard reagents with trifluoromethanesulphenyl chloride.[209] The trifluoromethanesulphenyl

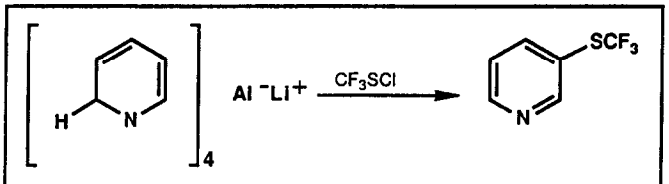


Figure 9.15

chloride is added to the Grignard reagent at 0 °C and results in the formation of not only the trifluoromethylthio compound but also aromatic halides (Figure 9.16). If an aryl magnesium bromide was used and significantly cooled, the yield of aryl trifluoromethyl sulphide decreased while that of aryl bromide increased. Mechanistic studies have attempted an explanation in that although attack of the carbanion is primarily on sulphur, the similar electronegativities of chlorine and sulphur allow formation of some trifluoromethylthiolate anion.[209] At lower temperatures, the very polarizable bromide can then compete with the trifluoromethanethiolate ion for displacement. Furthermore, when aryl magnesium iodides are used, yields are considerably lower.

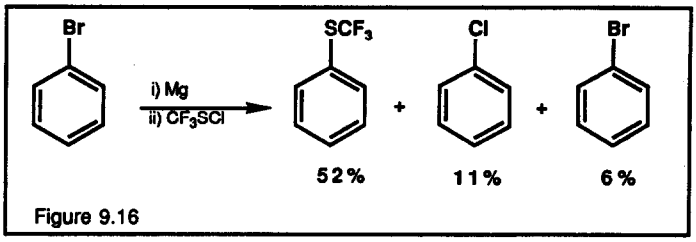


Figure 9.16

An alternative synthesis of aryl trifluoromethyl sulphides was based on the previously reported method of preparing aryl sulphides via the condensation of sulphenyl chlorides with aromatic compounds.[210b, 210c] The reaction was extended to include trifluoromethanesulphenyl chloride and proved to be useful particularly for aromatics containing electron donating substituents.[210a]

The reaction takes place at room temperature with yields of between 58-75%. In the case of benzene, substitution occurred only under forced conditions in the presence of a catalyst. Although substitution occurred almost always in the para position for electron donating substituents, as in the case of toluene and halobenzene, the products formed under forced conditions included all three isomers (Figure 9.17).

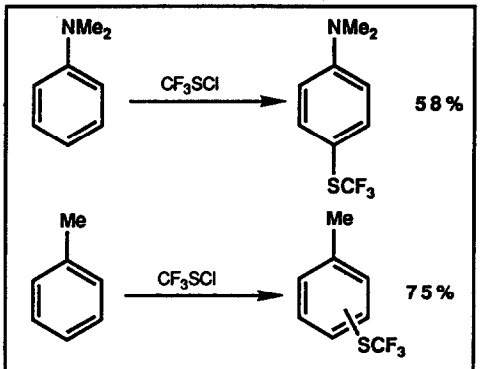


Figure 9.17

The free radical addition of trifluoromethanethiol (CF_3SH) to olefins results in the formation of trifluoromethylthiol alkanes and their corresponding oligomers.[211] The direction of attack can be attributed to intermediate radical stability.[212] For example, in the

addition of trifluoromethanethiol to chlorotrifluoroethylene and 2-methylpropene, the single products formed are those predicted by radical stability theory (Figure 9.18).

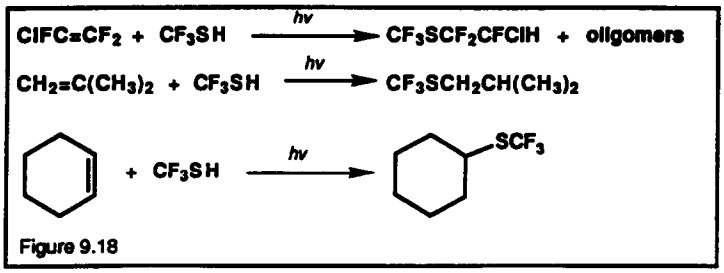


Figure 9.18

A final example of direct incorporation of the trifluoromethyl thiol unit is the free radical addition of pentafluoroiodobenzene to *bis*(trifluoromethyl)disulphide (Figure 9.19).[213] The presence of trifluoromethyl iodide and the perfluorophenylmethyl disulphide in the product mixture suggest that the pentafluorophenyl radical attacks the *bis*(trifluoromethyl)disulphide displacing a trifluoromethyl radical which subsequently abstracts an iodine atom.[213]

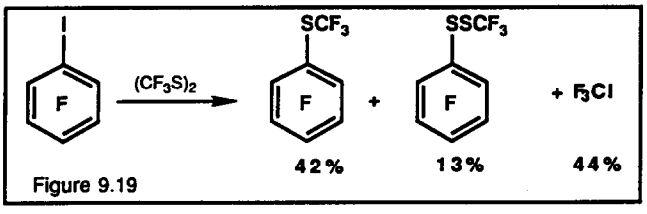


Figure 9.19

9.3 Trifluoromethylation of Thiols and Related Compounds

Alkyl trifluoromethyl sulphides can be prepared by irradiation of iodotrifluoromethane with dialkyldisulphides (Figure 9.20).[213]

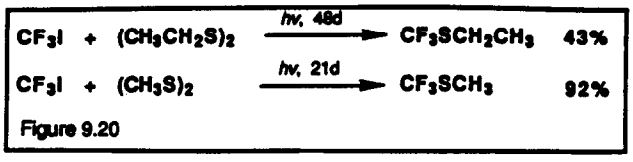


Figure 9.20

The formation of trifluoromethane, due to the increased number of hydrogens available for abstraction, has resulted in considerably lower yield in the reaction of

diethyldisulphide with iodotrifluoromethane for trifluoromethyl ethyl sulphide. Further, alkyl and aryl trifluoromethyl thiols have been synthesized from iodotrifluoromethane in 52 to 85% yield using the phase transfer catalyst benzyltriethylammonium chloride (Figure 9.21).[226]

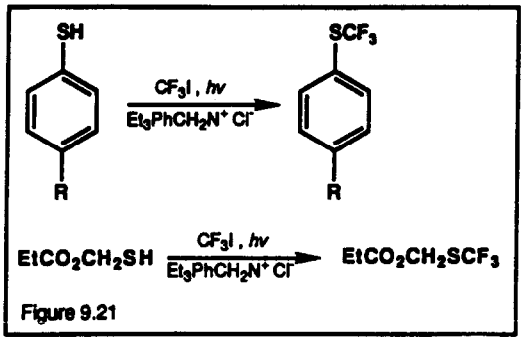


Figure 9.21

Trithiols may also be trifluoromethylated with iodotrifluoromethane to yield the corresponding tris(trifluoromethyl)thiol compounds (Figure 9.22).[214] This type of reaction may be extended to heteroaromatics such as pyrazine and pyrimidine.[215]

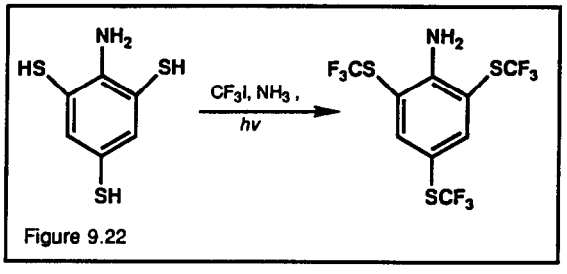


Figure 9.22

Trifluoromethyl aryl sulphides can be obtained by the reaction of arenethiolates with bromotrifluoromethane at a pressure of about two atmospheres, with yields varying from 7 to 75%.[216, 217] Substitution on the ring may vary, although the best yields are observed when electron donating substituents are present.[217] When bromotrifluoromethane is reacted with thiophenoxide in the presence of nitrobenzene, inhibition occurs suggesting an $S_{RN}1$ mechanism (Figure 9.23).[216]

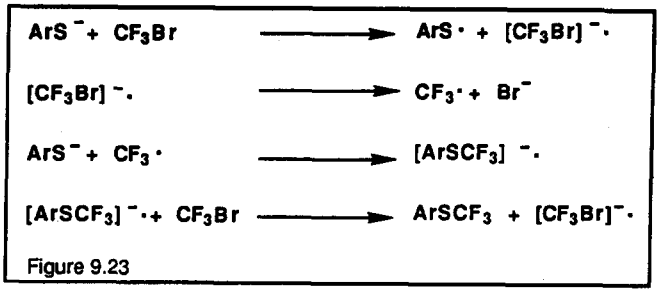


Figure 9.23

Alternatively, aliphatic and aromatic disulphides, when taken with bromotrifluoromethane in the presence of the sulphur dioxide radical anion, will produce trifluoromethyl thiol compounds in reasonable yields (31-93%).[187] The sulphur dioxide radical anion is derived from sodium dithionite ($Na_2S_2O_4$) and sodium hydroxymethane sulphinate (NaO_2SCH_2OH). The reaction takes place at room temperature in DMF/water and requires the presence of disodium hydrogenphosphate to neutralize the sulphur dioxide formed. In this case, it is clear that the disulphides are not reduced, which strongly substantiates the existence of a radical mechanism.[187] The low cost of bromotrifluoromethane (compared to iodotrifluoromethane) and the much lower reaction times (hours rather than days) makes these methods attractive.

The belief that compounds containing eliminatable heteroatoms between a perfluoroalkyl group and a good leaving group could act as trifluoromethylating agents[80] led to the development of a series of novel nitrogen containing compounds summarized in Figure 9.24.[42,80,86]

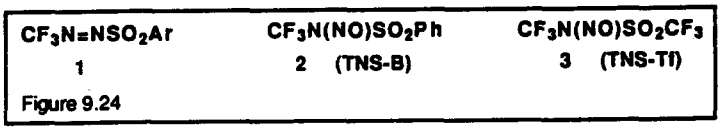


Figure 9.24

The first of the complexes, N-trifluoromethylazosulphonyl-benzene(1), prepared by the reaction of nitrosomethane and phenylsulphonamide in the presence of base, will react with disulphides to give trifluoromethylthio arenes.[86] Similarly, when irradiated, N-trifluoromethyl-N-nitrosophenylsulphonamide (TNS-B) in the presence of a disulphide substrate and biacetyl sensitizer resulted in trifluoromethyl iodide.[80] However, TNS-B

Substrate	Solvent	Time/hrs	Product	Yield
$(S\text{-}n\text{-}C_{10}H_{21})_2$	$(CH_3)_2CO$	6	$CF_3S\text{-}n\text{-}C_{10}H_{21}$	55
$(SCH_2COOH)_2$	"	14	CF_3SCH_2CDOH	63
$(SCH_2CH_2COOH)_2$	"	3.5	$CF_3SCH_2CH_2COOH$	50
$(SCH_2CH_2CH(NHCOCF_3)COOCH_3)_2$	"	7	$CF_3SCH_2CH_2CH(NHCOCF_3)COCH_3$	59
$(SCH_2CH(OAc)\,CH_2OAc)_2$	CH_3CN	14	$CF_3SCH_2CH(OAc)CH_2OAc$	64

Table 9.2: Reaction of N-Trifluoromethyl-N-Nitrosophenylsulphonamide with Disulphides.

produces better yields of the desired product with shorter reaction times. In addition, crystalline TNS-B is easier to handle than iodotrifluoromethane gas. A summary of reactions involving TNS-B is given in Table 9.2.[80]

Following the development of TNS-B as a trifluoromethylating agent, it was believed that the reactivity could be enhanced by replacing the aryl group with a perfluoroalkyl group. N-trifluoromethyl-N-nitrosotrifluoromethane sulphonamide (TNS-Tf) is prepared by reaction of nitrosomethane and hydroxylamine at -65 °C in DMF followed by addition of trifluoromethanesulphonyl fluoride in the presence of sodium hydride.[42] TNS-Tf is useful in the trifluoromethylation of thiols and disulphides resulting in generally higher yields and shorter reaction times that its TNS-B counterpart. For example, the synthesis of $CF_3SCH_2CH(NHCOCF_3)COOCH_3$ (a precursor to a methionine activation inhibitor) was increased from 30% with TNS-B to 71% with TNS-Tf. This is most likely due to the fact that both trifluoromethyl groups of TNS-Tf are used in the reaction.[42]

A final source of the trifluoromethyl group is derived from compounds containing the trifluoromethyl sulphonium ion. (Trifluoromethyl)dibenzothiophenium triflate and its seleno analog are prepared from 2-trifluoromethylthio(seleno) biphenyl in 75% yield according to Figure 9.25.[218] The mononitro- and dinitro- derivatives are synthesized using two or three equivalents of nitronium triflate respectively. When reacted with the

sodium salt of alkane thiols, these compounds will produce trifluoromethylthio ethers in fair yield (47-87%).

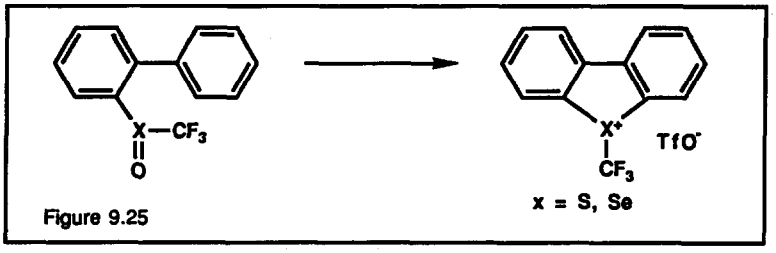


Figure 9.25

Similarly, trifluoromethyl 4-chlorophenyl sulphoxide reacts with trifluorosulphonium hexafluoroantimonate to give phenyl(trifluoromethyl)-fluorosulphonium hexafluoroantimonate, which subsequently reacts with m-xylene to give the trifluoromethyl sulphonium salt (I) shown in Figure 9.26.[219] As also described in Figure 9.26, this compound may be further reacted to produce trifluoromethyl thiols.

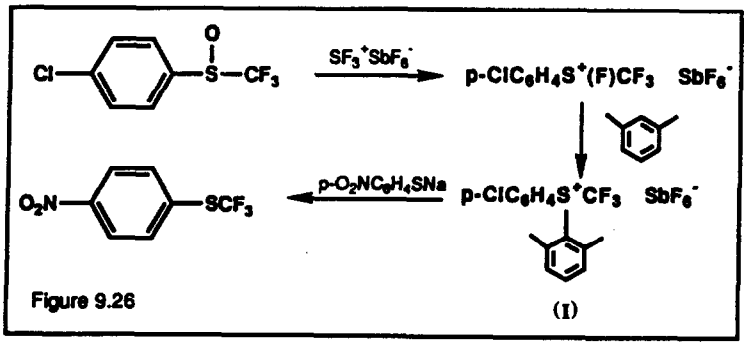


Figure 9.26

10. Preparation of Trifluoromethylsulphones (Triflones)

Interests in the pharmaceutical and agrochemical industries lies not only with trifluoromethylthiols, but with their oxidation product, the corresponding sulphones.[187] The strong electron withdrawing properties of the sulphonyl group coupled with the electronegativity of fluorine, renders the trifluoromethyl sulphonyl group one of the strongest electron withdrawing substitutents.[178,195]

10.1 Oxidation of -SCF_3

In general, the oxidation of aryl and heteroaryl trifluoromethyl sulphides will generate the desired sulphone[188,201] (see Figure 10.1). The temperatures and reaction times are critical in this type of synthesis since the resulting sulphonyl group is more reactive that its thiol precursor.[201] A disadvantage of this method lies in the fact that prior to oxidation, the sulphide must be prepared, requiring multi-step synthesis and expensive reagents (see Section 9).

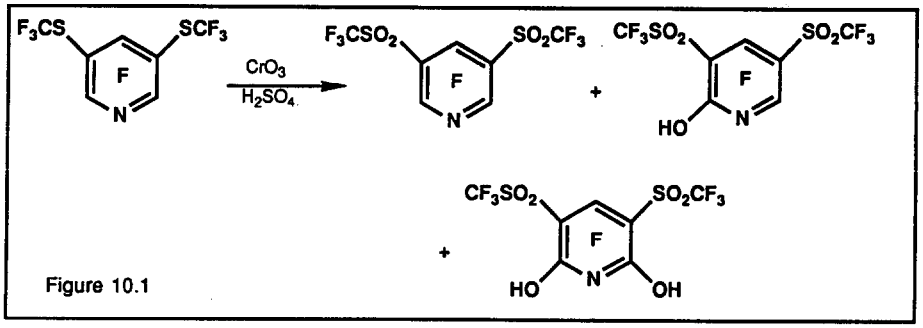


Figure 10.1

10.2 Direct Incorporation of -SO_2CF_3

A number of electrophilic trifluoromethane sulphonyl sources such as triflic anhydride $(CF_3SO_2)_2O$, trifluoromethyl sulphonyl chloride (CF_3SO_2Cl) and phenylbis(trifluoromethylsulphonyl)amine ($PhN(SO_2CF_3)_2$) provide a convenient route to the preparation of alkyl and aryl trifluoromethyl sulphones.[220]

Primary and secondary trifluoromethyl sulphones may be synthesized by the reaction of these electrophiles with organolithium reagents (Figure 10.2).[220]

However, tertiary and phenyllithium reagents resulted in no trifluoromethyl sulphone formation, though aryl trifluoromethyl sulphones may be prepared via the Friedel-Crafts reaction of arenes with triflic anhydride and aluminium chloride (Figure 10.3).[220]

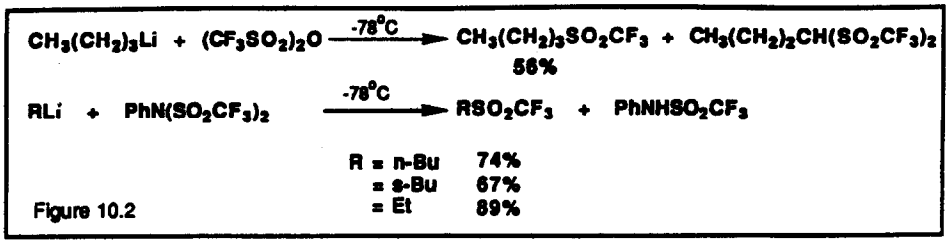


Figure 10.2

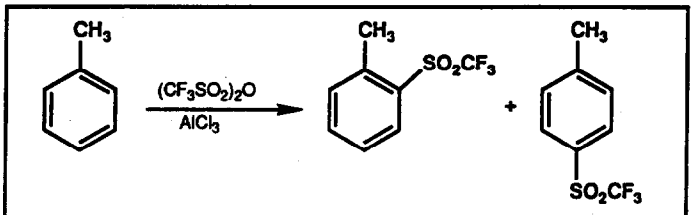


Figure 10.3

Attempts to prepare alkynyl trifluoromethyl sulphones using alkynyllithium silane or aluminium compounds proved unsuccessful due to low yields or inherent side reactions (oxidative coupling of the metal alkynide in the presence of the anhydride). It is only when the sodium salt of the alkyne is reacted with triflic anhydride that products are obtained in respectible yields (Figure 10.4).[228]

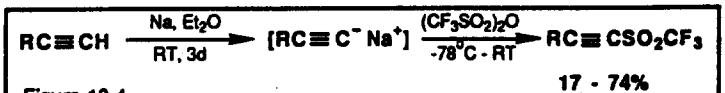


Figure 10.4

This method of synthesizing alkynyl trifluoromethyl sulphones may be used with most terminal alkynes, with the exception of those containing heteroatom substituents on the alkyl side chain. The triple bond of the product is particularly reactive towards nucleophiles such as water and amines and readily forms Diels-Alder adducts with cyclopentadiene.

10.3 Carbene Insertion

A more recent investigation has reported the use of *tris*(dimethylamino)sulphonium difluoromethylsilane (TASF) in conjunction with trifluoromethyl silanes or stannanes in order to prepare trifluoromethylsulphones (Figure 10.5).[227]

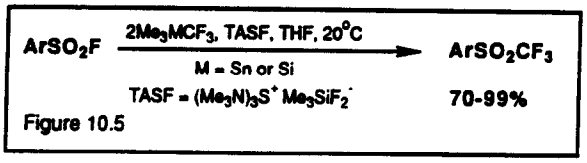


Figure 10.5

The mechanism of reaction involves the formation of difluorocarbene, which inserts into the sulphur-fluorine bond. The reaction gives high yields of aryl trifluoromethyl sulphones from readily prepared starting materials. It has been shown that the yield is not affected by electron withdrawing or donating substituents on the aromatic ring, but does depend on the method by which the reagents are introduced into the reaction medium. Further, when trifluoromethyl silanes are used, a variety of solvents may be used. In contrast, when trifluoromethyl stannanes are employed, the nature of the solvent significantly affects the product yield, and it has been concluded that the stannane intermediate in the reaction is stabilised by solvents of low polarisability.

10.4 Other Methods

The previously discussed N-trifluoromethylazophenylsulphones (Section 9.3) undergo thermal elimination of nitrogen, followed by radical cage recombination to yield the trifluoromethyl aryl sulphone in approximately 40% yield (Figure 10.6).[86]

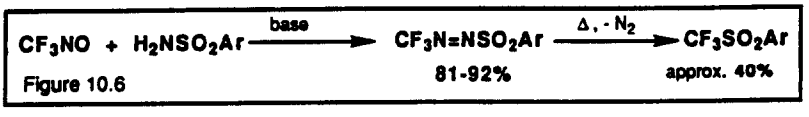


Figure 10.6

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