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Recent studies at Durham on direct fluorination

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Abstract

Developments in direct fluorination are described, which changed our perception of the viability of this methodology for selective introduction of carbon–fluorine bonds. Use of acids as solvent media is a valuable technique for electrophilic fluorination, especially with aromatic systems. Fluorinations of 1,3-dicarbonyl compounds proceed well and techniques for promoting reactivity in other carbonyl derivatives are described. 'In-situ' formation of other reagents, e.g. by reaction of fluorine with other halogens and with water, provides convenient methodology for halogenation and oxidation.

Keywords: Fluorine; Halogenation; Oxidation; Electrophilic fluorination

1. Introduction

A prejudice against the idea that reactions of elemental fluorine can be controlled, to introduce fluorine selectively into an organic compound, has built up since fluorine was discovered over 100 years ago. Indeed, many of us have unwittingly fostered this prejudice by demonstrations of fluorine igniting organic compounds and materials. However, we believe that this image is changing rapidly due to the work of several research groups [1–5], and the use of elemental fluorine in the manufacture of 5-fluorouracil which has demonstrated the opportunities available at the industrial scale. Here we review our own contributions to this changing perception which have been made over a period of almost a decade.

In Durham, we have used fluorine for many years. Initially, fluorine was generated using an ICI designed cell, of a traditional type, where minor 'explosive incidents' occurred which, we believe, were due to the fluorine being contaminated with oxygen difluoride arising from moisture in the cell electrolyte. These incidents were virtually eradicated by running the cell for 10–15 min to 'dry' the electrolyte before employing the fluorine generated in chemical reactions. The advent of high quality fluorine and fluorine–nitrogen mixtures being commercially available in cylinders largely eliminates the problem of oxygen difluoride — although fluorine under pressure should not be used unless the laboratory is appropriately equipped.

In 1990, British Nuclear Fuels plc (BNFL) established a subsidiary company (now named F2 Chemicals) to exploit (for non-nuclear purposes) their great skill and experience in fluorine technology that had been acquired in the nuclear industry. It is, of course, well known that fluorine is used in the manufacture of uranium hexafluoride which, in its turn, is used for the gaseous separation of isotopes of uranium. As part of the development of F_2 chemicals, the University of Durham was invited to conduct basic research into the use of fluorine in organic chemistry on behalf of the Company, with a view to providing a skill-base for the Company after a few years. It is a frequently unrecognised fact that the principal product of basic research, and the justification for financing the latter in academia and in industry, is the creation and maintenance of skill-bases. A company beginning work in a completely new area is most able to recognise this fact.

One of our early objectives was to use fluorine as an electrophile. Of course, this had already been achieved very successfully by use of the splendid N–F compounds, which are especially valuable in the laboratory [6]. However, these and other electrophilic fluorinating reagents e.g. acyl hypofluorites, caesium fluoroxy sulphate, xenon difluoride etc., are made by using fluorine and it is clear, therefore, that for scale-up especially, it would be preferable if fluorine could be used directly, rather than via an intermediate fluorinating reagent.

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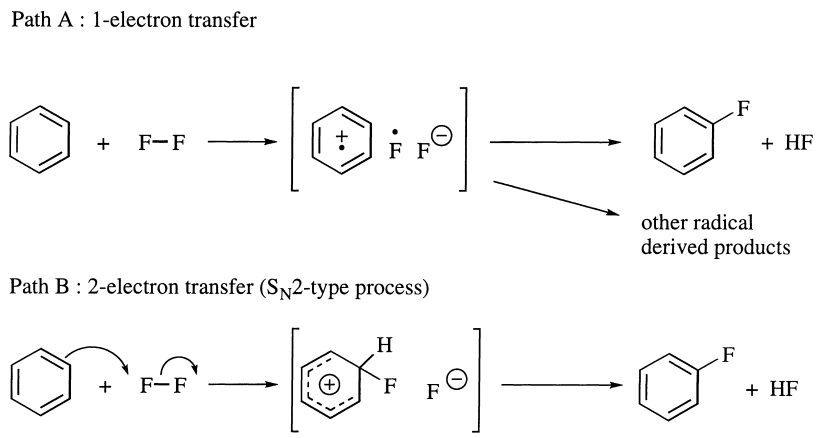


Scheme 1. Mechanism of direct fluorination of aromatic compounds.

2. Direct fluorination of aromatic systems

The reaction of fluorine with aromatic systems had been investigated by several groups [7–12] before we carried out our work in this area and the evidence suggested that fluorination occurs by both one (Scheme 1, Path A) and two (Scheme 1, Path B) electron transfer processes [5].

With a view to promoting the two electron process, i.e. encouraging the apparent electrophilicity of fluorine (Scheme 1, Path B), we investigated the effect of solvent on fluorination. It was found that electrophilic fluorination of aromatic compounds is favoured by the use of 98% concentrated sulphuric or formic acids as reaction media, although it is most probably the combination of both their high acidity and high dielectric constant which is especially effective in promoting the reaction. We envisage that it is the interaction of acid with fluorine that makes fluorine more susceptible towards nucleophilic attack (Scheme 2).

Of course, in aromatic systems that are more susceptible to electrophilic attack, sulphuric acid cannot be used as a solvent because sulphonation competes effectively. Furthermore, it is not a suitable medium when there is a nitrile group on the ring because hydrolysis occurs, but for the fluorination of deactivated systems, such as 2,4-difluorobenzoic acid, concentrated sulphuric acid as reaction medium results in the formation of 2,3,4,5-tetrafluoro- and even some pentafluoro- benzoic acid [13]. Consequently, a degree of 'tailoring' of the solvent to suit the substrate may be envisaged which is a situation familiar in reactions involving various other electrophiles.

Some examples are shown in Scheme 3 and, it is clear that either sulphuric acid or formic acid may be the more appropriate solvent, depending on the substrate.

In contrast, direct fluorination of monosubstituted, and 1,2- and 1,3-disubstituted aromatic compounds is not a particularly useful route to their corresponding mono-fluorinated derivatives since mixtures of regioisomers are produced. We may summarise, therefore, that when there are two substituents on an aromatic ring which both direct fluorine to the same site, as is the case with many 1,4-disubstituted aromatic compounds, then direct fluorination affords a convenient method for the preparation of fluoroaromatic compounds.

This picture is complicated by certain substrates being less reactive towards fluorine than we might have expected. For example, the fluorinations of 4-methylanisole and *para*-xylene proceed more slowly than does fluorination of the normally less reactive 4-nitroanisole. Moreover, mesitylene is fluorinated very slowly indeed. These latter results demonstrate that although fluorine acts in many situations as a simple electrophile, there is clearly much yet to learn about the range of mechanistic preferences [14].

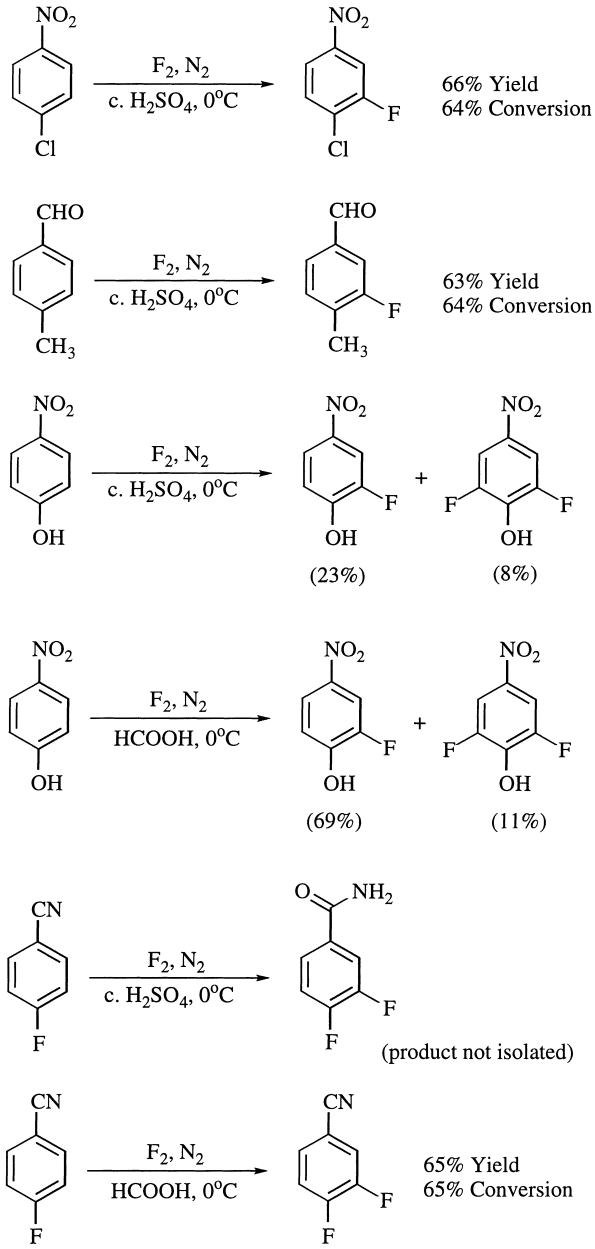
$$\overset{\delta+}{F}\!-\!\overset{\delta-}{F}\cdots\overset{\delta+}{H}$$

Scheme 2. Polarisation of fluorine by acid.

3. Preparation of α-fluorocarbonyl compounds

α-Fluorocarbonyl compounds are very versatile and useful 'building-blocks' in the preparation of more complex molecules, such as pharmaceuticals, which contain a fluorine atom. Previously, direct fluorination had been used to only a limited extent in reactions with carbonyl compounds and this was usually at low temperatures (−78°C) [15]. Not surprisingly, we found that all carbonyl compounds are not equally reactive towards fluorine and that the ease of fluorination depends on the nature and proximity of other functional groups. First, we will discuss the preparation of those compounds which can be obtained simply by exposing the parent compounds to fluorine and then we will describe the various methods we have used to convert the less reactive compounds to the required fluorinated derivatives, using fluorine directly.

Scheme 4 gives an indication of the relationship between structure of carbonyl compounds and reactivity towards fluorine but, as we shall see, within the various types there is considerable variation in reactivity.



Scheme 3. Reaction of fluorine with aromatic compounds.

3.1. 1,3-Dicarbonyl compounds which react readily with fluorine

Generally, compounds which exist in their enol form or compounds that enolise rapidly in the reaction medium, react with fluorine at a convenient rate. It is well known that cyclic 1,3-dicarbonyl compounds form enols more readily than acyclic analogues and therefore, cyclic 1,3-diones, such as dimedone (**1a**), react rapidly with fluorine to give mono- and di-fluorinated products, with the relative amounts of each depending on the amount of fluorine used in the reaction (Scheme 5, Table 1). Perhaps more remarkably, the fluorination of phloroglucinol (**2a**) gives the perfluorinated analogue [16] which was isolated as the trihydrate (**2b**) (Scheme 6).

Table 1
Reaction of fluorine with cyclic 1,3-diketones

F_2:Substrate, **1a**	Reaction time (h)	Yield (%)		Conversion (%)
		1b	**1c**	
2.2:1	4.25	–	75	100
1.1:1	1.0	40	33	70

Table 2
Reaction of fluorine with cyclic 1,3-diketones

	R^1	R^2 (**a**)	R^3	Yield (%)			Conversion (%)
				b	**c**	**d**	
3	CH_3	H	CH_3	70	11	3	90
4	CH_3	CH_3	CH_3	76	9	–	90
5	CH_3	Cl	CH_3	65	7	–	85
6	$-(CH_2)_4-$		CH_3	70	10	–	95

The situation with acyclic 1,3-diones, such as 1,3-pentanedione (**3a**) and ethyl acetoacetate (**7a**), is slightly different because the mono-fluoro- compounds do not readily enolise and consequently, difluorination is very much slower than mono-fluorination [17] (Scheme 7, Table 2; Scheme 8, Table 3).

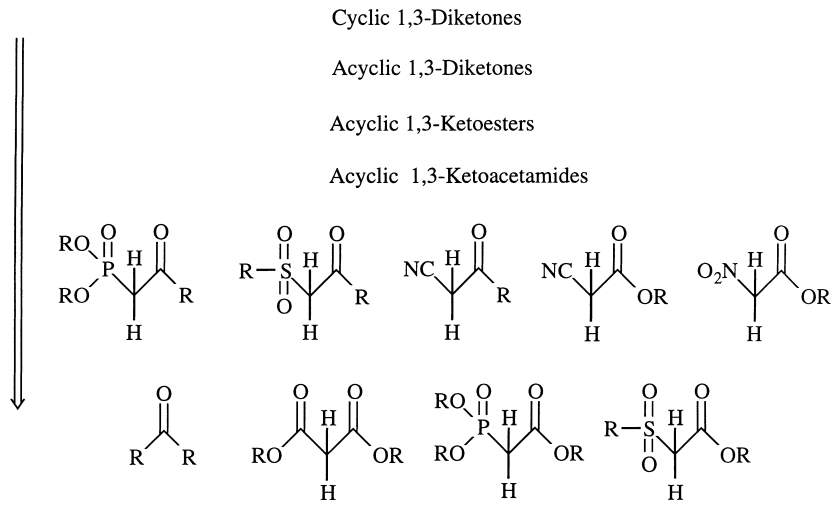
The case of ethyl-2-chloroacetoacetate (**9a**) is interesting in that initially, about 15% of the compound exists in its enol form in the reaction medium (formic acid), but its rate of enolisation is very slow [17]. This results in rapid fluorination until the enol form has all reacted and then no further reaction takes place. In this case, therefore, the conversion is a direct reflection of the enol content of the starting material.

3.2. Methodologies for enhancing reactivity of carbonyl derivatives towards fluorine.

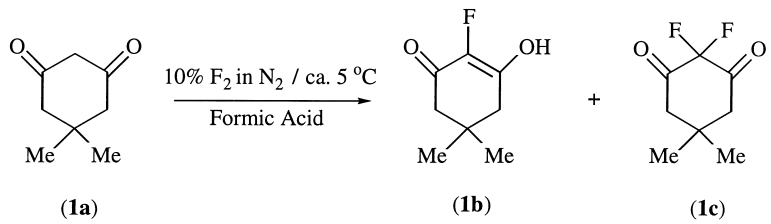
The remaining types of carbonyl compound outlined in Scheme 4 do not undergo significant reaction with molecular fluorine, but we have explored several means of bringing about the required transformations into their fluorinated analogues.

Table 3
Reaction of fluorine with 1,3-ketoesters

	R^1	R^2 (**a**)	R^3	Yield (%)			Conversion (%)
				b	**c**	**d**	
7	C_2H_5O	H	CH_3	80	10	1	60
8	C_2H_5O	CH_3	CH_3	85	5	–	25
9	C_2H_5O	Cl	CH_3	85	5	–	15
10	$-(CH_2)_4-$		C_2H_5O	90	1	–	90
11	$-O(CH_2)_2-$		CH_3	80	4	–	70

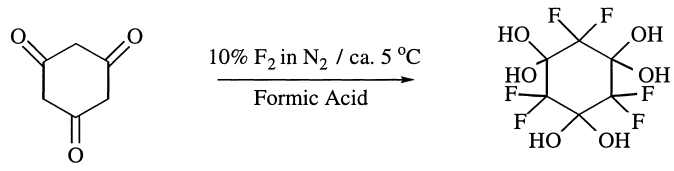


Scheme 4. Ease with which 'Carbonyl' compounds can be fluorinated with fluorine.



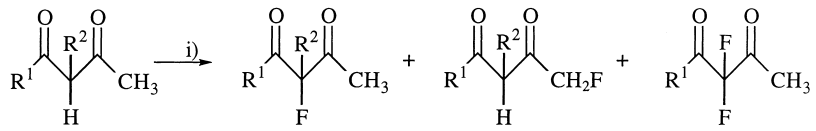
(**1a**) (**1b**) (**1c**)

Scheme 5. Reaction of fluorine with cyclic 1,3-diketones.



(**2a**) (**2b**)

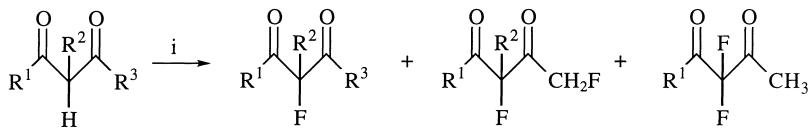
Scheme 6. Reaction of fluorine with phloroglucinol.



(**a**) (**b**) (**c**) (**d**)

i) 0.05 mol F_2 (10% in nitrogen) / 0.025 mol substrate in 50 ml formic acid / ca. 10 °C

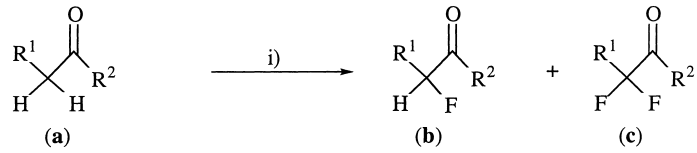
Scheme 7. Reaction of fluorine with cyclic 1,3-diketones.



(**a**) (**b**) (**c**) (**d**)

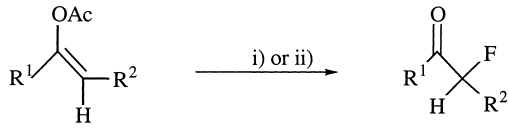
i) 0.05 mol F_2 (10% in nitrogen) / 0.025 mol substrate in 50 ml formic acid / ca. 10 °C

Scheme 8. Reaction of fluorine with 1,3-ketoesters.



Substrate, (20mmol)/ F_2, (54mmol over 4 hrs.)/anhydr.KF, (80mmol)/CH_3CN, (50ml)/ ca. 5 °C

Scheme 9. Base promoted reactions of fluorine with carbonyl compounds.



i), Substrate, (20mmol) / F_2, (50mmol over 110 min.) / CH_3CN, (50ml)/ ca. 5 °C
ii), Substrate, (20mmol) / F_2, (64mmol over 240 min.) / CH_3CN, (50ml)/ ca. 5 °C

Scheme 10. Fluorination of enol acetates.

Table 4
Base promoted reactions of fluorine with carbonyl compounds

	R^1	R^2 (**a**)	Yield (%)		Conversion (%)
			b	**c**	
12	NC	$C(CH_3)_3$	45	6	100
13	CH_3SO_2	CH_3	43	4	90
14	$(CH_3O)_2P{\cdot}O$	CH_3	43	7	70
15	NC	OC_2H_5	40	24	62
16	O_2N	OC_2H_5	50	7	100

Table 5
Fluorination of enol acetates

	Conditions	R^1	R^2	Yield **b** (%)	Conversion (%)
17	I	$-(CH_2)_4-$		56	>95
	II	$-(CH_2)_4-$		71	75
18	I	$-(CH_2)_6-$		66	>95
	II	$-(CH_2)_6-$		61	>95
19	I	C_4H_9-	C_3H_7-	61	>95
	II	C_4H_9-	C_3H_7-	71	64

3.2.1. Addition of base

Reaction of fluorine with those compounds having relatively acidic protons, i.e. cyanoketones e.g. (**12**), ketosulphones, e.g. (**13**), ketophosphonates, e.g. (**14**), cyanoesters, e.g. (**15**) and nitroesters, e.g. (**16**) can be promoted by carrying out the reaction in the presence of excess potassium fluoride [18] (Scheme 9, Table 4).

3.2.2. Formation of enol derivatives

For the preparation of simple fluoro ketones, treatment of the parent enol acetates with fluorine gives the required fluoro derivatives in good to fair yield [19] (Scheme 10, Table 5). Fluorination of trimethylsilyl ethers had been reported prior to our work [15] but reaction conditions involved inconveniently low temperature (−78°C/$CFCl_3$). We found that while fluoroketones are formed from trimethylsilylethers (ca. 0°C), the yields are not as high as those from the fluorination of enol acetates.

3.2.3. Formation of carbanions

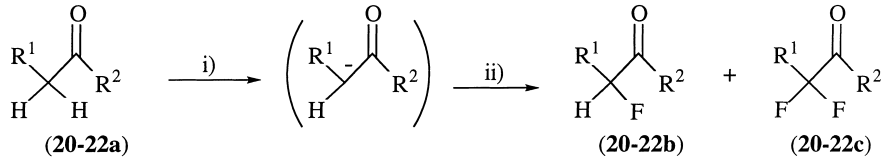
The remaining "unreactive" carbonyl compounds, i.e. 1,3-diesters, 1,3-phosphonoesters and 1,3-sulphonyl esters, can be successfully converted into their fluoro- analogues by first generating their carbanions and then treating these with fluorine [20,18] (Scheme 11, Table 6).

3.2.4. Catalysis by salts of transition metals

Most recently, we have found that the fluorination of many carbonyl compounds can be catalysed by salts of transition metals, presumably by accelerating the enolisation process [18] (Scheme 12). Generally, reactions need to be carried out in acetonitrile and catalytic activity is limited to hydrated copper (II) and nickel (II) nitrates. However, for the fluorination of one specific substrate i.e. ethyl-2-chloroacetoacetate (**9a**), a whole range of salts are effective catalysts, when the reaction is carried out in formic acid, giving a high yield (>90%) of **9b** with a 100% conversion of the starting material (Scheme 13). A very significant

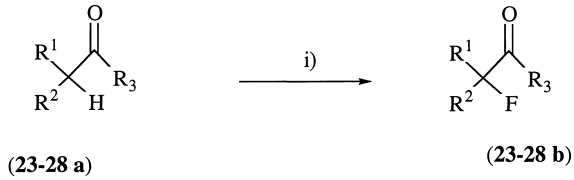
Table 6
Fluorination of carbanions

	a		Yield (%)		Conversion (%)
	R^1	R^2	**b**	**c**	
20	$C_2H_5OCO{\cdot}$	C_2H_5O	37	23	71
21	CH_3SO_2	C_2H_5O	36	7	62
22	$(C_2H_5O)_2P{\cdot}O$	C_2H_5O	35	15	70



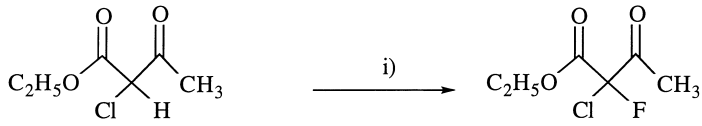
i) NaH or NaOEt / CH_3CN
ii)Excess F_2 / CH_3CN / ca. 5 °C

Scheme 11. Fluorination of carbanions.



i) Substrate, 20mmol./ $Cu(NO_3)_2$, 0.04 mmol./ F_2, 32 mmol./ CH_3CN, 50 ml.

Scheme 12. Catalysis by salts of transition metals.



i) Substrate, 20mmol./catalyst*, 0.04 mmol./ F_2, 32 mmol./formic acid, 50 ml.

Catalysts* include $Cr(NO_3)_3.9H_2O$; $Mn(NO_3).H_2O$; $Fe(NO_3)_3.6H_2O$; $Co(NO_3)_3.6H_2O$; $Ni(NO_3)_2.3H_2O$; $Cu(NO_3)_2.2.5H_2O$; $Zn(NO_3)_{2\cdot 6}.H_2O$; $CuCl_{2\cdot 2}.H_2O$; and $CuSO_4.5H_2O$

Scheme 13. Catalysis of salts of transition metals.

Table 7
Catalysis by salts of transition metals[a]

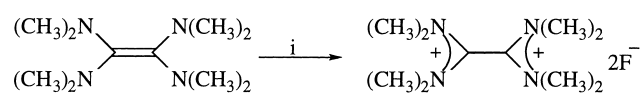
	R^1	R^2	R^3	Yield (**b**) (%)	Conversion (%)
23	$C_2H_5OCO\cdot$	H	OC_2H_5	78	100
24	$C_2H_5OCO\cdot$	NO_2	OC_2H_5	76	100
25	$C_2H_5OCO\cdot$	F	OC_2H_5	–	ca. 5
26[b]	CH_3SO_2	H	CH_3	45	87
27[b]	NO_2	H	OC_2H_5	52	54
28[b]	CN	H	OC_2H_5	50	46

[a] Under these conditions in the absence of catalyst, no more than approx. 12% of the substrate was converted.
[b] In the reactions of substrates **24**, **25** and **26**, there was also formed 5%, 20% and 8%, respectively, of the difluoro- compounds.

fluorination that can be catalysed is that of diethyl malonate (**23a**) which gives only the mono-fluorinated compound in high yield, Table 7. This is in contrast to the fluorination of the carbanion derived from this same compound which gives both mono- and di- fluorinated products (*vide supra*, Table 6) [20].

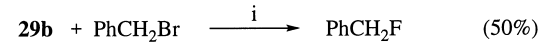
4. Electron rich alkenes

The highly electron rich alkene tetrakis(dimethylamino)ethylene (TDAE, **29a**) has a reducing capacity variously described as between zinc and potassium [21], and it is a measure of how perceptions change that we had the courage to fluorinate this compound. Indeed, TDAE reacts very efficiently with fluorine to provide an anhydrous fluoride ion salt (**29b**) (Scheme 14). The $TDAE^{2+}$ $2F^-$ salt is partially soluble in some organic solvents and can



i, F_2 (10% in N_2), CH_3CN, room temp.

Scheme 14. Reaction of fluorine with TDAE.



i, Sulpholane, 48 h, 80 °C.

Scheme 15. Fluorination of benzyl bromide.

effect a number of halogen exchange processes [22] (Scheme 15).

5. 'In-situ' generation of other electrophilic reagents using fluorine

Hydrogen bonding to fluorine is, of course, very effective and, as we have seen, the presence of acid makes molecular fluorine more susceptible to nucleophilic attack. This led us to consider the effect of acid on reagents, such as IF, BrF and HOF, generated '*in-situ*' (Scheme 16).

5.1. Iodination and bromination of aromatic compounds

Reactions of iodine with aromatic systems, at room temperature or below, were induced simply by passing fluorine through the system in the presence of acid [23]. The examples shown in Scheme 17 demonstrate that the system is a remarkably effective new iodinating agent.

Brominations are induced in an analogous way but BrF is more reactive than IF and it is possible to brominate highly deactivated aromatic compounds, such as 2,4-difluoro-nitrobenzene and 2,4-dinitro-fluorobenzene, which cannot be iodinated (Scheme 18).

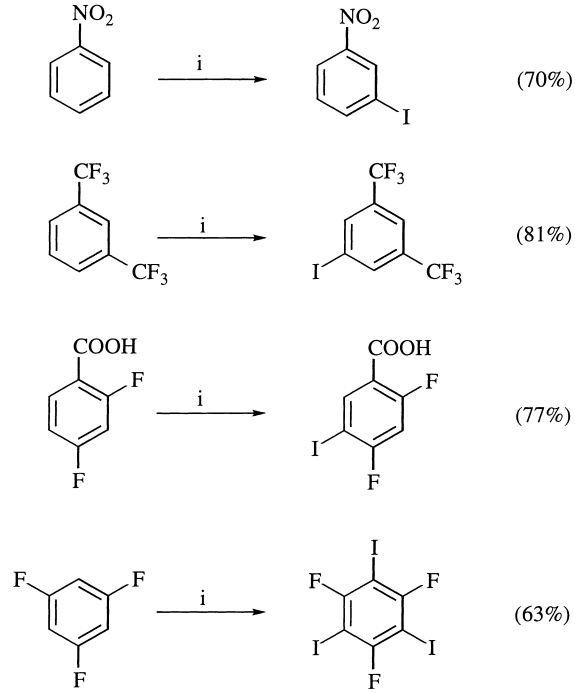
5.2. Oxidation

The reaction of fluorine with water gives HOF and this can be stabilised with acetonitrile and then used to oxidise various species [24]. We have found that, in some cases, it is unnecessary to pre-prepare the reagent and that oxidations can be carried out simply by passing fluorine through aqueous solutions of the substrate in acetonitrile. We also find that the presence of organic acid promotes these reactions. In principle, peroxy-acids could be generated by the reaction of fluorine with aqueous organic acids but we concluded that the oxidant is essentially HOF, and that its reactivity is significantly enhanced by the presence of acid (Scheme 19).

Thus, Baeyer–Villiger reactions can be achieved simply by passing fluorine through solutions of ketones in aqueous acetonitrile or acid, e.g. Scheme 20.

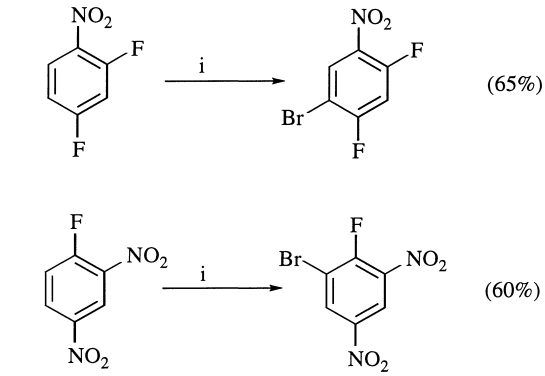
The oxidation of secondary alcohols can be smoothly accomplished to give good yields of ketones simply by

Scheme 16.



i, F_2, I_2, conc. H_2SO_4, r.t.

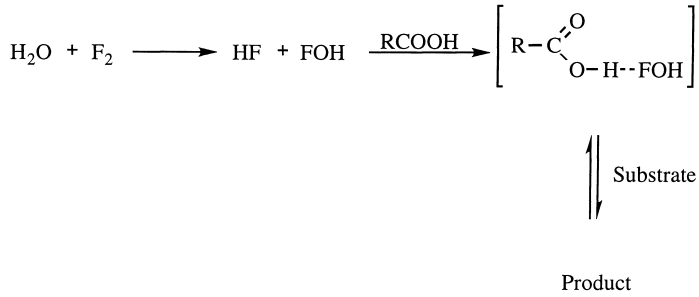
Scheme 17. Iodination of aromatic compounds.



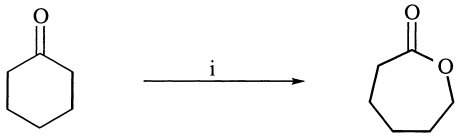
i, F_2, Br_2, conc. H_2SO_4, r.t.

Scheme 18. Bromination of aromatic compounds.

passing fluorine through solutions of alcohols in anhydrous acetonitrile (Schemes 21 and 22). (NB: the use of wet acetonitrile results in Baeyer–Villager oxidation of the ketone to an ester — *vide supra*) (Scheme 20). Interestingly, 1,2-diols do not yield 1,2-diones but rather, give 2-hydroxyketones (Scheme 22). It is likely that the hydroxyl group in α-hydroxyketones is resistant to further oxidation because of electron withdrawal by the carbonyl group. This effect of electron-withdrawing groups is also reflected in the



Scheme 19. HOF formation in the presence of acid.



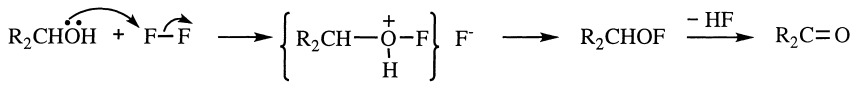
i, F_2 (10% in N_2), aq. CH_3CN or aq. HCOOH

Scheme 20.

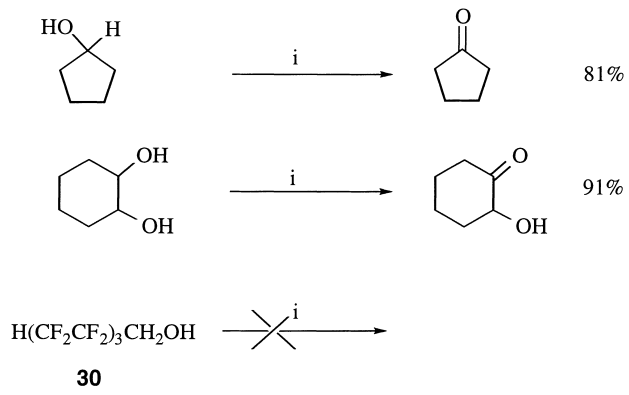
resistance to oxidation of the telomer alcohol (**30**), where there is electron withdrawal from the hydroxyl group by the fluorocarbon group. In contrast, similar treatment of primary alcohols with fluorine gives complex mixtures of products [25].

5.3. Fluorination of heterocyclic compounds

In the absence of acid, 'IF' generated *in-situ* acts as a source of both iodonium and fluoride ions which, on reaction with nitrogen heterocyclic compounds, provides a

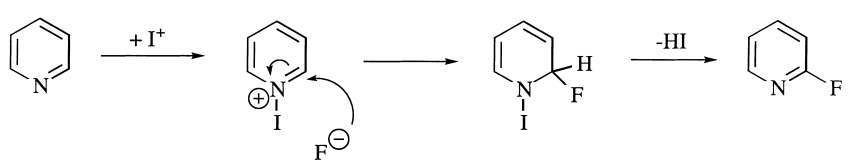


Scheme 21. Oxidation of alcohols.

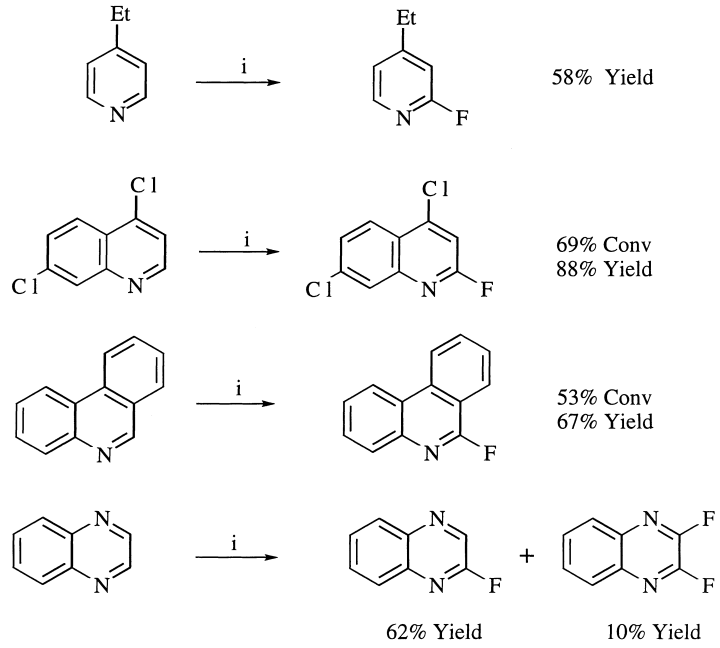


i, F_2 (10% in N_2), Dry acetonitrile

Scheme 22. Oxidation of alcohols.

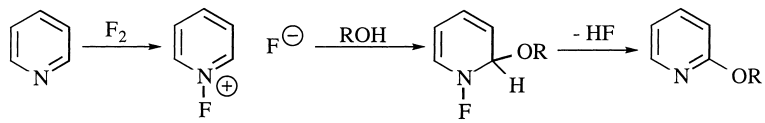


Scheme 23. Fluorination of heterocyclic compounds.

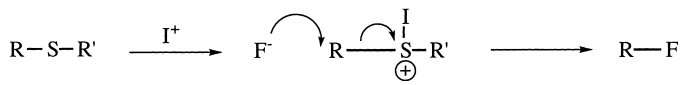


i, F_2, I_2, Et_3N, $CF_2ClCFCl_2$, r.t.

Scheme 24. Fluorination of heterocyclic compounds.



Scheme 25. Alkoxylation of heterocyclic compounds.

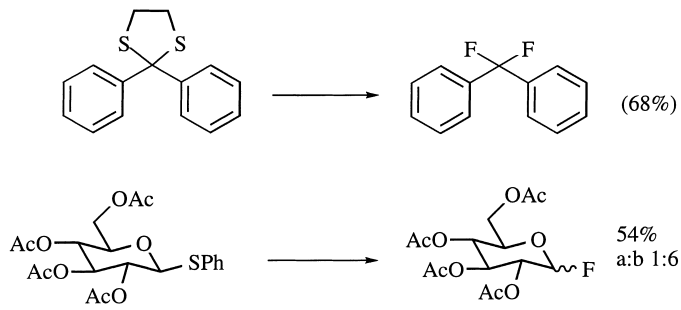


Scheme 26. Desulphurisation.

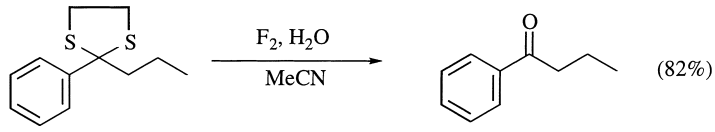
novel route to the corresponding α-fluorinated compounds (Schemes 23 and 24). Remarkably, the addition of tertiary amine to the system promotes the elimination of hydrogen iodide and results in improved yield. The process outlined in Scheme 23 is, overall, a nucleophilic displacement of hydrogen induced by fluorine.

5.4. Alkoxylation of heterocyclic compounds

Meinert and co-workers established that when fluorine is passed into pyridine, a solid is obtained which explodes on raising the temperature to −2°C [26]. However, related to the above, we have found that reactions of fluorine with



Scheme 27. Desulphurisation.



Scheme 28. Deprotection of dithiolanes.

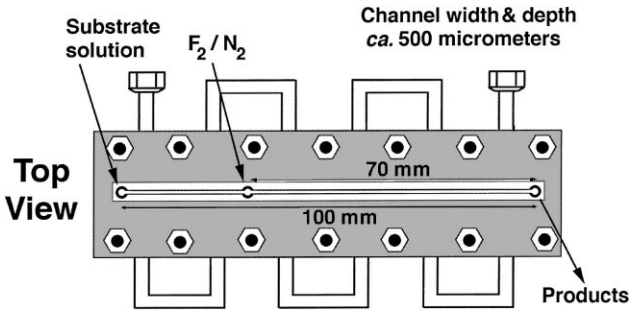


Fig. 1.

pyridine in the presence of alcohols, at room temperature, lead to the corresponding α-alkoxy compounds in good yield. Again, the overall result is nucleophilic displacement of hydrogen, but in this case by an alkoxy group (Scheme 25) (cf. the Chichibabin reaction).

5.5. Fluorodesulphurisation reactions

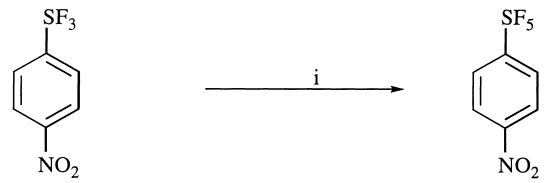
Carbon–sulphur bonds may be transformed into carbon–fluorine bonds upon reaction with 'IF', generated *in situ*, by reaction of iodine and fluorine (Schemes 26 and 27). Such fluorodesulphurisation reactions allowed the preparation of geminal difluoride and glycosyl fluoride derivatives (Scheme 27).

By a similar mechanism, a combination of fluorine and aqueous acetonitrile provided an effective reagent for the deprotection of dithiolanes (Scheme 28).

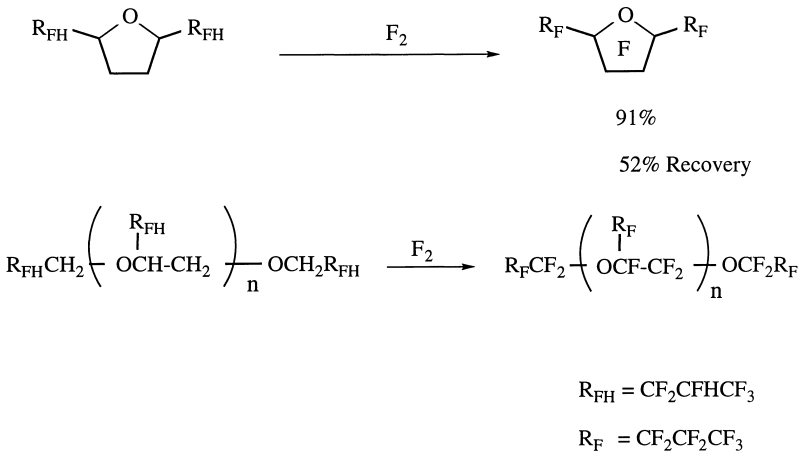
6. New techniques for direct fluorination — continuous flow and micro-reactors

Scale-up of very exothermic direct fluorination reactions will always present problems of safe-handling and temperature control and we sought to develop a continuous flow reactor as an attempt to address these problems.

There is currently much interest in the development of micro-reactors for chemical processing [27], because the benefits would include arithmetic scale-up from the performance of a single reactor to a theoretically unlimited number and, in principle, this scale-up could be achieved by the techniques of the electronics industry.



Scheme 29. I. CH_3CN, 5 ml hr^{-1}, 10% F_2 in N_2, 10 ml min^{-1}, R.T.



Scheme 30. Perfluorination of ethers.

After much development, we have designed a simple micro-reactor (Fig. 1) [28]. All of the liquid–gas mixing proceeds via cylindrical flow (the term is intended to indicate that the liquid forms an outer cylinder, coating the reactor surface). This offers enormous advantages in that it provides very large surface to volume ratios for the liquid phase which is highly beneficial for efficient reaction heat control. Using this system, we have successfully carried out various selective fluorinations, for example (Scheme 29). Fluorination of β-dicarbonyl compounds proceeded with high efficiency and, moreover, these reactions clearly demonstrated a catalytic effect by the fluorinated metal surface. Continuous flow [29] and micro-reactors [28] have also been adapted to carry out exhaustive perfluorination of several substrates (Scheme 30).

7. Conclusions

Over the course of this work, we have changed our perceptions of the opportunities available for the use of elemental fluorine in organic synthesis and we anticipate significant further developments, especially in the area of selective fluorination.

Acknowledgements

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