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Electrolytic fluorination of organic compounds

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Contents

1. Introduction

Partially fluorinated organic compounds have unique properties that make them suitable for diverse applications in agrochemistry, materials science and in the pharmaceutical industry.[1–10] This is attributed to the high electronegativity of the fluorine atom combined with the relatively similar size of fluorine to hydrogen and the high lipophilicity of the C–F bond.[11] In addition, fluorine can participate in hydrogen bonding interactions as an electron donor.[11] Efficient methods for the synthesis of fluorinated organic compounds are, therefore, becoming increasingly important. The two fundamentally different strategies by which fluorine can be introduced into target molecules are by chemical methods and by electrochemical methods. The chemical methods are as follows.

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1.1. Introduction of fluorine by the application of fluorine-containing building blocks[2]

This is an effective methodology for the preparation of complex molecules based on multiple molecular conversions of commercially available fluorinated compounds such as CF_3COCF_3, CF_3COMe, CF_3COOEt and CF_2Br_2. The disadvantages of this method are: (i) the limitation of commercially available fluorinated compounds; (ii) the shortage of monofluorinated precursors, though the incorporation of perfluorinated (e.g., trifluoromethyl and perfluoroalkyl) groups is well developed; and (iii) that fluorinated substrates are always costly.

1.2. Direct fluorination[12–15]

Direct substitution of hydrogen by fluorine generally requires the handling of elemental fluorine, either in a direct reaction with the substrate or in the preparation of fluorinating reagents. The fluorinating reagents are divided into two groups.

(A) *Nucleophilic fluorinating reagents*. Many reagents have been developed to overcome problems such as the poor nucleophilicity of F^-, and lowering the toxicity and increasing the stability of the fluorinating reagents. The most commonly used nucleophilic reagents are HF, BrF_3, XeF_2, SF_4, SiF_4, alkali metal fluorides, AgF, HgF_2, CuF_2, ZnF_2, Et_2NSF_3 (DAST) and $R_3N.nHF$.

(B) *Electrophilic fluorinating reagents*. These reagents have been developed for introducing fluorine at centres of high electron density and, therefore, they offer an interesting alternative when nucleophilic sources of fluorine are inefficient or have failed. The ability of fluorine to behave as an electrophile (F^+) is not easily achieved, since fluorine is the most electronegative element. Ingenious ways for overcoming this problem have been achieved by either withdrawing electronic charge from fluorine through inductive effects or by the presence of an excellent leaving group adjacent to fluorine. Examples of electrophilic fluorinating reagents are F_2, $FClO_3$, CF_3OF, CF_3COOF, $CsSO_4F$ and *N*-fluoropyridinium triflates. The main disadvantages of these methods are: (i) the difficulties in handling the hazardous or troublesome fluorinating reagents; and (ii) the lack of selectivity (regio- and stereoselectivity).

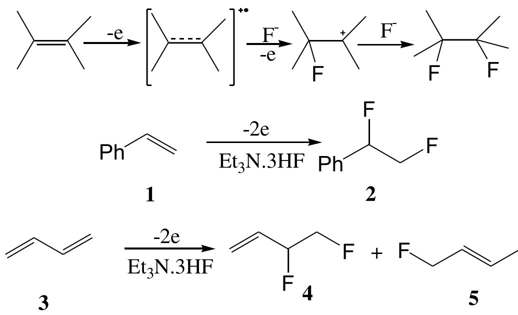
On the contrary, electrolytic fluorination methodology proved to be highly attractive and more promising than the above-mentioned methods and, consequently, it serves as a new tool in fluoro-organic synthesis.[16–19] Compared with the conventional chemical fluorination methods, electrolytic fluorination has the following advantages: (a) hazardous or toxic reagents are not required, the less corrosive fluoride salts compared with the other fluorinating reagents being widely used in electrolytic fluorination; (b) fluorination can be carried out in relatively simple equipment under mild conditions; (c) fluorination processes can be easily controlled by the applied potential, current and electricity; (d) it is a type of green chemistry, where the secondary pollution can be avoided because electricity is used as an oxidising reagent; and (e) it is an economic method, where a fluoride salt can be used as the fluoride ion source and supporting electrolyte and, in addition, some fluoride salts such as $Et_3N{\cdot}3HF$ can be easily recycled by simple distillation. Moreover, electrolytic reactions can be attempted using a simple battery as a power supply and glassware common to any synthetic laboratory.[20] Electrolytic fluorination processes are frequently employed to convert C–H to C–F bonds. Anhydrous HF (AHF) is the most common reagent used in electrolytic perfluorination, where all C–H bonds are converted to C–F bonds. AHF is, however, an extremely hazardous substance due to its low boiling point and high toxicity, in addition to giving poor yields of the electrochemically-perfluorinated products.[21,22] HF combined with organic bases, to form salts such as $Et_3N{\cdot}n$HF or $Et_4NF{\cdot}n$HF (n=2–5), have therefore, been widely utilised as the fluorine source and supporting electrolytes for the selective electrolytic partial fluorination of organic compounds.[23,24]

This review article covers the recent remarkable advances in the direct and indirect electrolytic partial fluorination of organic compounds such as olefins, aromatic compounds, carbonyl compounds, heteroatom compounds and heterocycles. Electrolytic perfluorination is also briefly described.

2. Electrolytic partial fluorination of organic compounds

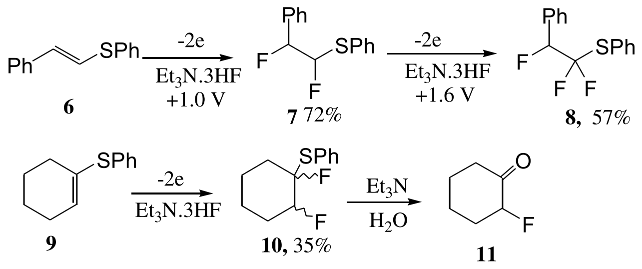
2.1. Direct electrolytic partial fluorination of organic compounds

2.1.1. Olefins. The electrolytic oxidation of double bonds in the presence of fluorinating agents proceeds predominantly through *cis* addition to give the corresponding *vicinal* difluorinated products.[25,26] Electrofluorination of styrene (**1**) in $Et_3N{\cdot}3HF$/MeCN gave the corresponding *vic*-difluorinated product **2** in 51% yield. Butadiene (**3**) gave a 1:2 mixture of the 1,2- and 1,4-adducts **4** and **5**, respectively[25] (Scheme 1).



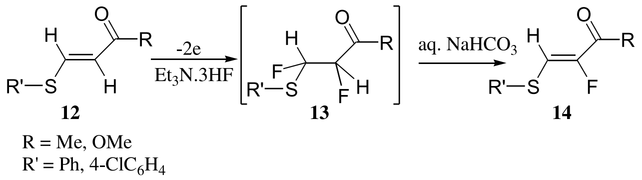
Scheme 1.

Electrolytic fluorination of 2-(phenylthio)styrene (**6**) in $Et_3N{\cdot}3HF$ under constant potential gave the *vic*-difluorinated product **7** which upon further fluorination at higher potential yielded the trifluorinated derivative **8**.[27] Electrofluorination of 1-(phenylthio)cyclohexene (**9**) resulted in the formation of the 1,2-difluoro-1-phenylthiocyclohexane (**10**) which is highly sensitive to acids and bases and could be converted into α-monofluorocyclohexanone (**11**) in the presence of traces of Et_3N,[27] as shown in Scheme 2.



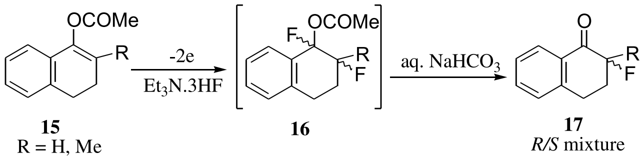
Scheme 2.

Vinyl sulfides **12** bearing carbonyl functions were also electrolytically fluorinated using $Et_3N \cdot 3HF$ in acetonitrile to give the monofluorinated vinyl sulfides **14** stereoselectively.[28] The latter products were obtained through dehydrofluorination of the adduct intermediate **13** (Scheme 3).



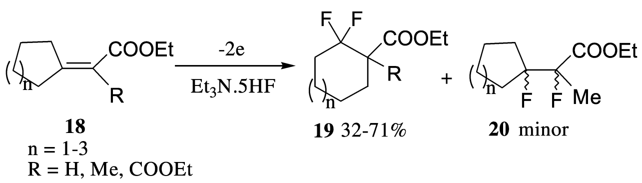
Scheme 3.

Anodic oxidation of 1-acetoxy-3,4-dihydronaphthalene derivatives **15**, in the presence of $Et_3N \cdot 3HF$, afforded the *vic*-difluorinated intermediates **16**, which were subsequently hydrolysed to give the α-fluoro cyclic ketones **17**,[29] as shown in Scheme 4.



Scheme 4.

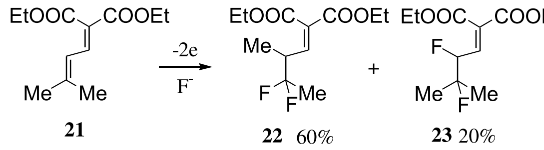
Yoneda and co-workers[30] found that electrolytic oxidation of the cyclic unsaturated esters **18** in $Et_3N \cdot 5HF$ resulted in fluorination and ring expansion to provide the *gem*-difluoro cycloalkanecarboxylates **19**, (Scheme 5), together with the minor product **20**.



Scheme 5.

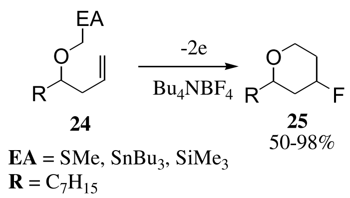
Electrolytic fluorination of the conjugated diene ester **21** occurred at the distal olefin moiety to give a mixture of the *vic*- and *gem*-difluorinated alkene esters **22** and **23**, respectively,[31] as demonstrated in Scheme 6.

Electrolytic fluorination accompanied by C–C bond formation has been achieved using silyl, stannyl or sulfenyl groups as electroauxiliaries (EA).[32–34] Anodic fluorination



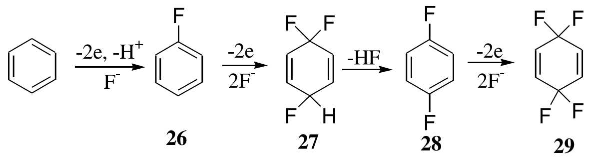
Scheme 6.

of the olefin derivatives **24** using Bu_4NBF_4 resulted in the loss of the electroauxiliaries and intramolecular cyclisation to one of the olefinic carbons and the introduction of fluoride ion to the other carbon to give the corresponding fluoropyran derivatives **25**[32] (Scheme 7).



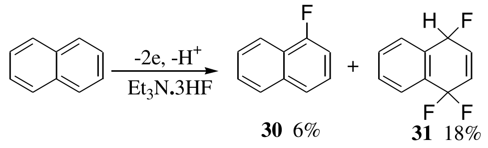
Scheme 7.

2.1.2. Aromatic compounds. Electrochemical fluorination of benzene, in $Et_4NF \cdot 4HF$/MeCN, afforded mainly monofluorobenzene (**26**) along with traces of 1,4-difluorobenzene (**28**).[35] Further fluorination of fluorobenzene (**26**) gave 3,3,6-trifluorocyclohexadiene (**27**) which undergoes dehydrofluorination to give 1,4-difluorobenzene (**28**). The latter compound was also electrolysed and converted into 3,3,6,6-tetrafluorocyclohexadiene (**29**),[36,37] as shown in Scheme 8. The compounds **28** and **29** could also be obtained as the final products during the electrofluorination of chloro- or bromobenzene.[38,39]



Scheme 8.

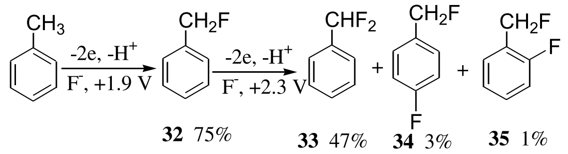
Meures et al.[25] have reported the electrolytic fluorination of naphthalene in $Et_3N \cdot 3HF$, which gave the corresponding mono- and trifluoro- derivatives **30** and **31** (Scheme 9).



Scheme 9.

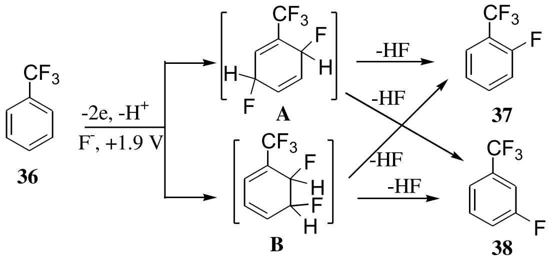
Electrolysis of toluene in the presence of neat liquid $Et_4NF \cdot 4HF$ was found to be highly regioselective and gave exclusively benzyl fluoride (**32**).[40,41] Further electrolysis of **32** afforded mainly difluoromethylbenzene (**33**), in addition to the ring-fluorinated byproducts **34** and **35**[40] (Scheme 10).

Trifluoromethylbenzene (**36**) was also electrolytically monofluorinated to give a mixture of the 2- and 3-fluoro-1-trifluoromethylbenzenes **37** and **38**, respectively, through



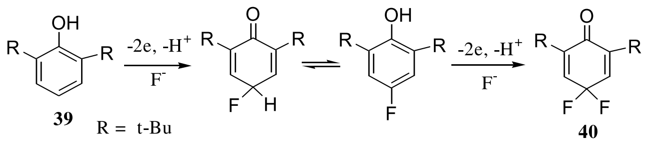
Scheme 10.

the dehydrofluorination of the intermediate adducts **A** or **B**[42] (Scheme 11).



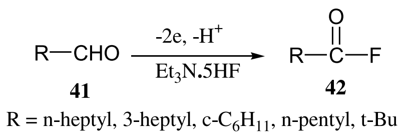
Scheme 11.

In the presence of $Et_3N{\cdot}5HF$ as the electrolyte, electrolytic fluorination of phenols such as **39** successfully afforded the 4,4-difluorocyclohexadien-1-one **40**, according to the reaction mechanism outlined in Scheme 12.[43,44]



Scheme 12.

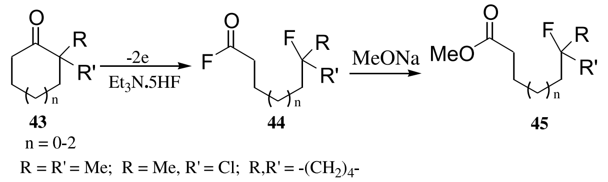
2.1.3. Carbonyl compounds. Yoneda and co-workers[45–47] reported a series of selective electrolytic fluorinations of aldehydes and ketones also using $Et_3N{\cdot}5HF$ as the electrolyte. The selective displacement of formyl hydrogen by a fluorine atom in the aliphatic aldehydes **41** took place electrolytically to give the corresponding acyl fluorides **42** in good yields.[45,47] The mechanism is depicted in Scheme 13.



Scheme 13.

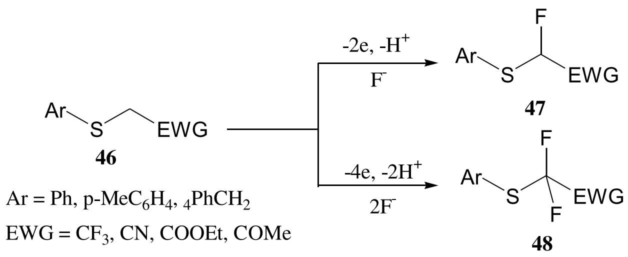
Selective electrolytic α-bond cleavage between the carbonyl carbon and the substituted α-carbon in the cyclic ketones **43** was attempted in the presence of $Et_3N{\cdot}5HF$ to give the fluoroacyl fluorides **44**, which upon esterification gave the corresponding fluoroacid esters **45**[46,47] (Scheme 14).

2.1.4. Aryl sulfides. The Fuchigami[48–54] and Laurent[55,56] groups found that the presence of an electron-withdrawing group (EWG) at the α-position to sulfur markedly facilitates the electrolytic α-fluorination of sulfides. In one example, electrolytic oxidation of aryl sulfides **46** in $Et_3N{\cdot}3HF$ or



Scheme 14.

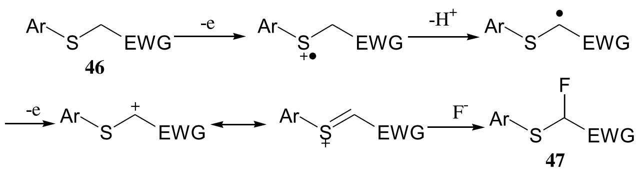
$Et_4NF{\cdot}3HF$ affords the corresponding α-monofluorinated sulfides **47** regioselectively (Scheme 15).



Scheme 15.

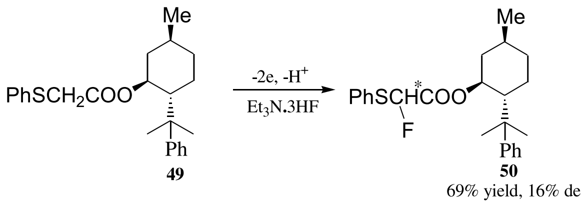
For the sulfides **46**, which have several positions susceptible to substitution by fluorine (Ar=*p*-MeC_6H_4 or $PhCH_2$), a fluorine atom was introduced exclusively α to the EWG and no fluorination of the tolyl or benzyl carbons was observed.[50] α-Fluorination of sulfides devoid of an EWG was also achieved electrolytically.[50,57,58] Passing double amount of the electricity in the fluorination of **46** resulted in the formation of the α,α-difluorinated products **48** (Scheme 15).[53,55–58]

An Electrochemical reaction–Chemical reaction–Electrochemical reaction–Chemical reaction (ECEC) mechanism was proposed for the α-fluorination of thioethers,[54] as shown in Scheme 16.

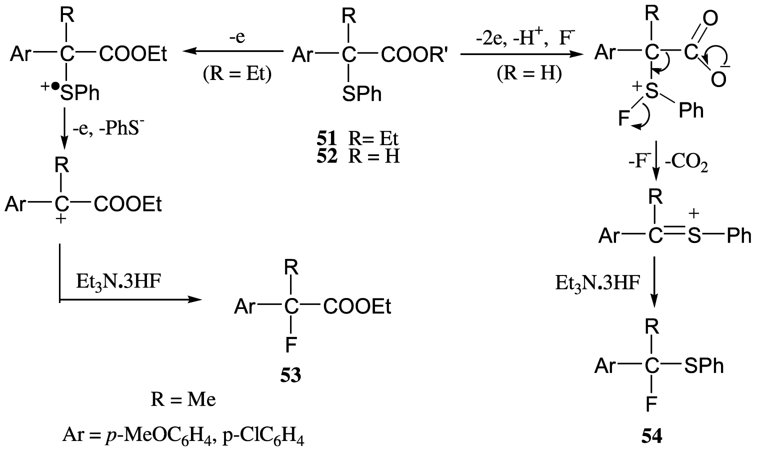


Scheme 16.

The diastereoselective electrolytic fluorination of an α-(phenylthio)acetate having a chiral auxiliary **49**, in the presence of $Et_3N{\cdot}3HF$, was found to give the corresponding fluorinated product **50**,[59] as shown in Scheme 17.



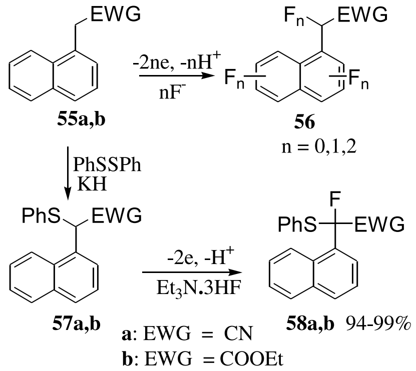
Scheme 17.



Scheme 18.

It is interesting that the electrolytic fluorinations of the α-(phenylthio)esters **51** and α-(phenylthio)acids **52** were reported to give the fluorinated products **53** and **54**, respectively, according to the different mechanisms postulated in Scheme 18.[60]

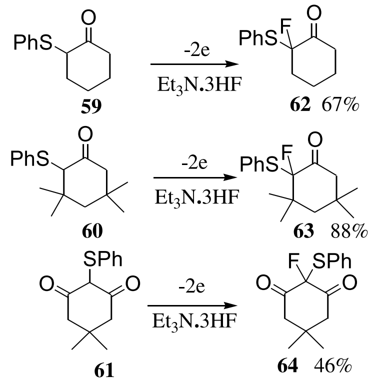
Attempts to electrochemically fluorinate 1-naphthaleneacetonitrile (**55a**) or ethyl 1-naphthaleneacetate (**55b**) met with failure and several polyfluorinated products **56** were detected, in very poor yields, without any selectivity.[61] This was attributed to the high oxidation potentials of **55a**,**b** and consequently they would be difficult to fluorinate electrolytically. Insertion of a phenylthio group at the α position of the naphthalene derivatives **55a**,**b**, however, to give **57a**,**b**, reduced the oxidation potential dramatically and the fluorination then became easy. The compounds **57a**,**b** were, therefore, selectively fluorinated at the α-carbon using $Et_3N \cdot 3HF$/MeCN to give **58a**,**b** in excellent yields, as shown in Scheme 19.[61]



Scheme 19.

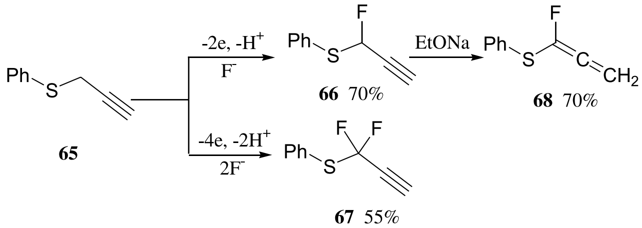
Electrolytic fluorination was extended to the α-(phenylthio)-substituted cyclic ketones **59–61** and found to be highly selective, the fluorine atom being selectively inserted at the α position to sulfur to give the corresponding monofluorinated ketones **62-64**, respectively, as shown in Scheme 20.[52]

Next, electrolytic fluorination of phenyl propargyl sulfide (**65**) using $Et_4NF \cdot 4HF$ in dimethoxyethane (DME) was found to be greatly dependent on the amount of electricity



Scheme 20.

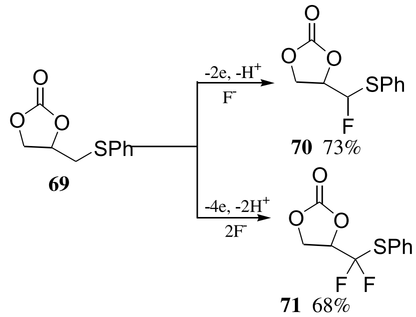
used.[62,63] When twice of the theoretical amount of electricity (4 Far/mol) was passed, the α-monofluorinated sulfide **66** was selectively formed in good yield. Passage of a large excess amount of electricity, however, resulted in the selective formation of α,α-difluoropropargyl sulfide **67**. Treatment of **66** with ethanolic sodium ethoxide solution afforded the corresponding fluoroallene **68** (Scheme 21).[62,63]



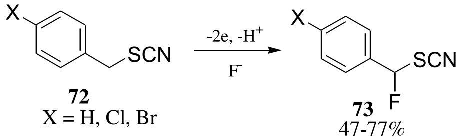
Scheme 21.

Anodic fluorination of 4-phenylthiomethyl-1,3-dioxolan-2-one (**69**) was successfully carried out in $Et_3N \cdot 3HF$ to provide the corresponding α-mono- or α,α-difluorinated sulfides **70** or **71**, respectively, based on the amount of electricity passed, as shown in Scheme 22.[64]

2.1.5. Benzyl thiocyanates. Benzyl thiocyanates **72** were also fluorinated, using $Et_4NF \cdot 4HF$, at the benzylic carbon to give the corresponding α-fluorothiocyanates **73** in moderate yields (Scheme 23).[65]

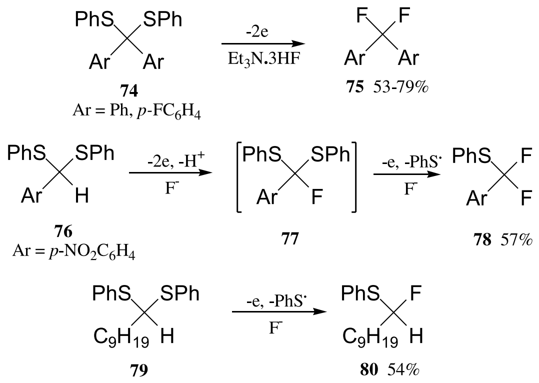


Scheme 22.



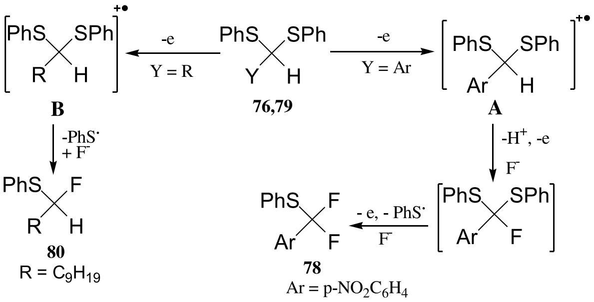
Scheme 23.

2.1.6. Dithioacetals and dithioketals. Electrolytic fluorodesulfurisation of dithioacetals and dithioketals has been reported,[66] and, in his study, electrolysis of the dithioketals **74** in the presence of $Et_3N\cdot 3HF$ provided the corresponding *gem*-difluoro compounds **75**. Dithioacetals of the aromatic aldehyde **76**, however, afforded via **77** the *gem*-difluorothioether **78** and those of the aliphatic aldehyde **79** gave the monofluorothioether **80**, as shown in Scheme 24.



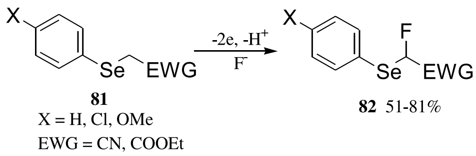
Scheme 24.

It is interesting to note that the electrolytic behaviour of the dithioacetal **76** is quite different from that of the dithioacetal **79**. This can be explained on the basis that deprotonation of the cation radical **A** seems to be easier than that of **B**, since the former α-hydrogen is more acidic than the latter (Scheme 25).[66]



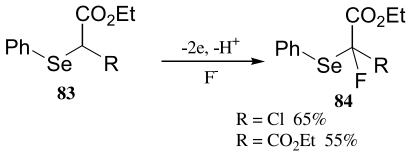
Scheme 25.

2.1.7. Organoselenium compounds. The phenylselenoethers **81** having an activated methylene group gave the corresponding α-monofluorinated derivatives **82** in good yields when electrolysed in the presence of $Et_3N\cdot 3HF$/MeCN, as shown in Scheme 26.[67,68]



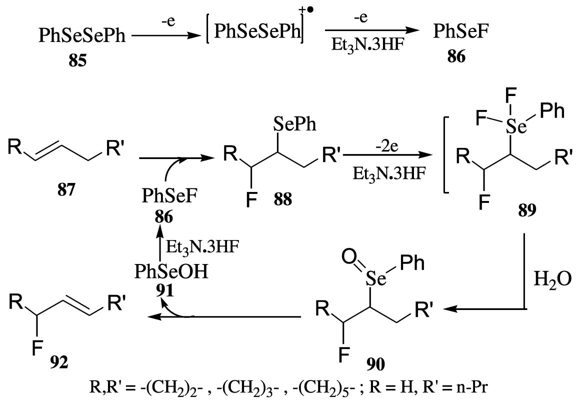
Scheme 26.

Similarly, selenides bearing two EWGs **83** were also electrolytically fluorinated to give the α-fluoroselenides **84** (Scheme 27).[67]



Scheme 27.

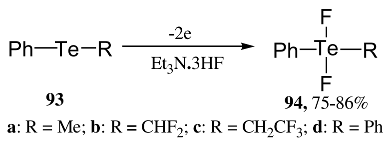
Uneyama et al.[69–72] reported the electrolytic fluorination of diphenyldiselenide (**85**), in the presence of $Et_3N\cdot 3HF$/CH_2Cl_2, to generate phenylselenyl fluoride (**86**). The latter compound underwent fluoroselenation with the olefins **87** to give the adducts **88**, which were subsequently oxidised via **99** to the selenoxides **90**. *syn*-Elimination of benzeneselenic acid (**91**) from **90** produced the allylic fluorides **92**, as shown in Scheme 28.[69]



Scheme 28.

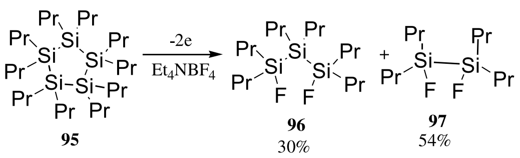
2.1.8. Organotellurium compounds. Electrolytic oxidation of the organotellurium compounds **93a–d** in the presence of fluoride ions using a divided cell resulted in difluorination of the tellurium atom selectively to give **94** in high yields. Even trifluoroethyl telluride **93c**, having an active methylene group, did not give any α-fluorination at carbon, as shown in Scheme 29.[73]

2.1.9. Organosilicon compounds. Electrolytic fluorination of deca-*n*-propylcyclopentasilane (**95**) in the presence of



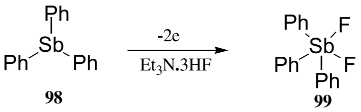
Scheme 29.

Et_4NBF_4 resulted in ring opining and Si–Si bond cleavage to give the difluorosilane derivatives **96** and **97** (Scheme 30).[74]



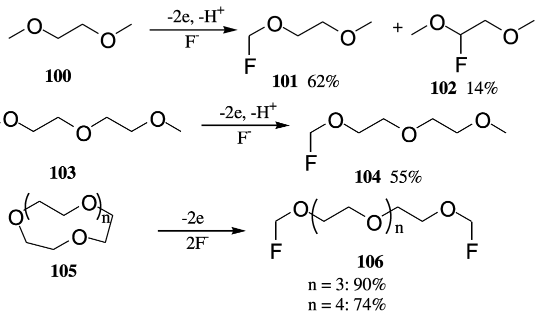
Scheme 30.

2.1.10. Organoantimony compounds. Electrofluorination of triphenylantimony (**98**) was conducted in the presence of the $Et_3N{\cdot}3HF$/MeCN system to give triphenylantimony difluoride (**99**) in excellent yield (Scheme 31).[75]



Scheme 31.

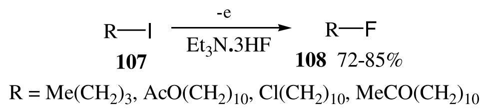
2.1.11. Ethers and cyclic ethers. Anodic fluorinations of ethers and crown ethers were reported by Fuchigami's group.[76,77] They found that electrolytic fluorination of dimethoxyethane (DME) (**100**) in $Et_3N{\cdot}5HF$ or $Et_4NF{\cdot}4HF$ gave a mixture of the two monofluorinated products **101** and **102** (Scheme 32). Similar fluorination of diethyleneglycol dimethylether (**103**) gave solely monofluorination at the terminal carbon, **104**. The crown ethers **105**, however, underwent carbon–carbon bond cleavage preferentially on fluorination to give the α,ω-difluorinated products **106**, as shown in Scheme 32.[76,77]



Scheme 32.

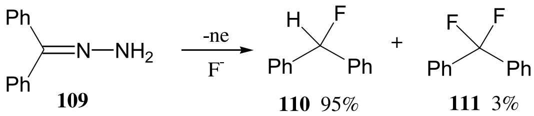
2.1.12. Alkyl iodides. Electrolytic fluorodeiodination of alkyl iodides **107** using $Et_3N{\cdot}n$HF (n=3–5) proceeds smoothly under mild conditions to give the corresponding alkyl fluorides **108** chemoselectively (Scheme 33).[78]

2.1.13. Hydrazones. Electrolysis of benzophenone hydrazone (**109**), in the presence of $Et_3N{\cdot}3HF/CH_2Cl_2$, was reported to afford mainly diphenylmonofluoromethane



Scheme 33.

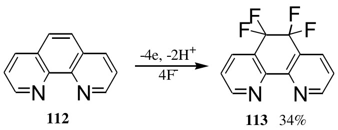
(**110**), in addition to its difluorinated derivative **111** as a byproduct (Scheme 34).[79]



Scheme 34.

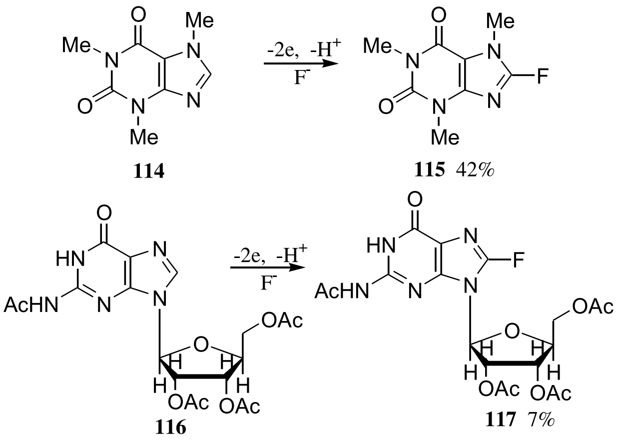
2.1.14. Heterocyclic compounds

2.1.14.1. Nitrogen-containing heterocycles. The electrolysis of 1,10-diazaphenanthrene (**112**) using $Et_3N{\cdot}3HF$ in absence of solvents resulted in the formation of its 5,5,6,6-tetrafluoro derivative **113** (Scheme 35).[25]



Scheme 35.

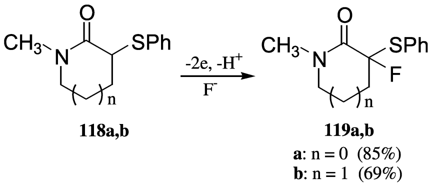
Caffeine (**114**) was fluorinated using $Et_3N{\cdot}3HF$ in acetonitrile to give 8-fluorocaffeine (**115**) in a reasonable yield (Scheme 36).[80,81] When guanosine tetraacetate (**116**) was oxidised under similar electrolytic conditions, 8-fluoroguanosine tetraacetate (**117**) was produced in a very low yield (Scheme 36).[80,81]



Scheme 36.

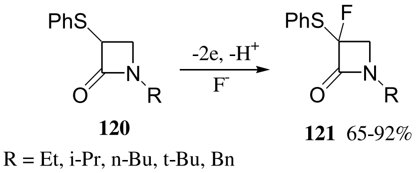
Five- and six-membered lactams **118a**,**b** bearing a phenylthio group were selectively fluorinated at the α position to the sulfur atom, to give the corresponding monofluorinated lactams **119a**,**b**, as shown in (Scheme 37).[82]

Electrolytic fluorination of α-phenylthio-β-lactams **120** in



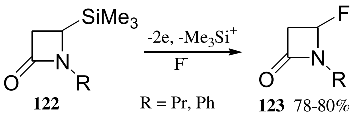
Scheme 37.

$Et_3N \cdot 3HF$ also led to the formation of the corresponding α-monofluorinated lactams **121** in high yields (Scheme 38).[83]



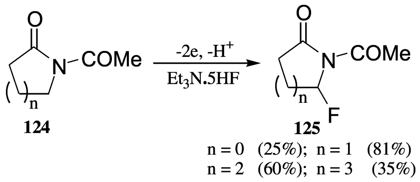
Scheme 38.

Suda et al.[84] have reported the electrolytic fluorodesilylation of (4-trimethylsilyl)azetidin-2-ones **122**, as shown in Scheme 39. In this reaction, the good leaving group (Me_3Si) greatly assisted the regioselective formation of the β-fluoro-β-lactams **123**.



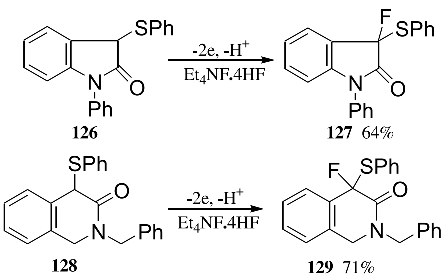
Scheme 39.

The lactams **124** having no sulfenyl or silyl groups in their rings were electrolytically fluorinated using $Et_3N \cdot 5HF$ by Yoneda's group.[85] In this work, fluorine atom was selectively inserted at the α position to the lactam nitrogen to give the desired products **125**, as outlined in Scheme 40.[85]



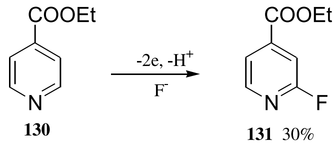
Scheme 40.

The oxindole and tetrahydroisoquinolinone derivatives **126** and **128**, activated with a phenylthio function α to the carbonyl group, were electrochemically fluorinated to give their monofluoro derivatives **127** and **129**, respectively, as depicted in Scheme 41.[86,87]



Scheme 41.

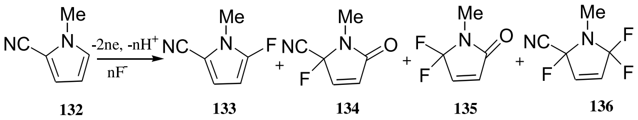
Ethyl 4-pyridinecarboxylate (**130**) underwent electrofluorination using $Et_3N \cdot 3HF$ to give ethyl 2-fluoro-4-pyridinecarboxylate (**131**) in low yield (Scheme 42).[88]



Scheme 42.

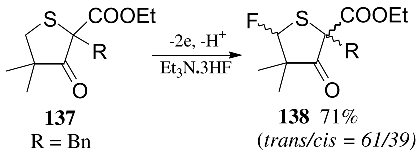
Recently, Tajima et al.[89] have reported that the electrolytic fluorination of 2-cyano-1-methylpyrrole (**132**) provides four ring-fluorinated products **133–136** and that the product selectivity was greatly dependent on both the fluoride salts and the solvents, as outlined in Scheme 43.[89]

2.1.14.2. Sulfur-containing heterocycles. Ethyl 2-benzyl-4,4-dimethyl-3-thiolanone-2-carboxylate (**137**) was reported to be electrolysed in $Et_3N \cdot 3HF/MeCN$ to give a mixture of *trans*/*cis* isomers of the highly biologically active 5-fluorothiolanone derivative **138** (Scheme 44).[90]



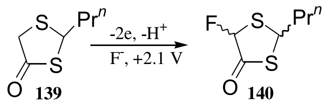
Fluoride salt/Solvent	Yield (%) 133	134	135	136
$Et_3N.5HF/CH_2Cl_2$	0	12	47	5
$Et_3N.4HF/CH_2Cl_2$	0	25	0	0
$Et_3N.3HF/CH_2Cl_2$	0	traces	traces	60
$Et_3N.2HF/CH_2Cl_2$	19	traces	traces	51
$Et_3N.2HF/MeCN$	20	traces	traces	32

Scheme 43.



Scheme 44.

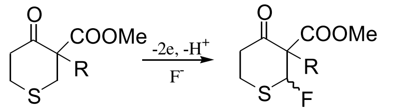
Electrolytic fluorination of 2-(*n*-propyl)-1,3-dithiolan-4-one (**139**) was performed using $Et_4NF \cdot 4HF/MeCN$ to afford a *cis*/*trans* mixture of 5-fluoro-2-(*n*-propyl)-1,3-dithiolan-4-one (**140**) in 72% yield (Scheme 45). The use of $Et_3N \cdot 3HF/MeCN$ also afforded compound **140**, but in very low yield (26%). This was explained on the basis that $Et_4NF \cdot 4HF/MeCN$ is highly stable against anodic oxidation up to 3 V vs. SCE, while $Et_3N \cdot 3HF/MeCN$ discharges around 2 V.[91]



$Et_4NF.4HF/MeCN$: 72%; *cis/trans* = 48/52
$Et_3N.3HF/MeCN$: 26%; *cis/trans* = 44/56

Scheme 45.

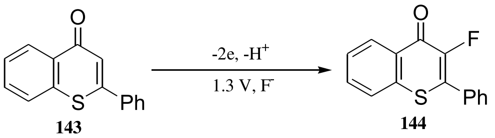
The 4-thianones **141** were similarly fluorinated at the 2-position to give the 2-fluoro-4-thianone derivatives **142** with a moderate to high diastereoselectivity (Scheme 46).[92]



R = Me: 7% (100% de)
R = Bn: 49% (44% de)

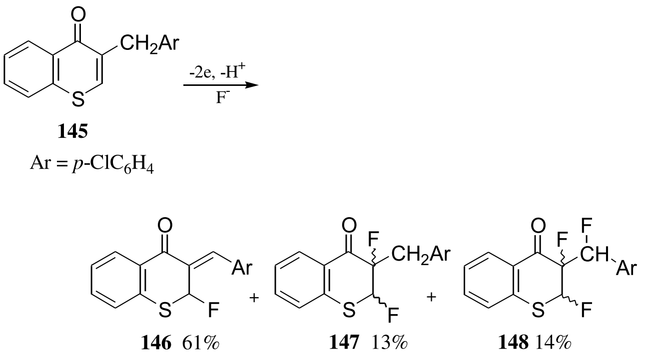
Scheme 46.

Thioflavone (**143**) was electrolytically fluorinated under controlled potential in the presence of $Et_3N{\cdot}3HF$ to afford 3-fluorothioflavone (**144**), as outlined in Scheme 47.[28]



Scheme 47.

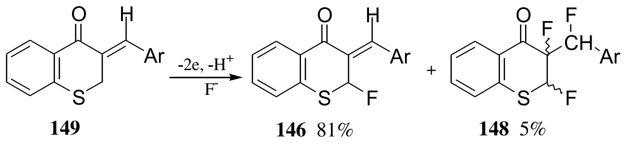
Recently, Dawood et al.[93] the reported that electrolytic fluorination of the homoisothioflavone derivative **145** proceeds in a different manner to that of thioflavone (**143**), in $Et_4NF{\cdot}4HF$/DME affording mainly the 2-fluoro-3-benzylidenethiochromanone derivative **146** in addition to its di- and trifluorinated derivatives **147** and **148**, respectively, as shown in Scheme 48.[93]



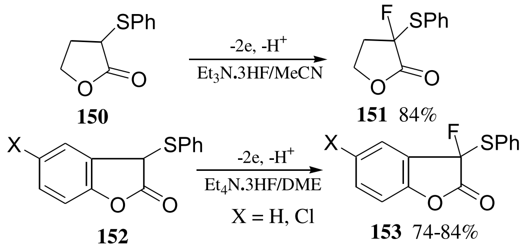
Scheme 48.

The mono- and trifluorinated thiochromanone derivatives **146** and **148** were alternatively obtained from the direct electrolytic fluorination of 3-arylidenethiochroman-4-ones **149** under similar electrolytic conditions (Scheme 49).[93]

2.1.14.3. Oxygen-containing heterocycles. The electrofluorination of 3-(phenylthio)tetrahydrofuran-2-one (**150**)[52] and 3-(phenylthio)-dihydrobenzofuran-2-one (**152**)[94] was successfully achieved in the presence of the appropriate fluoride salt to form the corresponding monofluorinated derivatives **151** and **153**, respectively, as shown in Scheme 50.

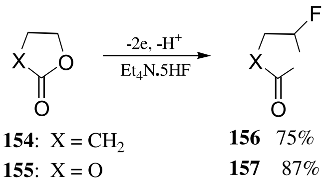


Scheme 49.



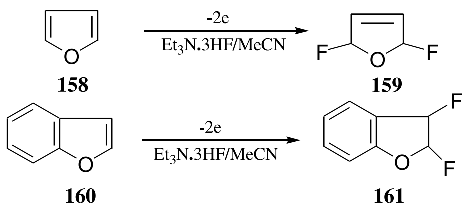
Scheme 50.

The regioselective anodic fluorination of γ-butyrolactone (**154**) and ethylene carbonate (**155**) was attempted using $Et_4NF{\cdot}5HF$ without a solvent to give the corresponding monofluorinated products **156** and **157**, respectively, in good yields (Scheme 51).[95]



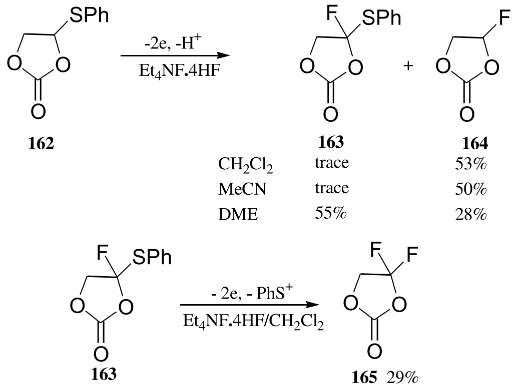
Scheme 51.

Difluorinated products were obtained in the electrolytic fluorination of furan (**158**) and benzofuran (**160**) using $Et_3N{\cdot}3HF$.[25] With furan, 1,4-addition of fluorine took place to give **159**, but 1,2-addition was observed in the fluorination of benzofuran to give **161** (Scheme 52).[25]



Scheme 52.

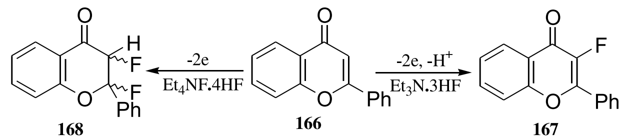
Electrolytic solvents played a significant role in the product selectivity during the fluorination of 4-phenylthio-1,3-dioxolan-2-one (**162**).[96,97] As shown in Scheme 53,



Scheme 53.

fluorodesulfurisation occurred to give 4-fluoro-1,3-dioxolan-2-one (**164**) selectively when CH_2Cl_2 or MeCN were used as the solvents; in dimethoxyethane (DME), however, α-fluorination took place to give **163** preferentially in addition to **164**. Further electrolytic fluorination of **163** in CH_2Cl_2 afforded 4,4-difluoro-1,3-dioxolan-2-one (**165**) (Scheme 53).[96,97]

Electrolytic fluorination of flavone (**166**) was found to be dependent on the type of fluoride salts used. In $Et_3N{\cdot}3HF$, it afforded 3-fluoroflavone (**167**), but using $Et_4NF{\cdot}4HF$ led to formation of 2,3-difluoro-2,3-dihydroflavone (**168**) (Scheme 54).[98,99]

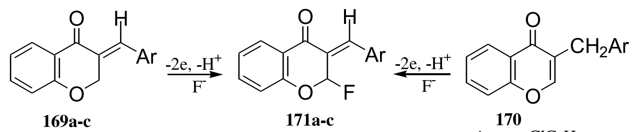


168 68% **166** **167** 58%

Scheme 54.

Highly regioselective electrolytic direct fluorination at the α-position to the ring-oxygen atom of the chroman-4-one derivatives **169a–c** was successfully performed using $Et_4NF{\cdot}4HF$/DME to give the corresponding 2-fluorochromanones **171a-c**.[100,101] The compound **171b** could also be obtained stereoselectively from an alternative electrofluorination of the homoisoflavone derivative **170**, as shown in Scheme 55.[100,101]

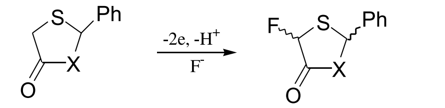
2.1.14.4. Heterocycles containing more than one heteroatom. The highly regioselective electrolytic fluorination of 3-benzyl-2-phenylthiazolidin-4-one (**172a**) was performed in $Et_3N{\cdot}3HF$/MeCN to give the corresponding monofluorinated product **173a** (Scheme 56).[102] When $Et_4NF{\cdot}4HF$/MeCN was used for the fluorination of the oxathiolan-4-one derivative **172b**, the monofluorinated product **173b** was obtained in 70% yield, while $Et_3N{\cdot}3HF$/MeCN resulted in no fluorination (Scheme 56).[103] The latter result was attributed to a severe passivation of the anode when $Et_3N{\cdot}3HF$/MeCN was used, due to the equilibrating existence of free Et_3N,[23] but no passivation was observed in the case of $Et_4NF{\cdot}4HF$/MeCN.[103]



169a-c **171a-c** 60-72% **170** Ar = p-ClC$_6$H$_4$

Ar; **a**: Ph; **b**: p-ClC$_6$H$_4$; **c**: p-BrC$_6$H$_4$

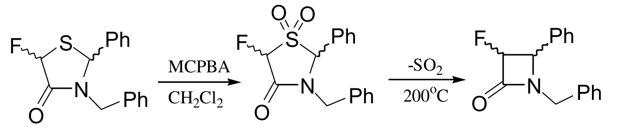
Scheme 55.



172a: X = NBn
172b: X = O
173a: 65% (*cis/trans = 46/54*)
173b: 70% (*cis/trans = 45/55*)

Scheme 56.

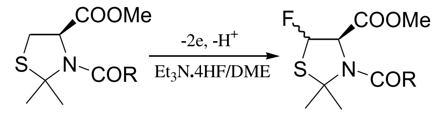
Treatment of **173a** with *m*-chloroperbenzoic acid (MCPBA) afforded the fluorosulfone **174** which, under thermolysis at 200 °C, resulted in the formation of the biologically active monofluorinated β-lactam **175** (Scheme 57).[102]



173a **174** 65% (*cis/trans = 46/54*) **175** 84% (*cis/trans = 19/81*)

Scheme 57.

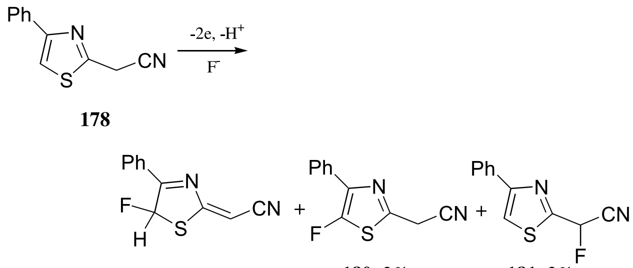
The thiazolidines **176** were also diastereoselectively electrolysed in dimethoxyethane using $Et_3N{\cdot}4HF$ to give the monofluorinated products **177** where a fluorine atom was selectively introduced at the α position to the sulfur atom (Scheme 58).[104]



176 R = Me, Ph, p-MeC$_6$H$_4$ **177** 53-91%, de 80-95%

Scheme 58.

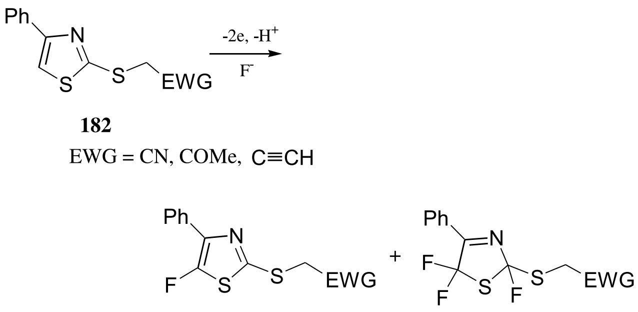
Electrolytic fluorination of 4-phenyl-2-thiazolylacetonitrile (**178**) was conducted in $Et_4NF{\cdot}5HF$/DME to give the monofluorinated products **179–181** as shown in Scheme 59.[105]



179 45% **180** 2% **181** 2%

Scheme 59.

Similarly, the thiazolyl sulfides **182** were electrochemically fluorinated at the thiazole ring to give the mono- and trifluorinated derivatives **183** and **184**, respectively (Scheme 60).[106]



183 8-25% **184** 23-50%

Scheme 60.

[redacted]

Sc[redacted]

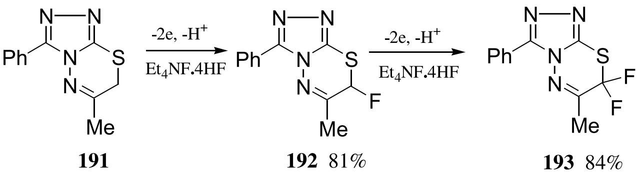
Si[redacted]
zin[redacted]
α p[redacted]
Sch[redacted]

Scheme 6[redacted]

Potentios[redacted] *b*]thiadiaz[redacted] using an [redacted] 7-monofluo[redacted] derivative **19**[redacted] tion of the [redacted] Scheme 64.[111][redacted]

2.1.14.5. Fluo[redacted]

Electrolytic mon[redacted] heterocyclic compo[redacted]y Fuchigami's group. [redacted] group attached to heterocycl[redacted]orinated to give the corresponding α-flu[redacted] products.[112–122] In one example, the 2-pyridyl sulfides **194** were fluorinated in $Et_3N{\cdot}3HF$ to give the corresponding α-fluorinated sulfides **195**, which were readily cyclised into the 2-fluoro-

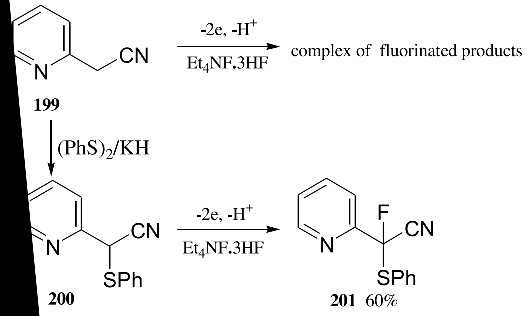


Scheme 64.

[redacted]thieno[2,3-*b*]pyridine derivative **198** in K_2CO_3/EtOH [redacted]olution through the intermediates **196** and **197**,[112,113] as [redacted]hown in Scheme 65.

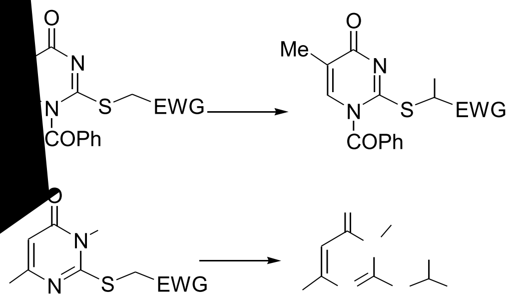
[redacted]**me 65.**

[redacted]ontrast, 2-pyridylacetonitrile (**199**) did not give the [redacted]ed fluorination. Its α-phenylthiolated derivative **200** [redacted]eeded smoothly, however, to give the corresponding [redacted]orinated product **201**[61] (Scheme 66).



[redacted]**.Scheme** **67.**

[redacted]imidyl sulfides **202** and **204** were similarly [redacted]d using $Et_4NF{\cdot}4HF$/DME to give **203** and **205**, [redacted]ely, in good yields (Scheme 67).[114]



Thiadiazolyl, oxadiazolyl and triazolyl sulfides **206-208** were successfully fluorinated to give **209–211**, respectively. The yield of the products was greatly affected by the type of heterocyclic ring system,[115] as shown in Scheme 68.

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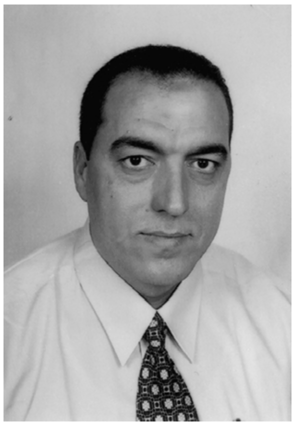
Biographical sketch



Kamal M. Dawood was born in 1965 in Kafr-Elsheikh, Egypt. He graduated from Cairo University, Egypt in 1987 then he joined Professor Ahmad M. Farag's research group to carry out his MSc and PhD studies under the supervision of Professor Farag, Cairo University. He received his PhD in 1995 in the applications of hydrazonoyl halides in heterocyclic chemistry. Then he was appointed as a Lecturer of Organic Chemistry at Cairo University and continued his research work on the topics of regioselectivity and reaction mechanisms of cycloaddition reactions of nitrilimines. In 1997 he was awarded the UNESCO Fellowship for one year at Tokyo Institute of Technology (TIT) and collaborated with Professor Toshio Fuchigami at TIT in the field of 'Electrochemical Partial Fluorination of Heterocyclic Compounds'. In 1999, he was awarded the JSPS (Japan Society for Promotion of Science) Fellowship for two years and worked again with Professor Fuchigami at TIT in the same field. During his stay at TIT he published ten articles in JOC, TL and JFC. In 2001 he returned back to Cairo and promoted to Assoc. Professor in 2002. In 2002 he received the Cairo University Award in Chemistry. In Aug. 2003 he was awarded the Alexander von Humboldt Fellowship at Hannover University with Professor Andreas Kirschning in the field of polymer-supported palladium catalysed hydrogenation of organic compounds.