<table>
<thead>
<tr>
<th>Title</th>
<th>Synthesis of fluorinated oxygen- and sulfur-containing heteroaromatics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Leary, Eileen M.; Jones, David J.; O'Donovan, Fiona P.; O'Sullivan, Timothy P.</td>
</tr>
<tr>
<td>Publication date</td>
<td>2015-06-11</td>
</tr>
<tr>
<td>Type of publication</td>
<td>Article (peer-reviewed)</td>
</tr>
<tr>
<td>Link to publisher's version</td>
<td><a href="http://dx.doi.org/doi:10.1016/j.jfluchem.2015.06.002">http://dx.doi.org/doi:10.1016/j.jfluchem.2015.06.002</a></td>
</tr>
<tr>
<td>Rights</td>
<td>© 2015 Elsevier B.V. This manuscript version is made available under the CC-BY-NC-ND 4.0 license <a href="http://creativecommons.org/licenses/by-nc-nd/4.0/">http://creativecommons.org/licenses/by-nc-nd/4.0/</a></td>
</tr>
<tr>
<td>Item downloaded from</td>
<td><a href="http://hdl.handle.net/10468/4118">http://hdl.handle.net/10468/4118</a></td>
</tr>
</tbody>
</table>

Downloaded on 2020-03-30T13:56:14Z
The published manuscript is available at the *Journal of Fluorine Chemistry* via

http://dx.doi.org/doi:10.1016/j.jfluchem.2015.06.002

© 2017. This manuscript version is made available under the CC-BY-NC-ND 4.0 license

http://creativecommons.org/licenses/by-nc-nd/4.0/
Synthesis of fluorinated oxygen- and sulfur-containing heteroaromatics

Eileen M. O’Leary\textsuperscript{a,b,c}, David J. Jones\textsuperscript{a,c}, Fiona P. O’Donovan\textsuperscript{a,c} and Timothy P. O’Sullivan\textsuperscript{a,b,c,*}.

\textsuperscript{a}Department of Chemistry, University College Cork, Cork, Ireland.

\textsuperscript{b}School of Pharmacy, University College Cork, Cork, Ireland.

\textsuperscript{c}Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland.

*Corresponding author. Tel +353 21 4901655; fax +353 21 4901656. Email tim.osullivan@ucc.ie

Keywords: Organofluorine chemistry, fluorobenzofurans, fluoropyrones, fluorocoumarins, fluoroflavones, fluorochromones, fluoroanthones, fluorothiophenes, fluorobenzothiophenes.

ABSTRACT

The incorporation of fluorine into a target molecule may have a considerable impact on its reactivity, selectivity, biological activity and physical properties. This is especially true in medicinal chemistry where fluorine is often employed as a bioisostere of hydrogen and where many important drug compounds also feature heteroaromatic rings. This work complements existing reviews on the synthesis of fluorinated, aromatic heterocycles, with a focus on less common oxygen-containing heteroaromatics as well as their sulfur-based analogues.
This review covers methods for the incorporation of fluorine into oxygen- and sulfur-containing heteroaromatic compounds.
## CONTENTS

1 INTRODUCTION 4

2 SYNTHESIS OF OXYGEN-CONTAINING HETERAROMATICS 5

2.1 SYNTHESIS OF FLUORINATED BENZOFURANS 5

2.2 SYNTHESIS OF FLUORINATED DIBENZOFURANS 12

2.3 SYNTHESIS OF FLUORINATED 2-PYRONES 15

2.4 SYNTHESIS OF FLUORINATED 4-PYRONES 18

2.5 SYNTHESIS OF FLUORINATED COUMARINS 18

2.6 SYNTHESIS OF FLUORINATED ISOCOUMARINS 26

2.7 SYNTHESIS OF FLUORINATED FLAVONES AND CHROMONES 28

2.8 SYNTHESIS OF FLUORINATED XANTHONES 36

3 SYNTHESIS OF SULFUR-CONTAINING HETERAROMATICS 40

3.1 SYNTHESIS OF 2- AND 5-FLUOROTHIOPHENES 40

3.2 SYNTHESIS OF 3- AND 4-FLUOROTHIOPHENES 47

3.3 SYNTHESIS OF PERFLUOROTHIOPHENES 52

3.4 SYNTHESIS OF FLUORINATED BENZOTHIOPHENES 54

4 CONCLUSIONS 58

ACKNOWLEDGEMENTS 59

REFERENCES 60
Fluorine is seldom found in natural products, with the antibiotic 4-fluorothreonine and the toxin fluoroacetate representing two rare examples [1]. Despite this fact, fluorine is present in a significant number of drug compounds, agrochemical products and novel materials. As testament to the importance of fluorine in the pharmaceutical industry in particular, there are 128 fluorinated compounds with US tradenames according to the World Drug Index [2]. Furthermore, it is estimated that about 15-20% of pharmaceuticals licensed each year (new chemical entities) contain a fluorine atom [3, 4]. The presence of a fluorine serves to increase drug lipophilicity [5, 6] which is especially important when designing drugs that are intended to cross the blood-brain barrier [7]. Fluorination of drug compounds also affects physical properties [8], and can alter binding affinities with enzymes and receptors [9], rate of metabolism [10], clearance, absorption and transport [11].

Scaffolds containing one or more heteroaromatic rings are common in medicinal compounds [12]. A high percentage of drugs contain either aromatic or aliphatic heterocycles [13]. For example, the top ten small drug molecules all contain heterocyclic moieties [14]. Oxygen-containing heterocyclic drugs are of particular medical relevance, forming an important class of building blocks in organic synthesis [15, 16].

It is not surprising, therefore, that the development of new methods for the incorporation of fluorine into heteroaromatic ring systems is an area of active research in chemistry. Both Furin and Burger et al. have reviewed approaches to the synthesis of fluorinated, nitrogen containing, heterocyclic compounds [17-20]. More recently, Serduyk et al. have presented an overview of methods for the synthesis of fluorofurans and perfluoroalkylfurans [21]. More general reviews on the preparation of polyfluorinated heterocyclic and heteroaromatic compounds have been compiled by both Brooke and Yakobson [22, 23]. The aim of this
work is to complement these existing reviews and to address the remaining gaps. Our focus is directed towards the incorporation of fluorine into less common, oxygen-containing heteroaromatic rings, as well as the synthesis of fluorinated, sulfur-containing rings.

This review is split into two major sections: firstly, oxygen-containing heteroaromatics and secondly, sulfur-containing aromatic heterocycles. Each section is sub-divided by ring-type. Within each sub-division, the initial focus is on methods for direct fluorination of heteroaromatic rings, followed by methods where fluorine participates in formation of the product (e.g. S_NAr displacement of fluoride) and finally, routes where fluorine is present in the substrate prior to cyclization. Examples where fluorine is effectively a bystander in the formation of the fluorinated product have been omitted.

2 SYNTHESIS OF OXYGEN-CONTAINING HETEROAROMATICS

2.1 SYNTHESIS OF FLUORINATED BENZOFURANS

Both De Luca and Rueckle have developed a methodology for the direct incorporation of fluorine into 2-position of a benzofuran [24, 25]. Lithiation of 1 with n-BuLi, followed by addition of N-fluorobenzenesulfonimide (NFSI) at -78°C, afforded the target compound 2 (Scheme 1). Yields for this reaction were not reported as the product was used in the next step without any further purification.

![Scheme 1](image_url)
Fluorodecarboxylation has been successfully used by a number of research groups to synthesise 2-fluorobenzofurans [26, 27]. In a typical example, Selectfluor® was added to a solution of 3 and sodium bicarbonate in water/ethyl acetate, from which fluorinated benzofuran 4 was isolated in 36% yield (Scheme 2).

![Scheme 2]

Widdowson *et al.* have demonstrated the fluorination of arylheteroaryl iodonium salts, prepared from the corresponding aryltrialkylstannanes [28]. This methodology was applied to stannane 5, which was converted to iodonium salt 6 with hydroxy(tosyloxy)iodobenzene (HTIB) in 98% yield, followed by subsequent fluorination with cesium fluoride to afford 2-fluorobenzofuran (7) (Scheme 3). Although actual yields are not quoted, the formation of 7 rather than fluorobenzene as the major product has been ascribed to a transition state where the 2-benzo[b]furyl group is equatorial, thus favouring fluorination of the heteroaryl ring.

![Scheme 3]
Ritter *et al.* have designed a strategy for the fluorination of aryl and heteraryl boronic acids using novel palladium complexes [29, 30]. These palladium complexes incorporate nitrogenous, bidentate ligands which resist oxidation by electrophilic fluorination reagents, can support high-valence aryl palladium fluorides for subsequent carbon–fluorine reductive elimination and do not induce competing nitrogen–fluorine reductive elimination. Complex 10, which was prepared from 2-benzofuranylboronic acid (8), was successfully fluorinated on treatment with Selectfluor® to furnish 7, albeit in a modest overall yield of 8% (Scheme 4).

![Scheme 4](image)

In their search for a straightforward preparation of fluorinated benzofurans, Plevey and co-workers discovered that cesium tetrafluorocobaltate is a highly effective reagent for the perfluorination of unsubstituted benzofurans [31]. Fluorination of benzofuran (11) at 380°C afforded polyfluorinated intermediate 12 as the major product in 20% yield (Scheme 5). Subsequent pyrolysis of 12 over nickel gauze at 580°C gave 2-fluorobenzofuran 13 in 7% yield along with 2,3-difluorobenzofuran 14.
Barton et al. have experimented with trifluorofluoro-oxymethane as a means of fluorinating benzofurans and indoles (Scheme 6). Accordingly, benzofuran (11) was converted to 15 in 19% yield on treatment with trifluorofluoro-oxymethane at -78°C [32]. Base-induced elimination with ethanolic potassium hydroxide afforded 3-fluorobenzofuran (16) in 61% yield.

Tagami et al. have described a route to 3-fluorobenzofurans in their work on the development of novel retinoic acid receptor agonists [33]. Bromination of 17, followed by halogen exchange with silver fluoride, afforded 18 in quantitative yield (Scheme 7). Installation of the double bond was accomplished with potassium tert-butoxide and 18-crown-6 giving 19 in 59% yield.
Khellin (20), a benzofuran-containing natural product, has long been of interest due to its many interesting medicinal properties (Scheme 8) [34]. Gammill and Nash found that treatment of 20 with *in situ* generated BrF afforded *trans*-3-bromo-2-fluoro-2,3-dihydrokhellin (21) in 84% yield (Scheme 8) [35]. The difluorinated derivative could in turn be prepared from 21 on treatment with silver fluoride affording the *cis*- and *trans*- isomers in a ratio of 51:36 respectively. The *cis*-isomer underwent DBU-mediated elimination to furnish the 3-fluorobenzofuran adduct 22 in 55% yield. 2-Fluorobenzofuran 23 was accessed directly from 21 on addition of potassium fluoride in 41% yield. The use of *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) as solvent was found to dramatically accelerate this reaction.
Methods for the incorporation of fluorine onto the benzene ring of benzofuran substrates have also been reported. Wang et al. used tetrafluoroboric acid to fluorinate benzofuran 24 via a Schiemann reaction (Scheme 9) [36, 37]. Over the course of the reaction, an aryldiazonium tetrafluoroborate forms and subsequently undergoes thermal decomposition to release boron trifluoride, producing the desired fluorinated benzofuran 25 in 45% yield.
Brooke et al. used intramolecular nucleophilic displacement of a fluorine atom by oxygen to prepare 4,5,6,7-tetrafluoro-benzofurans 28a-c from the enolates 27a-c of pentafluorobenzyl ketones 26a-c (Scheme 10) [38]. Yields varied depending on the nature of the substituent. 28c (R = Ph) was recovered in a yield of 76% due to the bulky phenyl group adopting a stable trans-configuration to the C6F5 group. Progressively lower yields of 33% and 13% were reported for 28b (R = Me) and 28a (R = H) respectively. Attempts to incorporate a fluorine atom into the 5-membered ring were unsuccessful; while it was possible to synthesise ethyl (2-ethoxycarbonyl-3,4,5,6-tetrafluorophenoxy)fluoroacetate from 2,3,4,5-tetrafluoro-6-hydroxybenzoate and ethyl chlorofluoroacetate, the subsequent cyclisation did not occur. The authors attribute this outcome to the unfavourable formation of a high energy carbanion.

![Scheme 10](image)

Ichikawa et al. have developed a novel synthesis of 2-fluorinated benzofurans from gem-difluorostyrenes [39]. Difluorovinylborane 30 was generated from 2,2,2-trifluoroethyl p-toluenesulfonate (29) in two steps (Scheme 11). Palladium-mediated coupling of 30 with o-iodoanisole and subsequent demethylation afforded gem-difluorostyrene 31 in 44% overall yield. 5-Endo-trigonal cyclisation of 31 was effected with sodium hydride in dimethylformamide resulting in an 84% yield of 2-fluorobenzofuran 32. The highly polarised difluorovinylidene bond in 31 displays significant single bond character which facilitates ring formation.
2.2 SYNTHESIS OF FLUORINATED DIBENZOFURANS

Zupan et al. have studied the effects of a range of fluorinating agents on the regioselective fluorination of dibenzofuran (33) (Table 1) [40]. A representative sample of reagents was tested including Selectfluor®, Accufluor®, N-fluoro-2,6-dichloropyridinium tetrafluoroborate (FPD-B) and NFSI. Selectfluor® and Accufluor® are of similar chemical structure; both are 4-fluoro-1,4-diazabicyclo[2.2.2]octane derivatives. Selectfluor® contains a chloromethyl group at the 1-position, whereas Accufluor® bears a hydroxyl group at the same location. Regioselectivity was found to be reagent dependent (entry 1 vs. entries 8 & 9, Table 1). The choice of solvent also proved crucial to the reaction outcome as no reaction was observed in either methanol or methylene chloride, whereas a mixture of polar solvents (acetonitrile and trifluoroacetic acid) resulted in the highest overall yield of 39%. No reaction was observed when NFSI was used as the fluorinating agent.
### Table 1

Effect of fluorinating reagent on product distribution

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Combined Yield (%)</th>
<th>34 (%)</th>
<th>35 (%)</th>
<th>36 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Selectfluor®</td>
<td>MeCN</td>
<td>35</td>
<td>27</td>
<td>42</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>Selectfluor®</td>
<td>MeCN, PhNO₂</td>
<td>34</td>
<td>28</td>
<td>41</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>Selectfluor®</td>
<td>MeCN, DCM</td>
<td>30</td>
<td>26</td>
<td>42</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>Selectfluor®</td>
<td>MeCN, MeOH</td>
<td>17</td>
<td>24</td>
<td>47</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>Selectfluor®</td>
<td>MeCN/CF₃CO₂H (9:1)</td>
<td>38</td>
<td>26</td>
<td>42</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>Selectfluor®</td>
<td>MeCN/CF₃CO₂H (1:1)</td>
<td>39</td>
<td>23</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>7</td>
<td>Selectfluor®</td>
<td>CF₃CO₂H</td>
<td>30</td>
<td>22</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>8</td>
<td>Accufluor®</td>
<td>MeCN</td>
<td>35</td>
<td>26</td>
<td>42</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>FPD-B</td>
<td>MeCN</td>
<td>38</td>
<td>18</td>
<td>53</td>
<td>29</td>
</tr>
</tbody>
</table>

Zupan has also investigated the use of xenon difluoride for the fluorination of dibenzofuran substrates [41]. Addition of xenon difluoride to 33 in dichloromethane at room temperature resulted in a mixture of regioisomeric, fluorinated products 34-36 in a low, combined yield of 17% (Table 2). An increase in yield to 30% was observed when boron trifluoride etherate was
employed as a catalyst. Interestingly, the use of boron trifluoride also affected regioselectivity, displaying a marked preference for fluorination at the 3-position.

**Table 2**

Fluorination of dibenzofurans with XeF₂

<table>
<thead>
<tr>
<th>Reagent</th>
<th>34 (%)</th>
<th>35 (%)</th>
<th>36 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XeF₂</td>
<td>25</td>
<td>31</td>
<td>44</td>
</tr>
<tr>
<td>XeF₂, BF₃.OEt₂, 0°C</td>
<td>23</td>
<td>23</td>
<td>54</td>
</tr>
<tr>
<td>XeF₂, BF₃.OEt₂, 20°C</td>
<td>26</td>
<td>21</td>
<td>53</td>
</tr>
</tbody>
</table>

Johnson *et al.* have indirectly prepared fluorinated dibenzofurans from the corresponding aminodibenzofurans *via* a Schiemann reaction [42]. Diazotisation of 2-aminodibenzofuran (2-NH₂-37) and 3-aminodibenzofuran (3-NH₂-37) with nitrous acid, followed by treatment with fluoroboric acid, afforded a diazonium fluoroborate intermediate which subsequently decomposed at elevated temperatures to afford 2-fluorodibenzofuran (35) or 3-fluorodibenzofuran (36) in yields of 39% and 80% respectively.
2.3 SYNTHESIS OF FLUORINATED 2-PYRONES

To the best of our knowledge, methods for the direct fluorination of 2-pyrones have not been reported in the literature. Fluorinated 2-pyrones may, however, be indirectly prepared from fluorine-containing precursors. An early example is provided by England et al. [43]. A [4+2] cycloaddition reaction between perfluoroacryloyl fluoride 39 with an aromatic acetylene 38 affords cycloadducts 40a-j (Table 3). This is followed by rearrangement to 41a-j and subsequent hydrolysis to afford fluorinated 2-pyrones 42a-j.

Table 3

Preparation of fluorinated 2-pyrones

<table>
<thead>
<tr>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Overall Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42a</td>
<td>H</td>
<td>H</td>
<td>F</td>
<td>2.5</td>
</tr>
</tbody>
</table>
The authors also report a second route to fluorinated 2-pyrones 45a-c in lower yields using a condensation reaction between either perfluoroacryloyl fluoride (39a) or perfluoromethacryloyl fluoride (39b) and either acetone (43a) or acetophenone (43b) (Scheme 13). The mechanism most likely involves conjugate addition of an α-carbon to the fluorinated double bond, followed by ring closure via the enol of 44a-c and subsequent loss of HF.

\[
\begin{align*}
43a : R^1 &= \text{CH}_3 \\
43b : R^1 &= \text{Ph} \\
39a : R^2 &= \text{F} \\
39b : R^2 &= \text{CF}_3 \\
44a : R^1 &= \text{CH}_3; R^2 &= \text{F} \\
44b : R^1 &= \text{CH}_3; R^2 &= \text{CF}_3 \\
44c : R^1 &= \text{Ph}; R^2 &= \text{F} \\
45a : R^1 &= \text{CH}_3; R^2 &= \text{F} (3\%) \\
45b : R^1 &= \text{CH}_3; R^2 &= \text{CF}_3 (29\%) \\
45c : R^1 &= \text{Ph}; R^2 &= \text{F} (6.7\%)
\end{align*}
\]

Scheme 13

Wang and Burton successfully synthesised a range of 3,4-difluoro-2-pyrones from (2E)-2,3-difluoro-3-iodoacrylic acid (46) and terminal acetylenes 47a-f in the presence of palladium and copper co-catalysts (Table 4) [44]. Iodoacid 46 reacts with alkyne 47 under Pd(0)
catalysis to produce ynenoic acid 48. 48 is not isolated but is instead converted in situ to pyrones 42a-b and 49a-d by Pd(II) catalysis. Both aromatic and aliphatic acetylenes were well tolerated as were heterocyclic acetylenes. The presence of either electron withdrawing or donating groups on the aromatic ring was not found to impact upon yields.

Table 4

Pd-Catalysed synthesis of 3,4-difluoro-2-pyrones

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42a</td>
<td>C₆H₅</td>
<td>24</td>
<td>62</td>
</tr>
<tr>
<td>42b</td>
<td>4-MeOC₆H₄</td>
<td>16</td>
<td>71</td>
</tr>
<tr>
<td>49a</td>
<td>n-C₅H₁₁</td>
<td>24</td>
<td>59</td>
</tr>
<tr>
<td>49b</td>
<td>C₆H₅CH₂CH₂</td>
<td>24</td>
<td>64</td>
</tr>
<tr>
<td>49c</td>
<td>4-CF₃C₆H₄</td>
<td>12</td>
<td>69</td>
</tr>
<tr>
<td>49d</td>
<td>2-Pyridyl</td>
<td>24</td>
<td>43</td>
</tr>
</tbody>
</table>

Fürstner et al. have developed a gold-containing catalyst which accelerates the cyclisation of widely available β-keto esters to furnish 4-hydroxy-2-pyrone [45]. Thus, β-keto ester 50 underwent cyclisation on exposure to catalyst 51 in acetic acid to afford 3-fluoropyrone 52 in 85% yield (Scheme 14).
2.4 SYNTHESIS OF FLUORINATED 4-PYRONES

As with the 2-pyrones, methods for the direct fluorination of 4-pyrones have not been reported in the literature. An indirect method has been reported by England and Krespan by way of a fluorinated lactone intermediate [46]. Methylketene 54 underwent a cycloaddition reaction with bis(trifluoromethyl)ketene (53) to afford lactone 55 in 61% yield (Scheme 15). Treatment of 55 with zinc chloride initiated hydrogen fluoride elimination and difluorinated 4-pyrene 56 was recovered in 25% yield.

\[
\text{Ph} \quad \text{F} \quad \text{O} \quad \text{Bu} \quad \xrightarrow{\text{AcOH, rt}} \quad \text{Ph} \quad \text{O} \quad \text{O} \quad \text{F} \quad 85\%
\]

Scheme 14

2.5 SYNTHESIS OF FLUORINATED COUMARINS
Rozen et al. employed acetyl hypofluorite as the fluorinating reagent in the electrophilic fluorination of coumarin (57) [47]. The product of electrophilic addition 58 tautomerises to its labile enol form 59, which readily undergoes elimination of acetic acid to produce 3-fluorocoumarin (60) in 95% yield (Scheme 16).

Scheme 16

Rozen and Brand fluorinated coumarin using elemental fluorine, at a concentration of 1% in N₂, in a mixture of fluorotrichloromethane, chloroform and ethanol (Scheme 17) [48]. Two products were isolated and identified as 3,4-dihydro-3,4-difluorocoumarin (61) (55% yield) and 3-fluorocoumarin (60) (15% yield) [48]. The authors noted that 61 could be quantitatively dehydrofluorinated to 60 by adsorbing it on a silica gel column for 24 hours. The easy elimination of HF is due to the anti configuration of the hydrogen and fluorine atoms resulting from syn addition of fluorine.

Scheme 17

A similar approach has been utilised by Sato et al., although they started with 4-chlorocoumarin (62) as their preferred substrate (Scheme 18) [49]. β-Chloro-enone 62 was firstly dissolved in the same solvent system employed previously by Rozen. On exposure to a stream of fluorine gas, 62 was then converted to difluorinated adduct 63. Purification of 63 on silica gel was accompanied by spontaneous elimination of HCl, affording 3,4-
difluorocoumarin (64) in 34% overall yield, along with a significant amount of starting material 62 (55%).

Scheme 18

In their investigation of the fluorination of coumarins in acidic solvents, Holling et al. found that fluorination of coumarin in sulfuric acid resulted in a mixture of products [50]. Fluorination of 57 gave five major products including 6-fluorocoumarin (65), 8-fluorocoumarin (66) and 7-fluorocoumarin (67) as well as smaller quantities of the difluorinated adducts 68 and 69 (Scheme 19). Only minute quantities of products arising from fluorination of the heterocyclic ring were observed, which would indicate that protonation of the oxygen atom by sulfuric acid deactivates the heterocyclic ring towards electrophilic fluorination.

Scheme 19
The same authors further reported that 6-methylcoumarin (70) may be selectively fluorinated ortho to the methyl group in synthetically useful yields (Scheme 20). By contrast, the fluorination of 7-methoxycoumarin (72a) is dependent on the amount of fluorine used (Table 5). The highest yields are obtained with 5 equivalents of fluorine, whereas 10 equivalents leads to an increase in the formation of the gem-difluoroketone side product 74.

![Scheme 20](image)

**Table 5**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Equiv. of F₂</th>
<th>Yield 73 (%)</th>
<th>Yield 74 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>5</td>
<td>66</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>10</td>
<td>trace</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>5</td>
<td>55</td>
<td>26</td>
</tr>
</tbody>
</table>

In their search for novel anti-inflammatory compounds, Curini et al. attempted the direct fluorination of umbelliferone [51]. Treatment of 75 with Selectfluor® in refluxing acetonitrile for 30 minutes furnished 76 in 52% yield (Scheme 21).
Jabin et al. have successfully demonstrated the direct fluorination of selected coumarins and psoralens, albeit in low yields [52]. They examined the fluorination of 77 and 79 using three different N-F electrophilic fluorinating reagents, namely NFSI, N-fluoropyridinium triflate and Selectfluor® (Scheme 22). Monitoring of these reactions via GC-MS confirmed that fluorinated products had formed using all three of the reagents. However, the desired products were isolated only when Selectfluor® was employed as the fluorinating agent. Fluorocoumarin 78 and fluoropsoralen 80 were obtained in 12% and 14% yields respectively, with substantial amounts of starting material also recovered in both cases.
Employing a ring-closing metathesis (RCM) reaction, Marhold et al. have prepared 3-fluorocoumarin (60) in 16% yield from 2-vinylphenyl-α-fluoroacrylate 81a (R = H) and ruthenium-based catalyst 82 (Scheme 23) [53]. Additionally, 44% of a homodimer involving the non-fluorinated double bonds was isolated. High-dilution experiments over a range of concentrations from 0.5M to 0.05M did not show a significant change in the product ratio. On replacing hydrogen with a methyl group in the precursor, 81b (R = Me) underwent RCM in a similar manner to afford 60 in a significantly increased yield of 79% [54, 55].

![Scheme 23](image)

Shi et al. have demonstrated that 2-fluoro-3-methoxyprop-2-enoyl chloride serves as a useful intermediate in the synthesis of fluorinated coumarins and other heteroaromatic ring systems (Scheme 24) [56]. In a typical example, acid chloride 84, which may be readily prepared from 1,2-dimethoxy-1-trimethylsilyloxyethene (83) [57], reacted with phenol to form advanced ester adduct 85. Exposure of 85 to sulfuric acid in chloroform afforded 60 in 90% yield.
The von Pechmann cyclisation is a popular route to the preparation of novel coumarins [58, 59]. For example, Harada et al. synthesised several substituted coumarins for use in the treatment of prostate cancer using this approach [60]. Reaction of resorcinol (87) and commercially available ethyl 2-fluoroacetoacetate (86) in the presence of methanesulfonic acid or trifluoroacetic acid afforded 88 in yields of 20-40% (Scheme 25). Other research groups have also reported synthesising fluorocoumarins in this manner [61, 62].

In an investigation of novel anti-HIV drug candidates, Xie et al. synthesised 90 by firstly reducing ketone 89 with sodium borohydride to the corresponding methylene derivative (Scheme 26) [63]. Subsequent von Pechmann condensation with ethyl 2-fluoroacetoacetate (86), using boron trifluoride diethyl etherate as a catalyst, afforded dihydroseselin 90 in 66% overall yield.
Scheme 26

α-Fluoro-β-ketoesters are highly versatile substrates and are particularly useful for the synthesis of fluorinated coumarins. Pasceri et al. have developed a novel methodology for the preparation of α-fluoro-β-ketoesters from α-diazo-β-ketoesters [64]. A series of α-diazo-β-ketoesters \(91a-c\) was treated with HBF\(_4\) to furnish α-fluoro-β-ketoesters \(92a-c\) in yields of 51-82% (Table 6). The use of flow chemistry reduced the hazards normally associated with diazo compounds. Addition of α-fluoro-β-ketoesters \(92a-c\) to \(93\) in the presence of trifluoracetic acid afforded fluorocoumarins \(94a-c\) in average to excellent yields.

**Table 6**

Synthesis of 3-fluorocoumarins

<table>
<thead>
<tr>
<th>α-Diazo-β-ketoester</th>
<th>R</th>
<th>Yield (92) (%)</th>
<th>Yield (94) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(91a)</td>
<td>Ph</td>
<td>82</td>
<td>92</td>
</tr>
<tr>
<td>(91b)</td>
<td>2-thienyl</td>
<td>76</td>
<td>83</td>
</tr>
<tr>
<td>(91c)</td>
<td>CH(_2)CH(_2)Ph</td>
<td>51</td>
<td>51</td>
</tr>
</tbody>
</table>
In a similar vein, Jabin et al. adapted the methodology developed by Banks [52] for the preparation of α-fluoro-β-ketoesters as precursors to fluorocoumarins [65]. Ethyl acetoacetate (95) was fluorinated with Selectfluor® in acetonitrile to afford 86 which then underwent von Pechmann condensation with 93 to produce 96 in 84% yield (Scheme 27).

![Scheme 27]

2.6 SYNTHESIS OF FLUORINATED ISOCOUMARINS

Zonov et al. have developed a procedure for the conversion of perfluoroindanones to fluorinated isocoumarins using antimony pentafluoride [66, 67]. Perfluoroindanone 97 was heated to 125ºC in the presence of SbF₅ to produce a pair of isochromenyl salts which underwent hydrolysis to afford two isocoumarins, 98 and 99, isolated in a combined yield of 61% in a ratio of 84:16 respectively (Scheme 28). The authors determined that the reaction is under kinetic control, as when the temperature was elevated to 130ºC and the reaction time extended, isocoumarin 99 was not recovered.
This methodology has also been expanded to include tetralones [68]. Thus, when perfluorinated precursor 100a (R = CF₃) was heated with SbF₅ at 180°C and subsequently hydrolysed, isocoumarin 98 was formed in 72% yield (Scheme 29). Additionally, 100b (R = C₂F₅) was also shown to form 101 in 34% yield under the same conditions.

The TiCl₄-mediated [3+3] cyclisation of 2-fluoro-1,3-diones 102 and 1,3-bis(silyl enol ethers) 103 offers a useful synthetic route to fluorinated isocoumarins (Table 7) [69, 70]. Reaction of 102 with 103 proceeds by an initial Muaiyama-Michael reaction, followed by cyclisation via a Mukaiyama aldol reaction. Subsequent aromatisation by way of an elimination reaction affords fluorinated phenols 104a-d. Demethylation of 104a-d with boron tribromide and addition of a strong base effects lactonisation, furnishing fluorinated isocoumarins 105a-d. This reaction was also successfully carried out with the ethyl ester derivative of 104.
**Table 7**

Synthesis of fluorinated isocoumarins 105a-d

<table>
<thead>
<tr>
<th>Product</th>
<th>R₁</th>
<th>R²</th>
<th>Overall Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>105a</td>
<td>Me</td>
<td>H</td>
<td>91</td>
</tr>
<tr>
<td>105b</td>
<td>Me</td>
<td>Me</td>
<td>84</td>
</tr>
<tr>
<td>105c</td>
<td>nPr</td>
<td>H</td>
<td>47</td>
</tr>
<tr>
<td>105d</td>
<td>nPr</td>
<td>Me</td>
<td>55</td>
</tr>
</tbody>
</table>

2.7 SYNTHESIS OF FLUORINATED FLAVONES AND CHROMONES

As part of their ongoing efforts into the synthesis of novel heterocycles, Médebielle et al. have developed a one-pot aldolisation-intramolecular S_N_Ar process for the preparation of fluorinated flavones and quinolinones [71]. The first step involves bis-chlorodifluoroacetylation of N,N-dimethyl-1-naphthylamine (106) to afford key intermediate 107 in 75% yield (Scheme 30). Addition of TDAE (tetrakis(dimethylamino)ethylene) to 107 and eight equivalents of a suitable aromatic aldehyde results in the formation of fluorinated flavone products 108a-d in yields ranging from 18% to 68% (Table 8).
Scheme 30

Table 8

Preparation of fluorinated flavones from 107

<table>
<thead>
<tr>
<th>Product</th>
<th>Ar</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>108a</td>
<td>Ph</td>
<td>65</td>
</tr>
<tr>
<td>108b</td>
<td>4-F-C₆H₅</td>
<td>68</td>
</tr>
<tr>
<td>108c</td>
<td>3-pyridinyl</td>
<td>52</td>
</tr>
<tr>
<td>108d</td>
<td>3,4-dimethoxyphenyl</td>
<td>18</td>
</tr>
</tbody>
</table>
The authors propose that the reaction proceeds by reduction of 107 by TDAE to the bis-enolate, followed by reaction with the aldehyde to form a bis-alkoxide (Scheme 31). This is accompanied by an intramolecular nucleophilic aromatic substitution and elimination of a dimethylamide anion. The strongly basic dimethylamide induces elimination of HF to furnish the desired target 108.

Scheme 31

Selective electrochemical fluorination is an efficient tool for the synthesis of fluorinated organic compounds. Hou et al. carried out a number of anodic fluorination experiments on several flavones [72]. Using a platinum electrode in anhydrous acetonitrile with Et$_3$N.3HF as the supporting electrolyte, substrates 109a-c were transformed to their fluorinated derivatives 110a-c in yields ranging from 19% to 62% (Table 9). The reaction was found to be dependent on temperature, with higher yields recorded when the reaction temperature was increased from room temperature to 30°C. While Et$_3$N.3HF led primarily to the desired 3-fluorinated product, use of Et$_3$NF.4HF as the supporting electrolyte resulted in the formation of 2,3-difluorinated products predominantly. In the paper, the authors note that 110a could also be
prepared by the reaction of 109a (R = H) with N-fluoropyridinium chloride in methylene chloride, albeit in a lower yield than their electrochemical fluorination methodology (21% vs. 43%).

Table 9
Influence of substituents and temperature on the electrochemical fluorination of flavones.

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>110a</td>
<td>H</td>
<td>rt</td>
<td>43</td>
</tr>
<tr>
<td>110a</td>
<td>H</td>
<td>30</td>
<td>58</td>
</tr>
<tr>
<td>110b</td>
<td>CH₃</td>
<td>rt</td>
<td>19</td>
</tr>
<tr>
<td>110b</td>
<td>CH₃</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>110c</td>
<td>Cl</td>
<td>rt</td>
<td>41</td>
</tr>
<tr>
<td>110c</td>
<td>Cl</td>
<td>30</td>
<td>62</td>
</tr>
</tbody>
</table>

Britton et al. have prepared a range of flavone derivatives in order to evaluate their potential as anti-prostate cancer agents [73]. They successfully incorporated fluorine into 111 using NFSI, affording fluorinated adduct 112 in 37% yield (Scheme 32). Acidification of 112 led to spontaneous cyclisation and elimination of water to furnish fluoroflavone 113 in excellent yield.
Menichincheri *et al.* have adopted a similar approach for the preparation of novel telomerase inhibitors [74]. They report the synthesis of a fluorinated flavone analogue from the reaction of fluorinated propanedione 115 with sulfuric acid, resulting in an 82% yield of the fluorinated chromone 116 (Scheme 33). Fluorine was introduced in the step prior to cyclisation by reaction of diketone 114 with NFSI, resulting in a 28% yield of the fluorinated propanedione 115.
The photocyclisation of 2-halo-1,3-diarylpropan-1,3-diones 117a-b to 3-haloflavones 118a-b is outlined in a paper by Kosmrlj and Sket (Scheme 34) [75]. Irradiation at 352 nm effected photocyclisation of 117a to form 3-fluoroflavone 118a in 55% after two hours. Extending the reaction time to four hours resulted in a quantitative yield of 118a. Photocyclisation of 117b was similarly successful. None of the alternative 3-chloroflavone products was detected, indicating that cleavage of the C-F bond was not an issue under these reaction conditions.
Buchwald et al. have developed a general method for the conversion of aryl triflates to aryl fluorides using Pd-mediated catalysis [76]. In a typical example, triflate 119 reacted with caesium fluoride in the presence of \([(\text{cinnamyl})\text{PdCl}_2]\) and the \(t\text{BuBrettPhos}\) ligand to furnish fluoroflavone 120 in 63% yield along with a small amount (2%) of the defluorinated by-product (Scheme 35).

![Scheme 35](image)

The proposed catalytic cycle is outlined in Scheme 36. A series of mechanistic studies by Grushin et al. had previously highlighted the challenges associated with formation of Ar-F bonds via reductive elimination [77-82]. The \(t\text{BuBrettPhos}\) ligand is crucial to the success of this methodology, as its large size both promotes reductive elimination of the Ar-F bond and also prevents the formation of unwanted dimeric \([\text{LPdAr(F)}]_2\) complexes.

![Scheme 36](image)
Nosova et al. have pioneered the intramolecular nucleophilic substitution of aryl fluorides as a synthetic route to polyfluorinated chromones [83]. The reaction of acyl chlorides 121a-b with acetoacetamides 122a-d at room temperature for 3 hours furnished chromones 123a-f in 63-76% yield (Table 10) [84]. Isothiocyanates may be used in place of acid chlorides affording the desired chromone target 123a in slightly improved yields (73%) [83].

Table 10
Synthesis of polyfluorinated chromones

<table>
<thead>
<tr>
<th>Product</th>
<th>R^1</th>
<th>R^2</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>123a</td>
<td>H</td>
<td>H</td>
<td>69</td>
</tr>
<tr>
<td>123b</td>
<td>H</td>
<td>CH_3</td>
<td>64</td>
</tr>
<tr>
<td>123c</td>
<td>H</td>
<td>H</td>
<td>67</td>
</tr>
<tr>
<td>123d</td>
<td>H</td>
<td>OCH_3</td>
<td>76</td>
</tr>
<tr>
<td>123e</td>
<td>F</td>
<td>CH_3</td>
<td>63</td>
</tr>
<tr>
<td>123f</td>
<td>F</td>
<td>H</td>
<td>68</td>
</tr>
</tbody>
</table>

More recently, a similar approach has been described using β-ketoesters in place of acetoacetamides [85]. Shcherbakov et al. prepared tri- and tetrafluorochromenes via a one-pot synthesis involving the acylation of β-ketoesters 125 with tetra- and penta-fluorobenzoyl chlorides 124 in the presence of magnesium ethoxide (Table 11). The reaction proceeds via the in situ formation of polyfluorinated benzoyl acrylates 126a-c which subsequently undergo
intramolecular nucleophilic aromatic substitution of the ortho fluorine with the hydroxyl group to give chromones 127a-c [86]. Varying the substituents on the β-ketoester had little effect on the yield (Table 11).

**Table 11**
Preparation of polyfluorinated chromones from β-ketoesters

<table>
<thead>
<tr>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>127a</td>
<td>H</td>
<td>Ph</td>
<td>66</td>
</tr>
<tr>
<td>127b</td>
<td>F</td>
<td>Ph</td>
<td>70</td>
</tr>
<tr>
<td>127c</td>
<td>H</td>
<td>Me</td>
<td>68</td>
</tr>
</tbody>
</table>

2.8 SYNTHESIS OF FLUORINATED XANTHONES

In their search for novel mGlu1 receptor enhancers, Vieira et al. synthesised several fluorinated xanthones using a synthetic methodology developed by Horne and Rodrigo [87, 88]. Friedel-Crafts acylation of para-substituted anisoles with 2-fluorobenzoic acid chlorides furnished 2-hydroxy-benzophenones 128a-f (Table 12). Base-induced cyclisation via displacement of fluoride afforded a series of xanthones 129a-f in quantitative yields.
Table 12
Preparation of fluorinated xanthones

<table>
<thead>
<tr>
<th>Product</th>
<th>X</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>129a</td>
<td>F</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>129b</td>
<td>F</td>
<td>H</td>
<td>2-F</td>
</tr>
<tr>
<td>129c</td>
<td>Br</td>
<td>H</td>
<td>3-F</td>
</tr>
<tr>
<td>129d</td>
<td>Br</td>
<td>H</td>
<td>4-F</td>
</tr>
<tr>
<td>129e</td>
<td>Br</td>
<td>5-F</td>
<td>4-F</td>
</tr>
<tr>
<td>129f</td>
<td>Br</td>
<td>3-F</td>
<td>6-F</td>
</tr>
</tbody>
</table>

Woydziak et al. have outlined a synthetic route to fluorinated xanthones starting from a common intermediate 130, which can be prepared in 92% yield from reaction of 2,4,5-trifluorobenzaldehyde and the Grignard derivative of 1-bromo-2,4,5-trifluorobenzene, followed by TEMPO-mediated oxidation (Table 13) [89]. Nucleophilic aromatic substitution of 130 with a range of oxygen and nitrogen nucleophiles afforded a range of symmetrical and unsymmetrical products 131a-i. A reduction in the reaction temperature (entry 3 vs. entry 4) or in the reaction time (entry 7 vs. entry 8) resulted in the formation of pentafluorinated, rather than tetrafluorinated, ketone intermediates (131d and 131h respectively). Heating 131a-i with aqueous sodium hydroxide in a sealed tube at 200ºC effected displacement of fluoride which was followed by cyclisation to the target xanthones 132a-j in good to excellent yields. It is noteworthy that when R\textsuperscript{2} was fluorine, it could be displaced by the hydroxide ion.
through an addition elimination mechanism presumably facilitated by the \textit{para}-ketone, whereas the two remaining fluorines remained intact \cite{90, 91}. Synthesis of the related thioxanthones was also reported in this paper.

**Table 13**

Synthesis of fluorinated xanthones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Temp. (°C)</th>
<th>Ketone</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
<th>Product</th>
<th>R³</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH₂OH</td>
<td>35</td>
<td>131a</td>
<td>NH₂</td>
<td>F</td>
<td>75</td>
<td>132a</td>
<td>OH</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>HNMe₂</td>
<td>60</td>
<td>131b</td>
<td>NMe₂</td>
<td>NMe₂</td>
<td>78</td>
<td>132b</td>
<td>NMe₂</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>HNEt₂</td>
<td>90</td>
<td>131c</td>
<td>NEt₂</td>
<td>NEt₂</td>
<td>85</td>
<td>132c</td>
<td>NEt₂</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>HNEt₂</td>
<td>26</td>
<td>131d</td>
<td>NEt₂</td>
<td>F</td>
<td>70</td>
<td>132d</td>
<td>OH</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>iPrNH₂</td>
<td>60</td>
<td>131e</td>
<td>iPrNH</td>
<td>iPrNH</td>
<td>92</td>
<td>132e</td>
<td>iPrNH</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>tBuNH₂</td>
<td>46</td>
<td>131f</td>
<td>tBuNH</td>
<td>tBuNH</td>
<td>82</td>
<td>132f</td>
<td>tBuNH</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>Piperidine</td>
<td>26</td>
<td>131g</td>
<td>Piperidine</td>
<td>Piperidine</td>
<td>91</td>
<td>132g</td>
<td>Piperidine</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>Piperidine</td>
<td>26</td>
<td>131h</td>
<td>Piperidine</td>
<td>F</td>
<td>76</td>
<td>132h^</td>
<td>OH</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>Morpholine</td>
<td>26</td>
<td>131i</td>
<td>Morpholine</td>
<td>Morpholine</td>
<td>81</td>
<td>132i</td>
<td>Morpholine</td>
<td>83</td>
</tr>
</tbody>
</table>

\(^{\text{reaction time of 3h}}\)

Dodean \textit{et al.} have demonstrated that difluorinated xanthones display higher anti-malarial activity than their non-fluorinated analogues \cite{92}. Treatment of 133 with Selectfluor\textsuperscript{®} provided 2,2-difluoro-1,3-hexanedione which was converted to 134 in 30\% overall yield (Scheme 37). Following elaboration of 134 to afford intermediate 135, monodemethylation
with boron trichloride and subsequent base-induced cyclisation afforded xanthone 136 in a combined yield of 51%.

Scheme 37
3 SYNTHESIS OF SULFUR-CONTAINING HETEROAROMATICS

3.1 SYNTHESIS OF 2- AND 5-FLUOROTHIOPHENES

Directional fluorination of thiophene (137) using elemental fluorine produces a mixture of 2- and 3-fluorinated products. For example, Cerichelli et al. achieved an 86% conversion of thiophene (137) to a mixture of 2-fluorothiophene (138) and 3-fluorothiophene (139) in a ratio of 57:43 (Scheme 38) [93]. Similar reactions with furan and pyrrole proved unsuccessful.

![Scheme 38](image)

One of the earliest reported syntheses of 2-fluorothiophene involved the incorporation of fluorine by reaction of 2-iodothiophene (140) with antimony trifluoride in nitromethane (Scheme 39) [94]. This transformation could be accomplished using 2-iodothiophene, albeit in low yield, but was unsuccessful when using the corresponding chlorinated or brominated substrates.

![Scheme 39](image)

Preferential reaction of electrophiles at the 2-position of thiophene is well established. Regioselective fluorination of the 2-position is generally achieved by the use of electrophilic sources of fluorine [95]. Banks et al. demonstrated that it is possible to deliver electrophilic fluorine using N-fluoroquinoxalinium fluoride (NFQNF) [96]. NFQNF may be prepared in ca. 90% yield by direct, low-temperature, liquid-phase fluorination of quinoxaline using elemental fluorine. Lithium salt 141, prepared from the reaction of thiophene with n-
butyllithium, was refluxed in the presence of NFQNF affording 2-fluorothiophene (138) in 10% yield (Scheme 40).

\[
\begin{align*}
\text{S} & \quad \text{Li} \\
\text{141} & \quad \text{F-Cl} \\
\text{Et}_2\text{O}, 0-20^\circ\text{C} & \quad \text{138} \\
\text{10\%} & 
\end{align*}
\]

**Scheme 40**

Lundbeck reported increased yields for the electrophilic fluorination of thiophene (137) by replacing NFQNF with NFSI as the fluorine source (Scheme 41) [97]. 2-Fluorothiophene (138) was recovered in a 44% yield which represents a significant improvement on previous efforts.

\[
\begin{align*}
\text{S} & \quad n-\text{BuLi}, \text{NFSI} \\
\text{137} & \quad \text{THF or Et}_2\text{O}, -70-0^\circ\text{C}, 1\text{ hr} \\
\text{138} & \quad \text{44\%} 
\end{align*}
\]

**Scheme 41**

Gobbi et al. have developed a novel one-pot preparation of thiophene derivative 143 for potential use as a dual-inhibitor of 5-HT$_{3A}$ and D$_3$ receptors (Scheme 42). Initial *in situ* fluorination of the dilithiated thiophene ring, followed by nucleophilic attack onto aldehyde 142, afforded alcohol 143 in 79% overall yield [98].

\[
\begin{align*}
\text{S} & \quad \text{137} \\
\text{O-K} & \quad \text{142} \\
\text{THF/Hexane, -78^\circ\text{C}} & \quad \text{143} \\
\text{143} & \quad \text{79\%} 
\end{align*}
\]

**Scheme 42**

The use of Selectfluor® is described in a patent on the development of a series thiophene-based matrix metalloproteinase 12 inhibitors 145a-e as potential therapies for the treatment of Chronic Obstructive Pulmonary Disease (COPD) (Table 14) [99]. In related work, Badland et
al. used a similar approach to synthesise additional matrix metalloproteinase 12 inhibitors which have also been incorporated into Table 14 [100].

Table 14

Fluorination of disubstituted thiophene substrates using Selectfluor®

<table>
<thead>
<tr>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>145a</td>
<td>p-CF₃OC₆H₄</td>
<td></td>
<td>41</td>
</tr>
<tr>
<td>145b</td>
<td>CH₃OOC</td>
<td>p-BrC₆H₄</td>
<td>40</td>
</tr>
<tr>
<td>145c</td>
<td>HC(O)</td>
<td>p-CF₃OC₆H₄</td>
<td>30</td>
</tr>
<tr>
<td>145d</td>
<td>CH₃OOC</td>
<td>Br</td>
<td>*90</td>
</tr>
<tr>
<td>145e</td>
<td>HC(O)</td>
<td>Br</td>
<td>*30</td>
</tr>
</tbody>
</table>

*Only % conversions (determined by HPLC) were reported by the authors for these compounds.

Synthesis of 2,3-difluorothiophene substrates has been achieved by way of selective, sequential halide exchange reactions [101]. Treating 2,3-dibromothiophene 146 with 1.3 equivalents of n-butyllithium and NFSI, afforded 2-fluorothiophene 147 in 83% yield (Scheme 43). This monofluorinated intermediate could be transformed into 2,3-difluorothiophene 148 in 80% yield under similar reaction conditions.
Rodmar et al. have demonstrated selective monofluorination at the 2-position of thiophene using perchloryl fluoride, a source of electrophilic fluorine. Treatment of thiophene (137) with ethyllithium in anhydrous ether at gentle reflux, followed by addition of perchlooyl fluoride at -15°C, provided the target compound (138) in approximately 36% yield (Scheme 44) [102].

Scheme 44

Nucleophilic fluorination has also been used in the preparation of 2-fluorothiophenes. Chambers and Marfat reported the displacement of a nitro group from 2-cyano-5-nitrothiophene (149) using potassium fluoride affording 2-cyano-5-fluorothiophene (150) in 63% yield (Scheme 45) [103]. Badland et al. also examined this route, but noted that the volatile nature of nitrile product 150 made scale-up difficult [100].

Scheme 45

The synthesis of 2-fluorothiophenes from bis-aryl-iodonium salts has been pioneered by Onys’ko [104]. This methodology proceeds via a cascade iodination-fluorination where thiophene (137) is initially converted to the bis(2-thienyl)iodonium salt 151 using...
tris(trifluoroaceoxy)-λ3-iodane, an electrophilic source of iodine (Scheme 46). Heating the salt in the presence of dry potassium fluoride furnishes the desired 2-fluorothiophene (138) in 37% yield. It was discovered that conversion to the hexafluorophosphate salt 151 is important as the trifluoroacetate salt leads to only trace amounts of the desired product, while the chloride salt results in formation of 2-chlorothiophene as the major product.

\[ \text{Scheme 46} \]

Expanding on this work, Ichiishi et al. have employed copper catalysts to selectively fluorinate the smaller aromatic ligand in unsymmetrical diaryliodonium salts [105]. The reaction shows broad substrate scope, including electron rich aromatic rings. Accordingly, 152 was converted to 2-fluorothiophene in 42% yield in the presence of copper triflate (Scheme 47). In the absence of the copper catalyst, the selectivity was reversed and mesityl fluoride 153 formed the major product in a 2:98 ratio. The authors postulate that the mechanism proceeds via a Cu(I)/Cu(III) catalytic cycle based on preliminary DFT (Density Functional Theory) calculations.

\[ \text{Scheme 47} \]

Chun et al. have employed diaryliodonium salts as substrates for the incorporation of \(^{18}\)F. While the focus of this work was the synthesis of radiolabelled benzene derivatives, 2-\(^{18}\)F-thiophene (2-\(^{18}\)F-137) was detected, albeit as a minor product in yields of less than 2% (Scheme 48) [106, 107].
As direct fluorination of the thiophene ring is not always possible, methods have also been developed for the introduction of fluorine prior to formation of the aryl ring. Petrov and Marshall have demonstrated how thietane 157 can be converted to 2-fluorothiophene (158) in 65% yield on exposure to activated aluminium powder (Scheme 49) [108]. Thietane 157 was prepared from commercially available 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (155) and 1,1-dimethoxyethylene (158) in the DMF in the presence of caesium fluoride catalyst. When the reaction was conducted in the absence of catalyst, the conversion took over three months to reach completion.

Burger et al. reported the synthesis of a series of 2-fluorothiophenes by way of an apparent 1,5-electrocyclisation process induced by phosphorous pentasulfide [109, 110]. The yields and conditions for these reactions are reported in Table 15. It was observed that higher reaction temperatures and longer reaction times resulted in considerably reduced yields of the 2-fluorothiophene products 161a-f.
Table 15

1,5-Electrocyclic route to 2-fluorinated thiophenes.

<table>
<thead>
<tr>
<th>Product</th>
<th>Ar</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>161a</td>
<td>Phenyl</td>
<td>55</td>
</tr>
<tr>
<td>161b</td>
<td>4-Fluorophenyl</td>
<td>46</td>
</tr>
<tr>
<td>161c</td>
<td>2-Fluorophenyl</td>
<td>32</td>
</tr>
<tr>
<td>161d</td>
<td>4-Chlorophenyl</td>
<td>59</td>
</tr>
<tr>
<td>161e</td>
<td>4-Methoxyphenyl</td>
<td>27</td>
</tr>
<tr>
<td>161f</td>
<td>2,4,6-Trimethylphenyl</td>
<td>30</td>
</tr>
</tbody>
</table>

The mechanistic explanation for this reaction, as proposed by the authors, is shown in Scheme 50. Conversion of α,β-unsaturated ketones 159a-f to β,γ-unsaturated ketone 160a-f is achieved using tin (II) chloride. Complexation of enones 159a-f with tin (II) chloride results in migration of the double bond and loss of fluoride to form the β,γ-unsaturated ketones 160a-f. The ketone then cyclises in the presence of phosphorus pentasulfide via an enethiol intermediate to form 161a-f.
3.2 SYNTHESIS OF 3- AND 4-FLUOROTHIOPHENES

While several methods for selectively fluorinating the 2-position on thiophene have been described in the literature, selective fluorination of the 3-position is more challenging. The most frequently employed strategy involves 2-protected thiophenes, thereby blocking reaction at the 2-position. An early use of this strategy is reported by Taylor and Zhou who prepared 3-fluorothiophene 164 using 2-carboxythiophene (162) as a starting material (Scheme 51) [111]. A standard NFSI fluorination was carried out, which normally would be expected to yield the 2- or 5-fluorothiophene; however under the conditions reported 3-fluorothiophene 164 was generated in 54% yield. This regioselectivity is explained by the authors as being a direct result of intramolecular chelation control of the lithiation step by the carboxylic acid.

![Scheme 51](image)

**Scheme 51**

Rodmar et al. achieved selective fluorination of thiophene at the 3-position by way of lithium-halide exchange [102]. Treatment of 3-bromothiophene (165) with ethyllithium, followed by reaction with perchloryl fluoride, furnished 3-fluorothiophene (139) in approximately 28% yield (Scheme 52).

![Scheme 52](image)

**Scheme 52**
An example of nucleophilic halide displacement as a way of incorporating fluorine can be seen in the work of El Kassmi et al. (Scheme 53) [112]. Chloride 166 is initially converted to fluoride 167 which then undergoes alkaline hydrolysis to furnish 2-carboxyl-3-fluorothiophene (164). Removal of the carboxylic acid group was achieved by heating 164 in the presence of copper dust, forming 3-fluorothiophene (139) in 93% yield.

\[ \text{Scheme 53} \]

An adaptation of the Schiemann reaction was reported as a means of accessing 3-fluorothiophene (139) by Pomerantz and co-workers [113]. Firstly, the diazonium salt 169 was prepared from 3-aminothiophene 168 in 93% yield (Scheme 54). Diazonium salt 169 was then mixed with sand and heated to 160-200°C to form 3-fluorinated thiophene 164 in 84% yield. Basic hydrolysis of the ester, followed by decarboxylation, afforded 3-fluorothiophene (139) in 93% yield.

\[ \text{Scheme 54} \]
Direct fluorination of the 3-position of thiophene is particularly challenging without chelation control or controlled halide-lithium exchange, as outlined above. Li et al. have overcome this obstacle by using gem-difluorohomopropargyl alcohol substrates, of which 171 below is an example (Scheme 55) [114]. Treatment of 171 with methanesulfonyl chloride and triethylamine to form the corresponding mesylate, followed by addition of sodium hydrosulfide, afforded 3-fluorothiophene 172 in 28% overall yield. This methodology has also been applied to the synthesis of 3-fluorofurans.

![Scheme 55](image)

In a similar vein, Hirotaki and Hanamoto have employed 2-bromo-3,3-difluoroallyl sulfides 174a-f with great success in the synthesis of a range 3-fluorothiophenes 175a-f (Table 16) [115]. These difluoroallyl sulfides may be readily synthesised from the S_N2 reaction of 2-bromo-3,3,3-trifluoropropene (173) with various thiols. The resulting difluoroallyls can be transformed into 2-aryl-3-fluoro-5-silylthiophenes in a one-pot synthesis. Yields were highest when chlorotriethylsilane was used as the silylating agent. It was also discovered that addition of triethylamine greatly accelerated cyclisation.

### Table 16

One-pot synthesis of 2-aryl-3-fluoro-5-silylthiophenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Difluoroallyl</th>
<th>Ar</th>
<th>Yield</th>
<th>Thiophene</th>
<th>R</th>
<th>Yield</th>
</tr>
</thead>
</table>

50
Sakamoto reported the synthesis of perfluorinated thiophene 181 using a series of Pd-mediated couplings (Scheme 56) [116]. 3,4-Dibromo-2,5-trimethylsilylthiophene (176) was converted to the difluoro compound 177 by initial formation of the lithium salt and subsequent fluorination with NFSI. 177 was then converted to the tributylstannane 183 via 182, both of which were subsequently used in later Stille coupling reactions. Conversion of 177 to dibromothiophene 178 and subsequent reaction with two equivalents of n-butyllithium, followed by treatment with both NFSI and tributylstannane chloride, yielded 179. 179 was coupled to 182 and then treated with N-bromosuccinimide in acetic acid to afford the 2-thienylthiophene 180. Lastly, 180 underwent an additional coupling reaction with 183 to furnish the perfluorinated polythiophene 181.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>(%)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>174a</td>
<td>Ph</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>174b</td>
<td>Ph</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>174c</td>
<td>Ph</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>174d</td>
<td>Ph</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>174e</td>
<td>p-C6H4Me</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>174f</td>
<td>p-C6H4OH</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>174g</td>
<td>p-C6H4OMe</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>174h</td>
<td>o-C6H4Cl</td>
<td>79</td>
</tr>
</tbody>
</table>
Andrés et al. accessed a range of α-carboxy-γ-fluorothiophenes 186a-g via reaction of two equivalents of methyl or ethyl thioglycolate anion 185 with a variety α-fluoroenones or α-fluoroenals 184 [117]. The yields varied from 41% to 85%, as summarised in Table 17. Formation of the cyclic product was not successful when only one equivalent of the thioglycolate anion was employed.
Table 17

Synthesis of α-carboxy-γ-fluorothiophenes

<table>
<thead>
<tr>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>186a</td>
<td>Me</td>
<td>H</td>
<td>Et</td>
<td>73%</td>
</tr>
<tr>
<td>186b</td>
<td>Me</td>
<td>Me</td>
<td>Et</td>
<td>54%</td>
</tr>
<tr>
<td>186c</td>
<td>Ph</td>
<td>Me</td>
<td>Et</td>
<td>85%</td>
</tr>
<tr>
<td>186d</td>
<td>H</td>
<td>Me</td>
<td>Et</td>
<td>41%</td>
</tr>
<tr>
<td>186e</td>
<td>H</td>
<td>t-Bu</td>
<td>Et</td>
<td>44%</td>
</tr>
<tr>
<td>186f</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>71%</td>
</tr>
<tr>
<td>186g</td>
<td>Ph</td>
<td>Me</td>
<td>Me</td>
<td>79%</td>
</tr>
</tbody>
</table>

3.3 SYNTHESIS OF PERFLUOROTHIOPHENES

Base-induced elimination of HF from fluorinated thiolane constitutes a short route to tetrafluorothiophenes. An early example is described by Burdon et al [118, 119]. Aqueous potassium hydroxide was not sufficiently reactive to effect aromatisation of hexafluorinated thiolane 187 – only on treatment with molten potassium hydroxide was 188 formed, albeit in a low yield of 10% (Scheme 57).

![Scheme 57](image)
In their search for novel fumigants, the Dow Chemical Company patented a method of synthesising tetrafluorothiophene 188 from polyhalogenated substrate 189, as shown in Scheme 58 [120]. The yields and intermediates in this route are not elaborated upon in the patent.

![Scheme 58](image)

An alternative route to 188 has been developed by Lemal et al. from a different starting point [121]. Reaction of commercially available diol 190 with tosyl chloride in pyridine afforded ditosylate 191 in 94% yield (Scheme 59). Subsequent cyclisation with sodium sulfide in dimethylformamide furnished 3,3,4,4-tetrafluorothiolane (192). Tetrafluorothiolane 192 then underwent tandem fluoro-Pummerer rearrangement on treatment with Selectfluor® in sulfolane to afford the hexafluorothiolane 193 as a mixture of cis- and trans-isomers. Sulfolane is sufficiently polar to dissolve Selectfluor®, but is non-nucleophilic and consequently does not compete for the electrophilic intermediates generated during the fluoro-Pummerer rearrangement. The proposed mechanism for the monofluorination step is outlined in Scheme 60.

![Scheme 59](image)

cis,trans 1.5:1
Interestingly, if only one equivalent of Selectfluor® is used in the penultimate step, pentafluorinated compound 194 is isolable and can be converted to 2,3,4-fluorothiophene (195) by reaction with potassium hydroxide in DMSO as shown in Scheme 61.

3.4 SYNTHESIS OF FLUORINATED BENZOTHIOPHENES

Few examples exist in the literature for the synthesis of fluorinated benzothiophenes to date. Fluorination of the 2-position of benzothiophene (196) is described in a 2007 patent on the development of substituted piperidines as potential renin inhibitors by Ehara et al., using the
familiar combination of n-butyllithium and NFSI (Scheme 62). No yields are reported for this reaction [122].

![Scheme 62](image)

**Scheme 62**

Ichikawa et al. synthesized 2-benzothiophene 201 by way of a 5-endo-trigonal cyclization, in an approach analogous to that reported earlier for benzofurans [39]. A methylsulfinyl group was introduced into aniline 198 via initial diazotization, followed by nucleophilic addition of sodium methylsulfide, affording 199 in 67% yield over two steps. Oxidation of 199 to sulfoxide 200 was carried out using hydrogen peroxide and titanium (III) chloride in 83% yield. Successive treatment of 200 with (i) trifluoroacetic anhydride and Et3N and (ii) K2CO3 in MeOH provided 2-fluorobenzo[b]thiophene 201 in 82% yield (Scheme 63).

![Scheme 63](image)

**Scheme 63**

As part of an investigation by Gorelsky et al. into palladium-catalysed arylation reactions, 3-fluorobenzothiophene was prepared from 3-bromobenzothiophene (202) using a LiCl-mediated Grignard reaction [123]. The reaction proceeds by way of a modified Grignard intermediate 203, followed by reaction with NFSI, to afford 3-fluorobenzothiophene (204) in
29% yield (Scheme 64). Addition of lithium chloride generally results in higher yields and greatly increased rates of formation of the Grignard intermediates [124].

Brooke has described the synthesis 4,5,6,7-tetrafluorobenzothiophene (207) by way of an intramolecular nucleophilic aromatic displacement of fluorine by sulfur as shown in Scheme 65 [125]. Initially, ketone 205 reacts with hydrogen sulphide and hydrogen chloride in 95% ethanol to yield gem-thiol 206 in 56% yield. Thiol 206 is subsequently refluxed in dry pyridine in the presence of a catalytic amount of potassium hydroxide affording target compound 207 in 87% yield. While unsure of the specific mechanism by which the potassium hydroxide catalyses the reaction, the authors report that in the absence of same a diminished yield of 47% is obtained.

Castle et al. reported the synthesis of benzothiophene 207 starting with rhodanine (209) and pentafluorobenzaldehyde (208) (Scheme 66) [126]. 208 and 209 were stirred in an aqueous solution of ammonium hydroxide to yield benzylidine 210 in 74% yield. Hydrolysis of 210 with sodium hydroxide generated the thiolate-carboxylate dianion intermediate, which subsequently underwent intramolecular cyclisation to form 4,5,6,7-tetrafluorobenzo[b]thiophen-2-carboxylic acid (211) in 69% yield. Finally, decarboxylation with copper-quinoline furnished 207 in 62% yield.
Fluorinated benzothiophenes may also be accessed by intramolecular nucleophilic aromatic displacement of fluorine by a carbanion [127]. Initially, treatment of 212 with $n$-BuLi generates the thiolate anion which undergoes Michael addition with 213 to form diester 214 in 50% yield (Scheme 67). Acid-mediated ester hydrolysis, followed by decarboxylation over copper-quinoline, furnishes 207 in 89% yield.
An analogous approach was employed in the synthesis of naphthothiophene 219 (Scheme 68) [128]. Michael addition of the anion of 216 to 217 afforded diester 218 in quantitative yield as the major regioisomer (92:8). Subsequent hydrolysis and decarboxylation produced naphthothiophene 219 in 57% yield.

Scheme 68

Related perfluorinated dibenzothiophenes have been synthesised by Chambers et al. (Scheme 69) [129]. Addition of two equivalents of n-BuLi to a mixture of 220 and 221 generated aryne 222 and thiolate 223 respectively. Nucleophilic addition of the thiolate to the aryne, followed by intramolecular cyclisation, resulted in a 70% yield of dibenzothiophene 224.

Scheme 69

4 CONCLUSIONS

As demonstrated in this review, several successful strategies have been employed to access fluorinated oxygen- and sulfur-containing heteroaromatics. Many selective methods have been developed for direct incorporation of fluorine into oxygen-containing heterocycles; however, it is also evident that some targets can only be accessed indirectly, using fluorinated substrates to access fluorinated heteroaromatic compounds.
Comparatively fewer procedures are present in the literature for the fluorination of sulfur-containing heterocycles in comparison to their oxygen analogues. This is, perhaps, a reflection of the greater level of interest in oxygen-based heteroaromatic targets.

In conclusion, a systematic review of the methods for accessing fluorinated oxygen and sulfur containing heterocycles has been presented which complements existing reviews in this area. The work presented here will be of broad interest to fluoroorganic chemists and those working in the field of heterocyclic synthesis.

ACKNOWLEDGMENTS

FPO’D would like to acknowledge the Irish Research Council for funding. DJJ would like to acknowledge University College Cork Strategic Research Fund for funding.
REFERENCES