C-F bond formation

Organofluorine chemistry has a wide variety of applications, from the manufacture of pharmaceuticals and agrochemicals through to polymers and fuel cells. The presence of fluorine atom(s) in an API can provide beneficial effects through increased efficacy, due to for example improved metabolic stability; lipophilicity and/or improved bioavailability through changes to its pK$_\text{a}$.[1] Although fluorination remains a critical technology for the pharmaceutical industry, very little is done in house – at least in process and manufacturing.[2]

In 2015 members of the CHEM21 project, Harsanyi and Sandford, based at Durham University published a perspective for the Green Chemistry Journal on fluorine sources, applications and sustainability.[3]

Organofluorine compounds are extremely rare in nature, and therefore the construction of carbon-fluorine bonds requires the use of synthetic fluorinating agents. The range of fluorinating agents used in chemical synthesis (see Figure 1) are ultimately all derived from the mineral fluorospar (CaF$_2$) which is used to make anhydrous hydrogen fluoride (aHF), (see Figure 1).[3]
There is a threat to the long term sustainability of organofluorine chemistry, as estimated reserves of fluorospar are set to last for approximately only another one hundred years. Therefore alternative sources of fluorine need to be explored. One route that has been suggested is the exploitation of a byproduct of the fertiliser industry ‘fluorosilic acid’, which is formed during the production of phosphoric acid from widely abundant phosphate rock.[3]

2. Fluorination key challenge in API synthesis (Last accessed: ).

Fluorinating agents

Fluorinating agents are, by their inherent highly reactive nature, not generally regarded as green or sustainable due to associated hazards and toxicity issues. However modern alternatives are being developed alongside safer handling techniques that facilitate safer halogenation reactions, with minimal impact on the environment.\[1\] Table 1 provides a summary of the main advantages and disadvantages of various fluorinating agents.\[1\]

<table>
<thead>
<tr>
<th>Fluorinating Agent</th>
<th>What is it used to fluorinate?</th>
<th>Why is it green? Advantages</th>
<th>Why is it not green? Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elemental Fluorine</td>
<td>Carbonyl compounds</td>
<td>Excellent atom economy</td>
<td>Highly reactive, toxic</td>
</tr>
<tr>
<td></td>
<td>Aromatics</td>
<td></td>
<td>Specialist handling needed</td>
</tr>
<tr>
<td></td>
<td>C-H bonds</td>
<td></td>
<td>Often generate HF byproducts</td>
</tr>
<tr>
<td>HF</td>
<td>Halide Displacements (S_N2)</td>
<td>Excellent atom economy</td>
<td>Extremely corrosive and hazardous</td>
</tr>
<tr>
<td>Fluoride Salts (e.g. KF, CsF)</td>
<td>Halide Displacements (S_N2)</td>
<td>Safe and easy to handle</td>
<td>Very hygroscopic but often needs to be dry for good reactivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excellent atom economy</td>
<td>Few by-products produced</td>
</tr>
</tbody>
</table>


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</thead>
<tbody>
<tr>
<td>N-F Reagents (e.g. Selectfluor, NFSI)</td>
<td>Carbonyl Compounds, Aromatics, Alkenes, Thioethers, Organometallic reagents (e.g. organotin)</td>
<td>Safe and easy to handle, Low toxicity</td>
<td>Derived from elemental fluorine, Expensive, Amine waste generated</td>
</tr>
<tr>
<td>Ruppert Reagent (CF$_3$SiMe$_3$)</td>
<td>Carbonyl compounds (nucleophilic), Aromatics</td>
<td>Safe and easy to handle</td>
<td>Silicon-containing waste generated, Expensive</td>
</tr>
<tr>
<td>Electrophilic trifluoromethylation reagents (e.g. Togni)</td>
<td>Carbonyl compounds (electrophilic), Aromatics, Alkenes, Alcohols/sulfides</td>
<td>Few other ways of doing many of these transformations</td>
<td>Iodoarene waste generated, Expensive, Reports of explosions</td>
</tr>
<tr>
<td>DAST / SF$_4$</td>
<td>Alcohol → CF, Carbonyl → CF$_2$</td>
<td>Few other ways of doing many of these transformations</td>
<td>Corrosive, Explosive byproducts at high temperatures</td>
</tr>
<tr>
<td>Fluoroform (CHF$_3$)</td>
<td>Carbonyl compounds</td>
<td>Using byproduct of Teflon production which otherwise needs to be disposed of</td>
<td>Very potent greenhouse gas, Normally incinerated producing H$_2$O, CO$_2$, HF</td>
</tr>
</tbody>
</table>

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</thead>
<tbody>
<tr>
<td>Trifluoroacetate Salts</td>
<td>Aromatics</td>
<td>CO₂ is only byproduct produced on decarboxylation</td>
<td>CO₂ is greenhouse gas</td>
</tr>
<tr>
<td></td>
<td>Carbonyl compounds</td>
<td></td>
<td>Produced using corrosive HF</td>
</tr>
</tbody>
</table>

Table 1: Advantages and disadvantages of range of fluorinating agents. Reproduced from [1] with permission from The Royal Society of Chemistry.


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This case study was provided by Prof. Graham Sandford from the Centre of Sustainable Processes at Durham University.

Although many pharmaceutically relevant molecules contain fluoro- or trifluoromethyl-aromatic functionalities, drug development now has evolved to require chemical entities that contain fluorine functionality at unaccessible sites and thus there continues to be a demand for the development of efficient, selective and economically viable methods for fluorination on industrial scale.[1][2][3][4]

Large scale manufacture of fluorinated compounds are carried out using expensive anhydrous hydrogen fluoride (aHF). However, the highly corrosive nature of this reagent limits fluorination reactions to structurally simple organic substrates, which have to be pre-functionalised with nitro- or chloro- groups through multistep procedures.[5] Ideally, the most efficient and direct way of achieving fluorination on large scale would be the selective conversion of a carbon-hydrogen bond to a carbon-fluorine bond using inexpensive fluorine gas.[6] Despite the recent advances seen in selective fluorination methods for both batch and flow processes, the use of fluorine gas for life science product manufacture has thus far been limited to the production of 5-fluoracil[7] as well an intermediate in the synthesis of Voricanazole (V-Fend, Pfizer).[8]

2-Fluoromalonate esters represent a class of potentially versatile building blocks for the synthesis of fluorinated compounds; various alkylations,[9] Michael additions,[10][11][12] and heterocycle formation reactions[13][14] have been reported for them, which gives a good indication of their utility in organic synthesis. There are three reasonable, low-cost synthetic strategies available for large scale manufacture of diethyl 2-fluoromalonate; the reaction of ethanol with hexafluoropropene (HFP),[15] halogen exchange (Halex)[16] and a selective direct fluorination process[17] (Scheme 1).
CHEM21 researchers have assessed and optimised the direct fluorination of diethyl malonate, catalysed by copper nitrate in flow, with the goal of intensifying the transformation and reducing its environmental impact. The optimised system for the selective fluorination process is shown in Scheme 2 and was applied successfully to related malonate esters in excellent yields.[13]

The CHEM21 researchers went further and investigated the green metrics of the optimised direct fluorination process as well as the other two approaches shown in Scheme 1. The group applied the CHEM21 metric toolkit [18] at first pass to all three approaches, the results for which are shown in Table 1.
The resultant metrics for the direct fluorination approach shows low material intensity with a PMI value of below 10, and other green metrics for this approach compare favourably with those of the HFP and Halex method in terms of environmental impact. These results demonstrate that the new optimised direct fluorination approach serves as an excellent benchmark figure for an efficient, effective and environmentally benign approach to the synthesis of fluoromalonates.


9. J. Dubois, C. Fourès, S. Bory, S. Falcou, M. Gaudry and A. Marquet, Synthesis of 5,5′-dihydroxyoxoacene and 4-fluoro 5,5′-dihydroxyoxoacene, the reduction products of 4-carboxyglutamic and 4-carboxy-4-fluoroglutamic acids, Tetrahedron, 1991, 47, 1001-1012.


Summary and further reading


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Advances are being made in