

HALO-ORGANICS

Fully functional fluorine

Dr Joel Swinson, senior research chemist at Halocarbon Products, looks at the advantages of using fluorinated intermediates in the life sciences

Nature makes very few compounds that contain fluorine. This is partly a result of the lack of free fluoride ions in the environment when compared to chloride; bacteria have evolved preferentially to incorporate that instead. Fluorine is also difficult to oxidise as a result of its high redox potential, which cuts out the use of a biosynthetic route analogous to the one bacteria generally use to introduce chloride.

However, fluorine's chemical properties mean that it is a common feature in synthetic active molecules, for both agrochemicals and pharmaceuticals. On the agro side, the three main classes of products – herbicides, insecticides and fungicides – all have many examples of active molecules that contain fluorine, including some of the most widely used products

Among the herbicides, diflufenican is a nicotinamide that acts by inhibiting carotenoid biosynthesis and contains five fluorines – two as phenyl substituents and a trifluoromethyl group. Fluroxypyr is a pyridine herbicide with a fluorine atom at the *ortho* position of the pyridine ring, while trifluralin is a dinitroaniline herbicide with an aromatic trifluoromethyl group.

Numerous common fungicides also contain fluorine atoms. Flusilazole is a triazole fungicide with a silicon atom at its core and two *para*-fluorophenyl groups attached to the silicon. Flutriafol also has two fluorophenyl groups, one with an *ortho* fluorine atom and the other with *para* substitution. Fludioxonil, commonly used as a seed treatment, has a difluoromethylene unit connecting two oxygen atoms on a benzene ring. The pyridines fluzinam and fluopicolide have trifluoromethyl groups attached to their cores.

Insecticides are well represented in the organofluorine universe too. λ -cyhalothrin is a pyrethroid ester insecticide with a vinyl trifluoromethyl group. Diflubenzuron has a pair of *ortho*-fluoro phenyl substituents. Numerous analogues have different fluorination patterns, such as triflumuron, with a trifluoromethoxy group, and hexaflumuron, which retains diflubenzuron's two aromatic fluorines and also has a 1,1,2-difluoroethyl group. Fipronil – commonly used to kill fleas on household pets – has two trifluoromethyl groups, one as a *para*-phenyl substituent, and the second as a trifluoromethyl sulfinyl unit

Around 20% of all the drugs on the market contain at least one fluorine atom, including three of the current top ten biggest selling medicines. Indeed, the world's current biggest selling drug, Pfizer's Lipitor (atorvastatin) has an aromatic fluorine atom. Two of the other big-selling cholesterol-lowering statin drugs also contain fluorine. Just like Lipitor, Lescol (fluvastatin) and Crestor (rosuvastatin) both have *para*-fluorophenyl groups.

As with the agrochemical fungicides, many antifungal medicines contain fluorine. Fluconazole – Pfizer's Diflucan – has two aromatic fluorines on one benzene ring, and Uriach's Micetal (flutrimazole) has two fluorines on separate phenyl groups. Fluorine also

features in Roche's antiprotozoal medicine Lariam (mefloquine), which is used to prevent and treat malaria.

Fluorine is a common element in antibiotic molecules, too. One of the biggest sellers in recent years – Bayer's Cipro (ciprofloxacin) has an aromatic fluorine substituent, as has norfloxacin (Noroxin from Dainippon) and levofloxacin (Levoquin), Ortho McNeil's single isomer version of the older drug ofloxacin.

A fourth class where fluorines are prevalent is the Cox-2 inhibitors, currently the focus of much regulatory attention because of their side effect problems. These anti-inflammatory drugs are designed to treat rheumatoid arthritis, and Pfizer's two drugs celecoxib (Celebrex) and valdecoxib (Bextra) both have trifluoromethyl units.

Fluorine has become a popular feature in drugs and agrochemicals because of the effects it exerts in molecules. The discovery process frequently involves taking a molecule that has some activity and modifying it to alter its properties – to make it more active, to increase its binding at a receptor or even to increase its bioavailability. Incorporating fluorine atoms is a great place to start.

Fluorine makes a good hydrogen mimic. Despite the fact that the atoms are larger, with a van der Waals radius of 1.35Å compared to 1.1Å for hydrogen, the additional steric demand of fluorine at receptor sites is minimal.¹ As the bond length between carbon and fluorine is not much greater than that between carbon and hydrogen, there is little change to the molecule's steric bulk either.

Electronically, though, the two atoms are totally different. Fluorine is the most electronegative of all the elements. It pulls electrons towards it, thus reducing the electron density at the carbon in a C-F bond. This also increases the acidity of nearby acid functionalities and the acidity of protons attached to the same carbon as the fluorine. It also affects the molecule's dipole moment and the molecule's overall stability.

Fluorine makes a good alternative to oxygen too. The van der Waals radius of oxygen is 1.40Å, so it makes little change to the size. Their electronegativities are similar too, 3.5 for oxygen and 4.0 for fluorine. The fluorine in fluoroalkanes and fluoroalkenes is isoelectronic to the oxygen in the corresponding alkanols and alkenols, giving a useful isosteric effect.

An alternative replacement for oxygen is a difluoromethylene unit. Here, the fluorines sit in the same place as the lone pairs would on oxygen, so it is still able to form hydrogen bonds. However, the C-C bonds are much stronger than the C-O ones would be, imparting increased stability to the molecule while retaining much of its steric and electronic character.

One of the most dramatic effects that the inclusion of fluorine substituents has is on lipophilicity. Fluorine substituents can greatly increase the fat solubility of molecules, which is particularly important in pharmaceuticals where it can increase their bioavailability. Including more fluorines amplifies the effect – the trifluoromethyl group is one of the most lipophilic known and is a regular feature in both drug and agrochemical actives.

Whilst numerous fluorinating reagents have been introduced in recent years, fluorination remains expensive, dangerous, difficult or all three. The simplest fluorinating reagents – F₂ and HF – are both extremely toxic and, because one is a gas and the other boils at ambient conditions, far from trivial to work with.

They are also an extremely unappealing prospect on a commercial manufacturing scale, as they pose significant containment challenges. Modern reagents are designed to be easier to handle, but are much more expensive, and can still be difficult to use. The fluoride in hydrogen fluoride behaves as a nucleophile, and many of the common reagents are sources of nucleophilic fluoride ions.

A good example is (diethylamino)sulfur trifluoride (DAST). This was developed by DuPont in the 1970s as an alternative to sulfur tetrafluoride, which is toxic and requires high temperatures and pressures to react. One of the fluorines was replaced with a diethylamine group and the result was a fluorinating reagent that will replace both hydroxyl and carbonyl oxygens with fluorine.

Another familiar nucleophilic fluorinating reagent is tetrabutylammonium trifluoride, (TBAF). It will replace good leaving groups such as tosylates and bromides with fluorine by nucleophilic substitution.

Electrophilic substitutions are more challenging. Whilst F₂ can behave as an electrophile, it is far too dangerous to be considered a routine reagent. Acetyl hypofluorite can be used to fluorinate enolisable β-diketones and β-diketoesters. Various pyridine derivatives have been created with N-F bonds that act as electrophilic fluorinating reagents. If electron-withdrawing substituents are introduced on the pyridine ring, this serves to increase the fluorine's reactivity.

Trifluoromethyl groups are common features in drug and agrochemical actives, but introducing them directly is not simple. There are few reagents that can add a trifluoromethyl group, and the one that is most common – CF₃-TMS or Ruppert's reagent – is now difficult to make because its fluorinated starting material, trifluoromethyl iodide, is frowned upon by the Montreal Protocol.

Because selective fluorination poses so many synthetic challenges, other strategies to create fluorinated molecules are clearly needed. Whether the active is an agrochemical or a pharmaceutical, the simplest and safest way to construct the molecule frequently involves the use of a commercially available fluorinated intermediate, such as those supplied by Halocarbon.

With these, the fluorination has already been carried out, and the intermediates can be used as building blocks to create more complex molecules with fluorine substituents. For example, numerous insecticides, including cyhalothrin, contain a vinyl trifluoromethyl group. This can be made using the intermediate 1,1,1-trichlorotrifluoroethane to introduce the trifluoromethyl group. Several different synthetic routes are possible.

One synthesis begins with the copper(I) chloride-catalysed addition of the fluorinated intermediate to ethyl-3,3-dimethyl-4-butenoate, as shown in Figure 1.² The adduct is treated with base to close the cyclopropane ring and eliminate hydrogen chloride to form the double bond. This route usually gives a mixture of *cis* and *trans* isomers, but careful choice of base can direct the synthesis.

An alternative which ensures only one isomer – the *trans* form – is isolated involves the carbonyl addition of a zinc carbenoid formed from the intermediate (Figure 2).³ The adduct is acetylated and then reduced with zinc dust, resulting in the desired cyclopropyl ester. The alternative *cis* isomer adduct forms as a lactone and so is simple to separate from the *trans* product.

Sumitomo Chemical has used ethyl trifluoroacetoacetate in the synthesis of pyridazine herbicides that are effective against a wide variety of weeds.⁴ A substituted aniline is first diazotised and the resulting derivative is reacted with ethyl trifluoroacetoacetate in the presence of sodium acetate. The ester group is then removed to give the required trifluoromethyl compound (Figure 3).

Trifluoroacetic anhydride is a particularly useful intermediate, especially for making drug molecules. An example is the selective human leukocyte elastase inhibitor ICI-200,880, which is based on a tripeptide backbone and has a trifluoromethyl ketone unit at its N terminus.

One way of creating the fluorinated part of the molecule starts with trifluoroacetic anhydride, which is reacted with an oxazolidinone. The resulting cyclic adduct is then treated with oxalic acid, giving the required N-protected fluorinated fragment ready for coupling with the rest of the peptide (Figure 4).⁵

Other potential syntheses use trifluoroacetaldehyde or Me₃Si-CF₃ catalysed by TBAF. Trifluoroacetaldehyde is a very useful building block, as it can be reacted with numerous different reagents including olefins, dienes, ketene silyl acetals, metal enolates and a variety of aromatic compounds. However, it is often much easier to use it in a hemiacetal form instead.

This is precisely the strategy employed by a group at Gifu University in Japan, who found that trifluoroacetaldehyde required high temperatures or an excess of concentrated sulfuric acid to make their reactions work.⁶ They started with the ethyl hemiacetal, and generated the free aldehyde from it *in situ* under very mild conditions. When this was mixed with an enamine at room temperature, the result was a β-hydroxy-β-trifluoromethyl ketone, with no need for any additives in the reaction mixture. The reaction could be carried out in either toluene or hexane as solvent.

A final example involves the synthesis of a range of trifluoromethyl amino acid derivatives.⁷ Amino acids are commonly used as building blocks in the synthesis of a variety of active molecules, so unnatural amino acids that contain trifluoromethyl groups have huge potential for the creation of fluorinated analogues. 3,3,3-trifluoropropene can be used to make both 4,4,4-trifluorovaline and 5,5,5-trifluoronorvaline, as shown in Figure 5.

The alkene is first converted into an aldehyde, where the trifluoromethyl group is in either the 2 or 3 position, using a cobalt-catalysed regioselective hydroformylation. If the aldehyde is then treated with acetamide, carbon monoxide and hydrogen and subsequently deprotected, the result is the fluorinated amino acid.

These are just a handful of examples of how fluorinated intermediates can be used to create active molecules that contain fluorine functionality. As chemists continue to include

fluorine in their agrochemical and pharmaceutical targets, the importance of fluorination – and the range of readily available fluorinated intermediates – is sure to grow in future.

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Figure 1 - Cu(I) chloride-catalysed addition of fluorinated intermediate to ethyl-3,3-dimethyl-4-butenolate

Figure 2 - Carbonyl addition of zinc carbenoid formed from fluorinated intermediate

Figure 3 – Use of ethyl trifluoroacetoacetate in synthesis of trifluoromethyl compound

Figure 4 – Fluorination of ICI-200,880

Figure 5 – Use of 3,3,3-trifluoropropene in 4,4,4-trifluorovaline & 5,5,5-trifluoronorvaline