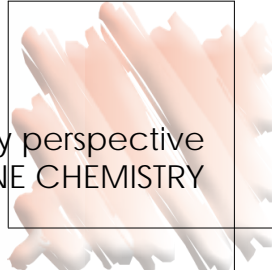




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# The Trifluoromethylgroup

## An overview of available synthetic methods at Solvias AG

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**ABSTRACT** This overview highlights some available methods for the introduction of a CF<sub>3</sub>-group into a molecule on laboratory and industrial scale. Thus, methods relying on transfer reagents for the nucleophilic and electrophilic trifluoromethylation are being discussed, while also industrial applicable efficient methods focusing on functional group inter-conversion are being highlighted.

### INTRODUCTION

Fluorinated molecules are increasingly used in the pharma and crop protection industry. This is due to the fact that strategically placed fluorine atoms often have a positive influence on the biological properties of active compounds (1). Figure 1 and Figure 2 are summarizing some of the best selling prescription drugs and agrochemicals containing Fluorine either as Aryl/Alkyl-F or -CF<sub>3</sub>, -SCF<sub>3</sub>, -OCF<sub>3</sub> functional groups.

For this reason synthetic methods for the selective preparation of specifically fluorinated intermediates and building blocks are of high importance (2).

This articles will summarize some of the most important and relevant methods for the introduction of a trifluoromethyl-group into a molecule applied on laboratory and industrial scale. Special emphasis will be given to industrial relevance and cost effective methods, while for sake of completion transfer reagents

(electrophilic and nucleophilic), which are more relevant on laboratory scale, will be discussed briefly as well. Especially, new developments in this area will be highlighted as they might find application on industrial scale in the near future.

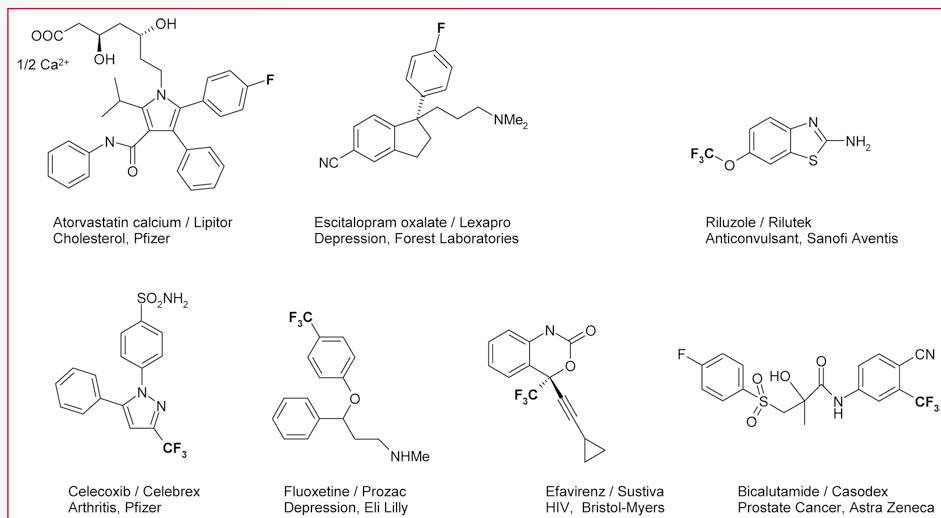


Figure 1. Fluorine containing active pharmaceutical products.

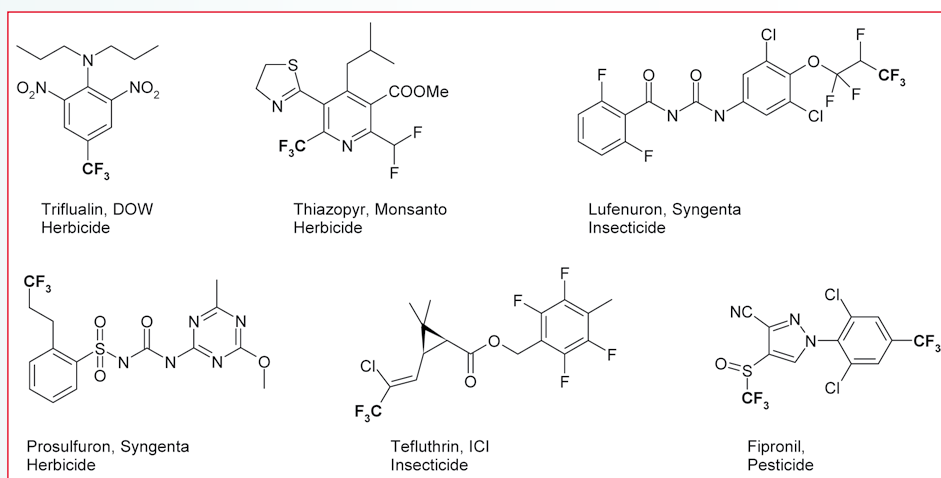


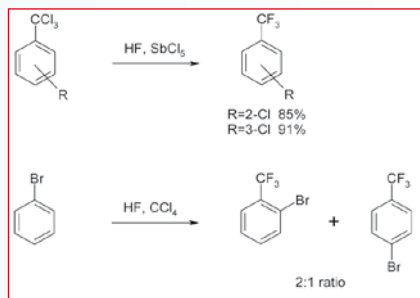
Figure 2. Fluorinated agrochemicals.



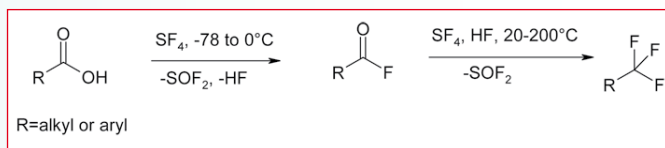
### Electrophilic trifluoromethylation

This interesting area is based on work by Yagupol'skii and was further developed by Umemoto who designed tunable electrophilic trifluoromethylation reagents as depicted in Figure 4 (8). These trifluoromethylchalcogenium salts (oxonium, sulfonium, selenium, telluronium) reagents are effective for the CF<sub>3</sub> group transfer to carbanions, enolates, enol ethers and other electron rich species (scheme 2). Recent progress in this area was made by Togni who succeeded in the development of a new family of hypervalent iodine compounds showing promising potential for the trifluoromethylation of several types of nucleophiles (9). In particular, promising results were obtained with β-keto ester, silyl enol ether, silyl ketene acetal and α-nitro ester, which represent novel examples of C-C bond forming process.

It is worth mentioning that electron rich aromatic systems can undergo direct trifluoromethylation of the aromatic ring using some of the reagents developed by Umemoto.



Scheme 3. Halogen exchange reaction for the synthesis of Ar-CF<sub>3</sub>.



Scheme 4. Reaction mechanism of sulfur tetrafluoride with carboxylic acids.

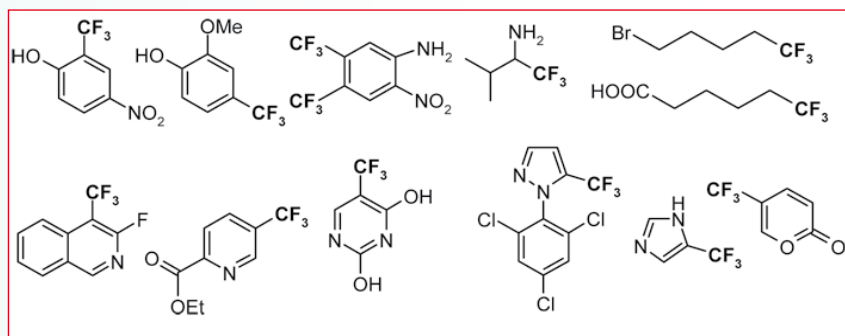
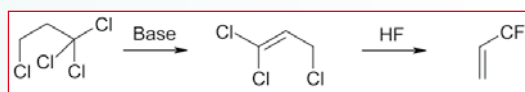


Figure 5. Selected product molecules with CF<sub>3</sub> groups prepared from carboxylic acids with SF<sub>4</sub>.



Scheme 5. Synthesis of 3,3,3-trifluoropropene.

## SOME INDUSTRIAL PROCESSES FOR THE SYNTHESIS OF ARYL AND ALKYL-CF<sub>3</sub>

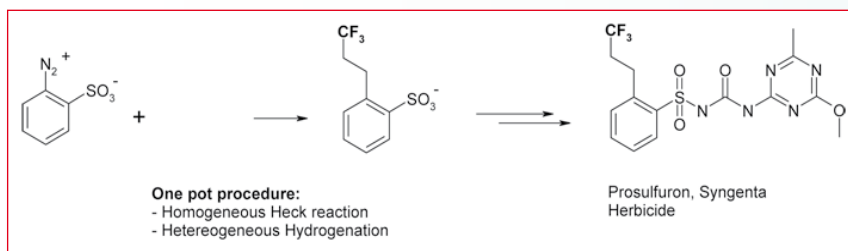
### Exchange of activated benzylic halogens

A cost effective and efficient way to manufacture Ar-CF<sub>3</sub> compounds is the complete replacement of chlorine atoms in the corresponding trichloromethyl-precursor. This reaction is possible under mild reaction conditions using anhydrous hydrogen fluoride and catalytic amounts of antimony(V)chloride (Scheme 3). Aromatic systems which are not substituted by an electron-withdrawing system can undergo a Friedel-Crafts type reaction with hydrogen fluoride/carbon tetrachloride to give access to the corresponding (trifluoromethyl)benzenes. In most cases the substitution pattern of the trifluoromethyl aromatic formed is in accordance with an electrophilic process (Scheme 3).

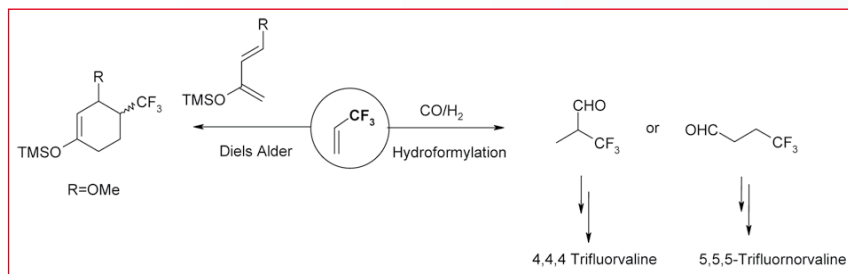
The fluorination of an aromatic trichloromethyl group is also accomplished in the presence of an excess of antimony(III)fluoride. Generally this chemistry (Swarts reaction) requires two to five equivalent of antimony(III) fluoride and compared to the use of anhydrous hydrogen fluoride, yields are generally slightly lower (10).

### Conversion of carboxylic acids and anhydrides

The reaction of sulfur tetrafluoride with carboxylic acids (aliphatic, aromatic and heterocyclic) is of particular importance as the most general and simplest route to trifluoromethyl derivatives. The reaction proceeds in two steps. The first step gives an acyl or aroyl fluoride, which is then in the second step transformed by catalytic amounts of hydrogen fluoride to the trifluoromethyl derivative (Scheme 4). The formation of the acyl fluoride occurs readily at low temperatures, while the second step requires considerably higher temperatures ranging from 20-200°C at pressure up to 60 bar. Therefore, carefully tuned reaction conditions are necessary to avoid the formation of tar-like or very impure products. Furthermore, the handling of sulfur tetrachloride requires special equipment and precautions in addition to experienced operators. Sulfur tetrachloride is a highly reactive, toxic and corrosive gas which has a LD<sub>50</sub> of 50 ppm (4h) and liberates hydrogen fluoride and thionyl fluoride on exposure to moisture. The combination of all necessary precautions and three decades of experience of Solvias in SF<sub>4</sub> chemistry ensures maximum safety and a high success rate for SF<sub>4</sub> fluorination which are routinely performed in batch sizes up to kilogram scale (Figure 5).



Scheme 6. Efficient synthesis of Prosulfuron.



Scheme 7. Efficient use of 3,3,3-trifluoropropene as a building block.

### Application of 3,3,3-Trifluoropropene

An interesting approach for the introduction of an alkyl  $\text{CF}_3$  groups represents the usage of the readily available 3,3,3-trifluoropropene as a building block. 3,3,3-trifluoropropene can be prepared starting from 1,3,3,3-tetrachloropropan via 1,1,3-trichloroprop-1-ene and subsequent HF addition as outlined in Scheme 5 (11).

3,3,3-Trifluoropropene has been successfully used in Heck-reactions. Prominent example is the elegant synthesis of Prosulfuron which relies on a pot procedure; a Pd-catalysed homogeneous Heck reaction followed by a heterogeneous hydrogenation of the resulting unsaturated compounds. Thus this

approach allows the facile and cost effective synthesis of the central building block for Prosulfuron and represents an elegant method for the synthesis of alkyl- $\text{CF}_3$  compounds (Scheme 6) (12). Also Diels Alder-reactions have been extensively reported using 3,3,3-trifluoropropene as a dienophile (13). In addition it undergoes highly regioselective hydroformylation to the corresponding aldehydes depending on catalyst employed. The resulting aldehydes have been successfully used for the synthesis of fluoro analogs of aliphatic amino acids such as 4,4,4-Trifluorvaline and 5,5,5-Trifluorvaline (14).

### CONCLUSIONS

This brief overview demonstrates that a variety of methods are available for the preparation of fluorinated compounds containing a  $\text{CF}_3$  group. Some transformations are feasible to be applied at kilogram scale or industrial scale. However, a drawback of most fluorinating chemistry is the toxic and sometimes aggressive nature of many fluorination reagents. For this reason special equipment and infrastructure is required and outsourcing the larger scale preparation and process development to companies specialized in handling such reagents can be an option.

### SOLVIAS' HAZARDOUS AND HIGH PRESSURE TEAM – FLUORINATION ON KG-SCALE

The Solvias chemical development/cGMP manufacturing group consists of a dedicated team handling hazardous- and high pressure chemistry including organofluorine chemistry. We provide rapid and comprehensive support to our customers in the life science industry ranging from process R&D to subsequent delivery of g to kg-amounts of intermediates and APIs. Solvias employs most synthetic methods (Deoxofluorination, Schiemann reaction, Halex reaction, direct fluorination) in organofluorine chemistry ( $\text{HF}$ ,  $\text{SF}_4$ ,  $\text{F}_2$ ) and can draw on more than 40 years of experience in this field. Over 10.000 reactions have been performed and reports are available, allowing a fast turnaround of our customers requests for fluorinated building blocks.

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