

Selective synthesis of fluorinated compounds on Kilogram scale

Methodology and equipment



Michael Quirnbach

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). For this reason synthetic methods for the selective preparation of specifically fluorinated intermediates and building are of high importance. Today, many fluorinated molecules are commercially available and can be used as building blocks for the synthesis of the desired fluorinated target molecule. In addition, a plethora of methods exist to selectively fluorinate a variety of substrate classes. However, in many cases either very toxic or otherwise dangerous reagents are needed, calling for particular know how and experience as well as specially equipped laboratories and reaction vessels. In this contribution we would like to discuss two aspects: i) The scope of selected fluorination methodologies and ii) the question of outsourcing the preparation of up to kg quantities of fluorinated intermediates to a specialized contractor such as Solvias.

USEFUL FLUORINATION METHODS

The following fluorination methods (2) have proven to be reliable for the selective formation of carbon-fluorine bonds in organic molecules on a preparative scale

- Fluorinations using SF₄
- Schiemann Reaction
- Electrophilic fluorination using F⁺-reagents (including enantioselective variants)
- Chlorine-Fluorine exchange reactions (Halax reaction)
- Direct fluorination using F₂

Here we will present a short overview on the first two reaction types which are by far the most important for the synthesis of fluorinated compounds on preparative scale.

Reactions using SF₄

SF₄ has proven to be a particularly useful reagent for the selective fluorination of a variety of oxygen and sulfur containing functional groups. Of particular interest are the preparation of CF₃ groups, starting from carboxylic acids (Figure 1), of difluorinated compounds using aldehydes and ketones as starting materials and of monofluorinated derivatives starting from alcohols (Figure 2). The two illustrations show "real-world" examples illustrating the broad range of substrates amenable to SF₄ chemistry encompassing aromatic, heteroaromatic as well as aliphatic substrates and the presence of a variety of functional groups. The reactions using SF₄ are usually carried out in presence of catalytic amounts of HF under carefully tuned conditions. Otherwise, formation of tar-like or very impure product will result. Apart from the prevention of side reactions, the toxicity of the reagent along with the reaction conditions ranging from -40°C to 160°C and pressures of up to 60 bar require rigorous safety measures. The combination of all necessary precautions and three decades of experience of Solvias in SF₄ chemistry ensures maximum safety and a high success rate for SF₄ fluorination which are routinely performed in batch sizes up to 500 grams.

Modified Schiemann Reaction: conversion of anilines to fluoro aromatics

The Baltz-Schiemann reaction, i.e., the thermal decomposition of isolated diazonium tetrafluoroborate salts, is the most important method to selectively introduce fluorine atoms into aromatic rings. Since fluorinated arenes are the most common motif found in biologically active compounds (1) it was of special importance to improve the methodology because the traditional Baltz-Schiemann only allows reactions on a gram scale. In the modified version, the diazotation step is usually performed with NaNO₂ in pyridine-HF or in anhydrous HF, where HF serves both as solvent and reagent. The substitution reaction is then carried by heating the reaction mixture above the decomposition temperature of the diazonium salt. With this modified version, a broad variety of carbo- and heterocyclic aromatic amines can be converted to fluoro aromatics on both laboratory and technical scale. A representative selection of preparative examples carried out in the Solvias laboratories is shown in Figure 3.

Preparative fluorinations

In contrast to chlorinated and brominated compounds, synthesis of fluorinated substances requires methods not readily applicable in standard organic laboratories. The reason lies in the toxicity and corrosivity of many fluorination reagents. Therefore, specially equipped laboratories or even closed boxes with high performance ventilation and gas washers and also special equipment such as plastic reactors or high pressure autoclaves

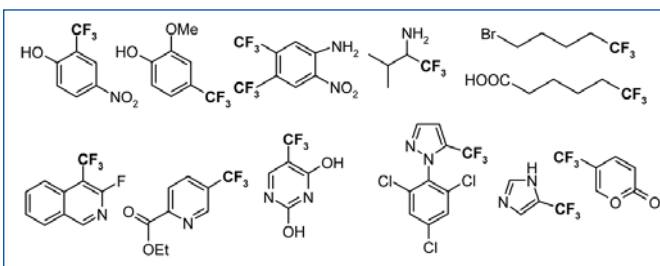


Figure 1. Selected product molecules with CF₃ groups prepared from carboxylic acids with SF₄.

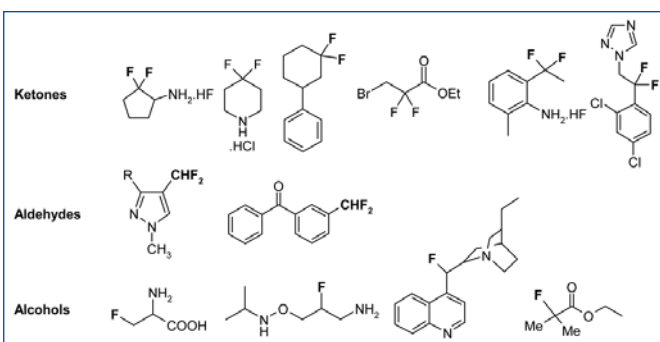


Figure 2. Selected product molecules prepared from ketones, aldehydes, and prim. sec. and tert. alcohols.

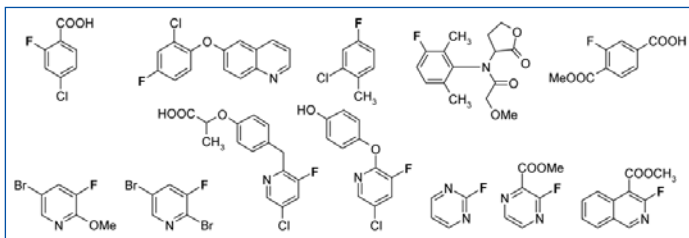


Figure 3. Scope of the modified Schiemann reactions to prepare fluoroaromatic compounds.

made of Monel 400® are often required. In addition, trained personnel with experience in handling toxic and aggressive chemicals as well as high-pressure apparatuses are a prerequisite as well.

This leads to the obvious question: If a fluorinated intermediate is not available commercially, do you prepare it yourself or outsource the preparation to a specialist? While many electrophilic fluorinations using F⁺-reagents such as Selectfluor®* can be carried out by experienced personnel on preparative scale without any special precaution, this is not recommendable for reactions with reagents such as HF or SF₄. For such preparations, outsourcing to a specialized company such as Solvias is clearly the method of choice.

For more than 30 years, a variety of different fluorination methods have been used at Solvias to prepare hundreds of fluorinated compounds on a preparative scale.

Fluorinations are routinely carried out in various scales up to 16 litres. We not only have all equipment required (several specialized vessels and autoclaves are depicted in Figure 4), but also the know-how and experience to successfully synthesize fluorinated target molecules on gram to kilogram scale and develop efficient processes for large-scale manufacturing.



Figure 4. 16 Litre autoclave for reactions between -70°C up to 300°C and up to 300bar, safe handling of toxic and aggressive chemicals.

Besides the transformations described above, Solvias can also perform reactions with almost every fluorination reagent, including diluted F₂ gas (e.g. 10 percent F₂ in N₂) under normal pressure and up to a 0,5 mol scale.

CONCLUSIONS

This brief overview demonstrates that a variety of methods are available for the preparation of selectively fluorinated compounds and that several transformations are feasible to be applied a kilogram scale. A drawback of most fluorinating chemistry is the toxic and sometimes aggressive nature of many fluorination reagents. For this reason outsourcing the larger scale preparation and process development to companies specialized in handling such reagents is highly recommended.

REFERENCES AND NOTES

1. For a recent review see S. Purser, P.R. Moore et al., *Chem. Soc. Rev.*, 37, p. 320 (2008).
2. For a comprehensive overview on synthetic methods see *Organic-Fluorine Compounds*, Houben-Weyl, E10a, Eb1, Eb2, 4th Ed., Thieme, Stuttgart (2000).

* Selectfluor is a registered trademark of Air Products and Chemicals, Inc.

**MICHAEL QUIRMBACH*, HEINZ STEINER,
HANS MEIER, HANS-ULRICH BLASER**

*Corresponding author

Solvias AG

P.O. Box

Basel, CH-4002, Switzerland