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Microreactors for elemental fluorine

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A microreactor has been designed for use with elemental fluorine, both for selective fluorination and for perfluorination of organic compounds.

Interest in the use of elemental fluorine directly, for the synthesis of fluorine-containing organic compounds, has increased dramatically in the last few years,[1–3] but scale-up will always present problems of safe handling and temperature control, for some of the most exothermic reactions in organic chemistry.

There is currently much interest in the development of microreactors for chemical processing,[4] because the benefits would include arithmetic scale-up from the performance of a single reactor to a theoretically unlimited number. Also, in principle, this scale-up could be achieved by the techniques of the electronics industry.

Microreactors have considerable attraction for application to direct fluorination processes because there is (i) a small inventory of fluorine in the reaction zone, (ii) opportunity for good mixing and temperature control, and (iii) simple scale-up. However, prior to this work, there was little knowledge available on the practicability of this approach.

After much development, we have now designed a simple micro-reactor, fabricated from a block of nickel (or copper), from which we have cut a groove as the micro-reactor; the design is indicated in Fig. 1, where the seal is provided by a block of polychlorotrifluoroethene, which also enables direct viewing of the reaction zone. Reactants and solvent were injected *via* a syringe and syringe-pump, while fluorine in nitrogen was introduced directly from a small cylinder *via* a mass-flow controller. Using this technique, all of the liquid–gas mixing that we carried out proceeded *via cylindrical flow* (the term is intended to indicate that the liquid forms an outer cylinder, coating the reactor surface, with the gas flowing through the centre) as opposed to *slug flow* (alternate slugs of liquid and gas), which might have been anticipated. Indeed, the former provides enormous advantages in that it provides very large surface to volume ratios for the liquid phase, which is highly beneficial for efficient reaction over a short distance in the reactor. There is also excellent mixing and very effective opportunities for heat control, through the cooling channels indicated. Furthermore, a surprisingly large through-put for such a small channel is possible, *e.g.* 0.5–5 ml h^{-1} have been used routinely.

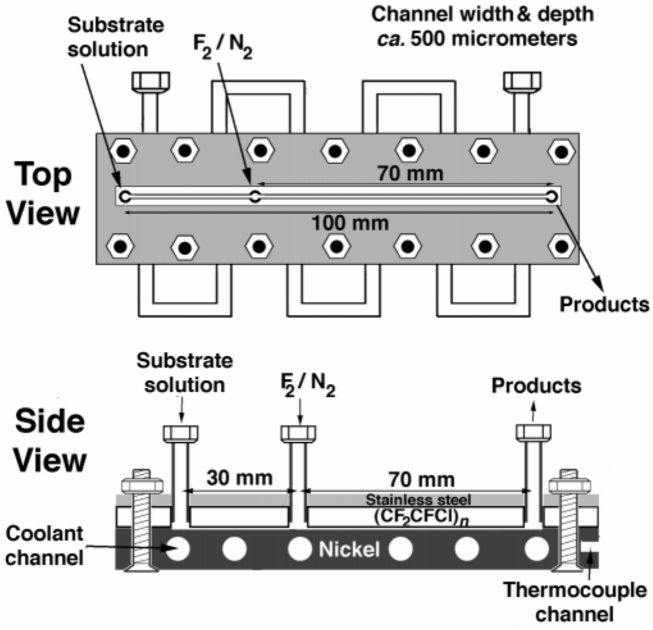
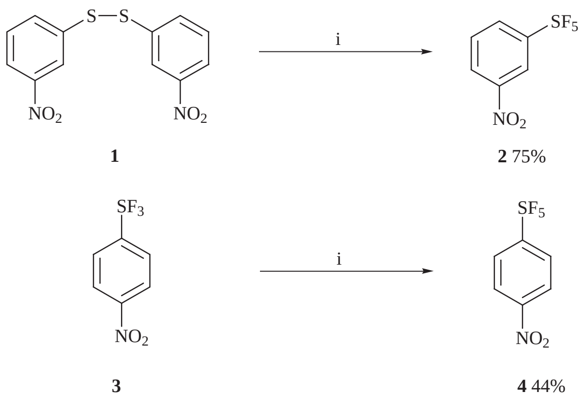


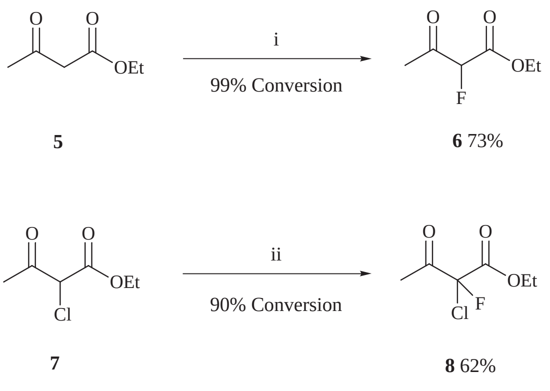
Fig. 1 Microreactor top and side view.

Products were trapped out in a half inch diameter FEP tube, cooled by either a salt–ice bath or an acetone–carbon dioxide slush bath. Residual gases were scrubbed in a soda-lime tower and any dissolved hydrogen fluoride was removed by either adding sodium fluoride to the product mixture or washing with water.

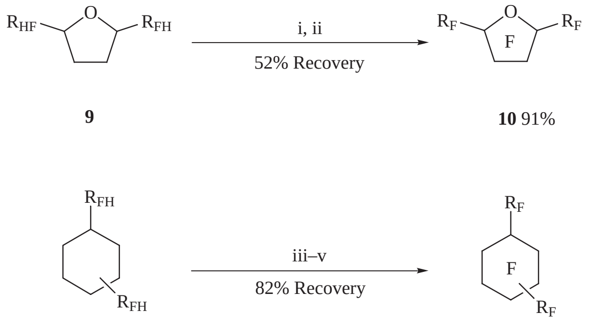
Using this system, we have successfully carried out various selective fluorinations, as shown in Schemes 1 and 2. Sulfur pentafluoride derivatives are of considerable interest[5] and



Scheme 1 *Reagents and conditions*: i, MeCN (5 ml h^{-1}), 10% F_2 in N_2 (10 ml min^{-1}), room temp.



Scheme 2 *Reagents and conditions*: i, 10% F_2 in N_2 (10 ml min^{-1}), 5 °C, HCO_2H (0.5 ml h^{-1}); ii, 10% F_2 in N_2 (10 ml min^{-1}), 5 °C, HCO_2H (0.25 ml h^{-1}).



9 **10** 91%

11 **12** 70%

$R_{FH} = CF_2CFHCF_3$

$R_F = CF_2CF_2CF_3$

Scheme 3 *Reagents and conditions*: i, 0.5 ml h^{-1}, 50% F_2 in N_2 (15 ml min^{-1}), room temp.; ii, 0.5 ml h^{-1}, 50% F_2 in N_2 (15 ml min^{-1}), room temp. then 280 °C; iii, 0.5 ml h^{-1}, 20% F_2 in N_2 (20 ml min^{-1}), room temp.; iv, 0.5 ml h^{-1}, 50% F_2 in N_2 (10 ml min^{-1}), room temp. then 50 °C; v, 0.5 ml h^{-1}, 50% F_2 in N_2 (15 ml min^{-1}) room temp. then 280 °C.

fluorination can be achieved directly from the di(*m*-nitrophenyl) disluphide **1**. However, for the *p*-nitro system **3**, due to its very low solubility in MeCN, preliminary fluorination (in bulk) to produce soluble trifluorides was performed and then the more difficult fluorination to pentafluorides was carried out in the microreactor.

Fluorination of β-dicarbonyl compounds proceeded with high efficiency and, moreover, these reactions demonstrated clearly a catalytic effect by the fluorinated metal surface. Fluorination is usually limited by either the concentration of enol, at equilibrium, or the rate constant for forming the enol. However, while bulk fluorination of ethyl 2-chloroacetoacetate **7** gives only low conversion to **8**,[6] the flow system is clearly efficient and the fluorinated metal surface obviously promotes the formation of enol.

We have also demonstrated that the technique can be used for *perfluorination*. In this case, however, we need an additional heated stage to complete the reaction and this is connected simply to the outlet of the reactor. Results are shown in Scheme 3 and there is no reason why these otherwise hazardous procedures could not be scaled up with safety. Traditionally, cobalt trifluoride (obtained using elemental fluorine) is used in industry to perfluorinate hydrocarbons, but for some of the examples shown here, the temperature required for perfluorination with elemental fluorine is significantly lower than that required for perfluorination using cobalt trifluoride.[7]

These experiments illustrate the significant potential for this approach to the use of elemental fluorine, both in the laboratory and at the industrial scale.

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Notes and references

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