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Epoxidation of alkenes using HOF·MeCN by a continuous flow process

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ABSTRACT

Continuous flow methodology is described which allows the in situ generation of the highly effective oxidising agent HOF·MeCN from fluorine and wet acetonitrile and immediate reaction with alkenes to afford epoxides in high yield. The HOF·MeCN continuous flow oxidising system provides an environmentally benign process that is suitable for large scale synthesis and is atom efficient, because the only by-product is hydrogen fluoride which, in principle, could be recycled to produce fluorine by electrolysis.

1. Introduction

In a series of publications, Rozen and co-workers demonstrated that the HOF·MeCN complex, formed by the reaction of elemental fluorine with water in acetonitrile at 0 °C, is a uniquely effective electrophilic oxygen transfer agent.[1–3] A wide range of oxidation reactions have been reported of, for example, amine, azide, sulfide, alcohol, ketone and N-heterocyclic substrates. All the reactions proceeded rapidly under very mild conditions to give the corresponding oxidation products in high yields. A further benefit of this oxidising system is that it is an environmentally benign process, replacing, for instance, toxic heavy metal oxidants for many transformations. It is also atom efficient, because the only by-product is hydrogen fluoride which, in principle, could be recycled to produce fluorine by electrolysis.

Rozen estimated that the HOF·MeCN complex has a half life of a few hours at 0 °C and thus the reagent must be produced when required immediately at the point of use. This requires 'batch' reaction of F_2 with wet acetonitrile to form a highly oxidising solution of HOF in acetonitrile. Furthermore, the resulting solution of HOF·MeCN and HF must be immediately analysed by titration to determine the concentration of oxidant. A combination of these factors could inhibit the development of this potentially very useful and powerful reagent for anything other than small scale laboratory synthesis and, indeed, applications in larger scale syntheses have not been developed.

In addition, highly exothermic, rapid oxidation processes can exhibit problems with reaction control when reagents are added into an excess of a highly oxidising medium. The scale-up of batch syntheses using unstable materials can be particularly difficult or even hazardous for processes where heat transfer, agitation, selectivity and tar formation are problematic. Consequently, the increased costs associated with conducting safe scale-up of many conventional oxidation processes in highly concentrated oxidising media can be prohibitive and so there is still a requirement for the development of reagents and/or processes that will allow safe, efficient oxidation to be performed on the laboratory and manufacturing scale.

In recent years, continuous flow microreactor devices[4,5] have been developed for a variety of synthetic procedures, usually with corresponding increases in yield, selectivity, controllability and safety. In conjunction with the possibility of arithmetic 'scale-out', there are clear benefits over conventional batch process technology. A key feature of using microreactor channels as the reaction 'vessels' is that the synthesis of large quantities of product is achieved by the operation of multiple channels and/or microreactor devices in parallel, avoiding many of the difficulties associated with traditional scale-up. In particular, the usual safety and chemistry issues associated with the decrease in efficiency of heat- and mass-transfers on increasing scale are avoided. In this context, we have demonstrated that gas/liquid reactions, particularly direct fluorination of a variety of organic substrates, can be achieved using continuous flow microreactor devices[6–10] and the scale-out of reactions involving the use of 30 channels in parallel has been successfully achieved for gas/liquid processes.[10]

We sought to use our continuous flow microreactor techniques for the development of effective oxidation methodology using HOF·MeCN, prepared in situ by direct fluorination. Such an approach avoids many of the problems associated with using HOF·MeCN in batch processes and could be suitable for scale-out beyond laboratory scale. We aimed to generate quantitatively the HOF·MeCN complex in situ in a microchannel and then react it immediately with an organic substrate so that the problems of concentration measurement, stability and storage would be avoided, making the process amenable to general use for both laboratory and manufacturing applications.

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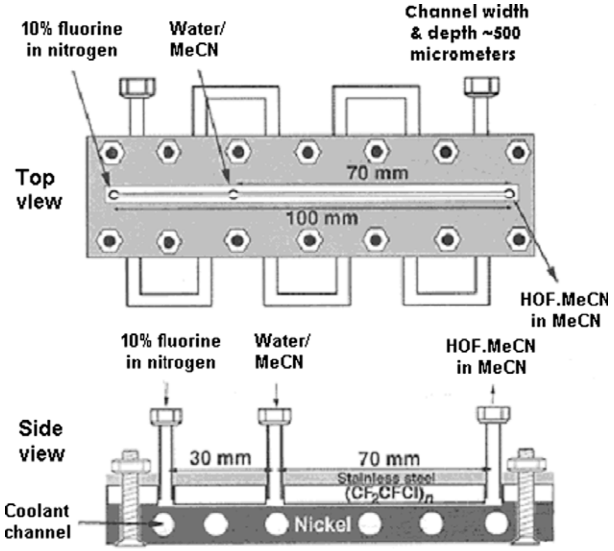
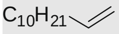
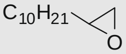
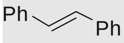
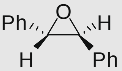
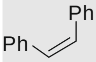
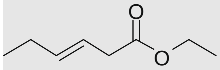
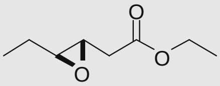
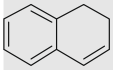
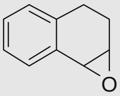
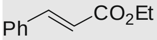
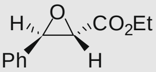
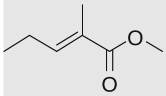
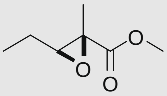
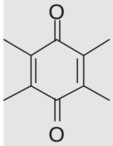
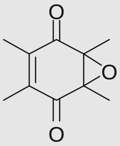
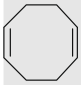
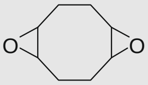


Figure 1. Single channel continuous flow reactor.

Table 1
Epoxidation of alkenes using HOF·MeCN in a continuous flow process

$$\text{Alkene} \xrightarrow[\textit{Continuous flow reactor}]{\text{HOF.MeCN, DCM, r.t.}} \text{Epoxide}$$

Alkene	Epoxide	Yield (%)
		98
		99
		81
		97
		82
		39[a] 63[b]
		99
		38
		94

[a] 1 equiv HOF·MeCN, NMR yield.
[b] 2 equiv HOF·MeCN, NMR yield.

In this Letter, we describe epoxidation reactions of a small series of alkenes where the HOF·MeCN is generated in situ in a continuous flow process using microreactor techniques to demonstrate this proof of concept.

For all the reactions involving the generation and reaction of HOF·MeCN described below, we used our single-channel microreactor, shown in Figure 1, and this apparatus and its operation had been described in detail previously.[6,7] Briefly, fluorine gas, diluted to 10% in nitrogen, was introduced into the microchannel using a mass flow controller set at a prescribed flow rate, and wet acetonitrile was added via a second inlet at a controlled rate by syringe pump (Fig. 2). The alkene was found to react preferentially with fluorine in the presence of HOF·MeCN, thus conditions for the complete reaction of fluorine with water had to be determined to prevent the production of fluorinated by-products.

Continuous flow epoxidation processes were carried out in which HOF·MeCN was generated in the microchannel and the alkene (in 1:1 v:v MeCN/dichloromethane solution) was added, via a T-piece connection at a controlled rate using a second syringe pump. We found that a throughput of 2.0 mmol h^{-1} channel^{-1} of HOF·MeCN was possible, based on the recovery of epoxide, in a 0.5 mm diameter, 125 mm reactor path length with a further 300 mm path length after the T-piece for oxidation of the alkene. Cooling of the microreactor and collection vessel was unnecessary because reactions proceeded with high control under ambient conditions with no reduction in yield. The product mixture flowed into a collection vessel that contained aqueous sodium hydrogen carbonate solution which quenched any excess HOF and HF immediately, minimising the risk of HF exposure and demonstrating that the reaction occurred in the flow system itself. Extraction of the aqueous solution with dichloromethane, drying and evaporation gave the desired epoxide, typically in greater than 80% yield without the need for any further purification.

A small series of alkenes was epoxidised in a similar manner and these results are collated in Table 1. Epoxidation of various mono-, di-, tri- and tetra-substituted alkenes demonstrates the potential of this technique.

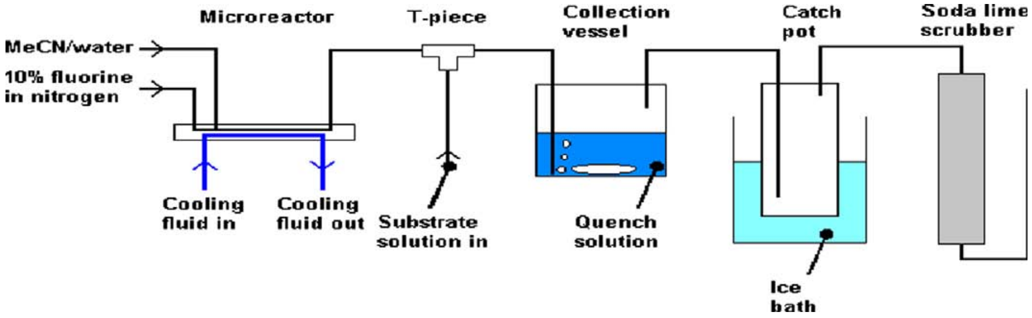


Figure 2. Gas/liquid continuous flow techniques.

Ethyl *trans*-cinnamate is known to be less reactive towards epoxidation processes, and our results are consistent with this observation.[11] Reaction with 2 equiv of HOF·MeCN, performed by halving the addition rate of the alkene solution, resulted in an increase in yield of approximately 50% as measured by ^{1}H NMR. Cyclooctadiene could be transformed into the corresponding di-epoxide upon reaction with an excess of in situ generated HOF·MeCN reagent.

In conclusion, we have demonstrated that HOF·MeCN can be generated and reacted immediately in situ in a continuous flow microreactor channel for the efficient oxidation of alkenes, removing the need to analyse the resulting, relatively unstable HOF·MeCN solution. This methodology, therefore, demonstrates that HOF·MeCN could be used for a number of continuous flow oxidations in microchannels, and given the potential for scale-out of microreactor systems, which we have already demonstrated for direct fluorination processes, the use of HOF·MeCN could be applied readily to larger scale synthesis.[12]

2. Experimental

Typical procedure. ***CAUTION***: Although 10% v/v fluorine in nitrogen is relatively easy to handle, it is still a potent oxidising agent and must be treated as such. Appropriate precautions must also be taken with regard to HF handling, including the provision of calcium gluconate antidote gel.

Fluorine (10% in N_2) was passed at an indicated rate of $20.0\ \mathrm{ml\ min^{-1}}$ (equating to $3.3\ \mathrm{mmol\ h^{-1}}$) into the microreactor channel via one inlet, and simultaneously, MeCN/H_2O (4:1, 10 ml) was added via syringe pump into a second inlet at a rate of $9.90\ \mathrm{ml\ h^{-1}}$ ($110.0\ \mathrm{mmol\ h^{-1}}$) while dodec-1-ene (0.34 g, 2.0 mmol) (in a 1:1 mixture of CH_2Cl_2/MeCN, 10 mL) was added via syringe pump into a third inlet at a rate of $9.90\ \mathrm{ml\ h^{-1}}$. After passage through the microreactor system, all reaction fluids were collected in a vessel containing dilute aq $NaHCO_3$ solution (50 mL). After purging the apparatus with nitrogen, the reaction mixture was added to $NaHCO_3$ solution (25 mL), extracted with CH_2Cl_2 (3 × 75 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure to yield 2-decyloxirane (0.36 g, 98%) as a yellow oil, with no further purification required; $\nu_{\max}$ ($\mathrm{cm^{-1}}$) 2923 (sp^3 C–H), 2854 (sp^3 C–H), 1466, 916, 833 (C–O–C), 722; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, $^3J_{HH}$ 6.4, $-CH_2CH_3$), 1.24 (15H, m, $-CH_2-$), 1.47 (3H, m, $-CH_2-$), 2.43 (1H, m, OCH_2), 2.71 (1H, m, OCH_2), 2.87 (1H, m, CHO); δ_C (100 MHz, $CDCl_3$) 14.0 (s, CH_3), 22.6, 25.9, 29.3, 29.4, 29.5, 29.6, 31.9, 32.4, 32.5 (all s, CH_2), 47.0 (s, OCH_2), 52.3 (s, OCH); *m/z* (EI) 184 ($[M]^+$, 2%), 169 ($[M-CH_3]^+$ 100%); as compared to literature data.[13]

Acknowledgement

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