Fluorination reactions in microreactors

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The DAST-mediated conversion of a range of alcohols to the corresponding fluorides in a microstructured device is described. This safe, practical fluorination method will facilitate reactions currently challenging on large scale.

Fluorinated organic compounds are emerging with increasing frequency as pharmaceutically active substances from the drug discovery process[1,2] owing to their unique physical and biochemical properties.[3,4] While organofluorine compounds are relatively rare in nature,[5] fluorine-containing molecules feature prominently in the agrochemical and pharmaceutical repertoire owing to their enhanced metabolic stability. In 2005 alone, half of the top ten pharmaceuticals contained fluorine;[6] a number that is expected to increase further. Among the numerous commercially available nucleophilic fluorinating reagents, DAST (diethylaminosulfur trifluoride) is perhaps the most widely utilised.[7] However, the use of DAST in large scale deoxyfluorination reactions is limited by its propensity to detonate at temperatures above 90 °C. The procurement of fluorinated intermediates and final products is thus hampered by safety concerns. Prompted by the need to find a safe, scalable method that allows for large quantities of fluorinated molecules to be prepared, we developed a microreactor-based deoxyfluorination method. Microreactors hold advantages when tackling hazardous reactions as heat transfer is more efficient in microstructured reaction vessels to control thermal runaway. Super-heating of solvents to accelerate reactions, and excellent mixing are further advantages. Explosive, highly toxic and corrosive reagents, intermediates or by-products (in this case HF) can be quenched *in situ*. Only small amounts of material are required to optimise reactions due to the small reactor volumes. Still, scale-up is simple under the flow-through regime. Reactions generally considered to be unattractive due to safety concerns are made more accessible using microreactors.[8,9]

Herein, we describe the development of a general method for the deoxyfluorination of a range of substrates, including alcohols, lactols, aldehydes and carboxylic acids, in a microstructured device (Fig. 1).[10] Pertinent features of this method include short reaction times (16 min), elevated temperature (70 °C) and *in situ* quenching of excess DAST and HF.

In order to establish general deoxyfluorination conditions, exploratory reactions were performed in toluene, dichloromethane and tetrahydrofuran. Dichloromethane was quickly identified as being the solvent of choice. Furthermore, the incorporation of a 75 psi HPLC back pressure regulator allowed the solvent to be super-heated to 70 °C resulting in shortened reaction times.[10] For economic reasons it was deemed prudent to use exactly 1 equivalent of DAST in the deoxyfluorination of alcohols and exactly 2 equivalents in the case of carbonyl-containing substrates. A residence time of 16 min was found to be optimal while 8 min residence time resulted in lower conversions as did 32 min (presumably due to product degradation).

Having established general deoxyfluorination conditions, preliminary experiments focused on the conversion of a range of benzylic and secondary alcohols to the corresponding fluorides (Table 1). Both electron rich and electron deficient benzylic alcohols were processed to the corresponding fluorides (entries 1 and 2, respectively) in good yield.[11,12] The naphthalene derivative (entry 3) reacted cleanly to give the desired product albeit in lower yield.[13] More complex secondary alcohols such as menthol and dihydrocholesterol were also tolerated (entries 4 and 5 respectively).[14–16]

Glycosyl fluorides are potent glycosylating agents that are typically prepared by treating the corresponding lactols with DAST. As part of an overall programme directed at simplifying oligosaccharide assembly[17] we explored whether glycosylating agents could be prepared in continuous flow. 2,3,4,6-Acetylated and benzylated glucoses undergo smooth conversion to the corresponding glycosyl fluorides[18–20] in excellent yield and do not require further purification prior to use (Table 2). Based on our interest in preparing 'activated' synthetic intermediates that may be used directly in subsequent transformations, we examined the conversion of a family of carboxylic acids to the corresponding acid fluorides (Table 3).[21] Substituted benzoic acids such as the 4-methoxy- and the 3,4-dimethyl- derivatives (entries 1 and 2) were quantitatively transformed to the desired acyl fluorides.[22] Similarly, aliphatic acids (entries 3, 4 and 5)[23] were converted to the expected products in excellent yield. Finally, the halogen exchange process (entry 6) was examined whereby an acid chloride was converted to the corresponding acid fluoride in high yield.[24]

To assess the scope of this method, the conversion of aldehydes and ketones to the corresponding *gem*-

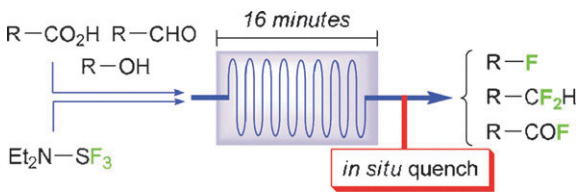

Fig. 1 Overview of the microreactor-based DAST fluorination process.

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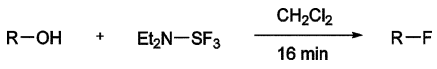
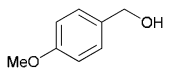
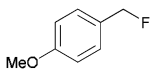
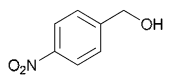
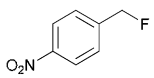
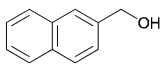
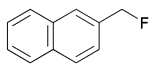
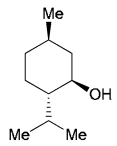
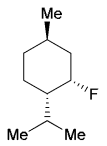
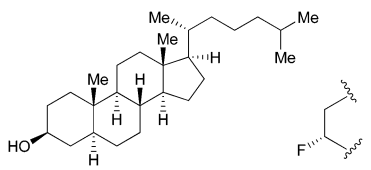
Table 1 DAST fluorination of selected benzylic and secondary alcohols[a]



Entry	Alcohol	Fluoride	Yield (%)
1			66
2			70
3			55
4			70[b]
5			61[c]

[a] *Reaction conditions*: Solutions of the alcohol and DAST (both 0.2 mol dm^{-3} in CH_2Cl_2) were simultaneously injected into a 16 cm^3 Syrris FRX microreactor and heated to 70 °C (retention time: 16 min). The outlet solution was subsequently mixed with a 10% aqueous solution of $NaHCO_3$. The product was extracted with ethyl acetate, washed with a saturated aqueous solution of $NaHCO_3$ and concentrated *in vacuo*. Purification by flash column chromatography on silica gel furnished the desired fluorides. [b] The product was isolated as a 6 : 1 mixture of diastereoisomers as determined by ^1H and ^{19}F NMR spectroscopy. [c] The product was isolated as a 5 : 1 mixture of diastereoisomers as determined by ^1H and ^{19}F NMR spectroscopy.

difluoromethylene adducts was explored and proved to be general for aldehydes (summarised in Table 4). The bulky *ortho*-substituted aldehyde (entry 1) was smoothly converted to the desired product in quantitative yield. Furthermore, electron rich (entries 2 and 3) and electron deficient (entry 4) aldehydes were transformed into the desired *gem*-difluoromethylene derivatives[25,26] in consistently high yield. Conversion of a straight-chain aliphatic aldehyde (entry 5) was also

Table 2 Facile preparation of glycosyl fluorides[a]

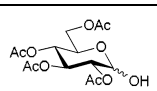
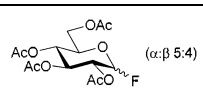
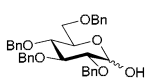
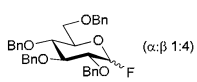
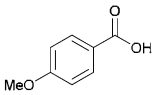
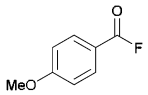
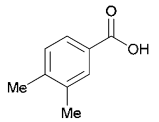
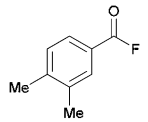
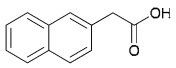
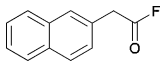
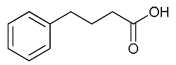
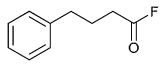
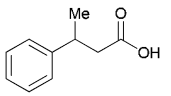
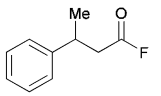
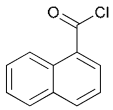
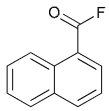
Entry	Lactol	Fluoride	Yield (%)
1		 (α:β 5:4)	89
2		 (α:β 1:4)	Quant.[b]

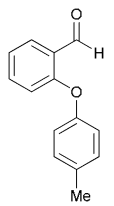
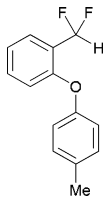
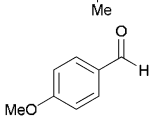
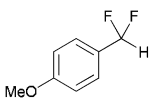
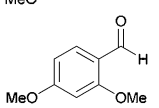
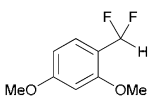
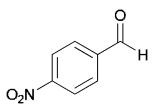
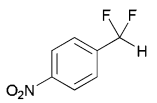
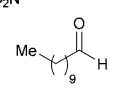
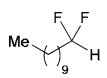
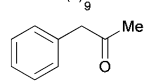
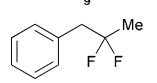
Table 3 Synthesis of a variety of acid fluorides[a]

Entry	Substrate	Fluoride	Yield (%)
1			Quant.[b]
2			95
3			Quant.[b]
4			93
5			81
6			80

[a] For experimental details see Table 1. [b] No purification required.

quantitative.[27] The conversion of ketones to the corresponding difluorides was less efficient (entry 6) and was not investigated further.[28] This finding may be attributed to the lower reactivity

Table 4 Conversion of carbonyl groups to the corresponding difluormethylenes

Entry	Substrate	Fluoride	Yield (%)
1			Quant.[b]
2			89
3			84
4			87
5			Quant.[b]
6			40[c]

[a] Experimental details are the same as those described in Table 1 with the exception that a 0.4 dm^{-3} solution of DAST in CH_2Cl_2 was used. [b] No purification required. [c] 40% conversion determined by ^1H NMR spectroscopy.

of ketones towards DAST, a reaction that typically requires elevated temperatures.[29]

In summary, we report a safe, practical and general method for deoxyfluorination of a range of substrates in a microstructured device. This synthetic method illustrates the utility of microreactors for modern synthetic organic chemistry.

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