The Use of Diethylaminosulfur Trifluoride (DAST) for Fluorination in a Continuous-Flow Microreactor

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Dedicated to Professor Sir Jack Baldwin, FRS, on the occasion of his 70th birthday

Abstract: The convenient and safe use of diethylaminosulfur trifluoride as a fluorinating agent in a continuous-flow microreactor is described using an in-line purification method to obtain clean reaction products.

Key words: microreactor, flow chemistry, immobilized reagents, fluorination, DAST

The introduction of fluorine into biologically active molecules is a well-recognized strategy for modifying and improving the pharmacokinetic properties of drug substances and agrochemical compounds.[1] Whilst diethylaminosulfur trifluoride (DAST) is the most commonly used reagent to effect the transformation of alcohols and carbonyl compounds to their corresponding fluoro derivatives, its use is not without associated problems. For example, it reacts violently with water, it is volatile, and is reported to be explosive when heated owing to its calorimetry profile and its rapid dismutation to SF_4 and $(Et_2N)_2SF_2$. Furthermore, its decomposition products are themselves highly reactive and will etch laboratory glassware. Accordingly, DAST must be used with extreme caution, and samples are recommended not to be heated above 90 °C.[2]

Flow-based microreactor technology is impacting significantly on the synthetic community by providing easy-to-use apparatus that offer many advantages in terms of processing flexibility and easy scaling factors as well as an increased safety profile. One of the main distinguishing characteristics of flow-based chemistry is the ability to handle hazardous components safely in a fully contained environment.[3] As a consequence we were attracted to the use of such devices for reactions involving the reagent DAST.[4]

Our group has already reported and built up considerable knowledge on the use of modular flow reactions for applications in organic synthesis[5] whereby products, even after several synthesis operations,[6] can be prepared cleanly using a combination of techniques from microfluidic chips,[7] flow coils,[8] packed reagent and scavenging flow tubes,[9] and phase-switch methods.[10] From this work we emphasize that it is the quality of the product generated that is important especially if this can be achieved without the need for expensive intermediate chromatographies, crystallizations, or aqueous workups. It should be remembered that the pumping devices and fluidic systems themselves are purely tools to aid the synthesis process.

In this work we report on the conversion of alcohols and carbonyl compounds into the corresponding mono- and difluoro counterparts together with the formation of oxazolines via hydroxylic precursors using DAST in a modular flow microreactor.

To perform the fluorination reactions in a convenient and safe way we decided to use the R2+/R4 combination flow reactor commercially available from Vapourtec.[11] Exploiting the injection loop system of the R2+ unit was found to be very valuable since any contact of the metal parts of the pumping system with the corrosive DAST reagent was thereby avoided. In addition due to the nature of the tubular reactor material (PEEK, PTFE, PFA) no degradation/destruction of the apparatus was observed during the investigation.

Initial test reactions using this reactor set-up identified dichloromethane as a suitable solvent for conducting the fluorination reactions. To extend the temperature range up to 90 °C a 6.9 bar (100 psi) backpressure regulator was attached in-line allowing accesses to the higher temperatures whilst depressing solvent boiling. For a typical fluorination reaction the substrate was dissolved in dry CH_2Cl_2 at concentrations ranging from 0.5–1.0 M and loaded into one of the two identical sample loops (2 mL internal volume; PEEK 0.76 mm i.d.). The second sample loop was then filled with a corresponding solution of DAST in CH_2Cl_2. The two solutions of starting materials were simultaneously injected into the system meeting and mixing in a T-piece. The combined flow stream was then pumped (flow rate of 150 µL/min each channel) through a convection flow coil (CFC, 9 mL internal volume, 1 mm i.d.) heated at temperatures between 70 °C and 90 °C resulting in a residence time of 30 minutes. After exiting the CFC the reaction stream was directed into an Omnifit glass column (10 mm i.d. bore by 150 mm length)[12] filled with a two-phase bed of firstly powdered calcium carbonate (2 g) and then a layer of silica gel (2 g, Figure 1).

In this arrangement it was found that the calcium carbonate was very effective at quenching the residual DAST reagent as well as other fluoride species generated in the reaction (i.e., through the formation of solid calcium fluo-

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ride which was trapped onto the silica gel). It was observed that as the reaction mixture entered the column an evolution of gas (CO_2) as well as the partial consumption of the solid calcium carbonate occurred. The desired fluorination product was then obtained directly following evaporation of the solvent without the need for any further purification as indicated by HPLC-MS and NMR. The sequestered product stream was also analyzed for inorganic fluoride content using a color standardized calibration test kit.[13] Concentration readings (<10 mg/L) indicated negligible ionic fluoride content across the range of tested reactions.

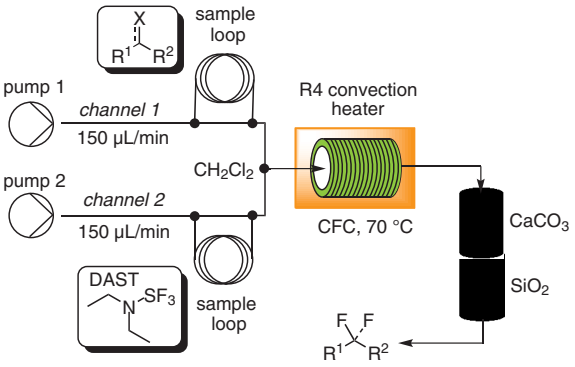


Figure 1 General flow reactor schematic

In a first series of transformations we converted a range of different alcohols into their corresponding monofluorides. By mixing stoichiometric amounts of both starting materials in the flow set-up described above followed by heating the reaction mixture in the CFC at 60 °C we were able to achieve complete conversion of the substrates into the fluoro compounds within a 30 minutes residence time. The desired products were readily isolated in good to excellent yields and purities (>95%) after evaporation of the solvent (Figure 2).

The conversion of benzylic and aliphatic alcohols into their corresponding fluoride species was found to be very chemoselective without affecting other sensitive functionalities such as acid-labile acetals. Furthermore, the fluorination of allylic alcohols such as geraniol gave the

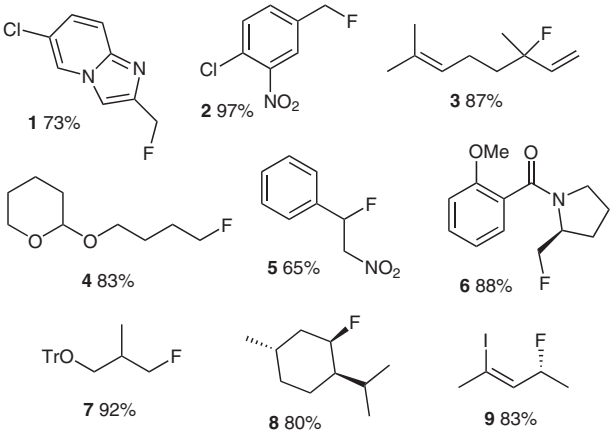
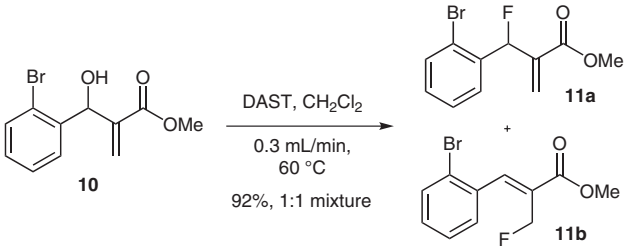


Figure 2 Fluorination products derived from alcohols

quaternary fluoride **3** with very high selectivity following a S_N2' mechanism as expected.

To further exemplify this methodology a more complex allylic alcohol based on a Baylis–Hillmann product **10** was subjected to the same flow fluorination procedure (Scheme 1). As expected, the methyl ester was not affected by the DAST reagent. However, a 1:1 mixture of allylic fluorides **11a** and **11b** was obtained, presumably resulting from competition between S_N1 and S_N2' mechanisms.



Scheme 1 Fluorination of allylic alcohol **10**

To further expand this procedure we investigated the conversion of a small collection of carbonyl compounds into their corresponding difluorides. All aldehydes were subjected to the standard flow procedure and smoothly underwent fluorination using two equivalents of DAST at 80 °C. It was found that electron-deficient aldehydes were transformed into the desired difluorides within 30 minutes, while electron-rich substrates required slightly longer residence times (45 min; equating to 100 µL/min per channel) in order to obtain complete conversion. In each case the products were isolated in excellent yields and purities after removing any fluoride contamination using the in-line calcium carbonate scavenging column (Figure 3).

Next we applied this continuous-flow method to the fluorination of less electrophilic species such as ketones. Although DAST is known to be less efficient for these substrates we were pleased to observe the clean formation

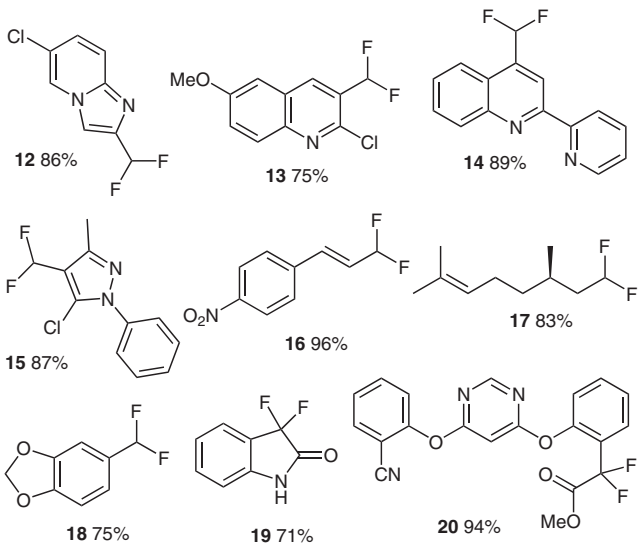
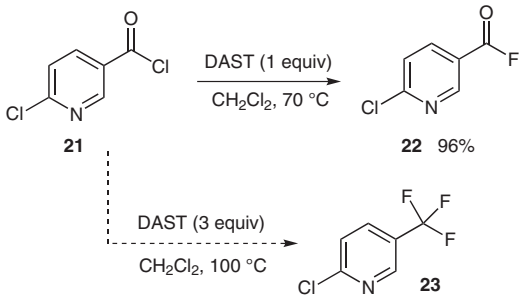


Figure 3 Fluorination products derived from carbonyls

of difluorides **19** and **20** (Figure 3) in good yields following the flow process. However, for the preparation of the isatin-derived compound **19** we were required to modify our procedure and use MeCN as a co-solvent due to much reduced solubility of the starting material in CH_2Cl_2. Pleasingly, it was found that by using a solution of the starting material in MeCN in one channel and mixing this with a stream containing the DAST reagent in CH_2Cl_2 furnished the desired product after in-line purification and solvent evaporation.

In order to investigate further the fluorination procedure the direct conversion of an acid chloride into its acyl fluoride derivative was examined. In the single evaluation study compound **22** was obtained in high yield within a 30 minutes residence time at 70 °C starting from 6-chloronicotinoyl chloride (**21**) (Scheme 2). In an extension, we treated the same starting acid chloride with a three equivalents excess of DAST aiming to convert the intermediate acid fluoride into the related trifluoromethyl compound **23**.[14] However, even when both the residence time and the temperature were increased (60 min at 100 °C) no formation of the desired trifluoromethyl product was observed. Despite this initial negative result it is obvious that this transformation would represent a strategically important sequence if a generic set of conditions could be developed. Consequently, we are testing other fluorinating conditions and reagents to facilitate this process.



Scheme 2 Fluorination of an acid chloride

As part of an ongoing research program in our group we require access to various oxazolines and related oxazole compounds for use in both natural product synthesis[15] and ligand encapsulation studies.[16] Therefore we examined the use of DAST as a dehydrating reagent to convert β-hydroxyamides into the corresponding oxazoline compounds.[17] Employing the standard flow procedure we were able to obtain both mono- **24** and bisoxazolines **25** in excellent yields and purities (Figure 4).

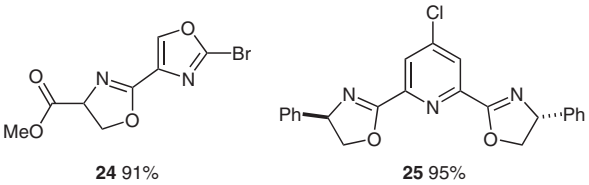


Figure 4 Cyclodehydration using DAST in flow

In conclusion, we have developed a safe and convenient protocol for the fluorination of various alcohols, aldehydes, and ketones using diethylaminosulfurtrifluoride (DAST) in the VapourTec R2+/R4 flow system. One of our main objectives, the reliable in-line purification of the reaction mixture, was accomplished using a glass column filled with equal amounts of solid calcium carbonate and silica gel. Collection of the reaction product followed by evaporation of the solvent furnished the desired products in high yields (65–97%) and purities (>95%) without the need of further purification. In addition, we have demonstrated the application of DAST as a cyclodehydration reagent in the flow synthesis of oxazolines. We are now examining other fluorinating agents and their compatibility with these flow microreactor devices in addition to developing scale-up opportunities.

In a typical procedure run on a 1 mmol scale; premade stock solutions of the substrate and DAST both dissolved in dry CH_2Cl_2 (2 mL, 0.5 M) were injected into separate injection loops of the R2+ unit of the Vapourtec flow system. Each channel comprising the flow stream was pumped at 150 μL/min equating to a residence time of 30 min. The reagent streams were combined in a standard T-piece and directed into a CFC (9 mL internal volume) heated at temperatures ranging between 70 °C and 90 °C using the R4 unit of the Vapourtec system. After leaving the CFC the reaction mixture was passed into an Omnifit glass column containing a plug of $CaCO_3$ (2 g) and a plug of silica gel (2 g) in order to quench and trap any fluoride contamination products. The pure product was collected and isolated after evaporation of the solvent.

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(11) Vapourtec R2+/R4 units are available from Vapourtec Ltd, Place Farm, Ingham, Suffolk, IP31 1NQ, UK. Website: http://www.vapourtec.co.uk. See also http://leyitc.ch.cam.ac.uk/equipment.html for images of the equipment.

(12) Commercially available Omnifit® glass chromatography columns with adjustable height-end pieces(plunger). Typically, the polymer-supported reagent is placed in an appropriately sized Omnifit® column, usually 10 mm bore by 150 mm length, or shorter and the plungers are adjusted to relevant bed heights and the polymer swelled/washed with solvent. Website: http://www.omnifit.com.

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