

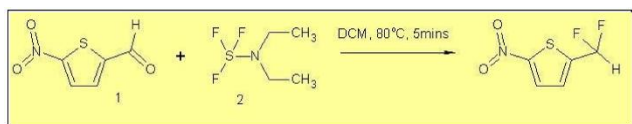
Application Note 26: Continuous Fluorination Reaction With Diethyl Amino Sulfur Trifluoride (DAST)

Produced by Vapourtec



Abstract

This application note illustrates the use of the Vapourtec R-Series system to pump highly reactive, moisture sensitive reagents in a safe and stable continuous reaction. Here we describe the continuous fluorination of a carbonyl group with diethylaminosulfur trifluoride (DAST) pumping directly through the R-Series acid resistant pump heads.



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Background

The addition of fluorine into pharmaceuticals and agrochemicals is an area of high importance and is illustrated by the number of top selling drugs containing fluorine (15 out of the top 100 selling pharmaceuticals by worldwide sales 2009). Its application also includes polymers and materials,

specialty solvents, performance fluids and in numerous reagents and intermediates for chemical synthesis.

The addition of fluorine is a well-known approach to alter chemical and biological profiles, including stability, lipophilicity, bioavailability and the blocking of metabolic degradation. As such there is an increased need for safe, selective and efficient methods to introduce fluorine into molecules.

The range of fluorinating reagents is numerous and diverse covering electrophilic, nucleophilic and electrochemical approaches. Of the nucleophilic fluorinating reagents the most commonly used is Diethylaminosulfur trifluoride (DAST), a reagent derived from SF₄. It is particularly useful for conversion of alcohols to alkyl fluorides, carboxylic acids to acyl fluorides and carbonyl compounds to gem-difluorides.

However the use of DAST for larger scale deoxyfluorination is limited due to it reacting violently with water and having a limited thermal stability. DAST itself is a fuming, volatile liquid and

difficult to handle in humid conditions and owing to its calorimetry profile can be explosive at temperatures above 90 °C. DAST therefore must be handled with care.

The application of flow chemistry offers several advantages here when undertaking hazardous reactions of this type including more efficient heat transfer to control thermal runaway, the ability to limit reaction volume, the decrease in handling explosive, highly toxic and corrosive reagents and the continuous replenishment of the reactants.

A further limitation of using these reagents in traditional batch methods are the by-products are often also highly reactive and will etch laboratory glassware. The use of the **Vapourtec R-Series** removes this issue as all reagents and by-products are only in contact with corrosion resistant components and PTFE tubing.

There are a number of publications that demonstrate the use of DAST in microfluidic systems where the reagent is introduced to the flowing stream after the pump via injection loops¹.

This study describes the use of the Vapourtec R-Series reactor to continuously feed the moisture sensitive fluorinating reagent DAST directly through the acid resistant **R2 C Plus** pump heads allowing a continuous, scalable reaction.

Method (Optimization)

As stated above, the use of injection loops after the pump head to introduce DAST to the reaction has been demonstrated. The aim here is to demonstrate the continuous pumping with no detrimental decomposition and no decrease in reactivity of the reagent. Initial experiments involved pumping small aliquots of both substrate

and fluorinating reagent through the pump head to measure this.

It is important that the drying procedure for running moisture sensitive reagents such as DAST is carried out as any residual moisture will result in decomposition of the reagent generating HF. Vapourtec have developed protocols for a variety of water and/or air sensitive reagents which are freely available to all Vapourtec R-Series users.

For this study the Vapourtec “DAST protocol” was used.

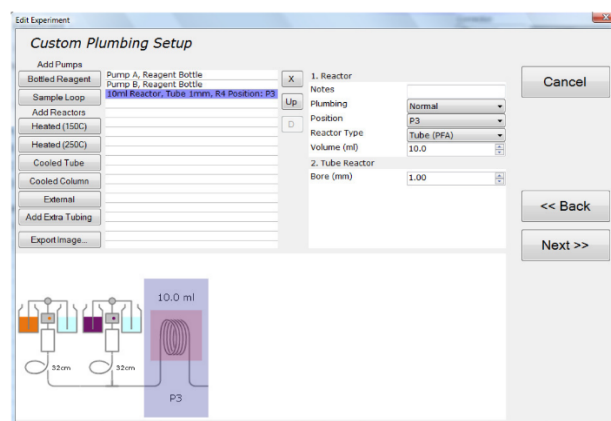


Fig 1. Flow control software setup for the experiment.

Setup

The flow reactor was configured using a combination of the **R2 C Plus** pump module and **R4** reactor module as shown in Figs 1.

A 10 ml PFA reactor was installed along with an 8 bar Vapourtec acid resistant back pressure regulator (BPR) fitted in-line between the reactor outflow and the collection valve.

A 20 ml stock solution of the reagents was prepared in anhydrous DCM;

Solution A

0.25 M of the substrate **1**, 5-Nitro-2-thiophenecarboxaldehyde (Aldrich 302295, CAS 4521-33-1)

Solution B

0.50 M Substrate **2**, diethylaminosulfurtrifluoride (DAST), (Aldrich 31942, CAS 38078-09-0)

System Parameters

System solvent:	DCM
Reagent A:	0.25 M substrate 1
Reagent B:	0.50 M substrate 2
Flow rate A:	variable (167 – 1000 $\mu\text{L}/\text{min}$)
Flow rate B:	variable (167 – 1000 $\mu\text{L}/\text{min}$)
Stoichiometry A:B	1:2
Reactor volume:	10 mL PFA reactor
Reactor temperature:	80 °C
Back pressure regulator:	~8 bar. Vapourtec Acid resistant BPR (with 1 mm bore throughout).

Then the following sequence of events was carried out for each reaction

1. The system was fully dried as per the protocol.
2. *Priming the pumps with anhydrous DCM:* Both selection valves were set to 'Solvent' and the pumps were primed with anhydrous DCM under a nitrogen atmosphere at 1.0 mL/min per pump.
3. *Priming the pumps with reagents:* The selection valve for line 1 was set to 'Reagent', the pumps set to 1 mL/min and the line connecting the valves to stock bottle 1 was filled with **Solution A**. The selection valve was set back to 'Solvent'

and anhydrous DCM pumped through the lines for 2 minutes. The same process was repeated with line 2, **Solution B** to fill the second reagent line.

4. *Reaction optimization:* A selective range of conditions were run using flow control software. Residence times of 5, 10, 15 and 30 minutes were run at with a fixed stoichiometry (2.0 eq DAST) in a 10ml reactor at 80 °C. A 4 ml aliquot of solution A (1.0 mM substrate 1) was reacted in each experiment.
5. *Work-Up and Analysis:* The collection stream was directed into a vial containing a 10 % solution of NaHCO_3 to quench the reaction. The product was extracted with DCM, washed with a saturated solutions of NaHCO_3 and then brine, dried (MgSO_4) and concentrated *in-vacuo* to dryness.

The reactions were followed by TLC (SiO_2 , 1:1 EtOAc:Hexane, UV detection) and RP HPLC.

The initial reaction conditions of a 30 min residence time at 80 °C with the 2.0 eq of DAST required showed a quantitative conversion to the desired product.

A reduction of residence time was explored (to increase the mass transfer). At residence times of 15, 10 and 5 minutes a quantitative conversion was also observed.

Again to increase mass transfer, the concentration of solution B was increased to 1.0 M. Note due to the solubility of substrate 1, the concentration of solution A could not be increased. Repeating the experiment at 5mins residence time, 80 °C and 2.0 eq DAST again gave a quantitative conversation by TLC/HPLC.

Fig 2 shows the flow control software reaction setup for this reaction.

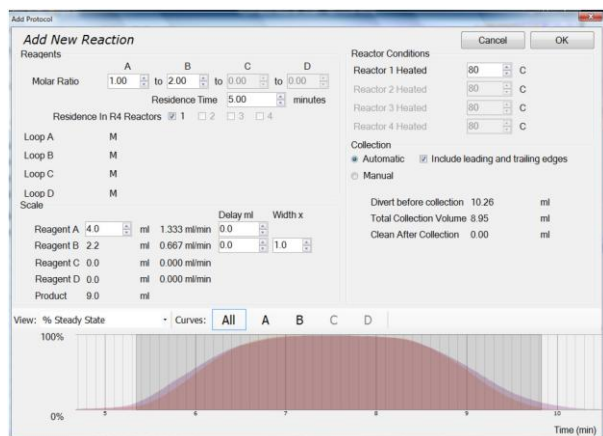


Fig 2. Reaction setup showing

- reaction conditions
- predicted dispersion profile at the collection point

Method (Steady State Conditions)

As described the optimum reaction conditions for reacting a dispersed 4 ml aliquot were 80 °C, 5 mins residence time with 2.0 eq DAST.

The predicted dispersion profile from this reaction (see base of fig 2) shows a significant steady state region and showed a quantitative conversion (by TLC/HPLC) with these conditions.

These two factors make it reasonable to assume that the reaction can be not only run in a continuous steady state but also scaled further by using the Vapourtec R-Series capabilities of placing four reactors in series, as shown in Fig 3.

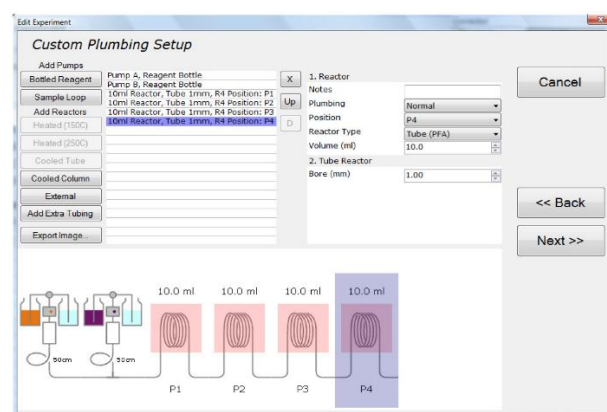


Fig 3 . Experimental Setup for scale-up

Setup

Fig 4 shows the reaction setup in flow control software.

Note that the 5 mins residence time is applied to the combined reactor formed by the four individual reactors in series.

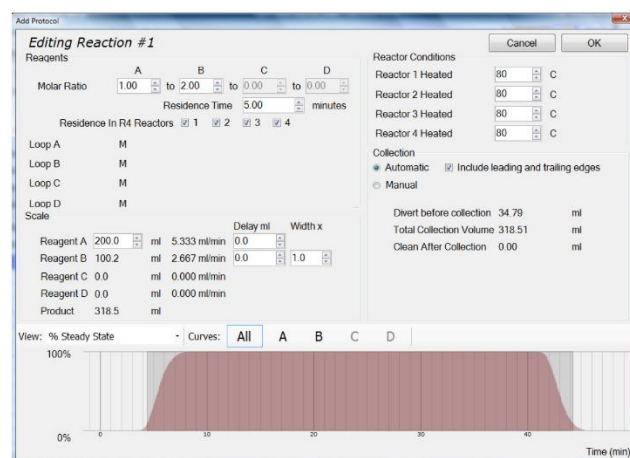


Fig 4 – Reaction set-up for scale-up

Stock solutions of the reagents were prepared in anhydrous DCM;

Solution A

0.25 M of the substrate **1**, 5-Nitro-2-thiophenecarboxaldehyde (Aldrich 302295, CAS 4521-33-1) (200 ml, 50 mM)

Solution B

1.00 M Substrate **2**, diethylaminosulfur trifluoride (DAST), (Aldrich 31942, CAS 38078-09-0) (100 ml, 100 mM)

System Parameters

System solvent:	DCM
Reagent A:	0.25 M substrate 1
Reagent B:	1.00 M substrate 2
Flow rate A:	5.333 mL/min
Flow rate B:	2.667 mL/min
Stoichiometry A:B	1:2
Reactor volume:	40 mL (4x 10 ml PFA reactor)
Reactor temperature:	80 °C
Back pressure regulator:	~8 bar. Acid resistant BPR used with 1 mm bore throughout.

The sequence of events was repeated from the optimization experiments.

1. The system was fully dried as outlined above. This was repeated to ensure the extra reactors used were fully dried.
2. *Priming the pumps with anhydrous DCM:* Both selection valves were set to 'Solvent' and the pumps were primed with anhydrous DCM under a nitrogen atmosphere at 1.0 mL/min per pump.
3. *Priming the pumps with reagents:* The selection valve for line 1 was set to 'Reagent', the pumps set to 1 mL/min and the line connecting the valves to stock bottle 1 was filled with **Solution A**. The selection valve was set back to 'Solvent' and anhydrous DCM pumped through the lines for 2 minutes. The same process was repeated with line 2, **Solution B** to fill the second reagent line.

4. *Steady State Reaction:* A residence times of 5 minutes was set at 80 °C with a stoichiometry (2.0 eq DAST) in a 40 ml reactor (4 x 10 ml PFA reactors in series). 200 ml of solution A was reacted.
5. *Work-Up and Analysis:* The collection stream was directed into a vial containing a 10% solution of NaHCO₃ to quench the reaction. The product was extracted with DCM, washed with a saturated solutions of NaHCO₃ and then brine, dried (MgSO₄) and concentrated *in-vacuo* to dryness.

Results

Optimisation Experiment

4 ml of **solution A** (1 mmol) was processed and collected over ~4.5 mins as shown above, fig. 2. After work-up the extracted material gave a straw coloured oil. Yield = 0.166g, 93%. Note the product was not purified further as NMR indicated 100% purity.

Steady State Experiment (Scale-Up)

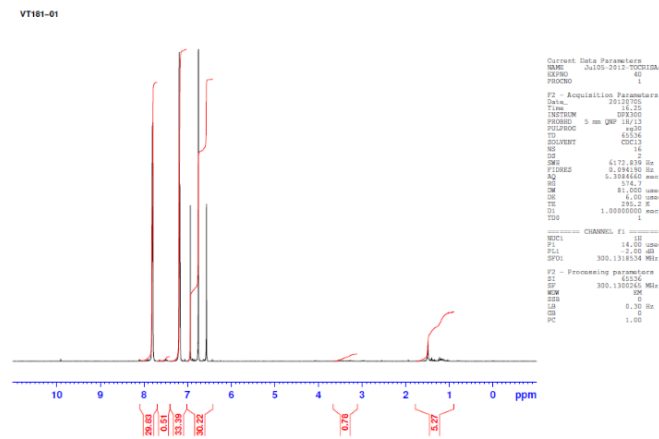
200 ml of **solution A** (50 mmol) was processed and collected over ~37.5 mins as shown above. After work-up the extracted material gave a straw coloured oil. Yield = 8.495 g, 95%. Note the product was not purified further as HPLC indicated 97.5% purity.

The yield of 8.5 g over just under 40 mins is equal to a mass transfer of ~13.6 g /hr. Extrapolating this experiment we can predict a yield of ~325 g/ 25hrs under continuous reaction conditions.

NMR Analysis

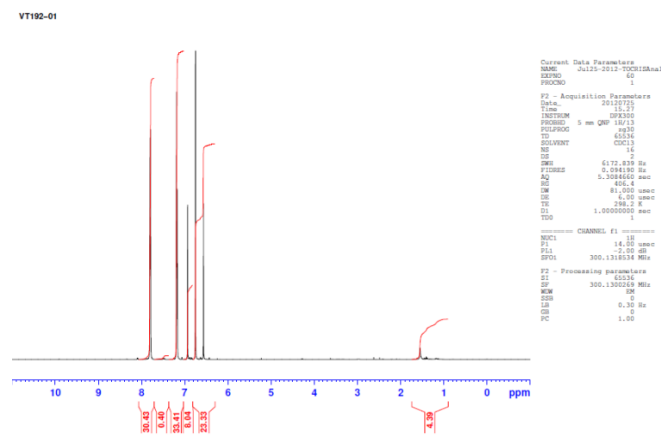
VT181-01 4 ml Optimization Experiment.

^1H NMR

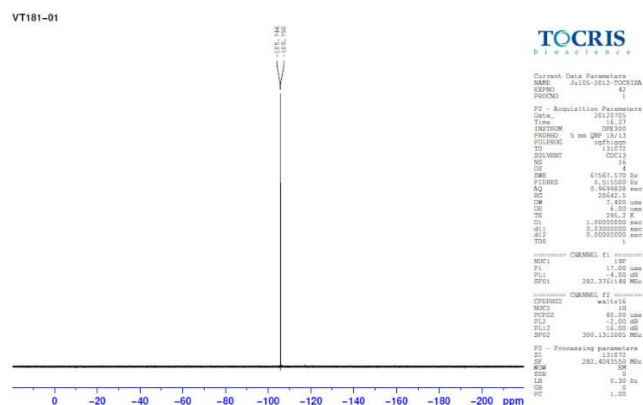


VT192-01 Steady State Experiment (Scale-Up)

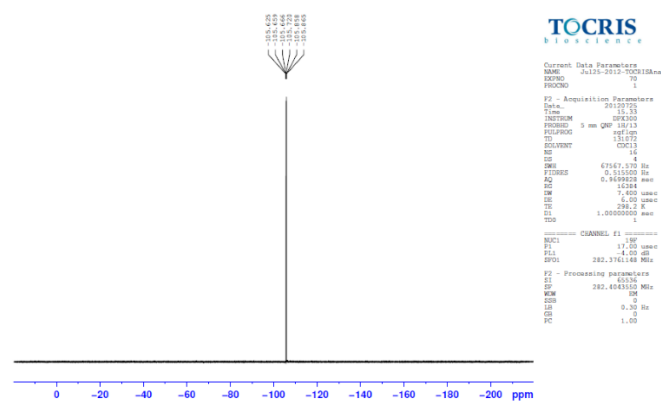
^1H NMR



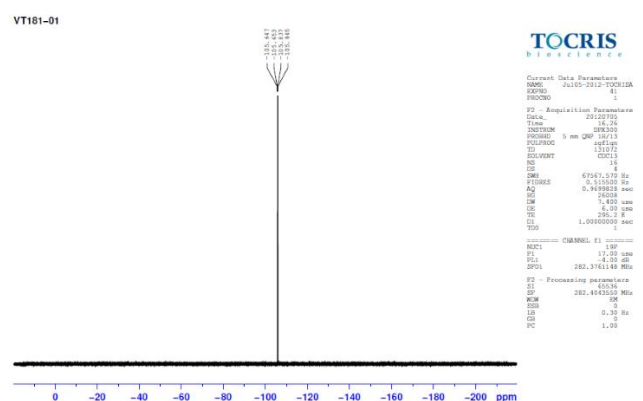
^{19}F NMR (F decoupled)



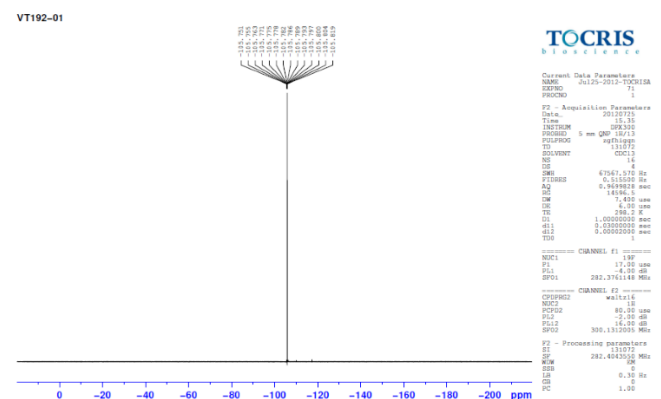
^{19}F NMR (F decoupled)



^{19}F NMR (F coupled)



^{19}F NMR (F coupled)



Waiting on NMR analysis for the larger scale reaction, should have these tomorrow.

- ⁱ (a) Marcus Baumannn, Ian R. Baxendale, Steven V. Ley, Synlett, **2008**, 14, 2111-2114;
- (b) Marcus Baumann, Ian R. Baxendale, Laetitia J. Martin, Steven V. Ley, Tetrahedron, **2009**, 65, 6611-6625;
- (c) Tomas Gustafsson, Ryan Gilmour, Peter H. Seeberger, **2008**, 3022-3024.