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Kinetics and Process Development for Deoxofluorination of a Steroid

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Abstract:

In this paper investigations for developing a continuous process for the fluorination of a steroid derivative with bis(methoxyethyl)-aminosulfurtrifluoride are presented. A kinetic model is suggested for this reaction. A simulation-based experimental design approach was implemented to find the optimum conditions for the flow reaction in a microreactor system.

Introduction

Most of the fine chemicals are produced through batch or semibatch processes. Batch processes have some inherent disadvantages compared to continuous processes, e.g., higher operating costs, fluctuating product quality, smaller throughput, etc. Also, in the case of hazardous reactions continuous processes can be safer owing to smaller reactor volume and provide more flexible scale-up options.[1] This is especially an advantage inherent to microreactors.[2,3] Synthesis under microreactor environment also allows optimum control over reaction parameters and, more importantly, the ease of handling potentially hazardous reagents due to smaller reaction volumes and channel sizes.[4]

Furthermore, in fine chemical industry the optimized processes are often designed on the basis of direct experimental data and experience. Following this approach, the optimum conditions can be found only with elaborate experimental efforts, and scaling up may not lead to desired optimum process conditions. In this work we have applied a model-based approach to develop a continuous process. A model fitted to batch reactor data was implemented to find optimum conditions for continuous process through simulations. Although initially time-consuming, this approach when applicable gives a better understanding of the reaction, helping in a better process design and scale-up. We have chosen the fluorination of the steroid molecule **1** to produce geminal difluoride **3a** as a model reaction. Fluorination reactions are gaining increasing interest in medicinal chemistry.[5]

The goal was maximization of conversion and the selection of optimal residence time, temperature, and reagent amount. In our initial experiments we used diethylaminosulfur trifluoride (DAST) as fluorinating agent, which is commonly used for selective deoxofluorination to produce geminal difluorides.[6,7] However, DAST is not recommended to be used at temperatures above 80 °C because of safety reasons, thus putting a limit on the reaction rate. Moreover it is also considered unsafe for industrial use because of its thermal instability.[8,9] A similar fluorinating agent reported to be safer than DAST is Deoxofluor (bis(methoxyethyl)-aminosulfurtrifluoride).[10] It was used successfully at higher temperatures, giving results similar to those with DAST. The deoxofluorinaton reaction investigated is represented in Figure 1. The steroid **1** also produced the byproduct **3b** besides the main product **3a**.

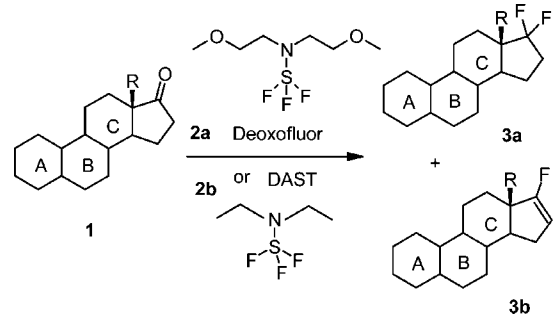

Figure 1. **Fluorination of steroid with DAST or Deoxofluor. Rings A, B, and C represent the rest of the steroid molecule that remains unchanged in the reaction.**

Results and Discussion

In an initial production campaign, a few kilograms of steroid **1** were fluorinated with DAST in a flow reactor. Further investigations were carried out with Deoxofluor substituted for DAST because of the reported safety advantage of the former over latter. All of the results discussed here were those obtained with Deoxofluor. In our work we carried out experiments in a batch reactor at different temperatures and Deoxofluor molar equivalents to prepare a kinetic scheme for this reaction. Experiments in a flow reactor were then carried out and optimized based on the simulations using the kinetic model.

Batch Process. *Reactor.* All reactions for collecting kinetic data were carried out in 50-mL glass reactors. A thermostatted oil bath was used for heating the reactor. The temperature of oil bath and inside the reactor was measured by PT 100 sensors. A new vessel was used for each reaction. Although we did not observe etching of glass after reaction, the use of glass is not

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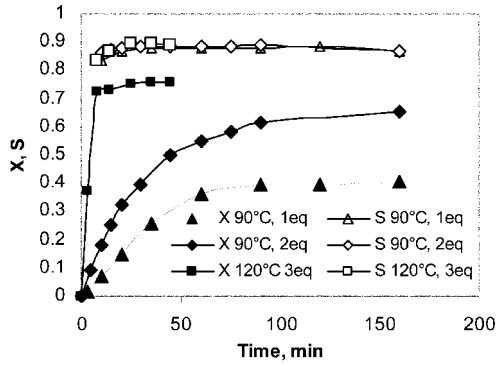

Figure 2. **Effect of molar equivalents of Deoxofluor 2a on conversion (X) and selectivity (S). Conversion is defined as moles of steroid 1 reacted per mole of 1 fed. Selectivity is defined as moles of difluoride 3a produced per mole of 1 reacted.**

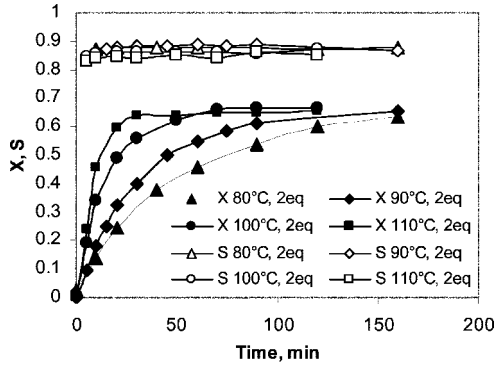

Figure 3. **Effect of temperature on conversion and selectivity; "2eq" represent 2 molar equiv of Deoxofluor 2a to steroid 1.**

recommended because of possible HF formation. The samples were analyzed by HPLC to get the concentration−time profile of the major reaction components.

Solvent Selection. The reactant **1** is a white powder at room temperature. As our aim was a continuous process, a solvent was required to dissolve **1** as a prerequisite to facilitate dosing of the reactants for continuous processing. Deoxofluor was supplied dissolved in toluene; therefore, as a first option toluene was used as a solvent for **1**, but its use at higher temperatures was limited by its boiling point. Mesitylene and tetralin were also tested in batch reactions at temperatures above 90 °C. We did not observe any difference in the reaction rates in different solvents. Tetralin was used for further experiments above 90 °C because of its lower cost. A 1:1 w/w mixture of steroid **1** and solvent was used in all of our reactions.

Deoxofluor Equivalents. Stoichiometrically 1 molar equiv of Deoxofluor or DAST is required to convert a ketone group into *gem*-difluoride, but in practice it is observed that higher molar equivalents are needed for a complete conversion. Figure 2 shows the effect of molar equivalents of Deoxofluor on conversion of the steroid. The selectivity of the main product **3a** was found not to vary significantly.

Reaction Temperature and Residence Time. Higher temperature leads not only to faster reaction rate but also to faster decomposition of Deoxofluor as a parallel side reaction. This puts a limit on the maximum attainable conversion of **1** after a reaction time depending on the operating temperature. The effect of operating temperature is shown in Figure 3. The temperature reported is the bath temperature. The observed reaction temperature was 2 ± 1.5 °C below bath temperature, except during the addition of Deoxofluor. As Deoxofluor was at room temperature, the reactor temperature dropped up to 15 °C below the bath temperature on adding Deoxofluor. The temperature was recovered within 1–2 min. At higher bath temperature (>110 °C) the reaction temperature exceeded the bath temperature by up to 5 °C between 2 and 5 min after adding Deoxofluor as a result of exothermic heat of the reaction. Consequently, Deoxofluor had to be added slowly over approximately 1 min to avoid higher temperature variations.

Reaction Kinetics. We analyzed the reaction products for the concentration of **1**, **3a**, and **3b**. Based on our results, the following reaction scheme is proposed:

Reaction 1: Steroid **1** + Deoxofluor **2a** $\xrightarrow{k_1}$ geminal difluoride **3a** + byproducts

Reaction 2: Steroid **1** + Deoxofluor **2a** $\xrightarrow{k_2}$ vinyl fluoride **3b** + byproducts

Reaction 3: Deoxofluor **2a** + Deoxofluor **2a** $\xrightarrow{k_3}$ byproducts

Reaction 4: Deoxofluor **2a** $\xrightarrow{k_4}$ byproducts

The term byproducts in the above equations refers to unidentified byproducts resulting from Deoxofluor. The thermal degradation mechanism of Deoxofluor is not well understood. First we assumed a second-order decomposition of Deoxofluor (Reaction 3) similar to that of DAST (7), but it was found inadequate to explain our batch data. The assumption of a first-order decomposition (Reaction 4) showed improved results, but a combination of both steps showed still better agreement with the experimental results. In the absence of a reliable method to measure the Deoxofluor concentration in the reaction mixture, we tested the thermal degradation of Deoxofluor by heating it for a length of time (up to 100 min) at one reaction temperature (120 °C) and then reacting it with the steroid **1** at 1:1 molar ratio at 100 °C for 3 h. It was observed that Deoxofluor heated for a longer time gave lesser conversion of the steroid. Heating Deoxofluor for more than 90 min at 120 °C destroyed its activity to deoxofluorinate the steroid **1**. If the concentrations of **1**, **2a**, **3a**, and **3b** are represented by C_1, C_{2a}, C_{3a} and C_{3b}, respectively, the mass balance in a batch reactor can be expressed as:

$$\begin{aligned}
\frac{dC_1}{dt} &= -k_1C_1C_{2a} - k_2C_1C_{2a} \\
\frac{dC_{2a}}{dt} &= -k_1C_1C_{2a} - k_2C_1C_{2a} - 2k_3C_{2a}^2 - k_4C_{2a} \\
\frac{dC_{3a}}{dt} &= k_1C_1C_{2a} \\
\frac{dC_{3b}}{dt} &= k_2C_1C_{2a}
\end{aligned} \tag{1}$$

The model parameters, viz., reaction rate constant and activation energy, were calculated by fitting the model to batch reaction data. Berkeley Madonna (Version 8.0.1) was used for parameter fitting and simulations. The initial concentrations required for the model were calculated from the measured initial amounts of **1** and **2a** added in the reactor and the measured

Table 1. **k and E_a values**

reaction number	k at 90 °C	E_a (kJ/mol)
1	1.85×10^{-4} ($Lmol^{-1}$ min^{-1})	62.67
2	2.63×10^{-5} ($Lmol^{-1}$ min^{-1})	66.90
3	3.14×10^{-6} ($Lmol^{-1}$ min^{-1})	69.59
4	2.25×10^{-4} (min^{-1})	73.76

volume of the reaction mixture in the reactor. The model was able to predict the conversion and selectivity within 10%. The values of the reaction constants and activation energy are given in Table 1. Figure 4 shows a comparison of model simulation with experimental batch data.

Continuous Process. The experimental setup is shown in Figure 5. A tube reactor was selected for continuous process because plug flow reactors are more efficient for positive order reactions than CSTR (continuous flow stirred tank reactor) etc. In our laboratory, 3 mm i.d. (inner diameter) stainless steel tube and 1.6 mm i.d. perfluoroalkoxy (PFA) tubes with lengths of 4–18 m were tested. The tube was immersed in a thermostatted oil bath. The temperature profile inside the tube was not measured because of installation difficulties. In some of the experiments it was observed that some byproducts tend to accumulate in the tube at low flow rates. We preferred the smaller diameter PFA tube as it is transparent, which allows an optical observation of the flow. We also found a more homogeneous flow in the smaller diameter PFA reactor, and it was also easier to clean probably owing to lesser wall friction compared to metal tubes.

The smaller diameter tube also facilitates heat transfer by providing higher heat transfer area per unit reaction mass. Since the reaction is exothermic, poor heat transfer would lead to a temperature rise in the reaction mixture, especially in the first section, that favours the decomposition of Deoxofluor, leading to a lower overall conversion. Formation of gas was also observed in the reaction that gave rise to a two-phase plug flow with alternating gas- and liquid-filled sections. Although small amounts of gas did not show any undesirable effect, higher gas fractions were undesirable as they also led to lower and unsteady residence time of liquid in the tube. A back pressure valve was installed at the reactor exit to suppress gas formation. An excess

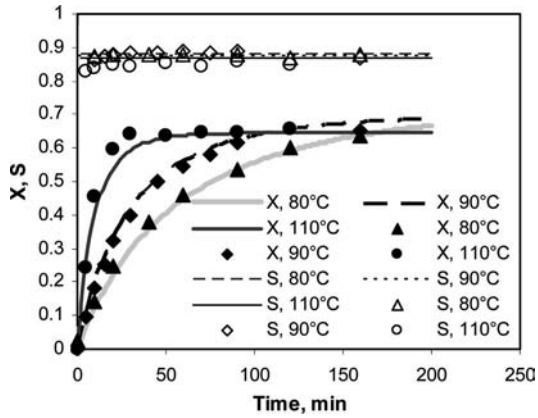

Figure 4. **Comparison of simulations and experimental data. Symbols represent experimental data, and lines represent simulated data.**

pressure of 0.5 bar was sufficient to achieve a uniform flow at 120 °C. The reactant−product ratio at the reactor exit was also monitored by ATR FT-IR. With online IR analysis, the onset of steady state could be easily monitored, and the predicted conversion by IR was within 6% of that obtained by HPLC. The steady-state conversion values obtained in different runs and the simulated profiles for comparison are represented in Figure 6. The reported temperature in Figure 6 is the oil bath temperature. The data shown is based on HPLC analysis.

Reaction in the tube reactor showed conversions higher than simulated data. This may be due to possible temperature differences in the actual reaction temperature profile inside the tube and in the batch reactor caused by differences in heat transfer conditions. Nevertheless, the model based on batch data could be reliably implemented to guide experiments towards finding optimum conditions. The effect of solvent amount, Deoxofluor equivalent, temperature, and residence time was investigated through computer simulations. Thus many unnecessary experimental conditions could be avoided, narrowing the range of experiments to be tested to find the optimum conditions. We found a residence time of 30 min at 120 °C to be an optimum. In our case 3 molar equiv of Deoxofluor was selected as we aimed to achieve a minimum of 75% conversion. Higher equivalents will lead to higher conversions but also to higher operating costs. An optimum depends on the particular requirements.

Conclusions

A continuous process for a deoxofluorination reaction has been developed and optimized. A kinetic model is suggested and was implemented to guide experiments in a flow reactor to optimize temperature, residence time, and Deoxofluor equivalents. The model is also a helpful tool for scaling up the process.

Experimental Section

Deoxofluor was supplied by Air Products as a 50% solution in toluene. The supplied Deoxofluor was distilled under vacuum at 60 °C to evaporate 50% of the weight before use in reaction. Toluene (≥99.9%, Merck), mesitylene (≥98%, Merck), acetonitrile (≥99.9%, Merck), and tetralin (≥96%, Merck) were used as supplied.

Procedure for Batch Reaction. Initially steroid **1** and the solvent were charged into the reactor. The reactor content was constantly stirred by magnetic stirrer. Deoxofluor was added when the desired temperature was reached. The time of addition of Deoxofluor was taken as the start time for the reaction. Samples were taken at different times and analyzed by HPLC.

Procedure for Continuous Reaction. The experimental setup is shown in Figure 5. Two feed tanks were employed. One carried the reactant **1** dissolved in tetralin in 1:1 w/w ratio and preheated to 90 °C. Deoxofluor was stored in a second feed tank at room temperature. The two liquids were pumped by calibrated rotary piston pumps through a micromixer (CPMM-R1200, IMM) into the tube reactor (1.6 mm i.d., 12 m length) that was initially filled with solvent only. The flow rates were set to get the desired Deoxofluor to steroid molar ratio and the required residence time in the tube. The micromixer

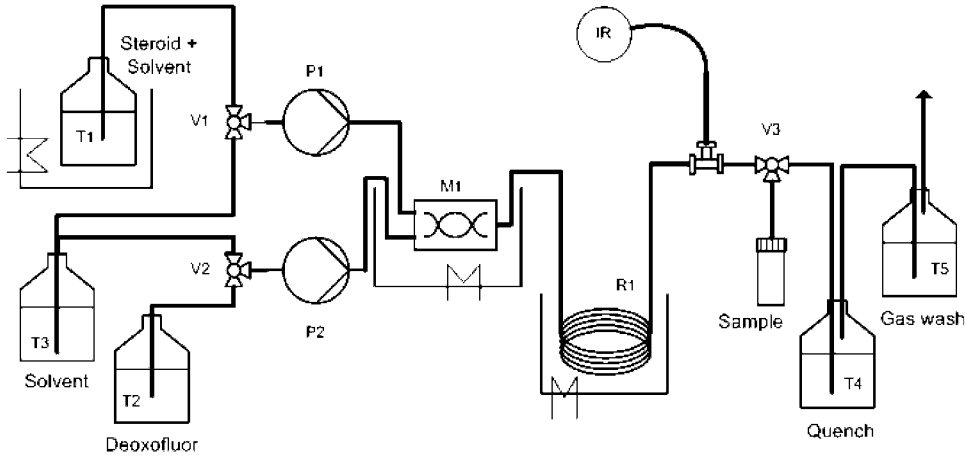

Figure 5. **Flowsheet for the continuous process. T1−T5, tanks; V1−V3, valves; P1 and P2, pumps; M1, micromixer; R1, coiled tube (reactor); IR, infrared spectrometer.**

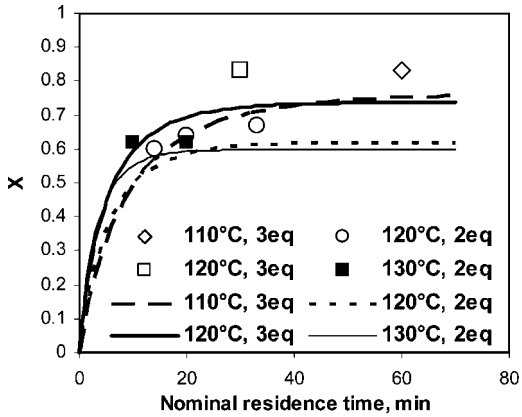

Figure 6. **Conversion in continuous process with different parameters. Symbols represent experimental data, and lines represent simulated data.**

was heated to 70 °C to prevent crystallization of the steroid, and the tube was immersed in the oil bath at the desired reaction temperature. The reactant−product ratio at the reactor exit was monitored by ATR FT-IR. After attaining steady state, samples were collected and analyzed by HPLC. The steady state values are reported in Figure 6.

Analytical Methods. The analysis of samples was performed by an HPLC (Hewlett-Packard 1100 Series) with a Zorbax-SB-C18 column (Agilent Technologies): length, 50 mm; i.d., 4.6 mm; liquid flow rate, 1 mL/min; Detector type, UV (220 nm); polar phase, water; nonpolar phase, acetonitrile. Before analysis, the reaction samples were quenched in a mixture of THF and 1 M NaOH (1:10 v/v). The organic phase was then diluted with acetronitrile and analyzed for **1**, **3a**, and **3b** by HPLC. During the continuous process online monitoring was performed by an FT-IR spectrometer (Nicolet 380 from Thermo Scientific).

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