

MICROFLUIDIC SYNTHESIS OF ENERGETIC COMPOUNDS

Dr. Joe Scavuzzo and Dr. Melissa Mileham

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Orbital ATK
Corinne, Utah

ABSTRACT

Microfluidic synthesis is the use of microliter scale flow reactors to manipulate reactive liquids or solutions to produce chemical transformations. Microfluidic synthesis processes have some advantages over traditional batch processes, particularly when producing energetic molecules. For example, microfluidic reactors contain only microliters of reactive solution, which greatly reduce risks associated with large volumes of energetic material. Further, because of the high surface area-to-bulk ratio in microfluidic reactors, heat is efficiently transferred away from the system. This is of particular importance for the synthesis of energetic molecules where exothermic nitrations and oxidations are common. The simplicity of microfluidic reactors also allows for easy scale-up and automation for remotely controlled processes. The present work deals with the design and fabrication of a microfluidic reactor used to produce energetic molecules. A nitrated precursor for an energetic polymer was chosen as the target molecule. The synthetic process contains two steps where organic molecule X1 is first nitrated to produce NO₂-X1. In the second step, NO₂-X1 undergoes an exothermic rearrangement to give the final product, NO₂-X2. Each step was performed and optimized individually on the microfluidic reactor. The optimized conditions were then used to perform the two steps in series on a single reactor.

INTRODUCTION

MICROFLUIDIC REACTOR BACKGROUND

Microfluidic reactors manipulate reactive liquids or solutions to produce chemical transformations under geometrically constrained environments with internal dimensions on the scale of micrometers.^[1] Microfluidic reactors contain microliter volumes of reaction solution, therefore only micrograms of energetic material are in process at any given time. This is particularly advantageous during the development stage of a new chemical process. Developmental operations involving new energetic materials and/or processes are inherently higher risk because of unknown behaviors and the potential for explosion. Accepting these risks can be reasonable if the consequence of an unexpected behavior is low. Because the process volumes of microfluidic reactors are restricted to microliters/gram scale, the consequences of unexpected behavior are more acceptable.

Microfluidic reactors provide some unique advantages over traditional synthesis methods. The reactor's high surface area-to-volume ratio allows for very efficient heat transfer from the reactor to the reactor's external environment. Highly exothermic reactions are commonplace in energetic material synthesis and efficient heat transfer translates to safer operations by mitigating the risk of self-heating runaway reactions.

Precise temperature control can also lead to higher purity reaction products by decreasing side reactions. [1]

These advantages are amplified in many self-contained commercially available systems because of the extensive characterization of reactor capabilities. Further, many commercially available systems are specifically designed for rapid process development (10 to 25 reaction conditions per day) and simple scale-up to the kilo or pilot-scale. It should be noted that scale-up is typically accomplished by operating reactors in parallel and/or extending the length of the microfluidic pathway. Kilo-scale operations can produce between 6 and 12 liters/hour of reaction solution while maintaining an active reactor volume of only ~200 μL .

Though commercially available reactors are impressive and offer many advantages, for the purposes of the research outlined in this work, a simple reactor was constructed in-house using basic laboratory equipment as a proof of concept. A target energetic molecule was chosen that requires two chemical reactions. The first reaction is the nitration of molecule X1 with 98% nitric acid to give NO₂-X1. Compound NO₂-X1 is then chemically transformed in a second reaction to give the target molecule NO₂-X2.

DEVELOPMENT STRATEGY

The development of the reactor was a three-step process as outlined in Fig. 1:

1. Optimize reactor parameters for nitration to produce NO₂-X1 (reaction step 1)
2. Optimize reactor parameters for chemical transformation of NO₂-X1 to NO₂-X2 (reaction step 2)
3. Perform reaction step 1 and reaction step 2 in series to transform X1 to NO₂-X2 in a single reactor

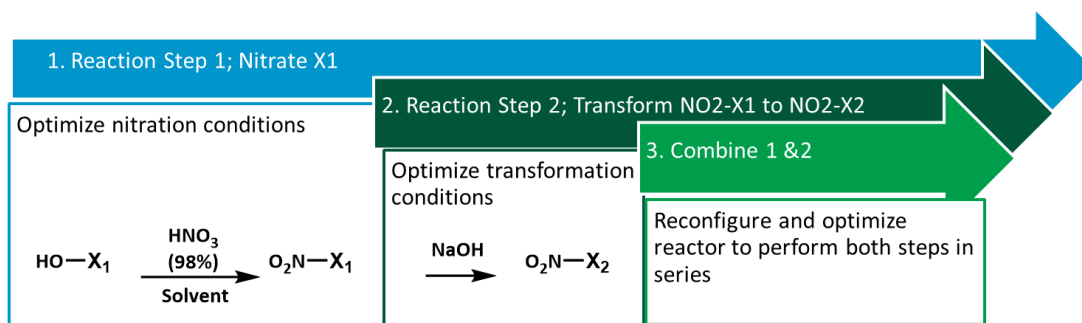


Fig. 1: Development strategy flow chart

RESULTS AND DISCUSSION

REACTOR DESIGN

The reactor is designed around critical design parameters and with flexibility in areas that allow for control over critical process control variables (Table 1). Reagents A and B are introduced to the system using syringe pumps set to constant flow rates. These reagents are pushed through acid resistant tubing (fluoropolymer) with an inner diameter of 0.79 mm to a T-Joint that combines reagents A and B into a single resonance tube. The resonance tube varies in length (30 to 140 cm) depending on the

operation and is coiled and submerged in a controllable constant temperature bath. Reagent feed ratios are controlled with different syringe sizes (Fig.2), or simply by using separate syringe pumps set to the desired flow rates. Resonance time is controlled by either resonance tube length or the combined flow rate of reagents A and B. Reaction product C is collected from the terminal end of the resonance tube into a glass vial for final analysis.

Table. 1: Reactor Design Parameters and Process Control Variables

Critical Design Parameters
Reagents A and B shall mix to produce product C ($A + B = C$).
Reagents A and B shall be introduced at a constant flow rate.
All wetted materials shall be resistant to oxidizing acids.
Reactor tube diameters shall be restricted to < 1mm diameter.
Reactor tube length must be of sufficient length to allow for reasonable resonance times.
Process Control Variables
Reaction temperature
Reagent feed ratios
Reaction solution resonance time



Fig. 2: Reactor design

REACTION STEP 1; X1 Nitration

The production of NO₂-X1 has traditionally been performed as a batch reaction, which requires extensive cooling to manage the exothermic nitration. Precise control over the reaction temperature, acid concentration and reaction time are required to ensure X1 is not under or over nitrated. The batch reaction conditions were used as a starting point for the microfluidic reactor conditions.

The reactor was configured as shown in Fig. 3 for the X1 nitration. Compound X1 was injected as reagent A and nitric acid or nitric acid/solvent solutions were injected as reagent B (Fig. 2 and 3). Reaction products were collected and analyzed by nuclear magnetic resonance (NMR) spectroscopy for percent conversion to NO₂-X1 and side products. Table 2 shows the process variables that were explored and the NMR analysis results. The first three experiments did not show any conversion of the starting material; it was determined that significantly longer reaction times are required. The resonance tube was extended from 30 cm to 412 cm for the remaining experiments. The data also shows higher acid concentrations are required for sufficient conversion to NO₂-X1. However, high acid concentrations also increase side reactions somewhat. Experiments 11 and 12 were conducted in order to demonstrate repeatability.

Statistical analysis was completed using JMP software to further understand the effects of changing process control variables. The analysis was a main effect analysis only for screening, which showed the acid concentration being the most significant factor, where lower amounts of solvent are best. The reactor size and retention time are close to significant ($P < 0.05$) and indicate smaller reactors and longer retention times are better. The results are shown in Tab. 2 and Fig. 4. The percent conversion and amount of side reaction product 1 present are in the same ranges expected for a batch reaction.

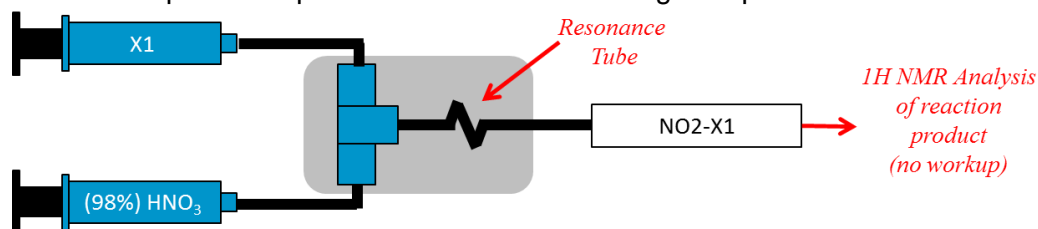


Fig. 3: X1 nitration reactor configuration

Table 2: X1 Nitration

Experiment	Temp (°C)	Acid Concentration (Solvent:HNO ₃)	Acid:X1	Flow Rate (mL/min)	Retention Time (min)	Molar % Conversion	% Side Rxn Product 1
1	15	2:3	4:1	0.11	2.05	0	0
2	25	2:3	4:1	0.11	2.05	0	0
3	30	2:3	4:1	0.11	5.65	0	0
4	20	1:3	4:1	0.15	21.6	19	14
5	20	1:5	4:1	1.23	2.68	13	12
6	20	1:5	4:1	0.25	13.4	14	12
7	20	1:5	4:1	0.125	26.0	54	13
8	27	1:5	4:1	1.23	2.68	22	13
9	20	0:1	4:1	1.23	2.68	68	14
10	20	0:1	4:1	0.25	13.4	43	7
11	20	0:1	4:0.68	0.76	4.23	78	39
12	20	0:1	4:0.68	0.152	21.0	74	18
11b	20	0:1	4:0.68	0.76	4.23	80	41
12b	20	0:1	4:0.68	0.152	21.0	75	27

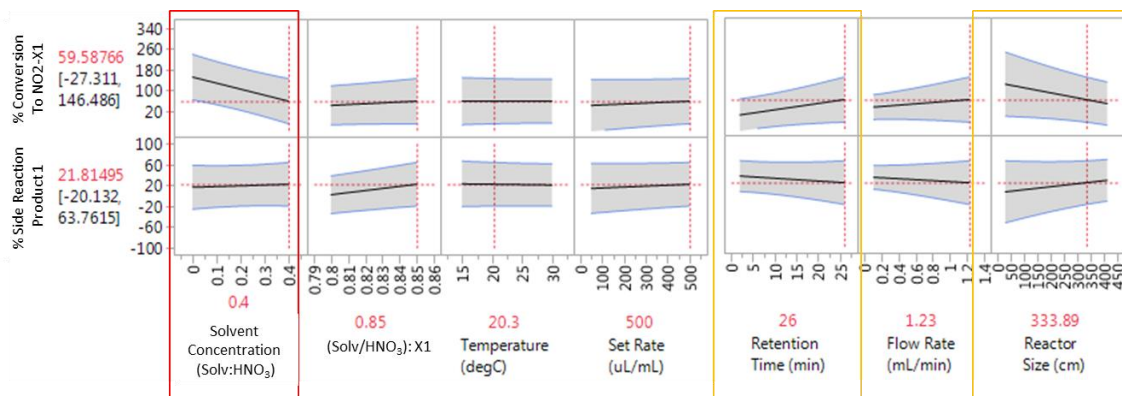


Fig. 4: Statistical analysis of NO₂-X1 conversion

NO₂-X2 STEP 2; NO₂-X1 CAUSTIC TREATMENT

The reactor configuration used for the nitration of X1 was also used for the NO₂-X1 transformation to NO₂-X2. However in this case, reagent A (Fig. 2) is an organic solution of NO₂-X1 and reagent B is a caustic solution. The reaction product of this step is the target material, X2-NO₂. For the experiments outlined in Table 3, the NO₂-X1 solution was prepared separately using a batch reaction set-up. The step 2 chemical transformation proved much easier in the microfluidic reactor than the nitration, with up to 100% conversion being achieved. It was also noted during the experiments that the reactor isothermal temperature bath remained at a constant temperature, indicating no apparent thermal runaways during the reaction. This is a key finding because the reaction involves the neutralization of any excess nitric acid from the previous step, which is an extremely exothermic reaction. Samples from each experiment were analyzed by NMR spectroscopy, with the percent conversion to NO₂-X2 and side products shown in Table 4. Statistical analysis was also completed for this data set, and determined the concentration of the NaOH, retention time and temperature were all important factors. The prediction model based on this analysis is shown in Fig. 5 and shows that maximizing NaOH concentration will increase NO₂-X2 conversion and yield with little impact on the amount of side product produced. Also, temperature offers minor improvements and a lower retention time increases yield while lowering the amount of side product.

Table. 3: Experiments conducted for conversion of NO₂-X1 to NO₂-X2

Experiment	NaOH:NO ₂ -X1	Temperature (°C)	Actual Flow Rate (mL/min)	Retention Time (min)
1	4:1	14	0.57	1.13
2	4:1	14	0.11	5.65
3	2.7:1	14	0.63	1.02
4	2.7:1	14	0.126	5.10
5	2.7:1	20	0.63	1.02
6	2.7:1	20	0.126	5.10
7	2.7:1	20	0.63	5.10
8	2.7:1	20	0.31	7.30
9	2.7:1	20	0.126	25.0
10	2.7:1	20	0.95	2.50
11	2.7:1	20	0.63	5.10

Table. 4: Conversion of NO₂-X1 to NO₂-X2 using a microfluidic reactor

Experiment	%Conversion (To NO ₂ -X2 or Side Product)	%Side Products	% Yield
1	20	0	20
2	20	0	20
3	83	0.6	82.4
4	92.4	2.6	89.8
5	94.7	2.2	92.5
6	97.3	3.9	93.4
7	100	5	95
8	100	9.3	90.7
9	100	40	60
10	93	6	87
11	97	13	84

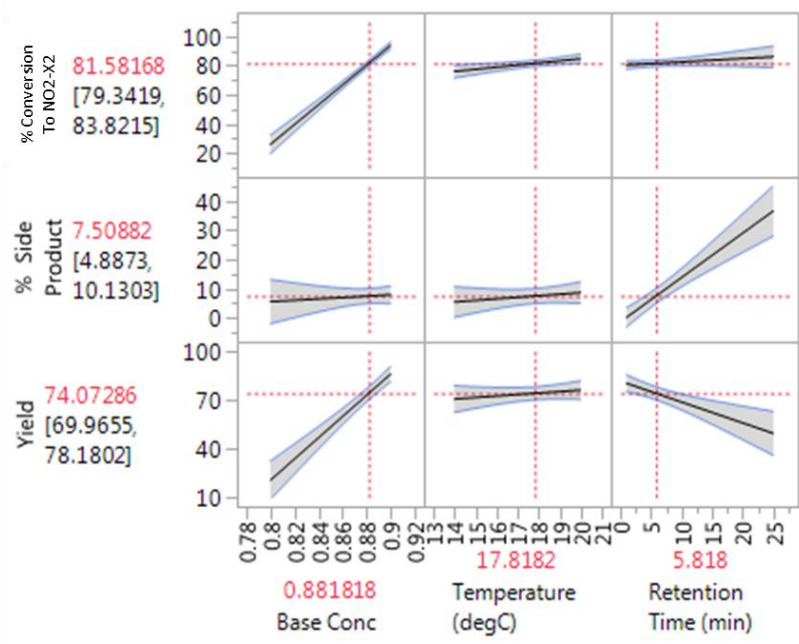


Fig. 5: Prediction model for ring closure step producing NO2-X2

STEP 1+2 IN SERIES; NITRATION AND CAUSTIC TREATMENT IN SERIES

In a final experiment, both steps of the NO2-X2 synthesis were performed in series on a single reactor. A schematic of the reactor is shown in Fig. 6. Compound X1 and nitric acid were injected into the T-joint under the optimized conditions discussed above to produce NO2-X1. The resonance tube containing NO2-X1 was then plumbed directly into a second T-joint where it was mixed with caustic and chemically transformed to NO2-X2. The specific conditions and results for each of the reactors are shown in Tables 5 to 7. NO2-X2 was produced at >75% yields. However, it is likely that additional optimization of process control variables would increase the reaction yield further. It should be noted that a 75% yield is in a similar range observed for batch conditions.

Table 5: Nitration conditions

Experiment	HNO3:X1	Temperature (°C)	Actual Flow Rate (mL/min)	Retention Time (min)
1	4:0.68	21	0.76	2.68
2	4:0.68	22	0.76	2.68
3	4:0.68	22	0.38	5.36

Table 6: Ring closure conditions

Experiment	NaOH Concentration	Temperature (°C)	NaOH Flow Rate (mL/min)	Retention Time (min)
1	3.4	22	0.774	1.2
2	7.2	22	0.774	1.2
3	7.2	32	2.4	0.7

Table 7: Experimental results from two-step microfluidic reactor producing NO₂-X₂

Experiment	%Conversion	% Side Products	Yield/Notes
1	N/A	N/A	Insufficient base
2	N/A	N/A	Inorganic precipitates
3	83	5.5	77.5

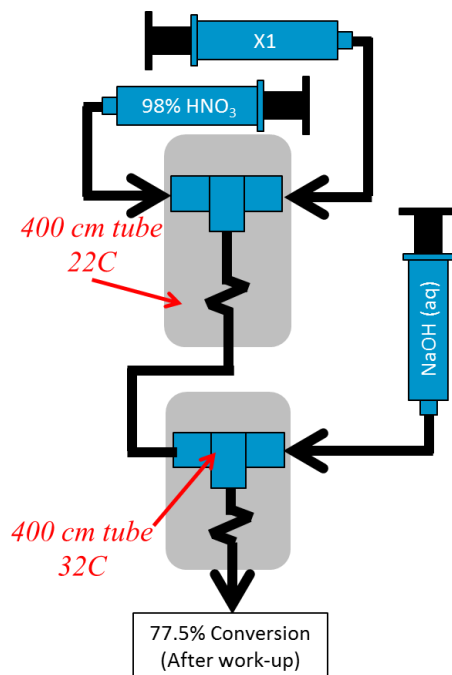


Fig. 6: Microfluidic reactor setup of two-step NO₂-X₂ synthesis

SUMMARY AND CONCLUSIONS

A microfluidic reactor was successfully constructed to meet the design parameters and required degree of control outlined in Table 1. The nitration of X₁ and caustic induced transformation of NO₂-X₁ have all been successfully completed using the current setup. Current methods for the nitration of X₁ are able to achieve at least an equivalent yield to the batch process, however, further optimization may increase the yield. The caustic induced transformation of NO₂-X₁ performed on the microfluidic reactor gave high yields of pure NO₂-X₂. When the reactor was reconfigured to perform both steps in series, NO₂-X₂ was successfully synthesized at a reasonable purity and yield. The in-house microfluidic reactor discussed here serves to prove that molecule NO₂-X₂ can be synthesized with microfluidics. Additional improvements in quality, and safety could be achieved with a more robust and properly characterized reactor.

REFERENCES

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AUTHORS

Dr. Joe Scavuzzo
Email: Joe.Scavuzzo@OrbitalATK.com
Office Phone: (435)863-8148

Address:
Orbital ATK
Building M-3
9160 UT-83
Corinne, UT 84307

Dr. Melissa Mileham
Email: Melissa.Mileham@OrbitalATK.com
Office Phone: (435)863-8399

Address:
Orbital ATK
Building M-3
9160 UT-83
Corinne, UT 84307