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LLNL-PROC-667843

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**May 18–21, 2015**

Insensitive Munitions and Energetic Materials Technology  
Symposium

Rome, Italy

This work performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344.

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# Microreactor flow synthesis of the secondary high explosive 2,6-diamino-3,5-dinitropyrazine-1-oxide (LLM-105)

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## Abstract:

*The secondary high explosive 2,6-diamino-3,5-dinitropyrazine-1-oxide, or LLM-105, has been synthesized using a commercially available flow microreactor system. Investigations focused on optimizing flow nitration conditions of the cost effective 2,6-diaminopyrazine-1-oxide (DAPO) in order to test the feasibility and viability of flow nitration as a means for the continuous synthesis of LLM-105. The typical benefits of microreactor flow synthesis including safety, tight temperature control, decreased reaction time, and improved product purity all appear to be highly relevant in the synthesis of LLM-105. However, the process does not provide any gains in yield, as the typical 50-60% yields are equivalent to the batch process. A key factor in producing pure LLM-105 lies in the ability to eliminate any acid inclusions in the final crystalline material through both a controlled quench and recrystallization. The optimized flow nitration conditions, multi-gram scale up results, analyses of sample purity, and quenching conditions for purity and crystal morphology control will be reported.*

*Keywords: LLM-105; Secondary High Explosive; Microreactor; Flow Synthesis*

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## Introduction

The nature of nitration chemistry has come a long way since the days of classical nitration by mixture of sulfuric acid and nitric acid (mixed acid), with the advent of powerful nitrate salts ( $\text{NO}_2\text{BF}_4$ )<sup>1</sup> and dinitrogen pentoxide<sup>2</sup>, in particular. However, despite the harsh nature of mixed acid, it is often necessary and unavoidable for the synthesis of many valuable commodities within areas such as energetic materials, fine chemicals, and pharmaceuticals.<sup>3</sup>

On any scale, mixed acid is hazardous to work with, but at larger scales, the ramifications due to runaway exothermic reactions (fume-offs) are of dire concern. The combination of necessity and unpredictable outcomes requires a scalable solution to mitigate the risk of this imbalance.

In the case of mixed acid, a fume-off is identified as a runaway exothermic nitration reaction caused by a build up of excess latent heat, which cannot be removed by the system.<sup>4</sup> This inability to remove heat leading to fume-offs is often due to two main culprits: inadequate cooling and mixing. Cooling and mixing are two difficult, but absolutely necessary parameters when scaling up highly exothermic reactions such as nitrations. One possible and growing field, which provides solutions to both of these issues, is the use of microfluidics.<sup>5-7</sup>

The use of microfluidics to conduct efficient, safe, and scalable reactions has seen a significant spike in interest, and has led to a number of commercially available microreactor systems allowing a wide variety of chemistries. Recent publications have described the benefits of microfluidics, plug flow reactors and other continuous flow systems for use in nitration scale-up processes.<sup>8-10</sup> For the majority, these papers discuss avoiding the production or isolation of energetic compounds toward their desired compound. However, one area, which can certainly benefit from flow nitration, would be the energetic materials field.<sup>11</sup>

2,6-Diamino-3,5-dinitropyrazine-1-oxide, or LLM-105, is a secondary explosive with nearly 80% the power<sup>12</sup> of HMX, but has the insensitivity characteristics of impact, spark, and friction closer to that of the extremely insensitive 1,3,5-triamino-2,4,6-trinitrobenzene (TATB). Within the arena of energetic materials, this combination of power and insensitivity are highly desired and just as difficult, if not more so, to attain. Interest in LLM-105 as an insensitive high explosive (IHE) to replace conventional high explosives (CHE) has led to a fundamental focus on understanding the synthesis and characteristics of this unique material since its first disclosure in 1995.<sup>13</sup> The synthesis of LLM-105 using a commercial microreactor would be highly advantageous due to the necessity for safety, and precise temperature control of this highly exothermic reaction.

## Experimental

**CAUTION:** 2,6-Diamino-3,5-dinitropyrazine-1-oxide (LLM-105) is an high explosive! Special care in the handling and synthesis of the 1.1D explosive LLM-105 shall be practiced. Chemists experienced in the synthesis and handling of explosives should only carry out synthesis of explosive compounds.

## General Experimental Methods

All reagents were used as received from commercial sources. The starting material, 2,6-diaminopyrazine-1-oxide (DAPO) was prepared under contract by Nalas Engineering (Centerbrook, CT) in accordance to the pending patent application.<sup>14</sup> Proton NMR spectra were recording on a 90 MHz or 600 MHz spectrometer, while <sup>13</sup>C spectra were recorded at 150 MHz. Chemical shifts were calibrated for deuterated DMSO in accordance with literature values.<sup>15</sup> The inserted static mixing tube is composed of a one-meter long (0.062 in. ID) length of ETFE tubing, packed with glass beads (425-600 mm avg. dia.) between the reactor chip and residence tubing (1.0 mm ID).

## Preparation of DAPO/10% Oleum (150 mg/ml)

Into a 1 L vessel equipped with thermometer, stirrer, and solid addition funnel, is added 95-98% sulfuric acid (125 ml). With vigorous stirring and cooling, 20% oleum (125 ml) is added while keeping the temperature below 20 °C. DAPO (37.5 g, 174 mmol) is added to the sulfuric acid in small portions, controlling solution temperature between 20-30 °C with external cooling. Once complete dissolution of DAPO is achieved, the solution volume is transferred to the reagent vessel.

### Preparation of Mixed Acid Solution with Potassium Nitrate (3 equiv.)

Into a 1 L vessel equipped with a thermometer and stirrer is added 95-98% sulfuric acid (125 ml). With vigorous stirring and cooling, 20% oleum (125 ml) is added while keeping the temperature below 20 °C. With vigorous stirring potassium nitrate (52.7 g, 522 mmol) is added to the sulfuric acid in small portions, controlling reaction temperature between 5-10 °C with external cooling. Once complete dissolution of the nitrate salt is achieved, the solution is transferred to the reagent vessel.

### Preferred Method for the Multigram-Scale Nitration of DAPO to LLM-105

The system was purged with a mixture of 20% oleum and 90% nitric acid in the desired ratio of 112:500  $\mu\text{L}/\text{min}$  to ensure the absence of water and bubbles throughout. The system is composed of a 3-input glass chip (1 mL volume) with a t-mixer, followed by a glass bead packed column (1 m, 0.062 in. ID, ETFE), residence tubing (1.0 mm ID, 8.5 mL volume, ETFE), backpressure regulator (1 bar), waste/collection switching valve, and a jacketed quench vessel (700 ml DI water, 0 °C) with a mechanical stirrer. The chip was heated (37 °C) with a commercial Peltier heater, while the static mixer and residence tubing were carefully coiled (no overlapping) and submerged in a stirred, temperature-controlled water bath (37 °C). The DAPO/10% oleum solution was pre-tared prior to running, and the lines and syringes were filled with the reagents during system equilibration with oleum and nitric acid. The DAPO/10% oleum was introduced at 500  $\mu\text{L}/\text{min}$  and a timer was started to determine the residence time ( $\tau$ , 8 min 45 s) from chip to backpressure regulator based on the yellow color of the LLM-105 in solution. At this time, the switch was changed from waste to collection in the chilled quench vessel. At the desired end time, the reagents were paused while the DAPO/10% oleum was replaced with concentrated sulfuric acid and the flow of reagents restarted. The run was allowed to continue for an additional 20 min until the reaction solution ran clear. During the final purging, the jacketed quench vessel was warmed to 40 °C in order to destroy any oxamide (30 min). The cooled solution was then filtered, washed (water, then ethanol), and dried by suction to give LLM-105 (17.2 g, 49% yield). 1H NMR (DMSO, 600 MHz):  $\delta$  9.06 (2H, s), 8.78 (2H, s). 1H NMR (DMSO, 90 MHz):  $\delta$  8.91 (4H, br s). 13C NMR (DMSO, 125 MHz):  $\delta$  144.7, 124.9.

### Results and Discussion

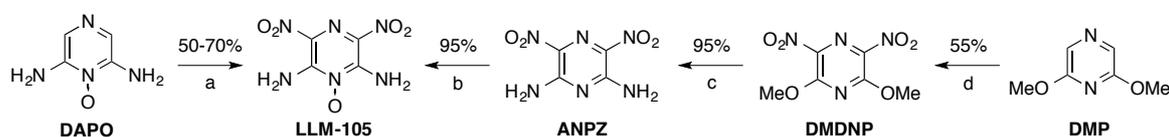
When evaluating the conversion of a batch reaction process to a microreactor, one must first determine if the potential benefits can actually be gained in the transition. Due to the small channel widths and precise temperature control, microreactors are superior at controlling highly exothermic reactions. The nitration of the starting material, 2,6-diaminopyrazine-1-oxide, or DAPO, is a highly involved and not fully understood process that involves a number of exothermic reaction pathways including: *N*-nitration, *C*-nitration, and multiple decomposition products leading to generation of carbon dioxide. Additionally, the dehydration of nitric acid by sulfuric acid to give the reactive nitronium intermediate, and the consummation of generated water by sulfur trioxide (oleum) are also highly exothermic processes. For these reasons alone, a microreactor would be beneficial for nitration using mixed acid. However, one must also consider the extent of mixing attained on the microscale.

For successful scaling of reactions between batch-scale and microscale, the efficiency and uniformity of mixing must be accurately modeled and properly controlled. Mixing efficiency can be estimated by the dimensionless Reynolds number ( $Re$ ), a ratio comparing the relative importance of inertial to viscous effects within a fluid flow system;

$$Re = \rho v D_H / \mu \quad (1)$$

where  $\rho$  is the fluid density,  $\mathbf{v}$  is the flow velocity,  $D_H$  is the hydraulic diameter and  $\mu$  is the fluid's dynamic viscosity. When  $Re < \sim 100$ , flow is fully laminar, and when  $Re > \sim 5000$  flow is turbulent, with a transition region in between. Reactant mixing at the batch scale is characterized by high values of  $Re$ , and the turbulent flows are complex to characterize, model and control. At the microscale, this task is made more manageable by the near absence of convection, described by low values of  $Re$ . Here, mixing can be extremely predictable and controllable. However, without convection, microscale mixing is dominated by diffusion, so at length scales greater than 10  $\mu\text{m}$ , it is slow and inefficient. To mitigate this, increasing the system's  $Re$  value is desirable.

In the case of a mixed acid system  $\rho$  and  $\mu$  cannot be altered, so the channel dimensions  $D_H$  and flow rate  $\mathbf{v}$  are the adjustable parameters. To achieve  $Re > 1,000$  in a cylindrical flow channel with a diameter of 500  $\mu\text{m}$ , at the relevant fluid density of 1.8 g/mL and viscosity of 20 mPa-s<sup>16</sup>, an estimated mean flow velocity of 25 m/s is required. This demands a pressure of 650 kPa (6.5 bars) for each cm of channel length, which greatly increases the hazards associated with the system. Many investigators have designed microfluidic devices that incorporate physical means of inducing convection to improve mixing efficiency<sup>17-19</sup>, while maintaining the uniformity and predictability advantages of microfluidic microreactors. In this work, a packed-bead column is incorporated for enhanced convection.



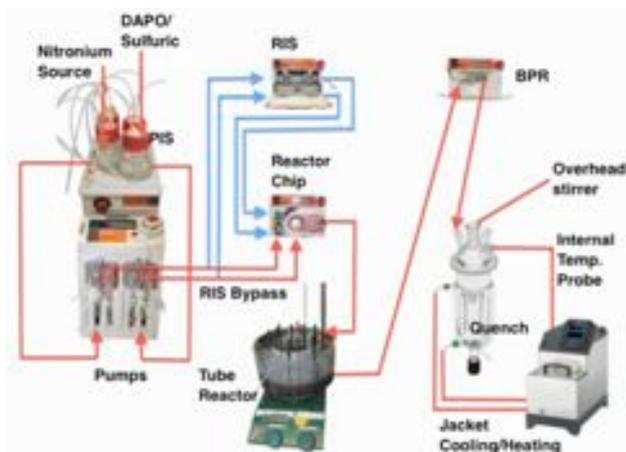
**Figure 1:** Batch Synthesis of LLM-105; a: 100% HNO<sub>3</sub>, 10% oleum, 2 h, 20-30 °C; b: H<sub>2</sub>O<sub>2</sub>/TFA, 10-20 °C, 45 °C 4 h, rt overnight; c: NH<sub>4</sub>OH, CH<sub>3</sub>CN, 60 °C, 1h; d: 10% oleum, 100% HNO<sub>3</sub>, 55%.

*Acronyms:* DAPO = 2,6-diaminopyrazine-1-oxide; ANPZ = 2,6-diamino-3,5-dinitropyrazine; DMDNP = 2,6-dimethoxy-3,5-dinitropyrazine; DMP = 2,6-dimethoxypyrazine.

The transitioning of a batch process to a microreactor is easiest when working with a system that has been optimized on multiple scales with an understanding of the system's chemistry. Although it is simple to run many small-scale flow reactions in a day, there are still many variables to consider including flow rates, temperature, pressure, molar equivalents, reagent concentrations, and more.

As mentioned, the batch synthesis of LLM-105 has been studied over nearly 20 years, and it has seen a number of methods for its production.<sup>20</sup> Two promising routes are depicted in Figure 1, while the DAPO process is favored over that of ANPZ for a variety of reasons. Ultimately, for practical use, one desires a certain level of purity and reproducible morphology. The oxidation of ANPZ to LLM-105 does not always go to completion due to the fact the oxidation reaction is heterogeneous from start to finish. Also, in the reaction pathway to LLM-105, there are three energetic materials (LLM-105 included), while there is only one in the case of the DAPO process. Obviously, there is more risk involved in a process requiring the handling of three energetic materials/intermediates versus only one, while the overall yield from the commercially prepared DMP or DAPO is comparable at 50% and 50-70%, respectively.

The microreactor synthesis of LLM-105 was modeled after some of the best batch procedures available. DAPO is first carefully dissolved in 10% oleum below 25 °C, and the nitrating reagent is best comprised of either 100% nitric acid or nitrate salts such as K<sup>+</sup>, Na<sup>+</sup>, or NH<sub>4</sub><sup>+</sup>, also added at a temperature below 30 °C. On the batch scale, the reaction is allowed to proceed over approximately three hours before being carefully quenched in ice. The three main variables include dissolving the DAPO in oleum, which nitronium source is used, and the reaction quench, and require a certain degree of chemical engineering in the transition to a microreactor system (Figure 2).



**Figure 2:** Microreactor setup for the mixed acid nitration and quenching of DAPO to LLM-105. PIS = pressurized input store, RIS = reagent injection system (for small scale reactions), BPR = backpressure regulator. Syrris<sup>®</sup> Asia system depicted above.

For the sake of safety, the less a chemist has to do in reagent preparation for the microreactor synthesis, the better. Therefore, it would be ideal if the only reagent preparation would be of the DAPO/oleum solution and not also the premixing of nitrate salts in sulfuric acid or oleum. It turns out that the DAPO solution is stable for as much as months at a time without significant loss in purity. Initial trial reactions in the microreactor were carried out on the two-milliliter scale in a single microreactor chip with a small residence tube reactor. Nitronium sources using nitric acid (90%), potassium nitrate in concentrated sulfuric acid, and ammonium nitrate in 20% oleum were all tried in the first small-scale trials (Table 1).

**Table 1:** Small-Scale Microreactor Nitration of DAPO to LLM-105 (2 mL)

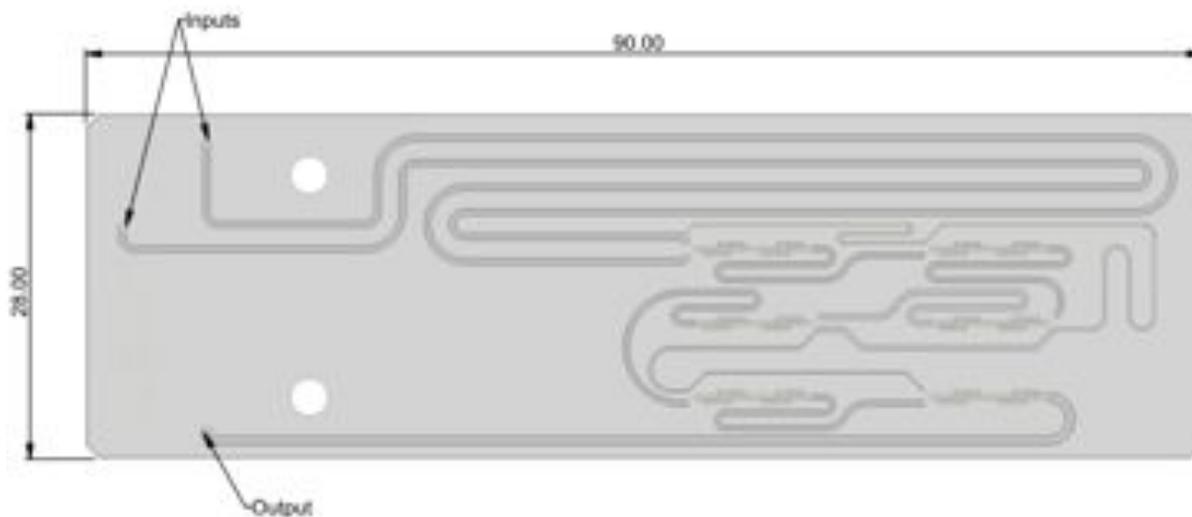
Entry	NO <sub>2</sub> <sup>+</sup> (eq.)	[DAPO] (mg/ml)	μl/min/ reagent	τ <sub>chip</sub> (min)	T <sub>chip</sub> (°C)	Yield <sup>c</sup> (%)
1	4.9 <sup>a</sup>	100	10	60	25	13 (N)
2	2.2 <sup>b</sup>	100	75	8	20-40	— (Y)
3	3 <sup>b</sup>	100	25	24	10	49 (Y)
4	3 <sup>b</sup>	100	25	24	40	51 (N)
5	3 <sup>b</sup>	100	33	18	50	43 (N)
6	4.9 <sup>a,e</sup>	100	25	19	40 <sup>f</sup>	16 (N)
7	4.9 <sup>a,e</sup>	100	25	19	40 <sup>f</sup>	23 (N) <sup>d</sup>
8	3 <sup>b,e</sup>	134	25	19	40 <sup>f</sup>	51 (N)

*a* 90% nitric acid in 10% oleum (1 mL total volume), *b* KNO<sub>3</sub> in 10% oleum, yield of LLM-105 (Y or N) = presence of mono-nitrated DAPO, *d* used 20% oleum instead of 10%, *e* nitronium broken into 1/6<sup>th</sup> portions over specially designed mixing chip, *f* 600 μL residence tube at 40 °C. 1 ml DAPO in 10% oleum, back pressure = 8.3 to 8.6 bar, 1 mL standard t-mixer 3-reagent chip (1 input plugged), additional residence time provided with 200 μL tubing at ambient temperature.

As can be seen in Table 1, the desire to use nitric acid as nitronium source (Entry 1) seemed initially thwarted. The yields were painfully low, and all cases using 90% nitric acid produced significant gas generation in the system, adversely affecting residence time (τ). Increasing the backpressure was not sufficient to suppress the generated gases throughout the entire reactor. Efforts moved toward the use of K<sup>+</sup> and NH<sub>4</sub><sup>+</sup> nitrate salts, which seemed to improve many aspects of the reaction on the batch scale.

Entries 2-4 show progressively better results with  $\text{KNO}_3$  as the nitronium source by using at least 3 equivalents and increasing the temperature to 40 °C. Temperatures exceeding 40 °C (entry 5) were detrimental to the yield despite the fact  $\tau$  could be reduced from 24 to 18 minutes, although in all instances, experiments using nitrate salts did not generate gases during the reaction. Results using  $\text{NH}_4\text{NO}_3$  are not given in Table 1, as the data was comparable to use of the potassium salts with the downside of significantly increased viscosity. This increase in viscosity will work on the small scale, but becomes a problem, as the viscous materials are much harder to pump at increased rates.

With promising results, the use of 90% nitric acid was reevaluated. It is understood that the best results on the batch scale use 100% nitric acid or nitrate salts in 10% oleum. The major difference between these conditions and 90% nitric is water content. Also, much of the losses in yield leads to decomposition products that go to carbon dioxide, and it is believed this decomposition is accelerated by the presence of water. Although the current results are significantly shorter than the batch process, it was thought that one could reduce  $\tau$  with a static mixer chip that also incorporates a sort of drop-wise addition effect in the design. Entries 6-8 use this specially designed “6-stage mixer” chip (Figure 3), which allows for the nitronium source to be introduced to the DAPO solution in 1/6<sup>th</sup> portions.



**Figure 3:** 6-stage mixer chip with pre-heating/cooling zone.

Overall pressure drop = 19.3 bar at 300  $\mu\text{L}/\text{min}$ . Chip designed by Dolomite Microfluidics.

Simply returning to 90% nitric acid in the 6-stage mixer chip (Entry 6) did not significantly increase the yield. However, dissolving the 90% nitric acid in 20% oleum (Entry 7) showed a 10% increase in yield over Entry 1. The additional mixing did have an effect of reducing  $\tau$  from 24 minutes to 19 minutes using potassium nitrate as seen in Entry 8. However, this reduction in residence time is not terribly significant, and may be the ceiling using nitrate salts, as is consistent with the batch nitration of DAPO.

The gains in LLM-105 yield between entries 1 and 7 of Table 1 reignited our desire to move back to 90% nitric acid as the nitronium source. In order to remove water from the reaction and reduce excessive decomposition, it was decided to use 20% oleum as a third component in the reaction in addition to 90% nitric acid and DAPO in 10% oleum. After deciding between a two-chip system and a single-chip system (Table 2), the simplicity of a standard t-mixed 3-reagent chip was chosen. It was found that premixing the 90% nitric acid with 20% oleum in the first chip was not advantageous over mixing all three components at once.

**Table 2:** Microreactor Nitration of DAPO Using Additional Oleum as a Third Component

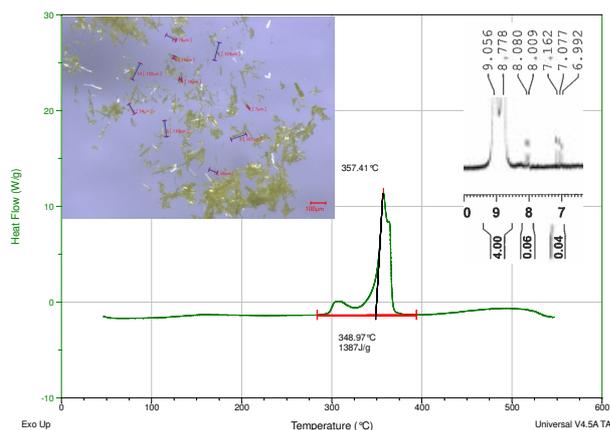
Entry	NO <sub>2</sub> <sup>+</sup> (eq.)	HNO <sub>3</sub> :DAPO: Oleum ( $\mu$ l/min)	$\tau$ (min)	Yield (%/g) <sup>e</sup>	% oxamide (NMR)
1 <sup>a</sup>	4.9	81:295:295	6	46, 6.8	25 <sup>g</sup>
2 <sup>a</sup>	3.7	62:295:295	6	59, 2.5	0 <sup>h</sup>
3 <sup>a</sup>	3.8	45:200:200	10	49, 2.8	0 <sup>i</sup>
4 <sup>b</sup>	4.9	27:98.3:98.3 <sup>d</sup>	10	— <sup>f</sup> , 2.5	0 <sup>h</sup>
5 <sup>c</sup>	3.8	112:500:500	9	39, 14.1	0 <sup>i</sup>
6 <sup>c</sup>	3.8	112:500:500	9	49, 17.2	0 <sup>j</sup>

*a* 90% nitric and oleum mixed in 1 mL 2-input t-mixed chip < 20 °C followed by addition of DAPO/10% oleum in 6-stage mixer (20 °C) and 37 °C tube reactor, *b* 250  $\mu$ L 3-input t-mixed chip plus 37 °C tube reactor, *c* same as *b*, with 1 mL 3-input t-mixed chip and 1 m glass bead packed column, *d* yield of LLM-105 excluding oxamide, *e* 3-input 250  $\mu$ L chip/overall flow rates reduced to prevent overpressure, *f* leak in system prevented from determining accurate yield, *g* quenched at 5 °C, *h* quench was allowed to self warm, *i* controlled quench with mechanical stirring at 40 °C/filtered at 40 °C, *j* quenched at 0 °C and stirred at 40 °C for 30 min,

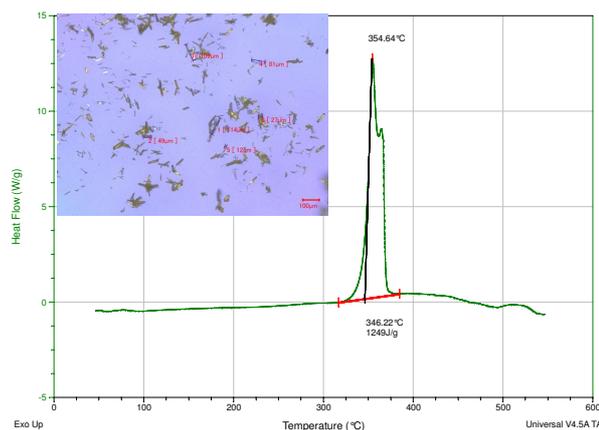
*k* varies due to lower DAPO concentration in beginning and end of run; over longer runs, the output will approach the theoretical rate of production. 150 mg/mL DAPO in 10% oleum, Back pressure = 0 to 4 bar.

The addition of an equal volume of 20% oleum to DAPO/10% oleum was necessary to eliminate gas production within the nitration reaction, and yields in line with the batch process were now attainable (Table 2). Also, it was found that reducing the chip and residence tube reactor temperatures to 37 °C aided in reducing decomposition. Streamlining of the process of reaction to quench lead to a consistent two-step process involving a jacketed collection vessel fitted with a mechanical stirrer and temperature probe (Figure 2). Entry 1 vs 2 and 4 made it clear that accurate control of the quenching conditions are critical to LLM-105 purity. When quenched cold, there were significant amounts of oxamide impurity along with the LLM-105. This impurity was known from the batch process, but has never been seen in such significant quantities as Entry 1. However, it was found in cases where the quench bath was not carefully controlled and allowed to warm, that there was no oxamide present. The difference in yield between entries 2 and 3 may have to do with the amount of time the product spends in the elevated quench temperatures, especially when compared to Entry 5. Therefore, a controlled quench temperature of 40 °C was used to aid in the decomposition of any oxamide, which was seen with the evolution of gas. The conditions used for Entry 6 were ultimately the preferred method of choice giving the highest purity as quenched material and the highest reproducible output of LLM-105.

In order to scale up to the rates seen in entries 5 and 6, it was necessary to add more mixing capabilities than just the t-mixer of the 3-reagent chip. Without additional mixing, the residence time exceeded 20 minutes due to relying on diffusion in the strictly laminar flow system. In order to achieve enough mixing without significantly increasing pressure restraints on the pumps, a one-meter long (0.062 in. ID) length of tubing packed with glass beads (425-600  $\mu$ m avg. dia.) was inserted between the reactor chip and residence tubing (1.0 mm ID). The packed bed column allows for a Reynolds value closer to transient mixing while still laminar.



**Figure 4:** DSC (main), <sup>1</sup>H NMR expansion showing ammonium salt impurity (top right), and micrograph of LLM-105 after quench at 40 °C (top left).



**Figure 5:** DSC and micrograph of LLM-105 after recrystallization from DMF/water.

In addition to refinement of the flow synthesis, full characterization of product purity is essential. LLM-105 is a bright yellow solid, which varies in appearance depending on its crystalline morphology or the nature of impurity. Simply relying on NMR and/or HPLC is not sufficient in determining the purity of LLM-105. In combination with the above, it is also necessary to collect the DSC of LLM-105 (Figures 4 and 5) to ensure purity.

When the LLM-105 reaction mixture is quenched at 40 °C, the crystals take on a high aspect ratio form (inset of Figure 4) similar to that of recrystallized material (inset Figure 5). However, as can be clearly seen by differential scanning calorimetry, there is a significant effect on the decomposition of LLM-105 in the as quenched material (Figure 4) with an appearance of an additional exothermic peak. The HPLC purity was determined to be 98.8% ( $\pm 1\%$ ), and the proton spectrum appears to be clean at first glance. However, at closer examination of a concentrated sample, there is a characteristic triplet at 7.08 ppm consistent with the presence of an ammonium salt (inset Figure 4). The impurity was suspected to be related to entrained acid based on our previous work. However, capillary electrophoresis detected less than 10 ppm sulfate ions and nearly no nitrate ions. This impurity was removed by recrystallization, as seen in Figure 5. Our preferred method, quenching at 0 °C and heating to 40 °C (Entry 6, Table 2), provides oxamide-free LLM-105 with small particle size, but still has a DSC similar to Figure 3. Further purification by recrystallization enhances the purity, but the particle size and morphology are altered.

## Conclusion

In conclusion, the safe nitration of 2,6-diaminopyrazine-1-oxide in mixed acid was demonstrated in a commercial micro-reactor with a maximum output of 3.34 g/h of the secondary high explosive, LLM-105. Additional oleum was necessary to maximize yield using 90% nitric acid in a 3-reagent system, and altering the quench conditions affected the purity and particle morphology in a controlled manner. Coupling the flow reactor with immediate quenching upon reaction completion at a controlled temperature leads to a superior quality material that is extremely reproducible. Ultimately, the benefits of heat transfer and precise reagent introduction in the microreactor negates the possibility of exothermic runaway leading to fume-off on the batch scale.

## Acknowledgements

The author's would like to thank Audrey Williams and Greg Klunder of the LLNL FSC for LCMS and capillary electrophoresis analysis of LLM-105 samples. Special thanks are due to,

Jennifer Montgomery, Fowzia Zaka, Socorro Painter, and Peter Hsu (LLNL) for their measurements of the DSC, TGA/DSC, HPLC, and particle size analysis. The authors would also like to thank the Joint DoD/DOE Munitions Program (JMP) and LLNL LDRD # 13-ER-051 for the funding to perform this work. This work performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344. LLNL-PROC-667843.

## References

- <sup>1</sup> J. P. Agrawal, R. D. Hodgson, *Organic chemistry of explosives*, John Wiley & Sons, Ltd, England, **2007**.
- <sup>2</sup> G. A. Olah, G. K. S. Prakash, Q. Wang, X. Li, *Nitronium tetrafluoroborate, E-EROS encyclopedia of reagents for organic synthesis*, John Wiley & Sons, Ltd, online, **2001**.
- <sup>3</sup> N. Kockmann, D. M. Roberge, Harsh reaction conditions in continuous flow microreactors for pharmaceutical production. *Chem. Eng. Technol.*, **32**, 1682–1694, **2009**.
- <sup>4</sup> F. Stoessel *Thermal safety of chemical processes: Risk assessment and process design*, Wiley-VCH, Weinheim, **2008**.
- <sup>5</sup> A. A. Kulkarni, Continuous flow nitration in miniaturized devices. *Beilstein J. Org. Chem.*, **10**, 405–424, **2014**.
- <sup>6</sup> K. S. Elvira, X. Casadevall i Solvas, R. C. R. Wootton, A. J. deMello, The past, present and potential for microfluidic reactor technology in chemical synthesis. *Nature Chemistry*, **5**, 905–915, **2013**.
- <sup>7</sup> V. Hessel, D. Kralisch, N. Kockmann, T. Noël, Q. Wang, Novel process windows for enabling, accelerating, and uplifting flow chemistry. *ChemSusChem*, **6**, 746–789 **2013**.
- <sup>8</sup> J. Antes, D. Boskovic, H. Krause, S. Loebbecke, N. Lutz, T. Tuercke, W. Schweikert, Analysis and improvement of strong exothermic nitrations in microreactors. *Trans IChemE*, **81**, 760–765, **2003**.
- <sup>9</sup> J. Pelleter, F. Renaud, Facile, Fast and safe process development of nitration and bromination reactions using continuous flow reactors. *Org. Process Res. Dev.*, **13**, 698–705, **2009**.
- <sup>10</sup> C. E. Brocklehurst, H. Lehmann, L. La Vecchia, Nitration chemistry in continuous flow using fuming nitric acid in a commercially available flow reactor. *Org. Process Res. Dev.*, **15**, 1447–1453, **2011**.
- <sup>11</sup> N. Zaborenko, E. R. Murphy, J. G. Kralj, K. F. Jensen, Synthesis and kinetics of highly energetic intermediates by micromixers: Direct multistep synthesis of sodium nitrotetrazolate. *Ind. Chem. Res.*, **49**, 4132–4139, **2010**.
- <sup>12</sup> T. D. Tran, P. F. Pagoria, M. D. Hoffman, J. L. Cutting, R. S. Lee, R. L. Simpson, Characterization of 2,6-Diamino-3,5-Dinitropyrazine-1-Oxide (LLM-105) as an insensitive high explosive material, in *Proceedings of 33rd International Annual Conference of ICT (Energetic Materials)*, Karlsruhe, Germany, June 25–28, **2002**.
- <sup>13</sup> P. F. Pagoria, A. R. Mitchell, R. D. Schmidt, R. L. Simpson, F. Garcia, J. Forbes, J. Cutting, R. Lee, R. Swansiger, D. M. Hoffman, Synthesis, Scale-up and experimental testing of LLM-105 (2,6-diamino-3,5-dinitropyrazine 1-oxide). *Insensitive Munitions & Energetic Materials Technology Symposium*, San Diego, CA, I-3-1 to I-3-5, **1998**.
- <sup>14</sup> P. F. Pagoria, M.-X. Zhang, Synthesis of pyrazines including 2,6-diaminopyrazine-1-oxide (DAPO) and 2,6-diamino-3,5-dinitropyrazine-1-oxide (LLM-105). US 20100267955 A1, April 20, **2009**.
- <sup>15</sup> H. E. Gottlieb, V. Kotlyar, A. Nudelman, NMR chemical shifts of common laboratory solvents as trace impurities. *J. Org. Chem.*, **62**, 7512–7515, **1997**.
- <sup>16</sup> N. F. H. Bright, H. Hutchison, D. Smith, The viscosity and density of sulphuric acid and oleum. *J. Soc. Chem. Ind.*, **65**, 385–388, **1946**.
- <sup>17</sup> A. D. Stroock, S. K. W.; Dertinger, A. Ajdari, I. Mezic, H.A. Stone, G.M. Whitesides, Chaotic mixer for microchannels. *Science*, **295**, 647–651, **2002**.

- <sup>18</sup> C.-Y. Lee, C.-L. Chang, Y.-N. Wang, L.-M. Fu, Microfluidic mixing: A review. *Int. J. Mol. Sci.*, **12**, 3263–3287, **2011**.
- <sup>19</sup> F. R. Pennella, M. Rossi, S. Ripandelli, M. Rasponi, F. Mastrangelo, M. A. Deriu, L. Ridolfi, C. J. Kähler, U. Morbiducci, Numerical and experimental characterization of a novel modular passive micromixer. *Biomed. Microdev.*, **14**, 849–862, **2012**.
- <sup>20</sup> A. J. Bellamy, The study of some potential new synthetic routes to LLM-105. (2,6-diamino-3,5-dinitropyrazine 1-oxide). *Cent. Eur. J. Energ. Mater.*, **4**, 33–57, **2007**.