Microreactor Flow Synthesis of the Secondary High Explosive 2,6-Diamino-3,5-dinitropyrazine-1-oxide (LLM-105)

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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, multigram scale-up results, analyses of sample purity, and quenching conditions for purity and crystal morphology are reported.

Keywords: flow nitration, microreactor, energetic materials, LLM-105

1. 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 (NO_2BF_4) [1] and dinitrogen pentoxide [2], 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 [3].

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 buildup of excess latent heat, which cannot be removed by the system [4]. This inability to remove heat leading to fume-offs is often due to two main culprits: inadequate cooling and mixing. The field of microfluidics is ideally suited for this issue, and there have been significant publications with regard to flow nitration [5–10]. 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 [11].

2,6-Diamino-3,5-dinitropyrazine-1-oxide, or LLM-105, is a secondary explosive with nearly 80% the power [12] 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 is highly desired and just as difficult, if not more so, to attain. Interest in LLM-105 as a secondary high explosive to replace conventional high explosives (CHE) has lead to a fundamental focus on understanding the synthesis and characteristics of this unique material since its first disclosure in 1995 [13]. 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.

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 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:

$$Re = \rho \mathbf{v} D_H / \mu \qquad (1)$$

where ρ is the fluid density, $\mathbf{v}$ is the flow velocity, D_H is the hydraulic diameter, and μ is the fluid's dynamic viscosity. In contrast to batch synthesis at the macroscale, where mixing is turbulent (Re > ~5000), microreactors typically exhibit laminar flow (Re < ~100). In this regime, since convection is nearly or completely absent, mixing is diffusion-dominated and, therefore, inefficient at length scales greater than 10 μm. To mitigate this, increasing the system's Re value is desirable.

In the case of the mixed acid system in this work, ρ and μ cannot be altered, so the channel dimensions D_H and flow rate $\mathbf{v}$ are the adjustable parameters. To achieve Re > 1000 in a cylindrical flow channel with a diameter of 500 μm, at the relevant fluid density of 1.8 g/mL and viscosity of 20 mPa·s [14], an estimated mean flow velocity of 25 m/s is required, which demands impractically high pressure. Many investigators have designed microfluidic devices that induce additional convection to improve mixing efficiency [15–17], even while nominal Re remains low. In this work, a packed-bead column is incorporated to achieve the goal of enhanced convection, while leveraging the uniformity and control benefits associated with microfluidic microreactors.

2. Results and Discussion

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 [18]. Two promising routes are depicted in Scheme 1, while the DAPO process is favored over that of ANPZ for a variety of reasons. Ultimately, for practical use, one desires

Scheme 1. Batch synthesis of LLM-105. 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
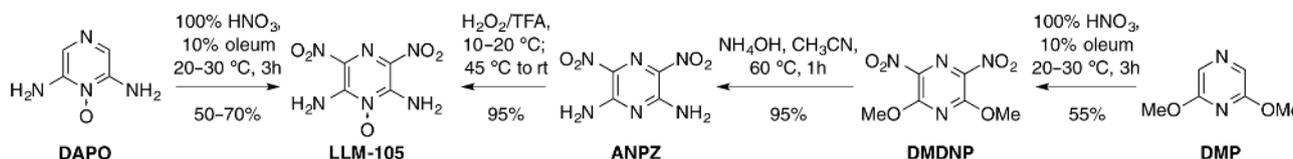
a certain level of purity and reproducible morphology. The oxidation of ANPZ to LLM-105 does not always go to completion due to the fact that the oxidation reaction is heterogeneous from start to finish. Also, in the reaction pathway to LLM-105, there are three energetic materials (LLM-105 included), 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.

To minimize hazardous reagent handling, 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).

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^+ and NH_4^+ nitrate salts, which seemed to improve many aspects of the reaction on the batch scale.

Entries 2–4 show progressively better results with KNO_3 as the nitronium source by using at least three equivalents and increasing the temperature to 40 °C. Temperatures exceeding 40 °C (entry 5) were detrimental to the yield despite the fact that τ could be reduced from 24 to 18 min although, in all instances, experiments using nitrate salts did not generate gases during the reaction. Results using NH_4NO_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 τ 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 1), which allows for the nitronium source to be introduced to the DAPO solution in 1/6th portions.

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 τ from 24 min to 19 min 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.

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 led 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 precipitated LLM-105. The presence of oxamide is likely due to the hydrolysis of the previously reported side product tetraketopiperazine [18], but oxamide 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

Table 1. Small-scale microreactor nitration of DAPO to LLM-105 (2 mL)

Entry	NO_2^+ (eq.)	[DAPO] (mg/mL)	µL/min/ reagent	τ_{chip} (min)	T_{chip} (°C)	Yield[c] (%)
1	4.9[a]	100	10	60	25	13 (N)
2	2.2[b]	100	75	8	20–40	– (Y)
3	3[b]	100	25	24	10	49 (Y)
4	3[b]	100	25	24	40	51 (N)
5	3[b]	100	33	18	50	43 (N)
6	4.9[a,e]	100	25	19	40[f]	16 (N)
7	4.9[a,e]	100	25	19	40[f]	23 (N)[d]
8	3[b,e]	134	25	19	40[f]	51 (N)

[a] 90% Nitric acid in 10% oleum (1 mL total volume).
[b] KNO_3 in 10% oleum.
[c] Yield of LLM-105 (Y or N) = presence of mono-nitrated DAPO.
[d] Used 20% oleum instead of 10%.
[e] Nitronium broken into 1/6th 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.
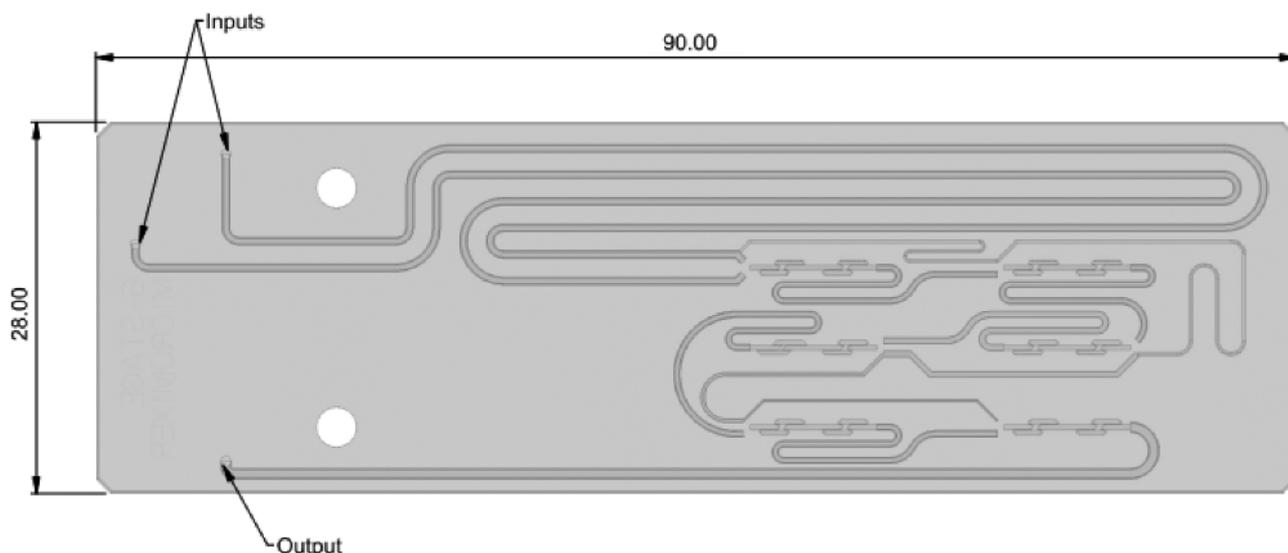
Figure 1. 6-Stage mixer chip with preheating/cooling zone. Overall pressure drop = 19.3 bar at 300 µL/min. Chip designed by Dolomite Microfluidics

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 min 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 glass bead packed column was inserted between the reactor chip and residence tubing (details in Experimental section) [19].

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 nuclear magnetic resonance (NMR) and/or high-performance liquid chromatography (HPLC) is not sufficient in determining the purity of LLM-105. In combination with the above, it is also necessary to collect the differential scanning calorimetric (DSC) of LLM-105 (Figure 3) 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 3A) similar to that of recrystallized material (inset,

Figure 3B). 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 3A) with an appearance of an additional exothermic peak at 349 °C. The exact cause or identity of impurity leading to this additional exotherm is currently unknown, but various analytical techniques provide some insight into the identity of the impurity. The purity determination by HPLC (98.8%, ±1%) along with a proton NMR spectrum that does not show any significant additional peaks other than LLM-105 let us initially suspect that entrained acid was the cause of the additional exotherm, based on previous work. However, capillary electrophoresis detected less than 10 ppm sulfate ions and nearly no nitrate ions. Upon closer examination of the proton NMR spectrum of a more concentrated sample, there is a characteristic triplet at 7.08 ppm consistent with the presence of an ammonium salt (inset, Figure 3A), which is likely related to the decomposition of oxamide to ammonium oxalate. Ultimately, the impurity was removed by recrystallization, as seen in Figure 3B. Our preferred method, quenching at 0 °C and heating to 40 °C (entry 6, Table 2), provides oxamide-free

Table 2. Microreactor nitration of DAPO using additional oleum as a third component

Entry	NO_2^+ (eq.)	HNO$_3$–DAPO–oleum (µL/min)	τ (min)	Yield (%/g)[e]	% Oxamide (NMR)
1[a]	4.9	81:295:295	6	46, 6.8	25[g]
2[a]	3.7	62:295:295	6	59, 2.5	0[h]
3[a]	3.8	45:200:200	10	49, 2.8	0[i]
4[b]	4.9	27:98.3:98.3[d]	10	–[f], 2.5	0[h]
5[c]	3.8	112:500:500	9	39, 14.1	0[i]
6[c]	3.8	112:500:500	9	49, 17.2	0[j]

[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 µL 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] 3-Input 250 µL chip/overall flow rates reduced to prevent overpressure.
[e] Yield of LLM-105 excluding oxamide.
[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. 150 mg/mL DAPO in 10% oleum, back pressure = 0 to 4 bar.
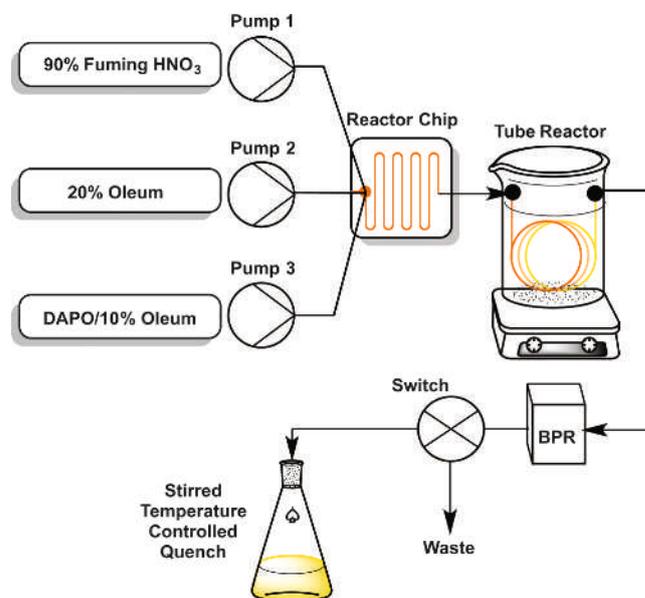

Figure 2. Flow nitration and quenching setup of DAPO to LLM-105. BPR = backpressure regulator
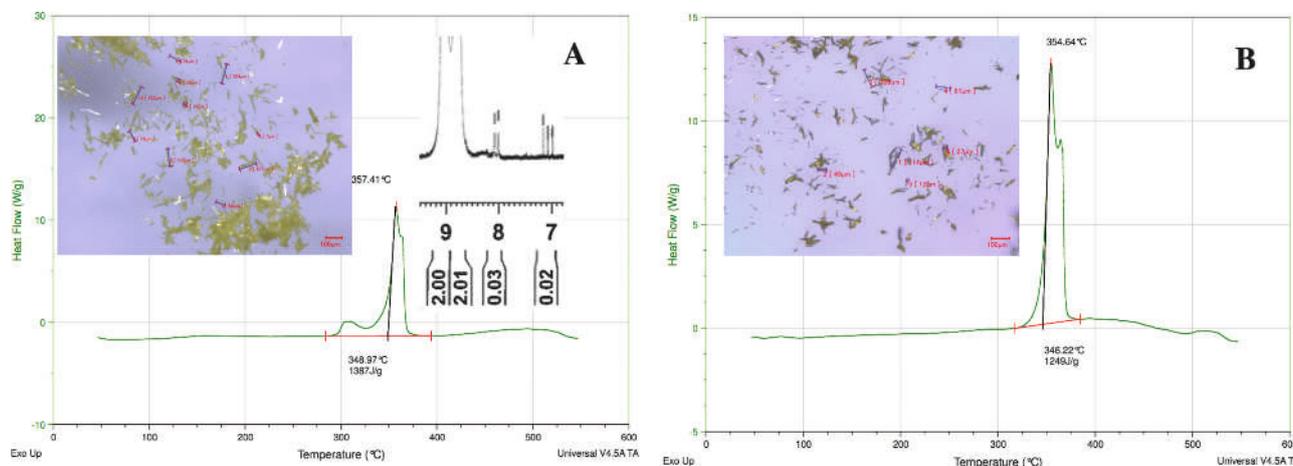
Figure 3. DSC and micrographs of LLM-105 after quench (A) and recrystallized from DMF–water (B)

LLM-105 with small particle size but still has a DSC similar to Figure 3A. Further purification by recrystallization enhances the purity, but the particle size and morphology are altered.

3. Conclusion

The safe nitration of 2,6-diaminopyrazine-1-oxide in mixed acid was demonstrated in a commercial microreactor 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 negate the possibility of exothermic runaway leading to fume-off on the batch scale.

4. Experimental

Caution: 2,6-Diamino-3,5-dinitropyrazine-1-oxide (LLM-105) is a high explosive. Special care in the handling and synthesis of the 1.1D explosive LLM-105 shall be practiced in accordance with U. S. Department of Energy M 440.1-1A, DOE Explosives Safety Manual. Only chemists experienced in the synthesis and handling of explosives should carry out synthesis of explosive compounds.

4.1. 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 [20]. Proton NMR spectra were recorded on a 90-MHz or 600-MHz spectrometer, while ^{13}C spectra were recorded at 150 MHz. Chemical shifts were calibrated for deuterated DMSO in accordance with literature values [21]. The inserted static mixing tube is composed of a one-meter long (0.062 in. ID, 1/8″ OD) length of ETFE tubing, packed with glass beads (425–600 μm avg. dia.) between the reactor chip and residence tubing (1.0 mm ID, 1/16″ OD, 10 m length).

4.2. 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 and 30 °C with external cooling. Once complete dissolution of DAPO is achieved, the solution volume is transferred to the reagent vessel.

4.3. 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 and 10 °C with external cooling. Once complete dissolution of the nitrate salt is achieved, the solution is transferred to the reagent vessel.

4.4. 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 500:112 μL/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), residence tubing (1.0 mm ID, 8.5 mL volume, ETFE), back-pressure 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 to 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 set at 37 °C (the timescale for heat transfer through the reaction tubing walls is ~5 s, and as such 100-fold shorter than the residence time in the tubing). The DAPO/10% oleum solution was pretared prior to running, and the lines and syringes were filled with the reagent during system equilibration with oleum and nitric acid. The DAPO/10% oleum was introduced at 500 μL/min, and a timer was started to determine the residence time (τ, 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). The supporting information contains proton and carbon spectra of pure LLM-105, as well as one that is contaminated with oxamide (quenched cold without further treatment). Also, the proton spectrum is expanded to show a small contaminant of what appears to be an ammonium salt of LLM-105. 1H NMR (DMSO, 600 MHz): δ 9.06 (2H, s), 8.78 (2H, s); 1H NMR (DMSO, 90 MHz): δ 8.91 (4H, br s); 13C NMR (DMSO, 125 MHz): δ 144.7, 124.9.

Supporting Information

Electronic Supplementary Material (ESM) containing data (HPLC, 1H and 13C NMR, SEM images, particle size reports, microreactor/chip specifications, electropherograms) associated with this article is available in the online version at doi: 10.1556/1846.2015.00016.

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