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High Output Continuous Nitration

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ABSTRACT: The design and use of a flow reactor for scaling up an exothermic nitration reaction in a safe manner on production scale is described. The flow reactor is made of a jacketed, stainless steel coil. Two charging methods, pump and nitrogen pressure were tested on a substituted pyridine substrate. The transfer from kilogram scale in the laboratory to 100-kg scale in the plant was successfully accomplished.

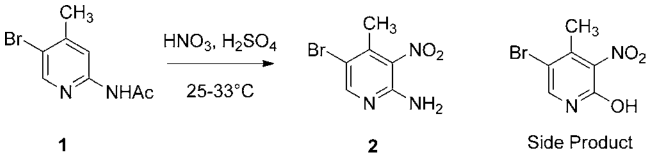
■ INTRODUCTION

The nitro derivatives of aromatic compounds have applications in a variety of fields and are synthesized in quantities ranging from bulk chemicals to fine chemicals to drug intermediates.[1] Nitration is the most common synthesis method for producing the nitro derivatives of aromatic compounds, which is often accompanied by a strong exotherm upon addition of the nitrating acid mixture. Performing such exothermic or hazardous reactions in a continuous flow reactor is advantageous because the reactant inventory at any given time is small, heat produced in a small reaction volume can be more rapidly dissipated, and exothermic runaway can be avoided. In addition, in a continuous process the reactive mixture can be quenched quickly, a feature with possible yield and safety advantages.

There are a number of literature examples of nitration reactions which have been performed under continuous conditions on lab scale. For example, Schwalbe et al. used a stainless steel microreaction system for the nitration of a key intermediate in the synthesis of sildenafil.[2,3] Pelletier details the nitration of 3-alkylpyrazoles on 100-g scale with an inexpensive continuous flow microreactor.[4] There is also a large body of patent literature describing industrial applications of flow nitrations. However, detailed reports in the open literature describing actual implementation in production for continuous nitrations are not as common. An exception is the DSM/Corning report of a highly efficient and selective nitration using Corning's microstructured device, resulting in the processing of 25 t of materials.[5]

We were interested in the development of a simple and practical flow reactor for nitration to produce hundreds or thousands of kilos of nitroaromatics. Nitropyridine **2**[6,7] was chosen for optimization in a flow system as large quantities were required as starting material for the synthesis of an active pharmaceutical ingredient (API) in clinical development. The nitropyridine can be prepared in a conventional batch process by treating a concentrated sulfuric acid solution of **1** with fuming nitric acid at 25−33 °C in 52−55% yield (Scheme 1). A calorimetry experiment on the batch reaction demonstrated a strong exotherm: 156 kJ/mol, in reasonable agreement with the calculated value of 167 kJ/mol and sufficient to produce an adiabatic temperature rise of 76 °C. Although differential scanning calorimetry revealed that pure **2** does not decompose exothermically at temperatures up to 200 °C, solutions of **2** in fuming nitric acid could be induced to decompose when heated above 80 °C, although the precise onset temperature could not be accurately pinpointed. The reaction was therefore deemed potentially hazardous for large-scale batch production, which prompted us to seek implementation of a continuous nitration system to produce the desired compound under safe conditions without compromising reaction yield. This report describes the results from the lab trial and plant run for the test of the flow reactor and preparation of **2** in a continuous nitration manner.

Scheme 1. Nitration of 1



■ RESULTS AND DISCUSSION

Operating System. A simple continuous flow reactor can be set up consisting of four main units: the feed vessels, the mixer, the residence loop, and a collecting vessel. All of these units were connected using stainless steel tubing and ports (see Figure 1).

Optimization of Continuous Processing Train. *Charging of Reactants Using Pumps.* The initial efforts used pumps to control the flow rate of two feed solutions. The pumping unit was a standard metering pump at 6 mL/min. Two solutions were prepared: solution A of 100 g of **1** in 300 g of H_2SO_4 (1/3 wt/wt) and solution B of HNO_3/H_2SO_4 (~1/12 wt/wt). Given a residence time of approximately 20 min, the bath temperature was set to 50−55 °C to ensure greater than 97% conversion.

Careful matching of addition rates of the two feed solutions was important for yield. The yield was significantly lowered as the nitric acid excess relative to **1** increased while the purity of isolated **2** only shifted slightly to a lower range (Table 1). The yield reduction was due to formation of the hydroxy pyridine side product (Scheme 1) generated by oxidation of the

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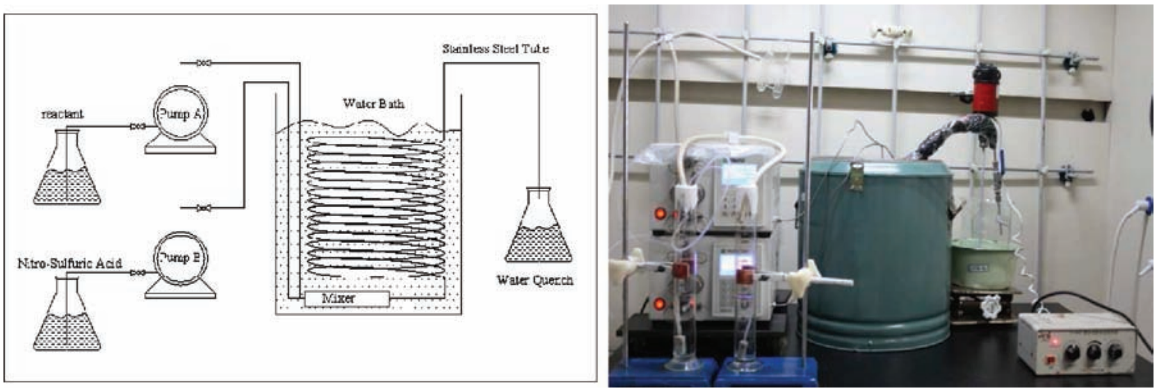

Figure 1. Nitration apparatus to prepare **2**. Ten meters of SS304 coil with 4 mm inner diameter. Water bath controlled at 50−55 °C.

Table 1. Impact of flow rates delivering excess nitric acid[a]

nitric acid excess (vs **1**) (%)	**2** purity (LC area %)	isolated yield (%)
3.8	82−87	68
6.4	80−85	60
9.0	78−82	51

[a] 100 g of **1** input; run time = 36 min.

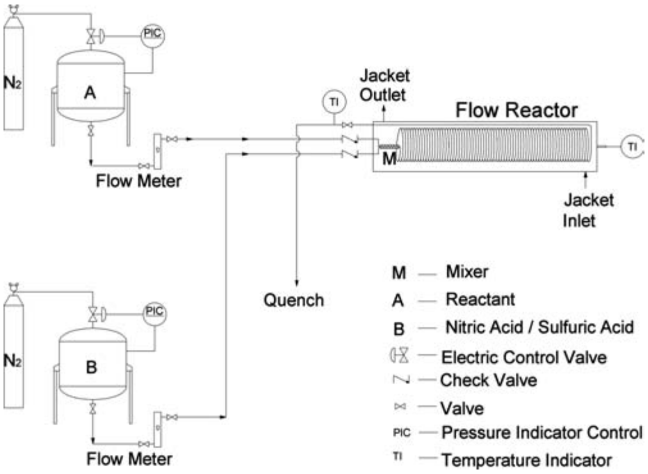

Figure 2. Schematic of pressure charge system.

aminopyridine by nitric acid. Unfortunately, attempts to reduce formation of the impurity by using stoichiometric or substoichiometric nitric acid were ineffective and came at the expense of large falloffs in conversion. These experiments allowed us to tune our feed rates to limit the excess nitric acid to <4%. Once optimized conditions were attained, reproducible results were demonstrated using this benchtop flow system (Table 2). These results indicated that by the 5−10 min range, the system attained an acceptable conversion and generated the best purity and yield of **2**.

Satisfied with this proof of concept, we examined a larger apparatus consisting of a reactor tube 45 m long of 15 mm inner diameter (total volume 7.95 L). A 1.5 kg (input **1**) demonstration run of 40 min produced 0.91 kg of product in >98% purity. However, the precise control of the flow rate of these viscous solutions became more difficult with the larger flow system. The difference in the amount delivered between two pumps in the 1.5 kg demonstration run reached 16%, auguring poorly for good control of the chemistry. In addition, the highly corrosive nature of the feed solutions poses additional challenges for achieving matched consistent flow rates with cost-effective and commercially available pumps. Facing time constraints, we elected to investigate charging by pressure.

Charging of Reactants with Pressure. We discovered that reactants could be charged accurately by applying modest nitrogen pressure on the feed tanks (Figure 2). The feed tanks were located only a few meters away and about 1 m higher than the flow reactor, so that the viscosity of the feed solutions proved unproblematic. Flow meters were used to regulate and match flow of the two streams into the reactor. Mechanically, this is much simpler than using pumps and permitted synchronized flows that differed by no more than 4% with monitoring.

Using this system, a 4-h trial was conducted charging 10 kg of **1** (Table 3). As with the benchtop system, stable performance over time was attained. Workup consisted simply of quenching into water followed by pH adjustment, filtration, and recrystallization. In this case, 59% isolated yield was achieved, a modest yield improvement compared with that of the batch reaction. The configuration of the equipment in the flow reactor gives significantly better heat dissipation relative to a batch reaction through increased surface area of the reactor and a large heat sink derived from the mass of water in the

Table 2. Nitration of 1 at different time points[a]

time (min)	unreacted **1** (area %)	product (area %)	assay yield of composite produced over the indicated time interval (%)
0−5	1.30	80.4	59
5	0.38	81.5	yields measured over time intervals only, not at discrete time points.
5−10	0.26	85.7	61
17	0.32	83.7	
17−22	0.32	83.6	60
23	1.09	81.8	

[a] Condition: 100 g input of **1**, H_2SO_4/HNO_3 = 22, 1.1 equiv of HNO_3 relative to **1**, 50−55 °C; flow rate = 6 mL/min.

Table 3. Ten kilogram demonstration run of nitration using pressure-charged reagents.[a]

sample time (min)	unreacted **1** (area %)	product (area %)	isolated yield
60	1.00	81.2	59%
120	0.26	83.8	
180	0.32	84.6	
240	0.25	83.2	

[a] Conditions: 10 kg input of **1**, H_2SO_4/HNO_3 = 22, 1.1 equiv of HNO_3 relative to **1**, 50−55 °C; flow rate = 70 mL/min.

jacket surrounding the coil. With a reactor volume of 7.95 L and efficient heat dissipation from coil to jacket, the contents of the reactor at any given time could produce a 1.8 °C temperature increase, and assuming adiabatic conditions (i.e., no active temperature control of the jacket) throughout a 10 kg run, the expected temperature rise is ~10 °C, giving further confirmation of the safety advantages afforded by switching to a flow reactor system for this type of reaction. In fact, the highest recorded temperature at the exit point of the flow reactor was 57 °C during the 10 kg run. Temperature measurements at other points along the coil were not attempted. Because a safe operating envelope was not carefully defined, users are warned that deviations from the conditions reported here could conceivably lead to a runaway reaction in the flow reactor.

Under these conditions, this apparatus has a theoretical output of ~28 kg/day. We have since operated this chemistry successfully in the flow reactor to generate 36.5 kg of **2** over a period of 2.5 days in 99.7% purity, albeit in only 50% yield because of less precise flow control during this run. Although when operated continuously for many hours periodic manual readjustment of the flow meters was needed to keep the addition rates synchronized, use of this expedient charging method allowed time lines to be met. Furthermore, the simple layout and design allows quick and inexpensive numbering up of this flow reactor.

■ CONCLUSIONS

A practical flow reactor has been constructed capable of supporting large-scale production of **2** by the use of nitrogen pressure to charge solutions. The significant heat of reaction for the desired chemistry was readily managed in the flow system, improving safety. Although only a modest yield improvement relative to the batch process was achieved in a 10 kg trial and actually fell slightly in a larger run, implementation enabled safe, rapid scale up and avoidance of a major capital expenditure for plant expansion. The system's simplicity, especially with regard to controlling flow into the reactor, makes it easily adaptable to other liquid/liquid flow reactions.

■ EXPERIMENTAL SECTION

All HPLC analyses were conducted on an Agilent 1200 using Eclipse XDB-C18 (150 mm × 4.6 mm, 5.0 μm) column; *T*: 40 °C; eluent: A = acetonitrile, B = 0.1% phosphoric acid in water; gradient: 0−15% from 90% B to 5% B, 15−20 min from 5% B to 0% B, flow rate: 1.5 mL/min; detection at 240 nm.

Preparation of 5-Bromo-4-methyl-3-nitro-pyridin-2-ylamine (batch reaction). 5-Bromo-2-amino-4-methylpyridine (**1**, 130 g, 0.57 mol) was dissolved in conc. H_2SO_4 (452 mL), and HNO_3 (14 mL) was added dropwise at 25−33 °C. The reaction mixture was stirred for 2 h. The mixture was poured into a mixture of ice (832 g) and water (832 g), and the pH was adjusted to 4−5 by addition of concentrated aq ammonium hydroxide (>20%). A light-yellow precipitate was collected by filtration that was washed with 10% aq NaOH (810 mL) and water (200 mL) twice. The filter cake was dissolved in THF (400 mL) at 60−70 °C and hot-filtered. Water (600 m L) was added to the filtrate; it was cooled to −10−0 °C, stirred for 1 h, and filtered. The filter cake was dried, and 72.4 g of the desired product as a yellow solid was obtained at >98% purity in 55% yield.[7] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H); 5.84 (s, 2H); 2.54 (s, 3H). IR (KBr): (cm^{-1}) = 3480, 3286, 3151, 1634, 1581, 1535, 1512, 1458, 1422, 1377, 1345, 1320, 1244, 1225, 1116, 1028, 990, 869, 779, 669.

Identification of side product 5-bromo-4-methyl-3-nitro-pyridin-2-ol proceeded as follows. The pH of the mother liquor from aq NaOH washing was adjusted to 6−7 with 3 N HCl at 0−20 °C. The aqueous phase was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to give the side product as an off-white solid (13.2 g). ^{1}H NMR (500 MHz, DMSO) δ 8.01 (s, 1H); 2.50 (br, 1H); 2.21 (s, 3H). MS: $C_6H_5BrN_2O_3$ required 231.95 (100%), 233.95 (98%). *m/z* found 235.11 (M + 1), 233.11 (M + 1).

For the continuous flow experiments, the experimental setup consisted of two pumps (TAUTO TBP5010T, China) connected to tubes (6 mm o.d.) through an inhouse developed and fabricated metal connector made of stainless steel (SS304). The two metallic tubes were subsequently connected to a micromixer followed by a residence time tube (6 mm o.d., 4 mm i.d., and 20 m long) made of SS304 (Tianjin, China). A digital thermometer (Thermocouple, United States) was also used (see Figure 1). The feed tanks were filled with the nitrating mixture and compound **1** in sulfuric acid, respectively. The SS304 tubes carrying the reactants, the micromixer, and the SS304 tube were immersed in a thermal bath. Flow of nitrating mixture and compound **1** were continuous. The reaction composition was varied by changing the flow ratio at the inlet and the composition of the nitrating mixture, while the temperature was changed by changing the bulk temperature in the jacket.

Preparation of 5-Bromo-4-methyl-3-nitro-pyridin-2-ylamine (10 kg flow reactor run). Reagent solution A: a solution of *N*-(5-bromo-4-methyl-pyridin-2-yl)-acetamide (10 kg, 43.86 mol) in H_2SO_4 (16.3 L). Reagent solution B: a solution of fuming HNO_3 (3.02 kg, 48.25 mol) in H_2SO_4 (20.1 L). The solutions A and B were added at 70 mL/min. The output rate was 1.24 kg/h. The reaction mixture flowed into a tank of ice (67 kg) and water (67 kg) for quenching at 0−20 °C. Following completion of the addition, the pH of the quenched reaction was adjusted to ~10 at 0−30 °C. After stirring for 90 min, the solid was filtered. The filter cake was dissolved in THF (40 L) at 60−70 °C and hot-filtered. Water (60 L) was added to the filtrate; it was cooled to −10−0 °C, stirred for 1 h, and filtered. The filter cake was dried, and 5.98 kg of product as a yellow solid was obtained at >98% purity in 59% yield.

Preparation of 5-Bromo-4-methyl-3-nitro-pyridin-2-ylamine (100 kg flow reactor run). Reagent solution A: a solution of *N*-(5-bromo-4-methyl-pyridin-2-yl)-acetamide (100 kg, 438.6 mol) in H_2SO_4 (163 L). Reagent solution B: a solution of fuming HNO_3 (30.3 kg, 482.5 mol) in H_2SO_4 (201 L). The solutions A and B were transferred to two 200-L stainless tanks, respectively, and added to the flow reactor at 70 mL/min. The output rate was 1.2 kg/h. The reaction mixture flowed into a tank of water (1340 kg) cooled initially to 0−5 °C. The production was run in five segments (80 L/11 h segment). The output from only 74% of the total feed solutions was quenched as described for product isolation, with the remainder removed for a separate experiment. The pH of the quenched reaction was adjusted to ∼10 at 0−30 °C. After the mixture stirred for 90 min, the solid was filtered. The filter cake was dissolved in THF (400 L) at 60−70 °C and hot-filtered. Water (600 L) was added to the filtrate; it was cooled to −10−0 °C, stirred for 1 h, and filtered. The filter cake was dried, and 36.5 kg of the product as a yellow solid was obtained at 99.7% purity and 50% yield based on input.

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Notes

The authors declare no competing financial interest.

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