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TECHNICAL NOTE

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Nitration Chemistry in Continuous Flow using Fuming Nitric Acid in a Commercially Available Flow Reactor

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ABSTRACT: The paper will describe the use of flow chemistry for scaling up exothermic or hazardous nitration reactions. Such reactions often cause time delays to the delivery of larger batches of intermediates or final compounds for medicinal chemistry projects, because considerable time is required for safety evaluation and, if necessary, modification of the procedure so that it can be scaled-up and run in a safe manner. A commercially available continuous flow reactor was used in the scale up of three challenging nitrations including a reaction involving a potentially explosive mixture of acetic acid and fuming nitric acid, with a productivity of 97 g/h.

INTRODUCTION

In recent years, continuous flow chemistry has emerged as a useful technology for research and development chemists within the pharmaceutical sector.[1−4] Highly efficient mixing is combined with superior heat exchange and narrowly distributed, well-defined, reaction times. One major advantage of flow reactors, in comparison to reactions in batch mode, is the small reaction volume, which allows the running of highly exothermic or hazardous reactions in a safer manner to provide >100 g quantities. Flow chemistry automation enables chemists to rapidly find optimized conditions for a reaction on trial scale. The refined conditions can then be directly translated to the production of larger amounts by increasing the volume of the reactor (and hence flow rate), using multiple reactors in parallel (numbering-up), and/or prolonging the running time of the system. The fast transfer of processes is in stark contrast to the typical scale-up of batch chemistry, which often requires additional time for the optimization of parameters.

Such technology is attractive for use in our Preparation Laboratories to aid the often time-critical supply of intermediates, building blocks, and final compounds in multihundred gram amounts to the Medicinal Chemistry laboratories of Novartis Research.

CONTROLLING ENERGY RELEASE USING FLOW CHEMISTRY

The Novartis Preparation Laboratories became interested in continuous flow chemistry in order to scale up exothermic or hazardous reactions. Hazardous chemistry often causes us delays and requires extensive safety assessments in order to scale up the batch reaction in a safe manner or to find alternative reaction conditions so that the hazard can be minimized when the reaction is performed on a larger scale in a batch reactor.[5] In order to fully understand the advantages of adapting batch chemistry to continuous flow, it is insightful to consider the kinetics of the reaction and the potential energy released in the case of a runaway reaction. Another important consideration is the speed at which the heat is released from a strongly exothermic reaction.

Differential scanning calorimetry (DSC) can provide valuable information about the onset temperature of a reaction or decomposition, and how much energy is released per gram of product. According to our internal safety guidelines, any reaction, starting material, or product showing an exotherm over 300 J g^{-1} is considered to require further safety assessment as it could result in an uncontrollable temperature rise within a reactor vessel. Performing such reactions in a microreactor or a continuous flow reactor is advantageous because the reaction takes place in narrow tubes, and any heat evolved is produced in a small reaction volume and can be more rapidly dissipated. Indeed, the heat-transfer rate between the reactor and the surrounding medium can be magnitudes of orders faster compared to that for a batch reactor.[6] In contrast to this, the scale-up of exothermic reactions in batch can be problematic due to low mixing efficiency and poor heat transfer, leading to the formation of hot spots and, as a further consequence, to the formation of undesired by-product.

LITERATURE EXAMPLES OF NITRATIONS IN CONTINUOUS FLOW

Nitration of aromatic compounds is not only fast but is often accompanied by a strong exotherm upon addition of the nitrating acid mixture, making these reactions interesting targets for adaptation to continuous flow. It is known that continuous processing can be used to control the reaction temperature and any selectivity of a given reaction with more precision. Nitration reactions are often performed using mixtures of nitric and acetic acids (sometimes with acetic anhydride) which are known to be potentially explosive.[7,8] Use of excess nitrating agent often results in polynitration, meaning that the accurate reaction times and

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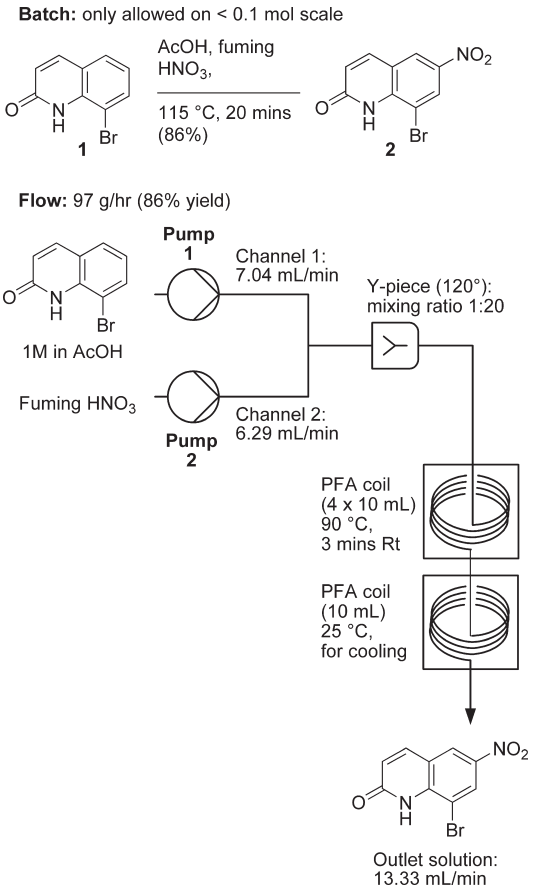
Scheme 1. Nitration of 8-bromo-1*H*-quinolin-2-one 1 in batch and under continuous flow



specific stoichiometry achievable in flow is particularly attractive. The precision of the reaction times in flow means that the nitrating mixture can be quenched before overreaction takes place. There are relatively few literature examples of nitration reactions which have been performed under continuous conditions. One reason is because of the lack of commercially available lab-scale equipment able to pump the corrosive acids that are required.

Schwalbe et al. used a stainless steel CYTOS microreaction system from Cellular Process Chemistry, for the nitration of a key intermediate in the synthesis of sildenafil, the active ingredient of Viagra.[9,10] By adapting this chemistry to flow, not only was the handling of the highly energetic reaction made easier, but also the selectivity of the reaction was improved. Exothermic decomposition via decarboxylation was avoided by utilizing accurate temperature control within the reactor. Further examples of nitrations in continuous flow include the nitration of toluene,[10−13] phenol,[14] benzaldehyde,[15] and salicylic acid[16] using a range of equipment, mainly including syringe pumps and self-made apparatus. In many of these literature examples, the aromatic component to be nitrated was used as the solvent, and the reaction was run under two-phase plug flow with the aqueous nitrating acid. A recent literature example (Pelleter et al. from AstraZeneca) details the nitration of 3-alkylpyrazoles on 100-gram scale with a productivity of 0.82 g/h.[6] A very impressive example for a nitration on production scale in flow is the nitration of a key intermediate in the synthesis of naproxcinod which was scaled to 25 tonnes by DSM and subsequently performed under cGMP using a Corning microreactor system.[17] The sensitive step in this reaction was not the nitration itself but the risk of exothermic decomposition of the nitrated product. The nitration utilized 65% nitric acid and involved the quenching of the outlet by stepwise addition of water and sodium hydroxide streams.

RESULTS AND DISCUSSION

The following section will outline the adaptation of three nitration examples to continuous flow and demonstrate the high productivity we have observed using relatively simple, commercially available equipment.[18] The first nitration we investigated is outlined in Scheme 1, showing the original batch conditions for the nitration of 8-bromo-1*H*-quinolin-2-one **1**, with the subsequent optimized flow conditions beneath. DSC of a mixture of fuming nitric acid and acetic acid showed a strong decomposition releasing 1374 J g^{-1} with an exotherm starting at 130 °C, presumably from the decomposition of acetyl nitrate. DSC of the reaction mixture after 50% addition of nitric acid showed a strongly exothermic decomposition starting at 105 °C, releasing 633 J g^{-1}, and after 100% addition, a second strongly exothermic decomposition releasing 1620 J g^{-1} with an onset at 225 °C. Under adiabatic conditions, the total energy released corresponds to a temperature rise of 840 °C. Reaction calorimetry also indicated that the reaction demonstrated the potential for accumulation.

The original nitration reaction had been performed on small scale by the Medicinal Chemistry team with the acidic solution at reflux (approximately 115 °C). The proximity of the reaction temperature to the onset of decomposition was unacceptable for scale up. For safety reasons, the scale of this reaction was limited to <0.1 mol for batch reactions, and we sought alternatives to be able to run this reaction on the required 250-g scale.

In adapting this nitration chemistry to continuous flow, not only would a relatively small quantity of high-temperature reaction mixture be present in the reactor at any one time, but also, should a temperature rise occur, the machine must be able to be manually stopped or will automatically stop if a rapid change in pressure is detected. Once product is formed in the reactor, it is continuously removed and pumped into the quench solution. There is therefore relatively little time for the nitrated product to undergo decomposition compared to the corresponding batch reaction.

As is often the case for adapting batch chemistry to flow, we started our trials with small-scale batch experiments. Not only does this provide us with information about the reaction rate (which was monitored by HPLC), but it also provides us with an opportunity to check whether the reaction is homogeneous. Figure 1 shows the reaction conversion at three different concentrations and the fourth experiment using diluted nitric acid. The rate of reaction using 65% nitric acid was deemed too slow for adaptation to flow: the reaction showing only approximately 50% conversion after one hour. However when the concentration was increased from 0.2 to 1 M, the reaction was complete in a matter of minutes in small-scale batch experiments.

A set of screening experiments using the Vapourtec R2C/R4 equipment was performed, using 1 M substrate in acetic acid and a second inlet stream of fuming nitric acid. The outlet stream was quenched by dripping directly into water and the resultant precipitate removed by filtration. The screen quickly revealed that only 3-min residency time (Rt) were necessary for near

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complete conversion (Table 1, entry 4). When the reactor temperature was varied and the 3-min residency time maintained, complete conversion was achieved at just 90 °C (Table 1, entry 5), a reduced temperature compared to that of batch. If the mixture was heated above this temperature, or reacted for longer than three minutes, a number of undefined baseline by-products were observed in HPLC. However a residency time of at least three minutes was required for >99% conversion (Table 1, entries 7 and 8), and when the equivalents of nitric acid were reduced, the reaction rate quickly dropped (Table 1, entries 9 and 10). Lower temperatures led to incomplete conversion.

The conditions which gave complete conversion (Table 1, entry 5) were chosen for scale-up trials with 3-min residency time at 90 °C using a 20-fold excess of fuming nitric acid. The reaction was stepwise scaled up by first using a 2-mL reactor followed by increasing reactor length until the maximum reactor size of 40 mL for the Vapourtec equipment was reached. At each stage the power usage of the R4 unit was observed to check that the unit was able to cope with the heat evolved from the reaction. The pumps were monitored over longer reaction times and were found to reliably pump the required flow rates over 2 h or more. For the largest-scale run, an additional 10-mL reactor coil at room temperature was attached behind the reaction coils at 90 °C so that the outlet stream had time to cool before reaching the back-pressure regulator. The maximum scale up is outlined in Scheme 1 with an outlet flow rate of 13.3 mL/min. Filtration of the quenched reaction mixture gave 86% yield of high-purity product in comparable yield to the original batch procedure. In total, 201 g of material was produced over 124 min, giving a satisfying production rate of 97 g/h. Not only were the screening experiments complete within a matter of hours, but we were also able to produce the required 250 g of material in just one day's work (including workup) using the Vapourtec setup. The flow reaction shows a considerable time saving compared to the batch experiment which required two months of safety evaluation and a subsequent week to safely perform the chemistry in a 2.5-L reactor using a trifluoroacetic/nitric acid alternative as the nitrating mixture.

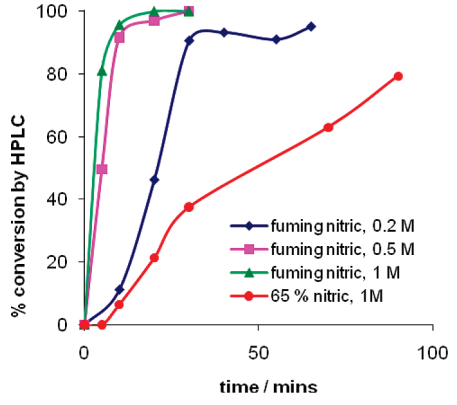

Figure 1. Batch conversion with time for varying substrate concentrations and 65% nitric acid for the nitration of 8-bromo-1*H*-quinolin-2-one **1**.

The second nitration reaction which was performed is outlined in Scheme 2. Initial scale-up trials were performed under batch conditions using an analogue procedure described in literature.[20] The method gave varying results and considerable by-product formation, leading to a gummy product which was difficult to purify and which could not be used directly for further reactions. When the reaction was scaled up in batch, to >100-g scale, it became difficult to keep the relevant reaction parameters (e.g., temperature, dosing time, stoichiometry) under precise control, and it was not possible to obtain a constantly high quality of product. Either dosing the nitric acid slowly at low temperature in order to control the heat evolution, or adding the acetic anhydride too early in the reaction led to the formation of acylated by-product **5** in significant quantities. The formation of by-product **5** made isolation of the product by precipitation or the workup extremely challenging. The by-product was removed for the next reaction step by additional crystallization, which in turn led to a significant loss in yield. We once again measured the DSC of the neat reaction product and observed two large exotherms, the first with an onset at 140 °C and a potential energy release of 641 J g^{-1}, the second with an onset at 220 °C and an energy release of 559 J g^{-1}. The first exotherm was considered risky for scale up in batch.

Following the success of the previous nitration in continuous flow, and knowing that the reaction was homogeneous, we directly ran a screening experiment using the Vapourtec equipment in which we varied temperature, stoichiometry, and residency time. Suitable conditions for a two-step reaction using three inlet streams, including our additional R1 pumping unit, were found after only a few hours of screening experiments, the time bottleneck often being the running of HPLC analytics. For the scale-up reaction, 2-amino-4-bromo-benzoic acid methyl ester **3**, as a 0.8 M solution in acetic acid, was mixed with a 6-fold excess of fuming nitric acid and then subjected to a 1.3-min

Table 1. Screening experiments for the nitration of 8-bromo-1*H*-quinolin-2-one 1 using a 2-mL PFA coil and collecting the outlet in water[19]

entry	Rt (mins)	temp. (°C)	stoichio-metric ratio (**1**:HNO_3)	**1** (%)[a]	**2** (%)[a]	by-product (%)[a,b]
1	5	120	1:20	1	96	3
2	5	105	1:20	0	98	2
3	5	90	1:20	1	97	2
4	3	120	1:20	1	97	2
5	3	90	1:20	0	100	0
6	3	70	1:20	8	92	0
7	2	90	1:20	2	98	0
8	1	90	1:20	2	98	0
9	5	90	1:15	11	86	3
10	5	90	1:11	52	47	1

[a] Area percentage determined from HPLC (254 nm). [b] Baseline impurities in HPLC of which the structures were not confirmed.

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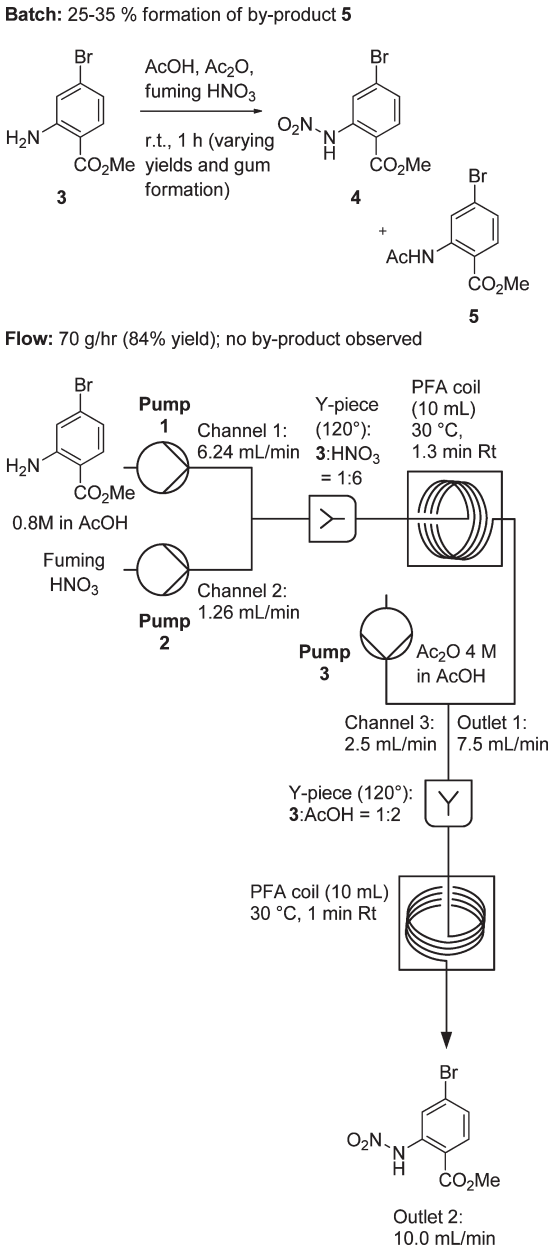
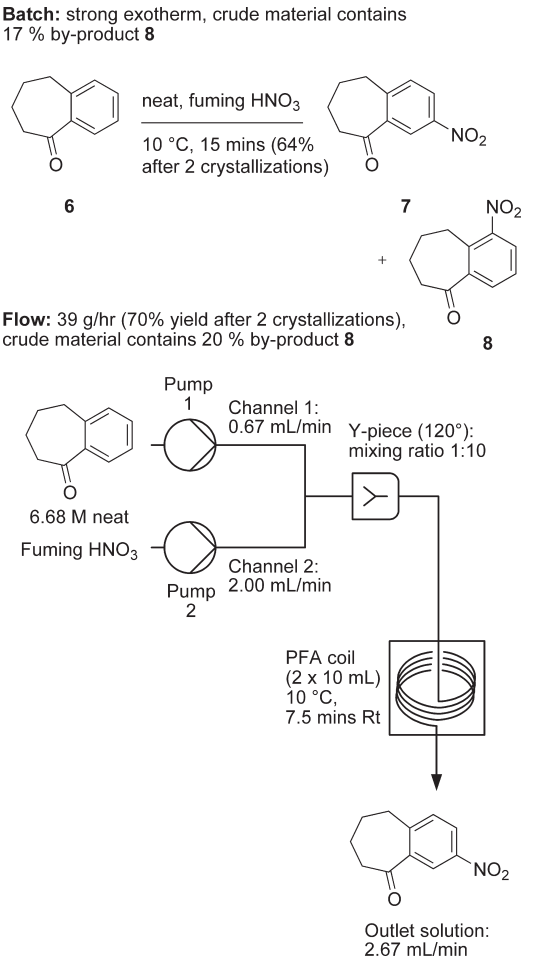
Scheme 2. Nitration of 2-amino-4-bromo-benzoic acid methyl ester 3 in batch and under continuous flow



Scheme 3. Nitration of 1-benzosuberone 6 in batch and under continuous flow



residency time in the first reactor. After this time, the outlet from the first reactor was mixed with the third inlet of a 4 M solution of acetic anhydride in acetic acid in 2-fold excess relative to the substrate. The reaction was subjected to a second residency time of one minute to give an outlet stream of 10 mL/min which was quenched directly by flowing into stirred ice−water. Formation of a crystalline solid was greatly influenced by the temperature of the quench water. Gum formation was observed when room temperature water was used for the quench, but a fine crystalline solid was obtained when ice was used. Filtration of the quenched reaction mixture gave 84% yield of a crystalline solid containing no by-product and pure enough to be used directly in the next step. In total, 123 g of material was produced over 105 min giving a production rate of 70 g/h. The flow experiment provided pure material, in contrast to the varying quality of product obtained from batch reactions. It is also noteworthy that the total lab time taken for screening, analytics, and subsequent scale-up was only one week. Since our group is concerned with the time-critical supply of intermediates, building blocks and final compounds in multihundred gram amount, time savings of this type can be directly translated into cost benefits.

The third nitration, outlined in Scheme 3, uses neat 1-benzosuberone and fuming nitric acid. The reaction in batch showed a strong exotherm and formation of approximately 20% of an ortho-substituted by-product. DSC of the dried crude material from a batch procedure showed a large exothermic decomposition of 983 J g^{-1} with a slow onset, beginning at approximately 150 °C. Although the reaction was run at low temperature in batch, addition of 1-benzosuberone **6** to a stirred reactor containing fuming nitric acid was very exothermic, and we did not want to work in a temperature regime anywhere close to the exothermic decomposition observed in the DSC. By using flow chemistry, we sought to adequately control this reaction and in doing so to possibly reduce by-product formation. Neat 1-benzosuberone (at 6.68 M) was mixed with fuming nitric acid at a range of residency times and stoichiometric ratios using a 5-mL PFA coil in a chilled reactor according to Table 2.

The outlet stream was dosed into stirred ice−water and the product removed by filtration for analysis by NMR. As previously observed for the other nitrations, a large excess of nitric acid

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Table 2. Screening experiments for the nitration of 1-benzosuberone 6 using a 5-mL PFA coil and collecting the outlet in ice−water

entry	Rt (mins)	temp. (°C)	stoichio-metric ratio (**6**:HNO_3)	**6** (%)[a]	**7** (%)[a]	**8** (%)[a]
batch	15	10	1:10	0	83	17
1	2.5	10	1:2.5	23	65	12
2	2.5	10	1:5	9	71	20
3	2.5	10	1:10	0	78	22
4	2.5	0	1:10	5	79	16
5	5	10	1:10	0	79	21
6	7.5	10	1:10	0	80	20

[a] Percentage from NMR integration.

(in this case 10 equiv) was required for high conversion, and we observed similar quantities of the by-product compared to that from batch (Table 2, entries 1−3). No significant change was observed when the reaction was run at lower temperatures or for longer residency time (Table 2, entries 4−6). Appropriate conditions were found to be 2.5-min residency time at 10 °C, and so we scaled up to the equipment maximum of 20 mL in two 10-mL PFA coils. When the flow rates were increased proportionally by a factor of 4 relative to the screening experiments (to a total flow rate of 8 mL/min), the dry ice-chilled air cooling unit was not able to maintain the reaction temperature of 10 °C, and the internal temperature rose to 30 °C. The reaction was immediately manually stopped. The reaction was performed with 5-min residency time (with a total flow rate of 4 mL/min), but again the temperature of 10 °C could not be maintained by the cooling unit, the internal temperature rose to 15 °C, and the reaction was again stopped. The fastest we were able to perform this reaction in a safe manner was at a total flow rate of 2.67 mL/min, equating to a residency time of 7.5 min. It would be possible to dilute this reaction so that the energy released from the reaction per centimeter of tubing would be reduced; however, this would result in a proportionally lower productivity. Experiments in which the 1-benzosuberone **1** was diluted with a solvent (e.g., acetic acid), or using a stainless steel reactor to aid heat transfer, were not attempted.

Using a residency time of 7.5 min, crude product was isolated in quantitative yield at 78% purity. The by-product was removed by crystallization of the crude material to give a final isolated yield of 70%; a comparable yield to that of the batch procedure. As a proof of concept, 12 g of >97% purity material (after crystallization) was prepared over 19 min at a production rate of 39 g/h.

CONCLUSIONS

The Novartis Preparation Laboratories have demonstrated the scale up of three nitration reactions using commercially available equipment at high production rates. All nitration solutions were homogeneous which is in contrast to some literature examples which utilize biphasic, organic, and nitrating acid mixtures in two-phase plug flow. In our experience, it is not necessary to employ a complex micromixer or chip, and in the three examples chosen, a simple Y-piece was sufficient in to effect efficient mixing and high conversion. It should also be noted that acetic acid or acetic anhydride with fuming nitric acid mixtures provides an alternative to traditional nitrating mixtures, such as a mixture of nitric and sulfuric acids. Despite the low corrosive nature of the latter (making it possible to use stainless steel reactors) the viscosity is high and thus limits the maximum flow rates that can be achieved in continuous mode.

In all three examples detailed above, comparable yields to that of batch were observed using continuous processing. In the second example, an additional advantage was that by-product formation was completely avoided under flow conditions. The impurity profile was improved, and this may have been due to the exact stoichiometry at the mixing point and the accurately defined reaction times before the quench. Selectivity was not altered or improved in the other two examples.

In summary, scaling up nitrations to produce some hundreds of grams was shown to be possible in a rapid manner (within a 1- to 2-week time frame, including screening) using the Vapourtec equipment. Three real examples of challenging chemistry encountered by our research group, which showed problems on scale-up, have been transferred to continuous flow with good results. Nitrations in continuous flow provide a safe alternative to running dangerous exothermic reactions in batch and show significant time savings, especially in the screening of reaction parameters to find the optimal conditions.

EXPERIMENTAL PROCEDURES

All chemicals were purchased from Fluka or Sigma-Aldrich unless otherwise mentioned. Fuming nitric acid was anhydrous and 100% concentration. 8-Bromo-1*H*-quinolin-2-one **1** was prepared according to a procedure by Schlosser et al.[21] Reverse phase HPLC analyses were performed on an Agilent-1100 machine using a Zorbax Eclipse XDB-C18 column, 4.6 mm × 50 mm, 1.8 μm, using acetonitrile and water as eluent (both containing 0.05% TFA), a column temperature of 35 °C, a flow rate of 1.0 mL/min, and measuring at 216 nm. The standard gradient used was 5 to 100% MeCN over 6 min, 100% MeCN for 1.5 min, followed by 100 to 5% MeCN over 0.5 min. GC was performed on an Agilent 7890A GC system with a BGB Silaren column (30 m × 0.32 mm ID, 0.12 μm film). The standard 12-min run started at 40 °C which was held for 0.3 min, followed by a temperature ramp at 25 °C/min up to 220 °C and a second ramp of 40 °C/min up to 280 °C, and this temperature was held for 3 min. The hydrogen flow was 2 mL/min, the front inlet temperature was 220 °C, and the front detection temperature was 300 °C. NMR was performed using a 400 MHz Varian machine, AS 400 Oxford. ^{1}H shifts were referenced to d_6-DMSO at 2.49 ppm and $CDCl_3$ at 7.26 ppm. ^{13}C shifts were referenced to d_6-DMSO at 39.52 ppm and $CDCl_3$ at 77.16 ppm. MS was measured using VG Platform (Fisons Instruments), Spectraflow 783 detector, HP 1100 series HPLC. Melting points were measured using a Büchi B-545 machine.

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Differential scanning calorimetry was measured on a Mettler Toledo DSC823 machine. A sample of the starting material, product, or reaction mixture was heated in a steel capsule, plated with 5 μm of gold, starting from 35 °C and increasing to 400 °C at a rate of 5 °C/min.

Specifications of the Vapourtec Equipment. A Vapourtec R2C/R4/R1C setup was used for all three flow experiments. The R2C unit is the pumping unit containing two adapted Knauer pumps which are able to pump highly concentrated and corrosive acids. The tubing and machine parts are all made from perfluoroalkoxy (PFA) or polytetrafluoroethylene (PTFE or Teflon) plastics, and the pump heads are ceramic. The liquid stream does not come into contact with metal parts, and corrosion can be avoided. The R4 is the heater unit with four heating positions and two cooling positions. The R1C pump is an additional pump (again adapted for corrosive reagents) which was used when three inlet streams were required. The tubing used was PFA with an internal diameter of 1 mm and kept to a minimum between reactors to avoid unwanted heat transfer. The Y-piece sits exterior to the heated reactors and inside the cooled reactors, the latter allowing the chilling of inlet streams prior to mixing. The Y-pieces are made of PTFE and have an inner diameter of 1 mm and no narrow point where crystallization can occur. Each reactor unit contains PFA tubing wrapped around into a coil (for example, a 10-mL reactor contains 13 m of tubing). The temperature sensor sits on the wall of the PFA tubing, approximately in the middle of the reactor. The reactor manifold, surrounding the reactor coil, is approximately 400 cm^3.

In order to fill the R2C pumping unit with the strongly corrosive acids, the following pumping protocol was followed. The system was flushed with isopropyl alcohol followed by water and finally glacial acetic acid with all pumps flowing at 2 mL/min and for 5 min for each inlet. The back of the pump heads were flushed with water followed by acetic acid. After the reaction the pumps were flushed in the reverse order. The system was flushed with glacial acetic acid followed by water, 0.1 M NaOH, and water again, and finally isopropyl alcohol with all pumps flowing at 2 mL/min and for 5 min for each inlet. The back of the pump heads were flushed with water followed by isopropyl alcohol. The machine was left to stand in isopropyl alcohol.

8-Bromo-6-nitro-1*H*-quinolin-2-one 2. The flow reactor was configured using a combination of the R2C pump module and R4 heater/chiller module. Four 10-mL PFA tubing reactors were installed in the R4 module, plus an additional 10-mL coil at room temperature to allow the outlet to cool, along with an 8-bar ceramic back-pressure regulator fitted in-line between the reactor outflow and the collection valve. The solvent bottle was filled with glacial acetic acid, and the reagent stock bottles were filled with 8-bromo-1*H*-quinolin-2-one **1** in acetic acid (1 M) and fuming nitric acid (22.4 M), respectively. The equipment was set to flow with a substrate:nitric acid ratio of 1:20. Pump 1 delivered 7.04 mL/min substrate solution and 6.29 mL/min fuming nitric acid to give a residency time of 3 min at 90 °C and a final outlet flow rate of 13.3 mL/min.

The outlet stream was collected for 124 min and poured directly into stirred water (8 L). When collection stopped, the yellow suspension was stirred for 30 min before filtering and washing with water (2 × 1 L). The solid was dried under a filter paper in the vacuum oven at 50 °C for 2 h then under a filter paper in the fume cupboard overnight to give a pale-yellow solid (201 g, 86%). Rate of production = 97.2 g/h. ^{1}H NMR (400 MHz, d_6-DMSO) δ 6.75 (1H, d, J = 9.09), 8.16 (1H, d, J = 9.35), 8.55 (1H, d, J = 2.53), 8.73 (1H, s), 11.21 (1H, br s). HPLC (Zorbax XDB-C18) r_t = 3.73 min; >99% purity. ^{13}C NMR (101 MHz, d_6-DMSO) δ 124.3, 124.8, 125.0, 128.5, 140.6, 140.9. HRMS (FAB) calcd for $C_9H_5BrN_2O_3$ + H: 268.95563, found: 268.95548/270.95344; calcd for $C_9H_5BrN_2O_3$ + Na: 290.93758, found: 290.93741/292.93533.

Methyl 4-bromo-2-(nitroamino)benzoate 4. The flow reactor was configured using a combination of the R2C pump module, the R1C pump module, and R4 heater/chiller module. Two 10-mL PFA tubing reactors were installed in the R4 module along with an 8-bar ceramic back-pressure regulator fitted in-line between the reactor outflow and the collection valve. The solvent bottle was filled with glacial acetic acid, and the reagent stock bottles were filled with **3** in acetic acid (0.8 M), fuming nitric acid (22.4 M), and acetic anhydride in acetic acid (4 M), respectively. The equipment was set to flow with a substrate/HNO_3/Ac_2O ratio of 1:6:2. Pump 1 delivered 6.24 mL/min substrate solution and 1.26 mL/min fuming nitric acid to give a residency time of 1.3 min at 30 °C in the first reactor. The outlet of the first reactor had a flow rate of 7.5 mL/min. The third pump delivered 2.50 mL/min of the acetic anhydride solution to give a residency time of 1 min at 30 °C in the second reactor.

The outlet stream was collected for 105 min and poured directly into stirred ice water (8 L). When collection stopped, the cream-colored suspension was stirred for 10 min before filtering and washing with water (2 × 500 L). The solid was dried under a filter paper in the vacuum oven at 40 °C overnight to give a cream-colored crystalline solid (123 g, 84%). Rate of production = 70 g/h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (3H, s), 7.41 (1H, dt, J = 8.60, 1.95), 7.94 (1H, dd, J = 8.59, 1.56), 8.42 (1H, t, J = 1.95), 13.37 (1H, br s). HPLC (Zorbax XDB-C18) r_t = 4.72 min; >99% purity. ^{13}C NMR (101 MHz, d_6-DMSO) δ 53.1, 126.4, 126.4, 130.7, 132.2, 132.8, 135.7, 165.3. HRMS (FAB) calcd for $C_8H_7BrN_2O_4$ − H: 272.95165, found: 272.95169/274.94938.

8-Nitro-1-benzosuberone 7. The flow reactor was configured using a combination of the R2C pump module and R4 heater/chiller module. Two 10 mL PFA tubing reactors were installed in the R4 module in chilled reactors along with an 8-bar ceramic back-pressure regulator fitted in-line between the reactor outflow and the collection valve. The chilled reactors were cooled with nitrogen which had been passed over dry ice. The solvent bottle was filled with glacial acetic acid, and the reagent stock bottles were filled with neat 1-benzosuberone (6.68 M) and fuming nitric acid (22.4 M), respectively. The equipment was set to flow with a substrate/nitric acid ratio of 1:10. Pump 1 delivered 0.67 mL/min substrate solution and 2.00 mL/min fuming nitric acid to give a residency time of 7.5 min at 10 °C and a final outlet flow rate of 2.67 mL/min.

The outlet stream was collected for 18.7 min and poured directly into stirred ice water (500 mL). When collection stopped, the yellow suspension was stirred for 10 min before filtering and washing with water (2 × 50 mL). The solid was dried under a filter paper in the vacuum oven at 40 °C overnight to give a pale-yellow solid (17.2 g, >99%). The crude material (containing approximately 20% of the ortho-nitrated isomer) was crystallized twice with 10% TBME in heptane (2 × 80 mL) and the resultant solid dried in the vacuum oven at 40 °C overnight to give a pale-yellow solid (12.0 g, 70%). Rate of production = 39 g/h. ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.67−1.74 (4H, m), 1.78−1.85 (4H, m), 2.67−2.77 (2H, m), 3.03−3.07 (2H, m), 7.60 (1H, d, J = 8.53), 8.27 (1H, s), 8.29 (1H, d, J = 2.51). HPLC (Zorbax XDB-C18) r_t = 4.55 min; >99%

purity. GC (BGB Silaren) r_t = 9.20 min; 97.3% purity. ^{13}C NMR (101 MHz, d_6-DMSO) δ 20.5, 24.8, 31.8, 40.4, 123.2, 126.7, 132.2, 139.7, 146.8, 149.4, 203.6. HRMS (FAB) calcd for $C_{11}H_{11}NO_3$ + H: 206.08117, found: 206.08110.

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