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Facile, Fast and Safe Process Development of Nitration and Bromination Reactions Using Continuous Flow Reactors

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Abstract:

Chemists working in a pilot plant often face safety issues during scale-up operations. With the help of emerging microfluidic applications and microdevices, running hazardous, highly exothermic or potentially unstable reactions can be easily transposed into a safe continuous flow mode. This paper describes how a potentially hazardous pyrazole nitration and the bromination of a variety of electron-rich heteroaromatic substrates were efficiently performed using a cheap and easily available system for bench chemists. Advantages of the continuous flow mode in organic synthetic chemistry will be exemplified by the large-scale production of raw materials under safe, green and reproducible conditions.

1. Introduction

Due to the fast-paced industrial environment, scale-up chemists need to solve quickly the safety, cost and environmental issues they face when optimising chemical processes. Through the implementation of emerging technologies like microfluidics, microreactors and continuous flow chemistry,[1,2,13] synthetic chemists can develop fast, efficient and safe organic processes. In modern pharmaceutical research, there is a routine demand to scale-up processes to produce large quantities of key intermediates for further derivatisation. However, some reactions performed at the bench are often potentially more hazardous on larger scales due to, for example, high exotherms, unstable mixtures and/or toxic issues of the intermediates generated during the reaction itself. We faced such problems recently with a pyrazole nitration and the bromination of imidazo[1,2-*a*]-pyridine. The implementation of a continuous flow reactor helped us to synthesise these key intermediates under safe conditions, without compromising reaction yield. After an initial period of reaction optimisation to find the best process in solution, we determined suitable operating parameters and produced the required compounds on large scales under reproducible conditions. This report describes some examples of the raw materials we have produced via a microfluidic continuous flow system. The syntheses of the following key intermediates will be described (Figure 1).

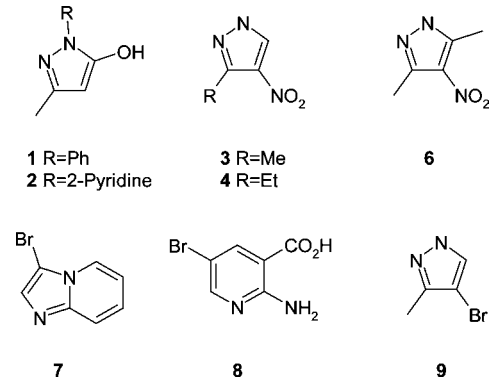

Figure 1. **Compounds scaled up and produced using a microfluidic continuous flow reactor.**

Table 1. **Parameter comparison of a tank reactor vs a microreactor**[1a]

	tank reactor	microfluidic system
internal structure	few milliliters to thousands of liters	<1 mL
type of flow	turbulent	laminar
mixing times	∼10 s	ms range (t < 1 s)
specific surface	∼100 (m^2/m^3)	5000−50 000 (m^2/m^3)
heat-transfer rate	∼2000 ($W/m^2/K$)	5000−25000 ($W/m^2/K$)

2. Results and Discussions

2.1. Operating System. A simple continuous flow reactor can be set up using easily available spare parts consisting of four main units: the pumps, the micromixer, the residence loop and a collecting vessel. All of these inexpensive units can be connected using standard low-diameter HPLC tubing and ports. As described in Table 1, laminar flow is crucial to limit mixing times to the minimum, while the miniaturisation of dimensions maximises heat exchange. The size of the internal channels provides the major advantage of a microfluidic device. The laminar flow generated in the microreactor impacts on the global reaction parameters such as the specific surface and the heat-tranfer rate. These parameters compared with a classical batch tank reactor are summarized in Table 1.

The pumping unit could be a syringe pump or a standard HPLC pump, commonly used in research laboratories. A key consideration is the pressure profile generated in the system.

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(1) (a) Jähnisch, K.; Hessel, V.; Lowe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406–446. (b) Ehrfeld, W.; Hessel, V.; Löwe, H. In *Microreactors in Organic Synthesis and Catalysis*; Wirth, T., Ed. Wiley-VCH: Weinheim, 2008. (c) Wirth, T., Ed. *Microreactors in Organic Synthesis and Catalysis*; Wiley-VCH: Weinheim, 2008.

(2) Brian, P.; Mason, K.; Price, J.; Bogdan, A.; Tyler McQuade, D. *Chem. Rev.* **2007**, *107*, 2300–2318.

(3) (a) Austin, M.; Blackborow, J.; Ridd, J.; Smith, B. *J. Chem. Soc*, **1965**, 1051–1057. (b) Habraken, C. *J. Org. Chem.* **1971**, *36*, 3081–3084. (c) Janssen, J.; Habraken, C.; Louw, R. *J. Org. Chem.* **1976**, *41*, 1758–1762. (d) Buchanan, G.; Stobie, A.; Wightman, R. *Can. J. Chem.* **1980**, *58*, 2624–2627.

(4) (a) Dale, D.; Dunn, P.; Golightly, C.; Hughes, M.; Levett, P.; Pearce, A.; Searle, P.; Ward, G.; Wood, A. *Org. Proc. Res. Dev.* **2000**, *4*, 17–22. (b) Lothrop, W.; Handrick, R. *Chem. Rev.* **1949**, *44*, 419–445.

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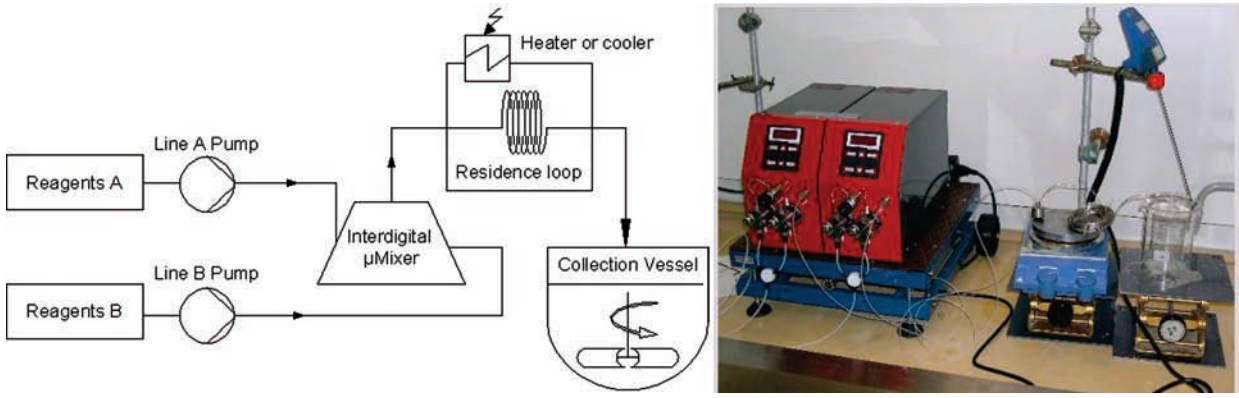


Figure 2. **System configuration.**

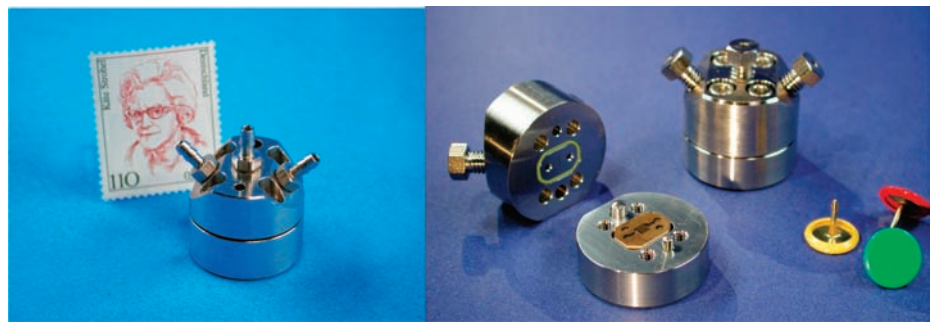


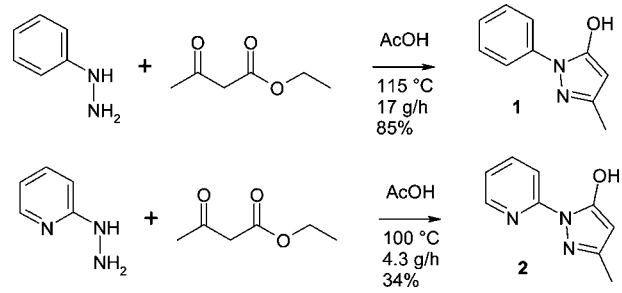
Figure 3. **IMM slit interdigital micromixer.**

In order to reach optimal mixing conditions under laminar flow, the inner pressure must be stable and continuous, which a syringe type system can generate. A syringe injection unit, however, has a considerable limitation which is the low capacity of the syringe resulting in a batch-like process, even if the advantages of laminar flow are maintained. Considering the quantities of material we intended to prepare, particularly for compounds **7** and **8**, a system connected to standard HPLC pumps was more suitable for our applications. At the beginning of our experiments, we assembled a system with two single-head piston pumps. In this case however, the pressure profile generated in the system was too unstable. Fluid was knocking in the system and upset the internal flow, which was visible by the blow out of the reaction fluid from the system. The accuracy of the continuous flow reactor was then reduced, which impacted the reproducibility of experiments. The current system is mounted with Syrrys FRX double-headed pumps on each line. Using this type of pump, the fluid flow delivered into the system is more accurate, even in the case of viscous mixtures. In order to inject corrosive materials solubilized in various organic solvents, we opted for stainless steel piston heads. Our system is able to deliver a range of reagent flow rates between 0.1 to 10 mL/min per injection line. (Figure 2).

The mixing unit is the key part of the system; this device is etched with channels designed on the micrometer scale which ensures the reagent streams mix at the millisecond range. After considering the range of likely operating conditions and chemicals that would be injected into the system, we opted for stainless steel mixers. A number of different types of stainless steel mixers are commercially available, and we chose a mixer from IMM (Institut für Mikrotechnik, Mainz) which best suited our requirements (temperature range from −40 to 220 °C, resistance to highly corrosive reagents, etc.). For a broad range of possible pressures and temperatures during operations, we acquired a slit interdigital micromixer for the handling of clear and low-viscosity solutions. Maintenance of such stainless steel units is easy to perform as the system can be opened and the channels cleaned by flushing the internal microstructures with aqueous or organic solvents, acids or bases. As it is made of stainless steel and Hastelloy, it is also possible to burn any impurities or clots generated in the microreactor. All of the reactions described in this work were processed through our IMM slit interdigital micromixer (Figure 3) followed by a residence loop.

The residence module constitutes the last unit of our system. The task of this unit is to maintain the mixed reagent stream under the chosen reaction conditions. A simple coil of stainless steel HPLC tubing was used as residence module. The simplicity of such a unit offers the opportunity to have a wide range of internal volumes available. Even if wide types of residence module can be used (for example, Ley et al.[7] implemented a plastic microcapillary reactor), a stainless steel residence module was selected because we anticipated carrying out reactions under harsh conditions. We commonly use 5, 10, or 18 mL coils as residence loops, which are easily connected to the micromixers with standard HPLC ports. The most important parameter of this unit is the internal diameter.[1,2] In order to maximize the exchange rate between the thermostatted environment and the reaction mixture, a residence loop of internal diameter of 1/16 in. was chosen. At the end of the coil, a HPLC back-pressure valve regulator can be mounted in order to avoid any pressure drop when solvents are heated above their boiling points. The reaction flow is then dripped into a flask which can simply be a container, but it could also be a cold quenching media, a reagent solution or a stirred mixture which precipitates the desired compounds or reaction byproduct.

Scheme 1. **Pyrazole ring closure**



The micromixer and the residence module can be easily thermostatted by a water bath, an oil bath or a chilling unit. The system could also be immersed in a heated sandpit or in a standard HPLC convective heater.

2.2. Chemistry Conducted. *2.2.1. Pyrazole Chemistry.* In order to test and validate our in-house system, we first synthesise the pyrazoles **1** and **2** on a reasonable scale using the exothermic ring closure between an acetoacetate and a hydrazine as a probe reaction. We transposed the in-house bench conditions used for the synthesis of **1** to a continuous mode and successfully produced the two desired pyrazoles **1** and **2** (Scheme 1). No batch synthesis of **2** was performed, and the reaction was directly tested in flow chemistry. The system configuration we used is that described in Figure 2. Although the obtained yield using flow chemistry was lower compared to the yield obtained by the batch procedure (85% versus 98%), the great advantage we saw was the easy handling of our system for scaling up when larger amounts of materials were needed to be produced via an exothermic reaction.

Following our successful first experiences of continuous flow chemistry, we decided to apply the microreactor technology to solve the problems we were facing in the lab concerning more hazardous and/or highly exothermic reactions.

2.2.2. Nitration of 3-Alkyl-pyrazoles: Safety Issues. The first real application concerned the nitration of 3-alkylpyrazoles. These nitro derivatives, after a reduction step, give the corresponding 4-amino-3-alkylpyrazole building blocks, which are no longer commercially available.

The most straightforward synthetic pathway to access the key intermediates proceeds via the nitration of 3-methylpyrazole[3] and 3-ethylpyrazole. The nitration of aromatics, including pyrazoles, is widely described in the literature.[3,5] However, the high potential energy of several nitrated heteroaromatics could lead to scale-up issues.[4a] A practical example of the potential safety issues which could result from pyrazole nitration during scale-up was reported and discussed by Dale et al.[4a] As the continuous flow nitration of organic compounds was already described in the literature,[5] we decided to investigate pyrazole nitration in a continuous flow mode.

Safety consideration: Following the studies of Lothrop and Handrick,[4b] the oxygen balance of the nitropyrazoles **3** and **4** were calculated as −107 and −144 respectively. These values

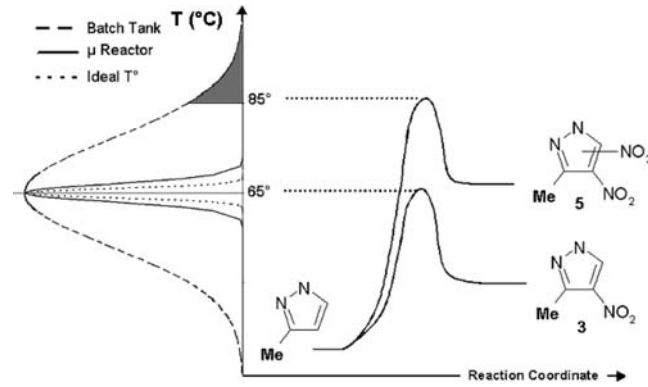


Figure 4. **Temperature population in a batch reactor vs a microreactor and impact on byproduct generation.[2]**

classified 3-methyl-4-nitropyrazole (**3**) and 3-ethyl-4-nitropyrazole (**4**) as compounds which could show detonating properties under severe confinement. Even though the oxygen balance calculation does not consider these nitropyrazoles as explosive materials, the compounds could still be classified as potentially dangerous materials. Before scaling up the chemistry, we synthesised a small amount of 3-methyl-4-nitropyrazole (**3**) following the experimental conditions reported by Smith et al.,[3] using a mixture of nitric and sulfuric acid. Using these conditions, a 12 g batch of 3-methyl-4-nitropyrazole (**3**) was synthesised under temperature-controlled conditions. A DSC study with **3** showed a small endotherm (14 J/g) which was seen from 107 °C that led into a larger endotherm from 126 °C with a peak at 134 °C which was assumed to be the melting point of the sample. The heat of decomposition of 2160 J/g, associated with an exotherm seen from 312 °C is well above the value of 800 J/g used to indicate a potential explosive. A potential explosive is also indicated if the time taken for the pressure to rise from 200 to 400 psi is less than 100 ms. In the case of 3-methyl-4-nitro-1H-pyrazole (**3**), the time taken was 252 ms, i.e. the decomposition is still very fast but not fast enough to indicate an explosive. Although 3-methyl-4-nitropyrazole is not itself an explosive, during the course of the reaction an unstable *N*-nitro derivative and dinitropyrazole derivative (**5**) are also observed if the temperature is not well controlled. Therefore, this reaction could be potentially hazardous to run on a large scale due to the presence of local hot spots which could be generated in a batch tank reactor under mechanical agitation (Figure 4).

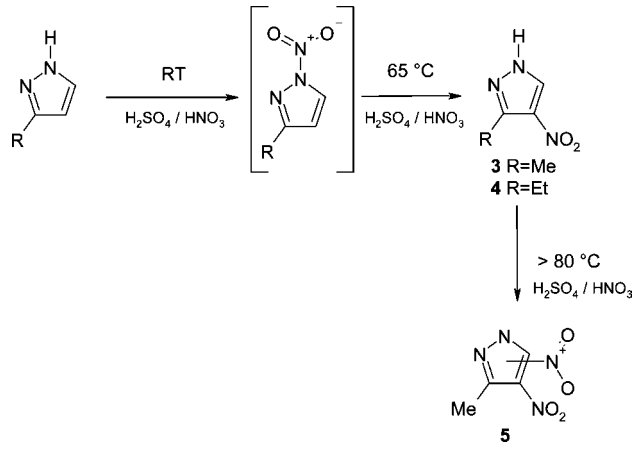
As described in the literature,[3] the *N*-nitropyrazole is formed first (Scheme 2). The reactive intermediate leading to pyrazole nitration is shown in scheme 2. The initial step is the formation of *N*-nitropyrazole.

Conditions involving a cold mixture of acetic acid and nitric acid were not envisaged because the *N*-nitro derivate is generated.[3c,d] A thermal sigmatropic rearrangement then occurs in nitric acid/sulfuric acid mixtures at elevated temperatures, affording the 3-alkyl-4-nitropyrazoles **3** and **4**. Habraken et al.[3] reported that the sigmatropic rearrangement occurred at 140 °C.

Our safety experiments were run in the system described in Figure 2. The micromixer was connected to a 10 mL residence loop, and the flow rates were maintained at 0.4 mL/min. Under these conditions the residence time is 25 min. We did not

(5) (a) Halder, R.; Lawal, A.; Damavarapu, R. *Catal. Today* **2007**, *125*, 74–80. (b) Ferstl, W.; Klahn, T.; Schweikert, W. *Chem. Eng. Technol.* **2007**, *30*, 370–378. (c) Panke, G.; Schwalbe, T.; Stirner, W. *Synthesis* **2003**, *18*, 2827–2830. (d) Antes, J.; Boskovic, D.; Krause, H. *Chem. Eng. Res. Des.* **2003**, *81*, 760–765. (e) Burns, J. R.; Ramshaw, C. *Chem. Eng. Commun.* **2002**, *189*, 1611–1628.

Scheme 2. **Temperature-dependent pyrazole nitration**



observe any nitro group migration at temperatures below 65 °C using the continuous flow process. However, compared with the reported batch-operating temperature of 140 °C,[3] it is possible to achieve high conversions by maintaining the temperature at 65 °C. Not only is this process easier to run practically, but in addition a lower operating temperature also decreases drastically the potential hazards as it avoids the accumulation of the dinitro derivative **5**. This potentially hazardous byproduct **5** was observed during a continuous flow process when the reaction mixture was heated above 65 °C. For safety reasons, the dinitro derivative was not isolated but was clearly identified by LC/MS. The structure of the dinitro derivative was not fully characterized, although under these conditions, the 1,4-dinitro-3-methylpyrazole probably undergoes a sigmatropic rearrangement to give 3-methyl-4,5-dinitropyrazole.[3] As the calculated oxygen balance of −55.8 for 3-methyl-4,5-dinitropyrazole or 3-methyl-1,4-dinitropyrazole classified these compounds as detonating explosives, we decided not to isolate the dinitro entity, but instead, we investigated the effect of the reactor temperature on the formation of **5** (Figure 5). At an operating temperature of 65 °C, only a trace of the dinitro derivative was observed, but above 80 °C, the dinitro byproduct becomes a significant impurity (Figure 5).

This highlighted the safety advantages of the continuous flow microreactor. The reaction mixture at any time before quenching, is under confinement in a very low volume. In the case of a hazardous reaction, the risk of an incident is minimised as the accumulation of potentially dangerous intermediates is avoided.

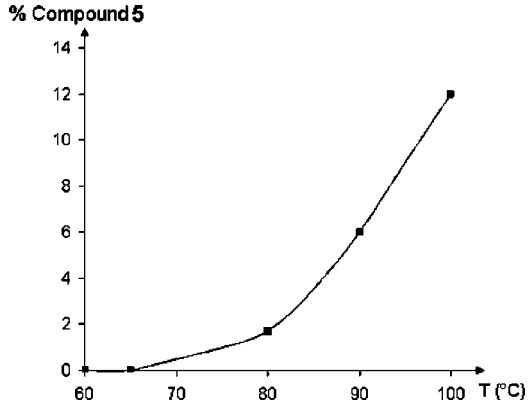


Figure 5. **Percent of dinitropyrazole vs operating temperature.**

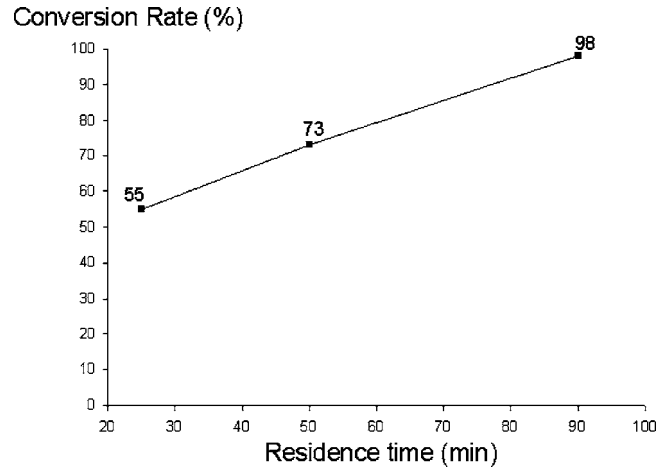


Figure 6. **Conversion rate (%) vs residence time (min) at 65 °C. 3-Methylpyrazole in sulfuric acid (1.2 M) reacting with 13 equiv of concentrated nitric acid.**

Using the method described by Schwalbe et al.[6] which considers the temperature distribution in a batch tank reactor vs a microfluidic reactor, we can graphically transpose the nitration conditions (Figure 4).

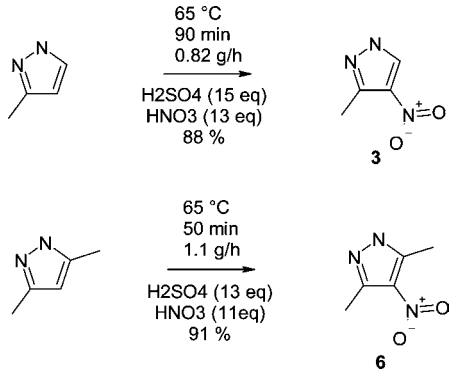
Figure 4 also explains the absence of dinitropyrazole **5** at 65 °C and correlates with measurements showed in Figure 5. In a microreactor, local hotspots are avoided due to the narrow range of temperature which eliminate the formation of the dinitropyrazole **5**.

2.2.3. Nitration of 3-Alkyl-pyrazoles: Continuous Flow Synthesis. The system was run as described in Figure 2 using a IMM SIMM-V2 micromixer connected to two upstream pumps. One pump injects concentrated nitric acid, while the other one injects a solution of the pyrazole dissolved in sulfuric acid. After mixing has occurred in the micromixer, the reaction is confined in a residence loop with the reaction time determined by the flow rate and the residence module internal volume. Optimization of the process can be done by modification of the reaction parameters directly in line. The modification of flow rate impacts both the reaction stoichiometry and/or the residence time. Our investigations started with a 10 mL residence loop and, for safety reasons described above in section 2.2.2, an operating temperature set to 65 °C. The flow rate was adjusted to modify the residence time. The optimal flow range in a IMM SIMM-V2 is 0.04−2.5 L/h, we must admit that pyrazole nitration was not carried out following the provider requirements.

Our first batch was 3-ethyl-4-nitropyrazole (**4**), the system was run using the conditions described in section 2.2.2. In operation, the 10 mL residence loop was immersed in a temperature-controlled bath at 65 °C. The reactor output was collected in a cold stirred vessel containing a quenching solution. At this stage, another advantage of a continuous process can easily be understood: On pilot scale, a reaction mixture neutralization or hydrolysis can be highly exothermic and very

(6) Schwalbe, T.; Autze, V.; Hohmann, M.; Stirner, W. *Org. Process Res. Dev.* **2004**, *8*, 440–454.
(7) Hornung, C.; Mackley, M.; Baxendale, I.; Ley, S. *Org. Process Res. Dev.* **2007**, *11*, 399–405.

Scheme 3. **3-Methyl and 3,5-dimethyl pyrazole nitration**



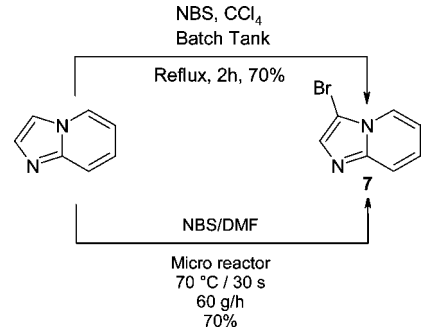
long to perform. At the end of our nitration process, the reaction mixture was quenched in-line by allowing the reaction mixture to drop into the collection vessel which contained a cold aqueous saturated potassium carbonate solution. After workup, the pure desired compound **4** was obtained as a white solid in a reasonable yield of 55%. Even though the throughput was not very high (2.5 g/h), we generated multigram quantities of 3-ethyl-4-nitropyrazole (**4**) under this fully safe production mode. However, due to project priorities, unlike the parent 3-methylpyrazole, the nitration of 3-ethylpyrazole was not optimized further.

Instead we were faced with an increasing demand for the delivery of large amounts of 3-methyl-4-nitropyrazole (**3**), so the nitration process for the synthesis of 3-methylpyrazole was investigated further.

The ratios of equivalents of [pyrazole/sulfuric acid/nitric acid] were modified. No yield improvement was noticed between [1/15/13] and [1/15/26] reagent ratios. Nevertheless, modification of the residence time allowed us to achieve the total conversion of 3-methylpyrazole into 3-methyl-4-nitropyrazole (**3**). Decreasing the flow rate while increasing the residence module internal volume allowed us to measure the impact of the residence time. The conversion rate improvement is shown in Figure 6. More than 100 g of 3-methyl-4-nitropyrazole (**3**) was then produced at a flow rate of 0.2 mL/min using an 18 mL residence coil. The resulting residence time of 90 min led to 98% of conversion of the starting material by reacting a 1.2 M solution of 3-methylpyrazole in sulfuric acid with 13 equiv of concentrated nitric acid. The output was 0.82 g/h, and the yield was 88% after workup. The impact of the concentration of the reaction mixture was not fully investigated. However, compared to the 98% conversion rate obtained with a 1.2 M solution, running the reaction with a 3 M solution of pyrazole in sulfuric acid with 6 equiv of nitric acid gave only 25% yield at the same flow rate of 0.2 mL/min with a residence time of 90 min at 65 °C. Only the starting material and the awaited 3-methyl-4-nitropyrazole (**3**) were identified in the reaction mixture without any trace of impurity or byproduct.

The nitration of 3,5-dimethylpyrazole (Scheme 3) was also investigated. On the basis of the previous example, we directly applied the reaction conditions used for the synthesis of compound **3** to synthesise 3,5-dimethyl-4-nitropyrazole (**6**). No batch trial was tested, and the synthesis of **6** was run directly on our continuous flow system (Figure 2).

Scheme 4



After 19 h, at a 1.1 g/h flow rate, it was possible to synthesise 20 g of pure 3,5-dimethyl-4-nitropyrazole (**6**).

Greater amounts of material could be produced by increasing the number of mixers or running the system for longer periods of time.

The nitration of pyrazoles illustrates several advantages of a continuous flow reactor for the safe handling of hazardous and exothermic reactions.

2.2.4. Additional Examples: Electrophilic Bromination. Halogenation is one of the most convenient ways to functionalise heterocycles. These reactions are widely described in the literature and are frequently performed in organic chemistry. We faced some safety issues concerning the bromination of imidazo[1,2-*a*]pyridine (Scheme 4). On the bench scale, imidazo[1,2-*a*]pyridine is easily brominated by *N*-bromosuccinimide (NBS) in refluxing carbon tetrachloride (CCl_4) for 2 h. (Scheme 4).

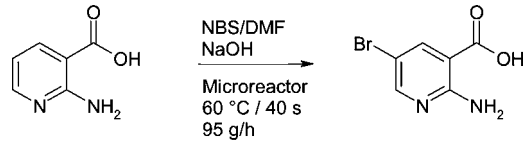
While scaling up the above bromination, a sudden and strong exotherm was noticed during the heating phase. The reaction mixture was very unstable and led to a near-miss incident where the majority of reaction contents were ejected out of the reactor, thus contaminating the fume cupboard environment. In order to safely produce large amounts of this key intermediate and on the basis of our first experiences described in section 2.2.3, we decided to attempt the reaction in a continuous flow mode. We encountered some possible limitations of our system. Both starting materials are insoluble in CCl_4 as is the generated succinimide, which precipitates during the reaction and could lead to particles clotting the system. Clearly to transfer to continuous flow mode, the reaction conditions needed to be modified. Moreover, from a pilot plant or production point of view, carbon tetrachloride has toxic and environmental issues and must be replaced if possible. The NBS/DMF solution complex was selected as an alternative bromination agent.[8−12] The key point is that NBS, the starting material, the reaction product and the succinimide are all souble in DMF, even at high concentrations. On a small scale at the bench, the reaction was complete in 5 min at room temperature using a batch

(8) Paquette, L., Ed. *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1995; Vol. 1, p 773.
(9) Mitchell, R. H.; Lai, Y. H. *J. Org. Chem.* **1979**, *44*, 4733–4735.
(10) Gutthrie, A. E.; Semple, J. E. *J. Org. Chem.* **1982**, *47*, 2369–2376.
(11) Danieli, B.; Lesma, G.; Palmisano, G. *J. Chem. Soc. Perkin Trans. 1* **1987**, 155–161.
(12) Groenen, L.; Verboom, W.; Nijhuis, W. H. *Tetrahedron* **1988**, *44*, 4637–4644.
(13) Baxendale, I.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K. *Chem. Commun.* **2006**, 2566–2568.

Table 2. **Batch bromination vs microfluidic bromination**

	batch	microreactor
solvent	CCl_4	DMF (less toxic)
dilution	high	low
output rate	vessel dependent	60−100 g/h
yield	70%	69%

Scheme 5



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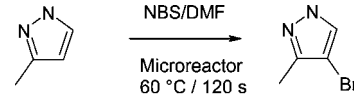
process. At this stage, a large batch synthesis was possible. The continuous mode was tested by injection of the two solutions mixed together in our SIMM-V2 IMM mixer. The two lines were fed, respectively, with imidazo[1,2-*a*] in DMF and NBS in DMF. The transfer to continuous mode was performed by setting, at the same concentrations, the residence time to 5 min. However, in addition to the advantages of microreactors in safety terms, in this case moving to our microreactor system allowed us to improve dramatically the reaction throughput after confinement in the residence loop at higher temperatures. A batch reaction was not tested at higher temperatures, but the reaction temperature effects were directly tested in-line by analysis of the output after temperature and flow-rate modification. The optimal conditions, with a 5 mL residence loop, were determined to be 70 °C at a flow rate of 10 mL/min. We were able to produce pure 3-bromo-imidazo[1,2-*a*]pyridine (**7**) with an output rate of 60 g/h. After work up, the desired product was obtained in a 70% yield with a purity of 99%(w/w) as determined by ^{1}H-NMR. (Scheme 4).

Using this method, several hundreds of grams of brominated product were produced. Compared to the batch process, even in the case of **7**, the yield was not improved, but the practical operating conditions (Table 2) demonstrated clear advantages in terms of process safety, greener chemistry with less waste (higher concentrations, no undesirable CCl_4) and higher rates of reaction outputs. These advantages are allied with a robust process which can be run easily for larger productions by running the system for longer.

Following our first and safe successful bromination, we directly applied these conditions to other scale-up brominations without any initial batch trial. Our second example of bromination was performed on the commercially available 2-amino nicotinic acid (Scheme 5).

The zwitterionic 2-amino nicotinic acid does not react as rapidly as imidazo[1,2-*a*]pyridine described above. The solubility of 2-amino nicotinic acid is also low in DMF, and with the zwitterionic form, obtaining complete conversion was difficult to attain. This issue was overcome by the addition of sodium hydroxide to the zwitterion in DMF to give a clear solution prior to injection into the micromixer. The sodium salt of 2-amino nicotinic acid showed greater solubility and reactivity than the corresponding zwitterionic entity without any solubility issues. Several hundred grams of **8** was produced using these basic conditions at a 95 g/h throughput.

Scheme 6



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An additional application of the bromination conditions was for the synthesis of 3-methyl-4-bromopyrazole (**9**). 3-Methylpyrazole was brominated using the standard continuous flow conditions (Scheme 6) described above without any initial batch trial.

The chlorination of imidazo[1,2-*a*]pyridine was also tested by simple duplication of the bromination conditions. The chlorination of imidazo[1,2-*a*]pyridine was also easily performed by replacing NBS with *N*-chlorosuccinimide (NCS) in DMF. The operating conditions were not optimized further and showed a lower throughput than for the bromination reaction. Using these conditions, the pure chloro derivative was obtained with a conversion rate of just 40%. In this case, the flow rates would need to be reduced and/or the residence time increased in order to reach reaction completion.

The advantage of a continuous flow bromination is evident. Compared to the batch procedure, even if yields are not improved, the use of the continuous mode gave access to large amounts of material while controlling the exotherm by the injection of the correct stoichiometry at any time in the process.

3. Conclusion

We have developed a versatile and inexpensive continuous flow microreactor unit capable of producing large quantities of material with minimal development effort. In this report, we have demonstrated its use for exothermic electrophilic substitution reactions, and in the near future, we hope to apply more complicated chemistry to this simple continuous flow reactor.

Experimental Section

The described system is equipped with FRX pumps provided by Syrris Ltd. (www.syrris.com). The micromixer from the Institut für Mikrotechnik in Mainz (www.imm-mainz.de) is an interdigital micromixer SIMM-V2 type. The residence loop, directly connected to the micromixer outlet, is a coil-shaped stainless steel tube with 1/16 in. as internal diameter. The operating flow rates are determined by the reaction conversion rate and directly relate to the residence module internal volume.

Flash chromatography was carried out on Merck Kieselgel 50 (art. 9385). NMR spectra were obtained on a Bruker Avance 500 (500 MHz) spectrometer. Chemical shifts are expressed in δ (ppm) units, and peak multiplicities are expressed as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; bs, broad singlet; m, multiplet. Mass spectrometry was carried out on an analytical Waters LC/MS system with positive and negative electrospray ion data collected automatically. NMR and mass spectra were run on isolated products and were consistent with the proposed structures and compounds described in the literature.

Pyrazoles Ring Closure. *Preparation of 3-Methyl-1-phenyl-1H-pyrazol-5-ol (1). Batch Procedure.* To a stirred solution of phenylhydrazine (91 mL, 925 mmol) in acetic acid (250 mL)

at room temperature was added dropwise over a 1 h period ethyl acetoacetate (124 mL, 971 mmol). During the addition, the reaction mixture was stirred while the internal temperature increased to 70 °C. After complete addition, the reaction mixture was stirred for an additional hour and concentrated. The resulting oil was diluted in petroleum ether (500 mL) until 3-methyl-1-phenyl-1H-pyrazol-5-ol (158 g, 98%) precipitated as a pale-yellow solid.

Continuous Flow Procedure. Reagent solution A: a solution of phenylhydrazine (50 mL, 508 mmol) in acetic acid (220 mL). Reagent solution B: a solution of ethylacetoacetate (68 mL, 534 mmol) in acetic acid (200 mL). The solutions A and B were filtered through a 0.45 μm filtration disk prior to the experiment. The reagent solutions A and B were pumped at 1 mL/min for each line into an IMM SIMM-V2 micromixer followed by a 1/16 in. diameter residence loop of 10 mL immersed in a 115 °C oil bath, corresponding to a residence time of 5 min. The output rate was 17 g/h. Once the reagent injection had finished, the acetic acid was evaporated, and the resulting oil was triturated with petroleum ether (200 mL) until 3-methyl-1-phenyl-1H-pyrazol-5-ol (75 g, 85%) precipitated as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.20 (s, 3H), 3.43 (s, 2H), 7.18 (t, 1H, J = 7.4 Hz), 7.4 (dd, 2H, $J1$ = 7.4 Hz, $J2$ = 8.0 Hz), 7.86 (d, 2H, J =8.0 Hz).

Preparation of 3-Methyl-1-(pyridin-2-yl)-1H-pyrazol-5(4H)-one (2). Reagent solution A: a solution of 2-hydrazinopyridine dihydrochloride (20 g, 110 mmol) in acetic acid (85 mL) and triethylamine (31 mL, 222 mmol). Reagent solution B: a solution of ethylacetoacetate (14 mL, 110 mmol) in acetic acid (120 mL). The solutions A and B were filtered through a 0.45 μm filtration disk prior the experiment. The reagent solutions A and B were pumped at 1.5 mL/min for each line into an IMM SIMM-V2 micromixer followed by a 1/16 in. diameter residence loop of 5 mL immersed in a 100 °C oil bath, corresponding to a residence time of 1.7 min. The output rate was 4.3 g/h. Once reagent injection was complete, the reaction mixture was concentrated, and the resulting oil was diluted with water. The pH was adjusted to 7.0 with solid sodium bicarbonate, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried on magnesium sulfate, filtered and concentrated to afford an oil which was triturated in 1:1 mixture petroleum ether/diethylether until 3-methyl-1-(pyridin-2-yl)-1H-pyrazol-5(4H)-one (6.5 g, 37.1 mmol, 34%) precipitated as a brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.26 (s, 3H), 5.43 (s, 1H), 7.12 (dd, 1H, $J1$ = 5.0 Hz, $J2$ = 8.5 Hz), 7.83−7.89 (m, 2H), 8.25 (d, 1H, J =5.0 Hz).

Pyrazole Nitration. *Preparation of 3-Methyl-4-nitro-1H-pyrazole (3).* Reagent solution A: a solution of 3-methylpyrazole (25 g, 305 mmol) in sulfuric acid (250 mL, 4700 mmol). Reagent solution B: concentrated nitric acid (69% HNO_3, 250 mL, 3968 mmol). The reagent solutions A and B were pumped respectively at 0.1 and 0.1 mL/min into an IMM SIMM-V2 micromixer followed by a 1/16 in. diameter residence loop of 18 mL immersed in a 65 °C water bath, corresponding to a residence time of 90 min. The reaction was immediately quenched by continuous pouring into a saturated aqueous solution of potassium carbonate (1 L). Once the reagent injection was complete, the pH was ajusted to 1.0 with an aqueous solution of sodium hydroxide and extracted with ethyl acetate (2 × 500 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated to afford 34 g (88%) of 3-methyl-4-nitro-1H-pyrazole as a white solid with an output rate of 0.82 g/h. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.58 (s, 3H), 7.03 (bs, 1H), 8.21 (s, 1H).

Preparation of 3-Ethyl-4-nitro-1H-pyrazole (4). Reagent solution A: a solution of 3-ethyl-1H-pyrazole (1.6 g, 16.64 mmol) in sulfuric acid (30 mL, 562.81 mmol). Reagent solution B: concentrated nitric acid (69% HNO_3, 35 mL, 555.44 mmol). The reagent solutions A and B were pumped at 0.2 mL/min for each line into an IMM SIMM-V2 micromixer followed by a 1/16 in. diameter residence loop of 10 mL immersed in a 65 °C water bath, corresponding to a residence time of 25 min and an output rate of 0.5 g/h. The reaction was immediately quenched by continuous pouring into a saturated aqueous solution of potassium carbonate (100 mL), and the pH was ajusted to 1.8. The aqueous layer was extracted with DCM (2 × 100 mL). The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated to afford 1.3 g (55%) of 3-ethyl-4-nitro-1H-pyrazole as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (t, 3H), 3.13 (q, 2H), 8.21 (s, 1H).

Preparation of 3,5-Dimethyl-4-nitro-1H-pyrazole (6). Reagent solution A: a solution of 3,5-dimethylpyrazole (15 g, 156 mmol) in sulfuric acid (112 mL, 2101 mmol). Reagent solution B: concentrated nitric acid (69% HNO_3, 112 mL, 1778 mmol). The reagent solutions A and B were pumped respectively at 0.1 and 0.1 mL/min into an IMM SIMM-V2 micromixer followed by a 1/16 in. diameter residence loop of 18 mL immersed in a 65 °C water bath, corresponding to a residence time of 90 min. The reaction was immediately quenched by continuous pouring into a saturated aqueous solution of potassium carbonate (1 L). Once reagent injection was complete, the pH was ajusted to 5.0 with a saturated aqueous solution of sodium hydrogencarbonate and extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated to afford 20 g (91%) of pure 3,5-dimethyl-4-nitro-1H-pyrazole as a pale-yellow crystalline solid. ^{1}H NMR (500 MHz, DMSO): δ 2.45 (s, 6H), 11.5 (bs, 1H).

Heterocyle Bromination. *Preparation of 3-Bromoimidazo(1,2)-pyridine (7). Batch Procedure.* To a stirred solution of imidazo(1,2)-pyridine (500 μL, 4.9 mmol) in DMF (5 mL) was added *N*-bromosuccinimide (878 mg, 4.9 mmol). The resulting solution was stirred at room temperature for 5 min. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated to afford 730 mg (73%) of 3-bromoimidazo(1,2)-pyridine (7) as a white solid.

Continuous Flow Procedure. Reagent solution A: imidazo[1,2-*a*]pyridine (75 mL, 740 mmol) in DMF (425 mL). Reagent solution B: NBS (132 g, 740 mmol) in DMF (368 mL). The solutions A and B were filtered through a 0.45 μm filtration disk prior the experiment. The reagent solutions A and B were pumped at 5 mL/min for each line into an IMM SIMM-

V2 micromixer followed by a 1/16 in. diameter residence loop of 5 mL immersed in a 70 °C water bath, corresponding to a residence time of 30 s. The collected solution was diluted with water (2 L). The aqueous layer was extracted with diethylether (3 × 1 L). The combined organic layers were washed with water (3 × 2 L), brine, dried on MgSO4, filtered and concentrated to afford the crystalline 3-bromoimidazo[1,2-*a*]pyridine (100 g, 69%) with an output rate of 60 g/h. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (ddd, 1H, *J*1 = 1.0 Hz, *J*2 = 6.8 Hz, *J*3 = 6.6 Hz), 7.25 (ddd, 1H, *J*1 = 1.0 Hz, *J*2 = 6.6 Hz, *J*3 = 9.0 Hz) 7.62 (ddd, 1H, *J*1 = 9.0 Hz, *J*2 = 1.0 Hz, *J*3 = 1.0 Hz), 7.63 (s, 1H), 8.13 (ddd, 1H, *J*1 = 6.8 Hz, *J2* = 1.0 Hz, *J3* = 1.0 Hz).

Preparation of 2-Amino-5-bromonicotinic Acid (8). Reagent solution A: 2-amino nicotinic acid (250 g, 1810 mmol) in DMF (650 mL) and 6 N sodium hydroxide (302 mL, 1810 mmol). Reagent solution B: NBS (322 g, 1810 mmol) in DMF (850 mL). The solutions A and B were filtered through a 0.45 μm filtration disk prior the experiment. The reagent solutions A and B were pumped at 7 mL/min for each line into an IMM SIMM-V2 micromixer followed by a 1/16 in. diameter residence loop of 10 mL immersed in a 60 °C water bath, corresponding to a residence time of 40 s. The collected solution was diluted with water (5 L) and acetic acid (207 mL, 3620 mmol). The white precipitate was collected by filtration and then stirred with water (2 L) at 50 °C for 3 h. The white solid was collected by filtration, washed with water and dried under vacuum to afford 2-amino-5-bromonicotinic acid (270 g, 69%) with an output rate of 95 g/h. ^{1}H NMR (500 MHz, DMSO): δ 8.09 (d, 1H), 8.25 (d, 1H), 7.35 (s, 2H).

Preparation of 4-Bromo-3-methylpyrazole (9). Reagent solution A: 3-methyl-1H-pyrazole (24.51 mL, 304.49 mmol) in DMF (150 mL). Reagent solution B: NBS (54.2 g, 304.49 mmol) in DMF (125 mL). The solutions A and B were filtered through a 0.45 μm filtration disk prior the experiment. The reagent solutions A and B were pumped at 2.5 mL/min for each line into an IMM SIMM-V2 micromixer followed by a 1/16 in. diameter residence loop of 10 mL immersed in a 60 °C water bath, corresponding to a residence time of 2 min. The collected solution was diluted with water (500 mL). The aqueous layer was extracted with diethylether (3 × 500 mL). The combined organic layers were washed with brine, dried on $MgSO_4$, filtered and concentrated to afford an oil which solidified as an impure material. The crude material was purified on silica, eluting with 25% of AcOEt in CH_2Cl_2 to afford 4-bromo-3-methyl-1H-pyrazole (24 g, 49%) as a white solid with an output rate of 21 g/h. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34 (s, 3H), 7.51 (s, 1H).

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