A two-step continuous flow synthesis of 4-nitropyridine

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4-Nitropyridine, a key intermediate in medicinal products, was successfully prepared from pyridine *N*-oxide in a two-step -approach. Pyridine *N*-oxide was nitrated with HNO_3 and H_2SO_4 to give 4-nitropyridine *N*-oxide, followed by reaction with PCl_3 to give the final product. The continuous flow methodology was used to minimise accumulation of the highly energetic and potentially explosive nitration product to enable the safe scale-up of 4-nitropyridine with no 2-nitropyridine by-product. By employing continuous extraction in the nitration step and applying the optimised conditions, a throughput of 0.716 kg 4-nitropyridine product per day from pyridine *N*-oxide with 83% yield and high selectivity in a continuous flow system was achieved.

Keywords: 4-nitropyridine, continuous flow system, nitration reactions, continuous extraction, microreaction technology

4-Nitropyridine can be an excellent starting material for the preparation of pyridine derivatives, which are important synthetic intermediates for new pesticides and medicines.[1,2] The pathway to 4-nitropyridine via the pyridine *N*-oxide involves two steps,[3, 4] including a nitration step and a reduction step. The nitration reaction is a key step and with the use of HNO_3–H_2SO_4 mixed acid as the nitration reagent is usually exothermic and at higher temperatures, which can result in polynitration.[5, 6] In addition, the scale-up of the synthesis of nitration products in batch can lead to the formation of hot spots and, as a further result, to the formation of undesired by-products and low productivity due to inefficient mixing and poor heat transfer.[7]

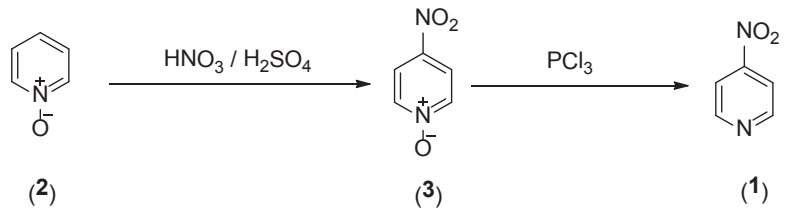
Employing microreaction technology is one way to increase the process safety and efficiency of fast highly exothermic reactions.[8-17] In recent years, microreaction technology has emerged as a useful approach for the synthesis of fine chemicals and key pharmaceutical intermediates where either the poor selectivity of the product is inevitable in batch or there are situations where the reactions are highly exothermic.[11-13] Compared with reactions in batch mode, one major advantage of the microreactor is the submillimetre dimensions of flow structures, which permits chemical reactions to proceed with higher quality, on account of highly efficient mixing and excellent heat absorption. As a result, reaction temperature control can be accurate and thus avoid hot spots often the cause of the formation of by-products, and with respect to traditional batch procedures, hazardous reactions can be handled more safely. Some of the important initial studies include the following: (1) Ducry and Roberge[5] have reported the nitration of phenol in continuous flow with a glass reactor (channel width <0.5 mm and 2.0 mL internal volume). The nitration of phenol in a microreactor yields a better fraction of the mononitration product of phenol and, as a further consequence, a reduction in the formation of polymerised products. (2) The nitration of toluene using HNO_3–H_2SO_4 mixed acid (T=65 °C, t=15 min, conversion of more than 98%), and with $Ac_2O/H_2SO_4/HNO_3$ as the nitrating agent (T=300 °C, t=70 min, conversion of 100%) in the CYTOS microreaction system was reported by Gerhard *et al*.[14] [NOTE: There may be significant additional safety implications when AC_2O and HNO_3 are involved together in a nitrating agent.[15-17]](3) The nitration of 3-alkylpyrazoles on 100 g scale with a productivity of 0.82 g h^{-1} was developed by Pelleter and Renaud[18] as a continuous process. (4) Kulkarni *et al*.[19,20] have reported the nitration of benzaldehyde and salicylic acid in continuous flow in equipment involving syringe pumps and self-made apparatus.

We now describe how all of these challenges have been overcome by careful selection of the reaction conditions, we report an efficient two-step flow synthesis of 4-nitropyridine (**1**). The investigated method includes two reaction steps: at first, pyridine *N*-oxide (**2**) was converted into 4-nitropyridine *N*-oxide (**3**) by heating it with a mixture of fuming nitric acid and conc. sulfuric acid. Secondly, the reaction of 4-nitropyridine *N*-oxide (**3**) with PCl_3 led to the formation of 4-nitropyridine (**1**) (Scheme 1).

Experimental

Batch model: The experiments were carried out not only in batch mode but also in continuous mode. To confirm our approach, the initial experiments in batch mode were mainly conducted based on the literature [3, 4] which provides us with information about the reaction rate (which was monitored by HPLC), especially an opportunity to check whether the reaction is homogeneous.

Continuous flow procedure: An overview of the two-step continuous flow process is depicted in Scheme 2. The reaction takes place by pumping pyridine *N*-oxide (**2**, 20 g, 0.212 mol) dissolved in conc.H_2SO_4 (200 mL) through one HPLC pump (TBp 5010T, Shanghai Tanto Biotech Co., Ltd. flow rate: 0.23 mL min^{-1}), and the fuming HNO_3 (40 mL, 0.96 mol) in H_2SO_4(200 mL) through a



Scheme 1 Reaction sequence for the preparation of 4-nitropyridine.

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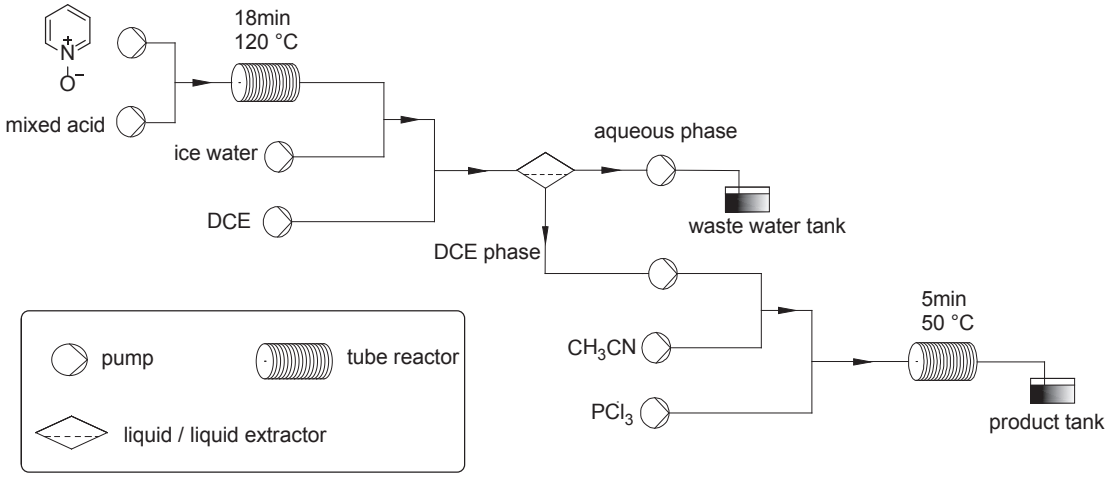

Scheme 2 Overview of the two-step continuous flow synthesis of 4-nitropyridine (**1**).

second pump(flow rate: 0.6 mL min^{-1}). The acids were premixed with great care at low temperatures (–10 to –5 °C), the conc.H_2SO_4 being added dropwise into fuming HNO_3 with vigorous stirring. In the first 15 mL polytetrafluoroethylene (PTFE, i.d.=1.0 mm) tube coil the reaction mixture is heated to 120 °C with a residence time of 18 min. The outgoing stream is mixed with ice water (flow rate: 1.25 mL min^{-1}) immediately. This rapid dilution of the concentrated acidic solution is a good safety feature. Then the mixture is pumped into a tailor-made continuous flow liquid/liquid extractor[21] to eliminate 4-nitropyridine *N*-oxide (**3**) from the previous step. At the same time, 1,2-dichloroethane (flow rate: 2.29 mL min^{-1}) is pumped into the extractor using another pump. After extraction, the 1,2-dichloroethane (DCE) phase containing 4-nitropyridine *N*-oxide (**3**) is injected through a pump to a second 37 mL tube coil PTFE(I.D.=2.1 mm). Simultaneously, CH_3CN (flow rate: 2.29 mL min^{-1}) and the solution of PCl_3 (36.73 g, 0.267 mol, flow rate: 2.82 mL min^{-1}) in 2454 mL CH_3CN are pumped into the PTFE tube using two separate pumps. The reduction reaction takes place in this second coil at 50 °C and a residence time of 5 min. The output flow of production from the coil continued directly into the product tank. After cooling, and then adding water, the reaction mixture was made alkaline by addition of Na_2CO_3 and was extracted with DCE. The DCE solution was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The two-step total yield of 4-nitropyridine was 21.7 g (83%); m.p. 49–50 °C (lit.[3] 50 °C). ^{1}H NMR (400 Hz, $CDCl_3$): δ 8.92 (dd, J_1 = 4.7Hz, J_2 = 1.5 Hz, 2H), 8.01 (dd, J_1 = 4.7 Hz, J_2 = 1.6 Hz, 2H).

In the nitration step, the samples were withdrawn at different time intervals and analysed using HPLC (Agilent model 1260, equipped with a Zorbox Bonus-RP 4.6 mm×150 mm column). The mobile phase used for analysis consisted of 66% H_2O and 34% acetonitrile. The HPLC analysis was carried out at the wavelength of 235 nm; the column temperature was maintained at 15 °C and the flow rate was set at 0.5 mL min^{-1}. In the reduction step, the analysis of the samples was done by HPLC on an Agilent-1260 system with a Eclipse XDB-C18 4.6 mm×250 mm column (Agilent). The mobile phase used for analysis consisted of 70% H_2O and 30% acetonitrile. The HPLC analysis was carried out at the wavelength of 235 nm, the column temperature was maintained at 20 °C and the flow rate was set at 1.0 mL min^{-1} ^{1}HNMR spectra were recorded on a Bruker AM-400 spectrometer with TMS as an internal standard and $CDCl_3$ as solvent.

Melting points were determined using a XT5A apparatus and were uncorrected.

Results and discussion

In order to study the preparation process of 4-nitropyridine in the microreactor, a series of experiments were performed. Figures 1, 2 and 3 show the yield of 4-nitropyridine *N*-oxide with different operating conditions and the conversions into 4-nitropyridine are depicted in Figs 4 to 6.

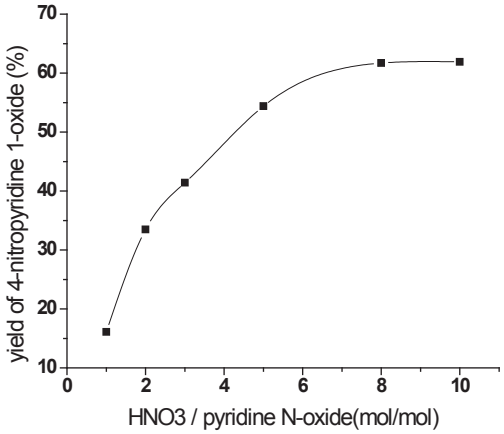

Fig. 1 Effect of HNO_3/pyridine *N*-oxide molar ratio on the yield of 4-nitropyridine *N*-oxide. The reaction was carried out at 120 °C, with a residence time of 6.6 min.

Effect of HNO_3/pyridine N-*oxide molar ratio on the yield of 4-nitropyridine* N-*oxide*

Figure 1 shows the yield of 4-nitropyridine *N*-oxide on the basis of HNO_3/pyridine *N*-oxide molar ratio from 1:1 to 10:1 with a residence time of 6.6 min at 120 °C. It can be seen that the yield of 4-nitropyridine *N*-oxide increased rapidly when the molar ratio of HNO_3/pyridine *N*-oxide was increased from 1:1 to 8:1 as the amount for NO_2^+ present was enhanced. Further increase of the HNO_3/pyridine *N*-oxide molar ratio to 10:1 resulted in almost no change of 4-nitropyridine *N*-oxide yield. For the synthesis of 4-nitropyridine *N*-oxide, the yield was close to 62% when the HNO_3/pyridine *N*-oxide molar ratio changed from 1:1 to 10:1. Therefore, the appropriate HNO_3/pyridine *N*-oxide molar ratio was 8:1 for 4-nitropyridine *N*-oxide under such reaction conditions.

4-Nitropyridine N-oxide (**3**): M.p.159–160.5 °C (lit.[3] 159 °C). ^{1}H NMR (400 Hz, $CDCl_3$): δ 8.23 (d, *J* = 7.6 Hz, 2H), 8.13 (d, *J* = 7.6 Hz, 2H).

Effect of reaction time on the yield of 4-nitropyridine N-*oxide*

When the nitration reaction was conducted at 120 °C with an HNO_3/pyridine *N*-oxide molar ratio of 8:1, the residence time was changed from 6.6 min to 28 min. The yield of 4-nitropyridine *N*-oxide increased with the increase of the residence time (Fig.2). For the synthesis of 4-nitropyridine *N*-oxide, the yield increased sharply when the residence time increased from 6.6 to 18 min, and the yield had an increase of

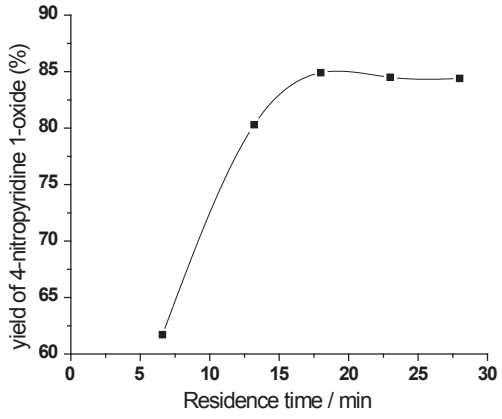

Fig. 2 Effect of reaction time on the yield of 4-nitropyridine *N*-oxide. The reaction was carried out at 120 °C, with HNO_3/pyridine *N*-oxide molar rate of 8:1.

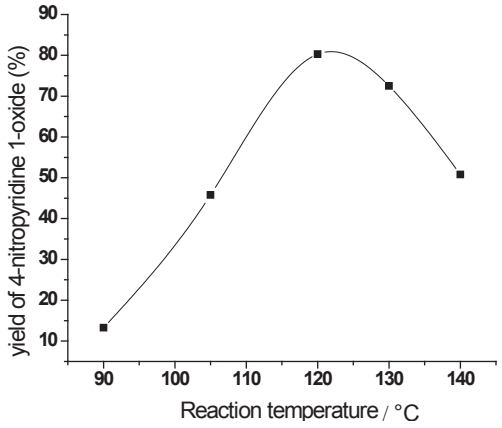

Fig. 3 Effect of reaction temperature on the yield of 4-nitropyridine *N*-oxide. The reaction was carried out with a residence time of 13.2 min and a molar ratio of HNO_3/pyridine *N*-oxide of 8:1.

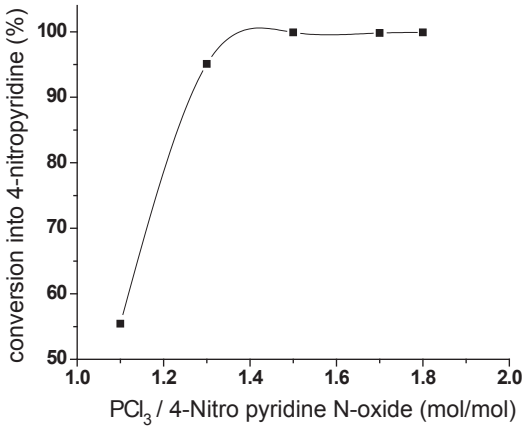

Fig. 4 Effect of PCl_3/4-nitropyridine *N*-oxide molar ratio on conversion into 4-nitropyridine. The reaction was carried out at 50 °C with a residence time of 5 min.

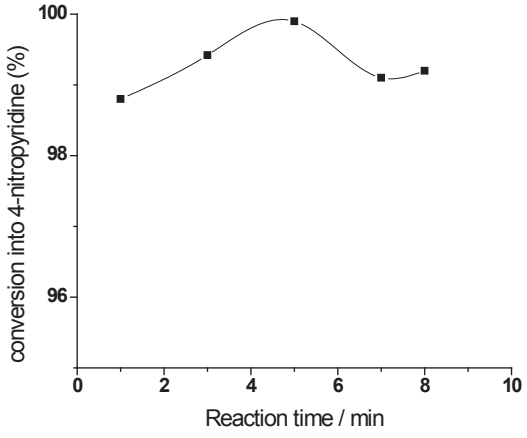

Fig. 5 Effect of reaction time on the conversion into 4-nitropyridine. The reaction was carried out at 50 °C with a PCl_3/4-nitropyridine *N*-oxide molar rate of 1.5:1.

23%. Further increase of the residence time to 28 min led to the slight increase or decrease of 4-nitropyridine *N*-oxide. The reasonable residence time was 18 min and at such reaction time a high yield of 85% of 4-nitropyridine *N*-oxide could be obtained. However, for the same reaction performed in the conventional batch reactor, it took at least 210 min with the yield of 72%,[19] indicating that the reaction time was much shorter under the continuous process.

Effect of reaction temperature on the yield of 4-nitropyridine N-oxide

In this part, the microreactor temperatures were varied from 90 °C to 140 °C, with the molar ratio of HNO_3/pyridine *N*-oxide of 8:1 and at a residence time of 13.2 min as shown in Fig. 3. It was observed that the yield of 4-nitropyridine *N*-oxide increased with the reaction temperature from 90 to 120 °C resulting from the increase of the generation of the nitronium ion. However, the yield of 4-nitropyridine *N*-oxide decreased when the reaction temperature increased to 140 °C and a certain amount of by-product (2-nitropyridine *N*-oxide) was found by HPLC.

2-Nitropyridine N-*oxide***.** M.p. 85–86°C (lit.[22] 85–86 °C). ^{1}H NMR (400 Hz, $CDCl_3$): δ 8.29 (dd, J_1 = 6.4 Hz, J_2 = 0.8 Hz, 1H), 7.69 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.48 (m, 1H), 7.41 (td, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H).

Effect of PCl_3/4-nitropyridine N-oxide molar ratio on the conversion into 4-nitropyridine

The effect of PCl_3/4-nitropyridine *N*-oxide molar ratio on the conversion into 4-nitropyridine from 1.1:1 to 1.8:1 with a residence time of 5 min at 50 °C was shown in Fig. 4. It could be seen that the conversion of 4-nitropyridine increased sharply when the molar ratio of PCl_3/4-nitropyridine *N*-oxide increased from 1:1.1 to 1:1.5. Further increased the PCl_3/4-nitropyridine *N*-oxide molar ratio resulted in almost keeping constant and no other products were observed with high PCl_3/4-nitropyridine *N*-oxide molar ratio.

Effect of reaction time on the conversion into 4-nitropyridine

Figure 5 shows the effect of reaction time on the conversion into 4-nitropyridine at a temperature of 50 °C, with PCl_3/4-nitropyridine *N*-oxide molar ratio of 1.5:1 when the reaction times were changed from 1 to 8 min. With the increase of the reaction time, the conversion into 4-nitropyridine is in slight increase or decrease and the yields were not lower than 99%. The above results indicated that the reaction time had little effect on the conversion into 4-nitropyridine. The reasons might be no "backing-mixing" in the microreactor and the reduction reaction, which took place under the continuous process, could be regarded as an irreversible reaction.

Effect of reaction temperature on the conversion into 4-nitropyridine

The reduction reaction was conducted at a residence time of 5 min with a PCl_3/4-nitropyridine *N*-oxide molar ratio of 1.5:1 and the reaction temperature was changed from 25 °C to 80 °C (Fig. 6). As shown in Fig.6, the conversion into 4-nitropyridine rapidly increased from 83 to 100% when the reaction temperature increased from 25 to 50 °C. Further increase of

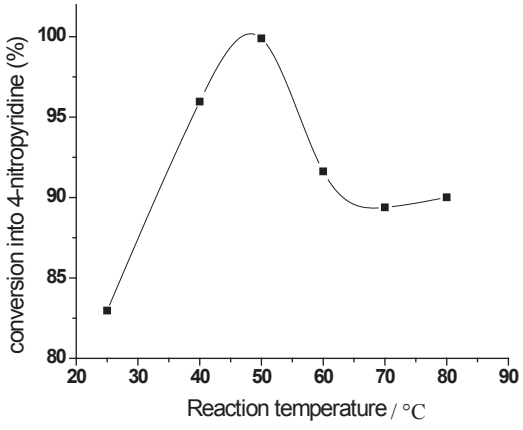

Fig. 6 Effect of reaction temperature on conversion into 4-nitropyridine. The reaction was carried out with a residence time of 5 min and a molar ratio of PCl_3/4-nitropyridine *N*-oxide of 1.5:1.

the reaction temperature to 80 °C resulted in a slight decrease in conversion and some uncertain impurities were detected by HPLC.

Conclusions

In general, the two-step continuous flow synthesis of 4-nitropyridine using commercially available equipment has been demonstrated and an additional advantage was that undesired by-products are almost avoided under continuous flow as a result of the high mixing efficiency and the accurately defined reaction times. The overall yield of the continuous process is 83%, which is much more than the 57% overall batch yield originally described in the literature.[3,4] With the exception of the increased overall yield and the environmental and safety advantages inherent to the microreaction technology, any off-line purification of intermediates was not required in our method.

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