Organic Process Research & Development

Technical Note

pubs.acs.org/OPRD

A High-Output, Continuous Selective and Heterogeneous Nitration of *p*-Difluorobenzene

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ABSTRACT: A practical continuous nitration process for 2,5-difluoronitrobenzene via nitration of *p*-difluorobenzene with fuming nitric acid in 98% yield has been developed. The excellent yield of this liquid/liquid biphasic reaction resulted from the advantages of a continuous flow system. The 2.0 equiv sulfuric acid could be used three times directly with product yields in the range of 96−98%, and further recycling of waste acid could be partly achieved by adjusting the concentration of sulfuric acid. Reaction time could be brought down to 2 min by increasing the reaction temperature and thereby taking advantage of superior mass and heat transfer of this continuous flow system.

INTRODUCTION

Nitroaromatics are widely used in various fields and are produced in quantities from bulk to kilogram scale.[1] Electrophilic nitration is the major synthetic route to nitroaromatics; however, the reaction is often difficult to control due to the strong exothermic nature. It presents serious hazardous particularly in large-scale production. In addition, inefficient heat transfer in large reaction vessel leads to more undesired side reactions such as further nitration, sulfonation, nucleophilic substitution, oxidation, and other reactions (Scheme 1).[2]

Over the last 10 years, rapid development of continuous flow technology has opened new horizons both in academia and industry. In comparison to the batch reactor, the continuous flow reactor offers several advantages such as better mass and heat transfer, fewer transport limitations, more precise control of reaction variables, safer operation, and easier scaling-up.[3] Nitration of aromatics is particularly advantageous when carried out in continuous flow reactors. The reactor dimensions are smaller, reactant inventory at any given time is less, diffusion is much faster, and surface-to-volume ratio is higher, which significantly reduces the possibility of side-product formation, and significantly improves the yield of the main product.

Several reports of nitration in continuous microreactors on lab scale are in the literature. For example, (a) Panke et al.[4] used a stainless steel microreactor for the high energetic nitration reactions. (b) Burns and Ramshaw[5] reported the nitration of benzene and toluene using mixed acids in a microreactor. (c) Pelletier and Renaud[6] detailed the nitration of 3-alkylpyrazoles with an inexpensive continuous flow microreactor. (d) Kulkarni et al.[7] described the nitration of benzaldehyde and salicylic acid with continuous flow stainless steel microreactors. (e) Ducry et al.[8] reported the nitration of phenol using a glass microchannel reactor. There are also many patents describing industrial applications of these continuous flow nitration reactors. However, detailed reports in the open literature describing actual implementation of nitration on large-scale production with continuous flow reactors are scarce. Notable exceptions are as follow: Braune and coworkers[9] reported an industrial nitration process with high efficiency and selectivity. Gage et al.[10] scaled up a continuous nitration of a pyridine derivative to 100-kg scale successfully; however, no obvious improvement of yield was achieved, and no mention of the recycling of waste acid was made.

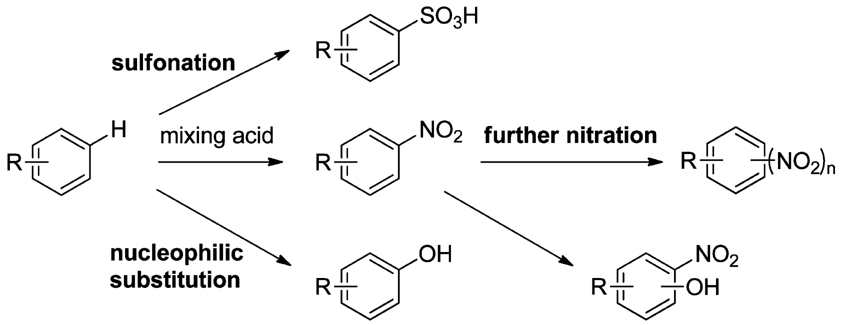
We have previously reported expeditious and kilogram-scale continuous flow synthesis of 7-ethyltryptophol and *o*-difluorobenzene both in high yield and purity.[11] Herein, we have developed a facile and practical continuous flow nitration reactor for nitroaromatics. *p*-Difluorobenzene (**1**) was chosen for this study, and its mononitration product (**2**) is useful in the pharmaceutical and liquid crystal industry.[12] Compound **2** can be prepared in conventional batch reactors by adding a mixed concentrated sulfuric acid and fuming nitric acid to **1** in 80% yield, the side products being the dinitro compound **3**, phenols **4**, and **5** (Scheme 2). This motivated us to explore a more selective and continuous nitration system under safer conditions.[13]

RESULTS AND DISCUSSIONS

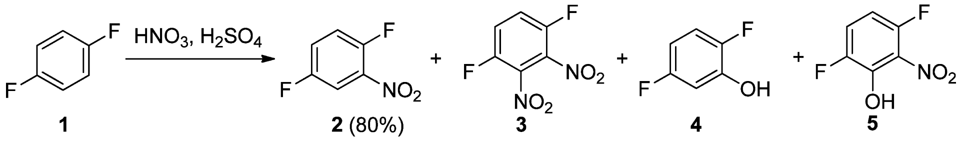
Process A. The initial process designed was the direct conversion of commonly used batch technology to a heterogeneous continuous flow system. The equipment consists of two peristaltic pumps (P_1, P_2, Baoding Longer, China) loaded with tubing connected by a T-joint to a mixer which was connected to the reacting tube (SS316, 4 mm i.d., 6 mm o.d.).[14] The reacting tube was immersed in a thermostat-controlled water bath (Scheme 3). Nitrating acid mixture (2.0 equiv concentrated sulfuric acid and 1.1 equiv fuming nitric acid) and *p*-difluorobenzene were pumped into the reactor at room temperature by P_1 and P_2, respectively. After a residence time in the reacting tube, the stream flowed through the outlet. The reaction was quenched by ice water (~20 mol mol^{-1} reactant) in the collection vessel. The mixture was extracted with EtOAc. The combined organic extracts were neutralized

Received: December 5, 2012
Published: February 11, 2013

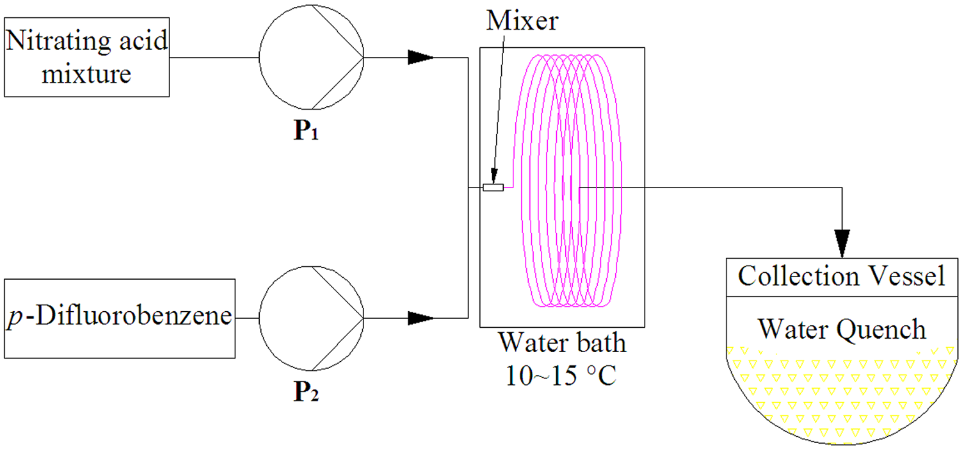
Scheme 1. Main side reactions of nitration reaction



Scheme 2. Nitration of *p*-difluorobenzene 1 in batch affords the mononitro 2 as the main product, with some dinitro 3 and difluorophenols 4 and 5 as side products



Scheme 3. Schematic of process A; coil is SS316 coil with 4 mm i.d. and 6 mm o.d.



with saturated sodium bicarbonate.[15] Mononitro product **2** was obtained after solvent removal and was analyzed by GC.

Different residence times were investigated by adjusting tube lengths while maintaining the same flow rate. The results (shown in Figure 1) indicated that the isolated yields of **2** and **3** increased with prolonged residence times. However, very little **4** or **5** was found, which supposedly resulted from the superior heat transfer of the continuous flow reactor. However, the dinitro **3** was still generated at about 5% yield, even the yield of **2** was only 71%, and nearly 24% of **1** remained at 8 min. The selectivity was not satisfactory. A possible explanation is that the biphasic stream gradually separates again downstream from the mixer, resulting in increasingly inefficient mass transfer and low selectivity. On the basis of the results of 1.1 equiv of nitric acid, we thought that the reduction of nitric acid could restrain further nitration. However, whether the amount of nitric acid was increased (1.3 equiv) or decreased (1.04 equiv) had hardly any effect on the reaction selectivity. This fact confirms the literature's argument that the biphasic nitration is a mass transfer-controlled reaction.[16] The inefficient mass transfer rate can account for the low selectivity. In addition, quenching the reaction by water resulted in a large amount of diluted waste acid which was difficult to handle.

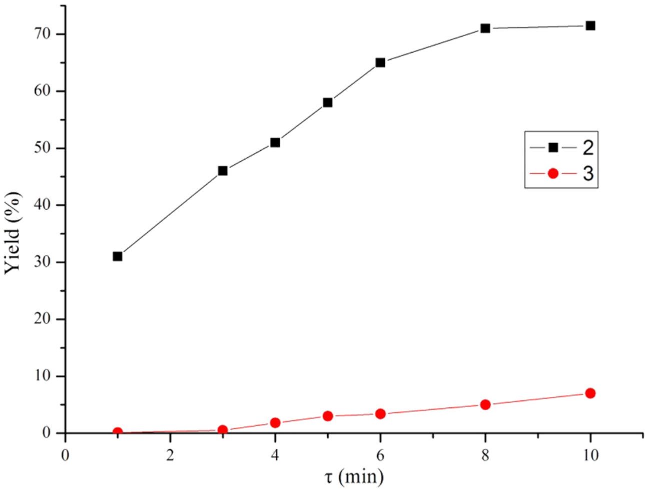
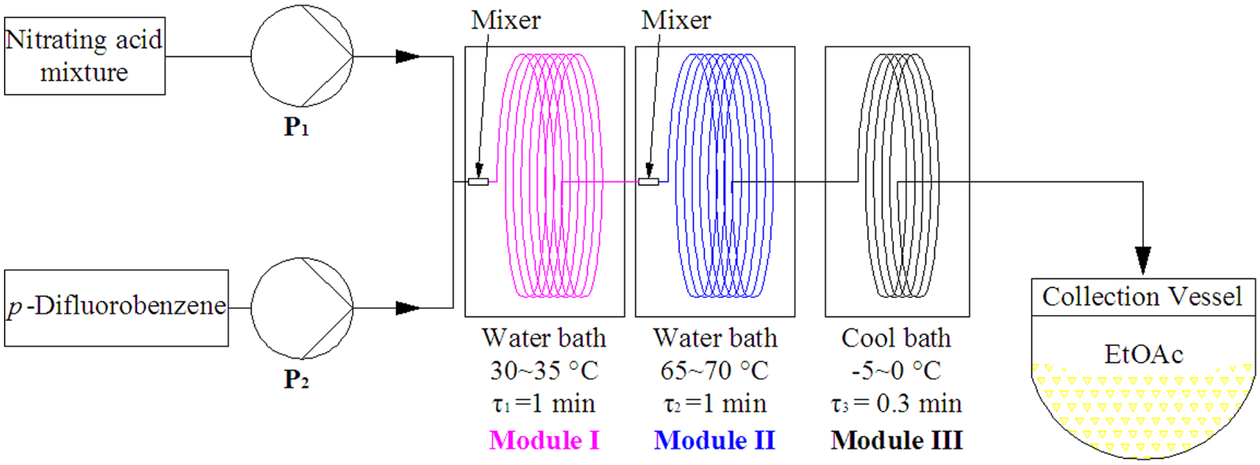


Figure 1. Change of yields of **2** and **3** with residence time in process A. As the reaction proceeds, the concentration of the reactants decreases, and the reaction rate is very slow, so the yield of product **2** increased very slowly. All yields are isolated yields. The rest of the composition remains the starting material.

Scheme 4. Schematic of process B: coil is SS316 coil with 4 mm i.d. and 6 mm o.d.[a]



[a] Due to the high concentration of reactants at the initial stage, the nitration rate is fast and accompanied with a rapid exotherm, and therefore a 30−35 °C bath was used to remove the heat (Module I). As the reaction proceeds, the concentration of the reactants becomes low, the nitration rate is slow, and another mixer and a higher temperature bath (Module II) were used to accelerate the reaction; however, the amounts of side products were not significantly increased in 1 min. In a cooling bath (Module III), the amount of the reactants is less, and the reaction rate becomes very slow, and a "quench" zone can be seen.

Process B. With the problems of process A in mind, an improved process was developed by connecting two reacting modules and a cooling module in series (Scheme 4). Nitrating acid mixture (2.0 equiv concentrated sulfuric acid and 1.1 equiv fuming nitric acid) and *p*-difluorobenzene were pumped into the reactor by $\mathbf{P_1}$ and $\mathbf{P_2}$ at the flow rates of 106 mL/min and 67 mL/min, respectively. The two-phase stream flowed through reacting module I which was immersed in 30−35 °C water bath with a residence time of 1 min (τ_1), and then flowed though reacting module II which was immersed in 65−70 °C water bath with another residence time of 1 min (τ_2). The reaction was quenched by rapid cooling to below 0 °C and extracting with EtOAc in collection vessel. Product **2** was obtained in 98% yield with 99% GC purity. Byproducts were hardly generated in this process due to the superior mass and heat transfer and more precise control of reaction variables. Under these conditions, this apparatus has an output of 6.25 kg/h.

Different tube diameters (1.5−6 mm) were studied using the premise of $\tau_1 = \tau_2 = 1$ min and $\tau_3 = 0.3$ min at the same feeding mole ratio and temperatures in process B. Results are shown in Table 1. All these small-scale biphasic flow systems have Reynolds numbers significantly less than 2000, which means these systems demonstrate laminar flow. The lack of turbulence and recirculation eddies in the reactor means that radial mixing is strictly due to diffusion.[17] The solution to Fick's law (eq 1) is frequently cited as a characteristic mixing time (τ_{mix}) where d_t is the tube diameter and D is the diffusion coefficient. Fick's law shows that the mixing time increases with tube diameter. In our experiments, the smaller diameter yielded more side products, whereas the larger diameter led to lower conversion rates. On the basis of nitration being a mass transfer-controlled reaction, the explanation could be that the mass transfer of the smaller-diameter tube is more efficient and leads to more side products within the same residence time; however, the inefficient mass and heat transfer of the larger-diameter tube results in worse selectivity and conversion. In other words, the residence time is too long in thinner tubes, and 6 mm of diameter is too large.

$$\tau_{\text{mix}} = \frac{d_t^2}{4D} \tag{1}$$

Table 1. Results of different tube diameters[18]

		yield (%)	
tube diameter (mm)	flow rate (mL/min)	**2** (%)	**3** (%)
1.5[a]	25	81	12
2[a]	42	86	9
4	167	98	<1
6[b]	376	82	6

[a] Some other side-products were also detected. [b] ~10% of *p*-difluorobenzene was not reacted.

Comparative Batch Experiment. For comparison, a typical batch nitration reaction was run under conditions analogous to those used in the continuous flow system (4 mm i.d.). Experimental details can be found in the Experimental Section. Results are shown in Table 2. Obviously, the continuous flow nitration process was established successfully with higher yield, and higher efficiency.

Table 2. Comparison of results

operate manner	continuous flow	batch
yield (%)	98	80
purity (%)	99 (crude product)	99.5 (after distillation)
reaction time	2.3 min	stirred for another hour after completing the addition of mixed acid
output	6.25 kg/h	based on the volume of vessel

Recycling of Waste Acid. Recycling experiments were carried out using the conditions of process B with the addition of 1.0 equiv HNO_3 to the waste acid in every run.[19] The results are shown in Table 3. The waste acid collected from process B consists of H_2SO_4, H_2O, and HNO_3. On the basis of the assumption of 100% conversion and addition of 1.0 equiv HNO_3 to the waste acid after each run, the theoretical and measured ratios of waste acid after nitration are shown in Table

Table 3. Results of recycling of waste acid

recycling times	yield (%) 2	yield (%) 3
1	98	<1
2	96	<1
3	77	<1
4	45	<1

4. With an increased ratio of water in the acid mixture, the yield of **2** decreased, but not much more dinitro **3** was generated. The reaction selectivity did not decrease, although the nitration reaction rate was slower at a lower concentration of acid. In other words, the 2.0 equiv sulfuric acid could be recycled two times directly with excellent product yields, and further recycling of waste acid can be partly achieved by adjusting the concentration of sulfuric acid to more than 80 wt % (H_2SO_4 wt % = $H_2SO_4/(H_2SO_4 + H_2O)$) with concentrated sulfuric acid. This was confirmed by operating the nitration reaction using the adjusted acid, and all five runs yielded 97–98% of **2** at 98–99% GC purities. The amount of sulfuric acid can be cut down from 2.5 mol of H_2SO_4 per mol of product **2** to 0.68 mol of H_2SO_4 per mol of product **2** based on two direct recycles of waste acid.

CONCLUSIONS

In summary, a green and practical continuous heterogeneous nitration process for **2** has been developed. Excellent yield was achieved with the use of a continuous flow system. The 2.0 equiv of sulfuric acid can be used three times directly, and further recycling of waste acid can be partly achieved by adjusting the concentration of sulfuric acid. The simplicity, especially with regard to controlling flow into the reactor, makes it easily amenable for other liquid/liquid heterogeneous flow reactions and for scaling up by operating several reactors in parallel with higher output in parallel.

EXPERIMENTAL SECTION

All GC analysis was conducted on an Agilent 7890A. GC conditions: HP-INNOWAX column, 30 m × 0.25 mm ×0.25 μm, Carrier gas: helium (1.5 mL/min), Injection temp.: 250 °C, Detector temp.: 260 °C, Oven: 100 °C (3 min hold) → 280 °C (10 °C/min, 10 min hold). ^{1}H and ^{19}F spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS, $\delta = 0$) as an internal standard at ambient temperature on a Varian 400 MHz spectrometer at 400 and 376.5 MHz, respectively.

Batch Experiment. *p*-Difluorobenzene (114 g, 1 mol) was placed in a 1-L glass jar which was immersed in an ice–water bath. A mixture of fuming nitric acid (73 g, 1.1 mol) and concentrated sulfuric acid (200 g, 2 mol) was prepared at room temperature. When **1** was cooled to 10 °C, the mixed acid was added to it. Nitration was initiated by the slow addition of the mixed acid, the temperature was kept below 15 °C. The mixture was stirred vigorously for another 1 h when addition was complete. The reaction was quenched by pouring the mixture into the ice–water bath to keep the temperature below 10 °C. The mixture was extracted with EtOAc (50 mL × 2), and the combined organic extracts were neutralized with 100 mL of saturated sodium bicarbonate and washed with 100 mL of water. The brownish-yellow liquid was obtained after solvent removal. Crude product was distilled in vacuo, and 127 g of yellowish liquid in 80% yield and 99.5% GC purity was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.81–7.77 (m, 1H), 7.40–7.34 (m, 1H), 7.33–7.27 (m, 1H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ/ppm: −114.72, −122.74.

Continuous Flow Experiment. A mixture of fuming nitric acid (730 g, 11 mol) and concentrated sulfuric acid (2000 g, 20 mol) was prepared. The mixed acid and *p*-difluorobenzene (1140 g, 10 mol) were pumped into the reactor (Scheme 4) by $\mathbf{P_1}$ and $\mathbf{P_2}$ at the flow rates of 106 mL/min and 67 mL/min, respectively. The stream flowed through the first mixer with a residence time of 1 min in reacting module I which was immersed in a 30–35 °C water bath, and then flowed through the second mixer with another residence time of 1 min in reacting module II which was immersed in a 65–70 °C water bath. Then the mixture was immediately cooled to below 0 °C (within 0.3 min) when flowed through the cooling tube in module III, and was extracted with EtOAc (500 mL × 2) in the collection vessel. The combined organic extracts were neutralized with 1 L saturated sodium bicarbonate and washed with 1 L water. An amount of 1558 g of yellowish liquid was obtained after solvent removal in 98% yield and 99% GC purity. The waste acid (about 2290 g) was collected for recycling.

Recycling of Waste Acid. Fuming nitric acid (663 g, 10 mol) was added to the collected acid. The experiment was carried out under identical conditions (residence time, feeding mole ratio, and total flow rate) and operations in first run, and resulted in a 98% yield of product **2** with 99% GC purity. Further recycling experiments were run analogously.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful for the National Natural Science Foundation of China (No. 21176222) and Zhejiang Technology and Service Platform of New Drug Innovation (PNDI) (No. 2011E61003) for financial support.

Table 4. Theoretical and measured ratios of waste acid

waste acid	theoretical ratios (wt %) HNO_3	theoretical ratios (wt %) H_2SO_4	theoretical ratios (wt %) H_2O	measured ratios (wt %) HNO_3	measured ratios (wt %) H_2SO_4	measured ratios (wt %) H_2O
waste acid 1	2.8	87.4 (89.9[a])	9.8	2.9	87.2 (89.8[a])	9.9
waste acid 2	2.5	78.6 (80.6[a])	18.9	2.6	78.1 (80.2[a])	19.3
waste acid 3	2.3	72.5 (74.2[a])	25.2	2.5	70.4 (72.2[a])	27.1
waste acid 4	2.2	67.2 (68.7[a])	30.6	–	–	–

[a] H_2SO_4 wt % = $H_2SO_4/(H_2SO_4 + H_2O)$

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(13) A calorimetry experiment on the batch reaction demonstrated a strong exotherm: 138 kJ/mol sufficient to produce an adiabatic temperature rise of 129 °C (2.0 equiv concentrated sulfuric acid and 1.1 equiv fuming nitric acid).

(14) The basis for choosing this tube diameter is the following: The pipe resistance should be less than the pumping force of the peristaltic pump, and it should be easy to achieve large-scale production with the reactor.

(15) The resident acid was neutralized by saturated sodium bicarbonate, and products remained in the organic phase.

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(18) The nitration is a mass transfer-controlled reaction. The thinner tube will have better mass transfer and a faster reaction rate, and thus the conversion in 6 mm tube was incomplete.

(19) There is an increase of the overall volume of acid, and we kept the same residence time and mole ratio by adjusting the flow rates (total rate unchanged). Slight change of concentrations did not affect the results with recycling two times.