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Org. Process Res. Dev., Just Accepted Manuscript • DOI: 10.1021/acs.oprd.5b00374 • Publication Date (Web): 06 Jan 2016 Downloaded from http://pubs.acs.org on January 11, 2016

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Continuous-Flow Process for Selective Mononitration of

1-Methyl-4-(methylsulfonyl)benzene

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ABSTRACT: An expeditious process for selective nitration of 1-methyl-4-(methylsulfonyl)benzene *via* a continuous-flow reactor in 98% yield was described. The continuous-flow mononitration ran well in adiabatic condition with 80 wt% sulfuric acid, and residence time was brought down to 5 s. The short residence time can significantly reduce byproducts. Dinitration was also studied for optimization of the mononitration. The spent acid could be reused for several times after concentrated in vacuum.

KEY WORDS: Continuous-flow; Mononitration; Adiabatic nitration; 1-Methyl-4-(methylsulfonyl)benzene

INTRODUCTION

Nitroaromatic derivatives are an important class of compounds with wide applications in pharmaceuticals, pesticides, dyes, perfumes, explosives, *etc.*¹ For example, the title reaction product 1-methyl-4-(methylsulfonyl)-2-nitrobenzene is an important material for the synthesis of Mesotrione (Figure 1), which is a herbicide used to control some grass and broad-leaved weeds mainly in maize crops.² Nitroaromatics are generally produced by nitration of aromatic derivatives. These nitration reactions are extremely hazardous due to highly exothermic thermodynamics as well as possible decomposition and explosion of nitro compounds.³ The heat of reaction per electrophilic substitution by a nitronium ion is typically -100 kJ/mol, and it presents serious hazards particularly in large-scale production. In the chemical industry, to carry out the reaction in a mild way, large quantities of diluents of waste solvents.⁴ Also, selectivity is not satisfying due to easy over-nitration or oxidation when reagents and products are both exposed to the reaction conditions over a long residence time.⁵ Still, the safety risk is not eliminated owing to mass and heat transfer limitations in conventional batch reactors.



Figure 1. Structure of Mesotrione.

The great demand of nitroaromatic compounds provides enormous impetus for extensive study of nitration reactions. Recently, one solution complementary to the conventional batch or semi-batch mode is to employ a continuous and selective nitration mode. There are a number of reports of nitration reactions which have been performed under continuous flow conditions.^{4, 6}

It is well proved that continuous-flow technology offers many advantages over batch methods', including precise control of stoichiometry, residence time, and temperature; high reproducibility; easy scale up; and often better reaction yields. The much higher surface area to volume ratio under flow conditions renders highly efficient heat transfer. Furthermore, safety hazards in handling exothermic reactions associated with explosive reagents are minimized.⁸ 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 safety.

Motivated by these advantages, our group has been committed to the continuous-flow synthesis technology, and has reported several practical kilogram-scale continuous-flow processes⁹. Herein, we have this technology applied to the mononitration of 1-methyl-4-(methylsulfonyl)benzene (1) in both isothermal and adiabatic condition (Scheme 1).

Scheme 1. Mononitration of 1-Methyl-4-(methylsulfonyl)benzene



RESULTS AND DISCUSSION

In the batch preparation¹⁰ of mononitrated product **2**, mixing acid (composed of concentrated sulfuric acid and nitric acid) was added dropwise into sulfuric acid solution of **1** at ≤ 10 °C, followed by stirring at room temperature for several hours, then solid product was obtained by introducing the reaction mixture into large amount of cold water. The heat of reaction had to be removed by external cooling, thus avoiding the over-nitration and oxidation side reactions. In the design of continuous-flow process for **2**, our original objectives were to shorten the long reaction time and reduce the amount of waste.

Isothermal Nitration Process

From the beginning of our investigation, commercial nitric acid (98 wt% HNO₃) was selected as the nitrating agent and sulfuric acid solution of **1** was prepared in acid tank. Scheme 2 shows the continuous-flow reactor experimental setup. The equipment consists of two peristaltic pumps (P₁, P₂, Baoding Longer, China) loaded with tubing connected by a T-mixer (SS316, 1.5 mm i.d.) that was connected to residence loop (SS316, 3 mm i.d., 5 mm o.d.). The reacting tube was immersed in a thermostat-controlled water bath. The flow rate of water being very high compared to the flow rate of the reactants, which would take the reactor to near isothermal conditions. Nitric acid and sulfuric acid solution were pumped into the reactor. After a residence time (τ) in reacting tube, reacting mixture was introduced into dilution tank and the reaction was quenched by cold water. Solid product was precipitated and samples were analyzed by HPLC.

Scheme 2. Schematic of Experimental Setup of Isothermal Nitration Process



The optimization of experimental parameters started from varying residence time (τ) and temperature (*T*). Reaction conditions: 98% sulfuric acid, molar feed ratio of **1** : HNO₃ : H₂SO₄ ($F_1 : F_N : F_S$) was 1 : 1.2 : 2.5, flow rates of nitric acid and sulfuric acid solution were 11.2 mL/min and 60.4 mL/min, respectively. This procedure was greatly facilitated by continuous-flow conditions, and a significant number of runs were rapidly conducted in a sequential manner. For the purpose of high efficiency, we hope to shorten the reaction time to less than one minute. Figure 2 showed the results of the influence of temperature and residence time on nitration. As we all know, on the basis of Arrhenius equation, the reaction product was detected, and excellent selectivity (over 98%) of mononitraction product **2** was obtained along with low conversion rate. As raised reaction temperature (higher than 55 °C), conversion of **1** can be completed immediately, however, dinitration product **3** and oxidation product **4** (Figure 3) emerged. When T = 75 °C, the reaction completed within 15 s and the selectivity was only 90% (about 9% of **3**, and nearly 0.5% of **4**).



Figure 2. Effect of temperature and residence time on nitration when $F_1 : F_N : F_S = 1 : 1.2 : 2.5$, flow rates of nitric acid and sulfuric acid solution were 11.2 mL/min and 60.4 mL/min. Conversion was

determined by HPLC.



Figure 3. Oxidated by-product 4.

Based on the above results, for primary purpose of reaction selectivity, we tried to change the acids dosage at low reaction temperature. The molar feed ratio was then studied (Table 1), when flow rate of nitric acid was 11.2 mL/min, and reaction temperature was about 40 °C. Flow rate of sulfuric acid solution was adjusted to adapt to the molar feed ratio, and reactor volume was not changed (10 m tube length). Reaction was accelerated obviously when F_S/F_1 increased, and selectivity was still excellent unless the ratio value reached 10 (entries 1-5, Table 1). Shortening the residence time resulted in lower conversion (entries 2-3, Table 1). Decreasing of F_N/F_1 affected the conversion rate (entries 6-7, Table 1). Due to excellent heat transfer efficiency, the reactions were run at accurate temperature, and almost no dinitrated or oxidated side reactions occurred in such short residence times.

entry	F_1 : F_N : F_S^a	τ (s)	Conv. $(\%)^b$	Sel. $(\%)^b$
1	1:1.2:2.0	65	96	100
2	1:1.2:2.5	60	100	99
3 ^{<i>c</i>}	1:1.2:2.5	30	93	99
4	1:1.2:5.0	43	100	99
5	1:1.2:7.5	33	100	98
6	1:1.2:10.0	27	100	97
7	1:1.1:5.0	39	99	99
8	1:1.05:5.0	38	94	99
^{<i>a</i>} Molar fe	ed ratio of 1 : HNO ₃ : H ₂ S	SO ₄ . ^b Determined	l by HPLC. ^c 5 m tube le	ength.

Table 1. Effect of molar feed ratio on nitration when T = 40 °C.

The success with 98 wt% nitric acid and 98 wt% sulfuric acid prompted us to study the influence of another process parameter, i.e. LHSV (liquid hourly space velocity). Studies¹¹ have proved that nitration reaction was controlled by mass transfer, for an increase in LHSV could lead to an increase in Reynolds numbers, which finally improved the mass transport on the reaction process. When the nitration

temperature was low, the reaction rate was slow, so the reaction was controlled by reaction kinetics. But as the temperature was raised, the reaction rate was raised as well. If the reaction rate reached to a certain point, the reaction was instantaneous in a macroscopical way of observation, in that case, the reaction was controlled by the mass transport. Table 2 showed the results of effect of LHSV on nitration when $F_1 : F_N : F_S = 1 : 1.2 : 2.5$ and T = 40 °C. LHSV value of 240 h⁻¹ provided better result (entry 3, Table 2). This phenomenon validated that at low LHSV, the flow regime was laminar flow which mixing was relative slow, so the reaction need a longer τ to complete conversion (entries 1-2, Table 2). As LHSV raised, the *Re* number raised as well, and the flow regime was transited from laminar flow to turbulent flow which improved mixing efficiency, therefore conversion can completed in a shorter τ (entries 3-6, Table 2). But when LHSV was too high, the reaction became drastically, that may cause some hotspots which led to dinitration, decreased selectivity (entries 5-6, Table 2). With these continuous-flow reaction parameters, excellent isolated yield of **2** was achieved (ranging from 96% to 98%).

entry	τ (s)	LHSV (h^{-1})	Conv. $(\%)^a$	Sel. $(\%)^a$
1	60	60	99	99
2	6	60	86	99
3	20	180	100	99
4	15	240	100	99
5	10	360	100	98
6	6	600	99	97
^a Determin	ed by HPLC.			

Table 2. Effect of LHSV on nitration when $F_1 : F_N : F_S = 1 : 1.2 : 2.5$ and T = 40 °C.

The objective of shorten reaction time was achieved. However, the amount of waste, especially diluted sulfuric acid was still needed to be reduced. As stated in nitration mechanism, sulfuric acid is just catalyst and dehydration agent. Theoretically, no sulfuric acid was consumed during nitration reaction, and we aimed to establish a continuous-flow nitration and sulfuric acid recycled process was possible. The key to achieve this goal was the recycling of sulfuric acid. Concentration of sulfuric acid was then studied when fuming nitric acid was used, and flow rate of nitric acid was 44.8 mL/min. Flow **ACS Paragon Plus Environment**

rate of sulfuric acid solution was adjusted to adapt to the molar feed ratio ($F_N/F_1 = 1.2$). Tube length was adjusted to keep 240 h⁻¹ of LHSV value. Results in Table 3 reveal that decrease of concentration of sulfuric acid lead to decrease of conversion, and increase of F_S/F_1 together with reaction temperature at low concentration of sulfuric acid won't generate more by-products. The concentration of 80 wt% H₂SO₄ can keep the purposes of conversion rate and selectivity in balance (entry 5, Table 3).

entry	H ₂ SO ₄ (wt%)	$F_{\rm S}/F_1$	$T(^{\circ}C)$	Conv. $(\%)^b$	Sel. $(\%)^a$
1	90	2.5	40	86	99
2	90	2.5	60	97	98
3	80	2.5	60	32	99
4	80	4.5	80	76	99
5	80	7.5	80	99	99
6	80	7.5	100	100	97
7	75	7.5	80	77	100
8	75	12.5	80	86	99
9	70	7.5	80	28	100
^{<i>a</i>} Determined	l by HPLC.				

Table 3. Effect of concentration of sulfuric acid on nitration when LHSV = 240 h⁻¹ and $F_N/F_1 = 1.2$.

Study of dinitration

An extra nitration test of mononirated product **2** (Scheme 3) was systematically investigated by varying reaction temperature, and residence time with the above optimized conditions, *i.e.* 80 wt% sulfuric acid, 98 wt% nitric acid, $F_2 : F_N : F_S = 1 : 1.2 : 7.5$, LHSV = 240 h⁻¹. The experiments were conducted in the same setup as shown in Scheme 2. It was found that dinitration reaction rate was not so fast within the first few seconds, which makes possible an adiabatic nitration process by shortening the reaction time within 5 s (Figure 4).

Scheme 3. Nitration of 1-methyl-4-(methylsulfonyl)-2-nitrobenzene





Figure 4. Study on nitration of 2 with optimized mononitration conditions.

Adiabatic Nitration Process

Bearing in mind that few byproducts generated in a very short residence time, adiabatic process was then undertaken. Experiment setup was shown in Figure 5, nitric acid and sulfuric acid solution of **1** were pumped into the flow reactor, and outlet of the reacting tube was connected to a dilution tank. PTFE tube was used as reacting tube and wrapped by thermal insulation cotton. Thermal conductivity of PTFE is only 0.25 W/(m·K), and nitration reaction can be done in a few seconds with an adiabatic temperature rise of excess than 60 °C, so the continuous-flow nitration can be regarded as adiabatic reaction. Reaction conditions were same with optimized isothermal reaction parameters, *i.e.* 80 wt% sulfuric acid, 98 wt% nitric acid (44.8 mL/min), $F_1 : F_N = 1 : 1.2$. As shown in Figure 6, the results revealed that adiabatic nitration was complete within 5 s with 99% selectivity when F_S/F_1 was 3.5. Mononitration of **1** ran well at adiabatic condition (high *T*, short τ). The isolated yield of mononitrated product **2** was about 98%. In addition, increase of sulfuric acid dosage lead to decrease of conversion, and the reason may be the decrease of adiabatic temperature elevation.



Figure 5. Experiment setup of adiabatic nitration process.



Figure 6. Effect of $F_{\rm S}/F_1$ on adiabatic nitration.

At this point, adiabatic nitration parameters can be summarized as follows: 80 wt% sulfuric acid and 98 wt% nitric acid were used, $F_1 : F_N : F_S = 1 : 1.2 : 3.5$, all reagents were fed at room temperature, total flow rate was 395.3 mL/min, residence time was 5 s, the i.d. of reacting tube was 3 mm, length of reacting tube was 4.6 m, and isolated yield of **2** was about 98%. To underline the advantages of the proposed flow synthesis, a comparison with the reaction performed in a batch manner was summarized in Table 4. Continuous-flow synthesis reduced byproducts and saved energy consumption obviously.

 Table 4 Comparison of the Batch Process with Continuous-flow Processes

operate manner	batch	isothermal continuous-flow	adiabatic continuous-flow
yield (%)	97	98	98
purity (%)	96	99	99

reaction time	stirred for hours after completing the addition of mixing acid	within 15 s	within 5 s
reaction temperature	addition: ≤ 10 °C (need cooling) reaction: r.t.	feeding: r.t. reaction: 80 °C	feeding: r.t. reaction: adiabatic

Recycling of spent acid

Based on the results of adiabatic nitration process, the target of establishing a recycled nitration process was fulfilled (Figure 7). Recycling experiments were carried out under adiabatic nitration conditions. The spent acid collected from adiabatic process consists of sulfuric acid, water, and trace of nitric acid. Concentration of sulfuric acid in spent acid was about 40 wt%. The diluted acid was condensed to 80 wt% under vacuum at about 140 °C. Higher temperature, which led to carbonation of organic solutes¹², resulted in the decrease of purity. Recycled water (about 0.1 wt% of sulfuric acid) was reused for dilution. The results were shown in Table 5. The sulfuric acid and water could be recycled several times without obvious decrease of product quality.



Figure 7. Schematic of recycled nitration process.

Recycle run	Yield of 2 (%)	Purity of 2 (%)
1	98	99
2	98	99
3	100	99
4	99	98

Table 5. Results of recycling experiments

5	100	97
6	95	94

CONCLUSION

In summary, an expeditious and high-yielding process for selective mononitration of 1-methyl-4-(methylsulfonyl)benzene *via* a continuous-flow reactor has been set up. The flow technology applied in this study increases the quality of nitration product, and the adiabatic flow process reduces the amount of sulfuric acid and saves energy consumption apparently. Using of moderate concentration of sulfuric acid makes the recycling process easy to implement. The process is readily adapted for preparation of analogous compounds and can easily be scaled up by increasing the reactor size or operating several reactors with high-throughput in parallel.

EXPERIMENTAL SECTION

All chemicals were purchased from commercial sources and were used without further purification. Melting points were determined on a Buchi 540 melting point apparatus and were uncorrected. ¹H NMR spectra was recorded on Varian 400 MHz spectrometer using tetramethylsilane (TMS) as the internal standard. High-performance liquid chromatography (HPLC) analysis was carried out on an Agilent 1200 system equipped with a SB-Aq 150 mm × 4.6 mm × 5 μ m column and detected at 216 nm, eluted with 30 : 70 CH₃CN / H₂O at 1.0 mL/min.

Continuous-Flow Experimental Procedure of Adiabatic Nitration Process. As shown in Figure 5, a mixture of 1 (340 g, 2 mol), water (158 mL), and concentrated sulfuric acid (700 g, 7 mol) was prepared. The mixed solution and fuming nitric acid (154 g, 2.4 mol) were pumped into the reactor by two pumps at the flow rates of 350.5 mL/min and 44.8 mL/min, respectively. The stream flowed through the mixer with a residence time of 5 s in reacting tube which was wrapped by thermal insulation cotton. The temperature of the reaction mixture at outlet of the reactor was raised to 100 °C immediately while the adiabatic temperature rise was about 70 °C. Then the mixture was introduced into the dilution tank and the reaction was quenched by cold water (900 mL). White solid was precipitated immediately.

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Then the mixture was cooling to room temperature. An amount of 421 g solid product was obtained after filtration and drying in 98% yield and 99% purity: mp 117–119 °C; ¹H NMR (400 MHz, CDCl₃) δ /ppm: 8.50 (s, 1H), 8.04 (d, 1H, *J* = 8.0 Hz), 7.06 (d, 1H, *J* = 8.0 Hz), 3.11 (s, 3H), 2.71 (s, 3H).

Recycling of Spent Acid. The waste acid (about 1680 g, about 40 wt% sulfuric acid) collected from above procedure was concentrated in vacuum at 140 °C until the concentration of sulfuric acid reached 80 wt%. At the same time, 830–840 g water (about 0.1 wt% sulfuric acid) was collected. Both the acid and water were reused, and a small amount of water was added to keep the reactants ratio of first run. 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% purity. Further recycling experiments were run analogously.

ACKNOWLEDGMENT

We are grateful to the National Natural Science Foundation of China (No. 21406203) for financial support.

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- (12) There was a little product in the filtrate. It could be carbonated if the temperature of concentration was too high with concentrated sulfuric acid, and the concentrated liquid became black. After recycling runs, the carbonated impurities might bring into the product.