# **Supporting Information**

Safe, efficient and selective synthesis of dinitro herbicides via a continuous-flow microreactor: one-step dinitration with nitric acid as agent\*\*

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## 1. General reagent information

Nitric acid and 1,2-dichloroethane (AR) were obtained from Kermel Chemical Reagent Company (China). 3,4-Dimethyl aniline (99% purity) was obtained from Aladdin Chemical Co., Ltd (China). Pure water and acetonitrile (Fisher Scientific, HPLC grade) were obtained for HPLC analysis. Acetone, 2-butanone, 3-pentanone and cyclopentanone (AR) were obtained from Sinopharm Chemical Reagent Co., Ltd (China). Anilines **1-4** (>98% purity) were prepared in lab by reductive amination of respective ketone with 3,4-dimethyl aniline, which were described in detail at **S3**. These reagents were used without further purification.

Aniline derivative	Chemical structure
1	
2	
3	
4	

# 2. General analytic methods

<sup>1</sup>H-NMR spectra were recorded on a Bruker 400 MHz instrument. Chemical shifts ( $\delta$ ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, and m are used to indicate singlet, doublet, triplet, and multiplet. Mass

spectra were obtained on an Agilent 6890N-5973N (GC-MS) instrument using electron ionization in positive mode. Analytical HPLC (eliteHPLC EC2000, China) analysis (UV detector at 220 nm) was carried out on a C18 reversed-phase analytical column (DIKMA Inertsil ODS-3 column,  $250 \times 4.6$  mm, particle size 5 µm) at 25°C using a mobile phase (water/acetonitrile 30:70 (v/v) + 0.1% triethylamine) at a flow rate of 1.0 mL/min, and nitrobenzene was used as internal standard. All the reagents and products studied in this work are known in the literature. Pendimethalin (**1a**), N-nitrosopendimethalin (**1b**) and anilines **2-4** have been characterized by <sup>1</sup>H-NMR and MS spectroscopy and identified by comparison of spectra reported in the literature. All the reagents and products have compared with standard samples offered by Shenyang Research Institute of Chemical Industry, which have shown the same retention time in HPLC analysis.

#### 3. Synthesis of parent aniline derivatives (Anilines 1-4)



The anilines 1-4 was synthesized using literature reported method of reductive amination of ketone.<sup>1</sup>

General procedure: 0.2 mol of 3,4-dimethyl aniline, 0.3 mol of ketone, 1.2 g of 5% platinum supported on carbon catalyst and 0.45 g of  $\beta$ -naphthalene sulfonic acid were mixed in a 200 ml autoclave in a batch process. The equipment was closed and purged with nitrogen and then charged with hydrogen to the operating pressure of 0.5-1.0 MPa. The reaction temperature was kept at 60-70°C for 1 h. Then the pressure was carefully vented in a fume hood and full cooling was applied. The reaction mixture was withdrawn, filtered, concentrated under vacuum and analyzed by GC (Agilent 7890). A yield of more than 98% was obtained in all cases. The 5% Pt/C catalyst can be recycled by washing with hydrochloric acid, rinsing with water and drying in oven.

#### 4. Conventional two-step synthesis of pendimethalin



In chemical industry, the method for introduction of two nitro-groups to aromatic ring is extensively two-step nitration process, that is, mononitration step in which momonitration reaction mainly takes place and the second nitration step in which mainly second nitration of mononitrated compounds takes place. One classic case of two-step nitration is the production for dinitrotoluenes (2,4-dinitrotoluene and 2,6-dinitrotoluene), which are the key intermediates for production of explosive of TNT (2,4,6-trinitrotoluene). The industrial two-step production of pendimethalin in chlorinated solvent has been reported<sup>2</sup>: the aniline **1** is treated with dilute nitric acid as the first step, after separation of organic phase from spent acid phase, the organic phase is then treated with more concentrated nitric acid as the second step, obtains with 89% yield of **1a** and **1b** and molar ratio for **1a**:**1b** of 7:3. The total reaction time is 4 h, and **1e** is produced in a significant amount since **1b** can be further converted into **1e** under long reaction time. Our experiment result demonstrated similar yield of **1a** and **1b** of 88% in two-step batch process. First step:  $[HNO_3]=35$  wt.%, [aniline 1]=30 wt.%,  $HNO_3$ :aniline 1=0.95:1(mol/mol),  $T=40^{\circ}$ C, t=1 h; second step:  $[HNO_3]=68$  wt.%,  $HNO_3$ :aniline 1=2:1(mol/mol),  $T=55^{\circ}$ C, t=3 h.



Figure S1. Schematic of conventional two-step synthesis of pendimethalin.

## 5. Microreactor information and experimental set-up

The microreactor used in this study was fabricated in stainless steel plate by micromachining technology in our CNC Machining Center. It mainly contained one reaction plate with 16 micro reaction channels and two heat exchanging

plates. The reaction plate was clamped by the two heat exchanging plate. The mixing, reaction and heat exchange units had been integrated in this microreactor system. Both the aniline and nitric acid inlets had a microstructure of 16 distribution channels. The diameter of mixing micropores is *ca*. 400  $\mu$ m. The width, depth and length of each micro reaction channel are 500  $\mu$ m, 400  $\mu$ m and 57 mm, respectively. The total reaction volume of these microchannels is *ca*. 0.2 ml. The picture of the compact multifunctional microreactor, the schematic diagrams of aniline and nitric acid fluids routes in the reaction plate and heat transfer plate are shown in Figure S2.





**Figure S2.** Picture of the compact multifunctional microreactor (a), schematic diagrams of aniline and NB fluids routes in the reaction plate (b) and heat transfer plate (c)

### 6. Methods for conversion of N-nitroso-pendimethalin to pendimethalin

N-Nitroso compounds are usually unstable and may be carcinogenic to mammal species. From both economic and environmental point of view, N-nitroso-pendimethalin are required to be converted into pendimethalin or other environment-friendly compounds so that the content of N-nitroso-pendimethalin in the final product is below 135 ppm (the standard was established by US Environmental Protection Agency). Tremendous methods have been reported for the disposal of N-nitroso compounds, and one traditional approach has been performed in our lab and proved that N-nitroso-pendimethalin has been converted into pendimethalin in a yield of more than 99%.<sup>3</sup> In our experiments, the disposal procedure was always performed with the crude product, thus the separation procedure of compounds **1a** and **1b** was not needed. The content of N-nitroso-pendimethalin decreased to <100 ppm (step 1). Subsequent treatment with heating at 180°C for 10 min resulted that the content of N-nitroso-pendimethalin decreased to <10 ppm (step 2). The separation procedure of compounds **1a** and **1b** was only conducted by column chromatography to obtain standard samples, using ethyl acetate and petroleum ether as eluent.



(>99% yield, N-nitroso-pendimethalin <100 ppm)

(50% yield, N-nitroso-pendimethalin<1 ppm)

## 7. One-step dinitration for synthesis of pendimethalin via a microreactor

General procedure: Anilines 1 (80 wt.%, in CH<sub>2</sub>ClCH<sub>2</sub>Cl) and HNO<sub>3</sub> (65 wt.%, in water) were loaded into an organic tank and an acid tank, respectively. The anilines 1 and HNO<sub>3</sub> streams from the respective tank were fed into the microreactor by two HPLC pumps (Chrom Tech, Series II, USA). The streams were divided into 16-branch flows via two fluid distributions, then mixed at the mixing micropores and reacted in the following microchannels. The microreactor was immersed in water bath, and the reaction temperature (40-90°C) was controlled by water bath and heat exchange fluids via a thermostat (Yuhua, China) and temperature of the reaction mixture outlet was monitored by a thermocouple (K-type) to compare with the water bath temperature. The residence time (0.8-40 s) was regulated by changing the reagents flow rates. After a steady state was reached, the effluent products were poured into cold acetonitrile solvent for 30 seconds to quench the reaction and diluted to 25 ml to form homogeneous sample solutions.

These sample solutions were analyzed by HPLC with an internal standard.



Figure S3. Experimental set-up of the microreactor system for continuous one-step dinitration of aniline compounds.

### 8. Process parameters study for one-step dinitration approach

Dinitration of aniline 1 were selected as a model reaction from preliminary study. Initial conditions were adopted under similar conditions mainly from two-step nitration procedure. 1,2-Dichloroethane was selected as solvent and concentration of aniline 1 was fixed as 30 wt.% in the organic tank. The nitrating agent was chosen as concentrated nitric acid (65 wt.%), mixed acid (15 wt.% nitric acid, 77 wt.% sulfuric acid, 18 wt.% water) and fuming nitric acid (98 wt.%), respectively. It was seen that 24% conversion was determined for 65 wt.% nitric acid (Table S1, entry1). The mixed-acid was so reactive that all the reactant 1 was converted to unidentified by-products. Moderate conversion (40%-85%) could be obtained with 98 wt.% nitric acid (Table S1, entries 2-3). Bearing in mind that increase in substrate concentration in microreactors may result in improved conversion, the concentration of aniline 1 was increased to 80%. It seems that conversion increased with the increase of temperature when it varied from  $40^{\circ}$ C to  $60^{\circ}$ C (Table S1, entries 4-6). Amazingly, 100% conversion and 92% selectivity was obtained at a residence time of 9 s and temperature of  $60^{\circ}$ C. (Table S1, entry 6) However, further increasing the concentration of reactant 1 would make the organic feed so viscous that the feed was hard to convey and the flow rate was difficult to measure accurately. Thus, the concentration of reactant 1 in the organic phase was finally fixed at 80%. We found that the molar ratio of **1a:1b** was always less than 0.5 when 98 wt.% nitric acid was employed, which meant large amounts of 1b were required to be converted into 1a in the downstream process. When the concentration of nitric acid was changed back to 65%, 100% conversion and 98% selectivity were obtained and the molar ratio of **1a:1b** turned out as high as 3.6 (Table S1, entry 7).

			<b>-</b>						
Entry	Т	ť	LHSV	[aniline 1]	[HNO₃]	HNO <sub>3</sub> :1	Conv. <sup>b</sup>	Sel.⁵	1a:1b°
-	(°C)	(s)	(10 <sup>3</sup> h <sup>-1</sup> )	(wt.%)	(wt.%)	(mol/mol)	(%)	(%)	(wt./wt.)
1	80	6.1	0.6	30	65	3.0	24	72	1.1
2	80	9.0	0.4	30	98	3.0	85	64	0.4
3	80	40	0.1	30	98	3.0	40	57	0.3
4	40	7.2	0.5	80	98	3.1	61	89	0.5
5	50	7.2	0.5	80	98	3.1	74	90	0.4
6	60	9.0	0.4	80	98	4.3	100	92	0.2
7	70	6.1	0.6	80	65	3.9	100	98	3.6
<sup>a</sup> Residence time. <sup>b</sup> Determined by HPLC. <sup>c</sup> in all cases, <b>1e</b> was not determined.									

Table S1: Initial study of one-step dinitration of aniline 1 in a continuous-flow microreactor

The success with 65% nitric acid and 80% aniline **1** solution prompted us to study the influence of other process parameters, such as LHSV (Liquid Hourly Space Velocity), reaction temperature and initial HNO<sub>3</sub>:aniline **1** molar ratio. In all cases, the fluid outlet temperatures were almost the same with reaction temperature, for variations of temperature were always within  $2^{\circ}$ C. The process parameters study have been mentioned in the article.

#### 9 Process optimization for one-step dinitration approach

After on process parameters study, the suitable initial molar ratio of  $HNO_3$  to aniline 1 is probably between 2.7 and 3.1. Table S2 demonstrated the optimization results. The optimum reaction condition was finally selected as  $HNO_3$ :aniline 1 molar ratio of 3.0 ( $HNO_3$ : 6.0 ml min<sup>-1</sup>, aniline solution: 7.8 ml min<sup>-1</sup>), temperature of 60°C and LHSV of 4100 h<sup>-1</sup>, and 100% conversion and 97% were obtained (Table S2, entry 4).

Table S2: Further process optimization of one-step dinitration of aniline 1 in a continuous-flow microreactor<sup>a</sup>

Entry	T	t <sup>b</sup>	LHSV	HNO <sub>3</sub> : <b>1</b>	Conv.°	Selec. <sup>c</sup>	<b>1a:1b</b> <sup>d</sup>	Output
	(°C)	(s)	(10 <sup>3</sup> h <sup>-1</sup> )	(mol/mol)	(%)	(%)	(wt./wt.)	(kg h <sup>-1</sup> )
1	70	1.0	3.5	2.9	100	92	2.7	0.45

2	70	1.0	3.4	3.0	100	92	2.9	0.43
3	60	1.0	3.4	3.0	99	97	4.8	0.45
4	60	0.8	4.1	3.0	100	97	4.2	0.54
<sup>a</sup> General conditions: the concentration of nitric acid, 65 wt.%; the concentration of aniline <b>1</b> , 80 wt.%.								
<sup>b</sup> Residence time. <sup>c</sup> Determined by HPLC. <sup>d</sup> in all cases. <b>1e</b> was not determined.								

### 10. Stable test for one-step dinitration approach for an hour

To test the stability of our microreactor system under this condition, the flow process was run continuously for 1 h, obtaining 0.54 kg of target products (**1a** and **1b**) in 97% yield as expected (isolated yield). This corresponds to an output of 12.96 kg day<sup>-1</sup> or 4.32 t per year (considering 8000 h running time in a year) for the target products (**1a** and **1b**). The reaction proceeded smoothly without evaporation of solvent or clogging of the microchannel.

### 11. Numbering-up for the microreactor by a factor of 100

Scale-up can be realized by a factor of 100 with numbering-up method (pile-up method, i.e. plate-to-stack method),<sup>4,5</sup> thus it corresponds to an output of 432 t per year, which approaches to factory-scale. Actually, the 16-channel microreactor in this study can be considered as  $16 \times$  numbering-up compared with single-channel microreactor. The design principle of numbered-up microreactor was depicted in Figure S7, which mainly contained of 100 reaction plates and 101 heat exchange plates (alternating arrangement of reaction plate and heat exchanging plate). The similar industrial microreactor with process capacity of 100 kt per year to produce monoammonium phosphate has been developed by our group and has been running stably more than three years since April 2009.<sup>[6]</sup> This microreactor consists of over 100 reaction plates. The photo of industrial production of monoammonium phosphate was also added in Figure S4. However, the scale-up experiment for this procedure has not been tried yet.



**Figure S4.** Design principle of numbered-up microreactor by a factor of 100 (a), industrial microreactor with process capacity of 100 kt per year to produce monoammonium phosphate (b).

### 12. One-step dinitration of other aniline derivatives (Anilines 2-4)

Two other N-alkyl substituted derivatives (anilines 2 and 3) underwent complete conversion and high selectivity even under solvent-free conditions (Table S3, entries 2 and 3). The reaction temperature for anilines **2** and **3** were improved to  $90^{\circ}$ C and  $80^{\circ}$ C, respectively. Sterically hindered aniline **4** was also tested and its conversion was slightly reduced (Table S3, entry 4).

Table S3. One-step dinitration of aniline derivatives using the continuous-flow microreactor

Aniline derivative		T (°C)	Conc. (wt.%.)	t <sup>a</sup> (s)	Conv. <sup>b</sup> (%)	Sel. <sup>b</sup> (%)	<b>a/b</b> (wt./wt.)	
1		60	80	0.8	100	97	4.2	
2	, Cy→ <sup>H</sup> N→	90	100	1.3	100	98	1.1	
3		80	100	1.5	100	99	2.8	
4		80	80	0.9	90	99	1.5	
<sup>a</sup> Residence time. <sup>b</sup> Determined by HPLC.								

## 13. Spectral data

## N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitroaniline (pendimethalin,1a)

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ =8.1 (s, 1H, Ar-H), 7.6 (s, 1H, N-H), 3.2 (s, 1H, -CHN), 2.3 (s, 3H, Ar-CH<sub>3</sub>), 2.2 (s, 3H, Ar-CH<sub>3</sub>), 1.3-1.6 (m, 4H, 2-CH<sub>2</sub>-), 0.8-0.9 (t, 6H, 2-CH<sub>3</sub>); **Simplified MS (EI)**: m/z calculated for C<sub>13</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub> M<sup>+</sup> 281, found 281

N -nitroso-N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitroaniline (N-nitroso-pendimethalin,1b)

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ =8.0 (s, 1H, Ar-H), 4.0 (m, 1H, -CHN), 2.5 (s, 3H, Ar-CH<sub>3</sub>), 2.25 (s, 3H, Ar-CH<sub>3</sub>), 1.75-2.2 (m, 4H, 2-CH<sub>2</sub>-), 0.8-1.1 (m, 6H, 2-CH<sub>3</sub>); **Simplified MS (EI**): m/z signal of N-nitroso-pendimethalin was not obtained due to decomposition of N-nitroso-pendimethalin in the GC instrument.

## N-(1-methylethyl)-3,4-dimethyl-aniline (aniline 2)



<sup>1</sup>**H-NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$ =7.0 (s, 1H, Ar-H), 6.3-6.5 (d, 2H, Ar-H), 3.62 (s, 1H, N-H), 3.25(s, 1H, -CHN), 2.3 (s, 3H, Ar-CH<sub>3</sub>), 2.2 (s, 3H, Ar-CH<sub>3</sub>), 1.25 (s, 6H, -(CH<sub>3</sub>)<sub>2</sub>); **Simplified MS (EI**): m/z calculated for C<sub>11</sub>H<sub>17</sub>N M<sup>+</sup> 163, found 163

N-(1-methylpropyl)-3,4-dimethyl-aniline (aniline 3)



<sup>1</sup>**H-NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$ =7.0 (s, 1H, Ar-H), 6.3-6.5 (d, 2H, Ar-H), 3.3-3.5 (s, 1H, N-H), 2.3-2.5 (s, 1H, -CHN), 2.2-2.3 (d, 6H, Ar-2CH<sub>3</sub>), 1.3 (s, 2H, -CH<sub>2</sub>-), 1.2 (d, 3H, -CH<sub>3</sub>), 1.0 (s, 3H, -CH<sub>3</sub>); **Simplified MS (EI)**: m/z calculated for C<sub>12</sub>H<sub>19</sub>N M<sup>+</sup> 177, found 177

# N-cyclopentyl-3,4-dimethyl-aniline (aniline 4)



<sup>1</sup>**H-NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$ =7.0 (s, 1H, Ar-H), 6.4-6.6 (d, 2H, Ar-H), 3.7-3.9 (s, 1H, N-H), 3.2-3.6 (s, 1H, -CHN), 2.2-2.3 (d, 6H, Ar-2CH<sub>3</sub>), 2.0-2.2 (s, 2H, -C H<sub>2</sub>-), 1.6-1.8 (d, 4H, 2-CH<sub>2</sub>-), 1.6 (s, 2H, -CH<sub>2</sub>-); **Simplified MS (EI)**: m/z calculated for C<sub>13</sub>H<sub>19</sub>N M<sup>+</sup> 189, found 189





















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