

Electronic Supplementary Information

An intensified chlorination process of 4-nitroaniline in liquid-liquid microflow system

Zhou Lan, Yangcheng Lu*

State Key Laboratory of Chemical Engineering, Department of Chemical Engineering,
Tsinghua University, Beijing 100084, China

*Corresponding author email: luyc@tsinghua.edu.cn

Dissolution and reaction of chlorine gas in 1,2-dichloroethane

Carbon tetrachloride, commonly used to dissolve Cl_2 , was banned due to environmental issues. Other chlorinated solvents included tetrachloroethane, petroleum ether, chlorobenzene, cyclohexane, *n*-hexane, dichloroethane, chloroform, chlorobutane, etc. For this reaction system, the following factors were mainly considered in the choice of solvent: (a) the solvent can dissolve Cl_2 well; (b) it does not react with Cl_2 and the substrate; (c) it is easy to separate after the reaction.

1,2-Dichloroethane (DCE) was placed in a 300 mL high-pressure reactor (316L; Anhui Kemi Machinery Technology Co., Ltd.), and added a certain amount of Cl_2 to absorb and dissolve under different temperatures and pressures with 500 rpm magnetic stirring.

The amount of Cl_2 dissolved in DCE was determined by the titration method.¹ A part of the dissolved solution was placed in the KI solution; dissolved Cl_2 reacted with I^- to obtain I_2 . Then the content of I_2 was titrated by $\text{Na}_2\text{S}_2\text{O}_3$ solution to determine the content of dissolved Cl_2 .

The reaction situation of Cl_2 and DCE was determined by the GC method. The solution after the reaction was taken as the GC sample for analysis. The GC sample (0.5 μL) was injected in the GC-2014 instrument (Shimadzu) equipped with a DB-FFAP column (length, 30 m; ID, 0.320 mm; film thickness, 0.25 μm). The oven temperature was maintained at 50 $^\circ\text{C}$ for 5 min, then increased to 240 $^\circ\text{C}$ by 15 $^\circ\text{C}/\text{min}$, and then held for 5 min. The flow rate of the nitrogen as the carrier gas was 1.0 mL/min with a split ratio of 30:1; the injector and FID detector temperatures were set to 280 $^\circ\text{C}$ and 300 $^\circ\text{C}$, respectively. The content of unreacted DCE was determined by using the area normalization method.

The dissolution and reaction of Cl_2 in DCE was shown in Table S1. When the reaction temperature was lower than or equal to 60 $^\circ\text{C}$, DCE hardly reacted with Cl_2 even if extending the reaction time, and the unreacted DCE content remains over 96 wt% (Entry 2, Table S1). And the dissolved Cl_2 content could be adjusted by controlling the temperature and pressure during absorption and dissolution (Entries 7-9, Table S1). For example, when the dissolving temperature was 40 $^\circ\text{C}$, the dissolved Cl_2 content

corresponding to the pressure of 0.1 MPa and 0.25 MPa was 5.0 wt% and 14.8 wt%, respectively. It indicated that DCE was a solvent that can dissolve Cl₂ and did not react with Cl₂.

To this end, the dissolution of Cl₂ in DCE was controlled at a lower temperature (like 40 °C) to obtain a DCE solution with a certain chlorine content, and then the flow reaction at a high temperature (60 °C) was carried out. Since Cl₂ basically did not react with DCE at lower temperatures (≤ 40 °C), and the residence time at high temperatures was extremely short (only a few seconds), it can be considered that the reaction of Cl₂ with DCE in the entire reaction process can be neglected. And the boiling point of DCE (83.7 °C) is higher than the reaction temperature, and it is easy to transport during the reaction and separate by vacuum distillation after the reaction. Therefore, DCE is a potential solvent to dissolve Cl₂ to carry out the liquid phase chlorination reaction.

Table S1. Situations of Cl₂ dissolved in DCE and reacted with DCE under different temperature and pressure

Entry	Temperature /°C	Time /h	Pressure /MPa	Dissolved Cl₂ /wt%	Unreacted DCE /wt%
1	70	2	0.52	8.0	90.6
2	60	2	0.61	10.4	96.6
3	50	2	0.76	18.7	97.1
5	40	5	0.50	28.5	99.6
6	30	3	0.55	42.2	99.5
7	40	2	0.25	14.8	99.7
8	40	2	0.20	10.1	99.7
9	40	2	0.10	5.0	99.8

HPLC-MS results analysis

Combining the results of HPLC-MS and existing standard compounds, the obtained products were analyzed to obtain the information of by-products. The obtained results are shown in Figure S1 and Table S2.

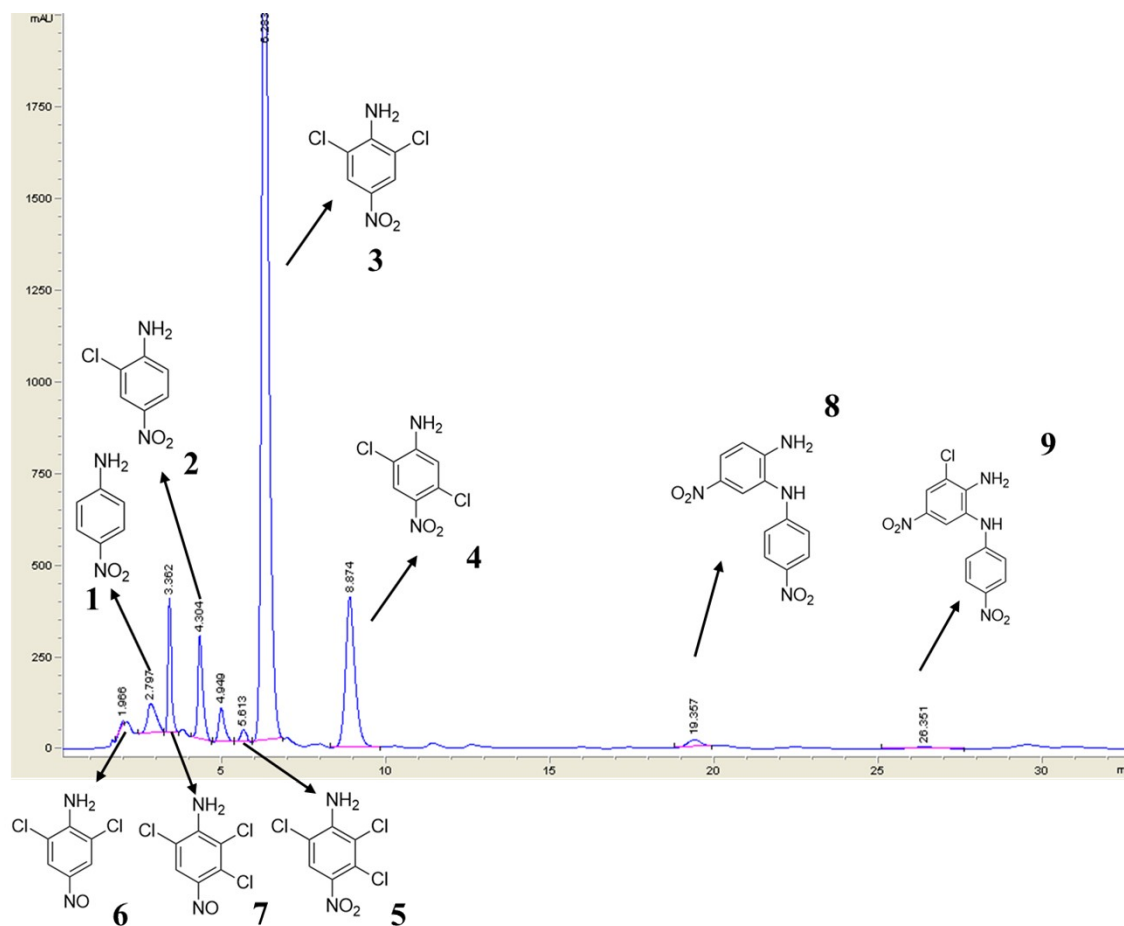


Fig. S1. HPLC-MS spectra

Table S2. Information of reacted sample by HPLC-MS analysis

NO.	Name	Chemical Formula	HRMS-ESI (m/z) ([M - H] ⁻)	
			Calcd	Found
1	4-nitroaniline	C ₆ H ₆ N ₂ O ₂	137.04293	137.03558
2	2-chloro-4-nitroaniline	C ₆ H ₅ ClN ₂ O ₂	171.00396	170.99660
3	2,6-dichloro-4-nitroaniline	C ₆ H ₄ Cl ₂ N ₂ O ₂	204.96498	204.95761
4	2,5-dichloro-4-nitroaniline	C ₆ H ₄ Cl ₂ N ₂ O ₂	204.96498	204.95753

5	2,3,6-trichloro-4-nitroaniline	$C_6H_3Cl_3N_2O_2$	239.92601	239.90256
6	2,6-dichloro-4-nitrosoaniline	$C_6H_4Cl_2N_2O$	188.97007	188.96283
7	2,3,6-trichloro-4-nitrosoaniline	$C_6H_3Cl_3N_2O$	222.93110	222.92377
8	5-nitro- <i>N</i> ¹ -(4-nitrophenyl)benzene-1,2-diamine	$C_{12}H_{10}N_4O_4$	273.07020	273.06296
9	<i>N</i> ¹ -(2-chloro-4-nitrophenyl)-5-nitrobenzene-1,2-diamine	$C_{12}H_9ClN_4O_4$	307.03123	307.02386

Interpretation on side reactions

To explore the effect of different additives on the stability of the product 2,6-dichloro-4-nitroaniline (DCNA) during the reaction, the product and different additives were reacted under batch conditions, and the result is as shown in Table S3. When there are acid and iron powder at the same time (Entries 2-5 in Table S3), the HPLC results indicated that a certain amount of 4-nitroaniline (PNA) appeared after the reaction. This may be due to the dechlorination reaction of DCNA in the environment of acid and metal ions. For this reason, the introduction of metal ions should be avoided as much as possible during the reaction, such as the use of non-metallic pipe fittings.

Table S3. Effect of different additives on the product

Entry	Annexing agent				Mass fraction/%				
	H ₂ SO ₄	DCE	HCl	Fe power	PNA 1	CNA 2	DCNA 3	Isomer 4	Nitrous 6, 7
1	✓	✓	✓		0.01	0.22	95.9	3.13	0.56
2	✓	✓		✓	6.89	0.18	89.0	2.44	0.48
3	✓		✓	✓	9.22	0.14	87.2	2.46	0.69
4		✓	✓	✓	5.84	0.16	90.6	2.67	0.59
5	✓			✓	36.4	0.11	60.1	2.12	1.03
6	✓		✓		0.08	0.18	95.4	3.05	1.21
7		✓	✓		0.00	0.24	95.8	3.33	0.44
8		✓		✓	0.03	0.25	95.2	3.72	0.70

Reference conditions: Batch reaction with 500 rpm magnetic stirring; temperature, 50 °C; time, 4 h; usages of each substance: 3 g DCNA, 12 ml 98 wt% H₂SO₄, 22.8 g DCE, 1.81 g HCl, 1 g Fe power; dilute, neutralize and extract after the reaction. Sulfuric acid was used here to better dissolve the product for the reaction.

Furthermore, Table S4 shows the stability of the product under continuous flow using the DCNA as the raw material. When there was no Cl₂ in the DCE phase, the product was stable after passing through the reaction tube under the environment of acid and DCE. However, when there was Cl₂ in the DCE phase, the mass fraction of DCNA after the reaction was significantly reduced, and there appeared by-products like isomers, dimers, and nitrous substances. These results indicated that when excess chlorine was present, the product DCNA was more prone to participating in side reactions. They may be some reduction reactions involving some metal ions activated by Cl₂ in the system (some pipe fittings are inevitably made of metal). Therefore, on the one hand, it is necessary to control the use of chlorine; and on the other hand, it is required to quench the reaction in time to avoid side reactions.

Table S4. Effect of Cl₂ on products under continuous flow

Entry	Acid phase	DCE phase	Mass fraction/%					Nitrous 6, 7
			PNA 1	CNA 2	DCNA 3	Isomer 4	Dimer 8, 9	
1	1 g DCNA in 4 ml H ₂ SO ₄	DCE	0.09	0.18	95.6	2.91	0.00	1.15
2	1 g DCNA in 4 ml H ₂ SO ₄ and 1 ml HCl	DCE	0.08	0.19	95.8	2.94	0.00	0.96
3	1 g DCNA in 4 ml H ₂ SO ₄	DCE with 10 wt% Cl ₂	0.82	0.14	15.4	36.4	23.2	24.1

Reference conditions: reaction tube, micropacked-bed reactor with 0.177-0.25 mm packing; reaction temperature, 60 °C; residence time, 20.4 s; flow rate of acid phase and DCE phase, 1.96 and 3.44 ml/min; dilute, neutralize and extract after the reaction. Sulfuric acid was used here to better dissolve the product for the reaction.

References

- 1 N. W. Taylor and J. H. Hildebrand, *J. Am. Chem. Soc.*, 1923, **45**, 682-694.